ไกลโคซิเลชันของ 2-ไนโตรไกลแคลที่เร่งกัมมันต์ด้วยด้วยเกลือไดไทโอคาร์เบเมต

นางสาวปาริชาติ สวัสดิ์ธีรกุล

จุฬาลงกรณ์มหาวิทยาลัย
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ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

GLYCOSYLATION OF 2-NITROGLYCALS ACTIVATED BY DITHIOCARBAMATE SALT

Miss Parichat Sawatteerakul

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science Program in Chemistry

Department of Chemistry

Faculty of Science

Chulalongkorn University

Academic Year 2016

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Thesis Title	GLYCOSYLATION OF 2-NITROGLYCALS ACTIVATED BY DITHIOCARBAMATE SALT
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Field of Study	Chemistry
Thesis Advisor	Assistant Professor Panuwat Padungros, Ph.D.

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ปาริชาติ สวัสดิ์ธีรกุล : ไกลโคซิเลชันของ 2-ไนโตรไกลแคลที่เร่งกัมมันต์ด้วยด้วยเกลือไดไทโอคาร์เบเมต (GLYCOSYLATION OF 2-NITROGLYCALS ACTIVATED BY DITHIOCARBAMATE SALT) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.ภาณุวัฒน์ ผดุงรส, 99 หน้า.

2-ไนโตรไกลแคลเป็นสารตั้งต้นที่สำคัญสำหรับใช้สังเคราะห์น้ำตาลชนิดดีออกซีแอมิโน ซึ่งเป็นน้ำตาลที่พบมากในกลุ่มของสารประกอบไกลโคโปรตีนหรือออลิโกแซ็กคาไรด์ที่มีฤทธิ์ทางชีวภาพ นอกจากนั้น 2-ไนโตรไกลแคลยังเป็นสารขั้นกลางทางเคมีสังเคราะห์ที่เหมาะสมต่อการนำไปใช้ทำปฏิกิริยาไกลโคซิเลชันผ่านปฏิกิริยาการเติมแบบไมเคิล (Michael addition) โดยเป็นปฏิกิริยาการเติมของนิวคลีโอไฟล์ลงบนพันธะคู่ของ 2-ไนโตรไกลแคล ให้ผลิตภัณฑ์ที่เป็นของผสมไอโซเมอร์ที่แตกต่างกันได้ถึง 4 รูปแบบ เนื่องจากเกิดคาร์บอนชนิดไม่สมมาตรขึ้นใหม่ 2 ตำแหน่ง ทำให้ผลิตภัณฑ์จากการเติมของนิวคลีโอไฟล์ที่ตำแหน่งแอนนอเมอริกเป็นไปได้ทั้งแบบแอลฟา-ไกลโคไซด์และเบต้า-ไกลโคไซด์ ในงานวิจัยนี้ คณะผู้วิจัยได้รายงานการทำปฏิกิริยาการเติมแบบไมเคิลของ 2-ไนโตรไกลแคลโดยไม่ใช้เบสหรือกรดแก่เป็นตัวเร่งปฏิกิริยาดังที่มีรายงานมาก่อน แต่เลือกใช้เกลือไดไทโอคาร์เบเมตเป็นสารเร่งกัมมันต์แทน งานวิจัยเริ่มจากการสังเคราะห์ 2-ไนโตรไกลแคลจากสารประกอบไกลแคลด้วยปฏิกิริยาไนเตรชันโดยใช้ซิลเวอร์ไนเตรตและโพรพิออนิล คลอไรด์ ให้ผลิตภัณฑ์อยู่ในช่วงร้อยละ 27–44 เมื่อเปลี่ยนวิธีไนเตรชันไปใช้ของผสมระหว่างแอเซติก แอนไฮดรายด์และกรดไนตริก จากนั้นจึงทำปฏิกิริยากำจัดออก พบว่าให้ผลิตภัณฑ์ 2-ไนโตรไกลแคลในร้อยละ 45 ขั้นต่อไปจึงศึกษาปฏิกิริยาการเติมแบบไมเคิลที่เร่งกัมมันต์ด้วยเกลือโซเดียมไดเอทิลไดไทโอคาร์เบเมตกับซัลเฟอร์นิวคลีโอไฟล์ ไนโตรเจนนิวคลีโอไฟล์และออกซิเจนนิวคลีโอไฟล์ พบว่าสารประกอบซัลเฟอร์นิวคลีโอไฟล์ให้ผลิตภัณฑ์ไทโอไกลโคไซด์ในปริมาณสูงที่สุด รวมถึงยังให้ผลิตภัณฑ์ที่มีความจำเพาะของสเตอริโอเคมีอีกด้วย ผลิตภัณฑ์ไทโอไกลโคไซด์ที่สังเคราะห์ได้นั้น สามารถใช้เป็นสารตั้งต้นในการสังเคราะห์คาร์โบไฮเดรตที่มีโครงสร้างซับซ้อนต่อไป ปฏิกิริยาการเติมแบบไมเคิลบน 2-ไนโตรไกลแคลที่พัฒนาขึ้นในงานวิจัยนี้เป็นการเร่งกัมมันต์ด้วยเกลือโซเดียมไดไทโอคาร์เบเมตในสภาวะที่ไม่รุนแรงและไม่ว่องไวต่อความชื้นในบรรยากาศ สามารถให้ผลิตภัณฑ์ที่มีความจำเพาะของสเตอริโอเคมี โดยเมื่อใช้ซัลเฟอร์ชนิดแอลิฟิติกซึ่งมีความเป็นนิวคลีโอไฟล์สูง จะให้ผลิตภัณฑ์เป็นแอลฟา-ไทโอไกลโคไซด์ ในปริมาณร้อยละ 61–98 ในทางกลับกัน หากใช้แอโรแมติกซัลเฟอร์หรือเฮเทอโรไซคลิกซัลเฟอร์ที่มีความเป็นนิวคลีโอไฟล์ต่ำกว่า จะให้ผลิตภัณฑ์เป็นเบต้า-ไทโอไกลโคไซด์ในปริมาณร้อยละ 75–93 โครงสร้างของไทโอไกลโคไซด์ที่ได้นั้น ทำการยืนยันด้วยเทคนิค เอ็นเอ็มอาร์ สเปกโตรสโคปี และยืนยันสเตอริโอเคมีที่ตำแหน่งแอนนอเมอริกด้วยการวิเคราะห์โครงสร้างผลึกสามมิติด้วยเทคนิคเอกซเรย์ คริสตัลโลกราฟี

ภาควิชา เคมี ลายมือชื่อนิสิต .....

สาขาวิชา เคมี ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ปีการศึกษา 2559

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KEYWORDS: 2-NITROGLYCAL / MICHAEL ADDITION

PARICHAT SAWATTEERAKUL: GLYCOSYLATION OF 2-NITROGLYCALS ACTIVATED BY DITHIOCARBAMATE SALT. ADVISOR: ASST. PROF. PANUWAT PADUNGROS, Ph.D., 99 pp.

2-nitroglycals are important precusors for the synthesis of many amino deoxy sugars, which are ubiquitous in several biologically active molecules such as glycoproteins or oligosaccharides. 2-Nitroglycals are also valuable synthetic intermediates as they readily undergo Michael addition. There are four possible Michael addducts from this reaction as it generates two new stereogenic carbons on the pyranoside. Both, an α- and β-glycoside can be generated from the addition of a nucleophile at the anomeric position. Herein, we report a novel method for stereoselective Michael addition of 2-nitroglycals without using strong base or acid as catalysts. Firstly, 2-nitroglycals were synthesized from glycals by a modified nitration method using combination of silver nitrate and propionyl chloride resulted in 27–44% yield. Nitration on glycals by acetic anhydride and nitric acid followed by elimination afforded the desired 2-nitroglycals in 45% yield over 2 steps. Next, Michael additions of 2-nitroglycals were demonstrated with *S*-, *N*-, and *O*-nucleophiles using sodium diethyldithiocarbamate (NaDTC; $Na^{+-}SC(S)NEt_2$) as an activator. Activation of 2-nitroglycals by NaDTC proceeded smoothly with various *S*-nucleophiles and resulted in thioglycosides in high yield and selectivities. The thioglycosides are valuable intermediates for complex carbohydrate synthesis. The use of sodium diethyldithiocarbamate as the activator allows the glycosylation to be performed under mild and non-anhydrous conditions which is more convenient than previously described anhydrous procedures. Interestingly, α-thioglycosides were obtained in 61–98 % yield when highly nucleophilic aliphatic thiols were used. On the other hand, β-thioglycosides were formed in 75–93 % yield when heterocyclic or aromatic thiols were used. The stereochemisrty of the thioglycosides were identified by NMR spectroscopy and confirmed by X-ray crystallography.

Department: Chemistry
Field of Study: Chemistry
Academic Year: 2016

Student's Signature .....

Advisor's Signature .....

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LIST OF ABBRIVIATIONS

br	broad signal
δ	chemical shift
d	doublet
dd	doublet of doublet
DMF	*N,N*-dimethylformamide
dt	doublet of triplet
equiv	equivalent
ESI	electrospray ionization
J	coupling constant
m	multiplet
m/z	mass-to-charge ratio
MS	mass spectrometry
DTC	diethyldithiocarbamate
NMR	nuclear magnetic resonance
o/n	overnight
p	para
ppm	part per million
rt	room temperature
s	singlet
TEMPO	(2,2,6,6-tetramethylpiperidine-1-yl)oxyl
TLC	thin layer chromatography

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CHAPTER I

INTRODUCTION

1.1 2-Nitroglycals as synthetic intermediates

2-Nitroglycals are important precursors for the synthesis of amino sugars, which are constituents of glycoproteins and many biological active compounds.[1-4] The structure of 2-nitroglycals consist of an enol ether moiety with the double bond located between carbon 1 and carbon 2 (C1- and C-2) position and the nitro group at carbon position 2. 2-Nitroglycals have been previously reported as starting materials for the synthesis in many reactions including Michael addition, with different type of nucleophiles, such as *O*-, *S*-, *P*-, and *N*-nucleophiles (Figure 1.1).[5-8]

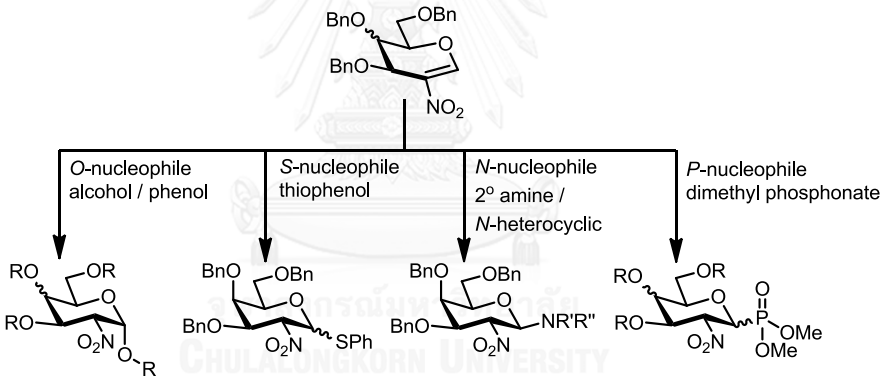

Figure 1.1 Michael addition of 2-nitroglycals with various nucleophiles.

1.2 Michael addition of 2-nitroglycals

Michael addition is a conjugate addition of a nucleophile to the electron-deficient unsaturated bond with a stabilized group such as carbonyl or nitro group. Michael addition on nitroalkene is a powerful method for organic synthesis since the procedure is simple and able to generate two new stereogenic carbons in one operation (Figure 1.2). Generally, Michael addition on a nitroalkene usually proceeds under catalysis of base by deprotonation on nucleophile resulted in higher nucleophilicity of nucleophile. The deprotonated nucleophile attacks at β-carbon of nitro group followed by protonation to yield Michael adduct. Michael addition can also be performed by protonation/hydrogen-bond formation of the nitro group on nitroalkene in order to increase its electrophilicity and then undergoes addition by a nucleophile.

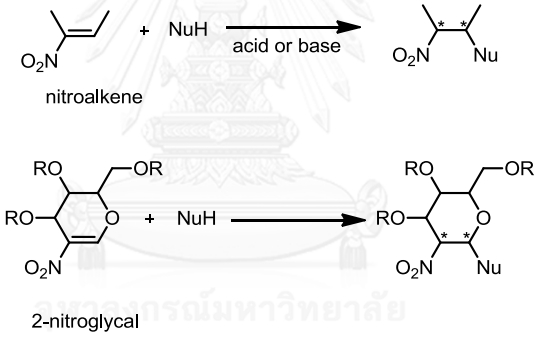

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Figure 1.2 General Michael addition of a nucleophile to nitroalkene and 2-nitroglycal.

1.2.1 Michael addition activation of nucleophile

The first step is to deprotonate the nucleophile with strong base. Then the nucleophile attacks at the anomeric position of 2-nitroglycal, which is the electrophilic center of the molecule. Finally, protonation will provide the Michael adduct of 2-nitroglycal. Schmidt and Das[9] have reported the Michael addition of 2-nitrogalactal with primary alcohols using a metal alkoxide base (Figure 1.3a). Potassium *tert*-butoxide (KO^{t}Bu) or sodium methoxide (NaOMe) were added into the reaction between a primary alcohol and 2-nitrogalactal resulting in the α-anomer as the major product. In the presence of weak base such as Et_3N, however, the β-anomer was obtained as the major product instead. In case of a bulkier nucleophile, steric hindered strong base such as potassium hexamethyl disilazide (KHMDS) was required to exclusively yield the α-anomer.[9] In 2003, Schmidt and coworkers[8] reported the methodology of Michael addition with phenol derivatives such as tyrosine. The use of strong base in toluene as a solvent resulted in Michael adducts in high yield with high α-selectivity (Figure1.3b).

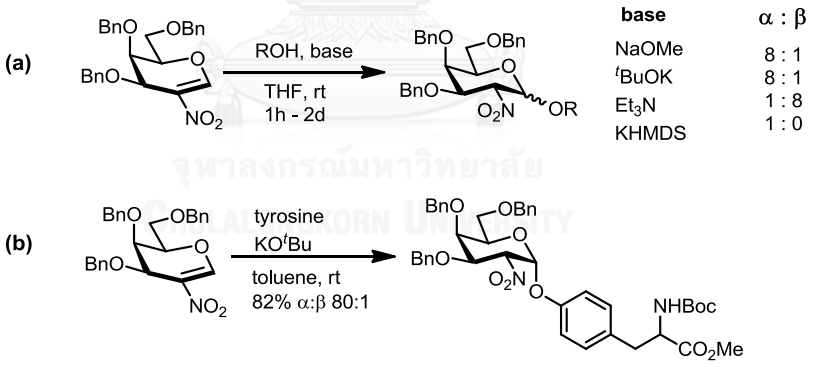

Figure 1.3 Michael addition to 2-nitrogalactal under basic conditions. (a) Addition with primary alcohols. (b) Addition with phenol derivatives.

Schmidt and coworkers[7] also reported the Michael addition of 2-nitrogalactal with *N*-heterocyclic substrates using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in THF. These conditions provided β-*N*-glycoside as a single isomer in 60–91% yield (Figure 1.4a). In 2011, Liu and coworkers[6] used excess secondary amines as nucleophiles for Michael addition of 2-nitroglycals in CH_2Cl_2 in the absence of a catalyst. Only a secondary amine nucleophile provided β-*N*-glycoside in excellent yield and selectivity (Figure 1.4b).

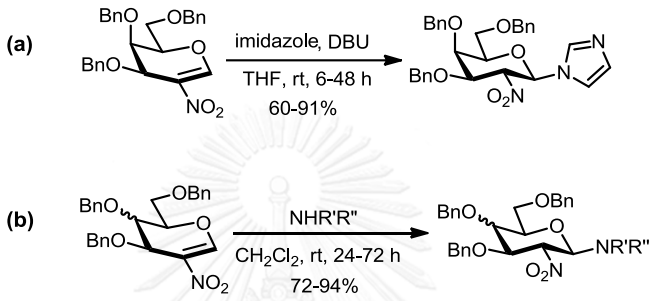

Figure 1.4 Michael additions of 2-nitroglycals with *N*-nucleophiles. (a) Addition with *N*-heterocycles. (b) Addition with secondary amines.

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Schmidt and coworkers[10] reported a Michael addition of thiophenol on 2-nitroglycal using potassium *tert*-butoxide (KO^{t}Bu) as a catalyst in toluene. They found that stirring the reaction for 30 minutes provided the β-thioglycoside with good yield but stirring the reaction for longer reaction time produced a mixture of α- and β-thioglycoside (Figure 1.5a). Schmidt and coworkers[11] changed the catalyst from a strong base into a weaker base such as Et_3N. In contrast, the α-thioglycoside was obtained as the major product due to reversibility between 2-nitroglycal precursor and the thioglycoside product, especially when the reaction time was left longer than 30 minutes (Figure 1.5b).

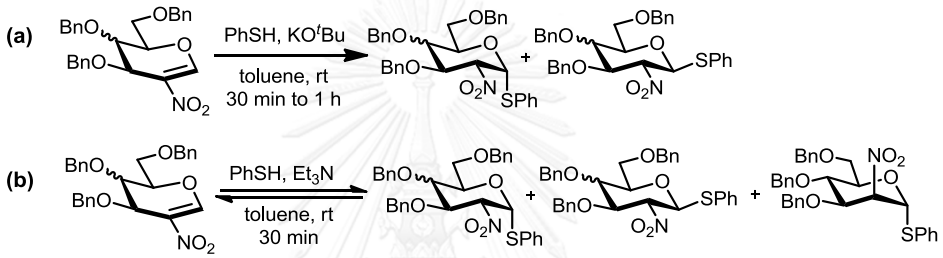

Figure 1.5 Michael addition of 2-nitrogalactal with thiophenol.

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1.2.2 Michael addition activation of electrophile

Michael addition of 2-nitroglycals can be catalyzed by a nucleophile to activate the 2-nitroglycal by enhancing its electrophilicity. From the report in 2009, Yu and coworkers[12] used *N*,*N*-dimethylaminopyridine (DMAP) as a catalyst for the Michael addition between perbenzylated-2-nitrogalactal and alcohols in CH_2Cl_2 (Figure 1.6). These conditions provided the β-*O*-glycoside in excellent yields and high selectivity. On the other hand, piperidinylpyridine (PPY) was used in case of 2-nitroglucal and gave good β-selectivity of the products. When the protecting group of 2-nitroglycal at C-3 is an acetyl group, the Ferrier rearrangements were obtained instead of the Michael addition products under the same conditions.

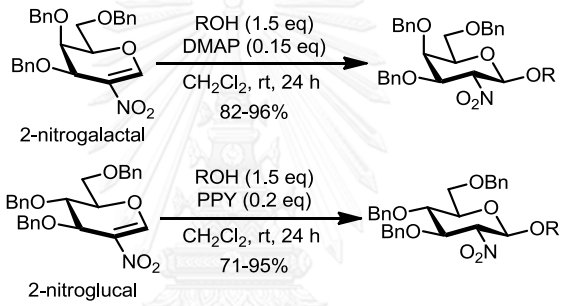

Figure 1.6 Base catalyzed Michael addition of 2-nitrogalactals.

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1.2.3 Michael addition activation of electrophile by hydrogen bond donor

Recently, thiourea was used in the Michael addition reaction as an organocatalyst, acting as hydrogen-bond donor to activate 2-nitroglycals. Schmidt and coworkers[11] used thiourea in Michael addition as a catalyst. Under a combination of Et_3N and symmetric thiourea or asymmetric chiral thiourea, Schmidt's group expected these conditions should improve the selectivity of products, however only the rate of the reaction was improved (Figure 1.7a).

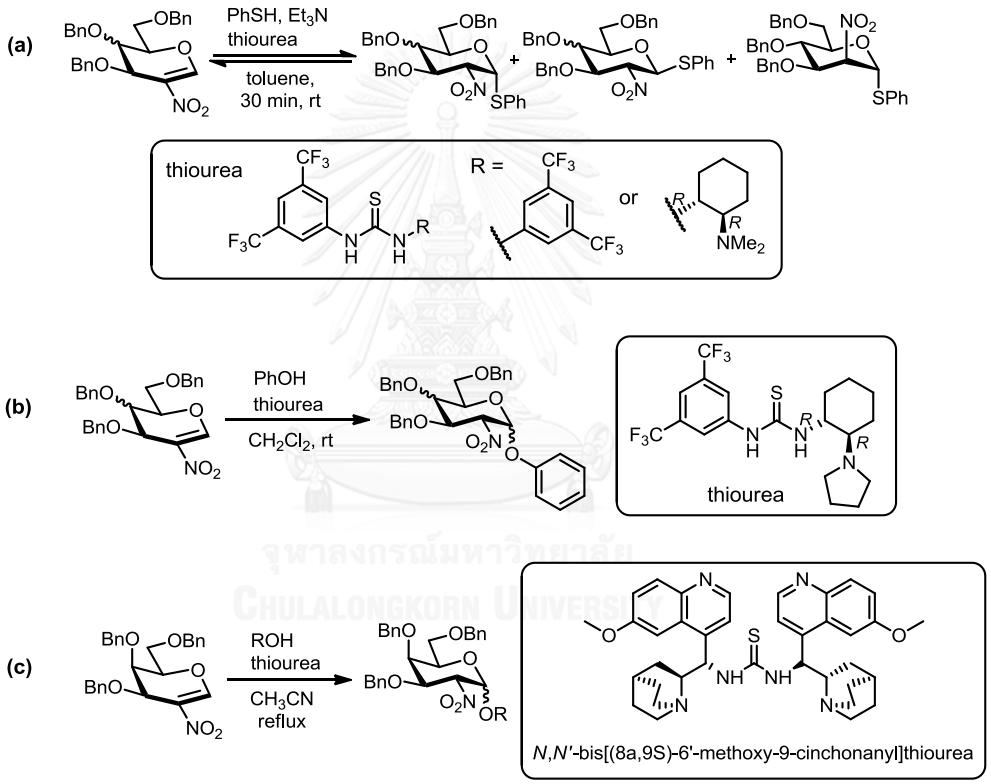

Figure 1.7 H-bond donor catalyzed Michael addition of 2-nitroglycals. (a) Addition with Et_3N and thiourea catalyst. (b) Addition with asymmetric thiourea (c) Addition with symmetric thiourea as an organocatalyst.

In 2016, Yoshida and coworkers[13] reported Michael addition of 2-nitroglycals with phenol derivatives using only asymmetric chiral thiourea to catalyze the addition in CH_2Cl_2. This asymmetric chiral thiourea formed H-bonding with the nitro group to activate the reaction and also improve the stereoselectivity. Thus, these conditions provided the *O*-glycoside in moderated to high yields and high α-selectivity (Figure 1.7b).

Recently in 2016, Galan and coworker[14] reported Michael addition of 2-nitrogalactals with alcohols using symmetric chiral thiourea. The reactions were dissolved in acetonitrile heated to reflux. This reaction provided α-*O*-glycoside as the major product (Figure 1.7c).

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1.3 Synthesis of 2-nitroglycals

2-nitroglycals was first synthesized in 1968 by Lemieux and coworkers[15] using glycals as starting material and dinitrogen tetroxide (N_2O_4) as a strong oxidizing agent. However, the use of N_2O_4 should be avoided as it is toxic and hazardous to the environment (Figure 1.8a). An alternative method was developed in 1988 by Holzapfel and coworkers[16] using nitronium tetrafluoborate (NO_2BF_4) in dimethylethylene (DME) at –40 °C. The second step involved elimination of hydrogen fluoride (HF) by 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to provide the 2-nitroglycals in moderate to excellent yields (Figure 1.8b).

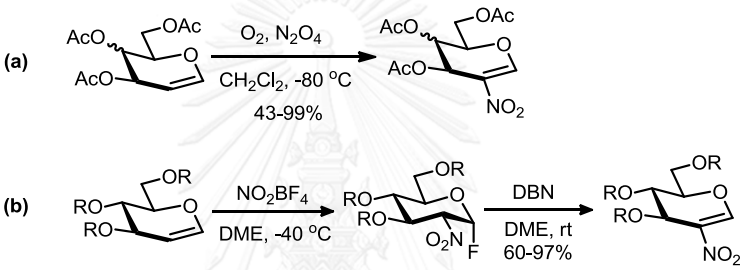

Figure 1.8 Synthesis of 2-nitroglycals from glycals. (a) One-pot nitration of glycals by Lemieux's group. (b) 2-Step synthesis of 2-nitroglycals by Hozapfel's group.

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Mild conditions for the synthesis of 2-nitroglycals have been previously reported using acetyl nitrate as a nitrating agent which was generated *in situ* manner. In 1998, Schmidt and coworkers[9] prepared acetyl nitrate from concentrated nitric acid (conc. HNO_3) in acetic anhydride at –33 °C under nitrogen atmosphere. The adduct was obtained in 70–75% yields before further elimination by triethylamine (Et_3N) resulting in 2-nitroglycals in 81 % yield (Figure 1.9a).

In 2011 Vankar and coworkers[17] reported a one-pot reaction to synthesize 2-nitroglycals. Silver nitrate and acetyl chloride were used to generate acetyl nitrate. At 55 °C in acetonitrile, the addition of acetyl nitrate and elimination occurred in one step with 55–94% yield. Nevertheless, lower reaction temperature provided lower yield and the generation of byproduct was observed (Figure 1.9b).

Recently in 2013, Vankar and coworkers[18] generated acetyl nitrate from tetrabutylammonium nitrate (TBAN) and trifluoroacetic anhydride (TFAA) at 0 °C under nitrogen atmosphere. Elimination was later occurred after warmed up the reaction to room temperature and then added Et_3N for elimination.

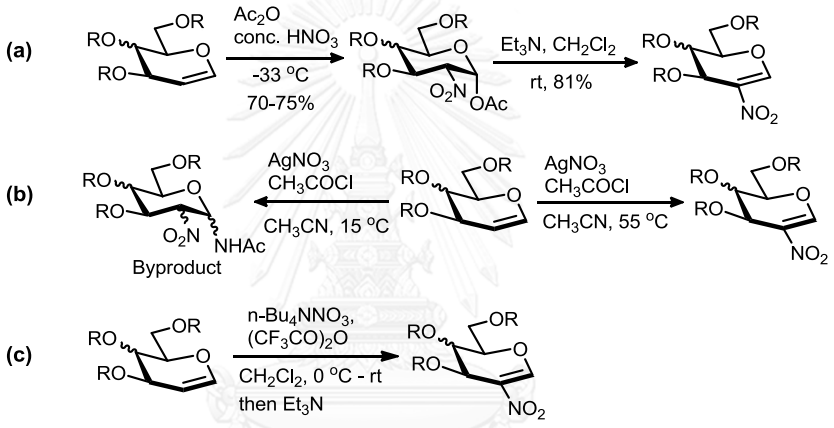

Figure 1.9 Synthesis of 2-nitroglycals from glycals. (a) 2-Step nitration of glycals by Schmidt and coworkers. (b) One-pot nitration of glycals by Vankar and coworkers. (c) Nitration of glycals using tetrabutylammonium nitrate.

1.3 Dithiocarbamate salt as an activator for Michael addition of 2-nitroglycals

Our research group[19-20] has previously reported the synthesis of glycosyl dithiocarbamate (DTC) and its use as a glycosyl donor. Glycosyl DTCs were generated *in situ* from epoxyglycal, which was obtained from dimethyldioxirane (DMDO) epoxidation of glycals. Then diethylamine (Et_2NH) and carbon disulfide (CS_2) were added to generate diethyldithiocarbamate (DTC) salt that reacted with the epoxyglycal, resulting in β-glycosyl DTC. Glycosyl DTC was easy to activate with various Lewis acid. It was activated by Cu(I)OTf in the presence of tri-*tert*-butylpyrimidine (TTBP) base. The reaction provided β-selective glycosylation with various acceptors in good to excellent yields (Figure 1.10).

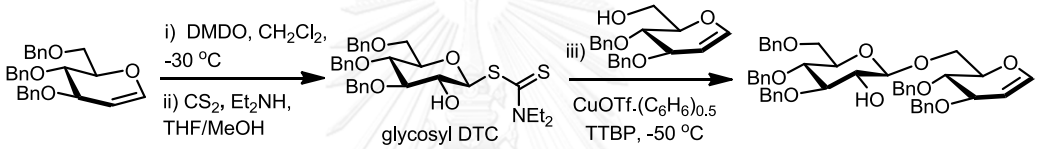

Figure 1.10 Synthesis of glycosyl DTC and using glycosyl DTC as a glycosyl donor.

Our group has an extensive experience in using dithiocarbamate salt (DTC) as a nucleophile from the synthesis of glycosyl DTCs. Originally, we envisage that dithiocarbamate salt could serve as a good nucleophile for the synthesis of 2-nitroglycosyl DTC *via* Michael addition since it exhibits very high nucleophilicity and also tolerates with non-anhydrous reaction conditions (Figure 1.11). Next, we plan to use 2-nitroglycosyl DTC for further propagation of oligosaccharide with a nitro group at C2 position. Finally, the nitro group could be reduced into amino group and provide amino sugar polymer such as chitosan.

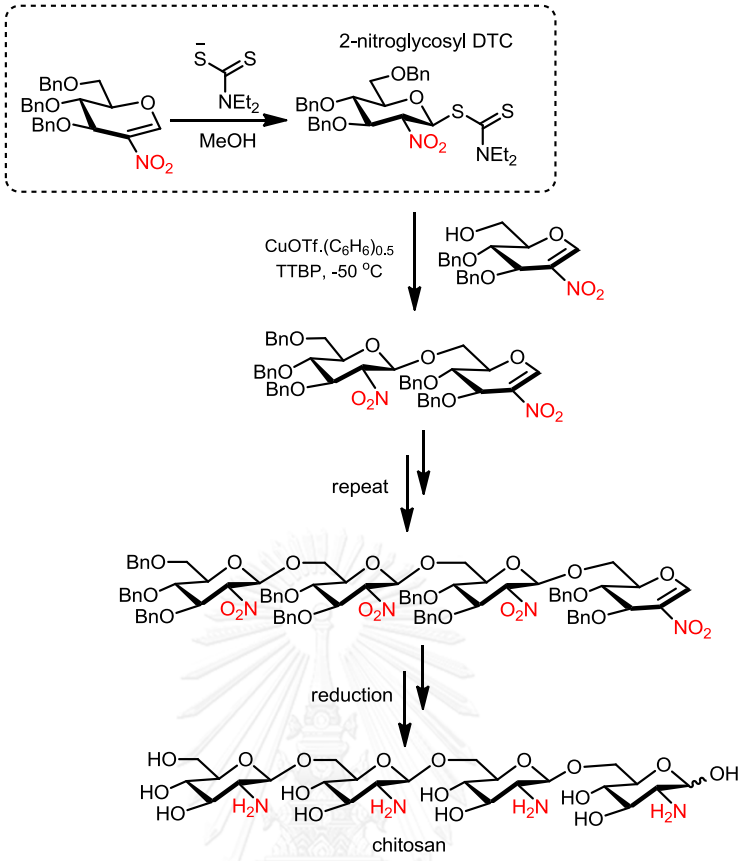

Figure 1.11 Original plans for synthesis of 2-nitroglycosyl DTC.

Preliminary experiment for the synthesis 2-nitroglycosyl DTC was performed using 2-nitrogalactal and sodium diethyldithiocarbamate (NaDTC) salt in methanol as a solvent (Figure 1.12). Surprisingly, the reaction provided Michael addition of methanol solvent instead of addition of DTC nucleophile as expected.

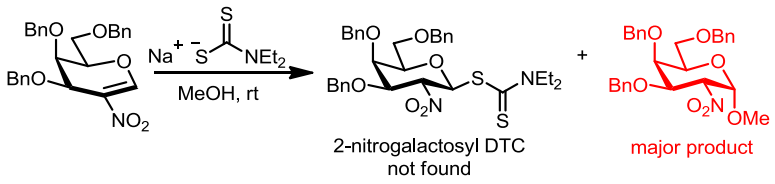

Figure 1.12 Addition of methanol on 2-nitrogalactal in the presence of NaDTC.

From this result, Michael addition of methanol was occurred in the presence of NaDTC. Next, Michael addition of 2-nitrogalactal with methanol was investigated without the addition of NaDTC. The consumption of 2-nitrogalactal starting material was not observed even after stirring reaction mixture for overnight (Figure 1.13). This evidence supported a crucial role of NaDTC as an activator or catalyst in the Michael addition of 2-nitroglycal.

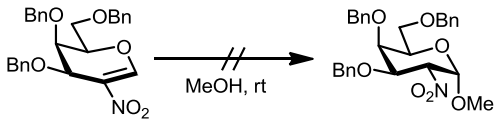

Figure 1.13 Michael addition of 2-nitroglycals with methanol without NaDTC.

Previously, Michael additions of 2-nitroglycals were performed under basic/acidic and required rigorous anhydrous conditions. In this work, we propose to use dithiocarbamate salt as an activator or catalyst for Michael addition of 2-nitroglycal substrates. We hope that this novel methodology will provide a mild and simple operation compared to previous reports which were required rigorous anhydrous conditions and strong basic or acidic catalyst.

