SYNTHESIS OF CELLO-OLIGOSACCHARIDES
—INFLUENCE OF SUBSTITUENT GROUPS ON STEREOSELECTIVE GLYCOSYLATION REACTION—

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LIST OF ABBREVIATIONS

Ac = acetyl $-COCH_3$

All = allyl $-CH_2CH=CH_2$

Bz = benzoyl $-COC_6H_5$

Bzl = benzyl $-CH_2C_6H_5$

Car = carbamoyl $-CONHC_6H_5$

DBU = 1,8-diazabicyclo[5.4.0]-7-undecene

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

D.P. = degree of polymerization

DPM = diphenylmethyl $-CH(C_6H_5)_2$

MCA = monochloroacetyl $-COCH_2Cl$

eq = equivalent

MOM = methoxymethyl $-CH_2OCH_3$

MTM = methylthiomethyl $-CH_2SCH_3$

m.p. = melting point

Ph = phenyl $-C_6H_5$

Piv = pivaloyl $-COC(CH_3)_3$

pMBzl = p-methoxybenzyl $-CH_2C_6H_4OCH_3$

P-TLC = preparative TLC

p-TsOH = p-toluenesulfonic acid

Rf = distance travelled by zone, divided by distance travelled by solvent front

r.t. = room temperature

TMSCl = trimethylsilyl chloride

Tr = trityl $-C(C_6H_5)_3$

triflate = trifluoromethanesulfonate

INTRODUCTION

Cello-oligosaccharides are generally defined as oligosaccharides consisting of two to ten D-glucopyranosyl residues jointed through β-1,4-glucosidic bonds which are readily hydrolyzed under acidic conditions to yield the constituent glucose.[76] These cello-oligosaccharides are not present free in nature but present only as structural units of cellulose.

Since Payen named "cellulose" for a polymer of D-glucose as a cell wall component of the higher plants in 1838, many studies on cellulose have been conducted for 150 years up to date.[60] Nevertheless, there still remains several fundamental problems related to cellulose chemistry such as mechanisms of biosynthesis and biodegradation, crystal structure, mechanism of mercerization, relationship between chemical structure of cellulose derivatives and their physicochemical properties and so on. These problems may be clearly solved by the use of cellulose model compounds such as cello-oligosaccharides. Biodegradation mechanism for lignin as a complex macromolecule recently, has been elucidated by the use of low molecular weight model compounds "oligo-lignols".[35] Hence, cello-oligosaccharides may play an important role in the future on fundamental cellulose research.[64]

These cello-oiligosaccharides are obtainable by both partial degradation of cellulose and chemical synthesis from D-glucose.[106] Since cellobiose octaacetate was first

prepared by Franchimont[17] in 1879, many researchers reported the preparation of the cello-oligosacchrides from cellulose by acetolysis, acid-catalyzed hydrolysis and enzymatic hydrolysis.[106] Miller et al.[63] prepared a series of cello-oligosaccharides up to celloheptaose in 1960. However, the yield of the cello-oligosaccharides by the partial degradation was extremely low for oligomers with high molecular weight, and isolation and purification of a series of the cello-oligosaccharide are tedious and not so easy.

On the other hand, chemical synthesis could be reliable and useful to obtain a pure cello-oligosaccharide, although there are many synthetic problems such as selections of the protective groups and glycosylation reaction to be solved.

The first synthesis of cellobiose was carried out by Freudenberg and Nagai[19] in 1933 and therafter many studies have been reported on the synthesis of cellobiose and cellotriose.[31),95] Cellotetraose was synthesized by Schmidt and Michel[82] in 1982 and by Takeo et al.[96] in 1983. However, higher cello-oligosaccharides than tetramer have not yet been synthesized and will not be obtained readily by their methods because these methods require many reaction steps. At present, the general synthetic method for cello-oligosaccharides has not been established.

The first synthetic approach toward cellulose was tried by Schlubach and Luhrs[81] in 1941. Since then, many researchers have attempted to synthesize cellulose. In spite

of the enormous effort devoted to cellulose synthesis, there has been no paper which completely solved the synthetic problems for cellulose.[70),71),94)] Therefore, the synthetic methods tried so far for cellulose can not be directly applied for the synthesis of cello-oligosaccharides, although some useful information could be obtained.

In principle, there are three problems to be solved for the synthesis of a cello-oligosaccharide; (1) regiospecific control: glycosylation of the hydroxyl group at the O-4 position of the glucopyranosyl residue has to be performed, (2) stereospecific control: glucosidic linkage of glucopyranosyl residues of β-configuration has to be made, (3) control of degree of polymerization (D.P.): the desired sequence of units has to be formed. The first problem could be solved by use of 2,3,6-tri-O-substituted glucopyranose derivative as a starting material, the second by the stereospecific glycosylation reaction, and the third by the stepwise condensation method. However, the main obstacle in the synthesis lies in the second problem, glycosylation reaction.[73),107)]

Newly-developed glycosylation methods and extensive data on glycosylation reactions have made possible to prepare several complex oligosaccharides such as hexa- and nona-saccharides fragments of the O-antigenic polysaccharide,[15)] heparin-like penta-saccharide,[51)] xylo- and malto-oligosaccharides.[49),80)] However, the glycosylation reaction is complicated and there still remain many problems for the highly stereoselective glycosylation with high yield, such

as selection of the leaving groups at anomeric center, activating reagents, solvents used and so on. Although there are no systematic studies from this point of view, the effects of the protective groups of both aglycon (hydroxyl component) and glycon (glycosyl component) on the stereoselective glycosylation reactions have been considered extremely important.

Substituent effect of the aglycon on glycosylation of N-acetyl glucosamine derivative by Koenigs-Knorr method has been reported by Sinay.[87] However, it is not known whether the result of Sinay[87] is applicable to cello-oligosaccharides synthesis.

Paulsen[73),74)] discussed the influence of glycon protective groups in the synthesis of β-D-manno- and β-L-rhamnoglycosidic derivative. While Boeckel et al.,[3),4),5)] reported substituent-effects of α-D-gluco- and α-D-manno-pyranosyl bromides on glycosylation by insoluble salts. However, the results obtained by Paulsen is not neccesarily agreed with those by Boeckel et al.. It is uncertain whether these results are applicable to glycosylation method other than Koenigs-Knorr method.

Therefore, a systematic investigation of the effect of the protective groups of aglycon and glycon on β-glycosylation is needed in the cello-oligosaccharides synthesis.

In the present thesis, the author focused on the influence of substituent groups of the aglycon and glycon on

glycosylation reaction (especially, β-1,4 glucosidic bond formation) for the synthesis of cello-oligosaccharides.

Chapter 1 contains a general synthetic design of cello-oligosaccharides and the synthesis of acyl 2,3,6-tri-O-substituted glucose derivative and its glycosylation according to this design.[67),89),90)]

In Chapter 2, the synthesis of aglycons with various protective groups and the influence of the substituent groups of the aglycon on glycosylation reaction are described.[90),92)]

In Chapter 3, the synthesis of glycons with different substituent pattern and the substituent effect of the glycon on glycosylation reactions are described.[91)] In addition, the selection of the most suitable starting material for the synthesis of cello-oligosaccharides and the future possible usage of the compound is discussed.[93)]

The detailed experimental methods and data of compounds are summarized in EXPERIMENTAL.

Chapter 1 Synthesis of starting material for regiospecific glycosylation

1-1. Basic synthetic design for cello-oligosaccharide

Nakatsubo et al.[67] proposed a synthetic design of cello-oligosaccharides from D-glucose as shown in Figs. 1 and 2.

In the synthetic design the substituted glucose derivative 1, which has three kinds of protective groups, X-, Y- and R-groups, is required as a starting material for the regulation of regiospecificity. Here, X- and Y-groups are "temporary" protective groups, and R-group is a "persistent" protective group.[18),27)] The temporary protective groups should be removed independently without giving any influence on the other functional groups before glycosylation reaction. It is prerequisite for the selection of these three protective groups that the Y-and R-groups or X- and R-groups must not be changed on the removal of the temporary protective X- or Y-groups, respectively. The persistent protective group is removed at the final step of the synthesis for the cello-oligosaccharide with the expected degree of polymerization (D.P.). Therefore, the R-group should be fairly stable under various conditions, but the removal conditions do not cause decomposition of the hydroxyl groups or β-glucosidic bonds in the synthesized cello-oligosaccharides. It should be considered that the selection of the R-group determines the choice of X- and Y-groups and vice versa.

The synthesis of cello-oligosaccharides is conducted from the starting material **1** by two reactions; deprotection of X- or Y-groups and β-glycosylation. The removal of X- or Y-groups from the starting material **1** gives glycon **2** or aglycon **3**, respectively. β-Glycosylation between glycon **2** and aglycon **3** leads to the formation of cellobiose derivative **4** which has the same protective system as starting material **1**. Cellobiose derivative **4** is further converted into glycon **5** and aglycon **6** by deprotection of X- or Y-groups, respectively. Here, two major synthetic methods are conceivable for the synthesis of cello-oligosaccharides; a linear synthetic method and a convergent synthetic method.[102),103)] In the former method (Fig. 1), β-glycosylation is performed between glycon **5** and aglycon **3** or between glycon **2** and aglycon **6** to afford cellotriose derivative **7** which also has the same protective system as compound **1**. Compound **7** is combined with compound **2** or **3** to give cellotetraose derivative **8**. After repeating the above two reactions, a series of cello-oligosaccharide (whose D.P.= 1,2,3,4....) could be theoretically obtained in this method. In the latter method (Fig. 2), β-glycosylation is conducted between glycon **5** and aglycon **6** to give cellotetraose derivative **8** with the same protective system as compound **1**. Further, the two compounds **8** are combined to afford the cellooctaose derivative. Thus, in this method, a series of cello-oligosaccharide (whose D.P.= 1,2,4,8....) could be prepared theoretically by repeating of the two

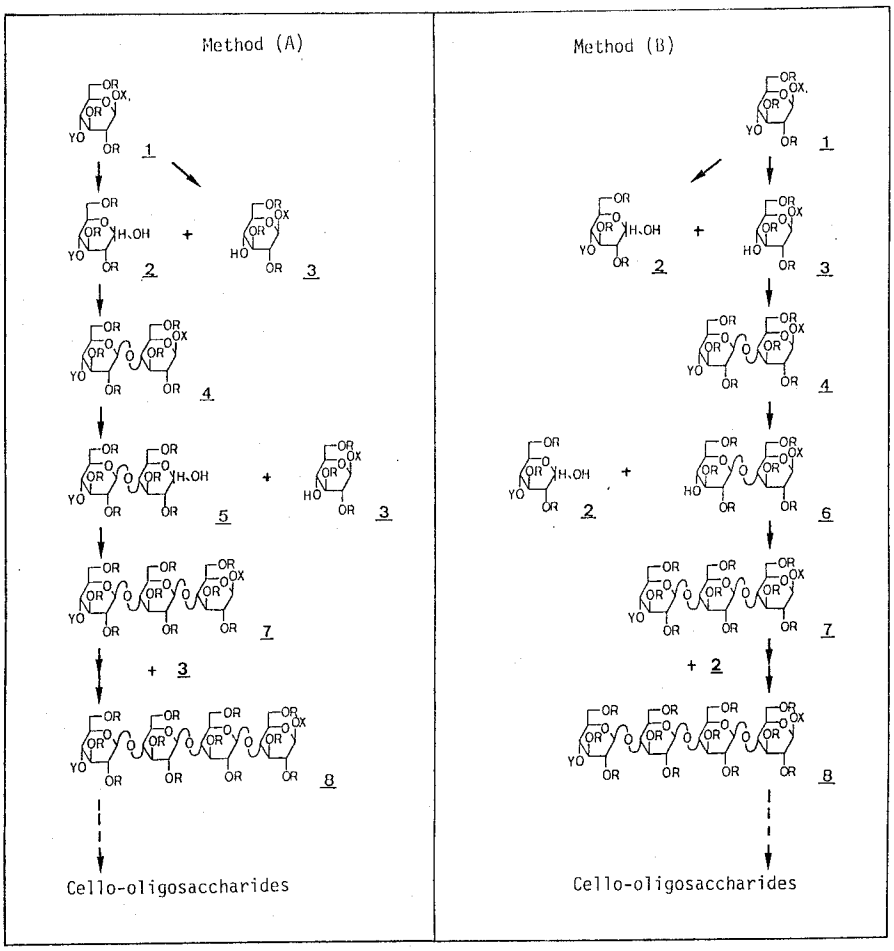


Figure 1. Linear synthetic method for cello-oligosaccharides.

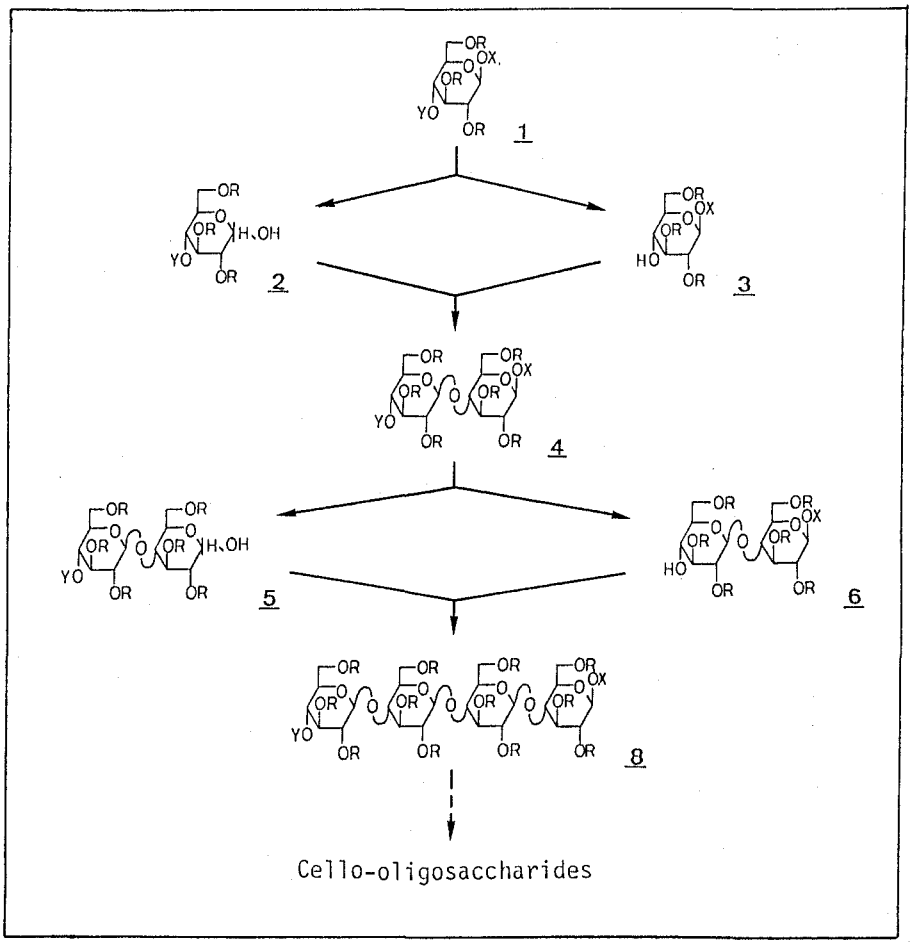


Figure 2. Convergent synthetic method for cello-oligosaccharides.

reactions.

Since the first synthesis of an O-glycoside was carried out by Michael in 1879,[62] a number of methods for the synthesis of O-glycoside have been proposed,[2),40),48),101] i.e., alcoholysis of free sugars (Fischer method) and syntheses from 1-halo sugars (Koenigs-Knorr method), from 1-O-acyl sugars (Helferich method), from 1,2-orthoesters (Orthoester method), from 1-fluoro sugars (Fluoride method), from 1-imidate sugars (Imidate method) and so on. However, no universal glycosylation methods have been established for the oligosaccharide synthesis so far.

The trichloroacetimidate method (hereafter imidate method) was selected in the present investigation for the following four reasons;[83),84)] [1] Glycosylation can be conducted under a very mild reaction condition (for example, at $-78^{\circ}C$ for about 30 min). [2] A S_N-2 reaction mechanism has been proposed to give only the β-glycoside from the α-imidate at low temperature with boron trifluoride etherate catalysis. [3] By the selection of catalysts and protective groups, reactivities that are comparable to those obtained for the glycosyl halide / silver triflate system (Koenigs-Knorr method) can be expected. [4] Schmidt and Michel[82] used this method for the synthesis of cellotetraose derivative and Kawada et al.[44] successfully synthesized the cellobiose derivative in high yield.

In the present synthetic design, synthesis of the substituted glucose derivative 1 (namely, the introduction and removal of the protective groups) and β-glycosylation

reaction are very important.

1-2. Synthesis of acyl 2,3,6-tri-O-substituted glucose derivatives

1-2-1. Selection of protective groups

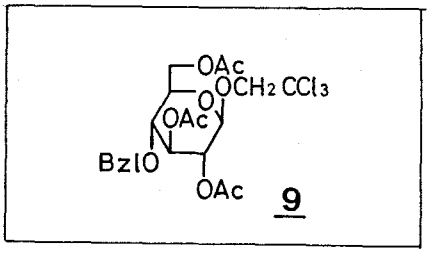
In the previous section, the basic synthetic design for cello-oligosaccharides was proposed. The first step in this design is the synthesis of the substituted glucose derivative 1.

Acetyl group was selected as the persistent protective R-group for the following advantages in this investigation. They are; [1] It could be easily introduced and removed. [2] The acetyl group introduced into the O-2 position of a glucose derivative (glycon) is expected to have a favorable effect on the formation of β-glucosidic bond by way of neighbouring group participation.[2] [3] Acetyl glucose derivatives have good solubility in organic solvents and could be easily crystallized. [4] Acetyl glucose derivatives are relatively easy to determine their chemical structure by their NMR spectra analysis. [5] Enough information on cellulose acetate is available, because it is widely used in the field of cellulose chemistry. However, the acetyl group also has several drawbacks such as the possible intramolecular migration, the instability under basic conditions and the lack of UV absorption.

On the other hand, 2,2,2-trichloroethyl and benzyl groups were chosen as the X- and Y-groups, respectively.

2,2,2-Trichloroethyl group of the sugars with acetyl and benzyl substituents can be selectively removed by zinc powder in acetic acid, and was used for the protection of the anomeric hydroxyl group by Lemieux and Driguez.[55),56)] Benzyl group can be deblocked by catalytic hydrogenolysis independently. Benzyl derivative could be observed on TLC under UV-light. This makes it possible to easily follow progress of the reaction and to purify the expected compound by TLC. Kovac[49)] used benzyl group for the protection of C-4 hydroxyl group in the synthesis of xylo-oligosaccharides.

Thus, 2,2,2-trichloroethyl 2,3,6-tri-O-acetyl-4-O-benzyl-β-D-glucopyranoside (**9**) was selected as a starting material 1.



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1-2-2 Synthesis of the acetyl derivatives

The synthetic route for compound **9** from D-glucose (**10**) is shown in Fig. 3. The key compound of this route is compound **17** which has a free hydroxyl group at the C-4 position of D-glucose. Many synthetic methods for such glucose derivatives, e.g. acyl group migration,[6),33)] selective acylation,[86),100)] reductive cleavage of 4,6-O-benzylidene derivative[24),25)] and use of a 4-O-nitro

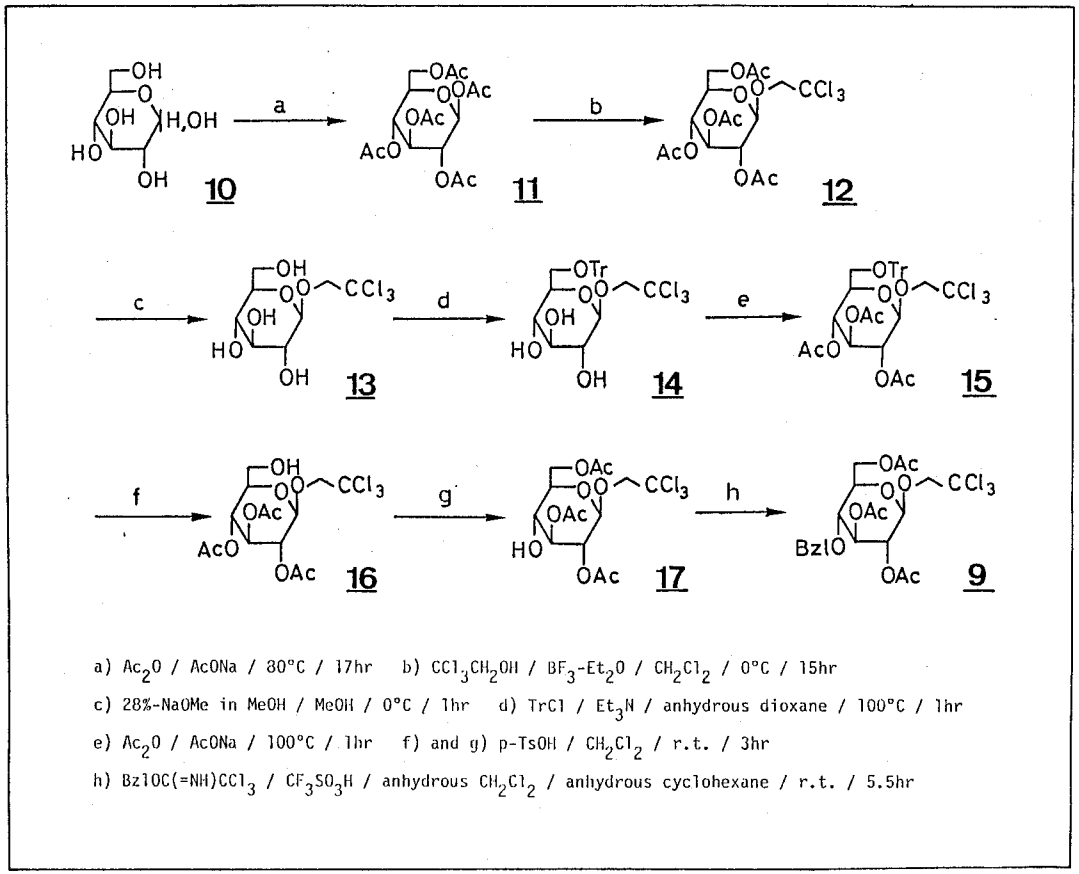


Figure 3. Synthetic route for compound **9** from compound **10**.

intermediate,[32] have been reported. Considering their yields, the number of reaction steps and simplicity of the preparation, a modified acyl group migration was applied to obtain compound 17 in this investigation.

Compound 12 was prepared from glucosepentaacetate (11) which was a mixture of α-and β-anomers (about 1:5) prepared by acetylation of compound 10 with acetic anhydrous / sodium acetate. First, Koenigs-Knorr reaction between tetra-O-acetyl-α-D-glucopyranosyl bromide, which was synthesized from compound 11 by the treatment with 25% hydrogen bromide acetic acid solution, and 2,2,2-trichloroethanol was examined in the presence of a silver or mercury salt such as silver carbonate, silver sulfate and mercury (II) bromide. However, yield of the expected glycoside was about 20%, probably because of poor nucleophilicity resulting from the large electron-attracting effects of the three chlorine atoms and large steric hindrance of 2,2,2-trichloroethanol. Then, a modified Helferich method[65] was tried. Compound 11 and 2,2,2-trichloroethanol were fused in the presence of catalytic amounts of p-toluenesulfonic acid at 100°C under 100mmHg to afford the expected glycoside in about 40% yield. Finally, the method reported by Magunusson et al.[59] was found to be the best method in respect to the yield and simplicity of the reaction. The solution of peracetyl glucose 11 and 2,2,2-trichloroethanol was treated with boron trifluoride etherate at room temperature for about 12 hours. After recrystallization, compound 12 was obtained in about 60% yield. This method was also useful for large scale

experiments using 78g (0.2 mol) of the starting material 11.

Compound 13, obtained by the deacetylation of compound 12 with sodium methoxide, was tritylated by the use of tritylchloride / pyridine system in a standard manner[34] to afford trityl ether 14 in a maximum of 67% yield, but the reproducibility of this method was poor. A possible reaction mechanism for the tritylation by this method is shown in Fig. 4.

Chaudhary and Hernandes[8] suggested that the formation of the N-tritylpyridinium salt (18) is the rate determining step in this reaction. Furthermore, it was found that the treatment of compound 14 with pyridinium hydrochloride (19)

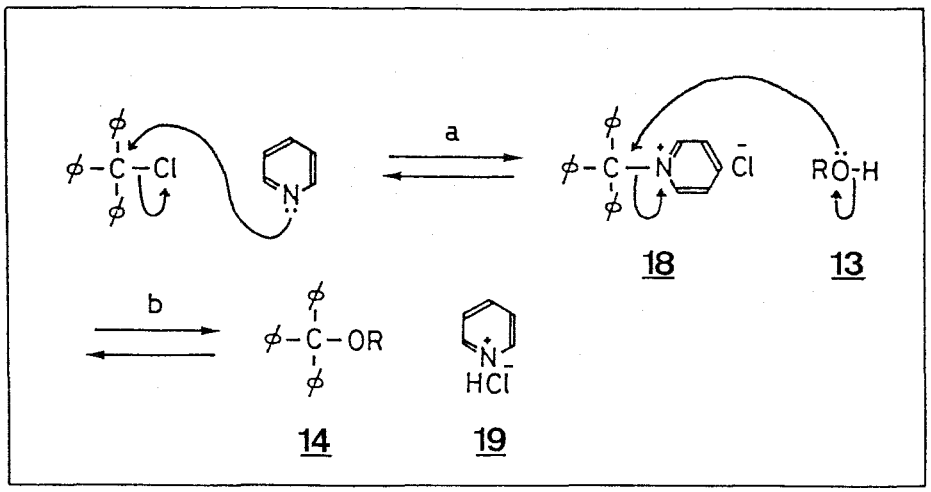


Figure 4. Reaction mechanism for tritylation with trityl chloride / pyridine.

