Highly Efficient Glycosylation of Sapogenins

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Introduction

Saponins are widely distributed in many plants and intimately involved in our daily lives.[1] They exist in relatively high quantities in many significant food and beverage plants, including oats, peanuts, soybeans, lentils, mung beans, garlic, onions, spinach, asparagus, jujube, quillaja, tea, etc. Saponins also figure prominently as active constituents in many well-known herbal medicinal plants, especially those from the Orient, such as ginseng, notoginseng, licorice, horse chestnut, red clover, senegae, and primula.[1] Saponins exist in the plants in such a complicated manner that one plant species normally contains more than several dozen structurally similar saponins.[1] Isolation of a single pure saponin from plants, especially in considerable amounts, is extremely formidable. Consequently, many saponin extracts from herbs have been directly used to treat various human diseases without evaluation of the pharmacological activities of each component. Chemical synthesis would provide a realistic way to obtain homogeneous saponins and therefore opportunities for understanding the actions of a saponin on the human body.

Structurally, saponins contain two quite distinct parts, a sugar part and a sapogenin part that is a steroid or triterpene. The chemical syntheses of both parts have been extensively studied. Therefore, the key to synthesizing a saponin turns out to be the glycosylation of the corresponding sapogenin. In most saponins, the sugar moiety is attached to the 3-OH of a sapogenin via the 1,2-*trans*-glycosidic bond.[1] The coupling of a sugar moiety to the 3-OH of a sapogenin has shown to be problematic. The use of 2-OAc glycosyl donors, such as glycosyl bromide,[2] fluoride,[3] trichloroacetimidate,[4] and acetate,[5] led to the corresponding saponins in low to moderate yields as a result of acetyl group transfer and ortho ester formation side reactions. The use of glycosyl donors without the participation of a neighboring group commonly produced a mixture of α and β anomers, which were difficult to separate.[6] Recently, Nishizawa applied thermoglycosylation,[7] Danishefsky used a 1,2-anhydro sugar,[8] and Gin employed a glycal[9] in the construction of the glycosidic bond between a monosaccharide and the 3-OH of a sapogenin. We report here a highly efficient and practical procedure for the glycosylation of sapogenins.

Results and Discussion

In our previous synthesis of diosgenyl saponins,[10] we attached the first glucose residue to diosgenin first and then extended the sugar chain sequentially. By using several different types of glycosyl donors in each glycosylation step, a family of diosgenyl saponins was readily synthesized. In those cases, we employed benzoyl group protected ethyl 1-thioglucopyranoside[10a] and glucopyranosyl bromide[10b] donors for the glycosylation of diosgenin. The use of a benzoyl group in place of an acetyl group completely avoided the acyl group transfer, and ortho ester formation was found to be dependent on the promoter used. To prepare large quantities of diosgenyl saponins for animal testing, we needed a practical method to prepare the starting saponin, i.e., diosgenyl β-D-glucopyranoside (trillin). The use of the previous protocols is obviously not the choice because of the expensive and toxic promoters used and the moderate yields that resulted during the glycosylation reactions. Fortunately, we disclosed a method that utilized 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **1a**[11] as the glycosyl donor and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.05 equiv) as a promoter[12] that produces the corresponding saponin quantitatively. This reaction was successfully scaled up to the preparation of 35 g of trillin in high yields (Scheme 1). Moreover, it was found that this reaction is complete within 5 min, and no special care is needed regarding, for example, the amount of TMSOTf used, the addition sequence, the addition speed, and the reaction temperature (from 0 to 25 °C or at ambient temperature). In this procedure, only two factors are essential: the benzoyl protection and the TMSOTf promotion. The use of BF_3-OEt_2 as a promoter led to relatively complex products.

Encouraged by the above results, we examined the generality of the present procedure for the glycosylation of sapogenins. To this end, we chose the glycosyl trichlo-

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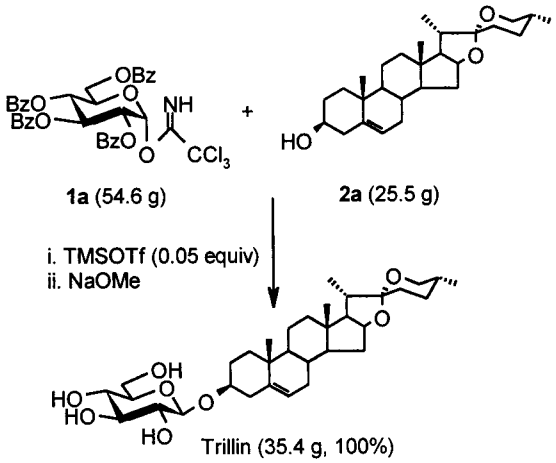
Scheme 1. Practical Preparation of Trillin



