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An Efficient Way for Glycosylation of Spirostanol

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Abstract: Using thioglycosides as donors, trimethylsilyl trifluoromethanesulfonate (TMSOTf) and N-iodosuccinimide(NIS) as promoter, a modified procedure for the glycosylation of spirostanol was developed. A series of saponins were synthesized in mild condition with excellent yields.

Keywords: Spirostanol glycoside, glycosylation, trimethylsilyl trifluoromethanesulfonate, ethyl 1-thioglycoside, N-iodosuccinimide.

Spirostanol glycosides are naturally occurring glycosides and as active constituents in many well-known herbal medicinal plants[1]. Some of them have been shown to be antidiabetic[2], antitumor[3], antitussive[4], and platelet aggregation inhibitor[5]. Structurally, the sugar moiety was attached to the 3 position of the aglycone through 1, 2–*trans* glycosidic bond.

To synthesize steroidal saponins, many 2-acetyl sugars had been used as donors for the glycosylation of the aglycone[6]. However, because of acetyl migration and ortho ester formaion, those reactions gave the corresponding saponins in low to moderate yields. Many researchers have reported various methods for this purpose with high yields[7-11]. Here we report our work for the glycosylation of steroid.

Thioglycosides were often used as donors in the synthesis of oligosaccharides. Biao Yu and co-workers had used 1-thioglycosides as one of donors to extend the sugar chain of diosgenin saponins *via* 'one-pot' manner [12].

We turned the monosaccharides into corresponding protected ethyl 1-thioglycosides by the method reported before[13]. Using the thioglycosides as dononrs, three different spirostanols tigogenin **1**, diosgenin **2** and hecogenin **3**, were glycosylated in excellent yields. The coupling result was shown in **Table 1**. During the process of the glycosylation for the three spirostanols, no acyl transfer products or ortho esters had been found. All the structures of the products were confirmed by ^{1}H-NMR and the spectra data proved that the glycosidic bonds between the sugar moiety and aglycone were exclusively 1, 2-*trans*.

Myszka[14] employed N-tetracholorophthaloyl protected D-glucosamine bromide promoted by AgOTf to couple with diosgenin giving the product **2d** in moderate yield. In

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Table 1 Glycosylation of spirostanol

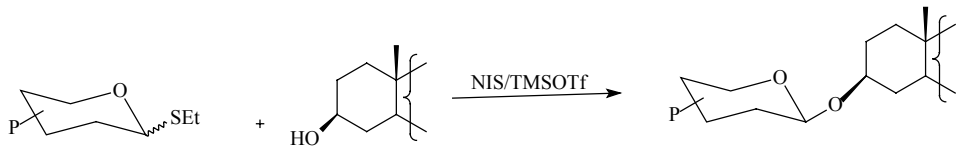
Entry	Donors	Acceptors	Products	δ_H(*ppm*)	$J_{1,2}$ (Hz)	Yield
1	**a**	**1**	**1a**	5.44	8.7	92%
2	**a**	**2**	**2a**[15]	5.46	8.7	Quantitative
3	**a**	**3**	**3a**	5.45	8.7	Quantitative
4	**b**	**1**	**1b**	4.90	7.5	91%
5	**b**	**2**	**2b**	4.90	8.1	93%
6	**b**	**3**	**3b**	4.88	7.5	Quantitative
7	**c**	**1**	**1c**	5.15	1.8	95%
8	**c**	**2**	**2c**	5.16	1.8	95%
9	**c**	**3**	**3c**	5.16	1.5	92%
10	**d**	**2**	**2d**[14]	5.47	8.4	93%
11	**e**	**2**	**2e**[16]	4.89	7.9	95%
12	**f**	**1**	**1f**	4.84	8.1	92%

the present glycosylation procedure, the yield of the corresponding product **2d** was 93%. Using N-phthaloyl protected D-glucosamine bromide, Zou[15] got the protected diosgenin saponin **2a** in the yield of 82%. Applying 1-thioglycoside as donor, we got the product **2a** quantitatively. Deng[16] applied NIS-AgOTf as promoter to couple a 1-thioglucoside with diosgenin offering the product **2e** in the yield of 55%. With our glycosylation procedure, the yield of **2e** was 95%. This reaction was successfully scaled up to the preparation of tigogenyl-2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside in excellent yield, which was the key intermediate for our parallel synthesis of tigogenyl glycosides.