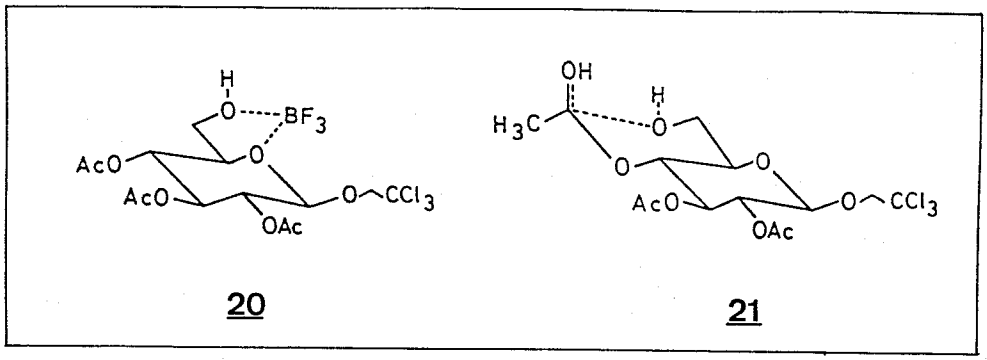
in pyridine gave the starting compound **13**. This experimental result indicates that this reaction is reversible as shown in Fig. 4.

Therefore, the following three points are extremely important to increase the reaction rate and to shift the equilibrium toward the product: [1] The use of a base stronger than pyridine (e.g. 4-dimethylaminopyridine, triethylamine , etc.) is recommended for accelerating the formation of the salt **18**. [2] The use of a solvent in which compound **19** is insoluble will cause compound **19** to precipitate and will force the reaction to completion. [3] Anhydrous conditions are essential to avoid the hydrolysis of tritylchloride and the expected compound **14**. Keeping in mind the above points, the synthesis of compound **14** was attempted using many combinations of bases and solvents. Among these, the triethylamine / dioxane system was found to be the best. When compound **13** was heated with triethylamine in anhydrous dioxane at 100°C for 1 hour, triethylamine hydrochloride was effectively removed from the reaction system as a precipitate, and then compound **14** was obtained in 86.9% yield. This method was found to be the most satisfactory method, with respect to both reproducibly high yield and simplicity of the preparations. The purification of trityl ether **14** by silica gel column chromatography should be carried out as rapidly as possible, because silica gel catalyzed detritylation has been reported.[54)]

In general, trityl ethers are cleaved by a number of methods, including acidic hydrolysis and catalytic,

chemical, or electrolytic reduction.[28] Here, acid-catalyzed reactions using a Lewis acid or a protonic acid were examined. The use of boron trifluoride etherate gave preferentially the detritylation compound **16** with the production of only a small amount (less than 5% yield) of compound **17** resulted from acetyl group migration. On the other hand, when compound **15** was treated with p-toluenesulfonic acid, both the detritylation and subsequent acetyl group migration proceeded smoothly; compound **17** was obtained in 86.8% yield without any residual amount of compound **16**. Similar results were obtained using Amberlyst H-15 (H+) or DL-camphor-10-sulfonic acid, but the reaction proceeded very slowly. Thus, the detritylation with a Lewis acid gave preferentially the detritylation compound **16**, whereas the detritylation with a protonic acid afforded exclusively compound **17**.

These results could be attributed to the coordination of boron trifluoride with the ring oxygen and O-6 as shown in intermediate **20**. Such coordination would reduce the electron density on O-6 and inhibit the free rotation of the C-6

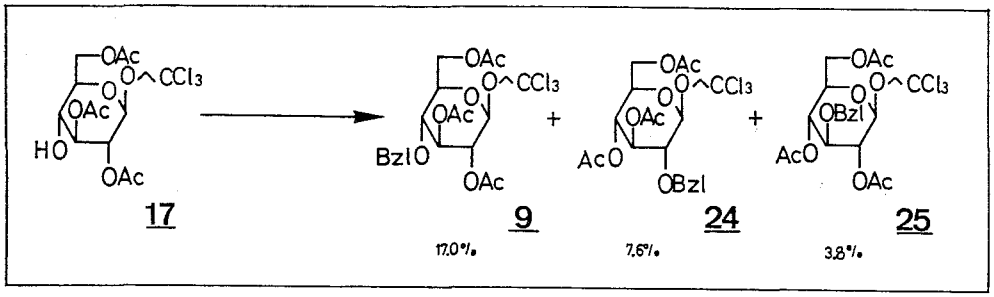


20 **21**

hydroxyl group around the C_5-C_6 linkage, thus preventing the formation of the desired cyclic orthoester intermediate **21**, from which compound **17** was derived. It seems that this coordination is similar to that of zinc bromide in detritylation[47),61)] or demethoxymethylation.[10)]

All of the above detritylations were carried out in methylene chloride. In 20% methanol-methylene chloride with the presence of a Lewis acid or a protonic acid, acetyl group migration did not occur at all. The detritylation compound **16** was obtained in over 95% yield in both cases. This result is interesting, but a satisfactory explanation is not available at this time.

When compound **17** was treated with benzyl bromide / silver oxide in N,N-dimethylformamide (DMF), which is a typical benzylation method in carbohydrate chemistry,[28)] the expected benzyl ether **9** was obtained in only 20% yield with several by-products. The low yield is attributed to the low reactivity of the C-4 hydroxyl group,[46)] and to the possibility of acetyl group migration under these reaction conditions.[29),88)] An alternative method which involves acetyl group migration from O-4 to O-6 and simultaneous benzylation[85)] was applied to compound **16**, but the expected compound **9** was obtained in only 20% yield. The benzylation of compound **17** with benzyl bromide / sodium hydride at 0°C for a short time (30 min) gave compound **9** in 17% yield with many by-products. Interestingly, 2,2,2-trichloroethyl 3,4,6-tri-O-acetyl-2-O-benzyl-β-D-glucopyranoside (**24**) and 2,2,2-trichloroethyl 2,4,6-tri-O-acetyl-3-O-benzyl-β-D-



glucopyranoside (**25**) were identified as by-products. The conversion of the compound **17** to the compound **24** indicates, that intramolecular acetyl group migration from the O-2 position to the O-4 position via an intermediate **22** taking 1C-conformation occurs and is then followed by the benzylation of the resulting free hydroxyl group at the C-2 position of the intermediate **23** as shown in Fig. 5.

All of the above investigations suggest that the benzylation of the C-4 hydroxyl group cannot be carried out in high yield under neutral or basic conditions, and that the introduction of a protective group is only possible under acidic conditions. Then, the benzylation by a Friedel-Crafts type reaction[79] and treatment with the benzyltrichloroacetimidate / trifluoromethanesulfonic acid system (benzylimidate method)[41),104] were examined. Compound **17** was treated with benzyl alcohol / phosphorus pentaoxide (P_2O_5), but the expected benzyl ether **9** was only obtained in a maximum of 20% yield, and the results were not reproducible. On the other hand, compound **17** was benzylated by the benzylimidate method, and the yield of compound **9** increased to about 50%. At present, no benzylation method

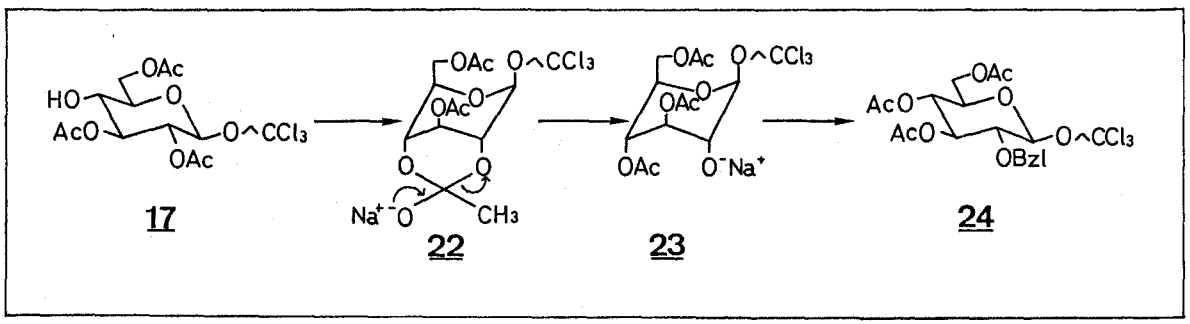


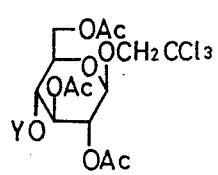
Figure 5. Reaction mechanism of the formation of compound **24** from compound **17**

has been found for compound **17** superior to the benzylimidate method.

Since the introduction of the benzyl group into the C-4 hydroxyl group was so difficult, methylthiomethyl (MTM),[77),78)] diphenylmethyl (DPM),[52)] or methoxymethyl (MOM)[20)] group was examined as the Y-group. The MTM, DPM, and MOM groups could be introduced by Friedel-Crafts type reactions and removed selectively by the use of mercury chloride, neutral hydrogenolysis, or a catalytic amount of hydrochloric acid, respectively.

Methylthiomethylation of compound **17** with acetic anhydride / acetic acid / dimethylsulfoxide (DMSO) gave the MTM ether **26** in 63.4% yield. But the MTM group was unstable in the presence of zinc powder / acetic acid, with which the trichloroethyl group was removed,[28)] compound **26** was not suitable for the purpose. However, the MTM group is a useful protective group for the C-4 hydroxyl group of glucose.

Treatment of compound **17** with benzhydrol / P_2O_5 or methyral / P_2O_5 gave the DPM ether **27** or the MOM ether **28** in 70.3% or 87.6% yield, respectively. The satisfactory yield from these reactions indicates that the respective



26 Y = $-CH_2SCH_3$ (-methylthiomethyl, -MTM)

27 Y = $-CH(C_6H_5)_2$ (-dipheylmethyl, -DPM)

28 Y = $-CH_2OCH_3$ (-methoxymethyl, -MOM)

cations may be produced readily and that side reactions do not occur appreciably under these reaction conditions. Thus, these results indicate that the introduction of a functional group into C-4 hydroxyl group of an acetylated glucose derivative proceeds in high yield only under acidic conditions.

1-2-3 Synthesis of the benzoyl derivatives

Either compound **27** or **28** described above is thought to be useful as a starting material **1** for the synthesis of cello-oilgosaccharides. However, the absence of UV absorption in compound **28** is inconvenient to follow the progress of a reaction and to purify the expected compound on TLC. Therefore, the introduction of benzoyl group instead of acetyl group as the R-group was examined. The merits of the benzoyl group are similar to those of the acetyl group, although the former has greater steric hindrance than the latter. The synthesis of 2,2,2-trichloroethyl 2,3,6-tri-O-benzoyl-4-O-methoxymethyl-β-D-glucopyranoside (**30**) was carried out via two synthetic routes as shown in Fig. 6.

First, compound **30** was synthesized from compound **28**. Deacetylation of compound **28** with sodium methoxide, followed by benzoylation with benzoyl chloride / anhydrous pyridine gave compound **30** in 63.5% yield.

Then, compound **30** was prepared from compound **14** by the method similar to that used for the synthesis of compound **28**. Compound **14** was converted into compound **31** in 87.1%

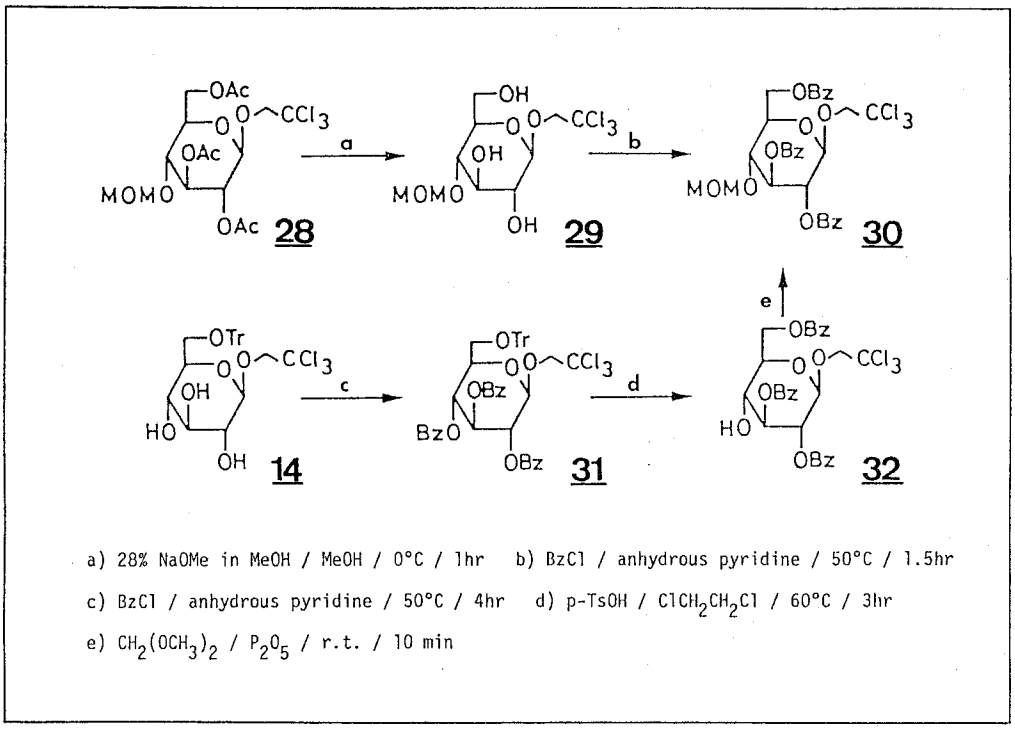
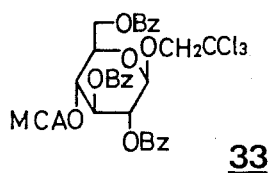


Figure 6. Synthetic route for compound **30** from compound **14** or **28**.

yield by the use of benzoyl chloride / anhydrous pyridine. In general the benzoyl group migrates less readily than the acetyl group.[1] Indeed, the detritylation of compound **31** with p-toluenesulfonic acid in dichloromethane at room temperature gave 2,2,2-trichloroethyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside in 63.7% yield. Benzoyl group migration did not occur. However, when compound **31** was treated with p-toluenesulfonic acid in 1,2-dichloroethane at 50°C, the benzoyl group migrated from O-4 to O-6 to give compound **32** in 70.7% yield. Thus, the benzoyl group is better than the acetyl group as the R-group for the synthesis of a glucose derivative which has a free hydroxyl group at the C-6 position. The methoxymethylation of compound **32** with methyral / P_2O_5 gave compound **30** in 77.5% yield.

Finally, the introduction of the monochloroacetyl group into the C-4 hydroxyl group was conducted. The monochloroacetyl (MCA) group is useful because it is selectively removed by thiourea but is resistant to acidic conditions which are necessary for the bromination of the anomeric hydroxyl group in Koenigs-Knorr type glycosylation.[9),28)] Compound **32** was converted into the MCA ether **33** in 81.0% yield by the use of chloroacetic anhydride / pyridine.[23)]



33

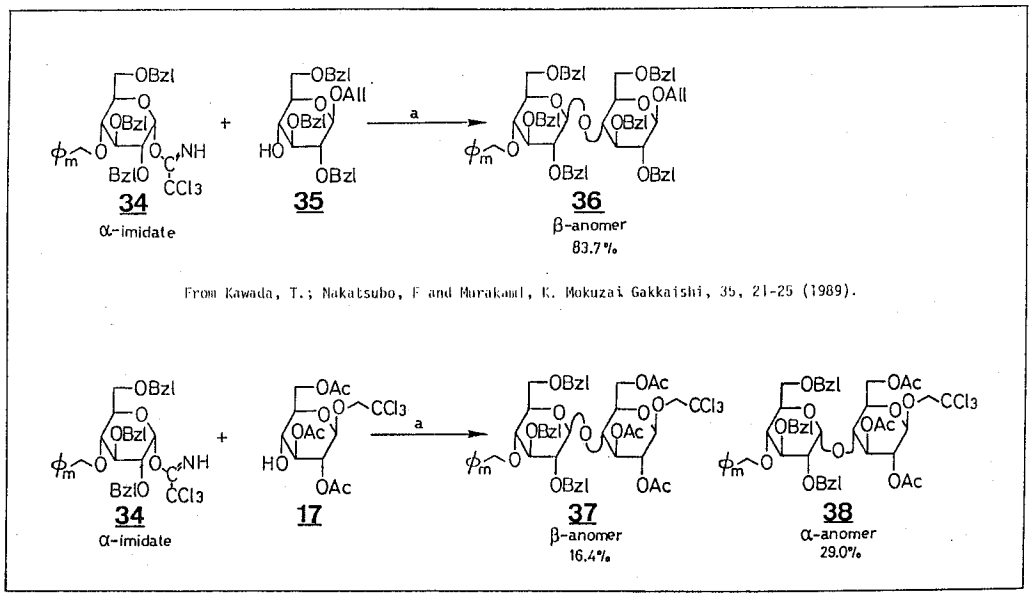
-MCA = -monochloroacetyl
(-$COCH_2Cl$)

1-2-4 Glycosylation of acyl derivatives

The second step in the design described in Section 1-1 is the synthesis of cellobiose derivative by the use of the synthesized glucose derivative.

Kawada et al.[44] reported that the glycosylaton between 2,3,6-tri-O-benzyl-4-O-p-methoxybenzyl-α-D-glucopyranosyl trichloroacetimidate (**34**) and allyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside (**35**) gave the corresponding cellobiose derivative **36** in 83.7% yield. Then, glycosylation of aglycon **17** with glycon **34** was made under the same reaction conditions reported by Kawada et al..[44]

Imidate **34** and aglycon **17** were dissolved in anhydrous dichloromethane containing molecular sieves 4A; then the solution was cooled below -70°C; boron trifluoride etherate in anhydrous dichloromethane was added; after 2 hours, the reaction mixture was worked-up and purified by TLC to give



compound **37** and compound **38** in 16.4% and 29.0% yield, respectively.

The products were identified by ^{1}H- and ^{13}C-NMR spectroscopies. The characteristic signals, derived from the 2,2,2-trichloroethyl and p-methoxybenzyl groups in the ^{1}H-NMR spectra of compounds **37** and **38**, provide the structual proof that glycosylation occurred between glycon **34** and aglycon **17**. The peaks of compound **37** that appear at 4.26 (1H, d, J=8.0) and 102.8 (C-1') conclusively indicate the β-configuration. And the peaks of compound **38** that appear at 4.80 (1H, d, J=3.5) and 99.1 (C-1') also indicate the α-configuration.

This result obviously indicates that the glycosylaton is tremendously affected by the protective groups pattern of the aglycon, and that aglycon **17** is unsuitable in the glycosylation by the imidate method. Therefore, before the synthesis of cello-oligosaccharides, it is required to examine the effect of the protective groups of the aglycon and glycon on glycosylation reaction in order to select the best protective group pattern.

1-3 Summary

For the synthesis of cello-oligosaccharide, regiospecific and stereospecific glycosylation reaction should be conducted. In this chapter, the basic prerequisite of starting material was discussed at first. The substituted glucose derivative should be protected by three kinds of protective groups, X-, Y- and R-groups as a starting

material (Section 1-1).

Then, 2,2,2-trichloroethyl 2,3,6-tri-O-acyl-β-D-glucopyranoside derivatives, which were satisfied with the basic prerequisite, were selected as a starting material and their synthetic route was investigated (Section 1-2-1 to 1-2-3). In the course of these syntheses, it turned out that trityl chloride / triethylamine / dioxane system was the most satisfactory method for tritylation with respect to the yield and the simplicity of preparation (Fig. 3, step d). It was also found that acetyl group migration occurred with a protonic acid, but did not with a Lewis acid (Fig. 3, step g). These results will give useful information in cellulose chemistry, because the tritylation and detritylation reactions are very important reaction for the preparation of regioselective substituted cellulose derivatives, and acetyl derivative is quite common in cellulose chemistry.

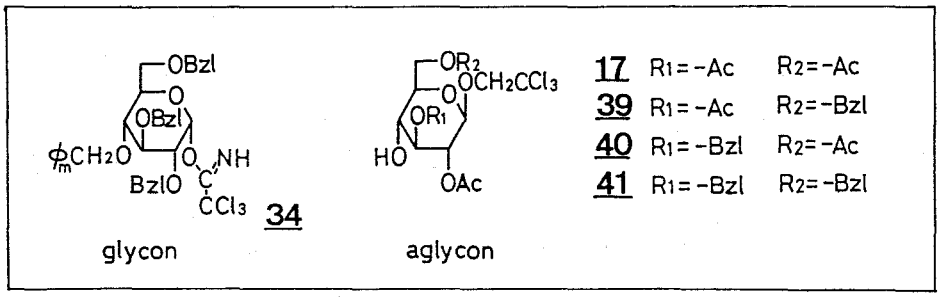
Next, the synthesis of cellobiose derivative was tried by the use of the acyl derivative synthesized (Section 1-2-4). However, contrary to the result reported by Kawada et al., the glycosylation of acyl glucose derivative by the imidate method gave a mixture of β- and α-glycosides. This result obviously indicated that the stereochemistry of the product on glycosylation reaction was tremendously affected by the protective group pattern of aglycon.

Chapter 2 Substituent-effect of aglycon on glycosylation reaction

2-1 Substituent-effect of acetyl and benzyl groups

In Chapter 1 (Section 1-2-4), it was described that the glycosylation is greatly influenced by the substituent pattern of protective groups in aglycon. Sinay[87] reported that the presence of C-3 ether substituent of the aglycon was very effective for increasing the yield of β-D-(1 → 4) linked disaccharide derivatives. Takeo et al.[96], in consideration of the results obtained by Sinay[87], recently reported the high yield syntheses of cellobiose, cellotriose and cellotetraose. On the other hand, Paulsen[73),74)] reported that alkyl substituted derivative are more reactive than those bearing acyl substituents. But, no systematic investigation has been reported for the substituent-effect of aglycon on stereospecific glycosylation reaction.

In this section, four aglycons **17**, **39**, **40** and **41** were selected for the glycosylation reaction with glycon **34**. The C-3 and C-6 hydroxyl groups of these aglycons were protected with different combinations of the electron-donating benzyl



group and the electron-withdrawing acetyl group in order to investigate the effect of these protective groups on the anomer ratio in the glycosylation reactions with glycon **34**.

2-1-1 Synthesis of 3-O-acetyl derivatives

The synthetic route for aglycons **17** and **39** from glucopentaacetate (**11**) is shown in Fig.7. The synthesis of compound **17** was described in detail in the previous chapter (Chapter 1, Section 1-2-2). The key reaction in the synthesis of compound **39** was the reductive cleavage of 4,6-O-benzylidene glucopyranoside (Fig. 7, step h).

Garegg *et al.*[24),25)] reported that the highly regioselective, reductive cleavage of 4,6-O-benzylidene hexopyranoside with sodium cyanoborohydride ($NaCNBH_3$) - HCl(gas) in tetrahydrofuran gave the 6-O-benzyl ether, which has a free hydroxyl group at the C-4 position, in high yield. On the other hand, Johansson and Samuelsson[42)] reported that the reductive ring-opening of 4,6-O-p-methoxybenzylidene hexopyranosides with $NaCNBH_3$-trifluoroacetic acid (CF_3COOH) in N,N-dimethylformamide (DMF) or with $NaCNBH_3$-trimethylsilyl chloride (TMSCl) in acetonitrile gave the 6- or 4-O-p-methoxybenzyl ether derivative, respectively, in high yield with good regioselectivity.

Since the use of HCl(gas) requires tedious handling, the $NaCNBH_3$-CF_3COOH and $NaCNBH_3$-TMSCl systems were examined in the present investigation. Compound **43** was treated with $NaCNBH_3$-CF_3COOH in DMF for 12 hours to afford only compound

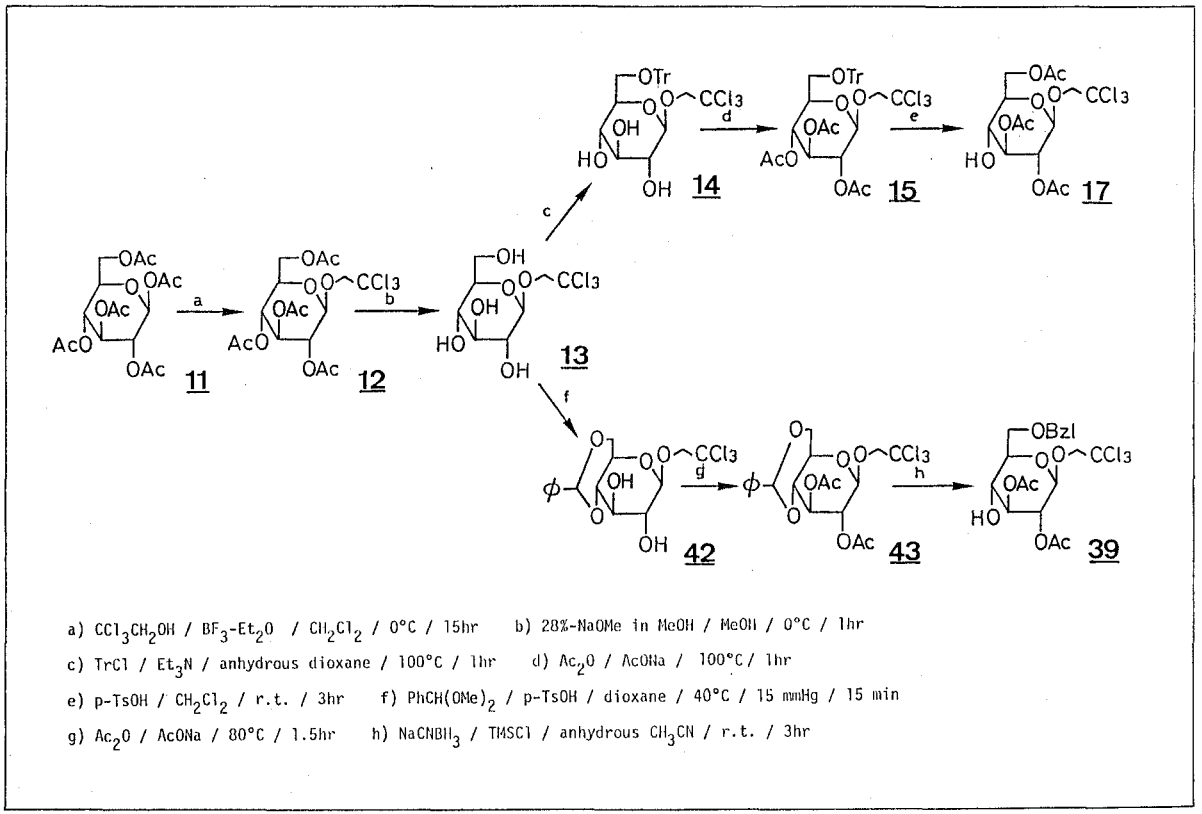


Figure 7. Synthetic route for **17** and **39** from compound **11**.

