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Zirconium tetrachloride as a convenient catalyst for the glycosylation of sterols with 2,3,4,6,6′-penta-*O*-acetyl-5-hydroxymethylgalactosyl fluoride

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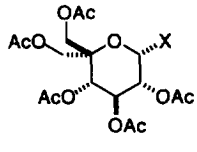
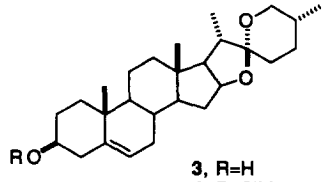
Abstract: Zirconium tetrachloride was found to catalyze glycosylation of various sterols with peracetylated 5-hydroxymethylene galactosyl fluoride. © 1997 Elsevier Science Ltd

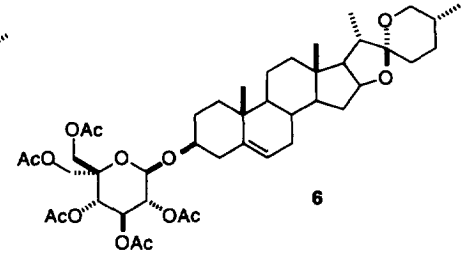
In the course of our work on cholesterol-lowering glycosides[1] we have experienced low yields of the glycosylation reaction using 5-substituted peracetylated galactosyl bromide **1**, diosgenin (**3**) and mercury cyanide in acetonitrile.[1b,2] The low yields, attributed to low thermal stability of **1** and general low reactivity of sterols, directed our attention to galactosyl fluorides known for considerably higher stability and good reactivity.[3] In fact crystalline **2**,[4] prepared in 75% yield from the corresponding hexaacetate using HF–pyridine,[5] was found to be stable at room temperature for many months. However, when it was used in a $BF_3 \bullet Et_2O$ catalyzed glycosylation reaction[6] with diosgenin or its trimethylsilyl ether **4**, several products were formed with the acetylated diosgenin **5** as the main one. This transesterification, frequently a predominant course of reaction, was the apparent reason for rather low yields (20%) of the desired product **6**. Other glycosylation promoters offered little improvement except $AgClO_4$–$SnCl_2$ which increased the yield by 5–10% but required longer reaction times compared to BF_3–Et_2O catalyzed reaction. Also, silver based reagents are typically not the first choice due to economic and toxicological reasons.



1, X=Br
2, X=F



3, R=H
4, R=$SiMe_3$
5, R=Ac



6

The need for a better catalyst prompted us to investigate several halides of titanium, tin, vanadium, zinc and zirconium searching for a Lewis acid with the right balance of acidity and transesterification properties. As a result of this search we found that zirconium tetrachloride[7] is the catalyst that can efficiently promote glycosylation reaction of **2** and **4** with little formation of the transesterification side product **5**.

With such promising results obtained with zirconium tetrachloride and diosgenin we decided to investigate other sterols using their trimethysilyl ether derivatives as glycosyl acceptors.

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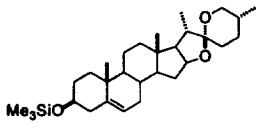
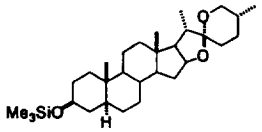
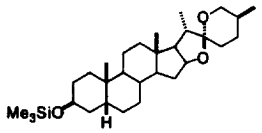
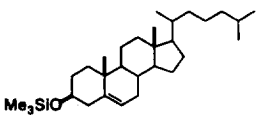
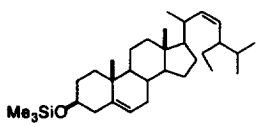
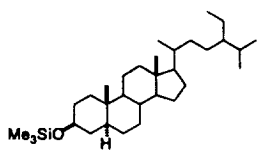
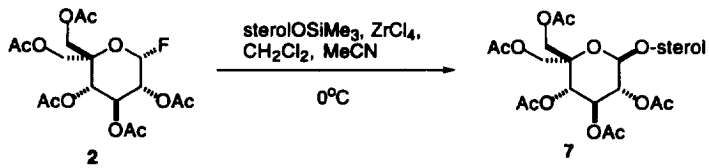
Table 1. Glycosylation of sterols with peracetylated 5-hydroxymethylene galactosyl fluoride[8]

entry	sterol	glycosyl acceptor	product	yield (%)[a,b]
1	diosgenin		**6**	58
2	tigogenin		**7a**	45
3	sarsasapogenin		**7b**	27
4	cholesterol		**7c**	43
5	stigmasterol		**7d**	62
6	stigmastanol		**7e**	64

[a] Isolated yields after silica gel chromatography,

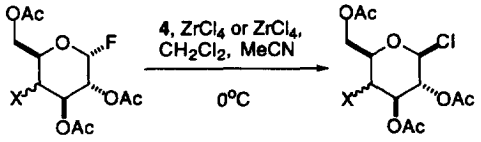
[b] Satisfactory ^1H, ^{13}C NMR and MS spectra, and elemental analysis were obtained for all glycosides.



