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Stannylene acetal-mediated regioselective open glycosylation of methyl β-D-galactopyranoside and methyl α-L-rhamnopyranoside

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Abstract

Open glycosylation of stannylated methyl β-D-galactopyranoside with per-*O*-benzoyl or -pivaloyl-glucopyranosyl bromide and -glucuronyl bromide, promoted by Ag-silica alumina, afforded regio- and stereoselectively glycosyl-β(1→6)-galactose and its orthoester derivative in good yield. Similar glycosylation of unprotected methyl α-L-rhamnopyranoside with per-*O*-pivaloylglucuronyl bromide provided glucuronyl-β(1→3)-rhamnose in moderate yield. © 1999 Elsevier Science Ltd. All rights reserved.

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A practical, chemical synthesis of complex oligosaccharides remains to be developed, since the necessity of using protective groups for differentiation of various hydroxyl groups makes the overall synthetic scheme lengthy and impractical. Regioselective glycosylation of unprotected sugars, so-called 'open glycosylation',[1] would be a solution to the problem. This methodology allows a short-step assembly of oligosaccharides, since open glycosylation can reduce the multi-steps involved in the protection–deprotection processes which have so far been employed in general oligosaccharide synthesis.

For regioselective acylation or alkylation of unprotected sugars, stannylated sugars have been successfully utilized for preferential protection. As regards methyl β-D-galactopyranoside, for example, the C3-hydroxyl group rather than the C6-hydroxyl group can be protected.[2–4] Hence, stannylene activation of sugar hydroxyl groups followed by electrophilic attack by a glycosyl donor would be most probably applicable to open glycosylation, a general procedure of which is depicted in Scheme 1.

Although methods for open glycosylation have been achieved by several groups,[1,5–7] the main products obtained therein are limited to glycosyl-α/β(1→6)-linked disaccharides. Therein lies the drawback to these methods; other disadvantages are the low regioselection of some couplings as well as low accessibility of some acceptor hydroxyl groups.

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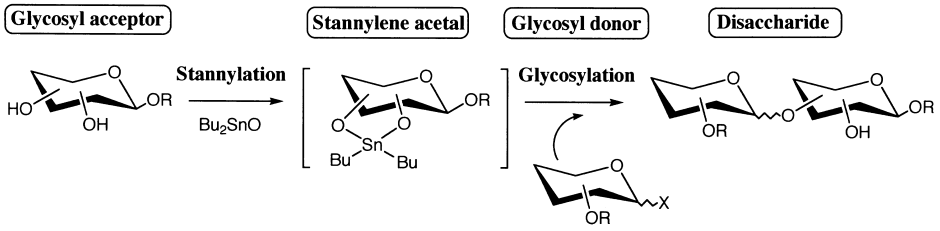


Scheme 1. Open glycosylation using stannylene activation method

We wish to report here an alternative stannylene-activated, regioselective glycosylation of methyl β-D-galactopyranoside **1** and methyl α-L-rhamnopyranoside **4** as acceptors with methyl 1-bromo-α-D-glucopyranuronates **5** and **7** and α-D-glucopyranosyl bromides **6** and **8** as donors using Ag-silica alumina as an effective promoter. By this methodology, we have developed a facile access to β(1→6)- and β(1→3)-linked disaccharides comprising glucuronic acid, glucose, galactose, and rhamnose units.

First, we examined reaction conditions for open glycosylation of totally unprotected methyl β-D-galactopyranoside **1** with per-*O*-benzoylated glucuronyl bromide **5** — this set of sugar units constitutes a common terminal disaccharide chain on N-CAM (neural cell adhesion molecule)[8] and immunologically relevant NK-cells.[9]

The stannylene acetal, generated in situ from **1**, was glycosylated with methyl tri-*O*-benzoyl-1-bromo-α-D-glucopyranuronate **5**[10] in the presence of several kinds of promoters as shown in Table 1 (Entries 1–4). Silver silica alumina[11] (Entry 4) best facilitated the reaction to yield β(1→6)-disaccharide **9** (39%) and the corresponding orthoester **13** (24%).[12] Such a relatively higher effectiveness of silver silica alumina in glycosylation with various glycosyl bromides has also been observed in our previous studies.[13] The structures of **9** and **13** were elucidated on the basis of their ^{1}H and ^{13}C NMR spectra, where the interglycosidic (1→6)-bond was definitely determined by the deuterium-induced differential isotope shift (DIS) technique[14] of the ^{13}C NMR. HMBC and NOESY data of the corresponding 2,3,4-tri-*O*-acetyl derivative **20** of **9** also supported the above assignment. The orthoester **13** could be converted to **20**, via the corresponding acetate, by treatment with a catalytic amount of TMSOTf[15] in 76% yield.

