Synthesis of Terminal Pentasaccharide Motif A Reminiscent of Mycobacterial Cell Wall

MS Thesis

submitted to

Indian Institute of Science Education and Research Pune in fulfilment of the requirements for the MS Chemistry Degree Program

by

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Certificate

Certified that the work incorporated in the thesis entitled, “Synthesis of terminal pentasaccharide motif, A reminiscent of Mycobacterial cell wall” submitted by **Sumit** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or institution.

Prof. Srinivas Hotha
(Supervisor)

Prof. H.N Gopi
(Expert)

Dedicated to my family and friends…

Declaration

I hereby declare that the matter embodied in the report entitled, '**Synthesis of terminal pentasaccharide motif, a reminiscent of Mycobacterial cell wall**' are the results of the work carried out by me at the Department of Chemistry, Indian Institute of Science Education & Research (IISER) Pune, under the supervision of Prof. Srinivas Hotha, and the same has not been submitted elsewhere for any other degree.

Sumit

Date: 15 March 2026

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Acknowledgments

First and foremost, I would like to sincerely thank my mentor, research supervisor, Prof. Srinivas Hotha (IISER Pune), a person of integrity, compassion, and exceptional standards and my project expert Prof. H N Gopi (IISER Pune). I am truly grateful for their constant encouragement, exceptional guidance, and for generously imparting their vast knowledge and experience, which have significantly enriched my skills. The successful completion of this journey would not have been achievable without their invaluable supervision. I would like to extend my thanks to all the past and present members of the Hotha lab for fostering a supportive and positive environment. I am especially grateful to my lab colleagues for contributing to the friendly and collaborative atmosphere in the lab. I am truly thankful to my batchmates and friends who have been my pillars of mental peace and strength. I am thankful to IISER Pune for providing me world-class research facilities. I would like to extend my gratitude to the operators of NMR, MALDI, HRMS, SEM, and TEM for their invaluable contributions to my MS journey. Finally, I dedicate this achievement to my family, who have stood by me through every high and low.

Abstract

The thesis titled "Synthesis of Terminal Pentasaccharide Motif A Reminiscent of Mycobacterial Cell Wall" is organized into three chapters. Chapter 1 provides an overview of the importance of carbohydrates, glycosylation, glycosidic linkages, stereoselectivity in chemical glycosylation, gold catalysis in glycosylation and conformational analysis of carbohydrates. Chapter 2 details the synthesis of the pentasaccharide motif A, mycobacterial glycan using [Au]/[Ag]-catalyzed glycosylation. Chapter 3 gives the references.

Chapter 1: **Introduction of Glycosylation, Glycomaterials, and their importance:**

Carbohydrate research has shifted significantly from viewing these molecules as metabolic fuel to recognizing them as sophisticated regulators of complex biological phenomena. Carbohydrates, often existing as diverse glycoconjugates such as glycoproteins, glycolipids, and proteoglycans, are important components of cell membranes and extracellular matrices. These biomolecules serve as the primary interface for essential biological activities, including cell-to-cell recognition, viral and bacterial pathogenesis, inflammatory responses, and the progression of tumor metastasis.

Despite their biological prominence, the study of glycans presents unique challenges that distinguish them from proteins or nucleic acids. The inherent micro-heterogeneity and structural complexity of naturally occurring glycoconjugates make their isolation in a chemically pure state. Unlike the linear assembly of DNA or the predictable folding of peptides, carbohydrates exhibit intricate branching patterns and specific glycosidic linkage requirements that necessitate precise chemical and chemo-enzymatic synthesis to achieve exact structural specifications.

Chemical glycosylation reaction process involves the nucleophilic displacement of a leaving group at the anomeric carbon of a glycosyl donor, typically facilitated by a promoter or activator. The resulting oxocarbenium ion intermediate is subsequently attacked by a glycosyl acceptor to form a new glycosidic bond. Achieving absolute regioselectivity and stereoselectivity of synthetic carbohydrate chemistry. While regioselectivity is often managed through strategic protecting group manipulations, stereoselectivity is governed by a delicate balance of stereoelectronic effects and anchimeric assistance, particularly at the C-2 position.

In recent decades, the emergence of gold-catalyzed glycosylation has revolutionized the field by providing a mild and efficient alternative to traditional Lewis acid-mediated methods. These advancements have paved the way for the development of novel glycomaterials - synthetic analogues designed to mimic the secondary structures of natural glycans. By adjusting the properties of these materials, researchers can create chiral, self-assembled systems with directional control, offering a powerful toolkit for probing glycan-protein interactions. As our ability to synthesize and analyse these complex structures matures, the development of pure, structurally defined glycoconjugates continues to be instrumental in understanding the molecular basis of disease and developing targeted therapeutic interventions.

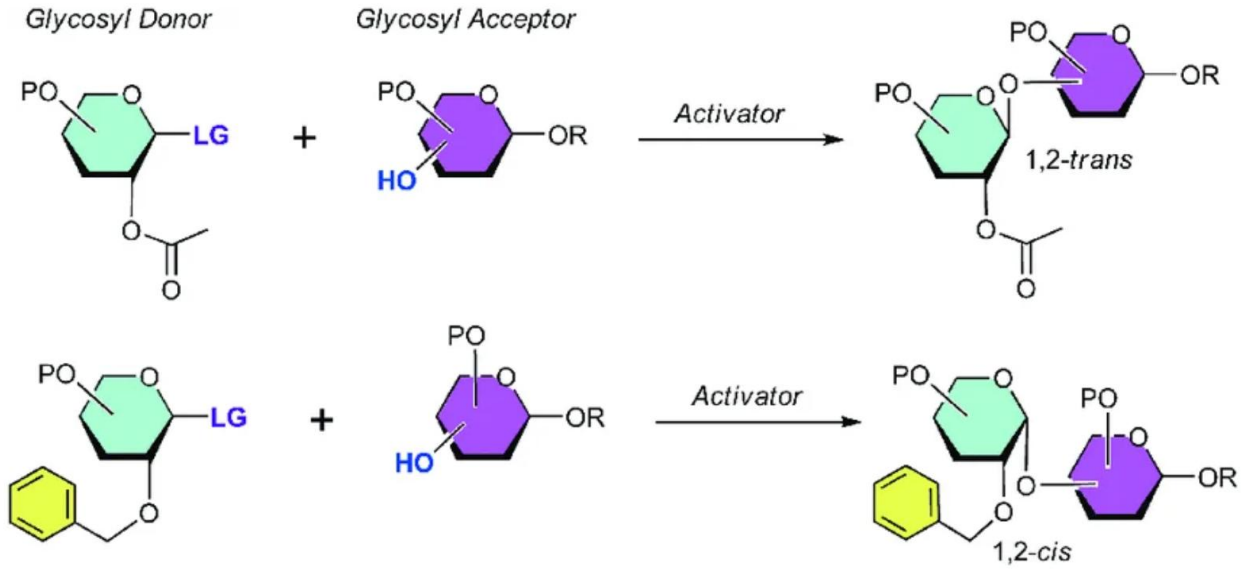


Figure 1: General representation of the glycosylation reaction. LG denotes the anomeric leaving group, P and R protecting groups. The stereodirecting effect of 2-*O*-protecting groups is presented in a simplified way as both 1,2-*cis* and 1,2-*trans* glycosides can be formed in each case. Note that common designations of glycosidic bonds as α- and β -relate to absolute D- and L-configuration of sugars, e.g. α-D-galactopyranoside is a 1,2 -*cis* -and α-L-arabinopyranoside is a 1,2-*trans* -glycoside.

Chapter 2: The glycolipid library was created through the process of [Au]/[Ag] catalyzed glycosylation and regioselective esterification. Mycobacterium tuberculosis (MTb) cell wall structure distinctively displays its glycolipid content which includes mycolyl arabinogalactan that contains Arabinofuranosyl (Araf), galactofuranose (Galf) and mycolic acid. The arabinogalactan (AG) terminal region features motif A which contains

a pentaarabinofuranoside that has two β-1,2 linkages and one α-1,5 and α-1,3 linkages. The C5 positions of motif A are mycolic acids which have been modified through distinctive cyclopropane groups. We used an [Au]-[Ag] catalyzed glycosylation method to create a range of MTb cell wall glycolipids which are derived from motif A. The glycolipid collection contains different forms of arabinofuranosides which include di, tri, tetra, and penta saccharides that contain α or β-(1→2, 3, or 5) Araf linkages and their saturated or doubly unsaturated or cyclopropanated long-chain fatty acid esterifications. The study used naturally occurring linoleic acid as the lipid component because it contains two cis olefin bonds. The chapter shows how scientists used trans glycosidic linked glycolipids for regioselective esterification while demonstrating hydrophobic component cis and trans cyclopropanation through a modified Simmons-Smith reaction. The literature review supported the chirality determination of cyclopropanated linoleic acids which *Tomoyuki Nishizaki* studied in 2011 (Cell Physiol. Biochem. 2011, 27, 149-158) through his research. The study involved the chemoenzymatic creation of all four cyclopropanated linoleic acid derivatives. *Nishizaki* explained that the determination of stereochemistry for cyclopropanated esters presents significant difficulties which need to be solved through further research.

Chapter 3: References

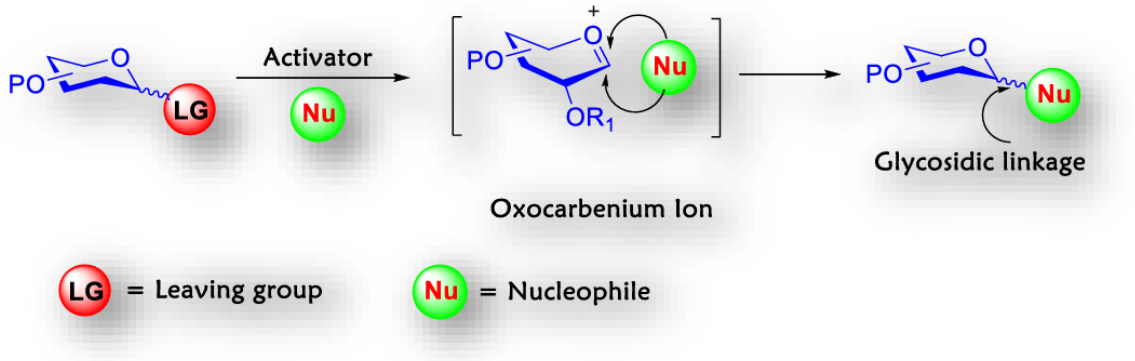
Chapter 1

1.1 Introduction of carbohydrates

From being thought of as basic energy sources, carbohydrates are now crucial regulators of intricate biological processes like cell signaling and fertilization. Even though they are widely distributed in nature, frequently as glycoconjugates. It is very challenging to isolate them due to their low concentrations and structural complexity. As a result, scientists rely on lab synthesis; however, unlike proteins or DNA, carbohydrates pose special difficulties because of their complex branching, particular linkage requirements, and the complex chemical strategies required to construct them.

