

HETEROCYCLES, Vol. 79, 2009, pp. 163 - 194. © The Japan Institute of Heterocyclic Chemistry
Received, 30th September, 2008, Accepted, 8th December, 2008, Published online, 12th December, 2008.
DOI: 10.3987/REV-08-SR(D)4

REACTIONS AND USES OF ARTIFICIAL KETOSES[#]

Takashi Yamanoi* and Sho Matsuda

The Noguchi Institute, 1-8-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan

E-mail: tyama@noguchi.or.jp

Abstract – Some artificial ketoses having a naturally occurring aldose backbone can be readily prepared by the addition of RLi or RMgX to aldonolactone derivatives. They are expected to be a novel class of carbohydrate reagents for synthesizing valuable compounds. In order to utilize these ketoses completely, we must elucidate the reaction characteristics influenced by the ketose's specific structures. In particular, it is important to understand the reaction specificities of the nucleophilic substitutions at the anomeric carbons of these ketoses to produce various ketosides. This review describes the nucleophilic reactions to form the ketosidic linkages from the artificial ketoses, focusing mainly on our recent research results.

1. INTRODUCTION

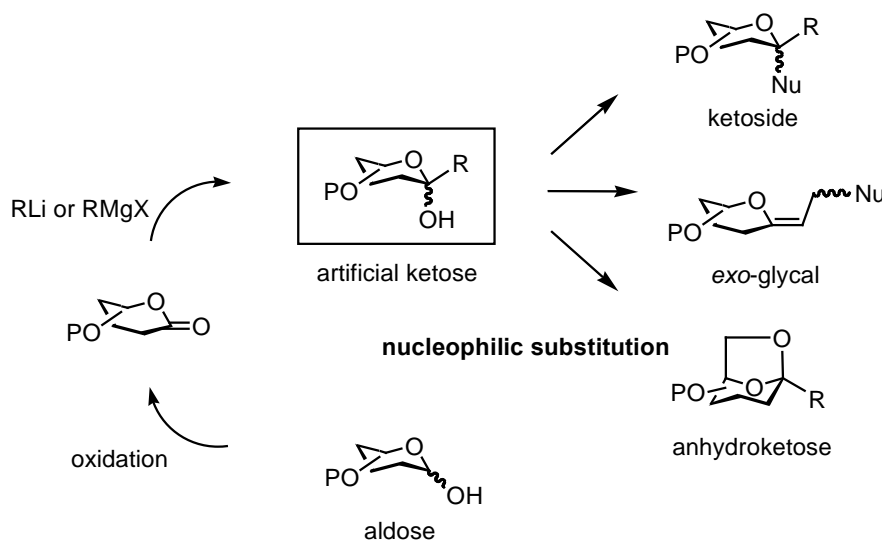
Carbohydrates play important roles in biological processes.¹ They are also chemically useful materials.² Non-natural carbohydrates derived by chemical modifications of natural carbohydrates are frequently utilized as reagents for preparing valuable compounds in synthetic organic chemistry.³

The addition reactions of RLi (or RMgX) to sugarlactone derivatives produced by oxidation of aldoses can readily produce various artificial ketoses whose anomeric carbons are bound to alkyl, alkynyl, alkene, aryl or other groups via a carbon–carbon linkage.⁴ The ketoses prepared by this method from naturally occurring aldoses possess the ring structures of the starting aldoses. Such ketoses, regarded as aldose analogues, are often used as precursors for preparing *C*-glycosides by reduction procedures.⁴ Recent studies show that some useful compounds, such as enzyme inhibitors,⁵ oligosaccharide mimics⁶ and spiroketals⁷ were prepared from these ketoses. These compounds are expected to form a new class of carbohydrate reagents useful for synthesizing more valuable and complicated compounds.

In order to utilize these ketoses completely, we must elucidate the reaction characteristics influenced by the ketose's specific structures. In particular, it is important to understand the specificities of the reactions to produce various ketosides from these ketoses by nucleophilic substitutions at the anomeric carbons of the ketoses. Since their anomeric carbon atoms are bound directly to functional groups, steric and electron effects of the functional groups easily influence the anomeric carbons. These factors make the reaction behaviour of the nucleophilic substitutions at the anomeric carbons of these ketoses remarkably different from those of aldoses.

We have devoted our considerable effort to investigating nucleophilic reactions at the anomeric carbons of artificial ketoses having a naturally occurring aldohexopyranose backbone.⁸ As a result, we successfully elucidated their nucleophilic reaction specificities and developed efficient synthetic methods for several types of ketopyranosides. In addition, as shown in Scheme 1, the findings from these studies contributed to the development of novel synthetic approaches for valuable carbohydrate compounds such as *exo*-glycals,⁹ trehalose mimics¹⁰ and anhydroketopyranoses¹¹ from these ketoses.

This paper summarizes our recent studies on nucleophilic substitutions to form ketopyranosidic linkages from artificial ketoses with a naturally occurring aldohexopyranose backbone as well as reviews the reports from other research groups.



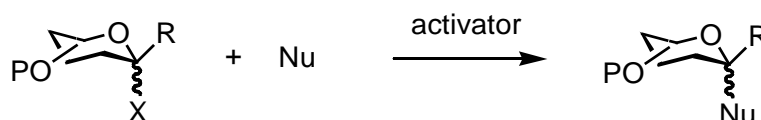
Scheme 1

(Nomenclature in this review)

For convenience, the artificial ketoses are defined as follows for easy understanding of the ketose's ring conformation. The general ketose with a naturally occurring aldohexopyranose backbone is named as '1-*C*-modified hexopyranose'. For example, the ketose with a methyl group at the anomeric carbon and a D-glucopyranose backbone is named as '1-*C*-methyl-D-glucopyranose'. The location number of the anomeric carbon atoms of these ketoses is defined in the same manner as that of the aldose.

2. FORMATION OF THE KETOPYRANOSIDIC LINKAGES FROM 1-C-MODIFIED HEXOPYRANOSSES

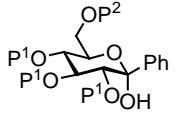
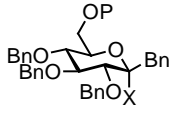
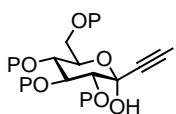
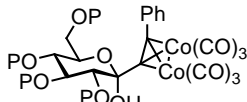
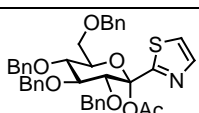
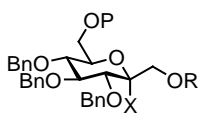
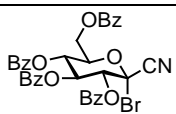
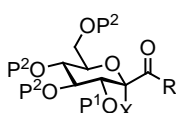
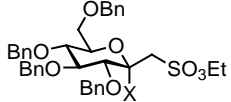
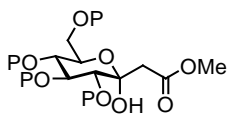
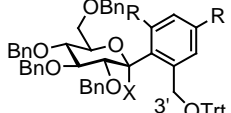
In this section, we summarize published reports on the formation reactions of ketopyranosidic linkages from 1-*C*-modified hexopyranoses, as shown in Scheme 2. Table 1 lists the ketose structures, nucleophiles and activators used, in addition to the reference numbers.

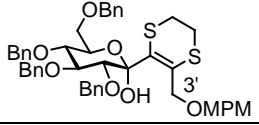
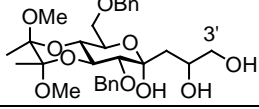
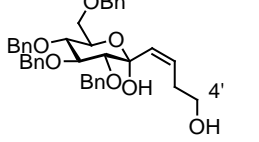
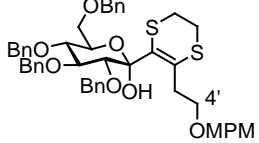
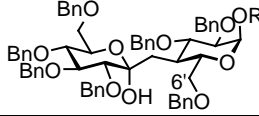
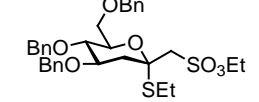
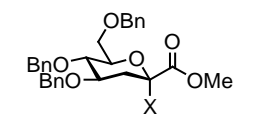
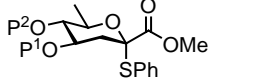
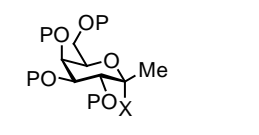
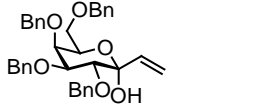
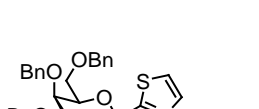
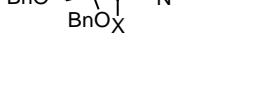
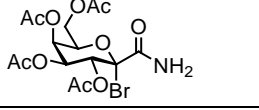
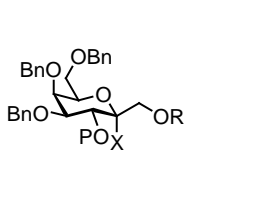


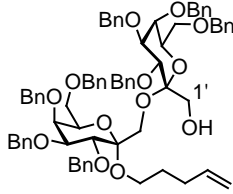
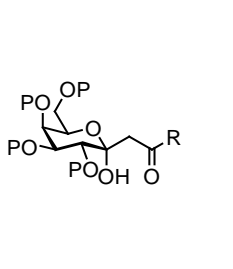
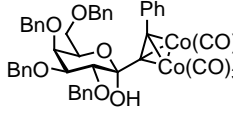
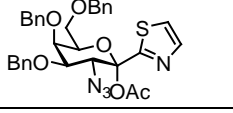
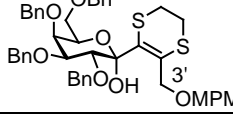
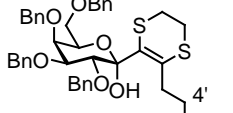
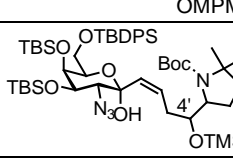
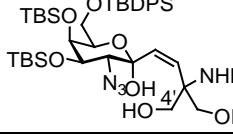
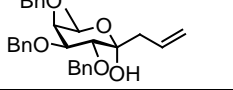
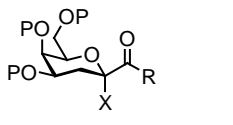
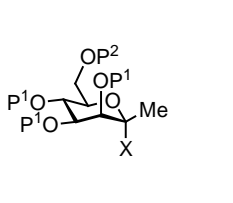
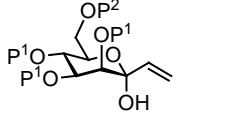
Scheme 2

Table 1. Formation of ketopyranosidic linkages from 1-*C*-modified hexopyranoses

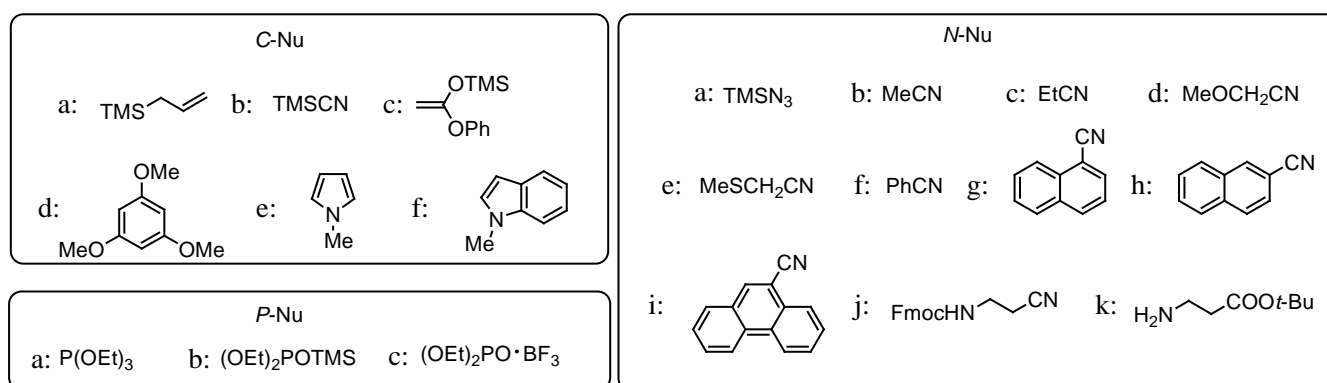
Ketopyranose	Nucleophile	Activator	Reference	
 X= OH, P ¹ = P ² = Bn X= OMe, P ¹ = P ² = Bn X= OMe, P ¹ = P ² = Ac X= OAc, P ¹ = P ² = Bn X= OMpt, P ¹ = P ² = Bn X= OH, P ¹ = Bn, P ² = H X= OH, P ¹ = Bn, P ² = TBS X= SEt, P ¹ = P ² = Bn	ROH	TMSOTf	12	
	ROH	Tf ₂ NH	8b,c,10	
	ROH	Bi(OTf) ₃	10	
	<i>C</i> -Nu _a	TMSOTf	8f	
	<i>C</i> -Nu _{a-c} , <i>N</i> -Nu _a	TMSOTf	8a	
	<i>C</i> -Nu _{a-c} , <i>N</i> -Nu _a	BF ₃ ·OEt ₂	13	
	ROH	Cl ₂ SO	14	
	ROH	SnCl ₄	12	
	ROH	SnCl ₄	12	
	ROH	TMSOTf	15	
 X= OAc X= OH	ROH	Sc(OTf) ₃	8b,e	
	<i>C</i> -Nu _a	TMSOTf	8f	
	<i>C</i> -Nu _{a-c} , <i>N</i> -Nu _a	TMSOTf	8a	
	 P= Bn P= TBS	ROH	TMSOTf	12
		ROH	K-10	7b,17,18,19
		ROH	BF ₃ ·OEt ₂	20
 X= OH, P= Bn X= OTMS, P= Bn X= OH, P= TBS X= OH, P= H	ROH	Bi(OTf) ₃	21	
	ROH	K-10	22,23	
	ROH (<i>C</i> -6)	TfOH	11a	
	ROH	TfOH	8d	
 X= OH, P= Bn X= OAc, P= Bn X= OH, P= H	<i>C</i> -Nu _a	TMSOTf	8f	
	<i>C</i> -Nu _{a-c} , <i>N</i> -Nu _a	TMSOTf	8a	
	ROH	Sc(OTf) ₃	8b,e	
	ROH (<i>C</i> -6)	TfOH	8d	