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1.4 Objectives

1. To synthesize 2-nitroglycals from glycals using a one-pot nitration by Vankar's method (Figure 1.14a) and 2-step nitration by Schmidt's method (Figure 1.14b).

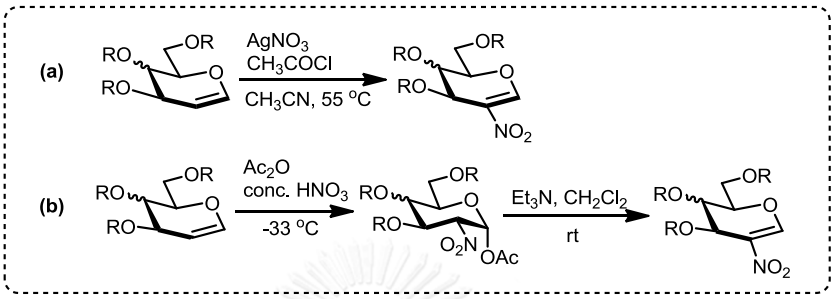

Figure 1.14 Synthesis of 2-nitroglycals from glycals. (a) One-pot nitration of glycals by Vankar's method. (b) 2-Step nitration of glycals by Schmidt's method.

2. To investigate Michael addition of 2-nitroglycals with various nucleophiles using sodium diethyldithiocarbamate (NaDTC) as an activator or catalyst. Optimization of nucleophiles, solvents, temperature, and reaction time will be carried out (Figure 1.15).

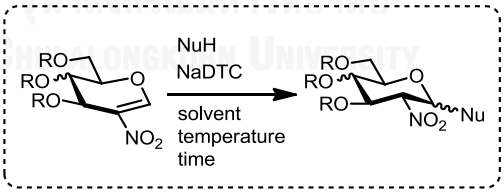

Figure 1.15 Michael addition of 2-nitroglycals with various nucleophiles.

CHAPTER II

EXPERIMENTAL SECTION

2.1 Chemicals and materials

Chemicals for the synthesis of this work were purchased from Carbosynth, Sigma-Aldrich, Fluka or Merck. Organic solvents from RCI Lab Scan were used for performing the reaction and for column chromatography. Solvents were dried with activated 4 Å molecular sieves. Reaction monitoring by thin layer chromatography (TLC) was performed on Macherey-Nagel aluminium sheets pre-coated with silica gel 0.20 mm UV254. Preparative thin layer chromatography was 0.5 mm thickness coated by silica gel 60 GF254 from Merck. Chemical spots on TLC were observed under UV light at 254 nm or by staining with p-anisaldehyde staining solution. Silica gel 60 (70-230 mesh) from Merck was used for column chromatography. Solvents for NMR experiments were purchased from Cambridge Isotope Laboratories or Euriso-top.

2.2 Instruments and equipment

EYELA rotary evaporator model N-1000 together with digital water bath model SB-1000 and pump form SIBATA circulating aspirator model WJ-20 was used to concentrate the solutions to dryness. Compounds were azeotroped with toluene prior to use by using a Buchi Rotavapor model R210, heating bath model B493 and a DAIKAWA vacuum pump model 2Vp-180L 0.5 Pa. High temperature reactions were performed by AccuBlock Digital dry bath model D1100 (Labnet, USA). Low temperature reactions were performed using an immersion cooler model EK90 (Thermo Fisher scientific, USA). Flash column chromatography was performed with Interchim PuriFlash model 4250-250 (Interchim, France). The ^{1}H NMR spectra were recorded operating at 400 MHz on Varian Mercury-400 plus or Bruker Avance 400 and 100 MHz for ^{13}C NMR spectra. Exact mass of new compounds were detected by high resolution mass spectroscopy (HRMS) operating on a MicroQTOF (Bruker) spectrometer.

2.3 Synthesis of 3,4,6-tri-*O*-benzyl-D-glucal

Commercially available 3,4,6-tri-*O*-acetyl-D-glucal (530 mg, 1.93 mmol) was used as starting material for the synthesis of D-glucal (Figure 2.1). The acetate protecting groups were removed by using potassium carbonate (K_2CO_3) (56 mg, 0.4 mmol) in methanol.[21] The concentration of the reaction was approximately 0.1 M. After 1 hour, TLC indicated complete consumption of the starting material (10% methanol in CH_2Cl_2 eluent; R_f = 0.21). The methanol solvent was removed by using a rotatory evaporator and eliminated traces amount of methanol and moisture by azeotroping with toluene. The crude D-glucal **1** from deacetylation reaction was dried *in vacuo* and was subjected to benzylation without further purification. D-Glucal **1** (0.373 g, 2.5 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF) (0.15 M) and cooled to 0 $^{\circ}$C. Tetrabutylammonium iodide (184 mg, 0.5 mmol) was added into a solution followed by addition of benzyl bromide (BnBr) (1.2 mL, 10 mmol). Sodium hydride (NaH, 60% dispersion in mineral oil) (400 mg, 10 mmol) was added into the reaction in the last step while the reaction was stirred in ice-bath.[22] Reaction was left stirring at room temperature overnight. The reaction was monitored by TLC (15% ethyl acetate in hexanes eluent; R_f = 0.3). After the reaction was complete, saturated $NaHCO_3$ was added at 0 $^{\circ}$C to neutralize the reaction and then extracted with diethyl ether (Et_2O) three times. The organic layer was collected and washed with distilled water five times to remove residual DMF. The combined organic extracts were washed with saturated NaCl, and concentrated to dryness. The crude residue was purified with silica gel on column chromatography. Solvents for elution were gradually increased from hexanes, 5% ethyl acetate in hexanes up to 20% ethyl acetate in hexanes. 3,4,6-tri-*O*-benzyl-D-glucal (**2**) was obtain as a white solid (770 mg) in 74% yield over 2 steps. Spectroscopic data (^{1}H NMR) of compound **2** was consistent with previous report.[23]

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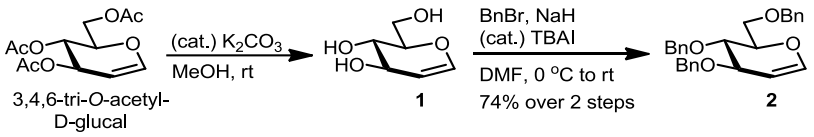

Figure 2.1 Synthesis of D-glucal (**2**) from 3,4,6-tri-*O*-acetyl-D-glucal.

2.4 Synthesis of 3,4,6-tri-*O*-benzyl-D-galactal

3,4,6-Tri-*O*-benzyl-D-galactal (**6**) was synthesized from β-D-galactosepentaacetate (Figure 2.2). First, β-D-galactose pentaacetate was treated with 4 equivalents of hydrobromic acid in acetic acid (HBr in CH_3COOH) using CH_2Cl_2 as a solvent. The crude galactosyl bromide (**3**) was dissolved in ethyl acetate and saturated NaH_2PO_4 (1:1), then activated zinc was added into reaction mixture as reducing agent. 3,4,6-Tri-*O*-acetyl-D-galactal (**4**) was obtained in 48% yield over 2 steps as a colorless syrup. Compound **4** (1.0 g, 3.6 mmol) was deacetylated under base-catalysis using K_2CO_3 (50 mg, 0.36 mmol) in methanol (0.1 M).[21] Crude D-galactal (**5**) was co-evaporated with toluene under high vacuum. Then crude **5** was protected as the benzyl ether under basic conditions in DMF. Catalytic amount of TBAI (230 mg, 0.72 mmol) was added into a solution, followed by benzyl bromide (1.5 mL, 13 mmol). NaH (520 mg, 13 mmol) was added into reaction mixture in the last step while the reaction was stirred in ice-bath, then continued stirring the reaction mixture at room temperature for overnight.[22] The reaction was monitored by TLC (20% ethyl acetate in hexanes eluent; R_f = 0.34). The reaction was quenched with saturated $NaHCO_3$, and then the aqueous layer was extracted with Et_2O three times. The organic layer was collected and washed with water five times to remove residual DMF. The combined organic layers were washed with brine and concentrated to dryness to afford crude **6** as a pale yellow syrup. The product was purified using silica gel column chromatography starting with hexanes, 5% ethyl acetate in hexanes and gradually increased polarity up to 25% ethyl acetate in hexanes. 3,4,6-Tri-*O*-benzyl-D-galactal (**6**) was obtained as a white solid (1.44 g) in 96% yield over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.21 (m, 15H), 6.37 (d, *J* = 6.1 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 2H), 4.68–4.58 (m, 3H), 4.46 (dd, *J* = 32.7, 11.9 Hz, 2H), 4.18 (s, 2H), 3.94 (s,

1H), 3.81–3.74 (m, 1H), 3.64 (dd, *J* = 10.1, 5.2 Hz, 1H). Spectrocopic data (^{1}H NMR) of compound **6** was consistent with previous report.[23]

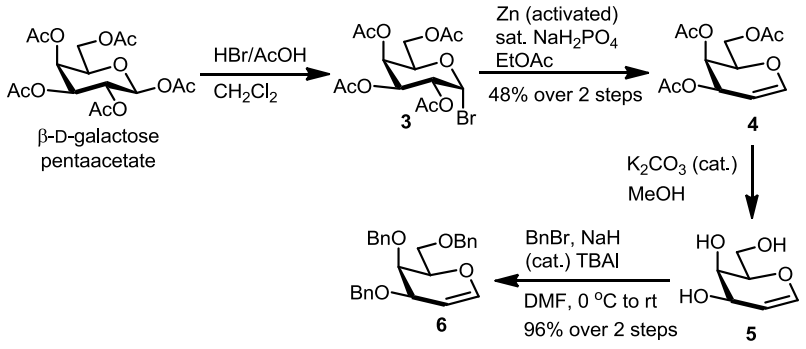

Figure 2.2 Synthesis of D-galactal (**6**) from β-D-galactose pentaacetate.

2.5 Nitration of glycals

2.5.1 Attempted nitration of glycals by silver nitrite/TEMPO

Following the recent report from Maity and coworkers in 2014,[24] silver nitrite ($AgNO_2$) was used as the nitrating agent for the nitration of an olefin using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as the catalyst. This method was applied to the synthesis of 3,4,6-tri-*O*-acetyl-D-glucal (**7**) (Figure 2.3).

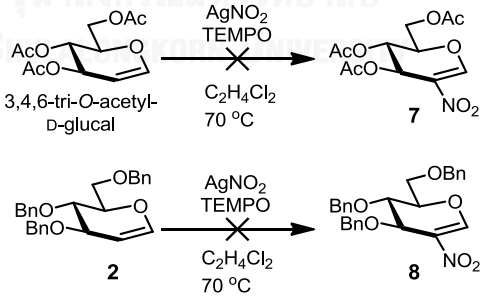

Figure 2.3 Attempted synthesis of 2-nitro-D-glucal by Maity's method.

Flame dried reaction tube and 4 Å molecular sieves were required in this reaction. 3,4,6-Tri-*O*-acetyl-D-glucal (48 mg, 0.18 mmol) were dissolved in dichloroethane (1 mL) and then treated with silver nitrite (161 mg, 1.0 mmol) and TEMPO (10 mg, 0.06 mmol) respectively. The reaction was stirred in an oil-bath at

70 °C overnight but the reaction was still not complete. After adding additional $AgNO_2$ and TEMPO and stirring for further 5 hours, silver precipitates and NO_2 gas were observed in the reaction tube. Monitoring the reaction by TLC indicated new spots but the starting material still remained. The reaction mixture was allowed to cool to room temperature. The silver precipitates was filtered through Celite in a fritted funnel and washed with CH_2Cl_2. All the filtrate was collected and neutralized with saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 three times. Washing was done with saturated NaCl and dried with Na_2SO_4, the solution was concentrate by rotary evaporator. Crude ^1H NMR of reaction mixture showed the starting material as the major component accompanied with unidentified able compounds.

In view of these results, we next exchanged the acetate protecting groups for benzyl ethers group to increase the reactivity of the glucal. Unfortunately, nitration of glucal (**2**) did not proceed under these reaction conditions as well.

2.5.2 Nitration by silver nitrate/acetyl chloride at high tempterature

2.5.2.1 Optimization of nitration by silver nitrate and proprionyl chloride

The method for nitration of glycals previously reported by Kancharla and coworker[17] was used acetyl chloride (CH_3COCl) and silver nitrate ($AgNO_3$) at 55 °C. In this work, propionyl chloride (CH_3CH_2COCl) was used instead of acetyl chloride due to prohibition of acetyl chloride by Thai narcotic laws, thus the optimization was needed.

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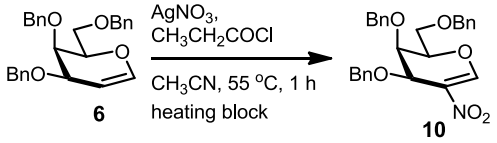
Table 2.1 Optimization of nitration on glycals.



Entry	$AgNO_3$ (equiv.)	CH_3CH_2COCl (equiv.)	Yield
1	1	1	6 %
2	1.5	1.5	16 %
3	2	2	22 %

3,4,6-Tri-*O*-benzyl-D-galactal (**6**) was used as a model substrate for optimization of this reaction. Glycal **6** (0.200 g, 0.48 mmol) was dried by co-evaporation with toluene and then dissolved in 5 mL acetonitrile. Silver nitrate and propionyl chloride were added into a solution of compound **6** with different amounts in each experiment. In entry 1 (Table 2.1), one equivalent of silver nitrate and propionyl chloride (82 mg, 0.48 mmol and 42 μL, 0.48 mmol, respectively) were added into the reaction mixture. In entry 2, 1.5 equivalents of silver nitrate and proprionyl chloride (122 mg, 0.72 mmol and 63 μL, 0.72 mmol, respectively) were added into a solution. Entry 3, amount of silver nitrate and propionyl chloride were increased up to 2 equivalents (164 mg, 0.96 mmol and 84 μL, 0.96 mmol, respectively). After addition of propionyl chloride into the reaction mixture, white precipitate was observed. The reaction mixture was then heat to 55 °C in a heating block. The reactions were monitored by TLC for every 30 minutes (20% ethyl acetate in hexanes eluent; R_f = 0.27). Those three reactions (entries 1-3) were completed within 1 hour. After cooling to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel with gradient elution using hexanes to 10% ethyl acetate in hexanes (20% ethyl acetate in hexanes eluent, R_f = 0.28, p-anisaldehyde). The highest yield was obtained by using 2 equivalents of the reagents as shown in Table 2.1 (entry 3). 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal were obtained as a turbid white syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s,

1H), 7.44—7.20 (m, 15H), 4.90 (d, *J* = 3.3 Hz, 1H), 4.82 (dd, *J* = 27.8, 10.7 Hz, 2H), 4.66 (dd, *J* = 37.3, 11.9 Hz, 3H), 4.51 (dd, *J* = 37.1, 11.9 Hz, 2H), 3.93 (m, 3H). Spectroscopic data (^{1}H NMR) of compound **10** was consistent with previous report.[17]

2.5.2.2 Synthesis of 3,4,6-tri-*O*-acetyl-2-nitro- D-glucal (**7**)

3,4,6-Tri-*O*-acetyl-D-glucal (200 mg, 0.73 mmol) was dissolved in dried acetonitrile (Figure2.4). Under the optimization conditions, silver nitrate (248 mg, 1.46 mmol) and propionyl chloride (128 μL, 1.46 mmol) were added into the reaction mixture. After addition of propionyl chloride into the reaction mixture, a white precipitate was observed. The reaction mixture was then heat to 55 °C in a heating block. The reaction was complete within 1 hour, monitored by TLC (30% ethyl acetate in hexanes eluent, p-anisaldehyde, R_f = 0.15). After cooling to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 1:9 eluent. Compound **7** was obtained as a pale yellow syrup (103 mg, 44%) (30% ethyl acetate in hexanes 2 times, p-anisaldehyde, R_f = 0.19) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 5.93 (dd, *J* = 2.6, 1.7 Hz, 1H), 5.19—5.15 (m, 1H), 4.40 (dd, *J* = 12.3, 8.4 Hz, 1H), 4.13—4.01 (m, 2H), 2.05 (s, 6H), 2.04 (s, 3H). Spectroscopic data (^{1}H NMR) of compound **7** was consistent with previous report.[17]

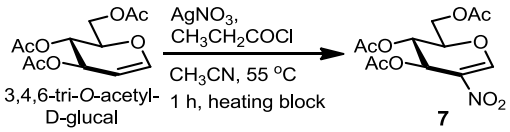


Figure 2.4 Synthesis of 3,4,6-tri-*O*-acetyl-2-nitro-D-glucal.

2.5.2.3 Synthesis of 3,4,6-tri-*O*-acetyl-2-nitro-D-galactal (**9**)

3,4,6-Tri-*O*-acetyl-D-galactal (300 mg, 1.1 mmol) was dissolved in dried acetonitrile 10 mL (Figure 2.5). Under optimization conditions, silver nitrate (374 mg, 2.2 mmol) and propionyl chloride (193 μL, 2.2 mmol) were added into a reaction mixture. After addition of propionyl chloride into a reaction mixture, a white

precipitates was observed. The reaction mixture was then heat to 55 ºC in heating block. The reaction was complete within 1 hour, monitored by TLC (ethyl acetate:hexanes = 3:7 eluent, ρ-anisaldehyde; R_f = 0.19). After cooling to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 3:2 eluent. Compound **9** was obtained as a colorless syrup (106 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 6.32 (d, *J* = 3.9 Hz, 1H), 5.47 (t, *J* = 4.4 Hz, 1H), 4.64–4.58 (m, 1H), 4.47 (dd, *J* = 12.5, 8.9 Hz, 1H), 4.33 (dd, *J* = 12.6, 3.2 Hz, 1H), 4.22–4.06 (m, 1H), 2.12 (s, 1H), 2.10 (s, 1H). Spectroscopic data (^{1}H NMR) of compound **9** was consistent with previous report.[17]

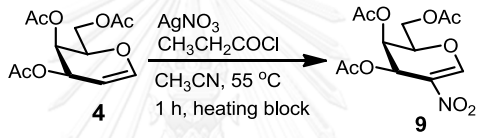


Figure 2.5 Synthesis of 3,4,6-tri-*O*-acetyl-2-nitro-D-galactal.

2.5.2.4 Synthesis of 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal (**8**)

3,4,6-Tri-*O*-benzyl-D-glucal **2** (1.0g, 2.4 mmol) was dissolved in dried acetonitrile (Figure 2.6). Under the optimization conditions, silver nitrate (815 mg, 4.8 mmol) and propionyl chloride (421 μL, 4.8 mmol) were added into the reaction mixture, a white precipitate was observed. The reaction mixture was then heat to 55 ºC in a heating block. The reaction was complete within 1 hour, monitored by TLC (ethyl acetate:hexanes = 1:4 eluent, R_f = 0.4). After cooling to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 3:7 eluent. Compound **8** was obtained as a colorless syrup (310 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.36–7.21 (m, 15H), 4.74–4.64 (m, 4H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.51–4.40 (m, 4H), 3.89–3.84 (m, 1H), 3.72 (dd, *J* = 10.6, 7.7 Hz, 1H), 3.60 (dd, *J* = 10.7,

5.3 Hz, 1H). Spectroscopic data (^{1}H NMR) of compound **8** was consistent with previous report.[17]

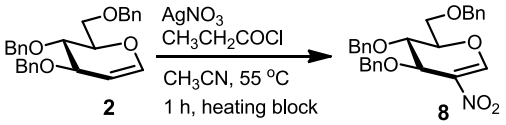


Figure 2.6 Synthesis of 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal.

2.5.2.5 Synthesis of 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**10**)

3,4,6-Tri-*O*-benzyl-D-galactal 6 (300 mg, 0.72 mmol) was dissolved in dried acetonitrile (Figure 2.7). Under the optimization conditions, silver nitrate (244 mg, 1.44 mmol) and propionyl chloride (126 μL, 1.44 mmol) were added into a reaction mixture, a white precipitate was observed. The reaction mixture was then heat to 55 ºC in a heating block. The reaction was complete within 1 hour, monitored by TLC (ethyl acetate:hexanes = 1:9, eluent, p-anisaldehyde, R_f = 0.15). After cooling to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 1:9 eluent. Compound **10** was obtained as a turbid white syrup (102 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.44–7.20 (m, 16H), 4.90 (d, *J* = 3.3 Hz, 1H), 4.82 (dd, *J* = 27.8, 10.7 Hz, 2H), 4.66 (dd, *J* = 7.3, 11.9 Hz, 3H), 4.51 (dd, *J* = 37.1, 11.9 Hz, 2H), 3.93 (dt, *J* = 8.9, 7.6 Hz, 3H). Spectroscopic data (^{1}H NMR) of compound **10** was consistent with previous report.[17]

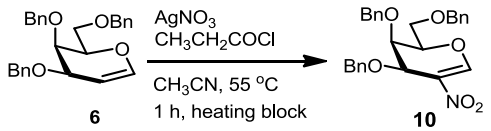


Figure 2.7 Synthesis of 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal.

2.5.3 Nitration of glycals using acetic anhydride and nitric acid at low temperature.

3,4,6-Tri-*O*-benzyl-D-galactal (**6**) was a substrate for nitration followed the protocol previously reported.[9] First, acetic anhydride (0.4 mL) was stirred in isopropanol bath; pre-cooled by immersion cooler at –10 ºC (Figure 2.8). Concentrated nitric acid (70% w/v, 142 μL, 2.4 mmol) was slowly added into the cooled acetic anhydride while stirring in isopropanol bath at –10 ºC. After the addition of nitric acid was complete, the temperature was cooled down to –35 ºC. The reaction mixture was frozen when the temperature reached to –25 ºC. Then a solution of galactal **6** (100 mg, 0.24 mmol) in acetic anhydride (0.6 mL) was slowly added to the mixture while stirred at –25 ºC. The reaction was left stirring at –25 ºC for 30 minutes, the the reaction mixture was slowly warmed up to room temperature. The reaction mixture was poured into ice-water and extracted with diethylether (Et_2O). After evaporate the solvent, crude mixture was dissolved in toluene and evaporated under vacuum then dissolved in dichloromethane (CH_2Cl_2). Triethylamine (40 μL, 0.288 mmol) was added into a reaction mixture, and then stirred at room temperature for overnight. The reaction was quenched with saturated NH_4Cl, extracted with CH_2Cl_2 and washed with saturated NaCl. The desired 2-nitrogalactal **10** was not observed from the crude mixture when analyzing by TLC compared with the authentic compound.

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A brand new bottle of acetic anhydride was used for the nitration and under argon gas atmosphere in order to prevent atmospheric moisture. A mixture of acetic anhydride and nitric acid was cooled down to –30 ºC before a solution of galactal **6** was added**.** Follow the method from Das and Schmidt,[9] after all reagents were mixed together at –30 ºC and stirred for 30 minutes, the reaction mixture was then removed from isopropanol bath to ice-bath at 0 ºC. Then the reaction was quenched by pouring the reaction mixture into ice-water. Acetic acid which was by-product from the reaction must be carefully removed by dissolving the reaction mixture in toluene and co-evaporated under vacuum. Then elimination reaction was performed using triethylamine as base. However, only trace amount of product was observed from this reaction.

The method was applied from the original procedure. Acetic anhydride (0.8 mL) was cooled in isopropanol bath at –10 ºC and kept the temperature inside round bottom flask at lower than 10 ºC. Then concentrated nitric acid (67 μL, 0.67 mmol) was added dropwise into the cooled acetic anhydride, and then stirred for 30 minutes. After that, the reaction mixture was cooled down to –30 ºC and added by the pre-cooled solution of galactal **6** (100 mg, 0.24 mmol) in acetic anhydride (1.2 mL). The reaction was stirred for 30 minutes at –30 ºC then removed from the isopropanol bath to ice-bath at 0 ºC. The reaction was monitored by the consumption of starting material on TLC. The reaction was quenched by pouring into ice-water, neutralized with saturated $NaHCO_3$, extracted with Et_2O and washed with saturated NaCl. Crude was concentrated and acid residual removed by dissolving in toluene and co-evaporation under high vacuum. After the acid was removed, the crude was obtained as a white solid of 2-nitro-1-acetylgalactoside intermediate. Crude from the reaction was dissolved in CH_2Cl_2 (2 mL). Triethylamine (40 μL, 0.29 mmol) was added into a solution, and then stirred at room temperature, the reaction mixture was complete within 30 minutes, monitored by TLC (ethyl acetate:hxanes = 1:4 eluent, ρ-anisaldehyde, R_f = 0.24). The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 1:4 eluent. Compound **10** was obtained as a white turbid syrup 50 mg (45%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.00 (s, 1H), 7.30–7.16 (m, 15H), 4.82 (d, *J* = 3.3 Hz, 1H), 4.74 (dd, *J* = 27.8, 10.7 Hz, 2H), 4.67–4.51 (m, 3H), 4.43 (dd, *J* = 37.1, 11.9 Hz, 2H), 3.90 – 3.80 (m, 3H). Spectroscopic data (^{1}H NMR) of compound **10** was consistent with previous report.[9]

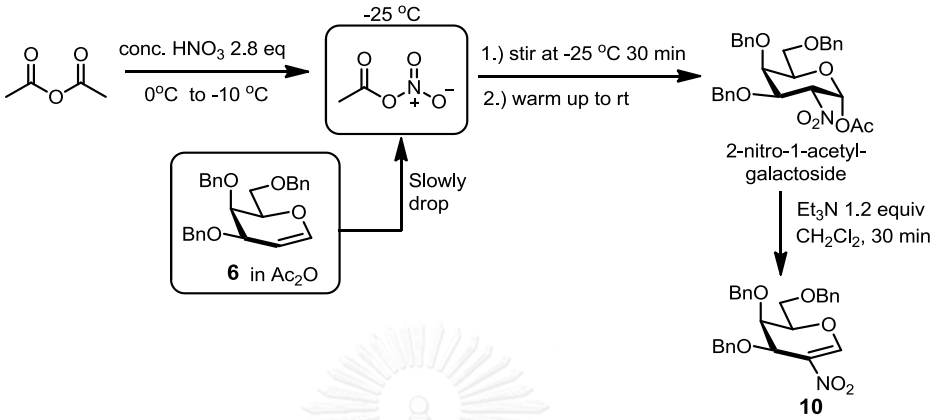

Figure 2.8 Nitration of galactal **6** using acetic anhydride and nitric acid.

2.6 Michael addition of 2-nitroglycals

2.6.1 Glycosylation with alcohol and amine

2-Nitrogalactal **10** (37 mg, 0.08 mmol) was dried by azeotropic distillation with toluene then dissolved in methanol (Figure 2.9). Sodium diethyldithiocarbamate (NaDTC, 28 mg, 0.12 mmol) was added into the reaction mixture. The reaction was purged with argon gas before left stirring at room temperature for overnight. The reaction was monitored by TLC (ethyl acetate:hexanes = 1:9 eluent 4 times, p-anisaldehyde, R_f = 0.28). After the reaction was complete, the solution was concentrated under rotary evaporator. Crude from the reaction was purified by short plug column chromatography on silica gel with ethyl acetate:hexanes = 0:1 to 1:9. Compound **12** was obtained as a yellow syrup (12 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.14 (m, 1H), 5.13 (d, *J*=4.1 Hz, 1H), 4.93 (dd, *J*=10.6, 4.1 Hz, 1H), 4.77 (d, *J*=11.2 Hz, 1H), 4.66 (s, 1H), 4.38 (dt, *J*=23.3, 11.6 Hz, 1H), 3.93–3.88 (m, 1H), 3.49 (d, *J*=6.5 Hz, 1H), 3.29 (s, 1H). ESI-MS: m/z calculated for $C_{28}H_{32}NO_7^+$ 494.22 [M+H^+]; found 494.20.

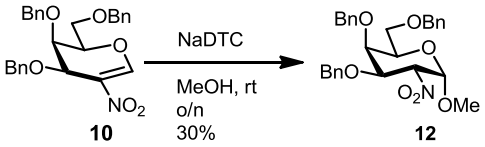

Figure 2.9 Michael addition of 2-nitrogalactal (**10**) with methanol.

From the result, Michael addition of 2-nitrogalactal by methanol was occurred when NaDTC 1.5 equivalents was used. Without the addition of NaDTC, the reaction of 2-nitrogalactal **10** (20 mg, 0.04 mmol) with excess methanol as a solvent (0.5 mL) did not proceed after being left overnight at room temperature. After that, 0.5 equivalent of NaDTC (4.5 mg, 0.02 mmol) was added in catalytic amount. The desired product appeared on the TLC but starting material did not completely consume after 3 days. On the other hand, increasing the amount of NaDTC from catalytic to stoichiometric accelerated the reaction time.

Michael addition of 2-nitrogalactal **10** (50 mg, 0.1 mmol) with isopropanol (1 mL) as nucleophile was set up by using isopropanol as solvent (Figure 2.10). NaDTC (34 mg, 0.15 mmol) was added and left the reaction stirred at room temperature for overnight. The reaction was worked-up by evaporation of the solvent. Crude was obtained as a yellow syrup. The reaction was provided trace amount of desired product, identified by Mass spectroscopic data. ESI-MS: m/z calculated for $C_{30}H_{36}NO_7^+$ 522.61 [M+H^+]; found 522.44.

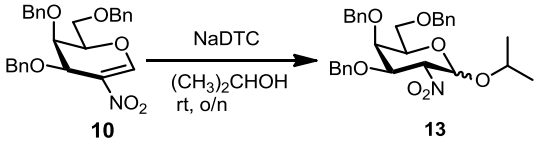

Figure 2.10 Michael addition of 2-nitrogalactal (**10**) with isopropanol.

2-Nitrogalactal **10** (40 mg, 0.087 mmol) was dissolved in dried CH_3CN (1 mL) as solvent (Figure 2.11). NaDTC (30 mg, 0.13 mmol) was added to the solution follow by benzyl alcohol (14 μL, 0.13 mmol). The reaction was stirred at room temperature overnight and monitored using TLC but there was no conversion observed.

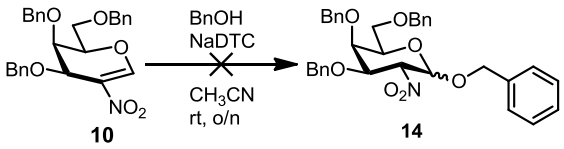

Figure 2.11 Michael addition of 2-nitrogalactal (**10**) with benzyl alcohol.

2-Nitrogalactal **10** (25 mg, 0.054 mmol) was dissolved in dried CH_3CN (1.0 mL), NaDTC (18 mg, 0.081 mmol.) was added (Figure 2.12). Piperidine (8 μL, 0.081 mmol) was dropped into the solution. The reaction was stirred at room temperature under argon atmosphere for overnight. The reaction was monitored by TLC (ethyl acetate:hexanes = 3:20 eluent, p-anisadehyde, R_f = 0.37), the reaction was complete after overnight. Neutralization was done by saturated $NaHCO_3$ then extracted with CH_2Cl_2 (5 mLx3). Combined organic layer was washed with saturated NaCl and dried over $NaSO_4$. Crude **15** was purified by column chromatography on silica gel (ethyl acetate:hexanes = 0:1 to 1:9 eluent). Compound **15** was obtained as a yellow syrup (20 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 15H), 5.13 (t, *J*=9.9 Hz, 1H), 4.85 (d, *J*=11.5 Hz, 1H), 4.62 (d, *J*=11.5 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 1H), 4.51–4.45 (m, 3H), 4.27 (d, *J*=9.4 Hz, 1H), 4.09 (dd, *J*=10.4, 2.7 Hz, 1H), 4.07–3.95 (m, 2H), 3.62–3.55 (m, 2H), 2.93–2.86 (m, 2H), 2.58–2.51 (m, 2H), 1.52–1.22 (m, 6H). Spectroscopic data (^{1}H NMR) of compound **15** was consistent with previous report.[6]

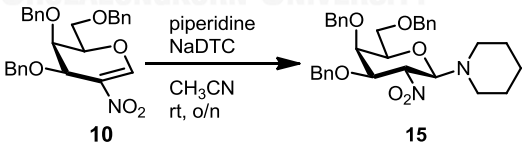

Figure 2.12 Michael addition of 2-nitrogalactal (**10**) with piperidine.

2.6.2 Glycosylation with thiol

2-Nitrogalactal **10** (40mg, 0.086 mmol) was dissolved in acetonitrile (Figure 2.13). Under the optimization conditions, NaDTC (30 mg, 0.13 mmol) and 1-dodecanethiol (25 μL, 0.1 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, p-anisaldehyde, R_f = 0.41). The reaction

mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 1:5 eluent. Compound **16** was obtained as a white solid (106 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.13 (m, 15H), 5.63 (d, *J* = 6.0 Hz, 1H), 5.20 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.76 (d, *J* = 11.1 Hz, 1H), 4.64 (s, 1H), 4.38 (m, 3H), 4.29 (t, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.93 (d, *J* = 2.2 Hz, 1H), 3.54–3.43 (m, 2H), 2.56–2.42 (m, 2H), 1.53–1.44 (m, 5H), 1.20 (broad s, 15H), 0.81 (t, *J* = 6.7 Hz, 3H). ESI-MS: m/z calculated for $C_{39}H_{53}NO_6SNa^+$ 686.90 [M+Na^+]; found, 686.38.

