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Regioselectivity shift from β-(1→6)- to β-(1→3)-glycosylation of non-protected methyl β-D-galactopyranosides using the stannylene activation method

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Abstract—Regio- and stereoselective glycosylation of non-protected methyl β-D-galactopyranoside has been developed using the stannylene acetal mediator, allowing a one-pot assembly of glucosyl-β-(1→6)-galactose and glucosyl-β-(1→3)-galactose. Remarkable regioselectivity shift from β-(1→6)- to β-(1→3)-glycosylation has been observed by addition of Bu_4NF etc. to the reaction medium. The method requires no tedious, lengthy manipulation being employed for the conventional protection–deprotection method.

Usual regioselective glycosylation has been achieved by the protection–deprotection method, which requires tedious, multi-step manipulation to prepare appropriately protected glycosyl acceptors.[1] For β-(1→6)-linked disaccharides, for example, glycosyl acceptors possessing fully protected hydroxyl groups other than 6-hydroxyl group must be arranged and then provided to glycosylation. The protective groups have to be removed in a later step. A new method for efficient, short-step assembly of oligosaccharides is desired as an alternative to the protection–deprotection method.

One solution might be regioselective glycosylation of non-protected glycosyl acceptors. It is well known that the stannylene-activated hydroxyl group increases the nucleophilicity of the oxygen atom to react with various electrophiles, so that tin-mediated regioselective acylation,[2] alkylation,[3] and other functionalization[4]

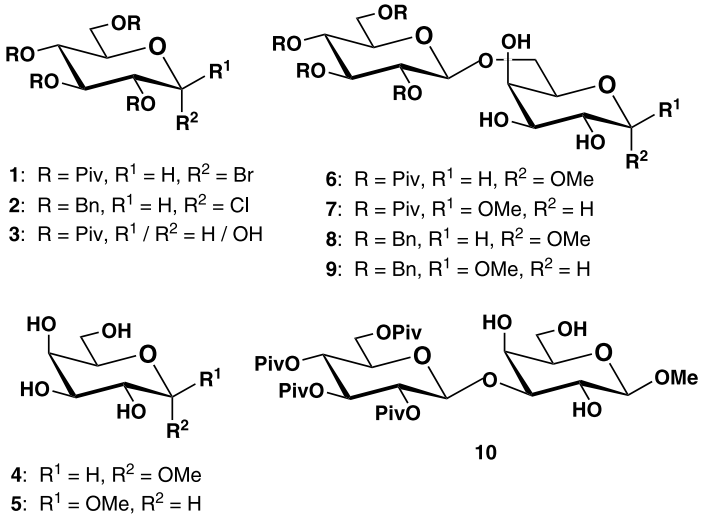

Figure 1. Glycosyl donors, acceptors, and disaccharides.

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have been amply demonstrated. However, few reports[5] have appeared for tin-mediated regioselective glycosylation of non-protected glycosyl acceptors. For glucosyl or galactosyl acceptors, the preceding methods are limited to afford α/β-(1→6)-linked disaccharides only as the major product. Apparently, regioselective glycosylation of the secondary hydroxyl group of non-protected glycoses is requested even in the presence of primary hydroxyl group. Generation of glycosyl-β-(1→3)-galactose moiety is of particular preference, since the disaccharide unit is well known as a core unit of many immunologically active oligosaccharides.[6] This paper reports regio- and stereoselective glycosylation of non-protected methyl α- and β-D-galactopyranosides, providing not only glucosyl-β-(1→6)-galactose but also glucosyl-β-(1→3)-galactose, the latter of which is the first selectively prepared as a major product by the stannylene activation method.

To elucidate the relations between regioselectivity and structures of glycosyl acceptors as shown in Figure 1, we first examined the glycosylation of methyl β-D-galactopyranoside (**5**) with 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (**1**) in the presence of Ag(I)-silica alumina.[7,8] Optimum reaction conditions were examined as shown in Table 1, where glucosyl-β(1→6)-galactose derivative (**7**) was obtained in 73% yield (entry 3).

