Contribution

Application of Saccharides to the Synthesis of Biologically Active Compounds

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1. Introduction

Chemistry laboratories at universities are often given a unique nickname based on their research areas such as “metal catalyst specialist” or “natural product specialist” with or without knowing. Our laboratory might be called “sugar specialist”.

Generally, saccharides have been synonymous for a “formidable” project for many chemists. They misunderstand that the laboratory dealing with saccharides must require specialized techniques. However, if one understands the properties of saccharides, the methods commonly used in organic chemistry can be applied. Our laboratory is currently engaged in two research areas - saccharide chemistry and process chemistry. Although these two areas may seem totally different, they share fundamental principles of chemistry and are closely related to each other. From this standpoint, we have applied saccharide chemistry as a basis of synthetic chemistry to approach various projects.

In this article we will describe our recent research for the synthesis of biologically active compounds from saccharides and their usefulness in the organic synthetic chemistry and pharmaceutical chemistry. We would be delighted if the readers would have a chance to feel more familiar with saccharide chemistry through this article.

2. Chemistry of Saccharides

Various macromolecules that make up living systems can be roughly divided into proteins, lipids, polysaccharides and nucleic acids, each constituted of amino acids, fatty acids, monosaccharides and nucleotides, respectively. Importance of saccharides may be emphasized by the fact that both monosaccharides and nucleotides contain D-ribose as their constituting unit. Carbohydrate chemistry widely ranges from monosaccharides to polysaccharides. It is important to apply physical and chemical properties of monosaccharides to understand more complicated polysaccharides. For example, saccharide chemistry includes stereochemistry of monosaccharides (micro-perspective) as well as macro-perspective physical analysis of structural polysaccharides such as peptideglycans in the cell wall. Chemistry of saccharides is thus closely related to biological activities, and at the same time it extends to all the range of synthetic chemistry. In the next section we will discuss several important aspects of saccharide chemistry and especially synthetic chemistry using saccharides.

Saccharides contain multiple functional groups *e.g.* hydroxy and amino groups linked to their backbone, forming chiral compounds. Due to this chirality, saccharides can be stereochemically complicated. Such compounds should undergo reactions under mild conditions that are also used for various chemicals. For example, reactions that can take place even when hydrated or complete at a neutral pH are preferable. Such limitation may seem to hinder the experiment. But from our point of view, it means that synthetic methods used for saccharides can be truly practical for almost all other chemicals. Those are the “synthetic” reactions in the strict sense of the word.

If we understand such characteristics of saccharides, we can benefit a lot from them. For example, being inexpensive and easily accessible, saccharides are often used to synthesize chiral natural compounds.[1] The essential role of saccharide chains and derivatives as biologically active compounds draws an extensive attention in hopes of use for therapeutic drugs. Researchers engaged in saccharide chemistry are able to participate in truly useful chemistry by applying elementary reactions to the synthesis of saccharide chains or various compounds that are potentially bioactive. The next section describes our approaches to the synthesis of saccharide-derived biologically active compounds, in which we fully enjoyed the essence of organic synthetic chemistry.

3. Development of the synthetic method for optically active, multisubstituted cyclohexane and its application to the synthesis of biologically active compounds

As D-saccharides, typified by D-glucose, are inexpensive and easily obtainable in large quantities, effective application of these compounds to the synthesis of optically active compounds is an indispensable task in organic synthetic chemistry along with development of therapeutic drug in future. We especially focused on the development of multisubstituted cyclohexane which is universally useful in the total synthesis of biologically active compounds.

3.1 Development of the ring conversion reaction for saccharides using palladium chloride[2]

There are many reports on the synthetic methods for optically active, multisubstituted cyclohexane. Especially since Ferrier developed a cyclization reaction of saccharides using mercurate[3] [Ferrier (II) reaction] in 1979, the ring conversion of 5- and 6-membered rings using saccharides has been intensively studied.[4] Because naturally-occurring, biologically active compounds often contain a ring structure with multiple functional groups, stereochemical control of chiral centers on these rings becomes crucial in the total synthesis of these compounds. Meeting this requirement, it is not too much emphasis to mention that Ferrier (II) reaction is remarkably useful for the total synthesis of compounds with a complicated conformation.[5]

The Ferrier (II) reaction converts 5-enopyranosides to cyclohexanone rings by a stoichiometric quantity of mercurate in hydrous solvent (Fig. 1).

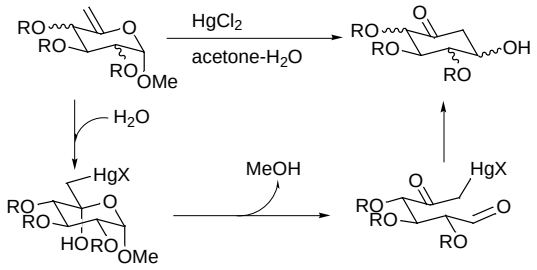
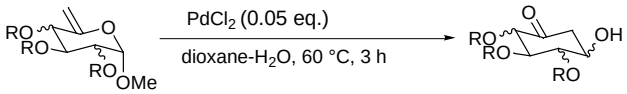


Fig. 1.

This is a ring conversion reaction from a tetrahydropyran ring to a cyclohexane ring, and the reaction steps start with oxymercuration of olefin by mercurate, followed by dealcoholization and ring opening of the resulting unstable hemiacetal, and intramolecular aldol condensation of diketone. Since biogenesis of inositols from saccharides uses similar reaction mechanism,[6] there is an increasing attention to the reaction. Thus, Ferrier (II) reaction poses interesting aspects in its reaction mechanism. At the same time, however, use of mercurate has been a serious concern. Although a catalytic quantity of mercurate was recently reported to be sufficient by Lukacs *et al.*[7] and Ogawa *et al.*,[8] from the viewpoint of both organic synthetic chemistry and drug chemistry, it is necessary to develop more practical methods that will meet current needs for environmental consideration and human health. Thus, we analyzed the Ferrier (II) reaction using other metallic salts.

We focused on the first step of the reaction, addition of water to olefin, and searched for transition metals that catalyzes oxymetallation similarly to mercury. As a result, we found that divalent palladium has a favorable activity, and especially that the catalytic activity of palladium chloride is as high as mercuric trifluoroacetate. The use of palladium chloride in Ferrier (II) reaction was only reported by Adam in 1988,[9] but its general application has not been discussed.[10] However, because this reaction undergoes in solvent at around neutral pH, there is no possibility of side reactions such as β-elimination of oxygen groups or elimination of blocking groups. In addition, palladium chloride is easily handled. Based on these aspects, we chose palladium chloride as a catalyst for the Ferrier (II) reaction.

Table 1.



Entry	5-eno pyranoside (R)	Yield (%)	α : β
1	Glc (Bz)	68	>99 : 1
2	Glc (Bn)	81	3 : 1
3	Gal (Bz)	68	>99 : 1
4	Gal (Bn)	94	9 : 1
5	Man (Bz)	95	>99 : 1
6	Man (Bn)	91	>99 : 1

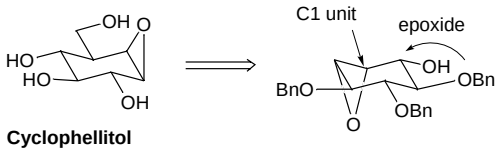
Although stability of palladium chloride was concerned at the beginning, we found that the compound remains stable in hydrated dioxane. As shown in Table 1, with 0.05 equivalent amount of palladium chloride, various substrates derived from glucose, galactose and mannose were converted to cyclohexanones at a high yield.

5-Enopyranoside derived from glucose and galactose showed a difference in reactivity between benzoyl and benzyl forms. Moreover, we found that stereochemical selectivity of newly formed hydroxy groups varies with each substrate (**Entry 1-4**). In contrast, the mannose-originated substrate did not show any difference between the protecting groups, and corresponding cyclohexanone was obtained with α-selectivity at a very high rate (**Entry 5, 6**).

This ring conversion completes by a catalytic quantity (0.05 equivalent) of palladium chloride. This reaction are more advantageous than the conventional methods, because 1) it is highly universal and applicable to the ring conversion of various saccharides, 2) it proceeds under very mild conditions, and 3) it produces various isomers through different stereochemical selectivity that arises from a mechanism different from that of mercury. Moreover, because the catalyst palladium chloride and solvent do not require purification, the reaction is practical and applied to the industrial manufacture. Using these advantages, we applied the method to the total synthesis of biologically active compounds.

3.2 Total synthesis of cyclophellitol[11]

Cyclophellitol is a β-D-glucosidase inhibitor isolated by Umezawa *et al.* in 1990.[12] In recent years, it has been found that saccharide-related enzymes are closely related to the intercellular recognition,[13] and inhibitors for these enzymes have been the focus of research for development of therapeutic drugs for various diseases.[14] Especially, cyclophellitol is known to have high activity, and its application has been expected to extend from an antivirus and anti-HIV agent to an inhibitor of cancer metastasis.[15] The structure of cyclophellitol, an epoxy ring in the β-position on a multisubstituted cyclitol in the glucose-conformation, resembles that of β-D-glucoside.[16] Development of synthetic methods for cyclophellitol has been widely studied all over the world[17]. We investigated synthetic methods of not only cyclophellitol but also its epimers, ultimately aiming at the study of structure activity relationship.



