University of Alberta

Towards the synthesis of glucose-containing fluorous oligosaccharides

by

Santu Mandal

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

Spring 2014
Edmonton, Alberta

Abstract

Fluorous phase chemistry is an emerging field in terms of new separation techniques. A highly fluorinated compound tends to dissolve in a fluorinated solvent rather than in a common organic solvent. Fluorophilic solid phase separation (F-SPE) techniques are also well established. Our goal is to explore the fluorous binding ability of highly fluorinated cyclic and acyclic glucopyranoside oligosaccharides against fluorinated lipids. For this purpose we have selected two families of targets: fluorinated cyclodextrins, α-(1→4)-linked cyclic glucose-containing oligosaccharides, and their open chain counterparts. Fluorinated cyclodextrins have previously been synthesized and shown to bind to *p*-trifluoromethyl phenol and inspiration for the latter class of compounds comes from bacteria. Some mycobacteria produce α-(1→4)-linked 6-*O*-methylated glucopyranose residues. These species form 1:1 complexes with long-chain fatty acids and acyl-coenzyme A derivatives *in vitro.* We envisioned that fluorinated derivatives of these molecules might bind to fluorinated lipids.

We developed synthetic routes to prepare fluorinated oligosaccharides with variable number of glucopyranose residues. Our synthetic approach was focused on using cyclodextrins as the starting materials. These compounds were synthesized through a route that does not require protecting group chemistry. These cyclic molecules will serve as the precursors to the acyclic molecules through the use of a reported cyclodextrin cleavage method. In addition, we explore the preparation of derivatives from a bottom-up approach via the synthesis of mono- and disaccharide derivatives containing fluorinated moieties.

Acknowledgement

The thesis would not have completed without the constant help and support of my supervisor, Dr. Todd L. Lowary. I would like to express my sincere gratitude and thanks to him. I can not express my heartfelt appreciation through words for his invaluable support in past three and half years during my graduate study. He is the most helpful and amazingly wonderful person I have met so far.

I would also like to thank the past and present Lowary group members whom I have worked with. I would like to give special thanks to Dr. Maju Joe for helping me out while troubleshooting any reaction condition or purification. My appreciation also goes to Dr. Kamar Sahloul for proof reading my thesis, Dr. Joern Saupe and Dr. Huu-Anh Tran for troubleshooting.

I am indebted to Alberta Glycomics Centre and Department of Chemistry for providing resources, analytical and instrumentation facilities during my research.

Finally, I would like to thank Neha Khanna for her trust in me and for always being by my side. I really appreciate the continued encouragements she gave me in past few years, which means a lot. Last but not least, my special thanks to my parents for relying on my decisions and their support.

Table of Contents

List of Schemes

List of Figures

List of Abbreviations

[α]	specific rotation
Ac	acetyl
AgOTf	silver trifluoromethane sulfonate
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
^{F}Boc	fluorous-tagged *tert*-butoxycarbonyl
Bu_2BOTf	dibutylboron trifluoromethane sulfonate
Bz	benzoyl
CD	cyclodextrin
CSA	camphorsulfonic acid
COSY	correlation spectroscopy
DBU	1,8-diazabicycloundec-7-ene
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMF	*N,N'*-dimethylformamide
DPPA	diphenylphosphoryl azide
Et	ethyl
ES-MS	electrospray ionization mass spectrometry

FBC	fluorous biphasic catalysis
FDA	food and drug administration (US)
F-SPE	fluorous solid phase extraction
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HMBC	heteronuclear multiple-bond correlation
HSQC	heteronuclear single quantum coherence
Me	methyl
MGLP/MGP	methyl glucose lipopolysaccharide
MMP	methyl mannose polysaccharide
MsCl	methanesulfonyl chloride
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
pK_a	ionization constant
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
Py	pyridine
R_f	retention factor
SCX-2	strong cation exchanger (version-2)
SPE	solid phase separation

TBAF	tetrabutylammonium fluoride
TBS/TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMAD	tetramethylazodicarboxamide
TLC	thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid
Tr	trityl

Chapter 1: Introduction

1.1 Introduction

The efficiency of a chemical reaction is determined by degree of conversion and ease of separation of the desired product.[1,2] In many cases, although the degree of conversion is good, a loss of product occurs due to poor purification methods, which results in bad yield of the desired product. Often chemists are challenged by a product's physical properties, such as similarity in polarity with starting material and inability to recrystallize, which makes the separation difficult. The usual separation or purification techniques such as liquid–liquid or solid–liquid phase separations, normal and reverse phase chromatography or ion exchange chromatography yield good results in most cases. However, to improve the cost-effectiveness and efficiency of purifications, there is a need to tune current methods to make them more effective and easier.

Fluorinated compounds play an important role in drug discovery. This is because of the unusual properties of the highly electronegative fluorine atom and the hydrophobic nature of fluorocarbon moiety. In fact, one of the top selling drugs in past several years is Lipitor® (**Figure 1-1**) by Pfizer/Astellas, which is a fluorinated molecule.[3]

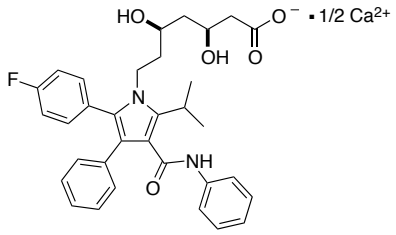


Figure 1-1. Structure of Lipitor®

In addition, about 25% of all marketed drugs contain fluorine and therefore fluorine-containing molecules are very important in the pharmaceutical industry. It is not exaggerating to state that almost all drug development programs aim at exploring fluorine-containing candidate molecules.[4] A couple of more examples of fluorinated drugs are shown in **Figure 1-2**.

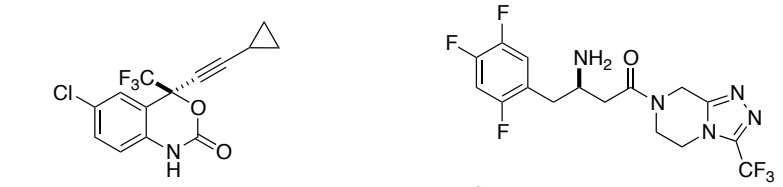


Figure 1-2. Examples of FDA approved fluorine-containing drugs

Sometimes usual silica gel chromatographic separations based on polarity of components of a reaction mixture are not easy. This happens due to similarity in the polarity of the molecuels and the way they interact with the solid support, leading to similar R_f values. To obtain a pure product one might have to do several separations and often the yield is not good. Here lies the necessity for developing quicker separation techniques to make separations, including those used in drug discovery, more feasible. Many groups have worked on so-called 'fluorous' chemistry as a means to improve the separation or purification methods of fluorine-containing compounds.

1.2 Fluorous phase chemistry

1.2.1 What is fluorous chemistry?

Fluorinated, in particular highly fluorinated, molecules have the property of associating with each other in a fluorophobic environment such as water, due to fluorophobic interactions.[5] On the other hand, the affinity of fluorous materials for other fluorinated molecules is termed fluorophilicity. These interactions can be used as a the basis of a purification method often referred to as 'fluorous' chemistry.[1] More specifically, fluorinated compounds tend to dissolve in fluorinated solvents such as perfluorinated hexane and these solvents are usually immiscible with hydrocarbon solvents and water at room temperature or lower temperatures.

This phenomenon provides an approach for separating fluorinated compounds from other organic molecules, which dissolve preferably in hydrocarbon solvents (see **Figure 1-3**). However, on an industrial scale, this technique becomes prohibitive due to the environmental aspects of fluorous solvents as they are toxic and not-biodegradable. Even if burnt like other hydrocarbons, these solvents produce fluorocarbons that may contribute to depletion of the ozone layer. Another drawback for this extraction method is that it only works with compounds with 60% or more fluorine content, which is usually not a desirable situation in most organic reactions.[1] Hence, there has been an interest in developing new fluorous purification approaches.

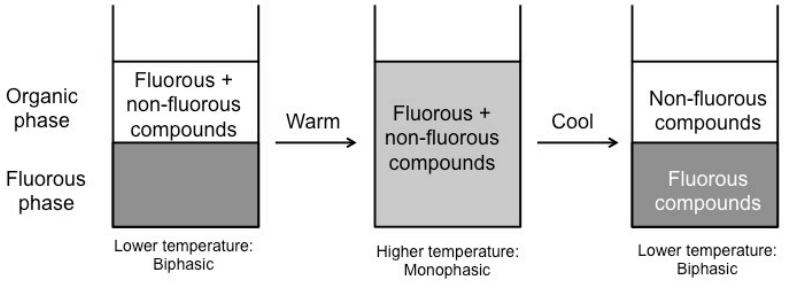


Figure 1-3. Schematic showing fluorous phase extraction process

1.2.2 Fluorous solid-phase extraction (F-SPE)

In 1997, Curran and coworkers[6] developed fluorocarbon-containing ($Si(CH_2)_2C_8F_{17}$) silica gel, which was introduced to the consumer market as Fluoro*Flash*® fluorous solid-phase extraction (F-SPE) cartridges by Fluorous Technologies, Inc.[7]

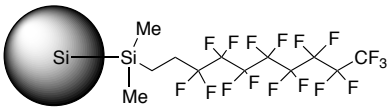


Figure 1-4. Schematic of fluorous silica gel

This solid–liquid extraction technique gained popularity because it is quick, easy and reusable. Another attractive feature is that there is no need for fluorinated solvents to perform a separation using F-SPE. The fluorinated compound binds strongly to the adsorbent when a complex reaction mixture is added to the F-SPE silica gel. Passing a solution containing 5–20% H_2O in either CH_3OH or DMF through the cartridge, results in elution of organic materials with no fluorine

content.[8] This happens because fluorous materials repel water, which is an inherent property of fluorocarbons. Later, passing organic solvent such as THF or CH_3OH through the F-SPE cartridge, lead to elution of the fluorinated compounds. The cartridges can be regenerated after washing with THF and acetone.

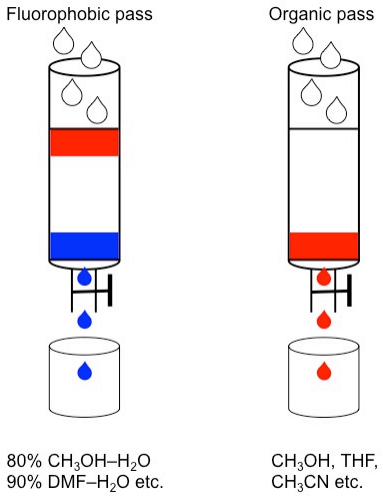
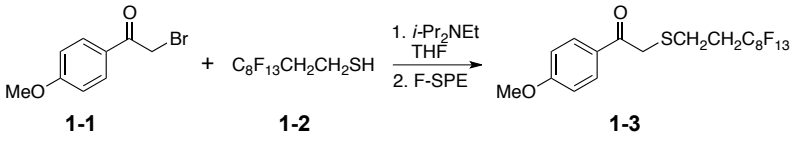


Figure 1-5. Schematic of the F-SPE technique. Red indicates the fluorous fraction and blue indicates the organic fraction

In the reaction below (**Scheme 1-1**), the displacement of the bromide in **1-1** was carried out using the fluorous-tagged thiol **1-2**. The thioether product **1-3** was then easily separated employing the F-SPE separation technique.[19]



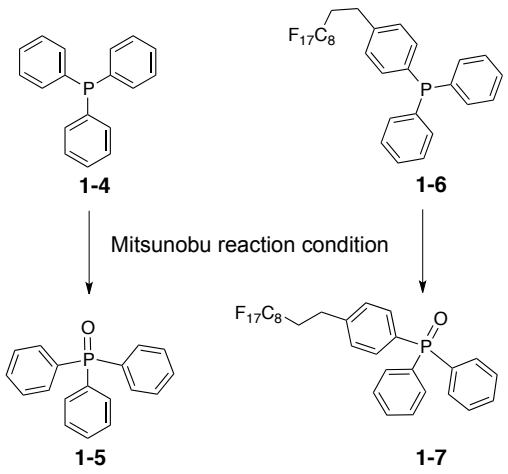
1-1 **1-2** **1-3**

Scheme 1-1. Use of the F-SPE technique to separate a fluorous product[19]

1.2.3 Use of fluorous reagents to ease the separation of hard to remove by-products

In the field of reaction discovery or method development, fluorous tags have been studied and used extensively.[1] Fluorous tags are placed in reagents or reactants such that they do not affect the reactivity of the molecule. This is done by strategically choosing a spacer group that keeps the tag away from the reaction centre so that the high electronegativity of fluorine does not affect reactivity. After the reaction, the tagged materials can be easily removed or separated from the reaction mixture by means of fluorous phase separation or F-SPE.

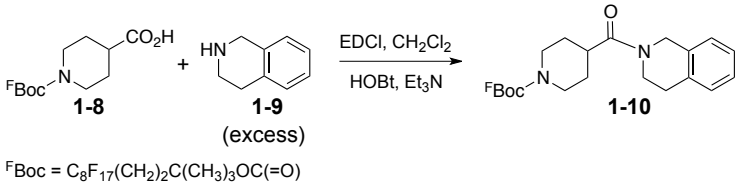
For example, a Mitsunobu reaction is a common reaction performed by organic chemists and a phosphine oxide is a by-product in this reaction. Traditionally, phosphine oxides such as **1-5** are difficult to remove from a reaction mixture. However, using fluorous phosphine reagents such as **1-6**, which produce a fluorous phosphine oxide (e.g., **1-7**), can solve this problem.[1,12] Here, the spacer group used is a phenyl ring. This fluorous by-product can be easily removed either by simple liquid–liquid extraction with a fluorous solvent or by removing it by F-SPE.[12]



Scheme 1-2. Example of a fluorous phosphine that can be removed easily using fluorous phase extraction[12]

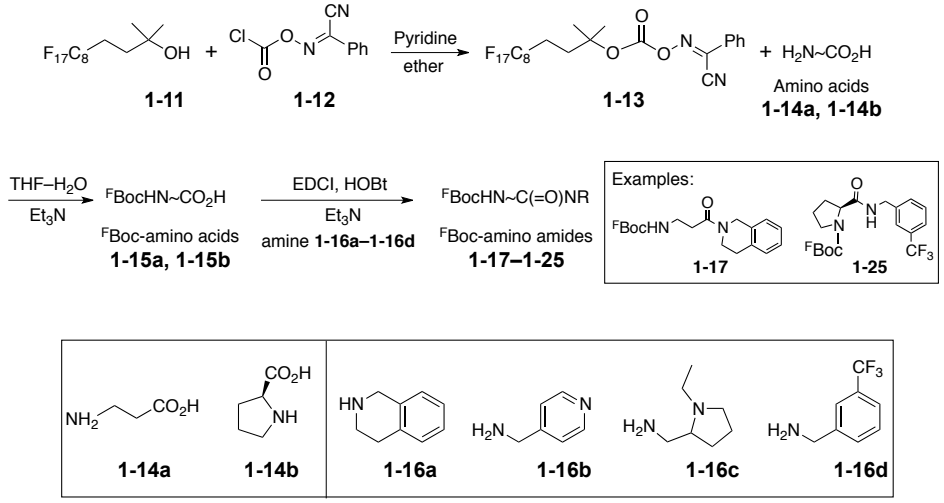
1.2.4 Use of fluorous-tagged reagents in efficient multi-step syntheses

In multistep syntheses, substrates tagged with fluorous protecting groups can reduce the time for efficient separation of products and improve the overall yield.[9] This advantage of F-SPE has already been successfully used in many simple or complex reactions. **Scheme 1-3** shows an example of an amide forming reaction[10] between a secondary amine **1-9** and fluorous-tagged carboxylic acid **1-8**. In this reaction, the product formed was isolated with ease by F-SPE. The excess reagents and by-products were removed by elution with a fluorophobic mobile phase (20% H_2O in CH_3OH) and the fluorous-tagged product, **1-10**, was collected in upon elution with a fluorophilic mobile phase (CH_3OH).



Scheme 1-3. Use of a fluorous-tagged Boc protecting group in amide coupling[10]

Also, in particular, parallel syntheses for the preparation of compound libraries have become more convenient with the use of fluorous-tagged reagents.[10] **Scheme 1-4** shows an example of adapting a fluorous-tagged reagent by Luo and coworkers. The fluorous-tag transfer reagent or "^{F}Boc" reagent **1-13** was prepared from fluorous-tagged alcohol **1-11** and **1-12**. The ^{F}Boc transfer reagent was used to tag amino acids to afford ^{F}Boc-amino acids (**1-15a** and **1-15b**). These ^{F}Boc-amino acids were coupled to various amines (**1-16a–1-16d**) to yield desired amides, **1-17–1-25**. Being fluorous-tagged these amides were separated quickly using the F-SPE technique.



Scheme 1-4. Efficient parallel synthesis using a fluorous-tagged Boc (^{F}Boc) protecting group[10]

1.2.5 Fluorous biphasic catalysis (FBC) for the facile recovery of fluorous-tagged catalysts

The term fluorous biphasic catalysis (FBC) gained the attention of the scientific community after Horváth and coworkers published their work[11] on fluorous biphasic reactions in 1994. The principle behind FBC is the use of two apparently immiscible liquid phases that form a single liquid phase when slightly heated. In the case of FBC, the two liquid phases are an organic phase containing reactants and a fluorous phase containing the fluorous-tagged catalyst. The key feature is that when warmed these form a single homogenous phase allowing the catalyst to catalyze the reaction. When the reaction is complete, the reaction mixture is cooled and again forms two liquid phases. This permits the easy separation of the catalyst, which can be reused without further purification. The product then can be extracted from the organic phase.

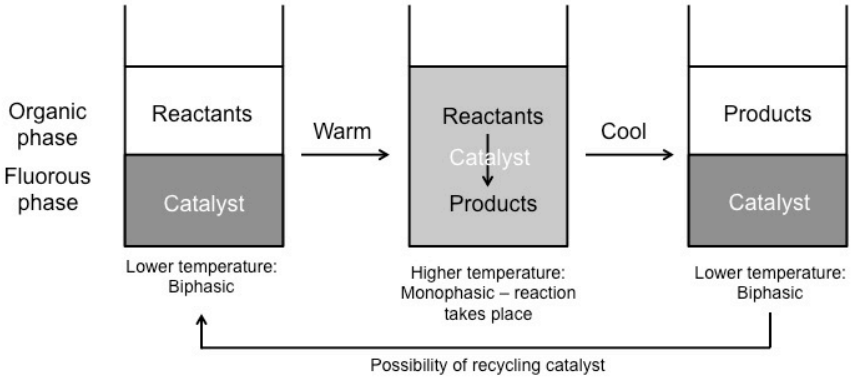
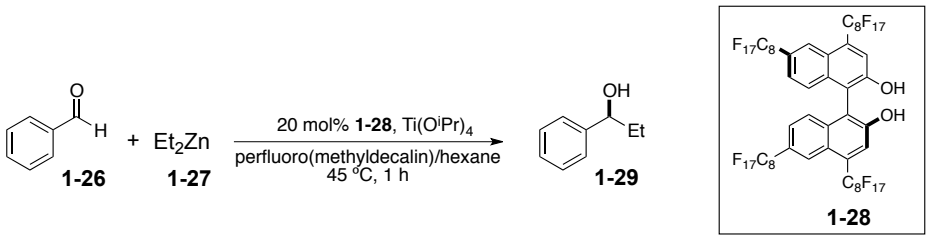


Figure 1-6. Schematic of the FBC technique

One of the numerous examples of this strategy is an asymmetric C–C bond forming reaction published by Tian and coworkers (**Scheme 1-5**).[13] Use of the fluorous chiral BINOL catalyst **1-28** was key in this instance.



1-26 **1-27** **1-29** **1-28**

Scheme 1-5. Example of FBC[13]

1.3 Thesis goals: Our approach towards developing novel carbohydrate-based fluorous materials

1.3.1 Inspiration by mycobacteria

Some mycobacteria, including *M. smegmatis, M. phlei and M. tuberculosis*, produce unique carbohydrates with both structural oddities and little known physiological functions.[14] One class of these unusual carbohydrates is polymethylated polysaccharides (PMPs). Two families of PMPs have been reported[15] – 3-*O*-methyl-mannose polysaccharides (MMPs) and 6-*O*-methyl-glucose lipopolysaccharides (MGLPs). PMPs form stable 1:1 complexes with long-chain fatty acids *in vitro*.[15] These moieties have been proposed to be involved in lipid biosynthesis of these organisms[15], however a definitive biological role has not been clearly established.

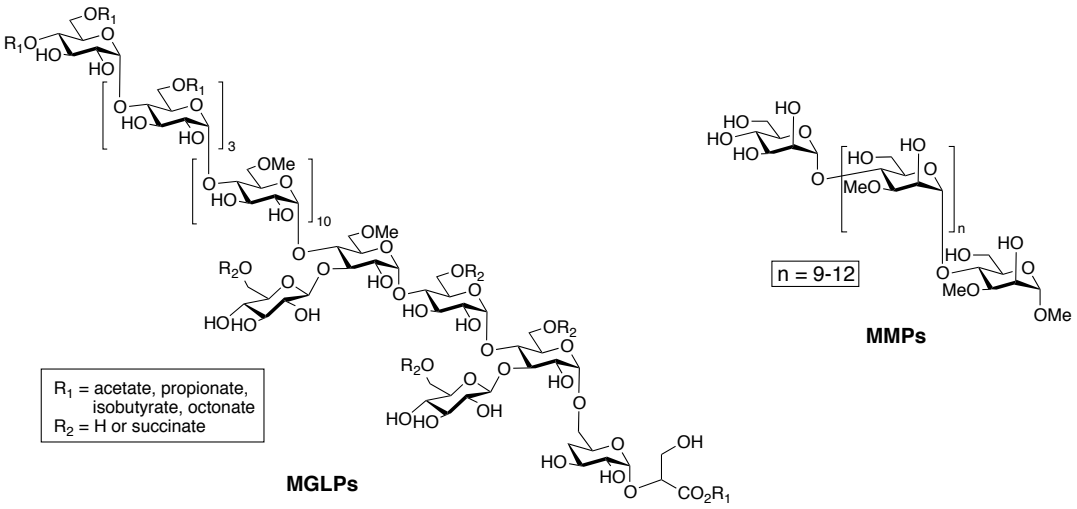


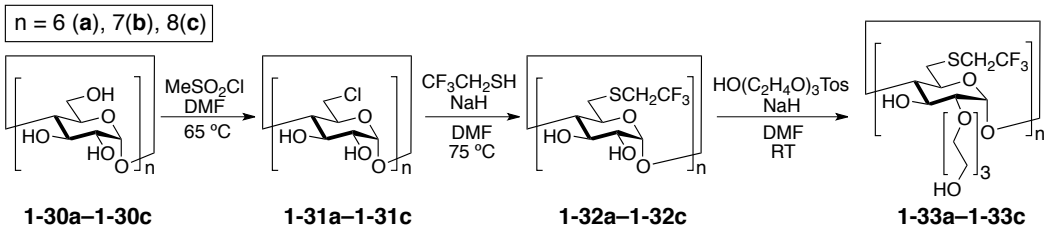
Figure 1-7. 6-*O*-Methyl-glucose lipopolysaccharides (MGLPs) and 3-*O*-methyl-mannose polysaccharides (MMPs)[16]

In my thesis, I explored the preparation of fluorous version of MGLPs, which we anticipated would bind to fluorinated molecules. These fluorous oligosaccharides could be new potential anchors for the generation of solid-phase adsorbents that could be used in F-SPE techniques.

1.3.2 Previous works by others

Cyclodextrins, *α*-(1→4) linked cyclic glucopyranosides, are amongst the most used molecules in host–guest interaction studies.[20] Due to their special structure, these molecules have hydrophobic interior and hydrophilic exterior. Because of this particular property cyclodextrins and its derivatives has use in lipophilic drug delivery.[18,20]

To date, there have been some investigations on the preparation of fluorinated cyclodextrins, but the number of reports is small. There are reports of synthesizing MGLPs by Meppen M. *et al*[17] and fluorinated cyclodextrins by Becker M. M. *et al*.[18] The study, carried out by Becker and coworkers[18] reported the synthesis of fluorinated cyclodextrins and studied their ability to bind to fluorine-containing molecules. The reported compounds were water-soluble and these produced host–guest complexes with *p*-trifluoromethylphenol stabilized by the fluorophobic effect.

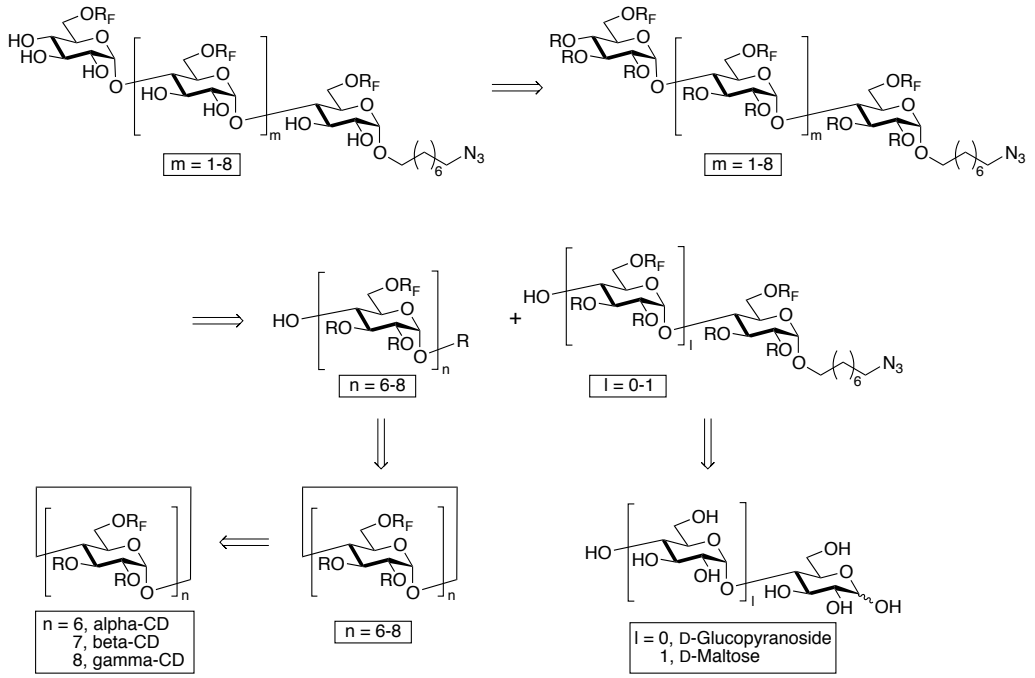


Scheme 1-6. Synthesis of fluorinated cyclodextrins by Becker and coworkers[18]

1.3.3 Our strategy to develop fluorous oligosaccharides

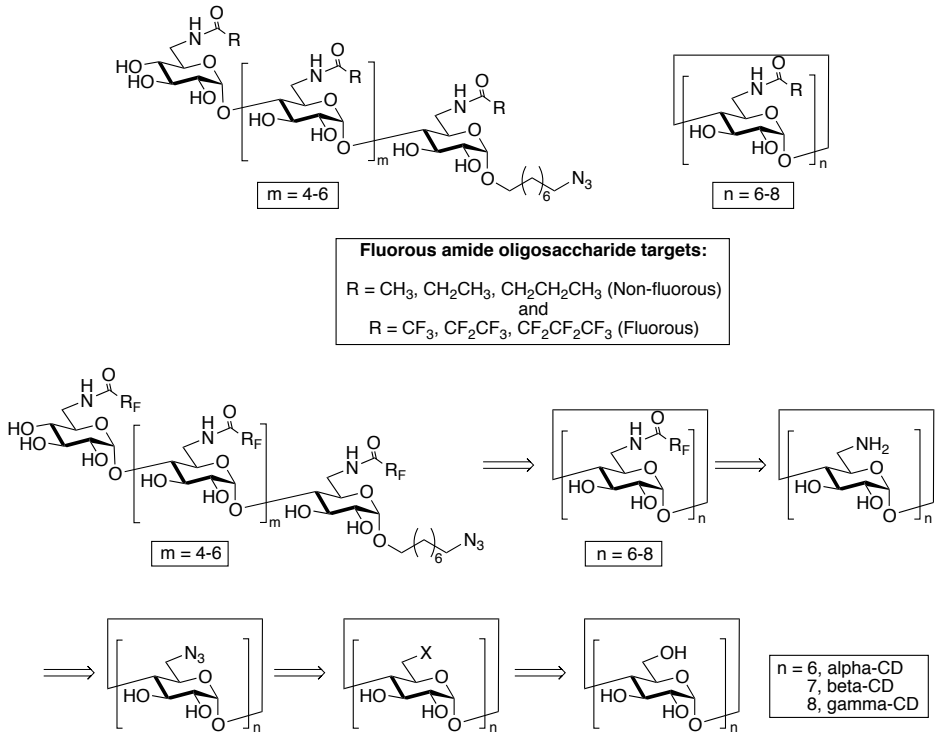
Inspired by the MGPLs, we aimed at preparing synthetic derivatives containing fluorinated groups. Once in hand, our goal was to test the binding abilities of these derivatives towards compounds such as fluorous lipids and fluorinated small molecules. We choose MGPLs because of affordable and easily available starting materials such as cyclodextrins, maltose and glucose were available for their preparation. The first two are already *α*-(1→4) linked glucopyranosides and are naturally abundant. The glucose unit can be used to increase the chain length.

