HETEROCYCLES, Vol. 78, No. 1, 2009, pp. 19 - 44. © The Japan Institute of Heterocyclic Chemistry
Received, 24th July, 2008, Accepted, 9th September, 2008, Published online, 11th September, 2008.
DOI: 10.3987/REV-08-638

CHEMISTRY OF 1-METHYLENESUGARS: SYNTHETIC UTILIZATIONS TO 1'-*C*-METHYL-SACCHARIDES AND RELATED CARBOHYDRATES

Rie Namme and Shiro Ikegami*

School of Pharmaceutical Sciences, Teikyo University, Sagamihara, Kanagawa 229-0195, Japan. e-mail: somc@pharm.teikyo-u.ac.jp

Abstract – The efficient synthesis of protected 1-methylenesugars and their acid-catalyzed *O*-glycosidation are mentioned in connection with that of 1-C-methyl-pyranoses. Application of this process to synthesis of the pentasaccharide PI-88 analogue was accomplished in a protected form. Also the syntheses of trehalose analogues and ulsonic acid derivatives were successful in the similar process. 1,3-Dipolar cycloaddition with nitrones provides the new types of *spiro*-heterocycles combined with carbohydrates. The closely related methylene-carbohydrates also provide a novel synthetic process for cyclitols that are useful synthetic intermediates for voglibose and related drugs.

INTRODUCTION

The important biological significance and potential chemotherapeutic value of carbohydrate compounds have stimulated much research activity on glycoside synthesis.

Our group has worked on the development of various sugar mimics such as ketosides, orthoester sugars, carbacyclins, aza-sugars, thia-sugars, and artificial oligosaccharides such as carbamate- and urea-linked saccharides.[1,2] In this review, we mention the chemistry and synthetic utilities of unique sugars introduced a C-1 unit at anomeric position.

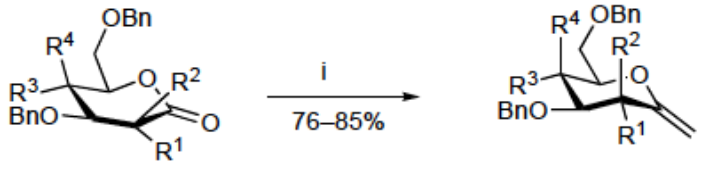
1. Glycosidation to 1-Methylenesugars

exo-Glycals, which have exocyclic olefin at anomeric position, have been actively examined about their preparation and utilization.[3] *exo*-Methylenesugars, that is one of the simplest exo-glycals, are useful precursors for synthesizing *C*-glycosides and other *C*-glycosyl derivatives.[4] Although *C*-glycosidations of *exo*-glycals have been well examined, their *O*-glycosidations were rarely reported until obtaining our observation. In this section, we describe the introduction of C-1 unit to pyranose as 1-*exo*-methylenesugars and its ability as glycosyl donors.

1-1 Preparation of 1-Methylenesugars

1-*exo*-Olefin-sugars have been prepared by several procedures, such as the Meyers' variant of the Ramberg-Becklund reaction[5], multiple step process with addition-elimination reactions[6], and methylenation of sugar lactones by Tebbe's reagent[7] or dimethyltitanocene.[8]

Perbenzyl-1-exo-methylenesugars can be readily prepared by Tebbe-type methylenation (Petasis modification) of corresponding lactones. The reactions of D-gluco-, D-galacto, and D-mannono-1,5-lactones **1a–c** with dimethyltitanocene afforded the corresponding tetra-*O*-benzyl-1-*exo*-methylenesugars **2a–c** in high yields (Scheme 1).[9]



1a–c **2a–c**

a : R^1=OBn, R^2=H, R^3=OBn, R^4=H (Glc)
b : R^1=OBn, R^2=H, R^3=H, R^4=OBn (Gal)
c : R^1=H, R^2=OBn, R^3=OBn, R^4=H (Man)

Scheme 1. *Reagents and conditions*: (i) Cp_2TiMe_2, toluene, 90°C

As the best way to elucidate the structure of the product, the X-ray single crystallographic structure of 1-methylenesugar **2a** is represented in Fig.1 by ball and stick model. It is shown that 1-methylenesugar **2a** is in chair conformation, which is also agreed with the ^{1}H-NMR coupling constant. By NMR analysis, galacto- and manno-derivatives **2b** and **2c** were also suggested to be in a chair form.

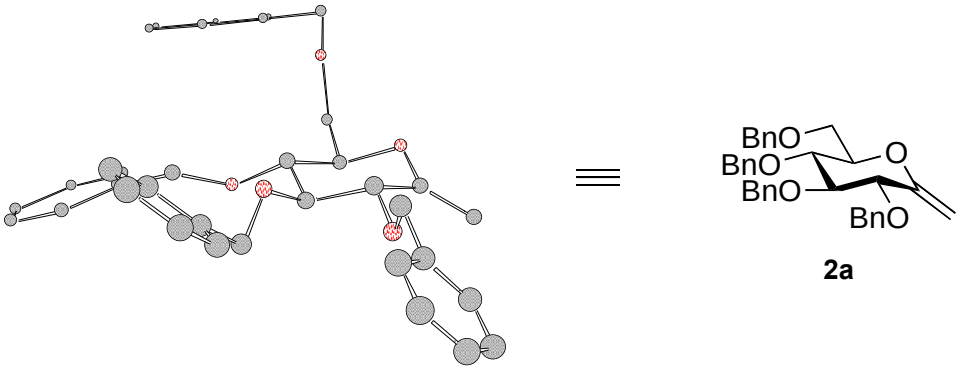
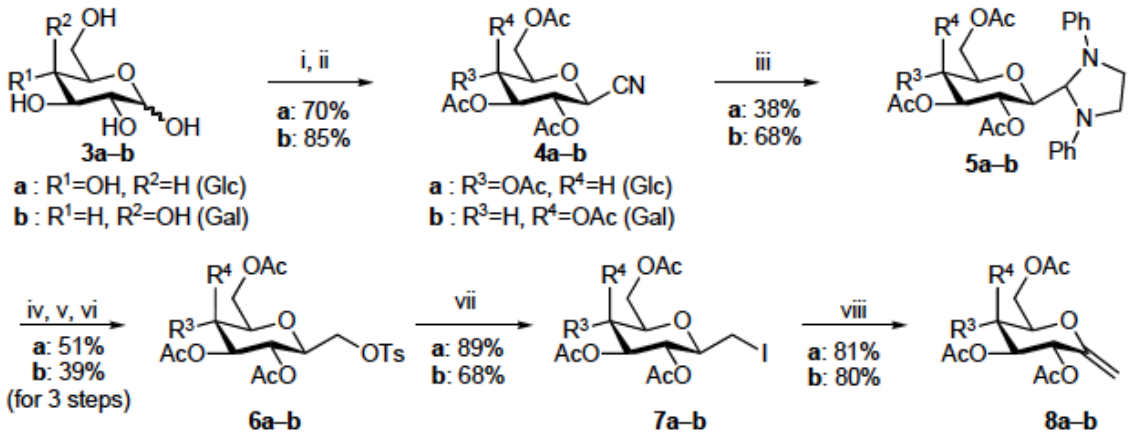


Figure 1. X-Ray crystallographic structure of **2a**. Hydrogen atoms are omitted for clarity.

On the other hand, this direct methylenation for the synthesis of peracetylglyconolactones could not be applied because they involve the ester function. Thus, multiple step synthesis was needed for preparing the *O*-acetyl-1-methylensugars.[10] As shown in Scheme 2 for the preparation of acetylated methylenesugars **8**, the subsequent procedures of aceylation, bromination and cyanation of the pyranose **3** afforded the compound **4**. Then, the compound **4** was reductively converted into diphenylimidazolidine **5** with Raney-Ni and *N*,*N'*-diphenylethylenediamine. Acidic cleavage of the imidazolidine **5** gave the aldehyde, which was reduced to alcohol with $NaBH(OAc)_3$, and then tosylated. The resulting tosylate **6** was treated with sodium iodide to afford the iodide **7**. Then, dehydorohalogenation of **7** with AgF provided tetra-*O*-acetyl-1-methylenesugars **8**.

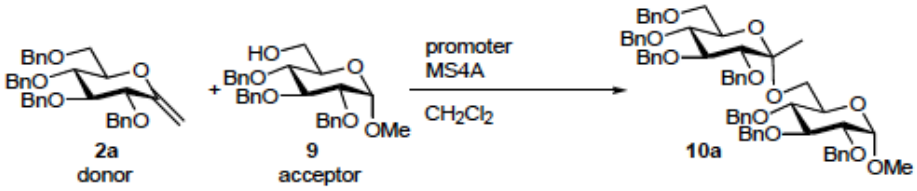


Scheme 2. *Reagents and Conditions*: (i) Ac_2O, $HClO_4$, P(red), Br_2; (ii) $Hg(CN)_2$, $MeNO_2$ rt; (iii) Raney-Ni, Py, $AcOH/H_2O$, NaH_2PO_2, $(PhNHCH_2)_2$, 40°C; (iv) $TsOH{\cdot}H_2O$, CH_2Cl_2/acetone, 0°C; (v) $NaBH(OAc)_3$, benzene, reflux; (vi) TsCl, pyridine, rt; (vii) NaI, Ac_2O, 125°C; (viii) AgF, pyridine, rt.

1-2 *O*-Glycosidation of 1-Methylenesugars

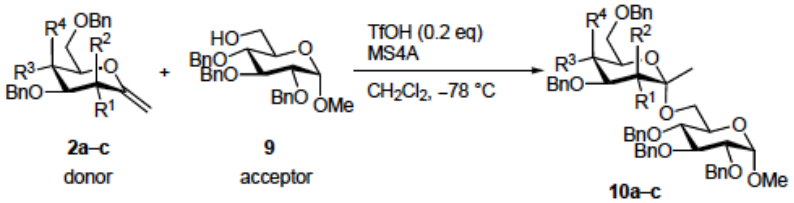
Firstly, the ability of 1-methylenesugars as powerful glycosyl donors in the glycosidation reactions was investigated. The acid-promoted *O*-glycosidation of 1-methylenesugar **2a** with methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside **9** was tried, affording 1-*C*-methyldisaccharide **10a** in complete α-selectivity (Table 1). Reaction conditions in this reaction were examined precisely and optimized using **2a** and **9**. It was found that the glycosidation proceeded effectively with trifluoromethanesulfonic acid (TfOH) in dichloromethane at –78°C (entry 2). Other Lewis acids also promoted this glycosidation, but the yield was lower than the reaction with TfOH (entries 5–8). Furthermore, the addition of a dehydrating agent was effective in proceeding glycosidation, and MS4A (one of the molecular shieves) was the most effective and suitable additive for this reaction. It should be noted that α-disaccharide was obtained as a single isomer even with any promoters in other solvents such as diethyl ether and toluene (entries 3–4).

Table 1. Acid-promoted *O*-glycosidation of 1-methylenesugar **2a** under various conditions



entry	promoter (eq)	solvent	temp.	time	yield (%)
1	TfOH (0.05)	CH_2Cl_2	0°C	5 min	83
2	TfOH (0.05)	CH_2Cl_2	–78°C	30 min	98
3	TfOH (0.2)	Et_2O	–78°C	30 min	93
4	TfOH (0.05)	$PhCH_3$	0°C	20 min	80
5	$ZnCl_2$ (0.2)	CH_2Cl_2	rt	48 h	31
6	$SnCl_4$ (0.1)	CH_2Cl_2	rt	2 h	78
7	TMSOTf (0.1)	CH_2Cl_2	0°C	15 min	78
8	BF_3•Et_2O (0.1)	CH_2Cl_2	0°C	1 h	76

Under optimized conditions, the glycosidation of galacto- and manno-derivertives **2b–c** was performed with acceptor **9** (Scheme 3). 1-Methylenesugars **2b** and **2c** exhibit similar glycosidation reactivity as the glycosyl donors and the corresponding 1'-*C*-methyl-α-disaccharides **10b–c** were obtained in high yields. In both cases, α-glycoside was obtained exclusively and β-glycoside was not detected.