Cyclophellitol
β-D-glucosidase inhibitor
IC_{50} < 0.8 μg / mL

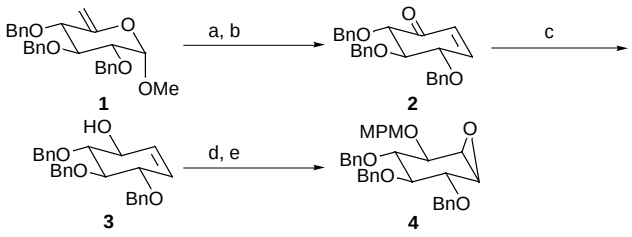
Fig. 2.

Fig. 2 shows the strategy for the synthesis of cyclophellitol and its epimers. Saccharides is used as the initial substrate in Ferrier (II) reaction and converted to a cyclohexane ring, and then an epoxy ring is formed stereoselectively. Then, using the regio- and stereoselective nucleophillic addition to the epoxy ring, a hydroxymethyl group is introduced as C1. Finally, an elimination reaction forms a β-configuration epoxy ring to complete the total synthesis of cyclophellitol, in which all the substituents are stereochemically controlled. This route allows synthesis of various epimers of cyclophellitol.

In our experiment, 5-enoglucopyranoside **1**[18] obtained by the conventional method was first used in Ferrier (II) reaction using a catalytic quantity of palladium chloride to obtain a cyclohexanone. The obtained cyclohexanone was converted to an enone **2** *via* elimination. The enone was reduced under Luche's condition[19] to obtain a β-alcohol **3**. Then α-form epoxide was formed stereoselectively, and the hydroxyl group was protected by an MPM group to obtain an intermediate, epoxide **4** (Fig. 3).

The key reaction in this total synthetic pathway is the regio-selective and nucleophilic attack of hydroxymethyl group to epoxide **4**. Generally, a nucleophile predominantly attacks at the axial position of epoxide in the open-ring reaction of cyclohexane.[20] Therefore, we expected that the nucleophilic substitution to this epoxide would occur at the axial position, C5, and would not show desired regio-selectivity[21] (Fig. 4).

We then thought that if we could change the conformation of the epoxide, we would be able to introduce hydroxymethyl group from the C6 position.



Reagents and Conditions: a)$PdCl_2$, dioxane - H_2O, 60 °C, 3 h, 81%; b) MsCl, Et_3N, CH_2Cl_2, r.t., 9 h, 74%; c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 15 min, 87%; d) *m*CPBA, Na_2HPO_4, CH_2Cl_2, r.t., 4 days, quant.; e) NaH, MPMCl, DMF - THF, r.t., 2 h, 93%.

Fig. 3.

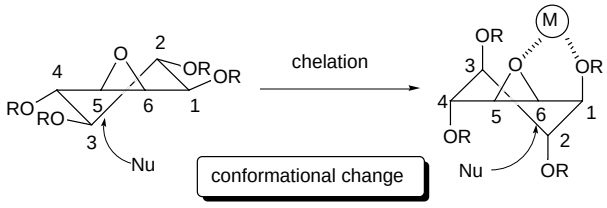
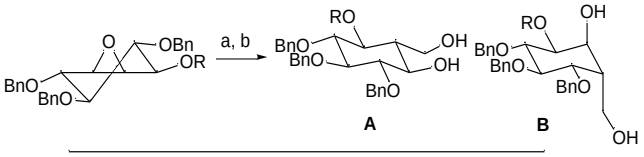


Fig. 4.

In other words, as shown in Fig. 4, chelation between metals and oxygen atoms of the epoxide and ether may drastically change the conformation of the cyclohexane ring, resulting in the axial nucleophilic attack at the C6 position, not C5. For such chelation, we used a boric reagent Mes_2BCH_2Li to replace hydroxymethyl and studied the regio selectivity of ring cleavage of the epoxide using substrates that are protected at C1, a coordinative position of attack, with various protecting groups (Table 2).[22]

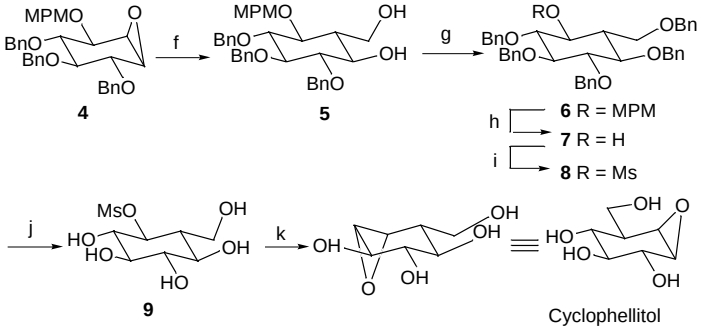
Table 2.



R	Yield (%)	Regioselectivity A : B
Bn	60	>99 : 1
MPM	78	>99 : 1
BOM	65	94 : 6
TBDMS[c]	83	<1 : 99
Ac	0	–

Reagents and Conditions: a) Mes_2BCH_2Li (10.0 eq), THF, r.t., 6 h; b) NaOH, H_2O_2, THF - MeOH, r.t., c) Oxidation condition: *m*CPBA (9.0 eq), Na_2HPO_4 (10.0 eq), r.t., 30 h

Unfortunately, because acyl protective groups react with the boric reagent, we did not obtain hydroxymethyl added products. Hydroxymethyl addition, however, occurred at a high rate in the substrate with an ether protective group. Very interestingly, the substrate protected with benzyl, MPM and BOM groups produced hydroxymethyl product **A** at the opposite position due to the chelation, but protection by TBDMS groups resulted in **B**. We assume that the bulky TBDMS group might block oxygen atom of the ether, and as a consequence, the conformation of cyclohexane was not converted. Based on these results, we selected the MPM group as the most appropriate protective group, and carried out the synthesis illustrated below (Fig. 5).



Reagents and Conditions: f) Mes_2BCH_2Li, THF, r.t., 6 h; NaOH, H_2O_2, THF - MeOH, r.t., 1 day, 78%; g) NaH, BnBr, DMF - THF, r.t., 4 days, 93%; h) DDQ, CH_2Cl_2 - H_2O, 0 °C, 1.5 h, 96%; i) MsCl, Et_3N, CH_2Cl_2, r.t., 12 h, 91%; j) $Pd(OH)_2$/C, MeOH, r.t., 1 day, 77%; k) 1.0*M* NaOH, 1 h, 82%.

Fig. 5.

After diol **5** was obtained through hydroxymethylation, it was protected by a benzyl group, and the methyl group was exchanged with an MPM group. Then, all the benzyl groups were deprotected by catalytic hydrogenation to obtain pentaols **9**. The pentaols readily underwent cyclization of epoxide under alkaline condition, and cyclophellitol was synthesized from **1** at the total yield of 14%.

In this synthetic method, the initial saccharides readily give rise to various epimers depending on the conformation of saccharides and types of protective groups. The same method successfully produced the epimer of cyclophellitol with a different configuration at C3.[23]

3.3 Synthesis of all isomers of inositol[24]

Inositol is one of the biologically active compounds found in both animals and plants, and it exhibits a variety of function involved in cell proliferation and carcinogenesis.[25] There are nine types of inositol stereoisomers (Fig. 6), and *myo*-inositol has received special attention since recent advances in understanding intracellular signaling pathways.[26,27]

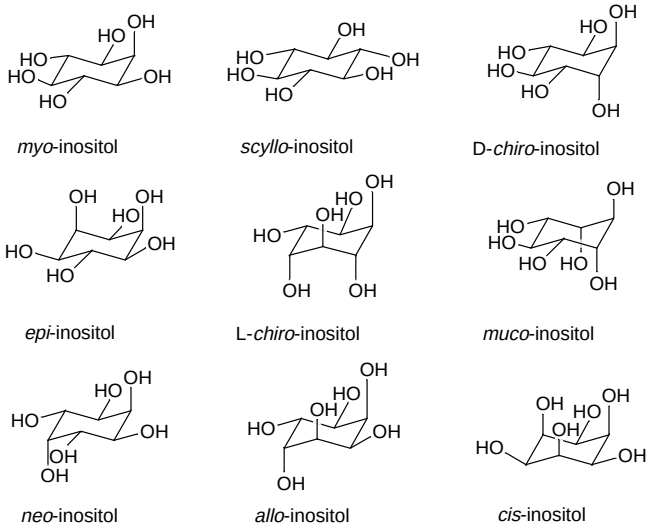


Fig. 6.

For example, in response to the extracellular stimulus, *myo*-inositol-1,4,5-triphosphate [Ins (1,4,5) P_3] mobilizes Ca^{2+} to increase cellular Ca^{2+} concentration.[28] Also, *myo*-inositol-1,3,4,5-tetraphosphate [Ins (1,3,4,5) P_4] takes up Ca ions from outside the cell.[29] Since inositol polyphosphates exert various functions by changing the intracellular Ca^{2+} concentration through these mechanisms, they are called second messengers. Although more *myo*-inositol polyphosphates have been found recently, their activation mechanisms remain elusive because of their low concentration and difficulty for isolation.[30] Therefore, there is a pressing need to obtain inositol derivatives that act as a ligand for inositol receptors.[31] However, there are only four kinds of naturally-occurring inositol stereoisomers (*scyllo*-, *neo*-, D-*chiro*-, and L-*chiro*-inositols), which may function as an agonist or an antagonist of *myo*-inositols, and the other four (*cis*-, *allo*-, *epi*- and *muco*-inositols) are only obtained through chemical synthesis. Of those, only two types are easily obtained but they are very costly. This solely owes to the rare existence of inositol isomers and less practical synthetic methods. To establish a facile synthetic method for all nine types of inositol isomers including the ones which were not the focus of previous studies, we designed a synthetic pathway as shown in Fig. 7.

