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Stereoselective glycosylations using benzoylated glucosyl halides with inexpensive promoters

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Abstract—Reactions of O-benzoylated glucopyranosyl halide (I, Br), isolated or generated in situ from per-benzoylated glucose (**8a**) and trimethylsilyl halide, with various alcohols were efficiently promoted by zinc halide (Cl, Br) or *N*-bromosuccinimide with a catalytic ZnI_2 to give the corresponding 1,2-*trans*-β-glucosides in good to high yields. When the anomeric halogenation of **8a** was carried out in the presence of reactive alcohols, 1,2-*cis*-α-glucosides were selectively formed.

Keywords: Glycosylation; Disarmed glycosyl halides; Lewis acids; NBS; Anomer

1. Introduction

Glycosylation of alcohols (O-glycosylation)[1] is an essential process for the synthesis of oligosaccharides and glycoconjugates such as glycolipids. In the last three decades, a variety of glycosyl donors[2] have been developed, including thioglycosides[3] and 1-*O*-trichloroacetimidates.[4] Nevertheless glycosyl halides, especially bromides, are still commonly employed as donors since the pioneering work of Koenigs and Knorr.[5] Glycosyl fluorides have now been widely employed for O-glycosylations[6] due to the high thermal and chemical stability, whereas glycosyl iodides have been considered impractical reagents in glycosylation reactions due to their instability.[7] However, in recent years, the anomeric iodides have attracted some interest[8] and have been extensively studied by Gervay-Hague's group.[9] Highly reactive 'armed' (typically *O*-benzyl protected) glycosyl iodides are generated from the 1-chloride,[8a] 1-acetate,[9] 1-phosphate,[8c] or 1-silyl ether,[10] and are reacted in situ with nucleophiles by S_N2 displacement in the presence or absence of catalyst.

In contrast, acyl-protected, 'disarmed' glycosyl iodides have proved to be rather stable.[11,12] These can be purified by silica gel chromatography and be stored for months.[11h,12b,c] Their reactions with alcohols have usually been performed by using conventional Koenigs–Knorr promoters such as AgOTf and $Hg(CN)_2$.[13] To avoid the use of those heavy metals, iodonium reagents and/or Lewis acids have recently been employed.[14] However, the scope of these glycosylations has not been well studied.

In the course of our synthetic studies of glycolipids, we were involved in 1,2-trans-glycosylation reactions using sugar peracetates by neighboring-group participation.[15] Although the glycosylations promoted by $ZnCl_2$ in toluene have proved to be convenient, the yields are moderate (40–65%) and the glycosyl acceptors are limited to simple alcohols. Our attention was then turned to the reactivity of disarmed glycosyl iodides. In this paper, we describe efficient glycosylation processes from per-benzoylated glucose via the iodide, using inexpensive and safe promoters such as $ZnBr_2$ and *N*-bromosuccinimide (NBS). These promoters have also been found to activate less reactive tetra-*O*-benzoyl-α-D-glucopyranosyl bromide to give the 1,2-trans-glucosides in good-to-high yields. In addition, unexpected 1,2-cis-selective

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glucosylation has been observed when the anomeric halogenation is carried out in the presence of reactive alcohols.

2. Results and discussion

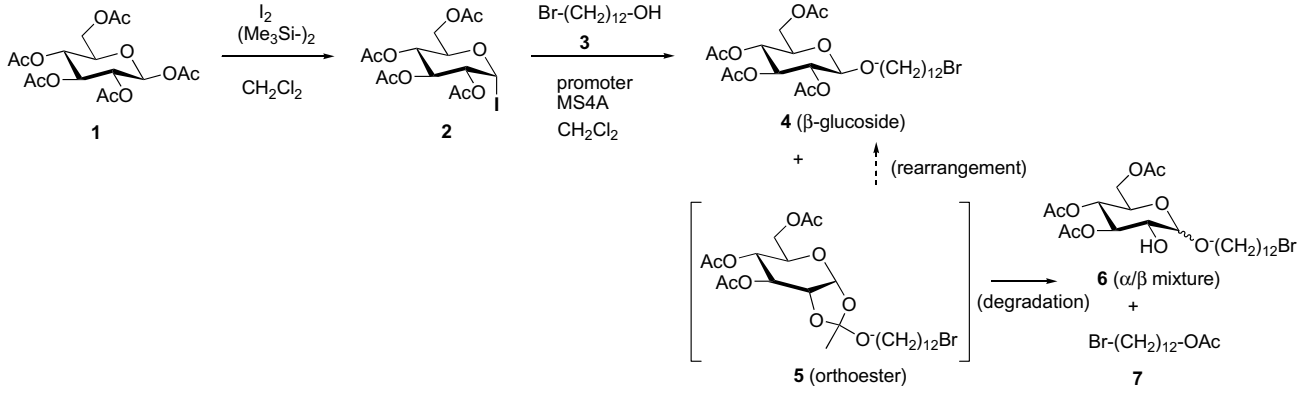
2.1. Glycosylation with acetylated glucosyl iodide

Disarmed glycosyl iodides reported thus far are primarily the acetyl-protected ones.[11] These have been prepared from the corresponding sugar peracetates with iodotrimethylsilane (TMS-I)[9b,11a,c,f] or other HI equivalents.[11b,e,g] Since TMS-I is unstable and expensive, in situ generation from iodine and hexamethyldisilane (HMDS)[16] would be preferable for practical synthesis.[11d,h]

According to the literature,[11h] β-glucose pentaacetate **1** was treated with iodine (0.6 equiv) and HMDS (0.6 equiv) in CH_2Cl_2 at rt to give tetra-*O*-acetyl-α-D-glucopyranosyl iodide (**2**) in essentially pure form by solvent evaporation or simple extractive workup (Scheme 1). With iodide **2** in hand, we examined the reactions with 12-bromo-1-dodecanol (**3**) using activators other than Ag and Hg salts. Iodonium reagents such as *N*-iodosuccinimide (NIS) and I_2 have been employed for the activation of glycosyl halides.[17] However, to our knowledge, bromonium reagents have not been used with such donors. We first employed *N*-bromosuccinimide (NBS) as a promoter because NBS is more stable and much cheaper than NIS. Thus, to a mixture of **2** and **3** (1.2 equiv) in CH_2Cl_2 with 4A MS was added NBS (1.2 equiv) at 5 °C. The mixture soon turned to reddish-brown, and **2** was consumed with the appearance of two major products on TLC. The polar product was the expected β-glucoside **4** (30–40% yield based on **2**) and the less polar product was orthoester **5** (30–40%), indicating that the NBS can activate the glucosyl iodide **2**. Since orthoesters would be rearranged to β-glycosides under Lewis acid conditions,[18] a catalytic amount of a Lewis acid such as trimethylsilyl triflate (TMSOTf) was added to the mixture before or during the reaction (e.g., entries 1 and 2 in Table). However, **4** did not increase (<50% yields), while 2-O-deacetylated glucosides **6** (α/β mixture) and O-acetylated alcohol **7** increased. Next, instead of NBS, several Lewis acids were employed as promoter (e.g., entries 3 and 4). The glycosylation proceeded at rt, but the yields of **4** were generally lower (20–40%). Therefore, the glycosylation with iodide **2** has proved less efficient than the direct glycosylation of **3** with the β-acetate **1** promoted by $ZnCl_2$: **4** was obtained in 58% yield.[15]

2.2. Preparation of benzoylated glucosyl iodide and a one-pot glycosylation process

There have been reported an increasing number of unsuccessful examples of glycosylations[17d,19] with an acetate group at C-2 owing to the formation of 1,2-orthoacetates, which would be decomposed to major byproducts, 2-O-deacetylated glycosides (α/β mixture) and O-acetylated alcohols as shown in Scheme 1. Such byproducts can be reduced by using either a benzoyl[19a,b] or a pivaloyl[19c] group at C-2. Therefore we set out to prepare *O*-benzoyl-protected glycosyl iodides.



