GLYCOSYLATION OF THIOGLYCOSIDES WITH BROMODIETHYLSULFONIUM BROMOPENTACHLOROANTIMONATE AS NOVEL ACTIVATOR

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ไกลโคซิเลชันของไทโอไกลโคไซด์ด้วยโบรโมไดเอทิลซัลโฟเนียมโบรโมเพนตะคลอโรแอนติโมเนตเป็นตัวกระตุ้นชนิดใหม่

น.ส.ลดาวัลย์ พันธ์รัมย์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	GLYCOSYLATION OF THIOGLYCOSIDES WITH BROMODIETHYLSULFONIUM BROMOPENTACHLOROANTIMONATE AS NOVEL ACTIVATOR
By	Miss Ladawan Punrum
Field of Study	Chemistry
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ลดาวัลย์ พันธ์รัมย์ :
ไกลโคซิเลชันของไทโอไกลโคไซด์ด้วยโบรโมไดเอทิลซัลโฟเนียมโบรโมเพนตะคลอโรแอนติโมเนตเป็นตัวกระตุ้นชนิดใหม่. (GLYCOSYLATION OF THIOGLYCOSIDES WITH BROMODIETHYLSULFONIUM BROMOPENTACHLOROANTIMONATE AS NOVEL ACTIVATOR) อ.ที่ปรึกษาหลัก : ผศ. ดร.ภาณุวัฒน์ ผดุงรส

ไกลโคซิลเลชันเป็นปฏิกิริยาเคมีที่มีความสำคัญในการสังเคราะห์คาร์โบไฮเดรตเช่น ไกลโคลิพิด ไกลโคโปรตีน และ โอลิโกแซคคาร์ไรด์ ไทโอไกลโคไซด์นิยมใช้เป็นสารตั้งต้นในการสังเคราะห์โอลิโกแซคคาร์ไรด์ เนื่องจากการสังเคราะห์ได้ง่าย มีความเสถียรสูงและสามารถถูกกระตุ้นได้หลายวิธี คณะผู้วิจัยได้รายงานไกลโคซิลเลชันทางเคมีของไทโอไกลโคไซด์กระตุ้นด้วยโบรโมไดเอทิลซัลโฟเนียมโบรโมเพนตะคลอโรแอนติโมเนต (BDSB) จากการศึกษาสภาวะและพารามิเตอร์ต่างๆ เช่นตัวทำละลาย และอุณหภูมิ พบว่าไกลโคซิลเลชันกระตุ้นด้วยโบรโมไดเอทิลซัลโฟเนียมโบรโมเพนตะคลอโรแอนติโมเนตเพียงอย่างเดียว ในตัวทำละลายอะซิโตไนไตรล์ ที่อุณหภูมิ –35 องศาเซลเซียสจนถึงอุณหภูมิห้อง ให้ผลิตภัณฑ์ร้อยละ 41 จากนั้นศึกษาโดยใช้ซิลเวอร์ทริเฟตเป็นตัวกระตุ้นร่วม พบว่าได้ผลิตภันฑ์สูงขึ้นเป็นร้อยละ 79 และมีสเตอริโอเคมีแบบเบต้าเพียงอย่างเดียว จากนั้นจึงนำสภาวะที่เหมาะสมนี้มาใช้ศึกษาปฏิกิริยาไกลโคซิลเลชัน ด้วยไกลโคซิลโดเนอร์ และไกลโคซิลแอคเซพเตอร์ชนิดต่างๆ พบว่าเมื่อใช้ไกลโคซิลโดเนอร์ต่างชนิดกัน ให้ผลิตภัณฑ์ร้อยละ 27 ถึง 85 นอกจากนี้เมื่อใช้ไกลโคซิลแอคเซพเตอร์ต่างชนิดกัน เกิดเป็นผลิตภัณฑ์ร้อยละ 20 ถึง 85 และจากการศึกษาตัวกลางที่เกิดขึ้น พบว่าเป็น ไกลโคซิลคลอไรด์ ซึ่งถูกยืนยันโครงสร้างด้วยเทคนิคเอ็นเอ็มอาร์ สเปกโตรสโคปี

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Ladawan Punrum : GLYCOSYLATION OF THIOGLYCOSIDES WITH BROMODIETHYLSULFONIUM BROMOPENTACHLOROANTIMONATE AS NOVEL ACTIVATOR. Advisor: Asst. Prof. Panuwat Padungros, Ph.D.

Glycosylation is an important reaction in carbohydrate synthesis of complex molecules such as oligosaccharides, glycoproteins, and glycolipids. Thioglycosides are widely used as precursors in oligosaccharide synthesis due to their ease of preparation, high stability towards protecting group manipulations and variety of activation methods. Recently, bromodiethylsulfonium bromopentachloroantimonate (BDSB) was reported as a novel source of highly electrophilic bromine. It was used to efficiently initiate cation-π cyclizations of polyene at low temperature. Herein, we report a chemical glycosylation of thioglycosides activated by BDSB. Firstly, armed and disarmed glycosyl donors and glycosyl acceptors were synthesized by using modified previous method. Next, several reaction conditions and parameters are investigated. It is found that treatment of reaction mixture with only BDSB in acetonitrile at –35 ^{o}C to room temperature gives the desired *O*-linked disaccharide in 41% yield and selectivity. However, applying BDSB in combination with stoichiometric silver triflate (AgOTf) provides the disaccharide in 79% yield and exclusive β selectivity without using neighboring participation group at C2. Moreover, glycosylation of disarmed thioglycosides are performed under the optimal conditions to give disaccharides in 27-85% yield. Next, glycosylation with several alcohols are performed and gave the desired products in 20-85% yield. The glycosyl chloride intermediate in this glycosylation activated with BDSB is isolated and identified by NMR spectroscopy.

Field of Study:	Chemistry	Student's Signature .....
Academic Year:	2018	Advisor's Signature .....

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Ladawan Punrum

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α	alpha
β	beta
br	broad signal
δ	chemical shift
d	doublet
dd	doublet of doublet
DMF	*N,N*-dimethylformamide
dt	doublet of triplet
Hz	hertz
J	coupling constant
m	multiplet
NMR	nuclear magnetic resonance
o/n	overnight
ppm	part per million
rt	room temperature
s	singlet
THF	tetrahydrofuran
TLC	thin layer chromatography

CHAPTER I

INTRODUCTION

1.1 Glycosylation of thioglycosides

Glycosylation is an important reaction in carbohydrate synthesis of complex molecules such as oligosaccharides, glycoproteins, and glycolipids.[1-3] These carbohydrates play an important role in biological processes and have been applied in pharmaceutical industry.[4-5] Chemical glycosylation is a reaction between glycosyl donor (electrophile) and glycosyl acceptor (nucleophile) with a formation of a glycosidic bond. Thioglycosides are widely used as precursors in oligosaccharide synthesis due to their ease of preparation, high stability towards protecting group manipulations and variety of activation methods. Thioglycosides can be activated by both of Lewis acid and thiophilic reagent (Figure 1.1).[6-7] Ferrier and co-workers first introduced mercury salt, $HgSO_4$, as an activator for glycosylation of thioglycosides.[8] Since then several kinds of Lewis acids such as $HgCl_2$, AgOTf, $Cu(OTf)_2$, $Yb(OTf)_3$, $La(OTf)_3$, and $Eu(OTf)_3$ were examined as activators. Thiophilic reagents are also powerful activators. The most common thiophilic activators are methyl triflate (MeOTf), dimethyl(methylthio)sulfonium triflate (DMTST), iodonium dicollidine perchlorate (IDCP), and *N*-iodosuccinimide (NIS), these activators often used together with triflic acid (TfOH) or silver triflate (AgOTf).

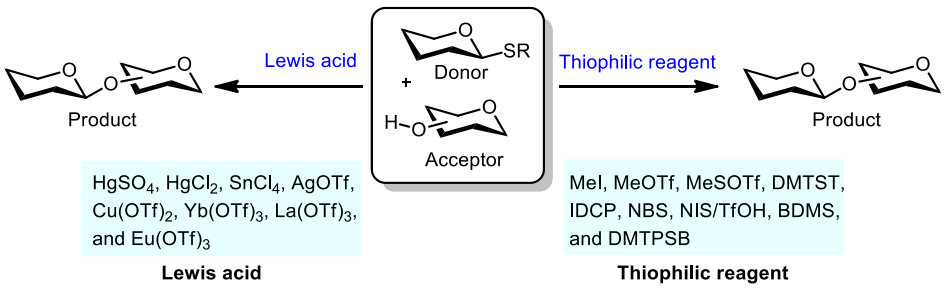


Figure 1.1 Glycosylation of thioglycosides activated with Lewis acids or thiophilic reagents.

1.2 Thiophilic reagents

Several studies reported the use of thioglycosides as glycosyl donors which were activated by thiophilic reagents. For example, Toshima and co-workers[9] reported glycosylation of 2-deoxy thioglycoside activated by NBS (*N*-bromosuccinimide) in dichloromethane in 1991. The product **1** was obtained in 95% yield with α isomer as a major product (Figure 1.2a). Roush and co-workers[10] also used NBS as an activator of 2-deoxy thioglycoside (Figure 1.2b). Glycosylation was performed smoothly to obtained disaccharide **2** in 92% yield with high α-selectivity.

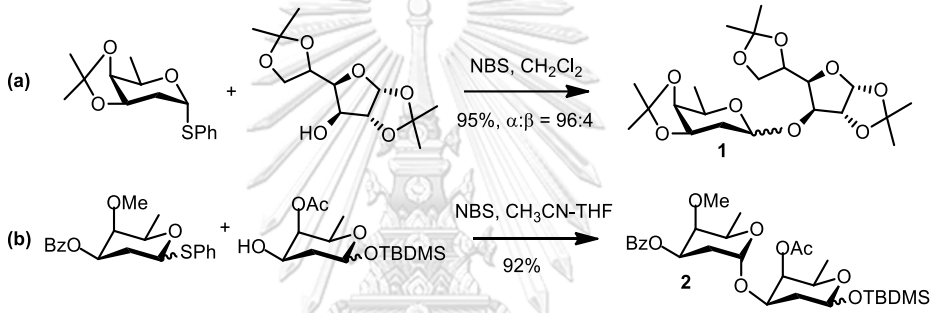
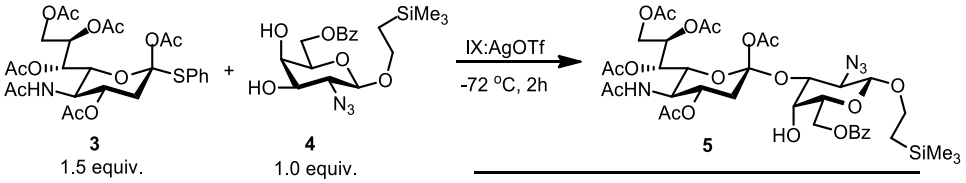


Figure 1.2 Glycosylation of 2-deoxy thioglycosides activated by NBS.

In 2002, Meijer and Ellervik[11] examined the activation of thioglycosides with interhalogen/AgOTf under low temperature. In this work, glycosylation between thioglycoside **3** and acceptor **4** was performed under ICl/AgOTf or IBr/AgOTf. The result showed that using ICl/AgOTf and IBr/AgOTf with 1.5:1.5 mole ratio obtained product **5** in 50% and 87%, respectively. Increasing the mole ratio of IBr/AgOTf (2.0:3.0) obtained **5** in up to 97% yield (Figure 1.3).



IX (activator)	IX:AgOTf (mole ratio)	Yield (%)
ICl	1.5:1.5	50
IBr	1.5:1.5	87
IBr	2.0:3.0	97

Figure 1.3 Glycosylation of thioglycoside **3** activated with IX/AgOTf.

Recent years later, bromodimethylsulfonium bromide (BDMS) in a combination with silver triflate was reported as a new efficient activator for thioglycosides by Ye and co-workers.[12] However, BDMS alone was not powerful enough to activate thioglycosides (Figure 1.4). From this study, authors used ethyl thioglycosides and glycosyl acceptor **46** for glycosylation to afford disaccharides **7** and **8** in good yields (78% and 79%, respectively).

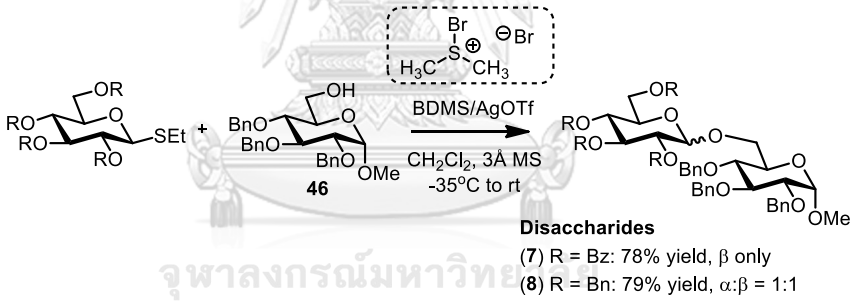


Figure 1.4 Glycosylation of thioglycosides activated with BDMS/AgOTf.

Moreover, Peng and Ye[13] reported *O*,*O*-dimethylthiophosphonosulfenyl bromide (DMTPSB) as a new activator for activation of thioglycosides. Glycosylation of thioglycosides and acceptor **49** by using DMTPSB in the combination with AgOTf was smoothly performed to obtain disaccharides **7** and **8** with high yield in 89% and 85%, respectively (Figure 1.5).

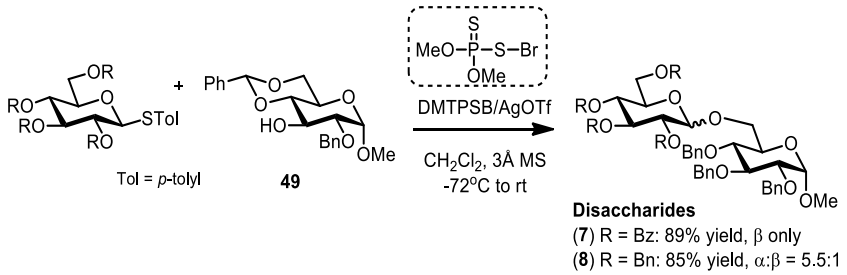


Figure 1.5 Glycosylation of thioglycosides activated with DMTPSB/AgOTf.

Fraser-Reid and co-workers[14] first introduced the concept of armed-disarmed effect for oligosaccharide synthesis. Glycosyl donors protected at hydroxyls with ether protecting groups (electron neutral or donating group) are called armed donors. In contrast, disarmed donors are glycosyl donor which hydroxyls protected with ester groups (electron withdrawing group). Competitive glycosylation between armed donor **10** and disarmed donor **11** with methanol were activated with IDCP or NIS/Et_3SiOTf. In both cases, products **12** derived from donor **10** was obtained as major product (Figure 1.6). This study presented that the armed glycosyl donor is more reactive than the disarmed donor.

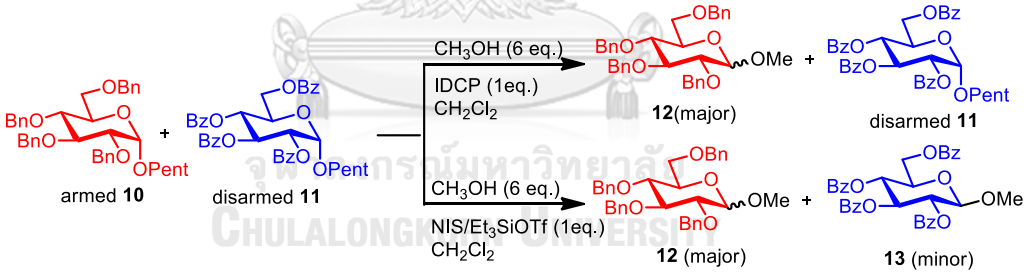
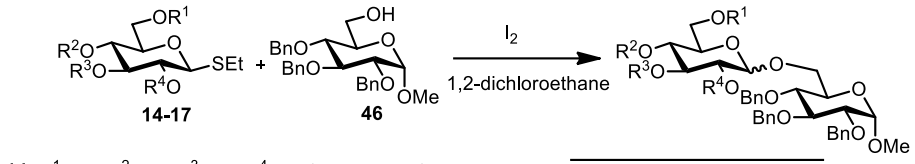


Figure 1.6 Competitive glycosylation of armed and disarmed glycosyl donor activated with IDCP or NIS/Et_3SiOTf.

Moreover, Kamkhachorn and co-workers[15] also reported the armed-disarmed effect of thioglycosides. In this work, glycosylation between glycosyl donors (**14–17**) and glycosyl acceptor **46** were proceeded by activating with iodine in 1,2-dichloroethane. The result showed that superarmed donor **14** is more reactive than armed donor **15**, disarmed donor **16**, and superdisarmed donor **17**, respectively (Figure 1.7).



14: R^1=Bn, R^2=Bn, R^3=Bn, R^4=Bz (superarmed)
15: R^1=Bz, R^2=Bz, R^3=Bz, R^4=NHTroc (armed)
16: R^1=Bz, R^2=Bz, R^3=Bz, R^4=NPhth (disarmed)
17: R^1=Bz, R^2=Bz, R^3=Bz, R^4=Bn (superdisarmed)

Entry	Time	Yield (α/β)
1	15 min	97% (β only)
2	8 h	72% (β only)
3	24 h	61% (β only)
4	24 h	41% (>19/1)

Figure 1.7 Glycosylation of superarmed, armed, disarmed, and superdisarmed thioglycosides activated with iodine.

1.3 Solvent and temperature effect

Furthermore, solvents and temperature also effect to the selectivity of glycosylation. Demchenko and Boons[16] reported the effect of diethyl ether solvent in glycosylation. In this study, ethyl thioglycosides **34b** and glycosyl acceptor **19** was activated with IDCP at room temperature. The result showed that using dichloromethane as solvent gave mixture of α and β disaccharide **20** (α:β = 0.7:1). When using dichloromethane in combination with diethyl ether, the α selectivity of **20** increase with the ratio of α:β = 2:1. Increasing the mole ratio of diethyl ether gave α selectivity of **20** in up to α:β = 3.5:1 (Figure 1.8).

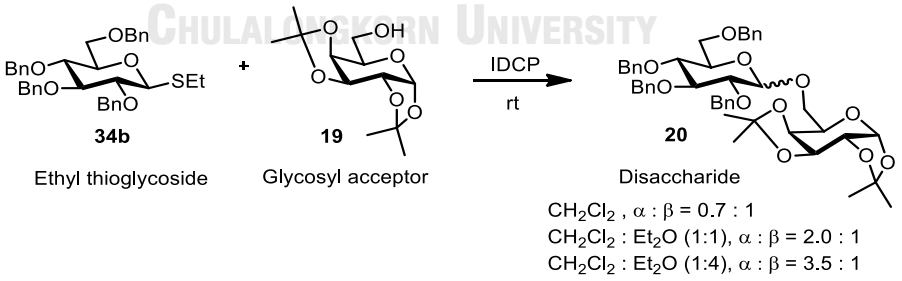
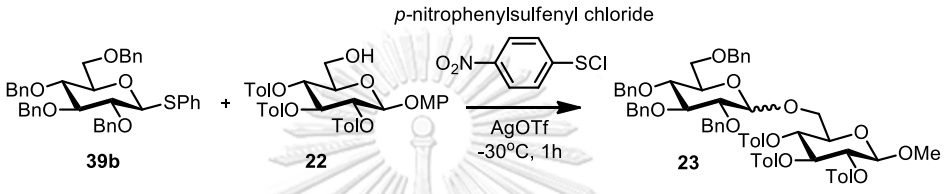


Figure 1.8 Glycosylation of ethyl thioglycoside **34b** and glycosyl acceptor **19** activated with IDCP.

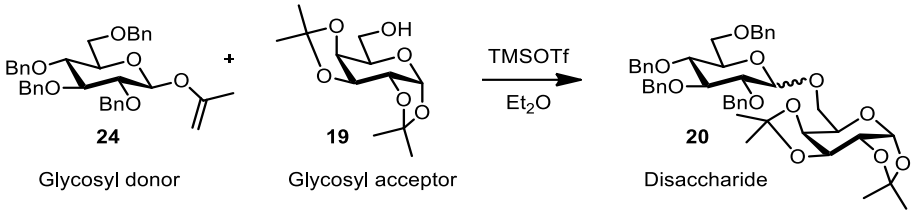
Satoh and co-workers[17] studied the solvent effect on glycosylation between phenyl thioglycosides **39b** and glycosyl acceptor **22** in different solvents such as acetonitrile (CH_3CN), diethyl ether (Et_2O), toluene, and dichloromethane (CH_2Cl_2). The activator was *p*-nitrophenylsulfenyl chloride/AgOTf. Results demonstrated that higher β selectivity of disaccharide **23** observed when acetonitrile or toluene was used. In the other hand, using diethyl ether or dichloromethane as solvent provided a mixture of α- and β-glycosides in 50:50 or 44:56 ratio, respectively (Figure 1.9).



Entry	**Solvent**	α:β
1	CH_3CN	18:82
2	Et_2O	50:50
3	toluene	24:76
4	CH_2Cl_2	44:56

Figure 1.9 Glycosylation of phenyl thioglycoside **39b** and glycosyl acceptor **22** in different solvents.

Chenault and co-workers[18] reported temperature effect on glycosylation. Glycosylation of glycosyl donor **24** and glycosyl acceptor **19** was activated with TMSOTf in diethyl ether. The results showed that glycosylation was smoothly proceeded to obtain disaccharide **20** in moderate to high yield. Moreover, increasing of β selectivity was observed when low temperature (–78 °C) was applied (Figure 1.10). The generation of stable glycosyl triflate intermediate at low temperature allowed acceptor **19** to attack on the β face.[19]



Temp. (°C)	Yield (%)	α:β
35	96	5:1
rt	84	7:1
-30	95	6:1
0	90	2.5:1.0
-78	50	1:3

Figure 1.10 Glycosylation of glycosyl donor **24** and glycosyl acceptor **19** at low temperature.

1.4 Mechanistic study of intermediate for glycosylation

To understand the mechanism of glycosylation, several glycosyl intermediates were monitored by NMR spectroscopy. In 2011, Mydock and co-workers[20] reported glycosyl sulfonium intermediate **26** as an intermediate when activation of ethyl thioglycoside **25** with MeOTf. ^{1}H NMR spectra showed that the anomeric H1 doublet signal of **26** shifted downfield to 5.27 ppm compared with H1 signal of **25**. This stable intermediate **26** (survived on preparative TLC) can be further applied as a donor to probe mechanism of thioglycoside with different conditions.

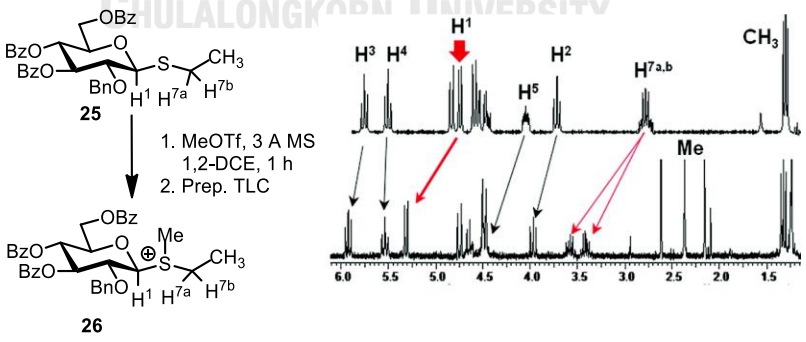


Figure 1.11 Mechanistic study of glycosyl sulfonium intermediate monitored by ^{1}H NMR.

Nokami and co-workers[21] also studied the intermediate of glycosylation. Glycosyl intermediate **29**/**30** were prepared by the addition of sulfides to an electrochemically generated glycosyl triflate **28** under low temperature as shown in Figure 1.12. The NMR result showed the proton signal of H1 of intermediate **29** was shifted to high field. Moreover, when dimethyl sulfide (Me_2S) was added to a solution of glycosyl triflate **28**, a single peak of β isomer was detected (Figure 12b). In contrast, when methyl phenyl sulfide (MeSPh) was added to a solution of glycosyl triflate **28**, the glycosyl sulfonium intermediate **30** was obtained. The ^{1}H NMR showed that the peaks of anomeric proton were attributed to the two signals hence there were 2 typed of intermediates (Figure 12c).

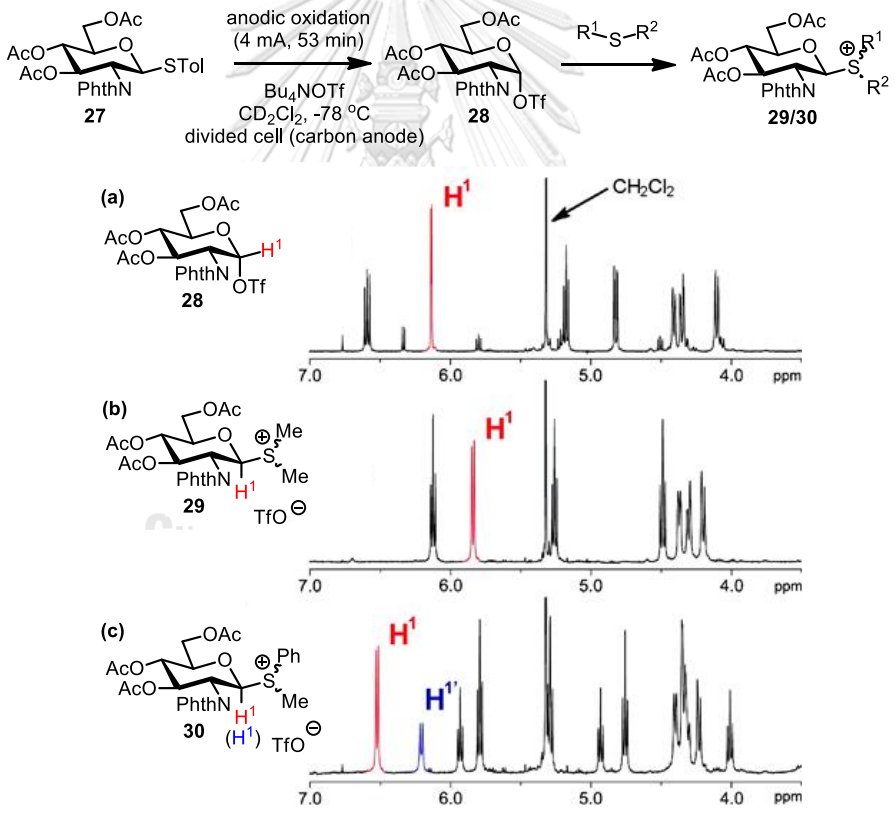


Figure 1.12 ^{1}H NMR spectra of (a) glycosyl triflate **28**, (b) glycosyl sulfonium ion **29**, and (c) glycosyl sulfonium ion **30**.

Furthermore, Kaeothip and co-workers[22] reported a generation of glycosyl bromide **32**. Ethyl thioglycoside **31** was activation with bromine in $CDCl_3$. The glycosyl bromine **32** was detected by ^1H NMR. When the reaction was proceeded for 5 minutes, the mixture of α and β glycosyl bromine was observed (α:β = 1:11). These anomeric proton signal of **32a** and **32b** were shifted to downfield. Next, when the reaction was monitored at 3 and 10 hours, the increasing of α selectivity was observed (Figure 1.13).

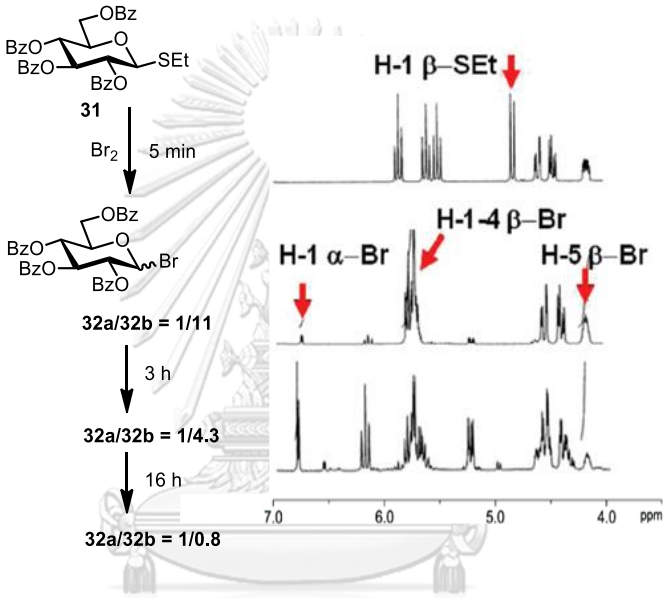
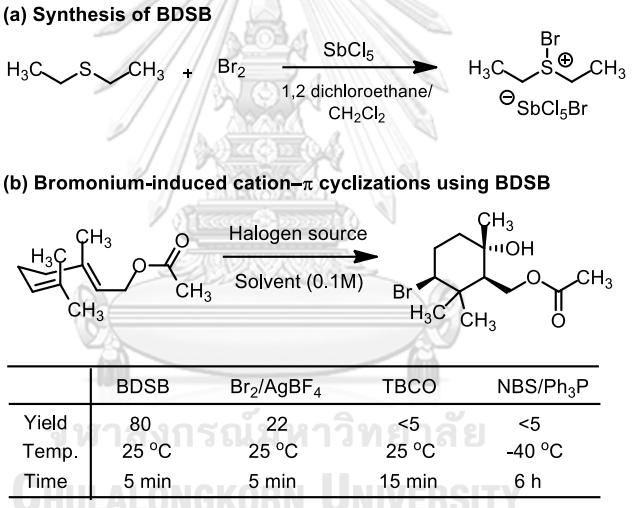


Figure 1.13 *In situ* generation of glycosyl bromide monitored by NMR.