Ketopyranose	Nucleophile	Activator	Reference
 <p>P¹ = P² = Bn P¹ = P² = Me P¹ = Bn, P² = H</p>	<p>C-Nu_{a,c}, N-Nu_a C-Nu_{a,c} ROH (C-6)</p>	<p>TMSOTf BF₃·OEt₂ TfOH</p>	<p>8a 13 8d</p>
 <p>X = OH, P = Bn X = OAc, P = Bn X = OH, P = H</p>	<p>C-Nu_a ROH C-Nu_{a,c}, N-Nu_a ROH ROH (C-6)</p>	<p>TMSOTf Tf₂NH TMSOTf Sc(OTf)₃ TfOH</p>	<p>8f 8b,c 8a 8b,e 8d</p>
 <p>R = Ph, P = Bn R = Ph, P = Me R = TMS, P = Bn R = P = Me R = H, P = Me R = Me, P = Bn</p>	<p>C-Nu_{a,c,d} C-Nu_{a-d}, N-Nu_a R'OH R'OH R'OH R'OH</p>	<p>BF₃·OEt₂ BF₃·OEt₂ SnCl₄-AgClO₄ K-10 K-10 K-10 TMSOTf</p>	<p>13,24 13,24 25 7a 7a 7a 26</p>
 <p>P = Me P = Bn</p>	<p>C-Nu_{a,b,d}, N-Nu_a C-Nu_{a,e,g}</p>	<p>BF₃·OEt₂ BF₃·OEt₂</p>	<p>27 27</p>
	<p>ROH P-Nu_a</p>	<p>TMSOTf TMSOTf</p>	<p>28 29</p>
 <p>X = F, R = CH₂CPh₃, P = TBDPS X = OEt, R = H, P = Bn X = Br, R = Ac, P = Bn X = F, R = P = Bn X = OH, R = H, P = Bn</p>	<p>R'OH R'OH R'OH R'OH R'OH R'OH R'OH N-Nu_{b-e} R'OH</p>	<p>SnCl₂-AgClO₄ TMSOTf Hg(CN)₂ Cp₂ZrCl₂-AgBF₄ TfOH TsOH-TfONa BF₃·OEt₂ BF₃·OEt₂</p>	<p>30 31 32 32 7c 7c 33 33</p>
	<p>NaN₃</p>		<p>34</p>
 <p>X = Cl, R = OMe, P¹ = TBS, P² = Bn X = Br, R = NH₂, P¹ = P² = Ac</p>	<p>R'OH (Me)₂CO DMSO</p>	<p>MgBr₂ Ag₂CO₃ AgF</p>	<p>35 36 36</p>
 <p>X = SEt X = OH</p>	<p>ROH N-Nu_a</p>	<p>NIS-TfOH BF₃·OEt₂</p>	<p>16,37-39 16</p>
 <p>P = Bn P = Me</p>	<p>C-Nu_b ROH N-Nu_{b,f} C-Nu_b</p>	<p>TMSOTf BF₃·OEt₂ TMSOTf TMSOTf</p>	<p>40 40 41,42 40</p>
 <p>R = H R = OMe</p>	<p>R'OTrt (C-3') R'OTrt (C-3')</p>	<p>BF₃·OEt₂-Et₃SiH BF₃·OEt₂-Et₃SiH</p>	<p>7d,43 7d</p>

Ketopyranose	Nucleophile	Activator	Reference
	ROMPM (<i>C</i> -3')	BF ₃ ·OEt ₂	44
	ROH (<i>C</i> -3')	HOAc	45
	ROH (<i>C</i> -3')	CSA	45
	ROH (<i>C</i> -4')	CSA	7e
	ROMPM (<i>C</i> -4')	BF ₃ ·OEt ₂	46
	R= Me R= Bn	R'OBn (<i>C</i> -6')	BF ₃ ·OEt ₂ BF ₃ ·OEt ₂
	ROH	NIS-TfOH	16
	X= SPh X= Cl	ROH ROH ROH ROH	NBS Hg(OAc) ₂ HgCl ₂ Ag ₂ SO ₄
	P ¹ = TBS, P ² = Bn P ¹ = P ² = Bn	ROH ROH	HgCl ₂ AgOTf
	X= OH, P= Bn X= OMe, P= Bn X= OMe, P= Ac X= OAc, P= Bn	ROH ROH ROH ROH	TMSOTf SnCl ₄ SnCl ₄ TMSOTf
	ROH ROH	TMSOTf BF ₃ ·OEt ₂	12 52
	X= OAc X= OP(OEt) ₂	ROH P-Nu _a N-Nu _a ROH P-Nu _{b,c} P-Nu _{b,c}	TMSOTf TMSOTf TMSOTf BF ₃ ·OEt ₂ TMSOTf BF ₃ ·OEt ₂
	(Me) ₂ CO DMSO	Ag ₂ CO ₃ AgF	36 36
	X= F, R= P= Bn X= SEt, R= P= Bn X= F, R= MOM, P= Bz X= F, R= MOM, P= Bn X= OH, R= H, P= Bn	R'OH R'OH R'OH R'OH R'OH R'OH	BF ₃ ·OEt ₂ IDCP Cp ₂ ZrCl ₂ -AgOTf Cp ₂ ZrCl ₂ -AgOTf TfOH TsOH-TfONa

Ketopyranose	Nucleophile	Activator	Reference
	ROH (C-1')	NIS-TMSOTf	31
	R= OH, P= Bn R= OMe, P= Bn R= OMe, P= Me R= OBn, P= Bn	N-Nu _f N-Nu _{f-i} N-Nu _{b,f,j,k} N-Nu _{b,f} C-Nu _b R'OH C-Nu _b C-Nu _b	TMSOTf TMSOTf TMSOTf TMSOTf TMSOTf BF ₃ ·OEt ₂ TMSOTf TMSOTf
	C-Nu _{a,e,f}	BF ₃ ·OEt ₂	27
	P-Nu _a	TMSOTf	29
	ROMPM (C-3')	BF ₃ ·OEt ₂	44
	ROMPM (C-4')	BF ₃ ·OEt ₂	46
	ROTMS (C-4')	CSA	60
	R= H R= DMB	R'OH (C-4') R'OH (C-4')	CSA CSA
	ROH	K-10	7b
	X= OH, R= OH, P= H X= SPh, R= OMe, P= TBS	R'OH R'OH R'OH R'OH	Dowex 50W(H ⁺) NBS HgCl ₂ Hg(OAc) ₂
	X= OH, P ¹ = P ² = Bn X= OMe, P ¹ = P ² = Bn X= OMe, P ¹ = P ² = Ac X= OAc, P ¹ = P ² = Bn X= OH, P ¹ = Bn, P ² = H	ROH ROH ROH ROH ROH ROH (C-6)	Bi(OTf) ₃ TMSOTf SnCl ₄ SnCl ₄ TMSOTf TfOH
	P ¹ = P ² = Bn P ¹ = Bn, P ² = TBS	ROH ROTBS (C-6)	TMSOTf TfOH

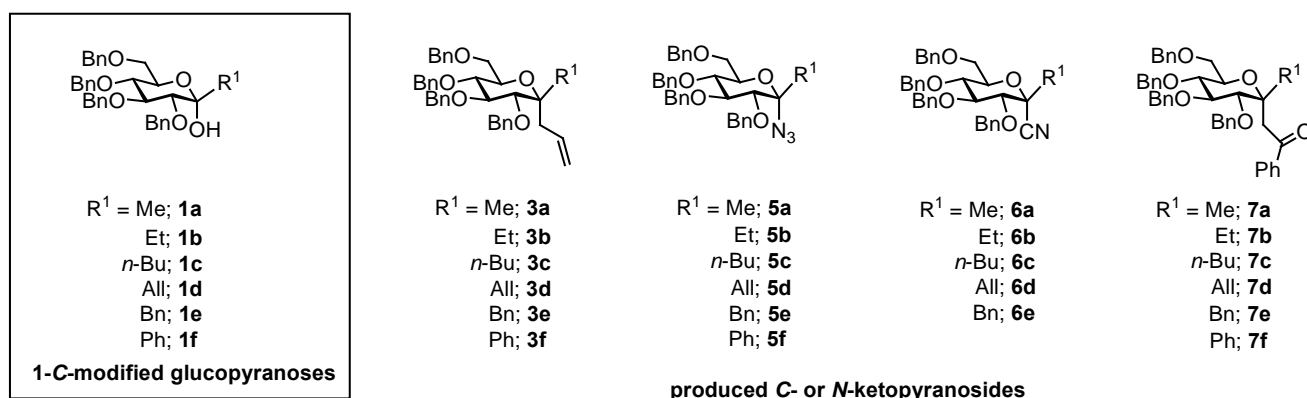
Ketopyranose	Nucleophile	Activator	Reference
	ROH (C-6)	TfOH	11a
	P= Bn	TfOH	7c
	ROH	TsOH-TfONa	7c
	P= H	HCl	65
	P= Me	AgOTf-pyridine	66
	P= Bn	AgOTf-pyridine	66
	P= CH ₂ CH=CH ₂	AgOTf-pyridine	66
	ROH	AgOTf-DBMP	66
	ROMPM (C-3')	BF ₃ ·OEt ₂	44
	ROMPM (C-4')	BF ₃ ·OEt ₂	46
	ROH	K-10	7b
	ROTBS (C-6)	TfOH	11a,b
	ROTBS (C-6)	TfOH	11a
	X= OH	BF ₃ ·OEt ₂	56
	X= SEt	IDCP (IDCT)	56
	ROH	NIS	67
	ROH	NIS	67
	R= TBDPS	IDCP (IDCT)	56
	R= SEM	IDCP (IDCT)	56
	N-Nu _f	TMSOTf	41,42
	ROH	NIS-TfOH	38



3. NUCLEOPHILIC SUBSTITUTIONS AT THE ANOMERIC CARBONS OF 1-C-MODIFIED HEXOPYRANOSE AND THEIR APPLICATIONS TO USEFUL COMPOUNDS

We have investigated nucleophilic reactions at the anomeric carbons of 1-*C*-modified hexopyranoses with various types of nucleophiles. As a result, the nucleophilic reaction specificities and development of efficient synthetic methods for various types of ketopyranosides were clarified.⁸ In addition, we succeeded in developing novel synthetic approaches to valuable carbohydrate compounds such as *exo*-glycals,⁹ trehalose mimics¹⁰ and anhydroketopyranoses¹¹ from the 1-*C*-modified hexopyranoses. This section describes these results.

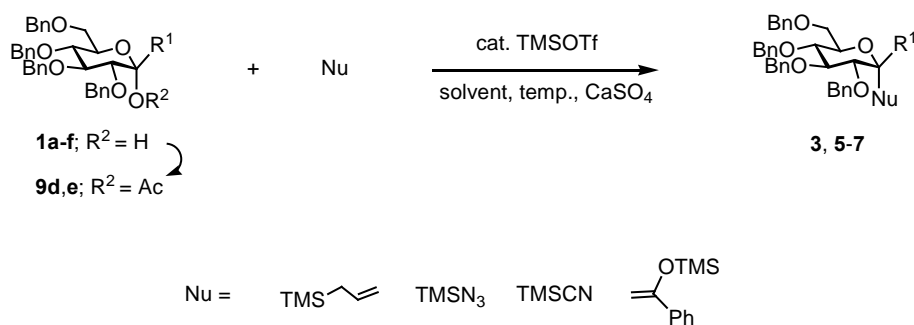
3.1 Formation of *C*- and *N*-ketopyranosidic linkages from 1-*C*-modified D-glucopyranose



Scheme 3

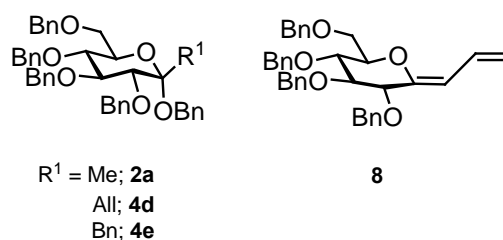
In this section, we describe the *C*- and *N*-ketosidations of the 1-*C*-modified D-glucopyranose derivatives with several nucleophiles.^{8a,8f} Scheme 3 shows the utilized glucopyranose derivatives (**1a–f**) carrying the methyl, ethyl, *n*-butyl, allyl, benzyl and phenyl groups at the anomeric carbon centres as well as the ketopyranosides synthesized in the study. We used allyltrimethylsilane, trimethylsilyl azide (TMSN₃), trimethylsilyl cyanide (TMSCN) and 1-phenyl-1-(trimethylsilyloxy)ethylene as the nucleophiles.

We first investigated *C*-allylation of **1a** with allyltrimethylsilane in the presence of TMSOTf as the activator, as shown in Scheme 4. Although the reaction gave the desired *C*-allylated glucopyranoside **3a**, the benzyl 1-*C*-methylated *O*-glucopyranoside **2a** was also obtained as a major by-product. This was attributable to the benzyl alcohol produced with the degradation of **1a** under the given reaction conditions. It acted as a glycosyl acceptor of **1a** and afforded **2a**. Then, we modified the reaction conditions such as the solvents, reaction temperatures and amounts of reagents. The reaction conditions using 3 equiv. of allyltrimethylsilane in MeCN at $-40\text{ }^{\circ}\text{C}$ in the presence of 20 mol% TMSOTf and the drying agent, CaSO_4 , successfully increased the yield of **3a** up to 88% with almost no production of **2a**. The reaction conditions were also effective for the *C*-allylation of **1b**, **1c** and **1f** having an ethyl, an *n*-butyl or a phenyl group to afford the *C*-allylated glucopyranosides **3b**, **3c** and **3f**, respectively, in the good yields of 88-95%. Under the given reaction conditions, however, *C*-allylation using **1d** and **1e** yielded the desired products **3d** and **3e** in only 31% and 18%. The reactions using **1d** and **1e** still produced the benzyl *O*-glucopyranosides **4d** and **4e**, as shown in Scheme 5, as the major by-products in ca. 20% yields, respectively. Apparently, the electronic or steric effect of the functional groups at the anomeric centers of **1d** and **1e** influenced the leaving ability of the hemiacetal hydroxy group and thereby the productions of **4d** and **4e**.