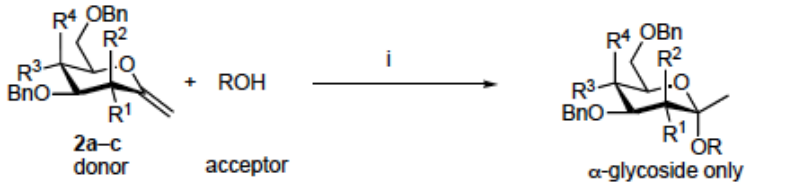


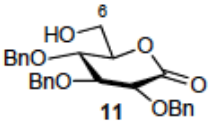
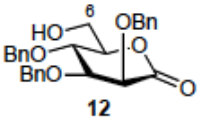
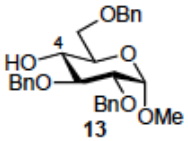
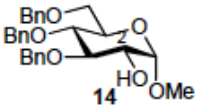
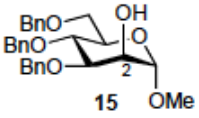
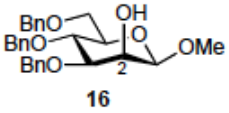
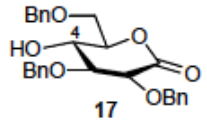
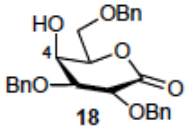
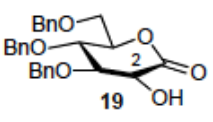
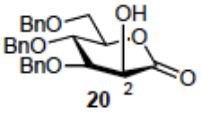
entry	donor	yield (%)
1	**2a** (Glc)	98
2	**2b** (Gal)	94
3	**2c** (Man)	90

Scheme 3

To examine the scope of this reaction, the glycosidation of **2a–c** with various sugar alcohols in pyranoses and glycono-1,5-lactones was carried out (Table 2).[11] Similarly in the case of methyl pyranoside **9**, the

Table 2. Glycosidation of 1-methylenesugar **2a–c** with various alcohols



entry	donor	acceptor (ROH)	product	yield (%)
1	**2a**	 **11**	**21a**	72
2	**2c**	 **12**	**22c**	79
3	**2a**	 **13**	**23a**	80
4	**2b**		**23b**	71
5	**2c**		**23c**	75
6	**2a**	 **14**	**24a**	94
7	**2a**	 **15**	**25a**	34
8	**2a**	 **16**	**26a**	26
9	**2a**	 **17**	**27a**	99
10	**2b**		**27b**	94
11	**2c**		**27c**	97
12	**2a**	 **18**	**28a**	81
13	**2b**		**28b**	82
14	**2c**		**28c**	97
15	**2a**	 **19**	**29a**	89
16	**2b**		**29b**	99
17	**2c**		**29c**	89
18	**2a**	 **20**	**30a**	86
19	**2b**		**30b**	98
20	**2c**		**30c**	89

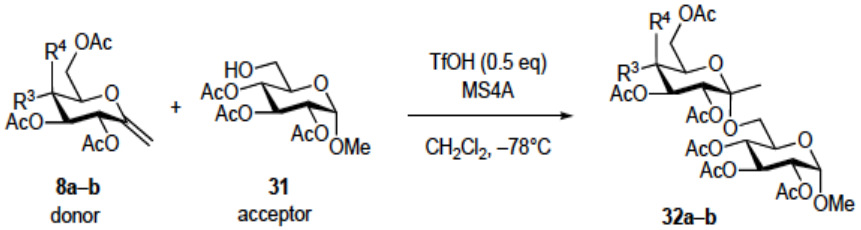
(i) TfOH (0.1 eq), MS4A, CH_2Cl_2, –78°C.

primary hydroxy group at the 6-position (6-OH) of D-galactono-1,5-lactone **11** and D-mannono-1,5-lactone **12** were well glycosylated (entries 1–2) . The equatorial secondary alcohols in **13** and **14** were also glycosylated in high yields (entries 3–6). On the other hand, the axial secondary alcohols at the **4** or **2** position (4-OH or 2-OH), 2-OH in mannopyranoside **15** and **16**, were less reactive and the corresponding 1'-*C*-methyldisaccharides were obtained only in 26–34% yield (entries 5–6). The axial hydroxyl group would generally be less reactive for glycosylation.

Next, the glycosidation of 1-methylenesugars with glycono-1,5-lactones **17–20** were examined. It was expected that the reactivity of 4-OH in galactono-1,5-lactone **18** or 2-OH in mannono-1,5-lactone **20** could be affected by the conformational change of a pyran ring. The glycosidation of 1-methylenesugars **2a–c** with glucono-1,5-lactone **17** and galactono-1,5-lactone **18** was carried out and corresponding disaccharides were obtained in high yield without any stereochemical change of alcohols to be glycosylated. In the similar way, both **19** and **20** showed good reactivity in the glycosidation of **2a–c**.

In all cases, the corresponding products as 1'-C-methyldisaccharide **21–30** were obtained in complete α-selectivity and β-glycosides were not detected.[12]

To investigate this unusually high stereoselectivity, we examined the glycosidation using peracetylated 1-methylensugars **8a–b** in which the acyl group attached to C-2 of glycosyl donor (Scheme 4). If neighboring group participation by an acetyl group are present in the reaction, β-isomers of 1'-C-methyldisaccharides might be obtained. The glycosidation of **8a–b** with acceptor **31** in the presence of TfOH gave the anomerically single α-disaccharides **32a–b** in moderate yields. The low yield of **32a** was due to the migration of an acetyl group in the acceptor **31**. These results suggest that the stereoselectivity in this reaction is not affected by the 2-*O*-acetyl group of the glycosyl donors **8a–b**.



entry	donor	yield (%)
1	**8a** (Glc)	51
2	**8b** (Gal)	82

Scheme 4

1-3 Stereochemistry at Anomeric Center

The configurations at the anomeric position of ketosides were confirmed finally by determination by X-ray crystallographic analyses and NMR study.

It is known that the magnitude of three-bond carbon-proton coupling constant $^{3}J_{\text{C-1,3-H}}$ depends on the

dihedral angle between the C-1/C-2 bond and C-3/3-H bond.[13] In 1-*C*-methylpyranoside, the 1-*C*-methyl exocyclic carbon and 2-H axial proton are oriented synclinally in α-ketoside and antipeliplanarly in β-ketoside (Figure 2). Therefore, the configuration of gluco- and galacto-ketopyranosides was determined by the analysis of vicinal C-H coupling constants $^{3}J_{C,H}$ in NMR spectra. Chemical shifts of 1-*C*-methyl and anomeric carbon were also compared.

By comparison of chemical shift and coupling constant $^{3}J_{1\text{-Me},2\text{-H}}$ of disaccharides **21a** and **21a**(β)[14] with those of known compound **33**α and **33**β[15], major isomer of **21a** was assigned to α-glycoside (Table 3). The vicinal coupling constant $^{3}J_{1\text{-Me},2\text{-H}}$ were measured for other 1' -*C*-methyldisaccharides, which were approximately 1.8 ~ 2.0 Hz. The result inidicates that newly formed glycosidic bonds have the α-configuration in gluco- and galacto-ketopyranosides.

Figure 2

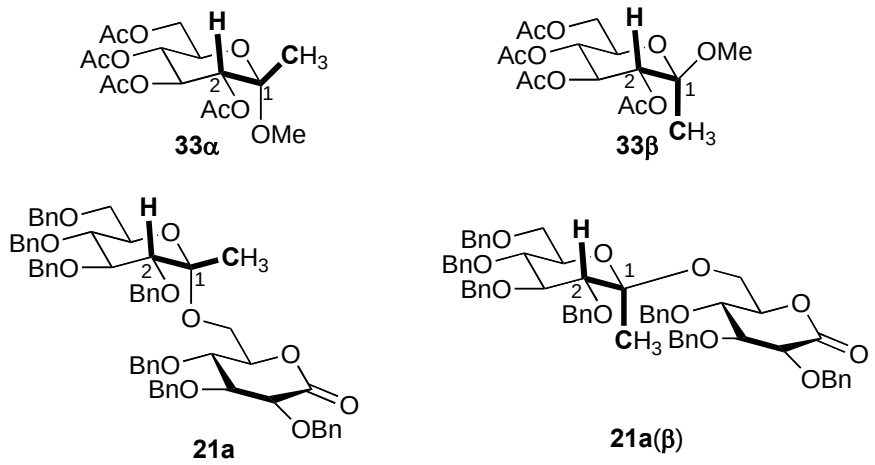
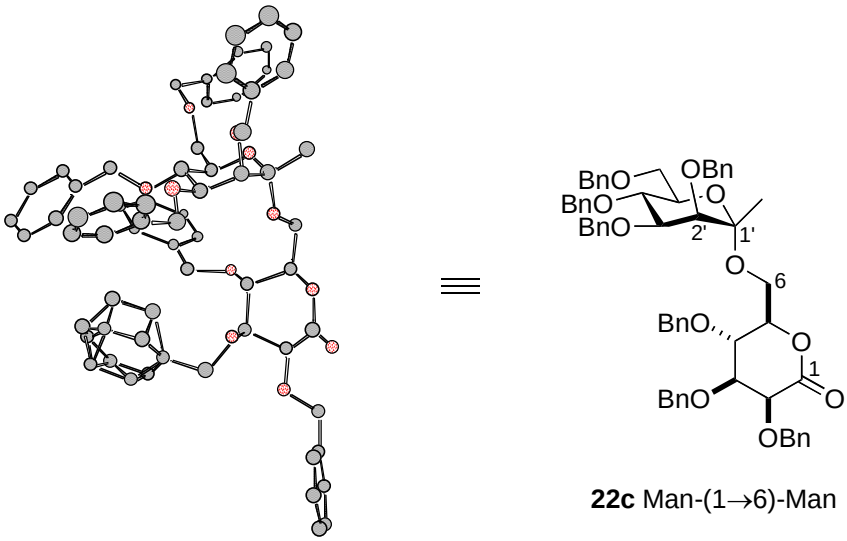


Table 3. The chemical shifts and coupling constants of nuclei and angles indicated in Fig. 2

	^{1}H (ppm)	^{13}C (ppm)		coupling constant
compound	C*H*$_3$	1-*C*H$_3$	C-1	$^{3}J_{1\text{-Me},2\text{-H}}$
21a	1.33	21.1	100.9	2.03 Hz
21a(β)	1.41	17.8	102.3	2.6 Hz
33α	1.35	19.49	99.53	1.6 Hz
33β	1.47	17.98	100.28	2.5 Hz

manno-Derivative of 1,6-linked disaccharide **22c** was obtained as colorless crystals. The X-ray crystallographic structure is shown in Figure 3. This X-ray analysis elucidated that manno-pyranoside possessed a chair conformation and α-anomeric configuration. This result suggests that the other 1-*C*-methyl-manno-pyranosides also possess the α-configuration because only single isomer was formed in every case. Thus, we could be fairly certain that the TfOH-promoted *O*-glycosidations of gluco-, galacto- and manno-1-methylenesugars give α-glycosides selectively.



22c Man-(1→6)-Man

Figure 3. X-Ray crystallographic structure of **22c** based on a disordered arrangement at C_3-*O*-benzyl group is showed. Hydrogen atoms are omitted for clarity.