1.5 Bromodiethylsulfonium bromopentachloroantimonate (BDSB)

Recently, a new brominating reagent, bromodiethylsulfonium bromopentachloroantimonate (BDSB) was first introduced by Snyder and Treitler (Figure 1.14a).[23] It was synthesized by bromination of diethylsulfide in the presence of Lewis acid, $SbCl_5$. It was used as an electrophilic brominating source for the cation-π cyclizations of polyene. In 2009, cyclizations of geraniol derivatives were performed by using different halogen sources such as BDSB, $Br_2/AgBF_4$, TBCO, and NBS/Ph_3P. The results showed that using BDSB as brominating reagent, cyclizations were completed in 5 minutes and products were obtained in high yield (80%) compared with other halogen sources (Figure 1.14b).[24]



	BDSB	$Br_2/AgBF_4$	TBCO	NBS/Ph_3P
Yield	80	22	<5	<5
Temp.	25 °C	25 °C	25 °C	-40 °C
Time	5 min	5 min	15 min	6 h

Figure 1.14 (a) Synthesis of bromodiethylsulfonium bromopentachloroantimonate (BDSB) and (b) cation-π cyclizations of geraniol derivatives.

Hence, this result indicated such high electrophilicity of BDSB. Moreover, lower cost, stability, and structural similarity of BDSB compared to that of bromodimethylsulfonium bromide (BDMS) convinced us to examine the use of BDSB as an activator in glycosylation. Herein we first examined the use of BDSB as a novel activator of thioglycosides for glycosylation. Second, the scope of substrates was investigated. Finally, the glycosyl intermediate of this reaction was studied through NMR spectroscopy.

1.6 Objectives

1. To Investigate the optimal conditions of glycosylation by using BDSB as a novel activator. The effect of activator, solvent, and temperature for glycosylation will be studied.

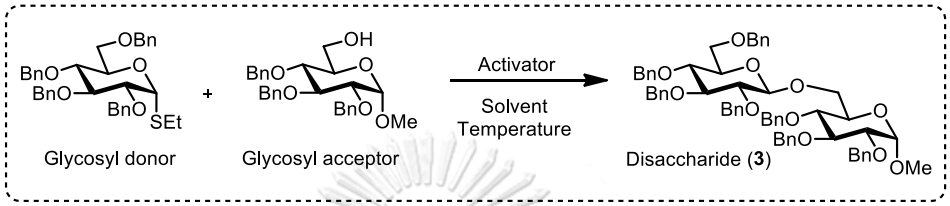


Figure 1.15 Glycosylation between glycosyl donor and glycosyl acceptor in various conditions.

2. To investigate scope of substrates in the glycosylation by using the optimal condition . Glycosylation with various donors and acceptors will be studied.

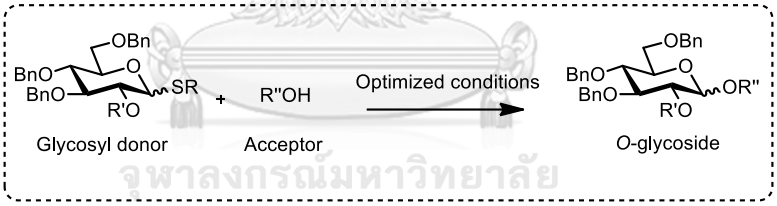


Figure 1.16 Investigation of glycosyl donors and acceptors for glycosylation.

CHAPTER II

EXPERIMENTAL SECTION

2.1 Chemicals and materials

All chemicals were purchased and used without further purification. Commercial organic solvents were used for column chromatography. For glycosylation, all glassware was flame-dried under vacuum and backfilled with argon gas. Reactions were performed under positive pressure by using argon balloon. Activated molecular sieves (3 Å) were used for anhydrous conditions and glycosylations. Dried solvents were taken from a solvent purification system and kept over 4 Å molecular sieves prior to use. All reactions were monitored by thin layer chromatography (TLC). Compounds on TLC plates were detected by UV lamp at 254 nm or staining with *p*-anisaldehyde solution and heated. Column chromatography was performed on silica gel 60 (70-230 mesh). Deuterated solvents such as $CDCl_3$ and CD_3CN were used for NMR experiments.

2.2 Instruments and equipment

NMR spectra were recorded on Varian Mercury 400 MHz, Bruker Avance 400 MHz and Jeol EZC 400 MHz. EYELA rotary evaporator model N-1000 together with digital water bath model SB-1000 and pump form SIBATA circulating aspirator model WJ-20 were used to concentrate the solutions to dryness. Buchi Rotavapor model R210, heating bath model B493 and a DAIKAWA vacuum pump model 2Vp-180L 0.5 Pa. were used for azeotropic distillation to remove trace of moisture.

2.3 Synthesis of glycosyl donors

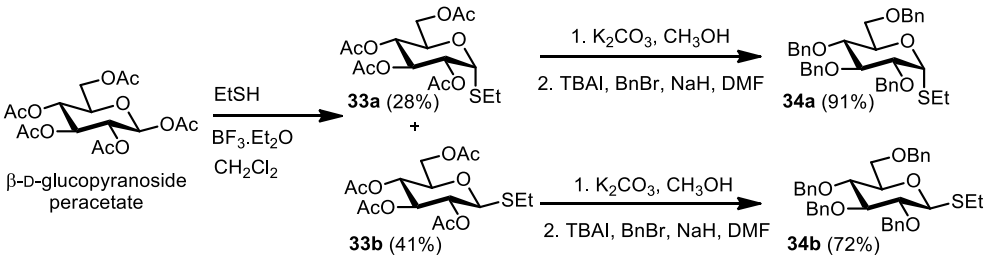


Figure 2.1 Synthesis of ethyl thioglucopyranosides **33a**, **33b**, **34a**, and **34b**.

2.3.1 Synthesis of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (**33a**) and ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**33b**)

Ethane thiol (1.1 mL, 14.9 mmol) and 3 Å MS (500 mg) were added into the solution of β-D-glucopyranoside peracetate (5 g, 12.8 mmol) in dried dichloromethane (CH_2Cl_2, 0.1 M) and the reaction was stirred for 30 minutes under positive pressure. After that, the reaction was cooled in the ice bath and $BF_3.Et_2O$ (3.2 mL, 25.9 mmol) was added by using gastight syringe. The reaction was stirred continuously at room temperature for overnight. After reaction was complete, reaction was neutralized by addition of saturated sodium hydrogen carbonate ($NaHCO_3$) 15 mL and extracted with CH_2Cl_2 three times (3x15 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with sodium sulfate (Na_2SO_4) and concentrated under reduced pressure to give crude as a pale yellow syrup. The crude product was purified by silica gel chromatography using 0, 5, 10, 20, 30, and 35% ethyl acetate/hexanes (EtOAc/hex) gradients. A mixture of α and β anomer were obtained as white solid. To separate α and β products, the mixture was recrystallized with diethyl ether/hexanes (Et_2O/hex) three times to get a white solid of α anomer **33a** (1.40 g, 3.57 mmol, 28%). After that, the filtrate was evaporated to remove solvents to get a white solid of β product **33b** (2.04 g, 5.20 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) of **33a**: δ 5.68 (d, *J* = 5.8 Hz, 1H), 5.36 (t, *J* = 9.8 Hz, 1H), 5.10–4.98 (m, 2H), 4.44 (m, 1H), 4.30 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.08 (dd, *J* = 12.3, 2.0 Hz, 1H), 2.66–2.48 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.27 (t, *J* = 7.4 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) of **33b**: δ 5.22 (t, *J* = 9.4

Hz, 1H), 5.14–4.97 (m, 2H), 4.50 (d, *J* = 10.0 Hz, 1H), 4.24 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.14 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.71 (m, 1H), 2.80–2.61 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.27 (t, *J* = 7.4 Hz, 3H).

2.3.2 Synthesis of ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (**34a**)

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside **33a** (701 mg, 1.79 mmol) was deprotonated by catalytic potassium carbonate (K_2CO_3, 26 mg, 0.19 mmol) in methanol (0.1 M) at room temperature for 3 hours. After removal of methanol, tetrabutylammonium iodide (TBAI, 66 mg, 0.18 mmol) was added. The mixture was then azeotroped with toluene and acetonitrile. After that, the mixture was treated with benzyl bromide (BnBr, 1 mL, 8.41 mmol) and sodium hydride (NaH, 60% dispersion in mineral oil, 572 mg, 14.3 mmol) in dimethyl formamide (DMF, 0.2 M) at 0 °C. The reaction was warmed slowly to room temperature by overnight stirring in the ice bath. The reaction was neutralized by addition of saturated $NaHCO_3$ 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a light brown syrup. The crude product was purified by silica gel chromatography using 0, 5, and 10% EtOAc/hex gradients to yield a white solid **34a** (948 mg, 1.62 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) of **34a**: δ 7.43–7.07 (m, 20H), 5.41 (d, *J* = 4.5 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.86–4.57 (m, 5H), 4.46 (dd, *J* = 11.4, 5.6 Hz, 2H), 4.19 (m, 1H), 3.89–3.80 (m, 2H), 3.76 (dd, *J* = 10.7, 3.7 Hz, 1H), 3.64 (t, *J* = 8.8 Hz, 2H), 2.64–2.45 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H).[25]

2.3.3 Synthesis of ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**34b**)

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **33b** (500 mg, 1.27 mmol) was deprotonated by catalytic K_2CO_3 (24 mg, 0.17 mmol) in methanol (0.1 M) at room temperature for 3 hours. After removal of methanol, TBAI (47 mg, 0.13 mmol) was added. The mixture was then azeotroped with toluene and acetonitrile. After that, the mixture was treated with BnBr (730 μL, 6.14 mmol) and NaH (412 mg, 10.3 mmol) in DMF (0.2 M) at 0 °C. The reaction was warmed slowly to room

temperature by overnight stirring in the ice bath. The reaction was neutralized by addition of saturated $NaHCO_3$ 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a light brown syrup. The crude product was purified by silica gel chromatography using 0, 5, and 10% EtOAc/hex gradients to get a white solid **34b** (532 mg, 0.91 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) of **34b**: δ 7.41–7.13 (m, 20H), 4.98–4.78 (m, 4H), 4.74 (d, *J* = 10.2 Hz, 1H), 4.64–4.52 (m, 3H), 4.47 (d, *J* = 9.8 Hz, 1H), 3.78–3.65 (m, 3H), 3.61 (t, *J* = 9.3 Hz, 1H), 3.46 (dd, *J* = 16.7, 7.5 Hz, 2H), 2.87–2.67 (m, 2H), 1.33 (t, *J* = 7.4 Hz, 3H).[26]

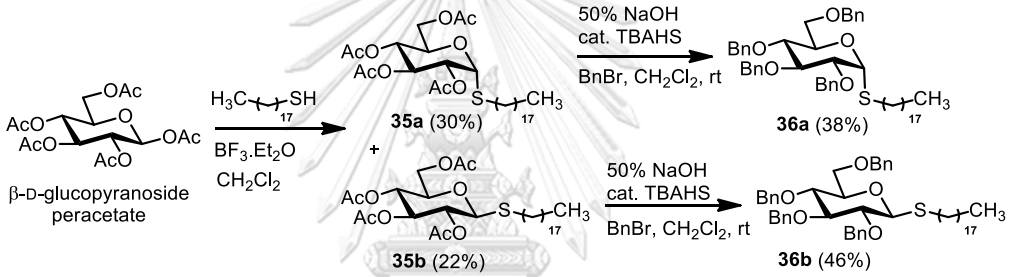


Figure 2.2 Synthesis of octadecyl thioglucopyranosides **35a**, **35b**, **36a**, and **36b**.

2.3.4 Synthesis of octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (**35a**) and octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**35b**)

Octadecane thiol (880 mg, 3.07 mmol) was added into the solution of β-D-glucopyranoside peracetate (1 g, 2.56 mmol) in dried CH_2Cl_2 (0.4 M) and the reaction was stirred for 30 minutes under positive pressure. After that, the reaction was cooled in the ice bath and $BF_3.Et_2O$ (800 μL, 6.48 mmol) was added by using gastight syringe. The reaction was stirred continuously at room temperature for overnight. At that point, reaction was neutralized by addition of saturated $NaHCO_3$ 10 mL and extracted with CH_2Cl_2 three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by recrystallization (three times) with Et_2O/hex (1/100 ratio) to

get a white solid of β product **35b** (348 mg, 0.56 mmol, 22%). After that, the filtrate was concentrated and purified by silica gel chromatography using 0, 5, 10, 15, and 20% EtOAc/hex gradients to get a white solid of α product **35a** (477 mg, 0.77 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) of **35a**: δ 5.65 (d, *J* = 5.8 Hz, 1H), 5.36 (t, *J* = 9.8 Hz, 1H), 5.08–4.98 (m, 2H), 4.43 (m, 1H), 4.30 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.07 (dd, *J* = 12.3, 2.1 Hz, 1H), 2.62–2.41 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.57 (m, 2H), 1.39–1.17 (m, 28H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) of **35b**: δ 5.21 (t, *J* = 9.4 Hz, 1H), 5.05 (m, 2H), 4.47 (d, *J* = 10.0 Hz, 1H), 4.24 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.13 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.70 (m, 1H), 2.74–2.58 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.64–1.49 (m, 2H), 1.42–1.16 (m, 30H), 0.87 (t, *J* = 6.8 Hz, 3H).[27]

2.3.5 Synthesis of octadecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (**36a**)

BnBr (172 μL, 1.45 mmol) and tetrabutylammonium hydrogen sulfate (TBAHS, 27 mg, 0.08 mmol) were added to the solution of 50% sodium hydroxide (50% NaOH, 1.6 mL). The reaction mixture was stirred vigorously for 30 minutes. After that, octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside **35a** (100 mg, 0.16 mmol) and CH_2Cl_2 (3 mL) were added. The reaction was stirred for overnight at room temperature. After the reaction was monitored by TLC and found that half of substrate was still remained. The reaction was stirred more for 4 days. At that point, the reaction was neutralized by addition of saturated ammonium chloride (NH_4Cl) 10 mL and extracted with CH_2Cl_2 three times (3x5 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a brown syrup. The crude product was purified by silica gel chromatography using 0 and 5% EtOAc/hex gradients to get a white solid **36a** (50 mg, 0.06 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) of **36a**: δ 7.44–7.06 (m, 23H), 5.36 (d, *J* = 4.8 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 4.86–4.54 (m, 5H), 4.18 (d, *J* = 8.5 Hz, 1H), 3.84 (m, 2H), 3.76 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.67–3.54 (m, 2H), 2.51 (m, 2H), 1.31 (m, 32H), 0.88 (t, *J* = 6.7 Hz, 3H).[27]

2.3.6 Synthesis of octadecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**36b**)

BnBr (800 μL, 6.73 mmol) and TBAHS (137 mg, 0.40 mmol) were added to the solution of 50% NaOH (8 mL). The reaction mixture was stirred vigorously for 30 minutes. After that, octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **35b** (500 mg, 0.81 mmol) and CH_2Cl_2 (8 mL) were added. The reaction was stirred for overnight at room temperature. After the reaction was monitored by TLC and found that half of substrate was still remained. So, the reaction was stirred more for 3 days. At that point, the reaction was neutralized by addition of saturated NH_4Cl 10 mL and extracted with CH_2Cl_2 three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude as a brown syrup. The crude product was purified by silica gel chromatography using 0, 5 and 10% EtOAc/hex gradients to get a white solid **36b** (297 mg, 0.37 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) of **36b**: δ 7.42–7.08 (m, 20H), 4.92 (dd, *J* = 10.7, 2.5 Hz, 2H), 4.87–4.78 (m, 2H), 4.73 (d, *J* = 10.2 Hz, 1H), 4.65–4.49 (m, 3H), 4.43 (d, *J* = 9.7 Hz, 1H), 3.66 (m, 4H), 3.44 (m, 2H), 2.81–2.64 (m, 2H), 1.72–1.60 (m, 2H), 1.31 (m, *J* = 53.8 Hz, 30H), 0.87 (t, *J* = 6.6 Hz, 3H).[27]

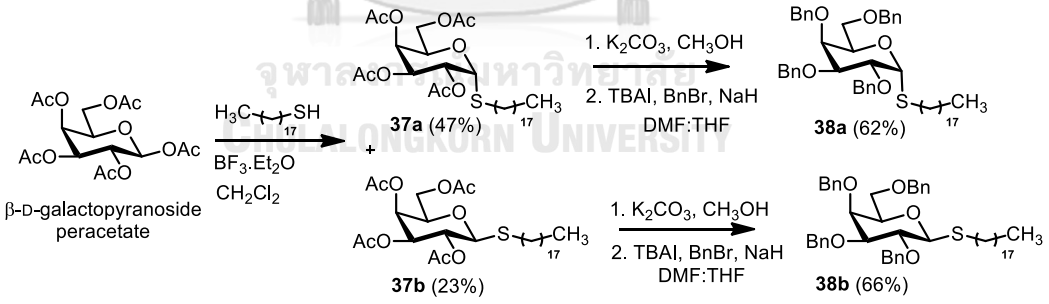


Figure 2.3 Synthesis of octadecyl thiogalactopyranosides **37a**, **37b**, **38a**, and **38b**.

2.3.7 Synthesis of octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-galactopyranoside (**37a**) and octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**37b**)

Octadecane thiol (880 mg, 3.07 mmol) was added into the solution of β-D-galactopyranoside peracetate (1 g, 2.56 mmol) in dried CH_2Cl_2 (0.4 M). The reaction was stirred for 30 minutes under positive pressure. After that, the reaction was

cooled in ice bath and $BF_3.Et_2O$ (790 μL, 6.40 mmol) was added by using gastight syringe. The reaction was stirred continuously at room temperature for overnight. At that point, reaction was neutralized by addition of saturated $NaHCO_3$ 10 mL and extracted with CH_2Cl_2 three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by silica gel chromatography using 0, 5, 10, 15, and 20% EtOAc/hex gradients to get white solid of α product **37a** (746 mg, 1.21 mmol, 47%) and β product **37b** (372 mg, 0.60 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) of **37a**: δ 5.71 (d, *J* = 5.2 Hz, 1H), 5.44 (d, *J* = 2.5 Hz, 1H), 5.24 (m, 2H), 4.58 (t, *J* = 6.5 Hz, 1H), 4.10 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.52 (m, 2H), 2.14 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.43–1.15 (m, 30H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) of **37b**: δ 5.42 (d, *J* = 3.1 Hz, 1H), 5.23 (t, *J* = 10.0 Hz, 1H), 5.04 (dd, *J* = 10.0, 3.3 Hz, 1H), 4.47 (d, *J* = 9.9 Hz, 1H), 4.13 (qd, *J* = 11.3, 6.7 Hz, 2H), 3.92 (t, *J* = 6.6 Hz, 1H), 2.78–2.55 (m, 2H), 2.15 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.98 (s, 3H), 1.46–1.14 (m, 32H), 0.87 (t, *J* = 6.7 Hz, 3H).

2.3.8 Synthesis of octadecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-galactopyranoside (**38a**)

Octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-galactopyranoside **37a** (400 mg, 0.65 mmol) was deprotonated by catalytic K_2CO_3 (9 mg, 0.07 mmol) in methanol (0.1 M) at room temperature for 3 hours. After removal of methanol, TBAI (25 mg, 0.07 mmol) was added. The mixture was azeotroped with toluene and acetonitrile before using. After that, the mixture was dissolved in 2:1 mixture of DMF:THF (6 mL). Then BnBr (530 μL, 4.50 mmol) and NaH (318 mg, 8.0 mmol) was added at 0 °C. The reaction was warmed slowly to room temperature by overnight stirring in an ice bath. The reaction was neutralized by addition of saturated NH_4Cl 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a brown syrup. The crude product was purified by silica gel chromatography using 0, 5, and 10% EtOAc/hex

gradients to get a white solid **38a** (324 mg, 0.40 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) of **38a**: δ 7.46–7.15 (m, 20H), 5.46 (d, *J* = 5.5 Hz, 1H), 4.94 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.78–4.63 (m, 3H), 4.62–4.53 (m, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.35–4.22 (m, 2H), 3.93 (m, 1H), 3.80 (dd, *J* = 9.9, 2.8 Hz, 1H), 3.59–3.47 (m, 2H), 2.51 (m, 2H), 1.64–1.48 (m, 2H), 1.42–1.15 (m, 30H), 0.88 (t, *J* = 6.8 Hz, 3H).

2.3.9 Synthesis of octadecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (**38b**)

Octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **37b** (200 mg, 0.32 mmol) was deprotonated by catalytic K_2CO_3 (7 mg, 0.05 mmol) in methanol (0.1 M) at room temperature for 3 hours. After removal of methanol, TBAI (12 mg, 0.03 mmol) was added. The mixture was azeotroped with toluene and acetonitrile. After that, the mixture was dissolved in 2:1 mixture of DMF:THF (3 mL). Then BnBr (290 μL, 1.4 mmol) and NaH (167 mg, 4.2 mmol) were added at 0 °C. The reaction was warmed slowly to room temperature by overnight stirring in an ice bath. The reaction was neutralized by addition of saturated NH_4Cl 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a brown syrup. The crude product was purified by silica gel chromatography using 0, 5, and 10% EtOAc/hex gradients to get a white solid **38b** (172 mg, 0.21 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) of **38b**: δ 7.44–7.18 (m, 20H), 4.95 (d, *J* = 11.7 Hz, 1H), 4.88 (d, *J* = 10.1 Hz, 1H), 4.79 (d, *J* = 10.1 Hz, 1H), 4.73 (s, 2H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.43 (m, 3H), 3.96 (d, *J* = 2.3 Hz, 1H), 3.82 (t, *J* = 9.4 Hz, 1H), 3.57 (m, 4H), 2.79–2.60 (m, 2H), 1.71–1.58 (m, 2H), 1.41–1.16 (m, 30H), 0.88 (t, *J* = 6.7 Hz, 3H).

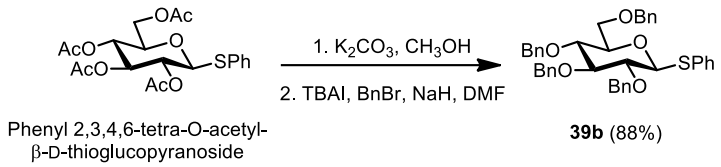


Figure 2.4 Synthesis of phenyl thioglucopyranoside **39b**.

2.3.10 Synthesis of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**39b**)

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (500 mg, 1.14 mmol) was deprotonated by catalytic K_2CO_3 (16 mg, 0.12 mmol) in methanol (0.1 M) at room temperature for 3 hours. After removal of methanol, TBAI (48 mg, 0.13 mmol) was added. The mixture was azeotroped with toluene and acetonitrile. After that, the mixture was dissolved in DMF (0.1 M) then treated with BnBr (650 μL, 5.47 mmol) and NaH (365 mg, 9.13 mmol) at 0 °C. The reaction was warmed slowly to room temperature by overnight stirring in the ice bath. The reaction was neutralized by addition of saturated NH_4Cl 20 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by silica gel chromatography using 0, 5, 10, and 15% EtOAc/hex gradients to get a white solid **39b** (637 mg, 1.01 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) of **39b**: δ 7.61 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.45–7.18 (m, 23H), 4.89 (m, 4H), 4.75 (d, *J* = 10.3 Hz, 1H), 4.69 (d, *J* = 9.7 Hz, 1H), 4.60 (m, 3H), 3.85–3.78 (m, 1H), 3.78–3.63 (m, 3H), 3.53 (t, *J* = 9.1 Hz, 2H).[28]

2.4 Synthesis of glycosyl acceptors

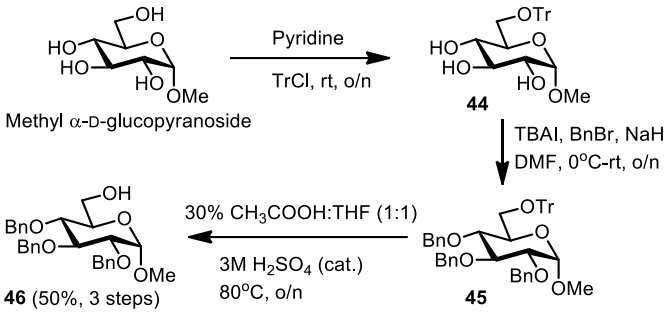


Figure 2.5 Synthesis of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **46**.

2.4.1 Synthesis of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**46**)

Methyl α-D-glucopyranoside (1.04 g, 5.36 mmol) and trityl chloride (TrCl, 3 g, 10.8 mmol) were azeotroped with toluene prior to use. Dried pyridine (0.3 M) was added and the reaction was stirred at room temperature for overnight. After the reaction was completed, pyridine was evaporated under reduced pressure by using toluene and acetonitrile as cosolvent to get a yellow syrup of **44**. TBAI (198 mg, 0.54 mmol) was added into the reaction flask of **44** and then the mixture of crude and TBAI was azeotroped with toluene and acetonitrile. After that, the mixture was dissolved in DMF (0.2 M) then the reaction was treated with BnBr (4.6 mL, 38.6 mmol) and NaH (2.6 g, 65.0 mmol) at 0 °C. The reaction was slowly warmed to room temperature by overnight stirring in an ice bath. The reaction was neutralized by addition of saturated NH_4Cl 50 mL and extracted with EtOAc three times (3x20 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a dark brown syrup. The crude product was purified by silica gel chromatography using 0, 5, 10, 20, 30, and 35% EtOAc/hex gradients to get compound **45** as a pale yellow solid (yield of **45** was not calculated because the TrCl was still remained with compound **45**).

To deprotect of trityl group at C6 of compound **45**, THF (25 mL, 0.05 M) and 30% acetic acid (25 mL, 0.05M) were added to **45** and then 3 M of H_2SO_4 was added as a catalytic. The reaction was stirred at 80 °C for overnight. The reaction was

neutralized by addition of saturated $NaHCO_3$ 10 mL and extracted with EtOAc three (3x20 mL) times. The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by silica gel chromatography using 0, 10, 20, 30, 40, 50, and 60% EtOAc/hex gradients to get compound **46** as a white solid (1.25 g, 2.70 mmol, 50% over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) of **46**: δ 7.41–7.24 (m, 15H), 4.99 (d, *J* = 10.9 Hz, 1H), 4.92–4.77 (m, 3H), 4.65 (m, 2H), 4.57 (d, *J* = 3.5 Hz, 1H), 4.01 (t, *J* = 9.2 Hz, 1H), 3.77 (dd, *J* = 11.5, 2.2 Hz, 1H), 3.73–3.61 (m, 2H), 3.56–3.44 (m, 3H), 3.36 (s, 3H).[29]

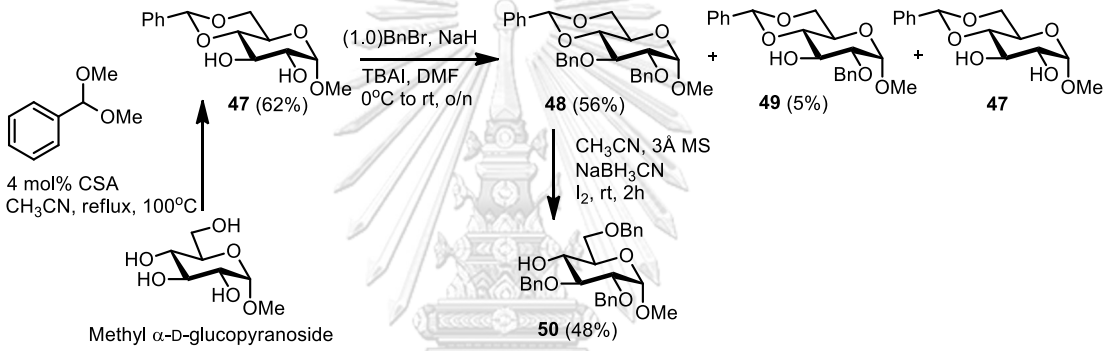


Figure 2.6 Synthesis of glycosyl acceptors **49** and **50**.

