Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 10383–10392

Synthesis of 1-*C*-alkyl-α-D-glucopyranosides by Lewis acid- or Brønsted acid-catalyzed O-glycosidation

Takashi Yamanoi,[a,*] Yoshiki Oda,[a] Sho Matsuda,[a,b] Ippo Yamazaki,[a] Kazuhide Matsumura,[a] Kaname Katsuraya,[c] Mikio Watanabe[b] and Toshiyuki Inazu[d]

[a]*The Noguchi Institute, 1-8-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan*
[b]*Department of Chemistry, School of Science, Tokai University, Kitakaname 1117, Hiratsuka, Kanagawa 259-1292, Japan*
[c]*School of Home Economics, Wayo Women's University, Chiba 272-8533, Japan*
[d]*Department of Applied Chemistry, School of Engineering, Institute of Glycotechnology, Tokai University, Kitakaname 1117, Hiratsuka, Kanagawa 259-1292, Japan*

Received 5 July 2006; revised 9 August 2006; accepted 21 August 2006
Available online 8 September 2006

Abstract—We prepared several kinds of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose derivatives containing methyl, ethyl, *n*-butyl, and benzyl groups as the alkyl groups at their anomeric positions. The Lewis acid- or Brønsted acid-catalyzed O-glycosidations using them as the glycosyl donors to synthesize 1-*C*-alkyl-D-glucopyranosides were investigated. Using 10 mol % of triphenylmethyl perchlorate efficiently catalyzed the glycosidation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl dimethylphosphinothioate. The glycosidation using the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl acetates smoothly proceeded in the presence of only 5 mol % of scandium(III) trifluoromethanesulfonate. The dehydration–condensation type glycosidation using the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses was significantly promoted using 5 mol % of bis(trifluoromethane)sulfonimide. These glycosidations successfully afforded various 1-*C*-alkyl-α-D-glucopyranosides in good yields with high α-stereoselectivities.

1. Introduction

The 1-*C*-alkyl-sugars, which have alkyl groups at their anomeric carbon centers, are considered to be a novel class of artificial ketoses, which replace naturally occurring aldoses. Their glycosylated compounds, i.e., 1-*C*-alkyl-glycosides, are expected to show biological functions different from those of natural compounds.[1] Therefore, considerable attention has been paid to developing glycosidation methods for synthesizing the 1-*C*-alkyl-*O*-glycosides.[2]

The reported methods for synthesizing the 1-*C*-alkyl-*O*-hexopyranosides involve glycosidations using the *exo*-glycal or 1-*C*-alkyl-sugar derivatives as the glycosyl donors. Although a few *exo*-glycals are conveniently utilized as the glycosyl donors in both enzymatic and chemical glycosidations,[3] there appears to be limitations in the use of the *exo*-glycals due to their synthetic difficulty. On the other hand, various kinds of 1-*C*-alkyl-sugar derivatives could be readily prepared by the reactions of the corresponding glycono-1,5-lactones with organometallic reagents such as organolithium reagents or Grignard reagents.[4] To the best of our knowledge, however, only a few O-glycosidations using 1-*C*-alkyl-hexopyranose derivatives as the glycosyl donors have ever been reported.[5]

We previously studied the glycosidations using 1-*O*-dimethylphosphinothioyl sugars[6] and 1-*O*-acetyl sugars[7] as the glycosyl donors. The former study showed that the glycosidations using the dimethylphosphinothioyloxy function as the leaving group were activated by a catalytic amount of triphenylmethyl perchlorate ($TrtClO_4$). In the latter study, ytterbium(III) triflate ($Yb(OTf)_3$) was found to be an effective activator for the glycosidations using the acetoxy function as the leaving group.

Our recent interest in the formation reaction of 1-*C*-alkyl-hexopyranosidic linkages by the O-glycosidation prompted us to start an investigation of the catalytic synthesis of 1-*C*-alkyl-hexopyranosides using our newly developed glycosidation methods. Part of the study was reported in a preliminary letter about the synthesis of 1-*C*-alkyl-glucopyranosides by the glycosidation of the 1-*C*-alkyl-D-glucopyranosyl donors having the acetoxy function as a leaving group. The reaction was activated by a catalytic amount of

Keywords: 1-*C*-Alkyl-glycopyranose; Ketopyranoside; Glycosidation; Lewis acid; Brønsted acid.
* Corresponding author. Tel./fax: +81 3 5944 3213; e-mail: tyama@noguchi.or.jp

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.08.059

scandium(III) triflate ($Sc(OTf)_3$).[8] The following letter describes the Brønsted acid-catalyzed glycosidation used to synthesize 1-*C*-alkyl-glucopyranosides. During the glycosidation, the anomeric hydroxyl function of the glycosyl donors, the 1-*C*-alkyl-D-glucopyranoses, was conveniently utilized as the leaving group.[9] In these letters were mentioned some of the interesting glycosidation properties based on these 1-*C*-alkyl-D-glucopyranosyl donor's reactivities. However, we considered that the 1-*C*-alkyl-hexopyranosyl donors would have some unknown reactivities and their elucidation would be important for their utilization in synthetic carbohydrate chemistry.

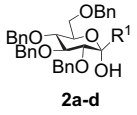
In order to develop efficient synthetic methods for producing 1-*C*-alkyl-hexopyranosides, in this full paper, we summarize the glycosidations using the glycosyl donors of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dimethylphosphinothioates, 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetates, and 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoses in the presence of catalytic amounts of Lewis acids or Brønsted acids as the activators.

2. Results and discussion

2.1. Glycosidation of the 1-*C*-alkyl-D-glucopyranosyl dimethylphosphinothioate derivatives

We describe the preparation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dimethylphosphinothioates and their catalytic O-glycosidation to synthesize the 1-*C*-alkyl-D-glucopyranosides.

2.1.1. Preparation of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses. According to the reported method, several 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses (R^1=alkyl; methyl: **a**, ethyl: **b**, *n*-butyl: **c**, benzyl: **d**) were prepared in high yields by the addition of the RLi or RMgX reagent to 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**)[10] (Scheme 1; Table 1).



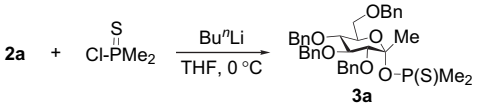
2a-d

Scheme 1.

Table 1. 1-*C*-Alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose

Entry	R^1	1-*C*-Alkyl-D-glucopyranose derivatives
1	Me	**2a**
2	Et	**2b**
3	Bu^n	**2c**
4	CH_2Ph	**2d**

2.1.2. Preparation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dimethylphosphinothioates. We examined the preparation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dimethylphosphinothioates from **2a–d**, according to our previously reported method for preparing the aldopyranosyl dimethylphosphinothioates.[6] The reaction of **2a** with dimethylphosphinothioyl (Mpt) chloride (1.2 equiv) using Bu^nLi (1.2 equiv) in THF at 0 °C produced 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl dimethylphosphinothioate (**3a**) in 55% yield (Scheme 2). However, similar reaction conditions using **2b** and **2c** gave the corresponding dimethylphosphinothioates in very poor yields. It is possible that the steric hindrances on the anomeric centers of **2b** and **2c** and the bulkiness of Mpt-Cl prevented introduction of the Mpt group into **2b** and **2c**. Compound **3a** was not as stable as the aldopyranosyl dimethylphosphinothioates that we had previously prepared. Therefore, **3a** was used in the glycosidation reaction immediately after the purification using thin-layer chromatography.

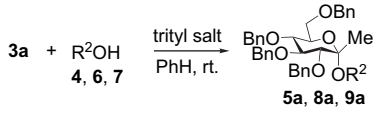


3a

Scheme 2.

2.1.3. Glycosidation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl dimethylphosphinothioate (3a).[11] The reactivity of **3a** as a glycosyl donor was expected to be high because the electron donating effect of the methyl group in **3a** would stabilize the glycosyl cation intermediate generated from **3a** in spite of its tertiary anomeric carbon center's steric hindrance.