Entry	Promoter (equiv)	Conditions	Yield (% based on **2**)		
			4	**6**	**7**
1	NBS (1.2), TMSOTf (0.4), TMU (0.2)	5 °C to rt, 4 h	38	20	42
2	NBS (1.2), $Cu(OTf)_2$ (0.12)	5 °C to rt, 28 h	47	19	31
3	$ZnCl_2$ (1.4)	rt, 12 h	24	16	46
4	CuOTf (1.2)	5 °C, 2 h	28	22	32

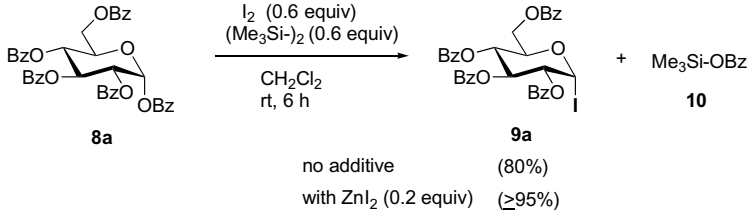
Scheme 1. Glycosylation with acetylated glucosyl iodide.

Stachulski's group[12c] and Field's group[14b] reported that perpivaloylated methyl β-glucuronate and perbenzoylated glucose are converted to the α-anomeric iodides by treatment with I_2 (0.6 equiv) and HMDS (0.6 equiv) in CH_2Cl_2 at room temperature for 5–6 h, respectively. In our hands, however, the iodination of α-D-glucopyranose pentabenzoate **8a**[20] under identical reaction conditions was incomplete at rt for 12 h (ca. 80% conversion). As shown in Scheme 2, we found that the addition of ZnI_2 (0.1–0.3 equiv) as a cheap Lewis acid iodide source accelerated the reaction to afford iodide **9a**[21] in nearly quantitative yield. Molecular sieves were not included in the reaction mixture since these retarded the rates of the reaction considerably. Trimethylsilyl benzoate **10**, a byproduct necessarily generated from **8a** and TMSI, can be removed by extractive workup with aq $NaHCO_3$–$Na_2S_2O_3$, and iodide **9a** is isolated in a sufficiently pure form. Addition of $ZnBr_2$ instead of ZnI_2 gave a mixture of **9a** and the α-glucosyl bromide **9b**.

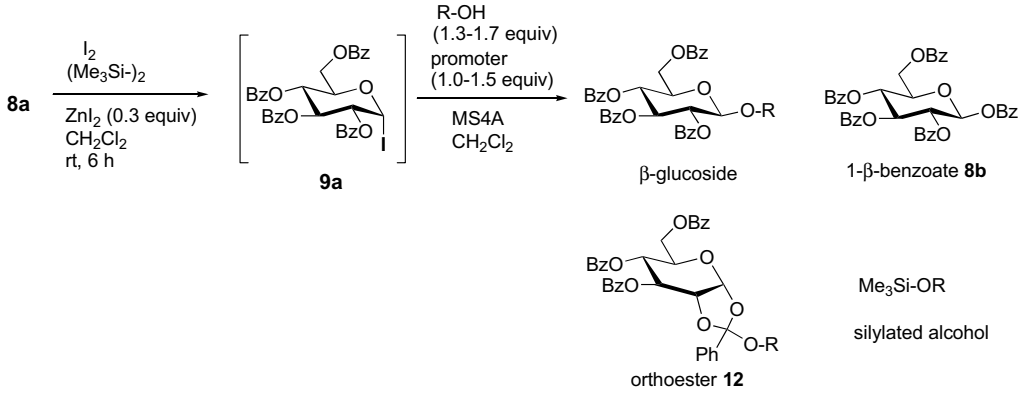
We initially examined a one-pot glycosylation process from **8a** without the isolation of iodide **9a** since **9a** is essentially pure and ZnI_2 in the reaction mixture might serve as an acid catalyst, which is often necessary for the *N*-halosuccinimide-promoted glycosylations.[22] Thus, to this reaction mixture at 5 °C were added 12-bromododecanol (**3**, 1.5 equiv) and NBS (1.2 equiv) with 4A molecular sieves (Scheme 3) Color of the reaction mixture turned reddish-purple and **9a** soon decreased. To our delight, β-glucopyranoside **11** (in Fig. 1) was obtained in 62% yield. Although **8a** disappeared at the iodination stage, β-glucose pentabenzoate **8b** was obtained in 18% yield. Byproduct **8b** would be formed by the reaction of **9a** with trimethylsilyl benzoate (**10**). Other byproducts were orthoester **12** (7%) and trimethysilylated alcohol. Neither 2-O-debenzoylated glucoside nor O-benzoylated alcohol was obtained.

This NBS-promoted one-pot glucosylation was applied to other alcohols (in Fig. 1), and the results are summarized in Table 1. Addition of 2-phenylethanol (**13**), cyclohexanol (**15**), and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (Ip-Gal-OH, **17**) afforded the corresponding β-glucosides in good yields (entries 2–4). In contrast, *N*-Cbz-serine methyl ester (*Z*-Ser-OMe, **19**) gave glucoside **20** in very low yield (10%) under identical conditions, along with several byproducts: orthoester **12S** (40%), β-benzoate **8b** (30%), iodide **9a** (15%), and trimethysilylated alcohol (36%) (entry 5). Formation of larger amounts of **8b** and orthoester **12S** would result from the lower reactivity of **19** compared to the other alcohols. Polt and co-workers reported that N-acylated β-amino-alcohols such as *N*-Cbz-serine derivatives have decreased nucleophilicity due to an unfavorable hydrogen-bonding pattern.[23]

Under Lewis acid conditions, a 1,2-orthoester can be rearranged to the β-glycoside, and a trimethylsilylated alcohol can be glycosylated.[24] Thus we examined the effect of Lewis acids in place of NBS. To the reaction



Scheme 2. Preparation of benzoylated glucosyl iodide.



Scheme 3. One-pot glucosylation via the anomeric iodide **9a**.

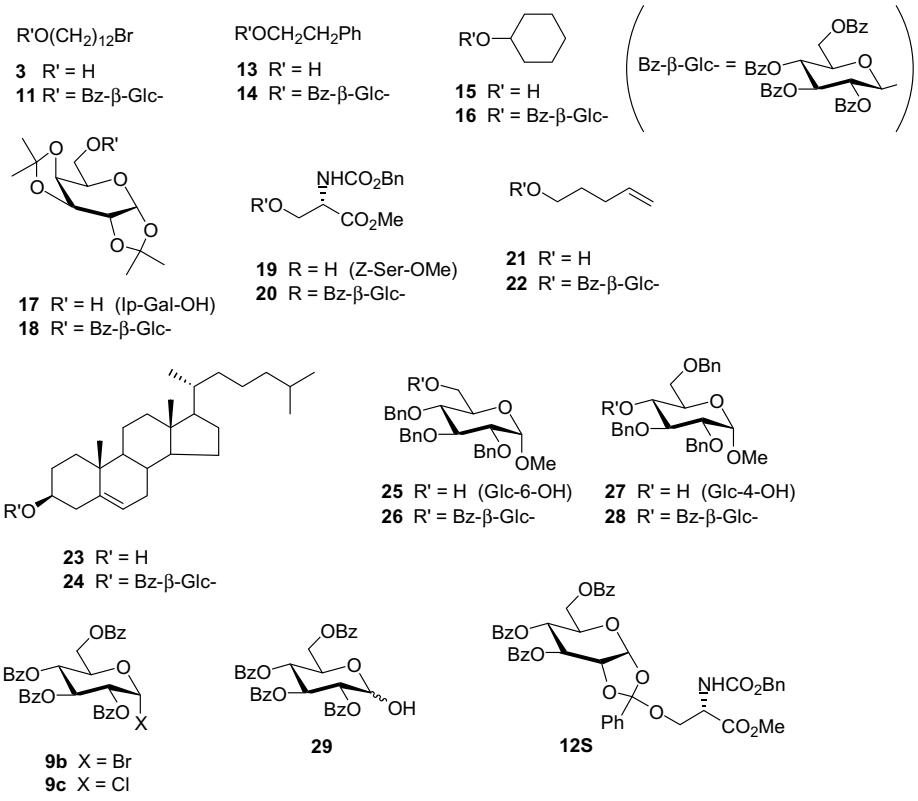


Figure 1. Acceptor alcohols and products in Tables 1 and 2.

