การสังเคราะห์ไทโอฟิวราโนไซด์โดยดีไฮเดรทีฟไกลโคซิเลชันในตัวกลางไมเซลล์

นางสาวตรีชฎา รัฐจักร์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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SYNTHESIS OF THIOFURANOSIDES BY DEHYDRATIVE GLYCOSYLATION IN MICELLAR MEDIA

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A Thesis Submitted in Partial Fulfillment of the Requirements
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ตรีชฎา รัฐจักร์ : การสังเคราะห์ไทโอฟิวราโนไซด์โดยดีไฮเดรทีฟไกลโคซิเลชันในตัวกลางไมเซลล์ (SYNTHESIS OF THIOFURANOSIDES BY DEHYDRATIVE GLYCOSYLATION IN MICELLAR MEDIA) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ศ. ดร. ธีรยุทธ วิไลวัลย์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ผศ. ดร. ภาณุวัฒน์ ผดุงรส, 124 หน้า.

คณะผู้วิจัยได้พัฒนาการสังเคราะห์สารไทโอฟิวราโนไซด์ด้วยปฏิกิริยาดีไฮเดรทีฟไกลโคซิเลชันในตัวกลางไมเซลล์ โดยใช้น้ำเป็นตัวทำละลาย ซึ่งเป็นการสังเคราะห์ที่เป็นมิตรกับสิ่งแวดล้อม สารในกลุ่มไทโอฟิวราโนไซด์นั้นมีประโยชน์สามารถนำไปประยุกต์ใช้ได้อย่างหลากหลายเช่น เป็นสารตั้งต้นในการสังเคราะห์สารประกอบคาร์โบไฮเดรต เป็นสารออกฤทธิ์ทางชีวภาพและเป็นสารลดแรงตึงผิวเลียนแบบธรรมชาติโดยงานวิจัยนี้ คณะผู้วิจัยเลือกใช้ dodecylbenzenesulfonic acid (DBSA) ซึ่งเป็นสารลดแรงตึงผิวที่มีฤทธิ์เป็นกรด หาซื้อได้ง่ายและราคาถูก DBSA สามารถก่อตัวเป็นไมเซลล์ในตัวทำละลายที่เป็นน้ำ จึงช่วยเพิ่มประสิทธิภาพการละลายของสารประกอบอินทรีย์ได้ ช่วยเพิ่มอัตราเร็วของการเกิดปฏิกิริยาไกลโคซิลเลชัน ซึ่งงานวิจัยนี้ ผู้วิจัยศึกษาปฏิกิริยาดีไฮเดรทีฟไกลโคซิเลชันของน้ำตาลฟิวราโนไซด์และไพราโนไซด์กับสารประกอบไทออลชนิดอะลิฟาติก อะโรเมติกและเฮทเทอโรไซคลิก โดยใช้การกระตุ้นด้วยคลื่นไมโครเวฟ ทำให้ช่วยลดระยะเวลาในการสังเคราะห์และได้ปริมาณผลิตภัณฑ์เพิ่มขึ้นด้วย นอกจากนั้น ผู้วิจัยได้ศึกษาอุณหภูมิและปริมาณ DBSA ที่เหมาะสมต่อการสังเคราะห์และพบว่า เมื่อใช้ DBSA ปริมาณ 100 mol% ที่อุณหภูมิ 80 องศาเซลเซียส สามารถสังเคราะห์ไทโอฟิวราโนไซด์ได้ทั้งชนิดที่เป็นอะลิฟาติกและอะโรเมติกจากสารตั้งต้นแลคทอลในปริมาณปานกลาง (24–72%) อีกทั้งการสังเคราะห์ที่พัฒนาขึ้นนั้น ไม่พบผลิตภัณฑ์ข้างเคียงชนิดไดไทโออะซิแทล ซึ่งเกิดจากการเปิดวงน้ำตาลเหมือนกับรายงานที่มีมาก่อนหน้านี้ ท้ายที่สุดวิธีการสังเคราะห์ใหม่นี้สามารถทำได้ง่าย สะดวก และไม่จำเป็นต้องใช้สภาวะที่ปราศจากน้ำเหมือนวิธีที่รายงานมาก่อนหน้า

ภาควิชา เคมี	ลายมือชื่อนิสิต .....
สาขาวิชา เคมี	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
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TRICHADA RATTHACHAG: SYNTHESIS OF THIOFURANOSIDES BY DEHYDRATIVE GLYCOSYLATION IN MICELLAR MEDIA. ADVISOR: PROF. TIRAYUT VILAIVAN, D.Phil., CO-ADVISOR: ASST. PROF. PANUWAT PADUNGROS, Ph.D., 124 pp.

Green and aqueous-based dehydrative glycosylation of thiofuranosides in micellar media was developed. The thiofuranosides are useful as precursors for carbohydrate synthesis, biological active molecules, and bio-surfactants. Dodecylbenzenesulfonic acid (DBSA), a commercially available Brønsted acid-surfactant, was employed to increase solubility of substrates and enhance rate of the glycosylation. Herein, we report the dehydrative glycosylation of furanosides and pyranosides with aliphatic, aromatic, and heterocyclic thiols in aqueous media to afford the thiofuranosides. Microwave irradiation led to improved yields and shorter reaction times. Other reaction parameters such as temperature and the amount of acid used were also optimized. Aliphatic and aromatic thiofuranosides were prepared from lactol precursors in moderate yields (24–72%) when using 100 mol% DBSA. Noteworthy, the open-chain dithioacetal which is a common by-product from the dehydrative glycosylation was not detected under these reaction conditions. Moreover, the methodology was simple and convenient to set up without the requirement for anhydrous conditions.

Department:	Chemistry	Student's Signature	.....
Field of Study:	Chemistry	Advisor's Signature	.....
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List of Abbreviations and Symbols

$[\alpha]_D$	specific rotation
Ac	acetyl
AcOH	acetic acid
anh.	anhydrous
Bn	benzyl
BS	bio-surfactant
$CDCl_3$	deuterated chloroform
δ	chemical shift
d	doublet
DBSA	dodecylbenzenesulfonic acid
DBSNa	sodium dodecylbenzenesulfonate
dd	doublet of doublet
DMF	*N*,*N*-dimethylformamide
2,4-DNP	2,4-dinitrophenylhydrazine
DPA	decaprenolphophoarabinose
equiv	equivalent
HCl	hydrochloric acid
J	coupling constant
LASCs	Lewis acid surfactant combined catalysts
μwave	microwave
m	multiplet
m/z	mass-to-charge ratio
MALDI-TOF	matrix assisted laser desorption ionization-time of flight
MS	mass spectrometry
NMR	nuclear magnetic resonance

o	ortho
O/N	overnight
p	para
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
psi	pounds per square inch
PTS	polyoxyethanyl α-tocopheryl sebacate
p-TSA	*p*-toluenesulfonic acid
R_f	retention factor
rpm	round per minute
rt	room temperature
s	singlet
TB	tuberculosis
TBAI	tetrabutylammonium iodide
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSBr	trimethylsilyl bromide
TTBP	2, 4, 6-tri-*tert*-butylpyrimidine
UV	ultraviolet
UV-vis	ultraviolet-visible
WERC	water exchange rate constant

CHAPTER I

Introduction

1.1 Organic synthesis in water

Stringent environmental concerns have demanded cleaner reaction process that use water instead of harmful organic solvents such as ethyl acetate, dichloromethane, methanol, and tetrahydrofuran according to the 12 green chemistry principles.[1] In particular, there are various advantages to use water as solvent. Firstly, water is safe and cheap compared to other organic solvents. Next, water has the largest heat capacity among solvents which facilitates controlling of reaction temperature.[2] In 1980, Breslow's research group was the first to adopt these concepts and reported Diels-Alder reactions in water (Figure 1.1a).[3] Rate of cycloaddition was accelerated by hydrophobic interaction of these poorly soluble starting materials. However, the cycloaddition proceeded smoothly only when vigorous stirring was applied since it helped prevent the precipitation of precursors. In 1985, Grieco and co-workers reported Aza Diels-Alder reactions of diene with iminium salt. The cycloaddition gave high yield but needed longer reaction time (up to 48 hours, Figure 1.1b).[4] Since then, several studies of organic reaction in water have gained considerable more attention.[2, 5-8]

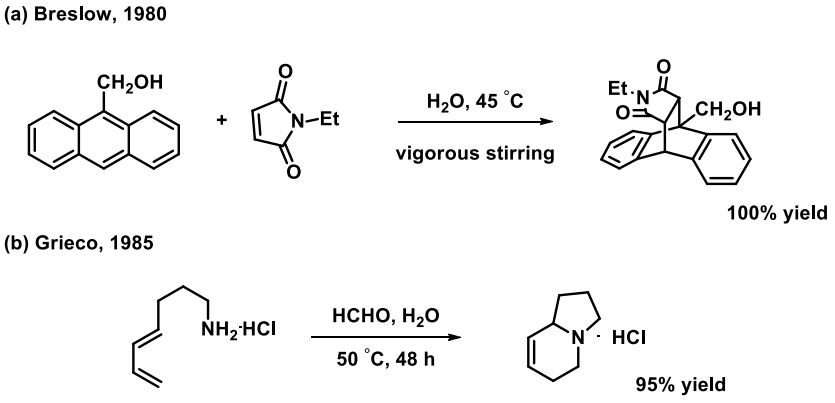


Figure 1.1. Water as media in organic synthesis. (a) Diels-Alder reaction reported by Breslow's group. (b) Aza Diels-Alder reaction reported by Grieco's group.

The challenge of using water as media in organic synthesis is poor solubility of organic molecules in water. Thus, longer reaction time, higher temperature, or vigorous stirring are required to perform reaction in water.

1.2. Micellar surfactant

Recently, concept of using micellar surfactant in organic synthesis was developed and showed promising results.[9] Surfactant molecules possess a polar head and a nonpolar tail within the same molecule are called amphiphilic molecules. It can generate micelle in water such as spherical and bilayer micelle (Figure 1.2). They exhibit interfacial activity usually consisting in their ability to lower the surface tension of liquid or the interfacial tension between two liquids of different polarity. Due to their unique properties, they are widely used in many household and industrial applications such as detergents, wetting agents, dispersants, emulsifiers, foaming agents.[10]

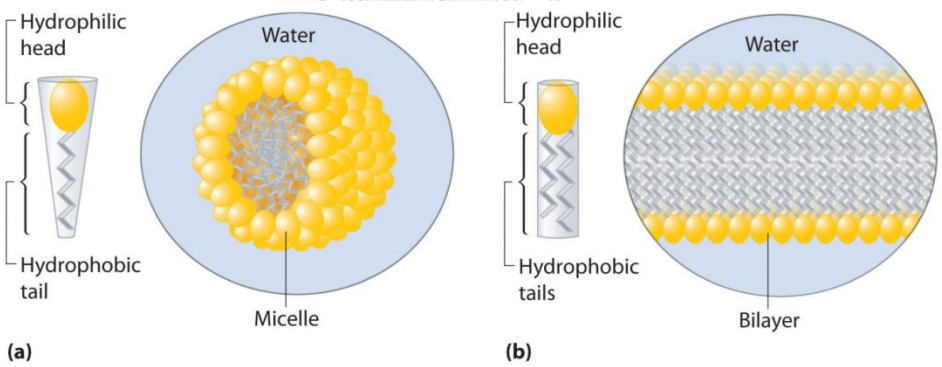


Figure 1.2. Structure of micelle and bilayer surfactant.[11]

A surfactant-type BrØnsted acid dodecylbenzenesulfonic acid (DBSA) has been widely used as a surfactant in aqueous solution.[9, 12-14] In 2001-2002, Kobayashi and co-workers[15-17] developed several dehydration reactions such as dehydrative esterification, etherification, thioetherification, and dithioacetalization in water (Figure 1.3). In these reactions, DBSA and hydrophobic substrates assemble through

hydrophobic interaction to form emulsion droplets whose interior is hydrophobic enough to expel water molecules generating during dehydration out of the droplets.

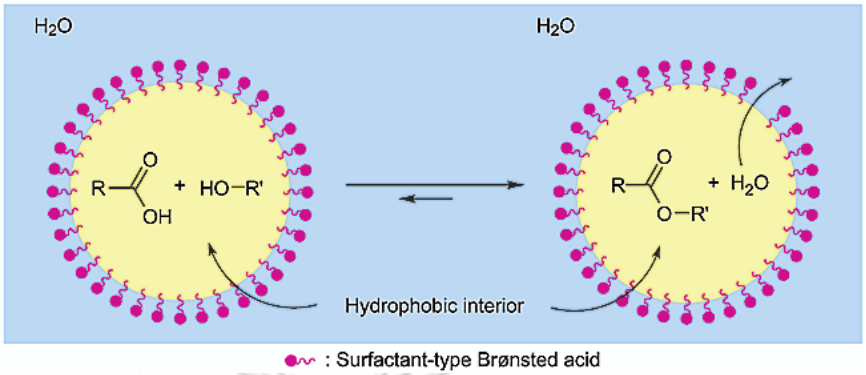


Figure 1.3. Illustration of dehydrative esterification by Kobayashi and co-workers.

This catalytic dehydration in water was applied to various substrates, for example dehydrative esterification as shown in Table 1.1. Several hydrophobic substrates were successfully esterified by DBSA in water. Not only α-monosubstituted carboxylic acids but also α-disubstituted and α-trisubstituted acids gave the corresponding ester products in high yields. Primary alcohols reacted smoothly, but the reactions were very slow in the case of secondary alcohols. Functional groups such a double bond also survived under these reaction conditions.

Table 1.1. DBSA-catalyzed esterification of various substrates in water[15]

RCOOH + HOR' $\xrightarrow[H_2O]{\text{DBSA (10 mol%)}}$ RCOOR'

40 °C, 48 h

Entry	R	R'	Yield (%)[a]
1	$CH_3(CH_2)_{10}$-	-$(CH_2)_3$Ph	89
2	$CH_3(CH_2)_{10}$-	-CH_2Ph	82
3	$CH_3(CH_2)_{10}$-	-$(CH_2)_{11}CH_3$	97
4	$CH_3(CH_2)_{10}$-	-$(CH_2)_{13}CH_3$	>99
5	$CH_3(CH_2)_{10}$-	*c*-HEX	46[b], 70[c]

6	$CH_3(CH_2)_{16}$-	-$(CH_2)_{11}CH_3$	98
7	$PhCH_2$-	-$(CH_2)_{11}CH_3$	92
8	$Ph(CH_2)_4$-	-$(CH_2)_{11}CH_3$	91
9	$Ph(CH_2)_4$-	-$(CH_2)_{12}Br$	91
10	$CH3(CH_2)_7CH=CH(CH_2)_7$-	-$(CH_2)_{11}CH_3$	95
11	*c*-HEX	-$(CH_2)_{11}CH_3$	90
12	1-adamantyl	-$(CH_2)_{11}CH_3$	93[d]

[a] Isolated yield. [b] For 96 h. [c] For 288 h. [d] At 60 °C.

Using DBSA as a catalyst, reaction mixture became a white turbid emulsion (Figure 1.4a), in which the formation of white turbid mixtures was important to attain good yields of the desired products.[17] The formation of emulsion droplets was confirmed by optical microscopy (Figure 1.4b). The emulsion formation is attributed to the property of DBSA as a surfactant, and as shown in Figure 1.3, this property is crucial to accelerate the rate of the dehydrative esterification.

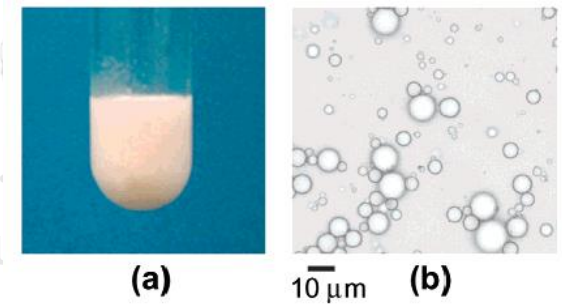


Figure 1.4. (a) Reaction mixture of the DBSA-catalyzed esterification of lauric acid with 3-phenyl-1-propanol in water. (b) Optical micrograph of the reaction mixture.[15]

Moreover, dehydrative glycosylations of both furanoside and pyranoside in water were also reported by Kobayashi's group. The glycosylations were performed between lactols (1-hydroxy sugars) and alcohols nucleophile with catalytic DBSA to afford the desired adducts in good yields (Figure 1.5).

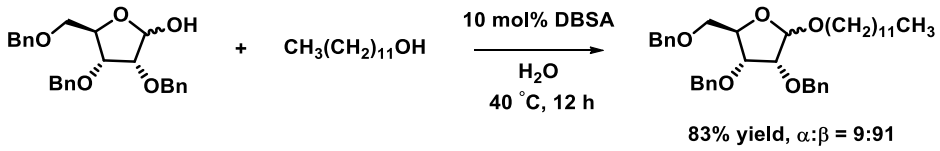


Figure 1.5. DBSA-catalyzed dehydrative glycosylation.[18]

Additionally, *C*-glycosylation between lactols and varieties of carbon- and heteroatom-centered nucleophiles using catalytic DBSA in water was reported.[18] Because of biological and synthetic importance of *C*-glycosides and *C*-nucleosides, the development of methods for their stereoselective generation has been later extensively studied.[19-20] To test the viability of the methodology, glycosylation between 1-hydroxy-D-ribofuranoside and electron-rich heteroaromatic or aromatic compounds were carried out. It was shown that the reactions proceeded smoothly to afford the corresponding *C*-nucleosides in good yields with excellent β-selectivity (Figure 1.6).

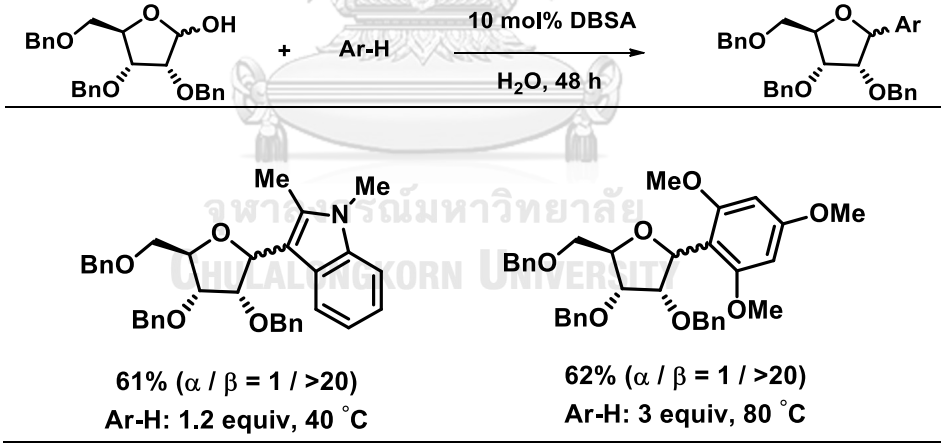
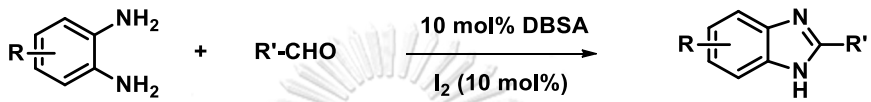


Figure 1.6. DBSA-catalyzed *C*-glycosylations of lactol in water.[18]

Furthermore, a practical and green method has been demonstrated for a chemoselective synthesis of 2-substituted benzimidazoles in aqueous media using DBSA as catalyst and iodine as co-catalyst. A broad range of 2-substituted benzimidazoles have been synthesized from *O*-diaminoarenes and a variety of

aldehydes using this method (Table 1.2). The operational simplicity, excellent yields of the products, and high chemoselectivity are the merits of this method. The primary roles of DBSA are assisting organic substrates to solute in aqueous media by forming micelles and acting as a catalyst to promote condensation of *O*-diaminoarene with the aldehyde.[21]

Table 1.2. DBSA–I_2 catalyzed synthesis of 2-substituted benzimidazoles[21]



Entry	R	R′	Time	Yield (%)[a]
1	H	Ph	2.0	92[b]
2	H	4-$NO_2C_6H_4$	1.0	94[b]
3	4-Methyl	Thiophene-2-yl	2.5	86[c]
4	4-Nitro	Cyclohexyl	6.0	81[c,d]
5	4-Chloro	2-$CH_3C_6H_4$	5.0	93[b]

[a] All yields refer to isolated product, characterized by melting point, ^{1}H NMR and mass, and also ^{13}C NMR and HRMS for new entries. [b] Isolated as sole product. [c] 3–5% of 1,2-Disubstituted benzimidazole was also isolated. [d] The reactions are carried out at 40 °C.

Sodium dodecyl benzenesulfonate (DBSNa) is the most abundant surfactant used worldwide. Different generations of this surfactant exist on the market: the first generation of so-called hard DBSNa surfactants, is highly branched, polydisperse molecule whereas soft DBSNa is mostly bearing narrowly distributed linear alkyl chains. Their solubility in water is generally total at usual concentrations but the latter family often requires heating to accelerate their solubilization.[22] Hard DBSNa surfactants, with a polydisperse and hyperbranched structure, combined with different rare earth metal salts generate highly water-dispersible catalytic system called Lewis Acid Surfactant Combined Catalysts (LASCs). This platform of new

complexes promotes fast, efficient cationic polymerization of industrially relevant monomers in direct emulsion at moderate temperature.[23-24] Homopolymerization and copolymerization of *p*-methoxystyrene (*p*-MOS), styrene and isoprene were synthesized by using the LASCs. The LASCs-catalyzed process does not require high shearing, prolong polymerization time, or large catalyst loading. It allowed reproducible generation of high-molar-mass homopolymers as well as random or multiblock copolymers in a simple and straightforward one-pot reaction (Figure 1.7).[25] Hyperbranched polydisperse DBSNa (hb-DBSNa) interacted with $YbCl_3$, and generated a LASC complex that micellizes in water. Propagation proceeds inside the droplets to generate polymers of high-molar-mass.[25]

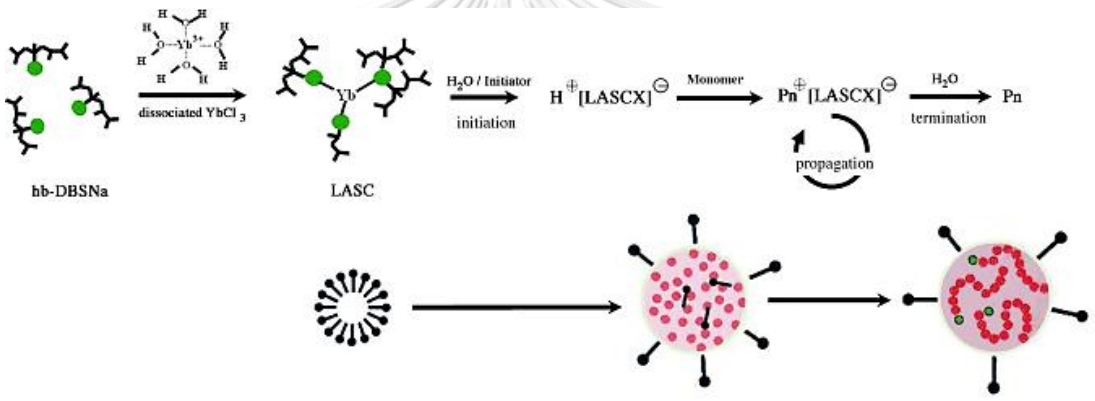


Figure 1.7. Chemical transformation (top) and physical illustration (bottom) of the hb-DBSNa-catalyzed polymerization. X=OH or C_6Cl_5O (initiator: H_2O or C_6Cl_5OH, respectively); P_n and P_n^+ —terminated and growing polymer chain, respectively.

Recently, Lipshutz's research group has introduced series of environmentally benign surfactants. The first generation "designer surfactant" was PTS (polyoxyethanyl α-tocopheryl sebacate). PTS was regarded as a generally useful nanoparticle-forming reagent. TPGS-750-M was later introduced as a second generation surfactant which is a diester composed of racemic α-tocopherol, PEG-750-M, and succinic acid, has been designed and readily prepared as an effective nanomicelle-forming species (Figure 1.8).

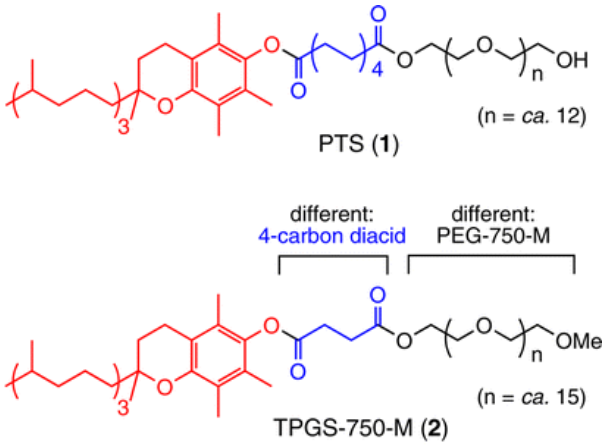
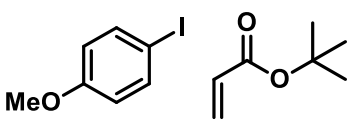
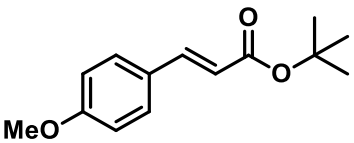
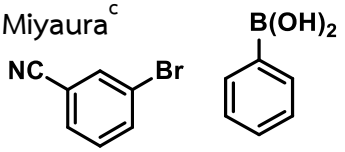
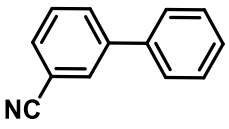
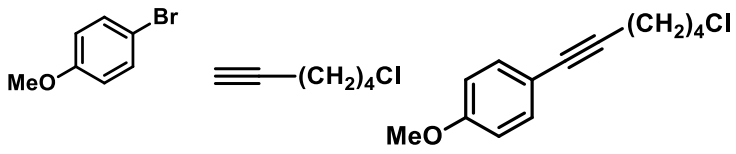
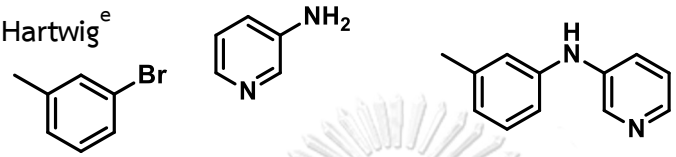


Figure 1.8. Chemical structure of PTS (**1**) and TPGS-750-M (**2**).

These Lipshutz's surfactants have been applied for various coupling reactions in aqueous media such as Heck, Suzuki-Miyaura, Sonogashira, and Buchwald-Hartwig couplings (Table 1.3).[26]

Table 1.3. Pd-catalyzed cross-couplings with PTS and TPGS-750-M in water at room temperature

Entry	Aryl Halide	Partner	Product	PTS Yield (%)[a]	TPGS-750-M Yield (%)[a]
1	Heck[b] 			96	97
2	Suzuki-Miyaura[c] 			78	93

3	Sonogashira[d] 	55	66
4	Buchwald-Hartwig[e] 	83	98

[a] Isolated yield of chromatographically pure materials. [b] Reactions were carried out for 4-12 h using aryl iodide (1 equiv), acrylate or styrene (2 equiv), triethylamine (3 equiv), catalyst Pd(P(*t*-Bu)$_3$)$_2$ 2 mol%), and 5 wt% of surfactant/H_2O. [c] Reactions were carried out for 2-24 h using aryl bromide (1 equiv), arylboronic acid (1.5-2 equiv), triethylamine (3 equiv), catalyst $PdCl_2$(dtbpf) (2 mol%), and 2 wt% of surfactant/H_2O. [d] Reactions were carried out for 21-25 h using aryl bromide (1 equiv), alkyne (1.5 equiv), triethylamine (2 equiv), catalyst $Pd(CH_3CN)_2Cl_2$ (1 mol%), X-Phos (2.5 mol%), and 3 wt% of surfactant/H_2O. [e] Reactions were carried out for 19-20 h using aryl bromide (1 equiv), aryl amine (1.2 equiv), KO-*t*-Bu (1.5 equiv), catalyst [(π-allyl)PdCl]$_2$ (0.5 mol%), cBRIDP (2 mol%), and 2 wt% of surfactant/H_2O.

Furthermore, Pictet–Spengler reactions of β-arylethyl carbamates with aldehydes in water was reported by using perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), as Brønsted acid–surfactants catalyst (Figure 1.9).[27] Fluorinated surfactants that contain hydrophobic perfluoroalkyl chain can form micelles at low concentrations. Due to very strong C–F bonds, they can also be used in harsh conditions that are too severe for hydrocarbon-based surfactants. These unique properties make fluorinated surfactants suitable for many industrial processes and consumer applications.[28]

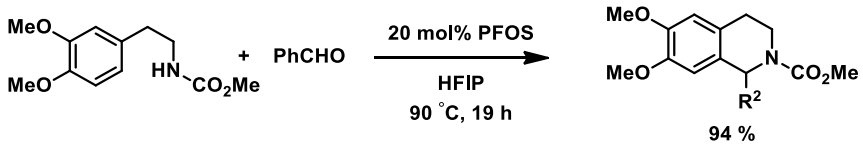


Figure 1.9. The Pictet–Spengler reactions of β-arylethyl carbamate derivatives with aldehydes in water using PFOS as surfactant

1.3. Decaprenolphosphoarabinose (DPA) analogue

Tuberculosis (TB) is caused by bacteria *Mycobacterium tuberculosis* that most often affects lungs of a patient. Tuberculosis is curable and preventable. TB spreads from person to person through air. A person needs to inhale only a few of these germs to become infected. People infected with TB bacteria have a 5–15% lifetime risk of falling ill with TB. When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months.[29] Cell walls of mycobacteria contain two polysaccharides, lipoarabinomannan and arabinogalactan, which are crucial to mycobacterial viability.[30-31] In 2004, Lowery and co-workers first reported the synthesis of decaprenolphophoarabinose (DPA, Figure 1.10 a), which is potential inhibitor of mycobacterial cell wall biosynthesis.[32] After that, Fairbank and co-workers reported the synthesis of series β-arabinofuranose glycosyl sulfones as putative mimics of DPA (Figure 1.10b), together with anti-bacterial activity.[33]

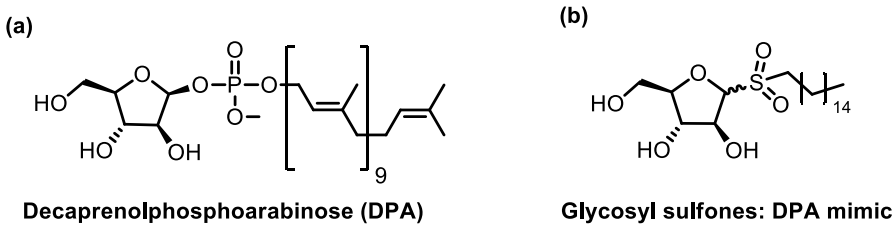


Figure 1.10. (a) Decaprenolphosphoarabinose (DPA). (b) glycosyl sulfones structures.

For the preparation of glycosyl sulfones (Figure 1.11), it started with Fischer glycosylation (**a**–**b**, step 1), benzylation (**a**–**b**, step 2), hydrolysis (**b**–**c**), and conversion to the glycosyl bromide (**c**–**e**). Then, glycosylation gave the desired thioglycoside product (**e**–**f**). Finally, oxidation and subsequent de-protection (**f**–**g**) were performed to yield the glycosyl sulfone products.

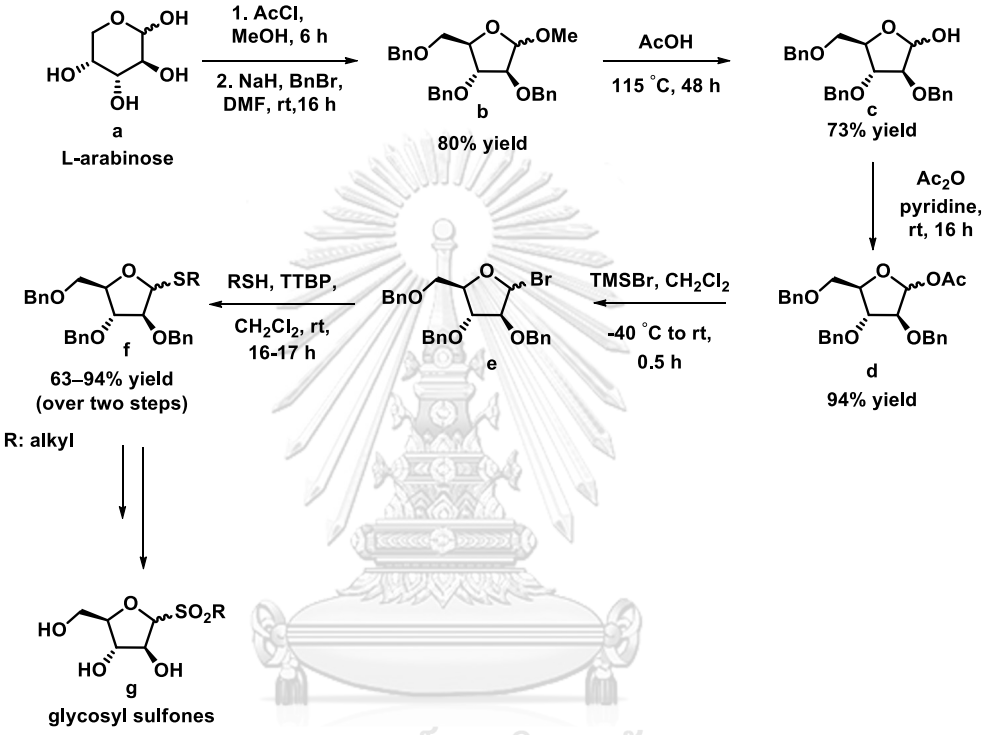


Figure 1.11. Synthesis of glycosyl sulfones **g** as DPA mimic.

It can be observed that the synthetic route from compound **c**–**f** was not efficient. Theoretically, direct glycosylation was possible to achieve furanoside **f** in only single step from lactol **c**. Fairbank and co-workers pursued this idea by applying direct dehydrative glycosylation using hydrochloric acid according to the method reported earlier by Wong's group (Figure 1.12).[34] However, the reaction gave mixtures of the desired thiofuranoside **f** (as minor product) and side-product of opened-chain dithioacetal (as major product) instead. To avoid the formation of dithioacetal, Fairbank and co-workers conducted the substitutions over 3 steps; acetylation, bromination, and thioglycosylation; to gain the desired thiofuranoside **f**. There were

several disadvantages for this route such as it took prolonged reaction time, used harmful organic solvents and reagents, and generated large amount of organic wastes.

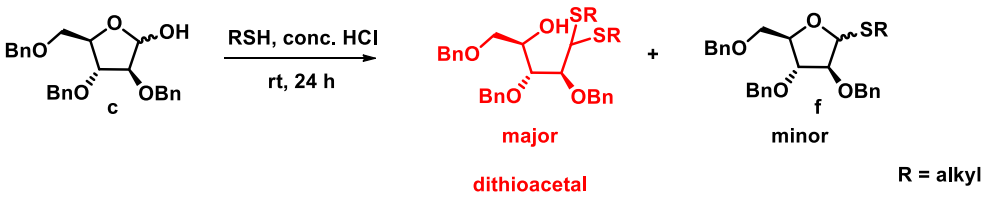


Figure 1.12. Dehydrative glycosylation of lactol **c** reported by Fairbank's group.

1.4 Dithioacetal formation from glycosylation

Formation of the open-chain dithioacetals from dehydrative glycosylation was a major hurdle and it has been reported in literature. Imbatch's[35] and Voss's[36] research groups reported the synthesis of 4-thio-D-ribofuranose and 4-thio-D-xylofuranose using hydrochloric acid as Brønsted acid and gave dithioacetals as major product in good yields (Figure 1.13).

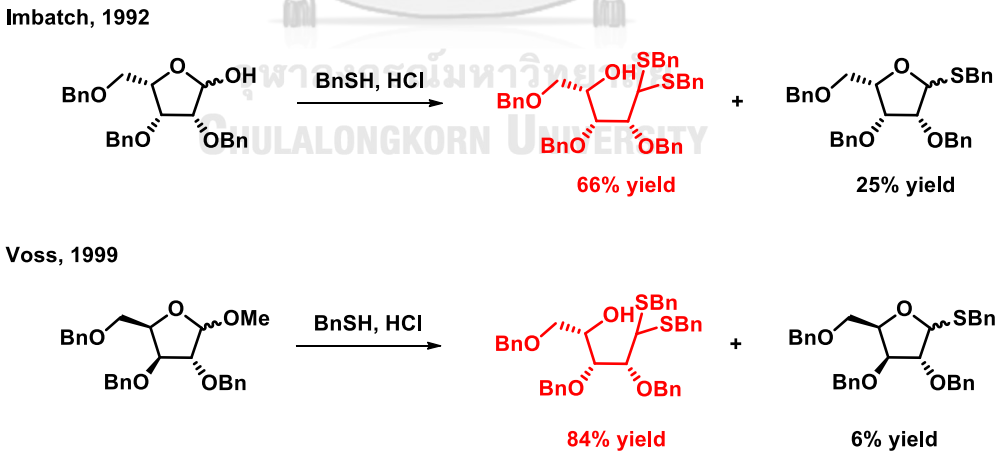


Figure 1.13. Dithioacetal formation by using Brønsted acid as catalyst.

Additionally, Montgomery's research group[37] described the synthesis of 4-thio-D-ribofuranose by using $SnCl_4$ as Lewis acid afforded dithioacetal product in

good yield. Wei's group reported the synthesis of thioethyl D-fucoside[38] in the presence of $BF_3{\cdot}OEt_2$ as Lewis acid. This reaction was found to be sensitive to reagent stoichiometry; using two or more equivalents of ethanethiol and $BF_3{\cdot}OEt_2$ produced dithioacetal as major product instead in 75% yield (Figure 1.14). In summary, dithioacetals frequently obtained from dehydrative glycosylation either by using BrØnsted or Lewis acids.