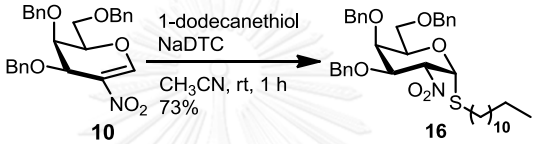

Figure 2.13 Michael addition of 2-nitrogalactal (**10**) with 1-dodecanethiol.

2-Nitrogalactal **10** (80 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.14). Under the optimized conditions, NaDTC (67 mg, 0.3 mmol) and 1-pentanethiol (30 μL, 0.24 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, p-anisaldehyde, R_f = 0.45). The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography on silica gel using gradient ethyl acetate:hexanes 0:1 to 3:7 eluent. Compound **17** was obtained as a yellow syrup (97 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.14 (m, 15H), 5.72 (d, *J* = 6.0 Hz, 1H), 5.28 (dd, *J* = 10.9, 6.0 Hz, 1H), 4.85 (d, *J* = 11.2 Hz, 1H), 4.77–4.67 (m, 2H), 4.46 (dt, *J* = 19.2, 8.7 Hz, 3H), 4.37 (t, *J* = 6.5 Hz, 1H), 4.30 (dd, *J* = 10.9, 2.9 Hz, 1H), 4.01 (d, *J* = 2.4 Hz, 1H), 3.64–3.45 (m, 2H), 2.67–2.43 (m, 2H), 1.65–1.47 (m, 2H), 1.37–1.17 (m, 4H), 0.87 (t, *J* = 6.9 Hz, 3H). ESI-MS: m/z calculated for $C_{32}H_{39}NO_6SNa^+$ 588.24 [M+Na^+]; found, 588.26.

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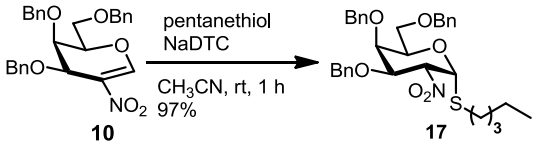

Figure 2.14 Michael addition of 2-nitrogalactal (**10**) with 1-pentanethiol.

2-Nitrogalactal **10** (80 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.15). Under the optimized conditions, NaDTC (67 mg, 0.3 mmol) and 1-octadecanethiol (71 mg, 0.24 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, p-anisaldehyde, R_f = 0.57). The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl, and concentrated to dryness. The crude mixture was purified by automated flash column chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 3:7 eluent. Compound **18** was obtained as a white solid (113 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.10 (m, 15H), 5.63 (d, *J* = 6.0 Hz, 1H), 5.20 (dd, *J* = 10.9, 6.0 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.68 – 4.58 (m, 2H), 4.46–4.31 (m, 3H), 4.29 (t, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 10.9, 2.9 Hz, 1H), 3.92 (d, *J* = 2.2 Hz, 1H), 3.59–3.41 (m, 2H), 2.61–2.39 (m, 2H), 1.55–1.42 (m, 2H), 1.20 (d, *J*=17.8 Hz, 30H), 0.80 (t, *J* = 6.8 Hz, 3H). ESI-MS: m/z calculated for $C_{45}H_{65}NO_6SNa^+$ 770.44 [M+Na^+]; found, 770.42.

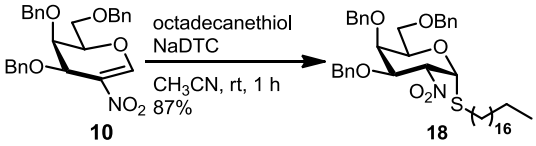

Figure 2.15 Michael addition of 2-nitrogalactal (**10**) with 1-octadecanethiol.

2-Nitrogalactal **10** (82 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.16). Under the optimized conditions, NaDTC (68 mg, 0.3 mmol) and cyclohexanethiol (30 μL, 0.24 mmol) were added into a reaction mixture and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, 2 times, p-anisaldehyde, R_f = 0.46). The

reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography using gradient ethyl acetate:hexanes = 0:1 to 2:3 eluent. Compound **19** was obtained as a colorless syrup (62 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.03 (m, 15H), 5.82 (d, *J* = 6.1 Hz, 1H), 5.28 (dd, *J* = 10.8, 6.1 Hz, 1H), 4.85 (d, *J* = 11.2 Hz, 1H), 4.79–4.67 (m, 2H), 4.54–4.34 (m, 4H), 4.28 (dd, *J* = 10.9, 2.9 Hz, 1H), 4.00 (d, *J* = 2.4 Hz, 1H), 3.75–3.45 (m, 2H), 2.81 (dd, *J* = 12.0, 8.5 Hz, 1H), 1.93 (brs, 2H), 1.71 (brs, 2H), 1.46–1.13 (m, 6H). ESI-MS: m/z calculated for $C_{33}H_{39}NO_6SNa^+$ 600.24 [M+Na^+]; found, 600.32.

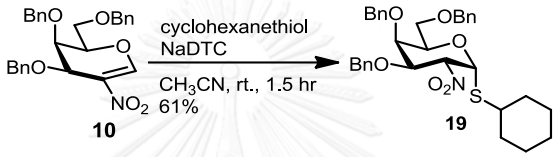

Figure 2.16 Michael addition of 2-nitrogalactal (**10**) with cyclohexanethiol.

2-Nitrogalactal **10** (86 mg, 0.18 mmol) was dissolved in acetonitrile (Figure 2.17). Under optimized conditions, NaDTC (68 mg, 0.3 mmol) and *tert*-butylthiol (27 μL, 0.24 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:haxanes = 1:5 eluent, 2 times, p-anisaldehyde, R_f = 0.5). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography using gradient ethyl acetate:hexanes = 0:1 to 2:3 eluent. Compound **20** was obtained as a colorless syrup (68 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.15 (m, 15H), 5.89 (d, *J* = 6.3 Hz, 1H), 5.29 (dd, *J* = 10.9, 6.2 Hz, 1H), 4.86 (d, *J* = 11.1 Hz, 1H), 4.81–4.68 (m, 2H), 4.53–4.43 (m, 4H), 4.41 (t, *J* = 6.6 Hz, 1H), 4.21 (dd, *J* = 10.9, 2.9 Hz, 1H), 4.03 (d, *J* = 2.5 Hz, 1H), 3.63 (t, *J* = 8.5 Hz, 1H), 3.52 (dd, *J* = 9.1, 5.6 Hz, 1H), 1.34 (s, 9H). ESI-MS: m/z calculated for $C_{31}H_{37}NO_6SNa^+$ 574.22 [M+Na^+]; found, 574.25.

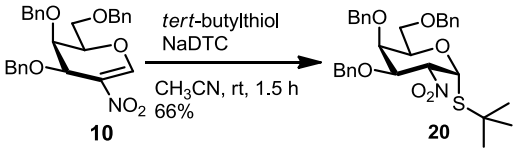

Figure 2.17 Michael addition of 2-nitrogalactal (**10**) with *tert*-butylthiol.

2-Nitrogalactal **10** (75 mg, 0.16 mmol) was dissolved in acetonitrile (Figure 2.18). Using the optimized reaction conditions, NaDTC (67 mg, 0.3 mmol) and 2-phenylethanethiol (32 μL, 0.24 mmol) were added into the reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, p-anisaldehyde, R_f = 0.37). The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with saturated NaCl, and concentrated to dryness. The crude mixture was purified by automated flash column chromatography using gradient ethyl acetate:hexanes = 0:1 to 1:4 eluent afforded compound **21** as a pale yellow syrup (89 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–6.97 (m, 20H), 5.63 (d, *J* = 5.9 Hz, 1H), 5.19 (dd, *J* = 10.8, 5.9 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.62 (s, 2H), 4.36 (dt, *J* = 20.9, 7.9 Hz, 3H), 4.26 (t, *J* = 6.3 Hz, 1H), 4.20 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.90 (d, *J* = 2.5 Hz, 1H), 3.52–3.41 (m, 2H), 2.83–2.72 (m, 3H), 2.72–2.65 (m, 1H). ESI-MS: m/z calculated for $C_{35}H_{37}NO_6SNa^+$ 622.22 [M+Na^+]; found, 622.25.

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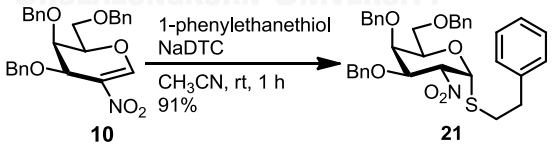

Figure 2.18 Michael addition of 2-nitrogalactal (**10**) with 2-phenylethanethiol.

2-Nitrogalactal **10** (50 mg, 0.108 mmol) was dissolved in acetonitrile (Figure 2.19). Under the optimized conditions, NaDTC (36 mg, 0.16 mmol) and benzenemethanethiol (15 μL, 0.13 mmol) were added into the reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 1:4 eluent, p-anisaldehyde, R_f = 0.34). The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2

and washed with saturated NaCl. The crude mixture was purified by preparative TLC using ethyl acetate:hexanes = 1:9 eluent system. Compound **22** was obtained as a pale yellow syrup (41 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.11 (m, 20H), 5.46 (d, *J* = 6.0 Hz, 1H), 5.15 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.61 (s, 2H), 4.42–4.32 (m, 3H), 4.30–4.21 (m, 2H), 3.91 (s, 1H), 3.70 (d, *J* = 13.4 Hz, 1H), 3.61 (d, *J* = 13.4 Hz, 1H), 3.49–3.42 (m, 1H), 3.34 (dd, *J* = 9.1, 6.1 Hz, 1H). ESI-MS: m/z calculated for $C_{34}H_{35}NO_6SNa^+$ 608.21 [M+Na^+]; found, 608.26.

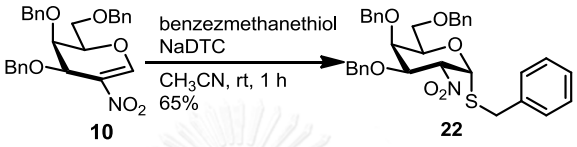

Figure 2.19 Michael addition of 2-nitrogalactal (**10**) with benzenemethanethiol.

2-Nitrogalactal **10** (100 mg, 0.22 mmol) was dissolved in acetonitrile (Figure 2.20). Under the optimized conditions, NaDTC (74 mg, 0.33 mmol) and 4-methylthiophenol (33 mg, 0.065 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 1:9 eluent 3 times, p-anisaldehyde, R_f = 0.2). The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by flash column chromatography on silica gel using gradient elution (ethyl acetate:hexanes = 0:1 to 1:3 eluent). Compound **23** was obtained as a colorless syrup (90 mg, 77%). Compound **23** was recrystallized with ethyl acetate:hexanes = 1:20 to afford white crystals which were characterized by X-ray crystallography (Figure A24). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38–7.26 (m, 14H), 7.22 (d, *J*=6.7 Hz, 2H), 7.17 (d, *J*=7.2 Hz, 2H), 7.11 (d, *J*=8.0 Hz, 2H), 5.19 (d, *J*=10.1 Hz, 1H), 4.72 (dd, *J*=16.6, 11.6 Hz, 2H), 4.62 (t, *J*=10.2 Hz, 1H), 4.55–4.42 (m, 4H), 4.37 (dd, *J*=10.2, 2.4 Hz, 1H), 4.23 (d, *J*=2.0 Hz, 1H), 4.10 (t, *J*=6.2 Hz, 1H), 3.60 (d, *J*=6.0 Hz, 2H), 2.27 (s, 3H). ESI-MS: m/z calculated for $C_{34}H_{35}NO_6SNa^+$ 608.70 [M+Na^+]; found, 608.22.

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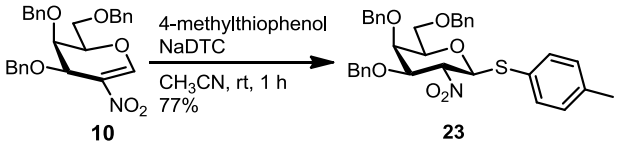

Figure 2.20 Michael addition of 2-nitrogalactal (**10**) with 4-methylthiophenol.

2-Nitrogalactal **10** (55 mg, 0.12 mmol) was dissolved in acetonitrile (Figure 2.21). Under the optimized conditions, NaDTC (41 mg, 0.18 mmol) and 4-methoxythiophenol (20 mg, 0.14 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by TLC (CH_2Cl_2:hexanes = 1:1 eluent, p-anisaldehyde, R_f = 0.46). Reaction was mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. Compound **24** was purified by recrystallization, and a mixture of **24**α and **24**β as a white crystals (52mg, 73%) were obtained. Compound **24**α; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.37–7.21 (m, 15H), 5.70 (d, *J* = 6 Hz, 1H), 5.30 (dd, *J* = 6.0, 10.8 Hz, 1H), 4.88 (d, *J* = 8 Hz, 1H), 4.77 (d, *J* = 4 Hz, 2H), 4.59–4.56 (m, 1H), 4.50–4.45 (m, 3H), 4.34 (dd, *J* = 2.4, 11.2 Hz, 1H), 4.03 (d, *J* = 2.4 Hz, 1H), 3.75 (s, 3H), 3.59 (m, 2H). ^{1}H NMR spectra indicated mixture of compound **24** (Appendix, Figure A25).

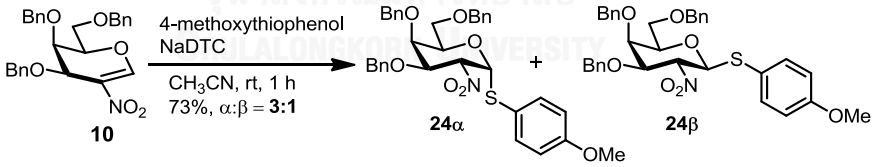

Figure 2.21 Michael addition of 2-nitrogalactal (**10**) with 4-methoxythiophenol.

2-Nitrogalactal **10** (80 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.22). Under the optimized conditions, NaDTC (70 mg, 0.31 mmol) and 2-thiazoline-2-thiol (48 mg, 0.4 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within overnight, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent 2 times, p-anisaldehyde, R_f = 0.27). The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column

chromatography on silica gel using gradient ethyl acetate:hexanes = 0:1 to 1:1 eluent. Compound **25** was obtained as a colorless syrup (93 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.18 (m, 15H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.07 (t, *J* = 9.9 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.56 (dd, *J* = 11.3, 2.7 Hz, 1H), 4.48 (dd, *J* = 21.2, 12.0 Hz, 2H), 4.34 (dd, *J* = 10.3, 2.6 Hz, 2H), 4.23–4.03 (m, 3H), 3.87 (t, *J* = 6.7 Hz, 1H), 3.61 (p, *J* = 9.1 Hz, 2H), 3.32–3.19 (m, 2H). ESI-MS: m/z calculated for $C_{30}H_{32}N_2O_6S_2Na^+$ 603.16 [M+Na^+]; found, 603.21.

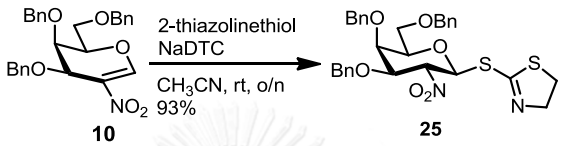

Figure 2.22 Michael addition of 2-nitrogalactal (**10**) with 2-thiazoline-2-thiol.

2-Nitrogalactal **10** (50 mg, 0.108 mmol) was dissolved in acetonitrile (Figure 2.23). Under the optimized conditions, NaDTC (36 mg, 0.16 mmol) and 2-mercaptobenzothiazole (22 mg, 0.13 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 4 days, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent 4 times, p-anisaldehyde, R_f = 1.5). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by preparative TLC on silica gel using ethyl acetate:hexanes = 1:9 to 3:7 eluent system. Compound **26** was obtained with unknown impurities as a pale yellow solid (42 mg, 62%). ESI-MS: m/z calculated for $C_{34}H_{32}N_2O_6S_2Na^+$ 651.16 [M+Na^+]; found, 651.22.

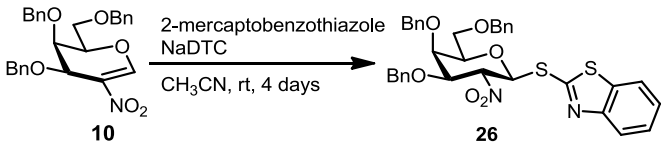

Figure 2.23 Michael addition of 2-nitrogalactal (**10**) with 2-mercaptobenzothiazole.

2-Nitroglucal **8** (80 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.24). Under the optimized conditions, NaDTC (59 mg, 0.26 mmol) and 1-dodecanethiol (49 μL, 0.20 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:hexanes = 1:9 eluent, p-anisaldehyde, R_f = 0.33). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The rude mixture was purified by automated flash column chromatography using gradient ethyl acetate:hexanes = 0:1 to 1:5 eluent. Compound **28** was obtained as a white solid (71 mg, 62%). ^{1}H NMR spectra indicated mixture of compound **28** (Appendix, Figure A30).

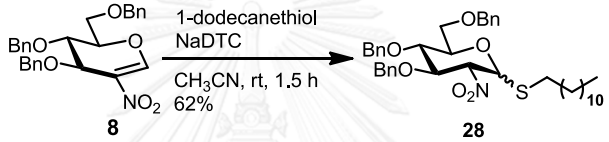

Figure 2.24 Michael addition of 2-nitroglucal (**8**) with 1-dodecanethiol.

2-Nitroglucal **8** (80 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.25). Under the optimized conditions, NaDTC (59 mg, 0.26 mmol) and 4-methylthiophenol (25 mg, 0.20 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, p-anisaldehyde, R_f = 0.33). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography using gradient elution with ethyl acetate:hexanes = 0:1 to 1:1 eluent. Compound **29** was obtained as a white solid (56 mg, 55%). ^{1}H NMR spectra indicated mixture of compound **29** (Appendix, Figure A32).

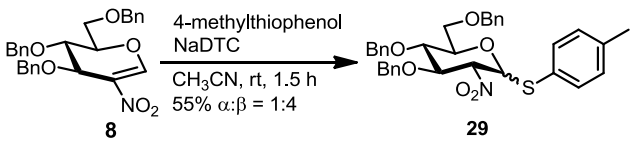

Figure 2.25 Michael addition of 2-nitroglucal (**8**) with 4-methylthiophenol.

2-Nitroglucal **8** (80 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 2.26). Under the optimized conditions, NaDTC (59 mg, 0.26 mmol) and 2-phenylethanethiol (28 μL, 0.20 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:hexanes 1:5 eluent, p-anisaldehyde, R_f = 0.17). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography using gradient ethyl acetate:hexanes = 0:1 to 1:1 eluent. Compound **30** was obtained as a pale yellow syrup (18 mg, 28%). ^{1}H NMR spectra indicated mixture of compound **30** (Appendix, Figure A34).

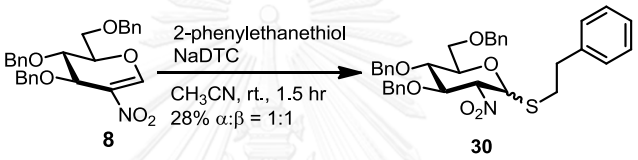

Figure 2.26 Michael addition of 2-nitroglucal (**8**) with 2-phenylethanethiol.

2-Nitrogalactal **10** (54 mg, 0.12 mmol) was dissolved in acetonitrile (Figure 2.27). Under the optimized conditions, NaDTC (41 mg, 0.18 mmol) and 6-mercapto-1-hexanol (20 μL, 0.14 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:hexanes = 1:5 eluent, p-anisaldehyde, R_f = 0.48). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by preparative TLC using ethyl acetate:hexanes = 1:5 to 2:5 eluent system. A mixture of compound **31** and **32** (4:1) was obtained as a pale yellow syrup (54 mg, 76%). ^{1}H NMR of **31** (400 MHz, $CDCl_3$) δ 7.30–7.12 (m, 15H), 5.63 (d, *J*=6.0 Hz, 1H), 5.20 (dd, *J*=10.8, 6.0 Hz, 1H), 4.76 (d, *J*=11.1 Hz, 1H), 4.64 (s, 2H), 4.43–4.32 (m, 3H), 4.28 (t, *J*=6.4 Hz, 1H), 4.21 (dd, *J*=10.8, 2.8 Hz, 1H), 3.92 (d, *J*=2.2 Hz, 1H), 3.56–3.46 (m, 4H), 2.56–2.44 (m, 2H), 1.70 (s, 2H), 1.56–1.39 (m, 2H), 1.30–1.19 (m, 4H). ESI-MS: m/z calculated for $C_{33}H_{41}NO_7SNa^+$ 618.25 [M+Na^+]; found, 618.30.

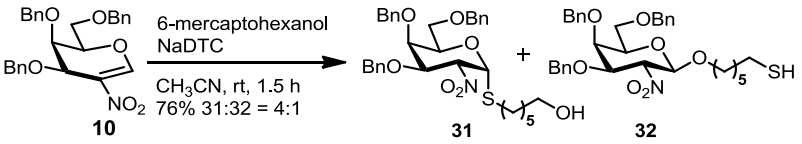

Figure 2.27 Michael addition of 2-nitrogalactal (**10**) with 6-mercapto-1-hexanol.

2-Nitrogalactal **10** (50 mg, 0.11 mmol) was dissolved in acetonitrile (Figure 2.18). Under the optimized conditions, NaDTC (37 mg, 0.17 mmol) and 2-mercaptoethanol (10 μL, 0.14 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within 1.5 hours, monitored by TLC (ethyl acetate:hexanes = 2:3 eluent, p-anisaldehyde, R_f = 0.32). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by preparative TLC using ethyl acetate:hexanes = 1:9 to 1:5 eluent system. Compound **33α** and **33β** were obtained as a yellow syrup in the first fraction 10 mg (1:2) of chromatography collection and second fraction consisted of compound **33α** and compound **34** 1:1.3 (34 mg) which were accounted for 74% yield for combined fraction. ^{1}H NMR of **33α** (400 MHz, $CDCl_3$) δ 7.31–7.09 (m, 15H), 5.70 (d, *J* = 6.1 Hz, 1H), 5.21 (dd, *J* = 10.9, 6.1 Hz, 1H), 4.75 (dd, *J* = 18.4, 10.6 Hz, 2H), 4.64 (d, *J* = 5.0 Hz, 2H), 4.49 (dd, *J* = 23.2, 11.6 Hz, 2H), 4.19 (dd, *J* = 10.9, 2.8 Hz, 1H), 3.82 (d, *J* = 2.7 Hz, 1H), 3.56–3.48 (m, 1H), 3.42 (dd, *J* = 9.2, 6.8 Hz, 1H), 3.32 (dd, *J* = 9.6, 5.1 Hz, 1H), 2.87 (dt, *J* = 14.7, 4.8 Hz, 2H), 2.76–2.64 (m, 2H). ESI-MS: m/z calculated for $C_{29}H_{33}NO_7SNa^+$ 562.19 [M+Na^+]; found, 562.23.

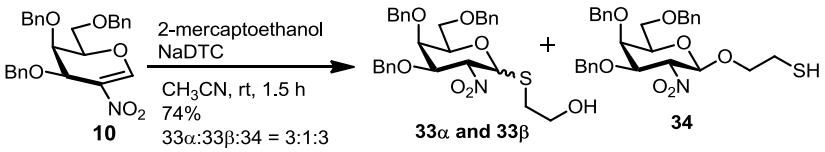

Figure 2.28 Michael addition of 2-nitrogalactal (**10**) with 2-mercaptoethanol.

2-Nitrogalactal **10** (100 mg, 0.2 mmol) was dissolved in acetonitrile (Figure 2.29). Under the optimized conditions, NaDTC (68 mg, 0.3 mmol) and 2-mercaptoethanol (18 μL, 0.24 mmol) were added into a reaction mixture, and then

stirred at room temperature. The reaction was complete within an hour, monitored by TLC (ethyl acetate:hexanes = 3:2 eluent, p-anisaldehyde, R_f = 0.57). The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. Crude from the reaction was azeotrope with toluene under vacuum then further acylation by acetic anhydride (0.5 mL) in anhydrous pyridine (1.5 mL). The reaction was stirred at room temperature. The reaction was complete within overnight, monitored by TLC (ethyl acetate:hexanes 1:4 eluent 2 times, R_f = 0.18). After the reaction was complete, 1 mL of methanol was added into the reaction mixture and stirred for 30 minutes. The reaction mixture was concentrated under a high vacuum evaporator to remove pyridine from the reaction. The crude oil was dissolved in CH_2Cl_2 (5 mL) and then neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes = 1:9 to 1:5 eluent. 2-Nitrogalactal **10** precursor was obtained 10 mg (ethyl acetate:hexanes = 1:5 eluent 2 times, p-anisaldehyde, R_f = 0.35) in first fraction. In second fraction, compound **35** was obtained as colorless syrup 66 mg (ethyl acetate:hexanes = 1:5 eluent 2 times, p-anisaldehyde, R_f = 0.17). The overall yield over 2 steps was 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 1H), 5.01 (t, *J* = 10.1 Hz, 1H), 4.88 (dd, *J* = 18.3, 10.8 Hz, 2H), 4.62 (dd, *J* = 21.0, 11.5 Hz, 2H), 4.50 (dd, *J* = 18.1, 10.1 Hz, 1H), 4.25 (dd, *J* = 12.7, 6.4 Hz, 1H), 4.14 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.08 (s, 1H), 3.76 (t, *J* = 6.5 Hz, 1H), 3.65 (d, *J* = 6.1 Hz, 2H), 3.00 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.88 (dt, *J* = 13.8, 6.8 Hz, 1H), 2.07 (s, 3H). ESI-MS: m/z calculated for $C_{31}H_{35}NO_8SNa^+$ 604.20 [M+Na^+]; found, 604.25.

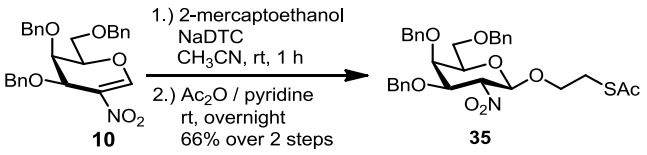

Figure 2.29 Michael addition of 2-nitrogalactal (**10**) with 2-mercaptoethanol then acetylation.

2-Nitrogalactal **10** (75 mg, 0.16 mmol) was dissolved in acetonitrile (Figure 3.30). Under the optimized conditions, NaDTC (68 mg, 0.3 mmol) and cysteamine hydrochloride (27 mg, 0.24 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by completely consumption of starting material on TLC. The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography using gradient ethyl acetate:hexanes = 1:9 to 1:1 eluent with 1% acetic acid. Unfortunately, we could not isolate the desired product.

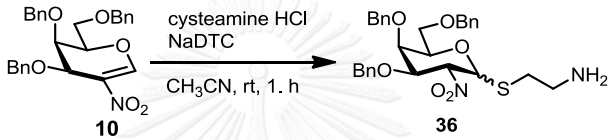

Figure 2.30 Michael addition of 2-nitrogalactal (**10**) with cysteamine.

The reaction was repeated using 2-nitrogalactal **10** (100 mg, 0.2 mmol) dissolved in acetonitrile (Figure 3.31). Under the optimized conditions, NaDTC (68 mg, 0.3 mmol) and cysteamine hydrochloride (28 mg, 0.24 mmol) were added into the reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by the disappearance of starting material on TLC. The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. Amine group of crude **36** was protected using di-tert-butyl dicarbonate (Boc_2O, 70 μL) and Et_3N (30 μL) dissolved in CH_2Cl_2. The reaction was stirred at room temperature for overnight. After that, the conversion was not complete. Boc_2O (30 μL) and Et_3N (40 μL) were added into the reaction mixture and stirred for further 12 h. After 2 days, TLC indicated complete consumption of the starting material and saturated NH_4Cl was added in order to neutralize the solution and extracted with CH_2Cl_2 (8 mL x 3). The combined organic layer was washed with saturated NaCl and dried with Na_2SO_4. The crude product was obtained as an orange-yellow syrup. It was separated into 2 portions and purified a portion by preparative TLC. Unfortunately, we could not identify the product from this reaction.

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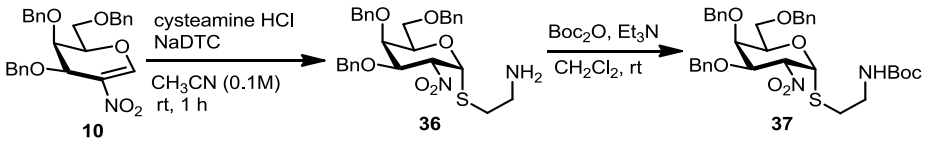

Figure 2.31 Michael addition of 2-nitrogalactal (**10**) with cysteamine then Boc-protection.

2-Nitrogalactal **10** (78 mg, 0.17 mmol) was dissolved in acetonitrile (Figure 3.32). Under the optimized conditions, NaDTC (68 mg, 0.3 mmol) and L-cysteine (29 mg, 0.24 mmol) were added into a reaction mixture, and then stirred at room temperature. The reaction was complete within an hour, monitored by disappearing of starting material on TLC. The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl. The crude mixture was purified by automated flash column chromatography of **38** using gradient ethyl acetate:hexanes = 1:1 to 3:1 eluent with 1% Acetic acid. After purification, compound **38** was obtained with unknown impurities. ESI-MS analysis m/z calculated for $C_{30}H_{35}N_2O_8S^+$ 583.21 $[M+H^+]$; found 583.41.

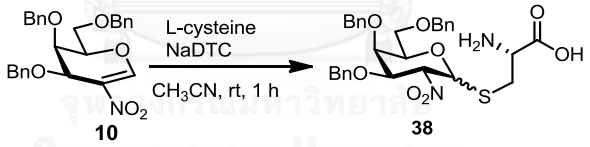

Figure 2.32 Michael addition of 2-nitrogalactal (**10**) with L-cysteine.

2-Nitrogalactal **10** (78 mg, 0.17 mmol) was dissolved in CH_3CN (2 mL) with NaDTC (68 mg, 0.3 mmol) (Figrue 3.33). 2-Naphthalenethiol (31 μL, 0.24 mmol) was added into a solution and stirred at room temperature for 3 days. TLC indicated no consumption of the starting material.

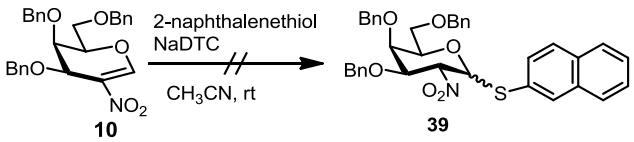

Figure 2.33 Michael addition of 2-nitrogalactal (**10**) with 2-naphthalenethiol.

2-Nitrogalactal **10** (41 mg, 0.09 mmol) was dissolved in CH_3CN (2 mL) with NaDTC (31 mg, 0.14 mmol) (Figure 3.34). 2-mercaptopyridine (12 mg, 0.11 mmol) was added into a solution and stirred at room temperature for 3 days. TLC indicated no consumption of the starting material.

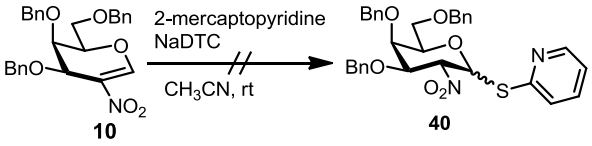

Figure 2.34 Michael addition of 2-nitrogalactal (**10**) with 2-mercaptopyridine.

2-Nitrogalactal **10** (50 mg, 0.108 mmol) was dissolved in CH_3CN (2 mL) with NaDTC (36 mg, 0.16 mmol) (Figure 2.35). 4-mercaptopyridine (14 mg, 0.13 mmol) was added into a solution and stirred at room temperature for 3 days. TLC indicated no consumption of the starting material.

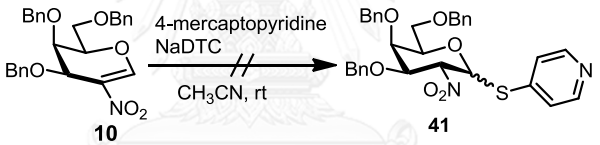

Figure 2.35 Michael addition of 2-nitrogalactal (**10**) with 4-mercaptopyridine.

2-Nitrogalactal **10** (50 mg, 0.11 mmol) was dissolved in CH_3CN (2 mL) with NaDTC (36 mg, 0.16 mmol) (Figure 2.36). 2-Thiosalicylic acid (14 mg, 0.13 mmol) was added into a solution and stirred at room temperature. TLC indicated no consumption of the starting material.

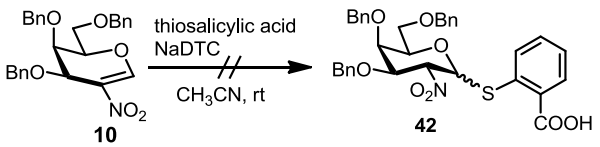

Figure 2.36 Michael addition of 2-nitrogalactal (**10**) with 2-thiosalicylic acid.