Table 1. One-pot glycosylation of alcohols with benzoylated glucosyl iodide **9a** prepared in situ from the pentabenzoate **8a**

Entry	(For glycosylation)		Conditions[b]	Yield[c] (%)			
	R–OH[a]	Promoter (equiv)		β-Glucoside		**8b**	**12**
1	$Br(CH_2)_{12}$–OH (**3**)	NBS (1.2)	5–10 °C, 6 h	**11**	62	18	7
2	$Ph(CH_2)_2$–OH (**13**)	NBS (1.1)	5–10 °C, 6 h	**14**	67	22	0
3	Cyclohexanol (**15**)	NBS (1.5)	5 °C, 3 h	**16**	86	0	0
4	Ip-Gal-OH (**17**)	NBS (1.2)	5–10 °C, 6 h	**18**	67	7	20
5	*Z*-Ser-OMe (**19**)	NBS (1.5)	5 °C, 4 h	**20**	10[d]	30	40
6	**3**	ZnI_2 (1.0)	40 °C, 5 h	**11**	82[e]	7	
7	**3**	$ZnCl_2$ (1.6)	rt, 5 h	**11**	79	16	
8	4-Penten-1-ol (**21**)	$ZnCl_2$ (1.1)	rt, 20 h	**22**	84	14	
9	**15**	$ZnCl_2$ (1.2)	rt, 6 h	**16**	84	6	
10	**17**	$ZnBr_2$ (1.4)	rt, 30 h	**18**	70	15	
11[f]	**3**	$ZnBr_2$ (1.0)	rt, 4 h	**11**	78	11	
12[f]	**3**	NBS (1.5)	rt, 4 h	No reaction			

[a] Alcohol used was 1.3–1.7 equiv to **8a**.
[b] Reaction was carried out in CH_2Cl_2 until **9a** was consumed. However, in several entries, a small amount (3–6%) of the donor remained as a mixture of **9a** and **9b** or **9a** and **9c**.
[c] Isolated yield after chromatography, based on **8a**.
[d] **9a** was recovered (15%).
[e] α-Anomer was obtained in 4% yield.
[f] TMSBr was employed instead of I_2–HMDS.

mixture of the glucosyl iodide containing ZnI_2 (0.3 equiv) in CH_2Cl_2 were added 12-bromododecanol (**3**, 1.5 equiv) and ZnI_2 (1.0 equiv) with 4A molecular sieves. The reaction was slow at rt, but proceeded at 40 °C to give glucoside **11** in 82% yield (entry 6). A small amount of the α-glucoside **11α** was obtained (4%). Addition of $ZnCl_2$ instead of ZnI_2 was found to promote the reaction at rt, giving **11** in 79% yield along with **8b** (entry 7). Under Lewis acid conditions, the orthoester was not obtained. This $ZnCl_2$-promoted one-pot glycosylation

was applied to other alcohols: 4-pentenol **21**, which cannot be used with NBS, and cyclohexanol **15** afforded the corresponding β-glucopyranosides in high yields with no α-anomer (entries 8 and 9). Thus $ZnCl_2$ would be a more effective promoter than ZnI_2. However, when the reaction proceeded slowly with $ZnCl_2$, anomeric halogen exchange occurred to give less reactive glucosyl chloride **9c**.

The halogen exchange from I (**9a**) to Br (**9b**) occurred in the NBS-activation as well as the $ZnBr_2$-activation (entry 10), and a small amount (3–6%) of the mixture (**9a** and **9b**) was recovered in several entries. These results led us to examine the reaction of glucopyranosyl bromide **9b** with 12-bromododecanol **3** in the presence of NBS or $ZnBr_2$. Treatment of **8a** with TMSBr (1.6 equiv) and $ZnBr_2$ (0.3 equiv) gave bromide **9b** in nearly quantitative yield,[11a,c,25] though the bromination of **8a** required a longer reaction time (at rt for 18 h) than the iodination (rt, 5 h). To this mixture were added **3** (1.3 equiv) and promoter (1.0 equiv) with molecular sieves 4 A. Addition of $ZnBr_2$ afforded the glucoside **11** in 78% yield (entry 11), whereas the addition of NBS did not promote the reaction (entry 12). These results suggest that the NBS-activation of glycosyl bromides would require 'I' source to form more active species such as NIS or I–Br.[17b,d]

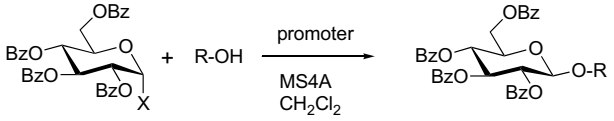
2.3. Comparison of reactivities

Due to the presence of non-volatile trimethylsilyl benzoate **10**, this convenient one-pot glycosylation should give significant amounts of β-benzoate **8b** as shown in Table 1. Gervay-Hague reported that magnesium oxide effectively deactivates TMSOAc to suppress the formation of a protected glucose β-acetate.[26] In our case, however, MgO (1 equiv) suppressed the glycosylation. Addition of $CaCO_3$ in the place of MgO showed little effect for the deactivation of TMSOBz.

As mentioned above, essentially pure glucosyl iodide **9a** was obtained simply by treatment with aqueous $NaHCO_3$–$Na_2S_2O_3$ to remove TMS-OBz **10** and excess TMS-I. Thus we employed the isolated iodide **9a**, and compared the donor reactivity to tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **9b**. Bromide **9b** is more stable than iodide **9a**, and it is easily available from **8a** with HBr–AcOH[20a] or from a commercial source.

We examined the glucosylation using either NBS with a catalytic amount of acid or Lewis acid alone (ZnX_2) as

Table 2. Glycosylation of various alcohols with glucosyl bromide **9b** or iodide **9a**



9a X = I
9b X = Br

β-glucoside

Entry	R–OH[a]	Promoter (equiv)	Conditions		Yield (%) of β-glucoside	
					From **9b**[b] (X = Br)	From **9a**[c] (X = I)
1	**3**	NBS (1.3) + ZnI_2 (0.2)	5 °C to rt, 24 h	**11**	85	83
2	**13**	NBS (1.5) + ZnI_2 (0.3)	5 °C to rt, 14 h	**14**	90	90
3	**13**	NBS (1.5) + $Zn(OTf)_2$ (0.3)	5 °C to rt, 20 h	**14**	7[d]	83
4	**13**	NBS (1.5) + TMSOTf (0.3)	5 °C to rt, 3 h	**14**	0[d]	64[e]
5	**17**	NBS (1.5) + ZnI_2 (0.3)	5 °C to rt, 5 h	**18**	90	87
6	**19**	NBS (1.5) + ZnI_2 (0.6)	5 °C to rt, 5 h	**20**	31[f]	na[h]
7	**19**	NBS (1.5) + ZnI_2 (0.3) + TMSOTf (0.5)	5 °C, 3 h to rt, 6 h	**20**	na[h]	48[g]
8	Glc-6-OH **25**	NBS (1.1) + TMSOTf (0.5)	5 °C, 3 h	**26**	na[h]	56[e]
9	**3**	$ZnCl_2$ (1.5)	rt, 4 h	**11**	85	91
10	**17**	$ZnCl_2$ (2.0)	rt, 48 h	**18**	84[i]	75[i]
11	**19**	$ZnBr_2$ (2.5)	40 °C, 8 h	**20**	60[j]	55[j]
12	**21**	$ZnBr_2$ (1.5)	rt, 3 h	**22**	90	85
13	Cholesterol **23**	$ZnBr_2$ (1.8)	40 °C, 6 h	**24**	93	90
14	**25**	$ZnBr_2$ (2.0)	rt, 10 h	**26**	75	74
15	Glc-4-OH **27**	$ZnBr_2$ (2.0)	rt, 24 h	**28**	53[j]	48[j]

[a] Alcohol used was 1.3–1.7 equiv to **9**, except for **19** and **27** (2 equiv).
[b] Isolated yield based on **9b**.
[c] Overall yield from benzoate **8a**, not based on **9a**.
[d] Donor **9b** was recovered (ca. 90%).
[e] A mixture of **9a**/**9b** was recovered (ca. 20%).
[f,g] A mixture of mono-hydroxy-glucoses was obtained (f: 66%, g: 50%).
[h] Not attempted.
[i] A small amount (<10%) of glucosyl chloride **9c** was obtained.
[j] 1-Hydroxy-glucose **29** was obtained (25–40%).

promoter. The results are summarized in Table 2. As expected, the yields of β-glucosides from the isolated iodide **9a** were higher than those by the one-pot process. We were pleased to find that bromide **9b** also reacted with a variety of alcohols by both promoter systems to give the β-glucosides with high stereoselectivity in comparable good yields except entries 3 and 4, in which little or no glucoside **14** was obtained from **9b** by the NBS-activation. These entries and entry 12 in Table 1 have revealed that a catalytic 'I' source such as ZnI_2 is necessary for the activation of glycosyl bromides with NBS.