Scheme 4

All the reactions of **1a–c** and **1f** with TMSN_3 , TMSCN and 1-phenyl-1-(trimethylsilyloxy)ethylene under the stated reaction conditions successfully produced the desired glucopyranosides **5a–c** and **5f**, **6a–c**, and **7a–c** and **7f** in the high yields of 78-99%. In contrast, the yields obtained by ketosidation using **1d** and **1e** depended on the species of the nucleophiles. The reactions using TMSN_3 afforded **5d** and **5e** both in 80% yield. The reactions using TMSCN gave **6d** and **7d** and those using 1-phenyl-1-(trimethylsilyloxy)ethylene gave **6e** and **7e** in moderate yields of 53–73%. The yields of the *C*- and *N*-ketosidations using **1d** and **1e** were lower than those using **1a–c** and **1f**.

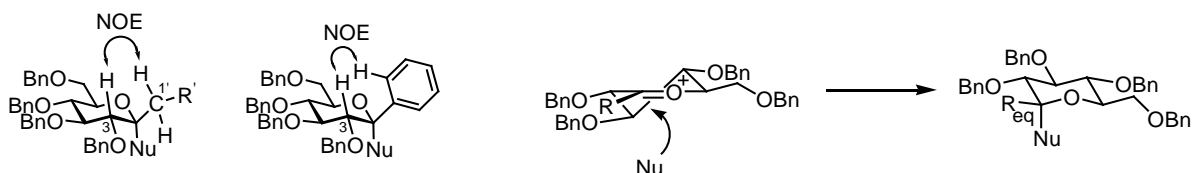


produced *by-products*

Scheme 5

Our next effort was directed towards improving the yields of the reactions of **1d** and **1e** with allyltrimethylsilane. Although the use of excess amounts of the reagents increased the yields of **3d** and **3e** to 53% and 78%, respectively, they were not satisfactory. In addition, the *exo*-glycal derivative **8**⁵⁸ was obtained as a novel by-product in 16% yield by the reaction using **1d**. Therefore, we attempted to use the glucopyranosyl acetates **9d** and **9e**. These acetates were expected to have high leaving abilities of the anomeric acetoxy group and were produced by the reactions of **1d** and **1e** with acetic anhydride using *n*-butyllithium in THF. The yield of **3e** obtained by the reaction of **9e** with allyltrimethylsilane increased up to 80% in the presence of 20 mol% TMSOTf in MeCN/CH₂Cl₂ (v/v = 1/1) at -78 °C. Under similar conditions, all the reactions of **9d** and **9e** with allyltrimethylsilane, TMSN₃, TMSCN and 1-phenyl-1-(trimethylsilyloxy)ethylene produced the corresponding glucopyranosides **3d** and **3e**, **5d** and **5e**, **6d** and **6e**, and **7d** and **7e**, respectively, in excellent yields. These results are shown in Table 2.

All the ketopyranosides were produced as single isomers, and the measurement of their NMR spectra indicated the NOE interactions between the proton of H-1' (or aromatic H) and H-3. The ketosidations proceeded with α -stereoselectivities. The α -side attack was advantageous for direct formation of the chair conformation from oxocarbenium cation intermediates, and forced the original anomeric functional groups of **1a-f** to assume an equatorial orientation. These conformational changes would contribute to the stabilization of the formation of the ⁴C₁ conformation, as shown in Scheme 6.



Scheme 6

These *C*- and *N*-ketosidation methods developed by us are potentially useful for synthesizing the subunits of naturally occurring products and chiral intermediates in organic chemistry.

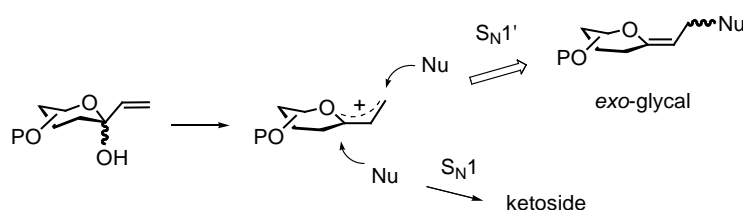
Table 2. *C*- or *N*-Ketosidation using 1-*C*-modified D-glucopyranoses

Entry ^a	Ketose	Nucleophile	Solvent	Temp/ °C	Product	Yield/%
1 ^b	1a	TMSCH ₂ CH=CH ₂	CH ₂ Cl ₂	-10	3a	49 (30) ^c
2 ^b	1a	TMSCH ₂ CH=CH ₂	Et ₂ O	-10	3a	Trace (25) ^c
3 ^b	1a	TMSCH ₂ CH=CH ₂	MeCN	-10	3a	67 (15) ^c
4 ^d	1a	TMSCH ₂ CH=CH ₂	MeCN	-10	3a	76 (9) ^c
5 ^e	1a	TMSCH ₂ CH=CH ₂	MeCN	-10	3a	63 (9) ^c
6 ^d	1a	TMSCH ₂ CH=CH ₂	MeCN	0	3a	69 (14) ^c
7 ^d	1a	TMSCH ₂ CH=CH ₂	MeCN	-20	3a	79 (7) ^c
8 ^d	1a	TMSCH ₂ CH=CH ₂	MeCN	-40	3a	84 (3) ^c
9 ^f	1a	TMSCH ₂ CH=CH ₂	MeCN	-40	3a	40 (7) ^c
10	1a	TMSCH ₂ CH=CH ₂	MeCN	-40	3a	88
11	1b, 1c, 1f	TMSCH ₂ CH=CH ₂	MeCN	-40	3b, 3c, 3f	88-95
12	1d	TMSCH ₂ CH=CH ₂	MeCN	-40	3d	31 (17) ^g
13	1e	TMSCH ₂ CH=CH ₂	MeCN	-40	3e	18
14 ^h	1d	TMSCH ₂ CH=CH ₂	MeCN/CH ₂ Cl ₂ = 1/1	-78	3d	53 (16) ⁱ
15 ^j	1e	TMSCH ₂ CH=CH ₂	MeCN/CH ₂ Cl ₂ = 1/1	-78	3e	78
16	1a-c, 1f	TMSN ₃	MeCN	-40	5a-c, 5f	94-99
17	1d	TMSN ₃	MeCN	-40	5d	80
18	1e	TMSN ₃	MeCN	-40	5e	80
19	1a-c	TMSCN	MeCN	-40	6a-c	90-95
20	1d	TMSCN	MeCN	-40	6d	65
21	1e	TMSCN	MeCN	-40	6e	73
22	1a-c, 1f	H ₂ C=C(OTMS)Ph	MeCN	-40	7a-c, 7f	78-98
23	1d	H ₂ C=C(OTMS)Ph	MeCN	-40	7d	53
24	1e	H ₂ C=C(OTMS)Ph	MeCN	-40	7e	61
25	9e	TMSCH ₂ CH=CH ₂	MeCN	-40	3e	66 (10) ^k
26	9e	TMSCH ₂ CH=CH ₂	MeCN/CH ₂ Cl ₂ = 1/1	-78	3e	80
27	9d	TMSCH ₂ CH=CH ₂	MeCN/CH ₂ Cl ₂ = 1/1	-78	3d	72
28	9d	TMSN ₃	MeCN/CH ₂ Cl ₂ = 1/1	-78	5d	94
29	9e	TMSN ₃	MeCN/CH ₂ Cl ₂ = 1/1	-78	5e	91
30	9d	TMSCN	MeCN/CH ₂ Cl ₂ = 1/1	-78	6d	95
31	9e	TMSCN	MeCN/CH ₂ Cl ₂ = 1/1	-78	6e	86
32	9d	H ₂ C=C(OTMS)Ph	MeCN/CH ₂ Cl ₂ = 1/1	-78	7d	93
33	9e	H ₂ C=C(OTMS)Ph	MeCN/CH ₂ Cl ₂ = 1/1	-78	7e	91

^a Reaction conditions molar ratio; ketopyranose: nucleophile: TMSOTf= 1: 3: 0.2. Reaction time; 2-3 h. ^b Molar ratio; ketopyranose: allyltrimethylsilane: TMSOTf= 1: 2: 0.1. ^c The value in parenthesis is the yield of the by-product **2a**. ^d Molar ratio; ketopyranose: allyltrimethylsilane: TMSOTf= 1: 2: 0.2. ^e Molar ratio; ketopyranose: allyltrimethylsilane: TMSOTf= 1: 2: 0.05. ^f Molar ratio; ketopyranose: allyltrimethylsilane: TMSOTf= 1: 1.5: 0.2. ^g The value in parenthesis is the yield of the by-product **4d**. ^h Molar ratio; ketopyranose: allyltrimethylsilane: TMSOTf= 1: 6: 0.2. ⁱ The value in parenthesis is the yield of the by-product **8**. ^j Molar ratio; ketopyranose: allyltrimethylsilane: TMSOTf= 1: 6: 0.4. ^k The value in parenthesis is the yield of the by-product **4e**.

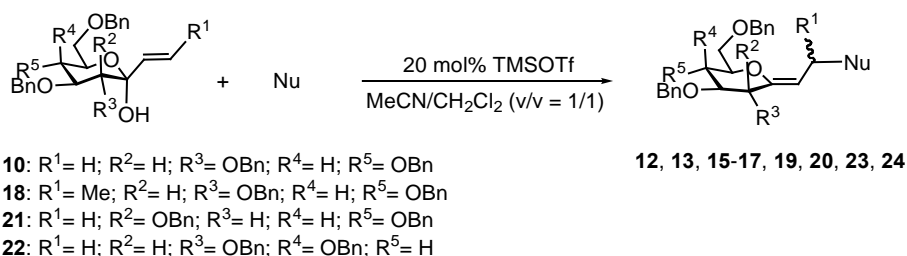
3.2 Formation of *exo*-glycals from 1-*C*-vinyl-hexopyranose derivatives

In this section, we describe our synthetic approach to *exo*-glycals^{18,20,68,69} from 1-*C*-vinyl-hexopyranose derivatives.² We speculated that the 1-*C*-vinyl-hexopyranose derivatives were likely to generate the specific glycosyl oxocarbenium cation intermediates stabilized by their resonance forms and that this effect would allow the nucleophiles to attack not only the anomeric carbons as stated above but also the terminal olefinic carbons, as shown in Scheme 7. The latter nucleophilic substitution, i.e. the S_N1'-type substitution was expected to produce the *exo*-glycal structures. All previously published reports, however, involved the S_N1-type ketosidation using alcoholic nucleophiles to synthesize 1-*C*-vinyl-*O*-hexopyranosides from 1-*C*-vinyl-hexopyranose derivatives.^{7b,11a,11b,12,17,18,19,20,21,22,23} We therefore anticipated that changing the species of the nucleophiles would make it possible to form *exo*-glycals from the 1-*C*-vinyl-hexopyranose derivatives via an S_N1'-type substitution mechanism.



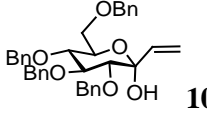
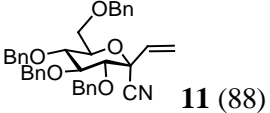
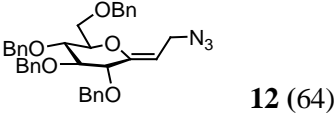
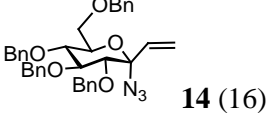

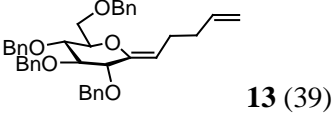


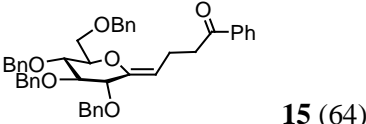
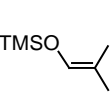
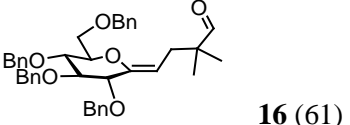

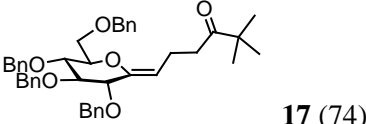
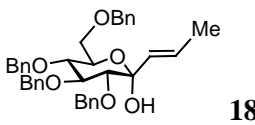

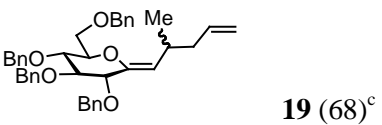

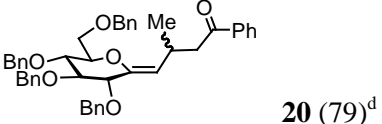
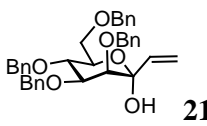

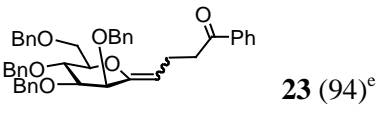
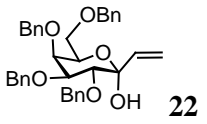

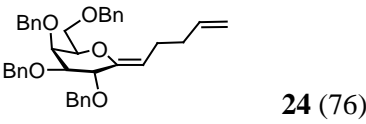
Scheme 7

We investigated the reactions between **10** and several nucleophiles, such as TMSCN, TMSN₃ and allyltrimethylsilane, using 20 mol% TMSOTf in MeCN at -40 °C, as shown in Scheme 8. The reaction using TMSCN gave only the ketopyranoside **11** in 88% yield by the S_N1-type substitution. When TMSN₃ and allyltrimethylsilane were used, the desired (*Z*)-*exo*-glycals **12** and **13** were stereoselectively obtained in 64% and 39% yields, respectively. Although the reaction using TMSN₃ gave **12** along with the ketopyranoside **14** in 16% yield, the reaction using allyltrimethylsilane produced **13** as a single product. We found that the differences in the species of the nucleophiles markedly influenced the nucleophilic characteristics of the reaction systems. Furthermore, the yield of **13** increased to 58% under reaction conditions using 20 mol% TMSOTf in MeCN/CH₂Cl₂ (v/v = 1/1) at -78 °C. Table 3 lists these results.