1.2 Chemical Glycosylation

A chemical glycosylation reaction can be explained as a nucleophilic displacement of a leaving group attached to the anomeric carbon of a glycosyl donor, facilitated by various promoters such as (Lewis acids, Brønsted acids, neutral reagents, inorganic salts, etc). Once the leaving group is displaced, an oxocarbenium ion intermediate is generated, which is then attacked by a glycosyl acceptor (nucleophile) to create a new glycosidic



Scheme 1.1: General glycosylation reaction

Bond. The first two chemical synthesis challenges require researchers to achieve both regioselectivity and stereoselectivity throughout the entire process of producing new glycosidic bonds. The research team achieved regioselectivity by maintaining one hydroxyl group unprotected during the reaction process while using protecting groups to shield the glycosyl acceptor. Multiple stereoelectronic elements determine all aspects of stereospecificity which creates greater difficulties for researchers who need to establish

control over stereospecific outcomes. The stereochemical result at C-2 position of the glycosyl donor depends on its functional group because this connection determines whether the reaction will produce 1,2-*cis* or 1,2-*trans* glycoside. The C-2 carbonyl group which exists as an ester carbonate or carbamate creates 1,2-*trans* glycosides through anchimeric assistance that produces an acycloxonium ion system with increased stability. The incoming nucleophile can only approach from one side because the trioxolenium ion intermediate restricts its movement, which results in the formation of 1,2-*trans* glycosides. Ethers at C-2 position which include benzyl, methyl or azide result in a mixture of 1,2-*trans* and 1,2-*cis* glycoside production. The oxocarbenium ion allows the acceptor to attack from both axial and equatorial positions which creates equal probability for the attack to happen. Stereoelectronic effects determine the specific distribution between 1,2-*trans* and 1,2-*cis* glycosides.

1.3 Gold catalysis in glycosylation

Most gold-catalyzed reactions involve gold in the +1 and +3 oxidation states as Au(0) is generally inert. The use of gold catalysis in glycoside synthesis was entirely unexplored until 2006. *Hotha and Kashyap* reported the first activation of an anomeric propargyl glycosyl donor (2006) through their study of the Au(III)-catalyzed Ferrier-type reaction which used a 3-*O*-propargyl derivative. The Zhu group showed that $AuCl_3$ could activate 2,2 dimethyl but-3-ynyl thioglycosides which contained alkyne groups while Hotha group studied glycosyl propargyl 1,2-*O*-orthoester donors to achieve 1,2-*trans* glycosylation which became important development in this research area. Hotha and Kayastha discovered that 1-ethynylcyclohexanyl glycoside donors can be activated at room temperature using $AuCl_3$ and AgOTf as a co-catalyst and these donors are noticed to be significantly more reactive than propargyl glycosides. The researchers *Vankar et al*. managed to activate the trichloroacetimidate donor by using Au(III) salts. The Yu group discovered *o*-hexynylbenzoate glycosyl donors that can be activated in the presence of $Ph_3PAuOTf$ or $Ph_3PAuNTf_2$ forming various glycosides and saccharide-containing natural products. *Mishra, Neralkar and Hotha* successfully developed a mild Au(I)/Ag(I) co-catalyzed glycosylation method using ethynylcyclohexyl glycosyl carbonate donors. Au(I)-catalyzed glycosylation methods are milder than traditional glycosylation approaches which often rely on strong Lewis acids or Brønsted acid activators. The new

methods provide researchers with better options to synthesize glycosides which normally prove challenging to create.

Chapter 2:

2.1 Introduction:

Tuberculosis (TB) continues to kill more people than any other disease across the globe while it remains one of the most lethal infectious diseases throughout human history. The cause of tuberculosis remained unknown until Dr. Robert Koch discovered the disease in 1882 and named the bacillus *Mycobacterium tuberculosis* (Mtb). Scientists estimate that about 2 billion people across the world were contracted M. tuberculosis. The WHO 2019 report listed tuberculosis as the 13th most common death cause worldwide while it became the main infectious disease threat that exceeded HIV/AIDS. *Mycobacterium tuberculosis* causes tuberculosis because infected people spread the bacteria through airborne particles that they release when they cough. Tuberculosis starts in the lungs as pulmonary TB but it can spread to other body parts as well. People who have HIV, diabetes, smokers or alcohol consumers excessively face increased chances of developing TB. The medical community identified isoniazid and rifampicin as the primary drugs for TB treatment. The Bacille Calmette-Guérin (BCG) vaccine which the scientific community developed almost 100 years ago now proves ineffective for TB prevention and has become a standard protection method against severe disease forms in children. No vaccine currently exists which can prevent TB in adults both before and after they contract the disease.

2.2 Structure of MTb cell wall

The bacterial cell wall is often referred to as the mycolyl-arabinogalactan-peptidoglycan (mAGP) complex. It consists of three main components: i) peptidoglycan, ii) lipopolysaccharides (including arabinogalactan, lipoarabinomannan, and lipomannan), and iii) the outer membrane (which contains mycolic acid, various glycolipids, and phthiocerol dimycocerosates)

2.2.1 Peptidoglycan: The peptidoglycan is found outside the mycobacterial inner or plasma membrane. It comprises alternating *N*-acetylglucosamine and muramic acid (which can be either *N*-acetylated or *N*-glycosylated) residues, connected by (1→4) bonds.

2.2.2 LM, LAM, and PIMs: The inner membrane of the mycobacterial cell wall contains a mixture of three lipoglycans: lipomannan (LM), lipoarabinomannan (LAM), and phosphatidyl *myo*-inositol mannosides (PIMs). PIMs are primarily linked to the two mannose units. LM consists of long chains of mannan or branches featuring the α-D-(1→2) mannopyranose units. LAM, the longest glycopolymer chain, is made up of D-mannan and D-arabinan, which are anchored to a phosphatidyl *myo*-inositol (PI) group in the mycobacterial cell wall. The highly branched mannan structure features an α-(1→6) linked mannopyranose (Man*p*) backbone, with single Man*p* units substituted at the C2 position.

2.2.3 Arabinogalactan: Arabinogalactan is a heteropolysaccharide covalently linked to the muramic acid residue of peptidoglycan through a phosphodiester bond. It is located between the cytoplasmic membrane and the outer mycolic acid layer of the Mtb cell. It consists of arabinose. The AG component is made up of roughly 30 linear alternating β-(1→5) and β-(1→6) Gal*f* residues, forming the D-galactose portion, which is further linked to the rhamnopyranosyl residue of the linker unit. The galactan region consists of a linear alternation of 5- and 6-linked β-D-Gal*f* residues. Three tricosarabinofuranoside (23mer) moieties are attached to the C5 hydroxyl group of the β(1→6) linked Gal*f* unit. This arabinan portion is highly branched, featuring a linear α(1→5) linked polysaccharide backbone with branching introduced by the 3,5-α-D-Ara*f* residue. Additionally, the non-reducing termini feature a structural motif [β-D-Ara*f*-(1→2)-α-D-Ara*f*]$_2$-3,5-α-D-Ara*f*-(1→5)-α-D-Ara*f* that forms a distinctive hexaarabinofuranose moiety.

2.2.4 Mycolic acid: As part of the outer membrane, trehalose-containing glycolipids and phthiocerol dimycocerosates are interspersed with mycolic acid. These components also play a vital role in the immune response when interacting with the host. Mycolic acids are key and distinctive lipid components of the mycobacterial cell envelope, playing a crucial role in the survival of mycobacterium species, which include the causative agents of tuberculosis and leprosy. Mycolic acid primarily consists of α-alkyl, and β-hydroxy long-

chain fatty acids (C_{70}–C_{90}) referred to as mycolic acids. These highly lipophilic fatty acids are classified based on the presence of unsaturation or cyclopropyl groups ("α-mycolic acid"), as well as modifications such as methoxy or keto functions in the main chain. Mycolic acids are found either as free acids or esterified to the arabinogalactan layer, trehalose, glucose (glucose mono mycolate, GMM) or glycerol. *Moody and co-workers* showed that the R,R- stereochemistry of the α-alkyl, β-hydroxy carboxylic acid is essential for T-cell recognition of glucose monomycolate. Cyclopropane fatty acids are common in mycobacteria, and their concentration increases when exposed to harsh environments, suggesting they play a role in protecting membranes. The impact of cyclopropane and unsaturated fatty acids, in both *cis* and *trans* configurations, on the packing, order, and fluidity of lipid bilayers is examined through molecular dynamics simulations. It has been demonstrated that cyclopropane fatty acids disrupt lipid packing, promote the formation of *gauche* defects in the chains, and increase lipid lateral diffusion, indicating they enhance fluidity. Specifically, an increase in the concentration of cyclopropane fatty acids in the membranes of various bacteria has been linked to tolerance against high osmotic pressure, elevated temperature, low pH, nutrient deprivation, and high alcohol concentrations. Cyclopropane mycolic acids also influence the host's innate immune response. The stereochemistry of the cyclopropane ring is crucial. Trans-cyclopropanated mycolic acids play a key role in regulating and limiting the virulence of M. tuberculosis. About 70% of the mycolic acid in Mycobacterium is α-mycolic acid, as the double bonds are especially prone to oxidation. It has been hypothesized that their methylenation enhances resistance to superoxide, singlet oxygen, ozonolysis.

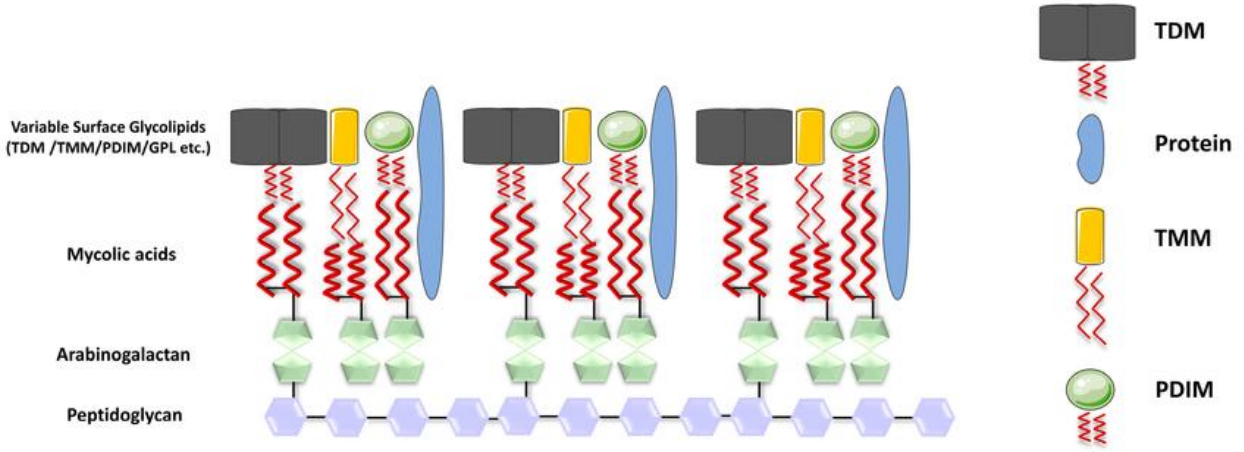


Figure 2: Structure of the cell wall of Mycobacterium tuberculosis. The cell wall of Mtb is formed by parallel arrangement of MA chains (represented by red wavy lines), which are linked to AG (depicted as green pentagons), while AG is covalently attached to peptidoglycan (PG) (shown as purple hexagons); the inner layer of the mycomembrane is presumably composed of free lipids, including TDM (depicted in gray), TMM (in yellow), and PDIM (in green spheres), along with the presence of proteins.

