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One-pot α-glycosylation pathway via the generation in situ of α-glycopyranosyl imidates in *N*,*N*-dimethylformamide

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Abstract—Divergent pathways are disclosed in the activation of 2-*O*-benzyl-1-hydroxy sugars by a reagent combination of CBr_4 and Ph_3P, all of which afford one-pot α-glycosylation methods. When this reagent is used in CH_2Cl_2, the 1-hydroxy sugar is converted to the α-glycosyl bromide in a conventional way and leads to the one-pot α-glycosylation method based on a halide ion-catalytic mechanism. In either DMF or a mixture of DMF and $CHCl_3$, however, alternative α-glycosyl species are generated. From the ^1H and ^{13}C NMR study of the products, as well as the reactions using Vilsmeier reagents $[(CH_3)_2N^+{=}CHX]X^-$ (X = Br and Cl), these were identified as cationic α-glycopyranosyl imidates having either Br^- or Cl^- counter ion. The cationic α-glycosyl imidate (Br^-), derived specifically in the presence of DMF, is more reactive than the α-glycosyl bromide and thus is responsible for the accelerated one-pot α-glycosylation. The one-pot α-glycosylation methodology performed in DMF was assessed also with different types of acceptor substrates including tertiary alcohols and an anomeric mixture of 1-OH sugars.

Keywords: α-Glycoside epitopes; Imidates; Solvent effects; Glycosylation; Trehalose; Glycolipids

1. Introduction

The development of practical α-glycosylation reactions is one of the meaningful challenges in organic chemistry.[1] This is mainly because a large part of mammalian oligosaccharides carry the corresponding α-glycoside epitope such as α-L-fucopyranoside and α-D-galactopyranoside in Lewis^X and globosyl antigens, respectively.[2] Also for the developing glycosylation methodologies, such as those based on semi-automatic,[3] solid-phase,[4] fluorous,[5] and modular syntheses,[6] simple and practical α-glycosylation reactions are essential. Among the popular α-glycosylation reactions hitherto reported,[7] the halide-ion catalytic α-glycosylation reaction established by Lemieux and his co-workers[8] seems to provide one of the most definitive pathways. A typical reaction utilizes a 2-*O*-benzyl-α-glycopyranosyl bromide as the glycosyl donor and *N*-tetraethylammonium bromide ($Et_4N^+Br^-$) as the catalyst. The α-glycosylation involves an in situ anomerization of the donor in the presence of the catalyst as the key step to give the β-glycosyl bromide in equilibrium. The β-species is more reactive than the α-glycosyl bromide, and therefore, it is able to serve as an actual donor in the α-glycosylation reaction. Moreover, it is notable from a practical viewpoint that this methodology requires none of the heavy metals and strong Lewis acids often seen in this type of reaction.

Also in our synthetic studies on the cell-membrane glycolipids (GGPLs)[9] of *Mycoplasma fermentans*,[10] we have applied the halide-ion catalytic method effectively. This method can be carried out under neutral conditions and is applicable to α-glycosylation with chiral epoxy alcohols [(*S*)- and (*R*)-glycidols] required for constructing the α-glycosyl-*sn*-glycerol skeleton. Along these lines, we have attempted to make the overall synthetic

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process simpler. In preceding papers,[11,12] we reported that the halide-ion catalytic α-glycosylation reaction could be conducted in a one-pot manner starting from a 2-*O*-benzyl-1-hydroxy sugar. For the one-pot α-glycosylation, the reagent combination of CBr_4 and Ph_3P, called the Appel–Lee reagent[13–15] in this paper, plays multiple roles such as conversion of the 1-hydroxy sugar into an α-glycosyl bromide, in situ anomerization, and dehydration of the reaction system. More recently, we found that an alternative α-glycosyl species was derived when the Appel–Lee reagent was used in DMF for the activation of the 1-hydroxy sugar.[16] The α-glycosyl species is labile to water and any isolation process, giving a mixture of the known α-glycosyl bromide and 1-hydroxy sugar. Moreover, the subsequent one-pot α-glycosylation was accelerated in comparison with the reactions conducted in CH_2Cl_2. These results have suggested that there may be an alternative α-glycosylation pathway in which the reactive α-glycosyl species serve as the glycosyl donor. In the present study, we examined the activation of the 1-hydroxy sugar by the Appel–Lee reagent in more detail, as well as the structure and possible role of the α-glycosyl species in the one-pot α-glycosylation conducted in DMF.

2. Results and discussion

2.1. Divergent activation pathways of a 2-*O*-benzyl-1-hydroxy sugar by the Appel–Lee reagent

The combination of CBr_4 and Ph_3P used in CH_2Cl_2 or $CHCl_3$ converts 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (**1**) to the α-glycosyl bromide (α-**2-Br**, Fig. 1a) giving $Ph_3P{=}O$ as a side product.[11,12] A similar conversion was reported also by Khatuntseva et al.[15] When this reagent was used in DMF-d_7, an alternative α-glycopyranosyl species α-**2-X** was derived (Fig. 1b). This species was highly sensitive to water and intolerable to isolation processes, being decomposed simultaneously to a mixture of α-**2-Br** and **1**. In a solvent mixture of 1:1 DMF-d_7 and $CDCl_3$, a third α-glycosyl species α-**2-Y** was derived (Fig. 1c), which is obviously different from the 2-*O*-benzyl-α-glycosyl chloride (α-**2-Cl**) reported in the literature.[17]

In ^{1}H NMR spectroscopy, the unknown α-glycosyl species (α-**2-X** and α-**2-Y**) gave H-1 signals at a remarkably low field (δ 7.12 and δ 6.72 ppm) (Table 1). The ^{1}H chemical shifts are unusual for the D-hexopyranosyl $^4C_1$ (ring) conformation. This indicates that these products carry a highly electron-withdrawing group at the anomeric position. From their ^{1}H and ^{13}C NMR data and chemical properties we have observed, we assigned them tentatively as cationic α-glycopyranosyl imidates, possessing bromide and chloride counter ions, respectively (Scheme 1).