39 in 60% yield, as expected. However, different from the results of Johansson and Samuelsson[42] treatment with $NaCNBH_3$-TMSCl in acetonitrile for 3 hours also gave only compound **39** in 60% yield. That is, the attack of either electrophile (CF_3COOH or TMSCl) occurred only on the O-4 position of the benzylidene group to result in the formation of only 6-O-benzyl ether **39** without any steric effect of the electrophile.

It has been reported that the regioselectivity from the reductive ring-opening of a benzylidene acetal is associated with the steric hindrance exerted by the C-3 substituent[57]. However, compound **49** with a bulky benzyl group at the O-3 position also gave only 6-O-benzyl ether **41** by the $NaCNBH_3$-TMSCl treatment, as described in the latter section (Fig. 8). Thus, the regioselectivity seems to also depend on the nature of the benzylidene used. For p-methoxybenzylidene kinetic control favors the attack of TMSCl on the O-6 position, resulting in the production of the 4-O-p-methoxybenzyl ether, but for benzylidene thermodynamic control favors the attack of TMSCl on the O-4 position, resulting in the production of the 6-O-benzyl ether. This difference is caused by the higher sensitivity of the p-methoxybenzylidene group, resulting from the electron-donating effect of its methoxyl group.

2-1-2 Synthesis of 3-O-benzyl derivatives

The synthesis of aglycons **40** and **41** was carried out by

methods similar to those used for the synthesis of aglycons **17** and **39**, respectively, as shown in Fig.8. The starting material **44** was prepared by the conventional method.[38),105)]

Interestingly, the acetyl group at the O-2 position of compound **25** was found to be stable toward methanolysis in the presence of a catalytic amount of sodium methoxide (0.1 eq) in methanol at 0°C for one hour; 2,2,2-trichloroethyl 2-O-acetyl-3-O-benzyl-β-D-glucoside was obtained in 95% yield. A similar result was reported by Takeo and Tei[98)] in the methanolysis of benzyl 2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranoside. Under the above conditions, both acetyl groups of 2,2,2-trichloroethyl 2,4-di-O-acetyl-3,6-di-O-benzyl-β-D-glucopyranoside (which was obtained from compound **41**) were also stable; the extent of the deacetylation was only about 5% based on TLC. On the other hand, compound **12** and 2,2,2-trichloroethyl 2,3,4-tri-O-acetyl-6-O-benzyl-β-D-glucopyranoside (which was obtained from compound **39**) were readily deacetylated to give compound **13** and 2,2,2-trichloroethyl 6-O-benzyl-β-D-glucopyranoside, respectively, in a quantitative yield.

These experimental results indicate that the benzyl group introduced into the O-3 position makes the acetyl groups at the O-2 and O-4 positions (i.e. adjacent to the benzyl group) stable toward such a mild methanolysis, but the benzyl group introduced into the O-6 position does not exert such a stabilization effect for the acetyl group. However, with compound **25** it seems that the acetyl group at the O-6 position is first subjected to methanolysis, thus

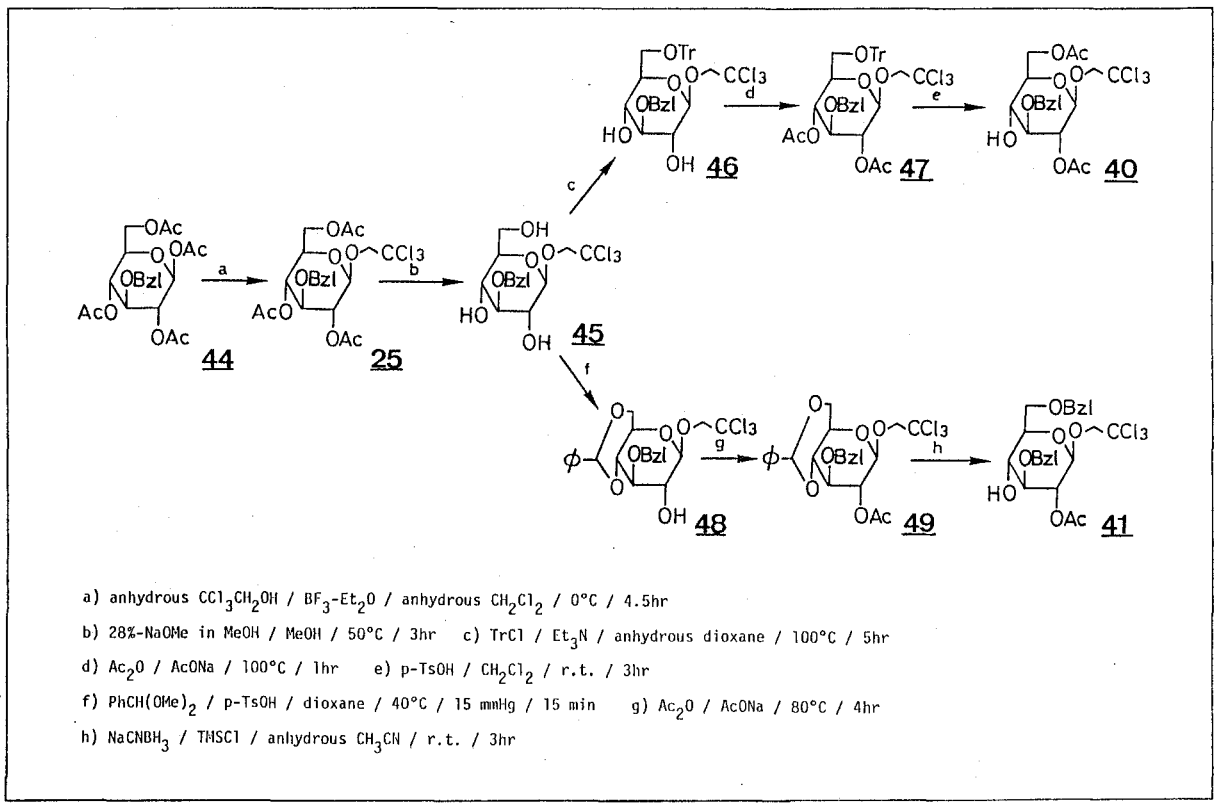
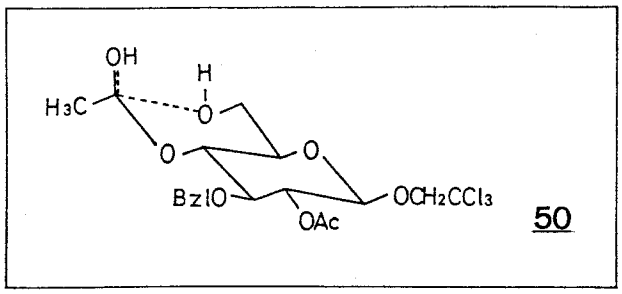


Figure 8. Synthetic route for compounds **40** and **41** from compound **44**.



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creating a free hydroxyl group. This free hydroxyl group makes possible the methanolysis of the acetyl group at the O-4 position, via a six-membered ring transition state (**50**). In this way the methanolysis of both acetyl groups (at O-4 and O-6) proceeds smoothly. Stabilization of the acetyl group should be attributable to steric or electronic factors, but not to conformational changes in the pyranose ring, because no significant difference in the ^{1}H- or ^{13}C-NMR data was observed between compounds **12** and **25**. The benzyl group probably hinders sterically the approach of the methoxide anion to the acetyl group, but this effect should be minor because the methoxide anion is not very large. Thus, the electronic factor should be more important. That is, the δ-characteristic of the acetyl-carbonyl carbon is thought to be smaller because of the electron-donating effect of the benzyl group. In other words the electron density of the acetate oxygens linked to the pyranose ring becomes abnormally high by the introduction of the benzyl group into the O-3 position.

Compound **25** was converted to compound **45** in over 90% yield under more drastic conditions (use of 5.0 eq of sodium methoxide at 50°C for 3 hours). The reductive cleavage of

compound **49** with $NaCNBH_3$-TMSCl in acetonitrile gave the desired 6-O-benzyl ether **41** in 60% yield.

2-1-3 Glycosylation of 3-O-acetyl and 3-O-benzyl derivatives

The glycosylation reactions between α-imidate **34** and aglycons **17,39-41** were conducted under the reaction conditions reported by Kawada et al..[44]

A solution of α-imidate **34** (2.0 eq) and the respective aglycon (1.0 eq) dissolved in anhydrous methylene chloride was added dropwise to a suspension of molecular sieves 4A in anhydrous methylene chloride below $-70^{\circ}C$. Boron trifluoride etherate (0.2 eq) in anhydrous methylene chloride was added dropwise to the above suspension below $-70^{\circ}C$. After the prescribed time (Table 1), the reaction mixture was worked up and the product was purified by preparative TLC. The configuration of the glucosidic center produced was determined by ^{1}H- and ^{13}C-NMR spectroscopies. The results are summarized in Table 1.

At low temperature in the presence of boron trifluoride catalysis, highly stereoselective conversion of the α-imidate to the β-glycoside generally proceeds smoothly with Walden inversion at the glycosidic center.[83),84)] Different from this general result, the glycosylation of aglycons **17** and **39** (with an acetyl group at the O-3 position) with α-imidate **34** gave preferentially the α-glycoside (α/β ratio = about 1.8 and 2.5, respectively). Furthermore, the total yield was low (about 50% yield) and about 50% of the

Table 1. Results of glycosylation reactions between α-imidate **34** and aglycons **17**, **39-41**

Aglycon	R_1*	R_2**	Reaction time (h)	Products	Yield (%) β	Yield (%) α
17	-Ac	-Ac	2	**37**(β) **38**(α)	16.4	29.0
39	-Ac	-Bzl	2	**51**(β) **52**(α)	13.0	33.0
40	-Bzl	-Ac	1	**53**(β)	94.2	--
41	-Bzl	-Bzl	1	**54**(β)	96.0	--

* R_1 = 3-O substituent group

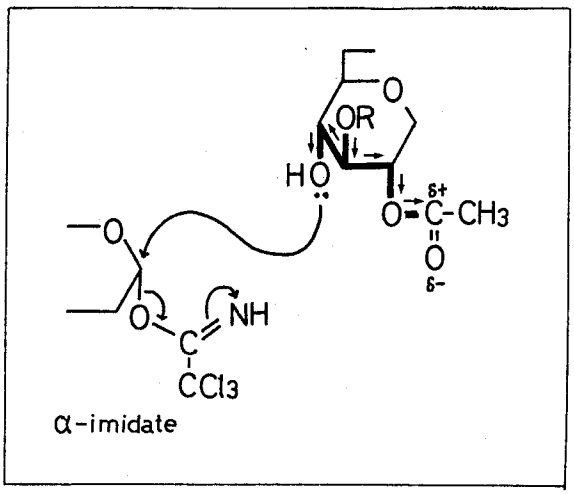
** R_2 = 6-O substituent group

starting aglycon was recovered. Contrary to these results, the glycosylation of aglycons **40** and **41** (with a benzyl group at the O-3 position) with α-imidate **34** gave only the β-glycoside in extremely high yield. The effect of the benzyl group introduced into the O-6 position on the α / β ratio seems to be small. These results coincide well with those reported by Sinay[87]. Thus, it is clear in the present experiments that the benzyl substituent at the O-3 position of the aglycon is indispensable to obtain a β-D-(1 → 4) linked glycoside with excellent yield.

The differences in the reactions that occur with the different aglycons may be explained as follows. The electron-donating benzyl group introduced into the O-3 position (aglycons **40** and **41**) seems to increase the electron

density of the hydroxyl group at the C-4 position, i.e., the hydroxyl group becomes more nucleophilic. As the result, substitution by the aglycons (**40** and **41**) via a complete S_N2 mechanism at the glucosidic center becomes favorable to afford only the β-glycoside. In contrast, the electron-withdrawing acetyl group at the O-3 position reduces the nucleophilicity of the hydroxyl group attached to the C-4 position of aglycon. Therefore, substitution by the aglycons (**17** and **39**) is thought to proceed with an S_N1-like mechanism, i.e., elimination of the trichloroacetimidoyl group in α-imidate **34** is followed by a reaction between the aglycons (**17** and **39**) and the resulting carbonium ion (or oxonium ion) intermediate to afford preferentially the α-glycoside, which is thermodynamically more stable than the β-glycoside.

The stabilization of the acetyl group in compound **25** and the results obtained from the above glycosylation experiments may be explained by the same electronic factor.



α-imidate

The benzyl group introduced into the O-3 position acts to increase the electron densities of the adjacent oxygen atoms (O-2 and O-4) to contribute to the stabilization of the acetyl groups at these positions with respect to mild methanolysis. At the same time, an increase in the nucleophilicity of the adjacent hydroxyl groups favors a complete S_N2 reaction in the glycosylation with α-imidate **34**. If such reasoning is correct, the presence of a benzyl (or other alkyl) group at the O-3 position of the aglycon will be important for the synthesis of a β-(1→2) glycoside and the presence of a benzyl (or other alkyl) group at the O-2 and/or the O-4 position of the aglycon will be important for the synthesis of a β-(1→3) glycoside.

It is clear that in the present work the α/β ratio produced by the glycosylation largely depends on the protective groups of the aglycons, even if the imidate method is used.

2-2 Substituent-effect of other alkyl and acyl groups

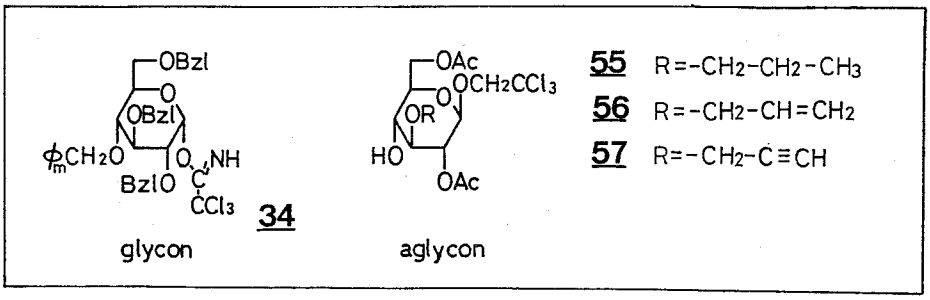
The substituent-effect of 3-O-benzyl group may be explained by the inductive effect of the electron-donating benzyl group, but the possible participation of π-electrons on the benzene ring such as π-complex formation,[14] a hydrogen-bond formation[66] and so on cannot be ruled out. The former part of this section describes the effects of the π-electron of the benzyl group on the glycosylation reaction.

On the other hand, the removal of acyl group is easier

than that of benzyl group, particularlly in the case of a high molecular weight compound. Therefore, the acyl group is more favorable as a persistent protective R-group. Then, the effect of the acyl groups other than acetyl group on the glycosylation reaction are also described in the latter part of this section.

2-2-1 Substituent-effect of 3-O-alkyl group

Three aglycons **55-57** were selected, for the glycosylation reaction with α-imidate **34**, in order to investigate the influence of the π-electron of the 3-O-benzyl substituent group on glycosylation reaction. Propyl, allyl and propargyl groups were chosen as typical models of single, double and triple bonds, respectively. The propargyl group can be converted into propyl and allyl groups by catalytic hydrogenation.



Synthesis of aglycons

The synthetic route for compounds **55-57** from 1,2,4,6-tetra-O-acetyl-3-O-propargyl-β-D-glucopyranose (**58**) is shown in Fig. 9. The starting material **58** was prepared via 1,2;5,6-di-O-isopropylidene-α-D-glucofuranose.[105] The

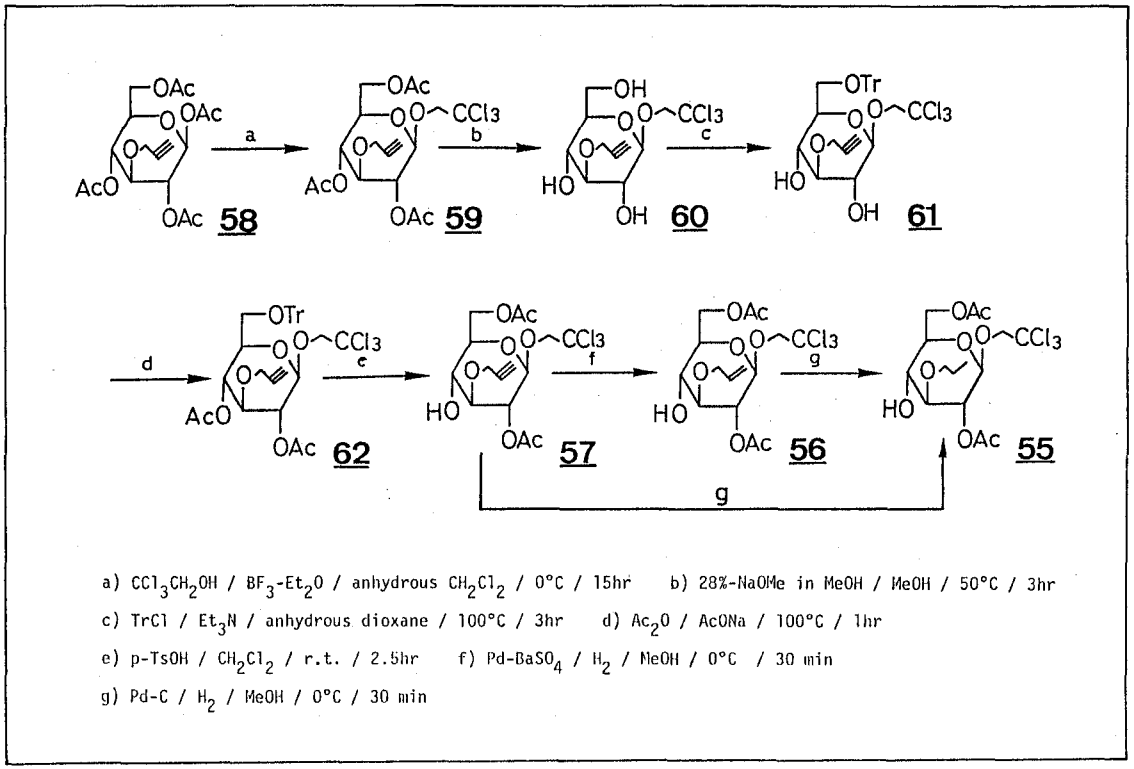


Figure 9. Synthetic route for compounds **55-57** from compound **58**.

synthesis of compound **57** was carried out by the methods similar to those used for the synthesis of compound **40**.

Compounds **55** and **56** were obtained from compound **57** by catalytic hydrogenation in methanol using palladium carbon (Pd-C) in about 60% yield and using Lindlar catalyst (Pd-$BaSO_4$)[11] in about 30% yield, respectively. The reaction time should be about 30 min, because 2,2,2-trichloroethyl group was found to be unstable under the reaction conditions.

Glycosylation

The glycosylation reaction between α-imidate **34** and aglycons **55-57** was conducted under the same reaction conditions described in the previous section (Reaction time was one hour.). The product was purified by preparative TLC. The configuration of the anomeric center was determined by ^{1}H-NMR and ^{13}C-NMR spectroscopies.

The results are summarized in Table 2, which also contains the substituent constants (σ_I) of R-groups[7] and pKa-values of R-OH predicted by the method of Perrin *et al.*[75]

As expected, three aglycons **55-57** gave only the β-glycoside in good yields, and 3-*O*-benzyl derivative **40** gave β-glycoside in an excellent yield as described in the previous section. Generally, the electron-donating ability of the C-3 functional group (R-) is evaluated by the substituent constant (σ_I) and the pKa-value of the corresponding alcohol (R-OH).[7),75] The yields of β-glycosides obtained by the reaction between glycon **34** and

Table 2. Results of glycosylation reactions between α-imidate **34** and aglycons **40**, **55-57**

Aglycon	-R*	Product	Yield (%)	σ_I**	pKa***
55	$-CH_2CH_2CH_3$	**63** (β)	79.3	-0.01	16.1
56	$-CH_2CH{=}CH_2$	**64** (β)	72.5	0.02	15.9
57	$-CH_2C{\equiv}CH$	**65** (β)	71.7	0.14	14.7
40	$-CH_2C_6H_5$	**53** (β)	94.2	0.03	15.5

* -R = 3-O substituent group

** σ_I = substituent constant for -R

*** pKa = value of R-OH

aglycons **55-57** seem to increase with decreasing of the σ_I-constant and with increasing of pKa-values. The yield of β-glycoside apparently is affected only by the inductive effect of the C-3 functional groups, not by the effect of the π-electrons of the C-3 functional groups.

Although σ_I-constant of benzyl group (0.03) is the similar to that of allyl group (0.02), the yield of β-glycoside from aglycon **40** is different from that from aglycon **56**. If the yield of the β-glycoside is affected only by the inductive effect of the C-3 functional group, both yields from aglycon **40** and **56** should be almost the same. Therefore, the excellent yield in the case of aglycon **40** should be affected not only by the inductive effect, but also by the other effect, i.e. by some through-space

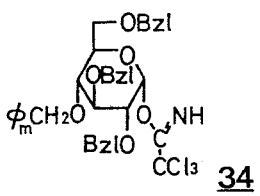
interaction[7] such as π-complex or a hydrogen bond formation between 3-O-benzyl and C-4 hydroxyl groups.

It is concluded that the benzyl group has a special function different from the other alkyl groups on β-glycosylation reaction. Benzyl group is especially useful for the protection of C-3 hydroxyl group of aglycon.

2-2-2 Substituent-effect of the 3-O-acyl group

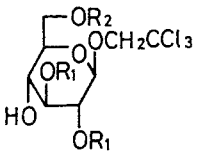
Carbamoyl and pivaloyl groups which are more electron-donating than acetyl group may be more useful for protection of the starting glucose derivative **1**. In fact, carbamoyl group has been used for the protection of the starting glucose derivative in the synthesis of cellulose-like polymer by Husemann and Müller[39] and by Hirano.[37] And pivaloyl group has been conveniently used for the β-glycosylation instead of acetyl group recently.[50] On the other hand, the use of electron-withdrawing protective group of aglycon at O-3 position may be favorable for the formation of α-glycoside; namely the more electron-withdrawing acyl group such as monochloroacetyl group may be useful for the synthesis of malto-oligosaccharides.

Then, four aglycons **66**-**69** were selected for the present investigation. Carbamoyl derivative **65** has poor solubility for dichloromethane used as a solvent in the glycosylation reaction. Since the aglycon **66** requires tedious handling, the aglycon **67** was also prepared as a carbamoyl derivative.



34

glycon



aglycon

66 $R_1 = R_2 =$ -Car

67 $R_1 =$ -Car $R_2 =$ -Ac

68 $R_1 = R_2 =$ -Piv

69 $R_1 = R_2 =$ -MCA

-Car = -carbamoyl (-CONHPh)
-Piv = -pivaloyl ($-COC(CH_3)_3$)
-MCA = -monochloroacetyl ($-COCH_2Cl$)

Synthesis of aglycons

The synthetic route for compounds **66-69** from 2,2,2-trichloroethyl β-D-glucopyranoside (**13**) is shown in Fig. 10. Since carbamoyl and pivaloyl groups seem to migrate less readily than acetyl group,[99] the C-6 hydroxyl group was acylated selectively to lead to compounds **66-68**. The selective carbamoylation[36),68)] of compound **72** was carried out by the treatment with phenyl isocyanate in anhydrous pyridine at 50°C to give compound **66** in 58.9% yield. In this reaction, anhydous pyridine was used to prevent the formation of by-products. The selective acetylation[86),100)] of compound **72** was performed by the treatment with acetyl chloride / 2,6-lutidine in ethyl acetate at 0°C to afford compound **67** in 64.5% yield. The selective pivaloylation[22),58)] of compound **73** was conducted by the treatment with pivaloyl chloride / pyridine in chloroform at 50°C to form compound **68** in 64.3% yield. The synthesis of compound **69** was conducted by the methods similar to those used for the synthesis of compound **17**.