Similar glycosylation of **1** with per-*O*-benzoyl-α-D-glucopyranosyl bromide **6** in CH_2Cl_2 afforded the β(1→6)-disaccharide **10** and the orthoester **14** in the ratio of 1:8 in 52% combined yield (Entry 5). In contrast to the above results, the glycosylation without stannylene activation resulted in only 10% formation of **14** along with complex products. In the THF solution instead of CH_2Cl_2 the set of products was varied to **14** and **16** in the ratio of 2:1, albeit in low yield (Entry 6).

Although intersugar orthoesters can be converted to the corresponding disaccharides in satisfactory yield,[15] the simplest access to the disaccharide would be provided by direct formation of the glycoside bond. In this context, the protecting group of the glycosyl donor should be changed to a pivaloyl group which is known to scarcely generate orthoesters. In fact, open glycosylation of **1** with per-*O*-pivaloylglucuronyl bromide **7** gave the β(1→6)-disaccharide **11** in 77% yield along with the orthoester **15** in only 2% yield (Entry 7). Similar treatment of **1** with per-*O*-pivaloylglucosyl bromide **8** afforded the disaccharide **12** in 72% yield as the sole product (Entry 8). Thus, the practical utility of this method has been exemplified by these results.

Aside from the β(1→6)-linkage, we tried to obtain β(1→3)-linked disaccharide, for which 6-*O*-protected galactoside such as **2** and **3** would be conceivable candidates. To test the hypothesis we examined glycosylation of 6-*O*-trityl- and 6-*O*-TBS-galactosides **2** and **3** with the bromide **6** by the stannylene activation method, which resulted in the formation of intersugar orthoesters **17** and **18**

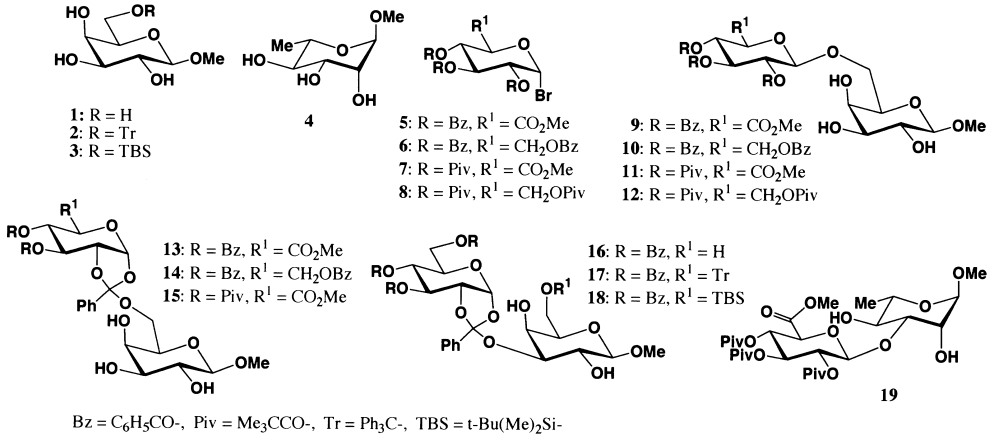
Table 1
Open glycosylation using stannylene activation[a]

Entry	Ac.	Do.	Ac./ Do.[b]	Promoter[c]	Solvent	Temp./ Time (°C) (h)	Product (Yield, %) Disaccharide / Orthoester
1	**1**	**5**	1.0	A	DMF	r. t. / 48	— / —
2	**1**	**5**	1.0	B	CH_2Cl_2	r. t. / 48	**9** (< 5) / **13** (< 5)
3	**1**	**5**	1.0	C	CH_2Cl_2	r. t. / 18	**9** (< 6) / **13** (< 6)
4	**1**	**5**	0.5	D	CH_2Cl_2	r. t. / 96	**9** (39) / **13** (24)
5	**1**	**6**	1.0	D	CH_2Cl_2	r. t. / 18	**10** (6) / **14** (46)
6	**1**	**6**	1.0	D	THF	r. t. / 120	— / **14** (18), **16** (9)
7	**1**	**7**	0.5	D	CH_2Cl_2	50 / 39	**11** (78) / **15** (2)
8	**1**	**8**	0.5	D	CH_2Cl_2	50 / 22	**12** (72) / —
9	**2**	**6**	0.5	D	CH_2Cl_2	r. t. / 18	— / **17** (24)
10	**3**	**6**	0.5	D	CH_2Cl_2	r. t. / 18	— / **18** (32)
11	**4**	**7**	0.5	D	CH_2Cl_2	r. t. / 96	**19** (46) / —