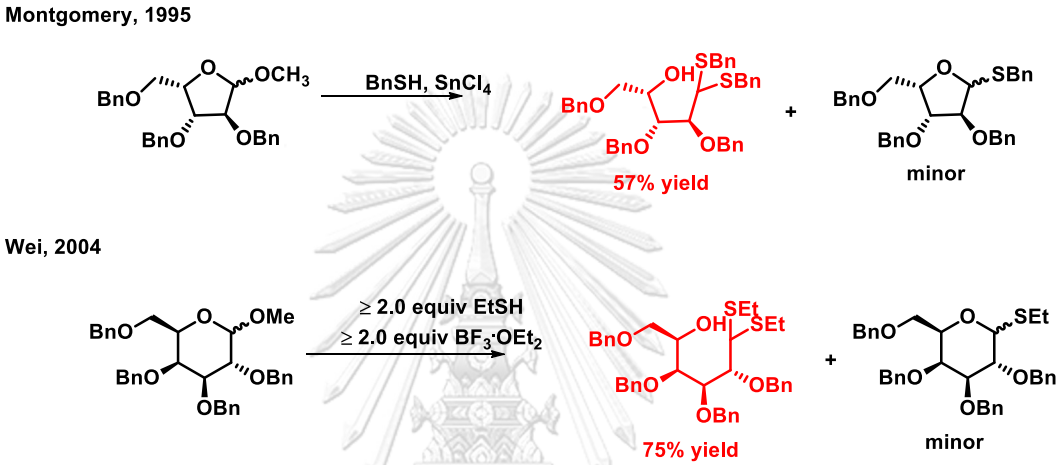


Figure 1.14. Dithioacetal formation by Lewis acids as activators.

Mechanism for dithiacetal generation showed in Figure 1.15. Firstly, protonation was occurred at the hydroxyl group of anomeric position. Water was generated as leaving group resulting in oxocarbenium ion intermediate. Then, thiol attacked at the sp^2 carbon of furanoside ring, deprotonated and led to the formation of thiofuranoside intermediate. Next, the second protonation occurred at oxygen atom on furanose ring contributed to the cleavage of C-O bond. Concomitantly, sulfonium ion intermediate was generated. Finally, the second molecule of thiol attacked at sp^2 carbon, deprotonation and formation of dithioacetal were proceeded.

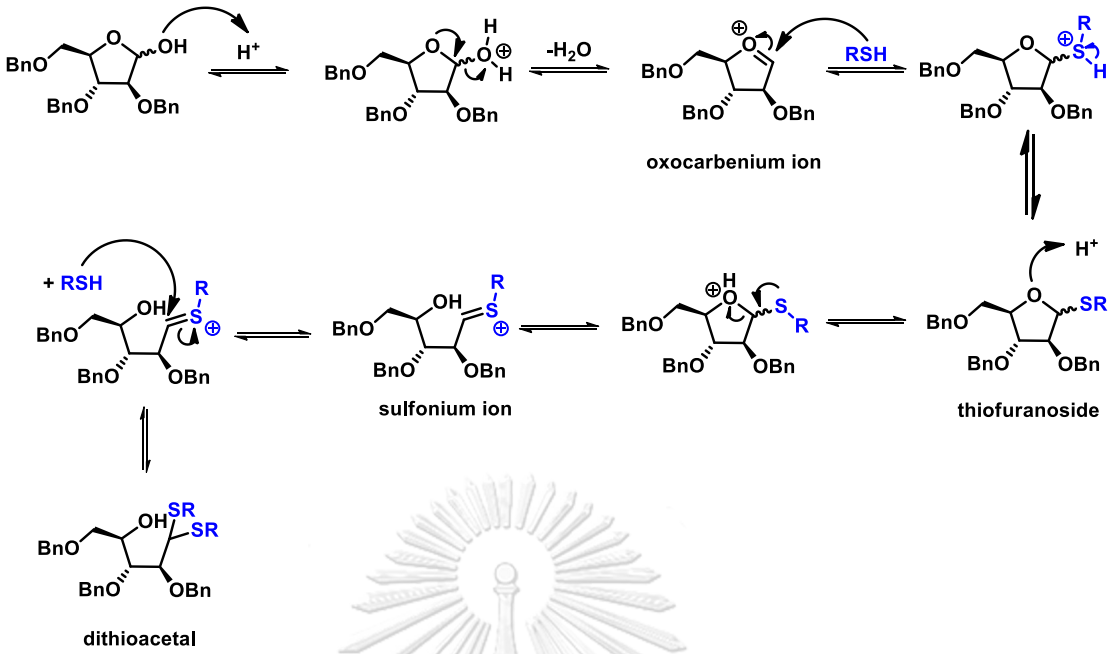


Figure 1.15. Mechanism for dithiacetal generation by dehydrative glycosylation.

1.5 Thioglycoside as bio-surfactants

Bio-surfactants (BS) produced by a variety of microorganisms show unique properties such as multi-functionality, high environmental compatibility compared to other chemical analogues. Numerous advantages of BS have prompted applications in food, cosmetic, and pharmaceutical industries. Glycolipid bio-surfactants are the most promising among all BS, due to high productivity from renewable resources and versatile interfacial and biochemical properties.[39-40] Glycolipid such as thioglycosides (*S*-glycosides) represent a diverse class of compounds typically found in biological membranes and are regarded as environmentally friendly bio-surfactants with broad use in cosmetics and potential therapeutic drug delivery systems. *S*-glycosides may be regarded as relatively inert moieties *in vivo*, or as chemical intermediates that can be oxidatively activated to generate glycoside donors.[41] For illustrate, synthesis of alkyl-β-D-thioglucopyranoside (Figure 1.16) was synthesized and reported for new types of detergent useful for biological applications.[42]

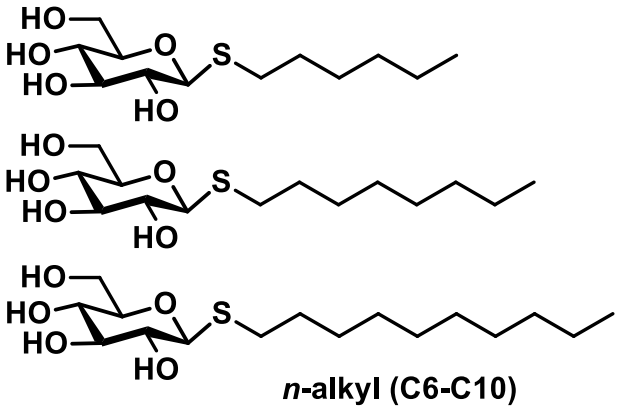


Figure 1.16. Alkyl-D-thiopyranoside as new types of detergents.

1.6 Lanthanide triflate as Lewis acid in water

Generally, Lewis acids are not used in aqueous media as most are unstable and undergo hydrolysis in water. However, lanthanide trifluoromethanesulfonates (lanthanide triflates) such as $La(OTf)_3$, $Yb(OTf)_3$, $Eu(OTf)_3$, $Gd(OTf)_3$, and $Sc(OTf)_3$ Lewis acids were reported to be stable in aqueous solution. Because of their large ionic radii contribute to the high stability in water and can act as catalyst. pK_h values (K_h = hydrolysis constant) of the cations are shown in Figure 1.17. Metal compounds have pK_h values from 4.3 to 10.08 are considered as tolerate in water.[43-44]

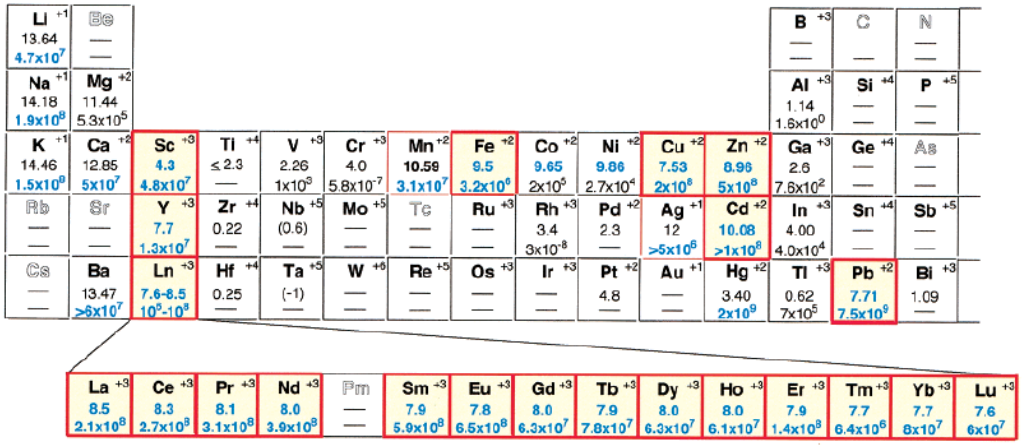
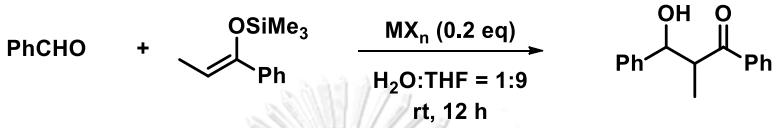


Figure 1.17. Hydrolysis constant and exchange rate constants for substitution of inner-sphere water ligands.[44]

Lanthanide triflates were screened in a Mukaiyama aldol reaction between benzaldehyde and (*Z*)-1-phenyl-1-(trimethylsiloxy)propene. It was found that Lewis acids based on the rare earths such as Sc(III), Yb(III), La(III) triflate were both stable and active as a catalyst in water (Table 1.4).

Table 1.4. Effect of rare earths metal salts in the aldol reaction.



Entry	MX_n	Yield (%)
1	$La(OTf)_3$	80
2	$Ce(OTf)_3$	81
3	$Pr(OTf)_3$	83
4	$Eu(OTf)_3$	88
5	$Gd(OTf)_3$	90
6	$Ho(OTf)_3$	89
7	$Tm(OTf)_3$	85
8	$Yb(OTf)_3$	92

From these literature reviews summarized above, the previous reports for synthesis of thiofuranoside under acid condition generated dithioacetal as by-product (Figure 1.12). In order to avoid this obstacle, alternative methods were conducted instead of three-step sequence to yield thiofuranosides (**c**–**f**, Figure 1.11). The reactions were experimented for long reaction time as well as used many harmful organic reagents and solvents. To mitigate these disadvantages, we are interested in development of green and novel method in the micellar media for synthesis of thiofuranosides. The dehydrative glycosylation of furanose and pyranose with variety of thiol nucleophiles will be investigated. Various reaction parameters such as type of surfactants, amount of surfactant, reaction temperature, reaction time, Lewis acids,

will be investigated for the optimal conditions. Study of substrate scope such as aliphatic, aromatic, and heterocyclic thiols will be carried out as well (Figure 1.18).

Figure 1.18. Illustration of dehydrative glycosylation between L-arabinose (model substrate) and thiols in the presence of dodecylbenzenesulfonic acid (DBSA).

1.7 Objective of this work

1. To synthesize thiofuranosides by dehydrative glycosylation in micellar media
2. To investigate optimal conditions for the synthesis of thiofuranoside
3. To study scope of furanoside and pyranoside as well as thiol nucleophile in thiofuranoside synthesis

CHAPTER II

Experimental section

2.1 Chemicals and materials

All reagent grade chemicals for the synthesis of this work were purchased from Acros, Merck, Sigma-Aldrich, or TCI. Laboratory grade organic solvents from RCI Lab Scan were used, thin-layer chromatography (TLC), and column chromatography. Solvents were dried with 3 Å molecular sieves for anhydrous reactions. Reaction monitoring by TLC were accomplished on silica gel 60 F254 0.2 mm pre-coated aluminium plates and purchased from Merck. Preparative thin layer chromatography was 0.5 mm thickness coated by silica gel 60 GF254 from Merck. Chemical spots on TLC were observed by visualization under 254 nm UV light or stained with *p*-anisaldehyde staining solution. Silica gel 60 (70-230 mesh) from Merck was used in purification by column chromatography. Solvents for NMR experiments were purchased from Cambridge Isotope Laboratories or Euriso-top. Milli-Q water was obtained from ultrapure water system with Millipak® 40 filter unit 0.22 μm, Millipore (USA).

2.2 Instrument and equipment

Reactions were irradiated over CEM Discover Labmate microwave reactor at 218 psi. pH values were measured by pH meter with ATC probe, SJ pH electrode and electrode stand from Eutech Instruments. The reaction mixture was centrifuged at 40 rpm for ten minutes by Hettich EBA20 Portable Centrifuge C2002. Solvents were concentrated to dryness by a Büchi Rotavapor R 200 together with Büchi Vacuum pump V 700 and water aspirator. Molecular sieve was activated with heating mantle under vacuum (Vacuubrand pump model RZ2). Starting materials were azeotroped prior to use by a Buchi Rotavapor model R210, heating bath model B493, and a DAIKAWA vacuum pump model 2Vp-180L 0.5 Pa. Optical rotations ($[\alpha]^{D}$) were obtained on a Jasco P-1010 Polarimeter using sodium light (D line, 589.3 nm).

Functional group determinations were confirmed by infrared (IR) spectroscopy on Nicolet 6700 instrument. Chemical structure identification was conducted by nuclear magnetic resonance (NMR) spectrometer on Bruker Avance 400 operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Exact masses of all new compounds were elucidated by high resolution mass spectroscopy (HRMS) operating on a SpiralTOF™ MALDI TOF Mass Spectrometer Revolutionary (Scientific and Technological Research Equipment Centre; STREC).

2.3 Synthesis of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside and methyl 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (3 and 4)[45]

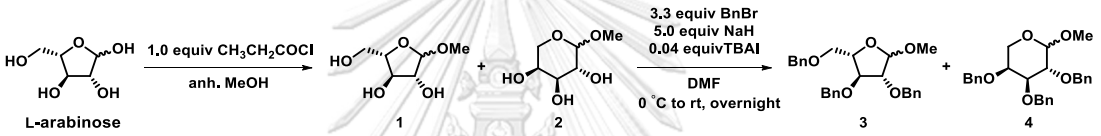


Figure 2.1. Synthesis of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside and methyl 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**3** and **4**).

Commercially available L-arabinose (5 g, 0.03 mol) was azeotroped prior to use for synthesis of methyl L-arabinose (**1** and **2**) with toluene and acetronitrile. Anhydrous methanol (50 mL) was added in a dried round bottom flask with magnetic bar and the azetroped L-arabinose followed by dropwise addition of propionyl chloride (2.6 mL, 0.03 mol) under nitrogen atmosphere. The reaction mixture was stirred for 4 h at room temperature. The reaction was monitored by TLC analysis (dichloromethane:methanol 2:1; *p*-anisaldehyde, R_f =0.20). After complete conversion was observed, pH of the reaction mixture was adjusted with $NaHCO_3$ to 8 and filtered. The filtered solution was evaporated over vacuum. The viscous colorless oily crude mixture (**1** and **2**, Figure 2.1) was obtained in 4.5 g.

The crude mixture of **1** and **2** was azeotroped with toluene and acetonitrile to remove the residual MeOH. Next, it was dissolved in DMF (40 mL) in an ice bath. Benzyl bromine (13 mL, 0.11 mol) and tetrabutylammonium iodide (TBAI, 0.5 g, 0.001

mol) were added and followed by the portion wise addition of NaH (60% dispersion in mineral oil, 4 g, 0.17 mol). The reaction mixture was stirred at 0 °C and allowed to warm up to room temperature for overnight. The reaction was monitored by TLC analysis (hexanes:ethyl acetate 2:1; *p*-anisaldehyde, R_f = 0.25). After completion, the solution was quenched with saturated $NaHCO_3$. Reaction mixture was extracted with diethylether (6×15 mL). The organic layer was combined and washed with distilled water to remove residual DMF. The combined organic extracts were washed with saturated NaCl. Then, it was dried over anhydrous magnesium sulfate ($MgSO_4$) and concentrated to dryness. Finally, the crude product was purified by column chromatography on silica gel using hexanes:ethyl acetate 4:1 as an isocratic mobile phase to obtain methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**3**) as a clear yellow oil in 60% (α:β = 50:50) over two steps; ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 3.45 (s, 3H), 3.60–3.67 (m, 2H), 3.92–3.95 (dd, *J* = 6.3, 2.8 Hz, 1H, 4.00-4.03 (dd, *J* =1.8 Hz, 1H), 4.21–4.27 (m,1H), 4.46–4.63 (m, 6H), 4.95–5.00 (s, 1H), 7.26–7.38 (m, 15H) and methyl 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**4**) as yellow clear oil in 25% (α/β = 50:50) over two steps; ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 3.30-3.37 (d, *J* = 12.6 Hz, 1H), 3.42 (s, 3H), 3.99–4.06 (m, 1H), 3.62–3.69 (d, *J* = 12.4 Hz, 1H), 3.80–3.90 (1H, m), 4.14–4.22 (1H, m), 4.68–4.85 (6H, m), 4.89–4.95 (1H, s), 7.30–7.48 (15H, m). ^{1}H NMR data of compound **3** and **4** were consistent with previous report.[46]

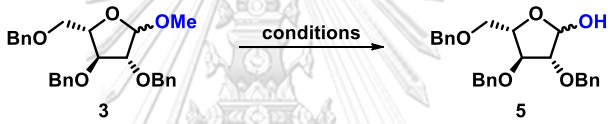
2.4 Synthesis of 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (5)

2.4.1 Optimization for acidic hydrolysis of 2,3,5-tri-O-benzyl-L-arabinofuranoside (5)

Compound **3** (500 mg, 1.15 mmol) and acid solutions (2.5 mL) were added in the microwave vessel. The reaction mixture was irradiated by microwave at 150 °C for 2 hours. The reaction was monitored by TLC analysis (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.15). After consumption of the starting material was observed, it was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 (5 × 3 mL), and washed once with saturated NaCl (3 mL). The organic layer was dried with $MgSO_4$,

filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 1:0 eluent. 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**5**, Table 2.1, entry 11) was obtained as a pale yellow solid as isomeric mixture of α:β = 50:50 (379 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$ α-anomer: δ_H 3.47–3.63 (m, 2H), 3.91–3.99 (m, 1H), 4.00–4.04 (m, 1H), 4.13–4.18 (m, 1H), 4.42–4.69 (m, 6H), 5.29–5.42 (s, 1H), 7.18–7.42 (m, 15H). ^{1}H NMR data of compound **5** was consistent with previous report.[46] The results and conditions are illustrated in Table 2.1.

Table 2.1. Optimization for the hydrolysis of methyl 2,3,5-tri-*O*-benzyl-L-arabino-furanoside (**3**).



3 5

Entry	Conditions	Temp (°C)	Time (h)	Yield[a]
1	CH_3COOH, 1.0 M H_2SO_4 (2:1)	70	72	trace[b]
2	CH_3COOH, 2.0 M H_2SO_4, THF (2:1:1)	100	48	trace[b]
3	0.1M HCl, dioxane (1:1)	60	48	NR[c]
4	0.1M DBSA, H_2O (1:1)	80	48	NR[c]
5	CH_3COOH:H_2O (1:4)	115	24	30%
6	0.1M HCl, dioxane (1:1)	70, μwave[d]	1	30%
7	CH_3COOH:H_2O (1:4)	115, μwave[d]	0.45	55%
8	CH_3COOH:H_2O (1:4)	115, μwave[d]	1	60%
9	CH_3COOH:H_2O (1:4)	125, μwave[d]	2	65%
10	CH_3COOH:H_2O (1:4)	130, μwave[d]	2	72%
11	CH_3COOH:H_2O (1:4)	150, μwave[d]	2	90%

[a] Isolated yield. [b] Yield was determined by TLC. [c] NR = No reaction; it was determined by TLC. [d] μwave = microwave irradiation.

2.5 Synthesis of 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (6)

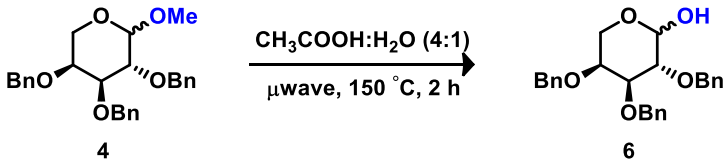


Figure 2.2. Hydrolysis of 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**6**).

Compound **4** (500 mg, 1.15 mmol) and acid solutions (2.5 mL) were added in the microwave vessel. The reaction mixture was irradiated by microwave at 150 °C for 2 hours. The reaction was monitored by TLC analysis (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.10). After complete consumption of starting material, it was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 (5 × 3 mL), and washed once with saturated NaCl (3 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 1:0 eluent. 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**6**) was obtained as a pale yellow solid as isomeric mixture of α:β = 50:50 (253 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 3.60–3.68 (d, *J* =11.0 Hz, 1H), 3.81–3.83 (s, 1H), 3.86–3.88 (m, 1H), 3.89–3.92 (m, 1H), 4.03–4.10 (m, 1H), 4.58–4.75 (m, 6H), 5.20–5.25 (s, 1H), 7.18–7.42 (m,15H). Spectroscopic data (^{1}H NMR) of compound **6** was consistent with previous report.[46]

2.6 Synthesis of 2,3,5-tri-O-benzyl-1-O-acetyl-L-arabinofuranoside (7)[47]

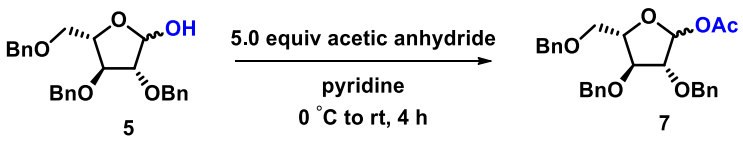
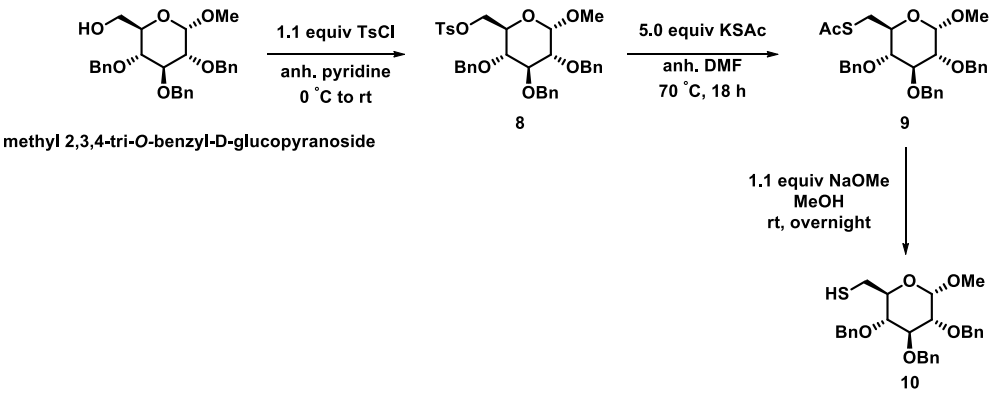


Figure 2.3. Synthesis of 2,3,5-tri-*O*-benzyl-1-*O*-acetyl-L-arabinofuranoside (**7**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside (**5**, 200 mg, 0.48 mmol) was dissolved in anhydrous pyridine (1.5 ml) and cooled down to 0 °C. Acetic anhydride (0.2 ml, 2.4 mmol) was then slowly added. The reaction was allowed to continue to stir at room temperature for 4 hours. The reaction was monitored by TLC analysis (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.35). After complete consumption, it was quenched by pouring into 1M HCl solution and diluted with ethyl acetate. Two layers were separated and the organic layer washed with 1M HCl solution, sat. $NaHCO_3$ (aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 1:0 eluent. 2,3,5-tri-*O*-benzyl-1-*O*-acetyl-L-arabinofuranoside (**7**) was obtained as colorless syrup (200 mg, 90%, α:β = 44:56). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 2.05–2.08 (s, 3H), 3.60–3.64 (d, *J* 5.0 Hz, 2H), 4.05–4.11 (s, 1H), 4.33–4.38 (m, 1H), 4.47–4.70 (m, 6H), 6.27–6.30 (d, *J* 4.0 Hz, 1H), 7.21–7.37 (m, 15H). ^{1}H NMR data of compound **7** was consistent with previous report.[46]

2.7 Synthesis of methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (10)[48-49]

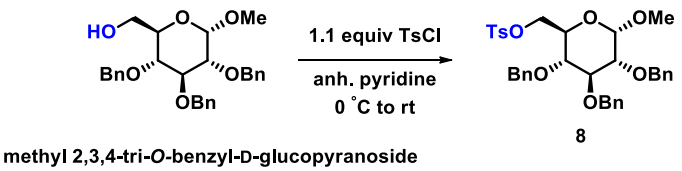
Methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**) can be prepared from methyl 2,3,4-tri-*O*-benzyl-D-glucopyranose precursor in 3 steps. Synthetic procedures were adapted from previously reports (Figure 2.4).[50-52]



methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside

Figure 2.4. Synthesis of methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**).

2.7.1 Methyl 6-tosyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside (8)



methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside

Figure 2.5. Synthesis of methyl 6-tosyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**8**).

Methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (368 mg, 0.8 mmol) was dissolved in anhydrous pyridine (1.5 mL) at 0 °C, and tosyl chloride (166 mg, 0.9 mmol) in anhydrous pyridine (0.5 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred overnight under nitrogen atmosphere. After consumption of the starting material by TLC monitoring (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.20), the reaction mixture was diluted with water, and extracted with ethyl acetate. The combined organic phases were washed with 2M HCl solution, water and brine, dried and concentrated to dryness. The crude product was purified by flash chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 1:0 eluent. Compound **8** was obtained as a white solid (420 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 2.35–2.42 (s, 3H), 3.26–3.33 (s, 3H), 3.36–3.49 (m, 2H), 3.75–3.79 (m, 1H), 4.17–4.20 (m, 1H), 4.51–4.53 (m, 1H), 4.63–4.65 (s, 1H), 4.73–4.85 (m, 6H), 4.97–5.00 (1s, H), 7.12–7.14 (d, 2H). 7.24–7.36 (m, 15H), 7.73–7.78 (2H, d). ^{1}H NMR data of compound **8** was consistent with previous report.[48-49]

2.7.2 Methyl 6-acetyl-6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (9)

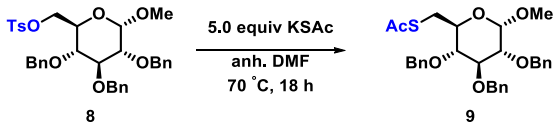


Figure 2.6. Synthesis of methyl 6-acetyl-6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**9**)

Methyl 6-tosyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside **8** (300 mg, 0.48 mmol) was dissolved in anhydrous DMF (3 mL), and the solution was heated to 70 °C. Potassium thioacetate (348 g, 3.05 mmol) was added in portions, and the reaction mixture was stirred at 70 °C for 18 h under nitrogen atmosphere. After consumption of the starting material by TLC monitoring (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.30), the resulting reaction mixture was diluted with water, extracted with ethyl acetate, and the combined organic phases were washed with water, brine, dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 1:0 eluent. Compound **9** was afforded as a white solid (199 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.30–2.34 (s, 3H), 3.02–3.07 (d, 1H), 3.29–3.33 (d, 1H), 3.34–3.37 (s, 3H), 3.47–3.54 (dd, 1H), 3.72–3.88 (m, 1H), 3.93–4.01 (m, 1H), 4.52–4.56 (d, 1H), 4.58–4.91 (m, 6H), 4.98–5.00 (s, 1H), 7.24–7.39 (m, 15H). Spectroscopic data (^{1}H NMR) of compound **9** was consistent with previous report.[48-49]

2.7.3 Methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (10)

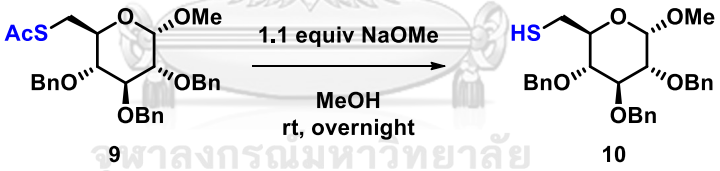


Figure 2.7. Synthesis of methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**).

Compound **9** (220 mg, 0.42 mmol) was dissolved in anhydrous DMF (2 mL), and the solution was heated to 70 °C. Sodium methoxide solution in methanol (1 mL, 0.462 mmol) was added in portions, and the reaction mixture was stirred at 70 °C for 18 h under nitrogen atmosphere. Consumption of the starting material was observed by TLC monitoring (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.20). Then reaction mixture was diluted with water, extracted with ethyl acetate, and the combined organic phases were washed with water, brine, dried and concentrated to dryness. The crude product was purified by flash chromatography on silica gel using

gradient elution with ethyl acetate:hexanes 0:1 to 1:0 eluent. Compound **10** was obtained as a white solid (234 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.70–2.79 (d, 1H), 3.14–3.18 (dd, 1H), 3.29–3.33 (d, 1H), 3.35–3.37 (s, 3H), 3.49–3.51 (d, 1H), 3.81–3.88 (d, 1H), 3.93–3.99 (d, 1H), 4.50–4.91 (m, 6H), 4.98–5.00 (s, 1H), 7.21–7.37 (m, 15H). ^{1}H NMR data of compound **10** was consistent with previous report.[48-49]

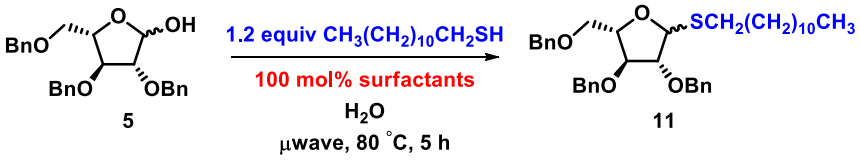
2.8 Dehydrative glycosylation in micellar system: A model study

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside (**5**) and 1-dodecanethiol were chosen as model compounds to investigate the optimal parameters for the dehydrative glycosylation to give dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**). The parameters were surfactant type, surfactant loading, reaction temperatures, and additional Lewis acids.

2.8.1 Effect of different surfactants

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of 100 mol% of different Brønsted acid-surfactants (0.5 M, 0.5 mL). Vessel was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3.0 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup. The results and conditions were shown in Table 2.2.

Table 2.2. Effect of different surfactants on dehydrative glycosylation



Entry	Surfactant	Yield (α:β)[a]
1	PFOS[b] (pka <1)	17% (71:29)
2	PFOA[c] (pka <1)	72% (71:29)
3	DBSA[d] (pka <1)	72% (50:50)
4	TPGS-750-M[e]	NR[f]
5	TPGS-750-M : *p*-TSA[g]	56% (91:9)
6	0.1 M H_2SO_4 (pka = 1.92)	trace[h]
7	CH_3COOH (pka = 4.75)	NR[f]
8	*p*-TSA (pka = -2.6)	17% (67:33)
9	4-hydroxybenzenesulfonic acid (pka < 1)	27% (71:29)

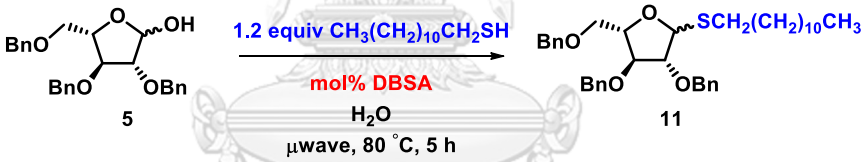
[a] yield and α:β selectivity were determined by ^{1}H NMR signal integration of anomeric proton. [b] PFOS = heptadecafluorooctanesulfonic acid ($CF_3(CF_2)_7SO_3H$). [c] PFOA = perfluorooctanoic acid ($CF_3(CF_2)_6COOH$). [d] DBSA = 4-dodecylbenzenesulfonic acid. [e] TPGS-750-M = DL-α-tocopherol methoxypolyethylene glycol succinate. [f] NR = No reaction; reaction mixture was observed by TLC. [g] *p*-TSA = *p*-toluenesulfonic acid. [h] Reaction mixture was observed by TLC. μwave = microwave irradiation.

2.8.2 Effect of DBSA amount

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of DBSA at various concentrations (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer

chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (105 mg, 72%, α:β = 1:1,). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.88 (t, *J* = 6.7 Hz, 3H), 1.15–1.45 (m, 18H), 1.65–1.73 (m, 2H), 2.50–2.76 (m, 2H), 3.44–3.77 (m, 2H), 3.98 (s, 1H), 4.04 (d, *J* = 3.8 Hz, 1H), 4.11–4.19 (m, 1H), 4.40–4.70 (m, 6H), 5.30–5.42 (m, 1H, anomeric proton), 7.14–7.42 (m, 15H). The results and conditions were illustrated in Table 2.3.

Table 2.3. Optimization of DBSA loading



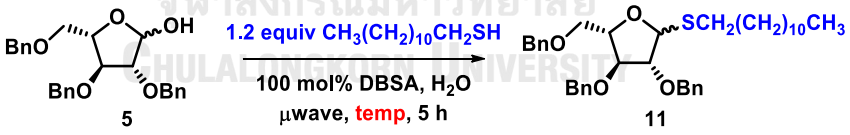
Entry	DBSA (mol%)	Yield (α:β)[a]	Brsm[b] Yield
1	10	36% (50:50)	40%
2	20	56% (50:50)	75%
3	30	51% (50:50)	98%
4	40	50% (50:50)	77%
5	50	54% (50:50)	78%
6	80	65% (50:50)	93%
7	100	72% (50:50)	99%
8	200	69% (50:50)	95%
9	0	NR[c]	NR[c]

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. [b] brsm = based on recovered starting material. [c] NR = No reaction; it was observed by TLC. μwave = microwave.

2.8.3 Effect of reaction temperatures

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of 10 mol% DBSA (0.5 mL). It was stirred in a microwave reactor at various temperatures for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes 0:1 to 3:7 eluent. Characterization of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was previously described.The results and conditions were summarized in Table 2.4.

Table 2.4. Optimization of reaction temperature



Entry	Temp (°C)	Yield (α:β)[a]	Brsm[b] Yield
1	40	44% (50:50)	99%
2	60	57% (50:50)	99%
3	80	72% (50:50)	99%
4	100	64% (50:50)	80%
5	120	decomposition[c]	-
6	80[d]	54% (50:50)	84%

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. [b] Brsm = based on recovered starting material. [c] Reaction mixture

decomposed at 120 °C within 1 h. [d] Product was obtained under conventional oil-bath heating for 28 h. μwave = microwave.

2.8.4 Dehydrative glycosylation by conventional heating

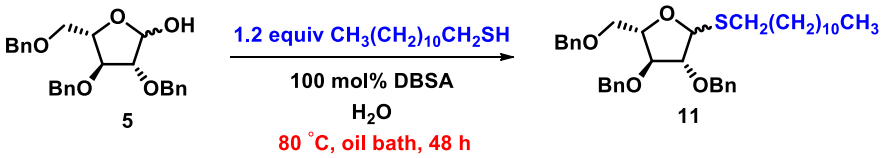


Figure 2.8. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) by conventional heating.

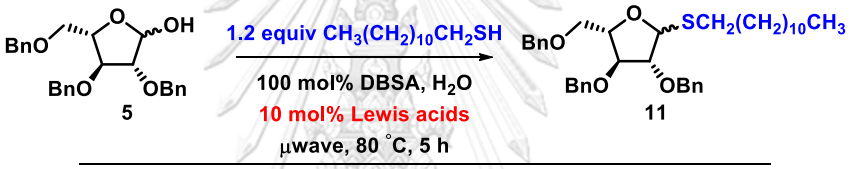
2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) was added in sealed-tube containing magnetic stirrer bar followed by 1-dodecanethiol (70 μL, 0.29 mmol). A stock solution of 100 mol% of DBSA was added. The reaction mixture was stirred at 80 °C in an oil bath for 48 h. It was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After complete conversion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-O-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (78 mg, 54%,α:β = 1:1)

2.8.5 Effect of Lewis acids

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and 10 mol% of Lewis acids were added in a microwave vessel followed by a stock solution of 10 mol% DBSA. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer

chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup. The results and conditions were concluded in Table 2.5.

Table 2.5. Optimization of additive Lewis acids



Entry	Lewis acids	Yield (α:β)[a]
1	$Sc(OTf)_3$	59% (50:50)
2	$Yb(OTf)_3$	63% (50:50)
3	$La(OTf)_3$	67% (50:50)
4	$Gd(OTf)_3$	64% (50:50)
5	$Nd(OTf)_3$	64% (50:50)
6	$Pr(OTf)_3$	56% (50:50)
7	$Cu(OTf)_2$	56% (50:50)
8	$Zn(OTf)_2$	15% (50:50)
9	$CrCl_3$	58% (50/50)

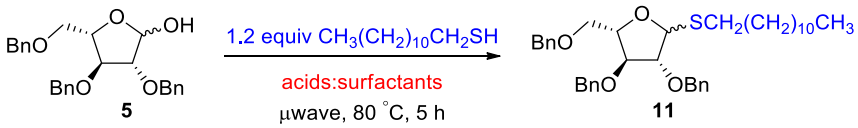
10	$SrCl_2$	56% (50/50)

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. μwave = microwave.

2.8.6 Effect of acids and other surfactants (DBSNa)

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of acids and surfactants. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup. The results and conditions are shown in Table 2.6.

Table 2.6. Effect of acids and surfactant.



Entry	Acid	Surfactant	Yield[a]
1	0.5 M *p*-TSA[b]	-	17
2	0.5 M *p*-TSA	5 mol% DBSNa[c]	55

3	0.5 M *p*-TSA	10 mol% DBSNa	60
4	0.5 M *p*-TSA	30 mol% DBSNa	43
5	0.5 M *p*-TSA	50 mol% DBSNa	38
6	0.5 M *p*-TSA	80 mol% DBSNa	44
7	0.5 M *p*-TSA	100 mol% DBSNa	36
8	-	100 mol% DBSNa	NR[d]
9	10 mol% $Sc(OTf)_3$	-	NR[d]
10	30 mol% $Sc(OTf)_3$	100 mol% DBSNa	trace[e]
11	100 mol% $Sc(OTf)_3$	100 mol% DBSNa	13[f]
12	30 mol% $Yb(OTf)_3$	100 mol% DBSNa	trace[e]

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton, α:β = 67:33. [b] *p*-TSA = *p*-toluenesulfonic acid. [c] DBSNa = sodium dodecylbenzenesulfonate. [d] NR = No reaction; it was monitored by TLC. [e] Reaction mixture was monitored by TLC. μwave = microwave.

2.9 Substrate scopes of glycosylation

2.9.1 Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (11) by optimal conditions

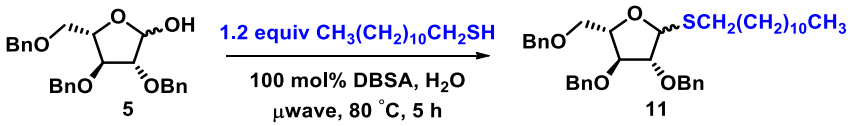


Figure 2.9. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) by optimal conditions.

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of acids and surfactants. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (105 mg, 72%, α:β = 50:50).

2.9.2 Study of leaving groups of furanoside donor

Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) from **3**

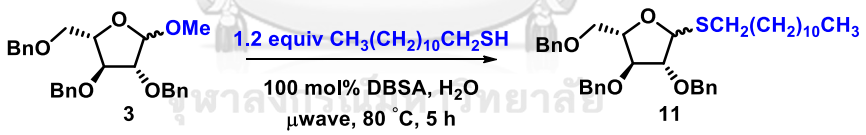


Figure 2.10. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**).

Methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **3** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of acids and surfactants. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator.

The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (14 mg, 10%, α:β = 91:9).

Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) from **7**

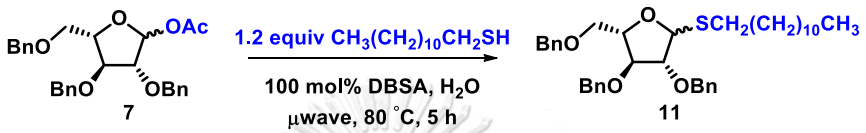


Figure 2.11. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) by optimal condition.

2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-L-arabinofuranoside **7** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of acids and surfactants. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (67 mg, 60%, α:β = 99:1).

2.9.3 Substrate scope of thiol acceptors

Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**11**)

Figure 2.12. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (50 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (105 mg, 72%, α:β = 50:50,). α-anomer: $[\alpha]_D^{26}$ +61.9° (c 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (t, *J* = 6.7 Hz, 3H), 1.15–1.45 (m, 18H), 1.65–1.73 (m, 2H), 2.50–2.76 (m, 2H), 3.44–3.77 (m, 2H), 3.98 (s, 1H), 4.04 (d, *J* = 3.8 Hz, 1H), 4.11–4.19 (m, 1H), 4.40–4.70 (m, 6H), 5.30–5.42 (m, 1H, anomeric proton), 7.14–7.42 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.14, 22.71, 29.03, 29.28, 29.38, 29.58, 29.65, 29.67, 29.69, 30.00, 30.92, 31.95, 71.43, 71.92, 72.39, 73.37, 82.09, 83.86, 84.39, 87.18, 127.75, 127.78, 127.91, 128.35, 128.41, 137.61, 137.90, 138.24. HRMS (MALDI-TOF): m/z calculated for $C_{38}H_{52}O_4SNa$ 627.3484 [M+Na^+]; found 627.3484. β-anomer: $[\alpha]_D^{25}$ -50.0° (c 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.78–0.84 (t, *J* = 6.6 Hz, 3H), 1.15–1.23 (m, 18H), 1.55–1.78 (m, 2H), 2.58–2.64 (t, *J* = 7.4 Hz, 2H), 3.54–3.59 (m, 2H), 3.85–3.90 (dd, *J* = 6.8, 3.1 Hz, 1H), 4.01–4.04 (s, 1H), 4.14–4.19

(m, 1H), 4.35–4.57 (m, 6H), 5.41–5.43 (s, 1H, anomeric proton), 7.13–7.31 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.09, 22.68, 28.54, 29.24, 29.34, 29.51, 29.59, 29.63, 29.65, 29.69, 31.92, 39.27, 69.84, 71.92, 72.17, 73.42, 81.23, 83.83, 87.97, 102.16, 127.56, 127.69, 127.72, 128.33, 128.40, 137.49, 137.89, 138.15. HRMS (MALDI-TOF): m/z calculated for $C_{38}H_{52}O_4SNa$ 627.3484 [M+Na^+]; found 627.3484.

Octylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**12**)

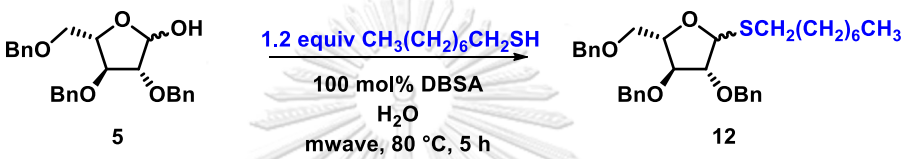


Figure 2.13. Synthesis of octylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**12**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-octanethiol (50 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Octylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**12**) was obtained as a yellow syrup (, 94 mg, 71%, α:β = 83:17). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.84-0.91 (t, *J* = 6.5 Hz, 3H), 1.22–1.32 (m, 10H), 1.59–1.66 (m, 2H), 2.62–2.68 (t, *J* = 6.8 Hz, 2H), 3.60–3.76 (m, 2H), 4.02–4.06 (t, *J* = 3.9 Hz, 1H), 4.12–4.18 (m, 2H), 4.47–4.64 (m, 6H), 5.36-5.39 (s, 1H, anomeric proton), 7.21–7.45 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.14, 22.71, 29.03, 29.28, 29.34, 29.59, 30.93, 31.93, 71.44, 71.93, 72.40, 73.38, 82.10, 83.88, 84.40, 87.19, 127.61, 127.76,

127.83, 128.36, 128.41, 137.52, 137.91, 138.26. HRMS (MALDI-TOF): m/z calculated for $C_{34}H_{44}O_4SNa$ 571.2858 [M+Na^+]; found 571.2859.

Decylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**13**)

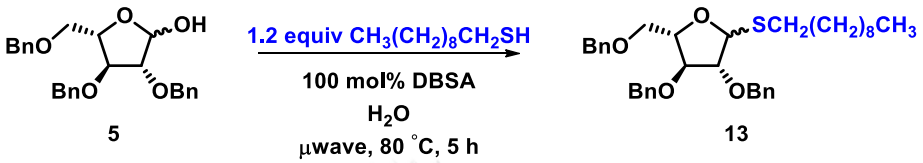


Figure 2.14. Synthesis of decylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**13**)

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-decanethiol (61 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Decylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**13**) was obtained as a yellow syrup (91 mg, 67%, α:β = 84:16). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.82-0.91 (t, *J* = 6.6 Hz, 3H), 1.21–1.33 (m, 14H), 1.59–1.66 (m, 2H), 2.63–2.67 (t, *J* = 7.0 Hz, 2H), 3.61–3.75 (m, 2H), 4.02–4.07 (t, *J* = 3.8 Hz, 1H), 4.12–4.18 (m, 2H), 4.45–4.65 (m, 6H), 5.36-5.39 (s, 1H, anomeric proton), 7.21–7.37 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.07, 22.64, 28.99, 29.13, 29.19, 29.69, 29.95, 30.89, 31.82, 32.30, 71.41, 71.90, 72.37, 73.35, 82.06, 83.84, 84.35, 87.15, 127.59, 127.75, 127.81, 127.88, 128.33, 128.39, 137.49, 137.89. HRMS (MALDI-TOF): m/z calculated for $C_{36}H_{48}O_4SNa$ 599.3171 [M+Na^+]; found 599.3161.

Tetradecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**14**)

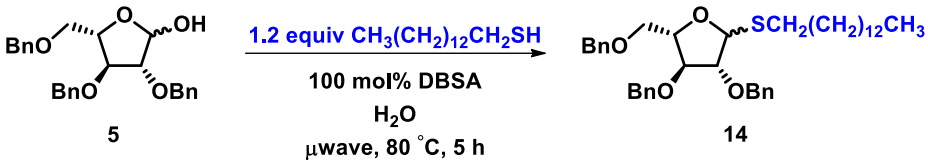


Figure 2.15. Synthesis of tetradecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**14**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-tetradecanethiol (79 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.41). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Tetradecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**14**) was obtained as a yellow syrup (99 mg, 65%, α:β = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.85-0.95 (t, *J* = 6.6 Hz, 3H), 1.19–1.33 (m, 22H), 1.58–1.65 (m, 2H), 2.61–2.69 (t, *J* = 6.8 Hz, 2H), 3.61–3.75 (m, 2H), 4.03–4.06 (t, *J* = 3.9 Hz, 1H), 4.11–4.18 (m, 2H), 4.44–4.64 (m, 6H), 5.36-5.40 (s, 1H, anomeric proton), 7.20–7.37 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.14, 22.72, 29.03, 29.28, 29.39, 29.59, 29.65, 29.69, 29.70, 29.71, 29.72, 30.00, 30.90, 31.96, 71.44, 71.93, 72.40, 73.38, 82.09, 83.88, 84.40, 87.19, 127.61, 127.78, 127.83, 127.91, 128.41, 137.62, 137.91, 138.26. HRMS (MALDI-TOF): m/z calculated for $C_{40}H_{56}O_4SNa$ 655.3797 [M+Na$^+$]; found 655.3788.

Pentadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**15**)

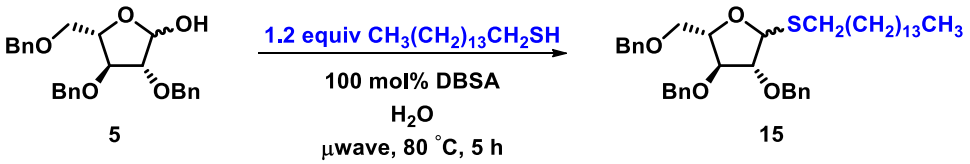


Figure 2.16. Synthesis of pentadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**15**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-pentadecanethiol (83 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.42). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Pentadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**15**) was obtained as a yellow syrup (90 mg, 58%, α:β = 92:8,). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.85-0.92 (t, *J* = 7.0 Hz, 3H), 1.17–1.33 (m, 24H), 1.57–1.65 (m, 2H), 2.61–2.68 (t, *J* = 6.8 Hz, 2H), 3.61–3.75 (m, 2H), 4.02–4.06 (t, *J* = 3.9 Hz, 1H), 4.11–4.19 (m, 2H), 4.47–4.65 (m, 6H), 5.36-5.40 (s, 1H, anomeric proton), 7.22–7.38 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.12, 22.70, 29.02, 29.27, 29.37, 29.57, 29.64, 29.67, 29.69, 29.70, 29.71, 29.72, 29.98, 30.91, 30.94, 71.42, 71.92, 72.38, 73.36, 82.07, 83.86, 84.37, 87.16, 127.60, 127.76, 127.90, 128.34, 128.40, 137.60, 137.88, 138.23. HRMS (MALDI-TOF): m/z calculated for $C_{41}H_{58}O_4SNa$ 669.3953 [$M+Na^+$]; found 669.3957.

Hexadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**)

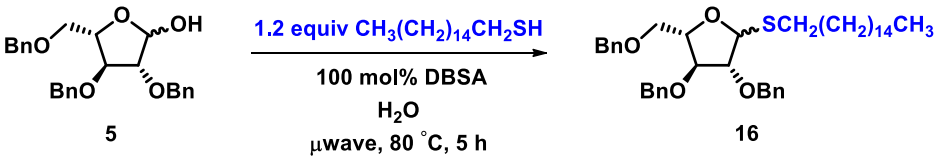


Figure 2.17. Synthesis of hexadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-hexadecanethiol (89 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.44). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Hexadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**) was obtained as a yellow syrup (92 mg, 58%, α:β = 54:46). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.84-0.90 (t, *J* = 6.7 Hz, 3H), 1.17–1.35 (m, 26H), 1.55–1.68 (m, 2H), 2.59–2.71 (m, 2H), 3.57–3.77 (m, 2H), 4.02–4.08 (t, *J* = 3.9 Hz, 1H), 4.10–4.20 (m, 2H), 4.43–4.66 (m, 6H), 5.36-5.41 (d, *J* = 4.9 Hz, 1H, anomeric proton), 7.21–7.41 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.16, 22.70, 28.96, 29.26, 29.27, 29.37, 29.57, 29.64, 29.67, 29.69, 29.71, 29.72, 29.98, 30.91, 30.93, 30.94, 71.42, 71.91, 72.38, 73.38, 82.07, 83.85, 84.36, 87.16, 127.60, 127.74, 127.90, 128.34, 128.40, 137.53, 137.88, 138.23. HRMS (MALDI-TOF): m/z calculated for $C_{42}H_{60}O_4SNa$ 683.4110 [M+Na^+]; found 683.4132.

Octadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**17**)

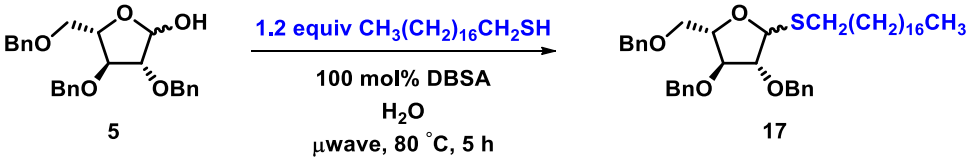


Figure 2.18. Synthesis of octadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**17**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-octadecanethiol (83 mg, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.48). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Octadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**17**) was obtained as a yellow syrup (104 mg, 63%, α:β = 90:10,). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.82-0.93 (t, *J* = 6.7 Hz, 3H), 1.19–1.35 (m, 30H), 1.56–1.66 (m, 2H), 2.61–2.70 (t, *J* = 7.4 Hz, 2H), 3.60–3.77 (m, 2H), 4.01–4.07 (t, *J* = 3.9 Hz, 1H), 4.10–4.20 (m, 2H), 4.46–4.65 (m, 6H), 5.36-5.40 (d, *J* = 4.9 Hz, 1H, anomeric proton), 7.21–7.41 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.98, 20.56, 26.88, 27.13, 27.23, 27.44, 27.51, 27.53, 27.54, 27.55, 27.56, 27.57, 27.58, 27.59, 27.60, 27.85, 28.77, 29.80, 69.28, 69.77, 70.24, 71.22, 79.93, 81.72, 82.24, 85.03, 125.46, 125.59, 125.76, 126.20, 126.29, 135.46, 135.75, 136.10. HRMS (MALDI-TOF): m/z calculated for $C_{44}H_{64}O_4SNa$ 711.4423 [M+Na^+]; found 711.4414.

Cyclohexylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**18**)

Figure 2.19. Synthesis of cyclohexylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**18**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-cyclohexanethiol (35 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.35). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Cyclohexylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**18**) was obtained as a yellow syrup (α/β = 50/50, 56 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 1.19-1.44 (m, 6H), 1.53–1.66 (m, 2H), 1.69–1.79 (m, 1H), 1.95–2.11 (m, 1H), 2.83–2.97 (m, 1H), 3.55–3.68 (m, 2H), 3.93–4.00 (m, 2H), 4.28–4.33 (m, 1H), 4.43–4.63 (m, 6H), 5.43-5.46 (d, *J* = 1.9 Hz, 1H, anomeric proton), 7.21–7.38 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.79, 29.69, 33.77, 33.98, 43.67, 56.24, 69.23, 72.20, 73.34, 79.83, 83.64, 89.20, 95.08, 96.23, 127.49, 127.72, 127.82, 128.34, 128.41, 137.59, 137.75, 137.87. HRMS (MALDI-TOF): m/z calculated for $C_{32}H_{38}O_4SNa$ 541.2388 [M+Na$^+$]; found 541.2384.

2-Phenylethylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**19**)

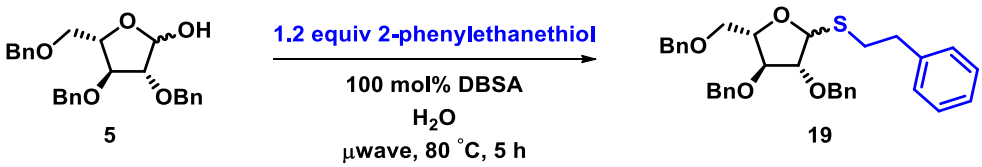


Figure 2.20. Synthesis of 2-phenylethylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**19**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 2-phenylethanethiol (34 mg, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.35). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (3 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. 2-Phenylethylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**19**) was obtained as a yellow syrup (54 mg, 42%, α:β = 60:40). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 2.86-2.99 (m, 4H), 3.58–3.74 (m, 2H), 3.93–3.98 (m, 1H), 4.00–4.07 (t, *J* = 4.0 Hz, 1H), 4.11–4.19, m, 1H), 4.44–4.61 (m, 6H), 5.35-5.40 (d, *J* = 4.9 Hz, 1H, anomeric proton), 7.17–7.37 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.13, 36.64, 71.36, 71.99, 72.39, 73.39, 82.08, 83.74, 84.33, 87.13, 126.31, 127.60, 127.76, 127.82, 127.85, 127.92, 127.97, 128.34, 128.40, 128.60, 137.59, 137.75, 137.87. HRMS (MALDI-TOF): m/z calculated for $C_{34}H_{36}O_4SNa$ 563.2232 [M+Na^+]; found 563.2285.

tert-Butylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**20**)

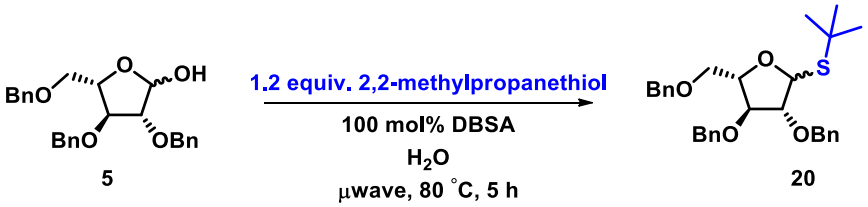


Figure 2.21. Synthesis of *tert*-butylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**20**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranose **5** (100 mg, 0.24 mmol) and *tert*-butylthiol (34 mg, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.35). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (3 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. *tert*-Butylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**20**) was obtained as a yellow syrup (28 mg, 24%, α:β = 50:50,). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 1.37-1.43 (s, 9H), 3.56–3.70 (m, 2H), 3.93–4.02 (m, 2H), 4.26–4.34 (m, 1H), 4.43–4.63 (m, 6H), 5.50-5.55 (d, *J* = 2.7 Hz, 1H, anomeric proton), 7.20–7.39 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.47, 31.48, 31.49, 44.27, 69.32, 72.06, 72.16, 73.28, 79.76, 83.48, 85.94, 89.50, 127.52, 127.67, 127.81, 128.33, 128.40, 137.59, 137.75, 138.26. HRMS (MALDI-TOF): m/z calculated for $C_{30}H_{36}O_4SNa$ 515.2232 [M+Na^+]; found 515.2239.

6-Thiopyranosyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**21**)

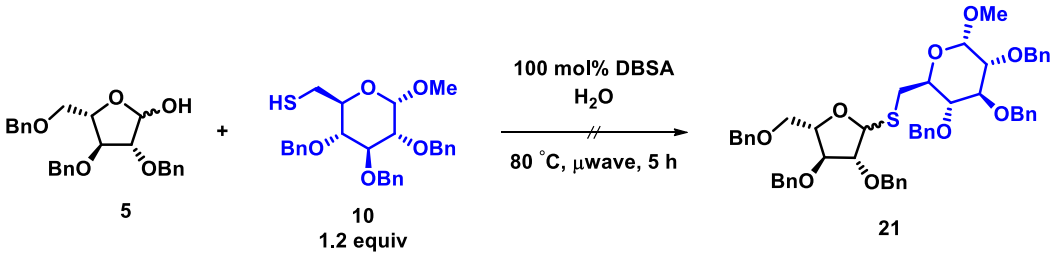


Figure 2.22. Synthesis of 6-thiopyranosyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**21**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside **10** (138 mg, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.27). After the starting material **5** was consumed, reaction mixture was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes 0:1 to 3:7 eluent. However, the desired product was not obtained.

4-Methylphenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**22**)

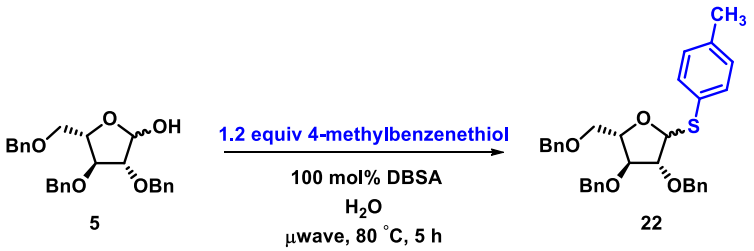


Figure 2.23. Synthesis of 4-methylphenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**22**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 4-methylbenzenethiol (36 mg, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.36). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. 4-Methylphenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**22**) was obtained as a yellow syrup (52 mg, 41%, α:β = 82:18,). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 2.27-2.35 (s, 3H), 3.65–3.82 (m, 2H), 4.07–4.11 (t, *J* = 3.6 Hz, 1H), 4.16–4.22 (m, 1H), 4.24–4.28 (m, 1H), 4.47–4.63 (m, 6H), 5.58-5.63 (d, *J* = 4.9 Hz, 1H, anomeric proton), 7.06–7.12 (d, *J* = 7.9 Hz, 2H), 7.22–7.45 (m, 17H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.70, 71.11, 71.89, 72.51, 73.59, 82.42, 83.47, 84.34, 90.36, 127.59, 127.78, 127.82, 127.94, 128.34, 128.43, 128.52, 131.62, 132.06, 136.99, 137.46, 137.81, 138.24. HRMS (MALDI-TOF): m/z calculated for $C_{33}H_{34}O_4SNa$ 549.2075 [M+Na$^+$]; found 549.2092.

4-Chlorophenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**23**)

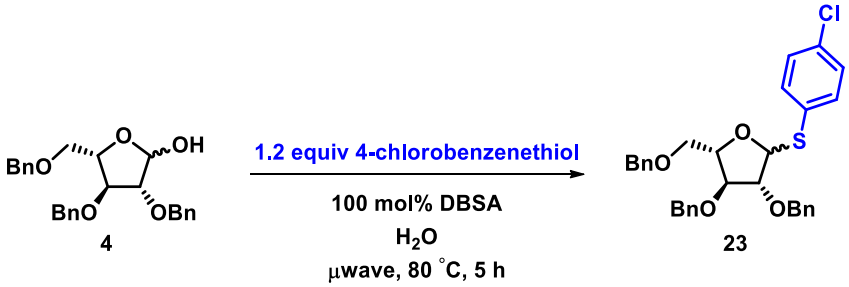


Figure 2.24. Synthesis of 4-chlorophenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**23**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 4-chlorobenzenethiol (34 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.35). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. 4-Chlorophenylhio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**23**) was obtained as a yellow syrup (57 mg, 43%, α:β = 86:14,). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 3.61–3.78 (m, 2H), 4.08–4.11 (t, *J* = 3.6 Hz, 1H), 4.18–4.24 (m, 1H), 4.24–4.28 (m, 1H), 4.45–4.62 (m, 6H), 5.60-5.65 (d, *J* = 7.5 Hz, 1H, anomeric proton), 7.21–7.39 (m, 17H), 7.41–7.46 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.89, 71.94, 72.58, 73.39, 82.61, 83.19, 84.28, 89.95, 127.65, 127.76, 127.85, 127.93, 127.99, 128.36, 128.45, 128.48, 128.97, 132.31, 137.25, 137.68, 138.12. HRMS (MALDI-TOF): m/z calculated for $C_{32}H_{31}ClO_4SNa$ 569.1529 [M+Na$^+$]; found 569.1531.

1-Napthylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**24**)

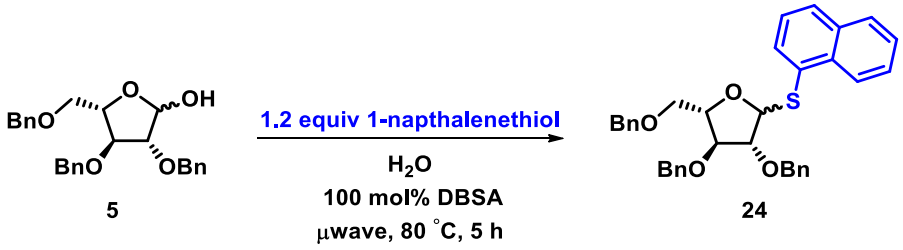


Figure 2.25. Synthesis of 1-napthylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**24**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and napthalenethiol (40 μL, 0.29 mmol) were added in a microwave vessel followed by a

stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.3). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. 1-Napthylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**24**) was obtained as a pale yellow solid (64 mg, 47%, α:β = 14:86,). ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ_H 3.62–3.68 (m, 2H), 4.02–4.06 (dd, *J* = 6.7, 3.1 Hz, 1H), 4.23–4.26 (t, *J* = 2.8 Hz, 1H), 4.43–4.60 (m, 7H), 5.58-5.62 (d, *J* = 2.2 Hz, 1H, anomeric proton), 7.21–7.37 (m, 15H), 7.38–7.56 (m, 3H), 7.77–7.87 (m, 3H), 8.44–8.49 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.18, 72.16, 72.31, 73.32, 80.86, 83.78, 88.77, 90.58, 125.53, 125.73, 126.18, 126.58, 127.57, 127.71, 127.75, 127.80, 127.89, 128.03, 128.31, 128.55, 131.68, 131.83, 134.04, 137.36, 137.78, 138.13. HRMS (MALDI-TOF): m/z calculated for $C_{36}H_{34}O_4SNa$ 585.2075 [M+Na^+]; found 585.2066.

2, 2-Thiazolylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**25**)

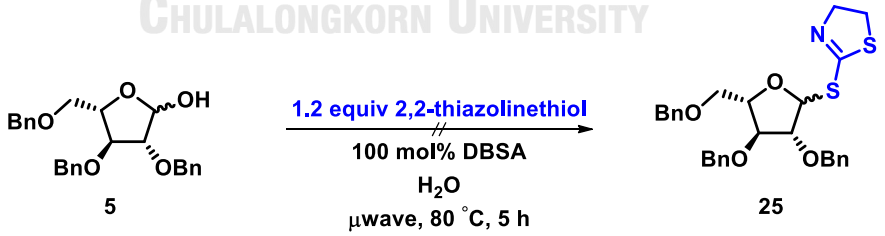


Figure 2.26. Synthesis of 2, 2-thiazolylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**25**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 2,2-thiazolinethiol (39 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5

h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.3). After the starting material **5** was consumed, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (3 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. However, there was no undesired product.

2-Benzothiazolylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**26**)

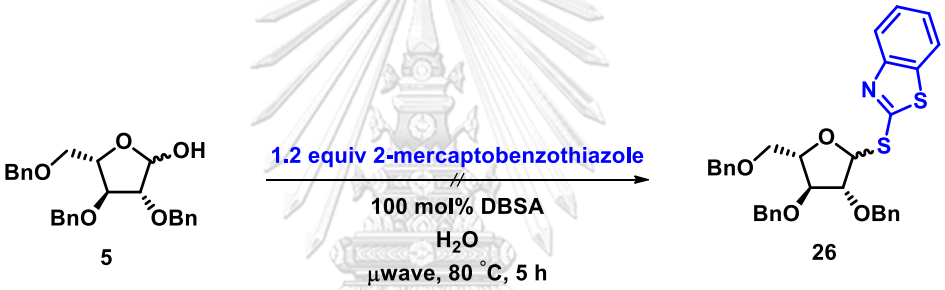


Figure 2.27. Synthesis of 2-benzothiazolylthio 2,3,5-tri-*O*-benzyl-L-arabino-furanoside (**26**).

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 2-mercaptobenzothiazole (48 mg, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.3). After the starting material **5** was consumed, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel

using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. However, there was no undesired product.

2.9.4 Substrate scope of furanoside and pyranoside donors

Dodecylthio 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside (**27**)

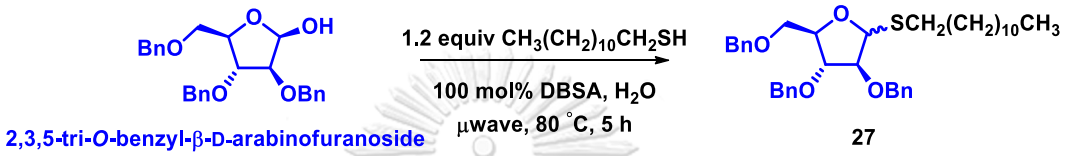


Figure 2.28. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside (**27**).

2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.4). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (**27**) was obtained as a pale yellow syrup (α/β = 83/17, 96 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.82–0.94 (t, *J* = 6.7 Hz, 3H), 1.21–1.34 (m, 18H), 1.56–1.65 (m, 2H), 2.62–2.68 (t, *J* = 6.7 Hz, 2H), 3.61–3.76 (m, 2H), 4.02–4.07 (t, d, *J* = 3.9 Hz, 2H), 4.11–4.19 (m, 2H), 4.47–4.61 (m, 6H), 5.36–5.40 (d, *J* = 4.9 Hz, 1H, anomeric proton), 7.22–7.36 (m, 15H). MALDI-TOF: m/z calculated for $C_{38}H_{52}O_4SNa$ 627.3484 [$M+Na^+$]; found 627.3466.

Dodecylthio 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**28**)

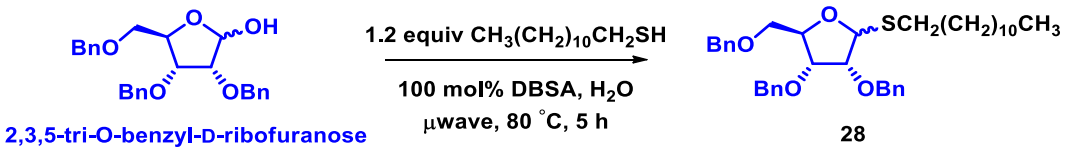


Figure 2.29. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**28**).

2,3,5-Tri-*O*-benzyl-D-ribofuranose (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.4). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-D-ribofuranose (**32**) was obtained as a pale yellow syrup (105 mg, 73%, α:β = 15:85,). ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ_H 0.86–0.90 (t, *J* = 6.7 Hz, 3H), 1.15–1.40 (m, 18H), 1.52–1.68 (m, 2H), 2.23–2.71 (m, 2H), 3.51–3.62 (m, 2H), 3.85–3.88 (m, 1H), 3.98–4.03 (m, 1H), 4.25–4.31 (m, 1H), 4.45–4.65 (m, 6H), 5.20–5.23 (m, *J* = 4.0 Hz, 1H, anomeric proton), 7.23–7.37 (m, 15H). MALDI-TOF: m/z calculated for $C_{38}H_{52}O_4SNa$ 627.3484 [M+Na^+]; found 627.3463.

Dodecylthio 2,3,5-tri-*O*-benzyl-D-xylofuranoside (**29**)

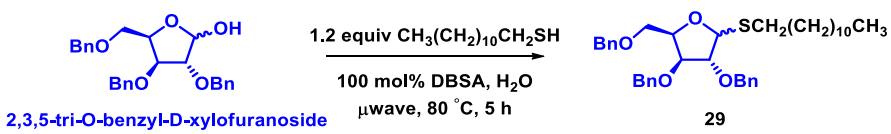


Figure 2.30. Synthesis of dodecylthio 2,3,5-tri-*O*-benzyl-D-xylofuranoside (**29**).

2,3,5-Tri-*O*-benzyl-D-xylofuranoside (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.4). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-D-xylofuranoside (**29**) was obtained as a pale yellow syrup (105 mg, 73%, α:β = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.85–0.90 (t, *J* = 6.6 Hz, 3H), 1.21–1.42 (m, 18H), 1.56–1.67 (m, 2H), 2.62–2.69 (t, *J* = 6.6 Hz, 2H), 3.64–3.85 (m, 2H), 3.96–4.01 (m, 1H), 4.06–4.11 (m, 1H), 4.12–4.16 (m, 1H), 4.42–4.66 (m, 6H), 5.52–5.55 (s, 1H, anomeric proton), 7.20–7.45 (m, 15H). MALDI-TOF: m/z calculated for $C_{38}H_{52}O_4SNa$ 627.3484 [M+Na$^+$]; found 627.3463.

Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**30**)

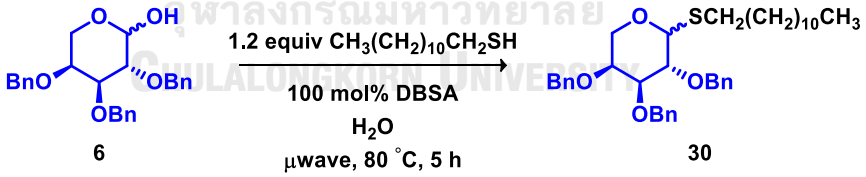


Figure 2.31. Synthesis of Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**30**).

2,3,5-Tri-*O*-benzyl-L-arabinopyranose **6** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 ×

2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**30**) was obtained as a pale yellow syrup (86 mg, 60%, α:β = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) α-anomer: δ_H 0.76–0.84 (t, *J* = 6.6 Hz, 3H), 1.09–1.32 (m, 18H), 1.46–1.62 (m, 2H), 2.42–2.65 (m, 2H), 3.58–3.67 (m, 2H), 3.70–3.77 (m, 1H), 3.84–3.96 (m, 2H), 4.51–4.65 (m, 6H), 5.11–5.15 (d, *J* = 3.5 Hz, 1H, anomeric proton), 7.17–7.32 (m, 15H). MALDI-TOF: m/z calculated for $C_{38}H_{52}O_4SNa$ 627.3484 [M+Na^+]; found 627.3485.

Dodecylthio 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (**31**)

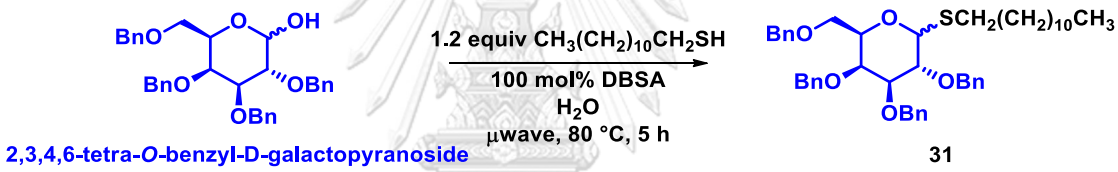


Figure 2.32. Synthesis of dodecylthio 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (**31**).

2,3,5-Tri-*O*-benzyl-D-galactopyranoside (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.32). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (**31**) was obtained as a pale yellow syrup (551 mg, 32%, α:β = 40:60,). ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ_H 0.84–0.91 (t, *J* = 6.7 Hz, 3H), 1.17–1.37

(m, 18H), 1.52–1.65 (m, 2H), 2.38–2.60 (m, 2H), 3.47–3.61 (m, 2H), 3.76–3.82 (m, 1H), 3.90–3.96 (m, 1H), 4.24–4.45 (m, 2H), 4.65–4.91 (m, 6H), 5.42–5.48 (d, *J* = 5.5 Hz, 1H, anomeric proton), 7.20–7.41 (m, 15H). MALDI-TOF: m/z calculated for $C_{46}H_{60}O_4SNa$ 747.4059 [M+Na^+]; found 747.4084.

Dodecylthio 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**32**)

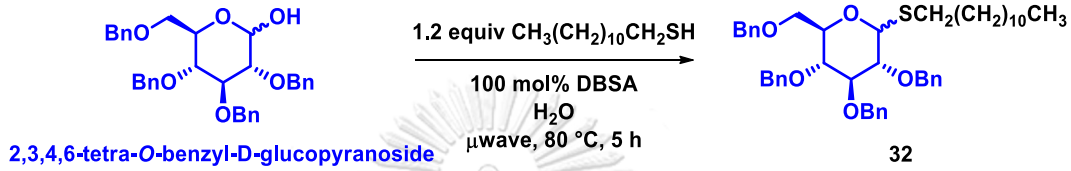


Figure 2.33 Synthesis of dodecylthio 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**32**).

2,3,5-Tri-*O*-benzyl-D-galactopyranoside (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of DBSA (0.5 mL). It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.32). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**32**) was obtained as a pale yellow syrup (551 mg, 45%, α:β = 40:60,). ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ_H 0.84–0.91 (t, *J* = 6.7 Hz, 3H), 1.19–1.40 (m, 18H), 1.54–1.66 (m, 2H), 2.43–2.60 (m, 2H), 3.41–3.49 (m, 1H), 3.57–3.70 (m, 2H), 3.72–3.78 (m, 1H), 3.80–3.89 (m, 2H), 4.40–4.87 (m, 6H), 5.35–5.39 (d, *J* = 4.9 Hz, 1H, anomeric proton), 7.12–7.39 (m, 15H). MALDI-TOF: m/z calculated for $C_{46}H_{60}O_4SNa$ 747.4059 [M+Na^+]; found 747.4035.

2.10 Mitigation of using organic solvent in work-up

2.10.1 Dilution with water

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of acids and surfactants. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, water (1.5 mL) was added and centrifuged. The precipitated phase was filtered and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup (48 mg, 33%, α:β = 50:50).

2.10.2 Dilution with saturated sodium hydrogen carbonate (sat. $NaHCO_3$)

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **5** (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by stock solutions of acids and surfactants. It was stirred in a microwave reactor at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography (hexanes:ethyl acetate 4:1; *p*-anisaldehyde, R_f = 0.40). After the reaction reached to the completion, sat. $NaHCO_3$ (1.5 mL) was added and then centrifuged. The emulsion phase was concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**) was obtained as a yellow syrup. (73 mg, 50%, α:β = 50:50).

CHAPTER III

Results and discussion

Here in, a facile and environmentally friendly method for the synthesis of thioglycosides by dehydrative glycosylation was developed. The dehydration was carried out using DBSA micellar system. This method was developed in order to reduce multi-step synthesis and generation of waste according to previous report.[33] Various reaction parameters such as surfactants, amount of surfactant, reaction temperature, and Lewis acids were investigated for the optimal conditions. Study of substrate scope of thiols (aliphatic, aromatic, and heterocyclic) and carbohydrates (furanoside and pyranoside) were also carried out (Figure 3.1).

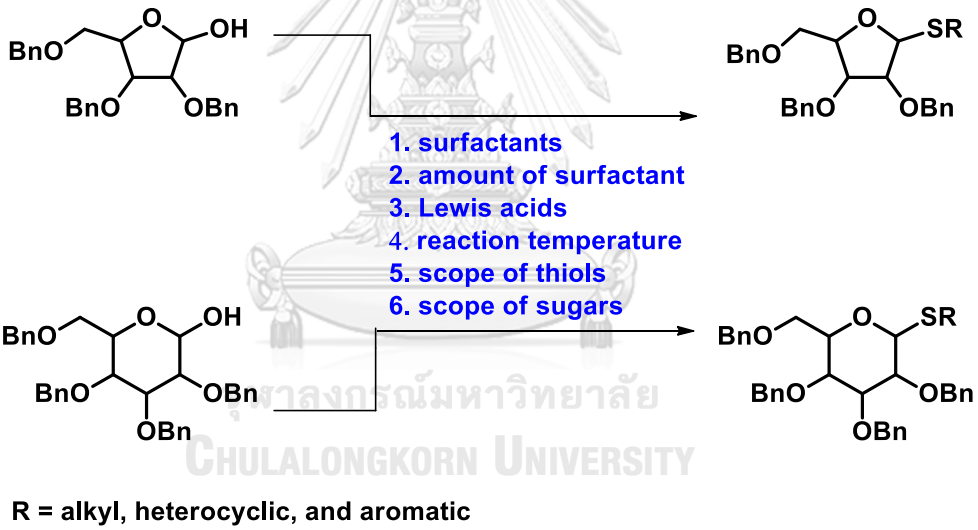


Figure 3.1. Scope of this work; dehydrative glycosylation in micellar system enabled by DBSA.

