HETEROCYCLES, Vol. 79, 2009, pp. 163 - 194. © The Japan Institute of Heterocyclic Chemistry
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REACTIONS AND USES OF ARTIFICIAL KETOSES[#]

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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]

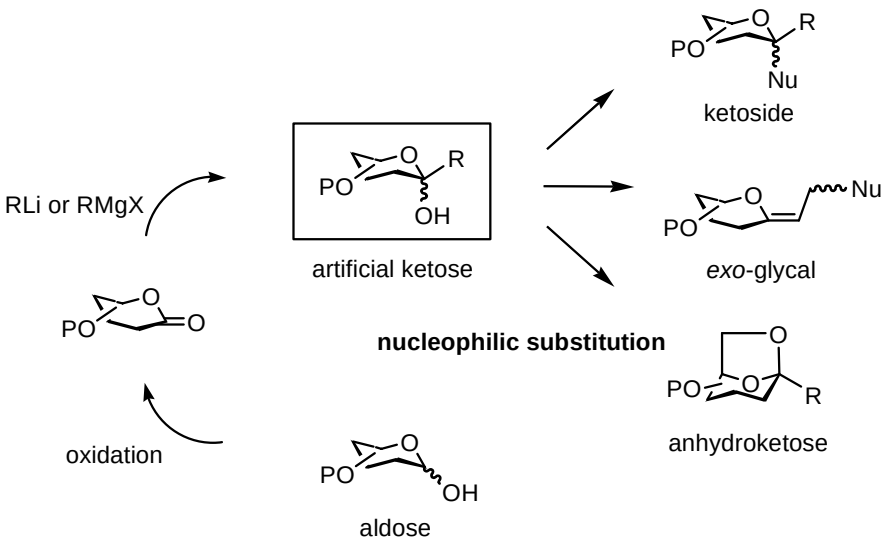
The addition reactions of RLi (or RMgX) to sugarlactone derivatives produced by oxidation of aldoses can readily produce various artificial ketoses whose anomeric carbons are bound to alkyl, alkynyl, alkene, aryl or other groups via a carbon–carbon linkage.[4] The ketoses prepared by this method from naturally occurring aldoses posses 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 mimics[6] and spiroketals[7] 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.

[#]This paper is dedicated to the memory of the late Dr. John W. Daly.

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 mimics[10] and anhydroketopyranoses[11] 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.



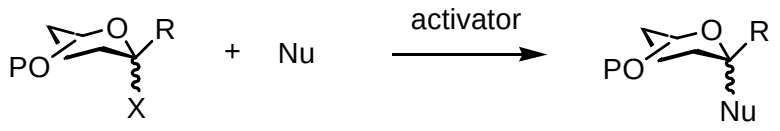
Scheme 1

(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.

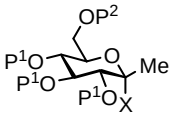
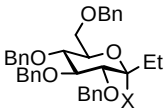
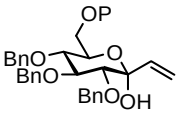
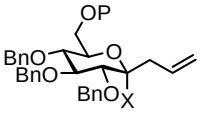
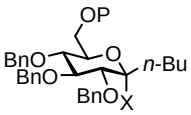
2. FORMATION OF THE KETOPYRANOSIDIC LINKAGES FROM 1-*C*-MODIFIED HEXOPYRANOSES

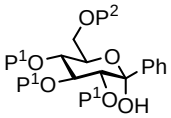
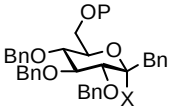
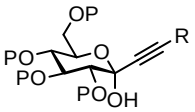
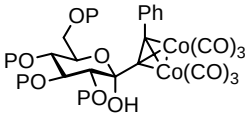
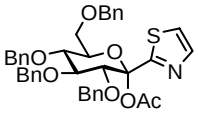
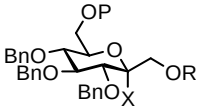
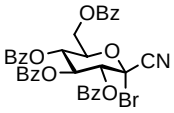
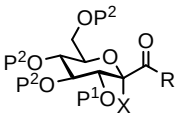
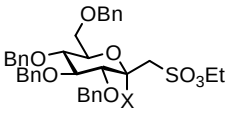
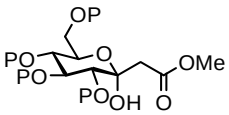
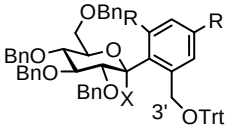
In this section, we summarize published reports on the formation reactions of ketopyranosidic linkages from 1-*C*-modified hexopyranoses, as shown in Scheme 2. Table 1 lists the ketose structures, nucleophiles and activators used, in addition to the reference numbers.

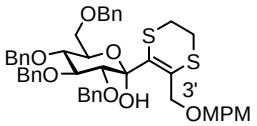
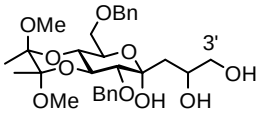
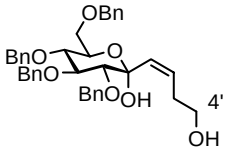
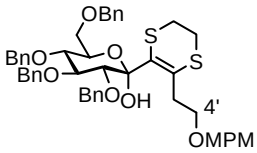
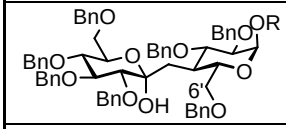
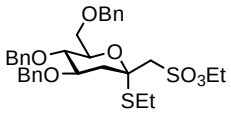
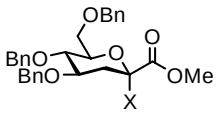
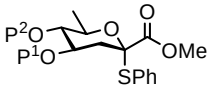
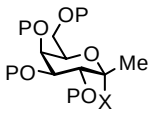
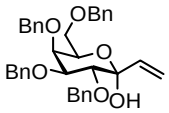
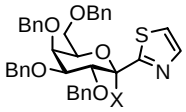
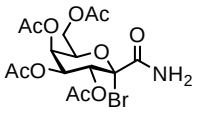
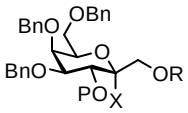


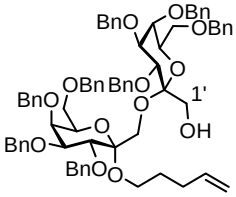
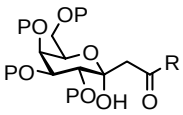
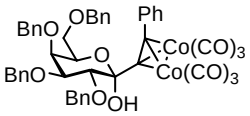
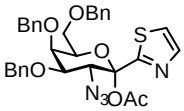
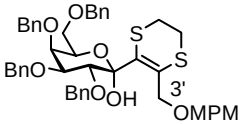
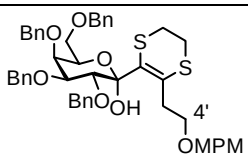
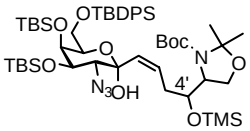
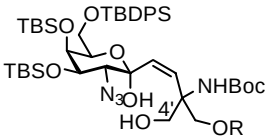
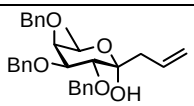
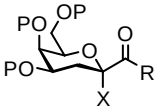
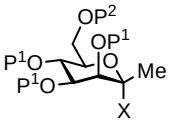
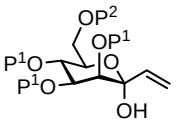
Scheme 2