Our target molecules included both cyclic and acyclic versions of fluorous-containing α-(1→4)-lined glucopyranosides. The smaller building blocks can be coupled together to give larger α-(1→4) linked oligosaccharides. On the other hand, cyclodextrins can be directly modified to afford cyclic versions of the targets as well as these can be cleaved to furnish acyclic α-(1→4) linked oligosaccharides. During the thesis related research work, we have explored two different kinds of target molecules. First we investigated the preparation of fluorous ether containing oligosaccharides (**Scheme 1-7**).



Scheme 1-7. Retrosynthetic plan for the synthesis of fluorous ether containing oligosaccharides

Next, we aimed at a different set of target molecules containing fluorous amide groups. **Scheme 1-8** shows how the synthesis of target molecules was planned.



Scheme 1-8. Retrosynthesis of fluorous and non-fluorous amide oligosaccharide targets

In the next chapters we will discuss the challenges faced during synthesis of these fluorinated oligosaccharides and how we overcame them.

1.4 Bibliography

(1) Dobbs A. P.; Kimberley M. R. *J. Fluor. Chem.* **2002**, *118*, 3.

(2) Fustero S.; Sancho A. M.; Aceña J. L.; Sanz-Cervera J. F. *J. Org. Chem.* **2009**, *74*, 6398.

(3) *MedAdNews 200 – World's Best-Selling Medicines, MedAdNews,* **July 2007**.

(4) Ojima I. *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell (Chichester, UK) **2009**, 4.

(5) Krafft M. P.; Riess J. G. *Chem. Rev.* **2009**, *109*, 1714.

(6) Curran D. P.; Hadida S.; He M. *J. Org. Chem.* **1997**, *62*, 6714.

(7) Fluorous Technology, Inc. (www.fluorous.com)

(8) Zhang W.; Curran D. P. *Tetrahedron* **2006**, *62*, 11837.

(9) Curran D. P. *AldrichimicaACTA* **2006**, *39*, 3.

(10) Lou Z.; Williams J.; Read R. W.; Curran D. P. *J. Org. Chem.* **2001**, *66*, 4261.

(11) Horváth I. T.; Ráábai J. *Science* **1994**, *266*, 72.

(12) Dandapani S.; Curran D. P. *J. Org. Chem.* **2004**, *69*, 8751.

(13) Tian Y.; Chan K. S. *Tet. Lett.* **2000**, *41*, 8813.

(14) Lee Y. C.; Ballou C. E. *J. Biol. Chem.* **1964**, *239*, 3602.

(15) Jackson M.; Brennan P. J. *J. Biol. Chem.* **2009**, *284*, 1949.

(16) (a) Xia L.; Lowary T. L. *J. Org. Chem.* **2013**, *78*, 2863. (b) Xia L.; Lowary T. L. *Biopolymers* **2013**, *99*, 697.

(17) Meppen M.; Wang Y.; Cheon H.; Kishi Y. *J. Org. Chem.* **2007**, *72*, 1941.

(18) Becker M. M.; Ravoo B. J. *Chem. Commun.* **2010**, *46*, 4369.

(19) Zhang W.; Curran D.; Chen C. H. *Tetrahedron* **2002**, *58*, 3871.

(20) Duo Z.; Xing H.; Xiao J. *Chem. Eur. J.* **2011**, *17*, 5373.

Chapter 2: Towards the synthesis of highly fluorinated ether analogues of methyl glucose oligosaccharides

2.1 Introduction

We have discussed methyl glucose lipopolysaccharides (MGLPs) in the first chapter of this thesis.[1,2] They are found in many mycobacterial species, and have possible involvement in the biosynthesis of lipids in those organisms.[2] Synthetic MGLPs have been prepared[3,4] and underwent binding studies with lipophilic molecules.[5] We planned to prepare fluorinated oligosaccharides in order test their binding abilities towards fluorous compounds such as fluorinated lipids and fluorinated small molecules.

In Chapter 1 we have discussed the importance of fluorinated compounds particularly in recent drug development efforts. This includes the synthesis of many fluorinated drug candidates,[6] and study of their physical properties using fluorous tags in reaction discoveries.[7] We aimed ultimately at devising a separation technique that could purify fluorinated compounds from a reaction mixture with ease and efficiency. The use of fluorous liquid phase extraction and phase separation using fluorous silica gel are well known.[8,9] We thought of preparing other fluorous materials using cheaply available oligosaccharides such as cyclodextrins, maltose and/or glucose as our starting materials. Moreover, being α-(1→4) glucopyranoside-containing oligosaccharides, they could be biodegradable. However, insertion of fluorous groups could prevent the oligosaccharide from enzymatic recognition. In this chapter we will discuss our attempts towards synthesizing fluorinated ether analogs of methyl glucose-containing oligosaccharides.

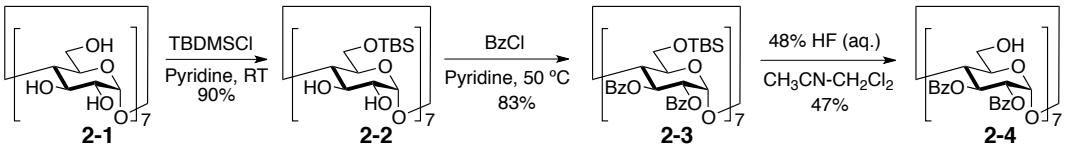
2.2 Results and discussion

2.2.1 Efforts to synthesize fluoroether derivatives of β-cyclodextrin

Our first attempt towards preparing fluorous ether-containing oligosaccharides started from β-cyclodextrin. β-Cyclodextrin is a commercially available naturally-occurring oligosaccharide with seven *α*-(1→4) glucopyranoside units where the first and seventh units are linked to form a cyclic, tub-shaped molecule. Cyclodextrins are well known for their host–guest inclusion chemistry and are widely used in drug delivery applications. The host–guest interaction is mainly based on lipophilic interaction with a guest molecule that fits in the cyclodextrin lipophilic cavity. The cyclic molecule has two faces, i.e., primary and secondary. The primary face contains the primary hydroxyl (6-OH) groups and the secondary face contains the secondary hydroxyl (2-OH and 3-OH) groups. Our objective was to modify the primary face of β-cyclodextrin. Cyclodextrins can be opened selectively cleaving only one glycosidic bond to get acyclic *α*-(1→4) linked oligosaccharide derivatives leading us to our secondary target molecules: acyclic fluorous ether oligosaccharides.

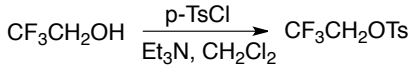
As illustrated in **Scheme 2-1**,[3] the 6-OH groups of β-cyclodextrin (**2-1**) were protected as *tert*-butyldimethylsilyl (TBS) ethers, by treatment with *tert*-butyldimethlysilyl chloride (TBDMSCl) in pyridine to furnish **2-2** in 90% yield. The secondary alcohol groups (2-OH and 3-OH) were then benzoylated using benzoyl chloride in pyridine to afford **2-3** in good yield, 83%. Finally, the TBS

groups were removed by treating **2-3** with 48% aqueous HF to provide **2-4** in 47% yield. The yield of the desired product was low due to unintended removal of one benzoyl group during treatment with aq. HF. This was determined by mass spectrometric analysis of the more polar spot on the TLC plate of the reaction.



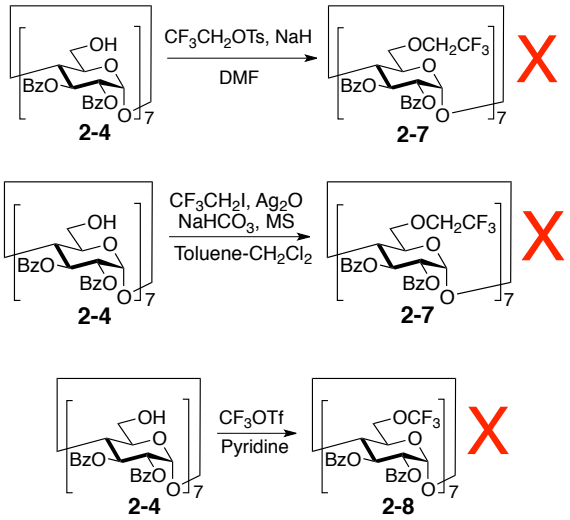
Scheme 2-1. Synthesis of **2-4** from β-cyclodextrin

Having obtained **2-4**, we next tested different reaction conditions (**Scheme 2-3**) to form fluorous ethers at the primary position. Our first trial was the substitution of trifluoroethyl compounds with good leaving groups by **2-4**. To explore this, trifluoroethyl tosylate (**2-6**) was synthesized from commercially available trifluoroethanol using *p*-tosyl chloride in the presence of triethylamine (TEA) in dichloromethane.[10] Substitution reactions of **2-4** and **2-6** under a range of basic conditions failed to afford the expected product, **2-7**. Under these conditions, extensive benzoyl group removal was observed, which made the purification of the expected products complicated. We also tried milder basic conditions such as $NaHCO_3$ and Ag_2O for the substitution reaction with CF_3CH_2I. This reaction did not yield expected product **2-7** either. Another effort was to use a triflate as leaving group in the substitution reaction but the starting material decomposed. When **2-4** was treated with CF_3OTf in pyridine no reaction occurred. So this approach to making the fluorous ethers was abandoned.



2-5 **2-6**

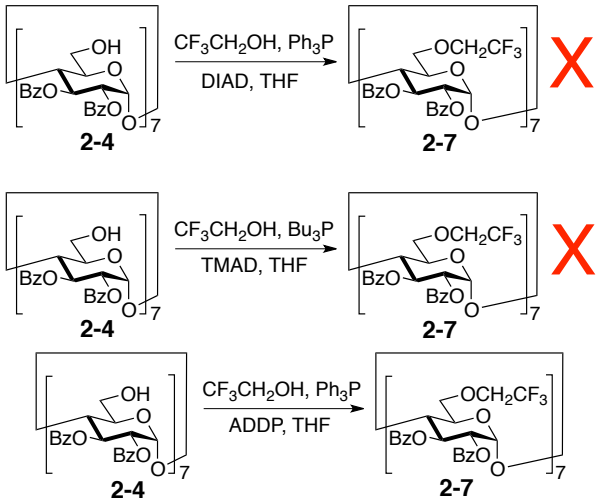
Scheme 2-2. Synthesis of tosylate **2-6** from trifluoroethanol (**2-5**)



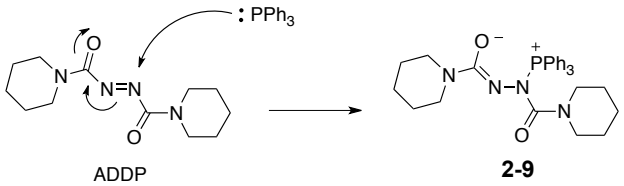
Scheme 2-3. Efforts to synthesize fluorous ethers from **2-4** using trifluoroethanol-based electrophiles

Having been unsuccessful in installing the fluoroalkyl groups using nucleophiles generated from **2-4**, we considered an alternate approach. This involved the Mitsunobu reaction on **2-4** and trifluoroethyl alcohol (**Scheme 2-4**). We used both diisopropyl azodicarboxylate (DIAD) and tetramethylazodicarboxamide (TMAD)[26] in these reactions, but we were unable to isolate the expected product. Different degrees of etherification took place and the products were inseparable. We looked for other Mitsunobu reagents, which had been reported for difficult substitutions, in particular 1,1'-(azodicarbonyl)dipiperidine (ADDP)[27] and found some success. Use of this reagent gave β-cyclodextrin derivatives with up to two out of seven primary hydroxyls substituted by a trifluoroethyl group. This was

plausibly because ADDP gives a more basic betaine intermediate (**2-9**) than the DIAD–PPh_3 or TMAD–PPh_3 betaine intermediate, as depicted in **Scheme 2-5**. This can abstract the proton of less acidic trifluoroethanol (pK_a 12.4)[11] more efficiently. However, it was never possible to force the reaction to give full substitution of all of the primary hydroxyls in β-cyclodextrin and thus the process of etherification was not successful.



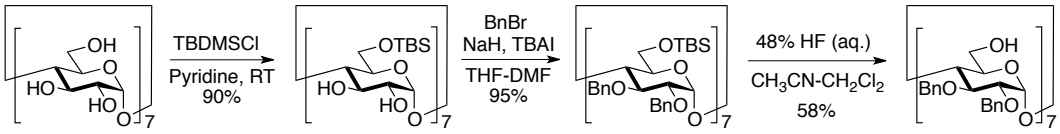
Scheme 2-4. Efforts to synthesize of fluorous derivatives of β-cyclodextrin using Mitsunobu reaction conditions



Scheme 2-5. Betaine intermediate generated from ADDP and triphenylphosphine

We postulated that the electron-withdrawing effect of benzoyl groups at C-2 and C-3 might be reducing the nucleophilicity of the 6-OH groups. Also, we wanted

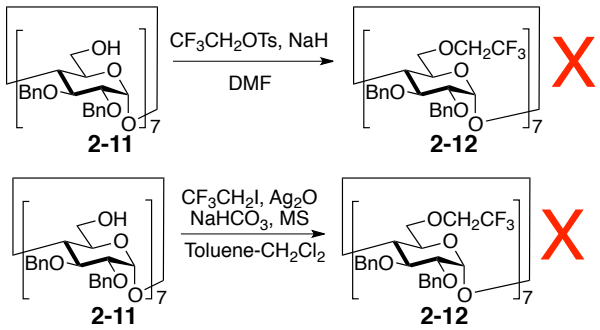
protecting groups that are more stable under basic conditions so as to survive substitution reaction conditions. Therefore, we decided to test derivatives that contained ether protecting groups at OH-2 and OH-3. β-Cyclodextrin-derivative (**2-11**) was synthesized from **2-2** in two steps in good yield as depicted in **Scheme 2-6**. First, we benzylated the secondary OH groups using benzyl bromide and NaH[12] to give **2-10** in very good yield, 95%. In the next step, the silyl protecting groups were removed by 48% aq. HF to afford **2-11** in 58% yield,



2-1 **2-2** **2-10** **2-11**

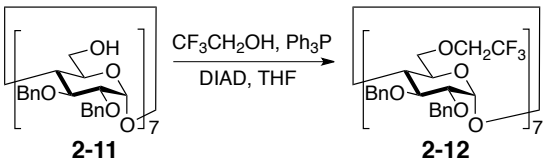
Scheme 2-6. Synthesis of benzyl derivatives of β-cyclodextrin

With compound **2-2** in hand, we explored the addition of the fluorous ethers. As illustrated in **Scheme 2-7**,we tried to produce nucleophiles of **2-11** at the primary hydroxyl group using different bases, NaH and Ag_2O, and to displace tosyl or iodide leaving groups at electrophilic centres of trifluoroethyl electrophiles. However, the substitution reactions did not give expected product **2-12**. The starting material decomposed and this was concluded from TLC that showed more polar spots than the starting material **2-11**.



Scheme 2-7. Substitution reactions between **2-11** and trifluoroethanol-derived electrophiles

Having failed at these traditional substitution reactions, the only glimpse of success was observed under Mitsunobu reaction conditions. As shown in **Scheme 2-8**, the reaction did not afford the fully substituted product. However, etherification was successful for up to five out of seven hydroxyl groups.



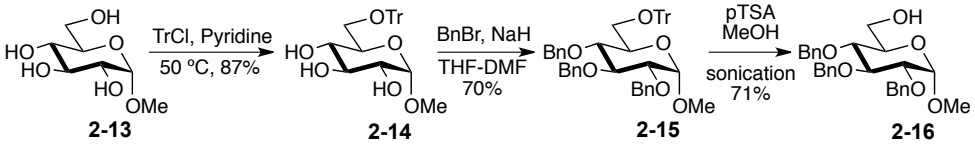
Scheme 2-8. Mitsunobu reaction of **2-11** using CF_3CH_2OH

2.2.2 Synthesis of fluoroether derivatives of glucopyranosides

With the partial success for the fluoroetherification of the primary hydroxyl groups of β-cyclodextrin, we decided to apply this approach on simpler systems such as monosaccharide and disaccharide glucopyranose derivatives, where complete substitution of all the reactive groups would be more likely. It was thought that if

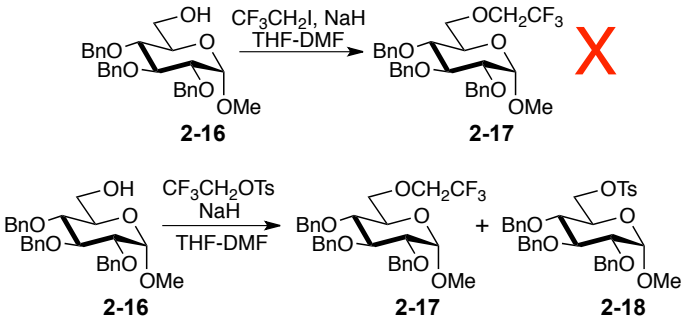
these reactions proceeded in good yield, the fluorinated building blocks could be assembled into larger compounds through glycosylation reactions.

To explore this possibility, the primary hydroxyl group of methyl *α*-D-glucopyranoside (**2-13**) was protected by a trityl group using trityl chloride in pyridine to afford compound **2-14** in good yield, 87% (**Scheme 2-9**). The secondary hydroxyl groups of **2-14** were benzylated using benzyl bromide and sodium hydride in THF and DMF to afford **2-15** in a moderate yield of 70%. Finally, intermediate **2-16** was obtained from **2-15** in 71% yield after deprotecting the trityl group under mild acidic conditions using *p*-TsOH in methanol[13] using sonication.



Scheme 2-9. Synthesis of glucopyranoside **2-16**

Using compound **2-16**, nucleophilic substitution of trifluoroethyl iodide by the primary OH group was attempted under basic conditions (**Scheme 2-10**). Unfortunately, this reaction did not give any of the expected product, **2-17** and the starting material decomposed. However, it was possible to obtain **2-17** under basic reaction conditions using trifluoroethyl tosylate. The product was contaminated with inseparable 6-tosyl derivative **2-18** as they had the same chromatographic R_f.



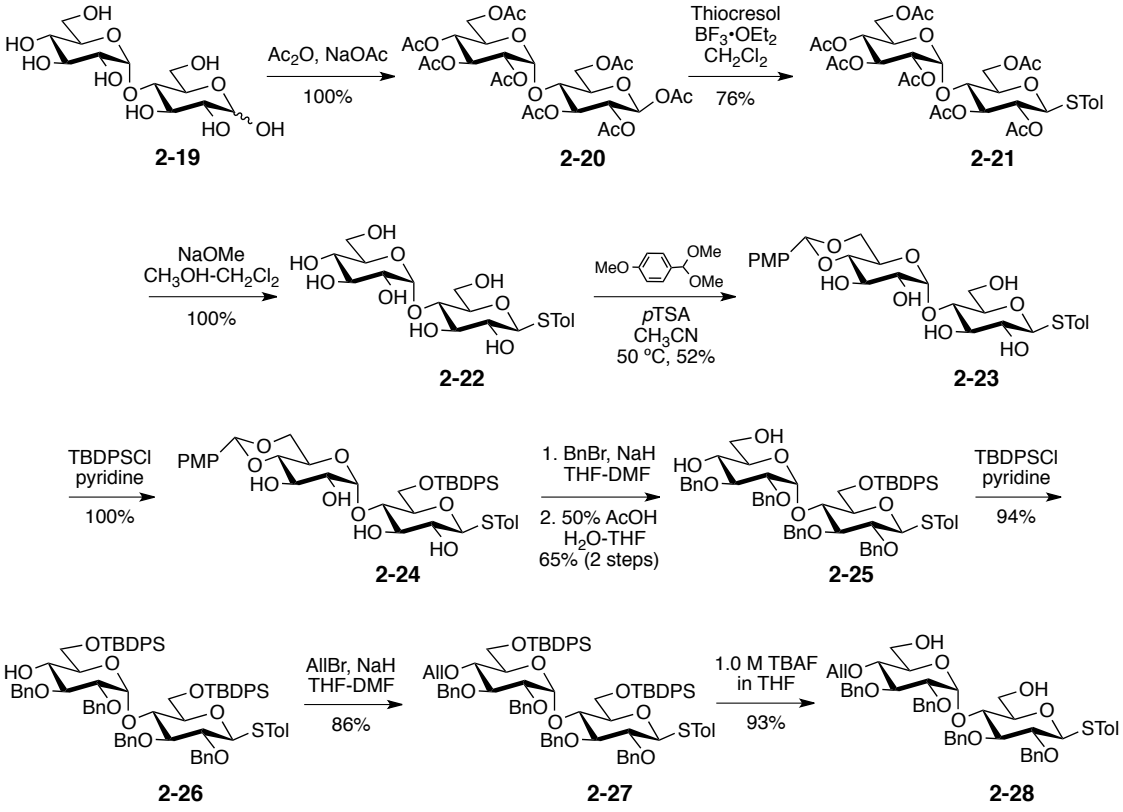
Scheme 2-10. Synthesis of fluorous glucopyranoside through substitution reactions from monosaccharide substrate **2-16**

Therefore we achieved success on the monosaccharide unit. We considered it as partial success because the separation of substituted and tosylated products was not possible. However, with this modest success we planned to test this reaction on a disaccharide unit, where separation might be easier.

2.2.3 Synthesis of fluoroether derivatives of maltose

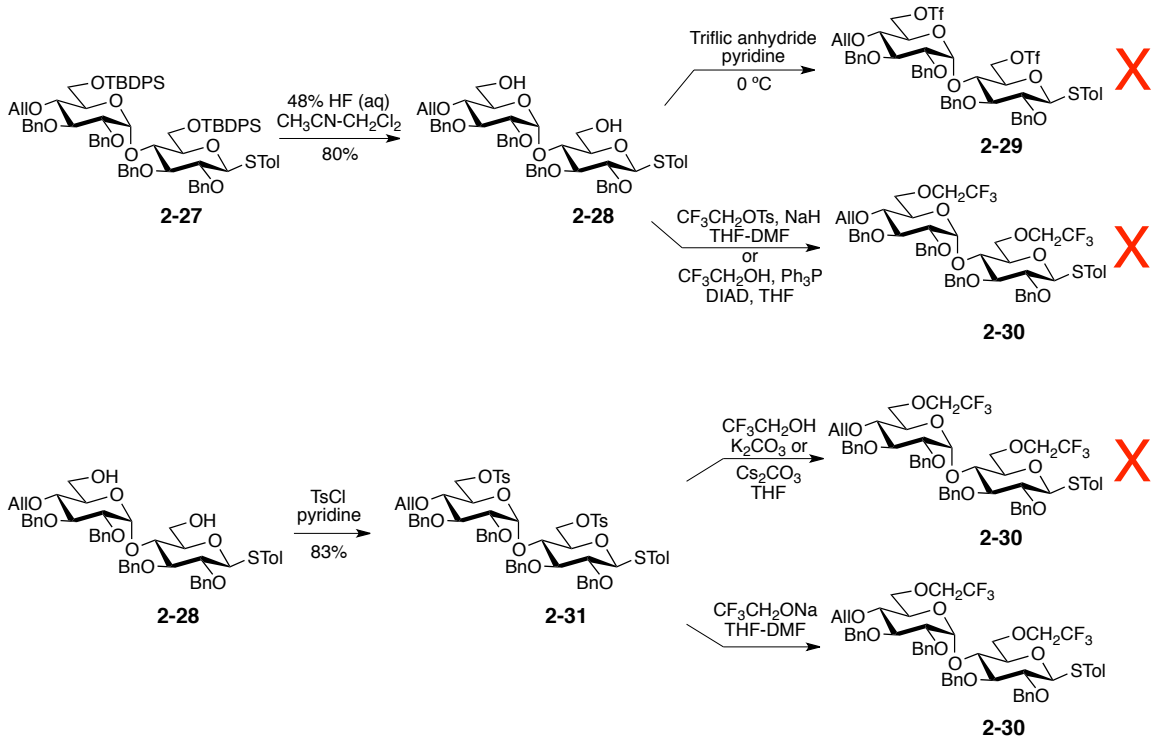
With the promising result using the monosaccharide unit, we explored this chemistry on the *α*-(1→4)-linked disaccharide, maltose, a naturally available and inexpensive disaccharide. As illustrated in **Scheme 2-11**,[14] maltose, was peracetylated using acetic anhydride and sodium acetate. The peracetylated product, **2-20,** was glycosidated using thiocresol to afford **2-21** in 76% yield. The acetyl groups were removed using Zemplén conditions to provide **2-22** in quantitative yield. Next, a *p*-methoxy-benzylidene acetal was installed using standard procedures[14] from **2-22** to form compound **2-23**. The primary hydroxyl of **2-23** was protected with a *tert*-butyldiphenylsilyl (TBDPS) group on treatment

with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in pyridine to furnish **2-24** in excellent yield.[15] The remaining secondary hydroxyl groups of **2-24** were then protected with benzyl groups using benzyl bromide and the benzylidene protecting group was removed by treating with 50% acetic acid in water–THF to furnish maltose derivative **2-25** in 65% yield over the two steps. The free primary hydroxyl group of **2-25** was then protected using TBDMSCl in pyridine to afford **2-26** in very good yield, 94%. The free secondary hydroxyl group of **2-26** was allylated using allyl bromide and sodium hydride in THF–DMF to give **2-27** in 86% yield. Finally, building block **2-28** with free primary hydroxyl groups was obtained from **2-27** upon deprotection of the silyl protecting groups by tetrabutylammonium fluoride (TBAF) in THF in very good yield, 93%.



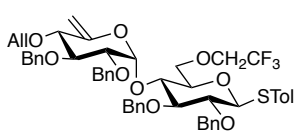
Scheme 2-11. Synthesis of maltose building block **2-28**

Our initial plan was to convert the primary alcohol groups in **2-28** to good leaving groups and then displace them with a fluorinated ether nucleophile (**Scheme 2-12**). However, the synthesis of trifluoromethanesulfonyl derivative **2-29** from **2-28** was not successful. This was not successful possibly because of decomposition of starting material during the reaction. Therefore, we changed our strategy and prepared a nucleophile from **2-28** that would be used to displace leaving groups from fluorinated alcohol derivatives. However, this attempt was unsuccessful as well and we could not obtain any expected product but instead decomposed starting material. A Mitsunobu reaction with **2-28** and CF_3CH_2OH was expected to yield fluoroether **2-30** also failed to afford expected product.

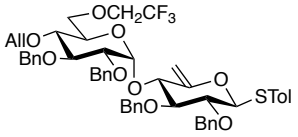


Scheme 2-12. Synthesis of fluorous ethers from maltose building block **2-30**

We therefore decided to prepare the ditosyl derivative of **2-28**, with the goal of displacing the tosyl leaving group with a trifluoroethanol-derived nucleophile. We could prepare tosylate **2-31** from **2-28** using *p*-toluensulfonylchloride in pyridine. With this tosylate in hand, we attempted to displace it by a trifluoroethylate nucleophile, prepared from alkali metal carbonate bases, for example, Cs_2CO_3 and K_2CO_3. These reactions failed; however, when sodium hydride was used to prepare the trifluoroethylate anion, the displacement reaction was successful. This reaction provided the expected product **2-30** together with an inseparable mixture of exo-ene products **2-30a** and **2-30b** (**Figure 2-1**).



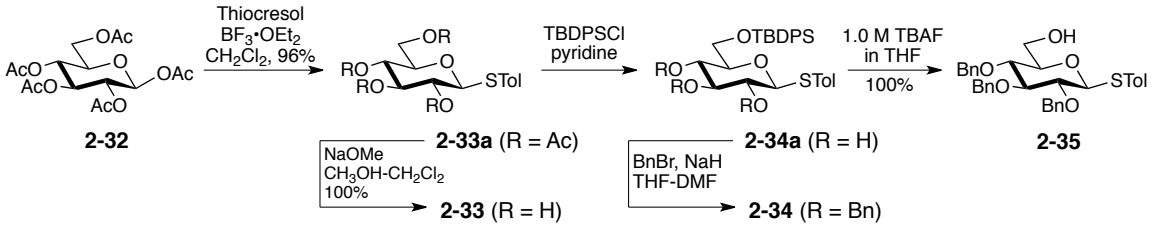
2-30a



2-30b

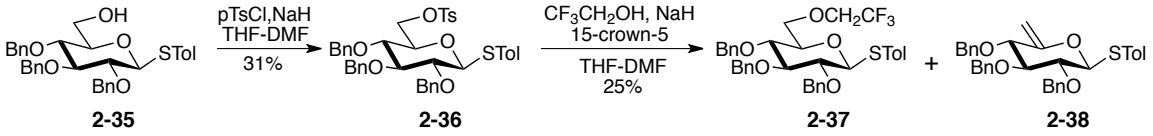
Figure 2-1. Exo-ene products formed from **2-30** due to elimination

We also explored this strategy on a monosaccharide (**Scheme 2-13**). Commercially available 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**2-32**) was glycosidated using thiocresol and then deacetylated under Zemplén conditions to afford **2-33** in excellent yield.[14] The primary alcohol of **2-33** was protected by *tert*-butyldiphenylsilyl group and the free secondary hydroxyl groups were protected with benzyl groups to give **2-34**. Building block **2-35** was synthesized by removing the TBDPS group with TBAF in tetrahydrofuran quantitatively.



Scheme 2-13. Synthesis of glucose building block **2-35**

With compound **2-35** in hand, the primary hydroxyl group was tosylated by treatment with *p*-tolenesulfonylchloride and sodium hydride to afford tosylate derivative **2-36**. The tosyl group was successfully displaced by trifluoroethylate nucleophile to furnish **2-37**. The expected product was formed along with elimination product. The yield was quite low due to the difficulty during chromatographic separation. The product and by-product exo-ene derivative **2-38** had very close chromatographic R_f.



