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A Practical Synthesis of β-D-Mannopyranosides

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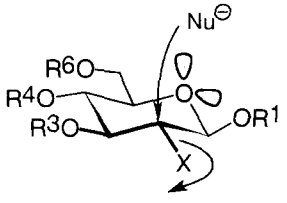
Abstract: An indirect yet highly efficient protocol for the β-**D**-mannosylation of sterically hindered alcohols is reported. Trichloroacetimidate **5** is used a key building block which is converted into the desired mannosides **9** via triflates **8** by an ultrasound promoted β-**D**-*gluco* → β-**D**-*manno* inversion process.

Keywords: Carbohydrates, Glycosidation, Trichloroacetimidates, Triflates, Sonochemistry

The formation of β-**D**-mannopyranosides in general is strongly disfavored by the anomeric effect of the pyranose ring as well as by eventual anchimeric assistance of acyl substituents on O-2. Despite some recent progress in "direct" mannosylation reactions [1], most entries into this particular type of glycoside still rely on "indirect" approaches. Particularly noteworthy among them are (i) stereoselective reductions of appropriately substituted hexopyranos-2-ulosides [2], (ii) glycosidations via an intramolecular aglycon delivery [3], and (iii) β-**D**-*gluco*→β-**D**-*manno* inversion reactions [4,5]. The latter, however, are severely impeded by the adverse stereoelectronic effect of the ring oxygen along the trajectory of the entering nucleophile. Therefore they have been usually carried out either by using special leaving groups or by running the reactions in an intramolecular – and hence entropically biased - way [4]. We now disclose, however, that S_N2 reactions at C-2 of a pyranose template can be significantly improved simply by means of ultrasound. The impact of the acoustic waves overrides the unfavorable stereoelectronic situation and renders this protocol highly efficient even for the mannosylation of unreactive or sterically hindered alcohols.



The differentially protected trichloroacetimidate **5** is used as a key building block. Its synthesis (Scheme 1) starts from acetobromoglucose which is converted into compound **1** in 85% yield on a multigram scale (EtOH, *n*-Bu_4NBr, collidine) [6]. Substitution of the O-acetyl for O-benzyl groups (**1**→**2**) followed by acid catalyzed hydrolysis of the orthoester leads to a mixture of **3** and α,β-**4**. No attempt was made to separate these compounds. Treatment of this mixture with trichloroacetonitrile and Cs_2CO_3 in CH_2Cl_2 overnight delivers the desired glycosyl donor **5** as the only reaction product in 92% yield. This outcome reflects an base-induced acetyl migration (**4**→**3**) preceding the formation of the thermodynamically more stable α-configurated trichloroacetimidate function ($J_{H1,H2}$ = 3.6 Hz, $J_{H2,H3}$ = 10.0 Hz) [7]. This route provides the valuable glycosyl donor **5** in only 4 steps from acetobromoglucose with an overall yield of 59% [8].

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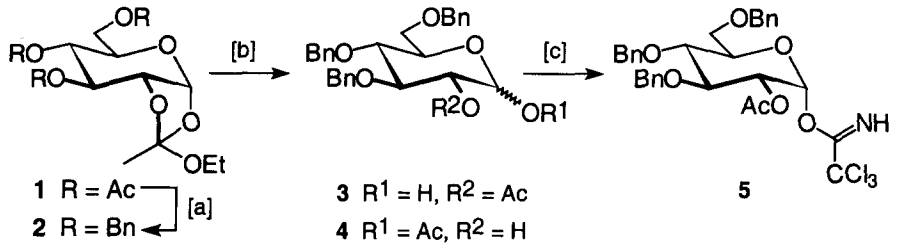
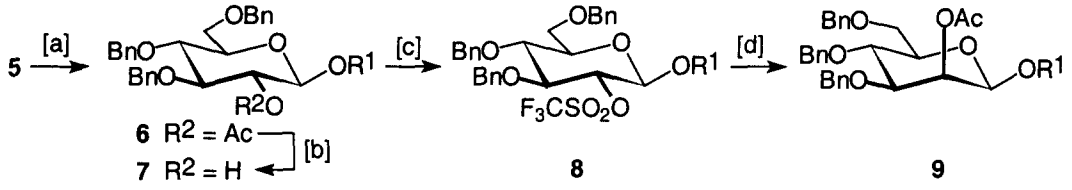


Scheme 1. [a] BnBr, KOH, THF, 81%; [b] aq. HOAc, 1h, 93%; [c] Cl_3CCN, Cs_2CO_3, CH_2Cl_2, 16h, 92%.