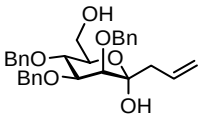
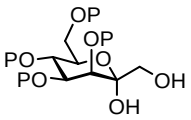
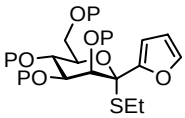
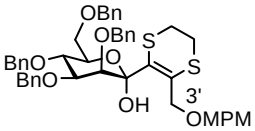
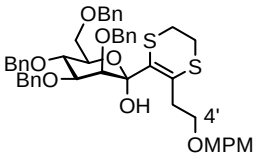
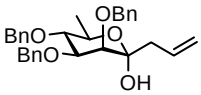
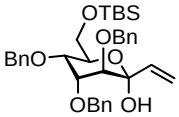
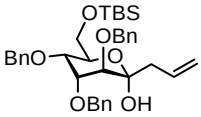
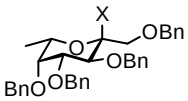
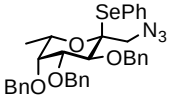
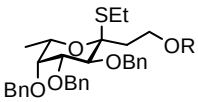
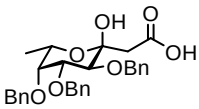
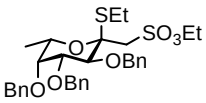
Table 1. Formation of ketopyranosidic linkages from 1-*C*-modified hexopyranoses

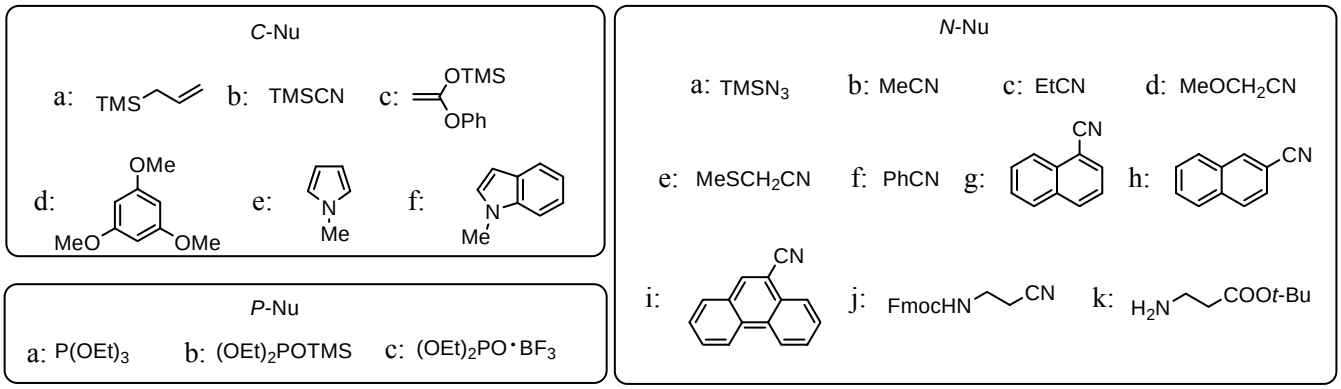
Ketopyranose		Nucleophile	Activator	Reference
	X= OH, P^1= P^2= Bn	ROH	TMSOTf	12
		ROH	Tf_2NH	8b,c,10
		ROH	$Bi(OTf)_3$	10
		C-Nu_a	TMSOTf	8f
		C-Nu_{a-c}, *N*-Nu_a	TMSOTf	8a
		C-Nu_{a-c}, *N*-Nu_a	$BF_3{\cdot}OEt_2$	13
		ROH	Cl_2SO	14
	X= OMe, P^1= P^2= Bn	ROH	$SnCl_4$	12
	X= OMe, P^1= P^2= Ac	ROH	$SnCl_4$	12
	X= OAc, P^1= P^2= Bn	ROH	TMSOTf	15
		ROH	$Sc(OTf)_3$	8b,e
	X= OMpt, P^1 = P^2 = Bn	ROH	$TrtClO_4$	8b
	X= OH, P^1= Bn, P^2= H	ROH (*C*-6)	TfOH	8d
	X= OH, P^1= Bn, P^2= TBS	ROTBS (*C*-6)	TfOH	8d
	X= SEt, P^1= P^2= Bn	ROH	NIS-TfOH	16
	X= OAc	ROH	$Sc(OTf)_3$	8b,e
	X= OH	*C*-Nu_a	TMSOTf	8f
		C-Nu_{a-c}, *N*-Nu_a	TMSOTf	8a
	P= Bn	ROH	TMSOTf	12
		ROH	K-10	7b,17,18,19
		ROH	$BF_3{\cdot}OEt_2$	20
		ROH	$Bi(OTf)_3$	21
	P= TBS	ROH	K-10	22,23
		ROTBS (*C*-6)	TfOH	11a
	X= OH, P= Bn	*C*-Nu_a	TMSOTf	8f
		C-Nu_{a-c}, *N*-Nu_a	TMSOTf	8a
		ROH	K-10	7b,17,19
	X= OTMS, P= Bn	ROH	$BF_3{\cdot}OEt_2$	17
	X= OH, P= TBS	ROH	K-10	22
	X= OH, P= H	ROH (*C*-6)	TfOH	8d
	X= OH, P= Bn	*C*-Nu_a	TMSOTf	8f
		C-Nu_{a-c}, *N*-Nu_a	TMSOTf	8a
	X= OAc, P= Bn	ROH	$Sc(OTf)_3$	8b,e
	X= OH, P= H	ROH (*C*-6)	TfOH	8d