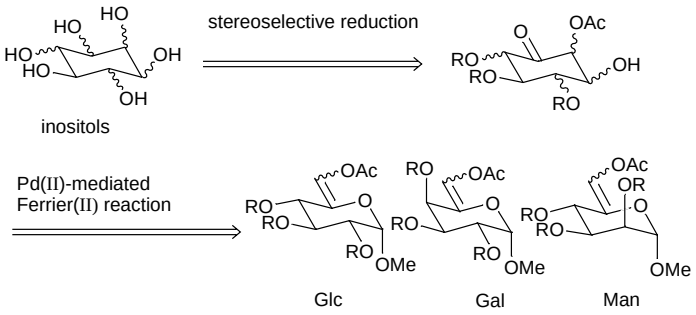


Fig. 7.

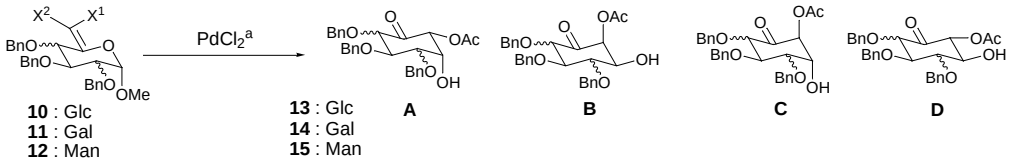
With this route, we predicted 5-enopyranoside containing an acetoxy group at C6 would be converted to cyclohexanone by Ferrier (II) reaction, and reduction of the ketone part of the obtained cyclohexanone would produce an inositol backbone.[32] Using substrates derived from glucose, galactose and mannose, this method would produce a great variety of isomers at the same time.

3.3.1 Examination on Ferrier (II) reaction of 6-*O*-acetyl-5-enopyranoside

First, Ferrier (II) reaction with the substrate, 6-*O*-acetyl-5-enopyranoside, using a catalytic quantity of palladium chloride was examined. We especially focused on the effect on stereochemistry of enol esters, and reactivity and stereoselectivity of *Z*- and *E*-form were compared (Table 3).

The *Z*-form of glucose-derived substrate **10** had higher reactivity than *E*-form, and produced a mixture of four corresponding stereoisomers. A similar result was obtained in the galactose-originated substrate **11**. For each saccharide, there was no effect of the C6 conformation on the ratio of formation of the four cyclohexanones obtained from *Z*-form or *E*-form. When mannose-derived substrate **12** was used, both *Z*- and *E*-form produced a single conformation of cyclohexanone. On the basis of these results, we found that any of these saccharides undergoes ring conversion effectively. We also found that depending on the conformation of the original saccharide, the ratio of cyclohexanone formation is different, that conformation of C6 of substrates is not retained, and that the conformation of C6 does not affect the conformation of newly formed chiral centers.[33] We analyzed the reaction also using Hg^{++}, but the reaction was slower than that of palladium chloride catalyzed, and produced different isomer ratios. Therefore, we concluded palladium chloride would bring a favorable outcome, and investigated the next steps.

Table 3.



10 : Glc
11 : Gal
12 : Man

13 : Glc
14 : Gal
15 : Man

A **B** **C** **D**

Entry	Substrates			$PdCl_2$	Solvent	Yield (%)	**A : B : C : D** [b]
1	Glc	**10a**	X^1=OAc, X^2=H	0.05 eq	dioxane - H_2O (4:1)	81	49 : 24 : 17 : 10
2		**10b**	X^1=H, X^2=OAc	0.05 eq	dioxane - H_2O (2:1)	N.R.	———
3				0.10 eq	dioxane - H_2O (2:1)	75	50 : 23 : 15 : 11
4	Gal	**11a**	X^1=OAc, X^2=H	0.05 eq	dioxane - H_2O (2:1)	88	40 : 11 : 42 : 7
5		**11b**	X^1=H, X^2=OAc	0.05 eq	dioxane - H_2O (2:1)	15	44 : 12 : 37 : 7
6	Man	**12a**	X^1=OAc, X^2=H	0.05 eq	dioxane - H_2O (2:1)	76	100
7		**12b**	X^1=H, X^2=OAc	0.05 eq	dioxane - H_2O (2:1)	58	100

[a] **Conditions** : 60 °C, 3 h

[b] The assignment of the ratio was based on the ^{1}H NMR (400 MHz) analysis of the diastereomixtures.

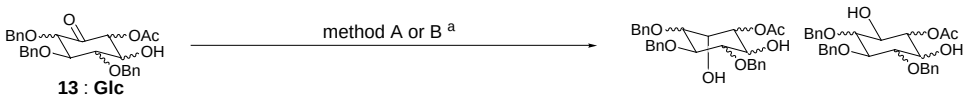
3.3.2 Examination on stereoselective reduction reaction

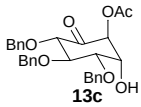
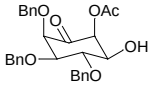
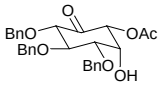
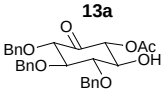
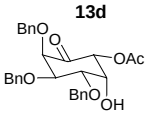
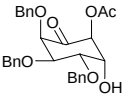
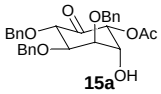
We tested two reduction methods for the cyclohexanones obtained above (Table 4). When $Me_4NHB(OAc)_3$ [34] was used, the reaction did not proceed with **14c** (Entry 11) but with others, produced alcohols that were reduced in *trans* manner at β-position of the carbonyl group. Especially with **13a**, **13c**, **14a** and **15a**, stereoselectivity was very high, and only β-form was obtained at high rate. We consider this is because the reduction started at the hydroxyl group at β-position of the carbonyl group. On the other hand, when sodium borohydride was used, the reaction proceeded at the position with less steric hindrance, and **13a**, **14a**, **14b**, **14c** and **15a** gave rise to reduced products with high selectivity. Because these two reduction reactions are complementary to each other, desired alcohols can be easily obtained by changing the reaction. Thus, the method to stereoselectively obtain eight out of nine inositol stereoisomers was established. The last isomer, *cis*-inositol was formed by **13a** that was obtained at the highest rate by ring conversion of the glucose-derived substrate.

As shown in Fig. 8, ketone of **13a** was reduced by sodium borohydride to obtain only α-form alcohol **13aa** at a high yield. Then, the benzyl group was deprotected, and an acetonide group was used to selectively protect the *cis*-diol. The configuration of the last hydroxy group was inverted to obtain *cis*-inositol derivative **17**. These inositol derivatives were all deprotected and confirmed to have similar values to those of previously reported for the naturally occurring derivatives.[36]

Thus, we succeeded in the stereoselective synthesis of all stereoisomers of inositol. This method uses various cyclohexanone isomers obtained by Ferrier (II) reaction using palladium chloride, and enables simultaneous synthesis of various isomers that cannot be obtained using mercuraic salt.

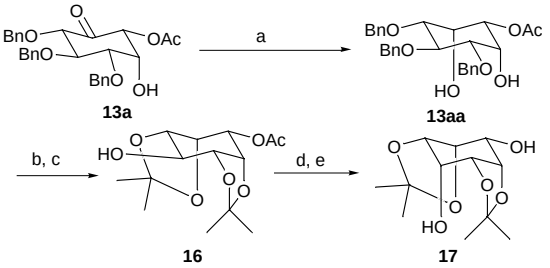
Table 4.



Entry	Substrate	Method	Conditions	Yield	α : β [b]	
1	 **13c**	A	0 °C, 3 h	91 %	<1 : 99	D-*chiro*-inositol
2		B	0 °C, 0.5 h	84 %	87 : 13	*muco*-inositol
3	 **14b**	A	r.t., 24 h	46 %	70 : 30	
4		B	-78 °C, 0.5 h	90 %	<1 : 99	*epi*-inositol
5	 **13a**	A	r.t., 3 h	94 %	<1 : 99	*myo*-inositol
6		B	0 °C, 0.5 h	97 %	>99 : 1	
7	 **13d**	A	r.t., 24 h	37 %	78 : 22	
8		B	0 °C, 0.5 h	86 %	22 : 78	*scyllo*-inositol
9	 **14a**	A	0 °C, 3 h	93 %	<1 : 99	*neo*-inositol
10		B	-78 °C, 0.5 h	88 %	98 : 2	
11	 **14c**	A	r.t., 48 h	N.R.	– : –	*allo*-inositol
12		B	0 °C, 0.5 h	96 %	<1 : 99	
13	 **15a**	A	0 °C, 3 h	92 %	<1 : 99	L-*chiro*-inositol
14		B	-40 °C, 0.5 h	92 %	98 : 2	

[a] **Conditions**, method A : $Me_4NBH(OAc)_3$ (5.0 eq), CH_3CN - AcO, method B : $NaBH_4$ (1.5 eq), MeOH

[b] The assignment of the ratio was based on the ^1H NMR (400 MHz) analysis of the diastereomixtures.