2-Nitrogalactal **9** (60 mg, 0.19 mmol) was dissolved in CH_3CN 2 mL (Figure 2.37). NaDTC (51 mg, 0.23 mmol) was added and followed by 1-dodecanethiol (40

μL, 0.17 mmol) as a limiting agent. Reaction was stirred at room temperature for overnight. The reaction was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with saturated NaCl, and concentrated to dryness. The crude mixture was purified by automated flash column chromatography, gradient with ethyl acetate:hexanes = 0:1 to 2:3 to afford compound **43** as a light-yellow syrup (39 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 5.16 (s, 1H), 4.65 (t, *J*=6.2 Hz, 1H), 4.40–4.26 (m, 2H), 3.99 (d, *J* = 1.6 Hz, 1H), 2.91–2.83 (m, 1H), 2.80–2.71 (m, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 1.76–1.63 (m, 2H), 1.25 (brs, 18H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=170.4, 160.0, 153.5, 130.4, 72.8, 67.9, 62.0, 39.3, 33.6, 32.0, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.3, 28.8, 22.8, 22.8, 20.9, 20.8, 14.2.

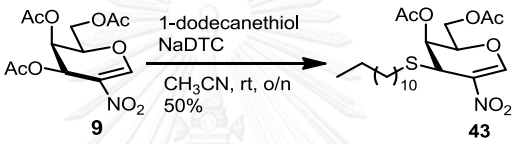

Figure 2.37 Ferrier rearrangement of acetyl-protected 2-nitrogalactal (**9**).

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CHAPTER III

RESULTS AND DISCUSSION

In this work, 2-nitroglycals were synthesized from glycals with modified method using propionyl chloride and silver nitrate in a one-pot reaction[17] or acetic anhydride and nitric acid then followed by elimination induced by trimethylamine.[9] Then the 2-nitroglycals were used as substrate for Michael addition with various nucleophiles activated by dithiocarbamate salt. Both of acetyl and benzyl protected 2-nitroglycals were studied. Michael adducts were obtained in high yield and stereoselectivities with different types of nucleophile (Figure 3.1).

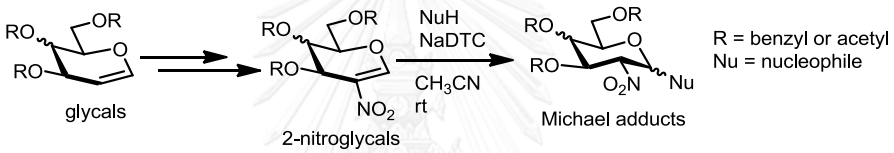

Figure 3.1 Scope of this work; synthesis and Michael addition of 2-nitroglycals.

2-Nitroglycals with various protecting groups and different types of sugar; 2-nitroglucal (**7** and **8**) and 2-nitrogalactal (**9** and **10**), were prepared by the modified methods from previous reports[9, 17] (Figure 3.2). The synthesis of 3,4,6-tri-*O*-acetyl-2-nitro-D-glucal (**7**) and also 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal (**8**) were started with commercially available 3,4,6-tri-*O*-acetyl-D-glucal. In the case of 2-nitrogalactals (**9** and **10**), the β-D-galactose pentaacetate was used as the precursor instead.

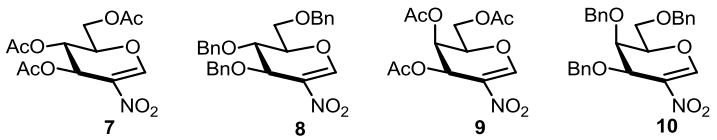

Figure 3.2 2-Nitroglycal derivatives prepared in this study.

3.1 Synthesis of 3,4,6-tri-*O*-benzyl-D-glucal (2)

3,4,6-Tri-*O*-benzyl-D-glucal (**2**) was synthesized by deprotection of acetyl group using catalytic potassium carbonate (K_2CO_3) in methanol of commercially available 3,4,6-tri-*O*-acetyl-D-glucal precursor (Figure 3.3).[21] Free hydroxyl glucal (**1**) was then installed with benzyl protecting group using benzyl bromide (BnBr) under catalytic tetrabutylammonium iodide (TBAI) in DMF.[22] 3,4,6-Tri-*O*-benzyl-D-glucal was obtained 74% yield as a white solid over 2 steps.

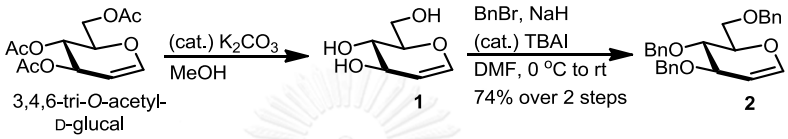

Figure 3.3 Synthesis of 3,4,6-tri-*O*-benzyl-D-glucal (**2**).

3.2 Synthesis of 3,4,6-tri-*O*-benzyl-D-galactal (6)

β-D-Galactose pentaacetate was used as starting material for the synthesis of galactal by bromide substitution and reductive elimination (Figure 3.4). Firstly, β-D-galactose pentaacetate was subjected to anomeric substitution with excess of hydrobromic acid in acetic acid to give glycosyl bromide (**3**) in good yield. The 2,3,4,6-tetra-*O*-acetyl-galactosyl bromide (**3**) was then treated with activated zinc in a biphasic reaction mixture between saturated monosodium phosphate (NaH_2PO_4) and ethyl acetate to provide 3,4,6-tri-*O*-acetyl-D-galactal (**4**) albeit in 48% yield over 2 steps. Hydrolysis of the reactive peracetyl galactosyl bromide (**3**) during reductive elimination might be responsible for the moderate yield of this transformation. The purified galactal **4** was subjected to acetyl deprotection under K_2CO_3 in methanol conditions.[21] After completion of the reaction monitored by TLC, methanol solvent was removed under high vacuum to provide crude galactal **5** as a light yellow viscous liquid. Due to nature of the viscosity of galactal **5**, trace of moisture and methanol could be trapped within the syrup thus deteriorating the efficiency of next benzylation step. Rigorous removal of residual moisture and methanol was performed by applying azeotropic distillation with a mixture of CH_3CN-toluene under

high vacuum rotary evaporator until the syrup galactal **5** became a white solid. Standard NaH/BnBr benzylation was then set under Argon atmosphere to prevent moisture in air entering to the reaction. Even though the moisture was already removed, excessed amount of NaH was also necessary in order to make sure that all of hydroxyl groups of galactal **5** were completely deprotonated.[22] The reaction was complete after stirring at room temperature overnight, followed by aqueous work up and purification. The 3,4,6-tri-*O*-benzyl-D-galactal was obtained as a white solid in 96% yield over 2 steps.

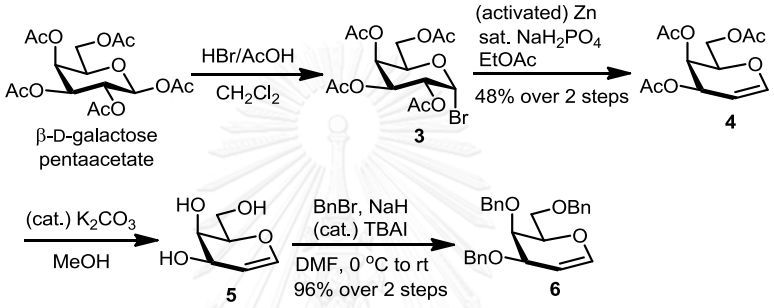

Figure 3.4 Synthesis of peracetyl galactal (**4**) and perbenzyl galactal (**6**) from β-D-galactose pentaacetate.

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3.3 Nitration of glycals

3.3.1 Attempt of nitration by silver nitrite/TEMPO at high temperature

Recently, Maiti and coworkers[24] reported efficient nitration of activated olefin under radical conditions. The nitration on alkene was done by employing silver nitrite ($AgNO_2$) as nitrating agent and catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) at high temperature. This nitration on alkene provided *E*-selectivity as show in Figure 3.5a. This selectivity was consistent with target molecule; 2-nitroglycals. So, this method was first applied for nitration with glucal as a substrate in our work (Figure3.5b).

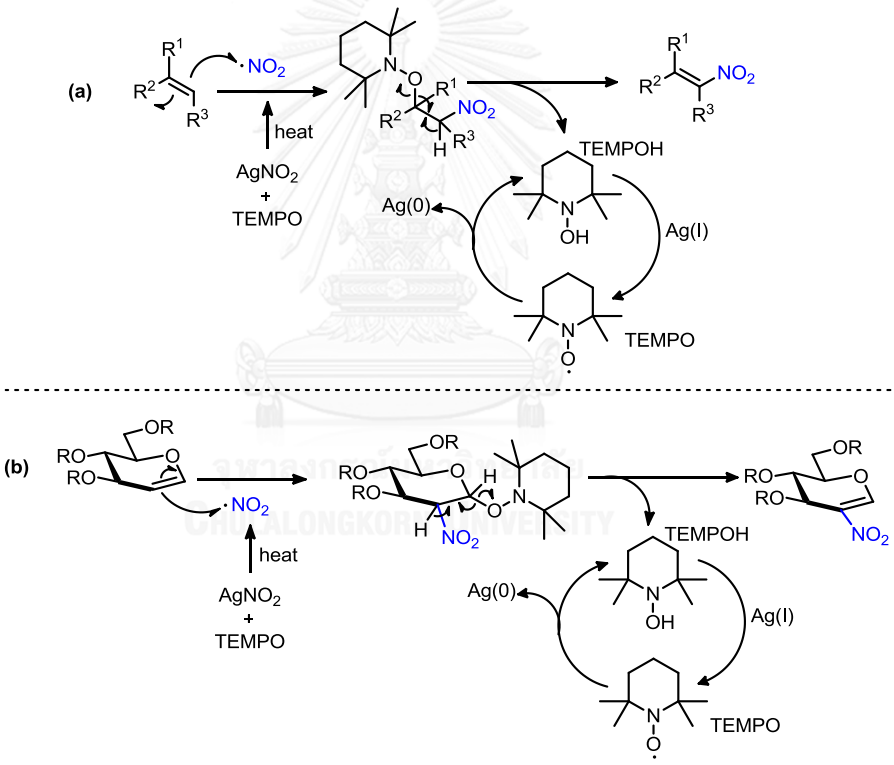

Figure 3.5 Mechanism of nitration with $AgNO_2$/TEMPO. (a) Nitration of alkene with $AgNO_2$/TEMPO. (b) Nitration of glycal with $AgNO_2$/TEMPO.

From the proposed mechanism (Figure 3.5), the nitro radical generated upon heating the reaction mixture underwent radical addition to the olefinic group of glucal and then TEMPO acted as single electron oxidant to form the intermediate adduct. Elimination of the intermediate produced the desired 2-nitroglucal. The TEMPO-H was released and later oxidized by Ag(I) ion from silver nitrite and regenerated TEMPO as a catalyst back again.

3,4,6-Tri-*O*-acetyl-D-glucal was treated with silver nitrite and TEMPO in dichloroethane ($C_2H_4Cl_2$) then heated to 70 °C for overnight (Figure 3.6). The reaction was monitored by TLC and revealed that the starting material was totally consumed but there was no formation of 2-nitroglucal product. We first hypothesized that the acetyl protecting group might not be compatible with these conditions since it is relatively labile and it also lowers electron density of olefinic moiety. Thus, perbenzylated glucal (**2**) was subjected to the above conditions. However, it also yielded only decomposition products without any desired 2-nitroglucal **8** (Figure 3.6).

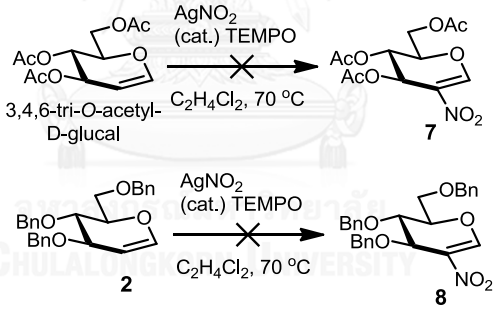

Figure 3.6 Synthesis of 2-nitroglucal by $AgNO_2$/TEMPO.

3.3.2. Nitration by silver nitrate/acetyl chloride at high temperature

Nitration of glycals by $AgNO_3$ and acetyl chloride has been reported by Vankar and coworkers in 2011.[17] Generation of a reactive nitrating agent, acyl nitrate, was achieved by mixing silver nitrate and acetyl chloride then heated to 55 ºC. The electrophilic acyl nitrate reacted with glycal and concomitantly underwent elimination to provide the 2-nitroglycal. Typically, high polar solvent such as acetonitrile was used in order to dissolve $AgNO_3$. At room temperature, the competitive nucleophilic addition of acetonitrile to the 2-nitro-oxonium intermediate also yielded 2-nitro-1-acetamido glycoside as a by-product. However, raising temperature up to 55 ºC speeded the elimination up thus produced 2-nitroglycal as a major product (Figure 3.7).

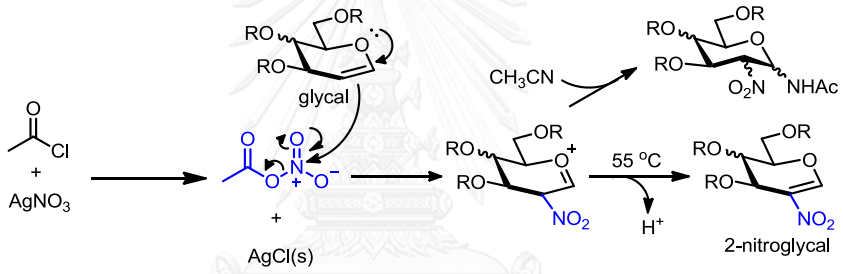

Figure 3.7 Mechanism for nitration of glycal by silver nitrate and acetyl chloride.

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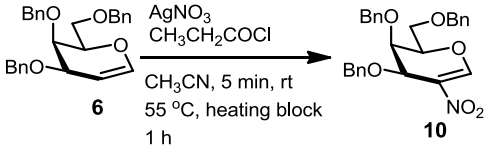
3.3.2.1 Optimization for nitration of glycals by silver nitrate and propionyl chloride

According to Vankar and coworkers report,[17] treatment of 3,4,6-tri-*O*-benzyl-D-galactal (**6**) with one equivalent of silver nitrate ($AgNO_3$) and acetyl chloride (CH_3COCl) at 55 ºC produced the desired 2-nitrogalactal in 62% yield. In this work, however, propionyl chloride (CH_3CH_2COCl) was used instead of acetyl chloride due to anti-narcotics law in Thailand prohibiting the purchase of acetyl chloride. Propionyl group was more bulkiness than acetyl group, so it might slow down the reaction rate and lower the yield. Thus optimization amount of reagent for nitration was setup. Increasing amount of silver nitrate and propionyl chloride from one equivalent to 1.5 and 2 equivalents were setup (Table 3.1).

Table 3.1 Optimization of nitration with silver nitrate and propionyl chloride.



Entry	$AgNO_3$ (eq.)	CH_3CH_2COCl (eq.)	Yield (%)
1	1	1	6
2	1.5	1.5	16
3	2	2	22

Three optimizations were set up in the same reaction scale which was 200 mg of 3,4,6-tri-*O*-benzyl-D-galactal **6** starting material for accurate comparison (Table 3.1, entries 1–3) . Propionyl chloride was slowly added into the clear solution mixture of galactal **6** and silver nitrate in CH_3CN at room temperature. White precipitate of AgCl was immediately formed during the addition of propionyl chloride. This appearance indicated the generation of propionyl nitrate intermediate. The reaction mixture was then heated to 55 °C by a heating block instead of oil bath. The heating block provided more accurate temperature control than oil bath method. The reaction was complete within an hour, monitored by the disappearing of starting material spot on TLC. The reaction mixture was allowed to cool down to room temperature and work-up. These three reactions were purified by column chromatography and product yields of entries 1, 2 and 3 were 6%, 16% and 22% respectively. It is worth noting that after reaction was heated for 10 minutes, reaction tube in entry 3 (Table 3.1) generation of nitrogen dioxide gas (NO_2) was observed as reddish-brown vapor in the reaction tube. This observation could imply the excess amount of propionyl nitrate that underwent decomposition during high temperature (Figure 3.8). Thus reaction condition of entry 3 was chosen to investigate with other glycals.

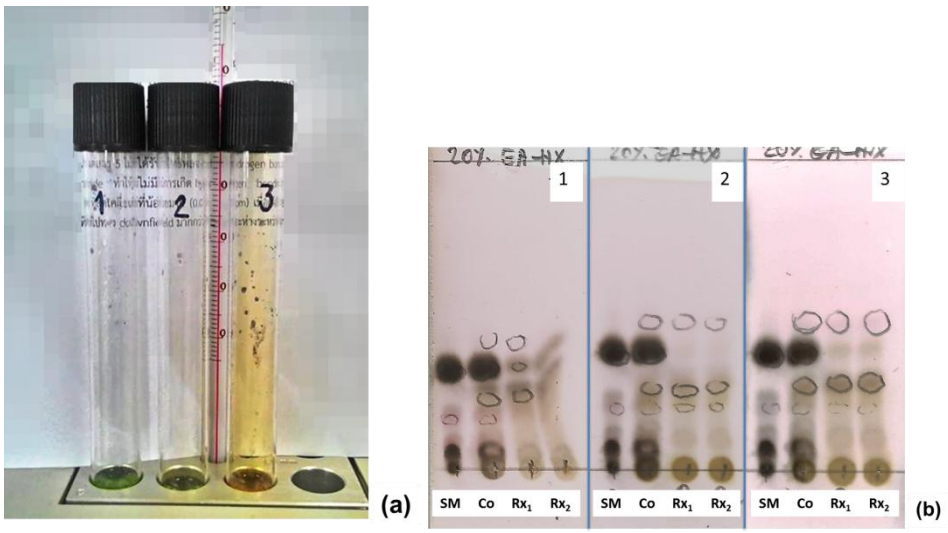


Figure 3.8 Optimization of nitration on galactal with $AgNO_3$ and propionyl chloride. (a) Reaction tube number 1, 2 and 3 represent reaction in entries 1, 2 and 3 (table 3.1) respectively. (b) ρ-anisaldehyde stained TLC, number 1, 2 and 3 represent reaction in entries 1, 2 and 3 respectively (Table 3.1) (SM = starting material, Co = co-spot, Rx = reaction spot).

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3.3.2.2 Synthesis of 2-nitro-D-glycals

Once the condition was established, 2-nitroglycals were synthesized by using 2 equivalents of silver nitrate and propionyl chloride. After purification, the obtained yields were low, except in the case of 3,4,6-tri-*O*-acetyl-D-glucal gave 3,4,6-tri-*O*-acetyl-2-nitro-D-glucal (**7**) in moderate yield. From the previous Vankar's report, this procedure should give the desired 2-nitrogalactal up to 62% yield. We hypothesize that bulkiness of reactive propionyl nitrate compared to that of acetyl nitrate might cause the lower yield. Moreover, *in situ* generation of propionyl nitrate could react with moisture and produced nitric acid (HNO_3) which later decomposed the galactal precursor. However, yield of galactal **10** was obtained in 30% which was slightly higher than the optimization experiment (entry 3, Table 3.1) due to a larger reaction scale thus the lost from purification process was decreased and provided higher yield.

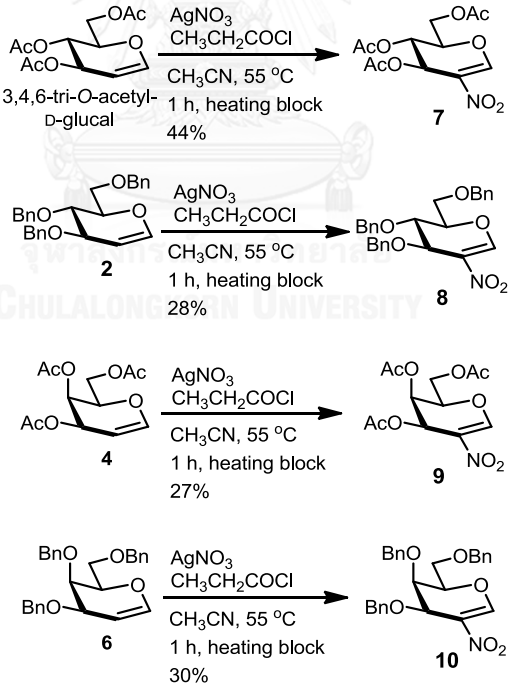

Figure 3.9 Synthesis of 2-nitro-D-glycals.

3.3.3 Nitration by acetic anhydride and nitric acid

Schmidt and coworkers[9] reported 2-step synthesis of 2-nitrogalactal *via* nitration and elimination in 1998 (Figure 3.10). Acetyl nitrate was *in situ* generated by a combination of acetic anhydride and concentrated nitric acid at low temperature. Then solution of glycal in acetic anhydride was added dropwise while the temperature was kept at around –30 °C. Addition of acetyl nitrate to glycal will occur in this step. After addition in first step was finished, crude from the reaction was azeotroped with toluene to eliminate acetic acid and trace moisture from the reaction mixture. 2-Nitro-1-acetyl-galactoside intermediate was further subjected to elimination using triethylamine (Et_3N) as a base to provide 2-nitroglycal as a product.

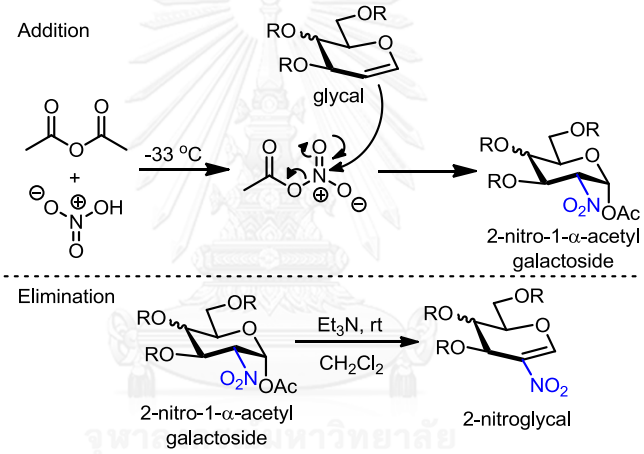

Figure 3.10 Mechanism for nitration of glycals by acetic anhydride and nitric acid.

In this reaction, the role of acetic anhydride was to activate nitric acid to be better and more reactive electrophile so that enol ether functional group of glycals can attack the nitrogen atom easier than that of nitric acid form. Schmidt and coworkers reported that 2-nitro-1-acetyl-galactoside intermediate was an α-anomer which then easily to proceed elimination *via* E2 mechanism.

3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal (**10**) was synthesized with this method. Following the protocol from Schmidt and coworkers,[9] concentrated nitric acid was slow dropped into pre-cooled acetic anhydride to generate acetyl nitrate in cooling bath under argon atmosphere. External temperature was maintained at –10 °C in

order to keep internal temperature lower than 20 ºC due to the exothermic reaction. Then solution was cooled down to –30 ºC, solution froze since temperature was down to –25 ºC. So, the reaction cannot cool down to –30 ºC, then the solution of galactal **6** was slowly added at –25 ºC. After galactal **6** was added, maintaining temperature at –25 ºC and stirred for 30 minutes. The reaction was allowed to slowly warm up to room temperature before quenching with saturated NaCl (Figure 3.11).

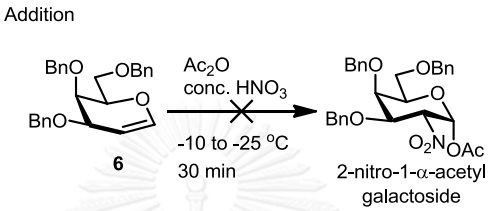

Figure 3.11 Attempt to synthesize 2-nitrogalatal (**10**).

We found the quality of acetic anhydride that was used in this reaction setup was poor (Figure 3.11). There was decomposition of acetic anhydride into acetic acid. However, ^{1}H NMR spectroscopy cannot clearly distinguish acetic anhydride and acetic acid. Later on, we found an easy way to check the quality of acetic anhydride was to use its melting point due to a large difference of melting point between acetic anhydride and acetic acid.

After several trials, the quality of acetic anhydride has been checked before using, argon atmosphere was also applied (Figure 3.12). Since under atmospheric conditions, moisture caused the decomposition of acetic anhydride, observing by the freezing of solution after cool down before its melting point. Reaction temperature of each step must be controlled precisely. Importantly, after the acid was completely added into acetic anhydride. The reaction mixture must be maintained at –10 ºC and stirred for 30 minutes. Then pre-cooled solution of galactal **6** in acetic anhydride was slowly added into a reaction mixture. After the reaction was complete, reaction was monitored by TLC. 2-Nitro-1-acetyl-galactoside crude was eliminated acetic acid residual by azeotropic distillation with toluene. The intermediate was obtained as a white solid.

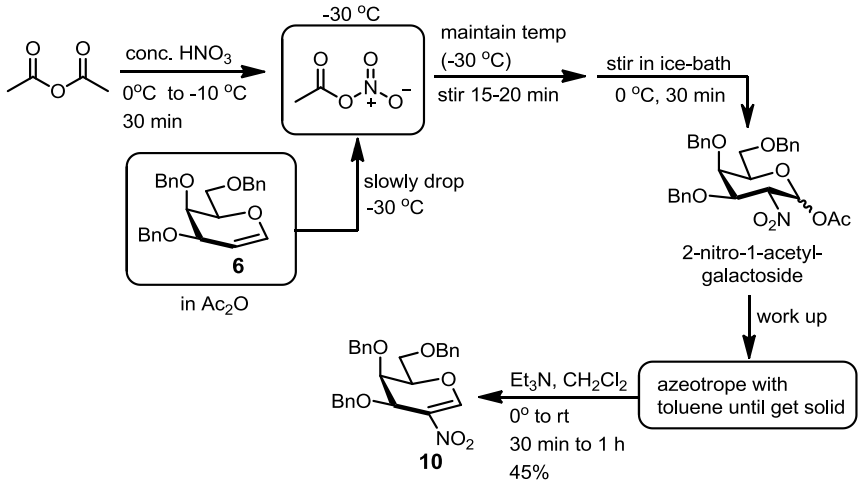

Figure 3.12 Synthetic procedure of 2-nitrogalactal by acetic anhydride and nitric acid.

From previous report, 2-nitro-1-acetyl-galactoside was obtained as α-isomer with reported chemical shift at 6.72 ppm with coupling constant of 4.1 Hz.[9] In our hand, ^{1}H NMR of intermediate 2-nitro-1-acetyl-galactoside was obtained as a mixture α- and β-isomer with chemical shifts 6.64 and 6.19 ppm, coupling constant of 4 Hz and 2.4 Hz respectively. The ratio of α:β was 1.8:1. Then α- and β-isomer of 2-nitro-1-acetyl-galactoside intermediate was taken to elimination using triethylamine (Et_3N), resulted in 2-nitrogalactal in 45% yield over 2 steps.

There was a hypothesis that 2-nitrogalactal product might be hydrolyzed in acidic silica gel while purification by column chromatography. Therefore, column chromatography was set by silica gel then authentic 2-nitrogalactal was loaded on a column and eluted compound to adsorb on silica gel and soaked for overnight. Then high polar solvent was used for washing the compound out of column to check whether 2-nitrogalactal decompose in silica gel or not. The obtained compound showed no significant difference from the authentic 2-nitrogalactal compared by TLC. So, we concluded that 2-nitrogalactal was stable enough on silica gel during chromatography.

In summary, 2-nitrogalactal was synthesized from a 2-step nitration using acetic anhydride and nitric acid, and a one-pot nitration using silver nitrate and

propionyl chloride. The obtained 2-nitroglycals will be used for investigation of Michael addition in the next step.

3.4 Michael addition of 2-nitroglycals

From preliminary result, Michael addition of 2-nitroglycals with methanol was not successful in the absence of NaDTC. In this case, Michael addition of 2-nitroglycals with thiol, a better nucleophile, was setup without addition of NaDTC again (Figure 3.13). After the reaction mixture was stirred for overnight, TLC indicated no consumption of the starting material as well.

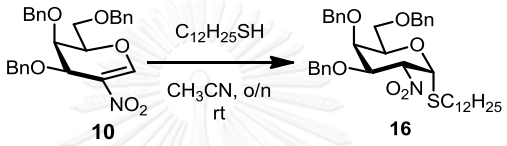

Figure 3.13 Addition of 1-dodecanethiol without NaDTC.

2-Nitrogalactal (**10**) was used for optimization of solvent and amount of NaDTC in Michael addition. 1-Dodecanethiol ($C_{12}H_{25}SH$) as *S*-nucleophile representative was first focused on this reaction.

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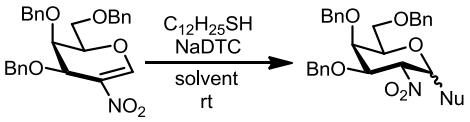
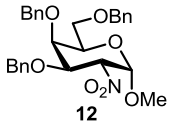
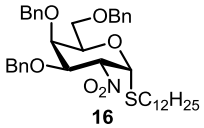
Table 3.2 Optimization of Michael addition on 2-nitrogalactal with 1-dodecanethiol.



10

Entry	Nucleophile	NaDTC (equiv)	Solvent	Time (h)	Product	Yield (%)
1	$C_{12}H_{25}SH$	1.5	MeOH	1	 **12**	93
2	$C_{12}H_{25}SH$	1.5	CH_3CN	1.5	 **16**	73
3	$C_{12}H_{25}SH$	0.5	CH_3CN	o/n	**16**	trace
4	$C_{12}H_{25}SH$	1.5	DMF	o/n	**16**	72
5	$C_{12}H_{25}SH$	1.5	THF	o/n	**16**	13
6	$C_{12}H_{25}SH$	1.5	$C_2H_4Cl_2$	1.5	**16**	52
7	$C_{12}H_{25}SH$	1.5	CH_2Cl_2	o/n	**16 +** unknown	N/A
8	$C_{12}H_{25}SH$	1.5	Toluene	o/n	no reaction	-
9	$C_{12}H_{25}SH$	1.5	Water	o/n	no reaction	-

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First, polar protic solvent such as methanol was used and the NaDTC was soluble in methanol (entry 1, Table 3.2). After the reaction was complete within an hour, the desired product was not observed. Methanolysis by methanol solvent was occurred instead even the 1-dodecanethiol nucleophile was also present in the reaction mixture. After purification, compound **12** was obtained in excellent yield and selectivity. Then acetonitrile and 1.5 eqiuvalents of NaDTC were used and provided the expected compound 2-nitro-1-α-thiogalactoside (**16**) in 73% (entry 2). However, the reaction with catalytic amount of NaDTC did not proceed smoothly. Only trace amount of product was observed from TLC and we were unable to purify the crude (entry 3). Another polar solvent; *N*,*N*-dimethylformamide (DMF) was tested and it dissolved all reagents very well. This reaction was complete after stirring overnight with good yield (entry 4). For entries 5 and 6, the use of tetrahydrofuran

(THF) and dichloroethane ($C_2H_4Cl_2$) partially dissolved NaDTC. The reaction in dichloroethane was complete after 1.5 hours with unsatisfactory yield. Reaction in THF was also completed after overnight with very low yield of desired product. Dichloromethane provided a mixture of desired products together with unknown carbohydrate compounds in moderate yield (entry 7). In entries 8 and 9, toluene and water were used as solvent which toluene did not dissolve NaDTC at all while water did not dissolve 2-nitroglycal and thiol. Under the use of toluene and water, conversion of product was not observed.

From the optimization, the best solvent for this reaction was acetonitrile and DMF, which were able dissolve both starting material and NaDTC. Especially, they provided good yield and gave stereoselective products. However, DMF was hard to remove by rotary evaporator due to its high boiling point at 154 °C. Thus acetonitrile (boiling point = 82 °C) was chosen for examination of the scope of nucleophile.

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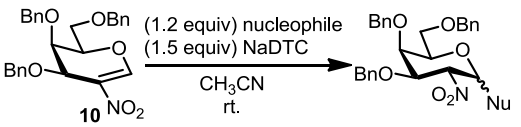
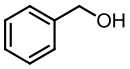
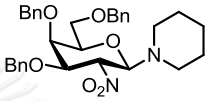
Table 3.3 Study of nucleophile scope in Michael addition of 2-nitroglycal.