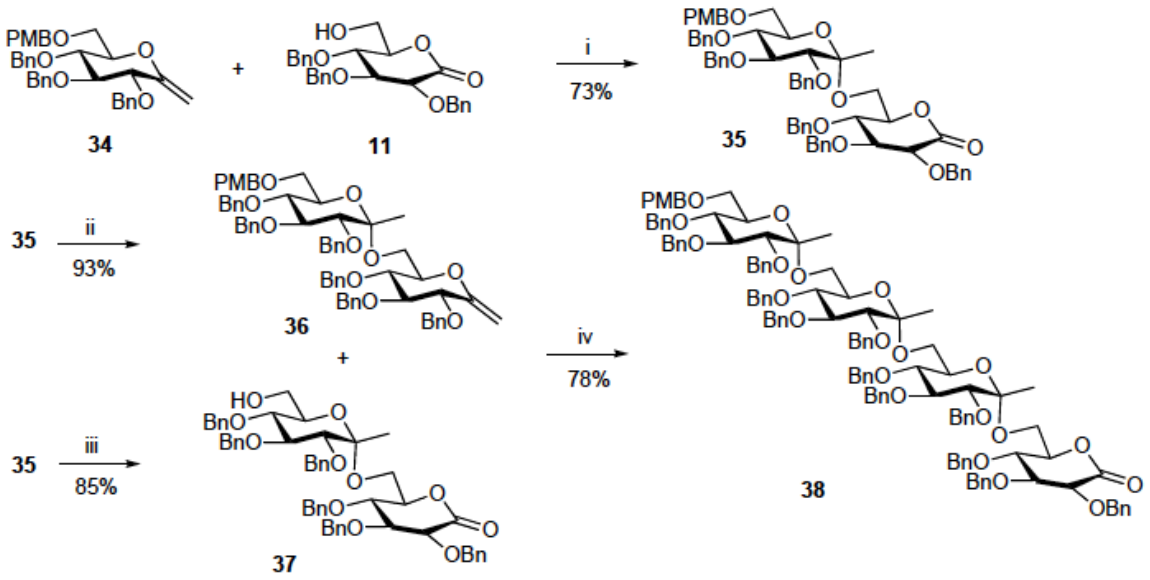
1-4 Synthetic Trial to Oligosaccharides (PI-88 Analogue)[16,17]

The acid-promoted *O*-glycosidation of 1-methylenesugars afforded 1'-*C*-methyldisaccharides not only in excellent yield but also in a completely α-stereoselective manner. Taking advantage of this α-selective glycosidation, we explored the synthesis of artificial α-glycosidic sugar chain.

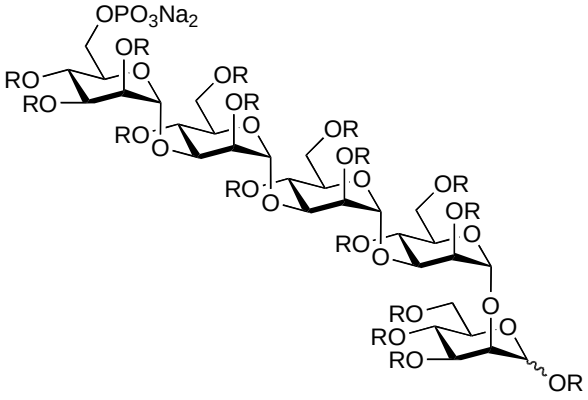
In order to examine the application to the oligosaccharide synthesis, the synthesis of Glc-α(1-6)-Glc linked 1-*C*-methyloligosaccharide was attempted (Scheme 5). 6-*O*-*p*-Methoxybenzyl (PMB)-protected 1-*exo*-methylenesugar **34** prepared for differentiating the 6-*O*-hydroxyl group from the other hydroxy groups was carried out under the established glycosidation conditions with hydroxylactone **11** and then the produced 1'-*C*-methyl-α-disaccharide **35** was converted into the corresponding glycosyl donor **36** by the methylenation. Disaccharide **35** was also converted into the acceptor **37** by the selective removal of PMB. Then, 2+2 glycosidation between **36** and **37** was performed and the tetrasaccharide **38** was obtained in complete α-selectivity. The result shows that this *O*-glycosidation of 1-methylenesugars could provide the preparative methodology to the new analogues of α-glycosidic oligosaccharides.

We next tried the synthetic application to the analogues of the bioactive sugar chains. Posphomannopentaose sulfate (PI-88), which was developed by Palish et al. in 1999 from the yeast P. holstii, shows potent heparanase inhibitory activity and antiangiogenesis properties.[18] As PI-88 consists of five mannose units with all α-glycoside linkages, we planed that 1-*C*-methyl-substituted PI-88 analogue could be synthesized utilizing the α-stereoselective *O*-glycosidation of *exo*-glycals.

PMB-Protected manno-methylenesugar **39** prepared selectively was carried out under the *O*-glycosidation with **20**. In this case, some modification of the rection conditions was needed. It was found that methanesulfonic acid (MsOH) was the best promoter to this glycosidation. Otherwise unexpected cyclized by-product was generated. The glycosidation of **39** with **20** in the presence of MsOH proceeded



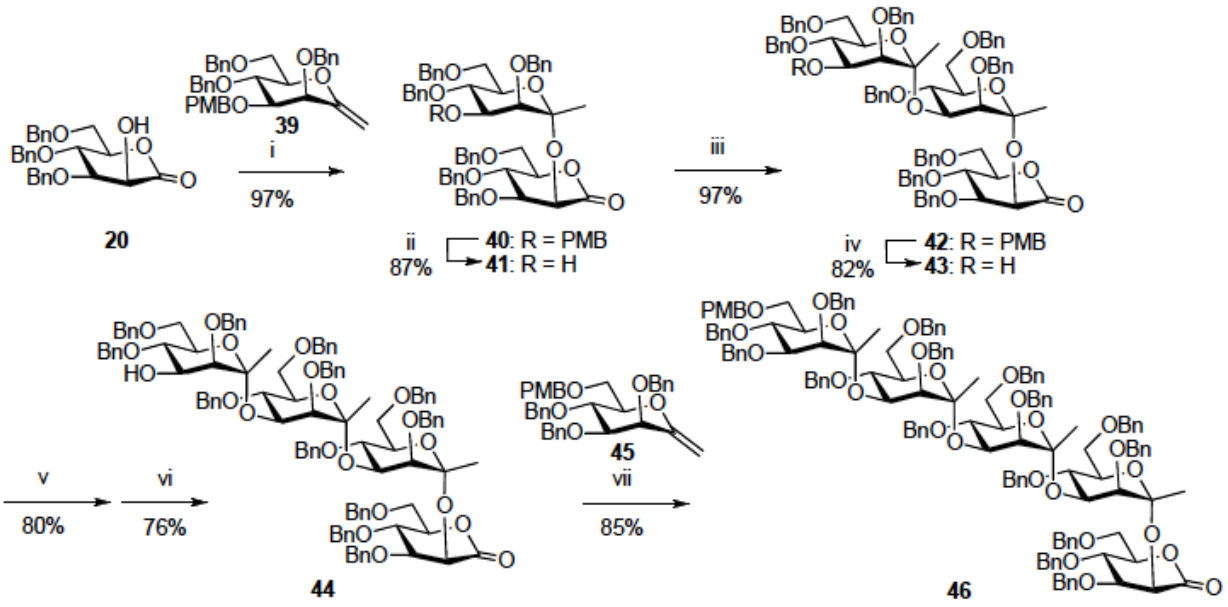
Scheme 5. *Reagents and conditions*: (i) **34**, **11** TfOH (0.05 eq), MS4A, CH_2Cl_2, –78°C; (ii) Cp_2TiMe_2, toluene, 70°C; (iii) CAN, CH_3CN/H_2O, rt.; (iv) **36**, **37**, TNSOTf (0.1 eq), MS4A, CH_2Cl_2, –78°C.



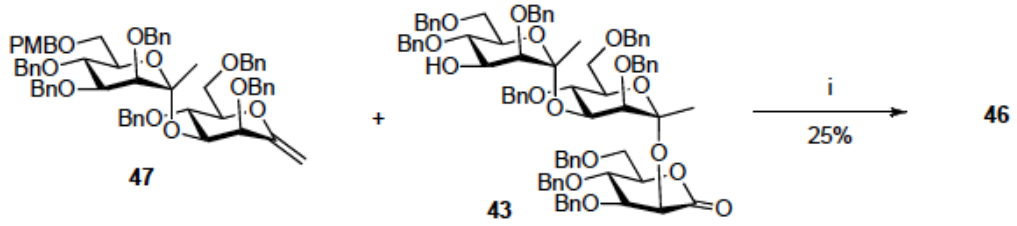
phosphomannopentaose sulfate (PI-88)
(R = SO_3Na or H)

smoothly, and the desired 1'-*C*-methyldisaccharide **40** was obtained α-stereoselectively in high yield. The removal of the PMB protection from the compound **40** with DDQ gave the disaccharidic glycosyl acceptor **41**, which was glycosylated again to afford trisaccharide **42** as a single isomer. Further chain-elongation sequentially involving the removal of PMB and glycosidation furnished the pentasaccharide **46** in complete α-selectivity (Scheme 6).

During the investigation of the synthesis of pentasaccharide **46**, 2+3 glycosidation was also examined. Disaccharidic donor **47** and trisaccharidic acceptor **43** were synthesized respectively and the glycosidation was performed. However, the glycosidation of **47** was rather unreactive and the desired pentasaccharide **46** was obtained only in 25% yield (Scheme 7). These results suggest that in some case, a step-by-step synthesis would be suitable in the synthesis of 1-*C*-methyl-oligosaccharide.



Scheme 6. Synthesis of pentasaccharide. *Reagents and Conditions:* (i) **39** (1.5 eq), MsOH, MS4A, CH_2Cl_2, –78°C; (ii) DDQ, CH_2Cl_2, H_2O, 0°C; (iii) **39** (1.5 eq), MsOH, MS4A, CH_2Cl_2, –78°C; (iv) DDQ, CH_2Cl_2, H_2O, 0°C; (v) **39** (1.5 eq), MsOH, MS4A, CH_2Cl_2, –78°C; (vi) DDQ, CH_2Cl_2, H_2O, 0°C; (vii) **45** (1.5 eq), MsOH, MS4A, CH_2Cl_2, –78°C.



Scheme 7. Synthesis of pentasaccharide. *Reagents and Conditions:* (i) MsOH, MS4A, CH_2Cl_2, –78°C

Finally, It would be hardly to say that we have not reached the final goal in this research. The final deprotection of the fully protected pentasaccharide **46** was not succeeded in spite of every successful trial because of the unexpectedly unstable glycosidic bonds presented in **46**.

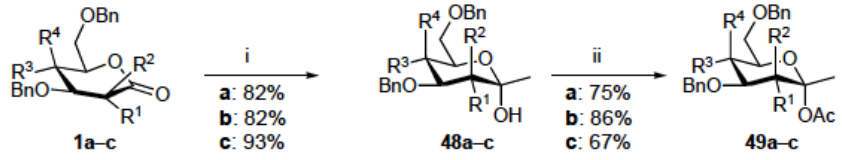
It is shown that the acid-promoted *O*-glycosidation by utilizing 1-methylenesugars provides a useful and efficient method, giving 1’-*C*-methyl-α-disaccharide with high α-selectivity in high yield. Furthermore, The method could be applied to the synthesis of the related α-oligosaccharide mimics.

2. Glycosidation of Ketopyranoses[19]

It is expected that the synthetic approach to 1-*C*-methyl-α-disaccharides can be accessed directly from ketopyranose. We also explored the glycosidation of ketoses and confirmed that 1-*C*-methyl-α-glycosides could be obtained as well. That is to say, the glycosidation of ketose is considered as another method to introduce C-1 unit at the anomeric position of the sugar chain. In this section, the preparation of ketopyranose and its conversion into ketoside-type disaccharides are mentioned.

2-1 Preparation of Ketopyranose

Ketopyranoses were readily prepared from lactones by the addition of alkyl group with organometallic reagents. Here, the lactones **1a–c** were treated with methyl lithium and converted into 1-*C*-methyl pyranose **48a–c**, respectively. The resulting ketoses were acetylated by treatment with acetic anhydride and butyl lithium.[20] These ketopyranoses were also used as glycosyl donors for 1-*C*-methyldisaccharide synthesis.



a : R^1=OBn, R^2=H, R^3=OBn, R^4=H (Glc)
b : R^1=OBn, R^2=H, R^3=H, R^4=OBn (Gal)
c : R^1=H, R^2=OBn, R^3=OBn, R^4=H (Man)

Scheme 8. *Reagents and conditions*: (i) CH_3Li (1.2 eq), THF, –78°C; (ii) Ac_2O, *n*BuLi, THF, –78°C.