2.3 Importance and biological function of AG-Mycolic acid

The physiological and pathogenic functions of Mycobacterium tuberculosis organisms depend on their cell envelope lipid composition which displays different types of lipids and their specialized structural features and essential functions. The specific characteristics of Mycobacterium tuberculosis pathogens determine how effective first- and second-line tuberculosis medications work, which includes isoniazid (INH) and ethionamide (ETH) drugs that block mycolic acid biosynthesis. Ethambutol (EMB) stops the development of arabinan sections which make up ManLAM and AG. Ethambutol (EMB) mainly affects the polymerization process which produces the arabinan part of *Mycobacterium smegmatis* cell wall arabinogalactan (AG) biosynthesis. The organism needs mycolic acids, AG and peptidoglycan to maintain its macromolecular structure. The multiple effects of EMB reach different body systems because its main effects occur at trehalose dimycolate (TDM), mycolate metabolism, AG synthesis, glucose metabolism and spermidine biosynthesis. Mycolic acid methyltransferases which need to function for M. tuberculosis survival serve as essential targets for drug development which protects the cell wall and develops intrinsic antibiotic resistance.

2.4 Present work:

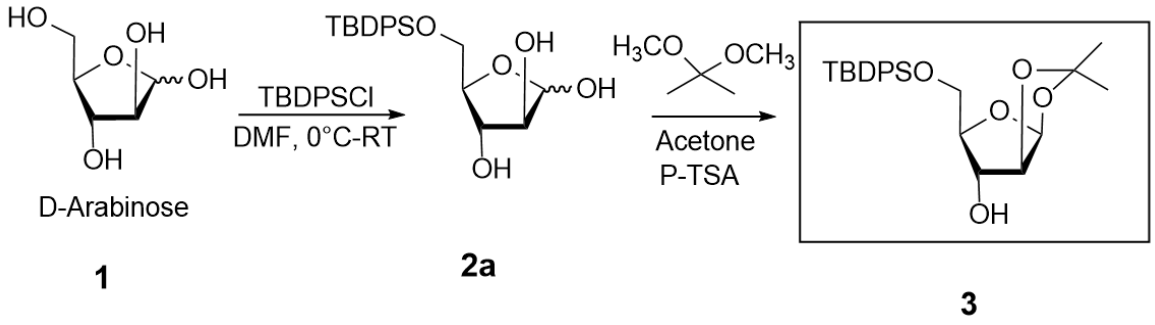
The cell wall of *Mycobacterium tuberculosis* (Mtb) is defined by its distinctive glycolipid composition particularly mycolyl arabinogalactan, which contains Ara*f*-, Gal*f*- and mycolic acid. My thesis focuses on the terminal portion of arabinogalactan (AG), motif A, a pentaarabinofuranoside characterized by two β-1,2 linkages and one each of α-1,5 and α-1,3 linkages. The C5 positions of motif A are esterified with mycolic acids, which are further modified by unusual cyclopropanes. In this study, we synthesized terminal motif A pentasaccharide.

2.5 Methods:

All reagents, starting materials, and dry solvents were acquired from commercial vendors and utilized exactly as supplied, without additional purification, unless otherwise noted. Every reaction was carried out in an environment of nitrogen. MERCK® SIL G/UV254 pre-coated Thin-layer Chromatography (TLC) sheets were used for TLC analyses. Visualization was accomplished with UV light (λ_{max} = 254 nm). Silica gel (200-300 and 100-200 mesh) was used for column chromatography. Either residual solvent [$CHCl_3$ (δ_H, 7.26 ppm, δ_C 77.2 ppm) as an internal standard were used to record the ^1H and ^{13}C NMR spectra on BRUKER 400 MHz (or 100 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hz. The signals' multiplicity is denoted by the following notations: s (singlet), d (doublet), t (triplet), td (triplet of doublet), q (quartet), sep (septet), m (multiplet). High-resolution mass spectra (HRMS) and infrared (IR) spectra were recorded using the BRUKER-ALPHA FT-IR spectrometer and HRMS-ESI-Q-Time of Flight LC/MS, respectively.

2.6 Scheme and Syntheses:

PART 1



Scheme 2: Synthesis of Acetonide protected sugar

2.6.1 TBDPS-Protection of Alcohol (1 to 2a):

To a solution of D-arabinofuranoside (26.29 mmol) in anhydrous DMF was added imidazole (78.87 mmol) at 25 °C. The resulting mixture was cooled to 0 °C, followed by the dropwise addition of *tert*-butyldiphenylsilyl chloride (TBDPSCl) (31.55 mmol). The reaction was allowed to warm to 25 °C and stirred for 4 h. Upon completion, the reaction was arrested by adding water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated

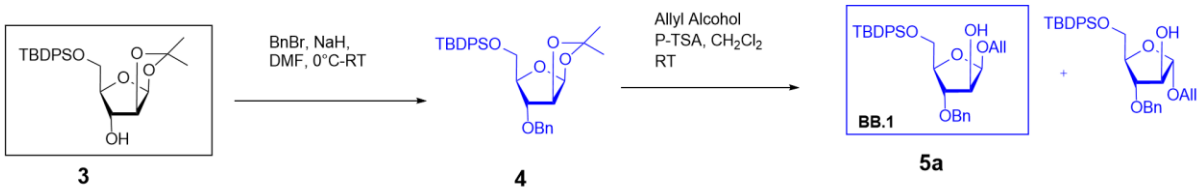
under reduced pressure. The crude oily residue was subjected to purification via silica gel column chromatography (EtOAc/petroleum ether) to afford the target compound as a clear oil (9.58 g, 85%).

2.6.2 1,2-*O*-isopropylidine-5-*O*-^{tert}butyldiphenylsilyl-D-arabinofuranose (2a to 3): To a stirred solution of 1,2-diol (149.28 mmol) in dry acetone (900 mL) were added 1,1-dimethoxypropane (298.56 mmol) and *p*-toluenesulfonic acid (p-TSA) (26.87 mmol). The reaction mixture was stirred at ambient temperature for 1 h. Upon completion, the reaction was neutralized with triethylamine (TEA) and the volatiles were removed under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford 1,2-*O*-acetonide-protected arabinofuranose (88% yield).

Synthesis of building block 1 (BB.1 or 5a):

2.6.3 1,2-*O*-isopropylidine-3-*O*-benzyl-5-*O*-^{tert}butyldiphenylsilyl-D-arabinofuranose (3 to 4): To a stirred solution of the alcohol (1.0 mmol) in anhydrous DMF at 0 °C was added NaH (60% dispersion in mineral oil, 1.2 mmol). After stirring for 10 min, benzyl bromide (1.2 mmol) and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI) were added. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h.

Upon completion, the mixture was poured into ice-cold water and extracted with EtOAc. The combined organic layers were washed sequentially with ice-cold water and brine, then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography to afford the desired benzyl ether.



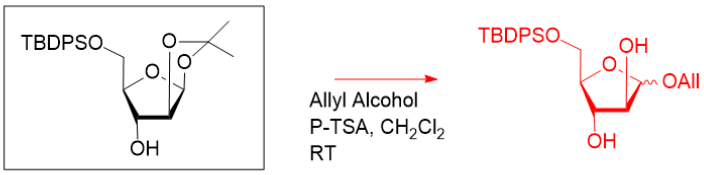
Scheme 3: Synthesis of Building Block 1

2.6.4 Allyl-3-*O*-benzyl-5-*O*-^{tert}butyldiphenylsilyl-β-D-arabinofuranose (BB1 or 5a): To a solution of the 1,2-acetonide-protected compound (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL/g) were added allyl alcohol (5.0 mmol) and *p*-toluenesulfonic acid (p-TSA) (0.2 mmol).

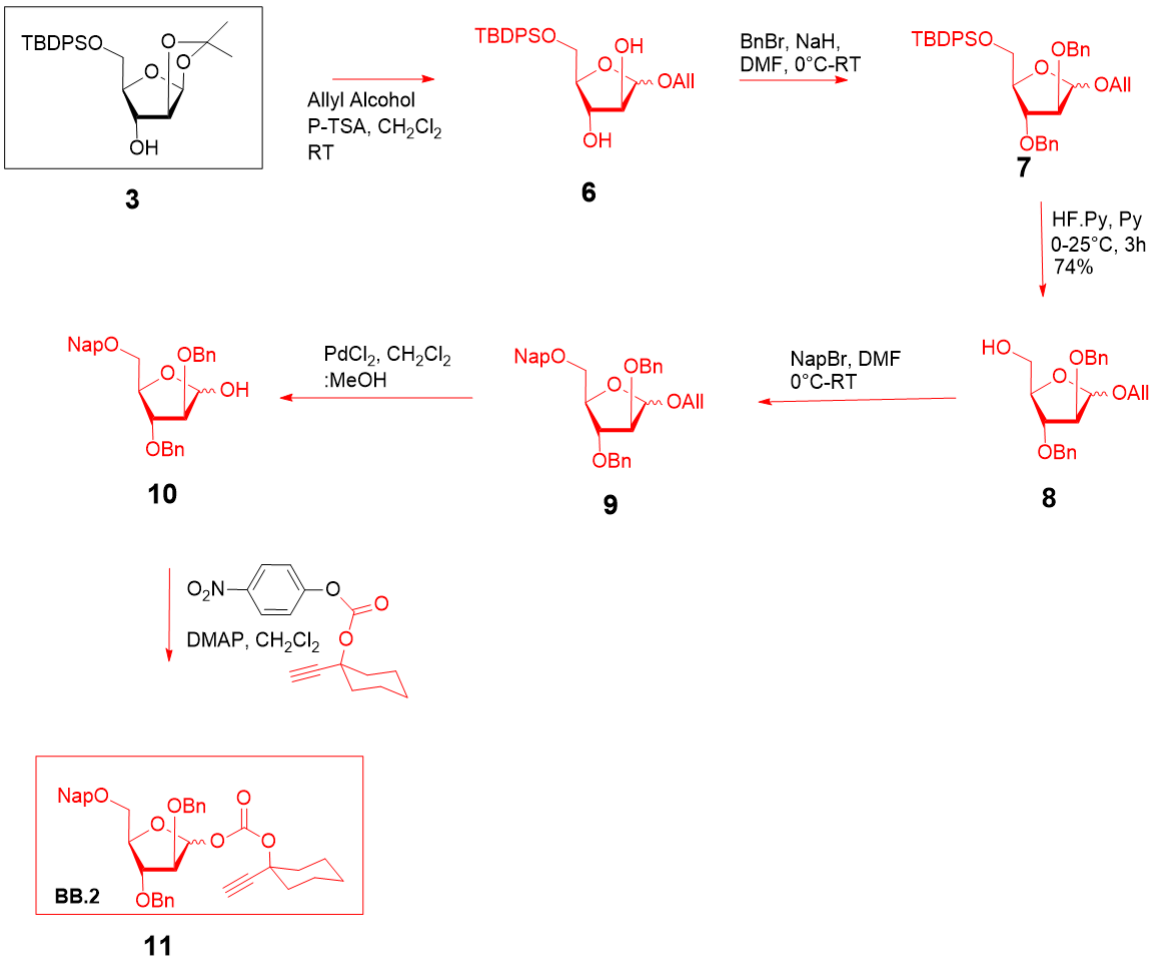
The reaction mixture was stirred at 60 °C for 2 h. Upon completion, the mixture was neutralized by the addition of triethylamine (TEA); the volatiles were removed under reduced pressure and the resulting crude residue was purified via silica gel column chromatography (hexane/EtOAc) to afford the desired allyl glycosides which are separated and characterized.

Synthesis of building block 2 (BB2)

2.6.5 Allyl-5-*O*-^{tert}butyldiphenylsilyl-α-D-arabinofuranose (3 to 6) (α isomer): To a solution of the 1,2-acetonide-protected **3** (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL/g) were added allyl alcohol (5.0 mmol) and *p*-toluenesulfonic acid (PTSA) (0.2 mmol). The reaction mixture was stirred at 60 °C for 2 h. Upon completion, the mixture was neutralized by the addition of triethylamine (TEA), the volatiles were removed under reduced pressure and the resulting crude residue was purified via silica gel column chromatography (hexane/EtOAc) to afford the desired allyl glycoside **6**.