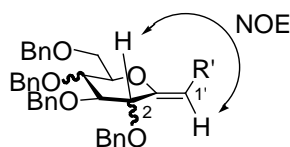
Scheme 8

Table 3. Synthesis of *exo*-glycols from 1-*C*-vinyl-*D*-glycopyranoses

Entry ^a	Ketose	Nucleophile	Product (Yield/%)
1 ^b		TMSCN	 11 (88)
2 ^b	10	TMSN ₃	 12 (64)  14 (16)
3 ^b	10	TMS 	 13 (39)
4	10	TMS 	13 (58)
5	10	TMSO 	 15 (64)
6	10	TMSO 	 16 (61)
7	10	TMSO 	 17 (74)
8		TMS 	 19 (68) ^c
9	18	TMSO 	 20 (79) ^d
10		TMSO 	 23 (94) ^e
11		TMS 	 24 (76)

^a Reaction conditions: solvent: MeCN/CH₂Cl₂ (v/v = 1/1); temperature: -78 °C; activator: 20 mol% TMSOTf. Molar ratio; 1-*C*-vinyl-glycopyranose derivative: nucleophile: TMSOTf = 1: 3: 0.2. ^b Reaction conditions: solvent: MeCN; temperature: -40 °C. ^c Diastereomer ratio = 3.5: 1. ^d Diastereomer ratio = 2: 1. ^e *Z*: *E* = 91: 9.

Next, we investigated the synthesis of various *exo*-glycal derivatives from the 1-*C*-vinyl-hexopyranoses **10**, **18**, **21** and **22** using several types of trimethylsilyl enol ethers, which were π -electron-related nucleophiles similar to allyltrimethylsilane. For the trimethylsilyl enol ethers, we used 1-phenyl-1-(trimethylsilyloxy)ethylene, 2-methyl-1-trimethylsilyloxy-1-propene, and 3,3-dimethyl-2-trimethylsilyloxy-1-butene. Under the stated reaction conditions, the reactions between **10** and the trimethylsilyl enol ethers afforded the corresponding (*Z*)-*exo*-glycals **15–17** by S_N1' -type substitution in good yields from 61% to 74% with no production of the corresponding ketopyranosides. The reactions of the 1-*C*-1-propenyl-glucofuranose **18** with allyltrimethylsilane or 1-phenyl-1-(trimethylsilyloxy)ethylene also produced the corresponding (*Z*)-*exo*-glycal **19** or **20** in 68% or 79% yield with a diastereomer ratio of 3.5/1 or 2/1, respectively. The reactions of the 1-*C*-vinyl-mannopyranose **21** with 1-phenyl-1-(trimethylsilyloxy)ethylene gave the corresponding *exo*-glycal **23** in a high yield of 94% with a geometric isomer ratio of *Z*:*E* = 91:9. The steric effect of the C-2 benzyloxy group slightly influenced the reaction stereoselectivity. The reactions between the 1-*C*-vinyl-galactopyranose **22** with allyltrimethylsilane stereoselectively afforded the (*Z*)-*exo*-glycal **24** in 76% yield. We observed the NOE interactions between H-2 and H-1' of the *exo*-glycals, as shown in Scheme 9, and determined their geometric isomers as the *Z* forms.



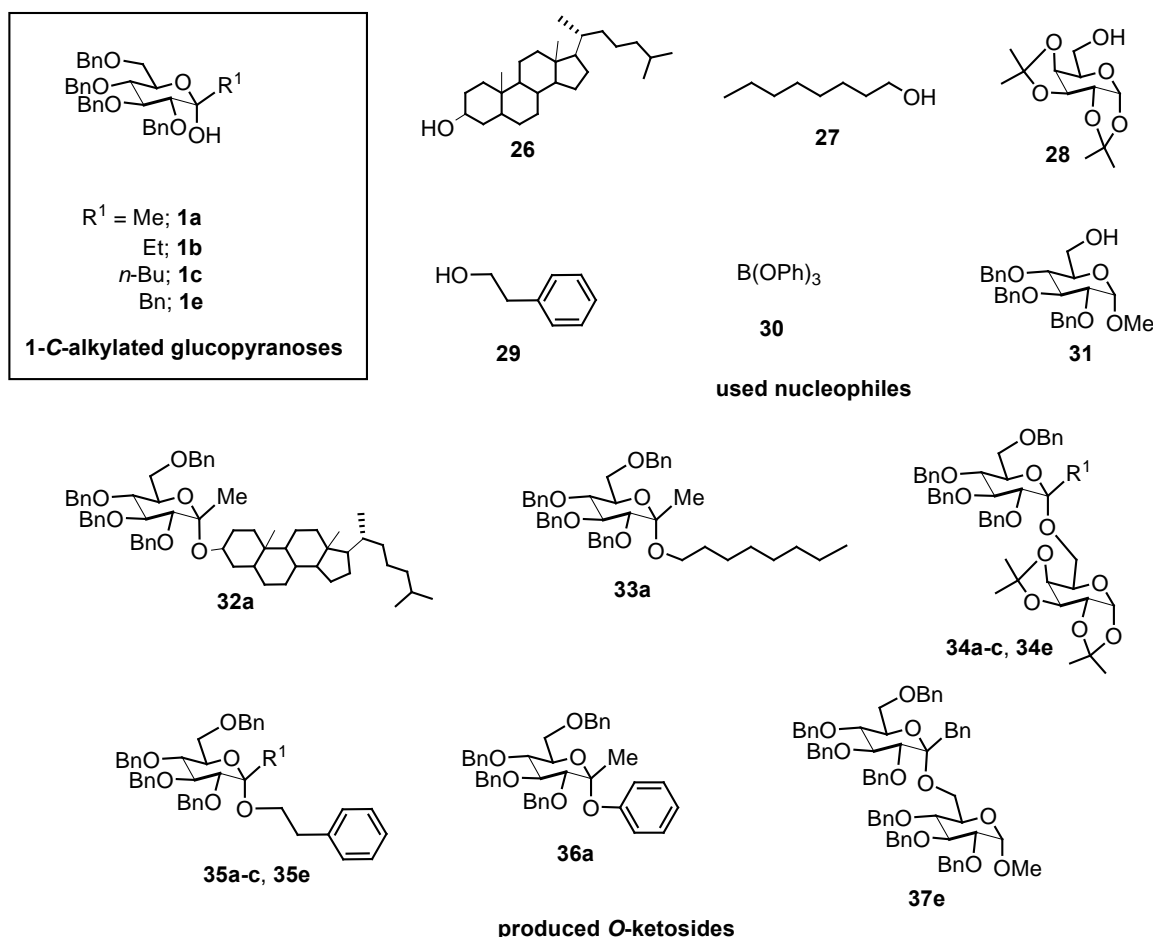
Scheme 9

To the best of our knowledge, this is the first synthetic approach to *exo*-glycals from the 1-*C*-vinyl-hexopyranoses by the S_N1' -type substitution mechanism. This method can provide various types of functionalized *exo*-glycals useful as synthetic intermediates in carbohydrate chemistry.

3.3 Formation of *O*-ketopyranosidic linkages from 1-*C*-modified D-glucofuranoses

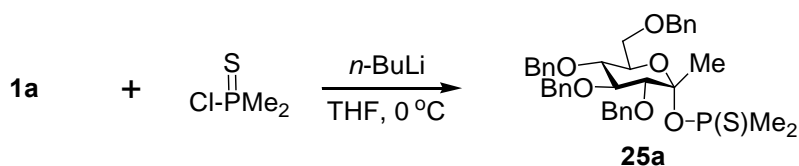
1-*C*-Modified *O*-glycosides are generally synthesized by glycosidations using 1-methylene sugars (*exo*-glycals) or 1-*C*-modified sugars as glycosyl donors. 1-Methylene sugars are convenient glycosyl donors and are utilized in both enzymatic and chemical glycosidations.^{6b,6b,69,69f,69g,70} However, there seems to be limitations in the use of *exo*-glycals because of their synthetic difficulty. In contrast, there is a wide variety of 1-*C*-modified sugars, and therefore, the *O*-ketosidation using 1-*C*-modified sugars can provide various types of *O*-ketosides. This section describes *O*-ketosidations using 1-*C*-modified D-glucofuranose derivatives. Scheme 10 shows the glucofuranose derivatives (**1a–c**, **1e**) carrying the

methyl, ethyl, *n*-butyl and benzyl groups at the anomeric carbon centers, utilized alcohols and produced *O*-ketopyranosides.



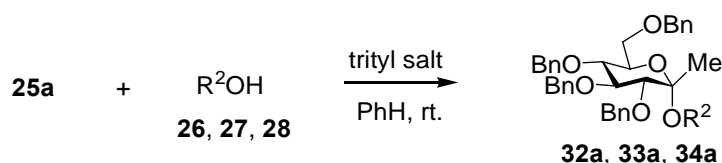
3.3.1 *O*-Ketosidation using dimethylphosphinothioate

We previously studied glycosidations using 1-*O*-dimethylphosphinothiyl sugars as the glycosyl donors.⁷¹ Our *O*-ketosidation study using 1-*C*-modified glucopyranoses started with the dimethylphosphinothioate method.^{8b,72} We examined the preparation of dimethylphosphinothioates from **1a–c** using dimethylphosphinothiyl (Mpt) chloride and *n*-BuLi in THF at 0 °C, according to our previously reported procedure shown in Scheme 11. Dimethylphosphinothioate **25a** was obtained from **1a** in a moderate yield of 55%. However, other dimethylphosphinothioates were obtained in very poor yields from **1b** and **1c**. In all likelihood, the steric hindrances on the anomeric centers of **1b** and **1c** and the bulkiness of Mpt-Cl prevented the introduction of the Mpt group into **1b** and **1c**. Compound **25a** was not as stable as the aldopyranosyl dimethylphosphinothioates we previously prepared.



Scheme 11

We next investigated the *O*-ketosidation of **25a** with the alcohols **26–28**, as shown in Scheme 12. The reactivity of **25a** as a glycosyl donor is expected to be high in spite of its anomeric carbon centre's steric hindrance because the electron donating effect of the anomeric methyl group stabilize the glycosyl cation intermediate. We then used some trityl salts as activators of **25a**, which were effective in the glycosidation of the highly reactive 2-deoxy-glycopyranosyl dimethylphosphinothioates. 3 β -cholestanol (**26**) smoothly glycosylated **25a** using 10 mol% TrtClO₄ in benzene at room temperature to afford **32a** in a high yield of 88% with an α -stereoselectivity. The reaction using 5 mol% TrtClO₄ slightly decreased the yield of **32a** to 71%. The reactions using 10 mol% of TrtSbCl₆, TrtBF₄ and TrtSnCl₅ as other trityl salts afforded **32a** in moderate yields from 34% to 43%. Under similar reaction conditions using 10 mol% TrtClO₄, we successfully performed glycosidation of **25a** with **27** and **28** to produce the *O*-glucosides **33a** and **34a** both in 82% yield with an α -stereoselectivity and an α/β ratio of 70/30. These results are indicated in Table 4.



Scheme 12

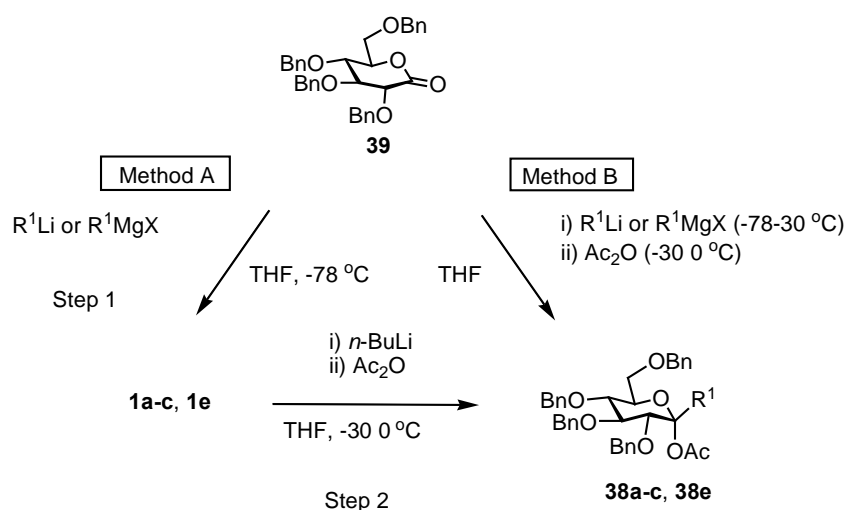
Table 4. *O*-Ketosidation using 1-*C*-methyl-D-glucopyranosyl dimethylphosphinothioate

Entry ^a	Trityl salt (mol%)	Alcohol	Product	Yield/% ^b
1	TrtClO ₄ (10)	26	32a	88
2	TrtClO ₄ (5)	26	32a	71
3	TrtSbCl ₆ (10)	26	32a	43
4	TrtBF ₄ (10)	26	32a	34
5	TrtPF ₆ (10)	26	32a	No reaction
6	TrtSnCl ₅ (10)	26	32a	43
7	TrtClO ₄ (10)	27	33a	82
8	TrtClO ₄ (10)	28	34a	82 ^c

^a Reaction conditions; molar ratio; **25a**: alcohol = 1: 1; reaction time; 1 h; reaction temperature; rt. ^b Only the α -ketoside was obtained. ^c The α/β ratio of glycoside was 70/30.