Scheme 2-14. Synthesis of fluorous ether **2-37** from glucose building block **2-35**

Although, the thioglycosides **2-30** and **2-37** could be obtained by this strategy, the generally low overall yields, particularly for the monosaccharide building block, suggested that this was not an ideal approach. We therefore discarded the devised route and did not proceed towards glycosylation to prepare larger oligosaccharides.

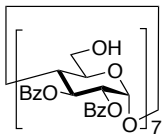
2.5 Conclusion

In this chapter we discussed the difficulties we encountered to obtain fluoroether oligosaccharide derivatives of MGLPs. We explained the challenges we faced during developing a method to synthesize fluorinated ether derivatives of both simple (e.g., monosaccharide) and complex (β-cyclodextrin) oligosaccharides. Although we could synthesize monosaccharide building block **2-30** and **2-37** with success, they were obtained in poor yield and elimination products were always present. Given this, we consider that this approach would not provide sufficient starting material to carry forward for making oligosaccharides. Hence, we abandoned the idea to synthesize fluorinated ether derivatives of MGLPs. Another approach for the preparation of fluorinated MGLP carbohydrates will be discussed in the next chapter.

2.4 Experimental details

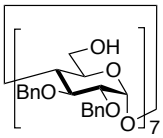
General methods for chemical synthesis: All reagents were purchased from commercial sources and were used without further purification unless noted otherwise. Reaction solvents were purified by successive passage through columns of alumina and copper under an argon atmosphere using Innovative Technology, Inc. PURE SOLV (SPS-400-7). All reactions were performed under a positive pressure of argon at room temperature unless specified otherwise. Reactions were monitored by TLC on silica gel 60-F_{254} (0.25 nm, Silicycle, Quebec, Canada) and visualization of the reaction components was achieved using UV fluorescence (254 nm) and/or by charring with acidified anisaldehyde

solution in ethanol or 5% H_2SO_4 in ethanol. Organic solvents were evaporated under reduced pressure at 40 ºC unless specified otherwise. Reaction products were purified by column chromatography on silica gel (230–400 mesh, Silicycle, Quebec, Canada) or Iatrobeads 6RS-8060 (Iatron Laboratories Inc., Tokyo) if the eluent system contained greater than 10% methanol. The yields reported are after purification. Optical rotations were measured in Perkin Elmer 241 polarimeter at 589 nm at ambient temperature and are in units of degree•mL/(g•dm). ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 or 500 MHz and chemical shifts were referenced to $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ at 125 MHz and chemical shifts were referenced to $CDCl_3$ (77.1 ppm). Assignments of the NMR spectra were based on one-dimensional experiments (APT, DEPT) and/or two-dimensional experiments (^{1}H–^{1}H COSY, HSQC and HMBC). Electrospray mass spectra (ES-MS) were recorded on Agilent Technologies 6220 TOF. For ES-MS spectra, samples were dissolved in $CHCl_3$ or CH_3OH and NaCl was added.

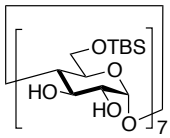


Heptakis(2,3-di-*O*-benzoyl)cyclomaltoheptaose (2-4): To a solution of **2-3** (1.15 g, 0.34 mmol) in CH_3CN–CH_2Cl_2 (20 mL, 3:1) in a plastic reactor was added 48% aq. HF (3.0 mL, 42 mmol) dropwise. The reaction mixture was stirred overnight, diluted with CH_2Cl_2 (25 mL) and then neutralized with saturated aq. $NaHCO_3$ (100 mL). The organic layer was separated and the aq. layer was

washed with CH_2Cl_2 (2 x 25 mL). The organic layers were combined, washed with brine (100 mL) and then dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and the resulting crude product was purified by flash silica gel chromatography (100% CH_2Cl_2 → 5:17 CH_3OH–CH_2Cl_2) to afford **2-4** (0.409 g, 47%) as a white solid. The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[3]

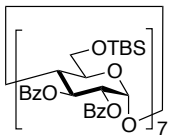


Heptakis(2,3-di-*O*-benzyl)cyclomaltoheptaose (2-11): To an ice cold solution of **2-10** (3.00 g, 0.81 mmol) in anhydrous THF (15 mL) in a plastic reactor was added HF–pyridine (2.0 mL) slowly. The mixture was stirred for 23 h and quenched by the addition of saturated aq. $NaHCO_3$ (180 mL). The mixture was partitioned between saturated aq. $NaHCO_3$ (180 mL) and EtOAc (80 mL). The organic layer was separated, washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash silica gel chromatography (100% CH_2Cl_2 → 3:22 CH_3OH–CH_2Cl_2) to furnish **2-11** (1.12 g, 58%) as a white solid. The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[16]



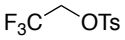
Heptakis(6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (2-2):

Cyclomaltoheptaose (7.0 g, 6.17 mmol) was dried under reduced pressure at 85 ºC overnight. This compound was dissolved in anhydrous pyridine (120 mL) cooled in an ice bath and then a solution of TBSCl (6.51 g, 43.19 mmol) in anhydrous pyridine (60 mL) was added dropwise. Another portion of TBSCl (1.31 g, 8.64 mmol) was added to the reaction mixture after 1 d and then the mixture was stirred for 4 d. The solution was concentrated under reduced pressure and the product was precipitated by adding the mixture to ice water (200 mL). The precipitate was further washed with ice water (400 mL). The product was dissolved in EtOAc (200 mL) and washed with 1 N HCl (100 mL), saturated aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was concentrated under reduced pressure and the product was recrystallized from EtOH to afford **2-2** (10.66 g, 90%) as a white powder. The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[3]

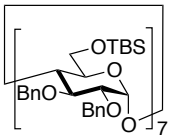


Heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-benzoyl)cyclomaltoheptaose (2-3): To an ice cold solution of **2-2** (10.65 g, 5.53 mmol) in anhydrous pyridine (330 mL) was added BzCl (36 mL, 310 mmol) slowly. The reaction mixture was

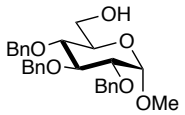
heated at 50 ºC and stirred for 5.5 d. The reaction mixture was concentrated under reduced pressure to a small volume (~100 mL). To this mixture was added saturated aq. $NaHCO_3$ (70 mL) at 0 ºC and the solution was stirred for 10 min. From this mixture, a sticky yellow solid was precipitated out by the addition of ice water (250 mL). The precipitate was filtered and it was further washed with cold water (200 mL). The solid was dissolved in CH_2Cl_2 (200 mL) and washed with 1 N HCl (200 mL), saturated aq. $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was concentrated under reduced pressure and the resulting residue was recrystallized from EtOH to furnish **2-3** (15.562 g, 83%) as a white solid. The ^1H NMR and ^{13}C NMR data were consistent with that previously reprted..[3]



1,1,1-trifluoroethyl-2-*O*-tosylate (2-6): A solution of 2,2,2-trifluoroethanol (1.00 g, 9.95 mmol) and TEA (3.63 g, 35.85 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to 0 ºC and *p*-TsCl (2.37 g, 12.45 mmol) was added. The reaction mixture was heated to room temperature and stirred overnight. The organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:9 CH_2Cl_2–hexane → 100% CH_2Cl_2) to afford **2-6** (1.865 g, 74%) as a colorless solid. The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[25]

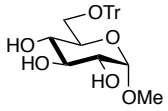


Heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-benzyl)cyclomaltoheptaose (2-10): To an ice-cold solution of **2-2** (2.00 g, 1.03 mmol) and BnBr (1.71 mL, 14.42 mmol) in anhydrous THF–DMF (15 mL, 1:1) was added NaH (60% dispersion in mineral oil, 0.577 g, 14.42 mmol). The mixture was heated to room temperature and stirred. Another portion of BnBr (1.71 mL, 14.42 mmol) and NaH (60% dispersion in mineral oil, 0.577 g, 14.42 mmol) were added to the reaction mixture after 23 h. The mixture was stirred for 27.5 h and quenched by the addition of CH_3OH (5 mL). The mixture was concentrated and partitioned between water (100 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash silica gel chromatography (100% hexane → 1:9 EtOAc–hexane) to give **2-10** (3.064 g, 95%) as a colorless sticky solid. R_f 0.46 (1:9 EtOAc–hexane). The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[16]

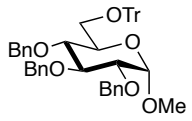


Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (2-16): To a mixture of **2-15** (340 mg, 0.48 mmol) in CH_3OH (3 mL) was added *p*-tolenesulfonic acid in CH_3OH (6 mL) (a solution of *p*-TsOH (50 mg) in CH_3OH (10 mL)) and the

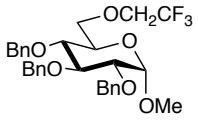
solution was sonicated for 55 min. The mixture was treated with TEA (1 mL) and then concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:4 EtOAc–hexane → 3:2 EtOAc–hexane) to afford **2-16** (157 mg, 71%) as a yellow sticky solid. R_f 0.32 (1:1 EtOAc–hexane). The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[17]



Methyl 6-*O*-trityl-α-D-glucopyranoside (2-14): To a solution of methyl α-D-glucopyranoside (1.942 g, 10.0 mmol), dried under reduced pressure at 50 ºC for 45 min in anhydrous pyridine (25 mL) was added TrCl (3.624 g, 13.0 mmol) and the mixture was stirred overnight at 50 ºC. The solution was cooled to room temperature and saturated aq. $NaHCO_3$ (30 mL) was added to quench excess HCl produced during the reaction. The solution was stirred for 15 min and then another portion of saturated aq. $NaHCO_3$ (70 mL) and CH_2Cl_2 (125 mL) were added. The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:19 CH_3OH–CH_2Cl_2 → 1:4 CH_3OH–CH_2Cl_2) to furnish **2-14** (3.755 g, 87%) as a white sticky solid. The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[18]

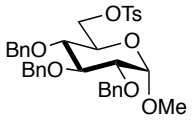


Methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside (2-15): To an ice cold solution of **2-14** (872 mg, 2.0 mmol) and BnBr (1.43 mL, 12.0 mmol) in anhydrous THF–DMF (25 mL, 4:1) was added NaH (60% dispersion in mineral oil, 480 mg, 12.0 mmol). The reaction mixture was stirred for 3 d and then partitioned between water (125 mL) and EtOAc (75 mL). The organic layer was washed with water (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1:9 EtOAc–hexane → 3:7 EtOAc–hexane) to furnish **2-15** (988 mg, 70%) as a yellow gum. The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[18]

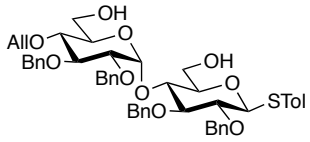


Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(1,1,1-trifluoro)ethyl-α-D-glucopyranoside (2-17): To an ice cold solution of **2-16** (46 mg, 0.1 mmol) in anhydrous THF–DMF (0.5 mL, 4:1) was added CF_3CH_2OTs (51 mg, 0.2 mmol) followed by NaH (60% dispersion in mineral oil, 6 mg, 0.15 mmol). Another portion of CF_3CH_2OTs (25 mg, 0.1 mmol) and NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol) were added to the reaction mixture after stirring for 40 h at RT. The reaction was further stirred for 24 h at RT and the excess NaH was quenched by the addition of CH_3OH (1 drop). The solvent was evaporated under reduced pressure and the

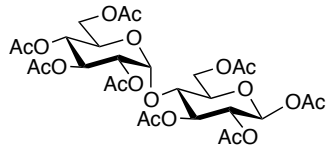
resulting residue was purified by flash silica gel chromatography (4:1 hexane–EtOAc → 3:1 hexane–EtOAc) to afford **2-17** (11 mg) as a colourless oil. R_f 0.40 (3:1 hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 15H), 4.99 (d, 1H, *J* = 10.8 Hz), 4.89 (d, 1H, *J* = 11.0 Hz), 4.81 (m, 2H), 4.66 (d, 1H, *J* = 12.1 Hz), 4.61–4.58 (m, 2H), 3.99 (app t, 1H, *J* = 9.3 Hz), 3.91–3.83 (m, 2H), 3.79–3.71 (m, 3H), 3.58–3.51 (m, 2H), 3.36 (s). ^{19}F NMR (500 MHz, $CDCl_3$) δ –73.98 ($C\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{30}H_{33}F_3O_6Na^+$) $[M+Na]^+$ 569.2121, found 569.2124.



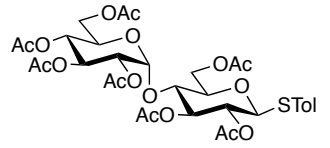
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranoside (2-18): To an ice cold solution of **2-16** (46 mg, 0.1 mmol) in anhydrous THF–DMF (0.5 mL, 4:1) was added CF_3CH_2OTs (51 mg, 0.2 mmol) followed by NaH (60% dispersion in mineral oil, 6 mg, 0.15 mmol). Another portion of CF_3CH_2OTs (25 mg, 0.1 mmol) and NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol) were added to the reaction mixture after stirring for 40 h at RT. The reaction was further stirred for 24 h at RT and excess of NaH was quenched by the addition of CH_3OH (1 drop). The solvent was evaporated under reduced pressure and the resulting residue was purified by flash silica gel chromatography (4:1 hexane–EtOAc → 3:1 hexane–EtOAc) to afford an inseparable mixture of **2-17** and **2-18** (30 mg) as a colourless sticky solid. R_f 0.28 (3:1 hexane–EtOAc). The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[12]



4-*O*-Allyl-2,3-di-*O*-benzyl-α-D-glucopyranosyl-(1→4)-*p*-tolyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (2-28): To a solution of **2-27** (1.45 g, 1.09 mmol) in dry THF (12 mL) was added a solution of 1 M TBAF in THF (4.36 mL, 4.36 mmol). The reaction mixture was stirred for 2 h and then concentrated under reduced pressure and the resulting residue was purified by flash silica gel chromatography (1:49 CH_3OH–CH_2Cl_2 → 1:19 CH_3OH–CH_2Cl_2) to furnish **2-28** (0.9 g, 93%) as a cream-color solid. R_f 0.27 (1:19 CH_3OH–CH_2Cl_2); ^{1}H NMR (500 MHz, , DMSO-d_6) δ 7.44–7.42 (m, 2H), 7.30–7.10 (m, 22H), 5.92–5.84 (m, 1H), 5.67 (d, 1H, *J* = 3.9 Hz), 5.23 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.16 (dd, 1H, *J* = 10.4, 1.1 Hz), 4.94–4.76 (m, 5H), 4.68–4.58 (m, 3H), 4.46 (d, 1H, *J* = 11.8 Hz), 4.30 (dd, 1H, *J* = 12.3, 5.7 Hz), 4.13–4.03 (m, 2H), 3.96–3.80 (m, 5H), 3.72–3.66 (m, 2H), 3.52–3.45 (m, 2H), 3.42 (dd, 1H, *J* = 9.8, 3.9 Hz), 3.31–3.27 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 139.2, 138.9, 138.6, 138.4, 137.0, 135.9, 131.2, 130.2, 128.7, 128.6, 128.6, 128.6, 128.2, 128.1, 127.9, 127.9, 127.8, 127.7, 127.1, 116.7, 96.2, 86.2, 81.5, 80.9, 79.4, 79.3, 77.6, 74.9, 74.3, 73.7, 73.4, 72.7, 72.6, 72.1, 60.8, 60.4, 21.1. HRMS (ES-MS) *m/z* calcd for ($C_{50}H_{56}O_{10}SNa^+$) $[M+Na]^+$ 871.3486, found 871.3476.

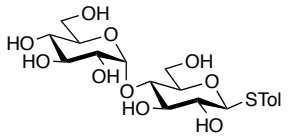


2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,2,3,5-tetra-*O*-acetyl-β-D-glucopyranose (2-20): To a mixture of D-(+)-maltose monohydrate (25.0 g, 70 mmol) and NaOAc (5.5 g) was added Ac_2O (140 mL). The reaction mixture was stirred for 23 h at 100 ºC. The reaction mixture was partitioned between saturated aq. $NaHCO_3$ (700 mL) and CH_2Cl_2 (600 mL) and this mixture was stirred for 4 h. The organic layer was separated, washed with saturated aq. $NaHCO_3$ (200 mL) and water (2 x 300 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **2-20** (54.4 g, 100%) as a white solid. R_f 0.32 (1:1 EtOAc–hexane). The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[20]

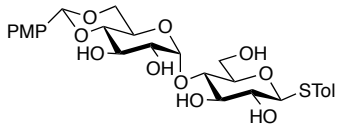


p-Toluyl 2,3,4,5-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,5-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2-21): To a mixture of **2-20** (25.2 g, 37.1 mmol), thiocresol (6.9 g, 55.65 mmol) and 4Å molecular sieves (15.0 g) in anhydrous CH_2Cl_2 (200 mL) was added $BF_3•Et_2O$ (22.9 mL, 185.5 mmol) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 17 h, at which point another portion of thiocresol (2.3 g, 18.55 mmol) and $BF_3•Et_2O$ (11.5 mL, 92.75 mmol) were added. After 24 h, $BF_3•Et_2O$ (11.5 mL, 92.75 mmol) was

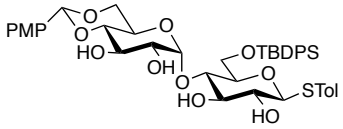
added to the reaction mixture. The reaction mixture was stirred for a further 16 h at RT and partitioned between cold saturated aq. $NaHCO_3$ (800 mL) and CH_2Cl_2 (200 mL). The resultant mixture was stirred for 40 min. The collected organic layer was washed with saturated aq. $NaHCO_3$ (200 mL), water (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:3 EtOAc–hexane → 1:1 EtOAc–hexane) to furnish **2-21** (21.07 g, 76%) as a white solid. R_f 0.44 (1:1 EtOAc–hexane). The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[19]



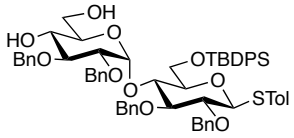
***p*-Toluyl α-D-Glucopyranosyl-(1→4)-1-thio-β-D-glucopyranoside (2-22):** To a solution of **2-21** (5.39 g, 7.26 mmol) in CH_3OH–CH_2Cl_2 (50 mL, 1:1) was added $NaOCH_3$ (196 mg, 3.63 mmol) and the mixture was stirred for 21 h. The reaction mixture was neutralized by adjusting the pH to 7 with Amberlite® IR120 resin. The solution was filtered and the filtrate was concentrated under reduced pressure to afford **2-22** (3.43 g, 100%) as a yellow solid. The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[21]



***p*-Toluyl 4,6-*O*-(4-Methoxy)benzylidene-α-D-glucopyranosyl-(1→4)-1-thio-β-D-glucopyranoside (2-23):** To **2-22** (3.816 g, 8.5 mmol) in anhydrous CH_3CN (16 mL) was added a mixture of *p*-TsOH (0.324 mg, 1.7 mmol) and 4-(dimethoxymethyl)methoxybenzaldehyde (5.8 mL, 34 mmol) in anhydrous CH_3CN (3 mL) and heated at 50 ºC. Another portion of *p*-TsOH (81 mg, 0.425 mmol) and 4-(dimethoxymethyl)methoxybenzaldehyde (2.2 mL, 12.75 mmol) were added to the mixture after 1 d. The reaction mixture was stirred for 2 d at 50 ºC. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash silica gel chromatography (100% CH_2Cl_2 → 3:22 CH_3OH–CH_2Cl_2) to provide **2-23** (2.465 g, 52%) as a white solid. R_f 0.37 (1:9 CH_3OH–CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39–7.35 (m, 4H) 7.12 (d, 2H, J = 8.1 Hz), 6.91–6.89 (m, 2H), 5.61–5.59 (m, 2H), 5.50 (s, 1H), 5.35 (d, 1H, J = 6.2 Hz), 5.27 (d, 1H, J = 5.2 Hz), 5.12 (d, 1H, J = 3.8 Hz), 4.66 (app t, 1H, J = 5.5 Hz), 4.58 (d, 1H, J = 9.7 Hz), 4.10 (dd, 1H, J = 9.3, 4.3 Hz), 3.74 (s, 3H), 3.73–3.62 (m, 3H), 3.58–3.49 (m, 3H), 3.39–3.36 (m, 3H), 3.10–3.05 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 136.7, 131.2, 131.0, 130.6, 129.9, 128.2, 113.8, 101.5, 101.3, 87.6, 81.3, 79.7, 79.5, 78.2, 73.4, 72.4, 70.5, 68.4, 63.8, 61.1, 55.6, 21.1. HRMS (ES-MS) *m/z* calcd for ($C_{27}H_{34}O_{11}SNa^+$) $[M+Na]^+$ 589.1714, found 589.1707.

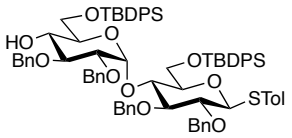


***p*-Toluyl 4,6-*O*-(4-Methoxy)benzylidene-α-D-glucopyranosyl-(1→4)-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (2-24):** To an ice-cold solution of **2-23** (2.235 g, 3.94 mmol) in anhydrous pyridine (25 mL) was added TBDPSCl (1.5 mL, 5.91 mmol). The reaction was warmed to room temperature and, after 5 h, another portion of TBDPSCl (0.5 mL, 1.97 mmol) was added. The reaction mixture was stirred for 21 h and then concentrated. The resulting residue was purified by silica gel column chromatography (100% CH_2Cl_2 → 3:22 CH_3OH–CH_2Cl_2) to afford **2-24** (3.374 g, 100%) as a white solid. R_f 0.50 (1:9 CH_3OH–CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86–7.84 (m, 2H), 7.78–7.76 (m, 2H), 7.50–7.38 (m, 10H), 7.05–7.03 (m, 2H), 6.91–6.89 (m, 2H), 5.46 (s, 1H), 5.17 (d, 1H, *J* = 3.8 Hz), 4.86–4.81 (br s, 1H), 4.49 (d, 1H, *J* = 9.7 Hz), 4.38–4.32 (br s, 1H), 4.01–3.94 (m, 3H), 3.84–3.75 (m, 4H), 3.81 (s, 3H), 3.66 (dd, 1H, *J* = 9.3, 3.6 Hz), 3.59–3.55 (m, 1H), 3.45–3.39 (m, 3H), 3.18–3.10 (br s, 1H), 2.94–2.88 (br s, 1H), 2.32 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 138.2, 136.0, 135.9, 135.7, 133.4, 133.1, 132.9, 129.8, 129.7, 129.7, 129.6, 129.1, 128.2, 128.2, 127.7, 127.7, 125.3, 123.8, 113.7, 102.3, 101.8, 88.1, 80.8, 80.6, 79.4, 77.5, 73.8, 71.6, 71.2, 68.7, 63.6, 62.5, 55.3, 26.8, 21.2, 19.3. HRMS (ES-MS) *m/z* calcd for ($C_{43}H_{52}O_{11}SSiNa^+$) $[M+Na]^+$ 827.2892, found 827.2885.



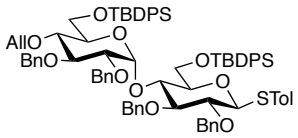
***p*-Toluyl 2,3-di-*O*-Benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (2-25):** To a solution of **2-24** (3.347 g, 4.15 mmol) and BnBr (2.96 mL, 24.9 mmol) in anhydrous THF–DMF (35 mL, 4:1) to 0 ºC, was added NaH (60% dispersion in mineral oil, 0.998 g, 24.9 mmol). The reaction mixture was stirred for 42 h before CH_3OH (1 mL) was added to quench the excess NaH. The mixture was concentrated under reduced pressure and the residue was then partitioned between EtOAc (200 mL) and water (300 mL). The organic layer was separated, washed with water (2 x 300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (100% CH_2Cl_2) to give a yellow oil product (5.0 g). To this product (5.0 g) was added AcOH–THF–water (200 mL, 2:1:1) and the mixture was stirred for 4 d. The reaction mixture was partitioned between saturated aq. $NaHCO_3$ (1600 mL) and EtOAc (500 mL) and this mixture was stirred for 30 min. The organic layer was separated, washed with saturated aq. $NaHCO_3$ (500 mL) and water (500 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (100% CH_2Cl_2 → 1:19 CH_3OH–CH_2Cl_2) to afford **2-25** (2.72 g, 65% over 2 steps) as a yellow solid. R_f 0.44 (1:19 CH_3OH–CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.76 (m, 4H), 7.51–7.49 (m, 2H), 7.44–7.21 (m, 26H), 7.06–7.04 (m, 2H), 5.59 (d, 1H, *J* =

3.6 Hz), 4.97–4.88 (m, 4H), 4.73 (d, 1H, *J* = 9.8 Hz), 4.67–4.62 (m, 2H), 4.56 (s, 2H), 4.09–4.03 (m, 3H), 3.82 (t, 1H, *J* = 8.7 Hz), 3.71–3.68 (m, 1H), 3.58–3.51 (m, 6H), 3.40 (dd, 1H, *J* = 9.7, 3.6 Hz), 2.35 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.6, 138.0, 137.9, 137.3, 136.0, 135.7, 133.7, 133.1, 131.8, 130.8, 129.7, 129.7, 129.6, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 127.8, 127.8, 127.7, 127.7, 127.7, 127.7, 127.3, 126.8, 97.1, 88.2, 86.5, 81.1, 79.7, 79.2, 75.3, 75.2, 74.6, 74.4, 73.0, 71.9, 70.3, 63.8, 62.2, 27.0, 21.1, 19.4. HRMS (ES-MS) *m/z* calcd for ($C_{63}H_{70}O_{10}SSiNa^+$) $[M+Na]^+$ 1069.4351, found 1069.4355.



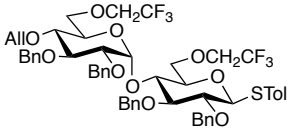
***p*-Toluyl 2,3-di-*O*-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (2-26):** To an ice-cold solution of **2-25** (2.69 g, 2.566 mmol) in dry pyridine (16 mL) was added TBDPSCl (1.31 mL, 5.132 mmol). The reaction mixture was stirred for 42 h at RT. Methanol (2 mL) was added to destroy excess TBDPSCl and the mixture was concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (9:1 hexane–EtOAc → 4:1 hexane–EtOAc) to furnish **2-26** (3.07 g, 94%) as a pale yellow solid. R_f 0.50 (4:1 hexane–EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.68 (m, 5H), 7.64–7.62 (m, 4H), 7.48–7.22 (m, 33H), 7.02–7.00 (m, 2H), 5.61 (d, 1H, *J* = 3.6 Hz), 4.95–4.84 (m, 4H), 4.71–4.65 (m, 3H), 4.57 (s, 2H), 4.05–3.98

(m, 3H), 3.80 (t, 1H, *J* = 8.7 Hz), 3.71–3.62 (m, 4H), 3.56–3.48 (m, 3H), 3.41 (dd, 1H, *J* = 9.4, 3.6 Hz), 2.31 (s, 3H), 1.06 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.8, 138.1, 138.0, 137.2, 135.8, 135.7, 135.6, 134.8, 133.6, 133.3, 133.2, 133.1, 131.7, 130.9, 129.7, 129.5, 129.5, 128.4, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 127.7, 127.7, 127.6, 127.6, 127.2, 126.8, 96.5, 88.3, 86.6, 81.2, 81.0, 81.0, 80.9, 79.8, 79.3, 76.5, 75.3, 75.2, 74.4, 73.8, 73.8, 73.0, 72.2, 71.3, 64.0, 63.9, 60.4, 27.0, 26.9, 26.6, 21.1, 19.4, 19.2. HRMS (ES-MS) *m/z* calcd for ($C_{79}H_{88}O_{10}SSi_2Na^+$) $[M+Na]^+$ 1307.5529, found 1307.5523.



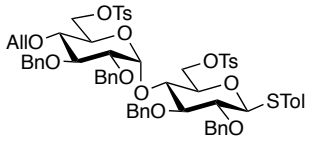
***p*-Toluyl 4-*O*-Allyl-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (2-27):** To an ice-cold solution of **2-26** (1.64 g, 1.275 mmol) in anhydrous THF–DMF (12 mL, 4:1) was added AllBr (0.43 mL, 5.1 mmol) followed by NaH (60% dispersion in mineral oil, 77 mg, 1.913 mmol). The reaction mixture was heated to room temperature and stirred for 20 h before another portion of AllBr (0.054 mL, 0.637 mmol) and NaH (60% dispersion in mineral oil, 26 mg, 0.637 mmol) were added. The reaction mixture was stirred for an additional 26 h. Methanol (1 mL) was added to quench the excess NaH and the mixture was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:19 EtOAc–hexane → 1:9 EtOAc–hexane) to afford

2-27 (1.45 g, 86%) as a colorless sticky solid. R_f 0.45 (1:9 EtOAc–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.59 (m, 10H), 7.42–7.20 (m, 32H), 6.98–6.96 (m, 2H), 5.88–5.80 (m, 1H), 5.64 (d, 1H, *J* = 3.7 Hz), 5.17–5.08 (m, 2H), 4.89–4.83 (m, 3H), 4.77–4.53 (m, 6H), 4.32–4.28 (m, 1H), 4.12–4.08 (m, 1H), 4.03–3.97 (m, 3H), 3.79 (t, 2H, *J* = 8.6 Hz), 3.60–3.49 (m, 6H), 3.40 (dd, 1H, *J* = 9.8, 3.7 Hz), 2.28 (s, 3H), 1.02 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.7, 138.1, 138.1, 137.0, 135.9, 135.8, 135.6, 135.5, 135.2, 133.8, 133.7, 133.7, 133.2, 131.5, 131.0, 129.6, 129.6, 129.5, 129.5, 129.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.0, 127.8, 127.6, 127.6, 127.6, 127.5, 127.5, 127.2, 126.8, 116.3, 96.1, 88.2, 86.6, 81.8, 81.0, 79.8, 79.6, 75.6, 75.2, 74.1, 73.8, 73.3, 73.0, 72.5, 64.6, 63.9, 62.5, 27.0, 26.8, 21.1, 19.4, 19.3. HRMS (ES-MS) *m/z* calcd for ($C_{82}H_{92}O_{10}SSi_2Na^+$) $[M+Na]^+$ 1347.5842, found 1347.5835.