Ketopyranose		Nucleophile	Activator	Reference
	P^1= P^2= Bn	*C*-$Nu_{a,c}$, *N*-Nu_a	TMSOTf	8a
	P^1= P^2= Me	*C*-$Nu_{a,c}$	$BF_3{\cdot}OEt_2$	13
	P^1= Bn, P^2= H	ROH (*C*-6)	TfOH	8d
	X= OH, P= Bn	*C*-Nu_a	TMSOTf	8f
		ROH	Tf_2NH	8b,c
	X= OAc, P= Bn	*C*-Nu_{a-c}, *N*-Nu_a	TMSOTf	8a
		ROH	$Sc(OTf)_3$	8b,e
	X= OH, P= H	ROH (*C*-6)	TfOH	8d
	R= Ph, P= Bn	*C*-$Nu_{a,c,d}$	$BF_3{\cdot}OEt_2$	13,24
	R= Ph, P= Me	*C*-Nu_{a-d}, *N*-Nu_a	$BF_3{\cdot}OEt_2$	13,24
	R= TMS, P= Bn	R'OH	$SnCl_4$-$AgClO_4$	25
		R'OH	K-10	7a
	R= P= Me	R'OH	K-10	7a
	R= H, P= Me	R'OH	K-10	7a
	R= Me, P= Bn	R'OH	TMSOTf	26
	P= Me	*C*-$Nu_{a,b,d}$, *N*-Nu_a	$BF_3{\cdot}OEt_2$	27
	P= Bn	*C*-$Nu_{a,e,g}$	$BF_3{\cdot}OEt_2$	27
		ROH	TMSOTf	28
		P-Nu_a	TMSOTf	29
	X= F, R= CH_2CPh_3, P= TBDPS	R'OH	$SnCl_2$-$AgClO_4$	30
	X= OEt, R= H, P= Bn	R'OH	TMSOTf	31
	X= Br, R= Ac, P= Bn	R'OH	$Hg(CN)_2$	32
	X= F, R= P= Bn	R'OH	Cp_2ZrCl_2-$AgBF_4$	32
	X= OH, R= H, P= Bn	R'OH	TfOH	7c
		R'OH	TsOH-TfONa	7c
		N-Nu_{b-e}	$BF_3{\cdot}OEt_2$	33
		R'OH	$BF_3{\cdot}OEt_2$	33
		NaN_3		34
	X= Cl, R= OMe, P^1= TBS, P^2= Bn	R'OH	$MgBr_2$	35
	X= Br, R= NH_2, P^1= P^2= Ac	$(Me)_2CO$	Ag_2CO_3	36
		DMSO	AgF	36
	X= SEt	ROH	NIS-TfOH	16,37-39
	X= OH	*N*-Nu_a	$BF_3{\cdot}OEt_2$	16
	P= Bn	*C*-Nu_b	TMSOTf	40
		ROH	$BF_3{\cdot}OEt_2$	40
		N-$Nu_{b,f}$	TMSOTf	41,42
	P= Me	*C*-Nu_b	TMSOTf	40
	R= H	R'OTrt (*C*-3')	$BF_3{\cdot}OEt_2$-Et_3SiH	7d,43
	R= OMe	R'OTrt (*C*-3')	$BF_3{\cdot}OEt_2$-Et_3SiH	7d

Ketopyranose		Nucleophile	Activator	Reference
		ROMPM(*C*-3')	$BF_3{\cdot}OEt_2$	44
		ROH(*C*-3') ROH(*C*-3') ROH(*C*-3')	HOAc CSA TfOH	45 45 45
		ROH (*C*-4')	CSA	7e
		ROMPM (*C*-4')	$BF_3{\cdot}OEt_2$	46
	R= Me R= Bn	R'OBn (*C*-6') R'OBn (*C*-6')	$BF_3{\cdot}OEt_2$ $BF_3{\cdot}OEt_2$	47 47
		ROH	NIS-TfOH	16
	X= SPh X= Cl	ROH ROH ROH ROH	NBS $Hg(OAc)_2$ $HgCl_2$ Ag_2SO_4	48,49 48,49 48 49,50
	P^1= TBS, P^2= Bn P^1= P^2= Bn	ROH ROH	$HgCl_2$ AgOTf	51 51
	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	12 12 12 15
		ROH ROH	TMSOTf $BF_3{\cdot}OEt_2$	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 $BF_3{\cdot}OEt_2$ TMSOTf $BF_3{\cdot}OEt_2$	28,31,53 29,31 54,55 31 31 31
		$(Me)_2CO$ DMSO	Ag_2CO_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	$BF_3{\cdot}OEt_2$ IDCP Cp_2ZrCl_2-AgOTf Cp_2ZrCl_2-AgOTf TfOH TsOH-TfONa	32,56 32,56 32,56 56 7c 7c

Ketopyranose		Nucleophile	Activator	Reference
		ROH (*C*-1')	NIS-TMSOTf	31
	R= OH, P= Bn	*N*-Nu_f	TMSOTf	57
		N-Nu_{f-i}	TMSOTf	58
		N-$Nu_{b,f,j,k}$	TMSOTf	41
		N-$Nu_{b,f}$	TMSOTf	42
	R= OMe, P= Bn	*C*-Nu_b	TMSOTf	40
		R'OH	$BF_3{\cdot}OEt_2$	40
	R= OMe, P= Me	*C*-Nu_b	TMSOTf	40,59
	R= OBn, P= Bn	*C*-Nu_b	TMSOTf	40,59
		*C*-$Nu_{a,e,f}$	$BF_3{\cdot}OEt_2$	27
		*P*-Nu_a	TMSOTf	29
		ROMPM (*C*-3')	$BF_3{\cdot}OEt_2$	44
		ROMPM (*C*-4')	$BF_3{\cdot}OEt_2$	46
		ROTMS (*C*-4')	CSA	60
	R= H	R'OH (*C*-4')	CSA	61
	R= DMB	R'OH (*C*-4')	CSA	62
		ROH	K-10	7b
	X= OH, R= OH, P= H	R'OH	Dowex 50W(H^+)	63
	X= SPh, R= OMe, P= TBS	R'OH	NBS	48,64
		R'OH	$HgCl_2$	48,64
		R'OH	$Hg(OAc)_2$	48
	X= OH, P^1= P^2= Bn	ROH	$Bi(OTf)_3$	10
		ROH	TMSOTf	12
	X= OMe, P^1= P^2= Bn	ROH	$SnCl_4$	12
	X= OMe, P^1= P^2= Ac	ROH	$SnCl_4$	12
	X= OAc, P^1= P^2= Bn	ROH	TMSOTf	15
	X= OH, P^1= Bn, P^2= H	ROH (*C*-6)	TfOH	8d
	P^1= P^2= Bn	ROH	TMSOTf	12
	P^1= Bn, P^2= TBS	ROTBS (*C*-6)	TfOH	11a

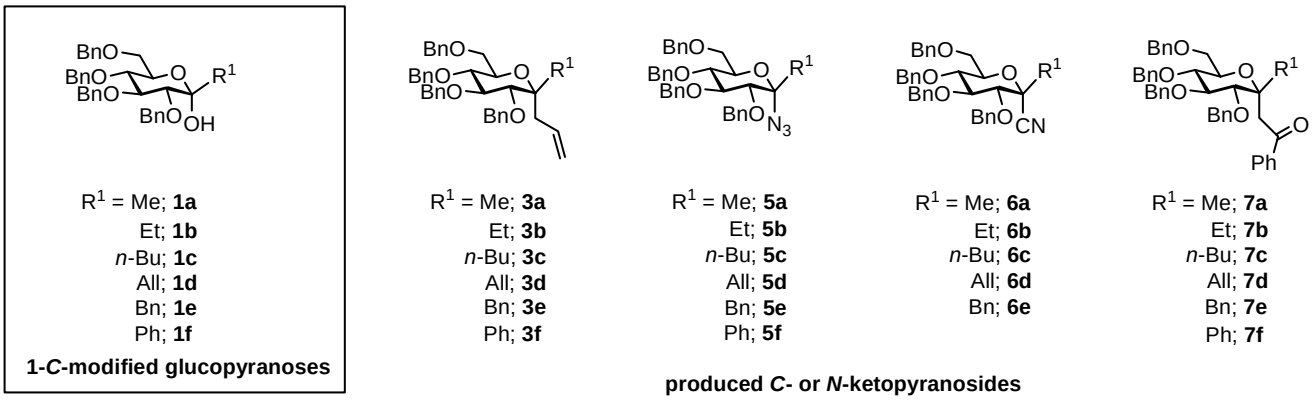
Ketopyranose		Nucleophile	Activator	Reference
		ROH (*C*-6)	TfOH	11a
	P= Bn P= H	ROH ROH ROH	TfOH TsOH-TfONa HCl	7c 7c 65
	P= Me P= Bn P= $CH_2CH{=}CH_2$	ROH ROH ROH ROH	AgOTf-pyridine AgOTf-pyridine AgOTf-pyridine AgOTf-DBMP	66 66 66 66
		ROMPM (*C*-3’)	$BF_3{\cdot}OEt_2$	44
		ROMPM (*C*-4’)	$BF_3{\cdot}OEt_2$	46
		ROH	K-10	7b
		ROTBS (*C*-6)	TfOH	11a,b
		ROTBS (*C*-6)	TfOH	11a
	X= OH X= SEt	ROH ROH	$BF_3{\cdot}OEt_2$ IDCP (IDCT)	56 56
		ROH ROH	NIS NIS	67 67
	R= TBDPS R= SEM	R’OH R’OH	IDCP (IDCT) IDCP (IDCT)	56 56
		*N*-Nu_f	TMSOTf	41,42
		ROH	NIS-TfOH	38



