Self-promoted Glycosylations with Trichloroacetimidate Glycosyl Donors: Synthesis of *N*-glycosides

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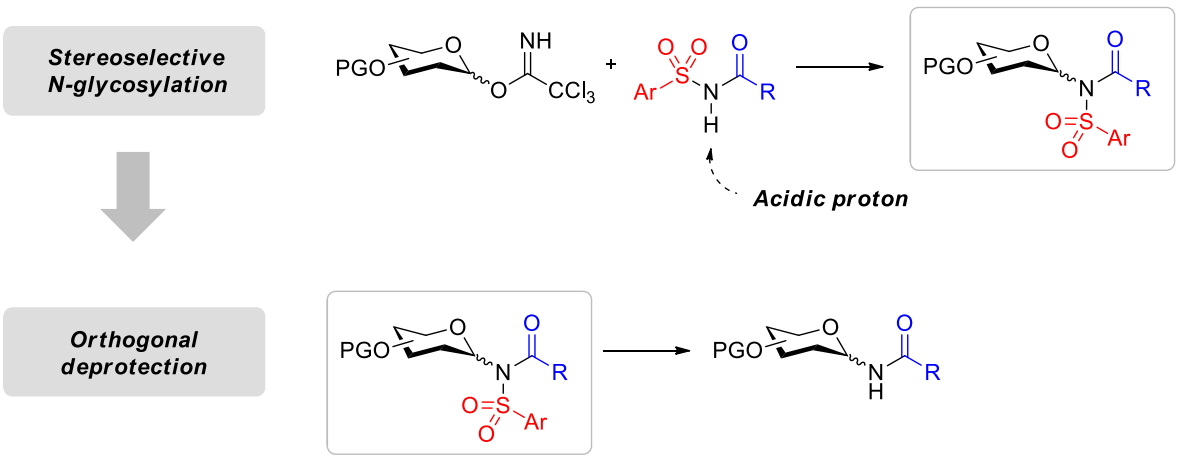
Abstract

Among the major classes of carbohydrates, *N*-glycosides are of immense importance. In nature, they are widely distributed as glycoconjugates, including *N*-glycoproteins bearing the glycosyl amide linkage. These biomolecules are ubiquitous in all known forms of life and have key roles in a multitude of life-sustaining biological processes. *N*-linked neo-glycoconjugates and glycomimetics, on the other hand, constitute non-natural *N*-glycosides. Numerous applications of these compounds have been reported, especially in the areas of chemical biology and medicinal chemistry. For instance, *N*-glycosyl sulfonamides have been shown to display significant inhibitory properties against carbonic anhydrase. Although a number of methods for the preparation of glycoconjugates have appeared, the synthesis of *N*-glycosides still poses a challenge in regard to yield, and most importantly, chemo- and stereoselectivity. In addition, the vast majority of reported methods apply additives such as catalysts, promoters and scavengers. In certain cases, the developed procedures also require harsh conditions. Thus, there is a great demand for new practical and general methods for synthesizing *N*-linked glycoconjugates.

Here we describe the development of a novel synthetic approach toward *N*-glycosides containing amide, sulfonamide and carbamate functions. The designed route involves the *N*-glycosylation step, which was the central subject of this study and the orthogonal protection strategy. Notably, the developed *N*-glycosylations are self-promoted, i.e., taking place without the need for any additives. The glycosidic bond formation can be therefore achieved by mixing only two compounds in a solvent. In this type of glycosylation, the acceptor acts as an activator of the glycosyl donor and nucleophile. A wide variety of acid-labile TCA (trichloroacetimidate) glycosyl donors and electron-poor acceptors, namely sulfonyl amides and carbamates, were employed in a series of self-promoted *N*-glycosylations. This enabled us to investigate the effect of different functional groups, anomeric configuration and steric bulk on the glycosylation outcome. In general, the reactions resulted in moderate to high yields. Noteworthy, the glycosylations were found to be highly selective toward 1,2-*trans*-glycosides when using α-glucosyl donors, making the developed method more attractive. In order to evaluate the orthogonality of the sulfonyl and amide or carbamate functions, several deprotection reactions were performed on a range of selected *N*-glycosylation products. The selective removal was eventually attained for *N*-glycosyl sulfonyl carbamates leading to target *N*-glycosyl sulfonamides and carbamates. The proposed methodology holds therefore some potential for the synthesis of *N*-functionalized sugars and we hope it will contribute to the development in the field of glycosylation chemistry.



Streszczenie

N-glikozydy stanowią jedną z głównych klas pochodnych węglowodanów o szczególnym znaczeniu. W naturze związki te są szeroko rozpowszechnione w postaci glikokoniugatów, w tym *N*-glikoprotein posiadających ugrupowanie amidowe w pozycji anomerycznej. *N*-glikoproteiny zaliczane do biomolekuł są wszechobecne we wszystkich znanych formach życia i odgrywają kluczową rolę w wielu procesach biologicznych podtrzymujących funkcje życiowe. Oprócz produktów naturalnych z wiązaniem *N*-glikozydowym, znane są również liczne *N*-glikozydy syntetyczne, takie jak neoglikokoniugaty oraz glikomimetyki. Tego typu związki znalazły szerokie zastosowanie w obszarach biologii chemicznej oraz chemii medycznej. Przykładowo udowodniono, iż *N*-glikozydowe sulfonamidy wykazują znaczące właściwości inhibicyjne względem anhydrazy węglanowej. Opracowano wiele metod otrzymywania glikokoniugatów, niemniej jednak synteza *N*-glikozydów wciąż stanowi wyzwanie pod kątem wydajności reakcji, a przede wszystkim chemo- oraz stereoselektywności. Ponadto, zdecydowana większość opublikowanych metod wymaga użycia dodatków, takich jak katalizatory, promotory oraz zmiatacze. W przypadku niektórych procedur syntetycznych konieczne jest także stosowanie drastycznych warunków reakcji. Istnieje zatem znaczna potrzeba prowadzenia badań ukierunkowanych na opracowanie praktycznych metod syntezy *N*-glikokoniugatów.

W niniejszej rozprawie przedstawiono nową strategię syntetyczną prowadzącą do otrzymania *N*-glikozydów posiadających ugrupowanie amidowe, sulfonamidowe oraz karbaminianowe. Zaprojektowana ścieżka syntezy obejmuje reakcję *N*-glikozylacji, która stanowiła główny przedmiot prowadzonych prac badawczych oraz koncepcję ortogonalnych grup ochronnych. Istotnie, opracowane *N*-glikozylacje są przykładem reakcji typu *self-promoted*, tj. zachodzących bez konieczności zastosowania dodatków. Do utworzenia wiązania glikozydowego dochodzi zatem w wyniku zmieszania dwóch substratów w rozpuszczalniku. W tego rodzaju glikozylacji akceptor pełni jednocześnie funkcję nukleofila oraz aktywatora donora glikozylowego. W ramach realizacji badań przeprowadzono serię reakcji *N*-glikozylacji z wykorzystaniem zróżnicowanych kwasowo-labilnych trichloroacetoimidanów glikozylu oraz akceptorów z elektronoakceptorowymi podstawnikami, mianowicie sulfonylowych amidów i karbaminianów. Reakcje te umożliwiły zbadanie wpływu obecności różnych grup funkcyjnych, konfiguracji w pozycji anomerycznej oraz zawady sterycznej na przebieg glikozylacji. W większości przypadków pożądane produkty otrzymano ze średnią lub wysoką wydajnością. Godnym uwagi jest fakt, iż glikozylacje z zastosowaniem α-glikozylowych donorów przebiegały z wysoką selektywnością, prowadząc głównie do 1,2-*trans*-glikozydów, co dodatkowo zwiększa atrakcyjność opracowanej metody. W celu zweryfikowania ortogonalności ugrupowania sulfonylowego oraz amidowego lub karbaminianowego, przeprowadzono reakcje odblokowania z wykorzystaniem wybranych produktów reakcji *N*-glikozylacji. Selektywne odblokowanie zostało osiągnięte dla reakcji z *N*-glikozylowymi sulfonylowymi karbaminianami, w wyniku których otrzymano docelowe *N*-glikozylowe sulfonamidy oraz karbaminiany. Zaproponowana strategia syntetyczna przejawia zatem potencjał do zastosowania w preparatyce *N*-glikozylowych pochodnych i mamy nadzieję, że wniesie istotny wkład w rozwój tego obszaru glikochemii.

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Author Information

Patrycja Mała received her Bachelor's degree in chemistry from the Adam Mickiewicz University in 2015 under the supervision of Prof. Henryk Koroniak, with a dissertation "The synthesis and the spectral analysis of fluorinated amides carbohydrates derivatives". Subsequently, she continued her studies in the same research group. In 2017, she defended the thesis entitled "Synthesis and Characteristic of Polymer Nanoparticles of Fluorescein Derivatives" and graduated with a Master's degree in biological chemistry. In that year, she was also awarded the Medal of Adam Mickiewicz University for her Master's diploma and academic achievements. During her graduate studies she did an academic internship within the Erasmus+ program in the prof. Stefan Braese group at the Karlsruhe Institute of Technology, where she acquired additional experience in glycochemistry and bioimaging. Meanwhile, she was an active member of the Scientific Association of Chemists at the Home University. After the graduation in 2017, she initiated her Ph.D. studies at the Adam Mickiewicz University under the supervision of Prof. Koroniak and Prof. Christian Marcus Pedersen within the international and interdisciplinary program ChemInter co-financed by the European Union. Her main research interests were focused on the development of new glycosylation methods. Throughout her doctoral studies, she was a visiting student in the Prof. Christian Marcus Pedersen group at the University of Copenhagen within the Erasmus+ and ChemInter programs. In 2019, she was also awarded the One-Year Grant for Doctoral Candidates by the German Academic Exchange Service for the project entitled "Glycosyl amides and sulfonamides as novel inhibitors of P. aeruginosa LecB", which was carried out in the Prof. Alexander Titz group at the Helmholtz Institute for Pharmaceutical Research Saarland. During her scientific career she has presented her work at several international and domestic conferences. She is also an author and co-author of the publications listed below.

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Abbreviations

$[\alpha]_D$	specific rotation at 589 nm (sodium D line)
1D	1-diamensional
2D	2-diamensional
Ac	acetyl
AcOH	acetic acid
Alloc	allyloxycarbonyl
Ar	generic aryl substituent
Asn	asparagine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
c	concentration
cat.	catalyst or catalytic (quantity)
Cbz	benzyloxycarbonyl
DCC	*N*,*N*'-dicyclohexylcarbodiimide
cm^{-1}	wavenumber
COSY	correlation spectroscopy
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylanimopyridine
DMAPA	3-(dimethylamino)-1-propylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
equiv.	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc-Cl	9-fluorenylmethoxycarbonyl chloride
GlcNAc	*N*-acetylglucosamine
h	hour(s)
hCA	human carbonic anhydrase
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IR	infrared
J	coupling constant
L	liter(s)
LG	leaving group

m	multiplet
MALDI	matrix-assisted laser desorption/ionization
Me	methyl
MeOH	methanol
mg	miligram(s)
mL	milliliter(s)
mmol	millimole(s)
NaOAc	sodium acetate
NBS	*N*-bromosuccinimide
NH_3	ammonia
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ns	nosyl
PG	protecting group
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Pyr	pyridine
quart	quartet
r.t.	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
TCA	trichloroacetimidate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOCSY	total correlation spectroscopy
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
δ	chemical shift
µl	microliter(s)
Φ	dihedral angle

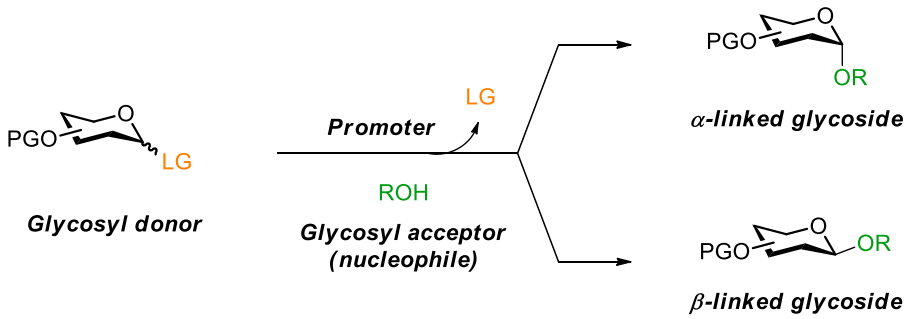
CHAPTER I

General Introduction

1.1. Introduction to Glycosylation Reactions

Existing in all known forms of life, carbohydrates are among the most ubiquitous organic compounds in nature. They occur in various locations of living systems carrying out critical functions in a myriad of fundamental biological events, such as cell growth, cell-cell recognition, adhesion, signal transduction and immune responses.[1–5] A vast number of these processes are driven and regulated by carbohydrate-protein interactions.[6–8] In nature, carbohydrates are typically attached to other molecules, most often proteins and lipids.[3] Therefore, structure elucidation of carbohydrates and a better understanding of their functions is also important in the context of these biomolecules. Due to the biological importance and molecular diversity, carbohydrates hold enormous potential for drug discovery and diagnostic-platform development.[9–13] Isolation of the naturally occurring carbohydrates is, however, complicated and usually results in complex mixtures of different compounds, making the analysis troublesome.[14] This prompted the development of chemical synthesis in the field of glycochemistry.[15] Nevertheless, despite tremendous progress within this area, especially in the past four decades, carbohydrates remain challenging synthetic targets, as their synthesis commonly involves a number of modifications and protecting groups manipulations.[16,17] Moreover, there is a need for controlling stereochemistry. The formation of anomeric mixtures not only reduces the reaction yield but also implies more extensive purification.

Since the pioneering work by Fisher at the end of the XIX century, chemical glycosylation has been the key transformation in carbohydrate chemistry serving as a powerful tool for the preparation of oligosaccharides and glycoconjugates.[18] Generally, glycosylation is a reaction between a carbohydrate equipped with a leaving group at the anomeric position and another compound, leading to the glycosidic bond formation (**Scheme 1.1**). Conventionally, a carbohydrate carrying the anomeric carbon involved in the glycosidic bond is referred to as the glycosyl donor, whereas the second reactant is defined as the acceptor.



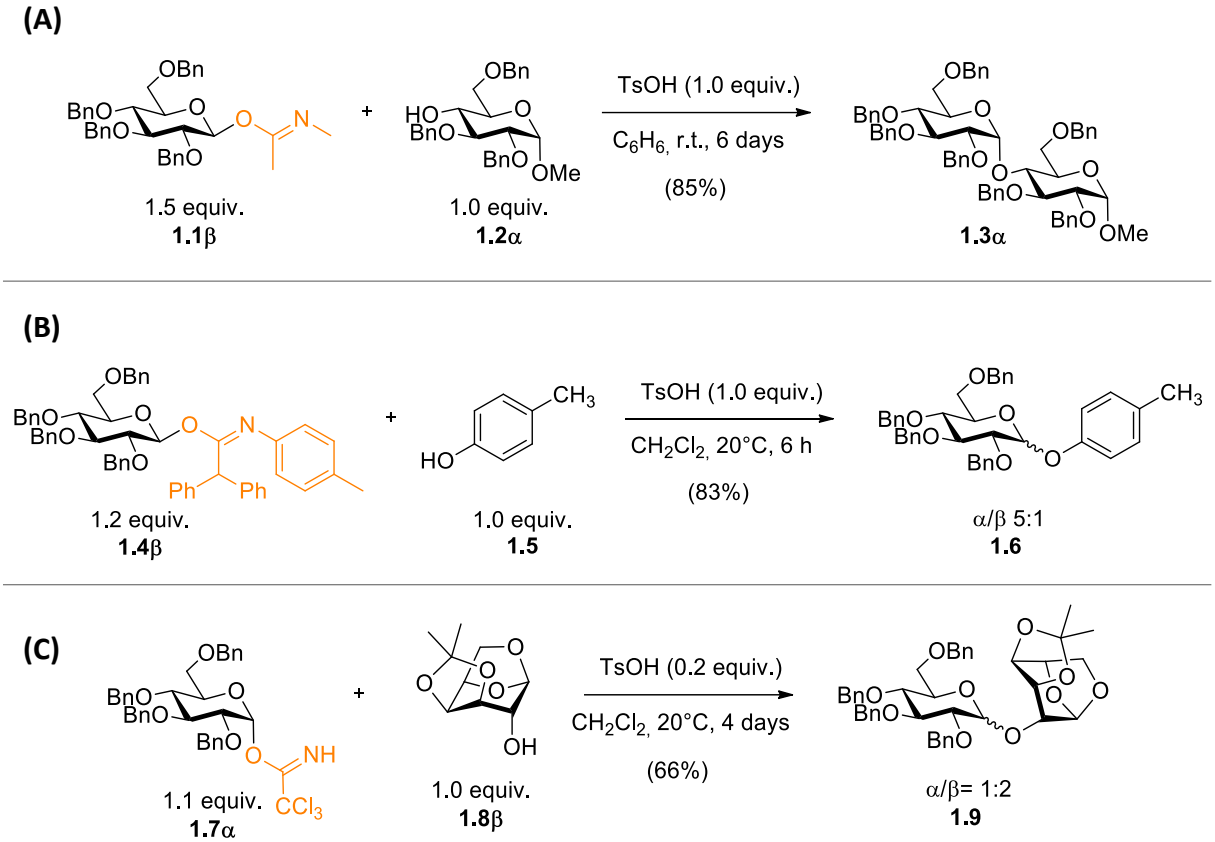
Scheme 1.1. Schematic representation of the glycosylation reaction.[19,20]

The majority of glycosylations take place in the presence of a suitable promoter capable of activating the glycosyl donor. Upon activation, the glycosyl donor typically acts as an electrophile, whereas the acceptor plays the role of a nucleophilic reagent.[15] There are, however, examples of umpolung reactivity.[21,22] In most cases, the glycosylation requires the prior installation of sufficient protecting groups, which may also influence the glycosylation outcome, for an instance by neighboring group participation.[19] Nonetheless, a vast number of glycosylations employing the unprotected glycosyl donors have been developed attracting significant interest from the synthetic community.[23,24] Since in the glycosylation the leaving group of the glycosyl donor is displaced by the acceptor, the reaction is usually considered as the nucleophilic substitution at sp^3 carbon proceeding through more S_N1 or S_N2 mechanism.[20] Besides the glycosyl donor, acceptor and promoter, the reaction pathway can be strongly affected by many factors including solvent, temperature and concentration. Hence, various intermediates can be formed under different glycosylation conditions and each glycosylation should be investigated as an independent case.[25] In general, glycosylations following the unimolecular mechanism involve the formation of carbenium ion intermediates, whereas the bimolecular reactions pass through associative transition states. However, it has been shown that the glycosylation pathway might be more complex and range between the two extreme mechanistic scenarios, proceeding via less or more solvent separated ion-pairs.[20] Although the determination of glycosylation mechanism is difficult and usually requires extensive kinetic studies it is of great importance. A deeper insight into the glycosylation mechanism provides knowledge essential to develop more efficient and stereoselective methods, and thus numerous efforts have been put in this direction.[26]

1.2. Trichloroacetimidate Glycosyl Donors

A natural consequence of the demand for new glycosylation methods was the development of a wide range of glycosyl donors, including commonly utilized thioglycosides, glycals, glycosyl halides, esters, orthoesters, phosphates and imidates. The latter ones have been of special interest over the last few decades, becoming the most extensively studied glycosyl donor type for catalytic glycosylations.[15,27,28]

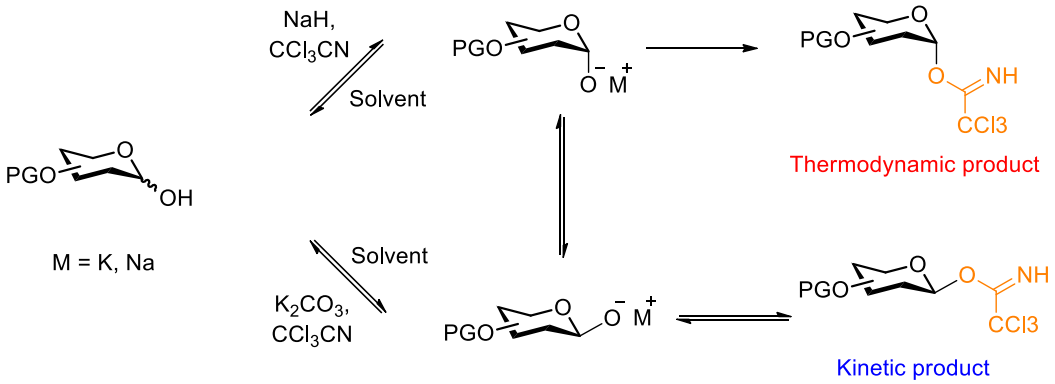
The first reports on the general synthesis of glycosyl imidate donors and their application in glycosylation reactions appeared in the late 1970's. Sinaÿ and co-workers introduced glycosyl (*N*-methyl)acetimidates, which were shown to be activated by *p*-toluenesulfonic acid and glycosylated with different sugar acceptors, giving rise to the di- and trisaccharides (**Scheme 1.2**).[29–32] Unlike many previously reported glycosylations, this method did not require heavy metal salts as promoters. However, stoichiometric amounts of the promoter were used for the activation of the glycosyl donors. Furthermore, glycosyl (*N*-methyl)acetimidates generally expressed low reactivity in glycosylation reactions. In addition, they were synthesized from other glycosyl donors, i.e., glycosyl halides in the presence of silver oxide. Due to these limitations, glycosyl (*N*-methyl)acetimidate donors have not really attracted considerable attention. Nonetheless, the findings by the Sinaÿ's group shortly after inspired Michel and Schmidt to introduce glycosyl trichloroacetimidates (TCAs) and ketenimidates, the former of which have become the most frequently used glycosyl imidate donors (**Scheme 1.2**).[33] In early studies, it was found that glycosylations employing TCA and ketenimidate glycosyl donors proceeded faster compared to reactions with the corresponding glycosyl (*N*-methyl)acetimidates. Both types of glycosyl imidate donors were shown to be activated by *p*-toluenesulfonic acid and $BF_3 \cdot OEt_2$. However, catalytic activation was only reported for glycosyl TCAs, making the donors more attractive. Over the years, a wide range of strategies have been developed for activating TCA glycosyl donors. The vast majority involve the use of Brønsted and Lewis acids, e.g., TMSOTf, $TMSNTf_2$, metal triflates, $AuCl_3$, $NHTf_2$, $HClO_4$, carboxylic acids and phosphoric acids. Most of the applied Lewis acids, however, are moisture-sensitive and necessitate rather low temperature conditions, which limits their usefulness.[15,28,34]



Scheme 1.2. Early examples of glycosylations with glycosyl (*N*-methyl)acetimidates (A), ketenimidates (B), and trichloroacetimidates (C).[30,33]

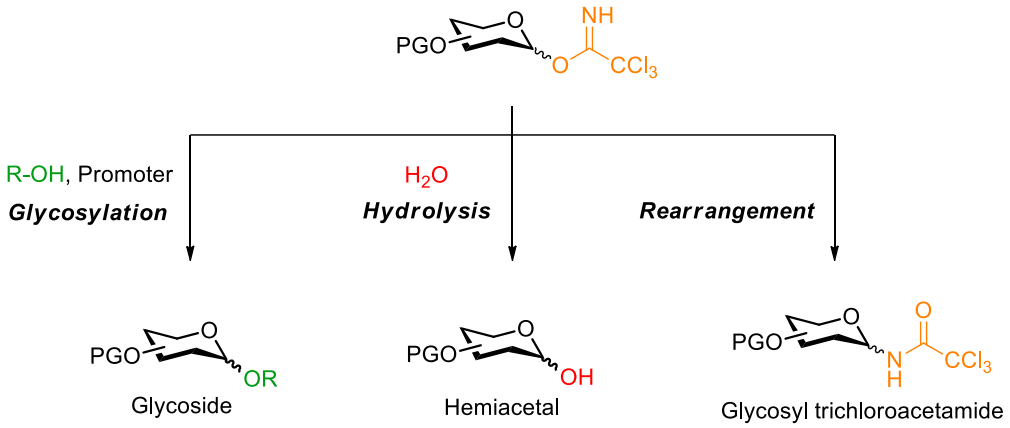
TCA glycosyl donors are generally synthesized by the base-catalyzed reaction of the appropriate hemiacetals with trichloroacetonitrile. Although the first procedure for the preparation of TCA glycosyl donors was described in the pioneer report by Michel and Schmidt, their formation was studied in greater detail in the follow-up publication.[33,35] During these studies, the same authors found that the synthesis of TCA glycosyl donors can be stereocontrolled by using different bases (**Scheme 1.3**). They early realized that the conversion of the hemiacetal to the corresponding β-TCA glycosyl donor proceeded faster than formation of its α-counterpart. The obtained results were justified by differences in the nucleophilicity of anomeric alkoxides formed initially upon addition of the base. The enhanced nucleophilicity of the β-alkoxide can be explained by dipole-dipole repulsions, resulting in increased accessibility of the lone pair on the exocyclic oxygen atom (O1).[36] It was therefore concluded that stronger bases, such as NaH, should favor the formation of the α-TCA donor, whereas weaker base, e.g., K_2CO_3, should give predominantly the β-anomer, which was confirmed experimentally. Furthermore, it was also found that the formation of the β-TCA donor is reversible in the presence of NaH and it can be converted to the corresponding α-TCA over an extended period of time. On the basis of these finding, two general procedures were developed for the

stereoselective synthesis of TCA glycosyl donors, which have been commonly applied in the following years. Worth mentioning are also other reported methods employing bases, such as DBU, NaOH and Cs_2CO_3, leading to the preferential formation of the thermodynamic α-TCA donor.[37–39]



Scheme 1.3. Stereocontrolled synthesis of TCA glycosyl donors.[35]

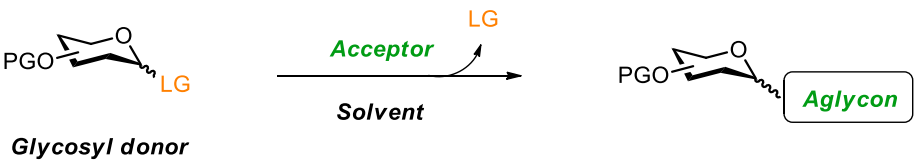
Depending on the glycosylation conditions, TCA glycosyl donors can undergo several side reactions, reducing the glycosylation yield.[40] Among the most occurring undesired reactions of the donor are hydrolysis and acid-catalyzed rearrangement (**Scheme 1.4**). During hydrolysis, the leaving group of the donor is substituted by H_2O, giving rise to the formation of a hemiacetal. In order to overcome or limit such decomposition of the donor, it is necessary to carry out the glycosylation under anhydrous conditions. The rearrangement, on the other hand, takes place when the leaving group competes with the proper nucleophile, leading to the glycosyl trichloroacetamide. The formation of this undesired byproduct is typically observed when glycosylating poor nucleophiles.[41–44] The rearrangement of TCA donors can be avoided or suppressed by replacing the solvent with a less polar medium or lowering the reaction temperature.[45–47] In some studies, the degree of rearrangement was also diminished by changing the type or amount of promoter.[48,49] In general, side reactions of TCA glycosyl donors can be circumvented by using an excess of TCA glycosyl donor. This solution usually provides an improvement in glycosylation yield.[25,50,51] Alternatively, the formation of by-products can be avoided by applying so-called "inverse conditions". In this case, the promoter is pre-mixed with the acceptor before a slow addition of the donor. These glycosylation conditions have been shown to be especially efficient for glycosylations employing highly reactive TCA glycosyl donors and poor nucleophiles.[52–55]



Scheme 1.4. General illustration of the competition between the glycosylation employing the TCA glycosyl donor and the two most common side reactions.[40]

1.3. Self-promoted Glycosylation Strategies

Glycosylation proceeding without any external activators, such as catalysts, promoters or scavengers, we refer to as "self-promoted" (**Scheme 1.5**).[56–59] In this type of reaction, the donor is activated by the acceptor, which acts also as a nucleophile. Self-promoted glycosylation is therefore a two-component reaction. The concept of activating the glycosyl donor by the acceptor is certainly advantageous for several reasons. First of all, self-promoted glycosylations are easy to perform as they employ only glycosyl donor, acceptor and a solvent, which are typically mixed under mild conditions. Furthermore, due to no need for additives, these reactions are appealing from an environmental as well as cost-efficiency standpoint. In contrast to self-promoted glycosylations, standard catalytic glycosylations require the addition of suitable catalysts or promoters. The latter ones have to be used in at least stoichiometric quantities, which generates significant amounts of chemical wastes.[15,28,60] Catalysts, on the other hand, are often relatively expensive. In most cases, the practical use of both catalysts and promoters is additionally impeded by their high toxicity, moisture and air sensitivity. Typically, low temperature is crucial for glycosylation due to their poor stability and volatility.[61–63] It should be also mentioned that the addition of activators, often revealing strong electrophilic nature, increases the possibility of generating other byproducts.[64–66]



Scheme 1.5. Schematic representation of the self-promoted glycosylation.[56–59]

Although self-promoted glycosylations might offer some improvements over conventional methods and have been known for decades since being introduced by Schmidt and Michel in 1980, these reactions have not piqued significant interest of the scientific community.[33] In fact, there have been only a few reports on self-promoted glycosylation methods, primarily enabling the synthesis of *O*-glycosides. Among those studies, several different glycosyl donors have been investigated (**Figure 1.1**).[31,33,67–71]

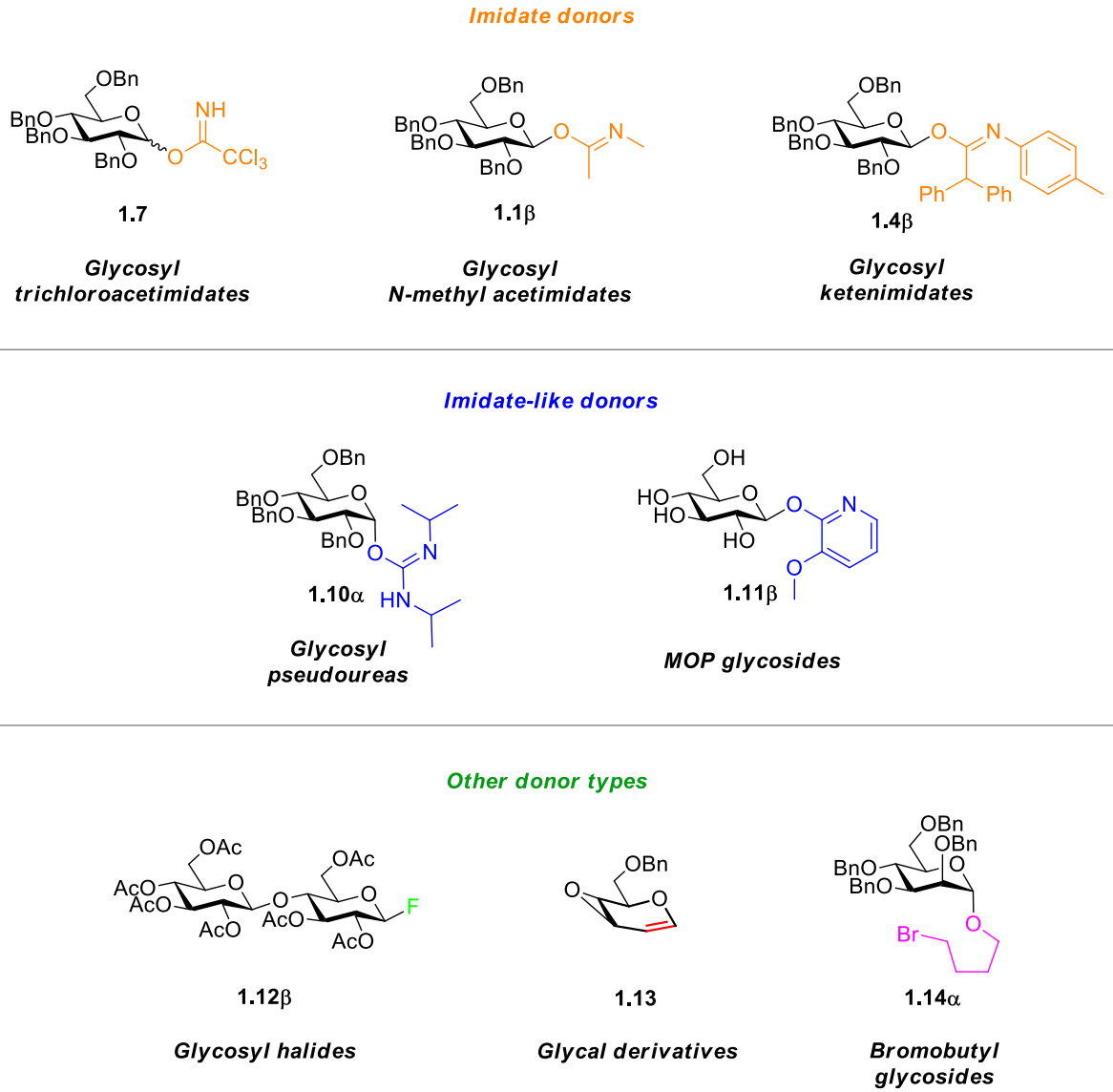


Figure 1.1. Selected examples of the glycosyl donor types studied in self-promoted glycosylations.[31,33,67–71]

Most of the developed glycosylations employ TCA glycosyl donors, which will be discussed in greater detail in the following section. In addition to TCA donors, other glycosyl imidates, i.e., *N*-methyl acetimidates and glycosyl ketenimidates, have also been proven to function as glycosyl donors in a self-promoted approach. In 1978, Sinaÿ and co-workers demonstrated that *N*-methyl acetimidates can be activated by carboxylic acid, *o*-nitrophenol and *o*-nitrothiophenol to give the corresponding *O*-glycosides with a complete inversion of the anomeric configuration.[31] Two years later, the self-condensation of the glycosyl ketenimidate **1.4β** and acetic acid appeared from Michel and Schmidt. The reaction was also highly invertive, leading to the preferential formation of the α-*O*-glycosyl ester (α/β > 19:1).[33]

The ability to react in a self-promoted manner has also been reported for glycosides that structurally resemble glycosyl imidates, i.e., pseudo-urea glycosyl donors and 2-(1,2-*trans*-glycopyranosyloxy)-3-methoxypyridines (MOP glycosides). The synthesis of the former ones was first reported by Ishido and co-workers in 1978, albeit the obtained glycosyl donors expressed high reactivity and hence could not be isolated.[67] On the basis of crude NMR spectra, it was, however, concluded that α-linked glycosyl donors were formed predominantly. In the same report and the follow-up paper, pseudo-urea glycosyl donors were shown to react with various acceptors in the absence of any additives, including phenols, thiophenols, carboxylic acids, aliphatic alcohols, theophylline and sugar alcohols.[67,72] It was observed that glycosylations were generally β-selective, with the exception of reactions employing aliphatic alcohols and sugar acceptors giving α-selectivity. Almost two decades after the introduction of pseudo-urea glycosyl donors, Hanessian and co-workers reported the first account of synthesizing and using other imidate-like donors, namely MOP glycosides.[68] Among those and further studies, it was found that activation of MOP glycosides can be achieved without the addition of any promoters by using acidic acceptors such as carboxylic acids, phosphoric acids, dibenzyl phosphate and uridine diphosphoric acid.[68,73] In all the glycosylations, inversion of the anomeric stereochemistry was observed, suggesting an S_N2-type mechanism. Notably, the scope of the glycosylation method was demonstrated on a range of different unprotected donors.

Besides glycosyl imidates and imidate-like donors, other glycosyl donor types have also been investigated in self-promoted glycosylation strategies. In 1997, Goggin and co-workers published the first and only report of using glycosyl halides as substrates for self-promoted glycosylations.[69] In an attempt to synthesize a biologically active glycoconjugate, the glycosyl fluoride donor **1.12β** was reacted with ticogenin and its TMS-protected derivative in a series of glycosylations. Although the reactions took place without external activators, elevated temperatures were necessary (112-190ºC). The reaction temperature was also found to affect the stereochemical outcome. In most cases, the reactions were selective toward the equatorial product. However, β-selectivity dropped with increasing the reaction temperature. Interestingly, no conversion into the desired glycoside was observed when using the N_2 sparging. It was therefore reasonable to hypothesize that the glycosylation could be catalyzed by the in situ formed HF.

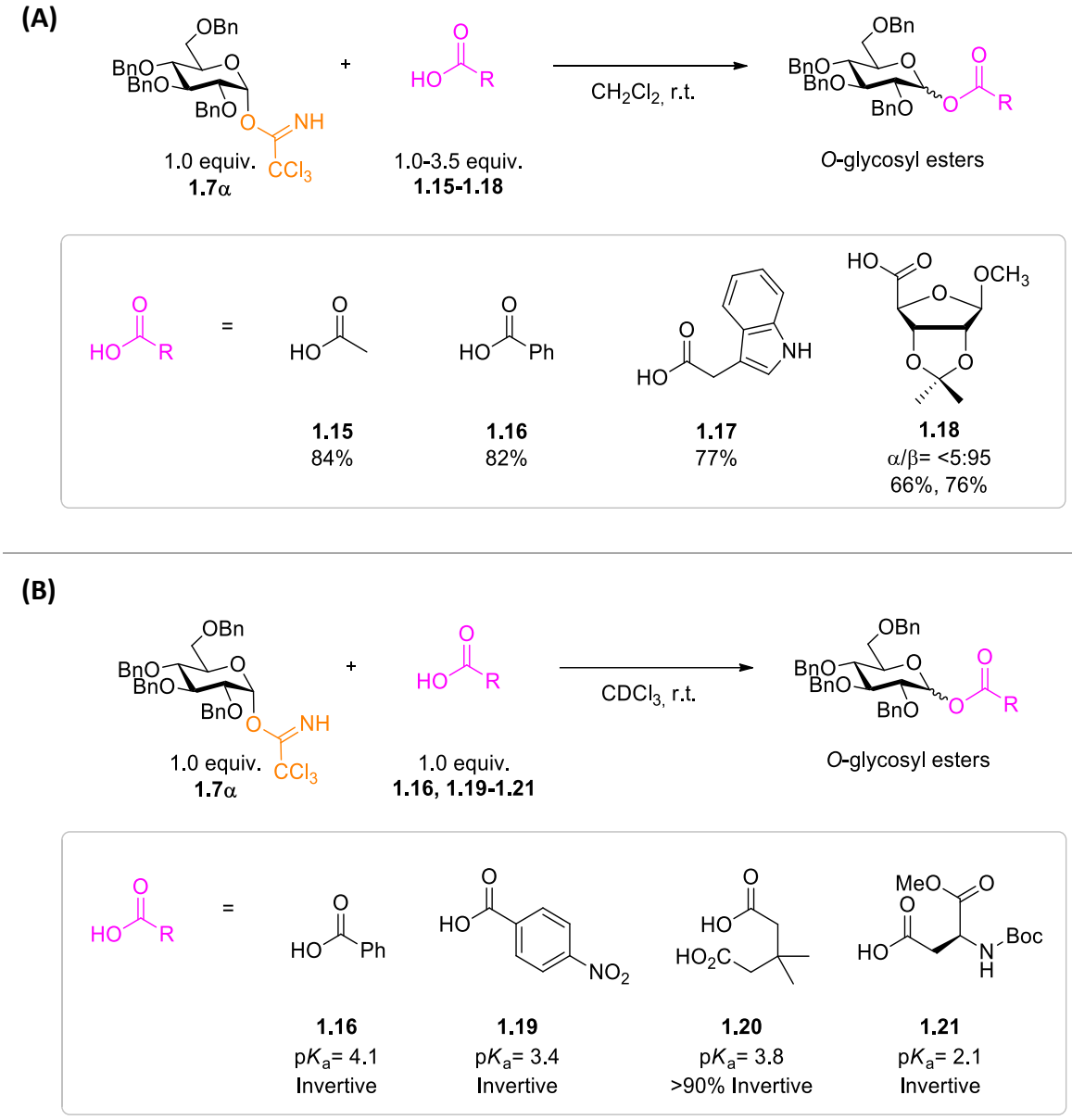
In the early 2000's, Crotti and co-workers were first to study glycals as glycosyl donors in self-promoted glycosylations.[70,74,75] They proposed a glycosylation strategy, which involved donors equipped with an epoxide function, i.e., α vinyl oxiranes. During their investigation, these epoxy glycals were found to undergo a regioselective 1,4-addition of alcohols and organolithium reagents leading to the corresponding 2,3-unsaturated *O*- and *C*-glycosides, respectively. Furthermore, it was observed that the stereochemical outcome of glycosylations is strongly influenced by the orientation of the oxirane ring. When using the α-faced epoxide, axial products were favored, whereas glycosylations with the β-oriented epoxide led to the preferential formation of equatorial glycosides. The authors rationalized this stereospecificity by interactions between the oxirane oxygen and incoming nucleophiles, such as hydrogen bonds and coordination through the metal.

Another variant of self-promoted glycosylation approach was introduced by Davis and co-workers in 2002.[71] They designed and investigated novel glycosyl donors, namely bromobutyl glycosides, which were found to display a unique ability to self-activate without the aid of an acceptor. According to the proposed mechanism supported by experimental data, the donor activation proceeds through the intramolecular nucleophilic substitution of the aglycon primary bromide by the anomeric *O*-1. This cyclization within the aglycon leads to the formation of a furanosyl cation, followed by the departure of the leaving group, giving rise to the oxocarbenium ion intermediate, which is the actual glycosylating agent. The scope of the glycosylation method was investigated on a range of two glycosyl donors, including the unprotected mannoside and two acceptors, i.e., methanol and primary sugar alcohol. In all cases, the reactions were found to be selective towards the thermodynamically favored α-products.

1.3.1. Self-promoted Glycosylations with Trichloroacetimidates

The first instance of the self-promoted glycosylation with TCA donor was reported by Schmidt and Michel in 1980 in their original work on glycosyl TCAs.[33] The perbenzylated glucosyl donor **1.7α** was reacted with the sugar acceptor carrying the carboxylic acid function (**1.18**) yielding the *O*-glycosyl ester with almost complete β-selectivity (**Scheme 1.6**). On the basis of the obtained result, it was realized that the acidic acceptor is capable of activating the TCA donor. Encouraged by this finding, the Schmidt group continued studies on self-promoted glycosylations with TCA glycosyl donors. In a follow-up paper, they demonstrated a series of glycosylations using the same glucosyl donor **1.7α** and a plethora of carboxylic acids bearing different moieties.[76] Likewise, the reactions gave rise to the corresponding *O*-glycosyl esters in good to excellent yields (70-96%) with a clear preference for the formation of β-products.

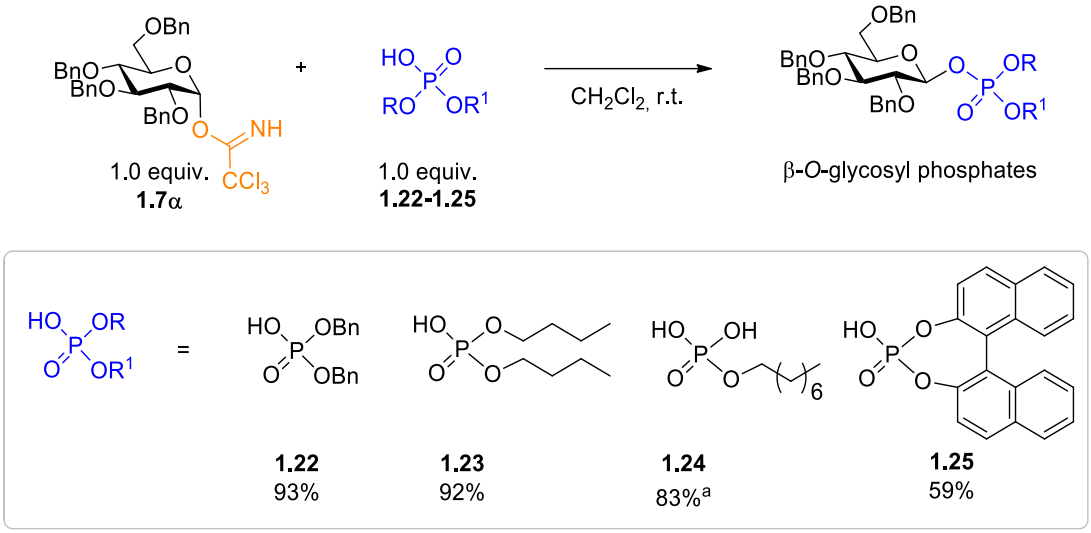
In 2013, carboxylic acids were further investigated by Miller and co-workers as catalytic activators for glycosylations with TCA glycosyl donors and alcohol acceptors (**Scheme 1.6**).[77] However, during their initial studies, it was found that carboxylic acids not only activated the TCA glycosyl **1.7α** but also competed in the glycosylation reaction with the actual acceptor. Due to the consumption of activator, no or poor conversion into the desired *O*-glycosylation products was observed along with the irreversible formation of the redundant *O*-glycosyl esters. The same carboxylic acids were subsequently utilized in stoichiometric amounts in a series of glycosylations employing the glucosyl donor **1.7α** without additional nucleophiles present. The reactions were monitored by ^{1}H-NMR which revealed broadening of the signal from the imidate NH proton upon addition of the carboxylic acid, indicating an interaction between the reactants. Furthermore, a negative correlation between the pK_a-values of the carboxylic acids and their relative reactivities was observed. In general, the reactions proceeded with a high degree of inversion of the anomeric configuration, similarly to the glycosylations reported by Schmidt and co-workers, suggesting a mechanism involving a close ion-pair.[76] In addition to prior experiments, a series of glycosylations using the donor **1.7α** and various alcohols were performed in the presence of the carboxylic acid **1.21** and $MgBr_2 \cdot Et_2O$, which was found to inhibit the undesired formation of *O*-glycosyl esters, presumably by coordination to the carboxylate ion.

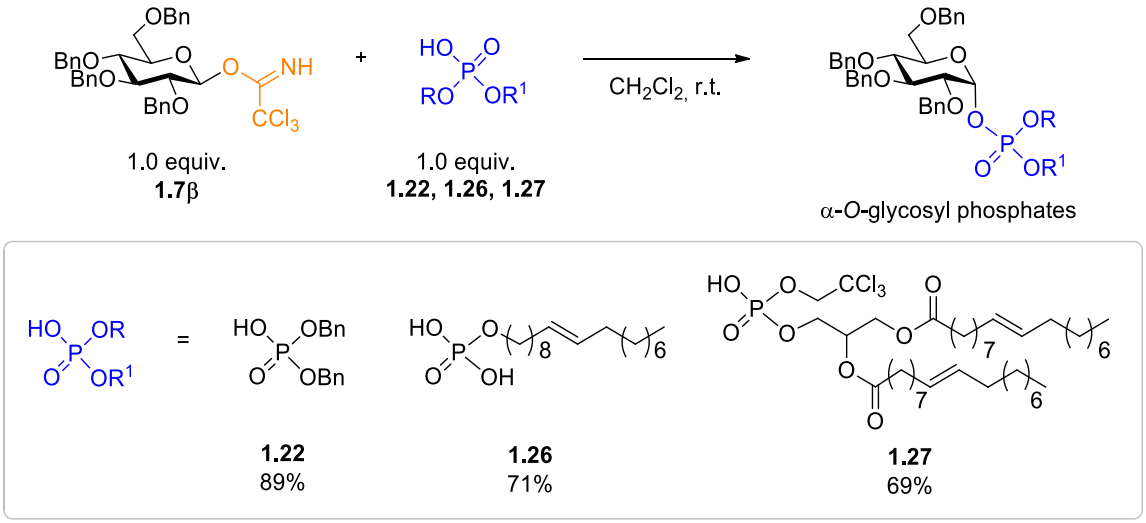


Scheme 1.6. Self-promoted glycosylations with TCA glycosyl donor and carboxylic acids reported by Schmidt and co-workers (A) and the Miller group (B).[76,77]

Shortly after the first publication describing the self-promoted glycosylation of the carboxylic acid with the TCA glucosyl donor, Schmidt and co-workers extended their studies to phosphoric acid derivatives. In the early 1980's, they reported the use of organic dihydrogen and hydrogen phosphates as both activators and acceptors for glycosylations with TCA glycosyl donors (**Scheme 1.7**).[78,79] During their investigation, several benzylated and acetylated donors with *gluco*, *manno* and *galacto* stereochemistry were reacted with various phosphoric acid-derived acceptors, leading to the formation of the desired *O*-glycosyl phosphates in yields ranging from 30 to 95%. The reactions with α-glucosyl donors were generally found to be

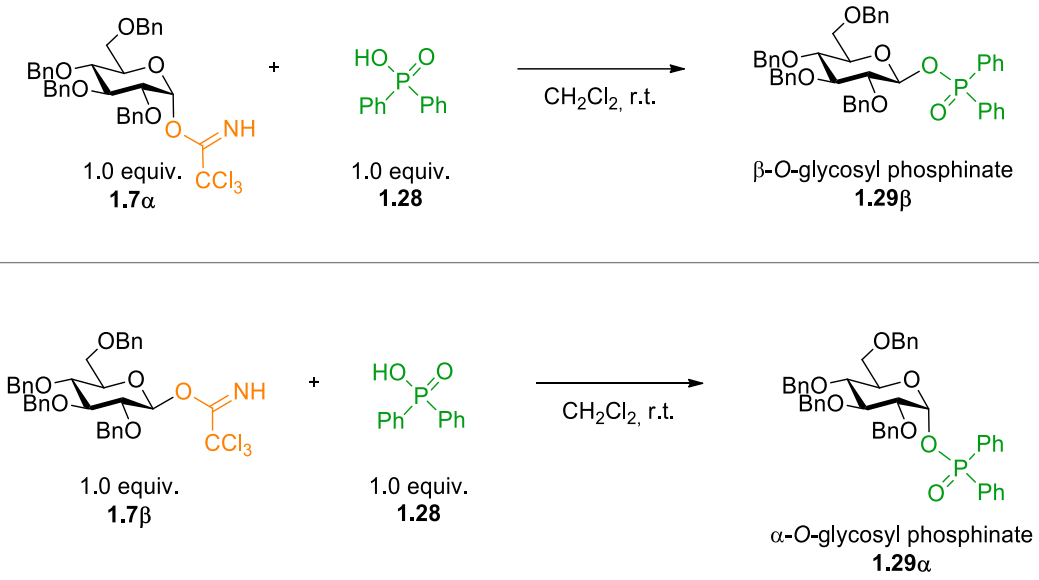
highly β-selective. However, some glycosylations facilitated exclusively α-linked products or gave an anomeric mixture. These results were justified by the anomerization of the initially formed β-glycoside to its α-counterpart catalyzed by the acceptor in the case of prolonged reaction time or acidic contaminations. Importantly, the anomerization was also observed upon the addition of a Lewis or Brønsted acid to the reaction mixture containing the β-product. Contrary to glycosylations using α-glucosyl donors, reactions with the β-glucosyl donor resulted in high selectivity toward the thermodynamic α-products.





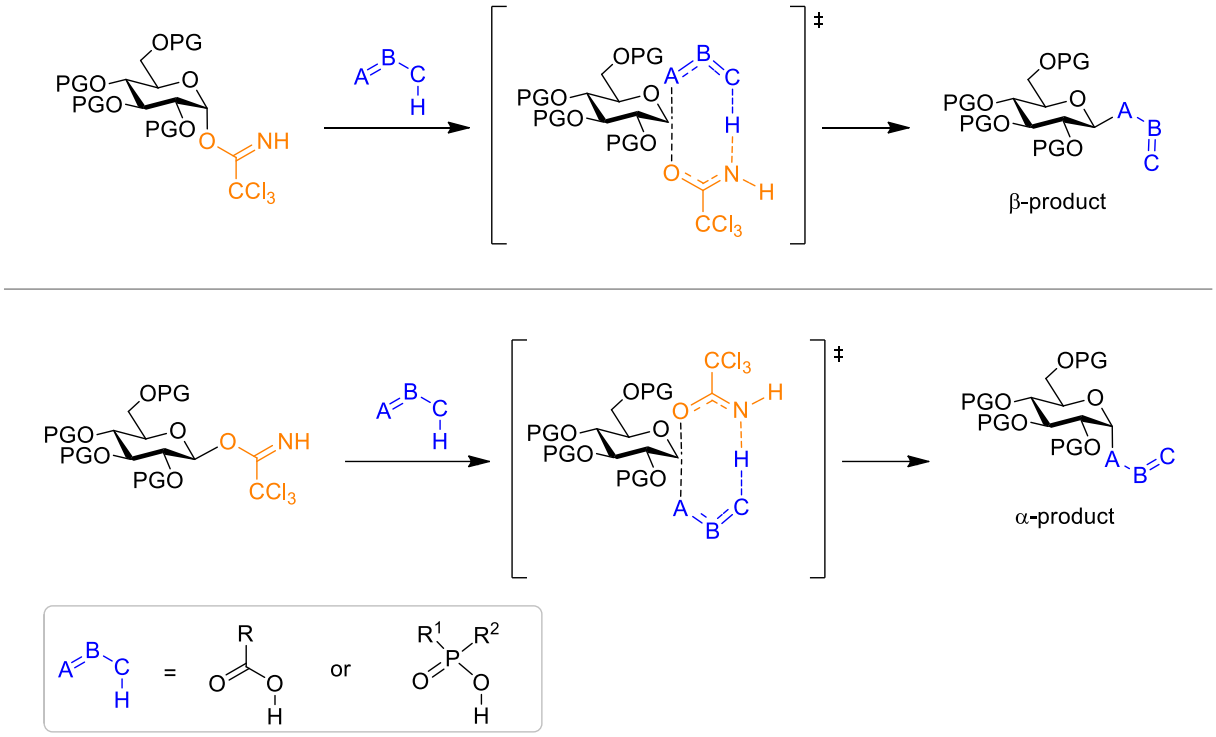
Scheme 1.7. Self-promoted glycosylations with organic dihydrogen and hydrogen phosphates investigated by Schmidt and co-workers.[78,79]

Later, the same research group broadened the scope of phosphorus-containing acceptors for self-promoted glycosylations with phosphinic, phosphonic and phosphoramidic acid derivatives (**Scheme 1.8**).[80] The glycosylation was investigated on a range of different TCA glucosyl donors varying in the protecting groups and anomeric stereochemistry. Likewise, the reactions proceeded in moderate to high yields (43-85%) and with a significant degree of inversion of the anomeric configuration.



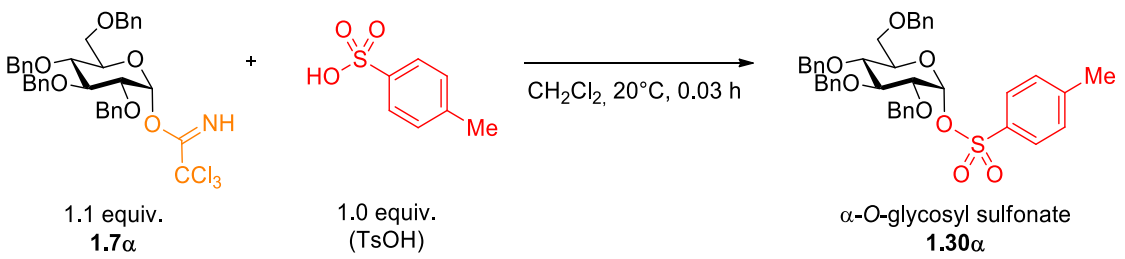
Scheme 1.8. Stereospecific formation of *O*-glycosyl phosphinates reported by the Schmidt group.[80]

The stereochemical outcomes of glycosylations using phosphorus-containing acceptors were much in line with those obtained for reactions with carboxylic acids. In most cases, the glycosylation products were formed with inversion of the anomeric stereochemistry. This stereospecificity was further explored by Schmidt and co-workers in 1990.[81] During their studies, they realized that these types of acceptors display structural similarities. On the basis of this, they introduced the concept of A=B-C-H systems, i.e., compounds which can adopt the suitable geometry enabling both activation of the TCA donor and nucleophilic substitution at the C-1 position (**Scheme 1.9**). According to the proposed mechanism, the reaction between the TCA donor and the A=B-C-H-like compound follows an S_N2-type pathway, involving the formation of a cyclic intermediate. In this intermediate, the anomeric centre is attacked by the A atom of the A=B-C-H system parallel to the protonation of the trichloroacetimidate nitrogen atom.



Scheme 1.9. Proposed mechanism of glycosylations with A=B-C-H systems justifying the selective formation of the β- and α-glycosides.[81]

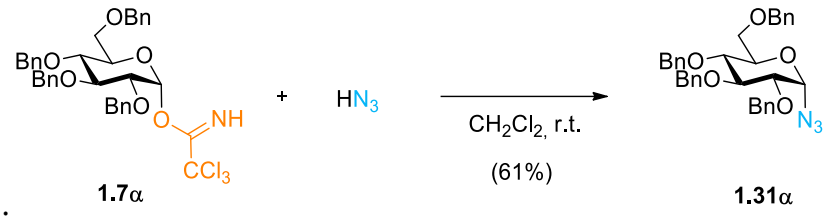
Although sulfonic acids and their derivatives have been extensively studied as catalytic activators of TCA glycosyl donors[15,33,77], there have also been examples of self-promoted glycosylations using these types of compounds.[76] Such reactants, however, cannot be classified as A=B-C-H systems. The first and only instance of a self-promoted reaction employing sulfonic acid appeared from Schmidt and co-workers in 1985 (**Scheme 1.10**). In contrast to other reported glycosylations with TCA glycosyl donors involving even stoichiometric amounts of *p*-toluenesulfonic acid, the reaction was carried out without additional nucleophilic agents present. It was found that *p*-toluenesulfonic acid is capable of activating the α-glucosyl donor (**1.7α**) and substituting its leaving group, leading to the exclusive formation of the thermodynamically favored α-*O*-glycosyl sulfonate (**1.30α**).



Scheme 1.10. The first example of self-promoted glycosylation with *p*-toluenesulfonic acid.[76]

Among other catalysts bearing the sulfonyl function used for activation of TCA glycosyl donors, TMSOTf proved to react in a self-promoted fashion similar to *p*-toluenesulfonic acid, giving rise to the corresponding *O*-glycosyl triflates. This self-condensation was first observed by Kim and co-workers using low-temperature NMR.[82] Although *O*-glycosyl triflates could not be isolated due their thermal instability, they have been successfully utilized as intermediates in β-mannosylations. During these studies, it was also found that their tendency to decompose can be diminished by installation of strongly electron-withdrawing protecting groups.

All previously described self-promoted approaches using TCA glycosyl donors enable the formation of *O*-glycosides. Despite the fact that *N*-glycosides constitute another important class of carbohydrates, we have found only one example of the self-promoted *N*-glycosylation with TCA donor reported prior to work by the Pedersen group, including the studies presented in this dissertation. In 1985, Schmidt and co-workers demonstrated that hydrazoic acid can react with the TCA donor (**1.7α**) without external additives, albeit not through the same pathway as A=B-C-H systems due to its linear geometry (**Scheme 1.11**).[76] The reaction resulted in the α-linked *N*-glycosyl azide (**1.31α**) in 61% yield. Besides a series of publications by Pedersen and co-workers[56–58], one more report appeared during the preparation of this thesis. In 2021, Mandal and Khanam reported a study on self-promoted glycosylations with TCA glycosyl donors and *N*-sulfonyl carbamates, which is a continuation of our work, and hence will not be discussed in detail.[83]

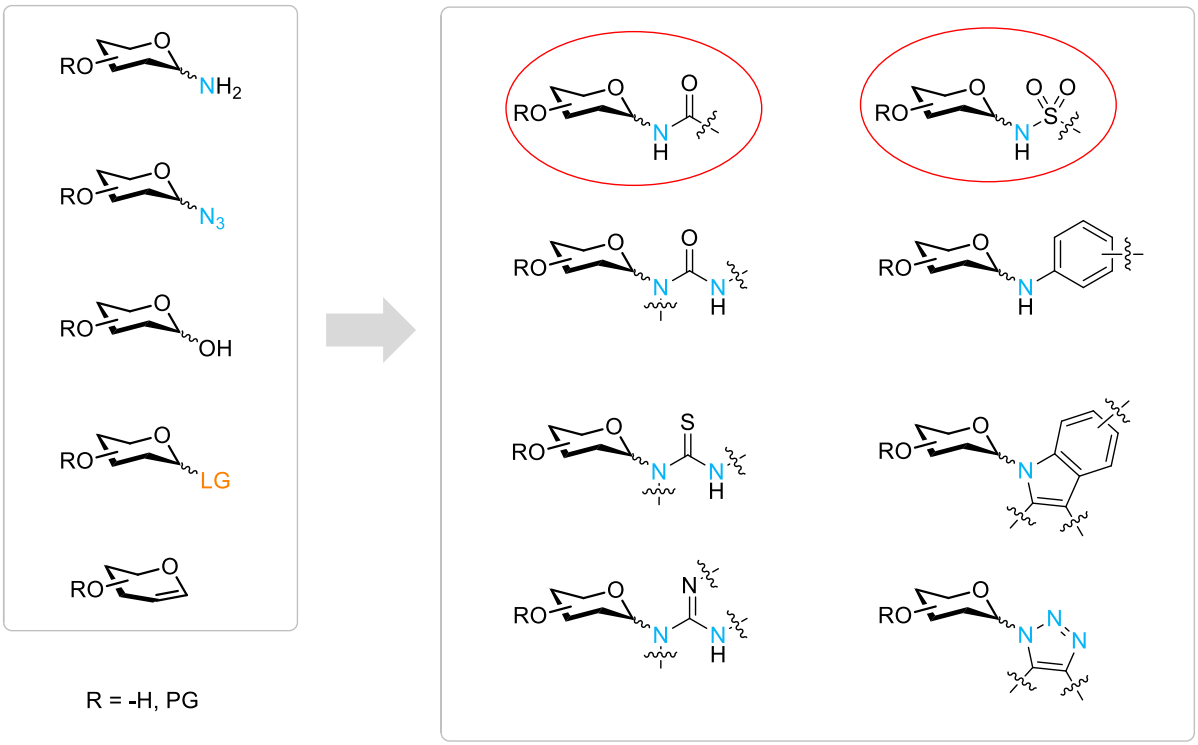


Scheme 1.11. The first instance of self-promoted *N*-glycosylation.[76]

1.4. *N*-glycosides as Important Targets in Organic Synthesis

N-glycosidic linkage is omnipresent in a broad spectrum of natural products, including complex biomolecules, i.e., nucleic acids and glycoproteins as well as smaller compounds with therapeutic properties such as antibiotics. The structural diversity of natural *N*-glycosides translates into a wide range of biological activities, frequently essential for life sustainability.[84–88] For this reason, *N*-glycosides have become an expanding field of research in the life sciences. Over the years, they have been extensively investigated to improve scientific understanding of their roles in living organisms, which has significantly contributed to the development of new therapeutic and diagnostic strategies.[89–91] Their biological relevance has also prompted scientists to discover non-natural *N*-linked glycoconjugates for numerous applications, especially in the area of medicinal chemistry. In fact, some of these compounds have been shown to offer great potential as antibacterial, antiviral, and anticancer agents[92,93]

The physicochemical properties of organic compounds, and hence their biological functions are closely related to their chemical structure. Thus, in order to achieve different characteristics, various structural motifs have been introduced in the anomeric position, which required scientists to develop new approaches for the *N*-functionalization of carbohydrate derivatives (**Scheme 1.12**). A vast number of methods have been reported which essentially can be categorized into three general strategies, namely functionalization of nitrogen-containing groups at the anomeric position, nucleophilic substitution of the leaving group, and inserting of an *N*-function into a sugar moiety devoid of anomeric substituent.[94] The first approach has gained special attention due to its utility for the preparation of biologically relevant glycopeptides and glycoproteins. This strategy typically involves the most popular synthetic precursors of *N*-glycosides, namely anomeric glycosylamines and glycosyl azides.[95–97] *N*-functionalization of sugars through nucleophilic substitution, on the other hand, has been attained using hemiacetals and different glycosyl donors, e.g., glycosyl imidates, thioglycosides, and glycosyl esters.[44,98–100] For the latter synthetic strategy, unsaturated sugar derivatives such as glycals have been the most commonly utilized substrates.[101–103] All the above-mentioned methodologies will be further discussed in context of the synthesis of *N*-glycosyl amides and sulfonamides, which were the central synthetic targets of our studies.



Scheme 1.12. Overview of important precursors of *N*-glycosides and common structural motifs found in *N*-functionalized carbohydrates.[94]

1.4.1. *N*-glycosyl Amides

N-glycosyl amides are an important class of *N*-glycosides with unique properties for a broad scope of applications (**Figure 1.3**). The *N*-glycoproteins represent the most ubiquitous group of such glycoconjugates in nature. In fact, they occur in all known forms of life.[5] These highly diverse and complex molecules contain oligosaccharides, namely *N*-glycans which are covalently attached to the protein through the *N*-glycosidic linkage. Typically, in natural *N*-glycoproteins the asparagine side chain is β-glycosylated with the GlcNAc sugar unit. Nevertheless, other different structural motifs have been also found in nature such as Glc-Asn, GalNAc-Asn, and Rha-Asn.[14] The attachment of sugars can affect the structure and activity of proteins, in some cases even their functions. For instance, the introduction of glycans was shown to stabilize the protein conformation through hydrogen bonds or hydrophobic interactions. Furthermore, such modification provides additional protection of protein surfaces against proteases.[3,104] Existing in various living organisms, *N*-glycans play crucial roles in a vast array of biological processes, including protein folding, signaling, immune response, cell recognition, and cell adhesion.[5,11,105] Therefore, glycosylation is considered one of the most important posttranslational modifications of proteins.

Another worth mentioning representatives of *N*-glycosyl amides are *N*-linked glycolipids which have found application in material science.[106] These amphiphilic glycoconjugates have been shown to self-assemble into nanotubes. The general structure of the self-assembling *N*-glycolipids consists of the hydrophilic carbohydrate moiety such as β-D-glucopyranosyl amine and a linear-hydrophobic chain. Glycol-bolaamphiphiles (**1.34β**) are a particularly interesting type of glycolipids forming nanostructures due to an additional hydrophilic group at the second end of the hydrocarbon chain. Moreover, amphiphilic *N*-glycosyl amides have also been successfully utilized as NICBS (non-ionic carbohydrate-based surfactants, **1.32β**), which are considered to be more environmentally friendly alternatives to polyethyleneglycol-type surfactants.[107,108]

Over the past three decades, *N*-glycosyl amides have been investigated as promising candidates for therapeutic applications.[6,109–111] For instance, α-linked so-called neo-glycoconjugates (**1.35α**) have been shown to inhibit carbohydrate-binding lectins in the micromolar range, including PA-IIL lectin from the opportunistic bacterium *Pseudomonas aeruginosa* responsible for severe infections associated with rates of high mortality.[112] The vast majority of naturally occurring *N*-glycosyl amides are β-linked. Therefore, in addition to the high affinity towards lectins, non-natural α-*N*-glycosyl amides are supposed to be more stable to hydrolytic enzymes compared to their β-counterparts. Among other biologically active *N*-glycosyl amides, β-*N*-glycosyl-thiophene-2-carboxamides (**1.33β**) proved to inhibit endothelial cell proliferation and hence might have potential in the treatment of angiogenesis-dependent diseases**.**[113,114] Furthermore, low molecular weight β-*N*-glucosyl amides (**1.36β**) have also been recognized as potent inhibitors of glycogen phosphorylase.[115,116]

N-glycosyl amides exhibit interesting properties and play fundamental roles in biological processes, especially *N*-glycoproteins. Expression of glycoproteins in cells commonly provides heterogeneous mixtures that are troublesome to separate.[14,86] This limits structural elucidation studies and further application. Therefore, there is a great need for development of efficient synthetic strategies which allow to obtain anomerically pure *N*-glycosyl amides.

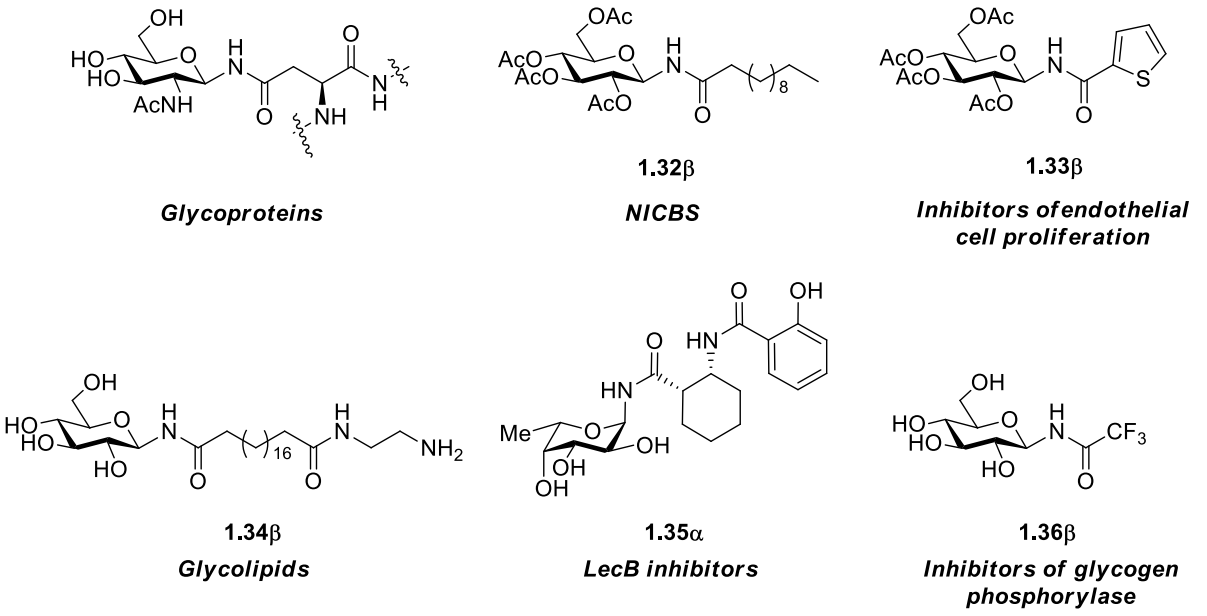


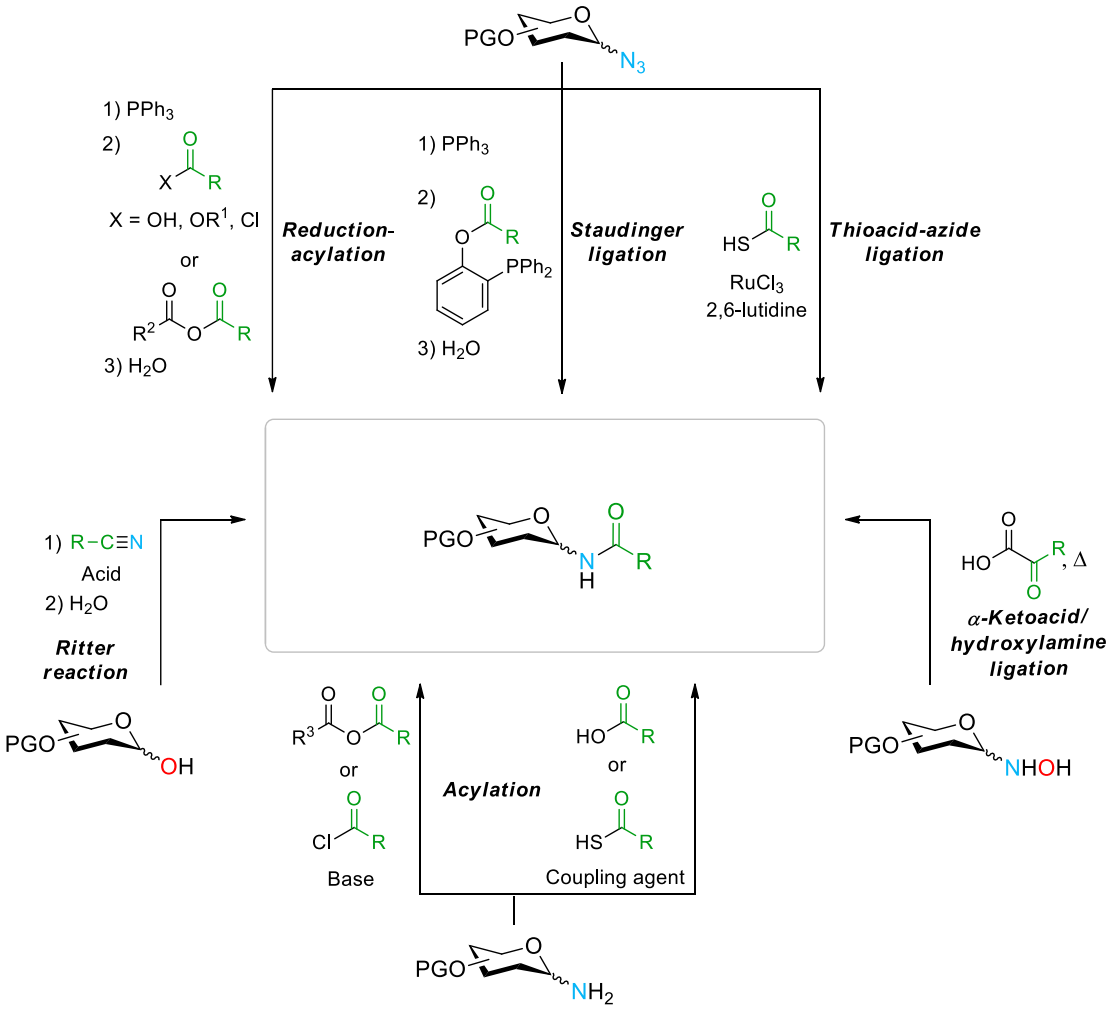
Figure 1.2. Representative examples of relevant natural and non-natural *N*-glycosyl amides.[14,106,107,112,114,116]

A lot of synthetic strategies have been developed for the synthesis of *N*-glycosyl amides (**Scheme 1.13**). However, many of these approaches facilitate the anomeric mixtures rather than the desired anomer. In addition, most of the developed methods have drawbacks, including the need for additives, harsh conditions, and low stability of the reactants. Early examples of synthesizing *N*-glycosyl amides hinged on the acylation of suitable hemiaminals using carboxylic acid derivatives such as acyl chlorides and anhydrides, typically in the presence of an additional base.[114,117–119] The general limitations of these methods lie in the poor stability of both the acylating agents and the glycosylamines, which are prone to undergo hydrolysis. This implies the necessity of anhydrous conditions and often using excessive amounts of acylating reagents. Furthermore, anomeric glycosylamines can anomerize under reaction conditions, leading to a drop in stereoselectivity. To overcome issues regarding the low stability of acylating reagents, *N*-glycosylamines have been condensed with more stable carboxylic acids or thioacids using coupling agents, most commonly *N*,*N*'-dicyclohexylcarbodiimide (DCC).[120–124] There have also been examples of photochemical couplings in which *N*-glycosylamines were reacted with photoreactive amides.[125]

Other important precursors of *N*-glycosyl amides are the anomeric azides, which generally reveal higher stability towards hydrolysis compared to the corresponding *N*-glycosylamines. Moreover, in contrast to glycosylamines, glycosyl amides do not undergo mutarotation and thus, in principle, provide better control of the stereochemical outcome. *N*-glycosyl azides can be converted to the amide-linked derivatives through a reduction-acylation reaction, referred to as the Staudinger reaction.[126–129] In this procedure, the glycosyl azide is initially reduced by the suitable organophosphine to the corresponding iminophosphorane intermediate, which is subsequently subjected to acylation by carboxylic acid or an activated derivative thereof. The resulting intermediate is then hydrolyzed to give the amide derivative. Although *N*-glycosyl azides do not anomerize, the preliminary formed iminophosphorane intermediates are prone to anomeric isomerization favoring β-anomers. It has been found that stereochemical information of the starting material can be retained only when using a highly reactive acylating agent which can trap the aza-ylid intermediate immediately.[126] To address the problem of stereoselectivity, another approach employing anomeric azides was

developed, namely the traceless Staudinger ligation.[130–132] This method, however, requires prior preparation of phosphine-functionalized acylating reagents.

In contrast to the Staudinger reaction, ligation involves an intramolecular acyl transfer which proceeds faster than the anomerization of the iminophosphorane intermediate. Thus, the reaction results in significant retention of the anomeric configuration. Glycosyl azides have also been effectively transformed into *N*-glycosyl amides by reaction with thioacids, i.e., thioacid-azide ligation.[133,134] Noteworthy, the reaction was found to proceed with an inversion of the anomeric configuration, which is in line with the suggested mechanistic scenarios involving formation of the 5-membered thiatriazoline intermediate.[135] This method, however, suffers from the need for additives such as 2,6-lutidine and in some cases $RuCl_3$ as a catalyst.



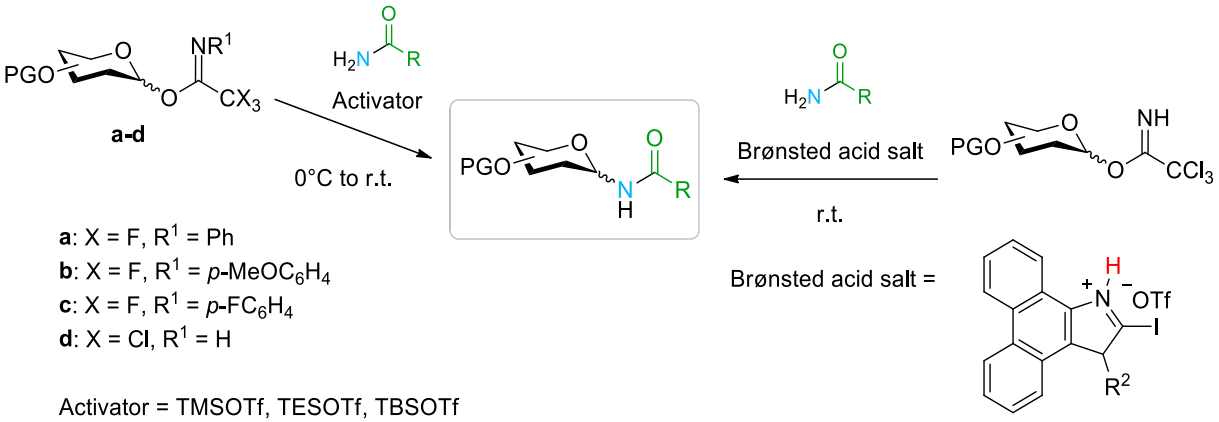
Scheme 1.13. Overview of selected methods for synthesizing *N*-linked glycosyl amides.[108,117,121,124,127,131,134,136]

Among the strategies for the synthesis of glycosyl amides, worth mentioning is the chemoselective reaction between *N*-glycosyl oximes and α-ketoacids, known as α-ketoacid-hydroxylamine ligation.[136] The clear advantage of this method relies on the fact that the reaction takes place without any additives. According to the proposed mechanism, the ligation proceeds through nitrone intermediates formed upon the nucleophilic attack of the oxime nitrogen on the keto group and the subsequent elimination of H_2O. The nitrone intermediates then undergo spontaneous rearrangement to the corresponding *N*-glycosyl amides with the release of CO_2. Although the reactions gave high β-selectivity, the products were obtained in rather poor yields, due to partial hydrolysis of the *N*-glycosyl oximes and the undesired formation of byproducts from α-ketoacids.

Furthermore, *N*-glycosyl amides have been derived from hemiacetals by reaction with the suitable nitriles in the presence of Brønsted or Lewis acid.[108,137] For this functionalization, termed the Ritter reaction, Wang and co-workers suggested a mechanistic pathway involving an oxocarbenium cation intermediate.[108] The following nucleophilic attack by the nitrile reagent leads to the formation of the nitrilium cation, which is first transformed into the imine intermediate and then hydrolyzed to the corresponding *N*-glycosyl amide. Importantly, the oxocarbenium cation intermediate was found to be preferentially attacked from the β-side in the *gluco* series. The reactions, however, resulted in low yields, which certainly limits the application of this method.

Glycosyl imidates have also been successfully utilized in the preparation of *N*-glycosyl amides (**Scheme 1.14**). In 2005, Takahashi and co-workers reported an *N*-glycosylation method for the synthesis of asparagine-linked glycopeptides employing glycosyl imidate donors and amide acceptors.[44] In the preliminary screening, a series of glycosylations were performed using β-galactosyl imidates, common organic solvents, and different triflates as activators. The reaction gave the best results in terms of yield when activating the glycosyl *N*-phenyltrifluoroacetoimidate with TMSOTf in a polar solvent, i.e., CH_3NO_2. The scope of glycosylation was investigated on a range of substrates, including the *N*-Troc-protected glucosamine derivative and the asparagine-containing tripeptide. In general, preferential formation of 1,2-*trans*-glycosides was observed in yields spanning from 10 to 92%. The selectivity, however, could arise from the neighboring group participation. Noteworthy, the methodology developed by Takahashi and co-workers was further explored under integrated microfluidic/batch conditions and for the synthesis of ribosylated amino acids.[138,139]

Another approach involving glycosyl imidates and amide acceptors has been proposed by Takemoto and co-workers in 2018.[140] They developed two catalytic systems for the activation of TCA glycosyl donors bearing an acyl protective group at the C-2 position. In both cases, the donors were activated under mildly acidic conditions. When using Schreiner's thioureas in combination with a co-catalyst, i.e., di-*N*-substituted 2-iodoazolium salts, the reaction predominantly led to the formation of *N*-acylorthoamides, which could then be rearranged to the corresponding *N*-glycosyl amides upon addition of an acidic activator. Direct *N*-functionalization, on the other hand, was attained by the use of Brønsted acid salt, i.e., mono-*N*-substituted 2-iodoazolium salt. Notably, these conditions allowed the authors to obtain various *N*-glycoconjugates in yields of 45-96%, including asparagine-linked glycopeptides. Likewise, high selectivity towards of 1,2-trans-glycosides was observed, which most likely relied on the neighboring group participation. In the follow-up paper, the *N*-glycosylation was also investigated with benzylated TCA glycosyl donors. During these studies, it was found that the stereochemical outcome is strongly affected by the choice of solvent.[42]



Scheme 1.14. Synthesis of *N*-glycosyl amides from glycosyl imidates.[44,140]

1.4.2. *N*-glycosyl Sulfonamides

Although *N*-linked glycosyl sulfonamides have not attracted as much attention as glycosyl amides, they certainly represent a unique and versatile class of glycoconjugates. In fact, these molecules have emerged as potential therapeutic targets against cancer. Notably, the 2-deoxy *N*-glycosides carrying a sulfonamide function have been shown to inhibit the growth of human hepatocellular carcinoma cells in the two-digit micromolar range (**Figure 1.3**).[141] Furthermore, *N*-glycosyl sulfonamides have been recognized as potent inhibitors of carbonic anhydrase, i.e., a zinc metalloenzyme which in living organisms occurs as different isoforms involved in a number of biological and pathological events (**Figure 1.3**).[142,143] In 2007, Supuran and co-workers reported a series of glycosyl sulfonamide inhibitors revealing nanomolar affinity towards four of the five tested human carbonic anhydrase (hCA) isoforms, including the tumor-associated hCA IX and XII.[143] Importantly, during their studies, it was found that the developed compounds displayed similar inhibitory activity to clinically used sulfonamide-containing drugs, namely acetazolamide and topiramate. In some cases, the developed inhibitors turned out to be even more potent than the aforementioned pharmaceuticals. In addition, one of the evaluated compounds was found to be isozyme-selective, displaying stronger affinity for tumor-associated isoforms hCA IX and XII. It should be mentioned that the reported examples of carbonic anhydrase *N*-glycosyl sulfonamide inhibitors shared the same aglycon, i.e., $NHSO_2NH_2$. However, the developed library consisted of diverse derivatives varying in sugar ring size, stereochemistry and functional groups.

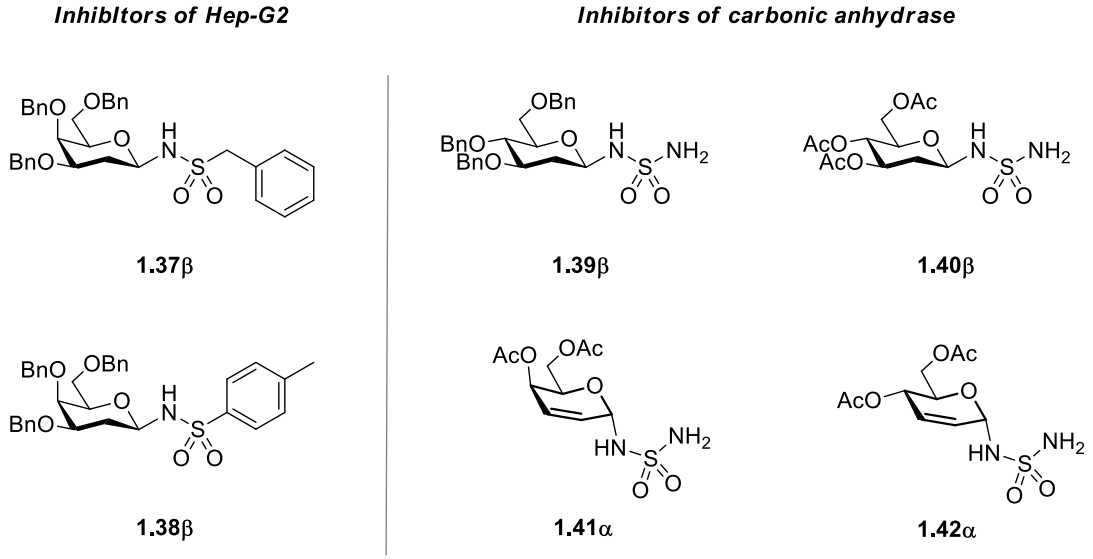


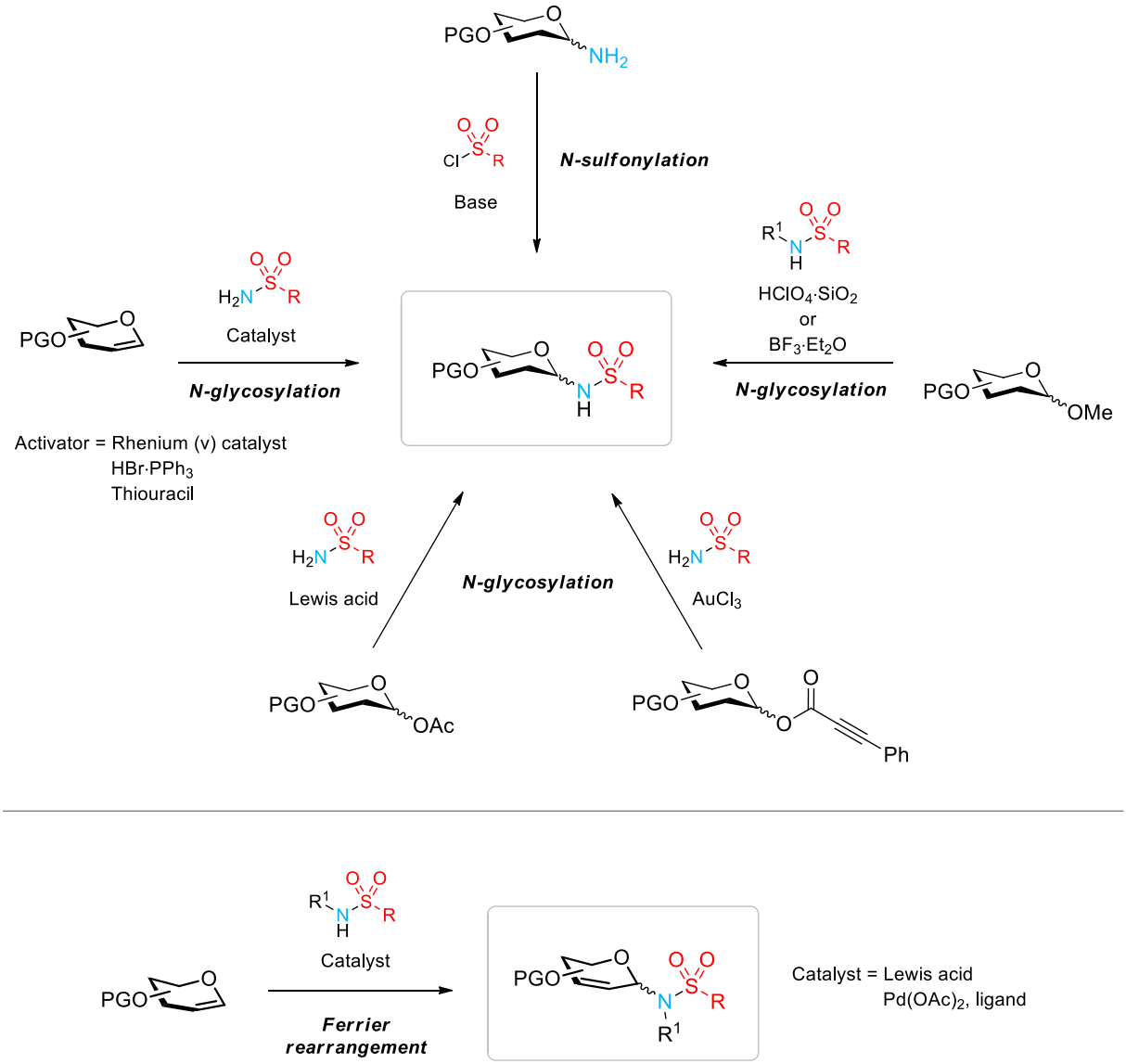
Figure 1.3. Representative examples of biologically active *N*-glycosyl sulfonamides.[141,143]

Since *N*-linked glycosyl sulfonamides have been demonstrated to possess promising biological activities and hence therapeutic potential, there is certainly a demand for efficient synthetic approaches toward these glycoconjugates. A lot of effort has been made in this field, especially in the past two decades. Analogously to the amide moieties, sulfonamide substituents have been introduced at the anomeric position by a reaction of suitable hemiaminals and sulfonyl chlorides in the presence of a base such as triethylamine and pyridine (**Scheme 1.15**).[144–146] However, as previously discussed, this method suffers from a low stability of the reactants towards hydrolysis and the intrinsic tendency to anomerization of glycosylamines, which may lead to a decrease in yield and stereoselectivity, respectively. In fact, according to examples from the literature, sulfonylation reactions usually resulted in poor and moderate yields.

Alternatively, *N*-linked glycosyl sulfonamides have been synthesized from glycals through *N*-glycosylation with sulfonamides (**Scheme 1.15**). Depending on the activation conditions, 2-deoxy or 2,3-unsaturated derivatives could be obtained. In general, Lewis acid catalysts, e.g., $BF_3 \cdot OEt_2$, $RuCl_3$, and triflates have been found to promote the allylic rearrangement, referred to as Ferrier rearrangement, leading to the 2,3-unsaturated products in good to excellent yields.[147–149] The reactions were often highly α-selective, albeit there was an example of the palladium-catalyzed Ferrier glycosylation facilitating predominantly β-glycosides.[150] 2-deoxy *N*-glycosyl sulfonamides, on the other hand, have been prepared via direct addition using several different catalytic systems, involving $PPh_3 \cdot HBr$, Re(V)-oxo complexes, and thiouracil.[141,151,152] Likewise, the reactions generally gave high yields. Nevertheless, in contrast to Ferrier glycosylations, a strong preference for the formation of β-glycosides was observed. In the report by Bravo and Colinas, this β-selectivity was rationalized by steric factors and the reverse anomeric effect.[141]

Furthermore, glycosyl esters have been employed as glycosyl donors for the synthesis of *N*-glycosyl sulfonamides (**Scheme 1.15**). In 2009, Bravo and co-workers showed that primary sulfonamides can be glycosylated with per-*O*-acetylated sugars upon Lewis acid activation.[153] During their preliminary studies, several promoters were investigated, of which $BF_3 \cdot OEt_2$ gave the best results in terms of yield. The optimized protocol involved the use of promoter in excessive amounts (2.0 equiv.), which seems to be the major limitation of this method. The scope of the glycosylation was studied using simple acceptors and anomeric mixtures of gluco-, galacto-, manno- and arabinosyl donors. All reactions facilitated corresponding *N*-glycosyl sulfonamides in high yields and with equatorial selectivity, which

the authors justified by the presence of unfavorable steric interactions in α-anomers. A decade after, stereoselective glycosylation with another glycosyl ester was published by Kumar and Shaw.[154] They proposed a general method for the synthesis of *O*- and *N*-linked 2-deoxy sugars employing deoxyphenylpropiolate glycosides as glycosyl donors. In their system, $AuCl_3$ was used for the activation of glycosyl donors, which can limit the application of the method considering cost-efficiency. A series of glycosylation were undertaken, however, including only one example of glycosylation with a sulfonamide acceptor. The reaction gave rise to the desired *N*-glycoside in a yield of 81% with high α-selectivity, which was explained by the favorable attack on the oxocarbenium ion while adopting a more stable half-chair conformation.



Scheme 1.15. Overview of selected synthetic approaches towards *N*-glycosyl sulfonamides.[144,150,151,153–155]

Besides glycosyl esters, methyl glycosides have also been investigated in *N*-glycosylations with sulfonamides (**Scheme 1.15**). In 2005, Colinas and Bravo reported early examples of such a reaction.[155] In their approach, methyl glycosides were activated with equivalent amounts of $BF_3 \cdot OEt_2$. The scope and limitations of the method were studied using a range of simple sulfonamides and benzylated glycosyl donors, including ribofuranosides and 2-deoxy sugars with *gluco* and *galacto* stereochemistry. The glycosylations were found to proceed in low to high yields, up to 85%. No significant anomeric selectivity was observed when reacting ribofuranosides, whereas glycosylations with 2-deoxy donors yielded almost exclusively β-products. In the follow-up paper by the same authors and Núñez, the reaction was further investigated using a different promoter, namely $HClO_4$-SiO_2, which is considered attractive in terms of cost-efficiency and easy to remove after the reaction.[156] Although the anomeric selectivity was not highly influenced by changing the promoter, an increase in yield could be achieved.

Goals of Research

Our paramount goal in this research was to develop an efficient and stereoselective approach involving a self-promoted glycosylation and the orthogonal protection strategy for the preparation of selectively functionalized *N*-glycosides. The pursued project can be divided into two parts, of which the first is dedicated to *N*-glycosyl sulfonamides and carbamates, and the second to *N*-glycosyl amides. At the onset of the project, we formulated several main objectives. To develop the glycosylation method, our initial goal was to investigate whether the *N*-sulfonyl carbamates and *N*-sulfonyl amides can activate the acid-labile TCA glycosyl donors in the presence of no additives. The following objective was to establish the optimal glycosylation procedure and to study its generality and versatility by testing various TCA glycosyl donors and electron-poor acceptors. During this part of the studies, we aimed to assess how different structural features of the reactants, such as size, stereochemistry and particular functional groups influence the reaction rate, yield and anomeric ratio. To complete the synthesis of target *N*-glycosides, we set the chemoselective removal of the sulfonyl and carbamate functions to be our last goal. Apart from the synthesis, this work aimed also to determine the structures and conformations of the obtained products using different spectroscopic methods.