Since our former research showed that the trityl salts were efficient activators for the highly reactive glycosyl donors such as the 2-deoxy-glycopyranosyl dimethylphosphinothioates, we used the trityl salts as the activators of **3a** in this glycosidation study. When **3a** was glycosylated with 3β-cholestanol (**4**) using 10 mol % of $TrtClO_4$ in benzene at room temperature (Scheme 3), the corresponding 1-*C*-methyl-D-glucopyranoside derivative (**5a**) was successfully obtained in high yield of 88% with an α-stereoselectivity. Even the reaction using only 5 mol % of $TrtClO_4$ could afford **5a** in 71% yield. When other trityl salts were used, the reactions using 10 mol % of triphenylmethyl hexachloroantimonate ($TrtSbCl_6$), triphenylmethyl tetrafluoroborate ($TrtBF_4$), and triphenylmethyl pentachlorotin ($TrtSnCl_5$) afforded **5a** in moderate yields from 34 to 43%. The maximum yield was attained from the reaction using 10 mol % of $TrtClO_4$. Although the combined use of I_2 and 10 mol % of $TrtClO_4$ was found to be an effective activating system for the glycosidation of several aldopyranosyl dimethylphosphinothioates, the reaction between **3a** and **4** using this activating system did not produce **5a** at all, but gave an unknown product.



5a, **8a**, **9a**

Scheme 3.

Next, the glycosidation of **3a** with *n*-octanol (**6**) or 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) as the

Table 2. The glycosidation of **3a** with alcohols (**4**, **6**, and **7**) in the presence of trityl salts[a]

Entry	Trityl salt (mol %)	Alcohol	Product	Yield (%)
1	$TrtClO_4$ (10)	**4**	**5a**	88
2	$TrtClO_4$ (5)	**4**	**5a**	71
3	$TrtSbCl_6$ (10)	**4**	**5a**	43
4	$TrtBF_4$ (10)	**4**	**5a**	34
5	$TrtPF_6$ (10)	**4**	**5a**	No reaction
6	$TrtSnCl_5$ (10)	**4**	**5a**	43
7	$TrtClO_4$ (10)	**6**	**8a**	82
8	$TrtClO_4$ (10)	**7**	**9a**	82[b]

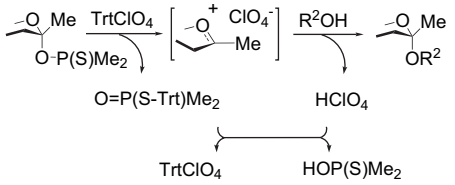
[a] Reaction conditions: molar ratio, **3a**:alcohol=1:1; reaction time, 1 h; reaction temperature, rt.
[b] The α/β ratio of glycoside was 70/30.

glycosyl acceptor was performed under similar reaction conditions using 10 mol % of $TrtClO_4$ in benzene. The corresponding *n*-octyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (**8a**) was obtained in 82% yield with an α-stereoselectivity, and 6-*O*-(2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9a**) was also obtained in 82% yield with an α/β ratio=70/30. The β-form of **9a** would be partially formed by the S_N2-like reaction mechanism. Judging from the glycosidation yields, **3a** expectedly worked as a highly reactive glycosyl donor in spite of its sterically hindered tertiary anomeric carbon center. These results are summarized in Table 2 (Fig. 1). The expected reaction mechanism is indicated in Scheme 4.

We found that the glycosidation of **3a** with several alcohols in the presence of 10 mol % of $TrtClO_4$ in benzene at room temperature smoothly proceeded to afford the 1-*C*-methyl-D-glucopyarnosides in good yields with high α-stereoselectivities.

2.2. Glycosidation of the 1-*C*-alkyl-D-glucopyranosyl acetate derivatives

In order to establish the method for producing the 1-*C*-alkyl-D-glucopyranosides having various kinds of alkyl groups, we



Scheme 4.

investigated the glycosidation of the 1-*C*-alkyl-D-glucopyranosyl donors having an acetoxy function as a leaving group using Lewis acids as activators. As the acetyl group was less bulky than the Mpt group, the acetyl group was expected to be smoothly introduced into **2a–d** in order to prepare the corresponding 1-*C*-alkyl-D-glucopyranosyl acetates. We describe the preparation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetates and the synthesis of various 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides by the Lewis acid-catalyzed O-glycosidation using them as the glycosyl donors.

2.2.1. Preparation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetates. We investigated the preparation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-D-glucopyranosyl acetate (**10a**)[12] by the acetylation of **2a** (Scheme 5). Although the ordinary acetylation of **2a** using Ac_2O/pyridine could not give **10a** at all, the use of Bu^{n}Li as a strong base in lieu of pyridine was effective. Compound **10a** was obtained in 69% yield by the reaction of **2a** with Bu^{n}Li followed by the addition of Ac_2O in THF at −78 °C. In the next experiment, the reaction temperature was gradually raised as follows. After the reaction of **2a** with Bu^{n}Li at −78 °C, Ac_2O was added to the reaction mixture at −30 °C, and the reaction was quenched at 0 °C. The yield of **10a** increased to 80%.[13]

As another convenient synthetic route, the one-pot synthesis of **10a** from **1** was examined (Scheme 5). When the reaction

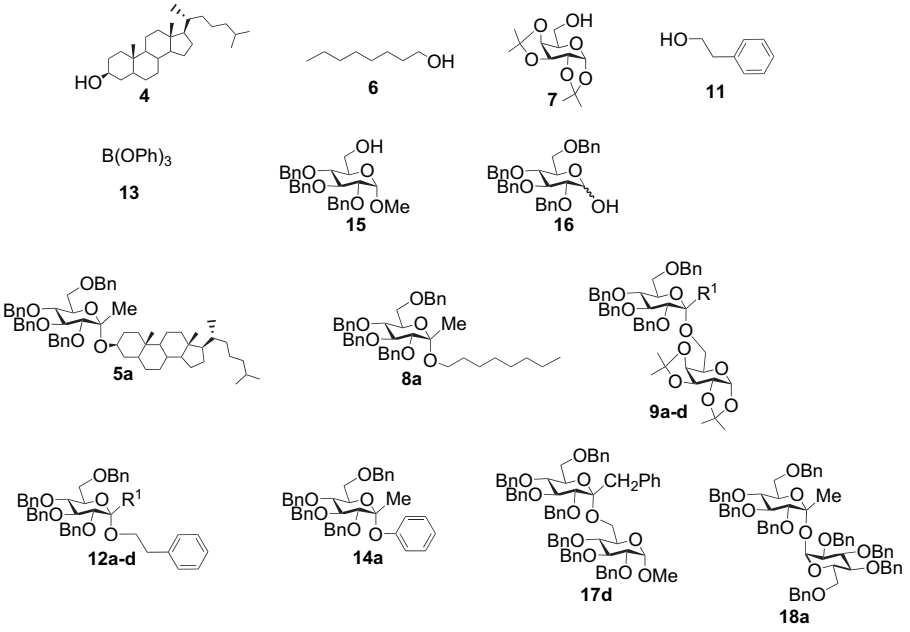
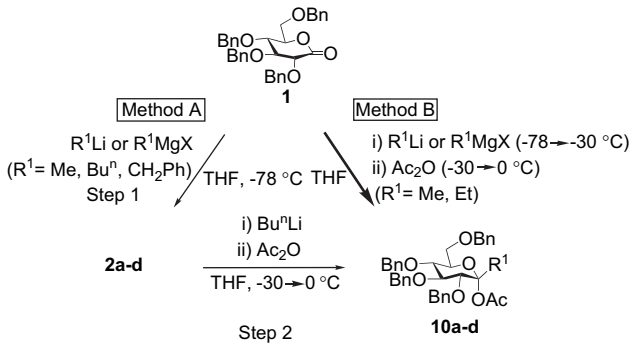


Figure 1. The acceptors utilized in the glycosidations and glycosides synthesized.



Scheme 5.

of **1** with MeLi was carried out at −78 °C in THF and Ac_2O was added at −30 °C, followed by quenching the reaction at 0 °C, **10a** was obtained in 73% yield.

Furthermore, we examined the preparation of the 2,3,4,6-tetra-*O*-benzyl-1-*C*-ethyl-α-D-glucopyranosyl acetate (**10b**), 2,3,4,6-tetra-*O*-benzyl-1-*C*-*n*-butyl-α-D-glucopyranosyl acetate (**10c**), and 1-*C*-benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl acetate (**10d**). The acetate **10b–d** were prepared in good yields with α-stereoselectivities by the acetylation of **2c** and **2d** using Bu^{n}Li and Ac_2O or by the one-pot synthesis from **1** using EtMgBr and Ac_2O (Scheme 5). These results are summarized in Table 3.

