Towards the Synthesis of Carrageenan Oligosaccharides

Kinnaert, Christine; Clausen, Mads Hartvig

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Christine Kinnaert

Department of Chemistry
Technical University of Denmark

Life isn't about waiting for the storm to pass…
It's about learning how to dance in the rain.

Vivian Greene

Preface

This thesis is the result of 3½ years research, as part of the Danish program to obtain a Ph.D. degree. The work has been carried out at the DTU Chemistry, Technical University of Denmark, under the supervision of Professor Mads Hartvig Clausen. As part of the Ph.D. program three months of external stay was carried out at UC Berkeley, California, under the supervision of Professor Dean Toste.

Chapter one is a brief introduction to the background of the project, including algae cell wall, carrageenans and their applications. Chapter two describes the synthesis strategy developed to afford ten targeted oligosaccharide carrageenans. Chapter three presents and discusses the results obtained towards the synthesis of these targets. In chapter four, work on catalysis that was carried out in Professor Toste's group at UC Berkeley is described. Chapter 5 gives a general conclusion and Chapter 6 contains experimental protocols and compounds data. A manuscript describing the work presented in chapter three will be written and submitted.

Acknowledgments

My time as a Ph.D. student has been very fruitful for me not only by means of education and achieving academic and technical qualifications but also with respect to personal development as an individual and as a scientist. Many people have contributed to the presented work.
First and foremost, I would like to express my gratitude to Professor Mads H. Clausen for giving me the opportunity to work in his group on a very interesting and challenging project. Thank you very much for the continues support and guidance during my studies but also for always having an open door to your office and caring so much for your students. Thank you for being a great mentor but also a friend with whom I have shared many memorable moments outside the lab, at a conference in India, or simply at our biannual group events really appreciated.
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I would like to thank Professor Dean Toste for giving me the opportunity to work within a different field of chemistry at UC Berkeley. The entire Toste's group, in particular Susumu Ito, Takahiro Horibe and Carolina Santana are thanked for tremendous help and great times in and outside the lab. Alexis Peschot, Luca Corno, Felix Petske and Kate Ito are thanks for making this stay in California a wonderful experience.
Xavier Kinnaert, Kim Mortensen, Faranak Nami, Martin Pedersen and Mathilde Daugaard are acknowledged for proof reading the whole or parts of the thesis. Thank you very much for your comments and criticism. I truly appreciate it.
Friends and family are acknowledged for all their support. A special word for my "Erasmus friends". Thank you for these weekends twice a year all around Europe sightseeing and having a lot of fun. I hope we will keep on finding new places to meet and catch up. Thanks to my group of friends from my engineering school (BDP), I know which whatsapp group to write to when I need a bit of laugh while working. Even though I don't see you that often I always feel I never left you when meeting you again. Thank to my childhood group of friends, it is always a pleasure to meet you again when spending some days back at my parents place. Special thanks to my best friend Lucille, you have been a huge help and support from far away during this whole PhD and our weekly skype talk always raised my mood. Another special thank goes to Ramona for her great support during this entire PhD and talks about all matters of life. If this Danish class did not succeed in making me being perfectly fluent in Danish, it made us at least meeting each other.

My deepest gratitude goes to my parents and my brother Xavier. Thank you Xavier for your support and our talks and catching up over skype. Thanks Mom and Dad for giving me the chance to study, and make me liking it. Thanks for being a great source of inspiration, if I did not end up being veterinarian like you it is mostly because I was a stubborn child that did not want to study the same thing as her parents but now I can say that chemistry is an as amazing field as medicine. If I am finishing this PhD today, it is only thanks to you.

Abstract

The plant cell walls represent almost 50% of the biomass found in plants and are therefore one of the main targets for biotechnological research. Many of their components already have important industrial applications in various fields, such as in the food and biomedical industry and in biofuel production. Therefore, it is necessary to optimize the plant production and its utilization. This will require a better understanding of the cell wall structure and function at the molecular level. Most of the studies achieved on plant cell wall structures and their biosynthesis have been focusing on land plants. Only very few reports are dealing with algae. However, land plants have algae ancestors and getting a better knowledge of algae cell walls could help understand the evolution of plant cell walls. Furthermore, some components specific to algae cell walls are very valuable in the industry. Indeed, the polysaccharides present in the plant cell wall vary depending on the plant species and change during the developmental stage of the plant. This makes it very challenging to address the function of individual components in living cells as well as study the physical properties of each particular molecule. Alternatively, structurally defined oligosaccharides can be used as models for the more complex polysaccharide components. This would enable to investigate a range of properties such as cell wall biosynthesis and protein-carbohydrate interactions, but also the physical properties of the pure oligosaccharides in order to optimize their applications in the industry. Chemical or enzymatic degradation of plant cell wall can provide some oligosaccharides but extensive purification is required and only a limited range of structures has so far been isolated. Chemical synthesis, on the other hand, is capable of producing structurally diverse oligosaccharides of excellent purity and in higher quantities.

This thesis presents the development of a synthetic strategy to produce ten different types of carrageenan oligosaccharides from one single precursor. These molecules are highly sulfated galactans, which are found in the cell wall of red algae and serve as gelling, stabilizing and viscosity-enhancing agents in many sectors ranging from the food industry to pharmaceuticals. A modular approach was chosen to enable the synthesis of carrageenan oligosaccharides with different lengths. Different protecting group patterns were tested to synthesize the oligosaccharide backbone. A protected tetrasaccharide precursor was synthesized and can be used to synthesize all ten carrageenan tetrasaccharides. Optimization of the deprotection steps as well as sulfation was done on a similar disaccharide and one disaccharide carrageenan was synthesized in the end. These steps were further translated successfully to the desired tetrasaccharide.

A work dealing with the development of an intramolecular catalyzed fluoroarylation is presented at the end of this thesis. A range of different allyl substituted aryl boronic acids substrates were synthesized in order to investigate the scope of a silver catalyzed reaction and some preliminary results of the catalytic reaction are presented.

Resumé

Plantecellevæggen udgør næsten 50% af plantens samlede biomasse og er derfor et vigtigt emne inden for bioteknologisk forskning. Mange af komponenterne har allerede vigtige industrielle anvendelser i diverse områder, såsom fødevare- og medicinal industrien såvel som i produktion af biobrændstof. Derfor er det vigtigt at optimere planteproduktionen og dets anvendelse. Dette kræver en bedre forståelse af plantecellevæggens struktur og funktion på et molekylært plan. De fleste studier omhandlende struktur og biosyntese af plantecellevægge har fokuseret på landplanter og kun få omhandler alger. Dog har landplanter algestamfædre og en bedre forståelse af algecellevægge kan hjælpe forståelsen af evolutionen af plantecellevægge. Ydermere er nogle specifikke komponenter af algecellevægge værdiful i industrien. Imidlertid varierer polysakkarider i plantecellevæggen afhængig af plantespecie og ændrer sig ydermere gennem plantens udviklingsstadie. Dette gør adresseringen af de enkelte komponenter i levende celler til en stor udfordring, hvilket studiet af de fysiske egenskaber af hvert enkelt molekyle ligeledes er. Alternativt kan strukturelt veldefinerede oligosakkarider fremstillet ved kemisk syntese bruges som model for de mere komplekse polysakkarider. Dette muliggør studier af en række egenskaber såsom biosyntese af cellevægge og protein-kulhydrat interaktioner, men også fysiske egenskaber af rene oligosakkarider for at optimere deres industrielle anvendelse. Kemisk eller enzymatisk nedbrydning af plantecellevægge kan give visse oligosakkarider men dette kræver omfattende oprensning og indtil videre er der kun isoleret et begrænset antal strukturer. Derimod muliggøre kemisk syntese produktionen af strukturel forskellige oligosakkarider af excellent renhed og i større mængder.

Denne afhandling præsenterer udviklingen af en syntesestrategi til at producere ti forskellige typer af carrageenan oligosakkarider fra et enkelt udgangspunkt i form af et beskyttet oligosakkarid. Carrageenaner er galaktaner med et stort antal sulfatgrupper og findes i plantecellevæggen hos røde alger og tjener som stivelse, stabilisator og viskositetsfremmende forbindelser i mange sektorer, som spænder fra fødevareindustrien til medicinalbranchen. En modulær fremgangsmåde var valgt til syntesen af carrageenan oligosakkarider af forskellige længder. Forskellige beskyttelsesgruppemønstre blev testet i syntesen af oligogalaktanerne. Et beskyttet tetrasakkarid blev syntetiseret og kan bruges i syntesen af alle ti carrageenan tetrasakkarider. Optimeringen af afbeskyttelsestrinnene såvel som indførsel at sulfatgrupperne blev udført på et lignende disakkarid, og et carrageenan disakkarid blev til sidst syntetiseret. Disse trin blev succesfuldt overført til det ønskede tetrasaccharid.

Et studium omhandlende udviklingen af en intramolekylær katalyseret fluoroarylering er præsenteret i sidste del af afhandlingen. En række forskellige allylsubstituerede substrater af aryl borsyrer blev syntetiseret for at studere potentialet af en sølv-katalyseret reaktion og nogle indledende resultater af den katalytiske reaktion er præsenteret.

List of abbreviations

Ac	Acetyl
AFM	Atomic force microscopy
All	Allyl
AQ	8-aminoquinoline
Aq.	Aqueous
Ara*f*	Arabinofuranosyl
Bn	Benzyl
br.	Broad
Bu	Butyl
Bz	Benzoyl
c	Concentration
CAN	Cerium(IV) ammonium nitrate
CGA	Charophycean green algae
ClAc	Chloroacetyl
cryo-SEM	cryo-Scanning electron microscopy
CSA	Camphor-10-sulfonic acid
d	Doublet
D	4-linked-α-D-galactopyranose
DA	3,6-Anhydro-D-galactose
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCMME	1,1-Dichloromethyl methyl ether
DCVC	Dry column vacuum chromatography
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
ddt	Doublet of doublet of triplets
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminum
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMTST	Dimethyl(methylthio)sulfonium trifluoromethanesulfonate
DNA	Deoxyribonucleic acid

dppb	1,4-Bis(diphenylphosphino)butane
dt	Doublet of triplets
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
dtbp	*Tert*-butylbipyridine
ECM	Extracellular matrix
Equiv.	Equivalents
ESI	Electron spray ionization
Et	Ethyl
f	Furanose
FCSPs	Fucose-containing sulfated polysaccharides
FTR	Fourier Transform Infrared
Fuc*p*	Fucopyranosyl
G	3-linked-β-D-galactopyranose
Gal*p*	Galactopyranosyl
Glu*p*	Glucopyranosyl
h	Hours
HMBC	Heteronuclear multiple bond correlation spectroscopy
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
IR	Infrared
J	Coupling constant
LG	Leaving group
L-Selectride	Lithium tri-*sec*-butylborohydride
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
min	Minutes
MS	Molecular sieves; Mass spectrometry
NAP	2-Naphthylmethyl
NBS	*N*-Bromosuccinimide
nc	Number of chains
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
p	Pyranose; Para
Ph	Phenyl
PhNCO	*N*-Phenyl isocyanate
Piv	Pivaloyl
*p*MP	para-Methoxyphenyl

ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
PTFAI	*N*-Phenyl trifluoroacetimidate
p-TSA	para-Toluenesulfonic acid
Py	Pyridine
q	Quartet
ref	Reference
R*f*	Retention factor
s	Singlet
sat.	Saturated
ST	Sulfuryltransferase
Super-hydride	Lithium triethylborohydride
t	Triplet
t	Tert
TBAB	Tetrabutyl ammonium bromide
TBAI	Tetrabutyl ammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TCECS	Trichloroethyl chlorosulfate
td	Triplet of doublet
temp	Temperature
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMDSO	Tetramethyldisiloxane
TMS	Trimethylsilyl
Tres	2,2,2-Trifluoroethanesulfonate
Ts	*p*-Toluene sulfonyl
TTBP	2,4,6-Tri-*tert*-butylpyrimidine
UDP	Uridine 5'-diphosphate
UV	Ultraviolet
δ	Chemical shift(s)
η	Viscosity
η_o	Viscosity of the solvent
η_{sp}	Specific viscosity
$[\eta]$	Intrinsic viscosity

Table of Contents

CHAPTER 1

1 Introduction

1.1 Structure and diversity of the plant cell walls

Plant cells belong to the family of eukaryotic cells, which mainly differ from cells of other eukaryotic organisms by the presence of a wall surrounding the cells. Plant cell walls are highly sophisticated fiber composite structures, dynamic and evolved to fulfill a wide range of biological roles necessary to keep the plant alive. Hence, the wall is the outer coat that provides a strong protective and supportive casting of the plant cell and at the same time define the size and shape of the cells. Not only do cell walls have a structural role, but they also play an important role in the wall expansion and defense response against pathogens.[1] However, cell walls display considerable variability in their fine structures. These differ depending on the species, but also within the plants, between the cell types and between cell wall microdomains.[2] Despite their diversity, the plant cell walls share some similarities in their rough structure. Nowadays, as a simplified model, they are generally divided into two categories: the primary and the secondary cell wall. While the primary cell wall is a thin and flexible structure that allows for the growth of the cell, the secondary cell wall, much thicker and stronger, is deposited on some specific cells when they have ceased to grow.

To understand how cell walls can perform their various functions, it is important to get an idea on how the different components are organized into a three dimensional functional matrix. Therefore several models have been proposed over the last years to explain the organization of wall components. Many of those models focus on understanding the organization of components in the primary cell walls of land plants.[3–5] A schematic representation of the primary cell wall of an angiosperm cell is presented in Figure 1-1. Angiosperms are commonly referred to as flowering plants which are part of the land plants. In the extracellular matrix (ECM), cellulose microfibrils are cross-linked by hemicellulose and this assembly is embedded non-covalently in a matrix of pectic polysaccharides. The interaction between hemicellulosic polysaccharides and cellulose microfibrils via hydrogen bonding are known as an important feature of the cell wall architecture.[6] However less is known about the interaction of pectic polysaccharides with the other components of the wall.[7,8,9] In the secondary walls, the embedding material is the phenolic polymer lignin.[5] Nevertheless, one should keep in mind that this division apply to two extreme states. Indeed, every individual cell has its own distinct and specialized cell wall as Keegstra points out in his review of plant cell walls.[7]

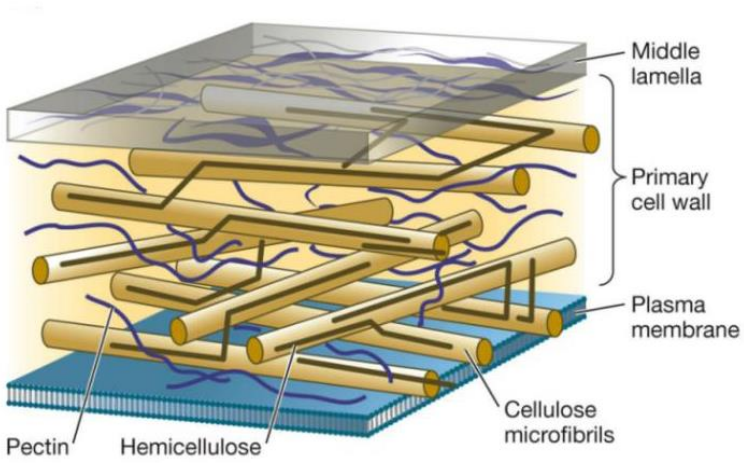


Figure 1-1. Schematic model of the primary cell wall of an angiosperms cell.[10]

1.1.1 Cell walls of algae and evolution of plant cell walls

Most models of plant cell walls fail to describe the dynamic nature of the wall, which is one of its most important features. Furthermore, cell walls from algae and primitive plants have only been studied recently: most of the previous works on structure and biosynthesis of cell walls have focused on angiosperms and crop plants.[7] One model of brown algae cell walls (from the order Fucales) has been proposed by Deniaud-Bouët *et al.*[11] (see Figure 1-2 a). In this model, cellulose microfibrils are sparse and with a ribbon shape. Alginates and fucose-containing sulfated polysaccharides (FCSPs) including sulfated fucans form the major part of the cell wall polymers. The structures of these polysaccharides is shown in Figure 1-2b. Cellulose is a neutral linear polysaccharide made of β-(1→4)-linked glucose (Glc*p*) with no branching.[6] Alginates consist of a linear block co-polymer of two uronic acid epimers, β-(1→4)-D-mannuronate (M) and α-(1→4)-L-guluronate (G).[12,13] G block-rich alginates are known to increase gel strength by forming "egg-box" junctions with calcium, bridging two antiparallel chains.[14] Most of the FCSPs found in brown algae are fucoidans which are heteropolymers of sulfated fucans. They contain long stretches of disaccharide repeating unit (1→4)-α-L-fucose-2,3-disulfate-(1→3)-α-L-fucose-2-sulfate.[15]

The FCSPs act as cross-linkers interlocking the cellulosic scaffold. However, the nature of the interactions between these highly charged polysaccharides and the neutral cellulosic chain remain elusive. It is hypothesized that hemicellulosic oligosaccharides might act as intermediates between the cellulose microfibrils and the FCSPs. However these hemicellulosic oligosaccharides have neither been isolated nor characterized yet. Some phenolic components are also found in this primary cell wall and likely to be associated with alginates and proteins.[16] Finally, a large amount of iodide is present but very little is known about its interaction and role. [11]

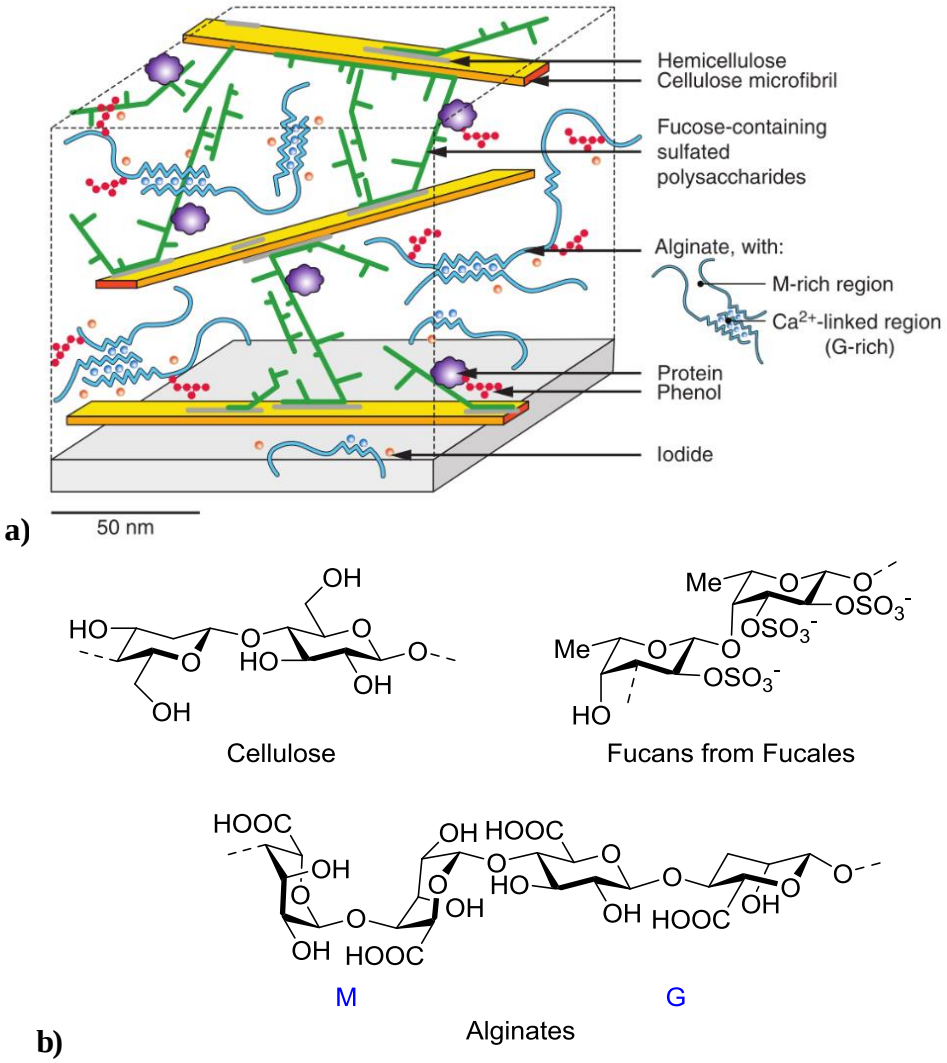


Figure 1-2. a) Cell wall model of brown algae from the order Fucales.[11] b) Repeating units of the major polysaccharides found in the cell wall of Fucales brown algae.

Land plants, red algae and green algae, all belong to the Archaeplastida phylum (see Figure 1-3b). This phylum evolved after an eukaryotic ancestor swallowed a photosynthetic cyanobacterium in a primary endosymbiotic event about 1500 million years ago.[17] Contrary, brown algae belong to a phylum (Stramenophiles), which arose only about a 1000 million years ago after a secondary endosymbiotic event, by which an unicellular red alga was captured by a heterotrophic protest as shown in Figure 1-3a.[18] These brown algae are therefore part of another eukaryotic supergroup called Chromalveolata. The proposed phylogenetic tree of eukaryotic organisms (Figure 1-3b) can explain why brown algae cell walls share polysaccharides with both plant (cellulose) and animal (sulfated fucans) ECM's, but also with some bacteria (alginates).[13]

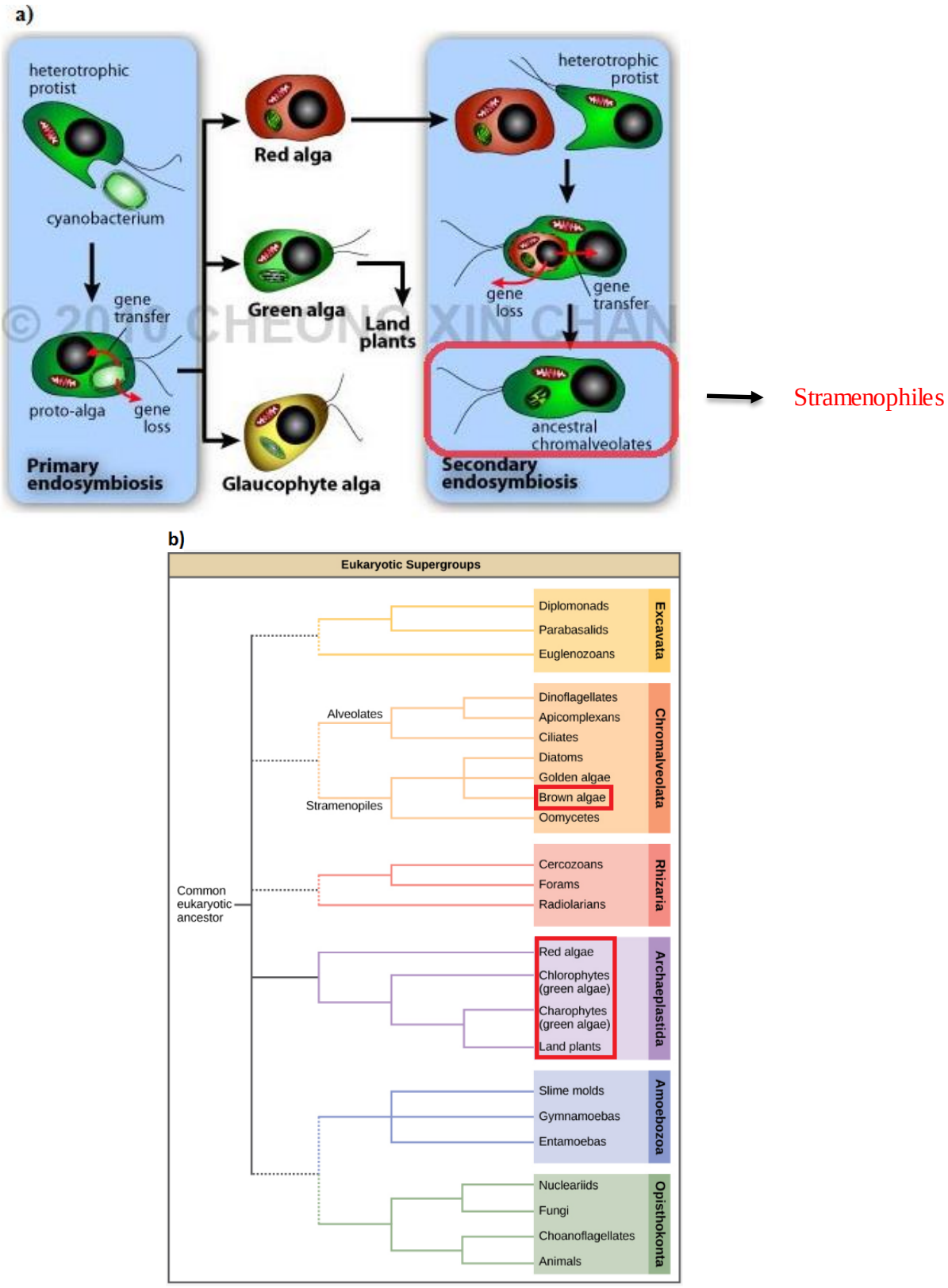


Figure 1-3. a) The origin of Stramenophiles phylum.[18] b) Representation of the Eukaryotic phylogenetic tree.[19]

Getting a better knowledge of different algal cell walls belonging to the Archaeplastida group will help us understand how the plant cell walls have evolved, as land plants have algal ancestors.[2,7,20] Land plants originate from some freshwater green algae, which emerged from their aquatic habitat and belonged to the Charophyceae taxa.[2,21,22] A scarce amount of papers have focused on algae and the majority of algal genomes that have been sequenced are unicellular.[23] This affords limited information concerning cell wall biosynthesis. Recently, the genome sequencing of a multicellular green alga Volvox carteri,[24] as well as the one of two members of the charophycean green algae (CGA)[25] provided additional tools to elucidate cell wall evolution in green plants. However, a big gap in the knowledge regarding eukaryotic algal phylogenies, algal cell wall compositions, and the machinery employed in algal cell wall biosynthesis still remains to be filled.[23] The cell wall components of both plants and algae are topic of intense research and several reviews give an overview of the occurrence of specific wall components in major plant and algal taxa.[2,20,26] The major polymers found in the cell wall of different plant and algal taxa are summarized in Table 1-1.[20] Even though the cell wall's composition of red and brown algae is notably different from the one of CGA and land plants, the complex relationships between land plants and algae explain some shared cell wall components such as cellulose. One can notice the presence of many different sulfated polysaccharides in the Rhodophyta and Phaeophyceae taxa which are not present in most of the Choroplastida taxa. On the other hand, pectin is not part of these red and brown algae. Agar, carrageenan and porphyran are the most important sulfated polysaccharides found in the red algae with homofucans in brown algae.

Taxa / **Polysaccharide**	**Chloroplastida**			**Rodophyta**	**Phaeophyceae**
	Embryophyceae (Land Plant)	**Charophyceae (Green algae)**	**Chlorophyta (Green Algae)**	**(Red Algae)**	**(Brown algae)**
Crystalline polysaccharides	Cellulose	Cellulose	Cellulose	Cellulose (1→4)-β-D-mannan (1→4)-β-D-xylan (1→3)-β-D-xylan	Cellulose
Hemicellulose	Xyloglucan Mannans Xylans MLG[a] (1→3)-β-glucan	Xyloglucan Mannans Xylans (1→3)-β-glucan	Xyloglucan Mannans Glucuronan (1→3)-β-glucan	Glucomannan Sulfated MLG[a] (1→3), (1→4)- β-D-xylan	Sulfated xylofucoglucan Sulfated xylofuco-Glucoronan (1→3)-β-glucan
Matrix carboxylic polysaccharides	Pectins	Pectins	Ulvans	-	Alginates
Matrix sulfated polysaccharides			Ulvans	Agars Carrageenans Porphyran	Homofucans

[a] MLG: β-(1→3),(1→4)-D-glucan 6-sulfate

Table 1-1: Major cell wall polymers present in different plant and algal taxa. [23]

As this thesis focus on carrageenans a more detailed description of the polysaccharidic components found in the cell wall of the Rhodophyta taxa will be given in the following section.

1.1.2 Polysaccharidic components of the primary cell wall of red algae (Rhodophyta)

The primary cell wall of marine red macrophytes consists mostly of water-soluble polysaccharides mainly composed of sulfated galactans such as agars, carrageenans and porphyrans which are linear sulfated α-(1→3),β-(1→4)-galactans. They differ in that agars and porphyrans, contain both D- and L-galactose units whereas carrageenans only contain D-galactose.[27] A more detailed description of the different types of carrageenans will follow in section Carrageenans1.1.2.1.

Only a small fraction of the constituents (5% to 15% dry weight) is made of fibrillary crystalline polysaccharides. These are mainly composed of cellulose, β-(1→4)-D-mannan, β-(1→4)-D-xylan and β-(1→3)-D-xylan, where amounts and localization depend on the species and the reproductive stage and life cycle of the plants.[28] The neutral crystalline fibers and the highly charged sulfated polysaccharides of the matrix are expected to be interconnected via other polysaccharides classified as hemicellulose as for higher plants. However, very little is known about the nature of these polysaccharides in the cell wall of red algae. Turvey *et al.*[29] characterized alkali-soluble β- (1→3),(1→4)-D-xylans from the cell wall of several red seaweeds. More recently, in 2000, Lahaye *et al.*[28] discovered two new kinds of hemicellulose in the cell wall of the red alga Kappaphycus Alvarezii, identified as β-(1→4)-D-glucomannan and mixed-linkage β-(1→3),(1→4)-D-glucan 6-sulfate (referred as sulfated MLG in Table 1-1). These hemicellulosic polysaccharides represent a minor part of the polysaccharides contained in the cell wall (4% of the algal dry weight) and their role in the construction and function of the cell wall remain to be established. In order to fully understand the dynamic nature of the walls and the function of each component, more molecular level information is needed.

1.1.2.1 Carrageenans

As mentioned earlier, carrageenans are a family of highly sulfated galactans found in the cell walls of certain red seaweeds of the Rhodophyceae class. This family of polysaccharides possesses the ability to form thermo-reversible gels or viscous solutions when added to salt solutions. Therefore, carrageenan polysaccharides serve as gelling, stabilizing and viscosity-enhancing agents in many sectors ranging from the food industry to pharmaceuticals.[30-31] They represent one of the major texturizing ingredients in the food industry. Their use in pharmaceutical products continues to be investigated, and recent applications in drug delivery systems are summarized in a review by S. Liang Li *et al.*[32] As one example owing to their physicochemical properties, carrageenans can be used as a matrix for preparation of extended-release tablets. Their application in polymeric microspheres for deliver of drugs in a rate-controlled and sometimes targeted manner is also being explored.[33] These are only two examples among many other applications, which have a therapeutic

focus and have been developed or are presently under investigations.[32] However, the use of carrageenan polysaccharides in the non-food field is limited by their high viscosity and therefore, it is desirable to obtain carrageenan oligosaccharides. Physical properties of carrageenans and especially their gelling and viscous enhancer abilities depend on the type of carrageenans. Carrageenan are divided into ten different types which differ mainly by their degree of sulfation and the presence or absence of 3,6-anhydrogalactose residues (Figure 1-5). Natural carrageenan is a mixture of non-homologous polysaccharides. This makes it challenging to produce homogenous oligosaccharides by chemical or enzymatic degradation of the algae cell wall. Although extensive studies have been conducted, only a limited range of structures is available, and the oligosaccharides obtained require extensive purification. On the other hand, as chemical synthesis can produce structurally defined oligosaccharides of excellent purity, we wished to produce well-defined carrageenan oligosaccharide structures this way. The aim of this project was to find an elegant way of synthesizing all ten types of known carrageenans.

1.1.2.1.1 Carrageenan structures and properties

1.1.2.1.1.1 Structure and diversity of carrageenans

This diverse family of polysaccharides shares a common galactan backbone of alternating 3-linked-β-D-galactopyranose (G) and 4-linked-α-D-galactopyranose (D). The disaccharide repetition moieties are called carrabiose units as shown in Figure 1-4.

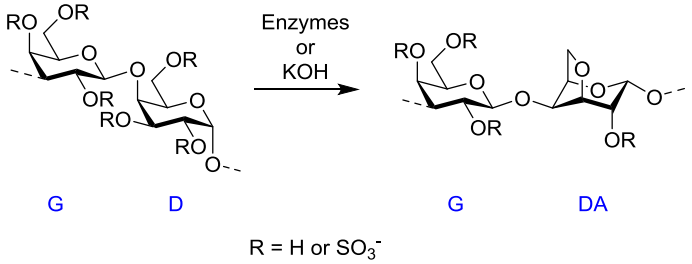


Figure 1-4. Carrabioses unit.

The carrabioses are classified according to the number and position of sulfate ester groups (S), as well as the occurrence of 3,6-anhydro-D-galactose (DA) obtained after the cyclization of the D units (see Figure 1-4). The nomenclature presented and used throughout this thesis was established by Knutsen, Myslabodski, Larsen, and Usov (1994) and integrated into the IUPAC rules.[34] 10 types of idealized carrabiose units are represented in Figure 1-5.

It has been shown that hot alkaline treatment of the D6S carrageenans (namely carrageenan having a 4-linked-α-D-galactopyranose residue sulfated at the 6 position) leads to cyclization to form the 3,6- anhydro rings (see Figure 1-4).[35,36] This chemical conversion can be achieved by either a solid state process using potassium hydroxide or in solution using calcium or sodium hydroxide below the melting temperature of the carrageenan.[36] In the same manner, this transformation is catalyzed by enzymes and therefore the 5 carrabioses D6S are biosynthetic precursors of the DA carrabioses. The anhydro ring formation probably results from a nucleophilic attack of the hydroxyl group on

the 3-position on C-6 sulfate ester.[37] Enzymes such as ‘‘sulfohydrolases’’[38,39] or galactose-6-sulfurylases[40] which catalyzed a similar reaction have been isolated from algal cells.

Different types of carrageenans are obtained from different species of Rhodophyta.[41] Furthermore, carrageenan structures also vary with the extraction procedures. A second level of carrageenan diversity comes from the co-occurrence of ideal carrabiose units (shown in Figure 1-5) in purified hybrid or copolymer chains. Therefore, carrageenans are usually heterogeneous structures containing several types of carrabiose units where proportion and distribution reflect the carrageenan biosynthetic pathway.[42,43] Hence, the term ‘disaccharide repeating unit’ refers to idealized structures.

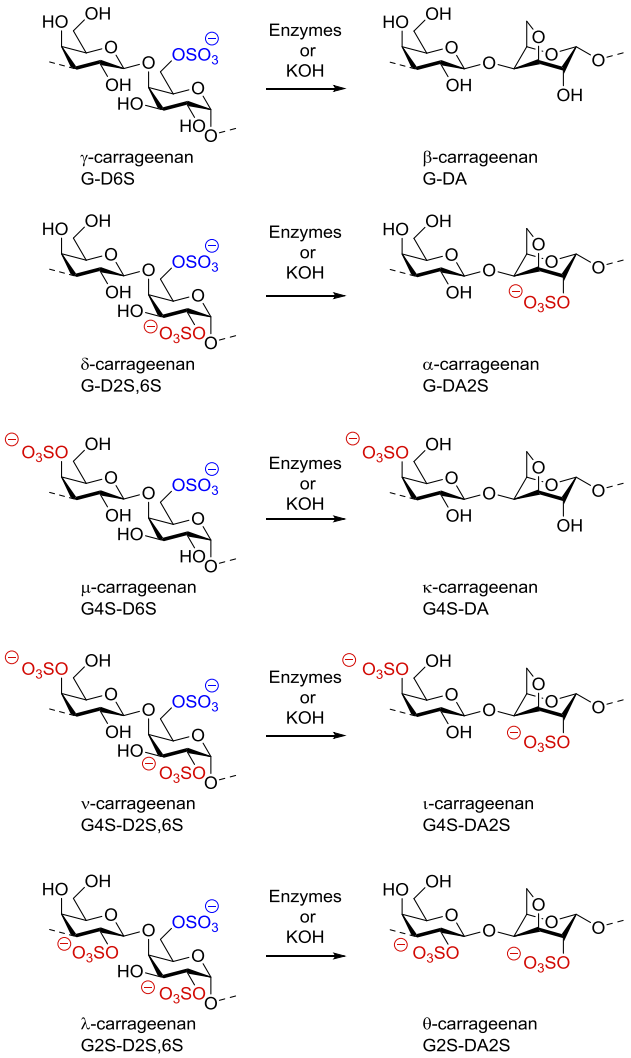


Figure 1-5. Ten types of idealized repeating units of carrageenans.[44]

1.1.2.1.1.2 Primary structure determination of carrageenan

Finding adequate analytical techniques to determine the amounts, the polydispersity, and the purity of carrageenans in food products and raw materials has been a challenge for many years and still remains a difficult task.[41] However, the development of Nuclear Magnetic Resonance

spectroscopy (NMR) helped to determine the primary structure of carrageenans. This determination includes mainly three different parts: a composition analysis, a linkage analysis and a sequence analysis. The whole set of analyses confirms the alternating structure of the backbone and elucidate the distribution of different repeating units along the polymeric chain.[27] NMR spectroscopy (both ^{1}H- and ^{13}C-NMR) is especially useful in the linkage analysis, while Infra Red spectroscopy (IR) is used to localize the sulfate group and anhydro group along the chain.[35] To complete the primary structural analysis an additional sulfate content determination can be performed. Acidic methanolysis to hydrolyze the sulfate groups followed by precipitation of sulfate as barium sulfate and quantification is often the method chosen to fulfill this task.

1.1.2.1.1.3 Physical properties of carrageenan

Physical properties of carrageenan such as gel strength, gelling and gel melting temperature are very important characteristics in regards to their use in industry. Therefore, parameters that have an impact on these properties have to be determined to optimize the process conditions for industrial production. It has been observed that structural parameters such as the degree of sulfation and the presence of 3,6-anhydro-α-D-galactose residues play a direct role on the gelling or viscous enhancing properties of carrageenan.[44]

In industry, seaweeds are usually extracted with alkali at elevated temperature. This treatment is typically called "cooking process". Different studies have been carried out to understand how the parameters of this process (such as alkali concentration, cooking temperature, cooking time) influence the yield and properties of extracted carrageenans. Rochmadi *et al.*[35] studied the effect of the concentration of potassium hydroxide during the extraction process upon properties of carrageenan from *Eucheuma cottonii*. This seaweed is known to be a good source of κ-carrageenan (G4S-DA), which has proved to form strong gel and therefore is highly valued in the dairy industry. Table 1-2 summarized the effect of KOH concentration on yield, sulfate content, gel strength, intrinsic viscosity, and finally molecular weight of extracted carrageenan.

Carrageenan type	Yield %	Sulfate %	Gel strength g/cm^2	[η] dL/g	M g/mol
Sigma (ref)	-	18.62	223.63	34.31	14.14×10^5
E.C.* in distilled water	46.43	15.80	nd	nd	nd
E.C.* 0.1N KOH	44.63	16.15	69.8	26.84	10.76×10^5
E.C.* 0.3N KOH	38.22	14.24	73.89	14.61	5.48×10^5
E.C.* 0.5N KOH	37.02	11.45	127.3	14.88	5.59×10^5

*Carrageenan extracted from *Eucheuma cottonii*

nd= not determined

Table 1-2. Influence of KOH concentration on the sulfate content, gel strength, intrinsic viscosity and molecular weight of extracted carrageenan (adapted from Rochmadi *et al.*[35]).

Fourier Transform Infrared spectra (FTIR spectra) of the extracted compound showed that extracted carrageenan had essentially κ-structure (G4S-DA) as the reference sample from Sigma Aldrich. The gel strength can be defined as a measure of the ability of a colloidal dispersion to develop and retain a gel form, based on its resistance to shear. It was measured according to the method used previously by Flashaw on agar species.[45] Sulfate content was determined by precipitation of the sulfates as barium sulfate. Finally, intrinsic viscosity was determined experimentally. To do so, viscosity of the solvent (η_0) and viscosities of dilute solutions of carrageenan (η) at different concentrations were measured first. The specific viscosities η_{sp} could then be calculated at each concentration (c) following $\boldsymbol{\eta_{sp} = \frac{\eta - \eta_0}{\eta_0}}$ Equation 1-2. With this in hand, $\frac{\eta_{sp}}{c}$ was plot as a function of the concentration (c). As the intrinsic viscosity [η] is defined as the viscosity of a infinitely dilute solution of the polymer, it could be deduced by extrapolation of this plot at a concentration of carrageenan equal to zero (following $\boldsymbol{[\eta] = \lim_{c \to 0} \frac{\eta_{sp}}{c}}$ Equation 1-1).

$$\boldsymbol{[\eta] = \lim_{c \to 0} \frac{\eta_{sp}}{c}} \quad \textbf{Equation 1-1}$$

$$\boldsymbol{\eta_{sp} = \frac{\eta - \eta_0}{\eta_0}} \quad \textbf{Equation 1-2}$$

According to these results, the concentration of alkali influences yield and properties of extracted carrageenan. Thus, increasing KOH concentration in the extraction process led to carrageenan containing fewer sulfate groups, having a lower intrinsic viscosity and a higher gel strength. The decrease of intrinsic viscosity value was in accordance with a decrease of mass which indicated that polymer degradation occurred during extraction at higher alkali concentration. Furthermore the diminution of sulfate content with the increase of alkali concentration can be related to the transformation of D6S residues of carrageenan to their corresponding anhydro DA one. Optimization of cooking process parameters to produce κ-carrageenan have also been explored by Ding *et al.*[46] Their experimental results showed the same trend as the one of Rochmadi *et al*[35], namely a similar opposite tendency of viscosity and gel strength when increasing the concentration of alkali solution during the extraction.

Another parameter that has been widely investigated in industrial treatment was the choice and influence of the counter ion used to jellify the carrageenan solution. Indeed changing counter ions led to variation of carrageenan gelation.[47] Large cations such as K^+, Rb^+ and Cs^+ are increasing the gelling properties of the molecules whereas smaller ones such as Na^+ and Li^+ have the opposite effect.[48] To address this issue, Thrimawithana *et al.*[49] conducted another study of texture and rheological properties of kappa and iota carrageenan (G4S-DA and G4S-DA2S respectively) in the presence of K^+ and Ca^{2+} by constructing partial ternary phase diagrams using Gibbs triangle shown in Figure 1-6.

To summarize the results presented in these phase diagrams, κ- and ι-carrageenan show different behavior in their responses to KCl and $CaCl_2 \cdot 2H_2O$. Indeed, while κ-carrageenan responds promptly to K^+ (low concentration of K^+ and only 0.2% (w/v) of k-carrageenan required for a sol-gel phase change at 22 °C (Figure 1-6 A), ι-carrageenan displays this transition at low concentration (only 0.4% (w/v) (Figure 1-6 D)) in the presence of low concentration of Ca^{2+}. Furthermore the formulation of κ-carrageenan in the presence of relatively high counter ion

concentration displayed syneresis whereas this phenomenon was not observed with ι-carrageenan formulation. Finally, when the concentration of counter ion was further increased, both systems showed partial gelling, resulting from an insufficient polymer concentration to form a uniform gel matrix.

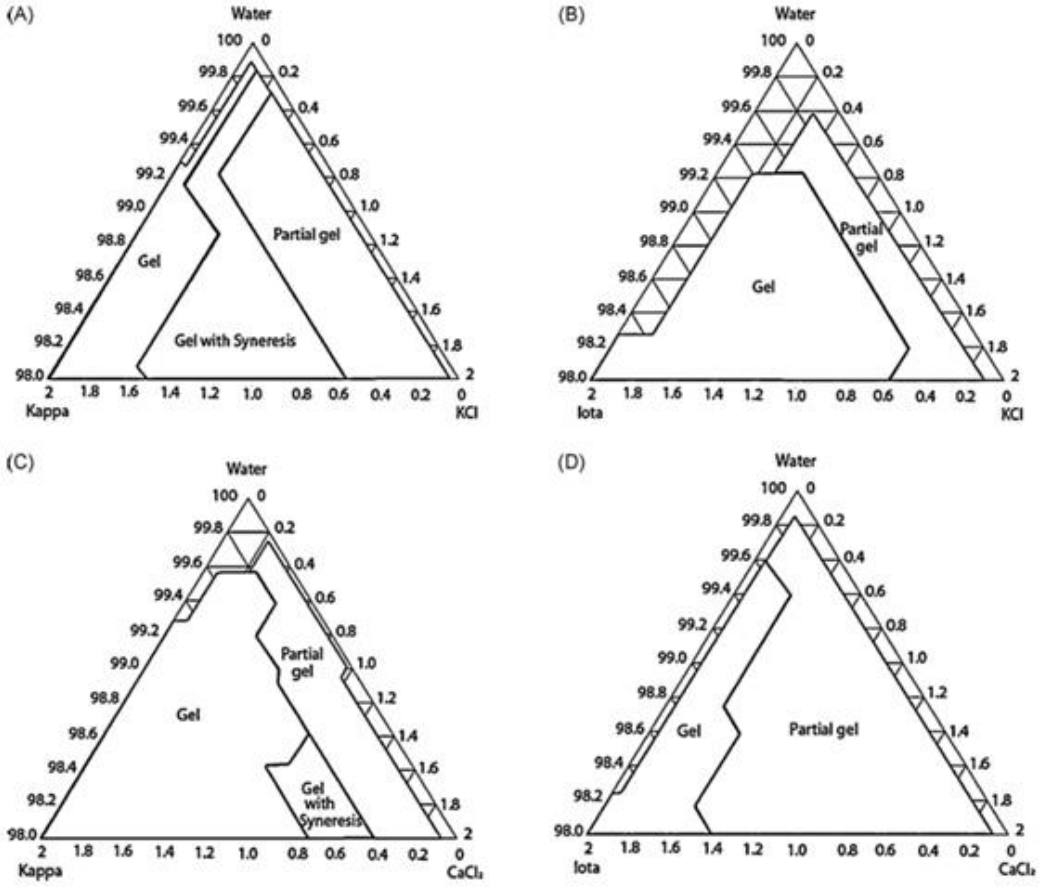


Figure 1-6. Partial ternary phase diagrams of κ-carrageenan (A and C) and ι-carrageenan (B and D) aqueous dispersions in the presence of KCl or $CaCl_2 \cdot 2H_2O$.[49]

To get a better understanding of these gelling properties it is important to relate them to the polymer gel structure and its three-dimensional network.

1.1.2.1.1.4 Elucidation of the three-dimensional structure of carrageenan

It has been shown that the conformation of carrageenan is related to their specific primary structure. Indeed the 3,6-anhydro residues of DA types of carrageenans (such as κ- and ι-carrageenan for example) both inverse the chair conformation of the pyranose rings from $^4C_1$ to $^1C_4$ and increases the hydrophobicity of the galactose residues. This allows the molecules to adopt a helical secondary structure in solution upon specific interactions with cations, such as K^+ or Ca^{2+}, and it has an impact on the rheological behavior of the carrageenan by increasing the gelling properties of that solution. [27,50,51] Contrarily, occurrence of disaccharide units without the 3,6-

anhydro ring, thus having a $^4C_1$-conformation, prevents the formation of any secondary structure such as helices by causing kinks in the primary structure.

Nakamura *et al.* suggested a cation-selective bridge formation to explain the helical conformation of κ-carrageenan in the presence of K^+ cation, (as shown in Figure 1-7).[48] To clarify some kind of cation specificity that have been observed previously in the sol-gel phase transition of κ-carrageenan, they suggested that this intramolecular chelation can only be formed with cations that have a radius big enough (K^+ or Ca^{2+} for example).

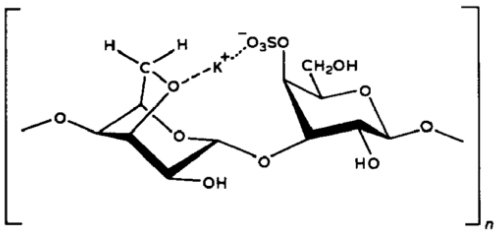


Figure 1-7. Possible mode of intramolecular, cation-selective "bridge" in the κ-carrageenan molecule in aqueous solution at low temperature.[48]

However, the cation-specifity is related to the type of carrageenan and the possible interactions involved. As a second example, Milas *et al.* showed that ι-carrageenan behavior can be explained by an electrostatic mechanism which implies a low ion selectivity and depends on the valence of the counter-ion, whereas in κ-carrageenan, in addition to the electrostatic long-range mechanism, a well-known specific role of K^+ counter-ions is shown and radius of the counter-ion seems to be important for possible interaction with the polysaccharide.[52]

Furthermore, temperature plays an important role in the behavior of polymer solution and the system can be characterized by a melting temperature corresponding to a coil-helix transition. This transition can be seen as the first event of gelation. The thermoreversible gelation of carrageenans in aqueous solution is believed to occur through a two-step process involving first an ion-induced helix formation followed by an association into a network. However, intermolecular interactions are necessary to form a cohesive network and this remains a highly debated and controversial topic. Indeed, many models have been proposed to describe the gelation process of polymers. At present, the "domain model" seems to be the one of choice for carrageenans and Figure 1-8 shows a mechanism of gelation proposed in 1979 by Morris *et al.*[47] according to this "domain model" gelation process.

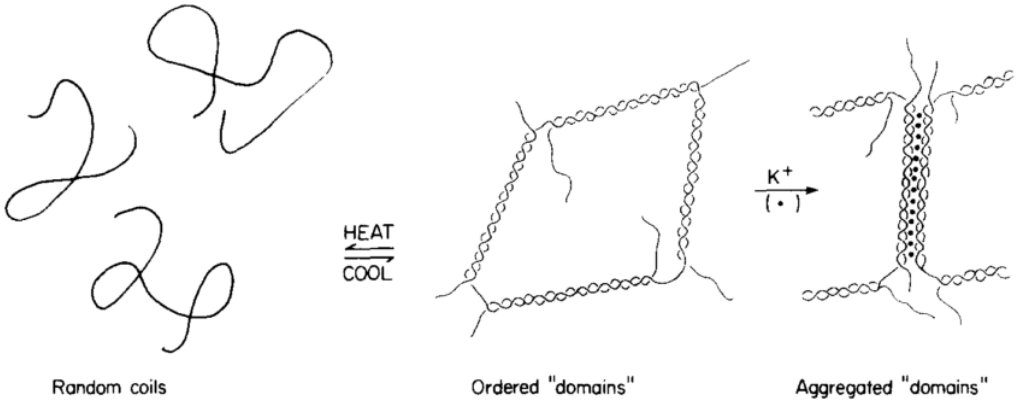


Figure 1-8. Schematic representation of the domain model of carrageenan gelation.[47]

It is assumed that, at high temperature in solution, carrageenans exist as random coils. By cooling down the solution, helix formation occurs, which leads to the apparition of small independent domains involving a limited number of chains via intermolecular association shown as ordered domains on Figure 1-8. However, when cations such as K^+ are incorporated, helices of different domains aggregate to enable long-range cross-linking and a cohesive network is formed. This quaternary aggregated domain structure contributes to the mechanical and rheological properties of the resulting gel. Different levels of chain association may be involved in the cross-linking process which can give a micro heterogeneous or "domain" character to the polymer gel structure.[47] Therefore, the microstructure of carrageenan solutions has to be analyzed to understand the gelation process at the molecular level. Many attempts have been done to elucidate this microstructure. One of them was a study achieved by Thrimawithana *et al.* on ι- and κ-carrageenan aqueous solution using cryo-scanning electron microscopy technique (cryo-SEM).[49] More recently, Schefer *et al.* used atomic force microscopy (AFM) to analyze the difference of microstructures between ι- and λ- carrageenan (respectively G4S-DA2S and G2S-D2S6S). [53] Figure 1-9 summarizes the results observed from the cryo-SEM analysis achieved by Thrimawithana and co-workers. As for the previously shown Gibbs phase diagrams in Figure 1-6, κ-carrageenan (E-H) and ι-carrageenan (A-D) show differences in the SEM images. ι-carrageenan dispersions in the absence of added cations does not display any cross-linking (A) and the polysaccharides are arranged as pleats. Contrarily, in the absence of added K^+, κ-carrageenan displays some regular order or cross-linking (E). Addition of respectively Ca^{2+} and K^+ for ι- and κ-carrageenan induced the appearance of cross-linked structures, with the formation of honeycomb like quaternary structure for ι-carrageenan (B and C) and rectangular pores for κ-carrageenan. However, a too high concentration of cations disrupted the cross-linking of both ι- and κ-carrageenan (D and H). This negative impact may be attributed to saturation of cross-linking zones, and aggregation of polymer groups which would disrupt the cohesive quaternary structure of the systems.

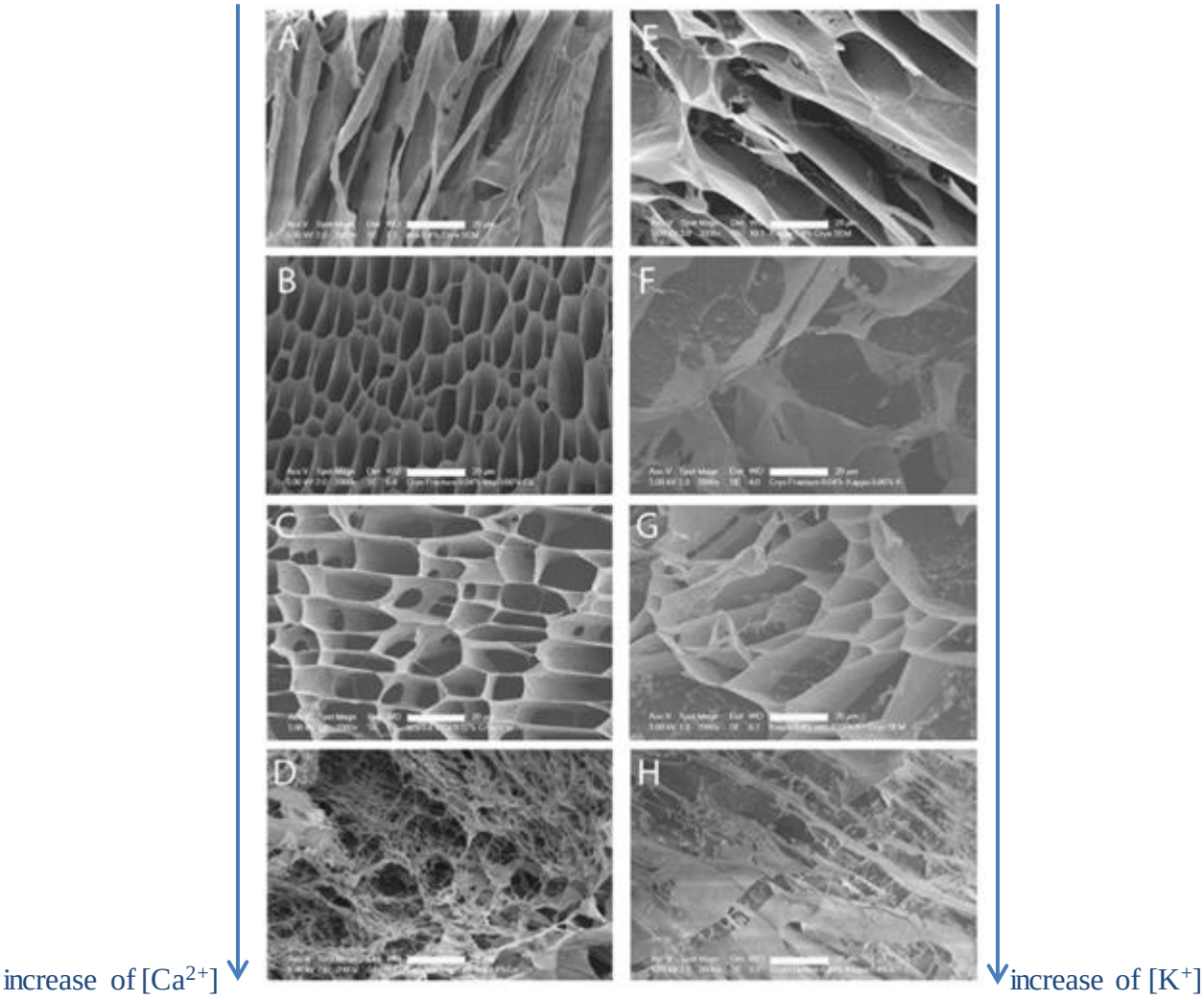


Figure 1-9. Cryo-SEM images of ι-carrageenan dispersions (0.4%, w/v) in the absence of added cations (A), and in the presence of 0.06%, w/v (B), 0.12%, w/v (C) and 0.4%, w/v (D) $CaCl_2 \cdot 2H_2O$ and κ-carrageenan dispersions (0.4%, w/v) in the absence of added cations (E) and in the presence of 0.06%, w/v (F), 0.12%, w/v (G) and 0.4%, w/v (H) of KCl (scale bars=20 µm). [49]

As the nature of the ordered state of carrageenan was still highly controversial, Schefer *et al.* attempted to resolve the disorder-order conformational transition in molecular solution of both λ- and ι-carrageenan by AFM imaging.[53] The carrageenans were chosen carefully for the study to be structurally diverse with one being a DA (ι) type and the other one a D6S type (λ).

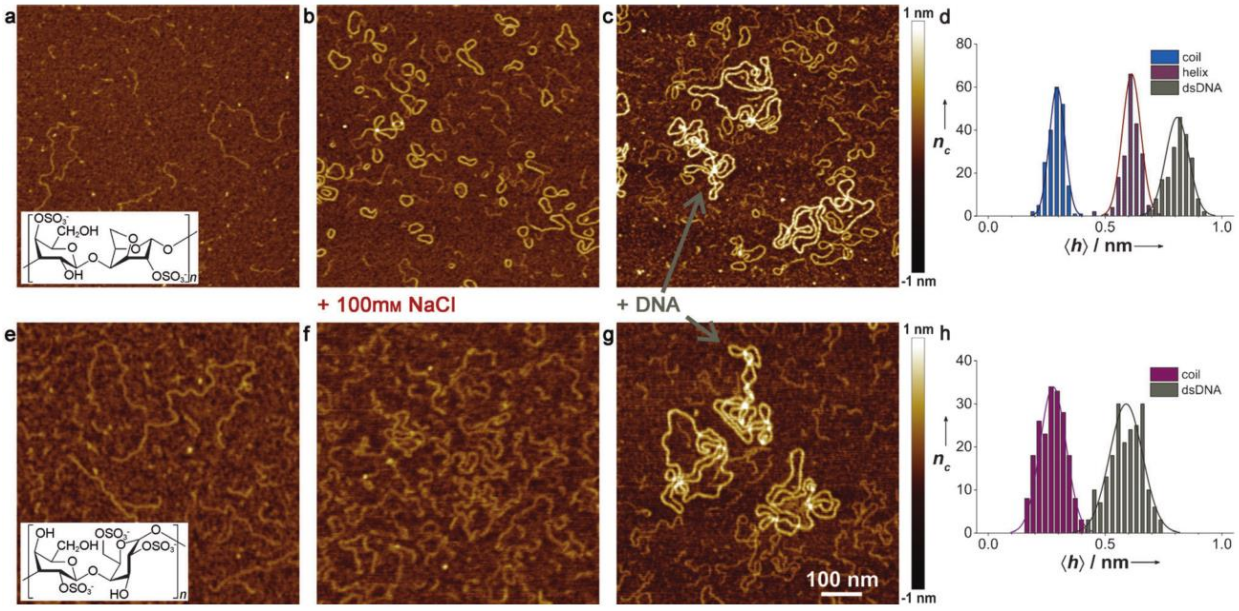


Figure 1-10. AFM height images of a–c) iota- and e–g) lambda-Na-carrageenan solutions, (a,e) as obtained after purification (0mm) and with insets of the idealized disaccharide repeating units of the polymers, (b,f) upon addition of 100mm NaCl, and (c,g) in the presence of dsDNA as internal height standard. The scale bars apply to all AFM images. d,h) Height histogram plots of averaged heights of number of chains (nc) of iota- and lambda-Na-carrageenan, respectively, extracted from the corresponding AFM images (c,g). [53]

First, and as expected, no conformational change and secondary structure of λ-carrageenan appeared while adding salt in the solution (Figure 1-10f). Contrarily, ι-carrageenan underwent dramatic changes (circular object coexisting with linear polymer chains) under these conditions (Figure 1-10b). Double-stranded DNA was then added to the salt solution as an internal standard to compare its height average with the one of ι-carrageenan. As the height of ι-carrageenan is around half the height of the double stranded DNA (see Figure 1-10c), it strongly supports that the ordered state of ι-carrageenan in salt solution consists of an intramolecular single-stranded helix conformation and not a double-stranded one as previously claimed. However, this doesn't exclude a possible intermolecular dimeric double helix formation when increasing the polymer concentration.

Thanks to a huge improvement in analytical techniques, many discoveries about the gelation process of carrageenan have been done throughout the last decades. Nonetheless, a lot remains to be done to get a better understanding of the process at the molecular level. This would lead to a fundamental knowledge about control of the polymer conformation transition, which would get an immediate application in their use, especially in pharmaceutical fields. For example, formulation of semi-solid system with requisite physical characteristics at a given temperature could become possible by fine-tuning carrageenan-to-cation ratio. These systems have potential applications in the investigation of drug delivery systems, where variation in counter ion concentration is likely to modify the rate of release of entrapped particles.[49]

1.1.2.1.2 Carrageenans biosynthesis

Experimental knowledge on carrageenan biosynthetic enzymes remains very limited and therefore, the biosynthethic pathway of carrageenans is only based on hypothesis. Craigie *et al.* characterized a galactose-6-sulfurylase from *C. crispus* in 1978 which catalyzes the 3,6-anhydrogalactose formation in κ-carrageenan and simultaneously release a stoichiometric amount of sulfate.[38] Two different galactose-2,6-sulfurylases from the same algae were discovered later by Genicot-Joncour *et al.*[54] In the same manner, these two enzymes catalyze the conversion of ν-carrageenan to ι-carrageenan. Based on the structures of carrabiose moieties that co-occur in the polysaccharide chains, it is usually assumed that three classes of enzymes are involved in the biosynthesis of these molecules: galactosyl transferases, sulfotransferases (ST) and galactose-6-sulfurylases. The latter is usually referred to as "sulfohydrolases" which are a novel class of enzymes so far only found in the red algal lineage. A coordinated activity of at least two galactosyltransferases is suggested to form the alternating β-1,4 and α-1,3 linkages making up the polymer backbone of carrageenan. Even though these reactions have been shown to take place in the Golgi apparatus, none of these enzymes have been isolated.[54] After polymerization of the backbone, sulfurylation is suggested to occur in the Golgi apparatus as well by the action of specific sulfotransferases which selectively introduce sulfate groups at different positions depending on the carrageenan type. These sulfated carrageenan precursors are then believed to be transported to the cell wall before the sulfohydrolases can act to cyclize the 3,6-anhydro residue. This last step remains the only one that has been biochemically demonstrated to date.[17]

While neutral β-1,4-linked galactose has been identified in carrageenan,[55] no neutral α-1,3-linked galactose moieties except from α-1,3-linked 3,6- anhydrogalactose have been found. Indeed, all galactans isolated from red algae contain either an α-1,3-linked 3,6-anhydrogalactose residue or α-1,3-linked-galactose-6-sulfate. This suggests that the presence of a 6-sulfate group on the α-1,3-linked galactose residues is systematic in the galactan precursor chain. Thus, an alternative scenario was suggested by Ficko-Blean *et al.*[17] as a hypothetical biosynthetic mechanism of seven carrageenans as shown in Figure 1-11. Only the two enzymes marked in red have been isolated and characterized as explained before. In this scenario two different pathways were proposed. Pathway 1 relies on the synthesis of D-galactose-6-sulfate-UDP from D-galactose-UDP. D-Galactose-6-sulfate and D-galactose are then incorporated into the growing carrageenan precursor in alternating α-1,3 and β-1,4-linkages by the action of specific galactosyltransferases. In pathway 2 a neutral galactan chain is synthesized by specific α-1,3/β-1,4 galactosyltransferases and simultaneously processed by a sulfuryltransferase forming the D-galactose-6-sulfate residue.[17] These biosynthesis pathways remain mainly hypothetical. Therefore, much more work need to be done in the characterization of the enzymes involved in the biosynthesis of carrageenan as well as in the understanding of their mechanisms of action to further relate this to the red algae cell wall biosynthesis. The synthesis of well-defined oligosaccharide carrageenans could provide valuable tools to study these enzymes and hopefully get a better understanding of the whole biosynthetic process.