CHAPTER II

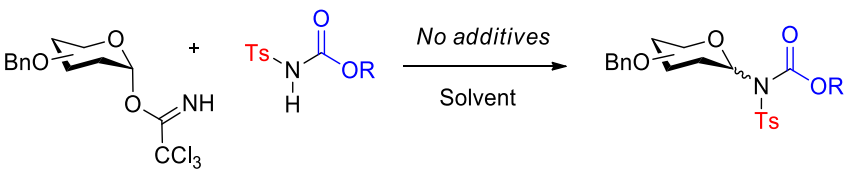
Self-promoted Glycosylation: Synthesis of *N*-glycosyl Sulfonamides and Carbamates

2.1. Introduction

Glycosyl sulfonamides display a wide range of biological activities and hence they have attracted much attention from the synthetic community. This class of glycosides has been recognized as promising antitumor agents.[157–159] Furthermore, glycosyl sulfonamides were found to possess inhibitory potency toward human carbonic anhydrase.[160] Although various synthetic strategies for such compounds have been reported, most of them require harsh conditions or additives such as catalysts and promoters.[150,156,161–163] In addition, these methodologies generally result in modest yields and stereoselectivities.[155,156,162,164] Thus, there is still a need for further development in this direction.

Although glycosyl carbamates have not gained significant popularity, they certainly represent another noteworthy class of glycosides. They have been studied as glycosyl donors, potential pharmaceuticals and surfactants.[165–168] Moreover, the application of glycosyl carbamates as multivalent ligands has also been investigated for studying carbohydrate-protein interactions.[169] There have been only a few reports dealing with the synthesis of anomeric glycosyl carbamates. One of the earliest and most commonly utilized methods employs hemiacetals and unstable isocyanates.[166–168] Alternative routes suffer from the need for catalysts or basic conditions.[170–172] Therefore, new mild and efficient strategies giving access to glycosyl carbamates are yet to be developed.

Since glycosyl sulfonamides and carbamates represent interesting targets in carbohydrate chemistry, we decided to develop an approach that could provide these derivatives in practical yields with the control of anomeric stereochemistry. Our synthetic strategy featured two key steps, i.e., *N*-glycosylation and the subsequent orthogonal deprotection. For the formation of the *N*-glycosidic bond, we turned our attention to the self-promoted glycosylations employing acid-labile TCA glycosyl donors.[77,78] Encouraged by the previously reported studies, we expected that electron-poor sulfonamides equipped with the carbamate function could also effectively activate TCA glycosyl donors and react with them giving rise to *N*-glycosyl sulfonyl carbamates (**Scheme 2.1**).



Scheme 2.1. Self-promoted *N*-glycosylation of *N*-sulfonyl carbamates.

As we anticipated, the acidic acceptors indeed allowed for the formation of *N*-glycosides without the need for any additives such as catalysts or promoters, making the developed glycosylation method particularly attractive. Noteworthy, the reactions led to the products in moderate to high yields. Furthermore, the *N*-glycosylation was found to proceed with a high degree of stereospecificity, facilitating excellent β-selectivity from the α-glucosyl donor. The obtained glycosylation products were then subjected to selective deprotection reactions which provided *N*-functionalized sulfonamides and carbamates in good yields and moderate to excellent β-selectivity. We, therefore, hope that the developed approach may have some potential for the future in the synthesis of interesting and valuable *N*-glycoconjugates.

2.2. Results and Discussion

The initial part of this section will be dedicated to the self-promoted *N*-glycosylation with emphasis on the structure of glycosylation products and the reaction mechanism. Furthermore, the results of *N*-glycosylations employing various glycosyl TCA donors and *N*-sulfonyl carbamate acceptors will be discussed. The last part of the section will focus on the orthogonal deprotection reactions, starting from the selective tosyl removal, followed by the carbamate functions cleavages.

To study the self-promoted *N*-glycosylation with sulfonyl carbamates we used a set of five commonly utilized in carbohydrate synthesis TCA donors, namely glucose, galactose and mannose benzylated derivatives (**Figure 3.2**). Importantly, the selected TCA glycosyl donors varied in stereochemistry, and hence enabled us to investigate whether the reactivity and stereochemical outcome depends on configurations of particular positions. Two sets of glucosyl and TCA galactosyl donors (**1.7α**, **1.7β**, **2.1α** and **2.1β**) were employed to study the influence of the anomeric configuration, whereas the α-TCA donors derived from three different monosaccharides (**1.7α**, **2.1α** and **2.2α**) allowed us to investigate the effect of the more distant C-2 and C-4 positions.

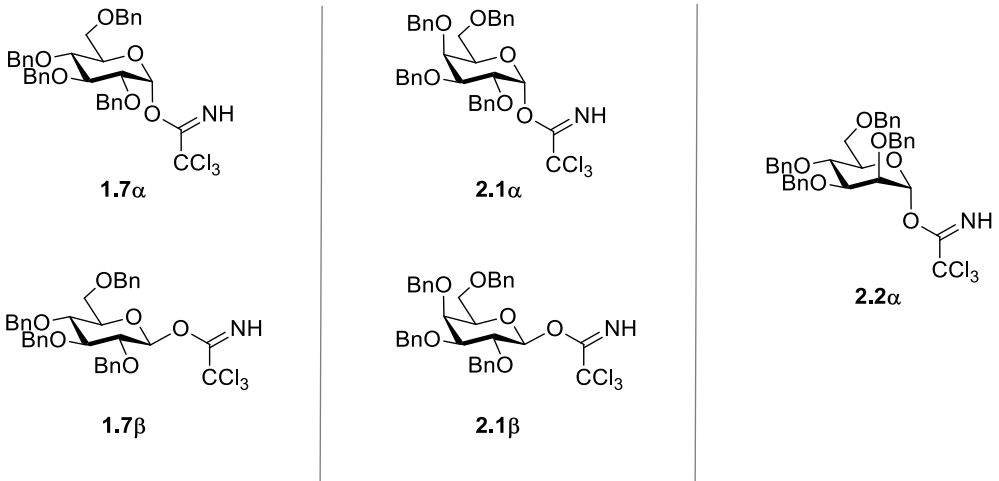
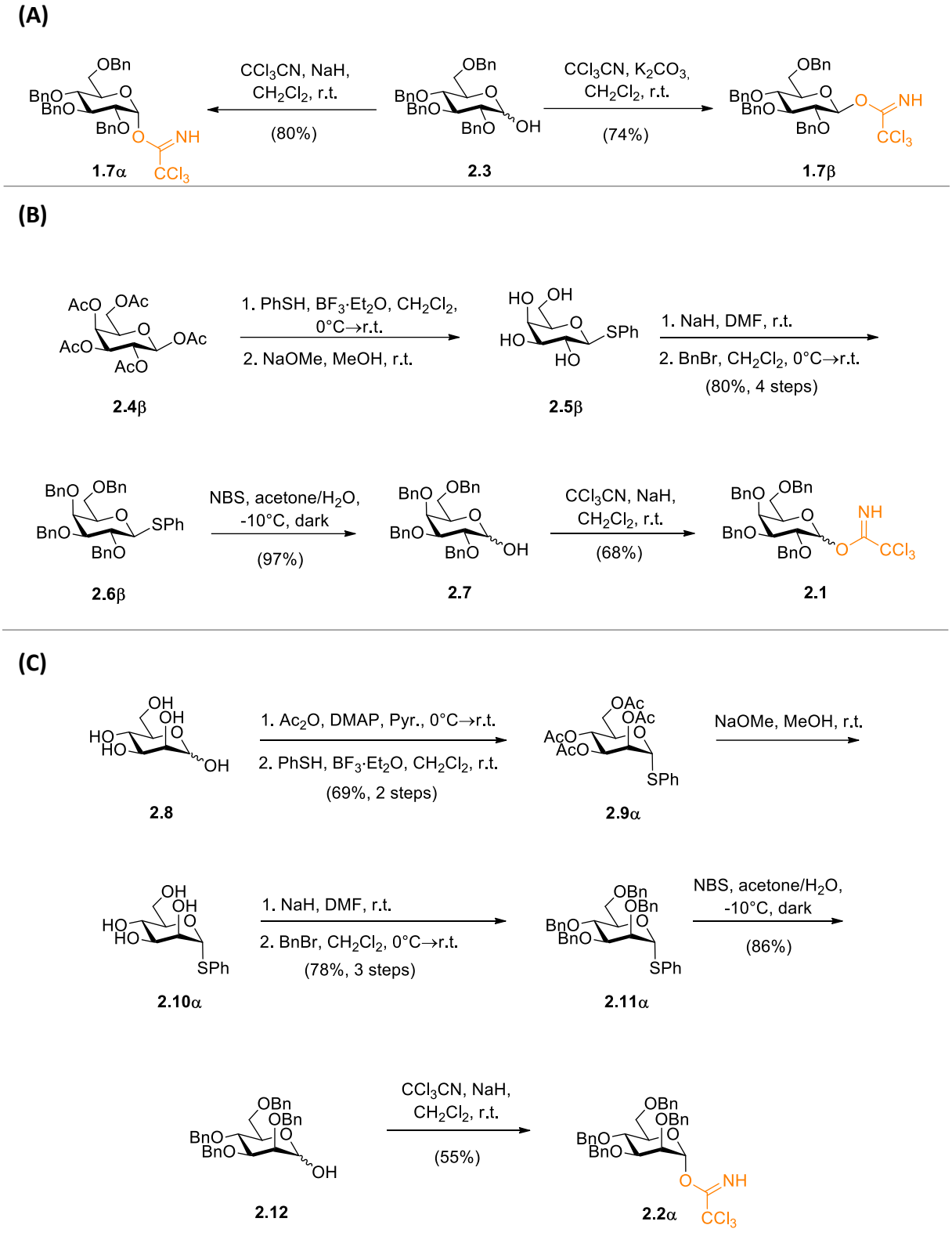


Figure 2.1. Glycosyl donors employed for self-promoted glycosylations with *N*-sulfonyl carbamates.

The synthetic routes of the glycosyl donors used in this study are summarized in **Scheme 2.2**. In order to obtain the target TCA donors, we first synthesized suitable hemiacetals with an exception from the commercially available hemiacetal **2.3**. Derivative **2.3** was directly transformed into the corresponding α- and β-TCA glucosyl donors (**1.7α** and **1.7β**) using trichloroacetonitrile and an inorganic base, i.e., NaH and K_2CO_3.[35] Both reactions gave access to the anomerically pure TCA donors in high yields of 80% and 74% respectively. The hemiacetals **2.7** and **2.12** were generally prepared in accordance with the same sequence of modifications besides the acetylation step which had to be performed solely for D-mannose (**2.8**). Synthesis of the galactosyl donors **2.1α** and **2.1β** involved six steps commencing from the peracetylated derivative **2.4β**, which was initially converted to the β-thioglycoside by glycosylation with thiophenol at the presence of Lewis acid.[173] The obtained product was then used without further purification in the next step, i.e., deacetylation under Zemplén's conditions. Subsequently, the obtained derivative **2.5β** was treated with NaH. The following benzylation with benzyl bromide facilitated the derivative **2.6β** in an 80% yield, over four steps.[174] Cleavage of the anomeric position was then attained by the oxidation reaction using NBS in a high yield (97%).[175] Further functionalization of the hemiacetal **2.7** by reaction with trichloroacetonitrile and NaH led to the both anomers of the galactosyl donor (**2.1α** and **2.1β)** in a total yield of 68%.[79] The TCA mannosyl donor **2.2α** was achieved in a seven-step synthesis from D-mannose (**2.8**) which was first subjected to acetylation by acetic anhydride and DMAP in dry pyridine.[176] Further Lewis acid-promoted thioglycosylation gave exclusively the α anomer of **2.9α** in a 69% yield, over two steps.[177] In analogy to the synthetic route of the galactosyl donors, the disarmed thioglycoside **2.9α** was then converted to the corresponding perbenzylated derivative **2.11α** by deacetylation and the following benzylation in a 78% yield, over three steps.[177] Subsequently, derivative **2.11α** was reacted with NBS giving access to the hemiacetal **2.12** in a very good yield (86%).[177] Finally, hemiacetal **2.12** was transformed into the target α-mannosyl TCA **2.2α** upon addition of trichloroacetonitrile under basic conditions (55%).[178]



Scheme 2.2. Synthesis of benzylated glucosyl (A), galactosyl (B) and mannosyl (C) TCA donors.*

* First four steps of the galactosyl donors synthesis were performed by Ph.D. Michael Martin Nielsen.[56]

The self-promoted *N*-glycosylation was investigated on a range of five different acceptors **2.13**-**2.17** (**Figure 2.2**) equipped with the carbamate and sulfonyl functions. These substituents were chosen for two principal reasons. First, we envisioned that the installation of the electron-withdrawing groups could provide sufficient acidity for the activation of the acid-labile TCA glycosyl donors. Second, it was found that the carbamate and sulfonyl moieties can be selectively removed under different conditions and hence used as temporary protecting groups. By taking advantage of this orthogonality, two selectively functionalized *N*-glycosides bearing either a sulfonyl or carbamate function could be obtained from one *N*-glycosylation product. In these studies, we put our focus on the acceptors featuring the same sulfonyl substituent, namely the tosyl group. Therefore, the selected acceptors varied exclusively in the carbamate moiety, generally considered a more convenient protecting group compared to the sulfonyl function. This choice of reactants enabled us to study the impact of the carbamate substituent on the acceptor's acidity, and thus its reactivity with the TCA glycosyl donors. To investigate the scope and limitations of the self-promoted *N*-glycosylation, we employed a set of carbamate-protected acceptors with different functional groups and steric hindrance. Noteworthy, due to these structural differences, the selected carbamate protecting groups can be cleaved using alternative procedures, which makes the developed approach more versatile.

In order to access the acidic properties of the selected *N*-sulfonyl carbamates, titration experiments were performed (**Figure 2.2**). These studies revealed that the electron-poor acceptors were indeed acidic with the pK_a-values spanning from 3.8 to 6.0 depending on the carbamate substituent. As expected, the acceptor bearing the most electron-withdrawing carbamate residue, i.e., Troc group (**2.16**) was found to be the most acidic one, whereas the lowest pK_a-value was observed for the Boc-protected acceptor (**2.17**).

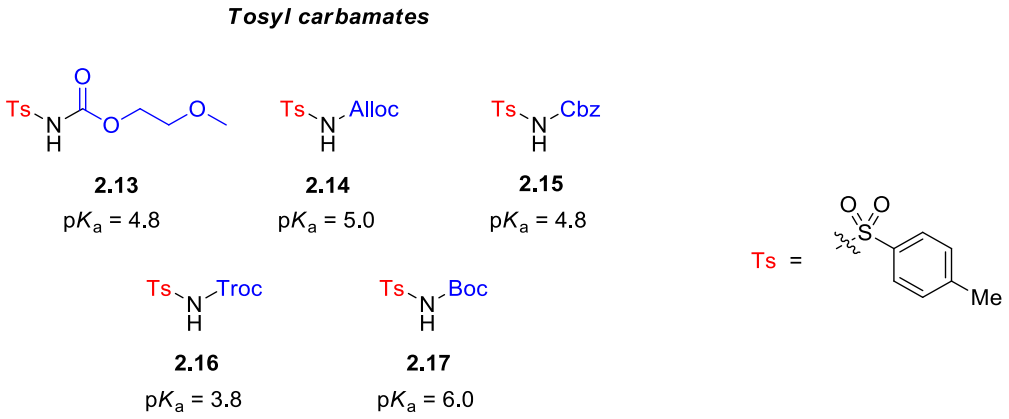
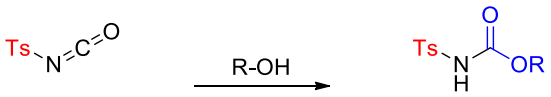


Figure 2.2. *N*-sulfonyl carbamates employed for self-promoted *N*-glycosylations and the determined pK_a-values.[†]

All tosylated carbamates were easily obtained in high yields (87-99%) from reacting the corresponding alcohol with tosyl isocyanate (**Table 2.1**).[179–182] Noteworthy, the reactions took place in absence of a solvent when using liquid alcohols at room temperature. In addition, the excess of alcohol could be then removed by distillation.

Table 2.1. Synthesis of *N*-sulfonyl carbamate acceptors.



2.18 **2.13-2.17**

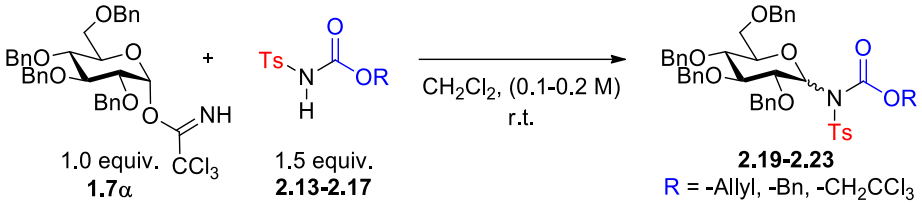
No.	R	Solvent	Temp. [°C]	Yield[a] [%]
2.13	-$CH_2CH_2OCH_3$	CH_2Cl_2	r.t.	91
2.14	-Allyl	-	0→r.t.	99
2.15	-Bn	-	0→r.t.	95
2.16	-CH_2CCl_3	-	0→r.t.	87
2.17	-*t*-Bu	-	r.t.	87

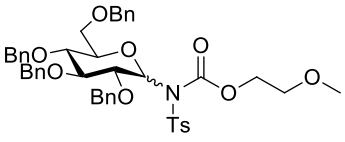
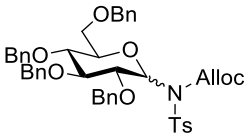
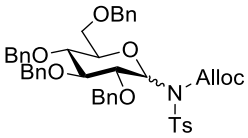
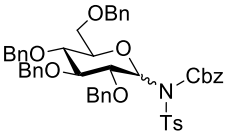
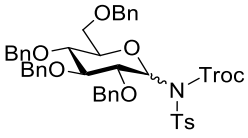
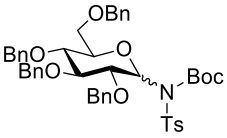
[a] Isolated yield.

[†] pK_a-values were determined from titration experiments performed by Ph.D. Michael Martin Nielsen.

To verify whether the obtained *N*-sulfonyl carbamates (**2.13**-**2.17**) can be efficiently glycosylated with the TCA glycosyl donors (**1.7α**, **1.7β**, **2.2α**, **2.2β** and **2.2α**) without the aid of additional catalysts or promoters, a series of *N*-glycosylation was carried out. We initiated our studies from glycosylations employing the commonly utilized in carbohydrate chemistry perbenzylated α-glucosyl donor (**Table 2.2**). Donor **1.7α** was first reacted with the tosyl carbamate **2.13** in CH_2Cl_2 at room temperature, using 50% excess of the acceptor. Notably, the preliminary glycosylation facilitated the desired *N*-glycoside not only in high yield (93%), but also with complete β-selectivity. Since our first attempt was successful, the same reaction conditions were further applied for glucosylation of the Alloc-derivative **2.14**. Although the reaction led to the exclusive formation of the β-product, the isolated yield was lower, compared to the previous glycosylation (80%). Subsequently, the reaction was investigated at a higher concentration of the donor using the same set of reactants (**1.7α** and **2.14**). As in self-promoted glycosylation the TCA donor is condensed with the acidic acceptor, we anticipated that the reaction could be concentration-dependent. Changing the concentration of the donor did not influence the reaction time and selectivity. However, the glycosylation at the higher concentration gave a better result in terms of yield (90%). Consequently, the initial glycosylation procedure was slightly modified and used for glucosylations of tosyl carbamates **2.15**-**2.17**. As expected, glycosylations under the optimized conditions were also found to proceed with inversion of the anomeric configuration, similarly leading to β-*N*-glycosides. In general, the reactions gave very high yields (>90%), with the exception of the glycosylation with Boc-derivative **2.17** (**Table 2.2**, **Entry 6**) which only led to a 35% yield. The reasoning behind this could be related to the bulkiness of the acceptor. Steric factors might therefore impose certain limitations on the developed *N*-glycosylation method. In addition, by-products were observed in crude ^{1}H-NMR suggesting cleavage of the Boc protecting group, which might be rationalized by its sensitivity to acidic conditions. There seems to be no significant dependence between the acidity of the acceptors and the reaction times. The glycosylation of the Boc-derivative **2.17** proceeded slower compared to the other glucosylations. However, the prolonged reaction time could be more associated with the size of the acceptor, as discussed above.

Table 2.2. Scope of self-promoted *N*-glycosylations using the benzylated glucosyl donor **1.7α** and tosyl carbamate acceptors **2.13**-**2.17**.



Entry	Acceptor	*c* [M]	*t* [h]	Product	α/β[a]	Yield[b] [%]
3	**2.13**	0.1	o.n.	 **2.19**	0:100	93
1	**2.14**	0.1	16	 **2.20**	0:100	80
2	**2.14**	0.2	16	 **2.20**	0:100	90
4	**2.15**	0.2	o.n.	 **2.21**	0:100	93
5	**2.16**	0.2	o.n.	 **2.22**	0:100	95
6	**2.17**	0.2	24	 **2.23**	0:100	35

[a] Determined from crude ^{1}H-NMR. [b] Isolated yield.

To expand our studies on the self-promoted glycosylation of *N*-sulfonyl carbamates, we investigated whether the stereochemical outcome of the reaction depends on the anomeric configuration of the donor. First, the β-glucosyl TCA (**1.7β**) was reacted with the Alloc-derivative **2.14** following the established glycosylation protocol (**Figure 2.3**). Unlike previously discussed glucosylations employing the α-donor (**1.7α**), this reaction facilitated two main products bearing the carbamate and the tosyl functions, suggesting the formation of an anomeric mixture. On the basis of crude NMR spectra, the compound revealing the higher anomeric coupling constant ($^3J_{H1,H2}$ 9.3 Hz) was identified as the β-linked *N*-glycoside (**2.20β**).

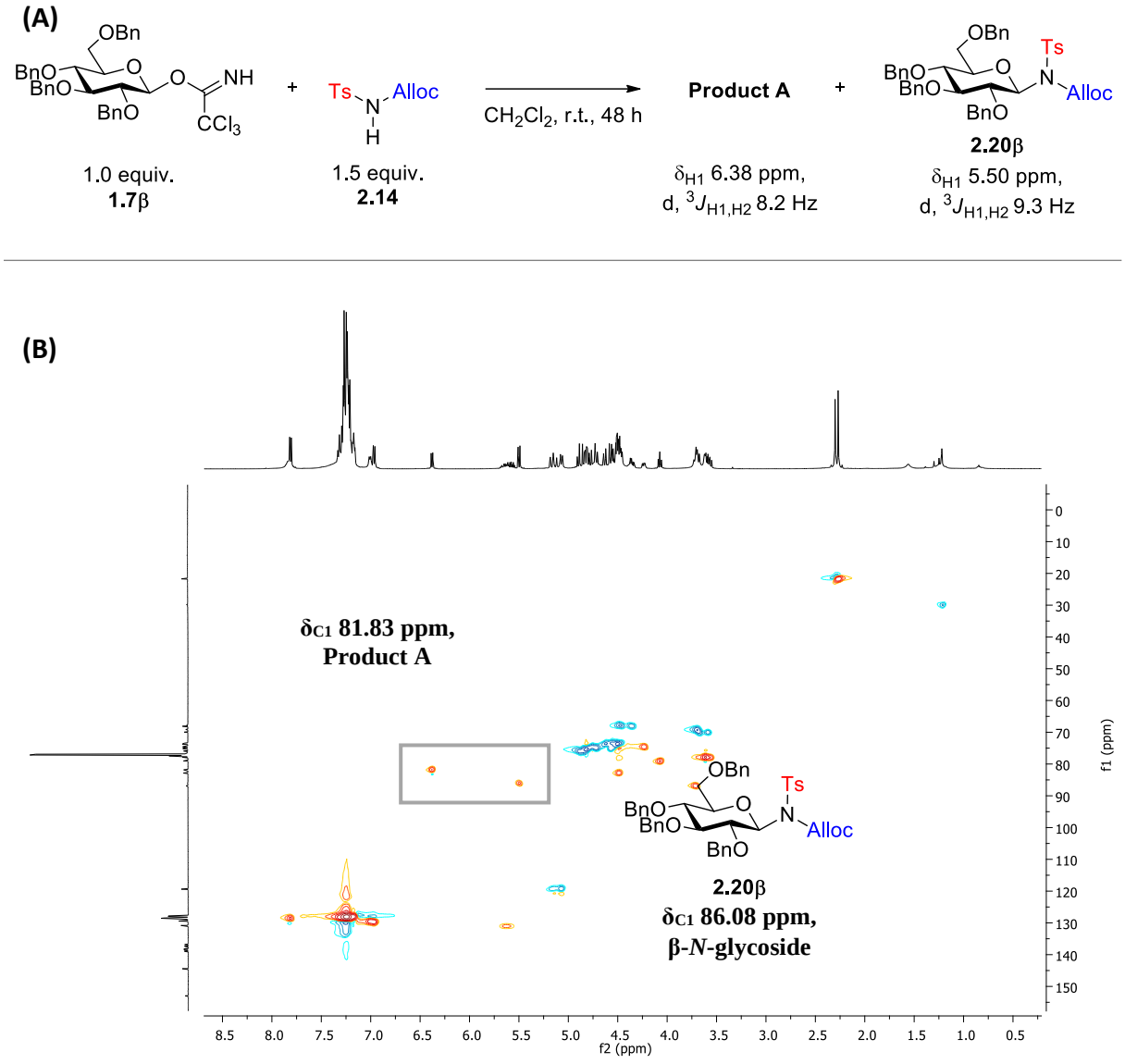
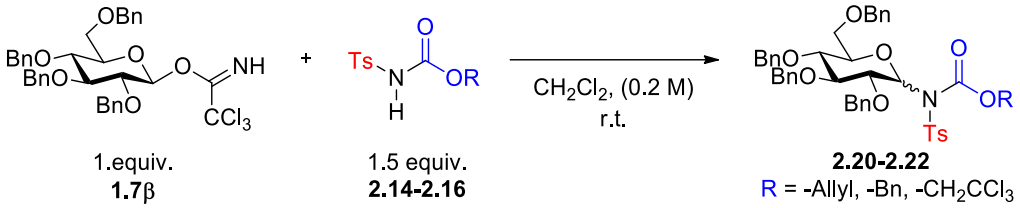
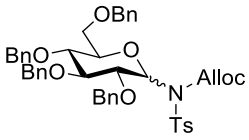
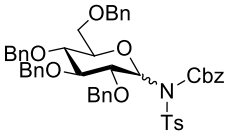
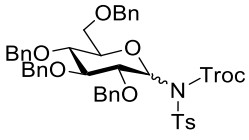


Figure 2.3. Self-promoted *N*-glycosylation with the glucosyl donor **1.7β** and the sulfonyl carbamate **2.14** (A). HSQC spectrum of the crude reaction mixture recorded at r.t. in $CDCl_3$. The anomeric region is highlighted in a rectangle (B).

Surprisingly, the second product resonating at δ_{H1} 6.38 ppm gave also a relatively high coupling constant ($^3J_{H1,H2}$ 8.2 Hz), which is unusual for 1,2-*cis* glycosides. It was, however, found that both glycosides revealed similar C-1 signals at δ_{C1} 86.08 and 81.83 ppm, respectively. Consequently, we ruled out the formation of the undesired *O*-glycosidic bond, which should generally give a more downfield anomeric carbon peak. The second product was eventually assigned to be the α-*N*-glucoside (**2.20α)**, despite the large anomeric coupling constant. The ratio between the *N*-glycosides **2.20α** and **2.20β** was found to be approximately 1:1. Similar results were obtained for glucosylations of the acceptors **2.15** and **2.16** (**Table 2.3**).

Table 2.3. Scope of self-promoted *N*-glycosylations using benzylated β-TCAs **1.7β** and sulfonyl carbamate acceptors **2.14-2.16**.



Entry	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**2.14**	16	 **2.20**	43:57	73
2	**2.15**	o.n.	 **2.21**	45:55	82
3	**2.16**	o.n.	 **2.22**	50:50	80

[a] Determined from crude ^{1}H-NMR. [b] Isolated yield.

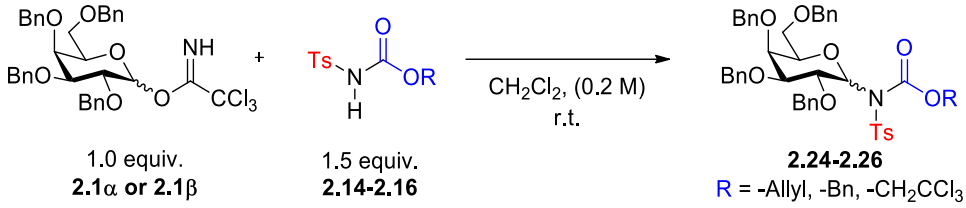
Although an increase in α-selectivity was observed when using the β-donor (**1.7β**), the glycosylations proceeded with a significantly lower degree of stereospecificity than the corresponding reactions with the α-TCA donor (**1.7α**). This led us to the conclusion that the

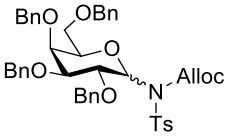
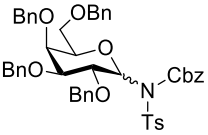
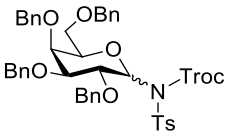
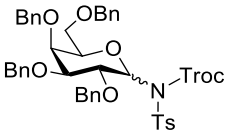
formation of 1,2-*cis*-glycosides is most likely unfavorable, which can be justified by the steric effect operating between the C-2 substituent and the bulky tosyl carbamates. Furthermore, it was found that the β-TCA donor (**1.7β**) reacted at comparable rates to its α-linked counterpart (**1.7α)**. Generally, the glycosylations resulted in good to high yields (73-80%), albeit slightly reduced compared to the reactions involving the α-glucosyl donor (**1.7α**).

In order to explore the scope of the self-promoted *N*-glycosylation method, the reaction was then tested on three of the synthesized acceptors (**2.14**-**2.16)** using the perbenzylated α-galactosyl donor (**2.1α**, **Table 2.4**). Generally, galactosyl donors have been reported as more reactive compounds than their glucosyl analogs.[183,184] From the TLC analysis it was, however, found that the α-galactosyl donor (**2.1α**) reacted at a similar rate as its glucosyl counterpart **1.7α** under the same reaction conditions. Whereas glycosylations with the α-glucosyl TCA (**1.7α**) resulted in a complete β-selectivity, galactosylations led to anomeric mixtures, although favoring the formation of β-*N*-glycosides. This drop in β-selectivity indicates that the axially oriented C-4 substituent could partially shield the β-face, making this side less accessible for the incoming acceptor. Noteworthy, the obtained α-products (**2.24**-**2.26α)** revealed similar anomeric coupling constants ($^3J_{H1,H2}$ 7.1-7.8 Hz) to those observed for the α-*N*-glucosides (**2.19**-**2.23α**). Furthermore, glycosylations employing the galactosyl donor **2.1α** gave lower yields compared to the corresponding glucosylations, albeit ranging from 61 to 81%. The highest yield was obtained in the case of glycosylation employing the most acidic acceptor, i.e., Troc-derivative **2.16**. Presumably, the glycosylation yield was also influenced by the steric interactions. The α-galactosyl donor (**2.1α**) with the axial substituent at the C-4 position could be less prone to react with the bulky tosyl carbamates than the α-glucosyl TCA (**1.7α**), and thereby slowly undergo the side reactions such as hydrolysis or rearrangement to the glycosyl trichloroacetamide.

The developed glycosylation procedure was also tested on the β-galactosyl donor (**2.1β**) using the Troc-derivative **2.16** as the acceptor (**Table 2.4**, **Entry 4**). From the TLC analysis it was concluded that the reaction proceeded with similar rate to the glycosylation with the α-glucosyl donor (**1.7α**). The glycosylation, however, turned out to be highly α-selective (α/β 83:17) and therefore more stereospecific compared to the corresponding glucosylation. It seems reasonable to assume that the glycosylation most likely went through a mechanism involving a more associated ion pair, which could be also related to the interactions between the β-faced C-4 substituent and the leaving group. Importantly, only a slight decrease in glycosylation yield was observed when using the β-galactosyl donor (**2.1β**).

Table 2.4 Scope of self-promoted *N*-glycosylations using benzylated galactosyl donors (**2.1α** and **2.1β**) and sulfonyl amide acceptors **2.14-2.16**.



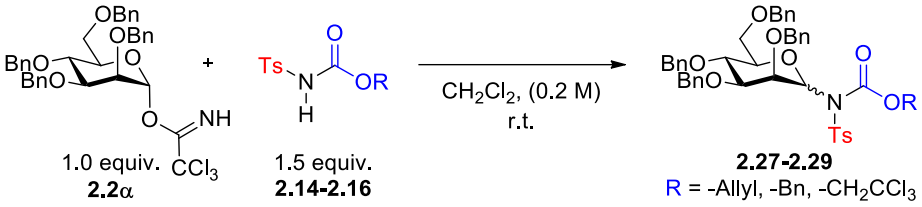
Entry	Donor	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**2.1α**	**2.14**	18, 16	 **2.24**	29:71	63
2	**2.1α**	**2.15**	16, o.n.	 **2.25**	34:66	61
3	**2.1α**	**2.16**	o.n.	 **2.26**	42:58	81
4	**2.1β**	**2.16**	o.n.	 **2.26**	83:17	69

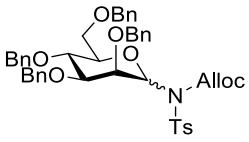
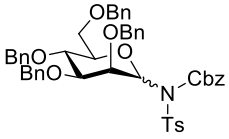
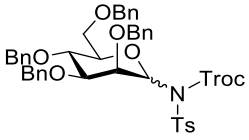
[a] Determined from crude ^{1}H-NMR. [b] Isolated yield.

The established *N*-glycosylation procedure was subsequently investigated using the same set of acceptors **2.14-2.16** and the benzylated α-mannosyl donor **2.2α** (**Table 2.5**). It was found that mannosylations of the less acidic tosyl carbamates **2.14** and **2.15** proceeded apparently slower than the corresponding glucosylations. Such results are in line with the previously reported studies comparing the reactivity of mannose derivatives and their glucosyl counterparts.[183] Furthermore, glycosylations performed with the mannose-derived donor **2.2α** turned out to be α-selective in contrast to glycosylations employing TCA gluco- and galactosyl donors (**1.7α** and **2.1α**). This clear preference for the formation of α-glycosides can be explained by the steric effect. It seems that the nucleophilic attack from the β-face was highly disfavored

due to the repulsive interactions between the axially oriented C-2 substituent and bulky acceptors. In general, mannosylations with α-donor (**2.2α**) resulted in moderate to good yields (64-74%). Nevertheless, the obtained yields were lower compared to the corresponding glucosylations, which supports the statement that mannosyl donors are generally less reactive than their glucosyl analogs.

Table 2.5. Scope of self-promoted *N*-glycosylations using the benzylated mannosyl donor **2.2α** and sulfonyl amide acceptors **2.14**-**2.16**.



Entry	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**2.14**	20	 **2.27**	100:0	64
2	**2.15**	24	 **2.28**	100:0	72
3	**2.16**	o.n.	 **2.29**	100:0	74

[a] Determined from crude ^{1}H-NMR. [b] Isolated yield.

In order to clarify the structures of the obtained *N*-glycosides, additional experiments were performed using different NMR spectroscopic methods. Since both the anomeric configuration and the ring conformation are related to the dihedral angles between the coupling protons, we aimed to estimate their values. Our initial studies were focused on the determination of the $^{3}J_{H,H'}$ coupling constants between the sugar ring protons. The observed values of the vicinal coupling constants were subsequently used to assess the torsion angles (ϕ) between the coupling protons, based on the Karplus curve, which represents the relationship between these two parameters.[185] In our structural and conformational analysis, we followed the curve corresponding to the general Karplus equation for protons bonded to the neighboring sp^3-hybridized carbon atoms (**Equation 2.1**, **Figure 2.4**).[186,187] Although the applied equation neglects the electronegativity and orientation of the substituents, and thus cannot be directly transferred to the pyranoside forms, we assumed that the general formula might serve as an estimation.

$$^{3}J_{HH'} = A + B \cos(\phi) + C \cos 2(\phi)$$

Equation 2.1. The general Karplus relationship. The equation parameterized for vicinal proton-proton coupling constants includes A = 4.22, B = 0.5, and C = 4.5 Hz.[185–187]

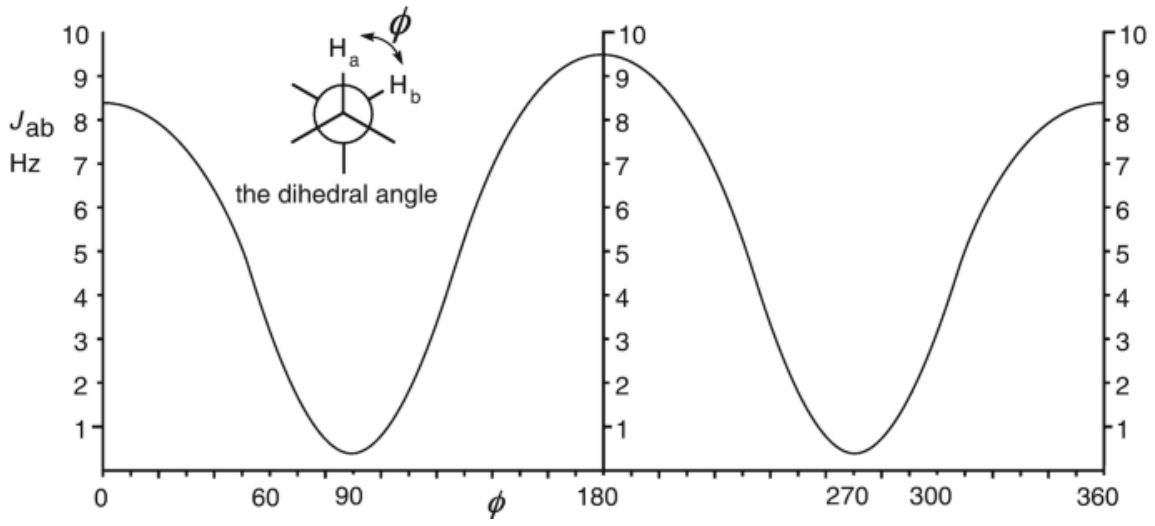


Figure 2.4. Karplus relationship for vicinal protons represented by a plot (see **Equation**).[188]

Our extended structural studies were focused mainly on the *N*-glucosylation products, for which the determination of coupling constants was somewhat troublesome due to the signals overlap. In addition, the α-linked glucosides giving unusual anomeric coupling constants (8.0-8.2 Hz) could not be isolated as pure anomers by column chromatography, making the structural

and conformational analysis more challenging. To investigate the stereochemistry of the *N*-glucosides, the anomeric mixture of the *N*-Troc-protected derivative (**2.22**) was chosen as a representative as it was obtained in an excellent yield (95%) and featured the lowest number of the hydrogen atoms in the carbamate moiety. In order to determine the vicinal coupling constants between the sugar ring protons selectively for each anomer, we performed total correlation spectroscopy (TOCSY) experiments using CD_3CN as a solvent due to the better spectral resolution compared to $CDCl_3$. From the recorded spectra it was found that whereas the anomeric couplings varied significantly, the rest of the ring protons revealed similar coupling constants, albeit generally smaller in the case of the α-anomer (**Table 2.6**). On the basis of the Karplus curve, the anomer with the higher anomeric constant ($^3J_{H1,H2}$ = 9.3 Hz) was confirmed to be a 1,2-*trans*-glycoside. Furthermore, the large vicinal coupling constants between the other ring protons clearly indicated that they are axially oriented and the β-anomer most likely adopted a relaxed $^4C_1$ chair conformation. This conformation was, however, excluded for the second anomer interpreted as the 1,2-*cis*-product. Its abnormally high anomeric coupling ($^3J_{H1,H2}$ = 7.6 Hz) constant did not correspond to the dihedral angle generally observed for the 1,2-equatorial-axial orientation of the protons in the chair form (nominally 60º). The relatively large value of $^3J_{H1,H2}$ was found to fit the dihedral angle larger than 0º and smaller than 60º. It was therefore deduced that H-1 and H-2 protons were presumably positioned in an orientation between the staggered and the eclipsed geometry. This finding together with other vicinal coupling constants slightly lower compared to the β-anomer, led us to the conclusion that the α-glucoside could adopt a skew boat conformation.

Table 2.6. Chemical shifts and coupling constants comparison between the α and β anomers of the Troc-derivative **2.22**. The presented values were determined from the 1D selective TOCSY spectra recorded in CD_3CN at room temperature.

Position	δ(^{1}H) [ppm]	Multiplicity	J^3 [Hz]
H-1α	6.42	d	7.6
H-3α	4.37	t	8.1
H-5α	4.30	broad dd	10.1, 5.5
H-2α	4.18	dd	8.1, 7.6
H-6α	3.78	broad d	10.8
H-6'α	3.67	dd	10.8, 5.5
H-4α	3.58	dd	10.1, 8.1
H-1β	5.62	d	9.3
H-2β	4.48	dd	9.3, 8.8
H-3β	3.84	t	8.8
H-5β, H-6β	3.72-3.80	m	-
H-6'β	3.62	dd	10.8, 6.1
H-4β	3.53	dd	10.6, 8.8

Our assignment was further validated by 1D and 2D NOESY experiments using the same mixture of anomers (**2.22**, **Table 2.7**). Correlations, observed in the 1D NOESY spectrum of the β-glucoside, between H-1, H-3 and H-5 confirmed the established anomeric configuration and the $^4C_1$ chair conformation. These signals were also visible in the 2D NOESY spectrum along with a cross-peak of H-2 with H-4, which additionally supported the initial assignment. In contrast, the correlations between H-3 and H-5 were not seen in both NOESY spectra of the second anomer, ruling out the $^4C_1$ chair conformation. Moreover, the anomeric proton was found to interact only with H-2, which is in line with the α-configuration. Since no cross-peak of H-1 with H-4 was observed, the boat conformation was also excluded.

Table 2.7. Correlations between sugar ring protons of the *N*-glycosides **2.22α** and **2.22β** observed in the 1D and 2D NOESY spectra recorded in $CDCl_3$ at 300 K. The key correlations are marked in red.

Position	δ(^{1}H)[a] [ppm]	2D NOESY correlations	1D NOESY correlations
H-1α	6.39	H-2	H-2, CH_2^{Troc}, Ar^{Ts}
H-2α	4.15	H-1	-
H-3α	4.34	-	-
H-4α	3.54	n.d.	-
H-5α	4.27	H-6	-
H-6α	3.74	n.d.	-
H-6'α	3.64	H-6	-
H-1β	5.59	H-2, H-3, H-5	H-3, H-5
H-2β	4.45	H-1, H-4	-
H-3β	4.81	H-1	-
H-4β	3.51	H-2	-
H-5β	3.74	H-1	-
H-6β	3.72	H-6'	-
H-6'β	3.59	H-6	-

[a]Chemical shift based on the 2D NOESY spectrum.

The NMR data such as vicinal coupling constants and the NOESY correlations between the ring protons provided some insight into the structures of the glycosylation products. They enabled us to clarify not only the anomeric configurations but also the sugar ring conformations. The 1,2-*trans*-glucosides (**2.19**-**2.23β**) were found to exist as the relaxed $^4C_1$ chair conformer, whereas the corresponding 1,2-*cis*-products were established to adopt the more uncommon $^1S_5$ skew-boat conformation, presumably to minimize the sterically repulsive interactions between the C-2 substituent and the bulky aglycon (**Figure 2.5**).

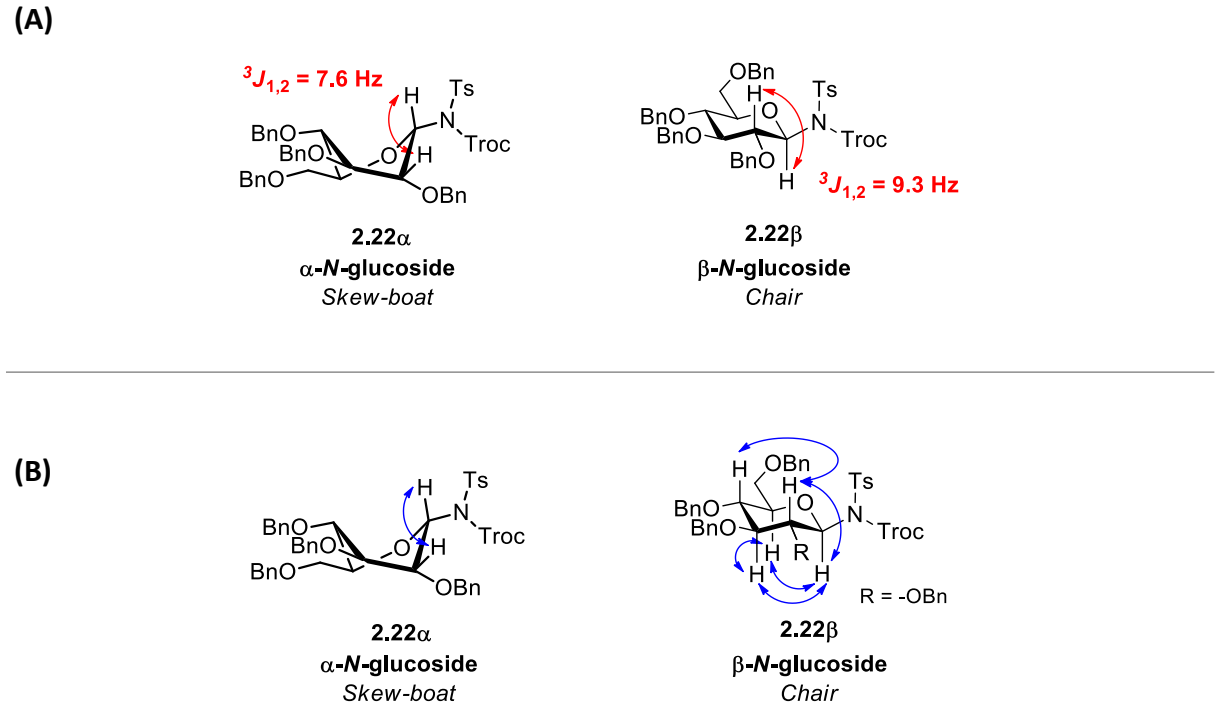


Figure 2.5. Established conformations of the α- and β-glucosides with the anomeric coupling constants (A) and key NOESY correlations (B). The conformations are shown for the Troc-derivative **2.22** as a representative.

Likewise, the analogous conformations were attributed to the *N*-functionalized galactosides (**2.24**-**2.26**). From the coupling constants, it was concluded that the α- and β-galactosides most likely adopted the $^1S_5$ skew-boat and $^4C_1$ chair conformations, respectively (**Figure 2.6**). Noteworthy, derivatives with *galacto* stereochemistry turned out to be separable by column chromatography in contrast to their *gluco* counterparts, allowing additional structural analysis by infrared (IR) spectroscopy. The IR data of the pure anomers **2.24α** and **2.24β** (see Experimental) showed very much the same absorption patterns and hence supported our preliminary statement that glycosylations with β-TCA donors led to the formation of *N*-linked stereoisomers.

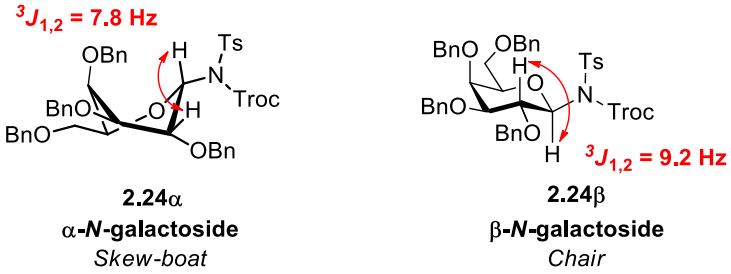
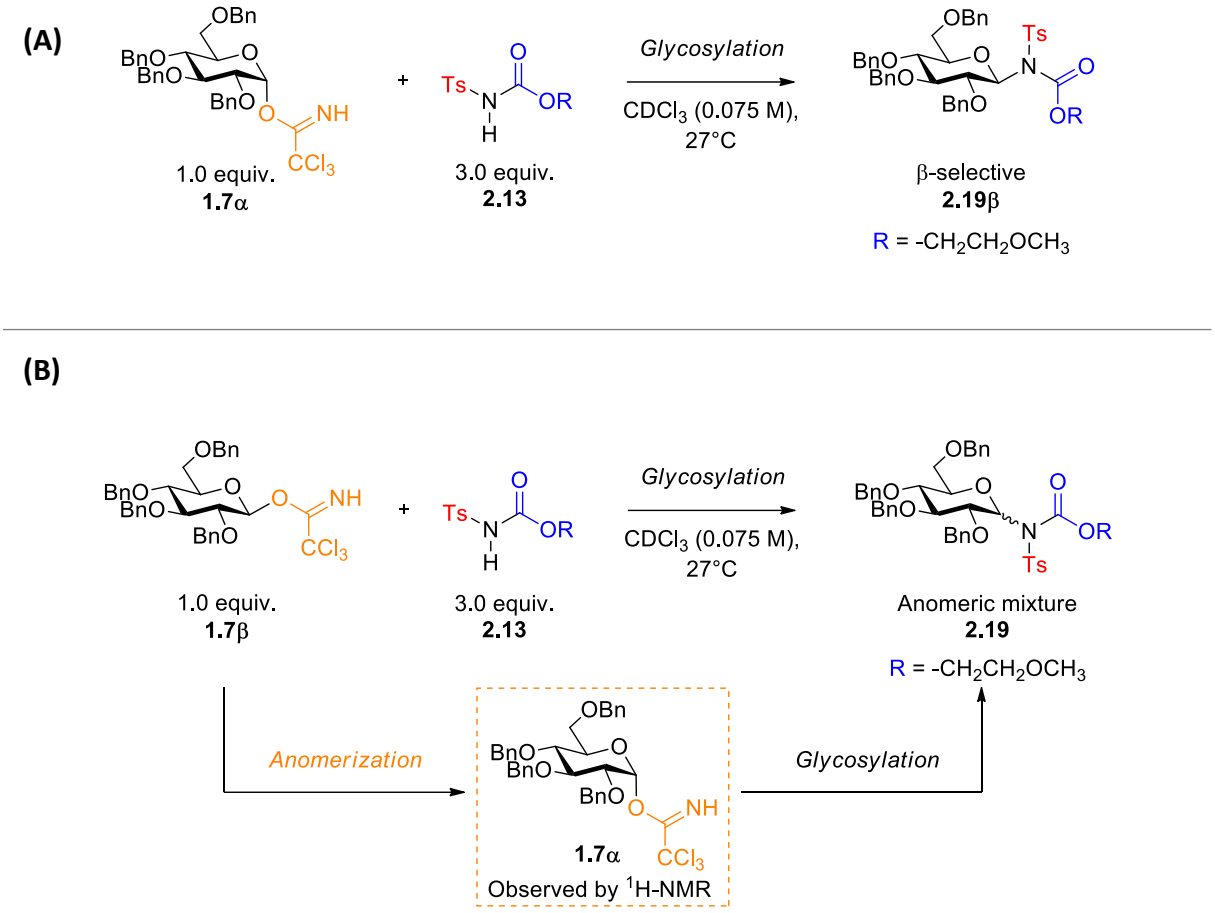


Figure 2.6. Most likely conformations of the α- and β-galactosides with the determined anomeric coupling constants. The established conformations are shown on the example of the Troc-derivative **2.24**.

In an attempt to understand how the anomeric configuration of the glycosyl donor influences the stereochemical outcome of the self-promoted *N*-glycosylation, we explored the reaction mechanism in a series of NMR experiments (see supporting information Ref.). The glycosylation was investigated by use of the anomeric set of the TCA glucosyl donors (**1.7α** and **1.7β**) and the acceptor **2.13** as the model reactants. Due to the moderate reactivity, compared to the other tosyl carbamates, the acceptor **2.13** enabled us to monitor the reaction progress over a relatively long period. In addition, the selected tosyl carbamate resonated at δ_{H1} 3.23 ppm as a singlet, assigned to the methoxy group, which can be easily distinguished from the other signals in crude NMR. As shown in **Scheme 2.3**, the mechanistic studies were carried out in the neutralized, deuterated chloroform at ambient temperature using an excess of the acceptor, resembling the established glycosylation conditions. Furthermore, mesitylene was employed as an internal standard in order to determine the concentration of the formed products, byproducts and intermediates. As expected, the ^{1}H-NMR data obtained for the glycosylation with the donor **1.7α** indicated the selective formation of the β-product (**2.19β**). Interestingly, when using the TCA **1.7β**, the recorded ^{1}H-NMR spectra revealed not only a conversion to the α-glucoside (**2.19α**) but also a partial is situ anomerization of the β-donor (**1.7β)** to its α-linked counterpart (**1.7α)**. This competing formation of the α-TCA, followed by the self-promoted glycosylation eventually gave rise to the β-glucoside (**2.19β**). Consequently, both α- and β-product were found in the reaction mixture by crude ^{1}H-NMR. It should be mentioned that the observed in situ anomerization of the TCA donor has been previously reported, albeit only for glycosylations in ionic liquids. The example of the anomerization taking place in the organic solvent might therefore be worth more attention and further studies.

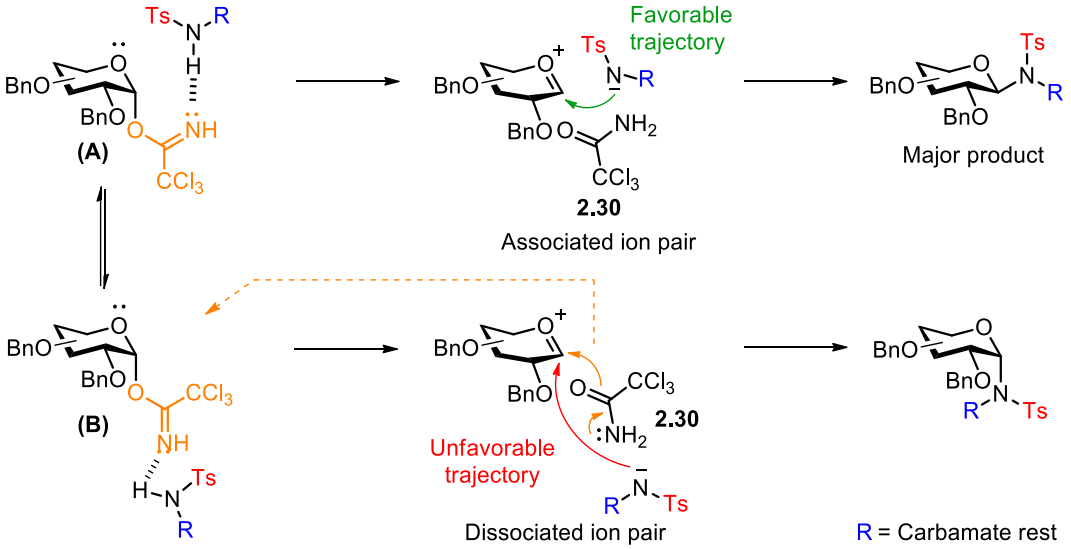


Scheme 2.3. Most pronounced differences in reactivity between the α- and β-glucosyl donors. The solvent used in the NMR experiments was pre-neutralized by passing it through basic Al_2O_3.

Although, the glycosylations proceeded with inversion of the anomeric configuration, indicating a bimolecular S_N2-like reaction, the kinetics of the glycosylation were found to be of first-order with respect to both glycosyl donor and acceptor. This led us to the conclusion that most likely the reaction follows the S_Ni-like pathway involving an ion-pair intermediate formed upon protonation of the TCA glycosyl donor. Recently, such a mechanism has been also proposed by Tanaka *et al.* for glycosylations of 1,2-anhydro donors.[189] Furthermore, on the basis of the NMR evidence, it was reasonable to assume that the glycosylation of α- and β-donor would lead to formation of different intermediates. Therefore, two mechanistic scenarios were proposed for glycosylation, depending on the donor used.

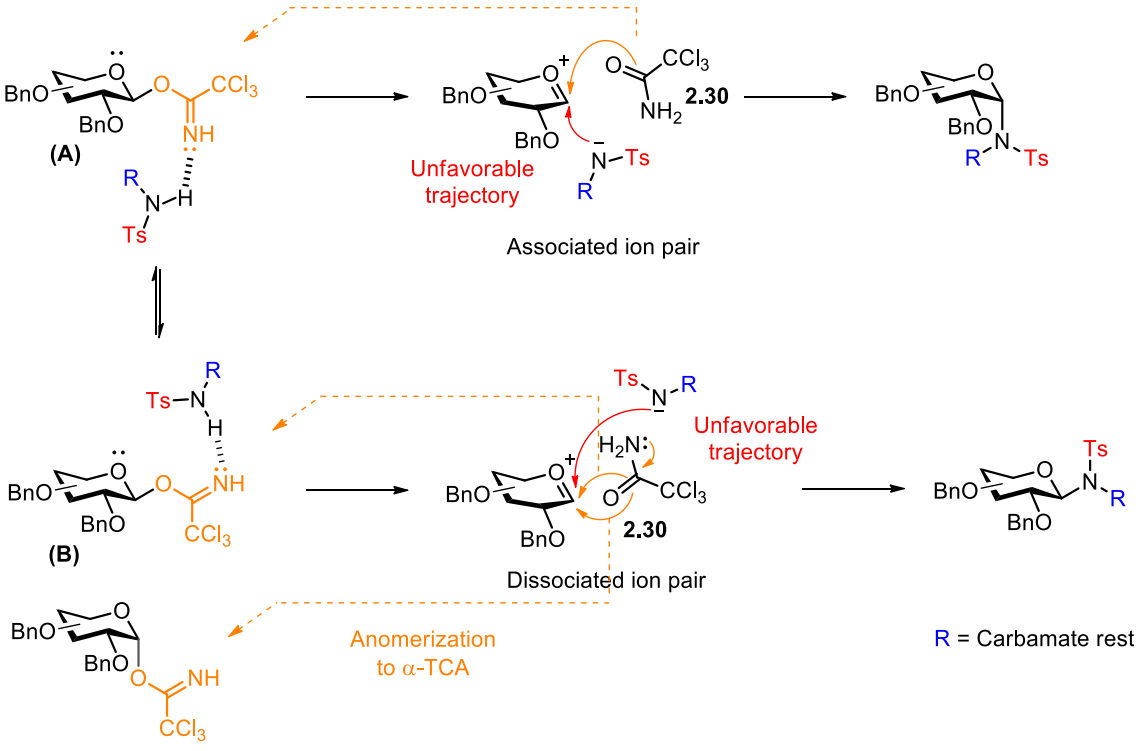
For the α-glycosyl donors, we suggested two alternative reaction pathways taking into account both conformers A and B (**Scheme 2.4a**). The first conformer, however, seems to exist preferentially, based on the previously reported studies on the TCA glycosyl donors.[81] From

the results and the glycosylation reactions and mechanistic experiments, it was concluded that activation of the conformer A most likely leads to the formation of an associated ion pair, whereas the activated conformer B should give a dissociated ion pair intermediate. It must be also mentioned, that the pre-formation of the stable glycosyl donor-acceptor complex was excluded since no ^{1}H shifts were observed for either the TCA glycosyl donor (**1.7α**) and acceptor (**2.13**) while titrating the solution of the donor solution with the solution of the acceptor. Furthermore, it was realized that the nucleophile should preferentially attack from the β-face for two main reasons. First, in the associated ion pair the sulfonamide anion is situated closer to the glycosyl cation. Second, the C-2 substituent can additionally shield the α-side, making this face less accessible for the incoming nucleophile. When the ion pair is more dissociated, the glycosyl cation can also react with the less distant trichloroacetamide **2.30**, giving rise to the TCA glycosyl donor. The proposed reaction pathway involving the associated ion pair as a favorable intermediate justifies the β-selectivity obtained for glycosylations in the *gluco* and *galacto* series. It is clear, however, that the corresponding mannosylations do not pass through the same intermediate as they resulted in complete α-selectivity. In this case, the formation of the dissociated ion pair intermediate seems to be more favored, due to the C-2 axial substituent hindering the β-facial attack.



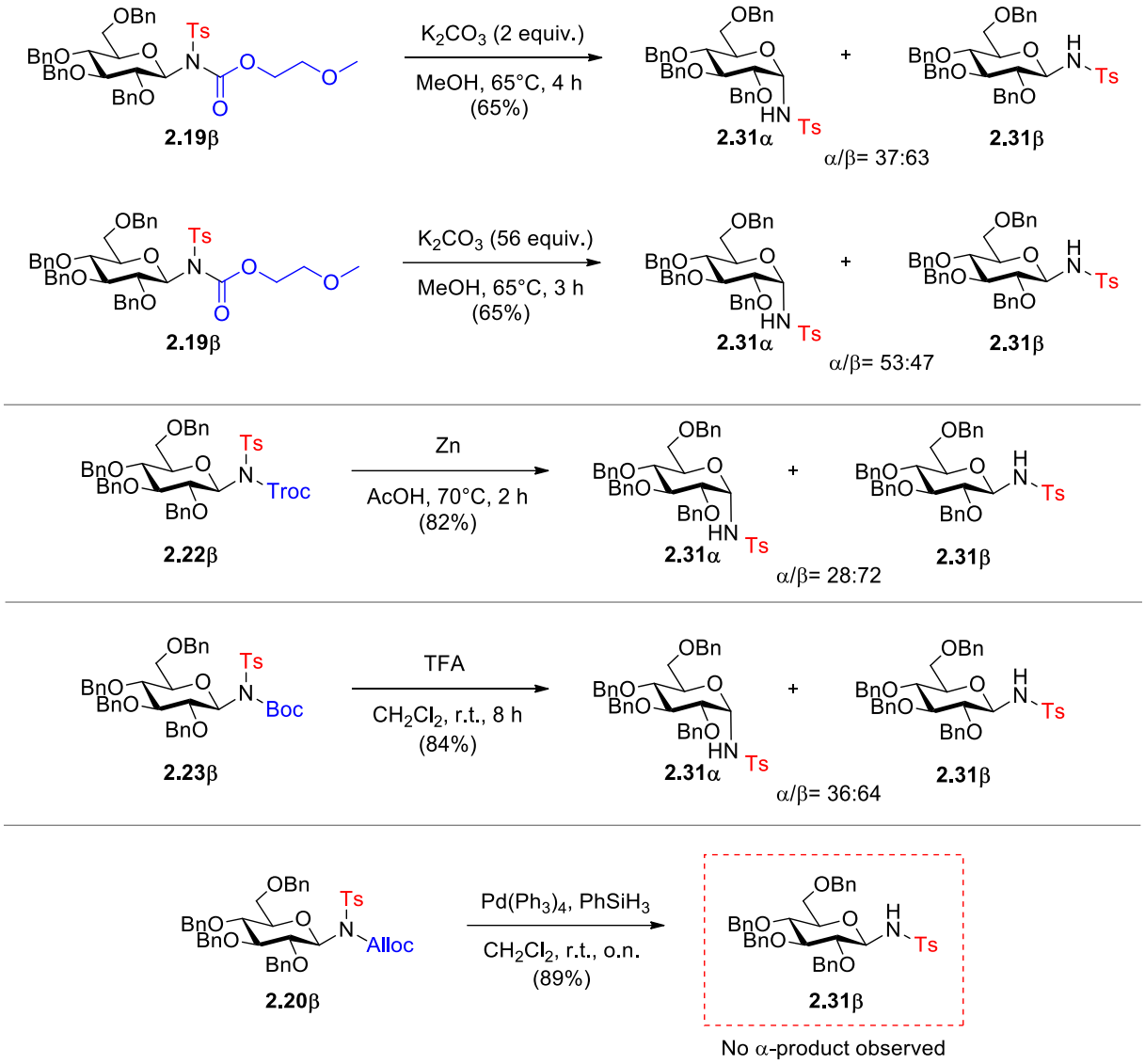
Scheme 2.4. Proposed mechanism of the self-promoted *N*-glycosylation employing the α-glycosyl donors.

The potential reaction pathways for glycosylations of the β-donors also involve two different conformers (A and B) as shown in **Scheme 2.5**, which upon activation would give the associated and dissociated ion pair intermediate, respectively. Whereas the first intermediate should be preferential when using the α-donors, it seems to be less favorable in glycosylations with the β-donors. The reasoning behind this is that in the associated ion pair formed from the activation of the A conformer the sulfonamide ion can only attack from the α-face, which is partly shielded by the equatorial C-2 substituent. Alternatively, as mentioned above, the leaving group can act as a nucleophile leading to the initial β-glycosyl donor. Formation of the dissociated ion pair intermediate is not likely to be favored either. Although the β-side is less sterically hindered, the sulfonamide ion is more remote from the glycosyl cation. In this case, the hydrogen bonds might be additionally formed between the nucleophile and the proximate trichloroacetamide **2.30**. Another aspect of the mechanism is the competing reaction of the glycosyl cation with the leaving group incoming either from the β- or α-side. In contrast to the formation of the β-glycosyl donor, the anomerization to the α-counterpart has an effect on the stereochemical outcome of the glycosylation. Thus, the lowered stereospecificity of the glycosylations employing the β-donors presumably arises not only from a lack of significant preference for any of the possible reaction pathways but also from the in situ anomerization.



Scheme 2.5. Proposed mechanism of the self-promoted *N*-glycosylation with the β-glycosyl donors.

Our next task was to investigate whether the carbamate or tosyl functions can be selectively removed from the obtained *N*-glycosylation products. We therefore undertook a series of appropriate deprotection reactions using various *N*-glucosides (**2.19**-**2.23β**). Our initial attempts were focused on the carbamate-deprotection of selected glucosides (**Scheme 2.6**). The orthogonality of the carbamate and tosyl groups was first studied with the derivative **2.19β** by applying the Zemplén's conditions under reflux. Although the deprotection gave access to the desired glycosyl sulfonamide **2.31** in a good yield (65%), the product was obtained as the anomeric mixture (α/β 37:63). The same carbamate deprotection was then performed using a large excess of the inorganic base. As expected, a mixture of anomers arose, albeit the anomeric ratio shifted to α/β 53:47. Subsequently, the selective deprotection was investigated using *N*-glycosides bearing different carbamates widely utilized as protecting groups in organic synthesis. The selective removal of the Troc function from the derivative **2.22β** was achieved at the elevated temperature with Zn in the presence of acetic acid, yielding the product **2.31** in a high yield (82%). However, the reaction led to the formation of both anomers in a ratio of α/β 28:72. Likewise, similar results were obtained in the case of the TFA-induced cleavage of the Boc-group, which gave rise to the tosyl-protected *N*-glycoside **2.31** in a high yield (84%) as an anomeric mixture. Eventually, the Alloc-deprotection was accomplished using a palladium catalyst and phenylsilane as the allyl scavenger. The reaction was highly efficient and most importantly, resulted in exclusive formation of the β-linked product (**2.31β**, 89%). Therefore, the Alloc group can be considered as the most suitable temporary protecting group among the tested carbamates.



Scheme 2.6. Selective removal of carbamate functions from the β-*N*-glucosides.

Since the α-product (**2.31α**) was obtained only from deprotections requiring either basic or acidic conditions, it was concluded that the initially formed β-glycosyl sulfonamide most likely underwent the *in situ* anomerization. Such anomerization can be rationalized by the acidic properties of the glycosyl sulfonamide due to the strong electron-withdrawing tosyl substituent directly attached to the anomeric nitrogen atom. In fact, other *N*-glucosyl sulfonamides have also been previously shown to anomerize during the deacetylation with NH_3 in MeOH.[190,191] The observed process has been referred as so-called mutarotation. To prove the anomerization and examine whether the β-glycosyl sulfonamide can be completely converted to its α-counterpart, we undertook further NMR experiments with a particular focus on the base catalysis (**Figure 2.7**). The anomerization studies were carried out in an NMR tube using a solution of the pure β-glycosyl sulfonamide (**2.31β**) in DMSO-d_6, which initially was treated

with K_2CO_3 at room temperature. Directly after addition of the base, a ^{1}H-NMR spectrum was recorded revealing the presence of the starting material. The sample was then heated to 50ºC and the progress of the anomerization was followed by ^{1}H-NMR until no changes were observed. It was found that the applied conditions indeed resulted in the appearance of new peaks assigned to the α-anomer of **2.31**, thereby confirming the anomerization of the tosyl-derivative. Furthermore, it was observed that the anomeric ratio was shifting over five days until an equilibrium between both anomers was attained (α/β 63:37).

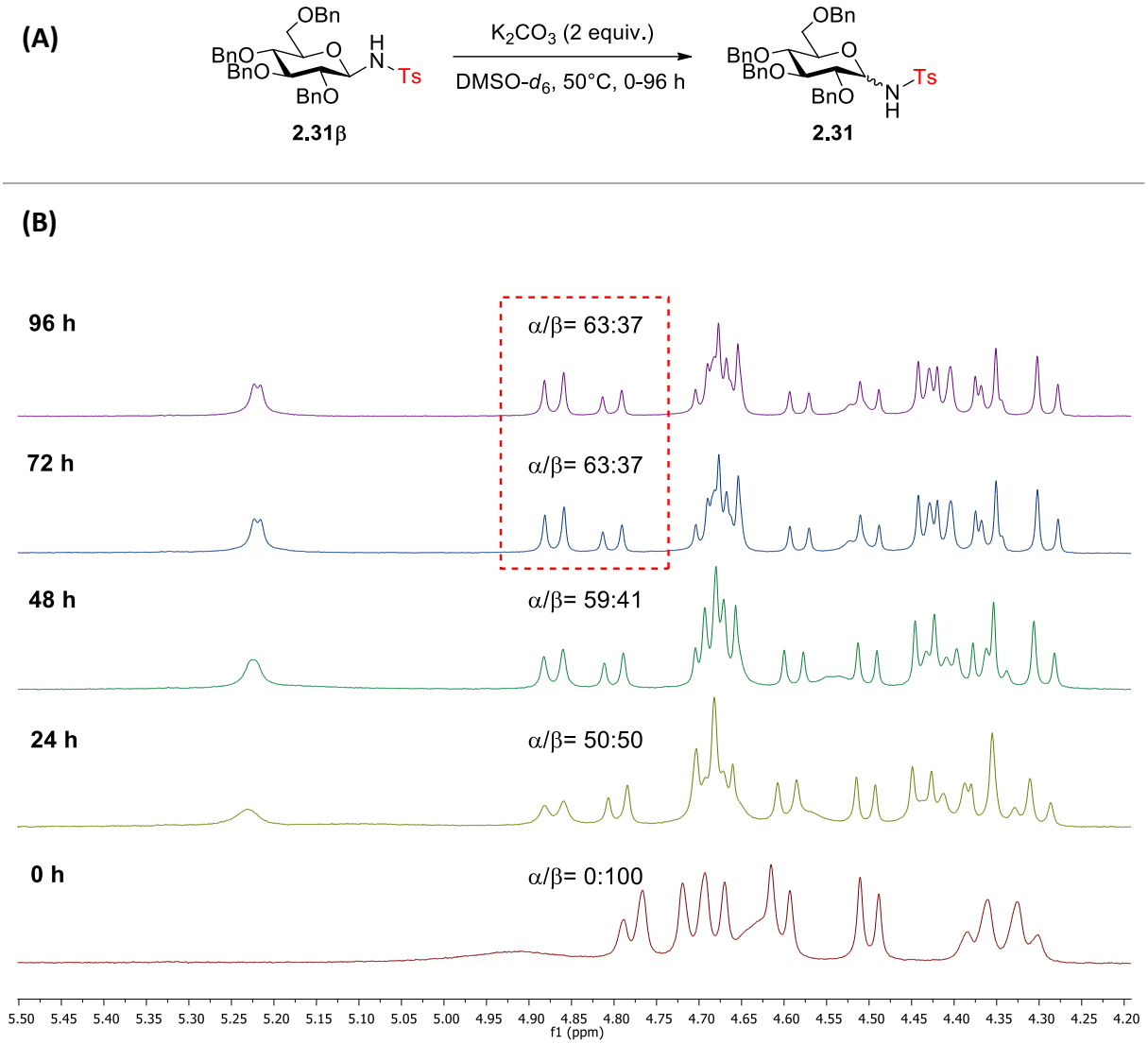
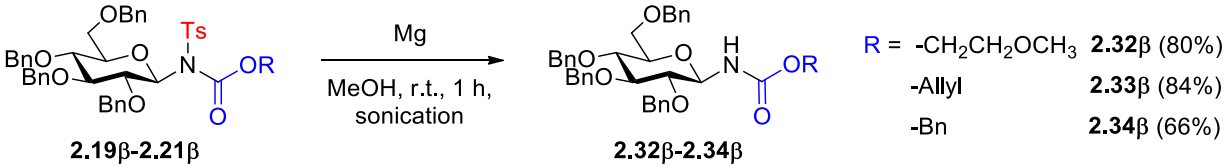


Figure 2.7. Studies on the anomerization of the β-glycosyl sulfonamide (**2.31β**) under basic conditions (A). Overview of the chemical shifts in the range δ_H 4.20-5.50 ppm observed in the ^{1}H-NMR spectra recorded over time (B).

To complete investigations of the orthogonal protection strategy, we turned our focus toward selective desulfonylation (**Scheme 2.7**). Although the tosyl group has been recognized as a versatile protecting group, particularly in the synthesis of heterocyclic compounds, its removal requires specific one-electron reductive conditions.[192–194] Thus, the tosyl moiety is generally difficult to cleave in a chemoselective manner. In order to access the carbamate-protected *N*-glycosides, the derivative **2.19β** was first reacted with lithium naphthalide at low temperature. However, our initial attempt resulted in a poor yield of 22%, and the glycosyl sulfonamide **2.31** was identified as the major byproduct. To improve the chemoselectivity, we applied different, milder conditions according to the protocol developed by Nyasse et al.[182] Derivatives **2.19**-**2.21β** were subjected to reduction using magnesium turnings and anhydrous MeOH with ultrasonication. Under these conditions, the corresponding *N*-glycosyl carbamates **2.32**-**2.34β** became the main products, giving yields of 80, 84 and 66%, respectively. The undesired cleavage of the carbamate function was still observed to take place, albeit as a side reaction. The deprotection using the Cbz-derivative **2.21β** resulted in the highest degree of the glycosyl sulfonamide formation, presumably due to the stronger electron-withdrawing nature of the carbamate substituent.



Scheme 2.7. Orthogonal desulfonylation of the β-*N*-glucosides.

2.3. Conclusions

Overall, we developed a synthetic approach toward the formation of *N*-glycosides featuring two key steps, i.e., the self-promoted *N*-glycosylation with TCA glycosyl donors and the orthogonal deprotection. During our studies of the *N*-glycosidic linkage forming step, we have shown that electron-poor acceptors can efficiently activate acid-labile TCA glycosyl donors giving rise to *N*-glycosyl sulfonyl carbamates. The reaction takes therefore place without any additives, which might be advantageous compared to the reported methods requiring catalysts or promoters. To investigate the glycosylation, various donors with *gluco*-, *galacto*- and *manno*-stereochemistry were reacted with different carbamate acceptors, leading to 11 *N*-glycosides in yields up to 95%. Importantly, all glycosylations proceeded at room temperature in a common organic solvent (CH_2Cl_2). Furthermore, the stereochemical outcome of the glycosylation was found to be strongly influenced by the stereochemistry of the donor, which can also be synthesized in a stereoselective manner, making this method more attractive. The highest stereospecificity was observed when using the α-glucosyl donor. In fact, the glycosylations resulted in complete inversion of the anomeric configuration. The stereospecificity dropped, when changing to the β-anomer of the same TCA donor. In order to elucidate the difference in reactivity between the anomeric pair of the TCA glycosyl donors, we undertook mechanistic studies, which led us to propose an S_Ni-type of mechanism. Noteworthy, our approach employs the orthogonal protection strategy, enabling the synthesis of more than one derivative from the same glycosylation product. Selective removal of carbamate substituents resulted in good and high yields, albeit the obtained product was found to anomerize under the reaction conditions involving either base or acid, which was further investigated. The undesired anomerization could be circumvent by installation of the Alloc moiety as a temporary protecting group, as its removal can be achieved without basic or acidic catalysis. Despite the fact that the selective cleavage of the tosyl group is generally difficult to attain, *N*-glycosyl carbamates were also obtained in good or high yields, leaving the anomeric configuration intact. Thus, the developed approach proved to be the selective and efficient synthetic route for the preparation of fully and partially functionalized *N*-glycosides.

Table 2.8. Summary of the developed approach.

Advantages	Drawbacks
- The glycosylation takes place without any additives at room temperature in CH_2Cl_2.	- Synthesis of the acceptors involves toxic and unstable isocyanates.
- Various acceptors can be used varying in size and functional groups.	- The glycosylation and deprotection reactions require dry conditions.
- Complete β-stereospecificity, when using the α-glucosyl donor.	- Poor yield of the glycosylation employing the Boc-protected acceptor.
- Generally, moderate to excellent yields in the glycosylation and the deprotection steps.	- In situ anomerization of the carbamate deprotection product in the presence of base or acid.
- The stereochemistry of the starting material is preserved during the Alloc and tosyl cleavage.	

2.4. Experimental

2.4.1. General Information

All reactions were carried out under an inert atmosphere of nitrogen in flame-dried glassware. Unless otherwise noted, chemicals and solvents were purchased from commercial suppliers (Sigma-Adrich, Fluka, TCI, ABCR, CarboSynth or Merck) and used without further purification. All solvents used for synthesis were HPLC-grade and dry. Dry CH_2Cl_2, acetonitrile, toluene, DMF and THF were obtained from an Innovative Technology PSMD-05 solvent drying system. Other solvents were dried with 4Å molecular sieves.

Thin layer chromatography (TLC) was performed on aluminum sheets coated with silica gel containing a fluorescence indicator (Merck 60 F254). TLC plates were visualized with UV-light (254 nm) or using a molybdate staining solution (Ce(IV)sulphate (10 g) and $(NH_4)_2MO_4$ (15 g) in 1000 mL 10 % H_2SO_4), 10% H_2SO_4 in methanol or vanillin staining solution (10 g, in 1000 mL 10 % H_2SO_4 in MeOH) followed by heating. For column chromatography ROTH 40-63 mesh and Kieselgel 230-400 mesh silica gel were used as stationary phase.

Nuclear magnetic resonance (NMR) spectroscopy was performed on Bruker 500 MHz Ultra Shield Plus spectrograph equipped with a cryo-probe.

Recorded spectra were referenced to the respective solvent peak as internal standard:

- $CDCl_3$ (^{1}H-NMR 7.260 ppm, ^{13}C-NMR 77.160 ppm)
- DMSO-d_6 (^{1}H-NMR 2.500 ppm, ^{13}C-NMR 39.520 ppm)
- CD_3CN (^{1}H-NMR 1.940 ppm, ^{13}C-NMR 1.320 ppm).

The reported TOCSY experiments were carried out under the same conditions at 26.85°C.

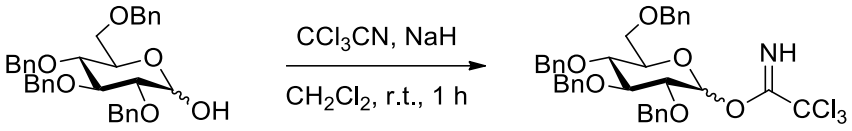
Infrared (IR) spectra were recorded using a Bruker Vertex 70 spectrometer equipped with the MIRacle Micro ATR accessory.

High resolution mass spectra (HRMS) were obtained from a Bruker SolariX XR 7T ESI/MALDI-FT-ICRMS instrument using matrix-assisted laser desorption ionization (MALDI).

Anton Paar polarimeter was used to determine optical rotations.

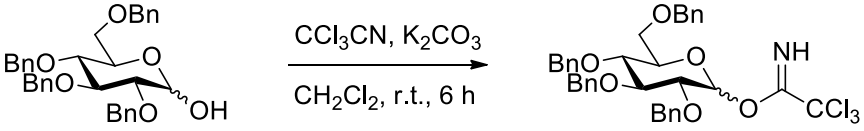
2.4.2. Synthesis of Glycosyl Donors

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (1.7α)



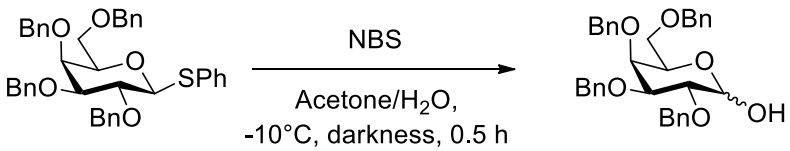
NaH (44.4 mg 60% in mineral oil, 1.11 mmol) and trichloroacetonitrile (2.3 mL, 23.1 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (2.50 g, 4.62 mmol) in dry CH_2Cl_2 (10 mL). The solution was stirred at r.t. for 1 h and evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:8 EtOAc/heptane + 0.5% Et_3N) to afford the major anomer (α) of compound **1.7α** (2.53 g, 3.69 mmol, 80%) as a colorless syrup. The NMR data of compound **1.7α** were consistent with the previously reported spectra. [35]

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (1.7β)



K_2CO_3 (2.05 g, 14.8 mmol) and trichloroacetonitrile (1.9 mL, 18.5 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (2.00 g, 3.70 mmol) in dry CH_2Cl_2 (12 mL). The solution was stirred at r.t. for 6 h and evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:7 EtOAc/heptane + 0.5% Et_3N) to afford the major anomer (β) of compound **1.7β** (1.86 g, 2.74 mmol, 74%). The NMR data of compound **1.7β** were consistent with the previously reported spectra. [35]

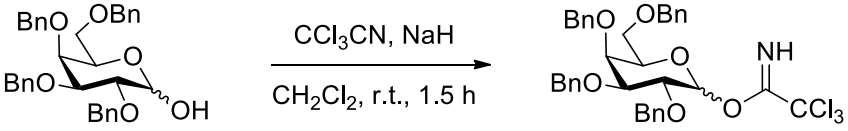
2,3,4,6-Tetra-*O*-benzyl-D-galactopyranose (2.7)



N-bromosuccinimide (1.01 g, 5.69 mmol) was added in the dark to a stirred solution of **2.6α** (3.00 g, 4.74 mmol) in a mixture of acetone and water (19:1, 60 mL) at -10°C. The solution was stirred at this temperature for 0.5 h. After completion, the reaction mixture was diluted with satd. aq. $NaHCO_3$ solution and extracted with EtOAc (2x 200 mL). The combined organic

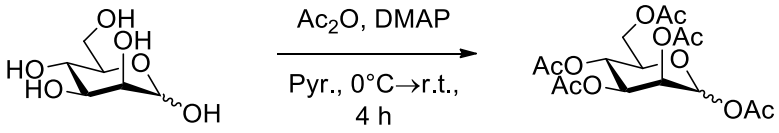
layers were dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash column chromatography (1:3→1:0 EtOAc/heptane) to yield the compound **2.7** (2.49 g, 4.60 mmol, 97%) as a colorless syrup. The NMR data of compound **2.7** were consistent with the previously reported spectra. [175]

2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl trichloroacetimidate (2.1)



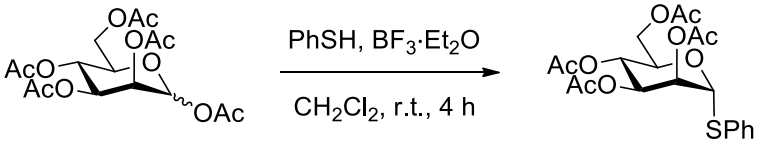
NaH (12.4 mg 60% in mineral oil, 0.31 mmol) and trichloroacetonitrile (0.7 mL, 6.47 mmol) was added to a stirred solution of **2.7** (700 mg, 1.29 mmol) in dry CH_2Cl_2 (7 mL). The solution was stirred at r.t. for 1.5 h and evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:8 EtOAc/heptane + 0.5% Et_3N) to yield two anomers (α/β 38:62) of compound **2.1** (599 mg, 0.87 mmol, 68%) as a colorless syrup. The NMR data of compound **2.1** were consistent with the previously reported spectra. [79,195]

1,2,3,4,6-Penta-*O*-acetyl-D-mannopyranose (2.8a)



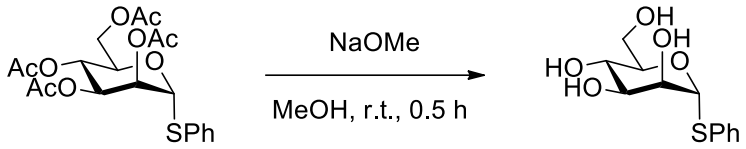
Ac_2O (39.4 mL, 416 mmol) was added to a solution of D-mannose (10.0 g, 55.5 mmol) in dry pyridine (60 mL) at 0°C. To the resulting mixture, DMAP (0.68 g, 5.55 mmol) was added. The reaction was allowed to warm up slowly to r.t. and stirred for 4 h. After completion, the reaction mixture was diluted with EtOAc (200 mL), washed with 1 M aq. HCl (5 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness to give a mixture of anomers of compound **2.8a** (21.5 g, 55.0 mmol, 99%) as a colorless syrup. The NMR data of compound **2.8a** were consistent with the previously reported spectra. [176]

Phenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-*α*-D-mannopyranoside (2.9α)



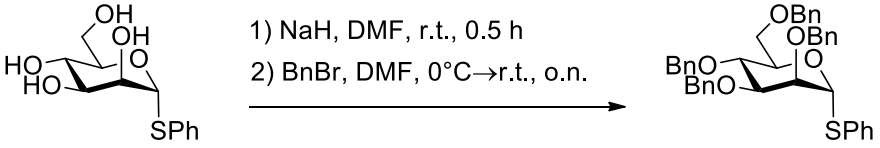
PhSH (8.6 mL, 83.3 mmol) was added to a solution of **2.8a** (21.7 g, 55.5 mmol) in dry CH_2Cl_2 (100 mL), followed by $BF_3 \cdot Et_2O$ (21.1 mL, 167 mmol). The resulting solution was stirred at r.t. for 4 h. After this time, the reaction mixture was washed with satd. aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and condensed *in vacuo*. The residue was crystallized from EtOH to afford the compound **2.9α** (17.1 g, 38.8 mmol, 70%) as a colorless crystalline solid. The NMR data of compound **2.9α** were consistent with the previously reported spectra. [177]

Phenyl 1-thio-*α*-D-mannopyranoside (2.10α)



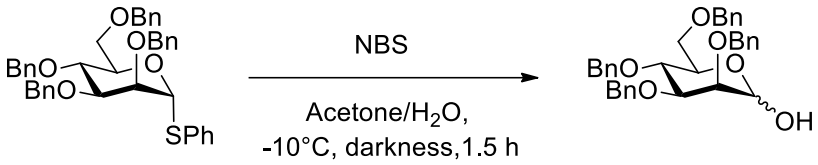
A 25% solution of NaOMe in MeOH (5.55 mL, 24.3 mmol) was added dropwise to a solution of **2.9α** (15.0 g, 34.1 mmol, 1 eq.) in dry MeOH (100 mL). The reaction mixture was stirred at r.t. for 0.5 h. After completion, the solution was neutralized with Amberlite IR-120 (H^+). The filtration and evaporation of solvent afforded the crude product **2.10α** as a white solid which was used in the next step without further purification. [177]

Phenyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-*α*-D-mannopyranoside (2.11α)



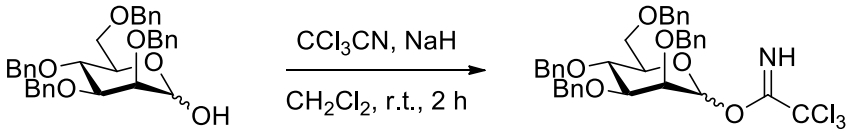
NaH (6.67 g 60% in mineral oil, 167 mmol) was added to a stirred solution of **2.10α** (9.06 g, 33.3 mmol) in dry DMF (100 mL). The resulting suspension was stirred at r.t. for 0.5 h. Then, the mixture was cooled down to 0°C and treated with BnBr (19.8 mL, 166 mmol). The suspension was allowed to warm up to r.t. and stirred overnight. After completion, the reaction was quenched with MeOH (20 mL) at 0°C. The solution was diluted with H_2O (500 mL) and extracted with Et_2O (3 x 300 mL). The combined organic layers were dried over Na_2SO_4, and condensed *in vacuo*. The residue was purified by flash column chromatography (1:8→1:4 EtOAc/heptane) to yield the compound **2.11α** (16.4 g, 26.0 mmol, 78%) as a colorless syrup. The NMR data of compound **2.11α** were consistent with the previously reported spectra. [177]

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose (2.12)



N-bromosuccinimide (4.22 g, 23.7 mmol) was added in the dark to a stirred solution of **2.11α** (5.00 g, 7.90 mmol) in a mixture of acetone and water (19:1, 200 mL) at -10°C. The solution was stirred at this temperature for 1.5 h. After completion, the reaction mixture was diluted with satd. aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash column chromatography (1:2→1:0 EtOAc/heptane) to yield the compound **2.12** (3.67 g, 6.79 mmol, 86%) as a colorless syrup. The NMR data of compound **2.12** were consistent with the previously reported spectra. [177]

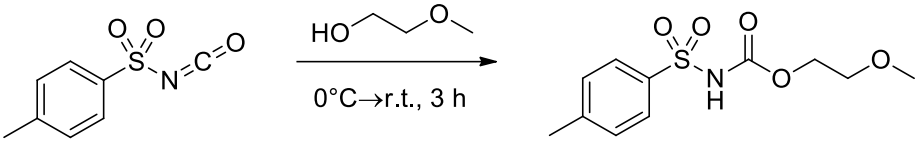
2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl trichloroacetimidate (2.2α)



NaH (64.6 mg 60% in mineral oil, 1.62 mmol) and trichloroacetonitrile (3.4 mL, 33.7 mmol) was added to a stirred solution of **2.12** (3.64 g, 6.73 mmol) in dry CH_2Cl_2 (15 mL). The solution was stirred at r.t. for 2 h and evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:8 EtOAc/heptane + 0.5% Et_3N) to afford the major anomer (α) of compound **2.2α** (2.52 g, 3.68 mmol, 55%) as a colorless syrup. The NMR data of compound **2.2α** were consistent with the previously reported spectra. [178]

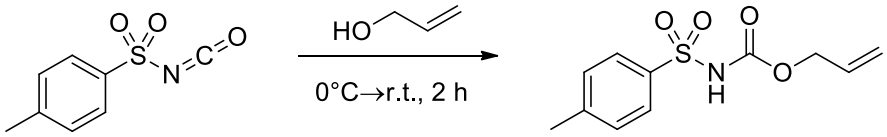
2.4.3. Synthesis of *N*-sulfonyl Carbamates

2-methoxyethyl *N*-(4-nitrophenylsulfonyl)carbamate (2.13)



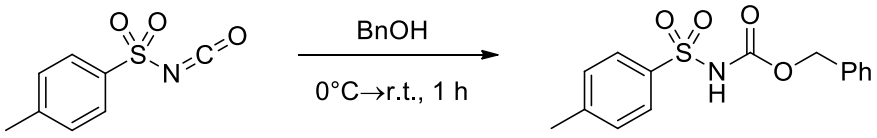
p-Toluenesulfonyl isocyanate (10.0 g, 50.7 mmol, 7.7 mL) was added slowly to a flask, in an ice bath, containing freshly distilled 2-methoxyethanol (20 mL, 254 mmol). The reaction mixture was allowed to reach r.t. and stirred for 3 h. After concentration *in vacuo,* the solid obtained was crystallized from CH_2Cl_2 and petroleum ether affording the compound **2.13** as a white crystalline solid (12.6 g, 46.1 mmol, 91%).‡ **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 11.99 (s, 1H, *N*H), 7.78 (d, *J* = 8.4 Hz, 1H, ArH^{Ts}), 7.43 (d, *J* = 7.8 Hz, 1H, ArH^{Ts}), 4.21 – 3.88 (m, 2H, CH_2), 3.57 – 3.37 (m, 2H, CH_2), 3.20 (s, 3H, *O*CH_3), 2.40 (s, 3H, CH_3^{Ts}) ppm. **^{13}C-NMR** (126 MHz, DMSO-d_6) δ 151.12 (C=O), 144.21 (ArC), 136.35 (ArC), 129.59 (2x ArCH), 127.48 (2x ArCH), 69.45 (CH_2), 64.80 (CH_2), 57.94 (*O*CH_3), 21.06 (CH_3^{Ts}) ppm. **HRMS** (MALDI+): Calculated for $C_{11}H_{15}NO_5SNa$+ m/z 296.05631; found m/z 296.05361.

Allyl *N*-(4-methylbenzenesulfonyl)carbamate (2.14)



Allyl alcohol (3.4 mL, 50.7 mmol) was cooled down in an ice bath. Then, *p*-toluenesulfonyl isocyanate (1.5 mL, 10.1 mmol) was added. The resulting solution was let to warm up to r.t. and stirred for 2h. After completion, an excess of alcohol was removed *in vacuo*. The crude product was purified by flash column chromatography with the eluent petroleum ether/ EtOAc (3:2) to afford the compound **2.14** (2.59 g, 10.1 mmol, 99%) as a white crystalline solid. The NMR data of compound **2.14** were consistent with the previously reported spectra. [179]

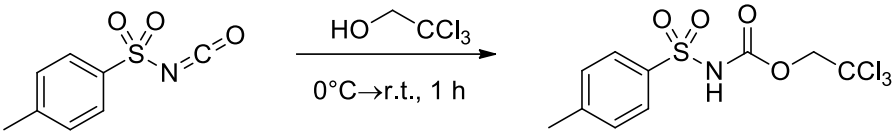
Benzyl *N*-(4-methylbenzenesulfonyl)carbamate (2.15)



‡ The compound **10** was synthesized by Prof. Christian Marcus Pedersen.