2.4.2 Synthesis of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**47**)

Methyl α-D-glucopyranoside (5 g, 25.8 mmol) and (–)-camphor-10-sulfonic acid (CSA, 250 mg, 1.08 mmol) were azeotroped with toluene and acetonitrile. The reaction was dissolved in dried acetonitrile (0.6 M). After that, the reaction was stirred at 90 °C for overnight. The reaction was quenched by addition of saturated $NaHCO_3$ 5 mL and extracted with EtOAc three times (3x30 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by crystallization (three times) with EtOAc/hex to get a white solid of **47** (4.23 g, 15.0 mmol, 58%). After that, the mother liquor was concentrated and purified by silica gel chromatography using 50, 60, 70, 80, 90, and 100% EtOAc/hex gradients to get more white solid of **47** (282 mg, 1.0 mmol, 4%). Methyl

4,6-*O*-benzylidene-α-D-glucopyranoside **47** was obtained in total of 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) of **47**: δ 7.49 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.37 (dd, *J* = 5.1, 1.9 Hz, 3H), 5.54 (s, 1H), 4.81 (d, *J* = 3.9 Hz, 1H), 4.30 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.94 (t, *J* = 9.2 Hz, 1H), 3.86–3.70 (m, 2H), 3.64 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.50 (t, *J* = 7.9 Hz, 1H), 3.47 (s, 3H).[30]

2.4.3 Synthesis of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**49**)

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **47** (2 g, 7.08 mmol) and TBAI (261 mg, 0.71 mmol) was azeotroped with toluene and acetonitrile. After that, the mixture was dissolved in DMF (0.2 M) then the reaction was treated with BnBr (900 μL, 7.57 mmol) and NaH (1.15 g, 28.75 mmol) at 0 °C. The reaction was warmed slowly to room temperature by overnight stirring in an ice bath. The reaction was neutralized by addition of saturated NH_4Cl 30 mL and extracted with EtOAc three times (3x20 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a brown syrup. The crude product was purified by silica gel chromatography using 10, 15, 20, 30, 40, 50, 60 and 80% EtOAc/hex gradients to get a white solid **48** (1.83 g, 3.94 mmol, 56%) and a yellow syrup **49** (128 mg, 0.34 mmol, 5%). Moreover, the starting material **47** was recovered in 173 mg. ^{1}H NMR (400 MHz, $CDCl_3$) of **48**: δ 7.54–7.21 (m, 15H), 5.55 (s, 1H), 4.87 (m, 3H), 4.70 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 3.7 Hz, 1H), 4.27 (dd, *J* = 10.1, 4.7 Hz, 1H), 4.05 (t, *J* = 9.3 Hz, 1H), 3.83 (td, *J* = 9.9, 4.7 Hz, 1H), 3.71 (t, *J* = 10.2 Hz, 1H), 3.60 (t, *J* = 9.5 Hz, 1H), 3.56 (dd, *J* = 9.3, 3.7 Hz, 1H), 3.41 (s, 3H).[30] ^{1}H NMR (400 MHz, $CDCl_3$) of **49**: δ 7.53–7.26 (m, 10H), 5.50 (s, 1H), 4.77 (d, *J* = 12.2 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 3.6 Hz, 1H), 4.25 (dd, *J* = 10.1, 4.7 Hz, 1H), 4.14 (t, *J* = 9.3 Hz, 1H), 3.80 (td, *J* = 9.9, 4.7 Hz, 1H), 3.69 (t, *J* = 10.2 Hz, 1H), 3.54–3.42 (m, 2H), 3.36 (s, 3H).[31]

2.4.4 Synthesis of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**50**)

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **48** (500 mg, 1.08 mmol) and molecular sieves (3 Å) in dried acetonitrile (0.1 M) were stirred at room temperature for 1 hour. Sodium cyanoborohydride ($NaBH_3CN$, 350 mg, 5.57

mmol) was added to the reaction and stirred for 5 minutes. After that, iodine (I_2, 965 mg, 3.80 mmol) was added. The reaction was completed in an hour. The reaction was quenched by addition of saturated $NaHCO_3$ 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by silica gel chromatography using 0, 10, 20, 30, 40, and 50% EtOAc/hex gradients to get compound **50** as a colorless syrup (240 mg, 0.52 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) of **50**: δ 7.41–7.23 (m, 15H), 5.00 (d, *J* = 11.4 Hz, 1H), 4.80–4.51 (m, 6H), 3.78 (t, *J* = 9.1 Hz, 1H), 3.74–3.64 (m, 3H), 3.59 (dd, *J* = 15.5, 6.2 Hz, 1H), 3.53 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.38 (s, 3H).[32]

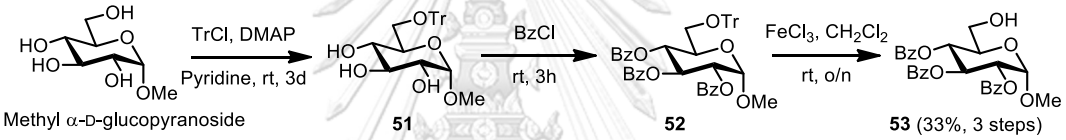


Figure 2.7 Synthesis of methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside **53**.

2.4.5 Synthesis of methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**53**)

Methyl α-D-glucopyranoside (200 mg, 1.03 mmol), TrCl (345 mg, 1.24 mmol), and 4-dimethylaminopyridine (DMAP, 63 mg, 0.52 mmol) were azeotroped with toluene prior to use. Dried pyridine (0.1 M) was added and the reaction was stirred at room temperature for 3 days. After complete reaction, the remaining hydroxy groups of **51** was protected by treating with BzCl (180 μL, 1.55 mmol) and the reaction was stirred for 3 hours under positive pressure of Ar. Pyridine was removed by evaporating with toluene and acetonitrile as cosolvent. After that, the concentrated solution was neutralized with saturated $NaHCO_3$ 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give crude **52** as a yellow syrup. The trityl group at C6 position of crude **52** was detritylated without purification. Ferric chloride ($FeCl_3$, 250 mg, 1.54 mmol) was added to the solution of crude **52** in CH_2Cl_2 (0.1 M). The reaction was

stirred at room temperature for overnight. The reaction was quenched by addition of saturated $NaHCO_3$ 10 mL and extracted with EtOAc three times (3x10 mL). The organic layers were washed with distilled water and brine. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to give crude as a yellow syrup. The crude product was purified by silica gel chromatography using 0, 10, 20, 30, 35, and 40% EtOAc/hex gradients to get compound **53** as a white solid (171 mg, 0.34 mmol, 33% over 3 steps). ^{1}H NMR (400 MHz,) of **53**: δ 8.00–7.94 (m, 4H), 7.87 (m, 2H), 7.53–7.46 (m, 2H), 7.42–7.32 (m, 5H), 7.29–7.23 (m, 2H), 6.23 (t, *J* = 9.7 Hz, 1H), 5.52 (t, *J* = 9.9 Hz, 1H), 5.28 (dt, *J* = 6.6, 3.6 Hz, 2H), 4.05 (m, 1H), 3.83 (dd, *J* = 12.9, 2.2 Hz, 1H), 3.74 (dd, *J* = 12.9, 3.8 Hz, 1H), 3.47–3.44 (m, 3H).[33]

2.5 Preliminary screening of glycosyl donor for glycosylation

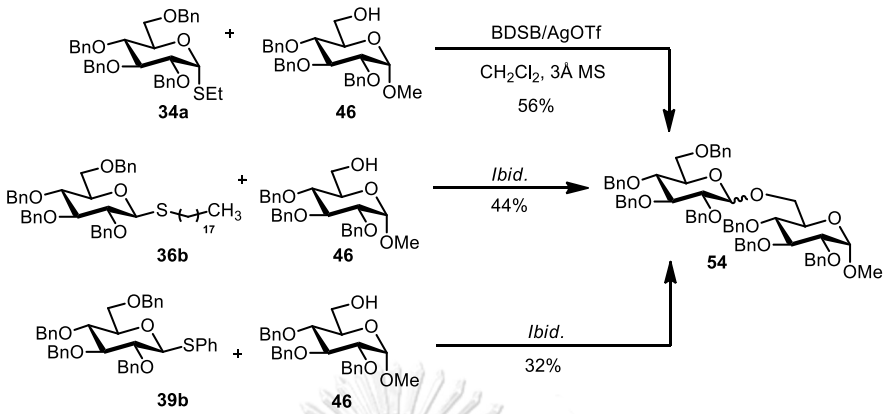


Figure 2.8 Glycosylation with three different glycosyl donors (**34a**, **36b**, and **39b**).

2.5.1 Glycosylation by using ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (**34a**) as glycosyl donor

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside **34a** (58 mg, 0.10 mmol) and glycosyl acceptor **46** (69 mg, 0.15 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried CH_2Cl_2 (0.1 M) were added and the reaction was stirred at room temperature for 30 minutes under argon balloon. The reaction was treated with dried AgOTf (42 mg, 0.16 mmol) and BDSB (90 mg, 0.16 mmol) at 0 °C and stirred for 35 minutes. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL then extracted with CH_2Cl_2 three times (3x1 mL). The combined organic layers were wash with distilled water and brine and dried with Na_2SO_4. The organic layer was concentrated to get crude as a yellow syrup. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25, and 30% EtOAc/hex gradients to get a white solid of product **54** (55 mg, 0.056 mmol, 56%, α:β = 40:60). ^{1}H NMR spectra of **54** is consistent with previous report.[34]

2.5.2 Glycosylation by using octadecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**36b**) as glycosyl donor

Octadecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **36b** (201 mg, 0.25 mmol) and glycosyl acceptor **46** (232 mg, 0.50 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried CH_2Cl_2 (0.1 M) were added and the reaction was stirred at room temperature for 30 minutes under argon balloon. The reaction was treated with dried AgOTf (97 mg, 0.38 mmol) and BDSB (206 mg, 0.38 mmol) at 0 °C. After that, the reaction was warmed slowly to room temperature for 1 hour. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL then extracted with CH_2Cl_2 three times (3x1 mL). The combined organic layers were washed with distilled water and brine and dried with Na_2SO_4. The organic layer was concentrated to get crude as a yellow syrup. The crude was purified by silica gel chromatography using 20, 25, and 30% EtOAc/hex gradients to get a white solid of product **54** (111 mg, 0.11 mmol, 44%, α:β = 50:50).

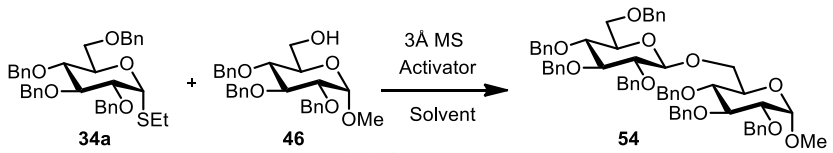
2.5.3 Glycosylation by using phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**39b**) as glycosyl donor

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **39b** (50 mg, 0.079 mmol) and glycosyl acceptor **46** (56 mg, 0.12 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried CH_2Cl_2 (0.1 M) were added and the reaction was stirred at room temperature for 30 minutes under argon balloon. The reaction was treated with dried AgOTf (38 mg, 0.15 mmol) and BDSB (68 mg, 0.12 mmol) at 0 °C. After that, the reaction was warmed slowly to room temperature for overnight. At that point, the reaction was quenched with $NaHCO_3$ 0.5 mL and extracted with CH_2Cl_2 three times (3x1 mL). The combined organic layers were wash with distilled water and brine and dried with Na_2SO_4. The organic layer was concentrated to give crude as a yellow syrup. The crude was purified by silica gel chromatography using 0, 5, 10, 15 and 20% EtOAc/hex gradients to get product **54** (25 mg, 0.025 mmol, 32%, α:β = 50:50).

2.6 Optimization conditions of glycosylation by using BDSB as an activator

2.6.1 Investigation of the optimal conditions for glycosylation

Table 2.1 Glycosylation of donor **34a** and acceptor **36** with different conditions.



Entry	Activator	Solvent	Temperature	Time	Yield (α:β)
1	BDSB	CH_2Cl_2	0 °C to rt	o/n	64% (55:45)
2	BDSB	CH_3CN	–35 °C to rt	o/n	41% (17:83)
3	BDSB/AgOTf	CH_2Cl_2	0 °C to rt	35 min	56% (40:60)
4	BDSB/AgOTf	CH_3NO_2	–20 °C to rt	o/n	76% (37:63)
5	BDSB/AgOTf	CH_3CN	–35 °C to rt	3 h	79% (β only)
6	BDSB/AgOTf	DMF	–35 °C to rt	o/n	trace

Investigation the optimal conditions of glycosylation by using BDSB as an activator. Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside **34a** (glycosyl donor) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **46** (glycosyl acceptor) were used in different solvent, temperature and activator (Table 2.1).

Entry 1: glycosyl donor **34a** (62 mg, 0.11 mmol) and glycosyl acceptor **46** (102 mg, 0.22 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried CH_2Cl_2 (0.1 M) were added then stirred at room temperature for 30 minutes under argon balloon. Cooling the reaction to 0 °C in an ice bath, BDSB (97 mg, 0.18 mmol) was added and stirred at room temperature for overnight. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction was extracted with CH_2Cl_2 three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried

with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to provide a white solid of disaccharide **54** (69 mg, 0.070 mmol, 64%) with the ratio of α:β = 55:45 (α:β ratio was determined by ^{1}H NMR).

Entry 2: glycosyl donor **34a** (80 mg, 0.14 mmol) and glycosyl acceptor **46** (50 mg, 0.11 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried acetonitrile (0.1 M) were added then stirred at room temperature for 30 minutes under argon balloon. The reaction was treated with BDSB (85 mg, 0.16 mmol) at –35 °C and stirred for 30 minutes. After that, the reaction was stirred and warmed to room temperature for overnight. The reaction was quenched with triethylamine (0.5 mL) and filtrated through a pad of Celite. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of disaccharide **54** (44 mg, 0.045 mmol, 41%) with the ratio of α:β = 17:83 (α:β ratio was determined by ^{1}H NMR).

Entry 3: glycosyl donor **34a** (58 mg, 0.10 mmol) and glycosyl acceptor **46** (69 mg, 0.15 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried CH_2Cl_2 (0.1 M) were added then stirred at room temperature for 30 minutes. The reaction was cooled to 0 °C in the ice bath and then BDSB (90 mg, 0.16 mmol) and dried AgOTf (42 mg, 0.16 mmol) were added. The reaction was stirred at room temperature for 30 minutes. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction was extracted with CH_2Cl_2 three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of disaccharide **54** (55 mg, 0.056 mmol, 56%) with the ratio of α:β = 40:60 (α:β ratio was determined by ^{1}H NMR).

Entry 4: glycosyl donor **34a** (94 mg, 0.16 mmol) and glycosyl acceptor **46** (51 mg, 0.11 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried nitromethane (CH_3NO_2, 0.1M) were added then stirred at room temperature for 30 minutes under argon balloon. After that, BDSB (94 mg, 0.17

mmol) and dried AgOTf (48 mg, 0.19 mmol) were added at –20 °C and stirred for 1 hour. The reaction was stirred and warmed to room temperature for overnight. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of disaccharide **54** (83 mg, 0.084 mmol, 76%) with the ratio of α:β = 37:63 (α:β ratio was determined by ^{1}H NMR).

Entry 5: glycosyl donor **34a** (94 mg, 0.161 mmol) and glycosyl acceptor **46** (50 mg, 0.108 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried acetonitrile (0.1 M) were added then stirred at room temperature for 30 minutes under argon balloon. BDSB (90 mg, 0.164 mmol) and dried AgOTf (48 mg, 0.187 mmol) were added at –35 °C and stirred for 1 hour. The reaction was stirred and warmed to room temperature for 3 hours. The reaction was quenched with triethylamine (1 mL) and filtrated through a pad of Celite. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of β-disaccharide **54b** (84 mg, 0.085 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) of **54b**: δ 7.26–7.06 (m, 35H), 4.89 (dd, *J* = 10.9, 4.8 Hz, 2H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.75–4.40 (m, 12H), 4.27 (d, *J* = 7.7 Hz, 1H), 4.10 (d, *J* = 9.9 Hz, 1H), 3.91 (t, *J* = 9.2 Hz, 1H), 3.79–3.70 (m, 1H), 3.66–3.32 (m, 9H), 3.24 (s, 3H). ^{1}H NMR spectra of **54b** is consistent with previous report.[42]

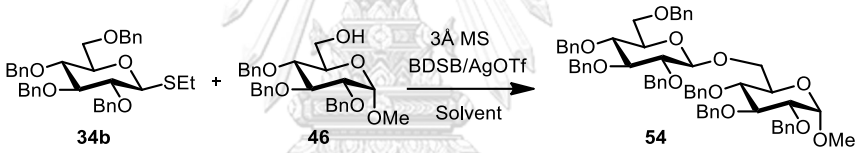
Entry 6: glycosyl donor **34a** (96 mg, 0.164 mmol) and glycosyl acceptor **46** (50 mg, 0.108 mmol) were azeotroped with toluene and acetonitrile. Activated molecular sieves (3 Å) and dried DMF (0.1 M) were added then stirred at room temperature for 30 minutes under argon balloon. BDSB (91 mg, 0.166 mmol) and dried AgOTf (52 mg, 0.202 mmol) were added at –35 °C and stirred for 1 hour. The reaction was stirred and warmed to room temperature for overnight. At that point, the reaction was monitored by TLC and observed there was no consumption of glycosyl acceptor **46** but all glycosyl donor 34a was disappeared. So, the reaction was stopped by quenching with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5

mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated to get the crude as yellow solid. NMR analysis of the crude mixture show only trace amount of the desired product.

After several optimizations, we found that the glycosylation of glycosyl donor **34a** and glycosyl acceptor **46** proceeded smoothly with BDSB/AgOTf in acetonitrile at –35 °C and then allowed to warm up to room temperature, to give disaccharide **54** in good yield and high β selectivity.

2.6.2 The solvent effect of glycosylation activated by BDSB/AgOTf

Table 2.2 Glycosylation of thioglycoside **34b** and acceptor **46** in different solvents.



Entry	Activator	Solvent	Temperature	Time	Yield (α:β)
1	BDSB/AgOTf	CH_2Cl_2	–35 °C to rt	o/n	68% (48:52)
2	BDSB/AgOTf	CH_3CN	–35 °C to rt	o/n	85% (β only)
3	BDSB/AgOTf	Toluene	–35 °C to rt	2d	33% (63:37)
4	BDSB/AgOTf	Et_2O	–35 °C to rt	o/n	66% (55:45)

To study the solvent effect of glycosylation, ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **34b** (glycosyl donor) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **46** (glycosyl acceptor) were used in different solvents such as CH_2Cl_2, acetonitrile, toluene, and Et_2O (Table 2.2).

Entry 1: glycosyl donor **34b** (97 mg, 0.166 mmol) and glycosyl acceptor **46** (51 mg, 0.110 mmol) were azeotroped with toluene and acetonitrile. 3 Å MS and dried CH_2Cl_2 (0.1 M) were added and stirred at room temperature for 30 minutes

under argon balloon. The mixture was activated with BDSB (91 mg, 0.166 mmol) and dried AgOTf (43 mg, 0.167 mmol) at –35 °C to room temperature for overnight. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction was extracted with CH_2Cl_2 three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of disaccharide **54** (74 mg, 0.075 mmol, 68%) with the ratio of α:β = 48:52 (α:β ratio was determined by ^{1}H NMR).

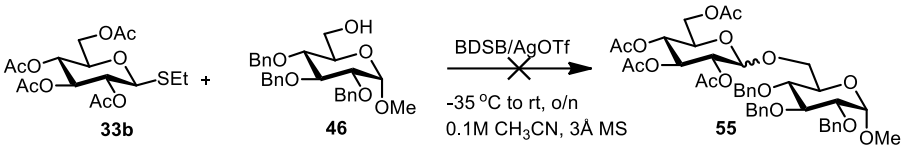
Entry 2: glycosyl donor **34b** (85 mg, 0.145 mmol) and glycosyl acceptor **46** (50 mg, 0.108 mmol) were azeotroped with toluene and acetonitrile. 3 Å MS and dried acetonitrile (0.1 M) were added and stirred at room temperature for 30 minutes under argon balloon. The mixture was activated with BDSB (94 mg, 0.171 mmol) and dried AgOTf (57 mg, 0.222 mmol) at –35 °C to room temperature for overnight. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of β-disaccharide **54b** (90 mg, 0.092 mmol, 85%).

Entry 3: glycosyl donor **34b** (58 mg, 0.099 mmol) and glycosyl acceptor **46** (31 mg, 0.067 mmol) were azeotroped with toluene and acetonitrile. 3 Å MS and dried toluene (0.1 M) were added and stirred at room temperature for 30 minutes under argon balloon. The mixture was activated with BDSB (55 mg, 0.100 mmol) and dried AgOTf (26 mg, 0.101 mmol) at –35 °C to room temperature for overnight. Reaction was monitored by TLC and found that half of glycosyl donor was still remained. So, more BDSB (55 mg, 0.100 mmol) and dried AgOTf (26 mg, 0.101 mmol) were added at –35 °C. The reaction was warmed slowly to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated

sodium potassium tartrate (2 mL) for 30 minutes. The reaction was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of disaccharide **54** (22 mg, 0.022 mmol, 33%) with the ratio of α:β = 63:37 (α:β ratio was determined by ^{1}H NMR).

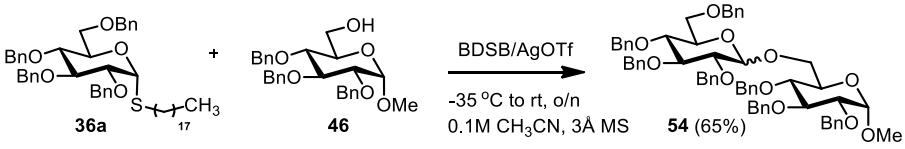
Entry 4: glycosyl donor **34b** (95 mg, 0.162 mmol) and glycosyl acceptor **46** (51 mg, 0.110 mmol) were azeotroped with toluene and acetonitrile. 3 Å MS and dried Et_2O (0.1 M) were added and stirred at room temperature for 30 minutes under argon balloon. The mixture was activated with BDSB (91 mg, 0.166 mmol) and dried AgOTf (43 mg, 0.167 mmol) in Et_2O at –35 °C to room temperature for overnight. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20 and 25% EtOAc/hex gradients to get a white solid of disaccharide **13** (72 mg, 0.073 mmol, 66%) with the ratio of α:β = 55:45 (α:β ratio was determined by ^{1}H NMR).

2.7 Examination of the substrates scope in glycosylation



2.7.1 Methyl 2,3,4-tris-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-α-D-glucopyranoside (**55**)

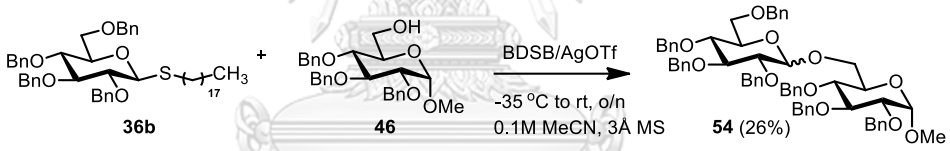
Glycosyl donor **33b** (65 mg, 0.166 mmol), glycosyl acceptor **46** (51 mg, 0.110 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (43 mg, 0.167 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (91 mg, 0.166 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. Reaction was monitored by TLC found that only glycosyl donor **33b** was consumed but glycosyl acceptor **46** was still remained in the reaction mixture. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 10, 15, 20, 25, 30 and 40% EtOAc/hex gradients to get a white solid of unidentified by-product mixture Moreover, glycosyl acceptor was recovered as a yellow syrup with 42 mg.



2.7.2 Methyl 2,3,4-tris-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (**54**)

Glycosyl donor **36a** (82 mg, 0.101 mmol), glycosyl acceptor **46** (32 mg, 0.069 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (27 mg, 0.105 mmol) at room

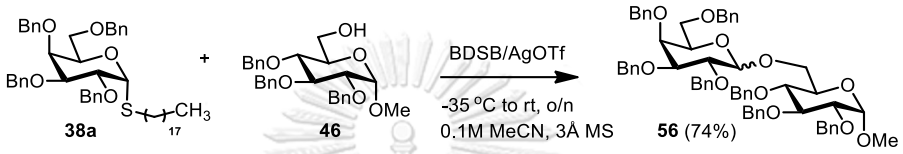
temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (57 mg, 0.104 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (2 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a white solid **54** (44 mg, 0.045 mmol, 65%) with the ratio of α:β = 12:88 (α:β ratio was determined by ^{1}H NMR). ^{1}H NMR (400 MHz,) of **54**: δ 7.43–7.00 (m, 207H), 5.05–4.86 (m, 21H), 4.86–4.42 (m, 72H), 4.35 (d, *J* = 7.8 Hz, 5H), 4.19 (dd, *J* = 10.7, 1.8 Hz, 5H), 4.04–3.92 (m, 7H), 3.88–3.78 (m, 8H), 3.78–3.38 (m, 54H), 3.36 (s, 1H), 3.33 (s, 7H). Moreover, glycosyl acceptor was recovered as a colorless syrup with 7 mg.



2.7.3 Methyl 2,3,4-tris-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (**54**)

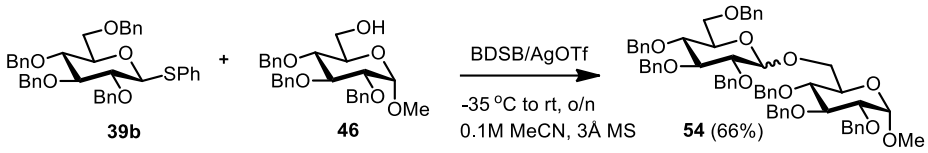
Glycosyl donor **36b** (78 mg, 0.096 mmol), glycosyl acceptor **46** (30 mg, 0.065 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (25 mg, 0.097 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (54 mg, 0.098 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (2 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15,

20, 25 and 30% EtOAc/hex gradients to get a white solid **54** (17 mg, 0.017 mmol, 26%) with the ratio of α:β = 21:79 (α:β ratio was determined by ^{1}H NMR). ^{1}H NMR (400 MHz,) of **54**: δ 7.37–7.09 (m, 69H), 5.01–4.93 (m, 4H), 4.93–4.87 (m, 2H), 4.78 (ddd, *J* = 9.0, 8.2, 4.2 Hz, 8H), 4.72 (d, *J* = 4.3 Hz, 1H), 4.70–4.46 (m, 12H), 4.42 (t, *J* = 11.1 Hz, 1H), 4.34 (d, *J* = 7.8 Hz, 1H), 4.18 (dd, *J* = 10.8, 1.8 Hz, 1H), 4.02–3.91 (m, 2H), 3.86–3.38 (m, 19H), 3.34 (s, 1H), 3.32 (s, 4H). Moreover, glycosyl acceptor was recovered as a colorless syrup with 15 mg.



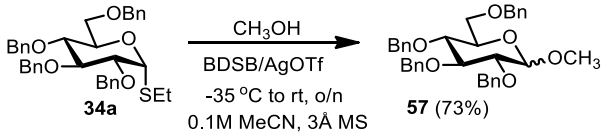
2.7.4 Methyl 2,3,4-tris-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (**56**)

Glycosyl donor **38a** (78 mg, 0.096 mmol), glycosyl acceptor **46** (30 mg, 0.065 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (25 mg, 0.097 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (54 mg, 0.098 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate for (2 mL) 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a white solid **56** (47 mg, 0.048 mmol, 74%) with the ratio of α:β = 33:67 (α:β ratio was determined by ^{1}H NMR). ^{1}H NMR (400 MHz,) of **56**: δ 7.44–7.07 (m, 154H), 5.04–4.87 (m, 14H), 4.86–4.48 (m, 45H), 4.49–4.34 (m, 9H), 4.32 (d, *J* = 7.7 Hz, 3H), 4.15 (dd, *J* = 10.8, 1.8 Hz, 3H), 4.06 – 3.72 (m, 22H), 3.67–3.39 (m, 27H), 3.31 (s, 4H), 3.30 (s, 1H). Moreover, glycosyl acceptor was recovered as a colorless syrup with 7 mg. ^{1}H NMR spectra of **56** is consistent with previous report.[34]



2.7.5 Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (**54**)

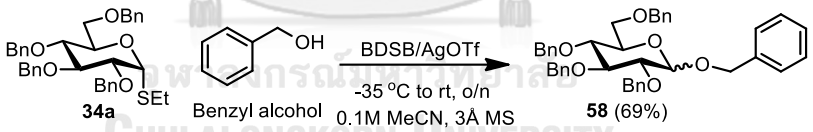
Glycosyl donor **39b** (63 mg, 0.100 mmol), glycosyl acceptor **46** (31 mg, 0.067 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (26 mg, 0.101 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (55 mg, 0.100 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (2 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a white solid **54** (43 mg, 0.044 mmol, 66%) with the ratio of α:β = 17:83 (α:β ratio was determined by ^{1}H NMR). ^{1}H NMR (400 MHz,) of 54: δ 7.39–7.08 (m, 96H), 5.03–4.87 (m, 9H), 4.85–4.39 (m, 32H), 4.35 (d, *J* = 7.8 Hz, 2H), 4.19 (dd, *J* = 10.7, 1.8 Hz, 2H), 4.05–3.93 (m, 3H), 3.88–3.39 (m, 28H), 3.35 (s, 1H), 3.33 (s, 5H). Moreover, glycosyl acceptor was recovered as a colorless syrup with 9 mg.