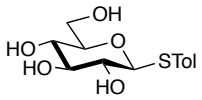
***p*-Toluyl 4-*O*-Allyl-2,3-di-*O*-benzyl-6-*O*-(1,1,1-trifluoro)ethyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-(1,1,1-trifluoro)ethyl-1-thio-β-D-glucopyranoside (2-30):** To a solution of **2-31** (11 mg, 0.0095 mmol) in anhydrous THF–DMF (0.1 mL, 1:1) was added freshly prepared CF_3CH_2ONa (mixture of CF_3CH_2OH (0.1 mL) and NaH (60% dispersion in mineral oil, 55 mg) in anhydrous THF–DMF (0.05 mL, 1:1)) at 0 ºC. The reaction mixture was warmed to room temperature and then another portion of CF_3CH_2OH (0.05 mL) and NaH (60% dispersion in mineral oil) (38 mg) in anhydrous DMF (0.1 mL)

were added after 4 h. The solution was stirred overnight and then CH_3OH (2 drops) was added. The mixture was concentrated and the resulting residue was purified by flash silica gel chromatography (1:4 EtOAc–hexane) to give **2-30** (6 mg) as a colourless sticky solid. The product **2-30** was contaminated with elimination products **2-30a** and **2-30b**. Data for **2-30**: R_f 0.52 (1:4 EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 2H), 7.31–7.25 (m, 22H), 7.22–7.11 (m, 14H), 5.94–5.84 (m, 1H), 5.32 (d, 1H, *J* = 3.6 Hz), 5.25–5.13 (m, 2H), 5.04 (d, 1H, *J* = 8.6 Hz), 4.89–4.84 (m, 2H), 4.81–4.72 (m, 7H), 4.63–4.46 (m, 5H), 4.36–4.29 (m, 2H), 4.13–3.62 (m, 15H), 3.53–3.41 (m, 3H), 2.36–2.35 (m, 4H). HRMS (ES-MS) *m/z* calcd for ($C_{54}H_{58}F_6O_{10}SNa^+$) $[M+Na]^+$ 1035.3547, found 1035.3538.



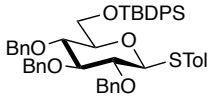
***p*-Toluyl 4-*O*-Allyl-2,3-di-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-tosyl-1-thio-β-D-glucopyranoside (2-31):** A mixture of **2-28** (153 mg, 0.18 mmol) and *p*-TsCl (120 mg, 0.63 mmol) in anhydrous pyridine (1 mL) was stirred for 18 h before being concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (2:3 EtOAc–hexane) to afford **2-31** (172 mg, 83%) as a white solid. R_f 0.34 (2:3 EtOAc–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.83 (m, 4H), 7.39–7.11 (m, 28H), 5.86–5.78 (m, 1H), 5.39 (d, 1H, *J* = 3.8 Hz), 5.23–5.13 (m, 2H), 4.84–4.74 (m, 5H), 4.59–4.51 (m, 3H), 4.44 (d, 1H, *J* = 11.8 Hz), 4.34–4.26 (m, 5H), 4.05–4.00

(m, 1H), 3.81 (t, 2H, *J* = 9.3 Hz), 3.75–3.69 (m, 2H), 3.53–3.50 (m, 1H), 3.42–3.33 (m, 3H), 2.44 (2x s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 144.8, 138.5, 138.4, 138.0, 137.7, 137.7, 134.4, 132.9, 132.8, 132.8, 130.0, 130.0, 129.9, 129.9, 129.7, 129.3, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.7, 127.7, 127.6, 127.6, 127.6, 127.3, 126.4, 117.3, 97.4, 87.5, 85.9, 81.4, 80.6, 78.8, 76.0, 75.4, 75.2, 74.3, 73.9, 73.7, 73.3, 69.9, 68.7, 68.6, 21.7, 21.2. HRMS (ES-MS) *m/z* calcd for ($C_{64}H_{68}O_{14}S_3Na^+$) $[M+Na]^+$ 1179.3663, found 1179.3649.



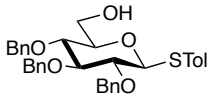
***p*-Tolyl 1-thio-β-D-glucopyranoside (2-33):** A mixture of β-D-glucose pentaacetate (10.0 g, 25.6 mmol), dried under reduced pressure in presence of P_2O_5 overnight, *p*-thiocresol (4.8 g, 38.4 mmol) and 4 Å molecular sieves (10.0 g) in anhydrous CH_2Cl_2 (150 mL) was cooled to 0 ºC. To this mixture was added BF_3•Et_2O (15.8 mL, 128 mmol). The reaction mixture was stirred for 18 h and then partitioned between saturated aq. $NaHCO_3$ (500 mL) and CH_2Cl_2 (100 mL). After stirring for 1 h, the organic layer was separated, washed with saturated aq. $NaHCO_3$ (200 mL), water (200 mL) and brine (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:3 EtOAc–hexane → 1:1 EtOAc–hexane) to afford *p*-toluyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **2-33a** (11.1 g, 96%) as a white solid. To a solution of **2-33a** (11.08 g, 24.4 mmol) in CH_3OH–CH_2Cl_2 (150 mL, 1:1) was added $NaOCH_3$ (658

mg, 12.2 mmol) and the mixture was stirred for 2 h. The solution was neutralized by adjusting pH to 7 using Amberlite® IR120 resin. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford **2-33** (7.03 g, 100%) as a white solid. R_f 0.20 (1:9 CH_3OH–CH_2Cl_2). The ^1H NMR and ^{13}C NMR data were consistent with that previously reported.[22]

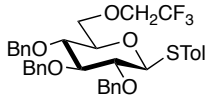


***p*-Tolyl 6-*O*-*tert*-butyldiphenylsilyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2-34):** To a solution of **2-33** (7.03 g, 24.5 mmol) in anhydrous pyridine, cooled to 0 ºC, was added TDBPSCl (12.6 mL, 49.0 mL) and the reaction mixture was stirred for 40 h. Methanol (3 mL) was then added and the mixture was concentered under reduced pressure. The product was purified by silica gel column chromatography (100% CH_2Cl_2 → 1:19 CH_3OH–CH_2Cl_2) to afford **2-34a** (13.50 g) as a yellow gum. Thioglycoside **2-34a** (13.5 g) and BnBr (13.1 mL, 110.25 mmol) were dissolved in anhydrous THF–DMF (180 mL, 4:1) and cooled to 0 ºC. To this mixture was added NaH (60% dispersion in mineral oil, 4.41 g, 110.25 mmol). The reaction mixture was warmed to room temperature and after 17 h of stirring, another portion of BnBr (2.2 mL, 18.37 mmol) and NaH (60% dispersion in mineral oil, 0.736 g, 18.37 mmol) were added. The reaction mixture was stirred for 21 h before CH_3OH (5 mL) was added to quench excess NaH. The mixture was concentrated under reduced pressure and partitioned between EtOAc (300 mL) and water (300 mL). The organic layer was separated, washed with water (2 x 300 mL), dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (1:9 EtOAc–hexane) to afford **2-34** (13.26 g, contained BnBr as impurity) as a yellow oil. R_f 0.30 (1:9 EtOAc–hexane). The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[15]

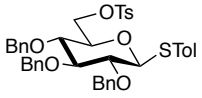


***p*-Tolyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2-35):** To a solution of **2-34** (19.23 g, 24 mmol) in anhydrous THF (150 mL) was added 1 M TBAF in THF (24 mL, 24 mmol). Another portion of 1 M TBAF in THF (18 mL, 18 mmol) was added to the mixture after 2 h. The reaction mixture was stirred for 5 h and then concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (2:3 EtOAc–hexane → 3:2 EtOAc–hexane) to afford **2-35** (11.0 g, 100%) as a white solid. R_f 0.33 (1:4 EtOAc–hexane). The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[23]



***p*-Tolyl 2,3,4-tri-*O*-benzyl-6-*O*-(1,1,1-trifluoro)ethyl-1-thio-β-D-glucopyranoside (2-37):** To a solution of **2-36** (65 mg, 0.09 mmol) and CF_3CH_2OH (13 µL, 0.18 mmol) in anhydrous THF–DMF (1 mL, 1:1), cooled to 0 ºC, was added NaH (60% dispersion in mineral oil, 7 mg, 0.18 mmol). The reaction was warmed to room temperature and, after 3 h, it was cooled again to 0

ºC. Next, additional CF_3CH_2OH (13 µL, 0.18 mmol) and NaH (60% dispersion in mineral oil, 7 mg, 0.18 mmol) were added, together with 15-crown-5 (178 µL, 0.9 mmol). After warming again to room temperature and stirring for 5 h, the solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (100% hexane → 1:4 EtOAc–hexane) to furnish **2-37** (14 mg, 25%) as a white solid. R_f 0.59 (1:4 EtOAc–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.47 (m, 2H), 7.45–7.43 (m, 2H), 7.38–7.28 (m, 13H), 7.15–7.13 (m, 2H), 4.95–4.93 (m, 2H), 4.39–4.37 (m, 2H), 4.79–4.78 (m, 1H), 4.65–4.61 (m, 2H), 3.93–3.71 (m, 5H), 3.61–3.58 (m, 1H), 3.51–3.46 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.1, 138.0, 137.9, 132.9, 129.8, 129.3, 128.5, 128.5, 128.5, 128.2, 128.0, 127.9, 127.9, 127.8, 127.8, 87.7, 86.7, 80.8, 79.1, 75.9, 75.5, 75.1, 71.1, 69.1, 21.1. ^{19}F NMR (500 MHz, $CDCl_3$) δ –74.4 ($C\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{36}H_{37}F_3O_5SNa^+$) $[M+Na]^+$ 661.2206, found 661.2198.



***p*-Tolyl 6-*O*-tosyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2-36):** To an ice cold solution of **2-35** (200 mg, 0.36 mmol) in anhydrous THF–DMF (2 mL, 1:1) was added NaH (60% dispersion in mineral oil) (21.6 mg, 0.54 mmol) followed by *p*-TsCl (103 mg, 0.54 mmol). The reaction mixture was heated to room temperature and stirred for 16 h before CH_3OH (0.1 mL) was added to quench excess of NaH. The solution was concentrated under reduced pressure

and the resulting residue was purified by flash silica gel chromatography (1:4 EtOAc–hexane) to provide **2-36** (65 mg, 31%) as a sticky solid. R_f 0.32 (1:3 EtOAc–hexane). The ^{1}H NMR and ^{13}C NMR data were consistent with that previously reported.[24]

2.5 Bibliography

(1) Jackson M.; Brennan P. J. *J. Biol. Chem.* **2009**, *284*, 1949.

(2) Lee Y. C.; Ballou C. E. *J. Biol. Chem.* **1964**, *239*, 3602.

(3) Meppen M.; Wang Y.; Cheon H.; Kishi Y. *J. Org. Chem.* **2007**, *72*, 1941.

(4) Cheon H. S.; Lian Y.; Kishi Y. *Org. Lett.* **2007**, *9*, 3327.

(5) (a) Cheon H. S.; Wang Y.; Ma J.; Kishi Y. *ChemBioChem* **2007**, *8*, 353. (b) Papaioannou N.; Cheon H. S.; Lian Y.; Kishi Y. *ChemBioChem* **2007**, *8*, 1775.

(6) Ojima I. *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell (Chichester, UK) **2009**, 4.

(7) Curran D. P. *Aldrichimica Acta* **2006**, *39*, 3.

(8) Curran D. P.; Hadida S.; He M. *J. Org. Chem.* **1997**, *62*, 6714.

(9) Zhang W.; Curran D. P. *Tetrahedron* **2006**, *62*, 11837.

(10) Gøgsig T. M.; Søbjerg L. S.; Lindhardt (neé Hansen) A. T.; Jensen K. L.; Skrydstrup T. *J. Org. Chem.* **2008**, *73*, 3404.

(11) Schrems O.; Oberhoffer H. M.; Luck W. A. P. *J. Phys. Chem.* **1984,** *88*, 4335.

(12) Burland P. A.; Osborn H. M. I.; Turkson A. *Bioorg. Med. Chem.* **2011**, *19*, 5679.

(13) A. Ichihara, M. Ubukata, and S. Sakamura, *Tetrahedron Lett*. **1977,** *18*, 3473.

(14) Miyabe H.; Nishiki A.; Naito T. *Chem. Pharm. Bull.* **2003**, *51*, 100.

(15) Lu G.; Wang P.; Liu Q.; Zhang Z.; Zhang W.; Li Y. *Chin. J. Chem.* **2009**, *27*, 2217.

(16) Bansal P. S.; Francis C. L.; Hart N. K.; Henderson S. A.; Oakenfull D.; Robertson A. D.; Simpson G. W. *Aust. J. Chem.* **1998**, *51*, 915.

(17) (a) Cox D. J.; Smith M. D.; Fairbanks A. J. *Org. Lett.* **2010**, *12*, 1452. (b) Sasaki E.; Lin C.; Lin K.; Liu H. *J. Am. Chem. Soc.* **2012**, *134*, 17432.

(18) Valente A.; Garcia M. H.; Marques F.; Miao Y.; Rousseau C.; Zinck P. *J. Inorg. Biochem.* **2013**, *127*, 79.

(19) Yan S.; Ding N.; Zhang W.; Wang P.; Li Y.; Li M. *J. Carbohydr. Chem.* **2012**, *31*, 571.

(20) Zhang J.; Zhang B.; Zhou J.; Li J.; Shi C.; Huang T.; Wang Z.; Tang J. *J. Carbohydr. Chem.* **2011**, *30*, 165.

(21) Joseph A. A.; Verma V. P.; Liu X. Y.; Wu C. H.; Dhurandhare V. M.; Wang C. C. *Eur. J. Org. Chem.* **2012**, *2012*, 744.

(22) Liu C. Y.; Chen H. L.; Ko C. M.; Chen C. T. *Tetrahedron* **2011**, *67*, 872.

(23) Yin Z. J.; Wang B.; Li Y. B.; Meng X. B.; Li Z. J. *Org. Lett.* **2010**, *12*, 536.

(24) Sun Y.; Zhang J.; Li C.; Guan H.; Yu G. *Carbohydr. Res.* **2012**, *355*, 6.

(25) Riss P. J.; Ferrari V.; Brichard L.; Burke P.; Smith R.; Aigbirhio F. I *Org. Biomol. Chem.* **2012**, *10*, 6980.

(26) Tsunoda T.; Kaku H. "*N*,*N*,*N*′,*N*′-Tetramethylazodicarbonxamide." *e-EROS Encyclopedia of Reagents for Organic Synthesis*, John Wiley & sons, Inc. **2003**.

(27) Humphries P. S.; Do Q. Q. T.; Wilhite D. M. *Beilstein J. Org. Chem.* **2006**, *2*, No. 21.

Chapter 3: Synthesis of glucose-containing oligosaccharides and their non-fluorinated analogues

3.1 Introduction

As was discussed in the previous chapter, given the difficulties we had with the synthesis of fluorous ether oligosaccharides, we changed our plans to look at different target molecules. Our goal was modified to synthesize fluorous amide oligosaccharides that might have similar physical properties (**Figure 3-1**). We envisioned that these fluorous amide analogues might be less challenging to synthesize, given the commercial availability of highly fluorinated carboxylic acid derivatives and the straightforward method for attachment to sugars (amidation reactions). We wanted to investigate the fluorous binding abilities of these fluorinated amide oligosaccharides and also wanted to compare them with the corresponding acyl (non-fluorinated) analogues. Therefore, a secondary goal was to synthesize non-fluorinated acyl derivatives of the targets.

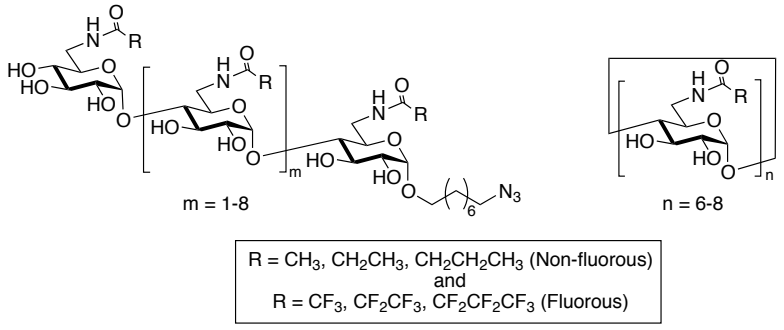


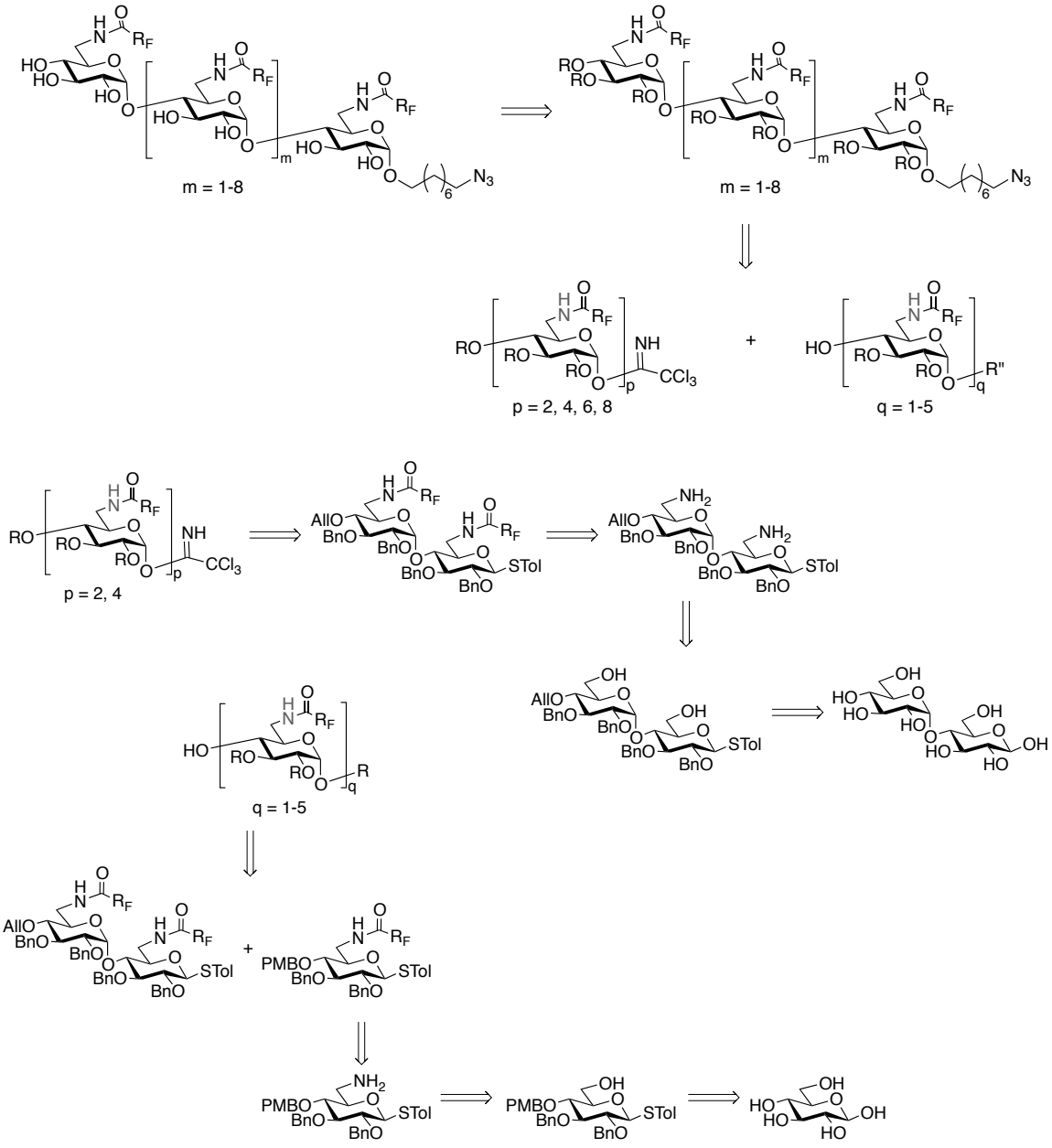
Figure 3-1. Targets for testing fluorous binding abilities of fluorous and non-fluorous oligosaccharides

First, we explored the synthetic route using mono- and disaccharides. Then, after the development of the route, it was further applied to larger *α*-(1→4) linked glucopyranosides. In this chapter we discuss the major challenges faced while

preparing fluorous amide oligosaccharides and how this was tackled by introducing a novel strategy to modify the primary face of cyclodextrins.

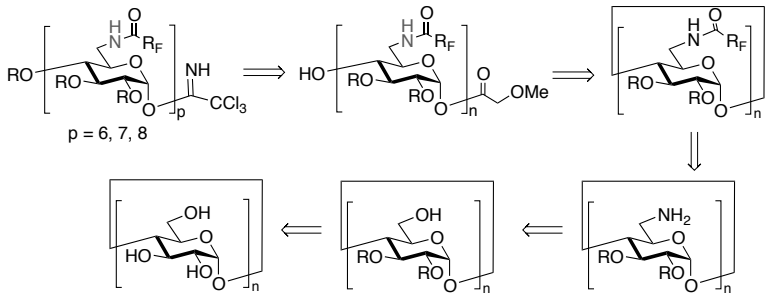
3.2 Retrosynthetic plan

Initially, we envisioned that the fluorinated glucose oligosaccharides could be synthesized from disaccharide (maltose) building blocks. We could couple two disaccharide units via glycosylation to afford *α*-(1→4) linked oligosaccharides. However, this would give only oligosaccharides containing an even number of glucopyranoside units. Therefore, we wanted to prepare monosaccharide building blocks to obtain oligosaccharides with an odd number of glucopyranoside units. The retrosynthetic approach is shown in **Scheme 3-1**.



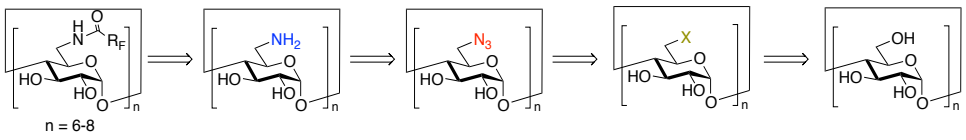
Scheme 3-1. Retrosynthetic analysis of target molecules from maltose and glucose building blocks

We also wanted to explore the synthesis of oligosaccharide targets from naturally occurring cyclic *α*-(1→4)-linked oligosaccharides, cyclodextrins. This approach could save time and reagents and would lead to both cyclic and acyclic oligosaccharide target molecules. It is possible to cleave cyclodextrins selectively to obtain linear *α*-(1→4)-linked glucopyranosides.[16]



Scheme 3-2. Retrosynthetic analysis of targets from cyclodextrins

Furthermore, we planned not to use any protecting groups to prepare our cyclic analogues through the approach outlined in **Scheme 3-3**. The reason behind this approach was, primarily, to synthesize fluorous amide oligosaccharides without the need for any deprotection step after the introduction of fluorous group. We envisioned that removing benzyl groups on these molecules would be difficult and the use of acyl protecting groups was also problematic, given that the fluoroamide bonds would likely be cleaved during de-*O*-acylation steps.

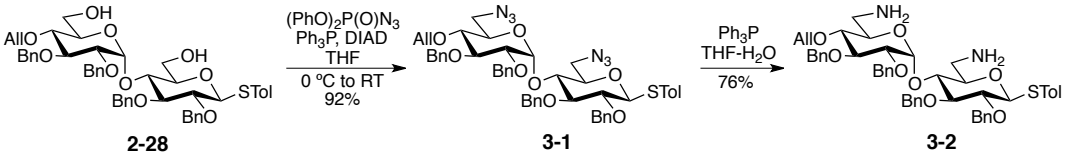


Scheme 3-3. Retrosynthetic analysis of targets from cyclodextrins without the use of protecting group chemistry

3.3 Results and discussion

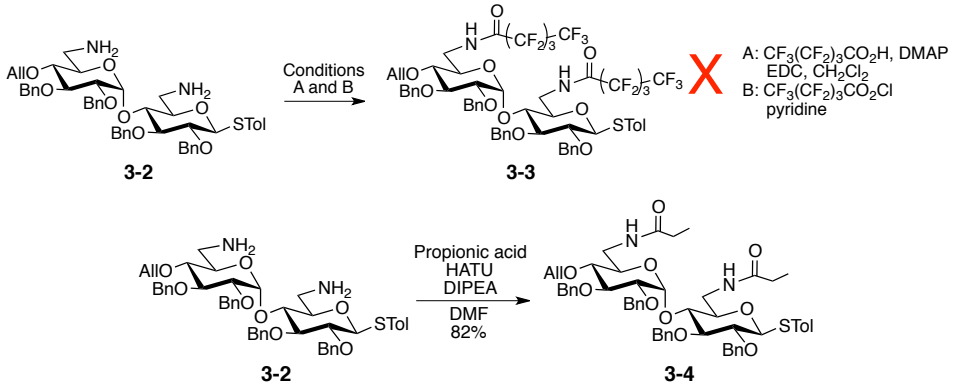
3.3.1 Experimentation on maltose, a disaccharide building block

As depicted in **Scheme 3-4**, we used the previously synthesized maltose building block **2-28** (see **Scheme 2-9**) as the starting material. Disaccharide **2-28** underwent Mitsunobu reaction with diphenylphosphoryl azide (DPPA) to form the diazido derivative **3-1** in 92% yield.[1] Compound **3-1** was then reduced to the corresponding diamine **3-2** using the Staudinger reaction, in 76% yield.[2] The amine was purified by SCX-2 cation exchange chromatography.[3]



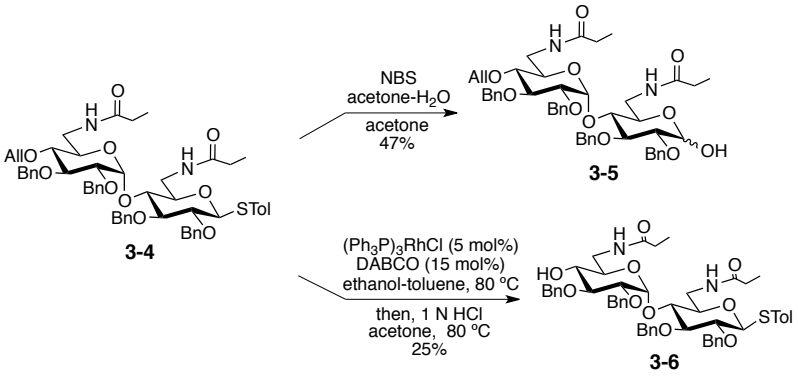
Scheme 3-4. Synthesis of maltose amine building block[1,2]

Acylation of amine **3-2** with fluorinated acid or acyl chlorides was unsuccessful (**Scheme 3-5**). TLC of the reaction mixture showed a highly polar spot that was unexpected for the product. However, amine **3-2** was successfully coupled with propionic acid using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as coupling reagent[4] along with Hunig's base in DMF to afford propanamide **3-4** in 82% yield.



Scheme 3-5. Preparation of non-fluorous amide via amide coupling[4]

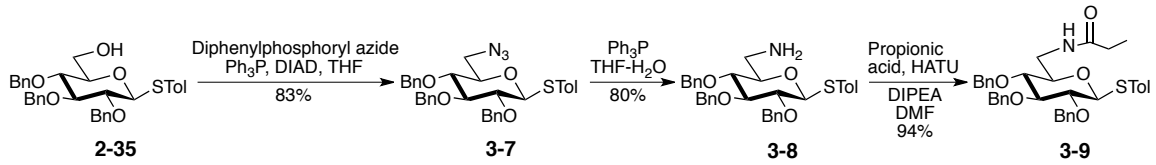
Having been successful in the preparation of **3-4**, our next goal was to prepare a disaccharide donor and a disaccharide acceptor, which could be coupled together to prepare larger structures (**Scheme 3-6**). We could prepare both the donor and acceptor from same building block **3-4**. The thiotolyl group can be cleaved and transformed into another donor that would be orthogonal to the thioglycoside donor. We planned to make an imidate donor. Treating propanamide **3-4** with *N*-bromosuccinimide (NBS) in acetone–water[5] provided reducing sugar **3-5** in a moderate 47% yield. Alternatively, cleavage of the allyl protecting group[6] provided acceptor **3-6** in a low yield of 25%. Having been successful in preparing acceptor and precursor to the imidate donor, we thought of testing our strategy on monosaccharide glucose unit. This was partially because of the lower yield obtained in the removal of allyl protecting group from **3-4**. We also wanted to test other orthogonal protecting group at 4–OH rather than allyl to improve overall yield.