The structure of **7** was elucidated based on its MS, ^{1}H and ^{13}C NMR spectra. The position of interglycosidic linkage was definitely determined by the deshielding effect of the ^{13}C-chemical shift, where *O*-glycosylated carbon atom resonates resonances at a sizably lower magnetic field, compared with the non-glycosylated carbons.[9] Furthermore, HMBC and NOESY data of **7** also supported the above assignment.

Analogous glycosylation was subjected to other galactosyl acceptors, e.g. methyl α-D-galactopyranoside (**4**), where the corresponding β-(1→6)-disaccharides were obtained in 41% yield (entry 7). From these facts we can assume that galactosyl acceptors employed favor the predominant formation of β-(1→6)-linked disaccharides in the above glycosylation reactions. To ascertain the stannylene activation effect, glycosylation reaction of **5** with **1** in non-stannylated conditions resulted in the recovery of **1**.

It is possible that the regioselectivity in the glycosylation depends on the kinetic reactivity of the stannylated glycosyl acceptors present in the equilibrium[10] as depicted in Figure 2. For example, 6-*O*-stannylated galactoside present in the equilibria would react faster than 3,4-*O*-stannylated galactoside to give β-(1→6)-disaccharide predominantly. On the contrary, simple acylation or alkylation of the galactose-derived stannylene acetal exceptionally gave 3-*O*-functionalized galactose only.[2,3] This is probably due to the significant reactivity of the acyl or alkyl electrophile, with which thermodynamically stable 3,4-*O*-stannylated galactoside reacts smoothly to afford 3-*O*-acylated/alkylated galactose. On the other hand, relatively unreactive and bulky electrophiles as glycosyl donors would react with faster-accessible 6-*O*-stannylated intermediate to occur 6-*O*-glycosylation.

Next, in order to realize 3-*O*-glycosylation of the stannylated galactose, we assumed two hypothetical concepts: (1) a more reactive glycosyl donor than **1** may facilitate 3-*O*-glycosylation rather than 6-*O*-glycosylation. (2) If the nucleophilicity of 3-OH of **5** were higher than that of the original stannylene acetal, glycosylation must occur at the 3-*O*-position. According to the former hypothesis, we selected 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**2**) as a reactive donor. The corresponding bromide was omitted because of its instability. When the chloride **2** was employed for glycosylation of methyl galactosides (**4**∼**5**), the major disaccharides provided were unexpected β-(1→6)-disaccharides as shown in Table 1 (entries 8∼9). It is noteworthy that β-linked disaccharides were preferably formed in these experiments, although the non-participating benzyl group was employed for 2-OH protection of the glycosyl donor. As proposed in the literature,[11] insoluble silver catalyst, e.g. Ag(I)-silica alumina would promote S_N2 type substitution at the anomeric center, providing β-anomers predominantly. Subsequently, on the hypothesis 2 enhancing the nucleophilicity of the

Table 1. Glycosylation of methyl α- and β-D-galactopyranosides by the stannylene activation method promoted by Ag(I)-silica alumina[a,b]

Entry	Donor	Acceptor	Solvent	Temp. (°C)	Time (h)	Product[c]	Yield (%)	α:β
1	**1**	**5**	$Cl(CH_2)_2Cl$	Rt	24	**7**	39	β
2	**1**	**5**	$Cl(CH_2)_2Cl$	50	24	**7**	66	β
3	**1**	**5**	$Cl(CH_2)_2Cl$	60	24	**7**	73	β
4	**1**	**5**	$Cl(CH_2)_2Cl$	70	24	**7**	68	β
5	**1**	**5**	THF	60	24	**7**	13	β
6	**1**	**5**	CH_3CN[d]	60	48	**7**	12	β
7	**1**	**4**	$Cl(CH_2)_2Cl$	50	20	**6**	41	β
8	**2**	**4**	$Cl(CH_2)_2Cl$	50	48	**8**	70	1:3
9	**2**	**5**	$Cl(CH_2)_2Cl$	50	48	**9**	60	1:6

[a] General stannylation: 1.5 equiv. Bu_2SnO to an acceptor, in MeOH, 50°C 3 h.
[b] Molar ratio of acceptor/donor = 0.5, Ag(I)-silica alumina 900 mg to 0.5 mmol of a donor.
[c] The 1-OH derivative (**3**) was also isolated as a byproduct in 30–50% yield.
[d] A 1:1 mixed solvent with $Cl(CH_2)_2Cl$.