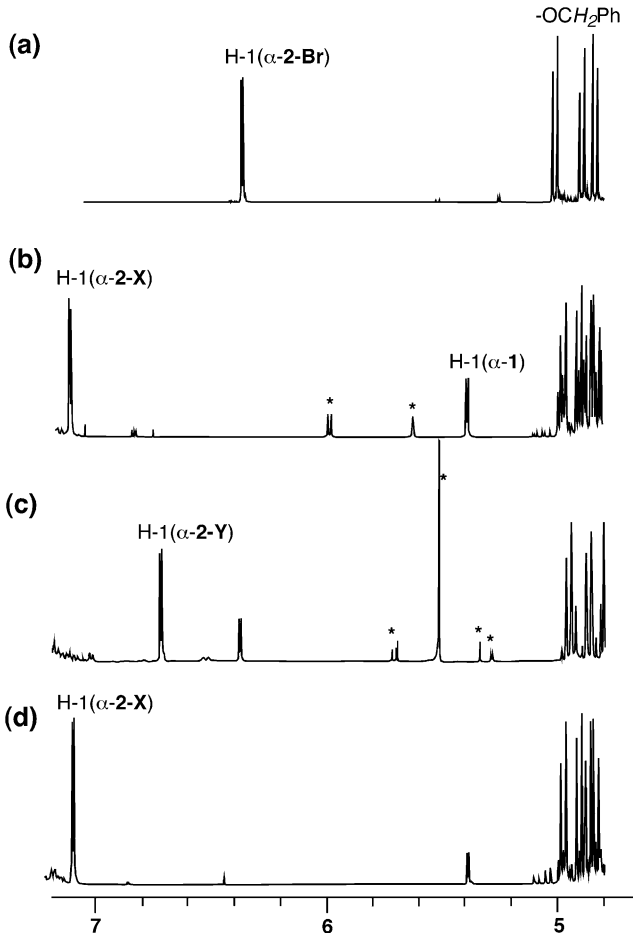


Figure 1. ^{1}H NMR spectra (500 MHz) of a mixture of **1** and (a) Appel–Lee reagent in $CDCl_3$, (b) Appel–Lee reagent in DMF-d_7, (c) Appel–Lee reagent in a mixture of 1:1 DMF-d_7 and $CDCl_3$, (d) Vilsmeier reagent (Br^--type) in DMF-d_7 solution. An asterisk (∗) denotes the signal of unidentified non-sugar products.

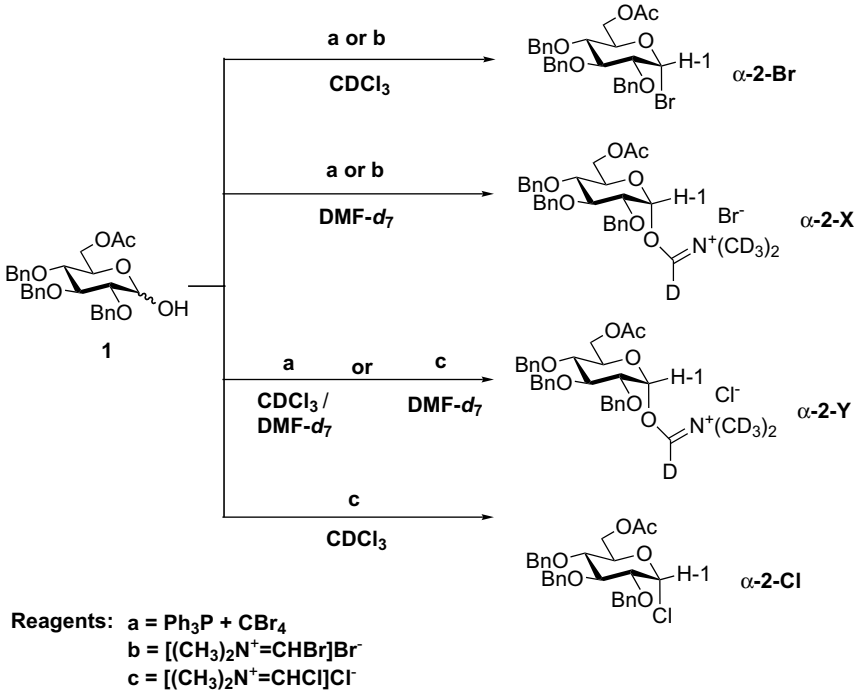
The assigned imidate structure is a kind of Vilsmeier–Haack intermediate having $[(CH_3)_2N^+{=}CH\text{-}OR]X^-$ as the general structure.[18] This intermediate is derived in reactions between an alkyl alcohol (R-OH) and a Vilsmeier reagent $[(CH_3)_2N^+{=}CHX]X^-$ (X = Cl or Br) on the way to forming alkyl halides (R-X).[19] Sugar OH groups are also known to give these intermediates including the anomeric imidate of 2,3:4,5-di-*O*-isopropylidene-D-mannofuranosyl imidates (Cl^- and *p*-TsO^- salts) derived with phosgene in DMF.[20]

To confirm the structures of α-**2-X** and α-**2-X**, we treated **1** with each of the bromide and the chloride types of Vilsmeier reagents (Aldrich). ^{1}H and ^{13}C NMR spectra of the main products accorded with the products derived with the Appel–Lee reagent. That is, the Br^- type of Vilsmeier reagent afforded α-**2-X** exclusively in DMF-d_7 (Fig. 1d), while it gave α-**2-Br** in $CDCl_3$. The Cl^- type of reagent gave α-**2-Y** in DMF-d_7 and α-**2-Cl** in $CDCl_3$. This means that the Appel–Lee reagent used in DMF generates the Vilsmeier reagents to afford the cationic