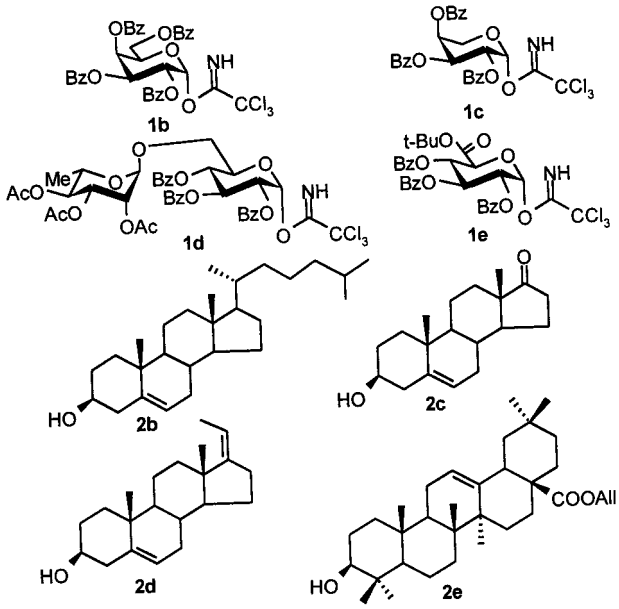


Figure 1. Selected donors and acceptors.

roacetimidates **1a**−**e** as the donors. These benzoyl-protected glycosyl imidates (**1a**−**e**), which were readily prepared from the corresponding 1-OH sugars,[11,13−14] were quite stable; no decomposition was detected after being stored at room temperature for more than 3 months. Diosgenin (**2a**), cholesterol (**2b**), dehydroisoandrosterone (**2c**), pregnadiene (**2d**), and allyl oleanate (**2e**) were chosen as the acceptors (Figure 1). The coupling results are listed in Table 1.

As shown in Table 1, all of the coupling reactions were complete within 15 min, providing the corresponding saponins in excellent yields (90−100%). No benzoyl group transfer products or ortho esters have been detected. The newly formed glycosidic bonds were proved to be exclusively 1,2-*trans* on the basis of their ^{1}H NMR spectra. Compared with a previous example, where coupling of diosgenin with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl (1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate led to the corresponding product in only moderate yield (43%),[6c] herein, glycosylation of diosgenin with disaccharide imidate **1d**, which has benzoyl protecting

Table 1. Glycosylation of Sapogenins[a]

entry	donors (1.2−1.3 equiv)	sapogenins (1.0 equiv)	products	yields[b] (%)
1	**1a**	**2a**	**3**	100
2		**2b**	**4**	90
3		**2d**	**5**	100
4		**2e**	**6**	100
5	**1b**	**2a**	**7**	92
6		**2b**	**8**	100
7		**2c**	**9**	92
8	**1c**	**2a**	**10**	92
9		**2b**	**11**	93
10		**2e**	**12**	91
11	**1d**	**2a**	**13**	100
12		**2b**	**14**	100
13		**2c**	**15**	93
14	**1e**	**2a**	**16**	90
15		**2b**	**17**	95
16		**2e**	**18**	90

[a] Conditions: donor **1a**−**e** (1.2−1.3 equiv), acceptor **2a**−**e** (1.0 equiv), 4 Å MS, CH_2Cl_2, TMSOTf (0.05 equiv), ambient temperature, 15 min. [b] Isolated yields.

groups, produced the corresponding saponin (**13**) quantitatively (entry 11). Glycosylation of the hindered 3-OH of allyl oleanate (**2e**), which has neighboring geminal methyl groups, also gave excellent yields of the corresponding products (entries 4, 10, and 16). The previous glycosylation attempts on the similar triterpene alcohols using glycosyl bromides[2b] and chlorides[6a,b] led to only moderate yields of the corresponding products. Moreover, the glucuronide moiety was also introduced into sapogenins in excellent yields by the present procedure (entries 14−16). Glycosylation with uronic acid donors has been found to be difficult[15] as a result of the electron-withdrawing 5-alkoxylcarbonyl group, which exerts a remarkable destabilizing effect on the incipient C-1 cation. Consequently, the alternative to synthesizing uronides has been employed by performing the glycosylation with a neutral hexose donor and oxidizing to the uronide afterward.[15] Recently, Oscarson developed ethyl thioglucuronides as glycosyl donors, which have activating benzyl groups at O-3 and O-4 and neighboring ester groups (acetyl, benzoyl, pivaloyl, and anisoyl) at O-2.[16] The present procedure should provide an easier entry to the uronic acid containing compounds. Finally, it is worth noting that the present procedure is within the scope of Schmidt glycosylation[12] and that the combined use of benzoyl group protected imidates as donors and TMSOTf as the promoter has occasionally been used in the past years;[17] however, this work provides clear advantages to the use of these systems in the synthesis of saponins.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds and reproduction of ^{1}H NMR spectra for compounds **4**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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