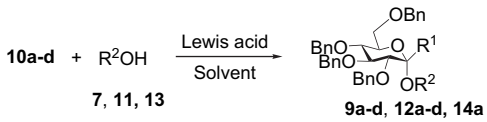
Table 3. Preparation of **10a–d**

Entry	Starting sugar derivative	Method[a]	Product	Yield (%)
1	**2a**	A	**10a**	80 (69)[b]
2	**1**	B	**10a**	73
3	**1**	B	**10b**	86
4	**2c**	A	**10c**	88
5	**2d**	A	**10d**	81

[a] Method A: after the reaction of **2a** (**2c** or **2d**) with Bu^{n}Li (1.1 equiv) was carried out in THF at −78 °C, Ac_2O (6 equiv) was added to the reaction mixture at −30 °C and the reaction was quenched by satd $NaHCO_3$ solution at 0 °C; Method B: after the reaction of **1** with MeLi or EtMgBr (1.2 equiv) was carried out in THF at −78 °C, Ac_2O (6 equiv) was added to the reaction mixture at −30 °C and the reaction was quenched by satd $NaHCO_3$ solution at 0 °C.

[b] The reaction was performed at −78 °C.

2.2.2. Glycosidation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl acetates (10a–d). We examined in detail the glycosidation of **10a** with phenethyl alcohol (**11**) in the presence of various Lewis acids (Scheme 6). When 5 mol % of a Lewis acid such as $Yb(OTf)_3$, $Sc(OTf)_3$, TMSOTf, $TrtClO_4$, and $BF_3\cdot OEt_2$ was used as the activator in dichloromethane at 0 °C, each Lewis acid could activate the glycosidation to give the corresponding glycoside **12a** in 67–80% yields with an α-stereoselectivity. $Yb(OTf)_3$ and $Sc(OTf)_3$ were especially effective for the activation of



Scheme 6.

10a. Even the reaction using only 1 mol % of $Sc(OTf)_3$ could afford **12a** in the yield of 73%, and only this reaction produced a small amount of the β-isomer (α/β=81/19). The effect of the solvents was also examined using CH_2Cl_2, $PhCH_3$, and CH_3CN. The reaction using $PhCH_3$ increased the yield of **12a** up to 89%, however, these solvents did not influence the glycosidation stereoselectivities at all.

Furthermore, we examined the glycosidation of the 1-*C*-alkyl-D-glucopyranosyl acetates (**10a–d**) with **11** or **7** under similar reaction conditions. The reactions of **10a–d** with **11** or **7** in the presence of 5 mol % of $Sc(OTf)_3$ in $PhCH_3$ stereoselectively afforded the corresponding phenethyl 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosides (**12b–d**) or 6-*O*-(1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoses (**9a–d**) in the yields from 73 to 89%, respectively.

Our recent study indicated that triaryloxyboranes worked as the reactive glycosyl acceptors of glycosyl acetates in the presence of a catalytic amount of $Yb(OTf)_3$ to afford the corresponding aryl O-glycosides.[7c] Therefore, the synthesis of phenyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (**14a**) was attempted by the reaction of **10a** with triphenoxyborane (**13**) using 5 mol % of $Yb(OTf)_3$ in CH_2Cl_2 at −78 °C. The desired **14a** was obtained in 80% yield with an α-stereoselectivity. These results are shown in Table 4 (Fig. 1). The proposed reaction mechanism is shown in Scheme 7.

Table 4. Synthesis of various 1-*C*-alkyl-α-D-glucopyranosides by the glycosidation of **10a–d** with acceptors (**7**, **11**, and **13**)[a]

Entry	Acetate	Alcohol	Activator	Solvent	Product	Yield (%)[b]
1	**10a**	**11**	$Yb(OTf)_3$	CH_2Cl_2	**12a**	76
2	**10a**	**11**	$Sc(OTf)_3$	CH_2Cl_2	**12a**	80
3	**10a**	**11**	TMSOTf	CH_2Cl_2	**12a**	69
4	**10a**	**11**	$TrtClO_4$	CH_2Cl_2	**12a**	74
5	**10a**	**11**	$BF_3\cdot OEt_2$	CH_2Cl_2	**12a**	67
6[c]	**10a**	**11**	$Sc(OTf)_3$	CH_2Cl_2	**12a**	73[d]
7	**10a**	**11**	$Sc(OTf)_3$	$PhCH_3$	**12a**	89
8	**10a**	**11**	$Sc(OTf)_3$	CH_3CN	**12a**	63
9	**10b**	**11**	$Sc(OTf)_3$	$PhCH_3$	**12b**	86
10	**10c**	**11**	$Sc(OTf)_3$	$PhCH_3$	**12c**	75
11	**10d**	**11**	$Sc(OTf)_3$	$PhCH_3$	**12d**	77
12	**10a**	**7**	$Sc(OTf)_3$	$PhCH_3$	**9a**	82
13[c]	**10a**	**7**	$Sc(OTf)_3$	$PhCH_3$	**9a**	87[e]
14	**10b**	**7**	$Sc(OTf)_3$	$PhCH_3$	**9b**	77
15	**10c**	**7**	$Sc(OTf)_3$	$PhCH_3$	**9c**	73
16	**10d**	**7**	$Sc(OTf)_3$	$PhCH_3$	**9d**	74
17[f]	**10a**	**13**	$Yb(OTf)_3$	CH_2Cl_2	**14a**	80

[a] Reaction conditions: molar ratio, **10a–d**:**11**:activator=1:1:0.05; **10a–d**:**7**:activator=1.5:1:0.075; reaction time, 1–3 h; reaction temperature, 0 °C.

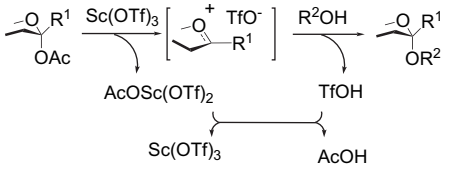
[b] Only the α-glycoside was obtained.

[c] $Sc(OTf)_3$ (1 mol %) was used.

[d] The α/β ratio of glycoside was 81/19.

[e] The α/β ratio of glycoside was 85/15.

[f] Reaction conditions: molar ratio, **10a**:**13**:activator=1:0.5:0.05; reaction time, 3 h; reaction temperature, −78 °C.



Scheme 7.

Inanaga et al. reported that lanthanide triflates could not activate at all the glycosidation using 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetate as the glycosyl donor.[14] This is quite different from our observations that any glycosidation using **10a–d** smoothly proceeded in the presence of only 5 mol % of $Sc(OTf)_3$. These results showed that **10a–d** indicated a much higher reactivity than the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetate as the glycosyl donor and the existence of the alkyl groups on **10a–d** remarkably increased their glycosyl donor's reactivities. Moreover, the species of the alkyl groups at the anomeric carbon centers of **10a–d** had almost no influence on the reactivities and stereoselectivities of the glycosidation. The reactivities of **10a–d** were similar to those of **3a**.

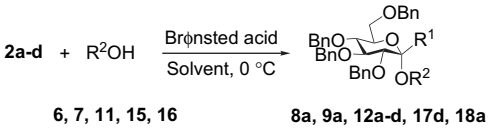
The high α-stereoselectivity of the glycosidation could be explained by the anomeric effect and the disadvantageous formation of β-glycosides due to the 1,3-diaxial interaction. It was also possible that the anomerization might occur and 1-*C*-alkyl-β-glucopyranosides might be converted to the corresponding α-glucopyranosides in the reaction system. In order to examine this point, the β-glycoside of **9a** (Table 4, entry 13) was added to the reaction in the presence of 10 mol % of $Sc(OTf)_3$ in toluene at room temperature overnight. No anomerization was observed in the reaction.

We found that **10a–d** worked as good glycosyl donors in the presence of only 5 mol % of $Sc(OTf)_3$ in toluene at 0 °C to afford various 1-*C*-alkyl-D-glucopyranosides in good yields with high α-stereoselectivities.