2-2 *O*-Glycosidation of Ketopyranose

We first investigated the reaction conditions for the *O*-glycosidation using **48a** by employing methyl glycoside **9** as a glycosyl acceptor.

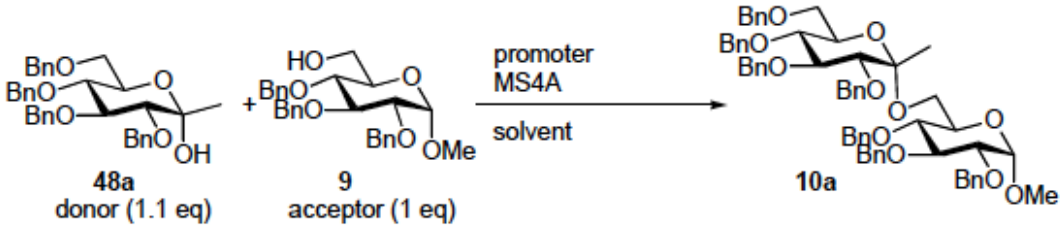
As the glycosidation of 1-methylenesugars was achieved in excellent yield by promoting with TfOH, the *O*-glycosidation of ketose **48a** was first examined under the same conditions. It was found that the *O*-glycosidation of **48a** with TfOH did not complete even in the use of 1.5 eq. of TfOH. After several attempts by changing Lewis acid promoters, it was found that TMSOTf was most effective for this glycosidation reaction. The best conditions were the use of 0.2 eq. of TMSOTf in dichloromethane in the presence of MS4A. The reaction also tried in other solvents such as diethyl ether and toluene, but the yield was moderate. It should be noted that the *O*-glycosidation of the 1-*C*-methyl-glucopyranose **48a** took place stereoselectively in the same manner and provided α-disaccharide **10a** as a sole product.

Following the above described conditions, the glycosidation of galacto- and manno-derivatives **48b** and **48c** with **9** was carried out and gave the corresponding α-disaccharides **10b** and **10c**, respectively, with complete α-stereoselectivity (Scheme 9). The results indicate that the stereochemistry of the resulting ketoside is not affected by stereochemistry of the 2- or 4- hydroxyl groups.

Starting from α-ketopyranose, α-ketoside was selectively formed. These results indicate that the *O*-glycosidation proceeds in S_N1 mechanism.

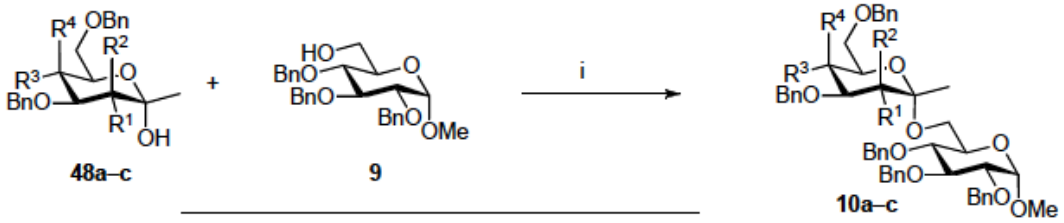
The transglycosidations of methyl 1-*C*-methylpyranosides **50a–c** were examined in the purpose of exploring the scope of this reaction. Because of the higher stability of the methyl glycosidic ether bond, stronger acidic condition was required to the transglycosidation and tin tetrachloride was effective for transglycosidation (Scheme 10).

Table 4. Effects of promoters on *O*-glycosidation reactions



48a donor (1.1 eq) + **9** acceptor (1 eq) → **10a**

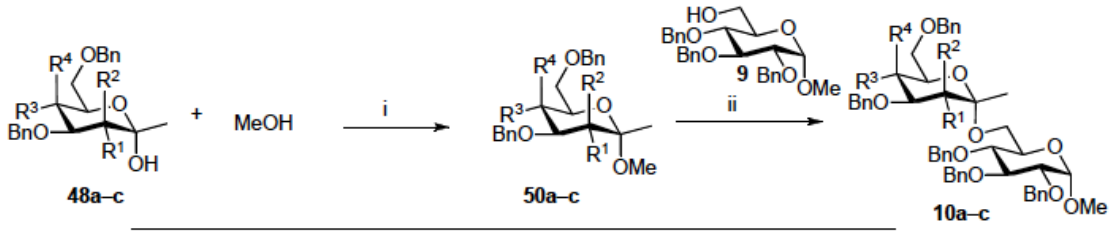
entry	promoter (eq)	solvent	temp.	yield (%)
1	TfOH (1.5)	CH_2Cl_2	–78°C, 3 h	75
2	TfOH (1.0)	CH_2Cl_2	–78°C, 1 h; 0°C, 1 h	79
3	TMSOTf (0.05)	CH_2Cl_2	0°C	72
4	TMSOTf (0.2)	CH_2Cl_2	0°C	90
5	TMSOTf (0.5)	CH_2Cl_2	0°C	86
6	TMSOTf (0.5)	Et_2O	0°C	83
7	TMSOTf (0.5)	THF	0°C	81
8	BF_3•Et_2O	CH_2Cl_2	0°C	78
9	$SnCl_4$ (1.0)	CH_2Cl_2	0°C	70
10	$TiCl_4$ (1.0)	CH_2Cl_2	0°C	74
11	$ZnCl_2$ (1.0)	CH_2Cl_2	0°C	77



48a–c + **9** → **10a–c**

entry	donor	yield (%)
1	**48a** (Glc)	90
2	**48b** (Gal)	89
3	**48c** (Man)	87

Scheme 9. *Reagents and conditions*: (i) TMSOTf (0.2 eq), MS4A, CH_2Cl_2, 0°C

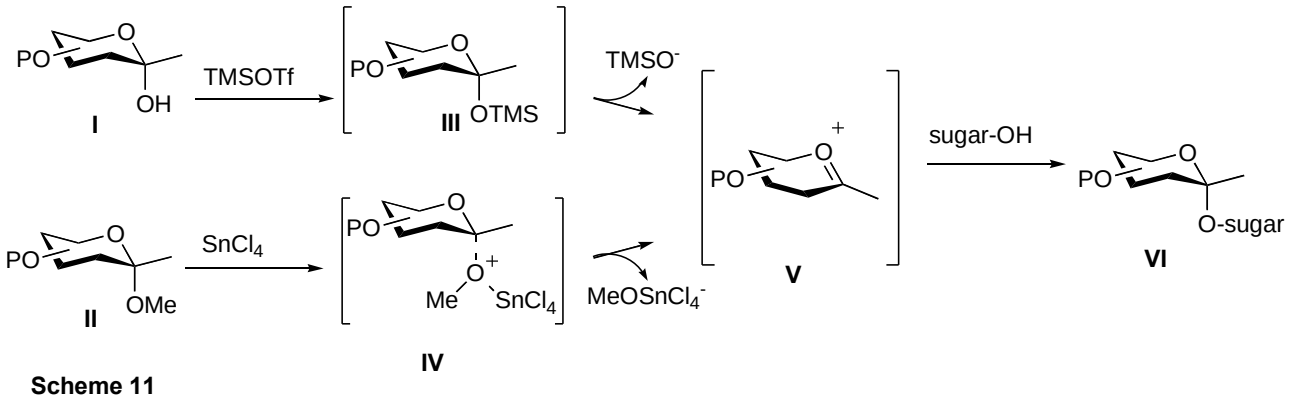


48a–c + MeOH → **50a–c** → **10a–c**

entry	donor	i yield (%)	ii yield (%)
1	**48a** (Glc)	92	81
2	**48b** (Gal)	95	78
3	**48c** (Man)	92	87

Scheme 10. *Reagents and conditions*: (i) TMSOTf (0.2 eq), MS4A, CH_2Cl_2, 0°C; (ii) $SnCl_4$ (1.0 eq), MS4A, CH_2Cl_2, 0°C, 3 h.

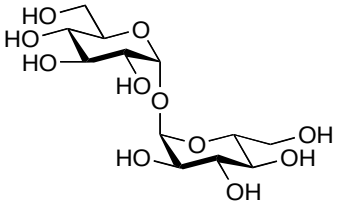
The *O*-transglycosidations afforded the corresponding α-glycosides as single isomers as well as the cases of 1-*exo*-methylenesugars and 1-*C*-methylsugars. In these glycosidations, a tertiary oxocarbenium ion **V** as a stable intermediate was generated from **II** or **III** and then combined with sugar alcohols to form the α-glycoside **VI**. The stability of the tertiary oxocarbenium ion **V** resulted in the α-stereoselectivity in the glycosidations due to the anomeric effect.[21]



Scheme 11

2-3 Application to Synthesis of Trehalose Analogues[22]

Utilizing α-selective *O*-glycosidation of 1-*C*-methyl-pyranose, we explored the synthesis of α-ketosyl α-aldosides. α-Ketosyl α-aldosides are 1,1’-linked non reducing disaccharide containing ketoside-bond, and they are regarded as 1-*C*-methyl analogues of trehalose.[23]

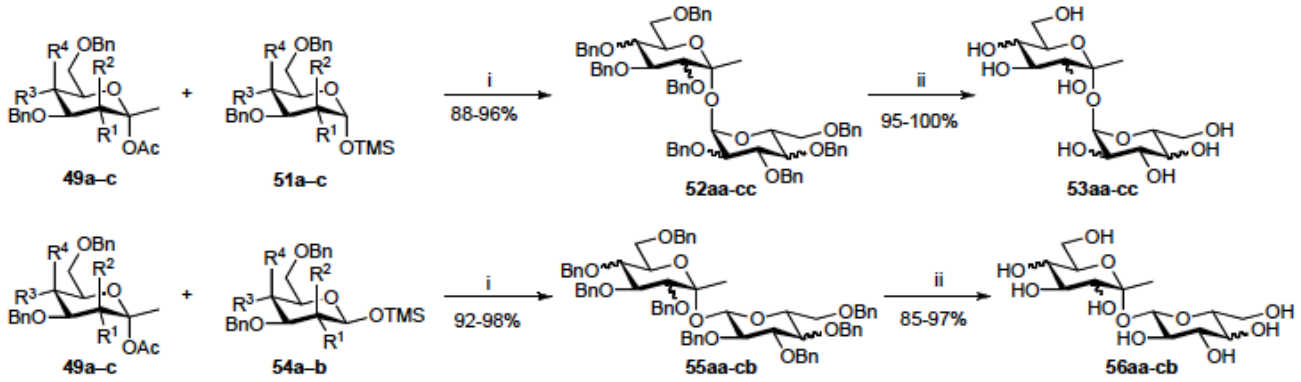


trehalose

We are also interested in whether or not the glycosidation proceeds in cross process between ketopyranose and aldopyranose. After detailed examination, it became clear that 1-*O*-acetyl-1-*C*-methylpyranoses **49a–c** were useful as glycosyl donors and trimethylsilyl α-pyranosides **51a–c** as glycosyl acceptors.[24] The glycosidation of ketose **49a–c** with **51a–c** was carried out in the presence of TMSOTf in a solution of dichloromethane. The reactions proceeded effectively in exclusive α-selectivity to give α-ketopyranosyl α-aldopyranoside **52aa–cc** in high yields. The stereochemistry of trimethylsilyl α-aldopyranoside was retained. However, only in the glycosidation of **49a** with **51a**, partially anomerization of α-aldopyranoside took place and then afforded the mixture of α,α-disaccharides **52aa** and α,β-disaccharides **55aa** in a ratio of **52a**a:**55aa**=10:1.