General procedure for glycosylation

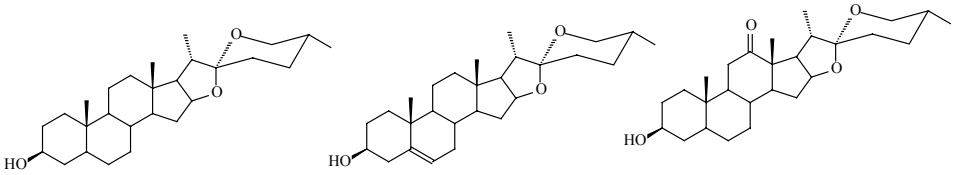
1 eq. of sapogenin, from 1.2 to 1.5 eq. of ethyl 1-thioglycoside was dissolved in anhydrous dichloromethane, powdered 4 Å molecular sieves was added and the reaction mixture was stirred at room temperature under argon for 30 min. At -15℃ 1.5 eq. NIS in dichloromethane was added, 15 min later 0.2 eq TMSOTf was injected into the mixture. When TLC showed the reaction was completed, a few drops of Et_3N were added, diluted with dichloromethane, filtered through celite and concentrated in vacuum. The residue was chromatographed on silica gel (petroleum ether/ ethyl acetate =10:1-4:1) giving white amorphous powder.

Figure 1 Selected donors and acceptors



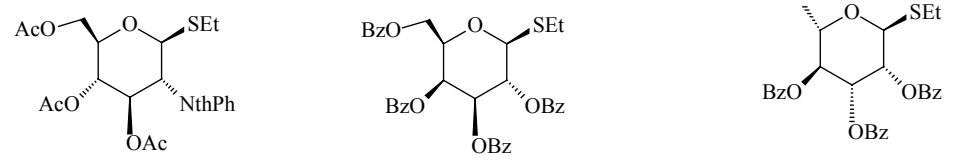
donors acceptors products

Acceptors:

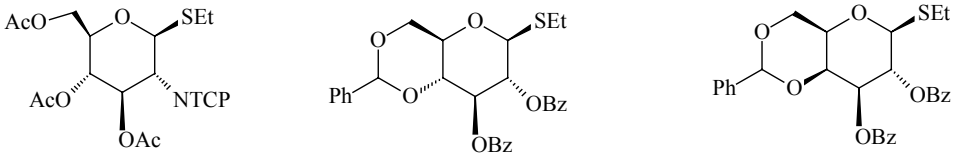


1 **2** **3**

Donors:



