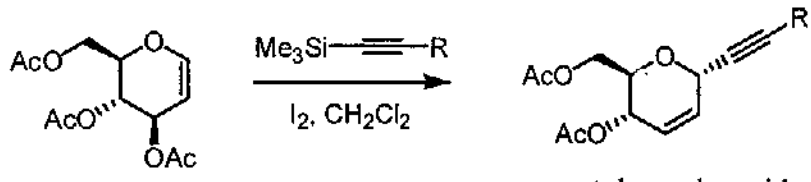
CHAPTER 5
CONCLUSION AND DISCUSSION

The purpose of this research was to study the iodine catalyzed glycosidation reaction of tri-O-acetoxy-D-glucal **1** with various nucleophiles. The glycosidation reactions of glucal with nucleophiles have been reported to proceed smoothly by using lewis acid as a catalyst. However, many of lewis acids are corrosive and moisture sensitive. The presence of even small amount of water causes lower yields of product. Therefore the development of reagents which are more efficient, easy to handle and convenient would be more advantaged.

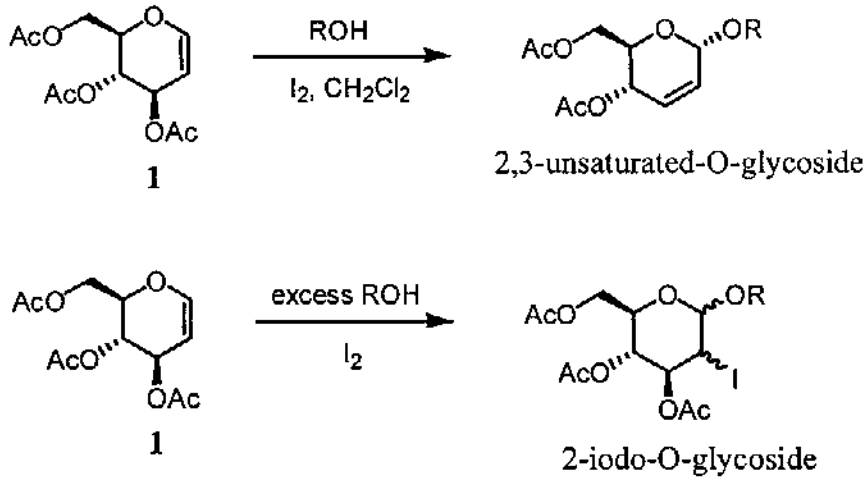
In part 1, the C-glycosidations of D-glucal were studied by using various silylacetylenes as nucleophiles and iodine (I_2) a catalyst. The reactions were performed in dichloromethane (CH_2Cl_2) at room temperature to afford exclusively the α-acetylene glycoside product in high yields (Scheme 25 and Table 1).



1 acetylene glycoside

Scheme 25 C-glycosidation of D-glucal **1** with various silylacetylenes by using iodine as a catalyst

In part 2, O-glycosidations of readily available D-glucal were studied by reacting with free hydroxy group nucleophiles. In the case of using dichloromethane as the solvent, 2,3-unsaturated-O-glycosides were obtained as the product in high yield. In the case of using excess alcohol, the O-glycosidation of D-glucal afforded only the 2-iodo-O-glycoside product in high yield. This new condition was performed without dichloromethane (Scheme 26 and Table 2).

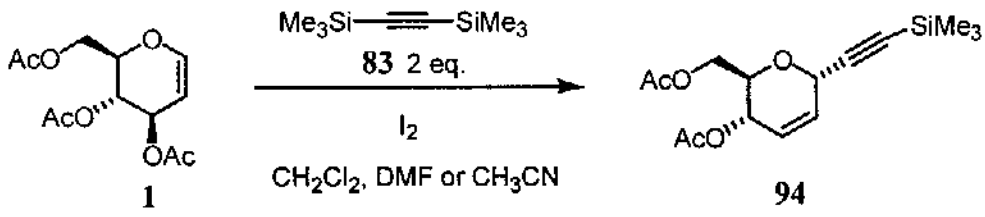


Scheme 26 O-glycosidation of D-glucal **1** with various alcohol by using iodine as a catalyst