In the NBS–ZnI_2 activation (entries 1, 2, 5–7), iodide **9a** was consumed faster (at 5 °C for 1 h) than bromide **9b** (at rt for several hours) to afford the β-glucoside and the orthoester, which was generally less polar than the former on TLC, in a variable ratio. The orthoester gradually decreased with the increase of β-glucoside by further stirring at rt for 5–24 h in most cases. In the case of *Z*-Ser-OMe **19** (entry 7), orthoester **12S** (ca. 80%) and β-glucoside **20** (ca. 10%) were formed at 5 °C within 1 h. To smoothly promote the rearrangement, TMSOTf (0.5 equiv) was added to the mixture, and the mixture was stirred at rt until **12S** disappeared. However, the yield of **20** was modest, and a mixture of 1-hydroxy- (**29**) and 2-hydroxy-benzoylated glucoses was obtained in 50% yield.

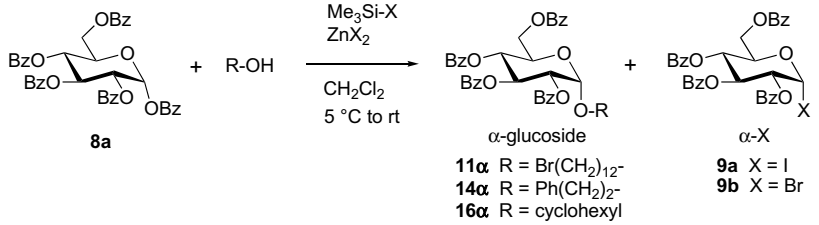
Since the orthoesters have not been obtained with ZnX_2 alone, the ZnX_2 activation seems more general and operationally simpler than the NBS activation. In the ZnX_2 activation, the reaction rates of **9b** with alcohols were similar to those of **9a**. Noteworthy is that yield from bromide **9b** was slightly higher than that from iodide **9a** in many entries. This result might be explained by two reasons: one is that the latter is not based on **9a**, but an overall yield from benzoate **8a**; the other reason is the hydrolytic instability of **9a**. Although $ZnCl_2$ and $ZnBr_2$ showed similar activities, $ZnBr_2$ would be preferred toward less reactive alcohols since $ZnCl_2$ would cause the halogen exchange of the donor to form less reactive glucosyl chloride **9c** (e.g., entry 10). By using $ZnBr_2$, cholesterol **23** reacted with donor **9a** or **9b** at 40 °C to afford the β-glucoside **24** in high yield (entry 13). For less reactive alcohols such as *Z*-Ser-OMe (**19**) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (Glc-4-OH, **27**) the yields of β-glucosides were still modest, and substantial amounts of 1-hydroxy-glucose **29** were obtained (entries 11 and 15).

Several Lewis acids,[27] including zinc halides,[12c,14a,28] have been reported to promote the reaction of disarmed glycosyl halides (mainly O-acetylated bromides, except glucosamine-type donors) with alcohols. However, these have not been widely employed for the O-glycoside synthesis, and the scope has not been sufficiently explored. For example, Stachulski and co-workers recently reported the glycosylation of various alcohols with pivaloylated glucuronate iodide using $FeCl_3$ with I_2 as promoters. They also reported the glucuronidation using Lewis acid alone [$ZnCl_2$, $CeCl_3$, or $Sc(OTf)_3$], but the substrate used was only 2-phenylethanol.[14a] The results described herein indicate that zinc halides and NBS would be promising substitutes for the Koenigs–Knorr promoters such as AgOTf. The present methods appear to be more dependent on the nucleophilicity of alcohols than the conventional Ag^+-promoted dehalogenative glycosylations, and thus the yields with reactive alcohols are comparable. Indeed, the yields of the β-glucosides **18** (84%), **22** (90%), and **24** (93%) by the ZnX_2-activation shown in Table 2 are higher than those reported for the AgOTf-promoted glucosylations (**18**: 75%,[19a] **22**: 68%,[29] **24**: 60%[19c]).

2.4. 1,2-cis-Selective glucosylation

We next attempted a tandem bromination and glucosylation process: the reaction of α-benzoate **8a** with TMSBr–$ZnBr_2$ in the presence of the alcohol **3**. The reaction proceeded smoothly at rt, and **8a** disappeared within 2 h. Two major products obtained were α-glucopyranosyl bromide **9b** (49%) and bromododecyl α-glucopyranoside **11α** (45%), and only a small amount of β-glucoside **11** (2%) was obtained. To examine this unexpected 1,2-cis-α-selectivity despite the presence of participating benzoyl group at C-2, other alcohols as well as the iodination reagents, TMSI–ZnI_2, were employed. The results are summarized in Table 3. The standard reaction was carried out with TMSBr (1.6 equiv) and $ZnBr_2$ (1.2 equiv) until **8a** was consumed. Under such conditions (entries 1, 5, 7, 9 and 10), reactive primary alcohols (**3**, **13**) afforded corresponding α-glucosides (**11α**, **14α**) and the α-bromide **9b** with a small amount of the β-glucosides. Cyclohexanol **15** gave glucoside **16α** in lower yield than the primary alcohols with a larger amount of **9b** (entry 7). In contrast, cholesterol **23** and *Z*-Ser-OMe (**19**) gave a little and no α-glucoside, respectively. Hence, the yield of α-glucosides appears to be dependent on the reactivity of the parent alcohols. In the presence of **23**, bromide **9b** was obtained in 83% yield (entry 9), whereas the yield of **9b** was only 20% in the presence of **19**, and 76% of **8a** was recovered (entry 10). These results suggest that acceptor **19** would deactivate the promoter $ZnBr_2$ due to its Lewis base nature, which can also be responsible for the low reactivity of **19** as shown in Tables 1 and 2. Longer reaction times at rt to promote further glucosylation and/or anomerization did not show a clear tendency. In all such cases (entries 2–4, 6 and 8) the α-halides **9a**/**9b** apparently decreased, and the α-glucosides increased in entries 3 (**3** with a catalytic amount of $ZnBr_2$) and 8 (**15** with TMSI–ZnI_2). However, the other entries did not have a positive effect, and significant amounts of the hydrolyzed product **29** were formed instead. TLC monitoring of the reactions indicated that