Scheme 3-6. Preparation of maltose donor[5] and acceptor[6]

3.3.2 Preparation of glucose (monosaccharide) building blocks

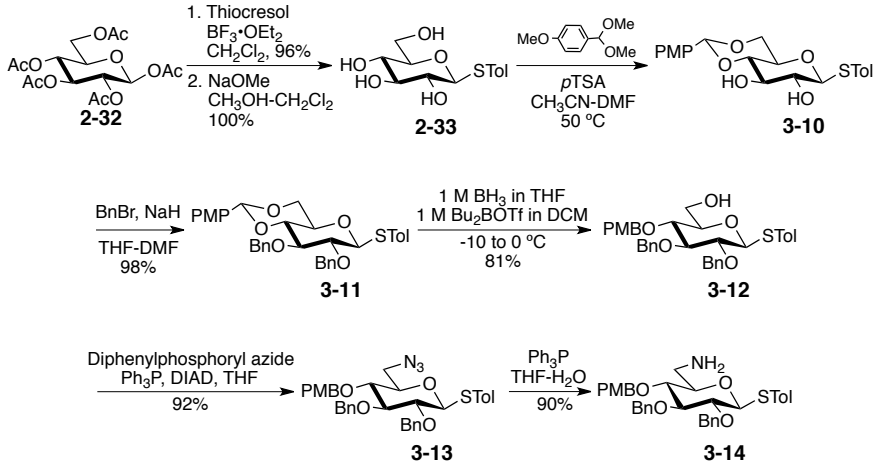
As we discussed in the previous section, to obtain targets with an odd number of carbohydrate moieties, we wanted to synthesize a monosaccharide glycosyl donor building block. To do this we started with the previously prepared glucose building block **2-35** (**Scheme 3-7;** see **Scheme 2-13** for the preparation of **2-35**). Monosaccharide **2-35** was converted to amine **3-8** by Mitsunobu reaction with DPPA[1] followed by Staudinger reduction.[2] Finally, propanamide **3-9** was prepared from amine **3-8** and propionic acid in 94% yield using standard HATU coupling[4] conditions. Glycosyl donor **3-9** could be used to extend the acyclic amide oligosaccharides by one glucopyranoside unit. But as there is no orthogonal protecting group at 4–OH position, we had to synthesize a monosaccharide unit with orthogonal protection at 4–OH. This will be discussed in next sections.



Scheme 3-7. Synthesis of propanamide derivative of glucose building block[2,4]

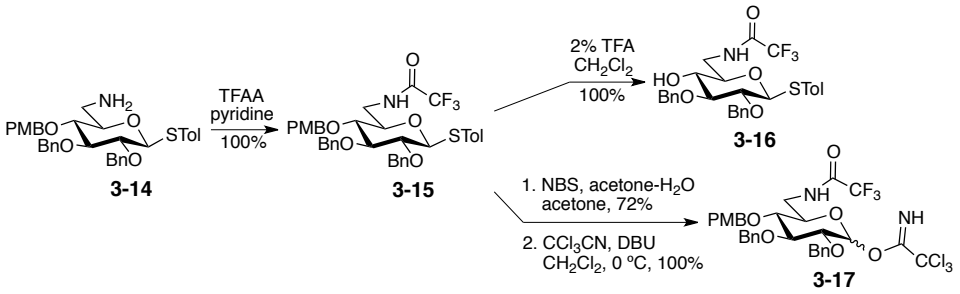
To prepare a suitable monosaccharide acceptor, it was necessary to orthogonally protect the 4-hydroxyl group of a glucose building block. Therefore as illustrated in Scheme **3-8**, β-D-glucopyranose pentaacetate (**2-32**, see **Scheme 2-13** for its preparation) underwent glycosidation with *p*-thiocresol and the resulting thioglycoside was deacetylated using Zemplén conditions furnishing **2-33**. The synthesis of the PMP benzylidene acetal **3-10** was achieved from **2-33** upon treatment with 4-methoxy-benzaldehyde dimethyl acetal in the presence of catalytic CSA.[8] Benzyl protection of the 2- and 3-hydroxyl groups of **3-10** provided **3-11** in 98% yield. Our goal was to selectively open the benzylidene ring to afford 6-hydroxy derivative **3-12** so that the primary alcohol group could be modified. This was achieved using 1 M BH_3 in THF and 1 M Bu_2BOTf in CH_2Cl_2 at low temperature.[9] This reaction yielded 98% of the expected product **3-12** from acetal **3-11**. The reaction also yielded a minor amount (<7% as determined by ^1H NMR spectroscopy) of the corresponding 4-hydroxy derivative. The regioselectivity of the selective deprotection was established by using 2-dimensional NMR spectroscopic techniques (HMBC and HSQC) and ^1H NMR spectroscopy. We determined the chemical shifts H-4, H-6a and H-6b for **3-11**

and compared with the chemical shifts of H-4, H-6a and H-6b for **3-12**. The monosaccharide amine building block **3-14** was synthesized in two steps from **3-12**. The primary alcohol group in **3-12** was converted to an azide using Mitsunobu reaction with DPPA in 92% yield.[1] Azide **3-13** was then reduced to amine **3-14** using triphenylphosphine and water in THF.[2]



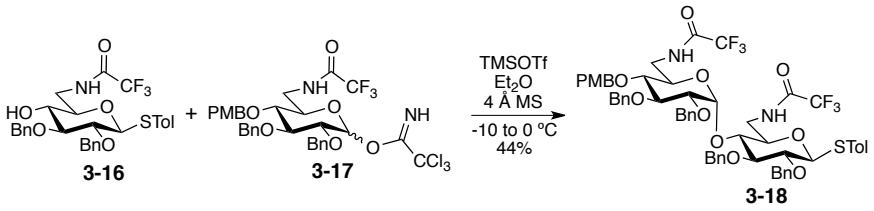
Scheme 3-8. Preparation of building block **3-14** from glucopyranose pentacetate

The first fluorinated amide **3-15** was derived from amine **3-14** using trifluoroacetic anhydride in anhydrous pyridine[10] in 100% yield (**Scheme 3-9**). Trifluoroacetamide **3-15** was then treated with 2% TFA in CH_2Cl_2 to afford acceptor **3-16** in which the PMB group was removed quantitatively.[11] Trichloroacetimidate donor **3-17** was synthesized from **3-15** by the hydrolysis of the anomeric sulfide group using NBS in acetone–water[5] followed by reaction with trichloroacetonitrile in the presence of DBU.



Scheme 3-9. Synthesis of donor[5] and acceptor[11] from trifluoroamide derivative **3-15**

With the appropriate donor and acceptor in hand, glycosylation of acceptor **3-16** with donor **3-17** (**Scheme 3-10**) using trimethylsilyltriflate[12] as the promoter furnished disaccharide **3-18** in modest (44%) yield, but with excellent α-selectivity.



Scheme 3-10. Glycosylation[12] between donor **3-17** and acceptor **3-16**

Having established a synthetic route to prepare fluorous amide derivatives and successfully coupled them to get a higher oligosaccharide, we wanted test our synthetic route on larger *α*-(1→4) linked glucopyranosides. Naturally available *α*-(1→4)-linked glucopyranosides, such as the cyclodextrins, were ideal for this purpose. Importantly, these cyclic moieties can be opened cleanly to afford

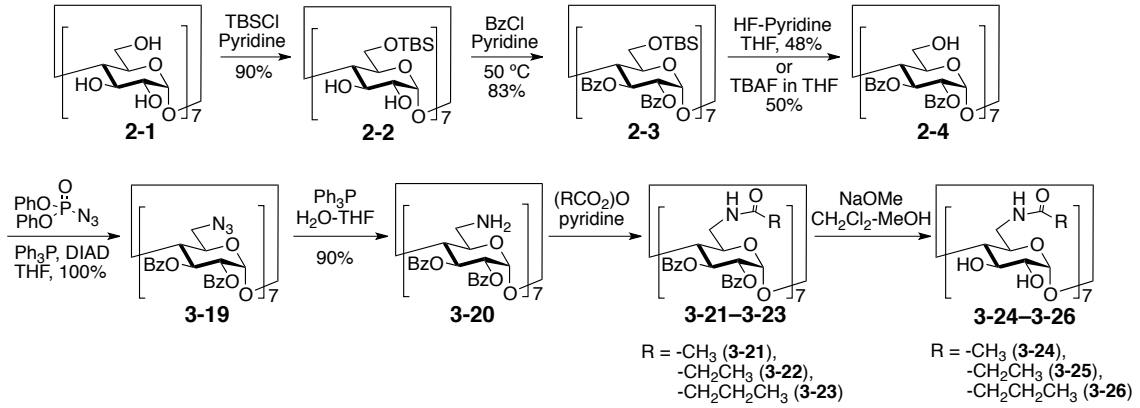
acyclic derivatives.[16] This would allow us to obtain higher oligosaccharides with ease and without the often low yielding and challenging glycosylation reactions.

3.3.3 Chemistry of cyclodextrins

3.3.3.1 Preparation of β-cyclodextrin analogues using protecting groups

As we discussed in the previous section, with the promising results obtained on simpler monosaccharides and in the preparation of an *α*-(1→4)-linked glucopyranose disaccharide derivative, we further investigated this approach on β-cyclodextrin, a cyclic oligosaccharide composed of seven *α*-(1→4)-linked glucopyranoside moieties. As outlined below, we could successfully synthesize amide derivatives of β-cyclodextrin, containing either fluorinated on non-fluorinated acyl groups.

With 2,3-dibenzyl β-cyclodextrin derivative **2-4**, already prepared (see **Scheme 2-1**), we started the amide formation chemistry. The primary hydroxyl groups of **2-4** was converted to azides[1], which were then was reduced to afford hepta-amine derivative **3-20** in 90% yield[2], as outlined in **Scheme 3-11**. Compound **3-20** was purified using SCX-2 cation exchange resin and was successfully coupled to several carboxylic acid anhydrides affording derivatives **3-21**–**3-23**. Removal of benzoyl groups using Zemplén conditions furnished target molecules **3-24–3-26**.



Scheme 3-11. Synthesis of non-fluorinated amide derivatives of β-cyclodextrin

Hence, the non-fluorinated acyl derivatives of the β-cyclodextrin targets were successfully synthesized. Next, we investigated the development of a novel route to synthesize fluorinated acyl derivatives of β-cyclodextrins, given concerns about protecting group compatibility (see next section) and a desire to minimize the number of steps and maximize the yield.

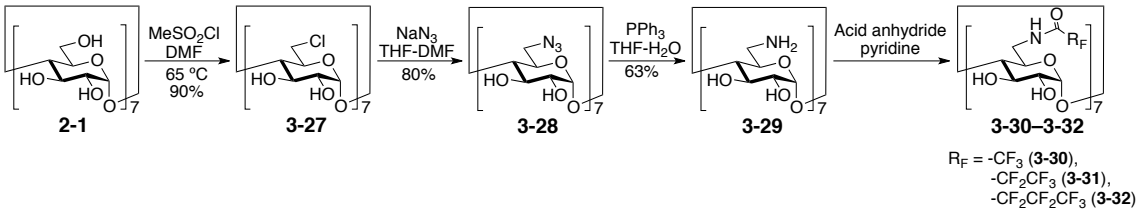
3.3.3.2 Preparation of fluorous β-cyclodextrin analogues without protecting groups

In the method described above to synthesize the non-fluorinated acyl derivatives, the last step was deacylation via the Zemplén method (sodium methoxide in methanol). We were concerned that the fluorinated amide derivatives, which are more susceptible to nucleophilic attack that their non-fluorinated counterparts, would not be stable under these conditions.[13] Therefore, we developed another route that does not require deprotection after the introduction of fluorous amide groups.

In developing such an approach, we found reports for the preparation of cyclodextrin derivatives without the use of protecting group manipulations.[14,20] In these reports it was claimed that they did not use any protecting group rather they just transformed primary hydroxyl group of cyclodextrins through a sequence of reactions to achieve target molecules. Based on this report, we developed a method that could selectively modify primary face of cyclodextrins without using any protecting groups. This route was applied to β-cyclodextrin and γ-cyclodextrin to prepare cyclic fluorinated and and non-fluorinated acyl derivatives. This method is environmentally friendly as there is no need of organic solvents and silica except for the purification of final product. The final products were purified by column chromatography using normal phase Iatrobeads or reversed phase C_{18} silica gel.

As depicted in **Scheme 3-12**, β-cyclodextrin (**2-1**) was heated with mesyl chloride in anhydrous DMF to afford heptakis(6-chloro-6-deoxy)cyclomaltoheptaose **3-27** in 90% yield.[20] Displacement of the chloro groups of **3-27** using sodium azide gave heptakis(6-azido-6-deoxy)cyclomaltoheptaose **3-28** in 80% yield.[14] Staudinger reaction conditions[2] were employed to reduce hepta-azide **3-28** to heptakis(6-amino-6-deoxy)cyclomaltoheptaose **3-29** in 63% yield. Fluorinated amides **3-30–3-32** were synthesized from **3-29** simply using various fluorous acid anhydrides in anhydrous pyridine.[10] Because of hydrophobic nature of these highly fluorinated amides, they could be precipitated from the reaction mixture by

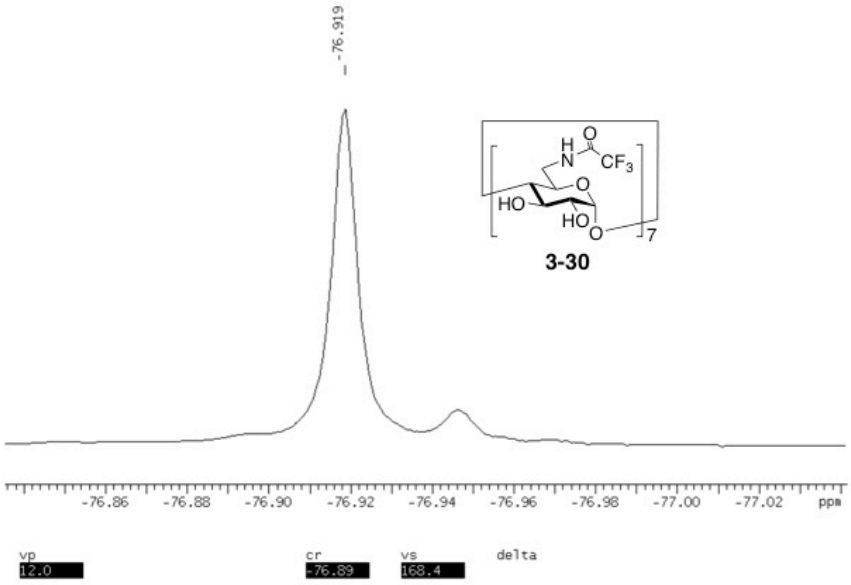
the addition of 1 N HCl. The residue was filtered and then purified by column chromatography using Iatrobeads.



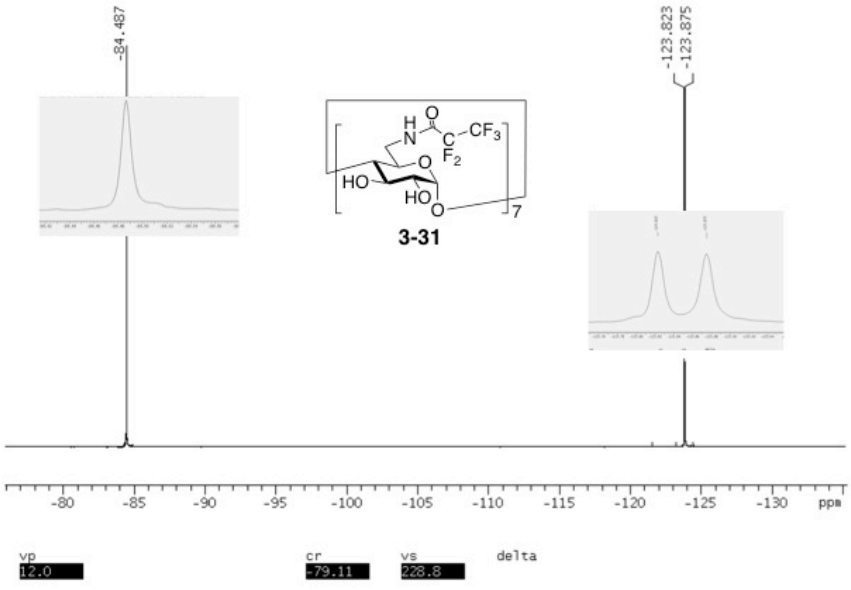
Scheme 3-12. Synthesis of fluorous amide derivatives of β-cyclodextrin[2,10,14,20]

3.3.3.3 Anomalous behavior of ^{19}F–^{19}F coupling in ^{19}F NMR spectra

When analyzing the ^{19}F NMR spectra of the products, the spin–spin coupling constants between neighboring fluorines in some of the derivatives were unexpected and surprising. In **3-30**, the CF_3 group appeared, as expected, as a singlet. For **3-31**, we expected CF_3 peak to be a triplet as a CH_3 group in a CH_3CH_2- group appears in an ^1H NMR spectrum. Both ^1H and ^{19}F are spin = ½ nuclei. But, to our surprise, the CF_3 appeared as a singlet and the signal for the CF_2 was a doublet. In case of **3-32**, which contains a $CF_3CF_2CF_2$ group, a higher analogue, couplings were observed partially. The CF_2 group near to the carbonyl centre was still a singlet but the other CF_2 group appeared as a quartet and the CF_3 group appeared as a triplet (see **Figure 3-2**).


-76.919
-76.86
-76.88
-76.90
-76.92
-76.94
-76.96
-76.98
-77.00
-77.02
ppm
vp
12.0
cr
-76.89
vs
168.4
delta

3-30


-84.487
-123.823
-123.875
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
ppm
vp
12.0
cr
-79.11
vs
228.8
delta

3-31

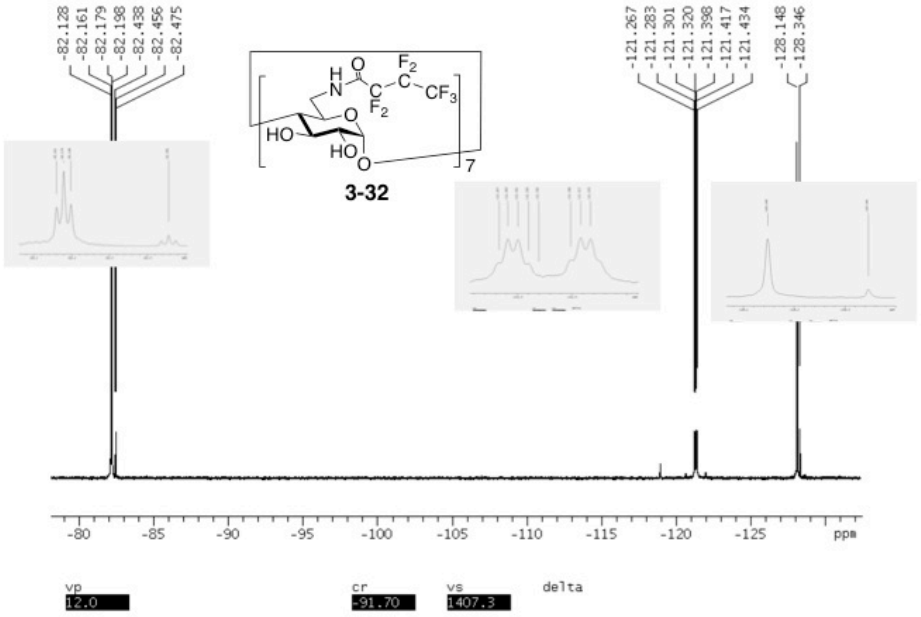


Figure 3-2. ^{19}F NMR spectra of fluorinated β-cyclodextrin analogues

To determine is this was caused by the chirality, we measured the ^{19}F NMR spectra for commercially available perfluorinated propionic, butyric and pentenoic acids as shown in **Figure 3-3**. This investigation revealed that as the chain length and number of fluorines increase, couplings start to appear and become even more complex than expected.

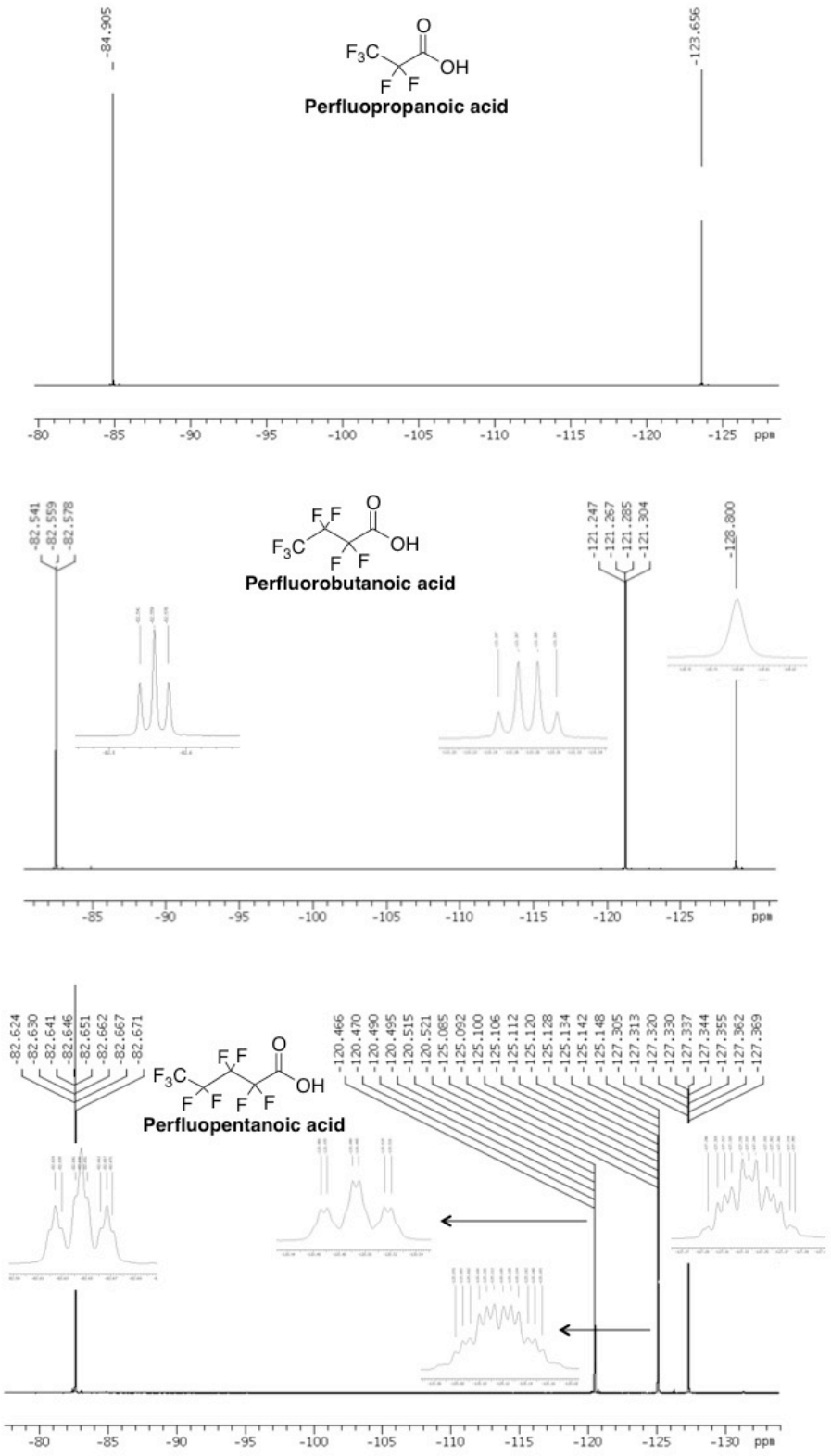


Figure 3-3. ^{19}F NMR spectra of perfluorinated carboxylic acids

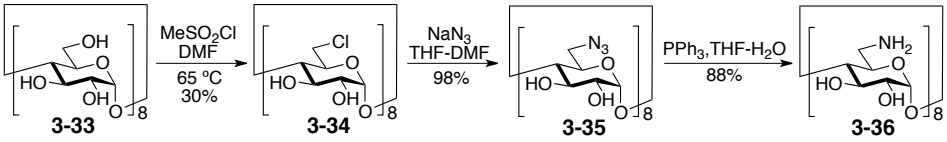
After a detailed search of the literature, and discussions with Dr. Ryan McKay in the University of Alberta NMR Spectroscopy laboratory, it was found to be a known phenomenon[15] for fluorinated compounds. Although the cause is unknown it may arise from the combination of the high electronegativity and small size of the fluorine atom.[7]

Ellis and coworkers[21] have studied ^{19}F NMR of perfluorocarboxylic acids to correlate their conformational and structural properties. The chemical shift, δ, for the terminal CF_3 and CF_2 adjacent to the carboxylic functionality changes rather drastically for up to C4 acids. However the changes in the same are less for the C5 or higher analogues. This is possibly due to higher degree of separation by $-CF_2-$ groups in longer chains. They have also mentioned that in shorter analogues (C4 or lower) have rigid zigzag structures but longer analogues (C5 or higher) tend to adopt partial helical conformations. These conformational features result in non-equivalence of the two fluorines on some of the CF_2 groups, which complicate the splitting patterns of the signals.

3.3.3.4 Preparation of γ-cyclodextrin derivatives without protecting group chemistry

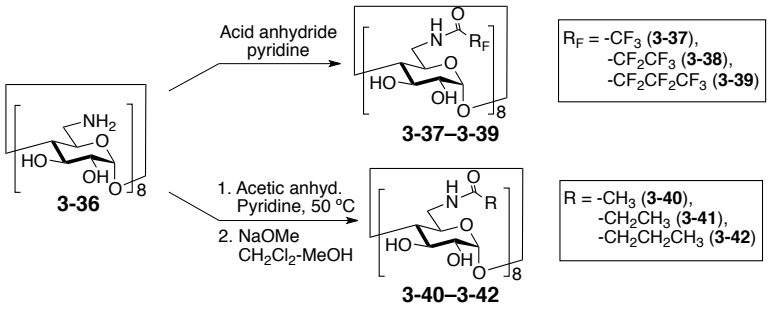
As outlined above, we were able to develop a route to the preparation of β-cyclodextrin-derivatives that did not involve the use of protecting groups. This chemistry was then applied to γ-cyclodextrin, which contains eight *α*-(1→4)-linked glucopyranose residues. Because of the simplicity of this approach, it was

used to prepare both the fluorinated and non-fluorinated derivatives. To begin, γ-cyclodextrin (**3-33**) was converted to octakis(6-chloro-6-deoxy)cyclomaltoctaose **3-34** in low yield of 30%.[20] Azide displacement on **3-34** afforded octakis(6-azido-6-deoxy)cyclomaltoctaose **3-35** in 98% yield.[14] The key intermediate, octakis(6-amino-6-deoxy)cyclomaltoctaose **3-36**, was achieved by Staudinger reaction[2] from azide **3-35** in 88% yield.



Scheme 3-13. Synthesis of amine derivative of γ-cyclodextrin[2,14,20]

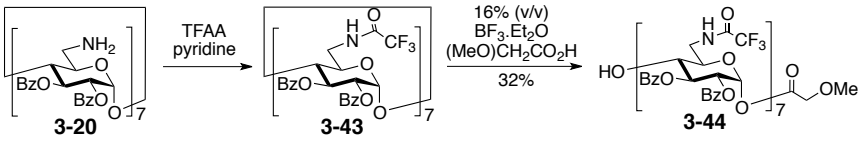
Fluorinated amide derivatives **3-37–3-39** were synthesized by treating amine **3-36** with the respective fluorous acid anhydrides in anhydrous pyridine.[10] The non-fluorinated γ-cyclodextrin analogues were obtained from **3-36** in two steps. Amine **3-36** was heated with acid anhydrides in anhydrous pyridine and then *O*-deacylation using Zemplén conditions afforded final compounds **3-40–3-42**. All these final products were purified by column chromatography using Iatrobeads or C_{18} silica gel.



Scheme 3-14. Synthesis of fluorinated[10] and non-fluorinated analogue amides of γ-cyclodextrin

3.3.3.5 Opening of β-cyclodextrin derivatives to acyclic derivative

Another goal of this project was to selectively open the cyclic structure of cyclodextrins to obtain acyclic fluorous amide oligosaccharides. The opening of cyclodextrin derivatives is well known[16] and has been recently investigated by the Kishi group.[17] According to a Kishi's work, per acylated cyclodextrins are the most suitable for selective opening, resulting in the cleavage of only one glycosidic bond. To explore this chemistry, the 6-amino-2,3-di-*O*-benzoyl-6-deoxy-β-cyclodextrin derivative **3-20** was treated with trifluoroacetic anhydride in anhydrous pyridine to prepare heptakis-trifluoroacetamide derivative **3-43**. This was then treated with $BF_3 \bullet Et_2O$ in methoxyacetic acid to cleave only one glycoside bond to yield acyclic derivative **3-44** in 32% yield. The lower yield can be explained by the fact that larger oligosaccharides must have cleaved to smaller fragments under the acidic condition of the reaction. This method needs to modified to obtain better yield and for more substrate scope. The ability to expand this to other substrate is important because under the basic conditions needed for deprotection of acyl groups, the fluorous amides would not be stable.



Scheme 3-15. Selective opening of a heptakis-trifluoroacetamide derivative of β-cyclodextrin to give a linear structure[16,17]

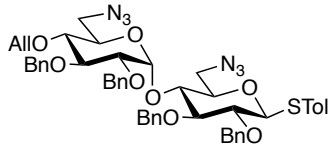
3.4 Conclusion

In summary, we developed approaches to prepare 12 cyclodextrin derivatives containing an amide or fluorinated amide-derivative at C-6 of each glycopyranose residue. Key to achieving this outcome was development of a route that did not require the use of protecting groups, and which was also devised such that silica and organic solvent wastes were minimized as there was no need of chromatography except for purification of target molecules at the last step. Opening of one β-cyclodextrin derivative to a linear heptasaccharide was successfully achieved. However, the opening chemistry needs to be optimized to improve the yield. In addition, the need for acyl protecting groups on the substrates to achieve good yields may hinder use of this approach in the future. Our initial studies based on simpler sugars such as glucose and maltose were applied on β-cyclodextrin initially before the development of protecting group free route. We synthesized 6 non-fluorinated amide derivatives of β-cyclodextrin with the approach we devised for mono and disaccharides. But as soon as we developed the protecting group free route, we did not follow the previously developed route.