2.3. Glycosidation of the 1-*C*-alkyl-α-D-glucopyranose derivatives

In order to develop a more convenient synthetic method for producing 1-*C*-alkyl-D-glucopyranosides, the direct glycosidation of the 1-*C*-alkyl-D-glucopyranoses **2a–d** without introducing any other leaving group was examined. We describe the dehydration–condensation type glycosidation of **2a–d** with alcohols using a catalytic amount of Brønsted acids as the activators.

2.3.1. Glycosidation of the 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses (2a–d). We investigated the dehydration–condensation type glycosidation using **2a** as a glycosyl donor and **11** as a glycoyl acceptor (Scheme 8). Brønsted acids were used as the activators for this glycosidation because they were expected to be potentially resistant to water. As the Brønsted acids, 5 mol % of camphorsulfonic acid, trifluoroacetic acid (CF_3CO_2H), and TfOH were used in dichloromethane at 0 °C in the presence of a drying agent, Drierite (anhydrous $CaSO_4$). Only TfOH could effectively activate the glycosidation to stereoselectively give the corresponding **12a** in 59% yield. The use of acetonitrile as the solvent slightly increased the yield of **12a** up to 73% with an α-stereoselectivity. Heptadecafluorooctanesulfonic acid



Scheme 8.

($C_8F_{17}SO_3H$) and bis(trifluoromethane)sulfonimide (Tf_2NH) as the Brønsted acid analogs of TfOH and tetrafluoroboric acid (HBF_4) were similarly effective for the glycosidation of **2a** under similar reaction conditions. Particularly, Tf_2NH gave **12a** in the maximum yield of 77%. Although 10 mol % of Tf_2NH hardly increased the yield of **12a**, the reaction even using 1 mol % of Tf_2NH gave **12a** in 56% yield.

We also investigated the glycosidation of **2b–d** with **11** in acetonitrile at 0 °C using 5 mol % of Tf_2NH in order to investigate how the difference in the alkyl groups at the anomeric carbon centers would influence the reactivity and stereoselectivity of the glycosidation. The desired **12b–d** were then obtained in yields ranging from 56 to 64% with high α-stereoselectivities. The difference in the alkyl groups at the anomeric carbon centers of **2a–d** had almost no influence on the glycosidation reactivity and stereoselectivity. This is similar to the above-mentioned glycosidation properties using **10a–d**.

Furthermore, we examined the glycosidation of **2a** (or **2d**) with **6**, **7**, and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**15**) in acetonitrile at 0 °C using 5 mol % of Tf_2NH or TfOH. The desired **8a**, **9a**, and methyl 6-*O*-(1-*C*-benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**17d**) were stereoselectively obtained in good yields of 78, 55, and 66%, respectively. Interestingly, even when the anomeric mixture of **16** was used as the glycosyl acceptor, the trehalose analog (**18a**), the product by the reaction of **2a** with **16** was obtained as a single isomer based on its NMR spectrum. In the ^1H NMR spectrum of **18a**, the anomeric proton of the glucopyranosyl residue was observed at 5.34 ppm with a doublet peak (J=3.4 Hz), and the value of the coupling constant indicated α. This suggested that the glycosidation strictly recognized the anomeric stereochemistry of the acceptor **16** and only the α-isomer of **16** was utilized as the glycosyl acceptor. These results are summarized in Table 5 (Fig. 1). The proposed glycosidation mechanism is indicated in Scheme 9.

We have successfully developed the direct dehydrative glycosidation using **2a–d** without introducing any other leaving group into them, and found that the glycosidation using **2a–d** was efficiently catalyzed using only 5 mol % of Tf_2NH or TfOH as the activators to afford various 1-*C*-alkyl-α-D-glucopyranosides in good yields.

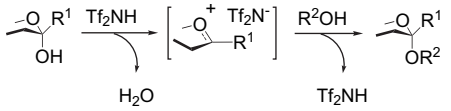
3. Determination of the anomeric configurations of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl donors and 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides

The anomeric configurations of all the 1-*C*-alkyl-D-glucopyranosyl donors (**2a–d**, **3a**, and **10a–d**) and 1-*C*-alkyl-D-glucopyranosides (**5a**, **8a**, **9a–d**, **12a–d**, **14a**, **17d**, and **18a**) were determined by their NMR spectra. The α-forms of them were determined by the measurement of the NOE interactions between H-2 and H-1′ of the alkyl groups of the 1-*C*-alkyl-D-glucopyranosyl rings as shown in Figure 2. The β-forms of **9a** and **12a** were determined by the measurements of the NOE interactions between H-3 (or H-5) and H-1′ of the methyl groups. Furthermore, the anomeric

Table 5. The glycosidation of **2a–d** with various alcohols (**6**, **7**, **11**, **15**, and **16**) in the presence of Brønsted acid[a]

Entry	1-*C*-Alkyl-glucopyranose	Alcohol	Brønsted acid (mol %)	Solvent	Product	Yield (%)
1	**2a**	**11**	Camphorsulfonic acid (5)	CH_2Cl_2	**12a**	No reaction
2	**2a**	**11**	CF_3CO_2H (5)	CH_2Cl_2	**12a**	No reaction
3	**2a**	**11**	TfOH (5)	CH_2Cl_2	**12a**	59
4	**2a**	**11**	TfOH (5)	CH_3CN	**12a**	73
5	**2a**	**11**	$C_8F_{17}SO_3H$ (5)	CH_3CN	**12a**	56
6	**2a**	**11**	Tf_2NH (5)	CH_3CN	**12a**	77
7	**2a**	**11**	HBF_4 (5)	CH_3CN	**12a**	73
8	**2a**	**11**	Tf_2NH (10)	CH_3CN	**12a**	69
9	**2a**	**11**	Tf_2NH (3)	CH_3CN	**12a**	65
10	**2a**	**11**	Tf_2NH (1)	CH_3CN	**12a**	56
11	**2b**	**11**	Tf_2NH (5)	CH_3CN	**12b**	57
12	**2c**	**11**	Tf_2NH (5)	CH_3CN	**12c**	64
13	**2d**	**11**	Tf_2NH (5)	CH_3CN	**12d**	56
14	**2a**	**6**	Tf_2NH (5)	CH_3CN	**8a**	78
15[b]	**2a**	**7**	Tf_2NH (5)	CH_3CN	**9a**	55
16[b]	**2d**	**15**	TfOH (5)	CH_3CN	**17d**	66
17[b]	**2a**	**16**	Tf_2NH (5)	CH_3CN	**18a**	47

[a] Reaction conditions: molar ratio, **2a–d**:alcohol (**6** or **11**):Brønsted acid=1:1:0.05; reaction time, 2 h; reaction temperature, 0 °C.
[b] Reaction conditions: molar ratio, **2a**,**d**:alcohol (**7**, **15** or **16**):Brønsted acid=1.5:1:0.075; reaction time, 3 h; reaction temperature, 0 °C.



Scheme 9.

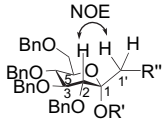


Figure 2. The determination of anomeric configurations of **3a**, **10a–d**, and glycosides.

configuration of **12a** could be determined by the NMR spectrum of the three bond coupling constants between the carbon of the 1′-*C*-methyl and the H-2 ($^3J_{C1',H2}$=2.5 Hz was α; $^3J_{C1',H2}$=1.5 Hz was β), according to the observations of Schlesselmann et al.[3e]

4. Conclusions

We have successfully developed the catalytic synthesis of various kinds of 1-*C*-alkyl-α-D-glucopyranosides carrying the methyl, ethyl, *n*-butyl, and benzyl groups as the alkyl groups at their anomeric positions by glycosidation using several 1-*C*-alkyl-D-glucopyranosyl donors with the dimethylphosphinothioyloxy, acetoxy, and hydroxyl functions as the leaving groups in the presence of $TrtClO_4$, $Sc(OTf)_3$, and Tf_2NH as the activators, respectively. We believe that this study can provide novel methods to synthesize biologically important neoglycoconjugates having 1-*C*-alkyl-sugar units.

5. Experimental

5.1. General

The NMR spectra were measured using an ECA-600 (JEOL) spectrometer at 600 MHz (^{1}H) and 150 MHz (^{13}C). The ^{1}H NMR chemical shifts are referenced to the internal standard TMS (δ_H=0.00). The ^{13}C NMR chemical shifts are referenced to the solvent signal (δ_C=77.0 for the central line of $CDCl_3$). The ESI-MS spectra were recorded on a Mariner (Applied Biosystems) spectrometer. Optical rotations were recorded using a JASCO DIP-360 digital polarimeter. All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates (0.25 mm).