Table 3. cis-Selective glucosylation of reactive alcohols



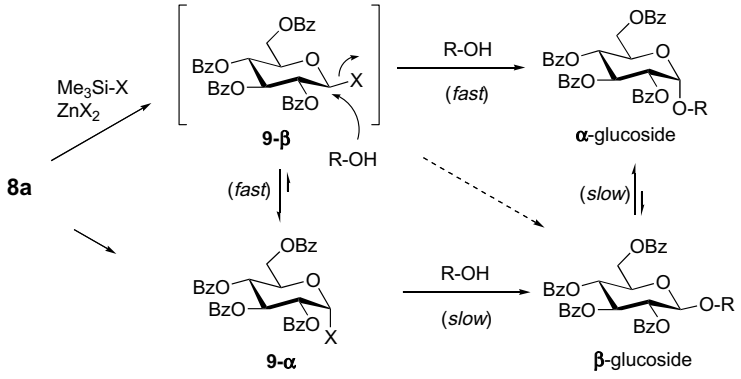
Entry	R–OH[a]	X[b,c]	Conditions	Yield[d] (%)		
				α-Glc	β-Glc	α-X
1	$Br(CH_2)_{12}$–OH (**3**)	Br	5 °C to rt, 2 h	45	2	49
2	**3**	Br	5 °C to rt, 24 h	48	3	32
3	**3**	Br[c]	5 °C to rt, 24 h	63	4	27
4	**3**	I	5 °C to rt, 48 h	47	5	25
5	$Ph(CH_2)_2$–OH (**13**)	Br	5 °C to rt, 2 h	68	2	16
6	**13**	I	5 °C to rt, 40 h	73	5	9
7	Cyclohexanol (**15**)	Br	5 °C to rt, 3 h	32	0	54
8	**15**	I	5 °C to rt, 70 h	58	0	20
9	Cholesterol (**23**)	Br	5 °C, 3 h	(2)[e]	0	83[f]
10	*Z*-Ser-OMe (**19**)	Br	5 °C to rt, 18 h	0	0	20[g]

[a] Alcohol used was 1.3–1.7 equiv to **8a**, except for **15** (2 equiv).
[b] TMS-X used was 1.5–2.0 equiv to **8a**, and TMSI was prepared from I_2 and HMDS.
[c] ZnX_2 was 1.1–1.5 equiv to **8a**, except entry 3 (0.3 equiv).
[d] Isolated yield after chromatography.
[e] The structure has not been confirmed.
[f] Cholesterol **23** was not recovered in this reaction since **23** reacted with the brominating agents to give a much less polar product.
[g] **8a** was recovered (76%).

the α-bromide **9b** was formed faster than the α-glucosides at lower temperatures (0–10 °C).

1,2-cis-Glycosylations in the presence of a participating group at C-2 have occasionally been observed with acetylated sugars.[27c,30] For example, Gutman and co-workers reported that, in the reaction of acetylated glucuronate bromide with 3-*O*-acetyl-morphine, cis-α-glycoside was selectively formed (α:β = 8:1) by using two and more equivalents of $ZnBr_2$ as promoter, whereas the β-glycoside was preferentially formed (α:β = 1:7) with 0.8 equiv of $ZnBr_2$.[28b] Field and co-workers reported that the iodine-promoted reaction of acetylated glucosyl iodide **2** with methanol gave the α-glucoside selectively (α:β = 7.5:1), whereas the benzoylated counterpart **9a** gave only the β-glucoside.[14b] These precedents suggest that particular reactants and/or conditions would be necessary for the 1,2-cis-selectivity. To our knowledge, cis-selective glycosylations with benzoylated sugars have rarely been reported.[31]

Preferential formation of the α-glucoside might be explained as shown in Scheme 4. Halogenation of **8a** would give β-halide **9**-β as a kinetically favored anomer, which quickly equilibrates to the more stable α-halide **9**-α under the acidic and halide-rich conditions.[9b] In the presence of a reactive alcohol, the β-halide **9**-β, being much more reactive than the α form **9**-α, would react



Scheme 4. Plausible reaction pathway.

with the alcohol in an S_N2 fashion to give α-glucoside. S_N1-type reaction of **9**-β by the assistance of a C-2 benzoyloxy group or the reaction of **9**-α with the alcohol described in the above sections, both leading to β-glucoside, seems to be much slower. Anomerization of the β-glucoside to the α anomer would also be slow.

3. Conclusions

We have developed comparatively mild, inexpensive, less-toxic, and efficient ways to prepare 1,2-*trans*-*O*-glucopyranosides from glucose pentabenzoate via the anomeric halides. Not only the glucosyl iodide but also the bromide can be activated by zinc halide or NBS with catalytic ZnI_2 to react with a variety of alcohols, indicating that these promoters would be promising substitutes for silver and mercury salts employed in the Koenigs–Knorr glycosylation.

4. Experimental

4.1. General methods

Melting points were determined with a Yanaco melting point apparatus MP-500D. Optical rotations were measured with a JASCO DIP-1000 polarimeter at 24 ± 2 °C, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-270 (270 MHz for ^{1}H and 67.8 MHz for ^{13}C) or a Varian INOVA 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in $CDCl_3$. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as the internal standard ($\delta = 0.0$) for ^{1}H NMR, and the central line of $CDCl_3$ ($\delta = 77.0$) for ^{13}C NMR spectra. Coupling constants (J) are given in Hertz. Elemental analyses were performed in the analytical section in this Institute (AIST). High-resolution mass (HRMS) and fast-atom-bombardment mass spectra (FABMS) were obtained on a Hitachi M80B and a JEOL MS600H mass spectrometer, respectively. Routine monitoring of reactions was carried out using E. Merck Silica Gel 60F_{254} TLC plates, and compounds were detected by UV absorbance (254 nm) and/or dipping the plates in 10% aq H_2SO_4 followed by heating. Column chromatography was performed with indicated solvents on silica gel (Kanto Chemicals, neutral, 100–210 μm, or Wakogel C-300, 45–75 μm).

4.2. 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide (9a)

To a mixture of α-D-glucopyranose pentabenzoate **8a** (284 mg, 0.40 mmol) and ZnI_2 (32 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added a solution of hexamethyldisilane (38 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL) followed by iodine (65 mg, 0.25 mmol). The deep-purple mixture was stirred at rt until **8a** was consumed and the color of the solution became pale pink. The resulting mixture was diluted with CH_2Cl_2 (20 mL) and an aq solution (20 mL) containing $NaHCO_3$ (120 mg) and $Na_2S_2O_3$ (80 mg), and was stirred for 10 min. The mixture was transferred into a separatory funnel, and the layers were separated. The organic layer was washed with aq NaCl (10 mL). The combined aq phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4.

Removal of the solvent gave the crude glucosyl iodide **9a** (285 mg, quantitative) as a colorless foam, which was used in the glycosylation step without further purification. Compound **9a**: $[\alpha]_D^{24}$ +140 (*c* 2.4, $CHCl_3$), lit.[14b] +138 (*c* 1, $CHCl_3$), lit.[20a] +139.5 ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.52 (m, 2H, H-5, 6a), 4.67 (m, 1H, H-6b), 4.74 (dd, 1H, $J_{1,2}$ 4.4, $J_{2,3}$ 9.8 Hz, H-2), 5.86 (t, 1H, $J_{3,4} = J_{4,5}$ 9.8 Hz, H-4), 6.19 (t, 1H, $J_{2,3} = J_{3,4}$ 9.8 Hz, H-3), 7.25 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 7.27–7.61 (m, 12H), 7.87 (m, 2H) 7.96 (m, 2H), 8.01 (m, 2H), 8.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 61.8 (C-6), 67.6, 71.0, 72.2, 73.0, 75.4 (C-1), 128.31, 128.33, 128.43, 128.46, 128.54, 128.73, 129.4, 129.7, 129.8, 129.9, 130.1, 133.2, 133.3, 133.6, 133.8, 165.0, 165.1, 165.5, 166.0. The ^{1}H and ^{13}C NMR data are in accord with those reported.[12b,14b]

4.2.1. General one-pot glycosylation procedure (A) via iodide 9a. To a mixture of α-D-glucose pentabenzoate **8a** (142 mg, 0.20 mmol) and ZnI_2 (16 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added a solution of hexamethyldisilane (18 mg, 0.12 mmol) in CH_2Cl_2 (0.2 mL) followed by iodine (31 mg, 0.12 mmol). The deep-purple mixture was stirred at rt until most of **8a** was consumed and the color of the solution became pale pink. To this mixture containing **9a** were added powdered 4A molecular sieves (200 mg), alcohol (ca. 0.3 mmol) in CH_2Cl_2 (1 mL), and promoter (0.2–0.6 mmol) in that order (when NBS was used as a promoter, the mixture was cooled in an ice-water bath before the addition). The resulting suspension was stirred until **9a** (or the orthoester if formed) was almost consumed (monitored by TLC). The reaction mixture was quenched by dilution with EtOAc (10 mL) and an aq solution (10 mL) containing $NaHCO_3$ (80 mg) and $Na_2S_2O_3$ (120 mg), and the mixture was stirred for 10 min, filtered through Celite, and washed thoroughly with EtOAc (10 mL). The combined filtrate and washings were transferred into a separatory funnel, and the layers were separated. The organic layer was washed with aq NaCl (10 mL). The combined aq layers were extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4. Removal of the solvent gave a

residue, which was purified by chromatography using an appropriate solvent system as indicated. When the separation was incomplete, the product ratio in fractions of the mixture was determined by ^{1}H NMR.