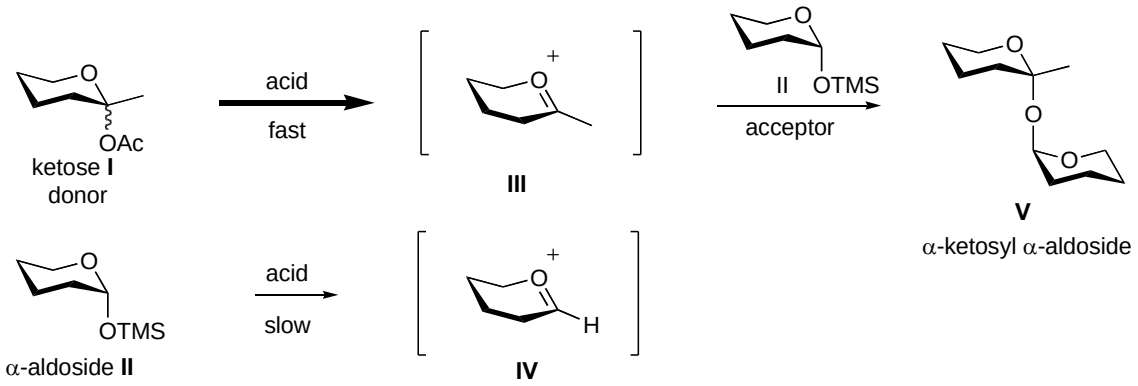
Similarly, we investigated the glycosidation using trimethylsilyl β-pyranoside **54a–c** as glycosyl acceptors. The glycosidation of ketoses **49a–c** with β-aldopyranoside **54a–b** proceeded α-selectively,

affording α-ketopyranosyl β-aldopyranosides **55aa–cb**. The anomerization of β-aldopyranoside **54a–b** to α-aldopyranosides **51a–b** was not observed and only α,β-disaccharides **55aa–cb** were formed in each cases. Therefore, both α,α- and α,β-disaccharides were selectively synthesized. α-Ketopyranosyl aldopyranoside **52aa–cc** and **55aa–cb** were deprotected respectively by palladium-catalyzed hydrogenolysis and corresponding trehalose analogues **53aa–cc** and **56aa–cb** were obtained nicely.



Scheme 12. *Reagents and conditions:* (i) TMSOTf (0.2 eq), MS4A, CH_2Cl_2, –78°C; (ii) $Pd(OH)_2$/C (50 wt%), basic alumina (25 wt%), H_2 (balloon),THF; MeOH.

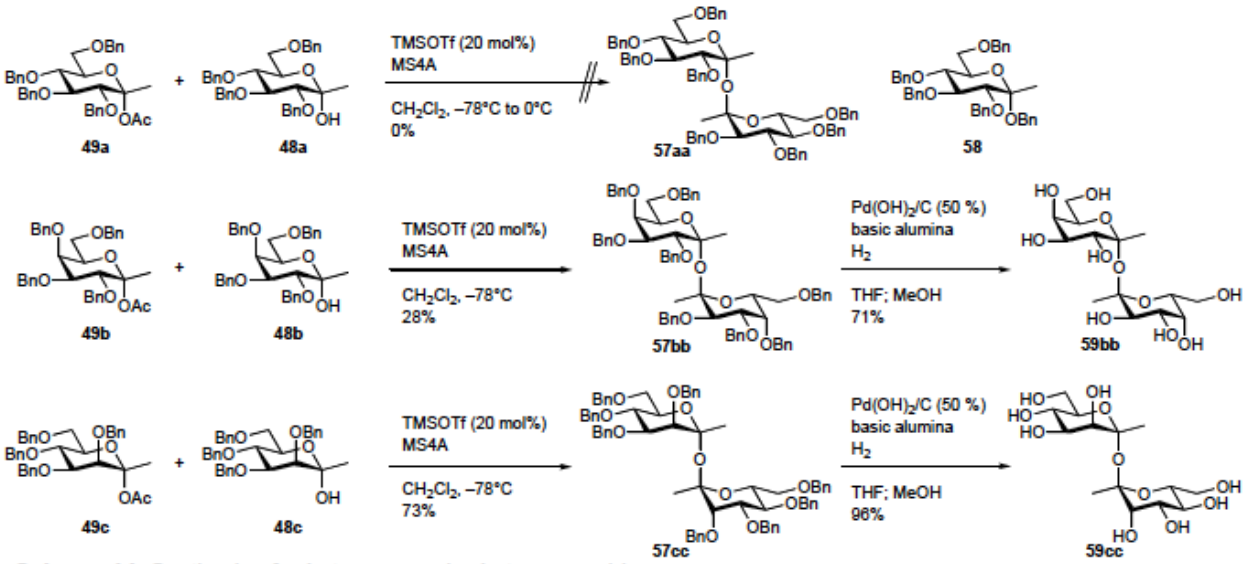
In this reaction, it is supposed that the formation of oxocarbenium intermediate **III** from ketose **I** is generated faster than **IV** from aldoside **II**, so that cross-linked ketosyl aldoside can be produced.



Scheme 13

We also tried the synthesis of dimethyl analogue of trehalose using ketoses **48a–c** as glycosyl acceptor. The glycosidation between gluco-derivatives did not give desired disaccharide **57aa** and afforded benzyl glucoside **58** instead. That is probably due to the bulkiness at the quaternary anomeric carbon. On the other hand, the glycosidation of galacto- and manno-derivatives afforded the corresponding disaccharides **57bb** and **57cc** respectively, of which deprotection produced 1,1'-dimethyl analogues of trehalose **59bb** and **59cc**.

Thus, we achieved the stereoselective synthesis of various 1-*C*-methyl analogues of trehalose by utilizing the glycosidation of ketoses.

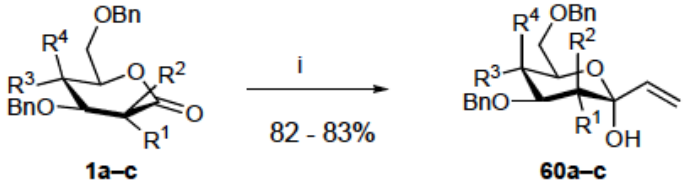


Scheme 14. Synthesis of α-ketopyranosyl α-ketopyranoside

2-4 Application to Synthesis of Ulosonic Acid Derivatives

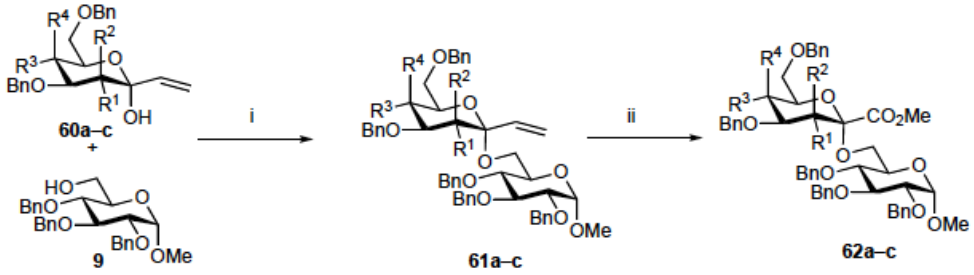
It is expected that the similar *O*-glycosidation of ketoses would proceed even in using other 1-*C*-alkyl-hexopyranoses and lead the various types of ketosides. Thus, we demonstrated the synthesis of ulosonic acid derivatives employing *O*-glycosidation of 1-*C*-vinyl-pyranose followed by ozonolysis of the olefin part.

1-*C*-vinyl-pyranoses **60a–c** were prepared by the reaction of lactones **1a–c** with vinylmagnesium bromide in good yields (Scheme 15). Under the above-mentioned conditions for 1-*C*-methyl-pyranose **48a–c**, the *O*-glycosidations of 1-*C*-vinyl-pyranoses **60a–c** with methyl glucoside **9** were carried out. The reaction was efficiently promoted by TMSOTf, and afforded corresponding disaccharides **61a–c** with exclusive α-selectivity. The conversion of 1-*C*-vinyl-glycoside **61a–c** to ulosonic acid derivatives was performed by a modification of Marshall's method. Ozonolysis of the olefinic bond in a solution of sodium hydroxide-methanol and dichloromethane provided directly the methyl esters **62a–c** (Scheme 16). In this way, the α-selective synthesis of ulosonic acid derivertives was succeeded.



a : R^1=OBn, R^2=H, R^3=OBn, R^4=H (Glc)
b : R^1=OBn, R^2=H, R^3=H, R^4=OBn (Gal)
c : R^1=H, R^2=OBn, R^3=OBn, R^4=H (Man)

Scheme 15. *Reagents and conditions*: (i) vinylmagnesium bromide (1.5 eq), THF, –78°C.



entry	donor	i yield (%)	ii yield (%)
1	**60a** (Glc)	88	33
2	**60b** (Gal)	71	30
3	**60c** (Man)	78	31

Scheme 16. *Reagents and conditions*: (i) TMSOTf (0.2 eq), MS4A, CH_2Cl_2, 0°C; (ii) NaOH/MeOH, CH_2Cl_2, O_3, –78°C.

3. Cycloaddition to 1-Methylenesugars

1-Methylenesugars can be also utilized for various structurally unique sugar compounds. In this section, the synthesis of spiro-sugars and their synthetic utilities are mentioned.

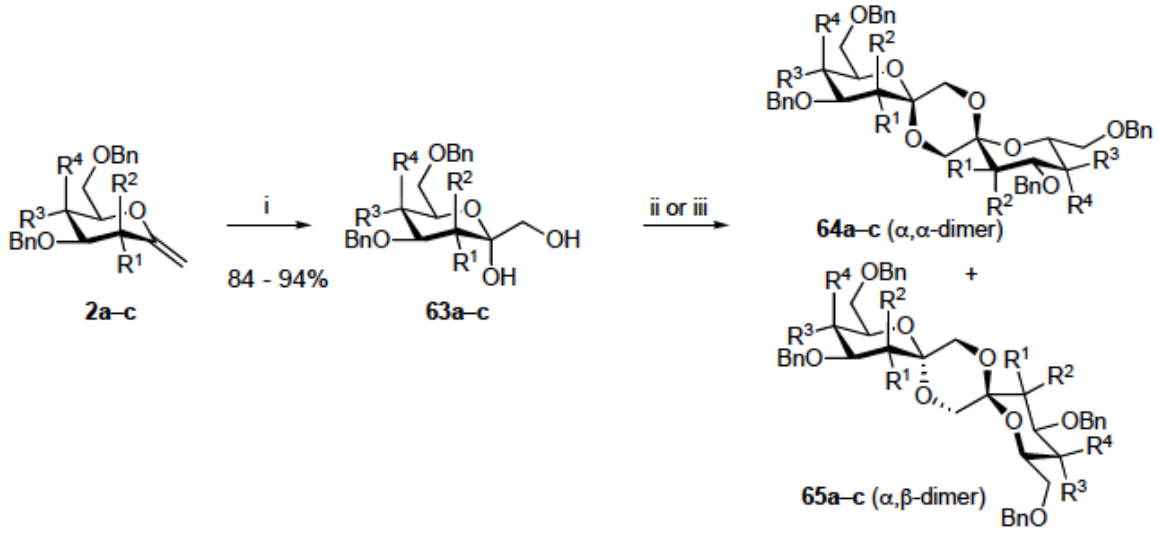
3-1 Synthesis of *spiro*-ketodisaccharides[25]

We mentioned the glycosidation of methylenesugars and ketoses under acidic conditions, in which the glycosidation took place α-stereoselectively and afforded α-ketosides in excellent yield. Taking adavantage of the α-selective glycosidation, we assumed that the glycosidation of 1-*C*-hydroxymethylpyranose in tandem manner of iterative glycosidation and intramolecular glycosidation would produce α-1,2-glycosyl-linked cyclic ketosaccharides. As various kinds of cyclodextrin have attracted greate attention, we demonstrated the stereoselective cycloglycosidation of ketose.

1-methylenesugars **2a–c** were converted into hept-2-ulopyranoses **63a–c** by the oxidation with *N*-methylmorpholine *N*-oxide and OsO_4. The reaction proceeded in high α-stereoselectivity with producing trace β-isomers (Scheme 17). Treatment of the diol **63a** with acids afforded two isomers of spiro-ketodisaccharide **64a** and **65a**. Various acids were scanned for the glycosidation and the effective formation of **64a** and **65a** was achieved with 1.5 eq. of TfOH in dichloromethane solution in a ratio of 1.1:1.0 (Table 5, entry 1). The ratio of **64a** and **65a** was influenced by the reaction temperature and **65a** became the major product as the reaction temperature increased. When the glycosidation of **63a** was performed under reflux conditions in diethyl ether using the combination of TsOH and TfONa, **64a** and **65a** were formed in 73% yield in a ratio of 1:7 (entry 2). The conditions at low temperature with TfOH and $CaSO_4$ (Method A) was benefit to the formation of **64a**, called kinetic control product and under the

reflux conditions in diethyl ether, the thermodynamic product **65a** was predominant.

