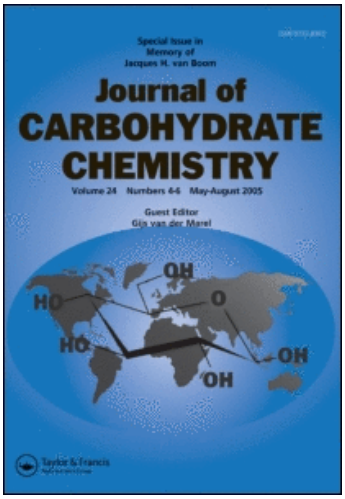

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COMMUNICATION

CONVENIENT ACCESS TO HALIDE ION-CATALYZED α-GLYCOSYLATION FREE FROM NOXIOUS FUMES AT THE DONOR SYNTHESIS

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Key Words: α-Glycosylation; Glycosyl bromide; Glycosyl glyceride

α-Selective glycosylation is a highly challenging and meaningful objective in carbohydrate chemistry.[1a-c] This is mainly because many biologically active oligosaccharides and other glycoconjugates in nature carry an α-glycoside linkage at the non-reducing terminal such as α-L-fucoside in sialyl Lewis^X antigens[2] and α-D-galactobioside in P^K antigens.[3a,b] However, α-glycosylation is not straightforward and requires optimization of the glycosyl donors, promoters, solvents, and other reaction conditions. In this respect, a halide ion-catalyzed α-glycosylation method proposed by Lemieux et al.[4] in 1975 has provided one of the few definitive ways. α-Selectivity is nearly perfect for many acceptor sugars so far examined as long as 2-*O*-benzyl glycosyl bromides are employed as donors.[5a–d] Moreover, the method requires no heavy metal promoters or strong Lewis acid catalysts. These properties are of high significance for large-scale production of ''sugar-based'' therapeutic agents and biochemical materials.

In our study on the structure and immunogenic activity of α-D-glucopyranosyl-*sn*-glycerophospholipids (GGPLs) isolated from *Mycoplasma fermentans*,[6a,b] we applied

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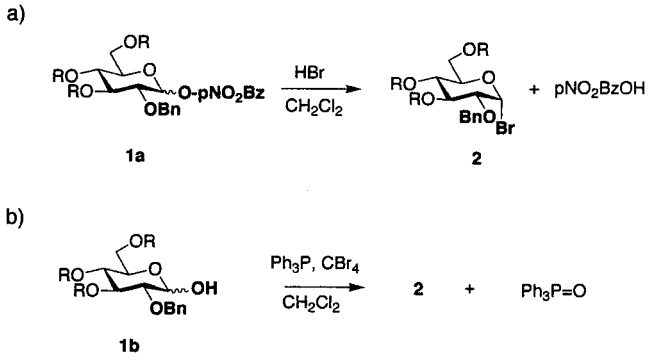
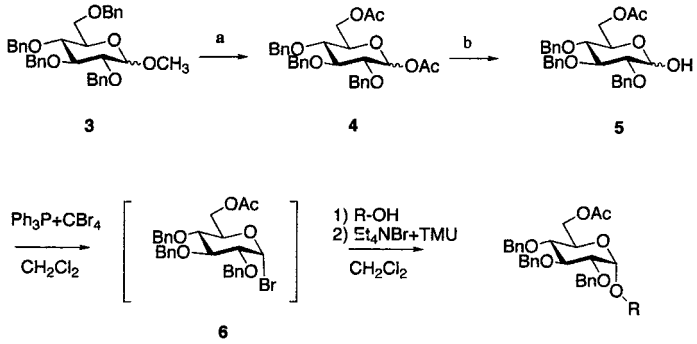


Scheme 1. Preparation of 2-*O*-benzyl glycosyl bromides 2. (a) Conventional bromination using noxious fumes of HBr. (b) Our proposal for bromination using Ph3P/CBr4.

the Lemieux method to stereoselective syntheses of GGPL-I and GGPL-III to elucidate their absolute structures.[7a,b] During this study, however, we experienced much trouble at the stage of preparing the 2-*O*-benzyl glycosyl bromides. In particular, the use of hydrogen bromide (HBr) from a steel tank requires special attention regarding noxious fumes. Such experiences prompted us to eliminate the difficulty prior to employing the excellent α-glycosylation methodology. In this paper, we describe a convenient access to 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide leading to a one-pot α-glycosylation reaction. The pathway allows us to perform a highly practical α-glycosylation without suffering from the noxious fumes.