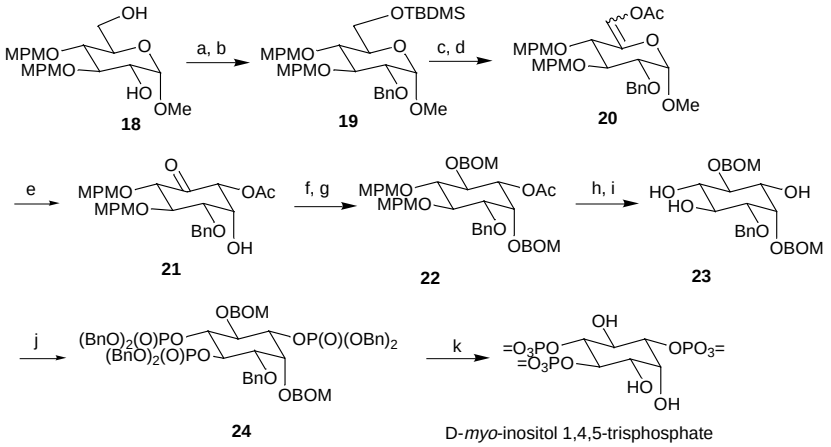


Reagents and Conditions: (a) $NaBH_4$, MeOH, 0 °C, 30 min, 97 %. (b) H_2, $Pd(OH)_2/C$, MeOH, r.t., 12 h, quant. (c) conc. H_2SO_4, acetone, 0 °C, 1 h, 83 %. (d) Tf_2O, pyridine, CH_2Cl_2, r.t., 1h, 89 %. (e) (i) CF_3COOCs, 18-crown-6, toluene, DMF, 80 °C, 1.5 h. (ii) sat. $NaHCO_3$, r.t., 1 h, 88 %.

Fig. 8.

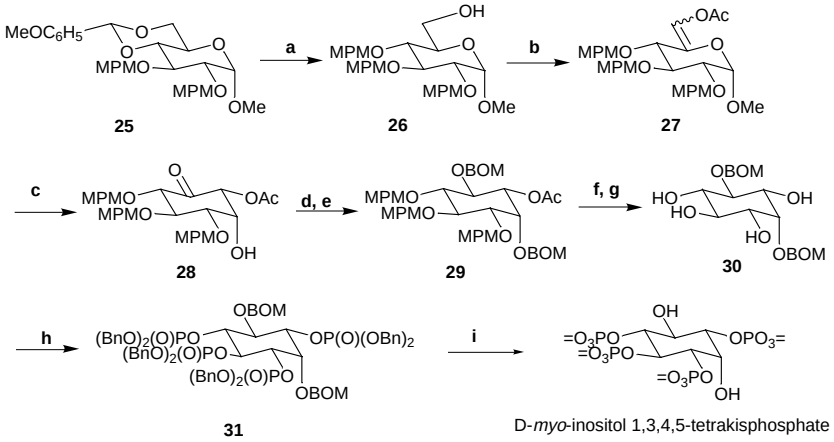
3.4 Synthesis of inositol polyphosphates

Next, we synthesized Ins (1,4,5) P_3 and Ins (1,3,4,5) P_4, as shown in Figs. 9 and 10.



Reagents and Conditions: a) TBDMSCl, imidazole, DMF, 0 °C, 30 min, 94 %; b) NaH, BnBr, DMF-THF, r.t., 30 min, 82 %; c) TBAF, THF, r.t., 1 h, 95 %; d) (i) DCC, DMSO, TFA, PhH, r.t., 12 h, (ii) Ac_2O, Et_3N, DMAP, $ClCH_2CH_2Cl$, reflux, 5 h, 80 %; e) $PdCl_2$, dioxane-H_2O, 60 °C, 8 h, 53 % ; f) $Me_4NBH(OAc)_3$, AcOH-CH_3CN, r.t., 3 h, 81 %; g) BOMCl, iPr_2NEt, $ClCH_2CH_2Cl$, reflux, 5 h, 78 %; h) NaOH, MeOH, 60 °C, r.t., 10 min, 81 %; i) DDQ, CH_2Cl_2-H_2O, r.t., 1 h, 80 %; j) (i) $(BnO)_2P(iPr_2N)$, tetrazole, CH_2Cl_2, r.t., 12 h, (ii) *m*CPBA, Na_2HPO_4, r.t., 1 h, 89%; k) H_2, $Pd(OH)_2$/C, MeOH, r.t., 12 h, 99 %.

Fig. 9.



a) TMSCl, $NaBH_3CN$, CH_3CN, -20 °C, 30 min, 64 %; b) (i) DCC, DMSO, TFA, PhH, r.t., 12 h, (ii) Ac_2O, Et_3N, DMAP, $ClCH_2CH_2Cl$, reflux, 5 h, 63 %; c) $PdCl_2$, dioxane-H_2O, 60 °C, 4 h, 29 % ; d) $Me_4NBH(OAc)_3$, AcOH-CH_3CN, r.t., 3 h, 96 %; e) BOMCl, iPr_2NEt, $ClCH_2CH_2Cl$, reflux, 3 h, 86 %; f) NaOH, MeOH-THF, r.t., 2 h, 94 %; g) DDQ, CH_2Cl_2-H_2O, r.t., 3 h, 98 %; h) (i) $(BnO)_2P(iPr_2N)$, tetrazole, CH_2Cl_2, r.t., 24 h, (ii) *m*CPBA, Na_2HPO_4, CH_2Cl_2, r.t., 2 h, 76 %; i) H_2, $Pd(OH)_2$/C, MeOH, r.t., 48 h, 98 %.

Fig. 10.

Ins (1,4,5) P_3 and Ins (1,3,4,5) P_4 obtained in this method showed consistency with values of naturally occurring compounds,[37,38] and their structures were confirmed.

In the next section, we will describe the effective application of lactone sugars to the synthesis of various biologically active compounds and sugar chains.

4. Application of glucono-D-lactone to the novel synthesis of L-sugars[39]

L-Saccharide occurs rarely in nature, but interestingly, it often plays a key role for the activity of biologically active compounds.[40] However, it is rare and the synthetic method has not been established, the study of L-saccharides is far behind that of D-saccharides. To overcome such situation and to bring about flourishing of chemistry of L-saccharides as in D-saccharides, we aimed at establishment of highly practical methods for L-saccharides. To approach to the chemical synthesis, we attempted effective conversion of D-form to L-form by inverting at the C5.

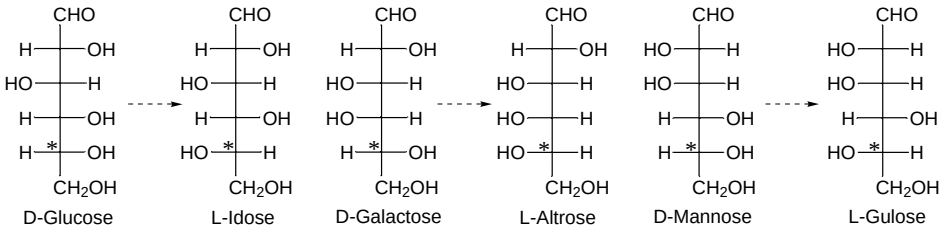


Fig. 11.

As shown in Fig. 11, inversion of D-glucose at C5 produces L-idose. Similarly, D-galactose can be converted to L-altrose, and D-mannose to L-gulose. Though L-idose and L-gulose are commercially available, they are very expensive. L-Altrose is not even on the market. Our method may utilize inexpensive and easily obtainable D-saccharides to effectively synthesize L-saccharides by simple steps. We attempted synthesis of L-saccharides by intramolecular cyclization of hydroxamic derivatives of gluco-D-lactones by Mitsunobu Reaction, a typical S_N2-type reaction in which D-saccharides are inverted at C5.

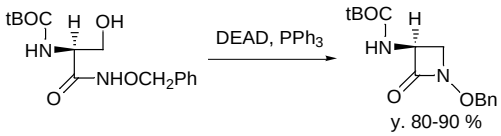


Fig. 12.

Miller *et al.* have already reported the intramolecular cyclization of β-hydroxyhydroxamic derivatives of amino acids.[41] This reaction has been used to synthesize various β-lactam antibiotics, because nucleophilic attack of the nitrogen atom of amides mainly produces beta-lactams (Fig. 12). However, not only the nitrogen atom of the amides, but also carbonyl oxygen may attack the compound. In fact, other substrates may produce lactones,[42] and we were interested in the outcome when saccharide-derived substrate was used (Fig. 13).

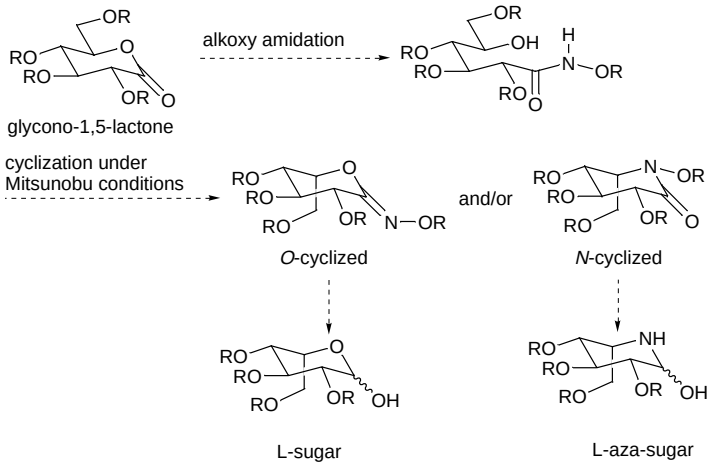
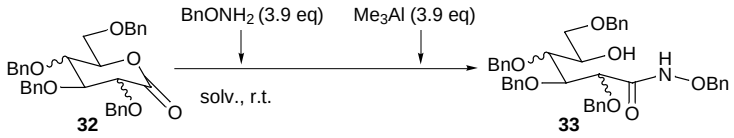


Fig. 13.