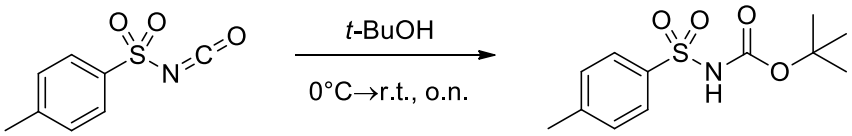
Benzyl alcohol (1.1 mL, 10.7 mmol) was cooled down in an ice bath. Then, *p*-toluenesulfonyl isocyanate (1.5 mL, 10.1 mmol) was added. The resulting solution was let to warm up to r.t. and stirred for 1 h. After completion, a crystallization was induced at -20°C from a mixture cyclohexane/CH_2Cl_2 (15:1) to afford the compound **2.15** (2.94 g, 9.63 mmol, 95%) as a white crystalline solid. The NMR data of compound **2.15** were consistent with the previously reported spectra. [180]

2,2,2-Trichloroethyl *N*-(4-methylbenzenesulfonyl)carbamate (2.16)



Trichloroethyl alcohol (4.9 mL, 50.7 mmol) was cooled down in an ice bath. Then, *p*-toluenesulfonyl isocyanate (1.5 mL, 10.1 mmol) was added. The resulting solution was let to warm up to r.t. and stirred for 1 h. After completion, an excess of alcohol was removed *in vacuo*. The crude product was purified by crystallization from a mixture cyclohexane/EtOAc (20:1) to afford the compound **2.16** (3.06 g, 8.81 mmol, 87%) as a white crystalline solid. The NMR data of compound **2.16** were consistent with the previously reported spectra. [181]

***t*-Butyl *N*-(4-methylbenzenesulfonyl)carbamate (2.17)**



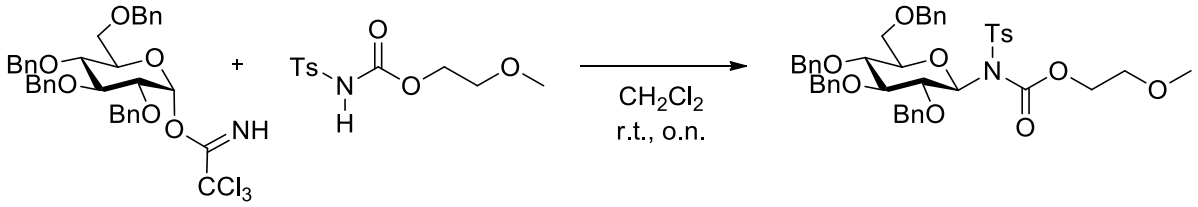
t-BuOH (9.6 mL, 101 mmol) was cooled down in an ice bath. Then, *p*-toluenesulfonyl isocyanate (1.5 mL, 10.1 mmol) was added. The resulting solution was let to warm up to r.t. and stirred overnight. After completion, an excess of alcohol was removed *in vacuo*. The crude product was purified by crystallization from a mixture cyclohexane/EtOAc (4:1) to afford the compound **2.17** (2.41 g, 8.86 mmol, 87%) as a white crystalline solid. The NMR data of compound **2.17** were consistent with the previously reported spectra. [196]

2.4.4. Self-promoted *N*-glycosylations

General procedure for glycosylations

Carbamate acceptor (1.5 equiv.) was added to a stirred solution of trichloroacetimidate glycosyl donor (1.0 equiv., 0.30 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere in flame-dried glassware. The reaction was stirred until no starting material was left. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The products were purified by flash column chromatography and evaporated *in vacuo* to dryness.

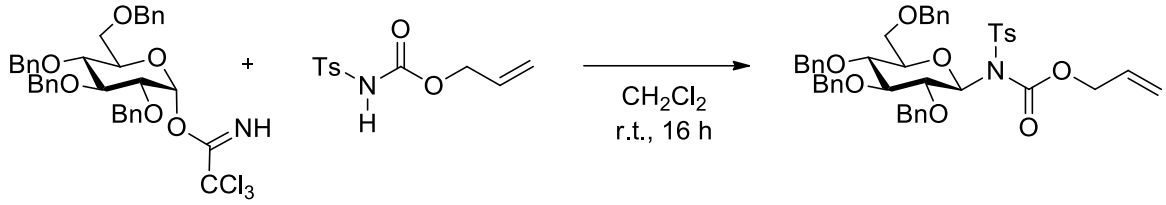
2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl 2-methoxyethyl tosylcarbamate (2.19β)



Carbamate **12** (89.5 mg, 0.33 mmol) was added to a stirred solution of **1.7α** (105 mg, 0.15 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:5 EtOAc/heptane) to yield the β anomer of compound **2.19** (113 mg, 0.25 mmol, 93%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H, 2x ArH^{Ts}), 7.38 – 7.26 (m, 18H, 18x ArH^{Bn}), 7.23 – 7.18 (m, 2H, 2x ArH^{Bn}), 7.07 – 7.01 (m, 2H, 2x ArH^{Ts}), 5.53 (d, *J* = 9.3 Hz, 1H, H-1β), 4.94 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.88 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.85 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.81 – 4.71 (m, 1H, CH_2^{Bn}), 4.61 (dt, *J* = 11.1, 6.1 Hz, 2H, CH_2^{Bn}), 4.55 (dd, *J* = 11.9, 3.1 Hz, 1H, H-2), 4.51 (d, *J* = 12.0 Hz, 2H, CH_2^{Bn}), 4.15 (dd, *J* = 5.7, 3.8 Hz, 2H, C(*O*)*O*CH_2), 3.75 (m, 2H, H-3, H-5, H-6a), 3.65 (m, 2H, H-4 H-6b), 3.41 (dd, *J* = 5.6, 3.8 Hz, 2H, *O*CH_2), 3.23 (s, 3H, *O*CH_3), 2.34 (s, 3H, CH_3^{Ts}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 144.22 (C=O), 138.56, 138.31, 138.07, 129.11, 128.41, 128.34, 128.28, 128.15, 127.94, 127.79, 127.69, 127.65, 127.57, 127.52 (6x ArC, 24x ArCH), 86.64 (C-3), 85.96 (C-1), 77.67 (C-2), 77.19 (2x C, C-4, C-5 same as $CDCl_3$), 75.59, 75.06, 73.30 (4x CH_2^{Bn}), 69.66 (*O*CH_2), 68.97 (C-6), 65.97

($C(O)OCH_2$), 58.69 (OCH_3), 21.60 (CH_3^{Ts}) ppm. **HRMS** (MALDI+): Calculated for $C_{45}H_{49}NO_{10}SNa+$ m/z 818.2969, found m/z 818.2970. $[\alpha]_D^{298}$= +8.52 (*c*=1.0, $CHCl_3$).

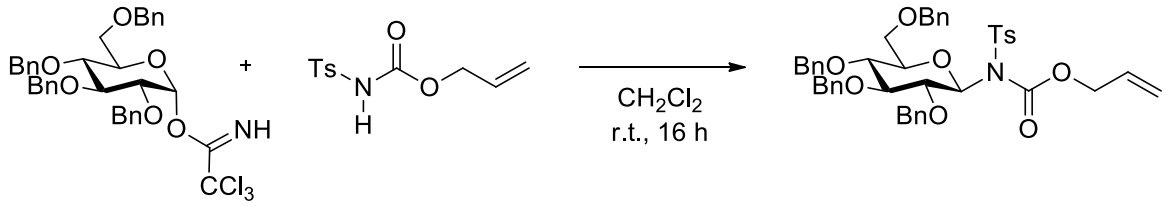
2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl allyl tosylcarbamate (2.20β)



Carbamate **2.14** (114 mg, 0.45 mmol) was added to a stirred solution of **1.7α** (204 mg, 0.30 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 16 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography ((1:7→1:6 EtOAc/heptane) to yield the β anomer of compound **2.20** (209 mg, 0.27 mmol, 90%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.84 (broad d, *J* ~ 7.4 Hz, 2H, 2x ArH^{Ts}), 7.41-7.16 (m, 20H, 20x ArH^{Bn}), 7.02 (d, *J* = 7.4 Hz, 2H, 2x ArH^{Ts}), 5.71-5.60 (m, 1H, =CH), 5.51 (d, *J* = 9.3 Hz, 1H, H-1), 5.17 (ddt, *J* = 17.2, 1.4, 1.4 Hz, 1H, $=CH_2^{trans}$), 5.09 (broad ddt, *J* ~ 10.6, 1.4, 1.4 Hz, 1H, $=CH_2^{cis}$), 4.91 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.86 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.83 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.78-4.67 (m, 2H, CH_2^{Bn}), 4.58 (d, *J* = 11.1 Hz, 2H, CH_2^{Bn}), 4.54-4.44 (m, 3H, H-2, CH_2^{Alloc}, CH_2^{Bn}), 4.42-4.34 (m, 1H, CH_2^{Alloc}), 3.77-3.66 (m, 3H, H-3, H-6, H-6'), 3.68-3.59 (m, 2H, H-4, H-5), 2.31 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.41 (C=O), 144.43 (ArC^{Ts}), 138.56 (ArC^{Bn}), 138.41 (ArC^{Bn}), 138.20 (ArC^{Bn}), 138.11 (ArC^{Bn}), 136.76 (ArC^{Ts}), 130.83 (=CH), 129.27 (2x $ArCH^{Ts}$), 128.74-127.67 (22x $ArCH^{Ts/Bn}$), 119.40 ($=CH_2$), 86.86 (C-3), 86.05 (C-1), 77.85, 77.56-76.79 (3x C, C-2, C-4, C-5, same as $CDCl_3$), 75.90 (CH_2^{Bn}), 75.21 (CH_2^{Bn}), 74.69 (CH_2^{Bn}), 73.44 (CH_2^{Bn}), 69.10 (C-6), 67.80 (CH_2^{Alloc}), 21.72 (CH_3) ppm.[§] **HRMS** (MALDI+): Calculated for $C_{45}H_{47}NO_9SNa^+$ m/z 800.2869; found m/z 800.2861. $[\alpha]_D^{298}$=+2.92° (*c*=0.480, $CHCl_3$).

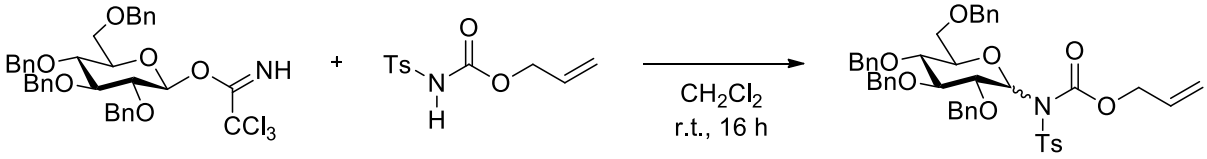
[§] The obtained compound **16** contained 2% of the α anomer.

2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl allyl tosylcarbamate (2.20β)



Carbamate **13** (112 mg, 0.439 mmol) was added to a stirred solution of **1.7α** (201 mg, 0.29 mmol) in dry CH_2Cl_2 (2.9 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 16 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography ((1:7→1:6 EtOAc/heptane) to yield the β anomer of compound **2.20** (182 mg, 0.23 mmol, 80%) as a colorless syrup. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

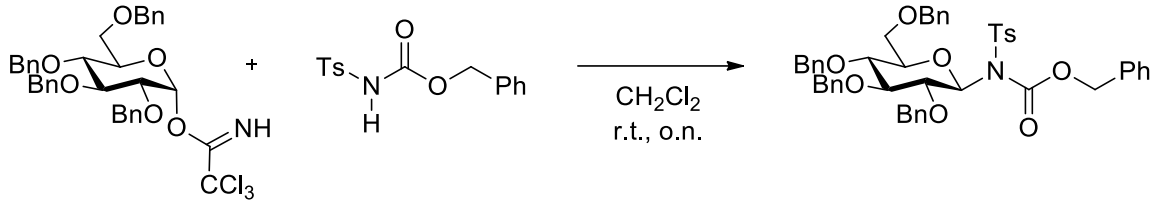
2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl allyl tosylcarbamate (2.20)



Carbamate **2.14** (83.6 mg, 0.33 mmol) was added to a stirred solution of **1.7β** (150 mg, 0.22 mmol) in dry CH_2Cl_2 (1.1 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 16 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:7→1:6 EtOAc/heptane) to yield the α/β mixture (43:57) of compound **2.20** (125 mg, 0.16 mmol, 73%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.88-7.86 (m, 4H, 4x ArH^{Ts}α/β), 7.37-7.14 (m, 40H, 40x ArH^{Bn}α/β), 7.01 (d, *J* = 7.5 Hz, 2H, 2x ArH^{Ts}β), 6.97 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}α), 6.38 (d, *J* = 8.2 Hz, 1H, H-1α), 5.69-5.60 (m, 1H, =CHβ), 5.63-5.54 (m, 1H, =CHα), 5.50 (d, *J* = 9.3 Hz, 1H, H-1β), 5.19-5.11 (m, 2H, $=CH_2^{trans}$α/β), 5.10-5.05 (m, 2H, $=CH_2^{cis}$α/β), 4.90 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}β), 4.84 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}β), 4.83 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}α), 4.82 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}β), 4.78 (d, *J* = 11.2 Hz, 1H, CH_2^{Bn}α), 4.76-4.69 (m, 2H, CH_2^{Bn}β), 4.63 (d,

J = 10.9 Hz, 1H, CH_2^{Bn}α), 4.57 (d, *J* = 11.1 Hz, 2H, CH_2^{Bn}β), 4.55-4.41 (m, 10H, H-2β, H-3α, CH_2^{Alloc}α/β, CH_2^{Bn}α/β), 4.41-4.32 (m, 2H, CH_2^{Alloc}α/β), 4.24 (ddd, *J* = 10.1, 5.0, 1.7 Hz, 1H, H-5α), 4.07 (t, *J* = 8.2 Hz, 1H, H-2α), 3.75-3.65 (m, 4H, H-3 β, H-6α/β, H-6'β), 3.66-3.54 (m, 4H, H-4α/β, H-5β, H-6'α), 2.30 (s, 3H, CH_3β), 2.27 (s, 3H, CH_3α) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 152.98 (C=Oα), 151.41 (C=Oβ), 144.44 (2x ArC^{Ts}α/β), 138.98 (ArC^{Bn}α), 138.60 (ArC^{Bn}α), 138.57 (ArC^{Bn}β), 138.43 (ArC^{Bn}β), 138.35 (ArC^{Bn}α), 138.21 (ArC^{Bn}β), 138.12 (ArC^{Bn}β), 137.37 (ArC^{Bn}α), 136.83 (ArC^{Ts}α), 136.77 (ArC^{Ts}β), 130.84 (=CHβ), 130.83 (=CHα), 129.43 (2x $ArCH^{Ts}$α), 129.28 (2x $ArCH^{Ts}$β), 128.74-127.65 (44x $ArCH^{Ts/Bn}$α/β), 119.40 (=CH_2β), 119.36 (=CH_2β), 86.87 (C-3β), 86.08 (C-1β), 82.86 (C-3α), 81.83 (C-1α), 79.04 (C-2α), 78.00 (C-4α), 77.86, 77.56-76.79 (3x C, C-2β, C-4β, C-5β, same as $CDCl_3$), 75.91 (CH_2^{Bn}β), 75.22 (CH_2^{Bn}β), 75.00 (CH_2^{Bn}α), 74.69 (CH_2^{Bn}β), 74.59 (CH_2^{Bn}α), 74.54 (C-5α), 73.76 (CH_2^{Bn}α), 73.64 (CH_2^{Bn}α), 73.45 (CH_2^{Bn}β), 69.98 (C-6α), 69.11 (C-6β), 68.12 (CH_2^{Alloc}α), 67.80 (CH_2^{Alloc}β), 21.73 (CH_3β), 21.67 (CH_3α) ppm. **HRMS** (MALDI+): Calculated for $C_{45}H_{47}NO_9SNa^+$ m/z 800.2869; found m/z 800.2856. $[\alpha]_D^{298}$=+12.88° (*c*=1.025, $CHCl_3$).

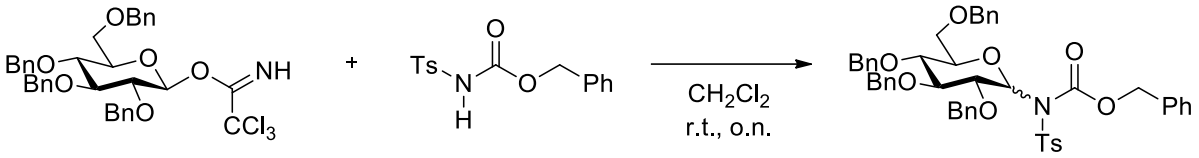
2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl benzyl tosylcarbamate (2.21β)



Carbamate **2.15** (142 mg, 0.46 mmol) was added to a stirred solution of **1.7α** (212 mg, 0.31 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:6 EtOAc/heptane) to yield the β anomer of compound **2.21** (244 mg, 0.29 mmol, 93%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.75 (broad d, *J* ~ 7.4 Hz, 2H, 2x ArH^{Ts}), 7.45-7.08 (m, 25H, 25x $ArH^{Bn/Cbz}$), 6.92 (d, *J* = 7.4 Hz, 2H, 2x ArH^{Ts}), 5.53 (d, *J* = 9.3 Hz, 1H, H-1), 5.05 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.96 (broad d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.91 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.86 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.82 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.72-4.54 (m, 4H, CH_2^{Bn}), 4.54-4.46 (m, 2H, CH_2^{Bn}, H-2), 3.79-3.68 (m, 3H, H-3, H-6, H-6'), 3.68-3.57 (m, 2H, H-4, H-5), 2.30 (s, 3H, CH_3)

ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.43 (C=O), 144.25 (ArC^{Ts}), 138.62 (ArC^{Bn}), 138.43 (ArC^{Bn}), 138.19 (ArC^{Bn}), 138.13 (ArC^{Bn}), 136.74 (ArC^{Ts}), 134.51 (ArC^{Cbz}), 129.22 (2x $ArCH^{Ts}$), 128.59-127.68 (27x $ArCH^{Ts/Bn/Cbz}$), 86.83 (C-3), 86.09 (C-1), 77.85, 77.55-76.72 (3x C, C-2, C-4, C-5, same as $CDCl_3$), 75.74 (CH_2^{Bn}), 75.19 (CH_2^{Bn}), 74.59 (CH_2^{Bn}), 73.49 (CH_2^{Bn}), 69.11 (CH_2^{Cbz}), 69.04 (C-6), 21.70 (CH_3) ppm.** **HRMS** (MALDI+): Calculated for $C_{49}H_{49}NO_9SNa^+$ m/z 850.3026; found m/z 850.3005. $[\alpha]_D^{298}$=+1.82° (*c*=1.210, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl benzyl tosylcarbamate (2.21)

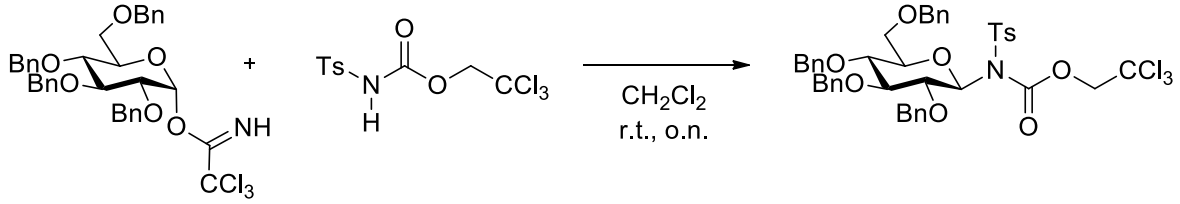


Carbamate **2.15** (102 mg, 0.33 mmol) was added to a stirred solution of **1.7β** (152 mg, 0.22 mmol) in dry CH_2Cl_2 (1.1 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:7→1:6 EtOAc/heptane) to yield the α/β mixture (53:47) of compound **2.21** (150 mg, 0.18 mmol, 81%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.76 (broad d, *J* ~ 7.4 Hz, 2H, 2x ArH^{Ts}β), 7.69 (d, *J* = 8.2 Hz, 2H, 2x ArH^{Ts}α), 7.42-7.16 (m, 46H, 46x $ArH^{Bn/Cbz}$α/β), 7.14 (d, *J* = 7.1 Hz, 2H, 2x $ArH^{Bn/Cbz}$α/β), 7.10 (d, *J* = 7.3 Hz, 2H, 2x $ArH^{Bn/Cbz}$α/β), 6.92 (d, *J* = 7.4 Hz, 2H, 2x ArH^{Ts}β), 6.84 (d, *J* = 8.2 Hz, 2H, 2x ArH^{Ts}α), 6.43 (d, *J* = 8.2 Hz, 1H, H-1α), 5.53 (d, *J* = 9.3 Hz, 1H, H-1β), 5.06 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}β), 5.02 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}α), 4.98 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}α), 4.97 (broad d, *J* ~ 12.1 Hz, 1H, CH_2^{Cbz}β), 4.91 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}β), 4.86 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}β), 4.83 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}β), 4.82 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}α), 4.80 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}α), 4.72-4.54 (m, 4H, CH_2^{Bn}β), 4.70 (d, *J* = 11.2 Hz, 1H, CH_2^{Bn}α), 4.65 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}α), 4.59-4.47 (m, 7H, H-2β, H-3α, CH_2^{Bn}α/β), 4.28 (ddd, *J* = 10.1, 4.8, 1.6 Hz, 1H, H-5α), 4.11 (t, *J* = 8.2 Hz, Hz, 1H, H-2α), 3.79-3.68 (m, 4H, H-3β, H-6α/β, H-6'β), 3.69-3.56 (m, 4H, H-4α/β, H-5β, H-6'α), 2.31 (s, 3H, CH_3β), 2.26 (s, 3H, CH_3α) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 153.22 (C=Oα), 151.44 (C=Oβ), 144.26 (ArC^{Ts}β), 144.21 (ArC^{Ts}α), 139.00 (ArC^{Bn}α), 138.62 (ArC^{Bn}β), 138.60 (ArC^{Bn}α), 138.43

** The obtained compound **17** contained 3% of the α anomer.

($ArC^{Bn}\beta$), 138.35 ($ArC^{Bn}\alpha$), 138.19 ($ArC^{Bn}\beta$), 138.13 ($ArC^{Bn}\beta$), 137.40 ($ArC^{Bn}\alpha$), 136.74 ($ArC^{Ts}\beta$), 136.69 ($ArC^{Ts}\alpha$), 134.51 ($ArC^{Cbz}\beta$), 134.35 ($ArC^{Cbz}\alpha$), 129.34 (2x $ArCH^{Ts}\alpha$), 129.23 (2x $ArCH^{Ts}\beta$), 128.74-127.64 (54x $ArCH^{Ts/Bn/Cbz}\alpha/\beta$), 86.83 (C-3β), 86.11 (C-1β), 82.82 (C-3α), 81.95 (C-1α), 79.13 (C-2α), 77.97 (C-4α), 77.85, 77.55-76.72 (3x C, C-2β, C-4β, C-5β, same as $CDCl_3$), 75.73 ($CH_2^{Bn}\beta$), 75.18 ($CH_2^{Bn}\beta$), 74.95 ($CH_2^{Bn}\alpha$), 74.58 ($CH_2^{Bn}\beta$), 74.56 ($CH_2^{Bn}\alpha$), 74.54 (C-5α), 73.71 ($CH_2^{Bn}\alpha$), 73.68 ($CH_2^{Bn}\alpha$), 73.49 ($CH_2^{Bn}\beta$), 69.88 (C-6α), 69.38 ($CH_2^{Cbz}\alpha$), 69.11 (CH_2^{Cbz}), 69.05 (C-6β), 21.70 ($CH_3\beta$), 21.64 ($CH_3\alpha$) ppm. **HRMS** (MALDI+): Calculated for $C_{49}H_{49}NO_9SNa^+$ m/z 850.3026; found m/z 850.3010. $[\alpha]_D^{298}$=+17.7° (*c*=0.825, $CHCl_3$).

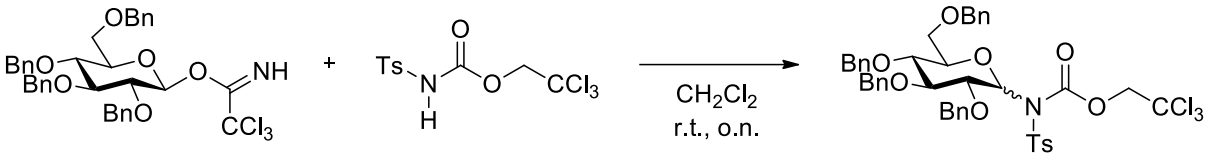
2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl 2,2,2-trichloroethyl tosylcarbamate (2.22β)



Carbamate **2.16** (158 mg, 0.46 mmol) was added to a stirred solution of **1.7*α*** (208 mg, 0.30 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:6 EtOAc/heptane) to yield the β anomer of compound **2.22** (250 mg, 0.29 mmol, 95%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.92 (broad d, *J* ~7.5 Hz, 2H, 2x ArH^{Ts}), 7.44-7.15 (m, 20H, 20x ArH^{Bn}), 7.04 (d, *J* = 7.5 Hz, 2H, 2x ArH^{Ts}), 5.60 (d, *J* = 9.3 Hz, 1H, H-1), 4.96 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.91 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.85 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.83-4.74 (m, 2H, CH_2^{Bn}), 4.65 (broad d, *J* = 11.3 Hz, 1H, CH_2^{Troc}), 4.61-4.45 (m, 5H, H-2, CH_2^{Bn}, CH_2^{Troc}), 3.78 (t, *J* = 8.9 Hz, 1H, H-3), 3.75 (broad d, *J* = 10.6 Hz, 1H, H-6), 3.72-3.66 (m, 1H, H-5), 3.66-3.55 (m, 2H, H-4, H-6'), 2.33 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 150.51 (C=O), 144.82 (ArC^{Ts}), 138.60 (ArC^{Bn}), 138.35 (ArC^{Bn}), 138.05 (ArC^{Bn}), 138.01 (ArC^{Bn}), 136.19 (ArC^{Ts}), 129.44 (2x $ArCH^{Ts}$), 128.59-127.74 (22x $ArCH^{Ts/Bn}$), 93.95 (CCl_3), 86.86 (C-3), 86.19 (C-1), 77.87, 77.69, 77.55-76.75 (3x C, C-2, C-4, C-5, same as $CDCl_3$), 75.85 (CH_2^{Bn}), 75.78

(CH_2^{Troc}), 75.18 (CH_2^{Bn}), 74.66 (CH_2^{Bn}), 73.46 (CH_2^{Bn}), 69.30 (C-6), 21.75 (CH_3) ppm.[††] **HRMS** (MALDI+): Calculated for $C_{44}H_{44}Cl_3NO_9SNa^+$ m/z 890.1700; found m/z 890.1682. $[\alpha]_D^{298}$=+1.36° (*c*=0.735, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl 2,2,2-trichloroethyl tosylcarbamate (2.22)

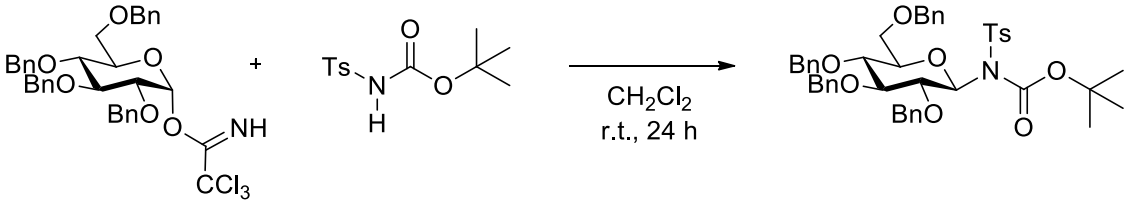


Carbamate **2.16** (115 mg, 0.33 mmol) was added to a stirred solution of **1.7β** (151 mg, 0.22 mmol) in dry CH_2Cl_2 (1.1 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:7→1:6 EtOAc/heptane) to yield the α/β mixture (50:50) of compound **2.22** (152 mg, 0.17 mmol, 80%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* =8.4 Hz, 2H, 2x ArH^{Ts}α), 7.91 (broad d, *J* ~7.5 Hz, 2H, 2x ArH^{Ts}β), 7.44-7.16 (m, 40H, 40x ArH^{Bn}α/β), 7.04 (d, *J* = 7.5 Hz, 2H, 2x ArH^{Ts}β), 7.02 (d, *J* =8.4 Hz, 2H, 2x ArH^{Ts}α), 6.48 (d, *J* = 8.0 Hz, 1H, H-1α), 5.60 (d, *J* = 9.3 Hz, 1H, H-1β), 4.95 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}β), 4.90 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}β), 4.86 (d, *J* = 11.4 Hz, 1H, CH_2^{Bn}α), 4.84 (d, J^2= 11.0 Hz, 1H, CH_2^{Bn}β), 4.83-4.74 (m, 2H, CH_2^{Bn}β), 4.81 (d, *J* = 11.2 Hz, 1H, CH_2^{Bn}α), 4.77 (d, *J* = 11.2 Hz, 1H, CH_2^{Bn}α), 4.72 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}α), 4.68 (d, *J* = 11.0, 1H, CH_2^{Bn}α), 4.64 (broad d, *J* = 11.3 Hz, 1H, CH_2^{Troc}β), 4.61-4.44 (m, 11H, H-2β, H-3α, CH_2^{Bn}α/β, CH_2^{Troc}α/β), 4.31 (ddd, *J* = 10.1, 5.1, 1.7 Hz, 1H, H-5α), 4.15 (t, *J* = 8.0 Hz, 1H, H-2α), 3.78 (t, *J* = 8.9 Hz, 1H, H-3β), 3.76-3.72 (m, 2H, H-6α/β), 3.72-3.66 (m, 1H, H-5β), 3.66-3.56 (m, 4H, H-4α/β, H-6'α/β), 2.33 (s, 3H, CH_3β), 2.31 (s, 3H, CH_3α) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 152.32 (C=Oα), 150.49 (C=Oβ), 144.81 (ArC^{Ts}β), 144.72 (ArC^{Ts}α), 138.81 (ArC^{Bn}α), 138.60 (ArC^{Bn}β), 138.47 (ArC^{Bn}α), 138.35 (ArC^{Bn}β), 138.29 (ArC^{Bn}α), 138.05 (ArC^{Bn}β), 137.99 (ArC^{Bn}β), 137.23 (ArC^{Bn}α), 136.56 (ArC^{Ts}α), 136.19 (ArC^{Ts}β), 129.66 (2x $ArCH^{Ts}$α) 129.43 (2x $ArCH^{Ts}$β), 128.58-127.73 (44x $ArCH^{Ts/Bn}$α/ β), 93.93 (CCl_3β), 93.91 (CCl_3α), 86.86 (C-3β), 86.17 (C-1β), 82.70 (C-3α), 82.52 (C-1α), 78.98 (C-2α), 77.94 (C-4α), 77.87, 77.69, 77.55-76.75 (3x C, C-2β, C-4β, C-5β, same as $CDCl_3$), 76.12 (CH_2^{Troc}α),

[††] The obtained compound **18** contained less than 1% of the α anomer.

75.85 (CH_2^{Bn}β), 75.78 (CH_2^{Troc}), 75.19 (CH_2^{Bn}β), 74.90 (C-5α, CH_2^{Bn}α), 74.67 (CH_2^{Bn}β), 74.58 (CH_2^{Bn}α), 73.91 (CH_2^{Bn}α), 73.75 (CH_2^{Bn}α), 73.46 (CH_2^{Bn}β), 69.99 (C-6α), 69.30 (C-6β), 21.74 (CH_3β), 21.68 (CH_3α) ppm. **HRMS** (MALDI+): Calculated for $C_{44}H_{44}Cl_3NO_9SNa^+$ m/z 890.1700; found m/z 890.1679. $[\alpha]_D^{298}$=+17.47° (*c*=0.790, $CHCl_3$).

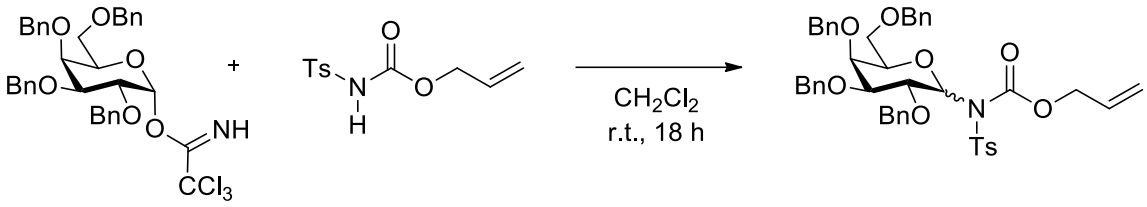
2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl *t*-butyl tosylcarbamate (2.23β)



Carbamate **2.17** (137 mg, 0.51 mmol) was added to a stirred solution of **1.7α** (231 mg, 0.34 mmol) in dry CH_2Cl_2 (3.0 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 24 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:6 EtOAc/heptane) to yield the β anomer of compound **2.23** (93.8 mg, 0.12 mmol, 35%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.00-7.72 (m, 2H, 2x ArH^{Ts}), 7.35-7.12 (m, 20H, 20x ArH^{Bn}), 7.10-6.92 (m, 2H, 2x ArH^{Ts}), 5.46 (d, *J* = 8.8 Hz, 1H, H-1β), 4.90 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.83 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.81 (d, J^2= 11.0 Hz, 1H, CH_2^{Bn}), 4.77-4.62 (m, 2H, CH_2^{Bn}), 4.62-4.55 (m, 2H, CH_2^{Bn}), 4.55-4.47 (m, 2H, H-2, CH_2^{Bn}), 3.78-3.65 (m, 3H, H-3, H-6, H-6'), 3.67-3.57 (m, 2H, H-4, H-5), 2.30 (s, 3H, CH_3^{Ts}), 1.26 (s, 9H, CH_3^{Boc}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 150.04 (C=O), 143.94 (ArC^{Ts}), 138.75 (ArC^{Bn}), 138.51 (ArC^{Bn}), 138.26 (ArC^{Bn}), 138.21 (ArC^{Bn}), 137.58 (ArC^{Ts}), 129.23 (2x $ArCH^{Ts}$), 128.54-127.61 (22x $ArCH^{Ts/Bn}$), 86.71 (C-3), 85.77 (C-1), 85.11 (C^{Boc}), 78.43 (C-2), 77.90, 77.76 (C-4, C-5), 75.76 (CH_2^{Bn}), 75.20(CH_2^{Bn}), 74.80(CH_2^{Bn}), 73.36 (CH_2^{Bn}), 69.00 (C-6), 27.93 (3x CH_3^{Boc}), 21.70 (CH_3^{Ts}) ppm.‡‡ **HRMS** (MALDI+): Calculated for $C_{46}H_{51}NO_9SNa^+$ m/z 816.3182; found m/z 816.3170. $[\alpha]_D^{298}$=+8.44° (*c*=0.545, $CHCl_3$).

‡‡ The obtained compound **19** contained 2% of the α anomer.

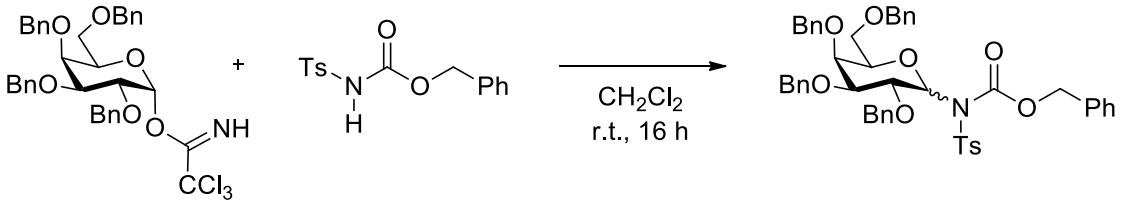
2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl allyl tosylcarbamate (2.24)



Carbamate **2.14** (112 mg, 0.44 mmol) was added to a stirred solution of **2.1α** (200 mg, 0.29 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 18 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:9→1:4 EtOAc/heptane) to yield the α/β mixture (29:71) of compound **2.24** (120 mg, 0.15 mmol, 53%) as a colorless syrup. **Anomer α ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.79 (broad d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 7.33-7.16 (m, 20H, 20x ArH^{Bn}), 6.98 (broad d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 6.51-6.46 (m, 1H, H-1), 5.61-5.52 (m, 1H, =CH), 5.12 (ddt, *J* = 17.2, 1.4, 1.4 Hz, 1H, $=CH_2^{trans}$), 5.07 (ddt, *J* = 10.5, 1.4, 1.4 Hz, 1H, $=CH_2^{cis}$), 4.91 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.74 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}), 4.67 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}), 4.63 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.57 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.55 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.47-4.36 (m, 6H, H-2, H-3, H-5, CH_2^{Bn}, CH_2^{Alloc}), 4.34 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1H, CH_2^{Alloc}), 3.94 (broad dd, *J* = 2.4, 1.3 Hz, 1H, H-4), 3.60 (dd, *J* = 10.6, 7.4 Hz, 1H, H-6), 3.47 (dd, *J* = 10.6, 4.5 Hz, 1H, H-6'), 2.26 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 153.06 (C=O), 144.24 (ArC^{Ts}), 138.93 (ArC^{Bn}), 138.78 (ArC^{Bn}), 138.28 (ArC^{Bn}), 137.83 (ArC^{Bn}), 137.06 (ArC^{Ts}), 130.87 (=CH), 129.36 (2x $ArCH^{Ts}$), 128.51-127.54 (22x $ArCH^{Ts/Bn}$), 119.20 ($=CH_2$), 82.68 (C-1), 79.74 (C-3), 75.94 (C-2), 74.77 (C-5), 74.48 (CH_2^{Bn}), 74.32 (CH_2^{Bn}), 74.18 (C-4), 73.63 (CH_2^{Bn}), 72.93 (CH_2^{Bn}), 70.06 (C-6), 67.95 (CH_2^{Alloc}), 21.63 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{45}H_{47}NO_9SNa^+$ m/z 800.2869; found m/z 800.2843. $[\alpha]_D^{298}$=+32.83° (*c*=0.335, $CHCl_3$). **Anomer β ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 7.34-7.14 (m, 20H, 20x ArH^{Bn}), 6.98 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 5.58-5.48 (m, 1H, =CH), 5.43 (d, *J* = 9.2 Hz, 1H, H-1), 5.08 (ddt, *J* = 17.2, 1.5, 1.5 Hz, 1H, $=CH_2^{trans}$), 4.93-4.87 (m, 2H, CH_2^{Bn}, $=CH_2^{cis}$), 4.78-4.71 (m, 2H, H-2, CH_2^{Bn}), 4.70 (s, 2H, CH_2^{Bn}), 4.61 (broad d, *J* ~ 11.0 Hz, 1H, CH_2^{Bn}), 4.53 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.45-4.36 (m, 3H, CH_2^{Alloc}, CH_2^{Bn}), 4.30-4.23 (m, 1H, CH_2^{Alloc}), 3.90 (d, *J* = 2.6 Hz, 1H, H-4), 3.70 (t, *J* = 6.4 Hz, 1H, H-5), 3.61 (dd, *J* = 9.2 Hz, 1H, H-3), 3.57 (d, *J* = 6.4 Hz, 2H, H-6, H-6'), 2.27 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.46 (C=O), 144.26

(ArC^{Ts}), 138.98 (ArC^{Bn}), 138.37 (ArC^{Bn}), 138.35 (ArC^{Bn}), 138.04 (ArC^{Bn}), 136.74 (ArC^{Ts}), 130.86 (=CH), 129.18 (2x $ArCH^{Ts}$), 128.69-127.50 (22x $ArCH^{Ts/Bn}$), 118.96 ($=CH_2$), 86.27 (C-1), 84.85 (C-3), 76.19 (C-5), 75.44 (C-2), 74.85 (CH_2^{Bn}), 74.64 (CH_2^{Bn}), 73.88 (CH_2^{Bn}), 73.58 (C-4), 72.97 (CH_2^{Bn}), 68.80 (C-6), 67.69 (CH_2^{Alloc}), 21.69 (CH_3) ppm.[§§] **HRMS** (MALDI+): Calculated for $C_{45}H_{47}NO_9SNa^+$ m/z 800.2869; found m/z 800.2844. $[\alpha]_D^{298}$=-5.96° (*c*=0.235, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl benzyl tosylcarbamate (2.25)

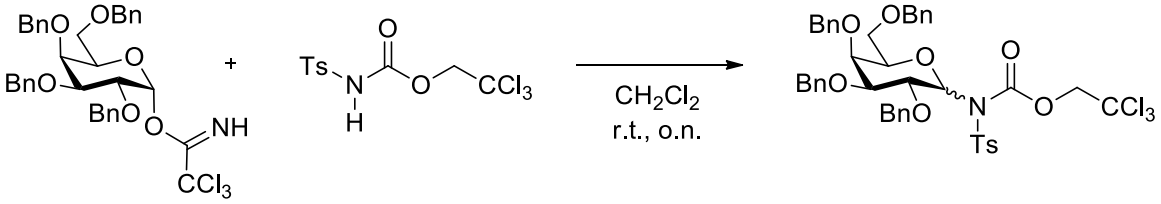


Carbamate **2.15** (135 mg, 0.44 mmol) was added to a stirred solution of **2.1α** (201 mg, 0.29 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 16 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:9→1:5 EtOAc/heptane) to yield the α/β mixture (37:63) of compound **2.25** (148 mg, 0.18 mmol, 61%) as a colorless syrup. **Anomer α ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ts}), 7.42-7.16 (m, 23H, 23x $ArH^{Bn/Cbz}$), 7.10-7.06 (m, 2H, 2x $ArH^{Bn/Cbz}$), 6.85 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ts}), 6.53 (d, *J* = 7.1 Hz, 1H, H-1), 5.00 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.95 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.94 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.73 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}), 4.66 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}), 4.65 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.60 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.58 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.50-4.39 (m, 5H, H-2, H-3, H-5, CH_2^{Bn}), 3.98-3.95 (m, 1H, H-4), 3.64 (dd, *J* = 9.5, 6.4 Hz, 1H, H-6), 3.50 (dd, *J* = 9.5, 6.3 Hz, 1H, H-6'), 2.25 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 153.29 (C=O), 144.03 (ArC^{Ts}), 139.02 (ArC^{Bn}), 138.82 (ArC^{Bn}), 138.32 (ArC^{Bn}), 137.93 (ArC^{Bn}), 136.95 (ArC^{Ts}), 134.48 (ArC^{Cbz}), 129.29 (2x $ArCH^{Ts}$), 128.55-127.55 (27x $ArCH^{Ts/Bn/Cbz}$), 82.80 (C-1), 79.80 (C-3), 76.04 (C-2), 74.79 (C-5), 74.48 (CH_2^{Bn}), 74.36 (CH_2^{Bn}), 74.26 (C-4), 73.62 (CH_2^{Bn}), 72.96 (CH_2^{Bn}), 70.01 (C-6), 69.24 (CH_2^{Cbz}), 21.62 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{49}H_{49}NO_9SNa^+$ m/z 850.3026; found m/z 850.3004.

[§§] Rotamers observed in NMR of the α anomer. Signal coming from H-1 appeared as multiplet in $CDCl_3$ and doublet in CD_3CN.

$[\alpha]_D^{298}$=+30.31° (*c*=0.640, $CHCl_3$). **Anomer β ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 7.40-7.07 (m, 25H, 25x $ArH^{Bn/Cbz}$), 6.91 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 5.46 (d, *J* = 9.2 Hz, 1H, H-1), 5.02 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.96-4.92 (m, 2H, CH_2^{Cbz}, CH_2^{Bn}), 4.83 (bt, *J* ~ 9.2 Hz, 1H, H-2), 4.73 (broad s, 2H, CH_2^{Bn}), 4.65-4.59 (m, 2H, CH_2^{Bn}), 4.48 (d, *J* = 11.7 Hz, 1H, CH_2^{Bn}), 4.45 (d, *J* ~ 11.8 Hz, 1H, CH_2^{Bn}), 4.42 (d, *J* = 11.7 Hz, 1H, CH_2^{Bn}), 3.95 (broad d, *J* = 2.2 Hz, 1H, H-4), 3.75 (bt, *J* = 6.3 Hz, H-5), 3.66-3.60 (m, 3H, H-3, H-6, H-6'), 2.29 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.50 (C=O), 144.10 (ArC^{Ts}), 139.02 (ArC^{Bn}), 138.43 (2x ArC^{Bn}), 138.09 (ArC^{Bn}), 136.75 (ArC^{Ts}), 134.67 (ArC^{Cbz}), 129.15 (2x $ArCH^{Ts}$), 128.62-127.54 (27x $ArCH^{Ts/Bn/Cbz}$), 86.30 (C-1), 84.85 (C-3), 76.28 (C-5), 75.49 (C-2), 74.77 (CH_2^{Bn}), 74.53 (CH_2^{Bn}), 73.75 (CH_2^{Bn}), 73.62 (C-4), 72.93 (CH_2^{Bn}), 68.84 (C-6), 68.76 (CH_2^{Cbz}), 21.68 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{49}H_{49}NO_9SNa^+$ m/z 850.3026; found m/z 850.3001. $[\alpha]_D^{298}$=-6.45° (*c*=0.620, $CHCl_3$).

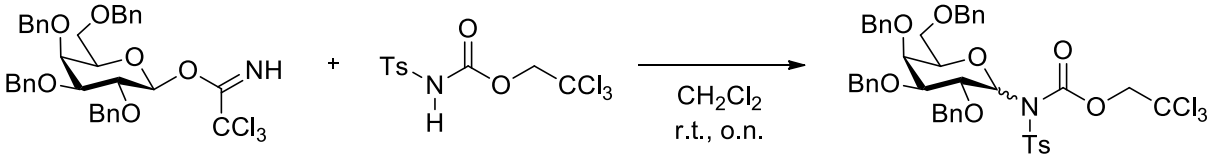
2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl 2,2,2-trichloroethyl tosylcarbamate (2.26)



Carbamate **2.16** (85.9 mg, 0.25 mmol) was added to a stirred solution of **2.1α** (113 mg, 0.17 mmol) in dry CH_2Cl_2 (0.8 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:7→1:6 EtOAc/heptane) to yield the α/β mixture (42:58) of compound **2.26** (116 mg, 0.13 mmol, 81%) as a colorless syrup. **Anomer α ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H, 2x ArH^{Ts}), 7.35-7.18 (m, 20H, 20x ArH^{Bn}), 6.99 (d, *J* = 8.4 Hz, 2H, 2x ArH^{Ts}), 6.56 (d, *J* = 7.8 Hz, 1H, H-1), 4.93 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.75 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}), 4.70 (d, *J* = 11.9 Hz, 1H, CH_2^{Bn}), 4.65 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.64 (d, *J* = 11.9 Hz, 1H, CH_2^{Troc}), 4.60 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.58 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.48-4.38 (m, 6H, H-2, H-3, H-5, CH_2^{Troc}, CH_2^{Bn}), 3.97 (dd, *J* = 2.7, 1.1 Hz, 1H, H-4), 3.63 (dd, *J* = 9.6, 6.5 Hz, 1H, H-6), 3.48 (dd, *J* = 9.6, 5.9 Hz, 1H, H-6'), 2.26 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 152.33 (C=O), 144.53 (ArC^{Ts}), 138.81 (ArC^{Bn}), 138.69 (ArC^{Bn}), 138.25 (ArC^{Bn}), 137.73 (ArC^{Bn}), 136.76 (ArC^{Ts}), 129.59 (2x

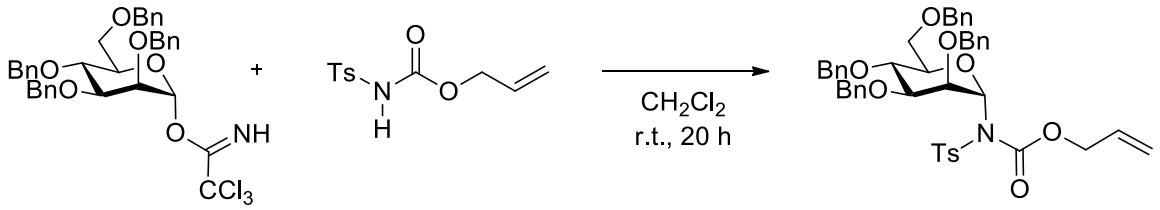
$ArCH^{Ts}$), 128.53-127.65 (22x $ArCH^{Ts/Bn}$), 93.93 (CCl_3), 83.44 (C-1), 79.58 (C-3), 76.05 (2x C, C-2, CH_2^{Troc}), 74.89 (C-5), 74.77 (CH_2^{Bn}), 74.52 (CH_2^{Bn}), 74.16 (C-4), 73.63 (CH_2^{Bn}), 72.85 (CH_2^{Bn}), 70.05 (C-6), 21.64 (CH_3) ppm. (MALDI+): Calculated for $C_{44}H_{44}Cl_3NO_9SNa^+$ m/z 890.1700; found m/z 890.1685. $[\alpha]_D^{298}$=+31.64° (*c*=0.670, $CHCl_3$). **Anomer β ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H, 2x ArH^{Ts}), 7.36-7.14 (m, 20H, 20x ArH^{Bn}), 6.99 (d, *J* = 7.9 Hz, 2H, 2x ArH^{Ts}), 5.50 (d, *J* = 9.2 Hz, 1H, H-1), 4.90 (d, *J* = 11.6 Hz, 1H, CH_2^{Bn}), 4.87 (t, *J* = 9.2 Hz, 1H, H-2), 4.81 (d, *J* = 10.9 Hz, 1H, CH_2^{Troc}), 4.74-4.68 (m, 3H, CH_2^{Bn}, CH_2^{Troc}), 4.58 (d, *J* = 11.5 Hz, 1H, CH_2^{Bn}), 4.56 (d, *J* = 11.6 Hz, 1H, CH_2^{Bn}), 4.45 (broad d, *J* ~ 11.5 Hz, 1H, CH_2^{Bn}), 4.44 (d, *J* = 11.7 Hz, 1H, CH_2^{Bn}), 4.40 (d, *J* = 11.7 Hz, 1H, CH_2^{Bn}), 3.90 (d, *J* = 2.3 Hz, 1H, H-4), 3.74 (dd, *J* = 6.7, 6.0 Hz, 1H, H-5), 3.64 (dd, *J* = 9.2, 2.3 Hz, 1H, H-3), 3.60 (dd, *J* = 9.3, 6.0 Hz, 1H, H-6), 3.55 (dd, *J* = 9.3, 6.7 Hz, 1H, H-6'), 2.28 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 150.61 (C=O), 144.62 (ArC^{Ts}) , 138.81 (ArC^{Bn}), 138.33 (2x ArC^{Bn}), 138.06 (ArC^{Bn}), 136.34 (ArC^{Ts}), 129.32 (2x $ArCH^{Ts}$), 128.65-127.63 (22x $ArCH^{Ts/Bn}$), 93.96 (CCl_3), 86.57 (C-1), 84.91 (C-3), 76.54 (C-5), 75.62 (C-2), 75.40 (CH_2^{Bn}), 74.97 (CH_2^{Troc}), 74.67 (CH_2^{Bn}), 73.86 (C-4), 73.59 (CH_2^{Bn}), 73.01(CH_2^{Bn}), 68.96 (C-6), 21.70 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{44}H_{44}Cl_3NO_9SNa^+$ m/z 890.1700; found m/z 890.1684. $[\alpha]_D^{298}$=-3.43° (*c*=0.525, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl 2,2,2-trichloroethyl tosylcarbamate (2.26)



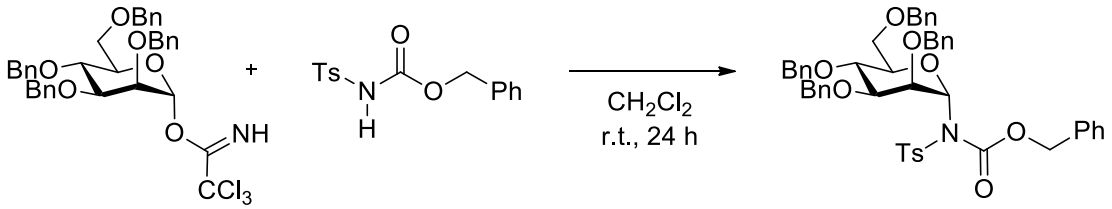
Carbamate **2.16** (110 mg, 0.32 mmol) was added to a stirred solution of **2.1β** (145 mg, 0.21 mmol) in dry CH_2Cl_2 (1.1 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:7→1:6 EtOAc/heptane) to yield the α/β (83:17) mixture of compound **2.26** (128 mg, 0.15 mmol, 69%) as a colorless syrup. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

2,3,4,6-tetra-*O*-benzyl-*α*-D-mannopyranosyl allyl tosylcarbamate (2.27α)



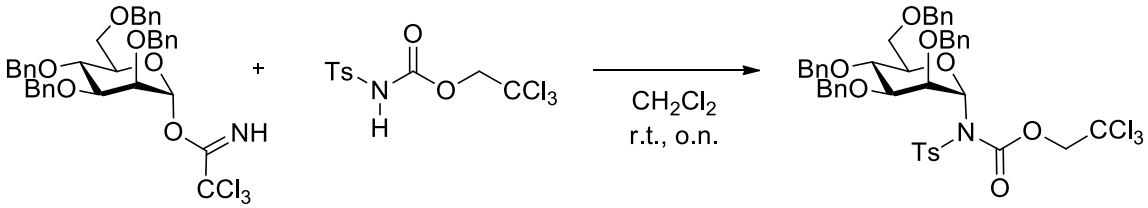
Carbamate **2.14** (113 mg, 0.44 mmol) was added to a stirred solution of **2.2α** (201 mg, 0.29 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 20 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:6 EtOAc/heptane) to yield α anomer of compound **2.27** (145 mg, 0.19 mmol, 64%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 7.35-7.18 (m, 20H, 20x ArH^{Bn}), 7.04 (d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 6.28 (d, *J* = 9.2 Hz, 1H, H-1), 5.68-5.59 (m, 1H, =CH), 5.16 (ddt, *J* = 17.2, 1.4, 1.4 Hz, 1H, $=CH_2^{trans}$), 5.05 (ddt, *J* = 10.5, 1.4, 1.4 Hz, 1H, $=CH_2^{cis}$), 4.76 (dd, *J* = 9.2, 2.9 Hz, 1H, H-2), 4.74 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.58 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.58-4.45 (m, 5H, CH_2^{Bn}, CH_2^{Alloc}), 4.45-4.33 (m, 4H, CH_2^{Bn}, H-5), 3.96 (t, *J* = 2.9 Hz, 1H, H-3), 3.88 (dd, *J* = 10.7, 7.3 Hz, 1H, H-6), 3.67 (dd, *J* = 10.7, 4.6 Hz, 1H, H-6'), 3.62 (dd, *J* = 3.8, 2.9 Hz, 1H, H-4), 2.33 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.90 (C=O), 144.10 (ArC^{Ts}) , 138.50 (ArC^{Bn}), 138.40 (ArC^{Bn}), 138.21 (ArC^{Bn}), 138.06 (ArC^{Bn}), 137.11 (ArC^{Ts}), 130.94 (=CH), 129.20 (2x $ArCH^{Ts}$), 128.70 (2x $ArCH^{Ts}$), 128.53-127.64 (20x $ArCH^{Bn}$), 119.12 ($=CH_2$), 81.27 (C-1), 76.59 (C5), 76.05 (C-4), 75.34 (C-3), 73.56 (C-2), 73.39 (CH_2^{Bn}), 73.19 (CH_2^{Bn}), 72.04(CH_2^{Bn}), 71.56 (CH_2^{Bn}), 69.23 (C-6), 67.68 (CH_2^{Alloc}), 21.70 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{45}H_{47}NO_9SNa^+$ m/z 800.2869; found m/z 800.2860. $[\alpha]_D^{298}$=+16.95° (*c*=0.755, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-*α*-D-mannopyranosyl benzyl tosylcarbamate (2.28α)



Carbamate **2.15** (137 mg, 0.45 mmol) was added to a stirred solution of **2.2α** (205 mg, 0.30 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 24 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:9→1:6 EtOAc/heptane) to yield α anomer of compound **2.28** (180 mg, 0.22 mmol, 72%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 7.42-7.08 (m, 25H, 25x $ArH^{Bn/Cbz}$), 6.92 (d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 6.29 (d, *J* = 9.2 Hz, 1H, H-1), 5.02 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.98 (d, *J* = 12.1 Hz, 1H, CH_2^{Cbz}), 4.74 (dd, *J* = 9.2, 2.8 Hz, 1H, H-2), 4.70 (d, *J* = 12.3 Hz, 1H, CH_2^{Bn}), 4.54 (d, *J* = 12.3 Hz, 1H, CH_2^{Bn}), 4.54 (d, *J* = 11.8 Hz, 1H, CH_2^{Bn}) 4.50 (d, *J* = 11.8 Hz, 1H, CH_2^{Bn}), 4.46-4.32 (m, 4H, CH_2^{Bn}, H-5), 4.35 (d, *J* = 11.8 Hz, 1H, CH_2^{Bn}), 3.91 (t, *J* = 2.8 Hz, 1H, H-3), 3.87 (dd, *J* = 10.7, 7.3 Hz, 1H, H-6), 3.66 (dd, *J* = 10.7, 4.6 Hz, 1H, H-6'), 3.61 (dd, *J* = 3.7, 2.8 Hz, 1H, H-4), 2.30 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.98 (C=O), 143.89 (ArC^{Ts}), 138.46 (ArC^{Bn}), 138.34 (ArC^{Bn}), 138.16 (ArC^{Bn}), 138.03 (ArC^{Bn}), 137.00 (ArC^{Ts}), 134.51 (ArC^{Cbz}), 129.10 (2x $ArCH^{Ts}$), 128.52-127.59 (27x $ArCH^{Ts/Bn/Cbz}$), 81.24 (C-1), 76.63 (C5), 75.93 (C-4), 75.34 (C-3), 73.56 (C-2), 73.32(CH_2^{Bn}), 73.08 (CH_2^{Bn}), 71.96 (CH_2^{Bn}), 71.52 (CH_2^{Bn}), 69.13 (C-6), 68.84 (CH_2^{Cbz}), 21.63 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{49}H_{49}NO_9SNa^+$ m/z 850.3026; found m/z 850.3009. $[\alpha]_D^{298}$=+19.64° (*c*=0.835, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-*α*-D-mannopyranosyl 2,2,2-trichloroethyl tosylcarbamate (2.29α)

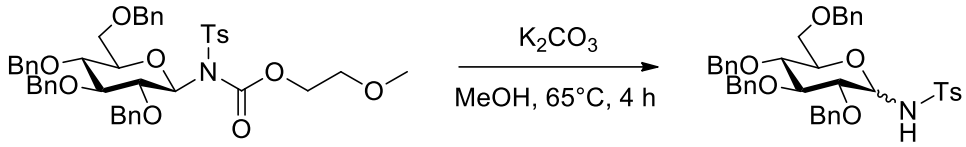


Carbamate **2.16** (154 mg, 0.44 mmol) was added to a stirred solution of **2.2α** (203 mg, 0.30 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with 0.5 M aq. NaOH (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated onto celite. The crude product was purified by flash column chromatography (1:9→1:6 EtOAc/heptane) to yield α anomer of compound **2.29α** (190 mg, 0.22 mmol, 74%) as a colorless syrup. **^{1}H-NMR** (500

MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 7.41-7.15 (m, 20H, 20x ArH^{Bn}), 7.02 (d, *J* = 8.3 Hz, 2H, 2x ArH^{Ts}), 6.34 (d, *J* = 9.3 Hz, 1H, H-1), 4.82 (dd, *J* = 9.3, 2.7 Hz, 1H, H-2), 4.72 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.65 (d, *J* = 11.9 Hz, 1H, CH_2^{Troc}), 4.62-4.48 (m, 6H, CH_2^{Bn}, CH_2^{Troc}), 4.44-4.39 (m, 2H, H-5, CH_2^{Bn}), 4.36 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 3.99 (t, *J* = 2.7 Hz, 1H, H-3), 3.88 (dd, *J* = 10.6, 7.4 Hz, 1H, H-6), 3.66 (dd, *J* = 10.6, 4.5 Hz, 1H, H-6'), 3.62 (dd, *J* = 3.9, 2.7 Hz, 1H, H-4), 2.31 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 151.06 (C=O), 144.42 (ArC^{Ts}), 138.41 (ArC^{Bn}), 138.30 (ArC^{Bn}), 138.13 (ArC^{Bn}), 137.94 (ArC^{Bn}), 136.71 (ArC^{Ts}), 129.35 (2x $ArCH^{Ts}$), 128 (2x $ArCH^{Ts}$), 128.55-127.69 (20x $ArCH^{Bn}$), 93.98 (CCl_3), 81.70 (C-1), 76.68 (C-5), 75.95 (C-4), 75.75 (CH_2^{Troc}), 75.21 (C-3), 73.73 (C-2), 73.43 (CH_2^{Bn}), 73.21 (CH_2^{Bn}), 72.02 (CH_2^{Bn}), 71.59 (CH_2^{Bn}), 69.17 (C-6), 21.71 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{44}H_{44}Cl_3NO_9SNa^+$ m/z 890.1700; found m/z 890.1681. $[\alpha]_D^{298}$=+15.71° (*c*=0.980, $CHCl_3$).

2.4.5. Deprotection Reactions

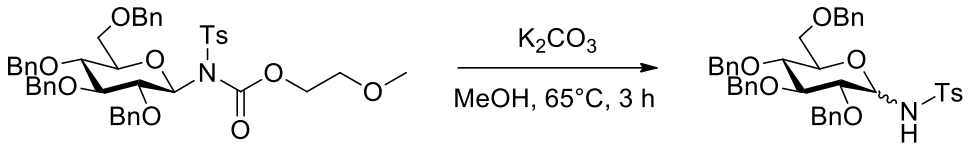
2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl *p*-toluenesulfonamide (2.31)



K_2CO_3 (46.0 mg, 0.33 mmol) was added to a solution of **2.19β** (131 mg, 0.16 mmol) in dry MeOH (10 mL). The resulting mixture was stirred at 65°C for 4 h. After this time, the crude product was evaporated *in vacuo* onto celite. The residue was purified by flash column chromatography (50:1 toluene/acetone + 1% HCOOH) to yield two anomers (α/β 37:63) of compound **2.31** (73.4 mg, 0.11 mmol, 65%) as a colorless syrup (anomer α) and a white solid (anomer β) [197]. **Anomer α ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H, 2x ArH^{Ts}), 7.36-7.17 (m, 18H, 18x ArH^{Bn}), 7.14 (d, *J* = 8.2 Hz, 2H, 2x ArH^{Ts}), 7.10-7.06 (m, 2H, 2x ArH^{Bn}), 5.34 (d, *J* = 2.7 Hz, 1H, *N*H), 5.31 (dd, *J* = 5.2, 2.7 Hz, 1H, H-1), 4.84 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.74 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.72 (d, *J* = 10.7 Hz, 1H, CH_2^{Bn}), 4.51 (broad s, 2H, CH_2^{Bn}), 4.46 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.42 (d, *J* = 10.7 Hz, 1H, CH_2^{Bn}), 4.37 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 3.67 (dd, *J* = 9.0, 5.2 Hz, 1H, H-2), 3.62 (t, *J* = 9.0 Hz, 1H, H-4), 3.57 (t, *J* = 9.0 Hz, 1H, H-3), 3.45 (dd, *J* = 10.7, 2.6 Hz, 1H, H-6), 3.41 (broad ddd, *J* ~ 9.0, 2.6, 1.9 Hz, 1H, H-5), 2.95 (dd, *J* = 10.7, 1.9 Hz, 1H, H-6'), 2.33 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 143.78 (ArC^{Ts}), 138.48 (ArC^{Bn}), 138.18 (ArC^{Bn}), 137.98 (ArC^{Bn}), 137.36 (ArC^{Bn}), 136.91 (ArC^{Ts}), 129.60 (2x $ArCH^{Ts}$), 128.74-127.72 (22x $ArCH^{Ts/Bn}$), 82.09 (C-3), 79.73 (C-1), 77.66 (C-2), 76.99 (C-4), 75.83 (CH_2^{Bn}), 75.22 (CH_2^{Bn}), 73.56 (CH_2^{Bn}), 72.75 (CH_2^{Bn}), 70.50 (C-5), 67.39 (C-6), 21.64 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{41}H_{43}NO_7SNa^+$ m/z 716.2658; found m/z 716.2650. $[\alpha]_D^{298}$= +54.00° (*c*=1.100, $CHCl_3$). **Anomer β ^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H, 2x ArH^{Ts}), 7.34-7.20 (m, 18H, 18x ArH^{Bn}), 7.16-7.13 (m, 2H, 2x ArH^{Ts}), 7.13-7.10 (m, 2H, 2x ArH^{Bn}), 4.92 (d, *J* = 9.8 Hz, 1H, *N*H), 4.87 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.82-4.78 (m, 2H, CH_2^{Bn}), 4.76 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.72 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.64 (dd, *J* = 9.8, 8.9 Hz, 1H, H-1), 4.49 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.39 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.31 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 3.66 (t, *J* = 8.9 Hz, 1H, H-3), 3.60-3.54 (m, 2H, H-4, H-6), 3.33-3.27 (m, 2H, H-5, H-6'), 3.27 (t, *J* = 8.9 Hz, 1H, H-2), 2.33 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 143.48 (ArC^{Ts}), 138.64 (ArC^{Bn}), 138.44 (ArC^{Bn}), 138.14 (ArC^{Bn}), 138.00 (ArC^{Bn}), 137.65 (ArC^{Ts}), 129.48 (2x $ArCH^{Ts}$), 128.68-127.44 (22x $ArCH^{Ts/Bn}$), 85.74 (C-3), 84.37 (C-1), 80.53 (C-2), 77.36 (C-4), 76.53 (C-5), 75.94 (CH_2^{Bn}), 75.06 (CH_2^{Bn}), 75.04 (CH_2^{Bn}), 73.73 (CH_2^{Bn}), 68.32 (C-6), 21.64

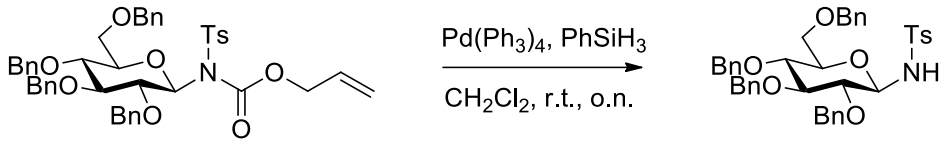
(CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{41}H_{43}NO_7SNa^+$ m/z 716.2658; found m/z 716.2652. $[\alpha]_D^{298}$= +10.57° (*c*=0.965, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl *p*-toluenesulfonamide (2.31)



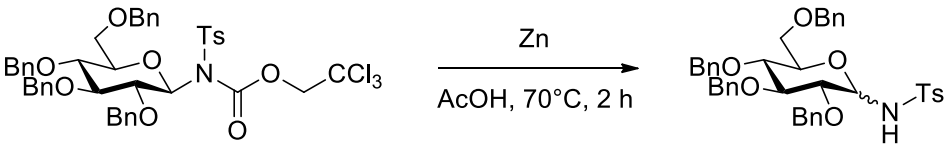
K_2CO_3 (1.08 g, 7.81 mmol) was added to a solution of **2.19β** (109 mg, 0.14 mmol) in dry MeOH (10 mL). The resulting mixture was stirred at 65°C for 3 h. After this time, the solvent was removed *in vacuo* and the residue diluted with CH_2Cl_2 (25 mL). The organic phase was washed with 0.5 M aq. HCl (15 mL), dried over Na_2SO_4 end evaporated to dryness. The crude product was purified by flash column chromatography (50:1→30:1 toluene/acetone) to yield two anomers (α/β 53:47) of compound **2.31** (62.2 mg, 0.09 mmol, 65%) as a colorless syrup (anomer α) and a white solid (anomer β) [197]. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl *p*-toluenesulfonamide (2.31β)



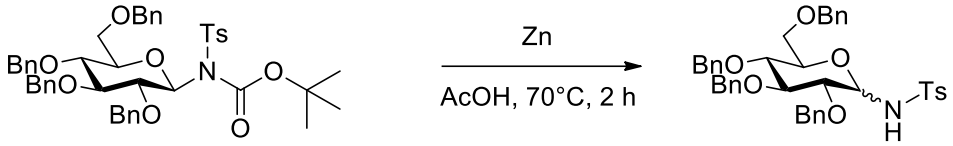
$PhSiH_3$ (0.1 mL, 0.88 mmol) was added to a solution of **2.20β** (172 mg, 0.22 mmol) in dry CH_2Cl_2 (3.0 mL) followed by $Pd(Ph_3)_4$ (12.8 mg, 0.01 mmol). The reaction mixture was stirred at r.t. overnight and after this time treated with MeOH (2 mL). Then, the solution was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (90:1→40:1 toluene/acetone) to yield the β anomer of compound **2.31** (136 mg, 0.20 mmol, 89%) as a white solid [198]. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl *p*-toluenesulfonamide (2.31)



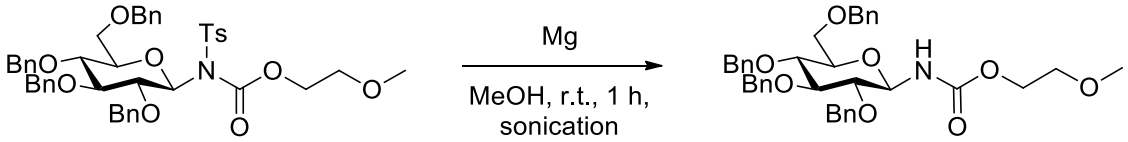
Zn powder (67.0 mg, 1.03 mmol) was added to a solution of **2.22β** (111 mg, 0.13 mmol) in AcOH (1.1 mL). The resulting suspension was stirred at 70°C for 2 h. After completion, the reaction mixture was filtered and the filtrate was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (100:1→10:1 toluene/acetone) to yield two anomers (α/β 28:72) of compound **2.31** (73.0 mg, 0.11 mmol, 82%) as a colorless syrup (anomer α) and a white solid (anomer β) [199]. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl *p*-toluenesulfonamide (2.31)



TFA (0.08 ml, 1.05 mmol) was added to a solution of **2.23β** (41 mg, 0.05 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred at r.t. for 8 h. After completion, the solution was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (100:1→10:1 toluene/acetone) to yield two anomers (α/β 36:64) of compound **2.31** (30.0 mg, 0.04 mmol, 84%) as a colorless syrup (anomer α) and a white solid (anomer β) [199]. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

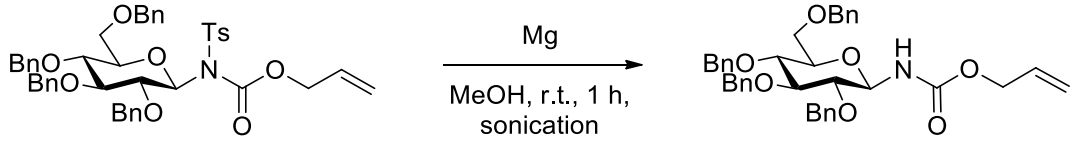
2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl 2-methoxyethyl carbamate (2.32β)



Mg powder (48.7 mg, 2.00 mmol) was added to a solution of **2.19β** (106 mg, 0.13 mmol) in dry MeOH (1.7 mL). The resulting suspension was sonicated under a nitrogen atmosphere for 1 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured into 0.5 M aq. HCl (10 mL). The organic phase was washed with 1M aq. $NaHCO_3$ (2 x 10 mL), brine (2 x 10 mL) and dried over Na_2SO_4. The crude product was purified by flash column chromatography (3:1→2:1 heptane/EtOAc) to afford the β anomer of compound **2.32** (68.3 mg, 0.11 mmol, 80%) as a white solid [182]. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.40-7.16 (m, 18H, 18x ArH), 7.15-7.07 (m, 2H, 2x ArH), 5.05 (broad d, *J* = 9.2 Hz, 1H, *N*H), 4.91-4.83 (m, 3H, H-1, CH_2^{Bn}), 4.78 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.77 (d, *J* = 11.3 Hz, 1H, CH_2^{Bn}), 4.70 (d, *J* = 11.3

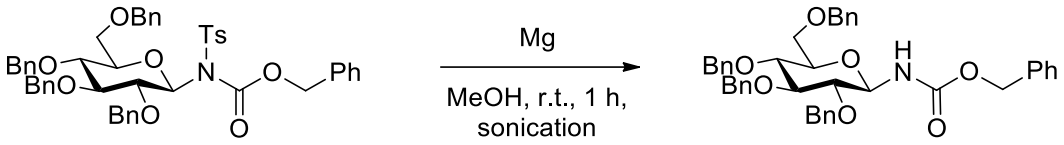
Hz, 1H, CH_2^{Bn}), 4.60 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 4.51 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.46 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 4.27-4.19 (m, 2H, C(*O*)*O*CH_2), 3.75-3.65 (m, 4H, H-3, H-4, H-6, H-6'), 3.56 (t, *J* = 4.7 Hz, 2H, *O*CH_2), 3.48 (broad dt, *J* ~ 2.4, 9.2 Hz, 1H, H-5), 3.36 (s, 3H, CH_3), 3.30 (t, *J* = 8.7 Hz, 1H, H-2) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.68 (C=O), 138.55 (ArC), 138.21 (ArC), 138.02 (ArC), 137.96 (ArC), 128.65-127.84 (20C, Ar), 86.05 (C-3), 81.93 (C-1), 80.66 (C-2), 77.69 (C-4), 76.44 (C-5), 75.84 (CH_2^{Bn}), 75.09 (CH_2^{Bn}), 74.96 (CH_2^{Bn}), 73.72 (CH_2^{Bn}), 70.86 ($CH_2^{Carbamate}$), 68.38 (C-6), 64.44 ($CH_2^{Carbamate}$), 59.08 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{38}H_{43}NO_8Na^+$ m/z 664.2886; found m/z 664.2872. $[\alpha]_D^{298}$= -4.71° (*c*=0.765, $CHCl_3$).

2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl allyl carbamate (2.33β)



Mg powder (31.3 mg, 1.29 mmol) was added to a solution of **2.20β** (66.7 mg, 0.09 mmol) in dry MeOH (1.5 mL). The resulting suspension was sonicated under a nitrogen atmosphere for 1 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and poured into 0.5 M aq. HCl (6.0 mL). The organic phase was washed with 1M aq. $NaHCO_3$ (2 x 10 mL), brine (2 x 10 mL) and dried over Na_2SO_4. The crude product was purified by flash column chromatography (4:1→2:1 heptane/EtOAc) to afford the β anomer of compound **2.33** (45.1 mg, 0.07 mmol, 84%) as a white solid [182]. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.37-7.16 (m, 18H, 18x ArH), 7.11-7.04 (m, 2H, 2x ArH), 5.85 (ddt, *J* = 17.1, 10.6, 5.6 Hz, 1H, =CH), 5.25 (ddt, *J* = 17.1, 1.5, 1.5 Hz, 1H, =CH_2^{trans}), 5.17 (broad d, *J* = 10.6 Hz, 1H, =CH_2^{cis}), 4.94 (broad d, *J* = 8.9 Hz, 1H, *N*H), 4.87-4.80 (m, 3H, H-1, CH_2^{Bn}), 4.75 (broad d, *J* ~ 11.1 Hz, 2H, CH_2^{Bn}), 4.65 (d, *J* = 11.4 Hz, 1H, CH_2^{Bn}), 4.56 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 4.53 (bt, *J* = 5.6 Hz, 2H, =CH_2), 4.47 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.41 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 3.71-3.63 (m, 4H, H-3, H-4, H-6, H-6'), 3.45 (broad dt, *J* = 9.1, 2.4 Hz, 1H, H-5), 3.27 (t, *J* = 8.6 Hz, 1H, H-2) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.52 (C=O), 138.52 (ArC), 138.20 (ArC), 137.97 (ArC), 137.90 (ArC), 132.60 (=CH), 128.67-127.86 (20C, Ar), 118.02 (=CH), 86.09 (C-3), 81.86 (C-1), 80.37 (C-2), 77.68 (C-4), 76.38 (C-5), 75.85 (CH_2^{Bn}), 75.07 (CH_2^{Bn}), 74.90 (CH_2^{Bn}), 73.70 (CH_2^{Bn}), 68.32 (C-6), 66.05 (CH_2^{Alloc}) ppm. **HRMS** (MALDI+): Calculated for $C_{38}H_{41}NO_7Na^+$ m/z 646.2781; found m/z 646.2770. $[\alpha]_D^{298}$= -8.44° (*c*=0.735, $CHCl_3$).

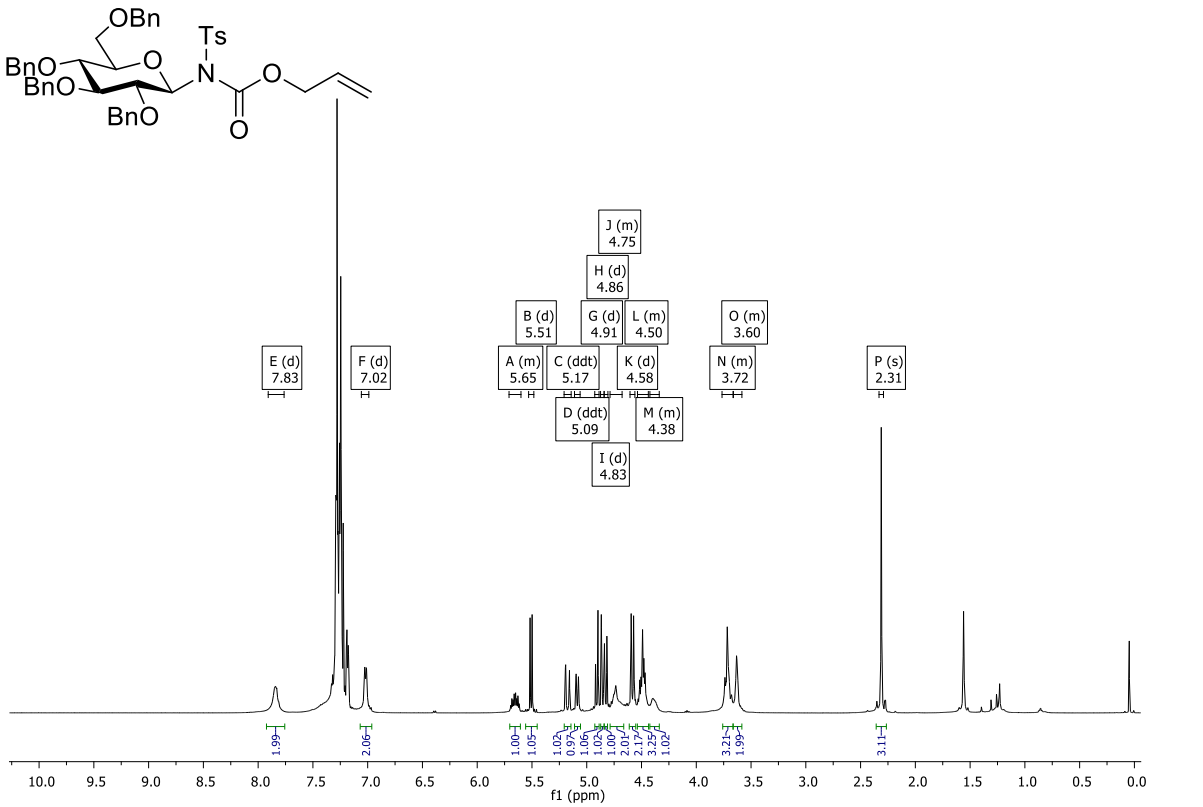
2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl benzyl tosylcarbamate (2.34β)

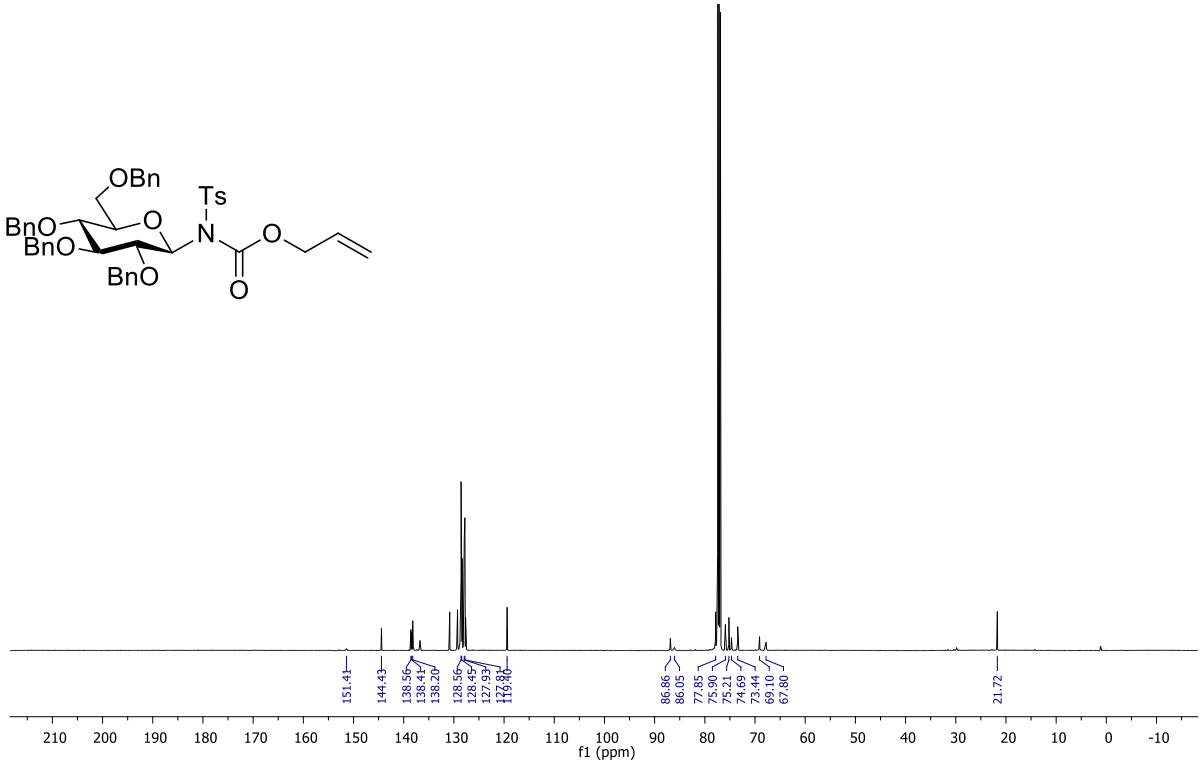


Mg powder (29.2 mg, 1.20 mmol) was added to a solution of **2.21β** (66.3 mg, 0.08 mmol) in dry MeOH (1.5 mL). The resulting suspension was sonicated under a nitrogen atmosphere for 1 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and poured into 0.5 M aq. HCl (6.0 mL). The organic phase was washed with 1M aq. $NaHCO_3$ (2 x 10 mL), brine (2 x 10 mL) and dried over Na_2SO_4. The crude product was purified by flash column chromatography (6:1→5:1 heptane/EtOAc) to afford the β anomer of compound **2.34** (35.5 mg, 0.05 mmol, 66%) as a white solid [182]. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.35-7.13 (m, 23H, 23x $ArH^{Bn/Cbz}$), 7.10-7.04 (m, 2H, 2x $ArH^{Bn/Cbz}$), 5.12 (d, *J* = 12.2 Hz, 1H, CH_2^{Cbz}), 5.02 (d, *J* = 12.2 Hz, 1H, CH_2^{Cbz}), 4.96 (broad d, *J* = 9.6 Hz, 1H, *N*H), 4.84-4.81 (m, 3H, H-1, CH_2^{Bn}), 4.75 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.73 (d, *J* = 11.3 Hz, 1H, CH_2^{Bn}), 4.63 (d, *J* = 11.3 Hz, 1H, CH_2^{Bn}), 4.56 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 4.47 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.42 (d, *J* = 12.1 Hz, 1H, CH_2^{Bn}), 3.71-3.62 (m, 4H, H-3, H-4, H-6, H-6‘), 3.45 (broad d, *J* = 7.6 Hz, 1H, H-5), 3.27 (t, *J* = 8.8 Hz, 1H, H-2) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 155.66 (C=O), 138.52 (ArC^{Bn}), 138.19 (ArC^{Bn}), 137.97 (ArC^{Bn}), 137.84 (ArC^{Bn}), 136.28 (ArC^{Cbz}), 128.67-127.87 (25x $ArCH^{Bn/Cbz}$), 86.09 (C-3), 81.89 (C-1), 80.37 (C-2), 77.68 (C-4), 76.40 (C-5), 75.86 (CH_2^{Bn}), 75.08 (CH_2^{Bn}), 74.92 (CH_2^{Bn}), 73.71 (CH_2^{Bn}), 68.33 (C-6), 67.21 (CH_2^{Cbz}) ppm. **HRMS** (MALDI+): Calculated for $C_{42}H_{43}NO_7Na^+$ m/z 696.2937; found m/z 696.2923.