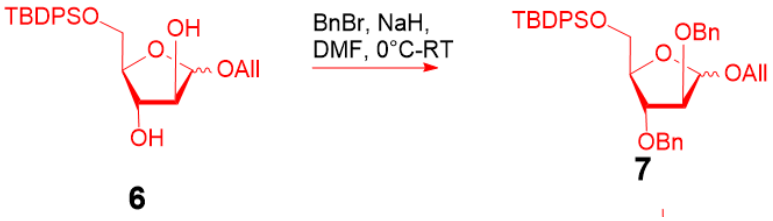


3 **6**



Scheme 4: Synthesis of building block 2

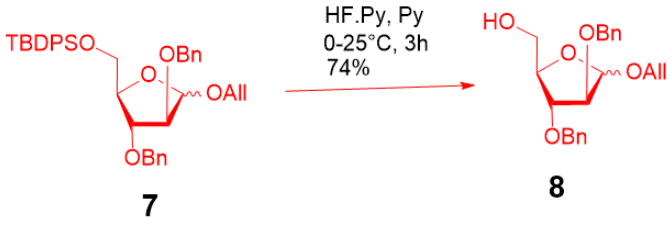
2.6.6 Allyl-2,3-O-dibenzyl-5-O-tertbutyldiphenylsilyl-α-D-arabinofuranoside (6 to 7):



To a stirred solution of the alcohol (1.0 mmol) in anhydrous DMF at 0 °C was added sodium hydride (60% dispersion in mineral oil, 1.2 mmol). The reaction mixture was stirred for 10 min, followed by the addition of benzyl bromide (1.2 mmol) and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI). The reaction was allowed to warm to room temperature and stirred for an additional 2 h. Upon completion, the reaction mixture was quenched by pouring into ice-cold water and extracted with EtOAc. The combined organic layers were washed sequentially with ice-cold water and brine, then dried over anhydrous Sodium Sulphate. The solvent was

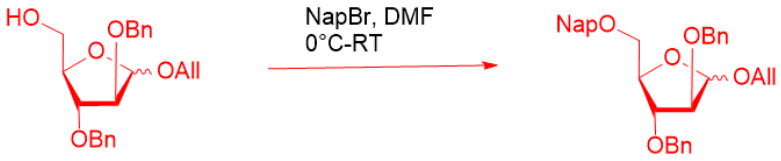
removed under reduced pressure, and the resulting crude residue was purified via silica gel column chromatography to afford the desired benzyl ether.

2.6.7: **Allyl 2,3-di-O-benzyl-D-ribofuranoside (7 to 8):** To a stirred solution of the TBDPS-protected silyl ether **7** (1.0 mmol) in anhydrous pyridine at 0 °C was added HF•py (3.0 mmol) dropwise under an inert atmosphere. The reaction mixture was allowed to warm to 25 °C and stirred for 5 h. Upon completion, the solution was cooled to 0 °C and quenched with 2*N* HCl. The aqueous phase was diluted with EtOAc and extracted. The combined organic layers were washed successively with ice-cold water, saturated aqueous sodium bicarbonate and brine. The organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography (EtOAc/hexanes) to afford the desired alcohol.



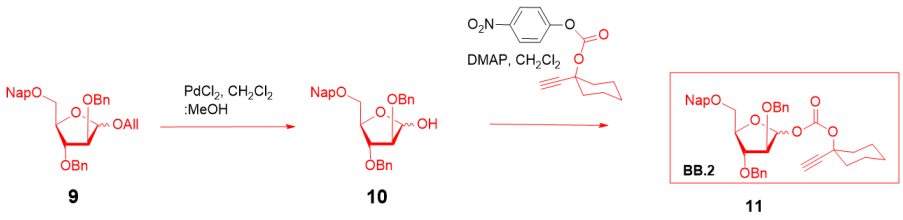
7 **8**

2.6.8 Allyl-2,3-*O*-dibenzyl-5-*O*-naphthylmethyl-α-D-arabinofuranoside (8 to 9) (α isomer): To a stirred solution of the alcohol **8** (2.5 g, 6.75 mmol) in anhydrous DMF (25 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 210 mg, 8.77 mmol). The mixture was stirred for 10 min, followed by the dropwise addition of 2-(bromomethyl)naphthalene (1.6 mL, 10.12 mmol) and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI). The reaction was allowed to warm to room temperature and stirred for an additional 2 h. Upon completion, the reaction mixture was diluted with EtOAc and quenched with ice-cold water. The organic phase was separated, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, resulting crude residue was purified by silica gel column chromatography (hexane/EtOAc) to afford the desired naphthyl ether **9** (2.8 g, 6.36 mmol, 94% yield).



8 **9**

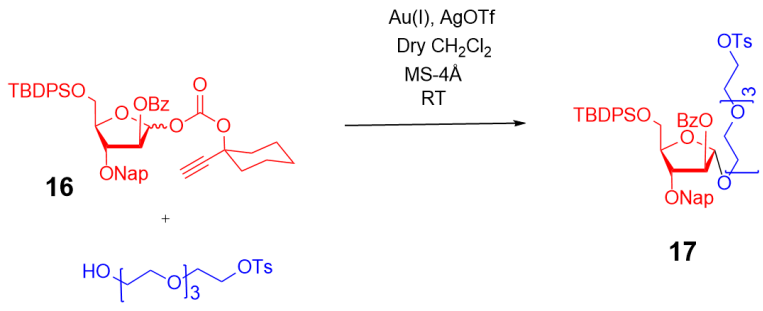
2.6.9:BB1:1-*O*-(((1-ethylnylcyclohexyl)oxy)carbonyl)-2,3-*O*-dibenzyl-5-*O*-naphthyl methyl-α-D-arabinofuranoside (9 to 11): A solution of allyl glycoside **9** (1.0 mmol) in a mixture of dichloromethane and methanol (3:1, 20 mL/g) was treated with palladium(II) chloride (0.2 mmol) added in portions under nitrogen atmosphere. The reaction mixture



was stirred vigorously for 2–3 h at room temperature. Upon completion, the reaction was neutralized with triethylamine, the resulting suspension was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure, the crude residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the corresponding hemiacetal. In continuation, the hemiacetal (1.0 mmol) was redissolved in dichloromethane (10 mL/g), 4-dimethylaminopyridine (1.2 mmol) and 1-ethynylcyclohexyl (4-nitrophenyl) carbonate (1.3 mmol) were added and solution was stirred at ambient temperature for 3 h. After the starting material was consumed, the solvent was removed under reduced pressure, and the residue was purified via silica gel column chromatography (hexane/ethyl acetate). To ensure the complete removal of 4-nitrophenol (by-product), the obtained material was redissolved in dichloromethane and washed with a saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and concentrated to yield the pure 1-ethynylcyclohexyl glycosyl carbonate donor.

Synthesis of Building block 3 (BB 3):

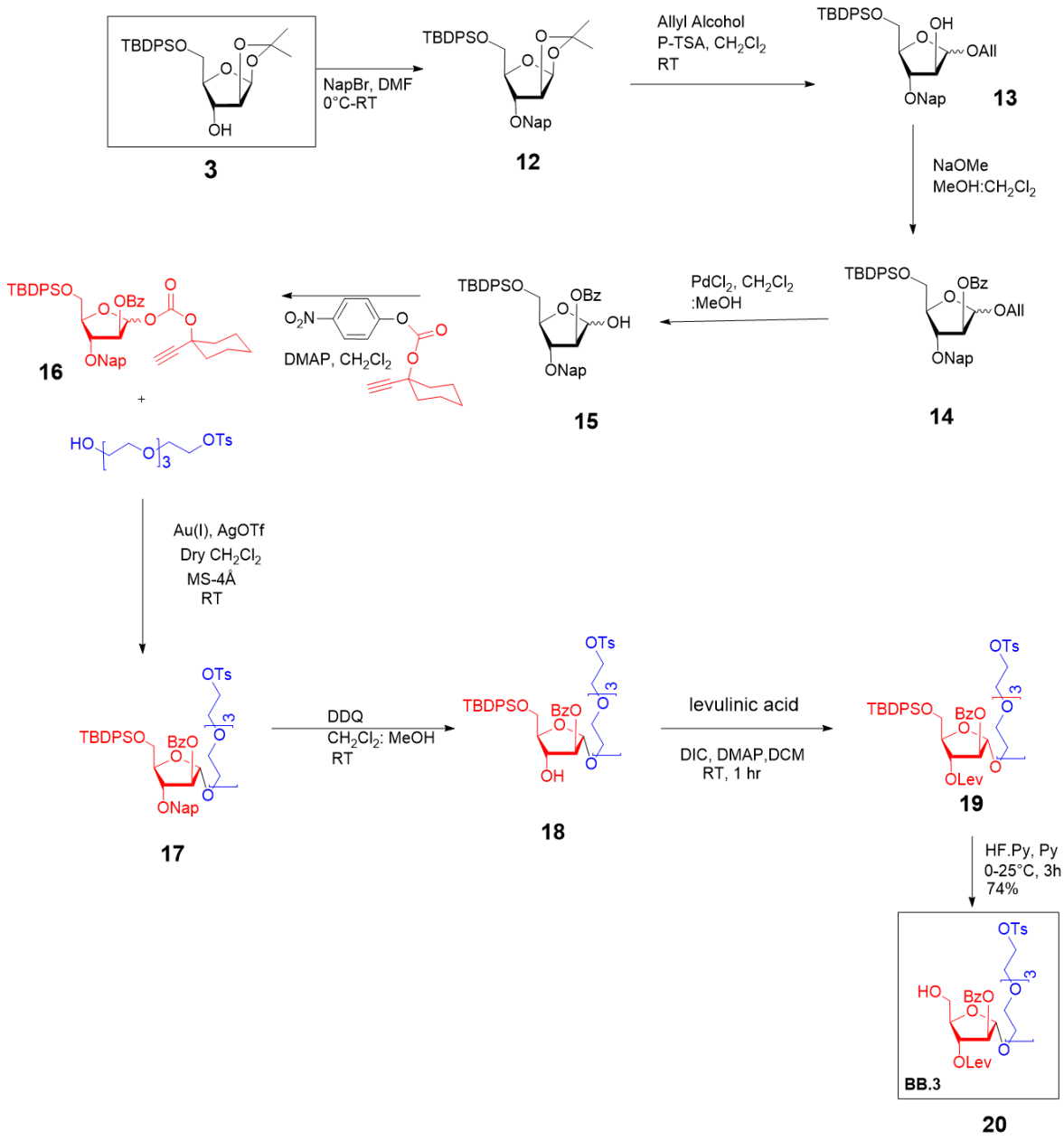
2.6.10 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-benzoyl-3-*O*-naphthylmethyl-5-*O*-*tert*butyldiphenylsilyl-α-D-arabinofuranoside.(16 to 17): A



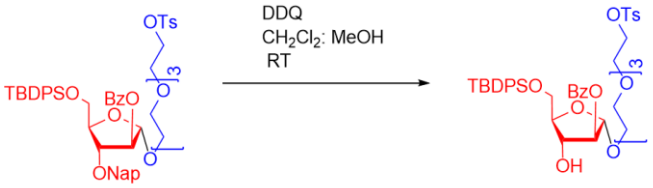
mixture of the glycosyl donor **16** (1.0 mmol) and acceptor (1.0 mmol) was dissolved in anhydrous dichloromethane, followed by the addition of freshly activated 4Å molecular sieves at 25 °C. After stirring

for 10 min, chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold(I) (8 mol %) and silver trifluoromethanesulfonate (8 mol %) were added to the reaction mixture. For reactions conducted at 25 °C, stirring was continued for 30 min. The reaction was quenched by the addition of excess triethylamine and the resulting suspension was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to afford the corresponding glycosides in 72–80% yield.