Table 1. ^{1}H and ^{13}C NMR data (δ ppm) of diverse α-glycosyl species derived in the reaction of **1** with Appel–Lee or Vilsmeier reagents[a]

	α-**2**-Br[b]	α-**2**-X[c]	α-**2**-Y[d]	α-**2**-Cl[e]
H-1	6.37 (d, 3.5 Hz)	7.12 (d, 3.5 Hz)	6.72 (d, 3.5 Hz)	6.04 (d, 3.5 Hz)
H-2	3.51 (dd, 3.5, 9.0 Hz)	3.71 (dd, 3.5, 9.0 Hz)	3.61 (dd, 3.5, 9.0 Hz)	3.71 (dd, 3.5, 9.0 Hz)
H-3	4.06 (dd, 9.0, 9.0 Hz)	3.95 (dd, 9.0, 9.0 Hz)	3.98 (dd, 9.0, 9.0 Hz)	4.06 (dd, 9.0, 9.5 Hz)
H-4	3.58 (dd, 9.0, 10.0 Hz)	3.72 (dd, 9.0, 10.0 Hz)	3.63 (dd, 9.0, 10.0 Hz)	3.55 (dd, 9.5, 10.0 Hz)
H-5	4.11 (ddd)	4.10 (m)	4.07 (m)	4.15 (ddd)
H-6 *proR*	4.29 (dd, 3.5, 12.0 Hz)	~4.3 (overlapped)	~4.3 (overlapped)	~4.27 (overlapped)
H-6 *proS*	4.27 (dd, 2.5, 12.0 Hz)	~4.3 (overlapped)	~4.3 (overlapped)	~4.27 (overlapped)
C-1	90.55	93.90	92.40	91.87
C-2	79.09	79.85	79.70	78.55
C-3	81.44	82.18	81.92	79.94
C-4	75.18	76.20	75.71	74.71
C-5	73.00	74.40	73.85	71.63
C-6	61.42	62.50	62.05	60.94

[a] The NMR data were taken from the spectra of a mixture of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucose (**1**) and the reagents as denoted in footnotes b–e, below.
[b] Appel–Lee reagent (3 mol equiv) in $CDCl_3$.
[c] Appel–Lee reagent (3 mol equiv) in DMF-d_7.
[d] Appel–Lee reagent (1.5 mol equiv) in 1:1 DMF-d_7:$CDCl_3$.
[e] Vilsmeier reagent (Cl^-) (3 mol equiv) in $CDCl_3$.



Scheme 1. Divergent activation of 1 by Appel–Lee (a) and Vilsmeier (b and c) reagents in different solvents.

α-glycosyl imidates α-**2**-X and α-**2**-Y from **1**. Accordingly, we have disclosed divergent activation pathways of **1** by either the Appel–Lee or the Vilsmeier reagent as summarized in Scheme 1. There, the mechanism of activation is largely determined by the solvent used.

2.2. One-pot α-glycosylation method carried out in DMF

As judged from the unique NMR chemical shift of C-1 and H-1, α-**2**-X is expected to undergo the in situ anomerization more readily than the conventional α-glycosyl bromide. This implies also that this species may serve as a prominent donor for the halide-ion catalytic pathway. Here, we examined several solvent and reagent conditions to examine the possible role of α-**2**-X with a final objective of establishing a one-pot α-glycosylation methodology carried out in DMF (Table 2). As acceptor substrates, we used cholesterol **3a** and *tert*-butyl alcohol **3b**. Every reaction was conducted in a one-pot manner using **1** as the donor with each of the acceptors and activating

reagents in 3-molar excess to this donor.[11,12,16] In entries 1 and 2, tetramethylurea (TMU) was used as a weak base in CH_2Cl_2 instead of DMF, which eliminates the occurrence of α-**2-X**. In entries 3 and 4, the reactions were conducted in DMF. In entries 5 and 6, the Br^- type of the Vilsmeier reagent was employed in lieu of the Appel–Lee reagent. In entries 7 and 8, a polymer-bound Ph_3P resin (Argonaut)[21] was employed.

As summarized in Table 2, every reaction gave the corresponding α-glycoside in high yield. Comparing the reaction time between entries 1 and 3 (or entries 2 and 4), it is obvious that the one-pot glycosylation is accelerated in DMF. As well as the usual solvent effect of DMF for promoting S_N2 reactions, we consider that the α-glycosyl imidate, derived specifically in this solvent, plays a key role in the acceleration. In entries 5 and 6, it is shown that the Vilsmeier reagent is also usable for the one-pot methodology. The reactions yielding no $Ph_3P{=}O$ were apparently cleaner than those by the Apple–Lee reagent.

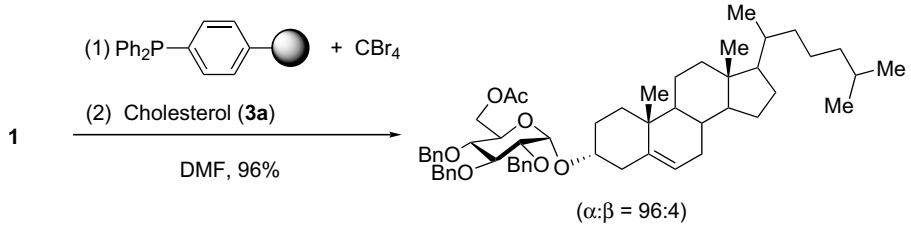
On the other hand, the 1-hydroxyl donor **1** was recovered as a side product without the reaction reaching completion. This result may be ascribable to the low capacity of the Vilsmeier reagent for trapping the water molecules that compete with the glycosylation reaction. A more significant difference may be in the fact that the Appel–Lee reagent can supply more Br^- anions than the Vilsmeier reagent can utilize for the in situ anomerization. Accordingly, the Apple–Lee reagent is a better $M–X_2$ (or M–X) type of reagent[16] that can activate a 1-hydroxy sugar while trapping the water molecules in a form of $Ph_3P{=}O$. In entries 7 and 8, it is shown that the polymer-bound Ph_3P works effectively for the one-pot methodology. With ^1H NMR spectroscopy, we observed that the polymer-bound Ph_3P also gave α-**2-X** in DMF-d_7. Actually, the use of the polymer reagent offers a remarkable advantage for purification of the glycosyl products, which definitely makes this an advanced one-pot α-glycosylation method (Scheme 2).