a) General stannylation : 1.5 eq. Bu2SnO, MeOH, reflux 2 h. b) Molar ratio of acceptor / donor.
c) A : Bu_4NBr; B : Ag_2CO_3, I_2 ; C : AgOTf, 1,1,3,3-tetramethylurea ; D : Ag-silica alumina

linking to the 3-position of the galactoside unit (Entries 9 and 10). Application of per-*O*-pivaloylglycosyl bromides to these acceptors will be examined further.

Next, we selected a 6-deoxysugar such as methyl α-L-rhamnopyranoside **4** as the glycosyl acceptor for β(1→3)-glycosylation. Stannylene-activated **4** was glycosylated with per-*O*-pivaloylglucuronyl bromide **7** to yield the expected β(1→3)-linked disaccharide **19** regioselectively in 46% yield (Entry 11). A similar glycosylation of **4** with **7** without stannylene activation gave a mixture of products in low yield.



Bz = C_6H_5CO-, Piv = Me_3CCO-, Tr = Ph_3C-, TBS = t-Bu$(Me)_2$Si-

It seems possible that the regioselectivity in the glycosylation of sugar stannylene acetal described in this study depends on the reactivity of various stannylated structures present in equilibria.[4,16] We assume that 6-*O*-stannylated galactoside present in the equilibria would react faster than 3,4-*O*-stannylated galactoside to give β(1→6)-disaccharides predominantly. On the other hand, in the case of 6-*O*-protected galactosides and unprotected rhamnoside, β(1→3)-linked disaccharides will be preferred due to the lack of a 6-hydroxyl group.

In summary, we have developed stannylene acetal-mediated open glycosylation of methyl β-D-galactopyranoside and α-L-rhamnopyranoside providing a regioselective entry to β(1→6)- and β(1→3)-linked disaccharides in a shorter, very simple process. Various extensions of this method are now in progress.[17]

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12. A general procedure: A mixture of methyl β-D-galactopyranoside **1** (48.6 mg, 0.25 mmol), dibutyltin oxide (93 mg, 0.38 mmol) in methanol (3.0 ml), was heated under reflux for 3 h. The mixture was evaporated in vacuo to give the crude stannylene acetal, which was used for the glycosylation. To a stirred suspension of the stannylene derivative in dry CH_2Cl_2 (5.0 ml) were added MS-3A (powder, 500 mg), Ag(I)-silica alumina (900 mg) and methyl 2,3,4-tri-*O*-benzoyl-1-bromo-α-D-glucopyranuronate **5** (292 mg, 0.50 mmol). The mixture was stirred in the dark for 4 days. After dilution with CH_2Cl_2 (30 ml), the mixture was filtered through Celite, and the filtrate was washed with 5% $NaHCO_3$ aq. (30 ml) and water (3×30 ml), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 10:1) to give the disaccharide **9** (68 mg, syrup, 39% yield) and the corresponding orthoester **13** (40 mg, syrup, 23% yield). Compound **9**: MS (FAB) *m/z*: 719 $[M+Na]^+$; ^{1}H NMR (300 MHz, pyridine-d_5) δ: 5.70 (1H, d, H-1′N), $J_{1'N,2'N}$=8.5 Hz; ^{13}C NMR (75 MHz, pyridine-d_5) δ: 70.4 (C-2), 71.4 (C-6), 72.3 (C-4), 75.0 (C-3), 75.4 (C-5), 106.0 (C-1); ^{13}C NMR (75 MHz, pyridine-d_5+D_2O) δ: 70.2 (C-2,), 71.4 (C-6), 72.1 (C-4), 74.8 (C-3), 75.4 (C-5), 106.0 (C-1).
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