5.2. Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl dimethylphosphinothioate (3a)

To a solution of **2a** (300 mg, 0.54 mmol) in dry THF (3 mL) at 0 °C was added a hexane solution of Bu^{n}Li (0.65 mmol) under an Ar atmosphere and stirred for 30 min. Mpt-Cl (88 mg, 0.69 mmol) was added to the solution, and stirred for 1 h at 0 °C. The reaction was then quenched by the addition of water. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (CH_2Cl_2/ethyl acetate/hexane=1/1/4) to give **3a** as a colorless oil (191 mg, 55%). $[\alpha]_D^{23}$ +48.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.87 (3H, d, J_{HCCOP}=0.6 Hz, CH_3), 1.90 (3H, d, J_{HCP}=6.2 Hz, PCH_3), 1.92 (3H, d, J_{HCP}=6.2 Hz, PCH_3), 3.19 (1H, dd, *J*=9.6 Hz, J_{HCCOC}=4.1 Hz, H-2′), 3.92–3.80 (2H, m, H-6), 3.74 (1H, t, *J*=9.6 Hz, H-4), 3.85 (1H, t, *J*=9.6 Hz, H-3), 3.87–3.90 (1H, m, H-5); ^{13}C NMR ($CDCl_3$): δ 24.3 (J_{CCOP}=4.3 Hz), 25.5 (J_{CP}=73.7 Hz), 26.0 (J_{CP}=70.8 Hz), 68.3, 73.0, 73.5, 75.2, 75.5, 75.7, 78.8, 82.8, 84.3 (J_{CCOP}=5.8 Hz), 105.8 (J_{COP}=10.1 Hz); HRMS (ESI) *m*/*z* calcd for $C_{37}H_{43}O_6PS\cdot Na^+$: 669.2410; found: 669.2443.

5.3. Preparation of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl acetates

5.3.1. Typical preparation by the acetylation of 1-*C*-alkyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoses. To a solution of **2a** (123 mg, 0.2 mmol) in dry THF (1 mL) at −78 °C was added a hexane solution of Bu^{n}Li (0.24 mmol) under an Ar atmosphere and the reaction temperature was raised to −30 °C for 1 h while stirring. Then, acetic

anhydride (0.3 mL) was added to the solution and the reaction temperature was gradually raised to 0 °C for 1 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **10a** as a colorless oil (111 mg, 85%).

5.3.2. Typical preparation from 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone. To a solution of **1** (288.8 mg, 0.54 mmol) in dry THF (3 mL) at −78 °C was added a diethyl ether solution of MeLi (0.64 mmol) under an Ar atmosphere and the reaction temperature was raised to −30 °C for 1 h while stirring. Acetic anhydride (0.6 mL) was then added to the solution, and the reaction temperature was gradually raised to 0 °C for 1 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **10a** as a colorless oil (233.7 mg, 73%).

5.3.3. 2,3,4,6-Tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl acetate (10a). $[\alpha]_D^{23}$ +45.2 (*c* 1.97, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.76 (3H, s, CH_3), 2.07 (3H, s, $C(O)CH_3$), 3.29 (1H, d, *J*=9.5 Hz, H-2), 3.55–3.58 (1H, m, H-5), 3.67 (1H, dd, *J*=3.2 Hz, *J*=11.1 Hz, H_a-6), 3.80 (1H, dd, *J*=3.2 Hz, *J*=11.1 Hz, H_b-6), 3.82 (1H, t, *J*=10.0 Hz, H-4), 4.02 (1H, t, *J*=9.3 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 22.1, 22.3, 68.1, 73.2, 73.5, 75.2, 75.5, 75.9, 77.6, 82.8, 84.0, 104.3, 168.7; HRMS (ESI) *m/z* calcd for $C_{37}H_{40}O_7\cdot Na^+$: 619.2672; found: 619.2602.

5.3.4. 2,3,4,6-Tetra-*O*-benzyl-1-*C*-ethyl-α-D-glucopyranosyl acetate (10b). Colorless oil; $[\alpha]_D^{23}$ +47.7 (*c* 2.45, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.88 (3H, t, *J*=1.6 Hz, CH_2CH_3), 2.05 (1H, m, $CH_aH_bCH_3$), 2.08 (3H, s, $C(O)CH_3$), 2.58 (1H, m, $CH_aH_bCH_3$), 3.52 (1H, d, *J*=8.9 Hz, H-2), 3.65 (1H, m, H-5), 3.70 (1H, dd, *J*=1.4 Hz, *J*=10.0 Hz, H_a-6), 3.80 (2H, m, H-4, H_b-6), 4.00 (1H, t, *J*=8.9 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 8.1, 22.3, 26.6, 68.4, 73.4, 73.5, 75.2, 75.3, 75.5, 77.8, 80.0, 83.1, 107.0, 168.7; HRMS (ESI) *m/z* calcd for $C_{38}H_{42}O_7\cdot Na^+$: 633.2823; found 633.2786.

5.3.5. 2,3,4,6-Tetra-*O*-benzyl-1-*C*-*n*-butyl-α-D-glucopyranosyl acetate (10c). Colorless oil; $[\alpha]_D^{23}$ +35.1 (*c* 7.16, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.83 (3H, t, *J*=7.6 Hz, $CH_2CH_2CH_2CH_3$), 1.15 (1H, m, $CH_2CH_aH_bCH_2CH_3$), 1.17 (1H, m, $CH_2CH_2CH_aH_bCH_3$), 1.25 (1H, m, $CH_2CH_2CH_aH_bCH_3$), 1.47 (1H, m, $CH_2CH_aH_bCH_2CH_3$), 2.02 (1H, m, $CH_aH_bCH_2CH_2CH_3$), 2.07 (3H, s, $C(O)CH_3$), 2.51 (1H, m, $CH_aH_bCH_2CH_2CH_3$), 3.51 (1H, d, *J*=8.9 Hz, H-2), 3.58 (1H, m, H-5), 3.68 (1H, dd, *J*=1.4 Hz, *J*=11.0 Hz, H_a-6), 3.77–3.82 (2H, m, H-4, H_b-6), 4.00 (1H, t, *J*=9.0 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 14.0, 22.3, 22.8, 25.9, 33.4, 68.4, 73.4, 73.4, 75.2, 75.3, 75.5, 77.8, 80.3, 83.2, 106.7, 168.7; HRMS (ESI) *m/z* calcd for $C_{40}H_{46}O_7\cdot Na^+$: 661.3136; found 661.3157.

5.3.6. 1-*C*-Benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl acetate (10d). Colorless oil; $[\alpha]_D^{23}$ +46.1 (*c* 1.37, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.14 (3H, s, CH_3), 3.25 (1H, d, *J*=13.7 Hz, CCH_aH_bPh), 3.30 (1H, d, *J*=8.9 Hz, H-2), 3.67–3.70 (1H, m, H-5), 3.73 (1H, t, *J*=9.0 Hz, H-4), 3.80 (1H, dd, *J*=2.0 Hz, *J*=11.0 Hz, H_a-6), 3.87 (1H, dd, *J*=2.8 Hz, *J*=11.0 Hz, H_b-6), 4.03 (1H, t, *J*=8.9 Hz, H-3), 4.20 (1H, d, *J*=13.8 Hz, CCH_aH_bPh); ^{13}C NMR ($CDCl_3$): δ 22.4, 39.9, 68.5, 73.3, 73.6, 74.5, 75.2, 75.5, 77.6, 79.5, 83.3, 106.8, 168.9; HRMS (ESI) *m/z* calcd for $C_{43}H_{44}O_7\cdot Na^+$: 695.2985; found: 695.2944.

5.4. Glycosidation

5.4.1. Typical glycosidation procedure using 3a as the glycosyl donor. To a stirred solution of $TrtClO_4$ (4 mg, 0.015 mmol) and 3β-cholestanol (58 mg, 0.15 mmol) in benzene (2 mL) at room temperature was added **3a** (96 mg, 0.15 mmol) in the presence of powdered 4 Å molecular sieves (ca. 100 mg). The resulting mixture was stirred for 1 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL), and the reaction mixture was filtered. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **5a** as a white solid (112 mg, 80%).