As shown in Fig. 13, nucleophilic attack of the amide N produces *N*-cyclized compounds, and nucleophilic attack of the oxygen atom gave *O*-cyclized products. In this case, Mitsunobu Reaction produces cyclic compounds all inverted at C5; *N*-cyclic compounds give L-aza sugar, and *O*-cyclic products yield L-saccharides. Based on this strategy, we analyzed intramolecular cyclization of δ-hydroxyalkoxamic derivatives of D-glycono-1,5-lactones.

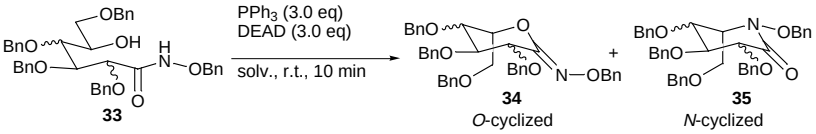
Table 5.



Entry	S.M.	Solv.	Time (min)	Yield (%)	Recovery of S.M. (%)
1	Glc	toluene	20	81	——
2	Glc	CH_2Cl_2	30	93	——
3	Glc	THF	30	57	38
4	Gal	CH_2Cl_2	50	92	——
5	Man	CH_2Cl_2	30	quant.	——

The substrate δ-hydroxyhydroxamic derivatives were synthesized by the reaction of D-gluconopyrano-lactone, D-galactono-pyrano-lactone and D-mannono-pyrano-lactone with benzyloxyamines. We predicted that this reaction might be facilitated by Lewis acids, and found that trimethylaluminum shows a remarkable accelerating effect to produce δ-hydroxyhydroxamic derivatives at a high yield as shown in Fig. 5.[43] Similarly, alkoxyamine hydrochloride showed a high yield, and proved effective for the synthesis of various δ-hydroxyhydroxamic derivatives. Provided these, we analyzed cyclization of the compound using Mitsunobu Reaction.

Table 6.



			Yield (%)[a]		
Entry	S.M.	Solv.	*O*-Cyclized	*N*-Cyclized	*O* / *N* Ratio
1	Glc	THF	71	13	5.5 : 1
2		CH_2Cl_2	67	28	2.4 : 1
3		DMSO	64	28	2.3 : 1
4	Gal	THF	68	30	2.3 : 1
5		CH_2Cl_2	44	53	1 : 1.2
6		DMSO	17	25	1 : 1.5
7	Man	THF	91	——	
8		CH_2Cl_2	96	——	
9		DMSO	79	——	

[a]Isolated yield.

Cyclization proceeded rapidly, and gave *O*-cyclized and *N*-cyclized δ-hydroxyalkoxamic derivatives at 71% and 13%, respectively, yielding *O*-cyclized form 5.5 times more than the *N*-cyclized. This was not consistent with the result by Miller *et al.* in which β-lactams were mainly obtained. The D-galactose-derived substrate also predominantly produced *O*-cyclized form. Interestingly, D-mannose produced only *O*-cyclized compounds but not *N*-cyclized product. Based on these results, we found that δ-hydroxyhydroxamic derivatives of saccharides always preferentially produce *O*-cyclized forms, though

the ratio of *O*- to *N*-cyclized products varies with the type of original sugars. In addition, detailed analysis of the effect of solvents revealed that the ratio of *O*- to *N*-cyclized products changes with the type of solvents when D-glucose and D-galactose were used. The suggested mechanism of this cyclization reaction is as follows (Fig. 14).

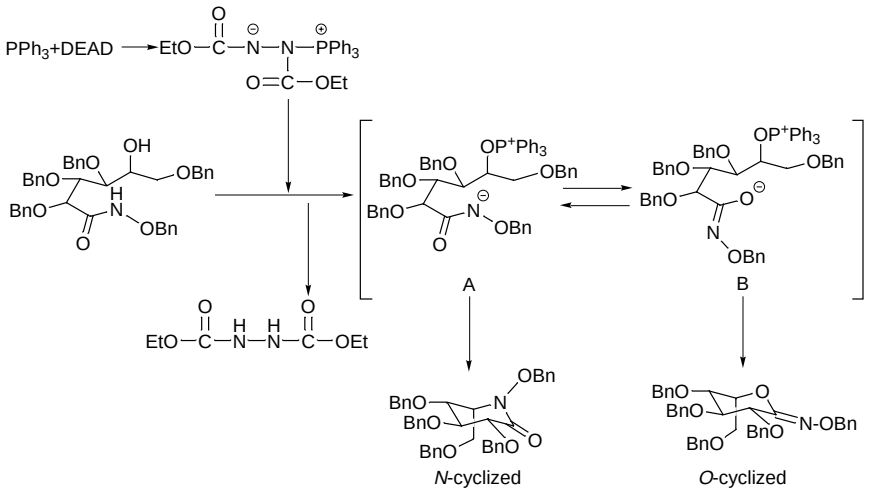


Fig. 14.

First, the complex contained through the Mitsunobu reagent draws amide hydrogen of δ-hydroxyhydroxamic derivatives to produce the intermediate **A** that contains a negative ionic charge on the nitrogen atom. The nucleophilic attack of this nitrogen atom to C5 results in an *N*-cyclized form. On the other hand, the intermediate **A** produces the intermediate **B** by transferring the negative charge to the oxygen atom. The nucleophilic attack of this oxygen forms *O*-cyclized products. So far the reason is still unclear, but the cyclization *via* intermediate **B** formation is predominant when δ-hydroxyhydroxamic derivatives of saccharides are used.

Provided that any saccharide we used preferentially produced *O*-cyclized forms, we synthesized L-pyranose (Fig. 15).

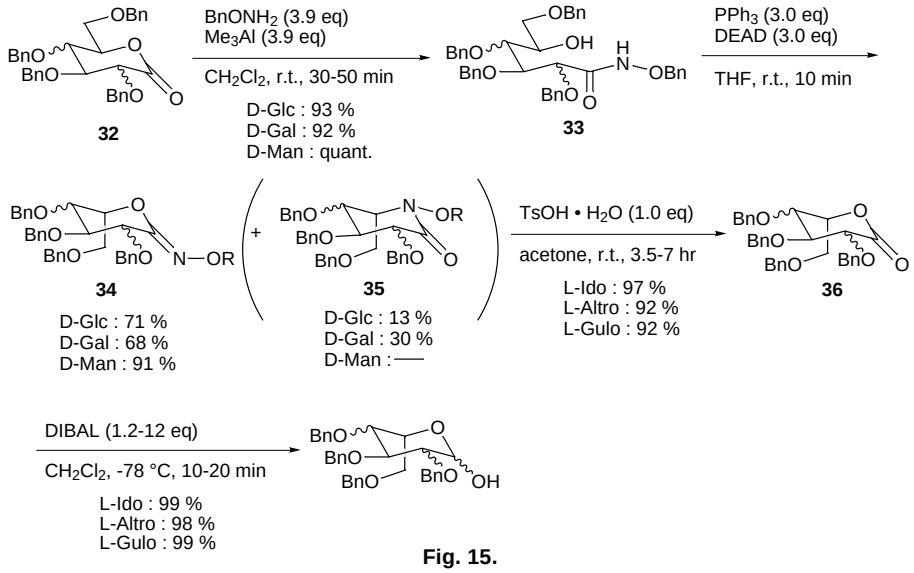


Fig. 15.

Because *O*-cyclized forms **34** derived from these three sugars are protected at C1 of L-pyranolactone, we deprotected this under acidic condition to produce L-idonolactone derivatives, L-altronolactone derivatives and L-gulonolactone derivatives, respectively, at a high yield. Then, the carbonyl group at C1 was reduced by DIBAL, and L-idose, L-altrose and L-gulose derivatives were effectively obtained. Especially, D-mannose showed 83% of total yield through the four steps, proving that this method is highly effective. The final product, L-pyranose derivative, is unprotected only at C1, and therefore it can be further used for glycosylation. Thus, we established the first synthetic method of rare L-saccharides from inexpensive and easily obtainable D-saccharides through simple steps.

Next, we attempted the synthesis of L-ribose by applying this cyclization method to 1,4-lactone derivatives of saccharides (Fig. 16). L-ribose is an enantiomer of D-ribose and very rarely occurs in nature. Recently, development of synthetic methods for L-ribose has been increasingly expected, because compounds containing L-ribose show various biological activities including antivirus effect.[44]

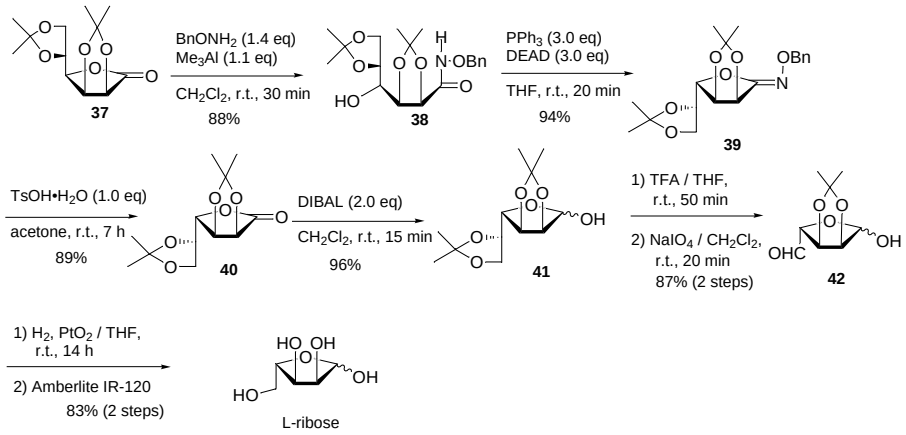


Fig. 16.