C-glycosidation

C-glycosidation of D-glucal with silylacetylenes

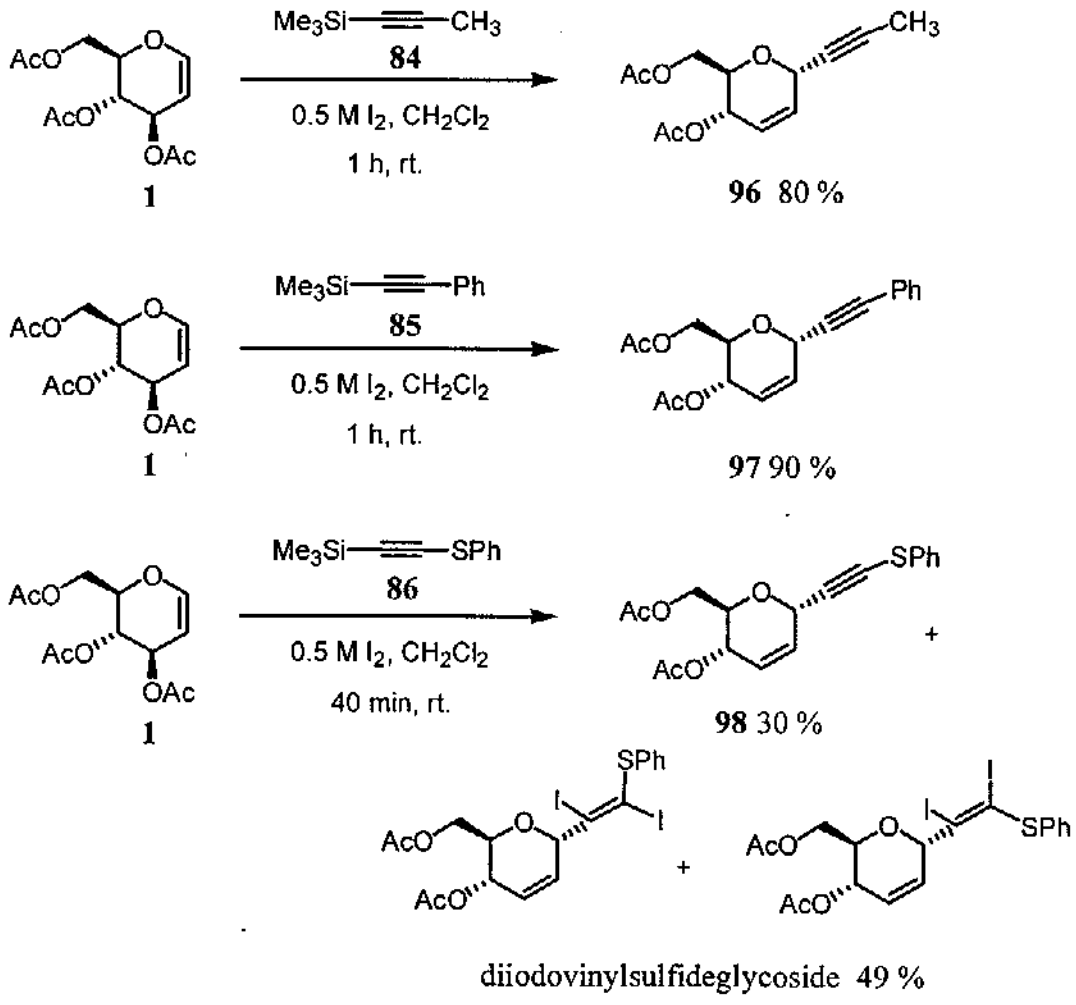
The application of iodine to the C-glycosidation of tri-O-acetyl-D-glucal **1** and silylacetylene with various types of R groups at the other end of acetylene moiety was studied (Scheme 25). Bis-trimethylsilylacetylene was used as the nucleophile to investigate the C-glycosidation by using iodine catalyst. The reaction was carried out in the presence of 0.5 M iodine in dichloromethane (condition a) to afford acetylene glycoside **94** in 78 % isolated yield. In a dilute concentration solution of iodine (0.08 M, condition b), only low yield of acetylene glycoside was observed. No desired product was obtained when using dimethylformamide (DMF) as the solvent (condition c). Complete reaction was observed in 40 min (condition d) in acetonitrile (CH_3CN). However the acetylene glycoside **94** was observed in lower yield than using dichloromethane (Scheme 27). According to these results, the condition a was used as a general procedure for the C-glycosidation of other silylacetylenes.



1 eq.		
condition a	0.5 M I_2 in CH_2Cl_2 (16 h)	78 %
condition b	0.08 M I_2 in CH_2Cl_2 (16 h)	11 %
condition c	0.5 M I_2 in DMF (16 h)	0 %
condition d	0.5 M I_2 in CH_3CN (40 min)	33 %

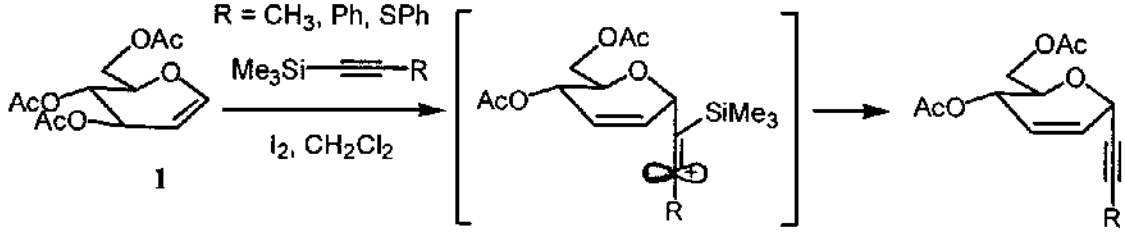
Scheme 27 C-glycosidation of D-glucal **1** with bis-trimethlsilylacetylene **83** in various conditions

The C-glycosidation reactions were completed by using condition a in 45 min to 1 h for the methyl, phenyl and phenylthio groups at the other end of silylacetylenes to afford exclusively the α-acetylene glycoside product **96** (80 %), **97** (90 %) and **98** (87 %), respectively (Scheme 28).



Scheme 28 C-glycosidation of the methyl, phenyl and phenylthio groups at the other end of silylacetylenes

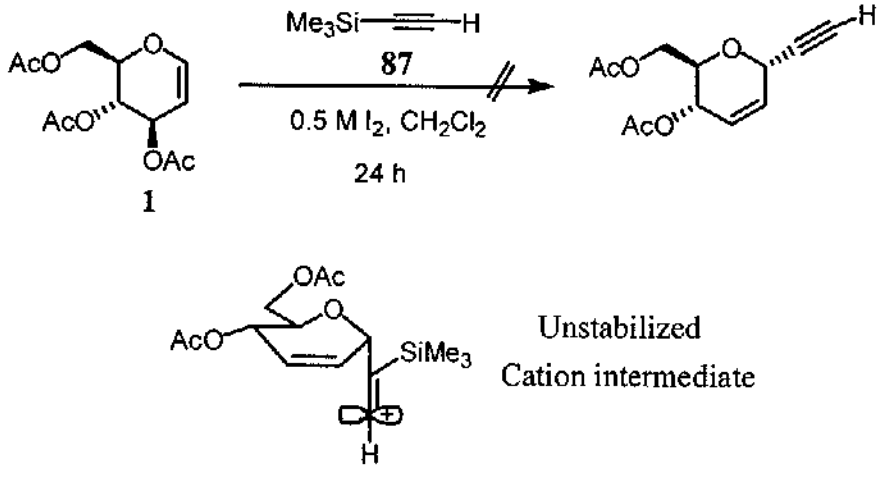
These complete reactions were observed in short time and gave the product in high yield because the electronic effect of the electron donating substituents accompanied with the β-silyl stabilized carbocation intermediate (Scheme 29).