Working mechanism of this work is based on micellar formation of DBSA surfactant. In aqueous media, formation of emulsion by DBSA surfactant generates hydrophobic pocket. This would concentrate acidic proton on the surface of the emulsion droplet and enhance the rate of dehydration to reach equilibrium. Water molecules generated during the dehydration is then removed from the droplet due

to the hydrophobic nature of their interior (Figure 3.2). As a result, the dehydration reaction would efficiently proceed even in the presence of large amount of water as solvent.[53]

Figure 3.2. Illustration of dehydrative glycosylation between L-arabinose model and thiols in the presence of dodecylbenzenesulfonic acid (DBSA).

3.1 Optimization for dehydrative glycosylation

3.1.1 Synthesis of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside and methyl 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (3 and 4) as glycosyl donors

L-arabinose was first used as a model substrate in this study due to its lower cost compared to other furanosides. Preparation of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**3**) and methyl 2,3,4-tri-*O*-benzyl-L-arabinopyranoside (**4**) was achieved following methanolysis and benzylation (Figure 3.3).[45] Methyl L-arabinofuranoside (**1**) was synthesized by dissolving commercially available L-arabinose in anhydrous methanol followed by dropwise addition of propionyl chloride. The *in situ* generated HCl in MeOH then acted as a catalyst to accelerate MeOH substitution at anomeric position of L-arabinose. The reaction mixture was stirred for 4 hours at room temperature to yield a mixture of methyl L-

arabinofuranoside and methyl L-arabinopyranoside. Reaction mixture was concentrated to dryness and subjected to next step without further purification.

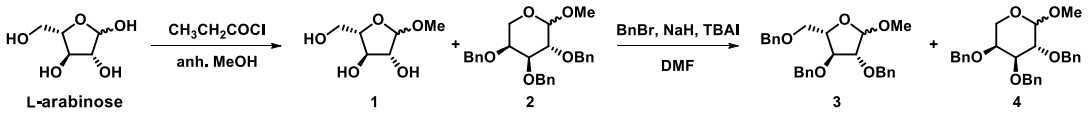


Figure 3.3. Synthesis of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside and methyl 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**3** and **4**).

Protection of the remaining free hydroxyl groups as benzyl ethers was performed by using standard benzylation conditions (BnBr, NaH, catalytic TBAI in DMF). Methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**3**) and pyranoside (**4**) were obtained as colorless syrup in 60% (α:β = 50:50) and 25% (α:β = 50:50), respectively over two steps.[54]

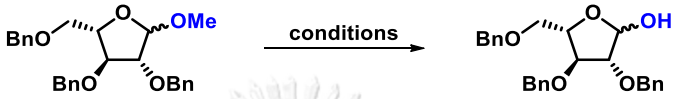
3.1.1.1. Synthesis of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (3)

Optimization for acidic hydrolysis reaction of 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (3)

Deprotection of the anomeric methoxy group was carried out under acidic conditions.[46] Surprisingly, the cleavage was not straightforward as originally expected due to the high stability of the *O*-methyl furanoside **3**. Several hydrolysis conditions were examined. The investigation of this deprotection was presented in Table 3.1. Initially, heating precursor **3** at 70 $^{\circ}$C in a mixture of 2:1 acetic acid and sulfuric acid provided only trace amount of the desired lactol product (**5**) monitored by TLC (entry 1). Addition of polar organic solvent such as tetrahydrofuran and increasing temperature were considered to enhance the solubility of furanoside **3** in the hydrolysis media (entry 2). However, the product was still detected in trace amount.

Then, a mixture of 1:1 HCl and dioxane was used, but there was no reaction occurred (entry 3).

Table 3.1. Optimization for the hydrolysis of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**3**)



3 5

Entry	Conditions	Temp (°C)	Time (h)	Yield[a]
1	CH_3COOH: 1.0 M H_2SO_4 (2:1)	70	72	trace[b]
2	CH_3COOH: 2.0 M H_2SO_4: THF (2:1:1)	100	48	trace[b]
3	0.1M HCl: dioxane (1:1)	60	48	NR[c]
4	0.1M DBSA: H_2O (1:1)	80	48	NR[c]
5	CH_3COOH:H_2O (4:1)	115	24	30%
6	0.1M HCl:dioxane (1:1)	70, μwave[d]	1	30%
7	CH_3COOH:H_2O (4:1)	115, μwave[d]	0.45	55%
8	CH_3COOH:H_2O (4:1)	115, μwave[d]	1	60%
9	CH_3COOH:H_2O (4:1)	125, μwave[d]	2	65%
10	CH_3COOH:H_2O (4:1)	130, μwave[d]	2	72%
11	CH_3COOH:H_2O (4:1)	150, μwave[d]	2	90%

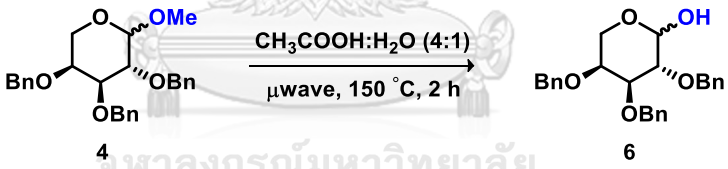
[a] Isolated yield. [b] Reaction mixture was monitored by TLC. [c] NR = No reaction; it was mornitored by TLC. [d] μwave = microwave irradiation

DBSA in water was applied for hydrolysis reaction (entry 4). Unfortunately, there was no reaction occurred. Next, 4:1 mixture of acetic acid and water was used, however only poor yield (30%) of the hydrolysis product was obtained (entry 5). Heating by microwave irradiation was then employed instead of conventional oil bath heating. The hydrolysis media in entry 3 (1:1 HCl: dioxane) was conducted again

by microwave irradiation instead of by oil bath. Nevertheless, the product was still obtained in low yield (entry 6). Thus, we decided to use 4:1 CH_3COOH: H_2O as hydrolysis media and the reaction temperature and reaction time were optimized (entries 7–11). It was found that the best conditions were CH_3COOH: H_2O (4:1) under microwave irradiation at 150 °C for 2 h (entry 11), which gave the desired lactol product **5** in 90% (α:β = 50:50).

3.1.1.2. Synthesis of 2,3,5-tri-O-benzyl-L-arabinopyranoside (6)

Methyl 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**4**) were hydrolyzed by the same hydrolysis conditions as previously described by using CH_3COOH: H_2O (4:1) under microwave irradiation at 150 °C for 2 hours (Figure 3.4). It gave the desired product **6** in 63% yield (α:β = 50:50) along with some staring material left over. Hydrolysis reaction did not proceed completely possibly due to conformational rigidity of the six-membered pyranoside ring.



4 6

Figure 3.4. Hydrolysis of 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**6**).

3.1.2 Reaction optimization

Dehydrative thioglycosylation in micellar system: A study model

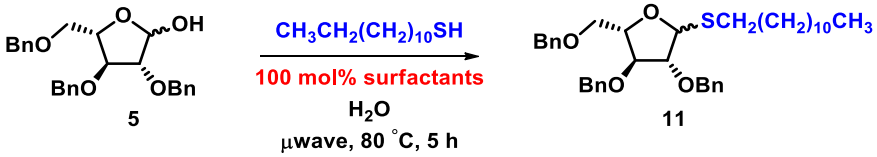
2,3,5-Tri-*O*-benzyl-L-arabinofuranoside (**5**) and 1-dodecanethiol were chosen for this optimization. Both precursors are relatively hydrophobic molecules thus they were selected as model substrates. Optimal reaction conditions for dehydrative glycosylation in the micellar media were investigated by varying several parameters

such as type of surfactants, amount of surfactant, reaction time, reaction temperature, and type of Lewis acid.

3.1.2.1. Effect of different surfactants

Effect of surfactants on the dehydrative glycosylation are shown in Table 3.2. Initial attempt was commenced by investigating Brønsted acid-type surfactants in the glycosylation between lactol **5** and 1-dodecanethiol, starting with DBSA surfactant. Thiofuranoside product was afforded in good yield without selectivity (entry 1). Then, perfluorooctanesulfonic acid (PFOS; $CF_3(CF_2)_7SO_3H$) and perfluorooctanoic acid (PFOA; $CF_3(CF_2)_6COOH$) were elucidated. Both of them (sulfonic and carboxylic acid) were reported as efficient Brønsted acid-type surfactants in emulsion polymerization. The results revealed that the desired dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside product (**11**) was obtained in low yield in the presence of PFOS (entry 2). On the other hand, yield was dramatically increased to 72% when using PFOA as surfactant (entry 3). In both cases the α–anomer was inferentially formed.

Table 3.2. Effect of different surfactants on dehydrative glycosylation

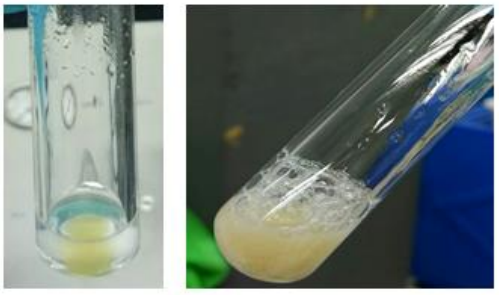


Entry	Surfactant	Yield (α:β)[a]
1	PFOS[b] (pka <1)	17% (71:29)
2	PFOA[c] (pka <1)	72% (71:29)
3	DBSA[d] (pka <1)	72% (50:50)
4	TPGS-750-M[e]	NR[f]
5	TPGS-750-M : *p*-TSA[g]	56% (91:9)

6	0.1 M H_2SO_4 (pka = 1.92)	trace[h]
7	CH_3COOH (pka = 4.75)	NR[f]
8	*p*-TSA (pka = -2.6)	17% (67:33)
9	4-hydroxybenzenesulfonic acid (pka < 1)	27% (71:29)

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. [b] PFOS = heptadecafluorooctanesulfonic acid ($CF_3(CF_2)_7SO_3H$). [c] PFOA = perfluorooctanoic acid ($CF_3(CF_2)_6COOH$). [d] DBSA = 4-dodecylbenzenesulfonic acid. [e] TPGS-750-M = DL-α-tocopherol methoxypolyethylene glycol succinate. [f] NR = No reaction; it was observed by TLC. [g] *p*-TSA = *p*-toluenesulfonic acid. [h] Reaction mixture was observed by TLC. μwave = microwave irradiation.

It's also worth mentioning that the reaction mixture of PFOS formed a bilayer between organic and aqueous phase (Figure 3.5a). However, when using PFOA the reaction mixture appeared as white turbid emulsion (Figure 3.5b). Formation of emulsion droplet is crucial for the promotion of the present dehydrative glycosylation. This could explain superior activity of PFOA over PFOS. Despite of good reaction yield, PFOA was not considered as a suitable surfactant in this study, since it is extremely persistent in environment, bio-accumulative and relatively toxic compared to other surfactants.[28]



(a) (b)

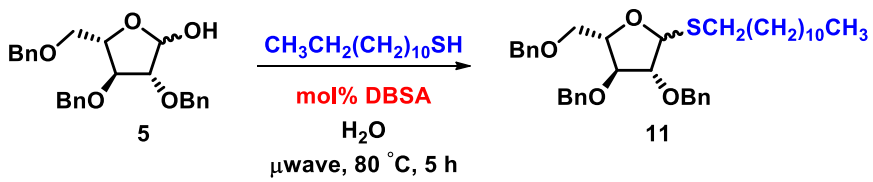
Figure 3.5. The reaction mixture vessels containing (a) PFOS (bilayer), (b) PFOA (yellow turbid emulsion).

Next, TPGS-750-M surfactant was applied in the glycosylation, but no reaction was occurred (entry 4). Addition of *p*-TSA to increase the acidity of the reaction gave moderate yield of the desired product (56%, entry 5). This clarify emphasizes the crucial roles of both Brønsted acid and surfactant. Other organic and inorganic Brønsted acids were also studied. The reaction performed with 0.1 M H_2SO_4 only provided product in trace amount (entry 6). When using short chain carboxylic acid; CH_3COOH, there was no product formation (entry 7). Next, small molecules of sulfonic acid such as *p*-toluenesulfonic acid (*p*-TSA) and 4-hydroxybenzenesulfonic acids were investigated (entries 8 and 9). The products were obtained in low yields in both cases, 17% and 27% respectively. It was clear that the micellar formation capability of Brønsted acid is necessary for successful dehydrative glycosylation. Therefore, this research will focus in using DBSA as Brønsted acid-type surfactants because of the highest yield and efficiency.

3.1.2.2 Effect of DBSA amount

Investigation of optimal DBSA loading was performed (Table 3.3). Addition of 10 mol% DBSA at 80 °C according to the previous reported,[17] afforded a mixture of anomeric products **10**, albeit in poor 36% yield (entry 1). From TLC monitoring, some starting material was not consumed and was recovered after column chromatography. Thus we also calculated the product yield in term of yield based on recovered starting material (brsm) in order to elucidate the reaction efficiency more accurately.

Table 3.3. Optimization of DBSA loading



Entry	DBSA (mol%)	Yield (α:β)[a]	Brsm[b] Yield

1	10	36% (50:50)	40%
2	20	56% (50:50)	75%
3	30	51% (50:50)	98%
4	40	50% (50:50)	77%
5	50	54% (50:50)	78%
6	80	65% (50:50)	93%
7	100	72% (50:50)	99%
8	200	69% (50:50)	95%
9	-	NR[c]	-

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. [b] brsm = based on recovered starting material. [c] NR = No reaction; it was observed by TLC. μwave = microwave.

When amount of surfactant was increased to 20–50 mol%, the product **10** was obtained in higher yield (entries 2–5). The yield were significantly improved when the amount of DBSA were used up to 80 and 100 mol% (entries 6–7). Employing excess DBSA (200 mol%) resulted in comparable yield, however the reaction mixture was viscous and very difficult to stir (entry 8). There was no formation of the product in the absence using DBSA (entry 9). Hence, the optimal DBSA loading for was 100 mol% which yielded product up to 72% isolated yield and 99% brsm yield (entry 7).

The reaction profile of DBSA loading in dehydrative reaction was illustrated in Figure 3.6. Firstly, the desired product was obtained poor yield of 10 mol% DBSA loading. Then, product yields were risen rapidly as catalytic amount of DBSA (20–50 mol%). The yields were enhanced considerably at 80–100 mol%. . It was becoming the highest yield at 100 mol% of DBSA, which was the optimal DBSA loading. Finally, yields were gradually decreasing at 200 mol% because of the high viscosity of the reaction.

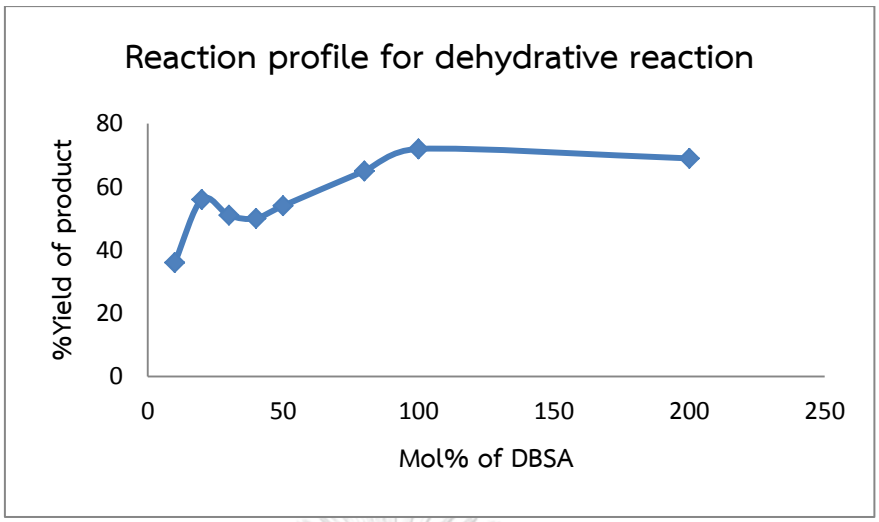
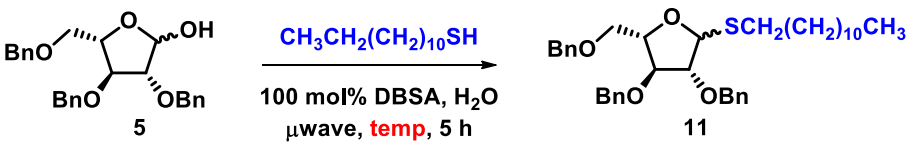


Figure 3.6. Reaction profile of dehydrative reaction in the presence of various concentration of DBSA.

3.1.2.3 Effect of reaction temperatures

With the optimal DBSA loading (100 mol%) in hand, we next examined the effect of reaction temperatures (Table 3.4). From the results, it was shown that yields of the dehydrative glycosylation were also affected by the reaction temperature. When the temperature was lowered from 80 °C (entry 3) to 60 °C and 40 °C, % yield decreased from 72 to 57 and 44, respectively (entries 1–2). On the other hand, when the temperature was raised to 100 °C, lower yield was obtained (entry 4) and at 120 °C the reaction mixture decomposed within 1 h (entry 5).

Table 3.4. Optimization of reaction temperature



Entry	Temp (°C)	Yield (α:β)[a]	Brsm[b] Yield
1	40	44% (50:50)	99%

2	60	57% (50:50)	99%
3	80	72% (50:50)	99%
4	100	64% (50:50)	80%
5	120	decomposition[c]	-
6	80[d]	54% (50:50)	84%

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. [b] brsm = based on recovered starting material. [c] NR = No reaction; it was observed by TLC. [C]The reaction mixture decomposed at 120 °C within 1 h. [d] The product was obtained under conventional heating for 28 h. μwave = microwave.

Dehydrative glycosylation was later conducted by conventional oil bath heating, in order to compare with microwave reactor's results (entry 6). The reaction mixture was stirred at 80 °C in oil bath for 48 hours. The obtained product (54%) was lower than using microwave reactor as well as the reaction time was much longer (48 h compared to 5 h). Thus, performing the reaction under microwave irradiation was more efficient since shorter reaction time and less energy consumption were required. Hence, the optimal reaction temperature for this reaction was 80 °C under microwave irradiation with 100 mol% DBSA loading (entry 3).

Figure 3.7 represents typical TLCs and reaction vessels of the dehydrative glycosylation described in Table 3.3 and Table 3.4. It showed that the milky suspension of 10 mol% DBSA at 80 ºC (Table 3.3, entry 1) gave low yield (Figure 3.7a). In contrast, high yield of the product was obtained from a pale-yellow suspension with 100 mol% DBSA at 80 ºC (Table 3.3, entry 7, Figure 3.7b). In addition, the reaction mixture decomposed within 1 hour of microwave irradiation and turned to black-brown solution at 120 ºC (Table 3.4, entry 5, Figure 3.7c).

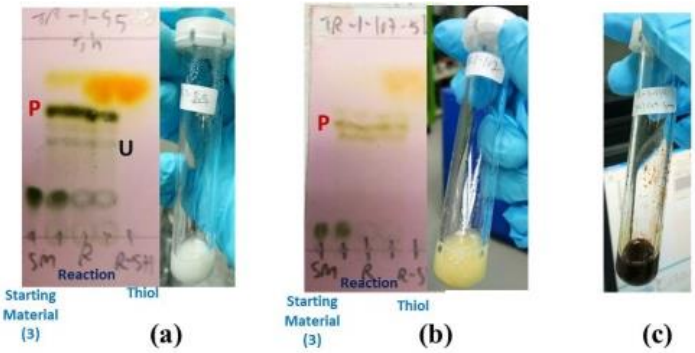
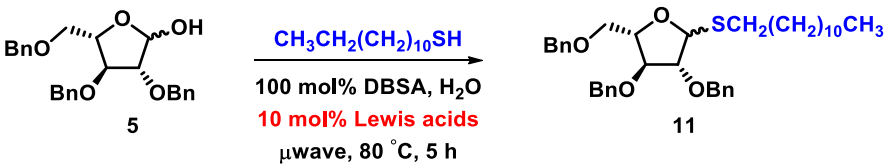


Figure 3.7. TLCs and reaction mixture vessels. (a) 10 mol% DBSA, 80 °C (Table 3.3, entry 1). (b) 100 mol% DBSA, 80 °C (Table 3.4, entry 3). (c) 100 mol% DBSA, 120 °C (Table 3.4, entry 5).

3.1.2.4 Effect of Lewis acids

Lanthanide salts have been reported as stable Lewis acids in aqueous solution. They were applied as catalysts in numerous chemical transformations.[44, 55] Glycosylation of lactol **5** with 1-dodecanethiol in the presence of triflate and chloride salts of metal group 1–11 as well as rare earth metals were screened; $Cu(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, $Pr(OTf)_3$, $CrCl_3$, and $SrCl_2$. The results are summarized in Table 3.5.

Table 3.5. Optimization of additive Lewis acids



Entry	Lewis acids	Yield (α:β)[a]
1	$Sc(OTf)_3$	59% (50:50)
2	$Yb(OTf)_3$	63% (50:50)

3	$La(OTf)_3$	67% (50:50)
4	$Gd(OTf)_3$	64% (50:50)
5	$Nd(OTf)_3$	64% (50:50)
6	$Pr(OTf)_3$	56% (50:50)
7	$Cu(OTf)_2$	56% (50:50)
8	$Zn(OTf)_2$	15% (50:50)
9	$CrCl_3$	58% (50:50)
10	$SrCl_2$	56% (50:50)

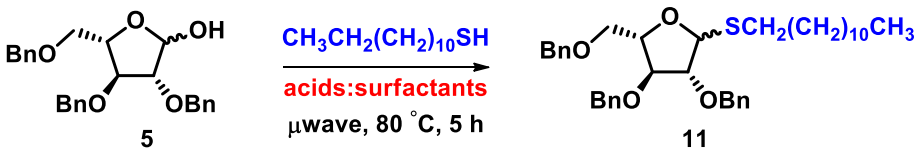
[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. μwave = microwave.

The effect of lanthanide salts were investigated under our standard dehydrative glycosylation conditions. Addition of 10 mol% lanthanide Lewis acid such as $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, and $Pr(OTf)_3$ all provided similar yields (56–67%) of the desired product **11** (entries 1–6). Other Lewis acids such as $Cu(OTf)_2$, $CrCl_3$, and $SrCl_2$ also gave comparable yield to the lanthanide Lewis acid (entries 7, 9–6). Interestingly, decomposition of lactol **5** was observed in the presence of $Zn(OTf)_2$, resulting in a much lower yield (entry 8). On the contrary of previous reports, additions of lanthanide Lewis acid did not show promotion of the glycosylation under the DBSA micellar condition since the products were obtained in a range of 50–60 %. This was lower that our optimized conditions without Lewis acid (entry 11, 72% yield), thus we concluded that Lewis acid was not necessary for our dehydrative glycosylation.

3.1.2.5 The effect of acids and surfactant (DBSNa)

It was shown that addition of DBSA was essential for the successful dehydrative glycosylation (entry 7, Table 3.3). In the absence of DBSA, no desired product was afforded (entry 9, Table 3.3). We wondered that this success was due to either micellar formation capability of dodecylbenzene sulfonate anion or acidity of the catalyst or both. Next, we set investigation to probe whether acid (Lewis/BrØnsted acid) or surfactant alone could generate the corresponding thioglycoside products **11** (Table 3.6). In case of *p*-toluenesulfonic acid (*p*-TSA) whose chemical structure and pK_a were similar to DBSA. However, it gave very low yield of the product (entry 1). The methyl group of *p*-TSA does not form micelles, even though it helps to solubilize organic molecule by the formation of hydrogen bond as hydrotropes. Hydrotropes have a much smaller size than micelles resulting in lower yield of the thioglycoside product.[56] Therefore, DBSNa (sodium dodecylbenzenesulfonate) was added to increase hydrophobic interiors forming larger micellar pockets and improve the yield of product. The amount of DBSNa was varied from 5 to 100 mol%. The results indicated that the yield increased evidently at of 5 mol% DBSNa (entry 2). When DBSNa was added up to 10 mol%, the highest yield was obtained in 60% yield (entry 3). When, DBSNa were used as stoichiometric levels, the yields were reduced gradually (entries 4–7). Importantly, no product was identified in the presence of DBSNa alone without acid (entry 8). The ionic distribution at charge aqueous interface has the influence with micelle structure. The more DBSNa added, the lower yield of products obtained and this might be a result of smaller size of micelle. [57]

Table 3.6. The effect of acids and surfactants



Entry	Acid	Surfactant	Yield[a]
1	100 mol% *p*-TSA[b]	-	17
2	100 mol% *p*-TSA	5 mol% DBSNa[c]	55
3	100 mol% *p*-TSA	10 mol% DBSNa	60
4	100 mol% *p*-TSA	30 mol% DBSNa	43
5	100 mol% *p*-TSA	50 mol% DBSNa	38
6	100 mol% *p*-TSA	80 mol% DBSNa	44
7	100 mol% *p*-TSA	100 mol% DBSNa	36
8	-	100 mol% DBSNa	NR[d]
9	10 mol% $Sc(OTf)_3$	-	NR[d]
10	30 mol% $Sc(OTf)_3$	100 mol% DBSNa	trace[e]
11	100 mol% $Sc(OTf)_3$	100 mol% DBSNa	13[f]
12	30 mol% $Yb(OTf)_3$	100 mol% DBSNa	trace[e]

[a] Yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton, α:β = 67:33. [b] *p*-TSA = *p*-toluenesulfonic acid. [c] DBSNa = sodium dodecylbenzenesulfonate. [d] NR = No reaction; it was observed by TLC. [e] Reaction mixture was observed by TLC. μwave = microwave.

$Sc(OTf)_3$ and $Yb(OTf)_3$ were chosen to study of the influence of Lewis acid. No reaction was occurred in the presence of 10 mol% of $Sc(OTf)_3$ by TLC monitoring

(entry 9). A combination of 100 mol% DBSNa and 30 mol% $Sc(OTf)_3$ or $Yb(OTf)_3$ gave only trace amount of the product (entries 10 and 11). When the amount of $Sc(OTf)_3$ was increased to 100 mol%, the product was obtained in 13% yield (entry 12). Consequently, from the results in Table 6, BrØnsted acid-surfactant has substantial influence over only either surfactant (DBSNa) or acid (BrØnsted and Lewis acid) to perform the desired thioglycoside product. When *p*-TSA was added without the association of surfactant (DBSNa), low yield of product was gained. On the other hand, it gave the good yield of product when DBSNa as used in catalytic amount.

3.2 Synthesis of 2,3,5-tri-O-benzyl-1-O-acetyl-L-arabinofuranoside (7)

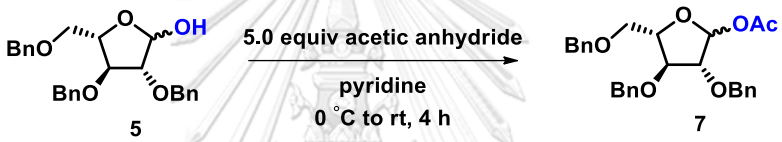


Figure 3.8. Synthesis of 2,3,5-tri-*O*-benzyl-1-*O*-acetyl-L-arabinofuranoside (**7**).

2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-L-arabinofuranoside (**7**) was prepared by acetylation reaction of **5** under acetic anhydride in pyridine at 0 °C to room temperature for 4 hours. The desired product **7** (Figure 3.8) was obtained as a clear yellow syrup in 90% yield (α:β = 44:56).

3.3 Synthesis of methyl 6-thio-2,3,4-tri-*O*-benzyl -D-glucopyranoside (10)

The study of glycosylation between lactol **5** and **10** as thiol acceptor was next explored. Methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**) was prepared from methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside precursor in 3 steps. The synthesis was adapted from previous reports.[50-52] The preparation of methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**) was shown in Figure 3.9. First, tosylation at a free hydroxyl of methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside was carried out. The reaction was conducted in anhydrous pyridine as solvent. TsCl in anhydrous pyridine was

added slowly at 0 °C and the reaction was stirred for overnight at room temperature under nitrogen atmosphere. The reaction gave the desired product **8** in 85% yield.

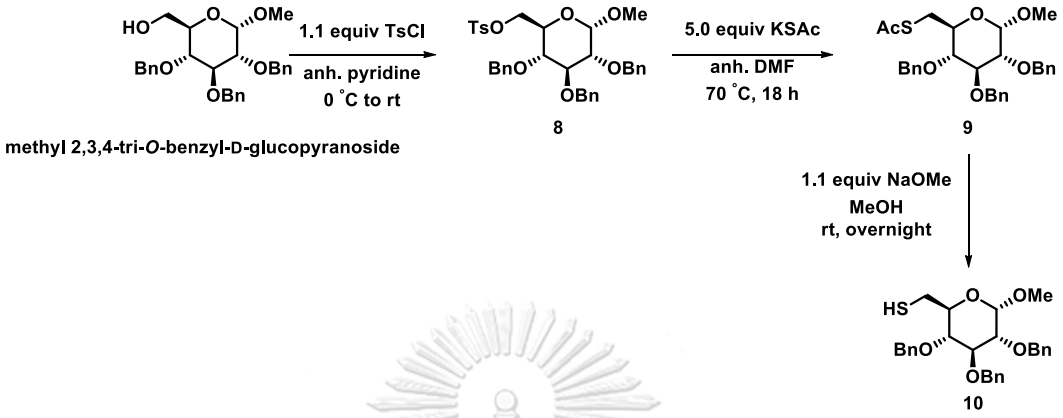


Figure 3.9. Synthesis of methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**).

Next, nucleophilic displacement of **8** with potassium thioacetate in dry DMF was conducted. Potassium thioacetate was added in several portions, and the reaction mixture was stirred at 70 °C for 18 h under nitrogen protection. The desired product methyl 6-thioacetyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**9**) was obtained in 98%. The last step for the preparation of **10** was deprotection of the thiol group in the presence of NaOMe in MeOH. Intermediate **9** was dissolved in MeOH. Then, sodium methoxide in MeOH was added dropwise, and the reaction mixture was stirred at room temperature overnight under nitrogen protection. It gave the product **10** as a clear yellow oil as in 88% yield.

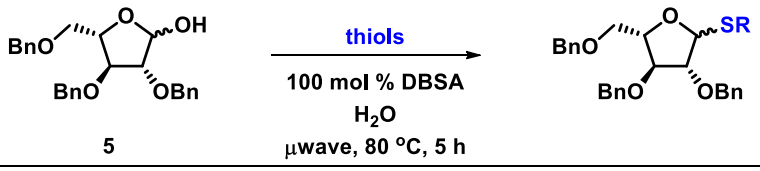
3.4 Substrate scopes of thioglycosylation

3.4.1 Thiofuranosides of aliphatic and aromatic thiols

The scope of the *S*-nucleophile was investigated as shown in Table 3.7 according to the optimal conditions. All reactions were performed in the presence of 100 mol% of DBSA under microwave irradiation at 80 °C for 5 h. The desired products from the primary and secondary aliphatic thiols (**11**–**19**) were obtained in the good

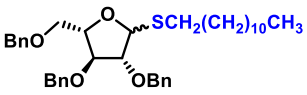
yields. Only the product (**20**) derived from tertiary aliphatic thiol was obtained in low yield. Unfortunately, thioglycosylation of the lactol **5** and methyl 6-thio-2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**) gave a pale yellow syrup (64 mg), that was not the desired product. Additionally, aromatic thiols bearing electron donating and withdrawing groups gave the moderate yields of the desired products (**22**–**23**). The product from of 1-napthalenethiol was also obtained in moderate yield (**24**). In case of the less reactive heterocyclic thiol nucleophiles, the products **25**–**26** could not be obtained. The reasons for low yielding of product may be explained by low hydrophobicity and reactivity of thiols. Nonetheless, highly water soluble tertiary aliphatic thiol such as *tert*-butylthiol did not penetrate into the micelle pockets, so the dehydrative glycosylation took place inefficiently resulting in low yield of product.

Table 3.7. Synthesis of thiofuranosides by dehydrative glycosylation with aliphatic and aromatic thiols

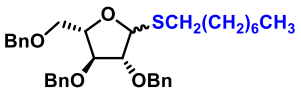


5

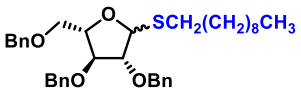
Aliphatic thiols[a]



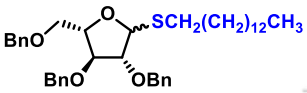
11 (α/β = 50/50, 72% yield)[a–b]



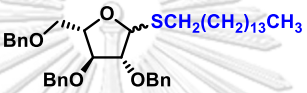
12 (α/β = 83/17, 71% yield)



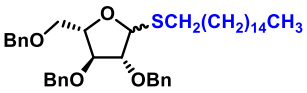
13 (α/β = 84/16, 67% yield)



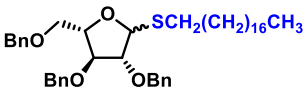
14 (α/β = 80/20, 65% yield)



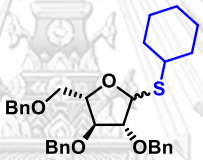
15 (α/β = 92/8, 58% yield)



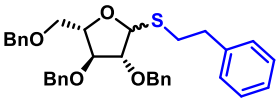
16 (α/β = 54/46, 58% yield)



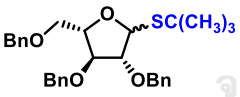
17 (α/β = 90/10, 63% yield)



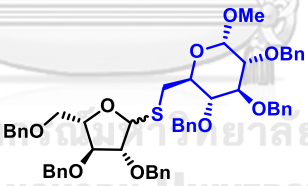
18 (α/β = 50:50, 45% yield)



19 (α/β = 60/40, 42% yield)

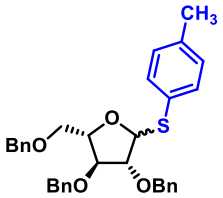


20 (α/β = 50/50, 24% yield)

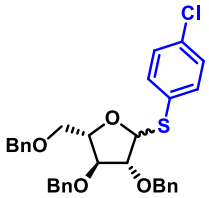


21
No desired product

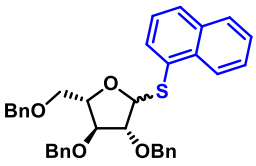
Aromatic thiols[a]



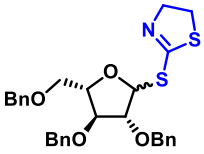
22 (α/β = 82/18, 41% yield)



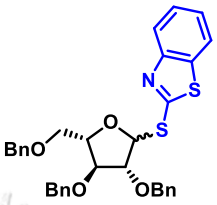
23 (α/β = 86/14, 43% yield)



24 (α/β = 14/86, 47% yield)



25 (No desired product)



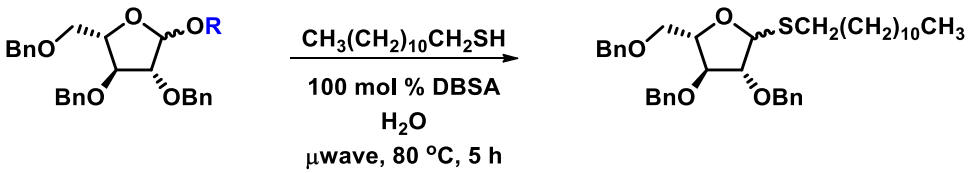
26 (No desired product)

[a] Isolated yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. μwave = microwave.

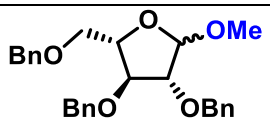
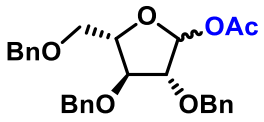
3.4.2 Effect of leaving group at anomeric carbon (C1)

Additionally, the effects of leaving groups at anomeric carbon were explored in both methoxy (**3**) and acetate (**7**) groups (Table 3.8). Acetate group provided decent yield of the product (entry 1), while methoxy as leaving group gave very poor yield (entry 2). It can be assumed that hydrolysis reaction may compete with dehydrative glycosylation and converse to hydroxyl group.

Table 3.8. Synthesis of furanosides by dehydrative glycosylation in various leaving groups



Entry	Furanoside	Yield (α:β)[a]
1		

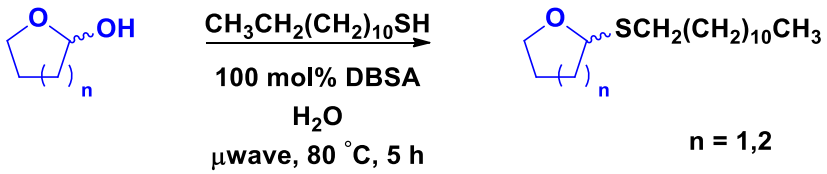
	 **3**	10 (91:9)
2	 **7**	60 (99:1)

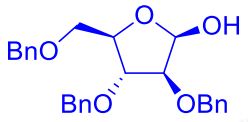
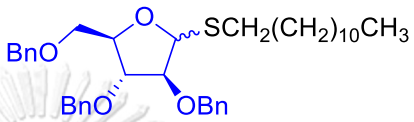
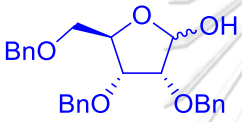
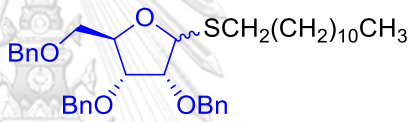
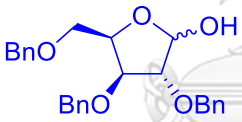
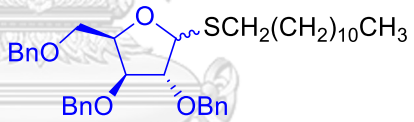
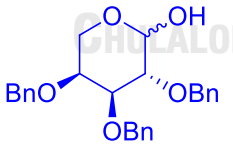
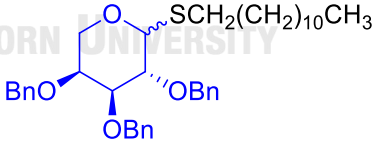
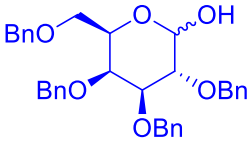
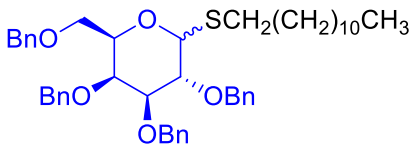
[a] Isolated yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. μwave = microwave.