Glycosylation

The glycosylation reactions between α-imidate **34** and

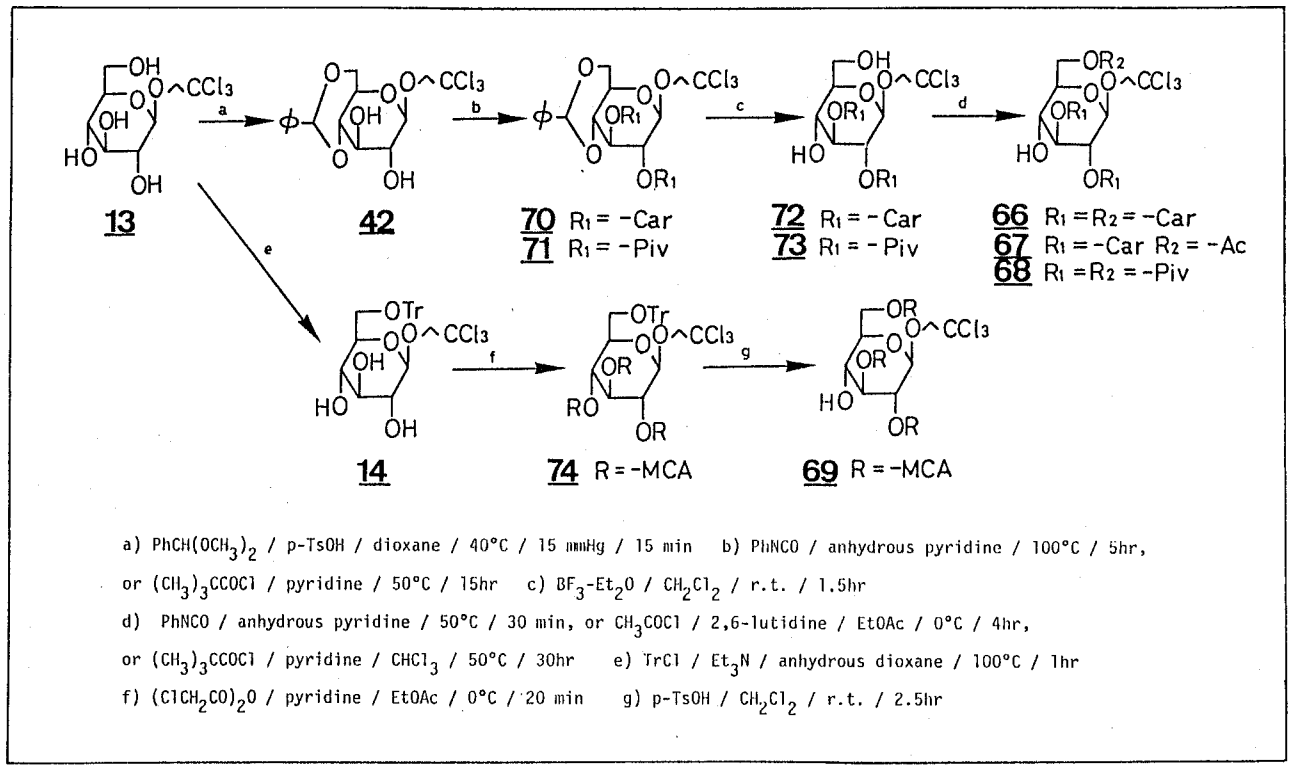


Figure 10. Synthetic route for compounds **66-69** from compound **13**.

aglycons **66-69** were performed under the same reaction conditions as those described in the previous section (Section 2-1-3). The results are summarized in Table 3.

Contrary to the expectation from its reaction mechanism for imidate method, four aglycons **66-69** gave both β-glycoside and α-glycoside. The S_N1 reaction mechanism seems to participate to some extent in all these reactions and the extent of the participation depends on the protective groups used. The total yields of glycoside incrased in the order of pivaloyl, carbamoyl, acetyl and monochloroacetyl groups. This result shows that the aglycon with more electron-donating acyl groups is more effective than that with more electron-withdrawing acyl group for the glycosylation reaction. Only carbamoyl derivatives **66** and **67** gave

Table 3. Results of glycosylation reactions between α-imidate **34** and aglycons **17**, **66-69**

Aglycon	$-R_1$*	$-R_2$**	Products	Yield (%)		
				β	α	total
66	-Car	-Car	**75**(β) **76**(α)	35.3	20.3	55.6
67	-Car	-Ac	**77**(β) **78**(α)	57.0	7.7	64.7
68	-Piv	-Piv	**79**(β) **80**(α)	23.8	55.6	79.4
69	-MCA	-MCA	**81**(β) **82**(α)	3.2	16.2	19.4
17	-Ac	-Ac	**37**(β) **38**(α)	16.4	29.0	45.4

* $-R_1$ = 2-O and 3-O substituent groups

** $-R_2$ = 6-O substituent group

preferentially the β-glycosides, though the other acyl derivatives afforded preferentially the α-glycosides.

Consequently, the effect of the C-3 substituent group of the aglycon on glycosylation by imidate method can be explained by the inductive effect. The C-3 electron-donating ether group seemes to increase the electron density and nucleophilicity of the hydroxyl group at the C-4 position, and a complete S_N2 reaction proceeds to afford only the β-glycoside. Especially, benzyl group with aromatic π-electron seems to have a special function such as through-space interaction. In contrast, on the glycosylation using aglycon with C-3 electron-withdrawing ester group, S_N1 type reaction proceeds to give a mixture of β-glycoside and α-glycoside. Thus, mainly, the inductive effect of the C-3 substituent of the aglycon is important factor to decide the configuration of the product in the glycosylation by imidate method. Further investigation of the interesting effect of aromatic π-electron of benzyl group may be needeed.

In the cello-oligosaccharides synthesis, the starting material 1 should be protected with benzyl group at O-3 position.

2-3 Summary

In this chapter, substituent-effect of aglycon on glycosylation reaction was investigated.

A series of aglycons with different combinations of benzyl and acetyl groups at the O-3 and O-6 positions were

synthesized with good yield and glycosylation reactions with imidate **34** were carried out to study the influence of substituent groups on the reactivity of C-4 hydroxyl group of aglycon (Section 2-1). The aglycon with benzyl group at O-3 position afforded only the β-glycoside in extremely high yield, but the aglycon with acetyl group at O-3 position gave preferentially the α-glycoside in about 30% yield (Table 1). The result revealed that the benzyl substituent at O-3 position of aglycon was indispensable to obtain only the β-D-(1→4) linked glycoside with excellent yield. The effect of 6-O-benzyl group on glycosylation reaction seemed to be small.

Although substituent-effect of 3-O-benzyl group can be explained by the inductive effect of the electron-donating benzyl group, the possible participation of π-electrons on benzene ring may also be important. Then, the influence of the π-electrons of the benzyl group on glycosylation reaction was studied (Section 2-2-1). As expected, all aglycons with 3-O-alkyl groups other than 3-O-benzyl group gave only the β-glycoside in good yields, and aglycon with 3-O-benzyl group afforded β-glycoside in the highest yield (Table 2). the results suggested that the aromatic π-electrons of 3-O-benzyl group, different from olefinic or acetylenic π-electrons, have a special function for increasing the yield of β-glycoside.

In addition, the effect of acyl group other than acetyl group was also investigated (Section 2-2-2). However, all aglycons with 3-O-acyl groups gave a mixture of β- and α-

glycosides (Table 3). Among the acyl groups investigated, carbamoyl group was effective for β-glycoside formation. Thus, it was concluded that benzyl group was especially useful for the protection of C-3 hydroxyl group of the aglycon.

Chapter 3 Substituent-effect of glycon on glycosylation reaction

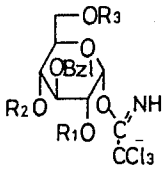
3-1 Substituent-effect of the α-imidate on glycosylation reaction

The benzyl group is necessary as the persistent group at the O-3 position of stating material 1 for the glycosylation reaction. However, the remaining protective groups at the O-2, O-4 and O-6 positions in the glycon (i.e., 3-O-benzyl-α-imidate) will affect on glycosylation reaction. In this section, therefore, the stability of 3-O-benzyl-α-imidates and the influence of the protective groups in the imidates on the reactivity in the glycosylation reaction were investigated.

In general an unstable material has a high reactivity. For example, α-imidate **34** was too unstable to decompose on silica gel during the purification[44], but gave β-glycoside in excellent yield. However, the unstability of compound **34** is inconvenient for handling, especially in the case of large scale preparation. Then, the faborable α-imidate used for the cello-oligosaccharides synthesis should be highly reactive, but should be nevertheless stable on silica gel. In the present study, typical electron-donating p-methoxybenzyl and electron-withdrawing monochloroacetyl groups as a temporary protective group at O-4 position, and benzyl, acetyl and pivaloyl groups as persistent protective groups at O-2 and O-6 positions were initially selected,

respectively. Thus, six imidates (glycons) **34,83-87** were prepared to investigate their stability and reactivity on the glycosylation reaction.

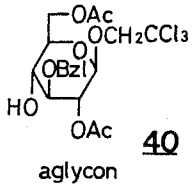
On the other hand, Boeckel et al.[3),4),5)] reported that the effects exerted by O-4 and O-6 substituent groups are reversed, though these substituent groups are separated by the same number of single bonds from the anomeric center. They demonstrated that a combination of the electron-withdrawing acyl group at the O-4 position and the electron-donating alkyl group at the O-6 position facilitate the formation of the β-glycoside. Paulsen[73),74)] reported that benzyl compounds are always more reactive than the acetylated or benzoylated derivatives, the position of benzyl groups being less important than their number. For the clarification of these effects, three imidates (glycons) **88-90** were also prepared.



glycon

34	R_1 = -Bzl	R_2 = -pMBzl	R_3 = -Bzl
83	R_1 = -Ac	R_2 = -pMBzl	R_3 = -Ac
84	R_1 = -Piv	R_2 = -pMBzl	R_3 = -Piv
85	R_1 = -Bzl	R_2 = -MCA	R_3 = -Bzl
86	R_1 = -Ac	R_2 = -MCA	R_3 = -Ac
87	R_1 = -Piv	R_2 = -MCA	R_3 = -Piv
88	R_1 = -Ac	R_2 = -Ac	R_3 = -pMBzl
89	R_1 = -Bzl	R_2 = -Ac	R_3 = -Ac
90	R_1 = -Ac	R_2 = -Ac	R_3 = -Ac

-pMBzl = -p-methoxybenzyl
-Piv = -pivaloyl
-MCA = -monochloroacetyl



aglycon **40**

Compound **40** was selected as an aglycon, since this compound gave β-glycoside in a high yield and was relatively easily prepared from compound **44** as described in the previous chapter (Chapter 2, Section 2-1).

3-1-1 Synthesis of the α-imidates

Synthesis of α-imidates [I]

Imidate **34** was prepared by the method reported by Kawada et al..[44] The synthetic route for imidates **83**,**84**,**88** and **90** from trichloroethyl 2,4,6-tri-O-acetyl-3-O-benzyl-β-D-glucopyranoside (**25**) is shown in Fig. 11. The key reaction in the synthesis of compound **83** and **84** is the reductive cleavage of 4,6-O-p-methoxybenzylidene glucopyranoside **93** and **94** (Fig. 11, step f).

Johansson and Samuelsson[42] reported that the reductive ring-opening of methyl 2,3-di-O-benzyl-4,6-O-p-methoxybenzylidene-α-D-glucopyranoside with $NaCNBH_4$-TMSCl in acetonitrile gave the 4-O-p-methoxybenzyl and 6-O-p-methoxybenzyl derivatives in 76% and 12% yields, respectively. However, different from the results of Johansson and Samuelsson[42], the acetyl derivative **93** afforded 4-O-p-methoxybenzyl ether **95** and 6-O-p-methoxybenzyl ether **96** in 38.5% and 30.0% yields by the treatment of $NaCNBH_4$-TMSCl in CH_3CN. On the other hand, the pivaloyl derivative **94** gave only compound **98** in 60.3% yield. The regioselectivity of the reductive cleavage of 4,6-O-p-methoxybenzylidene derivative seems to depend upon the electronic factor resulting from the subsituent groups

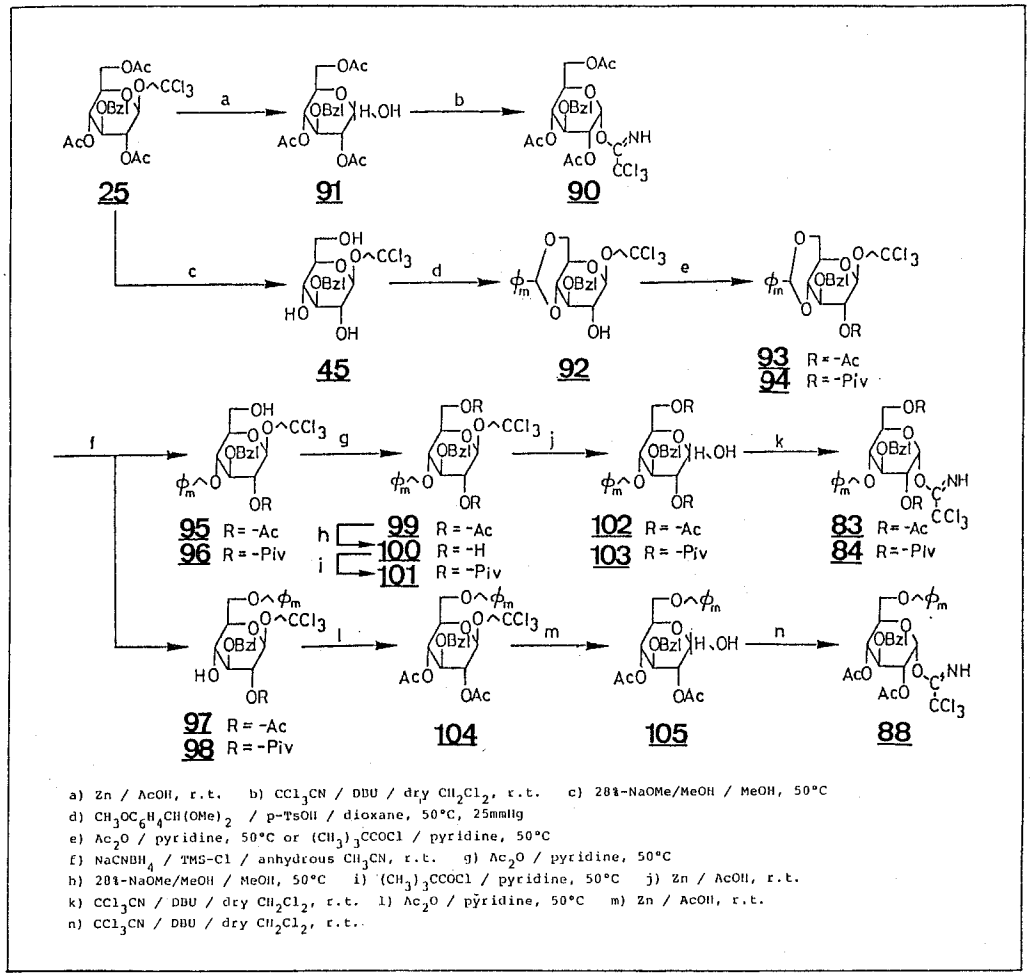


Figure 11. Synthetic route for **83**, **84**, **88** and **90** from compound **25**

at the O-1 or O-2 position. Thus, the substituent-effect on the reductive ring-opening reaction should be more studied.

Imidate **83** was prepared from compound **95** by acetylation, detrichloroethylation and imidoylation. Since compound **96** was not obtained by the selective cleavage of compound **94**, imidate **84** was prepared from compound **99** via compounds **100** and **101**. Imidates **88** and **90** were synthesized from compounds **97** and **25**, respectively.

Synthesis of α-imidates [2]

The synthetic route for imidates **85,86,87** and **89** is shown in Fig. 12. These imidates **85,86** and **87** were synthesized from compounds **35**, **40** and **113** by monochloroacetylation, deprotection at the C-1 position (deallylation or detrichloroethylation), and imidoylation, respectively.

Imidate **89** was prepared from allyl 2,3-di-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**106**).[43] The selective deallylation of compounds **108** and **111** with acyl group was done by the oxidative cleavage with selenium (IV) dioxide in acetic acid / dioxane[45] to give compounds **109** and **112** in about 60 % yields, respectively.

3-1-2 Stability of the α-imidates and their glycosylation

The stability of the respective imidate was evaluated by the stability on the purification by preparative TLC (layer thickness 2mm, Kiesel gel 60 F_{254} Merk) after imidoylation. The reactivities of imidates **34,83-90** were evaluated by the glycosylation reactions with aglycon **40**

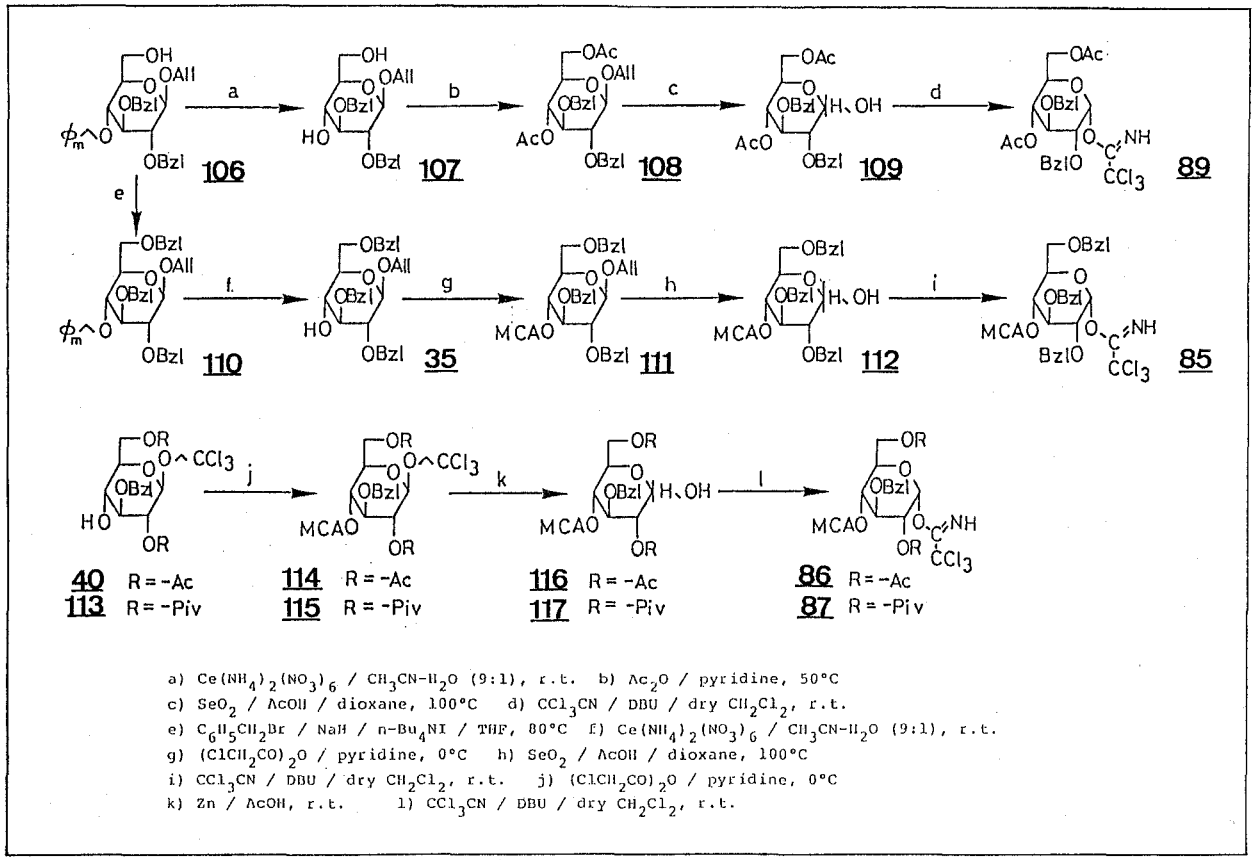


Figure 12. Synthetic route for compounds **85-87** and **89** from compounds **40**, **106** and **113**.

conducted under the similar reaction conditions as described previously; each imidate (1.0 eq) was reacted with aglycon **40** (2.0 eq) in the presence of a catalytic amount of BF_3-Et_2O (0.2 eq) below $-70^{\circ}C$ for one hour. The product was purified by a preparative TLC and identified by ^1H-NMR analysis. The results are summarized in Table 4. In the case of imidates **86-90**, the corresponding β-glycoside was not isolated by TLC; the yield was less than 1 % and only hydrolysis of the imidate was observed.

The introduction of the electron-withdrawing acyl group into α-imidate was found to contribute to the stabilization

Table 4. Results of the stability and reactivity of the α-imidates **34**, **83-90**

α-Imidate	-R_1*	-R_2**	-R_3***	Stability	Products	Yield (%)
34	-Bzl	-pMBzl	-Bzl	x	**53** (β)	82.0
83	-Ac	-pMBzl	-Ac	o	**118** (β)	60.0
84	-Piv	-pMBzl	-Piv	o	**119** (β)	57.8
85	-Bzl	-MCA	-Bzl	o	**120**(β)**121**(α)	13.5(β)3.0(α)
86	-Ac	-MCA	-Ac	o	--	--
87	-Piv	-MCA	-Piv	o	--	--
88	-Ac	-Ac	-pMBzl	o	--	--
89	-Bzl	-Ac	-Ac	o	--	--
90	-Ac	-Ac	-Ac	o	--	--

* -R_1 = 2-O substituent group
** -R_2 = 4-O substituent group
*** -R_3 = 6-O substituent group

of imidate, and to decrease the yield of β-glycoside. The replacement of the two benzyl groups at O-2 and O-6 positions of imidate **34** by acyl groups results in the stabilization of the imidate , and the β-glycosides were obtained in about 60% yields (imidates **83** and **84**). Generally, pivaloyl derivative is more effective for the β-glycosylation than the corresponding acetyl derivative,[50] but these two acyl derivatives, imidates **83** and **84**, have almost the same reactivity. Then, the replacement of 4-O-p-methoxybenzyl group of the imidate **34** by the electron-withdrawing monochloroacetyl group extremely decreases the yield of β-glycoside (imidate **85**). Thus, the electron-donating (p-methoxybenzyl) group at O-4 position of α-imidate is very important for the formation of β-glycoside. As expected from these results, the stable imidates **86** and **87** did not afford any β-glycoside.

The replacement with each other between p-methoxybenzyl group at O-4 position and acetyl group at O-6 position of imidate **83** results in the formation of imidate **88**. Contrary to the demonstration by Boeckel et al.,[3),4),5)] imidate **88** with the electron-withdrawing (acetyl) group at O-4 position and electron-donating (p-methoxybenzyl) group at O-6 position also did not afford β-glycoside. The result indicates that their demonstration is inapplicable to the present imidate method. Each of imidates **83**,**88** and **89** has two electron-donating (benzyl and/or p-methoxybenzyl) groups, but only imidate **83** gives the β-glycoside in a moderate yield. The comparison of these results indicate

that the most effective group for the synthesis of β-glycoside is the ether group at C-4 position of the α-imidate, and that C-2 and C-6 ether groups are not so effective.

Imidate **90** did not give β-glycoside. The additional introduction of benzyl group into O-2 position (imidate **89**) or O-6 position (imidate **88**) is not also effective, but the introduction of benzyl groups both into O-2 and O-6 positions results in the production of β-glycoside even if the strong electron-withdrawing monochloroaceyl group is introduced into O-4 position of the imidate (imidate **85**). Thus, both benzyl groups at O-2 and O-6 positions may synergistically effect for the glycoside formation.

Thus, it is concluded that the most effective group for the β-glycoside synthesis is an electron-donating ether group such as p-methoxybenzyl groups at O-4 position of α-imidate and that the other benzyl groups at O-2 and O-6 positions have synergistical effects.

It is interesting that both electron-donating groups at O-3 position of aglycon and at O-4 position of glycon are very effective for the β-glycosidic bond formation. Therfore, protective groups should be considered as "reaction directing groups", not simply as "blocking groups".

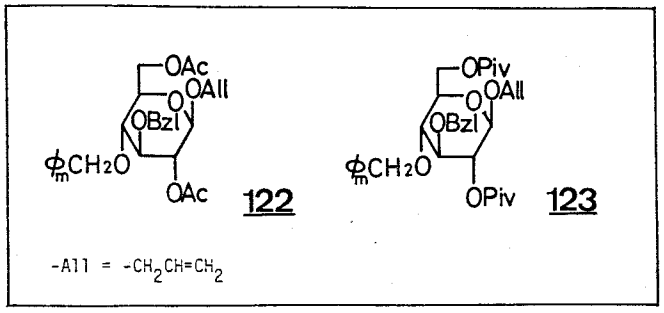
3-2 Conclusive selection of starting material for cello-oligosaccharides synthesis

In the synthetic design proposed (Chapter 1, Section 1-1), the starting material 1, which can be converted both into glycon and aglycon by simple operations, is required. This section describes the synthesis of actual starting material discussed in Chapter 2 and in the previous section of this chapter.

Among the α-imidates **34**,**83-90** investigated, α-imidates **83** and **84** are the most suitable in the presnt cello-oligosaccharides synthesis because of its stability and reactivity. In addition, the product synthesized from the combination of α-imidate **83** and aglycon **40** may be used for the preparation of regiospecific substituted cellulose derivaives.

However, there is a problem in the synthesis of compounds **83** or **84**, i.e.; the regioselectivity in the reductive cleavage of 4,6-O-p-methoxybenzylidene acetal. Kawada et al.[43] reported that the reductive ring-opening of allyl-2,3-di-O-benzyl-4,6-O-p-methoxybenzylidene-β-D-glucopyranoside with lithium aluminium hydride ($LiAlH_4$) - aluminium chloride ($AlCl_3$) gave the 4-O-p-methoxybenzyl ether derivative in 96.1% yield. On the other hand, Liptak[57] reported that regioselectivity in the reductive cleavage of benzylidene acetal with $LiAlH_4$-$AlCl_3$ is associated with the steric hindrance exerted by the C-3 substituent. However, 2,2,2-trichloroethyl group is unstable under the reaction conditions of the reductive cleavage with $LiAlH_4$-$AlCl_3$.[28),69)] Then, allyl group was selected as a temporary X-group instead of 2,2,2-trichloroethyl group.