Scheme 5: Synthesis of Building Block 3

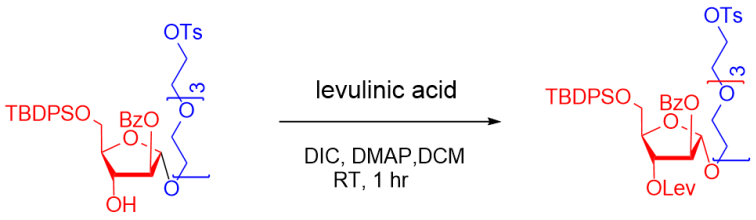


2.6.11 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-benzoyl-3-*O*-naphthylmethyl-α-D-arabinofuranoside(17 to 18): To a rapidly stirred solution of the alcohol (1.0 mmol) in a mixture of dichloromethane and methanol (1:4) at 25 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.0 mmol). The reaction mixture was stirred for 4 h, at which point the solution transitioned from a brown to a black color. The reaction was quenched by the addition of triethylamine, and the volatiles were removed under reduced pressure. The resulting crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the deprotected alcohol as a pale-yellow syrup.



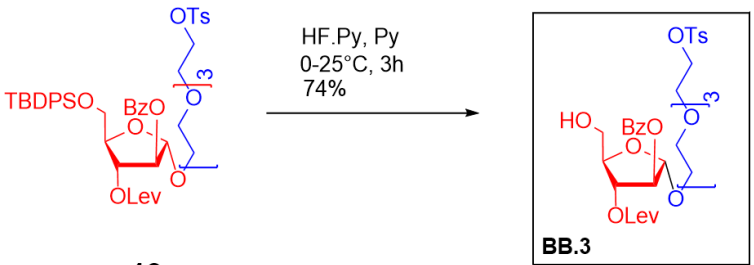
17 **18**

2.6.12 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-benzoyl-3-*O*-(4-oxopentanoyl)-5-*O*-^{tert}butyldiphenylsilyl-α-D-arabinofuranoside(18 to 19): To a stirred solution of the alcohol (1.0 mmol), 4-dimethylaminopyridine (0.5 mmol), and levulinic acid (1.3 mmol) in anhydrous dichloromethane at 0 °C was added *N*,*N*'- diisopropylcarbodiimide (1.5 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was gradually warmed to room temperature and stirred for 2 h. Upon completion, the solvent was removed under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the corresponding levulinate ester.



18 **19**

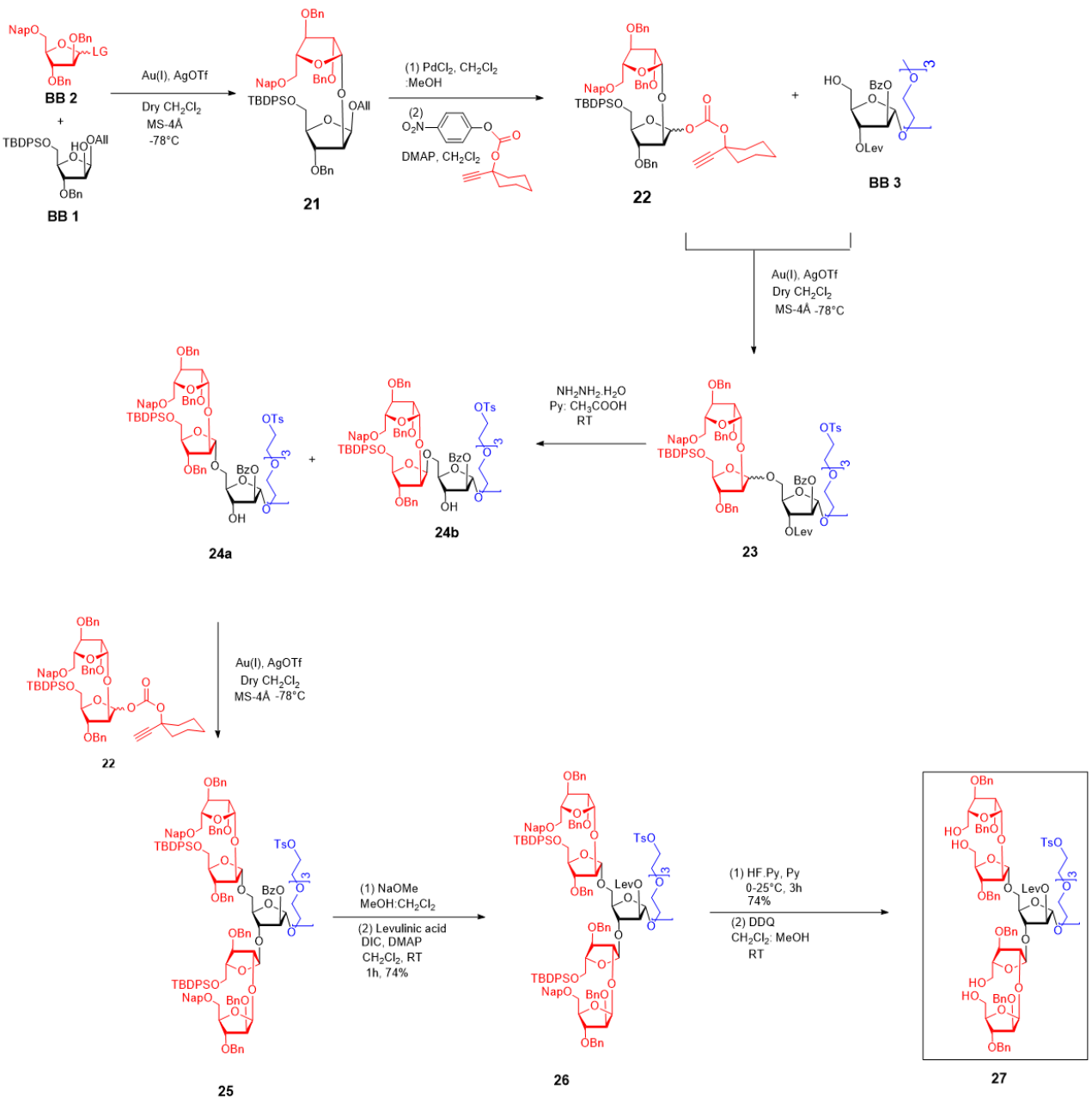
2.6.13:BB3:(2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-benzoyl-3-*O*-(4-oxopentanoyl)-α-D-arabinofuranoside.(19 to 20): Deprotection of the TBDPS-To a solution of the silyl ether (1.0 mmol) in anhydrous pyridine (threefold the volume of the reagent) at 0 °C was added hydrogen fluoride-pyridine (3.0 mmol) dropwise under an inert nitrogen atmosphere.



19 **20**

The reaction mixture was allowed to warm to 25 °C and stirred for 5 h. Upon completion, the mixture was cooled to 0 °C and quenched by the addition of 2*N* hydrochloric acid. The resulting mixture was diluted with ethyl acetate and the layers were separated. The organic phase was washed successively with ice-cold water, a saturated aqueous solution of sodium bicarbonate, and brine. The organic layer was then dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the corresponding alcohol.

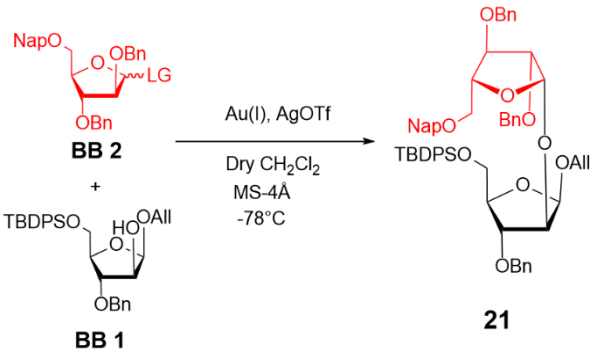
PART 2: Synthesis of pentasaccharide:



Scheme 6: Synthesis of protected pentasaccharide

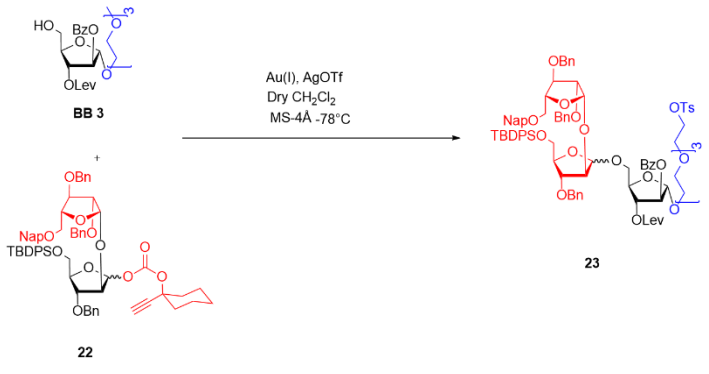
2.6.14: Allyl 2-*O*-(2,3-*O*-dibenzyl-5-*O*-naphthylmethyl-β-D-arabinofuranosyl)-3-*O*-benzyl-5-*O* *tert*butyldiphenylsilyl-β-D-arabinofuranoside (21): A mixture of the glycosyl donor (1.0 mmol) and acceptor (1.0 mmol) was dissolved in anhydrous dichloromethane, followed by the addition of freshly activated 4Å molecular sieves at 25 °C. After stirring for 10 min, chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold(I) (8 mol %) and silver trifluoromethanesulfonate (8 mol %) were added to the reaction mixture. For reactions conducted

at 25 °C, stirring was continued for 15–25 min, whereas reactions performed at –78 °C required 5–8 h for completion.



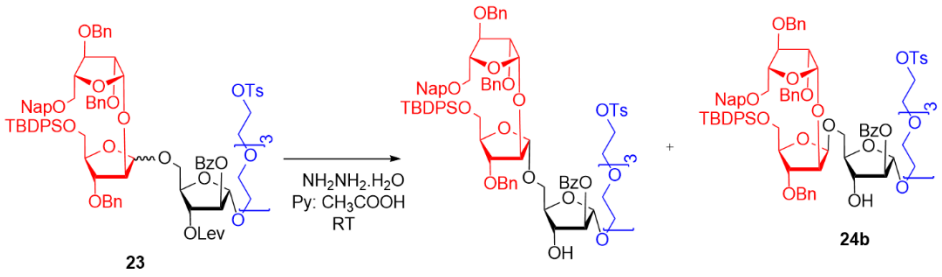
The reaction was quenched by the addition of excess triethylamine and the resulting suspension was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography (n-hexane/ethyl acetate) to afford the corresponding glycosides in 80% yield.

2.6.15 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-benzoyl-3-*O*-(4-oxopentanoyl)-5-*O*-(2-*O*-(2,3-*O*-dibenzyl-5-*O*-(naphthylmethyl)-β-D-arabinofuranosyl)-3-*O*-benzyl-5-*O* *tert*butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (22 to 23) both Isomers: A mixture of the glycosyl donor (1.0 mmol) and acceptor (1.0 mmol) was dissolved in anhydrous dichloromethane, to which freshly activated 4Å molecular sieves were added at 25 °C. After stirring for 10 min, chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold(I) (8 mol %) and silver trifluoromethanesulfonate (8 mol %) were introduced into the reaction mixture. For procedures conducted at 25 °C, the mixture was stirred for 15–25 min, while reactions performed at –78 °C were stirred for 5–8 h.