L-Ribose was synthesized based on the similar strategy. A lactone form **37** was derived from commercially available D-manno-1,4-lactone by a conventional method, and after the ring was cleaved, it was cyclized again by Mitsunobu Reaction. In this method, only *O*-cyclized form **39** that were inverted at C4 were produced at high yield, but not *N*-cyclized product. Considering that mannose-derived 1,5-lactones did not give *N*-cyclized product as described above, we concluded that in this method, mannose only specifically produces *O*-cyclized product. It is yet to be explained, but the conformation of hydroxy group at C2 of saccharides seems to affect the ratio of *O*- to *N*-cyclized products. Especially, the result of D-mannono-1,4-lactone was favorable for the synthesis of L-ribose, as L-ribose was effectively produced through several steps after the *O*-cyclized product obtained **39** were oxidatively cleaved at C6.

As described above, this method is able to derive aza-sugars from the *N*-cyclized product that are by-products of the intermolecular cyclization, and thus the application to the inhibitors of sugar related enzymes may be possible.

5. Synthesis of sugar derivatives using sugar ortho esters

Sugar ortho ester is produced by combining sugar lactones with sugar diols to form a spiro ring. Their unique structure was originally found in a series of orthosomycin antibiotics.[45] This characteristic bond, that is distinctive from glycoside bonds, has been studied along with the synthesis and structural analysis of orthosomycins, focusing on the method for formation of ortho ester bond. As a result, characteristics and reactivity of sugar ortho esters themselves have been left unknown as well as their applications. However, the strategic application of this specific reactivity to development of effective synthetic methods and use of ortho esters as sugar mimics with a fixed conformation seem to promise a lot of possibilities. From this point of view, we analyzed various synthetic methods for sugar ortho esters aiming at characterization of these compounds and their reactivity.

5.1 Development of the efficient synthetic method of sugar ortho esters[46]

When we started this research, there were only few reports on the synthesis of sugar ortho esters, and there were a limited number of synthetic sugar ortho esters. We therefore attempted to develop more effective methods. By analyzing the ketal synthetic method by Miyata *et al.*,[47] we found that sugar ortho ester is efficiently produced from sugar lactones and diols in the presence of the excess amount of methyl trimethylsilyl ether (TMSOMe) and a catalytic amount of trimethylsilyl triflate. Removal of by-product such as methanol and hexamethyldisilazane using toluene under reduced pressure during the reaction improved the yield, and enabled production of various sugar ortho esters when equal amount of lactones and diols were used (Fig. 17).

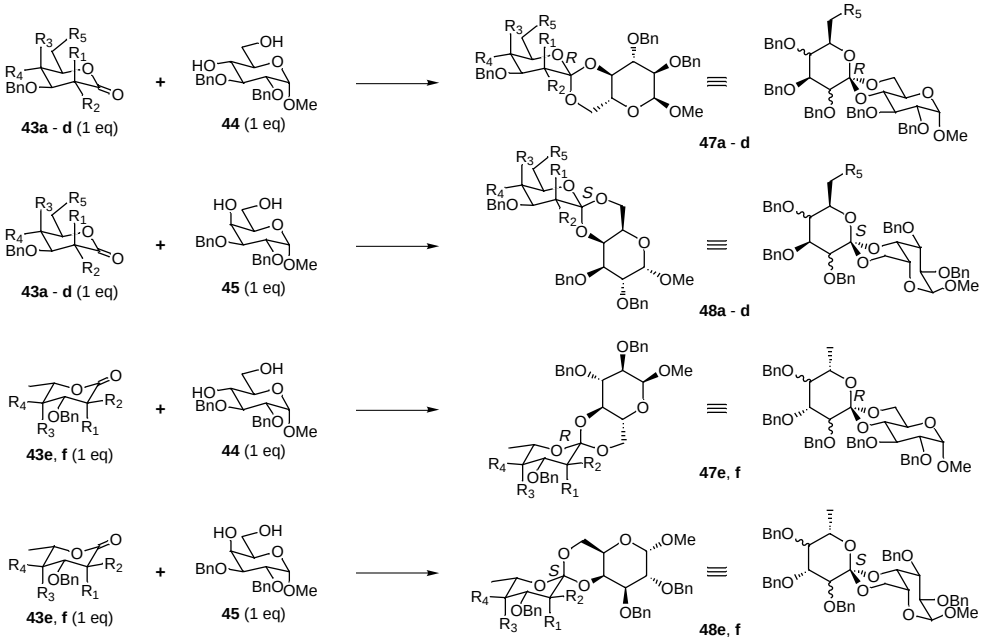


Fig. 17.

Sugar ortho ester forms two isomers based on the configurational structure around the spiro carbon. Either one of these two isomers was selectively produced for these sugar ortho esters (**47a-f**, **48a-f**, **49**).

5.2 Structural analysis of sugar ortho esters[48]

X-ray analysis is required to distinguish the configuration of two isomers of sugar ortho esters. We analyzed the structure of sugar ortho esters combining X-ray analysis and conformational analysis using a computer.

For the ortho esters with 3-ring backbone of pyran-dioxane-pyran described in the previous section, we analyzed the crystalline form **47c** as well as the acetyl derivatives of **47f**, **48c** and **48f** (**50-52**) by X-ray, and the conformation of the spiro carbon was determined as *R*, *R*, *S* and *S*, respectively (Fig. 18).

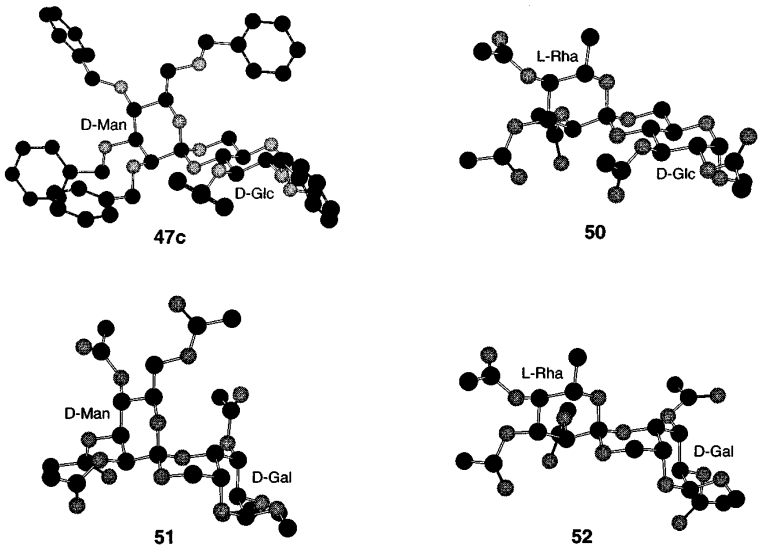


Fig. 18.

Next, presuming both *R* and *S*-conformation were obtained, we estimated the most stable conformation for all of the obtained ortho esters by the LOMD method[50] using MacroModel 6.0[49] at the specific force of mm2*. The more stable conformer was determined by calculating the energy for both conformations for each sugar ortho ester. In each compound, the difference between the energy of two isomers was sufficiently large, and **47a-f** were determined to have *R*-configuration, while **48a-f** were determined to have *S*-configuration at the spiro carbon. This result was consistent with the data reported by Yoshimura *et al.*[51]

Analysis of the calculated structure of the sugar ortho esters revealed that the energy difference between the two conformers stems from difference in stability of their backbone ring structures. Fig. 19 shows the estimated backbone ring structure of *R* and *S*-isomers of **47c**.

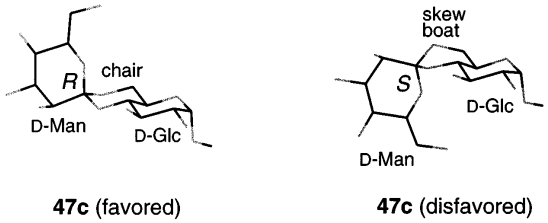


Fig. 19.

In the *R*-configuration, which was estimated to be more stable, the oxygen atom of the pyran ring from mannose is axial to the chair-form dioxane ring at the center, and this conformation is energetically preferred due to the anomeric effect.[52,53] Similarly in the other eleven sugar ortho esters, overall structure of either one of their conformers was more stable than the other. It was speculated that the isomer which was energetically unfavorable had a twisted boat-conformation of the dioxane ring to compensate the equatorial position of the pyran oxygen as shown in Fig. 19.

These results indicate that the difference in the conformation of hydroxyl groups, which is within the range that does not affect the pyran-ring structure, does not affect the configuration of the spiro carbon and conformation of the backbone rings of the conformer with the preferred structure. Therefore, the synthesized sugar ortho esters can be divided into four structural groups: D- or L-forms at the glycosyliden and glucose or galactose at the diol. As examples, Fig. 20 illustrates the structures of **47c**, **47f**, **48c** and **48f** viewed from two directions. In addition, when the conformation of **49** that is related to **47a** was analyzed, it was also estimated that it has an **A**-type ring structure.