Allyl group is stable under a variety of conditions and can be selectively removed easily by the methods such as mild two-step reactions (isomerization of the double bond and subsequent acid hydrolysis of the resultant enol ether), oxidative cleavage with selenium (IV) dioxide.[26),30),45)] The latter reaction conditions are applicable to the acetyl derivatives. For the protective group pattern except C-1 position, the protective group patterns of compounds **83** and **84** were chosen. The p-methoxybenzyl group selected as a temporary Y-group can be removed oxidatively by the use of ammonium cerium (IV) nitrate (CAN)[42)] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[72)] without any influence of persistent acetyl, pivaloyl and benzyl groups. Therefore, allyl 2,6-di-O-acetyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**122**) and allyl 2,6-di-O-pivaloyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**123**) were selected as starting material 1 in the present cello-oligosaccharides synthesis.



The synthetic route for compounds **122** and **123** from compound **44** is shown in Fig. 13. The key reaction in this

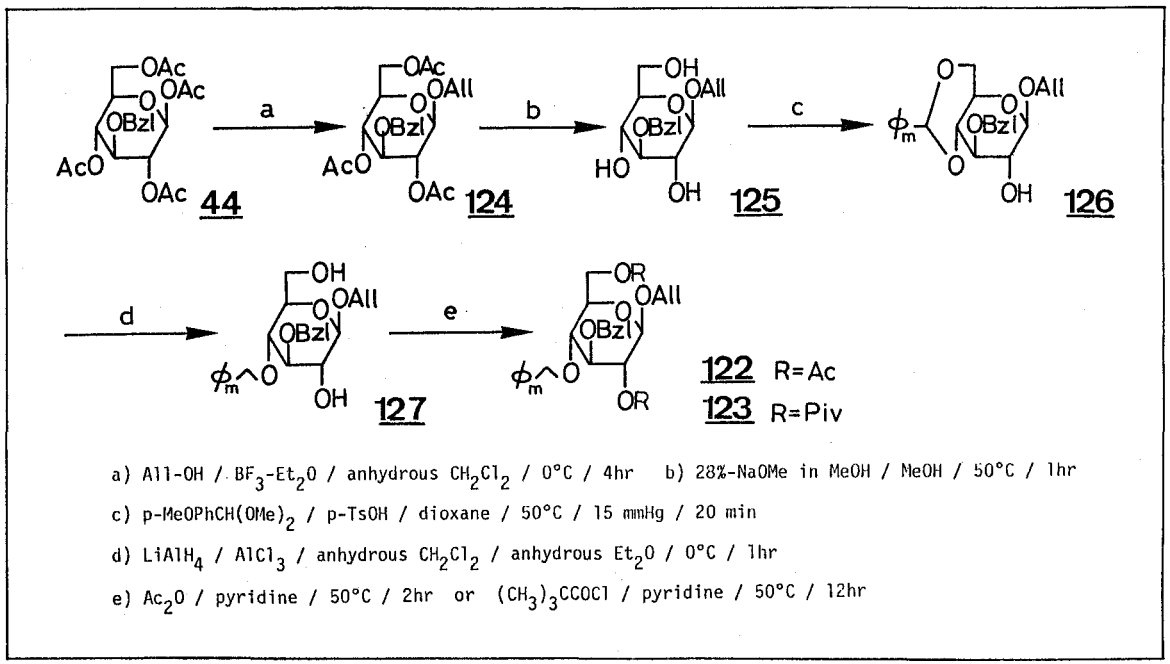


Figure 13. Synthetic route for compounds **122** and **123** from compound **44**

route is β-allylglycosylation (step a) and reductive ring-opening reaction (step d).

For the synthesis of β-allylglucopyranoside, a Koenigs-Knorr method in which acylglucosyl halide is reacted with allyl alcohol in the presence of a suitable catalyst such as silver carbonate[21] or mercuric cyanide[53] was tried. However, this method requires the additional halogenation step before glycosylation. Furthermore, 3-O-benzyl group of compound **44** was found to be partly removed under the halogenation reaction conditions. Then, the modified Magnusson's method[13),59] was examined. Compound **44** was treated with allyl alcohol / boron trifluoride etherate to afford compound **124** in 77.4% yield. 3-O-Benzyl group was stable under this reaction conditions. In this reaction, it was found that allyl alcohol and boron trifluoride etherate should be used in excess (5.0 eq and 10.0 eq) for completion of the reaction. Allyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside is also obtained from compound **11** in 70.5% yield. Thus, this procedure is a simple and highly stereoselective β-allylglycosylation method for the compound with benzyl ether.

The reductive ring-opening reaction of compound **126** using the $LiAlH_4$-$AlCl_3$ gave 4-O-p-methoxybenzyl ether derivative **127** in 83.6 % yield. Compound **127** was converted to the target material **122** and **123** by acetylation and by pivaloylation, respectively, in a quantitative yield.

The starting material **122** was converted into glycon **102** and aglycon **128** by the removal of the ally and p-

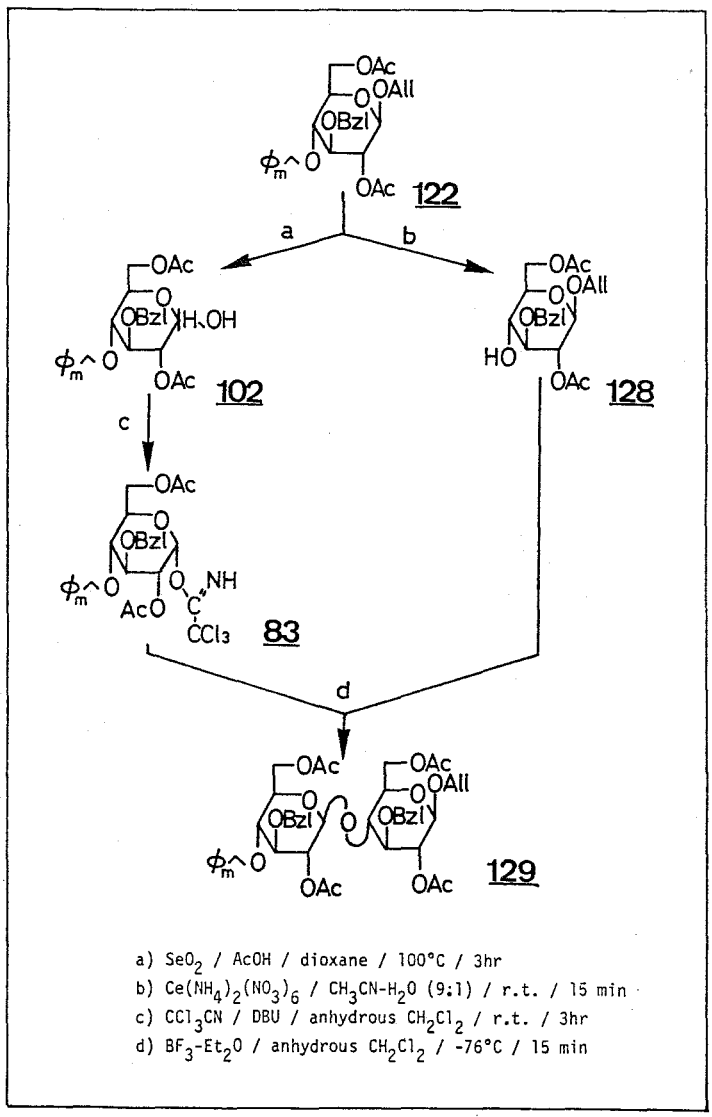


Figure 14.

Synthetic route for compound **129** from compound **122**

methoxybenzyl groups, respectively. The allyl group was removed by the oxidation with selenium (IV) dioxide to produce glycon **102** in 61.0% yield. For the removal of p-methoxybenzyl group, compound **122** was treated with cerium (IV) anmmonium nitrate to give aglycon **128** in 85.3% yield. Then, α-imidate **83** was obtained from compound **102**. Glycosylation between α-imidate **83** and aglycon **128** gave the β-glycoside **129** in about 50% yield.

3-3 Summary

In Chapter 3, the influence of the substituent groups of the glycon (α-imidate) on their stability and reactivity was investigated (Section 3-1). As the results, it was found that the introduction of an electron-withdrawing acyl group into the α-imidate contributes to stabilization of the α-imidate, but decreases the yield of β-glycoside, and that the electron-donating ether group such as p-methoxybenzyl group introduced into O-4 position of α-imidate was very effective. The 2-O- and 6-O-alkyl groups are not so effective for the β-glycoside formation.

Finally, a favorable starting material for the synthesis of cello-oligosaccharides was designed on the basis of the results mentioned above (Section 3-2). Allyl 2,6-di-O-acetyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**122**) and allyl 2,6-di-O-pivaloyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**123**) were proposed as a conclusive starting material for the synthesis of cello-

oligosaccharides.

CONCLUSIONS

There are two synthetic problems, regiospecific 1,4-bond formation and stereospecific β-linkage formation, have to be solved for the cello-oligosaccharides synthesis. The former problem will be solved by the use of a starting material which has special protective groups introduced by regiospecific control, the latter by the stereospecific β-glycosidic bond synthesis. The author investigated the synthetic methods for the starting materials and their glycosylation reaction in order to synthesize cello-oligosaccharides. The substituted glucose derivative **1** as a starting material should have three kinds of protective groups, X-, Y- and R-groups.

In Chapter 1, the synthesis of a starting material, in which acyl group is used as a R-group, and its glycosylation reaction for the regulation of regiospecificity were studied. The synthetic route for 2,3,6-tri-O-acetyl glucose derivatives from D-glucose (Fig. 3) was investigated at first. Here, two problems lay in tritylation at C-6 hydroxyl group (Fig. 3, step d) and acetyl group migration from O-4 to O-6 (Fig. 3, step g). The former problem was solved by the use of trityl chloride / triethylamine / dioxane system and the latter by the use of p-toluenesulfonic acid. 2,3,6-Tri-O-benzoyl glucose derivatives were also synthesized successfully. Then, the glycosylation between the acetyl derivative and α-imidate **34** was examined. As a result, it was found that the yield and α/β ratio of glycosides were

greatly affected by the protective group pattern.

In Chapter 2, a series of aglycons with different combinations of ether and ester groups at the C-3 and C-6 positions were successfully synthesized with good yields. Then, the glycosylation reactions with imidate **34** were conducted to investigate the influence of the substituent groups on the reactivity of the C-4 hydroxyl group of aglycons. The result indicated that the benzyl substituent at the O-3 position of the aglycon was indispensable to obtain only the β-D-(1→4) linked glycoside with excellent yield, by the effect of the π-electron of the benzene ring in addition to the inductive effect of the electron-donating benzyl group (Tables 1, 2 and 3).

In Chapter 3, the influence of the substituent groups of the glycon (α-imidate) on their stability and reactivity was investigated. It was found that the introduction of an electron-withdrawing acyl group into the α-imidate contributes to stabilization of the α-imidate, but decreases the yield of β-glycoside, and that the electron-donating ether group such as p-methoxybenzyl group introduced into O-4 position of α-imidate was very effective (Table 4). Thus, protective groups should be considered as "reaction directing groups" not simply as "blocking groups" from the present systematic investigation. The suitable selection and effective use of protective groups are very important for the synthesis of oligosaccharides and polysaccharides.

Finally, allyl 2,6-di-O-acetyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**122**) and allyl 2,6-di-O-pivaloyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (**123**) were proposed as a conclusive starting material for the synthesis of cello-oligosaccharides.

EXPERIMENTAL

GENERAL

All melting points are uncorrected. Optical rotations were determined with a Jasco DIP-4 polarimeter for solutions in $CHCl_3$ at 28°C, unless otherwise noted. UV spectra were recorded with a Shimadzu UV-365 spectrophotometer. IR spectra were recorded with a Shimadzu FT IR-4000 spectrophotometer. ^1H- and ^{13}C-NMR spectra were taken with a Varian XL-200 FT-NMR (200 MHz) and a JEOL FX-NMR (90 MHz) spectrophotometers, respectively, with TMS internal standard in $CDCl_3$. Chemical shifts and coupling constants are given in δ-value and Hz, respectively. Preparative TLC (hereafter "P-TLC") was done on silica gel plates (layer thickness 2 mm, Kieselgel 60 F_{254} Merck). Anhydrous CH_2Cl_2, anhydrous CH_3CN, anhydrous CCl_3CH_2OH and anhydrous pyridine were distilled from P_2O_5. Anhydrous dioxane was distilled from sodium metal. Anhydrous cyclohexane and anhydrous Et_2O were distilled from sodium hydride. The standard work-up included diluting with EtOAc, washing with a saturated $NaHCO_3$ solution and with a saturated NaCl solution (hereafter "brine"), drying over Na_2SO_4 and evaporating in vacuo.

1. EXPERIMENTAL (Chapter 1)

2,2,2-Trichloroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (12)

To a solution of glucosepentaacetate[105] (11) (78 g, 0.2M) and 2,2,2-trichloroethanol (57.6ml, 0.6M) dissolved in CH_2Cl_2 (100 ml), powdered molecular sieves 4A (20 g) was added. After stirring for 1 h at room temperature, BF_3-Et_2O (123ml, 1M) was added dropwise over a period of 1 h at 0°C. The reaction mixture was stirred for 15 h and then filtered. The residual molecular sieves was washed with EtOAc (200 ml). The combined filtrate and washings were worked-up by the standard method to give a colorless syrup which was crystallized from EtOH to afford colorless needles (60 g, 63.0% yield); m.p. 144-145°C (Lit. 143-145°C)[59], ^{1}H-NMR : 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.11 (3H, s), 3.72 (1H, ddd, J=10.0, 4.5, 2.4, C_5-H), 4.13 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.14 (1H, dd, J=12.0, 2.5, C_6-H_a), 4.26 (1H, dd, J=12.0, 4.5, C_6-H_b), 4.80 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.84 (1H, d, J=7.3, C_1-H), 5.10 (1H, broad t, J=10.0, C_2-H), 5.14 (1H, t, J=10.0, C_4-H), 5.24 (1H, broad t, J=10.0, C_3-H).

2,2,2-Trichloroethyl β-D-glucopyranoside (13)

To a suspension of 12 (4.79 g, 10 mM) in MeOH (70 ml), 28% NaOMe in MeOH (0.4 ml, 2 mM) was added at 0°C. The

reaction mixture was stirred for 1 h at room temperature. After treatment with Amberlite IR-120B (H+) ion-exchange resin, the resin was filtered off and washed with MeOH. The combined filtrate and washings were evaporated in vacuo to give a colorless syrup, which was triturated from EtOAc to afford colorless crystals (2.85 g, 91.4% yield); m.p. 148-149°C; $[\alpha]_D$ -36.3° (H_2O). Anal.Calcd.for $C_8H_{13}O_6Cl_3$: C, 30.82; H, 4.17. Found: C, 30.91; H, 4.25.

2,2,2-Trichloroethyl 6-O-trityl-β-D-glucopyranoside (14)

To a solution of **13** (2.49 g, 8 mM) and trityl chloride (2.68 g, 9.6 mM) in anhydrous dioxane, Et_3N (5.6 ml) was added dropwise. The solution was kept at 100°C for 1 h, then cooled and diluted with EtOAc. The organic layer was washed with a saturated NH_4Cl solution and with brine, dried over Na_2SO_4, and concentrated. The product was purified on a silica gel column (Wacogel C-100, 40 g, 12 cm x 3 cm) eluted with CH_2Cl_2 to give **14** as a syrup (3.84 g, 86.9% yield), which was triturated from n-hexane to afford colorless crystals; m.p. 74-76°C; $[\alpha]_D$ -17.3° (dioxane), UV λ_{max}^{EtOH} nm(ϵ): 260 (760), 254 (680). Anal. Calcd. for $C_{27}H_{27}O_6Cl_3$: C, 58.54; H, 4.88. Found: C, 58.82; H, 5.27.

2,2,2-Trichloroethyl 2,3,4-tri-O-acetyl-6-O-trityl-β-D-glucopyranoside (15)

Compound **14** (1.66 g, 3 mM) and NaOAc (986 mg, 12 mM) were dissolved in Ac_2O (40 ml). The reaction mixture was kept at 100°C for 1 h with vigorous stirring. The cooled

mixture was worked-up by the standard method. The residual Ac_2O was removed as the EtOH azeotrope. The viscous product was crystallized from EtOH / n-hexane to afford colorless crystals (1.84 g, 90.6% yield); m.p. 126-128°C; $[\alpha]_D$ 17.2°; UV λ_{max}^{EtOH} nm(ϵ): 262 (790), 255 (740) ; IR ν_{max}^{kBr} cm^{-1}: 1760 (C=O), 1220 (C-O); ^{1}H-NMR: 1.75 (3H, s), 2.01 (3H, s), 2.07 (3H, s), 3.11 (1H, dd, J=10.0, 4.5, C_6-H_a), 3.31 (1H, dd, J=10.0,2.5, C_6-H_b), 3.61 (1H, ddd, J=10.0, 4.5, 2.5, C_5-H), 4.23 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.46 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.84 (1H, d, J=7.5, C_1-H), 5.19 (1H, t, J=10.0, C_2-H), 5.24 (1H, t, J=10.0, C_4-H), 5.25 (1H, t, J=10.0, C_3-H), 7.34 (15H, broad, trityl). Anal. Calcd. for $C_{33}H_{33}O_9Cl_3$: C, 58.28; H, 4.86. Found: C, 58.27; H, 4.88.

2,2,2-Trichloroethyl 2,3,6-tri-O-acetyl-β-D-glucopyranoside (17)

A solution of compound **15** (1.02 g, 1.5 mM) in CH_2Cl_2 (20 ml) was stirred in the presence of p-toluenesulfonic acid (517 mg, 3 mM) at r.t. for 3 h. The solution was worked-up by the standard method. The product was purified on a silica gel column (Wacogel C-100, 20 g, 8 cm x 2.5 cm) eluted with CH_2Cl_2 to give **17** as an oil, which was crystallized from EtOH / n-hexane to afford colorless crystals (569 mg, 86.8% yield); m.p. 136-138°C ; $[\alpha]_D$ -59.2°; IR ν_{max}^{kBr} cm^{-1}: 3550 (OH), 1740 (C=O), 1230 (C-O); ^{1}H-NMR : 2.07 (3H, s), 2.11 (3H, s), 2.15 (3H, s), 3.54 (1H,

ddd, J=10.0, 4.5, 2.0, C_5-H), 3.58 (1H, broad, C_4-H), 4.15 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.34 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.41 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.51 (1H, dd, J=12.0, 4.5, C_6-H_b), 4.83 (1H, d, J=7.5, C_1-H), 5.06 (1H, t, J=9.5, C_2-H), 5.10 (1H, t, J=10.0, C_3-H). Anal. Calcd. for $C_{14}H_{19}O_9Cl_3$: C, 38.40; H, 4.34. Found: C, 38.70; H, 4.29.

2,2,2-Trichloroethyl 2,3,6-tri-O-acetyl-4-O-benzyl-β-D-glucopyranoside (9)

Compound 17 (44 mg, 0.1 mM) was dried over P_2O_5 in a vacuum desiccator, and molecular sieves 4A powder (100 mg) was dried over night in a 120°C oven before use. A solution of 17 in anhydrous CH_2Cl_2 (1 ml) was added to a stirred suspension of molecular sieves in anhydrous cyclohexane (1 ml). To this reaction mixture, benzyltrichloroacetimidate[12] (56 μl, 0.3 mM)[41] was added. After stirring this mixture at room temperature for 30 min, CF_3SO_3H (8 μl, 0.05 mM) was added. The reaction mixture was then kept at room temperature for an additional 5.5 h. The mixture was worked-up by the standard method to give a colorless oil. This oil was purified by P-TLC (EtOAc / n-hexane (1:4)) to give 9 (27.5 mg, 51.8% yield) which was crystallized from EtOH, m.p. 156-158°C; $[\alpha]_D$ -38.2° ; UV $\lambda_{max}^{dioxane}$ nm(ε): 259(180), 253 (140), 266(140); IR ν_{max}^{KBr} cm^{-1} : 1730 (C=O), 1230 (C-O) ; ^{1}H-NMR: 2.00 (3H, s), 2.06 (3H, s), 2.08 (3H, s), 3.62 (1H, ddd, J=10.0, 4.5, 2.0, C_5-H), 3.72 (1H, t, J=8.5, C_4-H), 4.13 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.22 (1H, dd, J=12.0, 4.0, C_6-H_a), 4.40 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.44 (1H, dd,

J=12.0,2.0, C_6-H_b), 4.46 (1H, d, J=11.0, benzyl), 4.56 (1H, d, J=11.0, benzyl), 4.82 (1H, d, J=7.5, C_1-H), 5.03 (1H, t, J=8.5, C_2-H), 5.31 (1H, d, J=8.5, C_3-H), 7.30 (5H, phenyl). Anal. Calcd. for $C_{21}H_{25}O_9Cl_3$: C, 47.78; H, 4.74. Found: C, 48.02; H, 4.73.

2,2,2-Trichloroethyl 3,4,6-tri-O-acetyl-2-O-benzyl-β-D-glucopyranoside (24) and 2,2,2-trichloroethyl 2,4,6-tri-O-acetyl-3-O-benzyl-β-D-glucopyranoside (25)

To a solution of the compound **17** (44 mg, 0.1 mM) and benzyl bromide (25.7 mg, 0.15 mM) dissolved in DMF (3 ml), NaH, 60% dispersion in mineral oil, (6 mg, 0.15 mM) was added at 0°C. After stirring for 30 min at 0°C, the reaction mixture was partitioned between Et_2O and brine. The Et_2O layer was dried over sodium sulfate and evaporated *in vacuo* to give a colorless oil which was purified by P-TLC (EtOAc / n-hexane (1:3)). The benzylated compound **9** (Rf-value = 0.5) was obtained in 17.0% yield (9 mg). Another separated fraction (Rf-value = 0.25, 8 mg) was further purified by P-TLC (CH_2Cl_2 / n-hexane (2:1) three times) to afford compound **24** (Rf-value = 0.47, 4 mg, 7.6% yield) and compound **25** (Rf-value = 0.40, 2 mg, 3.8% yield).

Compound **24**; ^{1}H-NMR: 1.94 (3H, s), 2.02 (3H, s), 2.10 (3H, s), 3.53 (1H, dd, J= 9.7, 7.7, C_2-H), 3.71 (1H, ddd, J= 9.5, 4.2, 2.2, C_5-H), 4.14 (1H, dd, J= 12.0, 2.2, C_6-H_a), 4.23 (1H, d, J= 11.7, $-OCH_2CCl_3$), 4.30 (1H, dd, J=12.0, 4.2, C_6-H_b), 4.53 (1H, d, J= 11.7, $-OCH_2CCl_3$), 4.68 (1H, d,

J=11.8, benzyl), 4.80 (1H, d, J=7.7, C_1-H), 4.95 (1H, d, J=11.8, benzyl), 4.99 (1H, t, J=9.5, C_4-H), 5.17 (1H, t, J=9.5, C_3-H), 7.26-7.44 (5H, m, phenyl).

Compound 25; ^{1}H-NMR: 1.98 (3H, s), 2.04 (3H, s), 2.10 (3H, s), 3.63 (1H, ddd, J=9.5, 4.5, 2.0, C_5-H), 3.74 (1H, t, J=9.5, C_3-H), 4.13 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.14 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.22 (1H, dd, J=12.0, 4.5, C_6-H_b), 4.40 (1H, d, J=12.0,$-OCH_2CCl_3$), 4.59 (1H, d, J=12.0, benzyl), 4.65 (1H, d, J=12.0, benzyl), 4.76 (1H, d, J=8.0, C_1-H), 5.15 (1H, t, J=9.5, C_4-H), 5.17 (1H, dd, J=9.5, 8.0, C_2-H), 7.20-7.42 (5H, m, phenyl).

2,2,2-Trichloroethyl 2,3,6-tri-O-acetyl-4-O-methylthiomethyl-β-D-glucopyranoside (26)

Compound 17 (44 mg, 0.1 mM) dissolved in dimethylsulfoxide (0.5 ml) was mixed with AcOH (0.5 ml) and Ac_2O (0.5 ml) and then heated at 100°C for 1 h. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The residual solvents were removed as the EtOH azeotrope. The product was crystallized from EtOH / n-hexane (31.7 mg, 63.4% yield), m.p. 141-143°C ; $[\alpha]_D$ 4.0°; IR ν_{max}^{KBr} cm^{-1} : 1740 (C=O), 1230 (C-O) ; ^{1}H-NMR: 2.05 (3H, s), 2.09 (3H, s), 2.13 (3H, s), 2.15 (3H, s), 3.60 (1H, ddd, J=10.0, 5.0, 2.5, C_5-H), 3.84 (1H, t, J=9.5, C_4-H), 4.13 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.35 (1H, dd, J=12.0, 4.0, C_6-H_a), 4.38 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.45 (1H, dd, J=12.0, 2.0, C_6-H_b), 4.68 (2H, s, $-CH_2SCH_3$), 4.82 (1H, d, J=9.0, C_1-H), 5.02 (1H, dd, J=9.5,7.5, C_2-H), 5.25

(1H, t, J=9.0, C_3-H). Anal. Calcd. for $C_{16}H_{23}O_9Cl_3S$: C,38.59; H, 4.62. Found: C, 38.73 ; H, 4.59.