2-*O*-Benzyl glycosyl bromides **2** are highly labile and intolerant to purification on silica gel columns and other purification processes. Therefore, 1-*O*-*p*-nitrobenzoyl sugars **1a**[8] and 1-thio glycosides[9] have been popularly employed as donor precursors (Scheme 1-a). Upon treatment of **1a** with HBr gas in CH_2Cl_2, the glycosylbromide **2** is produced and *p*-nitrobenzoic acid crystallizes from the solution. Though 1-thio gly-

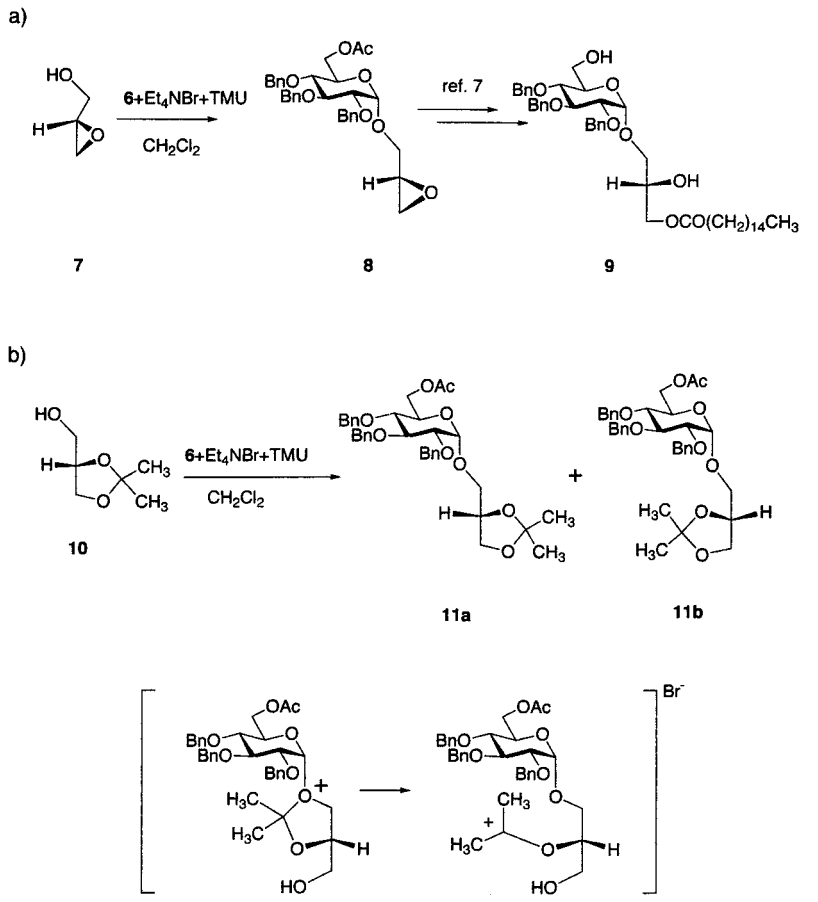


Reagent: (a) H_2SO_4, Ac_2O (92%); (b) piperidine/THF (80%)

Scheme 2. Convenient synthesis of the bromide donor 6 and its application for one pot α-glycosylation.

cosides are convertible to glycosyl bromides without using HBr gas, this approach seems to cause an analogous problem of malodorous thiols.[10] In the present study, we expected that anomeric free (1-OH) sugars **1b** might lead to the halide ion-catalytic α-glycosylation effectively by the use of an appropriate brominating agent. Among several candidates as brominating agents,[11,12a,b–14] we investigated triphenylphosphine/ carbon tetrabromide[14] as a reagent for replacing the 1-OH group with 1-Br (Scheme 1-b).