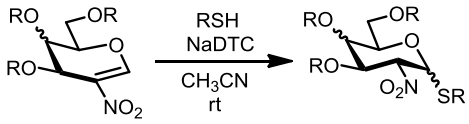
Entry	Nucleophile	Time (h)	Product	Yield (%)
1*		o/n	-	-
2		o/n	-	-
3		o/n	 **15**	67%

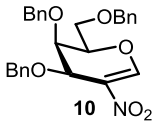
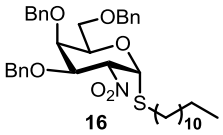
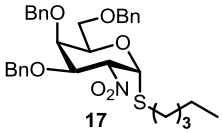
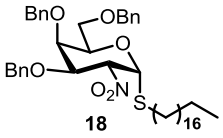
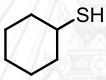
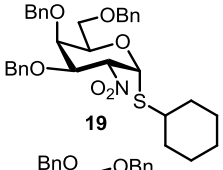
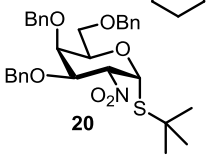
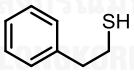
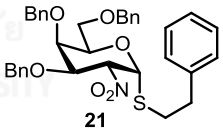
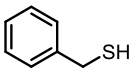
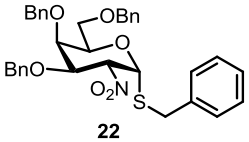
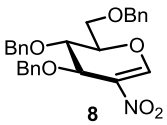
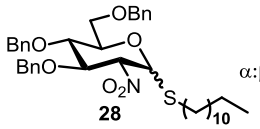
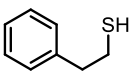
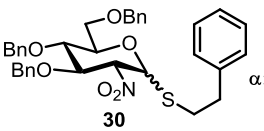
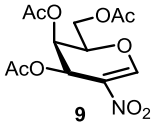
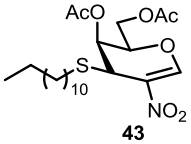
* Isopropanol was use as solvent and nucleophile.

In the study of nucleophiles, isopropanol was used as both nucleophile and solvent but no conversion was observed after reaction was left for overnight (entry 1 Table 3.3). Then benzyl alcohol was used as nucleophile in CH_3CN as solvent but there was no conversion after overnight (entry 2). Next, piperidine as a representative of *N*-nucleophile was examined in Michael addition. The reaction was complete within overnight and provided *N*-glycoside with β-selective (entry 3). The β-selectivity of *N*-glycoside was consistent with the previous report. Liu and coworkers[6] has been reported Michael addition of 2-nitroglycals with secondary amine and resulted in β-selectivity. Thus, we decided to focus only on the *S*-nucleophile since it has never been documented before. The investigation of Michael addition will be carried out by using NaDTC as an activator.

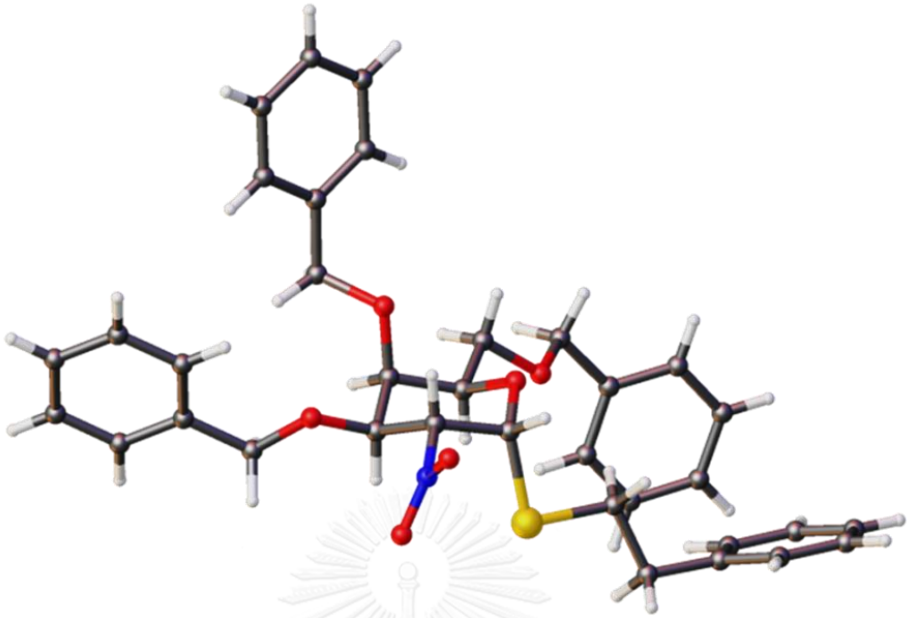
Next, aliphatic thiols will be examined on the Michael addition of 2-nitroglycals under the optimization conditions.

Table 3.4 Michael addition of 2-nitroglycals with aliphatic thiols.



Entry	2-nitroglycal	Nucleophile	Time (h)	Product	Yield (%)
1	 **10**	$C_{12}H_{25}SH$	1	 **16**	73
2	**10**	$C_5H_{11}SH$	1	 **17**	98
3	**10**	$C_{18}H_{37}SH$	1	 **18**	87
4	**10**		1.5	 **19**	61
5	**10**		1.5	 **20**	66
6	**10**		1	 **21**	88
7	**10**		1	 **22**	65
8	 **8**	$C_{12}H_{25}SH$	1.5	 **28**	62 α:β = 1:1
9	**8**		1.5	 **30**	28 α:β = 1:1
10	 **9**	$C_{12}H_{25}SH$	o/n	 **43**	50

As the result from optimization, aliphatic long chain 1-dodecanethiol provided good yield and α-selectivity (entry 1, Table 3.4). Then 1-pentanethiol and 1-octadecanethiol were demonstrated as a shorter aliphatic thiol and longer chain thiol nucleophile compared to the entry 1. Michael addition of 2-nitrogalactal (**10**) with 1-pentanethiol resulted in excellent yield (98%) and selectivity (entry 2). As same as the longer thiol nucleophile, 1-octadecanethiol resulted the Michael adduct with α-selectivity in 87% yield (entry 3). Then Michael addition using cyclohexyl thiol as a secondary thiol representative in order to test the versatility of reaction, the reaction provided α-thioglycoside in 61% yield (entry 4). Tertiary thiol using *tert*-butylthiol also gave the Michael adduct as α-thioglycoside in 66% yield (entry 5). 2-Phenylethanethiol in Michael addition with 2- nitrogalactal (**10**) provided α-selective product in 88% yield (entry 6). α-thioglycoside **21** was recrystallized in a mixture of ethyl acetate and hexanes, the crystal was analyzed by X-ray crystallography (Figure 3.14). The structure was confirmed as α-anomer which was consistent with the coupling constant in ^{1}H NMR of H1-H2 at 6.0 Hz. According to the Karplus equation, different of dihedral angle between H1-H2 shows the different coupling constant. The structure of other thioglycosides with the same stereochemistry possessed similar coupling constant as well. In case of α-anomer, dihedral angle between H1-H2 was approximately 60 degree. Coupling constants of α-anomer are observed between 2–6 Hz. Dihedral angle between H1-H2 of β-anomer proton was around 180 degree and observed the coupling constant in 10–13 Hz.



21

Figure 3.14 X-ray structure of compound **21** (α-anomer).

Benzyl thiol in Michael addition with 2-nitrogalactal (**10**) resulted α-thioglycoside in 65% yield (entry 7) Then 2-nitroglucal (**8**) was demonstrated in Michael addition with 1-dodecanethiol resulted in a mixture of α- and β-thioglycoside in 62% yield (entry 8). 2-Phenylethanthiol with 2-nitroglucal (**8**) also provided a mixture of α- and β-thioglycoside in 28% yield (entry 9). Under the same conditions, reaction of 2-nitrogalactal (**9**) with 1-dodecanethiol gave the Ferrier rearrangement product instead of the addition (Figure 3.15). C-O bond of acetyl-protected at C-3 of 2-nitrogalactal (**9**) was easy for cleavage and acetyl group was acted as a good leaving group. Ferrier rearrangement product was obtained in 50% yield (entry 10)

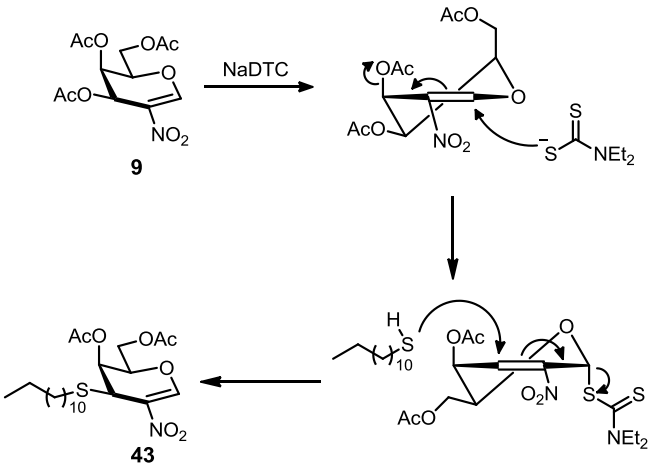


Figure 3.15 Proposed mechanism of Ferrier rearrangement of 2-nitrogalactal **9**.

Those Michael additions of 2-nitrogalactal (**10**) with primary aliphatic thiols proceeded within an hour with excellent α-selectivity. The reaction time of 2-nitrogalactal (**10**) with bulkier thiol such as secondary and tertiary thiol took longer time. While Michael addition of 2-nitroglucals (**8**) yielded a mixture anomer in a ratio of 1:1.

Next, we will focus on Michael addition of aromatic and heterocyclic thiols.

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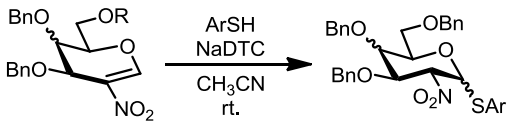
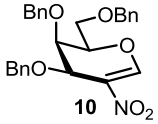
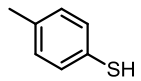
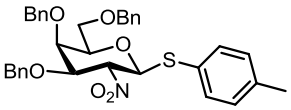
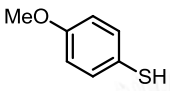
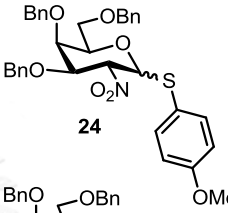
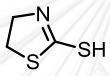
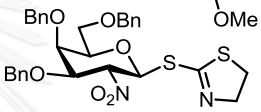
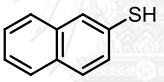
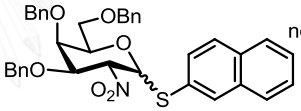
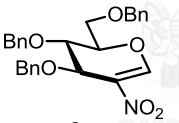
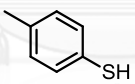
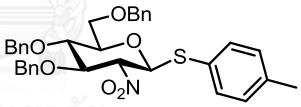
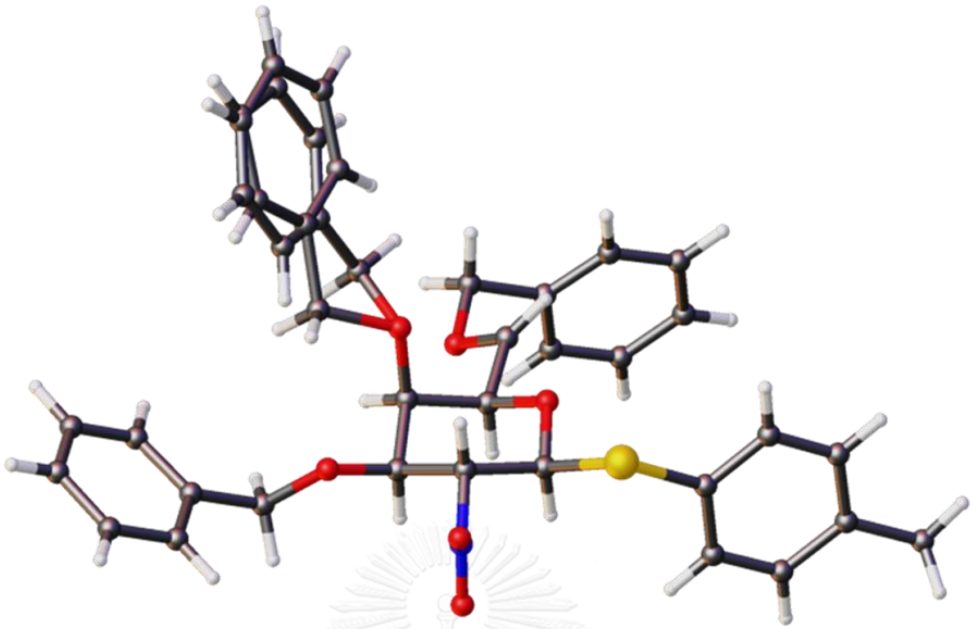
Table 3.5 Michael addition of 2-nitroglycals with aromatic and heterocyclic thiols.



Entry	2-nitroglycal	Nucleophile	Time (h)	Product	Yield (%)
1	 **10**		1	 **23**	77
2	**10**		1	 **24**	73 α:β = 3:1
3	**10**		1	 **25**	93
4	**10**		o/n	 **39**	no reaction
5	 **8**		1	 **29**	55 α:β = 1:4

Firstly, 4-methylbenzenethiol was demonstrated in Michael addition with 2-nitrogalactal. The reaction took an hour to complete, resulting in compound **23** in 77 % with β-anomer (entry 1, Table 3.5). Compound **23** was recrystallized in ethyl acetate and hexanes. The crystal was analyzed by X-ray crystallographic method (Figure 3.16). Compound **23** was assigned as β-anomer, with the coupling constant of H1-H2 = 10 Hz.



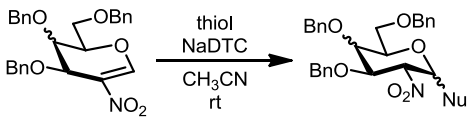
23

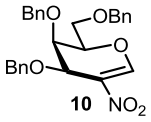
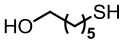
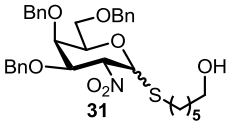
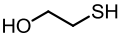
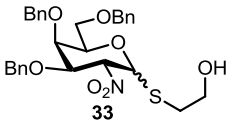
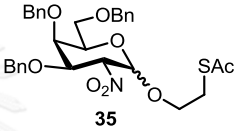
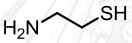
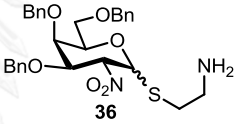
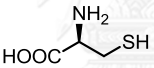
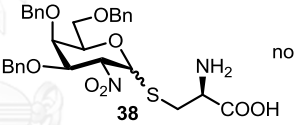
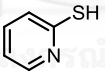
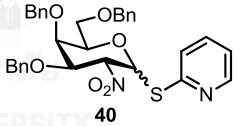
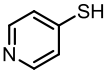
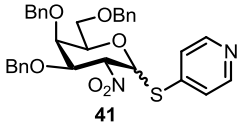
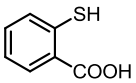
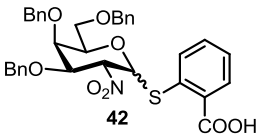
Figure 3.16 X-ray structure of compound **23** (β-anomer). Oxygen atom at C4 position exhibits as a trivalent atom due to molecular vibration at room temperature.

Michael addition of 2-nitrogalactal with 4-methoxybenzenethiol provided mixture of α- and β-glycoside in 73% yield, however, α-anomer was a major product of this reaction (entry 2). 2-Thiazoline-2-thiol gave excellent β-selectivity in 97% yield (entry 3). In case of 2-nitroglucal, Michael addition with 4-metylthiophenol resulted in β-glycoside with some mixture of α-anomer in 55% yield (entry 5). However, Michael addition of 2-nitrogalactal with 2-naphthalenethiol did not provided any conversion after the reaction was stirred overnight (entry 4).

Then bifunctional thiols were applied to Michael addition with 2-nitrogalactal (**10**), to extend the scope of the reaction.

Table 3.6 Michael addition of 2-nitroglycals with bifunctional thiols.



Entry	2-nitroglycal	Nucleophile	Time (h)	Product	Yield (%)
1	 **10**		1.5	 **31**	76% α:β = 8:1
2	**10**		1.5	 **33**	76 α:β = 4:1
3*	**10**		1.5	 **35**	66
4	**10**		1	 **36**	no reaction
5	**10**		1	 **38**	no reaction
6	**10**		o/n	 **40**	no reaction
7	**10**		o/n	 **41**	no reaction
8	**10**		o/n	 **42**	no reaction

*acetylation was applied after Michael addition.

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First, 6-mercaptohexanol, an unprotected hydroxyl thiol was examined in the reaction. We expected that under the activation of NaDTC, thiogalactoside will be a major product. After purification, *S*-galactoside **31α** was obtained as major product with trace amount of anomer **31β.** Overall yield was 76%. According to the previous experiment, alcohol was less reactive than thiol when the molecule was bulky or has some steric hindrance (entry 1, Table 3.6). Then Michael addition of 2-nitrogalactal (**10**) with 2-mercaptoethanol provided a mixture of α- and β-*S*-galactoside **33** and trace amount of unidentified compound (entry 2). To ease the purification of *S*-galactoside **33**, acylation of terminal hydroxyl group was carried out after Michael addition was complete. However, *O*-galactoside **35** was formed as a major product in 66% yield. According to the previous report from Liu and coworkers,[25] we proposed that intramolecular rearrangement from *S*-galactoside to *O*-galactoside was occurred (Figure 3.17).

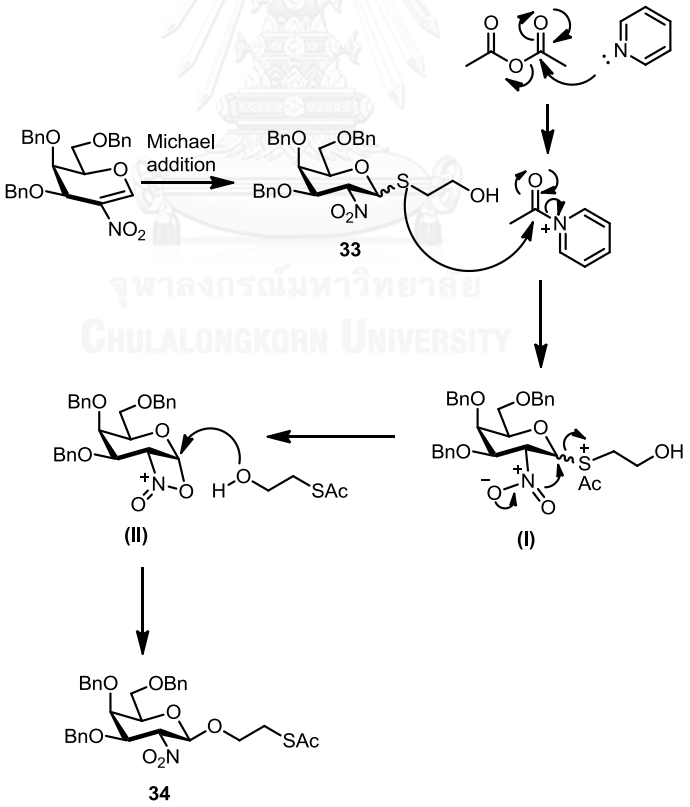

Figure 3.17 Proposed mechanism of intermolecular rearrangement from *S*-galactoside to *O*-galactoside.

Then Michael addition of 2-nitrogalactal (**10**) with cysteamine was performed. Starting material was consumed within an hour (entry 4). Unfortunately, we observed the conversion on TLC but we could not isolate the desired product (Figure 3.18).

Figure 3.18 TLC of the Michael addition of 2-nitrogalactal (**10**) with cysteamine.

L-Cysteine was next used in this Michael addition. The conversion was observed and the desired compound was obtained but could not get the purified product. The product was confirmed by mass spectrometer (entry 5). In entries 6–8, less reactive nucleophiles provided no conversion after the reaction was stirred for overnight (Table 3.6).

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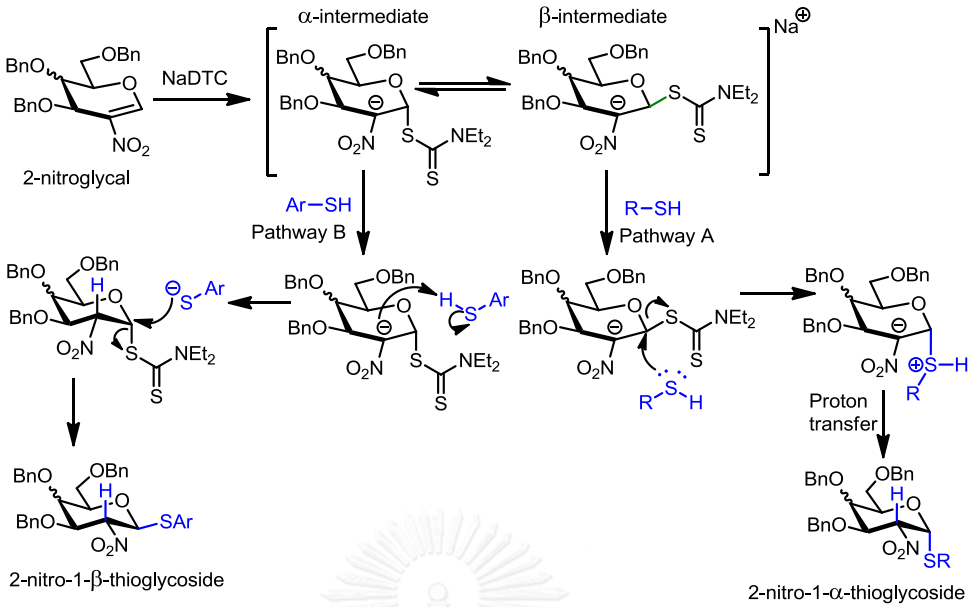

Figure 3.19 Proposed mechanism for Michael addition of 2-nitroglycals in this work.

According to our experimental results, we found the trend of the selectivity of this Michael addition. NaDTC could have activated 2-nitroglycals into the reactive intermediate, both α- and β-intermediate are also possible (Figure 3.19). Aliphatic thiols, strong nucleophiles, attack the DTC intermediate directly (Pathway A). Then the molecule will be stabilized by proton transfer. Due to the higher pK_a of aliphatic thiol, deprotonation was occurred after thiol already bonded with 2-nitroglycals. Since the acidity of proton was increased and easy to deprotonate. On the other hand, aromatic and heterocyclic thiols were deprotonated first in order to enhance their nucleophilicities before adding to the anomeric carbon (Pathway B) since their protons (lower pK_a) were easier to deprotonated. From the proposed mechanism, the different reactivity of thiols created different pathways of reaction and selectivity. This guideline could help us to select the appropriate nucleophile in order to synthesize thioglycosides *via* Michael addition. However, the explanation of this mechanism limited to only 2-nitrogalactal (**10**) substrates. While the selectivity of 2-nitroglucal (**8**) in Michael addition required further study.

CHAPTER IV
CONCLUSION

1. Synthesis of 2-nitroglycals was successfully accomplished by a modified one-pot nitration of glycals using silver nitrate and propionyl chloride to afford 2-nitroglycals (**7**–**9**) in 27–44% yield. Alternatively, benzyl-protected 2-nitrogalactal (**10**) was obtained in 45% yield over 2 steps by nitration using acetic anhydride and nitric acid followed by elimination with triethylamine (Figure 4.1).

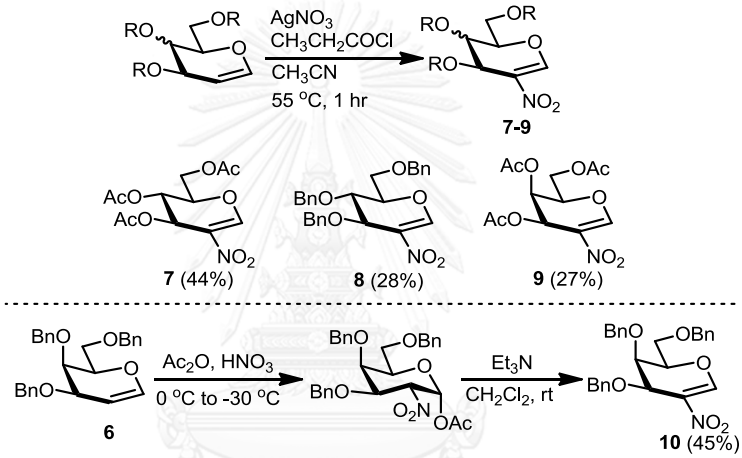

Figure 4.1 Synthesis of 2-nitroglycals from glycals.

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2. Michael addition of 2-nitroglycals was examined. 2-Nitroglycals were successfully activated by sodium diethyldithiocarbamate (NaDTC; $Na^{+-}SC(S)NEt_2$) in acetonitrile under mild conditions and without the need of drying the reaction solvents and reagents (Figure 4.2). In contrast with previous reports which required vigorous anhydrous conditions in order to provide high yields and selectivities.

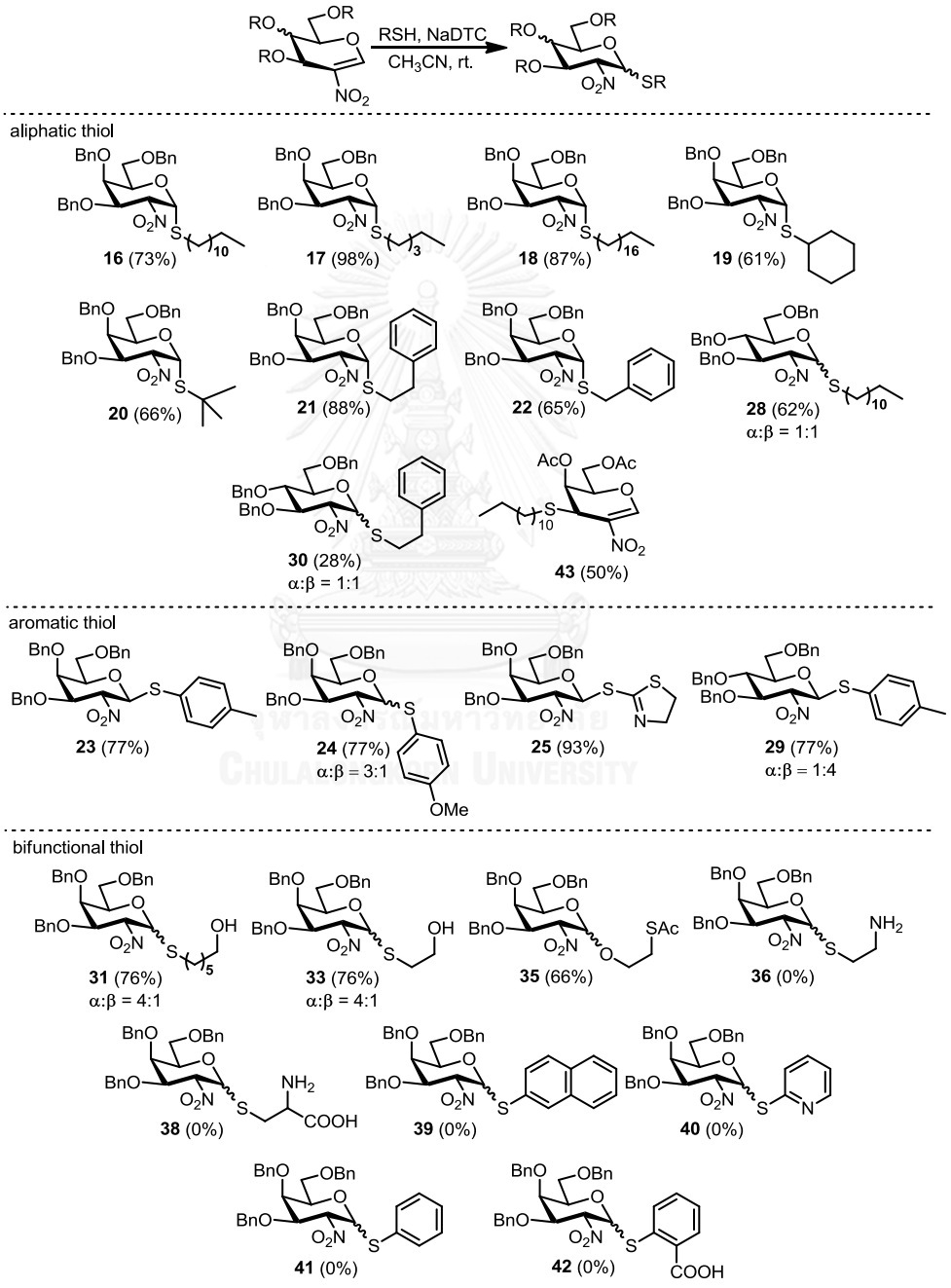

Figure 4.2 Thioglycosides from 2-nitroglycals with various thiols.

Michael addition of 2-nitrogalactal (**10**) with aliphatic thiols gave compound **16**–**22** in 61-98% yield with excellent α-selectivitiy. Michael addition of 2-nitroglucal (**8**) with aliphatic thiols gave poor selectivities, and thioglucoside **28** and **30** were obtained as a mixture of α- and β-anomer in 1:1 ratio in 62 and 28% yield, respectively. When the C-3 hydroxyl group was protected as acetyl group in 2-nitrogalactal (**9**), the Ferrier rearrangement product (**43**) was obtained in 50% yield. Michael addition of 2-nitroglycals with aromatic and heterocyclic thiols resulted in high β-selectivity, affording thiogalactoside **23**, **25**, and **29** in 55–93% yields except for 4-methoxybenzenethiol that anomeric mixture of thioglycoside **24** was obtained instead. Unprotected bifunctional thiol nucleophiles were next examined in the Michael addition with 2-nitrogalactal. Michael addition of 2-nitrogalactal with 6-mercaptohexanol was provided α-thiogalactoside as the major product. However, decreasing the chain length to 2-mercaptoethanol resulted in intramolecular rearrangement after acylation. Thiol nucleophiles which free amine, amino acid or carboxylic functional group were not successful under these reaction conditions. Chemical structure of the Michael adducts were elucidated by NMR spectroscopy and mass spectrometry. The α- and β-stereochemistry were confirmed by X-ray crystallography of the representative thiogalactoside **21** and **23**, and compared with the ^{1}H NMR coupling constants of the anomeric proton signals.

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APPENDIX

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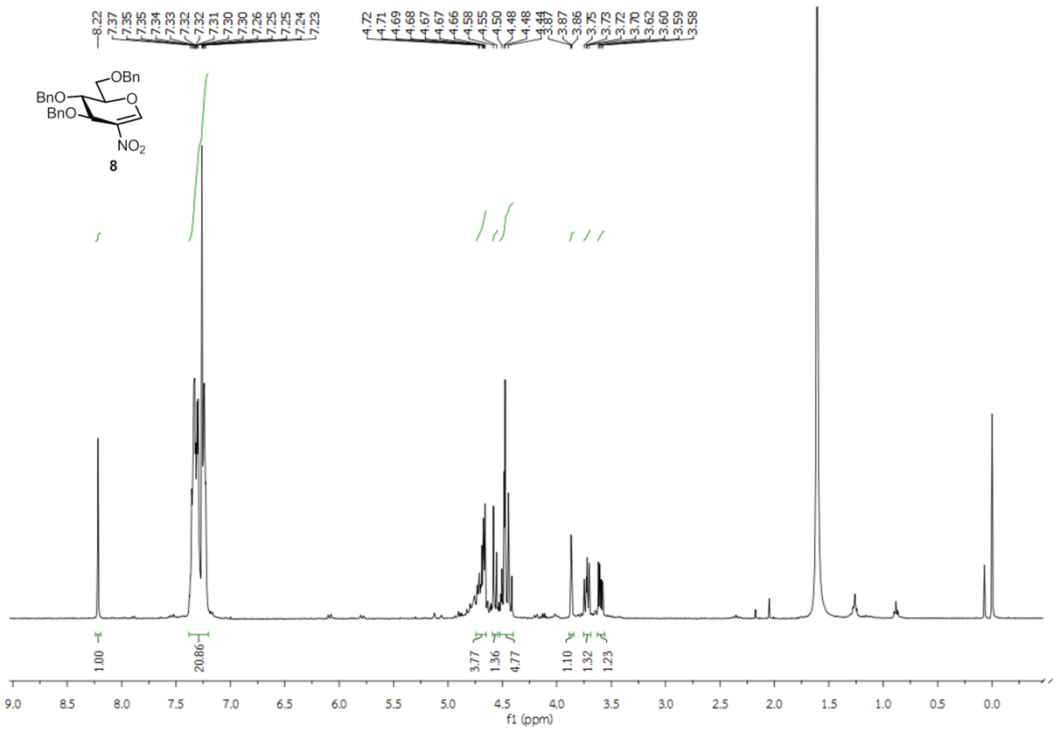

Figure A1 ^{1}H NMR spectrum of compound **8** (400 Hz, $CDCl_3$).