2,2,2-Trichloroethyl 2,3,6-tri-O-acetyl-4-O-diphenylmethyl-β-D-glucopyranoside (27)

To a solution of 17 (65 mg, 0.15 mM) and benzhydrol (138 mg, 0.75 mM) in anhydrous CH_2Cl_2 (1 ml), P_2O_5 (about 300 mg) was added, and the mixture was stirred at room temperature for 15 min. The mixture was poured into a stirred suspension of EtOAc (5 ml) and $NaHCO_3$ (300 mg), and then diluted with H_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by P-TLC (CH_2Cl_2 / n-hexane (2:1)) to yield colorless crystals (60.4 mg, 66.7% yield); m.p. 154-155°C; $[\alpha]_D$ 3.1°; UV $\lambda_{max}^{dioxane}$ nm(ϵ): 260(400), 254(350), 266(310) ; IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O), 1235 (C-O) ; ^{1}H-NMR : 1.66 (3H, s), 1.94 (3H, s), 2.03 (3H, s), 3.66 (1H, ddd, J=10.0, 4.0, 2.0, C_5-H), 3.84 (1H, dd, J=12.0, 4.0, C_6-H_a), 3.90 (1H, t, J=9.0, C_4-H), 4.10 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.23 (1H, dd, J=12.0, 2.0, C_6-H_b), 4.35 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.84 (1H, d, J=8.0, C_1-H), 4.96 (1H, dd, J=8.5,7.5, C_2-H), 5,35 (1H, t, J=9.0, C_3-H), 5.50 (1H, s, $-CH(C_6H_5)_2$), 7.24-7.29 (10H, m, phenyl). Anal. Calcd. for $C_{27}H_{29}O_9Cl_3$: C, 53.69 ; H, 4.80. Found: C, 53.69 ; H, 4.79.

2,2,2-Trichloroethyl 2,3,6-tri-O-acetyl-4-O-methoxymethyl-β-D-glucopyranoside (28)

To a solution of 17 (44 mg, 0.1 mM) and methyral (88 μl, 1 mM) in anhydrous CH_2Cl_2 (1 ml), P_2O_5 (about 200 mg) was added. The reaction mixture was stirred at room temperature for 10 min. The mixture was worked-up in the same way as that of 27 to give a colorless oil. The product was crystallized from EtOH /n-hexane (37.2 mg, 76.6% yield); m.p. 89-90°C; $[\alpha]_D$ -34.8°; IR ν_{max}^{KBr} cm^{-1} : 1745 (C=O) 1235 (C-O) ; ^{1}H-NMR : 2.06 (3H, s), 2.08 (3H, s), 2.12 (3H, s), 3.32 (3H, s, $-OCH_2OC\underline{H}_3$), 3.61 (1H, ddd, J=9.5, 4.5, 2.0, C_5-H), 3.74 (1H, dd, J=9.5, 9.0, C_4-H), 4.13 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.24 (1H, dd, J=12.0, 4.5, C_6-H_a), 4.39 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.42 (1H, dd, J=12.0, 2.5, C_6-H_b), 4.58 (1H, d, J=6.5, $-OC\underline{H}_2OCH_3$), 4.68 (1H, d, J=6.5, $-OC\underline{H}_2OCH_3$), 4.83 (1H, d, J=7.5, C_1-H), 5.01 (1H, dd, J=9.5, 8.0, C_2-H), 5.22 (1H, dd, J=9.0, 8.5, C_3-H). Anal. Calcd. for $C_{16}H_{23}O_{10}Cl_3$: C, 39.88 ; H, 4.78. Found: C, 38.83 ; H, 4.63.

2,2,2-Trichloroethyl 2,3,6-tri-O-benzoyl-4-O-methoxymethyl-β-D-glucopyranoside (30)

Method A: To a stirred solution of 28 (169 mg, 0.35 mM) in MeOH (4 ml), 28% NaOMe in MeOH (0.14 ml, 0.7 mM) was added at 0°C. The suspension was then stirred at room temperature for 1 h. The reaction mixture was worked-up in the same way as that of 13 to give a colorless oil. After the residue was dissolved in anhydrous pyridine (2 ml), benzoyl chloride (243 μl, 2.1 mM) was added. The solution was heated at 50°C for 1.5 h, cooled, and then worked-up by the standard method . The residual pyridine was

removed as the ethanol azeotrope. The product was purified by P-TLC (EtOAc / n-hexane (1:4)) to afford **30** (149.8 mg, 63.5% overall yield).

Method B: A solution of **32** (50 mg, 0.08 mM) in anhydrous CH_2Cl_2 (1 ml) was treated with methyral (88 μl, 1 mM) and P_2O_5 (about 200mg), and stirred at room temperature for 10 min. The mixture was worked-up in the same way as that of **27** to give a colorless oil (42.2 mg, 77.5% yield). The product was crystallized from EtOH.

Compound **30**; m.p. 84-85°C; $[\alpha]_D$ 51.5°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 275 (2680), 283 (2150) ; IR ν_{max}^{kBr} cm^{-1} : 1725 (C=O), 1275 (C-O); ^{1}H-NMR : 3.17 (3H, s, $-OCH_2OC\underline{H}_3$), 3.93 (1H, ddd, J=9.5, 4.0, 2.0, C_5-H), 4.11 (1H, t, J=9.5, C_4-H), 4.16 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.40 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.56 (1H, dd, J=12.0, 4.0, C_6-H_a), 4.57 (1H, d, J=7.0, $-OC\underline{H}_2OCH_3$), 4.69 (1H, d, J=7.0, $-OC\underline{H}_2OCH_3$), 4.75 (1H, dd, J=12.0, 2.5, C_6-H_b), 5.09 (1H, d, J=8.0, C_1-H), 5.48 (1H, dd, J=10.0, 7.5, C_2-H), 5.74 (1H, dd, J=9.5, 9.0, C_3-H), 7.25-8.12 (15H, m, phenyl). Anal. Calcd. for $C_{31}H_{29}O_{10}Cl_3$: C, 55.73 ; H, 4.34. Found: C, 55.32 ; H, 4.34.

2,2,2-Trichloroethyl 2,3,4-tri-O-benzoyl-6-O-trityl-β-D-glucopyranoside (31)

A solution of **14** (444 mg, 0.8 mM) dissolved in anhydrous pyridine (8 ml) was treated with benzoyl chloride (931 μl, 8 mM) at 50°C for 4 h. The solution was worked-up by the standard method. The residual pyridine was removed as the

EtOH azeotrope. The resulting brown oil was purified by P-TLC (EtOAc / n-hexane (1:4)) to give **31** as colorless crystals (604 mg, 87.1% yield). The crystals obtained were recrystallized from EtOH; m.p. 92-94°C; $[\alpha]_D$ -5.2° ; UV $\lambda_{max}^{dioxane}$ nm(ϵ) : 275 (3170), 283 (2430); IR ν_{max}^{KBr} cm^{-1} : 1740 (C=O), 1275 (C-O); ^{1}H-NMR : 3.29 (1H, dd, J=12.0,4.0, C_6-H_a), 3.44 (1H, dd, J=12.0, 2.0, C_6-H_b), 3.85-3.98 (1H, m, C_5-H), 4.29 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.52 (1H, d, J=12.0, $-OCH_2CCl_3$), 5.15 (1H, d, J=7.5, C_1-H), 5.65 (1H, dd, J=9.0, 7.5, C_2-H), 5.72 (1H, t, J=9.0, C_4-H), 5.84 (1H, t, J=9.5, C_3-H), 7.12-7.98 (30H, m, phenyl). Anal. Calcd. for $C_{48}H_{39}O_9Cl_3$: C, 66.55 ; H, 4.51. Found: C, 66.54 ; H, 4.52.

2,2,2-Trichloroethyl 2,3,6-tri-O-benzoyl-β-D-glucopyranoside (32)

To a solution of **31** (260 mg, 0.3 mM) in $ClCH_2CH_2Cl$ (3 ml), p-toluenesulfonic acid (206 mg, 1.2 mM) was added. After heating at 60°C for 3 h, the mixture was worked-up by the standard method. The residue was purified by P-TLC (EtOAc / n-hexane (1:4)) to afford **32** (129.5 mg, 69.1% yield), which was crystallized from EtOH / n-hexane; m.p. 192-193°C; $[\alpha]_D$ 42.3°; UV $\lambda_{max}^{dioxane}$ nm(ϵ): 275 (2760), 282 (2220) ; IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1725 (C=O), 1280 (C-O) ; ^{1}H-NMR : 3.77-4.02 (1H, m, C_5-H), 3.96 (1H, t, J=8.5, C_4-H), 4.19 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.43 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.66 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.83 (1H, dd, J=12.0, 4.0, C_6-H_b), 5.10 (1H, d, J=8.0, C_1-H), 5.42-5.63 (2H, m, C_2-H,C_3-H), 7.26-8.12 (15H, m, phenyl). Anal. Calcd.

for $C_{29}H_{25}O_9Cl_3$: C, 55.81 ; H, 4.01. Found: C, 55.83 ; H, 3.93.

2,2,2-Trichloroethyl 2,3,6-tri-O-benzoyl-4-O-monochloroacethyl-β-D-glucopyranoside (33)

A solution of **32** (50 mg, 0.08 mM) in EtOAc (2 ml) was treated with chloroacetic anhydride (136 mg, 0.8 mM) and pyridine (323 μl, 4 mM) at 0°C. After 10 min, the mixture was worked-up by the standard method. The residual pyridine was removed as the EtOH azeotrope. The resulting yellow oil was purified by P-TLC (EtOAc / n-hexane (1:4)) to afford colorless crystals (48.1 mg, 81.0% yield), which were recrystallized from EtOH; m.p. 169-170°C; $[\alpha]_D$ 47.1°; UV $\lambda_{max}^{dioxane}$ nm(ϵ) : 275 (2840), 283 (2280); IR ν_{max}^{KBr} cm^{-1} :1730 (C=O), 1255 (C-O); ^{1}H-NMR : 3.93 (1H, s, $-OCOCH_2Cl$), 3.94 (1H, s, $-OCOCH_2Cl$), 4.11 (1H, ddd, J=9.0, 5.0, 2.5, C_5-H), 4.19 (1H, d, J=12.0,$-OCH_2CCl_3$), 4.44 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.53 (1H, dd, J=12.5, 4.0, C_6-H_a), 4.66 (1H, dd, J=12.5, 2.5, C_6-H_b), 5.16 (1H, d, J=8.0, C_1-H), 5.58 (1H, t, J=9.5, C_4-H), 5.59 (1H, dd, J=9.0, 7.5, C_2-H), 5.77 (1H, t, J=9.5, C_3-H), 7.25-8.11 (15H, m, phenyl). Anal. Calcd. for $C_{31}H_{26}O_{10}Cl_4$: C, 53.14 ; H, 3.71. Found: C, 52.64 ; H, 3.60.

2,2,2-Trichloroethyl 2,3,6-tri-O-acetyl-2',3',6'-tri-O-benzyl-4'-O-p-methoxybenzyl-β-D-cellobioside (37) and 2,2,2-trichloroethyl 2,3,6-tri-O-acetyl-2',3',6'-tri-O-benzyl-4'-O-p-methoxybenzyl-β-D-maltoside (38)

Compound **34** (143 mg, 0.2 mM) and compound **17** (50 mg, 0.1 mM) were dried over P_2O_5 in a vacuum desiccator; and powdered molecular sieves 4A (220 mg) were dried overnight in a 120°C oven before use. A solution of **34** and **17** in anhydrous CH_2Cl_2 (1.5 ml) was added to a stirred suspension of molecular sieves in anhydrous CH_2Cl_2 (0.5 ml) below -70°C. To the resulting suspension, 0.1 ml of a solution of BF_3-Et_2O (2.46 μl, 0.02 mM) was added dropwise. The reaction mixture was kept below -70°C for 2 h, filtered and washed with EtOAc. The combined filtrate and washings were worked-up by the standard method to give a colorless syrup. This syrup was purified by P-TLC (EtOAc / n-hexane (1:4) three times and then EtOAc / benzene (5:95) three times) to afford compound **37** (17.3 mg, 16.4% yield) and compound **38** (30.7 mg, 29.0% yield).

Compound **37**; m.p. 86-88°C; UV $\lambda_{max}^{dioxane}$ nm(ϵ): 259 (830), 265(880), 269(900), 275(930), 282(790); IR ν_{max}^{KBr} cm^{-1}: 1753 (C=O), 1241 (C-O); ^{1}H-NMR: 1.99 (3H, s), 2.01 (3H, s), 2.06 (3H, s), 3.77 (3H, s, $-OC_6H_4OCH_3$), 3.81 (1H, t, J=9.0, C_4-H), 4.09 and 4.35 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.18 (1H, dd, J=12.0, 4.5, C_6-H_a), 4.26 (1H, d, J=8.0, C_1,-H), 4,45 (1H, dd, J=12.0, 2.0, C_6-H_b), 4.77 (1H, d, J=8.0, C_1-H), 5.04 (1H, dd, J=9.0, 8.0, C_2-H), 5.22 (1H, t, J=9.0, C_3-H), 6.82 (2H, d, J=8.0, $-OC_6H_4OCH_3$), 7.08 (2H, d, J=8.0, $-OC_6H_4OCH_3$); ^{13}C-NMR: 96.2 ($-CCl_3$), 101.3 (C-1), 102.8 (C-1'), 169.4, 170.1, 170.4 (-OAc). Anal. Calcd. for $C_{49}H_{55}O_{15}Cl_3$: C, 59.42; H, 5.56. Found: C, 51.02; H, 4.80.

Compound **38**: m.p. 173-174°C; UV $\lambda_{max}^{dioxane}$ nm(ϵ): 260

(1070), 266(1260), 269(1320), 276(1430), 282(1220); IR ν_{max}^{KBr} cm^{-1}: 1747(C=O), 1235(C-O); ^{1}H-NMR: 1.94 (3H, s), 2.01 (3H, s), 2.07 (3H, s), 3.77 (3H, s, $-OC_6H_4OC\underline{H}_3$), 3.86 (1H, t, J=9.0, C_4-H), 4.10 and 4.37 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.27 (1H, dd, J=12.0, 4.0, C_6-H_a), 4.60 (1H, dd, J=12.0, 2.0, C_6-H_b), 4.79 (1H, d, J=7.5, C_1-H), 4.80 (1H, d, J=3.5, C_1,-H), 5.07 (1H, dd, J=9.0, 7.5, C_2-H), 5.32 (1H, t, J=9.0, C_3-H), 6.81 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.04 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.2 ($-CCl_3$), 99.1 (C-1'), 101.1 (C-1), 169.4, 169.9, 170.2 (-OAc). Anal. Calcd. for $C_{49}H_{55}O_{15}Cl_3$: C, 59.42; H, 5.56. Found: C, 59.51; H, 5.58.

2. EXPERIMENTAL (Chapter 2. Section 2-1)

2,2,2-Trichloroethyl 4,6-O-benzylidene-β-D-glucopyranoside (42)

To a solution of compound **13** (218 mg, 0.7 mM) and benzaldehyde dimethylacetal[16] (167 μl, 1.1 mM) in dioxane (20 ml), p-toluenesulfonic acid (50 mg, 0.29 mM) was added. The solution was kept at 40°C under 15 mm Hg for 15 min. The solution was worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:2)) to afford compound **42**, which was crystallized from iso-PrOH / n-hexane to give colorless crystals (262 mg, 93.6% yield); m.p. 72-74°C; $[\alpha]_D$ -41.5°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 251(160), 257(190), 263(160), 268(70); ^{1}H-NMR: 2.90 (1H, broad d, J=2.5, C_2-OH), 3.01 (1H, broad s, C_3-OH), 3.49 (1H, td, J=9.5, 5.0, C_5-H), 3.60 (1H, t, J=9.0, C_3-H), 3.65 (1H, t, J=9.0, C_2-H), 3.81 (1H, dd, J=10.0, 9.5, C_6-H_{ax}), 3.87 (1H, t, J=9.0, C_4-H), 4.19 and 4.46 (2H, two d, J=11.0, $-OCH_2CCl_3$), 4.36 (1H, dd, J=10.0, 5.0, C_6-H_{eq}), 4.69 (1H, d, J=7.5, C_1-H), 5.55 (1H, s, $-CHC_6H_5$), 7.27-7.53 (5H, m, phenyl). Anal.Calcd. for $C_{15}H_{17}O_6Cl_3$:C,45.06;H,4.26. Found : C, 46.24;H,4.87.

2,2,2-Trichloroethyl 2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranoside (43)

Compound **43** was obtained from **42** by the standard acetylation method (Ac_2O / NaOAc, at 80°C for 1.5 h, a

quantative yield), and was crystallized from EtOH; m.p. 172-173°C; $[\alpha]_D$ -77.3°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 251(160), 257 (170), 261(150), 268(95); IR ν_{max}^{KBr} cm^{-1}: 1760(C=O), 1235 (C-O); ^{1}H-NMR: 2.07 (3H, s), 2.08 (3H, s), 3.57 (1H, td, J=9.5, 4.5, C_5-H), 3.75 (1H, t, J=9.0, C_6-H_{ax}), 3.83 (1H, t, J=10.0, C_4-H), 4.17 and 4.39 (2H, two d, J=12.0, -OCH_2CCl_3), 4.38 (1H, dd, J=10.0, 4.5, C_6-H_{eq}), 4.92 (1H, d, J=8.0, C_1-H), 5.14 (1H, dd, J=9.0,7.5, C_2-H), 5.38 (1H, t, J=9.5, C_3-H), 5.52 (1H, s, -CHC$_6$H$_5$), 7.35-7.44 (5H, m, phenyl). Anal. Calcd. for $C_{19}H_{21}O_8Cl_3$: C, 47.16; H, 4.34. Found : C, 47.29; H, 4.49.

2,2,2-Trichloroethyl 2,3-di-O-acetyl-6-O-benzyl-β-D-glucopyranoside (39)

Compound **43** (193 mg, 0.4 mM) and powdered molecular sieves 4A (200 mg) were dried over P_2O_5 in a vacuum desiccator before use. To a stirred suspension of **43** and molecular sieves in anhydrous CH_3CN (3 ml), $NaCNBH_3$ (265 mg, 4 mM) was added and then TMSCl (0.5 ml, 4 mM) in anhydrous CH_3CN (1 ml) was added dropwise. The reaction mixture was kept at room temperature for 3 h, filtered, and washed with EtOAc. The combined filtrate and washings were worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:2)) to afford **39** as a syrup (118 mg, 60.8% yield); m.p. 103-104°C; $[\alpha]_D$ -44.8°; IR ν_{max}^{KBr} cm^{-1}: 3424(OH), 1754 (C=O), 1235(C-O); ^{1}H-NMR: 2.06 (3H, s), 2.10 (3H, s), 2.94 (1H, broad d, J=3.5, -OH), 3.59 (1H, dt, J=10.0, 5.0, C_5-H), 3.75-3.85

(1H, m, C_4-H), 3.81 (2H, d, J=5.0, C_6-H_b), 4.14 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.38 (1H, d, J=12.0, $-OCH_2CCl_3$), 4.58 and 4.66 (2H, two d, J=11.0, benzyl), 4.82 (1H, collapsed d, J=8.0, C_1-H), 5.01-5.17 (2H, m, C_2-H, C_3-H). Anal. Calcd. for $C_{19}H_{23}O_8Cl_3$: C, 46.96; H,4.74. Found: C, 46.94; H, 4.70.

2,2,2-Trichloroethyl 2,4,6-tri-O-acetyl-3-O-benzyl-β-D-glucopyranoside (25)

Compound **44** (2.19 g, 5 mM) and powdered molecular sieves 4A (4 g) were dried over P_2O_5 in a vacuum desiccator before use. To a stirred suspension of compound **44** and molecular sieves in anhydrous CH_2Cl_2 (15 ml), anhydrous CCl_3CH_2OH (2.4 ml, 25 mM) was added, and then BF_3-Et_2O (3.1 ml, 25mM) was added dropwise over a period of 30 min at 0°C. The reaction mixture was stirred for an additional 4.5 h at 0°C. The molecular sieves were filtered off and washed with EtOAc. The combined filtrate and washings were worked-up by the standadrd method to give a colorless oil. The residual CCl_3CH_2OH was removed by distillation under reduced pressure. The viscous product was crystallized from EtOH to afford colorless crystals (1.68 g, 63.5% yield), m.p. 98.5-99.5°C; $[\alpha]_D$ -36.3°; UV λ_{max}^{EtOH} nm (ϵ): 253(190), 259 (230), 265(170); IR ν_{max}^{kBr} cm^{-1}: 1747(C=O), 1242(C-O). Anal. Calcd. for $C_{21}H_{25}O_9Cl_3$: C, 47.77; H, 4.74. Found: C, 48.04; H, 4.78.

2,2,2-Trichloroethyl 3-O-benzyl-β-D-glucopyranoside (45)

To a suspension of compound **25** (527 mg, 1mM) in MeOH (10 ml), 28%-NaOMe in MeOH (1 ml, 5 mM) was added. The reaction mixture was kept for 1 h at 50°C, and was neutralized with 1N-hydrochloric acid using 5% phenolphthalein / ethanol solution as an acid-base indicator, and then concentrated. The product was extracted with EtOAc, washed with a 1N-sodium hydroxide solution and with brine, dried over Na_2SO_4 and evaporated in vacuo to give a colorless syrup (362 mg, 90.2% yield), $[\alpha]_D$ -17.9° (MeOH) ; UV λ_{max}^{EtOH} nm (ϵ): 253(150), 259 (190), 265(140). Anal. Calcd. for $C_{15}H_{19}O_6Cl_3$: C, 44,83; H, 4.73. Found: C, 46.45; H, 5.00.

2,2,2-Trichloroethyl 3-O-benzyl-6-O-trityl-β-D-glucopyranoside (46)

To a solution of compound **45** (922 mg, 2.3 mM) and trityl chloride (1.42 g, 4.6 mM) in anhydrous dioxane (25 ml), Et_3N (1.6 ml, 11.5 mM) was added dropwise. The solution was stirred at 100°C for 5 h, cooled, and then diluted with EtOAc. The organic layer was washed with a saturated NH_4Cl solution and with brine, dried over Na_2SO_4 and concentrated. The product was purified on a silica gel column (Wacogel C-200, 60 g, 18 cm x 3 cm) eluted with EtOAc / n-hexane (1:9) to give a colorless oil (1.23 g, 83.1% yield), The prodct was crystallized from EtOH; m.p. 74-75°C; $[\alpha]_D$ -31.3°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 254(920), 259(970). Anal. Calcd. for $C_{34}H_{33}O_6Cl_3$: C, 63.40; H, 5.13. Found: C, 63.34; H, 5.12.

2,2,2-Trichloroethyl 2,4-di-O-acetyl-3-O-benzyl-6-O-trityl-

β-D-glucopyranoside (47)

Comound 47 was obtained from 46 by the standard acetylation method (Ac_2O / NaOAc at 100°C for 1 h, a quantitative yield), and was crystallized from EtOH / n-hexane; m.p. 144-145°C; $[\alpha]_D$ -5.3°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 254(990), 259(1040); IR ν_{max}^{KBr} cm^{-1}: 1754(C=O), 1222(C-O); ^{1}H-NMR: 1.70 (3H, s), 2.05 (3H, s), 3.12 (1H, dd, J=10.5, 5.0, C_6-H_a), 3.21 (1H, dd, J=10.5, 2.5, C_6-H_b), 3.45-3.56 (1H, m, C_5-H), 3.68 (1H, t, J=9.5, C_3-H), 4.22 and 4.46 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.56 and 4.62 (2H, two d, J=12.0, benzyl), 4.77 (1H, d, J=8.0, C_1-H), 5.20 (1H, t, J=9.3, C_4-H), 5.21 (1H, dd, J=9.5, 8.0, C_2-H), 7.19-7.49 (20H, m, phenyl). Anal. Calcd. for $C_{38}H_{37}O_8Cl_3$: C, 62.68; H, 5.09. Found: C, 63.57; H, 5.39.

2,2,2-Trichloroethyl 2,6-di-O-acetyl-3-O-benzyl-β-D-glucopyranoside (40)

To a solution of compound 47 (949 mg, 1.27 mM) in CH_2Cl_2 (30 ml), p-toluenesulfonic acid (437 mg, 2.54 mM) was added. The solution was stirred at room temperature for 3 h, and then worked-up by the standard method to give a yellow oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:4)) to afford compound 40 (504.6 mg, 78.6% yield), which was crystallized from EtOH / n-hexane; m.p. 110-111°C; $[\alpha]_D$ -43.0°; UV λ_{max}^{EtOH} nm (ϵ) :252(140), 258(170), 265(130); IR ν_{max}^{KBr} cm^{-1}: 3424(OH), 1747(C=O), 1248(C-O); ^{1}H-NMR: 2.05 (3H, s), 2.12 (3H, s), 3.43-3.55 (1H, m, C_5-H), 3.53-

3.65 (2H, m, C_3-H, C_4-H), 4.11 and 4.38 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.30 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.47 (1H, d, J=12.0, 4.0, C_6-H_b), 4.71 and 4.78(2H, two d, J=11.5, benzyl), 4.72 (1H, d, J=8.0, C_1-H), 5.07 (1H, colapsed dd, J=9.5, 8.0, C_2-H), 7.28-7.48 (5H, m, phenyl). Anal. Calcd. for $C_{19}H_{23}O_8Cl_3$: C, 46.96; H, 4.74. Found: C, 47.14; H, 4.80.