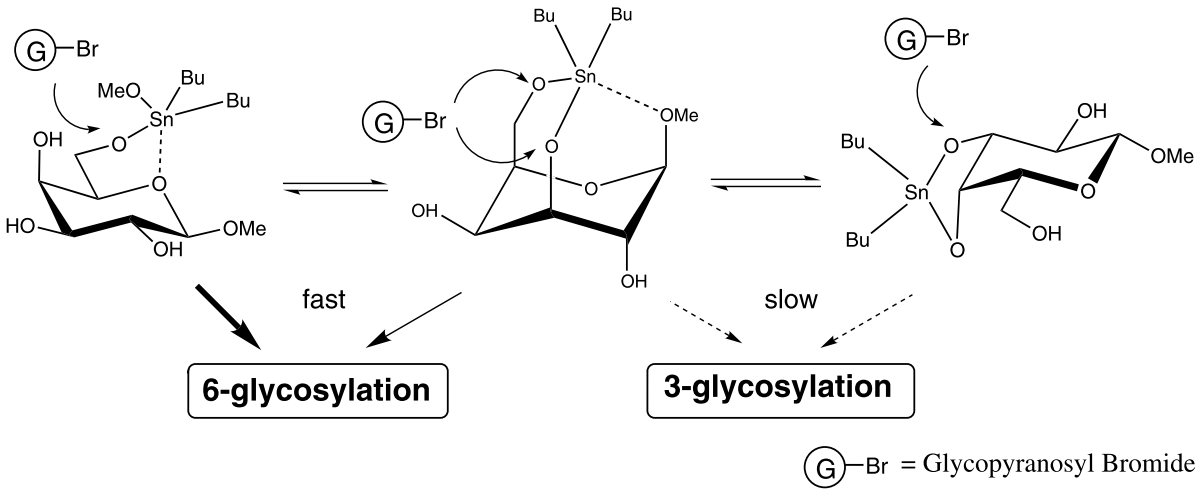

Figure 2. Relations between regioselectivity and structures of the stannylated methyl β-D-galactopyranoside.

3-OH group of galactose was examined using such additives as CsF[12] and tetrabutylammonium halides.[13] The results are summarized in Table 2.

Although cesium fluoride is recommended for facilitating tin-mediated substitution reaction,[12] we observed no improvement in regioselectivity or yield (entry 1). In contrast, a remarkable shift of the regioselectivity has been observed by the addition of tetrabutylammonium halides (entries 2∼5) or -acetate (entry 6), affording glucosyl-β-(1→3)-galactose derivative (**10**) predominant to the corresponding β-(1→6)-disaccharide (**7**). Once the additive was fixed upon tetrabutylammonium fluoride (TBAF), other reaction conditions have been optimized. At this stage the optimum yield is 42% (entry 10), however this result is comparable with the conventional protection method, where a glucosyl-β-(1→3)-galactose derivative has been prepared in less than 49% yield over four steps from methyl β-D-galactopyranoside (**5**),[14] even if the final glycosylation step proceeds quantitatively. In our case, on single recycling of the recovered bromide **1** (58% recovery),[15] the combined yield of **10** would be estimated at 66%.