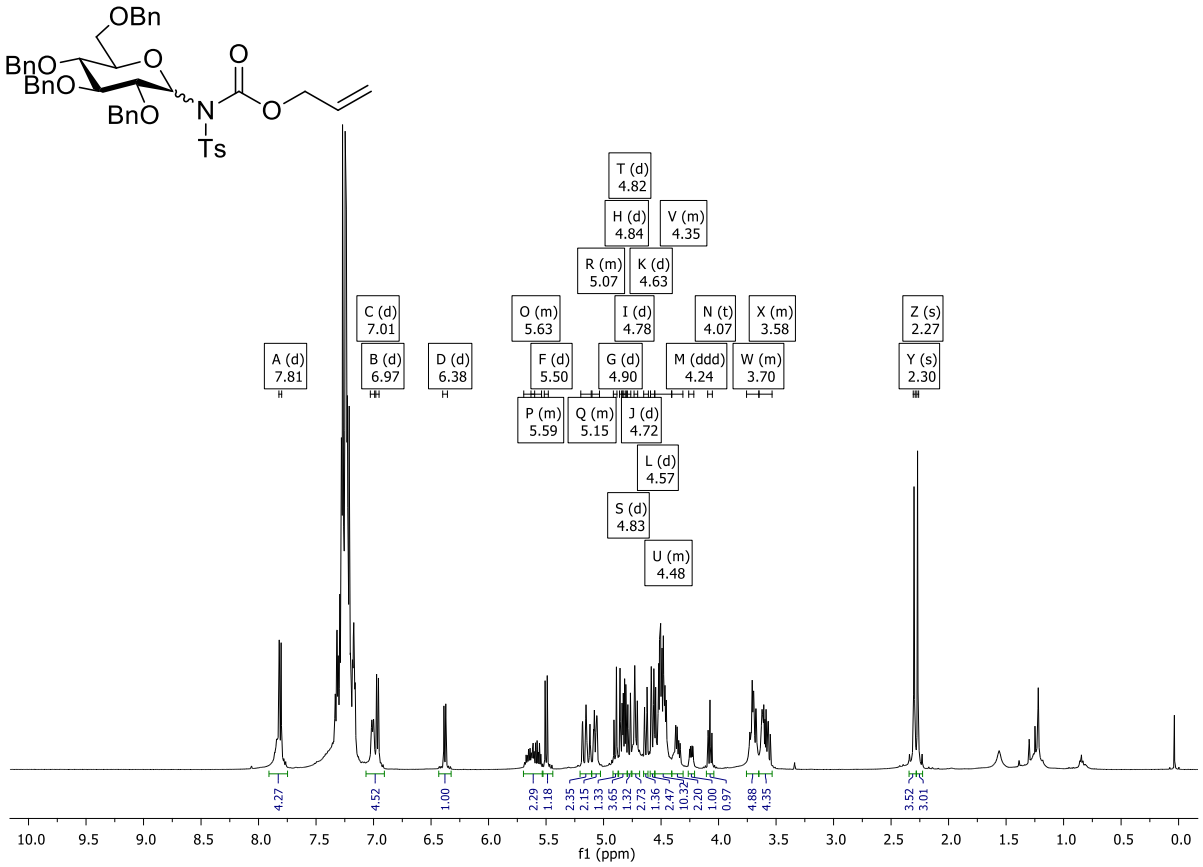
2.4.6. Appendix of ^{1}H and ^{13}C-NMR Spectra

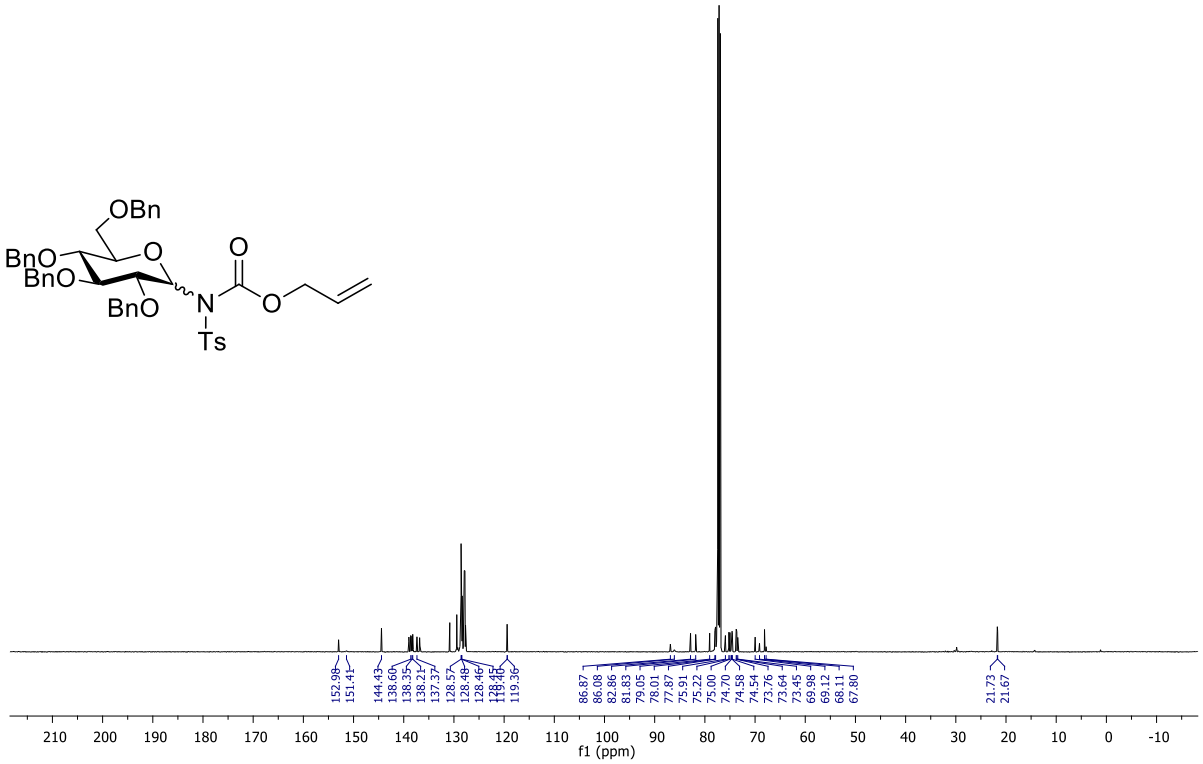
Compound 2.20β



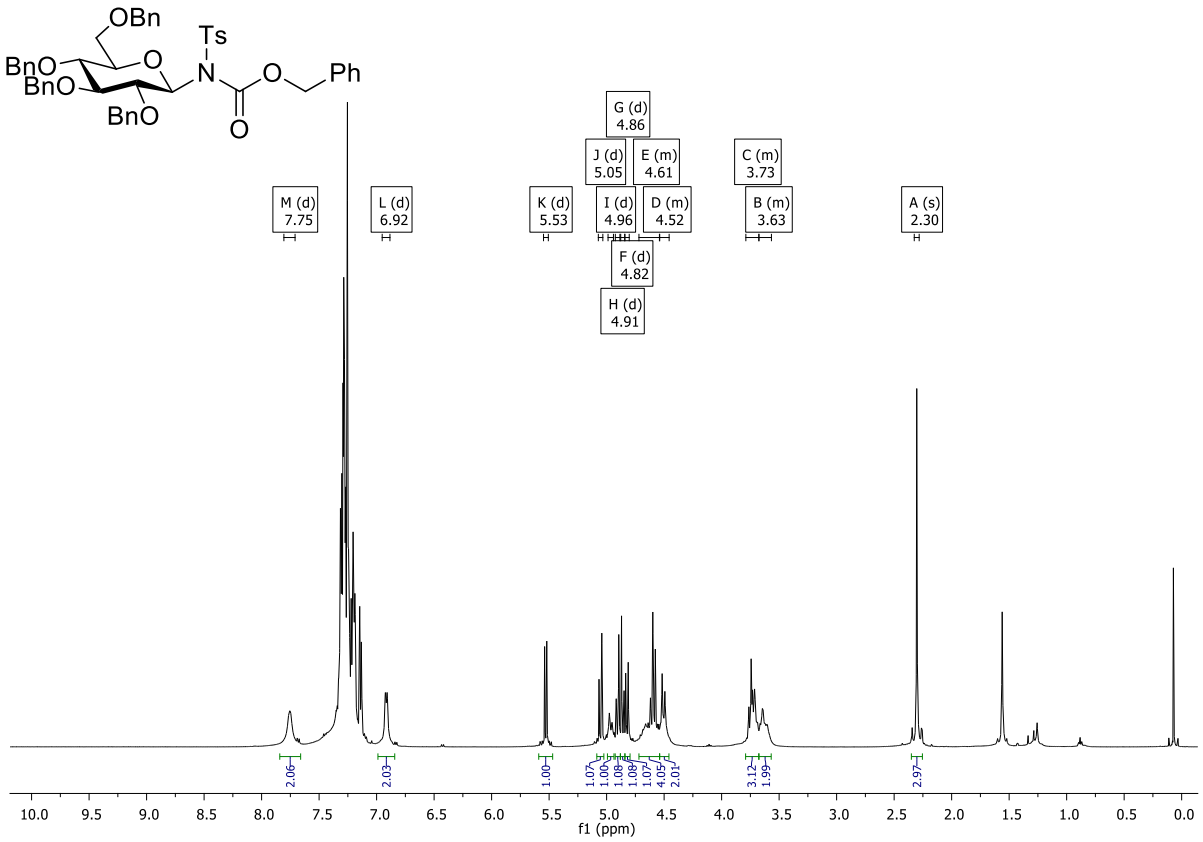


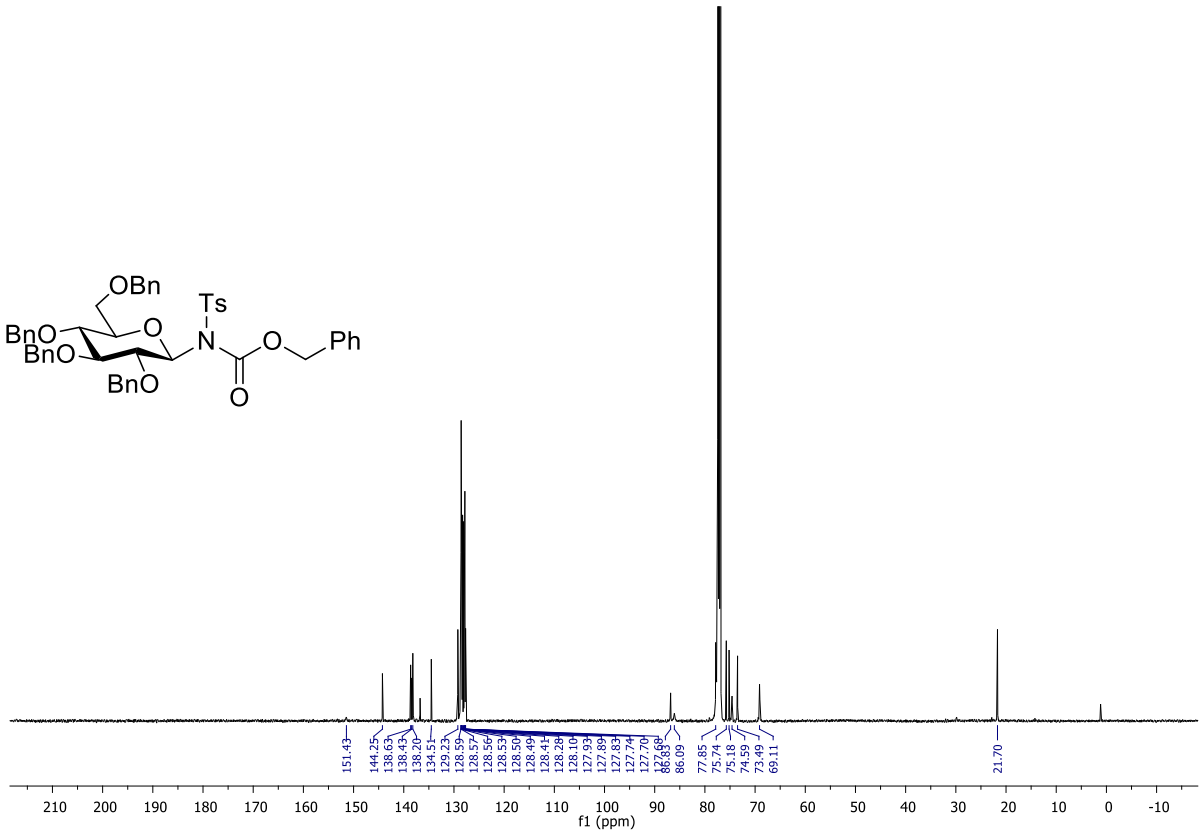
Compound 2.20



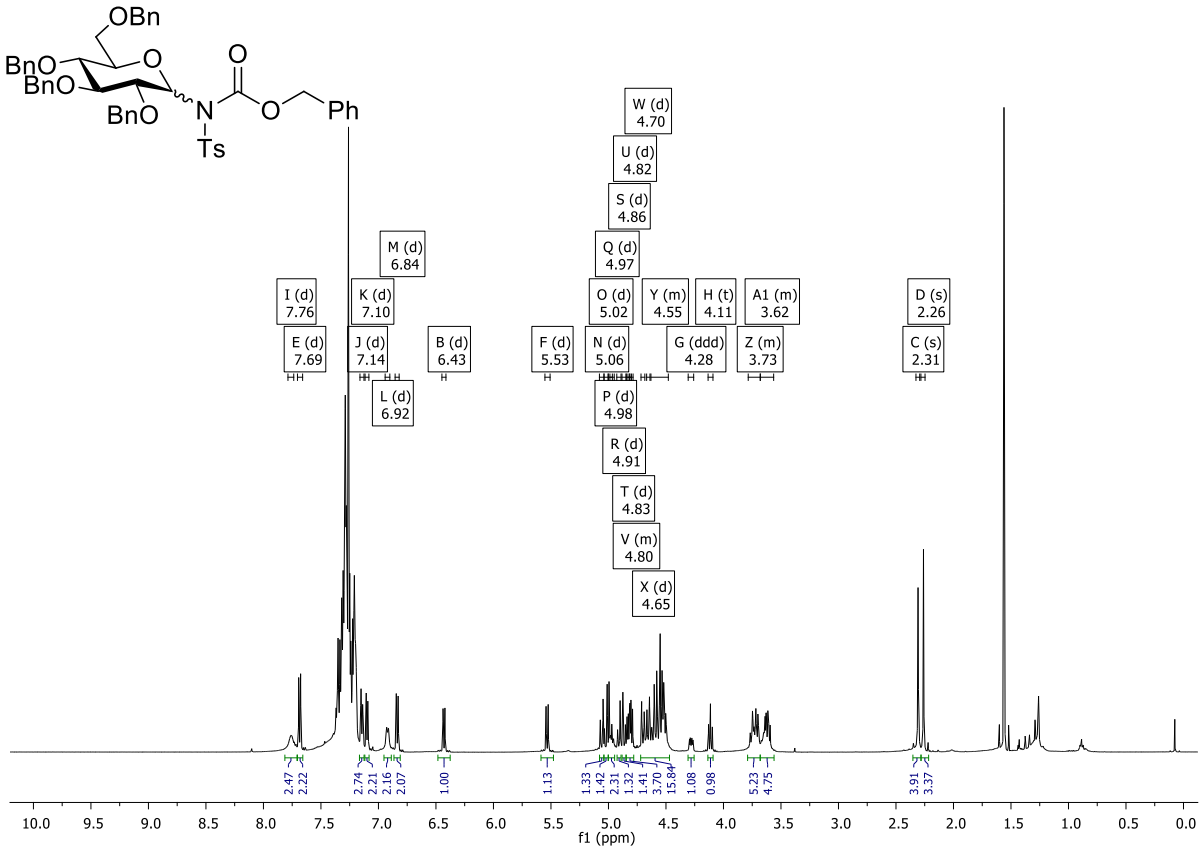


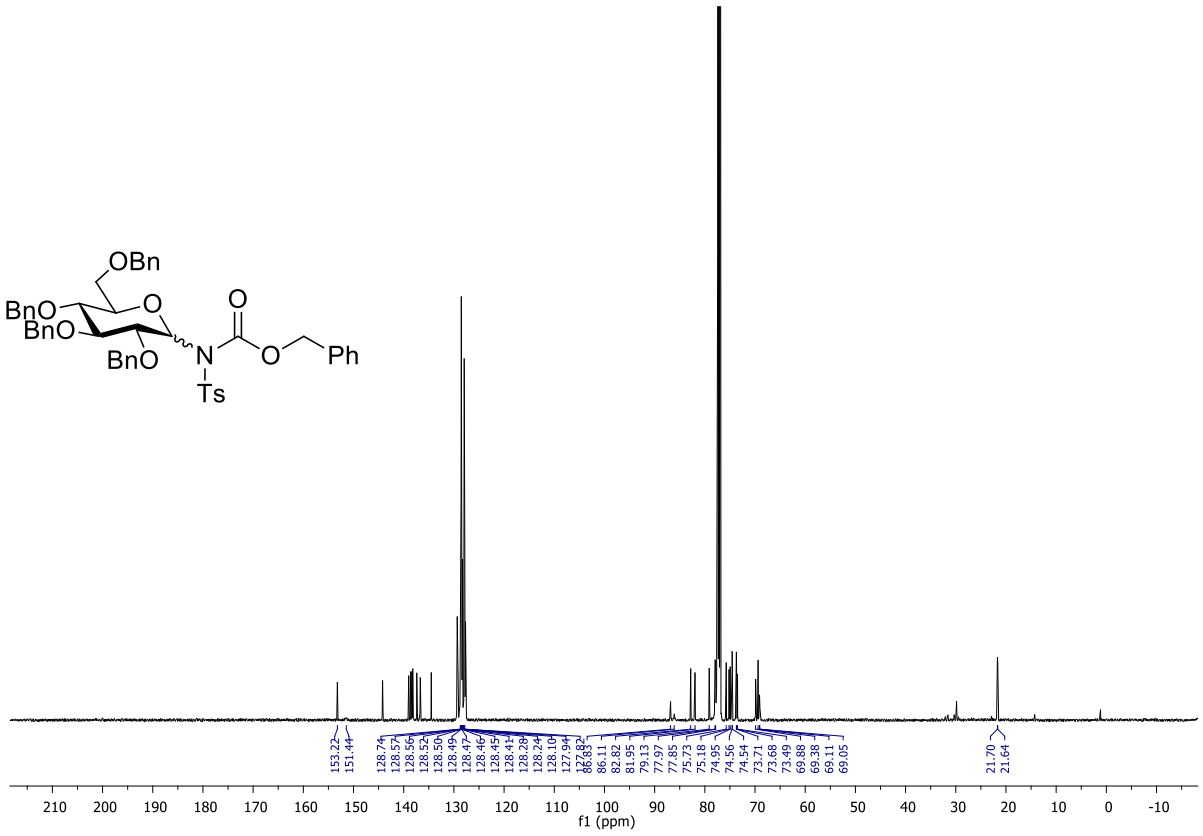
Compound 2.21β



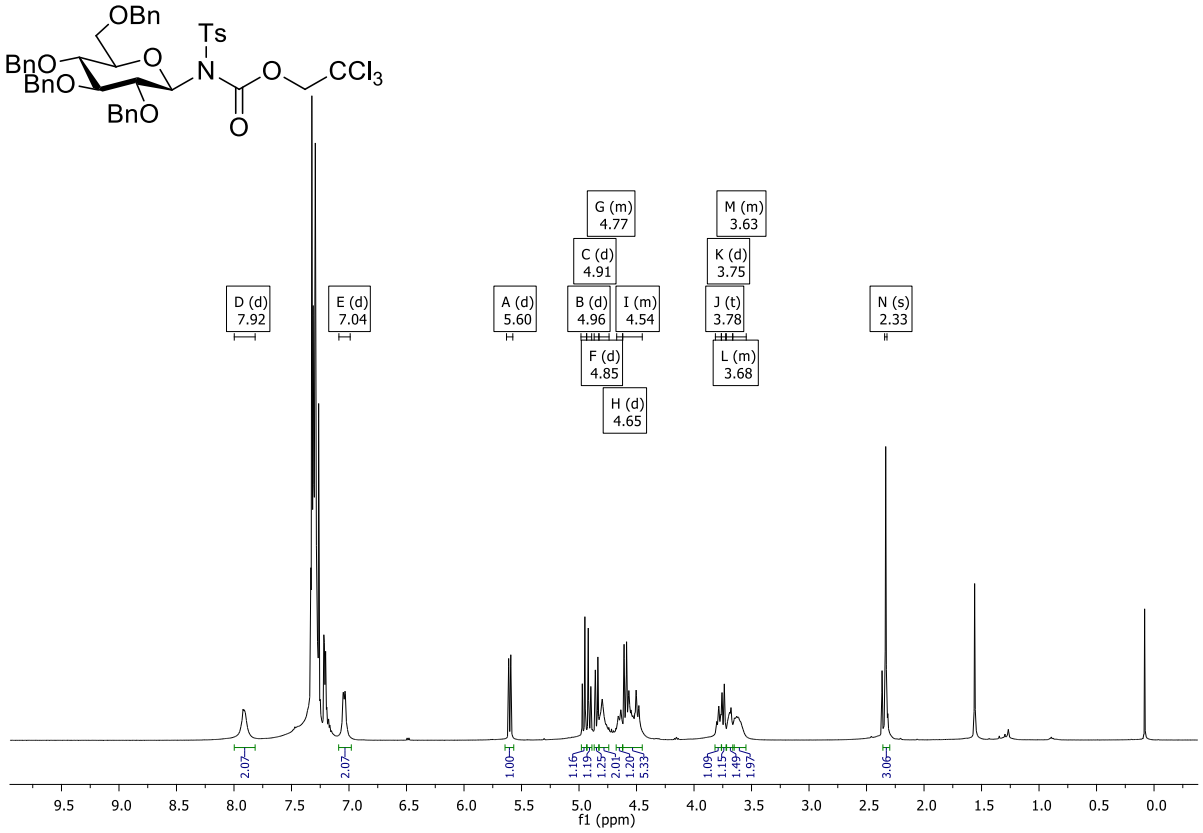


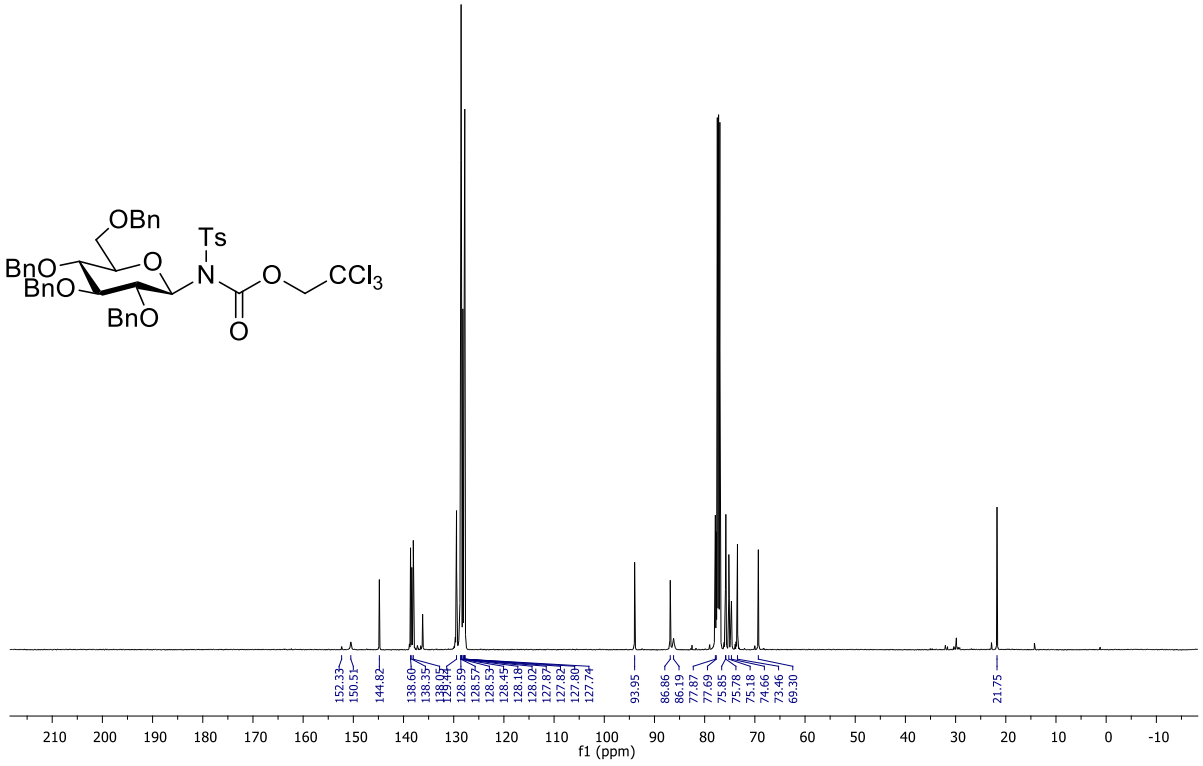
Compound 2.21



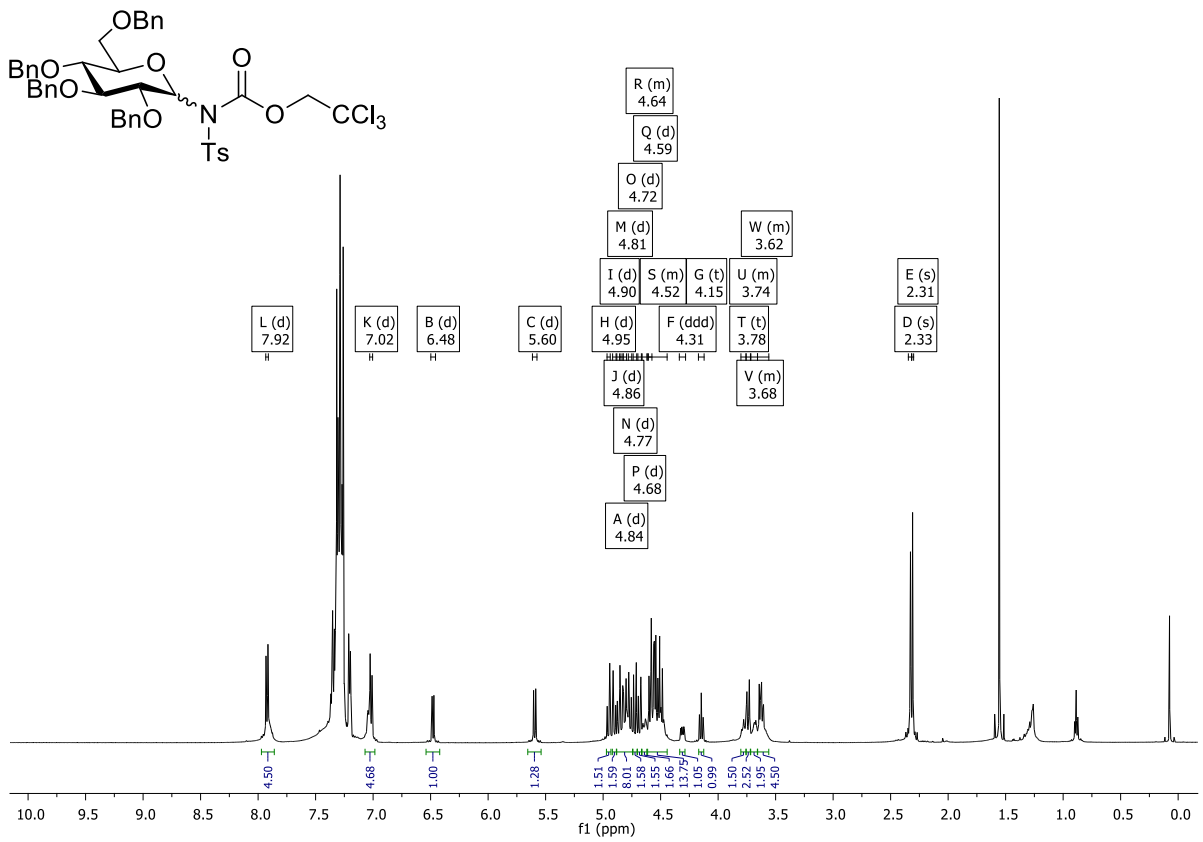


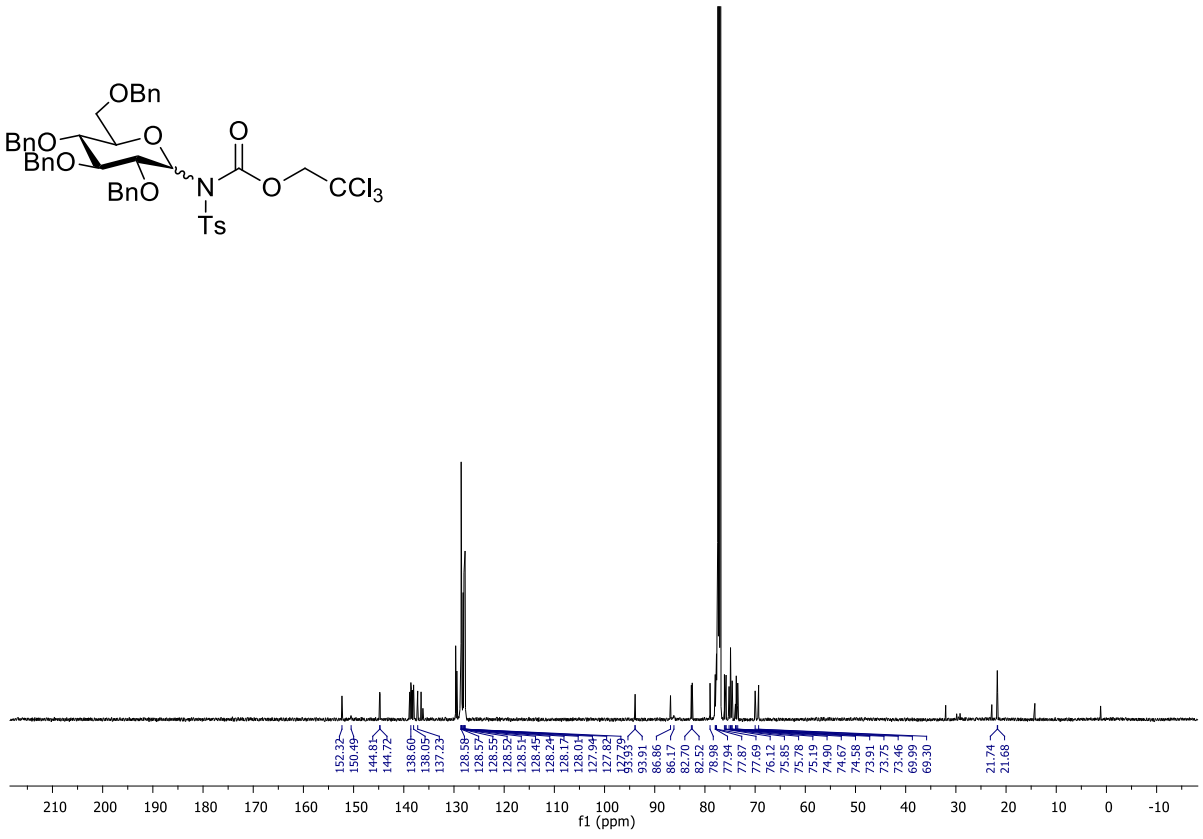
Compound 2.22β



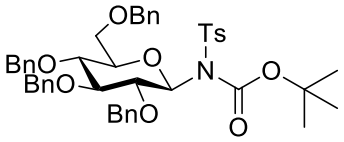


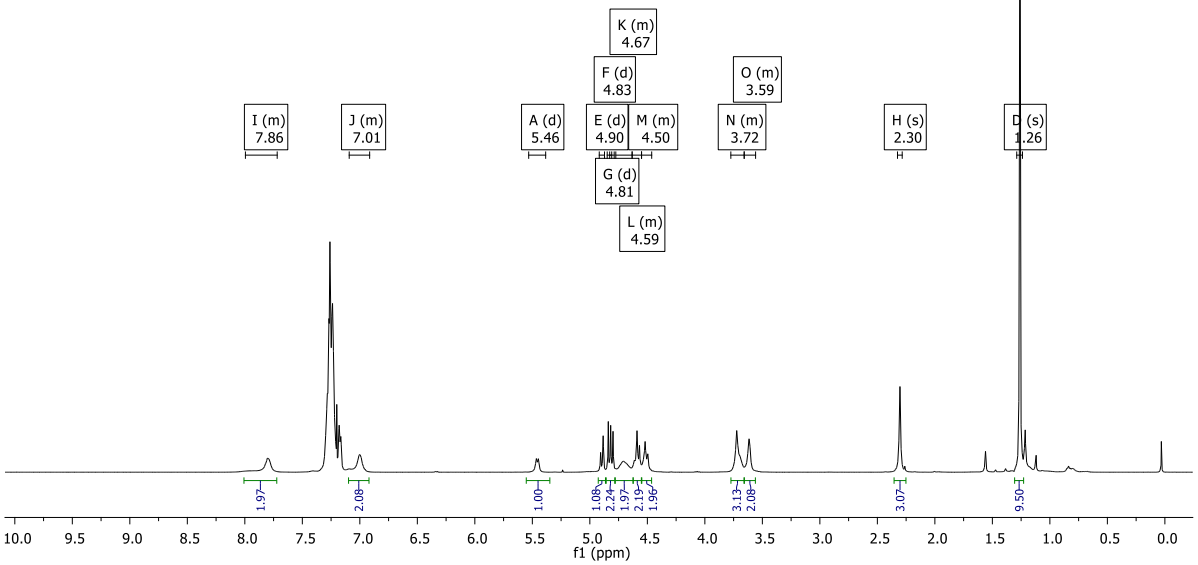
Compound 2.22

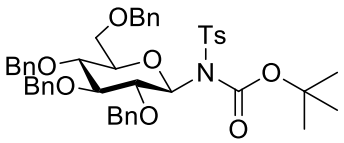




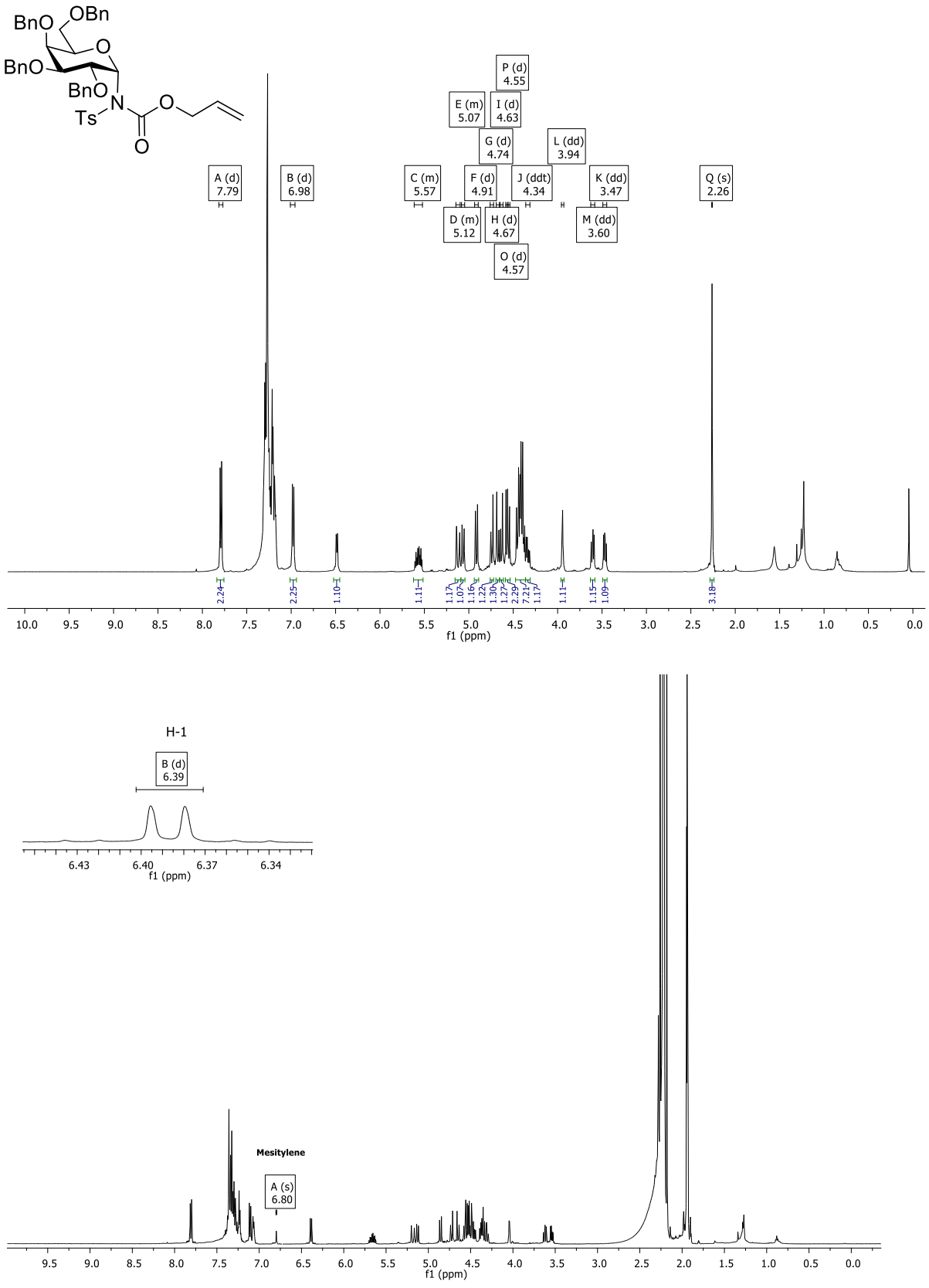
Compound 2.23β

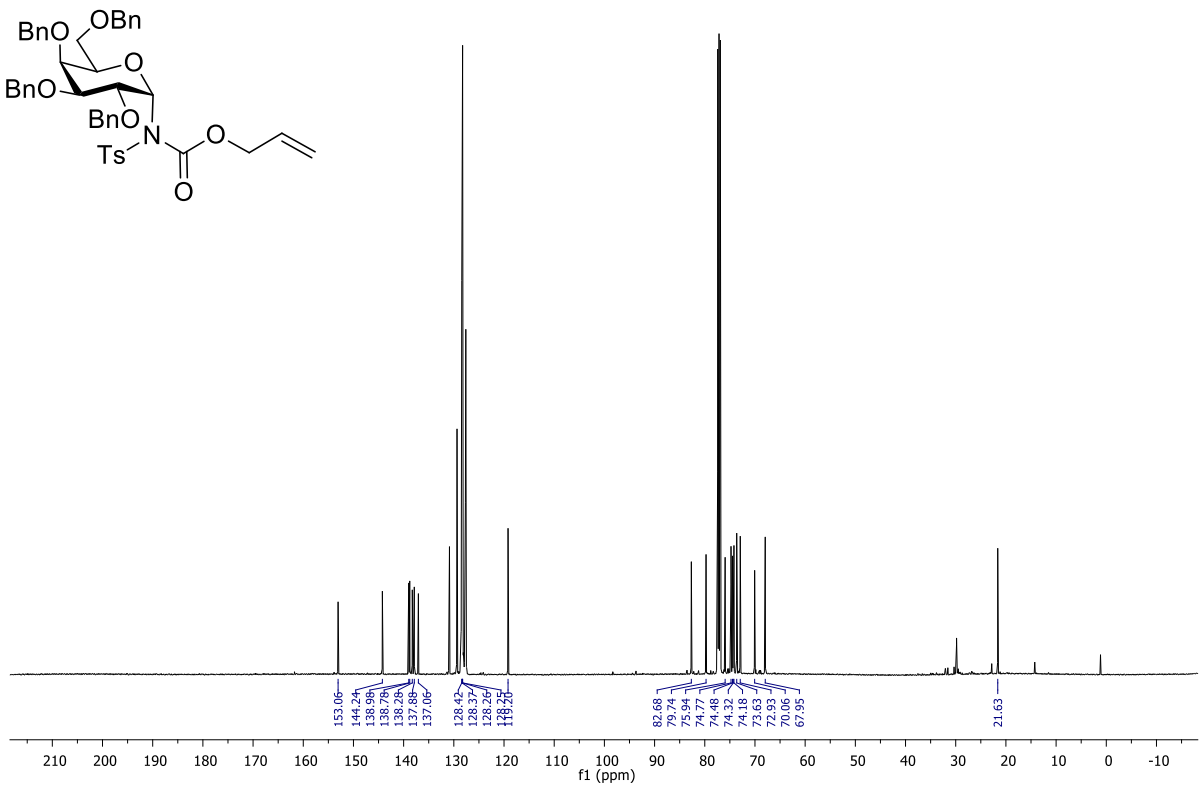




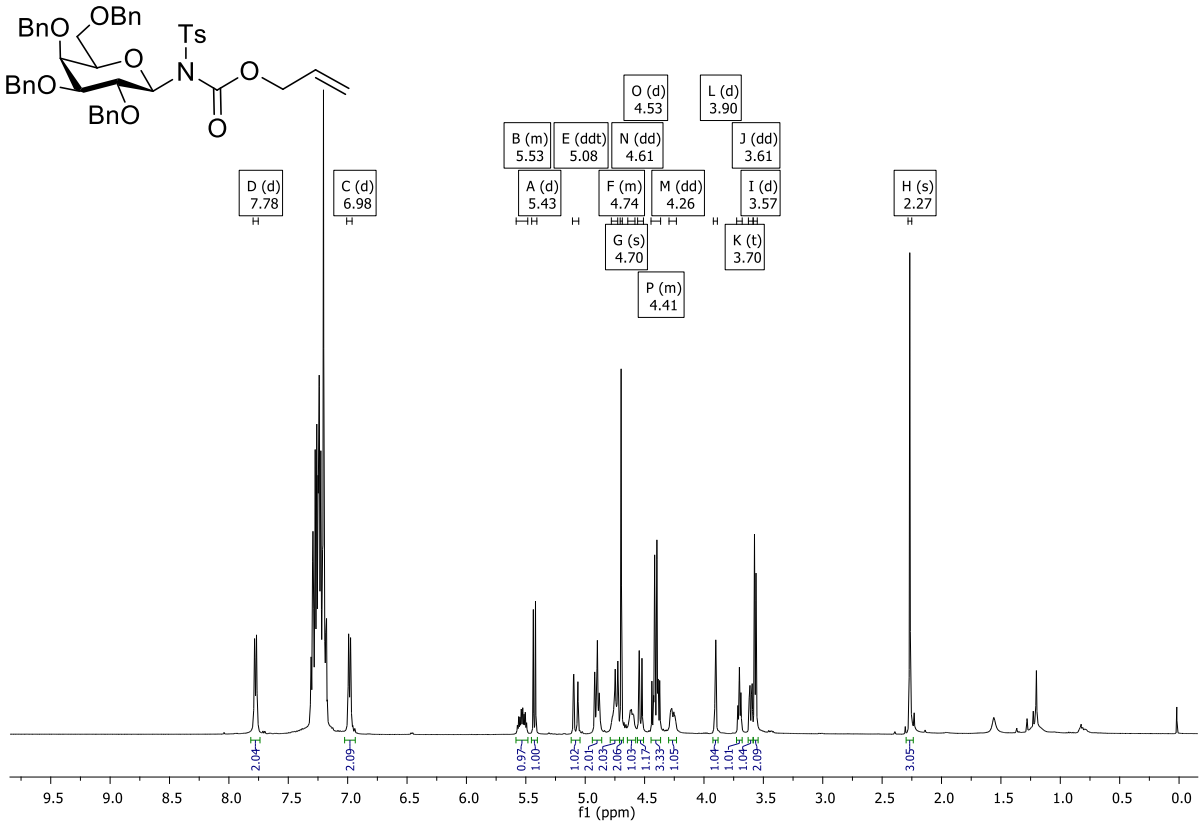


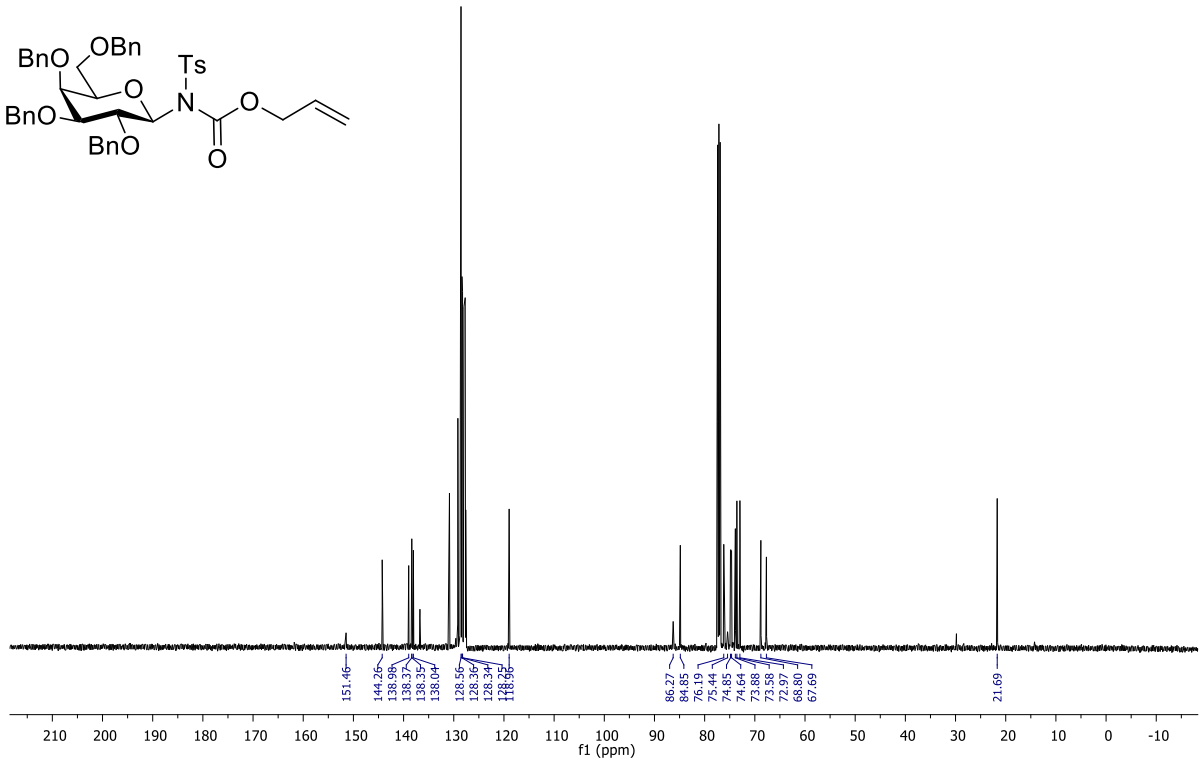
Compound 2.24α



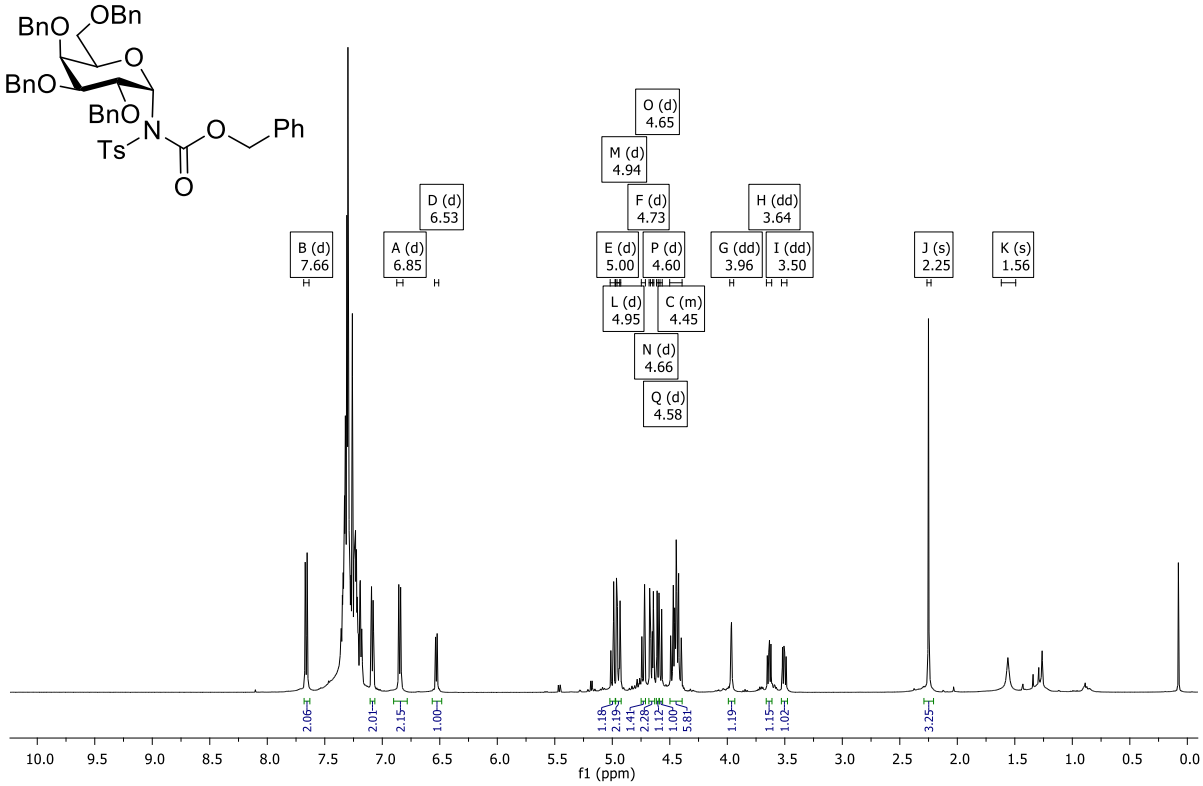


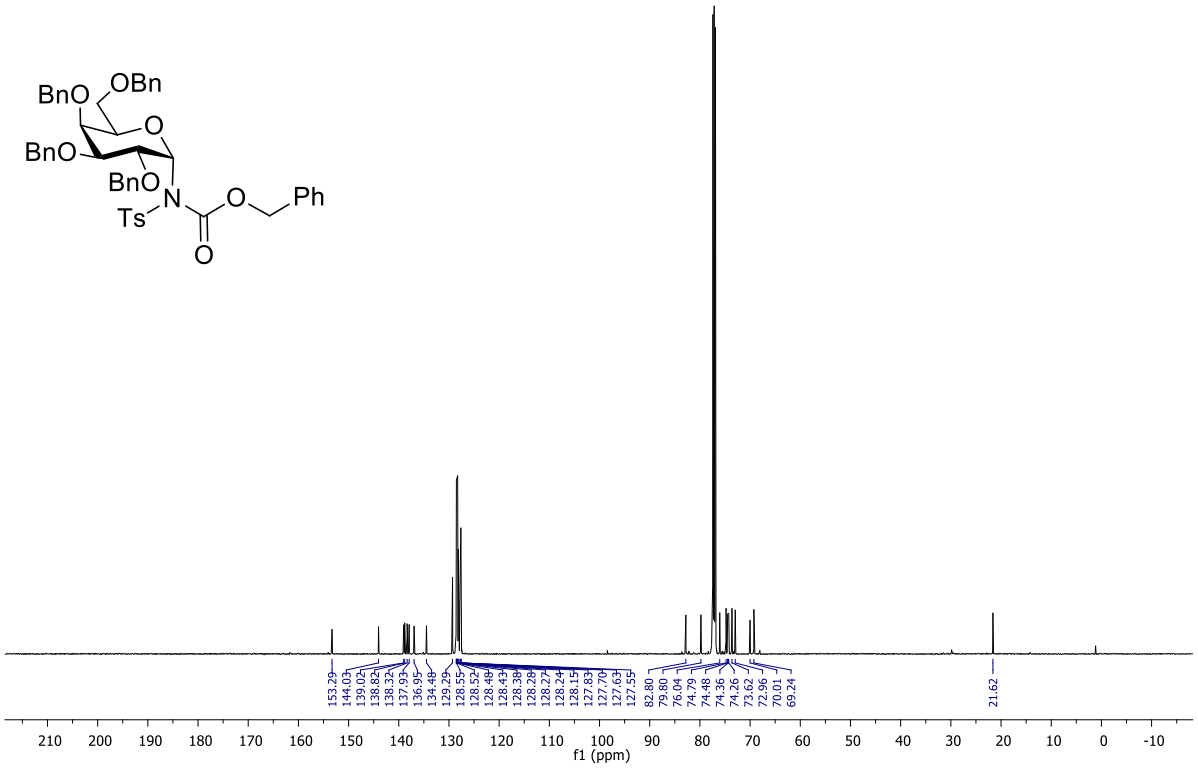
Compound 2.24β



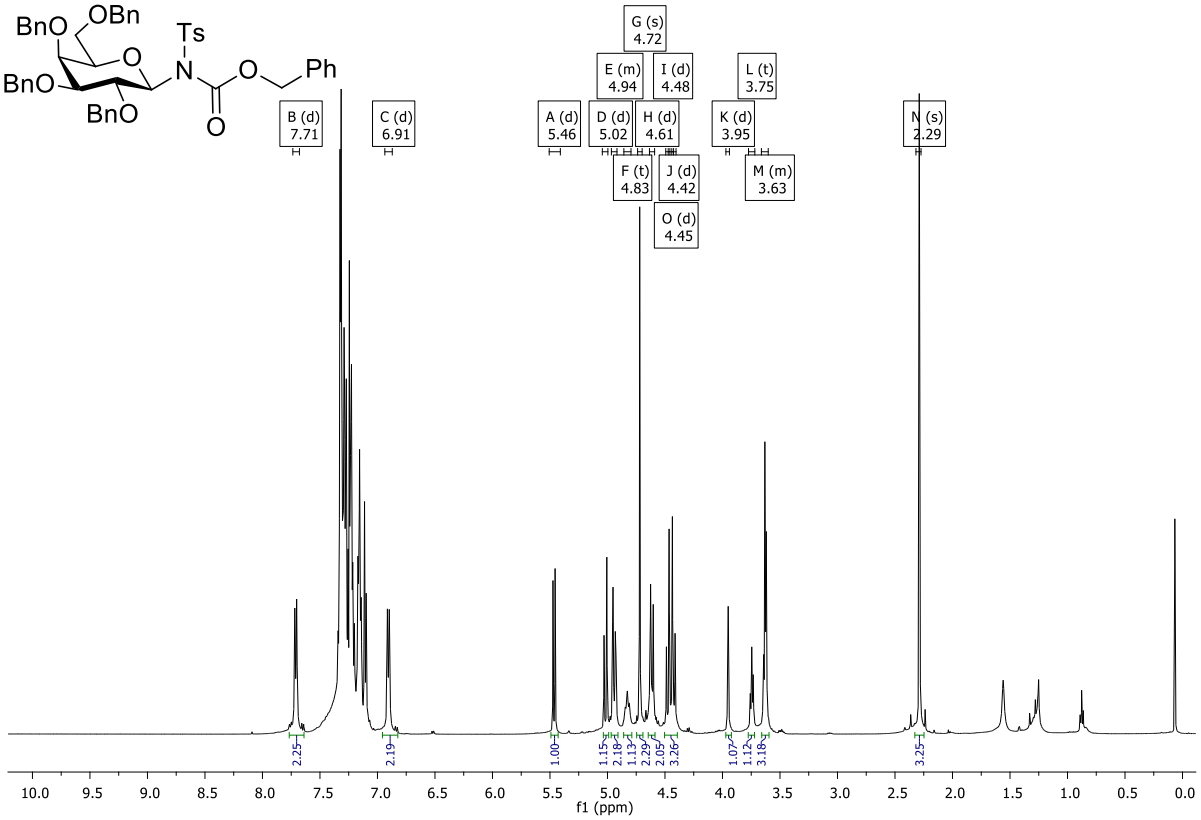


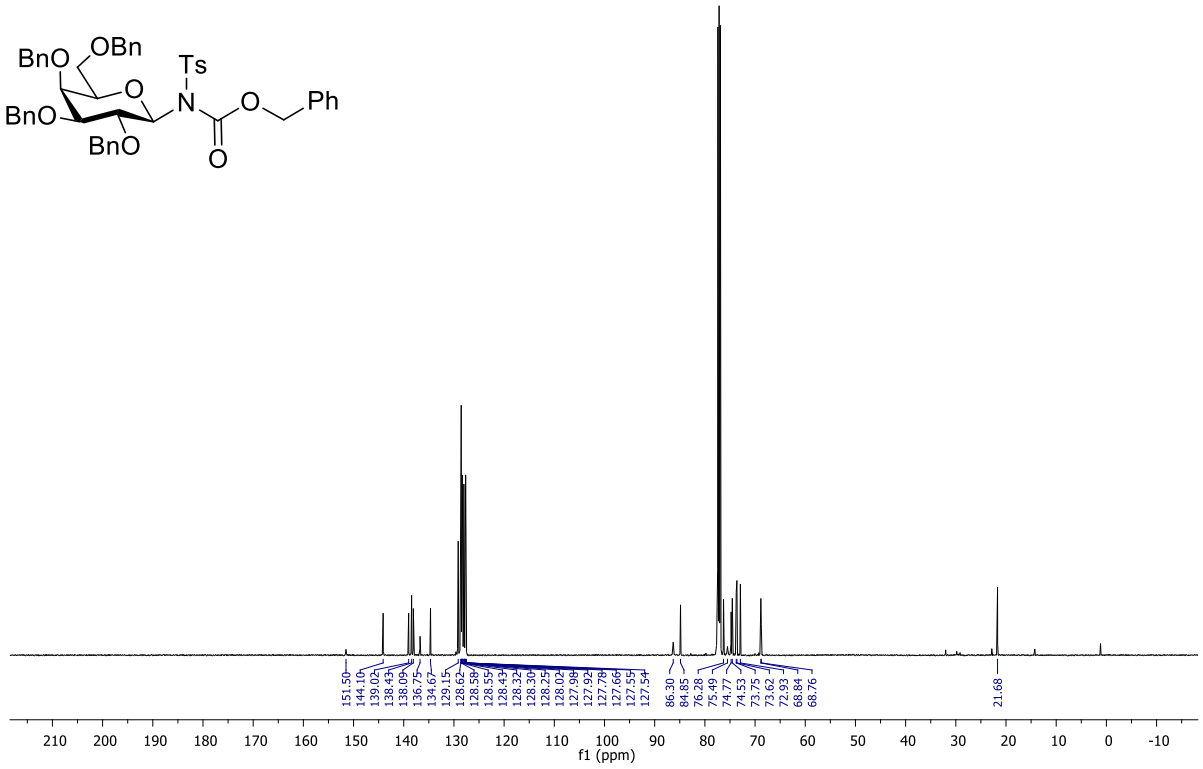
Compound 2.25α



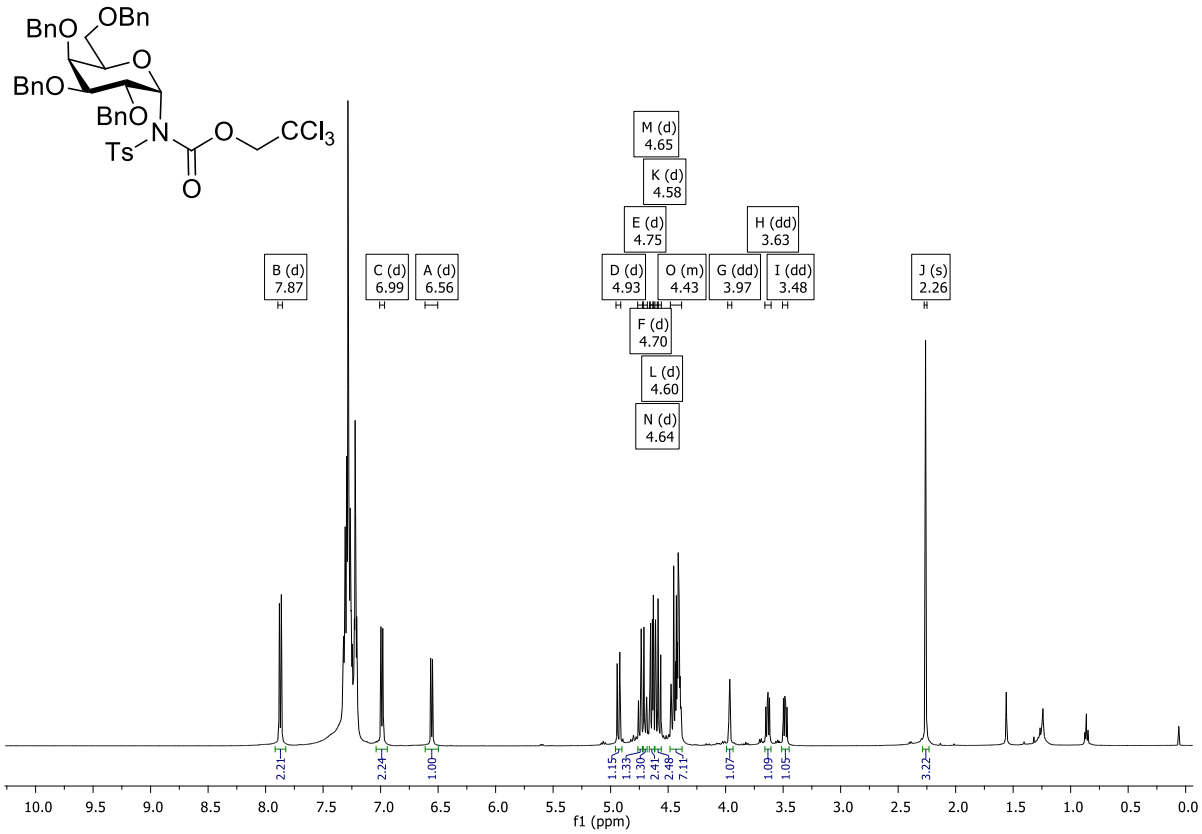


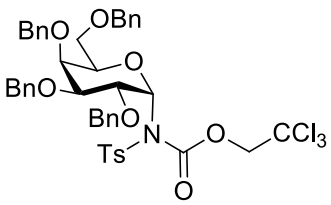
Compound 2.25β



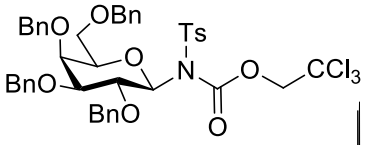


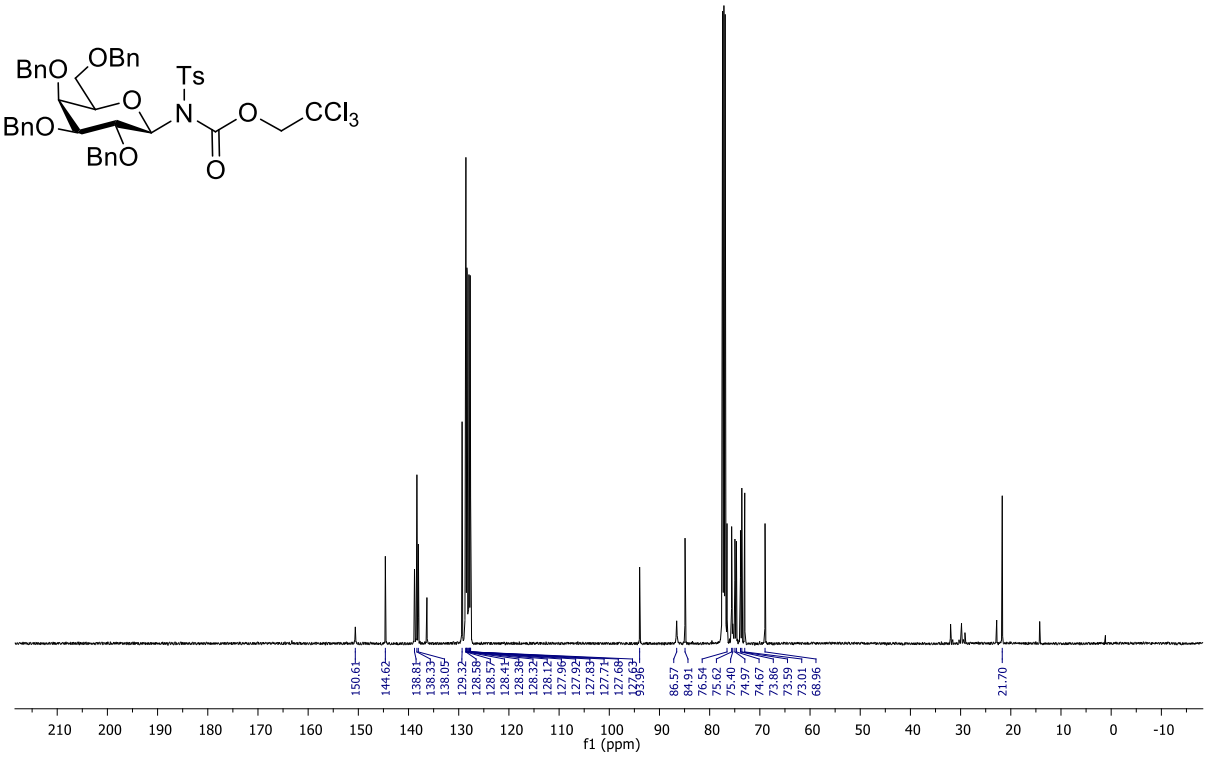
Compound 2.26α



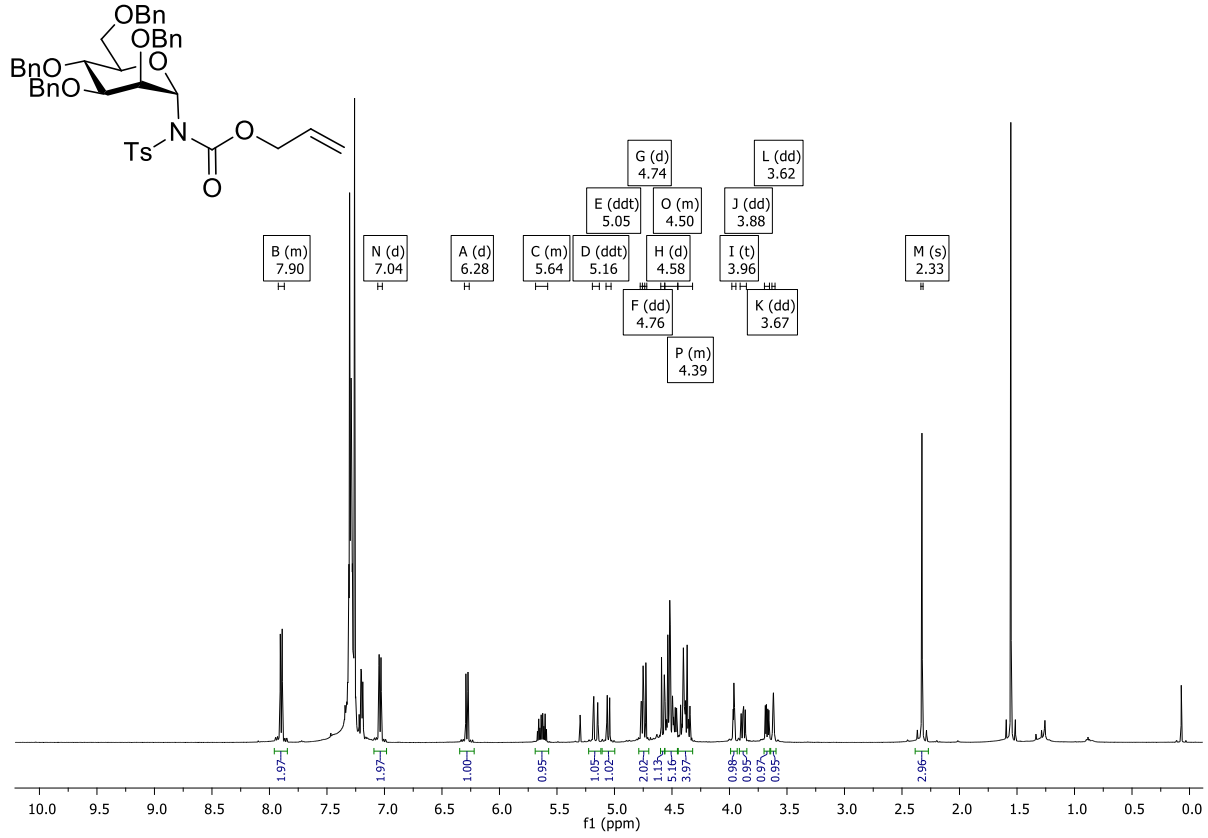


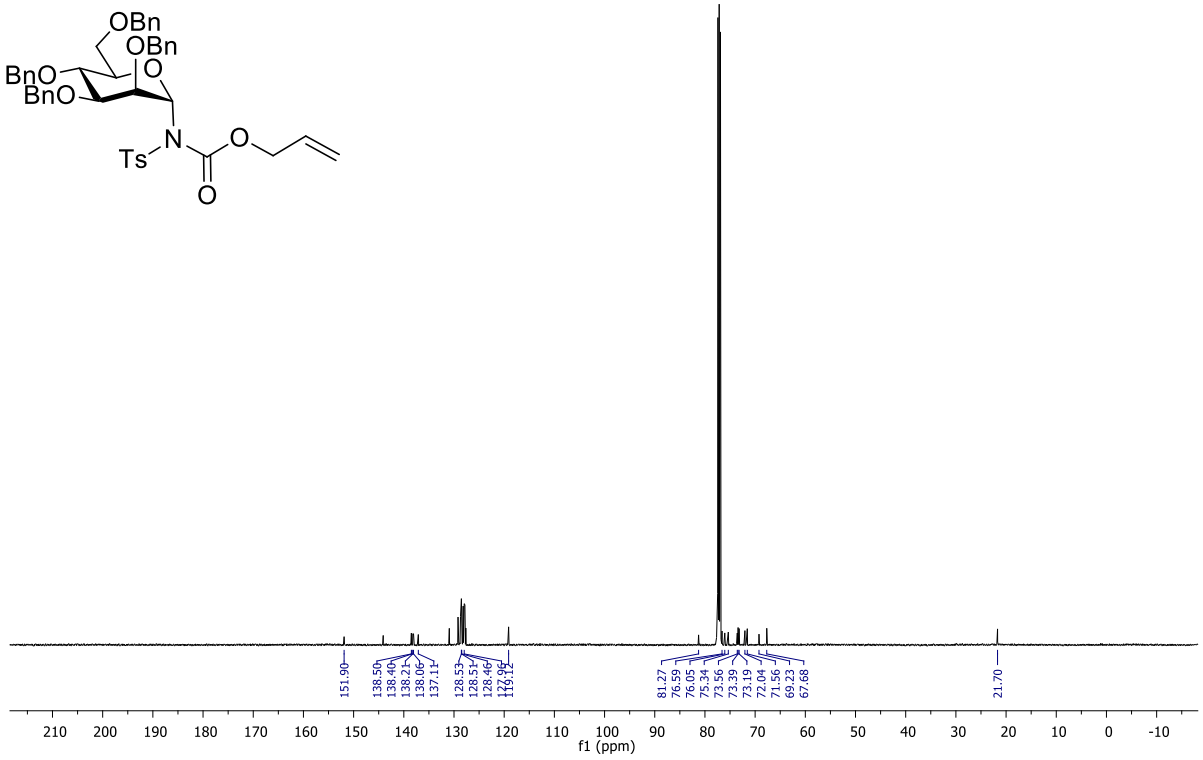
Compound 2.26β



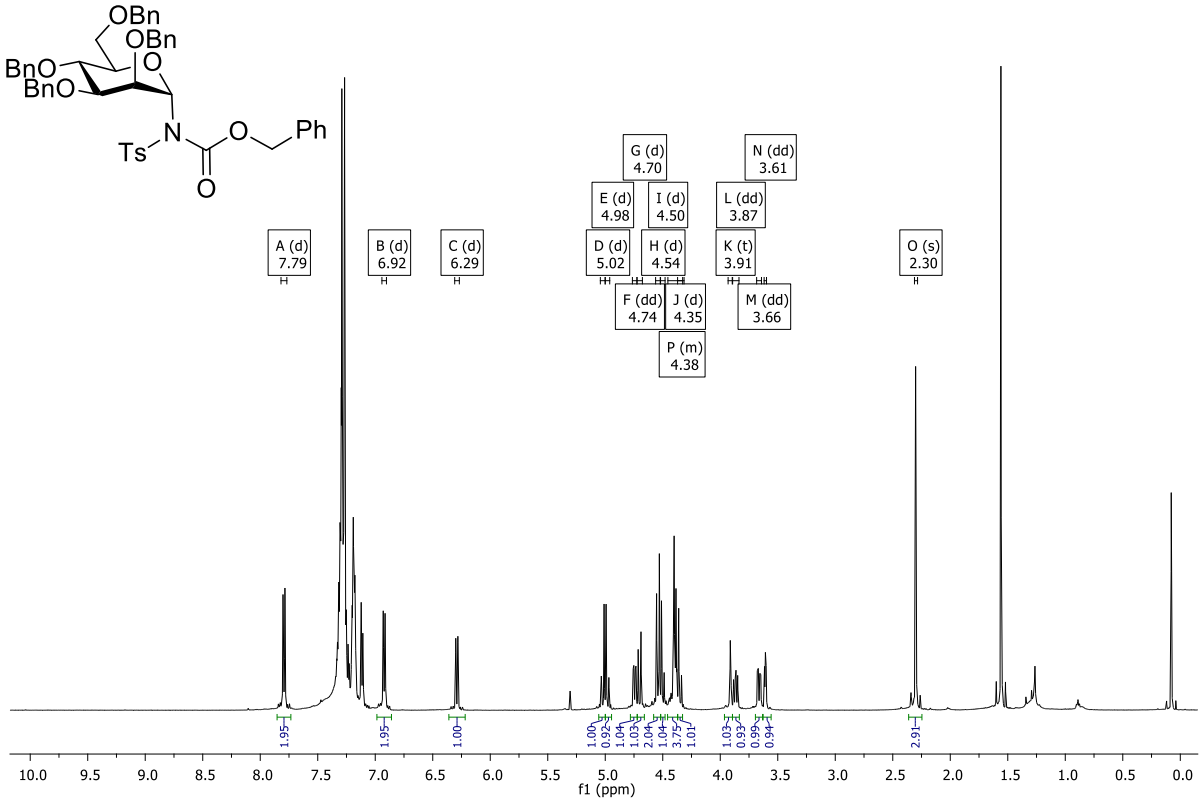


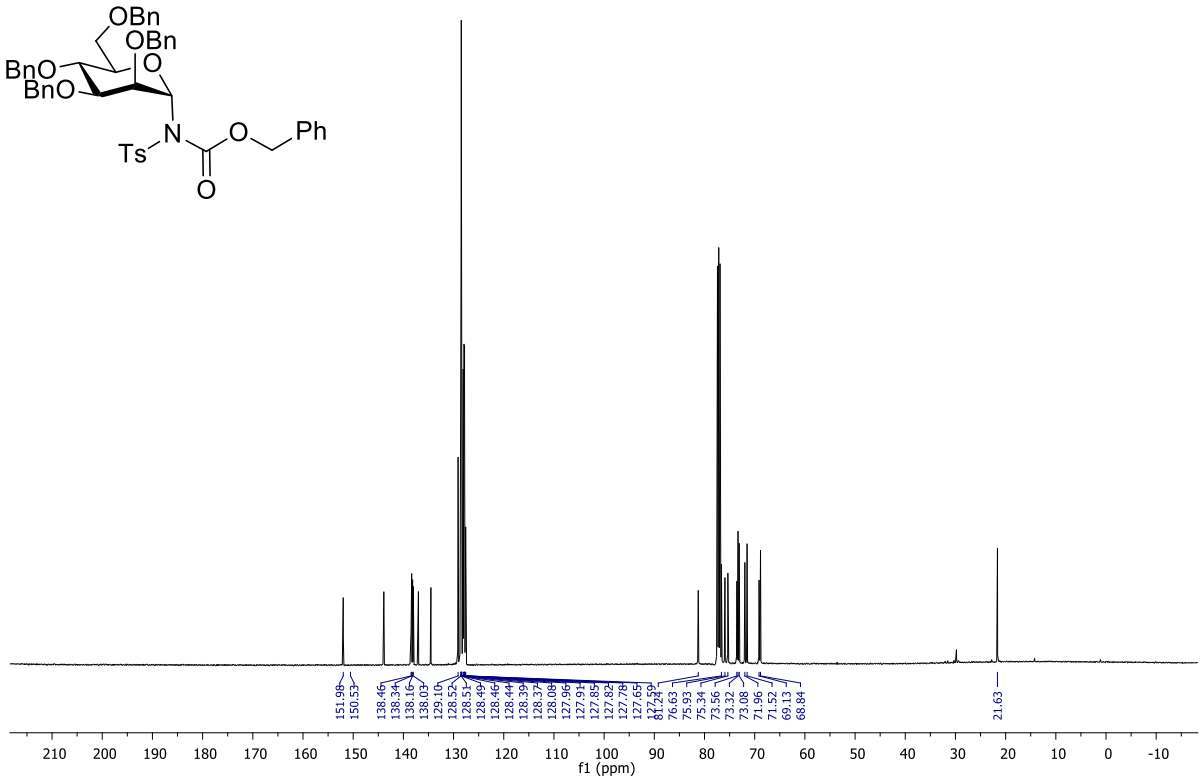
Compound 2.27α



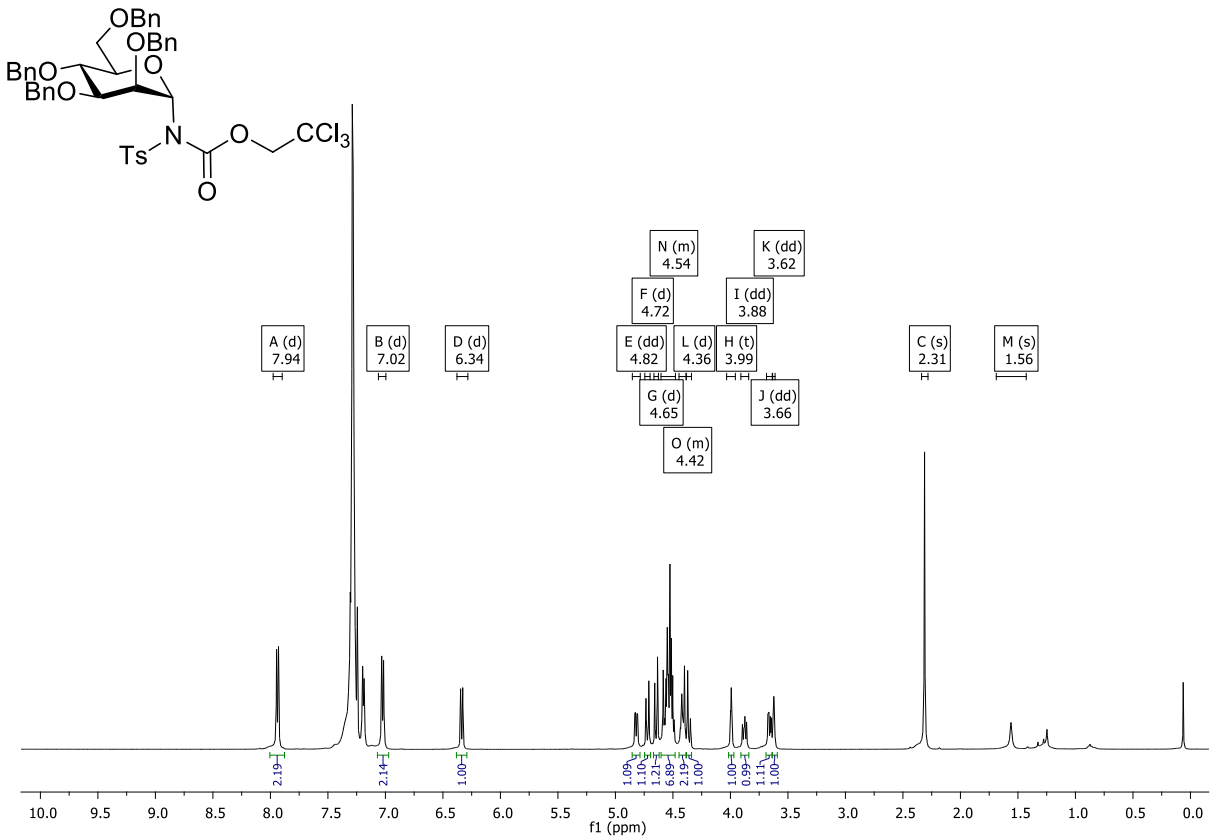


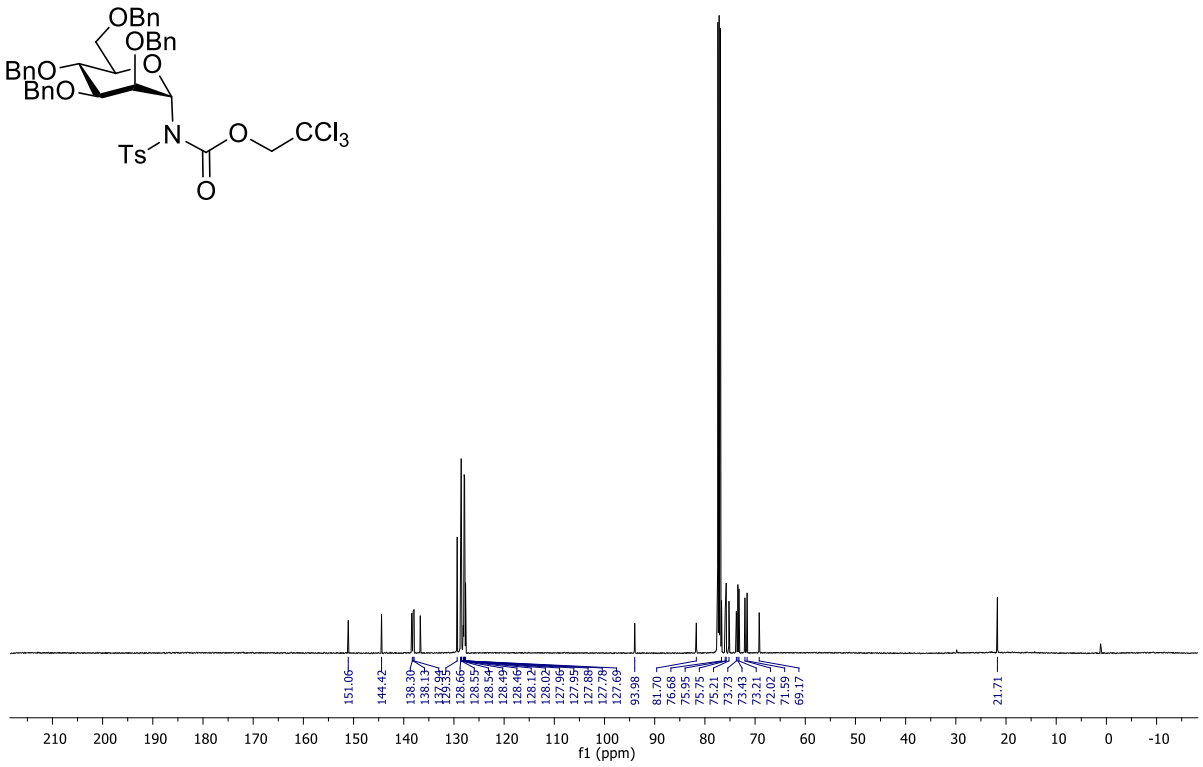
Compound 2.28α



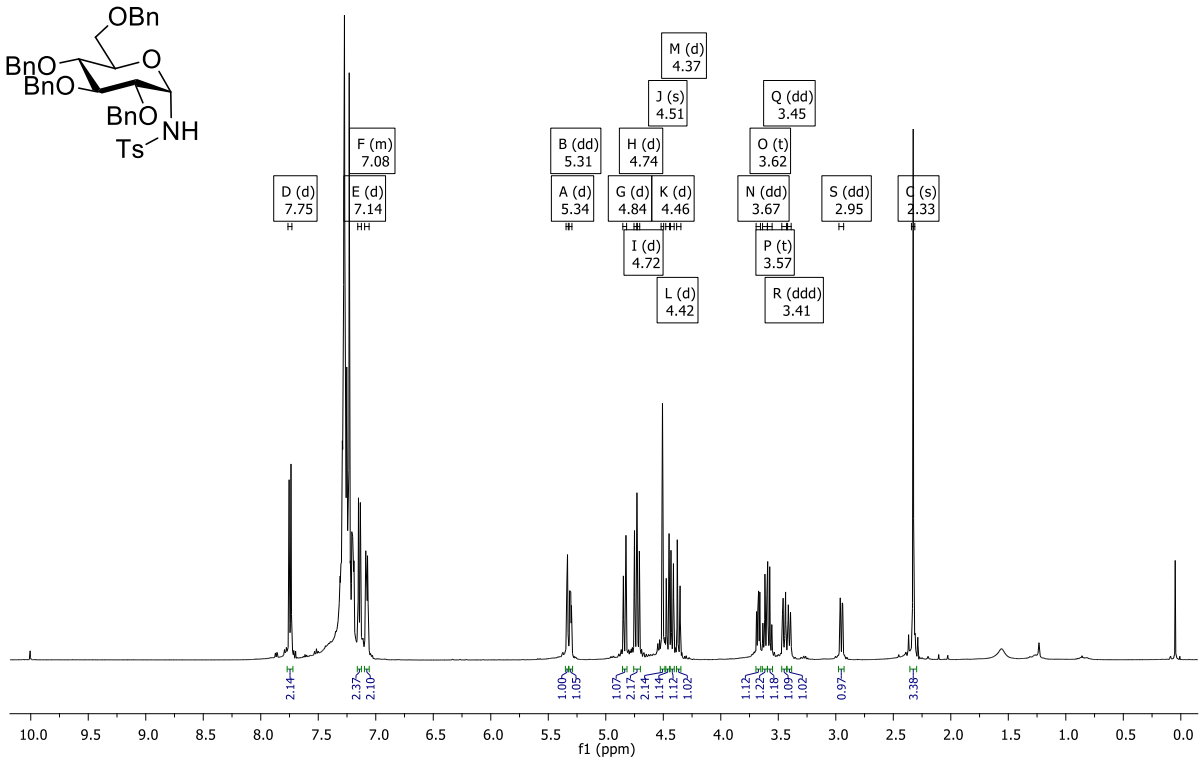


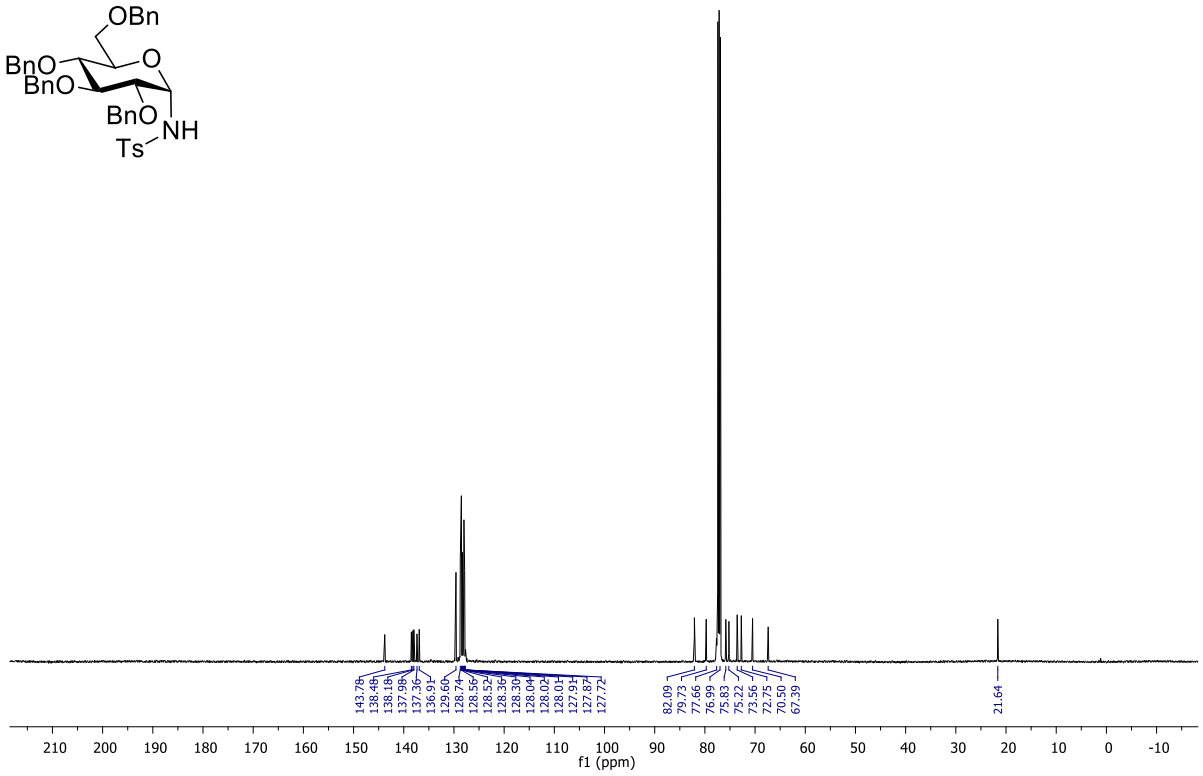
Compound 2.29α



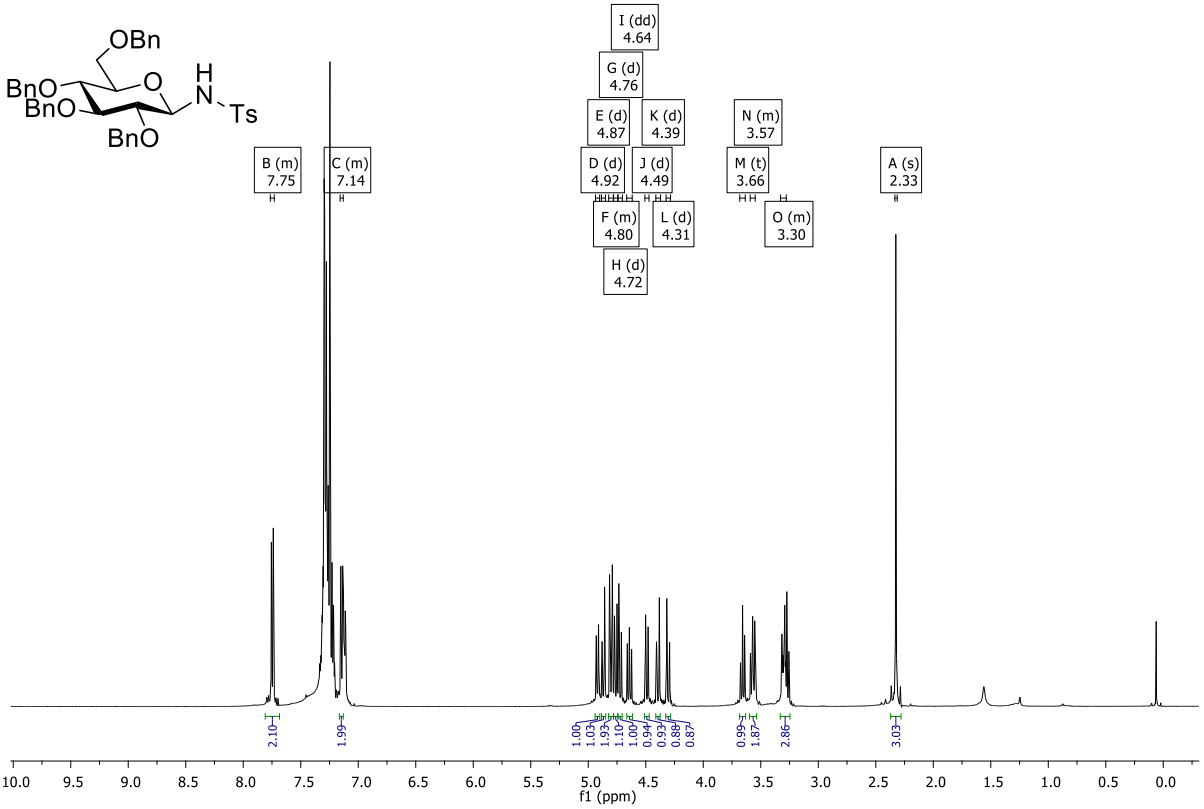


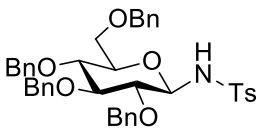
Compound 2.31α

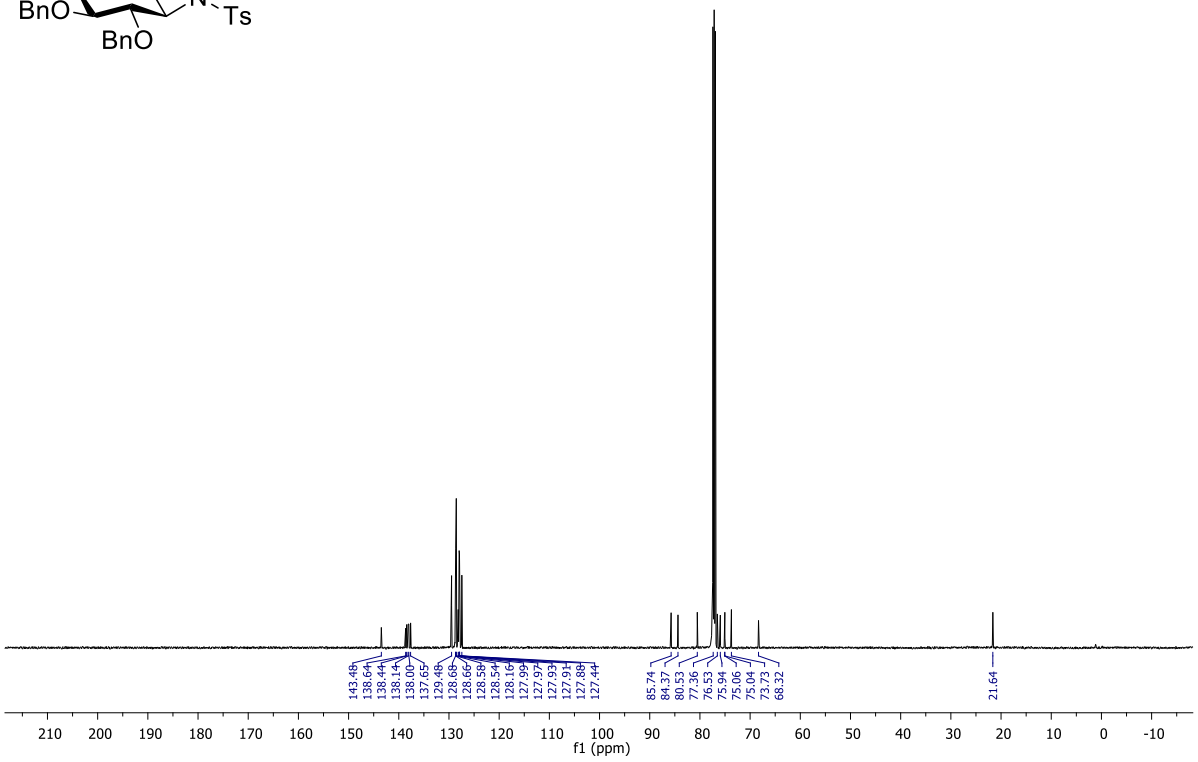




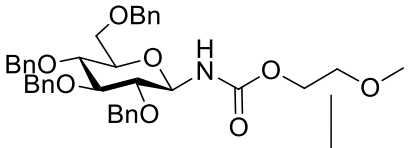
Compound 2.31β

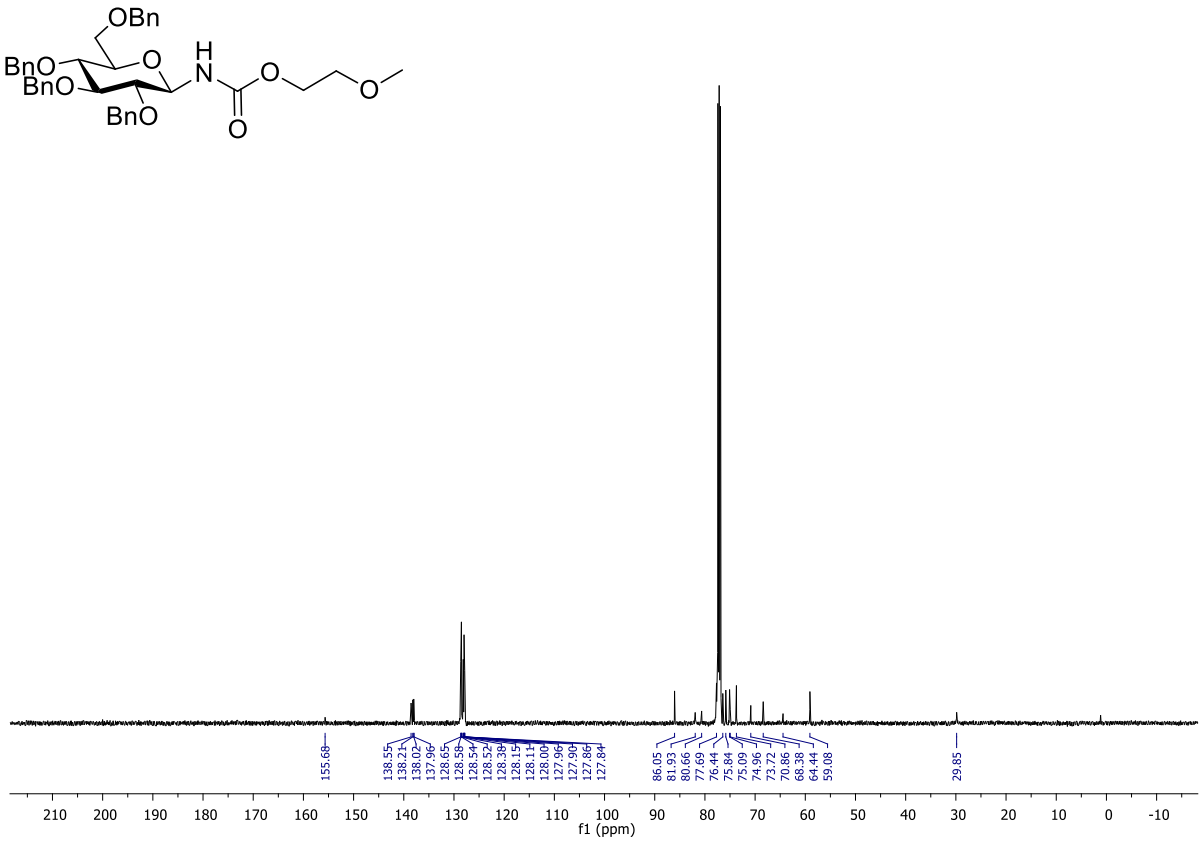




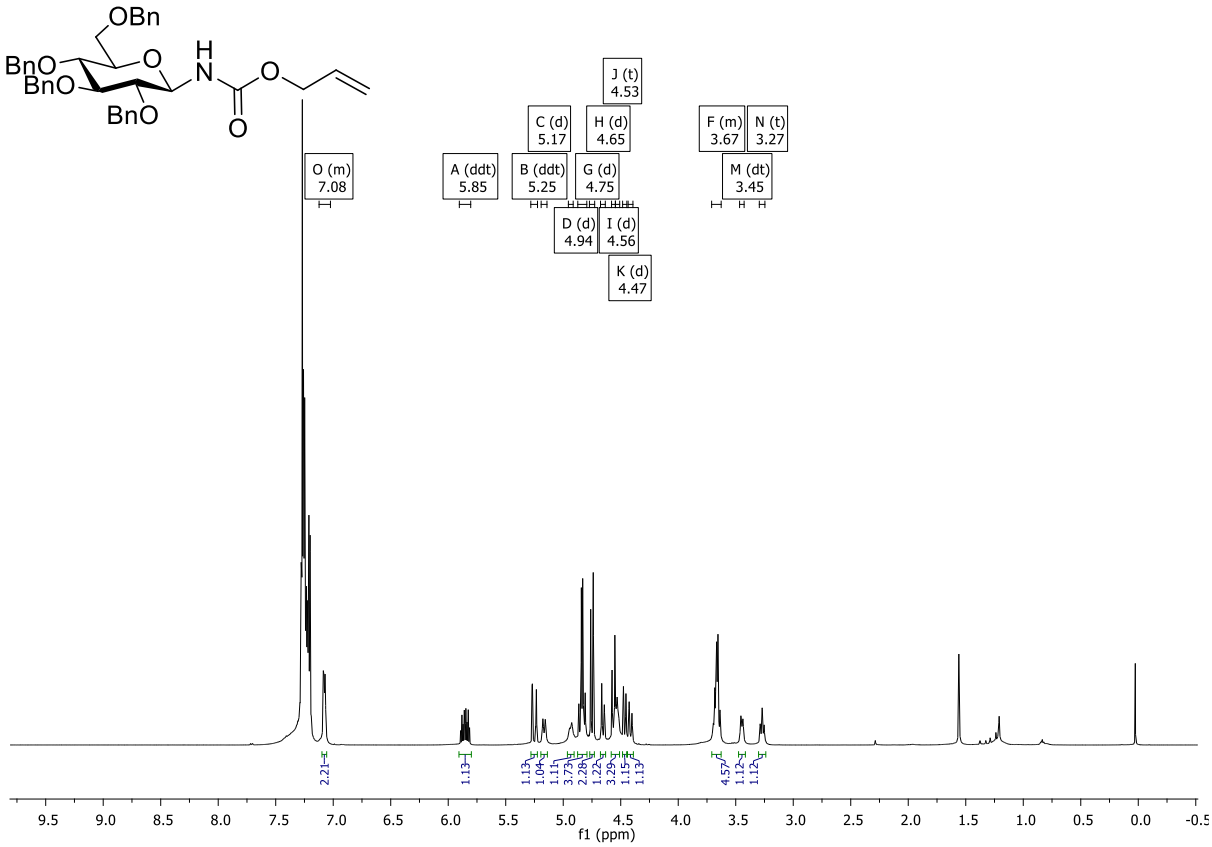


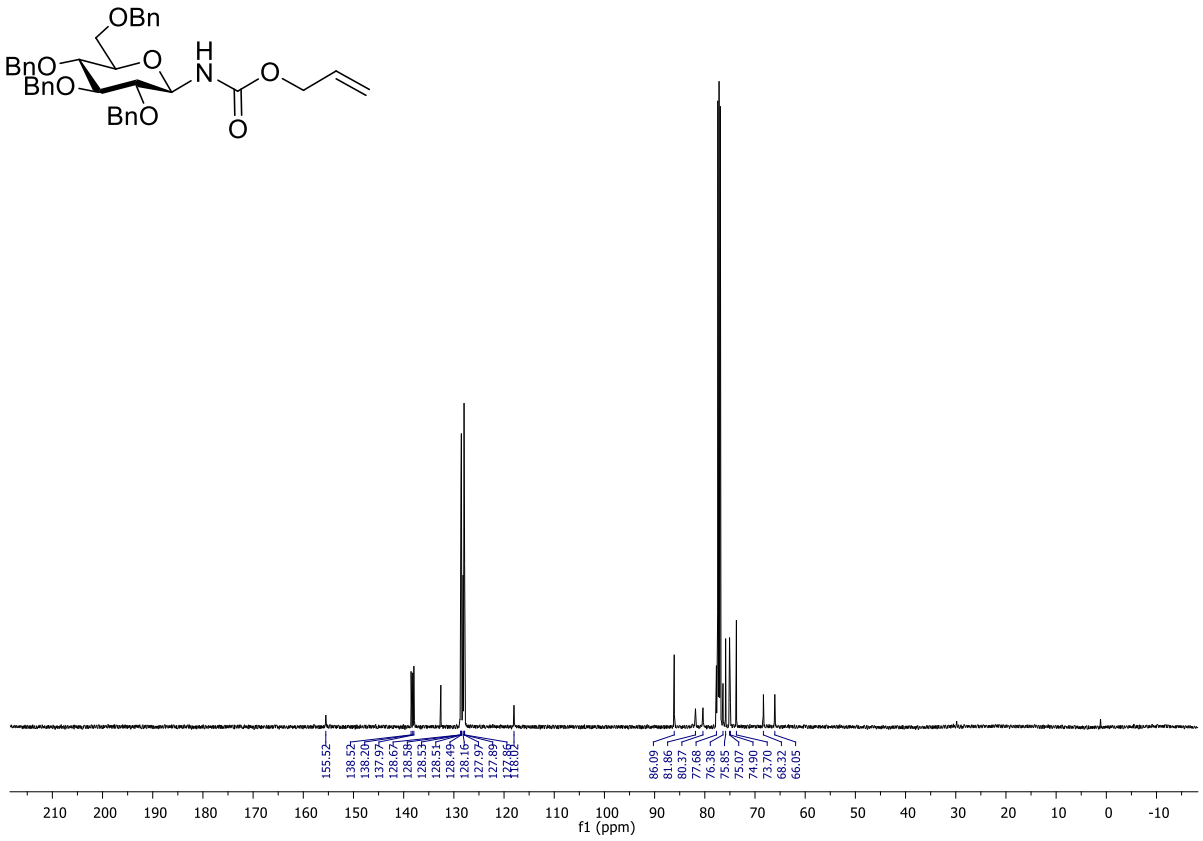
Compound 2.32β



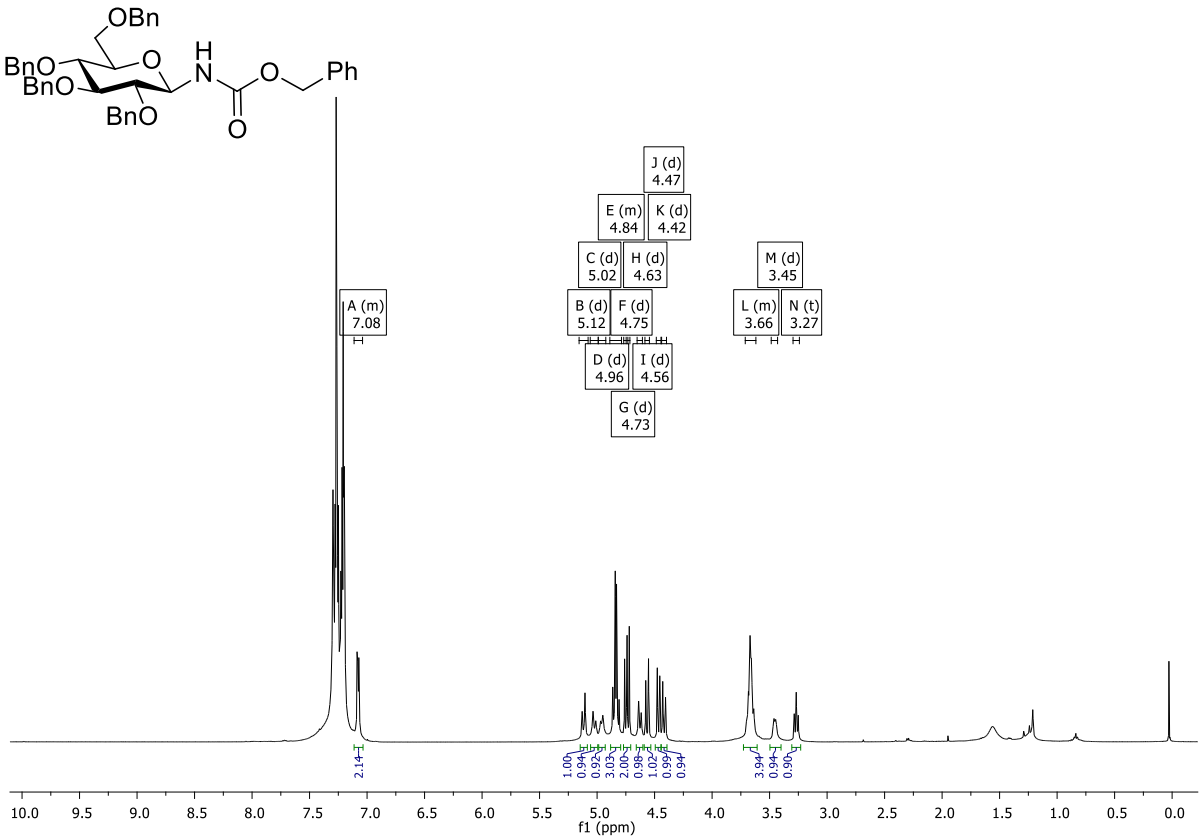


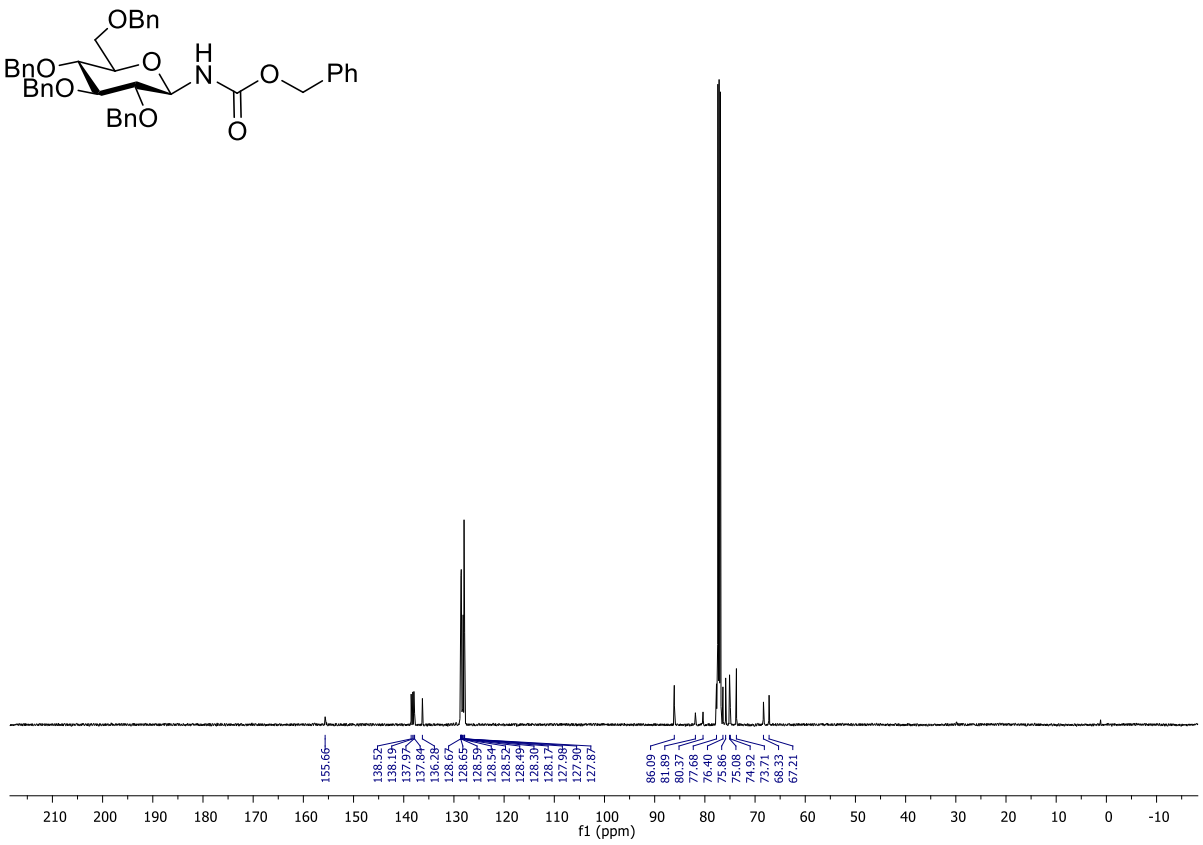
Compound 2.33β





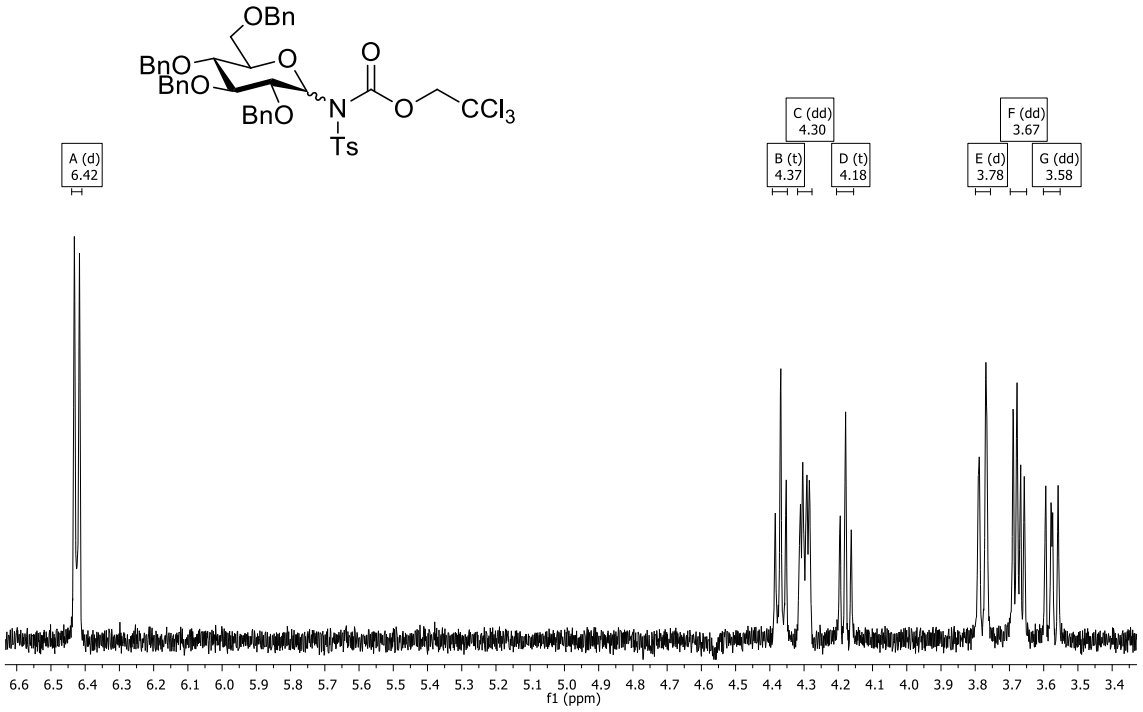
Compound 2.34β



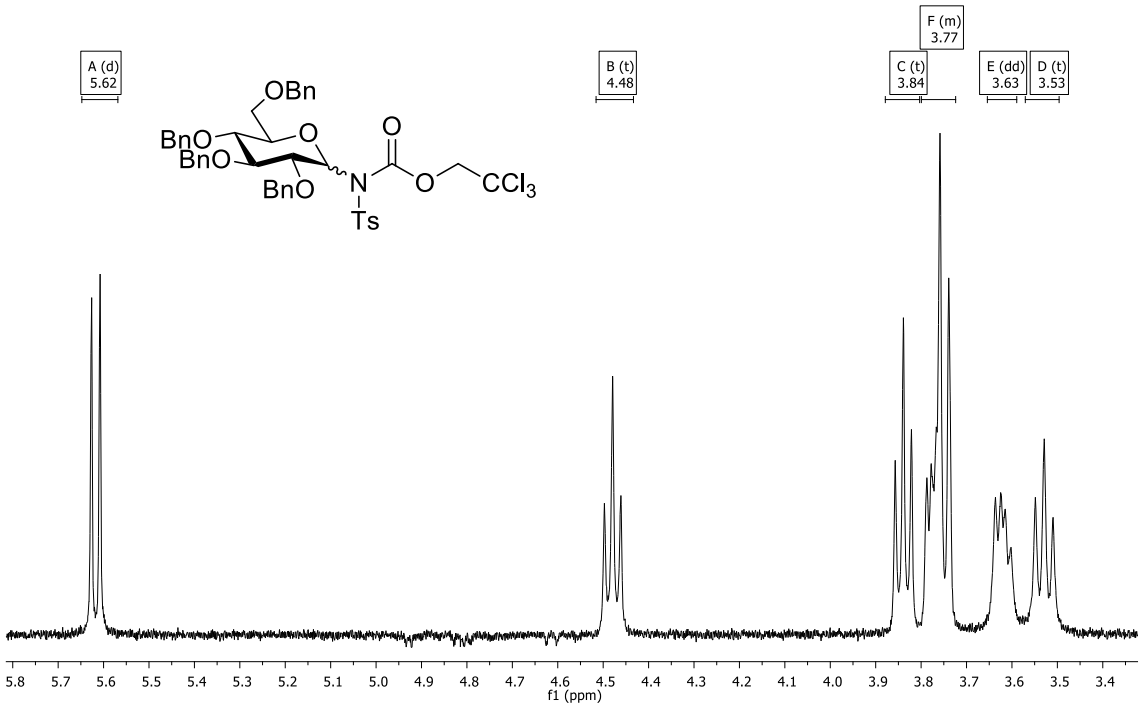

OBn
BnO
BnO
BnO
O
H
N
O
O
Ph
155.66
138.52
138.19
137.97
137.84
136.28
128.67
128.65
128.59
128.54
128.52
128.49
128.30
128.17
127.99
127.90
127.87
86.09
81.89
80.37
77.68
76.40
75.86
75.08
74.92
73.71
68.33
67.21
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

2.4.7. Appendix of TOCSY Spectra

The TOCSY spectrum of **compound 2.22** (α/β 23:77) in CD_3CN demonstrating correlations between H-1α and other sugar ring protons of the α-anomer. The spectrum was recorded at 26.85°C.