We have reported that the Appel–Lee reagent used in DMF in situ generates the cationic α-glycosyl imidate (Br^-). For rationalizing the observed α-glycosylation reaction, we assume that the α-glycosyl imidate will permit the in situ anomerization effectively under the optimized conditions (entries 3 and 4) and lead to an authentic halide-ion catalytic α-glycosylation pathway. According to the pioneering work of Lemieux et al.,[8] a 2-*O*-benzyl-α-glycopyranosyl bromide like α-**2-Br** undergoes a rapid equilibration with the β-glycosyl bromide in the presence of $Et_4N^+Br^-$, and the more reactive β-glycosyl bromide serves as the actual donor. Moreover, it is predicted that the β-glycosyl bromide takes an unusual ring conformation such as the $^1C_4$ (chair) and $B_{2,5}$ (boat) due to electrostatic effects termed as the anomeric effect. As judged from the NMR chemical shift of C-1 (93.90 ppm), as well as from the chemical

Table 2. One-pot α-glycosylation using either Appel–Lee or Vilsmeier reagent for the activation of **1**[a]

Entry	Reagents	Solvents	Acceptors	Time (h)[c]	α:β (%)[d]
1	Ph_3P+CBr_4	CH_2Cl_2+TMU[b]	**3a**	50	>99:1[e] (92)
2	Ph_3P+CBr_4	CH_2Cl_2+TMU[b]	**3b**	96	>99:1 (95)
3	Ph_3P+CBr_4	DMF	**3a**	18	95:5 (92)
4	Ph_3P+CBr_4	DMF	**3b**	24	97:3 (95)
5	$[(CH_3)_2N^+{=}CHBr]Br^-$	DMF	**3a**	>120[f]	97:3 (84)
6	$[(CH_3)_2N^+{=}CHBr]Br^-$	DMF	**3b**	>120[f]	>99:1 (72)
7	Poly-Ph_3P+CBr_4	DMF	**3a**	22	96:4 (96)
8	Poly-Ph_3P+CBr_4	DMF	**3b**	27	98:2 (96)

[a] Room temperature using **1** (0.2 mmol), DMF or CH_2Cl_2 (1.5 mL), Appel–Lee or Vilsmeier reagents (3 mol equiv for **1**), and the acceptor **3a** or **3b** (3 mol equiv).
[b] TMU (150 μL) was added to the CH_2Cl_2 solution together with the acceptor alcohol.
[c] Reaction time (h) after addition of the acceptor alcohol.
[d] Isolated yields (%) based on **1**; ^1H NMR analysis.
[e] No β-isomer was detected.
[f] The reaction was stopped after 120 h when a considerable amount of the 1-hydroxy sugar **1** was detected.



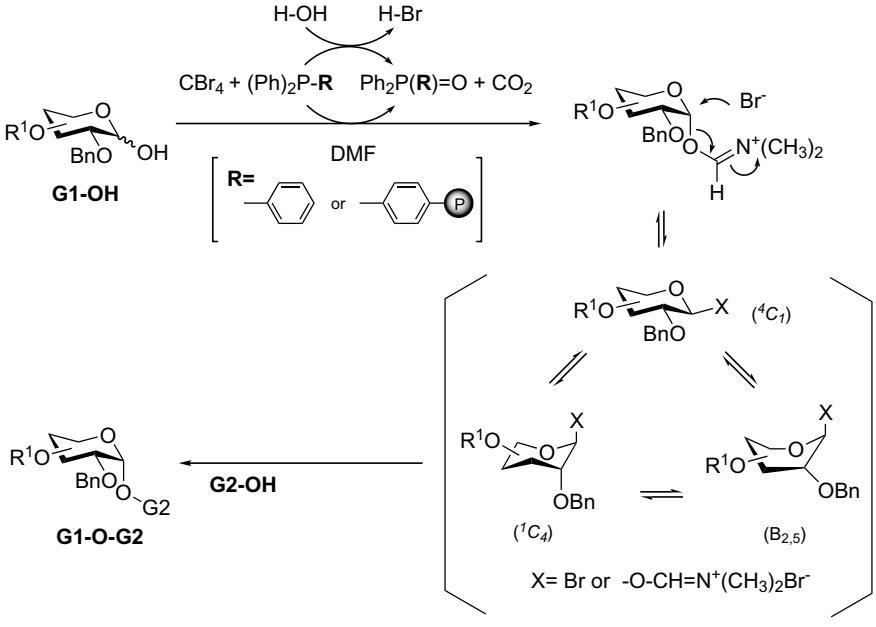
Scheme 2. An advanced one-pot α-glycosylation method using a combination of polymer-bound Ph_3P and CBr_4 in DMF.

behaviour of the Vilsmeier intermediate, it is reasonable to assume that the anomeric position of α-**2-X** can permit a nucleophilic bromination that leads to the in situ anomerization. Taking the overview of Lemieux et al. into account, we are able to propose a reaction pathway for the present one-pot α-glycosylation as summarized in Scheme 3. In the overall pathway, the in situ generation of the Vilsmeier reagent is omitted, and the occurrence of the β-glycosyl species with the unusual ring conformers is still considered speculative.