Scheme 29 The electronic effect of the electron donating substituents

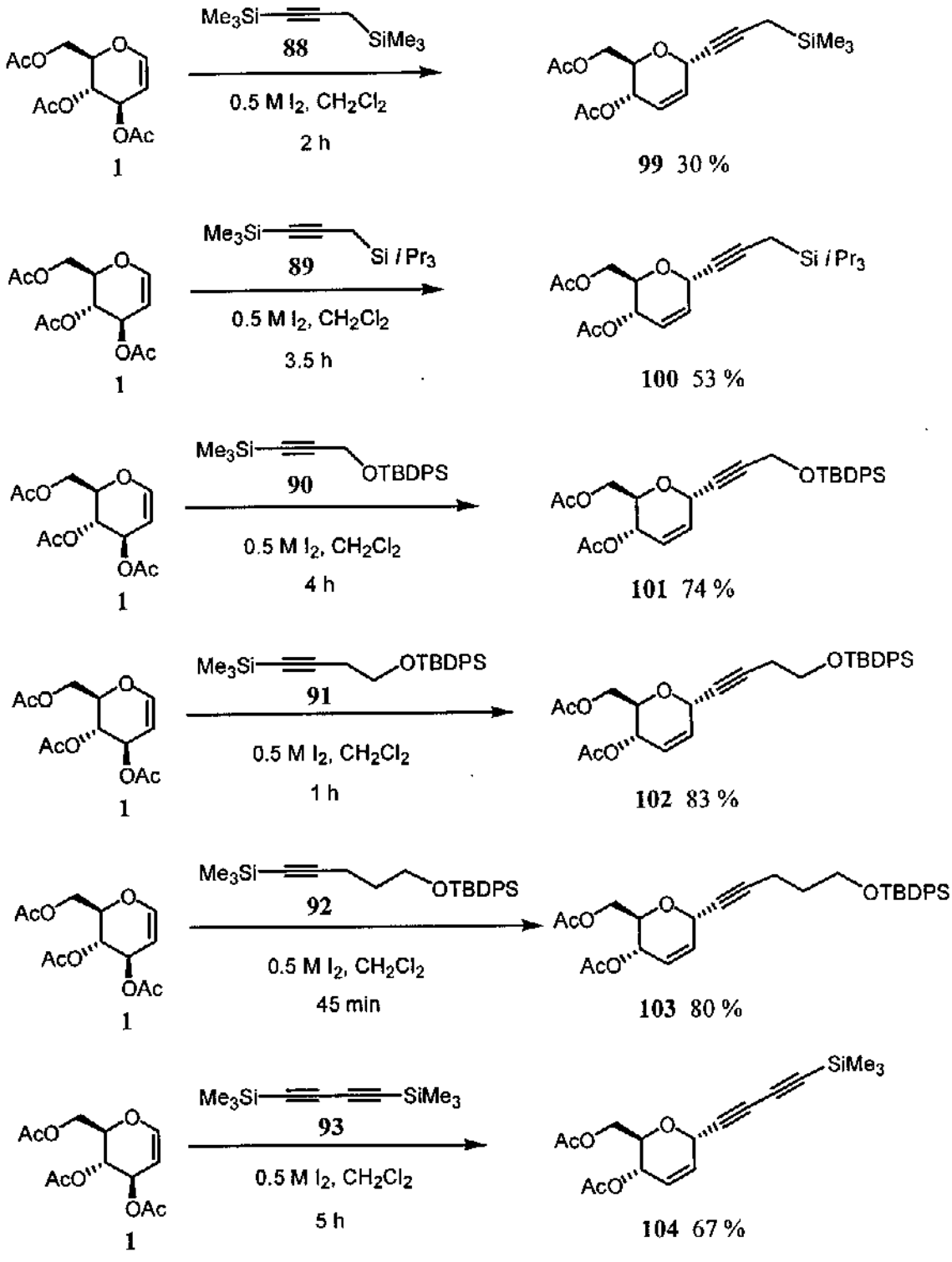
In the case of trimethylsilylphenylthioacetylene **86**, the 1 : 1.3 mixture of acetylene glycoside **98** and diiodovinylsulfideglycoside were obtained in 87 % total yield. The formation of diiodovinylsulfide mixture (49 %) was resulted from the iodine addition to acetylene moiety.

Without substituent at the end of acetylene, no desired product was observed due to the lack of substitution stabilized effect (Scheme 30).



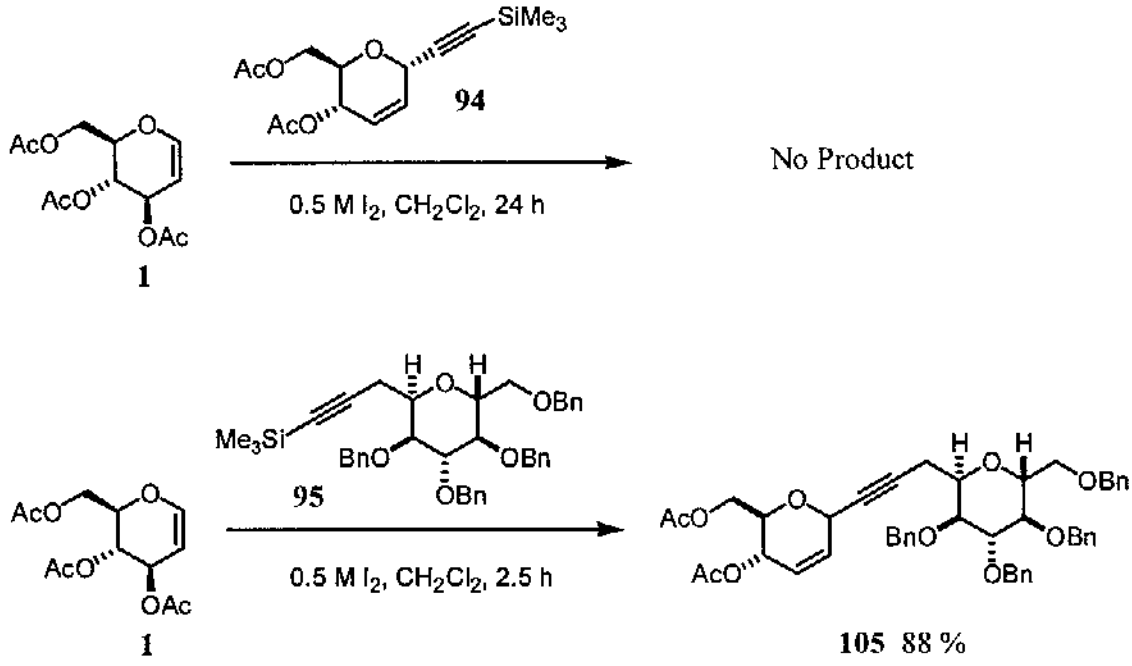
Scheme 30 The lack of substitution stabilized effect