Compound **5** reacts readily and stereoselectively with various glycosyl acceptors in the presence of catalytic amounts of $BF_3{\cdot}Et_2O$ (-25°C, CH_2Cl_2, MS 3Å) to the corresponding β-**D**-glucopyranosides **6** [7]. Deacetylation of the latter followed by treatment of the 2'-O-unprotected sugars **7** thus obtained with Tf_2O in CH_2Cl_2/pyridine affords the corresponding triflates **8** [9] in very high yields and sets the stage for the crucial β-**D**-*gluco* → β-**D**-*manno* inversion. Gratifyingly, the reaction proceeds smoothly provided that a mixture of triflate **8** and *n*-Bu_4NOAc in toluene is sonicated by means of an ultrasound cleaning bath (Scheme 2) [10]. Several representative β-**D**-mannopyranosides obtained in this way are compiled in Table 1. Only in the case of triflate **8a** a minor amount of the *gluco*-configurated acetate **6a** (7%) accompanies the formation of the desired β-**D**-mannoside **9a**; all other reactions took a completely stereoselective course. The anomeric configuration of **9a-e** can be unequivocally deduced from the $J_{H1',H2'} \leq 1$ Hz and the $J_{C1',H1'} = 153\text{-}160$ Hz, *i.e.* the typical range for β-**D**-mannopyranosides [11].

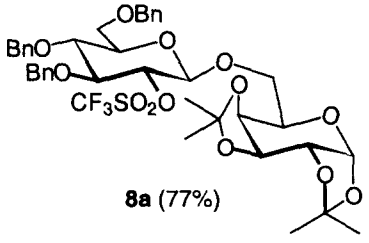
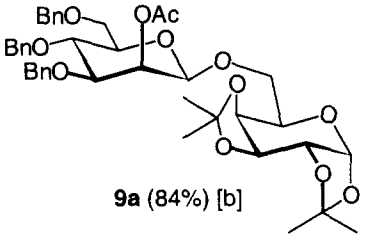
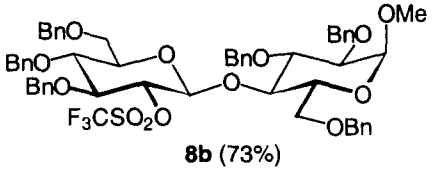
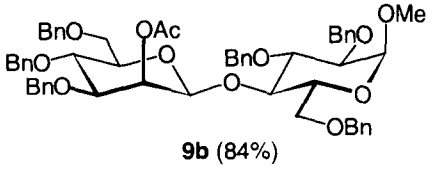
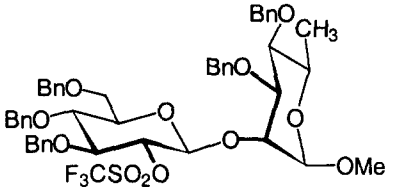
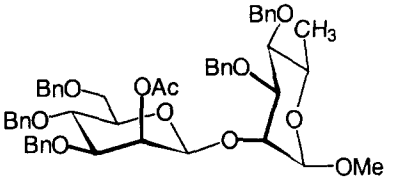
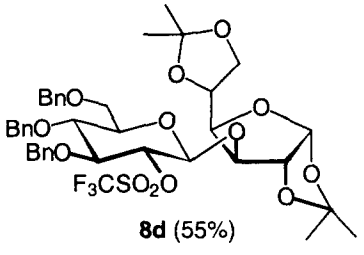
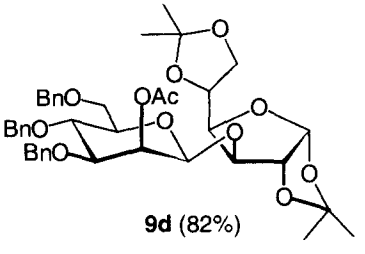
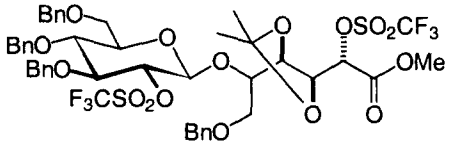
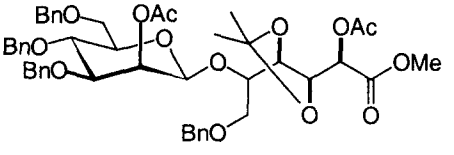