Despite several approaches, it was difficult to obtain clear evidence for the occurrence of the β-glycosyl species (imidate and bromide). For example, the ^{1}H NMR spectra of **2-X** and α-**2-Br** gave no signals corresponding to the β-isomers, and the ^{1}H–^{1}H coupling data were typical of the α-D-glucopyranosyl $^{4}C_{1}$ (ring) conformation. Apparently, the equilibration assumed here is rapid on the NMR time scale, and the β-isomer should be only a minor component (less than 5%), even if it exists. In ^{1}H–^{1}H COSY experiments, however, we might obtain some information on the β-isomer (Fig. 2). Both α-**2-X** and α-**2-Br** were found to give weak but substantial cross peaks between H-1 and H-3 as well as between H-1 and H-5. None of the α-glycosylated products from cholesterol (**3a**) and *tert*-BuOH (**3b**) gave such cross peaks under the same conditions. The cross peaks mean that the H-1 has a long-range coupling with the H-3 and H-5 protons.[22] On the other hand, such long-range coupling is not allowed for the α-glycopyranosyl species in any conformation. The long-range coupling is typical of the two protons located in a coplanar W-geometry or in an allylic position. We speculate a possibility that the unidentified β-isomers, taking the unusual ring conformation of $^{1}C_{4}$, may make the coplanar geometry and contribute to the observed long-range coupling.

As we have noted in the above study, the one-pot α-glycosylation carried out in DMF is very slow in comparison with the other glycosylation reactions using heavy metal promoters or Lewis acid catalysts. Under optimized conditions, we require the acceptor substrate and the Appel–Lee reagent in 3-molar excess amounts to the 1-hydroxy sugar. We predict, therefore, that the present α-glycosylation methodology will offer a major benefit to the large-scale assembly of simple α-glycosides rather than for complicated oligosaccharide linkages. For constructing the α-linked oligosaccharides such as Gb_3 and Lewis^{X}, we have proposed an alternative α-glycosylation reaction using *o*-methoxycarbonylphenyl 1-thioglycosides, which is non-malodorous and reactive with sugar acceptors, nevertheless, requiring a strong Lewis acid and a dehydrating reagent such as molecular sieves.[1e,23] We expect that the DMF solvent used in the present one-pot methodology can permit a wide range of acceptor substrates. Moreover, the slow reaction may be effective for inducing regio- and stereoselectivity. To examine these probabilities, we conducted two additional reactions (Scheme 4).

When glycerol was used as the acceptor substrate in a co-solvent system of 5:100 acetone–DMF, we obtained a mixture of 1-*O*- and 3-*O*-α-D-glucopyranosyl-*O*-isopropylidene-*sn*-glycerol derivatives[11] (**4a** and **4b**) directly in a 3:4 ratio. Though the diastereoselectivity in the prochiral C-1 and C-3 positions in glycerol was poor, the one-pot *O*-isopropylidenenation and α-glycosylation reaction should be unique to the present methodology. When the 1-hydroxy sugar **1** was used as the acceptor



Scheme 3. Overall reaction pathways in the one-pot α-glycosylation performed in DMF.

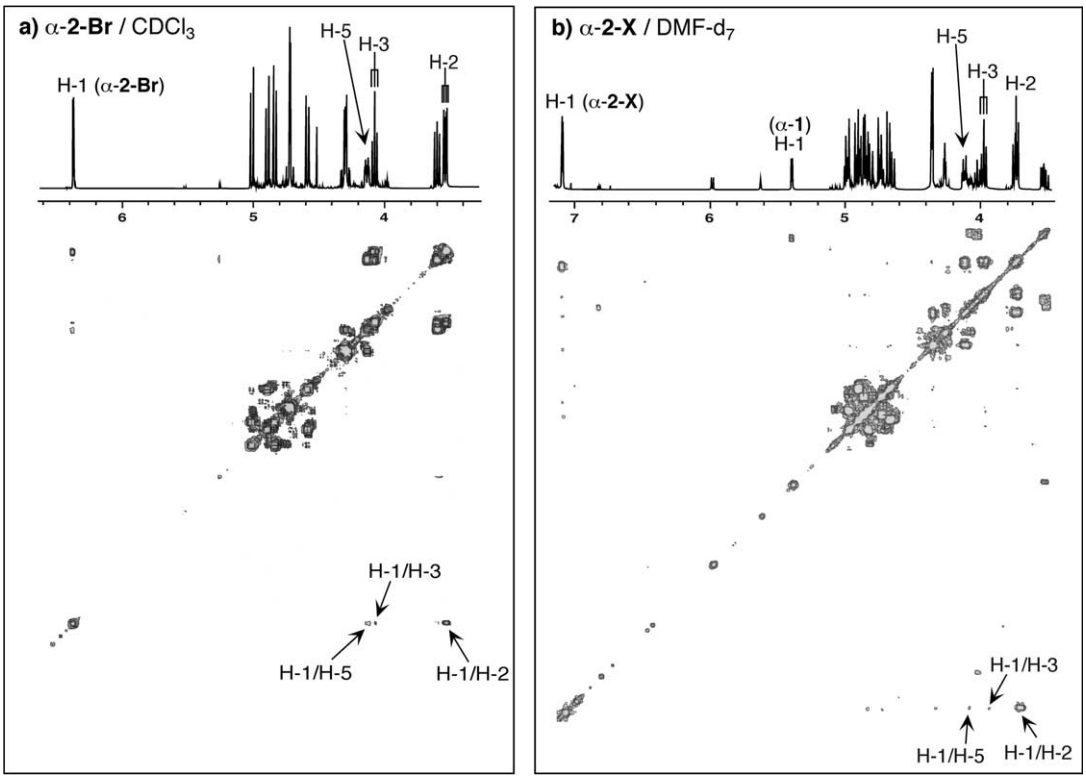
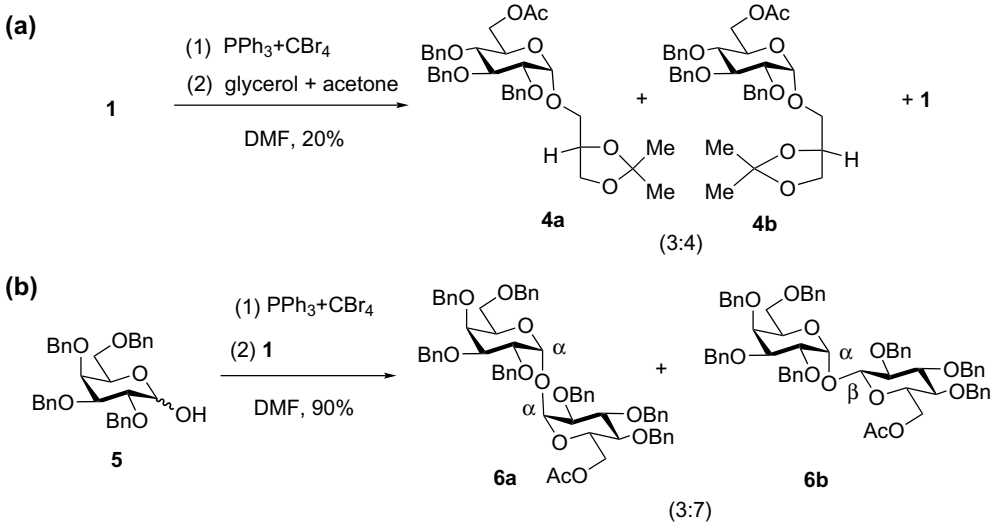