3. NUCLEOPHLIC 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 mimics[10] and anhydroketopyranoses[11] from the 1-*C*-modified hexopyranoses. This section describes these results.

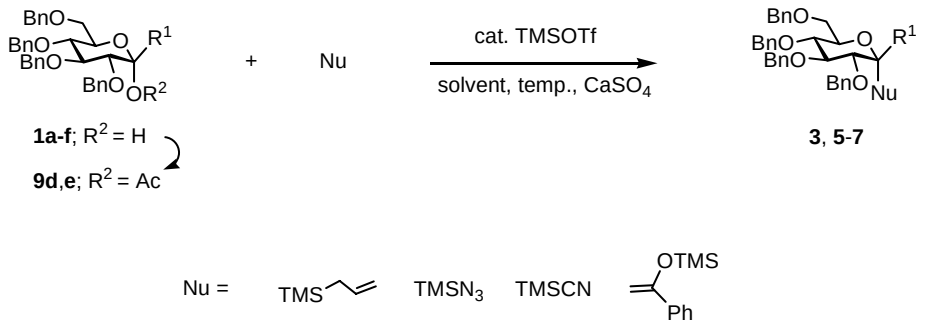
3.1 Formation of *C*- and *N*-ketopyranosidic linkages from 1-*C*-modified D-glucopyranose



Scheme 3

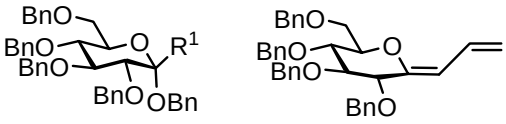
In this section, we describe the *C*- and *N*-ketosidations of the 1-*C*-modified D-glucopyranose derivatives with several nucleophiles.[8a,f] Scheme 3 shows the utilized glucopyranose derivatives (**1a**–**f**) carrying the methyl, ethyl, *n*-butyl, allyl, benzyl and phenyl groups at the anomeric carbon centres as well as the ketopyranosides synthesized in the study. We used allyltrimethylsilane, trimethylsilyl azide ($TMSN_3$), 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 °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**.



R^1 = Me; **2a**
All; **4d**
Bn; **4e**

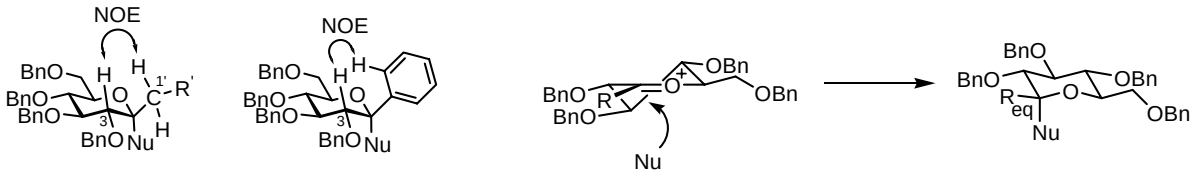
8

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 $MeCN/CH_2Cl_2$ (v/v = 1/1) at −78 °C. Under similar conditions, all the reactions of **9d** and **9e** with allyltrimethylsilane, $TMSN_3$, 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 $^4C_1$ 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.

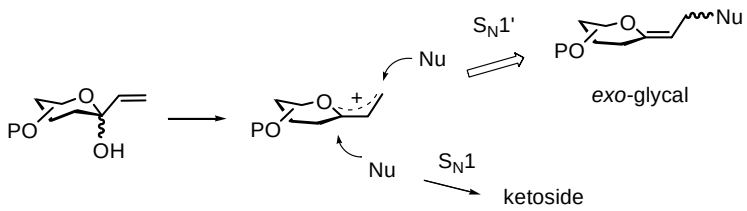
Table 2. *C*- or *N*-Ketosidation using 1-*C*-modified D-glucopyranoses

Entry[a]	Ketose	Nucleophile	Sovlent	Temp/ °C	Product	Yield/%
1[b]	**1a**	$TMSCH_2CH=CH_2$	CH_2Cl_2	-10	**3a**	49 (30)[c]
2[b]	**1a**	$TMSCH_2CH=CH_2$	Et_2O	-10	**3a**	Trace (25)[c]
3[b]	**1a**	$TMSCH_2CH=CH_2$	MeCN	-10	**3a**	67 (15)[c]
4[d]	**1a**	$TMSCH_2CH=CH_2$	MeCN	-10	**3a**	76 (9)[c]
5[e]	**1a**	$TMSCH_2CH=CH_2$	MeCN	-10	**3a**	63 (9)[c]
6[d]	**1a**	$TMSCH_2CH=CH_2$	MeCN	0	**3a**	69 (14)[c]
7[d]	**1a**	$TMSCH_2CH=CH_2$	MeCN	-20	**3a**	79 (7)[c]
8[d]	**1a**	$TMSCH_2CH=CH_2$	MeCN	-40	**3a**	84 (3)[c]
9[f]	**1a**	$TMSCH_2CH=CH_2$	MeCN	-40	**3a**	40 (7)[c]
10	**1a**	$TMSCH_2CH=CH_2$	MeCN	-40	**3a**	88
11	**1b, 1c, 1f**	$TMSCH_2CH=CH_2$	MeCN	-40	**3b**, **3c**, **3f**	88-95
12	**1d**	$TMSCH_2CH=CH_2$	MeCN	-40	**3d**	31 (17)[g]
13	**1e**	$TMSCH_2CH=CH_2$	MeCN	-40	**3e**	18
14[h]	**1d**	$TMSCH_2CH=CH_2$	MeCN/CH_2Cl_2 = 1/1	-78	**3d**	53 (16)[i]
15[j]	**1e**	$TMSCH_2CH=CH_2$	MeCN/CH_2Cl_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**	$H_2C=C(OTMS)Ph$	MeCN	-40	**7a-c**, **7f**	78-98
23	**1d**	$H_2C=C(OTMS)Ph$	MeCN	-40	**7d**	53
24	**1e**	$H_2C=C(OTMS)Ph$	MeCN	-40	**7e**	61
25	**9e**	$TMSCH_2CH=CH_2$	MeCN	-40	**3e**	66 (10)[k]
26	**9e**	$TMSCH_2CH=CH_2$	MeCN/CH_2Cl_2 = 1/1	-78	**3e**	80
27	**9d**	$TMSCH_2CH=CH_2$	MeCN/CH_2Cl_2 = 1/1	-78	**3d**	72
28	**9d**	$TMSN_3$	MeCN/CH_2Cl_2 = 1/1	-78	**5d**	94
29	**9e**	$TMSN_3$	MeCN/CH_2Cl_2 = 1/1	-78	**5e**	91
30	**9d**	TMSCN	MeCN/CH_2Cl_2 = 1/1	-78	**6d**	95
31	**9e**	TMSCN	MeCN/CH_2Cl_2 = 1/1	-78	**6e**	86
32	**9d**	$H_2C=C(OTMS)Ph$	MeCN/CH_2Cl_2 = 1/1	-78	**7d**	93
33	**9e**	$H_2C=C(OTMS)Ph$	MeCN/CH_2Cl_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**.