2.7.6 Methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**57**)

Glycosyl donor **34a** (50 mg, 0.086 mmol), dried methanol (36 μl, 0.890 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (34 mg, 0.133 mmol) at room

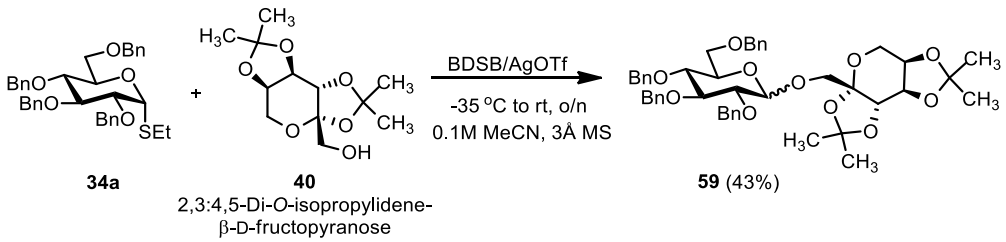
temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (73 mg, 0.133 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a colorless syrup of β product **57b** (30 mg, 0.054 mmol, 63%) and α product **57a** (5 mg, 0.009 mmol, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) of **57a**: δ 7.31–7.02 (m, 20H), 4.90 (d, *J* = 10.9 Hz, 1H), 4.79–4.64 (m, 3H), 4.62–4.47 (m, 3H), 4.46–4.31 (m, 2H), 3.90 (t, *J* = 9.3 Hz, 1H), 3.64 (m, 2H), 3.59–3.51 (m, 2H), 3.48 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.30 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) of **57b**: δ 7.31–7.04 (m, 20H), 4.85 (dd, *J* = 10.9, 1.5 Hz, 2H), 4.73 (t, *J* = 11.3 Hz, 2H), 4.63 (d, *J* = 11.1 Hz, 1H), 4.58–4.41 (m, 3H), 4.24 (d, *J* = 7.8 Hz, 1H), 3.68 (dd, *J* = 10.7, 1.6 Hz, 1H), 3.63–3.52 (m, 3H), 3.50 (s, 3H), 3.43–3.31 (m, 2H). ^{1}H NMR spectra of **57a** and **57b** are consistent with previous report.[35]



2.7.7 Benzyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**58**)

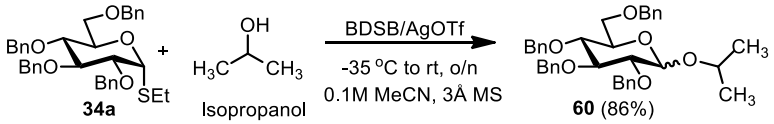
Glycosyl donor **34a** (170 mg, 0.291 mmol), benzyl alcohol (21 μl, 0.202 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (83 mg, 0.323 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (169 mg, 0.308 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with Et_3N and filtered through a pad of Celite. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients. The product was obtained as a white solid **58** (88 mg, 0.140 mmol, 69%). ^{1}H NMR

(400 MHz, $CDCl_3$) of **58**: δ 7.36–7.00 (m), 4.97–4.80 (m), 4.80–4.34 (m), 3.78–3.30 (m). ^{1}H NMR spectra of **58** is consistent with previous report.[36]



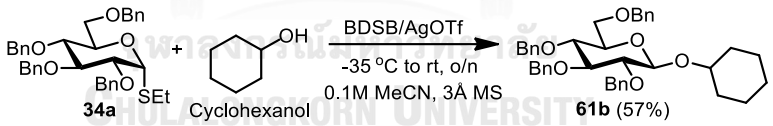
2.7.8 2,3,4,5-Di-*O*-isopropylidene-6-*O*-[2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl]-β-D-fructopyraoside (**59)**

Glycosyl donor **34a** (100 mg, 0.171 mmol), 2,3,4,5-di-*O*-isopropylidene-β-D-fructopyranose (30 mg, 0.115 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (44 mg, 0.171 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (96 mg, 0.175 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x2 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a white solid **59** (38 mg, 0.049 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) of **59**: δ 7.32–7.03 (m, 21H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.81–4.64 (m, 3H), 4.64–4.34 (m, 7H), 4.15 (d, *J* = 7.8 Hz, 1H), 3.92–3.80 (m, 3H), 3.72–3.46 (m, 5H), 3.46–3.30 (m, 2H), 1.45 (s, 2H), 1.44 (s, 1H), 1.41 (s, 1H), 1.37 (s, 2H), 1.34 (s, 2H), 1.29 (s, 1H), 1.23 (s, 2H).



2.7.9 Isopropyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**60**)

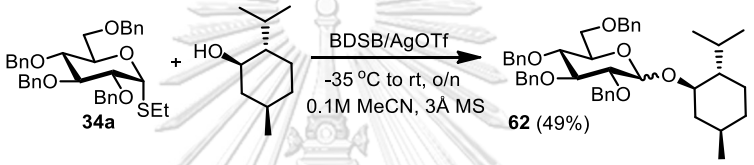
Glycosyl donor **34a** (50 mg, 0.086 mmol), isopropanol (65 μl, 0.850 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (38 mg, 0.148 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (76 mg, 0.138 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by prep TLC using 40% Et_2O/hex as an eluent. The product **60** was obtained as a white solid (43 mg, 0.074 mmol, 86%).^{1}H NMR (400 MHz, $CDCl_3$) of **60**: δ 7.34–7.01 (m, 20H), 4.96–4.78 (m, 2H), 4.78–4.66 (m, 2H), 4.66–4.56 (m, 1H), 4.56–4.42 (m, 3H), 4.38 (t, *J* = 6.1 Hz, 1H), 4.01–3.88 (m, 1H), 3.86–3.72 (m, 1H), 3.66 (dd, *J* = 10.7, 1.4 Hz, 1H), 3.62–3.51 (m, 2H), 3.51–3.44 (m, 1H), 3.44–3.27 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.1 Hz, 1H). ^{1}H NMR spectra of **60** is consistent with previous report.[37]



2.7.10 Cyclohexyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (**61b**)

Glycosyl donor **34a** (56 mg, 0.096 mmol), dried cyclohexanol (50 μl, 0.473 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (44 mg, 0.171 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (80 mg, 0.146 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30

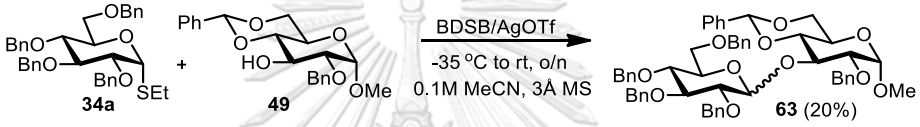
minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by prep TLC using 10% EtOAc/hex as an eluent. The product **61b** was obtained as a white solid (34 mg, 0.055 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) of **61b**: δ 7.33–7.04 (m, 20H), 4.92 (d, *J* = 10.9 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 10.9 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.57–4.40 (m, 4H), 3.70–3.52 (m, 4H), 3.47 (t, *J* = 9.2 Hz, 1H), 3.43–3.32 (m, 2H), 1.90 (dd, *J* = 30.6, 11.7 Hz, 2H), 1.67 (d, *J* = 4.1 Hz, 1H), 1.50–1.30 (m, 3H), 1.29–1.11 (m, 4H). ^{1}H NMR spectra of **61b** is consistent with previous report.[38]



2.7.11 (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**62**)

Glycosyl donor **34a** (181 mg, 0.310 mmol), L-menthol (36 mg, 0.230 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (77 mg, 0.230 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (159 mg, 0.230 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x2 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography using 0, 10, 20, 30 and 40% EtOAc/hex gradients. The α product **62a** (11 mg, 0.016 mmol, 7%) and β product **62b** (66 mg, 0.097 mmol, 42%) were obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) of **62a**: δ 7.26–7.17 (m, 18H), 7.09–7.02 (m, 2H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.90 (d, *J* = 10.9 Hz, 1H), 4.79–4.71 (m, 2H), 4.67–4.53 (m, 3H), 4.40 (d, *J* = 4.9 Hz, 1H),

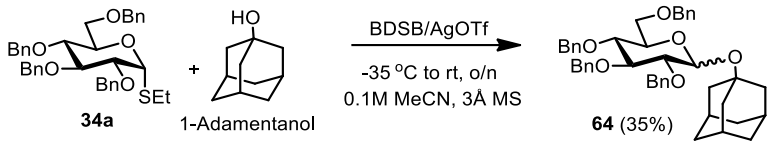
4.37 (d, *J* = 3.5 Hz, 1H), 3.98–3.86 (m, 2H), 3.68 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.60–3.52 (m, 2H), 3.47 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.28 (td, *J* = 10.6, 4.3 Hz, 1H), 2.42–2.26 (m, 1H), 2.11–1.99 (m, 1H), 1.59–1.48 (m, 4H), 1.24–1.13 (m, 8H), 1.02–0.70 (m, 11H), 0.63 (d, *J* = 6.9 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) of **62b**: δ 7.32–7.02 (m, 20H), 4.86 (t, *J* = 10.8 Hz, 2H), 4.72 (t, *J* = 11.0 Hz, 2H), 4.61 (d, *J* = 10.9 Hz, 1H), 4.56–4.43 (m, 3H), 4.40 (d, *J* = 7.8 Hz, 1H), 3.61 (d, *J* = 3.0 Hz, 2H), 3.59–3.49 (m, 2H), 3.42 (td, *J* = 10.6, 4.1 Hz, 1H), 3.33 (dd, *J* = 11.0, 5.0 Hz, 2H), 2.35–2.22 (m, 1H), 2.06 (d, *J* = 12.2 Hz, 1H), 1.58 (d, *J* = 11.6 Hz, 2H), 1.33–1.13 (m, 5H), 0.98–0.79 (m, 9H), 0.75 (d, *J* = 6.9 Hz, 4H). ^{1}H NMR spectra of **62a** and **62b** are consistent with previous report.[39]



2.7.12 Methyl 2-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (**63**)

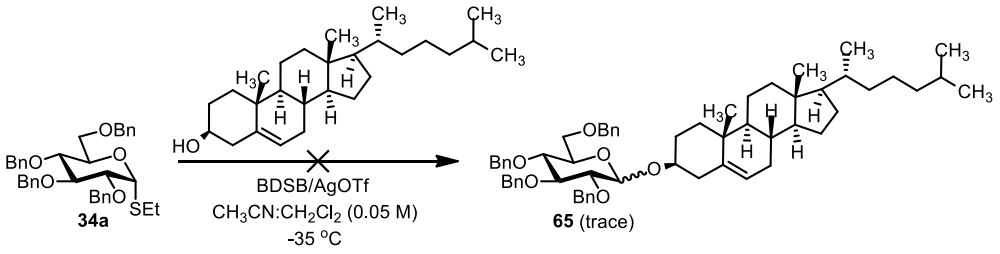
Glycosyl donor **34a** (121 mg, 0.207 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **49** (53 mg, 0.143 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (60 mg, 0.233 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (155 mg, 0.282 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x2 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients. The product was obtained as a white solid of β anomer **63b** (15 mg, 0.017 mmol, 12%) and mixture of α and β anomer **63** (10 mg, 0.011 mmol, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) of **63b**: δ 7.45–7.38 (m, 2H), 7.39–7.33 (m, 2H), 7.32–7.16 (m, 26H), 7.17–7.11 (m, 2H), 5.47 (s, 1H), 5.06 (d, *J* = 11.2 Hz, 1H), 4.90 (t, *J* = 9.0 Hz, 2H), 4.83–

4.68 (m, 4H), 4.56–4.41 (m, 5H), 4.36 (t, *J* = 9.1 Hz, 1H), 4.21 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.82 (td, *J* = 9.9, 4.6 Hz, 1H), 3.76–3.52 (m, 7H), 3.49 (t, *J* = 8.2 Hz, 1H), 3.35 (s, 3H), 3.24 (d, *J* = 9.1 Hz, 1H). ^{1}H NMR spectra of **63b** is consistent with previous report.[13]



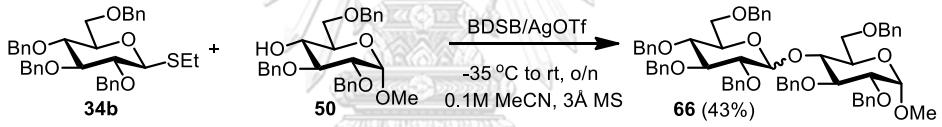
2.7.13 Adamantyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**64**)

Glycosyl donor **34a** (162 mg, 0.277 mmol), 1-adamantanol (30 mg, 0.197 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (79 mg, 0.307 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (190 mg, 0.346 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (3 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x2 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a white solid **64** (46 mg, 0.068 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) of **64**: δ 7.33–7.02 (m, 254H), 5.21 (d, *J* = 3.6 Hz, 4H), 4.92 (t, *J* = 9.5 Hz, 12H), 4.84 (d, *J* = 10.9 Hz, 9H), 4.79–4.43 (m, 81H), 4.38 (dd, *J* = 11.3, 6.9 Hz, 9H), 3.98–3.89 (m, 8H), 3.72–3.61 (m, 14H), 3.61–3.50 (m, 3H), 3.49–3.30 (m, 29H), 2.13–2.01 (m, 36H), 1.90–1.83 (m, 2H), 1.82–1.67 (m, 49H), 1.55 (s, 76H). ^{1}H NMR spectra of **64** is consistent with previous report.[40]



2.7.14 Cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**65**)

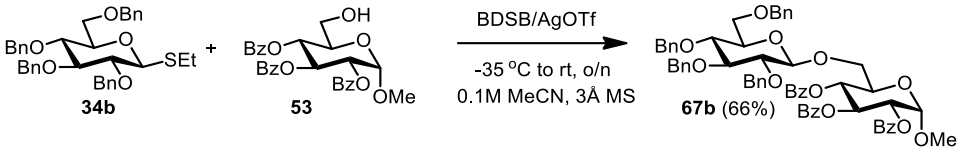
Glycosyl donor **34a** (91 mg, 0.156 mmol), dried cholesterol (40 mg, 0.104 mmol) and 3 Å MS in a mixture of 1:1 acetonitrile:CH_2Cl_2 (0.05 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (43 mg, 0.167 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (87 mg, 0.159 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point,reaction progress monitored by TLC found that several undesirable compounds were occurred.Reaction mixture was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with Na_2SO_4 and concentrated. NMR analysis of reaction mixture showed complex mixture.



2.7.15 Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (**66**)

Glycosyl donor **34b** (53 mg, 0.091 mmol), glycosyl acceptor **50** (28 mg, 0.060 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (24 mg, 0.093 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (50 mg, 0.091 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (2 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a colorless syrup **66** (26 mg, 0.026 mmol,

43%). Moreover, glycosyl acceptor was recovered as a colorless syrup with 13 mg. ^{1}H NMR spectra of **66** is consistent with previous report.[41]

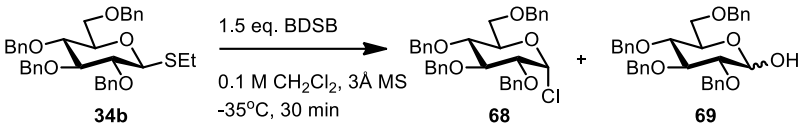


2.7.16 Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**67b**)

Glycosyl donor **34b** (52 mg, 0.089 mmol), glycosyl acceptor **53** (30 mg, 0.059 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. The reaction was treated with dried AgOTf (23 mg, 0.090 mmol) at room temperature. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (49 mg, 0.089 mmol). The reaction was stirred at –35 °C for 1 hour and allowed to warm up to room temperature for overnight. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. After that, the reaction was stirred with saturated sodium potassium tartrate (2 mL) for 30 minutes. The reaction mixture was extracted with EtOAc three times (3x1 mL) and washed with distilled water and brine. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 5, 10, 15, 20, 25 and 30% EtOAc/hex gradients to get a colorless syrup **67b** (40 mg, 0.039 mmol, 66%). Moreover, glycosyl acceptor was recovered as a white solid with 6 mg. ^{1}H NMR (400 MHz,) of **67b**: δ 7.98 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.94 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.85 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.54–7.46 (m, 2H), 7.45–7.23 (m, 31H), 7.19–7.09 (m, 2H), 6.18 (t, *J* = 9.8 Hz, 1H), 5.49 (t, *J* = 10.2 Hz, 1H), 5.26 (dd, *J* = 10.1, 3.6 Hz, 1H), 5.22 (d, *J* = 3.7 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.92 (d, *J* = 10.9 Hz, 1H), 4.84–4.74 (m, 2H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.49 (ddd, *J* = 26.2, 15.3, 9.7 Hz, 4H), 4.39 (ddd, *J* = 9.9, 6.1, 2.0 Hz, 1H), 4.13 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.82 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.69–3.56 (m, 4H), 3.50–3.40 (m, 2H), 3.38 (s, 3H). ^{1}H NMR spectra of **67b** is consistent with previous report.[42]

2.8 Glycosyl intermediate study

2.8.1 Glycosyl intermediate study of ethyl thioglycoside **34b** activated with BDSB in CH_2Cl_2



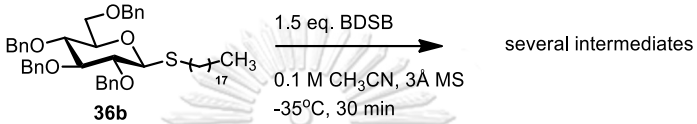
Glycosyl donor **34b** (65 mg, 0.111 mmol) and 3 Å MS in CH_2Cl_2 (0.1 M) were stirred at room temperature for 30 minutes. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (91 mg, 0.166 mmol). The reaction was stirred at –35 °C for 30 minutes. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. The reaction mixture was extracted with CH_2Cl_2 three times. The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 10, and 20% EtOAc/hex gradients to get a colorless syrup **68**. Moreover, hydrolysis by product **69** was observed as a white solid. ^{1}H NMR spectra of **68** and **69** are consistent with previous report.[43-44]

2.8.2 Glycosyl intermediate study of octadecyl thioglycoside **36b** activated with BDSB in CH_2Cl_2

Glycosyl donor **36b** (56 mg, 0.069 mmol) and 3 Å MS in CH_2Cl_2 (0.1 M) were stirred at room temperature for 30 minutes. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (57 mg, 0.104 mmol). The reaction was stirred at –35 °C for 30 minutes. At that point, the reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL 0.5 mL and saturated $NaHCO_3$ 0.5 mL. The reaction mixture was extracted with CH_2Cl_2 three times (3x1 mL). The organic layers were dried with

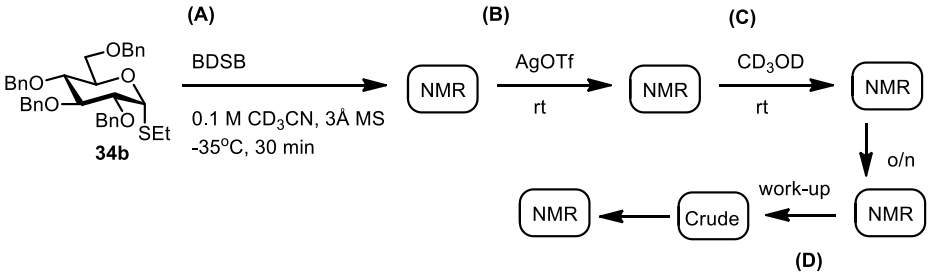
$MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 10, and 20% EtOAc/hex gradients to get a colorless syrup **68**. Moreover, hydrolysis by product **69** was observed as a white solid. ^{1}H NMR spectra of **68** and **69** are consistent with previous report.

2.8.3 Glycosyl intermediate study of octadecyl thioglycoside **36b** activated with BDSB in acetonitrile



Glycosyl donor **36b** (50 mg, 0.062 mmol) and 3 Å MS in acetonitrile (0.1 M) were stirred at room temperature for 30 minutes. After that, the reaction was cooled slowly to –35 °C then treated with BDSB (51 mg, 0.093 mmol). The reaction was stirred at –35 °C for 30 minutes. At that point, the reaction was monitored by TLC, several intermediate were observed on TLC. The reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. The reaction mixture was extracted with EtOAc three times (3x1 mL). The organic layers were dried with $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography using 0, 10, and 20% EtOAc/hex gradients. After purification, the intermediate was not observed due to decomposition. Moreover, hydrolysis by-product **69** was isolated as a white solid.

2.8.4 NMR monitoring of glycosylation of thioglycoside activated by BDSB/AgOTf



(**A**) Glycosyl donor **34b** (46 mg, 0.079 mmol) was azeotroped with toluene and acetonitrile prior use. 3 Å MS and acetonitrile-d3 (CD_3CN, 0.1 M) were added and stirred at room temperature for 30 minutes. After that, the mixture was cooled to –35 °C and then BDSB (69 mg, 0.126 mmol) was added. The reaction was stirred at –35 °C for 30 minutes. The reaction was transferred into NMR tube by using gastight syringe. The reaction was monitored at room temperature by NMR.

(**B**) The solution of AgOTf (32 mg, 0.124 mmol) in CD_3CN was added into reaction in the NMR tube. The reaction was monitored by NMR.

(**C**) Methanol-d4 (CD_3OD, 0.5 mL) was chosen as nucleophile and added into the reaction mixture at room temperature for 10 minutes. The reaction was monitored by NMR. At this point, the reaction was not complete. So, the reaction was stranded at room temperature for overnight and then monitored by NMR.

(**D**) Reaction was quenched with saturated $Na_2S_2O_3$ 0.5 mL and saturated $NaHCO_3$ 0.5 mL. The reaction mixture was extracted with EtOAc three times (3 x1 mL). The organic layers were dried over Na_2SO_4 and concentrated to obtain the crude product as a yellow syrup. The crude was determined by NMR.

CHAPTER III
RESULTS AND DISCUSSION

3.1 Synthesis of glycosyl donors and glycosyl acceptors

In this work, different glycosyl donors such as armed (**34a**, **34b**, **36a**, **36b**, **38a**, and **39b**) and disarmed (**33b**) donor were synthesized by using modified procedure from previous literature (Figure 3.1).[45-47]

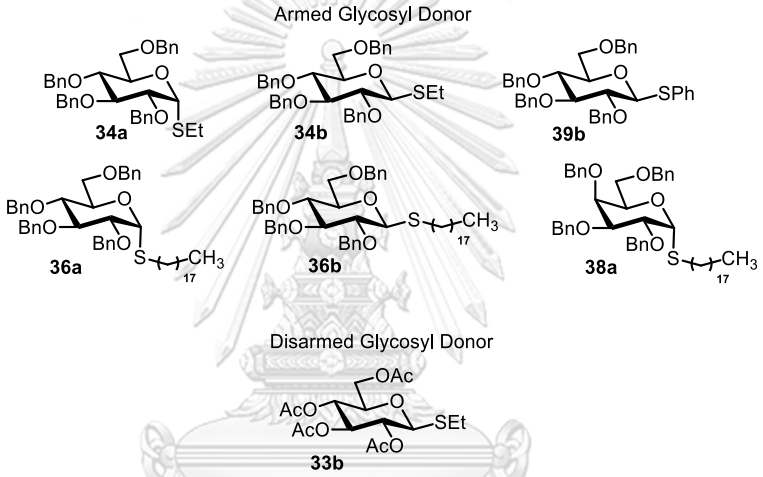


Figure 3.1 Glycosyl donors for glycosylation in this study.

Disarmed donor **33b** and armed donors **34a**, **34b**, **38a**, and **39b** were synthesized *via* two and three step reactions, respectively. First, the anomeric position of β-D-glucose pentaacetate was displaced with thiol and acetyl protecting groups were deprotected by catalytic K_2CO_3 in methanol. Finally, the protecting group manipulations on donors were performed *via* benzylation to provide the desired thioglycosides (Figure 3.2). Moreover, thioglycosides **36a** and **36b** were synthesized *via* deprotection by K_2CO_3 in methanol and then benzylation by phase transfer catalyzed with TBAHS, 50% NaOH, BnBr in dichloromethane.

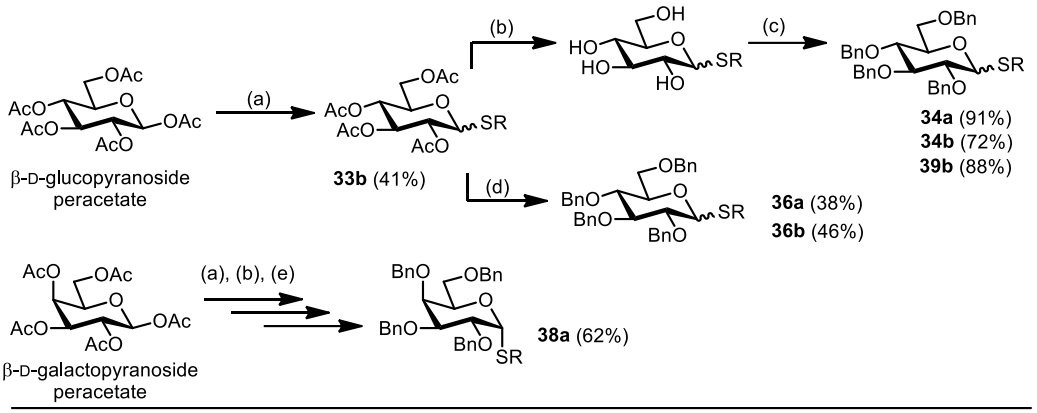
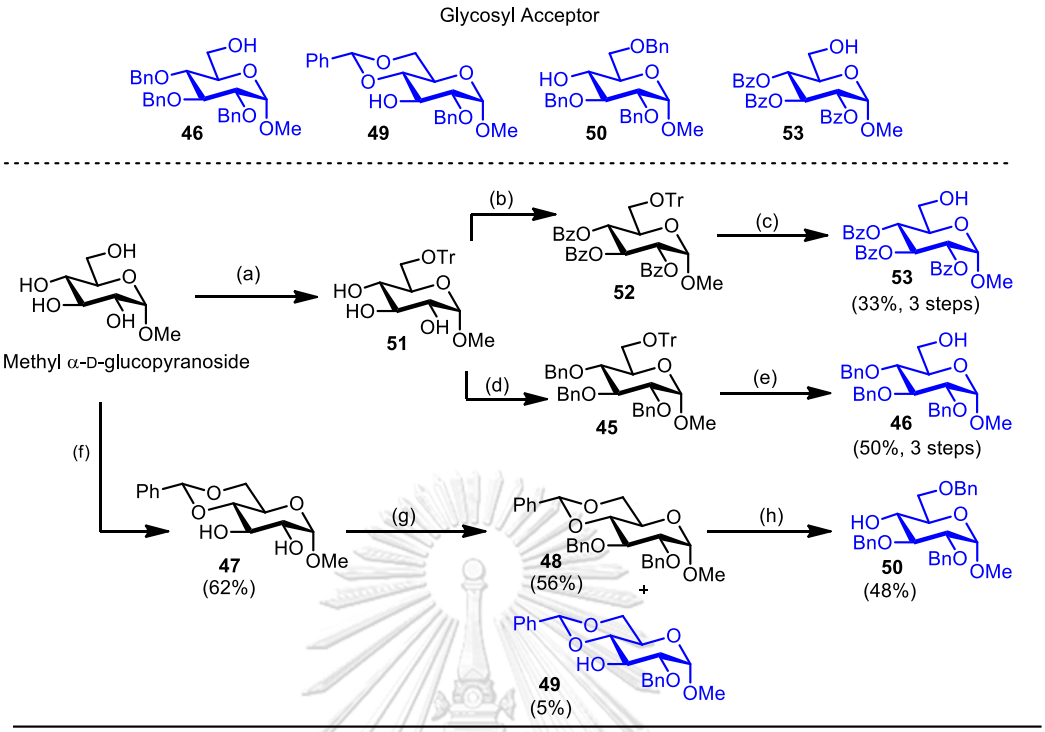


Figure 3.2 Synthesis of glycosyl donors.

Glycosyl acceptor **46**, **49**, **50**, and **53** were prepared by using modified procedure of previous reports.[48-49] Commercially available methyl α-D-glucopyranoside was used as precursor to provide the desired glycosyl acceptors (Figure 3.3). Primary alcohols **46** and **53** were synthesized in three steps. First, hyldroxy group at C6 of methyl α-D-glucopyranoside was tritylated by using TrCl in pyridine to generate **51**. Next, benzoylation of **51** was performed by treating with BzCl. Finally, trityl group of **52** was deprotected under acidic condition of acetic acid in THF to obtain **46** in 50% yield. Besides, **51** was benzylated by using BnBr, TBAI and NaH in DMF and then detritylated with $FeCl_3$ in dichloromethane, the acceptor **53** was obtained in 33% yield.



(a) TrCl, DMAP, pyridine, rt. (b) BzCl, pyridine, rt. (c) $FeCl_3$, CH_2Cl_2, rt. (d) BnBr, TBAI, NaH, DMF 0 °C to rt. (e) CH_3COOH, THF, 3M H_2SO_4, 80 °C to rt. (f) 4 mol% CSA, α,α-dimethoxytoluene, CH_3CN, 100 °C. (g) 1 eq. BnBr, TBAI, NaH, DMF, 0 °C to rt. (h) $NaBH_3CN$, I_2, CH_2Cl_2, 0 °C to rt.

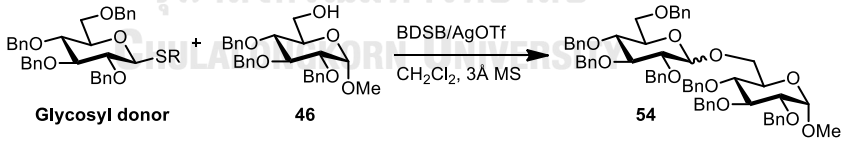
Figure 3.3 Glycosyl acceptors for glycosylation in this study.

Secondary alcohols **49** and **50** were synthesized. The hydroxy group at C4 and C6 of methyl α-D-glucopyranoside were treated with α,α-dimethoxytoluene and 4 mol% of CSA in acetonitrile to generate **47** in 62% yield. Next, compound **47** was benzylated by using 1.0 equivalent of BnBr, TBAI and NaH in DMF to obtain products **48** and **49** in 56% and 5% yields, respectively. Finally, reductive ring opening at benzylidene acetal protecting group of **48** was performed by using $NaBH_3CN$, I_2 in dichloromethane to obtain glycosyl acceptor **50** in 48% yield.

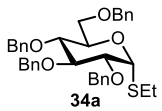
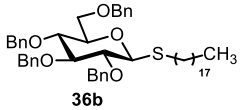
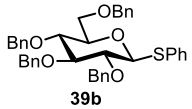
3.2 Preliminary screening of glycosyl donor for glycosylation

Preliminary study of glycosylation by using BDSB in combination with AgOTf as an activator was investigated (Table 2.1). Three different armed glycosyl donors (**34a**, **36b**, and **39b**) and glycosyl acceptor **46** were performed in CH_2Cl_2 at 0 °C to room temperature. These glycosyl donors were selected for preliminary screening based on their reactivities towards thiophilic activators. Order of reactivity from the highest to the lowest was ethyl thioglycosides **34a**, octadecyl thioglycosides **36b**, and phenyl thioglycosides **39b**, respectively. Firstly, glycosylation of ethyl thioglycosides **34a** was completed within 35 minutes to obtain disaccharide **54** in 56% yield with moderate selectivity (α:β = 40:60). Secondly, glycosylation of octadecyl thioglycosides **36b**, a long chain aliphatic glycosyl donor, was performed and finished in 1 hour to obtain disaccharide **54** in 45% yield with moderate selectivity (α:β = 50:50). Lastly, glycosylation of aromatic glycosyl donor, phenyl thioglycosides **39b**, was carried out for overnight to obtain disaccharide **54** in 32% yield with moderate selectivity (α:β = 50:50).