Figure 2. ^{1}H–^{1}H COSY spectrum of (a) α-**2-Br** produced from a mixture of **1** and an Appel–Lee reagent in $CDCl_3$, and (b) α-**2-X** from a mixture of **1** and an Appel–Lee reagent in DMF-d_7.



Scheme 4. One-pot α-glycosylation with glycerol in the presence of acetone (a) and with 1-OH sugar 1 in DMF (b).

substrate of D-galactosyl donor **5**, we obtained α-D-galactopyranosyl (1→1)-linked disaccharides as a mixture of **6a** and **6b** in the ratio of 3:7. The galactosylation reaction per se was α-specific, while we observed a unique stereoselectivity in the acceptor substrate **1**. The main product **6b** has a β-D-glucopyranosyl linkage. Since the acceptor **1** gives a 1:1 mixture of α and β anomers in DMF-d_7, it is obvious that the α-galactosylation favoured the β-anomer of **1** to afford **6b** as the major product. It is probable that a part of the α-anomer of **1** was anomerized to the β-isomer during the slow reaction (40 h). The non-reducing (1→1)-linked disaccharides have high potential in applications to biological and medicinal studies,[24] and the present α-glycosylation can provide promising access to the dissymmetric α-(1→1)-β-linked disaccharides.[25]

In conclusion, we have described divergent activation pathways of 2-*O*-benzyl-1-hydroxy sugars with the Appel–Lee reagent, in which the solvent determines the pathway of activation. In DMF solvent, the 1-hydroxy sugar is converted to the cationic α-glycosyl imidate (Br^-), which led to the one-pot α-glycosylation methodology that accepts both hydrophobic and hydrophilic acceptor substrates. The present one-pot α-glycosylation method is principally based on the halide-ion catalytic pathway established by Lemieux et al.[8] but it is different from the original authentic method with the effective use of 1-hydroxy sugars[26] and the M–X_2 type of activating reagents.[16] The reaction can be conducted at room temperature without special care for dehydration of the reaction system. The simple reaction is currently being applied to the practical synthesis of α-glycolipids from the cell-membrane of *M. fermentans*.

3. Experimental

3.1. General methods

All ^1H (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded at ambient temperature. ^1H chemical shifts are expressed in parts per million (ppm) based on internal TMS (0.00 ppm) in $CDCl_3$ or that of DMF-d_7 (2.91 ppm). ^{13}C chemical shifts are expressed in parts per million (ppm) based on solvent signal of $CDCl_3$ (77.00 ppm) or that of DMF-d_7 (30.10 ppm).

3.2. Experimental data (^1H and ^{13}C NMR spectroscopy and FAB mass spectrometry) of (a) α-2-Br, (b) α-2-X, (c) α-2-Y and (d) α-2-Cl

For details see Scheme 1 and Table 1.

3.2.1. 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide (α-2-Br). ^1H and ^{13}C NMR spectra were measured for a mixture of **1** and 3 mol equiv of CBr_4 and Ph_3P in $CDCl_3$, as well as for a mixture of **1** and 3 mol equiv of Vilsmeier (Br^-) reagent in $CDCl_3$. Both of the mixtures showed the occurrence of α-**2-Br** as the main product. δ_H and δ_C data obtained with CBr_4 and Ph_3P in $CDCl_3$ were as follows: δ_H 7.40–7.25 (m, 5H×3, –$CH_2C_6H_5$), 5.00, 4.88, 4.82, 4.72, 4.70 and 4.57 (d, 2H×3, –$CH_2C_6H_5$), 2.01 (s, 3H, –OAc); δ_C 164.93 (6-OAc; –*C*OCH$_3$), ~128 (18C, –CH_2-*Ph*), 74.99, 74.55, 72.12 (3C, –*C*H_2-Ph), 20.30 (6-OAc; –CO*C*H$_3$) (other proton data are listed in Table 1). FABMS spectra of the mixture of **1** and CBr_4 and Ph_3P in CH_2Cl_2 (*m*-nitrobenzyl alcohol+NaI): observed fragments were *m*/*z* 577 [M+Na^+] and 579 [M+2+Na^+], 650 [(*m*-nitrobenzyl glycoside)+$Na]^+$, 625 [(glycosyl iodide)+$Na]^+$, 515 [**1**+$Na]^+$, 498 [(**2-Br**)-Br+$Na]^+$, 497 [(**2-Br**)-HBr+$Na]^+$.