A postulated reaction mechanism for selective β-(1→3)-galactose formation is shown in Figure 3. Addition of fluoride ion to the stannylene acetal (**A**) would generate, via a pentacoordinated tin-complex **B**,[16] a more reactive alkoxide ion **C**, which reacts preferably with glycosyl donor **1** to give β-(1→3)-disaccharide (**10**). The 6-*O*-glycosylation also occurs with less reactive intermediate **A′** and/or **B′** to afford β-(1→6)-disaccharide as a very minor product. No isolation of β-(1→4)-disaccharide revealed that the intermediate **C′** would be the least reactive. Anyway, the 2-OH group would be less activated by stannylene acetal formation in the β-D-galactose system, according to the general concept that stannylene acetals are formed favorably in a *cis*-vicinal glycol system.[3,4]

In summary, the regioselective glycosylation of non-protected methyl α- and β-D-galactopyranosides was performed with per-*O*-pivaloyl- or benzyl-α-D-glucopyranosyl bromide or chloride using the stannylene activation method in the presence of Ag(I)-silica alumina to give β-(1→6)-disaccharides predominantly. Addition of an onium salt such as TBAF to the above system

Table 2. Effect of additives on glycosylation of methyl β-D-galactopyranoside **5** with per-*O*-pivaloyl-α-D-glucopyranosyl bromide **1** promoted by Ag(I)-silica alumina[a]

Entry	Additive	Equiv.[b]	Solvent	Product **7**:**10**	Combined yield (%)	Recovery **1** (%)
1	CsF	1	$Cl(CH_2)_2Cl$	9:1	57	–
2	Bu_4N-F	1	$Cl(CH_2)_2Cl$	1:7	25	58
3	Bu_4N-Cl	1	$Cl(CH_2)_2Cl$	1:7	17	71
4	Bu_4N-Br	1	$Cl(CH_2)_2Cl$	1:4	12	59
5	Bu_4N-I	1	$Cl(CH_2)_2Cl$	1:7	12	77
6	Bu_4N-OAc	1	$Cl(CH_2)_2Cl$	1:7	17	72
7	Bu_4N-F	0.2	$Cl(CH_2)_2Cl$	1:1	21	65
8	Bu_4N-F	0.5	$Cl(CH_2)_2Cl$	1:10	27	62
9	Bu_4N-F	0.5	THF	1:9	32	60
10	Bu_4N-F	0.5	CH_3CN	1:20	42	58
11[c]	Bu_4N-F	0.5	$Cl(CH_2)_2Cl$	–	–	92

[a] Reaction conditions: temp.: 50°C; time: 1 day.
[b] Molar equivalent of additives to acceptor **5**.
[c] A reaction without activation with Bu_2SnO resulted in the recovery of the bromide (**1**).