The C-glycosidation reactions of silylacetylene nucleophile were extended to the higher homologous of carbon bonds resulting in the formation of the acetylene glycosides in moderate to high yields. Both siylacetylenes **88** and **89** gave acetylene glycosides product **99** (30 %) and **100** (53 %) in moderate yield, respectively. In case of the C-glycosidation with silylpropargyl ether **90**, the glycoside product **101** was afforded in high yield (74 %) and when the homologation of carbon chain between the acetylene and TBDPS-ether was increased (**91** and **92**), the reaction was completed in the shorter time due to the relief of the destabilization effect by the ether group (Scheme 31). In the case of Bis-trimethysilyldiacetylene **93**, the silyl-diacetylene **104** was obtained in 67 % yield.



Scheme 31 C-glycosidation of D-glucal 1 with various silylacetylenes **88-93**

The efficiency of iodine was also tested to promote the C-glycosidation on the larger silylacetylene compounds **94, 95** (Scheme 32). The silylacetylene glycoside **94** failed to react with the D-glucal because of the destabilized effect of the ether ring oxygenation. Contrast to the result of silylpropargly-sugar **95**, the reaction proceeded smoothly to react with D-glucal to furnish exclusively the α-acetylene glycoside product **105** in 88 % yield. The glycoside **105** could be used as a precursor for further synthesis of cignatoxin.



Scheme 32 C-glycosidation of D-glucal **1** with the larger silylacetylene compounds

The stereochemistry at C-1 position of the acetylene glycoside products was proved to be exclusively α-orientation in all cases. The α-acetylene glycoside products were chemically proved to be partial hydrogenation of the acetylene group to the corresponding vinyl one, the vinyl α-proton showing NOE with the H-5 (Fig 3) which was reported by Tanaka, Tsukiyama and Isobe (1993). Here we have established an empirical rule as follows. The chemical shift at H-5 was found between 4.07-4.09 ppm in case of R = TMS, C:CTMS due to the anisotropic effect of the α-acetylene at C-1 (Fig 4). Comparing to the β-acetylene glycosides without

anisotropic effect, the chemical shift at the H-5 were observed between 3.74 and 3.75 which were summarized from a report by Tanaka, et al. from epimerization product *via* cobalt complex. All of the H-5 chemical shifts of acetylene glycoside products in our experiments were observed at 4.05-4.18 ppm. These results confirmed the α-orientation of the acetylene-glycoside products.

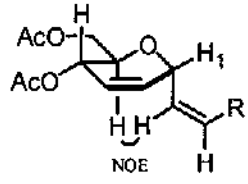
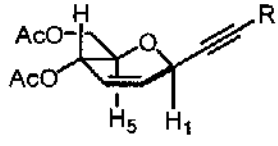


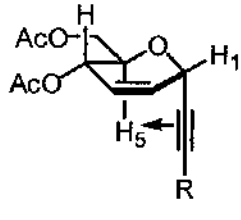
Figure 3 NOE of the vinyl α-proton with the H-5



β-acetylene glycoside

R= TMS, H-1 = 4.99
R= C:CTMS, H-1 = 5.04

R= TMS, H-5 = 3.75
R= C:CTMS, H-5 = 3.74



α-acetylene glycoside

R= TMS, H-1 = 4.96
R= C:CTMS, H-1 = 5.00

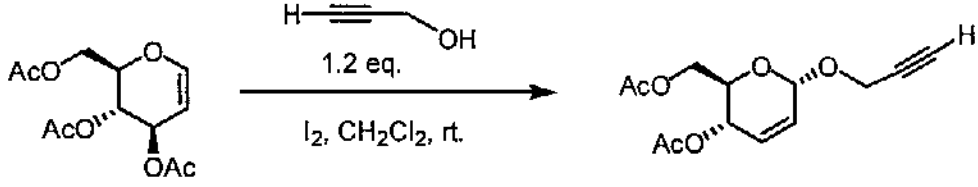
R= TMS, H-5 = 4.09
R= C:CTMS, H-5 = 4.07

Figure 4 Chemical shifts of the β-and α-acetylene glycosides

O-glycosidation

O-glycosidation of D-glucal with various alcohols

In part 2, the application of iodine in the O-glycosidation of tri-O-acetyl-D-glucal **1** and various alcohols were studied. The α-2,3-unsataturated-O-glycoside products were obtained in the presence of dichlomethane as a solvent at room temperature. The propargyl alcohol was used as a nucleophile to investigate the O-glycosidation. The propargyl ether glycoside product **106** was observed in 100 % yield for condition e, in a dilute concentration solution of 0.022 M iodine in dichloromethane. However, the glycoside product **106** was observed in lower yield in the higher concentration of iodine (condition f, 0.16 M iodine in dichloromethane). Thus condition e was used as a general procedure for study the O-glycosidation to obtain 2,3-unsaturated glycoside (Scheme 33).