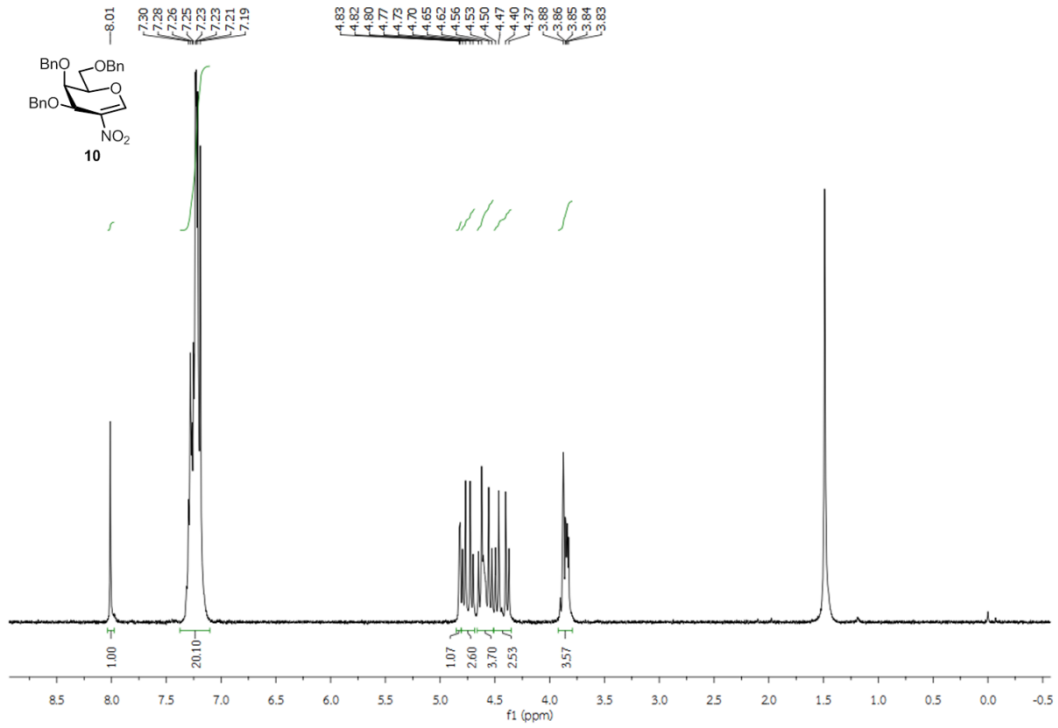

Figure A2 ^{1}H NMR spectrum of compound **10** (400 Hz, $CDCl_3$).

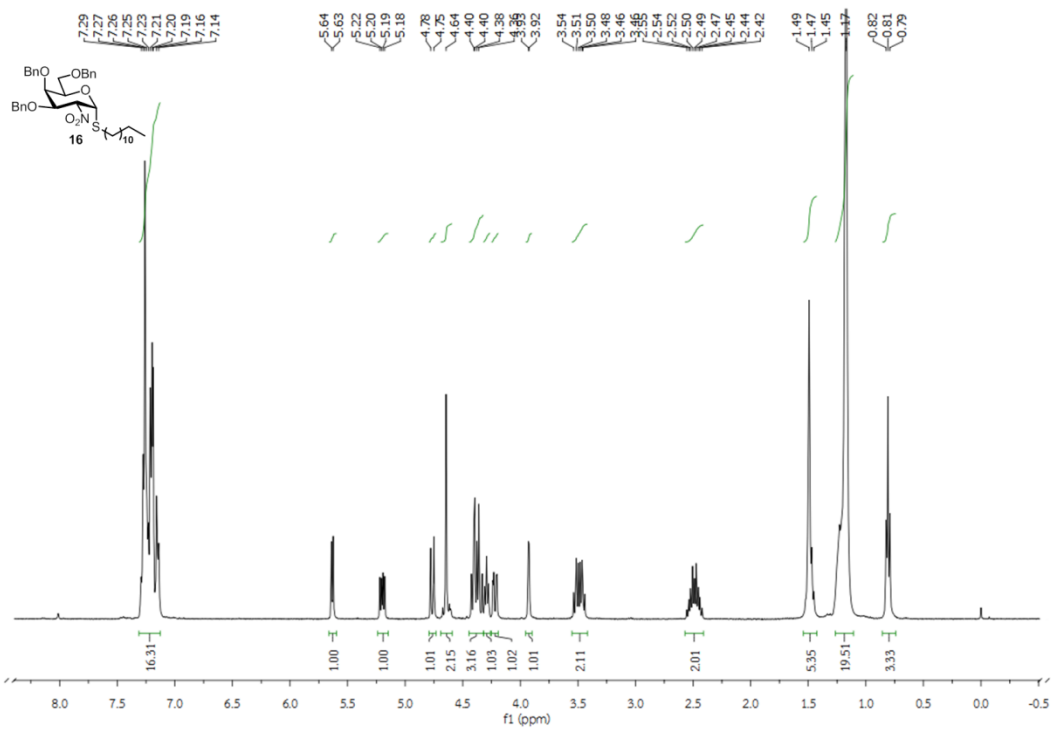

Figure A3 ^{1}H NMR spectrum of compound **16** (400 Hz, $CDCl_3$).

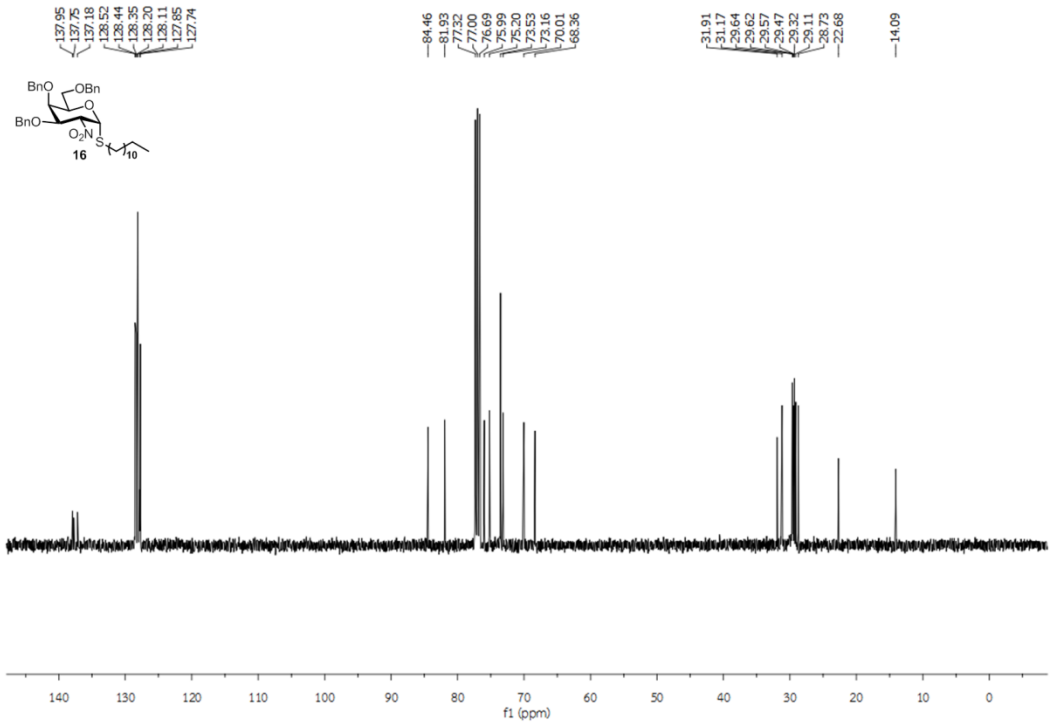

Figure A4 ^{13}C NMR spectrum of compound **16** (100 Hz, $CDCl_3$).

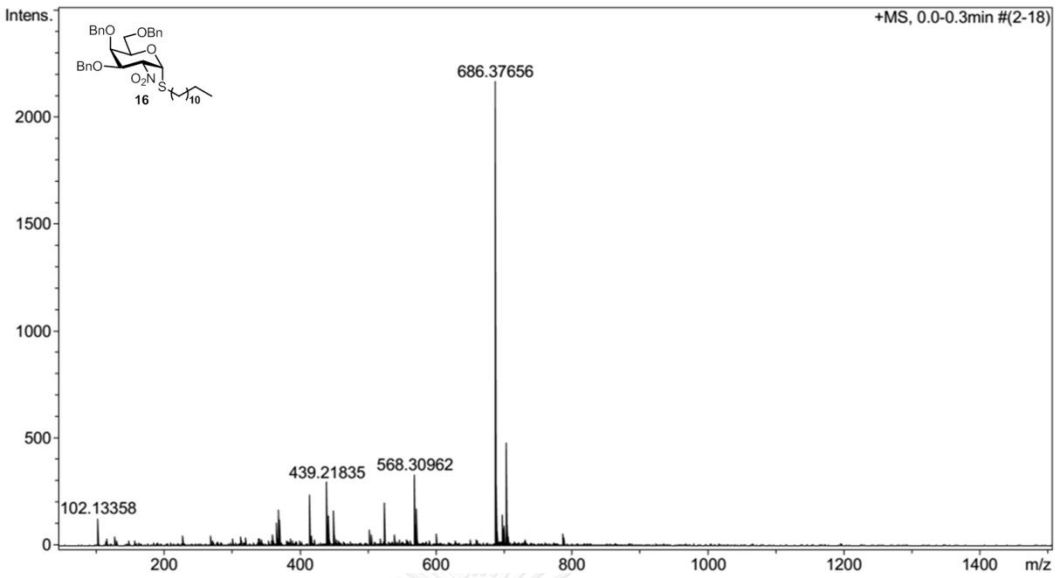

Figure A5 Mass spectrum of compound **16**.

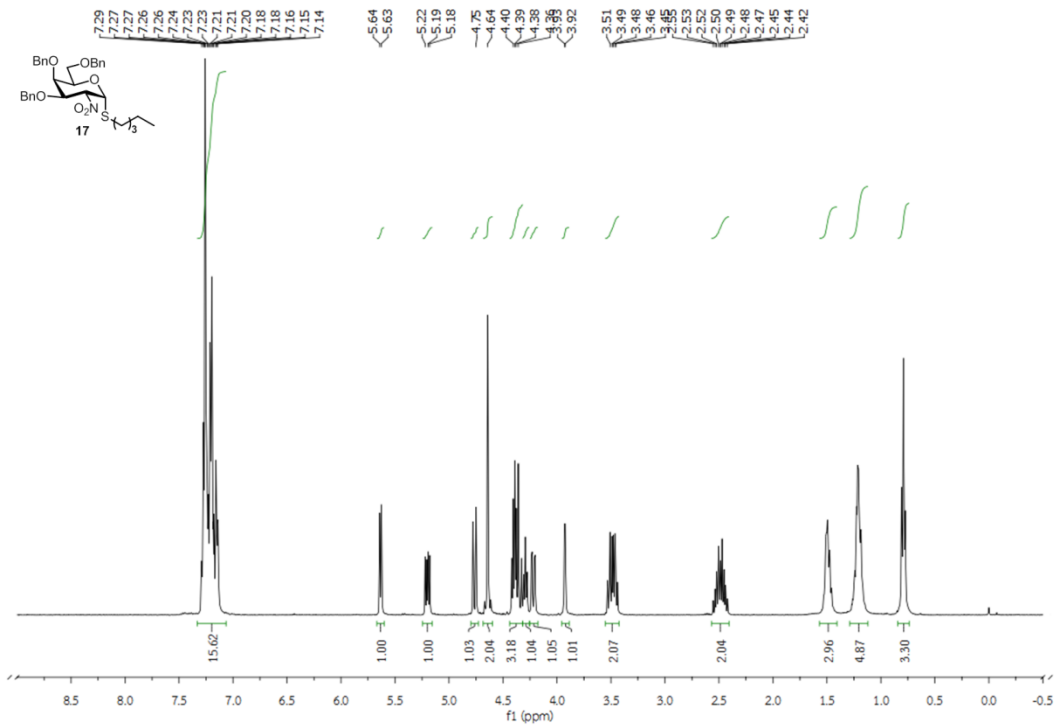

Figure A6 ^{1}H NMR spectrum of compound **17** (400 Hz, $CDCl_3$).

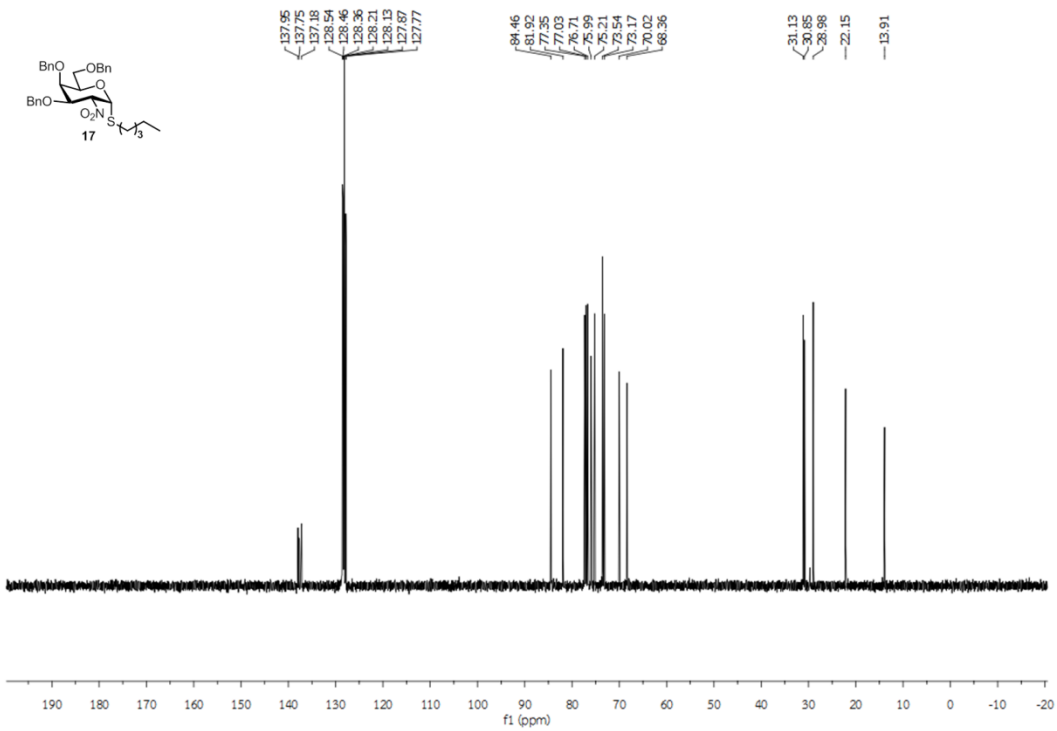

Figure A7 ^{13}C NMR spectrum of compound **17** (100 Hz, $CDCl_3$).

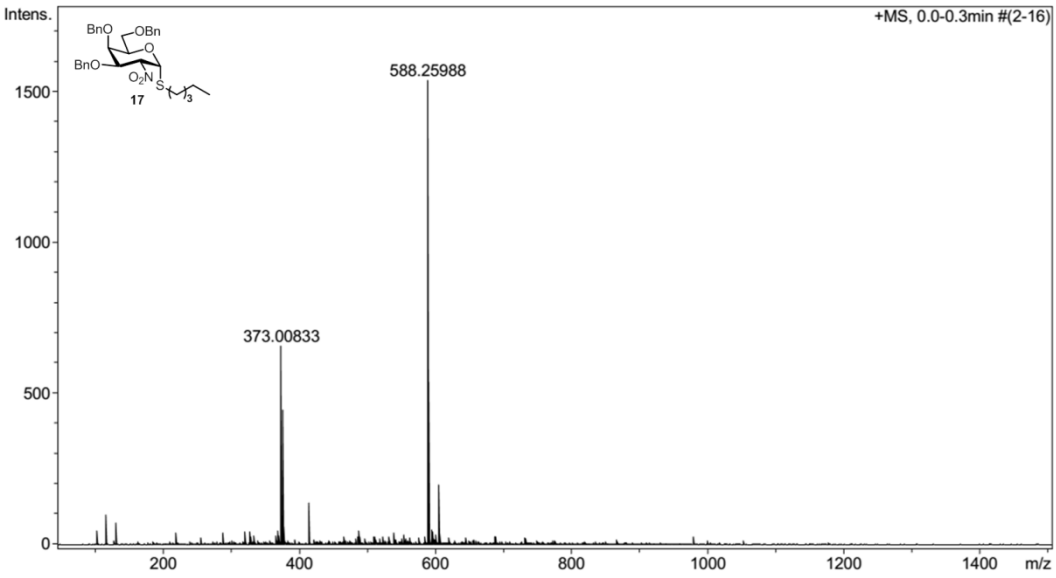

Figure A8 Mass spectrum of compound **16**.

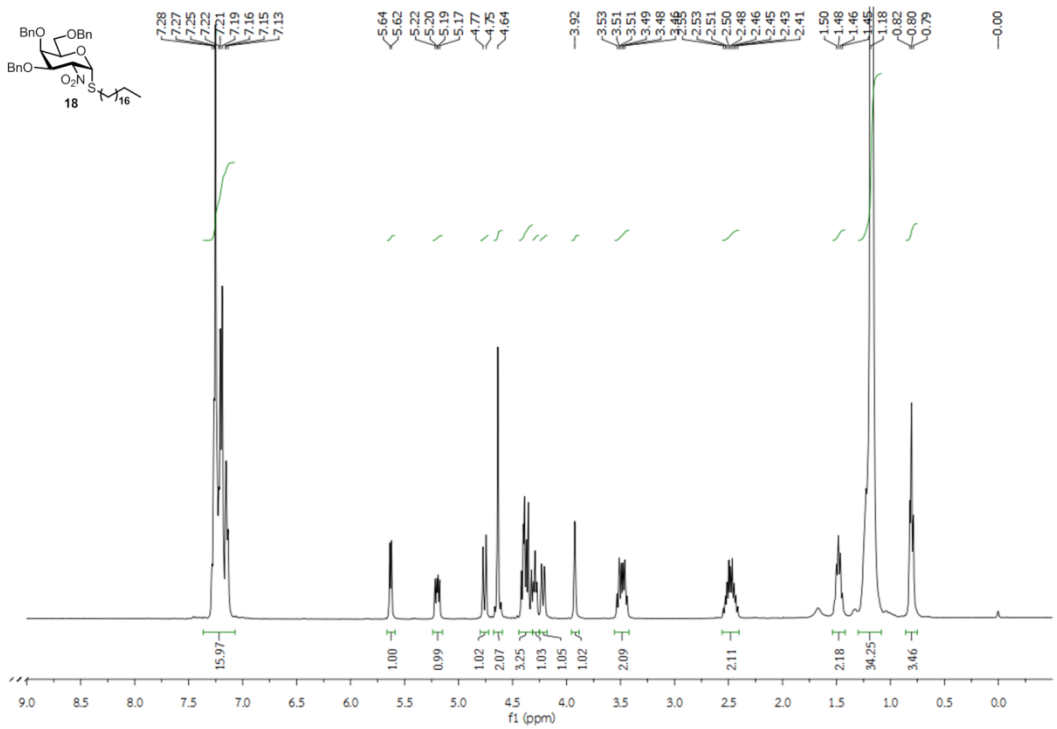

Figure A9 ^{1}H NMR spectrum of compound **18** (400 Hz, $CDCl_3$).

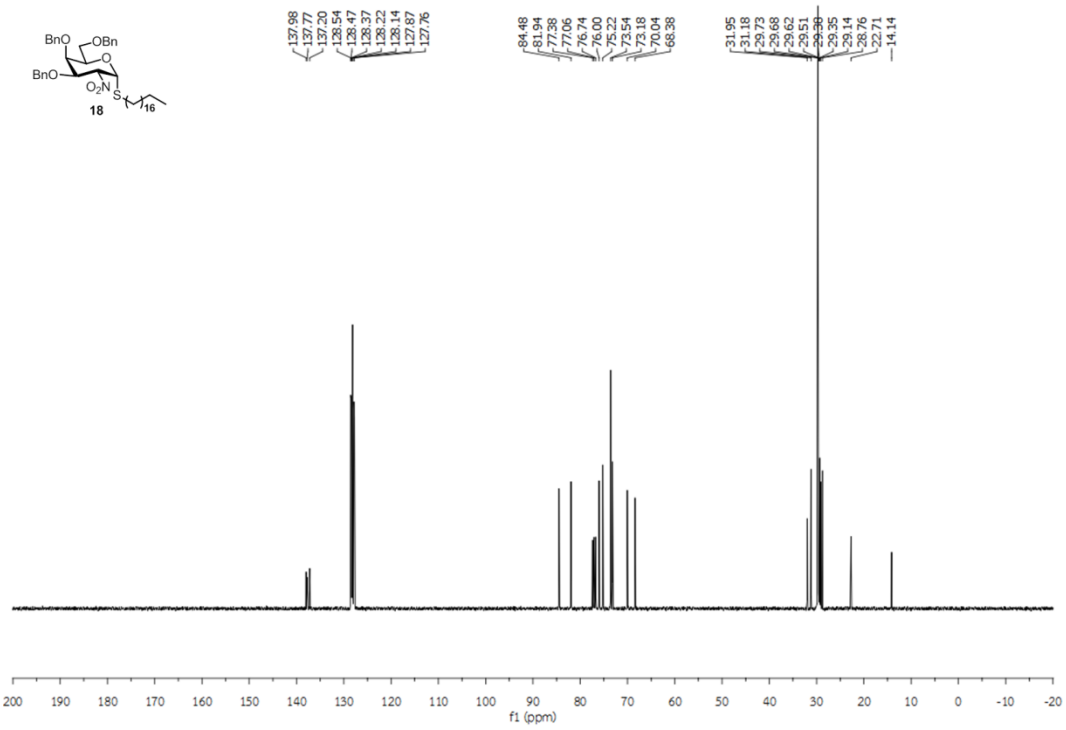

Figure A10 ^{13}C NMR spectrum of compound **18** (100 Hz, $CDCl_3$).

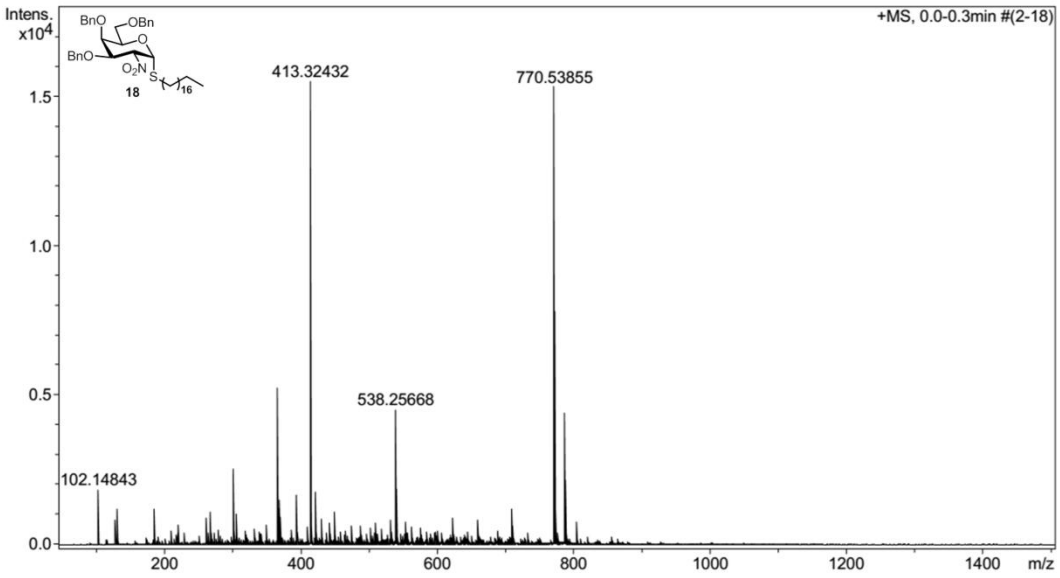

Figure A11 Mass spectrum of compound **18.**

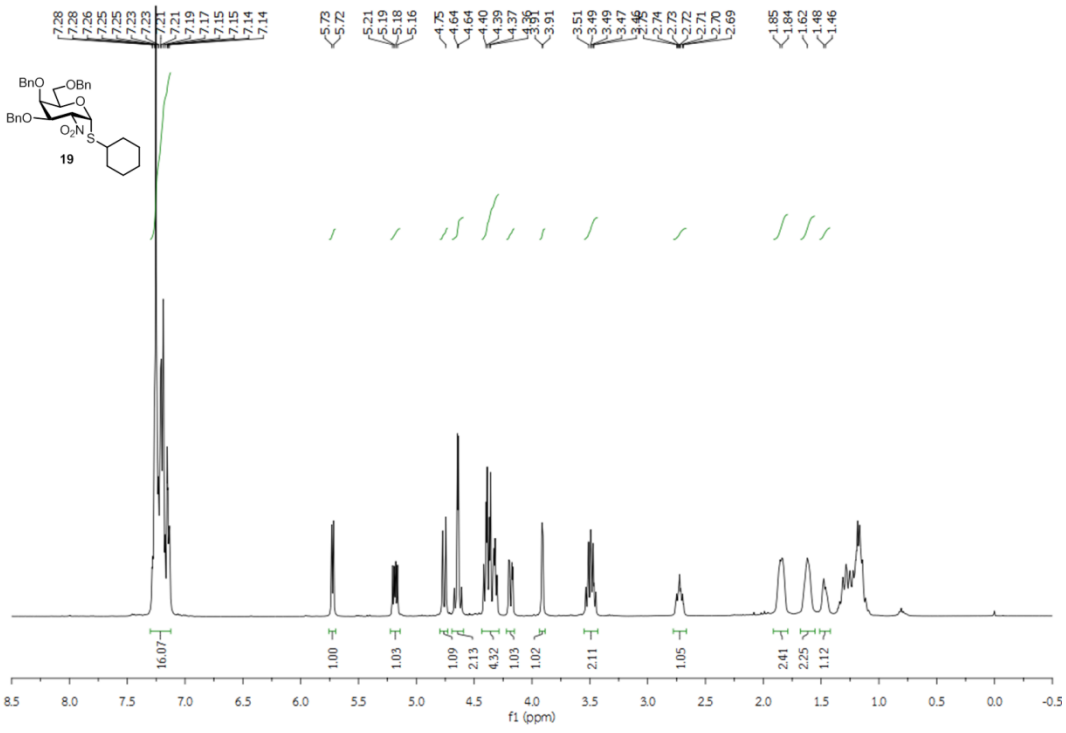

Figure A12 ^{1}H NMR spectrum of compound **19** (400 Hz, $CDCl_3$).

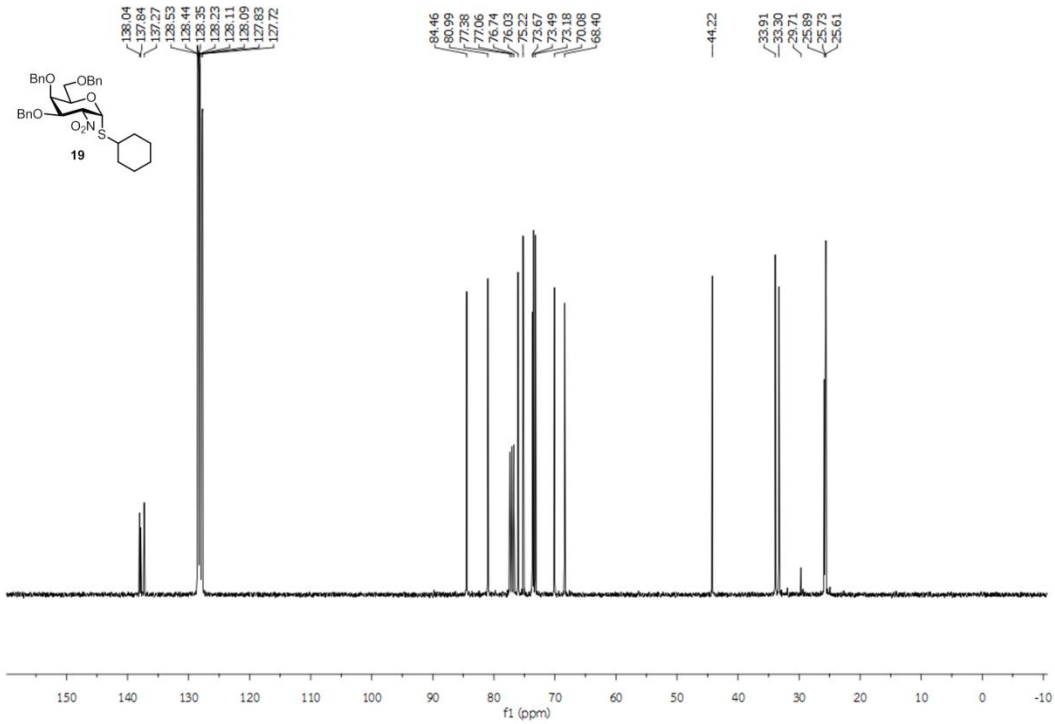

Figure A13 ^{13}C NMR spectrum of compound **19** (100 Hz, $CDCl_3$).

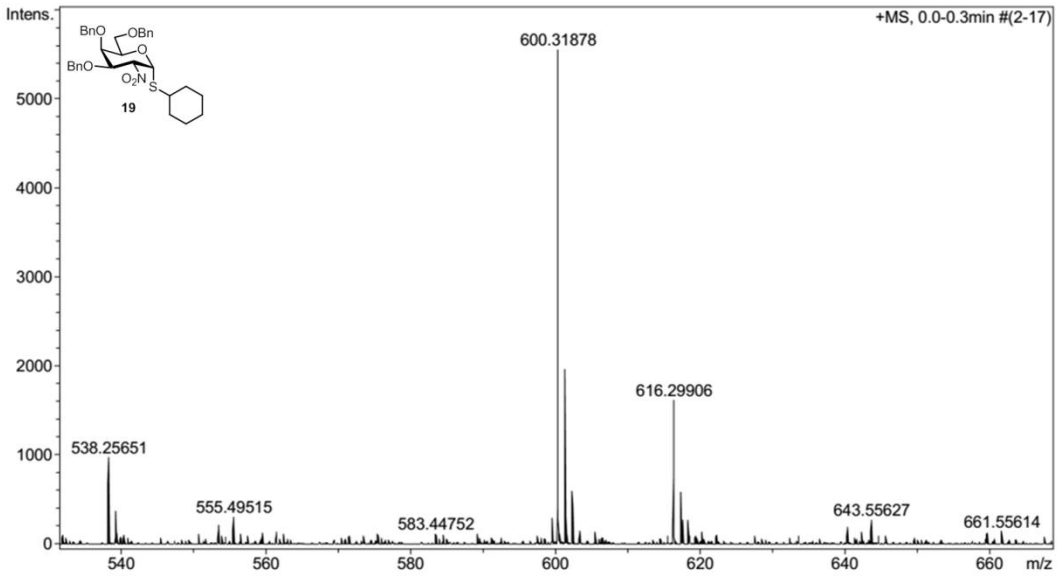

Figure A14 Mass spectrum of compound **19**.

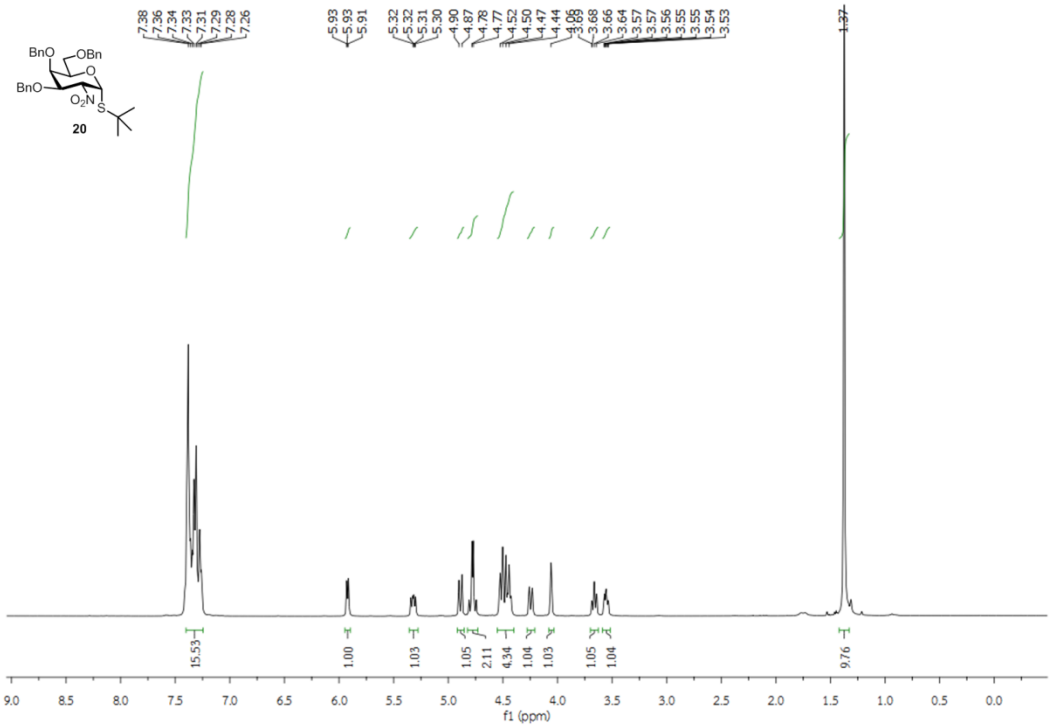

Figure A15 ^{1}H NMR spectrum of compound **20** (400 Hz, $CDCl_3$).