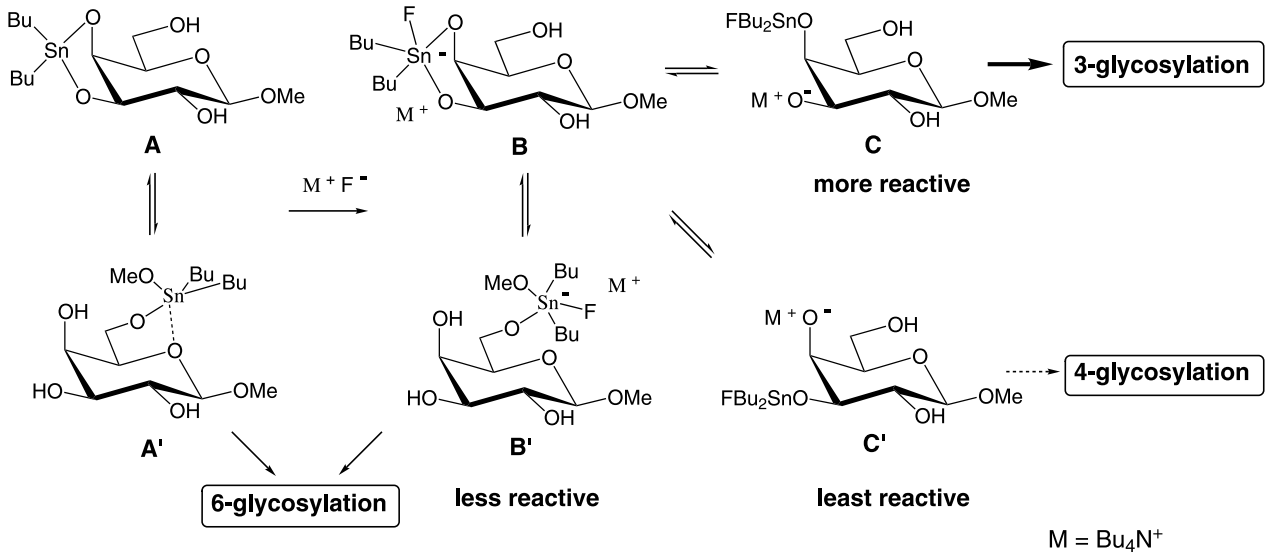

Figure 3. Proposed mechanism of the Bu_2SnO/F^- ion-mediated glycosylation.

brought forth a remarkable shift of the regioselectivity, providing glucosyl-β-(1→3)-galactose predominantly. The pentacoordinated tin-complex was conceivably formed by an attack of the fluoride ion, and acts as a key intermediate for the above described regioselective glycosylation. This method thus provides novel one-pot entry into glucosyl-β-(1→6)- and β-(1→3)-galactose units in regio- and stereoselective manner. Further application of this method to one-pot synthesis of various biologically active oligosaccharides is in progress.

Acknowledgements

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6. For example, sulfoglucuronyl paragloboside (SGPG) comprising GlcA-β-(1→3)-Gal unit is relevant to a neural cell adhesion molecule (N-CAM) and human natural killer cell (HNK-1): (a) McGarry, R. C.; Helfand, S. L.; Quarles, R. H.; Roder, J. C. *Nature* **1983**, *306*, 376; (b) Kruse, J.; Mailhammer, R.; Wernecke, H.; Faissner, A.; Sommer, I.; Goridis, C.; Schachner, M. *Nature* **1984**, *311*, 153.
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9. ^{13}C NMR chemical shift (100 MHz, δ in pyridine-d_5) and $\Delta\delta$ value of methyl β-D-galactopyranoside (**5**), glucosyl-β-(1→6)-galactoside (**7**), and glucosyl-β-(1→3)-galactoside (**10**) are listed as follows. For example, $\Delta\delta$ of C-6 between compounds **5** and **7** shows +7.8 ppm, whereas $\Delta\delta$ value of other non-glycosylated carbons are in the range of +0.1 ~ −1.6 ppm. The β-configuration of the newly formed intersaccharide linkage of **7** and **10** is apparent from the relatively large coupling constant (8.0 Hz) between H-1′ and H-2′.

	C-1	C-2	C-3	C-4	C-5	C-6
5	106.4	72.6	75.5	70.4	77.1	62.6
7	106.1	72.2	75.0	70.5	75.5	70.4
Δδ	- 0.3	- 0.4	- 0.5	+ 0.1	- 1.6	+ 7.8
10	106.4	71.6	82.5	69.4	76.9	62.6
Δδ	0.0	- 1.0	+ 7.0	- 1.0	- 0.2	0.0

10. Equilibrium of stannylated sugars including their dimeric structures has been proposed: Grindley, T. B.; Thangarasa, R. *Can. J. Chem.* **1990**, *68*, 1007. For simplification we showed only monomeric structures.

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14. Kohata, K.; Abbas, S. A.; Matta, K. L. *Carbohydr. Res.* **1984**, *132*, 127: methyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside is prepared from **5** in 49% yield over three steps.
15. The recovered bromide was identified on the basis of its MS and NMR spectra, indicating no conversion into the corresponding fluoride.
16. A similar ion pair mechanism involving penta-coordinated tin atom has been proposed in the regioselective benzylation of aliphatic diols by Ohno et al. See Ref. 12a.