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Regioselective glycosylation of alcoholic hydroxyl and phenolic hydroxyl

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ABSTRACT

A novel method for regioselective glycosylation of alcoholic hydroxyl and phenolic hydroxyl of polyhydroxyl compounds with the appropriate choice of the different reaction conditions has been developed. Alcoholic hydroxyl was selectively glycosylated using Ag_2CO_3/DCM catalyst system, while using Ag_2CO_3/quinoline catalyst system phenolic hydroxyl was selectively glycosylated.

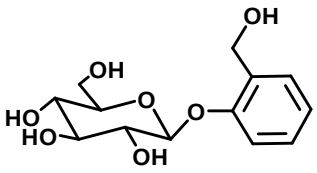
KEYWORDS

Glycosylation;
Regioselective;
Alcoholic hydroxyl;
Phenolic hydroxyl;
Pharmaceutical.

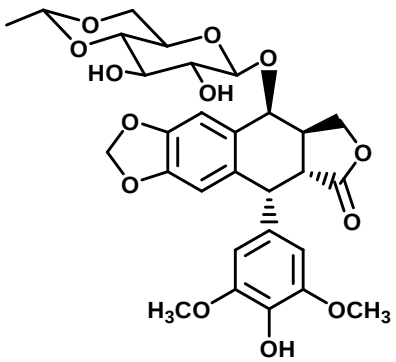
INTRODUCTION

Oligosaccharides and their conjugates with other biomolecules (glycoconjugates) play important in a wide variety of biological process and extensive studies are currently in progress to clarify the whole picture[1]. O-glycoside groups exist in a number of biologically important natural products and pharmaceuticals[2]. Their water solubility of hydrophobic molecules containing hydroxyl groups would influence their pharmacological properties, such as absorption, distribution, metabolism and excretion. Furthermore, glycosylation often reduces the irritability and toxicity of aglycone[3]. But aglycones of many drug molecules, such as salicin, etoposide, alcoholic hydroxyl and phenolic hydroxyl coexist[3,4] (Figure 1). To obtain these compounds, the development of efficient glycosylation reactions that can selectively protect and deprotect of hydroxyls is strongly required.

Using glycosyl halides as donors activating with a heavy metal ion, typically silver or mercury, is a traditional glycosylation method[2], such as the synthesis of rhamman oligosacchrides through highly regioselective 3-o-acylation of ally (or methyl) 4-o-benzoyl-α-L-rhamnopyranosides[6,7]. However, both alcoholic hydroxyl and phenolic hydroxyl can be easily glycosylated with Koenigs-Knorr method[8]. Selective glycosylation of alcoholic hydroxyl and phenolic hydroxyl has not been systematically reported up to now.