a **b** **c**



d **e** **f**

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17. Selected spectral data of synthesized new compounds:
    1a: ^{1}H-NMR ($CDCl_3$, δ_{ppm}), 7.87-7.75 (m, 4H, NthPh), 5.81(dd, 1H, $J_{3',4'}$ 9.0, $J_{2',3'}$ 10.5 Hz, H-3′), 5.44(d, 1H, $J_{1',2'}$ 8.7 Hz, H-1′), 5.12 (dd, 1H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 9.0 Hz, H-4′), 4.35(m, 1H, H-16), 4.25(m, 1H, H-2′), 4.15 (m, 2H, H-6′), 3.85(m, 1H, H-5′), 3.50-3.26 (m, 3H, H-3 and H-26), 2.10、2.02、1.85 （3s, 9H, $COCH_3$）, 0.94 (d,3H, J 6.6 Hz), 0.78 (d,3H, J 5.7 Hz), 0.71 (s, 3H), 0.66 (s, 3H). **1b**: ^{1}H-NMR ($CDCl_3$, δ_{ppm}), 8.11-7.21 (m, 20H, H-OBz), 5.96(d, 1H, $J_{3',4'}$ 3.3 Hz H-4′), 5.75 (dd, 1H, $J_{1',2'}$ 7.5, $J_{2',3'}$ 10.5 Hz, H-2′), 5.57(dd, 1H, $J_{2',3'}$ 10.5, $J_{3',4'}$ 3.3 Hz , H-3′), 4.90 (d, 1H, $J_{1',2'}$ 7.5 Hz, H-1′), 4.66 (dd, 1H, $J_{5',6'a}$ 6.9, $J_{5',6'b}$ 6.9 Hz, H-5′), 4.47 (m, 2H, H-6′), 4.30 (m, 1H, H-16), 3.61-3.44 (m, 3H, H-3 and H-26), 1.05 (d, 3H, J 7.8 Hz), 0.92 (d, 3H, J 6.0 Hz), 0.88 (s, 3H), 0.72 (s, 3H). **1c**: ^{1}H-NMR ($CDCl_3$, δ_{ppm}), 8.11-7.23 (m, 15H, H-OBz), 5.86(dd, 1H, $J_{2',3'}$ 2.4, $J_{3',4'}$ 9.9 Hz H-3′), 5.65 (t, 1H, J 9.9 Hz, H-4′), 5.58(dd, 1H, $J_{2',3'}$ 2.4, $J_{1',2'}$ 1.8 Hz H-2′), 5.15 (s, 1H, H-1′), 4.49 (m, 1H, H-16), 3.63-3.45(m, 3H, H-3 and H-26), 1.33 (d, 3H, $J_{5',6'}$ 6.3 Hz H-6′). **1f**: ^{1}H-NMR ($CDCl_3$, δ_{ppm}), 8.00-7.33(m, 15H), 5.80(dd, 1H, $J_{1',2'}$ 8.1, $J_{2',3'}$ 10.5 Hz , H-2′), 5.53(s, 1H, PhCH), 5.32(dd, 1H, $J_{2',3'}$ 10.5, $J_{3',4'}$ 3.6 Hz , H-3′), 4.84 (d, 1H, $J_{1',2'}$ 8.1Hz, H-1′), 4.57(d, 1H, $J_{3',4'}$ 3.6Hz, H-4′),4.38 (m, 2H, H-16 and H-5′), 4.12 (d, 1H, H-26a), 3.62 (m, 2H, H-6′), 3.48-3.32 (m, 2H, H-3 and H-26b).0.95(d, 3H, J 6.9Hz),0.78 (d, 3H, J 6.0Hz), 0.72(s, 3H), 0.68(s, 3H). **2b.** ^{1}H-NMR ($CDCl_3$, δ_{ppm}), 8.11-7.26(m, 20H, H-OBz), 5.97(d, 1H, $J_{3',4'}$ 3.6 Hz H-4′), 5.77 (dd, 1H, $J_{1',2'}$ 8.1, $J_{2',3'}$ 10.4 Hz, H-2′), 5.58(dd, 1H, $J_{2',3'}$ 10.4, $J_{3',4'}$ 3.6 Hz , H-3′), 5.21(d, 1H, $J_{5,6}$ 4.5 Hz H-6), 4.90 (d, 1H, $J_{1',2'}$ 8.1 Hz, H-1′), 4.67 (dd, 1H, $J_{5',6'a}$ 63, $J_{5',6'b}$ 6.3 Hz, H-5′), 4.44-4.36(m, 2H, H-6′), 4.32(q, 1H, H-16),3.57-3.33(m, 3H, H-3 and H-26), 2.18(m, 2H), 0.99(d, 3H, J 5.4 Hz), 0.92 (s, 3H), 0.78(d, 3H, J 6.3Hz), 0.76(s, 3H). **2c** ^{1}H-NMR ($CDCl_3$, δ_{ppm}), 8.11-7.23(m, 15H, H-OBz), 5.86(dd, 1H, $J_{2',3'}$ 3.6, $J_{3',4'}$ 9.7 Hz H-3′), 5.68 (dd, 1H, J 9.6 10.8 Hz, H-4′), 5.61(dd, 1H, $J_{2',3'}$ 3.6, $J_{1',2'}$ 1.8 Hz, H-2′),5.37(d, 1H, $J_{5,6}$ 4.5 Hz H-6) 5.16(s, 1H, H-1′),4.40(m, 1H, H-16), 4.25(m, 1H, H-5′), 3.59-3.38(m, 3H, H-3 and H-26), 1.33(d, $J_{5',6'}$ 6.3 Hz H-6′).
18. Data of compounds **3a** to **3c** were deposited in editorial office of CCL.
19. The spectral data of **2a**, **2d** and **2e** were the same as references 14, 15 and 16 reported.

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