Similarly, the cyclo-glycosidations of galacto- and manno-derivatives **63b** and **63c** were performed under the same conditions of Method A or Method B (entries 3–6). The reaction of **63a–c** showed similar reactivity under the both conditions. However, the α,α-stereoselectivity **64c** for **63c** was higher than that in the case of **63a** and **63b**. Thus, the corresponding *spiro*-ketodisaccharides were afforded.



Scheme 17. *Reagents and conditions*: (i) NMO, OsO_4 (5 mol%), acetone/H_2O, rt; (ii) (Method A) TfOH (1.5 eq), $CaSO_4$, CH_2Cl_2, –78°C→rt; (iii) (Method B) TsOH (1.0 eq), TfONa (1.0 eq), Et_2O, reflux.

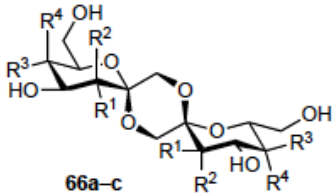
Table 5. Cyclo-glycosidation of 63a–c.

entry	63a–c	Method[a]	total yield (%)	64 : 65
1	**63a**	A	66	1.1 : 1.0
2	**63a**	B	73	1.0 : 7.0
3	**63b**	A	56	1.1 : 1.0
4	**63b**	B	76	1.0 : 5.1
5	**63c**	A	69	1.7 : 1.0
6	**63c**	B	78	1.0 : 1.6

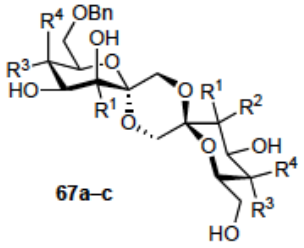
a) Method A: TfOH (1.5 eq), $CaSO_4$, CH_2Cl_2, –78°C (1 h)→rt; Method B: TsOH (1.0 eq), Et_2O, reflux, 3-5 h.

The compounds **64a–c** and **65a–c** were proved to be *spiro*-ketodisaccharides by mass spectral (FAB^+) and NMR analyses and their structures having the α,α- and α,β- anomeric conformation were determined by instrumental analysis of the deprotected compounds **66a–c** and **67a–c** (Figure 4).

Furthermore, the conformation of **65a–c** was confirmed finally by X-ray crystallographic analysis of the debenzylated compounds **67a–c** (Figure 5). These results show that all of compounds **67a–c** have a tricyclic chair-chair-chair form in thermodynamically stable conformation with the same α,β-anomeric configuration.



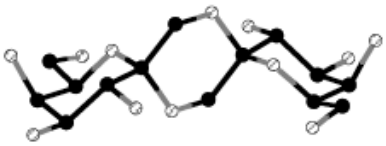
66a–c



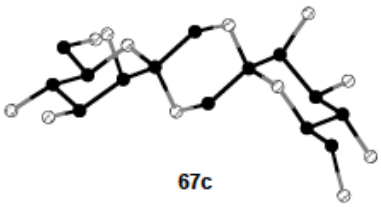
67a–c

Figure 4

67a



67b



67c

Figure 5. X-Ray crystallographic structures of α,β-spiro-ketodisaccharides **67a–c**

The structures of **64a–c** were elucidated by the comparison of the three bonds carbon-proton coupling constants $^{3}J_{C,H}$ and the NOE analysis for the acetylated compounds. The ^{1}H and ^{13}C NMR spectra showed that the pyranose ring adopted the normal $^{4}C_{1}$ chair form and the molecule had C2-symmetry. According to the coupling constant $^{3}J_{C,H}$, anomeric configuration of **66a–c** was revealed to be α,α-configuration. Taking account of the C2-symmetric conformation and the NOE measurement, the compounds **66a–c** were confirmed to possess a chair-boat-chair form for the spiro-tricycles.

This self condensation reaction might involve the two steps of glycosidation of **63a** in which α-glycosidic disaccharide is formed initially and then, the intramolecular cycloaddition takes place to give the products **64a** and **65a.** The formation of kinetically and thermodynamically less favorable β,β-spiroketodisaccharides were not observed. An attempt to prepare cyclic macroethers such as trimer, tetramer or more oligomers was unsuccessful in this glycosidation.

3-2 1,3-Dipolar Cycloaddition with Nitrones[26]

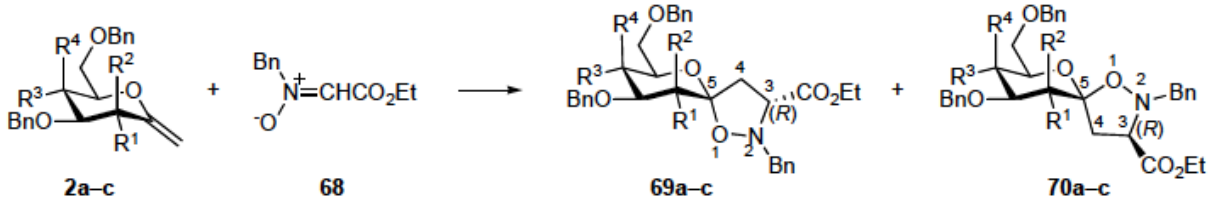
1,3-Dipolar cycloadditions of nitrons to alkenes have been widely used in organic synthesis. A stereoselective cycloaddition could be achieved by choosing an appropriate nitrone or alkene, which

contains either electron-donating or electron-withdrawing substituents. We describe here the stereoselective synthesis of glycosyl *spiro*-isoxazolidine by the 1,3-dipolar cycloaddition of nitrone to 1-methylenesugar and the further exploration in converting the *spiro*-isoxazolidine to new *C*-glcosyl amino acid.

The nitrone **68** was readily prepared according to the Dondoni's procedure[27] by the reaction of ethyl glyoxalate with the corresponding *N*-benzylhydroxylamine and *N*-methylhydroxylamine, respectively.

We firstly examined the cycloaddition of the 1-methylenesugar **2a** with the nitrone **68** under various conditions. This cycloaddition reaction in the presence of BF_3•Et_2O catalyst provided a mixture of α- and β-anomeric ketosyl *spiro*-isoxazolidines **69a** and **70a** with the α-isomer as predominant product (Scheme 18). This 1,3-dipolar cycloaddition proceeded diastereoselectively and gave only two isomers **69a** and **70a** possessing R-configuration at the C-3 position. In the presence of a catalytic amount of BF_3•Et_2O (0.3 eq) in dichloromethane, the cycloaddition at –78°C gave the adducts **69a** and **70a** in low yield and in a α,β-stereoselective ratio of 15.1:1 with the nearly 58% recovery of the starting material. The use of 1.3 eq of BF_3•Et_2O afforded the product **69a** and **70a** in 61% overall yield without remarkable change of α-streoselectivity. Moreover, increasing the reaction temperature up to 0°C after reacting at –78°C for 4 h resulted in 78% yield with satisfying α-stereoselectivity (α:β=11.3:1, Table 6, entry 1, Method A). It was found that the reactivity and selectivity were remarkably influenced by reaction temperature. In benzene solution at reflux, the reaction could efficiently proceed to afford **69a** and **70a** in excellent overall yield (96%) without any Lewis acid catalyst. Unfortunately, the stereoselectivity of the reaction was poor in this addition reaction (entry 2, Method B).

The 1,3-dipolar cycloaddition reactions of **2b–c** to **68** were also carried out in the above-mentioned procedures; Method A: 1-methylenesugar, nitrone **68** (1.25 eq), BF_3•Et_2O (1.3 eq), dichloromethane, –78°C, then 0°C; Method B: benzene, reflux. The results are summarized in Table 6. The results of gluco- and galacto-derivatives were similar in yields and stereoselectivity. In the case of manno-derivative possessing axial 2-hydroxy group, the reaction exhibited an increase of β-stereoselectivity.



2a–c **68** **69a–c** α-isomer **70a–c** β-isomer

a : R^1=OBn, R^2=H, R^3=OBn, R^4=H (Glc)
b : R^1=OBn, R^2=H, R^3=H, R^4=OBn (Gal)
c : R^1=H, R^2=OBn, R^3=OBn, R^4=H (Man)

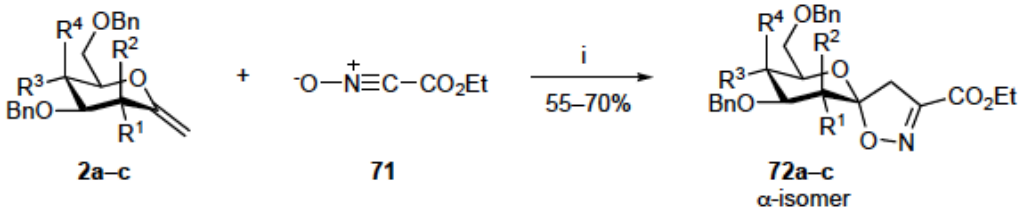
Scheme 18. 1,3-Dipolar cycloaddition of nitrone to 1-methylene sugars

Table 6. 1,3-Dipolar cycloaddition of **2a–c** with nitrone **68**

			Yield (%)		
entry	**2a–c**	Method[a]	**69a–c**	**70a–c**	α : β
1	**2a**	A	72	6	11.3 : 1.0
2	**2a**	B	43	52	1.0 : 1.2
3	**2b**	A	73	5	14.8 : 1.0
4	**2b**	B	31	32	1.0 : 1.0
5	**2c**	A	58	11	5.4 : 1.0
6	**2c**	B	23	42	1.0 : 1.8

a) Method A: **68** (1.25 eq), BF_3•Et_2O (1.3 eq), CH_2Cl_2, –78°C, 4 h→0°C; Method B: benzene, reflux, 24 h.

As another 1,3-dipolar cycloaddition, reactions with nitrile oxide were also studied. Nitrile oxide **71** was generated in situ from the corresponding ethyl chlorooximidoacetate under basic conditions and reacted with 1-methylenesugar **2a–c** in dichloromethane. The cycloadducts having *spiro*-isoxazoline structure **72a–c** were obtained in α-selectivity as a sole product. These stereoselective results are consistent with the RajanBabu's observation.[28]

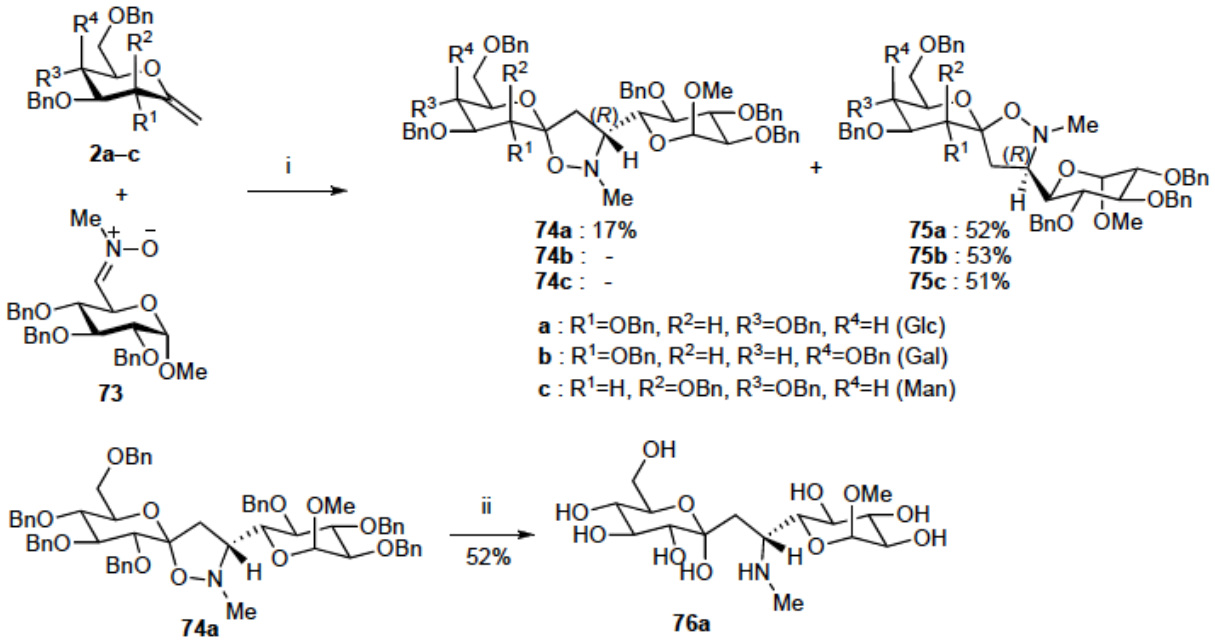


Scheme 19. *Reagents and conditions*: (i) CH_2Cl_2, rt.