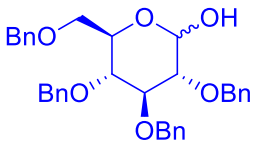
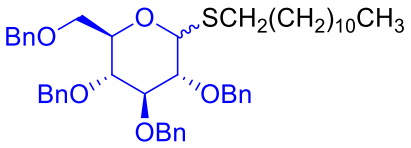
3.4.3 Dehydrative glycosylation of various furanoside and pyranoside

Next, dehydrative glycosylation of various substrates of both furanose and pyranose sugars by 1-dodecanethiol were investigated as shown in Table 3.9. 2,3,5-Tri-*O*-benzyl-β-D-arabinofuranoside, 2,3,5-tri-*O*-benzyl-D-ribofuranoside, and 2,3,5-tri-*O*-benzyl-D-xylofuranoside (entry 1–3) gave good yield of products (**27**–**29**) under the same optimal conditions. The pyranose sugar, 2,3,5-tri-*O*-benzyl-L-arabinopyranose (entry 4) also provided the desired product (**30**) in good yield. The corresponding products (**31**–**32**) from 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (entry 5–6) were obtained in low yield due to the poor reactivity of six-membered rings. Hence, the developed protocol for dehydrative glycosylation in micellar media can be applied for both furanose and pyranose sugars.

Table 3.9. Synthesis of thioglycosylation of various furanoside and pyranoside



Entry	Lactol	Product	Yield (α:β)[a]
1	 β-D-arabinofuranoside	 **27**	66% (83:17)
2	 D-ribofuranoside	 **28**	73% (15:85)
3	 D-xylofuranoside	 **29**	75% (50:50)
4	 L-arabinopyranoside	 **30**	60% (50:50)
5	 D-galactopyranoside	 **31**	32% (40:60)

6	 D-glucopyranoside	 **32**	45% (40:60)

[a] Isolated yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. μwave = microwave.

3.5 Mitigation of using organic solvent in work-up

Attempt to avoid from using organic solvents in work-up procedures was also considered in order to achieve a truly "green" synthesis. The experiments were carried out by using water and saturated $NaHCO_3$ instead of organic solvent extractions. Dilution the reaction mixture with water and saturated $NaHCO_3$ followed by centrifugation provided product **11** in only 10% and 50% respectively after column chromatography. Unfortunately, these methods gave diminished yield possibly due to a formation of emulsion phases and some of product was trapped in the aqueous layer. The reaction mixture separated into three phases after centrifugation (Figure 3.10). Emulsion phase of reaction at the top (the mixture of starting material and product), aqueous phase at the middle, and precipitated of inorganic salt at the bottom. To confirm the assumption that some of products were trapped in the aqueous phase, water layer was later extracted by ethyl acetate and analyzed by TLCs. It was found that some product was indeed present in the aqueous layer. Therefore, these procedures were not suitable replacement for organic extraction.

Figure 3.10. Work-up by using sat. $NaHCO_3$ (after centrifuge): emulsion phase of reaction at the top, aqueous phase at the middle, and precipitation at the bottom.

3.6 Proposed mechanism

According to the experiment results, we propose that the reaction begins by protonation of the anomeric hydroxyl group to form an oxocarbenium ion. The hydrophobic micelle core repels water and expulses it out of the micelle. Lastly, the thiol nucleophile attacks the oxocarbenium ion and the acid is regenerated[58] as shown in Figure 3.11.

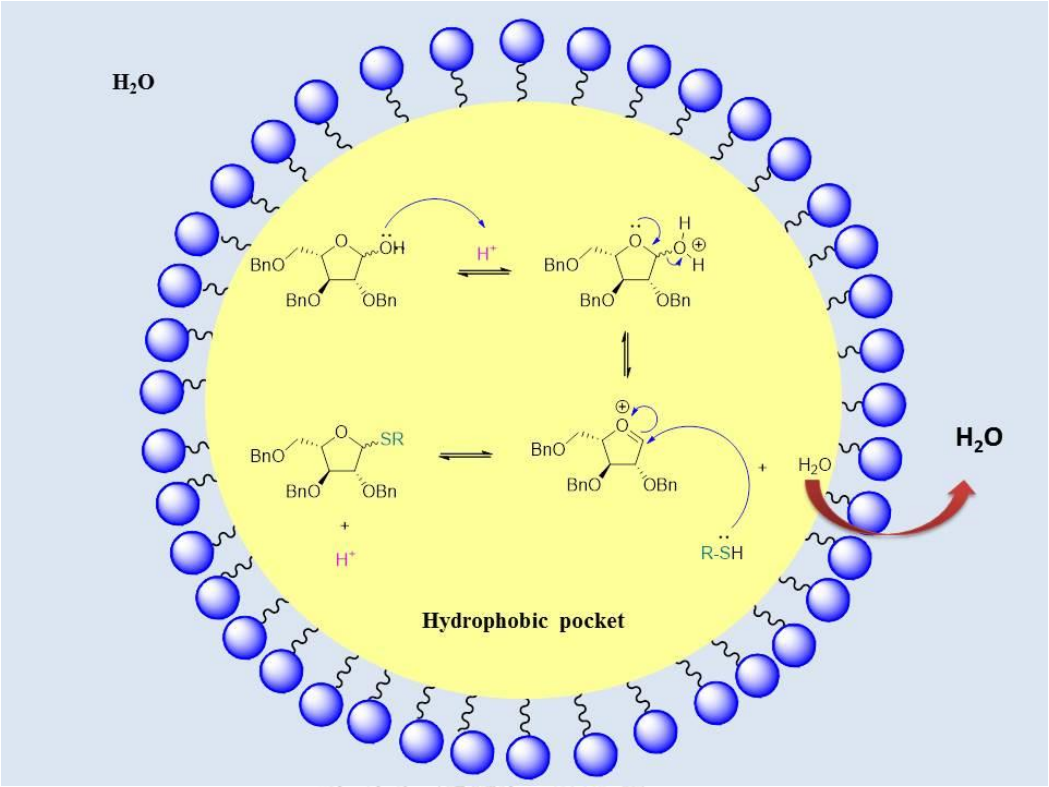


Figure 3.11. A proposed mechanism for the DBSA mediated synthesis of thiofuranoside in aqueous solutions.

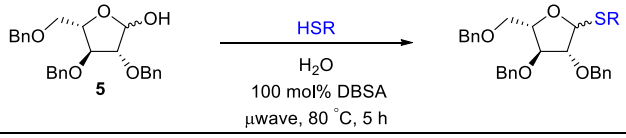
CHAPTER IV

Conclusion

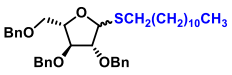
A novel and environmentally friendly method for the synthesis of dehydrative glycosylation in the presence of DBSA as a Brønsted acid-surfactant in water was developed. The use of water as the solvent makes the reaction very easy to perform without requiring anhydrous conditions and avoids the use of toxic and hazardous organic solvents. The emulsion hydrophobic pocket of DBSA surfactant was performed by hydrophobic interaction, when it was in water. The surfactant molecules would concentrate proton onto the surface of the emulsion droplets and then enhance the rate to reach equilibrium. Water molecules generated during the reaction would then be removed from the droplets due to the hydrophobic nature of their interior, making the reactions efficiently proceed even in the presence of a large amount of water as a solvent.

Performing the reaction in a microwave reactor significantly increased the yields and reduced the reaction times compared to conventional heating. The reaction conditions were optimized and it was found that the optimal condition was 100 mol% of DBSA in water at 80 °C under microwave irradiation for 5 hours afford the highest yield of the desired products. The study of effect of surfactant and acid confirmed that the reactions required the combination of Brønsted acid-surfactant. Either acids or surfactants alone were not efficient for generating the products. Addition of water-tolerated Lewis acids did not improve the yield.

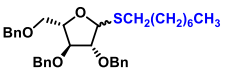
Table 4.1. Substrate scopes of dehydrative glycosylation.



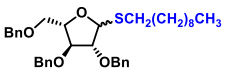
Aliphatic thiols[a]



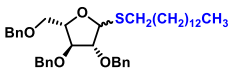
11 (α/β = 50/50, 72% yield)



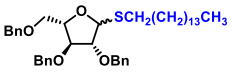
12 (α/β = 83/17, 71% yield)



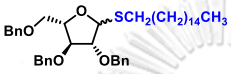
13 (α/β = 84/16, 67% yield)



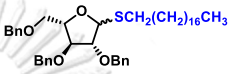
14 (α/β = 80/20, 65% yield)



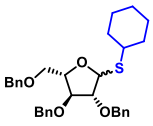
15 (α/β = 92/8, 58% yield)



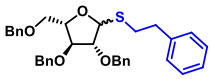
16 (α/β = 54/46, 58% yield)



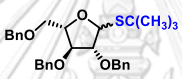
17 (α/β = 90/10, 63% yield)



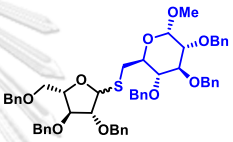
18 (α/β = 50/50, 45% yield)



19 (α/β = 60/40, 42% yield)

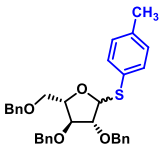


20 (α/β = 50/50, 24% yield)

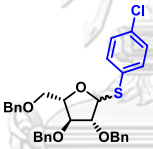


21 (No desired product)

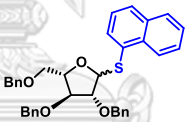
Heterocyclic and aromatic thiols[a]



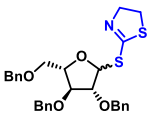
22 (α/β = 82/18, 41% yield)



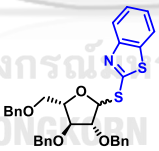
23 (α/β = 86/14, 43% yield)



24 (α/β = 14/86 47% yield)

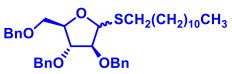


25 (No desired product)

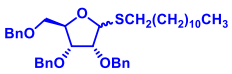


26 (No desired product)

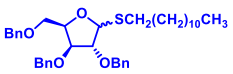
Furanosides and pyranosides[a]



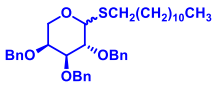
27 (α/β = 83/17, 66% yield)



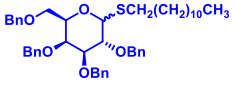
28 (α/β = 15/85, 73% yield)



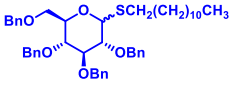
29 (α/β = 50/50, 75% yield)



30 (α/β = 50/50, 60% yield)



31 (α/β = 40/60, 32% yield)



32 (α/β = 40/60, 45% yield)

[a] Isolated yield and α:β selectivity was determined by ^{1}H NMR signal integration of anomeric proton. μwave = microwave.

As for the scope of substrates (Table 4.1), the reaction between the lactols could be performed with a wide variety of thiols, including primary, secondary, and tertiary alkyls as well as aryl, but not heterocyclic, thiols. Hydrophobic substrates gave better yields of the thiofuranoside products than hydrophilic substrates, which could not efficiently penetrate in the micelle pocket. Additionally, numerous *O*-benzyl-protected furanosides and pyranosides were elucidated as glycosyl donors. The thioglycoside products were generally obtained in moderate to good yield. The yields of thiopyranosides were lower than furanosides.

Noteworthily, the open-chain dithioacetal side product potentially obtained was not detected by using this protocol. The developed reaction needed neither dehydrating agents nor azeotropic removal of water. Moreover, this methodology avoided multi-step procedures to ensured anhydrous conditions compared to the previous reports. The simple and convenient preparation was easy to handle. Furthermore, since the solvent in the reactions are water, the reactions may lead to a method which solves some environmental problems. This work not only leads to a new reaction systems which works in water but also provides a new aspect of using micellar acidic catalyst for performing organic chemistry in water.

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APPENDIX

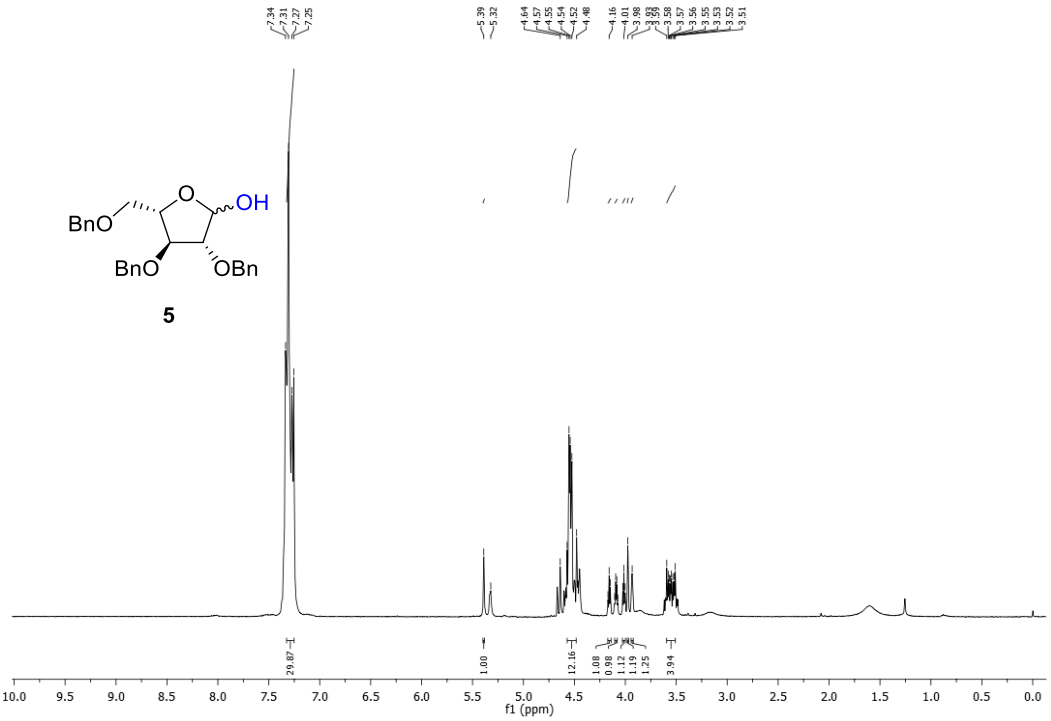

Figure A1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2,3,5-tri-*O*-benzyl-L-arabino-furanoside (**5**).

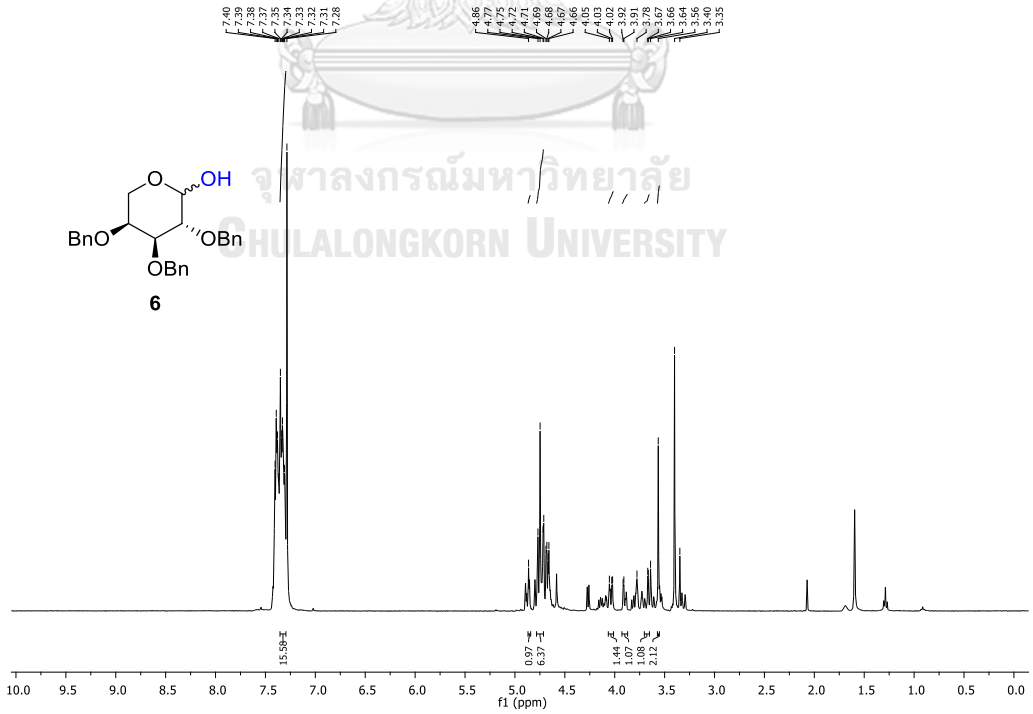

Figure A2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2,3,5-tri-*O*-benzyl-L-arabino-pyranoside (**6**).

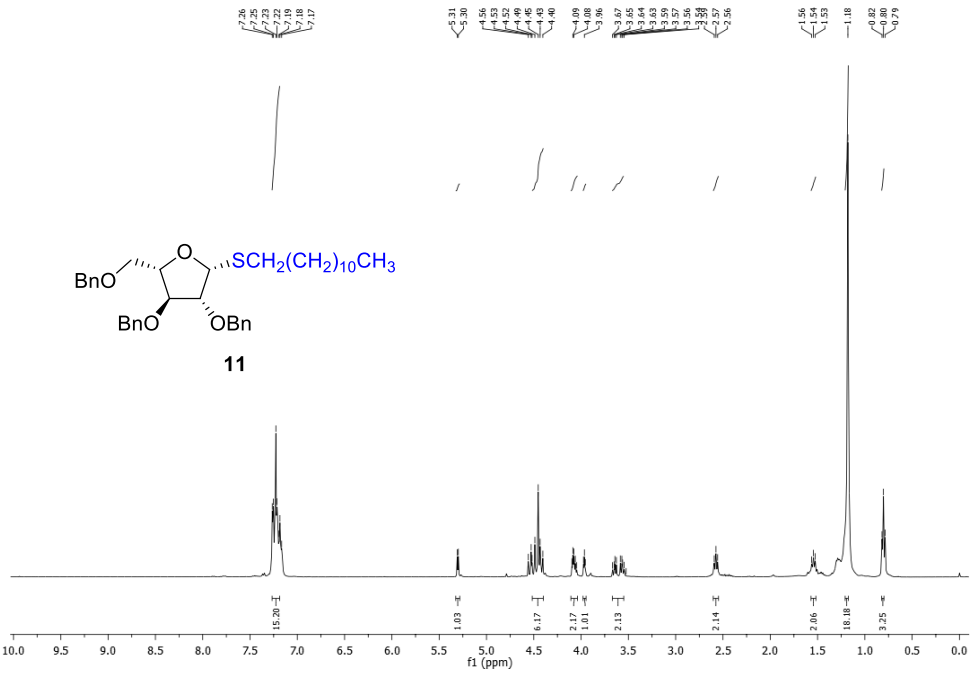

Figure A3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside (**11**).

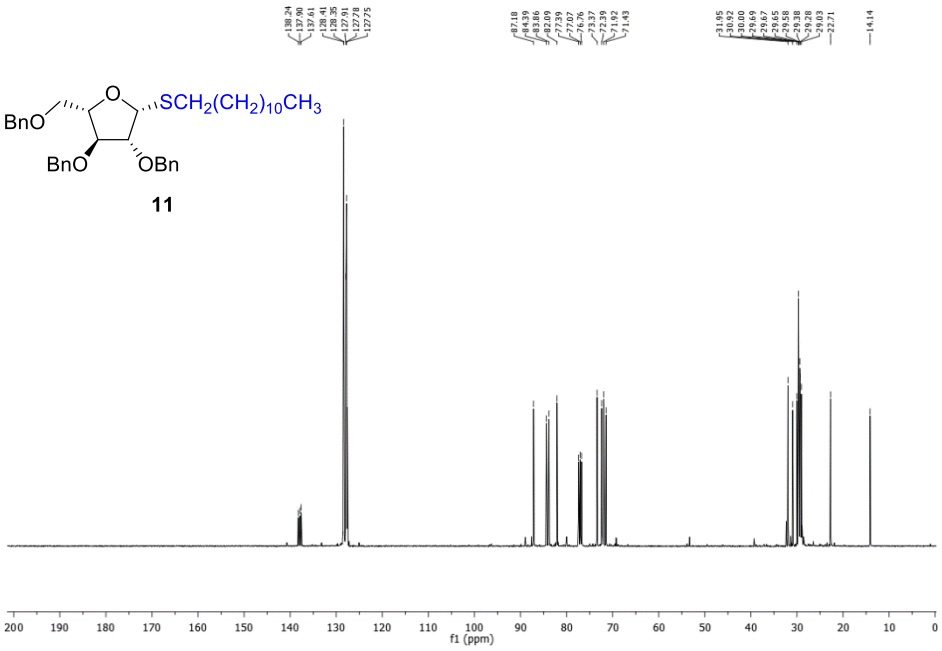

Figure A4. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside (**11**)

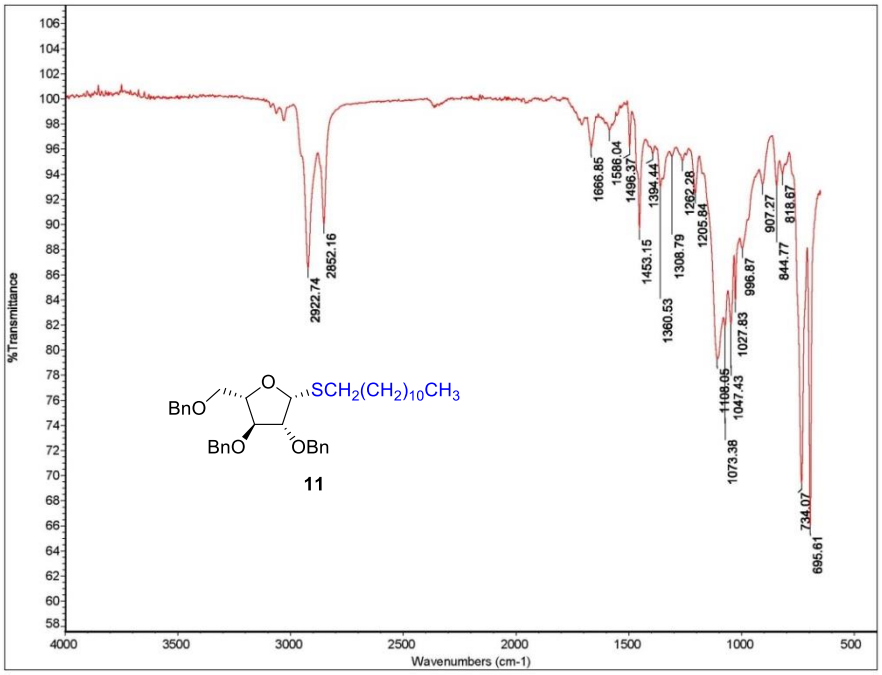

Figure A5. IR spectrum (ATR) of dodecylthio 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside (**11**)

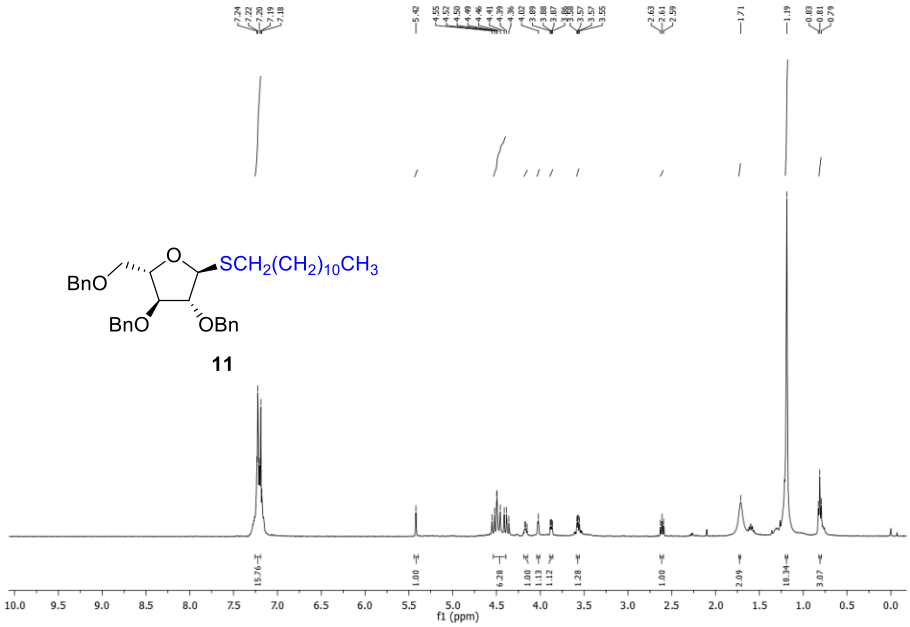

Figure A6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-β-L-arabinofuranoside (**11**).

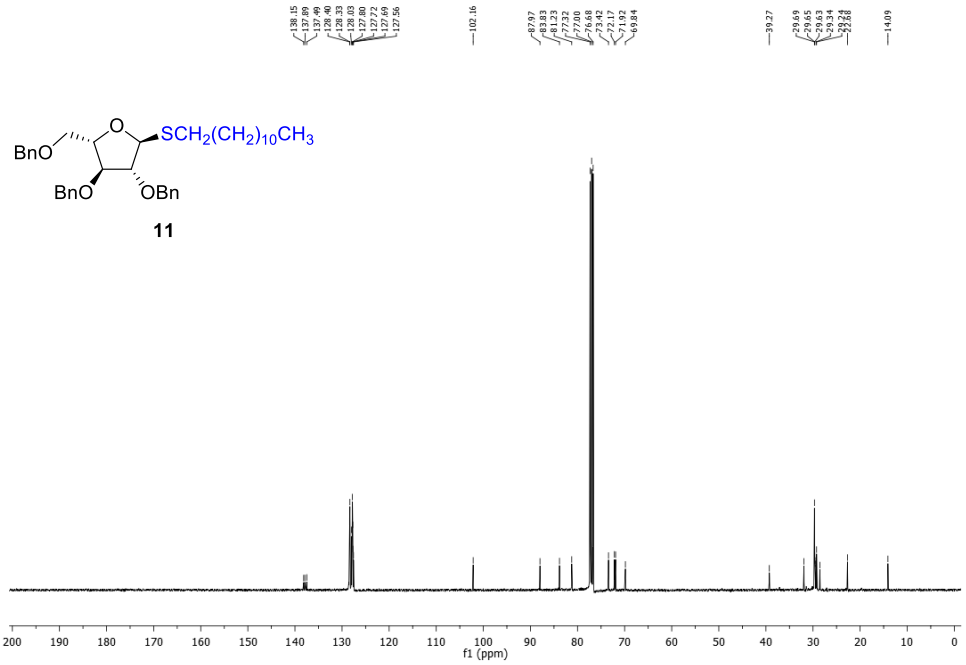

Figure A7. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-β-L-arabinofuranoside (**11**).

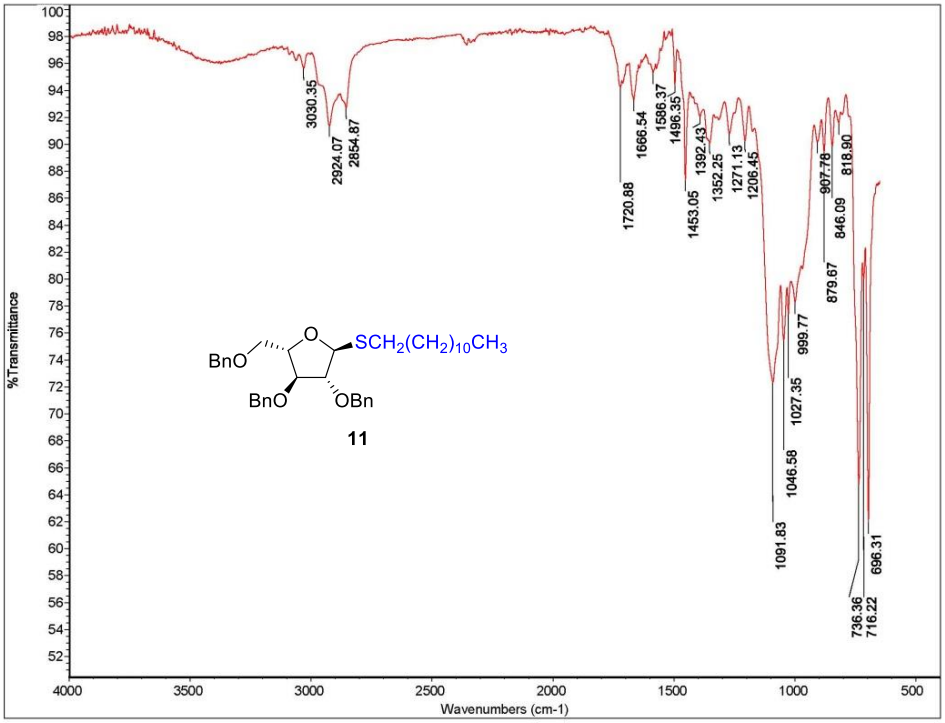

Figure A8. IR spectrum (ATR) of dodecylthio 2,3,5-tri-*O*-benzyl-β-L-arabinofuranoside (**11**).

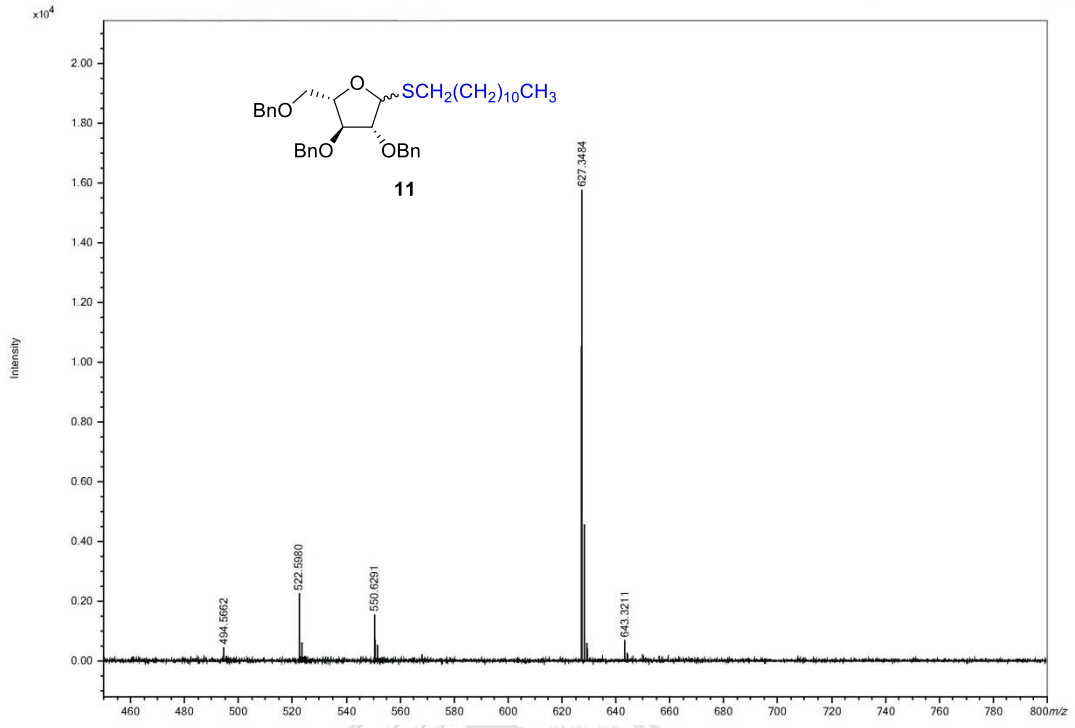

Figure A9. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**11**).

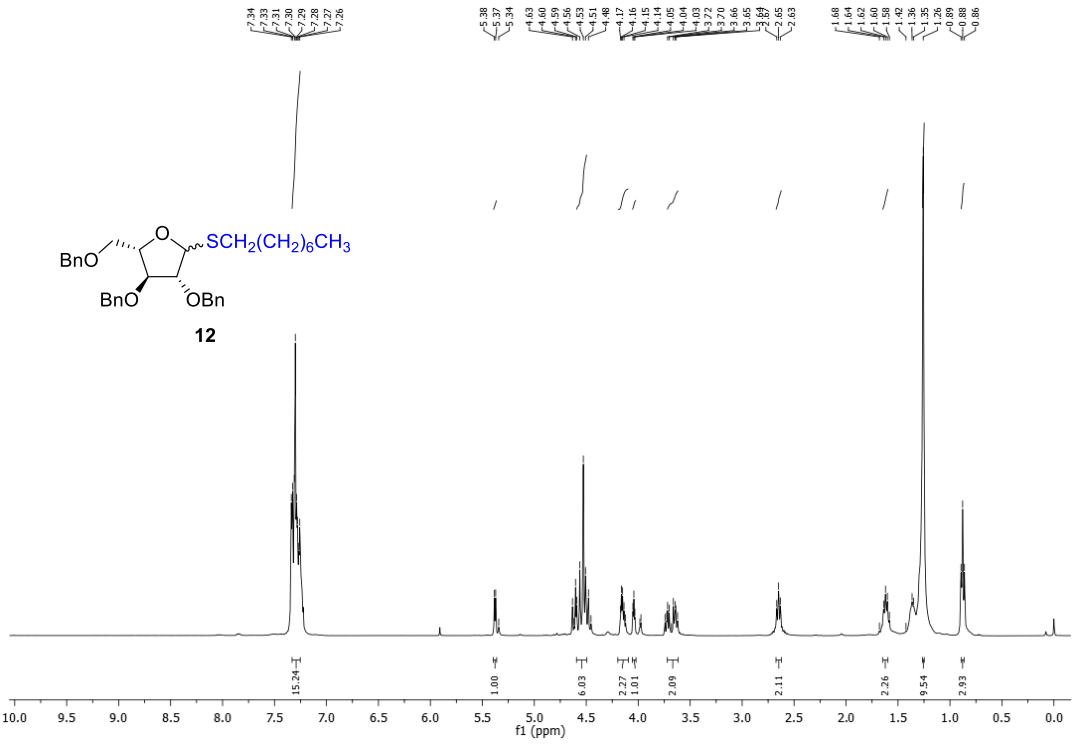

Figure A10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of octylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**12**).

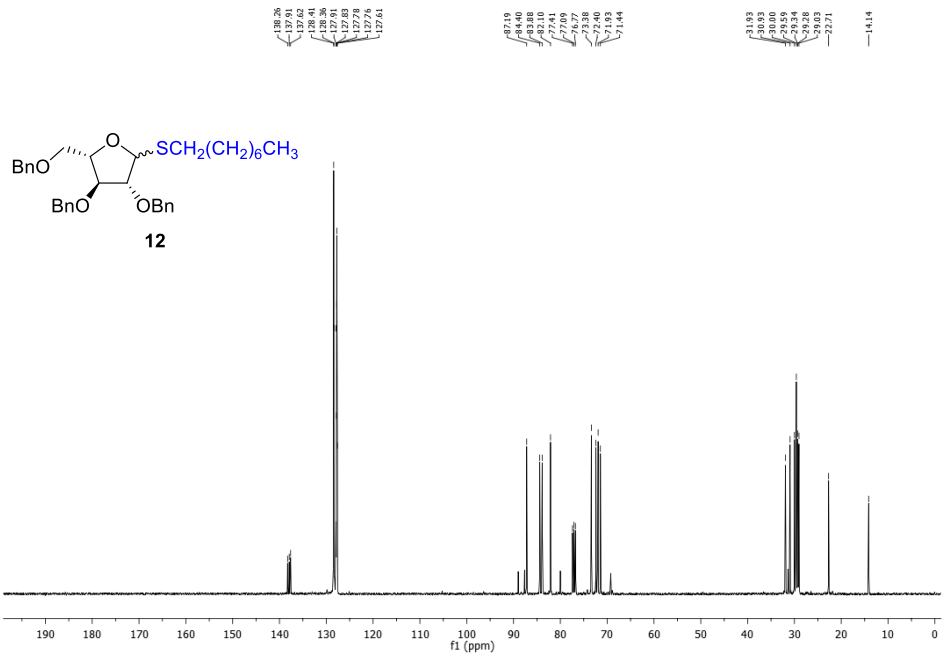

Figure A11. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of octylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (12).

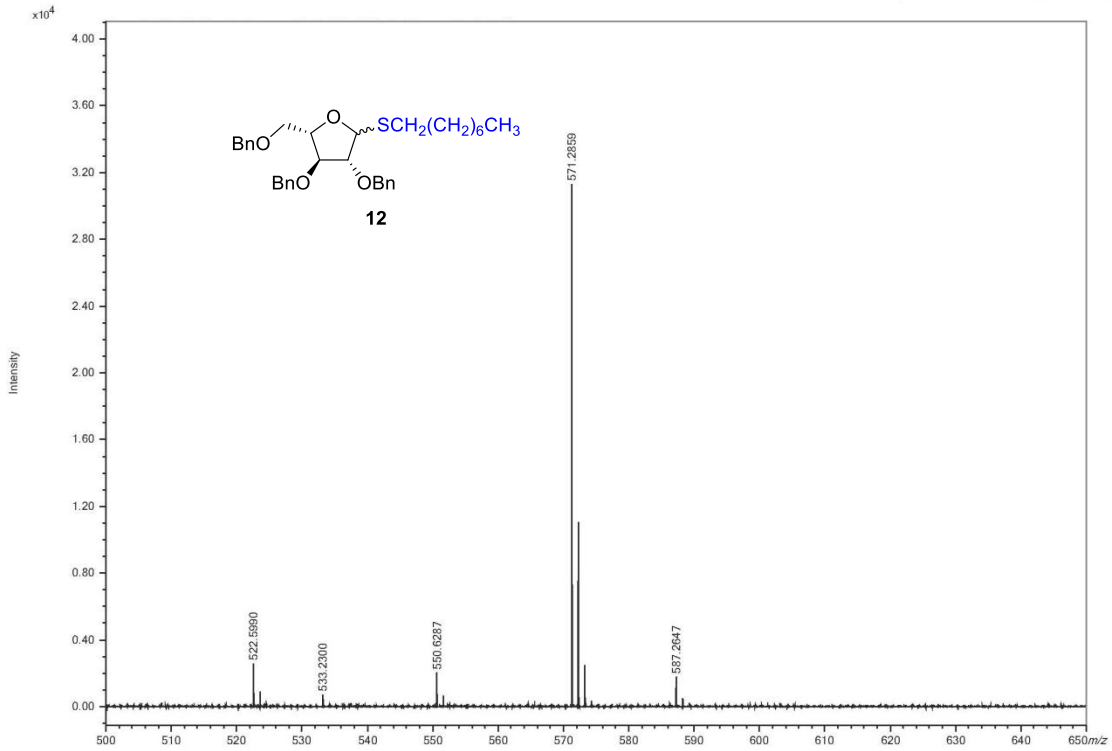

Figure A12. Mass spectrum of octylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**12**).