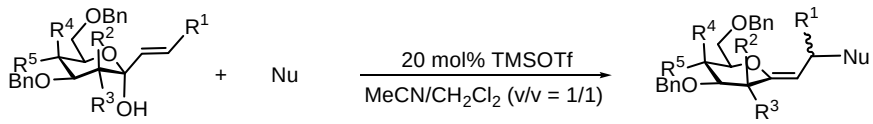
3.2 Formation of *exo*-glycals from 1-*C*-vinyl-hexopyranose derivatives

In this section, we describe our synthetic approach to *exo*-glycals[18,20,68,69] from 1-*C*-vinyl-hexopyranose derivatives.[9] 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,b,12,17-23] 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, $TMSN_3$ 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 $TMSN_3$ 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 $TMSN_3$ 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 $MeCN/CH_2Cl_2$ (v/v = 1/1) at −78 °C. Table 3 lists these results.

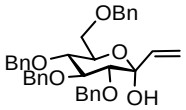
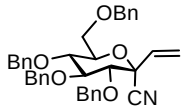
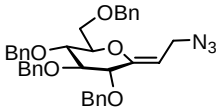
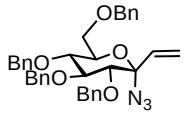
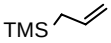
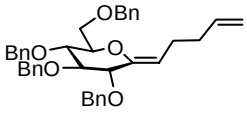
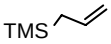
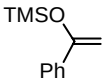
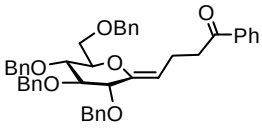
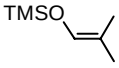
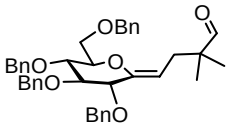
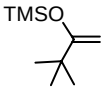
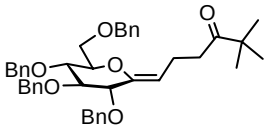
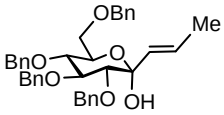
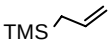
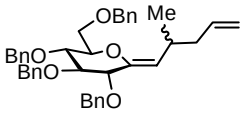
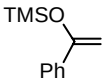
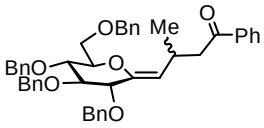
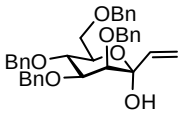
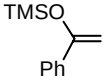
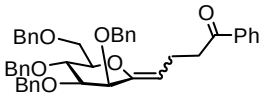
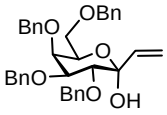
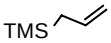
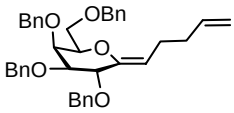


10: R^1= H; R^2= H; R^3= OBn; R^4= H; R^5= OBn
18: R^1= Me; R^2= H; R^3= OBn; R^4= H; R^5= OBn
21: R^1= H; R^2= OBn; R^3= H; R^4= H; R^5= OBn
22: R^1= H; R^2= H; R^3= OBn; R^4= OBn; R^5= H

12, **13**, **15-17**, **19**, **20**, **23**, **24**

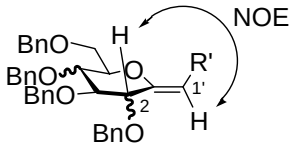
Scheme 8

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

Entry[a]	Ketose	Nucleophile	Product (Yield/%)	
1[b]	 **10**	TMSCN		 **11** (88)
2[b]	**10**	$TMSN_3$	 **12** (64)	 **14** (16)
3[b]	**10**		 **13** (39)	
4	**10**		**13** (58)	
5	**10**		 **15** (64)	
6	**10**		 **16** (61)	
7	**10**		 **17** (74)	
8	 **18**		 **19** (68)[c]	
9	**18**		 **20** (79)[d]	
10	 **21**		 **23** (94)[e]	
11	 **22**		 **24** (76)	

[a] Reaction conditions: solvent: $MeCN/CH_2Cl_2$ (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-glucopyranose **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.