3.2.2. 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyloxy-*N*-*N*-dimethylformamidinium bromide (α-2-X). ^1H and ^{13}C NMR spectra were measured for a mixture of **1** and 3 mol equiv of CBr_4 and Ph_3P in DMF-d_7. The observed spectra accorded with those derived from a mixture of **1** and 3 mol equiv of Vilsmeier (Br^-) reagent in DMF-d_7. However, several trials to detect signals of –O–CH=$N^+(CH_3)_2$ were unsuccessful because these signals were obscured in the DMF-d_7 solution system. δ_H and δ_C data obtained with CBr_4 and Ph_3P in DMF-d_7 were as follows: δ_H 7.47–7.29 (m, 5H×3, –$CH_2C_6H_5$), 4.96, 4.90, 4.86, 4.82, 4,73 and 4.66 (d, 2H×3, –$CH_2C_6H_5$), 2.03 (s, 3H, –OAc); δ_C 170.59 (6-OAc; –*C*OCH$_3$), ~128 (18C, –CH_2–*Ph*), 75.32, 74.99, 72.11 (3C, –*C*H_2-Ph), 20.47 (6-OAc; –CO*C*H$_3$) (other data are listed in Table 1). An FABMS study of the mixture of **1** and CBr_4 and Ph_3P in DMF detected no fragment of **2-X**. The observed fragments were adducts with matrix and **2-Br** were as follows; (*m*-nitrobenzyl alcohol+NaI): *m*/*z* 650 [(*m*-nitrobenzyl glycoside)+$Na]^+$, 625 [(glycosyl iodide)+$Na]^+$, 577 [(**2-Br**)+$Na]^+$, 579 [(**2-Br**)+2+$Na]^+$, 515 [**1**+$Na]^+$, 498 [(**2-Br**)-Br+$Na]^+$, 497 [(**2-Br**)-HBr+$Na]^+$. (2,2′-dithioethanol+NaI) (*m*/*z*): 651 [(2,2′-dithioethanyl glycoside)+$Na]^+$, 625 [(glycosyl iodide)+$Na]^+$, 577 [(**2-Br**)+$Na]^+$, 579 [(**2-Br**)+2+$Na]^+$, 515 [**1**+$Na]^+$, 498 [(**2-Br**)-Br+$Na]^+$, 497 [(**2-Br**)-HBr+$Na]^+$.

3.2.3. 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyloxy-*N*,*N*-dimethylformamidinium chloride (α-2-Y). ^1H and ^{13}C NMR spectra were measured for a mixture of **1** and 3 mol equiv of CBr_4 and Ph_3P in 1:1 DMF-d_7/$CDCl_3$ solution. The occurrence of α-**2-Y** was also derived from a mixture of **1** and 3 mol equiv of Vilsmeier (Cl^-) reagent in DMF-d_7 involving partial shifts due to the different solvent system as follows; ~7.30 (m, 5H×3, –$CH_2C_6H_5$), 6.67 (d, 1H, *J* 3.5 Hz, H-1), 4.96, 4.87, 4.80, 4.78, 4.67 and 4.61 (d, 2H×3, –$CH_2C_6H_5$), ~4.3 (m, 2H, H-6 *pro R* and *S*), 4.10 (m, 1H, H-5), 3.92 (dd, 1H, *J* 9.0 and 9.0 Hz, H-3), 3.64 (dd, 1H, *J* 9.0 and 10.0 Hz, H-4), 3.86 (dd, 1H, *J* 3.5 and 9.0 Hz, H-2), 2.02 (s, 3H, –OAc). δ_C 170.73 (6-OAc; –*C*OCH$_3$), ~128 (18C, –CH_2-*Ph*), 94.71 (C-1), 81.51 (C-3), 80.20 (C-2), 76.77 (C-4), 75.50, 75.11, 72.36 (3C, –*C*H_2-Ph), 72.70 (C-5), 62.85 (C-6), 20.47 (6-OAc; –CO*C*H$_3$). FABMS (*m*-nitrobenzyl alcohol+NaI): *m*/*z* 625 [(glycosyl iodide)+$Na]^+$, 533 [(**2-Cl**)+$Na]^+$ and 535 [(**2-Cl**)+2+$Na]^+$, 497 [(**2-Cl**)-HCl+$Na]^+$.

3.2.4. 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride (α-2-Cl).[21] When a mixture of **1** and 3 mol equiv of Vilsmeier (Cl^-) reagent in $CDCl_3$ was examined by ^1H NMR spectroscopy, both α- and β-glycosyl chlorides were observed (α:β = 5:2). α-**2-Cl**; δ_H 6.03 (d, 3.5 Hz, H-1), β-**2-Cl**; δ_H 5.23 (d, 8.0 Hz, H-1).

3.3. A general protocol for the one-pot α-glycosylation reaction

For details see Table 2.

3.3.1. General procedures. All reactions were conducted at ambient temperature (15–25 °C) in a glass vessel closed with a septum cap. Neither molecular sieves nor inert gas were used as long as the vessel was dried at 110 °C in an oven prior to the use. The reaction was terminated when the bromide donor was completely consumed as evidenced by TLC analysis. Four different conditions (Sections 3.3.2–3.3.5, below) were applied to glycosylation of **3a** and **3b** as follows.

3.3.2. Ph_3P+CBr_4 (Appel–Lee reagent) in tetramethylurea+CH_2Cl_2.[12] 6-*O*-Acetyl-2,3,4-tri*O*-benzyl-D-glucose[11] (**1**, 0.2 mmol) was dissolved in 1.5 mL of CH_2Cl_2 and treated with Ph_3P (3 mol equiv) and CBr_4 (3 mol equiv). The mixture was stirred for 3 h at room temperature. Then, tetramethylurea (TMU, 150 μL) and acceptor alcohol **3a** or **3b** (3 mol equiv) was added, and the reaction mixture was stirred at room temperature. The mixture was diluted with a mixture of toluene and EtOAc, washed with satd aq $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography on silica gel.