The 1,3-dipolar cycloaddition of 1-methylenesugar **2a–c** and sugar nitrone **73** also produced the cycloadduct by refluxing in toluene. The cycloaddition of **2a** afforded only two isomers **74a** and **75a**. Interestingly, the cycloaddition of galactose- and mannose-derivatives **2b** and **2c** with the nitrone **73** gave only β-isomers **75b** and **75c**, respectively. It should be mentioned that Lewis acids did not work as catalysts in this reaction. With the cycloadducts in hand, the reductive opening of isoxazoline ring was achieved by the treatment of **74a** with zinc powder in AcOH/Ac_2O. More directly, the cleavage of N-O bond and debenzylation were accomplished in one step by catalytic hydrogenation and a novel amino-*C*-ketosyl disaccharide **76a** was obtained in 52% yield.

3-3 Synthetic Utility of *spiro*-Sugars

In connection with chemistry of sugar ortho esters that we developed previously, we have extended these observations to the related sugar chemistry through their conversions into other functionalities.[2,29,30] Herein, an introduction of C-1 unit directly to ortho esters and their utilizations to other useful compounds were described.



Scheme 20. *Reagents and conditions*: (i) toluene, reflux; (ii) $Pd(OH)_2/C$, H_2, MeOH.

Ortho ester **78** prepared from lactone **1a** and neopentyl glycol **77** in 94% yield was treated with $AlMe_3$ in dichloromethane afforded enol ether **80**. By careful observation of the reaction, it is indicated that the first insertion of a methyl anion causes the cleavage of pyranose ring to afford ketal **79**, and then cleavage of dioxane ring occurs by proton elimination. In the reaction with small amount of $AlMe_3$, both ketal **79** and enol ether **80** were isolated. Actually, **79** was smoothly converted into **80** by treatment with $AlMe_3$ (Scheme 21).

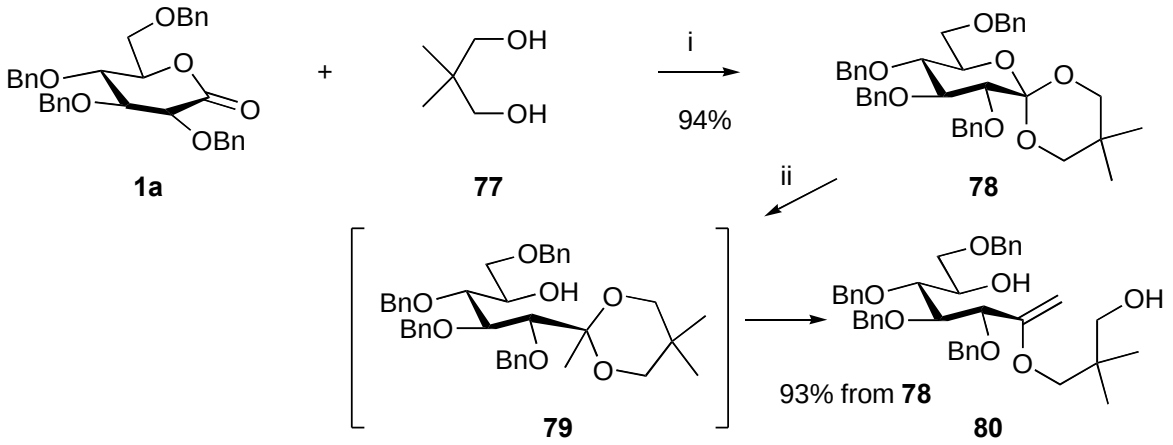
It seems to be a suitable precursor to cyclitols by chemical conversion of the resulting enol compound. We planned the development of a new method to the synthesis of cyclitols by intramolecular Aldol condensation. While Aldol condensation starting with silyl enol ethers has been well developed, there have been only a few reports on the condensation utilizing with alkyl enol ether.

The selective silyl (TBDMS) protection of **80** and consequent Swern oxidation produced the corresponding keto derivative **81**. After careful investigation by using various cyclization conditions, the intramolecular Aldol condensation of **81** was achieved in catalyzing by $ZnCl_2$ in THF-H_2O (19:1) under reflux to produce cyclitol derivative **82a** in 90% yield (Scheme 22). It should be noted that the addition of a small amount of H_2O is essential in facilitating the condensation. For more convenient and practical synthesis of cyclitols, Aldol condensation without silyl-protection was also examined. Diol **80** was directly oxidized to keto-aldehyde **83** and succeeding Aldol condensation of **83** catalyzed by $ZnCl_2$ in aqueous THF provided carbasugar **82a** in 83% yield. Fortunately, enol ether moiety of **83** selectively reacted with ketone in the sugar part instead of terminal aldehyde after another ketone generation by

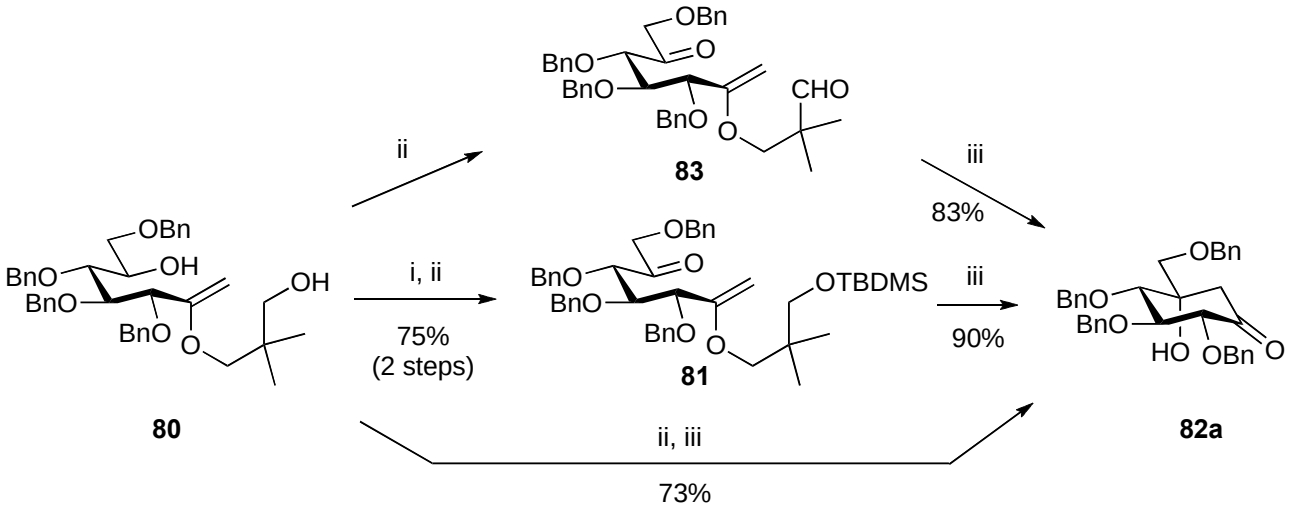
hydrolysis. More practically, oxidation of **80** and succeeding cyclization of the crude oxidized product afforded **82a** in 73% yield based on **80** (Scheme 22).

This procedure was applied to the conversion of galactonolactone and mannonolactone (Scheme 23). Starting from galactonolactone **1b**, the conversion through ortho ester formation, insersion of C-1 unit, oxidation and intramolecular Aldol condensation provided carbasugar **82b** in 64% overall yield. The structure of **82b** was confirmed by X-ray single crystallographic analysis (Figure 6). In the same way, manno-carbasugar **82c** was synthesized from **1c** in 56% total yield. In the case of manno-derivative **82c**, a small amount of stereoisomer also formed (major:minor = 10:1).

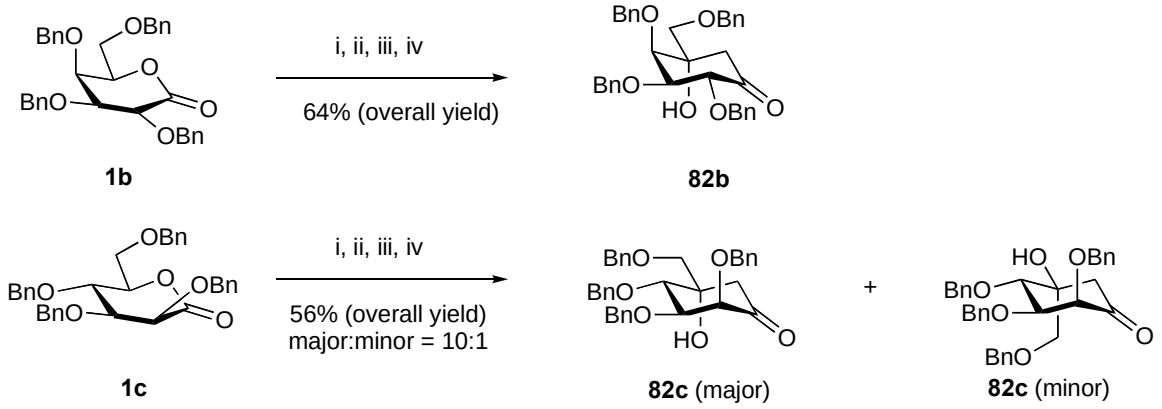
Cyclitol derivatives **82a–c** are versatile synthons for the synthesis of valiolamine and its derivatives including voglibose (Figure 7). The short steps synthesis presented here may be a new practical entry for the preparation of cyclitols.



Scheme 21. *Reagents and conditions*: (i) TMSOMe, TMSOTf, toluene, rt; (ii) $AlMe_3$, CH_2Cl_2, rt



Scheme 22. *Reagents and conditions*: (i) TBDMSCl, Et_3N, DMAP, DMF, rt; (ii) DMSO/Ac_2O, rt.; (iii) $ZnCl_2$, THF/H_2O (19:1), reflux



Scheme 23. *Reagents and conditions*: (i) **77**, TMSOMe, TMSOTf, toluene, rt; (ii) $AlMe_3$, CH_2Cl_2; (ii) DMSO/Ac_2O, rt.; (iv) $ZnCl_2$, THF/H_2O (19:1), reflux

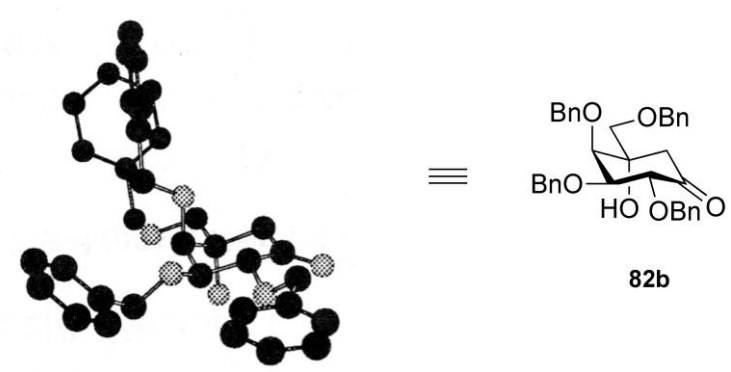


Figure 6. X-Ray crystallographic structure of carbasugar **82b**.