5.4.2. Typical glycosidation procedure using 10a–d as the glycosyl donors. To a stirred solution of $Sc(OTf)_3$ (4.4 mg, 0.0089 mmol) and phenethyl alcohol (20.7 mg, 0.17 mmol) in toluene was added **10a** (101.2 mg, 0.17 mmol) at 0 °C in the presence of Drierite (ca. 100 mg). The resulting mixture was stirred for 1 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **12a** as a colorless oil (99.2 mg, 89%).

5.4.3. Typical glycosidation procedure using 2a–d as the glycosyl donors. To a stirred solution of Tf_2NH (2.8 mg, 0.01 mmol) and **11** (24 mg, 0.2 mmol) in acetonitrile was added **2a** (111 mg, 0.2 mmol) at 0 °C in the presence of Drierite (ca. 100 mg). The resulting mixture was stirred for 2 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane=1/4) to give **12a** as a colorless oil (102 mg, 77%).

5.4.4. 3β-Cholestanyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (5a). $[\alpha]_D^{23}$ +39.0 (*c* 2.6, $CHCl_3$); mp: 159–159.5 °C; ^1H NMR ($CDCl_3$): δ 0.89–1.97 (47H, m, 3β-cholestanyl), 1.34 (3H, s, CH_3), 3.27 (1H, d, *J*=9.7 Hz, H-2), 3.58 (1H, t, *J*=9.5 Hz, H-4), 3.63–3.73

(2H, m, H-6), 3.92–3.93 (1H, m, H-5), 4.06 (1H, t, J=9.2 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 12.1, 12.4, 18.7, 21.2, 22.6, 22.9, 23.9, 24.3, 28.1, 28.3, 28.8, 30.3, 32.1, 35.5, 35.5, 35.8, 36.2, 36.4, 37.3, 39.5, 40.1, 42.6, 45.4, 54.4, 56.3, 56.5, 69.0, 71.2, 71.5, 75.4, 75.4, 73.3, 78.9, 83.1, 84.8, 100.8; Anal. Calcd for $C_{62}H_{84}O_6$: C, 80.48; H, 9.15. Found: C, 80.38; H, 9.39.

5.4.5. *n*-Octyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (8a). Colorless oil; $[\alpha]_D^{23}$ +26.8 (c 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, J=6.9 Hz, $CH_2(CH_2)_6CH_3$), 1.27–1.30 (13H, m, CH_3, $CH_2CH_2(CH_2)_5CH_3$), 1.55–1.63 (2H, m, $CH_2CH_2(CH_2)_5CH_3$), 3.32 (1H, d, J=9.6 Hz, H-2), 3.41 (2H, dd, J=6.9 Hz, J=7.6 Hz, $CH_2(CH_2)_6CH_3$), 3.62 (1H, dd, J=8.6 Hz, J=9.6 Hz, H-4), 3.63–3.72 (3H, m, H-5, H-6), 4.08 (1H, dd, J=8.9 Hz, J=9.6 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 14.1, 21.0, 22.7, 26.3, 29.3, 29.4, 29.7, 31.8, 60.8, 68.9, 71.4, 78.8, 83.2, 84.1, 100.2; HRMS (ESI) m/z calcd for $C_{43}H_{54}O_6\cdot Na^+$: 689.3813; found: 689.3828.

5.4.6. 6-*O*-(2,3,4,6-Tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9a). Colorless oil; $[\alpha]_D^{23}$ −10.4 (c 3.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.31 (3H, s, $C(CH_3)_2$), 1.32 (3H, s, $C(CH_3)_2$), 1.37 (3H, s, CH_3), 1.42 (3H, s, $C(CH_3)_2$), 1.51 (3H, s, $C(CH_3)_2$), 3.34 (1H, d, J=9.6 Hz, H-2′), 3.60–3.75 (4H, m, H-6′, H-6), 3.68 (1H, t, J=9.0 Hz, H-4′), 3.94 (1H, m, H-5′), 4.01 (1H, t, J=5.5 Hz, H-5), 4.08 (1H, t, J=9.6 Hz, H-3′), 4.27 (1H, m, H-2), 4.30 (1H, dd, J=2.0 Hz, J=8.2 Hz, H-4), 4.57 (1H, t, J=11.0 Hz, H-3), 5.50 (1H, d, J=5.5 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 20.9, 24.4, 25.0, 26.0, 26.2, 60.4, 67.3, 68.7, 70.7, 70.8, 71.2, 71.2, 73.3, 74.2, 75.1, 75.3, 78.6, 82.7, 84.2, 96.2, 100.6, 108.5, 109.1; HRMS (ESI) m/z calcd for $C_{47}H_{56}O_{11}\cdot Na^+$: 819.3715; found: 819.3764. Its β-form: colorless oil; $[\alpha]_D^{23}$ +23.5 (c 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, s, $C(CH_3)_2$), 1.31 (3H, s, $C(CH_3)_2$), 1.42 (3H, s, $C(CH_3)_2$), 1.48 (3H, s, CH_3), 1.57 (3H, s, $C(CH_3)_2$), 3.53 (1H, m, H-5′), 3.58 (1H, d, J=8.8 Hz, H-2′), 3.62 (1H, dd, J=8.9 Hz, J=9.6 Hz, H-4′), 3.65–3.69 (3H, m, H-3′, H-6′), 3.84 (2H, m, H-6), 4.00 (1H, m, H-5), 4.23 (1H, dd, J=1.8 Hz, J=7.9 Hz, H-4), 4.29 (1H, dd, J=2.4 Hz, J=5.0 Hz, H-2), 4.53–4.58 (3H, m, H-3, OCH_2Ph), 5.45 (1H, d, J=5.0 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 17.0, 24.3, 25.0, 26.0, 26.1, 60.7, 67.5, 69.4, 70.7, 70.7, 71.3, 73.4, 78.2, 83.2, 83.9, 96.4, 102.3, 108.5, 109.1; HRMS (ESI) m/z calcd for $C_{47}H_{56}O_{11}\cdot Na^+$: 819.3715; found: 819.3739.

5.4.7. 6-*O*-(2,3,4,6-Tetra-*O*-benzyl-1-*C*-ethyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9b). Colorless oil; $[\alpha]_D^{23}$ +11.3 (c 1.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.81 (3H, t, J=7.6 Hz, CH_2CH_3), 1.31 (3H, s, $C(CH_3)_2$), 1.32 (3H, s, $C(CH_3)_2$), 1.42 (3H, s, $C(CH_3)_2$), 1.52 (3H, s, $C(CH_3)_2$), 1.79 (1H, m, $CH_aH_bCH_3$), 1.88 (1H, m, $CH_aH_bCH_3$), 3.52 (1H, d, J=9.6 Hz, H-2′), 3.61–3.67 (3H, m, H-4′, H_a-6′, H_a-6), 3.75–3.79 (2H, m, H_b-6′, H_b-6), 3.96 (1H, m, H-5′), 4.01 (1H, t, J=5.5 Hz, H-5), 4.15 (1H, t, J=9.6 Hz, H-3′), 4.27 (1H, dd, J=2.0 Hz, J=4.8 Hz, H-2), 4.31 (1H, dd, J=2.0 Hz, J=7.6 Hz, H-4), 4.57 (1H, dd, J=2.1 Hz, J=7.6 Hz, H-3), 5.50 (1H, d, J=5.5 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 8.1, 24.4, 25.0, 25.5, 26.0, 26.2, 60.0, 67.4, 68.9, 70.7, 70.8, 71.2, 71.5, 73.1, 74.2, 74.4, 75.3, 78.7, 79.8, 83.0, 96.2, 102.2, 108.5, 109.1; HRMS (ESI) m/z calcd for $C_{48}H_{58}O_{11}\cdot Na^+$: 833.3877; found: 833.3872.

