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β-Selective Glycosylation with α-Mannosyl Fluorides Using Tin(II) Triflate and Lanthanum Perchlorate

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Abstract: A β-selective glycosylation with highly stable α-mannosyl fluorides and various acceptors has been found to be promoted by $Sn(OTf)_2$, with $La(ClO_4)_3 \cdot nH_2O$ as a coactivator.

One of the most important problems in carbohydrate chemistry concerns the direct construction of 1,2-*cis*-β-D-mannopyranosides, which possess the stereoelectronically disfavored anomeric equatorial *C-O* linkage.[1] Although direct glycosylation with a mannosyl bromide has been reported by Paulsen *et al.* to be the most practical approach,[2] this reaction requires both the use of a highly unstable mannosyl bromide as the donor, and also careful choice of protecting groups. Intramolecular aglycon delivery methods for obtaining the β-mannosides have been reported by Hindsgaul,[3] Stork,[4] and Ogawa[5] - however, although these methods proceed with complete stereocontrol they require a multi-step preparation of the starting material, resulting in low overall yields. Direct mannosylation using stable donors such as α-mannosyl fluorides is thus desirable for achieving a truly practical methodology. To the best of our knowledge, no β-selective direct glycosylation with α-mannosyl fluorides has been reported. We report herein the first such direct glycosylation, achieved by using a combination of $Sn(OTf)_2$ and $La(ClO_4)_3 \cdot nH_2O$ to promote the preparation of the desired β-mannosides.[6]

We recently succeeded in developing a new method for the glycosylation with glycosyl fluorides, promoted by either catalytic or stoichiometric amounts of rare earth salts, which has allowed us to carry out several notable glycosylation reactions.[7] However, the difficulty encountered in preparing β-mannosides selectively by glycosylation with α-mannosyl fluorides in these systems remained to be addressed.[7a,7c] In an attempt to further develop the β-mannosylation reaction, we have found that the use of tin(II) triflate and a rare earth perchlorate in combination effectively promotes the condensation of α-mannosyl fluoride **1** and primary acceptor **2**. Of the many types of rare earth salts which are available, we chose lanthanum perchlorate because of the increased fluorophilicity of the metal cations.[8] This salt, however, did not promote the condensation at all (Table 1, Entry 1). Moreover, in the case where $La(ClO_4)_3 \cdot nH_2O$ and $SnCl_2$ were used as a combined promoter, the reactivity of this system was still low (Entry 2).[9] Interestingly, this glycosylation reaction was found to proceed slowly when $Sn(OTf)_2$[10] alone was used as a promoter (Entry 3). As a consequence, we

examined the glycosylation reaction using $Sn(OTf)_2$ and various commonly used Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$, $La(OTf)_3$, $Yb(OTf)_3$ and $La(ClO_4)_3 \cdot nH_2O$ at -40 ℃ for 23 h. From the results shown in Entries 4 - 9 in Table 1, it appears that the combined system of $Sn(OTf)_2$ and $La(ClO_4)_3 \cdot nH_2O$ was the most effective promoter in this β-selective mannosylation. In fact, treatment of **1** with **2** in the presence of $Sn(OTf)_2$ (2.4 mol equiv) and $La(ClO_4)_3 \cdot nH_2O$ (1.2 mol equiv)[11] at -40 ℃ for 23 h gave **3a** (99% yield, α : β = 27 : 73, Entry 9). We assume that this β-selective mannosylation reaction proceeds via S_N2 type mechanism, i.e. some kind of active species is generated by the mixing of $Sn(OTf)_2$ and $La(ClO_4)_3 \cdot nH_2O$, and this then activates the fluoride and perhaps also the alcohol, thereby giving a facile reaction.