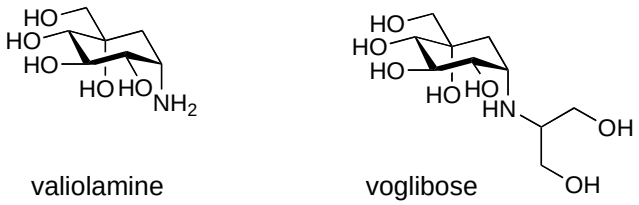


Figure 7. The structures of Valiolamine and Voglibose (Basen^R)

CONCLUSION

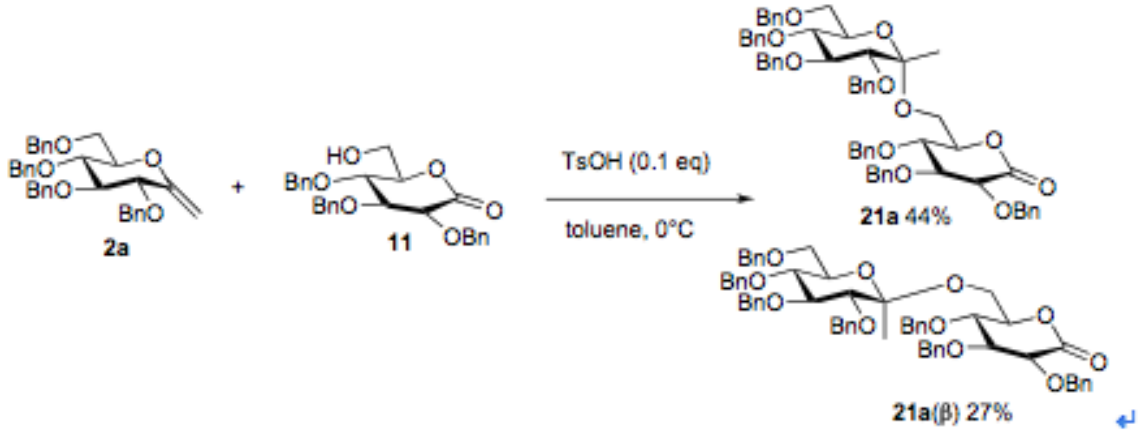
The introduction of one carbon atom to the anomeric position of pyranoses and their utilities toward various artificial sugar compounds were mentioned. The acid-catalyzed *O*-glycosidation of 1-methylenesugars or 1-*C*-methyl-pyranose produced 1'-*C*-methyldisaccharides in complete α-selectivity. This gycosidation was applied to the synthesis of ketoside-type artificial sugar chain, trehalose analogues, and ulosonic acid derivatives. Utilizing the synthetic property of 1-methylenesugars, the synthesis of conformationaly fixed *spiro*-ketosides and their conversion into sugar related compounds were achieved.

The highly stereoselective synthesis of these compounds provides useful sugar mimics in synthetic and biological fields. Chemistry concerning closely related compounds to methylene-sugar was also described.

REFERENCES AND NOTES

1. H. Takahashi, H. Kittaka, and S. Ikegami, *J. Synth. Org. Chem. Japan*, 2000, **58**, 120; D. Sawada, H. Takahashi, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, 2005, **46**, 2399; D. Sawada, S. Sasayama, H. Takahashi, and S. Ikegami, *Heterocycles*, 2005, **66**, 441; H. Takahashi, T. Shida, Y. Hitomi, Y. Iwai, N. Miyama, K. Nishiyama, D. Sawada, and S. Ikegami, *Chem. Eur. J.*, 2006, **12**, 5868; D. Sawada, S. Sasayama, H. Takahashi, and S. Ikegami, *Tetrahedron Lett.*, 2006, **47**, 7219; D. Sawada, S. Sasayama, H. Takahashi, and S. Ikegami, *Eur. J. Org. Chem.*, 2007, 1064; D. Sawada, S. Sasayama, H. Takahashi, and S. Ikegami, *Tetrahedron*, 2008, **64**, 8780.
2. H. Ohtake, X. Li, H. Takahashi, and S. Ikegami, *J. Synth. Org. Chem. Japan*, 2002, **60**, 206.
3. C. Taillefumier and Y. Chapleur, *Chem. Rev.*, 2004, **104**, 263.
4. L. Lay, F. Nicotra, L. Panza, G. Russo, and E. Caneva, *J. Org. Chem.*, 1992, **57**, 1304.
5. F. K. Griffin, P. V. Murohy, D. E. Paterson, and R. J. K. Taylor, *Tetrahedron Lett.*, 1998**,** **39**, 8179; M.-L. Alcaraz, F. K. Griffin, D. E. Paterson, and R. J. K. Taylor, *Tetrahedron Lett.*, 1998**,** **39**, 8183.
6. M. Brockhaus and J. Lehmann, *Carbohydr. Res.*, 1977, **53**, 21; J. Lehmann and C. Knapp, *Carbohydr. Res.*, 1978, **63**, 257; J. M. Lancelin, J. R. Pougny, and P. Sinay, *Carbohydr. Res.*, 1985, **136**, 369.
7. T. V. Rajan Babu and G. S. Reddy, *J. Org. Chem.*, 1986, **51**, 5458; C. S. Wilcox, G. W. Long, and H. Suh, *Tetrahedron Lett.*, 1984**,** **25**, 395.
8. C. R. Johson and B. A. Johons, *Synlett*, 1997, 1406; R. Csuk and B. I. Glänzer, *Tetrahedron*, 1991, **47**, 1655.
9. X. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Tetrahedron*, 2001, **57**, 4283.
10. E. J. Hehre, C. F. Brewer, T. Uchiyama, P. Schlesselmann, and J. Lehmann, *Biochemistry*, 1980, **19**, 3557.
11. R. Namme, T. Mitsugi, H. Takahashi, M. Shiro, and S. Ikegami, *Tetrahedron*, 2006, **62**, 9183.
12. For intramolecular glycosidation, see T. Kobayashi, C. S, Regens, and S. E. Denmark, *J. Synth. Org. Chem. Japan*, 2008, **66**, 616; R. W. Friesen and C. F. Sturino, *J. Org. Chem.*, 1990, **55**, 5808; E. Dubois and J. -M. Beau, *Tetrahedron Lett.*, 1990, **31**, 5165.
13. In *Advances in Carbohydrate Chemistry and Biochemistry*, ed. by D. Horton, Academic, San Diego, 1995; Vol. 51, pp. 15–61.
14. The glycosidation of 1-methylenesugar **2a** with 2,4,6-tri-O-benzyl-D-glycono-1,5-lactone (**11**) with

TsOH afforded α-disaccharide **21a** and a small amount of β-disaccharide **21a(β)**. This was the only substrate that we could obtain β-isomer. Our attempt to anomerize α-glycoside into β-glycoside was unsuccessful.



15. P. Schlesselmann, H. Fritz, J. Lehmann, T. Uchiyama, C. F. Brewer, and E. J. Hehre, *Biochemistry*, 1982, **21**, 6606.
16. R. Namme, T. Mitsugi, H. Takahashi, and S. Ikegami, *Tetrahedron Lett.*, 2005, **46**, 3033.
17. X. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Synlett*, 2001, 1885.
18. C. R. Parish, C. Freeman, K. J. Brown, D. J. Francis, and W. B. Cowden, *Cancer Res.*, 1999, **59**, 3433.; For a review, see: L. M. Khachigian and C. R. Parish *Cardiovasc. Drug Rev.*, 2004, **22**, 1.
19. X. Li, H. Ohtake, H. Takahashi, and S. Ikegami, *Tetrahedron*, 2001, **57**, 4297.
20. T. Yamanoi, Y. Oda, I. Yamazaki, M. Shinbara, K. Morimoto, and S. Matsuda, *Lett. Org. Chem.*, 2005, **2**, 242.
21. For example, Carbohydrate Chemistry, ed. by G.-J. Boons, Blakie Academic & Professional, London, 1998, pp. 10-16.
22. R. Namme, T. Mitsugi, H. Takahashi, and S. Ikegami, *Eur. J. Org. Chem.*, 2007, 3758.
23. L. M. Crowe and J. H. Crowe, *Biochim. Biophys. Acta*, 1988, **946**, 193; C. Colaço, S. Sen, M. Thangarelu, S. Pinder, and B. Roser, *Biotechnology*, 1992, **10**, 1007; C. A. L. S. Colaco, C. J. S. Smith, S. Sen, D. H. Roser, Y. Newman, S. Ring, and B. J. Roser, in *Formulations and Delivery of Proteins and Peptides*, ed. by J. L. Cleland and R. Langer, Symposium Series No. 567, American Chemical Society, Washington, DC, 1994, pp. 222–240.
24. L.-F. Tietze, R. Fischer, and H.-J. Guder, *Tetrahedron Lett.*, 1982, **23**, 4661; E. M. Nashed and C. P. J. Glaudemans, *J. Org. Chem.*, 1989, **54**, 6116; D. X. Qiu, F. Y. Wang, and M. S. Cai, *Synth. Commun.*, 1989, **19**, 3453; C. Kolar and G. Kneissl, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 809; W. Priebe, G. Grynkiewicz, and N. Neamati, *Tetrahedron Lett.*, 1991, **32**, 2079; T. Mukaiyama, K. Matsubara, *Chem. Lett.*, 1992, 1041; A. Kirschning, and G.-W. Chen, *Tetrahedron Lett.*, 1999, **40**, 4665.

25. X. Li, H. Takahashi, H. Ohtake, and S. Ikegami, *Tetrahedron*, 2001, **57**, 8053.
26. X. Li, H. Takahashi, H. Ohtake, and S. Ikegami, *Heterocycles*, 2003, **59**, 547; X. Li, H. Takahashi, H. Ohtake, and S. Ikegami, *Tetrahedron Lett.*, 2004, **45**, 4123.
27. A. Dondoni, S. Franco. F. Junquera, P. Merino, and T. Tejero, *Synth. Commun.*, 1994, **24**, 2537.
28. As only one example reported on the 1,3-dipolar cycloaddition, see T. V. RajanBabu and L. Toma, Carbohyd. Res., 1986, **51**, 5458.
29. H. Ohtake, N. Ichiba, M. Shiro, and S. Ikegami, *J. Org. Chem.*, 2000, **65**, 8164; H. Ohtake, N. Ichiba, and S. Ikegami, *J. Org. Chem.*, 2000, **65**, 8171.
30. H. Ohtake and S. Ikegami, *Org. Lett.*, 2000, **2**, 457; H. Ohtake, X. Li, M. Shiro, and S. Ikegami, *Tetrahedron*, 2000, **56**, 7109.

Miss Rie Namme was born in 1977. She received B.S. degree in 2000 and M.S. degree in 2002 from The University of Tokyo under the direction of Professor Masakatsu Shibasaki. In 2002, she joined Professor Shiro Ikegami's group at Teikyo University. Since 2006, she has worked in Professor Hideaki Natsugari's group. She is now a research associate of School of Pharmaceutical Sciences, Teikyo University. Her research interests are in general synthetic organic chemistry and in carbohydrate chemistry.

Professor Shiro Ikegami was born in 1936. He received Ph. D. degree in 1965 under the guidance of the late Professor Shun-ichi Yamada from The University of Tokyo. After spending 1.5 years as a Research Fellow granted from JSPS, he worked with the late Professor Herbert. C. Brown Purdue University, Indiana, USA as a Postdoctoral Research Associate in 1966-1968. After returning Japan in 1968, he spent a short time at Faculty of Pharmaceutical Sciences, The University of Tokyo as a Research Associate and then moved to National Institute of Radiological Sciences, Division of Pharmaceutical Sciences as Senior Scientist, where he was for 10 years. In 1978, he moved to School of Pharmaceutical Sciences, Teikyo University as a full Professor. He received The PSJ Award in 1997 from The Pharmaceutical Society of Japan and was a President of PSJ in 2002. He has retired in March 2006 and become Professor Emeritus, Teikyo University. His major research interests were on the three major subjects, 1. Design and Synthesis of Bioactive Substances, 2. Carbohydrate Chemistry, 3. Green Chemistry - Exploitation of New Polymer Catalysts.