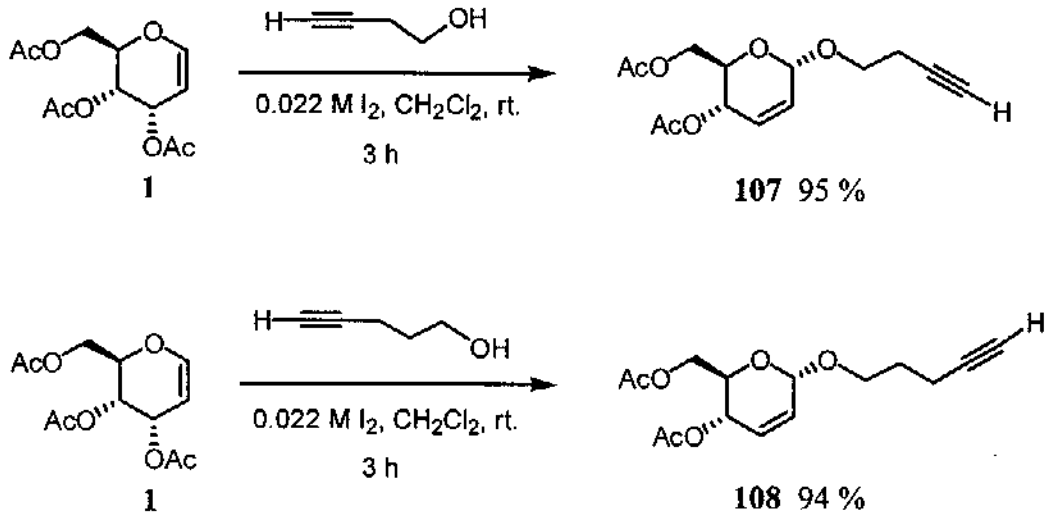
1
1 eq.

106

condition e	0.022 M I_2 (3 h)	100 %
condition f	0.16 M I_2 (3.5 h)	68 %

Scheme 33 O-glycosidation of D-glucal **1** with propargyl alcohol

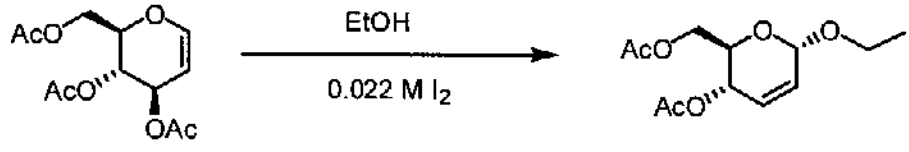
Other alkynyl alcohols such as 3-butyn-1-ol and 4-pentyn-1-ol were used as nucleophiles for the O-glycosidation to afford the α-2,3-unsaturated-O-glycoside products **107** and **108** in 95 and 94 % yield, respectively (Scheme 34).



Scheme 34 O-glycosidation of D-glucal **1** with alkyl alcohols

The homologation of carbon chain in alkynyl alcohols were not effected in the O-glycosidation.

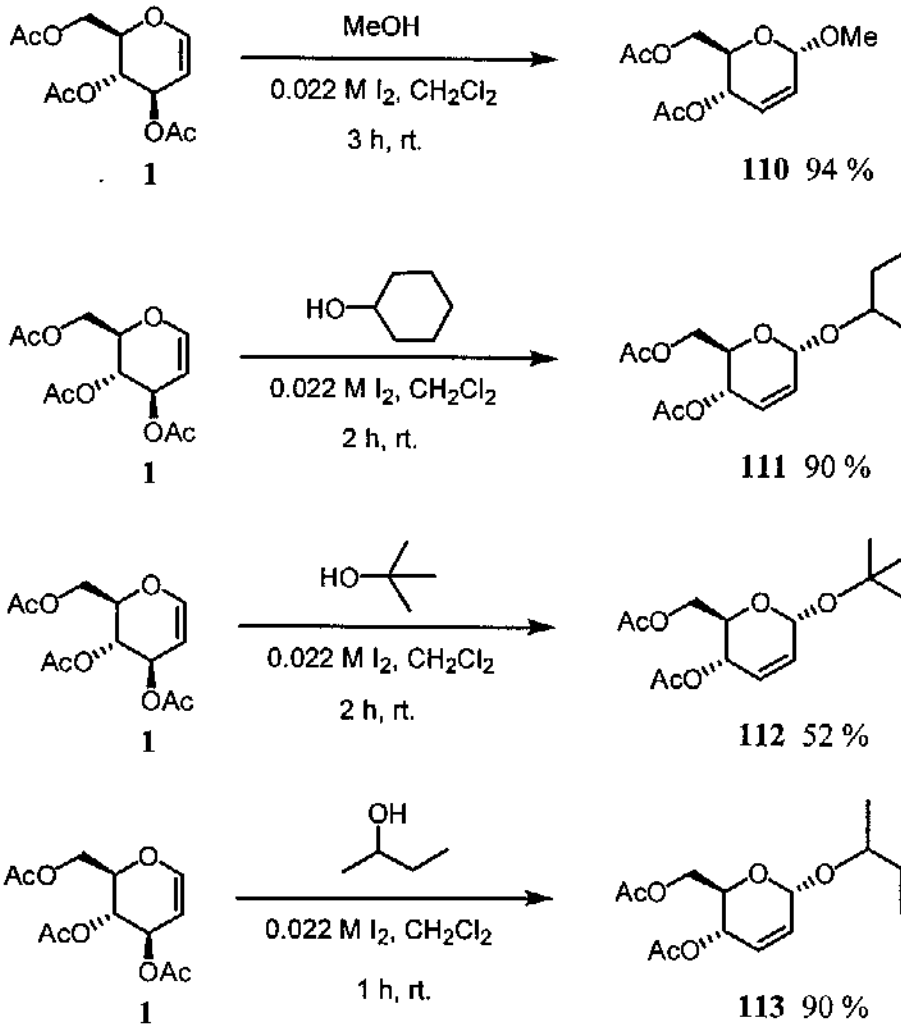
The O-glycosidation reactions with ethanol as a nucleophile were studied. In the presence of 0.022 M iodine, 2,3-unsaturated-O-glycoside was obtained in high yield and high stereoselectivity when dichloromethane was used as the solvent. Contrast to the result using acetonitrile as the solvent, the product was obtained in lower yield and lower stereoselectivity when dichloromethane was used. This result was due to solvent effect of acetonitrile coordinating with oxonium cation intermediate at the anomeric position C-1 from α-side forcing nucleophile attacked to the β-side. (Scheme 35).