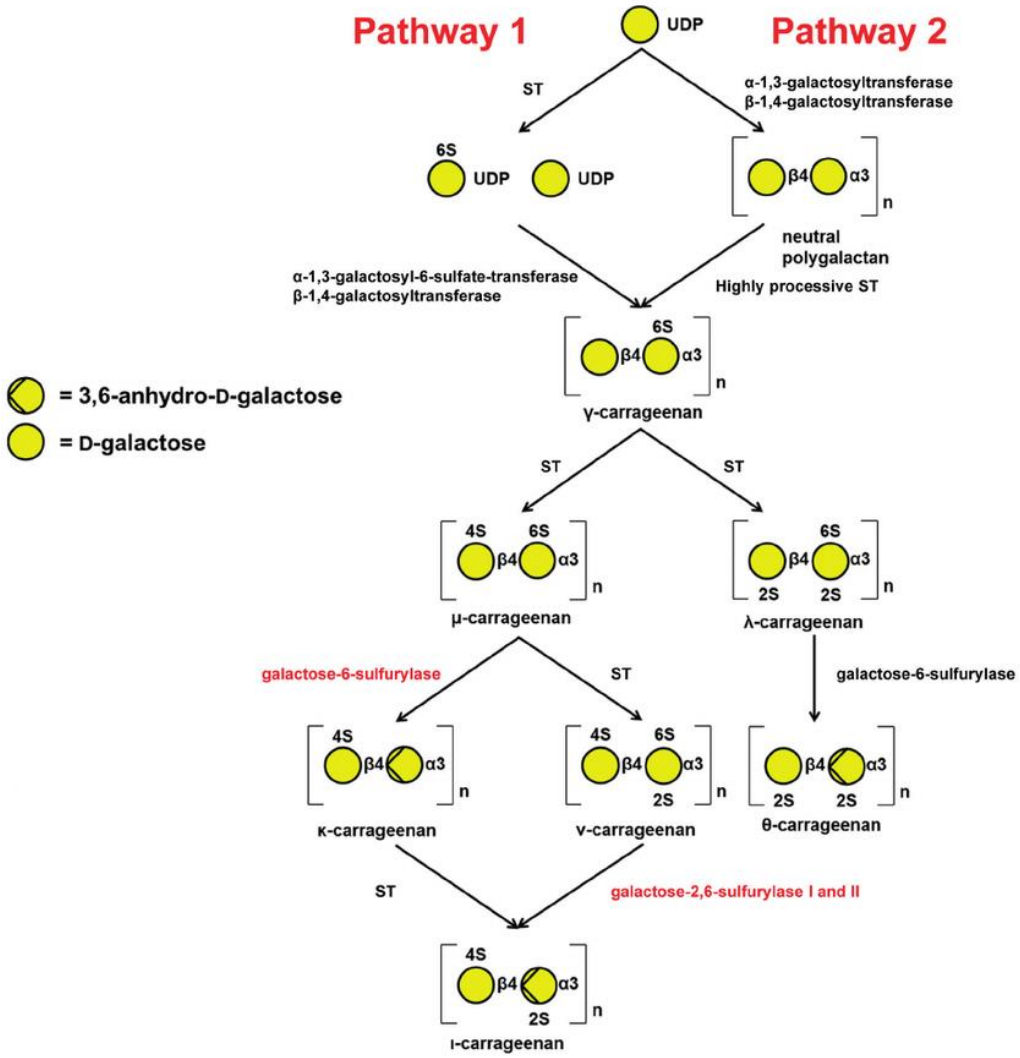


Figure 1-11. Two proposed carrageenan biosynthesis pathways by Ficko-Blean *et al.*[17]

1.1.2.1.3 Challenges in carrageenan chemical synthesis

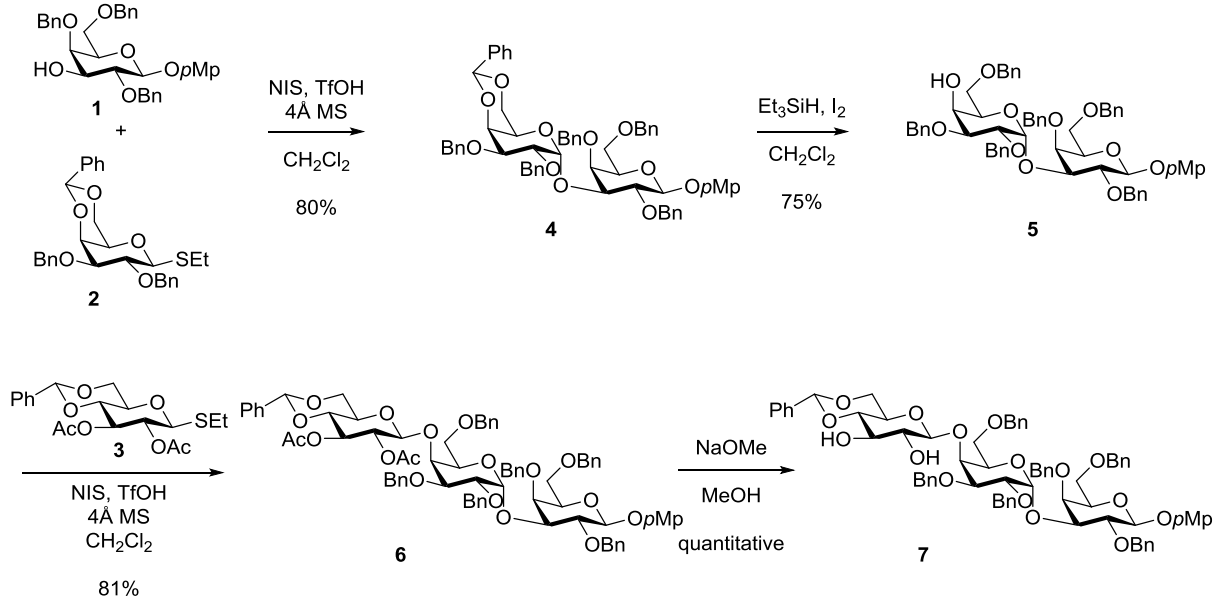
In general, the assembly of complex and well-defined glycans can be achieved by two strategies: enzymatically and/or via chemical synthesis. However, the enzymatic synthesis of polysaccharides requires the availability of the specific enzymes, and in this case, most of the enzymes remain to be discovered and/or isolated. Therefore, we wished to develop a chemical synthesis strategy that would enable us to synthesize well-defined oligocarrageenans. This requires the synthesis of an alternating 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose backbone, followed by the sulfation of various positions depending on the targeted carrageenan.

1.1.3 Previous studies of β-(1→4), α-(1→3)-D-galactan synthesis

1.1.3.1 Synthesis of alternating β(1→4), α(1→3) galactan

The only reported synthesis of an alternating 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose reached the protected trisaccharide β-D-Glu*p*-(1→4)-α-D-Gal*p*-(1→3)-β-D-Gal*p*- O*p*Mp (see Scheme 1-1). The latter was further used in the blockwise synthesis of a hexasaccharide present in the lipopolysaccharidic cell wall of *Azospirillum lipoferum*.[56]

β-(1→4),α-(1→3) linked trisaccharide **7** was synthesized from three monosaccharide building blocks **1**, **2** and **3**. First, stereoselective glycosylation of D-galactose-derived acceptor **1** and D- galactose thioglycoside donor **2** in the presence of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) gave the α-1,3 linked disaccharide **4** in 80% yield. A benzyl protecting group (Bn) was used as non-participating protecting group on the C-2 position of the thioethylgalactoside donor in order to control the 1,2-cis stereoselectivity of the reaction. An overview of stereocontrol in glycosylations is presented later in chapter 2. Regioselective reductive opening of the benzylidene acetal of compound **4** afforded a new disaccharide acceptor **5** in 75% yield. Stereoselective 1,2-trans glycosylation of disaccharide acceptor **5** with thioglucoside derivative **3** in the presence of NIS-TfOH afforded the β-1,4 linked trisaccharide derivative **4** in 81% yield. The stereochemical outcome of this reaction was controlled by the presence of a participating ester protecting group at the C-2 position of donor **3**. Trisaccharide **6** was then quantitatively converted into trisaccharide diol acceptor **7** after removal of the acetyl groups.



Scheme 1-1. Previous synthesis of β-D-Glu*p*-(1→4)-α-D-Gal*p*-(1→3)-β-D-Gal*p*-O*p*Mp.[56]

1.1.3.2 Previous studies of β-(1→4)-D-galactan synthesis

The preparation of well-defined β-(1→4)-D-galactans has previously proved to be challenging.

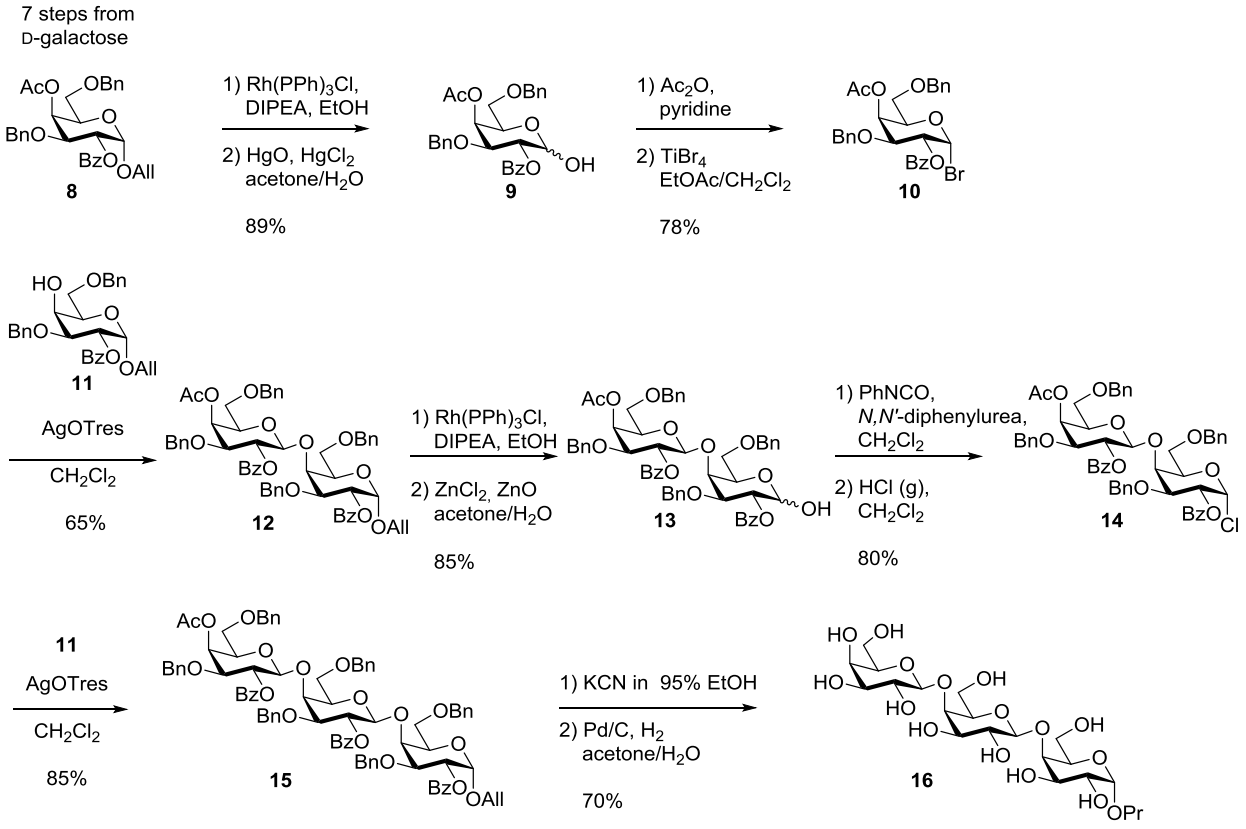
The chemical synthesis of β-(1→4)-D-galactans is difficult because of the low reactivity of the axially disposed C4-*OH* of galactosyl acceptors. Not only are axial hydroxyl groups less accessible towards glycosylation compared to primary and equatorial alcohols, but the acceptor must also be protected on the C3-*O* and C6-*O*, thereby making the C4-*OH* even more sterically hindered. Before 2016, only three groups had reported syntheses of β-(1→4)-D-galacto-oligosaccharides and two of them only reached the trisaccharide level (see Table 1-3).[57-58] Lately a small library of oligogalactans including linear tetra-, penta-, hexa-, and heptasaccharides as well as five (1→6) branched hepta- or octasaccharides have been synthesized by Dr. Mathias Andersen in our group.[59]

Table 1-3. Previous studies of β-(1→4)-D-galactan synthesis.

Synthetic oligosaccharide fragment	Year	Reference
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Gal*p*-OMe	1987	Kováč & Taylor[60]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Gal*p*-O^{n}Pr	1984	El-Shenawy & Schuerch[57]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-D-Gal*p*	2011	Komba *et al.*[61]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Gal*p*-OMe	2001	Lichtenthaler *et al.*[62]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-β-D-Gal*p*-OMp	2001	Lichtenthaler *et al.*[62]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_3$-β-D-Gal*p*-OMp *fully protected*	2001	Lichtenthaler *et al.*[62]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_4$-β-D-Gal*p*-OMp	2001	Lichtenthaler *et al.*[62]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_5$-β-D-Gal*p*-SPh *fully protected*	2002	Oberthür *et al.*[58]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_3$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_4$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_5$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-[β-D-Gal*p*-(1→6)]-β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-[β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)]-β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-[β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→6)]-β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-D-Gal*p*	2016	Andersen M. *et al.*[59]
L-Ara*f*-(1→4)-β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_4$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-[α-L-Ara*f*-(1→6)]-β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-D-Gal*p*	2016	Andersen M. *et al.*[59]
β-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-[α-L-Ara*f*-(1→5)- α-L-Ara*f*-(1→6)]-β-D-Gal*p*-(1→4)-{β-D-Gal*p*-(1→4)}$_2$-D-Gal*p*	2016	Andersen M. *et al.*[59]

1.1.3.2.1 First synthesis of linear β-(1→4) linked trisaccharide

The first reported synthesis of a linear β-(1→4)–D-galactan trisaccharide was developed by Schuerch & El-Shenawy[57] and is shown in Scheme 1-2.



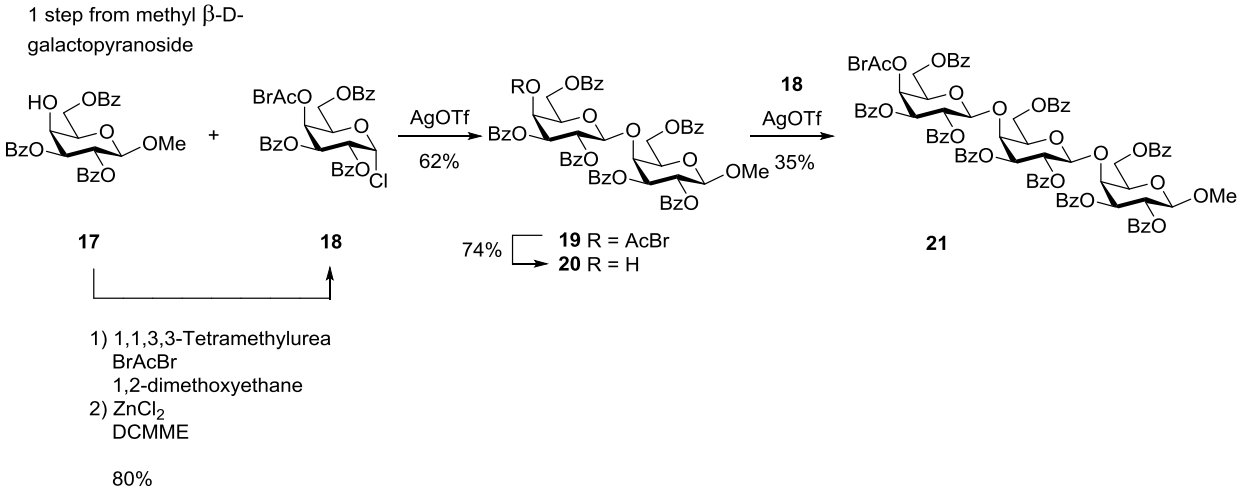
Scheme 1-2. Synthesis of protected β-(1→4)-D-galactotriose 16 by Schuerch & El-Shenawy.[57]

Their strategy was based on reactivation by exchange of an anomeric protecting group. Therefore, the allyl group (All) was chosen as an exchangeable protecting group at the anomeric position of the key building block **8**. This building block carried specific protecting groups. Hence, an acetyl group (Ac) was placed at the 4-position as it could selectively be removed in the presence of the other protecting groups. A benzoyl group (Bz) at the C-2 position would ensure neighboring group participation to control the stereochemical outcome of the glycosylation and form the desired β-linkage. Finally, a benzyl group (Bn) was used as a permanent protecting group for the remaining free hydroxyl groups. The acceptor **11** was coupled to glycosyl bromide **10** in a silver tresylate (2,2,2-trifluoroethanesulfonate, OTres) catalyzed glycosylation reaction providing the disaccharide **12** in a reasonable yield (65%). This disaccharide was then converted into the corresponding glycosyl chloride **14** in four steps. First, the allyl ether was removed by isomerization with $(PPh_3)_3RhCl$ and *N*,*N*-diisopropylethylamine (DIPEA) followed by hydrolysis of the enol ether with $ZnO/ZnCl_2$ to give the lactol **13**. This was converted to the corresponding glycosyl chloride by activation of the anomeric hydroxyl with *N*-phenyl isocyanate (PhNCO)

followed by treatment with HCl gas. A second glycosylation of the acceptor **11** with the disaccharide donor **14** afforded the trisaccharide **15** in 85% yield. Compound **15** was further de-esterified in the presence of KCN in ethanol and hydrogenated with Pd/C to give the unprotected trisaccharide **16**. However, this strategy had three main drawbacks. First of all, it was not possible to turn the di- and trisaccharide into acceptors, since selective acetyl deprotection of the C4-*O* could not be achieved. This would have enable to use them as building blocks to elongate the chain of the oligosaccharide in a fast and efficient way. Secondly, the reactivation of the anomeric group by three steps is both time consuming and results in low overall yield. Finally, glycosyl bromide **10** had to be synthesized by a laborious eleven-step procedure.

1.1.3.2.2 Alternative synthesis of a linear β-(1→4)-linked galactotriose by Kovác *et al.*

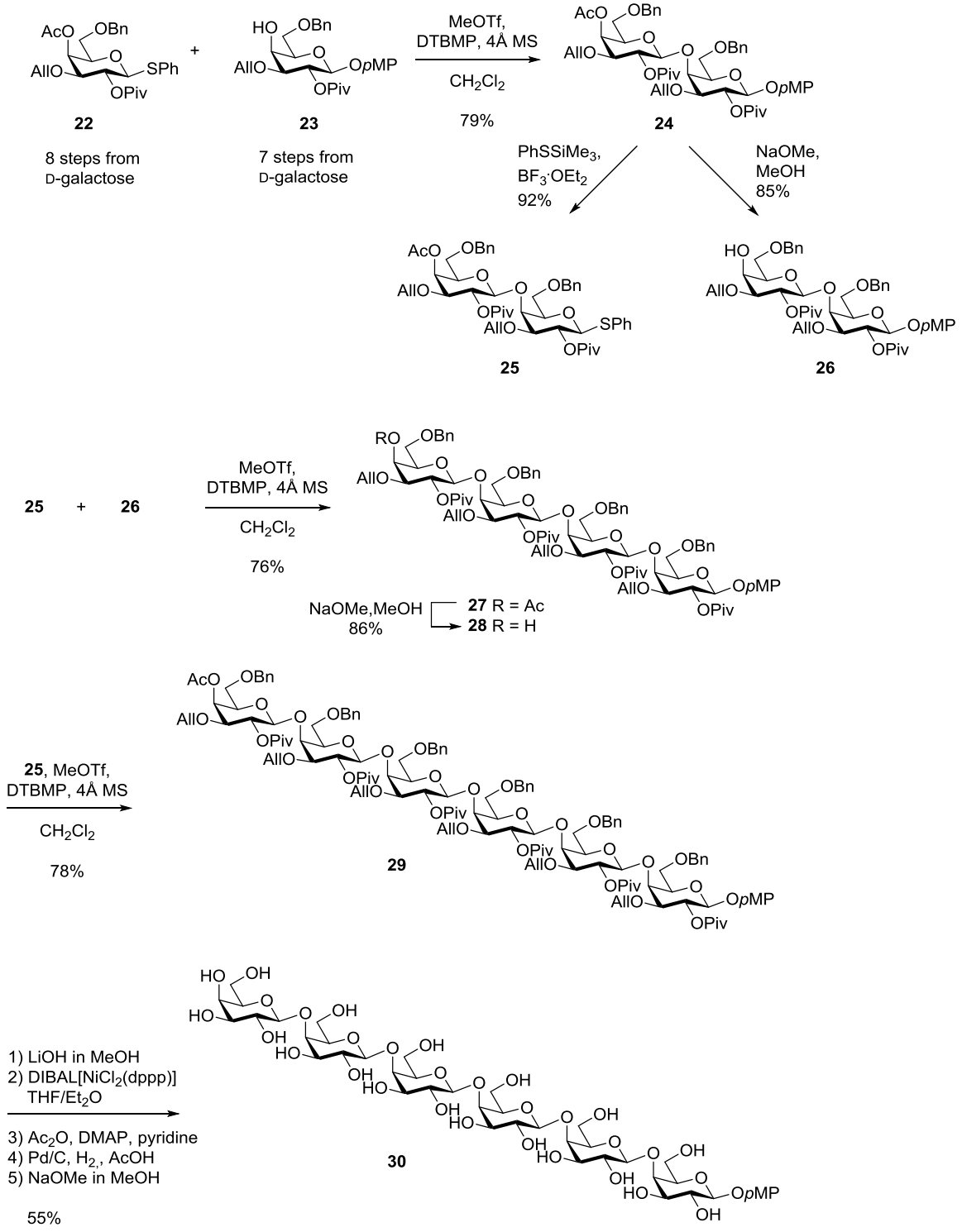
To improve the efficiency of this galactotriose synthesis, Kovác and co-workers suggested another approach starting from acceptor **17**, which could be easily synthesized by a one-step procedure from commercially available methyl β-D-galactopyranoside.[60] This was in turn converted to the glycosyl chloride **18** in two steps: introduction of the bromoacetyl group on the C-4 position followed by cleavage of the methyl anomeric center with 1,1-dichloromethyl methyl ether (DCMME) in the presence of zinc chloride (Scheme 1-3). Coupling of acceptor **17** and donor **18** promoted by silver trifluoromethanesulfonate (AgOTf) gave the desired disaccharide **19** in decent yield (62%). The bromoacetyl group was selectively removed with thiourea to give acceptor **20**, which was once again glycosylated with glycosyl chloride **18**. However, in this case, the glycosylation was slower and the trisaccharide **21** could only be obtained in 35% yield. Both the electron-withdrawing inductive effect of the ester protecting groups chosen and the size of the acceptor could help explain the low reactivity. Therefore, further elongation was also not feasible in this case.



Scheme 1-3. Synthesis of β-(1→4)–D-galactriose by Kovác *et al.*[60]

1.1.3.2.3 Synthesis of linear β-(1→4)-linked hexasaccharide

Lichtenthaler *et al.* published the first strategy by which longer β-(1→4)-linked galactans could be produced as shown in Scheme 1-4.[62]



Scheme 1-4. Synthesis of β-(1→4)–D-hexagalactoside (30) by Lichtenthaler *et al.* [62]

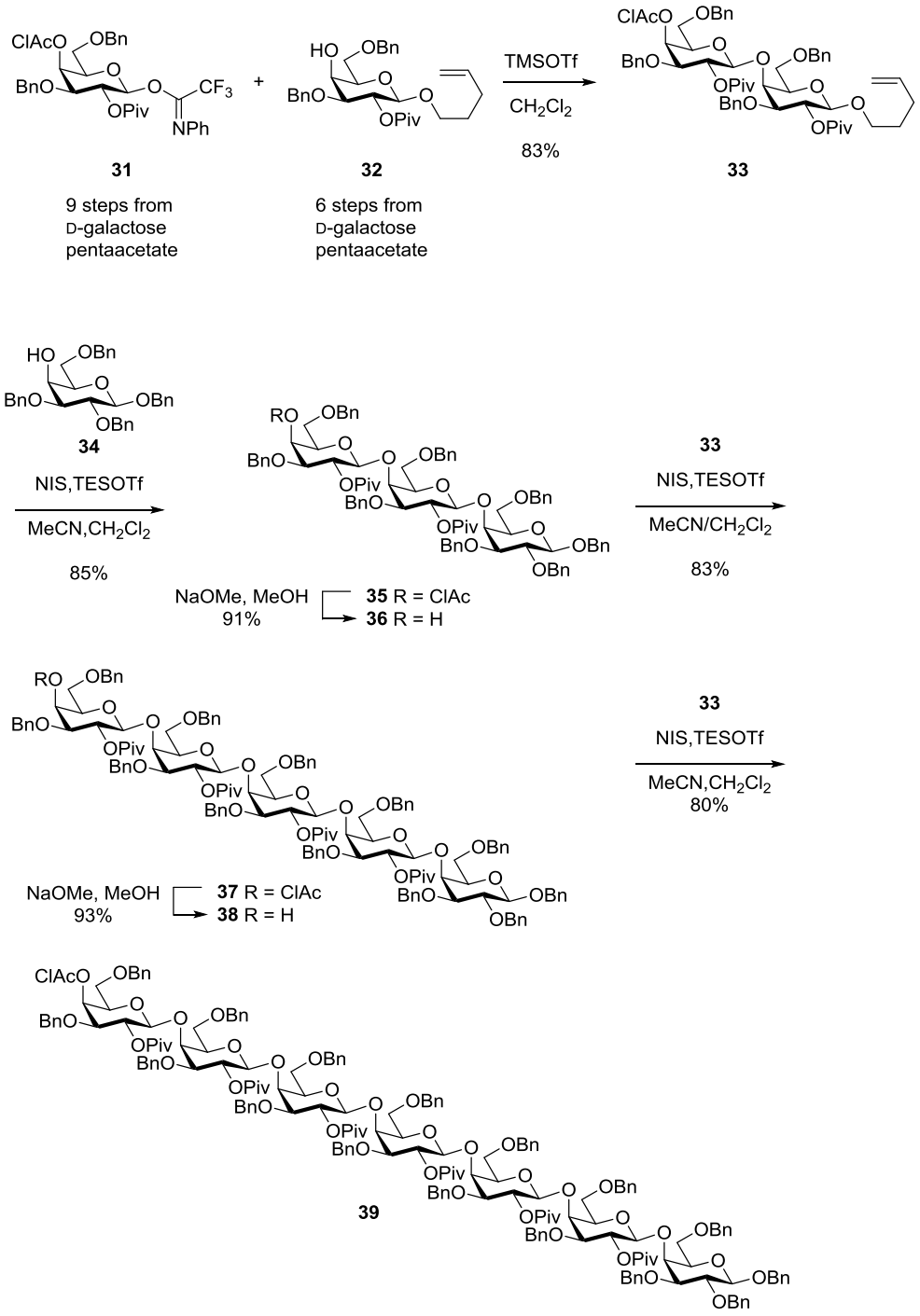
An iterative block strategy and easy interchange of donors and acceptors truly made this synthesis convergent. The method was also based on reactivation of donor by exchange of an anomeric protecting group. However, contrary to Schuerch and El-Shenawy,[57] thioglycosides were used for glycosylation and *p*-methoxyphenyl as the anomeric protecting group. Furthermore, the protecting group pattern was judiciously designed to minimize steric hindrance around the unreactive galactosyl-4-*OH*. Hence, allyl and/or benzyl groups were chosen as protecting groups for the C3-*O* and C6-*O* in order to enhance the accessibility as well as the nucleophilicity of the acceptor. In this case, the pivaloyl ester was used to protect the C2-*O* and participate in the glycosylation step in order to control its stereochemical outcome.. The acetyl group could then be chosen as temporary protecting group of the C4-*O* as mild deacetylation under Zemplén conditions is possible in the presence of the more stable pivaloyl ester.[63] *P*-methoxyphenyl can be converted to the corresponding thiophenylglycoside in a single step in good yield, contrary to the conversion of the allyl anomeric protecting in the case of Schuerch and El-Shenawy's synthesis.[57]

MeOTf-mediated glycosylation of thioglycoside building block **22** and acceptor **23** afforded the disaccharide **24** in a good yield (79%). This could then be turned both into a new disaccharide donor **25** by glycosylation with TMSSPh or a new disaccharide acceptor **26** by mild deacetylation under Zemplén conditions. Two rounds of glycosylation could then afford the hexasaccharide **29** on a gram scale. In a later report, the toxic MeOTf was replaced by triflic anhydride (Tf_2O) giving comparable glycosylation yields.[58] In comparison to the two previous studies, this strategy afforded a remarkable high yield of glycosylation taking into account the low reactivity of the C4- *OH* galactosyl acceptors. However, the deprotection of the different groups, especially the allyl group, turned out to be challenging, and a five-step procedure was necessary to fully deprotect the linear hexasaccharide. Furthermore, the final product is the unnatural *p*-methoxyphenyl galactoside and a low yielding "oxidative deprotection" is required to get the reducing sugar.

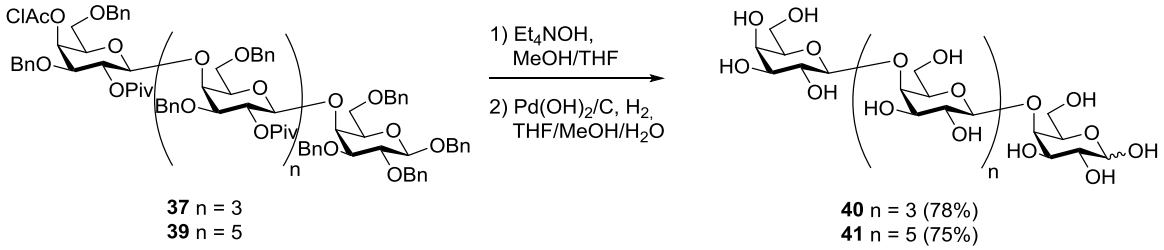
1.1.3.2.4 Synthesis of linear- and (1→6)-branched β-(1→4)–D-galactans.

Dr. Mathias Andersen in our group achieved the synthesis of a small range of β-D-galactooligosaccharides with a β-(1→4)-linked backbone and possibility of (1→6)-branching to mimic the structure of the galactan side-chains present in pectin. The strategy utilized a convergent block strategy where a pentenyl disaccharide donor **33** was prepared and used as a building block to get variable lengths of linear oligosaccharides. TMSOTf-mediated coupling of trifluoroacetimidate donor **31** and acceptor **32** afforded the key pentenyl disaccharide **33** in 83% yield (Scheme 1-5).[59] NIS-TESOTf-mediated glycosylation of disaccharide **33** with the reducing end monosaccharide acceptor **34** afforded trisaccharide **35** (Scheme 1-5). Selective deprotection of the chloroacetyl (ClAc) under mild Zemplén conditions followed by coupling with the disaccharide building block **33** enabled the synthesis of both a linear penta- and a heptasaccharide (**37** and **39**, respectively) in high yields. Final de-esterification of the two oligosaccharides by treatment with Et_4NOH followed by hydrogenolysis over $Pd(OH)_2/C$ gave the fully unprotected penta- and heptasaccharide targets in 78% and 75% yield, respectively (Scheme 1-6). Contrarily

to the strategy used by Lichtentaler *et al.*,[62] less deprotection steps were needed to reach the fully unprotected targets in an overall good yield.

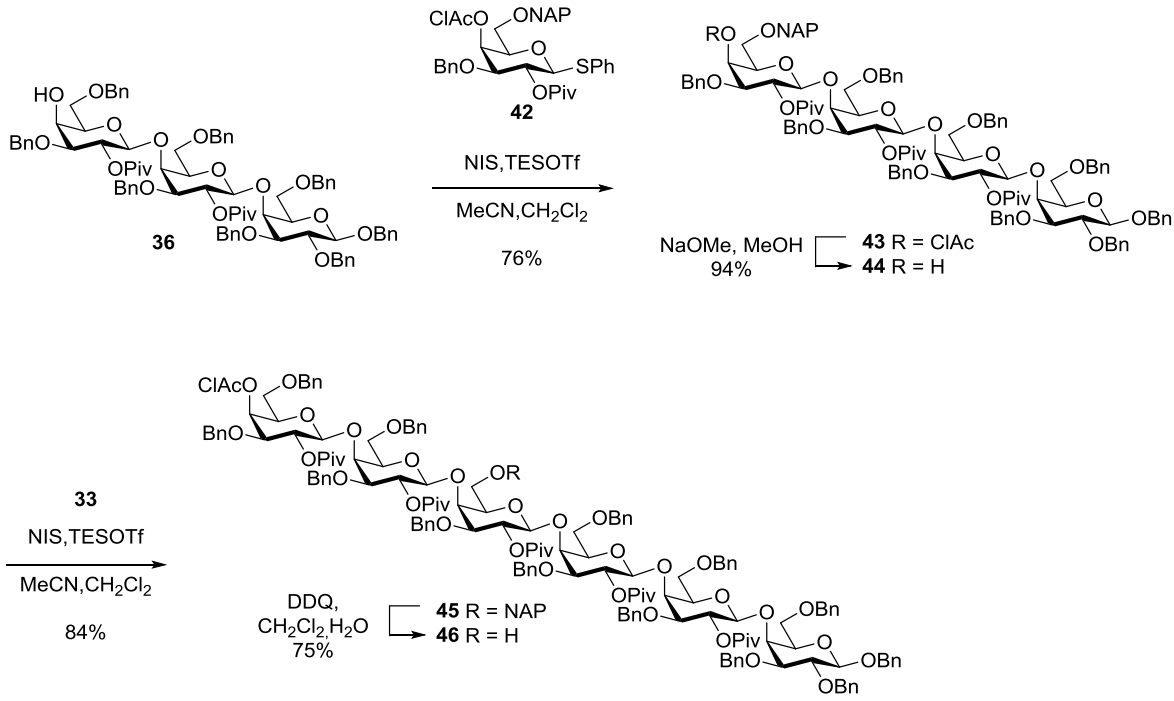


Scheme 1-5. Synthesis of linear β-(1→4)–D-penta- and heptasaccharides by Andersen *et al.* [59]



Scheme 1-6. Deprotection to afford linear β-(1→4)–D-penta- and heptasaccharides by Andersen *et al.* [59]

The same disaccharide donor **33** was used to prepare the branched oligosaccharides. In this case a branching point was installed at the fourth sugar moity by using a 2-naphthylmethyl (NAP) temporary protecting group on the C6-*O* position of this sugar, which could selectively be cleaved by oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). The synthesis of the β-(1→4) linked hexasaccharide **44** is shown in Scheme 1-7. This was then used as an acceptor in glycosylation with different monosaccharide or disaccharide donors to reach the various reducing branched hepta- and octasaccharides shown in Table 1-3.



Scheme 1-7. Synthesis of the protected 6-*OH* hexasaccharide (46) precursor of the various β-(1→6)-branched β-(1→4)–D-galactans. [59]

1.1.3.3 Previous studies of α-(1→3)-D-galactan synthesis

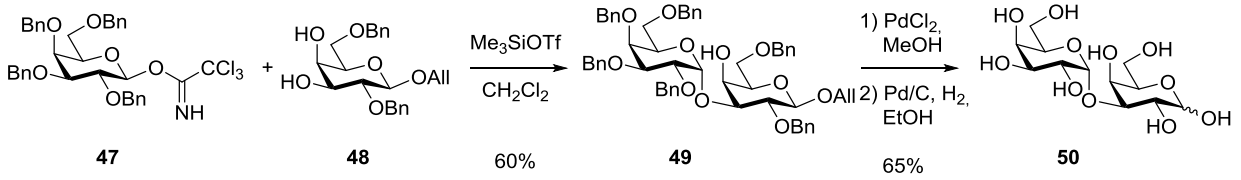
The equatorial C3-*OH* of D-galactose is significantly less hindered than the axial C4-*OH*. However, the higher reactivity due to increased nucleophilicity makes the glycosylation reactions faster and thus it becomes more difficult to control their stereochemical outcome. No α-(1→3)-linked oligosaccharide longer than disaccharide has been reported. A summary of the synthesized α-(1→3)-linked disaccharides is presented in Table 1-4 and some of the chemical synthesis strategy will be discussed in the next section. Several groups have studied the synthesis of isoglobotriaose which is a mammalian glycosphingolipid containing a galactose unit α-(1→3)-linked to lactose.[64–69]

Table 1-4. Previous studies of α-(1→3)-D-galactan synthesis.

Synthetic oligosaccharide fragment	Year	Reference
α-D-Gal*p*-(1→3)-α-D-Gal*p*	2000	Liaigre *et al.*[70]
α-D-Gal*p*-(1→3)-α-D-Gal*p*-O-Me	2002	Spangenberg *et al.*[71]
α-D-Gal*p*-(1→3)-α-D-Gal*p*-O-*p*-$NO_2C_6H_4$	2002	Spangenberg *et al.*[71]
α-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-D-Glc*p* (isoglobotriaose)	2014	Hsieh *et al.*[64]
	1992	Qiu *et al.*[69]
	2009	Yin *et al.*[66]
	2006	Xia *et al.*[67]
	1987	Koike *et al.*[65]
	1999	Zhang *et al.*[68]
α-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-D-GlcNAc	1981	Jacquinet *et al.*[72]
α-D-Gal*p*-(1→3)-β-D-Gal*p*-O-Me	1991	Sarkar *et al.*[73]

1.1.3.3.1 Chemical synthesis of α-(1→3)-D-digalactoside

Relying on the higher reactivity of the C3-*OH* compared to the C4-*OH*, Liaigre *et al.*[70] synthesized the digalactosides α-D-Gal*p*-(1→3)-α,β-D-Gal*p*-OAll by condensation of a trichloroacetimidoyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside donor with the 3,4-unprotected allyl 2,6-di-O-benzyl-α- or β-D-galactopyranoside acceptor. Trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) promoted reaction of donor **45** with the β-acceptor **46** afforded the desired α-(1→3)-linked disaccharide in a **47** decent yield (see Scheme 1-8). Furthermore, no (1→4)-linked regioisomer was observed in any case. The choice of a non-participating benzyl group at the C2-*O* position of the donor **45** was crucial to control the stereochemical outcome of the reaction. Furthermore, the benzyl groups most probably increased the reactivity of both donor **45** and acceptor **46** via electronic effects. Finally the disaccharide was fully deprotected using palladium chemistry.

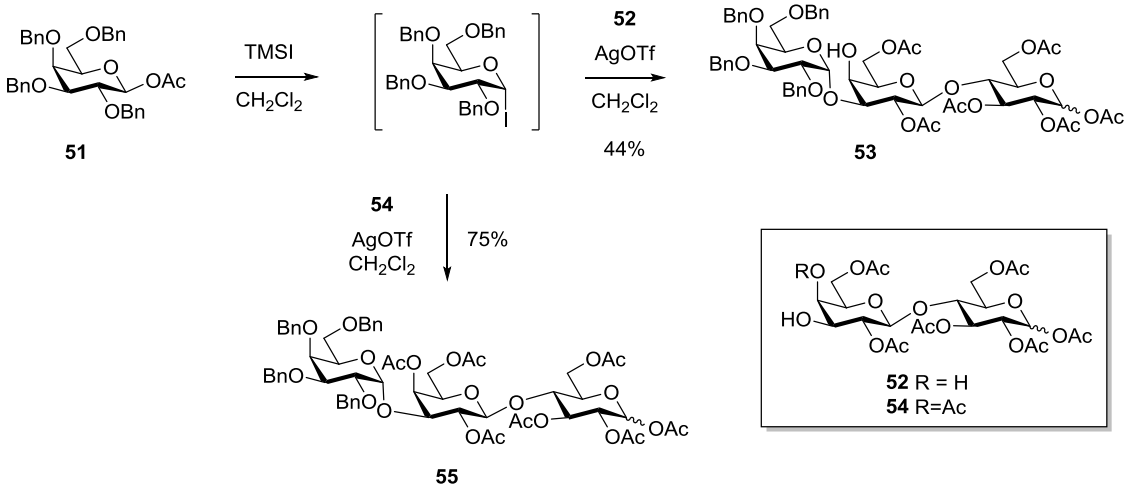


47 48 49 50

Scheme 1-8. Synthesis of α-(1→3)-linked disaccharide by Laigre *et al.*[70]

1.1.3.3.2 Chemical synthesis of α-(1→3)-linked galactose integrated in trisaccharides

The synthesis of isoglobotriaose requires the formation of an α-(1→3)-linkage between galactose and lactose. Most of the studies relied on the glycosylation between a 3',4'-unprotected lactose derivative and a galactosyl donor.[64–69] Here the focus is on one of the latest synthesis from 2014 by Hsieh *et al.*[64] This synthesis will be compared to works previously done in other groups. Among the previous synthesis of isoglobotriase, it has been shown that benzylated galactosyl donors improved the yield of the reaction over acetylated ones.[64–68] However low stereoselectivity was observed when using both thiomethyl or trichloroacetimidate donors. Therefore, Hsieh *et al.* decided to use an *O*-benzyl protected iodide donor in their synthesis, formed *in situ* from the acetyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside **49**. It was possible to obtain stereo- and regioisomer **51** in a decent yield (44%) starting from 3',4'-di-*OH* lactose acceptor **50**. However, a yield up to 75% could be reached when using selectively protected 3'-OH acceptor **52**. It is worth mentioning that both lactose acceptors **50** and **52** could be synthesized in only three and five steps respectively from per-TMS protected lactose. This increased the efficiency of the synthesis of isoglobotriose in comparison to other synthesis previously achieved, which all required between 6 and 12 steps to prepare the disaccharide acceptor.[64–69]



51 53 55

Scheme 1-9. Synthesis of isoglobotriaose by Hsieh et al.[64]

1.1.4 Overview of the sulfation methods developed in organic synthesis

In 1876, Eugen Baumann isolated a substance from horse urine, which he showed to be related to *m*- and *p*-phenol sulfonic acids.[74] Later, this substance was identified as potassium phenyl sulfate and proved to have a very low toxicity in the human body. After this discovery, the biochemistry and chemistry of molecule containing sulfate esters gained more and more interest. Metabolicly, sulfation is an important mechanism mostly used to remove potentially toxic agents from our body. Indeed, by introducing an anionic character in the molecule, it enhances its excretion properties.[75] Biochemical sulfation of molecules (especially carbohydrates) catalyzed by enzymes is another interesting mechanism of sulfation used to generate sulfated ligands with specific receptor-binding activity which induce specific biological responses.[76–78] Sulfate-protein interactions can be both specific and non-specific, via hydrogen-bonding interactions and pure electrostatic interactions respectively. Hence, it became of interest to modulate these interactions by designing appropriate non-natural sulfated ligands.[79–81] More generally, the synthesis of various sulfated scaffolds have proven great potential in biomedical and medical applications. Therefore, development of efficient sulfation methods was necessary.[82]

However, organic synthesis of sulfated molecules remains challenging as Al-Horani *et al.* points out in their review about chemical sulfation of small molecules, as introduction of sulfate groups changes the chemical properties of the molecule.[82] For example, sulfated molecules are mostly water soluble, which makes their purification more difficult. Furthermore, sulfate groups are labile under acidic conditions and high temperatures, and sulfated molecules are insoluble in most organic solvents. Therefore, few functional group manipulations can be performed after the introduction of sulfate esters. Polysulfation of small molecule scaffolds is another challenge. As the anionic crowding increases with the number of sulfate groups, repulsive forces make it difficult to drive the polysulfation to completion.[83]

Several methods of sulfation have been developed and are summarized in the review from Al-Horani *et al.*[82] First, sulfation used to be carried out with sulfuric acid (H_2SO_4) at moderate or low temperature. Alkenes, polyhydric alcohol and polysaccharides have been sulfated using H_2SO_4. A less reactive derivative of H_2SO_4, sulfamic acid (H_2NSO_3H), has been used later for synthesis of saturated monohydric alcohol sulfates and carbohydrate sulfates.[84] However H_2SO_4-based sulfation leads to many side reactions such as dehydration, non-selective sulfation and degradation of the starting material. Another similar method using dicyclohexylcarbodiimide (DCC) in combination with H_2SO_4 was then developed by Mumma *et al.*[85] and later on applied to carbohydrate derivatives for regioselective sulfation.[86,87] As DCC-sulfuric acid complex is rather bulky, sterically hindered hydroxyl groups are unlikely to be sulfated. Therefore, it can be used as a good sulfating agent for regioselective sulfation of the C-6 position of unprotected sugars for example. Nevertheless, this reaction leads to the formation of dicyclohexylurea, which can complicate the isolation of the desired sulfated product. Furthermore, considering the strong acidity of sulfuric acid, this reagent is not suitable for sulfation of acid sensitive molecules.

Sulfur trioxide (SO_3) amine complexes are the most widely employed reagents and can sulfate a variety of scaffolds containing alcoholic, phenolic, amine, thiol and other functionalities. They are much milder reagents than free SO_3 or even H_2SO_4.[75,88–90] Complexes of SO_3 with organic bases, such as triethylamine, trimethylamine and pyridine (Py) as well as amides such as dimethylformamide (DMF), have found extensive usage, especially in sulfation of carbohydrates residues.[91–94] For these complexes, the reactivity of the SO_3 can be directly modulated by the choice of the complexing amine/amide base. Indeed, the stability of the complex is proportional to the strength of the base used and therefore its reactivity should be inversely proportional to this strength. For example, the basic strengths of both Et_3N and Me_3N make these complexes much stronger and therefore expected to be less reactive than the Py one as shown in Table 1-5.[95] Even the weakest complex is a much milder reagent than free SO_3.

Table 1-5. Basic strengths of some amines used in SO_3·complexes, expected relative stability and reactivity of these complexes.

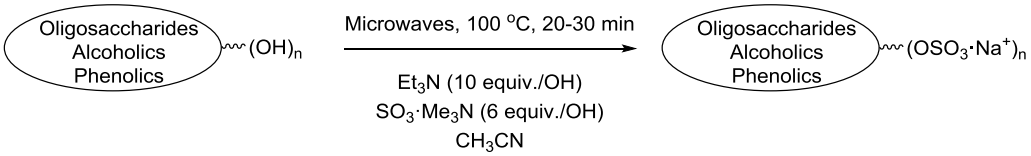
Expected increased reactivity of the SO_3-amine complex ↓

Amine	p*K*a, H_2O
Trimethylamine	10.72
Triethylamine	10.74
N-Ethylmorpholine	7.70
2,6-Dimethylpyridine	6.72
Diethylaniline	6.56
2-Methylpyridine	5.96
Pyridine	5.22
Dimethylaniline	5.06

↑ Increased stability of SO_3-amine

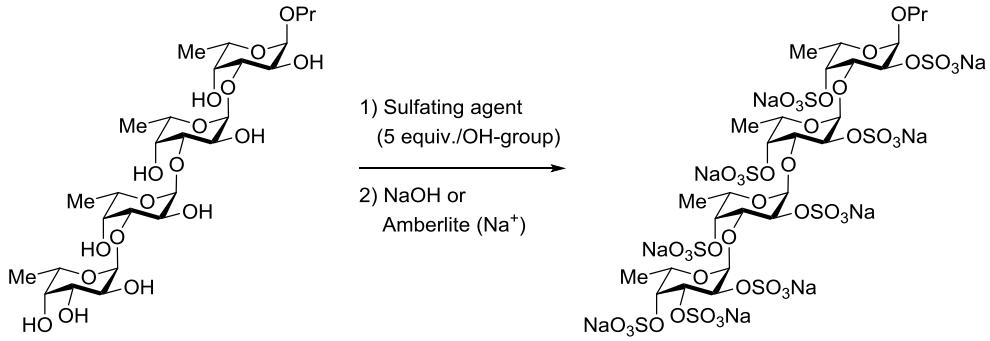
These SO_3·complexes have been the reagents of choice in the different studies of heparin/heparan synthesis.[96–100] In their work on modular synthesis of heparan sulfate oligosaccharides Boons *et al.* proved the stability of these sulfate esters towards some common deprotection steps in oligosaccharides synthesis such as saponification, Zémplen deacylation, desilylation using fluorides agents and hydrogenolysis.[96,97,100] These reagents have been successful in the synthesis of polysulfated scaffolds. In 2009, Chen *et al.* performed the simultaneous sulfation of seven positions using an excess of SO_3·Et_3N in their synthesis of idraparinux.[101] Nevertheless, polysulfation with SO_3·amine or amide complexes usually requires elevated temperature (up to 55 °C), a large excess of the reagent (5 to 10 equiv. per free -OH) and elongated reaction time (up to several days).

To enhance the rate of polysulfation a microwave-based protocol has been developed by Raghuraman *et al.* and the general procedure is presented in Scheme 1-10.[83] However, this method requires high temperature and is mainly convenient for small scale synthesis (< 10 mg of the per-sulfated products).



Scheme 1-10. Microwave-assisted sulfation of polyhydroxyl substrates by Raghuraman *et al.*[83]

In 2008, Krylov *et al.* attempted to synthesize the polysulfated tetrasaccharide **57** using SO_3·Py complex and different solvent combination and reaction time without any success (see entry 1-5 in Table 1-6).[102] Surprisingly, they figured out that, when performing the reaction with SO_3·Et_3N and adding 1.6 equiv. of TfOH per free hydroxyl group, the desired product was obtained in 77% yield. Furthermore, the addition of TfOH made it possible to carry out the reaction at 0 °C and reduce the reaction time. It was hypothesized that TfOH could liberate free SO_3 from the amine complex *in situ*, which is the most reactive sulfation agent. This is of great interest for the sulfation of substrates sensitive to high temperatures. They showed the efficiency of this TfOH promoted *O*-sulfation protocol on other polyol substrates as well.[102]



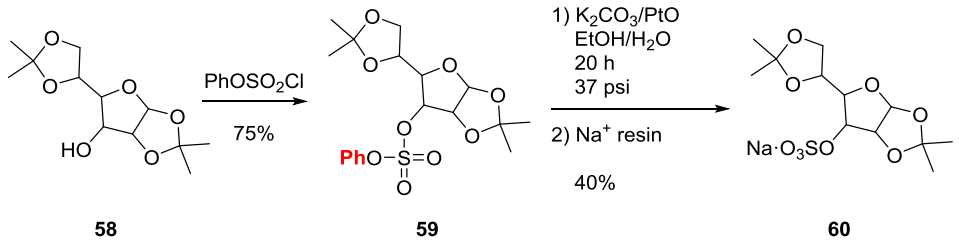
56 **57**

Table 1-6. Per-O-sulfation of tetrasaccharide 56.

Entry	Amount of TfOH (equiv./OH-group)	Temp (°C)	Time (h)	Sulfation agent	Solvent	Yield (%)
1	0	20	1	SO_3·Py	DMF	-
2	0	55	72	SO_3·Py	Py	-
3	0	55	72	SO_3·Py	DMF/Py (3/1)	-
4	0	55	72	SO_3·Py	DMF	-
5	0	55	72	SO_3·Et_3N	DMF	-
6	1.6	0	24	SO_3·Et_3N	DMF	77

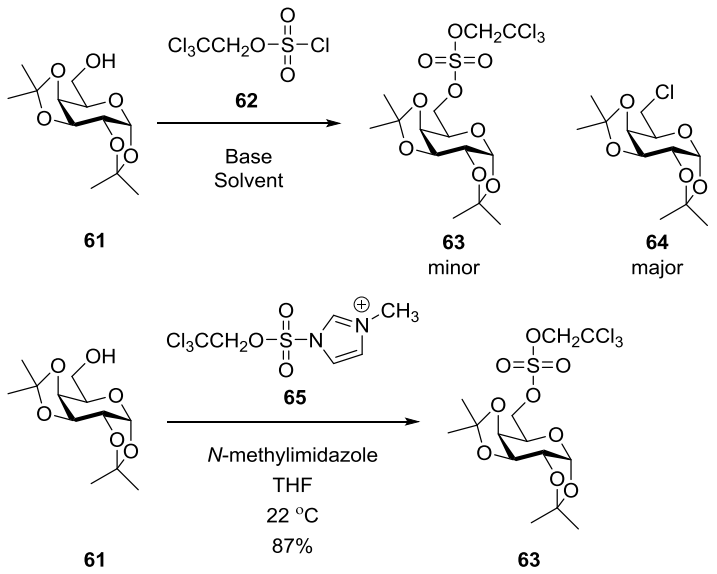
Sulfate esters are quite unstable towards a wide range of functional group transformations. This, together with their polarity, complicates the purification as well as further chemical transformations of sulfated substrates. Therefore, there is an increasing interest to introduce them

in a masked form. In 1981, Penney *et al.* developed a method using phenyl chlorosulfate to introduce a masked sulfate in monosaccharides as shown in the example in Scheme 1-11.[103] This phenyl chlorosulfate intermediate is expected to survive a number of chemical transformations including selective acid hydrolysis, acetolysis, deacetylation and fluoride-mediated removal of trialkylsilyl substituents, which are common deprotection steps in oligosaccharides synthesis. However, only a few reported synthesis have been using this opportunity until now. This must be explained by the low yielding deprotection step of the sulfate ester at the end as well as the high pressure equipment required to achieve this step.[104]



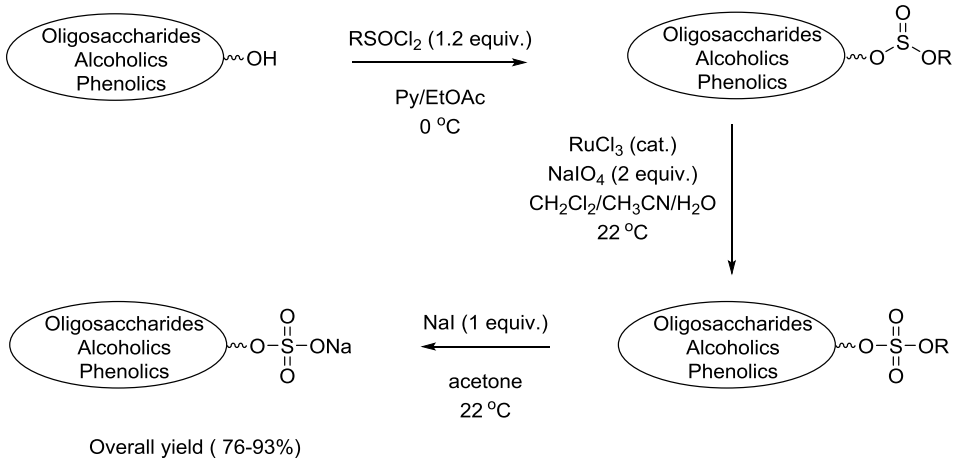
Scheme 1-11. Introduction of phenyl chlorosulfate as masked sulfate intermediate. [103]

Other protecting groups of the sulfate ester were then investigated. Proud *et al.* introduced the 2,2,2-trifluoroethyl which can be removed in high yield by *tert*-butoxide but requires high temperature.[105] Later on, Taylor *et al.* described the use of a 2,2,2-trichloroethyl (TCE) sulfate, which can be readily deprotected in excellent yield under neutral conditions with Pd/C or Zinc and ammonium formate.[106] This TCE-protected sulfate esters were first produced by reacting phenols with trichloroethyl chlorosulfate (TCECS), however this procedure failed in the synthesis of certain sulfated carbohydrates.[107] Indeed, TCECS (**62)** reaction with diisopropylidene-D-galactose **61** led to the formation of the corresponding chlorosugar **64** as a major by-product (see Scheme 1-12). It was then hypothesized that replacing the chloride group of TCECS with a non-nucleophilic leaving group would increase the yield of the desired TCE-protected sulfate esters **63**. Transforming the TCECS into a sulfuryl imidazolium triflate (**65**) and reacting it with diisopropylidene-D-galactose **61** afforded the desired product **63** in 87% yield.[107] This imidazolium salt **65** was reacted with a variety of other monosaccharides resulting in similar yields. Furthermore, the TCE-protected sulfates are stable to many of the conditions commonly encountered in carbohydrates chemistry such as debenzylation, acetylation, Zemplén deacetylation, reductive opening of benzylidene with either TfOH or dichlorophenylborane ($PhBCl_2$) in the presence of triethylsilane (Et_3SiH), acidic hydrolysis of the benzylidene using *p*-toluene sulfonic acid (TsOH) and formation of trichloroacetimidate derivative using catalytic amount of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU).[107] Therefore these TCE esters can be carried through several steps of a synthesis without decomposition, before final conversion to the sulfate monoester by reductive elimination.



Scheme 1-12. TCE protection of C-6 sulfate ester on diisopropylidene-D-galactose 61.

Finally a three-step sulfation strategy was developed by *Huibers et al.* [108] proceeding via sulfite- and sulfate diester intermediates as shown in Scheme 1-13. This protocol uses mild conditions: it can be carried out at 22 °C and requires near stoichiometric amounts of the reagents. The first step involves the formation of a diester sulfite derivative of the parent alcohol, which is then oxidized using sodium periodate and a catalytic amount of ruthenium (III) chloride ($RuCl_3$) to its sulfate diester form. The target sulfate monoester can then be released in high yield using sodium iodide. Unlike the sulfate monoesters of aliphatic alcohols, their corresponding sulfite and sulfate diesters are apolar, stable compounds, soluble in common organic solvents which allows standard purification by flash chromatography. Their stability towards typical conditions for *O*-protective group interconversion was then tested. They tolerated deacetalization conditions, as well as acetylation, silylation and desilylation. Nevertheless other transformations like acetonide hydrolysis using trifluoroacetic acid (TFA) and water, benzylation under either basic conditions (NaH, BnBr, TBAI) or acid-mediated (TMSOTf, $BnOC(NH)CCl_3$) led predominantly to decomposition. These findings demonstrate the potential of sulfite esters as sulfate precursors in organic sequences, but further optimization is still required to improve their compatibility with common reaction conditions.



Scheme 1-13. A three-step sulfation strategy: Sulfitylation-oxidation and release.

To summarize, a large number of methods have been developed to achieve sulfation of small molecules, however none is uniformly applicable with large consistency.

CHAPTER 2

2 Synthesis Strategy

We propose a synthetic approach to produce all ten types of carrageenans from a single precursor carrying different protecting groups that can be cleaved specifically to introduce the sulfate groups at various positions depending on the targeted carrageenan. As shown in Figure 2-1, a blockwise approach was chosen for the synthesis.

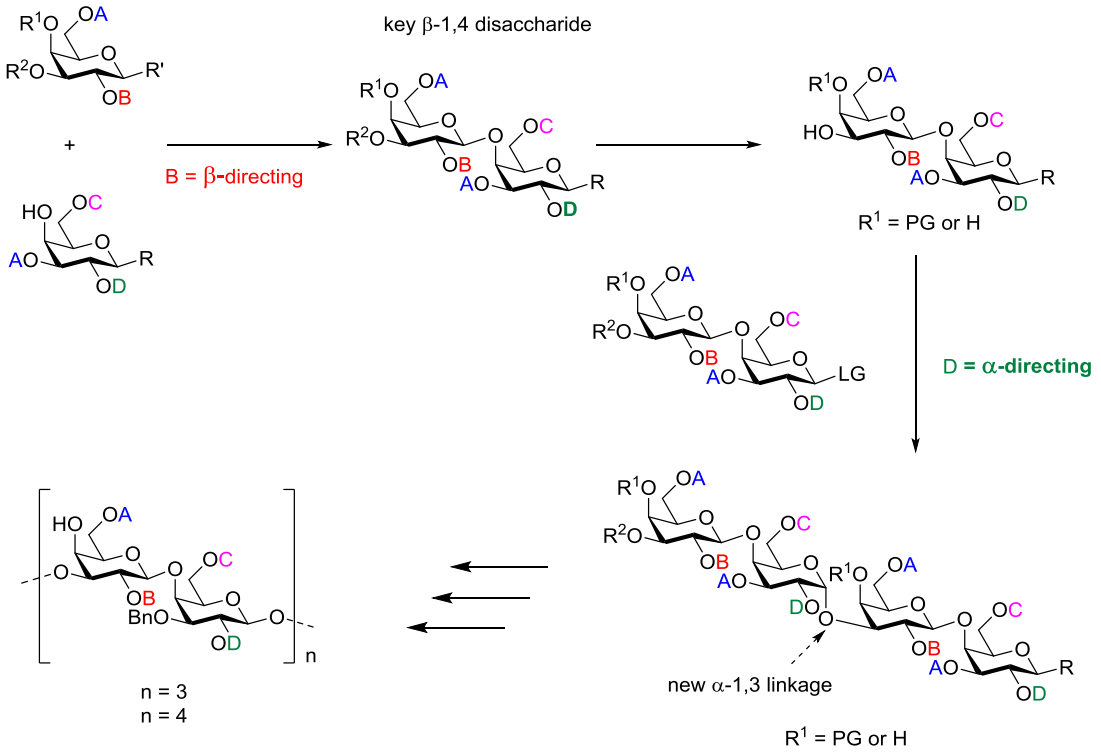


Figure 2-1. Synthetic strategy based on well-chosen protecting groups described in Table 2-1.

The synthetic strategy relies on the synthesis of a key β-1,4 linked disaccharide carrying suitable protecting groups. The chemical synthesis of β-1,4-D-galactans is difficult due to the low reactivity of the axially disposed C4-*OH* of galactosyl acceptors as already discussed. Not only are axial hydroxyls less accessible towards glycosylations compared to primary and equatorial alcohols, but the acceptor must also be protected on the C3-*O* and C6-*O*, thereby making the C4-*OH* even more sterically hindered. The key β-1,4 linked disaccharide will serve as a common building block. Each disaccharide will be α-1,3 linked to each other to build up the backbone of carrageenans consisting of D-galactose with alternating β-1,4 and α-1,3 glycosidic bonds. This modular approach gives a lot of flexibility on the length of the oligosaccharides. Thus, a hexasaccharide can be reached by

coupling a disaccharide to a tetrasaccharide, while an octasaccharide can result either from the coupling of a hexasaccharide with a disaccharide, or from the coupling between two tetrasaccharides. The chain could potentially be further elongated. The requirements for the different protecting groups are outlined in Table 2-1.

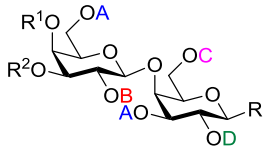
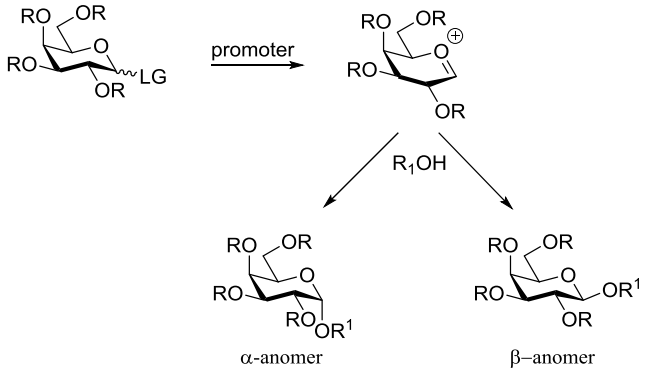


Table 2-1. Protecting group pattern requirements.