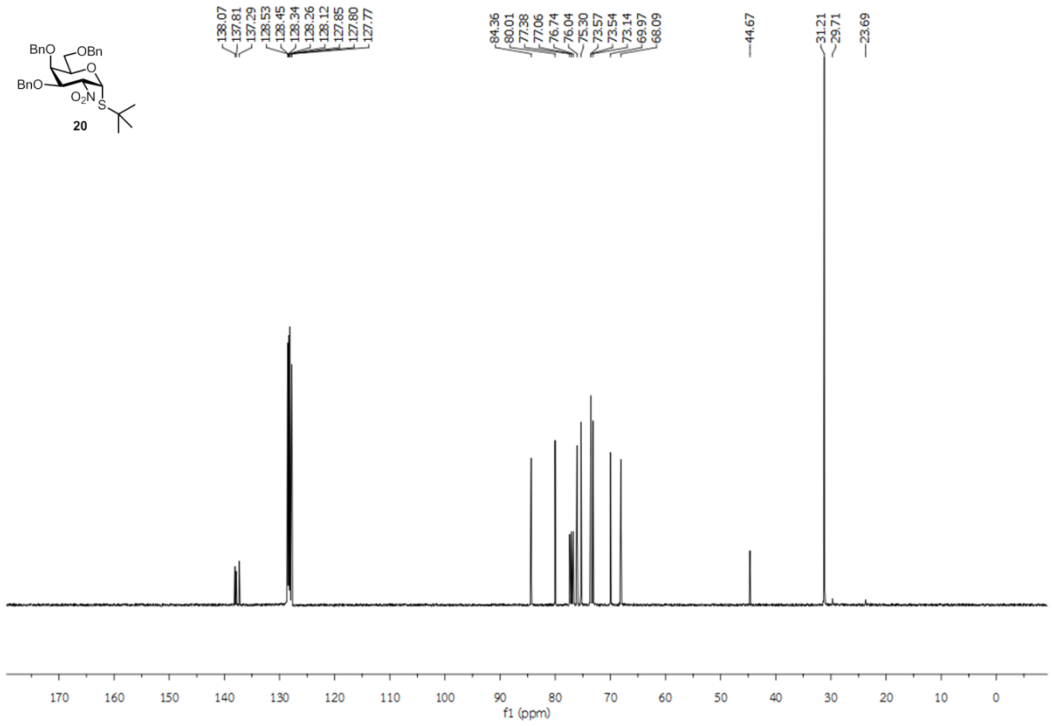

Figure A16 ^{13}C NMR spectrum of compound **20** (100 Hz, $CDCl_3$).

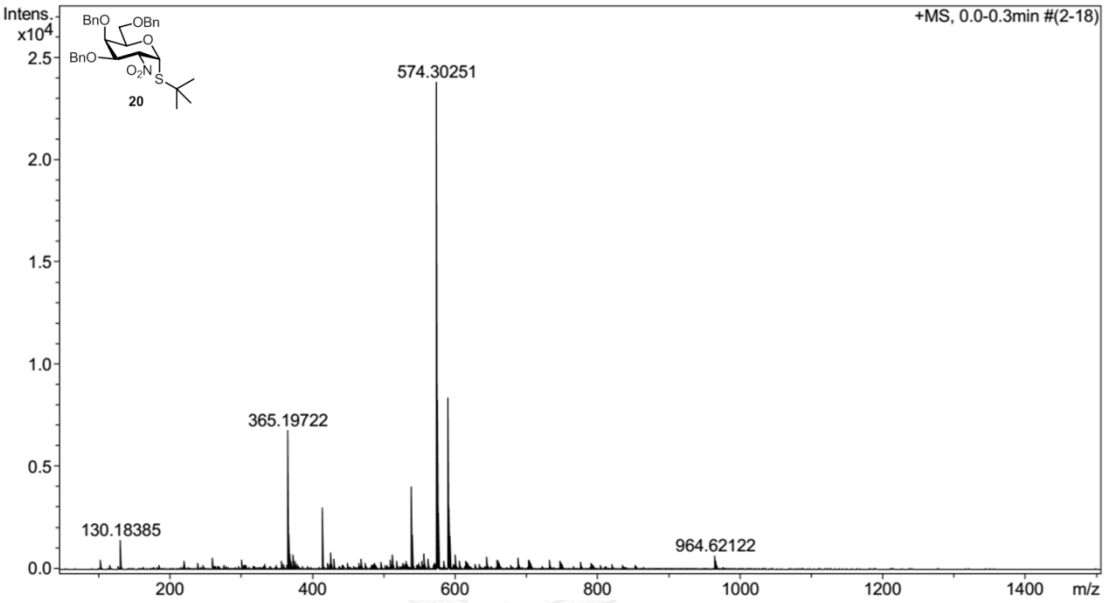

Figure A17 Mass spectrum of compound **20**.

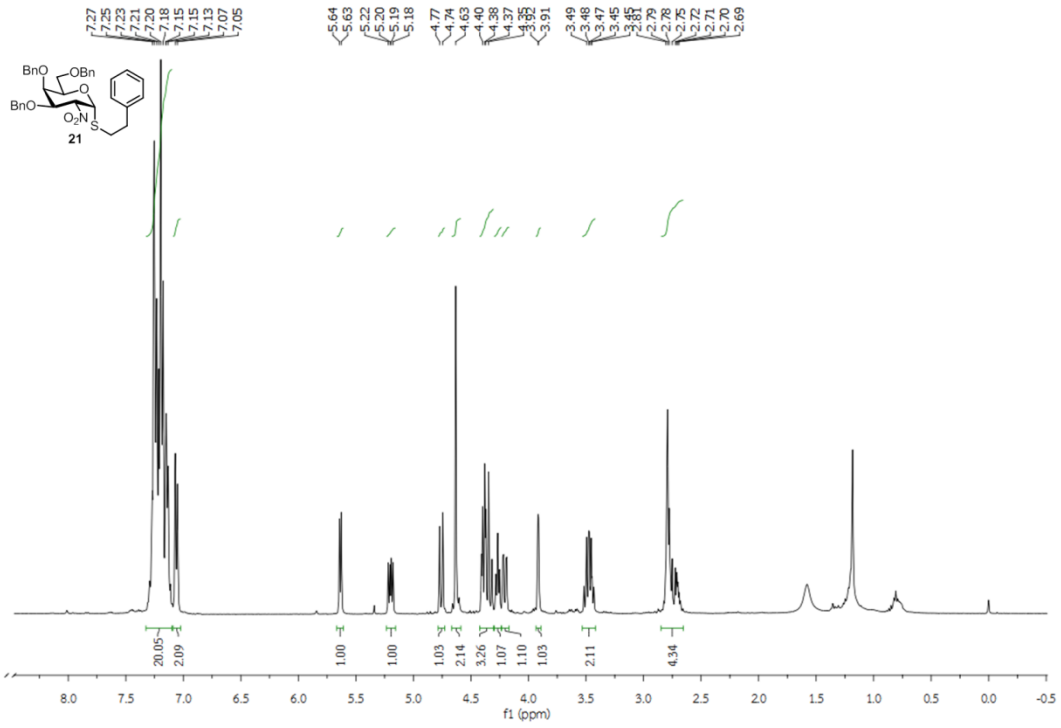

Figure A18 ^{1}H NMR spectrum of compound **21** (400 Hz, $CDCl_3$).

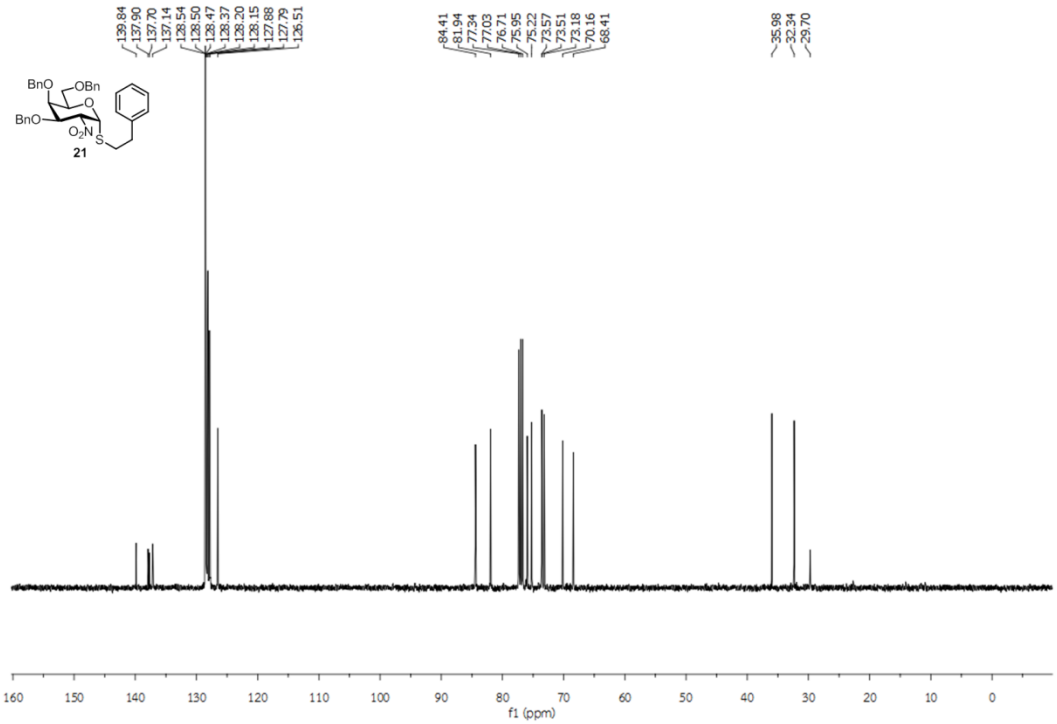

Figure A19 ^{13}C NMR spectrum of compound **21** (100 Hz, $CDCl_3$).

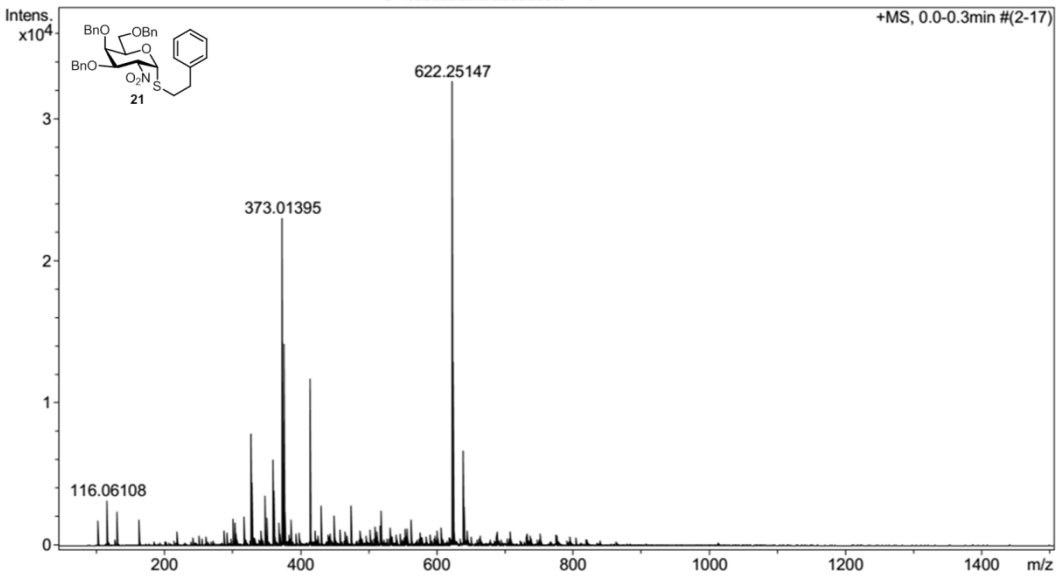

Figure A20 Mass spectrum of compound **21.**

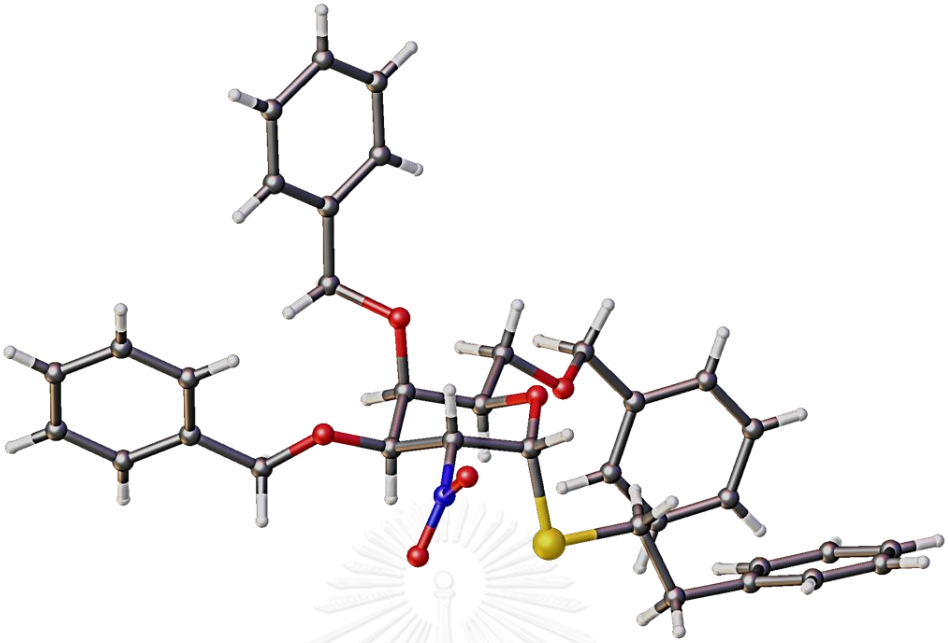

Figure A21 X-ray structure of compound **21**.

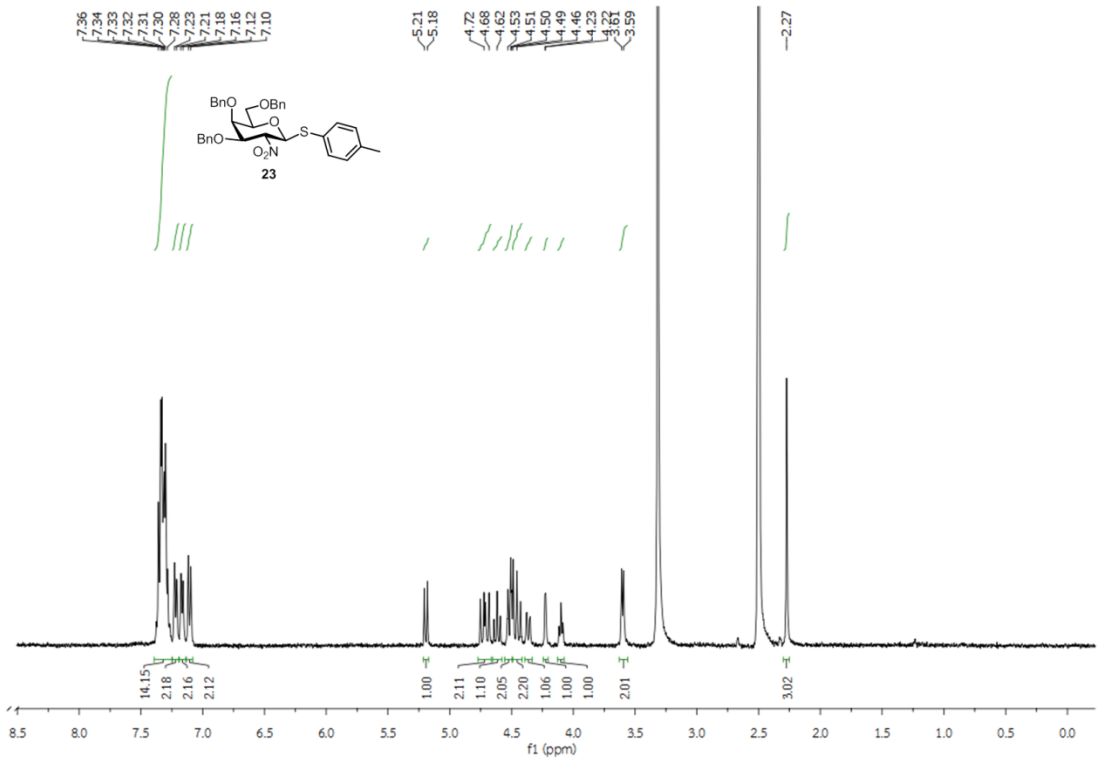

Figure A22 ^{1}H NMR spectrum of compound **23** (400 Hz, DMSO).

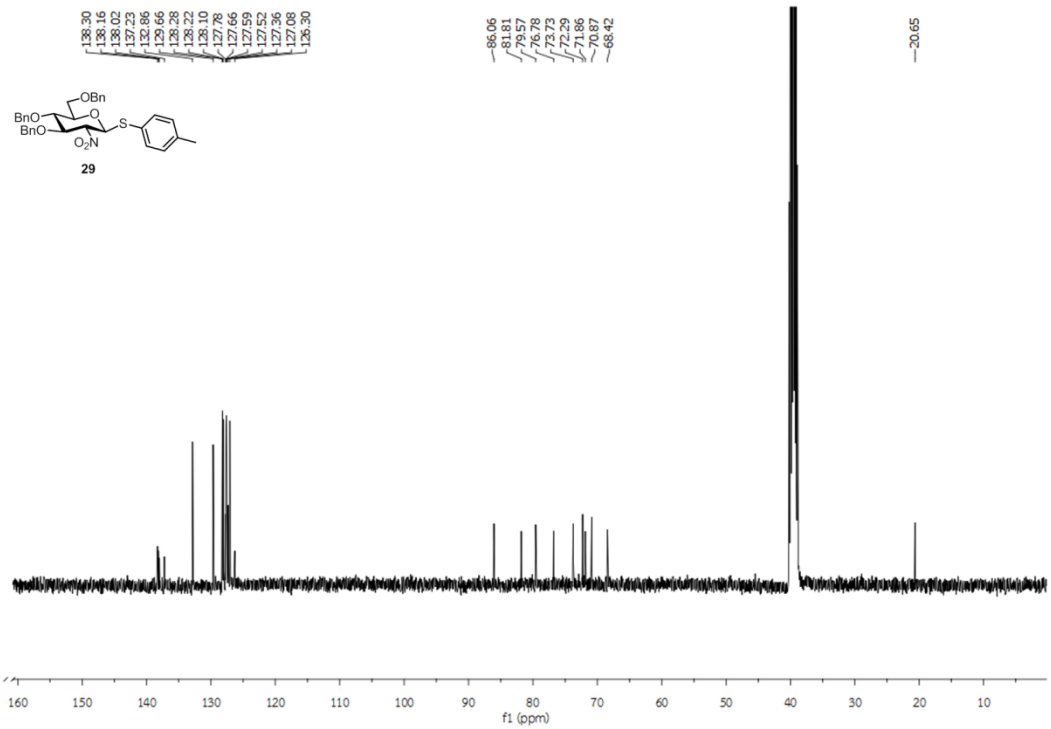

Figure A23 ^{13}C NMR spectrum of compound **23** (100 Hz, DMSO).

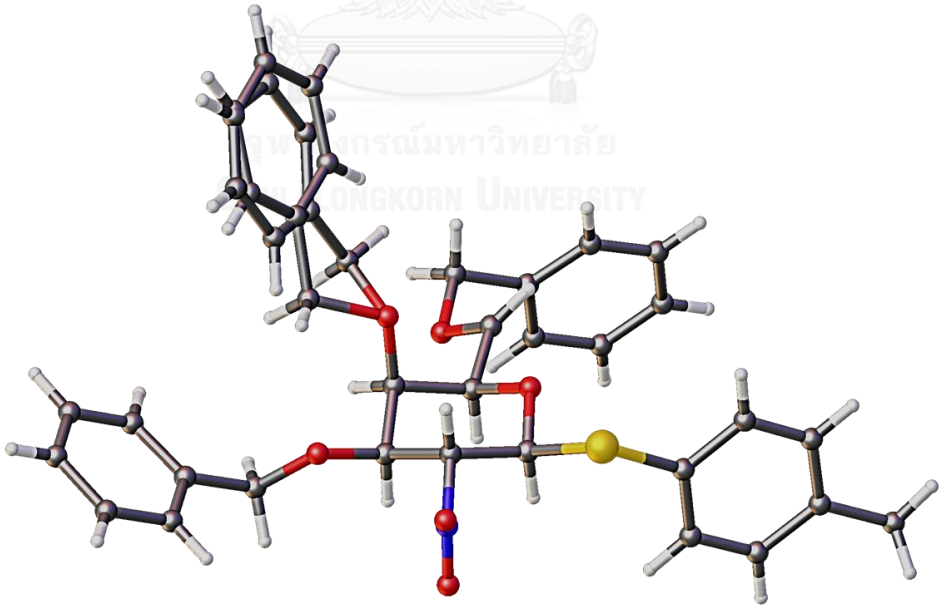

Figure A24 X-ray structure of compound **23**.

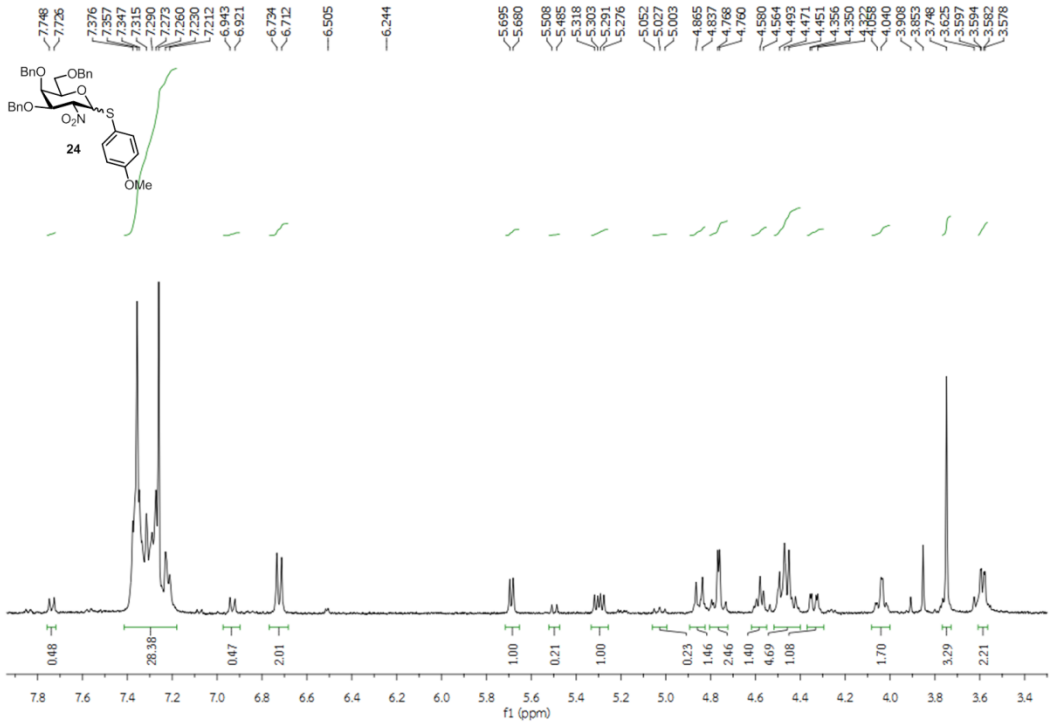

Figure A25 ^{1}H NMR spectrum of compound **24** (400 Hz, $CDCl_3$).

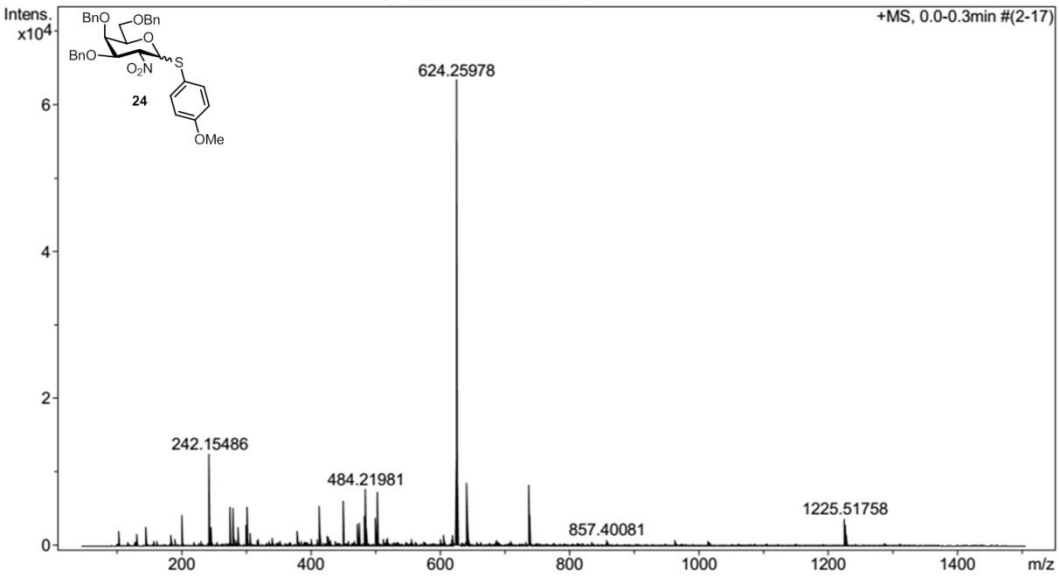

Figure A26 Mass spectrum of compound **24.**

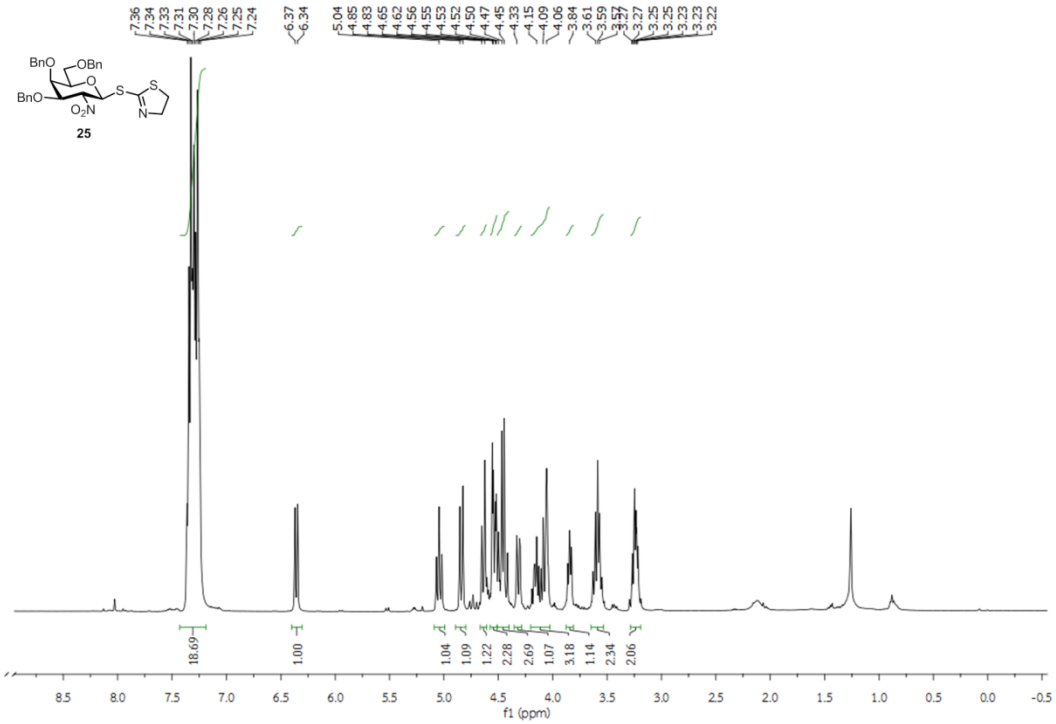

Figure A27 ^{1}H NMR spectrum of compound **25** (400 Hz, $CDCl_3$).

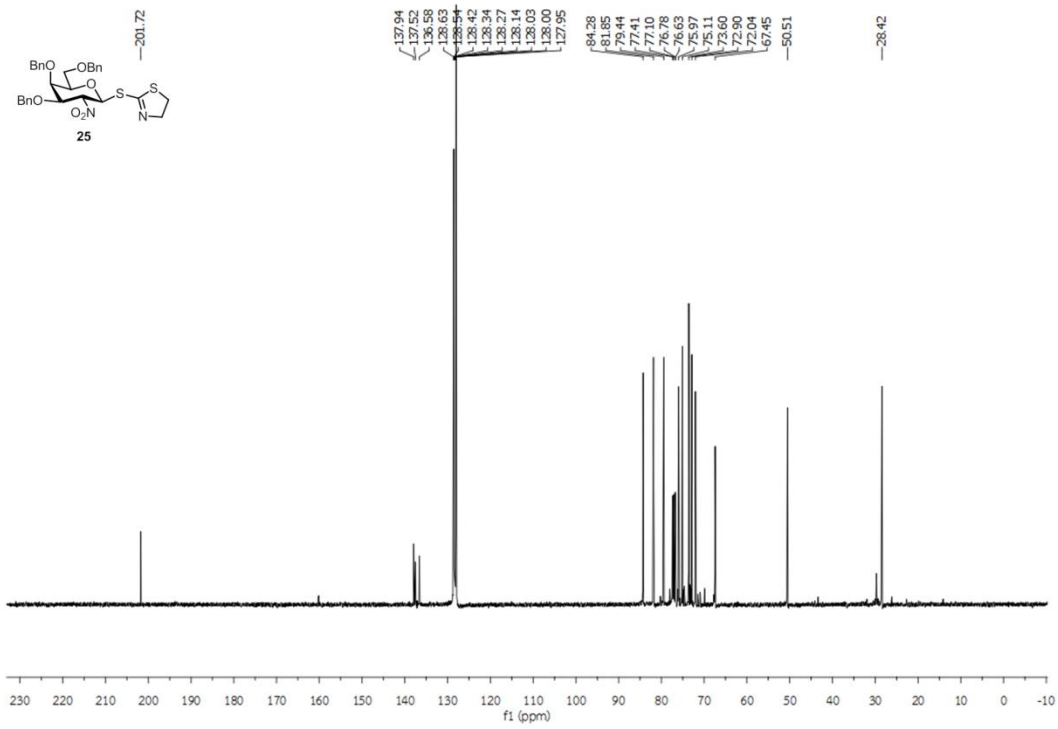

Figure A28 ^{13}C NMR spectrum of compound **25** (100 Hz, $CDCl_3$).

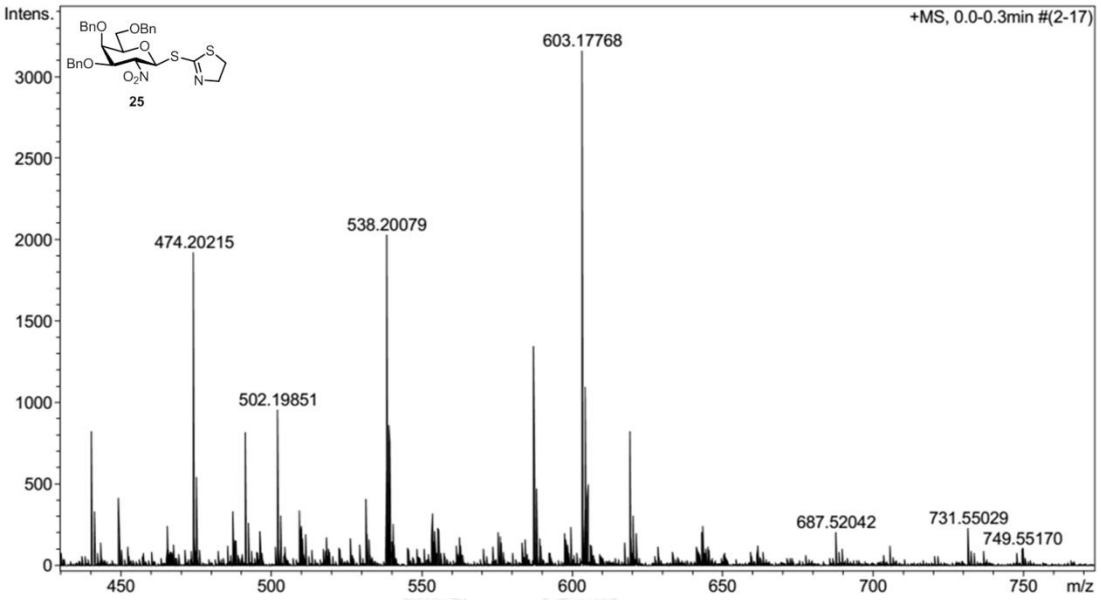

Figure A29 Mass spectrum of compound **25**.

