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Efficient synthesis of alkyl 2,3-unsaturated glucopyranosides from glycals mediated by ytterbium(III) triflate–trialkyl aluminum

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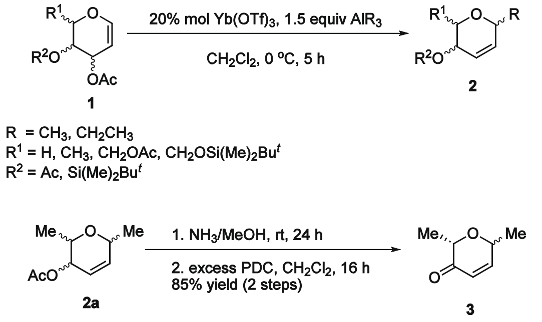
ABSTRACT

Treatment of glycals with trialkylaluminum in the presence of a catalytic amount of $Yb(OTf)_3$ leads to the corresponding alkyl 2,3-unsaturated glycosides in good to excellent yields. Reactions of protected glycals are achieved under very mild conditions.

C-Glycosides have attracted much attention because of their existence as subunits in biologically active natural products and as versatile chiral building blocks for the synthesis of bioactive molecules such as kendomycin,[1] angucyclines,[2] ciguatoxin,[3] and polycyclic ether marine metabolites.[4] Their synthetic manipulation, particularly the introduction of a carbon side-chain at the anomeric center of the sugar unit, has been investigated by several groups.[5] Carbon-Ferrier rearrangement, which involves Lewis acid-induced rearrangements of glycals in the presence of carbon nucleophiles, is one of the most useful transformations to access *C*-glycosides. Catalysts employed for the C-glycosidation of glycals include HF-pyridine,[6] PMA-SiO_2,[7] Montmorillonite K10,[8] I_2,[9] DDQ,[10] $BF_3{\cdot}OEt_2$,[11] TMSOTf,[12] $TiCl_4$,[13] $SnCl_4$,[14] AlR_3,[15] indium halides,[16] $In(OTf)_3$,[17] and $Bi(OTf)_3$.[18] Transition metal salts such as $FeCl_3$,[19] $Cu(OTf)_2$,[20] $Sc(OTf)_3$,[21] $ZrCl_4$,[22] organozinc species,[23] and $Pd(OAc)_2$[24] have also been successfully employed. There are only two examples of the use of lanthanide salts in the C-glycosidation of glycols, that is, $Yb(OTf)_3$[25] and $Er(OTf)_3$.[26] The success of these synthetic operations is case sensitive depending mainly on the catalysts, glycals, and the nucleophiles involved.

As part of our on-going efforts on the total synthesis of naturally occurring pyranonaphthoquinones,[27] we required an efficient method for the synthesis of *C*-alkylglycosides which could be eventually transformed into chiral enones **3** as shown in Scheme 1.

The synthesis of compound **2a** ($R^1 = Me$, $R^2 = OAc$ and $R = Me$) was reported[28] employing the combination of $TiCl_4$ and $AlMe_3$ in the C-glycosidation step. In our hands, this reaction led to a low yield of the *C*-methylglycoside product **2a** which was very difficult to purify. An effort to find a more efficient synthetic route led us to explore the use of other catalysts in combination with AlR_3 (R = Me, Et). Initial work was carried out with 3,4-di-*O*-acetyl-L-rhamnal **1a**, $AlMe_3$ and the Lewis acids screened included $In(OTf)_3$, $Sc(OTf)_3$, $Sm(OTf)_3$,[29a] $Hf(OTf)_4$,[29b] $Sn(OTf)_2$, $Cu(OTf)_2$, $Bi(OTf)_3$, and $Yb(OTf)_3$ (Table 1). Among these, $Yb(OTf)_3$ gave the highest yield and easily purified *C*-methylglycoside product. Optimum reaction conditions which led to a reproducible and highest yield of *C*-methylglycoside **2a** (92% yield) with good diastereoselectivity



Scheme 1. C-Glycosidation of glycals **1** and the synthesis of enone **3**.