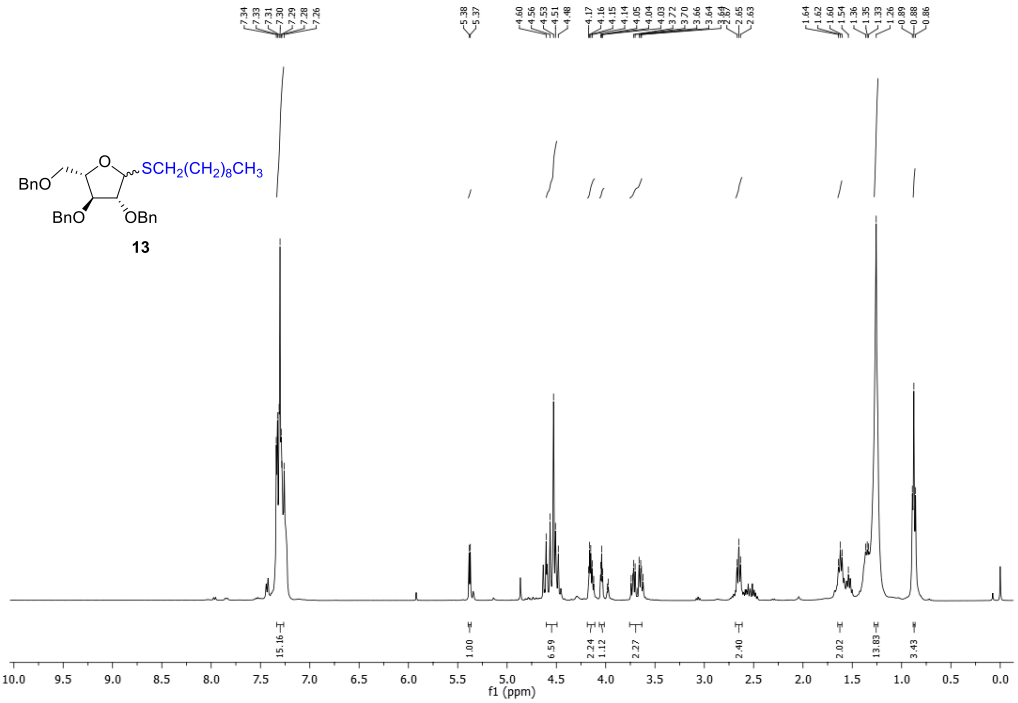

Figure A13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of decylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**13**).

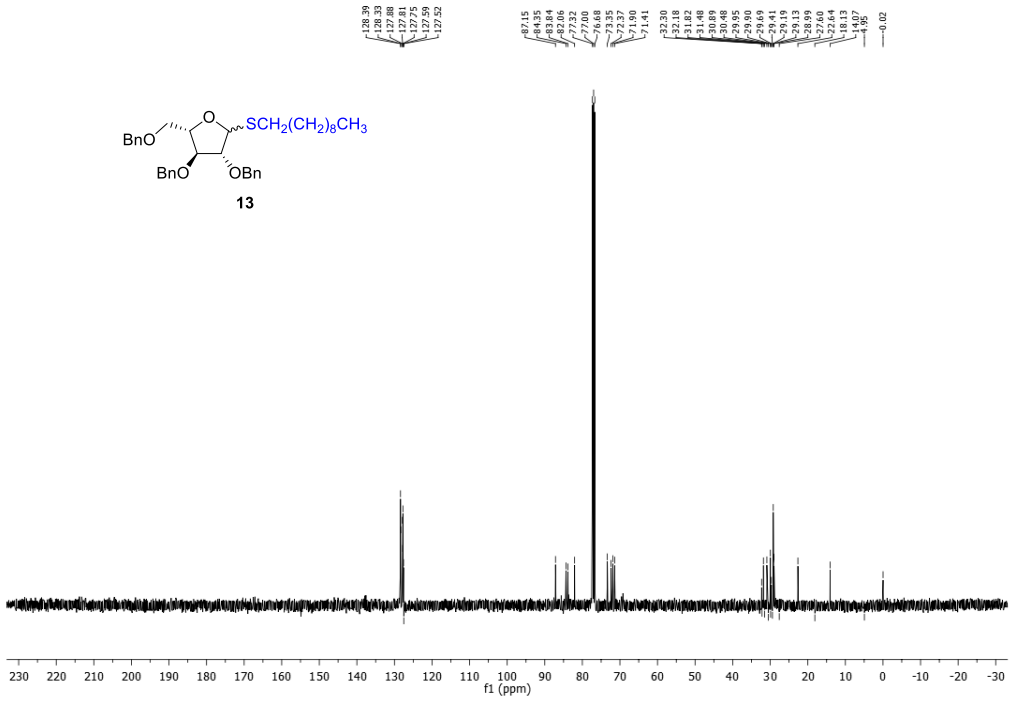

Figure A14. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of decylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**13**).

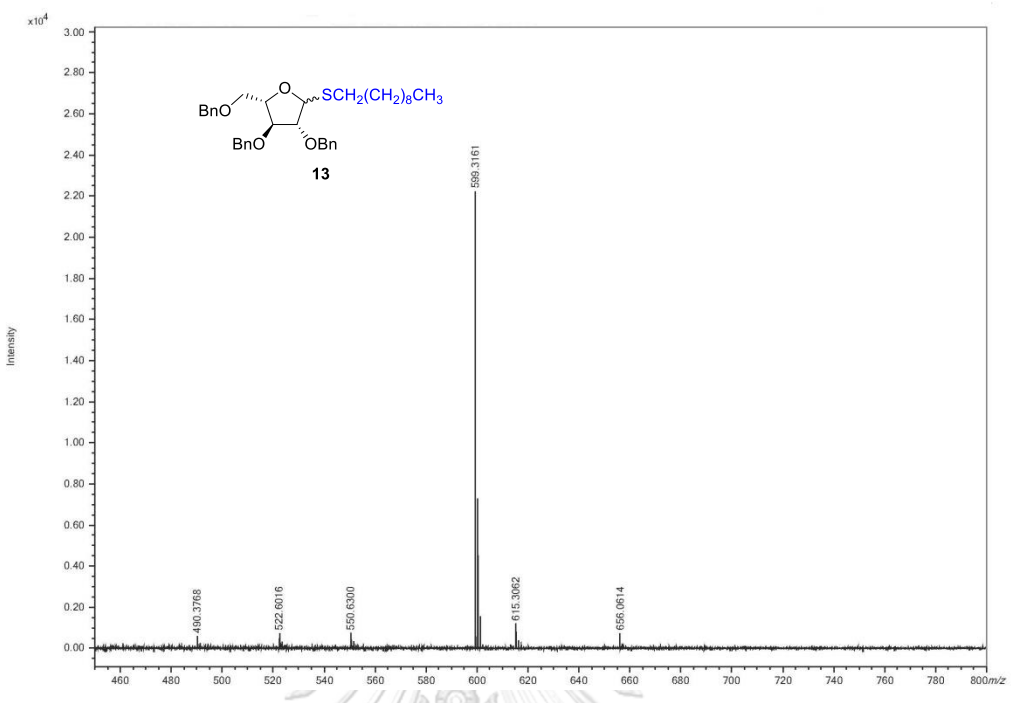

Figure A15. Mass spectrum of decylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**13**).

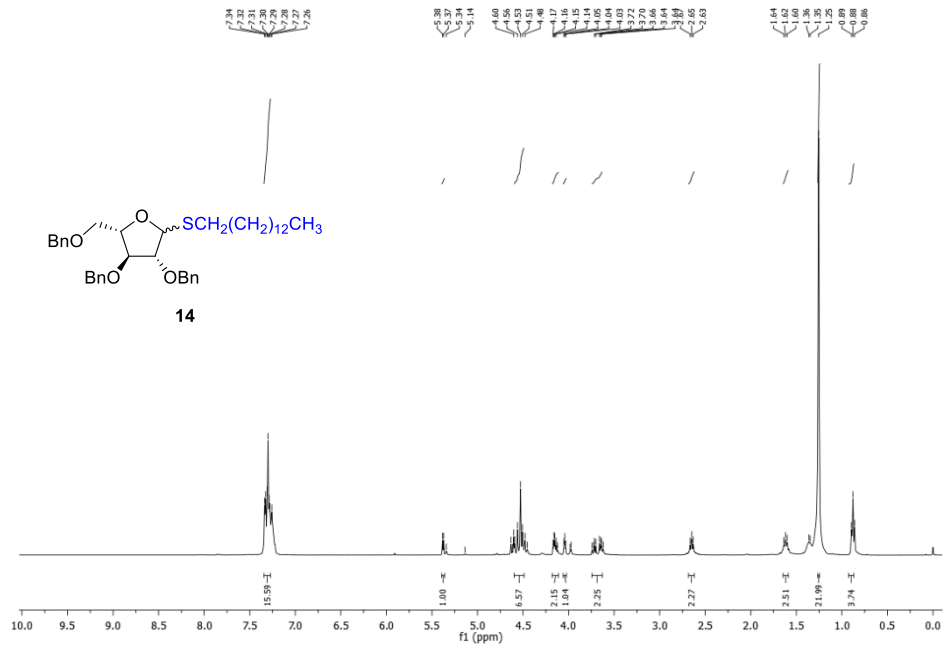

Figure A16. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of tetradecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**14**).

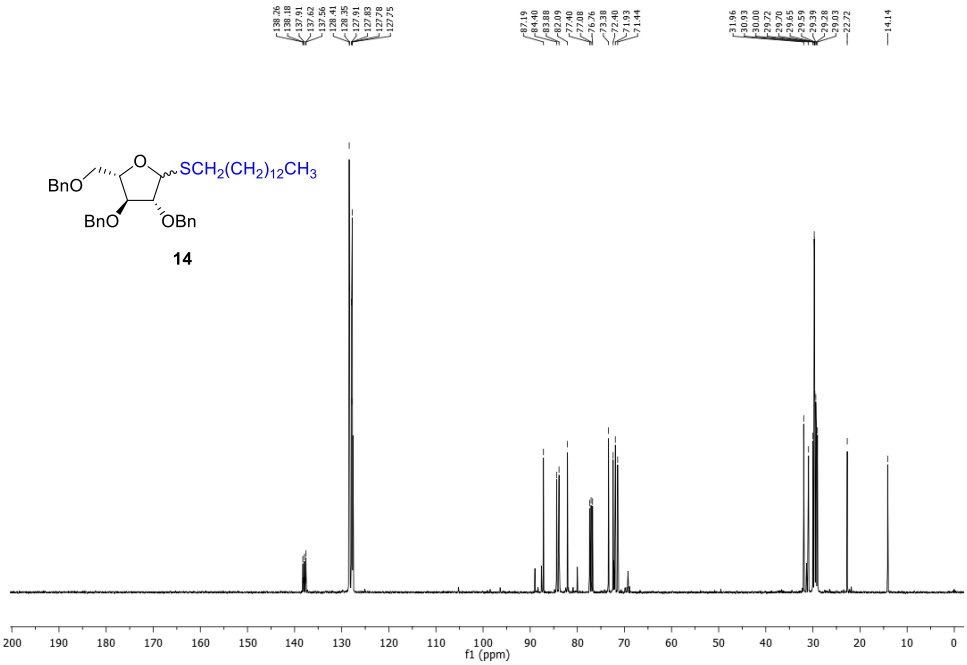

Figure A17. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of tetradecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**14**).

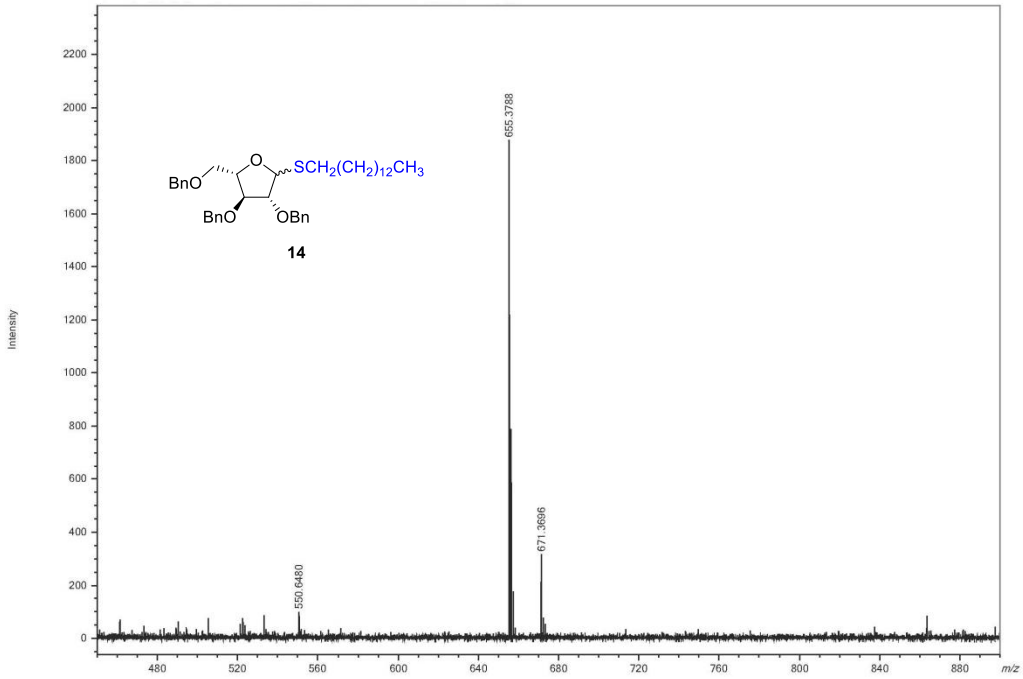

Figure A18. Mass spectrum of tetradecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**14**).

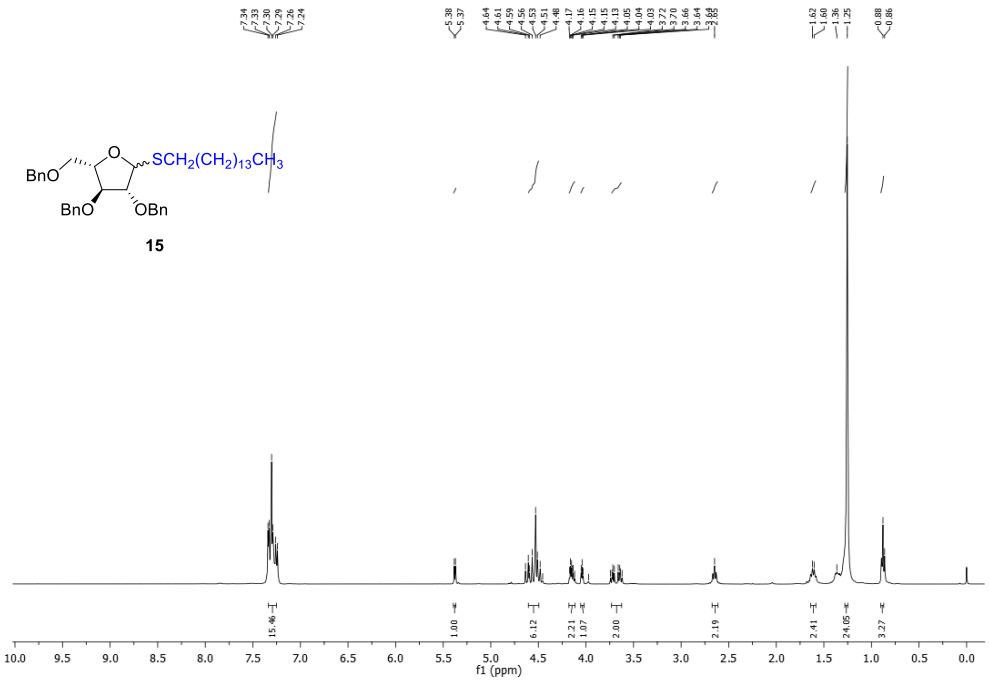

Figure A19. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of pentadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**15**).

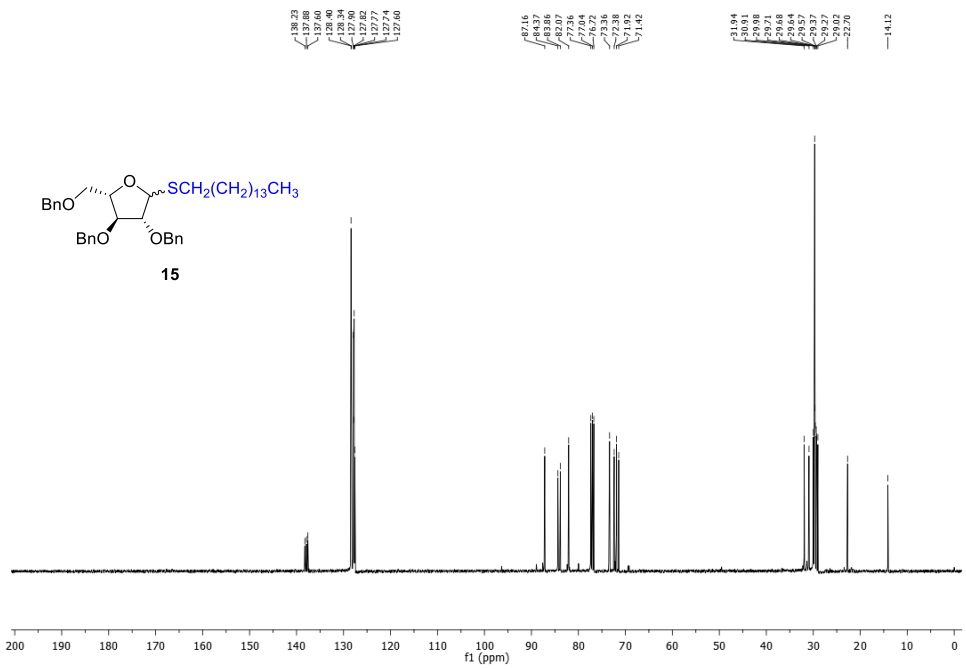

Figure A20. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of pentadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**15**).

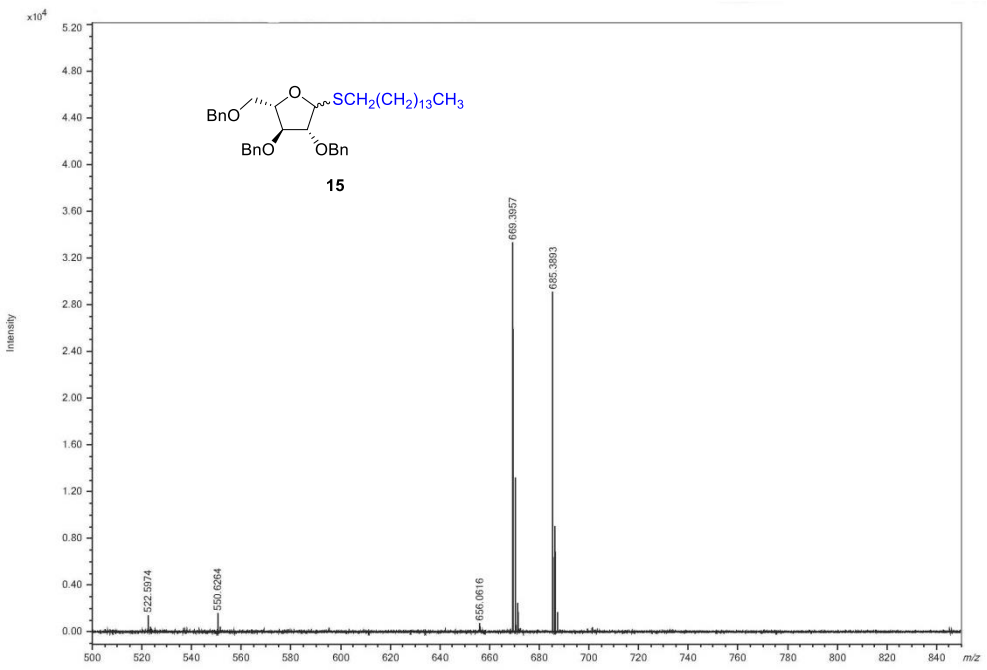

Figure A21. Mass spectrum of pentadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**15**).

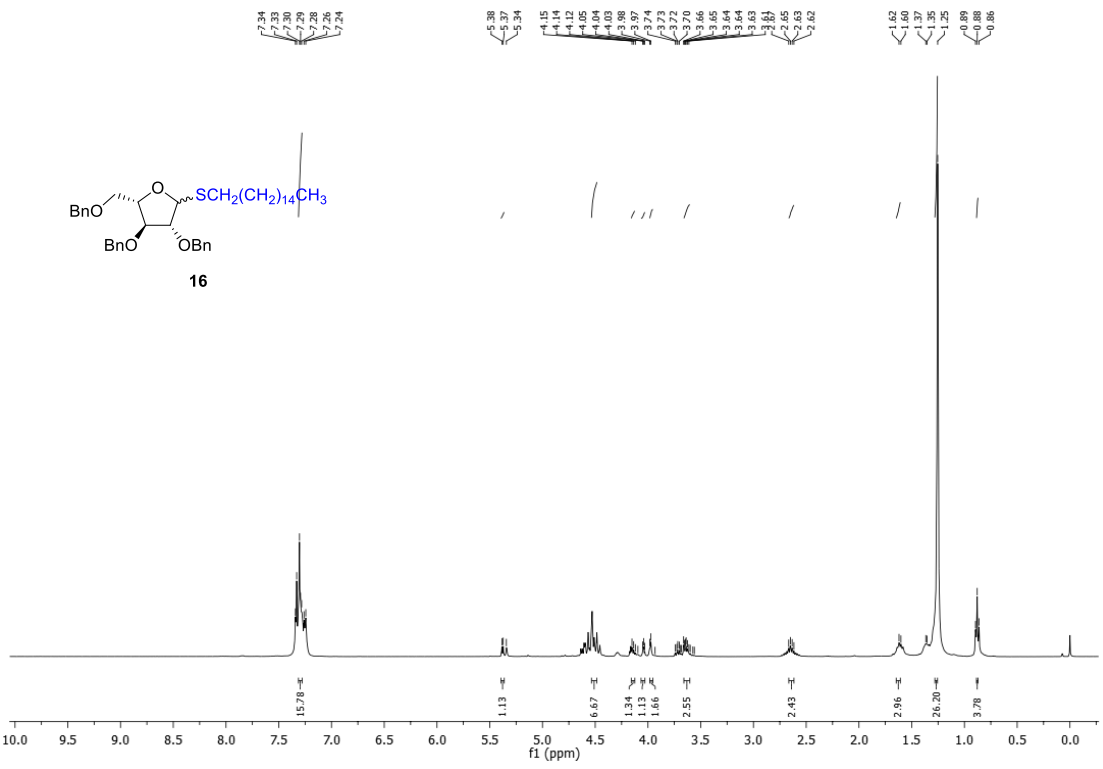

Figure A22. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of hexadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**).

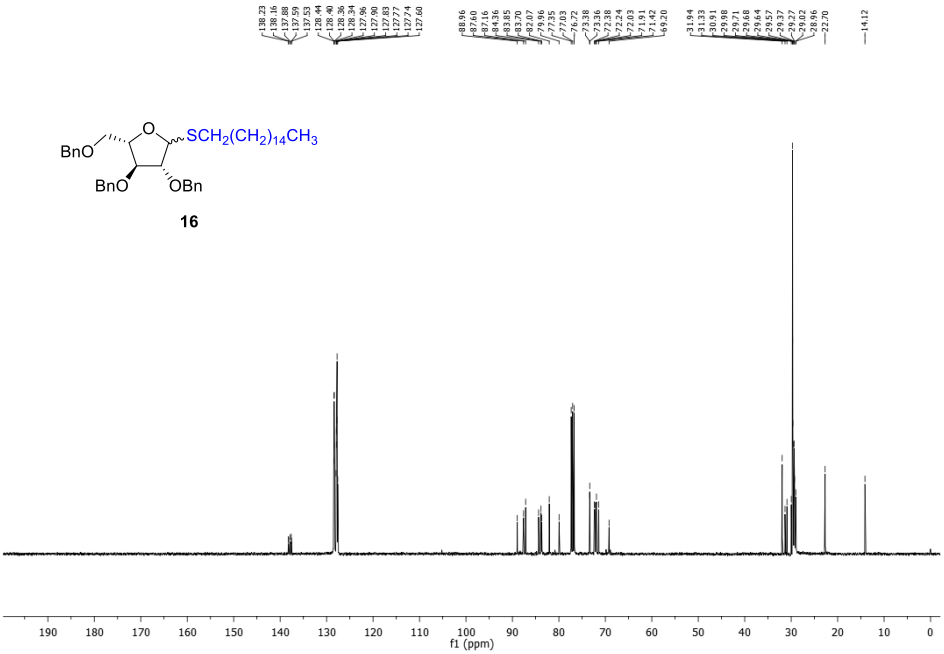

Figure A23. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of hexadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**).

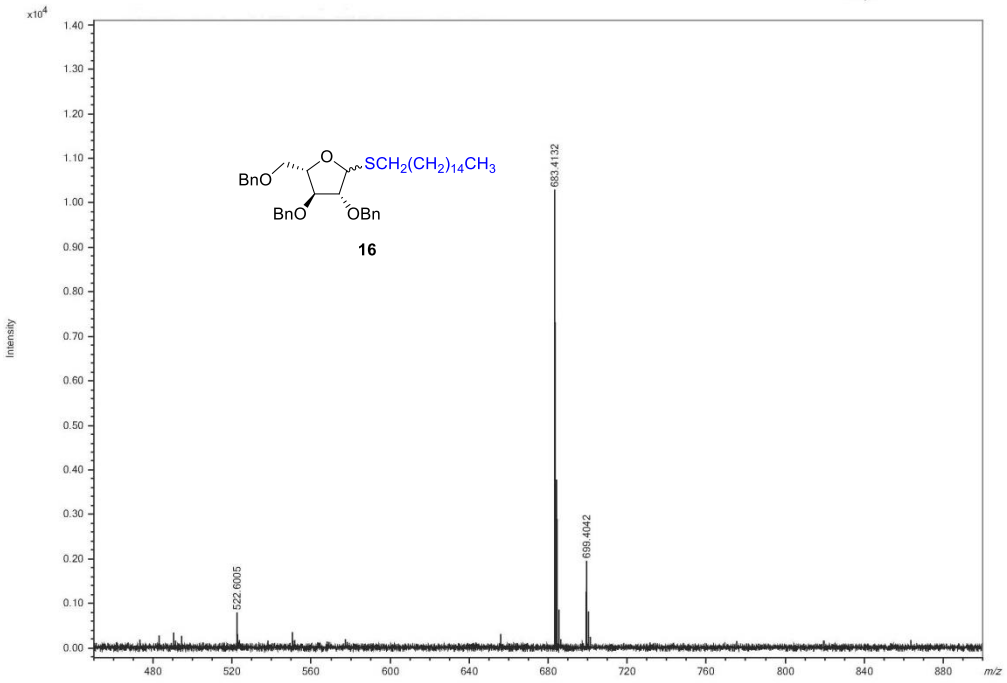

Figure A24. Mass spectrum of hexadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**).

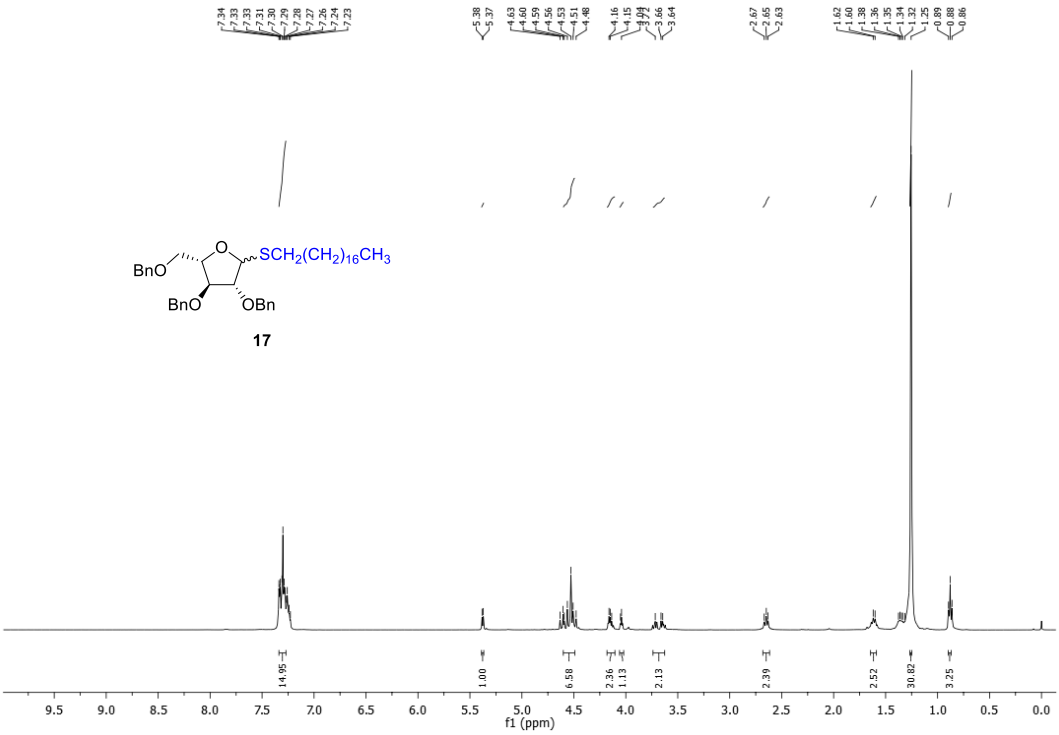

Figure A25. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of octadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**17**).

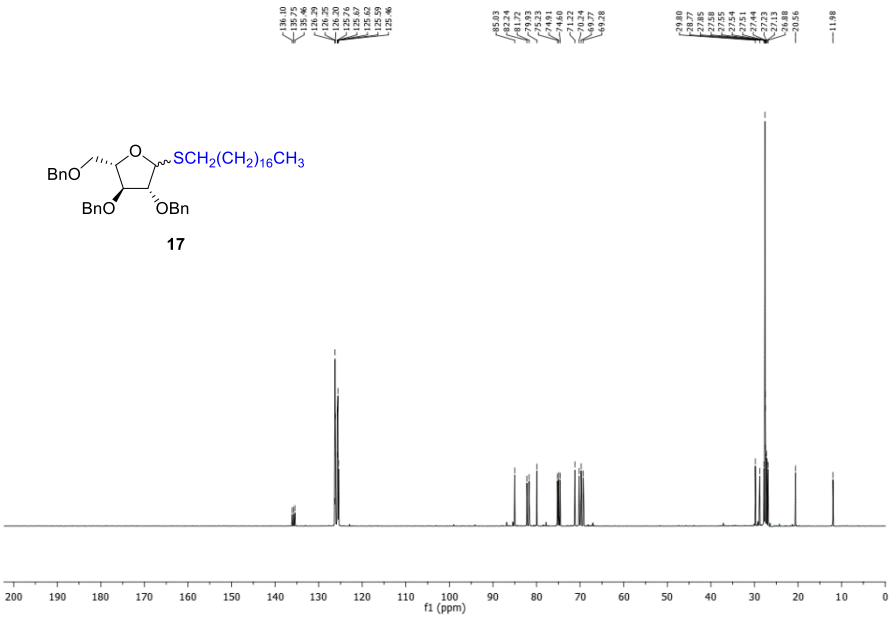

Figure A26. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of octadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**17**).

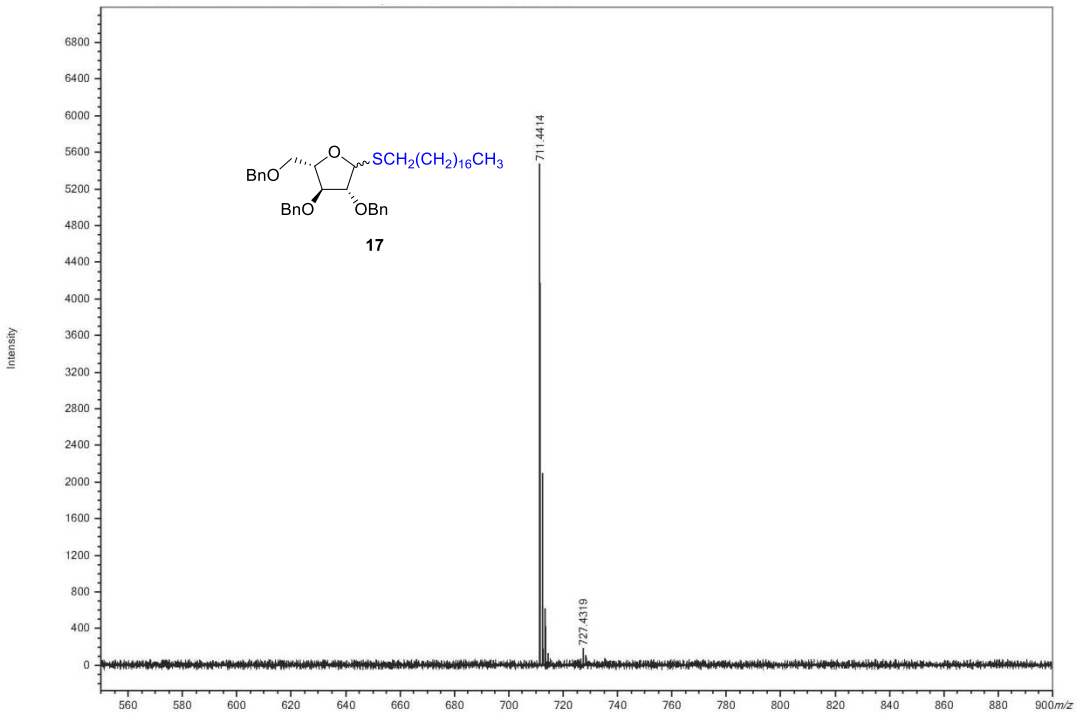

Figure A27. Mass spectrum of octadecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**17**).

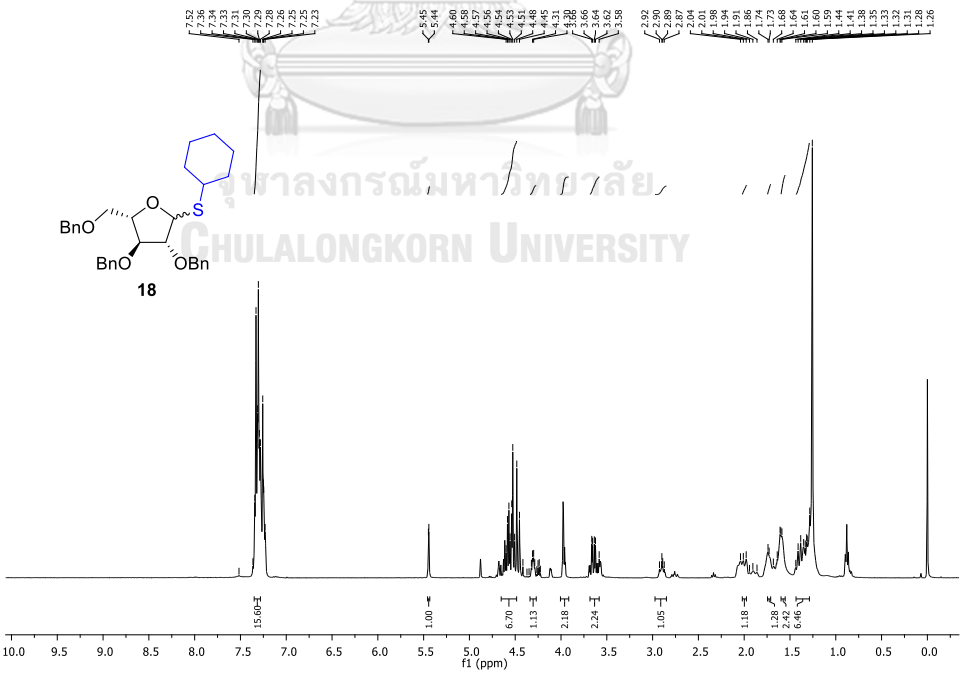

Figure A28. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of cyclohexylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**18**).

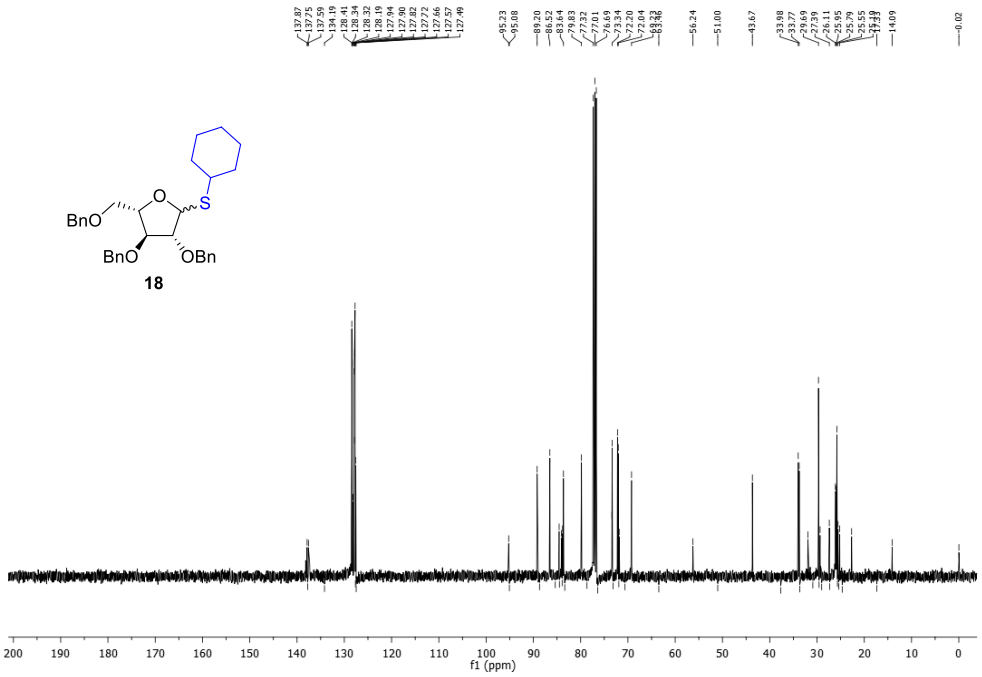

Figure A29. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of cyclohexylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**18**).