Table 3.1 Preliminary screening of glycosyl donors for BDSB/AgOTf-mediated glycosylation.



Glycosyl donor **46** **54**

Entry	Donor	Temperature	Time	Yield (α:β)[a,b]
1	 **34a**	0 °C to rt	35 min	56% (40:60)
2	 **36b**	0 °C to rt	1h	45% (50:50)
3	 **39b**	0 °C to rt	o/n	32% (50:50)

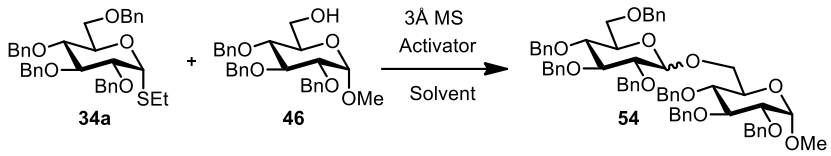
[a] α:β ratio determined by ^{1}H NMR integration
[b] donor (1.0 equiv.), acceptor (1.5-2.0 equiv.), AgOTf (1.5-1.6 equiv.), BDSB (1.5-1.9 equiv.)

Gratifyingly, these preliminary results indicated that combination of BDSB/AgOTf was capable of activating wide range of thioglycoside donors. Low α:β selectivity would probably come from the absence of neighboring participation at C2 on glycosyl donor which was frequently observed in chemical glycosylation. Ethyl thioglycoside **34a** was then selected as a glycosyl donor of choice for further glycosylation study due to its highest reactivity compared with donor **36b** and **39b**.

3.3 Investigation for optimal conditions for glycosylation

To investigate the optimal conditions for glycosylation of thioglycosides. Ethyl thioglycoside **34a** and glycosyl acceptor **36** were selected as a model. Glycosylation were performed at low temperature under several conditions. Firstly, we studied the efficiency of BDSB for activation of thioglycosides in CH_2Cl_2 and CH_3CN as solvent. The results showed that the glycosylation in CH_2Cl_2 provided the desired disaccharide **54** in 64% yield with moderate selectivity (α:β = 55:45) (Table 3.2, entry 1). When CH_3CN was used, the disaccharide **54** was obtained in 41% yield with good β selectivity (α:β = 17:83) (entry 2). However, both glycosylations (entries 1–2) took overnight to reach completion. BDSB (1.1 equiv.) in combination with AgOTf (1.1 equiv.) were used in CH_2Cl_2, yield of **54** was obtained in 56% with moderate selectivity (α:β = 40:60) (entry 3). The reaction time was significantly faster, it completed within 35 minutes. Finally, using CH_3CN as solvent and BDSB/AgOTf combination increased yield of **54** up to 79% yield with high β selectivity (entry 4).

Table 3.2 Optimization conditions of glycosylation with BDSB as activator.



Entry	Activator	Solvent (0.1 M)	Temperature	Time	Yield (α:β)
1	BDSB	CH_2Cl_2	0 °C to rt	o/n	64% (55:45)
2	BDSB	CH_3CN	–35 °C to rt	o/n	41% (17:83)
3	BDSB/AgOTf	CH_2Cl_2	0 °C to rt	35 min	56% (40:60)
4	BDSB/AgOTf	CH_3CN	–35 °C to rt	3 h	79% (β only)
5	BDSB/AgOTf	CH_3NO_2	–20 °C to rt	o/n	76% (37:63)
6	BDSB/AgOTf	DMF	–35 °C to rt	o/n	trace

Next, we focused to examine other polar solvents as media for glycosylation such as CH_3NO_2, and DMF. Using CH_3NO_2 (entry 5), the disaccharide **54** was obtained in good yield (76%) but the β selectivity (α:β = 37:63) was diminished compared to CH_3CN. On the contrary, glycosylation with DMF as solvent proceeded slowly and only small amount of product was detected (entry 6). TLC monitoring of glycosylation in DMF observed the stable unknown intermediate (Figure 3.4).

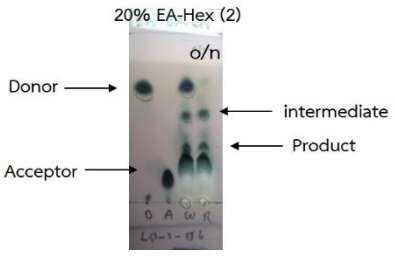


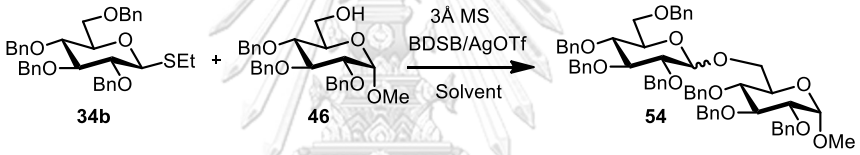
Figure 3.4 TLC monitoring of glycosylation between **34a** and **46** in DMF as solvent.

After several optimizations, we found that the glycosylation of **34a** and **46** proceeded smoothly and most productive with a combination of BDSB/AgOTf in acetonitrile at –35 °C and allowed to warm up to room temperature under argon atmosphere.

3.4 Study the effect of solvents for glycosylation with BDSB/AgOTf

Solvent effect on yield and selectivity of glycosylation was investigated under low temperature. Ethyl thioglycoside **34b** and glycosyl acceptor **46** were performed in different solvents such as CH_3CN, CH_2Cl_2, Et_2O, and toluene. The result showed that β thioglycoside **34b** was smoothly performed in acetonitrile at –35 °C to room temperature. The disaccharide **54** was obtained in high yield and high β selectivity (85% yield, β only) (Table 3.3, entry 1). This result was in accordance with using thioglycoside **34a** in acetonitrile. Thus this allowed us to conclude that the efficiency of glycosylation was independence on the anomeric linkage of donor.

Table 3.3 Solvents effect of glycosylation with BDSB/AgOTf.



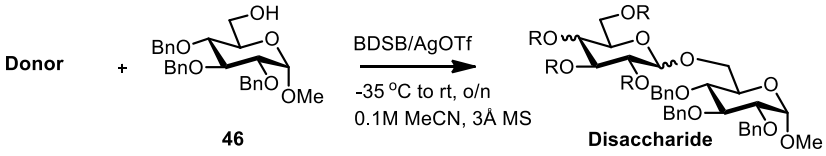
Entry	Activator	Solvent	Temperature	Time	Yield (α:β)
1	BDSB/AgOTf	CH_3CN	–35 °C to rt	o/n	85% (β only)
2	BDSB/AgOTf	CH_2Cl_2	–35 °C to rt	o/n	68% (48:52)
3	BDSB/AgOTf	Et_2O	–35 °C to rt	o/n	66% (55:45)
4	BDSB/AgOTf	toluene	–35 °C to rt	2d	33% (63:37)

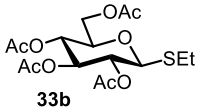
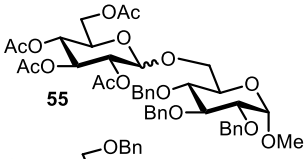
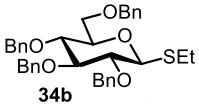
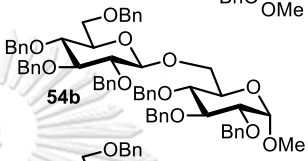
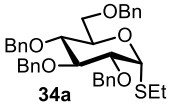
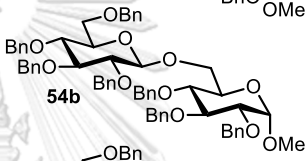
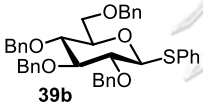
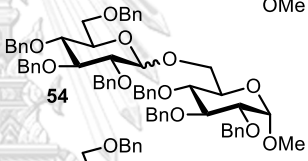
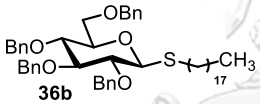
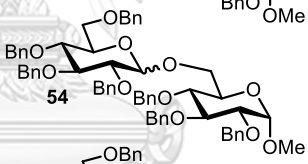
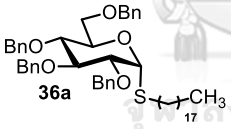
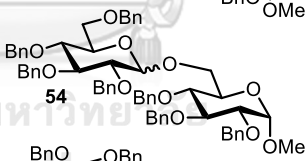
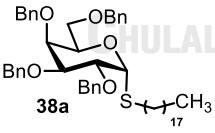
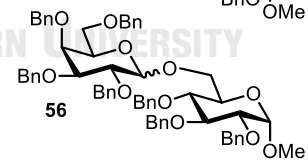
Next, using CH_2Cl_2 and Et_2O as solvent, the disaccharide **54** was obtained in moderate yield (68% and 66% yield, respectively). When Et_2O was used, the α selectivity of **54** was higher compared to CH_2Cl_2 as solvent (entries 2 and 3). Moreover, using toluene as solvent, increasing of the α selectivity was observed (α:β = 63:37). However, glycosylation of thioglycoside **34b** in toluene was sluggish and obtained **54** in low yield (33%) (entry 4). Thus, glycosylation of thioglycoside activated with BDSB/AgOTf in Et_2O is good conditions to increase the α selectivity for this work.

3.5 Scope of glycosyl donors

To study the glycosyl donor effect, disarmed (**33b**) and armed (**34a**, **34b**, **36a**, **36b**, **38a**, and **39b**) thioglycosides were used as donor under the optimal conditions (BDSB/AgOTf in acetonitrile at –35 °C to room temperature). Firstly, glycosylation between disarmed glycosyl donor **33b** and glycosyl acceptor **46** was performed. The result showed that the disarmed donor **33b** was consumed but acceptor **46** was remained and unidentified compounds were detected by TLC (Table 3.4, entry 1). Next, armed glycosyl donors were investigated. Ethyl thioglycosides **34b** and **34a** were used as donor, glycosylation was performed smoothly to generate disaccharide **54b** in high yield with β selectivity (85% and 79% yield, respectively) (entries 2 and 3). When using phenyl thioglycoside **39b** as donor, glycosylation was slower compared to using ethyl thioglycosides (**34b** and **34a**) and provided the disaccharide **54** with moderate yield and selectivity (65% yield, α:β = 17:83) (entry 4). Moreover, the bulky aliphatic thioglycosides **36b**, **36a**, and **38a** were studied. Effect of moisture in chemical glycosylation was conspicuous when carrying the reaction without azeotropic distillation of all precursors. The result showed that using **36b** as donor, disaccharide **54** was obtained in low yield (26%) because the glycosylation was performed without the azeotropic step (entry 5). Besides, glycosylation by using **36a** and **38a** were undergone smoothly to generate disaccharides **54** and **55** in good yield (65% and 74% yield, respectively). The good β selectivity of disaccharides **54** (α:β = 12:88) and **55** (α:β = 33:66) were observed (entries 6 and 7). To conclude, armed thioglycosides with short chain alkyl leaving group were activated with BDSB/AgOTf to provide disaccharides in good to high yields and good β selectivity.

Table 3.4 Investigation the scope of glycosyl donors for glycosylation.



Entry	Donor	Product	Yield (α : β)
1	 **33b**	 **55**	complex mixture
2	 **34b**	 **54b**	85% (β only)
2	 **34a**	 **54b**	79% (β only)
4	 **39b**	 **54**	65% (17 : 83)
5	 **36b**	 **54**	26% (21 : 79)
6	 **36a**	 **54**	65% (12 : 88)
7	 **38a**	 **56**	74% (33 : 67)

[a] α:β selectivity of disaccharides were determined by ^{1}H NMR

3.6 Scope of acceptors

The acceptor scope of the glycosylation was further investigated using several alcohols (Table 3.5). Firstly, glycosylation between a thioglycoside **34a** and glycosyl acceptor **46** was activated with BDSB/AgOTf to obtain **54b** in 79% yield and high β selectivity. Next, several primary alcohols were investigated as acceptors. Primary alcohols such as methanol, benzyl alcohol, and alcohol **40** were performed smoothly and obtained products in good to high yields (43–73%) with good β selectivities (Table 3.5, entries 2–4). When methanol was used, products were obtained in 73% yield with β anomer as major (α product **57a** = 10% and β product **57b** = 63%) (entry 2).

Secondary alcohol such as isopropanol, cyclohexanol, and L-menthol were proceeded to obtain products in moderate to high yield. When isopropanol was used, the product **60** was obtain in 86% yield (entry 5). Using cyclohexanol, only the β product of **61b** was isolated in 57% yield (entry 6). Glycosylation with L-menthol as an acceptor, the products were obtained in 49% yield with β anomer as major product (α product **62a** = 7% and β product **62b** = 42%) (entry 7). Moreover, using glycosyl acceptor **41**, the disaccharide **63** was obtained in low yield (20%) (entry 8). Analysis of by-products revealed that electrophilic bromonium oxidation to benzylidene acetal proton of acceptor **41** was occurred. Using 1-adamantanol as tertiary alcohol, the glycosylation was performed slowly and obtained low yield of product **64** in 35% yield (entry 9). Glycosylation with cholesterol as acceptor, donor and acceptors were consumed but no desired product was generated. Several unidentified by-products were observed probably due to a bromination of olefinic group on cholesterol during the reaction (Figure 3.5).

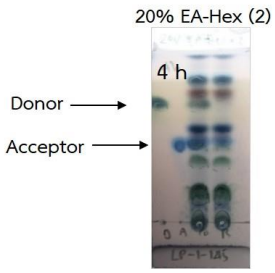
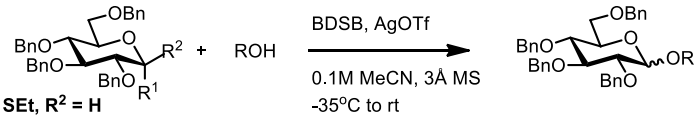
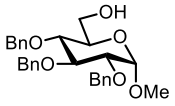
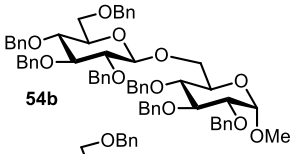
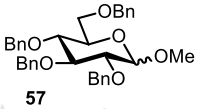
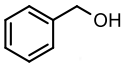
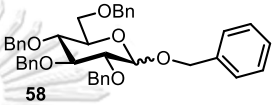
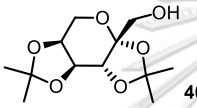
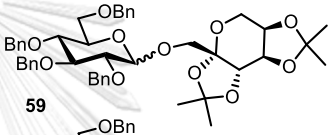
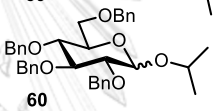
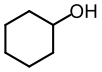
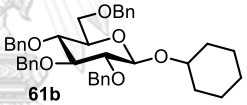
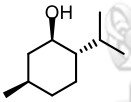
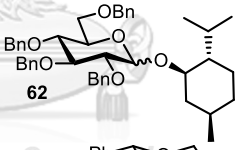
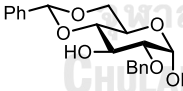
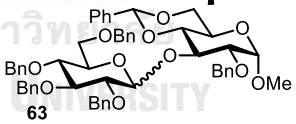
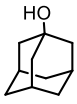
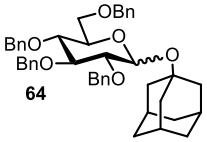
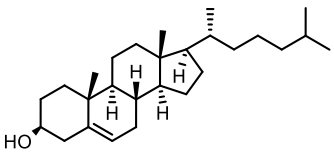
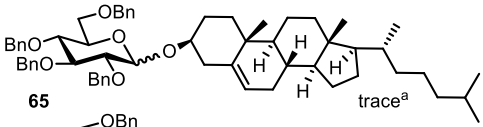
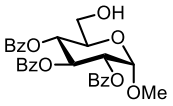
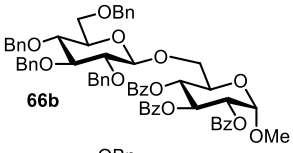
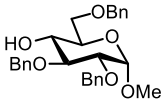
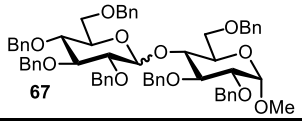


Figure 3.5 TLC analysis of glycosylation between **34a** and cholesterol.

Table 3.5 Investigation the scope of acceptors for glycosylation.



34a : R^1 = SEt, R^2 = H
34b : R^1 = H, R^2 = SEt

Entry	Acceptor	Product	Yield (α : β)
1		 **54b**	79% (β only)[a]
2	MeOH	 **57**	73% (14:86)[a]
3		 **58**	69%[a,c]
4	 **40**	 **59**	43%[a,c]
5		 **60**	86%[a,c]
6		 **61b**	57% (β only)[a]
7		 **62**	49% (14:86)[a]
8	 **41**	 **63**	20%[a,c]
9		 **64**	35%[a,c]
10		 **65**	trace[a]
11	 **53**	 **66b**	66% (β only)[b]
12	 **50**	 **67**	43%[b,c]

[a] Thioglycoside **34a** as donor [b] Thioglycoside **34b** as donor [c] Unable to determine α:β ratio

Moreover, disarmed glycosyl acceptor **53** and secondary glycosyl acceptor **50** were tested for glycosylation with ethyl thioglycoside **34b**. The results showed that glycosylations were proceeded to generate disaccharides **66b** and **67** in moderate yield (66% and 43%, respectively) (entries 11 and 12). When using disarmed glycosyl acceptor **53**, only β anomer was isolated (entry 11).

3.7 Glycosyl intermediate study

To study glycosyl intermediate in glycosylation, thioglycosides were activated with BDSB in the absence of acceptor. Firstly, glycosyl donor **34b** was treated with BDSB in CH_2Cl_2 at –35 °C for 30 minutes. After reaction was completed, glycosyl intermediate **68** was observed on TLC (Figure 3.5a). The reaction was quenched with $NaHCO_3$ and $Na_2S_2O_3$, extracted with ethyl acetate, and then purified by column chromatography. Glycosyl intermediate **68** was obtained as a colorless syrup and characterized by ^{1}H NMR (Figure 3.6a). Next, glycosyl donor **36b** was also studied by activating with BDSB in CH_2Cl_2 at –35 °C for 30 minutes, to provide glycosyl intermediate **68** as a colorless syrup (Figure 3.5b). Moreover, the hydrolysis by-product **69** was also collected as minor product (white solid) and characterized by ^{1}H NMR.

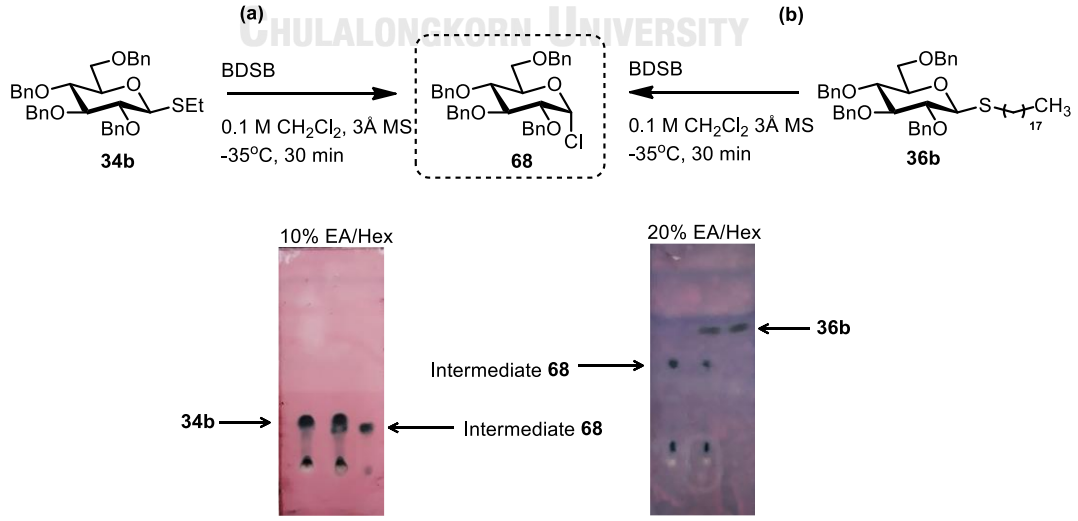
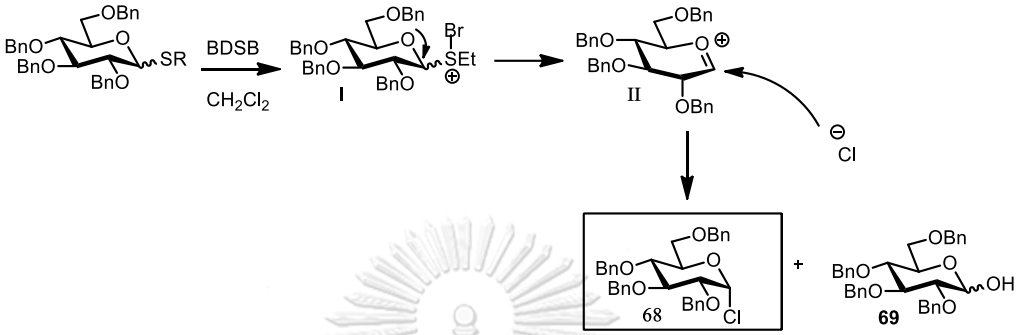


Figure 3.6 Glycosyl intermediate **68** was monitored by TLC.

The ^{1}H NMR analysis of glycosyl intermediate **68** showed chemical shift of anomeric proton at 6.02 ppm. Moreover, the *J*-coupling constants of the anomeric proton showed (*J* = 3.6 Hz and 3.8 Hz) that only α anomer was observed (Figure 3.6a and 3.6b).



From the results, we proposed that the chloride ion of BDSB added to the anomeric position of oxocarbenium intermediate (**II**). This glycosyl chloride **68** is an important intermediate in this glycosylation with BDSB. So, the mechanistic study of this glycosyl intermediate will be monitored by NMR in further detail.

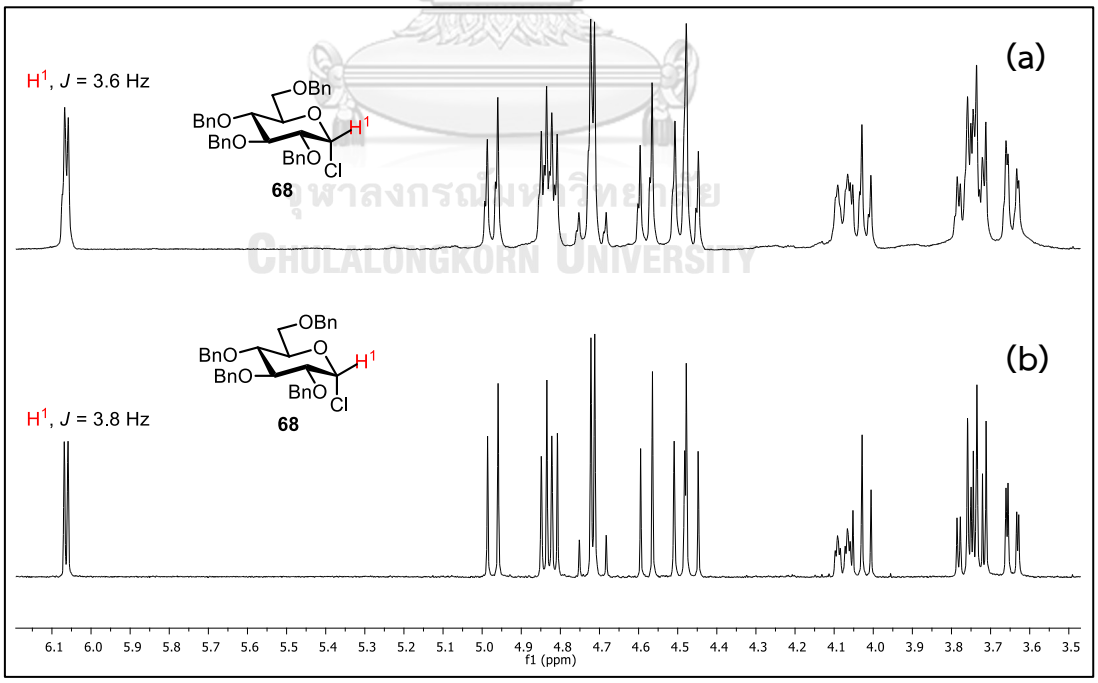


Figure 3.7 ^{1}H NMR spectra of glycosyl intermediate **68** (400 MHz, $CDCl_3$). (a) When glycosyl donor **34b** was used. (b) When glycosyl donor **36b** was used.

The mechanistic study of glycosylation of thioglycosides activated with BDSB/AgOTf was studied by using ^{1}H NMR spectroscopy (Figures 3.8 and 3.9). Firstly, thioglycoside **34a** was activated with BDSB in CD_3CN at –35 °C for 30 minutes (Figure 3.8b). Then, the reaction was monitored by NMR at room temperature. At this point, the two peaks of anomeric proton were detected at downfield position (6.75 and 6.38 ppm). The downfield peak at 6.75 ppm could be anomeric proton peak of glycosyl chloride intermediate **68**. Next, AgOTf in CD_3CN was added into the reaction and leaved it at room temperature for 5 minutes (Figure 3.8c). After monitoring the reaction, the peak at 6.75 ppm was disappeared. Since, the glycosyl chloride **68** might be activated by AgOTf.

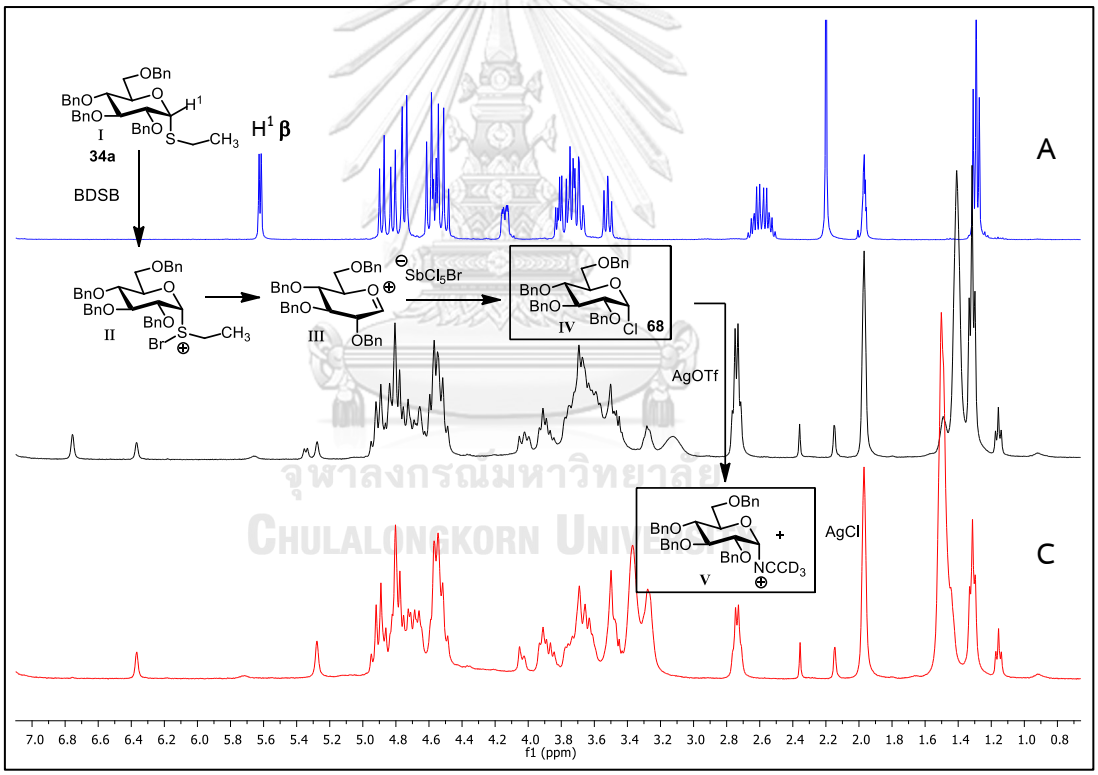


Figure 3.8 ^{1}H NMR monitoring of glycosylation of thioglycoside **34a** activated with BDSB/AgOTf (400 MHz, CD_3CN). (a) ^{1}H NMR spectrum of thioglycoside **34a**. (b) Thioglycoside **34a** activated by BDSB. (c) When AgOTf was added into the reaction.

Then, CD_3OD was added into the reaction mixture at room temperature for 10 minutes (Figure 3.9d). From the ^1H NMR result, only a small peak of β product was observed at 4.35 ppm. So, the reaction mixture was leaved for overnight to complete reaction (Figure 3.9e). Finally, the crude mixture of α and β product was identified by NMR (Figure 3.9f).