5.4.8. 6-*O*-(2,3,4,6-Tetra-*O*-benzyl-1-*C*-*n*-butyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9c). Colorless oil; $[\alpha]_D^{23}$ −4.6 (c 6.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.80 (3H, t, J=7.6 Hz, $CH_2CH_2CH_2CH_3$), 1.05 (1H, m, $CH_2CH_aH_bCH_2CH_3$), 1.13 (1H, m, $CH_2CH_2CH_aH_bCH_3$), 1.21–1.26 (2H, m, $CH_2CH_aH_bCH_aH_bCH_3$), 1.32 (3H, s, $C(CH_3)_2$), 1.33 (3H, s, $C(CH_3)_2$), 1.43 (3H, s, $C(CH_3)_2$), 1.52 (3H, s, $C(CH_3)_2$), 1.73–1.80 (2H, m, $CH_2CH_2CH_2CH_3$), 3.51 (1H, d, J=8.9 Hz, H-2′), 3.61–3.66 (3H, m, H-4′, H_a-6′, H_a-6), 3.75–3.78 (2H, m, H_b-6′, H_b-6), 3.96 (1H, dd, J=2.1 Hz, J=9.6 Hz, H-5), 4.02 (1H, t, J=5.5 Hz, H-5′), 4.14 (1H, t, J=9.6 Hz, H-3′), 4.27 (1H, dd, J=2.1 Hz, J=4.9 Hz, H-2), 4.31 (1H, dd, J=2.1 Hz, J=7.6 Hz, H-4), 4.58 (1H, dd, J=2.0 Hz, J=7.5 Hz, H-3), 5.51 (1H, d, J=4.9 Hz, H-1): ^{13}C NMR ($CDCl_3$): δ 14.0, 23.0, 24.3, 25.0, 25.9, 26.0, 26.2, 32.6, 60.0, 67.5, 68.9, 70.7, 70.8, 71.2, 71.5, 73.0, 74.2, 74.5, 75.2, 78.7, 80.3, 83.1, 96.2, 102.0, 108.5, 109.1; HRMS (ESI) m/z calcd for $C_{50}H_{62}O_{11}\cdot Na^+$: 861.4184; found: 861.4200.

5.4.9. 6-*O*-(1-*C*-Benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9d). Colorless oil; $[\alpha]_{465}^{23}$ +30.4 (c 1.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.34 (3H, s, $C(CH_3)_2$), 1.37 (3H, s, $C(CH_3)_2$), 1.46 (3H, s, $C(CH_3)_2$), 1.55 (3H, s, $C(CH_3)_2$), 3.09 (1H, d, J=13.8 Hz, CCH_aH_bPh), 3.25 (1H, d, J=9.1 Hz, H-2′), 3.27 (1H, d, J=14.4 Hz, CCH_aH_bPh), 3.57 (1H, t, J=9.6 Hz, H-4′), 3.75–3.79 (2H, m, H_a-6′, H_a-6), 3.84 (1H, dd, J=3.4 Hz, J=9.8 Hz, H_b-6′), 3.92–3.96 (2H, m, H-5′, H_b-6), 4.06 (1H, m, H-5), 4.13 (1H, t, J=9.6 Hz, H-3′), 4.31 (1H, dd, J=2.7 Hz, J=5.5 Hz, H-2), 4.40 (1H, dd, J=2.1 Hz, J=8.7 Hz, H-4), 4.59–4.64 (3H, m, H-3, OCH_2Ph), 5.55 (1H, d, J=5.5 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 24.4, 25.0, 26.0, 26.2, 39.5, 59.8, 67.2, 69.0, 70.7, 70.9, 71.1, 71.9, 73.1, 73.7, 74.5, 75.3, 78.6, 79.8, 83.2, 96.3, 102.5, 108.6, 109.1; HRMS (ESI) m/z calcd for $C_{53}H_{60}O_{11}\cdot Na^+$: 895.4028; found: 895.3995.

5.4.10. Phenethyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (12a). Colorless oil; $[\alpha]_D^{23}$ +45.5 (c 2.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, s, CH_3), 2.93 (2H, m, OCH_2CH_2Ph), 3.31 (1H, d, J=9.5 Hz, H-2), 3.36 (1H, m, H-5), 3.52–3.59 (3H, m, H-6, H-4), 3.61–3.66 (2H, m, OCH_2CH_2Ph), 4.07 (1H, t, J=9.3 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 21.0, 36.3, 62.0, 68.8, 71.4, 73.3, 74.7, 75.4, 75.5, 78.6, 83.0, 83.9, 100.3; HRMS (ESI) m/z calcd for $C_{43}H_{46}O_6\cdot Na^+$: 681.3192; found: 681.3197. Its β-form: colorless oil; $[\alpha]_D^{23}$ +21.4 (c 0.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, s, CH_3), 2.91 (2H, t, J=6.9 Hz, OCH_2CH_2Ph), 3.52–3.54 (1H, m, H-5), 3.55 (1H, d, J=8.9 Hz, H-2), 3.62 (1H, t, J=8.9 Hz, H-4), 3.65 (1H, t, J=8.9 Hz, H-3), 3.69 (2H, d, J=2.7 Hz, H-6), 3.86 (2H, m, OCH_2CH_2Ph); ^{13}C NMR ($CDCl_3$): δ 17.0, 36.7, 62.1, 69.4, 73.4, 73.4, 74.2, 75.0, 75.5, 78.2, 83.3, 83.9, 102.0; HRMS (ESI) m/z calcd for $C_{43}H_{46}O_6\cdot Na^+$: 681.3192; found: 681.3175.

5.4.11. Phenethyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-ethyl-α-D-glucopyranoside (12b). Colorless oil; $[\alpha]_D^{23}$ +54.0 (c 3.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.73 (3H, t, J=7.6 Hz,

CH_2CH_3), 1.75 (1H, m, $CH_aH_bCH_3$), 1.81 (1H, m, $CH_aH_bCH_3$), 2.92 (2H, m, OCH_2CH_2Ph), 3.41 (1H, dd, J=2.8 Hz, J=10.3 Hz, H-5), 3.50 (1H, d, J=9.7 Hz, H-2), 3.51–3.70 (4H, m, H-6, OCH_2CH_2Ph), 3.54 (1H, t, J=9.7 Hz, H-4), 4.12 (1H, t, J=9.6 Hz, H-3): ^{13}C NMR ($CDCl_3$): δ 8.1, 25.5, 36.5, 61.5, 68.9, 71.7, 73.2, 74.7, 74.7, 75.4, 78.8, 79.6, 83.3, 102.0; HRMS (ESI) m/z calcd for $C_{44}H_{48}O_6\cdot Na^+$: 695.3343; found: 695.3346.

5.4.12. Phenethyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-*n*-butyl-α-D-glucopyranoside (12c). Colorless oil; $[\alpha]_D^{23}$ +38.2 (c 1.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.76 (3H, t, J=6.8 Hz, $CH_2CH_2CH_2CH_3$), 0.91 (1H, m, $CH_2CH_aH_bCH_2CH_3$), 1.05 (1H, m, $CH_2CH_2CH_aH_bCH_3$), 1.15 (1H, m, $CH_2CH_2CH_aH_bCH_3$), 1.26 (1H, m, $CH_2CH_aH_bCH_2CH_3$), 1.69 (2H, t, J=8.2 Hz, $CH_2CH_2CH_aH_bCH_3$), 2.94 (2H, m, OCH_2CH_2Ph), 3.41 (1H, dd, J=3.4 Hz, J=10.3 Hz, H-5), 3.48 (1H, d, J=9.6 Hz, H-2), 3.53 (1H, t, J=9.6 Hz, H-4), 3.56 (1H, m, H_a-6), 3.60–3.63 (2H, m, H_b-6, $OCH_aH_bCH_2Ph$), 3.67–3.70 (1H, m, $OCH_aH_bCH_2Ph$), 4.11 (1H, t, J=9.6 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 14.0, 23.0, 25.9, 32.7, 36.5, 61.5, 69.0, 71.7, 73.2, 74.8, 74.8, 75.4, 78.8, 80.0, 83.5, 101.8; HRMS (ESI) m/z calcd for $C_{46}H_{52}O_6\cdot Na^+$: 723.3656; found: 723.3648.