The reaction was quenched by the addition of excess triethylamine and filtered through a pad of Celite. The resulting filtrate was concentrated under reduced pressure, and the crude residue was purified via silica gel column chromatography (n-hexane/ethyl acetate) to afford the desired glycosides in 72–80% yield.

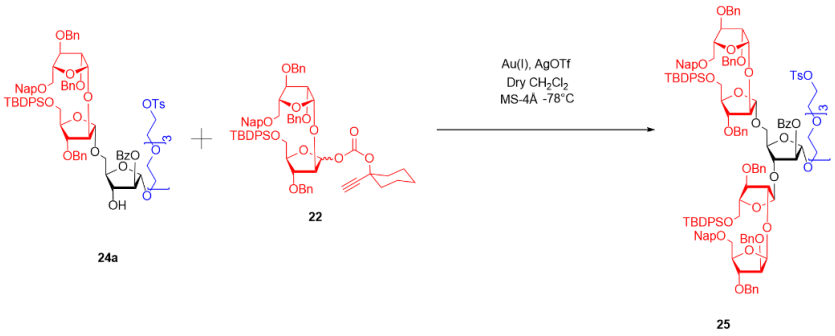
2.6.16 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-benzoyl-5-*O*-(2-*O*-(2,3-*O*-dibenzyl-5-*O*-(naphthylmethyl)-β-D-arabinofuranosyl)-3-*O*-benzyl-5-*O* *tert*butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside(23 to 24a): To a stirred solution of the levulinate ester (1.0 mmol) in dichloromethane at 25 °C were added hydrazine hydrate (4.0 mmol) and a buffer of pyridine-acetic acid. The reaction mixture was stirred for 45 min, after which the process was quenched by the addition of acetone.



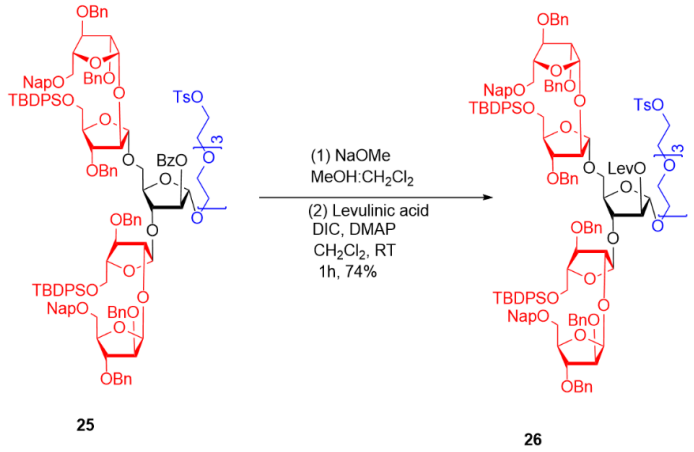
The mixture was diluted with ethyl acetate and washed successively with water, a saturated aqueous solution of sodium bicarbonate, and brine. The organic phase was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the desired alcohol.

2.6.17 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)2-*O*-benzoyl-3,5-di-*O*-(2-*O*-(2,3-di-*O*-benzyl-5-*O*-(naphthalen-1-ylmethyl)-β-D-arabinofuranosyl)-3-*O*-benzyl-5-*O*-*tert*butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (24a to 25):

A mixture of the glycosyl donor (1.0 mmol) and acceptor (1.0 mmol) was dissolved in anhydrous dichloromethane, followed by the addition of freshly activated 4Å molecular sieves at 25 °C. The reaction was quenched by the addition of excess triethylamine and the resulting suspension was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the crude residue was purified via silica gel column chromatography (n-hexane/ethyl acetate) to afford the corresponding glycosides in 78% yield.



2.6.18 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)2-*O*-(4-oxopentanoyl)-3,5-di-*O*-(2-*O*-(2,3-di-*O*-benzyl-5-*O*-(naphthalen-1-yl methyl)-β-D-arabinofuranosyl)-3-*O*-benzyl-5-*O*-*tert*butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (25 to 26): 1. Saponification of benzoates: To a solution of the benzoate (1.0 mmol) in methanol was added sodium methoxide (0.1 mmol per benzoate group). The reaction mixture was stirred at 25 °C for 8 h. Upon completion, the mixture was concentrated under reduced pressure to afford a crude residue, which was purified via silica gel column chromatography (ethyl acetate/hexanes) to yield the desired alcohol.

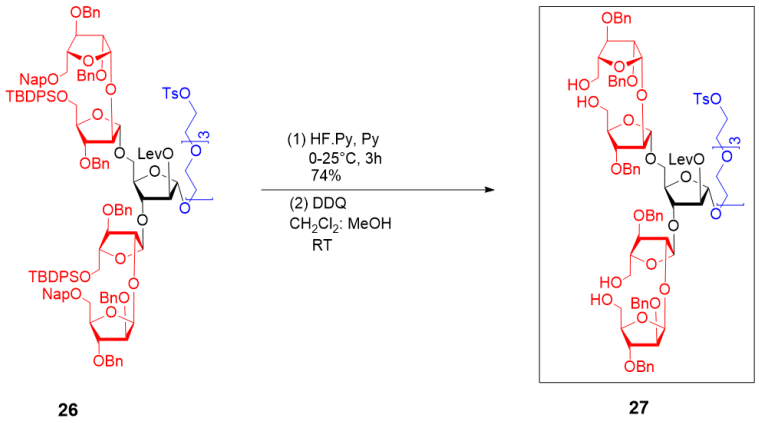


25 26

2. Synthesis of Levulinate Esters: To a stirred solution of the alcohol (1.0 mmol), 4-dimethylaminopyridine (0.5 mmol), and levulinic acid (1.3 mmol) in anhydrous dichloromethane at 0 °C was added N,N'-diisopropylcarbodiimide (1.5 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was gradually allowed to warm to room temperature and stirred for 2 h. Following the consumption of the starting material, the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to furnish the corresponding levulinate ester.

2.6.19 (2-(2-(2-(2-tosylethoxy)ethoxy)ethoxy)ethyl)-2-*O*-(4-oxopentanoyl)-3,5-di-*O*-(2-O-(2,3-di-*O*-benzyl-β-D-arabinofuranosyl)-3-*O*-benzyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (26 to 27) : To a solution of the silyl ether (1.0 mmol) in anhydrous pyridine (threefold the volume of the reagent) at 0 °C was added hydrogen fluoride-pyridine (3.0 mmol) dropwise under an inert nitrogen atmosphere. The reaction mixture was allowed to warm to 25 °C and stirred for 5 h. Upon completion, the mixture was cooled to 0 °C and quenched by the addition of 2 N hydrochloric acid. The resulting mixture was diluted with ethyl acetate and the phases were separated. The organic layer was washed successively with ice-cold water, a saturated aqueous solution of sodium bicarbonate, and brine. The organic phase was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the corresponding alcohol.

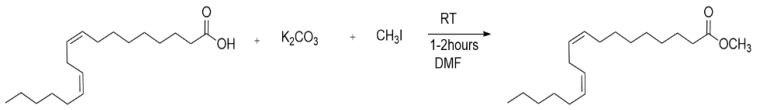
To a rapidly stirred solution of the alcohol (1.0 mmol) in a mixture of dichloromethane and methanol (1:4) at 25 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.0 mmol). The reaction was monitored for 4 h, during which time the mixture transitioned from a brown to a black coloration. The reaction was quenched by the addition of triethylamine, and the volatiles were removed under reduced pressure. The resulting crude residue was purified via silica gel column chromatography (ethyl acetate/hexanes) to furnish the alcohol as a pale-yellow syrup.



26 27

Part 3: Cyclopropanation part:

3.1 Synthesis of Methyl Linoleate (C2): To a stirred solution of linoleic acid C1 (1.00 eq) in anhydrous N,N-dimethylformamide (DMF), potassium carbonate (1.50 eq) was added at room temperature. The reaction flask was shielded from light using aluminium foil to prevent potential photo-oxidation of the diene system. Subsequently, methyl iodide (3.00 eq) was added dropwise to the suspension. The reaction mixture was allowed to stir at room temperature for 2 hours, during which the progress of the reaction was monitored by Thin Layer Chromatography (TLC).

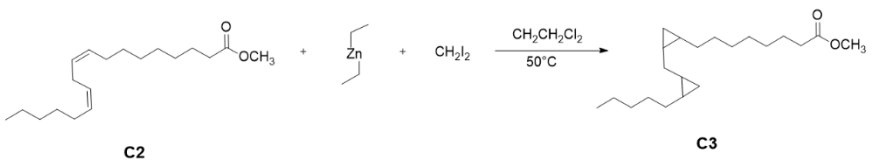


C1 C2

Upon completion, the reaction was quenched with water and the aqueous layer was extracted with an appropriate organic solvent (e.g., Ethyl Acetate or Diethyl Ether). The combined organic layers were washed thoroughly with water to remove residual DMF. To neutralize and remove any traces of unreacted iodine, the organic phase was washed with a saturated aqueous solution of sodium thiosulfate. The organic layer was then dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure to afford the methyl ester **C2**.

3.2 Synthesis of Methyl 9,10,12,13-diepoxyoctadecanoate derivative (C3): To a flame-dried round-bottom flask equipped with a magnetic stir bar and maintained under an inert atmosphere

of nitrogen, a solution of methyl linoleate (C2) (1.00 equiv.) in anhydrous dichloromethane was charged. The solution was cooled or maintained at a controlled temperature as diethylzinc (5.00 equiv.) was added via syringe. Subsequently, diiodomethane (10.00 equiv.) was added dropwise to the mixture.



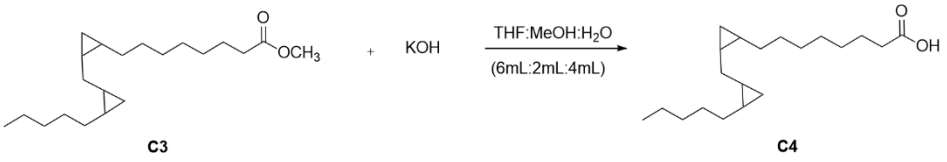
C2 C3

The reaction temperature was then raised to 50°C, and the mixture was stirred for the required duration to ensure the cyclopropanation of both alkene moieties. The progress of the reaction was monitored by TLC until the starting material C2 was fully consumed.

Upon completion, the reaction was cooled to 0°C and carefully quenched by the slow addition of saturated aqueous ammonium chloride to decompose the organozinc intermediates. The mixture was extracted with dichloromethane (3 x 15mL). The combined organic layers were washed with brine, dried over anhydrous Sodium Sulphate, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [Hexane/EtOAc] to afford the dicyclopropyl derivative C3.

3.3 Synthesis of 9,10,12,13-dicyclopropyloctadecanoic acid(C4): To a stirred solution of methyl ester C3 (1.00 equiv.) in a solvent mixture of THF and MeOH (6 mL : 2 mL), a solution of potassium hydroxide (3.50 equiv.) in 4 mL of Milli-Q water was added dropwise at room temperature. The resulting reaction mixture was allowed to stir at room temperature until the complete disappearance of the starting material was observed by TLC analysis.