Scheme 2. [a] R^1OH, $BF_3{\cdot}Et_2O$ cat., CH_2Cl_2/hexane, -25°C; [b] KOMe cat., MeOH, r.t.; [c] triflic anhydride, CH_2Cl_2/pyridine, r.t.; [d] *n*-Bu_4NOAc, toluene, ultrasound. For the yields obtained, *cf.* Table 1.

A few other aspects deserve mentioning: First, the choice of the nucleophile turned out to be of eminent importance. We noticed that *n*-Bu_4NOAc has a far superior reactivity than CsOAc or CsOAc/18-crown-6 previously described as the nucleophile in a similar context [12]. Likewise, reactions employing *n*-Bu_4N ONO rather than *n*-Bu_4NOAc (which lead to the corresponding 2-O-unprotected mannosides after hydrolysis of the nitrite esters primarily formed) were found to be distinctly less efficient. Secondly, ultrasound [13] is a key to success in the present mannosylation protocol, as „silent" reactions either fail to afford the products with reasonable rates or decompose the starting triflates when carried out under more forcing conditions. Finally, the formation of compound **9e** indicates that ultrasound-assisted triflate for acetate substitution reactions can be simultaneously carried out at two different sites in a given precursor.

The efficiency and practicality of this improved ultrasound-promoted entry into β-**D**-mannopyranosides is noteworthy, because it involves only routine steps and provides the desired products in good to excellent overall yields even in the case of sterically hindered acceptor alcohols [14].

Table 1. β-D-Mannoside Formation.

Triflate (Yield %, based on 5) [a]	β-D-Mannoside (Yield %)
 **8a** (77%)	 **9a** (84%) [b]
 **8b** (73%)	 **9b** (84%)
 **8c** (73%)	 **9c** (87%)
 **8d** (55%)	 **9d** (82%)
 **8e** (71%)	 **9e** (92%)

[a] Refers to the overall yield of the conversion **5** → **6** → **7** → **8**. [b] β-Glucoside **6a** was formed as a by-product (7%).

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[10] ***Representative procedure***: A mixture of triflate **8d** (237 mg, 0.29 mmol) and *n*-Bu_4NOAc (530 mg, 1.76 mmol) in toluene (8 mL) is sonicated with a laboratory cleaning bath (Brandelin Sonorex RK 514) for 16 h. Evaporation of the solvent and flash chromatography of the crude product with hexane/ethyl acetate (4/1→2/1) as the eluent affords product **9d** as a colorless syrup (174 mg, 82%). Characteristic data: IR: 1754 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.91 (d, 1H, *J* = 3.8 Hz, H-1), 4.60 (d, 1H, *J* = 0.9 Hz, H-1'); ^{13}C NMR ($CDCl_3$): δ = 170.3, 138.3, 138.1, 137.4, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 111.8, 108.3, 105.1, 97.3, 82.9, 80.6, 80.2, 80.1, 76.0, 75.2, 74.1, 73.7, 73.6, 71.5, 69.0, 67.8, 65.6, 26.7, 26.4, 26.2, 25.3, 21.0; $J_{C1',H1'}$ = 156.0 Hz.

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