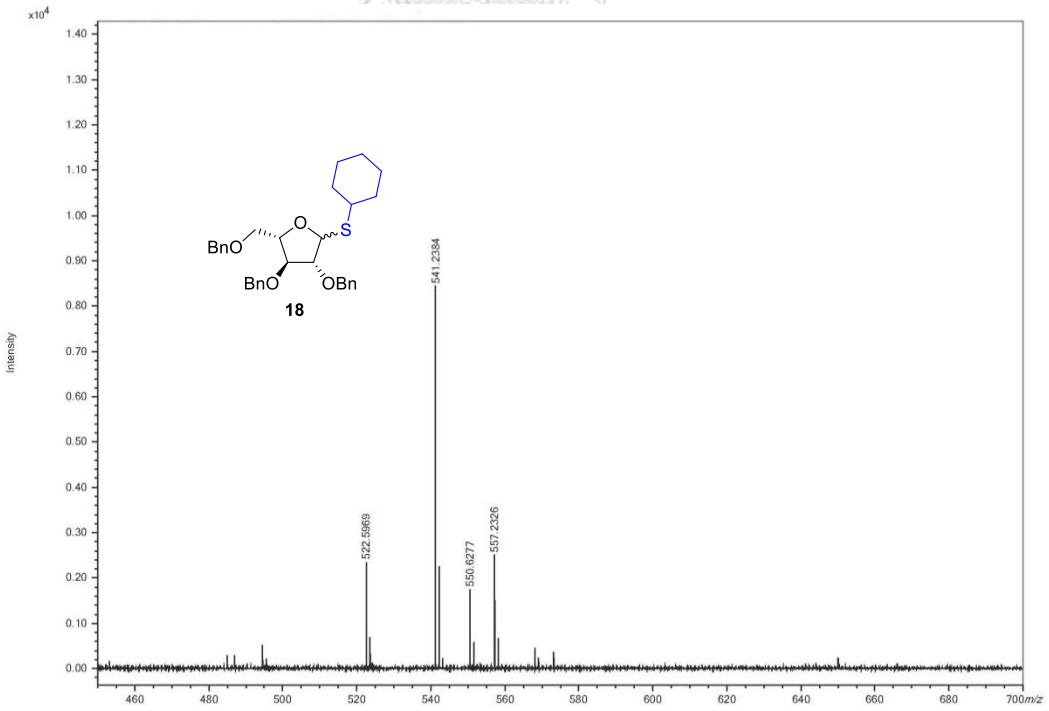

Figure A30. Mass spectrum of cyclohexylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**18**).

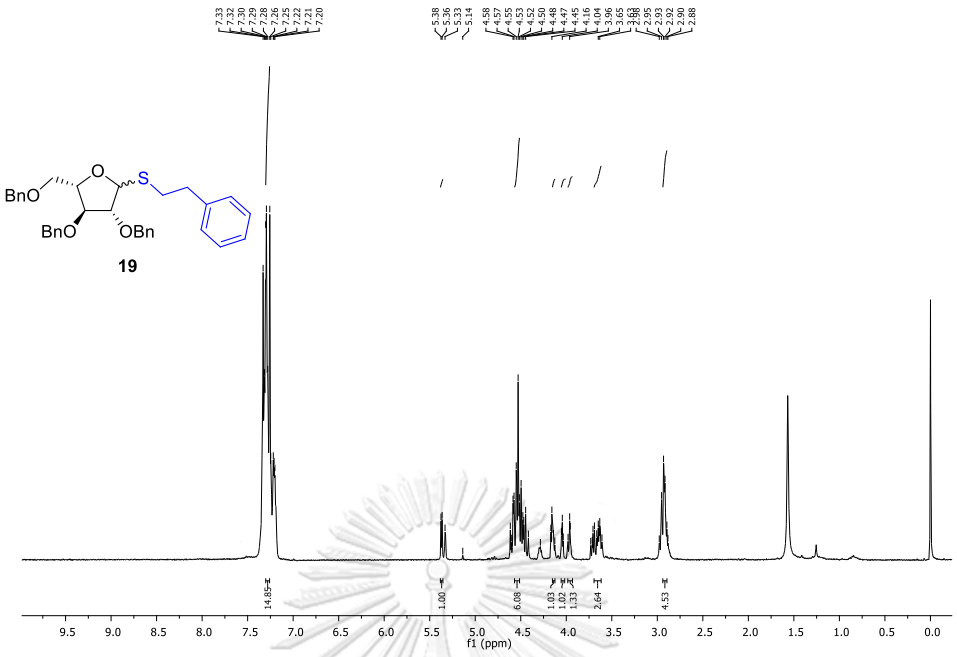

Figure A31. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-phenylethylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**19**).

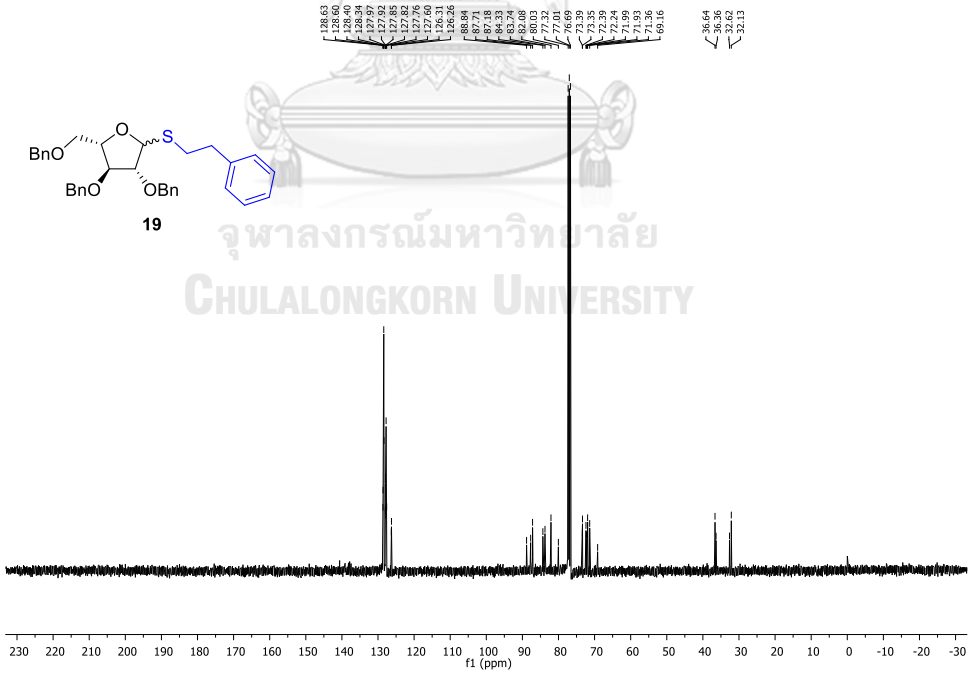

Figure A32. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 2-phenylethylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**19**).

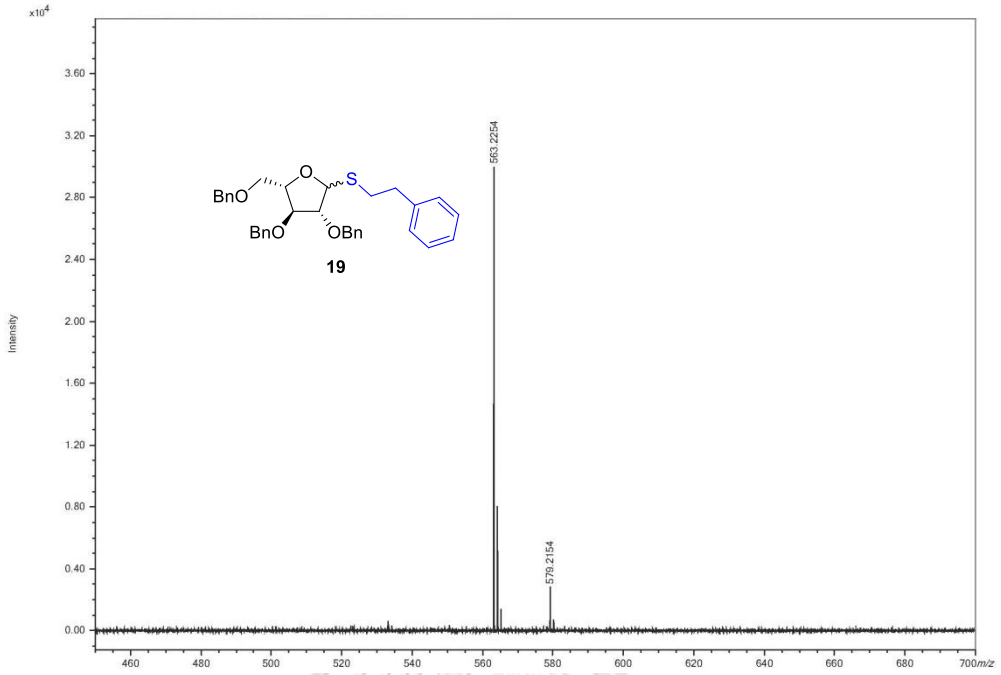

Figure A33. Mass spectrum of 2-phenylethylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**19**).

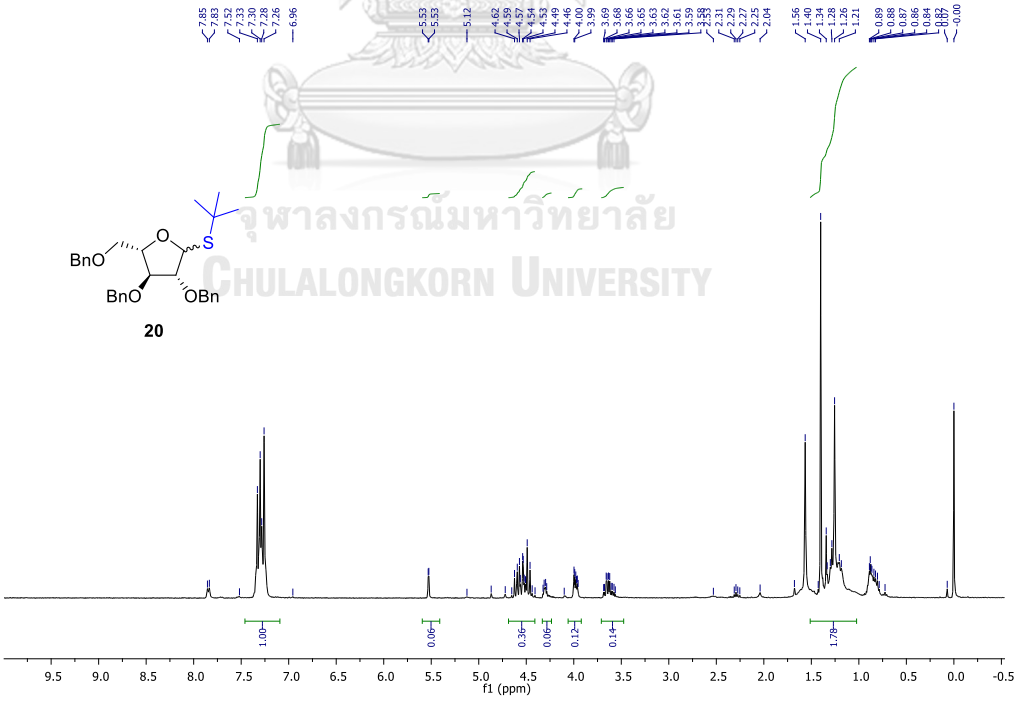

Figure A34. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2',2'-methylpropylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**20**).

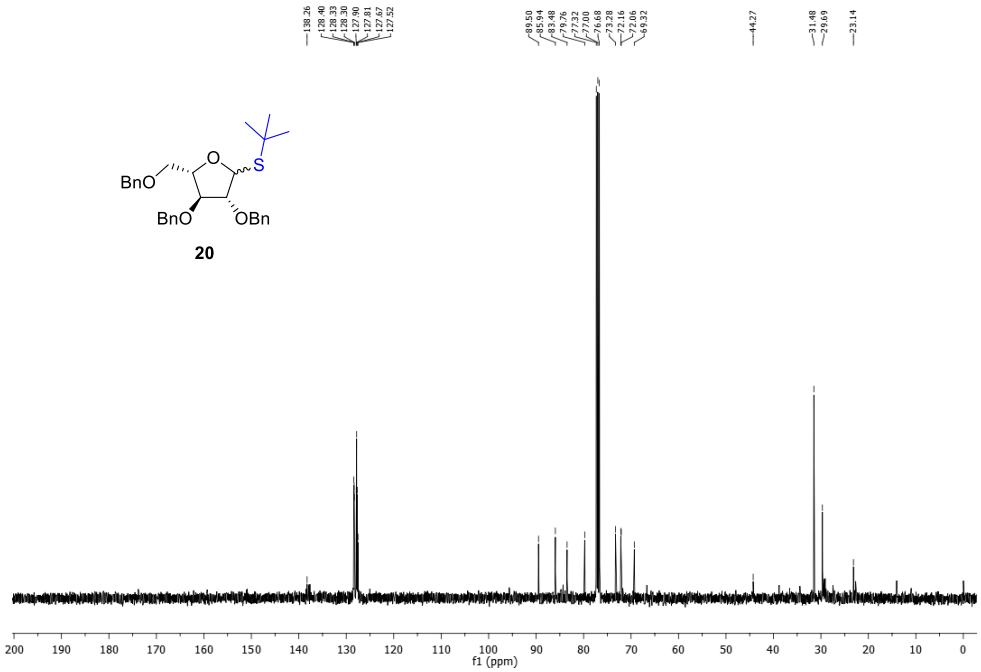

Figure A35. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 2',2'-methylpropylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**20**).

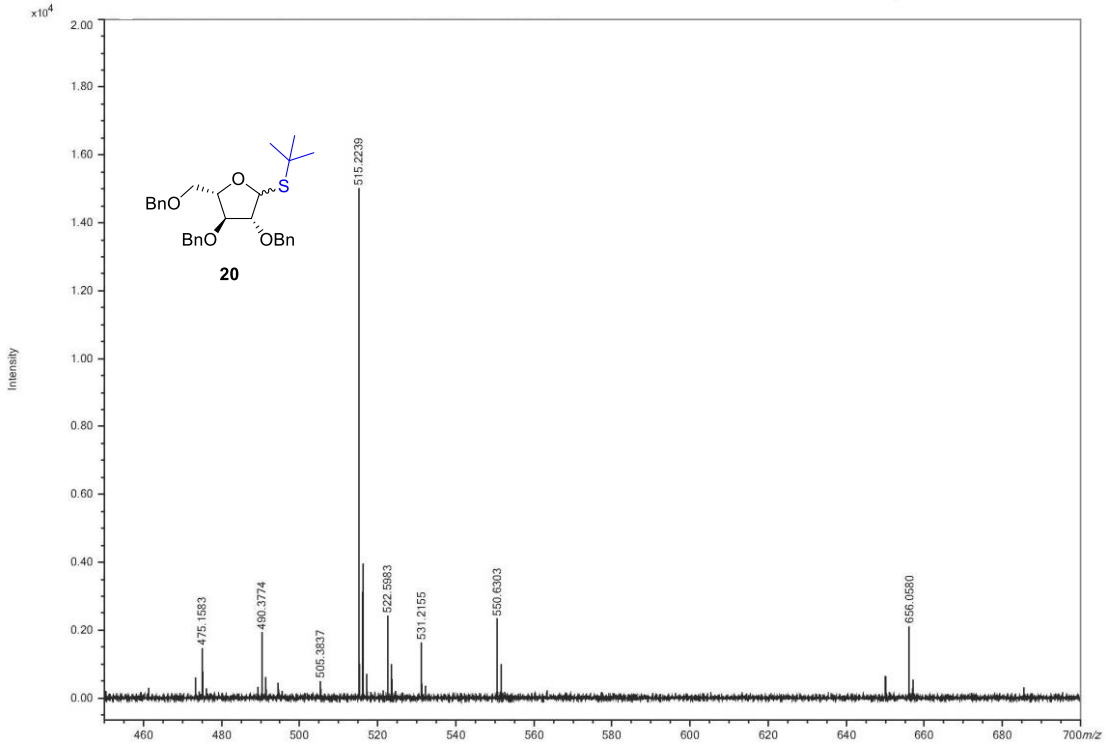

Figure A36. Mass spectrum of 2',2'-methylpropylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**20**).

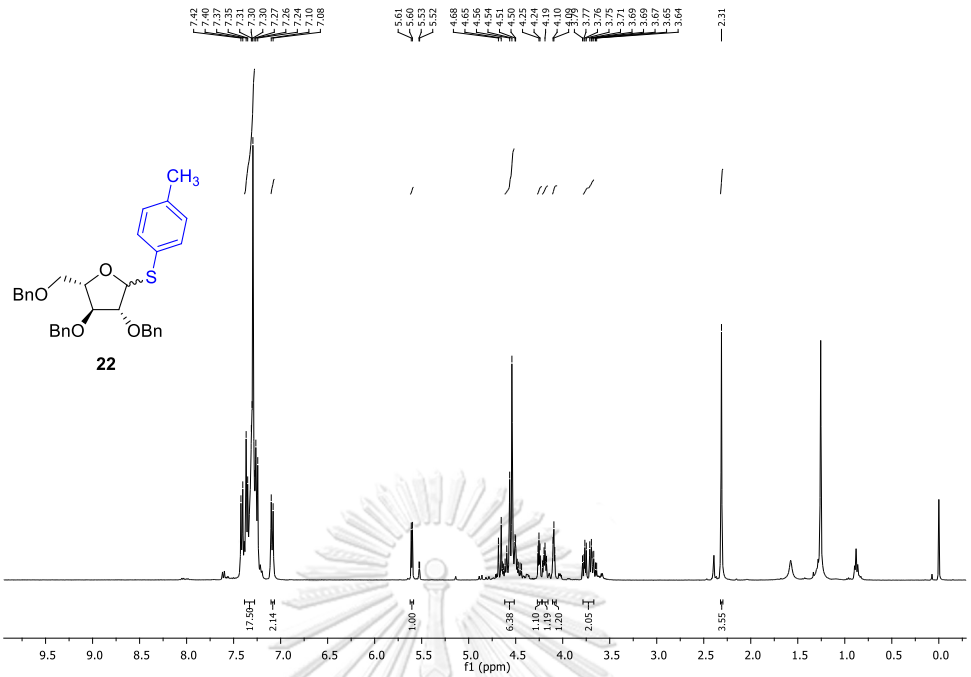

Figure A37. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-methylphenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**22**).

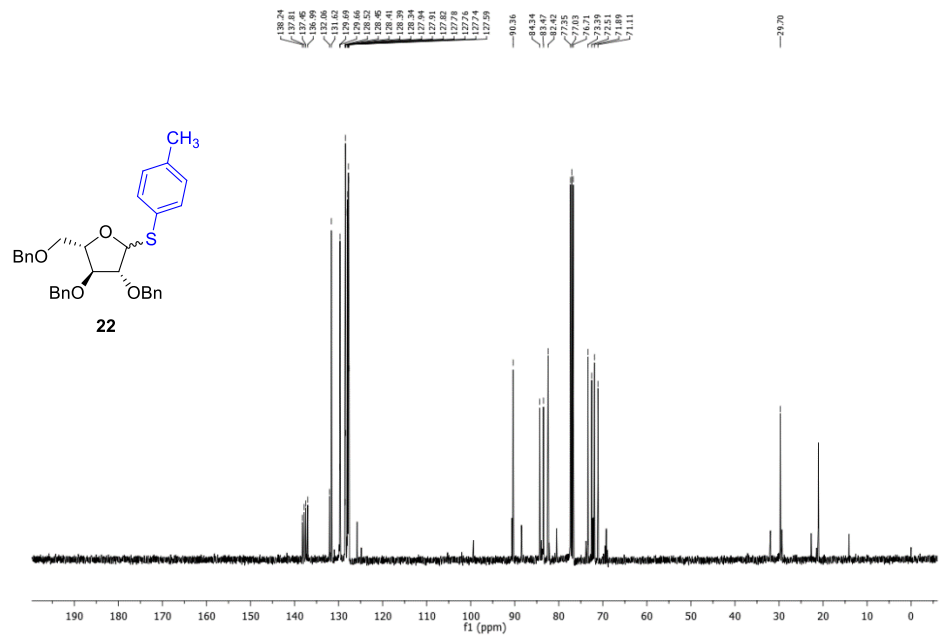

Figure A38. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4-methylphenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**22**).

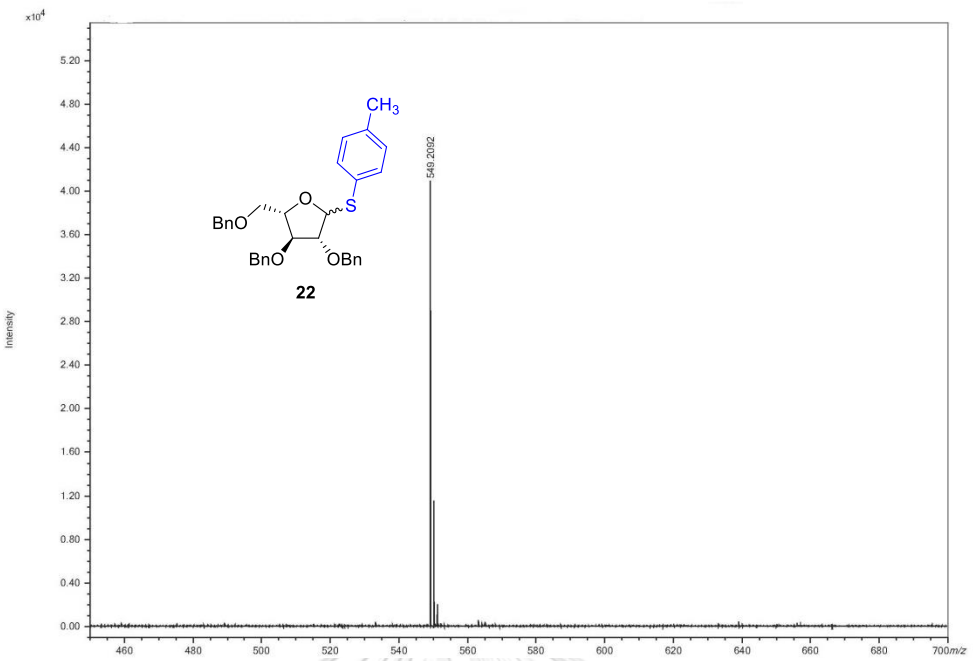

Figure A39. Mass spectrum of 4-methylphenylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**22**).

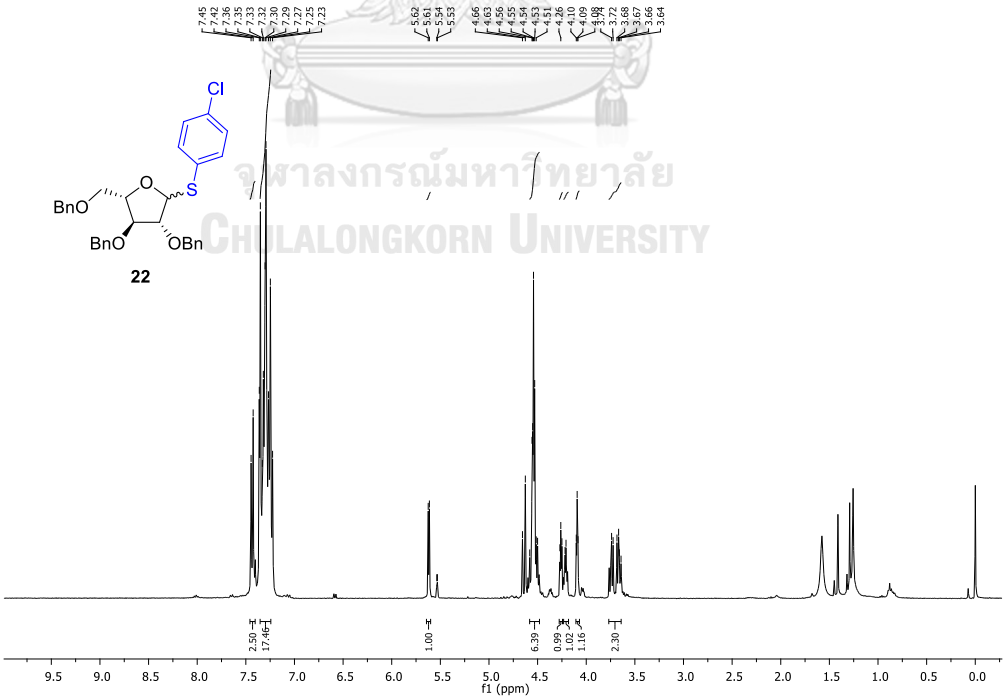

Figure A40. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-chlorophenyllthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**23**).

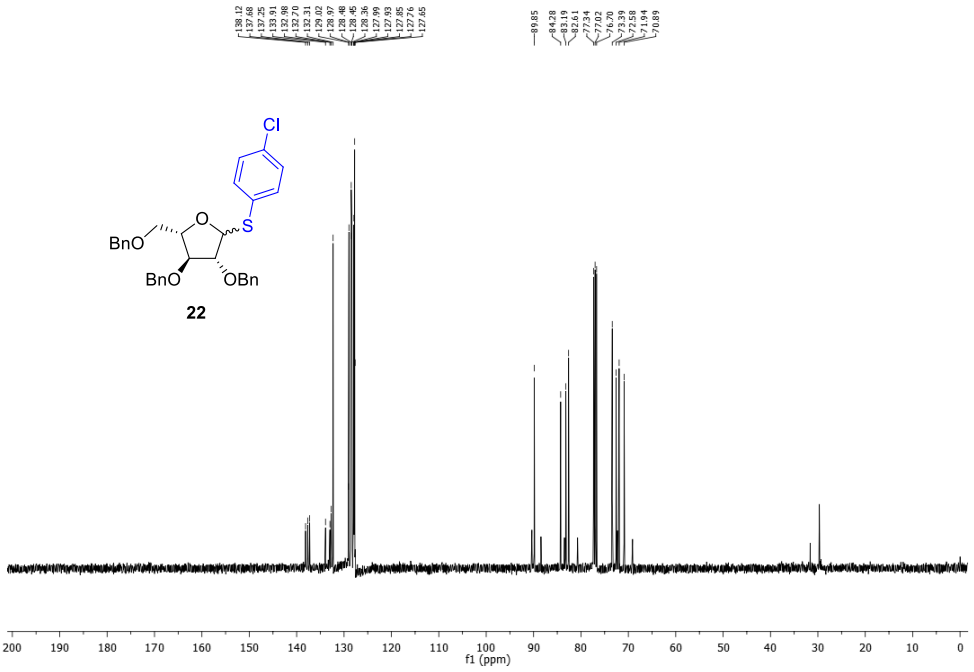

Figure A41. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 4-chlorophenyllthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**23**).

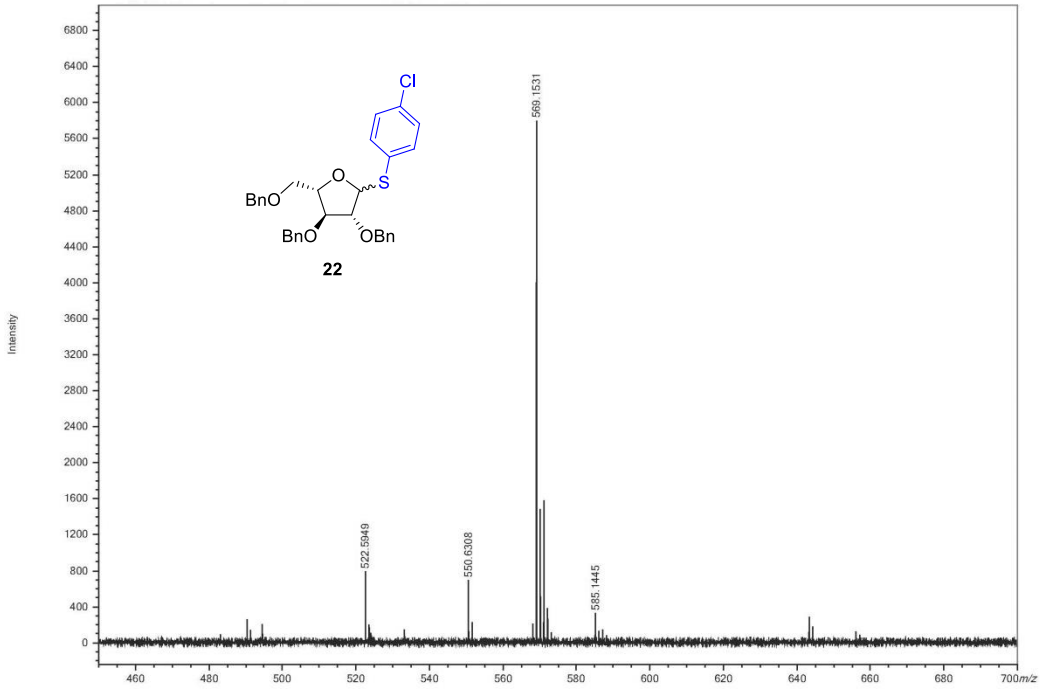

Figure A42. Mass spectrum of 4-chlorophenyllthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**23**).

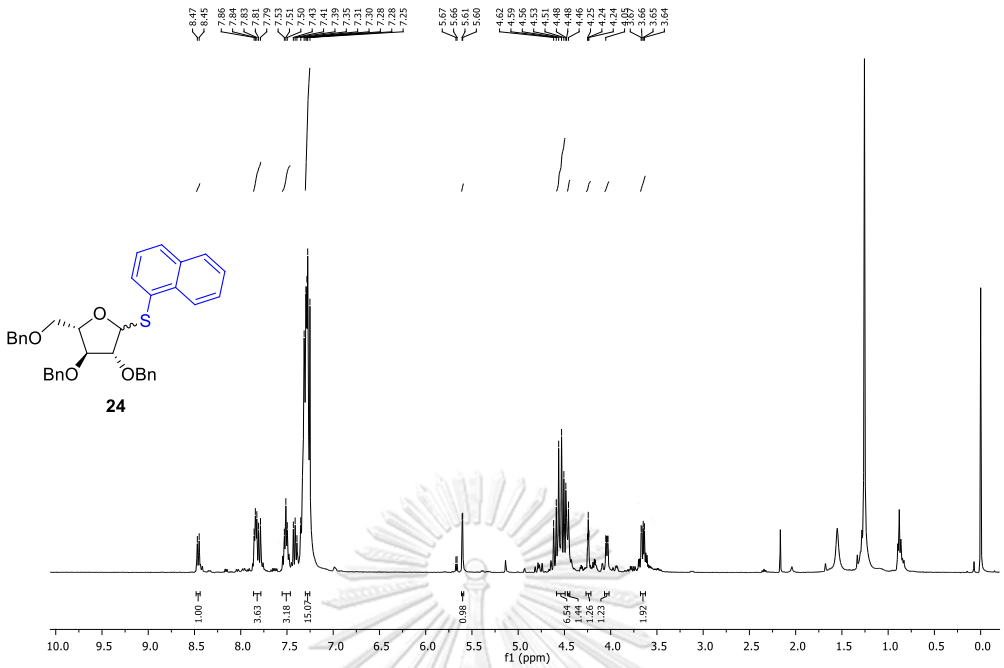

Figure A43. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-napthylthio 2,3,5-tri-*O*-benzyl-L-arabino-furanoside (**24**).

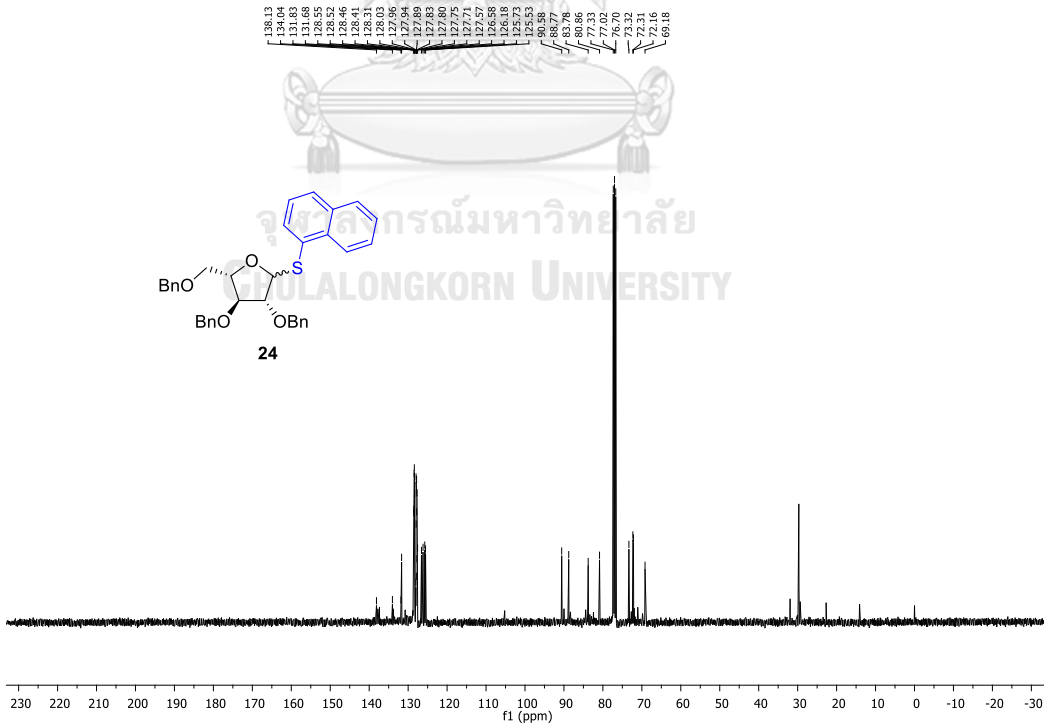

Figure A44. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of 1-napthylthio 2,3,5-tri-*O*-benzyl-L-arabino-furanoside (**24**).

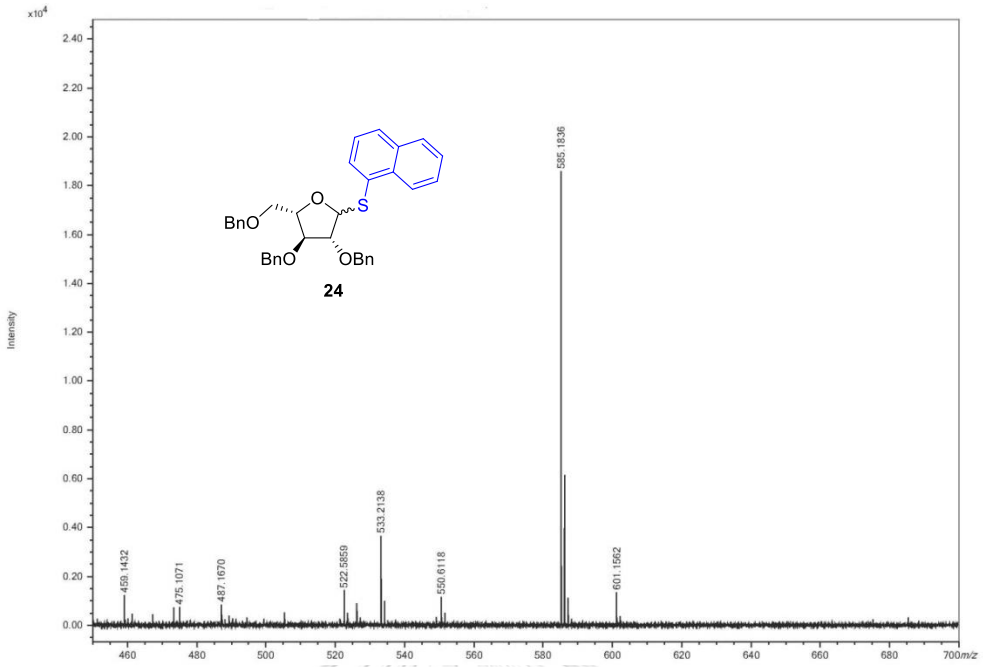

Figure A45. Mass spectrum of 1-napthylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**24**).

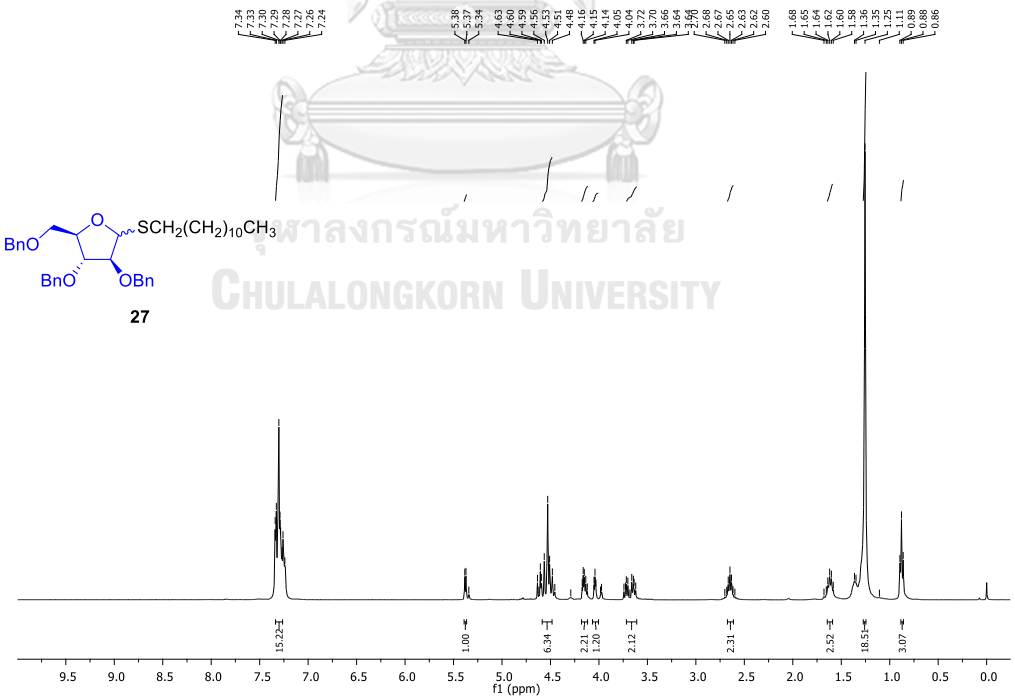

Figure A46. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (**27**).

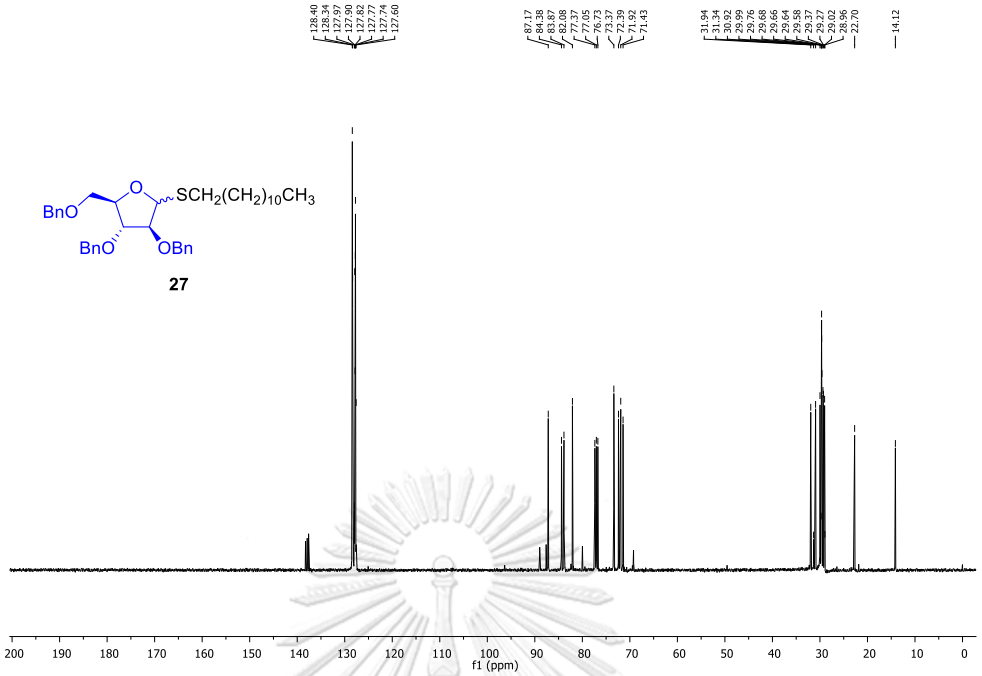

Figure A47. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (**27**).