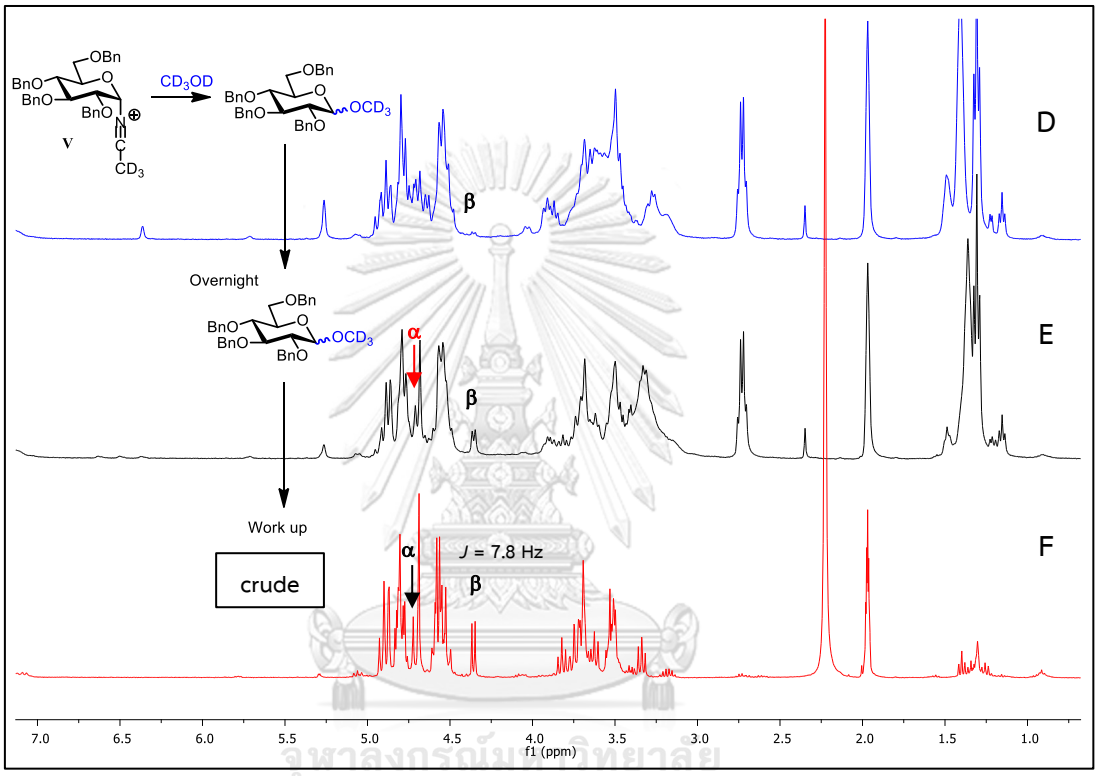


Figure 3.9 ^1H NMR monitoring of glycosylation of thioglycoside **34a** activated with BDSB/AgOTf (400 MHz, CD_3CN). (d) When CD_3OD was added at room temperature for 10 minutes. (e) overnight reaction at room temperature. (f) ^1H NMR spectrum of crude product after work-up.

According to the NMR monitoring of glycosylation, we proposed the possible glycosylation mechanism for this study (Figure 3.10). Firstly, thioglycoside (**I**) was activated by BDSB to generate oxocarbenium cation (**III**). Then, chloride ion of BDSB attacked the anomeric position of intermediate (**III**) to generate glycosyl chloride (**IV**) with α selectivity. When AgOTf was added and it was going to activate glycosyl chloride (**IV**). This step, the white precipitate of silver chloride (AgCl) was occurred.

For glycosylation in acetonitrile, acetonitrile would attack the oxocarbenium cation to generate a stable intermediate (**V**). The glycosylation *via* intermediate (**V**) to generate β product as a major.

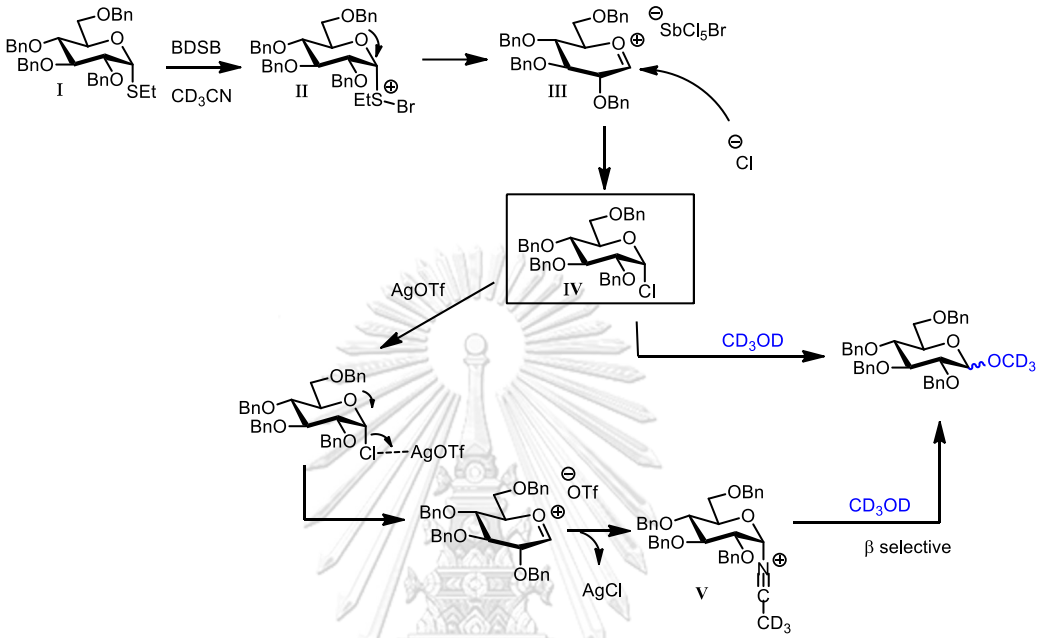
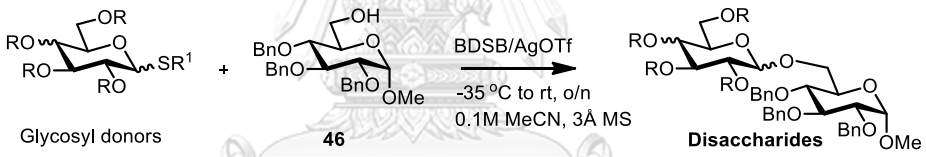


Figure 3.10 Proposed mechanism of glycosylation of thioglycosides activated with BDSB/AgOTf in the work.

CHAPTER IV
CONCLUSION

1. The glycosylation of ethyl thioglycoside and glycosyl acceptor activated by BDSB provided the disaccharide **54** in moderate yield. However, using BDSB in combination with AgOTf in acetonitrile at low temperature produced disaccharide **54** in high yield and β selectivity. The α selectivity was increased when using Et_2O and toluene as solvent.

2. Scope of thioglycosides was examined. Disarmed glycosyl donor was not successfully performed in this system of BDSB/AgOTf as activator. In contrast, armed glycosyl donors were smoothly performed under BDSB/AgOTf in acetonitrile at –35 °C to room temperature. Disaccharides (**54** and **56**) were obtained in low to high yields (26–85%) (Figure 4.1).



Armed donors: α-ethyl thioglucoside **34a** — Disaccharides: **54** = 79% yield
β-ethyl thioglucoside **34b** — **54** = 85% yield
α-octadecyl thioglucoside **36a** — **54** = 65% yield
β-octadecyl thioglucoside **36b** — **54** = 26% yield
α-octadecyl thiogalactoside **38a** — **56** = 74% yield
β-phenyl thioglucoside **39b** — **54** = 65% yield

Figure 4.1 The glycosyl donor scope of glycosylation with BDSB/AgOTf as activator.

Next, scope of acceptors was examined (Figure 4.2). Glycosylation of α ethyl thioglycoside **34a** and several acceptors was successfully performed and provided *O*-linked glycosides in low to high yields (20–79%) with good β selectivities. Primary glycosyl alcohol **46** was obtained **54b** in 79% with high β selectivity without using neighboring participation group at C2. Other primary alcohols were subjected to the glycosylation. The results indicated that glycosylations were proceeded smoothly to provide the *O*-linked glycosides **57–59** in moderate to high yields (43–73%). Glycosylation with secondary alcohols were investigated. When small molecule of

alcohol was used, the product **60** was obtained in high yield (86% yield). Using bulky secondary alcohols, the products (**61–63**) were obtained in low to moderate yields (20–57%). Next, using 1-adamantanol as tertiary alcohol, the glycosylation was proceeded slowly and obtained low yield of product **64** (35%). However, using unsaturated alcohol such as cholesterol as acceptor for this work was not successfully performed due to bromination of olefinic group.

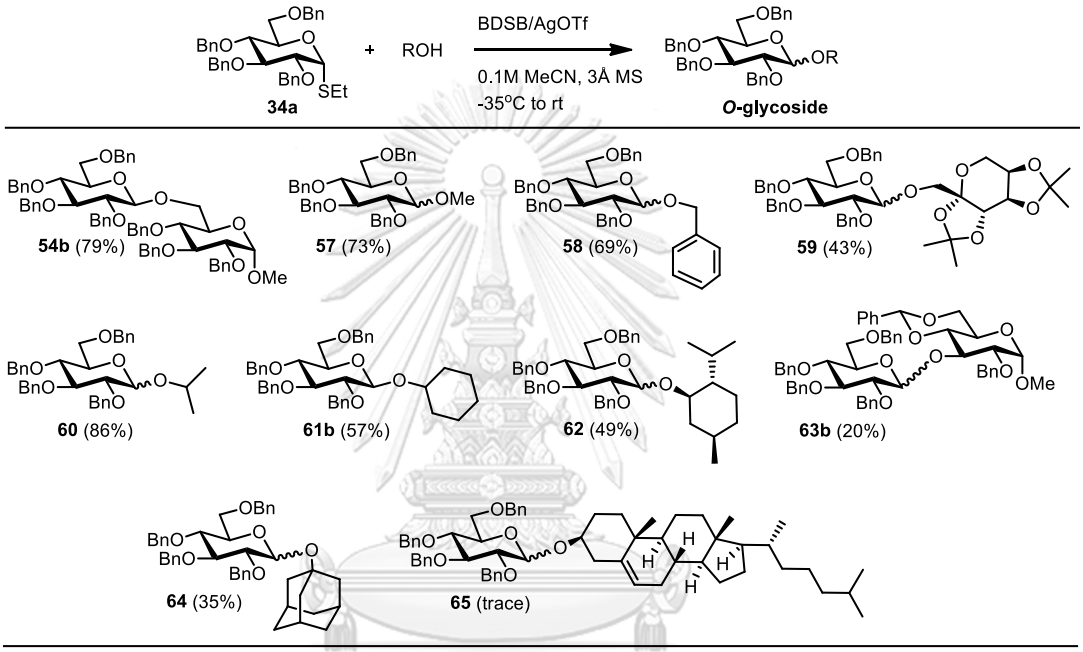


Figure 4.2 The acceptor scope of α-thioglycoside with BDSB/AgOTf as activator.

Moreover, glycosylations of β thioglycoside **34b** with different glycosyl acceptors were also examined (Figure 4.3). Glycosylation with primary alcohol **46** and **53** were proceeded to obtain disaccharides **54b** and **67b** in good to high yields (85% and 66%, respectively) with only β selectivities. Using secondary alcohol **50**, disaccharide **66** was obtained in moderate yield (43%).

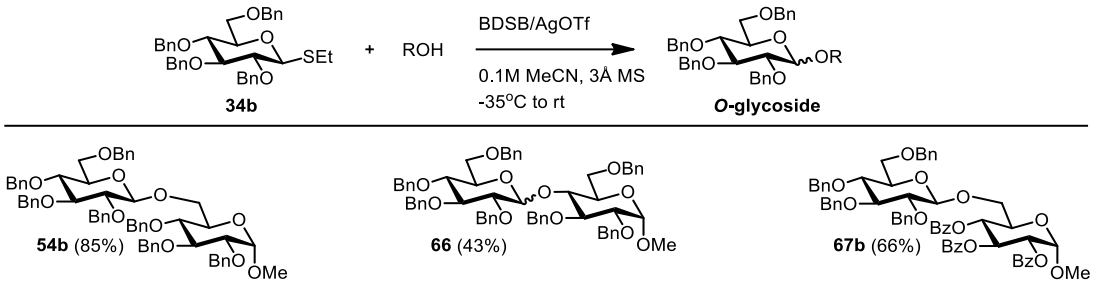


Figure 4.3 The acceptor scope of β-thioglycoside with BDSB/AgOTf as activator.

Finally, the intermediate from glycosylation of thioglycosides activated with BDSB was investigated. Glycosyl chloride intermediate **68** was isolated and confirmed by ^{1}H NMR.

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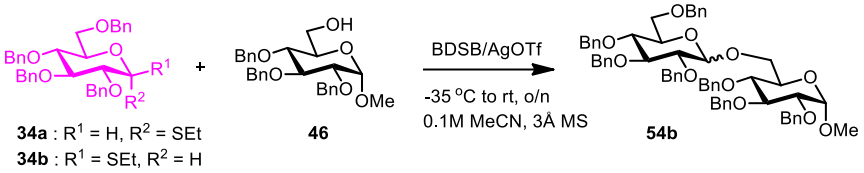
APPENDIC

Scope of glycosyl donors



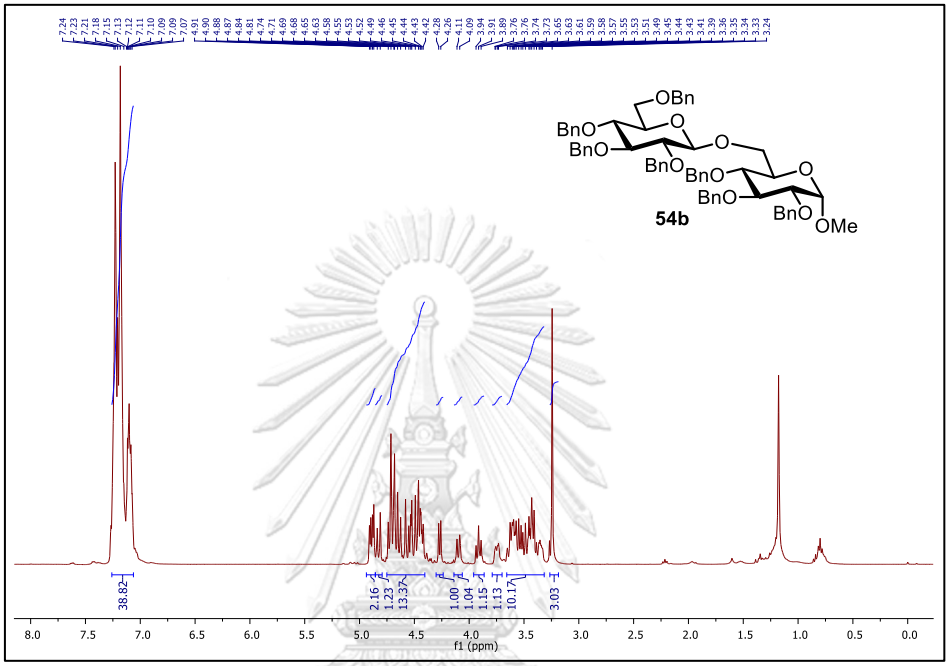


Figure A1 ^{1}H NMR spectrum of compound **54b** (400 Hz, $CDCl_3$).

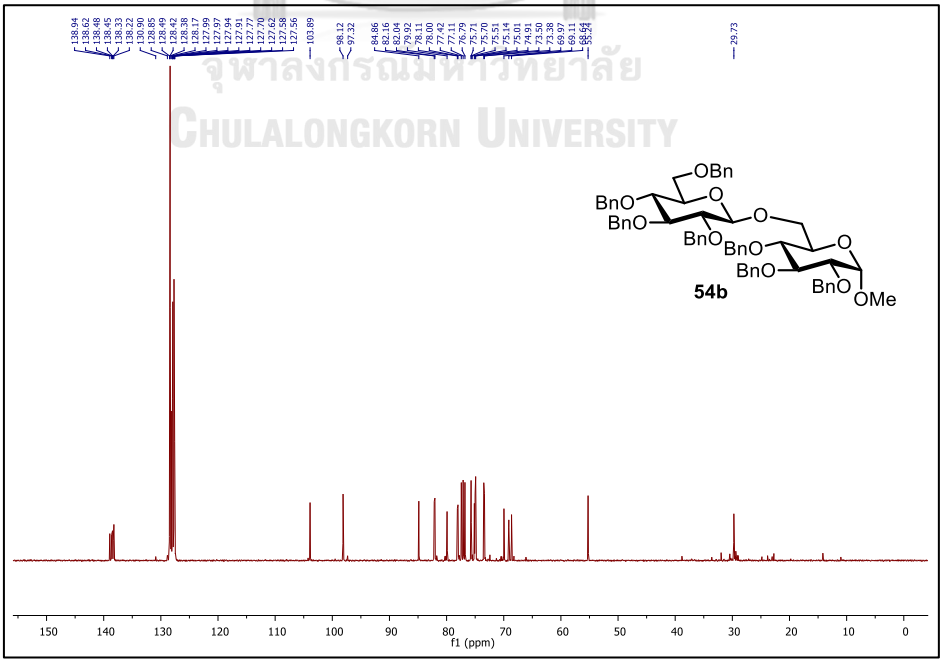


Figure A2 ^{13}C NMR spectrum of compound **54b** (100 Hz, $CDCl_3$).

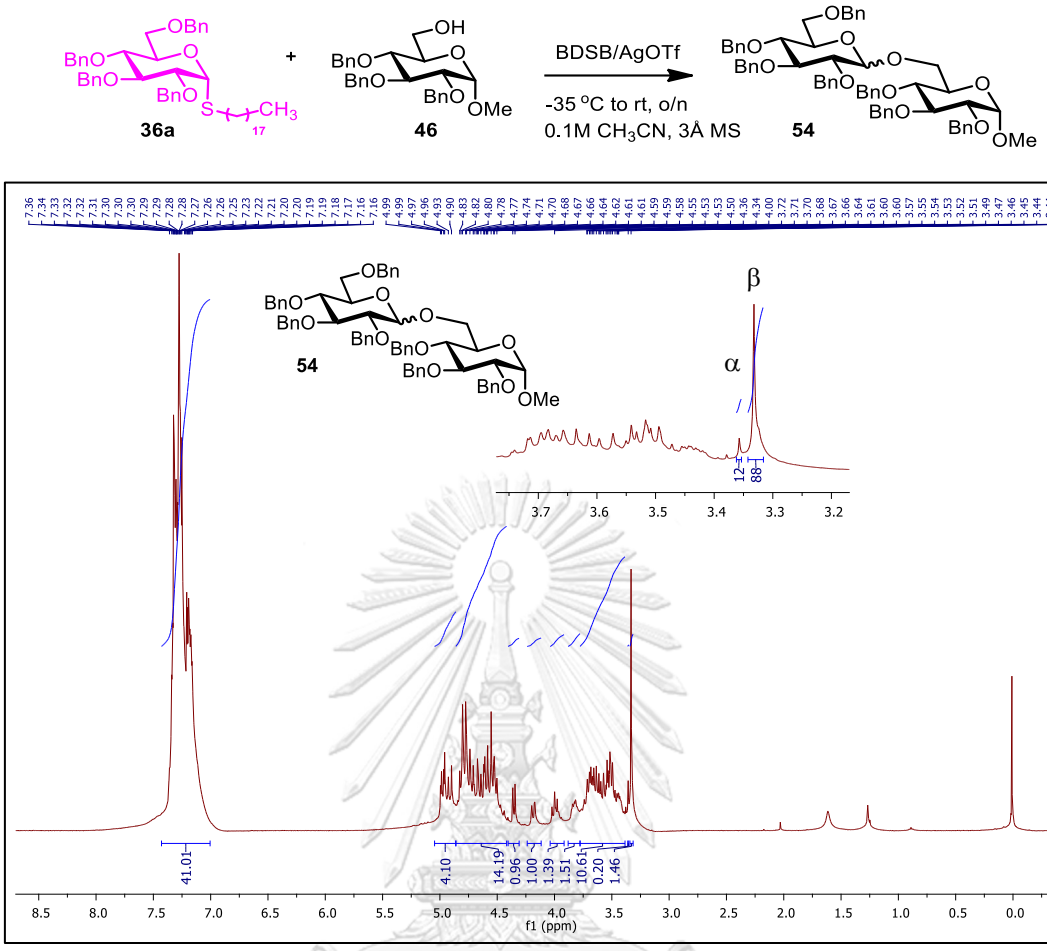


Figure A3 ^{1}H NMR spectrum of compound **54** (400 Hz, $CDCl_3$) using **36a** as donor.

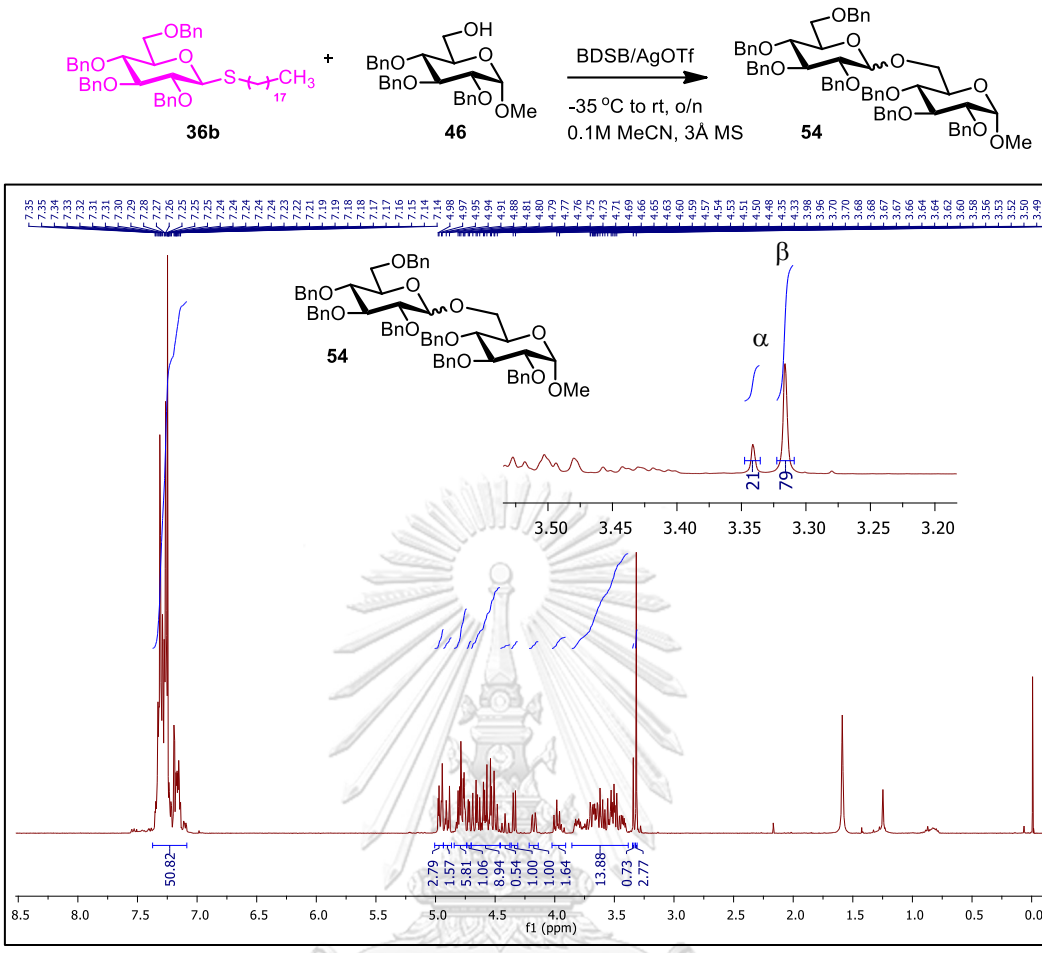


Figure A4 ^{1}H NMR spectrum of compound **54** (400 Hz, $CDCl_3$) using **36b** as donor.

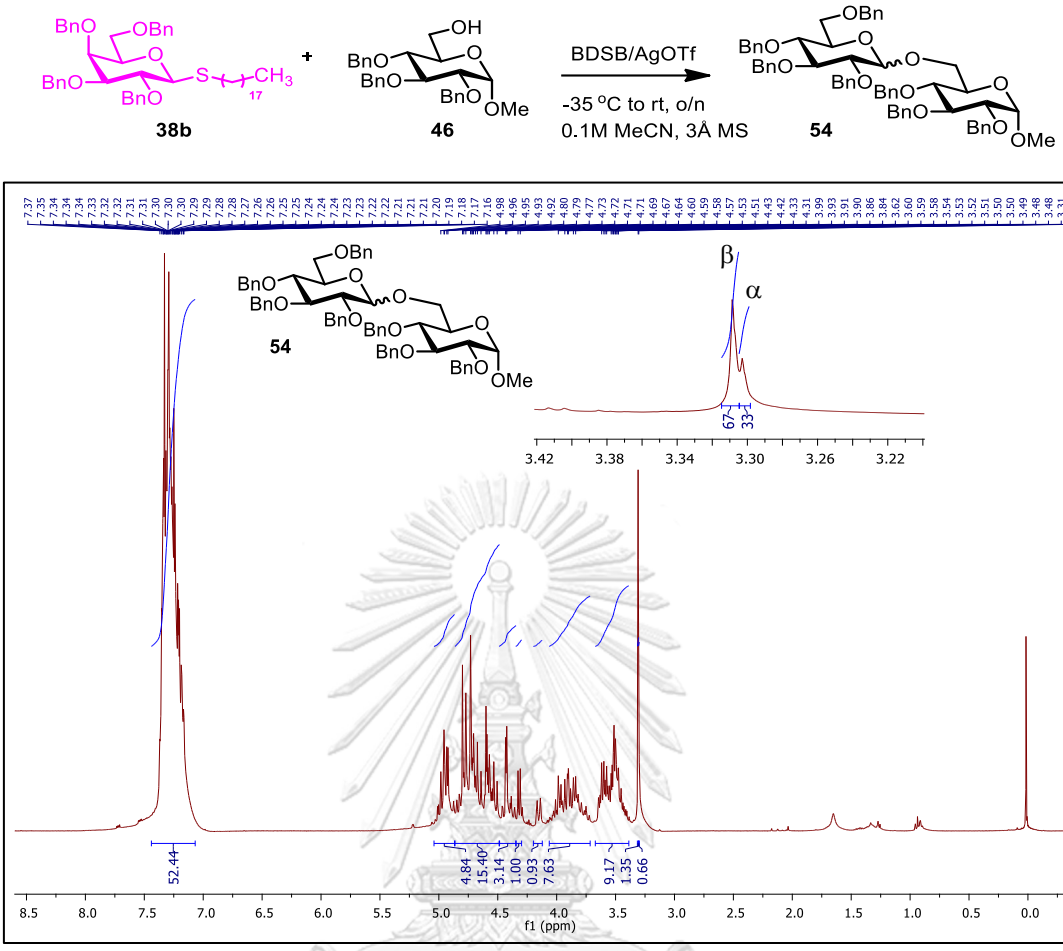


Figure A5 ^{1}H NMR spectrum of compound **54** (400 Hz, $CDCl_3$) using **38b** as donor.

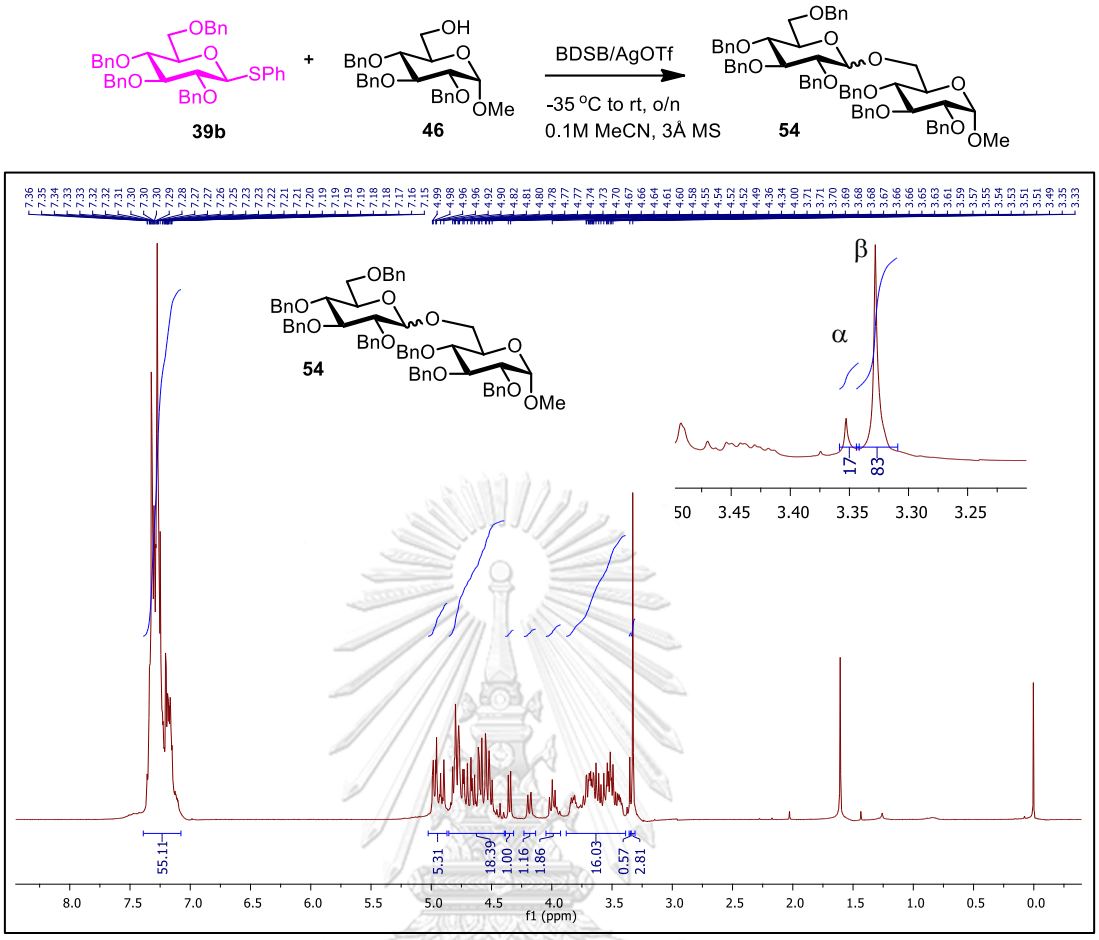


Figure A6 ^{1}H NMR spectrum of compound **54** (400 Hz, $CDCl_3$) using **39b** as donor.