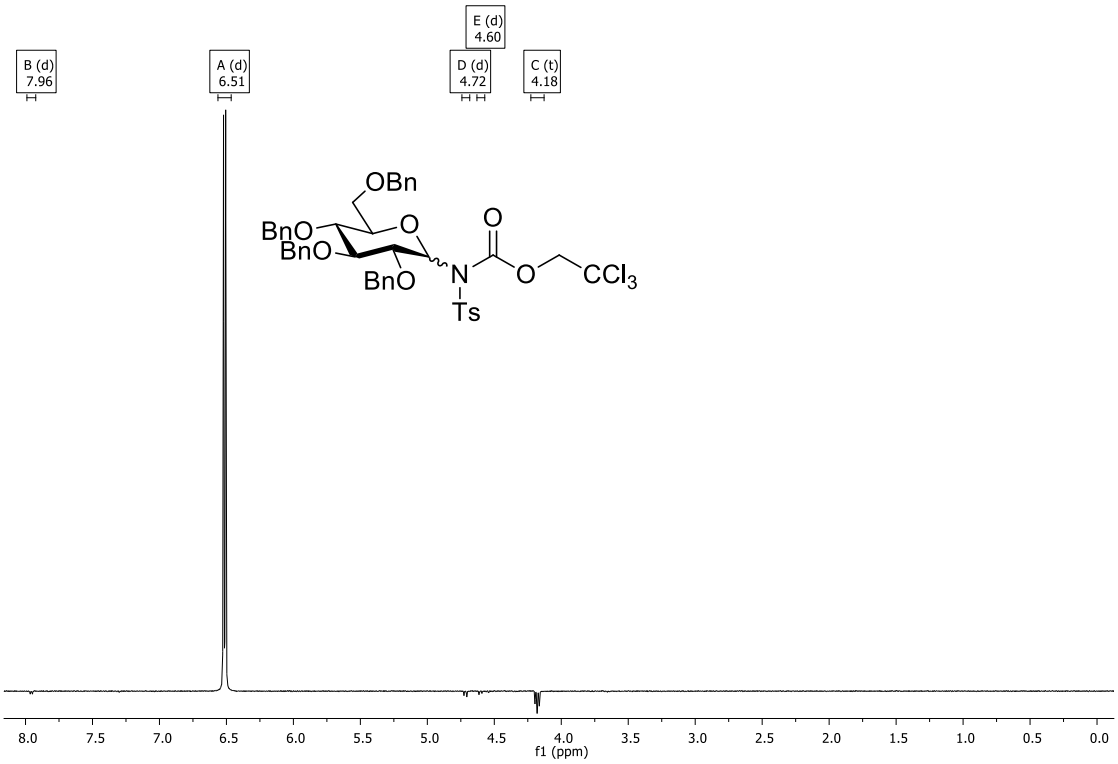


The TOCSY spectrum of **compound 2.22** (α/β 23:77) in CD_3CN demonstrating correlations between H-1β and other sugar ring protons of the β-anomer. The spectrum was recorded at 26.85°C.

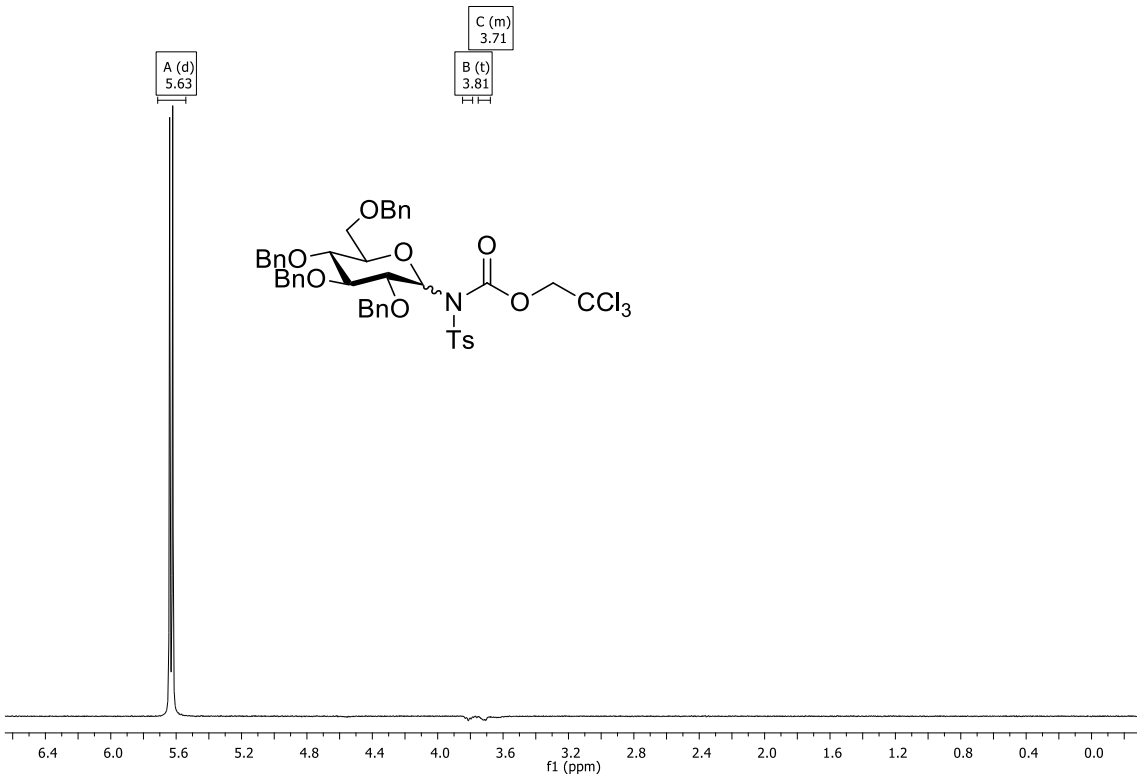


2.4.8. Appendix of 1D and 2D NOESY Spectra

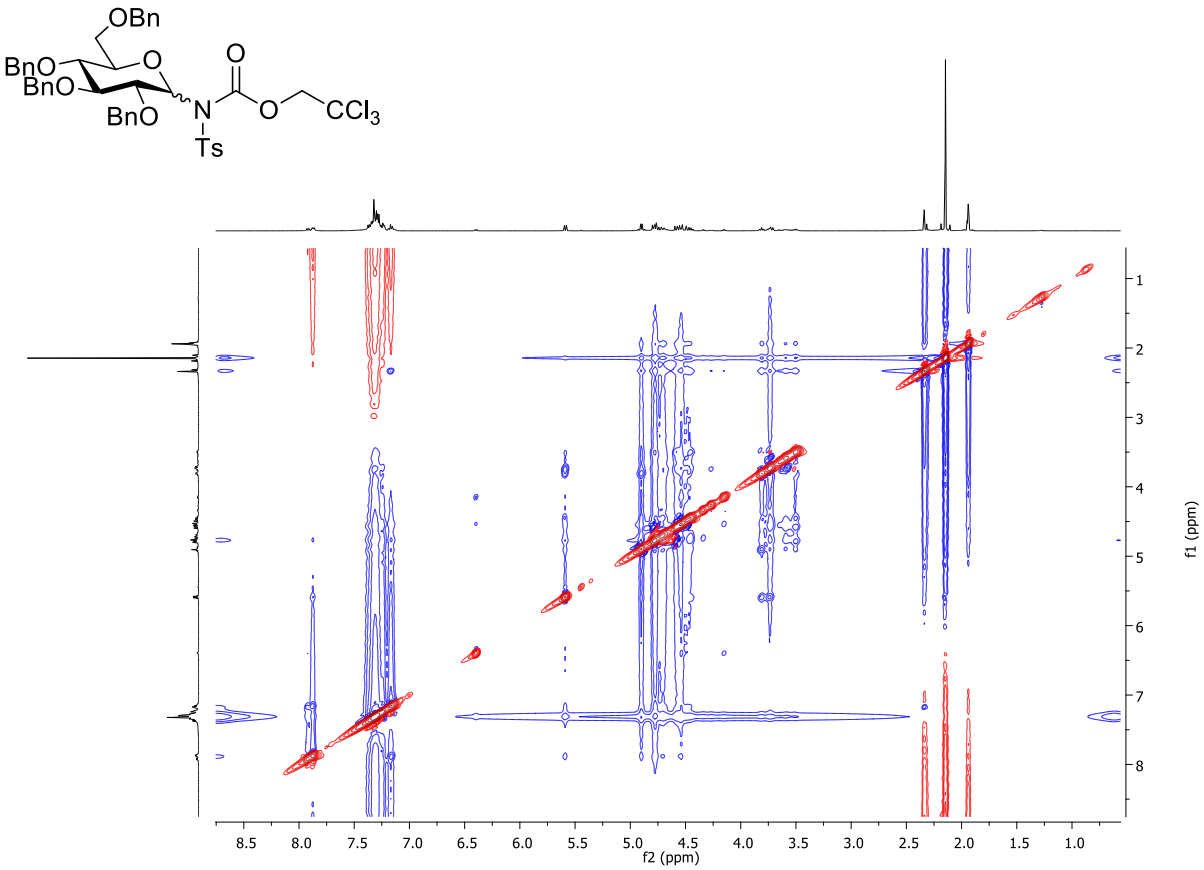
1D Selective Gradient NOESY spectrum of **compound 2.22** (α/β 23:77) in $CDCl_3$ demonstrating correlations between H-1α and the coupled protons. The spectrum was recorded at 26.85°C.



1D Selective Gradient NOESY spectrum of **compound 2.22** (α/β 23:77) in $CDCl_3$ demonstrating correlations between H-1β and the coupled protons. The spectrum was recorded at 26.85°C.

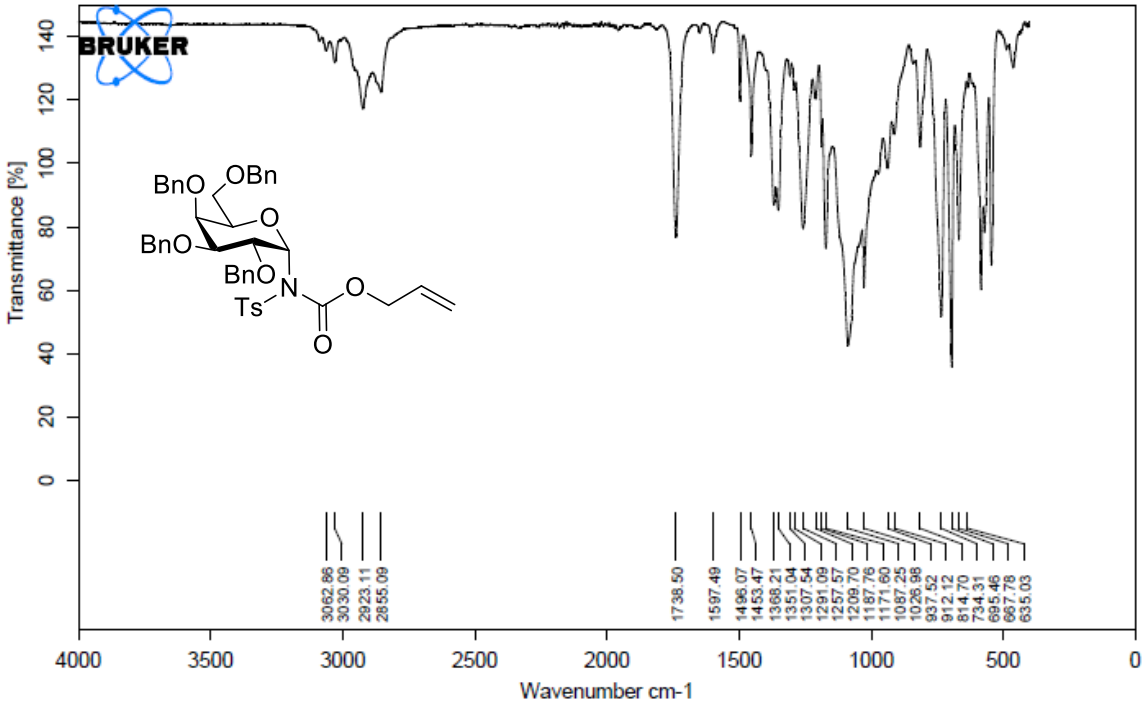


2D NOESY spectrum of **compound 2.22** (α/β 23:77) in $CDCl_3$ recorded at room temperature.

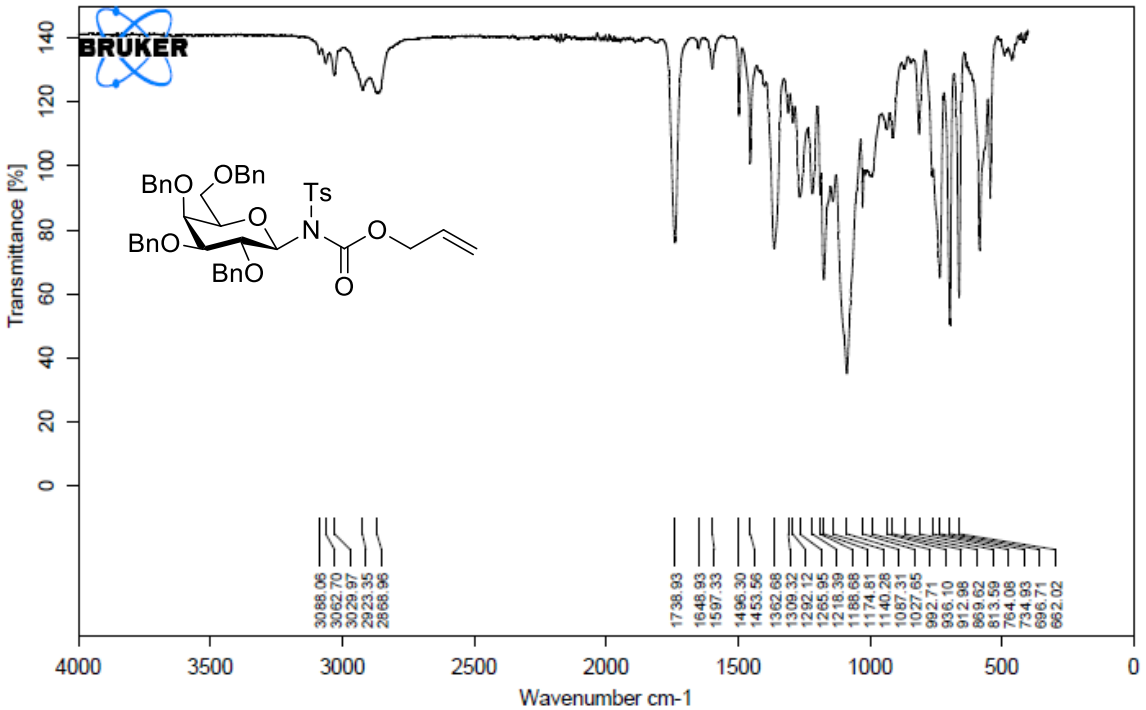


2.4.9. Appendix of IR Spectrum

Compound 2.24α



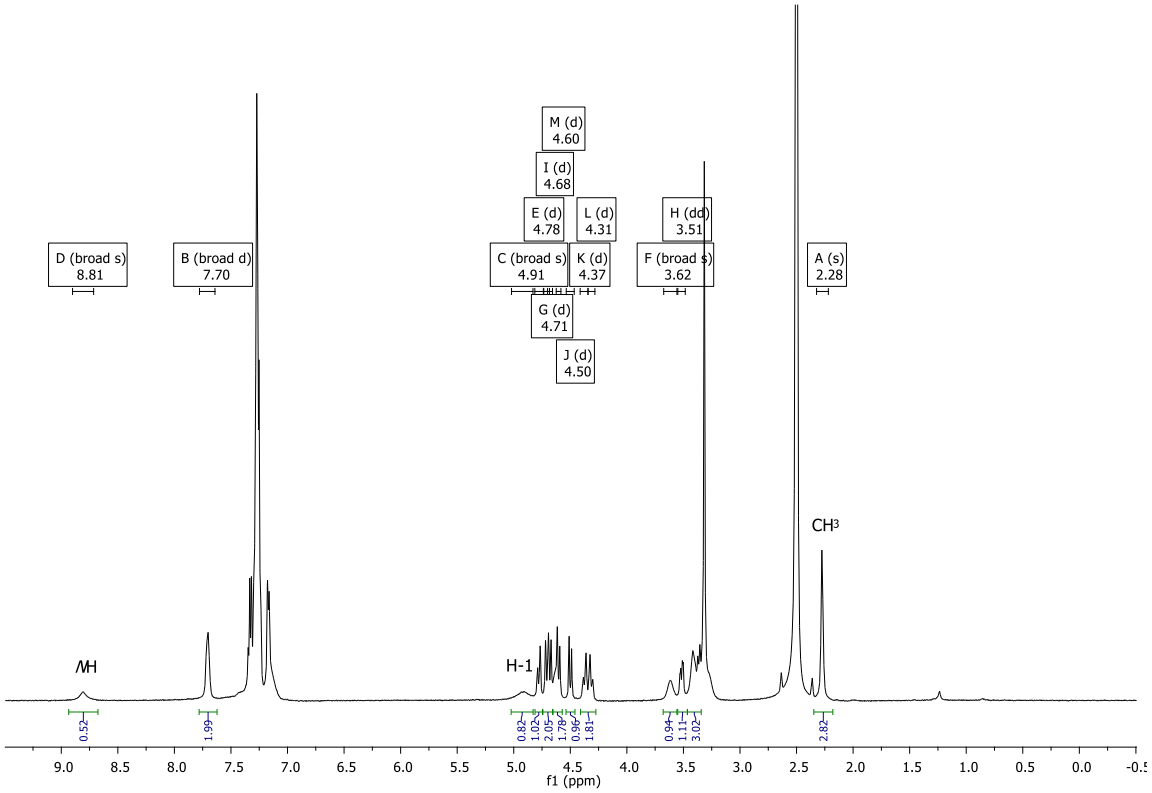
Compound 2.24β



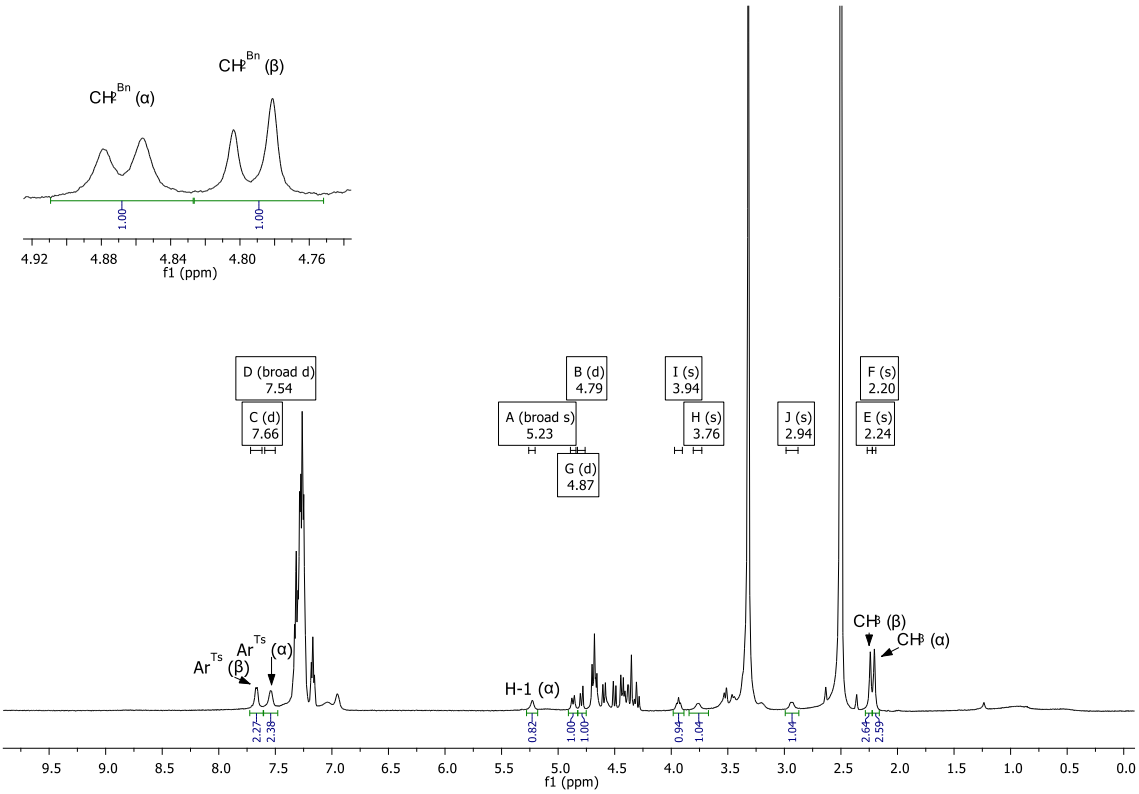
2.4.10. Appendix of Anomerization Studies

The compound **2.31β** (22.0 mg, 0.03 mmol) and DMSO-d_6 (0.7 ml) were placed in an NMR tube. Then, K_2CO_3 (8.0 mg, 0.06 mmol) was added at room temperature and ^{1}H-NMR was recorded directly. Subsequently, the NMR sample was heated at 50°C until no change in α/β ratio was observed (96 h). The anomerization process was monitored every 24 h by ^{1}H-NMR.

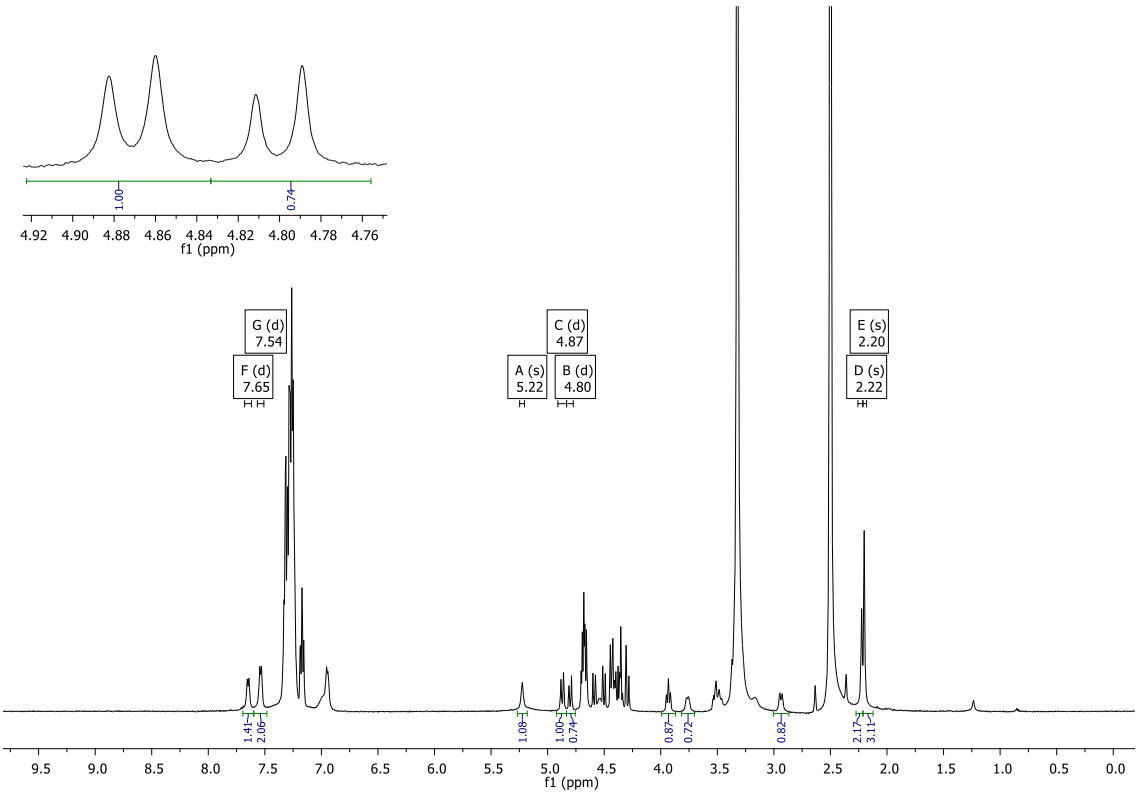
Spectrum of **compound 2.31** recorded directly after addition of K_2CO_3 at room temperature.



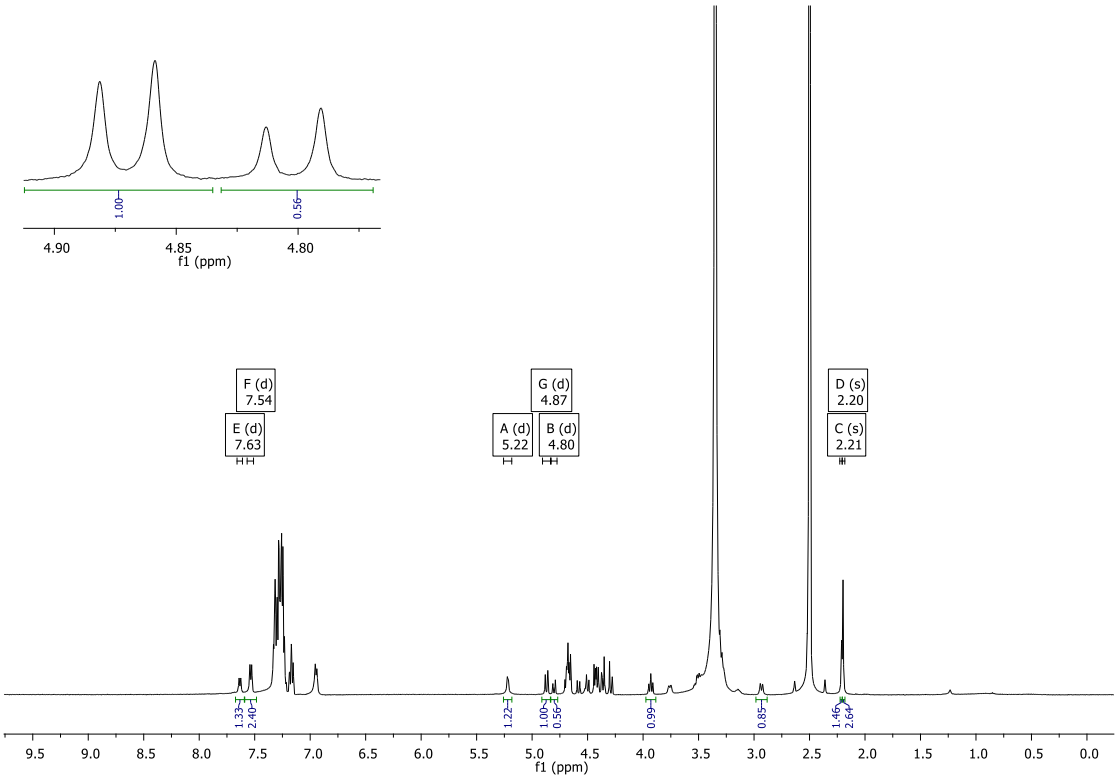
Spectrum of **compound 2.31** recorded after 24 h of heating at 50°C.



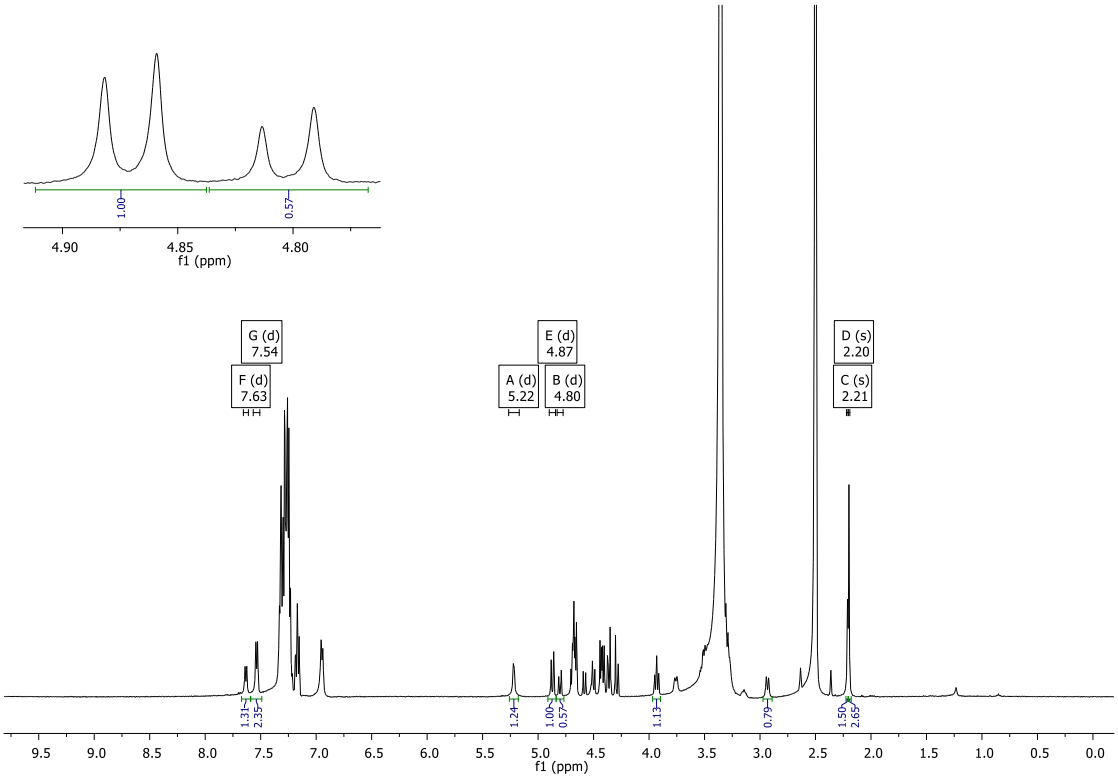
Spectrum of **compound 2.31** recorded after 48 h of heating at 50°C.



Spectrum of **compound 2.31** recorded after 72 h of heating at 50°C.



Spectrum of **compound 2.31** recorded after 96 h of heating at 50°C.



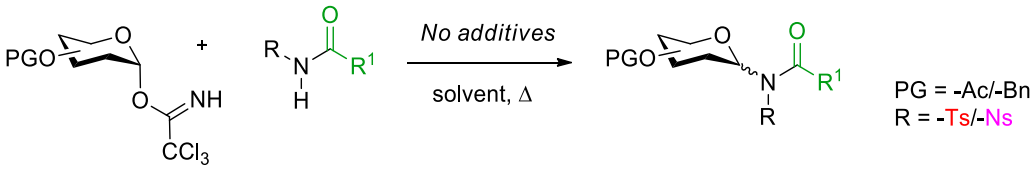
CHAPTER III

Self-promoted Glycosylation: Synthesis of *N*-glycosyl Sulfonyl Amides

3.1. Introduction

A great variety of glycosyl amides are found in nature playing crucial roles in essential biological processes.[5] In addition, a vast number of non-natural glycoconjugates bearing the amide function reveal biological activity.[109,110,200,112] Among the naturally occurring compounds, *N*-linked glycoproteins are of great interest, due to their participance in biological events on the cell surface. To better understand how glycoprotein structure influences their functions, effective synthetic methodologies are required. One of the major challenges in the synthesis of *N*-glycopeptides is the control of stereoselectivity. Most of the reported approaches providing *N*-glycosyl amides employ unstable glycosyl amines which rapidly undergo the anomerization leading to the troublesome in separation anomeric mixtures.[201,120,202] Furthermore, the application of the established methods is also limited by difficulties in preparing the starting materials, expensive catalysts, and coupling agents.[132,136,43,203]

In order to circumvent the common issues related to the synthesis of glycosyl amides, we aimed to develop a novel synthetic strategy featuring the stereoselective, self-promoted *N*-glycosylation method, followed by the orthogonal deprotection. The concept was based on the previously described approach. To provide access to the glycosyl amide derivatives, the general structure of the acceptors was modified by replacing the carbamate function with the amide moiety (**Scheme 3.1**).



Scheme 3.1. Self-promoted *N*-glycosylation of *N*-sulfonyl amides.

The established *N*-glycosylation method employs the acid-labile TCA donors which can be activated by the sufficiently acidic acceptors bearing the electron-withdrawing sulfonyl group. Thus, the *N*-glycosidic bond formation requires no additives such as catalysts or promoters. The two-component glycosylation might be a particularly advantageous alternative for the reported methods in the synthesis of the glycosyl amides. Importantly, the developed *N*-glycosylation method addresses the stereochemical issue. When α-TCA donors were used, the glycosylations resulted in stereoselective formation of various β-*N*-glycosyl sulfonyl amides including even more

complex molecules such as disaccharides and asparagine derivatives. In an attempt to obtain the target *N*-glycosyl amides, sulfonyl groups deprotection reactions were performed. However, the complete or significant amide bond cleavage was observed under the applied conditions. The deprotection procedure needs therefore optimization, which might be the subject of further investigations.

3.2. Results and Discussion

The first part of this section will focus on the self-promoted *N*-glycosylation, starting from test reactions with a simple glucosyl donor and the *N*-sulfonyl acetamide acceptors. Subsequently, the screening conditions will be discussed which allowed us to establish the optimized procedure, further applied to obtain a series of more complex *N*-glycosides. Lastly, our attempts to remove the sulfonyl function selectively will be described.

The scope of various glycosyl donors (**Figure 3.1**) was studied in a series of *N*-glycosylations. In order to study the stereospecificity of the self-promoted glycosylation, the α- and β-configured glucosyl TCAs (**1.7α** and **1.7β**) were reacted. Glycosylations employing the TCAs equipped with different protecting groups enabled us to assess their impact on the donor reactivity. In addition, the introduction of the acetyl group in the second position could enhance the β-selectivity, due to the neighboring group participation. To extend the set of donors with more complex TCAs, we used two disaccharide donors derived from the cellobiose (**3.4α** and **3.5α**). Also, two glucosamine derivatives **3.1α** and **3.2α** were investigated, due to their potential utility in the synthesis of the asparagine-linked *N*-glycosyl amides occurring in nature.

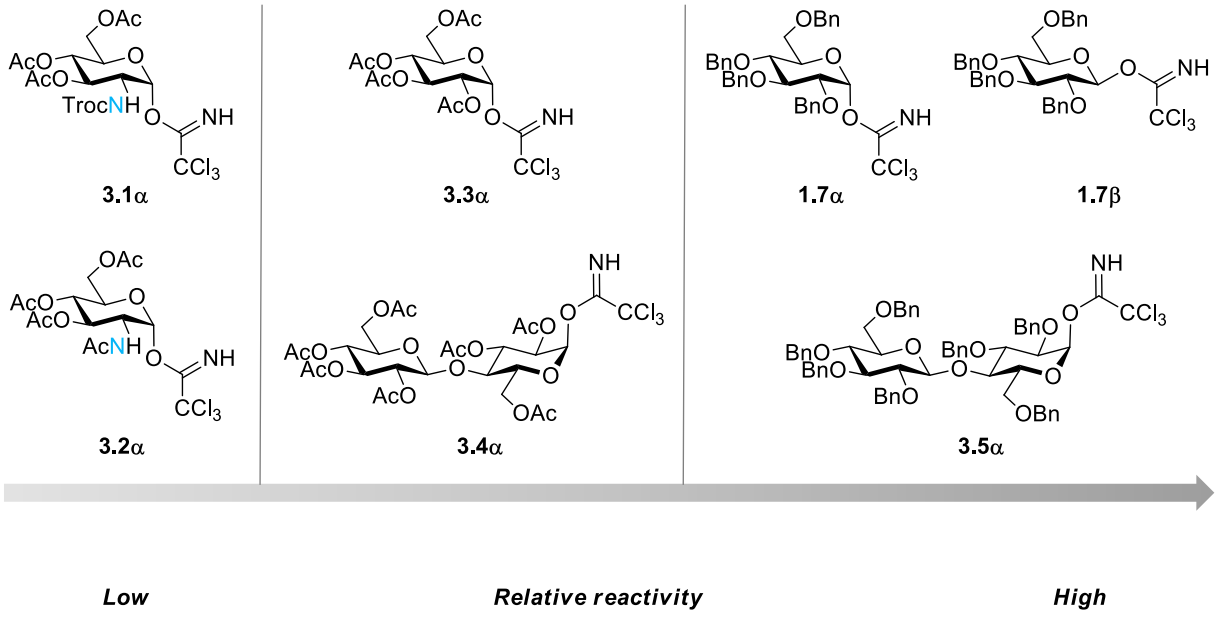
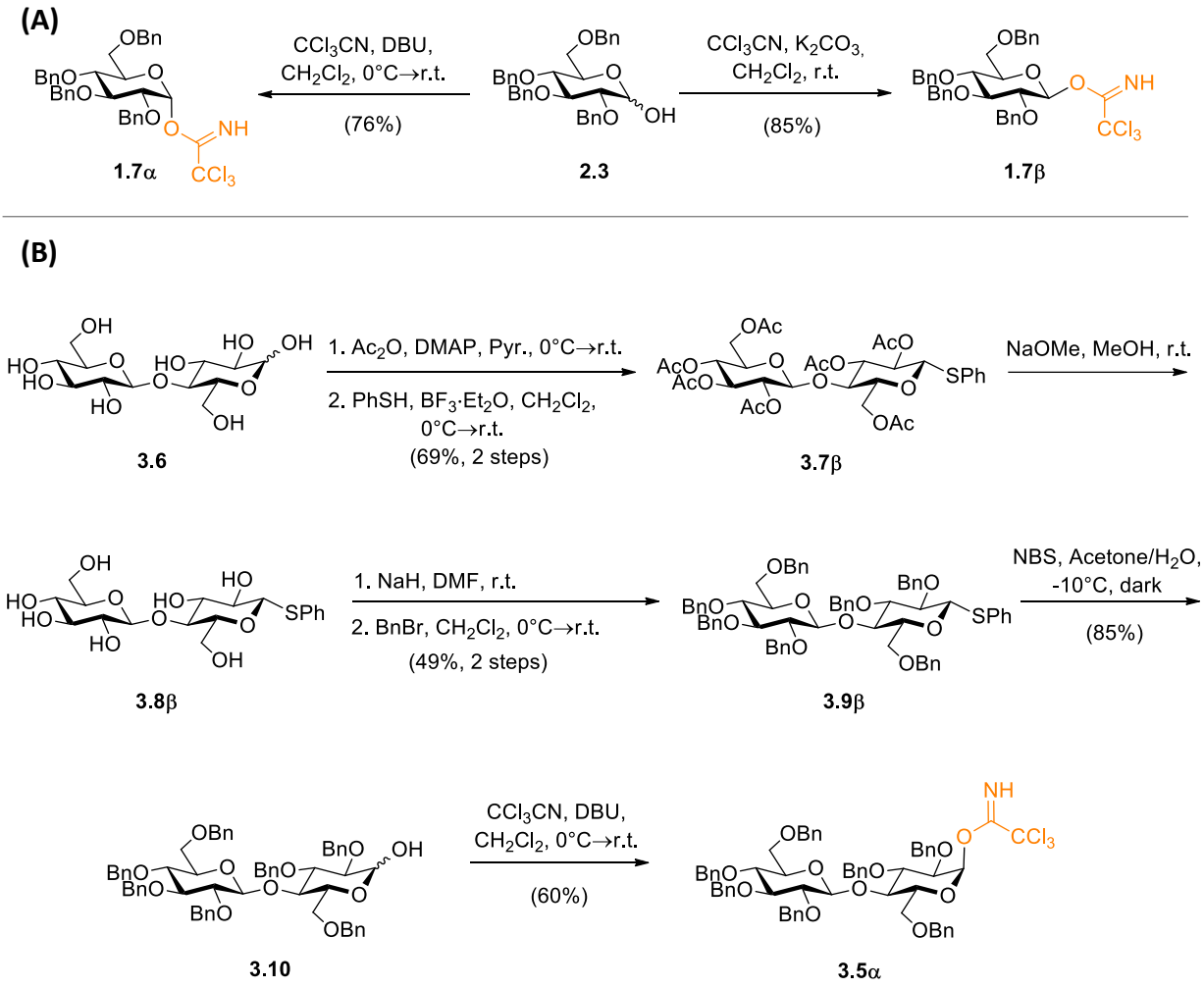


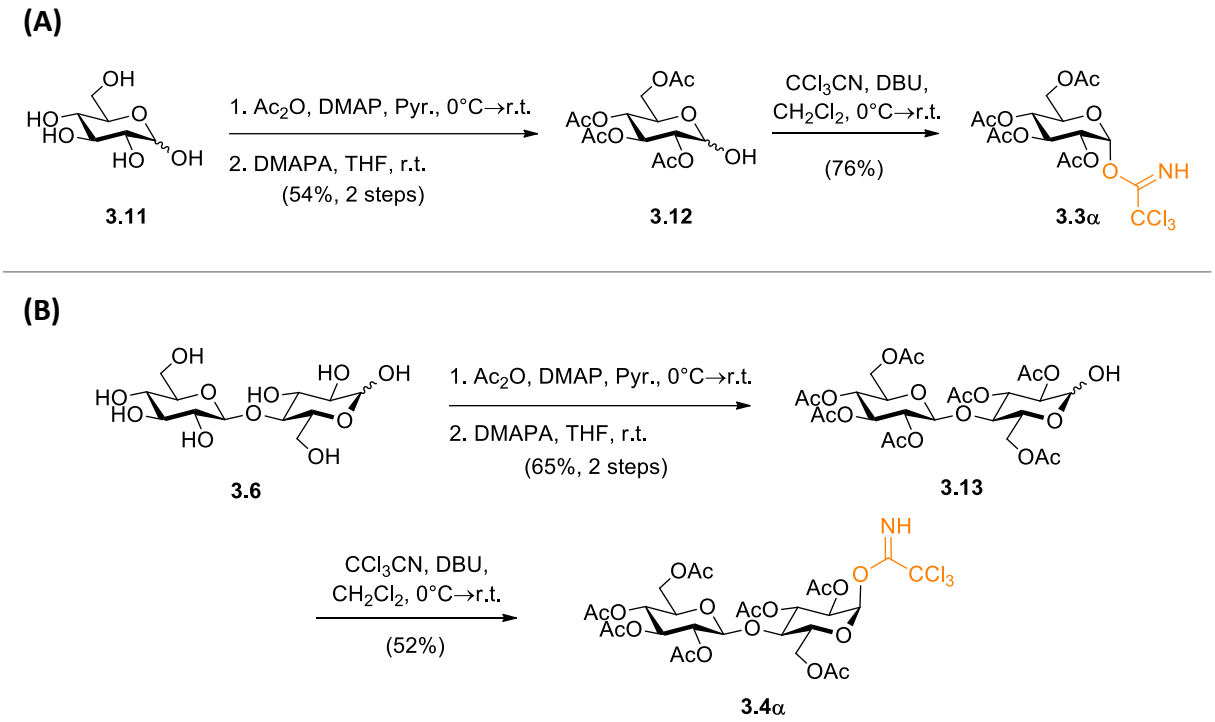
Figure 3.1. Glycosyl donors used in a series of self-promoted glycosylations with *N*-sulfonyl amides.

As discussed in chapter 1, the TCA glycosyl donors are synthesized from the corresponding hemiacetals in a reaction with trichloroacetonitrile under basic conditions. All hemiacetals used in this study were prepared beforehand, with the exception of glucose derivatives. The synthetic routes of the benzylated donors are summarized in **Scheme 3.2**. Starting with the commercially available hemiacetal **2.3**, the glucosyl donors **1.7α** and **1.7β** were obtained stereoselectively in one step. The α-TCA was formed primarily upon the addition of DBU to the mixture of **2.3** and trichloroacetonitrile.[204] The same reaction catalyzed by K_2CO_3 instead of DBU gave rise to the β-donor as the major product.[35] Both glucosyl TCAs were obtained in high yields. The disaccharide donor **3.5α** was synthesized in seven steps, commencing from D-cellobiose (**3.7**). First, the starting material was fully protected using acetic anhydride and DMAP in pyridine.[205] The following Lewis acid-promoted glycosylation with thiophenol afforded the thioglycoside **3.7β** in a high yield and β-selectivity (89%, α/β 1:>9).[206]



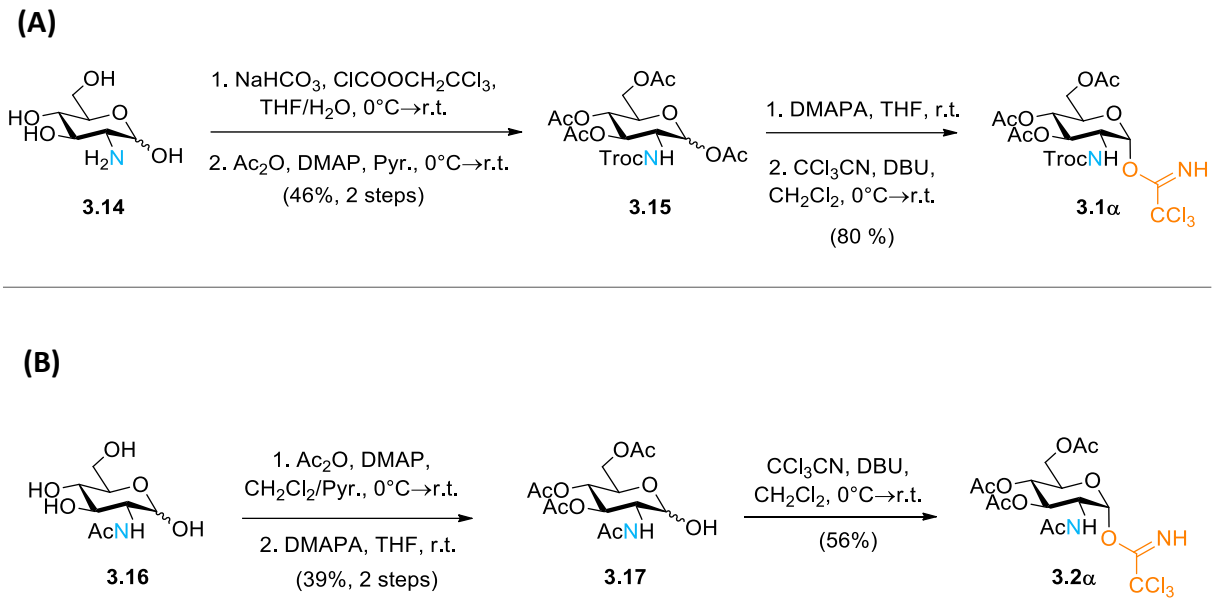
Scheme 3.2. Synthesis of benzylated glucosyl (A) and cellobiosyl (B) TCA donors.

Further removal of the acetates under Zemplén's conditions facilitated the deprotected thioglycoside **3.8β** which was used in the next step without purification.[206] Treatment of compound **3.8β** with NaH and subsequent benzylation with benzyl bromide furnished the derivative **3.9β** in a moderate yield (49%, over 2 steps).[207] Then, compound **3.9β** was converted to the corresponding hemiacetal **3.10** employing NBS as the oxidant (85%).[120] Final functionalization at the anomeric position was attained by reaction of **3.10** with trichloroacetonitrile and DBU to give the α-configured donor in a yield of 60%.[206] Although the product contained small amounts of an impurity (8%). The acetylated glucosyl and cellobiosyl TCAs were synthesized in accordance with the procedures described in **Scheme 3.3**. Synthesis of the glycosyl donor **3.3α** involved three steps and began with acetylation of D-glucose, leading to the peracetylated derivative in a good yield (71%).[208] Selective removal of the anomeric acetyl protecting group was performed following Jensen's procedure to provide the desired hemiacetal **3.12** (76%).[209] Compound **3.12** was then transformed into the target α-TCA donor **3.3α** with trichloroacetonitrile and DBU in a 76% yield.[210] The disaccharide α-TCA donor **3.4α** was synthesized from D-cellobiose according to the same sequence in an overall yield of 34% over three steps.[205,209,211]



Scheme 3.3. Synthesis of acetylated glucosyl (A) and cellobiosyl (B) TCA donors.

As outlined in **Scheme 3.4**, the protected glucosamine derivatives **3.1α** and **3.2α** were synthesized from D-glucosamine and *N*-acetyl-D-glucosamine in four and three steps respectively. Likewise, the synthetic routes involve modifications such as acetylation, anomeric deprotection and conversion to the corresponding TCA.[209,212–215] Preparation of the *N*-Troc-protected derivative **3.1α**, required an additional chemoselective protection of the amino function using 2,2,2-trichloroethyl chloroformate at the presence of base.[212] The four-step synthesis gave rise to the α-configured *N*-Troc-protected TCA **3.1α** in a 37% overall yield, while the GlcNAc donor **3.2α** was obtained in a yield of 22% over three steps.



Scheme 3.4. Synthesis of glucosamine-derived *N*-Troc-protected (A) and GlcNAc (B) TCA donors.

To study the self-promoted *N*-glycosylation in more detail, a set of five sulfonyl amide acceptors **3.18-3.22** with various functional groups were utilized (**Figure 3.2**). The general structure of the acceptors was analogous to the previously studied sulfonyl carbamates **2.13-2.17**. Similarly, in an attempt to provide acidity, sulfonyl substituents were installed serving as the electron-withdrawing temporary protecting groups. To diversify the scope of electron-poor amides, we selected two alternative sulfonyl substituents, namely tosyl and nosyl groups. The reasoning behind this was that these functions can be removed selectively under different conditions. In addition, the nosyl group has a stronger electron-withdrawing character than the tosyl substituent. Based on our previous pK_a measurements, the nosylcarbamates reveal superior acidic properties compared to their tosylated counterparts (**Figure 3.2**).

Thus, we envisioned that the employed sulfonyl amides would also vary in acidity which should influence their reactivity in glycosylation with the acid-labile TCA donors. To investigate, whether the nosylamides are more prone to react, we applied two pairs of sulfonyl amides with almost identical structures differing in the sulfonyl rest. We also studied if the self-promoted *N*-glycosylation depends on the size of the acceptor, using simple sulfonyl acetamides and more sterically hindered asparagine derivatives. The choice of asparagine acceptors as the more complex reactants seemed to be obvious, considering the potential application of the glycosylation method for the synthesis of *N*-glycopeptides. The sulfonyl acetamides were used as the model acceptors in the preliminary glycosylation studies and to optimize the reaction conditions.

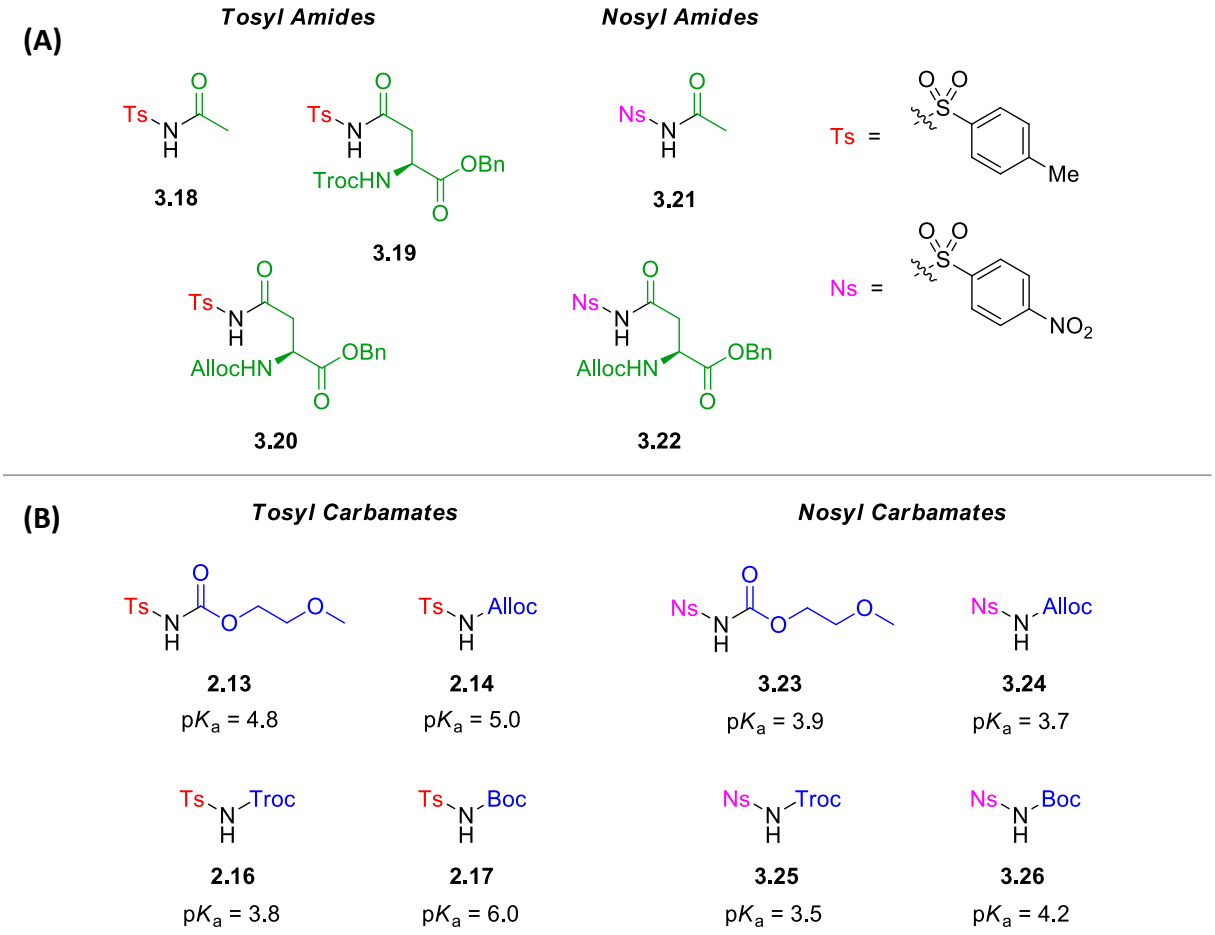
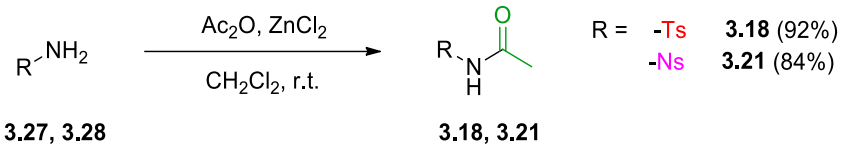


Figure 3.2. *N*-sulfonyl amides used in a series of self-promoted *N*-glycosylations (A). pK_a-values of the previously employed for self-promoted *N*-glycosylations *N*-sulfonyl carbamates (B).[***56]

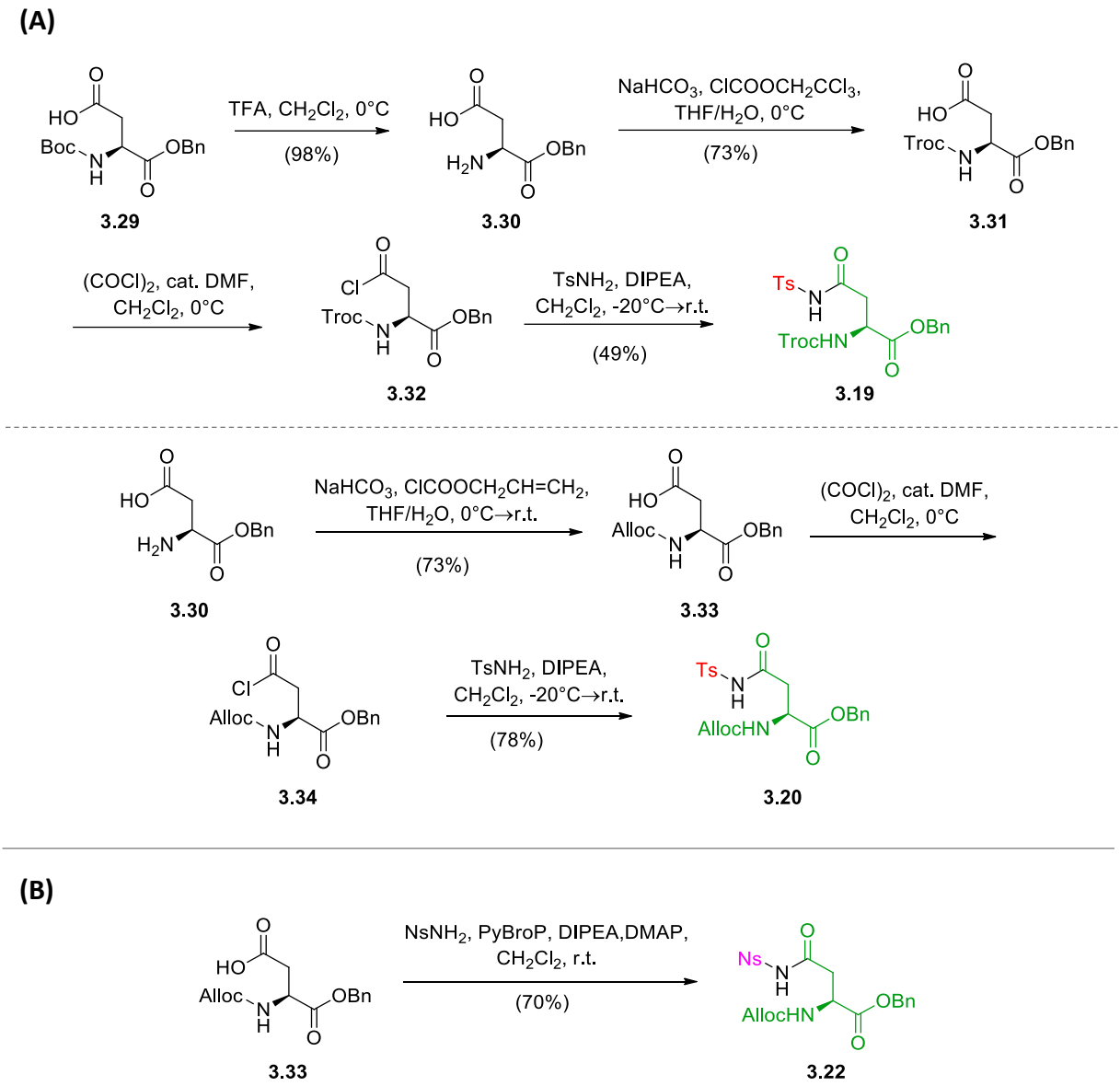
*** pK_a-values were determined from titration experiments performed by Ph.D. Michael Martin Nielsen.

Simple acceptors **3.18** and **3.21** were synthesized in a single step, by the *N*-acylation of the sulfonamide with acetic anhydrate in the presence of a catalytic amount of $ZnCl_2$ (**Scheme 3.5**).[216] Both tosyl- and nosyl derivatives were obtained in high yields of 92% and 84%, respectively.



Scheme 3.5. Synthesis of *N*-sulfonyl acetamide acceptors.

As shown in **Scheme 3.6**, synthesis of the asparagine acceptors commenced from the commercially available, *N*-Boc-protected starting material **3.29**. Since the self-promoted *N*-glycosylation requires acidic acceptors for the TCA activation, it seemed reasonable to exchange the Boc protecting group with a less acid-sensitive moiety. Therefore, the synthesis started from the quantitative Boc deprotection under acidic conditions.[217] The following reactions of **3.30** with two different chloroformates in the presence of base led to the *N*-Troc- and *N*-Alloc-protected derivatives **3.31** and **3.33** in equal yields of 73%. Subsequently, these compounds were converted to the corresponding acyl chlorides **3.32** and **3.34** which were used in the further step without purification. Treatment of the acyl chlorides with *p*-toluenesulfonamide and DIPEA as a base facilitated the target tosylated asparagine acceptors **3.19** and **3.20**. Likewise, the same synthetic strategy was employed for the preparation of the nosylated acceptor. However, the last step did not provide the desired compound. Consequently, we modified the synthetic route starting from the carboxylic acid derivative **3.33**. Our initial attempts to install the nosyl group, namely coupling using EDC in the presence of base and conversion of **3.33** to the corresponding anhydride, followed by the reaction with *p*-nitrobenzenesulfonamide were unsuccessful. Finally, sufficient activation of the carboxylic acid was achieved by the addition of the less commonly used PyBroP coupling agent. The reaction of **3.33** with *p*-nitrobenzenesulfonamide promoted by the phosphonium salt under basic conditions furnished the final nosylderivative **3.22** in 70% yield.



Scheme 3.6. Synthesis of asparagine-linked tosylated (A) and nosylated (B) acceptors.

With the sets of TCA donors **1.7α**, **1.7β**, **3.1α-3.5α** and sulfonyl amide acceptors **3.18-3.22** in hand, we began our investigation into the self-promoted *N*-glycosylation. Initially, we applied the previously established glycosylation procedure used for the synthesis of the carbamate-protected *N*-glycosides (**Figure 3.3**). While the glycosylation between the benzylated α-glucosyl donor **1.7α** and the tosylcarbamates proceeded smoothly under mild conditions (12-24 h), the same donor reacted significantly slower with the tosylamide acceptor **3.18**. Based on the TLC and crude ^{1}H-NMR spectrum, a full conversion was achieved after 48 hours. In addition, the reaction resulted in a mixture of three main glycosylation products bearing both tosyl and acetamido groups. Moreover, it was found that the glycosylation led to the hemiacetal and glycosyl trichloroacetamide byproducts (**2.3** and **3.36**) in a prominent

amount presumably due to the poor nucleophilicity of the acceptor. Since the glycosylation products revealed similar polarity, separation by column chromatography was unsuccessful providing a mixture of glycosides in a yield of 40%.

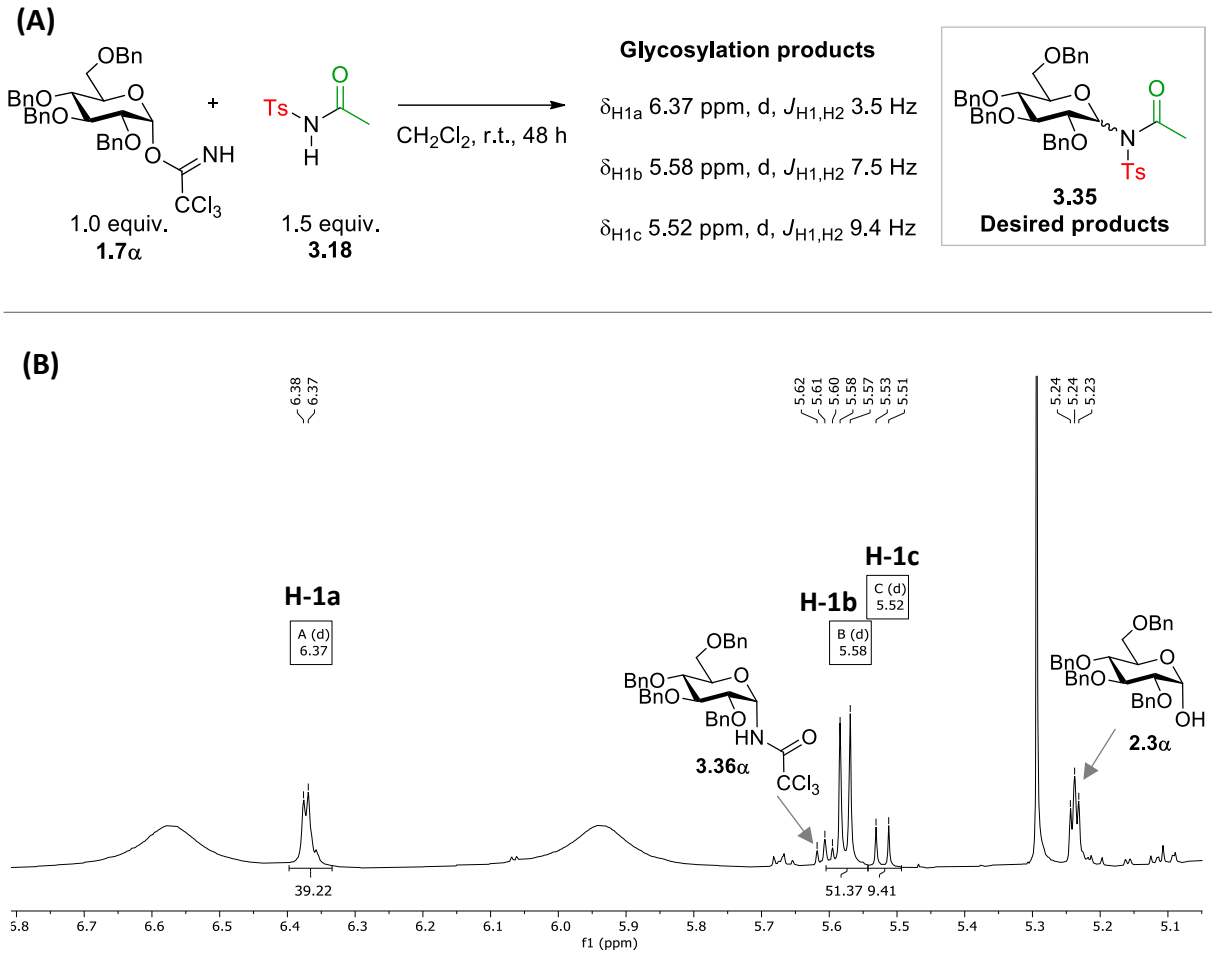


Figure 3.3. A) Preliminary self-promoted *N*-glycosylation with the glucosyl donor **1.7α** and the tosyl amide **3.18**. B) The anomeric region of the crude ^{1}H-NMR spectrum recorded at r.t. in $CDCl_3$.

Glycosylation using the same α-glucosyl donor **1.7α** and nosylamide acceptor **3.21** was investigated next to compare the reactivity of *N*-sulfonyl acetamides (**Figure 3.4**). To overcome the limitations of low acceptor solubility in CH_2Cl_2, glycosylation was carried out in refluxing solvent. As expected, the reaction time was shorter (12 h) compared to the preliminary glycosylation with **3.18** which could be related to the heating and superior reactivity of the nosyl acceptor. Crude NMR experiments revealed that the reaction led to the three major glycosylation products with aryl and acetamido substituents, similar to the previous glycosylation. Most importantly, these products were obtained in a different ratio compared to

the tosyl-derivatives. The undesired formation of the hemiacetal and trichloroacetamide (**2.3** and **3.36**) as byproducts was also observed in the crude ^{1}H-NMR spectrum, although not in vast amounts. Further attempts to isolate pure glycosylation products by column chromatography met with no success yielding a mixture of glycosides in a 25% yield. In addition, the predominant glycoside turned out to be relatively unstable under the purification conditions, degrading mostly to the hemiacetal and another unidentified compound. The analogous decomposition did not occur in the case of the tosyl-derivative. Such discrepancy in stability between the main tosylated and nosylated products could originate from the more electron-withdrawing nature of the nosyl substituent.

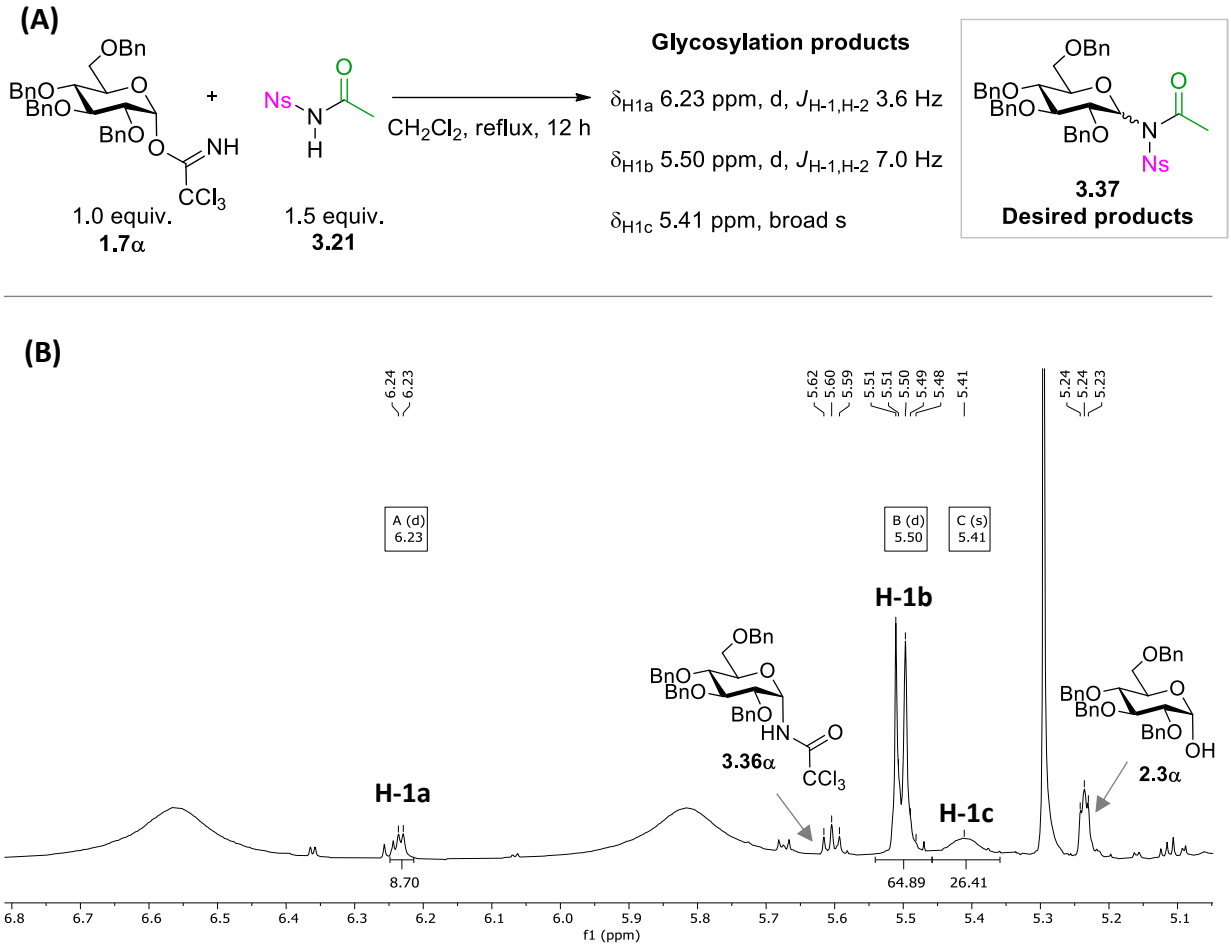


Figure 3.4. A) Self-promoted *N*-glycosylation with the glucosyl donor **1.7α** and the nosyl amide **3.21**. B) The anomeric region of the crude ^{1}H-NMR spectrum recorded at r.t. in $CDCl_3$.

Continuing our studies, we investigated how temperature influences the glycosylation (**Figure 3.5**). Due to the higher boiling point, 1,2-dichloroethane was chosen as a solvent instead of the similar in structure and polarity CH_2Cl_2. To compare the reactivity of the α-

glucosyl donor **1.7α** at different temperatures, we used the same tosylamide acceptor **3.18** as for the initial glycosylation. Unsurprisingly, increasing the temperature to 80ºC significantly shortened the reaction time (3 h). A mixture of the three tosylamide derivatives was again obtained, albeit in a different ratio compared to the reaction carried out at room temperature. It was found that higher reaction temperature favored the formation of glycosides with larger coupling constants for the anomeric protons whereas, under milder conditions the reaction occurred with a higher degree of selectivity toward the product with smaller $^{3}J_{H1,H2}$ value. Moreover, a pronounced change in the ratio of glycosides with high *J*-couplings between H-1 and H-2 was observed, from 85:15 to 67:33. Noteworthy, only trace of byproducts such as hemiacetal and trichloroacetamide (**2.3** and **3.36**) were found in crude ^{1}H-NMR. In addition, increasing the reaction temperature improved the yield to 83%. The isolated mixture of three compounds was further studied by NMR and IR to elucidate the structures of glycosylation products with a focus on the two predominant glycosides.

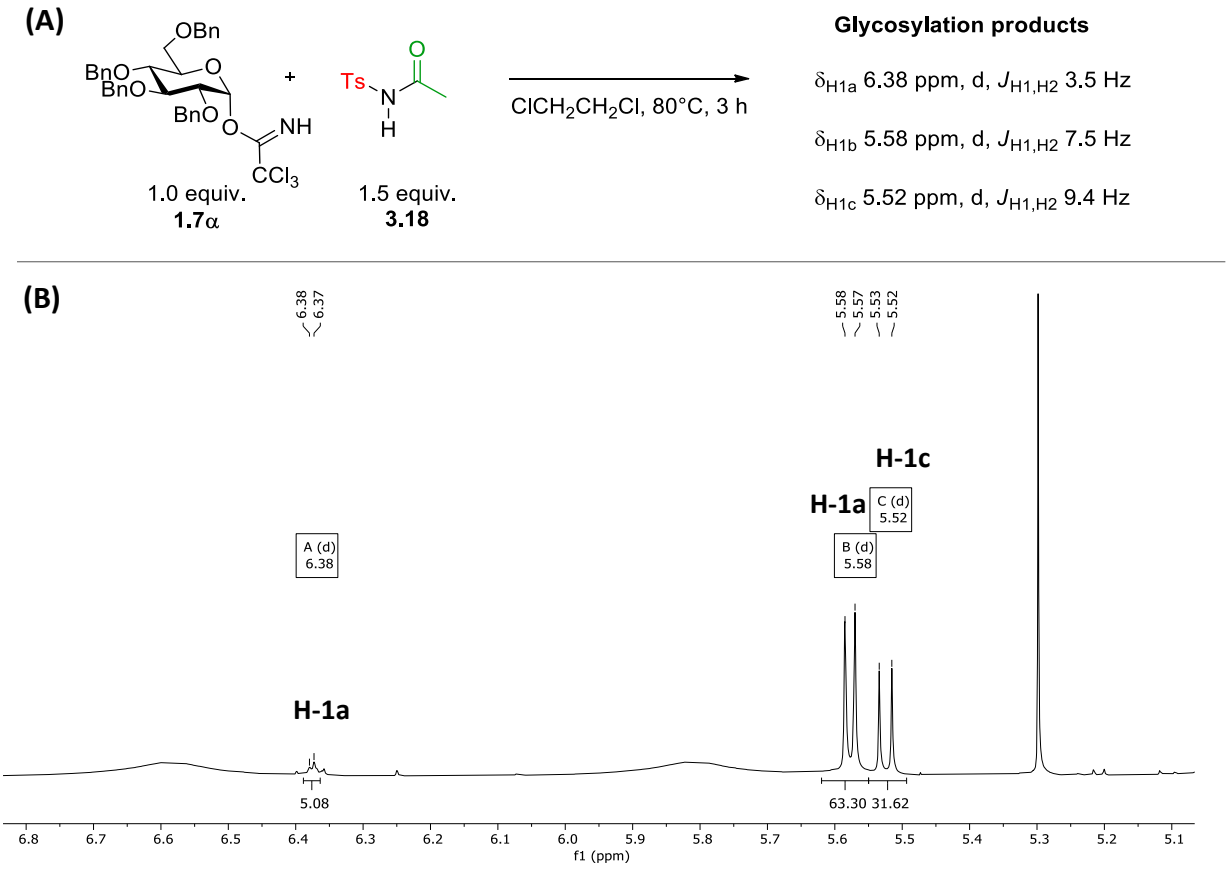


Figure 3.5. A) Self-promoted *N*-glycosylation with the glucosyl donor **1.7α** and the tosyl amide **3.18** at the elevated temperature. B) The anomeric region of the crude ^{1}H-NMR spectrum recorded at r.t. in $CDCl_3$.

By chemical shifts of the anomeric protons and $^{3}J_{H1,H2}$ values, it was concluded that the minor product revealing a small coupling constant is likely α-linked, while the other two were expected to be β-glycosides. Nevertheless, in some cases, *cis*-glycosides were found to adopt unusual conformations with relatively high coupling constants between H-1 and H-2. For instance, previously studied *N*-glycosyl carbamates adopting a skew-boat conformation with $^{3}J_{H1,H2}$ in range of 8.0-8.2 Hz. Thus, formation of more than one α-glycoside could not be entirely excluded. We next compared HSQC spectra of products obtained in the glycosylation employing the tosylamide acceptor with the spectrum recorded for the anomeric mixture of *N*-*N*-glycosyl carbamates. Interestingly, HSQC experiments revealed significant differences in ^{13}C chemical shifts of the main anomeric carbon signals (**Figure 3.6**). Indeed, the unusual for *N*-linked carbohydrates downfield shifts were observed in the case of two glycosides suggesting that these derivatives could be the products of the undesired *O*-glycosylation. As a comparison, the HSQC spectrum of the previously studied *N*-glycosyl carbamates bearing the tosyl substituent is shown in **Figure 3.7**. In general, anomeric carbon signals of the carbamate-protected *N*-glycosides spanned from 82 to 87 ppm.

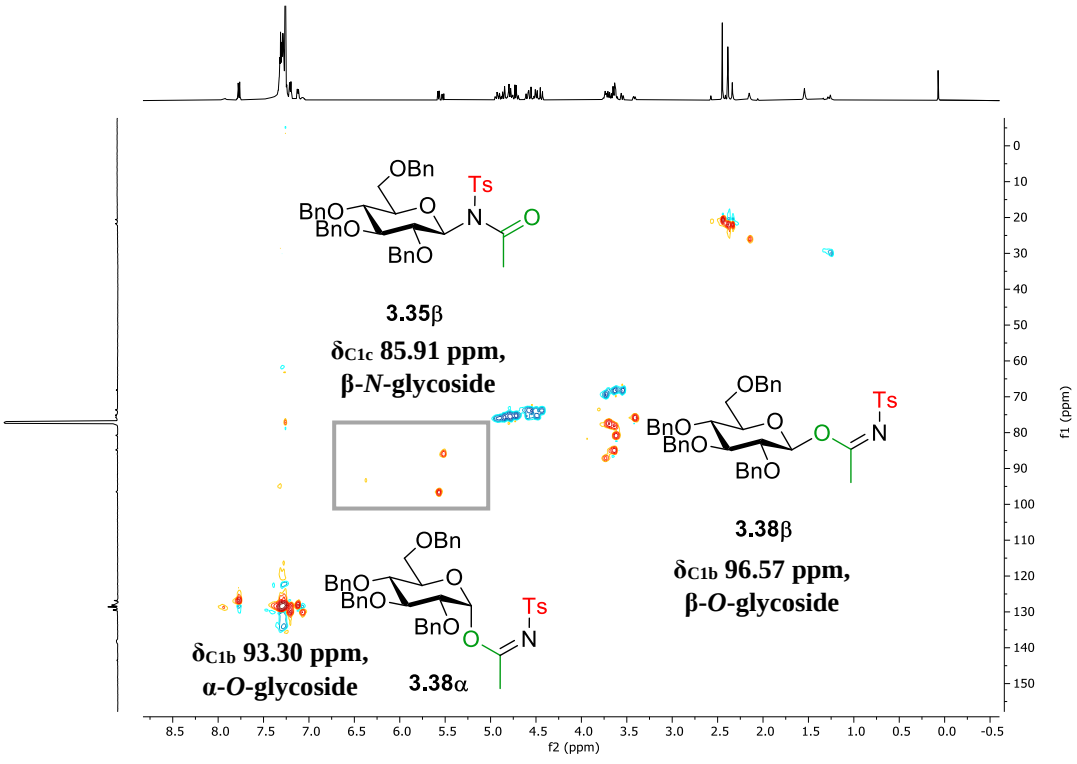


Figure 3.6. HSQC spectrum with the anomeric region indicated with a box. The spectrum was recorded at r.t. in $CDCl_3$ using the isolated mixture of glycosides obtained in the self-promoted glycosylation carried out at 80ºC.

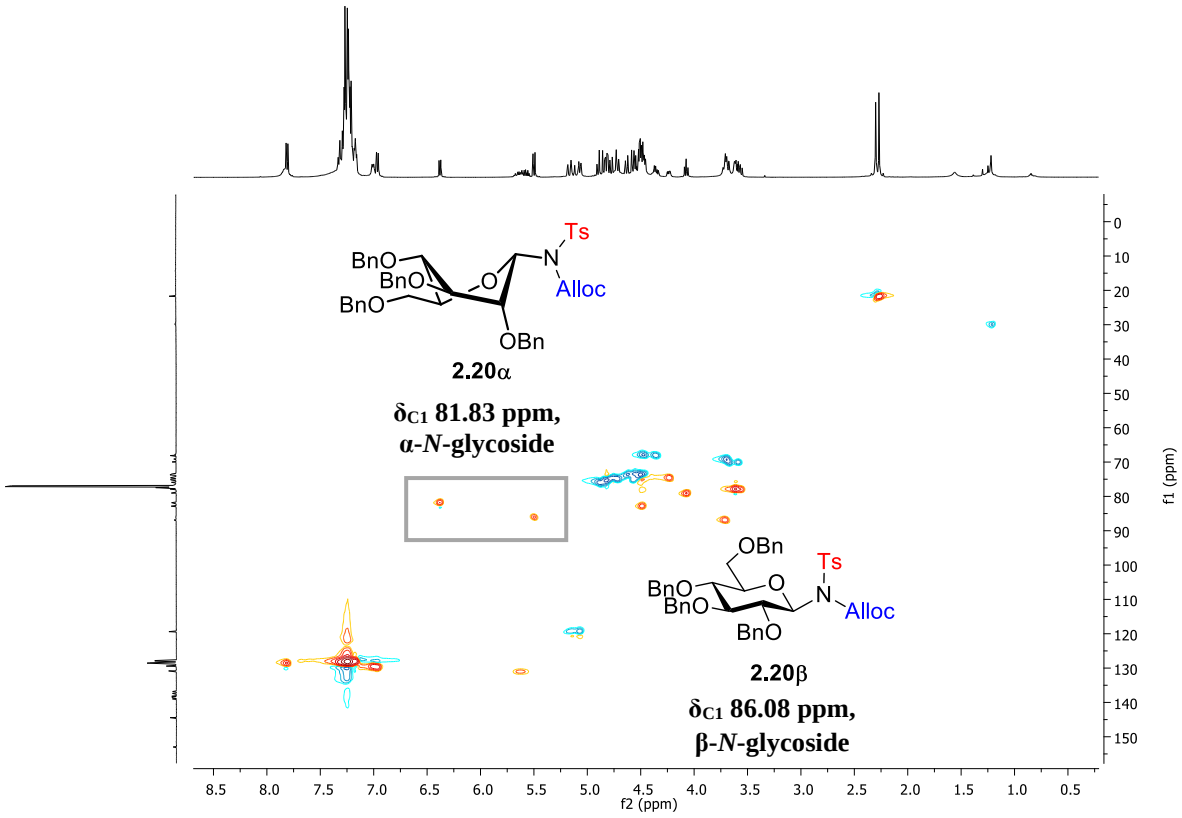


Figure 3.7. HSQC spectrum with the anomeric region indicated with a box. The spectrum was recorded at r.t. in $CDCl_3$ using the anomeric mixture of *N*-glycosides obtained in the self-promoted *N*-glycosylation with the glucosyl donor **1.7α** and the sulfonyl carbamate **2.14**.