The results obtained from reactions run according to a general procedure[8] are summarized in Table 1. Good isolated yields were obtained in all cases except sarsasapogenin (entry 3), the least reactive acceptor due to its cis decaline configuration of rings A and B which forces the 3-β silyloxy group into an axial position. Both unsaturated (entry 1, 4, 5) and saturated sterols (entry 2, 3, 6) worked well under the $ZrCl_4$ catalyzed glycosylation conditions. The spiroketal system (entry 1, 2, 3) was found to be compatible with the reaction conditions. All sterol glycosides formed exclusively as β

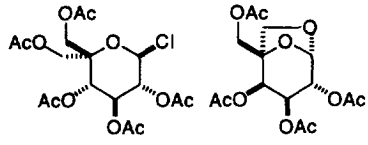
annomers based on ^1H and ^{13}C NMR spectra of crude reaction mixtures.[9] Transesterification leading to acetylated sterols was consistently a minor side reaction (<5%).

Once the new conditions for the glycosylation reaction had been established and further proven to work on multimolar scale, we decided to test the method for applicability to glycosyl fluorides derived from common sugars. Interestingly, no glycoside formed when peracetylated galactosyl fluoride **8** or glucosyl fluoride **9** were used in reaction with **4**. Instead, chlorides **10** and **11** respectively, with β-configuration at the anomeric center, were obtained in better than 90% yield.



8, X=α-OAc,
9, X=β-OAc

10, X=α-OAc,
11, X=β-OAc



12 **13**

Formation of **10** and **11** suggests that the $ZrCl_4$ catalyzed glycosylation involving **2** could also proceed through an intermediate chloride **12**. The higher reactivity of **12** over **10** or **11** could then be explained by the additional 1,3-neighboring group assistance of the C5 acetoxymethylene group. The fact that small amounts of anhydro-sugar **13** form during reactions with glycosyl acceptors of low reactivity (sterols) but not with more reactive primary alcohols like methanol or allyl alcohol seems to support such assistance.

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3. For example: a) Mukaiyama, T.; Hashimoto, Y.; Shoda, S. *Chem. Lett.* **1983**, 935; b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1383; c) Nicolau, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1994**, *106*, 4189–4192.
4. ^{13}C NMR ($CDCl_3$) data for the fluoride **2** were as follows: 169.76, 169.37, 105.87, 102.81, 78.48, 67.41, 66.71, 66.39, 64.71, 62.85, 61.85, 20.40, 20.28.
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8. The following procedure describing the preparation of **6** was used for all glycosylations mentioned in this paper: A round-bottomed flask is charged with 102.0 mg (0.241 mmol) of **5**-hydroxymethylene galactosyl fluoride (**2**), 118.1 mg (0.241 mmol) of trimethylsilyl diosgenin (**4**) and 5 ml of dried 1,2-dichloroethane. The homogenous solution is cooled to −20°C and 344 μL of 0.7 M zirconium tetrachloride solution in acetonitrile (Alfa) is slowly added causing the reaction mixture to turn yellow. The temperature is increased to 0°C and the mixture is stirred for 16 hr. At this time TLC analysis shows complete disappearance of the fluoride. The reaction mixture

is diluted with methylene chloride and the solution is washed with saturated aqueous sodium bicarbonate and brine, then dried over anhydrous sodium sulfate. The solution is concentrated on a rotary evaporator and the crude product is purified by silica gel column chromatography hexane–ethyl acetate) to give 114.4 mg (58% yield) of diosgenin 5-hydroxymethylene galactoside **6** as a colorless solid (mp 185–7°C; R_f=0.38, hexane:ethyl acetate 7:3).

9. ^{13}C NMR resonances ($CDCl_3$, ppm) corresponding to the anomeric carbon of sterol glycosides were as follows: **6**, 97.29; **7a**, 96.90; **7b**, 95.38; **7c**, 97.39; **7d**, 94.14; **7e**, 97.33.

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