Protecting Group	Requirements
A	- *Permanent* protecting group
B	- *β* directing group - Can be selectively removed
C	- Can be selectively removed
D	- *α* directing group - Can be selectively removed
R	- Stable under R' and LG activation (see Figure 2-1)
R^1	- Stable under R' and LG activation (see Figure 2-1)
R^2	- Stable under R' and LG activation (see Figure 2-1)
LG	- Leaving Group for a new glycosyl donor (see Figure 2-1)

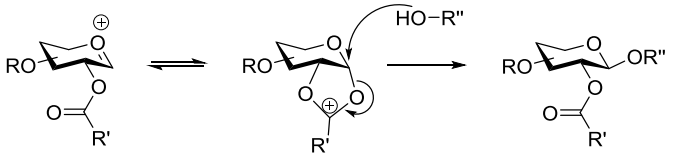
The permanent protecting group A would be used for positions that do not need to be sulfated at any point for any of the 10 targeted carrageenans. To build the D-galactose backbone of carrageenans with alternating β-1,4 and α-1,3 bonds a good stereocontrol of the glycosylations is needed. In theory any glycosylation reaction can lead to two stereosisomers : the α-anomer and the β-anomer as shown in Scheme 2-1. Typically, activation of a glycosyl donor leads to a glycosyl oxocarbenium ion,[109] which can then be attacked from either side by an acceptor and afford both α- and β-anomers. Under thermodynamic control, it has been observed that glycosylation reactions mostly afford the α-anomer.[110] This preference of the sterically unfavored axial position over the equatorial position at the anomeric center is called the endo-anomeric effect.[111,112] Two different explanations of this phenomenon are debated at present. The first one relying on a favourable dipole-dipole interactions for the α-anomer, while the second one proposes that the α-anomer is

stabilized by delocalization of an electron pair of the endocyclic oxygen atom to the periplanar C– X bond (X = electronegative atom) antibonding orbital.



Scheme 2-1. The two possible stereochemical outcomes of a glycosylation, exemplified on a galactose derivative.

Several parameters can influence the stereochemical outcome of a glycosylation. The most frequently employed tool to perform a 1,2-*trans* glycosylation is the use of participating groups on C-2 position, usually ester groups. This was first described by Lemieux in 1954.[113] Neighboring-group participation in sugar chemistry was later explained by Goodman *et al.*[114] The principle is explained for an ester participating group in Scheme 2-2. By generating an acyloxonium ion, this group can stabilize the oxocarbenium cation formed during the glycosylation step after activation of the donor by the promoter.

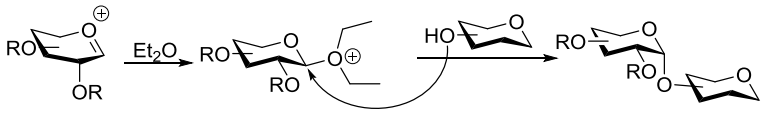


Scheme 2-2. Mechanism ester neighboring group participation.

In our case, to achieve a high stereocontrol of the β-1,4 linkage a participating protecting group B is needed at the C-2' position.

On the other hand, the α-1,3 linkage requires the formation of a 1,2-*cis* glycoside. Recently (2015) Demchenko *et al.* published a review which addresses the challenge of stereoselective 1,2-*cis* glycosylation.[115] Although , the presence of a non-participating group is required for the synthesis of 1,2-*cis* glycosides, this non-participating group alone can not ensure the stereoselectivity. Many other factors such as the solvent, the temperature, the type of donor used, the type of acceptor used, the amount and type of promoter, the protecting groups *etc* play an important role in the outcome of the glycosylation. Unfortunately, non comprehensive method is available for 1,2-*cis* glycosylation yet and refining reaction conditions for each particular glycosylation is necessary.

However, some guidelines are available to help choose these conditions. For example, ether-type solvents, *i.e.* Et_2O, THF or dioxane, are found to have a participating effect in some glycosylation processes leading towards the preferential formation of 1,2-*cis* glycosidic bonds.[115] These solvents are thought to interact with the oxocarbenium ion to form an equatorial intermediate, which can then undergo an S_N2-like displacement with the acceptor Scheme 2-3.[115]



Scheme 2-3. Proposed mechanism for the solvent participation in a 1,2-*cis* glycosylation.

Therefore, to increase the stereocontrol of the α-1,3 linkage in our strategy, a non-participating group D is used at the C-2 position. As the C-6 position needs to be sulfated in all cases, it requires a protecting group C, which can be cleaved selectively.

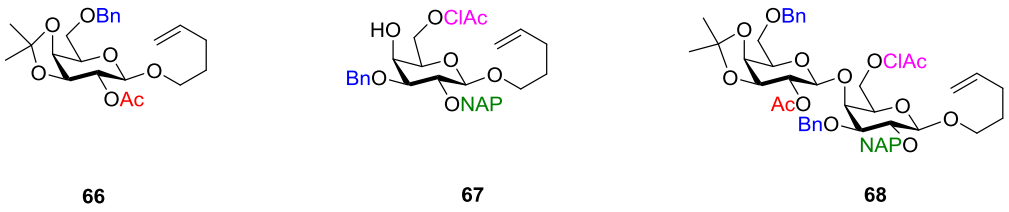
In order to establish the strategy, we aimed to synthesize the ten different type of tetrasaccharide carrageenans. This modular strategy could then be used to synthesize longer oligosaccharide carrageenans as explain before.

CHAPTER 3

3 Results and Discussion

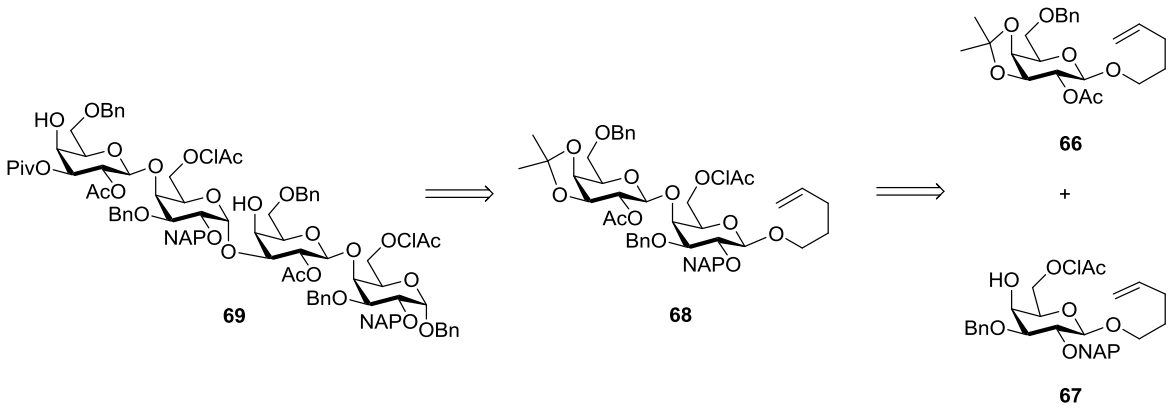
3.1 First protecting group strategy

The first idea was to synthesize the two differentially protected pentenyl galactosides **66** and **67** shown in Scheme 3-1. Employing the versatility of the pentenyl glycoside, which can be either used as a donor or as an acceptor, we would be able to start from the same pentenyl galactoside for the synthesis of both donor **66** and acceptor **67**. Using an orthogonal glycosylation strategy pentenyl galactoside **66** could be further converted into an other galactosyl donor while the second one **67** would be directly used as an acceptor to form the key β-1,4 linked disaccharide **68**. A ClAc group and a NAP group would be used as protecting groups that can be selectively deprotected using thiourea and an oxidative deprotection with DDQ, respectively.



66 **67** **68**

Scheme 3-1. Key monosaccharides 66, 67 and disaccharide 68 building blocks.

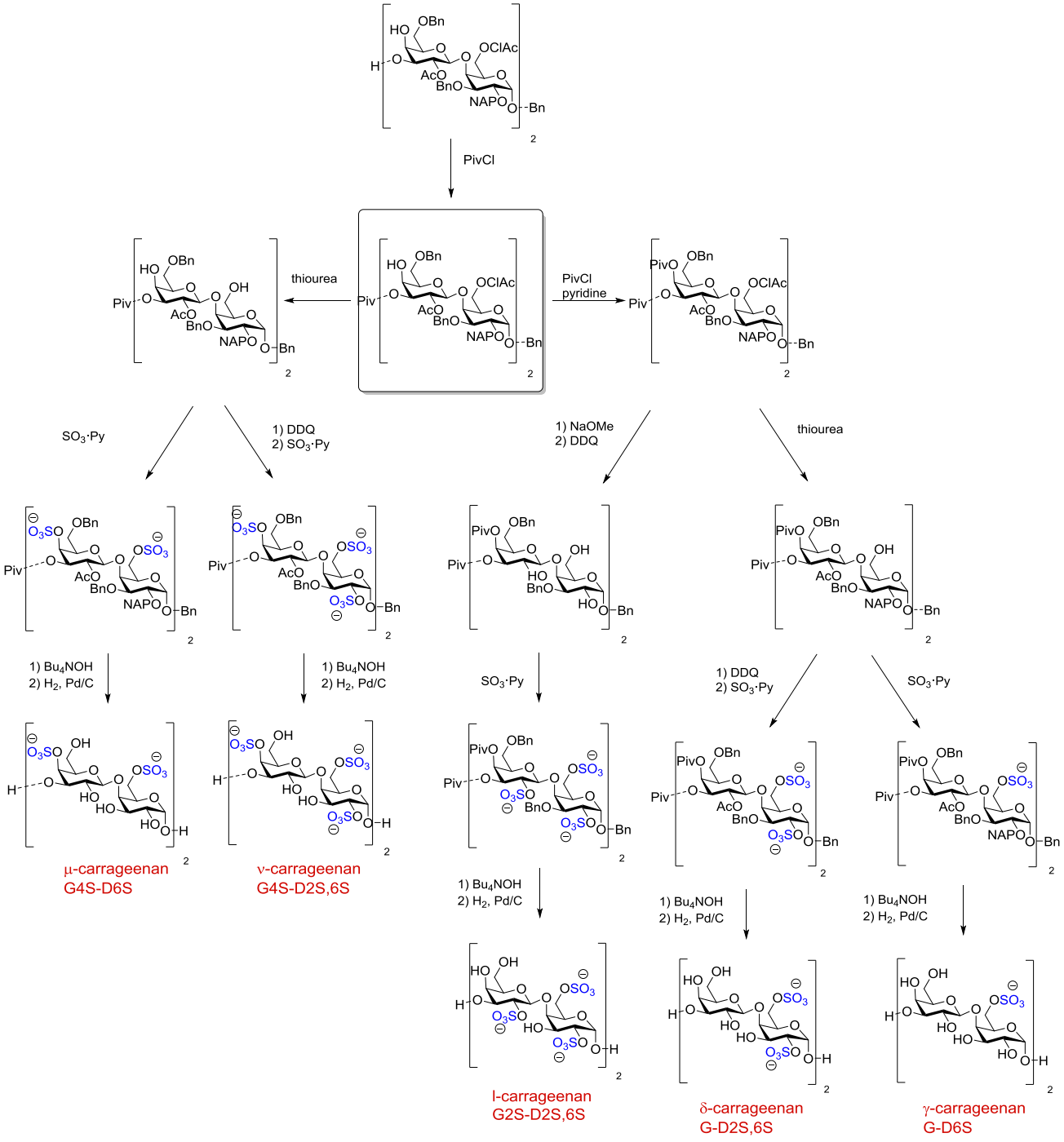


69 **68** **66** + **67**

Scheme 3-2. Retrosynthetic analysis of *n*-pentenyl glycoside-based strategy.

The retrosynthetic analysis of the targeted protected tetrasaccharide **69** is presented in Scheme 3-2. The strategy takes advantage of differential reactivity of the protecting groups as well as the use of a non-participating NAP group in the 2-position to promote α-stereoselectivity and the β- directing properties of the acetate in the 2'-position as explained in Chapter 2. It also takes

advantages of the versatility of the pentenyl group which can serve as a protecting group on the acceptor **67** in the first glycosylation to form the disaccharide and as a donor later on. A new disaccharide acceptor could be formed after hydrolysis of the pentenyl group followed by benzylation of the reducing end and removal of the isopropylidene protecting group, which would leave the 3'-position and the 4'-position unprotected. Relying on the higher reactivity of the 3- over the 4-position of galactose,[64,70,116] this disaccharide acceptor could be further coupled to the pentenyl donor **68**, forming an α-1,3 linkage to obtain the tetrasaccharide **69**.

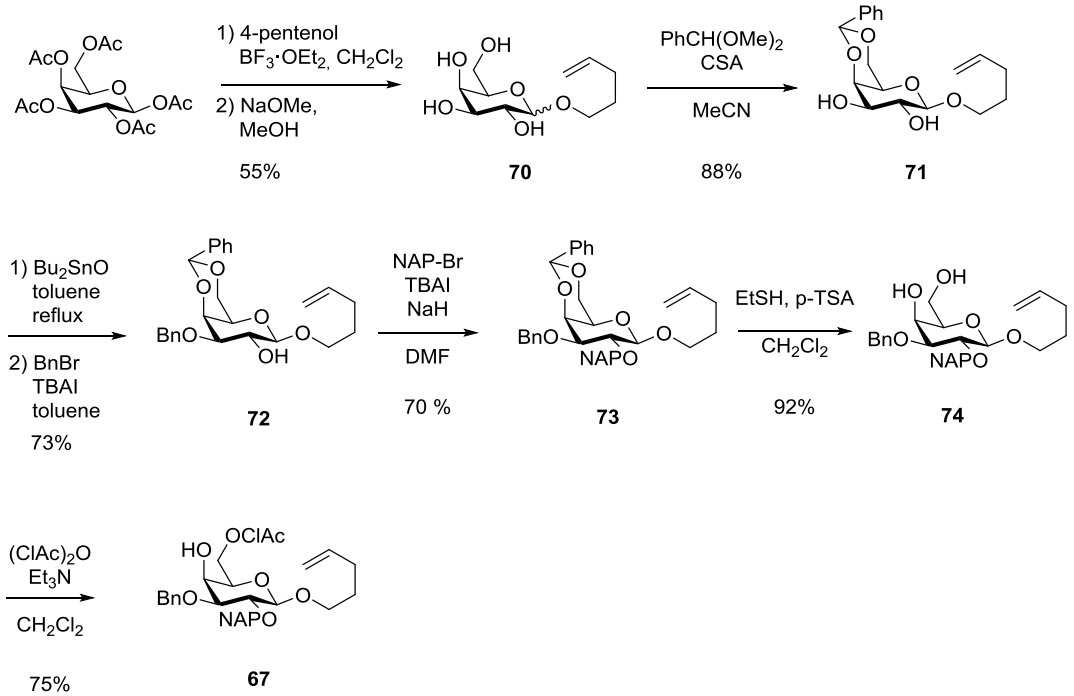


Scheme 3-3. Deprotection and sulfation steps.

Prior to deprotection and sulfation steps, a Piv group can first be installed regioselectively on the C-3'''-*OH* as selective acylation of 3,4-unprotected galactose proved to be feasible by tuning the reaction conditions.[117] With the protected tetrasaccharide in hand, it should be possible to prepare the five D6S carrageenans by applying 5 to 7 additional steps including regioselective deprotection of specific positions followed by introduction of sulfate groups on these unprotected positions, as shown in Scheme 3-3. The corresponding anhydro (DA) carrageenans could be synthesized from their D6S precursor by treating them with a hot alkaline solution or by "galactose-6-sulfurylase" enzymes to catalyze the cyclization.[35,37,40,42,43]

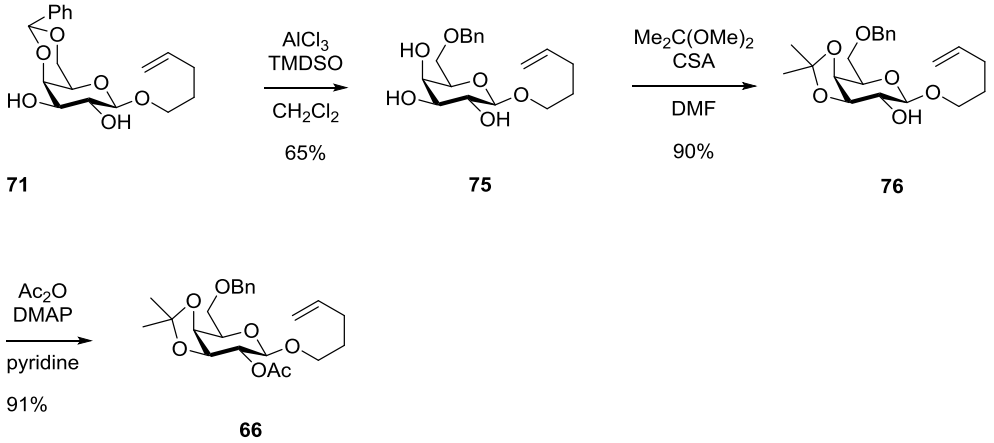
3.1.1 Synthesis of the pentenyl galactoside monosaccharide building blocks

The fully protected pentenyl glycoside **67** was prepared in seven steps from commercially available D-galactose pentaacetate (Scheme 3-4). $BF_3{\cdot}OEt_2$-mediated glycosylation of 4-penten-1-ol with β-D-galactose pentaacetate followed by Zemplén deacetylation afforded the unprotected pentenyl galactoside **70** as a 8:1 β/α-mixture. Treatment of **70** with benzaldehyde dimethylacetal and CSA gave the diol **71** in 88% yield. Activation of diol **71** with dibutyltin oxide (Bu_2SnO) followed by treatment with benzyl bromide (BnBr) gave the partially protected glycoside **72** in 73% yield. NAP protection of the remaining hydroxyl group position using 2-(bromomethyl)naphthalene (NAP-Br) in the presence of TBAI and sodium hydride (NaH) afforded the fully protected galactoside **73**. The benzylidene acetal was then hydrolyzed using ethanethiol (EtSH) combined with a catalytic amount of *para*-toluenesulfonic acid (*p*-TSA) giving diol **74** in 92% yield after only two hours of reaction[63] whereas standard conditions such as aq. AcOH resulted in moderate yields after prolonged reaction times. The C-6 position was finally regioselectively chloroacetylated by treatment of diol **74** with chloroacetic anhydride and triethylamine to afford acceptor **67** in 75% yield.



Scheme 3-4. Synthesis of pentenyl galactoside acceptor 67.

The fully protected pentenyl galactoside **66** was synthesized in 3 steps from diol **71 (**Scheme 3-5**)**. Regioselective reductive opening of the benzylidene acetal gave compound **75** in a reasonable yield by treatment with $AlCl_3$ and tetramethyldisiloxane (TMDSO)[118] whereas the slow hydrolysis of the benzylidene acetal was observed when using more common conditions such as $EtSi_3H$/TFA.[119] The identity of the product **75** was verified by heteronuclear multiple bond correlation spectroscopy (HMBC). Acetalization of the C-3 and C-4 positions of triol **75** in the presence of 2,2 dimethoxypropane and CSA afforded the cis 5-membered ring acetal **76** in 90% yield. Final acetylation of the remaining 2-hydroxyl group using acetic anhydride and DMAP in pyridine afforded the fully protected pentenyl galactoside **66** in 91% yield.



Scheme 3-5. Synthesis of pentenyl galactoside 66.

Next, the pentenyl glycoside **66** needed to be hydrolyzed in order to be further converted into an orthogonal galactosyl donor. Glycosyl imidate was chosen as donor type because of its high reactivity and ease of synthesis. Indeed, imidates can be synthesized from reducing sugars and even at a late stage of a synthetic sequence. Furthermore, imidates act as strong donors in the presence of only catalytic amounts of Brønsted or Lewis acids.[120] Contrary to glycosyl trichloroacetimidates that are prone to rearrange to trichloroacetamide during glycosylation prior to attack of the acceptor, glycosyl trifluoroacetimidate is not affected by this problem, since the leaving group is a poor nucleophile.[120,121] Therefore, glycosyl trifluoroacetimidate seemed to be a suitable choice of donor.

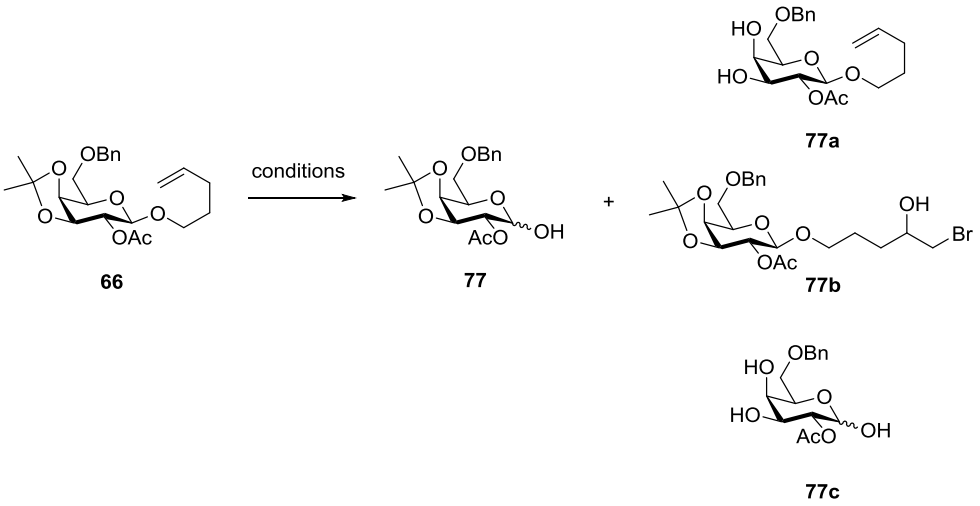
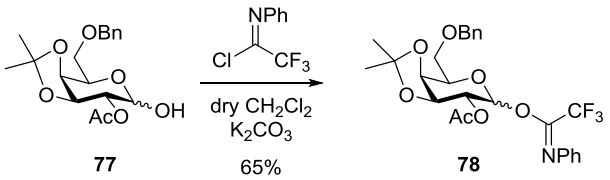


Table 3-1. Hydrolysis of pentenyl glycoside 66.

Entry	Conditions	Yield (%)			
		77	**77a**	**77b**	**77c**
1	NBS, H_2O 2,6-lutidine	-	-	74	-
2	Br_2 3eq Ag_2CO_3 acetone/water 4/1	28	-	-	40
3	Br_2 1.5 equiv. Ag_2CO_3 1.5 equiv. K_2CO_3 acetone/water 4/1	50	-	-	50
4	NIS, TESOTf, H_2O	-	50	-	-
5	NIS, TESOTf, H_2O K_2CO_3	52	-	-	-

The pentenyl hydrolysis turned out to be challenging due to the low reactivity of the donor **66** and the acid lability of the isopropylidene acetal. The optimization results are shown in Table 3-1. Hydrolysis with NBS/H_2O (entry 1) did not occur, due to the formation of halohydrin **77b**. A second attempt to hydrolyze the pentenyl group was to convert the pentenyl galactoside **66** into a galactosyl bromide by titration with bromine and hydrolyze the resulted glycosyl bromide afterwards. The pentenyl glycoside was thus titrated with bromine and the crude glycosyl bromide was treated with silver carbonate and water in acetone.[122] Unfortunately, the unstable isopropylidene protecting group was hydrolyzed during the reaction most probably due to the formation of HBr in the second step and optimization of the reaction conditions such as variation of the temperature and number of equivalent did not lead to the desired product **77** in a satisfactory yield (data not included in table). A last attempt of hydrolysis was performed by activating the pentenyl group with NIS/TESOTf in the presence of water (entry **4** and **5**), but hydrolysis of the isopropylidene group was still observed even in the presence of potassium carbonate and the yield was not significantly improved (52%).

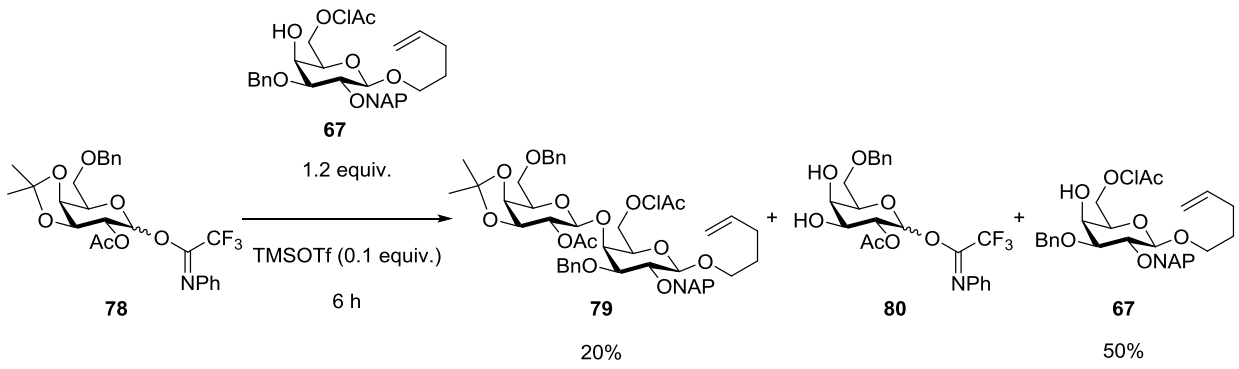
Even though the optimization of this reaction was not quite satisfying we decided to move on to the next step. Cyclic hemiacetal **77** was transformed into its corresponding trifluoroacetimidate donor by treatment with trifluoroacetimidoyl chloride and potassium carbonate leading to a mixture of both isomers as shown in Scheme 3-6.



Scheme 3-6. Trifluoroacetimidate donor 78 synthesis.

3.1.2 Towards the key β-1,4 linked disaccharide

The freshly synthesized imidate donor **78** could then be reacted with acceptor **67** using TMSOTf as promoter. However, as shown in Scheme 3-7, due to both low reactivity of the acceptor and acid lability of the isopropylidene protecting group the reaction afforded the side product **80** after consuming most of the donor and 50% of the acceptor **67** was recovered after termination of the reaction.



Scheme 3-7. Attempt of glycosylation between donor 78 and acceptor 67.

As the isopropylidene group had shown to be too labile it was then envisioned to replace it by a silylene acetal group such a di-*tert*-butyl silylene acetal as shown in Table 3-2.
Unfortunately, the silylene acetal product was not stable, most probably due to high strain, and decomposed on silica during the purification to give the corresponding mono silyl ether protected product.

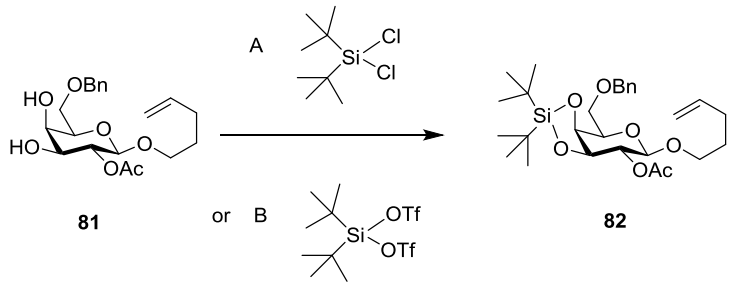


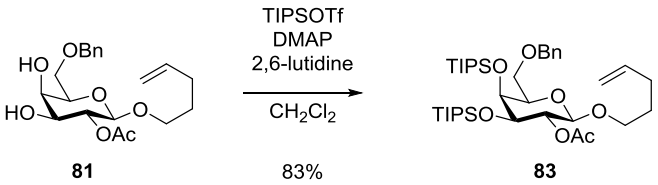
Table 3-2. Optimization table to introduce a silylene acetal protecting group.

Entry	Sylilation agent (equiv.)	Base (equiv.)	Solvent	Temp. (°C)	Reaction Time (h)	Yield 82 (%)
1	B	2,6-lutidine	CH_2Cl_2	22	4	-
2	B	Et_3N	CH_2Cl_2	0 to 30	7	8
3	A	HOBt	pyridine	90	20	-[a]
4	A	Imidazole	DMF	65	5	-[b]

[a] almost no conversion was observed

[b] decomposition on silica during purification

A silyl ether protecting group was then envisioned to replace the silylene acetal and triisopropylsilylether (TIPS) was chosen as shown in Scheme 3-8. Diol **81** was treated with an excess of triisopropylsilyltriflate (TIPSOTf) in the presence of 2,6-lutidine to afford the fully protected pentenyl galactoside **83**.



Scheme 3-8. Silyl ether protected pentenyl donor 16 synthesis

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As previously, the pentenyl group hydrolysis turned out to be difficult (see Table 3-3). It was first attempted to convert the pentenyl galactoside **83** into a galactosyl bromide by titration with bromine and then hydrolyze the resulted glycosyl bromide. The crude glycosyl bromide was treated with silver carbonate and water in acetone (entry 1) providing the product in 18% yield. It was then tried to react the crude glycosyl bromide with *tert*-butyl ammonium bromide (TBAB) and an excess of water, but this first led to migration of the acetyl group at the anomeric position and deprotection of one of the TIPS protecting group (entry 2). Adding 2,6-lutidine to neutralize the solution did not improve the yield of the reaction (entry 3).

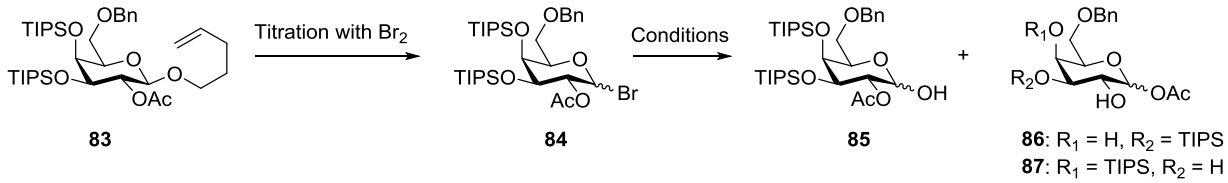
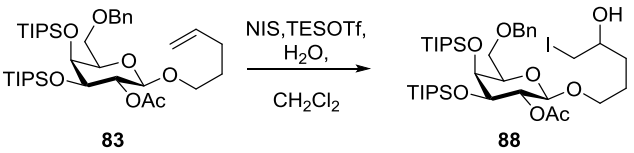


Table 3-3. Attempts to hydrolyze the pentenyl moiety.

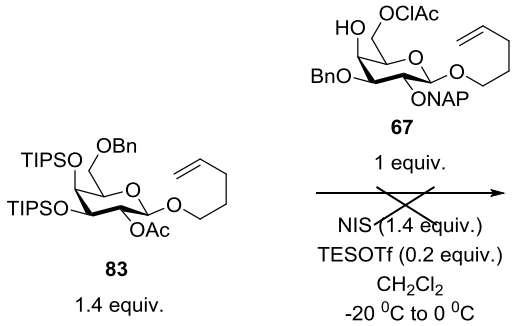
Entry	Reagents	Solvents	Temp. (°C)	Time (h)	Yield (%) 85	Yield (%) 86 or 87
1	Ag_2CO_3 (3 equiv.)	acetone/H_2O	22	3	18	-
2	TBAB (1 equiv.) H_2O (excess)	CH_2Cl_2/MeCN	0 to 22	3	-	20
3	TBAB (0.2 equiv.) H_2O (excess) 2.6-lutidine (1.3 equiv)	CH_2Cl_2/MeCN	0 to 22	3	-	-

In a last attempt of hydrolysis, the pentenyl group was activated with NIS/TESOTf in presence of H_2O, which would act as acceptor, but this only led to the corresponding halohydrin product **88** as shown in Scheme 3-9.



Scheme 3-9. Failed hydrolysis of the pentenyl group using NIS/TESOTf and water.

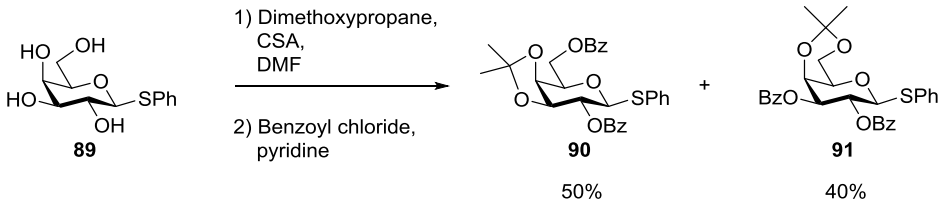
Due to the disappointing hydrolysis results we tried to use the pentenyl galactoside **83** directly as donor (see Scheme 3-10).



Scheme 3-10. Glycosylation trial between pentenyl donor 83 and pentenyl acceptor 67 .

This would follow an armed-disarmed glycosylation approach instead of the orthogonal glycosylation strategy that we envisioned. This concept rely on the effect of protecting groups on tuning chemoselectivity of glycosylation reaction. This phenomenon was first mentioned by Paulsen in 1982[123] and named by Fraser-Reid in 1988.[124] We hoped for a higher reactivity of pentenyl galactoside **83** that would be selectively activated in the presence of pentenyl galactoside acceptor **67**. This unfortunately did not lead to any successful result.

As a consequence of the many problems encountered the first protecting group strategy using the pentenyl anomeric protecting group was abandoned at that point. Instead of planning a new protecting group pattern, it was possible to conduct some test glycosylation experiments with different kinds of donors to investigate the possibilities of a new strategy. Since the anomeric thioacetal is stable towards a wide range of reaction conditions applied for the introduction of protecting groups, a thiophenyl galactoside donor appeared to be a promising choice. The thiophenyl galactoside donor **90** can easily be synthesized from thiophenyl galactoside **89**, carrying a benzoyl participating protecting group at C-2 position required for the stereoisomeric outcome of the first glycosylation. Thus, we decided to synthesize donor **90** and use it for test reactions (Scheme 3-11).



Scheme 3-11. Synthesis of monosaccharide building block 90.

The synthesis of **90** was achieved through a one pot acetalization of the C-3 and C-4 positions followed by benzoylation of the remaining free C-2 and C-6 positions. However, this also afforded the by-product **91** characterized by NMR.

The glycosylation experiments of thiophenyl galactoside donor **90** with our acceptor **67** are presented in Table 3-4.

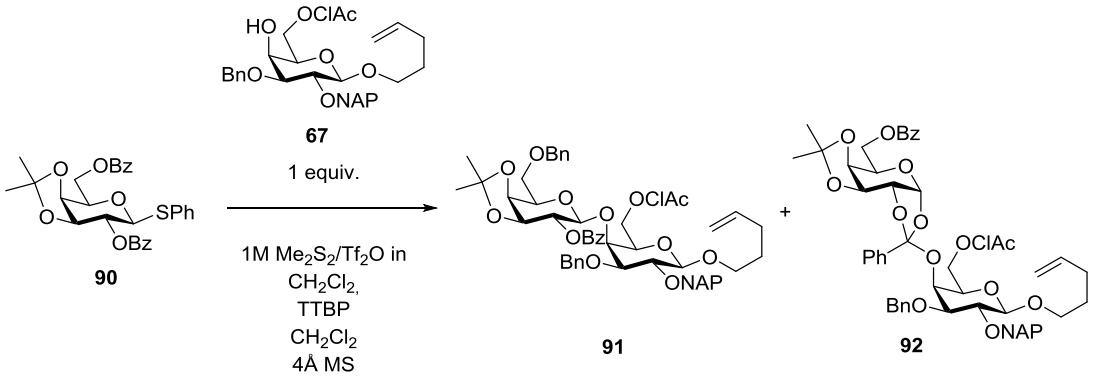


Table 3-4. Optimization of the glycosylation conditions between thiophenyl donor 90 and pentenyl acceptor 67.

Entry	A (equiv.)	TTBP (equiv.)	Promoter (equiv.)	Temp. (°C)	Time	91[a]	92[a]	90[a]
1	1.1	1.1	1.5	- 40	3 h	-	-	+
2	1.2	1.2	2.5	- 40	3 h	-	-	+
3	1.2	1.2	1.5	- 20	3 h		-	+
4	1.2	1.2	2.0	0	20 min	-	+	-
5	1.2	-	2.0	0	10 min	-	-	-

[a] indicated by TLC

A specific promoter suitable for thiophenyl glycosylation that would not activate the pentenyl acceptor **67** had to be chosen. The standard NIS-TESOTf promoter system does not fit this requirement as it can also activate the pentenyl group. Therefore, any kind of thiophilic promoter

such as electrophilic organosulfur compounds (like dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) or dimethyldisulfide-triflic anhydride (Me_2S_2/Tf_2O)) would be more appropriate.[125,126] To avoid the deprotection of the isopropylidene protecting group, 2,4,6- tri- *tert*-butylpyrimidine (TTBP) was added to neutralize the solution. Performing the reaction at lower temperature than 0 °C and varying the amount of promoter did not give good conversion of starting material (entry 1-3). Performing the reaction at 0 °C helped the conversion but unfortunately, the only product formed was the 1,2-orthoester **91** (entry 4). As orthoester formation is more likely to happen under basic conditions, we tried the reaction under the same conditions but without the TTBP. This led to full conversion of the starting materials within a few minutes but many by-products were formed that was related to the deprotection of the isopropylidene group.

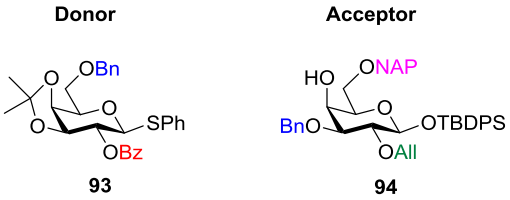
3.2 Second protecting group strategy

The protecting group pattern had to be changed taking into account both the problems encountered and some knowledge gained in the group in the since the first was devised. Table 3-5 gives an overview of the problems encountered during the first protecting group strategy.

Table 3-5. Summary of the first protecting group strategy Table 2-1.

Protecting Group	Requirements	First strategy	Problems encoutered
A	- *Permanent* protecting group	Bn	
B	- β directing group - Can be selectively removed	Ac	Migration during pentenyl hydrolysis
C	- Can be selectively removed	ClAc	Reduce reactivity of acceptor?
D	- α directing group - Can be specifically removed	NAP	Might be difficult to remove on oligosaccharide in the presence of Bn groups at 6-positions
R	- Stable under R' and LG activation	pentenyl	Hard to hydrolyze
R^1	- Stable under R' and LG activation	isopropylidene	Unstable under acidic glycosylation conditions
R^2	- Stable under R' and LG activation	isopropylidene	Unstable under acidic glycosylation conditions
LG	- Leaving Group for a new glycosyl donor	acetimidate	

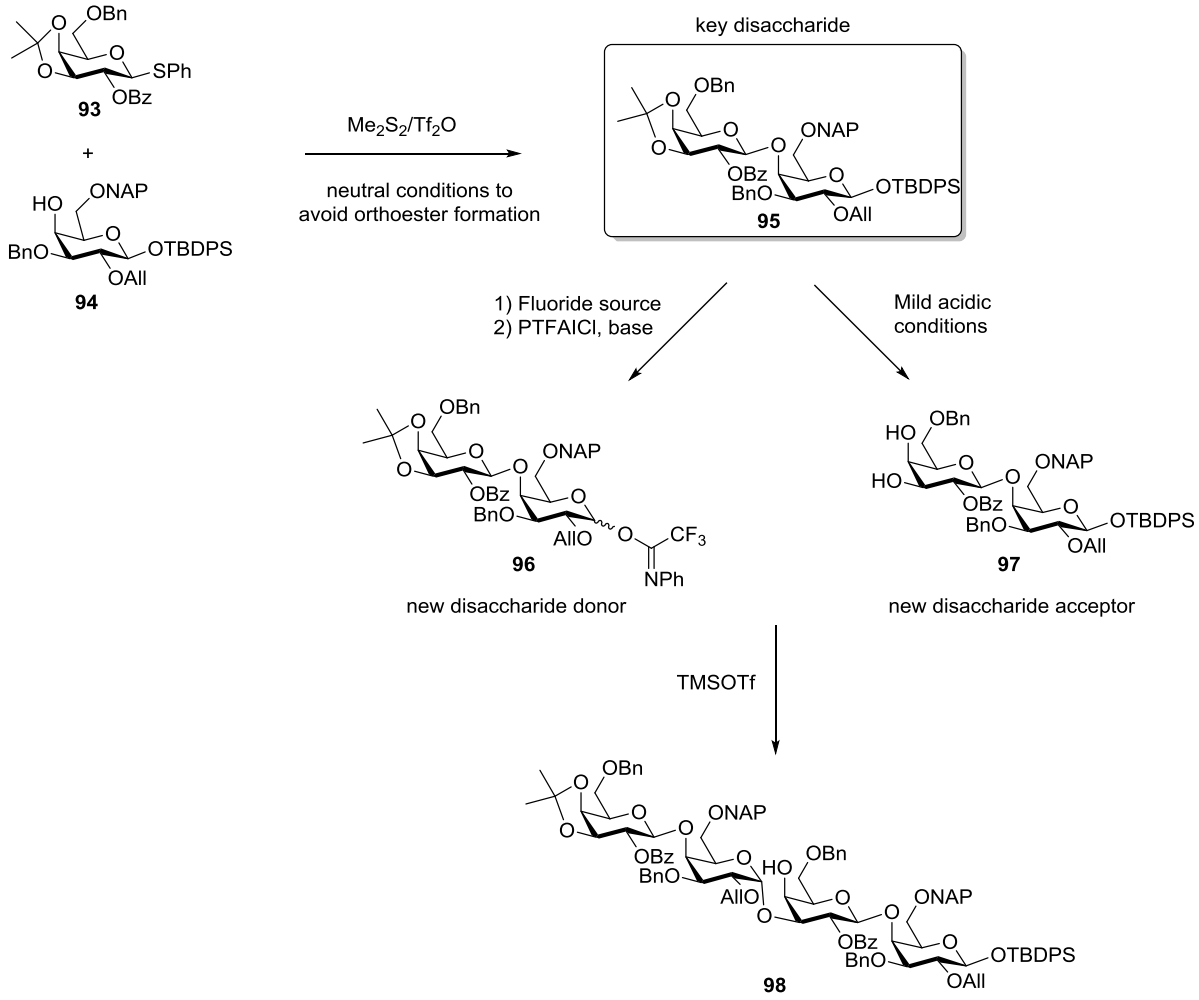
Taking the previous results into account, the two following monosaccharide building blocks were chosen for the new strategy (Scheme 3-12).



Scheme 3-12. New monosaccharide building blocks donor 93 and acceptor 94.

As donor, a thiophenyl galactoside was chosen due to its stability as previously mentioned. For example, whereas many other types of glycosyl donors such as glycosyl halides or glycosyl acetimidates, are unstable under deacetylation conditions, acetylated thioglycosides can be deprotected without degradation. Furthermore, most of the thioglycosides can be crystallized which makes them easy to handle. Activation of thioglycoside can be achieved using a wide variety of electrophilic promotors. The thioacetal function thus conveniently combines the role of an anomeric protective group and that of an efficient leaving group.[126–128] In this new strategy, a benzoyl group would be used as a neighboring group participating in the first glycosylation to form the β-1,4 glycosidic linkage. Hopefully, this would result in less migration than what had been observed with the acetyl group in some preliminary experiments. An allyl group would be used as a non-participating group to promote the formation of the α-1,3 linkage. Furthermore, allyl groups can be selectively removed by using for example $Pd(PPh_3)_4$.

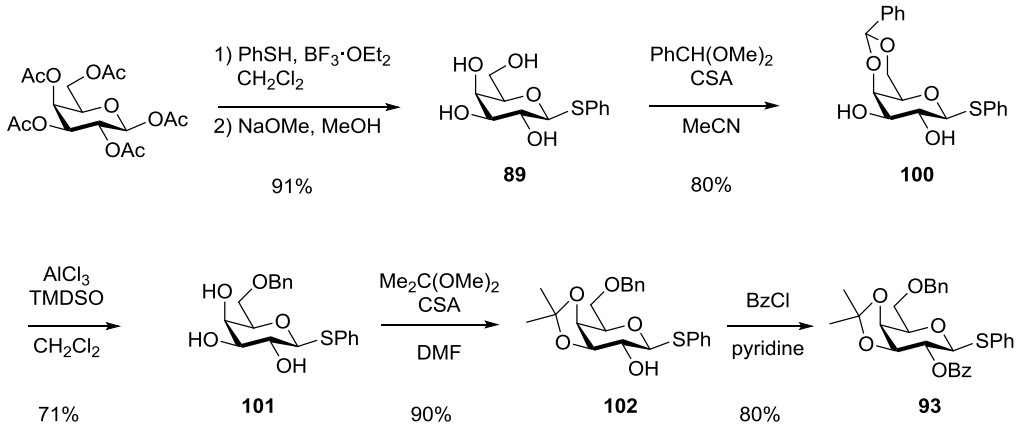
Scheme 3-13 shows the new synthesis strategy starting with these two new monosaccharide building blocks. The key TBDPS protected disaccharide **95** could, on one hand, be converted into a new disaccharide acceptor **97** after removal of the isopropylidene group under mild acidic conditions as for the previous strategy. On the other hand, it could also be transformed into a new disaccharide trifluoroacetimidate donor **96** after deprotection of TBDPS using a fluoride source. Following a blockwise strategy these two disaccharides **95** and **97** could then be coupled as previously to form an α-1,3 glycosidic linkage and reach the tetrasaccharide **98**.



Scheme 3-13. New synthesis strategy.

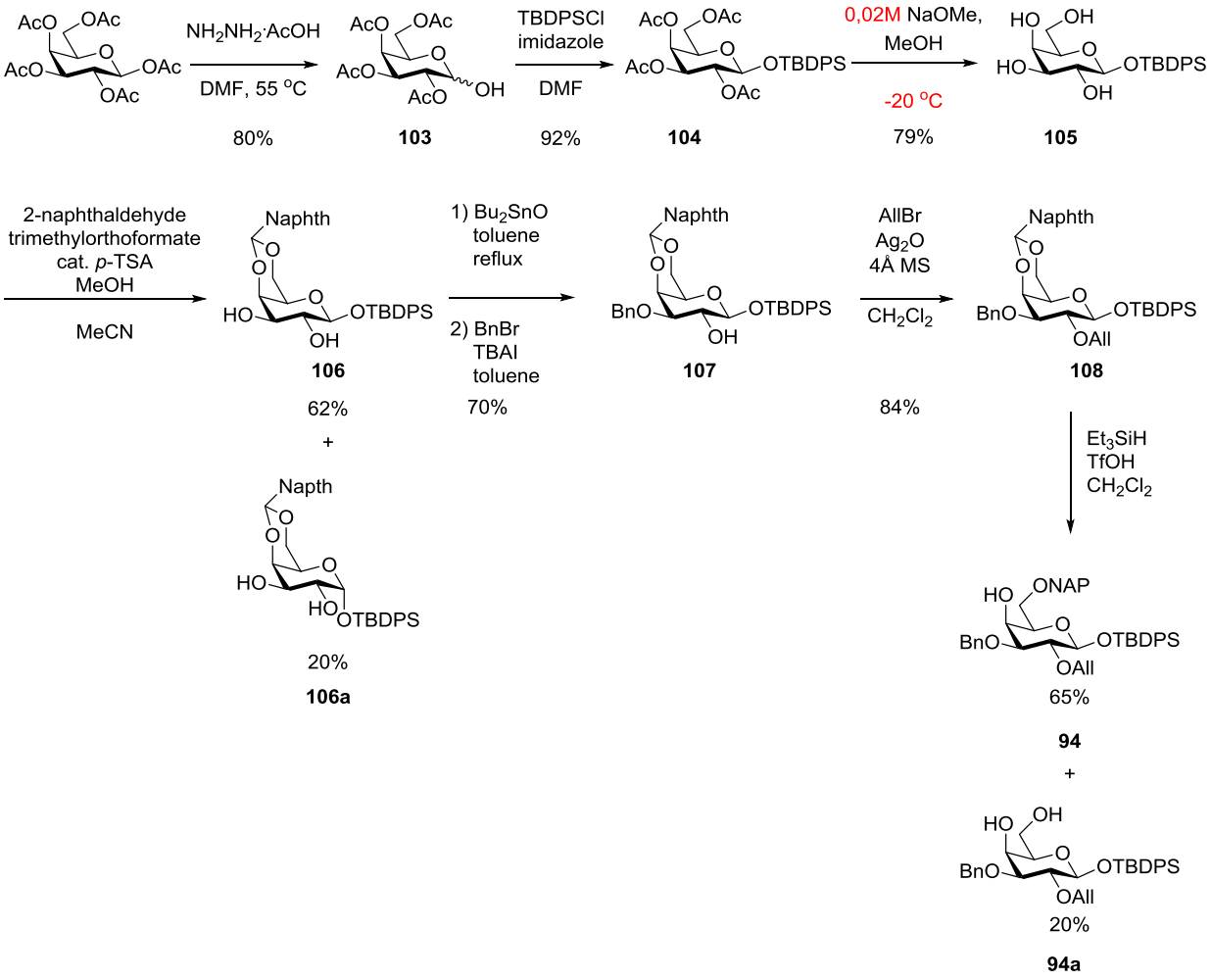
3.2.1 Synthesis of the monomeric building blocks

The synthesis of thiophenyl galactoside donor **93** is shown in Scheme 3-14. $BF_3 \cdot OEt_2$-mediated glycosylation of thiophenol with β-D-galactose pentaacetate followed by Zemplén deacetylation afforded the unprotected thiophenyl galactoside **89**. Treatment of this with benzaldehyde dimethylacetal and CSA gave the diol **100**. Regioselective reductive opening of the benzylidene acetal to give compound **101** was achieved in the same manner as in the previous strategy by treatment of **100** with aluminium trichloride and TMDSO. Acetalization of the C-3 and C-4 positions of **101** with 2,2 dimethoxypropane and CSA afforded the cis 5-membered ring acetal **102** in 90% yield. Benzoylation of the remaining hydroxy group using benzoyl chloride in pyridine afforded the fully protected thiogalactoside donor **93**.



Scheme 3-14. Synthesis of thiophenylgalactoside 93.

The synthesis of monosaccharide acceptor **94** followed the route shown in Scheme 3-15, starting with a selective anomeric deacetylation of galactose pentaacetate with hydrazine acetate in DMF affording hemiacetal **103** in 80% yield.[129] The anomeric center was further protected with a silyl ether by treatment with TBDPSCl and imidazole in DMF at 0 °C to give only the kinetic product, namely the β-anomer **104**. This time Zemplén deacetylation of the remaining acetyl groups had to be performed at low temperature and low concentration of sodium methoxide in methanol to avoid migration of the TBDPS group. As this protecting group is prone to migrate under both acidic and basic conditions, all the next steps had to be carried out under neutral conditions or with very low concentration of acid or base. Naphthylidene dimethylacetal was formed *in situ* by reacting 2- naphthaldehyde with trimethylorthoformate in methanol and a catalytic amount of *p*-TSA. This was used to acetalize the C-4 and C-6 positions of **105**. Unfortunately, isomerization of the starting material occurred during the reaction and the highest yield obtained was 62%. The presence of the α-anomer product **106a** was confirmed by NMR. This isomerization could be explained by the combination of a catalytic amount of acid and the known ability of silicon to stabilize β- carbocations such as the one present in the oxocarbenium ion formed by ring opening. Activation of diol **106** with Bu_2SnO followed by treatment with benzyl bromide in the presence TBAI gave the alcohol **107**. The identity of the product **107** was verified by HMBC.



Scheme 3-15. Synthesis of the acceptor 94.

The allylation step that followed was a bit more challenging as it had to be done under neutral conditions and therefore could not be performed through a standard Williamson ether synthesis. Instead a method developed by Sinou and co-workers derived from the well-known Tsuji-Trost reaction enables the introduction of allyl groups under neutral conditions with ethyl allyl carbonate and bis(dibenzylideneacetone)palladium(0) ($Pd_2(dba)_3$).[130] A summary of the allylation reaction conditions tested is presented in Table 3-6. Palladium catalyzed allylation (entry 1) yielded first the migrated product **108a** in 70% yield (characterized by NMR). This may be due to the production of a small amount of ethoxide during the catalytic cycle combined with the fast rate of migration of TBDPS. The reaction was repeated with addition of pyridinium *p*-toluenesulfonate (PPTS), used as a weak acid to neutralize the solution (entry 2). However, this time no formation of product was observed. Changing the allylating reagent to allyldiethylphosphate did not improve the outcome (entry 3). We finally decided to react **107** with silver oxide and allyl bromide and to our delight, this afforded the desired product **108** in 72% yield.

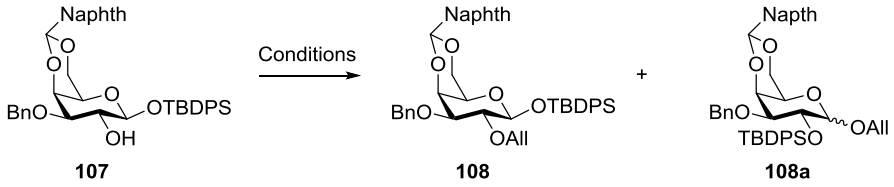
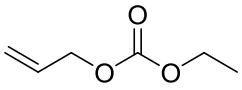
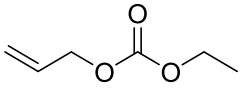
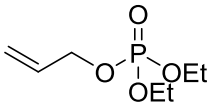
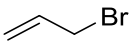


Table 3-6. Optimization conditions for the allylation.

Entry	Conditions	Outcome	
		108	**108a**
1	 $Pd_2(dba)_3$ dppb THF, 65 °C	-	+
2	 $Pd_2(dba)_3$ dppb PPTS as buffer THF, 65 °C	-	-
3	 $Pd_2(dba)_3$ dppb THF, 65 °C	-	-
4	 Ag_2O CH_2Cl_2 4Å MS 22 °C	+	-

The last step to get to the desired acceptor was a regioselective reductive opening of the naphthylidene group giving the NAP group on the C-6 position and the free 4-*OH*. This reaction was performed using triethylsilane (Et_3SiH) and triflic acid (TfOH) to afford the desired acceptor **94**. However, hydrolysis of the naphtylidene was also observed affording diol **94a** as major by product. (see Scheme 3-15)

3.2.2 Glycosylation step to get the key β-1,4 linked disaccharide

The results of the conditions tested for the first glycosylation are summarized in Table 3-7.
The glycosylation was first attempted with the NIS/TESOTf (A) promoter system which led to decomposition of the starting materials. As an addition of iodine to the double bond might occur, it was decided to switch to another thiophilic promoter. Several organosulfur-based activator systems are available for the "preactivation" of thioglycosides with an *in situ* formation of the reactive glycosyl triflate intermediate that can react with a wide range of acceptors.[128] Dimethyl disulphide-triflic anhydride (Me_2S_2/Tf_2O) promoter system (B) developed by Fügedi and co-workers[125] activates thioglycosides at low temperatures and can be prepared from non-expensive commercially available reagents. As the acid-lability of the isopropylidene protecting group had been an issue in the previous strategy, we first decided to try the reaction using 2,4,6-tri-*tert*-butylpyrimidine (TTBP), a non–nucleophilic and hindered base, to neutralize the solution (entry 2-4). Nevertheless, due to the very low reactivity of the acceptor no formation of product was observed until the temperature was raised to 0 °C and by-product **110a** was isolated and characterized by NMR. This by-product comes from an intramolecular reaction of the activated donor forming a 1,6-anhydro sugar and has been observed before.[131] It turned out that when omitting the TTBP the formation of this by- product was avoided. The separation by chromatography of the donor, acceptor and disaccharide was challenging and it was important to optimize the conditions to get full conversion of the donor. Finally, after varying the proportions of the donor, acceptor and promoter as well as the temperature and reaction time, the optimized conditions yielded the disaccharide **110** in 55% (entry 7), which was an acceptable yield taking the very poor reactivity of the acceptor into account.

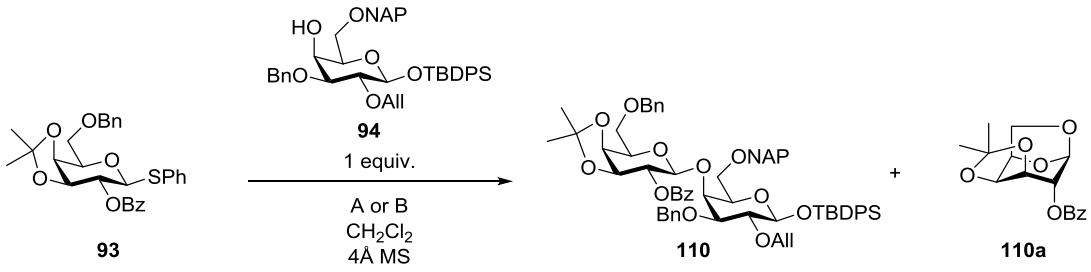
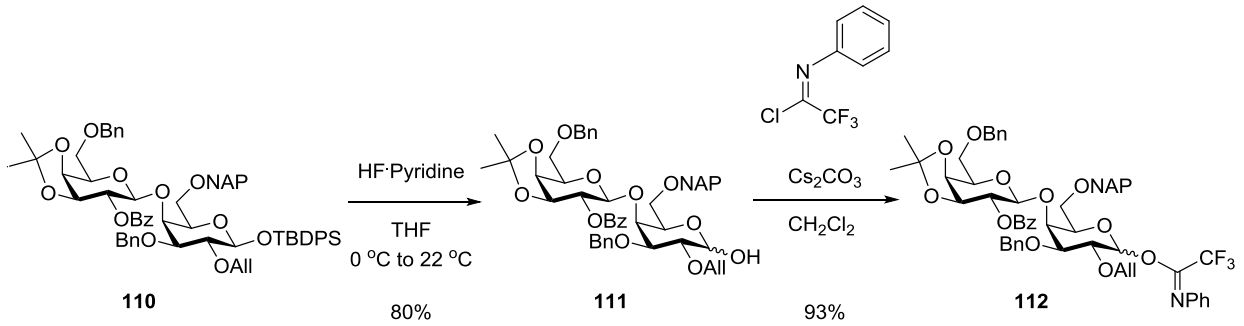


Table 3-7. Optimization conditions for glycosylation.

Entry	TTBP buffer	Donor (Equiv.)	A or B[a] (Equiv.)	Temp. (°C)	Time (h)	93 left	109 left	Yield 110 (%)	Yield 110a (%)
1	No	1.3	A	- 20 to -10	2	-	-	-	-
2	Yes	1.2	B (1.5)	- 40	4	+	+	-	traces
3	Yes	1.2	B (1.5)	- 20	2	+	+	< 10	traces
4	Yes	1.6	B (2.5)	0	0.5	-	+	30-50	20
5	No	1.6	B (2.5)	- 40	2	+	+	40-50	-
6	No	1.6	B (2.5)	- 40 to -20	2	-	-	-	-
7	No	1.3	B (2.5)	- 40	1	-	+	55	-

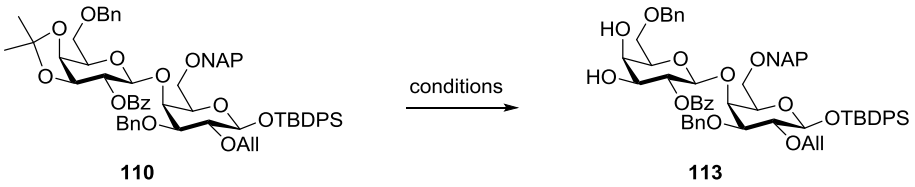
[a] A = NIS/TESOTf; B = Me_2S_2/Tf_2O

Disaccharide **110** could then be converted into both a donor and an acceptor. To derivatize the disaccharide into a new donor, the TBDPS protecting group of the anomeric center had to be hydrolyzed to give a cyclic hemiacetal. A new leaving group could then be installed at this unprotected anomeric position. Glycosyl trifluoroacetimidate was chosen because of its high reactivity and ease of synthesis as explained in 3.1.1. Deprotection of the anomeric TBDPS group was achieved in 80% yield by reacting disaccharide **110** with a HF·pyridine complex. Cyclic hemiacetal **111** could then be reacted with *N*-phenyl trifluoroacetimidoyl chloride in the presence of cesium carbonate to give the desired trifluoroacetimidate donor **112** in 93% yield (see Scheme 3-16).[132]



Scheme 3-16. To the trifluoroacetimidate donor 112.

Additionally, disaccharide **110** could be transformed into a new 3-*OH* acceptor by hydrolyzing the isopropylidene acetal (Table 3-8). As the axial 4-*OH* is supposed to be less reactive, we envisioned that it could remain unprotected during the glycosylation reaction. The hydrolysis was first tried using standard mild acidic conditions such as 80% acetic acid in water and adding dioxane as co-solvent to help the solubility (entry 1). Surprisingly, this did not hydrolyze the acetal at 22 °C and even when increasing the temperature and reaction time full conversion was not observed (entry 2). The reaction proceeded better when using a 1M aqueous HCl solution in methanol and dioxane and afforded the new acceptor **113** in 75% yield.



110 **113**

Table 3-8. Conditions to hydrolyze the isopropylidene acetal.

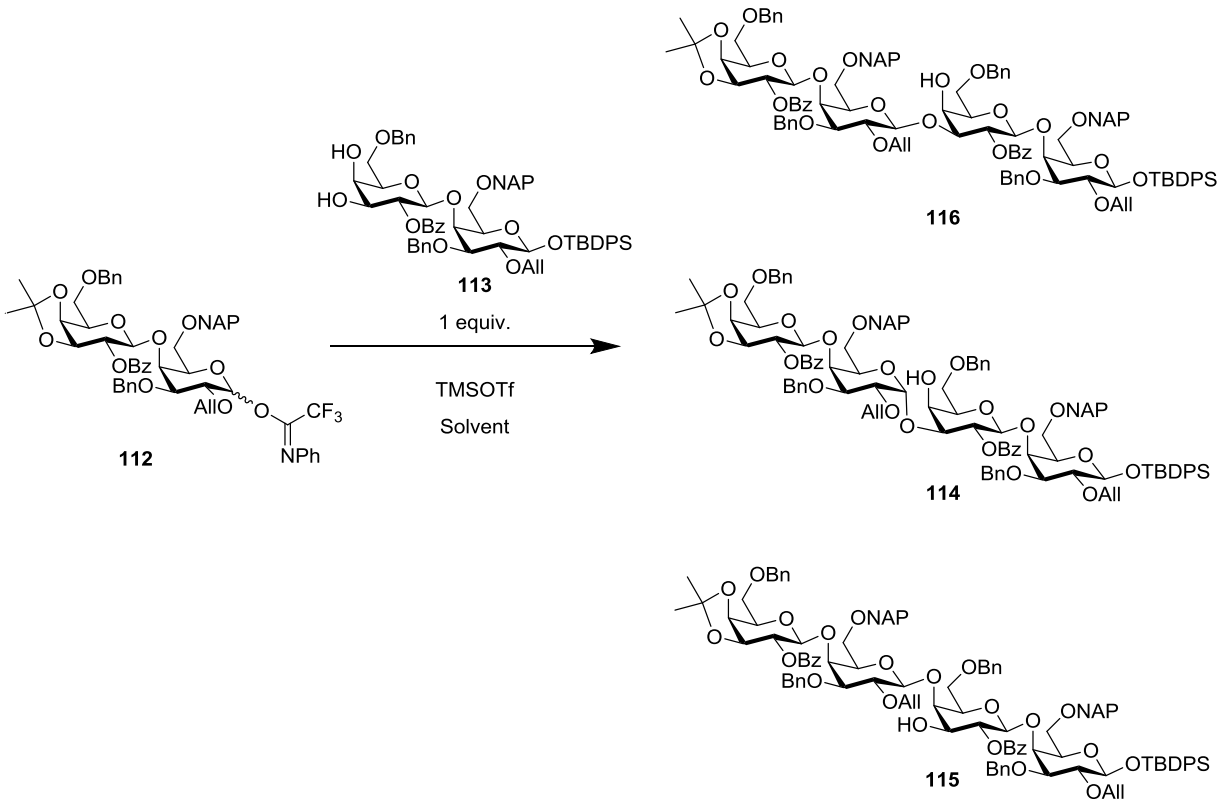
Entry	Conditions	Temperature (°C)	Time (h)	Yield (%)
1	$AcOH/H_2O$/dioxane 4/1/4	22	24	5
2	$AcOH/H_2O$/dioxane 4/1/4	60	48	56
3	1M HCl aq./methanol/dioxane	40	2	75

3.2.3 Attempt of synthesis of the key α-1,3 linked tetrasaccharide

With the new acetimidate disaccharide donor **112** and the free 3,4-*OH* disaccharide acceptor **113** in hand, a second glycosylation step could be performed. Relying on the higher reactivity of the equatorial 3-*OH* in comparison to the usually poor reactivity of the axial 4-*OH* of galactose, it was expected that the desired 3-linked regioisomer product would be favored. Furthermore, the stereoselectivity should be controlled by the combination of a non-participating allyl group at the second position of the disaccharide donor **112** and the anomeric effect enhancing α-selectivity.

Different glycosylation conditions were screened (see

Table 3-10) mainly affording the three isomers **114**, **115** and **116** in varying proportions Scheme 3-17.



Scheme 3-17. Glycosylation affording mainly the three regio- and stereoisomers 114, 115 and 116.