To support the NMR data an IR spectrum was recorded for the same mixture of glycosylation products. In contrast to the IR spectra of *N*-glycosyl carbamates, two distinctive peaks were identified within the functional group region (~1715 cm^{-1}, ~1627 cm^{-1}) which were assigned to the carbonyl and carbon-nitrogen double bonds respectively (**Figure 3.8**). Considering the same range (1600-1750 cm^{-1}) in spectra recorded for carbamate-protected *N*-glycosides, only one pronounced peak around 1738 cm^{-1} was observed and attributed to the carbonyl bond.

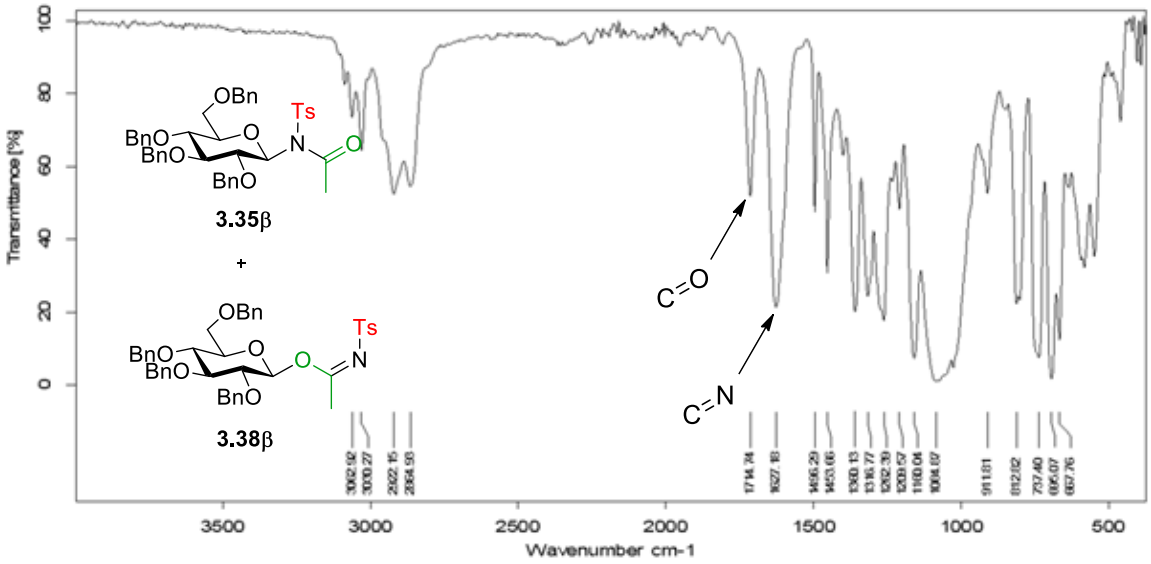
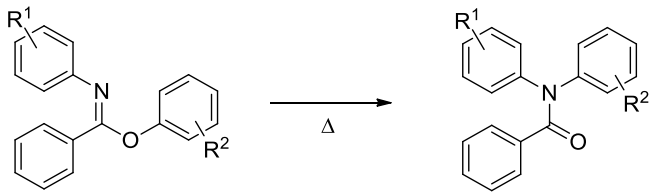


Figure 3.8. HSQC spectrum with the indication of the most characteristic signals within the functional group region. The spectrum was recorded at r.t. in $CDCl_3$ using the isolated mixture of glycosides obtained in the self-promoted glycosylation carried out at 80ºC.

On the basis of evidence from NMR and IR experiments, we concluded that the glycosylation carried out at 80ºC resulted mainly in the formation of isomeric 1,2-*trans*-glycosides. As discussed in the prior chapters, TCA glycosyl donors were found to rearrange to the corresponding trichloroacetamides typically as byproducts.[41,218,219] However, the amide formation from imidate has been known before the first application of glycosyl imidates.[220–223] An early example of such a conversion, referred to as the Chapman rearrangement, was demonstrated for aryl-*N*-arylbenzimidates (**Scheme 3.7**).[224,225] The formation of amides have been achieved at harsh high temperatures and/or using Lewis acids.[223–225] Although the rearrangement was shown to take place in various solvents, it is favored in the ones with higher polarity.[226]



Scheme 3.7. General representation of the classical Chapman rearrangement.[224,225]

In analogy to examples reported in literature, we envisioned that the obtained *O*-imidate glycosylation product could undergo the same type of rearrangement. Typically, the conversion of glycosyl TCAs to the isomeric trichloroacetamides have been observed as a side reaction in Lewis acid-promoted glycosylations. Nevertheless, the paramount goal of our investigations was to develop a self-promoted glycosylation with no need for any additives. Thus, we decided to prompt the rearrangement by using a polar solvent such as DMSO and increasing the temperature. In order to study the rearrangement, the isolated mixture of isomeric *O*- and *N*-glycosides was dissolved in dry DMSO-d_6 and heated at 110ºC for an hour. After this time, a ^{1}H-NMR spectrum was recorded which revealed a significant disparity in stability between the two major β-glycosides (**Figure 3.9**).

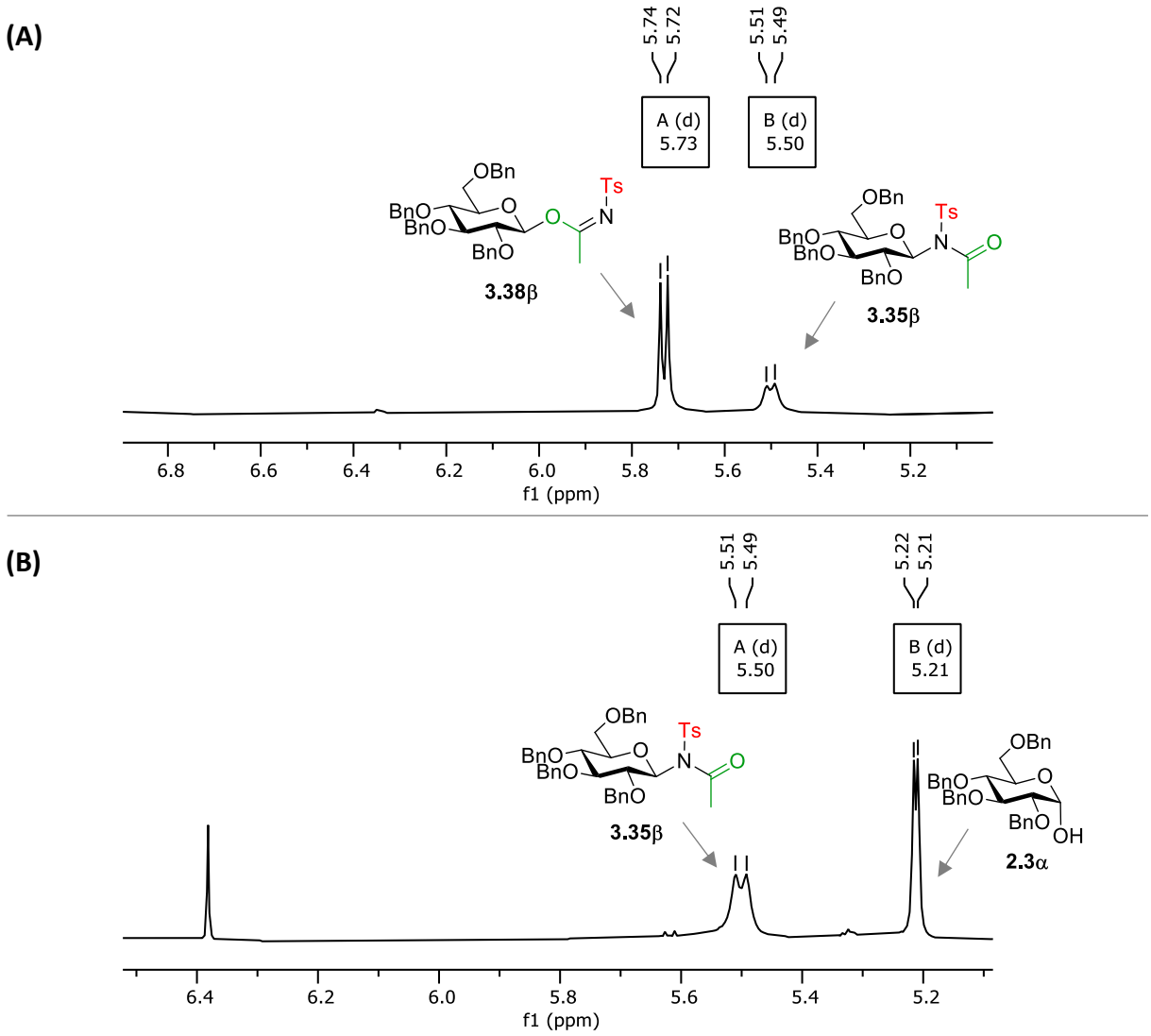


Figure 3.9. Heating experiment employing a mixture of glycosides obtained in the self-promoted glycosylation carried out at 80ºC and DMSO-d_6 as a solvent. Anomeric regions of the ^{1}H-NMR spectra recorded at r.t. in DMSO-d_6 before (A) and after (B) heating.

The NMR experiment carried out in DMSO-d_6 provided valuable information about the stability of the glycosylation products. The obtained data confirmed that the *O*-glycoside was more prone to hydrolysis compared to the isomeric *N*-glycoside. Therefore, it was reasonable to assume that the glycosylation reaction did indeed result in the formation of *O*-glycosyl imidate, which was expected to be less stable than the corresponding *N*-glycosyl amide. However, the experiment did not allow the desired rearrangement to be achieved. Consequently, the experiment was repeated using a less hygroscopic solvent, i.e., dry toluene (**Figure 3.10**). Since the rearrangement was found to proceed slower in less polar solvents, the heating time was increased to 24 h.

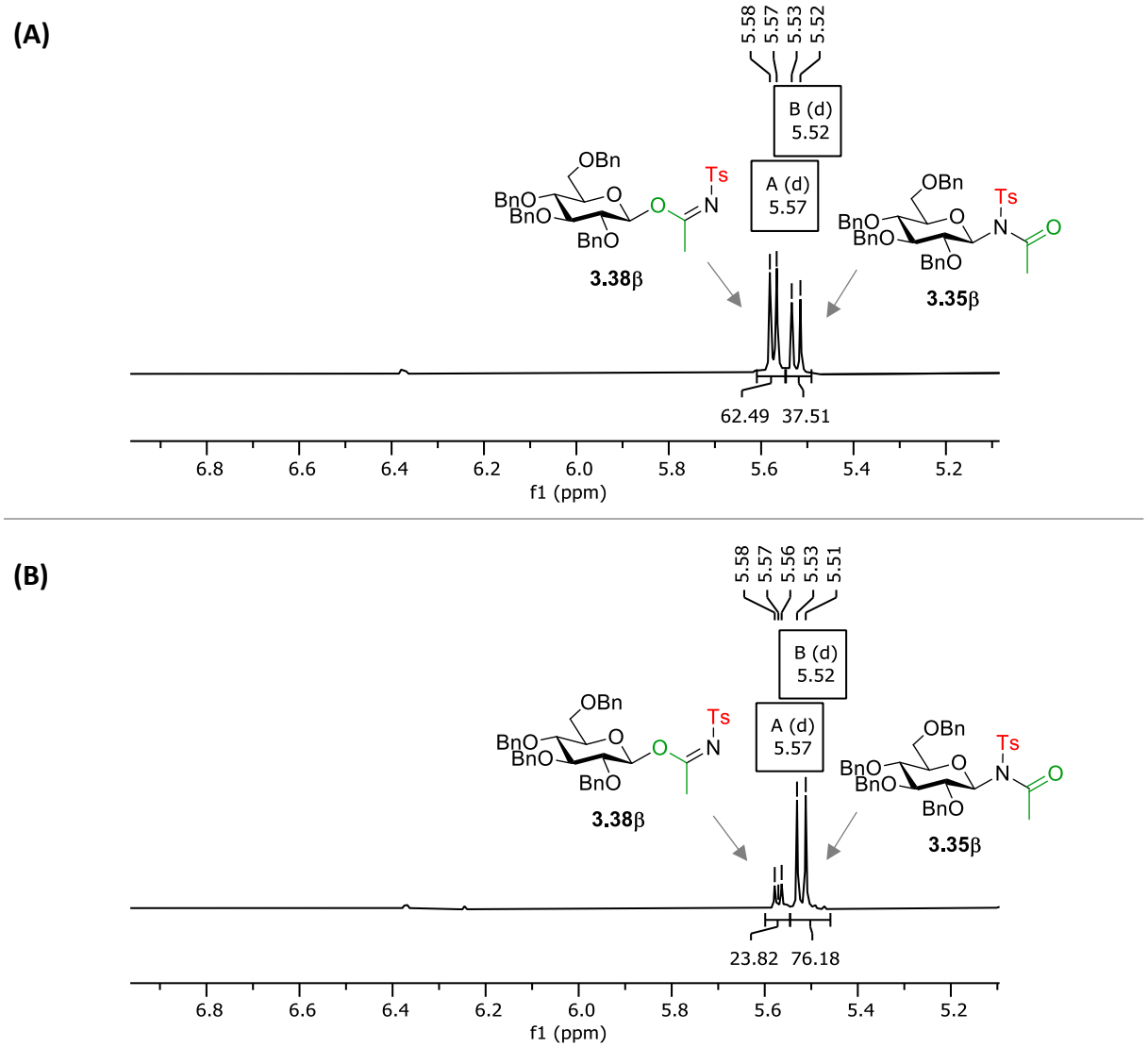
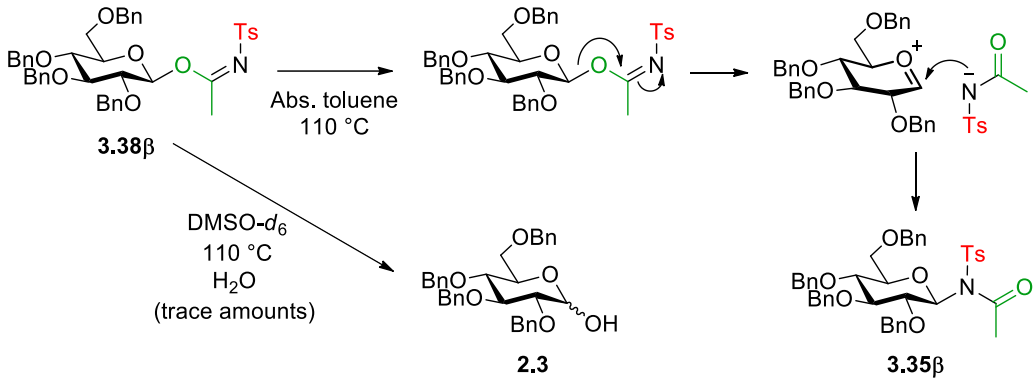


Figure 3.10. Heating experiment employing a mixture of glycosides obtained in the self-promoted glycosylation carried out at 80ºC and dry toluene as a solvent. Anomeric regions of the ^{1}H-NMR spectra recorded at r.t. in $CDCl_3$ before (A) and after (B) heating.

Subsequently, the resulting mixture was investigated by ^{1}H-NMR-spectroscopy to clarify whether the rearrangement occurred. As expected, the ratio between the *O*- and *N*-glycoside changed dramatically from 62:38 to 24:76 (**Figure 3.10**). Importantly, no additional signals appeared upon heating the sample. These results suggest that the varied ratio originated from the stereoselective rearrangement, excluding the decomposition. In conclusion, the experiment proved that the *O*-glycosyl imidates can be transformed to the thermodynamically more stable isomeric *N*-glycosyl amides at high temperature under anhydrous conditions (**Scheme 3.8**).



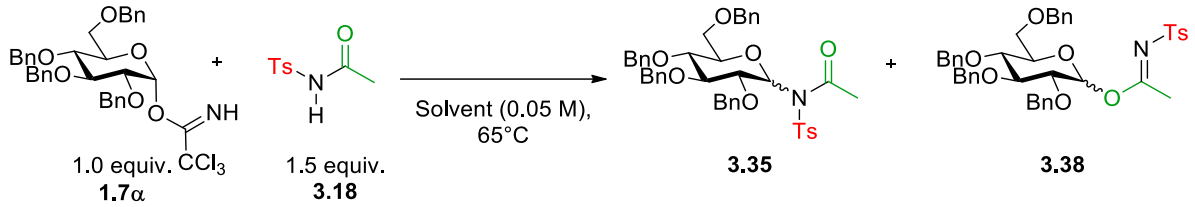
Scheme 3.8. Conversions of the *O*-glycosyl acetimidate under different conditions.

Armed with this knowledge, we next focused our studies on screening for glycosylation conditions. In efforts to optimize the procedure, a series of *N*-glycosylation reactions was performed employing the α-glucosyl donor **1.7α** and the simple tosyl amide acceptor **3.18**. The goal was to investigate the influence of reaction conditions such as solvent, temperature and concentration on the glycosylation and the following rearrangement. Based on ^{1}H-NMR spectra of the crude reaction mixtures, the chemo- and stereoselectivity was determined.

Initially, solvents were screened at the same temperature (65ºC) and concentration of the donor (*c*= 0.05 M). **Table 3.1** gives an overview of the obtained results. The reactions were monitored by TLC until a full conversion of the starting material. The completion times spanned from 3 to 8 hours depending on the solvent used. In general, the glycosylations carried out in more polar solvents gave higher reaction rates. The choice of solvent was found to be critical as the reaction in THF provided neither the *O*-glycosyl imidate nor the desired *N*-glycosyl amide. A mixture of the isomeric products was observed in the case of the other solvents used in the screening. In addition, when acetonitrile was used as a solvent the reaction resulted in byproducts formed from a nucleophilic addition to the nitrilium cation (**Scheme 3.11**). Chemoselectivity turned out to be strongly dependent on the solvent chosen. It was found that

the reaction in DMF gave the highest chemoselectivity towards the *N*-glycosides. The *O*-glycosyl imidates were predominant, while using the less polar solvents. It was also realized that the anomeric ratio of the *O*-glycosides was influenced by the choice of solvent, whereas the *N*-glycosides were obtained as β-anomers exclusively. A clear preference for the formation of β-*O*-glycosides was observed for the reactions carried out in the least polar solvents, i.e., 1,2-dichloroethane and toluene. The high degree of β-selectivity suggested that the mechanism involving more associated ion-pair was dominating in nonpolar solvents.

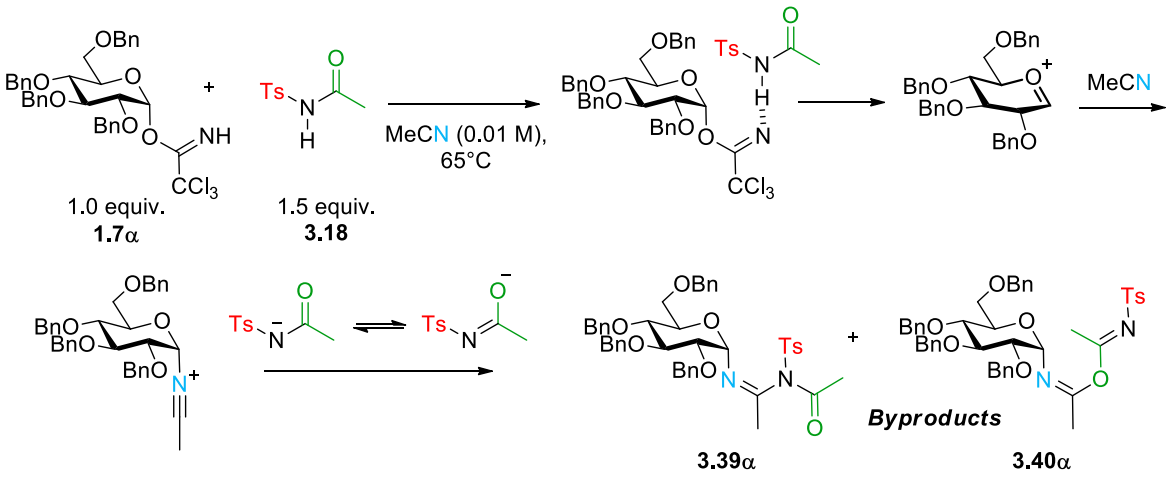
Table 3.1. Overview of self-promoted glycosylations using various solvents.



Solvent	*t* [h][a]	*O*/*N*-Glc	α/β *O*-Glc[b]	α/β *N*-Glc[b]
$C_2H_4Cl_2$	8h	2.2:1	0.03:1	0:1
THF	3h	-	-	0:1
DMF	3h	0.3:1	2.7:1	0:1
MeCN	4h	2.8:1	0.2:1	0:1
Toluene	7h	2.4:1	0.05:1	0:1
$MeNO_2$	8h	3.6:1	1:1	0:1

[a] Glycosylations were monitored by TLC until a full conversion of the starting material. [b] Determined from crude ^{1}H-NMR.

When switching to the more polar solvents, the selectivity dropped giving mixtures of the α- and β-*O*-glycosides with α/β ratios ranging from 0.2:1 to 2.7:1. Considering the chemoselectivity towards the target *N*-glycosides, DMF served as the best solvent, hence was used in the further optimization.

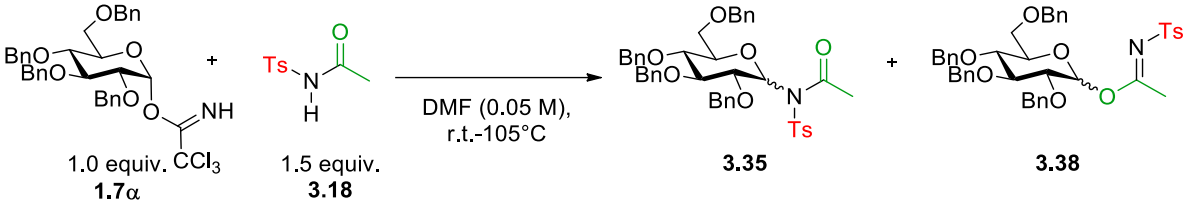


Scheme 3.11. In situ formation of the nitrilium cation when using MeCN as a solvent, followed by the nucleophilic addition leading to the side products **3.39α** and **3.40α**.

Screening for glycosylation conditions was then extended to the reactions at different temperatures (**Table 3.2**). Using high boiling DMF as a solvent enabled us to investigate the reaction within the broad scope of temperatures up to 105ºC. The glycosylations were carried out at the same concentration of the donor as in the previous screening (0.05 M). At room temperature, the reaction proceeded slowly. Full conversion of the TCA donor was attained after 6 days. Increasing temperature shortened the reaction time up to an hour. In addition, a strong temperature dependence on chemoselectivity was observed. The reaction performed at the highest temperature was found to give the best results in terms of the *O*/*N* selectivity (0:1 ratio). Generally, the chemoselectivity towards the *N*-glycosides dropped with decreasing temperature, with an exception of the reaction at room temperature. The obtained at the elevated temperatures *N*-selectivity could result from the glycosylation itself. However, it seems likely that most of the *N*-glycosyl amide was formed in the subsequent rearrangement, which was found to be faster at higher temperatures. The reaction at room temperature, in contrary to the general trend in chemoselectivity, resulted in a lower *N*-selectivity than the reaction carried out at 45°C. Nevertheless, the reaction times of these two glycosylations varied significantly. Glycosylation under milder conditions proceeded much slower, hence other processes could occur in parallel to the glycosylation affecting the ratio of *O*- and *N*-glycosides. Until a full conversion of the starting material, the already formed glycosyl imidate could either rearrange to the *N*-glycoside or decompose to the hemiacetal. Importantly, the reaction at room temperature gave rise to the hemiacetal as the main product. However, the reasoning behind this could be also related to the partial hydrolysis of the TCA glycosyl donor. Formation of the

hemiacetal side product was reduced by increasing the temperature. Furthermore, it was observed that the stereoselectivity was temperature-dependent. The exact anomeric ratios were difficult to determine due to signal overlap. Nevertheless, it was found that higher reaction temperatures generally favored the β-linked *O*- and *N*-glycosides.

Table 3.2. Overview of self-promoted glycosylations at different temperatures.



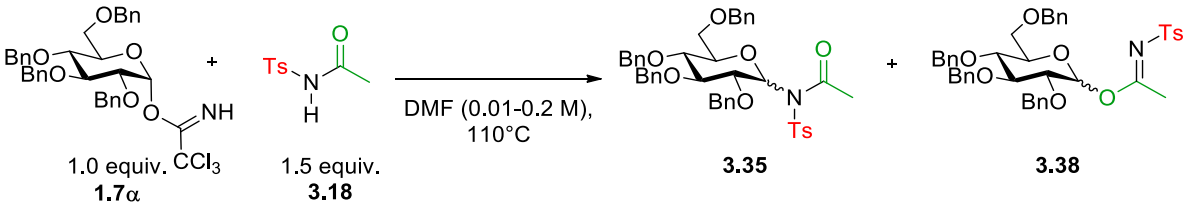
Temp. [°C]	*t* [h][a]	*O*/*N*-Glc[b]
r.t.	144	1:1
45	10	1:0.7
65	3	1:1
85	1	1:2.6
105	1	0:1

[a] Glycosylations were monitored by TLC until a full conversion of the starting material. [b] Determined from crude ^{1}H-NMR.

Continuing the optimization, the glycosylation was tested at multiple concentrations of the TCA glycosyl donor in the range from 0.01 M to 0.2 M (**Table 3.3**). As already shown, increasing the reaction temperature improved the *N*-selectivity, hence the glycosylations were performed at the elevated temperature (110°C). After an hour of reaction time, the crude ^{1}H-NMR spectra were measured. The experiments revealed a minor concentration dependence on the *O*/*N*-selectivity with a slightly higher preference for the *N*-glycoside in the more concentrated solutions (0.1 M and 0.2 M). The stereoselectivity was also moderately influenced by the concentration of the donor. The *N*-glycosylation was found to be β-selective at all concentrations used in the screening, whereas the *O*-glycosylation yielded different ratios of anomers. Higher concentrations of the donor led to the preferential formation of the β-*O*-glycoside. When using the more diluted solutions, the *O*-glycosylation was less 1,2-trans-selective. Thus, it could be concluded that at higher concentrations the donor reacts *via* the

reaction pathway involving two molecules of the acceptor. One acceptor acts as an activator of the TCA donor, whereas the second one plays the role of the nucleophile. A concentration of 0.1 M was chosen as the preferred value due to the limited solubility of the nosylated acceptors.

Table 3.3. Overview of self-promoted glycosylations at various concentrations. The reactions were stirred for 1 h.

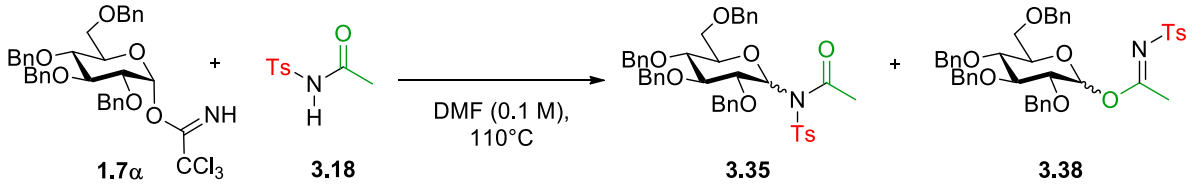


***c* [M]**	***O*/*N*-Glc[a]**	**α/β *O*-Glc[a]**	**α/β *N*-Glc[a]**
0.2	0.1:1	4:1	0:1
0.1	0.1:1	4:1	0:1
0.05	0.17:1	1:0	0:1
0.01	0.12:1	11:1	0:1

[a] Determined from crude ^{1}H-NMR.

Solvent, temperature, and concentration studies enabled us to establish a new glycosylation procedure. The optimized conditions were first applied in the glycosylation with the same reactants as those used in screening (**Table 3.4**). Following the well-established protocol, the reaction was carried out in DMF at 110ºC and 0.1 M concentration of the donor. Under these conditions, the reaction facilitated a mixture of α-*O*-glycoside and β-*N*-glycoside in a 5:95 ratio and a moderate yield of 65%.

Table 3.4. Comparison of glycosylations using 50% excess of either the glycosyl donor **1.7α** or tosyl acetamide **3.18**.



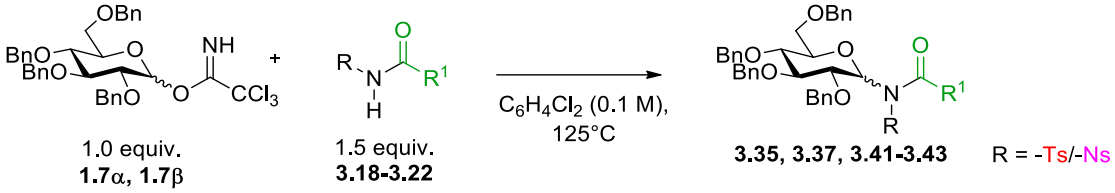
Entry	Donor (equiv.)	Acceptor (equiv.)	*t* [h]	α/β[a]	Yield[b] [%]
1	1.0	1.5	1.5	15:85	65[c]
2	1.5	1.0	1.5	14:86	75[d]

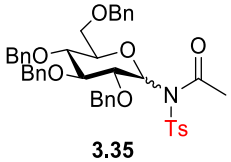
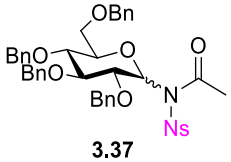
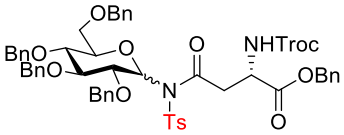
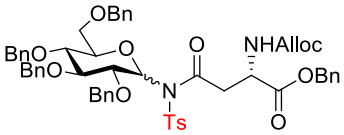
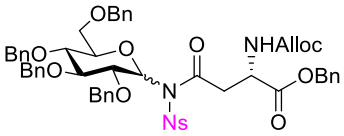
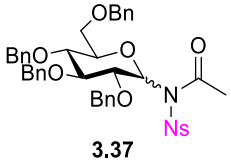
[a] Determined from crude ^{1}H-NMR with regard to *N*-glycosides. [b] Isolated yield. [c] Isolated compound contained 5% of the α-*O*-glycoside. [d] Isolated compound contained 8% of the α-*O*-glycoside.

Hydrolysis was found to be the major side reaction competing with glycosylation and the following rearrangement, hence lowering the yield. The molecular ratio between the donor and acceptor was therefore changed from 1:1.5 to 1.5:1. Using a 50% excess of the TCA glycosyl donor improved the yield of the glycosylation to 75%. However, the obtained mixture of glycosides contained higher amounts of the undesired α-*O*-glycoside (8%). Based on the previous solvent screening, *O*-glycosylation became more α-selective in polar solvents. Thus, in order to reduce the α-*O*-glycosylation, DMF was changed to the less polar and high-boiling *o*-dichlorobenzene. In addition, *o*-dichlorobenzene seemed to be a promising solvent in terms of yield due to its lower hygroscopicity compared to DMF. Since nonpolar solvents were found to decrease the rearrangement rate, the reaction temperature was elevated to 125ºC. The same reactants were employed in the glycosylation using *o*-dichlorobenzene as a solvent with a 50% excess of the acceptor. As anticipated, the crude ^{1}H-NMR spectrum revealed only a trace amount of the undesired hemiacetal. In fact, the glycosylation yield increased from 65% to 83%. Most importantly, the reaction led to the lower α-selectivity and thereby giving access to the pure β-*N*-glycoside.

Encouraged by the obtained results, we investigated the scope of the protocol using both anomers of the benzylated glucosyl donor (**1.7α** and **1.7β**) and five sulfonyl amide acceptors **3.18**-**3.22** (**Table 3.5**). In a series of *N*-glycosylations, nosyl amides reacted faster than the corresponding tosylated acceptors. Under the optimized conditions, the glycosylations with the α-TCA **1.7α** gave generally good yields, from 69% to 83%, and high β-selectivity (α/β 9:>91). The yield and selectivity seemed to be marginally dependent on the type of the sulfonyl substituent. Slightly better results were observed in the case of glucosylations with less electron-poor amides. The reaction was found to be more influenced by the steric factors. When bulkier asparagine derivatives were used as acceptors, the reaction resulted in lower yields. The steric bulk had however no significant impact on the β-selectivity which remained high. To investigate whether the glycosylation depends on the stereochemistry of the donor, the β-TCA **1.7β** was reacted with the acetamide acceptor **3.21** under the same conditions. Although the β-*N*-glycoside was formed predominantly, the selectivity towards the α-products increased resulting in the α/β ratio of 21:79 (**Figure 3.11**). The reaction was however less α-selective compared to the previously described glucosylations with sulfonyl carbamates. The stereochemical outcome was therefore modestly determined by the anomeric configuration of the glycosyl donor. The obtained results could be explained by a more dissociative mechanism in the case of glycosylation employing the less reactive sulfonyl amides.

Table 3.5. Scope of self-promoted *N*-glycosylations employing the benzylated glucosyl TCAs **1.7α** and **1.7β** and sulfonyl amide acceptors **3.18-3.22** in excess of 50%.



Entry	Donor	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**1.7α**	**3.18**	4	 **3.35**	4:96	83
2	**1.7α**	**3.21**	2	 **3.37**	3:97	81
3	**1.7α**	**3.19**	4	 **3.41**	2:98	69
4	**1.7α**	**3.20**	4	 **3.42**	9:>91	76
5	**1.7α**	**3.22**	2	 **3.43**	9:>91	71
6	**1.7β**	**3.21**	2	 **3.37**	21:79[c]	n.d.

[a] Determined from crude ^{1}H-NMR with regard to *N*-glycosides. [b] Isolated yield. [c] Determined from crude ^{1}H-NMR with regard to *N*-glycosides and *O*-imidates due to signal overlap.

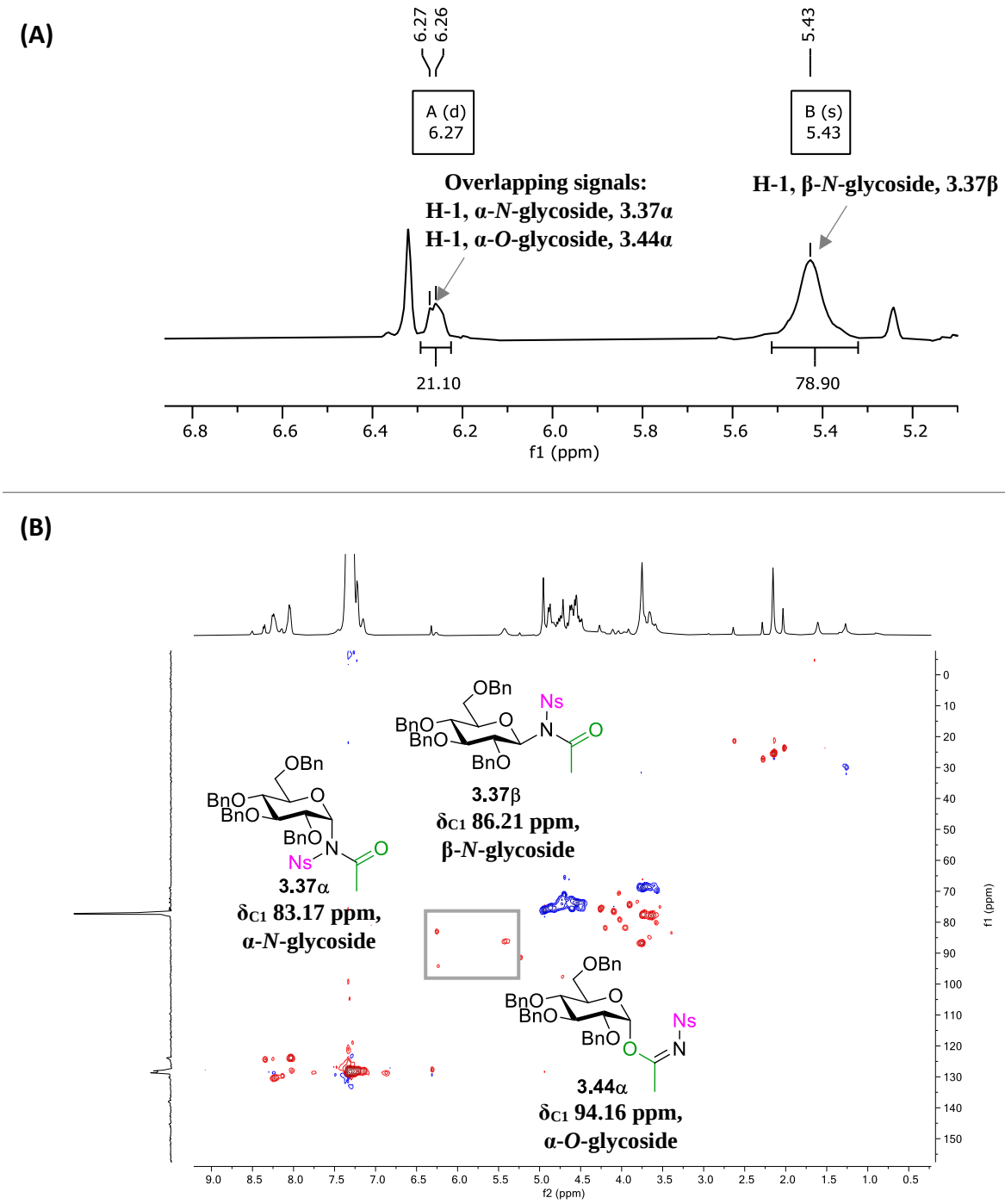
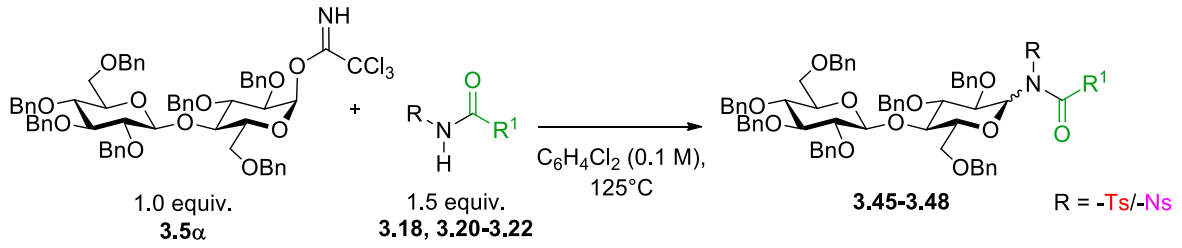
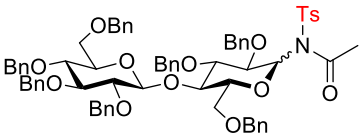
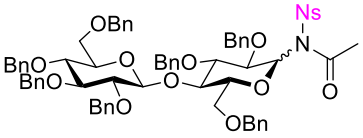
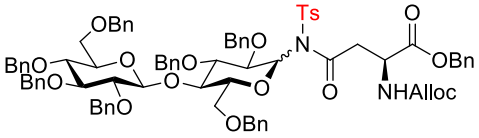
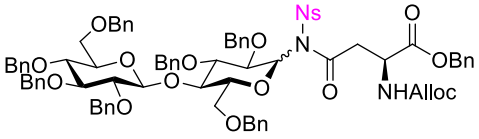


Figure 3.11. A) Anomeric region of the crude ^{1}H-NMR spectrum. B) HSQC spectrum with the anomeric region indicated with a box. The spectra were recorded at r.t. in $CDCl_3$ using a glycosides mixture obtained from the glycosylation with the β-glucosyl TCA **1.7β**.

The glycosylation was further studied using the more complex benzylated α-TCA donor, i.e., cellobiose derivative **3.5α** (**Table 3.6**). The glycosylations with disaccharide TCA proceeded with the same rate as the corresponding glucosylations. Nevertheless, the reactions gave generally lower yields, except the reaction employing the tosylated asparagine acceptor. When using the simple tosyl and nosyl acetamides, the products were obtained in comparable yields of 72% and 74% respectively. On the other hand, a pronounce difference in yields was observed for glycosylations using the asparagine derived counterparts (76% and 56%). Changing the glycosyl donor to the cellobiosyl derivative had almost no influence on the stereochemical outcome. The slightly lower β-selectivities were obtained for the glycosylations using the acetamide acceptors **3.18** and **3.21**. Moreover, there was no significant selectivity dependence on the sulfonyl rest and size of the acceptors.

Table 3.6. Scope of self-promoted *N*-glycosylations employing the benzylated α-cellobiosyl TCA **3.5α** and sulfonyl amide acceptors **3.18**, **3.20-3.22** in excess of 50%.

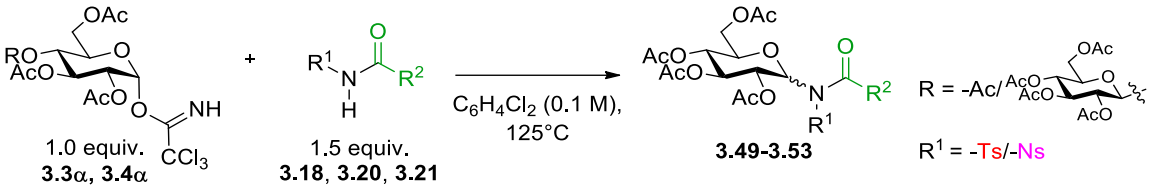


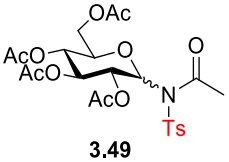
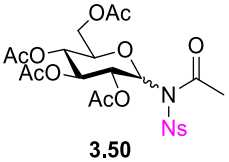
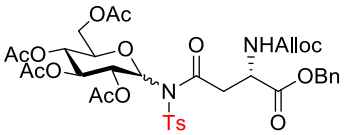
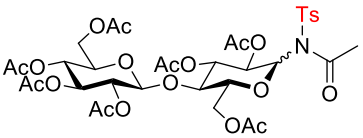
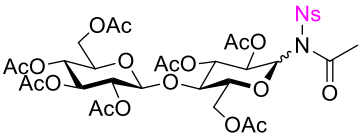
Entry	Donor	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**3.5α**	**3.18**	4	 **3.45**	6:94	72
2	**3.5α**	**3.21**	2	 **3.46**	7:93	74
3	**3.5α**	**3.20**	4	 **3.47**	8:92	76[c]
4	**3.5α**	**3.22**	2	 **3.48**	n.d.[d]	56

[a] Determined from crude ^{1}H-NMR with regard to *N*-glycosides. [b] Isolated yield. [c] Product isolated as the anomeric mixture (α/β=8:92). [d] α/β ratio was not determined due to signal overlap.

Continuing our studies, we tested the optimized protocol in glycosylations with the acetylated glucose **3.3α** and cellobiose derivatives **3.4α (Table 3.7)**. The disarmed donors were found to react slower with the less acidic tosylated acceptors compared to the corresponding benzylated TCAs. An exception from this trend was observed for the glycosylation with the asparagine acceptor **3.20**. On the other hand, while using the more acidic nosyl acetamide, the reaction times remained the same **3.21**. Furthermore, the sulfonyl substituent was found to be relevant in terms of the yield. In fact, the glycosylations employing the tosylated acceptors resulted in lower yields (56%-73%), whereas using the nosylated acceptor provided similar yields to the previously obtained (76%-84%). Also, the size of sulfonyl amides seemed to affect the glycosylation since the reaction with the bulkiest acceptor **3.20** gave the lowest yield. Although the reactivity varied depending on the donors and acceptors, the β-selectivity was excellent in all glycosylations and surpassed the values reported for the benzylated derivatives. The reasoning behind this, however, could be more related to the neighboring group participation commonly observed in glycosylations with acetylated donors. Eventually, the established procedure was employed in the synthesis of the glucosamine derivative (**Table 3.8**). Our initial attempt to glycosylate the acetylated GlcNAc donor **3.2α** using the nosyl acetamide acceptor **3.21** resulted in an exclusive formation of the oxazoline derivative. It was realized that the oxazoline derivative could not be further activated and hence reacted with the acceptor under the applied conditions. To circumvent this issue the acetyl moiety on the amino function was replaced with the Troc protecting group (**3.1α**). This strategy enabled us to obtain the desired glucosamine derivative in high β-selectivity and decent yield (49%).

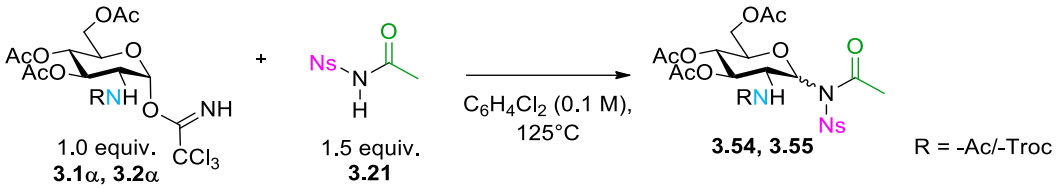
Table 3.7. Scope of self-promoted *N*-glycosylations employing acetylated α-TCAs **3.1α-3.4α** and sulfonyl amide acceptors **3.18**, **3.20**, **3.21** in excess of 50%.

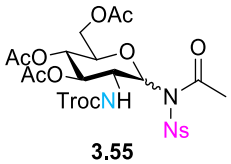


Entry	Donor	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**3.3α**	**3.18**	12	 **3.49**	2:98	73
2	**3.3α**	**3.21**	2	 **3.50**	2:98	84
3	**3.3α**	**3.20**	4	 **3.51**	n.d.	56
4	**3.4α**	**3.18**	10	 **3.52**	2:98	65
5	**3.4α**	**3.21**	2	 **3.53**	3:97	76[c]

[a] Determined from crude ^{1}H-NMR with regard to *N*-glycosides. [b] Isolated yield. [c] Isolated product contained 8% of an impurity.

Table 3.8. Scope of self-promoted *N*-glycosylations employing acetylated glucosamine derivatives **3.1α** and **3.2α** and sulfonyl amide acceptor **3.21** in excess of 50%.

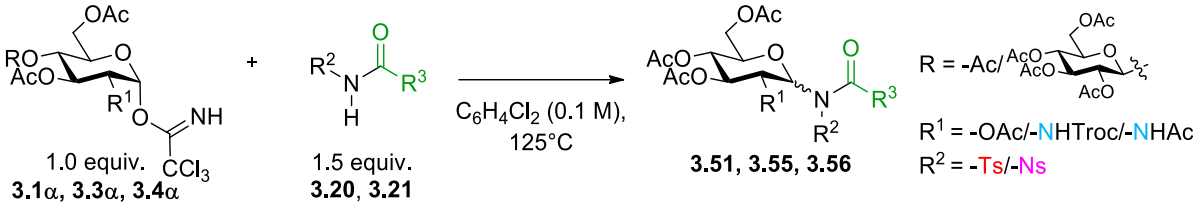


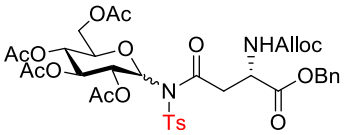
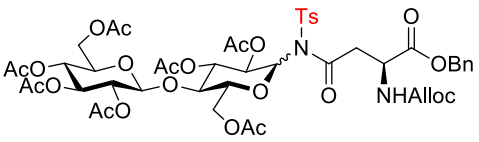
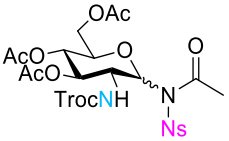
Entry	Donor	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**3.2α**	**3.21**	6	-	-	-
2	**3.1α**	**3.21**	2	 **3.55**	10:>90	49

[a] Determined from crude ^{1}H-NMR with regard to *N*-glycosides. [b] Isolated yield.

In order to investigate, whether altering the ratio between the reactants could improve the yield, additional glycosylations were performed using 50% excess of the glycosyl donor (**Table 3.9**). In these studies, the more disarmed acetylated donors were reacted with the sterically demanding asparagine derivative **3.20** and the nosyl acetamide **3.21**. The reaction time was prolonged only in the case of the glycosylations using the complex asparagine acceptor. Most importantly, the reactions using the glucosyl donor **3.3α** and the glucosamine derivative **3.1α** gave rise to the products in higher yields than previously obtained, 89% and 70% respectively. Noteworthy, the disaccharide derivative was obtained in the superior yield (66%), compared to the acetylated asparagine-linked monosaccharide (56%).

Table 3.9. Scope of self-promoted *N*-glycosylations employing acetylated α-TCAs **3.1α**, **3.3α**, **3.4α** in excess of 50% and sulfonyl amide acceptors **3.20**, **3.21**.



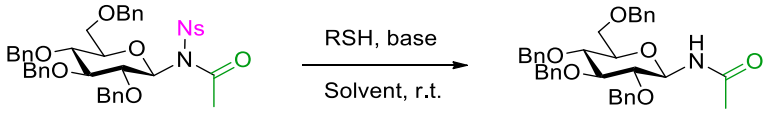
Entry	Donor	Acceptor	*t* [h]	Product	α/β[a]	Yield[b] [%]
1	**3.3α**	**3.20**	8	 **3.51**	n.d.	89
2	**3.4α**	**3.20**	8	 **3.56**	n.d.	66
3	**3.1α**	**3.21**	2	 **3.55**	n.d.	70

[a] Determined from crude ^{1}H-NMR with regard to *N*-glycosides. [b] Isolated yield.

The self-promoted glycosylation was shown to be useful in the synthesis of the β-*N*-glycosyl sulfonyl amides. Our next challenge was to remove the sulfonyl substituent in a chemoselective manner and thereby give access to the target *N*-glycosyl amides. The orthogonal deprotection of the tosyl group requires relatively harsh conditions. Therefore, this modification is usually considered as troublesome, especially in the case of the more complex compounds. It has been found that the orthogonal nosyl group removal can be achieved under milder conditions compared to the tosyl function using thiolates as the nucleophiles. Taking this into account, our initial attempts were focused on the nosyl group deprotection. The benzylated derivative **3.37β** was chosen as the model compound for the deprotection studies (**Table 3.10**).

The preliminary reaction was carried out in accordance with the most commonly utilized protocol employing thiophenol and potassium carbonate as a base. Nevertheless, the reaction led to the cleavage of the amide moiety instead of the sulfonyl substituent. In order to obtain the target *N*-glycosyl amide, the conditions were modified by changing the nucleophile, base, the ratio between reactants, solvent, and the reaction time. However, these attempts also turned out to be unsuccessful leading exclusively to the *N*-glycosyl sulfonamide.

Table 3.10. Overview of the nosyl group deprotection attempts.

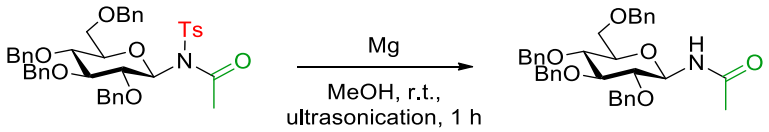


3.37β **3.57β**

Entry	Thiol (equiv.)	Base (equiv.)	Solvent	Temp. [°C]	t [h]	Yield [%][a]
1	PhSH (1.2)	K_2CO_3 (1.9)	DMF	r.t.	1	-
2	PhSH (3.0)	K_2CO_3 (4.0)	MeCN	r.t.	0.5	-
3	PhSH (4.0)	K_2CO_3 (1.0)	MeCN	r.t.	0.5	-
4	EtSH (5.0)	DBU (5.0)	MeCN	r.t.	0.5	-
5	C_6Cl_5SH (5.0)	DBU (5.0)	MeCN	r.t.	6	-

[a] Isolated yield.

Subsequently, we turned our focus toward the tosyl group removal (**Scheme 3.12**). Following the procedure successfully employed in preparation of the *N*-glycosyl carbamates, the reaction was carried out under ultrasonic irradiation using magnesium turnings and anhydrous methanol. Importantly, the desired *N*-glycosyl amide was observed in crude NMR spectra, however only in trace amount.



3.35β **3.57β**

Scheme 3.12. Tosyl group deprotection reaction conditions.

3.3. Conclusions

In conclusion, we developed a self-promoted *N*-glycosylation giving access to the *N*-glycosyl sulfonyl amides (**Table 3.11**). The glycosylation employs the commonly used TCA glycosyl donors and the sulfonyl amides. Notably, the investigated glycosylation is an example of a two-component reaction requiring no additives, since the electron-poor acceptors can act as activators of TCA donors. From screening conditions, the glycosylation was found to proceed in various aprotic organic solvents under dry conditions. Furthermore, the reaction gave the best results at high temperatures in terms of yield, chemo- and stereoselectivity, which might be considered the key limitation of this method. Noteworthy, the scope of the glycosylation was studied using armed and disarmed glycosyl donors including the glucosamine derivatives and disaccharides. In addition, different sulfonyl acetamide and asparagine derivatives varying in size and functional groups were investigated. Employing the optimized protocol, 22 derivatives were synthesized in yields ranging from 49% to 89%. The desired product was not obtained only in the glycosylation with the GlcNAc donor which led solely to the oxazoline derivative. Importantly, when using the α-TCA donors, the reactions resulted in high β-selectivity with α/β ratios spanning from 2:98 to 10:90. The glycosylation with the β-TCA donor was found to be less selective. Nevertheless, the self-promoted *N*-glycosylation with sulfonyl amides proceeded with a lower degree of stereospecificity compared to the previously demonstrated glycosylation with sulfonyl carbamates. The following removal of the sulfonyl groups turned out to be more troublesome than in the case of the carbamate-protected *N*-glycosides. Our attempts to deprotect the nosyl and tosyl functions were unsuccessful. Therefore, the deprotection step requires further studies with a focus on the reaction conditions or alternative sulfonyl substituents.

Table 3.11. Summary of the developed method.

Advantages	Drawbacks
- No need for additives. - The glycosylation takes place in various solvents. - Armed and disarmed donors can be used. - Tolerance for different functional groups. - Moderate to high yields. - High β-selectivity when using the α-donors.	- High temperature requirement. - Need for dry conditions. - No conversion for the GlcNAc donor. - Limited potential application due to challenging deprotection of sulfonyl groups.

3.4. Experimental

3.4.1. General Information

All non-aqueous reactions were carried out under an inert atmosphere of nitrogen in flame-dried glassware. Unless otherwise noted, chemicals and solvents were purchased from commercial suppliers (Sigma-Adrich, Fluka, TCI, ABCR, CarboSynth or Merck) and used without further purification. All solvents used for synthesis were HPLC-grade and dry. Dry CH_2Cl_2, acetonitrile, toluene, DMF and THF were obtained from an Innovative Technology PSMD-05 solvent drying system. Other solvents were dried with 4Å molecular sieves.

Thin layer chromatography (TLC) was performed on aluminum sheets coated with silica gel containing a fluorescence indicator (Merck 60 F254). TLC plates were visualized with UV-light (254 nm) or using a molybdate staining solution (Ce(IV)sulphate (10 g) and $(NH_4)_2MO_4$ (15 g) in 1000 mL 10 % H_2SO_4), 10% H_2SO_4 in methanol or vanillin staining solution (10 g, in 1000 mL 10 % H_2SO_4 in MeOH) followed by heating. For column chromatography ROTH 40-63 mesh and Kieselgel 230-400 mesh silica gel were used as stationary phase.

Nuclear magnetic resonance (NMR) spectroscopy was performed on Bruker 500 MHz Ultra Shield Plus spectrograph equipped with a cryo-probe.

Recorded spectra were referenced to the respective solvent peak as internal standard:

- $CDCl_3$ (^{1}H-NMR 7.260 ppm, ^{13}C-NMR 77.160 ppm)
- DMSO-d_6 (^{1}H-NMR 2.500 ppm, ^{13}C-NMR 39.520 ppm)
- CD_3CN (^{1}H-NMR 1.940 ppm, ^{13}C-NMR 1.320 ppm).

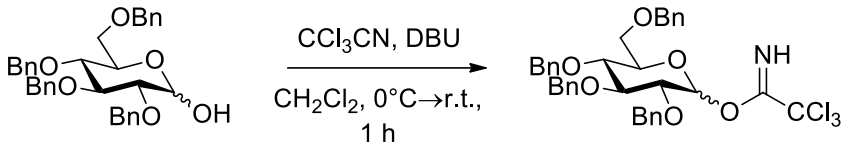
Infrared (IR) spectra were recorded using a Bruker Vertex 70 spectrometer equipped with the MIRacle Micro ATR accessory.

High resolution mass spectra (HRMS) were obtained from a Bruker SolariX XR 7T ESI/MALDI-FT-ICRMS instrument using matrix-assisted laser desorption ionization (MALDI).

Anton Paar polarimeter was used to determine optical rotations.

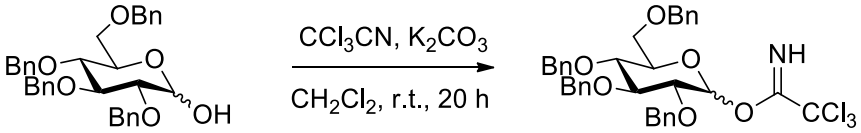
3.4.2. Synthesis of Glycosyl Donors

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (1.7α)



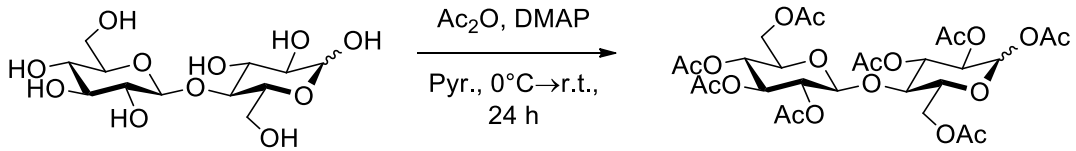
A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (2.00 g, 3.70 mmol) in dry CH_2Cl_2 (37 mL) was cooled down to 0°C. Then, trichloroacetonitrile (3.7 mL, 37.0 mmol) was added followed by DBU (0.3 mL, 1.85 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. for 1 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:6 EtOAc/heptane + 0.5% Et_3N) to afford the α anomer of compound **1.7** (1.91 g, 2.81 mmol, 76%) as a colorless syrup. The NMR data of compound **1.7α** were consistent with the previously reported spectra.[204]

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (1.7β)



K_2CO_3 (2.67 g, 19.4 mmol) and trichloroacetonitrile (3.8 mL, 37.4 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (2.41 g, 4.46 mmol) in dry CH_2Cl_2 (37 mL). The reaction mixture was stirred at r.t. for 20 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:6 EtOAc/heptane + 0.5% Et_3N) to afford the β anomer of compound **1.7** (2.60 g, 3.79 mmol, 85%). The NMR data of compound **1.7β** were consistent with the previously reported spectra.[35] The compound was prepared following an experimental procedure from the literature.[35]

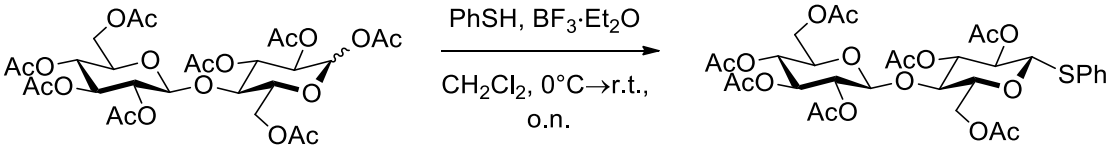
2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1→4)-1,2,3,6-tetra-*O*-acetyl-D-glucopyranoside (3.6a)



A solution of D-cellobiose (5.08 g, 14.8 mmol) in dry pyridine (74.2 mL) was cooled down to 0°C. Then, Ac_2O (37.1 mL, 392 mmol) was added followed by DMAP (0.18 g, 1.47 mmol).

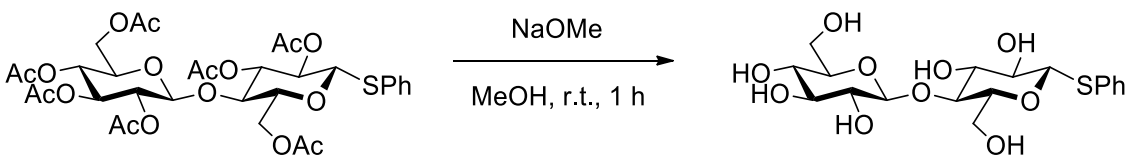
The reaction was slowly allowed to warm up and stirred at r.t. for 24 h. After completion, the reaction mixture was diluted with EtOAc (300 mL), washed with 1 M aq. HCl (5 x 200 mL), satd. aq. $NaHCO_3$ (2 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness yielding the anomeric mixture (α/β= 14:86) of compound **3.6a** (7.88 g, 11.6 mmol, 78%) as a colorless syrup. The NMR data of compound **3.6a** were consistent with the previously reported spectra.[227] The compound was prepared following a slightly modified experimental procedure from the literature.[205]

Phenyl 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-*β*-D-thioglucopyranoside (3.7)



PhSH (4.0 mL, 38.5 mmol) was added to a stirred solution of **3.6a** (17.4 g, 25.7 mmol) in dry CH_2Cl_2 (140 mL). Then, the solution was cooled down to 0°C and treated dropwise with $BF_3{\cdot}Et_2O$ (15.9 mL, 110 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. overnight. After this time, the solution was diluted with CH_2Cl_2 (500 mL), washed with satd. aq. $NaHCO_3$ (3 x 200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4 and condensed *in vacuo* to 100 mL. The resulting solution was poured into petroleum ether and kept at 4°C overnight. The obtained precipitate was filtered off, washed several times with petroleum ether and evaporated to dryness affording the β anomer of compound **3.7** (16.7 g, 22.8 mmol, 89%) as a pale orange solid. The NMR data of compound **3.7β** were consistent with the previously reported spectra.[206] The compound was prepared following an experimental procedure from the literature.[206]

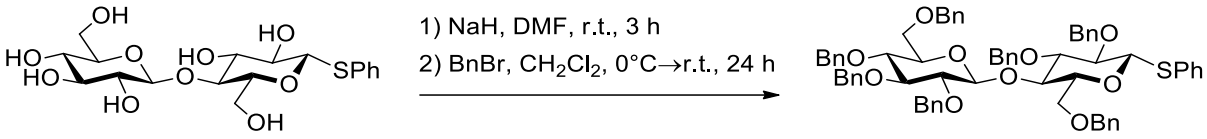
Phenyl *β*-D-glucopyranosyl-(1→4)-*β*-D-thioglucopyranoside (3.8β)



The 25% solution of NaOMe in dry MeOH (0.5 mL, 2.29 mmol) was added to a suspension of **3.7β** (16.7 g, 22.9 mmol). The reaction mixture was stirred at r.t. for 1 h. After completion, the solution was neutralized with Amberlite IR-120 (H^+), filtered and evaporated to dryness *in*

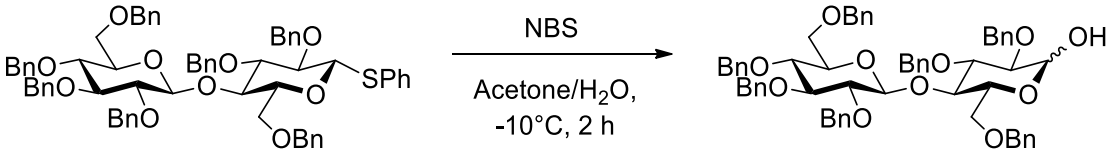
vacuo. The product was used in the next step without further purification.[206] The compound was prepared following an experimental procedure from the literature.[206]

Phenyl 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (3.9)



NaH (7.80 g 60% in mineral oil, 195 mmol) was added to a solution of **3.8β** (9.97 g, 23.0 mmol) in dry DMF (230 mL) and the reaction mixture was stirred at r.t. for 3 h. Then, the resulting suspension was cooled down to 0°C and treated dropwise with BnBr (23.2 mL, 195 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. for 24 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with H_2O (3 x 200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The obtained residue was dissolved in a min. amount of CH_2Cl_2, poured into Et_2O and kept at 4°C overnight. The precipitate was filtered off, washed several times with Et_2O and evaporated to dryness yielding the β anomer of compound **3.9** (12.0 g, 11.3 mmol, 49%) as a white solid. The NMR data of compound **3.9β** were consistent with the previously reported spectra.[207] The compound was prepared following an experimental procedure from the literature.[207]

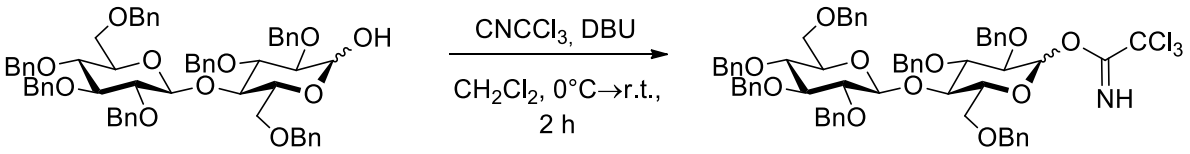
2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranose (3.10)



The compound **3.9β** (5.00 g, 4.69 mmol) was suspended in a mixture of acetone and H_2O (100 mL, v/v 19:1). The flask was coated with aluminium foil and the suspention was colled down to -10°C. Then, NBS (3.00 g, 16.9 mmol) was added and the reaction mixture was stirred at -10°C for 2 h. After this time, the reaction mixture was poured into satd. aq. $NaHCO_3$ (400 mL), extracted with AcOEt (2 x 300 mL). The organic layers were combined, washed with brine (200 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash column chromatography (1:3→1:2 EtOAc/heptane) to afford the anomeric mixture (α/β= 75:25) of compound **3.10** (3.87 g, 3.99 mmol, 85%) as a colorless syrup. The NMR data of

compound **3.10** were consistent with the previously reported spectra.[7] Anomer α: **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.48-7.09 (m, 35H, 35x ArH^{Bn}), 5.16 (d, *J* = 2.6 Hz, 1H, H-1a), 5.10 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.93-4.68 (m, 7H, CH_2^{Bn}), 4.64-4.50 (m, 3H, CH_2^{Bn}), 4.50-4.33 (m, 4H, H-1b, CH_2^{Bn}), 4.05-3.90 (m, 2H, H-4a, H-5a), 3.90-3.82 (m, 2H, H-3a, H-6a), 3.74-3.43 (m, 6H, H-2a, H-3b, H-4b, H-6a', H-6b, H-6b'), 3.43-3.23 (m, 2H, H-2b, H-5b), 2.36 (s, 1H, *O*H) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 139.51 (ArC^{Bn}), 138.73 (ArC^{Bn}), 138.64 (ArC^{Bn}), 138.53 (ArC^{Bn}), 138.42 (ArC^{Bn}), 138.08 (ArC^{Bn}), 137.96 (ArC^{Bn}), 128.58-127.32 (35x $ArCH^{Bn}$), 102.77 (C-1b), 91.51 (C-1a), 84.98 (C-3b), 82.82 (C-2b), 80.06 (C-3a), 79.07 (C-2a), 78.17 (C-4b), 76.61 (C-4a), 75.76 (CH_2^{Bn}), 75.34 (C-5b), 75.25 (CH_2^{Bn}), 75.09 (CH_2^{Bn}), 75.04 (CH_2^{Bn}), 74.94 (CH_2^{Bn}), 73.72 (CH_2^{Bn}), 73.47 (CH_2^{Bn}), 70.55 (C-5a), 69.14 (C-6b), 68.05 (C-6a) ppm. **HRMS** (MALDI+): Calculated for $C_{61}H_{64}O_{11}Na^+$ m/z 995.4346; found m/z 995.4323. $[\alpha]_D^{589}$= 26.6° (*c*= 1.2, $CHCl_3$).

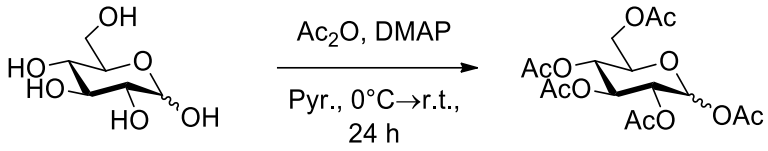
2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (3.5)



A solution of **3.10** (1.51 g, 1.55 mmol) in dry CH_2Cl_2 (14.2 mL) was cooled down to 0°C. Then, trichloroacetonitrile (0.6 mL, 6.21 mmol) was added followed by DBU (50.0 µL, 0.31 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. for 2 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:9→1:6 EtOAc/heptane + 0.5% Et_3N) to afford the α anomer of compound **3.5** (1.04 g, 0.93 mmol, 60%) as a colorless syrup.[†††] **HRMS** (MALDI+): Calculated for $C_{63}H_{64}Cl_3NO_{11}Na^+$ m/z 1138.3443; found m/z 1138.3406. $[\alpha]_D^{589}$= 63.2° (*c*= 0.6, $CHCl_3$). NMR data in accordance with litterature.[228]

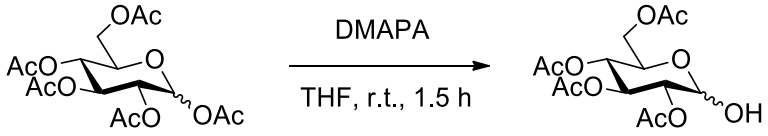
[†††] The isolated compound contained 8% of an impurity.

1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranoside (3.11a)



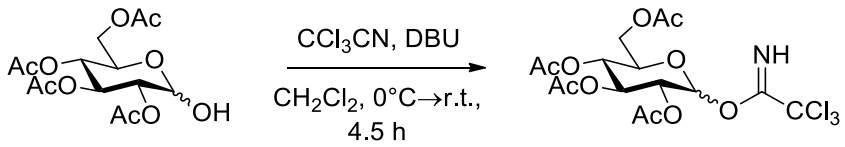
A solution of D-glucose (4.00 g, 18.1 mmol) in dry pyridine (7.3 mL) was cooled down to 0°C. Then, Ac_2O (8.5 mL, 90.4 mmol) was added followed by DMAP (0.22 g, 1.81 mmol). The reaction was slowly allowed to warm up and stirred at r.t. for 24 h. After completion, the reaction mixture was diluted with EtOAc (300 mL), washed with 1 M aq. HCl (5 x 200 mL), satd. aq. $NaHCO_3$ (2 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness yielding the anomeric mixture (α/β= 7:93) of compound **3.11a** (4.97 g, 12.8 mmol, 71%) as a colorless syrup. The NMR data of compound **3.11a** were consistent with the previously reported spectra.[208] The compound was prepared following a slightly modified experimental procedure from the literature.[208]

2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (3.12)



DMAPA (7.9 mL, 63.2 mmol) was added to a solution of **3.11a** (4.93 g, 12.6 mmol) in dry THF (63.2 mL). The reaction was stirred at r.t. for 1.5 h. After completion, the obtained solution was diluted with CH_2Cl_2 (300 mL), washed with 1 M aq. HCl (3 x 150 mL) and brine (150 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* yielding the anomeric mixture (α/β= 73:27) of compound **3.12** (3.33 g, 9.60 mmol, 76%) as a white solid. The NMR data of compound **3.12** were consistent with the previously reported spectra.[209] The compound was prepared following an experimental procedure from the literature.[209]

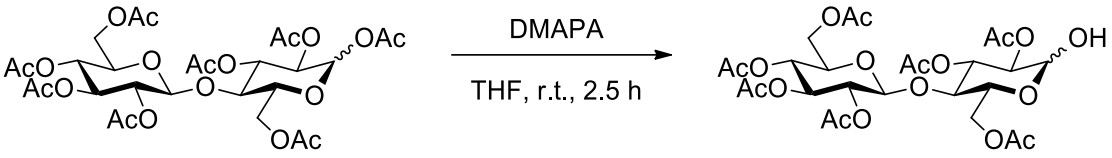
2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (3.3)



A solution of **3.12** (3.32 g, 9.53 mmol) in dry CH_2Cl_2 (51.1 mL) was cooled down to 0°C. Then, trichloroacetonitrile (3.8 mL, 38.1 mmol) was added followed by DBU (0.3 mL, 1.91 mmol).

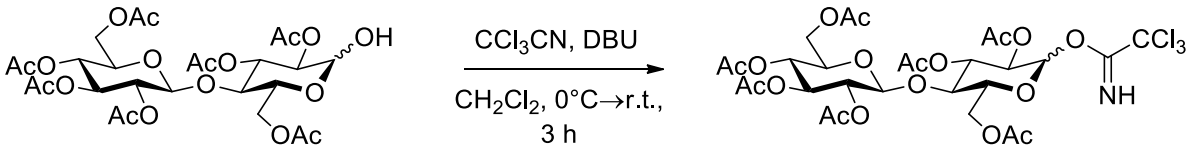
The reaction mixture was slowly allowed to warm up and stirred at r.t. for 4.5 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:3→1:2 EtOAc/heptane + 0.5% Et_3N) to afford the α anomer of compound **3.3** (3.57 g, 7.24 mmol, 76%) as a colorless solid. The NMR data of compound **3.3α** were consistent with the previously reported spectra.[210] The compound was prepared following an experimental procedure from the literature.[210]

2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranose (3.13)



DMAPA (7.3 mL, 58.0 mmol) was added to a solution of **3.6a** (7.87 g, 11.6 mmol) in dry THF (58.0 mL). The reaction was stirred at r.t. for 2.5 h. After completion, the obtained solution was diluted with CH_2Cl_2 (400 mL), washed with 1 M aq. HCl (3 x 250 mL) and brine (250 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* yielding the anomeric mixture (α/β= 69:31) of compound **3.13** (6.13 g, 9.63 mmol, 83%) as a white solid. The NMR data of compound **3.13** were consistent with the previously reported spectra.[229] The compound was prepared following an experimental procedure from the literature.[209]

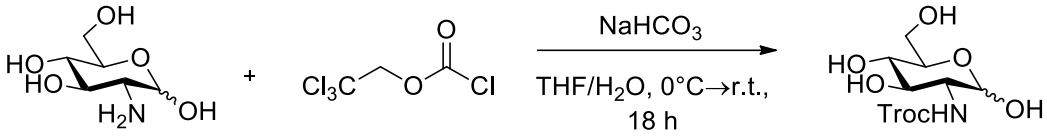
2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (3.4)



A solution of **3.13** (2.57 g, 4.04 mmol) in dry CH_2Cl_2 (29.0 mL) was cooled down to 0°C. Then, trichloroacetonitrile (1.6 mL, 16.2 mmol) was added followed by DBU (0.1 mL, 0.81 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. for 3 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:2→2:1 EtOAc/heptane + 0.5% Et_3N) to afford the α anomer of compound **3.4** (0.62 g, 2.10 mmol, 52%) as a colorless syrup. The NMR data of compound **3.4α** were

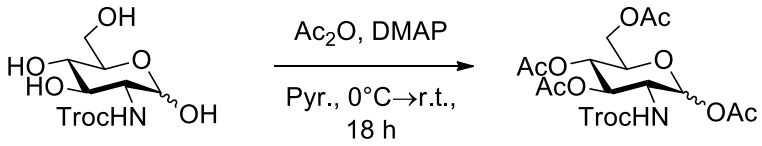
consistent with the previously reported spectra.[211] The compound was prepared following an experimental procedure from the literature.[211]

2-Deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (3.14a)



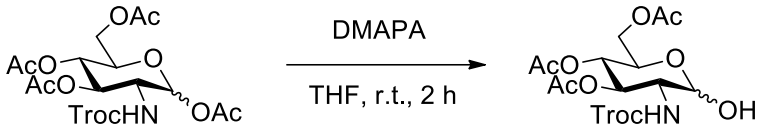
A solution of D-glucosamine hydrochloride (14.1 g, 65.5 mmol) in satd. aq. $NaHCO_3$ (600 mL) was cooled down in an ice bath. Then, 2,2,2- trichloroethyl chloroformate (17.8 mL, 129 mmol) was added dropwise. The reaction mixture was slowly allowed to warm up and stirred at r.t. for 18 h. After this time, the obtained, white precipitate was filtered off and evaporated to dryness *in vacuo*. The crude product **3.14a** was used in the next step without further purification. The compound was prepared following an experimental procedure from the literature.[212]

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranoside (3.15)



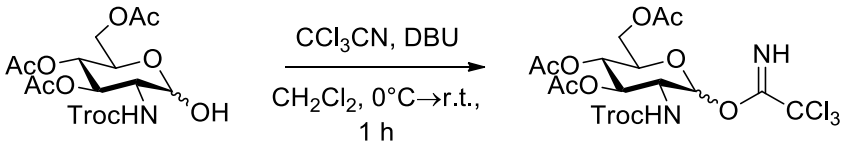
A solution of **3.14a** (23.2 g, 65.5 mmol) in dry pyridine (52.0 mL) was cooled down to 0°C. Then, Ac_2O (26.0 mL, 275 mmol) was added followed by DMAP (0.80 g, 6.55 mmol). The reaction was slowly allowed to warm up and stirred at r.t. for 18 h. After completion, the reaction mixture was diluted with EtOAc (1.0 L), washed with 1 M aq. HCl (5 x 500 mL), satd. aq. $NaHCO_3$ (2 x 500 mL) and brine (1 x 500 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness yielding the anomeric mixture (α/β= 9:91) of compound **3.15** (25.5 g, 48.5 mmol, 74%) as a pale-yellow solid. The NMR data of compound **3.15** were consistent with the previously reported spectra.[212] The compound was prepared following a slightly modified experimental procedure from the literature.[212]

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (3.15a)



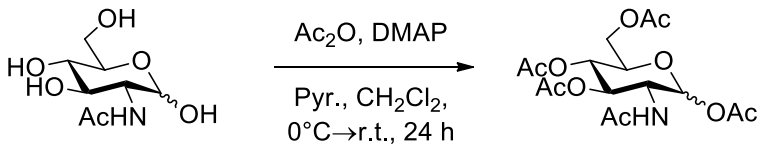
DMAPA (11.8 mL, 93.5 mmol) was added to a solution of **3.15** (9.77 g, 18.7 mmol) in dry THF (94.0 mL). The reaction was stirred at r.t. for 2 h. After completion, the obtained solution was diluted with CH_2Cl_2 (400 mL), washed with 1 M aq. HCl (3 x 250 mL) and brine (250 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) yielding the anomeric mixture (α/β= 87:13) of compound **3.15a** (5.61 g, 11.6 mmol, 62%) as a white solid. The NMR data of compound **3.15a** were consistent with the previously reported spectra.[230] The compound was prepared following an experimental procedure from the literature.[209]

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranosyl trichloroacetimidate (3.1)



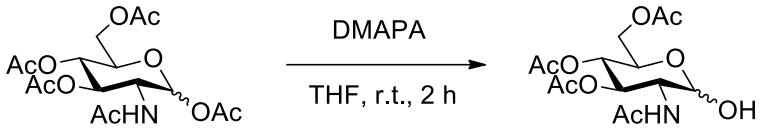
A solution of **3.15a** (3.18 g, 6.62 mmol) in dry CH_2Cl_2 (19.0 mL) was cooled down to 0°C. Then, trichloroacetonitrile (6.6 mL, 66.2 mmol) was added followed by DBU (0.2 mL, 1.65 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. for 1 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:2→1:1 EtOAc/heptane + 0.5% Et_3N) to afford the α anomer of compound **3.1** (3.33 g, 5.30 mmol, 80%) as a colorless syrup. The NMR data of compound **3.1α** were consistent with the previously reported spectra.[213] The compound was prepared following an experimental procedure from the literature.[213]

2-Amino-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranoside (3.16a)



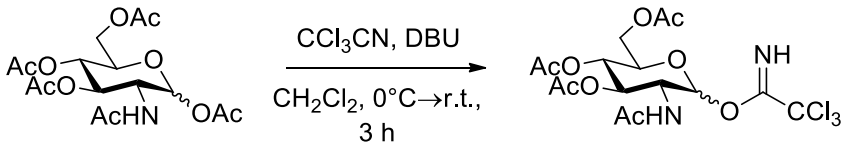
A solution of *N*-acetyl-D-glucosamine (4.00 g, 18.1 mmol) in dry pyridine (7.3 mL) and CH_2Cl_2 (17.0 mL) was cooled down to 0°C. Then, Ac_2O (8.5 mL, 90.4 mmol) was added followed by DMAP (0.22 g, 1.81 mmol). The reaction was slowly allowed to warm up and stirred at r.t. for 24 h. After completion, the reaction mixture was diluted with EtOAc (1.0 L), washed with 1 M aq. HCl (5 x 500 mL), satd. aq. $NaHCO_3$ (2 x 500 mL) and brine (1 x 500 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness yielding the anomeric mixture (α/β= 8:92) of compound **3.16a** (4.97 g, 12.8 mmol, 71%) as a pale-yellow solid. The NMR data of compound **3.16a** were consistent with the previously reported spectra.[231] The compound was prepared following a slightly modified experimental procedure from the literature.[214]

2-Acetamido--3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose (3.17)



DMAPA (7.2 mL, 57.5 mmol) was added to a solution of **3.16a** (4.48 g, 11.5 mmol) in dry THF (57.6 mL). The reaction was stirred at r.t. for 2 h. After completion, the obtained solution was diluted with CH_2Cl_2 (400 mL), washed with 1 M aq. HCl (3 x 250 mL) and brine (250 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash column chromatography (1:2→1:1 EtOAc/heptane) yielding the anomeric mixture (α/β= 91:9) of compound **3.17** (2.21 g, 6.33 mmol, 55%) as a white solid. The NMR data of compound **3.17** were consistent with the previously reported spectra.[232] The compound was prepared following an experimental procedure from the literature.[209]

2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (3.2)

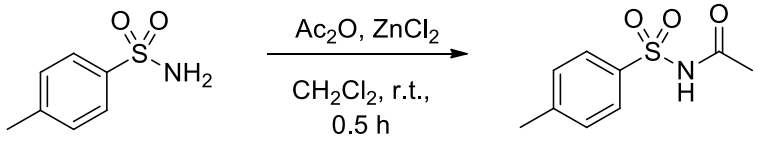


A solution of **3.17** (2.17 g, 6.25 mmol) in dry CH_2Cl_2 (33.2 mL) was cooled down to 0°C. Then, trichloroacetonitrile (2.5 mL, 25.0 mmol) was added followed by DBU (0.2 mL, 1.25 mmol). The reaction mixture was slowly allowed to warm up and stirred at r.t. for 3 h. After this time, the solvent was evaporated *in vacuo* onto celite. The crude product was purified by flash column chromatography (1:1 EtOAc/heptane + 0.5% Et_3N) to afford the α anomer of compound **3.2** (1.73 g, 3.50 mmol, 56%) as a pale-yellow solid. The NMR data of compound **3.2α** were

consistent with the previously reported spectra.[233] The compound was prepared following an experimental procedure from the literature.[215]

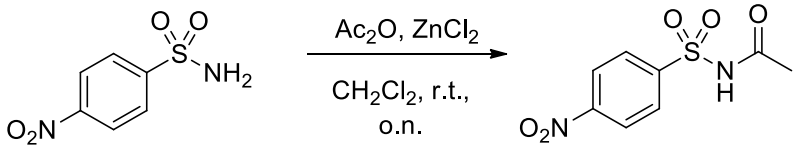
3.4.3. Synthesis of *N*-sulfonyl Amides

N-tosylacetamide (3.18)



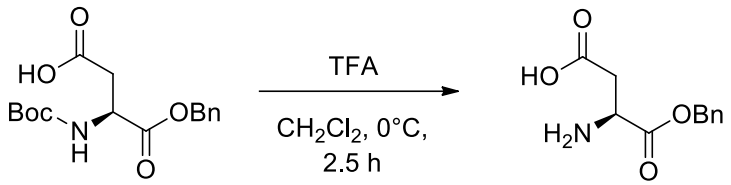
$ZnCl_2$ (0.04 g, 0.29 mmol) was added to a stirred solution of $TsNH_2$ (1.00 g, 5.84 mmol) and Ac_2O (1.1 mL, 11.7 mmol) in dry CH_2Cl_2 (2.0 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. for 0.5 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with H_2O (150 mL) and brine (150 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (2:3 EtOAc/heptane) to yield the compound **3.18** (1.14 g, 5.37 mmol, 92%) as a white solid. The NMR data of compound **3.18** were consistent with the previously reported spectra.[234] The compound was prepared following an experimental procedure from the literature.[216]

N-nosylacetamide (3.21)



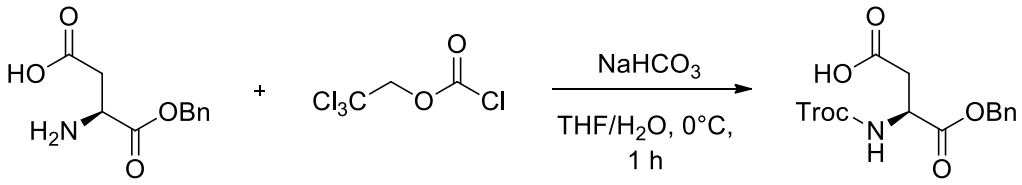
$ZnCl_2$ (0.03 g, 0.25 mmol) was added to a stirred solution of $TsNH_2$ (1.00 g, 4.95 mmol) and Ac_2O (0.7 mL, 7.42 mmol) in dry CH_2Cl_2 (2.0 mL) under a nitrogen atmosphere. The reaction was stirred at r.t. overnight. After completion, the reaction mixture was diluted with CH_2Cl_2 (300 mL), washed with H_2O (200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (2:3→1:0 EtOAc/heptane) to yield the compound **3.21** (1.02 g, 4.16 mmol, 84%) as a pale-yellow solid. The NMR data of compound **3.21** were consistent with the previously reported spectra.[235] The compound was prepared following an experimental procedure from the literature.[216]

L-aspartic acid benzyl ester (3.30)



A solution of N^{α}-(*tert*-butoxycarbonyl)-L-aspartic acid benzyl ester (500 mg, 1.55 mmol) in dry CH_2Cl_2 (18.0 mL) was cooled down to 0°C. Then, trifluoroacetic acid (6.0 mL, 78.4 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 2.5 h. After completion, the solution was poured into Et_2O and kept at 4°C overnight. The obtained precipitate was filtered off, washed three times with Et_2O and dried *in vacuo* affording the compound **3.30** (328 mg, 1.52 mmol, 98%) as a white solid. The NMR data of compound **3.30** were consistent with the previously reported spectra.[236] The compound was prepared following an experimental procedure from the literature.[217]

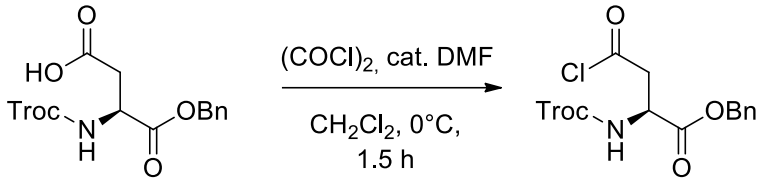
***N*$^{\alpha}$-(2,2,2-trichloroethoxycarbonyl)-L-aspartic acid benzyl ester (3.31)**



$NaHCO_3$ (4.52 g, 53.8 mmol) was added to a stirred solution of **3.30** (2.00 g, 8.96 mmol) in a mixture of THF and H_2O (100 mL, v/v 1:1). The resulting suspension was stirred at r.t. for 0.25 h. Then, it was cooled down to 0°C and treated dropwise with 2,2,2-trichloroethyl chloroformate (1.4 mL, 9.86 mmol). The reaction mixture was stirred at 0°C for 1 h. After this time, the obtained mixture was acidified with 0.05 M aq. $NaHSO_4$ to pH= 2-3 and extracted with EtOAc (3 x 200 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography (1:5→1:0 EtOAc/heptane) to afford the compound **3.31** (2.60 g, 6.54 mmol, 73%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.47-7.29 (m, 5H, 5x ArH^{Bn}), 5.98 (d, *J* = 8.7 Hz, 1H, *N*H), 5.21 (d, *J* = 3.0 Hz, 2H, CH_2^{Bn}), 4.77-4.72 (m, 2H, CH_2^{Troc}), 4.70 (dt, *J* = 8.7, 4.4 Hz, 1H, CH^{Asn}), 3.20-3.08 (m, 1H, CH_2^{Asn}), 3.05-2.92 (m, 1H, CH_2^{Asn}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 174.52 ($C{=}O^{Amide/Ester}$), 170.02 ($C{=}O^{Amide/Ester}$), 154.45 ($C{=}O^{Troc}$), 135.03 (ArC^{Bn}), 128.88 (2x $ArCH^{Bn}$), 128.80 (2x $ArCH^{Bn}$), 128.49 ($ArCH^{Bn}$), 95.35 (CCl_3), 74.95 (CH_2^{Troc}), 68.07 (CH_2^{Bn}), 50.57 (CH^{Asn}), 36.06 (CH_2^{Asn})

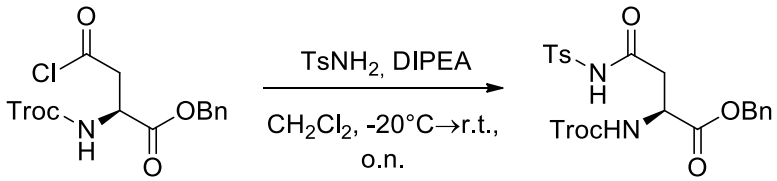
ppm. **HRMS** (MALDI+): Calculated for $C_{14}H_{14}Cl_3NO_6Na^+$ m/z 419.9784; found m/z 419.9767.

N$^{\alpha}$-(2,2,2-trichloroethoxycarbonyl)-L-aspartic acid acyl chloride benzyl ester (3.32)



A solution of the compound **3.31** (208 mg, 0.52 mmol) in dry CH_2Cl_2 (4.2 mL) was cooled down to 0°C. Then, the oxalyl chloride (53 μL, 0.63 mmol) was added dropwise followed by a catalytic amount of DMF. The reaction was stirred at 0°C for 1.5 h. After this time, the solution was evaporated to dryness at r.t. *in vacuo*. The obtained crude product was used in the next step without further purification.

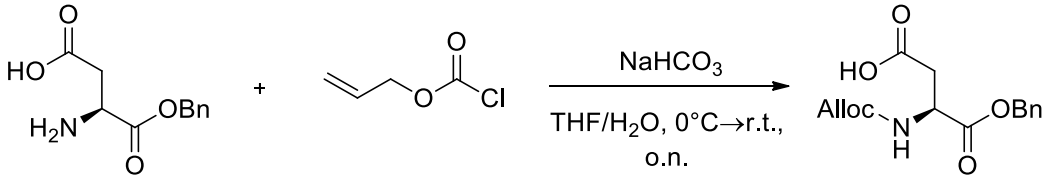
N$^{\alpha}$-(2,2,2-trichloroethoxycarbonyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.21)



A solution of $TsNH_2$ (0.41 g, 2.38 mmol) and DIPEA (0.8 mL, 4.77 mmol) in dry CH_2Cl_2 (20 mL) was cooled down to -20°C. Then, a solution of the acyl chloride **3.32** (0.99 g, 2.38 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was slowly allowed to warm up and stirred at r.t. overnight. After this time, the resulting solution was diluted with CH_2Cl_2 (100 mL) and washed with 1M aq. HCl (2 x 100 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was pourified by column chromatography (1:5→1:2 acetone/cyclohexane) to yield the compound **3.19** (0.64 g, 1.17 mmol, 49%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.43 (s, 1H, *N*H), 7.90 (d, *J* = 8.6 Hz, 2H, 2x ArH^{Ts}), 7.40-7.29 (m, 5H, 5x ArH^{Bn}), 7.26-7.21 (m, 2H, 2x ArH^{Ts}), 6.00 (d, *J* = 8.3 Hz, *N*H), 5.12 (d, *J* = 12.2 Hz, CH_2^{Bn}), 5.06 (d, *J* = 12.2 Hz, CH_2^{Bn}), 4.68 (s, 2H, CH_2^{Troc}), 4.59 (dt, *J* = 8.6, 4.5 Hz, 1H, CH^{Asn}), 3.04 (dd, *J* = 17.1, 4.5 Hz, 1H, CH_2^{Asn}), 2.88 (dd, *J* = 17.1, 4.5 Hz, 1H, CH_2^{Asn}), 2.44 (s, 3H, CH_3^{Ts}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 169.78 ($C{=}O^{Amide/Ester}$), 168.21 ($C{=}O^{Amide/Ester}$), 154.53 ($C{=}O^{Troc}$), 145.62 ($ArC^{Ts/Bn}$), 135.46 ($ArC^{Ts/Bn}$), 134.89 ($ArC^{Ts/Bn}$), 129.93 (2x $ArCH^{Bn}$), 128.80 (2x $ArCH^{Bn}$), 128.74 ($ArCH^{Bn}$), 128.44 (2x $ArCH^{Ts}$), 128.39 (2x

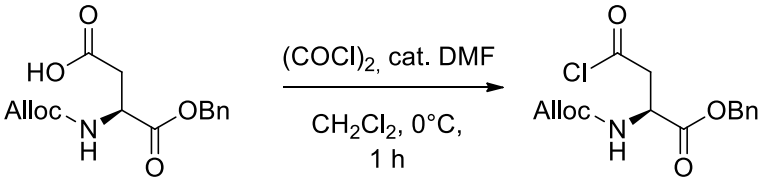
ArCH^{Ts}), 95.23 (CCl_3), 74.90 (CH_2^{Troc}), 68.14 (CH_2^{Bn}), 50.48 (CH^{Asn}), 38.03 (CH_2^{Asn}), 21.87 (CH_3^{Ts}) ppm. **HRMS** (MALDI+): Calculated for $C_{21}H_{21}Cl_3N_2O_7SNa^+$ m/z 573.0033; found m/z 573.0033. $[\alpha]_D^{589}$= 37.0° (*c*= 0.7, $CHCl_3$).

N$^{\alpha}$-(alloxycarbonyl)-L-aspartic acid benzyl ester (3.33)



$NaHCO_3$ (4.56 g, 54.3 mmol) was added to a stirred solution of **3.30** (2.02 g, 9.05 mmol) in a mixture of THF and H_2O (100 mL, v/v 1:1). The resulting suspension was stirred at r.t. for 0.5 h. Then, it was cooled down to 0°C and treated dropwise with allyl chloroformate (1.1 mL, 9.95 mmol) over 0.5 h. The reaction mixture was slowly allowed to warm up and stirred at r.t. overnight. After this time, the obtained mixture was acidified with 1 M aq. HCl to pH= 2-3 and extracted with EtOAc (3 x 200 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography (1:1 EtOAc/heptane) to afford the compound **3.33** (2.03 g, 6.61 mmol, 73%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H, 5x ArH^{Bn}), 5.90 (ddt, *J* = 16.6, 11.0, 5.7 Hz, 1H, =CH^{Alloc}), 5.75 (d, *J* = 8.5 Hz, 1H, *N*H), 5.31 (d, *J* = 16.6 Hz, 1H, =CH_2^{Alloc}), 5.26-5.15 (m, 3H, =CH_2^{Alloc}, CH_2^{Bn}), 4.67 (dt, *J* = 8.5, 4.6 Hz, 1H, CH^{Asn}), 4.63-4.54 (m, 2H, CH_2^{Alloc}), 3.10 (dd, *J* = 17.5, 4.6 Hz, 1H, CH_2^{Asn}), 2.92 (dd, *J* = 17.5, 4.6 Hz, 1H, CH_2^{Asn}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.81 (C=O$^{Amide/Ester}$), 170.49 (C=O$^{Amide/Ester}$), 156.02 (C=O^{Alloc}), 135.21 (ArC^{Bn}), 132.51 (=CH^{Alloc}), 128.75 (2x ArCH^{Bn}), 128.65 (ArCH^{Bn}), 128.41 (2x ArCH^{Bn}), 118.23 (=CH_2^{Alloc}), 67.86 (CH_2^{Bn}), 66.26 (CH_2^{Alloc}), 50.39 (CH^{Asn}), 36.51 (CH_2^{Asn}) ppm. **HRMS** (MALDI+): Calculated for $C_{15}H_{17}NO_6Na^+$ m/z 330.0954; found m/z 330.0940.