Scope of acceptors

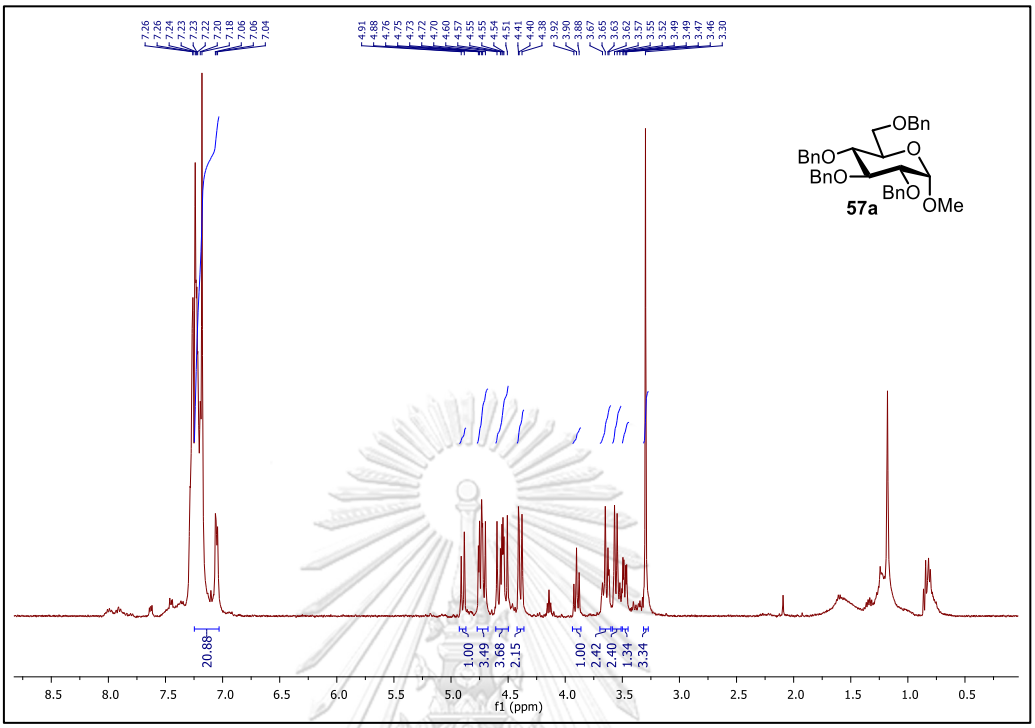


Figure A7 ^{1}H NMR spectrum of compound **57a** (400 Hz, $CDCl_3$).

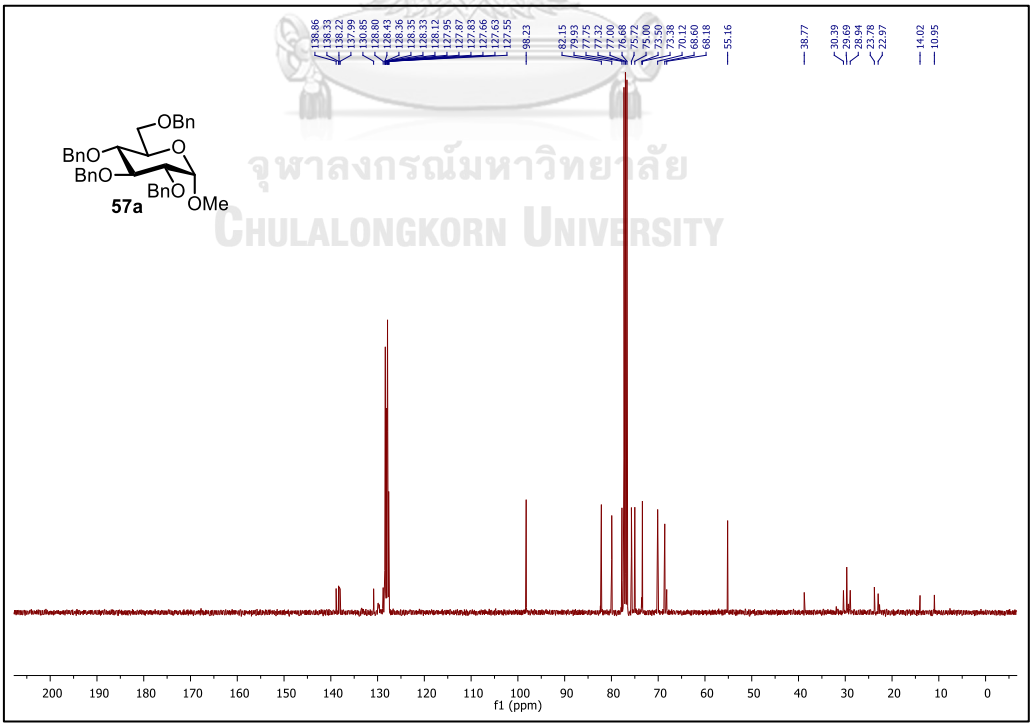


Figure A8 ^{13}C NMR spectrum of compound **57a** (100 Hz, $CDCl_3$).

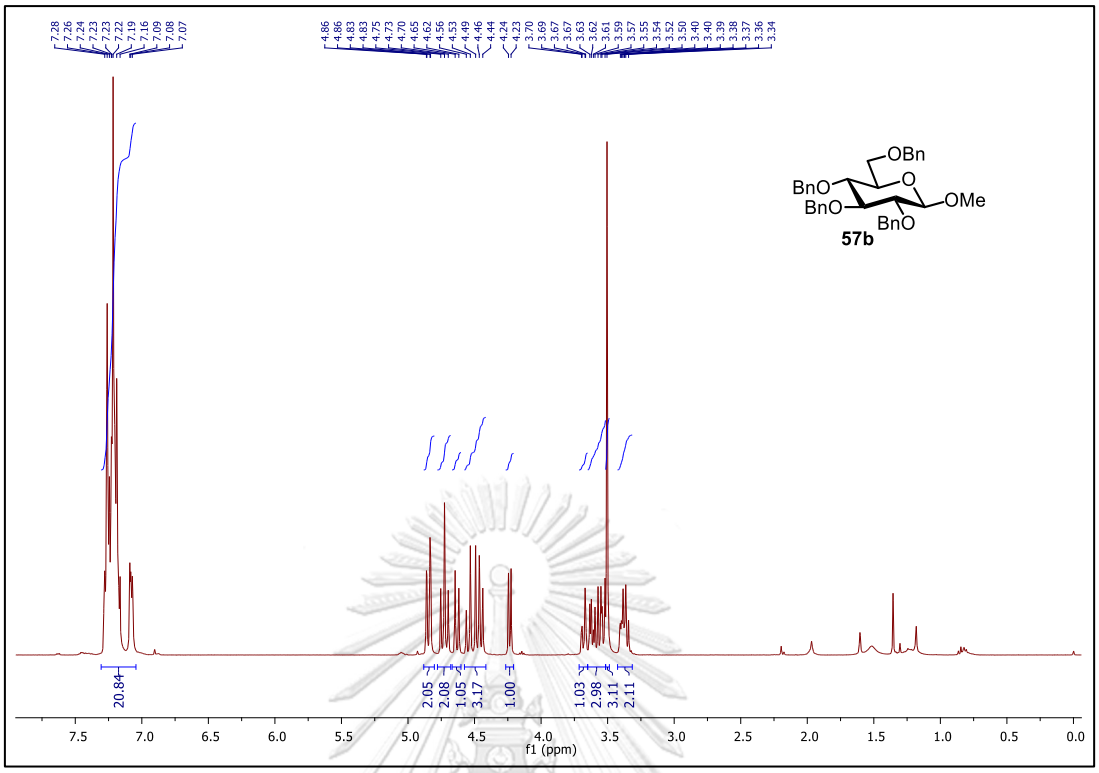


Figure A9 ^{1}H NMR spectrum of compound **57b** (400 Hz, $CDCl_3$).

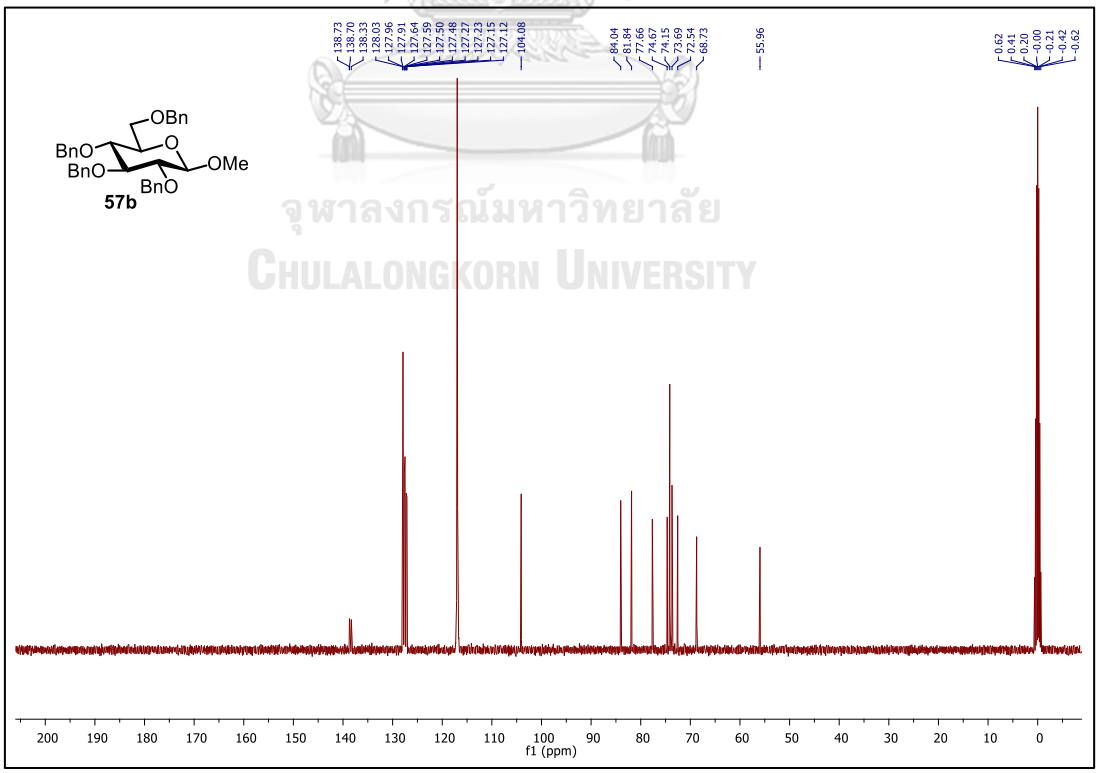


Figure A10 ^{13}C NMR spectrum of compound **57b** (100 Hz, CD_3CN).

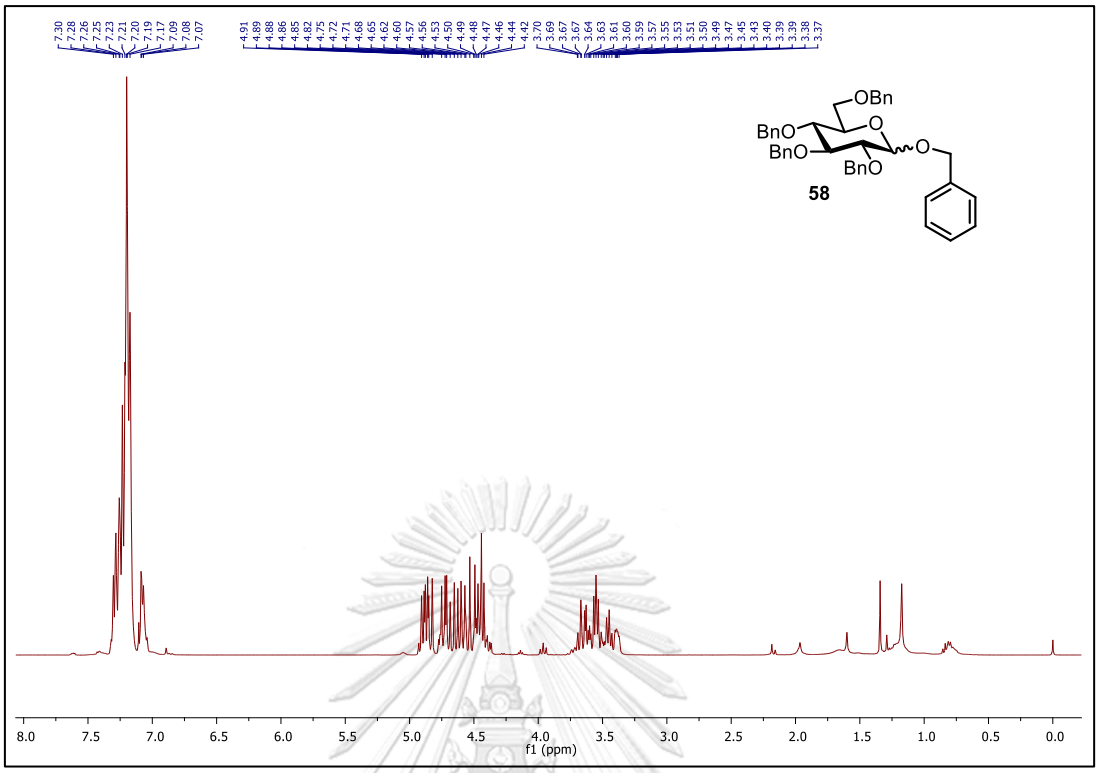


Figure A11 ^{1}H NMR spectrum of compound **58** (400 Hz, $CDCl_3$).

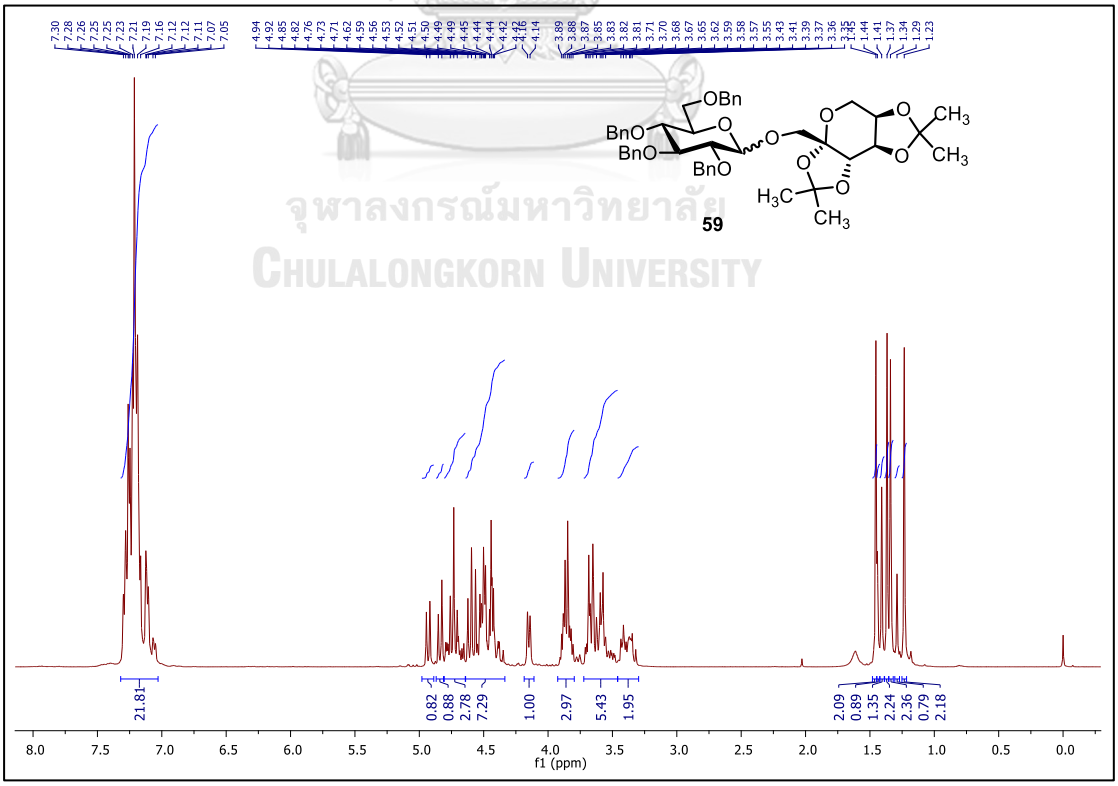


Figure A12 ^{1}H NMR spectrum of compound **59** (400 Hz, $CDCl_3$).

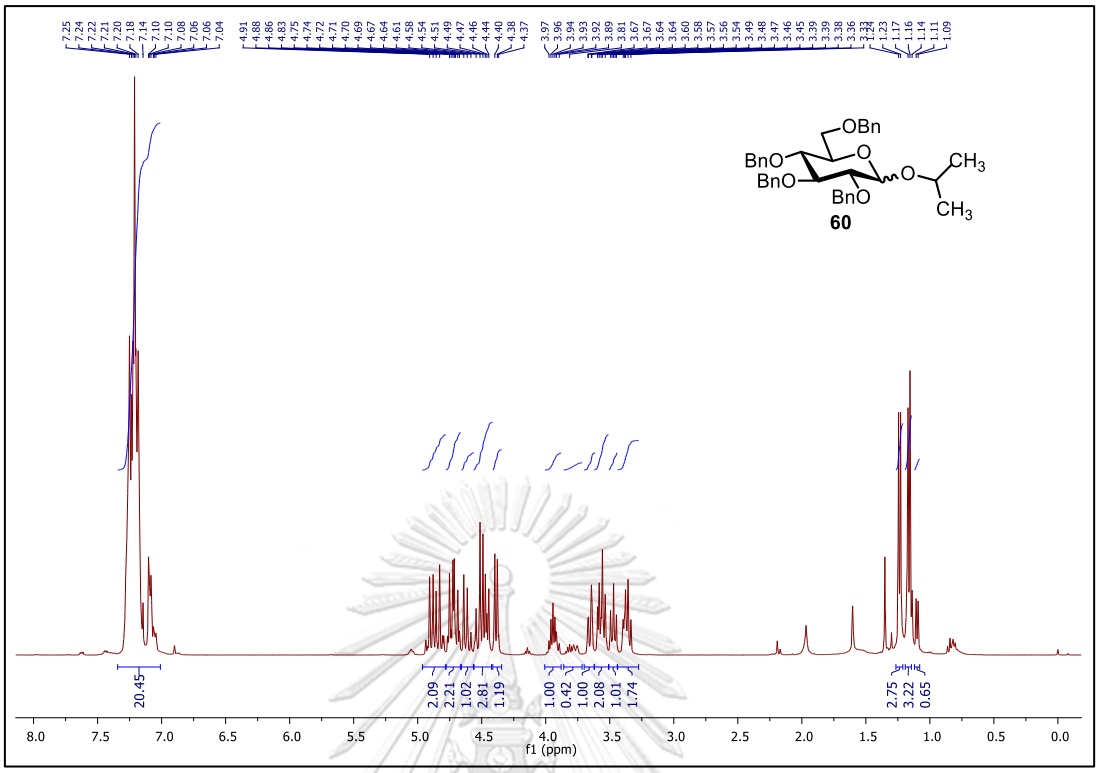


Figure A13 ^{1}H NMR spectrum of compound **60** (400 Hz, $CDCl_3$).

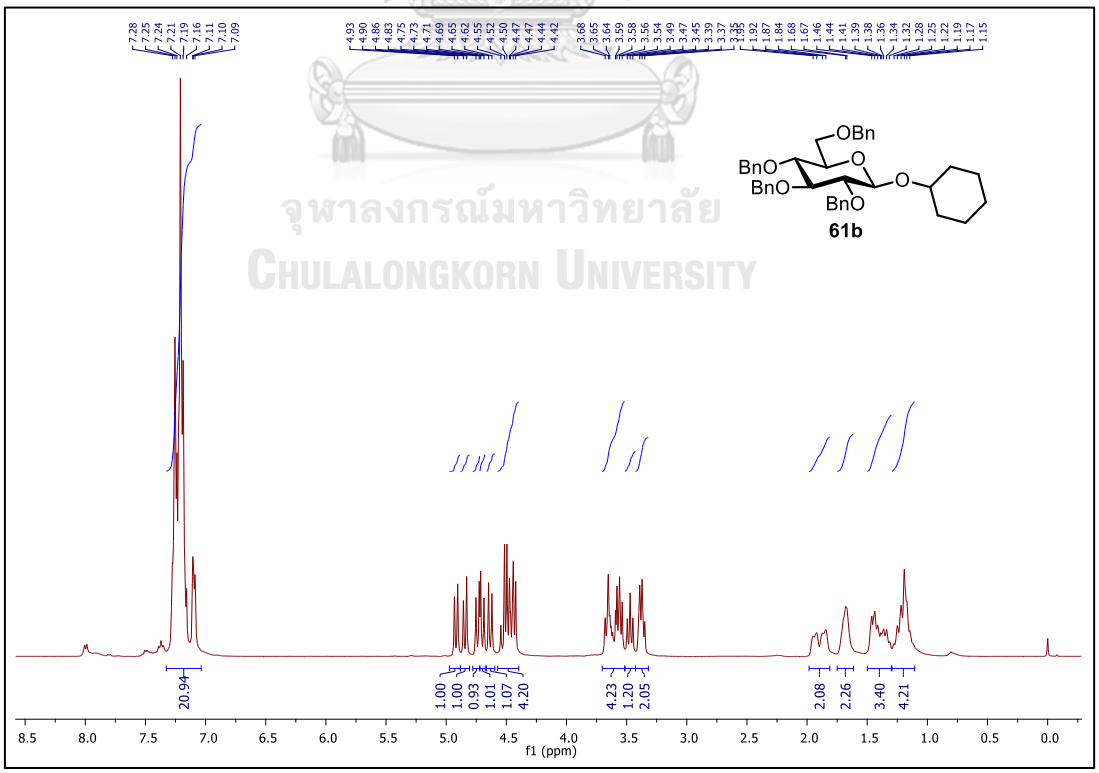


Figure A14 ^{1}H NMR spectrum of compound **61b** (400 Hz, $CDCl_3$).

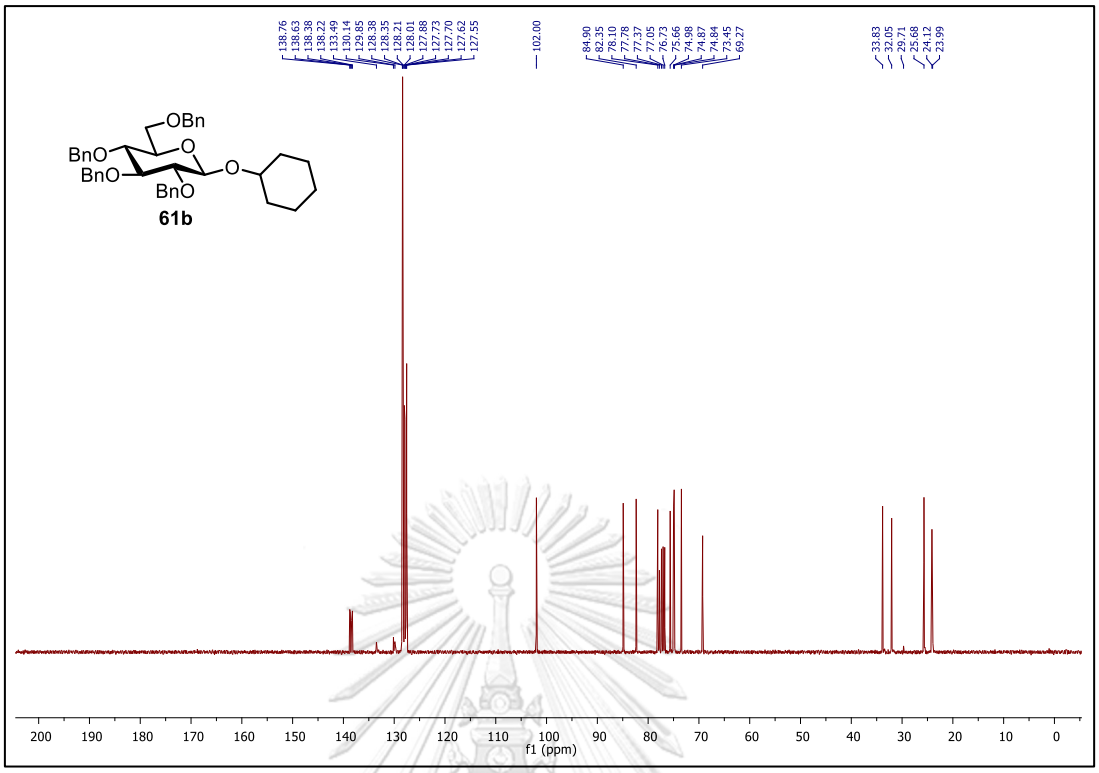


Figure A15 ^{13}C NMR spectrum of compound **61b** (100 Hz, $CDCl_3$).

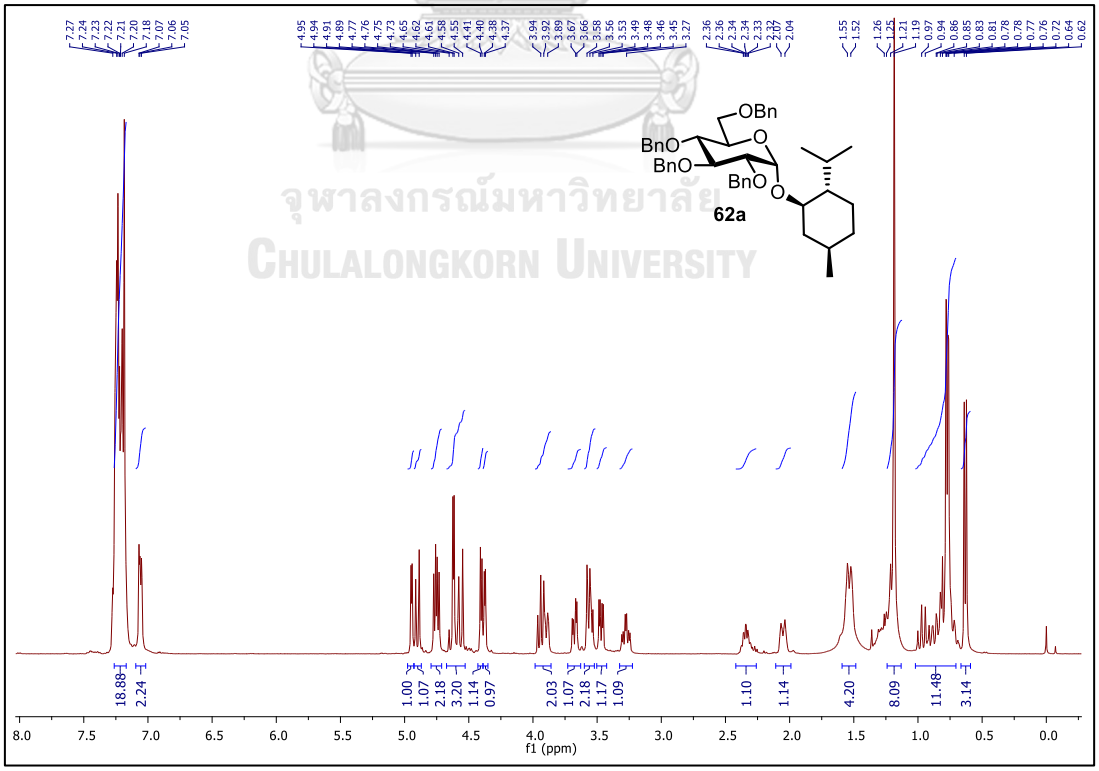


Figure A16 ^{1}H NMR spectrum of compound **62a** (400 Hz, $CDCl_3$).

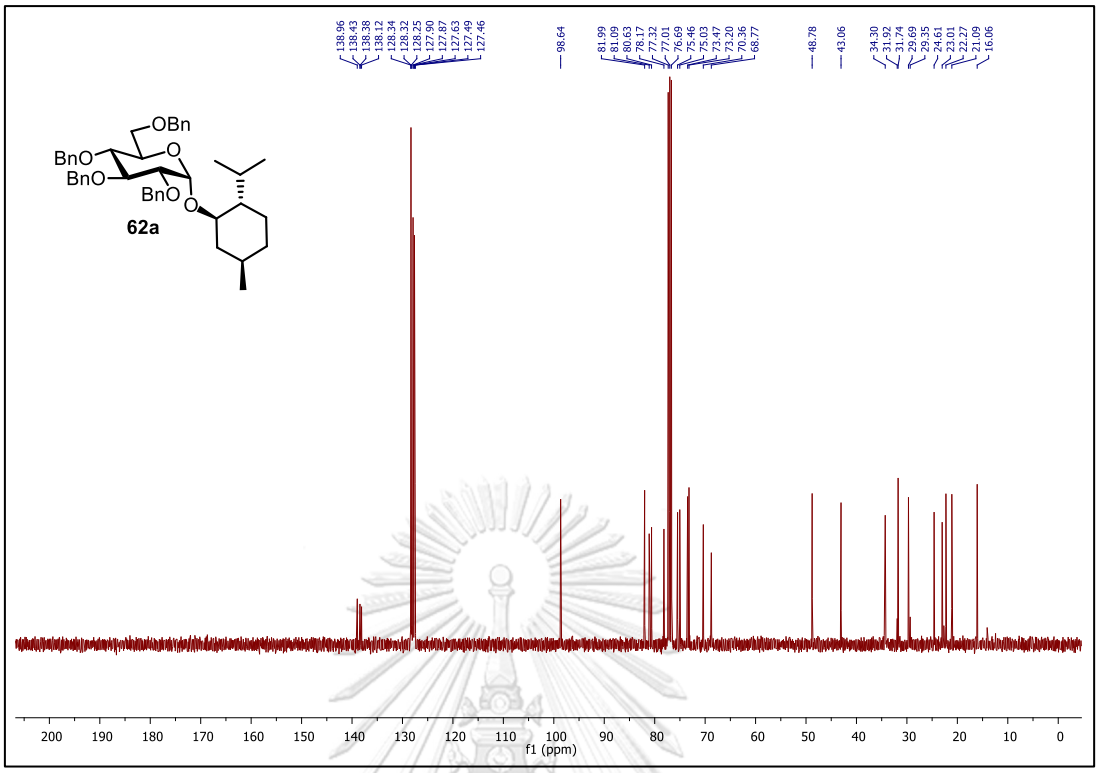


Figure A17 ^{13}C NMR spectrum of compound **62a** (100 Hz, $CDCl_3$).