2,2,2-Trichloroethyl 3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (48)

Compound **48** was obtained from compound **45** in the same way that compound **42** was obtained from compound **13**, ($PhCH(OMe)_2$ / p-TsOH / dioxane at 40°C under 15 mmHg for 20 min, 89.3% yield); m.p. 103-104°C; $[\alpha]_D$ -37.3°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 252(230), 258(280), 262(260); ^{1}H-NMR: 2.61 (1H, broad s, -OH), 3.48 (1H, m, C_5-H), 3.67-3.75 (3H, m, C_2-H, C_3-H, C_4-H), 3.81 (1H, t, J=10.0, C_6-H_{ax}),4.18 and 4.44 (2H, two d, J=11.5, $-OCH_2CCl_3$), 4.36 (1H, dd, J=10.0, 5.0, C_6-H_{eq}),4.67 (1H, collapsed d, J=7.5, C_1-H), 4.82 and 4.92 (2H, two d, J=11.5, benzyl), 5.58 (1H, s, $-CHC_6H_5$), 7.25-7.53 (10H, m, phenyl). Anal. Calcd. for $C_{22}H_{23}O_6Cl_3$: C, 53.93; H, 4.70. Found: C, 53.81; H, 4.72.

2,2,2-Trichloroethyl 2-O-acetyl-3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (49)

Compound **49** was prepared from **48** by the standard acetylation method (Ac_2O / NaOAc at 80°C for 4 h, a quantitative yield), and was crystallized from EtOH; m.p.

132-133°C; $[\alpha]_D$ -21.7°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 252(130), 258(180), 263(140); IR ν_{max}^{KBr} cm^{-1}: 1747(C=O), 1242(C-O); ^{1}H-NMR: 2.02 (3H, s), 3.47 (1H, t, J=9.0, C_5-H), 3.75 (1H, t, J=8.5, C_3H), 3.81 (1H, t, J=9.0, C_4-H), 3.83 (1H, t, J=10.0, C_6-H_{ax}), 4.12 and 4.36 (2H, two d, J=12.0, -OCH_2CCl_3), 4.36 (1H, dd, J=10.0, 5.0, C_6-H_a), 4.68 and 4.88(2H, two d, J=12.0, benzyl), 4.78 (1H, d, J=7.5, C_1-H), 5.12 (1H, colapsed t, J=8.5, C_2-H), 5.59 (1H, s, -CHC_6H_5), 7.29-7.47 (10H, m, phenyl). Anal. Calcd. for $C_{24}H_{25}O_7Cl_3$: C, 54.19; H, 4.70. Found: C, 54.28; H, 4.68.

2,2,2-Trichloroethyl 2-O-acetyl-3,6-di-O-benzyl-β-D-glucopyrnoside (41)

Compound 41 was obtained as a syrup from 49 in the same way that compound 39 was obtained from compound 43, ($NaCNBH_3$ / TMSCl / anhydrous CH_3CN at r.t. for 15 h, about 60% yield); $[\alpha]_D$ -23.2°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 252(340), 258 (420), 263(320), 266(300), 268(210); IR ν_{max}^{KBr} cm^{-1}: 3488(OH), 1747(C=O), 1241(C-O); ^{1}H-NMR: 2.04 (3H, s), 2.68 (1H, broad s, -OH), 3.49 (1H, dt, J=10.0, 5.0, C_5-H), 3.55 (1H, t, J=9.0, C_3-H), 3.70 (1H, broad t, J=10.0, C_4-H), 3.76 (2H, d, J=5.0, C_6-H), 4.12 and 4.37 (2H, two d, J=11.5, -OCH_2CCl_3), 4.56 and 4.63 (2H, two d, J=12.0, benzyl), 4.71 (1H, d, J=8.0, C_1-H), 4.71 and 4.77 (2H, two d, J=11.5, benzyl), 5.08 (1H, dd, J=9.5, 8.0, C_2-H). Anal. Calcd. for $C_{24}H_{27}O_7Cl_3$: C, 53.98; H, 5.06. Found: C, 54.13; H, 5.10.

Glycosylation between imidate 34 and aglycons 39-41

Imidate **34** (143 mg, 0.2mM) and aglycon (0.1 mM) were dried over P_2O_5 in a vacuum desiccator; and powdered molecular sieves 4A (220 mg) were dried overnight in a 120°C oven before use. A solution of imidate and aglycon in anhydrous CH_2Cl_2 (1.5 ml) was added to a stirred suspension of molecular sieves in anhydrous CH_2Cl_2 (0.5 ml) cooled below -70°C. To this reaction mixture, BF_3-Et_2O (2.46 μl, 0.02 mM) in anhydrous CH_2Cl_2 (0.1 ml) was added dropwise over a period of 10 min below -70°C. The reaction mixture was then kept below -70°C for the prescribed time (Table 1), and then filtered. The residual molecular sieves were washed with EtOAc. The combined filtrate and washings were worked-up by the standard method to give a yellow oil. The oil was purified by P-TLC developed with the following solvent combinations (v/v) to afford the corresponding glycoside: aglycon **39**, EtOAc / n-hexane (1:4) twice and then EtOAc / benzene (5:95) five times; aglycon **40**, EtOAc / n-hexane (1:2) twice; aglycon **41**, EtOAc / n-hexane (1:4) twice.

Compound 51 (β-anomer, 13.0% yield); m.p. 85-87°C; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 254(1140), 259(1450), 263(1540), 276 (1540); IR ν_{max}^{KBr} cm^{-1}; 1760(C=O), 1248(C-O); ^{1}H-NMR: 1.99 (3H, s), 2.06 (3H, s), 3.78 (3H, s, $-OC_6H_4OC\underline{H}_3$), 3.97 (1H, t, J=9.5, C_4-H), 4.12 and 4.38 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.31 (1H, d, J=8.0, C_1-H), 4.78 (1H, d, J=7.5, C_1-H), 5.08 (1H, dd, J=9.5, 7.5, C_2-H), 5.22 (1H, t, J=9.5, C_3-H), 6.80 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.10 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$). Anal. Calcd. for $C_{54}H_{59}O_{14}Cl_3$: C, 62.46; H,

5.69. Found: C, 62.38; H, 5.58.

Glycoside 52 (α-anomer, 33.0% yield); UV $\lambda_{max}^{dioxane}$ nm (ϵ) 254(1890), 259(2110), 269(2110); IR ν_{max}^{KBr} cm^{-1}: 1760(C=O), 1248(C-O); ^{1}H-NMR: 1.90 (3H, s), 2.06 (3H, s), 3.79 (3H, s, $-OC_6H_4OC\underline{H}_3$), 3.96 (1H, dd, J=11.0, 4.0, C_6-H_a), 4.08 (1H, t, J=9.0, C_4-H), 4.13 and 4.40 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.78 (1H, d, J=8.0, C_1-H), 5.01 (1H, d, J=4.0, $C_{1'}$-H), 5.08 (1H, dd, J=9.0, 8.0, C_2-H), 5.35 (1H, t, J=9.0, C_3-H), 6.80 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.02 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$). Anal. Calcd. for $C_{54}H_{59}O_{14}Cl_3$: C, 62.46; H, 5.69. Found: C, 61.97; H, 6.41.

Glycoside 53 (β-anomer, 94.2% yield); m.p. 105°C; $[\alpha]_D$ 2.9°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 260(1510), 266(1710), 269(1740), 275(1790), 282(1510); IR ν_{max}^{KBr} cm^{-1}: 1747(C=O), 1235(C-O); ^{1}H-NMR: 1.93 (3H, s), 2.01 (3H, s), 3.77 (3H, s, $-OC_6H_4OC\underline{H}_3$), 3.93 (1H, t, J=9.0, C_4-H), 4.05 and 4.32(2H, two d, J=12.0, $-OCH_2CCl_3$), 4.23 (1H, dd, J=12.0, 4.5, C_6-H_a), 4.47 (1H, d, J=10.0, $C_{1'}$-H), 4.49 (1H, dd, J=12.0,2.5, C_6-H_b), 4.67 (1H, d, J=9.0, C_1-H), 5.04 (1H, dd, J=9.0, 7.5, C_2-H), 6.83 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.12 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.5 ($-CCl_3$), 101.4(C-1), 102.8(C-1'), 169.3,170.3 (-OAc). Anal. Calcd. for $C_{54}H_{59}O_{14}Cl_3$: C, 62.46; H, 5.69. Found: C, 62.70; H, 5.70.

Glycoside 54 (β-anomer, 96.0% yield); $[\alpha]_D$ 3.9°; UV $\lambda_{max}^{dioxane}$ nm (ϵ): 254(970), 260(1240), 265(1310), 278(1240); IR ν_{max}^{KBr} cm^{-1}: 1754(C=O), 1235(C-O); ^{1}H-NMR: 1.93 (3H, s), 3.78 (3H, s, $-OC_6H_4OC\underline{H}_3$), 4.09 and 4.35 (2H, two d,

J=12.0, $-OCH_2CCl_3$), 4.47 (1H, d, J=9.0, C_1,-H), 4.67 (1H, d, J=8.0, C_1-H), 5.06 (1H, dd, J=9.0, 8.0, C_2-H), 6.79 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.07 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$); ^{13}C-NMR:96.6($-CCl_3$),101.6 (C-1), 102.6 (C-1'), 169.3 (-OAc). Anal. Calcd. for $C_{59}H_{63}O_{13}Cl_3$: C, 65.22; H, 5.80. Found. C, 64.92; H, 5.61.

3. EXPERIMENTAL (Chapter 2. Section 2-2)

2,2,2-Trichloroethyl 2,4,6-tri-O-acetyl-3-O-propargyl-β-D-glucopyranoside (59)

Compound **59** was prepared from compound **58** in the same way that compound **25** was prepared from compound **44**, (CCl_3CH_2OH / BF_3-Et_2O / anhydrous CH_2Cl_2, at 0°C for 15 h, 57.9% yield).

2,2,2-Trichloroethyl 3-O-propargyl-β-D-glucopyranoside (60)

Compound **60** was obtained from compound **59** in the same way that compound **45** was obtained from compound **25**, (28%-NaOMe in MeOH / MeOH, at 50°C for 3 h, a quantitative yield).

2,2,2-Trichloroethyl 3-O-propargyl-6-O-trityl-β-D-glucopyranoside (61)

Compound **61** was synthesized from compound **60** in the same way that compound **46** was synthesized from compound **45**, (TrCl / Et_3N / anhydrous dioxane, at 100°C for 3 h, 73.0% yield).

2,2,2-Trichloroethyl 2,4-di-O-acetyl-3-O-propargyl-6-O-trityl-β-D-glucopyranoside (62)

Compound **62** was obtained from compound **61** by the standard acetylation method, (Ac_2O / AcONa, at 100°C for 1 h, a quantitative yield).

2,2,2-Trichloroethyl 2,6-di-O-acetyl-3-O-propargyl-β-D-

glucopyranoside (57)

To a solution of compound **62** (1427 mg, 2.1 mM) in CH_2Cl_2 (20 ml), p-toluenesulfonic acid (730 mg, 4.2mM) was added. The solution was stirred at room temperature for 2.5 h, and then worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:2)) to afford compound **57** (764 mg, 83.2% yield), which was crysallized from EtOH / n-hexane; m.p. 126-127°C; ^{1}H-NMR: 2.15 (3H, s), 2.16 (3H, s), 2.51 (1H, t, J=2.5, -C-C=CH), 3.04 (1H, d, J=2.0, -OH), 3.46-3.72 (3H, m, C_3-H, C_4-H, C_5-H), 4.13 and 4.40 (2H, two d. J=12.0, $-OCH_2CCl_3$), 4.31 and 4.47 (2H, two dd, J=17.0, 2.5, $-CH_2C{=}C$), 4.33 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.48 (1H, dd, J=12.0, 3.5, C_6-H_b), 4.75 (1H, d, J=8.0, C_1-H), 5.02 (1H, dd, J=9.0, 8.0, C_2-H). Anal. Calcd. for $C_{15}H_{19}O_8Cl_3$: C, 41.52; H, 4.38. Found: C, 41.45, H, 4.50.

2,2,2-Trichloroethyl 2,6-di-O-acetyl-3-O-allyl-β-D-glucopyranoside (56)

A solution of compound **57** (15 mg, 0.03 mM) in MeOH (0.7 ml) was treated with 5% $Pd/BaSO_4$ (1 mg) under H_2 at 0°C for 30 min. The reaction mixture was filtered, and evaporated in vacuo to give a oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:2) twice), and then was crystallized from EtOH / n-hexane to give compound **56** (4.6 mg, 30.5% yield) as colorless crystals; m.p. 123-124°C; ^{1}H-NMR: 2.11 (3H, s), 2.13 (3H, s), 2.90 (1H, d, J=4.0, -OH), 3.36-3.63 (3H, m,

C_3-H, C_4-H, C_5-H), 4.11 and 4.38 (2H, two d, J=12.0, -OCH_2CCl_3), 4.21 and 4.22 (2H, two d, J=5.5, -CH_2-C=C), 4.32 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.47 (1H, dd, J=12.0, 2.0, C_6-H_b), 4.72 (1H, d, J=8.0, C_1-H), 5.02 (1H, dd, J=9.0, 8.0, C_2-H), 5.18 (1H, dd, J=10.5, 1.5, -C-C=CH_2cis), 5.26 (1H, dd, J=17.5, 1.5, -C-C=CH_2trans), 5.87 (1H, dddd, J=17.5, 10.5, 5.5, 5.5, -C-CH=C). Anal. Calcd. for $C_{15}H_{21}O_8Cl_3$: C, 41.33; H, 4.82. Found: C, 41.29; H, 4.81.

2,2,2-Trichloroethyl 2,6-di-O-acetyl-3-O-propyl-β-D-glucopyranoside (55)

A solution of compound **57** (94 mg, 0.2mM) in MeOH (2 ml) was treated with Pd-C (63 mg) under H_2 at 0°C for 30 min. The reaction mixture was filtered and concentrated to afford a oil. The oil was crystallized from EtOH / n-hexane (56.2mg, 59.1% yield); m.p. 118-119°C; ^{1}H-NMR: 0.91 (3H, t, J=7.2, -C-C-CH_3), 1.58 (2H, ddddd, J=7.2, 7.2, 7.2, 7.2, 7.2, -C-CH_2-C), 2.12 (3H, s), 2.14 (3H, s), 2.85 (1H, broad d, J=3.0, -OH), 3.39 (1H, t, J=9.5, C_3-H),3.46-3.73 (4H, m, C_4-H, C_5-H,-CH_2-C-C), 4.12 and 4.39 (2H, two d, J=12.0, -OCH_2CCl_3), 4.33 (1H, dd, J=12.0, 2.0, C_6-H_a), 4.45 (1H, dd, J=12.0, 4.0, C_6-H_b), 4.72 (1H, d, J=8.5, C_1-H), 5.00 (1H, dd, J=9.5, 8.5, C_2-H). Anal. Calcd. for $C_{15}H_{23}O_8Cl_3$: C, 41.14; H, 5.26. Found: C, 41.07; H, 5.27.

2,2,2-Trichloroethyl 4,6-O-benzylidene-2,3-di-O-carbamoyl-β-D-gluopyranoside (70)

To a solution of compound **42** (2.36 g, 5.9mM) in pyridine

(15 ml), PhNCO (3.2 ml, 29.5 mM) was added. The solution was kept at 100°C for 5 h. The reaction did not complete, and then PhNCO (1.6 ml, 14.75 mM) was added again. The reaction mixture was kept at 100°C for another 1 h. The excess PhNCO was decomposed by the addition of MeOH (2 ml) at 100°C for 30 min. The reaction mixture was diluted with EtOAc, washed with a 1N-hydrochloric acid solution and with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was exracted with CH_2Cl_2, and then filtered. The filtrate was concentrated to give colorless crystals (2.72 g, 72.2% yield).

2,2,2-Trichloroethyl 4,6-O-benzylidene-2,3-di-O-pivaloyl-β-D-glucopyranoside (71)

To a solution of compound **42** (582 mg, 1.45 mM) in pyridine (7 ml), $(CH_3)_3CCOCl$ (1.8 ml, 14.5 mM) was added. The solution was kept at 50°C for 15 h, and worked-up in the same way as that for compound **70** to give a oil. The product was crystallized from EtOH to afford colorless crystals (596 mg, 72.1% yield).

2,2,2-Trichloroethyl 2,3-di-O-carbamoyl-β-D-glucopyranoside (72)

To a solution of compound **70** (2.7 g, 4.2mM) in 20%-MeOH / CH_2Cl_2 (20 ml), BF_3-Et_2O (2.58 mM, 21mM) was added at 0°C. The solution was stirred at room temperature for 1.5 h, and worked-up by the standard method to afford colorless

crystals which were recrystallized from EtOH / n-hexane (1.7g, 73.0% yield).

2,2,2-Trichloroethyl 2,3-di-O-pivaloyl-β-D-glucopyranoside (73)

Compound **73** was obtained from compound **71** in the same way that compound **72** was obtained from compound **70**, (BF_3-Et_2O / 20%-MeOH / CH_2Cl_2, at r.t. for 3 h, 61.5% yield).

2,2,2-Trichloroethyl 2,3,6-tri-O-carbamoyl-β-D-glucopyranoside (66)

To a solution of compound **72** (60 mg, 0.11 mM) in anhydrous pyridine (2 ml), PhNCO (96 μl, 0.88 mM) was added. The solution was kept at 50°C for 30 min. The excess PhNCO was decomposed by the addition of MeOH (1 ml) at 50°C for 30 min. The solution was extracted with EtOAc, washed with a 1N-hydrochloric acid solution and with brine, dried over Na_2SO_4, and concentrated to give colorless crystals. The product was purified on silica gel column (Wacogel C-200, 24g, 2.5cm x 9.0cm) eluted with EtOAc/n-hexane (1:2) to give compound **66** as crystals (43 mg, 58.9% yield); m.p. 199-200°C; ^{1}H-NMR: 3.20-3.32 (1H, m, C_5-H), 3.30-3.60 (1H, broad s, -OH), 3.60 (1H, t, J=7.5, C_4-H), 4.10 and 4.33 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.36 (1H, broad d, J=11.0, C_6-H_a), 4.43 (1H, broad d, J=11.0, C_6-H_b), 4.81 (1H, d, J=7.5, C_1-H), 4.86 (1H, dd, J=8.0, 7.5, C_2-H), 4.96 (1H, dd, J=8.0, 7.5, C_3-H), 6.94-7.13 (3H, m, -CONHPh), 7.16-7.31 (15H, m, phenyl). Anal. Calcd. for $C_{29}H_{28}O_9Cl_3N_3$: C, 52.06; H, 4.19.

Found: C, 51.79; H, 4.17.

2,2,2-Trichlroethyl 6-O-acetyl-2,3-di-O-carbamoyl-β-D-glucopyranoside (67)

To a solution of compound **72** (121 mg, 0.22 mM) in EtOAc (3 ml), CH_3COCl (63 μl, 0.88 mM) and 2,6-lutidine (128 μl, 1.1 mM) were added. The solution was stirred at 0°C for 4 h, and then worked up in the same way as that for **66** to give a colorless oil. The oil was purified by P-TLC ($MeOH/CH_2Cl_2$ (5:95)) to afford compound **67** (84 mg, 64.5% yield), which was crystallized from EtOH/n-hexane; m.p. 157-159°C; ^{1}H-NMR: 2.14 (3H, s), 3.55-3.80 (2H, m, C_4-H, C_5-H), 4.18 and 4.42 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.41 (1H, broad s, C_6-H_a), 4.43 (1H, broad s, C_6-H_b), 4.88 (1H, d, J-8.0, C_1-H), 4.95-5.15 (2H, m, C_2-H, C_3-H), 7.00-7.12 (2H, m, -CONHPh), 7.14-7.40 (10H, m, phenyl). Anal. Calcd. for $C_{24}H_{25}O_9Cl_3N_2$: C, 48.69; H, 4.23. Found: C, 49.38; H, 4.42.

2,2,2-Trichloroethyl 2,3,6-tri-O-pivaloyl-β-D-glucopyranoside (68)

To a solution of compound **73** (192 mg, 0.4 mM) in $CHCl_3$ (7 ml), $(CH_3)_3CCOCl$ (197 μl, 1.6 mM) and pyridine (162 μl, 2.0 mM) were added. The solution was kept at 50°C for 30hr, and then worked up in the same way as that for **66** to afford a colorless oil. The oil was crystallized from EtOH / n-hexane to give compound **68** (145 mg, 64.3% yield); m.p. 194-195°C; ^{1}H-NMR: 1.20 (9H, s), 1.22 (9H, s), 1.26 (9H, s), 3.15 (1H, d, J=5.0, -OH), 3.45-3.66 (2H, m, C_4-H, C_5-H),

4.14 and 4.32 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.37-4.44 (2H, broad, C_6-H_a, C_6-H_b), 4.87 (1H, collapsed d, J=8.0, C_1-H), 5.00-5.06 (2H, m, C_2-H, C_3-H). Anal. Calcd. for $C_{23}H_{37}O_9Cl_3$: C, 48.98; H, 6.57. Found: C, 48.80; H, 6.67.

2,2,2-Trichloroethyl 2,3-di-O-monochloroacetyl-6-O-trityl-β-D-glucopyranoside (74)

To a solution of compound **14** (101 mg, 0.18 mM) in EtOAc (4 ml), $(ClCH_2CO)_2O$ (468 mg, 2.74 mM) and pyridine (0.74 ml, 9.13 mM) were added at 0°C. The reaction mixture was stirred at 0°C for 20 min, and partitioned between EtOAc and brine. The EtOAc layer was dried over Na_2SO_4 and evaporated *in vacuo* to give an yellow oil which was purified by P-TLC (EtOAc / n-hexane (1:2)) to afford a colorless oil (107 mg, 75.0% yield).

2,2,2-Trichloroethyl 2,3,6-tri-O-monochlroacetyl-β-D-glucopyranoside (69)

To a solution of compound **74** (97 mg, 0.12mM) in CH_2Cl_2 (3.5 ml), p-toluenesulfonic acid (43 mg, 0.25 mM) was added. The reaction mixture was kept at room temperature for 2.5 h, and worked-up by the standard method. The product was purified by P-TLC (EtOAc / n-hexane (1:2)) to afford a colorless oil (47.1 mg, 70.1% yield); m.p. 125-126°C; ^{1}H-NMR: 3.60 -3.71 (1H, m, C_5-H), 3.73(1H, dd, J=9.5, 8.0, C_4-H), 4.06 (2H, s, $-COCH_2Cl$), 4.08 and 4.13 (2H, two d, J=9.0, $-COCH_2Cl$), 4.15 and 4.39 (2H, two d, J=12.0, $-CH_2CCl_3$), 4.16

(2H, s, $-COCH_2Cl$), 4.50-4.56 (2H, m, C_6-H_a, C_6-H_b), 4.91 (1H, d, J=7.5, C_1-H), 5.11 (1H, dd, J=9.5, 7.5, C_2-H), 5.22 (1H, dd, J=9.5, 8.0, C_3-H). Anal. Calcd. for $C_{14}H_{16}O_9Cl_6$: C, 31.05; H, 2.96. Found: C, 31.20; H, 2.92.

Glycosylation between imidate 34 and aglycons 55-57 and 66-69

Imidate **34** (2.0eq) and aglycon (1.0eq) were dried over P_2O_5 in a vacuum desiccator; powdered molecular sieves 4A were dried overnight in a 120°C oven before use. A solution of imidate and aglycon in anhydrous CH_2Cl_2 was added to a stirred suspension of molecular sieves in anhydrous CH_2Cl_2 below -70°C. To this reaction mixture, BF_3-Et_2O (0.2eq) in anhydrous CH_2Cl_2 was added dropwise over a period of 10 min below -70°C. The reaction mixture was kept below -70°C for 1hr, and then filtered. The residual molecular sieves were washed with EtOAc. The combined filtrate and washings were then worked-up by the standard method to afford a syrup. The product was purified by P-TLC developed with the following solvent combinations (v/v) to afford the corresponding glycoside: aglycon **55**, EtOAc/n-hexane (1:4) three times and then EtOAc/benzene (5:95) twice; aglycon **56**, EtOAc/n-hexane (1:2) and then EtOAc/benzene (5:95) twice; aglycon **57**, EtOAc/n-hexane (1:4) twice and then EtOAc/benzene (5:95) twice; aglycon **66**, EtOAc/n-hexane (1:2) twice and then CH_2Cl_2 four times; aglycon **67**, EtOAc/n-hexane (1:3) four times and then MeOH/CH_2Cl_2 (1:99) twice; aglycon **68**, EtOAc/n-hexane (1:4) twice; aglycon **69**, EtOAc/n-hexane

(1:4) twice and then EtOAc/benzene (5:95).

Glycoside 63 (β-anomer, 79.3% yield); m.p. 106-107°C; ^{1}H-NMR: 0.89 (3H, t, J=8.0, -C-C-CH_3), 1.35-1.56 (2H, m, -C-CH_2-C), 1.99 (3H, s), 2.09 (3H, s), 3.77 (3H, S, -OCH_3), 4.06 and 4.32 (2H, two d, J=12.0, -OCH_2CCl_3), 4.41 (1H, d, J=8.0, C_1,-H), 4.68 (1H, d, J=8.0, C_1-H), 5.00 (1H, dd, J=9.5, 8.0, C_2-H), 6.78 (2H, d, J=8.0, -$C_6\underline{H}_4OCH_3$), 7.06 (2H, d, J=8.0, -$C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.4 (-CCl_3), 101.4 (C-1), 102.6 (C-1'). Anal. Calcd. for $C_{50}H_{59}O_{14}Cl_3$: C, 60.64; H, 5.96. Found: C, 60.55; H, 5.87.