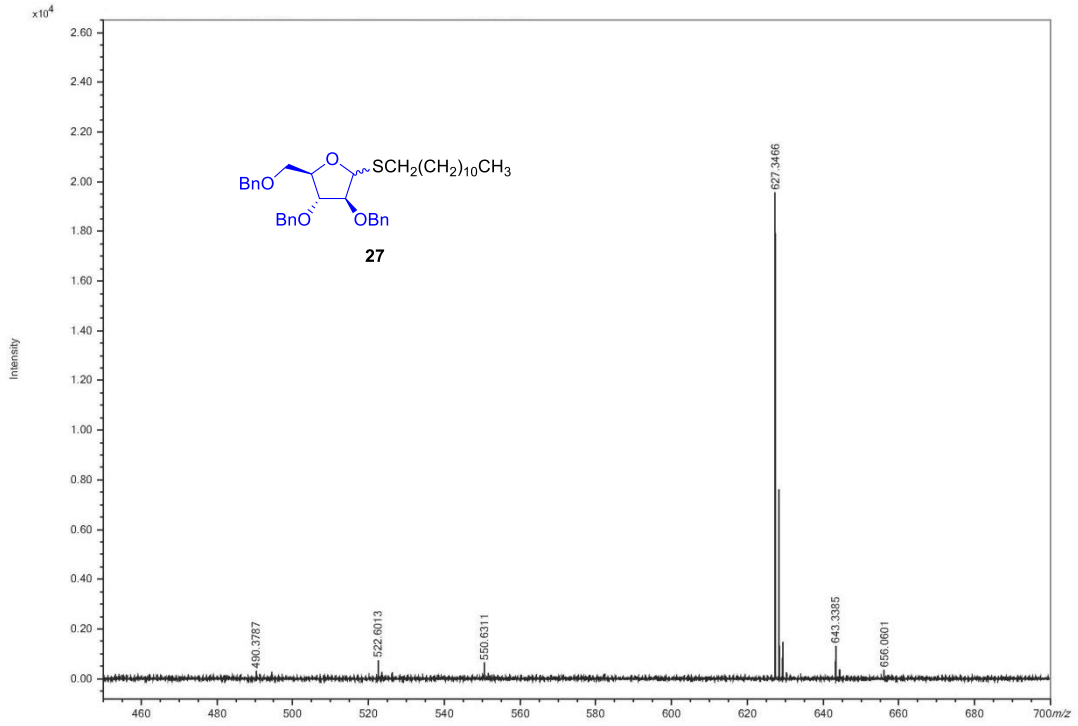

Figure A48. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (**27**).

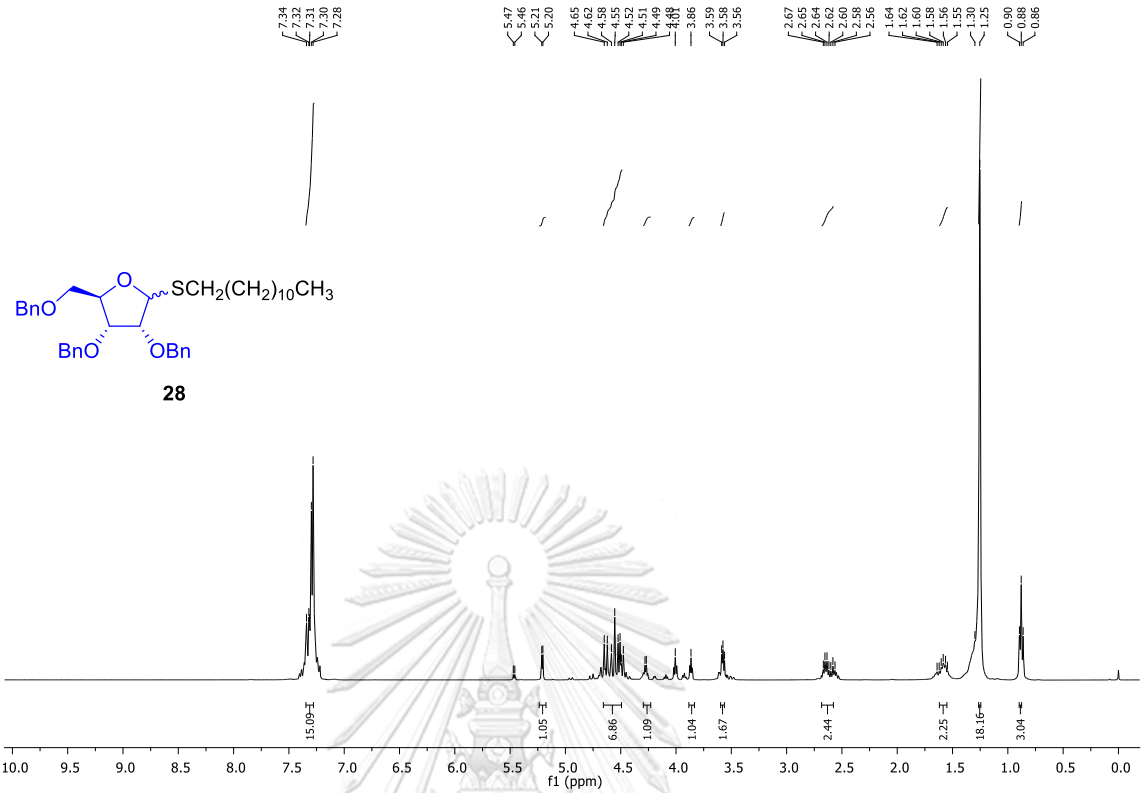

Figure A49. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**28**).

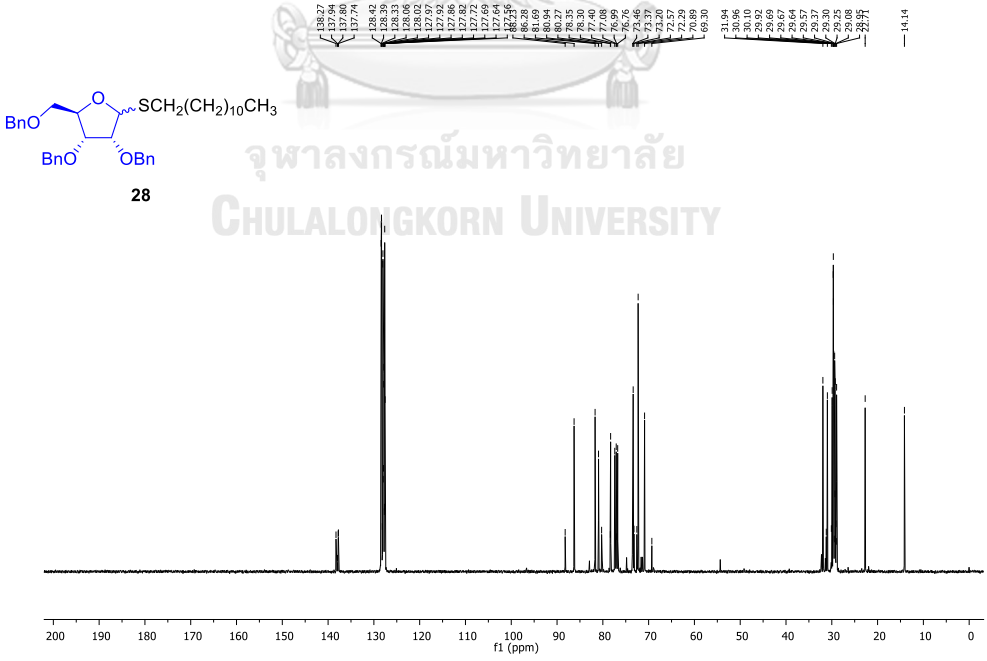

Figure A50. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**28**).

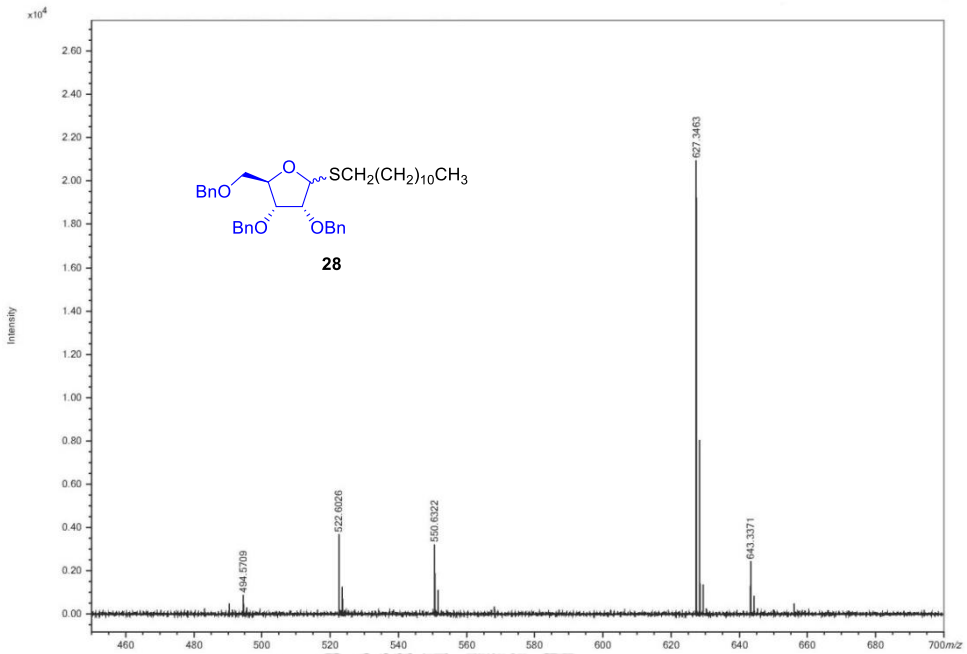

Figure A51. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**28**).

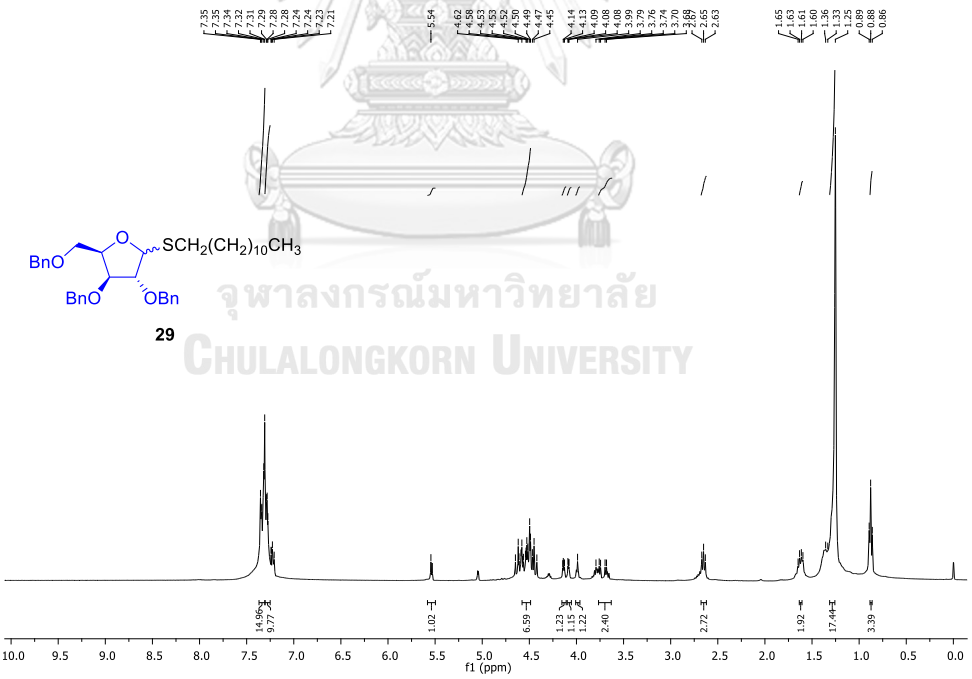

Figure A52. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-xylofuranoside (**29**).

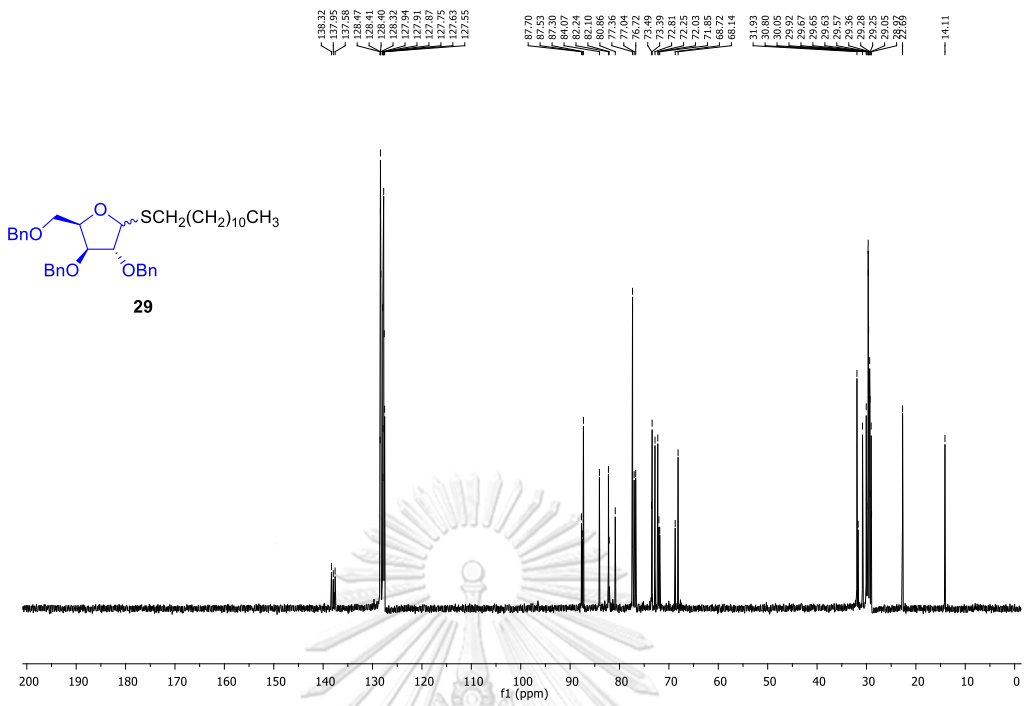

Figure A53. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-xylofuranoside (**29**).

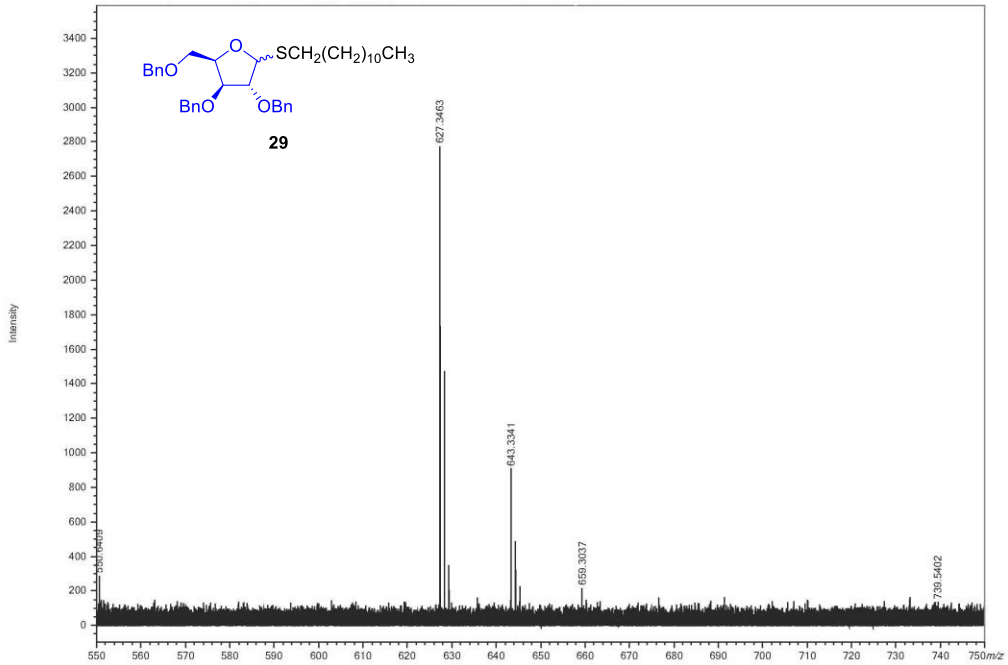

Figure A54. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-D-xylofuranoside (**29**).

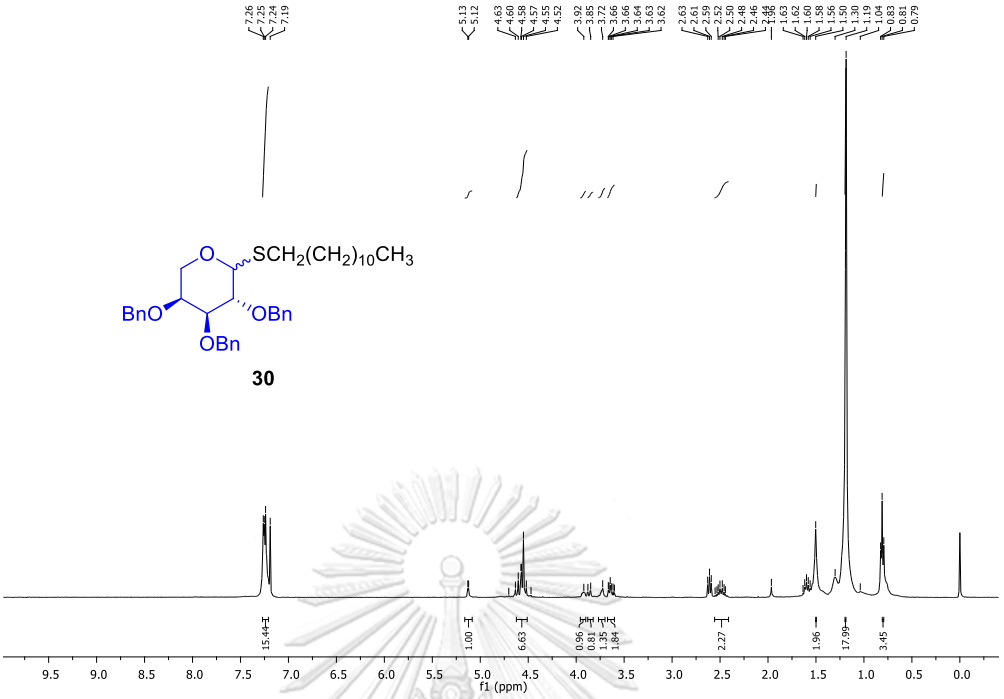

Figure A55. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**30**).

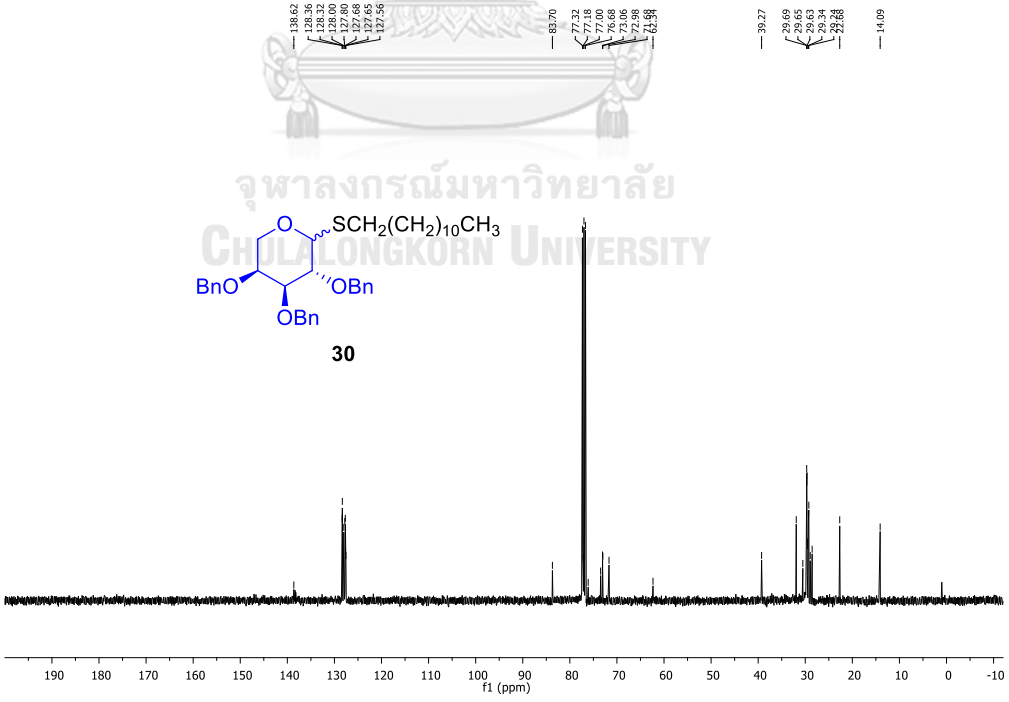

Figure A56. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**30**).

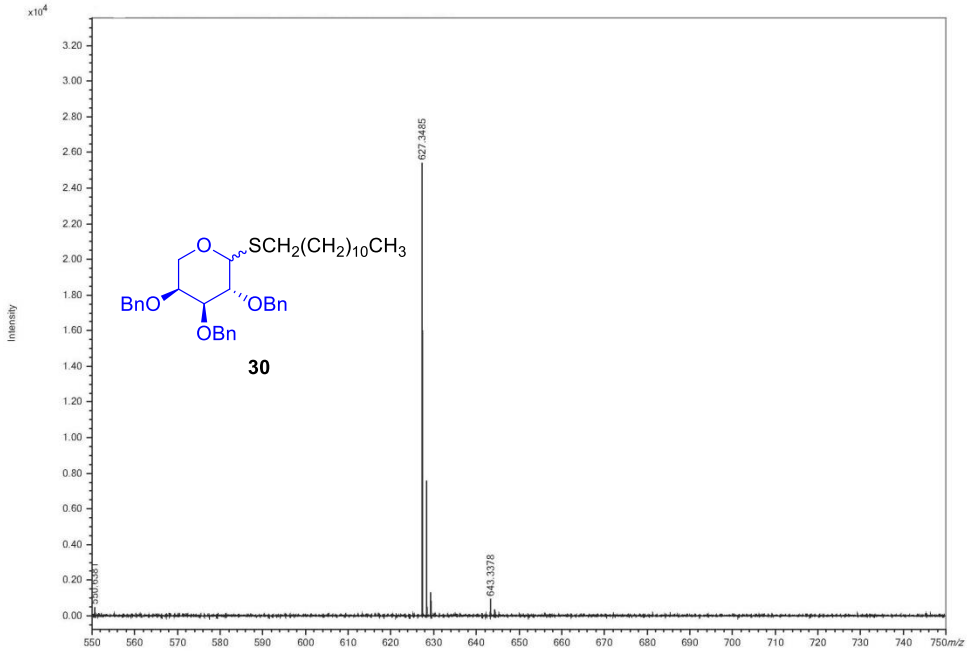

Figure A57. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinopyranoside (**30**).

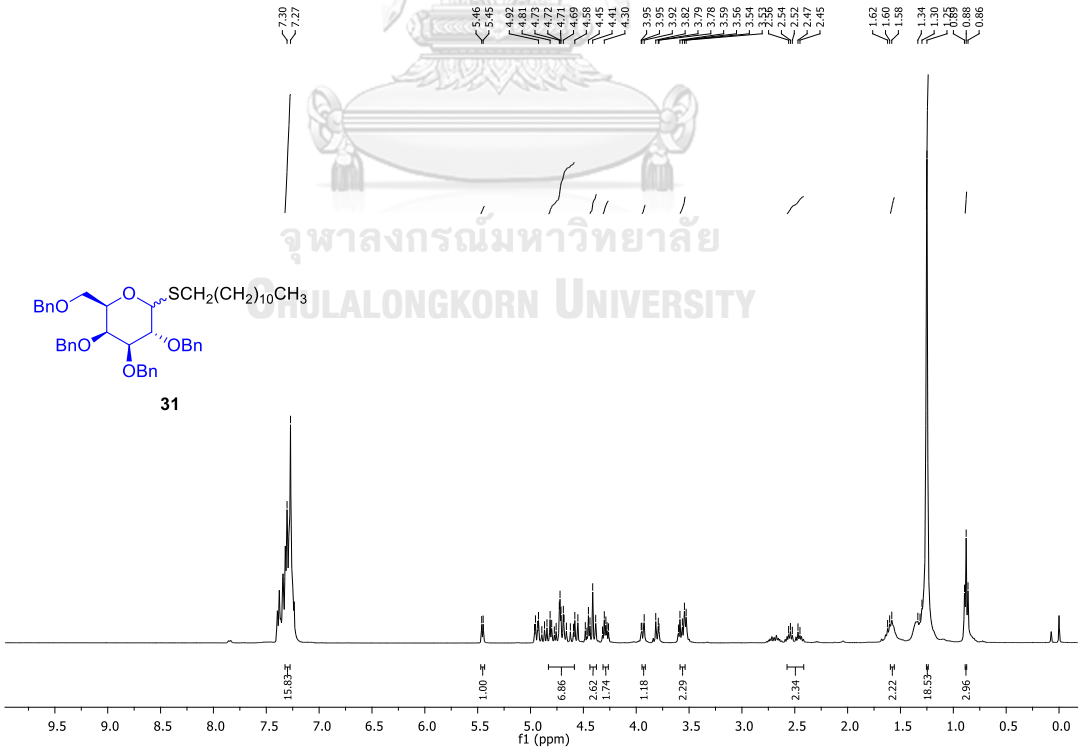

Figure A58. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-galactopyranoside (**31**).

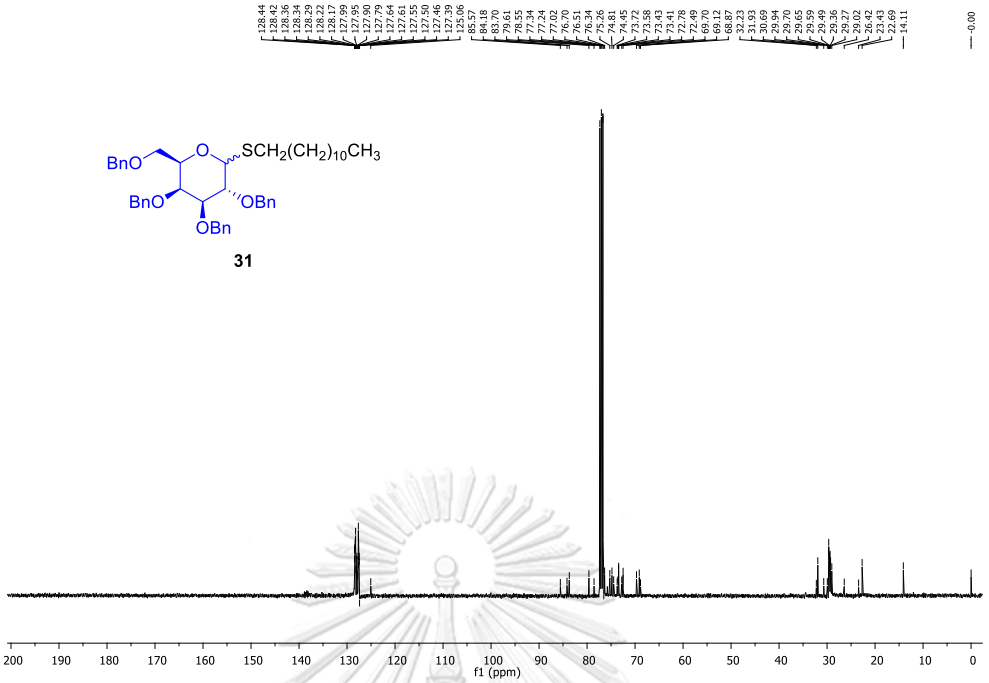

Figure A59. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-galactopyranoside (**31**).

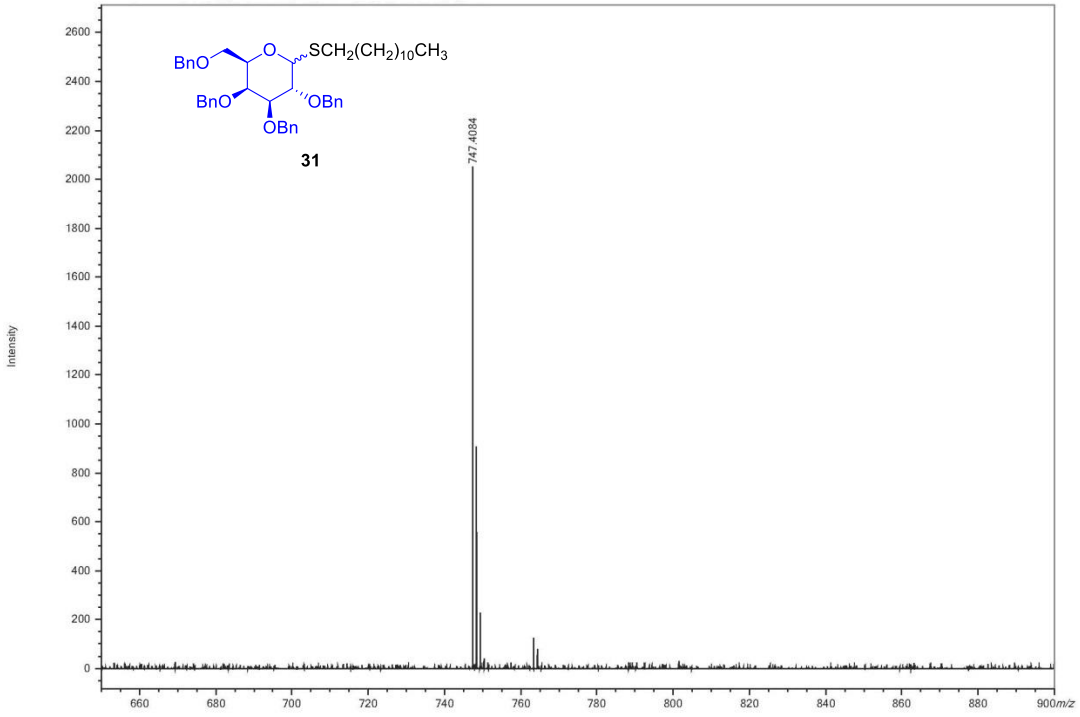

Figure A60. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-D-galactopyranoside (**31**).

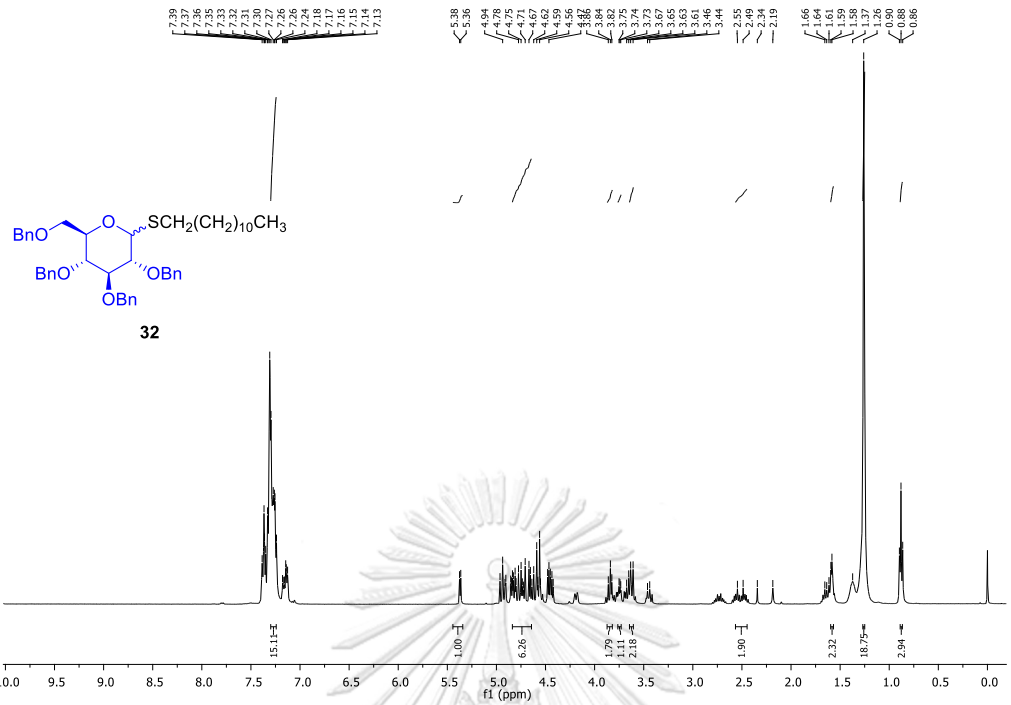

Figure A61. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-glucopyranoside (**32**).

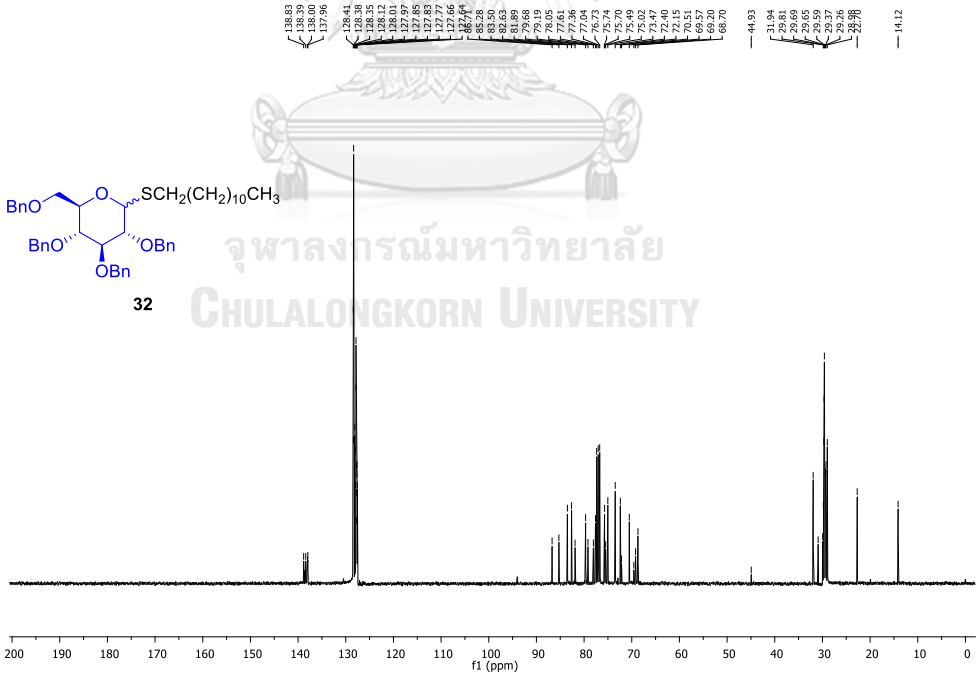

Figure A62. ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of dodecylthio 2,3,5-tri-*O*-benzyl-D-glucopyranoside (**32**).

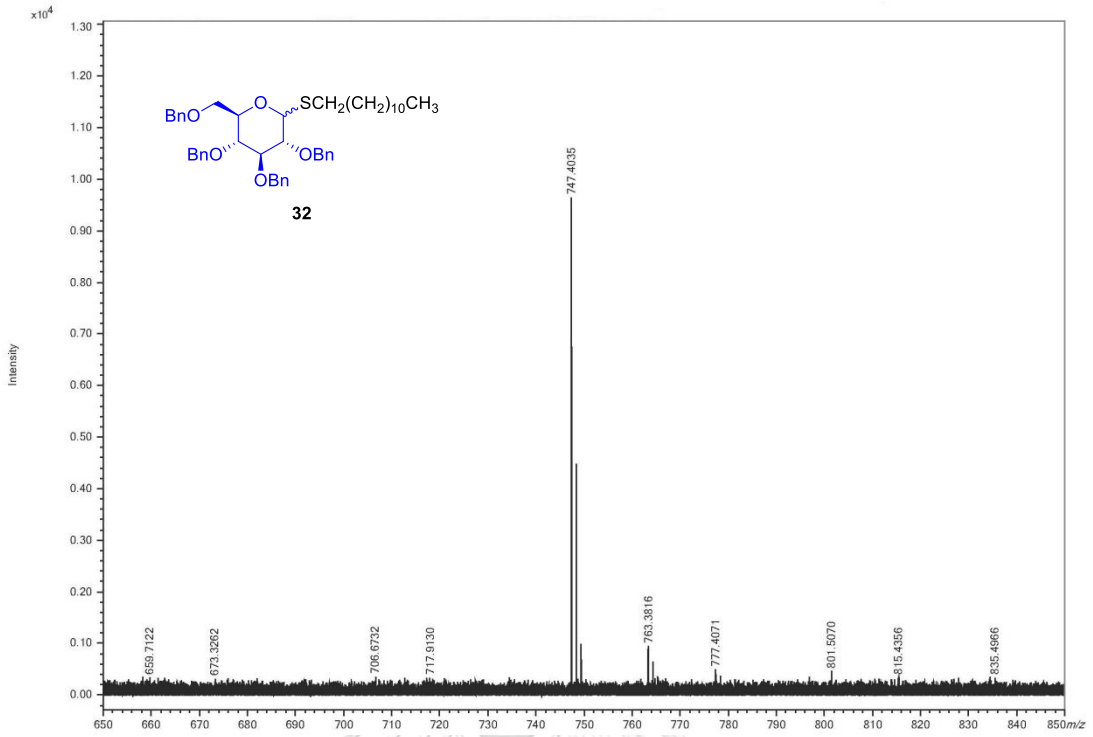

Figure A63. Mass spectrum of dodecylthio 2,3,5-tri-*O*-benzyl-D-glucopyranoside (**32**).

VITA

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