3.5 Experimental details

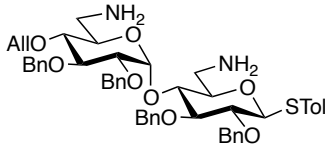
General methods for chemical synthesis: All reagents were purchased from commercial sources and were used without further purification unless noted. Reaction solvents were purified by successive passage through columns of alumina and copper under an argon atmosphere using a PURE SOLV (SPS-400-7) system from Innovative Technology, Inc. All reactions were performed under a positive pressure of argon at room temperature unless specified otherwise. Reactions were monitored by TLC on silica gel 60-F_{254} (0.25 nm, Silicycle, Quebec, Canada) and visualization of the reaction components was achieved using UV fluorescence (254 nm) and/or by charring with acidified anisaldehyde solution in ethanol or 5% H_2SO_4 in ethanol. Organic solvents were evaporated under reduced pressure at temperatures below 40 ºC unless specified otherwise. Reaction products were purified by column chromatography on silica gel (230–400 mesh, Silicycle, Quebec, Canada) or Iatrobeads 6RS-8060 (Iatron Laboratories Inc., Tokyo, Japan) if the eluent system contained greater than 10% methanol. Highly hydrophilic final products (**3-40** and **3-42**) were purified by column chromatography on C-18 silica gel (10% C_{18}; capped with TMS) (Toronto Research Chemicals Inc., Ontario, Canada). Amines were purified by cation exchange chromatography using SCX-2 cartridges (Silicycle, Quebec, Canada). SCX-2 cartridges were prewashed with 20 mL of 1:1 CH_3OH–CH_2Cl_2. The yields reported are after purification. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm at ambient temperature and are in units of degree•mL/(g•dm). ^{1}H NMR spectra were recorded at 500 or 600 MHz and

chemical shifts were referenced to $CHCl_3$ (7.26 ppm in $CDCl_3$), CHD_2OD (3.31 ppm, in CD_3OD) or HOD (4.79 ppm. ^{13}C NMR spectra were recorded at 125 MHz and chemical shifts were in reference to $CDCl_3$ (77.1 ppm) or CD_3OD (49.0 ppm). ^{19}F NMR spectra were recorded at 400 or 500 MHz. Assignments of the NMR spectra were based on one-dimensional experiments (APT, DEPT) and/or two-dimensional experiments (^1H–^1H COSY, HSQC and HMBC. Electrospray mass spectra (ES-MS) were recorded on an Agilent Technologies 6220 TOF. For ES-MS spectra, samples were dissolved in $CHCl_3$ or CH_3OH and NaCl was added.



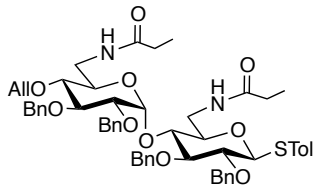
4-*O*-allyl-6-azido-6-deoxy-2,3-di-*O*-benzyl-α-D-glucopyranosyl-(1→4)-*p*-tolyl 6-azido-6-deoxy-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (3-1): A stirring solution of **2-28** (1.00 g, 1.178 mmol) and triphenylphosphine (0.926 g, 3.534 mmol) in anhydrous THF (12 mL) was cooled to 0 ºC using an ice-water bath and diphenylphosphoryl azide (0.612 mL, 2.827 mmol) was added followed by diisopropyl azodicarboxylate (DIAD) (0.684 mL, 3.534 mmol). The temperature was raised to RT as the ice in the ice-bath melted and then the reaction mixture was stirred for 17 h. The mixture was concentrated (with small amount of solvent left). The resulting crude material was purified by silica gel chromatography (100% hexane → 4:1 hexane–EtOAc) to give **3-1** (0.975 g, 92%) as a colorless sticky solid. R_f 0.53 (4:1 hexane–EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.53 (m, 2H), 7.45–7.41 (m, 1H), 7.33–7.15 (m, 21H), 5.93–5.90 (m, 1H), 5.58 (d, 1H,

J = 3.9 Hz), 5.26 (ddd, 1H, *J* = 17.1, 3.2, 1.5 Hz), 5.20 (ddd, 1H, *J* = 10.3, 2.8, 1.2 Hz), 4.93–4.83 (m, 4H), 4.77 (d, 1H, *J* = 10.8 Hz), 4.67–4.61 (m, 3H), 4.48 (d, 1H, *J* = 11.9 Hz), 4.35 (ddd, 1H, *J* = 12.3, 5.7, 1.3 Hz), 4.12 (ddd, 1H, *J* = 12.3, 6.1, 1.3 Hz), 3.98 (app t, 1H, *J* = 9.2 Hz), 3.84–3.79 (m, 2H), 3.71–3.44 (m, 8H), 3.37 (dd, 1H, *J* = 9.8, 0.7 Hz), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.4, 138.3, 137.8, 137.7, 134.4, 133.4, 130.1, 129.8, 128.9, 128.4, 128.4, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.3, 126.3, 117.5, 96.9, 87.8, 86.4, 81.5, 80.8, 79.2, 78.1, 77.7, 75.5, 75.3, 74.2, 73.7, 73.2, 71.1, 51.7, 51.4, 21.2. HRMS (ES-MS) *m/z* calcd for ($C_{50}H_{54}N_6O_8SNa^+$) $[M+Na]^+$ 921.3616, found 921.3605.



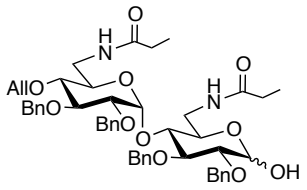
4-*O*-allyl-6-amino-6-deoxy-2,3-di-*O*-benzyl-α-D-glucopyranosyl-(1→4)-*p*-tolyl 6-amino-6-deoxy-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (3-2): To a solution of **3-1** (0.970 g, 1.097 mmol) in THF–H_2O (11 mL, 10:1) at RT was added triphenylphosphine (0.736 g, 2.805 mmol) and the mixture was stirred for 18.5 h. The reaction mixture was concentrated and the resulting residue was purified by silica gel chromatography (100% CH_2Cl_2 → 1:8 CH_3OH–CH_2Cl_2, containing 0.05% TEA) to afford **3-2** (0.688 g, 76%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.28–7.32 (m, 14H), 7.14–7.22 (m, 8H), 5.92–5.90 (m, 1H), 5.68 (d, 1H, *J* = Hz), 5.26 (ddd, 1H, *J* = Hz), 5.19 (dd, 1H, *J* = Hz), 4.94 (app t, 2H, *J* = Hz), 4.85 (d, 2H, *J* = Hz), 4.79 (d, 1H, *J* = Hz), 4.70 (d, 1H, *J*

= Hz), 4.64 (app t, 2H, *J* = Hz), 4.50 (d, 1H, *J* = Hz), 4.33 (dd, 1H, *J* = Hz), 4.12 (dd, 1H, *J* = Hz), 3.88–3.94 (m, 2H), 3.86–3.84 (m, 1H), 3.67 (ddd, 1H, *J* = Hz), 3.55 (app t, 1H, *J* = Hz), 3.42–3.47 (m, 2H), 3.25–3.23 (m, 2H), 3.12 (dd, 1H, *J* = Hz), 2.94 (dd, 1H, *J* = Hz), 2.85 (dd, 1H, *J* = Hz), 1.85–2.00 (br s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.6, 138.0, 137.9, 137.8, 134.7, 132.7, 129.8, 129.5, 128.4, 128.4, 128.3, 128.3, 128.3, 127.9, 127.8, 127.6, 127.5, 127.2, 126.3, 117.5, 96.7, 87.7, 86.9, 81.8, 81.5, 79.5, 79.3, 79.1, 75.5, 75.3, 74.1, 73.6, 72.7, 72.3, 43.2, 42.6, 27.0, 21.2. HRMS (ES-MS) *m/z* calcd for ($C_{50}H_{58}N_2O_8SNa^+$) $[M+Na]^+$ 869.38, found 869.38.



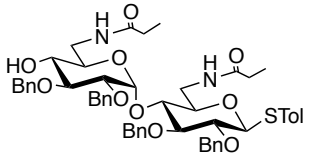
4-*O*-allyl-6-deoxy-2,3-di-*O*-benzyl-6-propanamido-α-D-glucopyranosyl-(1→4)-*p*-tolyl 6-deoxy-2,3-di-*O*-benzyl-6-propanamido-1-thio-β-D-glucopyranoside (3-4): To a stirring mixture of **3-2** (487 mg, 0.575 mmol), DIPEA (1.0 mL, 5.750 mmol) and propionic acid (129 μL, 1.725 mmol) in anhydrous DMF (2.7 mL) was added HATU (875 mg, 2.3 mmol). The reaction mixture was stirred for 1.5 h at RT and then partitioned between EtOAc (25 mL) and H_2O (50 mL). The organic layer was separated and further washed with water (50 mL) and saturated brine solution (50 mL) and then dried over anhydrous sodium sulfate. The organic layer was concentrated and the resulting residue purified by column chromatography (100 hexane → 1:1 hexane–EtOAc)

to furnish **3-4** (453 mg, 82%) as a cream-coloured solid. R_f 0.22 (1:1 hexane–EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 7.47–7.45 (m, 2H), 7.33–7.10 (m, 22H), 5.97–5.92 (m, 1H), 5.70 (dd, 1H, *J* = 7.5, 2.4 Hz), 5.28 (dd, 1H, *J* = 17.2, 1.3 Hz), 5.18 (d, 1H, *J* = 10.5 Hz), 5.11 (d, 1H, *J* = 11.4 Hz), 4.94 (d, 1H, *J* = 3.5 Hz), 4.87 (d, 1H, *J* = 10.5 Hz), 4.81–4.67 (m, 5H), 4.61 (d, 1H, *J* = 12.3 Hz), 4.36–4.31 (m, 2H), 4.17 (dd, 1H, *J* = 12.1, 5.9 Hz), 3.89 (app t, 1H, *J* = 9.3 Hz), 3.83–3.73 (m, 3H), 3.53 (dd, 2H, *J* = 16.4, 8.7 Hz), 3.42–3.36 (m, 2H), 3.30 (ddd, 1H, *J* = 18.2, 9.1, 2.6 Hz), 3.12 (app t, 1H, *J* = 9.3 Hz), 3.00–2.95 (m, 1H), 2.39 (s, 3H), 2.19–2.04 (m, 4H), 1.15–1.10 (m, 6H). ^{13}C NMR (125 MHz, CD_3OD) δ 174.2, 173.9, 138.9, 138.5, 138.3, 138.2, 137.7, 134.6, 132.9, 129.9, 129.3, 128.4, 128.4, 128.3, 128.2, 128.2, 127.9, 127.9, 127.9, 127.7, 127.6, 127.2, 126.9, 117.4, 99.1, 87.0, 85.2, 81.4, 81.0, 81.0, 79.9, 79.6, 77.8, 77.5, 75.6, 75.4, 75.2, 74.1, 73.5, 71.7, 41.4, 40.5, 29.5, 29.3, 21.1, 10.1, 9.7. HRMS (ES-MS) *m/z* calcd for ($C_{56}H_{66}N_2O_{10}SNa^+$) $[M+Na]^+$ 981.4330, found 981.4309.

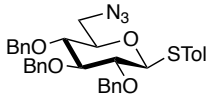


4-*O*-allyl-6-deoxy-2,3-di-*O*-benzyl-6-propanamido-α-D-glucopyranosyl-(1→4)-6-deoxy-2,3-di-*O*-benzyl-6-propanamido-D-glucopyranose (3-5): To a solution of **3-4** (100 mg, 0.104 mmol) in acetone (0.5 mL) was added acetone–water (1 mL, 9:1). To this mixture was added *N*-bromosuccinimide (37 mg, 0.208 mmol) in one portion. The reaction mixture was stirred for 16 h. The reaction was

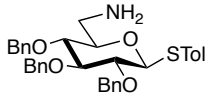
quenched by the addition of solid sodium bicarbonate (75 mg). The mixture was concentrated and the resulting residue was purified by column chromatography (100% CH_2Cl_2 → 1:19 CH_3OH–CH_2Cl_2) to furnish **3-5** (41 mg, 47%) as a colorless sticky solid. R_f 0.16 (4:1 EtOAc–hexane); HRMS (ES-MS) *m/z* calcd for ($C_{49}H_{60}N_2O_{11}Na^+$) $[M+Na]^+$ 875.41, found 875.41.



6-deoxy-2,3-di-*O*-benzyl-6-propanamido-α-D-glucopyranosyl-(1→4)-*p*-tolyl 6-deoxy-2,3-di-*O*-benzyl-6-propanamido-1-thio-β-D-glucopyranoside (3-6): To a solution of **3-4** (50 mg, 0.052 mmol) in EtOH–toluene (1.5 mL, 2:1) were added $(Ph_3P)_3RhCl$ (2.4 mg, 5 mol%) and DABCO (0.9 mg, 15 mol%). The mixture was heated at 80 ºC for 19 h. The solvent was evaporated under reduced pressure. The residue was stirred in 1 N HCl–acetone (3 mL, 1:9) at 80 ºC for 6 h. The reaction mixture was concentrated under reduced pressure. The product was purified by column chromatography (1:4 → 7:3 EtOAc–CH_2Cl_2) to afford **3-6** (11 mg, 25%) as a yellow sticky solid. R_f 0.17 (1:1 EtOAc–CH_2Cl_2); HRMS (ES-MS) *m/z* calcd for ($C_{53}H_{62}N_2O_{10}SNa^+$) $[M+Na]^+$ 941.4017, found 941.4004.

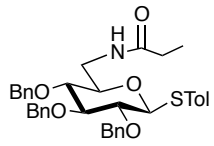


***p*-Tolyl 6-*O*-azido-6-deoxy-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (3-7):** A stirring solution of **2-35** (3.00 g, 5.39 mmol) and triphenylphosphine (2.12 g, 8.085 mmol) in anhydrous THF (35 mL) under argon was cooled to 0 ºC using an ice-water bath and diphenylphosphoryl azide (1.4 mL, 6.468 mmol) was added followed by DIAD (1.57 mL, 8.085 mmol). The reaction mixture was warmed to RT and then, after 27 hours, another portion of diphenylphosphoryl azide (0.23 mL, 1.078 mmol) was added. The reaction mixture was stirred for 44 h at RT. The mixture was concentrated (with small amount of solvent left) and the product was purified by silica gel chromatography (100% hexane → 1:9 EtOAc–hexane) to afford **3-7** (2.59 g, 83%) as a white solid. R_f 0.65 (1:4 EtOAc–hexane). The ^{1}H NMR, ^{13}C NMR and ES-MS data were consistent with previously reported data.[18]



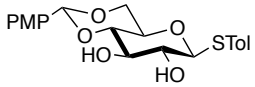
***p*-Tolyl 6-*O*-amino-6-deoxy-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (3-8):** To a solution of **3-7** (2.58 g, 4.435 mmol) in THF–H_2O (33 mL, 10:1) was added triphenylphosphine (1.51 g, 5.766 mmol) and stirred for 21 h. The mixture was concentrated under reduced pressure. The resulting crude product was purified by SCX-2 cation exchange chromatography. The SCX-2 cartridge was washed with CH_3OH–CH_2Cl_2 (50 mL, 1:1) and, thereafter, with 2 N NH_3 in

CH_3OH (50 mL). The ammonical fraction was concentrated under reduced pressure to furnish **3-8** (1.51 mg, 80%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.39 (m, 4H), 7.34–7.25 (m, 13H), 7.11–7.09 (m, 2H), 4.92–4.89 (m, 2H), 4.85–4.82 (m, 2H), 4.74 (d, 1H, *J* = 10.2 Hz), 4.62–4.59 (m, 2H), 3.69 (app t, 1H, *J* = 8.9 Hz), 3.46–3.37 (m, 2H), 3.25–3.21 (m, 1H), 3.04 (dd, 1H, *J* = 13.3, 2.7 Hz), 2.74 (dd, 1H, *J* = 13.4, 7.1 Hz), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.0, 138.0, 137.9, 132.8, 129.7, 129.6, 128.5, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 87.7, 86.8, 81.4, 78.9, 75.8, 75.5, 75.1, 43.3, 21.1.

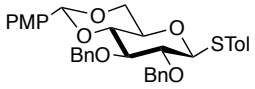


***p*-Tolyl 6-deoxy-6-propanamido-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (3-9):** To a stirring mixture of **3-8** (200 mg, 0.36 mmol), DIPEA (314 μL, 1.80 mmol) and propionic acid (40 μL, 0.54 mmol) in anhydrous DMF (1.7 mL), under an argon atmosphere, was added HATU (274 mg, 0.72 mmol). The reaction mixture was stirred for 1 h at RT and then partitioned between EtOAc (15 mL) and H_2O (30 mL). The organic layer was separated and further washed with H_2O (30 mL) and saturated brine solution (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and purified by column chromatography (1:1 hexane–EtOAc) to furnish **3-9** (207 mg, 94%) as a white solid. R_f 0.57 (1:1 EtOAc–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.43 (m, 4H), 7.40–7.30 (m, 13H), 7.18–7.16 (m, 2H), 5.64–5.62

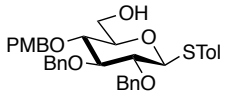
(m, 1H), 4.97–4.79 (m, 5H), 4.68–4.64 (m, 2H), 3.77–3.72 (m, 2H), 3.51–3.37 (m, 4H), 2.38 (s, 3H), 2.16–2.11 (m, 2H), 1.14 (t, 3H, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 138.3, 138.2, 137.9, 137.7, 133.1, 129.8, 129.2, 128.5, 128.5, 128.4, 128.2, 128.0, 128.0, 127.8, 87.4, 86.5, 81.2, 78.9, 77.6, 75.9, 75.5, 75.2, 40.1, 29.7, 21.1, 9.9. HRMS (ES-MS) *m/z* calcd for ($C_{37}H_{41}NO_5SNa^+$) $[M+Na]^+$ 634.2598, found 634.2585.



***p*-Tolyl 4,6-(4-methoxy)benzylidene-1-thio-β-D-glucopyranoside (3-10):** To a mixture of **2-33** (19.25 g, 51.2 mmol) in anhydrous CH_3CN–DMF (150 mL, 5:1) was added a mixture of *p*TSA (1.46 g, 7.68 mmol) and 4-(dimethoxymethyl)benzaldehyde (26.2 mL, 163.6 mmol) and the solution was heated at 50 ºC. Another portion of *p*TSA (0.49 g, 2.56 mmol) was added after 3 h. The solvent (~100 mL) was evaporated under reduced pressure and anhydrous CH_3CN (100 mL) was added. Another portion of 4-(dimethoxymethyl)benzaldehyde (17.5 mL, 102.4 mmol) was added to the mixture and the solution was stirred for 5 d at 50 ºC. The mixture was concentrated and purified by silica gel column chromatography (1:19 CH_3OH–CH_2Cl_2 → 1:4 CH_3OH–CH_2Cl_2) to give a yellow oil. The product was again purified by flash silica gel chromatography (100% CH_2Cl_2 → 1:19 CH_3OH–CH_2Cl_2) to furnish **3-10** (9.70 g, 47%) as yellow oil. R_f 0.61 (1:9 CH_3OH–CH_2Cl_2). The ^{1}H NMR, ^{13}C NMR and ES-MS data were consistent with previously reported data.[19]

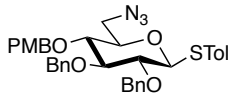


***p*-Tolyl 4,6-(4-methoxy)benzylidene-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (3-11):** To a solution of **3-10** (9.70 g, 23.5 mmol) in THF–DMF (90 mL, 1:1) cooled to 0 ºC, was added NaH (60% dispersion in mineral oil) (2.82 g, 70.5 mmol) in portions. The reaction mixture was heated to RT and stirred for 16 h and then CH_3OH (5 mL) was added to destroy excess NaH. The mixture was concentrated and partitioned between CH_2Cl_2 (200 mL) and H_2O (400 mL). The organic layer was separated, further washed with H_2O (400 mL) and saturated brine solution (400 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and the product was purified by column chromatography (100% hexane → 3:17 EtOAc–hexane) to furnish **3-11** (5.15 g) as a white solid. The ^{1}H NMR, ^{13}C NMR and ES-MS data were consistent with previously reported data.[19]



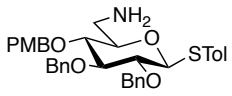
***p*-Tolyl 4-*O*-(4-methoxy)benzyl-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (3-12):** A round-bottomed flask containing **3-11** (3.00 g, 5.13 mmol), dried in presence of P_2O_5 overnight, was cooled to –10 ºC under an argon atmosphere and then 1M borane in THF (51.3 mL, 51.3 mmol) was added. The mixture was stirred for 15 min at –10 ºC before 1 M Bu_2BOTf in CH_2Cl_2 (10.3 mL, 10.3 mmol) was added and the solution was then warmed to 0 ºC gradually over a period of

10 min. The reaction mixture was stirred for 1 h at 0 ºC under argon. The solution was cooled to –10 ºC, treated with TEA (6.2 mL), quenched by the dropwise addition of CH_3OH (150 mL) and then stirred for 30 min at RT. The reaction mixture was concentrated under reduced pressure and co-evaporated with CH_3OH (2 x 50 mL) to remove of volatile impurities. The product was purified by flash column chromatography (100% hexane → 3:7 EtOAc–hexane) to furnish **3-12** (2.42 g, 81%) as a white solid. R_f 0.22 (1:4 EtOAc–hexane); $[\alpha]^{25}_D$ +1.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.42 (m, 4H, Ar–H), 7.39–7.33 (m, 8H, Ar–H), 7.24–7.22 (m, 2H, Ar–H), 7.16–7.15 (m, 2H, Ar–H), 6.89–6.87 (m, 2H, Ar–H), 4.97–4.90 (m, 3H, 3x Ar-C$\underline{H}_2$-O-), 4.80 (dd, 2H, *J* = 10.5, 7.7 Hz, 2x Ar-C$\underline{H}_2$-O-), 4.67 (d, 1H, *J* = 9.9 Hz, H-1), 4.61 (d, 1H, *J* = 10.6 Hz, Ar-C$\underline{H}_2$-O-), 3.91–3.86 (m, 1H, H-6b), 3.83 (s, 3H, -OC$\underline{H}_3$), 3.75–3.68 (m, 2H, H-4, H-6a), 3.57 (app t, 1H, *J* = 9.4 Hz, H-2), 3.49 (app t, 1H, *J* = 9.3 Hz, H-3), 3.39–3.36 (m, 1H, H-5), 2.38 (s, 3H, -C$\underline{H}_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 138.4, 138.1, 138.0, 132.7, 132.6, 130.0, 129.8, 129.8, 129.7, 129.5, 129.4, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 114.0 (24x Ar–C), 87.8 (C-1), 86.6 (C-4), 81.2 (C-3), 79.3 (C-5), 77.4 (C-2), 75.8, 75.5, 74.8 (3x Ar-$\underline{C}H_2$-O-), 62.3 (C-6), 55.3 (-O$\underline{C}H_3$), 21.1 (-$\underline{C}H_3$). HRMS (ES-MS) *m/z* calcd for ($C_{35}H_{38}O_6SNa^+$) $[M+Na]^+$ 609.2281, found 609.2271.



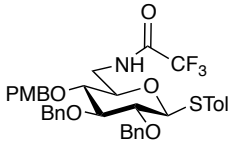
***p*-Tolyl 6-azido-4-*O*-(4-methoxy)benzyl-6-deoxy-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (3-13):** A mixture of **3-12** (360 mg, 0.614 mmol), Ph_3P (241.5 mg, 0.921 mmol) and diphenylphosphoryl azide (173 µL, 0.798 mmol) in anhydrous THF (4 mL) was cooled to 0 ºC and DIAD (178 µL, 0.921 mmol) was added. The ice bath was removed and solution was warmed to RT. Additional portions of diphenylphosphoryl azide (67 µL, 0.307 mmol), Ph_3P (80.5 mg, 0.307 mmol) and DIAD (59 µL, 0.307 mmol) were added after 17 h. The reaction mixture was then stirred for 44 h and concentrated under reduced pressure (with small amount of solvent left). The product was purified by flash column chromatography (100% hexane → 1:4 EtOAc–hexane) to yield **3-13** (342 g, 92%) as a white solid. R_f 0.54 (1:4 EtOAc–hexane); $[\alpha]^{25}_D$ +16.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H, Ar–H), 7.44–7.43 (m, 2H, Ar–H), 7.39–7.32 (m, 8H, Ar–H), 7.21–7.19 (m, 2H, Ar–H), 7.17–7.15 (m, 2H, Ar–H), 6.90–6.88 (m, 2H, Ar–H), 4.97–4.94 (m, 2x Ar-C$\underline{H}_2$-O-), 4.88 (d, 1H, *J* = 11.0 Hz, Ar-C$\underline{H}_2$-O-), 4.83–4.76 (m, 2x Ar-C$\underline{H}_2$-O-), 4.61 (d, 1H, *J* = 9.7 Hz, H-1), 4.56 (d, 1H, *J* = 10.6 Hz, Ar-C$\underline{H}_2$-O-), 3.83 (s, 3H, -OC$\underline{H}_3$), 3.70 (app t, 1H, *J* = 8.9 Hz, H-4), 3.56–3.48 (m, 3H, H-6a, H-6b, H-3), 3.45–3.42 (m, 1H, H-5), 3.35 (dd, 1H, *J* = 13.0, 5.5 Hz, H-2), 2.38 (s, 3H, -C$\underline{H}_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 138.3, 138.2, 138.0, 133.4, 129.9, 129.8, 129.7, 129.1, 128.5, 128.5, 128.2, 127.9, 127.8, 127.7, 114.0 (24x Ar–C), 88.0 (C-1), 86.7 (C-4), 78.1 (C-3), 77.8, 77.3 (2C, C-2, C-5), 75.8, 75.5, 74.9 (3x Ar-$\underline{C}H_2$-O-), 55.3 (-O$\underline{C}H_3$), 51.5 (C-6),

21.2 (-<u>C</u>H_3). HRMS (ES-MS) *m/z* calcd for ($C_{35}H_{37}N_3O_5SNa^+$) $[M+Na]^+$ 634.2346, found 634.2338.



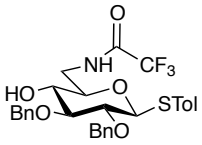
***p*-Tolyl 6-amino-4-*O*-(4-methoxy)benzyl-6-deoxy-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (3-14):** To a solution of **3-13** (1.77 g, 2.89 mmol) in tetrahydrofuran–water (22 mL, 10:1) was added Ph_3P (0.985 g, 3.757 mmol) at RT. Another portion of Ph_3P (152 mg, 0.578 mmol) was added after 16 h. The reaction mixture was stirred for 18.5 h and concentrated under reduced pressure. The product was purified using a SCX-2 cation exchange cartridge. Impurities were eluted using CH_3OH–CH_2Cl_2 (2 x 40 mL, 1:1). The amine product was eluted using 2 M NH_3 in CH_3OH (2 x 40 mL) to afford **3-14** (1.51 g, 90%) as a cream-coloured solid. R_f 0.32 (1:19 CH_3OH–CH_2Cl_2); $[\alpha]^{25}_D$ +16.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.43 (m, 4H, Ar–H), 7.39–7.31 (m, 8H, Ar–H), 7.23–7.22 (m, 2H, Ar–H), 7.16–7.14 (m, 2H, Ar–H), 6.89–6.87 (m, 2H, Ar–H), 4.96 –4.89 (m, 3x Ar-C<u>H</u>$_2$-O-), 4.82–4.78 (m, 2x Ar-C<u>H</u>$_2$-O-), 4.64 (d, 1H, *J* = 9.7 Hz, H-1), 4.58 (d, 1H, *J* = 10.6 Hz, Ar-C<u>H</u>$_2$-O-), 3.83 (s, 3H, -OC<u>H</u>$_3$), 3.72 (app t, 1H, *J* = 8.9 Hz, H-4), 3.48 (app t, 1H, *J* = 9.3 Hz, H-3), 3.42 (app t, 1H, *J* = 9.4 Hz, H-2), 3.27–3.23 (m, 1H, H-5), 3.07 (dd, 1H, *J* = 13.4, 2.6Hz, H-6b), 2.77 (dd, 1H, *J* = 13.4, 7.2 Hz, H-6a), 2.37 (s, 3H, -C<u>H</u>$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 138.5, 138.1, 138.0, 132.8, 130.1, 129.8, 129.7, 129.6, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 113.9 (24x Ar–C), 87.7 (C-1), 86.9 (C-4), 81.4 (C-3), 80.9 (C-5), 78.6 (C-2), 75.8, 75.5, 74.7 (3x Ar-<u>C</u>H$_2$-O-), 55.3 (-O<u>C</u>H$_3$), 43.3 (C-6),

21.1 (-$\underline{C}H_3$). HRMS (ES-MS) *m/z* calcd for ($C_{35}H_{39}NO_5SNa^+$) $[M+Na]^+$ 608.2447, found 608.2403.