4.2.2. General glycosylation procedure (B) using ZnX_2 as promoter. Zinc halide and powdered molecular sieves 4A were dried in vacuo at 110 °C for 1 h prior to use. To a mixture of sugar **9a** or **9b** (0.20 mmol), alcohol (0.3–0.4 mmol), ZnX_2 (0.3–0.6 mmol), and 4A molecular sieves (200 mg) was added CH_2Cl_2 (3 mL), and the suspension was stirred until **9a**/**9b** was almost consumed. The reaction mixture was worked up as described in procedure (A).

4.2.3. General glycosylation procedure (C) using NBS as promoter. To a mixture of sugar **9a** or **9b** (0.20 mmol), alcohol (0.3–0.4 mmol), ZnI_2 (0.04–0.06 mmol), and 4A molecular sieves (200 mg) was added CH_2Cl_2 (3 mL), and the mixture was cooled to 5 °C. NBS (0.22–0.30 mmol) was added in two portions, and the suspension was stirred at 5 °C to rt until most of **9a**/**9b** (or the orthoester if formed) was consumed. The reaction mixture was worked up as described in procedure (A).

4.3. 12-Bromododecyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (11)

Chromatographic purification on silica gel with 7:1:1 hexane–EtOAc–CH_2Cl_2 as eluent gave **11** as a colorless oil: $[\alpha]_D$ +14.8 (*c* 1.3, $CHCl_3$); R_f 0.32 (4:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 1.00–1.30 (m, 14H), 1.41 (m, 2H), 1.52 (m, 2H), 1.84 (quint, 2H, *J* 7.1 Hz), 3.40 (t, 2H, *J* 6.8 Hz, –C*H*$_2$Br), 3.54 (dt, 1H, *J* 9.6, 6.7 Hz), 3.92 (dt, 1H, *J* 9.6, 6.1 Hz), 4.17 (ddd, 1H, *J* 3.3, 5.0, 9.8 Hz, H-5), 4.51 (dd, 1H, *J* 5.1, 12.1 Hz, H-6a), 4.65 (dd, 1H, *J* 3.3, 12.1 Hz, H-6b), 4.85 (d, 1H, *J* 7.8 Hz, H-1), 5.54 (dd, 1H, *J* 7.8, 9.5 Hz, H-2), 5.69 (t, 1H, *J* 9.6 Hz, H-4), 5.92 (t, 1H, *J* 9.6 Hz, H-3), 7.30 (m, 2H), 7.35 (m, 2H), 7.40 (m, 4H), 7.52 (m, 4H), 7.84 (m, 2H), 7.90 (m, 2H), 7.96 (m, 2H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 25.7, 28.1, 28.7, 29.2, 29.36, 29.41, 29.43, 32.8, 34.1, 63.2, 69.8, 70.4, 71.9, 72.1, 72.9, 101.3 (C-1), 128.26, 128.32, 128.37, 128.8, 129.3, 129.6, 129.7, 129.8, 133.0, 133.1, 133.2, 133.4, 165.0, 165.2, 165.8, 166.1; FABMS (matrix NBA) *m*/*z* (%) 867 ([M(^{81}Br)+Na]$^+$, 25), 865 ([M(^{79}Br)+Na]$^+$, 21), 579 (100).

4.4. 2-Phenylethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (14)

Chromatographic purification with 30:1 CH_2Cl_2–EtOAc gave **14** as a colorless solid: mp 136–138 °C; $[\alpha]_D$ +27.4 (*c* 1.3, $CHCl_3$); R_f 0.33 (3:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.86 (m, 2H), 3.74 (dt, 1H, *J* = 9.8, 6.3 Hz), 4.14 (m, 2H), 4.50 (dd, 1H, *J* 5.2, 12.1 Hz, H-6a), 4.64 (dd, 1H, *J* 3.3, 12.1 Hz, H-6b), 4.83 (d, 1H, *J* 7.8 Hz, H-1), 5.55 (dd, 1H, *J* 8.1, 9.8 Hz, H-2), 5.67 (t, 1H, *J* 9.8 Hz, H-4), 5.88 (t, 1H, *J* 9.5 Hz, H-3), 7.04 (m, 5H), 7.28 (m, 2H), 7.38 (m, 6H), 7.52 (m, 4H), 7.83 (m, 2H), 7.91 (m, 4H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 35.9, 63.1, 69.8, 70.8, 71.8, 72.2, 72.9, 101.1, 126.1, 128.17, 128.27, 128.30, 128.36, 128.38, 128.75, 128.77, 129.3, 129.6, 129.71, 129.73, 129.81, 129.82, 133.11, 133.15, 133.21, 133.4, 138.2, 165.0, 165.2, 165.8, 166.1. Anal. Calcd for $C_{42}H_{36}O_{10}$: C, 71.99; H, 5.18. Found: C, 72.13; H, 5.12.

4.5. Cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (16)

Chromatographic purification with CH_2Cl_2 as eluent gave **16** as a colorless solid: mp 155–158 °C, lit.[32] mp 97.5–100 °C; $[\alpha]_D$ +12.3 (*c* 2.0, $CHCl_3$); R_f 0.29 (4:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 1.05–1.32 (m, 4H), 1.43 (m, 2H), 1.52–1.76 (m, 3H), 1.88 (m, 1H), 3.66 (tt, 1H, *J* 3.9, 9.1 Hz), 4.15 (ddd, 1H, $J_{5,6b}$ 3.4, $J_{5,6a}$ 5.6, $J_{4,5}$ 9.8 Hz, H-5), 4.51 (dd, 1H, $J_{5,6a}$ 5.6, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.62 (dd, 1H, $J_{5,6b}$ 3.4, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.94 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1), 5.51 (dd, 1H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.8 Hz, H-2), 5.64 (t, 1H, *J* 9.6 Hz, H-4), 5.90 (t, 1H, *J* 9.6 Hz, H-3), 7.25–7.45 (m, 8H), 7.51 (m, 4H), 7.84 (m, 2H), 7.91 (m, 2H), 7.96 (m, 2H), 8.01 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 23.5, 23.7, 25.3, 31.6, 33.2, 63.4, 70.0, 71.98, 72.03, 73.0, 78.5, 99.8, 128.24, 128.29, 128.36, 128.77, 128.80, 129.4, 129.58, 129.64, 129.66, 129.72, 129.78, 133.1, 133.2, 133.4, 165.0, 165.2, 165.8, 166.1. Anal. Calcd for $C_{40}H_{38}O_{10}$: C, 70.78; H, 5.64. Found: C, 70.84; H, 5.48.