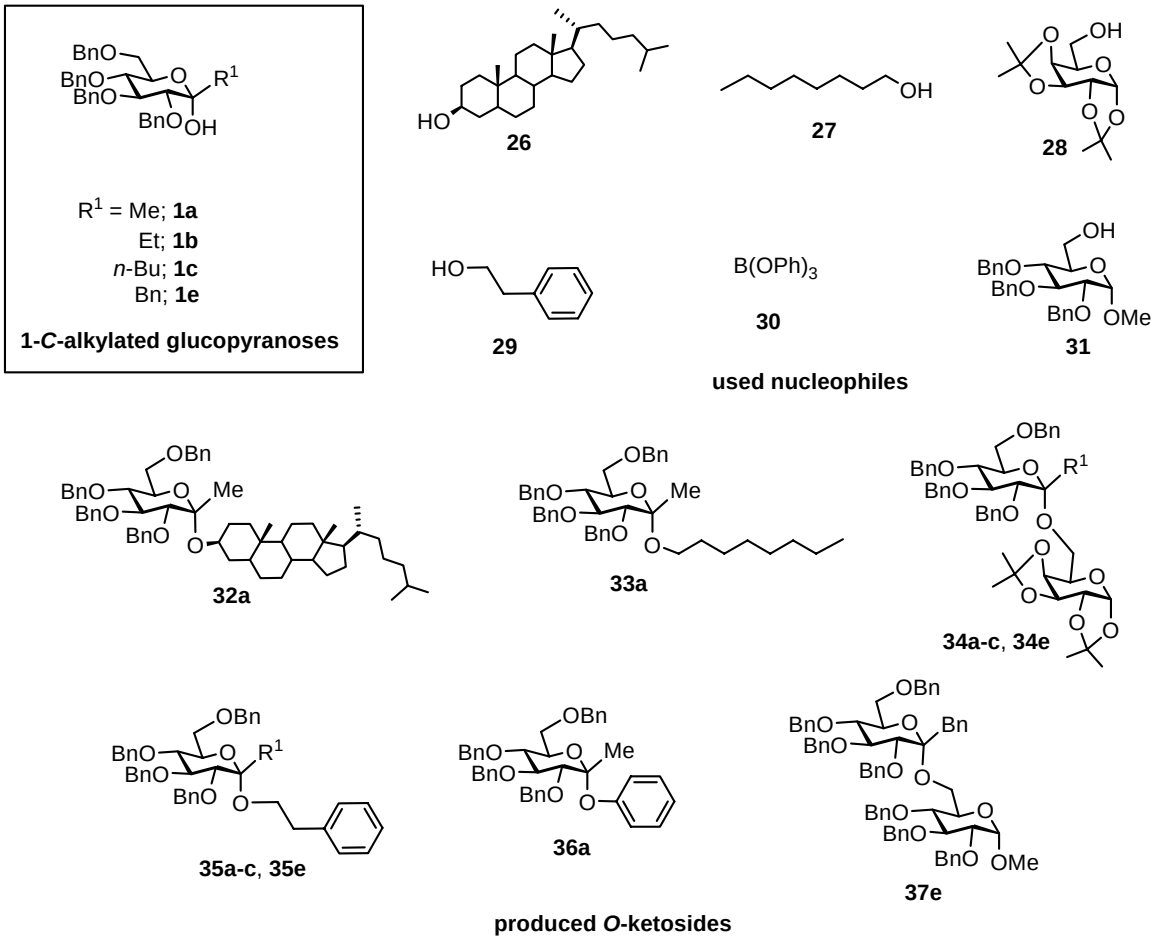
Scheme 9

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-glucopyranoses

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.[6a,b,69b,f,g,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-glucopyranose derivatives. Scheme 10 shows the glucopyranose derivatives (**1a**–**c**, **1e**) carrying the

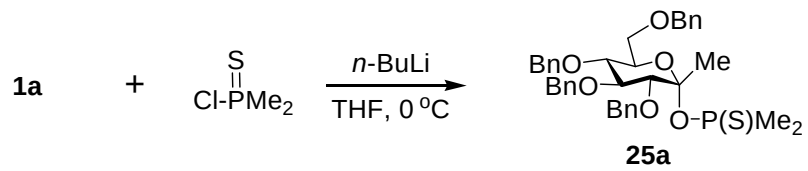
methyl, ethyl, *n*-butyl and benzyl groups at the anomeric carbon centers, utilized alcohols and produced *O*-ketopyranosides.



Scheme 10

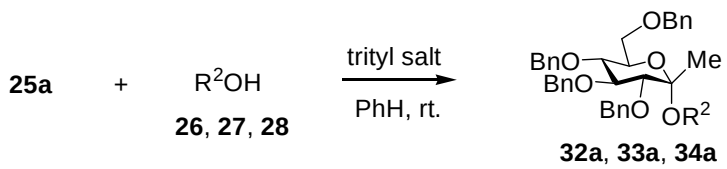
3.3.1 *O*-Ketosidation using dimethylphosphinothioate

We previously studied glycosidations using 1-*O*-dimethylphosphinothioyl 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 dimethylphosphinothioyl (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. 3β-cholestanol (**26**) smoothly glycosylated **25a** using 10 mol% $TrtClO_4$ in benzene at room temperature to afford **32a** in a high yield of 88% with an α-stereoselectivity. The reaction using 5 mol% $TrtClO_4$ slightly decreased the yield of **32a** to 71%. The reactions using 10 mol% of $TrtSbCl_6$, $TrtBF_4$ and $TrtSnCl_5$ as other trityl salts afforded **32a** in moderate yields from 34% to 43%. Under similar reaction conditions using 10 mol% $TrtClO_4$, 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

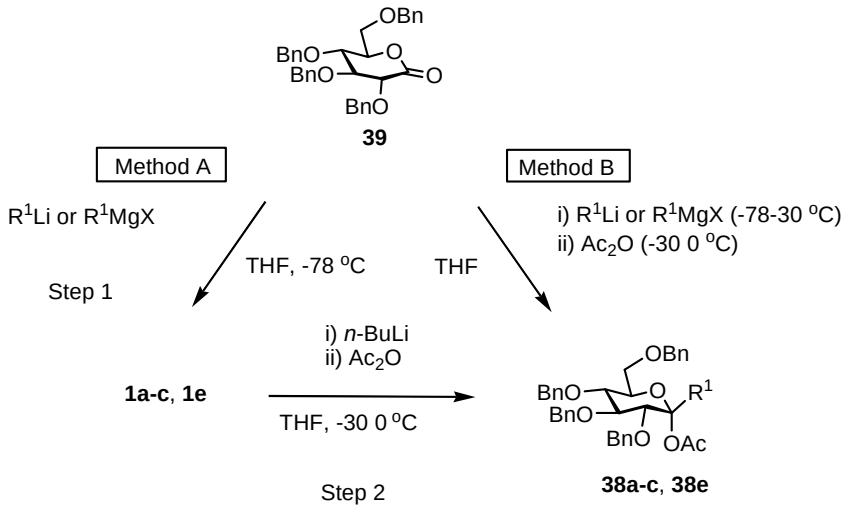
Table 4. *O*-Ketosidation using 1-*C*-methyl-D-glucopyranosyl dimthylphosphinothioate

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

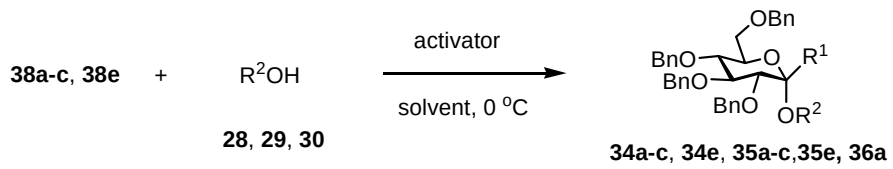
The acetyl group, less bulky than the Mpt group, could be smoothly introduced into **1a**–**c** and **1e** to prepare the corresponding acetates, as mentioned in the Section 3.1. Although the ordinary acetylation of **1a** using Ac_2O-pyridine could not give **38a** at all,[73] the use of *n*-BuLi as a strong base in lieu of pyridine was effective. We acetylated the compounds **1a**–**c** and **1e** with *n*-BuLi and Ac_2O 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 Ac_2O 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,e] 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, $TrtClO_4$ and $BF_3{\bullet}OEt_2$ as the activators in CH_2Cl_2 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 CH_2Cl_2, 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_2Cl_2	**35a**	76
2	**38a**	**29**	$Sc(OTf)_3$	CH_2Cl_2	**35a**	80
3	**38a**	**29**	TMSOTf	CH_2Cl_2	**35a**	69
4	**38a**	**29**	$TrtClO_4$	CH_2Cl_2	**35a**	74
5	**38a**	**29**	BF_3•OEt_2	CH_2Cl_2	**35a**	67
6[c]	**38a**	**29**	$Sc(OTf)_3$	CH_2Cl_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_2Cl_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.