condition e	in CH_2Cl_2	99 %
condition g	in CH_3CN	61 % (α : β ; 2 : 1)

Scheme 35 O-glycosidation of D-glucal **1** with ethanol

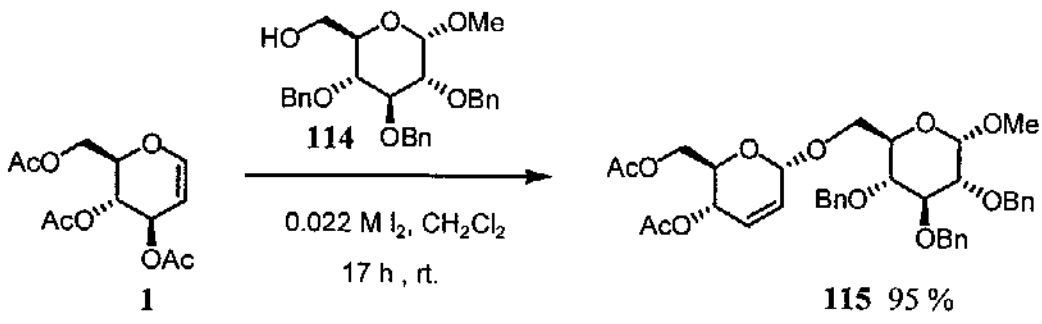
O-glycosidation reactions with various alcohols such as methanol, cyclohexanol, *tert*-butanol and 2-butenol were studied. 2,3-unsaturated-O-glycoside products were afforded in 94 %, 90 %, 52 % and 90 % yield, respectively. In the case of *tert*-butanol, 2,3-unsaturated-O-glycoside product **112** was afforded in low yield due to steric effect of the nucleophile (Scheme 36).



Scheme 36 O-glycosidation of D-glucal **1** with various alcohols

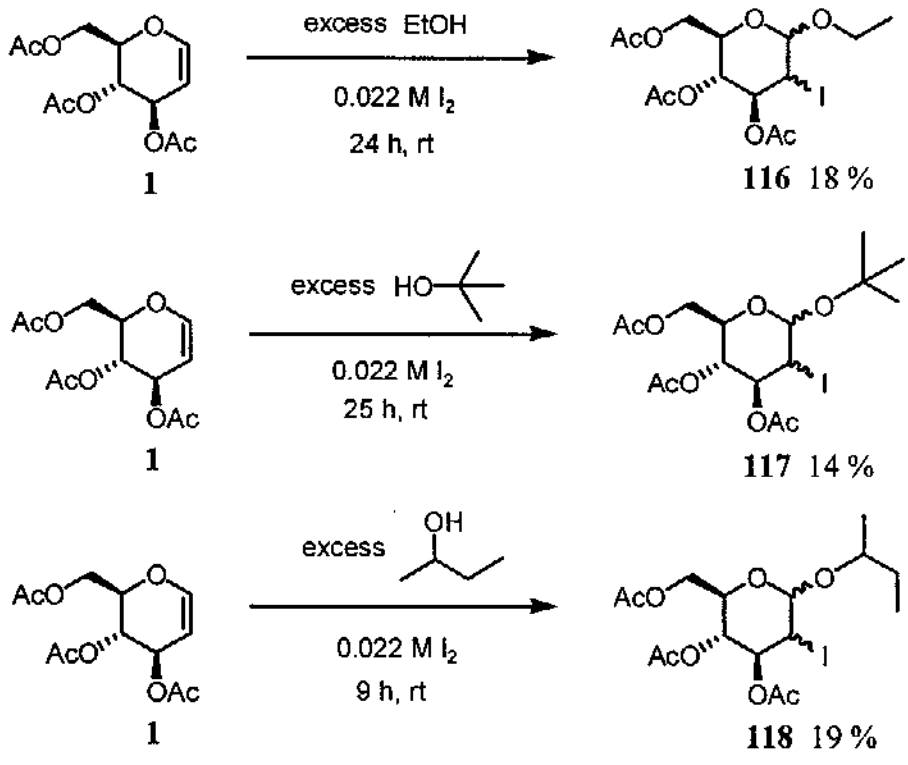
According to the previous result this works showed the efficiency of iodine in O-glycosidation with several alcohols. One free hydroxy sugar compound **114** was used as a nucleophile to synthesize the disaccharide product **115** in high yield (Scheme 37).

It was found that the O-glycosidation with sugar **114** proceeded smoothly in the presence of 0.022 M iodine in dichloromethane to obtain the disaccharide **115** in 95 % yield proving the generality of this O-glycosidation.