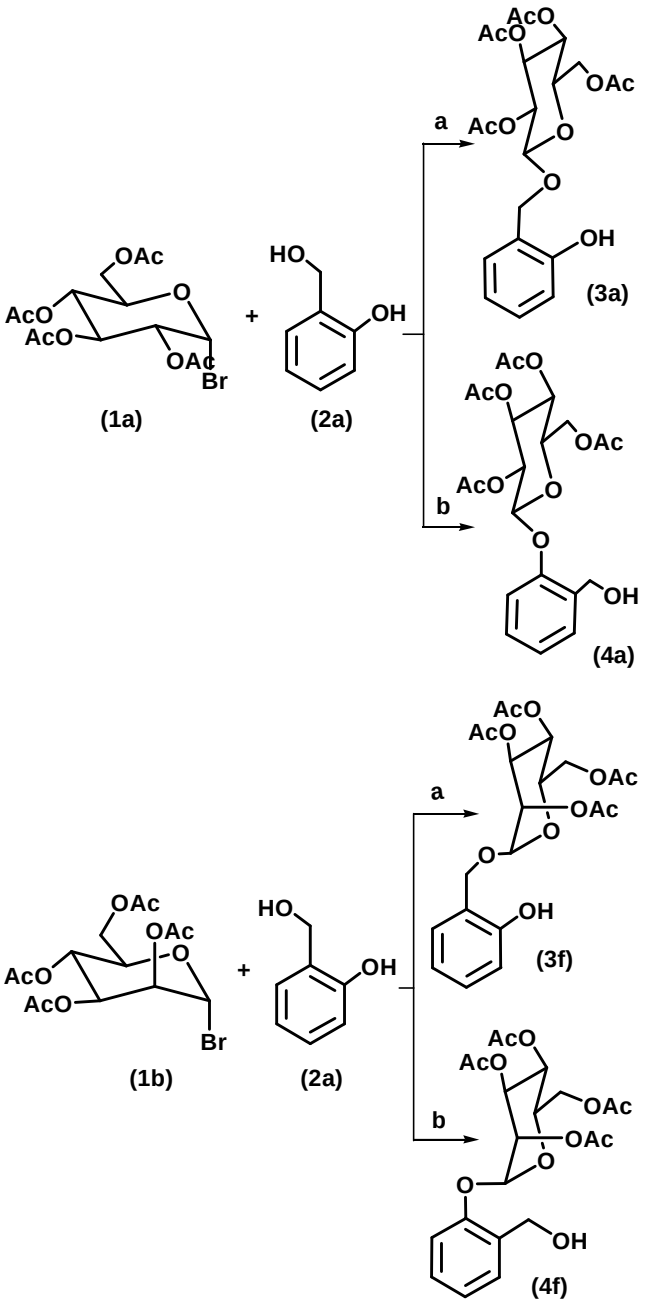
Salicin



Etoposide

Figure 1 : The structure of salicin and etoposide

Herein, we report a directly selective glycosylation of alcoholic hydroxyl and phenolic hydroxyl of polyhydroxyl compounds with the appropriate choice of the different experiment condition without the protection/deprotection strategy (Scheme 1).



Scheme 1 : Regant and condition: (a) Ag_2CO_3, DCM, rt; (b) Ag_2CO_3, Quinoline, rt

In a preliminary investigation, we found that 2,3,4,6-tetra-O-Acety-D-glucosyl bromide **(1a)** (1.0 equiv) reacted with saligenol **(2a)** (1.2 equiv) in the presence of Ag_2CO_3 and 4Å molecular sieves in DCM at room temperature give alcoholic hydroxyl glycosylated **(3a)** as a sole product in 67% yield, while phenolic hydroxyl of **(2a)** was selectively glycosylated to afford **(4a)** in 48% yield using quinoline as solvent. These results encouraged us to examine a number of other phenols containing alcoholic hydroxyl groups. As shown in TABLE 1, when Ag_2CO_3/DCM catalyst system was used, selective glycosylation of primary alcoholic hydroxyls of 4-hydroxy-phenylmethanol **(2b)** and 4-hydroxy-phenylethanol **(2c)** gave good yields (71% and 65%, entry 2 and 3), while glycosylation of the second alcohols 4′-hydroxy-1-phenylethanol **(2d)** and 4′-demethyl epipodophyllotoxin **(2e)** gave 42% (entry 4) and 36% yields (entry 5), respectively. When Ag_2CO_3/quinoline catalyst system was used, phenolic hydroxyls of **(2b-2e)** were glycosylated with moderate yields (30~55%) (entries 2~5).

To further demonstrate the generality of this strategy, 2,3,4,6-tetra-O-Acety-D-mannosyl bromide **(1b)** was chose as another glycosyl donor for the selective glycosylation. After D-mannosyl bromide **(1b)** was attached to saligenol **(2a)** under the two different conditions, **(3f)** (in 65% yield) and **(4f)** (in 47% yield) were obtained, respectively (TABLE 1, entry 6).

It is noteworthy that the glycosylation products of D-glucosyl bromide exhibits β-configuration (TABLE 1, entries 1-5), whereas the glycosylation products of mannosyl bromide possess α-configuration (TABLE 1, entry 6), which may be due to the neighboring-group participation of ester group at C-2[9].

