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Effective 1,2-*trans*-Glycosylation of Complex Alcohols and Phenols Using the Oximate Orthoester of *O*-Pivaloyl Glucopyranose

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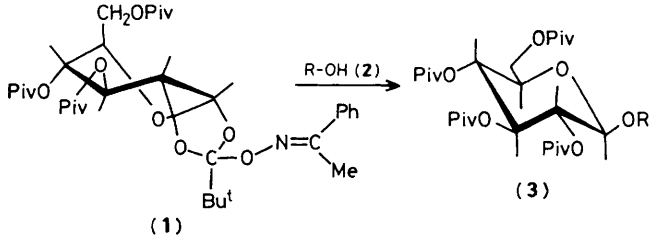
The highly stereoselective β-glycosylation of the complex steroid alcohols (**2b**)—(**2d**), the steroid phenol (**2e**), and the serine derivative (**2f**) is achieved in high yields using the new glycosyl donor 1,2-*O*-(1-*N*-1-phenylethylidene-amino-oxy)-2,2-dimethylpropylidene-3,4,6-tri-*O*-pivaloyl-α-D-glucopyranose (**1**) in the presence of boron trifluoride–diethyl ether.

Effective stereoselective glycosylation methods are required for the syntheses of model compounds for the investigation of drug metabolism and for the development of drug delivery systems.[1] Among the known 1,2-*trans*-glycosylations, the orthoester method of Kochetkov *et al.*[2] suffers from the disadvantage that, besides the desired glycoside, its corresponding orthoester and a second glycoside formed from the starting orthoester by rearrangement are also obtained. Modified procedures using the cyano-[3] or thio-analogues[4] of orthoesters, since they require the trityl ethers of the alcohols as substrates for glycosylation, are inefficient for the glycosylation of less reactive, sterically demanding aglycones.

Here, we report that the glucopyranose derivative (**1**) is a new, very effective glycosyl donor which, when used in glycosylation reactions, does not give rise to the unwanted side products normally produced in orthoester glycosylations. Furthermore, in contrast to other modern methods using 1-*O*-acetyl-monosaccharides for the glycosylation of alcohols[5] and 1-*O*-trimethylsilyl-sugars for the glycosylation of phenols,[6] each in the presence of trimethylsilyl trifluoromethanesulphonate, the oximate orthoester (**1**) allows the stereoselective glycosylation to take place of both alcoholic and phenolic hydroxy groups in complex molecules under identical conditions.



(1) (3)

Scheme 1. *Conditions:* $BF_3 \cdot Et_2O$, CH_2Cl_2. Piv = Bu^{t}CO.

The oximate orthoester (**1**) is easily obtained from acetophenone oxime and 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide[7] in the presence of silver carbonate or silver trifluoromethanesulphonate–s-collidine in dichloromethane. Compound (**1**)† is stable in the air for months and is also stable to acetic acid in methanolic solution for hours. Its ^{1}H n.m.r. spectrum ($CDCl_3$) reveals a relatively large H-1–H-2 *cis* coupling (6.0 Hz) (δ 6.2, H-1) and, consequently, a small H-2–H-3 *trans* coupling (3.0 Hz) (δ 4.67, H-2), both suggesting a twisted conformation for the crowded oximate orthoester (**1**).

In the presence of $BF_3 \cdot Et_2O$ (*ca.* 4 equiv.), needed for co-ordinative saturation of the ester carbonyl groups, the oximate orthoester (**1**) reacts with alcohols and phenols (**2**) in dichloromethane at room temperature within 5—30 min to give the corresponding β-glucosides stereoselectively (Scheme 1, Table 1).

The yields in Table 1 refer to analytically pure glycosides (**3**) purified by chromatography. The structures of the products (**3**) have been proved by their ^{13}C n.m.r. spectra.‡ In addition to its efficiency and selectivity, the method has the advantage

† (**1**): ^{13}C n.m.r. ($CDCl_3$): δ 125.8 (orthoester-C) and 99.1 (C-1).

‡ The signal of the anomeric carbon is proof of the structure: 100.6 MHz ^{13}C n.m.r. ($CDCl_3$): δ 99.5, (**3a**); 99.6, (**3b**); 99.79, (**3c**); 101.09, (**3d**); 99.54, (**3e**); 100.69 (**3f**).

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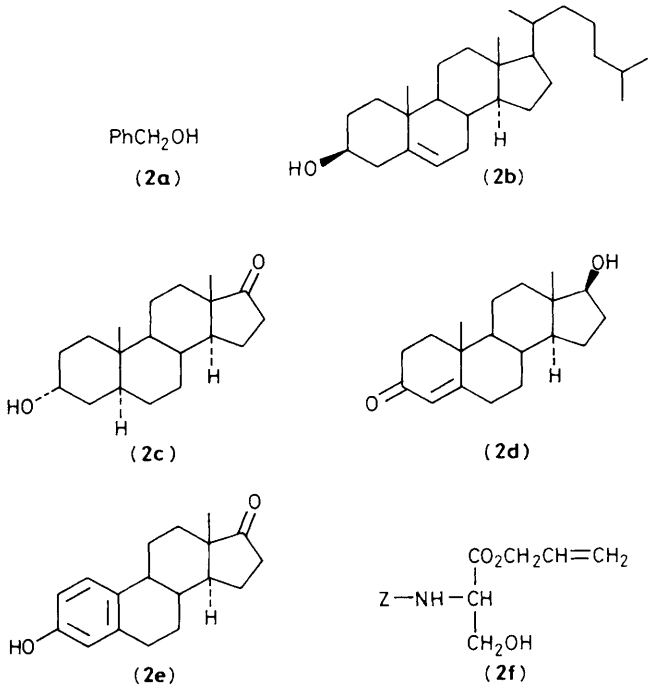

that both the glycosyl donor and the aglycone need only be used in equivalent amounts, whereas the normal orthoester procedure[2] requires an excess of the alcohol and in the classical glycosylations using tetra-*O*-acetyl-α-D-glucopyranosyl bromide[10] a large excess of the glycosyl donor is required. The reaction described here proceeds quickly and in homogeneous solution and the formation of the undesired orthoësters corresponding to the glycosides (**3**) is practically prevented. Complex alcohols, such as cholesterol (**2b**), androsterone (**2c**), and the sterically hindered testosterone (**2d**) are likewise converted into their β-glucosides as efficiently as the phenol estrone (**2e**). Also, the polar benzyloxycarbonyl serine allyl ester[8] (**2f**) is glycosylated in high yield. The blocking functions of this substrate are not affected which demonstrates the relatively mild acidic conditions during the reaction.

Table 1. Glycosylation of the hydroxy compounds (**2**) using the oximate orthoester (**1**) (Scheme 1).

R-OH	Glycoside	% Yield	M.p., *t*/°C	$[\alpha]_D^{26}$ [a]
(**2a**)	(**3a**)[b]	78	123	−24.1°
(**2b**)	(**3b**)[c]	82	196—197	−15.9°
(**2c**)	(**3c**)	73	165	+31.2°
(**2d**)	(**3d**)	68	198	+43.4°
(**2e**)	(**3e**)	81	240—241	+50.4°
(**2f**)[d]	(**3f**)	79	—	+4.5°[e]

[a] c = 1, $CHCl_3$. [b] Lit.[7] m.p. 124—125 °C, $[\alpha]_D^{26}$ −24.5°. [c] Lit.[7] m.p. 197—198 °C, $[\alpha]_D^{26}$ −14.9°. [d] Ref. 8. [e] Lit.[9] $[\alpha]_D^{26}$ + 4.9°.

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