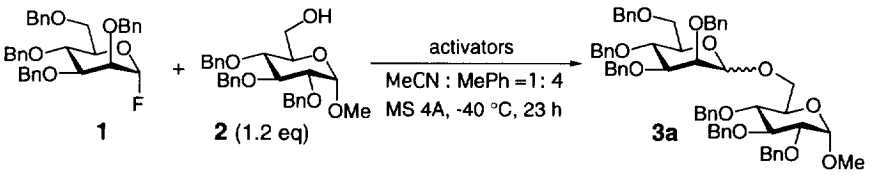


Table 1. β-Selective glycosylation with **1** and **2**

entry	activator (1.2 mol eq)	co-activator (1.2 mol eq)	yield (%)	α : β
1	$La(ClO_4)_3 \cdot nH_2O$	-	No reaction	
2	$La(ClO_4)_3 \cdot nH_2O$	$SnCl_2$	47	46 : 54
3	$Sn(OTf)_2$	-	11	44 : 56
4	$Sn(OTf)_2$	$BF_3 \cdot OEt_2$	80	39 : 61
5	$Sn(OTf)_2$	$TiCl_4$	54	76 : 24
6	$Sn(OTf)_2$	$La(OTf)_3$	33	40 : 60
7	$Sn(OTf)_2$	$Yb(OTf)_3$	25	40 : 60
8	$Sn(OTf)_2$	$La(ClO_4)_3 \cdot nH_2O$	85	29 : 71
9	$Sn(OTf)_2$[a]	$La(ClO_4)_3 \cdot nH_2O$	99	27 : 73

[a] 2.4 mol equiv was used.

We next examined the glycosylation with α-mannosyl fluoride and various primary acceptors. As expected, β-selective mannosylation reactions took place with primary acceptors derived from glucose (97% yield, α : β = 26 : 74), galactose (99% yield, α : β = 25 : 75) and mannose (92% yield, α : β = 28 : 72), in the case where 2 equivalents of starting fluoride **1** and 1 equivalent of the acceptors were used (Table 2, Entries 1, 2, and 3).

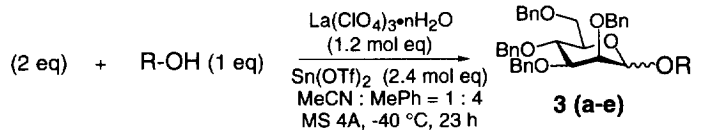
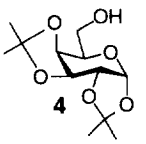
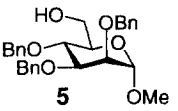
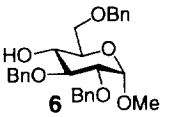
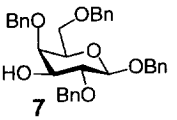


Table 2. β-Selective mannosylation with **1** and various acceptors

entry	R-OH	glycosides	yield (%) [a]	α : β [b]
1	**2**	**3a**	97	26 : 74
2	 **4**	**3b**	99	25 : 75
3	 **5**	**3c**	92	28 : 72
4	 **6**	**3d**	99	61 : 39
5	 **7**	**3e**	99	49 : 51

[a] Isolated yields after flash column chromatography. [b] Ratio was determined by ^{1}H-NMR analysis and/or weight by weight after separation.

Since a β-mannose residue linked to the secondary *C*-4 position of *N*-acetylglucosamine represents the core structure of asparagine (Asn)-linked oligosaccharides, the formation of secondary-type glycosidic linkages is of considerable significance in the field of glycoconjugate synthesis.[12] As shown in Table 2 (Entries 4 and 5), although the chemical yields of these glycosylation reactions were good, the β-selectivity was generally low. We assume that the lower selectivity in these mannosylation reactions is due to the decreased nucleophilicity of secondary acceptors such as **6** and **7**. However, the anomeric isomers of this mannosylation reaction with secondary acceptors were easily separated by standard flash column chromatography. We believe that, at the very least, this mannosylation reaction with secondary acceptors would be of value in the synthesis of oligosaccharides of biological interest.

In conclusion, we have succeeded in developing a direct mannosylation reaction using a combination of $Sn(OTf)_2$ and $La(ClO_4)_3 \cdot nH_2O$ as an activator. Moreover, the results described herein should be quite

instructive for future development of a general glycosylation reaction, using α and/or β glycosyl fluorides, for the synthesis of oligosaccharides.[13]

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13. A representative procedure is as follows: A mixture of $La(ClO_4)_3 \cdot 7H_2O$ (1.2 mol equiv to a donor or an acceptor), $Sn(OTf)_2$ (2.4 mol equiv) and MS 4A (100 mg) were dried at ca. 180 ℃ in vacuo for 2 h. An solution of mannosyl fluoride **1** (27.1 mg, 0.05 mmol) and acceptor **2** (27.9 mg, 0.06 mmol) in acetonitrile and toluene (1 : 4, 1 mL) was then added to the mixture at -40 ℃. After the reaction was complete, saturated aq. $NaHCO_3$ was added. Filtration to remove inorganic compounds and usual work up gave a product which was purified by flash column chromatography.

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