3.3.2 *O*-Ketosidation using acetates

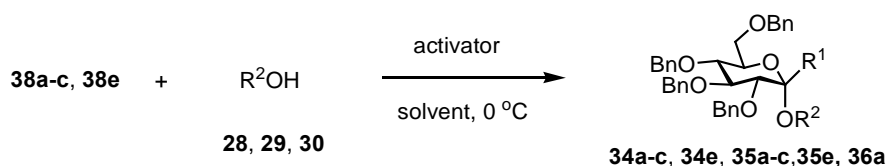
The acetyl group, less bulky than the Mpt group, could be smoothly introduced into **1a–c** and **1e** to prepare the corresponding acetates, as mentioned in the Section 3.1. Although the ordinary acetylation of **1a** using Ac₂O-pyridine could not give **38a** at all,⁷³ the use of *n*-BuLi as a strong base in lieu of pyridine was effective. We acetylated the compounds **1a–c** and **1e** with *n*-BuLi and Ac₂O at -78 – 0 °C to produce the acetates **38a–c** and **38e** in good yields. The one-pot synthesis of **38a–c** and **38e** was also achieved from the glucono-1,5-lactone derivative **39** by adding RLi (or RMgX) and subsequently Ac₂O in THF, as shown in Scheme 13.



Scheme 13

We then investigated *O*-ketosidation using the acetates **38a–c** and **38e** in the presence of a Lewis acid, as shown in Scheme 14.^{8b,8c} First, the reaction of **38a** with phenethyl alcohol (**29**) was examined in detail using 5 mol% of Lewis acids such as Yb(OTf)₃, Sc(OTf)₃, TMSOTf, TrtClO₄ and BF₃•OEt₂ as the activators in CH₂Cl₂ at 0 °C. Each Lewis acid activated the glycosidation to give the corresponding glucoside **35a** in 67–80% yields with α -stereoselectivities. Yb(OTf)₃ and Sc(OTf)₃ were especially effective for the activation of **38a**. Even the reaction using only 1 mol% of Sc(OTf)₃ could afford **35a** in a yield of 73% with an α/β ratio of 81/19. We also examined the effect of the solvents using CH₂Cl₂, PhMe and MeCN. The reaction using PhMe increased the yield of **35a** to 89%. However, these solvents did not influence the glycosidation stereoselectivities at all.

Under similar reaction conditions, the reactions of **38a–c** with **29** (**28**) stereoselectively afforded the α -*O*-glucoside **35a–c** (**34a–c**) and those of **38e** with **29** (**28**) stereoselectively afforded the α -*O*-glucoside **35e** (**34e**) in yields of 73–89%.^{74,75} B(OPh)₃ (**30**) worked as the reactive glycosyl acceptors of **38a** to stereoselectively afford the phenyl α -*O*-glucoside **36a** in 80% yield.^{75c} Table 5 displays these results.



Scheme 14

Table 5. *O*-Ketosidation using 1-*C*-modified D-glucopyranosyl acetates

Entry ^a	Acetate	Alcohol	Activator	Solvent	Product	Yield/% ^b
1	38a	29	Yb(OTf) ₃	CH ₂ Cl ₂	35a	76
2	38a	29	Sc(OTf) ₃	CH ₂ Cl ₂	35a	80
3	38a	29	TMSOTf	CH ₂ Cl ₂	35a	69
4	38a	29	TrtClO ₄	CH ₂ Cl ₂	35a	74
5	38a	29	BF ₃ •OEt ₂	CH ₂ Cl ₂	35a	67
6 ^c	38a	29	Sc(OTf) ₃	CH ₂ Cl ₂	35a	73 ^d
7	38a	29	Sc(OTf) ₃	PhMe	35a	89
8	38a	29	Sc(OTf) ₃	MeCN	35a	63
9	38b	29	Sc(OTf) ₃	PhMe	35b	86
10	38c	29	Sc(OTf) ₃	PhMe	35c	75
11	38e	29	Sc(OTf) ₃	PhMe	35e	77
12	38a	28	Sc(OTf) ₃	PhMe	34a	82
13 ^c	38a	28	Sc(OTf) ₃	PhMe	34a	87 ^e
14	38b	28	Sc(OTf) ₃	PhMe	34b	77
15	38c	28	Sc(OTf) ₃	PhMe	34c	73
16	38e	28	Sc(OTf) ₃	PhMe	34e	74
17 ^f	38a	30	Yb(OTf) ₃	CH ₂ Cl ₂	36a	80

^a Reaction conditions; molar ratio; **38a-c, 38e: 29**: activator = 1: 1: 0.05; **38a-c, 38e: 28**: activator = 1.5: 1: 0.075; reaction time; 1-3 h; reaction temperature; 0 °C. ^b Only the α -ketoside was obtained. ^c 1 mol% of Sc(OTf)₃ was used. ^d The α/β ratio of product was 81/19. ^e The α/β ratio of ketoside was 85/15. ^f Reaction conditions; molar ratio; **38a: 30**: activator = 1: 0.5: 0.05; reaction time; 3 h; reaction temperature; -78 °C.

Inanaga *et al.* reported that lanthanide triflates could not activate glycosidation using 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetate as the glycosyl donor.⁷⁶ This result greatly differ from our observations that any glycosidation using **38a-c** and **38e** smoothly proceeded using only 5 mol% Sc(OTf)₃. The existence of the alkyl groups on **38a-c** and **38e** markedly increased their reactivities as glycosyl donors. The species of the alkyl groups at the anomeric carbon centers of **38a-c** and **38e** had almost no influence on the reactivities and stereoselectivities of the glycosidation. These findings corresponded to the observations about the *C*- and *N*-ketosidation mentioned in Section 3.1.

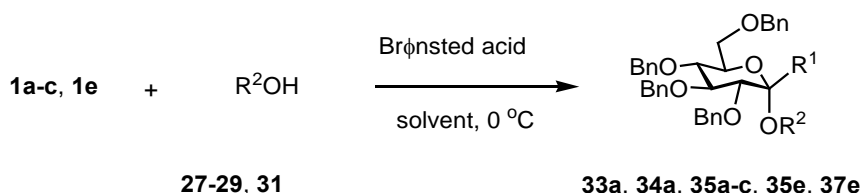
The high α -stereoselectivity of this reaction could be explained by the anomeric effect and by the inhibition of the β -glucoside formation by the 1,3-diaxial interaction. In addition, we examined the

possibility that the β -*O*-glucoside might be isomerized into the corresponding α -*O*-glucoside in the reaction system. No anomerization was observed in the reaction using the β -glucoside of **34a** to α -glucoside in the presence of 10 mol% Sc(OTf)₃ in PhMe at room temperature overnight.

3.3.3 Dehydrative *O*-ketosidation

We next examined direct *O*-ketosidation using the 1-*C*-modified hexopyranoses **1a–c** and **1e** without introducing any other leaving group, as shown in Scheme 15, in order to develop a more convenient method for producing *O*-ketosides.^{8b,8c} Dehydrative *O*-ketosidation of **1a–c** and **1e** was performed using a Brønsted acid expected to be resistant to water.

The reaction of **1a** with **29** was investigated using 5 mol% of camphorsulfonic acid, CF₃CO₂H and TfOH in CH₂Cl₂ at 0 °C in the presence of CaSO₄. Only TfOH was effective for the dehydrative *O*-ketosidation to give **35a** in 59% yield with an α -stereoselectivity. The use of MeCN as the solvent slightly increased the yield of **35a** to 73%. Similarly, we found C₈F₁₇SO₃H and Tf₂NH acting as the Brønsted acid analogues of TfOH, and HBF₄ to be effective under similar reaction conditions. In particular, Tf₂NH gave **35a** with a maximum yield of 77%.



Scheme 15

Under the given reaction conditions, ketosidation of **1b**, **1c** and **1e** with **29** gave the desired **35b**, **35c** and **35e**, respectively, in yields ranging from 56% to 64% with high α -stereoselectivities. We also found that the difference in the alkyl groups at the anomeric carbon centers of **1a–c** and **1e** had almost no influence on the dehydrative *O*-ketosidation reactivity and stereoselectivity. This observation is similar to that of Section 3.3.2. Moreover, **1a** and **1e** smoothly glycosylated the compounds **27**, **28** and **31** in good yields of 78%, 55% and 66%, respectively, with high α -stereoselectivities under the given reaction conditions. Table 6 lists these results.

Our *O*-ketosidation methods mentioned in Section 3.3 are useful for synthesizing various types of mimics of naturally occurring *O*-aldopyranosides, which are expected to show biological functions different from those of natural compounds.

Table 6. Dehydrative *O*-ketosidation using 1-*C*-modified D-glucopyranoses

Entry ^a	Ketose	Alcohol	Brønsted acid (mol%)	Solvent	Product	Yield/%
1	1a	29	Camphorsulfonic acid (5)	CH ₂ Cl ₂	35a	No reaction
2	1a	29	CF ₃ CO ₂ H (5)	CH ₂ Cl ₂	35a	No reaction
3	1a	29	TfOH (5)	CH ₂ Cl ₂	35a	59
4	1a	29	TfOH (5)	MeCN	35a	73
5	1a	29	C ₈ F ₁₇ SO ₃ H (5)	MeCN	35a	56
6	1a	29	Tf ₂ NH (5)	MeCN	35a	77
7	1a	29	HBF ₄ (5)	MeCN	35a	73
8	1a	29	Tf ₂ NH (10)	MeCN	35a	69
9	1a	29	Tf ₂ NH (3)	MeCN	35a	65
10	1a	29	Tf ₂ NH (1)	MeCN	35a	56
11	1b	29	Tf ₂ NH (5)	MeCN	35b	57
12	1c	29	Tf ₂ NH (5)	MeCN	35c	64
13	1e	29	Tf ₂ NH (5)	MeCN	35e	56
14	1a	27	Tf ₂ NH (5)	MeCN	33a	78
15 ^b	1a	28	Tf ₂ NH (5)	MeCN	34a	55
16 ^b	1e	31	TfOH (5)	MeCN	37e	66

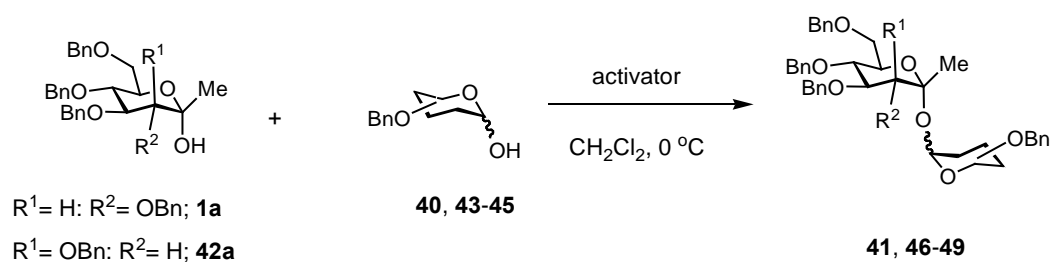
^a Reaction conditions; molar ratio; **1a-c**, **1e**: alcohol: Brønsted acid = 1:1: 0.05. Reaction time; 2 h; reaction temperature; 0 °C. ^b Reaction conditions; molar ratio; **1a**, **1e**: alcohol: Brønsted acid = 1.5:1: 0.075. Reaction time; 3 h; reaction temperature; 0 °C.

3.4 Formation of trehalose mimics by 1-*C*-methyl-hexopyranosylation

One of the interesting findings on the aforementioned *O*-ketosidation using 1-*C*-modified hexopyranoses was that the ketopyranosylation proceeded with high α -stereoselectivity. We expected this feature to be useful for synthesizing mimics of trehalose (α -D-glucopyranosyl α -D-glucopyranoside) as this natural non-reducing disaccharide is composed of two glucose molecules linked together by an α -glucopyranosidic linkage. Trehalose is well known for its various biological activities such as its suppressive effect on the progress of osteoporosis.

We attempted the dehydrative *O*-ketosidation method to synthesize some non-reducing disaccharides (trehalose mimics) into which 1-*C*-methyl-D-hexopyranoses were incorporated, as shown in Scheme 16.^{8b,8c,10} First, when we investigated the reaction of 1-*C*-methyl-D-glucopyranose (**1a**) with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**40**) using 5 mol% Tf₂NH in MeCN at 0 °C for 3 h in the presence of CaSO₄, the desired non-reducing disaccharide **41** was produced in 47% yield as a single isomer, and both of its glycosidic linkages were α -configured. This interesting observation urged us to make a further investigation into the ketosidation conditions of **1a** with **40**, including the stereoselectivity of the ketosidation and other effective activators in place of Tf₂NH.

When we changed the solvent from MeCN to CH₂Cl₂, the reaction of **1a** with **40** markedly increased the yield of **41** to 87%. This increase was due to the high solubility of **40** in CH₂Cl₂. We used Lewis acids, Yb(OTf)₃, Sc(OTf)₃ and Bi(OTf)₃, which were expected to be resistant to water. The reactions using Sc(OTf)₃ and Bi(OTf)₃ gave **41** in high yields of 80% and 89%, respectively. Bi(OTf)₃ was an efficient activator for this reaction,^{77,78} while BiCl₃ did not work at all.