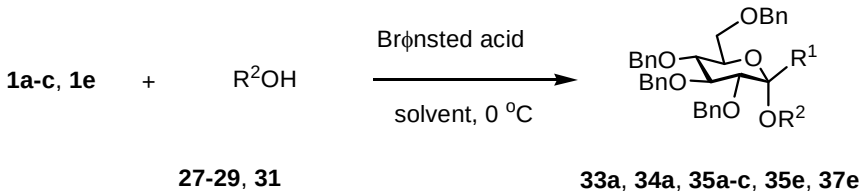
The high α-stereoselectivity of this reaction could be explained by the anomeric effect and by the inhibition of the β-glucoside formation by the 1,3-diaxial interaction. In addition, we examined the

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,c] Dehydrative *O*-ketosidation of **1a**–**c** and **1e** was performed using a Brϕnsted acid expected to be resistant to water.

The reaction of **1a** with **29** was investigated using 5 mol% of camphorsulfonic acid, CF_3CO_2H and TfOH in CH_2Cl_2 at 0 °C in the presence of $CaSO_4$. 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 $C_8F_{17}SO_3H$ and Tf_2NH acting as the Brϕnsted acid analogues of TfOH, and HBF_4 to be effective under similar reaction conditions. In particular, Tf_2NH 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*-modofied D-glucopyranoses

Entry[a]	Ketose	Alcohol	Brϕnsted acid (mol%)	Solvent	Product	Yield/%
1	**1a**	**29**	Camphorsulfonic acid (5)	CH_2Cl_2	**35a**	No reaction
2	**1a**	**29**	CF_3CO_2H (5)	CH_2Cl_2	**35a**	No reaction
3	**1a**	**29**	TfOH (5)	CH_2Cl_2	**35a**	59
4	**1a**	**29**	TfOH (5)	MeCN	**35a**	73
5	**1a**	**29**	$C_8F_{17}SO_3H$ (5)	MeCN	**35a**	56
6	**1a**	**29**	Tf_2NH (5)	MeCN	**35a**	77
7	**1a**	**29**	HBF_4 (5)	MeCN	**35a**	73
8	**1a**	**29**	Tf_2NH (10)	MeCN	**35a**	69
9	**1a**	**29**	Tf_2NH (3)	MeCN	**35a**	65
10	**1a**	**29**	Tf_2NH (1)	MeCN	**35a**	56
11	**1b**	**29**	Tf_2NH (5)	MeCN	**35b**	57
12	**1c**	**29**	Tf_2NH (5)	MeCN	**35c**	64
13	**1e**	**29**	Tf_2NH (5)	MeCN	**35e**	56
14	**1a**	**27**	Tf_2NH (5)	MeCN	**33a**	78
15[b]	**1a**	**28**	Tf_2NH (5)	MeCN	**34a**	55
16[b]	**1e**	**31**	TfOH (5)	MeCN	**37e**	66

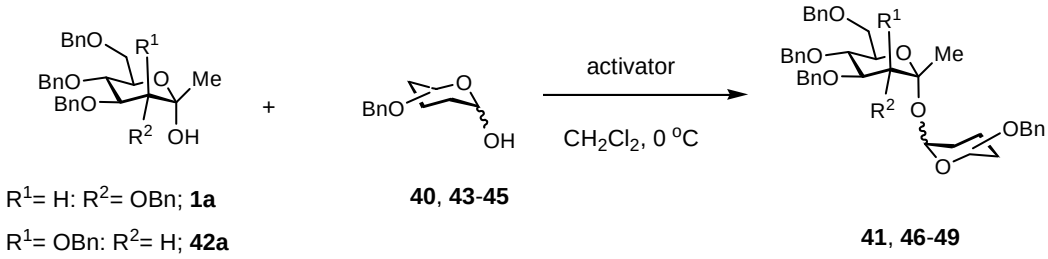
[a] Reaction conditions; molar ratio; **1a-c**, **1e**: alcohol: Brϕnsted acid = 1:1: 0.05. Reaction time; 2 h; reaction temperature; 0 °C. [b] Reaction conditions; molar ratio; **1a**, **1e**: alcohol: Brϕnsted acid = 1.5:1: 0.075. Reaction time; 3 h; reaction temperature; 0 °C.

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,c,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% Tf_2NH in MeCN at 0 °C for 3 h in the presence of $CaSO_4$, 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 Tf_2NH.

When we changed the solvent from MeCN to CH_2Cl_2, 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 CH_2Cl_2. 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 $BiCl_3$ did not work at all.



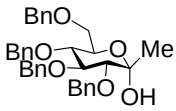
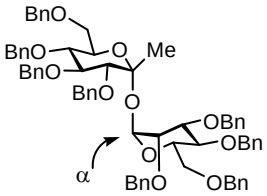
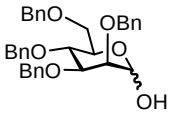
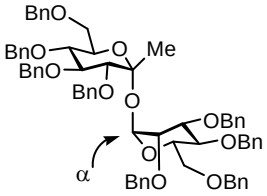
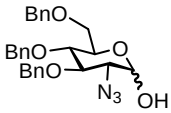
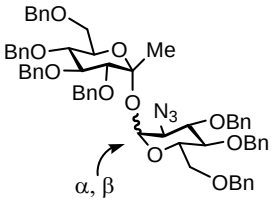
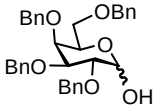
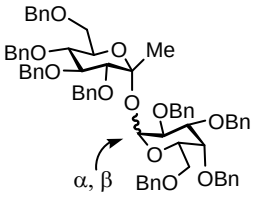
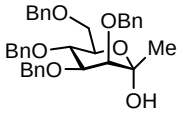
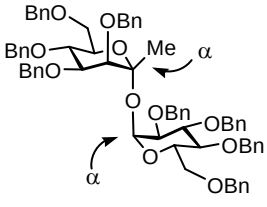
Scheme 16

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 Tf_2NH 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 CH_2Cl_2 solvent based on the NMR spectra. Compounds **40** and **43**–**45** were dissolved in CD_2Cl_2, 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.

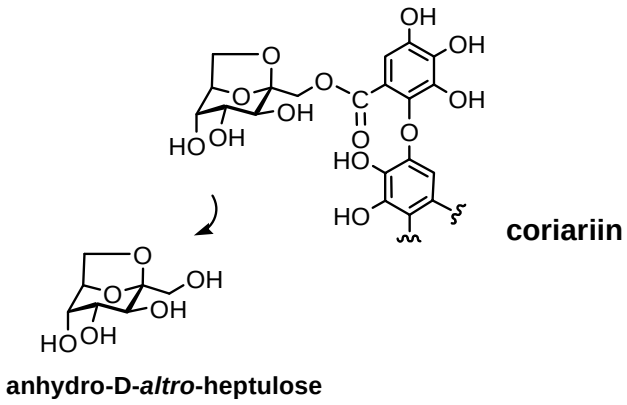
Table 7. Synthesis of trehalose mimics by 1-*C*-methyl-D-hexopyranosylation