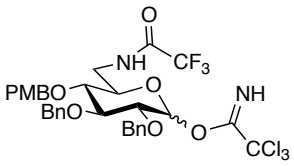
***p*-Tolyl 4-*O*-(4-methoxy)benzyl-6-deoxy-2,3-di-*O*-benzyl-6-trifluoroethamido-1-thio-β-D-glucopyranoside (3-15):** A solution of **3-14** (586 mg, 1.00 mmol) in anhydrous pyridine (11 mL) was cooled to 0 ºC using an ice bath and trifluoroacetic acid anhydride (278 μL, 2.00 mmol) was added. The ice bath was removed after 5 min and then the reaction mixture was stirred for 15 min. A small piece of ice was added to quench excess trifluoroacetic acid anhydride. The mixture was partitioned between EtOAc (40 mL) and H_2O (40 mL). The organic layer was separated, further washed with H_2O (40 mL), saturated brine solution (40 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated and the resulting residue was purified by flash column chromatography (1:1 EtOAc–hexane) to afford **3-15** (722 mg, 100%) as a yellow solid. R_f 0.45 (1:4 EtOAc–hexane); $[\alpha]^{25}_D$ -6.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.33 (m, 12H, Ar–H), 7.27–7.25 (m, 2H, Ar–H), 7.17–7.15 (m, 2H, Ar–H), 6.91–6.89 (m, 2H, Ar–H), 6.42 (br s, 1H, -C(O)N$\underline{H}$), 4.99–4.96 (m, 2x Ar-C$\underline{H}_2$-O-), 4.90 (d, 1H, *J* = 10.8 Hz, Ar-C$\underline{H}_2$-O-), 4.82–4.79 (m, 2x Ar-C$\underline{H}_2$-O-), 4.63 (d, 1H, *J* = 9.7 Hz, H-1), 4.55 (d, 1H, *J* = 10.4 Hz, Ar-C$\underline{H}_2$-O-), 3.83 (s, 3H, -OC$\underline{H}_3$), 3.79–3.71 (m, 2H, *J* = Hz, H-4, H-6b), 3.49 (app t, 1H, *J* = 9.3 Hz, H-3), 3.41–3.33 (m, 3H, H-2, H-5, H-6a), 2.38 (s, 3H, -C$\underline{H}_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6 (Ar–

C), 156.8 (C=O), 138.6, 138.1, 137.8, 133.2, 130.1, 129.9, 129.5, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 114.1 (23x Ar–C), 87.7 (C-1), 86.4 (C-4), 81.0 (C-3), 77.9, 76.5 (2C, C-2, C-5), 75.9, 75.6, 74.8 (3x Ar-$\underline{C}H_2$-O-), 55.3 (-O$\underline{C}H_3$), 40.6 (C-6), 21.1 (-$\underline{C}H_3$). ^{19}F NMR (500 MHz, $CDCl_3$) δ -75.85 (-C$\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{37}H_{38}F_3NO_6SNa^+$) $[M+Na]^+$ 704.2264, found 704.2254.

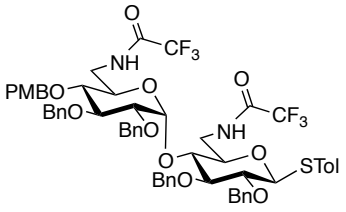


***p*-Tolyl 6-deoxy-2,3-di-*O*-benzyl-6-trifluoroethamido-1-thio-β-D-glucopyranoside (3-16):** To an ice-cold solution of **3-15** (330 mg, 0.484 mmol) in anhydrous CH_2Cl_2 (33 mL) was added drop wise trifluoroacetic acid (0.66 mL). The reaction mixture was heated to RT and stirred for 2 h. The mixture was partitioned between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ solution (aq.) (50 mL). The organic layer was separated, washed with saturated brine solution (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated and the resulting residue was purified by silica gel chromatography (100% hexane → 2:3 EtOAc–hexane) to afford **3-16** (270 mg, 100%) as a white solid. R_f 0.20 (1:4 EtOAc–hexane); $[\alpha]^{25}_D$ –46.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.33 (m, 12H), 7.16–7.14 (m, 2H), 6.68–6.66 (m, 1H), 4.98–4.92 (m, 2H), 4.80–4.77 (m, 2H), 4.64 (d, 1H, *J* = 9.7 Hz), 3.70–3.68 (m, 2H), 3.55–3.51 (m, 1H), 3.47–3.43 (m, 1H), 3.37–3.35 (m, 2H), 2.63 (br s, 1H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 138.6, 138.1, 137.8, 132.9, 129.9, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.1, 116.9, 114.0, 88.1, 85.3, 80.6, 75.7,

75.5, 71.2, 40.9, 21.1. HRMS (ES-MS) *m/z* calcd for ($C_{29}H_{30}F_3NO_5SNa^+$) $[M+Na]^+$ 584.1689, found 584.1677.

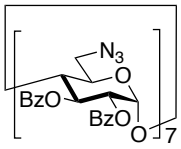


4-*O*-(4-methoxy)benzyl-6-deoxy-2,3-di-*O*-benzyl-6-trifluoroethamido-D-glucopyranosyl tricholoroacetimidate (3-17): Acetone–water (2.5 mL, 9:1) was added to a solution of **3-15** (311 mg, 0.456 mmol) in acetone (1.5 mL) and then *N*-bromosuccinimide (163 mg, 0.912 mmol) was added. The reaction mixture was stirred for 1 h being being quenched by adding solid $NaHCO_3$ (337 mg). The mixture was concentrated and the resulting residue was purified by flash silica gel column chromatography (100% hexane → 2:3 EtOAc–hexane). The product was found to contain impurities and was again purified by flash silica gel chromatography (100% hexane → 2:3 EtOAc–hexane, slow gradient) to afford **3-17a** (188 mg, 72%) as a white solid. An ice-cold solution of **3-17a** (43 mg, 0.0747 mmol) in anhydrous dichloromethane (0.7 mL) and trichloroacetonitrile (30 μL, 0.2988 mmol) was treated with DBU (0.5 μL, 0.5 mol%) (50 μL solution was added, 2 μL DBU in 200 μL CH_2Cl_2) and stirred for 1 h at 0 ºC. The reaction mixture was concentrated (not to complete dryness) and loaded onto a TEA prewashed (1:3 EtOAc–hexane, containing 0.1% TEA) silica gel column. The product was eluted using 1:3 EtOAc–hexane (containing 0.1% TEA) to afford **3-17** (59 mg, 100%) as a white sticky solid. R_f 0.26 (1:3 EtOAc–hexane, containing 0.1% TEA).



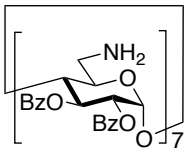
4-*O*-(4-methoxy)benzyl-6-deoxy-2,3-di-*O*-benzyl-6-trifluoroethamido-α-D-glucopyranosyl-(1→4)-*p*-tolyl 6-deoxy-2,3-di-*O*-benzyl-6-trifluoroethamido-1-thio-β-D-glucopyranoside (3-18): A mixture of **3-16** (33.5 mg, 0.0598 mmol), **3-17** (53 mg, 0.0747 mmol) and 4 Å molecular sieves in dry diethyl ether (1 mL) was cooled to –10 ºC. Trimethylsilyl triflate (1.1 μL, 10 mol%) was added to the mixture and heated up to 0 ºC. The reaction mixture was stirred for 45 minutes and TEA (2 μL) was added. The product was purified by column chromatography (100% hexane → 1:4 EtOAc–hexane) to afford **3-18** (35 mg, 44%) as a colorless sticky solid. R_f 0.44 (3:7 EtOAc–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.15 (m, 22H), 6.89–6.87 (m, 2H), 5.02–4.98 (m, 2H), 4.90–4.86 (m, 2H), 4.83–4.79 (m, 3H), 4.73–4.65 (m, 2H), 4.62–4.55 (m, 2H), 4.44 (d, 1H, *J* = 12.2 Hz), 4.29–4.24 (m, 1H), 3.95–3.92 (m, 1H), 3.85–3.81 (m, 5H), 3.74–3.71 (m, 1H), 3.62–3.58 (m, 1H), 3.53–3.48 (m, 2H), 3.45–3.42 (m, 1H), 3.67–3.33 (m, 1H), 3.23 (app t, 1H, *J* = 9.3 Hz), 3.15–3.10 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (Ar–C), 157.4, 157.3 (2x C=O), 138.7, 138.6, 138.2, 137.9, 137.6, 132.7, 130.1, 130.0, 129.9, 129.8, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.6, 127.4, 126.8, 126.8, 114.1, 114.0 (35x Ar–C), 98.9 (C-1'), 87.5 (C-1), 84.9, 81.4 (2C, C-4, C-4'), 80.8, 80.0 (2C, C-3, C-3'), 79.4, 78.4, 78.4 (3C, C-2', C-5, C-5'), 75.6, 75.4, 75.0, 74.8, 73.7 (5x Ar-CH_2-O-), 70.7 (C-2'), 55.3 (-

O<u>C</u>H_3), 41.7, 40.4 (2C, C-6, C-6'), 21.1 (-<u>C</u>H_3). ^{19}F NMR (500 MHz, $CDCl_3$) δ -75.62, -75.93 (2x <u>C</u>F_3). HRMS (ES-MS) *m/z* calcd for ($C_{59}H_{60}F_6N_2O_{11}SNa^+$) $[M+Na]^+$ 1141.3714, found 1141.3704.

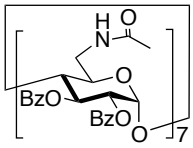


Heptakis(6-azido-6-deoxy-2,3-di-*O*-benzoyl)cyclomaltoheptaose (3-19): A stirring solution of **2-1** (667 mg, 0.257 mmol) and triphenylphosphine (708 mg, 2.6985 mmol) in anhydrous THF (6 mL) was cooled to 0 ºC and diphenylphosphoryl azide (0.47 mL, 2.1588 mmol) was added followed by DIAD (0.52 mL, 2.6985 mmol). The mixture thickened to form a cake and stopped stirring. The mixture was heated to RT, melted and started stirring again. The reaction mixture was stirred for 5 d at RT and then concentrated under reduced pressure (not to complete dryness) and purified by flash column chromatography (100% hexane → 1:1 EtOAc–hexane) to furnish **3-19** (804 mg, 100%) as a white solid. R_f 0.68 (1:1 EtOAc–hexane) $[\alpha]^{25}_D$ +119.7 (*c* 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.43 (m, 4H, Ar–H), 7.31–7.23 (m, 2H, Ar–H), 7.02 (t, 2H, *J* = Hz, Ar–H), 6.97 (t, 2H, *J* = Hz, Ar–H), 5.93 (dd, 1H, *J* = 10.3, 9.1 Hz, H-3), 5.50 (d, 1H, *J* = 3.8 Hz, H-1), 5.06 (dd, 1H, *J* = 10.5, 3.8 Hz, H-2), 4.47–4.44 (m, 1H, H-5), 4.10 (app t, 1H, *J* = 9.3 Hz, H-4), 4.04–4.01 (m, 1H, H-6a), 3.94 (dd, 1H, *J* = 13.5, 4.9 Hz, H-6b). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0 (C=O), 164.5 (C=O), 132.7, 132.4 , 129.9, 129.8, 129.8, 129.3, 128.3, 127.9, 127.7 (12x Ar–C), 97.1

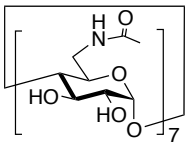
(C-1), 77.5 (C-4), 71.5, 71.3, 71.1 (3C, C-2, C-3, C-5), 51.9 (C-6). HRMS (ES-MS) *m/z* calcd for ($C_{140}H_{119}N_{21}O_{42}Na^+$) $[M+Na]^+$ 2788.7702, found 2788.7713.



Heptakis(6-amino-6-deoxy-2,3-di-*O*-benzoyl)cyclomaltoheptaose (3-20): To a solution of **3-19** (800 mg, ca. 0.25 mmol) in THF–H_2O (2.8 mL, 9:1) was added triphenylphosphine (688 mg, 2.625 mmol) and the reaction mixture was stirred for 2 d. The mixture was then concentrated and loaded onto a SCX-2 cation exchange cartridge. The cartridge was washed with CH_3OH–CH_2Cl_2 (30 mL, 1:1) and, thereafter, with 2 N NH_3 in CH_3OH (30 mL). The ammonical fraction was concentrated under reduced pressure to furnish **3-20** (610 mg, 94%) as cream-colored solid. $[\alpha]^{25}_D$ +89.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.50 (m, 4H, Ar-H), 7.28-7.25 (m, 1H, Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.02 (app t, 2H, *J* = 7.8 Hz, Ar-H), 6.96 (app t, 2H, *J* = 7.9 Hz, Ar-H), 6.01 (app t, 1H, *J* = 9.7 Hz, H-3), 5.55 (d, 1H, *J* = 3,7 Hz, H-1), 5.03 (dd, 1H, *J* = 10.4, 3.8 Hz, H-2), 4.51-4.48 (m, 1H, H-5), 4.17 (app t, 1H, *J* = 9.3 Hz, H-4), 3.43 (app d, 1H, *J* = 11.9 Hz, H-6a), 3.33 (dd, 1H, *J* = 13.6, 4.8 Hz, H-6b), 1.15-1.18 (br s, 2H, -NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1 (C=O), 164.5 (C=O), 132.6, 132.2, 132.2, 132.1, 129.9, 129.7, 129.7, 129.5, 128.5, 128.4, 127.6, 127.7 (12C, Ar–C), 96.9 (C-1), 77.5 (C-4), 72.3 (C-5), 71.9, 71.9 (2C, C-2, C-3), 42.8 (C-6). HRMS (ES-MS) *m/z* calcd for ($C_{140}H_{134}N_7O_{42}^+$) $[M+H]^+$ 2584.8559, found 2584.8528.

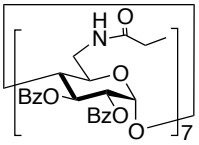


Heptakis(6-deoxy-2,3-di-*O*-benzoyl-6-ethanamido)cyclomaltoheptaose (3-21): To a stirring solution of **3-20** (100 mg, 0.0386 mmol) in anhydrous pyridine (1.3 mL) was added acetic anhydride (0.5 mL) and the mixture was heated at 50 ºC for 16 h. The mixture was cooled to RT and added to ice-cold 1 N HCl (20 mL). A precipitate formed, which was collected and washed with ice-cold water. The product was purified by column chromatography on Iatrobeads silica gel (100% CH_2Cl_2 → 1:4 CH_3OH–CH_2Cl_2) to afford **3-21** (24 mg, 22%) as a white solid. HRMS (ES-MS) *m/z* calcd for ($C_{154}H_{147}N_7O_{49}Na^+$) $[M+Na]^+$ 2900.91, found 2900.91.

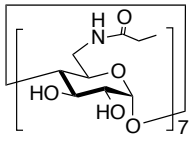


Heptakis(6-deoxy-6-ethanamido)cyclomaltoheptaose (3-24): To a solution of **3-21** (25 mg, 0.0087 mmol) in CH_3OH–CH_2Cl_2 (1 mL, 1:1) was added $NaOCH_3$ (6.5 mg, 0.1218 mmol) and stirred for 5 d at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (100% CH_2Cl_2 → 1:1 CH_3OH–CH_2Cl_2) to furnish **3-24** (13.5 mg, 100%) as a white solid. $[\alpha]^{25}_D$ +48.3 (*c* 0.20, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.93 (d, 1H, *J* = 3.6 Hz, H-1), 3.81–3.91 (m, 3H, H-3, H-5, H-6b), 3.51 (dd, 1H, *J* = 3.6, 9.8 Hz, H-2), 3.40 (dd, 1H, *J* = 7.2, 13.8 Hz, H-6a), 3.28 (app t, 1H, *J* =

9.1 Hz, H-4), 1.99 (s, 3H, C<u>H</u>$_3$, amide). ^{13}C NMR (125 MHz, CD_3OD) δ 172.2 (C=O, amide), 102.5 (C-1), 83.9 (C-4), 73.1, 72.8 (2C, C-2, C-3), 70.6 (C-5), 40.0 (C-6), 21.3 (<u>C</u>H$_3$, amide). HRMS (ES-MS) *m/z* calcd for ($C_{56}H_{91}N_7O_{35}Na^+$) $[M+Na]^+$ 1444.5448, found 1444.5449.

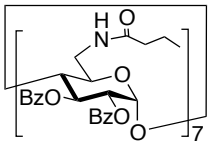


Heptakis(6-deoxy-2,3-di-*O*-benzoyl-6-propanamido)cyclomaltoheptaose (3-22): To a stirring solution of **3-20** (100 mg, 0.0386 mmol) in anhydrous pyridine (1.3 mL) was added propionic anhydride (0.5 mL) and heated at 50 ºC for 24 h. The mixture was cooled to RT and added to an ice cold 1 N HCl (20 mL). A precipitate formed that was collected via filtration and washed with ice-cold H_2O. The product was dissolved in CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **3-22** (106 mg, 92%) as an off-white solid. HRMS (ES-MS) *m/z* calcd for ($C_{161}H_{161}N_7O_{49}Na^+$) $[M+Na]^+$ 2999.02, found 2999.02.

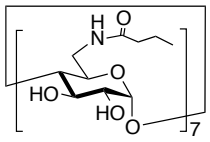


Heptakis(6-deoxy-6-propanamido)cyclomaltoheptaose (3-25): To a solution of **3-22** (100 mg, 0.0335 mmol) in CH_3OH-CH_2Cl_2 (2 mL, 1:1) was added $NaOCH_3$ (25 mg, 0.4690 mmol) and stirred for 6 d at RT. The reaction mixture

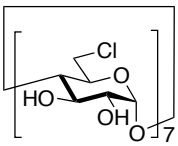
was concentrated under reduced pressure. The residue was purified by column chromatography (100% CH_2Cl_2 → 1:1 CH_3OH–CH_2Cl_2) to furnish **3-25** (23 mg, 45%) as a white solid. $[\alpha]^{25}_D$ +117.6 (*c* 0.20, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.92 (d, 1H, *J* = 3.6 Hz, H-1), 3.82-3.88 (m, 3H, H-3, H-5, H-6b), 3.52 (dd, 1H, *J* = 3.4, 9.7 Hz, H-2), 3.45 (dd, 1H, *J* = 7.3, 13.9 Hz, H-6a), 3.29 (app t, 1H, *J* = 9.3 Hz, H-4), 2.31-2.23 (m, 2H, C<u>H</u>$_2$, amide), 1.12 (t, 3H, *J* = 7.6 Hz, C<u>H</u>$_3$, amide). ^{13}C NMR (125 MHz, CD_3OD) δ 175.9 (C=O, amide), 102.5 (C-1), 83.9 (C-4), 73.0, 72.8 (2C, C-2, C-3), 70.6 (C-5), 39.9 (C-6), 28.7 (<u>C</u>H_2, amide), 9.2 (<u>C</u>H_3, amide). HRMS (ES-MS) *m/z* calcd for ($C_{63}H_{105}N_7O_{35}Na^+$) $[M+Na]^+$ 1542.6544, found 1542.6526.



Heptakis(6-deoxy-2,3-di-*O*-benzoyl-6-butanamido)cyclomaltoheptaose (3-23): To a stirring solution of **3-20** (80 mg, 0.0309 mmol) in anhydrous pyridine (1 mL) was added butyric anhydride (0.5 mL) and heated at 50 ºC for 3 d. The mixture was cooled to RT and added to an ice cold 1 N HCl (20 mL). The precipitate was collected via filtration and washed with ice-cold H_2O. The product was dissolved in CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **3-23** (67 mg, 71%) as a white solid. HRMS (ES-MS) *m/z* calcd for ($C_{168}H_{175}N_7O_{49}Na^+$) $[M+Na]^+$ 3097.13, found 3097.13.

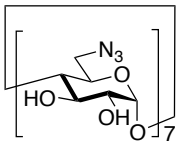


Heptakis(6-deoxy-6-butanamido)cyclomaltoheptaose (3-26): To a solution of **3-23** (67 mg, 0.0217 mmol) in CH_3OH-CH_2Cl_2 (1 mL, 1:1) was added $NaOCH_3$ (16 mg, 0.3038 mmol) and stirred for 6 d at room temperature (RT). The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (100% CH_2Cl_2 → 1:1 CH_3OH–CH_2Cl_2) to furnish **3-26** (32 mg, 91%) as a white solid. $[\alpha]^{25}_D$ +104.5 (*c* 0.25, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.95 (d, 1H, *J* = 3.5 Hz, H-1), 3.89–3.84 (m, 3H, H-3, H-5, H-6b), 3.52 (dd, 1H, *J* = 9.8, 3.5 Hz, H-2), 3.48 (dd, 1H, *J* = 14.3, 7.52 Hz, H-6a), 3.29 (app t, 1H, *J* = 9.4 Hz, H-4), 2.28-2.20 (m, 2H, C$\underline{H}_2$, amide), 1.69-1.62 (m, 2H, C$\underline{H}_2$, amide), 0.95 (t, 3H, *J* = Hz, CH_3, amide). ^{13}C NMR (125 MHz, CD_3OD) δ 174.9 (C=O, amide), 102.5 (C-1), 83.9 (C-4), 73.0, 72.7 (2C, C-2, C-3), 70.6 (C-5), 39.8 (C-6), 37.5 ($\underline{C}H_2$, amide), 19.1 ($\underline{C}H_2$, amide), 12.8 ($\underline{C}H_3$, amide). HRMS (ES-MS) *m/z* calcd for ($C_{70}H_{119}N_7O_{35}Na^+$) $[M+Na]^+$ 1640.7639, found 1640.7655.



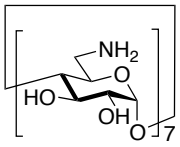
Heptakis(6-chloro-6-deoxy)cyclomaltoheptaose (3-27): To β-cyclodextrin (2.0 g, 1.76 mmol), dried under reduced pressure at 90 ºC overnight, in dry DMF (20 mL) was added methanesulfonyl chloride (1.44 mL, 18.48 mmol) and heated at 65 ºC. Another portion of methanesulfonyl chloride (0.48 mL, 6.16 mmol) was

added to the reaction after 4 d. The reaction mixture was stirred for 6 d. The reaction mixture was cooled to RT and CH_3OH (10 mL) was added to quench excess methanesulfonyl chloride. The mixture was concentrated under reduced pressure and re-dissolved in CH_3OH. pH of the mixture was adjusted between 9 to 10 by adding ca. 3 M $NaOCH_3$ in CH_3OH. The mixture was added to ice-water (400 mL) and precipitate formed. The precipitate was collected by filtration and washed with cold H_2O and CH_3OH. The product was dried under reduced pressure to afford **3-27** (1.99 g, 90%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.95 (d, 1H, J = 6.7 Hz, –OH), 5.85 (d, 1H, J = 2.2 Hz, –OH), 4.94 (d, 1H, J = 3.7 Hz, H-1), 4.06 (app d, 1H, J = 10.4 Hz, H-5), 3.85–3.76 (m, 2H, H-3, H-6b), 3.61 (app dt, 1H, J = Hz, H-6a), 3.39-3.34 (m, 2H, H-2, H-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ 102.5 (C-1), 84.1 (C-4), 72.9, 72.5 (2C, C-2, C-3), 71.7 (C-5), 45.5 (C-6). HRMS (ES-MS) *m/z* calcd for ($C_{42}H_{63}Cl_7O_{28}Na^+$) $[M+Na]^+$ 1283.1218, found 1283.1199.

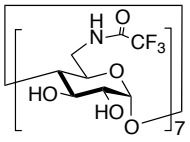


Heptakis(6-azido-6-deoxy)cyclomaltoheptaose (3-28): To a mixture of **3-27** (1.958 g, 1.549 mmol), KI (1.80 g, 10.843 mmol) and NaN_3 (2.147 g, 32.529 mmol) was added DMSO–H_2O (20 mL, 3:1) and heated at 80 ºC for 6 d. The mixture was added to ice-cold H_2O (400 mL) to crush out product. The precipitate was collected by filtration and washed with plenty of cold H_2O. The product was freeze dried to afford **3-28** (1.579 g, 78%) as a cream colored solid. ^{1}H NMR (500

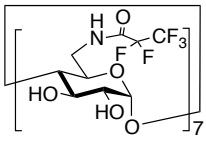
MHz, DMSO-d_6) δ 5.87 (d, 1H, J = 6.7 Hz, –OH), 5.73 (d, 1H, J = 2.1 Hz, –OH), 4.89 (d, 1H, J = 3.6 Hz, H-1), 3.69–3.77 (m, 2H, H-5, H-6b), 3.60–3.54 (m, 2H, H-3, H-6a), 3.38–3.28 (m, 2H, H-2, H-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ 102.5 (C-1), 83.6 (C-4), 73.0, 72.5 (2C, C-2, C-3), 70.8 (C-5), 51.8 (C-6). HRMS (ES-MS) *m/z* calcd for ($C_{42}H_{63}N_{21}O_{28}Na^+$) $[M+Na]^+$ 1332.4044, found 1332.4057.



Heptakis(6-amino-6-deoxy)cyclomaltoheptaose (3-29): To a mixture of **3-28** (241 mg, 0.184 mmol) in THF–H_2O (2 mL, 9:1) was added triphenylphosphine (506 mg, 1.932 mmol). The reaction mixture was stirred for 4 d. The mixture was concentrated and triturated with CH_2Cl_2 (3x 5 mL) and CH_3OH (3x 5 mL). The product was concentrated under reduced pressure to furnish **3-29** (130 mg, 63%) as a cream-colored solid. ^{1}H NMR (500 MHz, D_2O) δ 5.07 (d, 1H, J = 3.0 Hz, H-1), 3.97–3.90 (m, 1H, H-5), 3.88–3.82 (m, 1H, H-3), 3.62 (dd, 1H, J = 9.9, 3.4 Hz, H-2), 3.46 (app t, 1H, J = 9.2 Hz, H-4), 3.13–3.09 (m, 1H, H-6a), 2.93–2.87 (m, 1H, H-6b). HRMS (ES-MS) *m/z* calcd for ($C_{42}H_{78}N_7O_{28}^+$) $[M+H]^+$ 1128.4889, found 1128.4887.

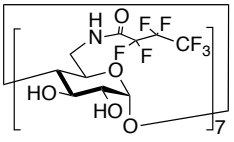


Heptakis(6-deoxy-6-trifluoroethanamido)cyclomaltoheptaose (3-30): A solution of **3-29** (20 mg, 0.0177 mmol) in anhydrous pyridine (0.6 mL) was cooled to 0 ºC and trifluoroacetic anhydride (35 μL, 0.2478 mmol) was added. The reaction mixture was heated to RT and stirred for 4 d. CH_3OH (1 mL) was added to quench excess trifluoroacetic anhydride and the mixture was concentrated under reduced pressure. The product was purified by column chromatography (100% CH_2Cl_2 → 2:3 CH_3OH–CH_2Cl_2) to afford **3-30** (8 mg, 25%) as a yellow solid. $[\alpha]^{25}_D$ +77.8 (*c* 0.70, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.02 (d, 1H, *J* = 3.6 Hz, H-1), 3.94–3.89 (m, 1H, H-5), 3.82–3.86 (m, 2H, H-3, H-6b), 3.61 (dd, 1H, *J* = 14.1, 7.1 Hz, H-6a), 3.51 (dd, 1H, *J* = 9.8, 3.5 Hz, H-2), 3.32–3.28 (m, 1H, H-4). ^{13}C NMR (125 MHz, CD_3OD) δ 158.1 (C=O), 116.1 ($\underline{C}F_3$, amide), 102.3 (C-1), 83.9 (C-4), 72.8 (C-3), 72.6 (C-2), 70.1 (C-5), 40.2 (C-6). ^{19}F NMR (500 MHz, CD_3OD) δ –76.92 ($C\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{56}H_{70}F_{21}N_7O_{35}Na^+$) $[M+Na]^+$ 1822.3500, found 1822.3475.



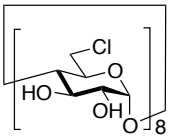
Heptakis(6-deoxy-6-pentafluoropropanamido)cyclomaltoheptaose (3-31): A solution of **3-29** (20 mg, 0.0177 mmol) in anhydrous pyridine (0.6 mL) was cooled to 0 ºC and pentafluoropropionic anhydride (48 μL, 0.2478 mmol) was added.

The reaction mixture was heated to RT and stirred for 4 d. CH_3OH (1 mL) was added to quench excess trifluoroacetic anhydride and the mixture was concentrated under reduced pressure. The residue was triturated with 1 N HCl and H_2O to remove excess pyridine and soluble salts. The product was purified by column chromatography (100% CH_2Cl_2 → 1:1 CH_3OH–CH_2Cl_2) to afford **3-31** (7.5 mg, 20%) as a yellow solid. $[\alpha]^{25}_D$ +61.2 (*c* 0.7, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.03 (d, 1H, *J* = 3.7 Hz), 3.94–3.90 (m, 1H, H-5), 3.88–3.84 (m, 2H, H-3, H-6b), 3.70 (dd, 1H, *J* = 14.1, 6.2 Hz, H-6a), 3.51 (dd, 1H, *J* = 9.7, 3.5 Hz, H-2), 3.31–3.28 (m, 1H, H-4). ^{13}C NMR (125 MHz, CD_3OD) δ 158.6 (C=O), 118.0 ($\underline{C}F_2$, amide), 106.9 ($\underline{C}F_3$, amide), 102.2 (C-1), 83.7 (C-4), 72.8 (C-3), 72.5 (C-2), 70.2 (C-5), 40.0 (C-6). ^{19}F NMR (500 MHz, CD_3OD) δ –84.49 ($C\underline{F}_3$), –123.85 ($C\underline{F}_2$). HRMS (ES-MS) *m/z* calcd for ($C_{63}H_{70}F_{35}N_7O_{35}Na^+$) $[M+Na]^+$ 2172.3246, found 2172.3225.