These isomers were characterized by NMR to identify the regio- and stereochemistry of the new linkage formed in each case. Thus, HMBC correlation between H-3' and C-1'' confirmed the 1-3 linkage formed for both product **114** and **116** while, in the case of **115**, a cross peak in the HMBC between H-4' and C-1'' showed the formation of a 1-4 linkage during the glycosylation step. To prove the stereochemistry observed for the three products, selected chemical shifts and coupling constants (*J*) for the new anomeric centers were analyzed as shown in Table 3-9.

Table 3-9. Characterization of 114, 115 and 116.

Product	$\delta_{C1''}$ (ppm) (^{13}C NMR)	$\delta_{H1''}$ (ppm) (^{1}H NMR)	$^{1}J_{C1'',H1''}$ (Hz) (from coupled HSQC)	$^{3}J_{H1'',H2''}$ (Hz) (from DQF-cosy)
114	95.6	4.62	169	4.8
115	104.9	4.26	160	10.5
116	104.7	4.42	160	10.0

According to Bock *et al.*[133] the one bond ^{13}C-^{1}H coupling constants in pyranoses is the most powerful tool to determine the anomeric configuration. Thus, for D sugars in the $^{4}C_1$ conformation, a $^{1}J_{C1,H1}$ of around 170 Hz indicates an α-anomeric sugar configuration whereas a $^{1}J_{C1,H1}$ of around

160 Hz indicates a β-anomeric sugar configuration. Furthermore, the ^{13}C chemical shift (δ_C) of the α-anomer is normally lower than the one of the β-anomer for D-pyranoses in $^4C_1$ conformation (in this case 95.6 ppm for **114** and around 105.0 ppm for **115** and **116**). Finally, the vicinal coupling constant between the anomeric H1 and the H2 ($^3J_{H1H2}$) indicates the relative orientation of the two protons. A smaller coupling constant is expected when these two protons are *cis* (corresponding to an α-anomeric configuration in the case of D-galactose) than *trans* (β-anomeric configuration in the case of D-galactose). The results shown in Table 3-9 match all these criteria supporting that the new glycosidic linkage formed in compound **114** is an α-linkage whereas the one in both compounds **115** and **116** are β-linkages.

In some of the conditions screened for the glycosylation, the formation of other by products was observed. However, the by-products without the isopropylidene protecting group were not fully characterized as they co-eluted with the hydrolyzed donor 111. Therefore, traces of a mixture of these products is marked as 112b in the

Table 3-10 summarizing attempts to optimize the reaction.

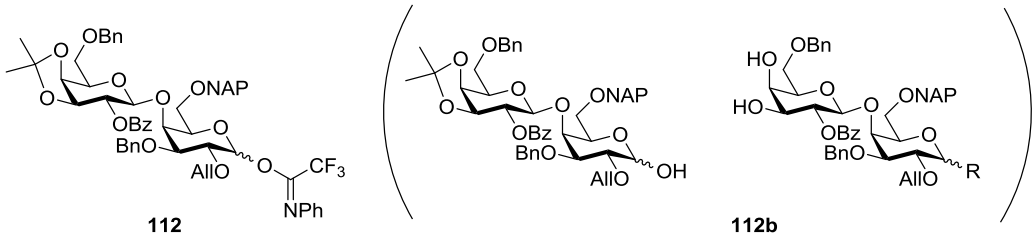


Figure 3-1. By products found during the glycosylation.

In all cases, TMSOTf was used as promoter. A first attempt of glycosylation was performed at -40 °C for 15 minutes using 1.2 equiv. of donor and 0.25 equiv. of promoter and gave a mixture of the three tetrasaccharide isomers, some hydrolyzed donor **111** and possibly some products without the isopropylidene group **112b** (entry 1). As it turned out to be very challenging to separate isomers **114** from **115** and **115** from **116** by flash chromatography, we next tried to avoid the formation of regioisomer **115** by decreasing the amount of donor and promoter (entry 2) and this seemed to be successful. However, some hydrolyzed donor **111** was still observed and therefore, the next choice was to add some molecular sieves to remove any traces of water present in the reaction mixture and reduce this common side reaction (entries 3 to 5). The aim was then to increase the stereoselectivity of the reaction. Some ether-type solvents, *i.e.* Et_2O, THF or dioxane, are found to have a participating effect in some glycosylation reactions leading towards the preferential formation of 1,2-*cis* glycosidic bonds as explained in Chapter 2.[115] Therefore, several attempts were done using Et_2O first, either alone or mixed with CH_2Cl_2 (entries 4 to 7). However, glycosylations in Et_2O are usually much slower than in CH_2Cl_2. Therefore, it turned out to be difficult to get the reaction to go to completion and in all these cases a significant amount of donor was recovered even when the amount of promoter and/or the temperature were increased (entry 7).

Table 3-10. Glycosylation conditions screened.

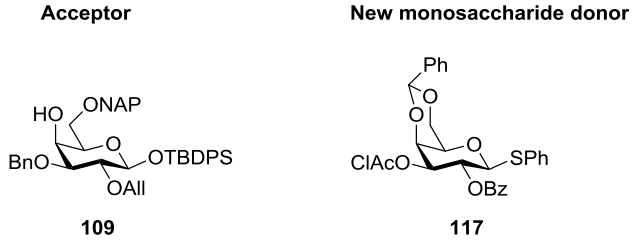
Entry	Donor[a] (Equiv.)	TMSOTf[a] (Equiv.)	Temp. (°C)	4 Å MS[b]	Solvent	Time	Outcome
1	1.2	0.25	- 40	-	CH_2Cl_2	15 min	**114**, **115**, **116**, **112b**[d]
2	1	0.1	- 40	-	CH_2Cl_2/Et_2O 1/1	25 min	**114**, **116**, **112b** [d]
3	1.2	0.25	- 40	+	CH_2Cl_2	15 min	**114** (10-30%) **115** (<10%) **116** (20%)
4	1	0.25	- 40	+	CH_2Cl_2/Et_2O 1/1	15 min	**114** (20%) **116** (45%)
5	1	0.25	0	+	Et_2O	20 min	**114** (10%) **116** (20%) **112**
6	1	0.25	0	-	Et_2O	90 min	**114** (10%) **116** (20%) **112** **112b**[d] (20%)
7	1	1	0-22	+	Et_2O	12 hours	**114**, **116**, **112**
8	1	0.5	0	+	toluene	30 min	**114** (20%) **116** (18%) **112**
9	1	0.5	22	+	dioxane	30 min	**114** (28%) **116** (13%) **112**, **112b**[d]
10	1	0.5	0	+	dioxane/Et_2O 1/1	75 min	**114** (40%) **116** **112**, **112b**[d]
11[c]	1	0.5	0	+	dioxane/Et_2O 1/1	2 hours	20% <**114**<60%[e] **116** **112**

[a]Molar ratio in respect to the acceptor. [b]Crushed 4 Å molecular sieves. [c]Add of 1 equiv. TTBP as buffer. [d]By-products defined in Figure 3-1. [e]Some product sticking to the column.

One attempt was even tried without molecular sieves as they are alkaline and therefore were thought to attenuate the reactivity but this resulted again in formation of hydrolyzed donor and deprotection of the isopropylidene group (entry 6). Switching to other solvent such as toluene or dioxane alone did not increase the yield of the desired product **114** (entries 8 and 9). As the melting point of dioxane is 11 °C, Et_2O was added as co-solvent to enable stirring at lower temperature (entries 10 and 11) and in the last attempt, TTBP was used to neutralize the reaction mixture and decrease the likelyness of isopropylidene deprotection. We figured out at that point that a portion of the products were not eluting properly from the column. After trying out different eluent systems without any satisfying results, we decided to move on to an easier strategy which would involve a 4-*O* protected disaccharide acceptor to avoid the possible formation of the 1,4-linked regioisomer by product (**115**) and make it easier to increase the relative amount of donor used to optimize the reaction conditions.

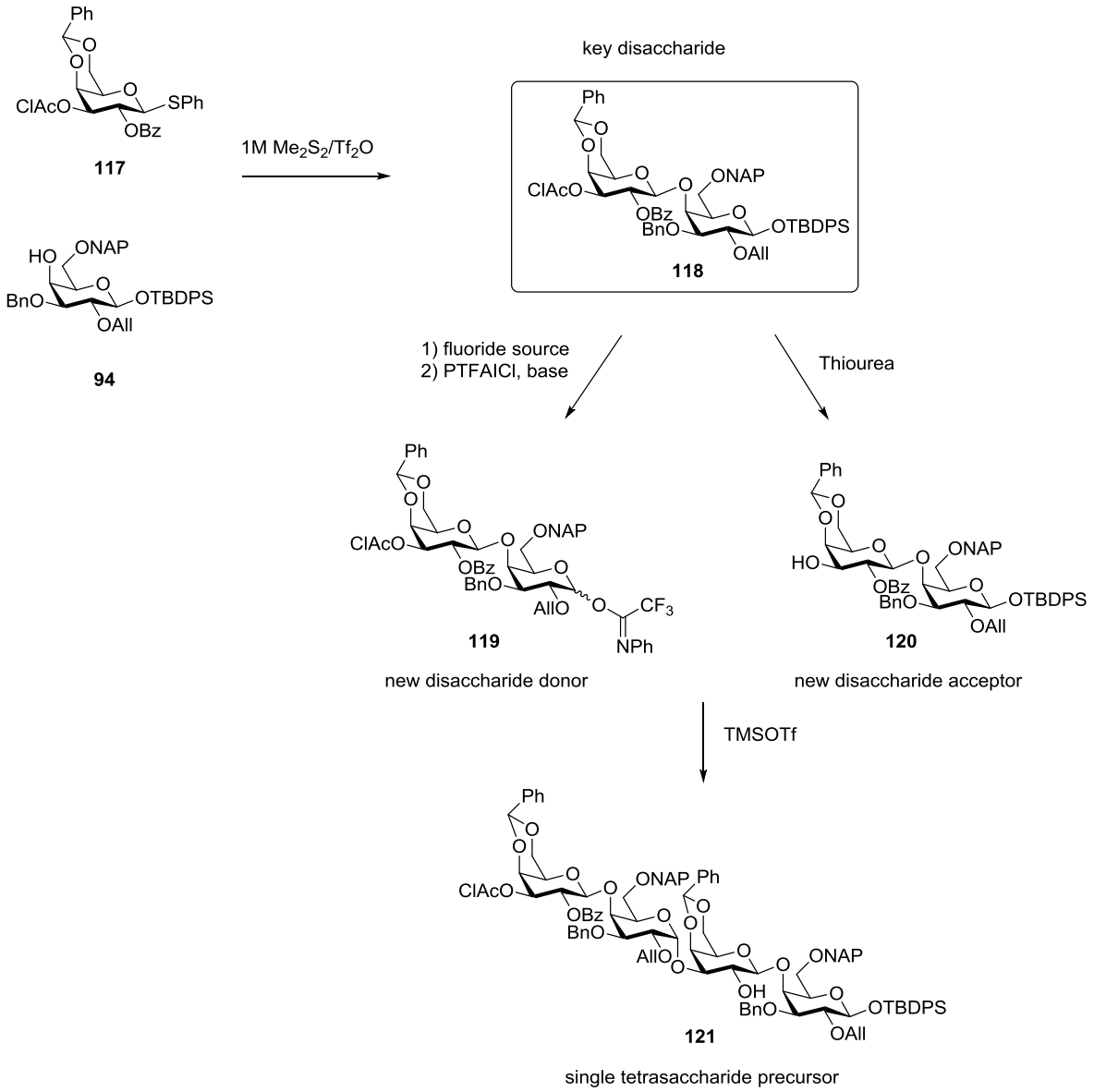
3.3 Third protecting group strategy

Whereas the monosaccharide acceptor **109** could be kept the same, a new monosaccharide donor had to be designed in order to fulfil the new requirement of a disaccharide acceptor, with a free 3-*OH* further in the synthesis (see Scheme 3-18).



Scheme 3-18. Monosaccharide building blocks.

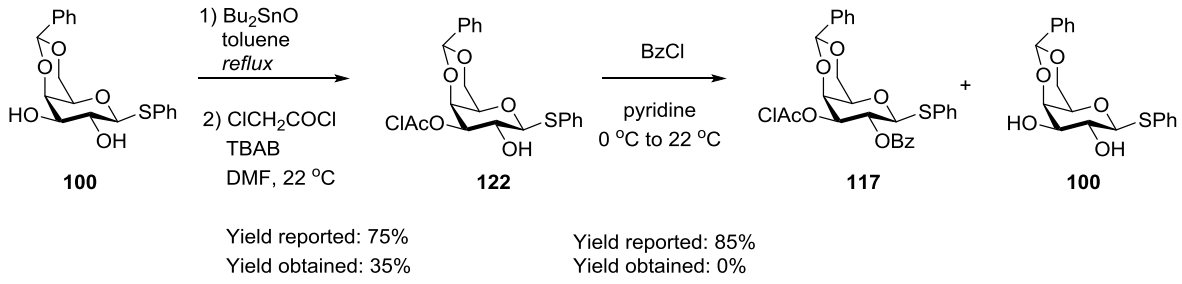
The ClAc group was chosen for temporary protection of the C-3 position since it can be selectively removed either with thiourea or under mild basic conditions.[134] The new synthetic strategy to get to the fully protected tetrasaccharide **121** is shown in Scheme 3-19 and very similar to the previous strategy shown in Scheme 3-13. The key disaccharide **118** will be converted into a new disaccharide donor **119** as previously and a new disaccharide acceptor **120** by selective removal of the chloroacetyl group. The following glycosylation step between both will afford the tetrasaccharide precursor **121** ready to be deprotected and sulfated in different order to get to the target molecules.



Scheme 3-19. New synthetic strategy.

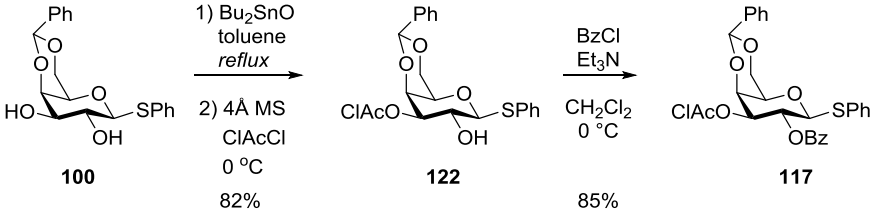
3.3.1 Synthesis of building block donor 117 and key disaccharide 118

The monosaccharide donor **117** was previously synthesized by T. Kanaya *et al.*[135] However, when following the same procedures starting from diol **100**, the yield of the regioselective chloroacetylation through the formation of a dibutyltin acetal intermediate was lower than reported. Furthermore, the benzoylation step used pyridine as solvent, which led to deprotection of the chloroacetyl group instead (see Scheme 3-20).



Scheme 3-20. First attempt to synthesize donor 117 following T. Kanaya .[135]

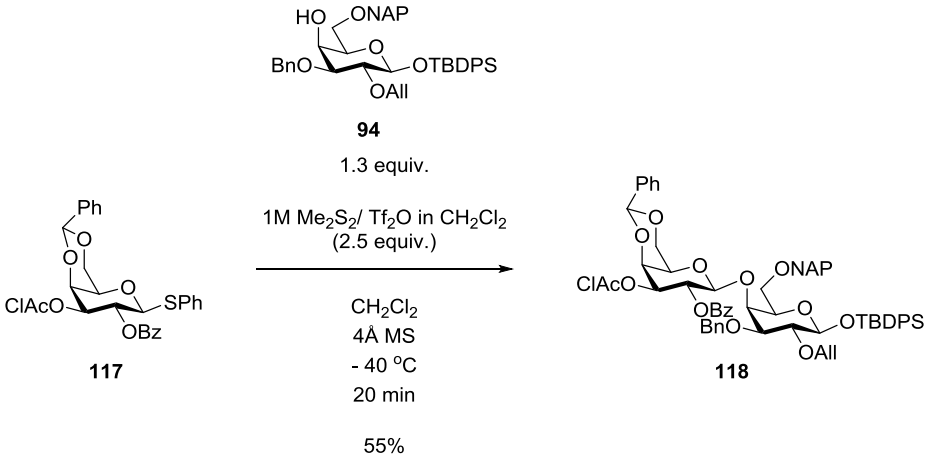
A second and more successful attempt was performed as shown in Scheme 3-21.



Scheme 3-21. Synthesis of building block 117.

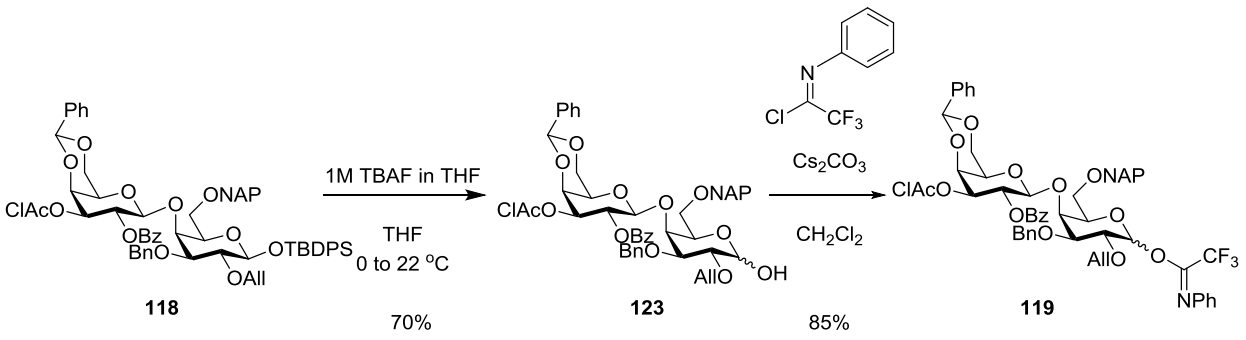
Thioglycoside **100** was regioselectively chloroacetylated via formation of the stannylene acetal with Bu_2SnO followed by treatment with chloroacetyl chloride and 4Å MS at 0 °C.[63] Benzoylation of the remaining unprotected hydroxyl group in dichloromethane at low temperature (0 °C) and using a stoichiometric amount of Et_3N afforded the desired fully protected thiogalactoside **117** in 85% yield.

The glycosylation between the new donor **117** and the acceptor **94** could then be performed using the optimized conditions previously found for the synthesis of disaccharide **110** as shown in Scheme 3-22, and afforded disaccharide **118** in 55% yield.



Scheme 3-22. Glycosylation to get the key disaccharide 118.

The conversion of disaccharide **118** into the corresponding trifluoroacetimidate donor was straightforward and done as previously described (see Scheme 3-23).



Scheme 3-23. Synthesis of trifluoroacetimidate donor 119.

Unfortunately, it turned out to be much more challenging to obtain the disaccharide acceptor by selectively removing the chloroacetyl protecting group (see Table 3-11).

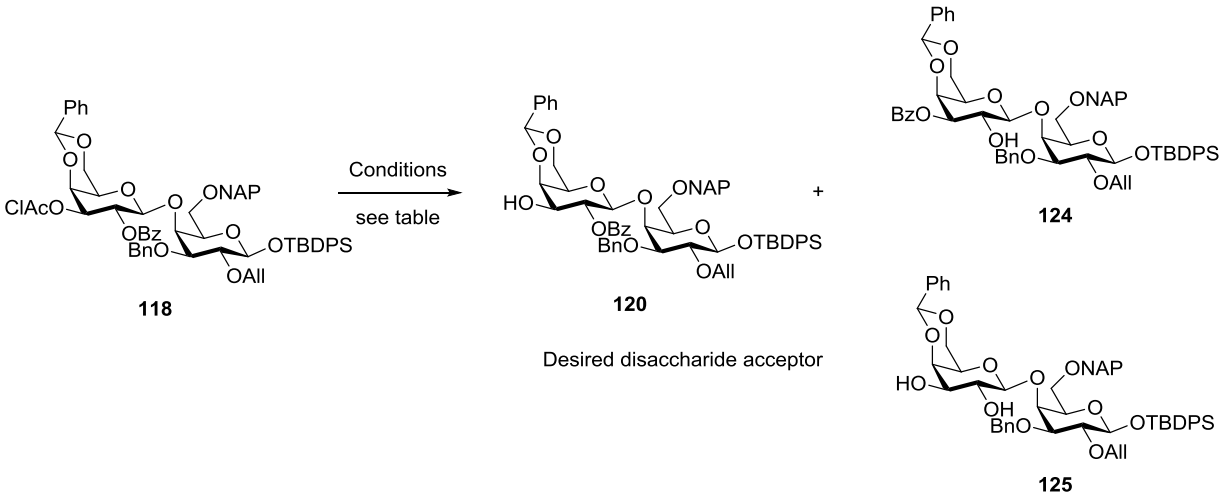


Table 3-11. Screening of different conditions to selectively remove the ClAc group.

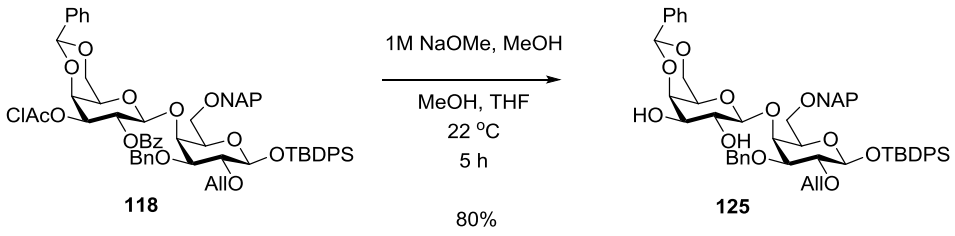
Entry	Conditions	Outcome[a]			
		120	**124**	**125**	**118**
1	Thiourea (3 equiv.), $NaHCO_3$ (3.5 equiv.), TBAI (0.2 equiv.) THF, 55 °C, 24 h	-	70%	-	+
2	Thiourea (5 equiv.) , THF, 22 °C,(12 h) to 55 °C (24 h)	-	+++	-	+++
3	Thiourea (5 equiv.), 2,6-lutidine (5 equiv.), DMF, 70 °C, 1 h	+	++	-	+++
4	DABCO (1 equiv. after 24 h add 12 equiv.), ethanol/THF 1:1, 22 °C	-	+++	-	+++
5	L-selectride (1M in THF), CH_2Cl_2, 0 °C, 2 h	20%	-	50%	+
6	L-selectride (1M in THF), CH_2Cl_2, -78 °C	-	-	-	+++
7	L-selectride (1M in THF), CH_2Cl_2, -40 °C	+	++	++	++
8	0.05M NaOMe in MeOH, 0 °C	+	-	+	++

[a] percentage indicates yield of reaction after purification by flash chromatographic while +/- indicates relative quantities estimated by TLC.

First, the removal of chloroacetyl group was tried by using the most common conditions, thiourea, $NaHCO_3$ and TBAI (entry 1).[134] However, this afforded mainly the migrated product **124**. An attempt to decrease the basicity of the solution by removing $NaHCO_3$ did not significantly change the outcome of the reaction (entry 2). A small improvement was observed when following the procedure given by H. Tanaka *et al.*[136] (entry 3). 1,4-Diazabicyclo[2.2.2]octane (DABCO) has

been previously used to cleave chloroacetyl protecting group,[137] nevertheless, no reaction occurred before adding a large excess of the reagent which led to the formation of mainly migrated product **124** (entry 4). Due to significant migration of the 2-*O*-acyl group under basic conditions, it was attempted to change the conditions more drastically and to remove the chloroacetyl by reduction (entries 5, 6 and 7). Li(*sec*-Bu)$_3$BH (L-selectride) was chosen as the reducing agent as it had given good results in our group previously and is less dangerous to use than superhydride.[138,63] Indeed, the corresponding borane is less volatile and therefore less likely to react with oxygen. Unfortunately, at 0 °C it was not possible to remove the chloroacetyl group selectively in the presence of the benzoyl group, resulting instead in diol **125** as the major product (entry 5). Hoping for higher selectivity, the temperature was lowered, but at -78 °C no reaction occurred (entry 6). Performing the reaction at -40 °C did not give any selectivity. A last attempt of selective deprotection using Zemplén conditions however modified by decreasing both the concentration of NaOMe and the temperature did not give satisfying result either.

At this point, we decided to deprotect both acyl group under Zemplén conditions (see Scheme 3-24). The obtained diol **125** would be used further as disaccharide acceptor in the next glycosylation, hoping that the 3-position would be more reactive than the more sterically hindered 2-position and, therefore afford the right regioisomer.

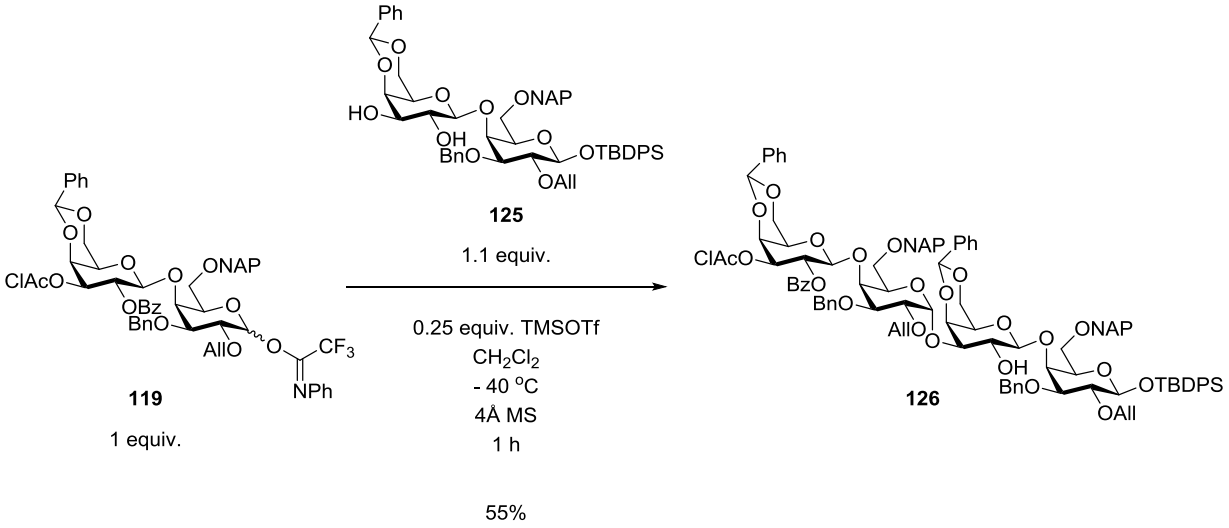


Scheme 3-24. Deprotection of acyl groups under Zemplén conditions.

3.3.2 Synthesis of key the α-1,3 linked tetrasaccharide

The glycosylation between disaccharide donor **119** and the diol disaccharide acceptor **125** could in principle lead to four different tetrasaccharide isomers, two regioisomers and each of them could be produced as two diastereoisomers (α- and β-linked). Furthermore, hexasaccharides could also be produced. Thus, we decided to use a small excess of acceptor **125** (1.1 equiv) to hopefully avoid the formation of hexasaccharides with selectivity for one regioisomer of the tetrasaccharides. We were dependent on one of the hydroxyl groups being more reactive than the other. The conditions used are presented in the Scheme 3-25 and afforded tetrasaccharide **126** in a surprisingly good yield (55%) taking into account the number of possible products. As previously, the stereo- and regiochemistry of the new glycosidic linkage were confirmed by 2D NMR experiments. Indeed,

HMBC correlations proved the 1-3 linkage while both ^{13}C and ^{1}H chemical shifts of the new anomeric center and coupling constants supported the α-stereochemistry of the newly formed bond (see Table 3-12).



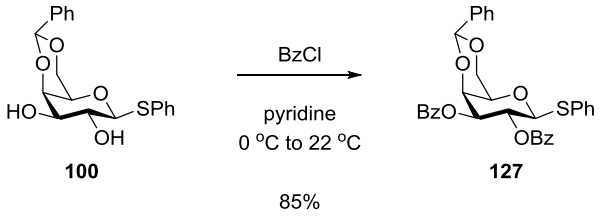
Scheme 3-25. Glycosylation to get the α-1,3 linked tetrasaccharide 126.

$\delta_{C1''}$ (ppm)	$\delta_{H1''}$ (ppm)	$^{3}J_{H1'',H2''}$ (Hz)	$^{1}J_{C1'',H1''}$ (Hz)
92.2	5.33	5.5	168

Table 3-12. NMR data of the new glycosidic linkage.

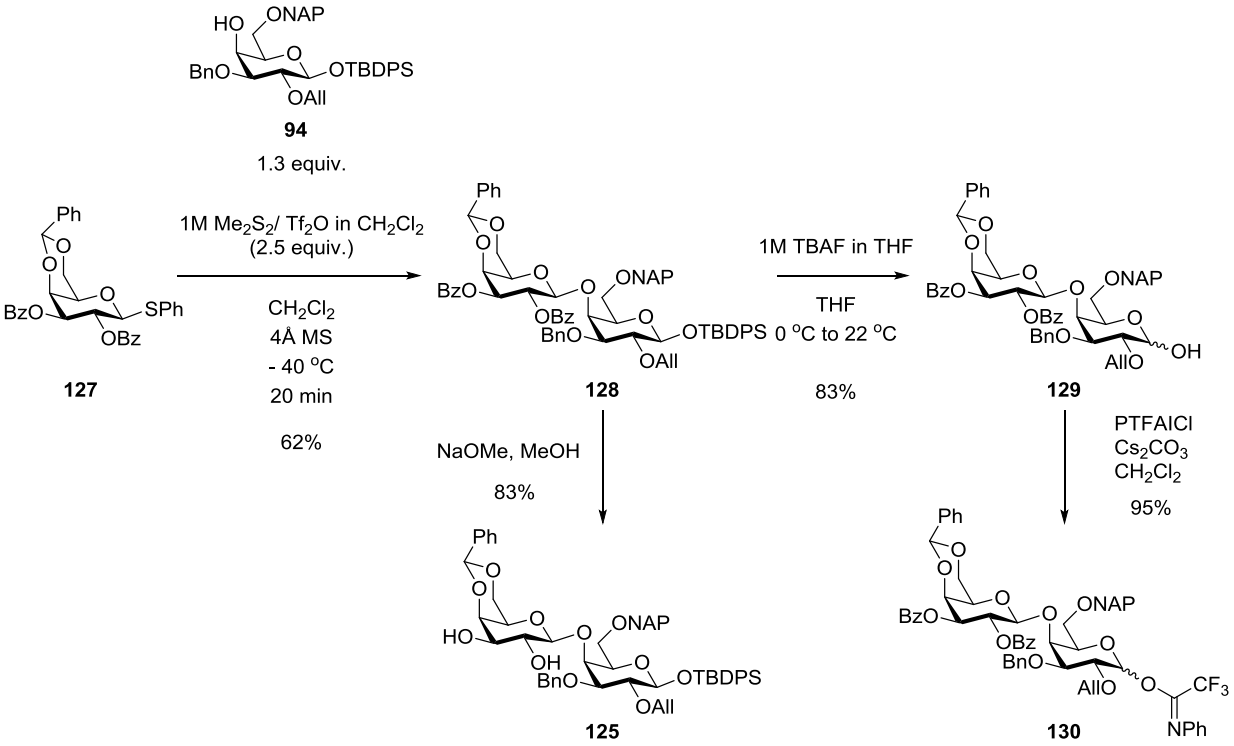
Not much time was left at that point to optimize the conditions for this glycosylation and therefore we decided to move on to the subsequent steps.

As this glycosylation unexpectedly worked out quite well, regioselective deprotection of the C-3' position of **118** was no longer required and a simpler dibenzoylated monosaccharide building block donor was synthesized as shown in Scheme 3-26.



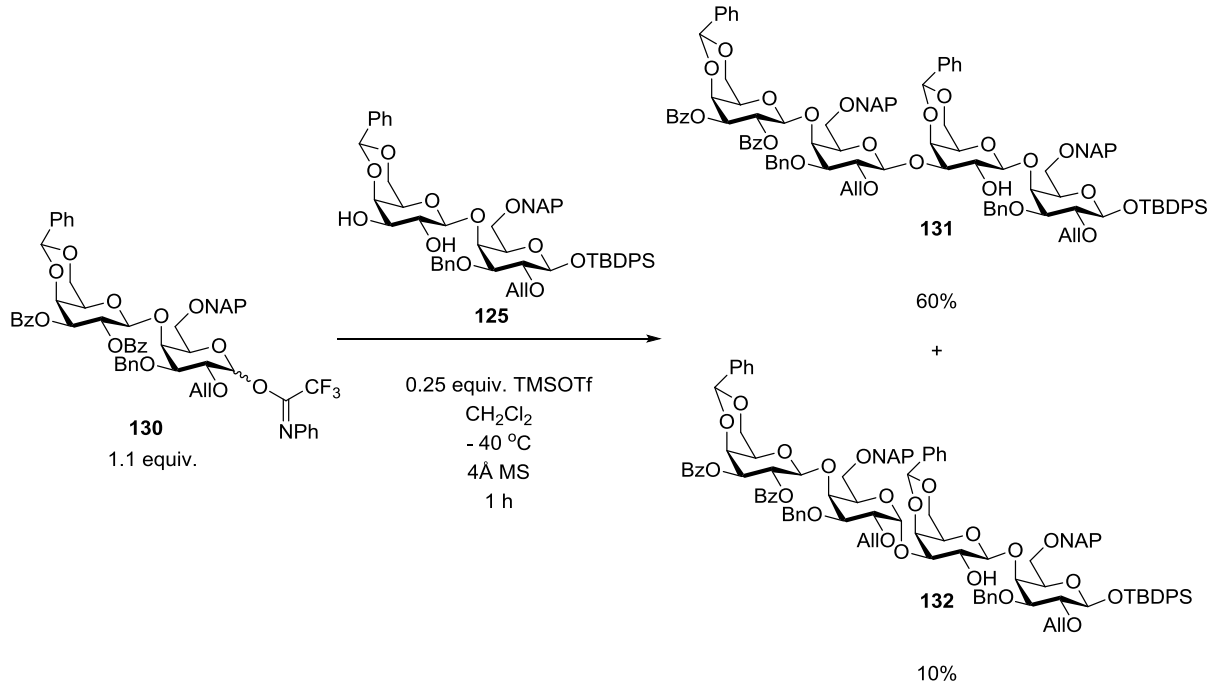
Scheme 3-26. Synthesis of monosaccharide donor 127.

Similar procedures starting from monosaccharide donor **127** and monosaccharide acceptor **94** could then be performed to get to the new trifluoroacetimidate disaccharide **130** and disaccharide acceptor **125**. (Scheme 3-27). A slightly better yield was obtained for the first glycosylation step using the new dibenzoylated thiophenylgalactoside donor (62% versus 55%).



Scheme 3-27. From monosaccharide building block 127 to disaccharide donor 130 and disaccharide acceptor 125.

Unexpectedly, the glycosylation between donor **130** and acceptor **125** did not proceed as well as with the previous chloroacetylated donor **119** (See Scheme 3-28).



Scheme 3-28. Glycosylation to get the tetrasaccharide 132.

Using the identical reation conditions, only 10% of the desired α-1,3 linked tetrasaccharide **132** was obtained, whereas the major product formed was the corresponding stereoisomer **131** (60% of β-1,3 linked product). This unpredictable outcome highlights the importance of protecting groups for glycosylation and demonstrates how, even remote, subtle differences can dramatically affect reactivity and stereoselectivity.

The tetrasaccharide **126** shown in Figure 3-2 was therefore chosen as precursor for all the target molecules.

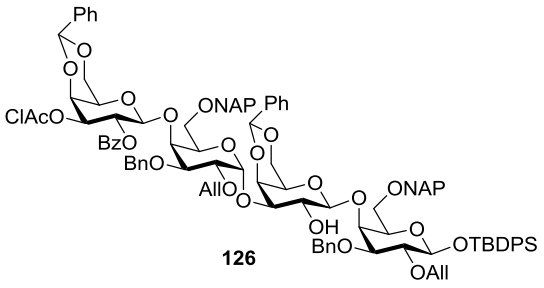
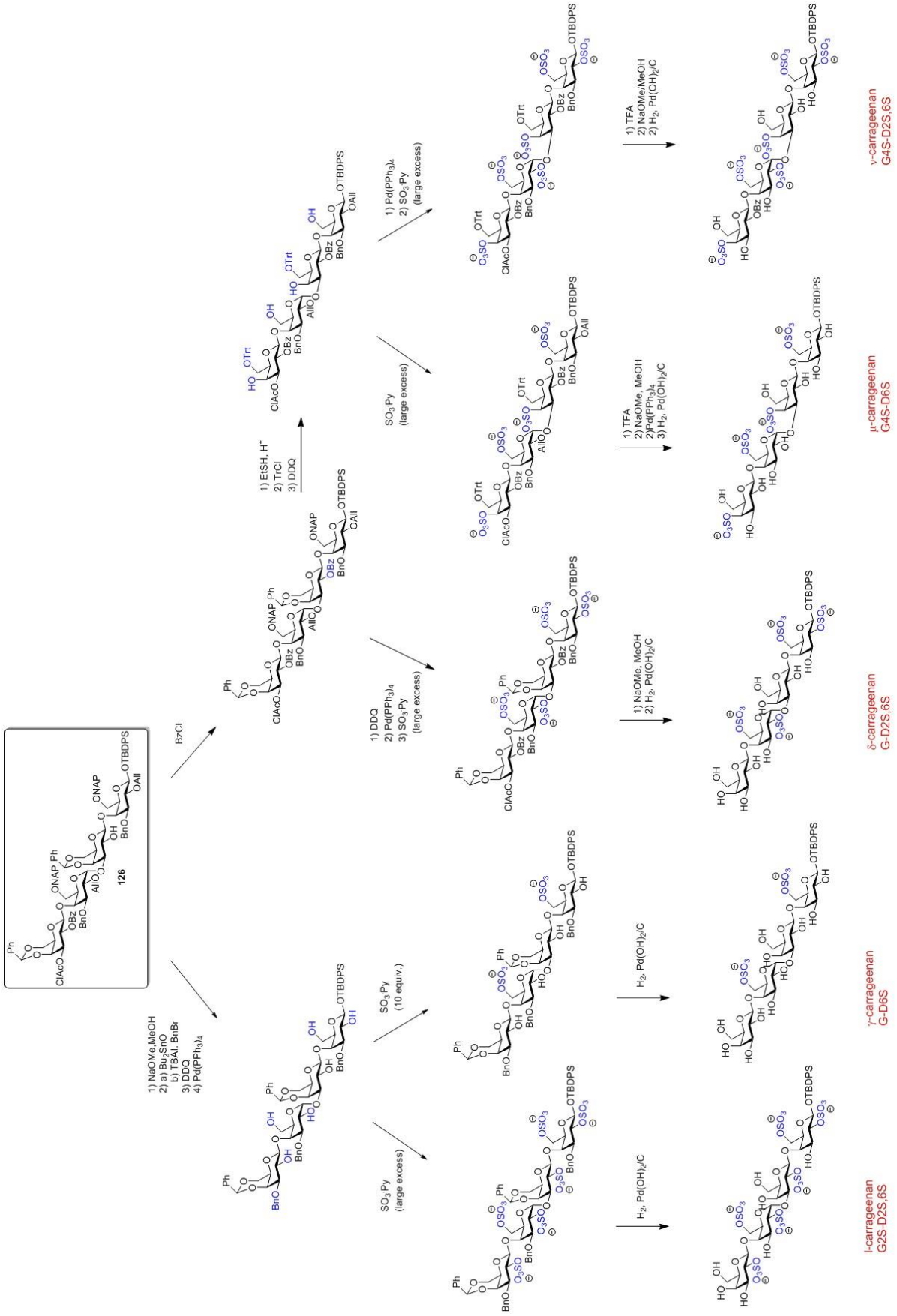


Figure 3-2. Protected tetrasaccharide precursor 126 of all targets molecule.

3.3.3 Investigation of deprotection and sulfation steps

With the protected tetrasaccharide **126** in hand it was believed to be possible to prepare the five D6S carrageenans by applying 6 to 9 additional steps to regioselectively deprotect some positions and introduce sulfate groups at these unprotected positions depending on the targeted carrageenan as shown in the following Scheme 3-29. The sulfation step and following deprotection were mostly inspired by the work of Boons *et al.* related to heparin synthesis.[96,97]

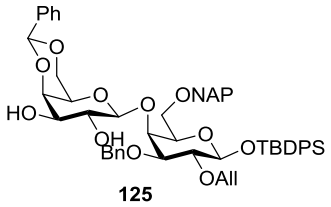
As explained in section 0, the NAP group and allyl group were chosen for their ability to be selectively removed by DDQ and palladium tetrakis ($Pd(PPh_3)_4$) respectively and were placed at positions where sulfation was eventually required. In the same manner, the benzylidene protecting group can be cleaved selectively under acidic conditions. In some cases, one more protecting step is needed prior to sulfation. For example, the C-3'''position of the tetrasaccharide has to be protected to arrive at carrageenans G2S-D2S,6S and G-D6S. Therefore, after Zemplén deprotection of the chloroacetyl and the benzoyl protecting groups, a regioselective benzylation of that position *via* the formation of a tin acetal could be performed. In the case of carrageenans G4S-D6S and G4S-D2S,6S, positions C-6' and C-6''' need to be protected before the sulfation step. Due to steric demands, trityl groups are easy to install selectively on primary alcohols in the presence of secondary alcohols, and therefore, this could be a wise choice of protecting group, which could later be removed under acidic conditions. Zemplén conditions would remove the remaining esters after sulfation while the last hydrogenation step would cleave the remaining benzyl and benzylidene protecting groups depending on the target.



Scheme 3-29. Deprotection and sulfation strategy.

3.3.3.1 Preliminary test experiments on disaccharide 125.

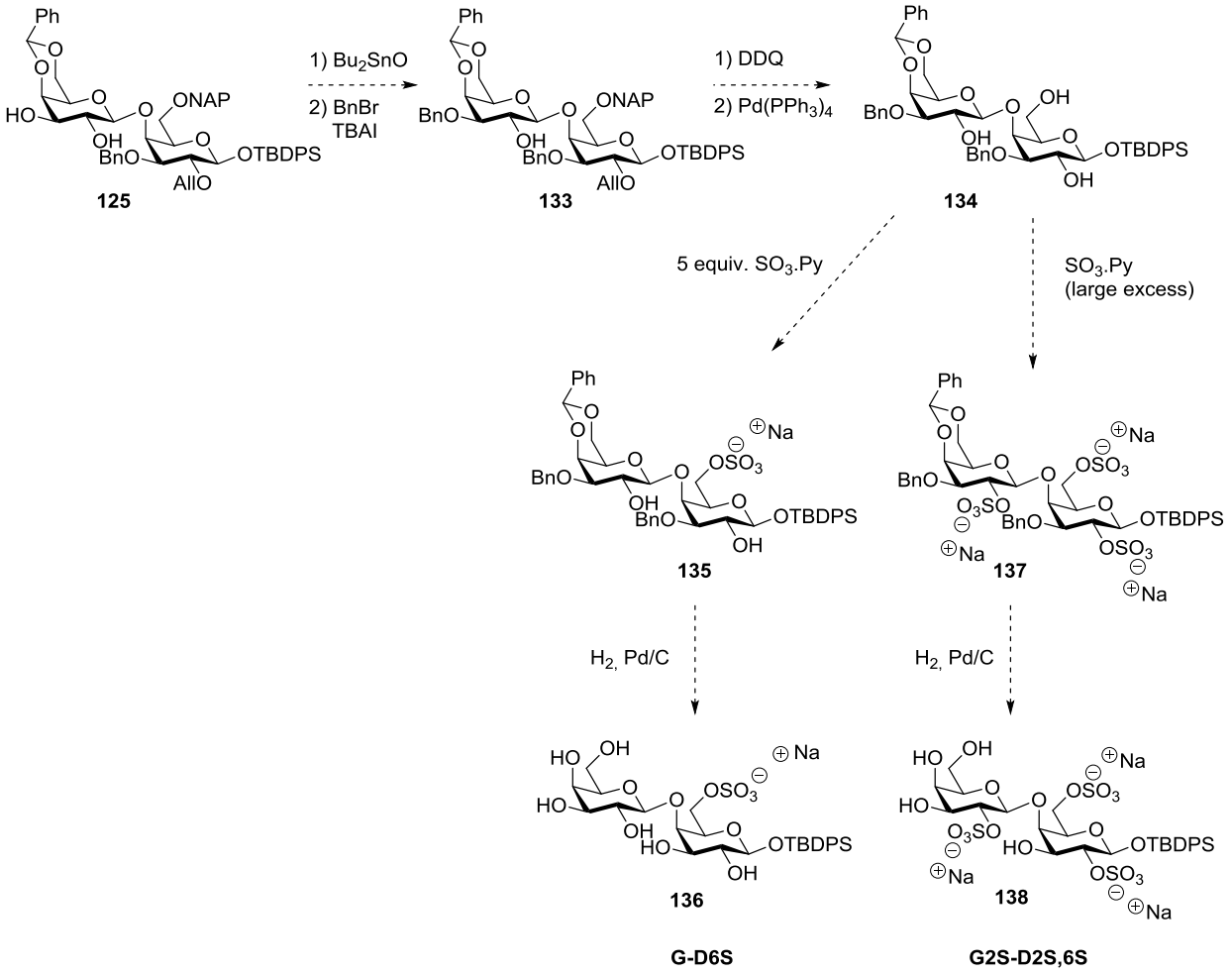
To ensure that the different selective deprotection steps would work and in order to get experience with the sulfation reaction, we decided to first perform some experiments with disaccharide **125** (Scheme 3-30) as it should have more or less the same reactivity and behaviour as the similarly protected tetrasaccharide **126**, in theory.



125

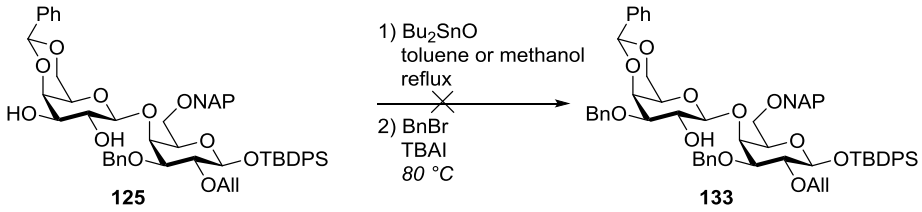
Scheme 3-30. Disaccharide 125 used as test substrate.

The first idea was to synthesize the λ-carrageenan disaccharide (G2S-D2S,6S) and see if a selective sulfation of the C-6 position in the presence of other secondary free hydroxy groups would be feasible to get γ-carrageenan (G-D6S) as shown in Scheme 3-31. A selective benzylation of the C-3' position followed by deprotection of the NAP group and the allyl group would give triol **134** ready for sulfation. Then, sulfation either of the C-6 position or of all remaining free hydroxy groups would afford respectively disaccharides **135** and **137** ready to be hydrogenated and give the desired products G2S-D2S,6S and G-D6S.



Scheme 3-31. Synthesis strategy to get to (G2S-D2S,6S) and (G-D6S) disaccharides.

The first step of the synthesis, namely stannylene-promoted regioselective benzylation of the diol **125**, did not proceed as expected with most of the starting material recovered. It was thought that the stannylene acetal formation was the limiting step due to the possible presence of water in the reaction mixture. Therefore more attempts were done to get as dry conditions as possible by adding 4 Å molecular sieves, changing solvent from toluene to methanol and drying the vessels more carefully, but none of them gave any satisfying result (Scheme 3-32).



Scheme 3-32. Unsuccessful regioselective benzylation.

Even though the benzyl protecting group would have been the wisest choice of protecting group to keep the number of deprotection step at a minimum, we needed to find another protecting group. As regioselective acylation of this position has been performed before, we chose a benzoyl group as new protecting group. However, several attempts needed to be performed before getting the desired regioselectivity as shown in Table 3-13.

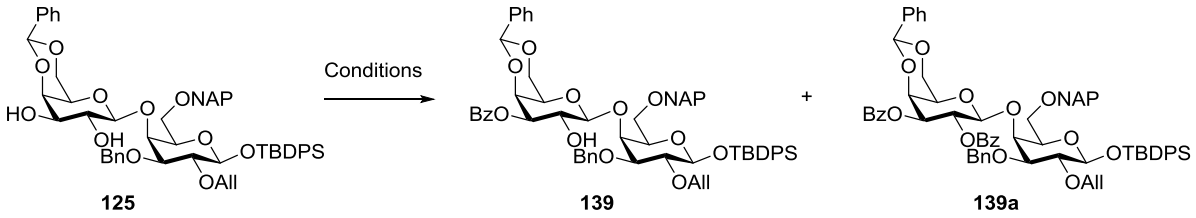


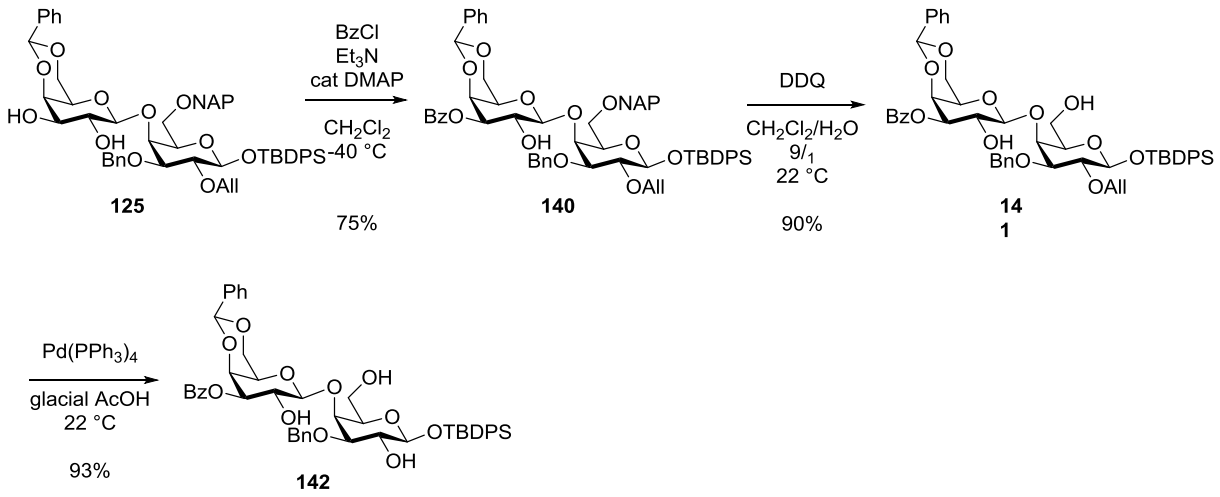
Table 3-13. Conditions tested for the regioselective benzoylation of diol 125.

Entry	Conditions	Outcome[a]		
		139	**125**	**139a**
1	BzCl (1.1 equiv.), pyridine (1.1 equiv.), CH_2Cl_2, -40 °C, 4 h	30%	50%	20%
2	BzCl (1.2 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, -40 °C, 4 h	+	+++	-
3	BzCl (1.2 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, 0 °C	++	++	+
4	BzCl (1.2 equiv.), Pyridine, 0 °C, 24 h	++	++	-
5	BzCl (1.1 equiv.), Et_3N (1.2 equiv.), cat. DMAP CH_2Cl_2, -40 °C	75%	-	15%

[a] percentage indicates yield of reaction after purification by flash chromatographic while +/- indicates relative quantities estimated by TLC.

Relying on the higher reactivity of the C-3' position as compared to the C-2' position, the regioselective benzoylation was first tried following Mandal *et al.*'s procedure, using pyridine as a base and performing the reaction in dichloromethane at -40 °C (entry 1).[139] However, the dibenzoylated adduct **139a** was formed in almost the same quantity as the desired product **139** and therefore some other conditions had to be screened. Finally, by adding a catalytic amount of DMAP and performing the reaction at low temperature in dichloromethane in the presence of a stoichiometric amount of triethylamine, the regioselectivity improved and the yield of the reaction increased to 75% (entry 5).

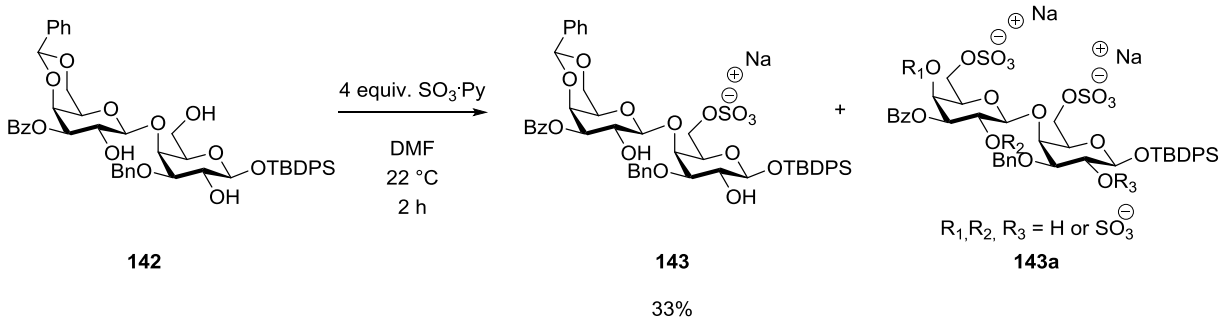
The triol **142** precursor of the sulfation could then be synthesized as shown in Scheme 3-33.



Scheme 3-33. Synthesis of triol 142 from disaccharide 125.

The 6-*O*-NAP protecting group was selectively cleaved by oxidation using DDQ in a good yield (90%).[140] Selective removal of the allyl group using palladium tetrakis finally led to triol **142** notably without migration of the TBDPS group or anomerization.

The first sulfation attempt was done by following a procedure often used in the synthesis of heparan sulfate oligosaccharides by Boons *et al.* (see Scheme 3-34).[97,141]

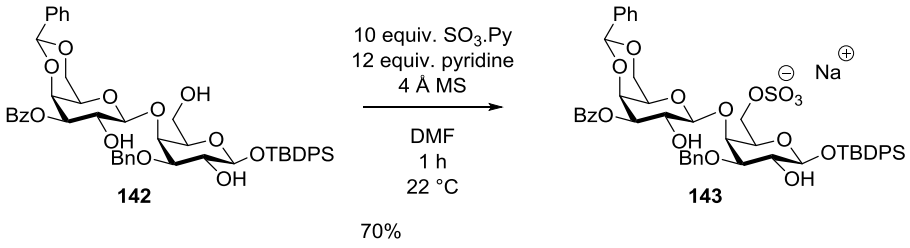


Scheme 3-34. First attempt of selective sulfation of the 6-position by using 4 equiv. of SO_3·Py complex.

A lower amount of SO_3·Py complex was used in our case in order to sulfate the C-6 position selectively. However, due to acid lability of the benzylidene protecting group, some by-products without benzylidene protecting group were isolated. The conditions needed to be optimize to quench any traces of acid and water present in the reaction mixture in order to avoid this side-reaction.

Therefore, we decided to add 4 Å MS as well as a few equivalents of pyridine to the reaction mixture and this afforded the monosulfated disaccharide **143** in 70% yield. (see Scheme 3-35). The sulfate ester at the C-6 position was identified by a downfield shift of the corresponding carbon

(~ 8 ppm) and protons (~ 0.5 ppm). According to previous syntheses of heparin oligosaccharides a downfield shift of ring protons H-2 and H-2' close to 1 ppm would indicate the formation of sulfate ester at the C-2 positions.[142,100] As the chemical shift of H-2 and H-2' did not change, we concluded that sulfation at these two positions did not occur.



Scheme 3-35. Optimized conditions for the selective sulfation.

Sulfation of all three hydroxyl groups turned out to be much more challenging than expected. First of all, as the polysulfated molecules are very polar, it was difficult to follow the reaction properly. It was however possible to follow the disappearance of the starting material as well as the presence of monosulfated adduct **143**. The idea was, therefore, to get full conversion of both of these before purifying the reaction mixture. The different conditions attempted are presented in Table 3-14. Several attempts were done using the same reagents as for the selective sulfation but a larger excess of sulfating agent (30 equiv. entry 1 and 60 equiv. entries 2 and 3 respectively). Neither adding more equivalents of reagent, nor increasing the temperature to 55 °C changed the amount of starting material and monosulfated adduct left in the reaction mixture significantly. To explain this observation, it was hypothesized that the C-2 positions were too sterically hindered to react with the sulfating agent (and especially C-2' position). Indeed, the C-2'position had previously shown a very low reactivity in the glycosylation to obtain the tetrasaccharide **126** (Scheme 3-25). Furthermore, one of the challenges of polysulfation is the repulsive intramolecular forces created by the sulfate groups which can make it difficult to drive the reaction to completion as explained by Al-Horani *et al.*.[82] Therefore, a more reactive sulfating agent might be needed to form the sulfate esters on these positions and further optimization remains to be done.

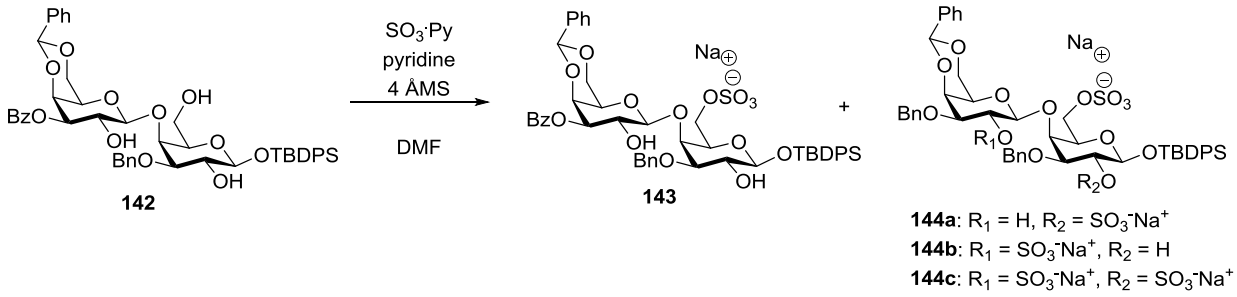


Table 3-14. Conditions tried for the full sulfation of triol disaccharide 142.

Entry	Reagents	Temp. (°C)	Time (h)	Outcome[a] 142	Outcome[a] 143
1	SO_3·Py (30 equiv.) pyridine (35 equiv.)	22	24	+	++
2	SO_3·Py (60 equiv.) pyridine (65 equiv.)	22 to 55	48	+	++
3	SO_3·Py (60 equiv.) pyridine (65 equiv.) DMAP (1 equiv.)	22 to 55	48	+	++

[a] Relative quantities estimated by TLC.

To get to the desired G-D6S disaccharide **136**, monosulfated disaccharide **143** could then be deprotected. First debenzoylation under Zemplén conditions was performed as shown in Table 3-15.

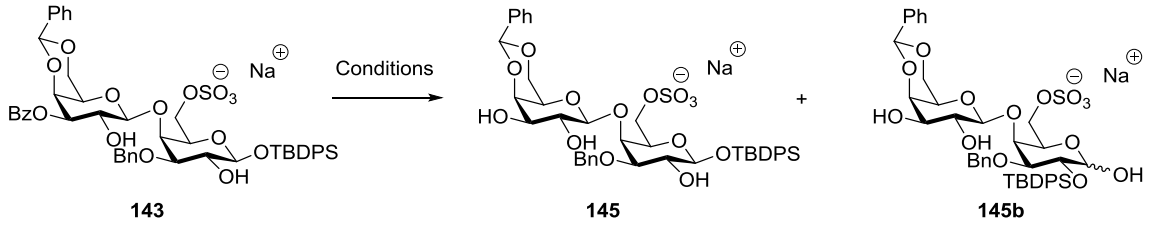
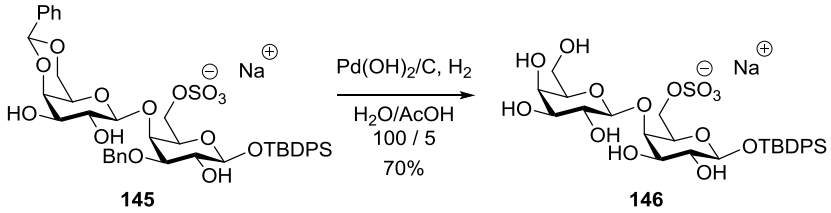


Table 3-15. Debenzoylation of monosulfated disaccharide 143.

Entry	Conditions	145 (%)	145b (%)
1	1 M NaOMe/MeOH in MeOH, 22 °C, 2 h	20	60
2	0.04 M NaOMe/MeOH in MeOH, -20 °C, 48 h	70	-

Due to fast migration of the TBDPS group, cleavage of the benzoyl group under standard Zemplén conditions afforded mostly the migrated hemiacetal product **145b**. (entry 1). Repeating the reaction at lower concentration of sodium methoxide and lower temperature solved the problem and gave the desired triol **145** in 70% yield (entry 2). Optimization of the concentration to decrease the reaction time would be advantageous.

The final step was a hydrogenation to get the unprotected monosulfated disaccharide following Boons's procedure.[97] A catalytic amount of acetic acid was added to decrease the reaction time and hopefully avoid deprotection of the sulfate group as this has been experienced in the heparin oligosaccharides synthesis when longer reaction times were necessary (see Scheme 3-36).[100] Both benzylidene and benzyl groups were successfully removed using these conditions without affecting the sulfate group.

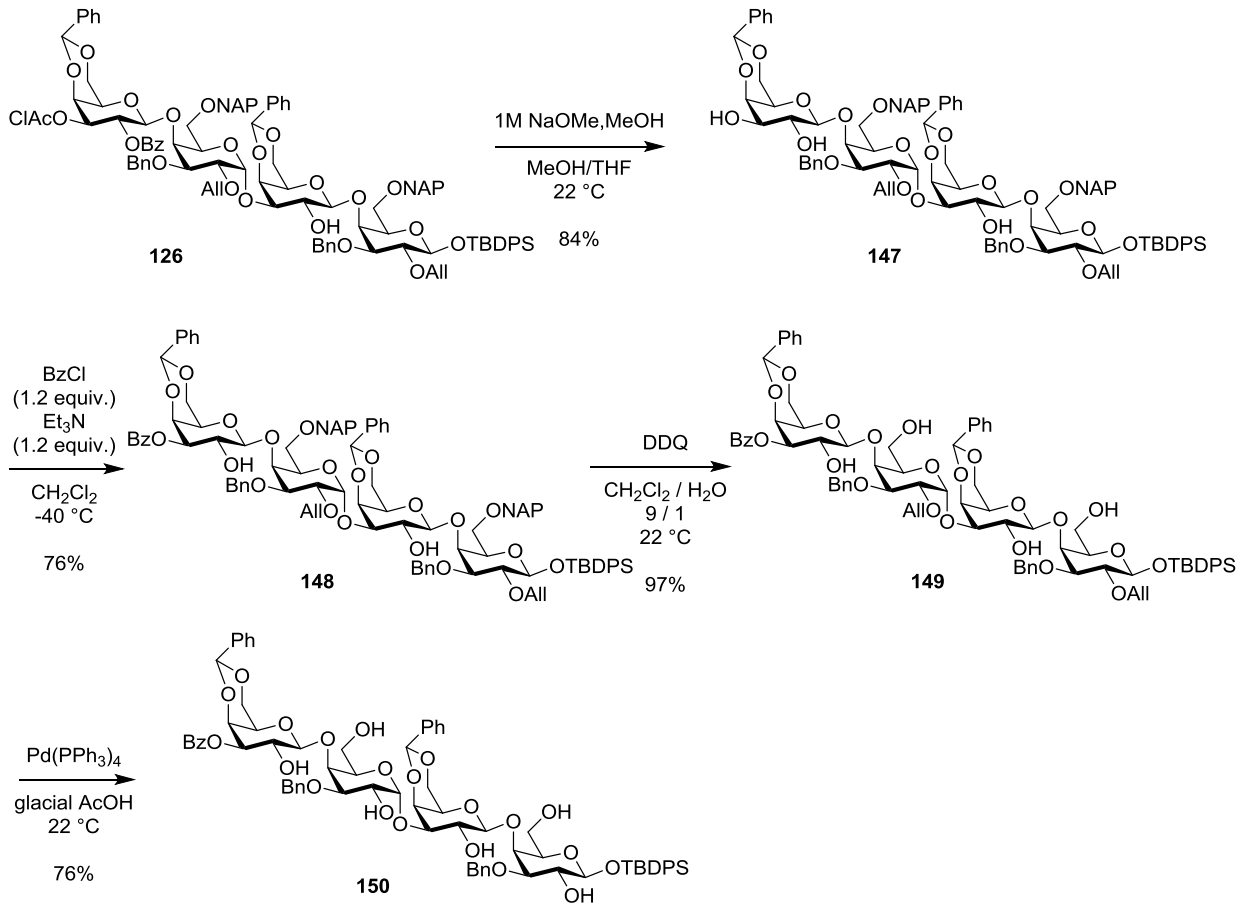


Scheme 3-36. Hydrogenation to get the unprotected monosulfated disaccharide G-D6S.