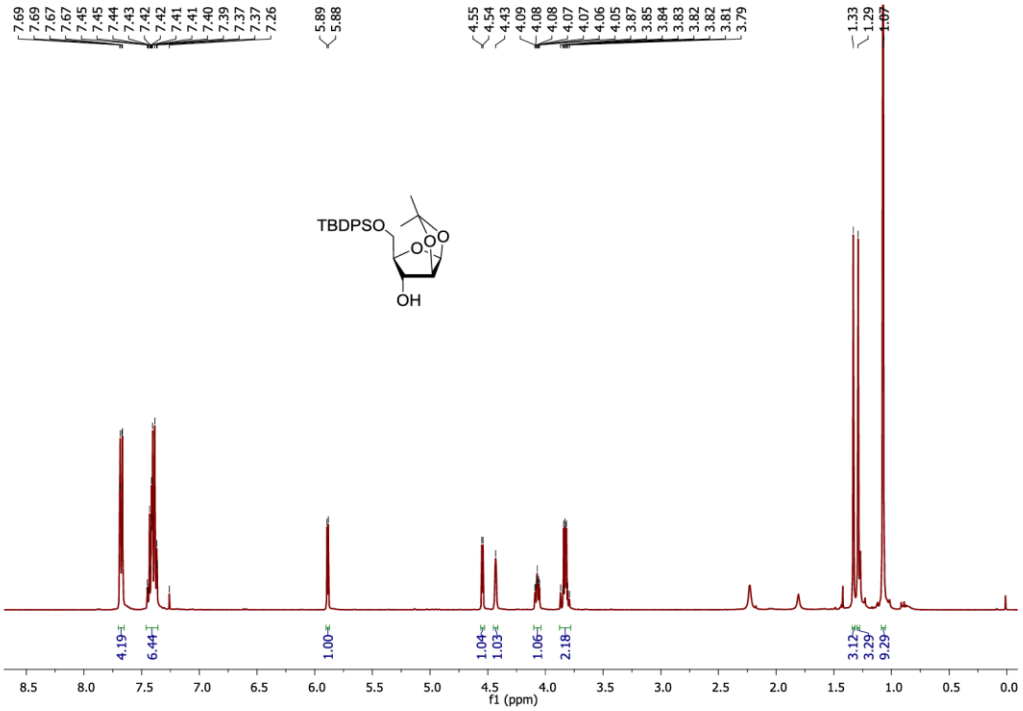
Upon completion, the organic solvents (THF and MeOH) were removed under reduced pressure. The remaining aqueous residue was cooled to 0°C and acidified to pH ~2 using a 1N HCl solution to precipitate the free carboxylic acid. The mixture was then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na2SO4, and concentrated under vacuum. The crude product was purified [mention method, e.g., via recrystallization or silica gel chromatography] to afford the dicyclopropyl acid.



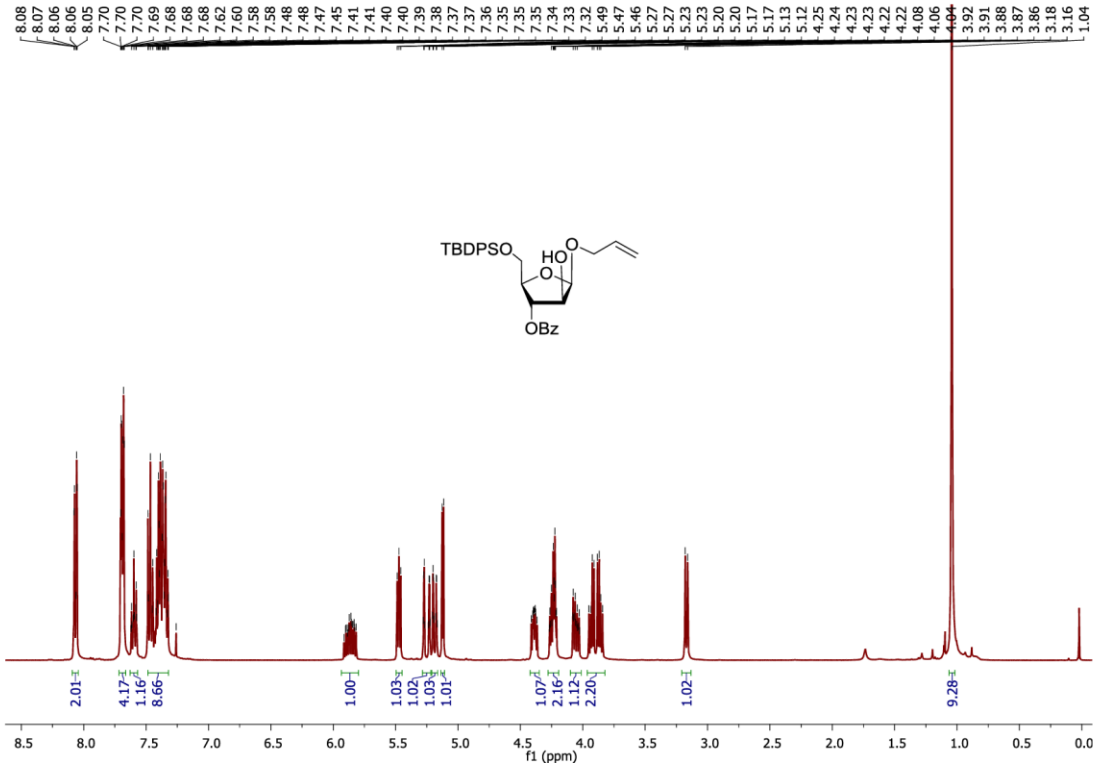
C3 C4

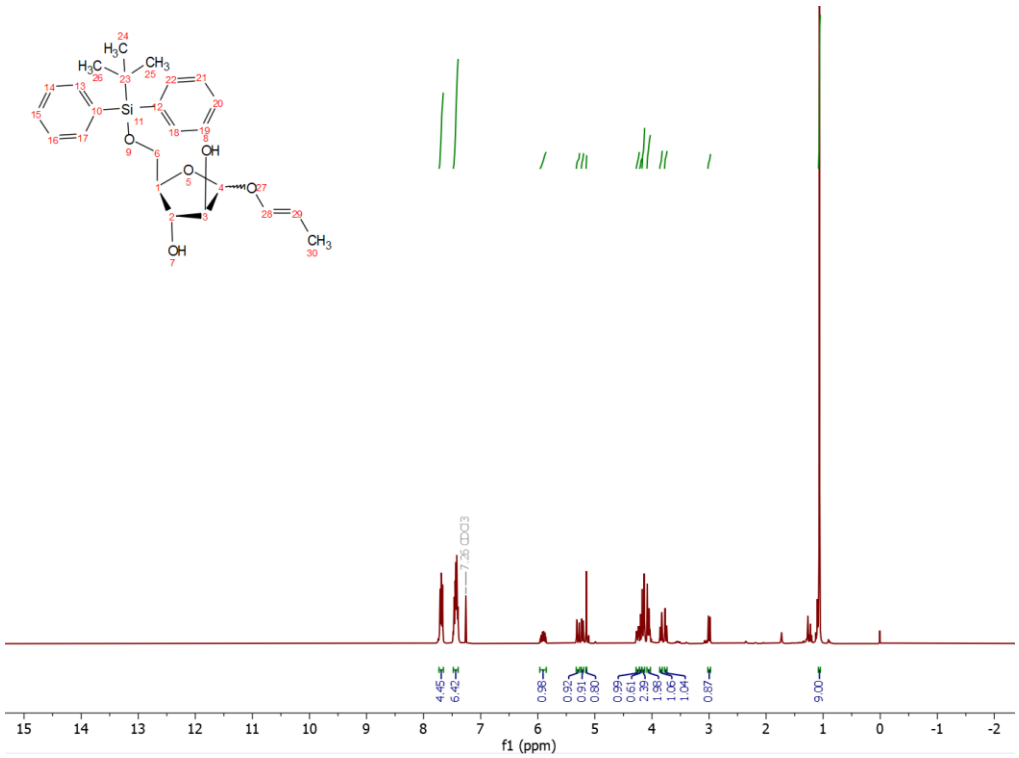
2.7 NMR spectra of compounds:

^{1}H Spectrum (400 MHz, $CDCl_3$) of **3:**

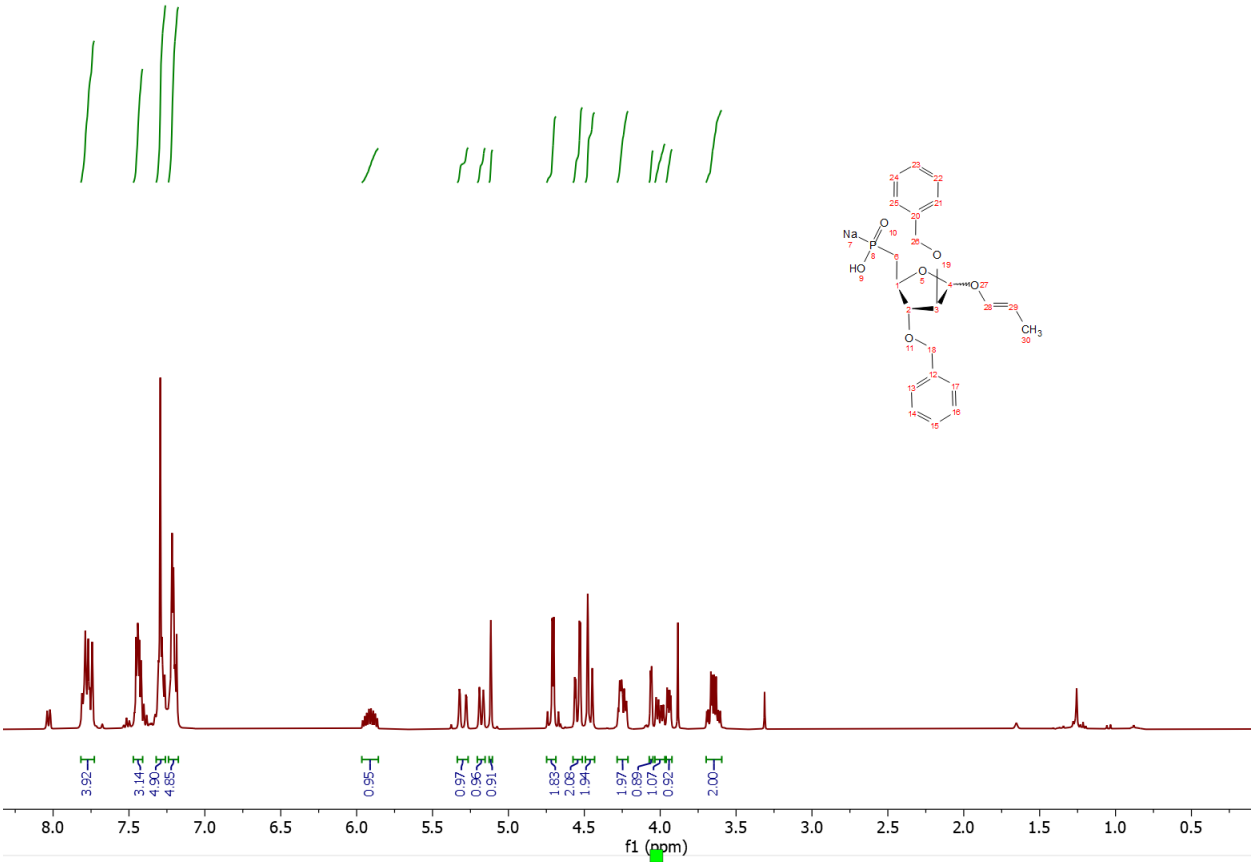


^{1}H Spectrum (400 MHz, $CDCl_3$) of 5 (BB1)