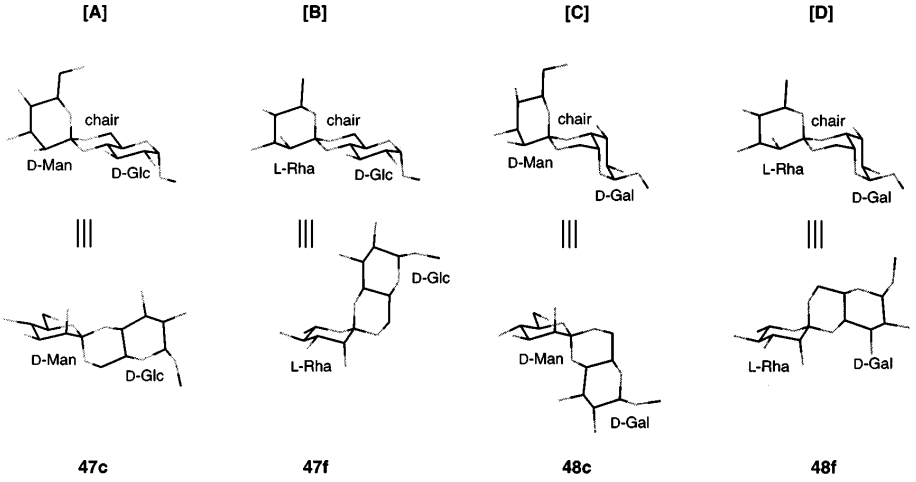


Fig. 20.

5.3 Development of reductive glycosylation *via* sugar ortho esters[54]

Organic chemical approaches to sugar ortho esters have been centered around their structural analysis, and their reactivity is little known. We analyzed the reactivity of ortho esters with hydride anions and methyl anions with the hope to develop a novel synthetic method.

Fig. 21 shows a generalized equation for the reaction of anions and sugar ortho esters.

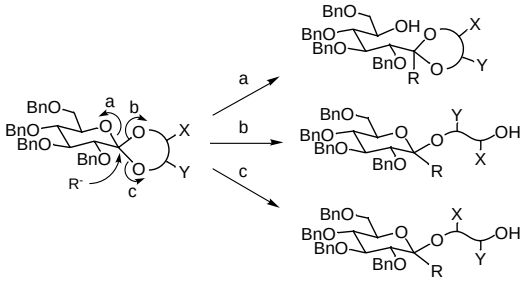
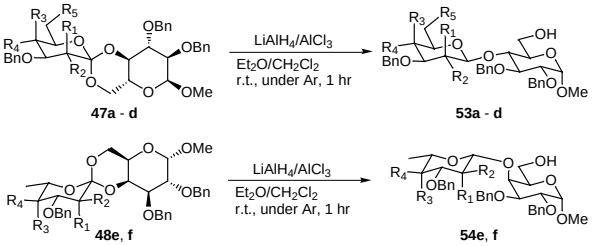


Fig. 21.

Attacked by anions, cleavage of the ring at **a**-position produces acetal or ketal compounds, while cleavage at **b**- or **c**-position yields glycosides. Each product has two conformers at the newly formed chiral center. If we could control the regio-selectivity of ring-opening and stereoselectivity of the anion attack, we would be able to develop a novel synthetic method for glycosylation. Although activation of glycosyl donors has been focused in the research for development of the glycosylation method[55], we attempted different approaches for more flexible strategy for sugar chain synthesis.

When the sugar ortho ester **47a** is reduced by hydride anion, there are four possible glycoside products which have either α (1→4), β (1→4), α (1→6) or β (1→6) bonding. When we evaluated various reducing agents for their efficiency, regio-selectivity and stereoselectivity, we found that two equivalent amount of lithium aluminum hydride ($LiAlH_4$) and aluminum chloride ($AlCl_3$) [56] in ethermethylene chloride selectively produced β (1→4) glycoside **53a** at 92% from **47a** (Table 7, **Entry 1**). In this case, the other predicted three glycosides were not formed, indicating highly regio-selective and stereoselective reaction. Using this method, reduction of sugar ortho esters **47b-d**, **48e** and **f** showed 92-99% yield and selectively produced β (1→4) glycoside **53b-d**, **54e** and **f** (Table 7). However, reduction of other sugar ortho ester **47e**, **f** and **48a-d** did not proceed efficiently. Reducing agents were further evaluated, and we found that sodium cyanoborohydride and aluminum chloride in toluene-acetonitrile[57] selectively produces β (1→6) glycoside **55a-d**, **56e** and **f** (Table 8). When we applied this method to the sugar ortho esters **47a-d**, **48e** and **f**, however, it did not give favorable products.

Table 7.

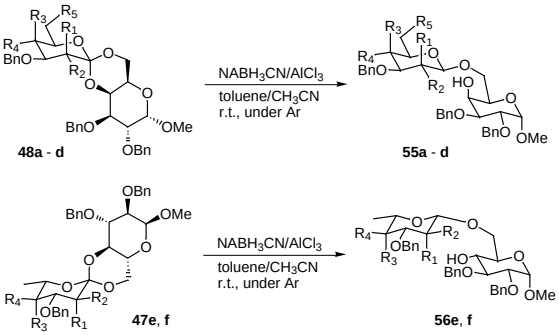


Entry	Orthoester	Glycoside	Yield (%) [a]
1	**47a**	**53a**	92
2	**47b**	**53b**	98
3	**47c**	**53c**	98
4	**47d**	**53d**	92
5	**48e**	**54e**	96
6	**48f**	**54f**	99

These reactions were carried out for 1 hr at r.t. under Ar in Et_2O/CH_2Cl_2 ([orthoester]=50 mM, $LiAlH_4$: 2 eq, $AlCl_3$: 2 eq).
a) Isolated yield.

a : R_1=H, R_2=OBn, R_3=H, R_4=OBn, R_5=OBn (Glc)
b : R_1=H, R_2=OBn, R_3=OBn, R_4=H, R_5=OBn (Gal)
c : R_1=OBn, R_2=H, R_3=H, R_4=OBn, R_5=OBn (Man)
d : R_1=H, R_2=OBn, R_3=OBn, R_4=H, R_5=H (D-Fuc)
e : R_1=H, R_2=OBn, R_3=OBn, R_4=H (L-Fuc)
f : R_1=OBn, R_2=H, R_3=H, R_4=OBn (Rha)

Table 8.



Entry	Orthoester	Glycoside	Time (hr)	Yield (%) [a]
1	**47a**	**55a**	2	93
2	**47b**	**55b**	2	97
3	**47c**	**55c**	48	42 [b]
4	**47d**	**55d**	2	88
5	**48e**	**56e**	1	88
6	**48f**	**56f**	12	78 [c]

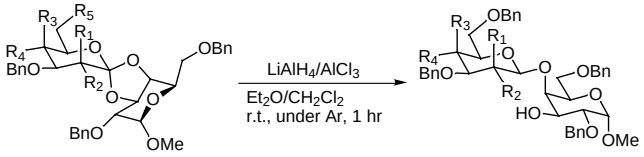
These reactions were carried out at r.t. under Ar in toluene/CH_3CN ([orthoester]=50 mM, $NaBH_3CN$: 7 eq, $AlCl_3$: 5 eq, MS3A: 100mg/2ml solvents). a) Isolated yield. b) 91% yield based on conversion.
c) α-(1→6)-Isomer was detected (6%).

a : R_1=H, R_2=OBn, R_3=H, R_4=OBn, R_5=OBn (Glc)
b : R_1=H, R_2=OBn, R_3=OBn, R_4=H, R_5=OBn (Gal)
c : R_1=OBn, R_2=H, R_3=H, R_4=OBn, R_5=OBn (Man)
d : R_1=H, R_2=OBn, R_3=OBn, R_4=H, R_5=H (D-Fuc)
e : R_1=H, R_2=OBn, R_3=OBn, R_4=H (L-Fuc)
f : R_1=OBn, R_2=H, R_3=H, R_4=OBn (Rha)

The difference in reactivity observed in these sugar ortho esters can be simply explained by their conformational differences as described above. The backbone ring structure of **47a-d**, **48e** and **f** are predicted to be **A** or **D** form in Fig. 20. The figure at the bottom has oxygen atom at C6 of the diol ring axial to the pyran ring of the lactone. On the other hand, the compounds **47e**, **f** and **48a-d** are predicted to have **B** or **C** form as shown in Fig. 20, but the C4 oxygen is axial. Due to the anomeric effect, we could predict the pyran ring has higher reactivity at axial compared to equatorial[58], but in each sugar ortho ester, the compound derived from axial cleavage was preferentially produced if used with appropriate reducing agents. The high β-selectivity can be explained by that the reducing agent and hydride approached from the same axial side.

We also carried out reduction of the sugar ortho ester **57a-c** by $LiAlH_4/AlCl_3$. When major forms of **57a-c** were used, C3 oxygen, which was predicted to be axial, was selectively reduced and selectively produced β (1→4) glycoside **58a-c** at 92-97% (Table 9).

Table 9.



57a - c (major) **58a - c**

a : R_1=H, R_2=OBn, R_3=H, R_4=OBn (Glc)
b : R_1=H, R_2=OBn, R_3=OBn, R_4=H (Gal)
c : R_1=OBn, R_2=H, R_3=H, R_4=OBn (Man)

Entry	Orthoester	Glycoside	Yield (%) [a]
1	**57a**	**58a**	95
2	**57b**	**58b**	92
3	**57c**	**58c**	97

These reactions were carried out for 1 hr at r.t. under Ar in Et_2O/CH_2Cl_2 ([orthoester]=50 mM, $LiAlH_4$: 2 eq, $AlCl_3$: 2 eq).
a) Isolated yield.