In order to examine the 1-bromination reaction, 6-*O*-acetyl–2,3,4-tri-*O*-benzyl-D-glucopyranose **5** was prepared from methyl tetra-*O*-benzyl-D-glucopyranoside **3** available from D-glucose in our reported way (72% yield for two steps).[15] Regioselective acetolysis of **3** cleaved the 1-*O*-Me and 6-*O*-Bn groups and afforded **4**, which was subjected to aminolysis by piperidine in THF to then give the 1-OH sugar **5** (Scheme 2). The bromination reaction of **5** with PhP_3 and CBr_4 was optimized at room temperature (15–20°C) by changing the solvents (CH_2Cl_2, toluene, THF, and diethyl ether) and the molar ratio of the bromination agents (1.0 ~ 3.0 mol equiv). The reaction was monitored by TLC on silica gel (*n*-hexane/ethyl acetate) to show that the 1-OH sugar **5** was consumed completely within 3 h and converted to glycosyl bromide **6** when CBr_4



Scheme 3. Application of 6 for one pot α-glycosylation to 3-*O*-α-D-glycosyl-*sn*-glycerides.

(3 mol equiv) and Ph_3P (3 mol equiv) were used in CH_2Cl_2.[a] Addition of diethyl ether caused precipitation of $Ph_3P{=}O$. Filtration followed by the evaporation of the solvent gave 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucosyl bromide **6** as a syrup.[16]

One-pot glycosylation was next examined for the reaction mixture without any isolation processes for the bromide donor **6** and $Ph_3P{=}O$. Commercially available (*S*)-glycidol **7** and 1,2-*O*-isopropylidene-*sn*-glycerol **10** were employed as glycosyl acceptors, taking their synthetic potential for GGPLs and other α-D-glycosyl-*sn*-glycerides into account (Scheme 3).[7,17,18] When the glycosylation was conducted at room temperature in the presence of tetraethylammonium bromide[4,5] (Et_4NBr, 1.5 mol equiv) and *N*,*N*,*N*′,*N*′-tetramethylurea (TMU, 10 mol equiv),[7] each of the glycosylated products **8** and **11** was isolated in satisfactory yields[b] (82% and 95%, respectively, based on the amount of 1-OH sugar **5**) after purification on silica gel column. Their ^{1}H NMR spectra[c] showed that both of the acceptors **7** and **10** permitted α-selective glycosylation affording no β-isomer. These results have shown that none of the brominating agents and possible side-products, including $Ph_3P{=}O$, affect the one-pot α-glycosylation under the halide ion-catalytic conditions. On the other hand, the reaction of **10** was found to cause epimerization at the glycerol moiety to give a mixture of two diastereomers **11a** and **11b** in *ca.* 3:2 ratio. Analogous isomerization was reported in glycosylation reactions using heavy metal promoters and regulated by the addition of an appropriate amine base.[17,18] In the present case, the epimerization is considered to proceed via the formation of an oxonium cation complex stabilized under the halide ion-catalytic conditions (Scheme 3-b). The addition of excess TMU could not avoid the

[a]The 1-bromination reaction at room temperature was sluggish in toluene and not detected in THF and diethyl ether in 2 h.

[b]In these reactions, glycosyl bromide **6** was consumed completely for α-glycosylation without any decomposition into 5. The low yield of **8** was ascribed to partial ring opening of the epoxide moiety by a bromide anion during the reaction.