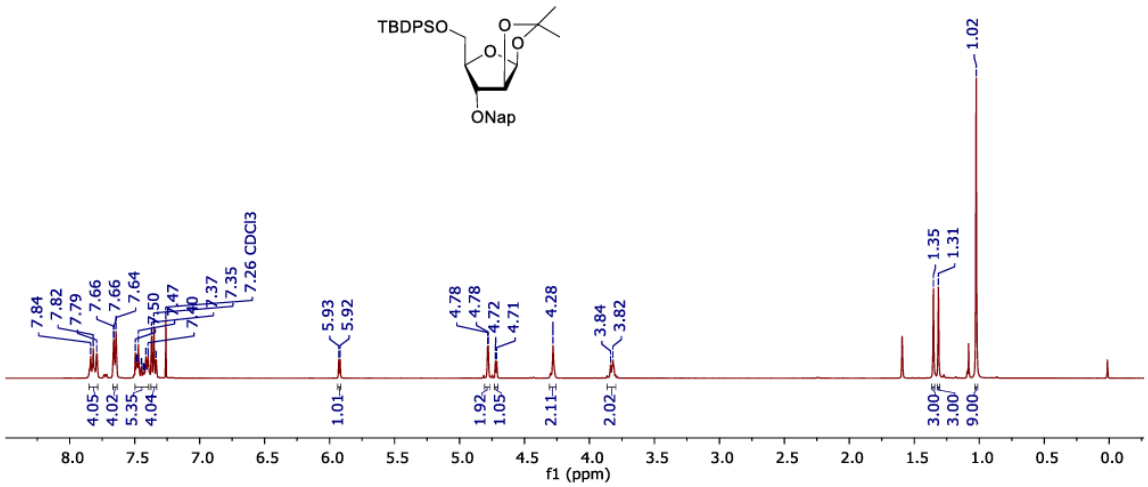




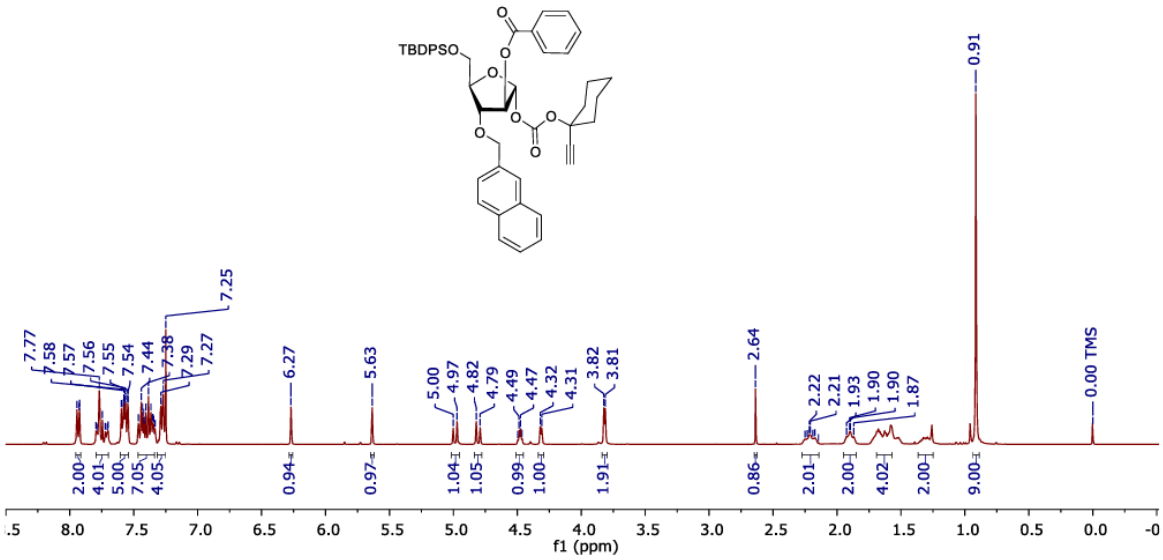
^{1}H NMR of Compound 6



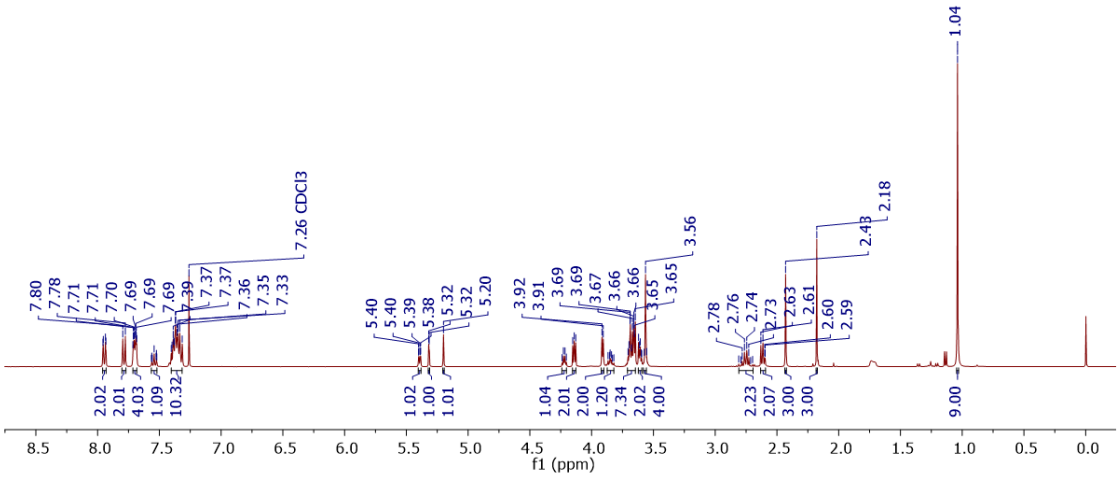
^{1}H NMR (400MHz, $CDCl_3$) of Compound 9



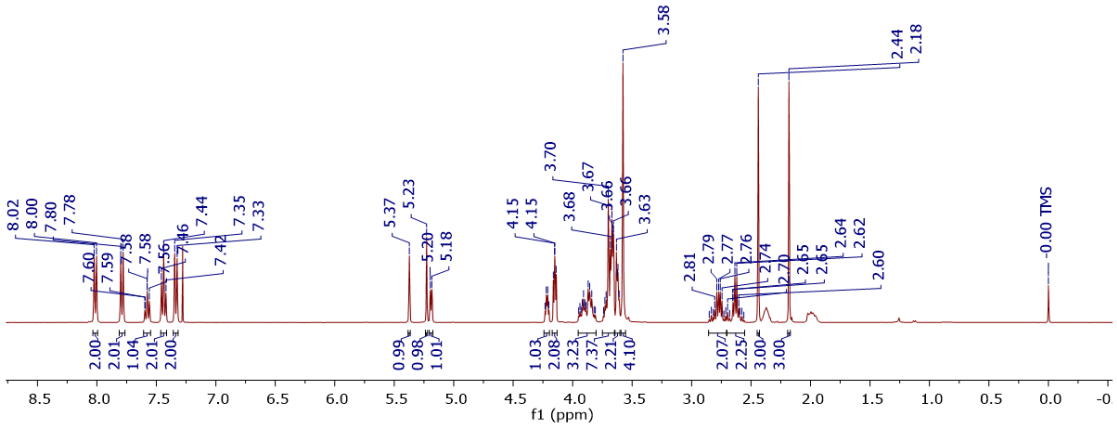
^{1}H NMR (400MHz, $CDCl_3$) of Compound 12



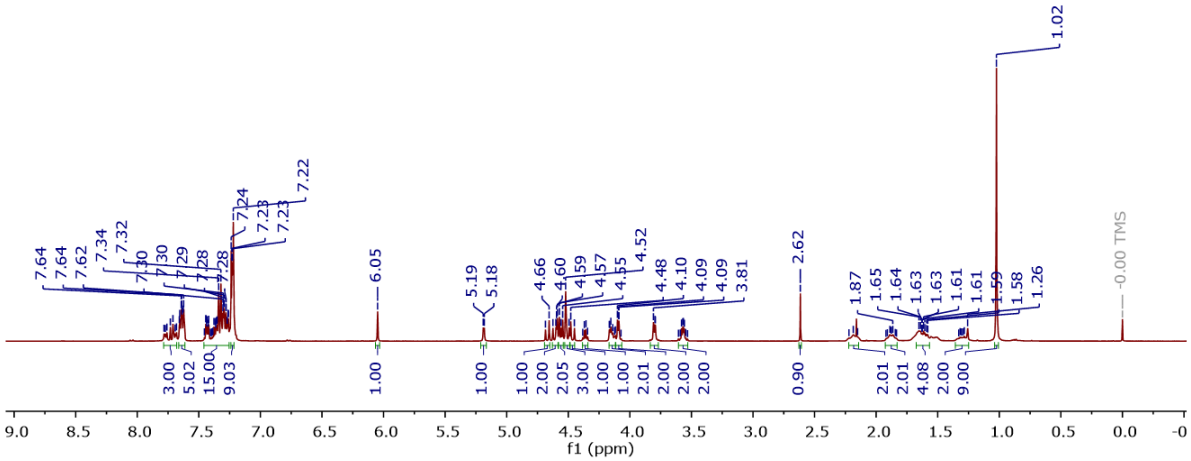
^{1}H NMR (400MHz, $CDCl_3$) of Compound16



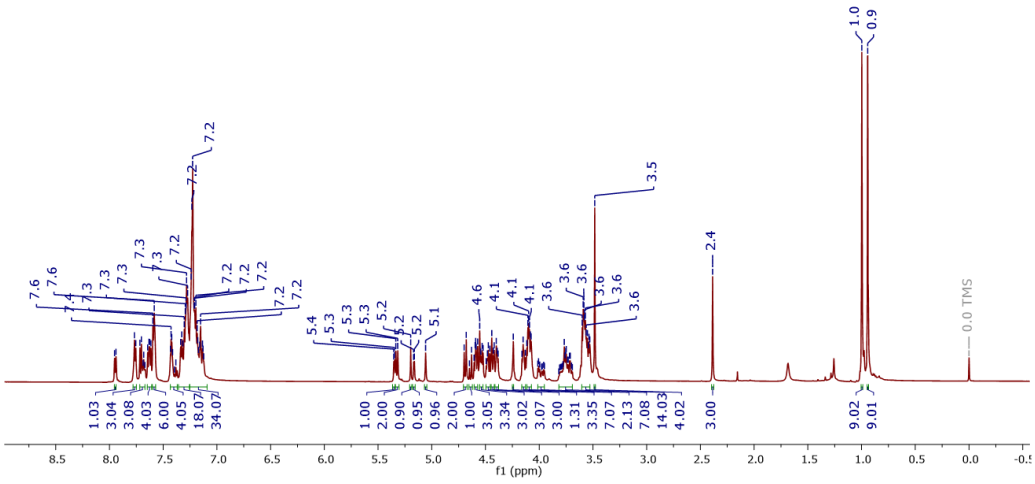
^{1}H NMR (400MHz, CDCl3) of Compound 19



^{1}H NMR (400MHz, $CDCl_3$) of Compound 20 (BB3)



^{1}H NMR (400MHz, $CDCl_3$) of Compound 22



^{1}H NMR (400MHz, $CDCl_3$) of Compound 25

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