4.6. 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (18)

Chromatographic purification with 30:1 CH_2Cl_2–EtOAc gave **18** as a colorless foam: $[\alpha]_D$ −15.3 (*c* 1.45, $CHCl_3$), lit.[19a] −18 ($CHCl_3$), lit.[22e] −15.7 (*c* 1.0, $CHCl_3$); R_f 0.38 (2:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 3H), 1.20 (s, 3H), 1.24 (s, 3H), 1.37 (s, 3H), 3.86 (dd, 1H, $J_{5,6a}$ 6.8, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.90 (m, 1H, H-5), 4.02 (dd, 1H, $J_{5,6b}$ 3.5, $J_{6a,6b}$ 10.5 Hz, H-6b), 4.10 (dd, 1H, $J_{4,5}$ 1.8, $J_{3,4}$ 8.0 Hz, H-4), 4.18 (ddd, 1H, $J_{5',6'b}$ 3.3, $J_{5',6'a}$ 5.3, $J_{4',5'}$ 10.0 Hz, H-5′), 4.22 (dd, 1H, $J_{2,3}$ 2.5, $J_{1,2}$ 5.1 Hz, H-2), 4.43 (dd, 1H, $J_{2,3}$ 2.3, $J_{3,4}$ 8.0 Hz, H-3), 4.49 (dd, 1H, $J_{5',6'a}$ 5.3, $J_{6'a,6'b}$ 12.1 Hz, H-6′a), 4.65 (dd, 1H, $J_{5',6'b}$ 3.1, $J_{6'a,6'b}$ 12.1 Hz, H-6′b), 5.05 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 5.42 (d, 1H, $J_{1,2}$ 5.1 Hz, H-1), 5.54 (dd, 1H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 9.6 Hz, H-2′), 5.68 (t, 1H, *J* 9.8 Hz, H-4′), 5.91 (t, 1H, *J* 9.6 Hz, H-3′), 7.27 (m, 2H), 7.31–7.44 (m, 6H), 7.50 (m, 4H), 7.83 (m, 2H), 7.90 (m, 2H), 7.98 (m, 2H), 8.03 (m, 2H); ^{13}C NMR data

were essentially identical with those reported.[22e] FABMS (matrix NBA) *m*/*z* (%) 861 ([M+Na]$^+$, 43), 579 (100).

4.7. *N*-Benzyloxycarbonyl-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-L-serine methyl ester (20)

Chromatographic purification with 2:1 hexane–EtOAc gave **20** as a colorless foam: $[\alpha]_D$ +31.4 (*c* 1.45, $CHCl_3$); R_f 0.25 (2:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 3.66 (s, 3H), 3.91 (dd, 1H, *J* 3.3, 10.3 Hz), 4.11 (ddd, 1H, *J* 3.2, 5.1, 10.3 Hz, H-5), 4.33 (dd, 1H, *J* 2.9, 10.3 Hz), 4.47 (dd, 1H, *J* 5.1, 12.2 Hz, H-6a), 4.48 (m, 1H, –C*H*–NH), 4.64 (dd, 1H, *J* 3.2, 12.2 Hz, H-6b), 4.83 (d, 1H, *J* 7.8 Hz, H-1), 4.96 and 5.04 (2 × d, 2H, J_{gem} 12.5 Hz, CH_2Ph), 5.48 (dd, 1H, *J* 7.8, 9.5 Hz, H-2), 5.56 (d, 1H, *J* 8.1 Hz, NH), 5.66 (t, 1H, *J* 9.8 Hz, H-4), 5.88 (t, 1H, *J* 9.6 Hz, H-3), 7.24–7.58 (m, 17H), 7.82 (m, 2H), 7.89 (m, 2H), 7.94 (m, 2H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 52.6, 54.2, 62.9, 66.9, 69.3, 69.4, 71.7, 72.3, 72.6, 101.3, 128.07, 128.11, 128.28, 128.38, 128.39, 128.47, 128.71, 128.72, 129.0, 129.5, 129.71, 129.76, 129.79, 133.1, 133.24, 133.29, 133.4, 136.2, 155.8, 165.04, 165.11, 165.7, 166.1, 169.8; FABMS (matrix NBA) *m*/*z* (%) 854.5 ([M+Na]$^+$, 20), 832.5 ([M+H]$^+$, 4), 579.3 (34).

4.7.1. 3,4,6-tri-*O*-benzoyl-α-D-glucopyranose orthoester (12S). Chromatographic purification with 40:1 CH_2Cl_2–EtOAc gave **12S** as a colorless foam: $[\alpha]_D$ +1.3 (*c* 1.65, $CHCl_3$); R_f 0.32 (2:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 3.63 (dd, 1H, *J* 3.3, 10.0 Hz), 3.70 (s, 3H), 3.72 (dd, 1H, *J* 3.1, 10.0 Hz), 4.08 (ddd, 1H, *J* 3.0, 5.0, 8.6 Hz, H-5), 4.36 (dd, 1H, *J* 5.1, 12.1 Hz, H-6a), 4.44 (m, 1H, –C*H*–NH), 4.51 (dd, 1H, *J* 2.8, 12.2 Hz, H-6b), 4.72 (m, 1H, H-2), 5.07 and 5.11 (2 × d, 2H, J_{gem} 12.2 Hz, CH_2Ph), 5.47 (d-like, 1H, $J_{4,5}$ 8.8 Hz, H-4), 5.58 (d, 1H, *J* 8.6 Hz, NH), 5.73 (dd, 1H, $J_{3,4}$ 1.6, $J_{2,3}$ 2.9 Hz, H-3), 6.01 (d, 1H, $J_{1,2}$ 5.1 Hz, H-1), 7.24–7.35 (m, 7H), 7.37–7.51 (m, 8H), 7.59 (m, 2H), 7.69 (m, 2H), 7.91 (m, 2H), 7.93 (m, 2H), 8.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 52.5, 53.8, 63.8, 64.0, 67.1, 67.6, 68.3, 69.0, 72.3, 97.6 (C-1), 121.1 (Ph–*C*O$_3$–), 126.2, 128.0, 128.1, 128.2, 128.39, 128.46, 128.53, 128.8, 129.0, 129.5, 129.6, 129.8, 129.9, 130.0, 133.0, 133.5, 133.7, 134.4, 136.1, 155.8, 164.5, 165.1, 165.9, 170.3; FABMS (matrix NBA) *m*/*z* (%) 854 ([M+Na]$^+$, 39), 832 ([M+H]$^+$, 2), 579 (100).

4.8. 4-Pentenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (22)

Chromatographic purification with 3:1 hexane–EtOAc gave **22** as a colorless solid: mp 112–114 °C, lit.[29] mp 113–114 °C; $[\alpha]_D$ +19.3 (*c* 2.1, $CHCl_3$), lit.[29] +18.7 (*c* 1, $CHCl_3$); R_f 0.35 (3:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 2H), 1.98 (m, 2H), 3.56 (dt, 1H, *J* 9.8, 6.7 Hz), 3.93 (dt, 1H, *J* 9.8, 6.2 Hz), 4.17 (ddd, 1H, $J_{5,6b}$ 3.3, $J_{5,6a}$ 5.1, $J_{4,5}$ 9.8 Hz, H-5), 4.51 (dd, 1H, $J_{5,6a}$ 5.2, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.65 (dd, 1H, $J_{5,6b}$ 3.3, $J_{6a,6b}$ 12.1 Hz, H-6b), 4.80 (m, 1H), 4.83 (m, 1H), 4.84 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1), 5.54 (dd, 1H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.8 Hz, H-2), 5.64 (tdd, 1H, *J* 6.6, 9.1, 18.2 Hz, –C*H*=CH$_2$), 5.69 (t, 1H, *J* 9.7 Hz, H-4), 5.92 (t, 1H, *J* 9.7 Hz, H-3), 7.27 (m, 2H), 7.38 (m, 6H), 7.50 (m, 4H), 7.84 (m, 2H), 7.90 (m, 2H), 7.97 (m, 2H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 28.5, 29.7, 63.2, 69.4, 69.8, 71.9, 72.1, 72.9, 101.2, 114.9, 128.25, 128.32, 128.36, 128.77, 128.78, 129.3, 129.6, 129.69, 129.71, 129.74, 129.78, 133.08, 133.16, 133.19, 133.4, 137.7, 165.0, 165.2, 165.8, 166.1. Anal. Calcd for $C_{39}H_{36}O_{10}$: C, 70.47; H, 5.46. Found: C, 70.34; H, 5.37.