3.3.3.2 Deprotection and sulfation steps to afford G-D6S tetrasaccharide

As the different deprotection and sulfation steps were optimized on the model disaccharide **125** and afforded G-D6S disaccharide in a good overall yield, these procedures were translated to the protected tetrasaccharide **126** to afford ι-carrageenan tetrasaccharide (G-D6S). The deprotection steps prior to sulfation were achieved as shown in Scheme 3-37.

First, deprotection of the two acyl group under Zemplén conditions afforded diol tetrasaccharide **147**. Regioselective benzoylation of the free C-3''' position under the conditions optimized for the disaccharide analogue gave the monobenzoylated adduct **148** in 76% yield. Oxidative cleavage of the NAP groups using DDQ, followed by deallylation with $Pd(PPh_3)_4$ afforded tetrasaccharide **150** in excellent yield ready for the sulfation step.



Scheme 3-37. Deprotection steps on tetrasaccharide 126.

The conditions optimized for the selective sulfation on disaccharide **142** needed to be adapted to enable disulfation of tetrasaccharide **150** as shown in the following Table 3-16.

The first attempt was performed by starting with 5 equiv. of the SO_3·Py complex and 6 equiv. of pyridine (entry 1). According to TLC analysis, a lot of starting material remained after 2 hours and therefore the same amounts of both reagents were added. TLC did not show any significant improvement after additional two hours and therefore, the same was repeated one more time. The reaction did not go to completion and was quenched after 8 hours and purified by flash chromatography. Some starting material was recovered and a mixture of monosulfated adduct **151a** and the desired disulfated tetrasaccharide **151** was obtained. A second experiment was started by adding more reagent from the beginning (12 equiv. of SO_3·Py) and after adding 10 more equiv. later, the reaction went to completion. The product was obtained in 60% yield and only a small amount of monosulfated adduct was isolated (10%). We have not repeated yet this experiment to confirm its reproducibility and the final optimization remains to be done.

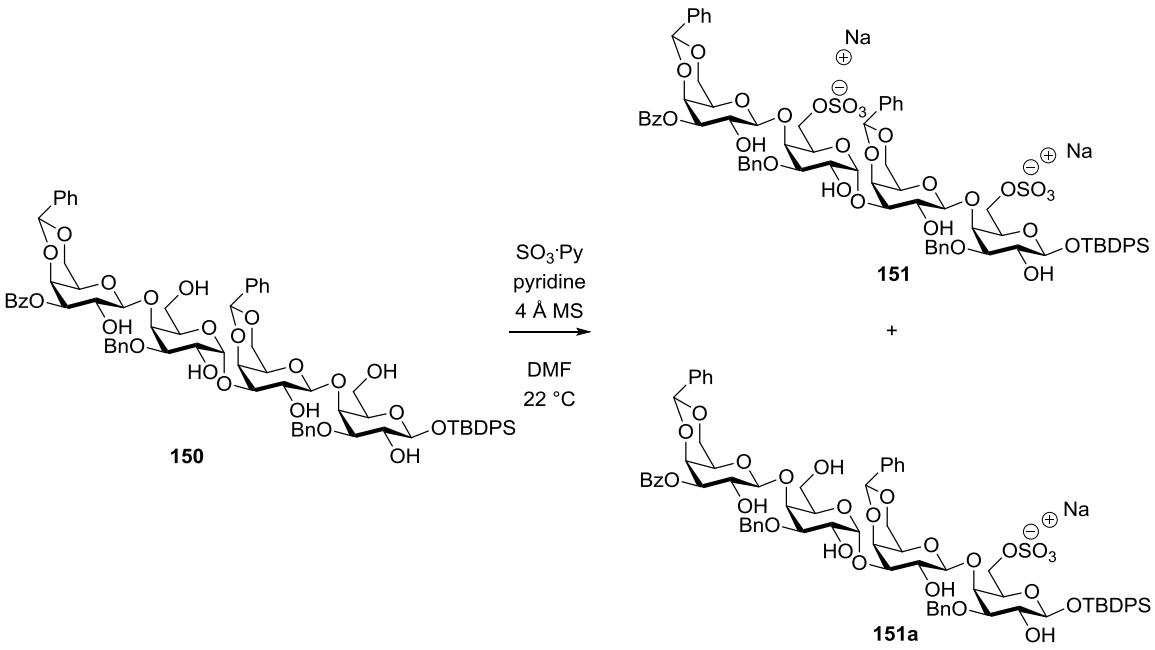


Table 3-16. Conditions tried for the selective sulfation of the C-6 positions.

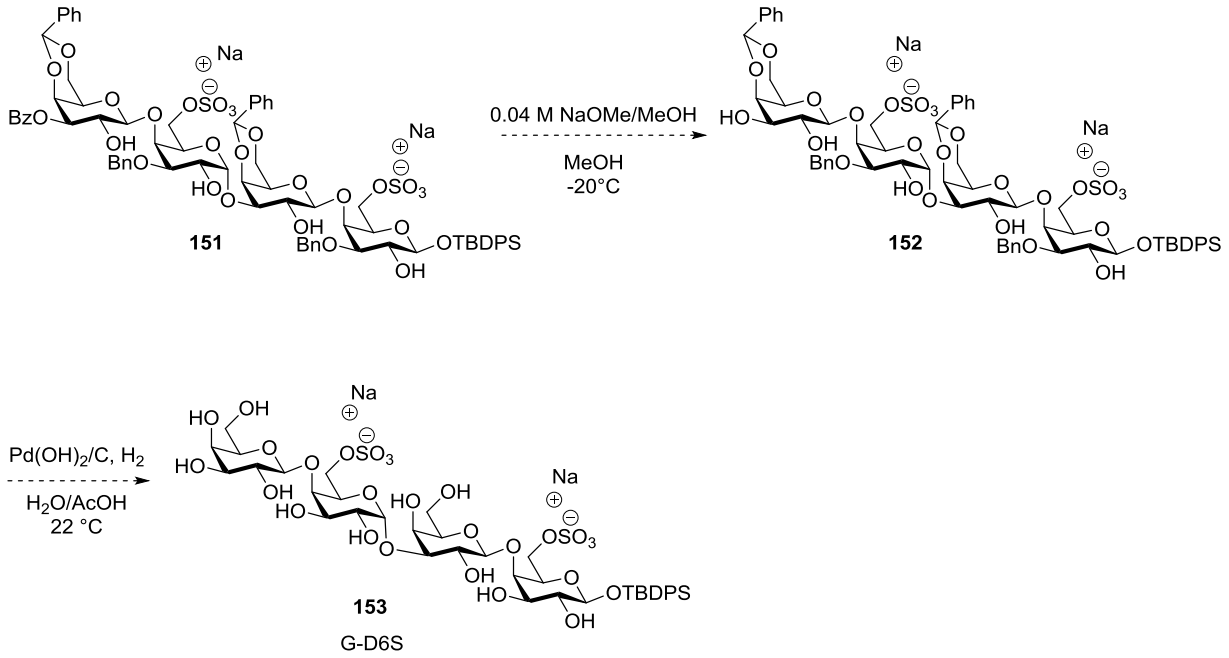
Entry	Reagents	Time (h)	Outcome[a] 150	151	151a
1	SO_3·Py (15 equiv. added in 4 times over 5 h) pyridine (18 equiv. added in 4 times over 5 h)	8	+	++	++
2	SO_3·Py (22 equiv. in 2 times over 2 h) pyridine (24 equiv.in 2 times over 2 h)	3	-	60%	10%

[a] percentage indicates yield of reaction after purification by flash chromatographic while +/- indicates relative quantities estimated by TLC.

Unfortunately, due to small amount of **151** we were not able to perform the debenzoylation and hydrogenation on this disulfated tetrasaccharide to reach the target molecule. However we note that conditions appear to translate well from disaccharide to tetrasacharide.

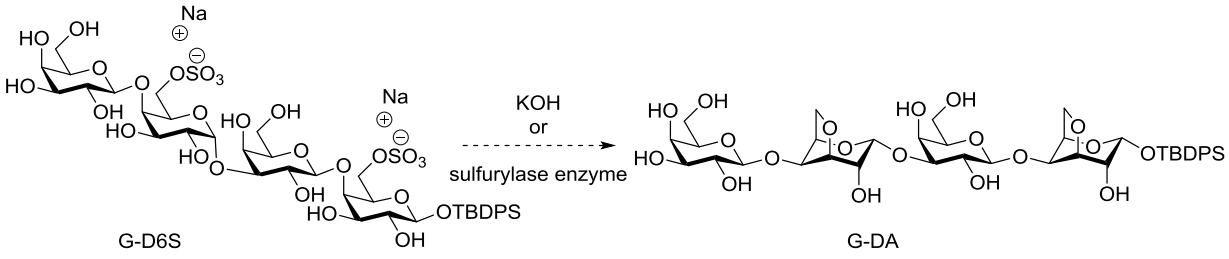
3.4 Future perspectives

After synthesizing some more of the disulfated tetrasaccharide **151**, deprotection of the ester as well as hydrogenation following the conditions tested on disaccharide **143** remain to be done to get the desired G-D6S tetrasaccharide as shown in Scheme 3-38.



Scheme 3-38. Synthesis of the G-D6S tetrasaccharide target.

The formation of the 3,6-anhydro ring could then be tested on the G-D6S tetrasaccharide to synthesize the corresponding G-DA tetrasaccharide (β-carrageenan) either by using an alkaline solution or through enzymatic conversion as shown in Scheme 3-39.[35,37,40,42,43]

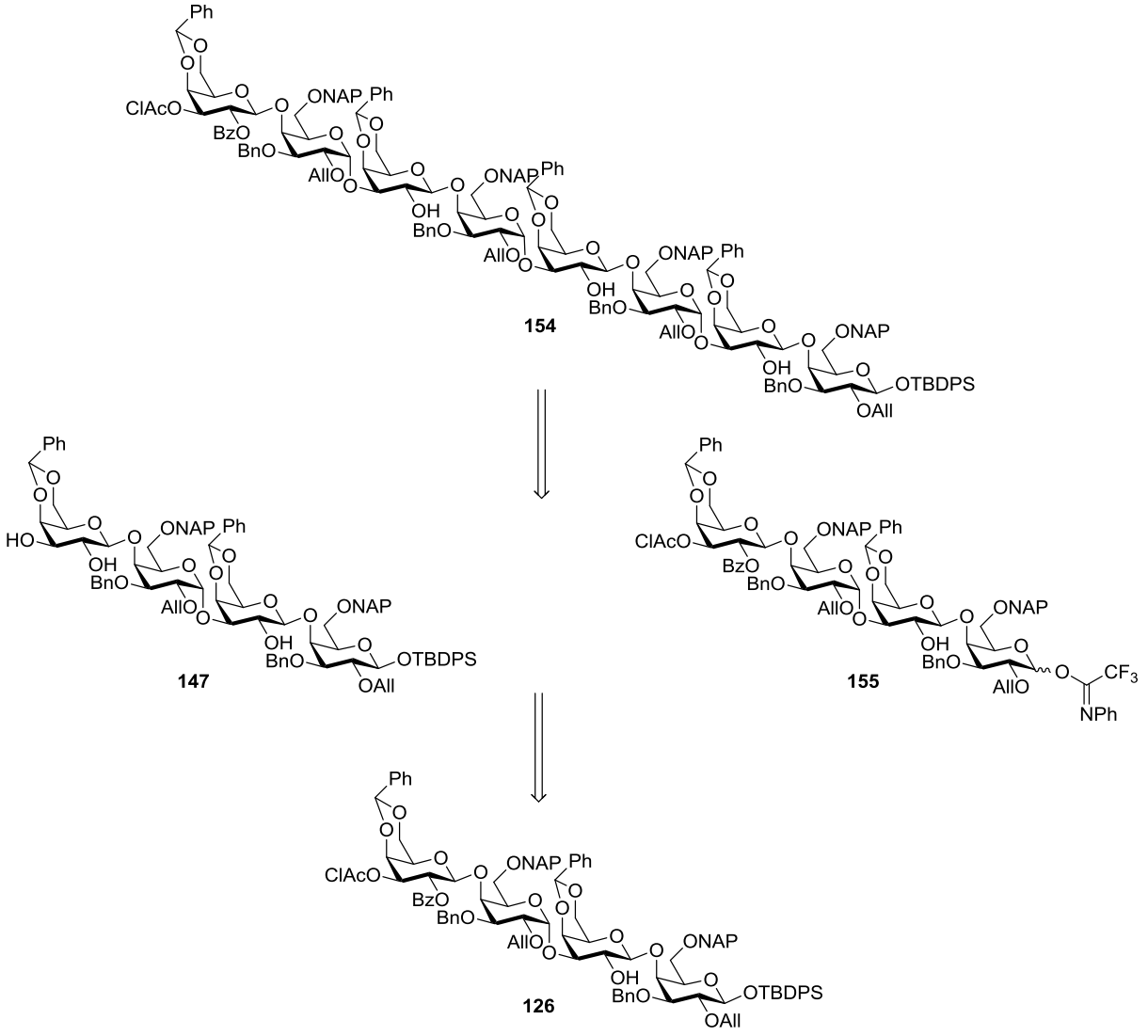


Scheme 3-39. Cyclization of the 3,6-anhydro residue to reach G-DA tetrasaccharide.

The eight other targeted carrageenans require polysulfation and sulfation of at least one secondary alcohol (either C-4' or C-2/C-2' positions as previously shown in Scheme 3-29). Therefore, a method to sulfate the sterically hindered C-2 and C-2' positions needs to be developed prior to synthesize the other target molecules. As explained in section 1.1.4, other sulfating agent such as

$SO_3{\cdot}NEt_3$ or $SO_3{\cdot}NMe_3$ have been used in the synthesis of sulfated oligosaccharides.[82] The basicity of both triethylamine and trimethylamine make these complexes more stable than the pyridine one as shown in Table 1-5.[95] Addition of TfOH in the reaction mixture may help sulfation carry out with one of those $SO_3{\cdot}$amine complexes as this previously solved the problem of polysulfation in the synthesis achieved by Krylov *et al.* [102] (see section 1.1.4). If a few more trials with these sulfating agents are not successful, we might have to change the conditions more drastically and find other non-sterically hindered sulfating agents compatible with our substrate. To help their purification as well as the success of subsequent deprotection steps in common organic solvent, it might be a good idea to introduce them as a masked formed as explained in 1.1.4. Once the polysulfation method is developed, the other carrageenan should be easily synthesized by following the deprotection/sulfation strategy showed in Scheme 3-29.

A longer perspective, would be to produce longer oligosaccharides such as octasaccharides, since DP=8 should provide an effective binding to antibodies and enzymes and would also enable structural studies of the oligomers.[143] Following our modular synthesis, they should be attainable through coupling of two tetrasaccharides building blocks as shown in Scheme 3-40.



Scheme 3-40. Retrosynthetic pathway to the octasaccharide precursor 154.

The described chemistry in this section is currently ongoing.

3.5 Concluding remarks

One of the main challenge in this project was the diversity of protecting group required in order to synthesize one single precursor for all ten types of carrageenan oligosaccharides. Therefore, the two first protecting group strategies did not succeed in the synthesis of the alternating 3-linked-β-D-galactopyranose (G) and 4-linked-α-D-galactopyranose (D) backbone of carrageenan. This was mainly due to the lability of some protecting groups such as the isopropylidene group, which was hydrolyzed during the glycosylation reactions. Moving on to a third set of orthogonal protecting groups, the desired tetrasaccharide precursor **126** was finally successfully synthesized. The deprotection and sulfation steps were then tested on disaccharide **125**. Conditions for a selective sulfation of the C-6 position of triol disaccharide **143** were optimized and afforded the desired

monosulfated disaccharide **143** in 70% yield. This one was successfully deacylated and hydrogenated to give the desired G-D6S disaccharide carrageenan. These promizing results were then translated on to tetrasaccharide **126** and the selective deprotection steps followed by regioselective sulfation of C-6 positions afforded disulfated tetrasaccharide **151** in an overall good yield. However, polysulfation of triol disaccharide **143** did not give any satisfying result yet and more work remains to be done in that perspective before starting the synthesis of the other target tetrasaccharide carrageenans.

CHAPTER 4

4 Catalyzed Intramolecular Fluoroarylation

Fluoroorganic compounds are eminently important in medicinal chemistry. The introduction of fluorine has attracted considerable attention from the synthetic community,[144] however, carbon-fluoride bond formation remains a challenging chemical transformation.[145] Enantioselective fluorinations are mostly achieved through α-fluorination of ketone and aldehyde derivatives,[146–149] or by ring-opening of strained heterocycles.[150–152] Few examples of enantioselective transition-metal-catalyzed fluorination exist.[146–149,153,154]

Pd-mediated C-F bond formation can be achieved through two main approaches: Pd^{0}/Pd^{II}-mediated nucleophilic fluorination or Pd-mediated electrophilic fluorination. The latter most probably goes through a reductive elimination from a high-valent Pd specie but further mechanistic insight about the oxidant-promoted C-F bond formation is still ongoing.[155,156] The two approaches differ by the source of fluorine used, either being of nucleophilic or electrophilic character respectively. Nucleophilic fluorination using fluoride is complicated by the relatively high basicity of the anion. It does not tolerate reaction involving protic functional groups such as alcohols, primary or secondary amines, and N-H-containing amides due to the strong H-F hydrogen bonding resulting in bifluoride formation.[157] Electrophilic fluorination on the other hand can be challenging with basic functional groups such as amines and sulfides due to side reactions with the electrophilic fluorinating reagent. Thus, the two approaches are complementary.[145]

C-F bond formation through reductive elimination using "F^{+}" oxidants goes through a Pd^{II}/Pd^{IV} catalytic cycle. This has been studied the last decades and Selectfluor (see Figure 4-1) proved to be a useful "F^{+}" oxidant reagent both in gold and palladium catalysis.[156]

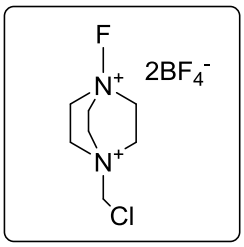
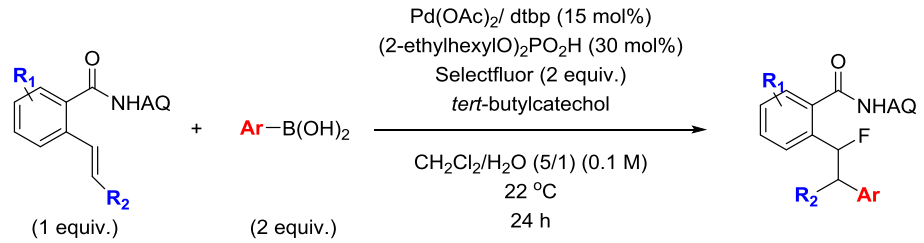


Figure 4-1. Selectfluor: a source of "F^{+}".[158]

4.1 Background of the project: Pd-catalyzed intermolecular fluoroarylation of styrenes

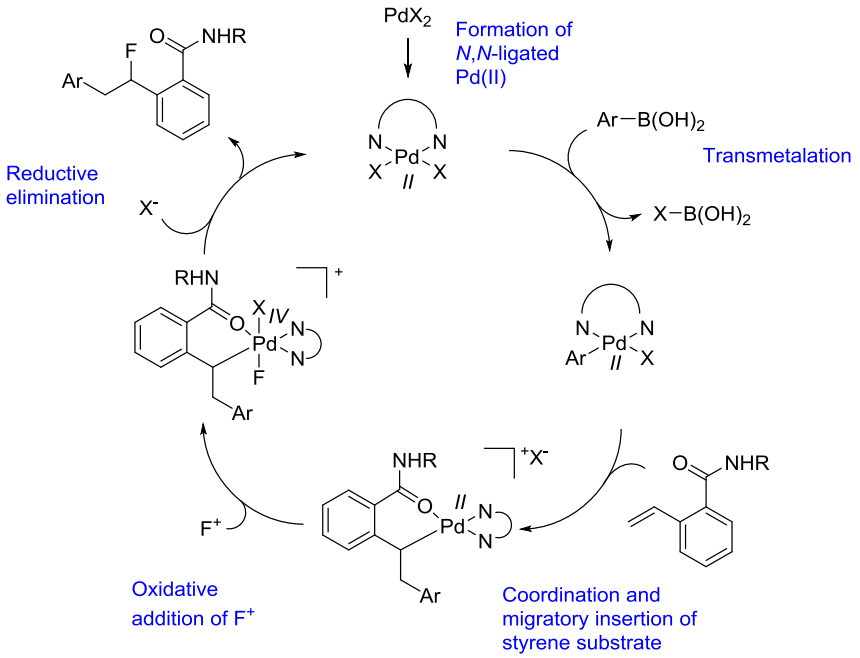
This project was inspired by previous results from the Toste group involving an asymmetric palladium-catalyzed directed intermolecular fluoroarylation of styrenes.[159] The reaction involved a three-component coupling of Selectfluor, a styrene and an aryl boronic acid. The optimized conditions for the regioselective Pd-catalyzed fluoroarylation of styrenes are shown in Scheme 4-1.



Scheme 4-1. Optimized conditions for Pd-catalyzed fluoroarylation of styrenes.[159]

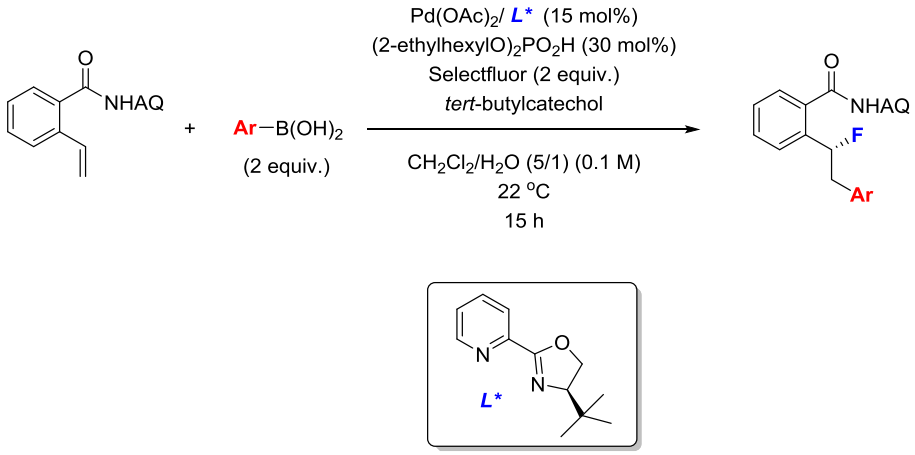
A directing group such as 8-aminoquinoline (AQ) was needed to control the regioselectivity of the reaction. *Tert*-butyl-bipyridine (dtbp) ligands had to be added to stabilize the high-valent metal intermediate and divert it from an oxidative Heck-type coupling reaction toward C-F bond formation. The electron rich character of bipyridine ligands facilitates oxidative addition of palladium and their steric bulk promotes reductive elimination. Furthermore, these bidentate ligands do not induce competing nitrogen-fluorine reductive elimination.[160] Aryl boronic acids were used as arylating reagents since boronic acids are compatible with a variety of functional groups and competent nucleophiles for transmetalation to palladium. Additionally, fluorination of arylboronic acids and derivatives has already been extensively studied.[161–163] The addition of water was important to solubilize the Selectfluor salt, and organic phosphate was added as phase transfer catalyst. Finally *tert*-butylcatechol was used as stabilizer and inhibitor of styrene polymerization. The yield of the reaction varied between 62% and 81%, depending on the substrates.

The mechanism shown in Scheme 4-2 was suggested to explain the outcome of the reaction. The catalytic cycle is initiated by the formation of an *N*,*N*-ligated Pd(II) specie. Transmetalation with the aryl boronic acid followed by coordination and migratory insertion of the styrene substrate affords a *β*-arylated Pd(II) intermediate. Stabilization of this intermediate via coordination with the directing group as well as a bipyridine ligand retards the competing *β*-hydride elimination reaction and promote the oxidative addition of "F^{+}" delivered by Selectfluor, affording a high-valent Pd(IV) specie. Finally, reductive elimination affords the desired monofluorinated product and regenerates the catalytic complex [N-N-$Pd^{(II)}$].



Scheme 4-2. Proposed catalytic cycle for the directed fluoroarylation of styrene.[159]

An enantioselective version of the reaction using chiral ligand *L** (shown in Scheme 4-3) was further developed and optimized giving good yields (up to 83%) and ee (up to 96).

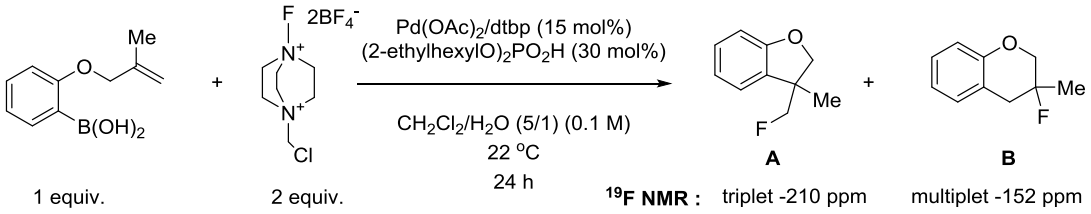


Scheme 4-3. Enantioselective Pd-catalyzed fluoroarylation of styrenes. [159]

Based on these results, we envisioned that it would be possible to develop an intramolecular version of this catalytic reaction which would involve a simultaneous cyclization and C-F bond formation.

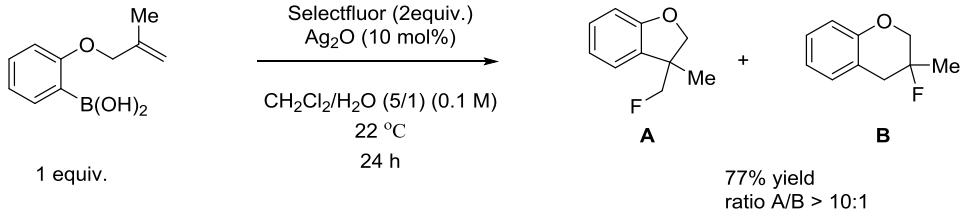
4.2 Development of a catalytic intramolecular fluoroarylation

Using the optimized conditions of the intermolecular fluoroarylation shown in Scheme 4-1, a first attempt of intramolecular fluoroarylation was tried using the same conditions (Scheme 4-4).



Scheme 4-4. First attempt of Pd-catalyzed intramolecular fluoroarylation.

The two regioisomers formed (**A** and **B**) were isolated and characterized by ^{19}F NMR.
To optimize the regioselectivity of the reaction, some additives had to be screened. Surprisingly, after adding silver oxide in the reaction mixture, we figured out that this additive could catalyze the fluorocyclization by itself (Scheme 4-5).



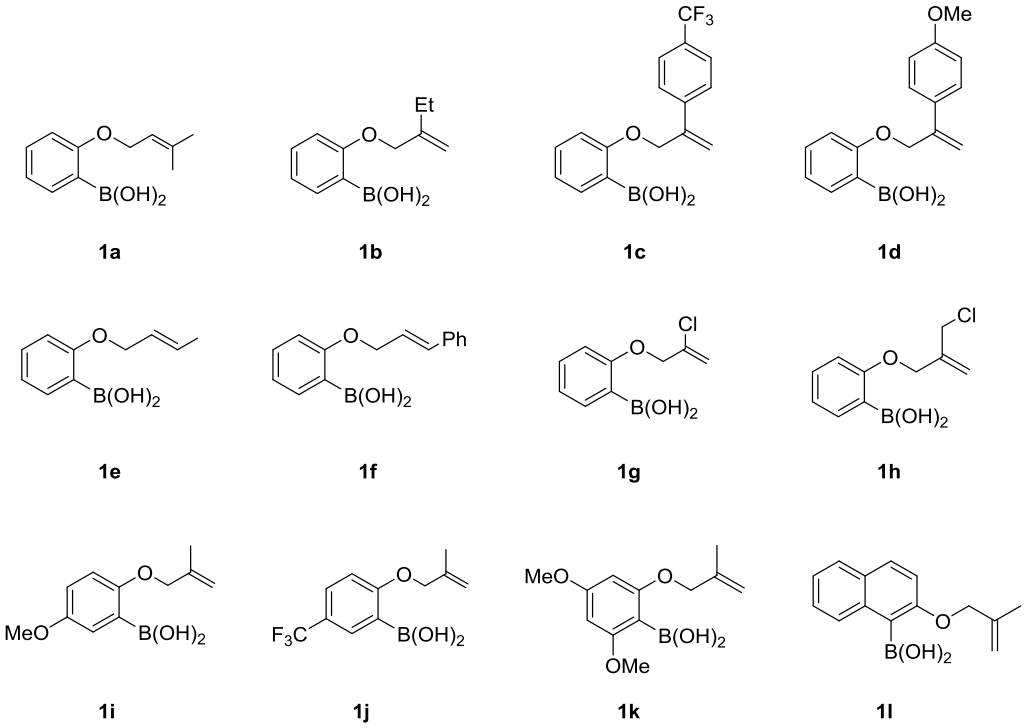
Scheme 4-5. Silver-catalyzed intramolecular fluoroarylation.

Silver is typically used as a non-redox active Lewis acid in homogeneous catalysis, and its redox catalysis is not well understood yet but hypothesized to proceed through an one eletron transfer pathway.[164] Radical fluorination has emerged during the last decade as a new tool in C(sp^3)- F bond formation as shown by the radical deboronofluorination of alkylboronic acids or their pinacol ersters developed by Li *et al.*[165] As silver oxide is an inexpensive Ag(I) source, we decided to explore this new kind of catalysis and try to develop a silver-catalyzed intramolecular fluoroarylation.

This first experience gave us the hope that the regioselective outcome of the reaction could be controlled by changing the electronic environment of both the aryl and the allyl functionalities by substituting them with electron-withdrawing or electron-donating groups.

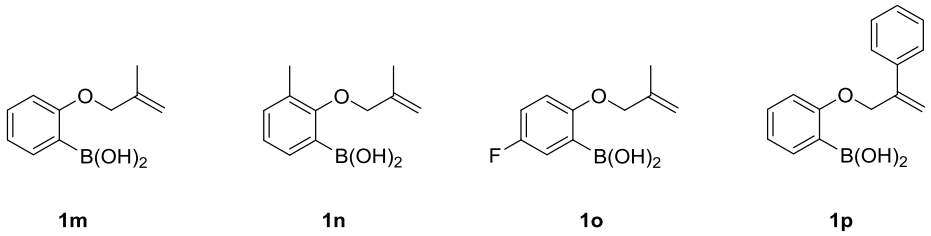
4.2.1 Substrates scope

The small library of substrates shown in Scheme 4-6 and Scheme 4-7 was designed to be synthesized.



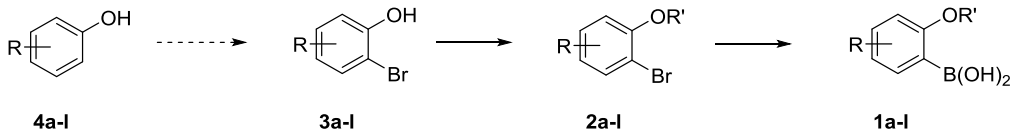
Scheme 4-6. Substrate scope.

The following additional substrates were synthesized at the same time by Dr. G. Schäfer.



Scheme 4-7. Additional substrates synthesized by Dr. G. Schäfer.

In principle the different substrates could be synthesized following the route shown in Scheme 4-8.

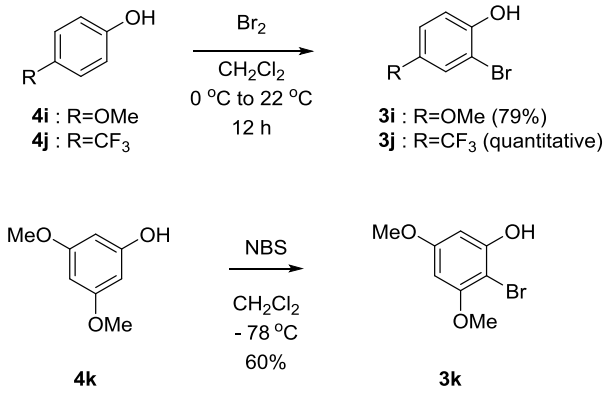


Scheme 4-8. Synthetic route for the different aryl boronic substrate derivatives.

Substrates **1a-h** could be synthesized from commercially available 2-bromophenol starting by an alkylation step either through nucleophilic substitution of R'X with the phenol or using a Mitsunobu reaction between 2-bromophenol and R'OH (in most cases commercially available except for the substrates **1c** and **1d**). In either cases the boronic acid would be installed on the alkylated substrate (**2a-l**) through a lithium bromide exchange followed by borate trapping known as the *in situ* quenched method developed by Reider *et al.*[166] For the substrates **1i-k** an additional bromination step onto the corresponding R-substituted phenol would be required prior to the alkylation. The last substrate **1l** could be synthesized through the same way but starting from commercially available 1-bromo-2-naphtol.

4.2.1.1 Synthesis of the substrates

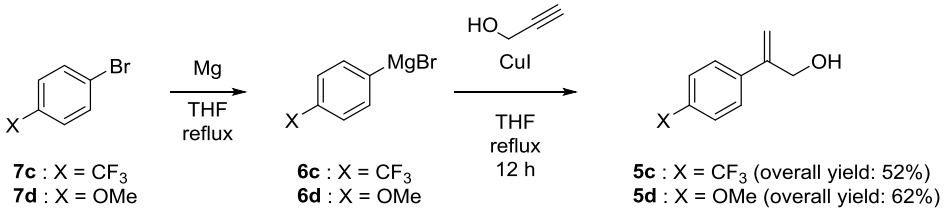
The bromination of the substituted phenols **4i-k** was done according to Scheme 4-9.



Scheme 4-9. Synthesis of the brominated substituted phenol 3j-l.

Substrates **3j-k** were synthesized following a standard bromination procedure using bromine while **3l** was synthesized from commercially available 3,5-dimethoxyphenol at low temperature using the electrophilic brominating reagent NBS to avoid multiple bromination.[167]

For substrates **1c** and **1d**, it was necessary to synthesize the alkylating reagents **5c** and **5d** prior to the alkylation reaction with **3c** and **3d**. Compounds **5c** and **5d** were prepared *via* a Grignard reaction reported in the literature as shown in Scheme 4-10.[168]



Scheme 4-10. Grignard reaction affording 5c and 5d.

The alkylation of all the substrates could then be achieved as described in Table 4-1. Substrates **2a**, **2c** and **2d** were synthesized via a Mitsonobu reaction between their phenol derivative

precursors and the required substituted unsaturated alcohol **B** (see path b). All the other substrates were obtained by nucleophilic attack of their corresponding R-substituted phenol precursors on the required substituted allyl-halogen reagent **B** (see path a). All the reactions afforded the desired compounds **2a-l** in satisfying yields (50%-98%) except for substrates **3g** and **3h.** No product was isolated for **3g** while **2h** dimerized to give compound **2h'** (shown in Scheme 4-11) as the major product.

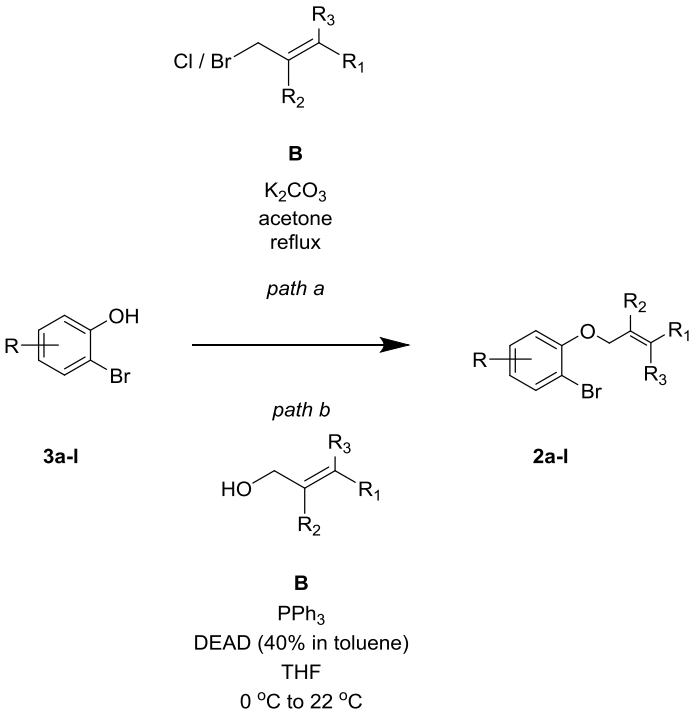
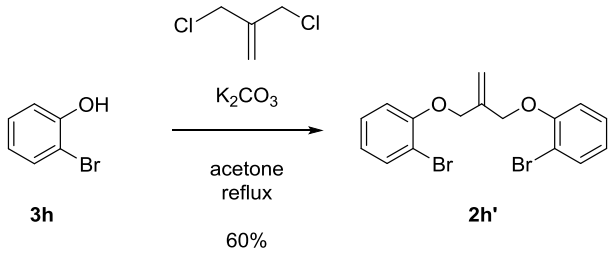


Table 4-1. Alkylation step.

Substrates 3	Path a/b	R	R_1	R_2	R_3	Yield (%)
3a	b	H	Me	H	Me	98
3b	a	H	H	Et	H	8
3c	b	H	H	*4*-$CF_3C_6H_4$	H	50
3d	b	H	H	*4*-$OMeC_6H_4$	H	95
3e	a	H	Me	H	H	75
3f	a	H	Ph	H	H	70
3g	a	H	H	Cl	H	-
3h	a	H	H	CH_2Cl	H	-[a]
3i	a	*4*-OMe	H	Me	H	76
3j	a	*4*-CF_3	H	Me	H	65
3k	a	*3,5*-OMe	H	Me	H	70
3l	a	3,4-$(CH)_4$	H	Me	H	65

[a]dimerization



Scheme 4-11. Dimerized product 2h' isolated.

The boronic acid could then be installed on the alkylated substrates **2a-f,i-l** as shown in Table 4-2. First, the reaction was tested on all the substrates **2a-f,i-l** by using the most common procedure[169] (*path a*) which involves a reaction between trimethylborate and the aryllithium substrate previously formed by lithium-bromide exchange of the corresponding arylbromide substrate. However, the reaction did not give a satisfying results for substrates **2c-d** and **2f-l**. Furthermore, the yields of the reactions were all quite low (maximum 45%). It has been shown before that some aryllithium intermediates are intrinsically unstable and this could explain the outcomes of these reactions.[166] Therefore, the *in situ* quench method (*path b*) developed by Reider *et al.*[166] was tried on substrates **2c-d**,**f-l**. In this case, *n*-butyllithium is added to a solution of the arylbromide and triisopropyl borate. The mixture is then quenched under acidic conditions. The procedure afforded the different products in maxium 50% yield. The general low yields of the reaction might be due to the challenging purification of these boronic acid derivatives.

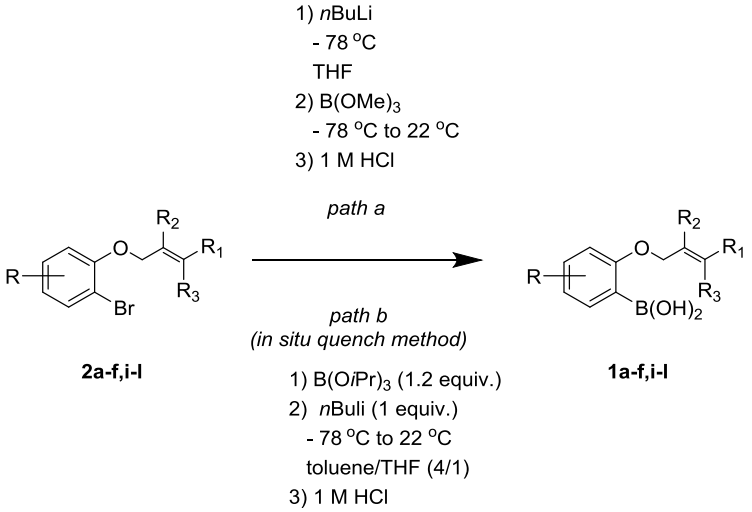


Table 4-2. Boronic acid formation.

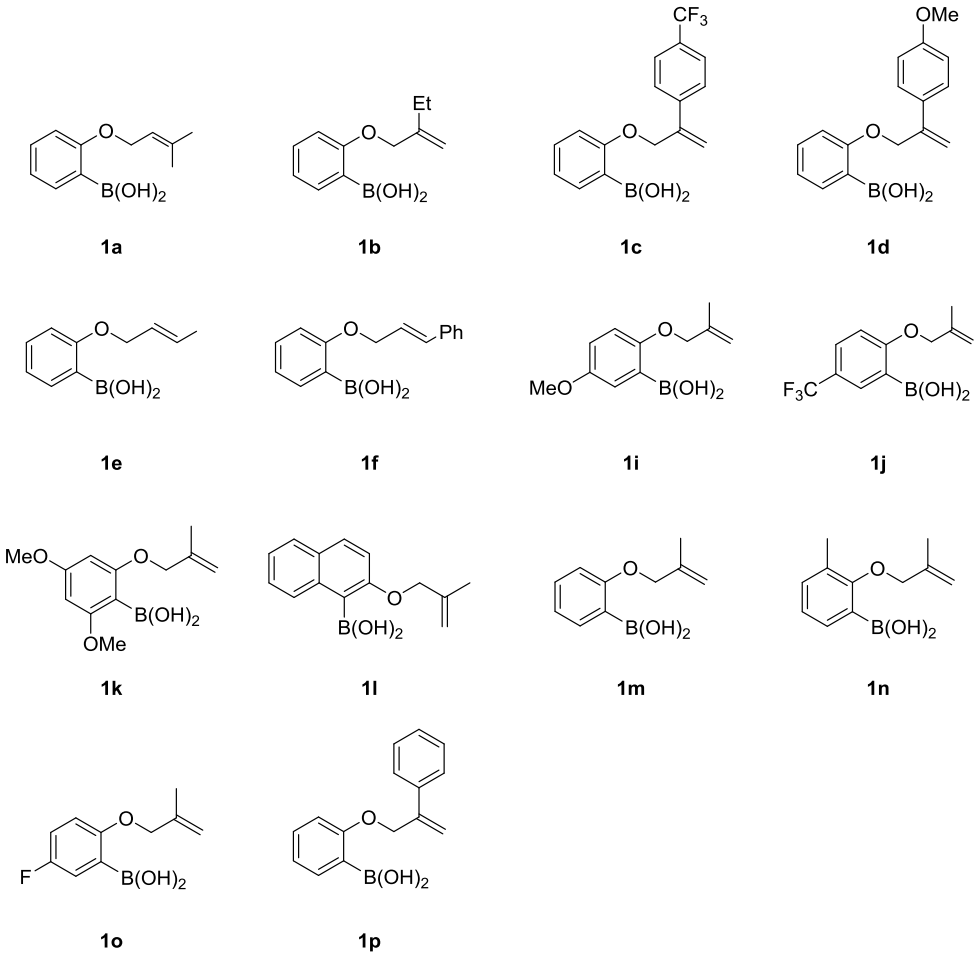
Substrates 2	Path a/b	R	R_1	R_2	R_3	Yield (%)
2a	a	H	Me	H	Me	35
2b	a	H	H	Et	H	40
2c	b	H	H	*4*-$CF_3C_6H_4$	H	50
2d	b	H	H	*4*-$OMeC_6H_4$	H	40
2e	a	H	Me	H	H	45
2f	b	H	Ph	H	H	50
2i	b	*4*-OMe	H	Me	H	32
2j	b	*4*-CF_3	H	Me	H	35
2k	b	*3,5*-OMe	H	Me	H	40
2l	b	3,4-$(CH)_4$	H	Me	H	35

4.2.1.2 Catalytic reaction: preliminary results

The boronic acids (see Scheme 4-12) were then subjected to the silver-catalyzed intramolecular fluoroarylation to investigate its scope and regioselective outcome.

The reaction was performed on 0.5 mmol scale except for **1i** and **1j** (entry 15 and 16). The results are presented in Table 4-3. In almost all cases, the reaction did not go to completion (except for compound **1n** (entry 12)). Ethyl and methyl substituents on the internal vinylic carbon seem to increase the yield of the reaction as well as its regioselectivity towards the 5-membered ring product in most of the cases (entries 2, 8, 11, 12 and 13). As the reaction might proceed through a radical pathway, the carbon radical is more likely to be formed on the more substituted carbon which means the non-terminal vinylic carbon. This can explain the favorited 5-membered ring product. Alkyl substituents such as methyl and ethyl groups are electron donating group and indeed, they can stabilize the radical formed on the adjacent carbon and therefore increase the yield and regioselectivity of the reaction. According to these results, we then hypothesized that forming a benzylic radical would improve the yield and regioselectivity of the reaction and therefore we tested the reaction on substrates **1c** and **1d** (entries 3 and 4). However, substitution of the allyl or the aryl functionalities did not give any satisfying result.

No significant correlation between the addition of electron-donating (OMe) or electron-withdrawing substituents (F, CF_3) on the aryl functionality and the outcome of the catalytic reaction could be deduced from this set of experiments.



Scheme 4-12. Boronic acids subjected to the silver catalyzed fluorocyclization.

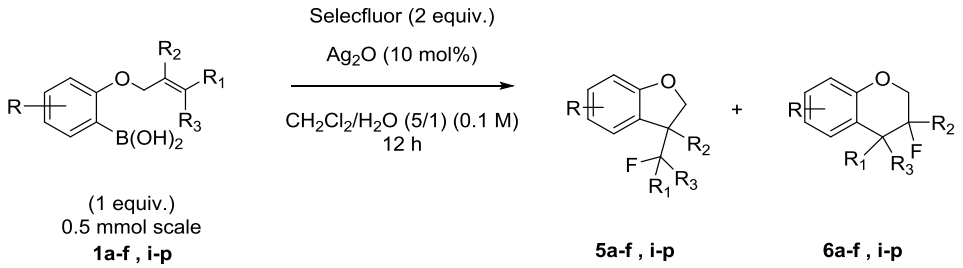


Table 4-3. Results of the Ag-catalyzed fluorocyclization on substrates shown in Scheme 4-12.

Entry	Substrates	Temp. (°C)	1a-f , i-p left[a]	Yield	Ratio 5/6
1	**1a**	22	+	-	-
2	**1b**	22	+	70%	>15:1
3	**1c**	22	+	-	-
4	**1d**	22	+	-	-
5	**1e**	22	+	-	-
6	**1f**	22	+	-	-
7	**1i**	22	+	-	-
8	**1j**	22	+	50%	>15:1
9	**1k**	22	+	-	-
10	**1l**	22	+	-	-
11	**1m**	22	+	77%	>10:1
12	**1n**	22	-	95%	1:1
13	**1o**	22	+	59%	5:1
14	**1p**	22	+	56%	1:1
15[b]	**1i**	45	+	nd	nd
16[b]	**1j**	45	+	nd	nd

[a] indicated by TLC

[b] 0.1 mmol scale, reaction mixture not purified

4.2.1.3 Concluding remarks and future perspectives

A variety of allyl substituted aryl boronic acids was synthesized and then tested in a silver-catalyzed intramolecular fluoroarylation. It seems like an alkyl substitution on the internal vinylic carbon of the allyl group can increase the yield of the reaction as well as guide it towards the formation of the 5-membered ring product. Contrarily, substituents on the aryl group do not seem to have any direct effect on the outcome of the reaction. The reaction needs more optimization and an additional mechanistic study could help us understand the scope of the reaction as well as designing suitable substrates. Furthermore, all the arylboronic substrastes synthesized could be tested in the palladium catalyzed reaction presented first.

CHAPTER 5

5 Conclusion

This project aimed at developing a strategy for the synthesis of ten different types of carrageenan oligosaccharides from one single precursor. A modular approach relying on the synthesis of a key β-1,4-linked digalactoside building block carrying suitable protecting groups was chosen to enable the synthesis of carrageenans with different lengths. Each disaccharide would be α-1,3-linked to each other to build up the carrageenans backbone consisting of D-galactose with alternating β-1,4 and α-1,3 glycosidic linkages. In order to establish the strategy, our objective was to synthesize ten different types of carrageenan tetrasaccharides. The strategy required the identification of a suitable set of protecting groups, which would enable the synthesis of the backbone of the carrageenans as well as the introduction of sulfate groups at various positions depending on the targeted carrageenan. This turned out to be the biggest challenge throughout the project and two protecting group strategies were unsuccessfully attempted. These strategies relied on the higher reactivity of the equatorial 3-*OH* compared to the axial 4-*OH* of galactose to form the α- 1,3- linkage. Therefore, the second glycosylation step was carried out between a trifluoroacetimidate disaccharide donor and a 3,4-*OH* disaccharide acceptor. However, the control of the regioselectivity and stereoselectivity of the desired α-1,3-linkage turned out to be more difficult than anticipated. Furthermore, the isopropylidene acetal used in these two strategies proved to be too labile making the first glycosylation reaction forming a β-1,4-linked disaccharide difficult to optimize. To our surprise, the third set of orthogonal protecting groups chosen afforded the desired protected tetrasaccharide by forming the regioselective α-1,3-linkage in 55% yield through a glycosylation between a 2,3-*OH* disaccharide acceptor and a trifluoroacetimidate disaccharide donor. The deprotection and sulfation step required to reach the different targets were first tested on the key disaccharide **125** giving the G-D6S disaccharide carrageenan successfully by a selective C-6 sulfation of triol disaccharide **142** in 70% yield followed by debenzoylation and hydrogenation. So far, the protecting group chosen performed well in the synthesis of the backbone and could be successively removed. The deprotection steps prior to the sulfation as well as the selective C-6 sulfation step were translated successfully to the tetrasaccharide **126.** Further debenzoylation and hydrogenation will afford the G-D6S tetrasaccharide. More work on polysulfation remains to be done in order to reach the remaining four D6S targets. The chemically or enzymatically catalyzed cyclization to form the anhydro residue DA needs to be developed to reach the corresponding five DA carrageenans. These experiments are currently ongoing. Once the tetrasaccharide targets will be reached, they will serve as model compounds for structural analysis to help our understanding of the gelation process at a molecular level. This would lead to a fundamental knowledge about control of the polymer conformational transition, which would get an immediate application in the industry. They could also be used to help characterize enzymes involved in their biosynthesis and increase the knowledge about algae/plant cell wall biosynthesis.

Longer oligomers, with a better binding affinity, could potentially be synthesized by applying the same block strategy if needed.

This work is a typical example of the challenges faced in oligosaccharide synthesis. The outcome of glycosylation reactions is hard to predict and this often makes extensive method development necessary. Indeed, each position in the pyranose ring has different reactivity and this is furthermore affected by the nature of the surrounding protecting groups. A systematic analysis of acceptor conformation and reactivity could result in a better understanding of chemical glycosylation reactions.

Inspired by work on catalyzed intermolecular fluoroarylation of styrene derivatives, a set of allyl substituted aryl boronic acids was synthesized and subjected to a similar silver-catalyzed intramolecular fluoroarylation reaction. It turned out that alkyl substituents on the internal vinylic carbon of the allyl group increased the yield of the reaction as well as guide it towards the formation of the 5-membered ring regioisomer product. Contrarily, substituents on the aryl group did not seem to have any direct effect on the outcome of the reaction. A mechanistic study could help understand these preliminary results and design a suitable set of substrates to improve the yield as well as the regioselectivity of the reaction.

CHAPTER 6

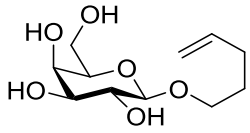
6 Experimental

6.1 General considerations

Starting materials, reagents and solvents were purchased from commercial suppliers and used without further purification. All solvents are HPLC-grade. The anhydrous solvents were obtained from Innovative Technology PS-MD-7 Pure-solv solvent purification system except for pyridine, which was dried over 4 Å activated molecular sieves for at least 24 hours (according to standard procedure).[170] Reactions requiring anhydrous conditions were carried out in flame-dried glassware under inert atmosphere. Thin-layer chromatography (TLC) was performed on Merck Aluminium Sheets pre-coated with silica, C-60 F_{254} plates. The plates were visualized under UV irradiations and/or by heating after dipping in cemol solution stain ($Ce(SO_4)_2$ (1.6 g) and $(NH_4)_6Mo_7O_{24}$ (4 g) in 10 % sulphuric acid (200 mL). Anysaldehyde stain (H_2SO_4 (10 ml) and *p*-anisaldehyde (10 ml) in EtOH 95% (200 mL)) was used instead of cemol to follow glycosylation reaction using a thiophenylglycosyl donor. Eluent systems are specified for each R_f-value, and ratios are given as volume ratios. Evaporation of solvents was performed with a VWR International Laborota 400 under reduced pressure (*in vacuo*) at temperatures ranging between 35-55 °C. Traces of solvents were removed under reduced pressure by means of a membrane pump. Flash column chromatography was performed using Geduran silica gel 60 Å (35-70 µm) as the stationary phase by the general procedure developed by Still *et al.*[171] Dry column vacuum chromatography (DCVC) was performed according to literature procedure.[172] Both for flash column chromatography and for dry column chromatography, the eluent systems are specified under the protocol for each synthesis. Eluent ratios are given as volume ratios. NMR-spectras were recorded on a Bruker Ascend 400 spectrometer with a Prodigy cryoprobe. Chemical shifts (δ) are reported in ppm downfield from TMS (δ = 0) using solvent resonance as the internal standard. The spectra were recorded in $CDCl_3$ or MeOD. Coupling constants (*J*) are reported in Hz and the field is reported in each case. Multiplicities are reported as singulet (s), doublet (d), triplet (t), broad singlet (br. s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd) , doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet (t), triplet of doublets (td), quartet (q), and multiplet (m). Optical rotation was measured on a Perkin Elmer Model 241 Polarimeter (cuvette 1.0 mL, 100 mm) using a sodium source lamp (589 nm, 20 °C). $CHCl_3$ was used as the solvent. HRMS spectra were performed on an UHPLC-QTOF system (Dionex ultimate 3000 and Bruker MaXis) with an electrospray ionization (ESI) source and controlled using DataAnalysis 4.2 software. Melting points were measured on a Stuart melting point SMP30 and reported in °C uncorrected. All compounds have been characterized by NMR using 1D and 2D experiments. All peaks on the spectra are assigned, however the protons on free hydroxyl groups are generally not assigned. The carbohydrate residues have been assigned from the monosaccharide in the reducing end. New compounds were characterized by NMR, HRMS, melting point (mp) and optical rotation.

6.2 Procedures

Pent-4-enyl-β-D-galactopyranoside (70)[173]

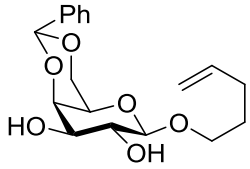


To a solution of galactose pentaacetate (50.0 g, 128.1 mmol) and pent-4-en-1-ol (30 ml, 281.8 mmol) in CH_2Cl_2 (350 ml) was added BF_3-OEt_2 (20 ml, 153.7 mmol). The mixture was stirred at 22 °C under an atmosphere of nitrogen for 12 h, and then diluted with CH_2Cl_2 (150 ml) and washed with saturated aq. $NaHCO_3$ (500 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The syrupy residue was dissolved in 0.04 M NaOMe in MeOH (430 ml) and the solution stirred for 3 h. The mixture was quenched with Amberlite IR-120(H^+) (20 ml) and stirred for an additional 30 min. The resin was filtered off and the filtrate concentrated, and purified by dry column vacuum chromatography (0–20% methanol in dichloromethane – 2% increments MeOH/CH_2Cl_2) to a greasy solid. Recrystallisation from EtOAc afforded **70** (18.0 g, 56%) as white crystals. The compound analyses were in accordance with data from the literature.

mp 88– 90 °C. $\mathbf{R}_f$ 0.30 (6:1 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, D_2O) δ 5.92 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, -C*H*=CH_2), 5.01 (d, 1H, *J* = 17.4 Hz, 0.5xCH=C*H*$_2$), 4.94 (d, 1H, *J* = 10.2 Hz, 0.5xCH=C*H*$_2$), 4.30 (d, 1H, *J* = 8.0 Hz, H-1), 3.84 –3.51 (m, 7H, OC*H*$_2$-CH_2-, H-3, H-4, H-5, H- 6ab), 3.42 (t, 1H, *J* = 8.9 Hz, H-2), 2.07 (m, 2H, -C*H*$_2$-CH=CH_2), 1.65 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2) ppm. **^{13}C NMR** (101MHz, D_2O) δ 139.1 (-*C*H=CH_2), 115.0 (-CH=*C*H_2), 103.0 (C-1), 75.3 (C-4), 73.1 (C-3), 71.0 (C-2), 70.1 (O-*C*H_2-CH_2-), 68.9 (C-5), 61.1 (C-6), 29.6 (-*C*H_2-CH=CH_2), 28.3 (-*C*H_2-CH_2-CH=CH_2) ppm.

Pent-4-enyl 4,6-*O*-benzylidene-β-D-galactopyranoside (71)[173]



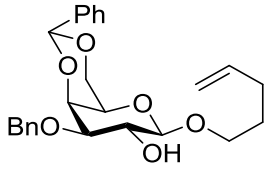
To a solution of benzaldehyde dimethylacetal (12.2 ml, 81.6 mmol) and camphor-10-sulfonic acid (CSA) (170 mg, 0.76 mmol) in acetonitrile (340 ml) was added **70** (13.5 g, 54.4 mmol). The flask was equipped with a distillation head and the mixture heated to reflux and stirred for 1.5 h during which time about 80 ml of a MeCN–MeOH mixture distilled off. The reaction mixture was quenched with Et_3N (0.7 mL) and concentrated to a solid, which was recrystallised from EtOAc to give **71** as a white solid (15.5 g, 85%). The compound analyses were in accordance with data from the literature.

mp 157–160 °C. $\mathbf{R}_f$ 0.57 (10:1 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H, ArH), 7.35 (m, 3H, ArH), 5.81 (m, 1H, C*H*=CH_2), 5.54 (s, 1H, PhC*H*O_2), 5.04 (dq, *J* = 17.1, 1.7 Hz, 1H, CH=C*H*$_2$), 4.97 (dq, *J* = 10.4, 1.7 Hz, 1H, CH=C*H*$_2$), 4.32 (dd, *J* = 12.5, *J* = 1.5 Hz, 1H, H- 6a), 4.26 (d, *J* = 7.3 Hz, 1H, H-1), 4.20 (dd, *J* = 3.6, 1.5 Hz, 1H, H-4), 4.07 (dd, *J* = 12.5, 1.5 Hz, 1H, H-6b), 3.98 (dt, *J* = 9.7, 7.0 Hz, 1H, 0.5xOC*H*$_2$-CH_2-), 3.74 (dd, *J* = 9.6, 7.3 Hz, 1H, H-2), 3.69 (dd, *J* = 9.6, 3.6 Hz, 1H, H-3), 3.52

(dt, *J* = 9.7, 7.0 Hz, 1H, 0.5xOC*H*$_2$-CH$_2$-), 3.46 (m, 1H, H-5), 2.24- 2.06 (m, 4H, 2-O*H*, 3-O*H*, -C*H*$_2$-CH=CH$_2$), 1.76 (m, 2H, -C*H*$_2$-CH$_2$-CH=CH$_2$) ppm. **^{13}C NMR** (101MHz, $CDCl_3$) δ 138.4 (-*C*H=CH$_2$), 137.8, 129.4, 128.4 (2C),126.7 (2C) (6 ArC), 115.1 (-CH=*C*H$_2$), 103.1 (C-1), 101.6 (Ph*C*HO$_2$), 75.7 (C-4), 73.0 (C-3), 72.0 (C-2), 69.6 (O-*C*H$_2$-CH$_2$), 69.4 (C-6), 66.9 (C-5), 30.4 (-*C*H$_2$-CH=CH$_2$), 28.9 (-*C*H$_2$-CH$_2$-CH=CH$_2$) ppm.

Pent-4-enyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (72)

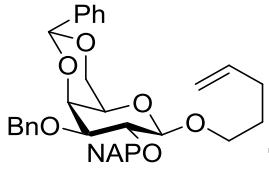


Di-*n*-butyl tin oxide (7.25 g, 29.13 mmol) was added to a solution of compound **71** (7.0 g, 20.8 mmol) in dry toluene (170 mL) and stirred under refluxing temperature for 12 h. The temperature was adjusted to 75-80 °C, and then *n*-Bu$_4$NI (11.53 g, 31.21 mmol) and benzyl bromide (3.71 ml, 31.21 mmol) were added in one portion; stirring was maintained at this temperature for 24 h. The mixture was concentrated and purified by flash chromatography (5:1 Toluene/EtOAc) to give **72** as transparent oil. Yield: 6.5 g (73%).

R$_f$ 0.24 (5:1 Toluene/EtOAc).

^{1}H NMR (400 MHz, C_6D_6) δ 7.71 – 7.66 (m, 2H, ArH), 7.44 (m, 2H, ArH), 7.23 – 7.06 (m, 6H, ArH), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C*H*=CH$_2$), 5.30 (s, 1H, PhC*H*O$_2$), 5.07 – 4.93 (m, 2H, -CH=C*H*$_2$), 4.69 (s, 2H, OC*H*$_2$Ph), 4.26 – 4.19 (m, 1H, H-2), 4.14 (d, *J* = 7.7 Hz, 1H, H-1), 4.08 (dd, *J* = 10.5, 1.4 Hz, 1H, H-4), 3.90 (dt, *J* = 10.5, 6.5 Hz, 1H, H- 3), 3.70 – 3.67 (m, 1H, H-6a), 3.41 (ddd, *J* = 9.0, 7.3, 4.4 Hz, 2H, OC*H*$_2$-CH$_2$-), 3.30 (dd, J = 9.6, 3.6 Hz, 1H, H-6b), 2.51 (m, 1H, 2-OH), 2.48 (s, 1H, H-5), 2.05 (m, 2H, -CH2-CH=CH2), 1.70 – 1.55 (m, 2H, C*H*$_2$-CH$_2$-CH=CH$_2$) ppm. **^{13}C NMR** (101MHz, C_6D_6) δ 139.7 (2C), 139.3 (2C), 138.9 (-*C*H=CH$_2$), 129.3 (2C), 129.0 (2C), 128.2 (2C), 127.2 (2C) (12 ArC), 115.3 (-CH=*C*H$_2$), 104.0 (C-1), 101.6 (Ph*C*HO$_2$), 79.9 (C-3), 74.1 (C-4), 72.0 (C-2), 71.1 (O*C*H$_2$Ph), 69.6 (O- *C*H$_2$- CH$_2$-), 69.1 (C-6), 67.1 (C-5), 30.9 (-*C*H$_2$-CH=CH$_2$), 29.5 (-*C*H$_2$-CH$_2$-CH=CH$_2$) ppm.

Pent-4-enyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-naphtyl)methyl-β-D-galactopyranoside (73)

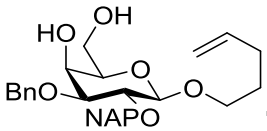


To a solution of **72** (11.5 g, 26.96 mmol) in DMF (150 ml) naphthylmethyl bromide (8.94 g, 40.45 mmol) and *n*-Bu$_4$NI (996 mg, 2.67 mmol) were added and the mixture was cooled down to 0 °C. Sodium hydride (1.62 g, 40.45 mmol, 60% in oil) was added and the mixture was stirred at 22 °C for 12 hours, before being quenched with MeOH (3 ml), partially concentrated, diluted with EtOAc (300 ml) and washed with water and brine. The organic phase was dried, concentrated, and the residue was recrystallised from EtOAc–Heptane to afford **73** as a white solid product (9.8 g, 65%).

R_f 0.17 (4:1 Hept/EtOAc).