[c]Selected analytical date of compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H7.40 ~ 7.23 (m, 5 H × 3, $-CH_2C_6H_5$), 4.55 ~ 5.02 (dd, 2 H × 3, $-CH_2C_6H_5$), 4.87 (d, 1 H, J = 4.0 Hz, H-1), 4.26 (dd, 1 H, J = 4.0 and 12.0 Hz, H-6$_S$), 4.22 (dd, 1 H, J = 2.5 and 12.0 Hz, H-6$_R$), 4.02 (t, 1 H, J = 9.0 and 9.5 Hz, H-3), 3.88 (m, 1 H, H-5), 3.76 (dd, 1 H, J = 3.5 and 12.0 Hz, glycidol H-3$_{proR}$), 3.48 (dd, 1 H, J = 6.0 and 12.0 Hz, glycidol H-3$_{proS}$), 3.53 (dd, 1 H J = 3.5 and 9.5 Hz, H-2), 3.20 (m, 1 H, glycidol H-2), 2.57 and 2.78 (dd, 1 H × 2, J = 4.0 and J = 5.0, J = 3.0 and 5.0 Hz, glycidol H-1$_{proR}$ or H-1$_{proS}$), 1.99 (s, 3 H, −Ac); HR MS (FAB): *m*/*z* calcd for $C_{32}H_{36}O_8Na$ [M + Na$^+$] 571.2308; found 571.2285. Compound **11a** (major product): ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.40 ~ 7.23 (m, 5 H × 3, $-CH_2C_6H_5$), 4.56 ~ l4.99 (dd, 2 H × 3, $-CH_2C_6H_5$), 4.83 (d, 1 H, J = 3.5 Hz, H-1), 4.35 (t, 1 H, J = 5.5 and 6.5 Hz, glycerol H-2), 4.20 ~ 4.28 (dd, 1 H × 2 H-6), 3.98 (t, 1 H, J = 9.0 and 9.5 Hz, H-3), 3.85 (m, 1 H, H-5), 4.07 and 3.74 (dd, 1 H × 2, J = 8.5 and 6.5, J = 6.0 and 8.0 Hz, glycerol H-3$_{proR}$ or H-3$_{proS}$), 3.60 and 3.55 (dd, 2 H, J = 6.0 and 10.5, J = 6.5 and 10.5 Hz, glycerol H-1$_{proR}$ or H-1$_{proS}$), 3.54 (dd, 1 H, J = 3.5 and 9.5 Hz, H-2), 3.47 (dd, 1 H, J = 9.0 and 10.0 Hz, H-4), 2.02 (s, 3 H, −Ac), 1.42 and 1.36 (s, 3 H × 2, isopropyl). Compound **11b** (minor product): ^{1}H NMR (500 MHz, $CDCl_3$): δ_H7.40 ~ 7.23 (m, 15 H, $-CH_2C_6H_5$), 4.56 ~ 4.99 (dd, 2 H × 3, $-CH_2C_6H_5$), 4.74 (d, 1 H, J = 3.5 Hz, H-1), 4.32 (t, 1 H, J = 5.5 and 6.5 Hz, glycerol H-2), 4.20 ~ 4.28 (dd, 1 H × 2, H-6), 4.00 (t, 1 H, J = 9.0 and 9.5 Hz, H-3), 3.88 (m, 1 H, H-5), 4.07 and 3.78 (dd, 1 H × 2, J = 6.5 and 8.5, J = 5.5 and J = 8.0 Hz, glycerol H-3$_{proR}$ or H-3$_{proS}$), 3.69 and 3.42 (dd, 1 H × 2, J = 6.0 and 10.5, J = 6.5 and 10.5 Hz, glycerol H-1$_{proR}$ or H-1$_{proS}$), 3.54 (dd, 1 H, J = 3.5 and 9.5 Hz, H-2), 3.48 (dd, 1 H, J = 9.0 and 10.0 Hz, H-4), 2.02 (s, 3 H, −Ac), 1.41 and 1.35 (s, 3 H × 2, isopropyl); HR MS (FAB): *m*/*z* calcd for $C_{35}H_{42}O_9Na$ [M + Na$^+$] 629.2727; found 629.2704.

epimerization. In any case, the use of (*S*)-glycidol **7** provides a more practical way towards 3-*O*-α-D-glycosyl-*sn*-glycerides, since a fatty acid can be introduced in an S_N2 fashion affording **9** regioselectively (Scheme 3-a).[7]

In conclusion, we have demonstrated a convenient access to 2-*O*-benzyl glucosyl bromide **6** starting from D-glucose leading to one-pot halide ion-catalyzed α-glycosylation. This approach has solved the difficulty in the chemical construction of α-D-glucopyranosyl-*sn*-glycerides widely distributed in bacterial cell walls. We expect that the present pathway will be extended to other glycosyl donors and acceptors to solve many of difficulties encountered in α-glycosylation chemistry. Additional studies are in progress in our group and will be reported elsewhere.

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