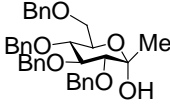
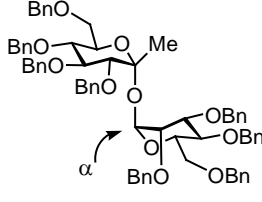
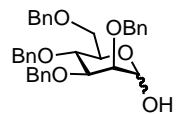
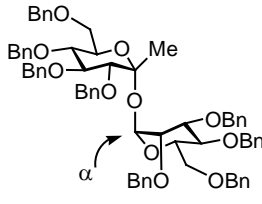
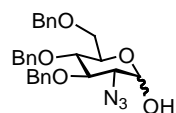
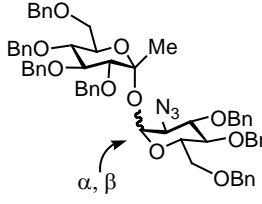
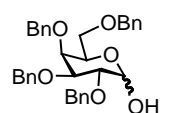
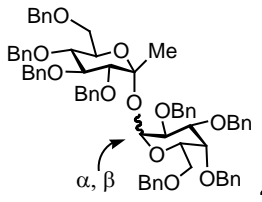
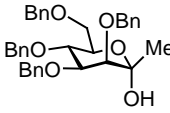
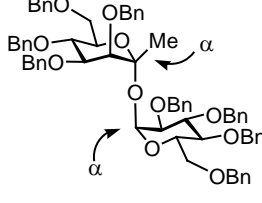
Scheme 16

The syntheses of several non-reducing disaccharides by 1-*C*-methyl-hexopyranosylation were examined using the 1-*C*-methyl-hexopyranoses **1a** or **42a** and the aldopyranoses **40** and **43–45** by employing both Tf₂NH and Bi(OTf)₃ as the activators. We obtained the corresponding non-reducing disaccharides **41** and **46–49** in good yields. Compounds **41**, **46** and **49** were obtained as single isomers. In addition, compound **47** was formed in the isomer ratios of 78/22 and 58/42, and compound **48** was formed in isomer ratios of 87/13 and 76/24. Table 7 displays these results. The anomeric configurations of all the formed ketopyranosidic linkages of **46–49** were α, which were determined by the observation of the NOE interactions between the methyl group and the H-2 of the 1-*C*-methyl-D-hexopyranosyl rings. The measurement of the coupling constants of H-1 determined the aldopyranosidic linkages of **47** and **48**.

In order to investigate the relation between the α/β-anomer ratios of the acceptors and those of the aldopyranosidic linkages of the products, we measured the α/β-anomer ratios of the aldohexopyranoses **40** and **43–45** in CH₂Cl₂ solvent based on the NMR spectra. Compounds **40** and **43–45** were dissolved in CD₂Cl₂, and the NMR spectra measured about 30 min later showed that **40** and **43** contained ca. 15–20% of the β-anomers and that **44** and **45** contained ca. 40% of the β-anomers. In spite of the presence of the β-anomers, the ketopyranosylations of **40** and **43** did not form products with β-aldopyranosidic linkages at all. This suggested that the α-anomers of **40** and **43** predominantly worked as reactive acceptors. The ketopyranosylations of **44** and **45** formed small amounts of **47** and **48** with β-aldopyranosidic linkages. This showed that their β-anomers partly participated in the ketopyranosylations, although the α-anomers were preferentially used as reactive acceptors.

To the best of our knowledge, this study is the first example of the incorporation of a 1-*C*-methyl-D-hexopyranose into a non-reducing disaccharide.⁷⁹ These trehalose mimics are expected to exhibit novel biological activities.

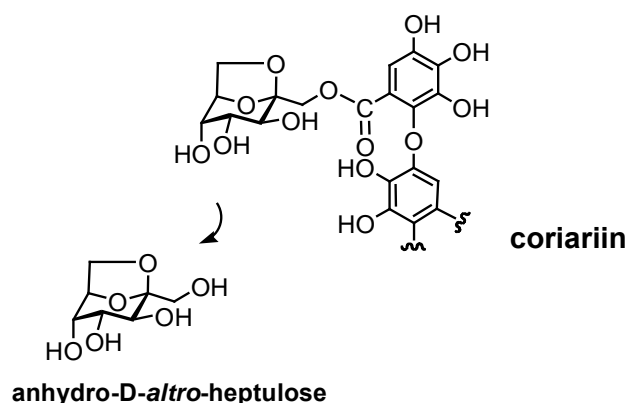
Table 7. Synthesis of trehalose mimics by 1-*C*-methyl-*D*-hexopyranosylation

Entry ^a	Ketose	Aldose	Solvent	Activator	Product (Yield/%)	α/β Ratio ^b
1	 1a	40	MeCN	Tf ₂ NH	 41 (47)	α only
2	1a	40	CH ₂ Cl ₂	Tf ₂ NH	41 (87)	α only
3	1a	40	CH ₂ Cl ₂	Yb(OTf) ₃	41 (21)	α only
4	1a	40	CH ₂ Cl ₂	Sc(OTf) ₃	41 (80)	α only
5	1a	40	PhMe	Sc(OTf) ₃	41 (61)	α only
6	1a	40	CH ₂ Cl ₂	Bi(OTf) ₃	41 (89)	α only
7	1a	40	CH ₂ Cl ₂	BiCl ₃	41 (Trace)	α only
8	1a	 43	CH ₂ Cl ₂	Tf ₂ NH	 46 (64)	α only
9	1a	43	CH ₂ Cl ₂	Bi(OTf) ₃	46 (75)	α only
10	1a	 44	CH ₂ Cl ₂	Tf ₂ NH	 47 (90)	78/22
11	1a	44	CH ₂ Cl ₂	Bi(OTf) ₃	47 (84)	58/42
12	1a	 45	CH ₂ Cl ₂	Tf ₂ NH	 48 (83)	87/13
13	1a	45	CH ₂ Cl ₂	Bi(OTf) ₃	48 (89)	76/24
14	 42a	40	CH ₂ Cl ₂	Tf ₂ NH	 49 (37)	α only
15	42a	40	CH ₂ Cl ₂	Bi(OTf) ₃	49 (80)	α only

^a Molar ratio; donor: acceptor: activator= 1: 0.67: 0.05. Reaction time; 3 h. Reaction temperature; 0 °C. ^b All the 1-*C*-methyl-hexopyranosidic linkages of **41** and **46-49** were α .

3.5 Formation of anhydroketopyranoses from 1-*C*-modified hexopyranoses

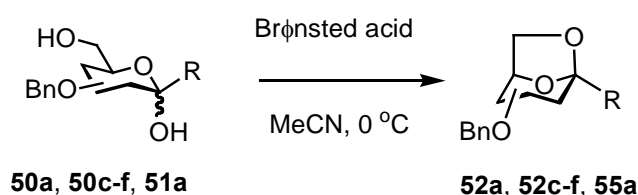
Several anhydroketopyranoses having 6,8-dioxabicyclo[3.2.1]octane structures are found in natural products such as *Sedum spectabile*,⁸⁰ *Smilax sonchifolius*,⁸¹ and *Coriaria japonica* A.⁸² Coriariin found in *C. japonica* A has an anhydro-*D*-*altro*-heptulose bound to a tannin molecule via an ester linkage, as shown in Scheme 17. Its analogues possess biologically important antitumour and antiviral activities. In addition, the 6,8-dioxabicyclo[3.2.1]octane structural anhydroketopyranoses are useful chiral building blocks in synthetic organic chemistry. This section 3.5 describes the general reaction characteristics of the formation of anhydroketopyranoses by intramolecular *O*-ketosylation, i.e. ‘anhydroketopyranosylation’ of 1-*C*-modified hexopyranoses and a synthetic approach to an anhydro-*D*-*altro*-heptulose derivative found in *C. japonica* A.



Scheme 17

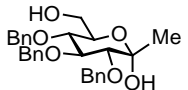
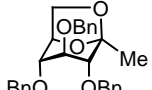
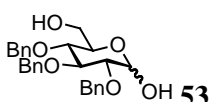
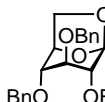
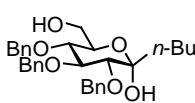
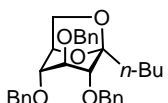
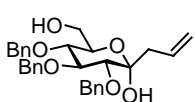
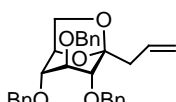
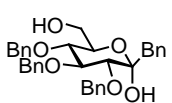
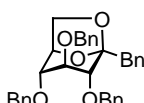
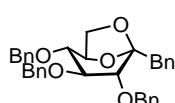
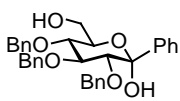
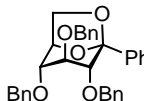
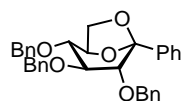
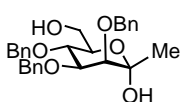
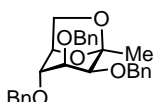
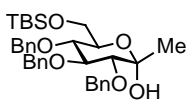
3.5.1 Formation of anhydroketopyranoses by the intramolecular *O*-ketosidation

6,8-Dioxabicyclo[3.2.1]octane structural anhydroketopyranoses can be regarded as intramolecular *O*-ketopyranosides. The 1-*C*-modified hexopyranoses are expected to be useful precursors for providing various types of anhydroketopyranoses having 6,8-dioxabicyclo[3.2.1]octane structures. Therefore, we investigated the formation of these anhydroketopyranoses by direct anhydroketopyranosylation of 1-*C*-modified hexopyranoses.^{8d}



Scheme 18

Table 8. Anhydroketopyranosylation of 1-*C*-modified D-hexopyranoses

Entry ^a	Ketose	Brønsted acid (mol%)	Product (Yield/%)
1 ^b	 50a	Camphorsulfonic acid (20)	 52a (59)
2	50a	Tf ₂ NH (20)	52a (82)
3	50a	TfOH (20)	52a (84)
4	50a	TfOH (5)	52a (93)
5	50a	TfOH (1)	52a (86)
6	50a	TfOH (0.5)	52a (68)
7	 53	TfOH (20)	 54 (Trace)
8	 50c	TfOH (5)	 52c (91)
9	 50d	TfOH (5)	 52d (95)
10	 50e	TfOH (5)	 52e (70)  52e' (26)
11	 50f	TfOH (5)	 52f (78)  52f' (14)
12	 51a	TfOH (5)	 55a (93)
13	 56a	TfOH (5)	52a (80)

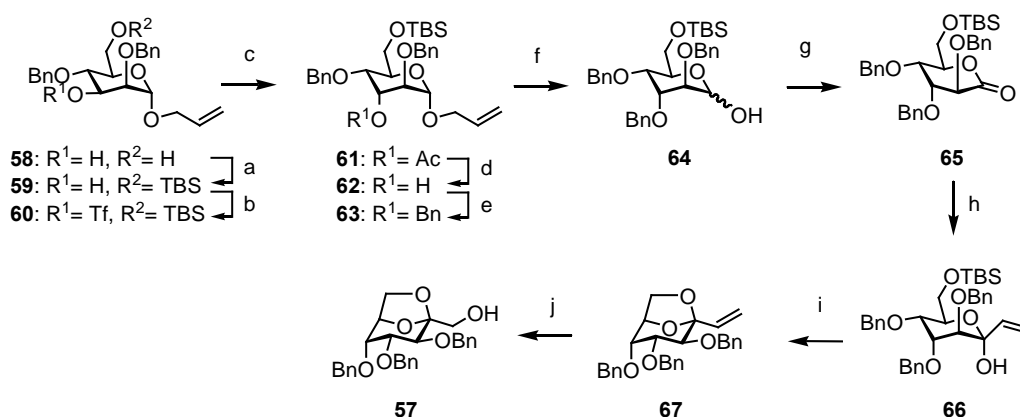
^a Reaction conditions; solvent: MeCN; reaction time: 2 h; reaction temperature: 0 °C.^b Reaction time: 30 h.

Several 1-*C*-modified D-hexopyranoses, **50a**, **50c–f** and **51a** carrying the methyl, allyl, *n*-butyl, phenyl and benzyl groups at the anomeric carbon centers and having a hydroxyl group at the C-6 position were utilized. We investigated the anhydroketopyranosylation of **50a** to afford the corresponding anhydroketopyranose **52a** using Brønsted acids as activators, as shown in Scheme 18, according to a concept similar to that mentioned in Section 3.3.3. Table 8 summarizes these results. Each reaction using 20 mol% of camphorsulfonic acid, Tf₂NH and TfOH as the Brønsted acid in MeCN at 0 °C gave the desired **52a** in 59%, 82% and 84% yields, respectively. Tf₂NH and TfOH were very efficient for this anhydroketopyranosylation. We then varied the amount of TfOH. The reactions using only 1 mol% or 0.5 mol% of TfOH proceeded to give **51a** in 86% and 68% yields, respectively. A maximum yield of 93% was attained in the reaction using 5 mol% of TfOH. Thus, the reactivity of **50a** was remarkably high, a fact corresponding to the ‘intermolecular’ *O*-ketosidation mentioned in Section 3.3.3. The reaction from 2,3,4-tri-*O*-benzyl-D-glucopyranose (**53**) to 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**54**) under similar reaction conditions scarcely proceeded. We considered that the presence of the anomeric methyl group of **50a** would promote not only the generation of the oxocarbenium cation intermediate from **50a** but also the conformation flip of the pyranosyl ring from ⁴C₁ into ¹C₄ because of its equatorial orientation in the anhydroketopyranose form.

We then demonstrated the synthesis of various types of anhydroketopyranoses (**52c–f**) by anhydroketopyranosylation of **50c–f**. The reactions using **50c** and **50d** in MeCN at 0 °C for 2 h in the presence of 5 mol% TfOH afforded the desired anhydroketopyranoses **52c** and **52d** in the excellent yields of 91% and 95%, respectively. The ¹C₄ conformational **52e** and **52f** were similarly obtained from **50e** and **50f** in 70% and 78% yields, respectively. Interestingly, in these two reactions, the twist-boat conformational isomers **52e'** and **52f'** were also formed in 26% and 14% yields. Therefore, the total yields of these glycosidations were 96% and 92%, respectively. These results showed that the difference in the 1-*C*-functional groups of **1a–e** had almost no influence on the anhydroketopyranosylation yields, although the benzyl and phenyl groups of **50e** and **50f** influenced the ring conformations of the anhydroketopyranoses.