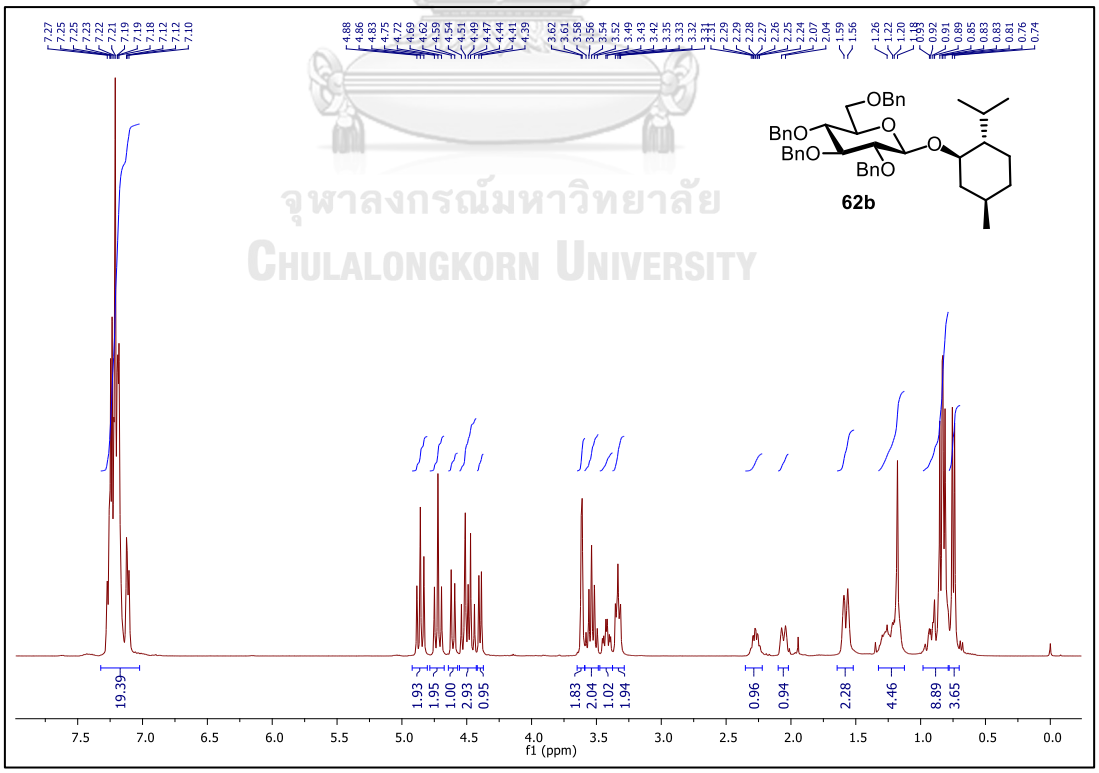


Figure A18 ^{1}H NMR spectrum of compound **62b** (400 Hz, $CDCl_3$).

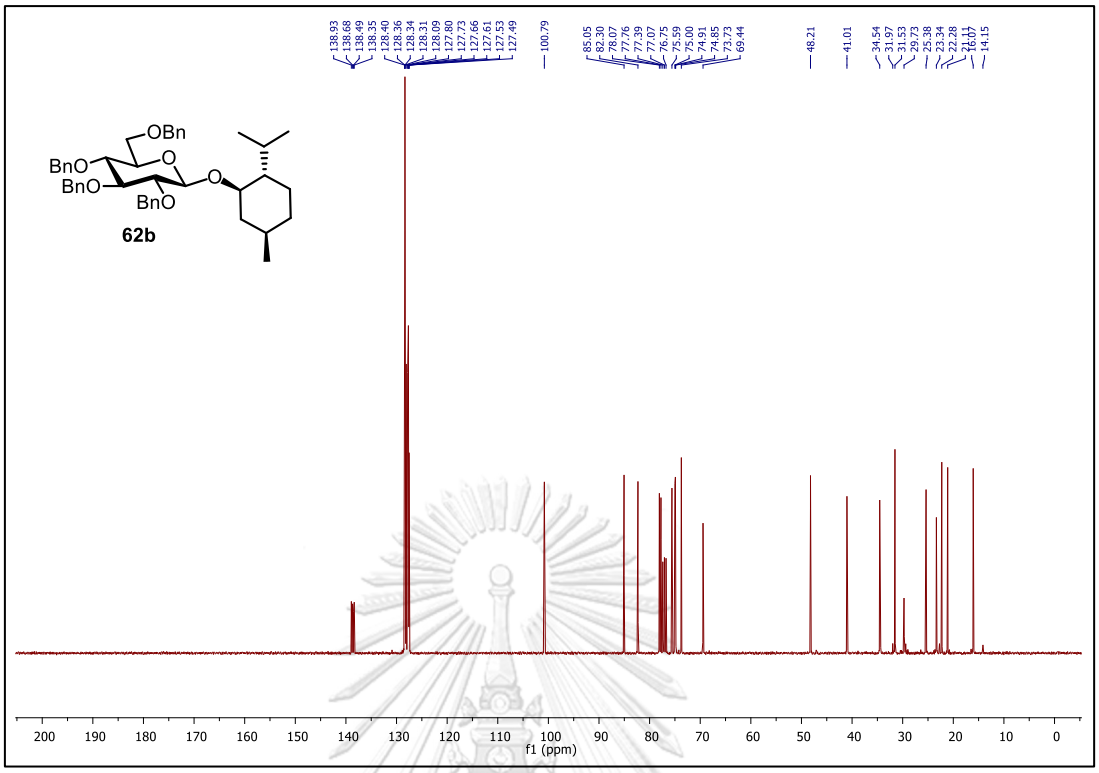


Figure A19 ^{13}C NMR spectrum of compound **62b** (100 Hz, $CDCl_3$).

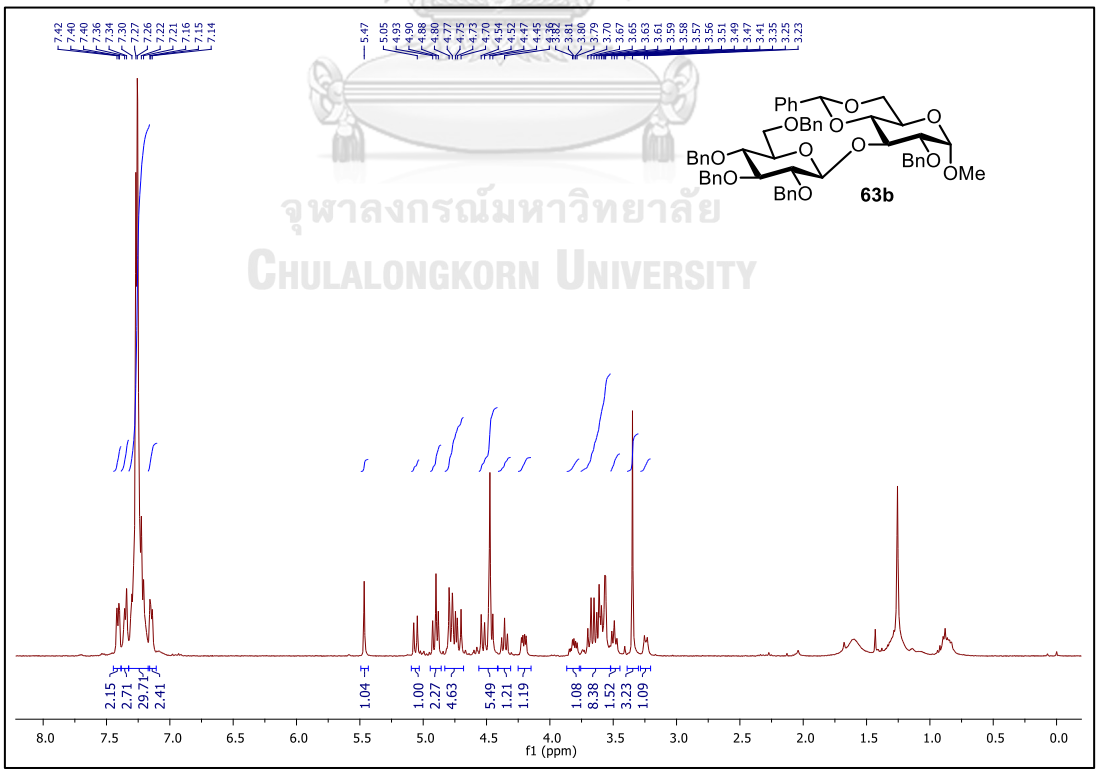


Figure A20 ^{1}H NMR spectrum of compound **63b** (400 Hz, $CDCl_3$).

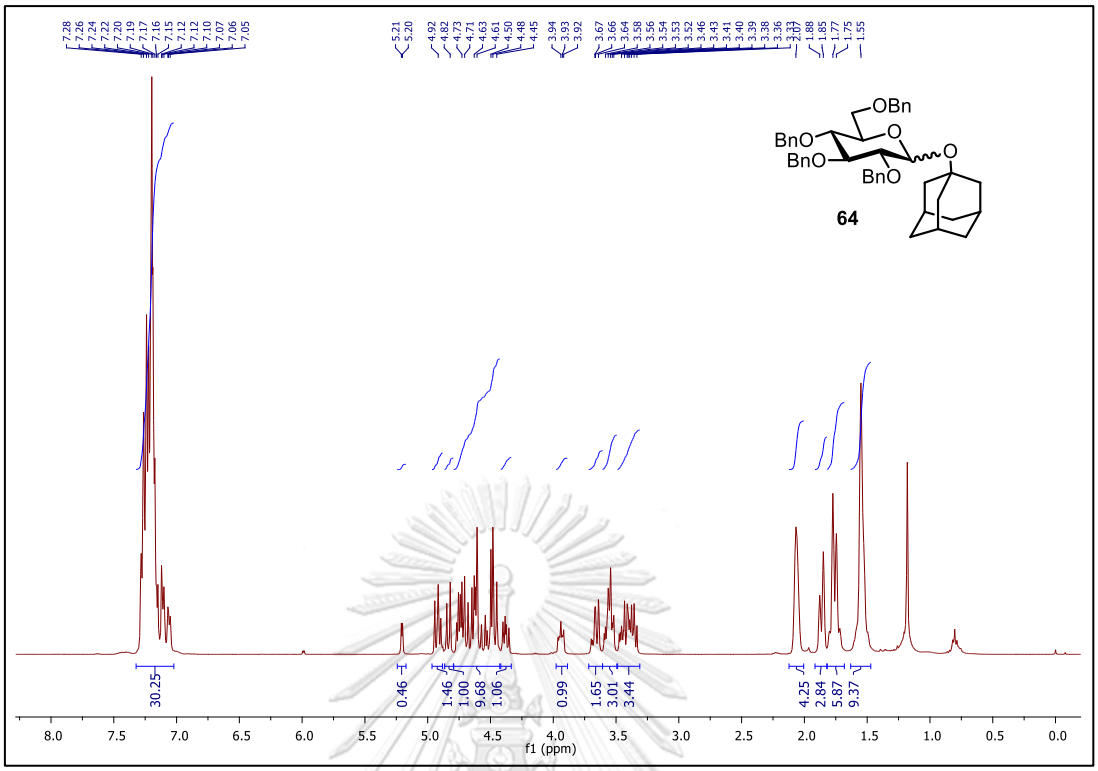


Figure A21 ^{1}H NMR spectrum of compound **64** (400 Hz, $CDCl_3$).

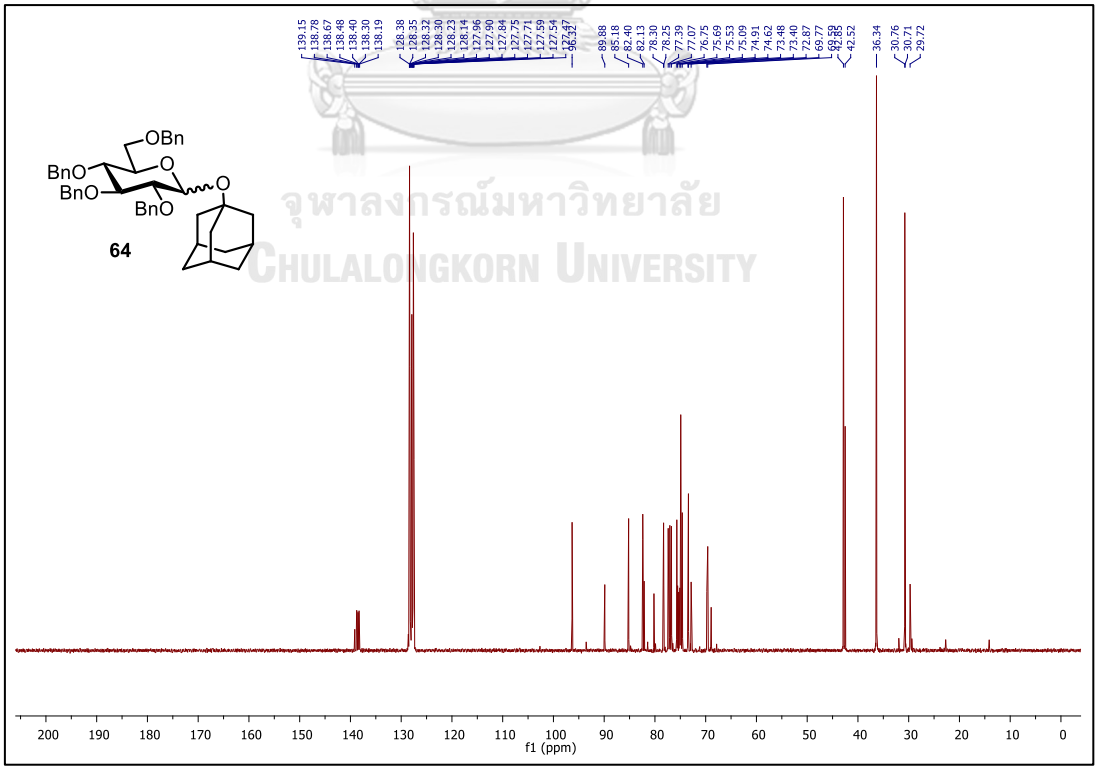


Figure A22 ^{13}C NMR spectrum of compound **64** (100 Hz, $CDCl_3$).

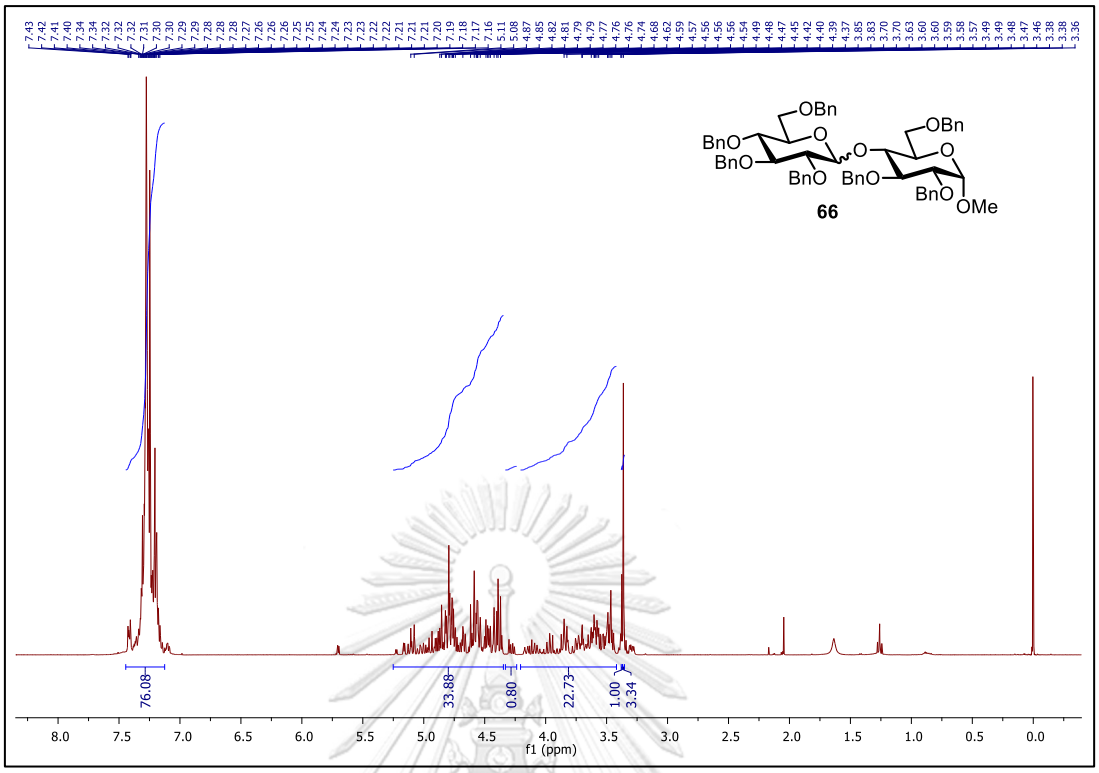


Figure A23 ^{1}H NMR spectrum of compound **66** (400 Hz, $CDCl_3$).

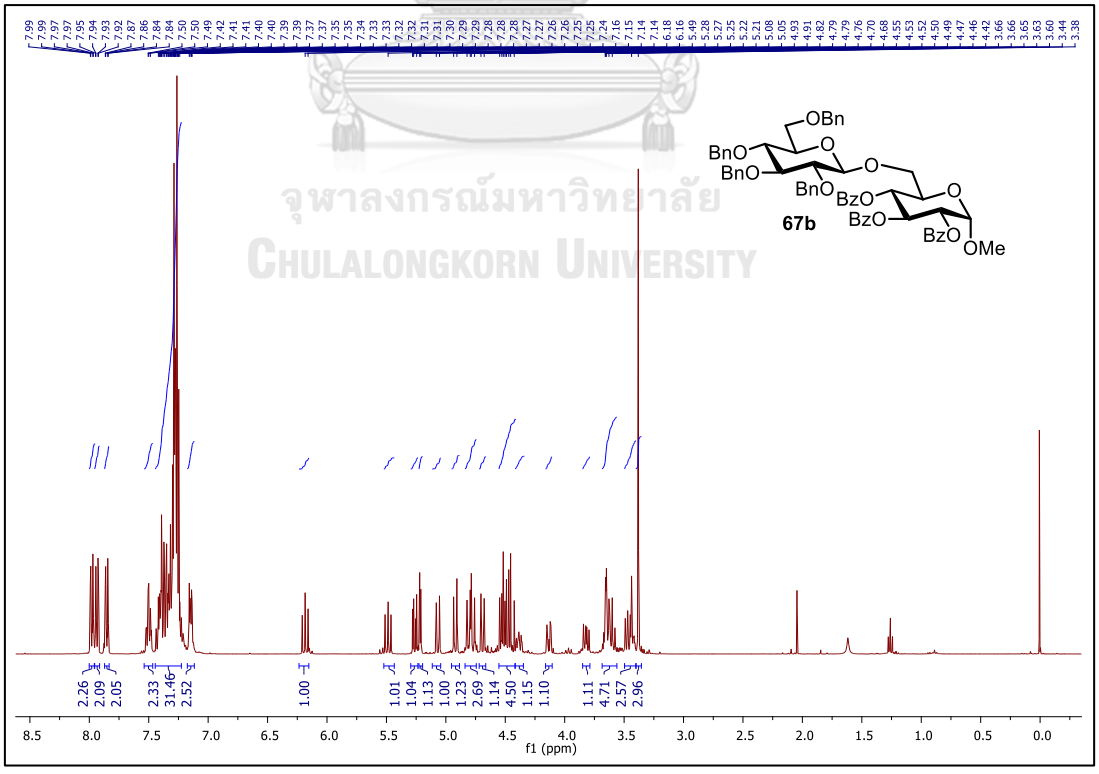


Figure A24 ^{1}H NMR spectrum of compound **67b** (400 Hz, $CDCl_3$).

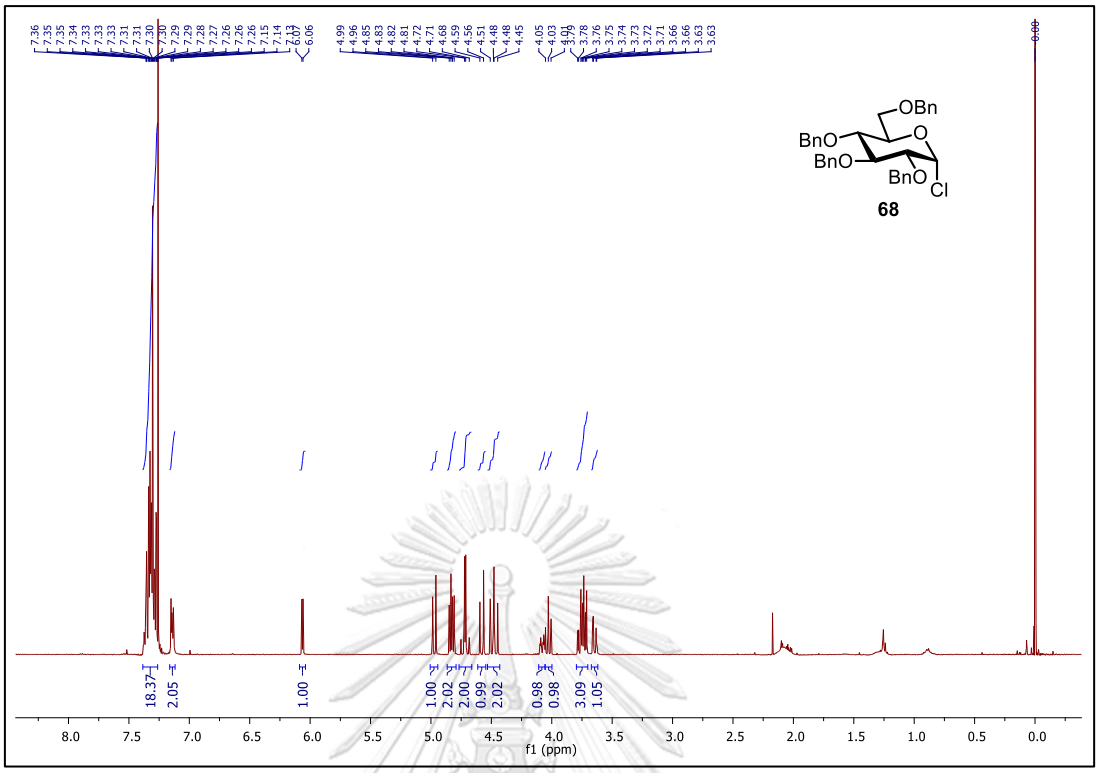


Figure A25 ^{1}H NMR spectrum of compound **68** (400 Hz, $CDCl_3$).

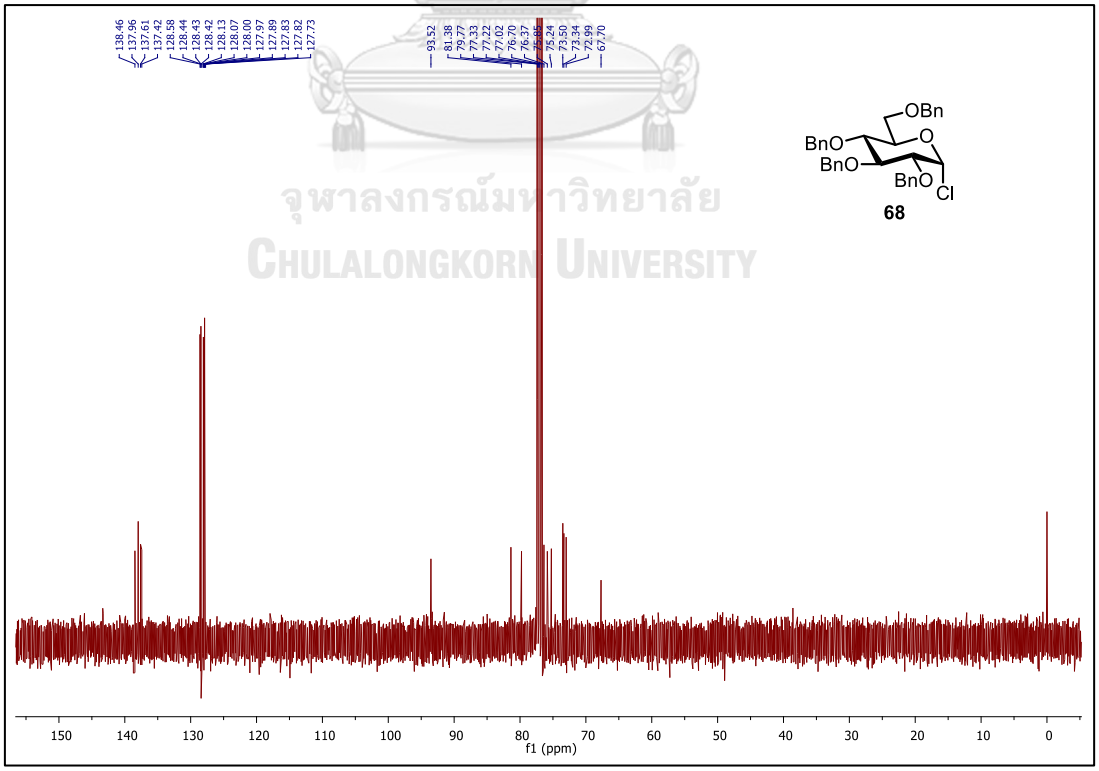


Figure A26 ^{13}C NMR spectrum of compound **68** (100 Hz, $CDCl_3$).

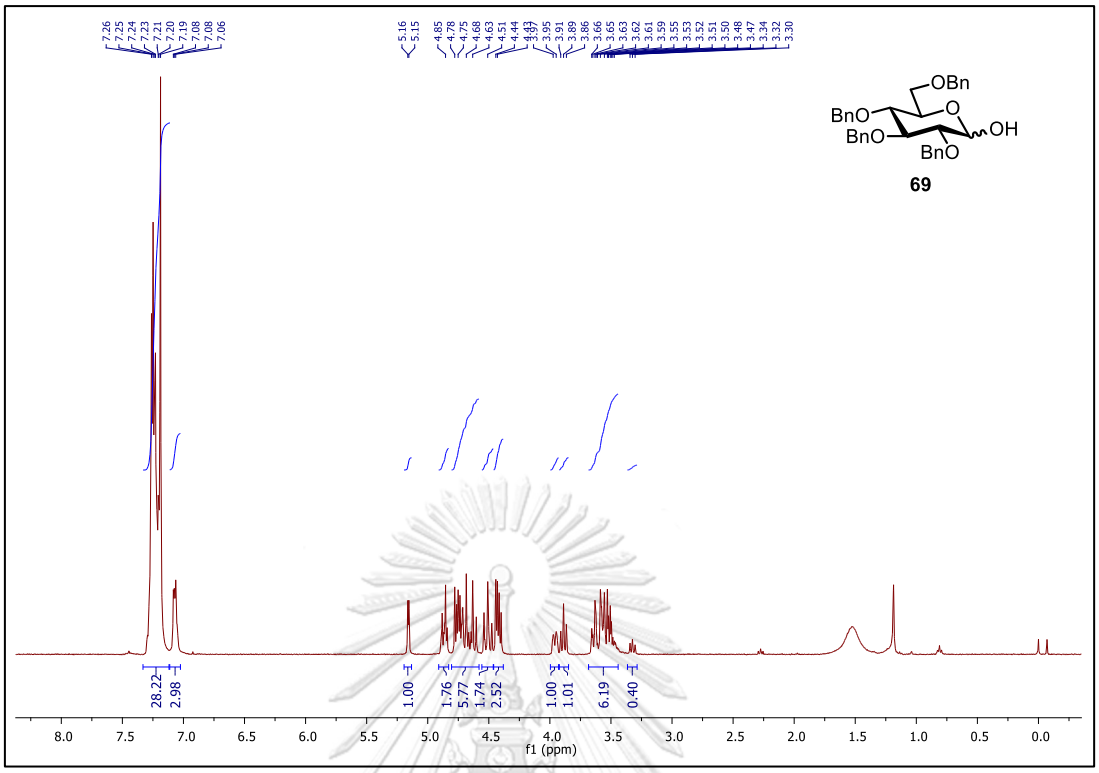


Figure A27 ^{1}H NMR spectrum of compound **69** (400 Hz, $CDCl_3$).

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