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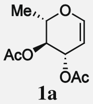
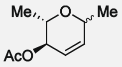
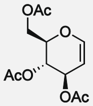
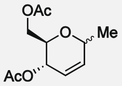
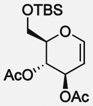
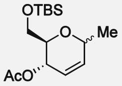
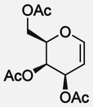
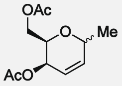
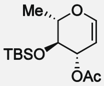
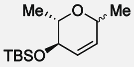
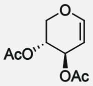
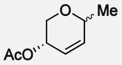
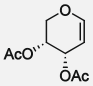
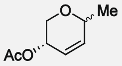
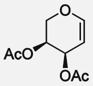
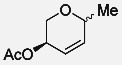
Table 1
Screening of $M(OTf)_3$ in the reaction of 3,4-di-*O*-acetyl-L-rhamnal **1a** with Lewis acids and $AlMe_3$

Entry	Lewis acid	Yield[a] (%) (α:β)[b]
1	$In(OTf)_3$	85 (25:75)
2	$Sc(OTf)_3$	86 (55:45)
3	$Yb(OTf)_3$	92 (80:20)
4	$Sm(OTf)_3$	90 (58:42)
5	$Hf(OTf)_4$	94 (21:79)
6	$Sn(OTf)_2$	67 (46:54)
7	$Cu(OTf)_2$	53 (44:56)
8	$Bi(OTf)_3$	78 (66:34)
9	1.1 equiv $TiCl_4$	50–70 (55:45)

[a] Isolated yields as diastereomeric mixtures.
[b] Ratio determined by ^1H NMR spectroscopy; configuration determined by an NOE experiment.

Table 2
C-Glycosidation of glycals **1a**–**h** with $Yb(OTf)_3$ and $AlMe_3$

Entry	Glycal	Product	Yield[a] (%) (α:β)[b]
1	 **1a**	 **2a**	92 (80:20)
2	 **1b**	 **2b**	94 (79:21)
3	 **1c**	 **2c**	88 (75:25)
4	 **1d**	 **2d**	87 (89:11)[c]
5	 **1e**	 **2e**	94 (50:50)
6	 **1f**	 **2f**	71 (85:15)
7	 **1g**	 **2g**	81 (85:15)
8	 **1h**	 **2h**	87 (84:16)

[a] Isolated yields as diastereomeric mixtures.
[b] Ratio determined by ^1H NMR spectroscopy.
[c] The reaction was carried out at rt for 12 h.

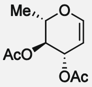
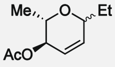
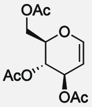
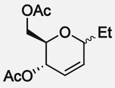
required $AlMe_3$ (1.5 equiv) and $Yb(OTf)_3$ (20 mol %) in CH_2Cl_2 at 0 °C (entry 3). The background reactions using $AlMe_3$ (1.5 equiv), and the combination of $AlMe_3$ (1.1 equiv) and of $Yb(OTf)_3$ (20 mol %) gave the product **2a** in 59% and 64% yields, respectively. The use of a lower catalyst loading led to a much lower yield of **2a**. $Sm(OTf)_3$ gave a good yield of product but with low selectivity (entry 4). It is notable that indium and hafnium triflates (entries 1 and 5) gave good yields of the product but with opposite diastereoselectivity to that of $Yb(OTf)_3$. $TiCl_4$ gave erratic yields and the product was very difficult to purify. It was found that the sequence of the addition of the reagents affects the yields significantly. The solution of $AlMe_3$ and $Yb(OTf)_3$ must be premixed and to this was added the glycal derivative in dichloromethane. We believe that the reaction involves the formation of an $AlMe_3$–$Yb(OTf)_3$ complex which induces the generation of an oxonium ion followed by methyl transfer to the anomeric carbon to produce **2a**. Recycling the catalyst, ($Yb(OTf)_3$) was also possible giving the desired product but in a slightly lower yield (80%).