4.9. Cholest-5-en-3β-yl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (24)

Chromatographic purification with CH_2Cl_2 gave **24** as a colorless solid: mp 205–208 °C, lit.[33a] 214–216 °C, lit.[19c] 204–206°C; $[\alpha]_D$ +17.3 (*c* 1.6, $CHCl_3$), lit.[33a] +15 (*c* 0.9, $CHCl_3$), lit.[33b] +14.1(*c* 0.71, $CHCl_3$), lit.[33c] +13.5 (*c* 1.0, $CHCl_3$); R_f 0.40 (4:1 hexane–EtOAc); ^{1}H and ^{13}C NMR data were essentially identical with those reported.[33c] Anal. Calcd for $C_{61}H_{72}O_{10}$: C, 75.91; H, 7.52. Found: C, 75.82; H, 7.39.

4.10. Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (26)

Chromatographic purification with 40:1 CH_2Cl_2–EtOAc gave **26** as a colorless foam: $[\alpha]_D$ +21.5 (*c* 2.2, $CHCl_3$), lit.[2e] +18 (*c* 1.4, $CHCl_3$), lit.[33b] +22.1 (*c* 2.7, $CHCl_3$), lit.[34] +21.7 (*c* 1.0, $CHCl_3$); R_f 0.40 (2:1 hexane–EtOAc); ^{1}H and ^{13}C NMR data were essentially identical with those reported.[2e,34] FABMS (matrix NBA) *m*/*z* (%) 1065 ([M+Na]$^+$, 31), 579 (100).

4.11. Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (28)

Chromatographic purification with 40:1 CH_2Cl_2–EtOAc gave **28** as a colorless foam: $[\alpha]_D$ −1.0 (*c* 2.6, $CHCl_3$), lit.[2e] +1 (*c* 1.5, $CHCl_3$), lit.[33b] −3.0 (*c* 1.7, $CHCl_3$), lit.[34] +1.0 (*c* 1.0, $CHCl_3$); R_f 0.36 (2:1 hexane–EtOAc); ^{1}H and ^{13}C NMR data were essentially identical with those reported.[2e,g,34] Anal. Calcd for $C_{62}H_{58}O_{15}\cdot 0.5H_2O$: C, 70.77; H, 5.65. Found: C, 70.78; H, 5.42.

4.12. General procedure for 1,2-cis selective glycosylation

To a cooled mixture of α-D-glucose pentabenzoate **8a** (0.20 mmol), alcohol (0.3–0.4 mmol), and $ZnBr_2$ (55 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added a

solution of bromotrimethylsilane (50 mg, 0.32 mmol) in CH_2Cl_2 (0.3 mL). The mixture was stirred at ca. 5 °C for 1 h, and then at rt until **8a** was consumed. The reaction was quenched by dilution with EtOAc (10 mL) and aq $NaHCO_3$ (10 mL), and the mixture was worked up as described in procedure (A).

4.12.1. 12-Bromododecyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (11α). The crude product mixture from the reaction of **8a** (144 mg, 0.20 mmol) and **3** (80 mg, 0.30 mmol) was purified by silica gel chromatography eluting with 5:1→4:1 hexane–EtOAc to give **9b** (65 mg, 49%) and **11α** (76 mg, 45%): colorless oil; $[\alpha]_D$ +67.0 (*c* 2.3, $CHCl_3$); R_f 0.39 (4:1 hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 1.10–1.35 (m, 14H), 1.41 (m, 2H), 1.61 (m, 2H), 1.84 (quint, 2H, *J* 7.1 Hz), 3.40 (t, 2H, *J* 6.8 Hz), 3.49 (dt, 1H, *J* 10.0, 6.6 Hz), 3.80 (dt, 1H, *J* 9.8, 6.4 Hz), 4.48 (m, 2H, H-5 and 6a), 4.61 (m, 1H, H-6b), 5.30 (dd, 1H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.0 Hz, H-2), 5.35 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.68 (t, 1H, *J* 9.6 Hz, H-4), 6.20 (t, 1H, *J* 9.8 Hz, H-3), 7.25–7.45 (m, 8H), 7.50 (m, 4H), 7.87 (m, 2H), 7.94 (m, 2H), 7.99 (m, 2H), 8.05 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 26.0, 28.1, 28.7, 29.25, 29.29, 29.35, 29.45, 32.8, 34.0, 63.1, 67.7, 68.8, 69.7, 70.6, 72.1, 95.9 (C-1), 128.23, 128.33, 128.35, 128.9, 129.1, 129.2, 129.64, 129.69, 129.71, 129.83, 129.86, 133.0, 133.28, 133.34, 165.3, 165.76, 165.78, 166.1; FABMS (matrix NBA) *m*/*z* (%) 866 ($[M+Na]^+$, 12), 843 ($[M]^+$, 4), 579 (100).

4.12.2. 2-Phenylethyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (14α). The crude product mixture from the reaction of **8a** (144 mg, 0.20 mmol) and **13** (40 mg, 0.34 mmol) was purified by chromatography eluting with CH_2Cl_2 to give **9b** (21 mg, 16%) and **14α** (95 mg, 68%): colorless foam; $[\alpha]_D$ +111 (*c* 1.6, $CHCl_3$); R_f 0.40 (3:1 hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 2.95 (t, 2H, *J* 6.5 Hz), 3.75 (dt, 1H, *J* 9.4, 6.1 Hz), 3.96 (m, 1H), 3.98 (dt, 1H, *J* 9.4, 6.8 Hz), 4.32 (dd, 1H, *J* 5.1, 12.1 Hz), 4.46 (dd, 1H, *J* 2.8, 12.1 Hz), 5.28 (dd, 1H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.1 Hz, H-2), 5.33 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.62 (t, 1H, *J* 9.9 Hz, H-4), 6.16 (t, 1H, *J* 9.9 Hz, H-3), 7.04 (m, 5H), 7.28 (m, 2H), 7.38 (m, 6H), 7.52 (m, 4H), 7.83 (m, 2H), 7.91 (m, 4H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 35.9, 62.8, 67.6, 68.8, 69.3, 70.4, 71.9, 95.5 (C-1), 126.3, 128.25, 128.33, 128.34, 128.38, 128.86, 129.02, 129.14, 129.62, 129.67, 129.82, 129.91, 133.06, 133.32, 133.37, 138.7, 165.16, 165.74, 165.79, 166.1; FABMS (matrix NBA) *m*/*z* (%) 723 ($[M+Na]^+$, 64), 700 ($[M]^+$, 12), 579 (100).

4.12.3. Cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (16α). The crude product mixture from the reaction of **8a** (144 mg, 0.20 mmol) and **15** (40 mg, 0.4 mmol) was purified by chromatography eluting with CH_2Cl_2 to give **9b** (71 mg, 54%) and **16α** (44 mg, 32%): colorless solid; mp 168–169 °C, lit.[32] mp 91–92 °C; $[\alpha]_D$ +88.0 (*c* 1.3, $CHCl_3$); R_f 0.37 (4:1 hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 1.08–1.33 (m, 4H), 1.46 (m, 1H), 1.53 (m, 1H), 1.62 (m, 1H), 1.71 (m, 2H), 1.96 (m, 1H), 3.62 (tt, 1H, *J* 3.9, 9.4 Hz), 4.47 (m, 1H), 4.59 (m, 2H), 5.28 (dd, 1H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.1 Hz, H-2), 5.51 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.65 (t, 1H, *J* 9.9 Hz, H-4), 6.21 (t, 1H, *J* 9.9 Hz, H-3), 7.28 (m, 2H), 7.32–7.45 (m, 6H), 7.52 (m, 4H), 7.88 (m, 2H), 7.96 (m, 2H), 7.99 (m, 2H), 8.05 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 23.6, 23.9, 25.4, 31.6, 33.4, 63.2, 67.8, 69.7, 70.6, 72.1, 77.5, 94.5 (C-1), 128.22, 128.31, 128.35 128.9, 129.1, 129.2, 129.63, 129.67, 129.77, 129.83, 133.0, 133.26, 133.34, 165.3, 165.8 (2C), 166.1. Anal. Calcd for $C_{40}H_{38}O_{10}$: C, 70.78; H, 5.64. Found: C, 70.78; H, 5.43.

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