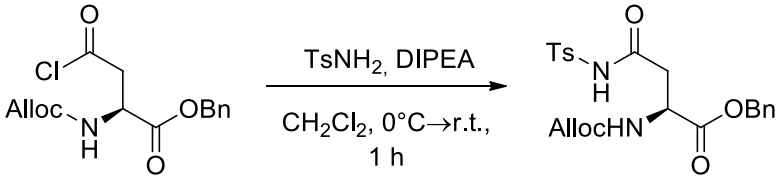
N$^{\alpha}$-(alloxycarbonyl)-L-aspartic acid acyl chloride benzyl ester (3.34)



A solution of the compound **3.33** (0.77 mg, 2.50 mmol) in dry CH_2Cl_2 (32.0 mL) was cooled down to 0°C. Then, the oxalyl chloride (0.4 mL, 5.01 mmol) was added dropwise followed by

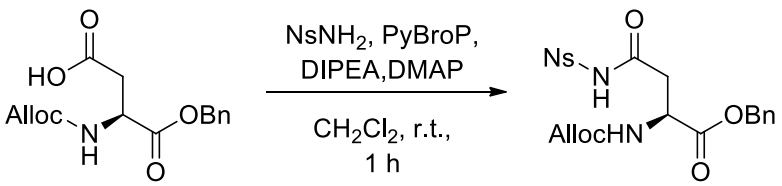
a catalytic amount of DMF. The reaction was stirred at 0°C for 1 h. After this time, the solution was evaporated to dryness at r.t. *in vacuo*. The obtained crude product was used in the next step without further purification.

N^{α}-(alloxycarbonyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.20)



A solution of $TsNH_2$ (0.47 g, 2.75 mmol) and DIPEA (0.9 mL, 5.01 mmol) in dry CH_2Cl_2 (18 mL) was cooled down to 0°C. Then, a solution of the acyl chloride **3.34** (0.82 g, 2.50 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise. The reaction mixture was slowly allowed to warm up and stirred at r.t. for 1 h. After this time, the resulting solution was diluted with CH_2Cl_2 and washed with 1M aq. HCl (2 x 100 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was pourified by column chromatography (1:5→1:2 acetone/cyclohexane) to yield the compound **3.20** (0.90 g, 1.95 mmol, 78%) as a pale-yellow solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.82 (s, 1H, *N*H), 7.90 (d, *J* = 8.6 Hz, 2H, 2x ArH^{Ts}), 7.39-7.28 (m, 5H, 5x ArH^{Bn}), 7.25 (d, *J* = 8.6 Hz, 2H, 2x ArH^{Ts}), 5.92-5.79 (m, 1H, $=CH^{Alloc}$), 6.79 (d, *J* = 8.0 Hz, *N*H), 5.27 (broad d, *J* = 17.1 Hz, $=CH_2^{Alloc}$), 5.19 (broad d, *J* = 10.2 Hz, 1H, $=CH_2^{Alloc}$), 5.12 (d, *J* = 12.1 Hz, CH_2^{Bn}), 5.05 (d, *J* = 12.1 Hz, CH_2^{Bn}), 4.60-4.48 (m, 3H, CH^{Asn}, CH_2^{Alloc}), 2.97 (broad d, *J* = 16.6 Hz, 1H, CH_2^{Asn}), 2.86 (broad d, *J* = 16.6 Hz, 1H, CH_2^{Asn}), 2.42 (s, 3H, CH_3^{Ts}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.4 ($C=O^{Amide/Ester}$), 168.6 ($C=O^{Amide/Ester}$), 156.2 ($C=O^{Alloc}$), 145.3 ($ArC^{Ts/Bn}$), 135.7 ($ArC^{Ts/Bn}$), 135.1 ($ArC^{Ts/Bn}$), 132.4 ($=CH^{Alloc}$), 129.8 (2x $ArCH^{Ts}$), 128.7 (2x $ArCH^{Bn}$), 128.6 ($ArCH^{Bn}$), 128.3 (2x $ArCH^{Bn}$), 118.1 ($=CH_2^{Alloc}$), 67.9 (CH_2^{Bn}), 66.3 (CH_2^{Alloc}), 50.4 (CH_2^{Asn}), 38.4 (CH_2^{Asn}), 21.8 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{22}H_{24}N_2O_7SNa^+$ m/z 483.1202; found m/z 483.1197. $[\alpha]_D^{589}$= 39.4° (*c*= 0.6, $CHCl_3$).

N^{α}-(alloxycarbonyl)-*N*-(nosyl)-L-asparagine benzyl ester (3.22)



PyBroP (1.54 g, 3.30 mmol) was added to a stirred solution of **3.33** (0.80 g, 2.59 mmol), $NsNH_2$ (0.48 g, 2.36 mmol), DIPEA (1.0 mL, 5.90 mmol) and DMAP (14.4 mg, 0.12 mmol) in dry CH_2Cl_2 (24 mL). The reaction mixture was stirred at r.t. for 1 h. After this time, the resulting solution was diluted with CH_2Cl_2 (100 mL) and washed with 1M HCl (2 x 100 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography (1:3→2:1 EtOAc/heptane) to yield the compound **3.22** (1.07 g, 1.65 mmol, 70%) as a pale-yellow solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 12.60 (broad s, 1H, *N*H), 8.40 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ns}), 8.15 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ns}), 7.74 (d, *J* = 8.1 Hz, *N*H), 7.40-7.21 (m, 5H, 5x ArH^{Bn}), 5.91-5.77 (m, 1H, $=CH^{Alloc}$),5.23 (broad d, *J* = 17.4 Hz, $=CH_2^{Alloc}$), 5.14 (broad d, *J* = 10.7 Hz, $=CH_2^{Alloc}$), 5.09-4.99 (m, 2H, CH_2^{Bn}), 4.51-4.33 (3H, CH^{Asn}, CH_2^{Alloc}), 2.87 (dd, *J* = 16.9, 5.8 Hz, 1H, CH_2^{Asn}), 2.66 (dd, *J* = 16.9, 7.9 Hz, 1H, CH_2^{Asn}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.7 ($C=O^{Amide/Ester}$), 169.0 ($C=O^{Amide/Ester}$), 150.2 ($C=O^{Alloc}$), 144.6 ($ArC^{Ns/Bn}$), 135.7 ($ArC^{Ns/Bn}$), 133.3 (CH^{Alloc}), 129.2 (ArCH), 128.4 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 124.4 (ArCH), 117.1 ($=CH_2^{Alloc}$), 66.2 (CH_2^{Bn}), 64.6 (CH_2^{Alloc}), 49.7 (CH_2^{Asn}), 37.3 (CH_2^{Asn}) ppm. **HRMS** (MALDI+): Calculated for $C_{21}H_{21}N_3O_9SNa^+$ m/z 514.0896; found m/z 514.0888.

3.4.4. Self-promoted *N*-glycosylations

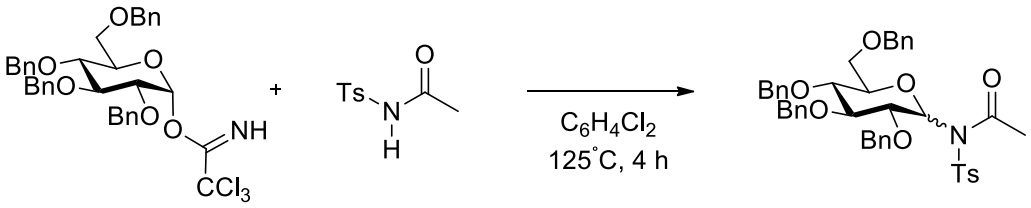
General procedure A for glycosylations

Amide acceptor (1.5 equiv.) was added to a stirred solution of trichloroacetimidate glycosyl donor (1.0 equiv., 0.2 mmol) in dry $C_6H_4Cl_2$ (2.0 mL) under a nitrogen atmosphere in flame-dried glassware. Depending on the glycosyl donor used, the reaction was stirred at 125 °C for h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) to remove trichloroacetamide and brine (50 mL). The products were purified by flash column chromatography and evaporated to dryness.

General procedure B for glycosylations

Amide acceptor (1.0 equiv.) was added to a stirred solution of trichloroacetimidate glycosyl donor (1.5 equiv., 0.2 mmol) in dry $C_6H_4Cl_2$ (2.0 mL) under a nitrogen atmosphere in flame-dried glassware. Depending on the glycosyl donor used, the reaction was stirred at 125 °C for h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) to remove trichloroacetamide and brine (50 mL). The products were purified by flash column chromatography and evaporated to dryness.

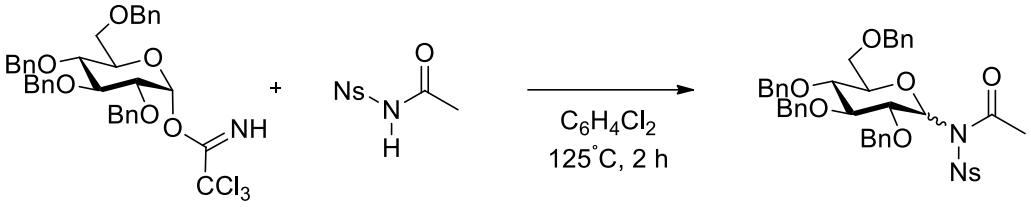
***N*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-*N*-tosylacetamide (3.35)**



3.18 (85.2 mg, 0.40 mmol) was added to a stirred solution of **1.7α** (183 mg, 0.27 mmol) in dry $C_6H_4Cl_2$ (2.7 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 4 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:4 EtOAc/heptane) to yield the β anomer of compound **3.35** (163 mg, 0.22 mmol, 83%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.93 (broad s, 2H, 2x ArH^{Ts}), 7.42-7.13 (m, 20H, 20x ArH^{Bn}), 7.06 (d, *J* = 7.9 Hz, 2H, 2x ArH^{Ts}), 5.52 (d, *J* = 9.4 Hz, 1H, H-1), 4.93 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.89 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.85 (d, *J* = 10.9 Hz,

1H, CH_2^{Bn}), 4.82-4.70 (m, 2H, CH_2^{Bn}), 4.59 (d, *J* = 10.9 Hz, 2H, CH_2^{Bn}), 4.55-4.41 (m, 2H, H-2, CH_2^{Bn}), 3.83-3.69 (m, 3H, H-3, H-6, H-6'), 3.68 (t, *J* = 9.5 Hz, 1H, H-4), 3.65-3.60 (m, 1H, H-5), 2.33 (s, 3H, CH_3^{Ts}), 2.15 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.71 (C=O), 144.68 ($ArC^{Ts/Bn}$), 138.54 ($ArC^{Ts/Bn}$), 138.31 ($ArC^{Ts/Bn}$), 138.12 ($ArC^{Ts/Bn}$), 137.98 ($ArC^{Ts/Bn}$), 137.02 ($ArC^{Ts/Bn}$), 129.60 (2x $ArCH^{Ts}$), 128.59-127.77 (24x $ArCH^{Ts/Bn}$), 86.89 (C-3), 85.87 (C-1), 77.93 (C-5), 77.80 (C-4), 7.75-76.50 (C-2, same as $CDCl_3$), 75.87 (CH_2^{Bn}), 75.26 (CH_2^{Bn}), 74.83 (CH_2^{Bn}), 73.53 (CH_2^{Bn}), 69.25 (C-6), 25.85 (CH_3^{Ac}), 21.72 (CH_3^{Ts}) ppm. **HRMS** (MALDI+): Calculated for $C_{43}H_{45}NO_8SNa^+$ m/z 758,2764; found m/z 758.2735. $[\alpha]_D^{589}$= 11.4° (*c*= 0.7, $CHCl_3$).

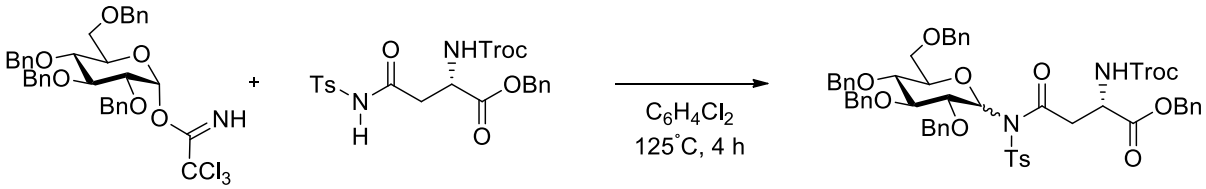
N-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-*N*-nosylacetamide (3.37)



3.21 (79.2 mg, 0.32 mmol) was added to a stirred solution of **1.7α** (148 mg, 0.22 mmol) in dry $C_6H_4Cl_2$ (2.2 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH (50 mL) solution and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:4 EtOAc/heptane) to yield the β anomer of compound **3.37** (134 mg, 0.18 mmol, 81%) as a pale-yellow solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.23 (broad s, 2H, 2x ArH^{Ns}), 8.04 (d, *J* = 8.5 Hz, 2H, 2x ArH^{Ns}), 7.50-7.16 (m, 20H, 20x ArH^{Bn}), 5.43 (broad s, 1H, H-1), 5.01-4.92 (m, 2H, CH_2^{Bn}), 4.92-4.84 (m, 2H, CH_2^{Bn}), 4.80-4.68 (m, 1H, CH_2^{Bn}), 4.60 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.57 (d, *J* = 11.8 Hz, 1H, CH_2^{Bn}), 4.52 (d, *J* = 11.8 Hz, 1H, CH_2^{Bn}), 4.45-4.22 (m, 1H, H-2), 3.87-3.69 (m, 4H, H-3, H-4, H-6, H-6'), 3.69-3.60 (m, 1H, H-5), 2.14 (s, 3H, CH_3) ppm. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 8.33-8.13 (m, 4H, 4x ArH^{Ns}), 7.52-7.05 (m, 20H, 20x ArH^{Bn}), 5.53 (d, *J* = 9.3 Hz, 1H, H-1), 4.86 (s, 2H, CH_2^{Bn}), 4.79 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.75 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.70-4.62 (m, 1H, CH_2^{Bn}), 4.61 (d, *J* = 12.0 Hz, 1H, CH_2^{Bn}), 4.57 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.53 (d, *J* = 12.0 Hz, 1H, CH_2^{Bn}), 4.38-4.08 (m, 1H, H-2), 3.92-3.81 (m, 2H, H-3, H-5), 3.79-3.67 (m, 2H, H-6, H-6'), 3.63 (t, *J* = 9.5 Hz, 1H, H-4), 2.26 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.77 (C=O), 150.44 ($ArC^{Ns/Bn}$), 145.31 ($ArC^{Ns/Bn}$), 138.23 ($ArC^{Ns/Bn}$), 137.91 ($ArC^{Ns/Bn}$), 137.87 ($ArC^{Ns/Bn}$), 137.53 ($ArC^{Ns/Bn}$),

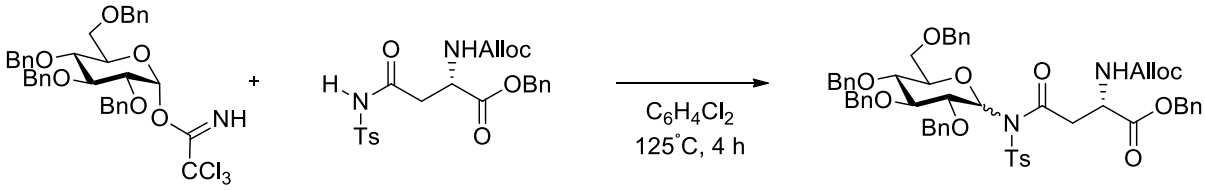
130.21 (2x $ArCH^{Ns}$), 128.70-127.80 (20x $ArCH^{Bn}$), 123.87 (2x $ArCH^{Ns}$), 86.75 (C-3), 86.21 (C-1), 77.91 (C-5), 77.53 (C-4), 7.75-76.50 (C-2, same as $CDCl_3$), 75.98 (CH_2^{Bn}), 75.36 (CH_2^{Bn}), 75.04 (CH_2^{Bn}), 73.62 (CH_2^{Bn}), 68.92 (C-6), 25.51 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{42}H_{42}N_2O_{10}SNa^+$ m/z 789.2458; found m/z 789.2427. $[\alpha]_D^{589}$= 14.1° (*c*= 0.7, $CHCl_3$).

N$^{\alpha}$-(2,2,2-trichloroethoxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.41)



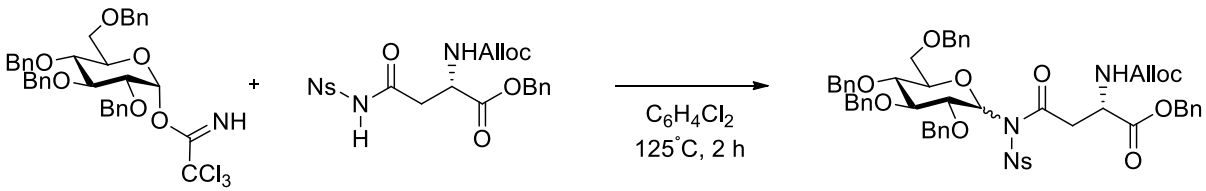
3.19 (132 mg, 0.24 mmol) was added to a stirred solution of **1.7α** (110 mg, 0.16 mmol) in dry $C_6H_4Cl_2$ (1.6 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 4 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH (50 mL) solution and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:4 EtOAc/heptane) to yield the β anomer of compound **3.41** (119 mg, 0.11 mmol, 69%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.19-7.68 (m, 2H, 2x ArH^{Ts}), 7.63-6.88 (m, 27H, 2x ArH^{Ts}, 25x ArH^{Bn}), 5.78 (broad s, 1H, *N*H), 5.47 (d, *J* = 9.3 Hz, 1H, H-1), 5.07 (d, *J* = 12.0 Hz, 1H, CH_2^{Troc}), 4.92 (d, *J* = 11.4 Hz, 1H, CH_2^{Bn}), 4.90 (d, *J* ~ 10.8 Hz, 1H, CH_2^{Bn}), 4.88 (d, *J* = 11.4 Hz, 1H, CH_2^{Bn}), 4.84 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.84 (d, *J* ~ 12.0 Hz, 1H, CH_2^{Troc}), 4.77-4.69 (m, 1H, CH_2^{Bn}), 4.65 (d, *J* = 12.0 Hz, 1H, CH_2^{Bn}), 4.59 (d, *J* = 10.8 Hz, 1H, CH_2^{Bn}), 4.58-4.23 (m, 5H, H-2, CH^{Asn}, CH_2^{Bn}), 3.92-3.64 (m, 4H, H-3, H-4, H-6, H-6'), 3.64-3.54 (m, 1H, H-5), 3.51-2.86 (m, 2H, CH_2^{Asn}), 2.30 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 171.67 ($C{=}O^{Amide/Ester}$), 170.02 ($C{=}O^{Amide/Ester}$), 154.36 ($C{=}O^{Troc}$), 144.99 ($ArC^{Ts/Bn}$), 138.50 ($ArC^{Ts/Bn}$), 138.20 ($ArC^{Ts/Bn}$), 138.04 ($ArC^{Ts/Bn}$), 137.92 ($ArC^{Ts/Bn}$), 136.46 ($ArC^{Ts/Bn}$), 135.22 ($ArC^{Ts/Bn}$), 129.82 (2x $ArCH^{Ts}$), 128.64-127.75 (27x $ArCH^{Ts/Bn}$), 95.28 (CCl_3), 86.79 (C-3), 86.34 (C-1), 77.98 (C-5), 7.75-76.50 (C-2, C-4, same as $CDCl_3$), 75.81 (CH_2^{Bn}), 75.29 (CH_2^{Bn}), 74.89 (CH_2^{Bn}), 74.77 (CH_2^{Bn}), 73.54 (CH_2^{Bn}), 69.08 (C-6), 67.55 (CH_2^{Troc}), 50.66 (CH^{Asn}), 40.47 (CH_2^{Asn}), 21.74 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{55}H_{55}Cl_3N_2O_{12}SNa^+$ m/z 1095.2439; found m/z 1095.2389. $[\alpha]_D^{589}$= 31.0° (*c*= 0.8, $CHCl_3$).

N^{α}-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.42)



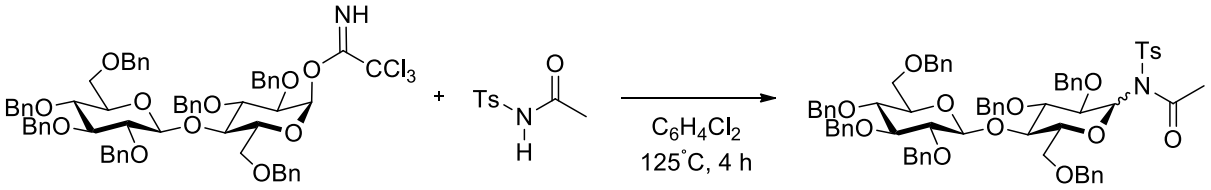
3.20 (116 mg, 0.25 mmol) was added to a stirred solution of **1.7α** (115 mg, 0.17 mmol) in dry $C_6H_4Cl_2$ (1.7 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 4 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:4 EtOAc/heptane) to yield the β anomer of compound **3.42** (125 mg, 0.13 mmol, 76%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.20-7.62 (m, 2H, 2x ArH^{Ts}), 7.52-6.82 (m, 27H, 2x ArH^{Ts}, 25x ArH^{Bn}), 5.77 (broad s, 1H, CH^{Alloc}), 5.54 (broad s, 1H, *N*H), 5.45 (d, *J* = 9.2 Hz, 1H, H-1), 5.20 (broad d, *J* = 17.2 Hz, 1H, $=CH_2^{Trans}$), 5.13 (broad d, *J* = 8.5 Hz, 1H, $=CH_2^{Cis}$), 5.07 (d, *J* = 12.2 Hz, 1H, CH_2^{Bn}), 4.95-4.79 (m, 5H, CH_2^{Bn}), 4.75-4.65 (m, 1H, CH_2^{Bn}), 4.59 (d, *J* = 10.6 Hz, 2H, CH_2^{Bn}), 4.56-4.42 (m, 4H, H-2, CH^{Asn}, CH_2^{Alloc}, CH_2^{Bn}), 4.42-4.32 (m, 1H, CH_2^{Alloc}), 3.86-3.62 (m, 4H, H-3, H-4, H-6, H-6'), 3.62-3.51 (m, 1H, H-5), 3.51-2.87 (m, 2H, CH_2^{Asn}), 2.29 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 171.78 ($C=O^{Amide/Ester}$), 170.50 ($C=O^{Amide/Ester}$), 155.89 ($C=O^{Alloc}$), 144.90 ($ArC^{Ts/Bn}$), 138.54 ($ArC^{Ts/Bn}$), 138.25 ($ArC^{Ts/Bn}$), 138.08 ($ArC^{Ts/Bn}$), 137.95 ($ArC^{Ts/Bn}$), 136.53 ($ArC^{Ts/Bn}$), 135.39 ($ArC^{Ts/Bn}$), 132.55 (CH^{Alloc}), 129.78 (2x $ArCH^{Ts}$), 128.66-127.76 (27x $ArCH^{Ts/Bn}$), 117.92 ($=CH_2^{Alloc}$), 86.75 (C-3), 86.31 (C-1), 78.01 (C-5), 7.75-76.50 (C-2, C-4, same as $CDCl_3$), 75.80 (CH_2^{Bn}), 75.27 (CH_2^{Bn}), 75.00 (CH_2^{Bn}), 73.54 (CH_2^{Bn}), 69.07 (C-6), 67.39 (CH_2^{Bn}), 65.99 (CH_2^{Alloc}), 50.44 (CH^{Asn}), 40.84 (CH_2^{Asn}), 21.73 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{56}H_{58}N_2O_{12}SNa^+$ m/z 1005.3608; found m/z 1005.3575. $[\alpha]_D^{589}$= 40.7° (*c*= 0.5, $CHCl_3$).

N^{α}-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-*N*-(nosyl)-L-asparagine benzyl ester (3.43)



3.22 (107 mg, 0.22 mmol) was added to a stirred solution of **1.7α** (99.8 mg, 0.15 mmol) in dry $C_6H_4Cl_2$ (1.5 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:4 EtOAc/heptane) to yield the β anomer of compound **3.43** (105 mg, 0.11 mmol, 71%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.41-7.80 (m, 4H, 4x ArH^{Ns}), 7.52-7.00 (m, 25H, 25x ArH^{Bn}), 5.82 (m, 1H, CH^{Alloc}), 5.55 (br, 1H, *N*H), ~5.42 (br, 1H, H-1), 5.25 (d, *J* = 17.1 Hz, 1H, $=CH_2^{Trans}$), 5.17 (d, *J* = 10.3 Hz, 1H, $=CH_2^{Cis}$), 5.10 (d, *J* = 12.4 Hz, 1H, CH_2^{Bn}), 4.96-4.65 (m, 6H, CH_2^{Bn}), 4.60 (d, *J* = 10.8 Hz, 2H, CH_2^{Bn}), 4.59-4.37 (m, 5H, H-2, CH^{Asn}, CH_2^{Alloc}, CH_2^{Bn}), 3.79-3.44 (m, 5H, H-3, H-4, H5, H-6, H-6'), 3.38-3.08 (m, 2H, CH_2^{Asn}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.38 ($C=O^{Amide/Ester}$), 155.88 ($C=O^{Amide/Ester}$), 150.45 ($C=O^{Alloc}$), 144.79 ($ArC^{Ns/Bn}$), 138.24 ($ArC^{Ns/Bn}$), 137.91 (2x $ArC^{Ns/Bn}$), 137.56 ($ArC^{Ns/Bn}$), 135.19 (2x $ArC^{Ns/Bn}$), 132.4 (CH^{Alloc}), 128.74-127.82 (27x $ArCH^{Ns/Bn}$), 123.91 (2x $ArCH^{Ns}$), 118.15 ($=CH_2^{Alloc}$), 86.54 (broad, C-3), 86.17 (broad, C-1), 77.99 (C-5), 77.90-76.50 (C-2, C-4, same as $CDCl_3$), 75.92 (CH_2^{Bn}), 75.36 (CH_2^{Bn}), ~75.00 (broad, CH_2^{Bn}), 73.61 (CH_2^{Bn}), 68.76 (C-6), 67.56 (CH_2^{Bn}), 66.14 (CH_2^{Alloc}), 50.42 (CH^{Asn}), ~40.00 (broad, CH_2^{Asn}) ppm. **HRMS** (MALDI+): Calculated for $C_{55}H_{55}N_3O_{14}SNa^+$ m/z 1036.3302; found m/z 1036.3271 $[\alpha]_D^{589}$= 56.0° (*c*= 0.4, $CHCl_3$).

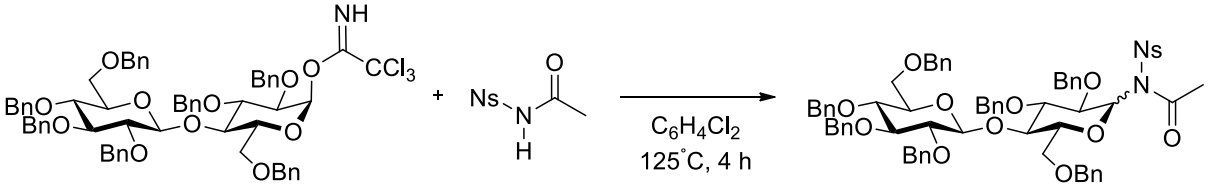
N-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranosyl)-*N*-tosylacetamide (3.45)



3.18 (32.8 mg, 0.15 mmol) was added to a stirred solution of **3.5α** (115 mg, 0.10 mmol) in dry $C_6H_4Cl_2$ (1.0 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 4 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:5 EtOAc/heptane) to yield the β anomer of compound **3.45** (86.5 mg, 0.07 mmol, 72%) as a colorless syrup. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.89 (broad s, 2H, 2x

ArH^{Ts}), 7.58-7.10 (m, 35H, 35x ArH^{Bn}), 7.03 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ts}), 5.51 (d, *J* = 9.5 Hz, 1H, H-1a), 5.19 (d, *J* = 11.3 Hz, 1H, CH_2^{Bn}), 4.91 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.83 (d, *J* = 11.3 Hz, 1H, CH_2^{Bn}), 4.81 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.81-4.76 (m, 3H, CH_2^{Bn}), 4.74 (d, *J* = 11.3 Hz, 1H, CH_2^{Bn}), 4.71-4.59 (m, 1H, CH_2^{Bn}), 4.57-4.49 (m, 3H, H-1b, CH_2^{Bn}), 4.44-4.32 (m, 4H, H-2a, CH_2^{Bn}), 4.09 (t, *J* = 9.5 Hz, 1H, H-4a), 3.87 (dd, *J* = 11.1, 4.3 Hz, 1H, H-6a), 3.75-3.66 (m, 3H, H-3a, H-6a', H-6b), 3.64 (t, *J* = 9.5 Hz, H-4b), 3.61-3.49 (m, 3H, H-3b, H-5a, H-6b'), 3.41 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2b), 3.33 (ddd, *J* = 9.5, 4.5, 1.9 Hz, 1H, H-5b), 2.32 (s, 3H, CH_3^{Ts}), 2.08 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.61 (C=O), 144.55 ($ArC^{Ts/Bn}$), 139.25 ($ArC^{Ts/Bn}$), 138.71 ($ArC^{Ts/Bn}$), 138.55 ($ArC^{Ts/Bn}$), 138.47 ($ArC^{Ts/Bn}$), 138.33 ($ArC^{Ts/Bn}$), 138.26 ($ArC^{Ts/Bn}$), 138.08 ($ArC^{Ts/Bn}$), 137.03 ($ArC^{Ts/Bn}$), 129.50 (2x $ArCH^{Ts}$), 128.52-127.38 (37x $ArCH^{Ts/Bn}$), 102.78 (C-1b), 85.75 (C-1a), 85.23 (C-3a), 85.10 (C-3b), 82.90 (C-2b), 78.30 (C-5a), 78.17 (C-4b), 7.75-76.50 (C-2a, same as $CDCl_3$), 76.54 (C-4a), 75.81 (CH_2^{Bn}), 75.48 (CH_2^{Bn}), 75.30 (CH_2^{Bn}), 75.22 (C-5b), 75.02 (CH_2^{Bn}), 74.77 (CH_2^{Bn}), 73.48 (CH_2^{Bn}), 73.32 (CH_2^{Bn}), 69.01 (C-6b), 68.31 (C-6a), 25.75 (CH_3^{Ac}), 21.70 (CH_3^{Ts}) ppm. **HRMS** (MALDI+): Calculated for $C_{70}H_{73}NO_{13}SNa^+$ m/z 1190.4700; found m/z 1190.4649. $[\alpha]_D^{589}$= 15.3° (*c*= 1.0, $CHCl_3$).

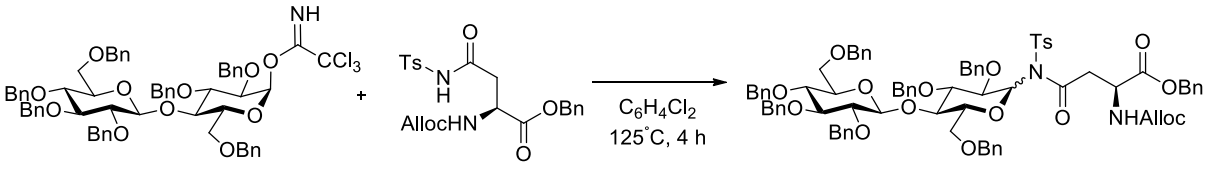
N-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranosyl)-*N*-nosylacetamide (3.46)



3.21 (38.3 mg, 0.16 mmol) was added to a stirred solution of **3.5α** (117 mg, 0.11 mmol) in dry $C_6H_4Cl_2$ (1.1 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:4 EtOAc/heptane) to yield the β anomer of compound **3.46** (93.0 mg, 0.08 mmol, 74%) as a pale-yellow solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H, 2x ArH^{Ns}), 7.97 (d, *J* = 8.5 Hz, 2H, 2x ArH^{Ns}), 7.57-7.04 (m, 35H, 35x ArH^{Bn}), 5.40 (broad d, *J* = 9.2 Hz, 1H, H-1a), 5.22 (d, *J* = 11.1 Hz, 1H, CH_2^{Bn}), 4.91 (d, *J* = 10.9 Hz, 1H, CH_2^{Bn}), 4.88-4.78 (m, 4H, CH_2^{Bn}), 4.75 (d, *J* = 11.2 Hz, 1H, CH_2^{Bn}), 4.68-4.54 (m, 1H, CH_2^{Bn}), 4.55 (d,

J = 10.8 Hz, 1H, CH_2^{Bn}), 4.52-4.46 (m, 2H, H-1b, CH_2^{Bn}), 4.46-4.40 (m, 2H, CH_2^{Bn}), 4.37 (d, *J* = 12.0 Hz, 1H, CH_2^{Bn}), 4.30-4.11 (m, 1H, H-2a), 4.11 (t, *J* = 9.5 Hz, 1H, H-4a), 3.88 (dd, *J* = 10.9, 4.1 Hz, 1H, H-6a), 3.78-3.65 (m, 3H, H-3a, H-6a', H-6b), 3.63 (t, *J* = 9.4 Hz, 1H, H-4b), 3.60-3.54 (m, 2H, H-3b, H-6b'), 3.51 (broad ddd, *J* = 9.5, 4.1, 2.2 Hz, H-5a), 3.43 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2b), 3.36 (ddd, *J* = 9.4, 4.7, 1.9 Hz, 1H, H-5b), 2.08 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.81 (C=O), 150.36 ($ArC^{Ns/Bn}$), 145.29 ($ArC^{Ns/Bn}$), 138.96 ($ArC^{Ns/Bn}$), 138.63 ($ArC^{Ns/Bn}$), 138.50 ($ArC^{Ns/Bn}$), 138.41 ($ArC^{Ns/Bn}$), 138.25 ($ArC^{Ns/Bn}$), 137.84 ($ArC^{Ns/Bn}$), 137.61 ($ArC^{Ns/Bn}$), 130.16 (2x $ArCH^{Ns}$), 128.69-127.57 (35x $ArCH^{Bn}$), 123.78 (2x $ArCH^{Ns}$), 102.86 (C-1b), 86.00 (C-1a), 85.09 (C-3a), 85.05 (C-3b), 82.89 (C-2b), 78.22 (C-5a), 78.13 (C-4b), 7.75-76.50 (C-2a, same as $CDCl_3$), 76.37 (C-4a), 75.84 (CH_2^{Bn}), 75.64 (CH_2^{Bn}), 75.38 (C-5b), 75.28 (CH_2^{Bn}), 75.06 (CH_2^{Bn}), 74.99 (CH_2^{Bn}), 73.49 (CH_2^{Bn}), 73.36 (CH_2^{Bn}), 69.07 (C-6b), 68.01 (C-6a), 25.44 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{69}H_{70}N_2O_{15}SNa^+$ m/z 1221.4395; found m/z 1221.4363. $[\alpha]_D^{589}$= 18.4° (*c*= 0.9, $CHCl_3$).

N^{α}-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranosyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.47)

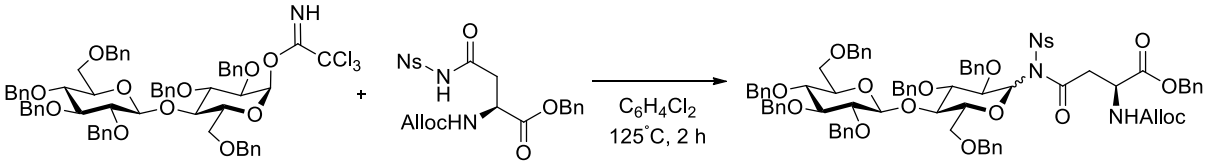


3.20 (63.6 mg, 0.14 mmol) was added to a stirred solution of **3.5α** (103 mg, 0.09 mmol) in dry $C_6H_4Cl_2$ (0.9 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 4 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:5 EtOAc/heptane) to yield the β anomer of compound **3.47** (98.9 mg, 0.07 mmol, 76%) as a colorless syrup.‡‡‡ **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.07-7.69 (m, 2H, 2x ArH^{Ts}), 7.69-7.07 (m, 40H, 40x ArH^{Bn}), 7.07-6.79 (m, 2H, 2x ArH^{Ts}), 5.89-5.67 (m, 1H, CH^{Alloc}), 5.60-5.47 (m, 1H, *N*H), 5.42 (d, *J* = 9.4 Hz, 1H, H-1a), 5.29-5.15 (m, 2H, $=CH_2^{Trans}$, CH_2^{Bn}), 5.12 (dd, *J* = 10.4, 3.7 Hz, 1H, $=CH_2^{Cis}$), 5.04 (d, *J* = 12.4 Hz, 1H, CH_2^{Bn}), 4.90 (d, *J* = 11.0 Hz, 1H, CH_2^{Bn}), 4.87-4.66 (m, 7H, CH_2^{Bn}), 4.60-4.44 (m, 6H, H-1b, CH^{Asn}, CH_2^{Alloc}, CH_2^{Bn}), 4.44-4.25 (m, 5H, H-2a, CH_2^{Bn}), 4.18-4.04 (m, 1H, H-4a), 3.93-3.78 (m, 1H, H-6a),

‡‡‡ Isolated compound contained 8% of α anomer.

3.76-3.60 (m, 4H, H-3a, H-4b, H-6a', H-6b), 3.60-3.53 (m, 2H, H-3b, H-6b'), 3.52-3.44 (m, 1H, H-5a), 3.41 (t, *J* = 8.5 Hz, 1H, H-2b), 3.36-3.18 (m, 2H, H-5b, CH_2^{Asn}), 3.17-2.96 (m, 1H, CH_2^{Asn}), 2.19 (s, 3H, CH_3) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 171.71 ($C{=}O^{Amide/Ester}$), 170.48 ($C{=}O^{Amide/Ester}$), 155.88 ($C{=}O^{Alloc}$), 144.80 ($ArC^{Ts/Bn}$), 139.23 ($ArC^{Ts/Bn}$), 138.71 ($ArC^{Ts/Bn}$), 138.53 ($ArC^{Ts/Bn}$), 138.47 ($ArC^{Ts/Bn}$), 138.34 ($ArC^{Ts/Bn}$), 138.22 ($ArC^{Ts/Bn}$), 138.09 ($ArC^{Ts/Bn}$), 136.57 ($ArC^{Ts/Bn}$), 135.38 ($ArC^{Ts/Bn}$), 132.55 (CH^{Alloc}), 129.69 (2x $ArCH^{Ts}$), 128.62-127.34 (42x $ArCH^{Ts/Bn}$), 117.89 ($=CH_2^{Alloc}$), 102.75 (C-1b), 86.21 (C-1a), 85.09 (C-3a/C-3b), 85.02 (C-3a/C-3b), 82.87 (C-2b), 78.39 (C-5a), 78.16 (C-4b), 7.75-76.50 (C-2a, same as $CDCl_3$), 76.31 (C-4a), 75.79 (CH_2^{Bn}), 75.44 (CH_2^{Bn}), 75.24 (CH_2^{Bn}), 75.19 (CH_2^{Bn}), 75.01 (C-5b, CH_2^{Bn}), 73.48 (CH_2^{Bn}), 73.33 (CH_2^{Bn}), 68.97 (C-6b), 68.14 (C-6a), 67.34 (CH_2^{Bn}), 65.96 (CH_2^{Alloc}), 50.39 (CH^{Asn}), 40.68 (CH_2^{Asn}), 21.70 (CH_3) ppm. **HRMS** (MALDI+): Calculated for $C_{83}H_{86}N_2O_{17}SNa^+$ m/z 1437.5545; found m/z 1437.5483. $[\alpha]_D^{589}$= 44.1° (*c*= 0.8, $CHCl_3$).

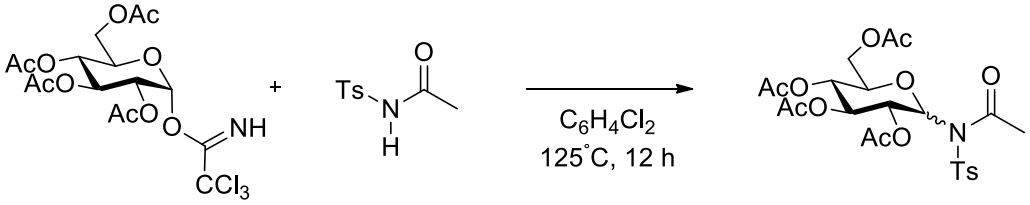
N^{α}-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-D-glucopyranosyl)-*N*-(nosyl)-L-asparagine benzyl ester (3.48)



3.22 (70.6 mg, 0.14 mmol) was added to a stirred solution of **3.5α** (107 mg, 0.10 mmol) in dry $C_6H_4Cl_2$ (1.0 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:7→1:5 EtOAc/heptane) to yield the β anomer of compound **3.48** (77.7 mg, 0.06 mmol, 56%) as a pale yellow syrup.**^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.31-7.98 (m, 2H, 2x ArH^{Ns}), 7.98-7.74 (m, 2H, 2x ArH^{Ns}), 7.69-6.91 (m, 40H, 40x ArH^{Bn}), 5.81 (ddt, 1H, *J* = 16.3, 10.7, 5.5 Hz, $=CH^{Alloc}$), 5.55 (d, 1H, *J* = 8.8 Hz, *N*H), 5.48-5.18 (m, 3H, H-1a, $=CH_2^{Trans}$, CH_2^{Bn}), 5.15 (d, 1H, *J* = 10.7 Hz, $=CH_2^{Cis}$), 5.06 (d, *J* = 12.4 Hz, 1H, CH_2^{Bn}), 4.98-4.76 (m, 7H, CH_2^{Bn}), 4.73 (d, 1H, *J* = 11.3 Hz, CH_2^{Bn}), 4.61-4.46 (m, 6H, H-1b, CH^{Asn}, CH_2^{Alloc}, CH_2^{Bn}), 4.45-4.28 (m, 5H, H-2a, CH_2^{Alloc}, CH_2^{Bn}), 4.14 (t, 1H, *J* = 9.6 Hz, H-4a),3.87 (dd, *J* = 11.1, 4.0 Hz, H-6a), 3.78-3.61 (m, 4H, H-3a, H-4b, H-6a', H-6b), 3.61-3.54 (m, 2H, H-3b, H-6b'), 3.53-3.45 (m, 1H, H-5a), 3.42 (dd, *J* = 8.8, 8.3 Hz, 1H, H-2b), 3.35 (ddd, *J* = 9.7, 4.5, 1.9 Hz, 1H, H-5b), 3.26 (broad d, *J* = 17.7 Hz, 1H, CH_2^{Asn}), 3.12 (broad d, *J* = 17.7 Hz, 1H, CH_2^{Asn}) ppm.

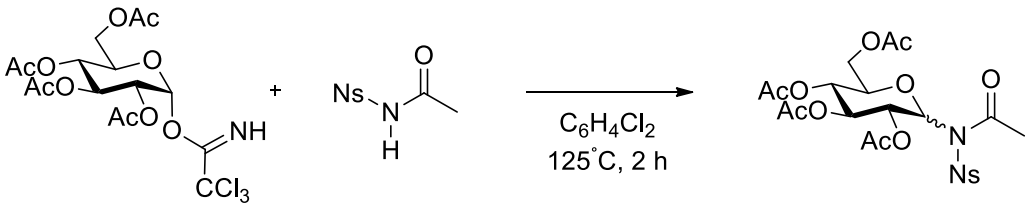
^{13}C-NMR (126 MHz, $CDCl_3$) δ 172.00 ($C{=}O^{Amide/Ester}$), 170.39 ($C{=}O^{Amide/Ester}$), 155.87 ($C{=}O^{Alloc}$), 150.37 ($ArC^{Ns/Bn}$), 144.75 ($ArC^{Ns/Bn}$), 138.95 ($ArC^{Ns/Bn}$), 138.63 ($ArC^{Ns/Bn}$), 138.44 ($ArC^{Ns/Bn}$), 138.40 ($ArC^{Ns/Bn}$), 138.26 ($ArC^{Ns/Bn}$), 137.80 ($ArC^{Ns/Bn}$), 137.70 ($ArC^{Ns/Bn}$), 135.18 ($ArC^{Ns/Bn}$), 132.43 (CH^{Alloc}), 130.02 (2x $ArCH^{Ns}$), 128.73-127.51 (40x $ArCH^{Bn}$), 123.83 (2x $ArCH^{Ns}$), 118.10 ($=CH_2^{Alloc}$), 102.86 (C-1b), 86.16 (C-1a), 85.07 (C-3b), 84.81 (C-3b), 82.84 (C-2b), 78.31 (C-5a), 78.09 (C-4b), 7.75-76.50 (C-2a, same as $CDCl_3$), 76.21 (C-4a), 75.82 (CH_2^{Bn}), 75.54 (CH_2^{Bn}), 75.28 (C-5b, CH_2^{Bn}), 75.25 (CH_2^{Bn}), 75.03 (CH_2^{Bn}), 73.46 (CH_2^{Bn}), 73.36 (CH_2^{Bn}), 68.99 (C-6b), 67.86 (C-6a), 67.50 (CH_2^{Bn}), 66.10 (CH_2^{Alloc}), 50.38 (CH^{Asn}), 40.45 (CH_2^{Asn}) ppm. **HRMS** (MALDI+): Calculated for $C_{82}H_{83}N_3O_{19}SNa^+$ m/z 1468.5239; found m/z 1468.5177. $[\alpha]_D^{589}$= 47.7° (*c*= 0.5, $CHCl_3$).

N-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-*N*-tosylacetamide (3.49)



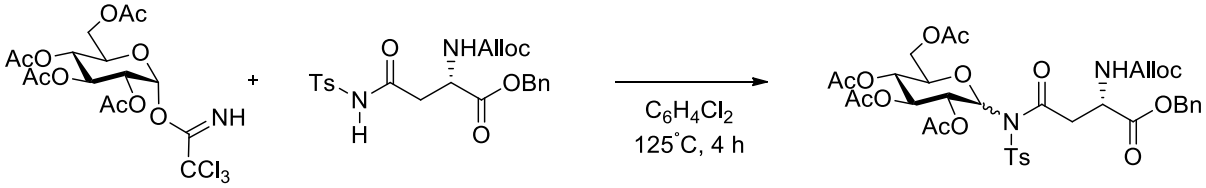
3.18 (117 mg, 0.55 mmol) was added to a stirred solution of **3.3α** (180 mg, 0.37 mmol) in dry $C_6H_4Cl_2$ (3.7 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 12 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.49** (144 mg, 0.27 mmol, 73%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ts}), 7.32 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ts}), 5.77 (t, *J* = 9.3 Hz, 1H, H-2), 5.68 (d, *J* = 9.3 Hz, 1H, H-1), 5.32 (dd, *J* = 9.6, 9.3 Hz, 1H, H-3), 5.18 (t, *J* = 9.6 Hz, 1H, H-4), 4.30-4.18 (m, 2H, H-6, H-6'), 3.91-3.83 (m, 1H, H-5), 2.44 (s, 3H, CH_3^{Ts}), 2.29 (s, 3H, CH_3^{Ac}), 2.09 (s, 3H, CH_3^{Ac}), 2.06 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 2.03 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.61 ($C{=}O^{Ac}$), 170.11 ($C{=}O^{Ac}$), 169.86 ($C{=}O^{Ac}$), 169.81 ($C{=}O^{Ac}$), 169.55 ($C{=}O^{Ac}$), 145.30 (ArC^{Ts}), 136.46 (ArC^{Ts}), 129.88 (2x $ArCH^{Ts}$), 128.26 (2x $ArCH^{Ts}$), 83.59 (C-1), 75.04 (C-5), 73.60 (C-3), 68.91 (C-2), 68.07 (C-4), 61.84 (C-6), 25.77 (CH_3^{Ac}), 21.82 (CH_3^{Ts}), 20.87 (CH_3^{Ac}), 20.73 (2x CH_3^{Ac}), 20.67 (CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{23}H_{29}NO_{12}SNa^+$ m/z 566.1308; found m/z 566.1294. $[\alpha]_D^{589}$= 50.1° (*c*= 0.8, $CHCl_3$).

***N*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-*N*-nosylacetamide (3.50)**



3.21 (121 mg, 0.49 mmol) was added to a stirred solution of **3.3α** (162 mg, 0.33 mmol) in dry $C_6H_4Cl_2$ (3.3 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.50** (160 mg, 0.28 mmol, 84%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 8.8 Hz, 2H, 2x ArH^{Ns}), 8.15 (d, *J* = 8.8 Hz, 2H, 2x ArH^{Ns}), 5.71 (d, *J* = 9.6 Hz, 1H, H-1), 5.67 (dd, *J* = 9.6, 9.4 Hz, 1H, H-2), 5.36 (t, *J* = 9.4 Hz, 1H, H-3), 5.19 (dd, *J* = 10.1, 9.4 Hz, 1H, H-4), 4.30 (dd, *J* = 12.6, 2.4 Hz, 1H, H-6), 4.25 (dd, *J* = 12.6, 4.4 Hz, 1H, H-6'), 4.12 (residual EtOAc), 3.92 (ddd, *J* = 10.1, 4.4, 2.4 Hz, 1H, H-5), 2.36 (s, 3H, CH_3^{Ac}), 2.09 (s, 3H, CH_3^{Ac}), 2.09 (s, 3H, CH_3^{Ac}), 2.07 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.44 ($C{=}O^{Ac}$), 169.97 ($C{=}O^{Ac}$), 169.92 ($C{=}O^{Ac}$), 169.82 ($C{=}O^{Ac}$), 169.49 ($C{=}O^{Ac}$), 150.75 (ArC^{Ns}), 144.94 (ArC^{Ns}), 129.78 (2x $ArCH^{Ns}$), 124.31 (2x $ArCH^{Ns}$), 83.29 (C-1), 75.39 (C-5), 73.19 (C-3), 68.99 (C-2), 67.75 (C-4), 61.47 (C-6), 25.37 (CH_3^{Ac}), 20.83 (CH_3^{Ac}), 20.69 (2x CH_3^{Ac}), 20.64 (CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{22}H_{26}N_2O_{14}SNa^+$ m/z 597.1002; found m/z 597.0978. $[\alpha]_D^{589}$= 54.2° (*c*= 0.7, $CHCl_3$).

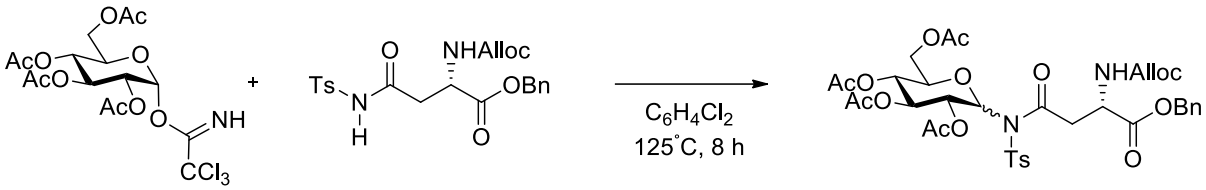
***N*$^{\alpha}$-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.51)**



3.20 (181 mg, 0.39 mmol) was added to a stirred solution of **3.3α** (129 mg, 0.26 mmol) in dry $C_6H_4Cl_2$ (2.6 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 4 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer

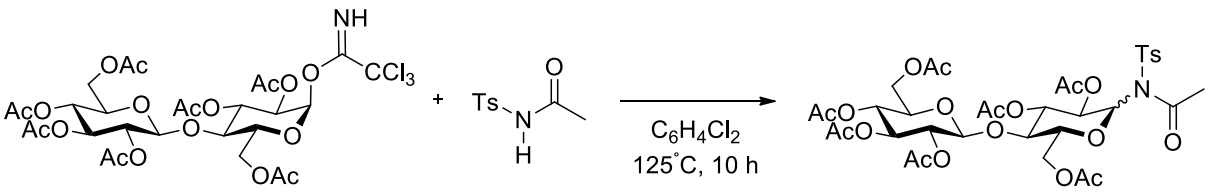
was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.51** (116 mg, 0.15 mmol, 56%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H, 2x ArH^{Ts}), 7.47-7.29 (m, 4H, 4x ArH^{Bn}), 7.29-7.15 (m, 3H, 2x ArH^{Ts}, ArH^{Bn}), 6.00-5.72 (m, 2H, H-2, $=CH^{Alloc}$), 5.67 (d, *J* = 8.7 Hz, 1H, *N*H), 5.53 (broad s, 1H, H-1), 5.39-5.24 (m, 2H, H-3, $=CH_2^{Alloc}$), 5.23-5.08 (m, 3H, H-4, $=CH_2^{Alloc}$, CH_2^{Bn}), 5.05 (d, *J* = 12.4 Hz, 1H, CH_2^{Bn}), 4.70-4.41 (m, 3H, CH^{Asn}, CH_2^{Alloc}), 4.26 (broad d, *J* = 12.5 Hz, 1H, H-6), 4.15 (broad d, *J* = 12.5 Hz, 1H, H-6'), 3.84-3.73 (m, 1H, H-5), 3.42-2.98 (m, 2H, CH_2^{Asn}), 2.39 (s, 3H, CH_3^{Ts}), 2.05 (s, 6H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.63 (2x $C=O^{Ester/Amide}$), 170.47 ($C=O^{Ester/Amide}$), 170.08 ($C=O^{Ester/Amide}$), 169.82 ($C=O^{Ester/Amide}$), 169.44 ($C=O^{Ester/Amide}$), 156.03 ($C=O^{Alloc}$), 145.58 ($ArC^{Ts/Bn}$), 135.92 ($ArC^{Ts/Bn}$), 135.53 ($ArC^{Ts/Bn}$), 132.84 ($=CH^{Alloc}$), 130.10 (2x $ArCH^{Ts}$), 128.57 (2x $ArCH^{Bn}$), 128.32 ($ArCH^{Bn}$), 128.13 (2x $ArCH^{Bn}$), 127.90 (2x $ArCH^{Ts}$), 117.54 ($=CH_2^{Alloc}$), 84.15 (C-1), 74.96 (C-5), 73.38 (C-3), 68.37 (C-2), 68.07 (C-4), 67.32 (CH_2^{Bn}), 65.87 (CH_2^{Alloc}), 61.80 (C-6), 50.34 (CH^{Asn}), 40.23 (CH_2^{Asn}), 21.79 (CH_3^{Ts}), 20.82 (CH_3^{Ac}), 20.71 (CH_3^{Ac}), 20.68 (CH_3^{Ac}), 20.59 (CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{36}H_{42}N_2O_{16}SNa^+$ m/z 813.2153; found m/z 813.2129. $[\alpha]_D^{589}$= 45.4° (*c*= 0.9, $CHCl_3$).

N$^{\alpha}$-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.51)



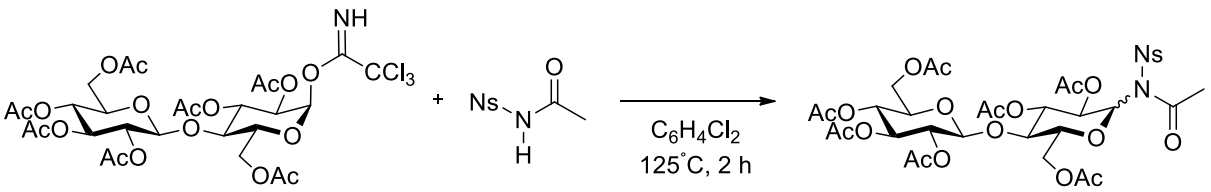
3.20 (106 mg, 0.23 mmol) was added to a stirred solution of **3.3α** (169 mg, 0.34 mmol) in dry $C_6H_4Cl_2$ (3.4 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 8 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.51** (161 mg, 0.20 mmol, 89%) as a white solid. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

***N*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranosyl)-*N*-tosylacetamide (3.52)**



3.18 (57.3 mg, 0.27 mmol) was added to a stirred solution of **3.4α** (140 mg, 0.18 mmol) in dry $C_6H_4Cl_2$ (1.8 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 10 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.52** (96.7 mg, 0.12 mmol, 65%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 7.33 (d, *J* = 8.0 Hz, 2H, 2x ArH^{Ts}), 5.77 (broad t, *J* = 9.2 Hz, 1H, H-2a), 5.60 (broad d, *J* ~ 9.2 Hz, 1H, H-1a), 5.27 (dd, *J* = 9.4, 9.2 Hz, 1H, H-3a), 5.16 (dd, *J* = 9.5, 9.2 Hz, 1H, H-3b), 5.08 (t, *J* = 9.5 Hz, 1H, H-4b), 4.95 (dd, *J* = 9.2, 8.1 Hz, 1H, H-2b), 4.70 (broad d, *J* = 12.1 Hz, 1H, H-6a), 4.55 (d, *J* = 8.1 Hz, 1H, H-1b), 4.40 (dd, *J* = 12.9, 3.9 Hz, 1H, H-6b), 4.17-4.02 (m, 2H, H-6'a, H-6'b), 3.88 (t, *J* = 9.4 Hz, 1H, H-4a), 3.80-3.71 (m, 1H, H-5a), 3.72-3.65 (m, 1H, H-5b), 2.44 (s, 3H, CH_3^{Ts}), 2.23 (s, 3H, CH_3^{Ac}), 2.11 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, CH_3^{Ac}), 2.04 (s, 6H, CH_3^{Ac}), 2.01 (s, 6H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.63 ($C{=}O^{Ac}$), 170.39 ($C{=}O^{Ac}$), 170.30 ($C{=}O^{Ac}$), 169.88 (2x $C{=}O^{Ac}$), 169.79 ($C{=}O^{Ac}$), 169.42 ($C{=}O^{Ac}$), 169.08 ($C{=}O^{Ac}$), 145.30 (ArC^{Ts}), 136.51 (ArC^{Ts}), 129.97 (2x $ArCH^{Ts}$), 128.08 (2x $ArCH^{Ts}$), 100.84 (C-1b), 83.67 (C-1a), 75.95 (C-5a), 75.89 (C-4a), 73.08 (C-3b), 73.04 (C-3a), 72.21 (C-5b), 71.73 (C-2b), 69.08 (C-2a), 67.87 (C-4b), 61.65 (C-6b), 61.42 (C-6a), 25.86 (CH_3^{Ac}), 21.78 (CH_3^{Ts}), 20.96 (CH_3^{Ac}), 20.80 (CH_3^{Ac}), 20.66 (5C, CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{35}H_{45}NO_{20}SNa^+$ m/z 854.2153; found m/z 854.2148. $[\alpha]_D^{589}$= 11.5° (*c*= 0.9, $CHCl_3$).

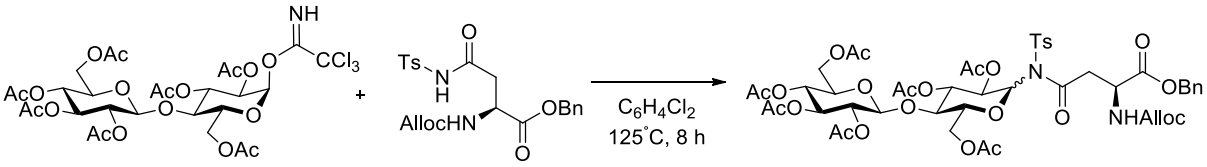
***N*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranosyl)-*N*-nosylacetamide (3.53)**



3.21 (52.9 mg, 0.22 mmol) was added to a stirred solution of **3.4α** (113 mg, 0.14 mmol) in dry $C_6H_4Cl_2$ (1.4 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.53** (94.5 mg, 0.11 mmol, 76%) as a white solid.[§§§] **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.7 Hz, 2x ArH^{Ns}), 8.16 (d, *J* = 8.7 Hz, 2x ArH^{Ns}), 5.68 (broad dd, *J* = 9.6, 9.3 Hz, 1H, H-2a), 5.62 (d, *J* = 9.6 Hz, 1H, H-1a), 5.30 (t, *J* = 9.3 Hz, 1H, H-3a), 5.17 (t, *J* = 9.4 Hz, 1H, H-3b), 5.09 (dd, *J* = 9.9, 9.4 Hz, 1H, H-4b), 4.95 (dd, *J* = 9.4, 8.0 Hz, 1H, H-2b), 4.78 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6a), 4.58 (d, *J* = 8.0 Hz, 1H, H-1b), 4.41 (dd, *J* = 12.5, 4.3 Hz, 1H, H-6b), 4.12 (dd, *J* = 12.3, 4.2 Hz, 1H, H-6'a), 4.07 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6'b), 3.90 (dd, *J* = 9.8, 9.3 Hz, 1H, H-4a), 3.79 (ddd, *J* = 9.8, 4.2, 2.1 Hz, 1H, H-5a), 3.69 (ddd, *J* = 9.9, 4.3, 2.3 Hz, 1H, H-5b), 2.27 (s, 3H, CH_3^{Ac}), 2.12 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, CH_3^{Ac}), 2.06 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.61 ($C{=}O^{Ac}$), 170.39 ($C{=}O^{Ac}$), 170.16 ($C{=}O^{Ac}$), 169.98 ($C{=}O^{Ac}$), 169.70 ($C{=}O^{Ac}$), 169.64 ($C{=}O^{Ac}$), 169.41 ($C{=}O^{Ac}$), 169.03 ($C{=}O^{Ac}$), 150.79 (Ar^{Ns}), 144.95 (Ar^{Ns}), 129.68 (2x $ArCH^{Ns}$), 124.46 (2x $ArCH^{Ns}$), 100.84 (C-1b), 83.59 (C-1a), 76.31 (C-5a), 75.57 (C-4a), 73.00 (C-3b), 72.77 (C-3a), 72.26 (C-5b), 71.75 (C-2b), 69.19 (C-2a), 67.83 (C-4b), 61.61 (C-6b), 60.88 (C-6a), 25.52 (CH_3^{Ac}), 20.96 (CH_3^{Ac}), 20.81 (CH_3^{Ac}), 20.71 (CH_3^{Ac}), 20.69 (CH_3^{Ac}), 20.68 (CH_3^{Ac}), 20.66 (CH_3^{Ac}), 20.64 (CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{34}H_{42}N_2O_{22}SNa^+$ m/z 885.1848; found m/z 885.1820. $[\alpha]_D^{589}$= 12.6° (*c*= 0.9, $CHCl_3$).

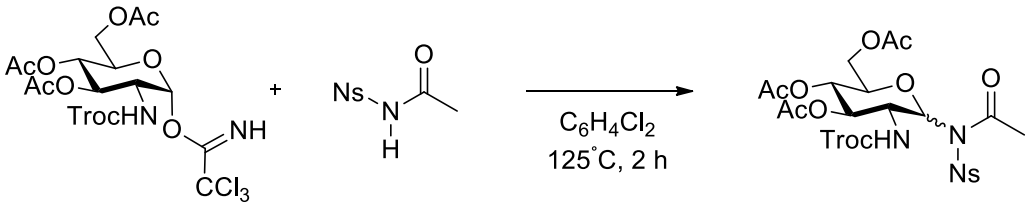
[§§§] The isolated product contained 8% of an unknown impurity.

N^{α}-(allyloxycarbonyl)-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-D-glucopyranosyl)-*N*-(tosyl)-L-asparagine benzyl ester (3.56)



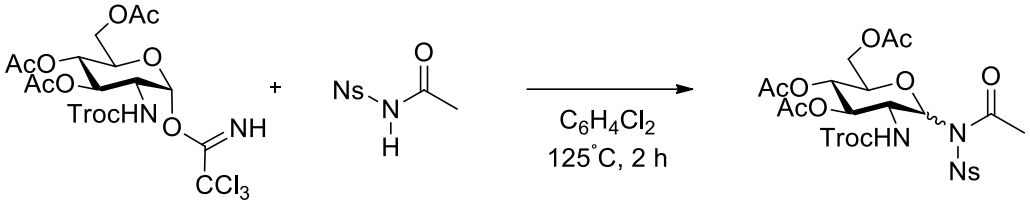
3.20 (58.4 mg, 0.13 mmol) was added to a stirred solution of **3.4α** (149 mg, 0.19 mmol) in dry $C_6H_4Cl_2$ (1.9 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 8 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.56** (91.0 mg, 0.09 mmol, 66%) as a white solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 7.37-7.30 (m, 3H, 3x ArH^{Bn}), 7.27 (d, *J* = 8.1 Hz, 2H, 2x ArH^{Ts}), 7.25-7.18 (m, 2H, 2x ArH^{Bn}), 5.95-5.82 (m, 1H, $=CH^{Alloc}$), 5.81-5.70 (m, 1H, H-2a), 5.66 (d, *J* = 8.6 Hz, 1H, *N*H), 5.47 (broad s, 1H, H-1a), 5.29 (broad d, *J* = 17.7 Hz, 1H, $=CH_2^{Trans}$), 5.26 (t, *J* = 9.6 Hz, 1H, H-3a), 5.22-5.11 (m, 3H, H-3b, $=CH_2^{Cis}$, CH_2^{Bn}), 5.08 (t, *J* = 9.6 Hz, 1H, H-4b), 4.99 (d, *J* = 12.3 Hz, 1H, CH_2^{Bn}), 4.94 (dd, *J* = 9.3, 8.2 Hz, 1H, H-2b), 4.70 (broad d, *J* = 12.3 Hz, 1H, H-6a), 4.62-4.47 (m, 4H, H-1b, CH^{Asn}, CH_2^{Alloc}), 4.43 (dd, *J* = 12.6, 4.3 Hz, 1H, H-6b), 4.09 (dd, *J* = 12.6, 2.2 Hz, 1H, H-6'b), 4.05 (dd, *J* = 12.3, 4.1 Hz, 1H, H-6'a), 3.87 (t, *J* = 9.6 Hz, 1H, H-4a), 3.75-3.63 (m, 2H, H-5a, H-5b), 3.40-3.03 (m, 2H, CH_2^{Asn}), 2.39 (s, 3H, CH_3^{Ts}), 2.10 (s, 3H, CH_3^{Ac}), 2.08 (s, 3H, CH_3^{Ac}), 2.05 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.98 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.82 ($C=O^{Amide/Ester}$), 170.63 ($C=O^{Amide/Ester}$), 170.54 ($C=O^{Amide/Ester}$), 170.40 ($C=O^{Amide/Ester}$), 170.29 ($C=O^{Amide/Ester}$), 170.08 ($C=O^{Amide/Ester}$), 169.75 ($C=O^{Amide/Ester}$), 169.43 ($C=O^{Amide/Ester}$), 169.07 ($C=O^{Amide/Ester}$), 156.07 ($C=O^{Alloc}$), 145.59 (ArC^{Ts}), 135.98 (ArC^{Ts}), 135.50 (ArC^{Bn}), 132.84 ($=CH^{Alloc}$), 130.17 (2x $ArCH^{Ts}$), 128.62 (2x $ArCH^{Bn}$), 128.36 ($ArCH^{Bn}$), 128.06 (2x $ArCH^{Bn}$), 127.85 (2x $ArCH^{Ts}$), 117.63 ($=CH_2^{Alloc}$), 100.95 (C-1b), 84.18 (C-1a), 75.91 (C-5a), 75.86 (C-4a), 73.12 (C-3b), 72.65 (C-3a), 72.29 (C-5b), 71.73 (C-2b), 68.47 (C-2a), 67.78 (C-4b), 67.24 (CH_2^{Bn}), 65.93 (CH_2^{Alloc}), 61.60 (C-6b), 61.24 (C-6a), 50.29 (CH^{Asn}), 40.30 (CH_2^{Asn}), 21.81 (CH_3^{Ts}), 20.94 (CH_3^{Ac}), 20.84 (CH_3^{Ac}), 20.69 (3x CH_3^{Ac}), 20.65 (CH_3^{Ac}), 20.63 (CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{48}H_{58}N_2O_{24}SNa^+$ m/z 1101.2998; found m/z 1101.2955. $[\alpha]_D^{589}$= 19.5° (*c*= 0.8, $CHCl_3$).

***N*-(2-(2,2,2-trichloroethoxycarbonylamino)-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranosyl)-*N*-nosylacetamide (3.55)**



3.21 (62.8 mg, 0.26 mmol) was added to a stirred solution of **3.1α** (107 mg, 0.17 mmol) in dry $C_6H_4Cl_2$ (1.7 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→2:3 EtOAc/heptane) to yield the β anomer of compound **3.55** (59.5 mg, 0.08 mmol, 49%) as a pale-yellow solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.8 Hz, 2H, 2x ArH^{Ns}), 8.18 (d, *J* = 8.8 Hz, 2H, 2x ArH^{Ns}), 5.70 (broad s, 1H, *N*H), 5.59 (d, *J* = 8.9 Hz, 1H, H-1), 5.49-5.25 (m, 1H, H-3), 5.20 (t, *J* = 9.7 Hz, 1H, H-4), 4.81 (d, *J* = 11.4 Hz, 1H, CH_2^{Troc}), 4.74-4.45 (m, 2H, H-2, CH_2^{Troc}), 4.31 (dd, *J* = 12.6, 2.2 Hz, 1H, H-6), 4.28-4.17 (broad dd, *J* = 12.6, 4.3 Hz, 1H, H-6‘), 3.90 (ddd, *J* = 9.7, 4.3, 2.2 Hz, 1H, H-5), 2.37 (s, 3H, CH_3^{Ac}), 2.09 (s, 3H, CH_3^{Ac}), 2.08 (s, 3H, CH_3^{Ac}), 2.07 (s, 3H, CH_3^{Ac}) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 169.81 ($C=O^{Ac}$), 169.38 ($C=O^{Ac}$), 169.14 ($C=O^{Ac}$), 168.32 ($C=O^{Ac}$), 153.58 ($C=O^{Troc}$), 149.60 (ArC^{Ns}), 143.87 (ArC^{Ns}), 128.70 (2x $ArCH^{Ns}$), 123.16 (2x $ArCH^{Ns}$), 94.12 (CCl_3), 83.53 (C-1), 74.29 (C-5), 73.71 (CH_2^{Troc}), 71.37 (C-3), 66.78 (C-4), 60.43 (C-6), 52.67 (C-2), 24.40 (CH_3^{Ac}), 19.71 (CH_3^{Ac}), 19.56 (2x CH_3^{Ac}) ppm. **HRMS** (MALDI+): Calculated for $C_{23}H_{26}Cl_3N_3O_{14}SNa^+$ m/z 728.0099; found m/z 728.0085. $[\alpha]_D^{589}$= 14.0° (*c*= 0.8, $CHCl_3$).

***N*-(2-(2,2,2-trichloroethoxycarbonylamino)-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranosyl)-*N*-nosylacetamide (3.55)**

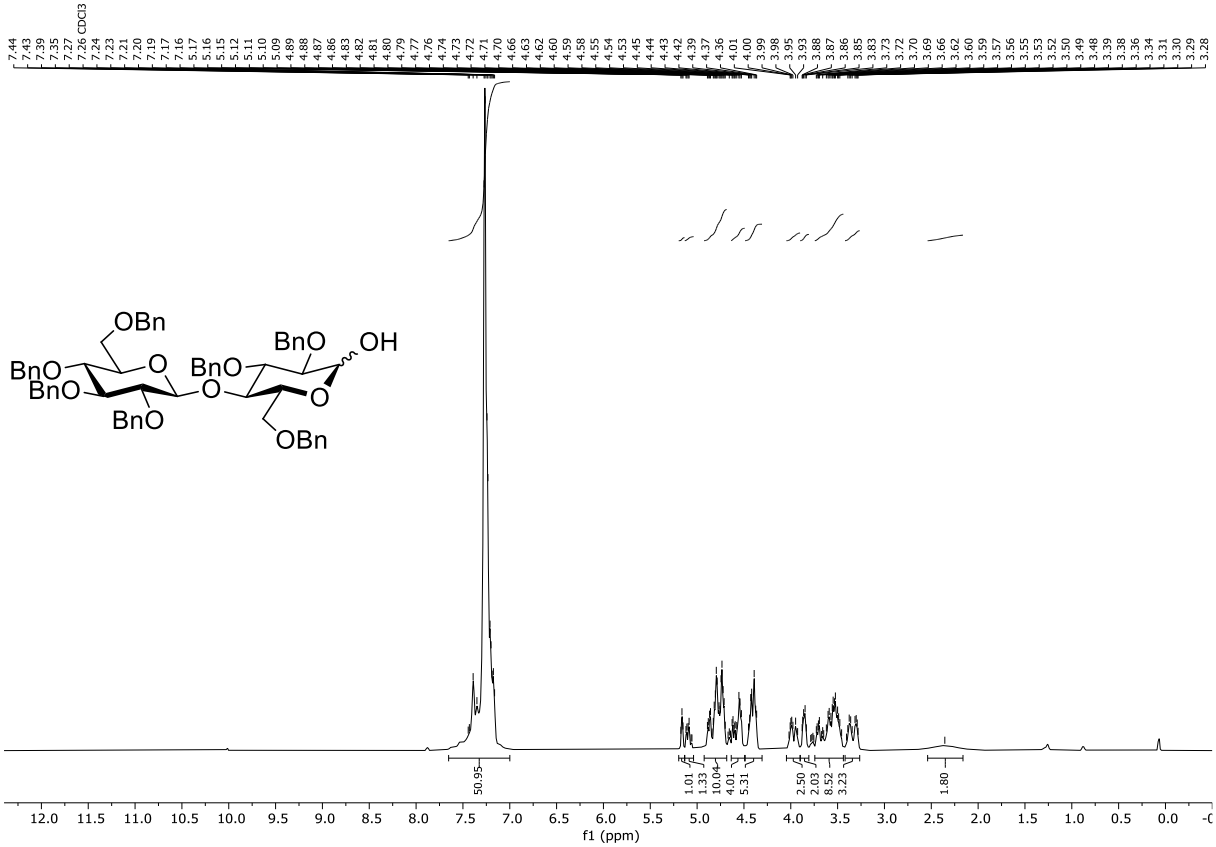


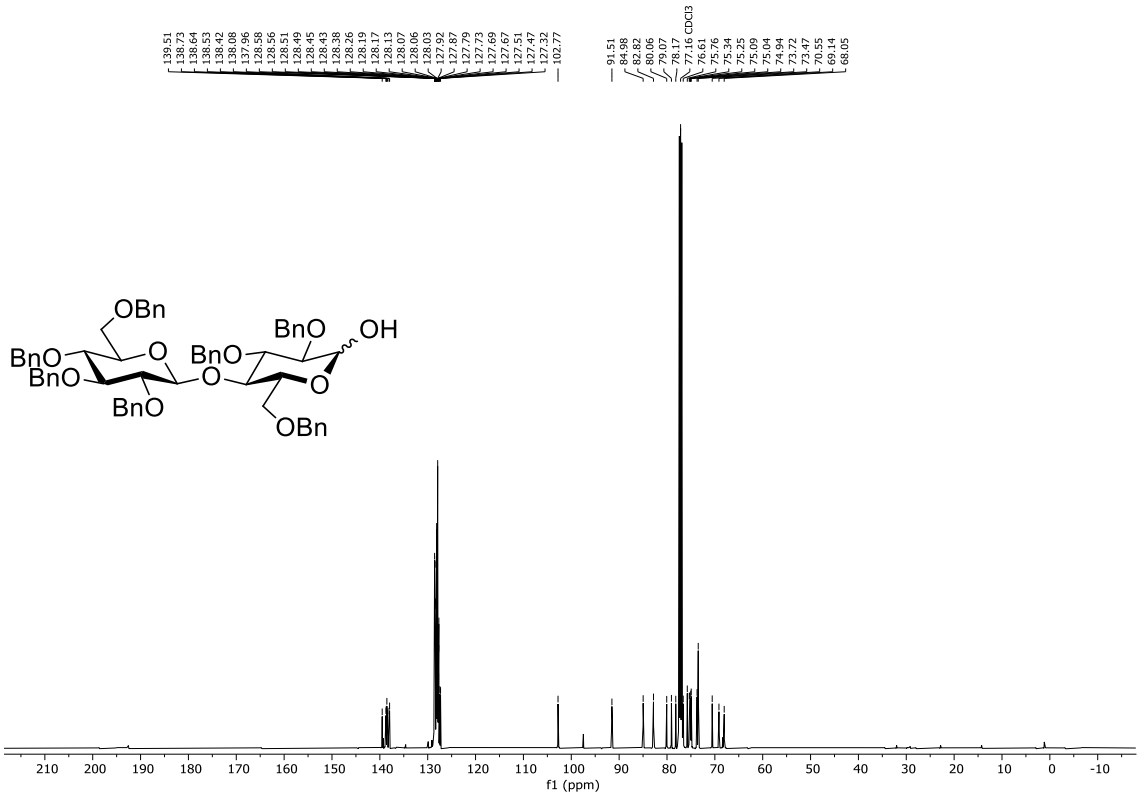
3.21 (45.5 mg, 0.19 mmol) was added to a stirred solution of **3.1α** (174 mg, 0.28 mmol) in dry $C_6H_4Cl_2$ (2.8 mL) under a nitrogen atmosphere. The reaction was stirred at 125 °C for 2 h. After

completion, the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aq. NaOH solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (1:3→1:1 EtOAc/heptane) to yield the β anomer of compound **3.55** (92.6 mg, 0.13 mmol, 70%) as a white solid. The ^{1}H-NMR data were in accordance with the spectrum of the identical compound previously reported in this experimental section.

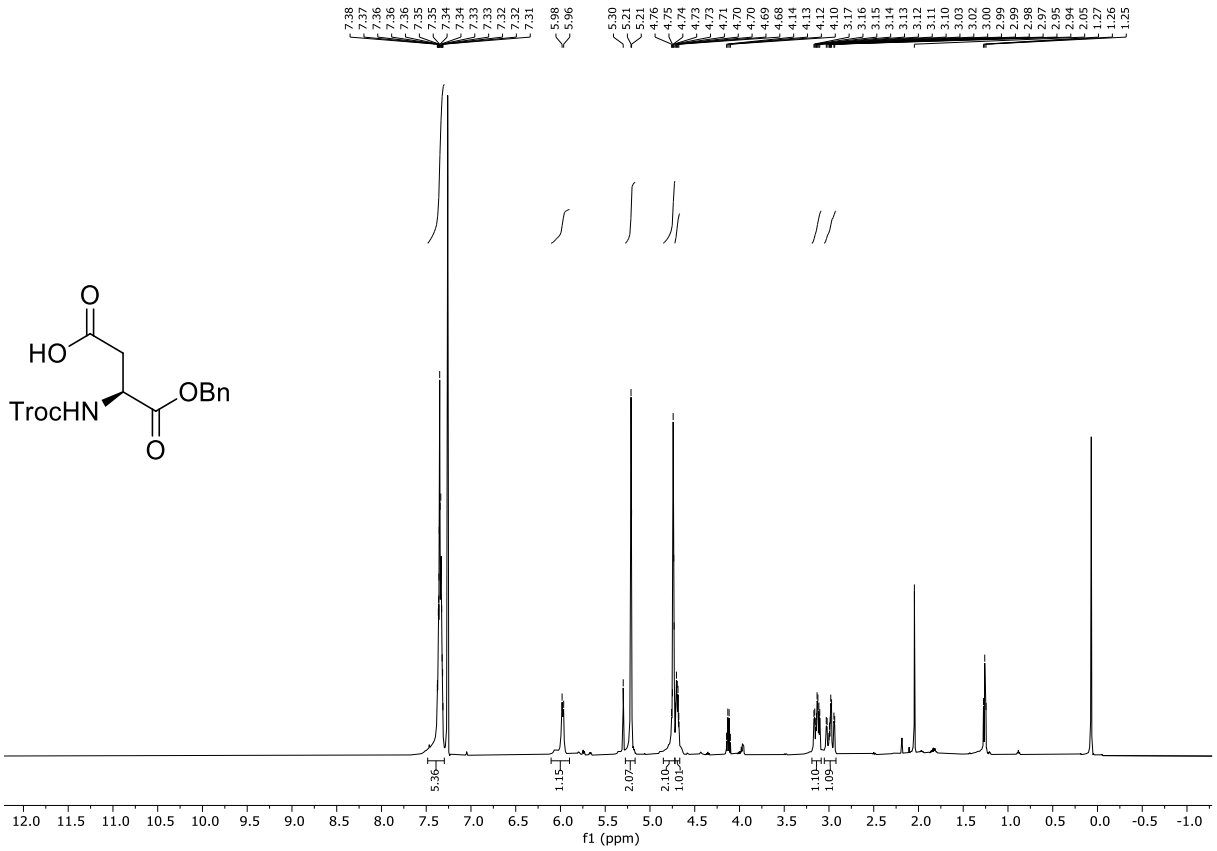
3.4.5. Appendix of ^{1}H and ^{13}C-NMR Spectra