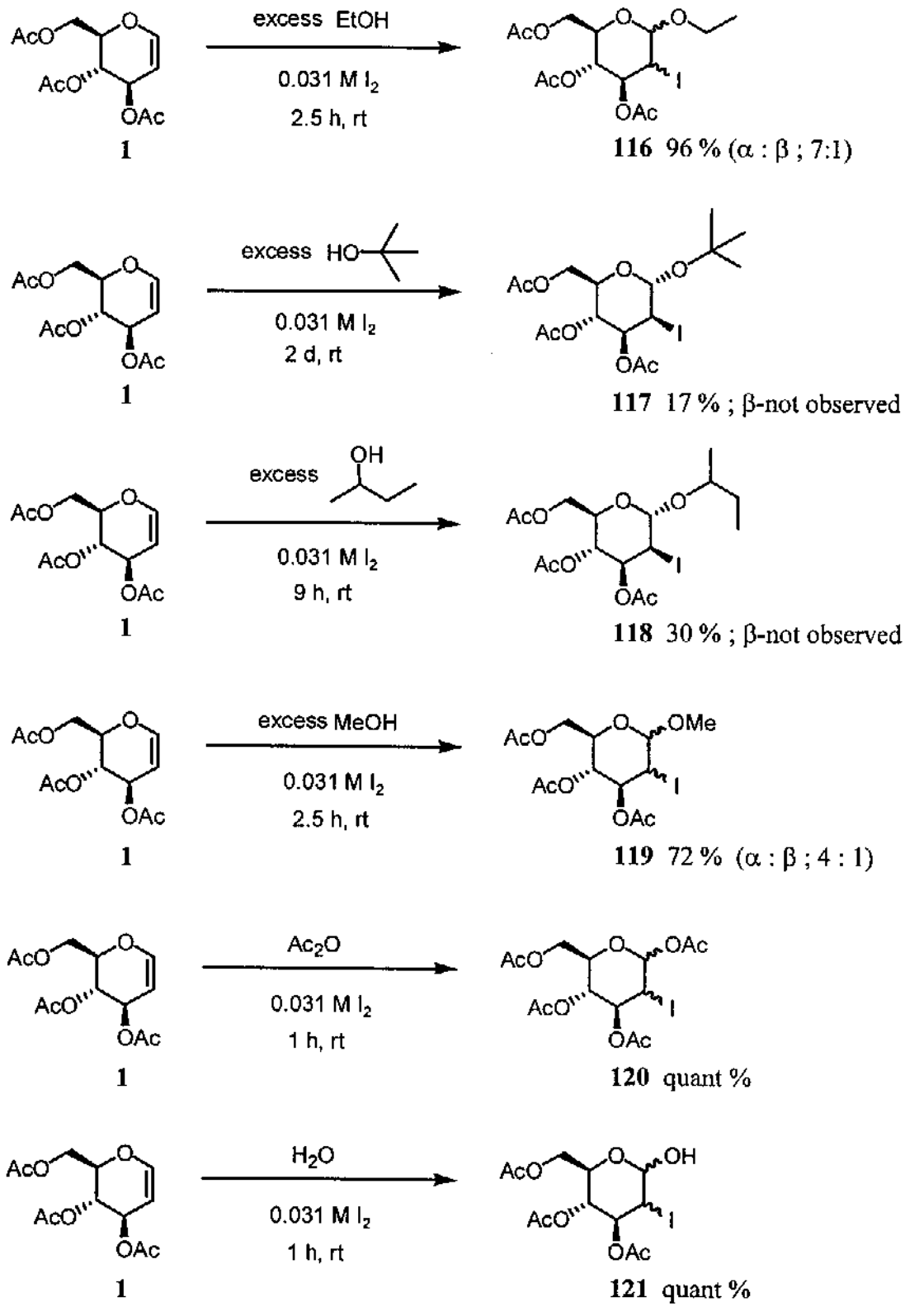
Scheme 37 O-glycosidation of D-glucal **1** with sugar **114**

The reaction appeared to be interesting. It turned out to afford only 2-iodo-O-glycoside as the product when the reaction was performed in excess alcohol as a solvent and a nucleophile. The reactions were first investigated by using 0.022 M iodine, condition h and 2-iodo-O-glycoside was obtained in low yield without 2,3-unsaturated-O-glycoside (Scheme 38).



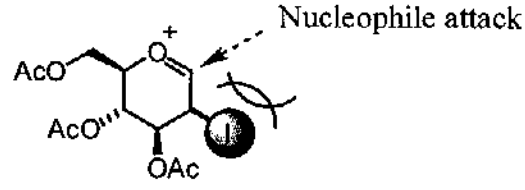
Scheme 38 O-glycosidation of D-glucal 1 with various excess alcohols by using 0.022 M iodine

The yield of 2-iodo-O-glycosidation was improved by using higher concentration of iodine (0.031 M iodine). 2-Iodo-O-glycoside product was observed in higher yield comparing to the condition of 0.022 M iodine. Therefore the highest concentration condition was used as a general procedure for the O-glycosidation to obtain exclusively 2-iodo-O-glycoside. Ethanol was used as a nucleophile and solvent to afford the 2-iodo-O-glycoside **116** in 96 % with high stereoselectivity (α : β = 7 : 1). With the same condition, nucleophiles such as *tert*-butanol, 2-butanol, methnol, acetic anhydride and water were treated with iodine affording 2-iodo-O-glycoside **117** (17 %), **118** (30 %), 119 (72 %), **120** (quant %) and **121** (quant %), respectively (Scheme 39).



Scheme 39 O-glycosidation of D-glucal **1** with various excess alcohols by using 0.031 M iodine

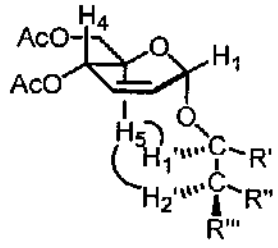
In the case of more hindered alcohols such as *tert*-butanol and 2-butanol, 2-iodo-O-glycosides, the desired product, was observed in low yield due to the steric effect of larger nucleophile attacking the iodo-oxonium carbocation intermediate as shown in Figure 5.