^{1}H NMR (400 MHz, C_6D_6) δ 7.86 (m, 1H, ArH), 7.78 – 7.71 (m, 2H, ArH), 7.71 – 7.60 (m, 3H, ArH), 7.60 – 7.53 (m, 1H, ArH), 7.45 (m, 2H, ArH), 7.29 – 7.21 (m, 2H, ArH), 7.21 – 7.05 (m, 6H, ArH), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C*H*=CH_2), 5.35 (s, 1H, PhC*H*O_2), 5.14 (d, *J* = 11.7 Hz, 1H, 0.5xOC*H*$_2$Naphth), 5.06 – 4.93 (m, 2H, -CH=C*H*$_2$), 4.90 (d, *J* = 11.7 Hz, 1H, 0.5xOC*H*$_2$Naphth), 4.75 – 4.63 (m, 2H, OC*H*$_2$Ph), 4.33 (d, *J* = 7.7 Hz, 1H, H-1), 4.20 – 4.08 (m, 2H, H-2, 0.5xOC*H*$_2$-CH_2-), 4.02 – 3.94 (m, 1H, H-6a), 3.74 (d, *J* = 3.4 Hz, 1H, H-4), 3.55 – 3.39 (m, 3H, H-3, H-6b, 0.5xOC*H*$_2$-CH_2-), 2.55 (s, 1H, H-5), 2.10 (m, 2H, -C*H*$_2$-CH=CH_2), 1.77 – 1.59 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 139.4, 139.0, 138.4 (-*C*H=CH_2), 137.6, 134.0, 133.5, 128.9, 128.6 (2C), 128.3 (2C), 128.2, 128.1 (2C), 127.9 (3C), 126.9 (2C), 126.6, 126.5, 126.1, 125.8 (22 ArC), 115.1 (- CH=*C*H_2), 104.1 (C-1), 101.2 (Ph*C*HO_2), 79.9 (C-3), 79.2 (C-2), 75.5 (O*C*H_2Naphth), 73.9 (C- 4), 71.7 (O*C*H_2Ph), 69.2 (O-*C*H_2-CH_2-), 68.9 (C-6), 66.6 (C-5), 30.6 (-*C*H_2-CH=CH_2), 29.4 (-*C*H_2-CH_2-CH=CH_2) ppm.

Pent-4-enyl 3-*O*-benzyl-2-*O*-(2-naphtyl)methyl-β-D-galactopyranoside (74)

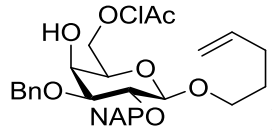


To a solution of compound **73** (7.35 g, 12.97 mmol) dissolved in 200 ml CH_2Cl_2 was added ethane thiol (4.68 ml, 64.85 mmol) and *p*-toluenesulfonic acid (247 mg, 1.30 mmol). The reaction mixture was stirred at 22 °C for 2 hours, quenched with Et_3N and concentrated *in vacuo*. The crude was purified by flash chromatography (1:1 EtOAc/Heptane) yielding a white solid product (5.7 g, 92%).

R_f 0.57 (2:3 EtOAc/Hexane).

^{1}H NMR (400 MHz, C_6D_6) δ 7.85 (s, 1H, ArH), 7.70 – 7.60 (m, 3H, ArH), 7.56 (dt, *J* = 8.4, 4.3 Hz, 1H, ArH), 7.31 – 7.20 (m, 4H, ArH), 7.20 – 7.04 (m, 3H, ArH), 5.73 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C*H*=CH_2), 5.18 (d, *J* = 11.8 Hz, 1H, 0.5xOC*H*$_2$Naphth), 4.99 (m 3H, 0.5xOC*H*$_2$Naphth, -CH=C*H*$_2$), 4.48 (s, 2H, OC*H*$_2$Ph), 4.27 (d, *J* = 7.8 Hz, 1H, H-1), 3.97 – 3.77 (m, 4H, H-6ab, H-2, 0.5xOC*H*$_2$-CH_2-), 3.70 (s, 1H, H-5), 3.43 (dt, *J* = 9.5, 6.6 Hz, 1H, 0.5xOC*H*$_2$-CH_2-), 3.27 (dd, *J* = 9.4, 3.5 Hz, 1H, H-3), 3.07 (m, 1H, H-4), 2.50 (s, 1H, 6-O*H*), 2.10 (m, 2H, -C*H*$_2$-CH=CH_2), 1.96 (s, 1H, 4-O*H*), 1.73 – 1.60 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 138.7, 138.4 (-*C*H=CH_2), 137.2, 134.0, 133.5, 128.7, 128.0, 127.9 (2C), 126.8 (2C), 126.5 (2C), 126.2 (2C), 126.0 (2C) (16 ArC), 115.1 (- CH=*C*H_2), 104.3 (C-1), 80.9 (C-3), 79.4 (C-2), 75.3 (O*C*H_2Naphth), 74.5 (C-4), 72.2 (O*C*H_2Ph), 69.1 (O-*C*H_2-CH_2-), 67.3 (C-5), 62.6 (C-6), 30.6 (-*C*H_2-CH=CH_2), 29.5 (-*C*H_2-CH_2-CH=CH_2) ppm.

Pent-4-enyl 3-*O*-benzyl-6-*O*-chloroacetyl-2-*O*-(2-naphtyl)methyl-β-D-galactopyranoside (67)

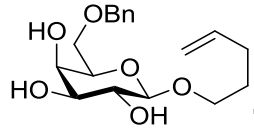


Diol **74** (5.7 g, 11.91 mmol) was dissolved in anhydrous CH_2Cl_2 (100 ml) and cooled in an ice bath. Et_3N (2.57 ml, 10.06 mmol) was added followed by chloroacetic anhydride (2.24 g, 13.10 mmol). The reaction mixture was stirred at 0 °C for 2 hours and then warmed up to 22 °C before being diluted with CH_2Cl_2 (100 ml), washed with ammonium chloride (3 x 100 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by flash chromatography (2:3 EtOAc/Heptane) to yield **67** as white solid (4.5 g, 68%).

R_f 0.22 (1:3 EtOAc/Heptane).

^{1}H NMR (400 MHz, C_6D_6) δ 7.84 (s, 1H, ArH), 7.71 – 7.61 (m, 3H, ArH), 7.55 (m, 1H, ArH), 7.31 – 7.20 (m, 4H, ArH), 7.19 – 7.06 (m, 3H, ArH), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C*H*=CH_2), 5.16 (d, *J* = 11.8 Hz, 1H, 0.5xOC*H*$_2$Naphth), 5.06 – 4.93 (m, 2H, -CH=C*H*$_2$), 4.91 (d, *J* = 11.8 Hz, 1H, 0.5xOC*H*$_2$Naphth), 4.59 – 4.37 (m, 4H, OC*H*$_2$Ph, H- 6ab), 4.22 (d, *J* = 7.8 Hz, 1H, H-1), 3.97 – 3.89 (m, 1H, 0.5xOC*H*$_2$-CH_2-), 3.85 (dd, *J* = 9.3, 7.8 Hz, 1H, H-2), 3.62 (dd, *J* = 3.4, 0.9 Hz, 1H, H-4), 3.50 (t, *J* = 3.8 Hz, 2H, C*H*$_2$-Cl), 3.49 – 3.40 (m, 1H, 0.5xOC*H*$_2$-CH_2-), 3.30 – 3.20 (m, 2H, H-3, H-5), 2.14 – 2.05 (m, 2H, -C*H*$_2$-CH=CH_2), 1.75 – 1.59 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 166.9 (OAcCl), 138.6 (-*C*H=CH_2), 138.3, 137.1, 134.0, 133.5, 128.7 (2C), 128.0 (2C), 126.8 (2C), 126.5 (2C), 126.3 (2C), 126.0 (2C) (16 ArC), 115.2 (-CH=*C*H_2), 104.1 (C-1), 80.5 (C-3), 79.2 (C-2), 75.2 (O*C*H_2Naphth), 72.4 (O*C*H_2Ph), 72.1 (C-5), 69.1 (O-*C*H_2-CH_2-), 67.0 (C-4), 65.4 (C-6), 40.7 (*C*H_2Cl), 30.6 (-*C*H_2-CH=CH_2), 29.4 (-*C*H_2-CH_2-CH=CH_2) ppm.

Pent-4-enyl 6-*O*-benzyl-β-D-galactopyranoside (75)[118]



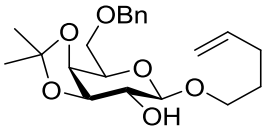
To a solution of diol **71** (8.00 g, 23.7 mmol) in CH_2Cl_2 (220 ml) was added $AlCl_3$ (4.76 g, 35.7 mmol) and 1,1,3,3-tetramethyldisiloxane (6.30 ml, 35.7 mmol) at –78 °C. After stirring at 22 °C for 12 hours, the mixture was diluted with CH_2Cl_2, washed with 1M aqueous HCl and water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was then purified by flash chromatography (1:10 MeOH/CH_2Cl_2) to yield compound **75** in 71% as a white solid. (5.69 g)

R_f 0.31 (1:10 MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 5H, ArH), 5.73 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, , -C*H*=CH_2), 5.01 – 4.83 (m, 2H, -CH=C*H*$_2$), 4.51 (s, 2H, OC*H*$_2$Ph), 4.14 (d, *J* = 7.6 Hz, 1H, H-1), 3.91 (d, *J* = 3.1 Hz, 1H, H-3), 3.88 – 3.79 (m, 1H, H-2), 3.74 – 3.42 (m, 6H, H-6ab, OC*H*$_2$-CH_2-CH_2-CH=CH_2, H-4, H-5), 2.76 (bs, 3H, 3xO*H*), 2.12 – 1.99 (m, 2H, - C*H*$_2$-CH=CH_2), 1.74 – 1.59 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.2 (-*C*H=CH_2), 138.0, 128.6 (2C), 128.0, 127.9 (2C) (6 ArC), 115.1 (-CH=*C*H_2), 103.2 (C-1), 73.8 (C-5), 73.7 (C-4),

73.6 (<u>C</u>H$_2$Ph), 72.0 (C-2), 69.6 (C-3), 69.5 (C-6), 69.3 (O-<u>C</u>H$_2$-CH$_2$-), 30.3 (- <u>C</u>H$_2$-CH=CH$_2$), 28.86 (-<u>C</u>H$_2$-CH$_2$-CH=CH$_2$) ppm.

Pent-4-enyl 6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (76)

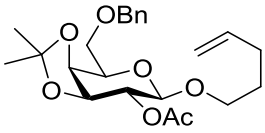


To a solution of **75** (8.63 g, 25.5 mmol) in anhydrous DMF (150 ml) was added 2,2-dimethoxypropane (9.37 ml, 76.5 mmol) and camphor sulfonic acid (1.18 g, 5.10 mmol). The mixture was stirred at 22 °C for 2 hours. Excess reagent was quenched with (0.9 ml) trimethylamine, stirred for an additional 30 minutes and concentrated. The crude was purified by flash chromatography (1:3 EtOAc/Heptane) to yield **76** as transparent oil in 90% (8.68 g).

R$_f$ 0.48 (2:3 EtOAc/Heptane).

^{1}H NMR (400 MHz, C$_6$D$_6$) δ 7.32 – 7.23 (m, 2H, ArH), 7.20 – 7.13 (m, 2H, ArH), 7.12 – 7.05 (m, 1H, ArH), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C<u>H</u>=CH$_2$), 5.07 – 4.90 (m, 2H, -CH=C<u>H$_2$</u>), 4.44 and 4.36 (ABq pattern, *J* = 12.2 Hz, 2H, OC<u>H$_2$</u>Ph), 4.05 – 3.92 (m, 2H, H-1, H-3), 3.91 – 3.66 (m, 6H, H-2, H-4, H-6ab, OC<u>H$_2$</u>-CH$_2$-CH$_2$-CH=CH$_2$), 3.33 (dt, *J* = 9.5, 6.6 Hz, 1H, H-5), 2.43 (d, *J* = 2.4 Hz, 1H, 2-O<u>H</u>), 2.01 (qd, *J* = 7.9, 3.9 Hz, 2H, -C<u>H$_2$</u>-CH=CH$_2$), 1.64 – 1.56 (m, 2H, -C<u>H$_2$</u>-CH$_2$-CH=CH$_2$), 1.44 (s, 3H, CH$_3^{isoprop}$), 1.22 (s, 3H, CH$_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C$_6$D$_6$) δ 139.0, 138.5 (-<u>C</u>H=CH$_2$), 128.6 (2C), 127.9, 127.8 (2C) (6 ArC), 115.0 (-CH=<u>C</u>H$_2$), 109.8 (<u>C</u>(CH$_3$)$_2$), 103.1 (C-1), 79.5 (C-2), 74.2 (2C, C-4 and C- 3), 73.6 (<u>C</u>H$_2$Ph), 72.9 (C-5), 70.0 (C-6), 69.0 (O-<u>C</u>H$_2$-CH$_2$-), 30.6 (-<u>C</u>H$_2$-CH=CH$_2$), 29.3 (-<u>C</u>H$_2$-CH$_2$-CH=CH$_2$), 28.4 (CH$_3^{isoprop}$), 26.6 (CH$_3^{isoprop}$) ppm.

Pent-4-enyl 2-*O*-acetyl-6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (66)



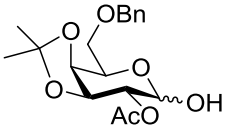
A solution of **76** (5.58 g, 15.0 mmol) was dissolved in anhydrous pyridine (60 ml). Acetic anhydride (2.83 ml, 30.0 mmol) and 4-dimethylaminopyridine (183 mg, 1.5 mmol) were added and the mixture was stirred at 22 °C for 12 hours. The reaction mixture was washed with water and the aqueous phase was extracted with dichloromethane. The organic phase was dried over MgSO$_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (1:3 EtOAc/Heptane) to yield product **66** as a transparent oil (91%, 5.74 g).

R$_f$ 0.26 (1:3 EtOAc/Heptane).

^{1}H NMR (400 MHz, C$_6$D$_6$) δ 7.29 (dd, *J* = 7.9, 1.0 Hz, 2H, ArH), 7.21 – 7.13 (m, 2H, ArH), 7.13 – 7.06 (m, 1H, ArH), 5.69 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, - C<u>H</u>=CH$_2$), 5.46 (t, *J* = 8.3 Hz, 1H, H-2), 5.03 – 4.90 (m, 2H, -CH=C<u>H$_2$</u>), 4.45 and 4.38 (AB$_q$ pattern, 12.2 Hz, 2H, OC<u>H$_2$</u>Ph), 4.17 (d, *J* = 8.3 Hz, 1H, H-1), 3.97 (dd, *J* = 7.6, 5.3 Hz, 1H, H-3), 3.90 – 3.78 (m, 4H, H-4, H-6ab, 0.5xOC<u>H$_2$</u>-CH$_2$-), 3.72 – 3.66 (m, 1H, H-5), 3.33 (ddd, *J* = 18.5, 10.5, 6.1 Hz, 1H, 0.5xOC<u>H$_2$</u>-CH$_2$-), 2.07 – 1.99 (m, 2H, -C<u>H$_2$</u>-CH=CH$_2$), 1.78 (d, *J* = 3.2 Hz, 3H, CH$_3^{Ac}$), 1.55 (m, 5H, CH$_3^{isoprop}$, -C<u>H$_2$</u>-CH$_2$-CH=CH$_2$), 1.20 (s, 3H, CH$_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C$_6$D$_6$) δ 169.0 (OAc), 139.0, 138.4

(-<u>C</u>H=CH_2), 128.6 (2C), 128.2, 127.9 (2C) (6 ArC), 115.0 (-CH=<u>C</u>H_2), 110.5 (<u>C</u>$(CH_3)_2$), 100.9 (C-1), 77.7 (C-3), 74.3 (C-4), 73.6 (<u>C</u>H_2Ph), 73.3 (C- 2), 72.7 (C-5), 69.9 (C-6), 68.4 (O-<u>C</u>H_2-CH_2-), 30.4 (-<u>C</u>H_2-CH=CH_2), 29.2 (-<u>C</u>H_2-CH_2-CH=CH_2), 28.0 ($CH_3^{isoprop}$), 26.7 ($CH_3^{isoprop}$), 20.67 (CH_3^{Ac}) ppm.

2-*O*-acetyl-6-*O*-benzyl-3,4-*O*-isopropylidene-D-galactopyranose (77)



Compound **66** (500 mg, 1.19 mmol) was dissolved in CH_2Cl_2 (12 ml). Water (20 µl, 1.3 mmol) was added and the mixture was cooled down to -20 °C. NIS (275 mg, 1.42 mmol), TESOTf (45 µl, 0.24 mmol) and K_2CO_3 (250 mg, 1.19 mmol) were added and the reaction was stirred for 1.5 hour at - 20 °C. The reaction mixture was then diluted with CH_2Cl_2, washed with $Na_2S_2O_3$ and with saturated aqueous $NaHCO_3$. The water phase was then extracted with CH_2Cl_2 and the combine organic phases were dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography to yield hemiacetal **77** in 52% (218 mg) (4:1 α/β).

R_f 0.45 (1:1 EtOAc/Heptane).

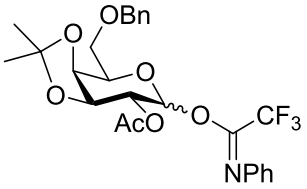
α-anomer:

^{1}H NMR (400 MHz, C_6D_6) δ 7.28 (d, *J* = 7.2 Hz, 2H, ArH), 7.20 – 7.12 (m, 2H, ArH), 7.09 (dt, *J* = 7.3, 4.3 Hz, 1H, ArH), 5.49 (t, *J* = 3.6 Hz, 1H, H-2), 5.31 (dd, *J* = 8.0, 3.2 Hz, 1H, H-5), 4.53 – 4.28 (m, 3H, OC<u>*H*$_2$</u>Ph, 1-O<u>*H*</u>), 4.17 (d, *J* = 3.6 Hz, 1H, H-1), 3.93 – 3.79 (m, 2H, H-3, H- 4), 3.76 – 3.65 (m, 2H, H-6ab), 1.73 (s, 3H, CH_3^{Ac}), 1.49 (s, 3H, $CH_3^{isoprop}$), 1.15 (s, 3H, $CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 170.3 (OAc), 138.5, 128.7 (2C), 128.2 (2C), 127.9 (6 ArC), 109.7 (<u>C</u>$(CH_3)_2$), 90.9 (C-1), 74.2 (C-3), 73.9 (C-4), 73.6 (O<u>C</u>H_2Ph), 72.6 (C-2), 70.2 (C- 5), 67.1 (C-6), 28.1 ($CH_3^{isoprop}$), 26.5 ($CH_3^{isoprop}$), 20.6(CH_3^{Ac}) ppm.

β-anomer:

^{1}H NMR (400 MHz, C_6D_6) δ 7.28 (d, *J* = 7.2 Hz, 2H, ArH), 7.20 – 7.12 (m, 2H, ArH), 7.09 (dt, *J* = 7.3, 4.3 Hz, 1H, ArH), 5.31 (dd, *J* = 8.0, 3.2 Hz, 1H, H-5), 5.22 (t, *J* = 7.8 Hz, 1H, H-2), 4.53 – 4.28 (m, 3H, OC<u>*H*$_2$</u>Ph, 1-O<u>*H*</u>), 3.93 – 3.79 (m, 3H, H-3, H-4, H-1), 3.76 – 3.65 (m, 2H, H- 6ab), 1.73 (s, 3H, CH_3^{Ac}), 1.49 (s, 3H, $CH_3^{isoprop}$), 1.15 (s, 3H, $CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 170.6 (OAc), 138.7, 128.6 (2C), 128.2 (2C), 127.9 (6ArC), 110.4 (<u>C</u>$(CH_3)_2$), 95.5 (C-1), 77.0 (C-3), 75.3 (C-4), 74.3 (O<u>C</u>H_2Ph), 73.6 (C-2), 72.5 (C-5), 69.8 (C-6), 28.0 ($CH_3^{isoprop}$), 26.4 ($CH_3^{isoprop}$), 23.1 (CH_3^{Ac}) ppm.

2-*O*-acetyl-6-*O*-benzyl-3,4-*O*-isopropylidene-D-galactopyranose *N*-phenyl trifluoroacetimidate (78)

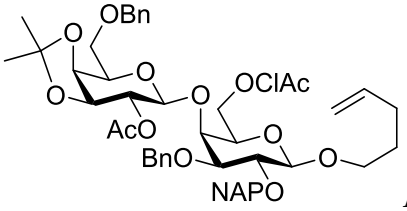


Hemiacetal **77** (600 mg, 1.70 mmol) was dissolved in CH_2Cl_2 (10 ml) and cooled to 0 °C. *N*-phenyl trifluoroacetimidoyl chloride (0.55 ml, 3.41 mmol) and cesium carbonate (1.11g, 3.41 mmol) were added and the reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The crude was purified by flash chromatography (1:4 EtOAc/Heptane) to yield a white solid (578 mg, 65%).

$\mathbf{R}_f$ 0.45 (1:3 EtOAc/Heptane).

^{1}H NMR (400 MHz, C_6D_6) δ 7.30 – 6.93 (m, 7H, ArH), 6.93 – 6.80 (m, 1H, ArH), 6.80 – 6.72 (m, 2H, ArH), 5.64 (t, *J* = 7.3 Hz, 1H, H-2), 4.40 and 4.32 (ABq, *J* = 12.0 Hz, 2H, OC$\underline{H_2}$Ph), 3.90 (t, *J* = 6.8 Hz, 1H, H-4), 3.78 (dt, *J* = 12.9, 4.2 Hz, 4H, H-3, H- 5, H-6ab), 1.70 (s, 3H, CH_3^{Ac}), 1.53 (s, 3H, $CH_3^{isoprop}$), 1.14 (s, 3H, $CH_3^{isoprop}$) (no signal for H- 1) ppm. **^{13}C NMR** (101 MHz, C_6D6) δ 169.6 (OAc), 144.0 (C*ipso*, NPh), 138.8, 129.3 (2C), 129.1 (2C), 128.6 (2C), 127.9 (2C), 124.6 (10 ArC), 119.7 (ArC, NPh), 110.1 ($\underline{C}(CH_3)_2$), 93.62 (C-1), 73.6, 73.2, 73.1, 70.6, 69.4 (C-5), 69.4 (C-6), 27.6 ($CH_3^{isoprop}$), 26.1 ($CH_3^{isoprop}$), 20.2 (CH_3^{Ac}) ppm (no signals for CF_3 and C=NPh).

Pent-4-enyl 2-*O*-acetyl-6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-chloroacetyl-2-*O*-(2-naphtyl)methyl-β-D-galactopyranoside (79)



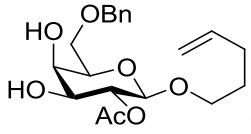
A mixture of donor **78** (100 mg, 0.19 mmol) and acceptor **67** (127 mg, 0.23 mmol) was co-evaporated with toluene and subjected to high vacuum overnight. The mixture was dissolved in CH_2Cl_2 (4 ml) and cooled down to - 40 °C. TMSOTf (1.81 µl, 0.01 mmol) was added and the reaction was stirred at - 40 °C until TLC showed full conversion of the donor (6 hours). The reaction was quenched by addition of trimethylamine (0.02 ml) concentrated *in vacuo* and purified by flash chromatography (10:1 EtOAc/Toluene) to yield disaccharide **79** in 24% (40 mg).

$\mathbf{R}_f$ 0.62 (1:4 EtOAc/Toluene).

^{1}H NMR (400 MHz, C_6D_6) δ 7.84 (m, 1H, ArH), 7.68 – 7.60 (m, 3H, ArH), 7.57 – 7.51 (m, 1H, ArH), 7.37 (m, 3H, ArH), 7.30 – 7.17 (m, 6H, ArH), 7.18 – 7.08 (m, 3H, ArH), 5.71 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C$\underline{H}$=CH_2), 5.42 – 5.31 (t, *J* = 8.0 Hz, 1H, H- 2'), 5.23 (dd, *J* = 11.7, 5.9 Hz, 1H, 0.5xOC$\underline{H_2}$Naphth), 5.08 – 5.00 (m, 1H, 0.5x-CH=C$\underline{H_2}$), 5.00 – 4.90 (m, 2H, 0.5xOC$\underline{H_2}$Naphth, 0.5x-CH=C$\underline{H_2}$), 4.73 (d, *J* = 8.0 Hz, 1H, H-1'), 4.65 (m, 2H, OC$\underline{H_2}$Ph'), 4.55 (m, 1H, H-6a), 4.53 – 4.45 (m, 2H, OC$\underline{H_2}$Ph), 4.41 (d, *J* = 12.0 Hz, 1H, H-1), 4.29 – 4.23 (m, 1H, H-6b), 4.00 – 3.81 (m, 5H, H-3, H-3', H-6ab', H-4), 3.80 – 3.66 (m, 3H, H-2, H-5', H-4'), 3.53 (d, *J* = 5.6 Hz, 2H, O-C$\underline{H_2}$-CH_2-), 3.51 – 3.43 (m, 2H, C$\underline{H_2}$Cl), 3.32 (dt, *J* = 8.9, 4.4 Hz, 1H, H-5), 3.26 (dd, *J* = 9.7,

2.9 Hz, 1H, H-3), 2.10 – 2.01 (m, 2H, -C$\underline{H_2}$-CH=CH_2), 1.80 – 1.73 (m, 3H, CH_3^{Ac}), 1.70 – 1.58 (m, 2H, -C$\underline{H_2}$-CH_2-CH=CH_2), 1.51 (d, *J* = 9.4 Hz, 3H, $CH_3^{isoprop}$), 1.24 – 1.03 (m, 3H, $CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 169.2 (OAc), 166.9 (OAcCl), 139.1 , 138.9, 138.4 (-$\underline{C}$H=CH_2), 137.2, 134.0, 133.5, 128.7 (4C), 128.5, 128.1 (4C), 128.0, 127.9 (2C), 127.7, 126.7, 126.4, 126.3, 126.0 (22 ArC), 115.1 (-CH=$\underline{C}H_2$), 110.5 ($\underline{C}(CH_3)_2$) 104.1 (C-1'), 101.3 (C-1), 81.7 (C-3), 79.6 (C-2), 77.2 (C-3'), 75.3 (O$\underline{C}H_2$Naphth), 74.1 (C-4'), 73.8 (2C, O$\underline{C}H_2$Ph', C-4), 73.5 (C-5), 73.2 (C-2'), 72.7 (O$\underline{C}H_2$Ph), 72.2 (C-5'), 70.1 (C-6') , 68.8 (O-$\underline{C}H_2$-CH_2-), 66.3 (C-6), 40.8 ($\underline{C}H_2$Cl), 30.6 (-$\underline{C}H_2$-CH=CH_2), 29.4 (-$\underline{C}H_2$-CH_2-CH=CH_2), 27.9 ($CH_3^{isoprop}$), 26.5 ($CH_3^{isoprop}$), 20.8 (CH_3^{Ac}) ppm.

Pent-4-enyl 2-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (81)

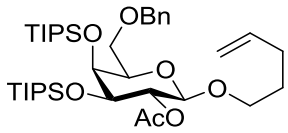


66 (4.64 g, 11.03 mmol) was dissolved in 80 % AcOH in water (100 ml) and stirred at 22 °C for 24 hours. The reaction mixture was extracted with dichloromethane and the organic phase washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (1:1 EtOAc/Heptane) to give **81** in 90% yield (3.77 g).

R_f 0.20 (1:1 EtOAc/Heptane).

^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (dd, *J* = 7.9, 1.0 Hz, 2H, ArH), 7.21 – 7.14 (m, 2H, ArH), 7.10 (m, 1H, ArH), 5.70 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H, -C$\underline{H}$=CH_2), 5.36 (t, *J* = 8.0 Hz, 1H, H-2), 5.00 (ddd, *J* = 17.1, 3.6, 1.2 Hz, 1H, 0.5x-CH=C$\underline{H_2}$), 4.94 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H, 0.5x-CH=C$\underline{H_2}$), 4.34 (s, 2H, OC$\underline{H_2}$Ph), 4.21 (d, *J* = 8.0 Hz, 1H, H-1), 3.88 – 3.79 (m, 1H, 0.5xOC$\underline{H_2}$-CH_2-), 3.77 (t, *J* = 4.3 Hz, 1H, H-5), 3.64 (m, *J* = 10.0, 5.6 Hz, 2H, H-6ab), 3.35 (dt, *J* = 9.6, 6.6 Hz, 1H, 0.5xOC$\underline{H_2}$-CH_2-), 3.16 (d, *J* = 8.0 Hz, 1H, H-3), 2.87 (d, *J* = 4.3 Hz, 1H, H-4), 2.07 – 1.99 (m, 2H, -C$\underline{H_2}$-CH=CH_2), 1.80 (d, *J* = 4.0 Hz, 3H, CH_3^{Ac}), 1.64 – 1.49 (m, 2H, -C$\underline{H_2}$-CH_2-CH=CH_2) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 170.9 (OAc), 138.7 (2C), 138.4 (-$\underline{C}$H=CH_2), 128.7 (2C), 127.9, 127.9 (2C) (6 ArC), 115.1(-CH=$\underline{C}H_2$), 101.4 (C- 1), 73.8 (C-4), 73.7 (C-3), 73.6 (O$\underline{C}H_2$Ph), 73.2 (C-2), 70.0 (C-5), 69.8 (C-6), 68.6 (O-$\underline{C}H_2$-CH_2-), 30.4 (-$\underline{C}H_2$-CH=CH_2), 29.3 (-$\underline{C}H_2$-CH_2-CH=CH_2), 20.8 (CH_3^{Ac}) ppm.

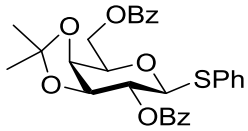
Pent-4-enyl 2-*O*-acetyl-6-*O*-benzyl-3,4-O-ditriisopropylsilyl-β-D-galactopyranoside (83)



Diol **81** (2 g, 5.26 mmol) was dissolved in CH_2Cl_2 (50 ml) and 4-dimethylaminopyridine (450 mg, 3.68 mmol) and 2,6-lutidine (1.69 g, 15.78 mmol) were added. The solution was cooled down to 0 °C and triisopropylsilyl trifluoromethanesulfonate (3.81 ml, 14.20 mmol) was added. The reaction mixture was stirred at 0 °C for 1 hour and 2 hours more at 22 °C before being quenched with methanol and concentrated *in vacuo*. The crude was purified by flash chromatography (1:6 EtOAc/Heptane) to yield **83** in 82% (3.0 g)

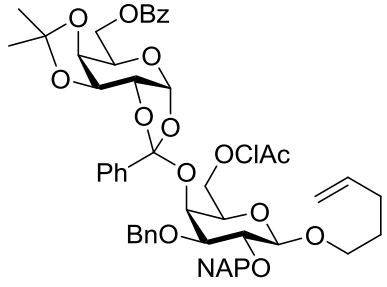
R_f 0.55 (1:3 EtOAc/Heptane).
^{1}H NMR (400 MHz, C_6D_6) δ 7.29 (d, *J* = 7.1 Hz, 2H, ArH), 7.18 (m, 2H, ArH), 7.12 – 7.06 (m, 1H, ArH), 5.71 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, -C*H*=CH_2), 5.57 (dd, *J* = 9.4, 8.0 Hz, 1H, H-2), 5.00 (ddd, *J* = 16.9, 3.4, 1.6 Hz, 1H, 0.5x- CH=C*H*$_2$), 4.97 – 4.92 (m, 1H, 0.5x-CH=C*H*$_2$), 4.41 (s, 2H, OC*H*$_2$Ph), 4.25 (d, *J* = 8.0 Hz, 1H, H-1), 3.97 – 3.80 (m, 4H, H-6ab, H-3, H-4), 3.53 (t, *J* = 6.1 Hz, 1H, H-5), 3.43 – 3.35 (m, 2H, OC*H*$_2$-CH_2-), 2.05 (q, *J* = 7.3 Hz, 2H, , -C*H*$_2$-CH=CH_2), 1.91 – 1.87 (s, 3H, CH_3^{Ac}), 1.67 – 1.47 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2), 1.13 – 0.99 (m, 18H, 9x$CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 168.8 (OAc), 139.0, 138.5 (-*C*H=CH_2), 128.6 (2C), 128.2, 127.9 (2C) (6 ArC), 115.0 (-CH=*C*H_2), 101.7 (C-1), 74.0 (C-5), 73.9 (C-3), 73.7 (O*C*H_2Ph), 72.4 (C-2), 70.1 (C-4), 69.5 (C-6), 68.2 (O-*C*H_2-CH_2-), 30.4 (-*C*H_2-CH=CH_2), 29.3 (-*C*H_2-CH_2-CH=CH_2), 21.0 (CH_3^{Ac}), 18.2 (2C, Cq^{TIPS}), 18.1 (2C, CH_3^{TIPS}), 18.1 (2C, CH_3^{TIPS}), 18.0 (2C, CH_3^{TIPS}) ppm.

Phenyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside[174] (90)



To a solution of phenyl 1-thio-β-D-galactopyranoside **89** (1.0 g, 3.68 mmol) in anhydrous dimethylformamide (40 ml) were added 2,2-dimethoxypropane (0.68 ml, 5.51 mmol) and camphor sulfonic acid (172 mg, 0.74 mmol). The reaction mixture was stirred at 22 °C for 12 hours. The reaction was then quenched with 0.5 ml triethylamine, diluted with EtOAc, washed with ammonium chloride, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in 25 ml of anhydrous pyridine, cooled down to 0 °C and benzoyl chloride (1.71 ml, 14.6 mmol) was slowly added. The reaction mixture was then warmed up to 22 °C and stirred for 12 hours. Water was then added to the mixture and the compound was extracted with diethyl ether. The organic phase was further washed with ammonium chloride, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:4 EtOAc/Heptane) yielding **90** as a white crystalline solid (1.2 g, 62%). The compound analyses were in accordance with data from the literature.
mp 129-.131 °C. **R_f** 0.55 (1:2 EtOAc/Hept).
^{1}H NMR (400 MHz, C_6D_6) δ 8.20 (ddt, *J* = 9.7, 6.5, 1.8 Hz, 4H ArH), 8.10 (dt, *J* = 8.5, 1.6 Hz, 1H, ArH), 7.52 – 7.47 (m, 2H, ArH), 7.16 – 7.04 (m, 3H, ArH), 7.02 – 6.96 (m, 2H, ArH), 6.92 – 6.81 (m, 3H, ArH), 5.72 (dd, *J* = 10.1, 7.3 Hz, 1H, H- 2), 4.75 (dd, *J* = 11.8, 3.4 Hz, 1H, H-6a), 4.66 (dd, *J* = 11.8, 8.4 Hz, 1H, H-6b), 4.56 (d, *J* = 10.1 Hz, 1H, H-1), 4.07 (dd, *J* = 7.2, 5.4 Hz, 1H, H-3), 3.78 (dd, *J* = 5.4, 2.2 Hz, 1H, H-4), 3.76 – 3.70 (m, 1H, H-5), 1.51 (s, 3H, $CH_3^{isoprop.}$), 1.16 (s, 3H, $CH_3^{isoprop.}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 166.2 (OBz), 165.5 (OBz), 133.7, 133.2, 132.2 (2C), 130.5 (2C), 130.2 (2C), 130.1 (2C), 129.0 (2C), 128.7 (2C), 128.6 (2C), 127.9, 127.6 (18 ArC), 111.1 (*C*$(CH_3)_2$), 86.1 (C-1), 77.6 (C- 3), 74.7 (C-5), 74.1 (C-4), 72.3 (C-2), 64.5 (C-6), 27.8 ($CH_3^{isoprop}$), 26.5 ($CH_3^{isoprop}$) ppm.

6-*O*-benzoyl-3,4-*O*-isopropylidene-1,2-(Phenyl 3-*O*-benzyl-6-O-chloroactyl-2-*O*-(2- naphtyl)methyl-β-D-galactopyranosidepent-4-enyl Orthoacetate) (92)



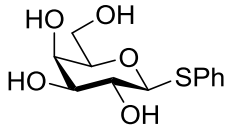
Preparation of 1 mL 1M Me_2S_2/Tf_2O in dichloromethane: Me_2S_2 (0.1 mL) was diluted in anhydrous dichloromethane (1 mL) and cooled down to 0 °C. Triflic anhydride (0.17 mL) was added and the mixture was stirred for 30 minutes at 0 °C.

Thiophenyl galactoside **90** (169 mg, 0.32 mmol) and acceptor **67** (150 mg, 0.27 mmol) were co-evaporated with toluene three times and subjected to high vacuum overnight. The mixture was dissolved in dichloromethane (6 ml) and stirred with 4 Å MS for 30 minutes. The reaction mixture was cooled down to - 40 °C, 1M Me_2S_2/Tf_2O in dichloromethane (0.54 mL) and TTBP (80.6 mg, 0.32 mmol) were added. The mixture was stirred for 20 minutes until TLC showed full conversion of the donor. The reaction was then quenched with triethylamine (0.3 mL). The mixture was diluted with dichloromethane, filtered through celite, washed with $NaHCO_3$. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the crude product was purified by flash chromatography (1:40 EtOAc/Toluene) to yield the orthoester product **92** in 18% yield (46 mg).

R_f 0.60 (1:5 EtOAc/Toluene).

^{1}H NMR (400 MHz, C_6D_6) δ 8.35 – 8.04 (m, 3H, ArH), 7.82 (dd, *J* = 14.2, 8.0 Hz, 2H, ArH), 7.76 (s, 1H, ArH), 7.74 – 7.58 (m, 3H, ArH), 7.50 – 6.93 (m, 13H, ArH), 5.92 (d, *J* = 5.1 Hz, 1H, H-1'), 5.79 – 5.62 (m, 1H, -C*H*=CH_2), 5.06 – 4.74 (m, 5H, H-2', OC*H*$_2$Naphth, -CH=C*H*$_2$), 4.72 – 4.25 (m, 6H, H-1, OC*H*$_2$Ph, H-6ab', H-6a), 4.25 – 4.05 (m, 2H, H-3', H-6b), 4.05 – 3.89 (m, 2H, 0.5xO-C*H*$_2$-CH_2-, H-4), 3.89 – 3.65 (m, 2H, H-5', H-2), 3.61 – 3.42 (m, 4H, C*H*$_2$Cl, 0.5xO-C*H*$_2$-CH_2-, H-4'), 3.42 – 3.32 (m, 1H, H-5), 3.32 – 3.19 (m, 1H, H-3), 2.15 – 2.02 (m, 2H, -C*H*$_2$-CH=CH_2), 1.76 – 1.57 (m, 2H, -C*H*$_2$-CH_2-CH=CH_2), 1.41 – 1.28 (s, 3H, $CH_3^{isoprop}$), 1.09 – 0.98 (s, 3H , $CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 166.6 (OAcCl), 165.9 (OBz), 139.0, 138.4 (-*C*H=CH_2), 137.4, 136.9, 133.9, 133.5, 132.9, 130.9, 130.2, 130.1, 129.5, 129.3, 128.9, 128.7 (2C), 128.6 (3C), 128.5, 128.4, 128.2 (2C), 127.9, 126.9, 126.8, 126.5, 126.2, 126.0, 125.7 (28 ArC), 121.7 (Ph*C*O_2), 115.1 (-CH=*C*H_2), 109.7 (*C*$(CH_3)_2$), 103.7 (C-1), 97.9 (C-1'), 80.2 (C-3), 78.5 (C-2), 74.9 (O*C*H_2Naphth), 72.5 (O*C*H_2Ph), 72.4 (C-5), 71.6 (C-2'), 71.0 (C-4'), 70.7 (C-3'), 69.0 (O-*C*H_2-CH_2-), 68.6 (C-4), 68.1 (C-5'), 65.8 (C-6), 64.4 (C-6'), 40.6 (*C*H_2Cl), 30.6 (-*C*H_2-CH=CH_2), 29.4 (-*C*H_2-CH_2-CH=CH_2), 26.1($CH_3^{isoprop}$), 24.3 ($CH_3^{isoprop}$) ppm.

Phenyl 1-thio-β-D-galactopyranoside[175] **(89)**

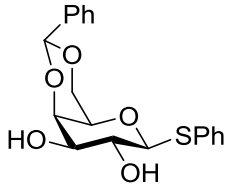


To a solution of galactose pentaacetate (30.0 g, 76.9 mmol) and thiophenol (8.75 mL, 85.8 mmol) in CH_2Cl_2 (250 mL) was added boron trifluoride diethyl etherate (9.75 mL, 76.9 mmol). The reaction mixture was stirred at 22 °C for 12 hours. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHCO_3$ (300 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Without further purification, the peracetylated thioglycoside was deacetylated. Na (1.28 g, 55.5 mmol) was dissolved in MeOH (130 mL) and the NaOMe/MeOH solution was slowly added to a solution of the peracetylated sugar in MeOH (100 mL). The reaction mixture was stirred at 22 °C until TLC showed full conversion (12 h). The reaction was quenched with Amberlite IR-120 H^+ (50 mL) and stirred for 1 h. The ion-exchange resin was filtered off, washed with MeOH and the filtrate was concentrated *in vacuo*. The product was recrystallized from EtOAc to give **89** as colorless crystals. Yield (over two steps) 19.0 g (91%). Its analytical data matched with those reported.[175]

mp 98 °C. $\mathbf{R_f}$ 0.48 (1:1 EtOAc/Acetone).

^{1}H NMR (400 MHz, DMSO) δ 7.42 (d, *J* = 7.4 Hz, 2H, ArH), 7.27 (t, *J* = 7.4 Hz, 2H, ArH), 7.17 (d, *J* = 7.4 Hz, 1H, ArH), 4.84 (d, *J* = 13.0 Hz, 1H, H- 1), 4.06 (d, *J*= 3.2 Hz, 1H, H-4), 3.85-3.75 (m, 4H, H-3, H-5, H-6ab), 3.70 (m, 1H, H-2) ppm. **^{13}C NMR** (101 MHz, DMSO) δ 136.3 (*ipso*-C, Ar), 129.8 (2C, *ortho*-C, Ar), 129.5 (2C, *meta*-C, Ar), 126.7 (*para*-C, Ar), 88.4 (C-1), 79.8 (C-5), 75.3 (C-2), 69.9 (C-3), 69.0 (C-4), 61.2 (C-6) ppm.

Phenyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside[176] **(100)**

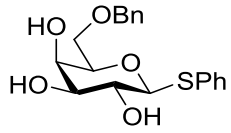


To a solution of benzaldehyde dimethyl acetal (12.6 mL, 83.8 mmol) and camphor sulphonic acid (0.13 g, 0.56 mmol) in MeCN (350 mL) was added **89** (15.22 g, 55.9 mmol). The flask was equipped with a distillation unit and the mixture was heated to reflux for 1.5 hour. During this period approximately 100 mL of MeCN-MeOH was distilled off. The distillation unit was replaced with a condenser and the reaction mixture was heated to reflux until TLC showed full conversion (1 h). The residue was then recrystallized from EtOAc yielding the desired product in 80% (16.12 g). Its analytical data matched with those reported.

mp: 148-150 °C. $\mathbf{R_f}$ 0.25 (19:1 CH_2Cl_2/MeOH).

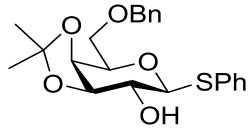
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 2H, ArH), 7.45 – 7.23 (m, 8H, ArH), 5.51 (s, 1H, PhC*H*O_2), 4.51 (d, *J* = 8.0 Hz, 1H, H-1), 4.38 (d, *J* = 12.5 Hz, 1H, H-6a), 4.21 (d, *J* = 1.3 Hz, 1H, H-3), 4.03 (d, *J* = 12.5 Hz, 1H, H-6b), 3.76 – 3.63 (m, 2H, H-5, H-4), 3.56 (s, 1H, H-2), 2.30 (s, 2H, 2-O*H*, 3-O*H*) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.8 , 133.9 (2C), 131.0, 129.6, 129.1 (2C), 128.5 (2C), 128.4, 126.8 (2C) (12 ArC), 101.6 (Ph*C*HO_2) 87.1 (C-1), 75.6 (C-4), 73.9 (C-3), 70.2 (C-5), 69.5(C-6), 68.9 (C-2) ppm.

Phenyl 6-*O*-benzyl-1-thio-β-D-galactopyranoside[118] **(101)**



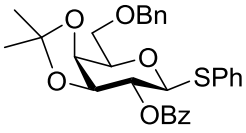
Diol **100** (14.38 g, 39.9 mmol) was co-evaporated three times with toluene and subjected to high vacuum for 2 hours. The compound was then dissolved in CH_2Cl_2 (330 ml) and $AlCl_3$ (7.89 g, 59.85 mmol) and 1,1,3,3-tetramethyldisiloxane (10.58 mL, 59.85 mmol) were added at –78 °C. After stirring at 22 °C for 12 hours, the mixture was diluted with CH_2Cl_2, washed with 1M aqueous HCl and water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was then purified by flash chromatography (1:15 MeOH/CH_2Cl_2) to yield compound **101** in 71% as a white solid (10.3 g). The compound analyses were in accordance with data from the literature.[177]
mp: 123-125 °C. $\mathbf{R}_f$ 0.62 (1:6 MeOH/CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H, ArH), 7.30 – 7.15 (m, 8H, ArH), 4.49 (m, 3H, H-1 and OC*H*$_2$Ph), 3.99 (d, *J* = 2.8 Hz, 1H, H- 3), 3.75 – 3.71 (m, 2H, H-6ab), 3.71 – 3.64 (m, 1H, H-2), 3.60 (dd, *J* = 11.4, 6.1 Hz, 1H, H-5), 3.55 (m, 2H, H-4 and 4-O*H*), 3.23 (d, *J* = 2.7 Hz, 1H, 2-O*H*), 3.20 (d, *J* = 4.1 Hz, 1H, 3-O*H*) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.9, 132.9, 132.3 (2C), 129.1 (2C), 128.6 (2C), 128.0, 127.9, 127.8 (2C), 88.8 (C-1), 77.5 (C-5), 75.0 (C-4), 73.8 (O*C*H$_2$Ph), 70.1 (C-2), 69.9 (C-6), 69.6 (C-3) ppm.

Phenyl 6-*O*-benzyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside[178] **(102)**



To a solution of **101** (9.74 g, 26.87mmol) in anhydrous dimethylformamide (150 mL) were added 2,2-dimethoxypropane (9.8 mL, 80.62 mmol) and camphor sulfonic acid (1.25 g, 5.37 mmol). The mixture was stirred at 22 °C for 3 hours. The acid was quenched with triethylamine (1.5 mL) and stirred for 30 additional minutes. The mixture was then concentrated *in vacuo* and the crude product was purified by flash chromatography (1:3 EtOAc/Heptane) yielding a white solid product in 90% (9.73 g). The compound analyses were in accordance with data from the literature.[178]
$\mathbf{R}_f$ 0.41 (2:3 EtOAc/Heptane).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H, ArH), 7.26 (t, *J* = 4.7 Hz, 4H, ArH), 7.25 – 7.16 (m, 4H, ArH), 4.60 – 4.46 (m, 2H, OC*H*$_2$Ph), 4.39 (d, *J* = 9.9 Hz, 1H, H-1), 4.13 (dd, *J* = 5.5, 2.1 Hz, 1H, H-4), 4.00 (dd, *J* = 7.1, 5.5 Hz, 1H, H-3), 3.90 (ddd, *J* = 6.7, 5.4, 2.1 Hz, 1H, H-5), 3.78 – 3.69 (m, 2H, H-6ab), 3.49 (dd, *J* = 9.9, 7.1 Hz, 1H, H-2), 2.44 (d, *J* = 1.0 Hz, 1H, 2-O*H*), 1.36 (d, *J* = 8.4 Hz, 3H, $CH_3^{isoprop}$), 1.26 (s, 3H, $CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.3, 132.6, 132.4, 129.1 (2C), 128.5 (2C), 128.1, 127.8, 127.7 (2C), 110.4 (*C*$(CH_3)_2$), 88.10 (C-1), 79.1 (C-5), 76.2 (C-4), 73.9 (O*C*H$_2$Ph), 73.7 (C-3), 71.7 (C-2), 69.7 (C-6), 28.19 ($CH_3^{isoprop}$), 26.5 ($CH_3^{isoprop}$) ppm.

Phenyl 2-*O*-benzoyl-6-*O*-benzyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (93)

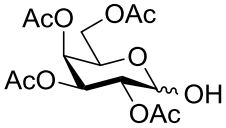


To a solution of alcohol **102** (12.7 g, 31.55 mmol) in anhydrous pyridine (200 mL) was added benzoyl chloride (7.3 mL, 63.11 mmol) dropwise at 0 °C. The reaction was stirred at 20 °C for 12 hours. Water (200 mL) was added and the product was extracted with diethyl ether (3x100 mL). The combined organic phases were washed three times with saturated aqueous NH_4Cl (3 x 200 mL) before being dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (1:3 EtOAc/Heptane) affording the product as a white solid in 96% yield (15.4 g).

mp = 102-105 °C. $\mathbf{R}_f$ 0.51 (1:2 EtOAc/Heptane). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$= 18.0° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, C_6D_6) δ 8.21 – 8.17 (m, 2H, ArH), 7.59 – 7.55 (m, 2H, ArH), 7.30 (d, *J* = 7.3 Hz, 2H, ArH), 7.22 – 7.15 (m, 2H, ArH), 7.14 – 6.91 (m, 7H, ArH), 5.74 (dd, *J* = 10.0, 7.2 Hz, 1H, H-2), 4.68 (d, *J* = 10.0 Hz, 1H, H-1), 4.43 and 4.35 (ABq pattern, *J* = 12.0 Hz, 2H, OC*H*$_2$Ph), 4.07 (dd, *J* = 7.2, 5.4 Hz, 1H, H-3), 3.91 – 3.84 (m, 2H, H-4, H-5), 3.79 – 3.70 (m, 2H, H-6ab), 1.54 (s, 3H, $CH_3^{isoprop}$), 1.19 (s, 3H, $CH_3^{isoprop}$) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 165.4 (OBz) , 139.0, 134.6 (2C), 133.1 (2C), 132.3 (2C), 130.7 (2C), 130.2 (2C), 129.1 (2C), 128.6, 127.9 (2C), 127.6 (2C) (18 ArC), 110.7 (*C*$(CH_3)_2$), 86.1 (C-1), 77.6 (C-5), 76.2 (C-4), 74.3 (O*C*H_2Ph), 73.6 (C-3), 72.5 (C-2), 70.0 (C-6), 27.9 ($CH_3^{isoprop}$), 26.57 ($CH_3^{isoprop}$) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{29}H_{30}NaO_6S$ 529.1655; found 529.1657.

2,3,4,6-O-tetraacetyl-D-galactopyranose[129] (103)

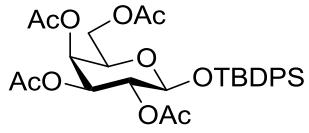


Galactose pentaacetate (70.0 g, 179.36 mmol) was dissolved in anhydrous DMF (300 mL) at 55 °C, hydrazine acetate (18.5 g, 200.91 mmol) was added and the mixture was stirred at 55 °C for 20 min. After cooling, 50% sat. aq. $NaHCO_3$ (1000 mL) was added and the suspension was extracted with EtOAc (4 x 200 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$ (400 mL) and H_2O (400 mL), evaporated on celite and purified by dry column vacuum chromatography (0–100% EtOAc in Toluene – 5% increments EtOAc/Toluene) to afford **103** as a white foam. Yield 50.0 g (80%) The compound analyses were in accordance with data from the literature.

$\mathbf{R}_f$ 0.55 (1:1/ EtOAc/Hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (d, *J* = 3.6 Hz, 1H, H-1α), 5.47 (d, *J* = 10.7 Hz, *J* = 3.6 Hz, 1H, H-2), 5.40 (d, *J* = 3.3 Hz,1H, H-4), 5.15 (dd, *J* = 10.7 Hz, *J* = 3.3Hz, 1H, H-3), 4.48 (t, *J* = 6.6 Hz, 1H, H-5), 4.38 (s, 1H, 1-O*H*), 4.11 (dd, *J* = 1.8 Hz, 1H, H-6b), 4.09 (m, 1H, H-6a), 2.15 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 170.4, 170.2, 170.0 (4 OAc), 90.5 (C-1), 68.4 (C-5), 68.2 (C-2), 67.2 (C-3), 65.9 (C-4), 61.7 (C-6), 20.7, 20.5 (3C) (4 CH_3^{Ac}).

***tert*-butyldiphenylsilyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (104)**

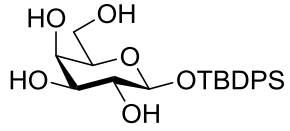


Hemiacetal **103** (55.0 g, 157.9 mmol) was dissolved in DMF (250 mL) and cooled down to 0 °C. To the solution were added tert-butyl diphenylsilyl chloride (51.3 mL, 197.4 mmol) and imidazole (26.9 g, 394.8 mmol). The reaction mixture was stirred at 0 °C for 1 hour and then at 22 °C for 18 hours. The mixture was diluted with Et2O (500 mL) and washed with water (4 x 500 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by dry column vacuum chromatography (0–100% EtOAc in Heptane – 5% increments EtOAc/Heptane) to give **104** as a white solid in 92% yield. (85.3 g)

R_f 0.65 (2:1 Toluene/EtOAc). $[\alpha]_D^{20}$= 2.1° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H, ArH), 7.59 – 7.53 (m, 2H, ArH), 7.41 – 7.25 (m, 6H, ArH), 5.29 – 5.19 (m, 2H, H-3, H-4), 4.79 (dd, *J* = 8.5, *J* = 3.5 Hz, 1H, H-2), 4.55 (d, *J* = 8.5 Hz, 1H, H-1), 3.93 (m, 2H, H-6ab), 3.55 (dt, *J* = *J* = 6.6, *J* = 1.2 Hz, 1H, H-5), 2.10 (s, 3H, CH_3^{Ac}), 1.89 (s, 3H, CH_3^{Ac}), 1.88 – 1.85 (m, 6H, 2x CH_3^{Ac}), 1.00 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3, 169.6 (4 OAc), 136.0 (2C), 135.8 (2C), 132.8, 132.7, 130.1 (2C), 127.8 (2C), 127.6 (2C) (12 ArC), 96.1 (C-1), 71.1 (C-5), 70.8 (C-2), 70.7 (C-3), 67.4 (C-4), 61.5 (C-6), 26.8 (3C, *tert*-butyl), 20.9, 20.8, 20.7 (2C) (4 CH_3^{Ac}), 19.2 *(tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{30}H_{38}NaO_{10}Si$ 609.2126; found 609.2123.

***tert*-butyldiphenylsilyl β-D-galactopyranoside (105)**

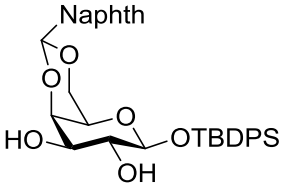


To a solution of **104** (80.0 g, 136.35 mmol) in MeOH (200 mL) at -20 °C was added a freshly prepared 0.04M NaOMe solution in methanol (200 mL). The reaction mixture was stirred at -20 °C for 12 hours, quenched with Amberlite 120-H^+ ion-exchange resin, filtered and concentrated *in vacuo*. The residue was purified by dry column vacuum chromatography (0– 100% EtOAc in Toluene – 7% increments EtOAc/Toluene) to give **105** as an transparent oil in 79% (50.7 g).

R_f 0.06 (2:1 Toluene/EtOAc). $[\alpha]_D^{20}$= 12.9° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 4H, ArH), 7.41 – 7.20 (m, 6H, ArH), 4.37 (d, *J* = 7.4 Hz, 1H, H-1), 4.17 (d, *J* = 5.6 Hz, 1H, 3- O*H*), 3.85 (d, *J* = 4.5 Hz, 1H, 4-O*H*), 3.79 – 3.72 (m, 1H, H-4), 3.62 (ddd, *J* = 9.4, *J* = 7.4, *J* = 3.4 Hz, 1H, H-2), 3.56 – 3.40 (m, 3H, H-6a, H-6b, 2-O*H*), 3.31 (ddd, *J* = 9.4, *J* = 5.6, *J* = 3.4 Hz, 1H, H-3), 3.01 (t, *J* = *J* = 6.0 Hz, 1H, H-5), 2.43 – 2.34 (m, 1H, 6-O*H*), 0.99 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.9 (2C), 135.8 (2C), 133.4, 132.9, 130.0, 129.9, 127.7 (2C), 127.5 (2C) (12 ArC), 97.9 (C-1), 74.2 (C-5), 73.4 (C-2), 73.4 (C- 3), 69.0 (C- 4), 61.5 (C-6), 27.0 (3C, *tert*-butyl), 19.2 *(tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{22}H_{30}NaO_6Si$ 441.1703; found 441.1704.

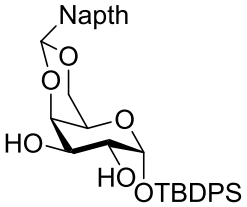
***tert*-butyldiphenylsilyl 4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranoside (106)**



Naphthaldehyde (21.7 g, 139.4 mmol) was suspended in 140 mL methanol before trimethyl orthoformate (24.64 g, 232.3 mmol) and *p*-toluenesulfonic acid mono hydrate (1.77 g, 9.29 mmol) were added at 22 °C. After 2 hours TLC showed full conversion of the starting material and the resulted mixture was concentrated *in vacuo*, dissolved in 100 mL anhydrous acetonitrile and added to a suspension of **105** (38.9 g, 92.9 mmol) in anhydrous acetonitrile (900 mL). The resulted mixture was heated to 60 °C and stirred for 8 hours. The acid was then neutralized with 10 mL Et_3N. The mixture was concentrated *in vacuo* and purified by flash chromatography (1:4 to 1:1 EtOAc/Toluene) to afford **106** as transparent crystals in 62% yield (32.1 g).

mp 85.1 °C. $\mathbf{R}_f$ 0.55 (1:1 Toluene/EtOAc). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$= -36.6° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H, ArH), 7.83 – 7.70 (m, 5H, ArH), 7.65 (dd, *J* = 7.5, 6.1 Hz, 2H, ArH), 7.56 (dd, *J* = 8.5, 1.5 Hz, 1H, ArH), 7.45 – 7.38 (m, 2H, ArH), 7.38 – 7.25 (m, 1H, ArH), 7.17 (dd, *J* = 10.2, 4.6 Hz, 2H, ArH), 7.08 (dd, *J* = 10.2, 7.7 Hz, 2H, ArH), 5.54 (s, 1H, NaphthC*H*O_2), 4.41 (d, *J* = 7.5 Hz, 1H, H-1), 3.98 (m, 2H, H-6a, H-4), 3.83 (d, *J* = 12.3 Hz, 1H, H-6b), 3.77 (dd, *J* = 9.6, 7.5 Hz, 1H, H-2) 3.45 (d, *J* = 7.5 Hz, 1H, H-3), 2.98 (s, 1H, H-5), 2.59 – 2.32 (m, 2H, 2-O*H*, 3-O*H*), 1.05 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.2, 135.9, 135.3, 133.9, 133.4, 133.0, 129.9, 129.8, 129.2, 128.5, 128.4, 128.3, 127.9, 127.7 (2C), 127.5 (2C), 126.6, 126.3, 126.0, 125.4, 124.1 (22 ArC), 101.5 (Naphth*C*HO_2), 97.8 (C-1), 75.5 (C-3), 74.0 (C-4), 72.7 (C-2), 69.1 (C-6), 66.6 (C-5), 27.1 (3C, *tert*-butyl), 19.4 (*tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{33}H_{36}NaO_6Si$ 579.2173; found 579.2173.



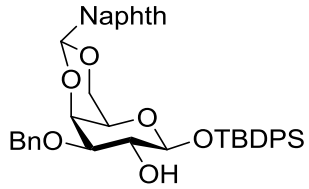
tert-butyldiphenylsilyl 4,6-*O*-(2-naphthyl)methylene-α-D-galactopyranoside **106a** was isolated in 20% yield as main by product of the reaction.

$\mathbf{R}_f$ 0.65 (1:1 Toluene/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H ArH), 7.76 – 7.49 (m, 7H, ArH), 7.48 – 7.40 (m, 1H, ArH), 7.40 – 7.19 (m, 5H, ArH), 7.19 – 6.99 (m, 3H, ArH), 5.49 (s, 1H, NaphthC*H*O_2), 5.40 (d, *J* = 3.2 Hz, 1H, H-1), 4.12 (m, 1H, H-4), 3.96 (m, 1H, H-5), 3.88 – 3.74 (m, 3H, H-6ab, H-2), 3.65 (s, 1H, H-3), 2.52 (d, *J* = 8.7 Hz, 1H ,3-O*H*), 2.03 (d, *J* = 7.6 Hz, 1H, 2-O*H*), 1.03 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.0 (2C), 136.0 (2C), 135.0, 133.8, 132.9, 132.7, 130.2, 130.1, 128.5, 128.2, 127.9 (2C), 127.8 (2C), 127.8, 126.5, 126.3, 125.8, 125.4, 123.9 (22 ArC), 101.3 (Naphth*C*HO_2), 94.6 (C-1), 76.1 (C-3), 70.7 (C-4), 70.0 (C-2), 69.3 (C-6), 63.1

(C-5), 27.1 (3C, *tert*-butyl), 19.5 *(tert*-butyl) ppm.

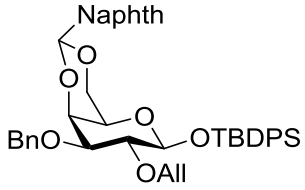
***tert*-butyldiphenylsilyl 3-*O*-benzyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranoside (107)**



Di-*n*-butyl tin oxide (15.81 g, 63.50 mmol) was added to a solution of compound **106** (32.14 g, 57.73 mmol) in dry toluene (500 mL) and stirred under refluxing temperature for 12 h. The temperature was adjusted to 75-80 °C, and then *n*-Bu_4NI (32.0 g, 86.59 mmol) and benzyl bromide (10.3 mL, 86.59 mmol) were added in one portion; stirring was maintained at this temperature for 24 h. The mixture was then washed with saturated sodium thiosulfate and the organic phase was then dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (25:1 Toluene/EtOAc) to give **107** as colorless oil. Yield: 28.7 g (70%). $\mathbf{R}_f$ 0.80 (2:1 Toluene/EtOAc).). $[\alpha]_D^{20}$= 28.4° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.7 Hz, 1H, ArH), 7.80 – 7.68 (m, 5H, ArH), 7.67 – 7.62 (m, 2H, ArH), 7.58 – 7.54 (m, 1H, ArH), 7.41 – 7.35 (m, 2H, ArH), 7.33 – 7.02 (m, 11H, ArH), 5.45 (s, 1H, NaphthC*H*O_2), 4.67 – 4.57 (m, 2H, OC*H*$_2$Ph), 4.41 (d, *J* = 6.6 Hz, 1H, H-1), 4.04 – 3.80 (m, 4H, H-6ab, H-4, H-2), 3.28 (dd, *J* = 9.7, 3.6 Hz, 1H, H-3), 2.93 (s, 1H, H-5), 2.26 (s, 1H, 2-O*H*), 1.06 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.3, 136.2, 136.0, 135.6, 133.9, 133.6, 133.5, 133.1, 129.8 (2C), 129.2, 128.5, 128.4 (2C), 128.1, 128.0 (2C), 127.9, 127.8, 127.7 (2C), 127.5 (2C), 126.4, 126.1, 126.0 , 125.4, 124.3 (28 ArC), 101.2 (Naphth*C*HO_2), 98.0 (C-1), 79.3 (C- 3), 73.4 (C-4), 72.3 (C-2), 71.6 (O*C*H_2Ph), 69.3 (C-6), 66.6 (C-5), 27.1 (3C, *tert*-butyl), 19.5 *(tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{40}H_{42}NaO_6Si$ 669.2642; found 669.2643.

***tert*-butyldiphenylsilyl 2-*O*-allyl-3-*O*-benzyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranoside (108)**

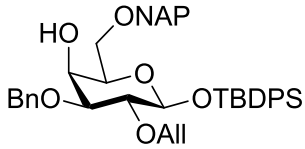


Compound **107** (20 g, 31.0 mmol) was dissolved in dichloromethane (200 mL) and stirred with 4 Å MS (20 g) for 30 minutes at 22 °C. Allyl bromide (18 ml, 216 mmol) was added and the mixture was stirred for 30 minutes more at 22 °C. The flask was then wrapped in aluminum foil, silver oxide (36 g, 155 mmol) was added and the reaction mixture was stirred for 24 h at 22 °C. The mixture was then filtered through a celite pad, concentrated *in vacuo* and the crude product was purified by flash chromatography (1:50 EtOAc/Toluene) to afford **108** as a transparent oil in 84% yield (17.9 g).