Under this reduction condition, the minor form of **57a-c** hardly underwent the reaction. Therefore, when the products were used for reduction without separating isomers, they gave β (1→4) glycoside without any practical problems.

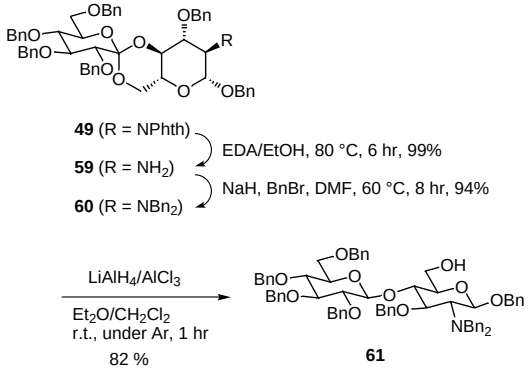


Fig. 22.

As shown in Fig. 22, ortho ester of glucosamine **49** was also analyzed. After converting **49** to dibenzyl-protected form **60**, reduction by $LiAlH_4/AlCl_3$ selectively produced β (1→4) glycoside **61**. Unfortunately glucosamine with a phthalimide group **49** or unprotected amino group **59** was not appropriate as a substrate for the reaction.

The most intriguing aspect of this glycosylation method is that β-mannoside and β-rhamnoside are obtained with remarkably high selectivity. It is difficult to produce *cis*-1,2-β-glycoside by the conventional method, but this novel strategy allowed selective production of β-glycoside from either mannose or rhamnose. The yield at both ortho ester formation and reduction was efficient, and it was equal to or higher than the other synthetic method for *cis*-1,2-β-glycoside.[59,60] Because this method produces unprotected hydroxyl groups that are available for further glycosylation, it can be used to produce a branch point of glycoside chains.

6. Development of the synthesis of carba-sugars using sugar ortho esters[61]

As previously described, the various synthetic methods for cyclitols have been extensively studied. We developed a simple-step synthesis of carba-hexose by applying reaction of ortho esters with methyl anions.

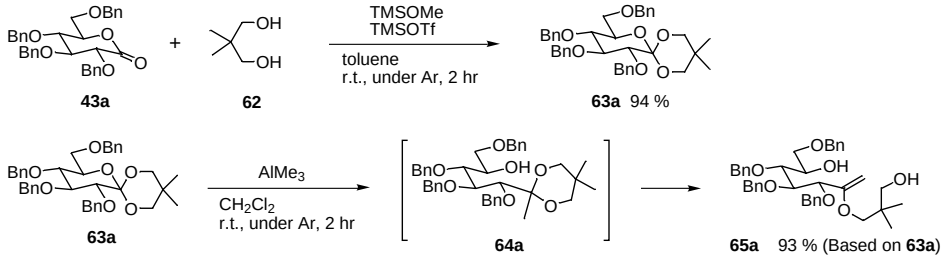


Fig. 23.

When the excess amount of sugar ortho ester **63a** was allowed to react with trimethyl aluminum, which is expected to be a methyl anion donor, an enol ether compound **65a** was obtained at 93% yield (Fig. 23). Because the ketal **64a** was isolated as an intermediate, the initial step of this reaction must be the ring cleavage by methyl anion introduction, shown as in Fig. 21. The reaction is followed by cleavage of the carbon-oxygen bond of the dioxane ring[62] along with deprotonation by trimethyl aluminum to produce an enol ether **65a**, and these are novel reaction observed with ortho esters. The formed enol ether **65a** have seven carbon atoms, and thus it is useful as a precursor of carba-hexose. We then attempted to convert **65a** to aketone **67a** (Fig. 24) and formation of cyclohexane ring by aldol condensation.[63]

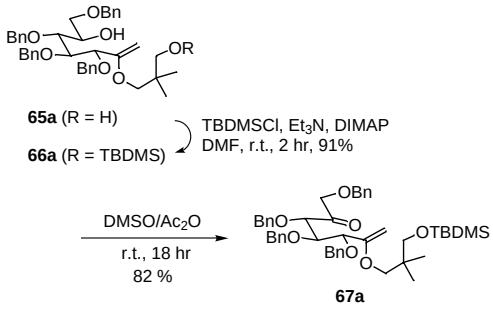
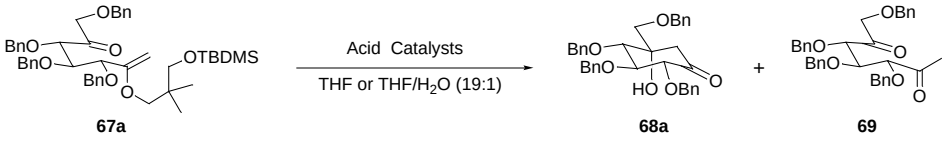


Fig. 24.

As a result of our evaluation of novel reaction conditions for aldol condensation for alkyl enol ethers, we found that heating with two equivalent amount of zinc chloride in hydrated tetrahydrofuran[64] converts **67a** to a carba-sugar **68a** at 90% yield (Table 10, **Entry 5**).

Table 10.



Entry	Reagent	Reagent / **67a**	Additive	Conditions	Time(h)	Yield (%) **68a**	**69**	**67a**
1	PPTS	1.0	–	rt	18	28	51	nd
2	BF_3•H_2O	1.0	–	rt	0.5	69	1	nd
3	$ZnCl_2$	1.0	–	rt	18	68	nd	nd
4	$ZnCl_2$	1.0	H_2O	rt	18	28	nd	67
5	$ZnCl_2$	2.0	H_2O	reflux	4	90	nd	nd
6	HCl	2.0	H_2O	rt	0.5	4	62	nd

As shown in **Entry 3**, when zinc chloride was used in the dehydrated solvent, the reaction proceeded rapidly but produced by-products, thus at the reduced yield of the desired compound. However, in the presence of small amount of water, interestingly it produced **68a** at a high yield (**Entry 5**). Also, when hydrochloric acid in hydrated tetrahydroflan was used, it predominantly produced a diketone **69** (**Entry 6**). When we omitted silyl protection to streamline the procedure and used crude products of direct oxidation of enol ether **65a** for aldol condensation, we obtained **68a** at 73% yield (Fig. 25).

The major product of the first oxidation reaction was dicarbonyl **70**, and after isolation and aldol condensation, ketone was selectively converted to **68a** (Fig. 25). Similarly, lactone of galactose **43b** and mannose **43c** produced carba-sugars **68b** and **c** at 64% and 56% total yield, respectively, *via* the simple-step procedure (Fig. 26).

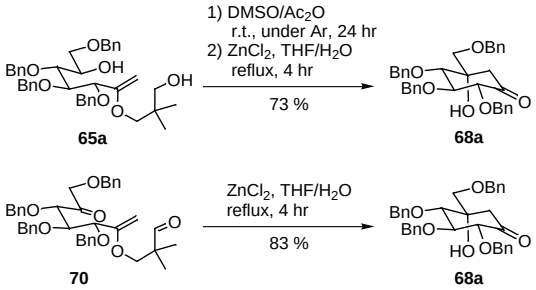
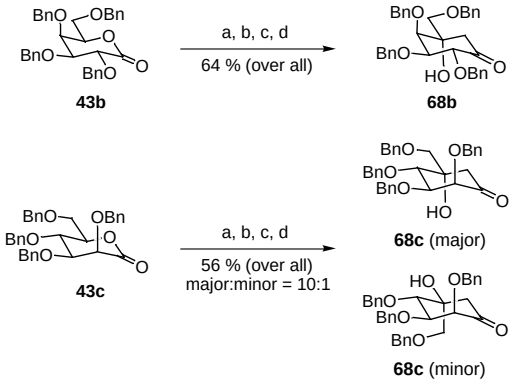


Fig. 25.

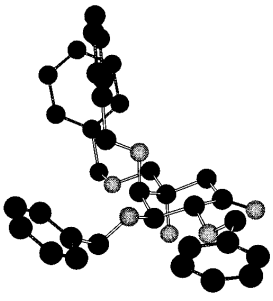


Reagents and Conditions: a) 2,2-dimethylpropanediol, TMSOMe, TMSOTf, toluene, r.t. b) $AlMe_3$, CH_2Cl_2, r.t.(or reflux) c) DMSO/Ac_2O, r.t. d) $ZnCl_2$, THF/H_2O, reflux

Fig. 26.

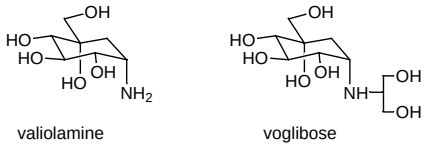
When **68c** was used, cyclization of aldol produced two isomers at 10 : 1. The conformation of two isomers of **68b** and **68c** were determined by X-ray analysis (Fig. 27) and by the formation of cyclic phenyl boronate derivatives.[65]

68a is a useful synton for the synthesis of the derivatives of valiolamines,[66,67] and we also produced voglibose (Fig. 28), a diabetic drug, *via* two steps according to the method by Fukase *et al*.[68]



68b

Fig. 27.



valiolamine voglibose

Fig. 28.

7. Conclusion

Although the synthetic methods described in this paper are all targeted at saccharides, we apply these methods to novel synthetic methods by focusing on enols or lactones within the sugars and by using common reactions. Saccharides are inexpensive and easily obtainable resources of optically active compounds. We believe the strategic use of these sugars may greatly contribute to the field of medical chemistry as well as organic synthetic chemistry. There are many areas left unexplored in the chemistry of saccharides, and we would like to encourage more researchers to tackle these problems.

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