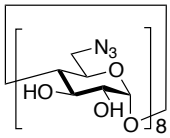
Heptakis(6-deoxy-6-heptaluorobutanamido)cyclomaltoheptaose (3-32): A solution of **3-29** (30 mg, 0.0266 mmol) in anhydrous pyridine (0.6 mL) was cooled to 0 ºC and heptafluorobutyric anhydride (91 μL, 0.3724 mmol) was added. The reaction mixture was heated to RT and stirred for 4 d. CH_3OH (1 mL) was added to quench excess trifluoroacetic anhydride and the mixture was concentrated under reduced pressure. The product was purified by column chromatography (100% CH_2Cl_2 → 1:1 CH_3OH–CH_2Cl_2) to afford **3-32** (6 mg, 10%) as orange

solid. $[\alpha]^{25}_{D}$ +48.3 (*c* 0.60, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 5.04 (d, 1H, *J* = 3.5 Hz, H-1), 3.96–3.91 (m, 1H, H-5), 3.88–3.84 (m, 2H, H-3, H-6b), 3.71 (dd, 1H, *J* = 14.1, 6.2 Hz, H-6a), 3.51 (dd, 1H, *J* = 9.9, 3.5 Hz, H-2), 3.31–3.28 (m, 1H, H-4). ^{13}C NMR (125 MHz, CD_3OD) δ 158.4 (C=O, amide), 117.5 ($\underline{C}F_3$, amide), 108.6 (2x $\underline{C}F_2$, amide), 102.2 (C-1), 83.6 (C-4), 72.8 (C-3), 72.5 (C-2), 70.2 (C-5), 40.1 (C-6). ^{19}F NMR (500 MHz, CD_3OD) δ -82.21 ($C\underline{F}_3$), -121.17 ($C\underline{F}_2$), -128.04 ($C\underline{F}_2$). HRMS (ES-MS) *m/z* calcd for ($C_{70}H_{70}F_{49}N_7O_{35}Na^+$) $[M+Na]^+$ 2522.3023, found 2522.3052.

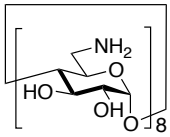


Octakis(6-chloro-6-deoxy)cyclomaltoctaose (3-34): To γ-cyclodextrin (1.0 g, 0.77 mmol), dried under reduced pressure at 85 ºC overnight, in dry DMF (9 mL) was added methanesulfonyl chloride (0.72 mL, 9.24 mmol) and heated at 70 ºC. Another portion of methanesulfonyl chloride (0.24 mL, 3.08 mmol) was added to the reaction mixture after 28.5 h. The mixture was stirred for 3 d. The reaction mixture was cooled to RT and CH_3OH (5 mL) was added to quench excess methanesulfonyl chloride. The mixture was concentrated under reduced pressure and re-dissolved in CH_3OH. pH of the mixture was adjusted between 9 to 10 by adding ca. 3 M $NaOCH_3$ in CH_3OH. The mixture was added to ice-H_2O (200 mL) and a precipitate formed. The precipitate was collected by filtration and washed with cold H_2O and CH_3OH. The product was dried under reduced pressure to

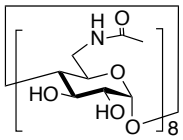
afford **3-34** (0.337 g, 30%) as a dirty white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.95 (d, 1H, J = 6.8 Hz, –OH), 5.90 (s, 1H, –OH), 4.97 (d, 1H, J = 3.8 Hz, H-1), 4.00 (d, 1H, J = 10.1 Hz, H-5), 3.81 (dd, 1H, J = 12.4, 7.5 Hz, H-6a), 3.58 (t, 1H, J = 9.3 Hz, H-2), 3.40-3.35 (m, 2H, H-4, H-6b). HRMS (ES-MS) *m/z* calcd for ($C_{48}H_{72}Cl_8O_{32}Na^+$) $[M+Na]^+$ 1463.1407, found 1463.1394.



Octakis(6-azido-6-deoxy)cyclomaltoctaose (3-35): To a mixture of **3-34** (330 mg, 0.228 mmol), TBAI (674 mg, 1.824 mmol) and NaN_3 (356 mg, 5.472 mmol) was added DMSO–H_2O (3 mL, 3:1) and heated at 80 ºC for 6 d. The mixture was added to ice-cold H_2O (200 mL) to crush out product. The precipitate was collected by filtration and washed with plenty of cold H_2O. The product was freeze dried to afford **3-35** (334 mg, 98%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.90 (d, 1H, J = 7.0 Hz, –OH), 5.85 (d, 1H, J = 2.4 Hz, –OH), 4.93 (d, 1H, J = 3.9 Hz, H-1), 3.76–3.71 (m, 2H, H-5, H-6b), 3.60–3.54 (m, 2H, H-3, H-6a), 3.40–3.32 (m, 2H, H-2, H-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ 102.5 (C-1), 83.1 (C-4), 72.9, 72.7 (2C, C-2, C-3), 70.9 (C-5), 51.6 (C-6). HRMS (ES-MS) *m/z* calcd for ($C_{48}H_{72}N_{24}O_{32}Na^+$) $[M+Na]^+$ 1519.50, found 1519.50.

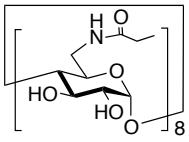


Octakis(6-amino-6-deoxy)cyclomaltoctaose (3-36): To a mixture of **3-35** (320 mg, 0.2137 mmol) in THF–H_2O (2.3 mL, 9:1) was added triphenylphosphine (673 mg, 2.5644 mmol). The reaction mixture was stirred for 5 d. The mixture was concentrated and triturated with EtOH (3x 5 mL), CH_3OH (3x 5 mL) and CH_2Cl_2 (3x 5 mL) The product was concentrated under reduced pressure to furnish **3-36** (242 mg, 88%) as a white solid. ^{1}H NMR (500 MHz, D_2O) δ 5.13 (br s, 1H, H-1), 3.87–3.83 (m, 2H, H-5, H-3), 3.66 (dd, 1H, *J* = 9.8, 3.6 Hz, H-2), 3.50 (t, 1H, *J* = 8.5 Hz, H-4), 3.16–2.90 (m, 2H, H-6a, H-6b). ^{13}C NMR (125 MHz, D_2O) δ 101.4 (C-1), 81.8 (C-4), 72.7, 72.2 (2C, C-2, C-3), 71.5 (C-5), 40.9 (C-6).



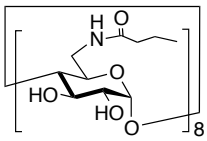
Octakis(6-deoxy-6-ethanamido)cyclomaltoctaose (3-40): To a solution of **3-36** (30 mg, 0.023 mmol), dried overnight under reduced pressure in presence of P_2O_5, in anhydrous pyridine (0.5 mL) was added acetic anhydride (0.25 mL) under an argon atmosphere and heated at 50 ºC for 5 d. The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and 1 N HCl (20 mL). The organic layer was separated and further washed with H_2O (20 mL), saturated $NaHCO_3$ solution (aq.) (20 mL) and saturated brine solution (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product

(37 mg, ca. 0.016 mmol) was dissolved in CH_3OH–CH_2Cl_2 (0.8 mL, 1:1) was added $NaOCH_3$ (21 mg, 0.384 mmol) and stirred for 5 d at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase column chromatography (1:4 → 1:1 CH_3OH–H_2O) to furnish **3-40** (6 mg, 16% over 2 steps) as a white solid after lyophilizing. R_f 0.85 (1:1 CH_3OH–H_2O); $[\alpha]^{25}_D$ +83.8 (*c* 0.50, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 5.14 (d, 1H, *J* = 3.9 Hz, H-1), 3.96–3.88 (m, 2H, H-3, H-5), 3.75 (app d, 1H, *J* = 12.3 Hz, H-6b), 3.64 (dd, 1H, *J* = 9.9, 3.7 Hz, H-2), 3.46 (app t, 1H, *J* = 9.4 Hz, H-4), 3.40 (dd, 1H, *J* = 8.0, 14.2 Hz, H-6a), 1.90 (s, 3H, C<u>H</u>$_3$, amide). ^{13}C NMR (125 MHz, D_2O) δ 174.1 (C=O), 101.2 (C-1), 82.0 (C-4), 72.6 (C-2), 72.2 (C-3), 70.1 (C-5), 40.0 (C-6), 21.9 (<u>C</u>H$_3$, amide). HRMS (ES-MS) *m/z* calcd for ($C_{64}H_{104}N_8O_{40}Na^+$) $[M+Na]^+$ 1647.6242, found 1647.6232.



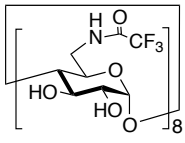
Octakis(6-deoxy-6-propanamido)cyclomaltoctaose (3-41): To a solution of **3-36** (30 mg, 0.023 mmol), dried overnight under reduced pressure in presence of P_2O_5, in anhydrous pyridine (0.5 mL) was added propionic anhydride (0.25 mL) and heated at 50 ºC for 2 d. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 1 N HCl (20 mL). The organic layer was separated and further washed with H_2O (10 mL), saturated $NaHCO_3$ solution (aq.) (10 mL) and saturated brine solution (10 mL). The organic layer was dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure. The product (52 mg, ca. 0.02 mmol) was dissolved in CH_3OH–CH_2Cl_2 (1 mL, 1:1) was added $NaOCH_3$ (26 mg, 0.48 mmol) and stirred for 5 d at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 100% CH_2Cl_2 as eluent. The product was further triturated with CH_2Cl_2 (3x 2 mL) and Et_2O (3x 2mL) to furnish **3-41** (20 mg, 50% over 2 steps) as a white solid. $[\alpha]^{25}_D$ +68.3 (*c* 0.40, CH_3OH); ^{1}H NMR (500 MHz, D_2O) δ 5.09 (H-1, *J* = 3.5 Hz), 3.89–3.85 (m, 2H, H-3, H-5), 3.74 (app d, 1H, *J* = 13.3 Hz, H-6b), 3.62 (dd, 1H, *J* = 9.8, 2.8 Hz, H-2), 3.45–3.32 (m, 2H, H-4, H-6a), 2.24–2.19 (m, 2H, C<u>H</u>$_2$, amide), 1.06 (t, 3H, *J* = 7.6 Hz, C<u>H</u>$_3$, amide). ^{13}C NMR (125 MHz, D_2O) δ 177.8 (C=O), 101.2 (C-1), 82.0 (C-4), 72.6 (C-2), 72.2 (C-3), 70.2 (C-5), 39.9 (C-6), 29.0 (<u>C</u>H_2, amide), 9.6 (<u>C</u>H_3, amide). HRMS (ES-MS) *m/z* calcd for ($C_{72}H_{120}N_8O_{40}Na^+$) $[M+Na]^+$ 1759.7494, found 1759.7526.



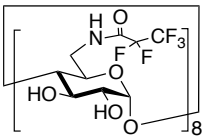
Octakis(6-deoxy-6-butanamido)cyclomaltoctaose (3-42): To a solution of **3-36** (30 mg, 0.023 mmol), dried overnight under reduced pressure in presence of P_2O_5, in anhydrous pyridine (0.5 mL) was added butyric anhydride (0.25 mL) and heated at 50 ºC for 5 d. The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and 1 N HCl (20 mL). The organic layer was separated and further washed with H_2O (20 mL), saturated $NaOCH_3$ solution (aq.) (20 mL) and saturated brine

solution (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product (57 mg, ca. 0.019 mmol) was dissolved in CH_3OH–CH_2Cl_2 (1 mL, 1:1) was added $NaOCH_3$ (25 mg, 0.456 mmol) and stirred for 5 d at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase column chromatography (1:4 → 1:1 CH_3OH–H_2O) to furnish **3-42** (15 mg, 35% over 2 steps) as white solid after lyophilizing. R_f 0.41 (1:1 CH_3OH–H_2O); $[\alpha]^{25}_D$ +133.1 (*c* 0.20, CH_3OH); ^1H NMR (500 MHz, D_2O) δ 5.14 (d, 1H, *J* = 3.7 Hz, H-1), 3.90–3.80 (m, 3H, H-6b, H-3, H-5), 3.63 (dd, 1H, *J* = 9.9, 3.7 Hz, H-2), 3.44 (app t, 1H, *J* = 9.4 Hz, H-4), 3.36 (dd, 1H, *J* = 13.7, 7.8 Hz, H-6b), 2.24–2.17 (m, 2H, C$\underline{H}_2$, amide), 1.62–1.54 (m, 2H, C$\underline{H}_2$, amide), 0.88 (app t, 3H, *J* = 7.3 Hz, C$\underline{H}_3$, amide). ^{13}C NMR (125 MHz, D_2O) δ 176.7 (C=O, amide), 100.9 (C-1), 81.7 (C-4), 72.7 (C-2), 72.1 (C-3), 70.3 (C-5), 39.9 (C-6), 37.7 ($\underline{C}H_2$, amide), 19.1 ($\underline{C}H_2$, amide), 13.1 ($\underline{C}H_3$, amide). HRMS (ES-MS) *m/z* calcd for ($C_{80}H_{136}N_8O_{40}Na_2^{2+}$) $[M+2Na]^{+2}$ 947.4319, found 947.4322.



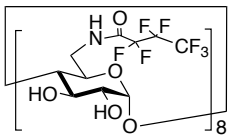
Octakis(6-deoxy-6-trifluoroethanamido)cyclomaltoctaose (3-37): A solution of **3-36** (20 mg, 0.0155 mmol) in anhydrous pyridine (0.5 mL) was cooled to 0 ºC and trifluoroacetic anhydride (27 μL, 0.1860 mmol) was added. The reaction mixture was heated to RT and stirred for 5 d. CH_3OH (1 mL) was added to quench excess trifluoroacetic anhydride and the mixture was concentrated under

reduced pressure. The product was purified by column chromatography (100% CH_2Cl_2 → 1:1 CH_3OH–CH_2Cl_2) to afford **3-37** (6.2 mg, 22%) as a yellow solid. $[\alpha]^{25}_D$ +86.6 (*c* = 0.60, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 5.10 (d, 1H, *J* = 3.5 Hz, H-1), 4.02 (ddd, 1H, *J* = 18.0, 10.3, 2.5 Hz, H-5), 3.83 (app t, 1H, *J* = 9.4 Hz, H-3), 3.55 (dd, 1H, *J* = 9.8, 3.5 Hz, H-2), 3.48–3.40 (m, 2H, H-6b, H-4), 3.17 (dd, 1H, *J* = 13.3, 8.4 Hz, H-6a). ^{13}C NMR (125 MHz, CD_3OD) δ 161.9 (C=O), 116.0 ($\underline{C}F_3$), 101.5 (C-1), 82.2 (C-4), 72.5(C-2), 72.3 (C-3), 68.2 (C-5), 40.4 (C-6). ^{19}F NMR (500 MHz, CD_3OD) δ –76.74 ($C\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{64}H_{80}F_{24}N_8O_{40}Na^+$) $[M+Na]^+$ 2079.3981, found 2079.3941.



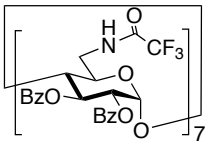
Octakis(6-deoxy-6-pentafluoropropanamido)cyclomaltoctaose (3-38): A solution of **3-36** (20 mg, 0.0177 mmol) in anhydrous pyridine (0.6 mL) was cooled to 0 ºC and trifluoroacetic anhydride (35 μL, 0.2478 mmol) was added. The reaction mixture was heated to RT and stirred for 4 d. CH_3OH (1 mL) was added to quench excess trifluoroacetic anhydride and the mixture was concentrated under reduced pressure. The product was purified by column chromatography (100% CH_2Cl_2 → 2:3 CH_3OH–CH_2Cl_2) to afford **3-38** (8 mg, 25%) as a yellow solid. $[\alpha]^{25}_D$ +65.1 (*c* = 0.80, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 5.04 (d, 1H, *J* = 3.9 Hz, H-1), 3.93–3.82 (m, 3H, H-6b, H-3, H-5), 3.64 (dd, 1H, *J* = 14.0, 7.1 Hz, H-6a), 3.54 (dd, 1H, *J* = 9.9, 3.7 Hz, H-2), 3.36–3.32 (m, 1H, H-4). ^{13}C NMR (125 MHz, CD_3OD) δ 158.6 (C=O), 118.0 ($\underline{C}F_2$), 106.9 ($\underline{C}F_3$), 102.4 (C-1), 83.7 (C-4),

72.9 (C-2), 72.5(C-3), 70.2 (C-5), 40.3 (C-6). ^{19}F NMR (500 MHz, CD_3OD) δ –84.54 ($C\underline{F}_3$), –123.87 ($C\underline{F}_2$). HRMS (ES-MS) *m/z* calcd for ($C_{72}H_{80}F_{40}N_8O_{40}Na^+$) $[M+Na]^+$ 2479.3725, found 2479.3677.



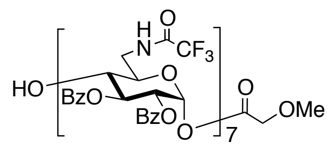
Octakis(6-deoxy-6-heptafluorobutananamido)cyclomaltoctaose (3-39): A solution of **3-36** (20 mg, 0.0155 mmol) in anhydrous pyridine (0.5 mL) was cooled to 0 ºC and heptafluorobutyric anhydride (91 μL, 0.3720 mmol) was added. The reaction mixture was heated to RT and stirred for 5 d. Ice-cold 0.5 N HCl was added to the mixture that turned the product in fine particles and did not precipitate. The water was removed and the mixture was freeze dried. The mixture was attempted to purify via fluorous phase separation using Fluoro*Flash*® cartridge. The cartridge loaded with reaction mixture was first eluted with H_2O–CH_3OH (30 mL, 80:20) and fluorinated product was eluted with CH_3OH (30 mL). The product was purified by column chromatography (1:1 CH_3OH–CH_2Cl_2) to afford **3-39** (2 mg, 5%) as a yellow solid. $[\alpha]^{25}_D$ +62.7 (*c* = 0.19, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.03 (d, 1H, *J* = 3.6 Hz, H-1), 3.92–3.81 (m, 3H, H-6b, H-3, H-5), 3.64 (dd, 1H, *J* = 13.9, 6.6 Hz, H-6a), 3.51 (dd, 1H, *J* = 9.8, 3.7, Hz, H-2), 3.35–3.32 (m, 1H, H-4). ^{13}C NMR (175 MHz, CD_3OD) δ 158.3 (C=O), 117.5 (2x $\underline{C}F_2$), 108.5 ($\underline{C}F_3$), 102.4 (C-1), 83.6 (C-4), 72.8 (C-2), 72.5 (C-3), 70.2 (C-5), 40.3 (C-6). ^{19}F NMR (125 MHz, CD_3OD) δ –82.22 ($C\underline{F}_3$), –121.38 ($C\underline{F}_2$), –128.15 ($C\underline{F}_2$). HRMS (ES-MS) *m/z* calcd for ($C_{80}H_{80}F_{56}N_8O_{40}Na^+$) $[M+Na]^+$ 2879.3470,

found 2879.3473.



Heptakis(6-deoxy-2,3-di-*O*-benzoyl-6-trifluoroethanamido)cyclomaltoheptaose (3-43): To a solution of **3-20** (210 mg, 0.0812 mmol) dissolved in anhydrous pyridine (3 mL), cooled to 0 ºC using an ice bath, was added trifluoroacetic anhydride (161 μL, 1.1368 mmol). Ice bath was removed and the reaction mixture was heated to RT. The reaction mixture was stirred for 20 h. The mixture was partitioned between EtOAc (20 mL) and 1 M HCl (40 mL). The organic layer was separated and washed with H_2O (40 mL), saturated $NaHCO_3$ solution (aq.) (40 mL) and saturated brine solution (40 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (100% hexane → 1:1 EtOAc–hexane) to give **3-43** (158 mg, 58%) as a pale yellow solid. R_f 0.17 (2:3 EtOAc–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.04 (m, 10H, Ar-H), 5.73–5.71 (m, 1H, H-3), 5.49 (d, 1H, J = 3.9 Hz, H-1), 5.13–5.11 (m, 1H, H-2), 4.46–4.44 (m, 1H, H-5), 4.24–4.21 (m, 1H, H-4), 3.94–3.91 (m, 1H, H-6a), 3.84–3.80 (m, 1H, H-6b). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8 (C=O), 164.5 (C=O), 158.4 (C=O, amide), 132.9, 132.6, 129.9, 129.8, 129.6, 129.1, 128.2, 128.1, 128.0, 127.8, 117.0, 114.8 (Ar–C), 98.3 (C-1), 80.0 (C-4), 70.9, 70.8, 70.7 (3C, C-2, C-3, C-5), 40.7 (C-6). ^{19}F NMR (500 MHz, $CDCl_3$) δ –75.64– –75.69 (7x

C$\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{154}H_{126}F_{21}N_7O_{49}Na_2^+$) $[M+Na]^{+2}$ 1650.8516, found 1650.8524.



2,3-di-*O*-benzoyl-6-deoxy-6-trifluoroacetamido-α-D-glucopyranosyl-(1 → 4)-2,3-di-*O*-benzoyl-6-deoxy-6-trifluoroacetamido-α-D-glucopyranosyl-(1 → 4)-2,3-di-*O*-benzoyl-6-deoxy-6-trifluoroacetamido-α-D-glucopyranosyl-(1 → 4)-2,3-di-*O*-benzoyl-6-deoxy-6-trifluoroacetamido-α-D-glucopyranosyl-(1 → 4)-2,3-di-*O*-benzoyl-6-deoxy-6-trifluoroacetamido-α-D-glucopyranosyl-(1 → 4)-2,3-di-*O*-benzoyl-6-deoxy-6-trifluoroacetamido-α-D-glucopyranosyl-(1 → 4)-2,3-di-*O*-benzoyl-6-deoxy-1-*O*-methoxyacetyl-6-trifluoroacetamido-α-D-glucopyranose (3-44): To **3-43** (102 mg, 0.0313 mmol) was added BF_3•Et_2O (0.7 mL) in methoxyacetic acid (3.4 mL) under an argon atmosphere and stirred for 24 h at RT. Saturated $NaHCO_3$ solution (aq.) (80 mL) was added to the reaction mixture to neutralize. The mixture was partitioned with EtOAc (30 mL). The organic layer was separated and washed with saturated brine solution (60 mL). The organic layer was further dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was purified by column chromatography using (100% hexane → 2:3 EtOAc–hexane) to furnish **3-44** (33 mg, 32%) as white solid. R_f 0.14 (2:3 EtOAc–hexane); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.62–7.10 (m, 70H), 5.88–5.86 (m, 2H), 5.79–5.65 (m, 5H), 5.59–5.50

(m, 7H), 5.28–5.20 (m, 3H), 5.15–5.07 (m, 6H), 4.41–4.36 (m, 6H), 4.20–4.18 (m, 5H), 4.10–3.66 (m, 20H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 168.7, 165.3–165.1 (4C), 164.7–164.6 (4C), 133.3–133.0 (7C), 130.0–129.3 (17C), 128.2–127.8 (13C), 117.1–117.1 (4C), 114.8–114.8 (3C), 98.0–96.7 (7C), 89.0–88.9 (3C), 76.7–76.7 (4C),76.7–76.7 (3C), 71.5–69.5 (20C), 59.2, 40.9–40.5 (7C), 29.7. ^{19}F NMR (500 MHz, CD_2Cl_2) δ –75.82, –75.86, –75.87, –75.89, –75.90, –75.91, –75.93 (7x $C\underline{F}_3$). HRMS (ES-MS) *m/z* calcd for ($C_{157}H_{132}F_{21}N_7O_{52}Na_2^+$) $[M+Na]^{+2}$ 1695.8674, found 1695.8697.

3.6 Bibliography

(1) Mangold S. L.; Carpenter R. T.; Kiessling L. L. *Org. Lett.* **2008**, *10*, 2997.

(2) Köhn M.; Breinbauer R. *Angew. Chem., Int. Ed*. **2004**, 43, 3106.

(3) www.silicycle.com/media/pdf/poster-p-sulfonic-acids-products-purification-needs.pdf (as of February 28, 2014)

(4) Valeur E.; Bradley M. *Chem. Soc. Rev.* **2009**, *38*, 606.

(5) Nicolaou K. C.; Mitchell H. J.; Fylaktakidou K. C.; Rodriguez R. M.; Suzuki H *Chem. Eur. J.*, **2000**, *20*, 3116.

(6) (a) Guibé F. *Tetrahedron* **1997**, *53*, 13509. (b) Mayer T. G.; Schimdt R. R. *Eur. J. Org. Chem.* **1999**, 1153.

(7) R. McKay, personal communication.

(8) Evans D. A.; Ng H. P. *Tetrahedron Lett.* **1993**, *34*, 2229.

(9) (a) Jiang L.; Chan T. H. *Tetrahedron Lett.* **1993**, *39*, 355. (b) Daragics K.; Fugedi P. *Tet. Lett.* **2009**, *50*, 2914.

(10) Prediger P.; Barbosa L. F.; Genisson Y.; Correia C. R. D. *J. Org. Chem.* **2011**, *76*, 7737.

(11) Bouzide A.; Sauve G. *Tetrahedron Lett.* **1999**, *40*, 2883.

(12) Mayer T. G.; Schimdt R. R. *Eur. J. Org. Chem.* **1999**, 1153.

(13) Wuts P. G. M.; Greene T. W. *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. (Hoboken, Jew Jersey) **2007**, 781.

(14) Hecht S.; Karginov V.; Fahmi N. *U. S. Patent US 7,851,457 B2*, Dec. 14, 2010.

(15) Newmark R. A. *J. Fluorine Chem.* **2009**, *130*, 389.

(16) (a) Sakari, N.; Wang, L.-X.; Kuzuhara, H. *J. Chem. Soc., Chem. Commun.* **1991**, 289. (b) Sakari, N.; Wang, L.-X.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 437. (c) Sakari, N.; Matsui, K.; Kuzuhara, H. *Carbohydr. Res.* **1995**, *266*, 263. (d) Sakairi, N.; Kuzuhara, H. *Carbohydr. Res.* **1996**, *280*, 139.

(17) Meppen M.; Wang Y.; Cheon H.; Kishi Y. *J. Org. Chem.* **2007**, *72*, 1941.

(18) Sun Y.; Zhang J.; Li C.; Guan H.; Yu G. *Carbohydr. Res.* **2012**, *355*, 6.

(19) Miyabe H.; Nishiki A.; Naito T. *Chem. Pharm. Bull.* **2003**, *51*, 100.

(20) Becker M. M.; Ravoo B. J. *Chem. Commun.* **2010**, *46*, 4369.

(21) Ellis D. A.; Denkenberger K. A.; Burrow T. E.; Mabury S. A. *J. Phys. Chem. A* **2004,** *108,* 10099.

Chapter 4: Summary and future work

4.1 Summary

Fluorous phase chemistry has come out to be a new and separation technique for fluorinated molecules.[1,2] Our goal was to synthesize fluorous glucose-containing oligosaccharides that as new adsorbents for fluorous solid phase extraction technique.

In the beginning we encountered difficulties in synthesizing fluorous ether oligosaccharides. We, thereafter, modified our goal to prepare fluorous amide group-containing oligosaccharides. We successfully synthesized 18 cyclic fluorous and non-fluorous glucose-containing oligosaccharides from β- and γ-cyclodextrins. Moreover, we developed a method that does not require any protecting group or silica gel chromatographic purification of intermediates.[3,4] We also carried out the selective ring opening of a β-cyclodextrin derivative under previously developed conditions[5,6] to afford linear glucose-containing oligomers.

4.2 Future work

With the cyclic fluorous and non-fluorous derivatives of glucose-containing oligosaccharides already synthesized, our target is to test their binding affinities towards fluorinated lipid molecules as well as fluorinated small molecules. These binding studies will be conducted in collaboration with the research group of Dr. John Klassen. The binding affinities will be studied via electrospray ionization mass spectrometry.

Additionally, we would like to further investigate the selective opening of the cyclodextrin moiety to synthesize linear versions of these derivatives. This is important in terms of aiming for higher yields for the opening reaction. Our goal would be to test the reaction with different protecting groups, Lewis acids and solvents.

Ultimately if the binding affinities of these synthesized fluorous oligosaccharides towards fluorinated molecules appear to be promising, they would be studied further so that we can anchor them to silica gel or resin. This will lead us to a novel fluorous solid phase separation materials.

4.3 Bibliography

(1) Curran D. P.; Hadida S.; He M. *J. Org. Chem.* **1997**, *62*, 6714.

(2) Fluorous Technology, Inc. (www.fluorous.com)

(3) Becker M. M.; Ravoo B. J. *Chem. Commun.* **2010**, *46*, 4369.

(4) Hecht S.; Karginov V.; Fahmi N. *U. S. Patent US 7,851,457 B2*, Dec. 14, 2010.

(5) (a) Sakari, N.; Wang, L.-X.; Kuzuhara, H. *J. Chem. Soc., Chem. Commun.* **1991**, 289. (b) Sakari, N.; Wang, L.-X.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 437. (c) Sakari, N.; Matsui, K.; Kuzuhara, H. *Carbohydr. Res.* **1995**, *266*, 263. (d) Sakairi, N.; Kuzuhara, H. *Carbohydr. Res.* **1996**, *280*, 139.

(6) Meppen M.; Wang Y.; Cheon H.; Kishi Y. *J. Org. Chem.* **2007**, *72*, 1941.