$\mathbf{R}_f$ 0.75 (10:1 Toluene/EtOAc). $[\alpha]_D^{20}$= 11.2° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H, ArH), 7.82 – 7.57 (m, 8H, ArH), 7.41 – 7.35 (m, 2H, ArH), 7.33 – 7.01 (m, 11H, ArH), 5.91 (ddd, *J* = 22.8, 10.7, 5.7 Hz, 1H, -C*H*=CH_2), 5.47 – 5.42 (s, 1H, NaphthC*H*O_2), 5.20 (dd, *J* = 17.2, 1.7 Hz, 1H, C*H*$_2$=CH_{trans}), 5.07 (dd, *J* = 10.7, 1.7 Hz, 1H, C*H*$_2$=CH_{cis}), 4.67 – 4.58 (m, 2H, OC*H*$_2$Ph), 4.48 (d, *J* = 7.5 Hz, 1H, H- 1), 4.35 (ddd, *J* = 39.8, 12.2, 5.7 Hz, 2H, OC*H*$_2$-CH=CH_2), 3.91 (d, *J* = 3.4 Hz, 1H, H-4), 3.82 – 3.68 (m, 3H, H-6ab, H-2), 3.31 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3), 2.78 (s, 1H, H-5), 1.05 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.7, 136.3 (2C), 136.0 (2C), 135.7, 135.5 (-*C*H=CH_2), 134.0, 133.9, 133.7, 133.1, 129.7, 129.6, 129.2, 128.5, 128.4 (3C), 127.8 (3C), 127.7, 127.5 (2C), 127.3 (2C), 126.3, 126.1, 124.4 (28 ArC), 116.6 (-CH=*C*H_2), 101.4 (Naphth*C*HO_2), 98.0 (C-1), 80.0 (C- 3), 79.4 (C-2), 74.3 (C-4), 74.2 (O*C*H_2CH=CH_2), 72.1 (O*C*H_2Ph), 69.1 (C-6), 66.3 (C-5), 27.1 (3C, *tert*-butyl), 19.4 *(tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{43}H_{46}NaO_6Si$ 709.2955; found 709.2955.

***tert*-butyldiphenylsilyl 2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (94)**

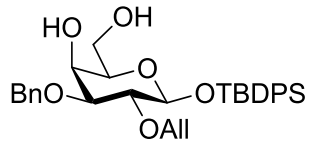


To a solution of fully protected galactoside **108** (16.1 g, 23.44 mmol) dissolved in 300 mL dichloromethane was added triethylsilane (18.8 mL, 117.2 mmol) and the mixture was cooled down to 0 °C. Triflic acid (8.98 mL, 117.2 mmol) was then added dropwise over 1 hour and the mixture was stirred at 22 °C for 3.5 hours. The reaction mixture was then diluted with dichloromethane and the organic phase was washed with $NaHCO_3$ and dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by flash chromatography (1:30 EtOAc/Toluene) to yield the product as a transparent oil in 65% yield (10.5 g).

R$_f$ 0.55 (20:1 Toluene/EtOAc). $[\alpha]_D^{20}$ = 6.4° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.54 (m, 9H, ArH), 7.43 – 7.35 (m, 2H, ArH), 7.34 – 7.07 (m, 17H, ArH), 5.94 – 5.82 (m, 1H, -C*H*=CH_2), 5.18 (dd, *J* = 17.2, 1.7 Hz, 1H, C*H*$_2$=CH_{trans}), 5.08 (dd, *J* = 10.4, 1.7 Hz, 1H, C*H*$_2$=CH_{cis}), 4.60 (s, 2H, OC*H*$_2$Ph), 4.53 – 4.40 (m, 3H, OC*H*$_2$Naphth, H-1), 4.40 – 4.20 (m, 2H, OC*H*$_2$-CH=CH_2), 3.86 (d, *J* = 3.0 Hz, 1H, H-4), 3.62 – 3.49 (m, 2H, H-2, H-6a), 3.38 (dt, *J* = 10.3, 5.7 Hz, 1H, H-6b), 3.27 (dd, *J* = 9.4, 3.0 Hz, 1H, H-3), 3.14 (t, *J* = 5.7 Hz, 1H, H-5), 1.01 (d, *J* = 6.3 Hz, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 136.2 (2C), 136.0 (2C), 135.7, 135.3 (-*C*H=CH_2), 133.7, 133.4, 133.3, 133.1, 129.8, 129.7, 128.6 (2C), 128.2, 128.0 (2C), 127.9 (2C), 127.8, 127.6 (2C), 127.4 (2C), 126.6, 126.2, 126.0, 125.9 (28 ArC), 116.8 (-CH=*C*H_2), 98.1 (C-1), 81.0 (C-3), 80.3 (C-2), 74.3 (O*C*H_2CH=CH_2), 73.8 (O*C*H_2Naphth), 73.1 (C-5), 72.5 (O*C*H_2Ph), 69.1 (C-6), 67.2 (C-4), 27.0 (3C, *tert*-butyl), 19.3 (*tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{43}H_{48}NaO_6Si$ 711.3112; found 711.3114.

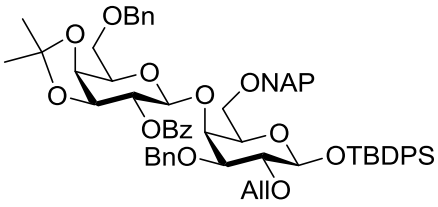
The main by-product was characterized as *tert*-butyldiphenylsilyl 2-*O*-allyl-3-*O*-benzyl-β-D-galactopyranoside (**94a**)



$\mathbf{R_f}$ 0.25 (20:1 Toluene/EtOAc). $[\alpha]_D^{20}$= 30.8° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (ddt, *J* = 13.9, 6.7, 1.5 Hz, 4H, ArH), 7.41 – 7.14 (m, 11H, ArH), 5.94 (ddt, *J* = 17.3, 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.24 (dt, *J* = 17.3, 1.7 Hz, 1H, C*H*$_2$=CH_{trans}), 5.12 (dt, *J* = 10.4, 1.7 Hz, 1H, C*H*$_2$=CH_{cis}), 4.61 (q, *J* = 11.7 Hz, 2H, OC*H*$_2$Ph), 4.54 (d, *J* = 7.5 Hz, 1H, H-1), 4.44 (ddt, *J* = 12.3, 5.7, 1.5 Hz, 1H, 0.5xOC*H*$_2$-CH=CH_2), 4.28 (ddt, *J* = 12.3, 5.7, 1.5 Hz, 1H, 0.5xOC*H*$_2$-CH=CH_2), 3.70 (d, *J* = 3.4 Hz, 1H, H-4), 3.61 – 3.50 (m, 2H, H-2, H-6a), 3.34 (m, 1H, H-6b), 3.29 (dd, *J* = 9.4, 3.4 Hz, 1H, H-3), 2.98 (m, H-5), 1.03 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0, 136.0 (2C), 135.9 (2C), 135.2 (-*C*H=CH_2), 134.1, 133.1, 129.9 (2C), 128.6 (2C), 128.1, 127.9 (2C), 127.8, 127.6 (2C), 127.5 (18 ArC), 116.9 (-CH=*C*H_2), 98.2 (C-1), 80.7 (C-3), 80.4 (C- 2), 74.6 (C-5), 74.4 (O*C*H_2CH=CH_2), 72.7 (O*C*H_2Ph), 67.5 (C-4), 62.4 (C-6), 27.01 (3C, *tert*-butyl), 19.2 (*tert*-butyl) ppm. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{32}H_{40}NaO_6Si$ 571.2486; found 571.2487.

***tert*-butyldiphenylsilyl 2-*O*-benzoyl-6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (110)**



Preparation of 20 mL 1M Me_2S_2/Tf_2O in dichloromethane: Me_2S_2 (2 mL) was diluted in anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C. Triflic anhydride (3.4 mL) was added and the mixture was stirred for 30 minutes at 0 °C.

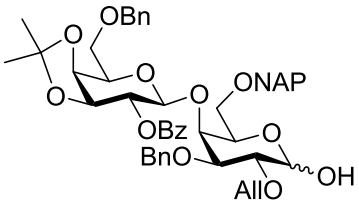
Thiophenyl galactoside **93** (3.15 g, 6.21 mmol) and acceptor **94** (3.29 g, 4.78 mmol) were co-evaporated with toluene three times and subjected to high vacuum overnight. The mixture was dissolved in CH_2Cl_2 (120 ml) and stirred with 4 Å MS (6 g) for 30 minutes. The reaction mixture was cooled down to - 40 °C, 1M Me_2S_2/Tf_2O in CH_2Cl_2 (15.5 mL) was added and it was stirred for 1 hour until TLC showed full conversion of the donor. The reaction was then quenched with Et_3N (8 mL). The mixture was diluted with dichloromethane, filtered through celite, washed with $NaHCO_3$. The organic phase was then dried over $MgSO_4$, concentrated *in vacuo* and the crude product was purified by flash chromatography (1:50 EtOAc/Toluene) to yield the product in 55% (2.85 g).

$\mathbf{R_f}$ 0.60 (10:1 Toluene/EtOAc). $[\alpha]_D^{20}$= -9.0° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.6, 6.4 Hz, 2H, ArH), 7.77 – 7.63 (m, 3H, ArH), 7.63 – 7.51 (m, 5H, ArH), 7.44 – 7.34 (m, 3H, ArH), 7.31 – 7.04 (m, 19H, ArH), 5.62 (dq, *J* = 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.23 (t, *J* = 8.0 Hz, 1H, H-2'), 4.99 – 4.90 (m, 2H, -CH=C*H*$_2$), 4.87 (d, *J* = 8.0

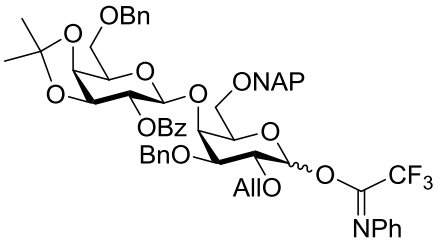
Hz, 1H, H-1'), 4.61 – 4.45 (m, 2H, OC$\underline{H_2}$Ph), 4.39 – 4.27 (m, 5H, H-1, OC$\underline{H_2}$Naphth, OC$\underline{H_2}$Ph'), 4.17 (m, 2H, H-3', H-4'), 3.97 (dd, *J* = 8.3, 1.7 Hz, 1H, H-3), 3.80 (tt, *J* = 6.0, 3.0 Hz, 1H, H-5'), 3.78 – 3.53 (m, 4H, H-6b, 0.5xOC$\underline{H_2}$-CH=CH_2, H-6ab'), 3.39 – 3.30 (m, 2H, H-6a, 0.5xOC$\underline{H_2}$-CH=CH_2), 3.21 – 3.10 (m, 3H, H-2, H-4, H-5), 1.61 (s, 3H, $CH_3^{isoprop.}$), 1.29 (s, 3H, $CH_3^{isoprop.}$), 0.92 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.4 (OBz), 138.8, 138.2, 136.3 (3C), 136.0 (2C), 135.3 (-$\underline{C}$H=CH_2), 134.0, 133.4, 133.3, 133.0, 132.9, 130.4, 130.2 (2C), 129.6, 129.4, 128.5 (2C), 128.5 (2C), 128.4, 128.0, 127.8 (4C), 127.7 (2C), 127.5 (4C), 127.2 (2C), 126.2, 126.0, 125.9, 125.8, 125.4 (40 ArC), 116.0 (- CH=$\underline{C}H_2$), 110.6 ($\underline{C}(CH_3)_2$), 100.5 (C-1'), 97.8 (C-1), 81.8 (C-3), 81.3 (C-2), 77.2 (C-3'), 74.1 (C-4'), 73.8 (2C, C- 2', O$\underline{C}H_2$CH=CH_2), 73.6 (O$\underline{C}H_2$Ph'), 73.6 (O$\underline{C}H_2$Naphth), 73.5 (C-5), 73.2 (O$\underline{C}H_2$Ph), 72.7 (C-4), 72.3 (C-5'), 70.0 (C-6), 69.4 (C-6'), 28.0 ($CH_3^{isoprop}$), 26.9 (3C, *tert*-butyl), 26.5 ($CH_3^{isoprop}$), 19.2 (*tert*-butyl) ppm.

2-*O*-benzoyl-6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-D-galactopyranose (111)



In a plastic container, disaccharide **110** (1.8 g, 1.66 mmol) was dissolved in THF (17 mL) and the solution was cooled to 0 °C. 20% HF-pyridine complex (4 mL) was added slowly while the temperature was maintained below 5 °C. The reaction mixture was then slowly heated to 22 °C and stirred for 4 hours. The mixture was cooled to 0 °C and quenched by adding dropwise sat. aq. $NaHCO_3$ (20 mL). The mixture was then poured into 150 mL sat. aq. $NaHCO_3$. and extracted with EtOAc (3x50 mL). The combined organic phases was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (1:5 EtOAc/Toluene) to afford hemiacetal **111** in 80% yield (1.12 g) (5:1 α/β).
R_f 0.20 (1:6 EtOAc/ Toluene).

2-*O*-benzoyl-6-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-D-galactopyranose *N*-phenyl trifluoroacetimidate

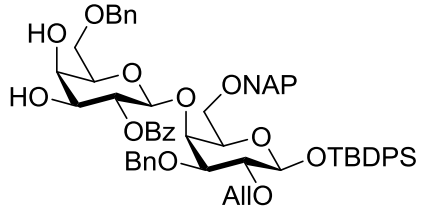


Hemiacetal **111** (600 mg, 0.71 mmol) was dissolved in dichloromethane (8 mL) and cooled to 0 °C. Cesium carbonate (463 mg, 1.42 mmol) was added followed by addition of *N*-phenyl trifluoroacetimidoyl chloride (0.23 mL, 1.42 mmol). The ice bath was removed and the reaction stirred at 22 °C for 2 hours. The mixture was then filtered

through celite and concentrated *in vacuo*. The crude was purified by flash chromatography (1:30 EtOAc/Toluene) to yield the product in 93% as a white solid (670 mg).

R_f 0.70 (1:4 EtOAc/ Toluene). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.03 (m, 24H, ArH), 7.01 – 6.89 (m, 1H, ArH), 6.65 (d, *J* = 7.7 Hz, 2H, ArH), 5.66 – 5.47 (m, 1H, -C*H*=CH_2), 5.16 (t, *J* = 7.9 Hz, 1H, H- 2'), 4.93 (d, *J* = 1.6 Hz, 1H, 0.5x-CH=C*H*$_2$), 4.89 (d, *J* = 1.6 Hz, 1H, 0.5x-CH=C*H*$_2$), 4.79 (d, *J* = 7.9 Hz, 1H, H-1'), 4.70 – 4.44 (m, 4H, OC*H*$_2$Ph', OC*H*$_2$Ph), 4.36 (s, 2H, OC*H*$_2$Naphth), 4.21 (dd, *J* = 7.2, 5.4 Hz, 1H, H-4'), 4.18 – 4.11 (m, 1H, H-3'), 4.01 (d, *J* = 2.2 Hz, 1H, H-4), 3.91– 3.48 (m, 7H, 0.5xOC*H*$_2$CH=CH_2, H6ab, H6ab', H-5', H-5) 3.31 (m, 3H, H-3, H- 2, 0.5xOC*H*$_2$CH=CH_2), 1.56 (s, 3H, CH_3^{isopro}), 1.27 (s, 3H, CH_3^{isopro}) ppm (no signal for H-1).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (OBz), 143.7 (C*ipso*, NPh), 138.4, 138.1, 136.1, 134.6 (- *C*H=CH_2), 133.4, 133.1, 133.0, 130.3, 130.2, 129.5, 129.2, 128.7, 128.5 (2C), 128.4, 128.3, 128.2, 128.1, 128.0, 127.9 (3C), 127.8 (3C), 127.7 (2C), 126.4, 126.1, 125.9 (2C), 125.4, 124.2 (32 ArC), 119.4 (ArC, NPh), 116.7 (-CH=*C*H_2), 110.6 (*C*$(CH_3)_2$), 101.1 (C-1'), 97.1 (br., C-1), 81.2 (C-3), 78.3 (C-2), 77.4 (C-3'), 75.0 (C-5), 74.0 (C-2'), 73.9 (O*C*H_2CH=CH_2), 73.8 (C- 4'), 73.7 (O*C*H_2Ph), 73.6 (O*C*H_2Ph'), 73.4 (O*C*H_2Naphth), 73.2 (C-4), 72.3 (C-5'), 69.7 (C-6), 69.4 (C-6'), 27.9 ($CH_3^{isoprop}$), 26.5 ($CH_3^{isoprop}$) ppm (no signals for *C*F_3 and *C*=NPh).

tert-butyldiphenylsilyl 6-*O*-benzyl-2-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2-*O*allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (113)

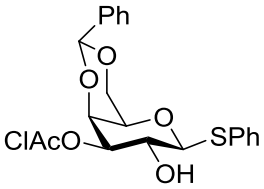


To a solution of disaccharide **110** (1.0 g, 0.92 mmol) in methanol (5 mL) and dioxane (5 mL) was added 1 mL of 1M aqueous HCl. The reaction mixture was heated to 50 °C and stirred for 3 hours. The mixture was then diluted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$ and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:5 EtOAc/ Toluene) to afford diol **113** in 75% yield (721 mg).

R_f 0.25 (1:5 EtOAc/ Toluene). $[\alpha]_D^{20}$= -12.0° (c 0.5, $CDCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.02 (m, 2H, ArH), 7.81 – 7.67 (m, 3H, ArH), 7.67 – 7.56 (m, 5H, ArH), 7.48 – 7.38 (m, 3H, ArH), 7.37 – 7.11 (m, 19H, ArH), 5.70 (dq, *J* = 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.24 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2'), 5.08 – 4.94 (m, 3H, H-1', -CH=C*H*$_2$), 4.62 and 4.52 (ABq pattern, *J* = 12.0 Hz, 2H, OC*H*$_2$Ph), 4.44 – 4.25 (m, 5H, H-1, OC*H*$_2$Naphth, OC*H*$_2$Ph'), 4.08 (s, 1H , H-4), 4.04 (d, *J* = 3.4 Hz, 1H, H- 4'), 3.90 (dd, *J* = 12.2, 5.6 Hz, 1H, 0.5xOC*H*$_2$CH=CH_2), 3.75 – 3.65 (m, 3H, H-6a', H-6a, H- 3'), 3.60 – 3.48 (m, 3H, H-6b', 0.5xOC*H*$_2$CH=CH_2, H-5'), 3.39 – 3.32 (m, 1H, H-6b), 3.32 – 3.24 (m, 2H, H-2, H-3), 3.21 (m, 1H, H-5), 0.97 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.27 (OBz), 138.7, 137.8, 136.2 (3C), 136.0 (2C), 135.3 (- *C*H=CH_2), 133.9, 133.4, 133.3, 133.2, 133.0, 130.4, 129.9, 129.6, 129.5, 129.2, 128.6 (2C), 128.5 (2C), 128.3 (3C), 128.0 (4C), 127.9, 127.8 (2C), 127.7 (2C),

127.5 (2C), 127.2 (2C), 126.1 (2C), 125.8 (40 ArC), 116.1 (-CH=$\underline{C}H_2$), 100.9 (C-1'), 98.0 (C-1), 82.0 (C-3), 81.3 (C-2), 74.4 (C-2'), 73.8 (O$\underline{C}H_2$CH=CH_2), 73.7 (O$\underline{C}H_2$Ph'), 73.6 (O$\underline{C}H_2$Ph), 73.5 (2C, O$\underline{C}H_2$Naphth, C-5), 73.2 (C-5'), 73.1 (C-3'), 72.8 (C-4), 69.7 (C-6), 69.6 (C-4'), 69.3 (C-6'), 26.9 (3C, *tert*-butyl), 19.2 (*tert*-butyl) ppm.

Phenyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranoside[135] **(122)**

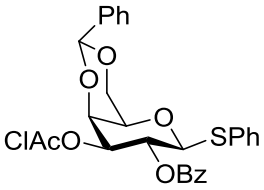


Di-n-butyl tin oxide (10.8 g, 43.7 mmol) was added to a solution of compound **100** (15.0 g, 41.6 mmol) in dry toluene (400 mL) and stirred under refluxing temperature for 12 h. The reaction mixture was cooled to 0 °C, and freshly activated 4Å MS (15 g) were added. After 30 min chloroacetyl chloride (3.41 mL, 42.87 mmol) was added dropwise and stirring was maintained at this temperature for 1 hour. The reaction was quenched by addition of MeOH, filtered through a pad of celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (10:1 to 5:1 Toluene/EtOAc) to give **122** as white crystals. Yield: 14.8 g (82%). The compound analyses were in accordance with data from the literature.[135]

R_f 0.55 (1:2 EtOAc/ Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H, ArH), 7.32 – 7.10 (m, 8H, ArH), 5.36 (s, 1H, PhC$\underline{H}O_2$), 4.86 (dd, *J* = 9.8, 3.4 Hz, 1H, H-3), 4.47 (d, *J* = 9.5 Hz, 1H, H-1), 4.32 – 4.24 (m, 2H, H-4, H-6a), 4.03 – 3.94 (m, 2H, C$\underline{H_2}$-Cl), 3.91 (dd, *J* = 12.5, 1.7 Hz, 1H, H-6b), 3.86 (m, 1H, H-2), 3.50 (m, 1H, H-5) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4 (OAcCl), 137.7, 133.8 (2C), 130.2, 129.3, 129.2 (2C), 128.6, 128.3 (2C), 126.5 (2C) (12 ArC), 101.1 (Ph$\underline{C}HO_2$), 87.6 (C-1), 76.6 (C-3), 73.5 (C-4), 69.9 (C-5), 69.2 (C-6), 65.6 (C-2), 41.0 ($\underline{C}H_2$Cl) ppm.

Phenyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranoside[135] (**117**)

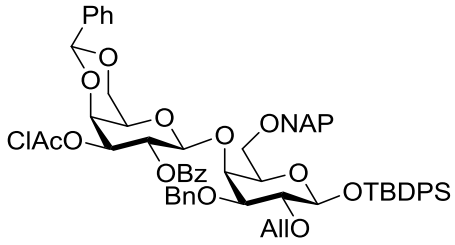


To a solution of alcohol **122** (14.8 g, 33.9 mmol) in CH_2Cl_2 (220 mL) was added Et_3N (9.5 ml, 67.8 mmol). The mixture was cooled down to 0 °C and benzoyl chloride (9.8 mL, 84. 7 mmol) was added dropwise. After stirring for 4 hours at 0 °C, the reaction was quenched by adding 10 ml of MeOH, diluted with 200 mL CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4, concentrated *in vacuo* and the crude product was purified by flash chromatography (1:15 EtOAc/Toluene) to afford fully protected monosaccharide **117** in 82% yield (15.2 g). The compound analyses were in accordance with data from the literature.[135]

R_f 0.65 (1:2 EtOAc/ Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 2H, Ar*H*), 7.58 – 7.51 (m, 2H, ArH), 7.47 – 7.41 (m, 1H, ArH), 7.33 – 7.14 (m, 10H, ArH), 5.50 (t, *J* = 9.8 Hz, 1H, H-2), 5.39 (s, 1H, PhC*H*O_2), 5.15 (dd, *J* = 9.8, 3.4 Hz, 1H, H-3), 4.72 (d, *J* = 9.8 Hz, 1H, H-1), 4.46 (dd, *J* = 3.4, 1.0 Hz, 1H, H-4), 4.32 (dd, *J* = 12.5, 1.7 Hz, 1H, H-6a), 4.00 – 3.84 (m, 3H, H-6b, C*H*$_2$-Cl), 3.61 (m, 1H, H-5) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1 (OAcCl), 165.9 (OBz), 137.6, 134.0 (2C), 133.7, 130.7, 130.1 (2C), 129.2, 129.0 (3C), 128.7 (2C), 128.5, 128.2 (2C), 126.5 (2C) (18 ArC), 101.0 (Ph*C*HO_2), 84.7 (C-1), 73.8 (C-3), 73.6 (C-4), 70.0 (C-5), 69.2 (C-6), 68.4 (C-2), 40.7 (*C*H_2Cl) ppm.

***tert*-butyldiphenylsilyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (118)**



Preparation of 10 mL 1M Me_2S_2/Tf_2O in dichloromethane: Me_2S_2 (1 mL) was diluted in anhydrous CH_2Cl_2 (10 mL) and cooled to 0 °C. Triflic anhydride (1.7 mL) was added and the mixture was stirred for 30 minutes at 0 °C.

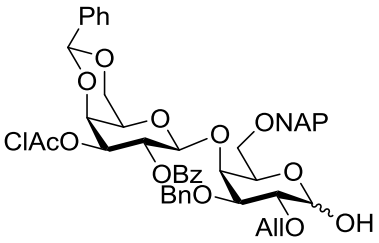
Thiophenyl galactoside **117** (1.68 g, 3.10 mmol) and acceptor **94** (1.64 g, 2.39 mmol) were co-evaporated with toluene three times and subjected to high vacuum for two hours. The mixture was dissolved in CH_2Cl_2 (65 ml) and stirred with 4 Å MS (3 g) for 30 minutes. The reaction mixture was cooled down to - 40 °C, 1M Me_2S_2/Tf_2O in CH_2Cl_2 (5.98 mL) was added and it was stirred for 30 min at - 40 °C until TLC showed full conversion of the donor. The reaction was then quenched with Et_3N (1.5 mL). The mixture was diluted with CH_2Cl_2, filtered through celite, and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:70 to 1:5 EtOAc/Toluene) to yield the product in 55% (1.48 g).

R_f 0.40 (1:5 EtOAc/ Toluene). $[\alpha]_D^{20}$= 26.8° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H, ArH), 7.74 – 7.56 (m, 8H, ArH), 7.54 – 7.44 (m, 2H, ArH), 7.43 – 7.02 (m, 20H, ArH), 5.87 (ddt, *J* = 17.4, 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.55 (dd, *J* = 10.4, 7.7 Hz, 1H, H-2'), 5.38 (s, 1H, PhC*H*O_2), 5.19 (dq, *J* = 17.4, 1.7 Hz, 1H, C*H*$_2$=CH_{trans}), 5.06 (m, 2H, C*H*$_2$=CH_{cis}, H-3'), 4.85 (d, *J* = 7.7 Hz, 1H, H-1'), 4.66 and 4.54 (ABq pattern, *J* = 12.2 Hz, 2H, OC*H*$_2$Ph), 4.50 – 4.33 (m, 5H, H-4',OC*H*$_2$Naphth, H-1, 0.5xOC*H*$_2$CH=CH_2), 4.19 (ddt, *J* = 12.4, 5.6, 1.5 Hz, 1H, 0.5xOC*H*$_2$CH=CH_2), 4.06 – 3.96 (m, 2H, H-4, H-6a'), 3.87 – 3.76 (m, 2H, H-6b', 0.5xC*H*$_2$-Cl), 3.73 (s, 1H, 0.5xC*H*$_2$-Cl), 3.71 – 3.64 (m, 1H, H-6a), 3.47 – 3.39 (m, 1H, H-2), 3.32 – 3.24 (m, 2H, H-3, H-5'), 3.21 (dd, *J* = 9.4, 5.1 Hz, 1H, H-6b), 3.13 (dd, *J* = 6.9, 5.1 Hz, 1H, H-5), 0.99 (s, 9H, 3xCH_3 ^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (OAcCl), 166.2 (OBz), 138.5, 138.0, 137.8 (2C), 136.2 (2C), 136.1, 136.0 (2C), 135.4 (-*C*H=CH_2), 133.8,

133.7, 133.5, 133.4, 133.0, 130.1, 129.7 (2C), 129.5, 129.3, 129.2, 128.7 (3C), 128.6, 128.4, 128.3 (3C), 128.0, 127.8, 127.5, 127.3, 126.5 (2C), 126.3, 126.0, 125.9, 125.8, 125.4 (2C) (40 ArC), 116.6 (-CH=$\underline{C}H_2$), 101.1 (Ph$\underline{C}HO_2$), 101.0 (C-1'), 98.3 (C-1), 82.0 (C-3), 81.2 (C-2), 74.3 (O$\underline{C}H_2CH=CH_2$), 73.7 (O$\underline{C}H_2$Naphth), 73.6 (O$\underline{C}H_2$Ph), 73.5 (2C, C-4', C- 4), 73.2 (C-5), 72.6 (C-3'), 71.1 (C-2'), 68.9 (C-6), 68.8 (C-6'), 66.3 (C-5'), 40.8 ($\underline{C}H_2$Cl), 27.1 (3C, *tert*-butyl), 19.3 (*tert*-butyl) ppm.

2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-D-galactopyranose (123)



To a solution of **118** (3.0 g, 2.68 mmol) in THF (30 mL) at 0 °C was added TBAF (2.68 mL, 1.0 M in THF). The resulting mixture was warmed up gradually to 22 °C and was stirred for 3 hours. The reaction was diluted with CH_2Cl_2, washed with sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (6:1 to 2:1 Toluene/EtOAc) to afford **123** as a transparent oil. Yield: 1.86 g (76%).

R_f 0.30 (5:1 Toluene/EtOAc). **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{49}H_{49}NaClO_{13}$ 903.2753; found 903.2748.

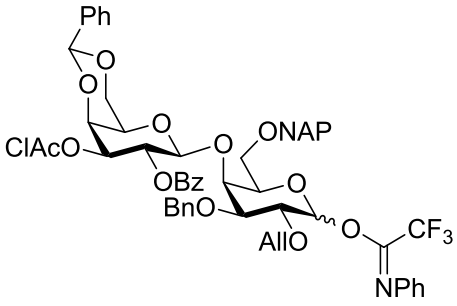
α-anomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 2H, ArH), 7.66 (m, 5H, ArH), 7.49 – 7.02 (m, 15H), 5.92 – 5.75 (m, 1H, -C$\underline{H}$=CH_2), 5.47 (m, 1H, H-2'), 5.39 (s, 1H, PhC$\underline{H}O_2$), 5.35 – 5.17 (m, 2H, H-1, C$\underline{H}_2$=CH_{trans}), 5.11 – 4.99 (m, 2H, C$\underline{H}_2$=CH_{cis}, H-3'), 4.73 – 4.59 (m, 4H, OC$\underline{H}_2$Ph, 0.5xOC$\underline{H}_2$CH=CH_2, H-1'), 4.54 – 4.50 (m, 1H, 0.5xOC$\underline{H}_2$CH=CH_2), 4.36 – 4.30 (m, 1H, H- 4'), 4.17 – 4.01 (m, 3H, OC$\underline{H}_2$Naphth, H-5), 4.00 – 3.68 (m, 6H, H-3, H-4, H-6ab, H-6ab'), 3.68 – 3.48 (m, 4H, C$\underline{H}_2$-Cl, H-2, H-5') ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (OAcCl), 166.3 (OBz), 138.5, 138.3, 138.0, 137.8 (2C), 135.9, 134.8, 133.7 (-$\underline{C}$H=CH_2), 133.3, 130.1, 129.2, 129.1, 128.7 (2C), 128.3 (2C), 128.2, 128.0, 127.9, 127.7, 126.8, 126.7 (2C), 126.5, 126.3, 126.1 (2C), 125.9, 125.4 (28 ArC), 117.5 (-CH=$\underline{C}H_2$), 101.9 (C-1'), 101.2 (Ph$\underline{C}HO_2$), 91.7 (C-1), 77.7 (C-3), 77.36 (C-2), 76.4 (C-4), 73.6 (O$\underline{C}H_2$Naphth), 73.3 (O$\underline{C}H_2$CH=CH_2), 72.5 (C-4'), 72.5 (O$\underline{C}H_2$Ph), 72.4 (C-3'), 71.0 (C-2'), 69.4 (C-6), 69.2 (C-5), 68.7 (C-6'), 66.1 (C-5'), 40.7 ($\underline{C}H_2$Cl) ppm.

β-anomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 2H, ArH), 7.66 (m, 5H, ArH), 7.49 – 7.02 (m, 15H), 5.92 – 5.75 (m, 1H, -C*H*=CH_2), 5.47 (m, 1H, H-2'), 5.39 (s, 1H, PhC*H*O_2), 5.35 – 5.17 (m, 1H, C*H*$_2$=CH_{trans}), 5.11 – 4.99 (m, 2H, C*H*$_2$=CH_{cis}, H-3'), 4.73 – 4.59 (m, 4H, OC*H*$_2$Ph, 0.5xOC*H*$_2$CH=CH_2, H-1'), 4.54 – 4.50 (m, 2H, 0.5xOC*H*$_2$CH=CH_2, H-1), 4.36 – 4.30 (m, 1H, H- 4'), 4.17 – 4.01 (m, 3H, OC*H*$_2$Naphth, H-5), 4.00 – 3.68 (m, 6H, H-3, H-4, H-6ab, H-6ab'), 3.68 – 3.48 (m, 4H, C*H*$_2$-Cl, H-2, H-5') ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (OAcCl), 166.3 (OBz), 138.5, 138.3, 138.0, 137.8 (2C), 135.9, 134.8, 133.7 (-*C*H=CH_2), 133.3, 130.1, 129.2, 129.1, 128.7 (2C), 128.3 (2C), 128.2, 128.0, 127.9, 127.7, 126.8, 126.7 (2C), 126.5, 126.3, 126.1 (2C), 125.9, 125.4 (28 ArC), 117.5 (-CH=*C*H_2), 101.9 (C-1'), 101.2 (Ph*C*HO_2), 97.8 (C-1), 77.7 (C-3), 77.36 (C-2), 76.4 (C-4), 73.6 (O*C*H_2Naphth), 73.3 (O*C*H_2CH=CH_2), 72.5 (C-4'), 72.5 (O*C*H_2Ph), 72.4 (C-3'), 71.0 (C-2'), 69.4 (C-6), 69.2 (C-5), 68.7 (C-6'), 66.1 (C-5'), 40.7 (*C*H_2Cl) ppm.

2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (119)



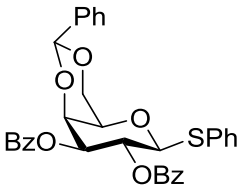
Hemiacetal **118** (1.80 g, 2.04 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. Cesium carbonate (1.33 g, 4.08 mmol) was added followed by addition of *N*-phenyl trifluoroacetimidoyl chloride (0.66mL, 4.08 mmol). The ice bath was removed and the reaction stirred at 22 °C for 3 hours. The mixture was then filtered through celite and concentrated *in vacuo*. The crude was purified by flash chromatography (1:15 to 1:3 EtOAc/Toluene) to yield the product in 93% as a white solid (2.1 g).

R_f 0.60 (4:1 Toluene/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H, ArH), 7.72 – 7.51 (m, 5H, ArH), 7.47 – 7.18 (m, 11H, ArH), 7.17 – 6.99 (m, 6H, ArH), 6.97 – 6.90 (m, 1H, ArH), 6.67 (d, *J* = 7.8 Hz, 2H, ArH), 5.83 (m, 1H, - C*H*=CH_2), 5.50 (m, 1H, H-2'), 5.37 (s, 1H, PhC*H*O_2), 5.22 – 5.17 (m, 1H, C*H*$_2$=CH_{trans}), 5.11 – 5.06 (m, 2H, H-3', C*H*$_2$=CH_{cis}), 5.04 (m, 1H, H-1), 4.79 (d, *J* = 7.8 Hz, 1H, H-1'), 4.74 – 4.52 (m, 4H, OC*H*$_2$Ph, OC*H*$_2$Naphth,), 4.40 – 4.33 (m, 1H, H-4'), 4.24 – 3.95 (m, 4H, OC*H*$_2$CH=CH_2, H-4, H-6a'), 3.94 – 3.25 (m, 9H, H-6b', H6ab, H-2, H-3, H-5, H-5', C*H*$_2$-Cl) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (OAcCl), 166.1 (OBz), 143.7 (C*ipso*, NPh), 138.0, 138.0, 137.7, 136.0, 134.8, 133.7, 133.4, 133.1, 130.1 (3C), 129.2, 129.1, 128.8 (2C), 128.7 (2C), 128.4, 128.3 (2C), 128.2, 128.1, 127.9, 127.8, 126.5 (3C), 126.1, 125.9 (2C), 125.4, 124.3 (32 ArC), 119.5 (ArC, NPh), 117.2 (-CH=*C*H_2), 101.4 (C-1'), 101.2 (Ph*C*HO_2), 97.4 (C-1), 81.5 (C-3), 78.2 (C-2), 77.4 (C-4), 74.4 (O*C*H_2CH=CH_2), 73.9 (O*C*H_2Naphth), 73.6 (O*C*H_2Ph), 73.4 (C-

4'), 72.5 (C-3'), 71.1 (2C, C-2' and C-6), 68.7 (C-6'), 66.7 (C-5), 66.4 (C-5'), 40.6 (<u>C</u>H_2Cl) ppm (no signals for <u>C</u>F_3 and <u>C</u>=NPh).

Phenyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranoside[179] **(127)**

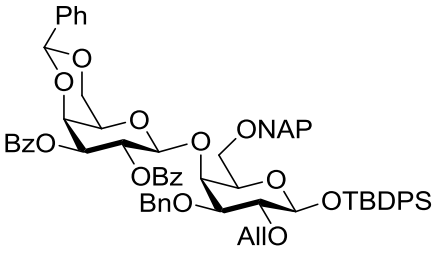


Diol **100** (19.0 g, 52.7 mmol) was dissolved in 300 mL pyridine and cooled down to 0 °C. Benzoyl chloride (18.4 mL, 158,2 mmol) was added dropwise and the mixture was stirred at 22 °C for 12 hours. The mixture was diluted with Et_2O (200 mL) and washed with water (3 x 200 mL) and NH_4Cl (3 x 200 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the crude product was purified by flash chromatography (1:50 EtOAc/Toluene) to yield the product as a white solid in 85% yield (25 g).

R_f 0.70 (1:2 EtOAc/Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 4H, ArH), 7.55 – 7.45 (m, 2H, ArH), 7.45 – 7.09 (m, 14H, ArH), 5.70 (t, *J* = 9.9 Hz, 1H, H-2), 5.41 (s, 1H, PhC<u>*H*</u>O_2), 5.26 (dd, *J* = 9.9, 3.4 Hz, 1H, H-3), 4.86 (d, *J* = 9.9 Hz, 1H, H-1), 4.49 (dd, *J* = 3.4, 0.9 Hz, 1H, H-4), 4.34 (dd, *J* = 12.4, 1.6 Hz, 1H, H-6a), 3.99 (dd, *J* = 12.4, 1.6 Hz, 1H, H-6b), 3.66 (s, 1H, H-5) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (OBz), 165.1 (OBz), 137.7, 134.0 (2C), 133.5, 133.3, 131.2, 130.1 (2C), 129.9 (2C), 129.8 (2C), 129.2 (3C) 128.9, 128.5, 128.4 (2C), 128.2 (2C), 126.6 (2C) (24 ArC), 101.0 (Ph<u>C</u>HO_2), 85.4 (C-1), 74.2 (C-3), 73.8 (C-4), 70.0 (C-5), 69.3 (C-6), 67.2 (C-2) ppm.

***tert*-butyldiphenylsilyl 2,3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (128)**



Preparation of 10 mL 1M Me_2S_2/Tf_2O in dichloromethane: Me_2S_2 (1 mL) was diluted in anhydrous CH_2Cl_2 (10 mL) and cooled to 0 °C. Triflic anhydride (1.7 mL) was added and the mixture was stirred for 30 minutes at 0 °C.

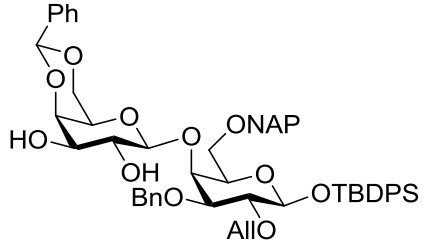
Thiophenyl galactoside **127** (1.93 g, 3.40 mmol) and acceptor **94** (1.56 g, 2.26 mmol) were co-evaporated with toluene three times and subjected to high vacuum for two hours. The mixture was dissolved in CH_2Cl_2 (50 ml) and stirred with 4 Å MS (3 g) for 30 minutes. The reaction mixture was cooled down to - 40 °C, 1M Me_2S_2/Tf_2O in CH_2Cl_2 (5.98 mL) was added and it was stirred for 30 min until TLC showed full conversion of the donor. The reaction was then quenched with Et_3N (2 mL). The mixture was diluted with CH_2Cl_2, filtered through celite and concentrated *in*

vacuo. The crude product was purified by flash chromatography (1:50 to 1:10 EtOAc/Toluene) to afford the product in 62% yield (1.60 g).

R_f 0.40 (1:20 EtOAc/Toluene). $[\alpha]_D^{20}$= 138.0° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 4H, ArH), 7.72 – 7.47 (m, 9H, ArH), 7.46 – 7.39 (m, 2H, ArH), 7.39 – 6.99 (m, 22H, ArH), 5.80 (dd, *J* = 10.5, 7.9 Hz, 1H, H-2'), 5.54 (ddt, *J* = 17.2, 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.40 (s, 1H, PhC*H*O_2), 5.16 (dd, *J* = 10.5, 3.6 Hz, 1H, H-3'), 5.10 (d, *J* = 7.9 Hz, 1H, H-1'), 4.91 – 4.82 (m, 2H, -CH=C*H*$_2$), 4.61 – 4.46 (m, 3H, 0.5xOC*H*$_2$Naphth, OC*H*$_2$Ph), 4.45 – 4.41 (m, 1H, H-4'), 4.36 (d, *J* = 12.2 Hz, 1H, 0.5xOC*H*$_2$Naphth), 4.31 (d, *J* = 7.2 Hz, 1H, H-1), 4.09 – 4.02 (m, 2H, H-4, H-6a'), 3.86 (dd, *J* = 12.4, 1.7 Hz, 1H, H-6b'), 3.71 – 3.62 (m, 2H, 0.5xOC*H*$_2$CH=CH_2, H-6a), 3.35 (s, 1H, H-5'), 3.25 – 3.14 (m, 3H, 0.5xOC*H*$_2$CH=CH_2, H-6b. H-3), 3.14 – 3.05 (m, 2H, H-2, H-5), 0.89 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5 (OBz), 165.1 (OBz), 138.9, 138.0, 137.9, 136.4, 136.2 (2C), 136.0 (2C), 135.3 (-*C*H=CH_2), 133.9, 133.5, 133.4 (2C), 133.0, 132.9, 130.2 (2C), 130.1, 129.6, 129.5, 129.4, 129.2 (2C), 129.1, 128.6 (2C), 128.5, 128.4 (2C), 128.3 (2C), 128.0, 127.9 (2C), 127.7, 127.5 (2C), 127.4, 127.2, 126.5 (2C), 126.3, 125.9 (2C), 125.7, 125.4 (2C) (46 ArC), 116.0 (-CH=*C*H_2) , 101.0 (Ph*C*HO_2), 100.9 (C- 1'), 97.8 (C-1), 82.0 (C-3), 81.5 (C-2), 73.7 (O*C*H_2Naphth), 73.6 (O*C*H_2CH=CH_2), 73.4 (2C, O*C*H_2Ph, C-4'), 73.1 (C-5), 73.0 (C-3'), 72.0 (C-4), 69.7 (C-2'), 68.8 (C-6'), 68.7 (C-6), 66.3 (C-5'), 27.0 (3C, *tert*-butyl), 19.2 (*tert*-butyl) ppm.

tert-butyldiphenylsilyl 4,6-_O_-benzylidene-β-D-galactopyranosyl-(1→4)-2-_O_-allyl-3-_O_-benzyl-6-_O_-(2-naphthyl)methyl-β-D-galactopyranoside (125)



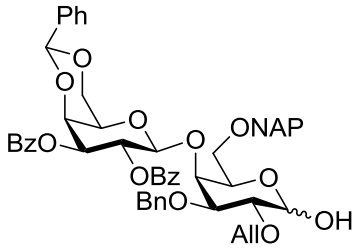
Dibenzoylated disaccharide **128** (2.43 g, 2.10 mmol) was dissolved in methanol (14 mL) and THF (10 mL) and 1.25 mL of freshly prepared 1M NaOMe in MeOH were added. The reaction mixture was stirred at 22 °C for 3 hours, quenched with Amberlite IR-120 (H^+), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (4:1 to 2:1 Toluene/EtOAc) to afford diol **125** in 86% yield (1.7 g).

R_f 0.15 (1:5 EtOAc/ Toluene). $[\alpha]_D^{20}$= -19.2° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.66 (m, 8H, ArH), 7.62 – 7.58 (m, 1H, ArH), 7.54 – 7.49 (m, 2H, ArH), 7.48 – 7.42 (m, 2H, ArH), 7.41 – 7.20 (m, 8H, ArH), 7.19 – 7.11 (m, 6H, ArH), 5.93 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H, -C*H*=CH_2), 5.58 (s, 1H, PhC*H*O_2), 5.31 – 5.12 (m, 2H, -CH=C*H*$_2$), 4.85 – 4.67 (ABq pattern, *J* = 12.2 Hz, 2H, OC*H*$_2$Ph), 4.61 – 4.39 (m, 4H, 0.5xOC*H*$_2$Naphth, OC*H*$_2$-CH=CH_2, H-1), 4.34 – 4.22 (m, 2H, H-1', 0.5xOC*H*$_2$Naphth), 4.11-3.98 (m, 2H, H-3', H-6a'), 3.89 – 3.78 (m, 4H, H-6b', H-2', H-6a, H-4), 3.69 (dd, *J* = 9.7, 7.5 Hz, 1H, H-2) 3.61 – 3.52 (m, 1H, H-4'), 3.39 (dd, *J* = 9.7, 3.2 Hz, 1H, H-3), 3.31 (dd, *J* = 9.0, 5.1 Hz, 1H,

H-6b), 3.22 – 3.08 (m, 2H, H-5, H-5'), 1.08 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0, 137.8, 137.7, 136.2 (2C), 136.1 (2C), 136.0, 135.1 (-$\underline{C}$H=CH_2), 133.6, 133.4, 133.0, 129.7 (3C), 129.3, 129.2 (2C), 128.6, 128.4 (3C), 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 126.5 (2C), 126.3, 126.1, 126.0, 125.5, 125.4 (34 ArC), 117.1 (-CH=$\underline{C}H_2$), 105.8 (C-1'), 101.4 (Ph$\underline{C}HO_2$), 98.2 (C-1), 80.9 (C-3), 80.8 (C-2), 77.8 (C-2'), 75.3 (C-3'), 74.3 (O$\underline{C}H_2$Naphth), 74.1 (O$\underline{C}H_2$Ph), 73.4 (C-4'), 73.3 (O$\underline{C}H_2$CH=CH_2), 72.8 (C-5), 72.5 (C-4), 69.2 (C-6'), 68.3 (C- 6), 66.9 (C-5'), 27.1 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

2,3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-D-galactopyranose (129)



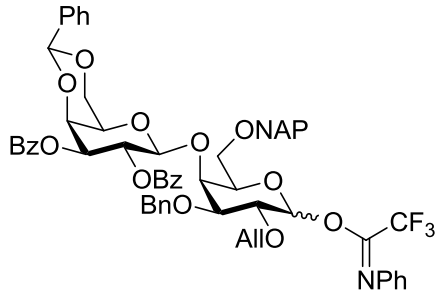
To a solution of **128** (700 mg, 0.61 mmol) in THF (10 mL) at 0 °C was added TBAF (0.61 mL, 1.0 M in THF). The resulting mixture was warmed gradually to 22 °C and was stirred for 2 h. The reaction was diluted with CH_2Cl_2, washed with sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (4:1 to 2:1 Toluene/EtOAc) to afford **129** as a transparent oil. Yield: 437 mg (80%).

R_f 0.24 (5:1 Toluene/EtOAc).

^{1}H NMR (400 MHz, , $CDCl_3$) δ 7.97 – 7.80 (m, 6H, ArH), 7.74 – 7.62 (m, 6H, ArH), 7.53 – 7.02 (m, 15H, ArH), 5.79 – 5.71 (m, 1H, H-2'), 5.51 – 5.41 (m, 2H, PhC$\underline{H}O_2$, -C$\underline{H}$=CH_2), 5.21 – 5.09 (m, 1.8H, H- 3', H-1α), 5.03 – 4.94 (m, 1H, H-1'), 4.92 – 4.51 (m, 7H, OC$\underline{H_2}$Ph, OC$\underline{H_2}$Naphth), 4.50 – 4.44 (m, 1.2H, H-4', H-1β), 4.16 – 4.03 (m, 3H, H-6a',H-4, H-5), 3.95 – 3.85 (m, 1H, H-6b'), 3.82 – 3.56 (m, 4H, H-6ab, H-3,), 3.54 – 3.28 (m, 4H, H-5', H-2, OC$\underline{H_2}$-CH=CH_2) ppm.

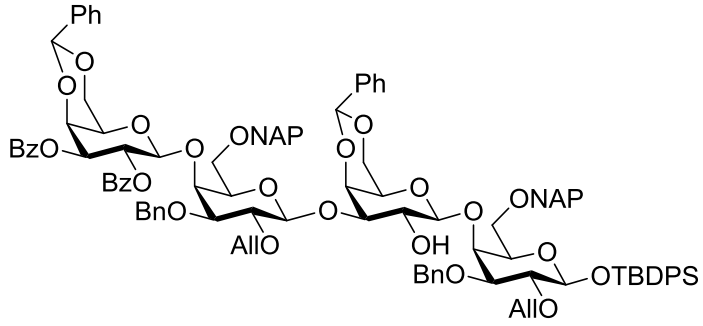
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (OBz), 165.2 (OBz), 138.8, 138.1, 136.0, 135.1, 134.7 (-$\underline{C}$H=CH_2), 134.1, 133.6, 133.5, 133.1, 133.0, 130.2, 130.1, 130.0, 129.9 (3C), 129.4, 129.2, 128.7, 128.6 (2C), 128.5, 128.4 (2C), 128.3 (2C), 128.2, 127.9, 127.8, 127.7, 126.8, 126.6, 126.2, 126.0, 125.9 (34 ArC), 116.7 (-CH=$\underline{C}H_2$), 101.4 (C-1'), 101.1 (Ph$\underline{C}HO_2$), 97.6 (C-1β), 91.9 (C-1α), 77.9 (C-3), 77.0 (C-2), 74.4 (C-4), 73.5 (2C, O$\underline{C}H_2$Naphth and O$\underline{C}H_2$Ph), 73.5 (C-4'), 73.1 (C-3'), 72.3 (O$\underline{C}H_2$CH=CH_2) , 69.6 (2C, C-2' and C-5), 69.3 (C-6), 68.8 (C-6'), 66.2 (C-5') ppm.

2,3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranose *N*-phenyl trifluoroacetimidate (130)



Hemiacetal **129** (400 mg, 0.45 mmol) was dissolved in dichloromethane (6 mL) and cooled to 0 °C. Cesium carbonate (290 mg, 0.89 mmol) was added followed by addition of *N*-phenyl trifluoroacetimidoyl chloride (0.14 mL, 0.89 mmol). The ice bath was removed and the reaction stirred at 22 °C for 3 hours. The mixture was then filtered through celite and concentrated. The crude was purified by flash chromatography (1:15 to 1:3 EtOAc/Toluene) to yield the product in 98% as a white solid (470 mg). The product was not further characterized and used directly in the next step.

***tert*-butyldiphenylsilyl 2,3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (131)**



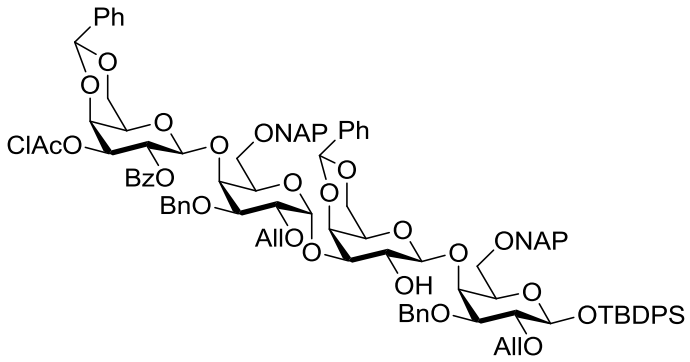
Trifluoroacetimidate donor **130** (100 mg, 0.094 mmol) and disaccharide acceptor **125** (72.8 mg, 0.078 mmol) were co-evaporated with toluene three times and subjected to high vacuum for two hours. The mixture was dissolved in CH_2Cl_2 (4 ml) and stirred with 4 Å MS for 30 minutes. The reaction mixture was cooled down to - 40 °C, and TMSOTf (3.53 µL, 0.019 mmol) was added. The mixture was stirred at -40 °C for 1 hour, quenched with 0.1 mL of triethylamine, diluted with CH_2Cl_2, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:10 to 1:5 EtOAc/Toluene) to yield tetrasaccharide **131** in 60% (91 mg).

R_f 0.55 (1:3 EtOAc/ Toluene).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 46.1, 8.3, 1.3 Hz, 5H, ArH), 7.87 – 7.67 (m, 12H, ArH), 7.65 – 7.07 (m, 37H, ArH), 6.01 – 5.88 (m, 2H, H-2’’’, -C*H*=CH_2), 5.70 – 5.52 (m, 3H, PhC*H*O_2, PhC*H*O_2’’, -C*H*=CH_2’’), 5.32 – 5.14 (m, 4H, H-1’’’, H- 3’’’, -CH=C*H*$_2$), 4.99 – 4.74 (m, 7H, H-1’’, OC*H*$_2$Naphth’’, OC*H*$_2$Naphth, -CH=C*H*$_2$’’), 4.70 – 4.38 (m, 8H, H-1, H-4’’’, OC*H*$_2$Ph, 0.5-C*H*$_2$-CH=CH_2’’, OC*H*$_2$Ph’’, 0.5x-C*H*$_2$-CH=CH_2), 4.36 – 4.22 (m, 4H, H-1’, H-

6a’’’, H- 4’’, 0.5x-C$\underline{H_2}$-CH=CH_2), 4.15 (d, *J* = 3.6 Hz, 1H, H-4’), 4.10 – 3.95 (m, 4H, H-6a’, H-6b’’’, H- 2’, 0.5x-C$\underline{H_2}$-CH=CH_2’’), 3.93 – 3.76 (m, 4H, H-6ab, H- 6b’, H-5), 3.73 – 3.55 (m, 5H, H-5’’’, H-6a’’, H-5’’, H-3’, H-2), 3.51 – 3.28 (m, 3H, H- 6b’’, H-3, H-3’’), 3.26 – 3.08 (m, 4H, H-5’, H- 2’’, 0.5x-C$\underline{H_2}$-CH=CH_2’’, H-4), 1.09 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5 (OBz), 165.3 (OBz), 139.2, 138.6, 138.1, 137.8, 136.2 (2C), 136.1, 136.0 (2C), 135.5 (-$\underline{C}$H=CH_2’’), 135.2 (-$\underline{C}$H=CH_2), 133.6, 133.4 (2C), 133.3, 133.0 (2C), 132.8, 130.1 (2C), 130.0, 129.7, 129.6, 129.4, 129.2, 129.1, 128.6, 128.5 (3C), 128.4, 128.3 (4C), 128.2, 128.1 (3C), 128.0 (4C), 127.7 (2C), 127.6 (3C), 127.5 (4C), 127.3, 126.9, 126.5 (4C), 126.4 (4C), 126.2, 126.1 (4C), 125.9, 125.7, 125.4 (68 ArC), 116.7 (-CH=$\underline{C}H_2$), 116.1 (- CH=$\underline{C}H_2$’’), 105.5 (C-1’), 103.4 (C-1’’), 101.5 (C-1’’’), 101.0 (Ph$\underline{C}HO_2$’’’), 100.5 (Ph$\underline{C}HO_2$’), 98.1 (C-1), 81.4 (C-3’’), 81.1 (C- 3), 81.0 (C-2), 79.8 (C-4), 77.0 (C- 3’), 76.6 (C-5), 75.7 (C-4’), 74.3 (O$\underline{C}H_2$CH=CH_2’’), 74.0 (O$\underline{C}H_2$Ph’’), 73.7 (O$\underline{C}H_2$Naphth, O$\underline{C}H_2$Naphth’’), 73.6 (C-4’’’), 73.5 (O$\underline{C}H_2$CH=CH_2), 73.3 (O$\underline{C}H_2$Ph), 73.2 (C-5’’), 73.2 (C-3’’’), 73.1 (C-4’’), 73.0 (C-2’’), 72.0 (C-2’), 69.6 (C- 2’’’), 69.0 (C-6’’’), 68.9 (C-6’), 68.6 (C-6), 68.5 (C-6’’), 67.0 (C-5’), 66.3 (C-5’’’), 27.0 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (126)**



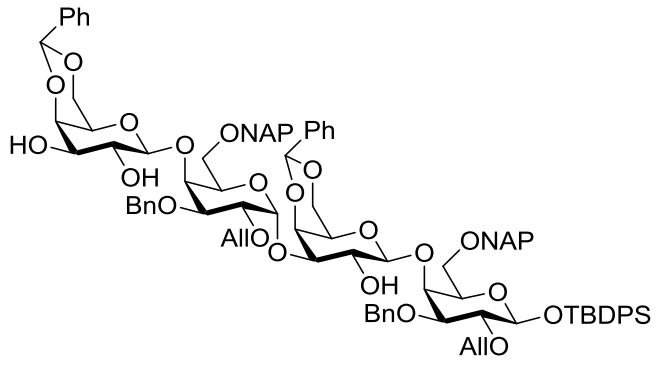
Trifluoroacetimidate donor **119** (1.72 g, 1.64 mmol) and disaccharide acceptor **125** (1.40 g, 1.49 mmol) were co-evaporated with toluene three times and subjected to high vacuum for two hours. The mixture was dissolved in CH_2Cl_2 (50 ml) and stirred with 4 Å MS for 30 minutes. The reaction mixture was cooled down to - 40 °C, and TMSOTf (67 µL, 0.37 mmol) was added. The mixture was stirred at -40 °C for 1 hour, quenched with 3 mL of triethylamine, diluted with CH_2Cl_2, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:12 to 1:5 EtOAc/Toluene) to yield tetrasaccharide **126** as a white solid in 55% (1.56 g).

mp 75.2 °C. $\mathbf{R}_f$ 0.40 (1:4 EtOAc/ Toluene). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$= 41.4° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 3H, ArH), 7.85 – 7.63 (m, 14H, ArH), 7.63 – 7.11 (m, 32H, ArH), 5.93 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H, -C$\underline{H}$=CH_2), 5.74 – 5.58 (m, 2H, H-2’’’,

- C<u>*H*</u>=CH_2''), 5.50 – 5.46 (m, 2H, PhC<u>*H*</u>O_2', PhC<u>*H*</u>O_2'''), 5.31 – 5.26 (m, 2H, H-1'', 0.5x-CH=C<u>*H*$_2$</u>''), 5.25 – 5.01 (m, 3H, 0.5x-CH=C<u>*H*$_2$</u>'', 0.5x-CH=C<u>*H*$_2$</u>, H-3'''), 4.94 (d, *J* = 10.4 Hz, 1H, 0.5x-CH=C<u>*H*$_2$</u>), 4.91 – 4.58 (m, 9H, H-1''', OC<u>*H*$_2$</u>Ph'', OC<u>*H*$_2$</u>Ph, -C<u>*H*$_2$</u>-CH=CH_2'', OC<u>*H*$_2$</u>Naphth), 4.57 – 4.26 (m, 6H, H-1, H-1', H-5'', H-4''', OC<u>*H*$_2$</u>Naphth''), 4.24 (d, *J* = 3.6 Hz, 1H, H-4'), 4.19 (d, *J* = 3.0 Hz, 1H, H-4''), 4.14 – 3.97 (m, 4H, H-3'', H-2', - C<u>*H*$_2$</u>-CH=CH_2), 3.96 – 3.58 (m, 13H, H-3', H-4, H-2'', H-2, C<u>*H*$_2$</u>Cl, H-6ab''', H-6ab'', H-6ab', H- 6a), 3.44 – 3.29 (m, 3H, H-5''', H-6b, H-3), 3.16 (dd, *J* = 7.4, 5.3 Hz, 1H, H-5), 3.06 (s, 1H, H-5'), 1.10 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5 (OAcCl), 166.3 (OBz), 139.0, 138.00 (2C), 137.9, 137.8, 136.5, 136.2, 136.0, 135.2 (-<u>*C*</u>H=CH_2), 135.1(-<u>*C*</u>H=CH_2''), 133.7, 133.6, 133.5, 133.4, 133.3, 133.0, 132.9, 130.1, 129.6, 129.2, 129.1, 129.0, 128.6, 128.5 (2C), 128.4, 128.3, 128.3, 128.3 (2C), 128.1, 128.0 (2C), 127.9, 127.8, 127.8, 127.7 (2C), 127.5 (2C), 127.3 (2C), 126.6 (2C), 126.5 (2C), 126.2, 126.2, 126.1 (2C), 125.9, 125.8, 125.6, 125.4 (49 ArC), 116.8 (- CH=<u>*C*</u>H_2''), 116.3 (-CH=<u>*C*</u>H_2), 106.2 (C-1'), 101.9 (C-1'''), 101.3 (Ph<u>*C*</u>HO_2'), 101.1 (Ph<u>*C*</u>HO_2'''), 98.1 (C-1), 92.3 (C-1''), 81.0 (C-2), 80.9 (C-3), 77.8 (C-3''), 77.6 (C-4), 76.5 (C- 2''), 76.4 (C-4''), 74.5 (C-3'), 74.3 (O<u>*C*</u>H_2Naphth''), 74.0 (O<u>*C*</u>H_2Ph''), 73.6 (O<u>*C*</u>H_2CH=CH_2''), 73.4 (O<u>*C*</u>H_2Naphth), 73.3 (O<u>*C*</u>H_2Ph), 73.2 (C-4'''), 72.9 (C-5), 72.6 (C-3'''), 71.3 (C-4'), 71.0 (O<u>*C*</u>H_2CH=CH_2), 70.9 (C-2'''), 70.1 (C-2'), 69.7 (C-6'), 69.4 (C-6''), 69.0 (C- 6'''), 68.8 (C-5''), 68.5 (C-6), 66.7 (C-5'), 66.1 (C-5'''), 40.7 (<u>*C*</u>H_2Cl), 27.1 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

tert-butyldiphenylsilyl 4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (147)

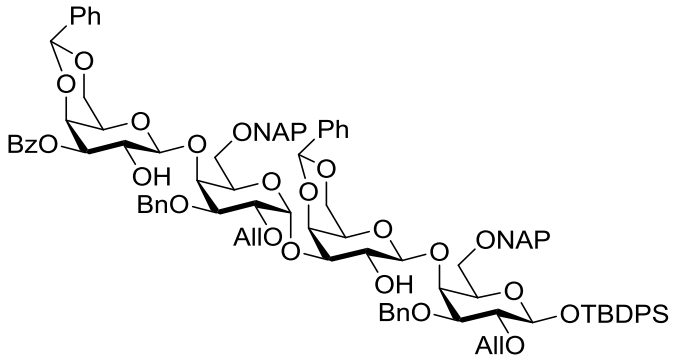


52 µl of 4.6 M NaOMe in MeOH was added to a solution of tetrasaccharide **126** (647 mg, 0.34 mmol) in methanol (3 mL) and THF (2 mL). The reaction mixture was stirred at 22 °C for 3 hours, quenched with Amberlite IR-120 (H^+), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (4:1 to 2:1 Toluene/EtOAc) to afford diol **147** in 89% yield (490 mg).