Anhydroketopyranosylation of **51a** under same reaction conditions smoothly proceeded to afford **55a** in a high yield of 93%. Furthermore, the reaction using 6-*O*-*tert*-butyldimethylsilyl-1-*C*-methyl-D-glucopyranose (**56a**) also afforded **52a** in 80% yield. In this reaction, TfOH not only promoted the anhydroketopyranosylation but also removed the TBS group of **56a**, which is a great advantage of this anhydroketopyranosylation. In none of the above reactions, we observed the production of oligosaccharides by intermolecular *O*-ketosidation.

3.5.2 Synthesis of an anhydro-D-*altro*-heptulose found in *C. japonica* A



Reagents and conditions: (a) TBSCl (2 equiv.), imidazole (2 equiv.), CH₂Cl₂, rt, 2 h, 88%; (b) Tf₂O (1.5 equiv.), pyridine, -20 °C~rt, 2.5 h, 93%; (c) CsOAc (2 equiv.), 18-crown-6 (2 equiv.), toluene, sonication, 30 °C, 24 h, 62%; (d) NaOMe (cat.), MeOH, rt, overnight, 95%; (e) BnBr (1.5 equiv.), NaH (4 equiv.), DMF, 0 °C~rt., overnight, 96%; (f) PdCl₂ (3 equiv.), AcOH-AcONa buffer, sonication, 30 °C, 4 h, 87%; (g) DMSO, Ac₂O, rt, overnight, 99%; (h) vinylMgCl (1.2 equiv.), CeCl₃ (1.2 equiv.), toluene, -78 °C, 1 h, 62%; (i) TfOH (0.05 equiv.), MeCN, 0 °C, 2h, 88%; (j) O₃, Ph₃P (5 equiv.), CH₂Cl₂, -78 °C, 45 min., then NaBH₄ (8 equiv.), THF, 0 °C, 3 h, 72%.

Scheme 19

We applied the aforementioned anhydroketopyranosylation to the synthesis of an anhydro-D-*altrio*-heptulose⁸³ found in *C. japonica* A.^{11a,b} Our synthetic target was the partially benzylated anhydro-D-*altrio*-heptulose derivative **57**, as shown in Scheme 19. Compound **57** is a useful unit for synthesizing coriariin because it has a free hydroxyl group that functions as a binding site with a tannin molecule, and its other hydroxyl functions are protected by benzyl groups. Our synthetic approach to **57** starts from a D-mannopyranose derivative **58**,⁸⁴ and consists of the following key reaction steps: (i) steric inversion at the C-3 position from a D-mannopyranose derivative to a D-*altrio*pyranose derivative, (ii) introduction of a vinyl group to the C-1 position of the *altrio*pyranose derivative to produce a 1-*C*-vinylated D-*altrio*pyranose derivative, (iii) anhydroketopyranosylation of the 1-*C*-vinylated D-*altrio*pyranose derivative to form the anhydroketopyranose structure and (iv) conversion of the vinyl group of the anhydroketopyranose to a hydroxymethyl group to produce the desired compound **57**.

We introduced a TBS group into the C-6 position of **58** using TBSCl-imidazole in CH₂Cl₂. Introduction of a Tf group to the C-3 position was performed using Tf₂O in pyridine. Steric inversion at C-3 of **60** to **61** was successfully achieved in 62% yield using AcOCs in the presence of 18-crown-6 in PhMe at 30 °C for 24 h under ultrasonic conditions. After the conversion of the acetyl group of **61** to a benzyl group, we removed the allyl group of **63** using PdCl₂ in AcOH-AcONa at 30 °C for 4 h under ultrasonic conditions. Oxidation of **64** using DMSO-Ac₂O produced the desired **65**. Introduction of the vinyl group to the C-1 position of **65** to produce **66** was successfully achieved in 62% yield using vinylmagnesium chloride in PhMe in the presence of CeCl₃ at -78 °C for 1 h. The anhydroketopyranosylation of **66** smoothly proceeded to afford the desired compound **67** in 88% yield using 5 mol% TfOH in the presence of CaSO₄ in MeCN at 0 °C for 2 h. It is unnecessary to remove the TBS group at C-6 of **66** prior to the

anhydroketopyranosylation because the TBS group was removed by TfOH during the anhydroketopyranosylation as mentioned above. We converted the vinyl group of **67** into a hydroxymethyl group to give the desired **57** in 72% yield by ozone oxidation of **67** and treatment with triphenylphosphine at $-78\text{ }^{\circ}\text{C}$ for 45 min and subsequent reduction using NaBH_4 at $0\text{ }^{\circ}\text{C}$ for 3 h.

CONCLUSIONS

This paper summarizes our recent studies on the nucleophilic substitutions to form the ketopyranosidic linkages from the artificial ketoses having a naturally occurring aldohexopyranose backbone. We also reviewed the reports from other research groups. We believe that this paper can contribute to the further development of novel utilizations of 1-*C*-modified sugars.

ACKNOWLEDGEMENTS

We thank Prof. Kaname Katsuraya (Wayo Women's University) for NMR analyses, and Prof. Toshiyuki Inazu (Tokai University) and Dr. Akihiro Yoshida (The Noguchi Institute) for their helpful discussions. We are also grateful to Mr. Ippo Yamazaki, Mr. Yoshiki Oda, Mr. Kenji Morimoto, Ms. Masae Shinbara, Mr. Kazuhide Matsumura, Ms. Yukari Nara and Mr. Ryo Inoue for their supports in experiments.

REFERENCES AND NOTES

1. 'Comprehensive Glycoscience. From Chemistry to Systems Biology', Vol. 1-3, ed. by J. P. Kamerling, G.-J. Boons, Y. C. Lee, A. Suzuki, N. Taniguchi, and A. G. J. Voragen, Elsevier Ltd., Oxford, 2007.
2. 'Carbohydrates in Drug Design', ed. by Z. J. Witczak and K. A. Nieforth, Marcel Dekker, Inc., New York, 1997.
3. 'Carbohydrate Mimics. Concepts and Methods', ed. by Y. Chapleur, H.-J. Altenbach, F. Chretien, J. M. Contelles, F. Nicotra, A. P. Rauter, and S. M. Roberts, Wiley-VCH, 1998.
4. 'The Chemistry of *C*-Glycosides', ed. by D. E. Levy and C. Tang, Pergamon, 1995.
5. (a) M. Benlifa, S. Vidal, D. Gueyrard, P. G. Goekjian, M. Msaddek, and J.-P. Praly, *Tetrahedron Lett.*, 2006, **47**, 6143; (b) D. Pan, J. Liu, C. Senese, A. J. Hopfinger, and Y. Tseng, *J. Med. Chem.*, 2004, **47**, 3075; (c) F. Stolz, M. Reiner, A. Blume, W. Reutter, and R. R. Schmidt, *J. Org. Chem.*, 2004, **69**, 665; (d) L. Somsák, L. Kovács, M. Tóth, E. Ösz, L. Szilágyi, Z. Györgydeák, Z. Dinya, T. Docsa, B. Tóth, and P. Gergely, *J. Med. Chem.*, 2001, **44**, 2843.
6. (a) R. Namme, T. Mitsugi, H. Takahashi, and S. Ikegami, *Tetrahedron Lett.*, 2005, **46**, 3033; (b) X. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Synlett*, 2001, 1885.
7. (a) Y. Yamamoto, K. Yamashita, T. Hotta, T. Hashimoto, M. Kikuchi, and H. Nishiyama, *Chem. Asian J.*, 2007, **2**, 1388; (b) P. A. V. van Hooft, F. E. Oualid, H. S. Overkleeft, G. A. van der Marel,

- J. H. van Boom, and M. A. Leeuwenburgh, *Org. Biomol. Chem.*, 2004, **2**, 1395; (c) X. Li, H. Takahashi, H. Ohtake, M. Shiro, and S. Ikegami, *Tetrahedron*, 2001, **57**, 8053; (d) S. Czernecki and M.-C. Perlat, *J. Org. Chem.*, 1991, **56**, 6289; (e) S. Hanessian and A. Ugolini, *Carbohydr. Res.*, 1984, **130**, 261.
8. (a) Y. Oda and T. Yamanoi, *Synthesis*, 2007, 3021; (b) T. Yamanoi, Y. Oda, S. Matsuda, I. Yamazaki, K. Matsumura, K. Katsuraya, M. Watanabe, and T. Inazu, *Tetrahedron*, 2006, **62**, 10383; (c) T. Yamanoi, S. Matsuda, I. Yamazaki, R. Inoue, K. Hamasaki, and M. Watanabe, *Heterocycles*, 2006, **68**, 673; (d) T. Yamanoi, K. Matsumura, S. Matsuda, and Y. Oda, *Synlett*, 2005, 2973; (e) T. Yamanoi, Y. Oda, I. Yamazaki, M. Shinbara, K. Morimoto, and S. Matsuda, *Lett. Org. Chem.*, 2005, **2**, 242; (f) T. Yamanoi and Y. Oda, *Heterocycles*, 2002, **57**, 229.
 9. T. Yamanoi, Y. Nara, S. Matsuda, Y. Oda, A. Yoshida, K. Katsuraya, and M. Watanabe, *Synlett*, 2007, 785.
 10. T. Yamanoi, R. Inoue, S. Matsuda, K. Katsuraya, and K. Hamasaki, *Tetrahedron: Asymmetry*, 2006, **17**, 2914.
 11. (a) S. Matsuda, T. Yamanoi, and M. Watanabe, *Tetrahedron*, 2008, **64**, 8082. (b) S. Matsuda, K. Matsumura, M. Watanabe, and T. Yamanoi, *Tetrahedron Lett.*, 2007, **48**, 5807.
 12. X. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Tetrahedron*, 2001, **57**, 4297.
 13. A. M. Gómez, C. Uriel, S. Jarosz, S. Valverde, and J. C. López, *Eur. J. Org. Chem.*, 2003, 4830.
 14. B. I. Glänzer and R. Csuk, *Carbohydr. Res.*, 1991, **220**, 79.
 15. R. Namme, T. Mitsugi, H. Takahashi, and S. Ikegami, *Eur. J. Org. Chem.*, 2007, 3758.
 16. G. Májer, A. Borbás, T. Z. Illyés, L. Szilágyi, A. C. Bényei, and A. Lipták, *Carbohydr. Res.*, 2007, **342**, 1393.
 17. M. A. Leeuwenburgh, C. C. M. Appeldoorn, P. A. V. van Hooft, H. S. Overkleeft, G. A. van der Marel, and J. H. van Boom, *Eur. J. Org. Chem.*, 2000, 873.
 18. K. Tomooka, Y. Nakamura, and T. Nakai, *Synlett*, 1995, 321.
 19. P. A. V. van Hooft, M. A. Leeuwenburgh, H. S. Overkleeft, G. A. van der Marel, C. A. A. van Boechel, and J. H. van Boom, *Tetrahedron Lett.*, 1998, **39**, 6061.
 20. L. Lay, M. Meldal, F. Nicotra, L. Panza, and G. Russo, *Chem. Commun.*, 1997, 1469.
 21. T. Yamanoi, Y. Oda, H. Muraishi, and S. Matsuda, *Molecules*, 2008, **13**, 1840.
 22. P. A. V. van Hooft, G. A. van der Marel, C. A. A. van Boechel, and J. H. van Boom, *Tetrahedron Lett.*, 2001, **42**, 1769.
 23. P. A. V. van Hooft, P. F. van Swieten, G. A. van der Marel, C. A. A. van Boechel, and J. H. van Boom, *Synlett*, 2001, 269.
 24. A. M. Gómez, C. Uriel, S. Valverde, S. Jarosz, and J. C. López, *Tetrahedron Lett.*, 2002, **43**, 8935.

25. F. E. McDonald, H. Y. H. Zhu, and C. R. Holmquist, *J. Am. Chem. Soc.*, 1995, **117**, 6605.
26. S. Groothuys, S. (B.) A. M. W. van den Broek, B. H. M. Kuijpers, M. IJsselstijn, F. L. van Delft, and F. P. J. T. Rutjes, *Synlett*, 2008, 111.
27. A. M. Gómez, C. Uriel, S. Valverde, and J. C. López, *Org. Lett.*, 2006, **8**, 3187.
28. A. Dondoni, A. Marra, I. Roji, and M.-C. Scherrmann, *Tetrahedron*, 1996, **52**, 3057.
29. A. Dondoni, S. Daninos, A. Marra, and P. Formaglio, *Tetrahedron*, 1998, **54**, 9859.
30. D. Noort, N. C. R. van Straten, G. J. P. H. Boons, G. A. van der Marel, X. Bossuyt, N. Blanckaert, G. J. Mulder, and J. H. van Boom, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 583.
31. A. Dondoni, A. Marra, M.-C. Scherrmann, and V. Bertolasi, *Chem. Eur. J.*, 2001, **7**, 1371.
32. B. M. Heskamp, D. Noort, G. A. van der Marel, and J. H. van Boom, *Synlett*, 1992, 713.
33. D. Noort, G. A. van der Marel, G. J. Mulder, and J. H. van Boom, *Synlett*, 1992, 224.
34. K. Czifrák, L. Kovács, K. E. Kövér, and L. Somsák, *Carbohydr. Res.*, 2005, **340**, 2328.
35. D. Crich and L. B. L. Lim, *Tetrahedron Lett.*, 1991, **32**, 2565.
36. L. Somsák, L. Kovács, V. Gyóllai, and E. Ósz, *Chem. Commun.*, 1999, 591.
37. A. Borbás, G. Szabovik, Z. Antal, P. Herczegh, A. Agócs, and A. Lipták, *Tetrahedron Lett.*, 1999, **40**, 3639.
38. A. Borbás, G. Szabovik, Z. Antal, K. Fehér, M. Csávás, L. Szilágyi, P. Herczegh, and A. Lipták, *Tetrahedron: Asymmetry*, 2000, **11**, 549.
39. A. Borbás, M. Csávás, L. Szilágyi, G. Májer, and A. Lipták, *J. Carbohydr. Chem.*, 2004, **23**, 133.
40. F. Schweizer, A. Otter, and O. Hindsgaul, *Synlett*, 2001, 1743.
41. M. Penner, D. Taylor, D. Desautels, K. Marat, and F. Schweizer, *Synlett*, 2005, 212.
42. M. Penner and F. Schweizer, *Carbohydr. Res.*, 2007, **342**, 7.
43. S. Czernecki and M.-C. Perlat, *J. Carbohydr. Chem.*, 1990, **9**, 915.
44. R. Caputo, A. Guaragna, G. Palumbo, S. Pedatella, and F. Solla, *Eur. J. Org. Chem.*, 2002, 534.
45. M. de Kort, A. D. Regenbogen, A. R. P. M. Valentijn, R. A. J. Challiss, Y. Iwata, S. Miyamoto, G. A. van der Marel, and J. H. van Boom, *Chem. Eur. J.*, 2000, **6**, 2696.
46. R. Caputo, U. Ciriello, P. Festa, A. Guaragna, G. Palumbo, and S. Pedatella, *Eur. J. Org. Chem.*, 2003, 2617.
47. R. Preuss, K.-H. Jung, and R. R. Schmidt, *Liebigs Ann. Chem.*, 1992, 377.
48. D. Crich and T. J. Ritchie, *J. Chem. Soc., Perkin Trans. 1*, 1990, 945.
49. D. Crich and T. J. Ritchie, *J. Chem. Soc., Chem. Commun.*, 1988, 1461.
50. D. Crich and T. J. Ritchie, *J. Chem. Soc., Chem. Commun.*, 1988, 985.
51. D. Crich and F. Hermann, *Tetrahedron Lett.*, 1993, **34**, 3385.
52. E. Modica, F. Compostella, D. Colombo, L. Franchini, M. Cavallari, L. Mori, G. De Libero, L.