Entry[a]	Ketose	Aldose	Solvent	Activator	Product (Yield/%)	α/β Ratio[b]
1	 **1a**	**40**	MeCN	Tf_2NH	 **41** (47)	α only
2	**1a**	**40**	CH_2Cl_2	Tf_2NH	**41** (87)	α only
3	**1a**	**40**	CH_2Cl_2	$Yb(OTf)_3$	**41** (21)	α only
4	**1a**	**40**	CH_2Cl_2	$Sc(OTf)_3$	**41** (80)	α only
5	**1a**	**40**	PhMe	$Sc(OTf)_3$	**41** (61)	α only
6	**1a**	**40**	CH_2Cl_2	$Bi(OTf)_3$	**41** (89)	α only
7	**1a**	**40**	CH_2Cl_2	$BiCl_3$	**41** (Trace)	α only
8	**1a**	 **43**	CH_2Cl_2	Tf_2NH	 **46** (64)	α only
9	**1a**	**43**	CH_2Cl_2	$Bi(OTf)_3$	**46** (75)	α only
10	**1a**	 **44**	CH_2Cl_2	Tf_2NH	 **47** (90)	78/22
11	**1a**	**44**	CH_2Cl_2	$Bi(OTf)_3$	**47** (84)	58/42
12	**1a**	 **45**	CH_2Cl_2	Tf_2NH	 **48** (83)	87/13
13	**1a**	**45**	CH_2Cl_2	$Bi(OTf)_3$	**48** (89)	76/24
14	 **42a**	**40**	CH_2Cl_2	Tf_2NH	 **49** (37)	α only
15	**42a**	**40**	CH_2Cl_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

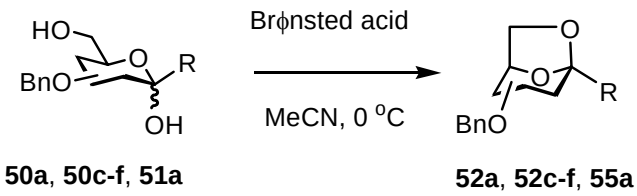
Several anhydroketopyranoses having 6,8-dioxabicyclo[3.2.1]octane structures are found in natural products such as *Sedum spectabile*,[80] *Smallanthus sonchifolius*,[81] and *Coriaria japonica* A.[82] Coriariin found in *C. japonica* A has an anhydro-D-*altro*-heptulose bound to a tannin molecule via an ester linkage, as shown in Scheme 17. Its analogues possess biologically important antitumour and antivirus 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

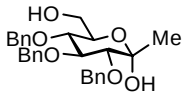
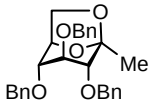
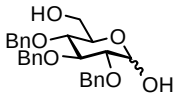
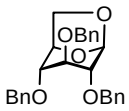
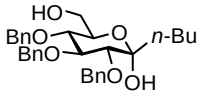
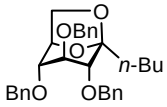
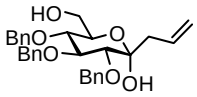
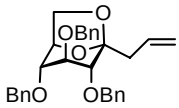
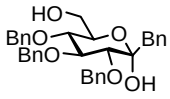
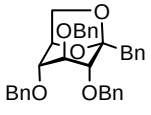
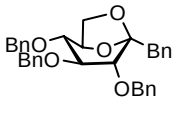
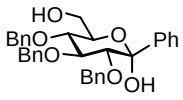
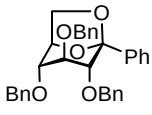
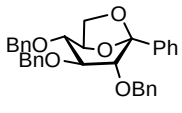
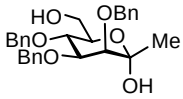
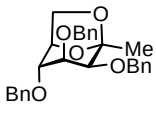
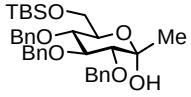
3.5.1 Formation of anhydroketopyranoses by the intramolecular *O*-ketosidation

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	Brϕnsted acid (mol%)	Product (Yield/%)
1[b]	 **50a**	Camphorsulfonic acid (20)	 **52a** (59)
2	**50a**	Tf_2NH (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)

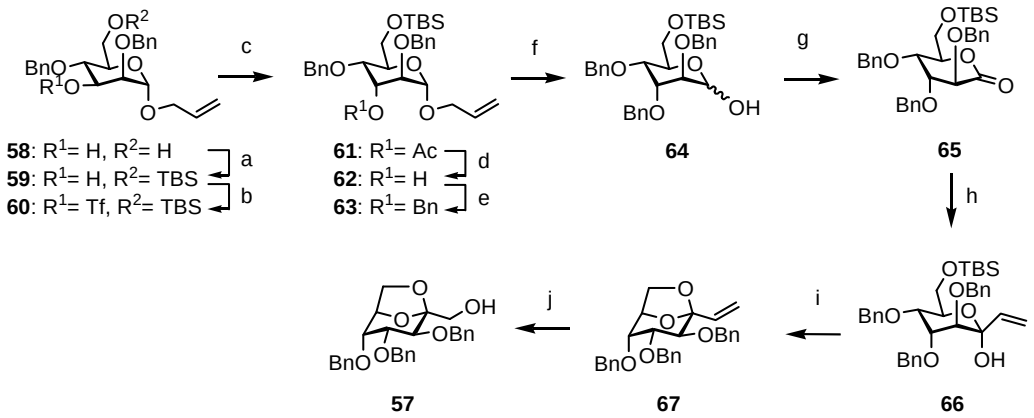
[a] Reaction conditions; solvent: MeCN; reaction time: 2 h; reaction temperature: 0 °C.
[b] Reaction time: 30 h.

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, Tf_2NH and TfOH as the Brønsted acid in MeCN at 0 °C gave the desired **52a** in 59%, 82% and 84% yields, respectively. Tf_2NH 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 $^4C_1$ into $^1C_4$ 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 $^1C_4$ 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.), CH_2Cl_2, rt, 2 h, 88%; (b) Tf_2O (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) $PdCl_2$ (3 equiv.), AcOH-AcONa buffer, sonication, 30 °C, 4 h, 87%; (g) DMSO, Ac_2O, rt, overnight, 99%; (h) vinylMgCl (1.2 equiv.), $CeCl_3$ (1.2 equiv.), toluene, -78 °C, 1 h, 62%; (i) TfOH (0.05 equiv.), MeCN, 0 °C, 2h, 88%; (j) O_3, Ph_3P (5 equiv.), CH_2Cl_2, -78 °C, 45 min., then $NaBH_4$ (8 equiv.), THF, 0 °C, 3 h, 72%.

Scheme 19

We applied the aforementioned anhydroketopyranosylation to the synthesis of an anhydro-D-*altro*-heptulose[83] found in *C. japonica* A.[11a,b] Our synthetic target was the partially benzylated anhydro-D-*altro*-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-altropyranose derivative, (ii) introduction of a vinyl group to the C-1 position of the altropyranose derivative to produce a 1-*C*-vinylated D-altropyranose derivative, (iii) anhydroketopyranosylation of the 1-*C*-vinylated D-altropyranose 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 CH_2Cl_2. Introduction of a Tf group to the C-3 position was performed using Tf_2O 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 $PdCl_2$ in AcOH-AcONa at 30 °C for 4 h under ultrasonic conditions. Oxidation of **64** using DMSO-Ac_2O 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 $CeCl_3$ 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 $CaSO_4$ 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 °C for 45 min and subsequent reduction using $NaBH_4$ at 0 °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.

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