In conclusion, we have developed a highly regioselective glycosylation method of the alcoholic hydroxyl or phenolic hydroxyl of phenols containing alcoholic hydroxyls. Using Ag_2CO_3/DCM catalyst system alcoholic hydroxyl was selectively glycosylated with D-glucosyl and D-mannosyl bromide as donors, while using Ag_2CO_3/quinoline system phenolic hydroxyl was selectively glycosylated.

ACKNOWLEDGMENTS

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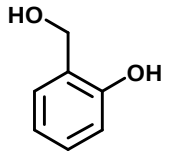
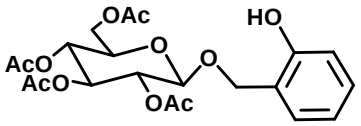
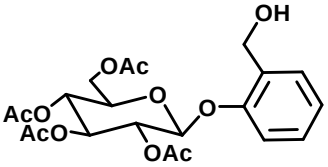
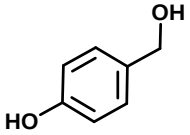
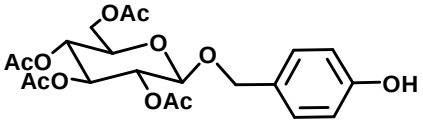
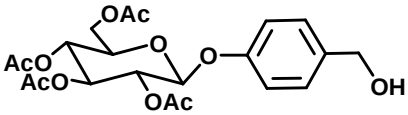
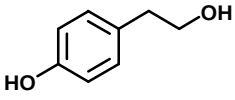
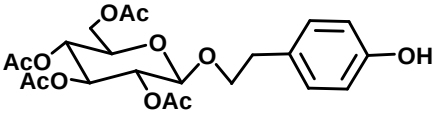
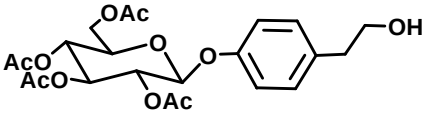
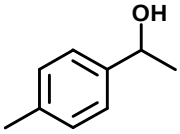
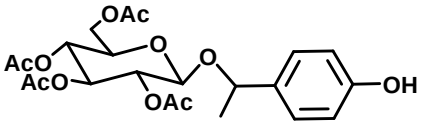
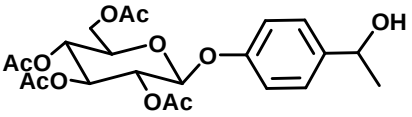
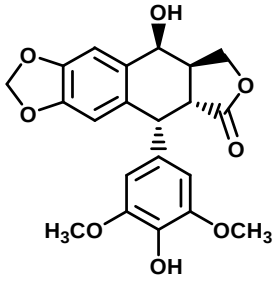
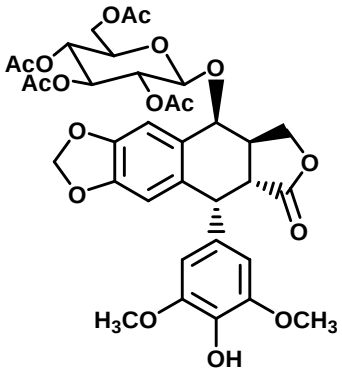
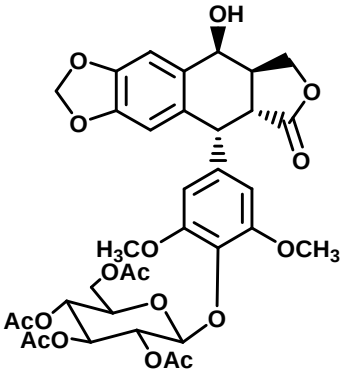
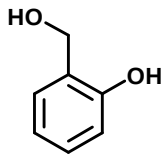
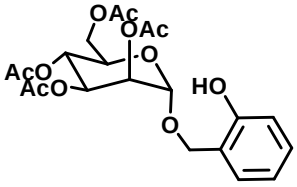
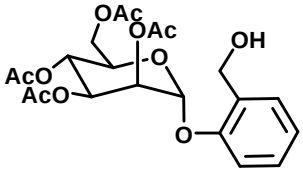
TABLE 1 : Selective glycosylation of alcoholic hydroxyl and phenolic hydroxyl with D-glucosyl (1a) or D-mannosyl bromides (1b)