5.4.13. Phenethyl 1-*C*-benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (12d). Colorless oil; $[\alpha]_D^{23}$ +48.6 (c 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.96 (1H, m, $OCH_2CH_aH_bPh$), 3.01 (1H, m, $OCH_2CH_aH_bPh$), 3.03 (1H, d, J=3.7 Hz, CCH_aH_bPh), 3.23 (1H, d, J=9.6 Hz, H-2), 3.27 (1H, d, J=3.7 Hz, CCH_aH_bPh), 3.47 (1H, t, J=9.6 Hz, H-4), 3.49 (1H, m, H-5), 3.66 (1H, d, J=11.0 Hz, H_a-6), 3.69 (1H, dd, J=3.4 Hz, J=10.3 Hz, H_b-6), 3.82–3.86 (2H, m, OCH_2CH_2Ph), 4.11 (1H, t, J=9.7 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 36.6, 39.7, 61.7, 69.1, 71.9, 73.2, 74.0, 74.8, 75.8, 78.6, 79.9, 83.4, 102.4; HRMS (ESI) m/z calcd for $C_{49}H_{50}O_6\cdot Na^+$: 757.3500; found: 757.3549.

5.4.14. Phenyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (14a). Colorless oil; $[\alpha]_D^{23}$ +70.0 (c 4.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, s, CH_3), 3.36 (1H, d, J=9.6 Hz, H-2), 3.63 (1H, t, J=9.6 Hz, H-4), 3.66–3.70 (2H, m, H-6), 4.02–4.04 (1H, m, H-5), 4.16 (1H, t, J= 9.0 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 21.1, 69.1, 71.9, 73.4, 74.8, 75.6, 75.6, 78.6, 83.1, 84.2, 103.3; HRMS (ESI) m/z calcd for $C_{41}H_{42}O_6\cdot K^+$: 669.2613; found: 669.2661.

5.4.15. Methyl 6-*O*-(1-*C*-benzyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17d). Colorless oil; $[\alpha]_D^{23}$ +50.0 (c 3.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.95 (1H, d, J=14.4 Hz, CCH_aH_bPh), 3.14 (1H, d, J=13.7 Hz, CCH_aH_bPh), 3.19 (1H, d, J=9.6 Hz, H-2′), 3.33 (1H, dd, J=8.9 Hz, J=9.6 Hz, H-3), 3.36 (3H, s, OMe), 3.47 (1H, t, J=9.6 Hz, H-4′), 3.46–3.52 (2H, m, H-2, H_a-6), 3.63 (1H, d, J=11.0 Hz, H_a-6′), 3.69 (1H, dd, J=3.4 Hz, J=11.0 Hz, H_b-6′), 3.86–3.90 (3H, m, H-5, H-5′, H_b-6), 3.98 (1H, t, J=8.9 Hz, H-4), 4.05 (1H, dd, J=8.9 Hz, J=9.6 Hz, H-3′), 4.56–4.59 (2H, m, H-1, OCH_aH_bPh); ^{13}C NMR ($CDCl_3$): δ 39.7, 55.0, 60.6, 69.1, 70.3, 71.8, 78.6, 78.7, 79.8, 80.2, 82.3, 83.4, 97.6, 102.4; HRMS (ESI) m/z calcd for $C_{69}H_{72}O_{11}\cdot Na^+$: 1099.4967; found: 1099.5003.

5.4.16. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranoside (18a). Colorless oil; $[\alpha]_D^{23}$ +70.0 (c 2.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.49 (3H, s, CH_3), 3.29 (1H, d, J=9.6 Hz, H-2′), 3.33–3.39 (3H, m, H_a-6, H_b-6, H_a-6′), 3.55–3.58 (1H, m, H_b-6′), 3.56 (1H, dd, J=3.4 Hz, J=10.3 Hz, H-2′), 3.64 (1H, dd, J=9.6 Hz, J=10.3 Hz, H-4), 3.68 (1H, t, J=9.6 Hz, H-4′), 4.03 (1H, t, J=10.3 Hz, H-3), 4.05 (1H, t, J=9.6 Hz, H-3′), 4.17–4.19 (1H, m, H-5′), 4.27–4.28 (1H, m, H-5), 5.34 (1H, d, J=3.4 Hz, H-1′); ^{13}C NMR ($CDCl_3$): δ 22.7, 68.3, 68.5, 70.0, 71.0, 78.0, 78.6, 80.1, 81.8, 82.7, 85.1, 90.2, 101.0; HRMS (ESI) m/z calcd for $C_{69}H_{72}O_{11}\cdot Na^+$: 1099.4967; found: 1099.5006.

References and notes

1. Brockhaus, M.; Lehmann, J. *Carbohydr. Res.* **1977**, *53*, 21–31.
2. Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Synlett* **2001**, 1885–1888.
3. For examples of chemical glycosidation, see: (a) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283–4295; (b) Lin, H.-C.; Yang, W.-B.; Gu, Y.-F.; Chen, C.-Y.; Wu, C.-Y.; Lin, C.-H. *Org. Lett.* **2003**, *5*, 1087–1089; (c) Chang, C.-F.; Yang, W.-B.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2002**, *43*, 6515–6519; (d) Lin, H.-C.; Du, W.-P.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2005**, *46*, 5071–5076; For enzymatic glycosidation, see: (e) Schlesselmann, P.; Fritz, H.; Lehmann, J.; Uchiyama, T.; Brewer, C. F.; Hehre, E. J. *Biochemistry* **1982**, *21*, 6606–6614.
4. For example, see: (a) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610–612; (b) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752–753.
5. (a) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4297–4309; (b) As the analogs of the 1-*C*-alkyl-hexopyranose derivatives, the glycosidation using the 1-*C*-alkoxyalkyl-hexopyranose derivatives was reported. See: Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 5657–5670; (c) As the 1-*C*-alkyl-hexofuranose derivative, the glycosidation using 2,3:5,6-di-*O*-isopropylidene-1-*C*-methyl-D-mannofuranosyl acetate was reported. See: Dondoni, A.; Marra, A.; Rojo, I.; Scherrmann, M.-C. *Tetrahedron* **1996**, *52*, 3057–3074.
6. (a) Inazu, T.; Yamanoi, T. *Chem. Lett.* **1989**, 69–72; (b) Yamanoi, T.; Inazu, T. *Chem. Lett.* **1990**, 849–852; (c) Yamanoi, T.; Nakamura, K.; Takeyama, H.; Yanagihara, K.; Inazu, T. *Chem. Lett.* **1993**, 343–346; (d) Yamanoi, T.; Nakamura, K.; Sada, S.; Goto, M.; Furusawa, Y.; Takano, M.; Fujioka, A.; Yanagihara, K.; Satoh, Y.; Hosokawa, H.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2617–2622; (e) Yamanoi, T.; Nakamura, K.; Takeyama, H.; Yanagihara, K.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1359–1366; (f) Yamanoi, T.; Fujioka, A.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1488–1491.
7. (a) Yamanoi, T.; Iwai, Y.; Inazu, T. *J. Carbohydr. Chem.* **1998**, *17*, 819–822; (b) Yamanoi, T.; Iwai, Y.; Inazu, T. *Heterocycles* **2000**, *53*, 1263–1267; (c) Yamanoi, T.; Yamazaki, I. *Tetrahedron Lett.* **2001**, *42*, 4009–4011.
8. Yamanoi, T.; Oda, Y.; Yamazaki, I.; Shinbara, M.; Morimoto, K.; Matsuda, S. *Lett. Org. Chem.* **2005**, *2*, 242–246.

9. (a) Yamanoi, T.; Matsuda, S.; Yamazaki, I.; Inoue, R.; Hamasaki, K.; Watanabe, M. *Heterocycles* **2006**, *68*, 673–677; (b) We also reported the Brønsted acid-catalyzed intramolecular β-glycosidation of 1-*C*-alkyl-D-hexopyranoses to form the anhydroketopyranoses; Yamanoi, T.; Matsumura, K.; Matsuda, S.; Oda, Y. *Synlett* **2005**, 2973–2977.
10. Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531–2534.
11. Inazu, T.; Yamanoi, T. Jpn. Kokai Tokkyo Koho, JP 02240093, 1990.
12. 2,3,4,6-Tetra-*O*-benzyl-1-*C*-methyl-α-D-glucopyranosyl acetate has also been synthesized from **1** by a multistep reaction sequence; Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3642–3650.
13. It was reported that the acetylation of a ketopyranose derivative with DMAP/Ac_2O gave the open ring compound; Heskamp, B. M.; Noort, D.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1992**, 713–715.
14. Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Tetrahedron Lett.* **1993**, *34*, 2791–2794.