The conversion of **2a** to enone **3** was achieved in 85% yield in two steps (Scheme 1).

The generality of the method was demonstrated using protected glycals **1b**–**h** under standard conditions resulting in the *C*-1 methylglycosides **2b**–**h**, respectively, in good to excellent yields with moderate to good diastereoselectivity (Table 2). The reaction of acid-sensitive 3-*O*-acetyl-4-*O*-(*tert*-butyldimethylsilyl)-L-rhamnal **1c** (Table 1, entry 3) under standard conditions afforded the corresponding methylglycoside **2c** in 88% yield but with moderate diastereoselectivity; when $TiCl_4$ was used as the Lewis acid, no identifiable product could be isolated. The glycal **1e** gave an excellent yield of **2e** but with no diastereoselectivity. For **1d** (entry 4), the reaction was complete in 12 h at room temperature. In all the reactions, the diastereoisomeric mixtures and the two anomers, including those of enones **3**, could be separated by radial chromatography. All products were fully characterized using spectroscopic data.

The utility of this method was further demonstrated by the reaction with metal triflates and $AlEt_3$. It is interesting to note that the reaction of glycals **1a** and **1b** with $AlEt_3$ (1.5 equiv) using 20 mol % of $Yb(OTf)_3$, $In(OTf)_3$, or $Hf(OTf)_4$ as catalyst at 0 °C gave

Table 3
C-Glycosidation of glycals **1a** and **1b** with metal triflates and $AlEt_3$

Entry	Glycal	Product	Lewis acid	Yield[a] (%) (α:β)[b]
1	 **1a**	 **2i**	$Yb(OTf)_3$ $In(OTf)_3)$ $Hf(OTf)_4$	95 (70:30) 75 (40:60) 91 (30:70)
2	 **1b**	 **2j**	$Yb(OTf)_3$ $In(OTf)_3$ $Hf(OTf)_4$	92 (70:30) 72 (38:62) 97 (35:65)

[a] Isolated yields as pure anomeric mixtures after radial chromatography.
[b] Anomeric ratio was determined from the ^1H NMR spectrum.

the products **2i** and **2j** in excellent yields with the same trend in diastereoselectivity as observed with $AlMe_3$ (Table 3).

In summary, the combination of ytterbium triflate and trialkylaluminum has been demonstrated to be a highly efficient catalyst system for effecting *C*-1 alkylation of glycals under very mild conditions. This procedure offers several advantages over traditional procedures employing $TiCl_4$ or other harsh Lewis acids; these include mild reaction conditions, high yields of the desired products, a simple experimental procedure and the ease of product isolation.

General procedure: A 100 mL round-bottomed flask was charged with $Yb(OTf)_3$ (20 mol %, 0.29 g, 0.47 mmol) and CH_2Cl_2 (4 mL). The resulting slurry was cooled to 0 °C before a solution of trimethylaluminum (2.0 M in hexanes, 1.75 mL, 3.5 mmol, 1.5 equiv) was added. The resulting mixture was stirred at 0 °C for 15 min until the fuming ceased. To this mixture was added dropwise a solution of glycal (2.34 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at 0 °C for 5 h before being quenched by slow addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (3 × 10 mL), brine (10 mL), and dried over $MgSO_4$. Filtration and solvent removal on a rotary evaporator afforded the crude product. The desired product was obtained upon purification using radial chromatography.

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29. To the best of our knowledge, this is the first report on the use of both samarium and hafnium triflates in C-glycosidation of glycals. For leading references, see: (a) Kawabata, H.; Kubo, S.; Hayashi, M. *Carbohydr. Res.* **2001**, *333*, 153–158; (b) Wu, Y.-C.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 9522–9524.