- Panza, and F. Ronchetti, [Org. Lett., 2006, 8, 3255](#).
53. A. Marra, A. Dondoni, and F. Sansone, [J. Org. Chem., 1996, 61, 5155](#).
54. A. Dondoni, M.-C. Scherrmann, A. Marra, and J.-L. Delépine, [J. Org. Chem., 1994, 59, 7517](#).
55. A. Dondoni and A. Marra, [Chem. Rev., 2000, 100, 4395](#).
56. B. M. Heskamp, G. H. Veeneman, G. A. van der Marel, C. A. A. van Boeckel, and J. H. van Boom, [Tetrahedron, 1995, 51, 5657](#).
57. F. Schweizer, A. Lohse, A. Otter, and O. Hindsgaul, [Synlett, 2001, 1434](#).
58. A. Lohse, F. Schweizer, and O. Hindsgaul, [Comb. Chem. High Throughput Screen., 2002, 5, 389](#).
59. F. Schweizer and O. Hindsgaul, [Carbohydr. Res., 2006, 341, 1730](#).
60. J. L. Koviach, M. D. Chappell, and R. L. Halcomb, [J. Org. Chem., 2001, 66, 2318](#).
61. J. W. Lane and R. L. Halcomb, [Tetrahedron, 2001, 57, 6531](#).
62. J. W. Lane and R. L. Halcomb, [J. Org. Chem., 2003, 68, 1348](#).
63. C.-C. Lin, M. Shimazaki, M.-P. Heck, S. Aoki, R. Wang, T. Kimura, H. Ritzèn, S. Takayama, S.-H. Wu, G. Weitz-Schmidt, and C.-H. Wong, [J. Am. Chem. Soc., 1996, 118, 6826](#).
64. D. Crich and T. J. Ritchie, [Carbohydr. Res., 1989, 190, C3](#).
65. F. P. Franke, M. Kapuscinski, and P. Lyndon, [Carbohydr. Res., 1985, 143, 69](#).
66. D. Crich, J.-T. Hwang, and H. Yuan, [J. Org. Chem., 1996, 61, 6189](#).
67. B. M. Heskamp, G. H. Veeneman, G. A. van der Marel, C. A. A. van Boeckel, and J. H. van Boom, [Tetrahedron, 1995, 51, 8397](#).
68. W.-B. Yang, Y.-Y. Yang, Y.-F. Gu, S.-H. Wang, C.-C. Chang, and C.-H. Lin, [J. Org. Chem., 2002, 67, 3773](#).
69. (a) B. Bourdon, M. Corbet, P. Fontaine, P. G. Goekjian, and D. Gueyrard, [Tetrahedron Lett., 2008, 49, 747](#); (b) M. Corbet, B. Bourdon, D. Gueyrard, and P. G. Goekjian, [Tetrahedron Lett., 2008, 49, 750](#); (c) X. Zhu, Y. Jin, and J. Wickham, [J. Org. Chem., 2007, 72, 2670](#); (d) G. S. Coumbarides, M. Motevalli, W. A. Muse, and P. B. Wyatt, [J. Org. Chem., 2006, 71, 7888](#); (e) R. J. K. Taylor, G. D. McAllister, and R. W. Franck, [Carbohydr. Res., 2006, 341, 1298](#); (f) C.-H. Lin, H.-C. Lin, and W.-B. Yang, [Current Topics in Med. Chem., 2005, 5, 1431](#); (g) C. Taillefumier and Y. Chapleur, [Chem. Rev., 2004, 104, 263](#); (h) P. A. Colinas, A. Ponzinibbio, A. Lieberknecht, and R. D. Bravo, [Tetrahedron Lett., 2003, 44, 7985](#); (i) P. A. Colinas, A. Lieberknecht, and R. D. Bravo, [Tetrahedron Lett., 2002, 43, 9065](#); (j) J.-P. Praly, G.-R. Chen, J. Gola, and G. Hetzer, [Eur. J. Org. Chem., 2000, 2831](#).
70. Enzymatic method; (a) E. M. H. Duke, S. Wakatsuki, A. Hadfield, and L. N. Johnson, [Protein Science, 1994, 3, 1178](#); (b) W. Weiser and J. Lehmann, [Biochemistry, 1988, 27, 2294](#); (c) H. W. Klein, M. J. Im, and D. Palm, [Eur. J. Biochem., 1986, 157, 107](#); (d) P. Schlessmann, H. Fritz, J.

- Lehmann, T. Uchiyama, C. F. Brewer, and E. J. Hehre, *Biochemistry*, 1982, **21**, 6606. Chemical method; (e) R. Namme, T. Mitsugi, H. Takahashi, M. Shiro, and S. Ikegami, *Tetrahedron*, 2006, **62**, 9183; (f) S.-J. Hsu, H.-C. Lin, and C.-H. Lin, *Carbohydr. Res.*, 2006, **341**, 1428; (g) H.-C. Lin, W.-P. Du, C.-C. Chang, and C.-H. Lin, *Tetrahedron Lett.*, 2005, **46**, 5071; (h) H.-C. Lin, C.-C. Chang, J.-Y. Chen, and C.-H. Lin, *Tetrahedron: Asymmetry*, 2005, **16**, 297; (i) G. V. M. Sharma, Rakesh, A. S. Chander, V. G. Reddy, M. H. V. R. Rao, and A. C. Kunwar, *Tetrahedron: Asymmetry*, 2003, **14**, 2991; (j) H.-C. Lin, W.-B. Yang, Y.-F. Gu, C.-Y. Chen, C.-Y. Wu, C.-H. Lin, *Org. Lett.*, 2003, **5**, 1087; (k) C.-F. Chang, W.-B. Yang, C.-C. Chang, and C.-H. Lin, *Tetrahedron Lett.*, 2002, **43**, 6515; (l) D. E. Paterson, F. K. Giffin, M.-L. Alcaraz, and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2002, 1323; (m) X. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Tetrahedron*, 2001, **57**, 4283; (n) M.-L. Alcaraz, F. K. Giffin, D. E. Paterson, and R. J. K. Taylor, *Tetrahedron Lett.*, 1998, **39**, 8183.
71. (a) T. Yamanoi, H. Hamada, Y. Oda, and K. Hattori, *Lett. Drug Design Discovery*, 2006, **3**, 547; (b) T. Yamanoi, J. Inagaki, M. Mizuno, and T. Inazu, *Heterocycles*, 2000, **52**, 921; (c) T. Yamanoi, A. Fujioka, and T. Inazu, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1488; (d) T. Yamanoi, K. Nakamura, H. Takeyama, K. Yanagihara, and T. Inazu, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1359; (e) T. Yamanoi, K. Nakamura, S. Sada, M. Goto, Y. Furusawa, M. Takano, A. Fujioka, K. Yanagihara, Y. Satoh, H. Hosokawa, and T. Inazu, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2617; (f) T. Yamanoi, K. Nakamura, H. Takeyama, K. Yanagihara, and T. Inazu, *Chem. Lett.*, 1993, 343; (g) T. Yamanoi and T. Inazu, *Chem. Lett.*, 1990, 849; (h) T. Inazu and T. Yamanoi, *Chem. Lett.*, 1989, 69.
72. T. Inazu and T. Yamanoi, Jpn. Kokai Tokkyo Koho, 1990, JP 02240093.
73. It was reported that the acetylation of a ketopyranose derivative with DMAP-Ac₂O gave the open ring compound. See ref. 32.
74. The ketosidation system using Sc(OTf)₃ was also successfully applicable to the *O*-ketosidation of D-fructofuranose derivatives. T. Yamanoi, N. Misawa, and M. Watanabe, *Tetrahedron Lett.*, 2007, **48**, 6458.
75. We also reported the glycosidation methods using glycosyl acetates. (a) T. Yamanoi, S. Nagayama, H.-K. Ishida, J. Nishikido, and T. Inazu, *Synth. Commun.*, 2001, **31**, 899; (b) T. Yamanoi and I. Yamazaki, *Tetrahedron Lett.*, 2001, **42**, 4009; (c) T. Yamanoi, Y. Iwai, and T. Inazu, *Heterocycles*, 2000, **53**, 1263; (d) T. Yamanoi, Y. Iwai, and T. Inazu, *J. Carbohydr. Chem.*, 1998, **17**, 819.
76. J. Inanaga, Y. Yokoyama, and T. Hanamoto, *Tetrahedron Lett.*, 1993, **34**, 2791.
77. There were several glycosidation reports using Bi(OTf)₃ as follows. (a) K. Ikeda, Y. Ueno, S. Kitani, R. Nishino, and M. Sato, *Synlett*, 2008, 1027; (b) S. Valerio, A. Iadonisi, M. Adinolfi, and A. Ravidà, *J. Org. Chem.*, 2007, **72**, 6097; (c) M. Adinolfi, A. Iadonisi, A. Ravidà, and S. Valerio, *Tetrahedron Lett.*, 2006, **47**, 2595; (d) J. Babu, A. Khare, and Y. Vankar, *Molecules*, 2005,

- [10, 884](#); (e) J. S. Yadav, B. V. S. Reddy, R. K. Srinivasa, L. Chandraiah, and V. Sunitha, *Synthesis*, 2004, 2523; (f) K. Ikeda, Y. Torisawa, T. Nishi, J. Minamikawa, K. Tanaka, and M. Sato, *Bioorg. Med. Chem.*, 2003, 11, 3073.
78. We also found that Bi(OTf)₃ was effectively catalyzed the glucosidation using 1-hydroxy sugars. (a) T. Yamanoi, R. Inoue, S. Matsuda, and K. Hamasaki, *Lett. Org. Chem.*, 2008, 5, 30. (b) T. Yamanoi, R. Inoue, S. Matsuda, K. Iwao, Y. Oda, A. Yoshida, and K. Hamasaki, *Heterocycles*, 2009, 77, 445.
79. A similar paper was reported. See ref. 15.
80. F. B. La Forge and C. S. J. Hudson, *Biol. Chem.*, 1917, 30, 61.
81. M. Takenaka and H. Ono, *Tetrahedron Lett.*, 2003, 44, 999.
82. T. Hatano, R. Yoshihara, S. Hattori, M. Yoshizaki, T. Shingu, and T. Okuda, *Chem. Pharm. Bull.*, 1992, 40, 1703.
83. Other synthetic approaches to an anhydro-D-*altro*-heptulose were as follows. (a) C. G. Francisco, A. J. Herrera, and E. Suárez, *J. Org. Chem.*, 2002, 67, 7439. (b) Z. Hricovíniová-Bíliková and L. Petruš, *Carbohydr. Res.*, 1999, 320, 31. (c) V. Dalmás and C. Demuynck, *Tetrahedron: Asymmetry*, 1993, 4, 1169.
84. T. Ogawa, S. Nakabayashi, and T. Kitajima, *Carbohydr. Res.*, 1983, 114, 225.



Takashi Yamanoi is a chief Scientist of the Synthetic Carbohydrate Chemistry Laboratory at The Noguchi Institute. He graduated from the Department of Chemistry, Tokyo University of Science in 1985 (MS), and started his career in the carbohydrate field as the research scientist at the Noguchi Institute. He obtained his Ph.D. from Tokyo University of Science in 1995. He has been a chief Scientist at The Noguchi Institute since 2002. He is a councilor of the Society of Cyclodextrins, Japan and the Japanese Society for Carbohydrate Research, and is also a member of the editorial advisory board of the journal 'Open Glycoscience' (Bentham Science Publishers

Ltd.).



Sho Matsuda is a researcher of the Synthetic Carbohydrate Chemistry Laboratory at The Noguchi Institute. He received B. S. degree in 2005 and M. S. degree in 2007 from Department of Chemistry, Tokai University. He joined the Supporting Program for Creating University Ventures (2007. 4 ~ 2008. 10, Japan Science and Technology Agency). His current research interests are synthetic organic chemistry and carbohydrate chemistry.