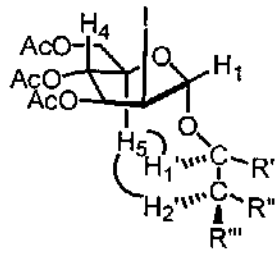
Iodo-oxonium carbohydrate intermediate

Figure 5 The steric effect of larger nucleophile

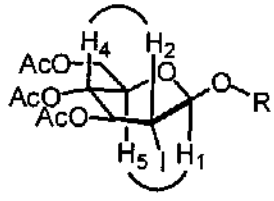
The stereochemistry of the major O-glycoside products at C-1 position was proved to be exclusively α-orientation in all cases. The iodo-substituent at C-2 in the case of α-2-iodo-O-glycoside product was located in the axial position. The minor product in the O-glycosidation was obtained as β-2-iodo-O-glycoside. The iodo-substituent at C-2 was observed in the equatorial position. The α-stereochemistry at C-1 of the product was proved by using the NOESY technique to observe the relationship between H-5 with H-1' and H-5 with H-2'. In addition, the lack of NOE between H-2 and H-4 strongly supported the α-stereomers. The β-2-iodo-O-glycoside configuration was firmly established by the presence of a clear NOE between H-5 and H-1. Moreover the presence of NOE between H-2 and H-4 confirmed the equatorial iodo- configuration which was absent in the corresponding α-stereoisomer as shown in Figure 6.



α-2,3-unsaturated-O-glycoside



α-2-iodo-O-glycoside

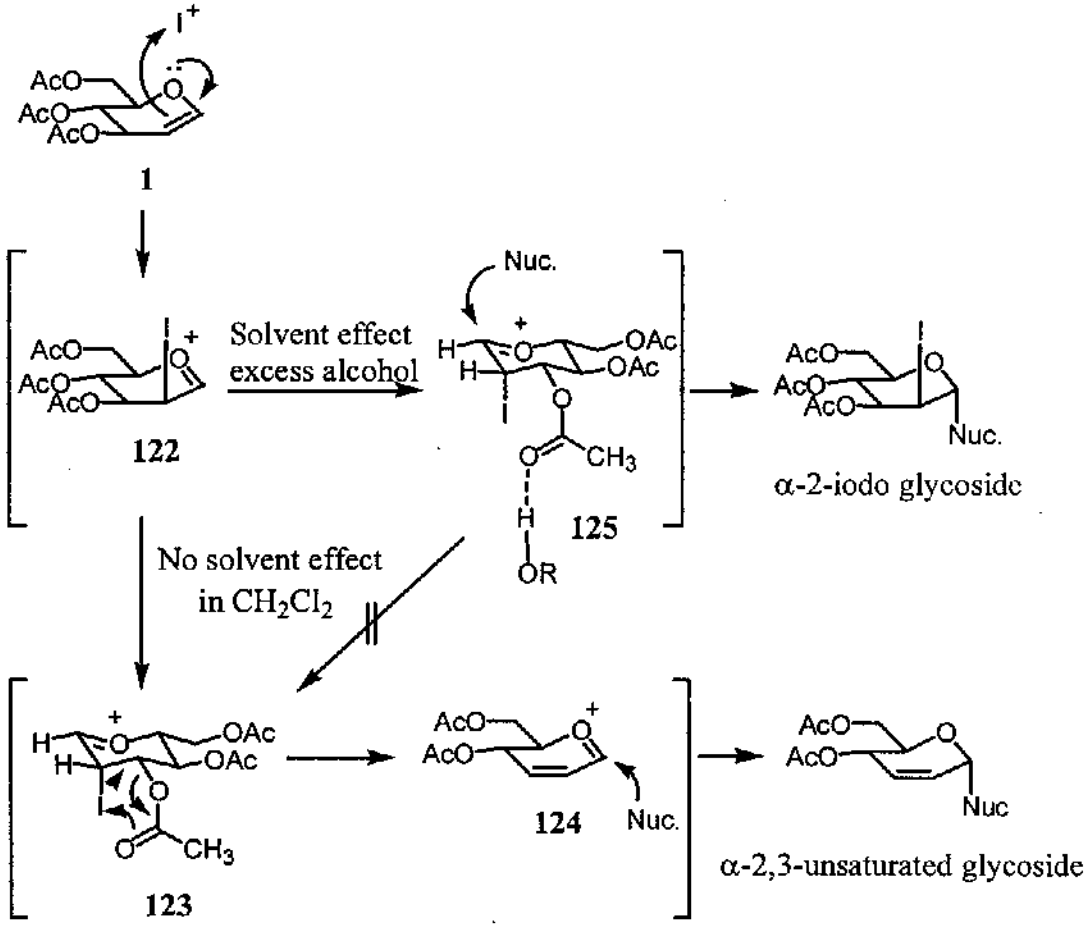


β-2-iodo-O-glycoside

Figure 6 NOE of α-2,3-unsaturated-O-glycoside, α-2-iodo-O-glycoside and β-2-iodo-O- glycoside

Mechanism

In terms of reaction mechanism, this process could involve the generation of different oxonium cation species from the Ferrier rearrangement of Lewis acid catalyzed C-glycosidation and O-glycosidation as depicted in Scheme 40.



Scheme 40 Mechanism of glycosidation reaction by using iodine as a catalyst

We believe the C- and O-glycosidation reactions were initiated by the attack of a soft electrophilic iodonium to the double bond of tri-O-acetyl-D-glucal **1** to form an iodo-oxonium carbocation **122** (Scheme 40) rather than to the acetate group at C-3 as Ferrier rearrangement. Concerted elimination of iodine and acetyl group at the C-3 position of intermediate **123** resulted in the formation of intermediate **124** which was more stable than **122** due to the resonance effect. This intermediate **124** and **125** could coordinate with silylacetylene or one free hydroxy compound at the anomeric position C-1 from the α-side to give the C-glycoside or O-glycoside product.

In the case of O-glycosidation in dichloromethane, the reaction proceeded *via* similar mechanism as C-glycosidation. The mechanism of O-glycosidation, in excess alcohol as a solvent and nucleophile, seemed to proceed *via* the intermediate **125** in which the alcohol was coordinated to acetate group at C-3 position. This

solvent effect retarded the iodo-acetate elimination process resulting in 2-iodoglycoside as the only product.

In conclusion, this thesis work reported the development of convenient and easy procedure with high stereoselectivity for the C-glycosidation with various acetylenes and O-glycosidation with various alcohols using iodine to promote the reaction. The possible iodo-oxonium mechanism was also proposed in this thesis including the empirical rule for NMR analysis of the α-C-glycoside.