Glycoside 64 (β-anomer, 72.5% yield); m.p. 100-102°C; ^{1}H-NMR: 1.99 (3H, s), 2.09 (3H, s), 3.78 (3H, s, -OCH_3), 4.05 and 4.33 (2H, two d, J=12.0, -OCH_2CCl_3), 4.41 (1H, d, J=8.0, C_1,-H), 4.68 (1H, d, J=8.0, C_1-H), 5.19 (1H, dd, J=8.5, 8.0, C_2-H), 5.24 (1H, dd, J=10.5, 1.5, -C-C=CHcis), 5.37 (1H, dd, J=17.0, 1.5, -C-C=CHtrans), 5.82 (1H, ddt, J=17.0, 10.5, 5.3, -C-CH=C), 6.79 (2H, d, J=8.0, -$C_6\underline{H}_4OCH_3$), 7.06 (2H, d, J=8.0, -$C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.5 (-CCl_3), 101.3 (C-1), 102.7 (C-1'). Anal. Calcd. for $C_{50}H_{57}O_{14}Cl_3$: C, 60.75; H, 5.77. Found: C, 60.24; H, 5.75.

Glycoside 65 (β-anomer, 71.7% yield); ^{1}H-NMR: 1.98 (3H, s), 2.11 (3H, s), 2.37 (1H, t, J=2.5, -CH_2-C=C), 3.77 (3H, s, -OCH_3), 4.07 and 4.33 (2H, two d, J=12.5, -OCH_2CCl_3), 4.41 (1H, d, J=8.0, C_1,-H), 4,72 (1H, d, J=8.5, C_1-H), 4.94 (1H, t, J=8.5, C_2-H), 6.78 (2H, d, J=8.0, -$C_6\underline{H}_4OCH_3$), 7.06 (2H, d, J=8.0, -$C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.4 (-CCl_3), 101.3 (C-1), 103.1 (C-1'). Anal. Calcd. for $C_{50}H_{55}O_{14}Cl_3$: C, 60.88;

H, 5.58. Found: C, 59.90; H, 5.41.

Glycoside 75 (β-anomer, 35.3% yield); ^{1}H-NMR: 3.32 (1H, dd, J=10.0, 8.0, C_2,-H), 3.82 (3H, s, $-OCH_3$), 4.18 and 4.42 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.36 (1H, d, J=8.0, C_1,-H), 4.94 (1H, d, J=7.5, C_1-H), 6.82 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.03 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$).

Glycoside 77 (β-anomer, 57.0% yield); ^{1}H-NMR: 2.09 (3H, s), 3.26 (1H, dd, J=9.0, 8.0, C_2,-H), 3.78 (3H, s, $-OCH_3$), 4.16 and 4.40 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.26 (1H, d, J=8.0, C_1,-H), 4.89 (1H, d, J=6.5, C_1-H), 6.85 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.06 (2H, d, J=8.0, $=C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.3 ($-CCl_3$), 101.6 (C-1), 103.4 (C-1').

Glycoside 78 (α-anomer, 7.7% yield); ^{1}H-NMR: 2.09 (3H, s), 3.46 (1H, dd, J=10.0, 3.5, C_2,-H), 3.77 (3H, s, $-OCH_3$), 4.16 and 4.42 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.88 (1H, d, J=7.5, C_1-H), 5.03 (1H, d, J=3.5, C_1,-H), 6.80 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.08 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$).

Glycoside 79 (β-anomer, 23.8% yield); ^{1}H-NMR: 1.20 (9H, s), 1.21 (9H, s), 1.27 (9H, s), 3.77 (3H, s, $-OCH_3$), 4.15 and 4.32 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.41 (1H, d, J=6.5, C_1,-H), 4.87 (1H, d, J=8.0, C_1-H), 6.82 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.06 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.1 ($-CCl_3$), 100.6 (C-1 and C-1').

Glycoside 80 (α-anomer, 55.6% yield); ^{1}H-NMR: 1.17 (9H, s), 1.19 (9H, s), 1.20 (9H, s), 3.77 (3H, s, $-OCH_3$), 4.10 and 4.27 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.85 (1H, d, J=7.0, C_1-H), 5.06 (1H, d, J=3.0, C_1,-H), 6.78 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.03 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 95.8 (C-

1'), 96.0 ($-CCl_3$), 99.8 (C-1).

Glycoside 81 (β-anomer, 3.2% yield); ^{1}H-NMR: 3.78 (3H, s, $-OCH_3$), 3.98 and 4.02 (2H, two d, J=6.5, $-COCH_2Cl$), 4.06 (4H, s, $-COCH_2Cl$), 4.09 and 4.33 (2H, two d, J=11.5, $-OCH_2CCl_3$), 4.26 (1H, d, J=8.0, C_1,-H), 4.83 (1H, d, J=7.5, C_1-H), 5.13 (1H. dd, J=9.5, 7.5, C_2-H), 6.82 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.04 (2H, d, J=8.0, $C_6\underline{H}_4OCH_3$); ^{13}C-NMR: 96.0 ($-CCl_3$), 100.1 (C-1), 100.8 (C-1').

Glycoside 82 (α-anomer, 16.2% yield); ^{1}H-NMR: 3.46 (1H, dd, J=9.5, 3.5, C_2,-H), 3.74 and 3.80 (2H, two d, J=7.0, $-COCH_2Cl$), 4.07 (2H, s, $-COCH_2Cl$), 4.08 (2H, s, $-COCH_2Cl$), 4.13 and 4.39 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.80 (1H, d, J=3.5, C_1,-H), 4.85 (1H, d, J=8.0, C_1-H), 5.35 (1H, dd, J=9.0, 8.0, C_2-H), 6.82 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.04 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$).

4.EXPERIMENTAL (Chapter 3.)

2,4,6-tri-O-acetyl-3-O-benzyl-D-glucopyranose (91)

A solution of compound **25** (300 mg, 0.57 mM) in Ac_2O (5 ml) was treated with zinc powder (930 mg, 14.2 mM) at room temperature for 2 h. The reaction mixture was filtered and washed with EtOAc. The filtrate and washings were worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:2)) to give compound **91** as a oil (154 mg, 68.3% yield).

2,2,2-Trichloroethyl 3-O-benzyl-4,6-O-p-methoxybenzylidene-β-D-glucopyranoside (92)

To a solution of compound **45** (10g, 32mM) and p-methoxybenzaldehyde dimethylacetal (11.7 ml, 64 mM) in dioxane (100 ml), p-toluenesulfonic acid (400 mg) was added. The reaction mixture was kept at 50°C under 15 mmHg for 20 min, and then worked-up by the standard method to give a colorless oil. The oil was crystallized from EtOH / iso-PrOH / n-hexane to afford colorless crystals (11.8 g, 85.5% yield).

2,2,2-Trichloroethyl 2-O-acetyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (95) and 2,2,2-trichloroethyl 2-O-acetyl-3-O-benzyl-6-O-p-methoxybenzyl-β-D-glucopyranoside (97)

Compound **93** (362mg, 0.64mM) and powdered molecular sieves 4A (200mg) were dried over P_2O_5 in a vaccum

desiccator before use. To a stirred suspension of compound **93** and molecular sieves 4A in anhydrous CH_3CN (5ml), $NaCNBH_4$ (243mg, 3.87mM) was added and then TMS-Cl (491 μl, 3.87mM) in anhydrous CH_3CN (1ml) was added dropwise. The reaction mixture was kept at room temperature for 30 min, filtered and washed with EtOAc. The combined filtrate and washings were worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC ($MeOH/CH_2Cl_2$ (1:99)) to afford compounds **95** (140mg, 38.5% yield) and **97** (109mg, 30.0% yield) as syrups.

2,2,2-Trichloroethyl 3-O-benzyl-6-O-p-methoxybenzyl-2-O-pivaloyl-β-D-glucopyranoside (98)

Compound **94** (121mg, 0.2mM) and powdered molecular sieves 4A (100mg) were dried over P_2O_5 in a vaccum desicator before use. To a stirred mixture containing compound **94** and molecular sieves 4A in anhydrous CH_3CN (2.5ml), $NaCNBH_4$ (75.6mg, 1.2mM) was added and then TMS-Cl (153μl, 1.2mM) in anhydrous CH_3CN (0.5mM) was added dropwise. After 3 h, the reaction did not complete yet, and then TMS-Cl (76 μl, 0.6mM) in anhydrous CH_3CN (0.5ml) was added dropwise. The reaction mixture was kept for another 30 min at room temperature, filtered and wored-up by the standard method to yield a colorless oil. The oil was purified by P-TLC ($MeOH/CH_2Cl_2$ (5:95)) to afford compound **98** (73.2mg, 60.3% yield) as a syrup; ^{1}H-NMR : 1.23 (9H, s), 3.46-3.81 (5H, m, C_3-H, C_4-H, C_5-H, C_6-H_a, C_6-H_b), 3.83 (3H, s, $-OCH_3$), 4.19 and 4.36 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.51 and 4.59 (2H, two d, J=12.0,

benzyl), 4.72 and 4.79 (2H, two d, J=12.0, benzyl), 4.80 (1H, d, J=8.0, C_1-H), 5.14 (1H, dd, J=10.0, 8.0, C_2-H), 6.92 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.29 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.30-7.44 (5H, m, phenyl).

2,3,6-tri-O-benzyl-4-O-monochloroacetyl-D-glucopyranose (112)

A mixture of compound 111 (519mg, 0.92mM), SeO_2 (111mg, 1.0mM) and AcOH (57 μl, 1.0mM) in dioxane (5ml) was heated under reflux for 2hr. The reaction mixture was worked-up by standad method to give a brown oil. The oil was purified by P-TLC (EtOAc/n-hexane (1:3)) to afford compound 112 (298mg, 61.9% yield) as crystals; m.p. 104-105°C; ^{1}H-NMR : 3.37-3.63 (2H, m, C_6-H_a, C_6-H_b), 3.52 and 3.63 (2H, two d, J=14.5, $-COCH_2Cl$), 3.62 (1H, dd, J=9.5, 3.5, C_2-H), 3.93 (1H, t, J=9.5, C_3-H), 4.09 (1H, dt, J=9.5, 3.5, C_5-H), 4.42 and 4.51 (2H, two d, J=11.5, benzyl), 4.63 and 4.88 (2H, two d, J=11.5, benzyl), 4.68 and 4.79 (2H, two d, J=11.5, benzyl), 5.06 (1H, dd, J=9.5, 9.5, C_4-H), 5.19 (1H, d, J=3.5, C_1-H), 7.20-7.44 (15H, m, phenyl).

Imidoylation of compounds 91,102,103,105,109,112,116 and 117

To a solution of the respective compound (1.0eq) in anhydrous CH_2Cl_2, DBU (0.2eq) and CCl_3CN (2.0eq) were added. The reaction solution was stirred for 3hr at room temperature, and then evaporated below 25°C to give a yellow oil. The oil was purified by P-TLC developed with the

following solvent combinations (v/v) to give the corresponding imidate: compounds **91,102,105,109** and **116**, EtOAc/n-hexane (1:2) ; compounds **103,112** and **117**, EtOAc/n-hexane (1:4).

Imidate 83; ^{1}H-NMR: 1.96 (3H, s), 2.05 (3H, s), 3.68 (1H, t, J=9.5, C_4-H), 3,82 (3H, s, $-OCH_3$), 3.97-4.11 (1H, m, C_5-H), 4.11 (1H, t, J= 9.5, C_3-H), 4.18-4.40 (2H, m, C_6-H_a, C_6-H_b), 4.53 and 4.80 (2H, two d, J=10.5, benzyl), 4.79 and 4.89 (2H, two d, J=11.0, benzyl), 5.04 (1H, dd, J=9.5, 4.0, C_2-H), 6.44 (1H, d, J=4.0, C_1-H), 6.85 (2H, d, J=8.0, -$C_6H_4OCH_3$), 7.20 (2H, d, J=8.0, -$C_6H_4OCH_3$), 7.25-7.41 (5H, m, phenyl), 8.58 (1H, s, $-C(=NH)CCl_3$).

Imidate 84; ^{1}H-NMR: 1.18 (9H, s), 1.21 (9H, s), 3.67 (1H, t, J=9.5, C_4-H), 3.82 (3H, s, $-OCH_3$), 4.02-4.16 (1H, m, C_5-H), 4.14 (1H, t, J=9.5, C_3-H), 4.24 (1H, dd, J= 12.0, 4.0, C_6-H_a), 4.38 (1H, dd, J= 12.0, 2.0, C_6-H_b), 4.49 and 4.78 (2H, two d, J=10.0, benzyl), 4.82 and 4.87 (2H, two d, J=11.5, benzyl), 5.06(1H, dd, J=10.0, 3.5, C_2-H), 6.52 (1H, d, J=3.5, C_1-H), 6.87 (2H, d, J=8.0, -$C_6H_4OCH_3$), 7.20 (2H, d, J=8.0, -$C_6H_4OCH_3$), 7.26-7.48 (5H, m, phenyl), 8.62 (1H, s, $-C(=NH)CCl_3$).

Imidate 85; ^{1}H-NMR : 3.44 (1H, dd, J=10.0, 3.5, C_6-H_a), 3.53(1H, dd, J=10.0, 3.5, C_6-H_b), 3.56 and 3.64 (2H, two d, J=14.5, $-COCH_2Cl$), 3.81 (1H, dd, J=9.5, 3.5, C_2-H), 3.97 (1H, t, J=9.5, C_3-H), 4.01 (1H, dt, J=10.0, 3.5, C_5-H), 4.40 and 4.50 (2H, two d, J=12.0, benzyl), 4.62 and 4.87 (2H, two d, J=12.0, benzyl), 4.68 and 4.75 (2H, two d, J=11.5, benzyl), 5.23 (1H, dd, J=10.0, 9.5, C_4-H), 6.49 (1H, d,

J=3.5, C_1-H), 7.18-7.42 (15H, m, phenyl), 8.64 (1H, s, -C(=NH)CCl_3).

Imidate 86; ^{1}H-NMR : 1.96 (3H, s), 2.13 (3H, s), 6.61 (1H, d, J=3.5, C_1-H), 8.74 (1H, s, -C(=NH)CCl_3).

Imidate 87; ^{1}H-NMR : 1.20 (9H, s), 1.22(9H, s), 3.66 and 3.85 (2H, two d, J=15.0, -$COCH_2Cl$), 4.02-4.24 (4H, m, C_3-H, C_5-H, C_6-H_a, C_6-H_b), 4.57 and 4.81 (2H, two d, J=11.5, benzyl), 5.08 (1H, dd, J=10.0, 3.5, C_2-H), 5.19 (1H, t, J=10.0, C_4-H), 6.60 (1H, d, J=3.5, C_1-H), 7.22-7.46 (5H, m, phenyl), 8.72 (1H, s, -C(=NH)CCl_3).

Imidate 88; ^{1}H-NMR : 1.91 (3H, s), 1.99 (3H, s), 3.42-3.58 (2H, m, C_6-H_a, C_6-H_b), 3.78 (3H, s, -OCH_3), 3.98-4.16 (1H,m, C_5-H), 4.05 (1H, t, J=9.5, C_3-H), 4.39 and 4.46 (2H, two d, J=12.0, benzyl), 4.62 and 4.71 (2H, two d, J=12.0, benzyl), 5.07 (1H, dd, J=9.5, 3.5, C_2-H), 5.23 (1H, t, J=9.5, C_4-H), 6.56 (1H, d, J=3.5, C_1-H), 6.88 (2H, d, J=8.0, -$C_6H_4OCH_3$), 7.20-7.40 (6H, m, phenyl), 8.63 (1H, s, -C(=NH)CCl_3).

Imidate 89; ^{1}H-NMR : 1.96 (3H, s), 2.05 (3H, s), 3.79 (1H, dd, J=10.0, 4.0, C_2-H), 3.97 (1H, t, J=10.0, C_3-H), 4.00-4.13 (1H, m, C_5-H), 4.06 (1H, dd, J=13.0, 2.5, C_6-H_a), 4.21 (1H, dd, J=13.0, 5.0, C_6-H_b), 4.66 and 4.88 (2H, two d, J=12.0, benzyl), 4.69 and 4.75 (2H, two d, J=12.5, benzyl), 5.10 (1H, t, J=10.0, C_4-H), 6.45 (1H, d, J=4.0, C_1-H), 7.24-7.33 (10H, m, phenyl), 8.64 (1H, s, -C(=NH)CCl_3).

Imidate 90; ^{1}H-NMR : 2.00 (3H, s), 2.01 (3H, s), 2.09 (3H, s), 3.95-4.16 (1H, m, C_5-H), 4.09 (1H, dd, J=13.0, 2.5,

C_6-H_a), 4.12 (1H, t, J=10.0, C_3-H), 4.21 (1H, dd, J=13.0, 5.0, C_6-H_b), 4.64 and 4.73 (2H, two d, J=11.5, benzyl), 5.08 (1H, dd, J=10.0, 4.0,C_2-H), 5.20 (1H, t, J=10.0, C_4-H), 6.54 (1H, d, J=4.0, C_1-H), 7.22-7.40 (5H, m,phenyl), 8.67 (1H, s, -C(=NH)CCl_3).

Glycosylation between imidates 34,83-90 and aglycon 40

The respective imidate (1.0eq) and aglycon **40** (2.0eq) were dried over P_2O_5 in a vacuum desiccator; powdered molecular sieves 4A were dried overnight in a 120 °C oven before use. A solution of imidate and aglycon in anhydrous CH_2Cl_2 was added to a stirred suspension of molecular sieves 4A in anhydrous CH_2Cl_2 below -70°C. To this reaction mixture, BF_3-Et_2O (0.2eq) in anhydrous CH_2Cl_2 was added dropwise below -70°C. The reaction mixture was then kept below -70°C for 1 hr, filtered and washed with EtOAc. The combined filtrate and washings were worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC developed with the following solvent combinations (v/v) to afford the corresponding glycoside : imidate **34**, EtOAc / n-hexane (1:4); imidate **83**, MeOH /CH_2Cl_2 (2:98); imidate **84**, EtOAc / n-hexane (1:2), imidate **85**, CH_2Cl_2.

Glycoside 53 (β-anomer, 82.0% yield).

Glycoside 118 (β-anomer, 60.0% yield); ^{1}H-NMR : 1.90 (3H, s), 1.91 (3H, s), 1.98 (3H, s), 2.13 (3H, s), 3.81 (3H, s, $-OCH_3$), 4.07 and 4.32 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.52 (1H, d, J=8.0, C_1,-H), 4.68 (1H, d, J=8.0, C_1-H), 6.87

(2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.19 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.20-7.46 (10H, m, phenyl).

Glycoside 119 (β-anomer, 57.8% yield); ^{1}H-NMR : 1.16 (9H, s), 1.20(9H, s), 1.89 (3H, s), 2.14 (3H, s), 3.81 (3H, s, $-OCH_3$), 4.07 and 4.34 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.46 (1H, d, J=8.0, C_1,-H), 6.86 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.16 (2H, d, J=8.0, $-C_6\underline{H}_4OCH_3$), 7.22-7.44 (10H, m. phenyl).

Glycoside 120 (β-anomer, 13.5% yield); ^{1}H-NMR : 1.98 (3H, s), 2.05 (3H, s), 3.48 and 3.59 (2H. two d, J=14.5, $-COCH_2Cl$), 4.07 and 4.33 (2H, d, J=12.0, $-OCH_2CCl_3$), 4.43 (1H, d, J=8.0, C_1,-H), 4.69 (1H, d, J=8.0, C_1-H), 7.18-7.40 (20H, m, phenyl).

Glycoside 121 (α-anomer, 3.0% yield); ^{1}H-NMR : 1.96 (3H, s), 2.05 (3H, s), 3.54 and 3.64 (2H, two d, J=14.5, $-COCH_2Cl$), 3.55 (1H, dd, J=9.5, 3.5, C_2,-H), 4.09 and 4.37 (2H, two d, J=12.0, $-OCH_2CCl_3$), 4.76 (1H, d, J=8.0, C_1-H), 5.39 (1H, d, J=3.5, C_1,-H), 7.10-7.40 (20H, m, phenyl).

Allyl 2,4,6-tri-O-acetyl-3-O-benzyl-β-D-glucopyranoside (124)

Compound **44** (1000mg, 2.28mM) was dried over P_2O_5 in a vacuum desiccator. To a solution of compound **44** in anhydrous CH_2Cl_2 (10 ml), allyl alcohol (0.78ml, 11.4mM) was added, and then BF_3-Et_2O (2.8ml, 22.8mM) was added dropwise at 0°C. The reaction solution was kept at 0°C for 4 h. The reaction mixture was worked-up by the standard method to give a yellow oil. The product was crystallized from EtOH / n-

hexane to afford **124** (770mg, 77.4%); m.p. 76-77°C; ^{1}H-NMR: 1.99 (s, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 3.58 (1H, ddd, J= 9.5, 5.0, 2,5, C_5-H), 3.70 (1H, t, J=9.5, C_3-H), 4.07 (1H, ddd, J=13.5, 6.0, 1.5, -CH_2-C=C), 4.11 (1H, dd, J=12.0, 2.5, C_6-H_a), 4.22 (1H, dd, J=12.0, 5.0, C_6-H_b), 4.33 (1H, ddd, J=13.5, 5.0, 1.5, -CH_2-C=C), 4.46 (1H, d, J=8.0, C_1-H), 4.57 (1H, d, J=12.0, benzyl), 4.63 (1H, d, J=12.0, benzyl), 5.09 (1H, dd, J=9.5, 8.0, C_2-H), 5.13 (1H, t, J=9.5, C_4-H), 5.18 (1H, dd, J=10.0, 1.5, -C-C=CHcis), 5.26 (1H, dd, J= 17.5, 1.5, -C-C=CHtrans), 5.84 (1H, dddd, J=17.5, 10.0, 6.0, 5.0, -C-CH=C), 7.20-7.40 (5H, m, phenyl). Anal. Calc. for $C_{22}H_{28}O_9$: C, 60.55; H, 6.42. Found: C, 59.75; H, 6.61.

Allyl 3-O-benzyl-β-D-glucopyranoside (125)

Compound **125** was prepared from compound **124** in the same way that compound **45** was prepared from compound **25**, (28% NaOMe in MeOH / MeOH, at 50°C for 1 h, 93.8% yield).

Allyl 3-O-benzyl-4,6-O-p-methoxybenzylidene-β-D-glucopyranoside (126)

Compound **126** was obtained from compound **125** in the same way that compound **92** was obtained from compound **45**, (p-MeOPhCH(OMe)$_2$ / p-TsOH / dioxane, at 50°C under 15 mmHg, for 20 min, 85.8% yield).

Allyl 3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (127)

To a solution of compound **126** (3.26 g, 7.6 mM) in

anhydrous CH_2Cl_2 (40 ml) and anhydrous Et_2O (20 ml), $LiAlH_4$ (1.45 g, 38.1 mM) was added. A solution of $AlCl_3$ (4.06 g, 30.4 mM) in anhydrous Et_2O (20 ml) was added dropwise at 0^oC over 30 min. The reaction mixture was stirred at 0^oC for 1 h, treated with H_2O (2.6 ml) in tetrahedrofuran (10 m) to decompose the excess reagents and then filtered with EtOAc. The combined filtrate and washings were worked-up by the standard method to give a colorless syrup. THe product was crystallized from EtOH / n-hexane to afford colorless crystals (2.74 g, 83.6% yield).

Allyl 2,6-di-O-acetyl-3-O-benzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (122)

Compound 122 was synthesized from compound 127 by the standard acetylation method, (Ac_2O / pyridine, at 50^oC, for 2 h, a quantitative yield); ^1H-NMR: 1.99 (3H, s), 2.06 (3H, s), 3.40-3.55 (1H, m, C_5-H), 3.56-3.73 (2H, m, C_3-H, C_5-H), 3.79 (3H, s, $-OCH_3$), 4.04 (1H, dd, J=13.5, 6.0, $-CH_2$-C=C), 4.20 (1H, dd, J=12.0, 4.0, C_6-H_a), 4.31 (1H, dd, J=13.5, 4.0, $-CH_2$-C=C), 4.34 (1H, dd, J=12.0, 2.0, C_6-H_b), 4.40 (1H, d, J=8.0, C_1-H), 4.49 (1H, d, J=10.5, benzyl), 4.69 (1H, d, J=11.0, benzyl), 4.76 (1H, d, J=10.5, benzyl), 4.82 (1H, d, J=11.0, benzyl), 5.01 (1H, dd, J=9.0, 8.0, C_2-H), 5.17 (1H, dd, J=10.5, 1.5, -C-C=CHcis), 5.24 (1H, dd, J=17.0, 1.5, -C-C=CHtrans), 5.74-5.96 (1H, m, -C-CH=C), 6.88 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.22 (2H, d, J=8.0, $-OC_6\underline{H}_4OCH_3$), 7.28-7.44 (5H, m, pheyl).

Allyl 2,6-di-O-pivaloyl-3-O-benzyl-4-O-p-mehoxybenzyl-β-D-glucopyranoside (123)

Compound **123** was obtained from compound **127** in the same way that compound **71** was obtained from compound **42**, ($(CH_3)_3CCOCl$ / pyridine / 50°C / 12 h, a quantitative yield).

2,6-Di-O-acetyl-3-O-benzyl-4-O-p-methoxybenzyl-D-glucopyranoside (102)

A mixture of compound **122** (252 mg, 0.49 mM), SeO_2 (60 mg, 0.54 mM) and AcOH (31 μl, 0.54 mM) in dioxane (2 ml) was heated under reflux for 3 h. The reaction mixture was worked-up by the standard method to give a yellow oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:1)) to afford compound **102** (140 mg, 60.3% yield).

Allyl 2,6-di-O-acetyl-3-O-benzyl-β-D-glucopyranoside (128)

To a solution of compound **122** (372 mg, 0.72 mM) in CH_3CN-H_2O (4 ml, 9:1), $Ce(NH_4)_2(NO_3)_6$ (1.19 g, 2.16 mM) was added. The reaction mixture was kept at room temperature for 15 min, and then worked-up by the standard method to give a colorless oil. The oil was purified by P-TLC (EtOAc / n-hexane (1:2)) to afford a colorless oil (243 mg, 85.3% yield).

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