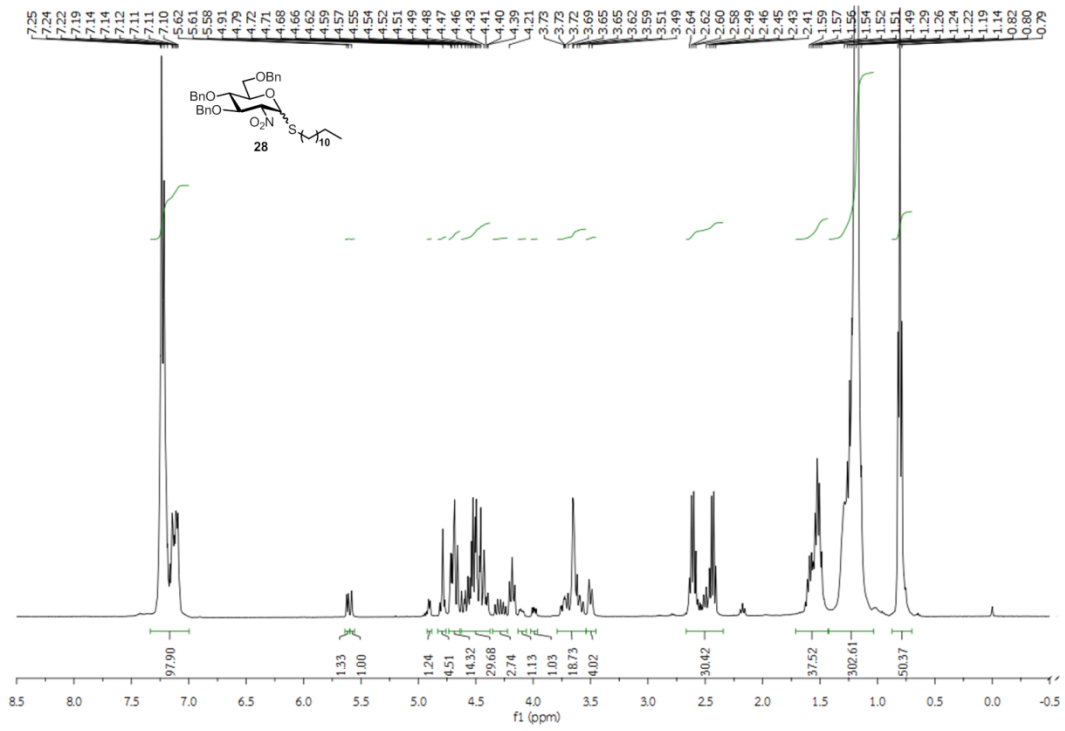

Figure A30 ^{1}H NMR spectrum of compound **28** (400 Hz, $CDCl_3$).

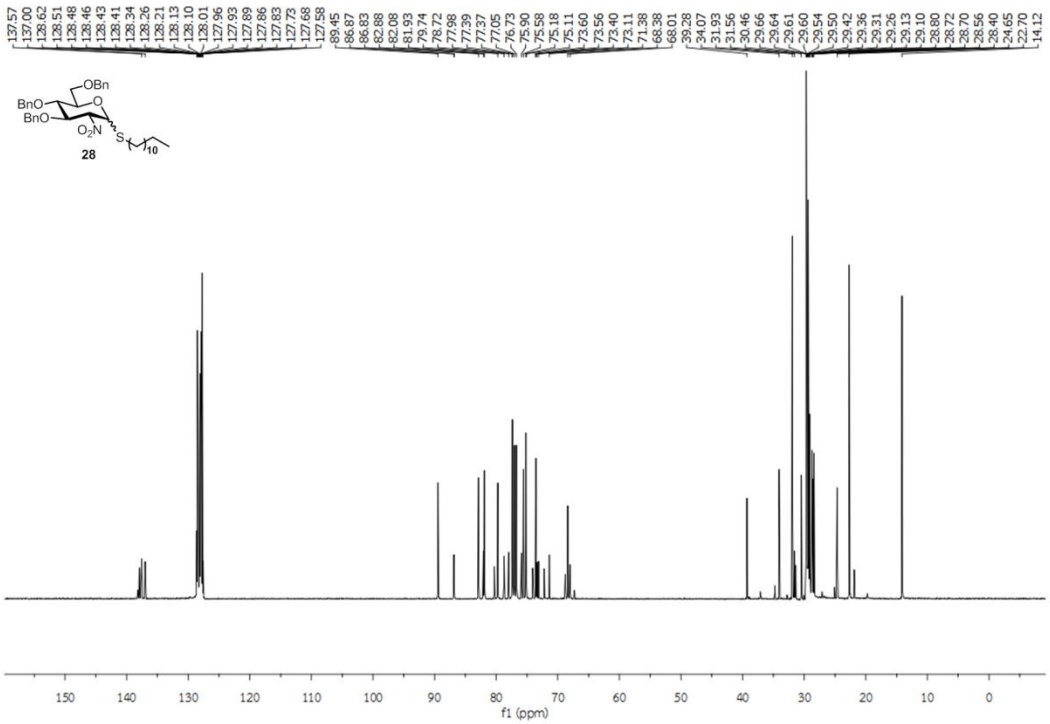

Figure A31 ^{13}C NMR spectrum of compound **28** (100 Hz, $CDCl_3$).

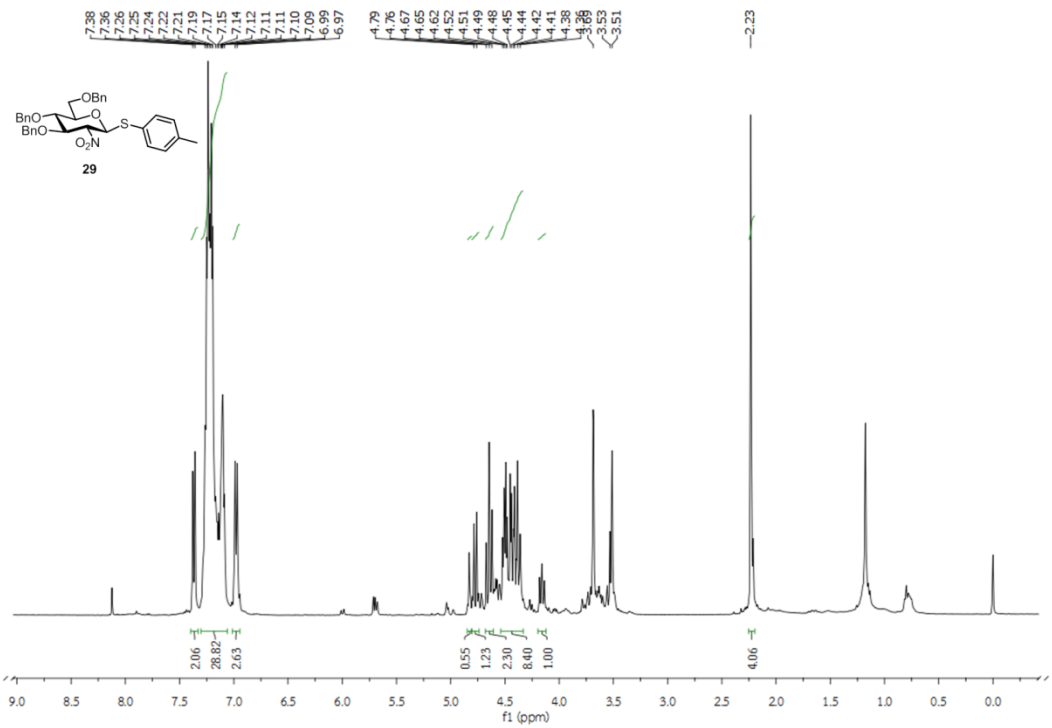

Figure A32 ^{1}H NMR spectrum of compound **29** (400 Hz, $CDCl_3$).

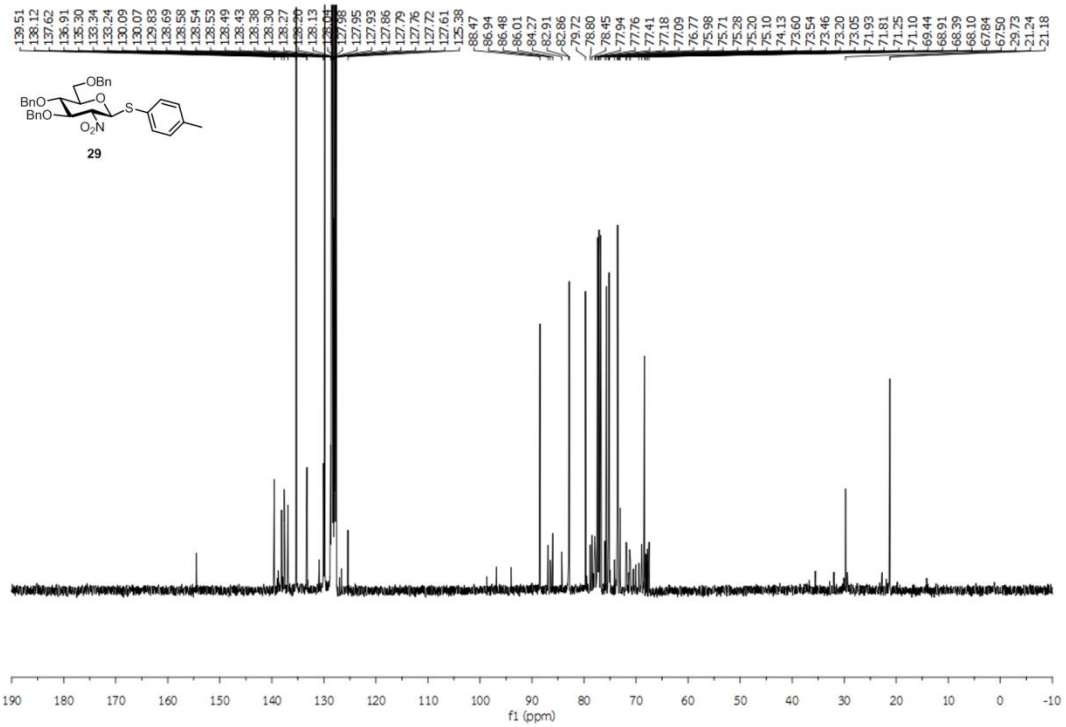

Figure A33 ^{13}C NMR spectrum of compound **29** (100 Hz, $CDCl_3$).

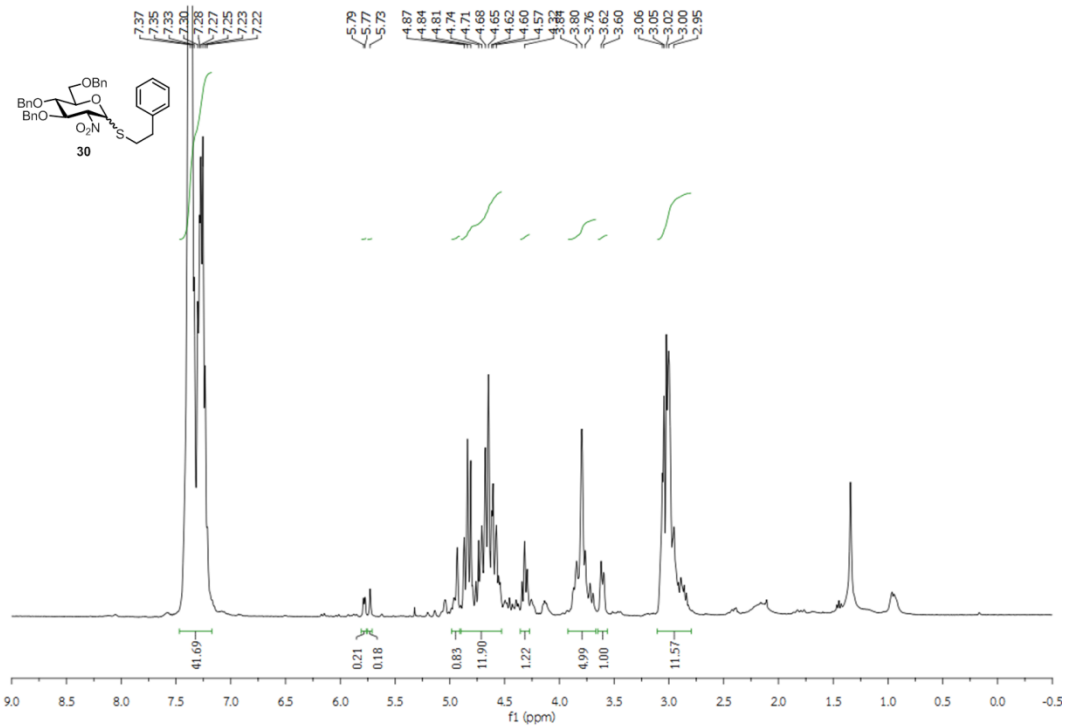

Figure A34 ^{1}H NMR spectrum of compound **30** (400 Hz, $CDCl_3$).

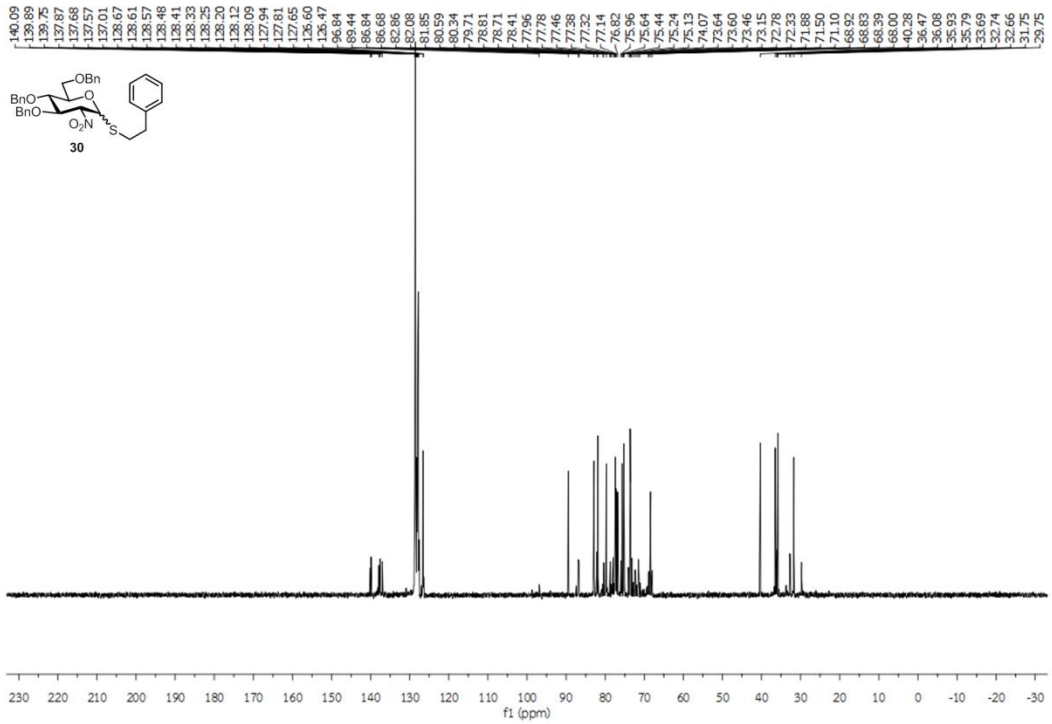

Figure A35 ^{13}C NMR spectrum of compound **30** (100 Hz, $CDCl_3$).

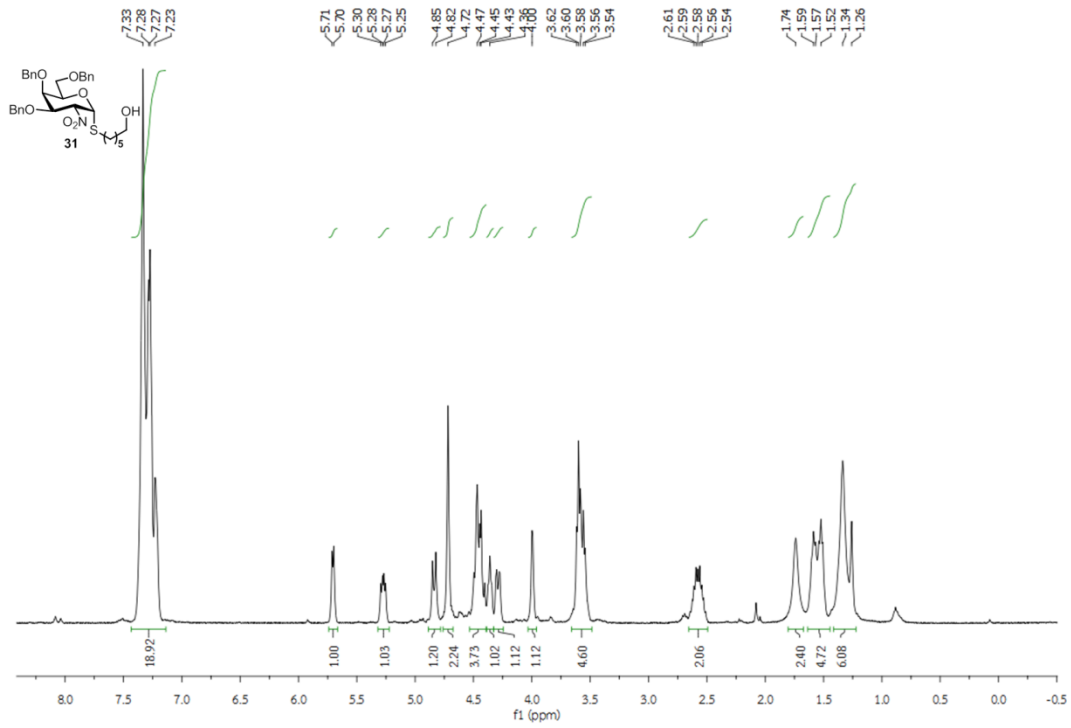

Figure A36 ^{1}H NMR spectrum of compound **31** (400 Hz, $CDCl_3$).

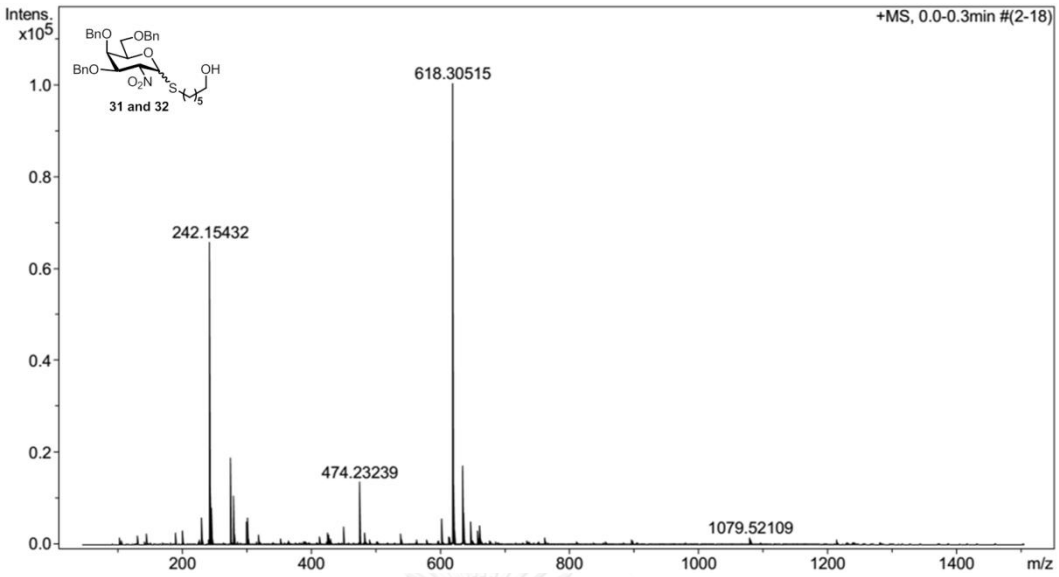

Figure A37 Mass spectrum of compound **31** and **32.**

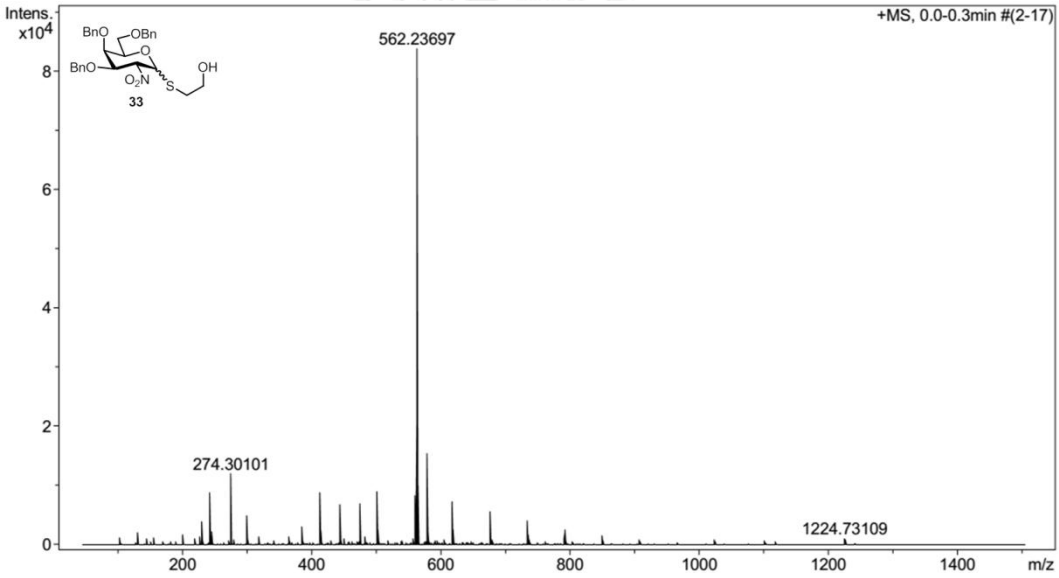

Figure A38 Mass spectrum of compound **33.**

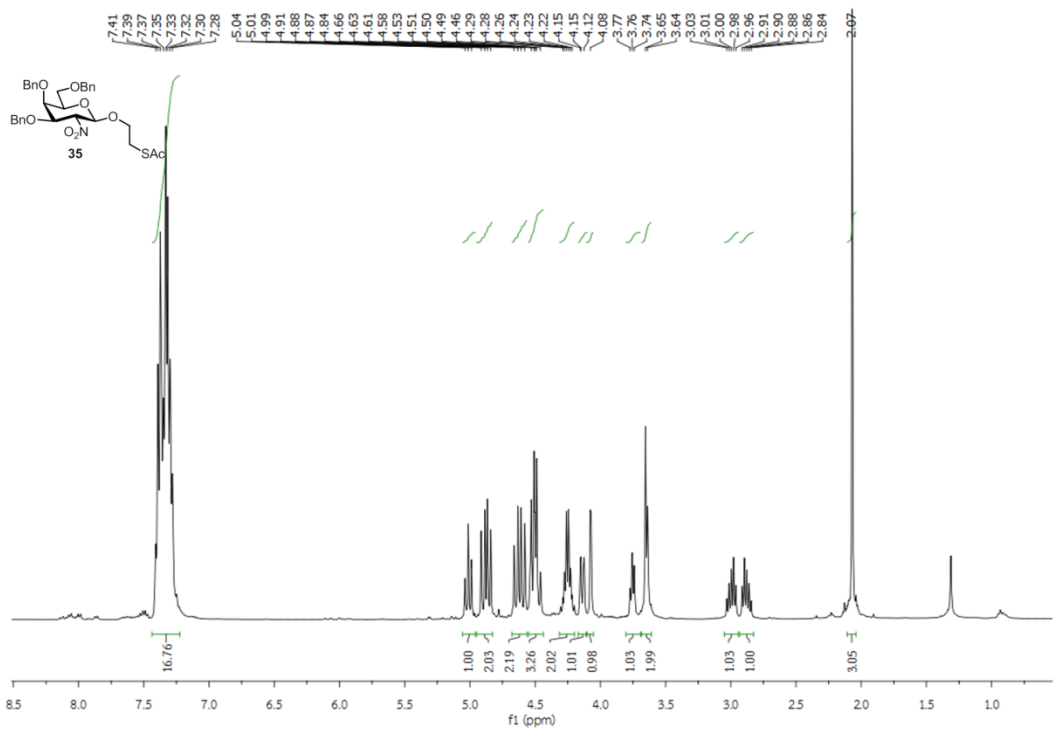

Figure A39 ^{1}H NMR spectrum of compound **35** (400 Hz, $CDCl_3$).

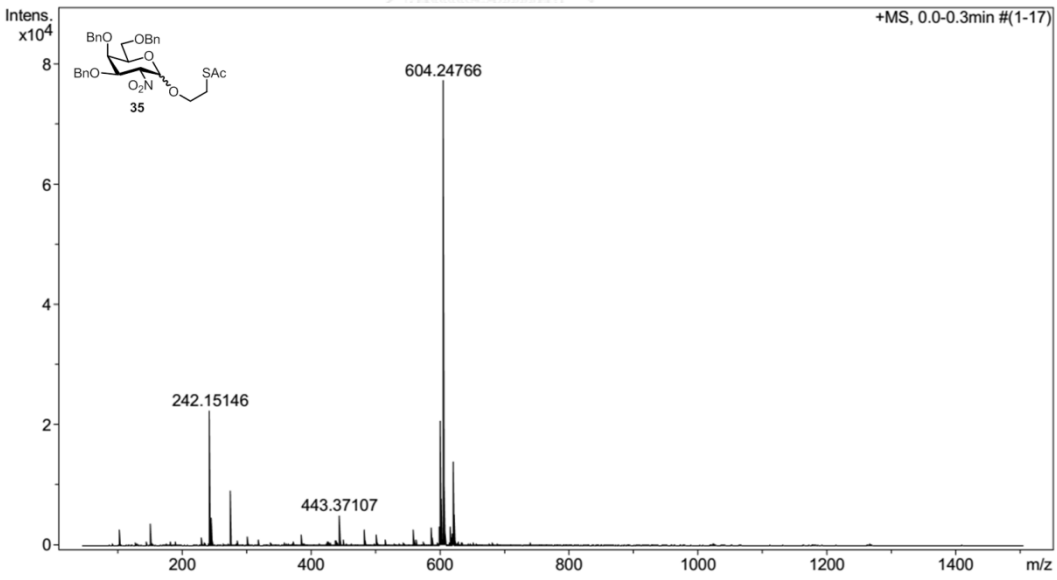

Figure A40 Mass spectrum of compound **35.**

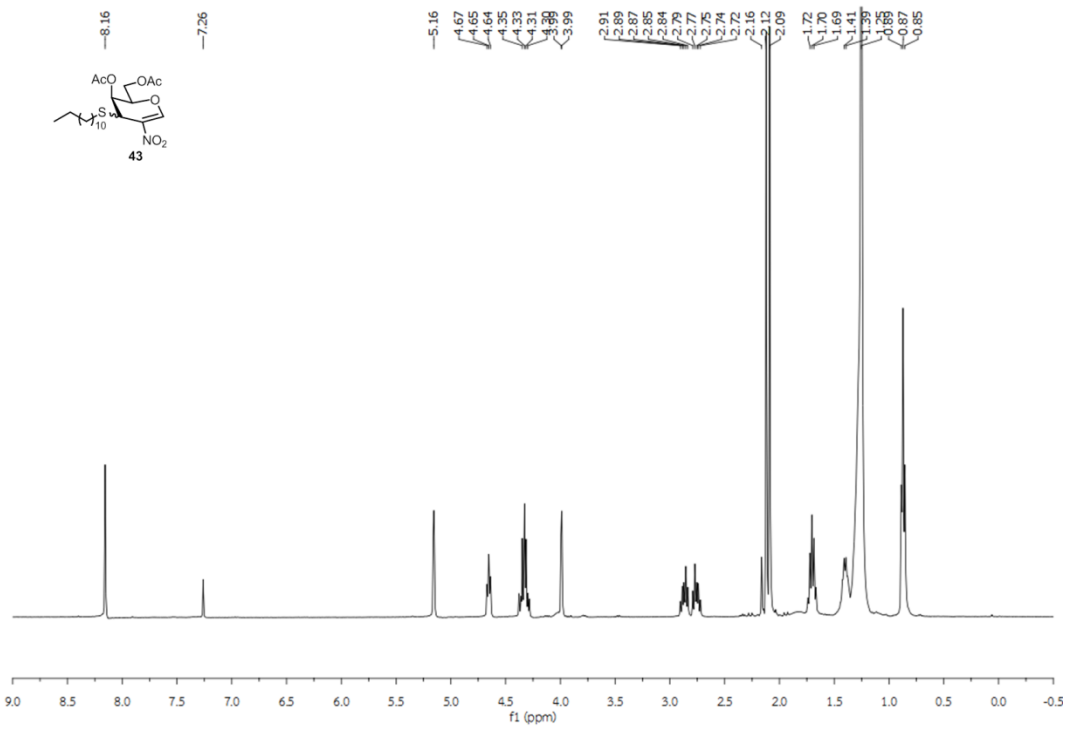

Figure A41 ^{1}H NMR spectrum of compound **43** (400 Hz, $CDCl_3$).

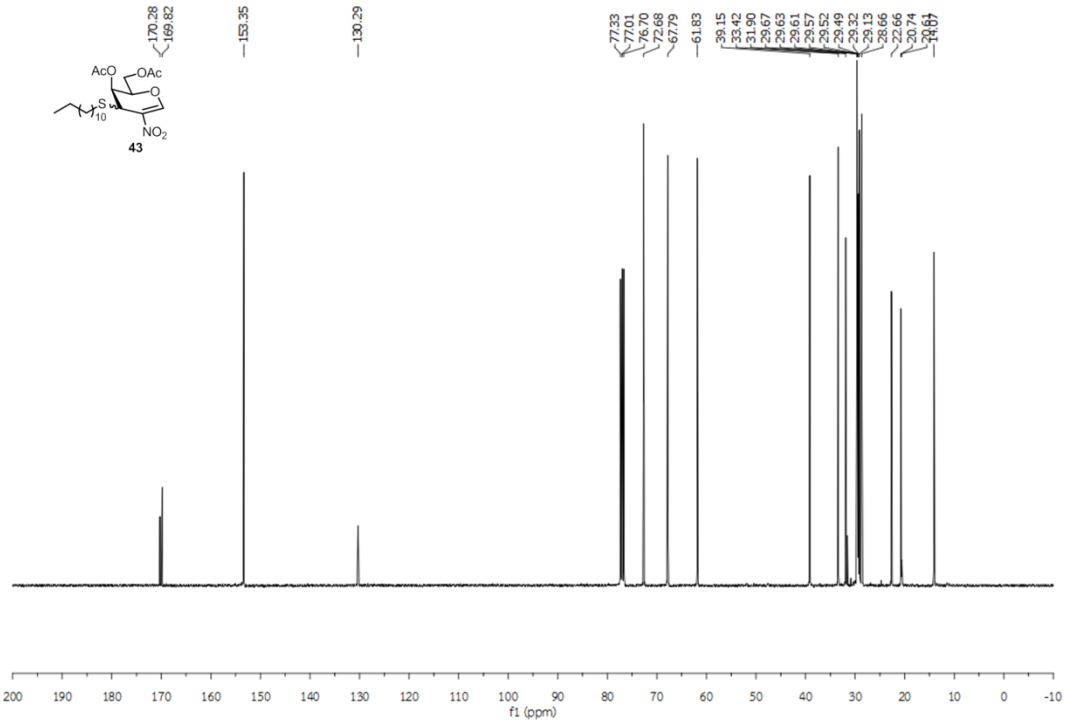

Figure A42 ^{13}C NMR spectrum of compound **43** (100 Hz, $CDCl_3$).

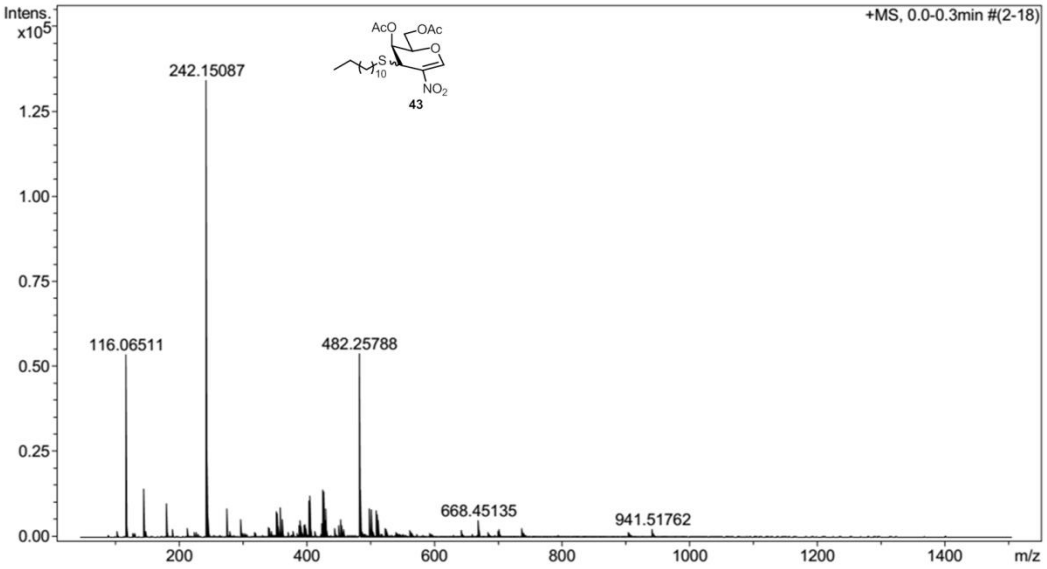

Figure A43 Mass spectrum of compound **43.**

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VITA

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