Entry	Substrate	Product of alcoholic glycosylation Isolated yield	Product of phenolic glycosylation Isolated yield
1	 **(2a)**	 **(3a)** (67%)	 **(4a)** (48%)
2	 **(2b)**	 **(3b)** (71%)	 **(4b)** (55%)
3	 **(2c)**	 **(3c)** (65%)	 **(4c)** (51%)
4	 **(2d)**	 **(3d)** (42%)	 **(4d)** (46%)
5	 **(2e)**	 **(3e)** (36%)	 **(4e)** (30%)
6	 **(2f)**	 **(3f)** (65%)	 **(4f)** (47%)

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[10] Typical procedure for the glycosylation of alcoholic hydroxyl. To a solution of 2,3,4,6-Tetra-o-acetyl-α-D-glucopyranosyl bromide **(1a)** (2.1 g, 5 mmol) in anhydrous DCM (25 ml) were added **(2a)** (0.744 g, 6mmol), Ag_2CO_3 (2.76 g, 10 mmol) and powdered 4Å molecular sieves (1.5g) at room temperature. The reaction mixture was stirred overnight in the dark at room temperature, and then filtered. The filtrate was condensed in vacuo, and the residue was diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. After evaporated in vacuo, the residue was purified by column chromatography with n-hexane/EtOAc to give pure **(3a)** as a white solid. 1H NMR (500 MHz, CDCl3): δ 2.00 (3 H, s), 2.03 (3 H, s), 2.05 (3 H, s), 2.12 (3 H, s), 3.72£- 3.75 (1 H, m), 4.18 (1 H, dd, J = 4.7, 12.3 Hz), 4.30 (1 H, dd, J = 2.3,12.3 Hz), 4.65 (1 H, d, J = 8.0 Hz), 4.74-5.00 (2 H, 2d, J = 12.3 Hz), 5.06-5.07 (1 H, m), 5.13 (1 H, t, J = 9.5 Hz), 5.20 (1 H, t, J = 9.5 Hz), 6.49 (1 H, s, OH), 6.89-7.24 (m, 4 H) ppm; ESI–MS: m/z = 477$[M + Na]^+$.

[11] Typical procedure for the glycosylation of phenolic hydroxyl. A solution of 2,3,4,6-Tetra-o-acetyl-α-D-glucopyranosyl bromide **(1a)** (2.1 g, 5 mmol), **(2a)** (0.744 g, 6 mmol), Ag_2CO_3 (2.76 g, 10 mmol) and powdered 4Å molecular sieves (1.5 g), quinoline (25 ml) was stirred at room temperature for 5 h, and then was poured into CH_3OH. The solution was filtered through a short pad of silica gel and evaporated in vacuo. The residue was dissolved into AcOEt and washed successively with 1 N HCl and brine, and dried over anhydrous Na_2SO_4. After evaporation, the resulting crude product was purified by flash column chromatography with n-hexane/AcOEt to afford pure **(4a)** as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 1.98 (3 H, s), 2.00 (3 H, s), 2.02 (3 H, s), 2.06 (3 H, s), 2.70 (1 H, s, OH), 3.83 (1 H, m), 4.13 (1 H, dd, J = 2.4, 12.3 Hz), 4.23-4.25 (1 H, m), 4.62 (2 H, 2×d, J = 12.2 Hz), 5.09 (1 H, t, J = 3.8 Hz), 5.12-5.16 (1 H, m), 5.29 (1 H, d, J = 10.0 Hz), 5.30-5.31 (1 H, m), 6.98-7.32 (m, 4 H) ppm; ESI–MS: m/z = 477$[M + Na]^+$.