3.3.3. Ph_3P+CBr_4 in DMF.[16] A solution of **1** (0.2 mmol) in DMF (1.5 mL) was treated with Ph_3P (3 mol equiv) and CBr_4 (3 mol equiv) and stirred for 3 h at room temperature. Then acceptor alcohol **3a** or **3b** (3 mol equiv) was added, and the mixture was stirred at room temperature and processed in the same way as described in Section 3.3.2, above.

3.3.4. Vilsmeier reagent (Br^-) in DMF. A solution of **1** (0.2 mmol) in DMF (1.5 mL) was treated with $[(CH_3)_2N^+{=}CH_2Br]Br^-$ (3 mol equiv) and stirred for 3 h at room temperature. The acceptor alcohol **3a** or **3b** (3 mol equiv) was then added, and the mixture was processed in the same manner as described in Section 3.3.2, above.

3.3.5. Poly–(Ph_3P)+CBr_4 in DMF. The DMF solution of **1** (0.2 mmol in 1.5 mL) was treated with diphenylphosphino-polystyrene (3 mol equiv) and CBr_4 (3 mol equiv) and stirred for 3 h at room temperature. Then, the acceptor alcohol (3 mol equiv) was added and processed in the same way as in Section 3.3.2, above.

3.3.6. Spectral data for *tert*-butyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside. IR (KBr film); 3031, 2938, 2867, 1741, 1457, 1369, 1238, 1155, 1072, 1031, 742, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ_H 7.40–7.23 (m, 5H×3, $-CH_2C_6H_5$), 5.09 (d, 1H, *J* 4.0 Hz, H-1), 4.99–4.53 (dd, 2H×3, $-CH_2C_6H_5$), 4.31 and 4.15 (dd, 1H×2, *J* 5.0 and 12.0, *J* 1.5 and 12.0 Hz, H-$6_{S\ and\ R}$), 4.05 (m, 1H, H-5), 4.02 (dd, 1H, *J* 9.0 and 9.0 Hz, H-3), 3.49 (dd, 1H, *J* 4.0 and 9.0 Hz, H-2), 3.46 (dd, 1H, *J* 9.0 and 9.5 Hz, H-4), 2.00 (s, 3H, -Ac), 1.25 (s, 3H×3, *t*-Bu). HRFABMS: Calcd for $C_{33}H_{40}O_7Na$ $[M+Na]^+$, *m*/*z* 571.2672; found, *m*/*z* 571.2661.

3.3.7. A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→1)-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (6a) and 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→1)-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (6b). A solution of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**5**, 1.1 g, 2.00 mmol) in 20 mL of DMF was treated with Ph_3P (3 mol equiv) and CBr_4 (3 mol equiv) and stirred for 3 h at room temperature. Then **1** (3 mol equiv) was added, and the mixture was stirred at room temperature and processed in the same way as described in the general protocol (Section 3.3) to give a mixture of **6a** and **6b**. IR (KBr film): 3347, 3062, 3031, 2924, 1739, 1453, 1364, 1240, 1100, 1025, 737, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): Compound **6b** (major product) δ_H 7.16–7.47 (m, 5H×7, $-CH_2C_6H_5$), 5.17 (d, 1H, *J* 3.0 Hz, H-1′), 4.97–4.30 (d, 2H×7, $-CH_2C_6H_5$), 4.59 (d, 1H, *J* 8.5 Hz, H-1), 4.28 (dd, 1H, *J* 2.0, 12.0 Hz, H-6), 4.25 (m, 1H, H-5′), 4.11–4.05 (m, 1H×2, H-4′ and H-6), 4.04 (dd, 1H, *J* 3.0, 10.0 Hz, H-2′), 4.03 (dd, 1H, *J* 2.5, 10.0 Hz, H-3′), 3.65 (dd, 1H, *J* 9.0 and 9.5 Hz, H-3), 3.58 (dd, 1H, *J* 8.0, 8.5 Hz, H-6′), 3.50 (dd, 1H, *J* 9.5 and 10.0 Hz, H-4), 3.46 (dd, 1H, *J* 8.5 and 9.0 Hz, H-2), 3.46–3.42 (m, 1H×2, H-6′ and H-5), 1.93 (s, 3H, -Ac); Compound **6a** (minor product) δ_H 7.41–7.18 (m, 5H×7, $-CH_2C_6H_5$), 5.22 (d, 1H, *J* 3.5 Hz, H-1), 5.22 (d, 1H, *J* 3.5 Hz, H-1′), 4.97–4.30 (d, 2H×7, $-CH_2C_6H_5$), 4.31 (m, 1H, H-5′), 4.24 (m, 1H, H-5), 4.10 (dd, 1H, *J* 3.5 and 10.0 Hz, H-2′), 4.09 (dd, 1H, *J* 4.0, 12.0 Hz, H-6), 4.05 (dd, 1H, *J* 2.5, 10.0 Hz, H-3′), 4.03 (dd, 1H, *J* 1.0, 2.5 Hz, H-4′), 4.00 (dd, 1H, *J* 9.0 and 9.5 Hz, H-3), 3.98 (dd, 1H, *J* 2.0, 12.0 Hz, H-6), 3.55 (dd, 1H, *J* 3.5, 9.5 Hz, H-2), 3.52 (dd, 1H, *J* 2.0, 9.5 Hz, H-6′), 3.48 (dd, 1H, *J* 3.0, 9.5 Hz, H-6′), 3.47 (dd, 1H, *J* 9.0 and 9.5 Hz, H-4), 2.04 (s, 3H, -Ac). HRFABMS: Calcd for $C_{63}H_{66}O_{12}Na$ $[M+Na]^+$, *m*/*z* 1037.4452; found, *m*/*z* 1037.4443.

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