R_f 0.15 (1:2 EtOAc/Toluene). $[\alpha]_D^{20}$= 11.2° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.64 (m, 11H, ArH), 7.64 – 7.10 (m, 33H, ArH), 5.92 (ddt, *J* = 16.2, 10.7, 5.6 Hz, 1H, -C*H*=CH_2''), 5.69 (ddt, *J* = 17.5, 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.48 (s, 2H, PhC*H*O_2', PhC*H*O_2'''), 5.26 (d, *J* = 3.2 Hz, 1H, H-1''), 5.23 – 5.02 (m, 2H, ,-CH=CH_2), 5.02 – 4.91 (m, 2H, ,-CH=CH_2''), 4.79 – 4.61 (m, 6H, OCH_2Naphth, OCH_2Ph, OCH_2Ph''), 4.59 – 4.38 (m, 5H, H-1, -CH_2-CH=CH_2, OCH_2Naphth''), 4.35 (m, 2H, H-1', H-1'''), 4.32 – 4.25 (m, 1H, H- 2'''), 4.21 (d, *J* = 3.6 Hz, 1H, H-5), 4.17 – 3.62 (m, 18H, H-4', H-4''', H-2', H- 3', H-2'', H- 4'', H-3'', H-4, H-2, H-6a, H-6ab'', H-6ab', H-6ab''', -CH_2-CH=CH_2''), 3.54 (dd, *J* = 9.6, 3.7 Hz, 1H, H-3'''), 3.37 (dd, *J* = 9.7, 3.2 Hz, 1H, H-3), 3.33 – 3.28 (m, 1H, H-6b), 3.21 – 3.03 (m, 3H, H-5', H-5'', H-5'''), 1.09 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 138.0 (2C), 137.9, 137.8, 136.2 (2C), 136.0 (4C) 135.1 (-*C*H=CH_2''), 134.9 (-*C*H=CH_2), 133.6, 133.4 (2C), 133.3, 133.0, 132.9, 129.3, 129.2 (3C), 129.0, 128.7, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.2, 128.1, 128.0 (2C), 127.9 (2C), 127.8 (2C), 127.6, 127.5 (2C), 127.3 (2C), 126.6 (2C), 126.5 (3C), 126.3, 126.2, 126.1, 126.0, 125.9, 125.6, 125.4 (56 ArC), 117.0 (-CH=*C*H_2''),, 116.8(-CH=*C*H_2), 106.0 (C-1'''), 105.8 (C-1'), 101.4 (Ph*C*HO_2'/Ph*C*HO_2'''), 101.2 (Ph*C*HO_2'/Ph*C*HO_2'''), 98.1 (C-1), 92.9 (C-1''), 81.0 (C-2), 80.9 (C-3), 79.3 (C-4), 77.6 (C- 3''), 77.36 (C-4''), 76.4 (C-2''), 75.3 (C-3'), 75.1 (C-2'), 74.5 (O*C*H_2Ph''), 74.3 (O*C*H_2CH=CH_2) 73.7 (O*C*H_2Ph), 73.4 (C-3'''), 73.3 (2C, O*C*H_2Naphth and O*C*H_2Naphth''), 72.9 (C-5''), 72.5 (C-2'''), 71.6 (C-5), 71.3 (C-4'''), 70.1 (C-4'), 69.35 (O*C*H_2CH=CH_2''), 69.1 (C- 6'''), 69.0 (C-6'), 68.5 (C- 6''), 68.4 (C-6), 66.9 (C-5'''), 66.8 (C-5'), 27.1 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (148)**



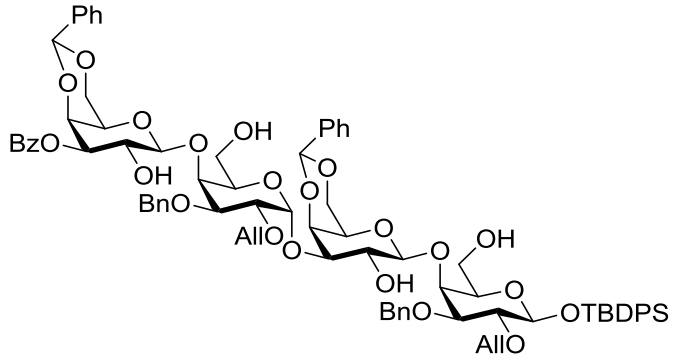
To a solution of triol **147** (680 mg, 0.42 mmol) in 15 mL of CH_2Cl_2 was added triethylamine (64 µL, 0.46 mmol). The solution was then cooled down to -40 °C, benzoyl chloride (54 µL, 0.46 mmol) and DMAP (15 mg, 0.13 mmol) were added. The reaction mixture was stirred at -40 °C for 3 hours until TLC indicated full conversion of the starting material. The mixture was then diluted with CH_2Cl_2 and washed with 1M HCl. The organic phase was further washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in*

vacuo. The crude product was purified by flash chromatography ((1:15 EtOAc/Toluene) to afford the product in 76% yield (550 mg).

R_f 0.50 (1:3 EtOAc/Toluene). $[\alpha]_D^{20}$= 57.8° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.04 (m, 2H, ArH), 7.85 – 7.63 (m, 13H, ArH), 7.62 – 7.12 (m, 34H, ArH), 5.92 (ddt, *J* = 17.2, 10.7, 5.6 Hz, 1H, -C*H*=CH_2), 5.67 (ddd, *J* = 17.3, 10.6, 5.3 Hz, 1H, -C*H*=CH_2''), 5.47 (s, 1H, PhC*H*O_2'/PhC*H*O_2'''), 5.43 (s, 1H, PhC*H*O_2'/PhC*H*O_2'''), 5.29 – 5.12 (m, 3H, H-1'',-CH=C*H*$_2$), 5.06 (dq, *J* = 17.3, 1.6 Hz, 1H, 0.5x-CH=C*H*$_2$''), 5.01 – 4.93 (m, 3H, H-3''', 0.5xOC*H*$_2$Ph'', 0.5x-CH=C*H*$_2$''), 4.91 (s, 1H, 0.5xOC*H*$_2$Ph), 4.79 – 4.61 (m, 4H, 0.5xOC*H*$_2$Ph, H-6ab'/H-6ab''', 0.5xOC*H*$_2$Ph''), 4.58 – 4.36 (m, 8H, H-1, H-1''', H-4''', H- 5'', - C*H*$_2$-CH=CH_2, H-6ab'/H-6ab'''), 4.34 (d, *J* = 7.6 Hz, 1H, H-1'), 4.32 – 4.16 (m, 4H, H-2''', H- 4', OC*H*$_2$Naphth), 4.16 – 3.99 (m, 7H, H-4'', H-3'', H-2', - C*H*$_2$-CH=CH_2'', OC*H*$_2$Naphth''), 3.99 – 3.62 (m, 7H, H-2, H-4, H-6a, H-3', H-2'', H-6ab''), 3.37 (dd, *J* = 9.7, 3.2 Hz, 1H, H-3), 3.33 – 3.24 (m, 2H, H-6b, H-5'/H-5'''), 3.16 (dd, *J* = 7.5, 5.3 Hz, 1H, H-5), 3.08 (d, *J* = 2.0 Hz, 1H, H-5'/H-5'''), 1.09 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7 (OBz), 138.1, 138.0, 137.8, 136.2 (3C), 136.1, 136.0 (2C), 135.1 (-*C*H=CH_2), 134.9 (-*C*H=CH_2''), 134.6, 133.7, 133.5, 133.4, 133.3, 133.2, 133.0, 132.1, 130.1 (2C), 129.9, 129.8, 129.6, 129.2 (2C), 129.1, 129.0, 128.9, 128.8, 128.6 (2C), 128.5 (2C), 128.4 (4C), 128.3 (2C), 128.2, 128.2 (3C), 128.1, 128.0 (2C), 127.9, 127.8, 127.7, 127.5 (2C), 127.3 (2C), 126.5, 126.4, 126.3, 126.2, 126.1, 126.0, 125.9, 125.6, 125.4 (62 ArC), 116.8 (2C, -CH=*C*H_2 and -CH=*C*H_2''), 106.1 (2C, C-1'and C-1'''), 101.2 (Ph*C*HO_2'/Ph*C*HO_2'''), 100.8 (Ph*C*HO_2'/Ph*C*HO_2'''), 98.1 (C-1), 92.96 (C-1''), 81.0 (C-2), 80.9 (C-3), 79.7 (C-4''), 77.6 (C- 3''), 77.4 (C-4), 76.6 (C-2''), 75.2 (C-3'''), 75.1 (C-3'), 74.5 (OC*H*$_2$Ph), 74.3 (-*C*H_2-CH=CH_2), 73.7 (2C, OC*H*$_2$Ph'', O*C*H_2Naphth), 73.4 (2C, O*C*H_2Naphth'', C-4'''), 73.3 (2C, C- 6' and C- 6'''), 72.9 (C-5), 71.6 (C-4'), 71.4 (-*C*H_2-CH=CH_2''), 70.1 (C-2'), 69.4 (C- 2'''), 69.0 (C- 6''), 68.5 (C-5''), 68.4 (C-6), 66.7 (2C, C-5' and C-5'''), 27.1 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-β-D-galactopyranoside (149)**



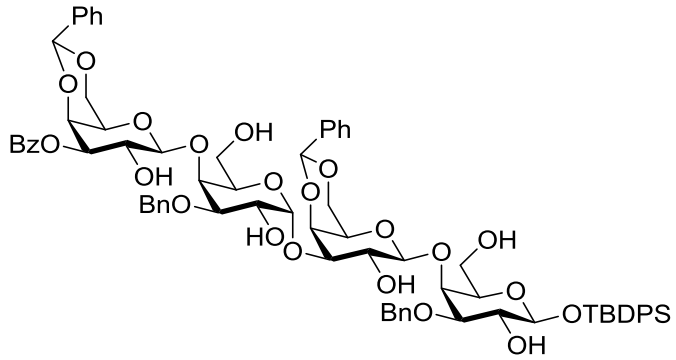
To a solution of **148** (482 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) and water (1 mL) was added DDQ (190 mg, 0.84 mmol). The mixture was stirred

for 1 hour at 22 °C in the dark, diluted with CH_2Cl_2 (30 mL), filtered through a high pad of celite and washed with sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (2:1 Toluene/EtOAc) afforded **149** in 97% yield (394 mg).

$\mathbf{R}_f$ 0.15 (1:1 EtOAc/Toluene). $[\alpha]_D^{20}$= 80.8° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 2H, ArH), 7.69 – 7.60 (m 5H, ArH), 7.50 – 7.15 (m, 28H, ArH), 5.89 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H, - C*H*=CH_2), 5.62 (ddt, *J* = 17.4, 10.8, 5.5 Hz, 1H, - C*H*=CH_2''), 5.40 (m, 2H, PhC*H*O_2', PhC*H*O_2'''), 5.24 (d, *J* = 1.7 Hz, 1H, 0.5x- CH=C*H*$_2$/0.5x-CH=C*H*$_2$''), 5.19 (d, *J* = 1.7 Hz, 1H, 0.5x-CH=C*H*$_2$/0.5x-CH=C*H*$_2$''), 5.13 (d, *J* = 3.6 Hz, 1H, H-1''), 5.10 (d, *J* = 1.7 Hz, 1H, 0.5x-CH=C*H*$_2$/0.5x-CH=C*H*$_2$''), 5.04 (d, *J* = 1.7 Hz, 1H, .5x-CH=C*H*$_2$/0.5x-CH=C*H*$_2$''), 4.97 – 4.89 (m, 2H, H-4'', 0.5x-CH=C*H*$_2$/ 0.5x- CH=C*H*$_2$''), 4.80 – 4.56 (m, 4H, OC*H*$_2$Ph, OC*H*$_2$Ph''), 4.50 (d, *J* = 7.7 Hz, 1H, H-1'''), 4.47 – 4.37 (m, 3H, H- 1, H-4''', 0.5x-C*H*$_2$-CH=CH_2), 4.34 (d, *J* = 7.7 Hz, 1H, H-1'), 4.27 – 4.05 (m, 4H, 0.5x-C*H*$_2$-CH=CH_2, H-2''', H-5, H-4'), 4.04 – 3.91 (m, 9H, H-3''', H-3'', - C*H*$_2$- CH=CH_2'', H-6ab', H- 6ab''', H- 2'), 3.85 – 3.64 (m, 4H, H-2'', H-4, H-6ab), 3.62 – 3.45 (m, 4H, H-6a'', H-5''', H- 2, H-3'), 3.33 (m, 2H, H-6b'', H-3), 3.26 (d, *J* = 2.0 Hz, 1H, H-5'), 3.05 – 2.98 (m, 1H, H-5''), 1.02 (s, 9H, 3xCH_3^{TBDPS}) ppm.**^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.63 (OBz), 138.0 (2C), 137.9, 137.8, 137.7, 136.1 (3C), 135.9 (2C), 135.11 (-*C*H=CH_2), 134.8 (- *C*H=CH_2''), 133.7, 133.4, 133.3, 130.1 (2C), 129.9, 129.8 (2C), 129.2, 129.1, 128.7 (2C), 128.5 (2C), 128.4 (4C), 128.3 (2C), 128.2 (3C), 128.1, 127.7, 127.6, 127.5 (3C), 126.4 (3C) (42 ArC), 116.9 (2C,-CH=*C*H_2 and -CH=*C*H_2''), 105.8 (C-1'''), 105.4 (C-1'), 101.4 (Ph*C*HO_2'), 101.0 (Ph*C*HO_2'''), 98.0 (C-1), 93.6 (C-1''), 81.0 (C-2), 80.7 (C-3), 79.4 (C-3'''), 77.4 (C-3'') 76.5 (C- 2''), 75.9 (C-4), 75.6 (C-3'), 75.0 (C-4''), 74.5 (O*C*H_2Ph''), 74.3 (O-*C*H_2-CH=CH_2), 74.2 (O*C*H_2Ph) 73.6 (C-5''), 73.2 (C-4'''), 71.6 (C-4'), 71.4 (O-*C*H_2-CH=CH_2''), 69.6 (C-2'), 69.2 (C- 6'), 69.1 (C-5), 69.0 (C-2'''), 68.9 (C-6'''), 66.9 (2C, C-5' and C-5'''), 61.3 (C-6), 60.2 (C-6''), 27.1 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-β-D-galactopyranoside (150)**

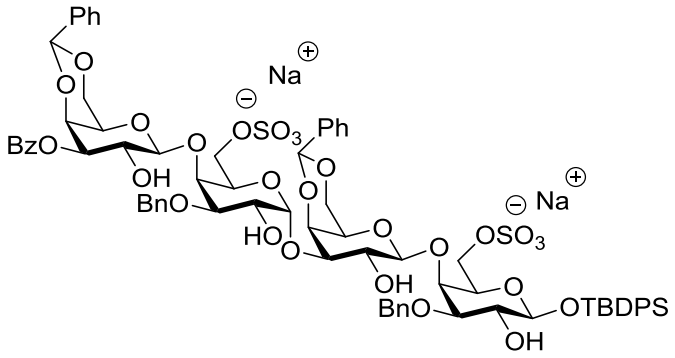


To a solution **149** (350 mg, 0.24 mmol) in 5 mL glacial acetic acid was added $Pd(PPh_3)_4$ (280 mg, 0.24 mmol). The mixture was degassed and stirred under nitrogen at 22 °C for 48 hours. The residue was co-evaporated three times with toluene and purified by flash chromatography (1:10 to 1:2 EtOAc/Toluene) to afford the desired compound in 76% yield (250 mg).

R_f 0.15 (1:1 EtOAc/Toluene). $[\alpha]_D^{20}$= 29.8° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H, ArH), 7.70 – 7.55 (m, 9H, ArH), 7.52 – 7.05 (m, 24H, ArH), 5.44 (s, 1H PhC*H*O_2'), 5.38 (s, 1H, PhC*H*O_2'''), 4.98 (d, *J* = 3.9 Hz, 1H, H-1''), 4.95 (dd, *J* = 10.1, 3.5 Hz, 1H, H-3'''), 4.83 – 4.71 (m, 2H, OC*H*$_2$Ph), 4.64 – 4.56 (m, 2H, OC*H*$_2$Ph''), 4.47 (d, *J* = 7.7 Hz, 1H, H-1'''), 4.39 (dd, *J* = 3.5, 1.0 Hz, 1H, H-4'''), 4.35 (m, 2H, H-1, H-1'), 4.20 – 4.01 (m, 4H, H-6a''', H-5, H-4', H-2'''), 4.00 – 3.89 (m, 5H, H-6b''', H-6ab' H-2'', H-4''), 3.87 (dd, *J* = 3.4, 1.4 Hz, 1H, H-4), 3.84 – 3.57 (m, 7H, H-6a'', H-6ab, H-2', H-2, H-3', H-3''), 3.50 – 3.42 (m, 2H, H-5''', H-6b''), 3.31 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3), 3.23 (s, 1H, H-5'), 3.15 (t, *J* = 7.4 Hz, 1H, H-5''), 1.02 (s, 9H, 3xCH_3 ^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.6 (OBz), 138.0, 137.8 (2C), 137.6, 137.5, 136.0 (2C), 135.9 (2C), 134.7, 133.3, 133.2, 133.0, 132.3, 132.2 (2C), 132.1 (3C), 132.0, 130.1, 130.0 (2C), 129.9, 129.4, 129.1 (2C), 128.8, 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 128.1, 127.8, 127.6, 126.4, 126.3, 125.4 (42 ArC), 105.7 (C- 1'''), 105.0 (C-1'), 101.3 (Ph*C*HO_2'), 101,0 (Ph*C*HO_2''') 97.9 (C-1), 96.4 (C-1''), 80.7 (C-3), 78.5 (C-4''), 78.1 (C-3''), 76.7(C-3'), 75.3 (C-4), 74.8 (C-3'''), 74.0 (C-2), 73.9 (OC*H*$_2$Ph), 73.8 (OC*H*$_2$Ph''), 73.7 (C-5''), 73.2 (C-4'''), 72.0 (C-4'), 69.9 (C-2''), 69.8 (C-5), 69.5 (C-2'), 69.0 (2C, C- 2''' and C-6'''), 68.9 (C-6'), 66.8 (C-5'''), 66.7 (C-5'), 61.2 (C-6), 60.2 (C-6''), 27.0 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-sulfonate-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-sulfonate-β-D-galactopyranoside (151)**

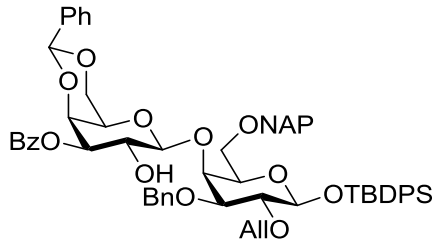


Tetrasaccharide **150** (122 mg, 0.09 mmol) was dissolved in 5 mL anh. DMF. The mixture was stirred at 22 °C for 30 min after pyridine (0.17 mL, 2.11 mmol) and 4 Å MS were added. SO_3·Py complex (311 mg, 1.95 mmol) was added in two times over 2 h and the reaction mixture was stirred 2 h at 22 °C until TLC showed full conversion of the starting material. The reaction was then quenched by addition of 1 mL of pyridine and 2 mL of methanol, diluted with CH_2Cl_2 and the molecular sieves were filtered off through celite. The filtrate was concentrated *in vacuo* and the crude product was purified by flash chromatography (gradient of 1 % MeOH in CH_2Cl_2). The fractions containing the product were stirred with Amberlite IR 120 (Na^+) resins for 15 minutes, the resin was filtered off and the fractions concentrated to yield disulfated product **151** in 60% (84 mg).

$\mathbf{R}_f$ 0.35 (1:8 MeOH/ CH_2Cl_2). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$= 123.2° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, MeOD) δ 8.09 – 8.04 (m, 2H, ArH), 7.89 – 7.78 (m, 5H, ArH), 7.64 – 7.54 (m, 4H, ArH), 7.53 – 7.24 (m, 24H, ArH), 5.63 (s, 1H, PhC*H*O$_2$'), 5.54 (s, 1H, PhC*H*O$_2$'''), 5.22 (d, *J* = 3.8 Hz, 1H, H-1''), 5.12 (dd, *J* = 10.1, 3.8 Hz, 1H, H-3'''), 4.85 – 4.69 (m, 5H, H-1''', OC*H*$_2$Ph, OC*H*$_2$Ph''), 4.59 (d, *J* = 7.7 Hz, 1H, H-1'), 4.54 – 4.23 (m, 10H, H-4''', H-4'', H-4' H-1, H-5', H-6a, H-6a'', H-6ab''', H-6a'), 4.17 – 4.07 (m, 5H, H-2'', H- 6b, H-6b'', H-4, H-6b'), 4.02 (dd, *J* = 10.1, 7.7 Hz, 1H, H-2'''), 3.97 (dd, *J* = 9.9, 2.9 Hz, 1H, H-3''), 3.92 – 3.85 (m, 2H, H-2, H-3'), 3.80 (dd, *J* = 9.9, 7.7 Hz, 1H, H-2'), 3.67 (d, *J* = 1.3 Hz, 1H, H-5/H-5''), 3.58 – 3.52 (m, 1H, H-5'''), 3.50 (q, *J* = 1.6 Hz, 1H, H-5/H-5''), 3.45 (dd, *J* = 9.8, 3.0 Hz, 1H, H-3), 1.12 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, MeOD) δ 167.6 (OBz), 139.7, 139.6, 139.4, 139.1, 137.2 (2C), 137.1 (2C), 134.7, 134.3, 134.2, 131.3, 130.8 (2C), 130.7, 129.9, 129.8, 129.7, 129.6 (2C), 129.5 (4C), 129.3 (2C), 129.1 (4C), 129.0 (3C), 128.9 (2C), 128.6 (2C), 128.5, 127.6 (2C), 127.3 (2C) (42 ArC), 106.1 (C-1'''), 106.0 (C-1'), 102.2 (Ph*C*HO$_2$'), 101.9 (Ph*C*HO$_2$'''), 99.6 (C-1), 96.2 (C-1''), 82.9 (C-3), 79.7 (C-3''), 78.9 (C-4''), 77.7 (C-4), 76.7 (C-3'), 76.0 (C-3'''), 75.0 (C-4'''), 74.6 (2C, O*C*H$_2$Ph and O*C*H$_2$Ph''), 74.2 (C-2), 73.8 (C-5'''), 73.2 (C-5'), 71.3 (C-2'), 70.9 (C-2'''), 70.5 (C-2''), 70.3 (C-6 or C-6''), 70.1 (2C, C-4' and C-6 or C-6''), 68.2 (C-5 or C-5''), 68.1(C-5 or C-5''), 67.8 (C-6'), 67.7 (C-6''') 27.4 (3C *tert*-butyl), 20.2 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-6-*O*-(2-naphthyl)methyl-β-D-galactopyranoside (140)**

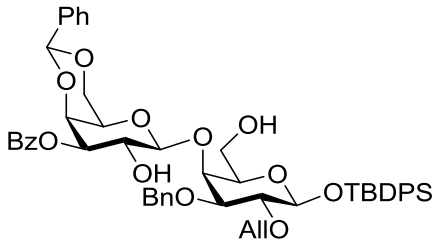


To a solution of diol **125** (1.12 g, 1.19 mmol) in 30 mL of CH_2Cl_2 was added triethylamine (0.20 mL, 1.43 mmol). The solution was then cooled down to -40 °C, benzoyl chloride (0.16 mL, 1.43 mmol) and DMAP (44 mg, 0.36 mmol) were added. The reaction mixture was stirred at -40 °C for 2 hours until TLC indicated full conversion of the starting material. The mixture was then diluted with CH_2Cl_2, washed with 1M HCl. The organic phase was further washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:30 to 1:10 EtOAc/Toluene) to afford the product in 75% yield (920 mg).

R_f 0.65 (1:3 EtOAc/Toluene). $[\alpha]_D^{20}$= 14.4° (c 1.0, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 2H, Ar*H*), 7.89 – 7.13 (m, 30H, Ar*H*), 5.95 (ddt, *J* = 16.2, 10.7, 5.7 Hz, 1H, -C*H*=CH_2), 5.47 (s, 1H, PhC*H*O_2), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H, 0.5x-CH=C*H*$_2$), 5.18 (dt, *J* = 10.4, 1.5 Hz, 1H, 0.5x-CH=C*H*$_2$), 5.05 (dd, *J* = 10.1, 3.7 Hz, 1H, H- 3'), 4.86 – 4.69 (ABq pattern, *J* = 12.2 Hz, 2H, OC*H*$_2$Ph), 4.64 – 4.38 (m, 5H, H-1, H-1', H-4', H-2', 0.5xOC*H*$_2$CH=CH_2), 4.36 – 4.26 (m, 1H, 0.5xOC*H*$_2$CH=CH_2,), 4.09 (dd, *J* = 12.5, 1.5 Hz, 1H, H- 6b), 3.96 – 3.81 (m, 3H, H-6a', H-6a, H-4), 3.70 (dd, *J* = 9.7, 7.4 Hz, 1H, H-2), 3.42 (dd, *J* = 9.7, 3.2 Hz, 1H, H-3), 3.31 (m, 2H, H-6b', H-5), 3.20 (dd, *J* = 7.8, 5.2 Hz, 1H, H-5'), 1.10 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7 (OBz), 138.0, 137.6, 136.2 (3C), 136.0 (3C), 135.1 (-CH=*C*H_2), 133.6 (2C), 133.4, 133.3, 133.0, 130.1 (3C), 129.7, 129.6, 129.2 (2C), 129.0, 128.7 (2C), 128.5 (2C), 128.4 (3C), 128.3 (2C), 128.2, 128.0, 127.8, 127.6, 127.4, 126.3 (2C), 126.1, 126.0, 125.5, 125.4 (40 ArC), 116.9 (-*C*H=CH_2), 106.1 (C-1'), 100.8 (Ph*C*HO_2), 98.1 (C-1), 81.0 (C-2), 80.8 (C-3), 78.2 (C-4), 75.2 (C-3'), 74.4 (O*C*H_2CH=CH_2), 74.0 (O*C*H_2Ph), 73.4 (O*C*H_2Naphth), 73.3 (C-4'), 72.8 (C-5'), 69.4 (C-2'), 69.1 (C-6), 68.3 (C-6'), 66.8 (C-5), 27.1 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-2-*O*-allyl-3-*O*-benzyl-β-D-galactopyranoside (141)**

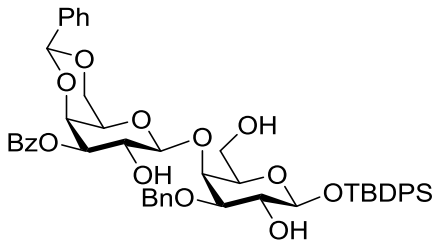


To a solution of **140** (872 mg, 0.85 mmol) in CH_2Cl_2 (25 mL) and water (2.5 mL) was added DDQ (290 mg, 1.28 mmol). The mixture was stirred for 1 hour at 22 °C in the dark, diluted with CH_2Cl_2 (30 mL), filtered through a high pad of celite and washed with sat. aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (4:1 to 2:1 Tol/EtOAc) afforded **141** as a white solid in 90% yield (697 mg).

$\mathbf{R_f}$ 0.25 (3:1 Tol/EtOAc). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$= 43.2° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 2H, ArH), 7.63 (m, 5H, ArH), 7.52 – 7.44 (m, 1H, ArH), 7.41 – 7.04 (m, 17H, ArH), 5.86 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, -C*H*=CH_2), 5.38 (s, 1H, PhC*H*O_2), 5.19 (dq, *J* = 17.2, 1.7 Hz, 1H, 0.5x-CH=C*H*$_2$), 5.09 (dq, *J* = 10.4, 1.4 Hz, 1H, 0.5x- CH=C*H*$_2$), 4.96 (dd, *J* = 10.1, 3.5 Hz, 1H, H-3'), 4.76 – 4.59 (ABq pattern, *J* = 12.2 Hz, 2H, OC*H*$_2$Ph), 4.42 – 4.36 (m, 4H, H-1, H-1', H-4', 0.5xOC*H*$_2$CH=CH_2), 4.25 – 4.17 (m, 2H, 0.5xOC*H*$_2$CH=CH_2, H-2'), 4.13 – 4.04 (m, 1H, H-6a'), 3.99 – 3.91 (m, 1H, H-6b'), 3.71 (m, 2H, H-4, 2'-O*H*), 3.59 – 3.47 (m, 2H, H-2, H-6a), 3.40 (d, *J* = 1.3 Hz, 1H, H-5'), 3.34 (m, 3H, H-3, H- 6b, 6-O*H*), 3.01 (m, 1H, H-5), 1.01 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7 (OBz), 137.8, 137.6, 136.1, 136.0, 135.1 (-*C*H=CH_2), 133.7, 133.4, 133.3, 130.1, 129.9 (2C), 129.8, 129.2, 129.1, 128.8, 128.6, 128.5, 128.4 (3C), 128.3 (2C), 127.7 (3C), 127.5 (3C), 126.3 (2C), 125.4 (30 ArC), 117.0 (-CH=*C*H_2), 105.7 (C-1'), 100.9 (Ph*C*HO_2), 98.0 (C-1), 80.9 (C-2), 80.4 (C-3), 77.4 (C-4), 74.9 (C-3'), 74.3 (2C, O*C*H_2Ph and O*C*H_2CH=CH_2), 73.5 (C-5), 73.3 (C- 4'), 69.0 (C-2'), 68.8 (C-6'), 66.9 (C-5'), 60.3 (C-6), 27.1 (3C *tert*-butyl),19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-β-D-galactopyranoside (142)**



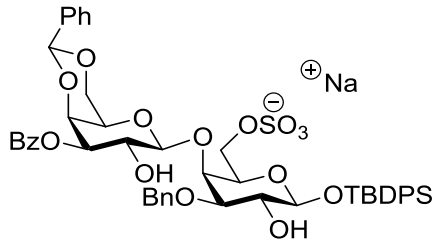
To a solution of diol **141** (679 mg, 0.75 mmol) in 6 mL glacial acetic acid was added $Pd(PPh_3)_4$ (434 mg, 0.37 mmol). The mixture was degassed and stirred under nitrogen at 22 °C for 12 hours. The residue was coevaporated three times with toluene and purified

by flash chromatography (1:10 to 1:2 EtOAc/Toluene) to afford the desired compound in 93% yield (608 mg).

R_f 0.25 (3:1 Toluene/EtOAc). $[\alpha]_D^{20}$= 34.0° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H, ArH), 7.68 – 7.58 (m, 4H, ArH), 7.51 – 7.44 (m, 1H, ArH), 7.42 – 7.22 (m, 10H, ArH), 7.21 – 7.03 (m, 8H, ArH), 5.38 (s, 1H, PhC*H*O_2), 4.96 (dd, *J* = 10.2, 3.7 Hz, 1H, H-3'), 4.76 – 4.59 (ABq pattern, *J* = 12.2 Hz, 2H, OC*H*$_2$Ph), 4.45 (d, *J* = 7.7 Hz, 1H, H-1'), 4.38 (d, *J* = 3.6 Hz, 1H, H-4'), 4.35 (d, *J* = 7.5 Hz, 1H, H-1), 4.17 (dd, *J* = 10.2, 7.7 Hz, 1H, H-2'), 4.00 (m, 2H, H-6ab') 3.87 – 3.79 (m, 2H, H-4, H-2), 3.68 (m, 1H, H-6b), 3.48 (m, 1H, H-6a), 3.40 (s, 1H, H-5'), 3.31 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3), 3.14 (s, 1H, H- 5), 2.76 (bs, 1H, O*H*), 1.02 (s, 9H, 3xCH_3^{TBDPS}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.6 (OBz), 138.0, 137.8, 137.7, 137.6, 136.0 (2C), 135.8 (2C), 133.4, 133.3, 133.2, 130.1, 130.0 (2C), 129.9, 129.2 (2C), 129.1, 128.8 (2C), 128.5, 128.4 (2C), 128. (2C), 128.2, 127.8, 127.6, 126.3, 125.4 (30 ArC), 105.4 (C-1'), 100.9 (Ph*C*HO_2), 97.9 (C-1), 80.3 (C-3), 75.9 (C-4), 74.7 (C-3'), 74.1 (C-2), 73.9 (O*C*H_2Ph), 73.8 (C-5), 73.2 (C-4'), 68.9 (C-2'), 68.8 (C-6'), 66.8 (C-5'), 60.2 (C- 6), 27.0 (3C *tert*-butyl), 19.3 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-sulfonate-β-D-galactopyranoside (143)**



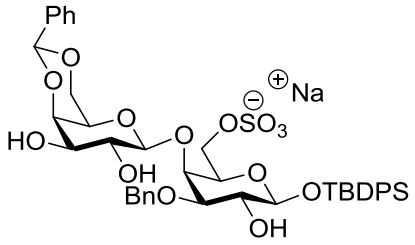
Triol **142** (200 mg, 0.23 mmol) was dissolved in 14 mL anh. DMF. The mixture was stirred at 22 °C for 30 min after pyridine (0.23 mL, 2.76 mmol) and 4 Å MS were added. SO_3.Py complex (369 mg, 2.30 mmol) was added and the reaction mixture was stirred 1 h at 22 °C until TLC showed full conversion of the starting material. The reaction was then quenched by addition of 1 mL of pyridine and 2 mL of methanol, diluted with CH_2Cl_2 and the molecular sieves were filtered off through celite. The crude product was purified by flash chromatography (gradient of 1 % MeOH in CH_2Cl_2). The fractions containing the product were stirred with Amberlite IR 120 (Na^+) resin for 15 minutes, the resin was filtered off and the product concentrated to yield monosulfated product **143** in 70% (155 mg).

R_f 0.40 (1:9 MeOH/CH_2Cl_2). $[\alpha]_D^{20}$= 1.6° (c 0.5, $CDCl_3$).

^{1}H NMR (400 MHz, MeOD) δ 8.10 – 8.05 (m, 2H, ArH), 7.83 (m, 4H, ArH), 7.65 – 7.58 (m, 1H, ArH), 7.53 – 7.24 (m, 18H, ArH), 5.55 (s, 1H, PhC*H*O_2), 5.10 (dd, *J* = 10.1, 3.8 Hz, 1H, H-3'), 4.80 (s, 2H, OC*H*$_2$Ph), 4.72 (d, *J* = 7.8 Hz, 1H, H-1'), 4.56 – 4.48 (m, 2H, H-4', H-1), 4.48 – 4.38 (m, 2H, H-6a', H-6a), 4.24 (d, *J* = 3.0 Hz, 1H, H-4), 4.14 – 4.03 (m, 3H, H-6b', H6b, H-2'), 3.91

(dd, *J* = 9.8, 7.5 Hz, 1H, H-2), 3.61 – 3.54 (m, 2H, H-5, H-5'), 3.47 (dd, *J* = 9.9, 3.0 Hz, 1H, H- 3), 1.12 (s, 9H, 3x$CH_3{}^{TBDPS}$) ppm. **^{13}C NMR** (101 MHz, MeOD) δ 168.2 (OBz), 140.3 , 139.9, 137.9 (2C), 137.8 (2C), 135.3, 134.9, 134.9, 131.9, 131.4 (4C), 131.3, 130.3 (2C), 130.1 (2C), 130.0 (2C), 129.6 (2C), 129.5, 129.2 (2C), 129.1 (2C), 128.0 (2C) (30 ArC), 106.7 (C-1'), 102.6 (Ph*C*HO_2), 100.3 (C-1), 83.7 (C-3), 78.2 (C-4), 76.6 (C-3'), 75.7 (C-4'), 75.2 (O*C*H_2Ph), 74.9 (C-2), 74.3 (C-2'), 71.3 (C-5), 70.7 (C-6'), 68.8 (C-5'), 68.2 (C-6), 28.0 (3C *tert*-butyl), 20.8 (*tert*-butyl) ppm.

tert-butyldiphenylsilyl 4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-3-*O*-benzyl-6-*O*-sulfonate-β-D-galactopyranoside (145)

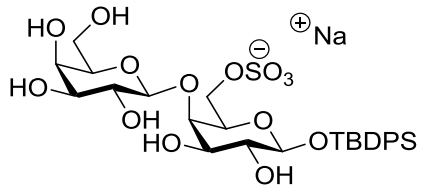


Monosulfated diol **143** (127 mg, 0.13 mmol) was dissolved in MeOH (1 mL) and the solution was cooled down to -20 °C. 1 mL of 0.04 M NaOMe in MeOH was added and the reaction was stirred at -20 °C for 24 hours. After addition of Amberlite IR 120 (H+), the mixture was stirred 30 minutes at -20 °C before the resin was filtered off. The reaction mixture was then stirred with Amberlite IR 120 (Na^+) for an additional 15 minutes and concentrated after filtering off the sodium resin. The crude product was purified by flash chromatography (gradient of 3 % MeOH in CH_2Cl_2) to afford triol **145** in 70% yield (77 mg).

R_f 0.30 (1:8 MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, MeOD) δ 7.86 – 7.80 (m, 4H ArH), 7.59 – 7.56 (m, 2H, ArH), 7.49 – 7.27 (m, 14H, ArH), 5.58 (s, 1H, PhC*H*O_2), 4.79 (s, 2H, OC*H*$_2$Ph), 4.53 (dd, *J* = 7.6, 1.8 Hz, 2H, H-1, H-1'), 4.45 (dd, *J* = 10.5, 6.5 Hz, 1H, H-6a), 4.37 (m, 1H, H-6a'), 4.20 – 4.14 (m, 2H, H-4, H-4'), 4.07 (m, 2H, H-6b', H-6b), 3.90 (dd, *J* = 9.8, 7.5 Hz, 1H, H-2), 3.72 (dd, *J* = 9.9, 7.6 Hz, 1H, H- 2'), 3.60 (m, 1H, H-3'), 3.54 (t, *J* = 6.4 Hz, 1H, H-5), 3.47-3.43 (m, 2H, H-3, H-5'), 1.12 (s, 9H, 3x$CH_3{}^{TBDPS}$). **^{13}C NMR** (101 MHz, MeOD) δ 139.72, 139.29, 137.21 (2C), 137.12 (2C), 134.6, 134.2, 130.8, 130.7, 129.8, 129.4 (2C), 129.3 (2C), 129.0 (2C), 128.9, 128.6 (2C), 128.5 (2C), 127.7 (2C), (24 ArC), 106.4 (C-1'), 102.4 (Ph*C*HO_2), 99.7 (C-1), 83.1 (C-3), 77.8 (C-4), 77.4 (C-4'), 74.6 (O*C*H_2Ph), 74.3 (C-2), 73.8 (C-3'), 73.7 (C-5), 73.2 (C-2'), 70.3 (C-6'), 68.4 (C- 5'), 67.6 (C-6), 27.4 (3C *tert*-butyl), 20.2 (*tert*-butyl) ppm.

***tert*-butyldiphenylsilyl β-D-galactopyranosyl-(1→4)-6-*O*-sulfonate-β-D-galactopyranoside (146)**

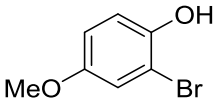


Triol **145** (60 mg, 0.07 mmol) was dissolved in distilled water (10 mL) and acetic acid (0.05 mL). 20% palladium hydroxide on carbon (90 mg) was added and the resulting mixture was placed under an atmosphere of hydrogen and stirred for 12 h at 22 °C. The mixture was then filtered through a celite pad and the filtrate was freeze dried to provide the compound **146** in 70% yield (32 mg). [97,100]

^{1}H NMR (400 MHz, MeOD) δ 7.78 (dd, *J* = 14.9, 6.5 Hz, 4H, ArH), 7.37 (d, *J* = 17.4 Hz, 6H, ArH), 4.55 – 4.29 (m, 3H, H-1, H-1', H-6a), 4.21 – 3.93 (m, 2H, H-6b, H-2), 3.92 –3.39 (m, 9H, H-6a', H-6b', H-3, H-4, H-5, H-2', H-3', H-4', H-5'), 1.04 (s, 9H, 3xCH_3^{TBDPS}) ppm.**^{13}C NMR** (101 MHz, MeOD) δ 137.2 (2C), 137.1 (2C), 134.6, 134.3, 130.8, 130.7, 128.6 (2C), 128.5 (2C) (12 ArC) , 107.0 (C-1'), 99.5 (C-1), 80.4 (C-2), 77.1 (C-4), 75.2 (C-3), 75.2 (C-2'), 75.1 (C-4'), 73.6 (2C, C-5 and C-3'), 70.9 (C-5'), 67.4 (C-6), 62.9 (C-6'), 27.4 (3C *tert*-butyl), 20.1 (*tert*-butyl) ppm.

6.3 Procedures for the substrates synthesis

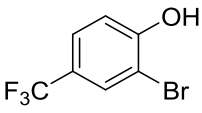
2-bromo-4-methoxyphenol (3i)[180]



Para-methoxyphenol (2.48 g ,20 mmol) was dissolved in 75 ml CH_2Cl_2 and cooled down to 0 °C. Bromine (1.13 ml, 22 mmol) was added dropwise and the reaction mixture was stirred at 22 °C for 12 hours. The reaction was then quenched with 30 ml of sat. aq. $Na_2S_2O_3$ and water (15 ml) and stirred 30 minute. The mixture was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (9:1 Hexane/ EtOAc) affording the product as a grey solid. Yield 3.20 g (79%).[180]

R_f 0.42 (1:7 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 2.9 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 1H), 6.80 (dd, *J* = 8.9, 2.9 Hz, 1H), 5.23 (s, 1H), 3.76 (s, 3H) ppm.

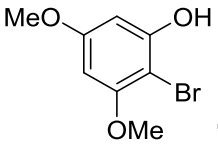
2-bromo-4-(trifluoromethyl)phenol (3j)[180]



To a solution of meta-trifluoromethylphenol (1.62 g, 10 mmol) in 10 ml CH_2Cl_2 was added bromine (0.54 ml, 10.5 mmol) dropwise at 0 ^{0}C. The mixture was warmed to 40 °C and stirred for 12 hours. The reaction was then quenched with 15 ml of sat. aq. $Na_2S_2O_3$ and water (15 ml) and an additional stirred 30 minutes. The mixture was extracted with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* and the crude product was purified by flash chromatography (4:1 Hexane/ EtOAc) to afford the product in quantitative yield. R_f0.25 (1:4 EtOAc/Hex). The crude product was used without any further purification

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.16 – 5.71 (bs, 1H) ppm.

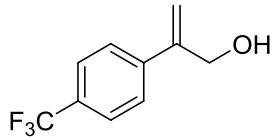
2-bromo-3,5-dimethoxyphenol (3k) [167]



To a solution of 3,5-dimethoxyphenol (1.54 g, 10 mmol) in 100 ml CH_2Cl_2 was added NBS (1.77g, 10 mmol) at -78 °C. The reaction was stirred at -78 °C for 5 hours, quenched with 10 % aqueous K_2CO_3 and warmed up to 22 °C. The mixture was then diluted with water and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ concentrated *in vacuo* and purified by flash chromatography (6:1 Hexane/ EtOAc) to afford the product in 60% yield. (1.34 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, *J* = 2.6 Hz, 1H), 6.10 (d, *J* = 2.6 Hz, 1H), 5.67 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H) ppm.

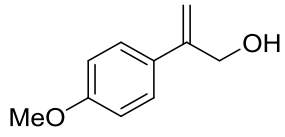
2-(4-(trifluoromethyl)phenyl)prop-2-en-1ol (5c)[168]



Magnesium turnings (912 mg, 37.5mmol ; flame dried and cooled under N_2 atmosphere) were immersed in 15 ml Et_2O. Two drops of dibromoethane were added followed by 1/20 of the 4-bromobenzotrifluoride (2.63 ml ; 18.75 mmol) solution in Et_2O (3.5 ml) until the reaction started. The reaction mixture was immersed in a water bath and the rest of the 4-bromobenzotrifluoride solution was added over 30 minutes via syringe pump at 22 °C. The reaction mixture was stirred for an additional hour at 22 °C. The Grignard solution was then added dropwise to a solution of propargyl alcohol (0.43 ml, 7.5 mmol) and CuI (143 mg, 0.75 mmol) in 15 ml Et_2O over 30 minutes at -5 °C. The reaction mixture was stirred under reflux for 15 hours before being cooled down to 0 °C and quenched with saturated aqueous NH_4Cl (12ml). The aqueous phase was further extracted with Et_2O (2 x 15 ml) and the combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford the desired product in 52% yield (789 mg) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 20.7, 8.4 Hz, 4H), 5.55 (s, 1H), 5.46 (s, 1H), 4.55 (s, 2H), 1.97 (bs, 1H) ppm.

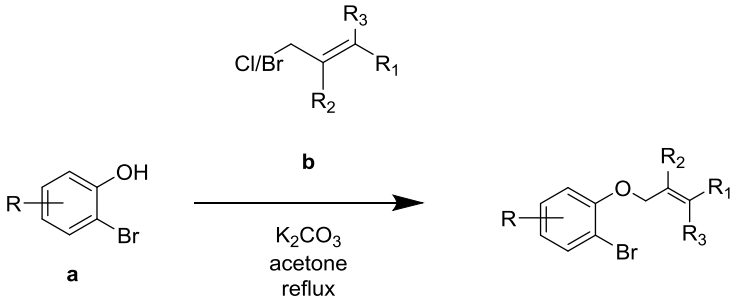
2-(4-(methoxyphenyl)prop-2-en-1-ol (5d)



Magnesium turnings (1.23 g, 50mmol ; flame dried and cooled under N_2 atmosphere) were immersed in 20 ml THF. Two drops of dibromoethane were added followed by 1/20 of the 4-bromoanisole (3.07 ml, 25.0 mmol) solution in THF (5 ml) until the reaction started. The reaction mixture was immersed in a water bath and the rest of the 4-bromoanisole solution was added over 30 minutes via syringe pump at 22 °C. The reaction mixture was stirred for an additional hour at 22 °C. The Grignard solution was then added dropwise to a solution of propargyl alcohol (0.57 ml, 10.0 mmol) and CuI (191 mg, 0.10 mmol) in 20 ml THF over 30 minutes at -5 °C. The reaction mixture was stirred under reflux for 15 hours before being cooled down to 0 °C and quenched with saturated aqueous NH_4Cl (15ml). The aqueous phase was further extracted with Et_2O (2 x 20 ml) and the combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by flash chromatography to afford the product in 62 % yield (1,02 g).

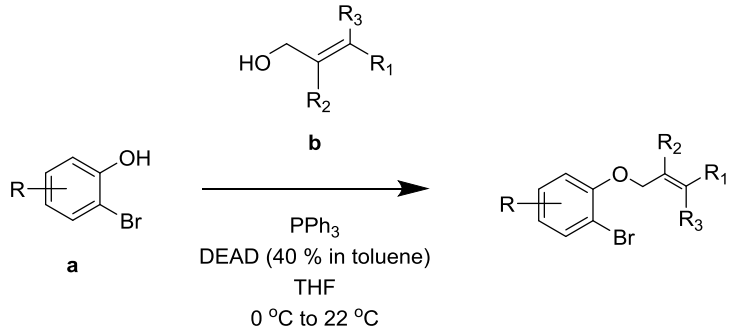
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.7 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 2H), 5.38 (s, 1H), 5.25 (s, 1H), 4.50 (s, 3H), 3.80 (s, 2H), 1.88 (bs, 1H) ppm.

General procedure for alkylation of substituted 2-bromophenol A



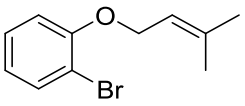
Bromophenol **a** (1.0 equiv.) was dissolved in acetone (0.2M) and potassium carbonate (2.5 equiv.) was added followed by allyl halide **b** (1.5 equiv.). The reaction mixture was stirred under reflux for 12 hours. Potassium carbonate was filtered off and the filtrate concentrated *in vacuo* and purified by flash chromatography.

General procedure for alkylation of substituted 2-bromophenol B



Bromophenol **a** (1.00 eq) and triphenylphosphine (1.2 equiv.) were dissolved in THF (0.3M). Allyl-alcohol **b** (1.1 equiv.) was added and the reaction mixture was cooled to 0 °C. Diethylazodicarboxylate (DEAD) (40 % in toluene, 1.7 equiv.) was added dropwise. The reaction mixture was stirred at 22 °C until TLC revealed full conversion. The reaction was quenched with 40 ml of water, extracted with washed with 2M NaOH, washed with brine and dried over $MgSO_4$. The crude was concentrated *in vacuo* and purified by flash chromatography (Hex/Et_2O)

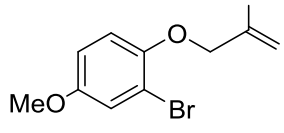
1-bromo-2-((3methylbut-2-en-1-yl)oxy)benzene (2b)



Compound **2b** was synthesized according to procedure **B**. to afford the product as transparent oil. Yield 1.19 g (98%).

R_f 0.72 (1:19 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 5.44 (t, *J* = 5.8 Hz, 1H), 4.53 (d, *J* = 6.5 Hz, 2H), 1.72 (s, 3H), 1.68 (s, 3H) ppm.

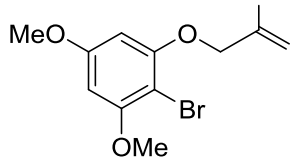
2-bromo-4-methoxy-1-((2-methylallyl)oxy)benzene (2i)



Compound **2i** was synthesized according to procedure **A**. The crude was purified by flash chromatography (20:1 Hexane/ EtOAc) to afford a slightly yellow liquid. Yield 740 mg (76%).

R*f* 0.65 (1:6 EtOAc/Hexane).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 5.2 Hz, 1H), 6.80 (dt, *J* = 9.0, 5.9 Hz, 2H), 5.14 (s, 1H), 5.00 (s, 1H), 4.43 (s, 2H), 3.75 (s, 3H), 1.85 (s, 3H).

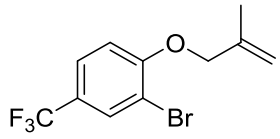
2-bromo-1,5-dimethoxy-3-((2-methylallyl)oxy)benzene (2k)



Compound **2k** was synthesized according to procedure **A**. The crude was purified by flash chromatography (30:1 Hexane/EtOAc) to afford **2k** in 70% yield (1.00 g).

R*f* 0.25 (1:30 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.16 (s, 2H), 5.17 (s, 1H), 5.01 (s, 1H), 4.47 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 1.85 (s, 3H).

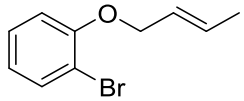
2-bromo-1-((2-methylallyloxy)-4-(trifluoromethyl)benzene (2j)



Compound **2j** was synthesized according to procedure **A**. The crude was purified by flash chromatography (40:1 Hexane/EtOAc) to afford **2j** in 65% yield (850 mg).

R*f* 0.50 (1:20 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.0 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 6.96 (dd, *J* = 19.4, 8.9 Hz, 1H), 5.17 (s, 1H), 5.06 (s, 1H), 4.56 (s, 2H), 1.87 (s, 3H) ppm. **^{19}F NMR**(50 MHz, $CDCl_3$) δ -60.59 (s) ppm.

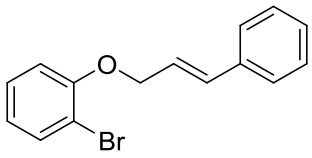
(*E*)-1-bromo-2(but-2en-1-yloxy)benzene (2e)



Compound **2e** was synthesized according to procedure **A** using crotyl chloride. The crude was purified by flash chromatography (40:1 Hexane/EtOAc) to afford **2e** in 70% yield (1.58 g).

R*f* 0.65 (1:20 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.24 (dd, *J* = 11.8, 4.4 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.01 – 5.67 (m, 2H), 4.54 (d, *J* = 5.7 Hz, 2H), 1.77 (dd, *J* = 9.0, 3.3 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0, 133.3, 128.8, 128.3, 125.5, 121.8, 113.6, 112.2, 69.7, 17.9 ppm.

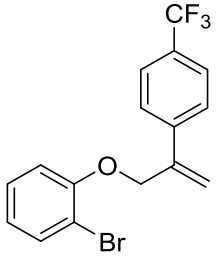
1-bromo-2(cinnamyloxy)benzene (2f)



Compound **2f** was synthesized according to procedure **A** using cynnamyl bromide as reagent. The crude was purified by flash chromatography (40:1 Hexane/EtOAc) to afford **2f** in 75% yield (2.16 g).

R_f 0.65 (1:20 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.42 – 7.33 (t, 2H), 7.33 – 7.24 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 16.0 Hz, 1H), 6.46 (dt, *J* = 16.0, 5.5 Hz, 1H), 4.80 (d, *J* = 5.5 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0, 136.4, 133.5, 133.0, 128.6, 128.5 (2C), 127.9, 126.6 (2C), 123.9, 122.1, 113.8, 112.4, 69.7 ppm.

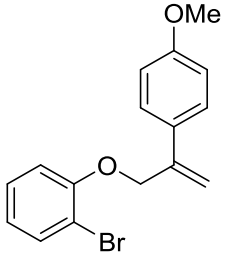
1-bromo-2-((2-(4-/trifluoromethyl)phenyl)allyl)oxy)benzene (2c)



Compound **2c** was synthesized according to procedure **B** using previously synthesized **5c** as alkylating reagent. The crude was purified by flash chromatography (40:1 Hexane/EtOAc) to afford **2c** in 50% yield (650 mg).

R_f 0.65 (1:20 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (s, 3H), 7.57 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.38 – 7.24 (m, 2H), 6.96 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.88 (td, *J* = 7.7, 1.4 Hz, 1H), 5.71 (d, *J* = 6.7 Hz, 2H), 4.96 (s, 2H) ppm.

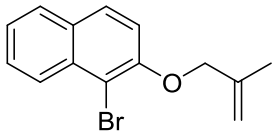
1-bromo-2-((2-(4-methoxyphenyl)allyl)oxy)benzene (2d)



Compound **2d** was synthesized according to procedure **B** using previously synthesized **5d** as alkylating reagent. The crude was purified by flash chromatography (40:1 Hexane/EtOAc) to afford **2d** in 95% yield (1.70 g)).

R_f 0.56 (1:20 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 –7.42 (m, 1H), 7.31 – 7.22 (m, 1H), 6.97 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.87 (td, *J* = 7.7, 1.2 Hz, 1H), 5.56 (s, 1H), 5.51 (d, *J* = 10.4 Hz, 1H), 5.31 (s, 1H), 4.94 (s, 2H), 3.84 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 154.9, 141.6, 133.4, 130.7, 128.3, 127.2 (2C), 122.1, 113.8 (2C), 113.7, 113.1, 112.4, 70.6, 55.3 ppm.

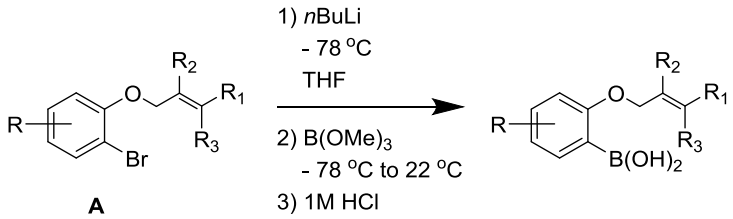
1-bromo-2-((2-methylallyl)oxy)naphthalene (2l)



Compound **2l** was synthesized according to procedure **A** starting from 1-bromo-2-naphtol. The crude was purified by flash chromatography (40:1 Hexane/EtOAc) to afford **2l** in 63% yield (1.73 g).

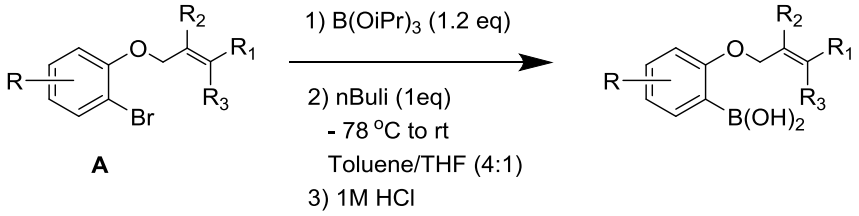
R_f 0.65 (1:20 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.9 Hz, 1H), 8.01 – 7.67 (d, 2H), 7.61 – 7.55 (m, 1H), 7.44 – 7.38 (m, 1H), 7.30 – 7.22 (m, 1H), 5.22 (d, *J* = 5.7 Hz, 1H), 5.05 (d, *J* = 5.9 Hz, 1H), 4.66 (d, *J* = 4.1 Hz, 2H), 1.91 (d, *J* = 5.8 Hz, 3H) ppm.

General procedure for synthesis of aryl boronic acid 1



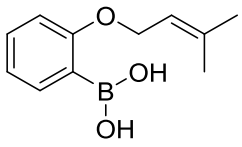
1 equiv. of **A** was dissolved in THF (0.2 M) under N_2 atmosphere and cooled down to -78 °C. *n*BuLi (1.1 equiv.; 2.5 M in hexane) was added dropwise over 10 minutes and the reaction mixture was stirred 30 min at -78 °C. 1.2 equiv. of trimethylborate was added in one portion and the reaction mixture was warmed to 22 °C and stirred an additional hour before being quenched with 1M aqueous HCl. The mixture was then stirred 15 minutes more and extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The crude was concentrated *in vacuo* and purified by flash chromatography. The purified product was washed several times with hexane and filtered off.

General procedure for synthesis of aryl boronic acid 2(*in situ* quench method)[166]



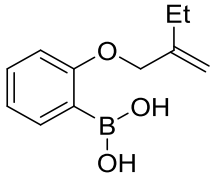
1 equiv. of **A** and 1.2 equiv. of triisopropylborate were dissolved in a mixture of 0.2 M Toluene/THF (4:1). The solution was cooled down to -78 °C and 1 equiv. of *n*BuLi was added via syringe pump over 30 min. The reaction mixture was stirred 30 minutes at -78 °C and 1 hour at 22 °C. The reaction was quenched with 1 M aqueous HCl. The mixture was then stirred 15 minutes more and extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The crude was concentrated *in vacuo* and purified by flash chromatography. The purified product was washed several times with hexane and filtered off.

(2-3-methylbut-2-en-1-yl)oxy)phenyl)boronic acid (1a)



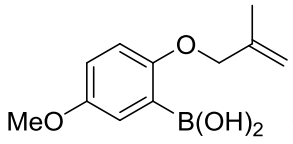
1a was synthesized according to the procedure **1** and starting from 5.0 mmol of 1- bromo-2-((3-mtehylbut-2-en-2-yl)oxy)benzene **2a** The crude was purified by flash chromatography (7:1 to 4:1 Hexane/ EtOAc) to afford a white solid. Yield 240 mg (35%).
R_f 0.54 (1:4 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.54 – 6.38 (m, 2H), 5.52 (ddd, *J* = 6.8, 5.6, 1.3 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 2H), 1.83 (s, 3H), 1.77 (s, 3H) ppm.

(2-(2-methylenebutoxy)phenyl)boronic acid (1b)



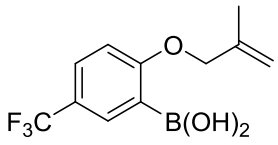
1b was synthesized according to the procedure **1**. The crude was purified by flash chromatography (9:1 to 5:1 Hexane/ EtOAc) R_f 0.26 (1:7 EtOAc/Hex). Yield 240 mg (40%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.20 – 8.14 (m, 1H), 7.79 (t, *J* = 7.1 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 1H), 5.83 (s, 1H), 5.34 (s, 2H), 2.94 (q, *J* = 7.7 Hz, 2H), 1.88 (td, *J* = 7.4, 2.8 Hz, 3H) ppm.

(5-methoxy-2-((2-methylallyl)oxy)phenyl)boronic acid (1i)



Boronic acid **1i** was synthesized according to the *in situ* quench procedure **2** and starting with 2.5 mmol of the corresponding aryl bromide. The crude was purified by flash chromatography (6:1 to 2:1 Petroleum ether/ EtOAc) to afford the product in 32% yield (160 mg).
R_f 0.26 (1:5 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 33.5, 3.2 Hz, 1H), 6.96 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.57 (s, 2H), 5.10 (s, 1H), 5.05 (s, 1H), 4.51 (s, 2H), 3.81 (s, 3H), 1.85 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9, 153.8, 140.1, 120.4, 118.7 (2C), 114.0, 112.6, 72.8, 55.7, 19.6 ppm.

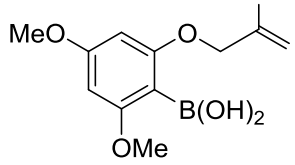
(5-trifluoro-2-((2-methylallyl)oxy)phenyl)boronic acid (1j)



Boronic acid **1j** was synthesized according to the *in situ* quench procedure **2.** The crude was purified by flash chromatography (6:1 to 2:1 Petroleum ether/EtOAc) to afford the product in 35% yield (250 mg).

R_f 0.26 (1:5 EtOAc/Hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 1.6 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.10 (s, 2H), 5.11 (d, *J* = 5.4 Hz, 2H), 4.61 (s, 2H), 1.87 (s, 3H), 1.69 (d, *J* = 17.6 Hz, 2H) ppm. **^{19}F NMR** (50 MHz, $CDCl_3$) δ -60.94 ppm.

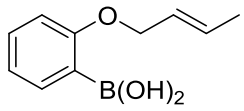
(2,4-dimethoxy-6-((2-methylallyl)oxy)phenyl)boronic acid (1k)



Boronic acid **1k** was synthesized according to the *in situ* quench procedure **2** The crude was purified by flash chromatography (Petroleum ether/EtOAc 6:1 to 2:1) to afford the product in 40% yield (353 mg)

R_f0.23 (1:5 EtOAc/Hex). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 (s, 2H), 6.13 (d, *J* = 23.1 Hz, 2H), 5.04 (d, *J* = 23.4 Hz, 2H), 4.52 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 1.84 (s, 3H) ppm.

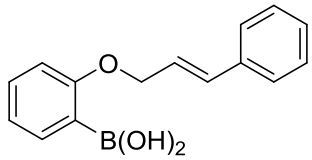
(E)-(2-(but-2-en-1-yloxy)phenyl)boronic acid (1e)



1e was synthesized according to the procedure **1**. The crude was purified by flash chromatography (Hex/ EtOAc 9:1 to 5:1) to afford the product in 45% yield (601 mg)

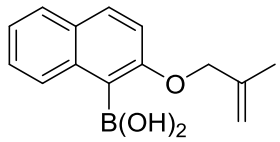
R_f 0.26 (1:7 EtOAc/Hexane). **^{1}H NMR** (400 MHz, CDCl3) δ 7.87 (d, J = 7.2 Hz, 1H), 7.44 (dd, J = 13.9, 6.8 Hz, 1H), 7.10 – 6.97 (m, 1H), 6.97 – 6.86 (m, 1H), 6.41 (s, 2H), 6.02 – 5.67 (m, 2H), 4.56 (d, J = 6.1 Hz, 2H), 1.78 (t, J = 7.4 Hz, 3H) ppm.

(2-(cinnamyloxy)phenyl)boronic acid (1f)



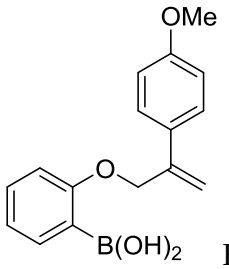
Boronic acid **1f** was synthesized according to the *in situ* quench procedure **2** The crude was purified by flash chromatography (Hexane/EtOAc) to afford the product in 50% yield (930 mg).

(2-((2-methylallyl)oxy)naphthalen-1-yl)boronic acid (1l)



Boronic acid **1l** was synthesized according to the *in situ* quench procedure **2** and starting with the corresponding aryl bromide. The crude was purified by flash chromatography (6:1 to 2:1 Hexane/ Petroleum ether) to afford yield 35% (212 mg)

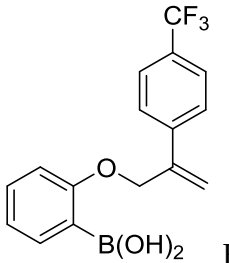
(2-((2-(4-methoxyphenyl)allyl)oxy)phenyl)boronic acid (1d)



Boronic acid **1d** was synthesized according to the *in situ* quench procedure. The crude was purified by flash chromatography (6:1 to 2:1 Hexane/ Petroleum ether) to afford the product in 40% yield (284 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.71 (m, 1H), 7.57 – 7.32 (m, 3H), 7.04 (dd, *J* = 15.5, 8.2 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.71 (s, 2H), 5.55 (s, 1H), 5.36 (s, 1H), 4.98 (s, 2H), 3.83 (s, 3H) ppm.

(2-((2-(4-(trifluoromethyl)phenyl)allyl)oxy)phenyl)boronic acid (1c)



Boronic acid **1c** was synthesized according to the *in situ* quench procedure. The crude was purified by flash chromatography (6:1 to 2:1 Hexane/ Petroleum ether) to afford the product in 50% yield (350 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 1.8 Hz, 1H), 7.67 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.23 (s, 2H), 5.11 (d, *J* = 4.9 Hz, 2H), 4.62 (s, 2H), 1.87 (s, 3H) ppm

CHAPTER 7

7 References

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