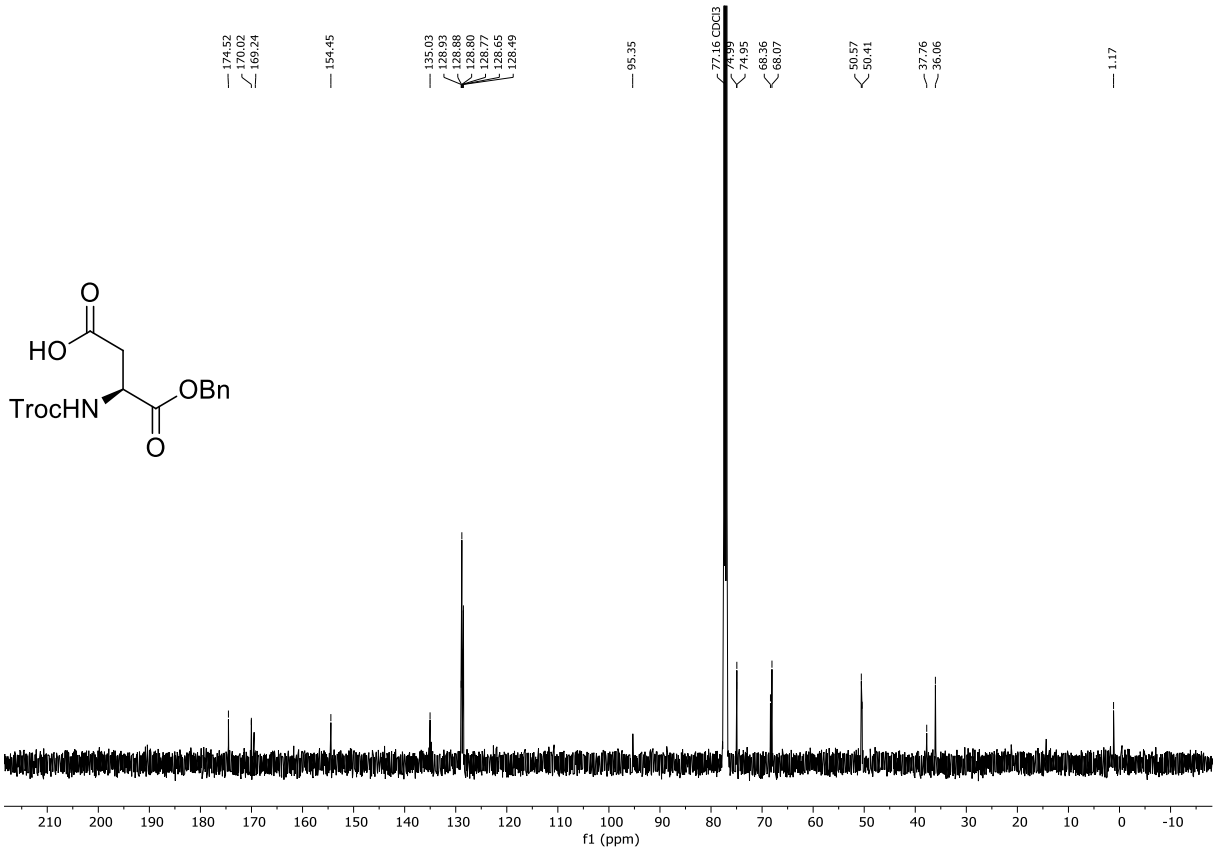
Compound 3.10



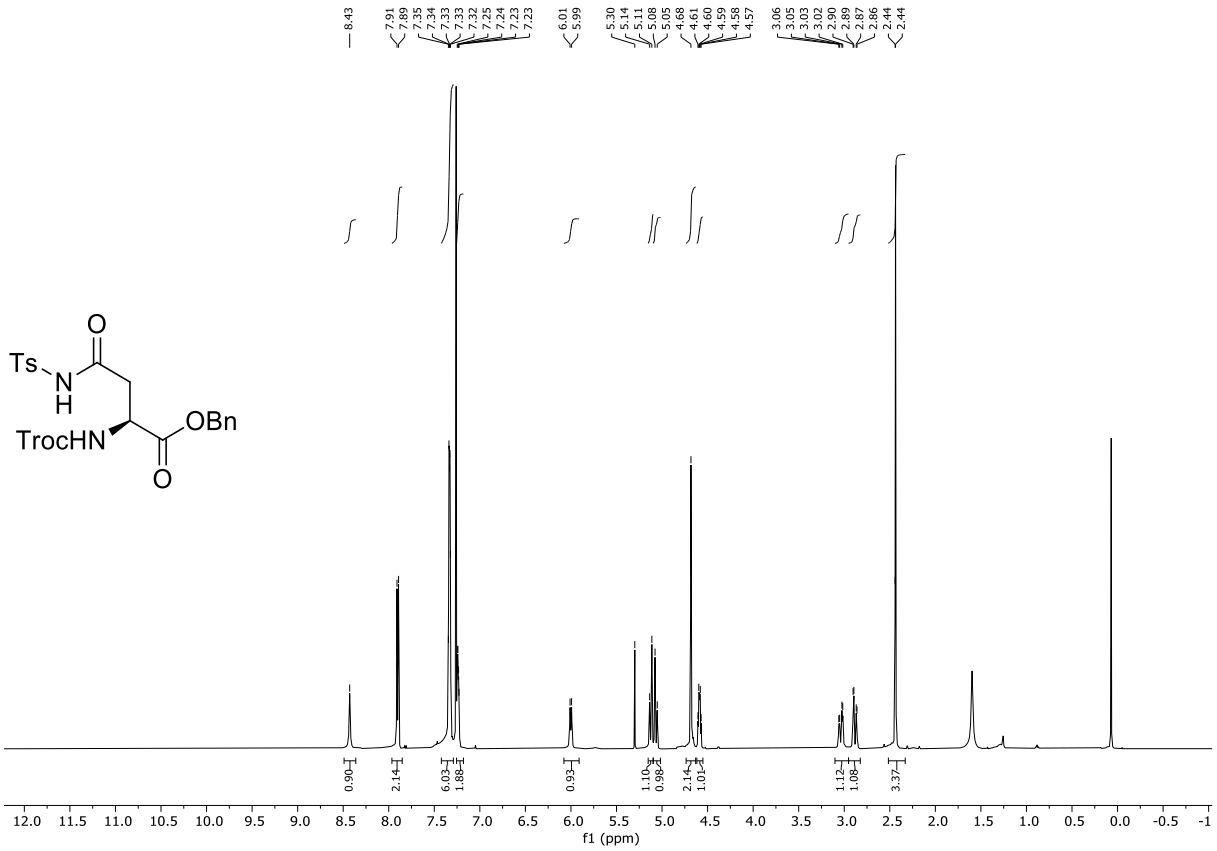


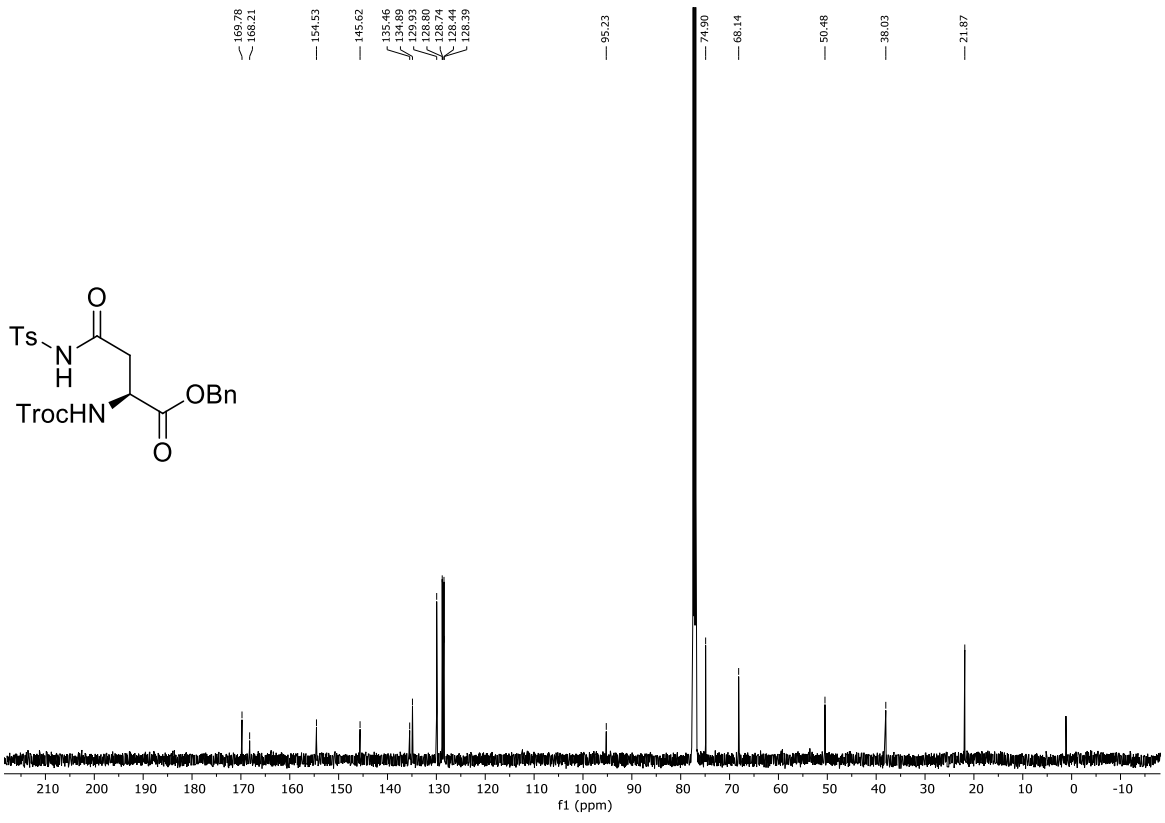
Compound 3.31



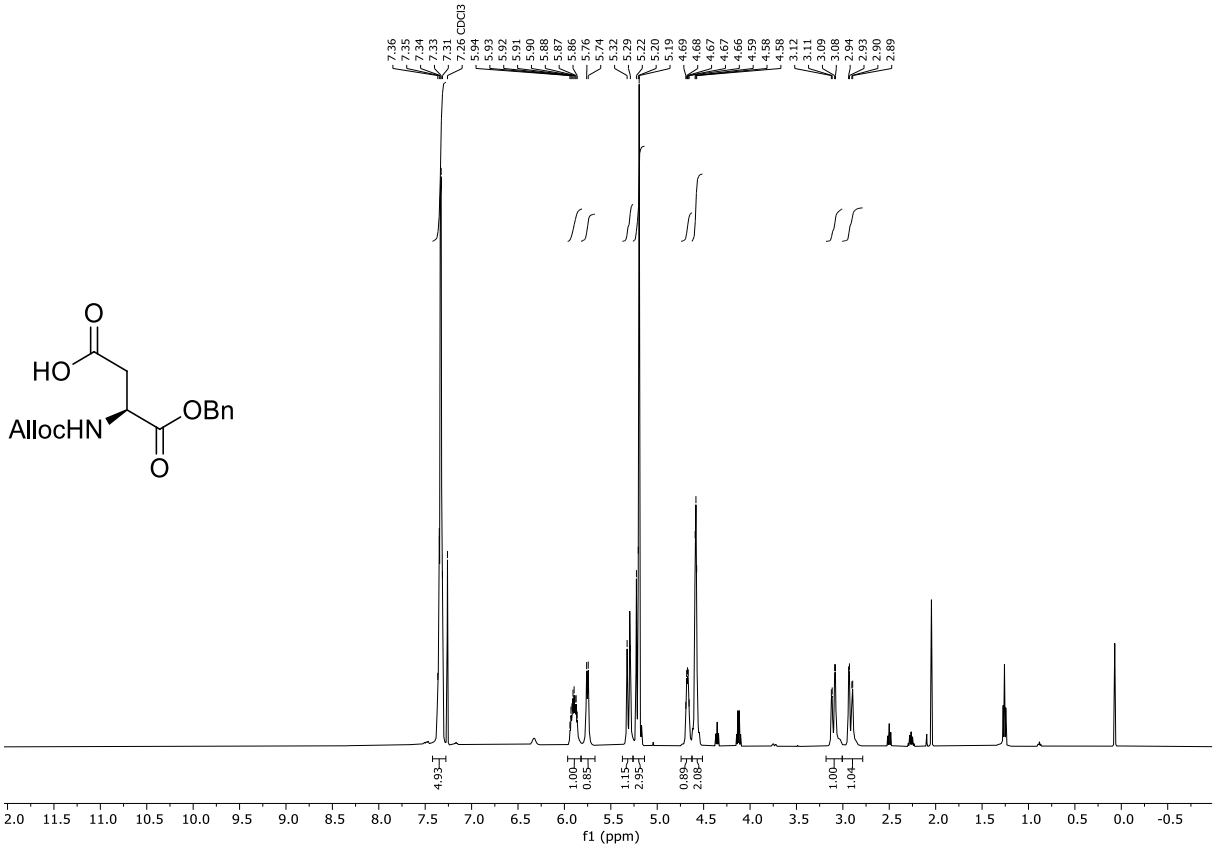


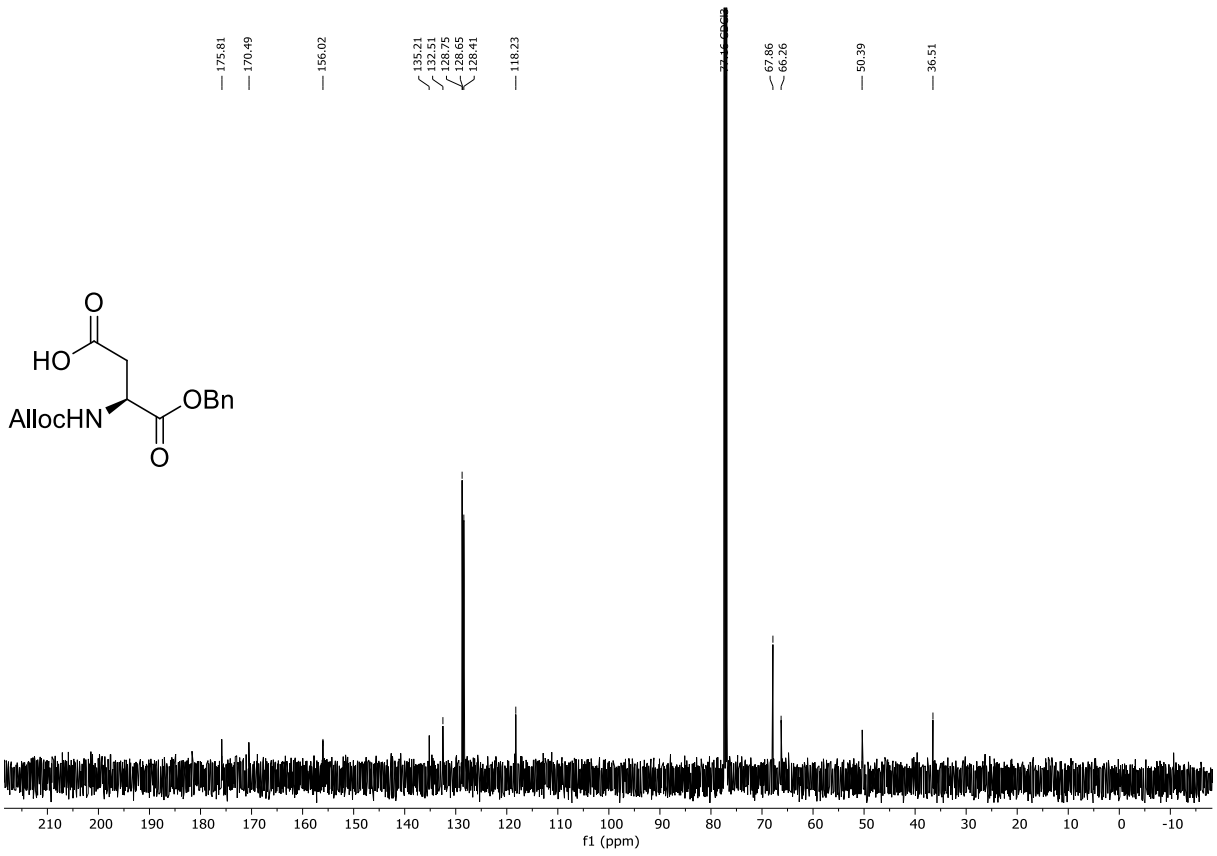
Compound 3.19



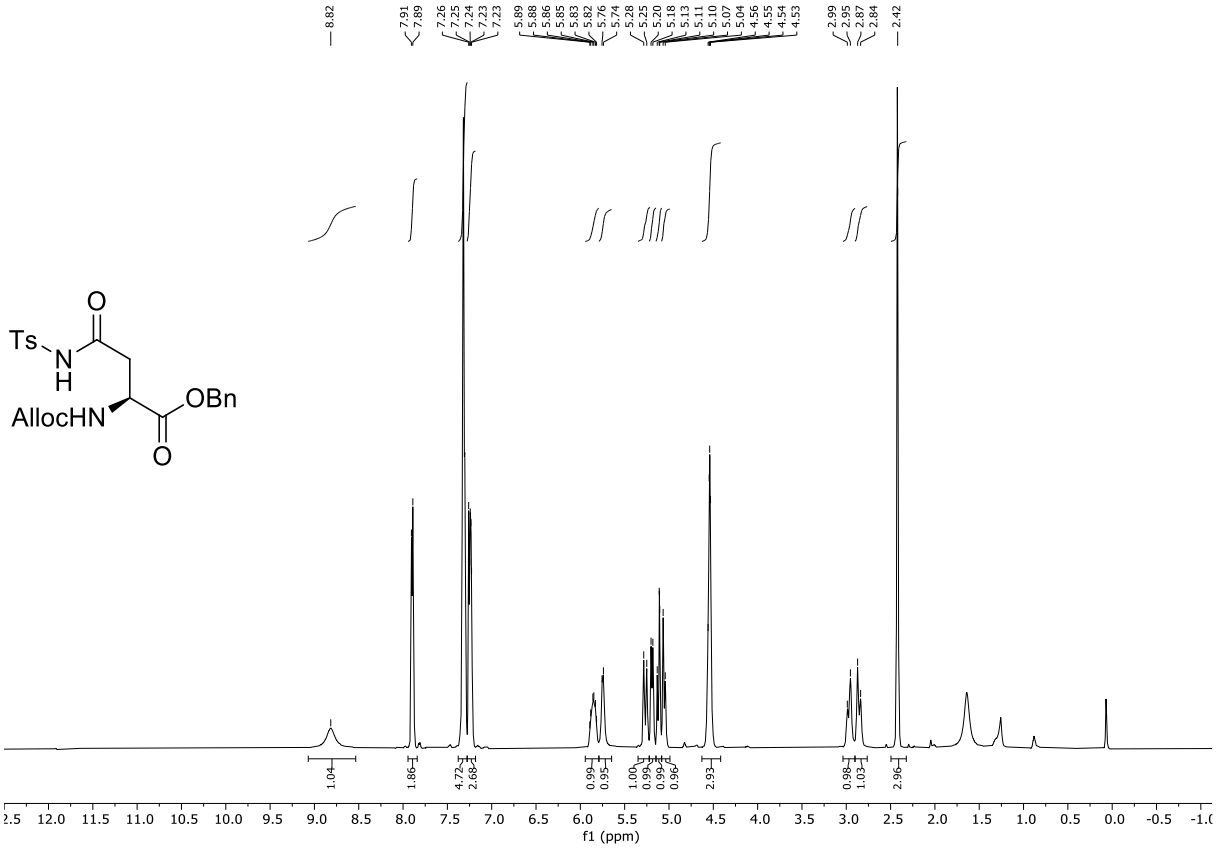


Compound 3.33

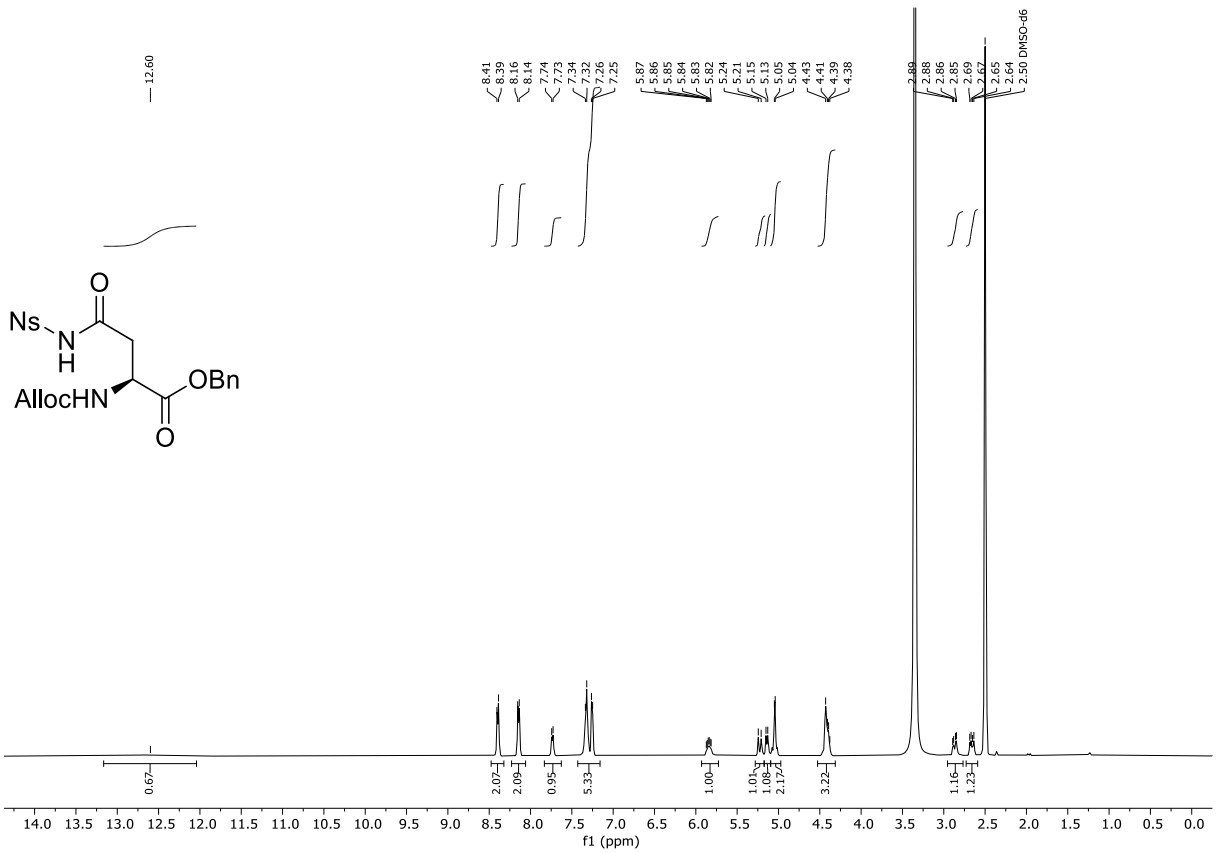




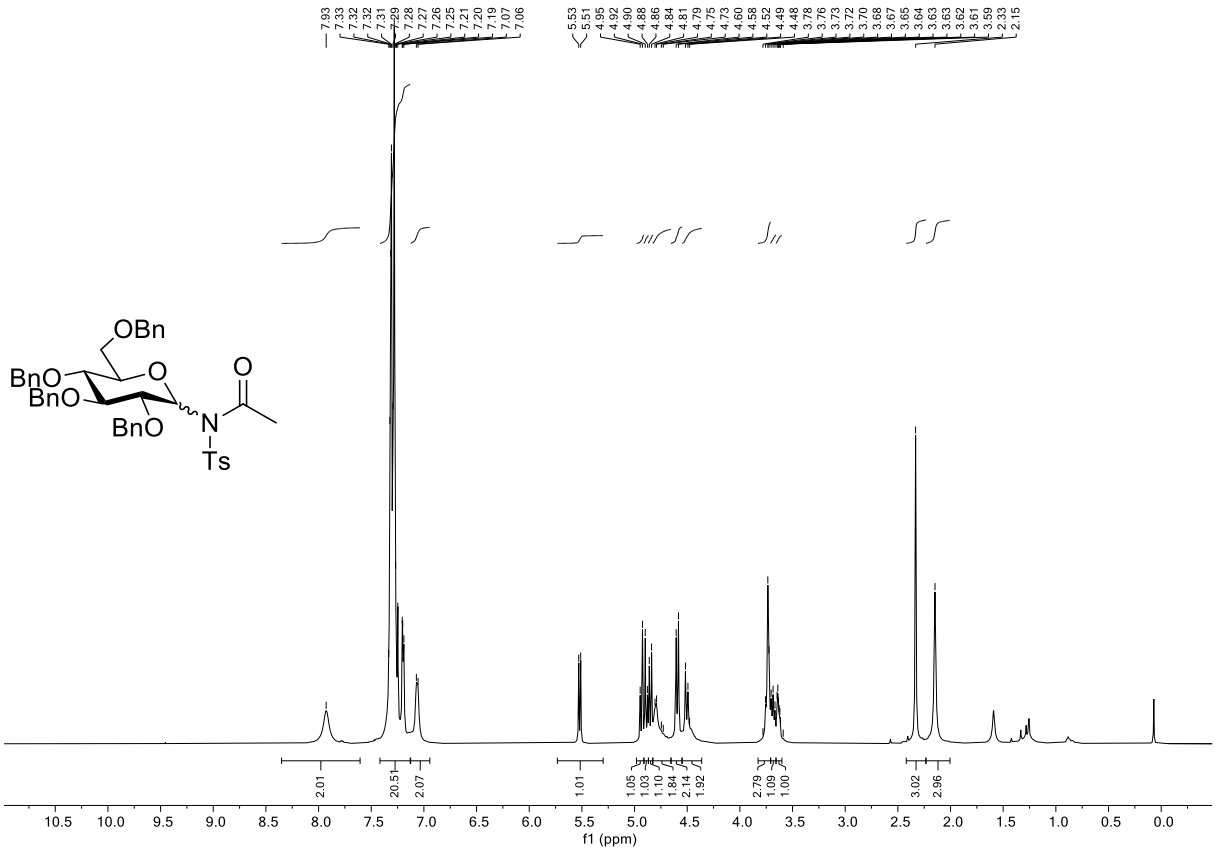
Compound 3.20

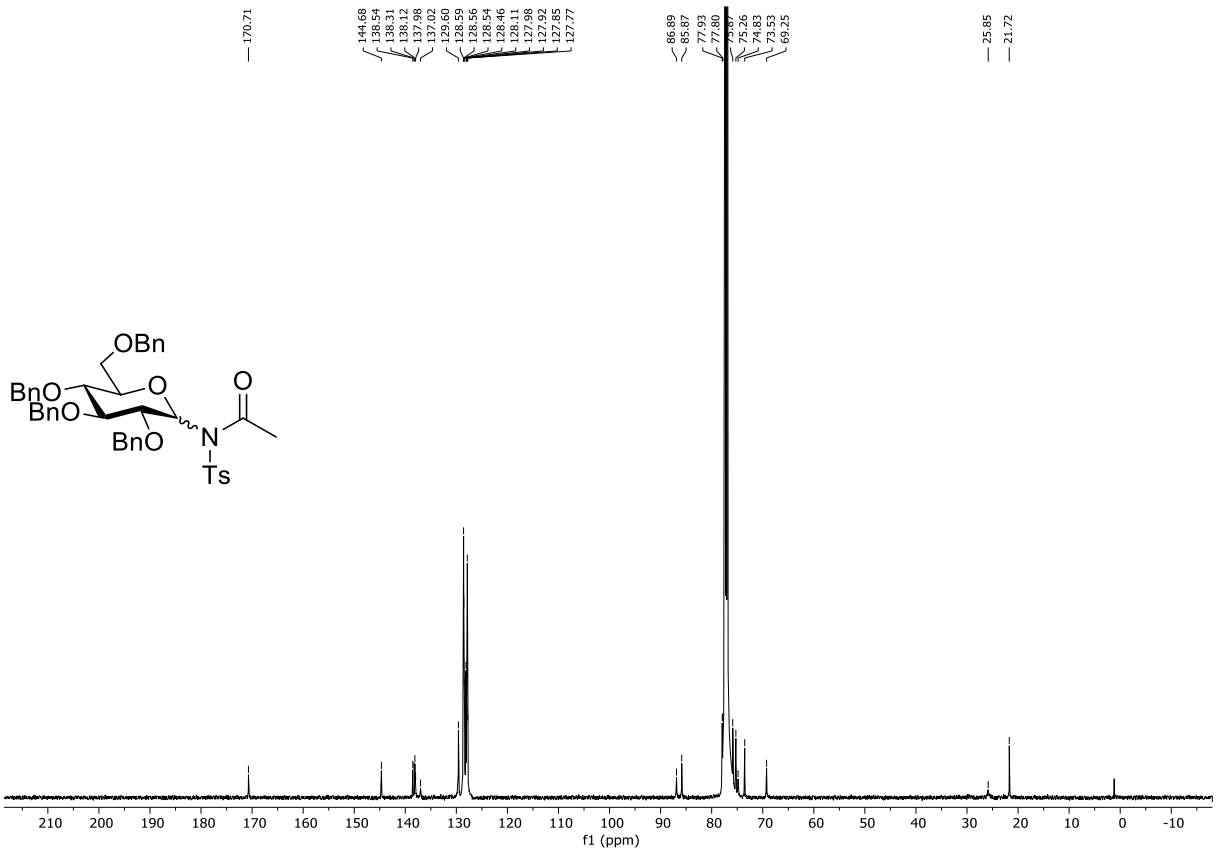


Compound 3.22

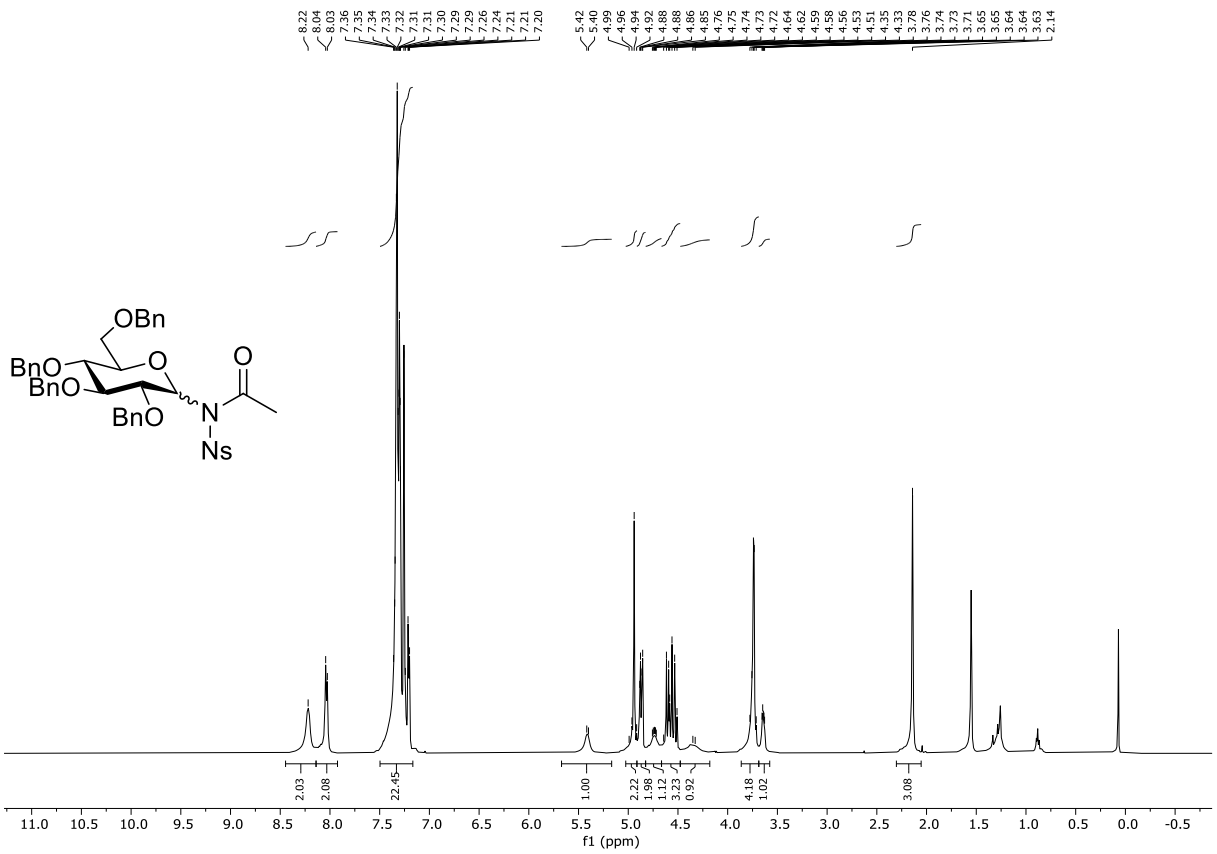


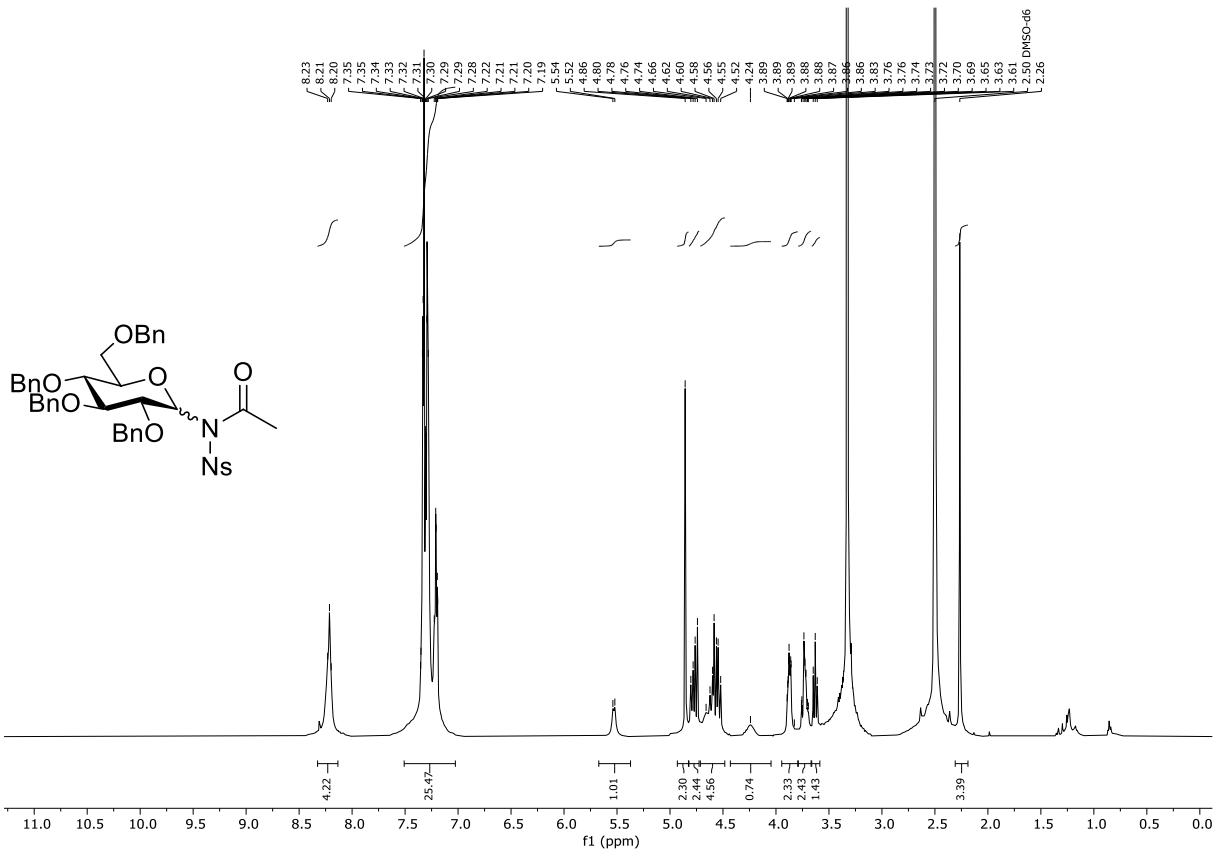
Compound 3.35

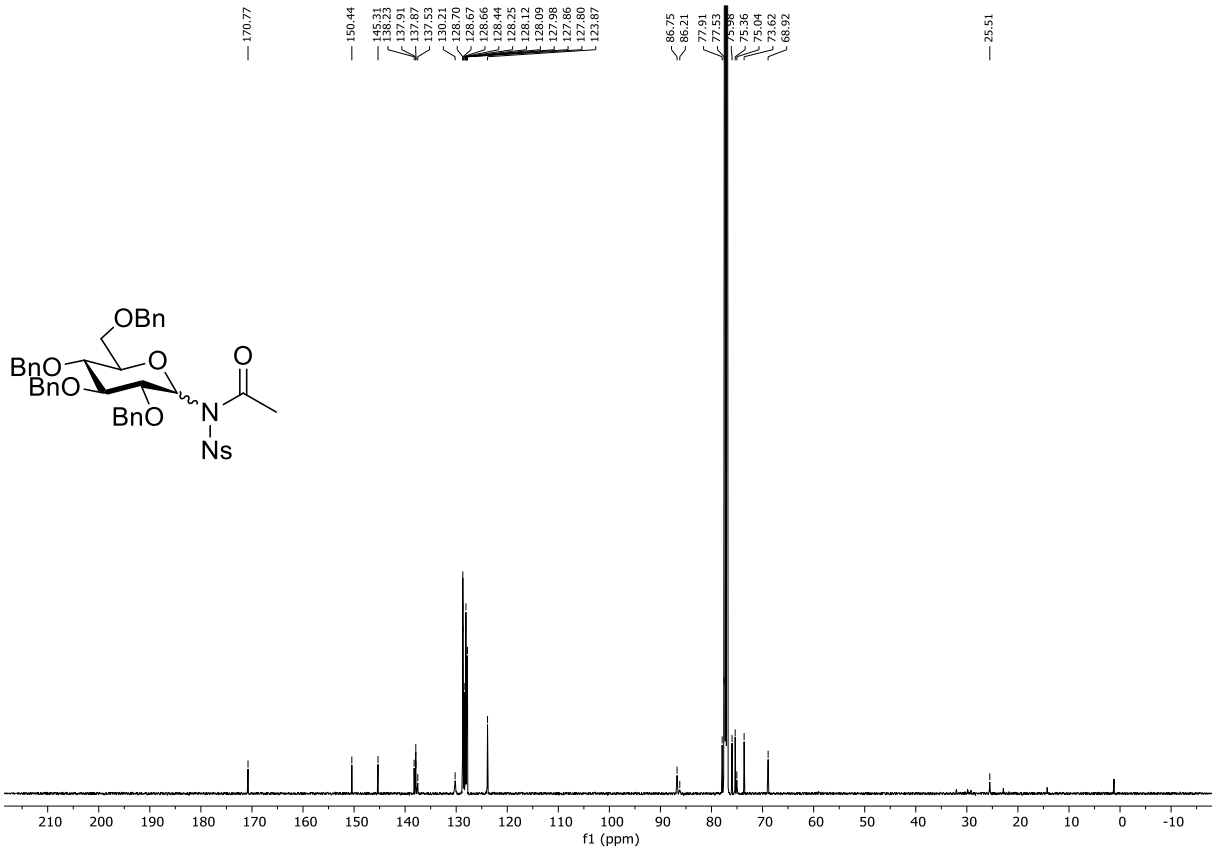




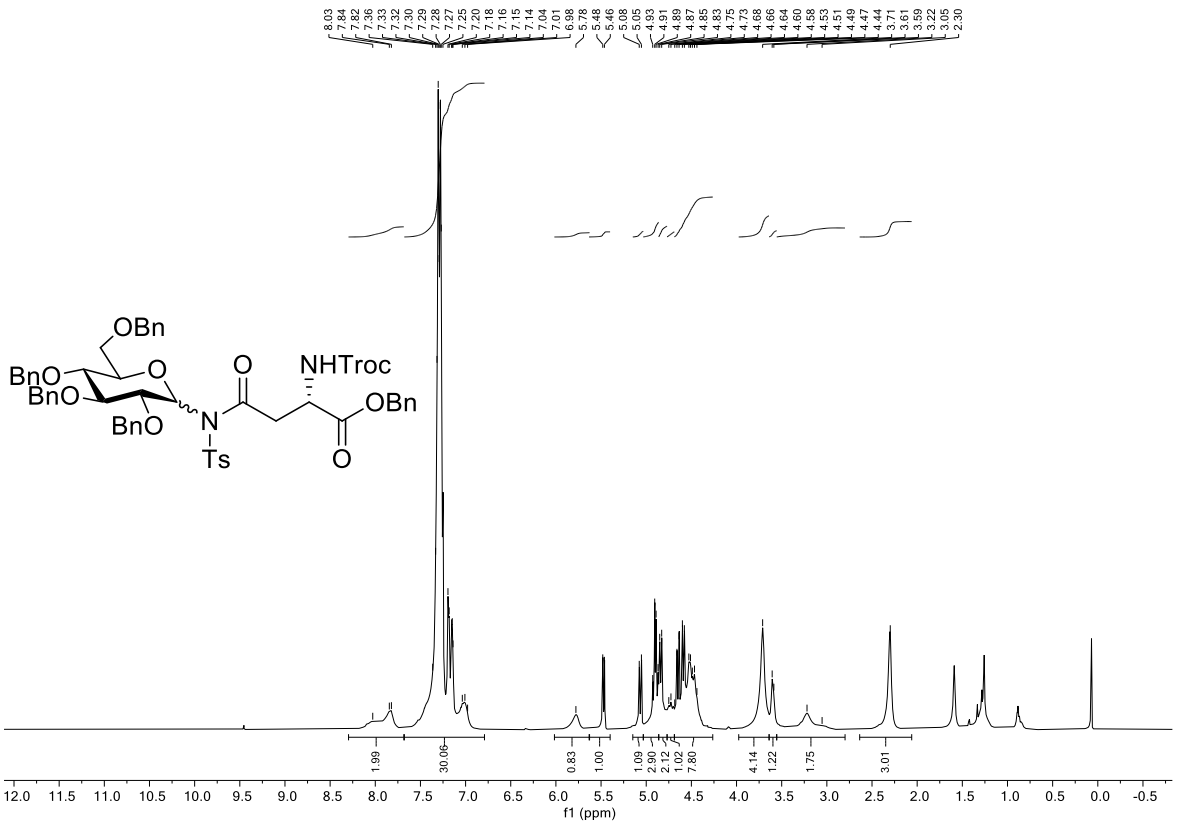
Compound 3.37

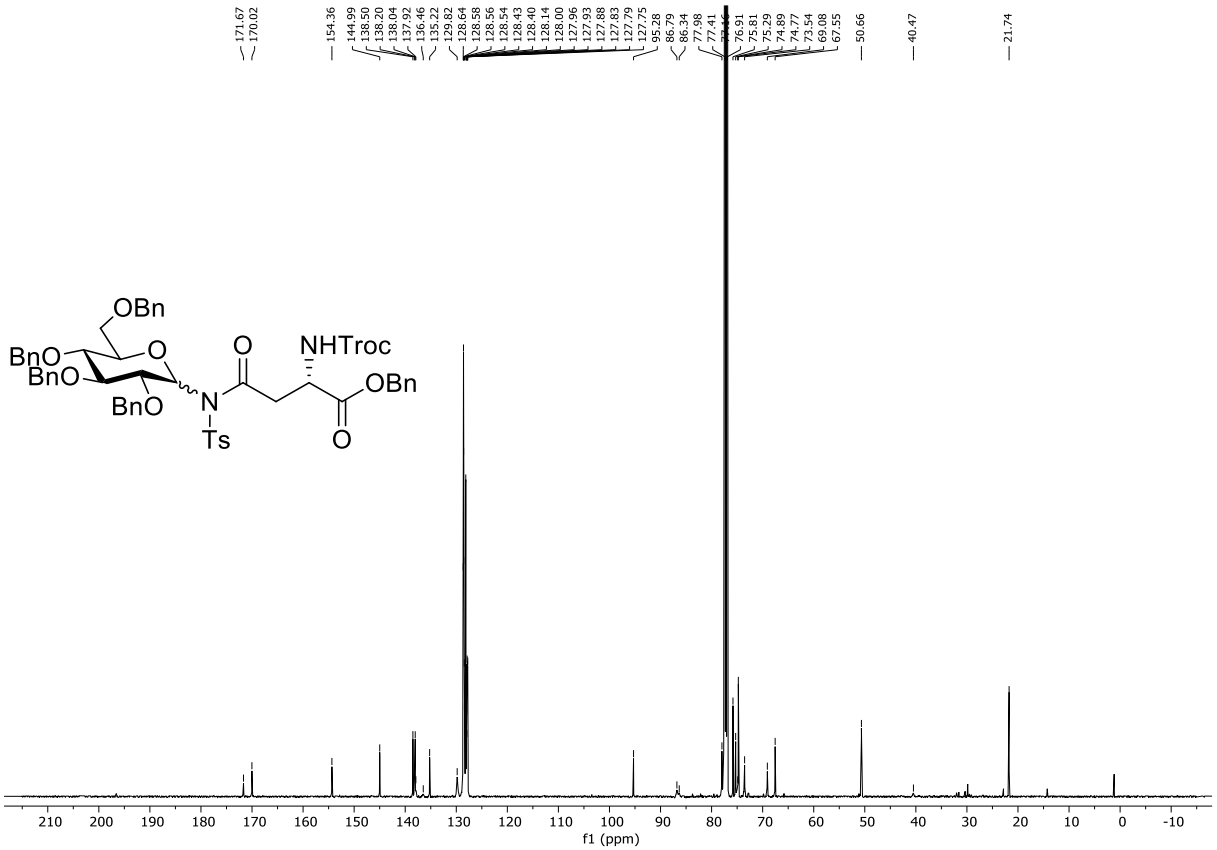




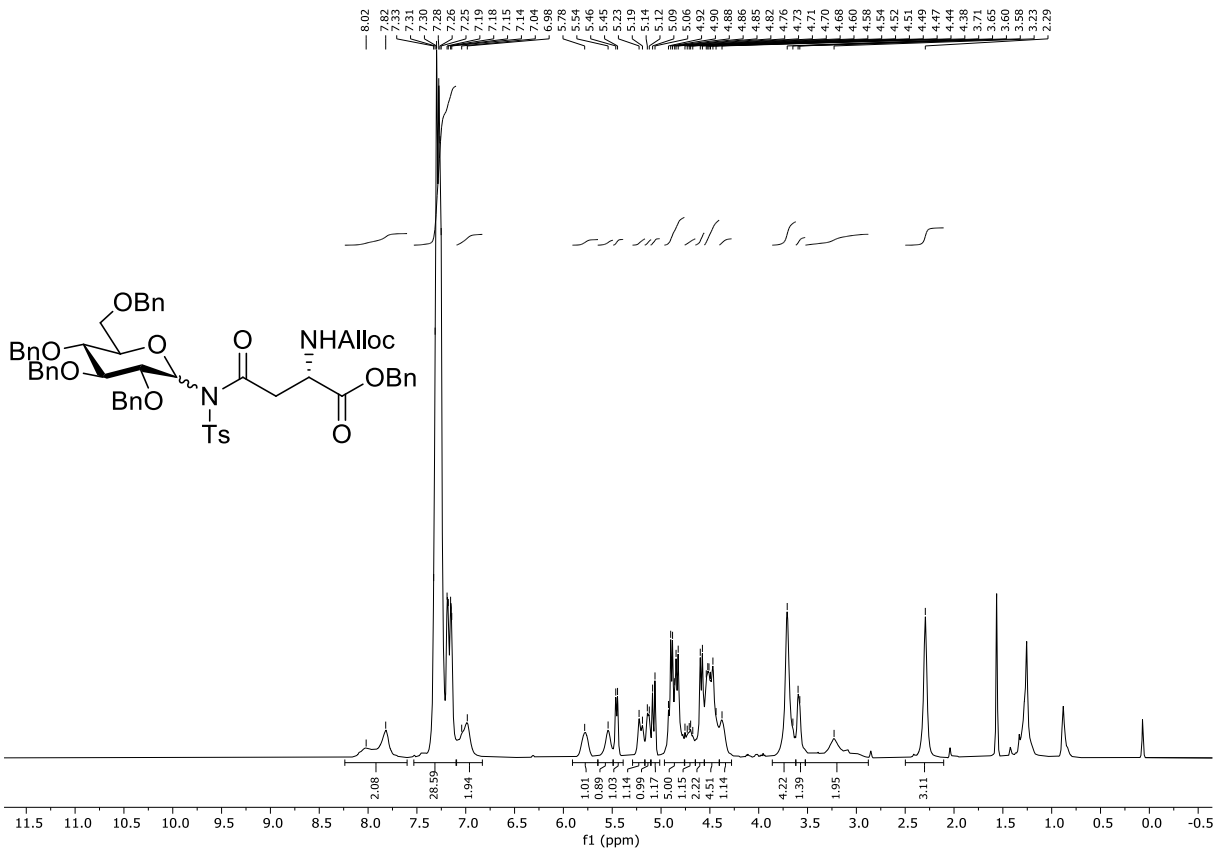


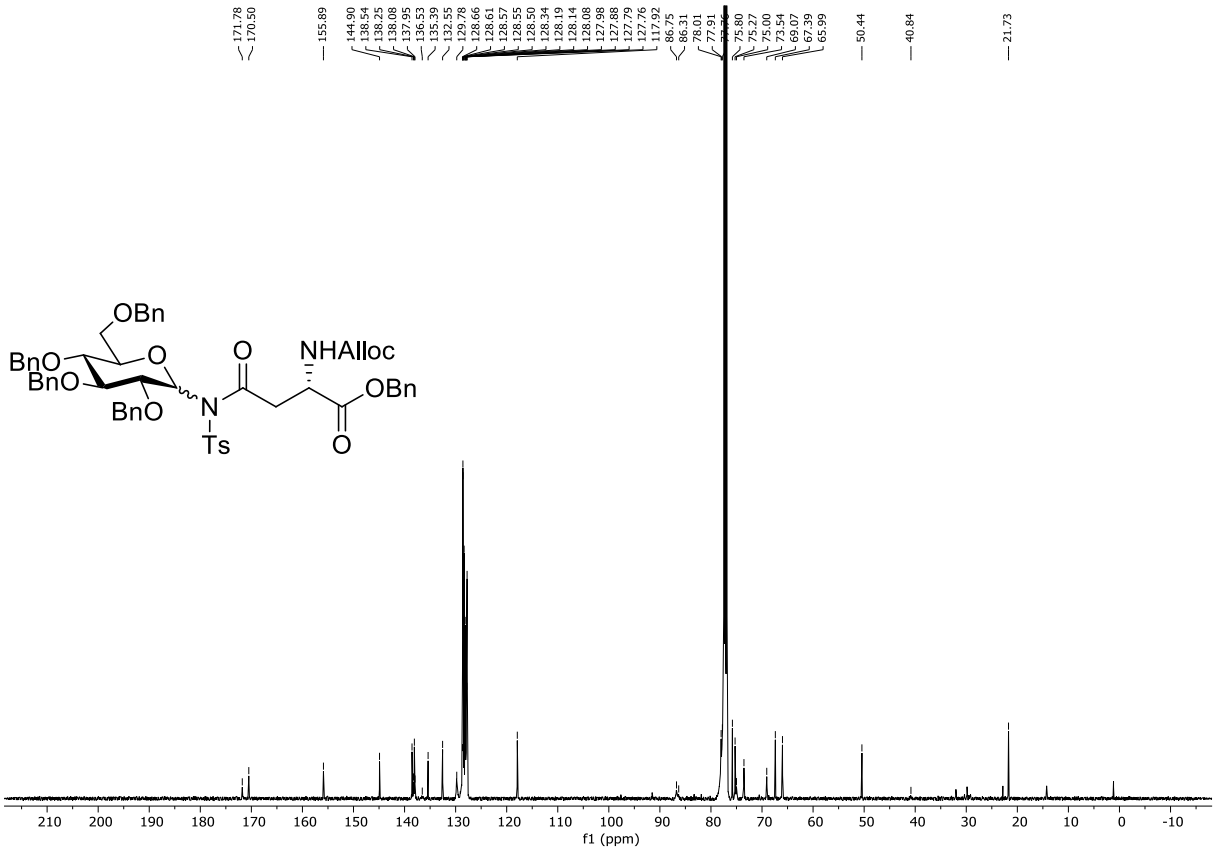
Compound 3.41



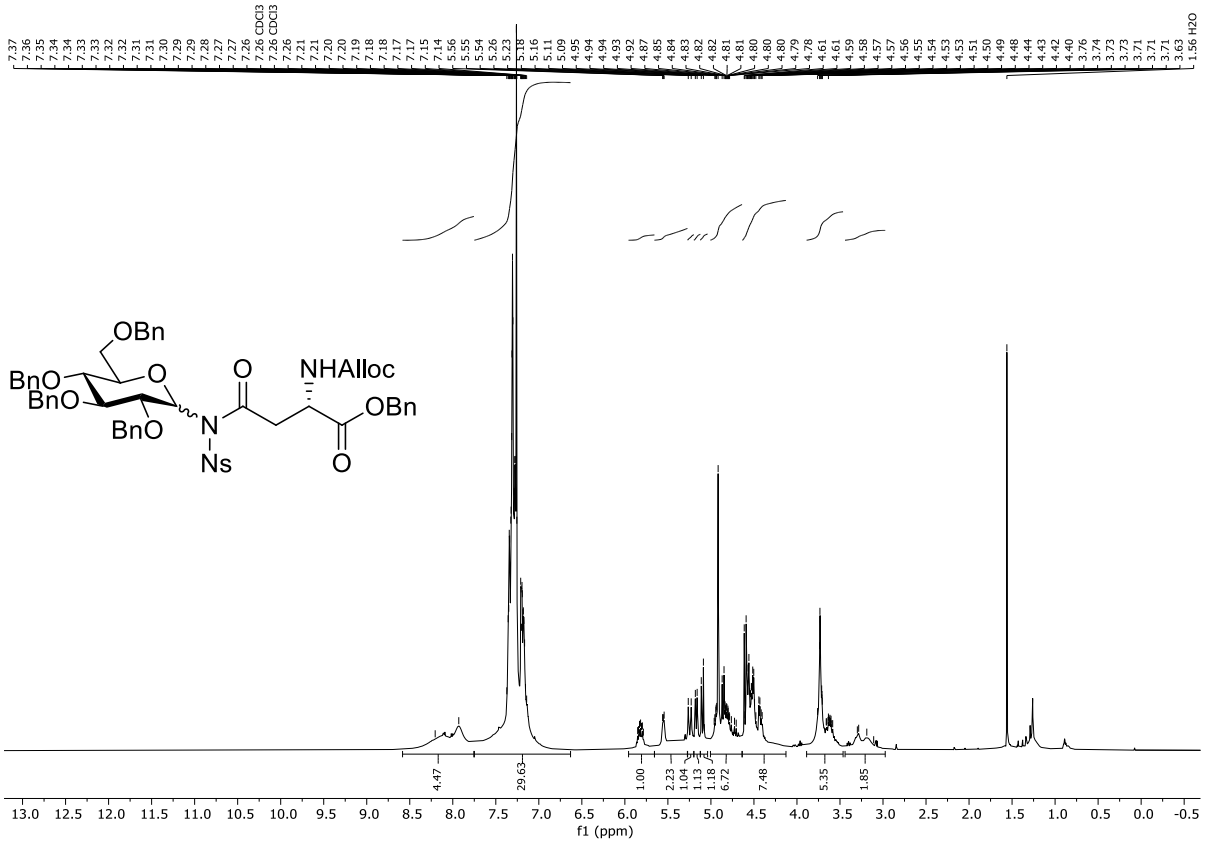


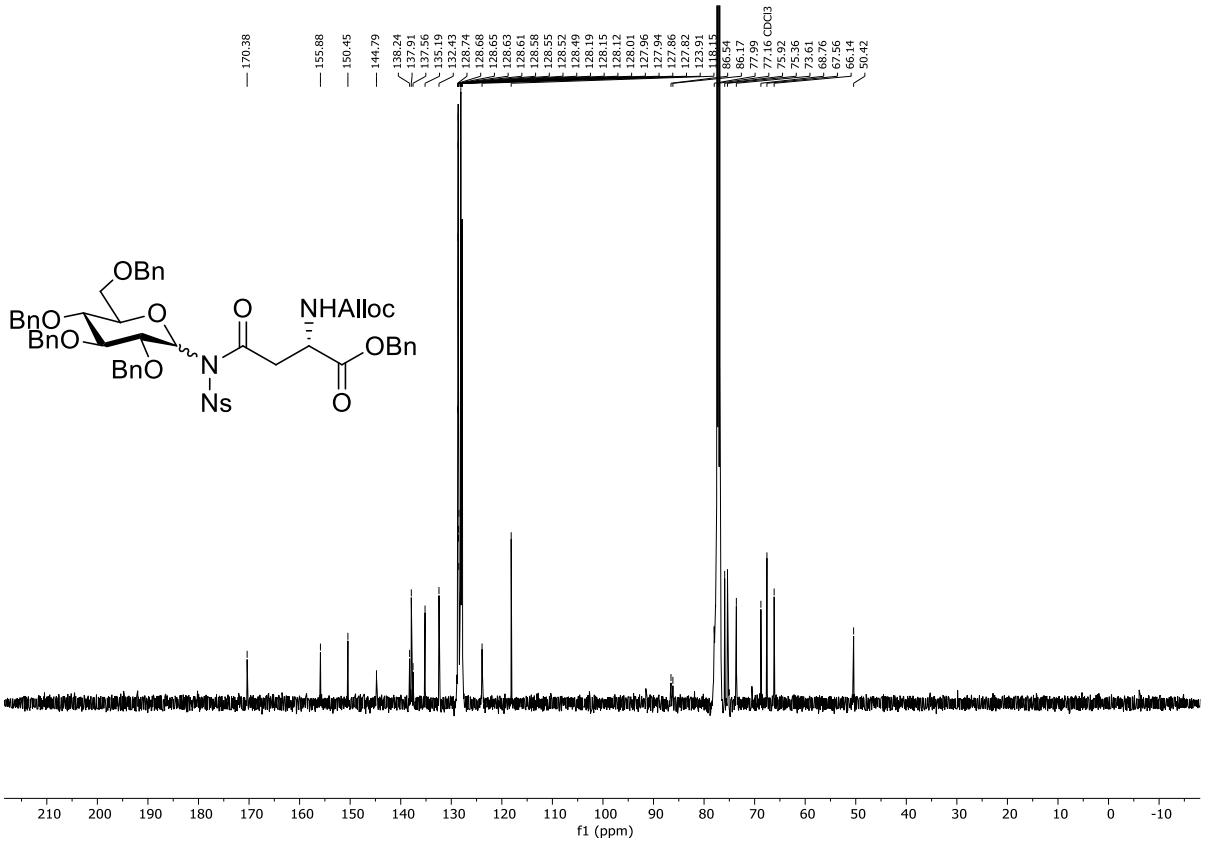
Compound 3.42



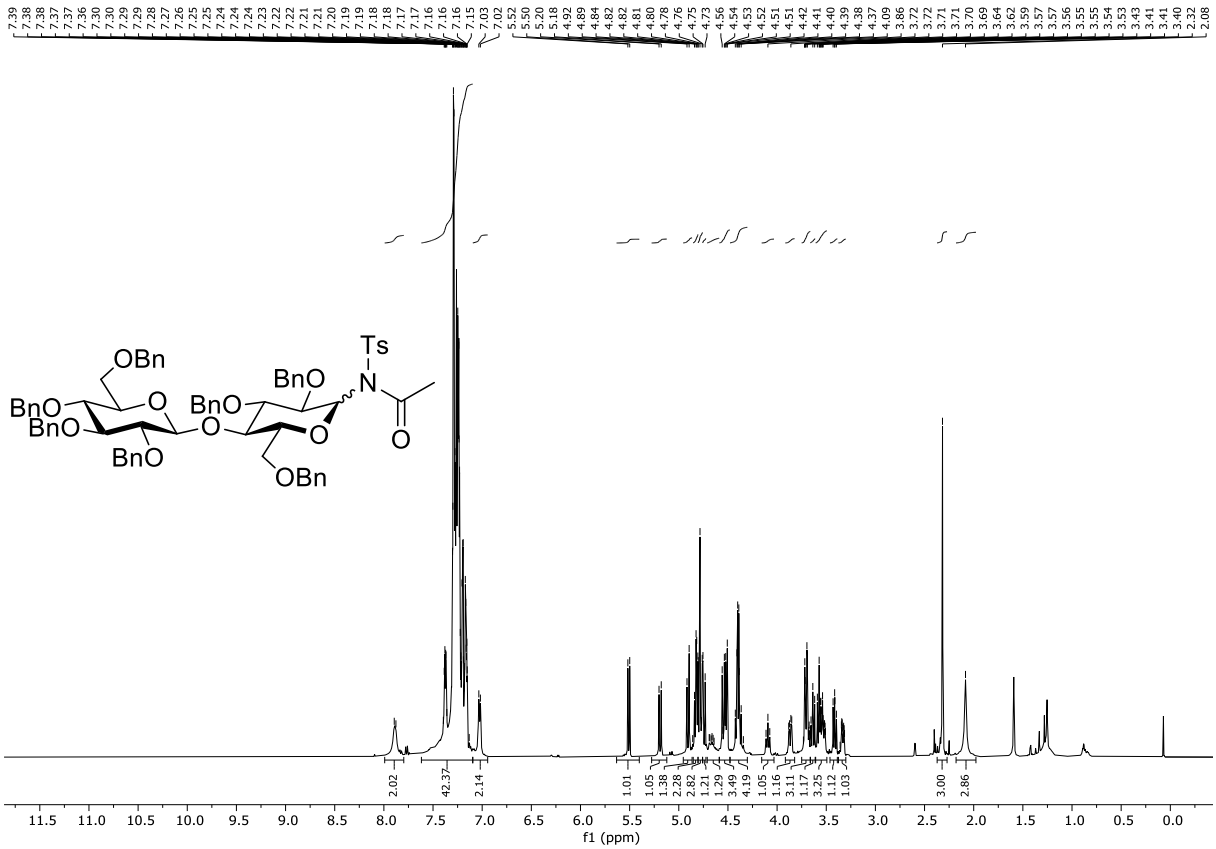


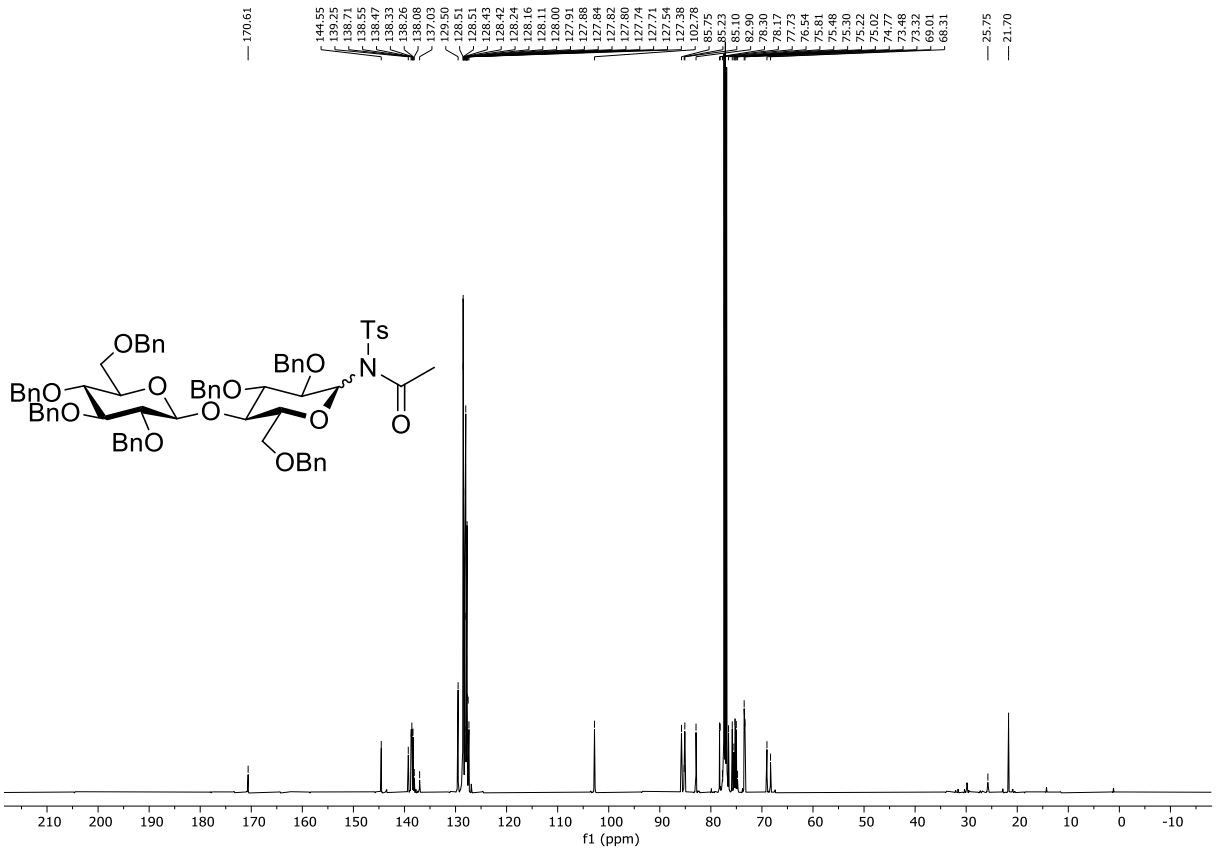
Compound 3.43



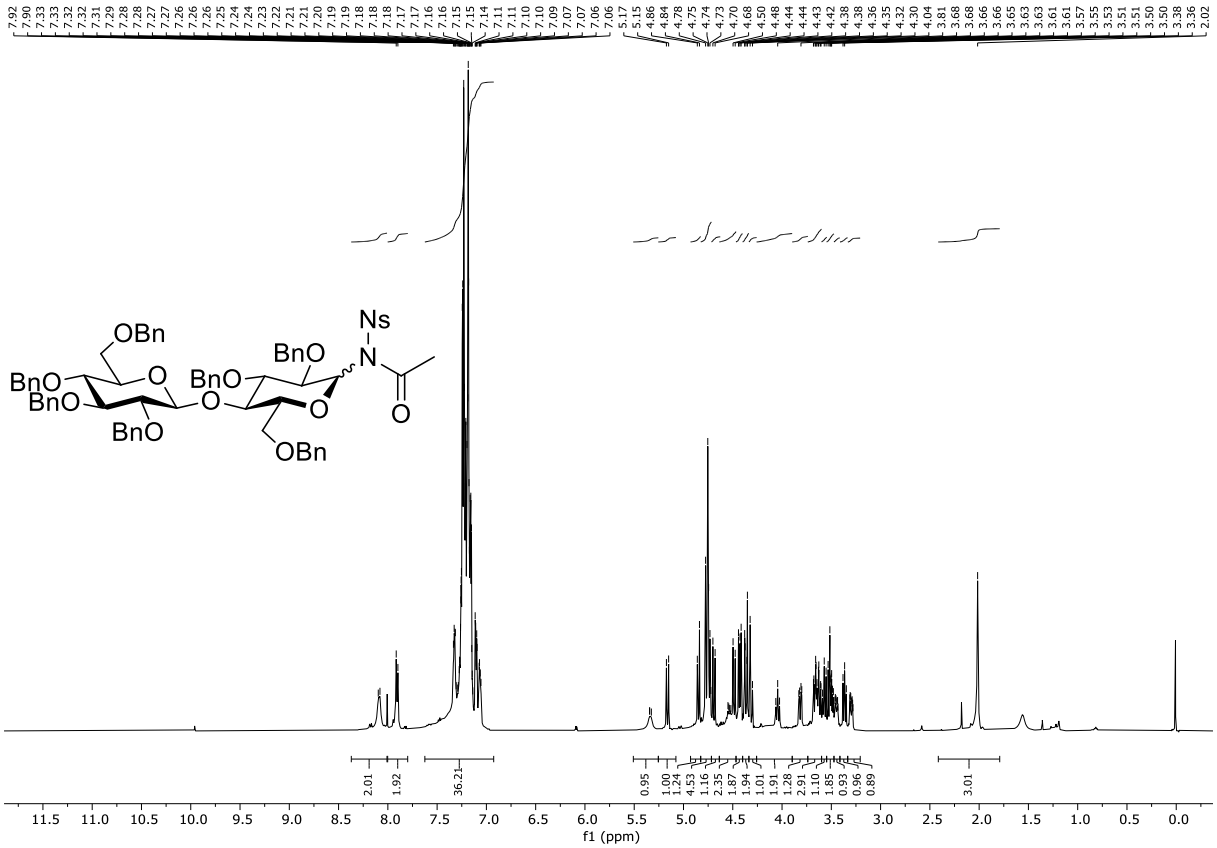


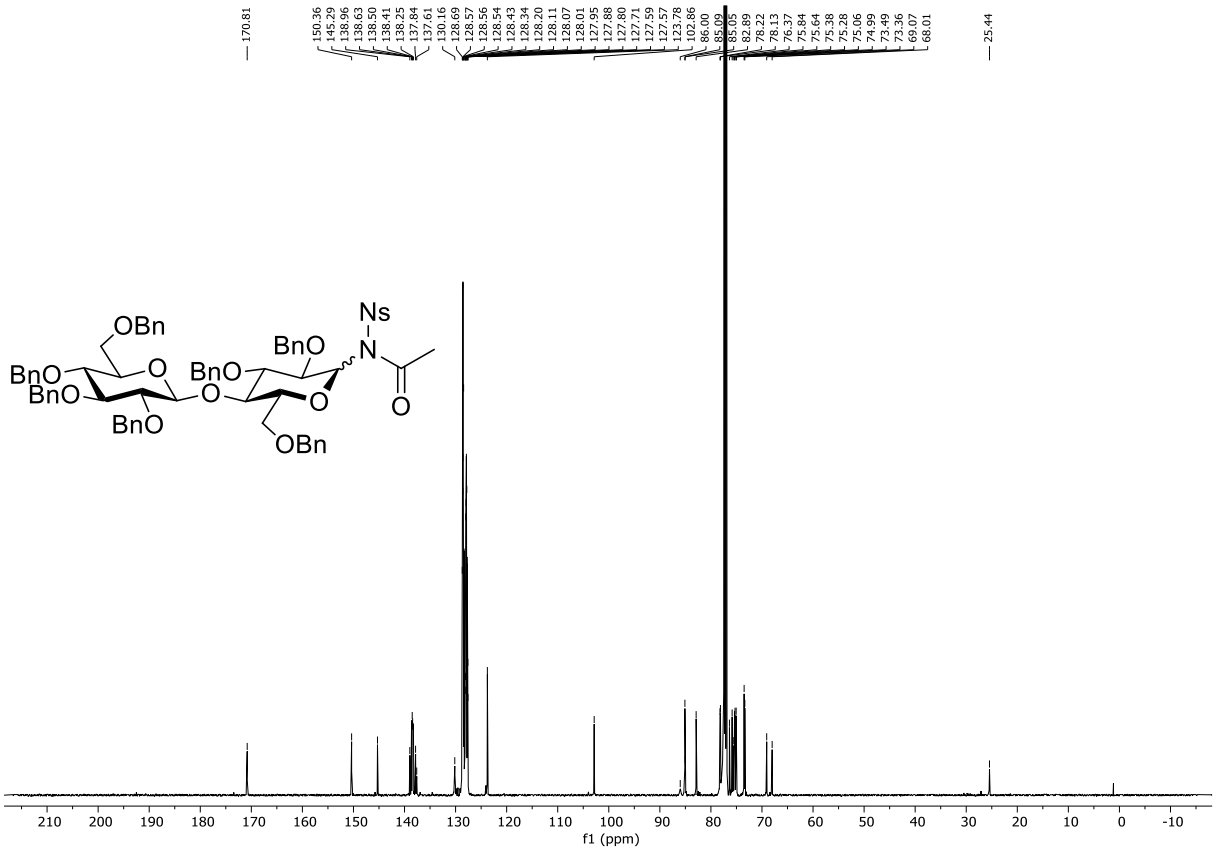
Compound 3.45



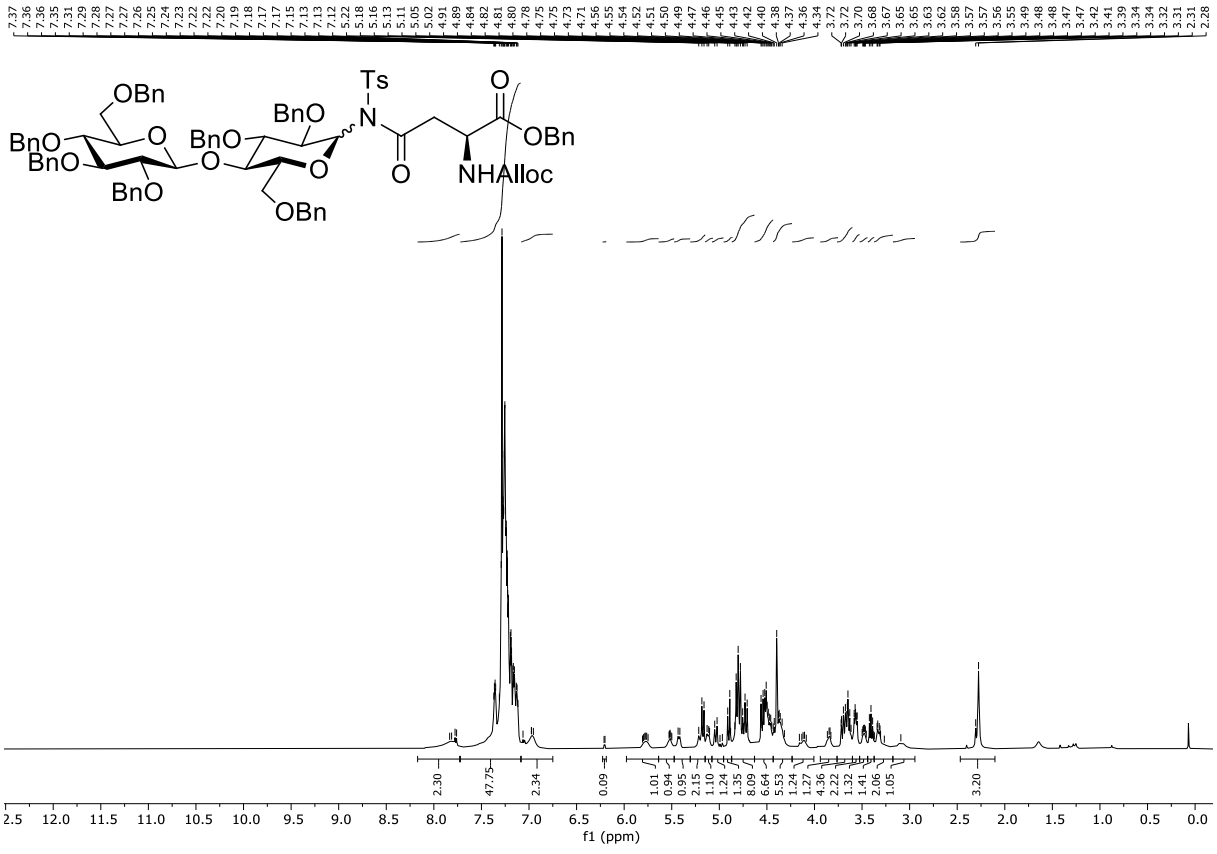


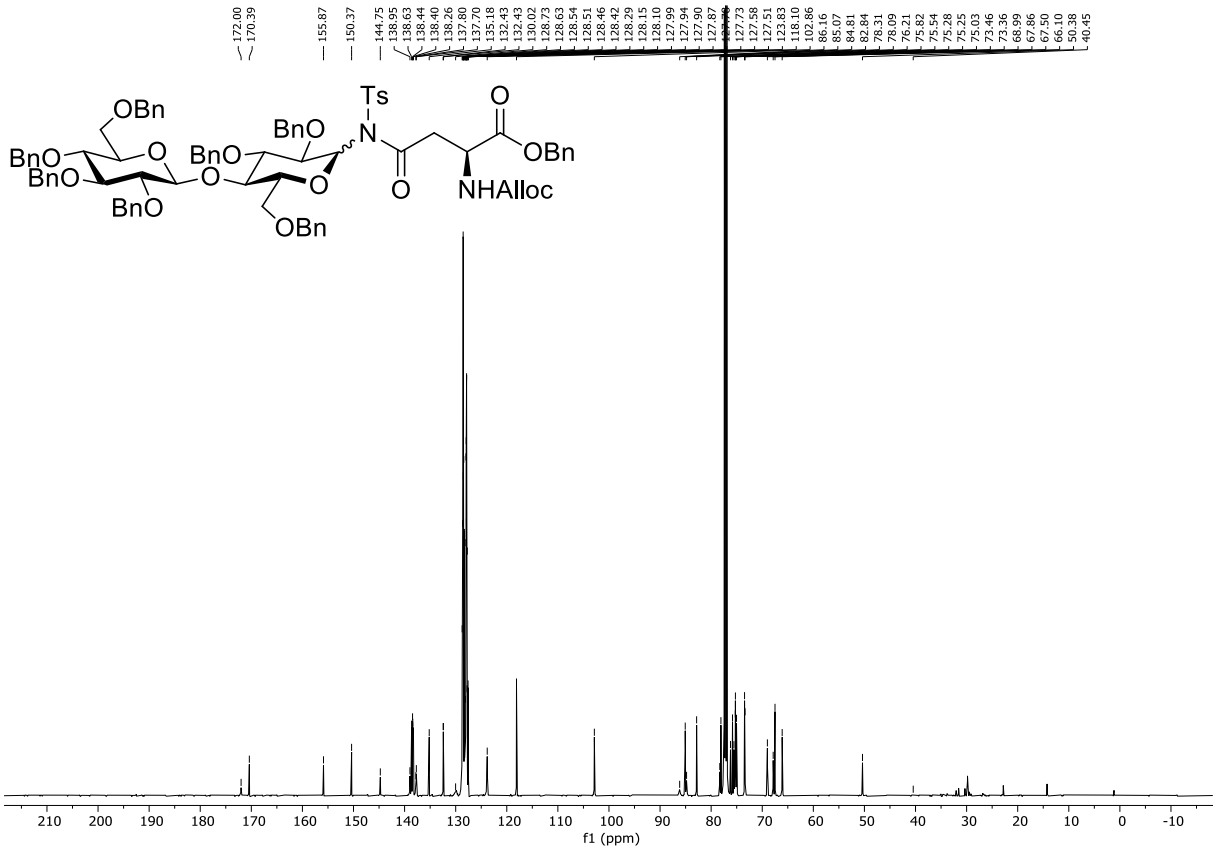
Compound 3.46



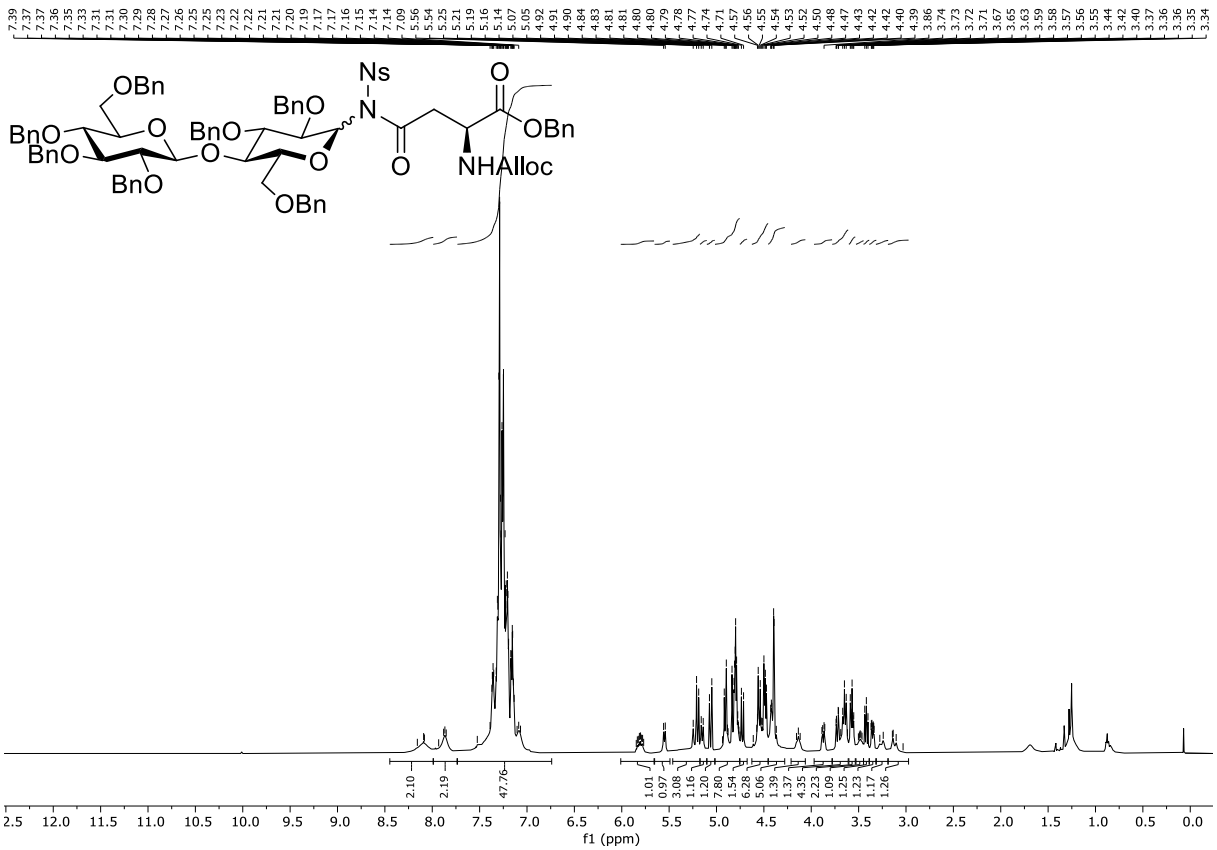


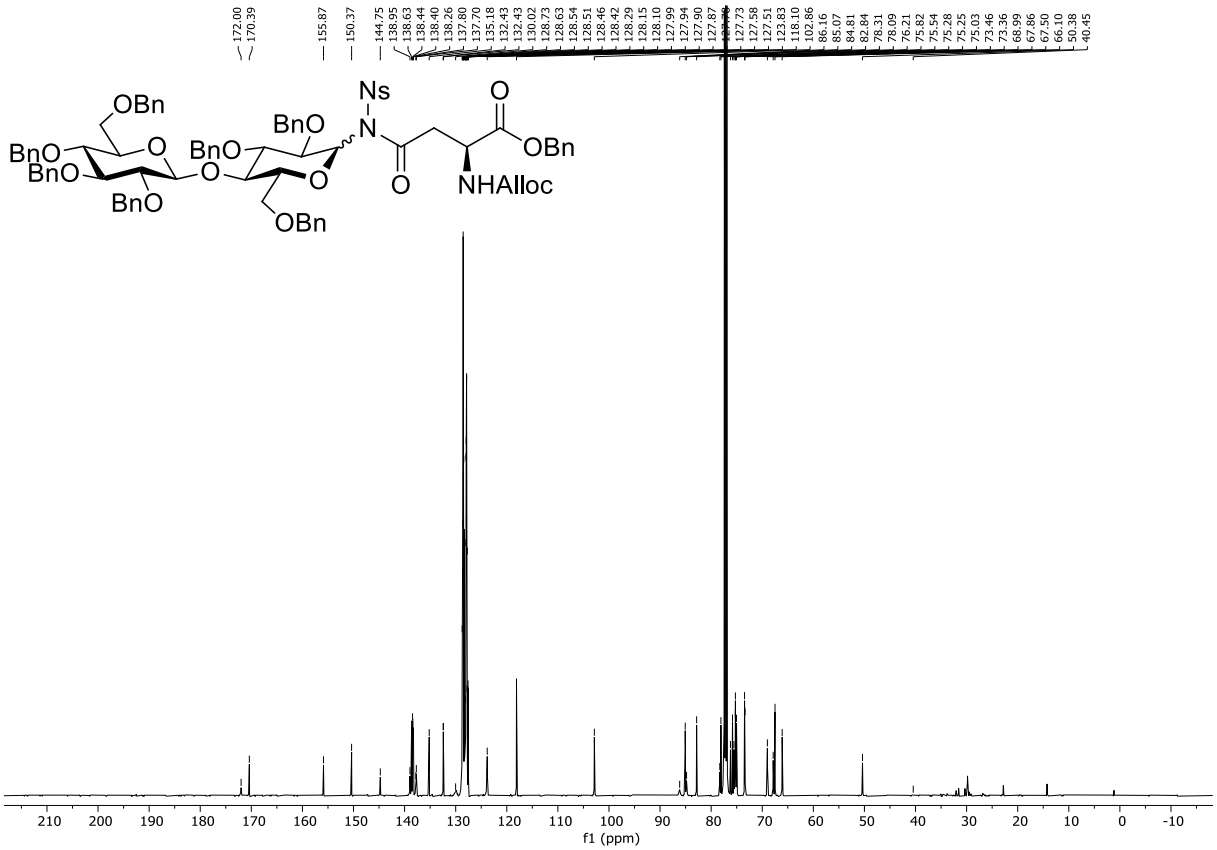
Compound 3.47



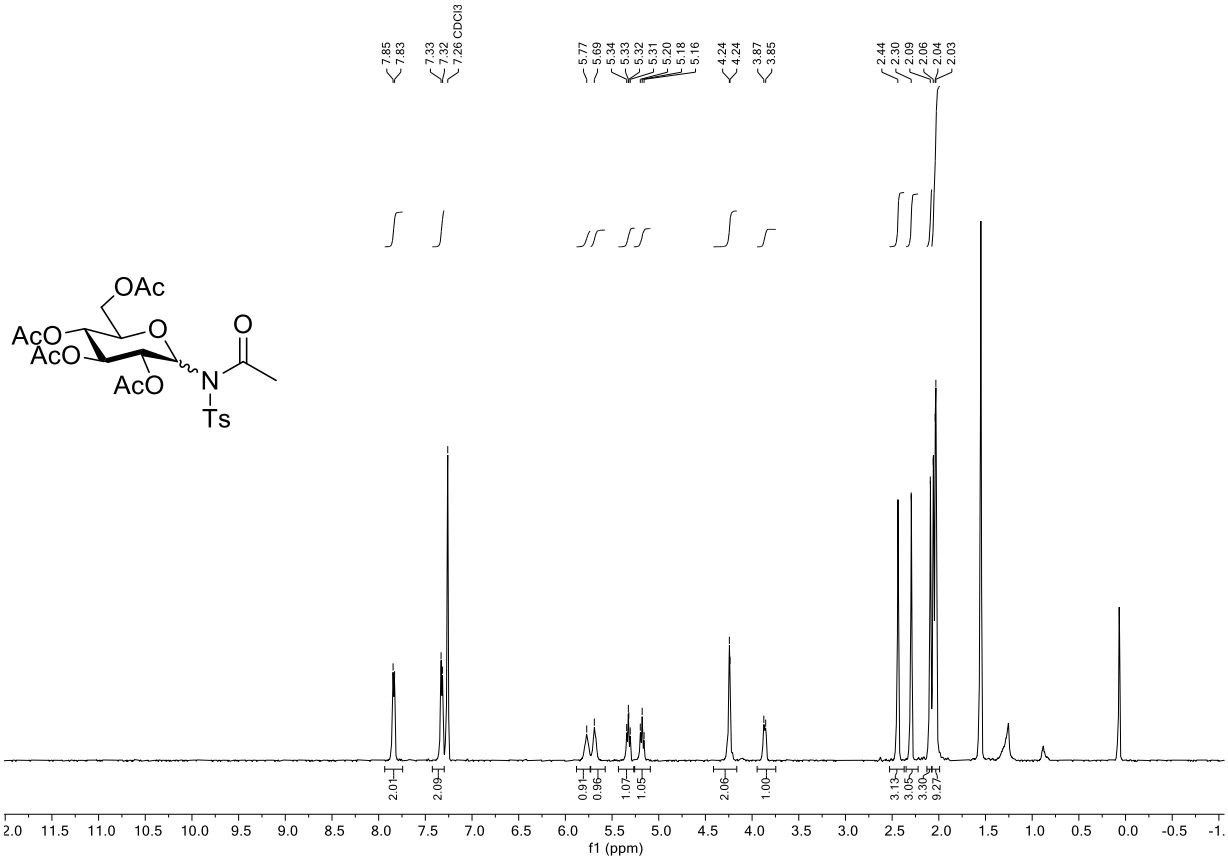


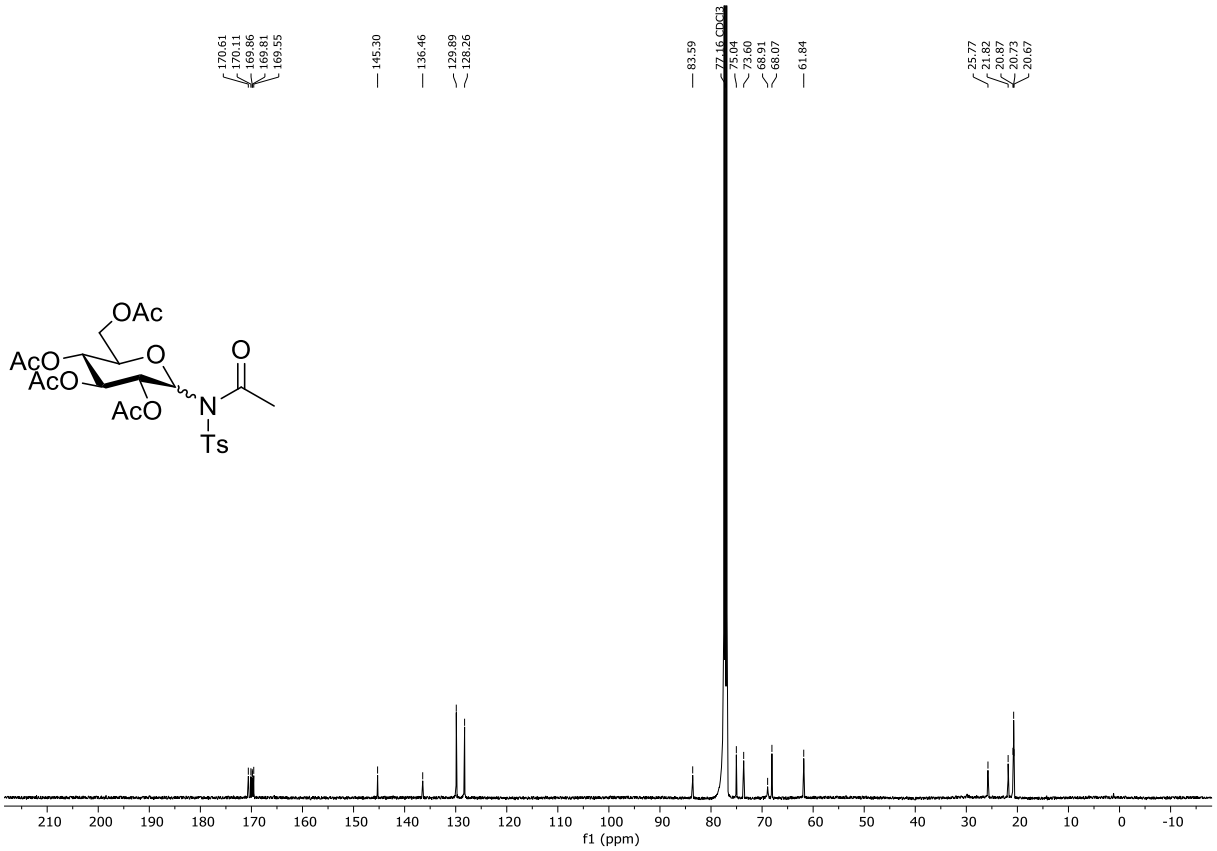
Compound 3.48



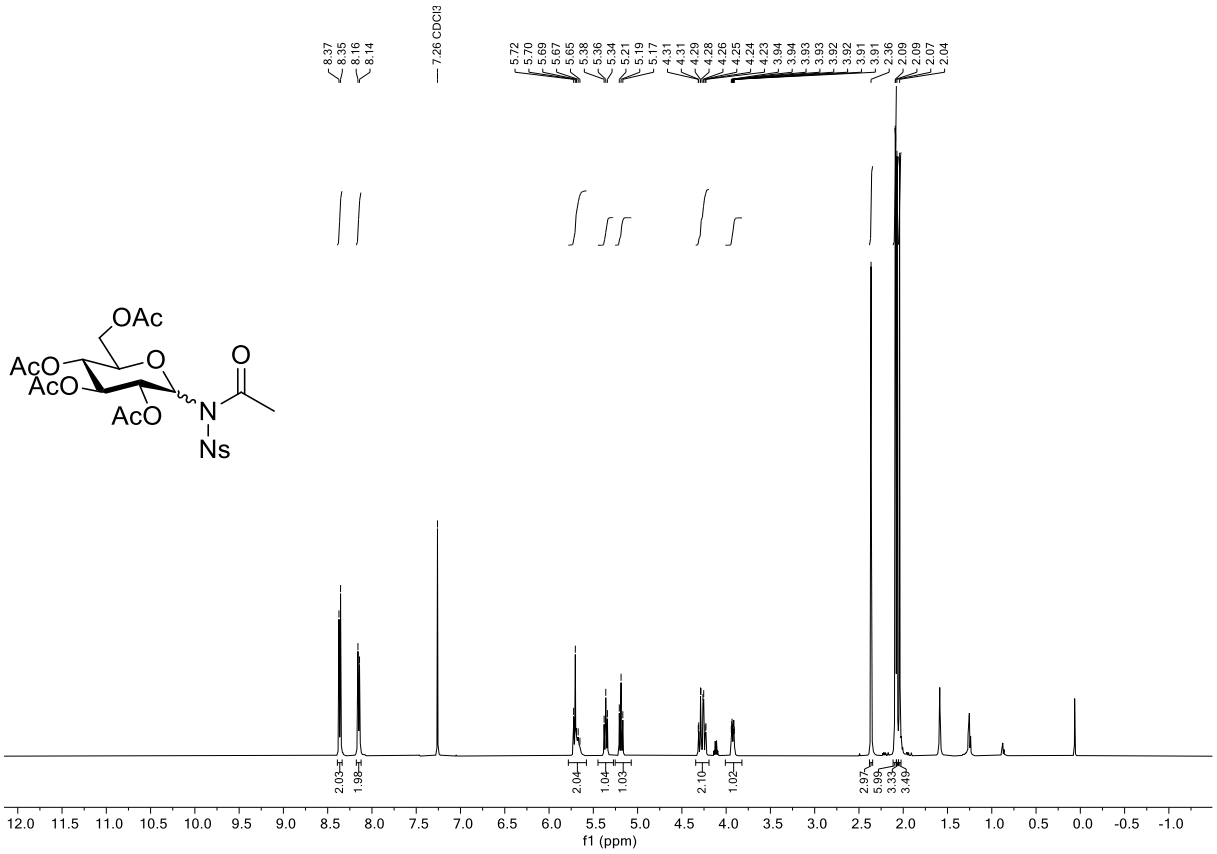


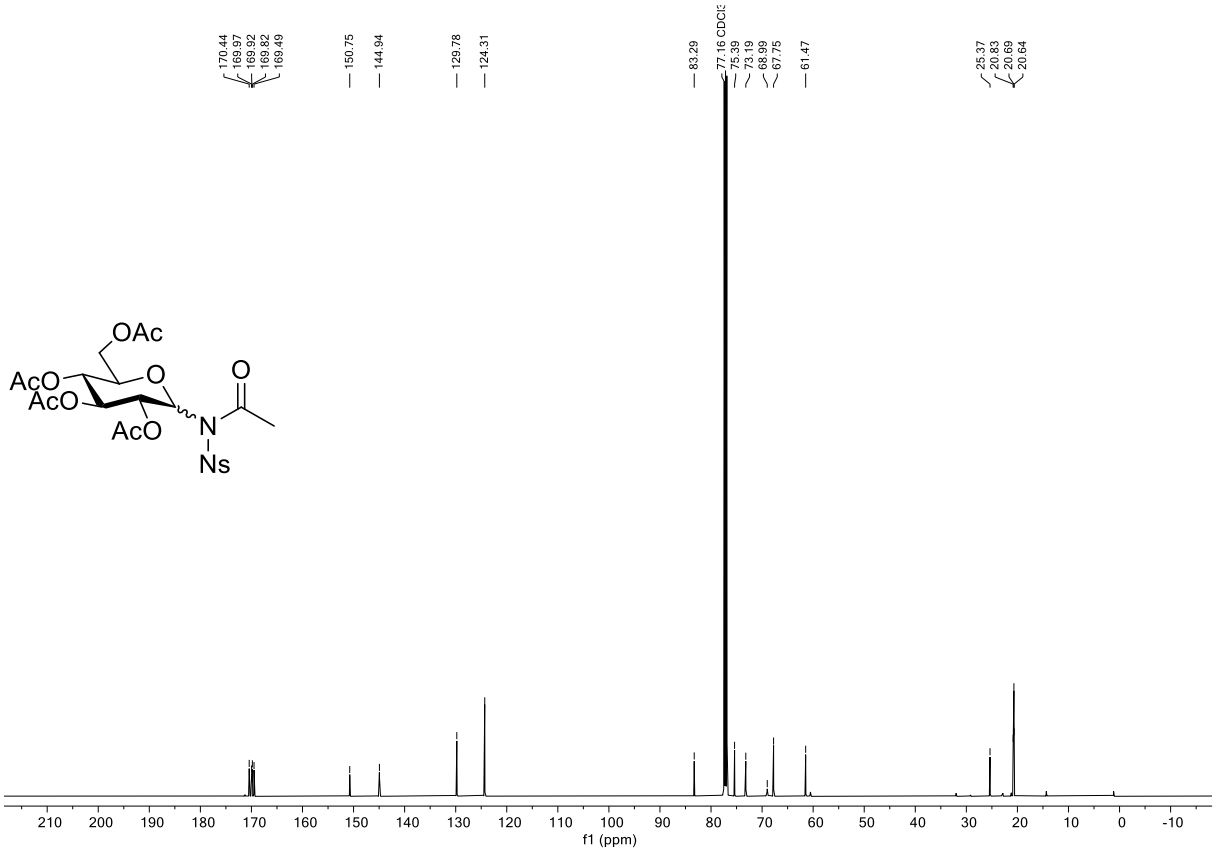
Compound 3.49



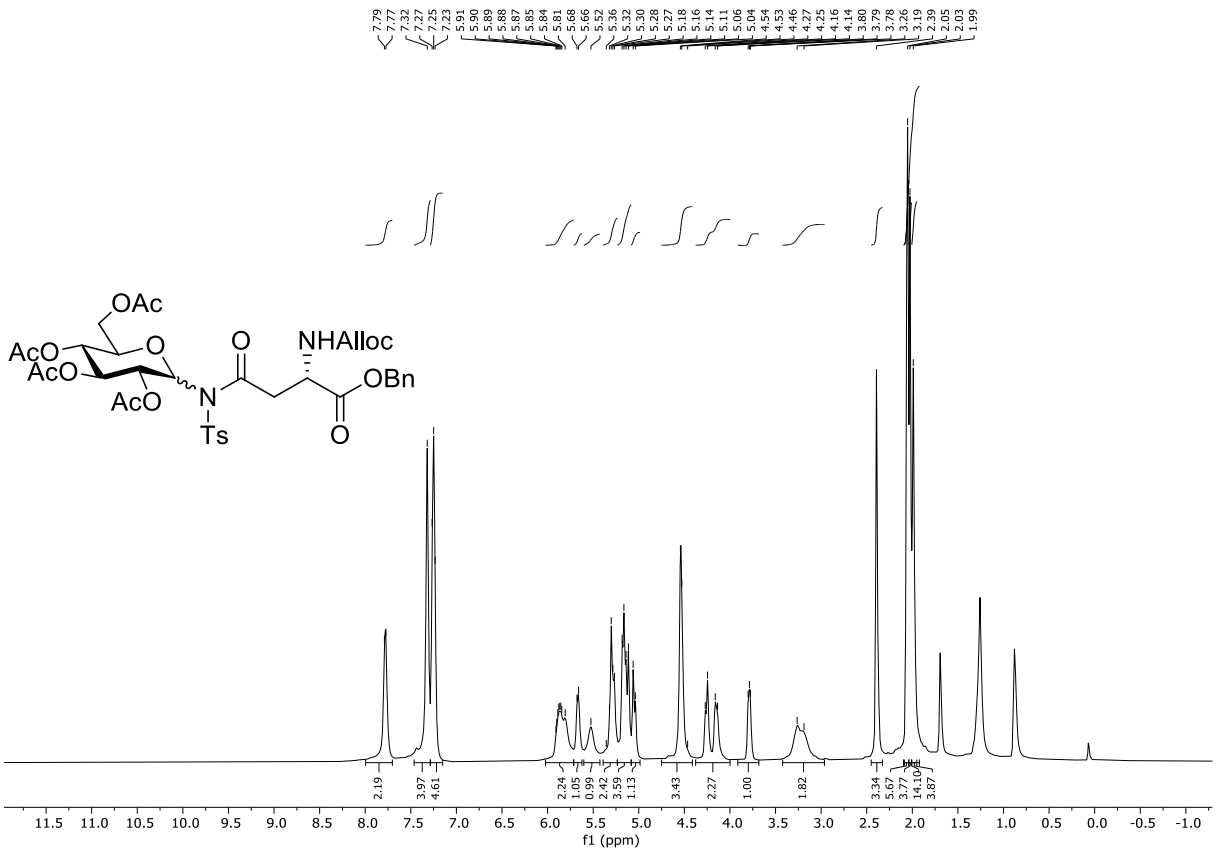


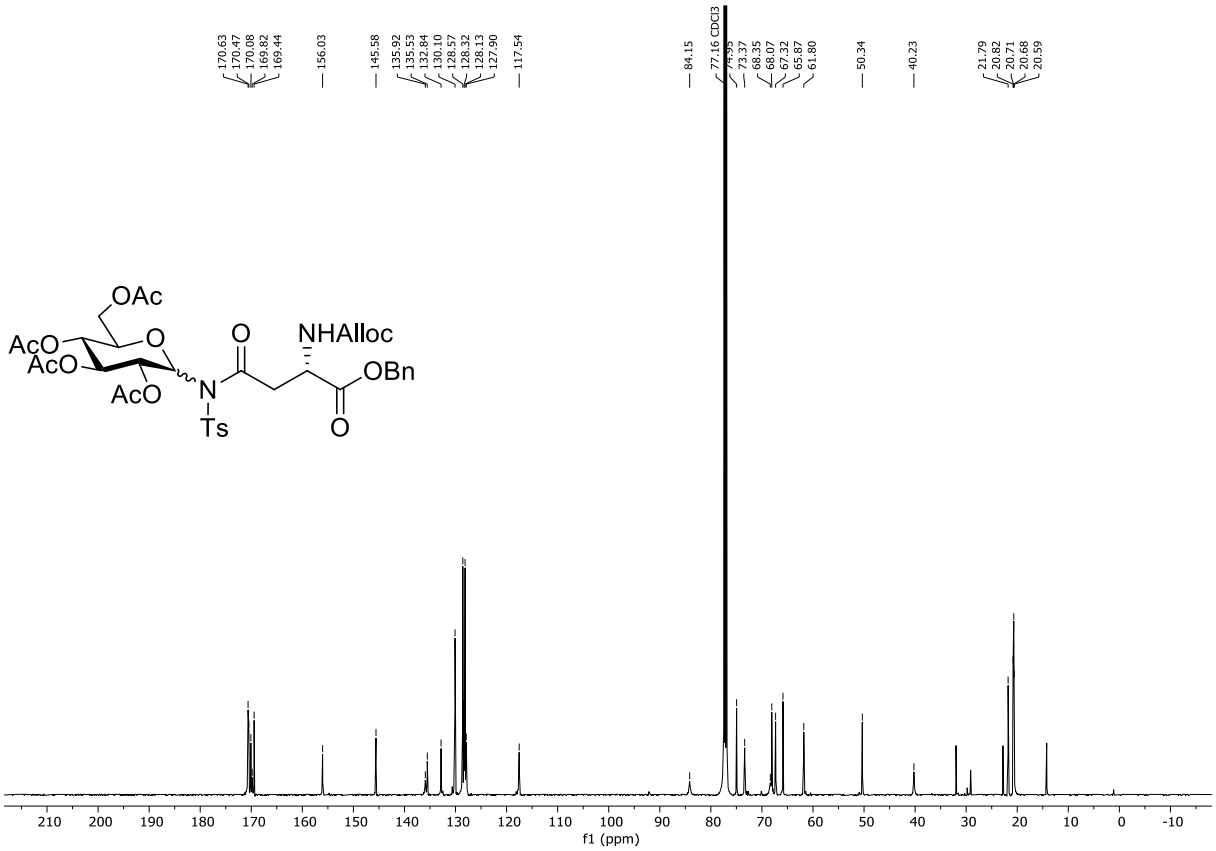
Compound 3.50



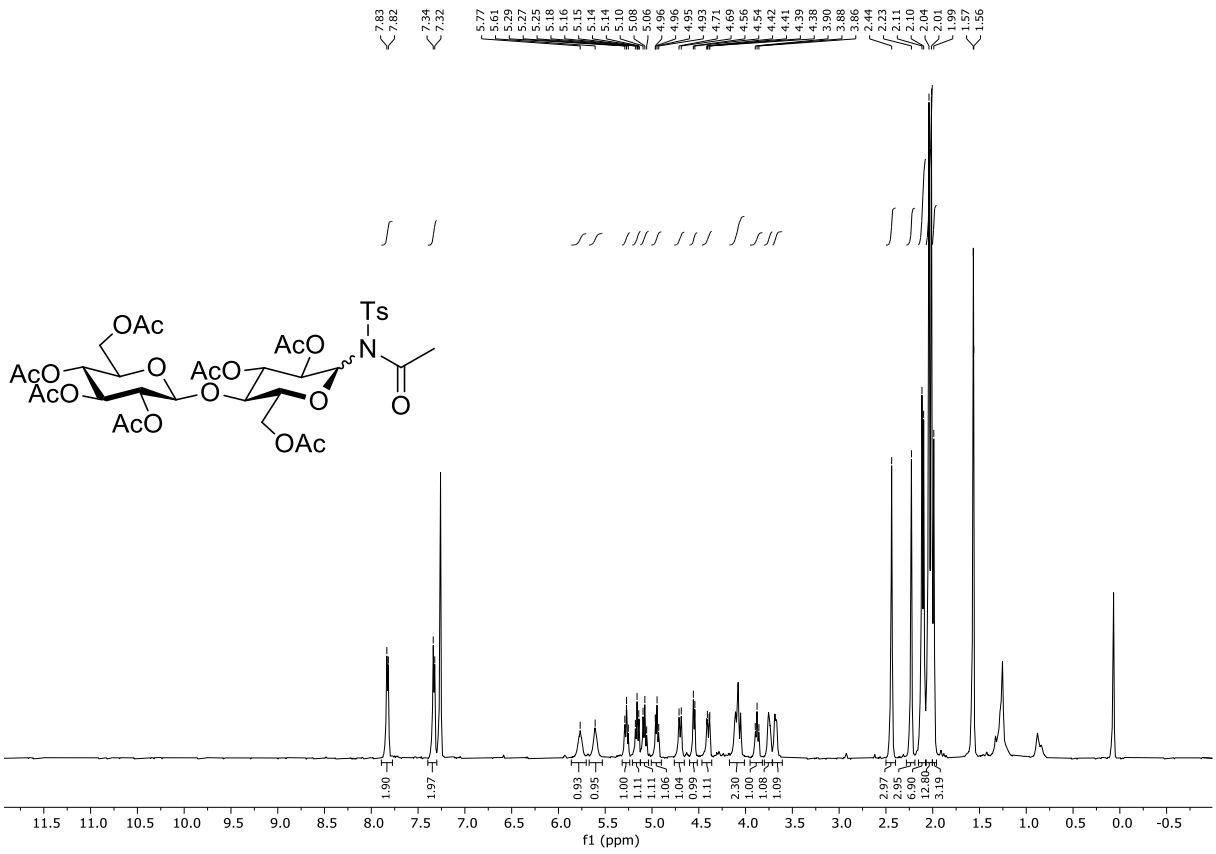


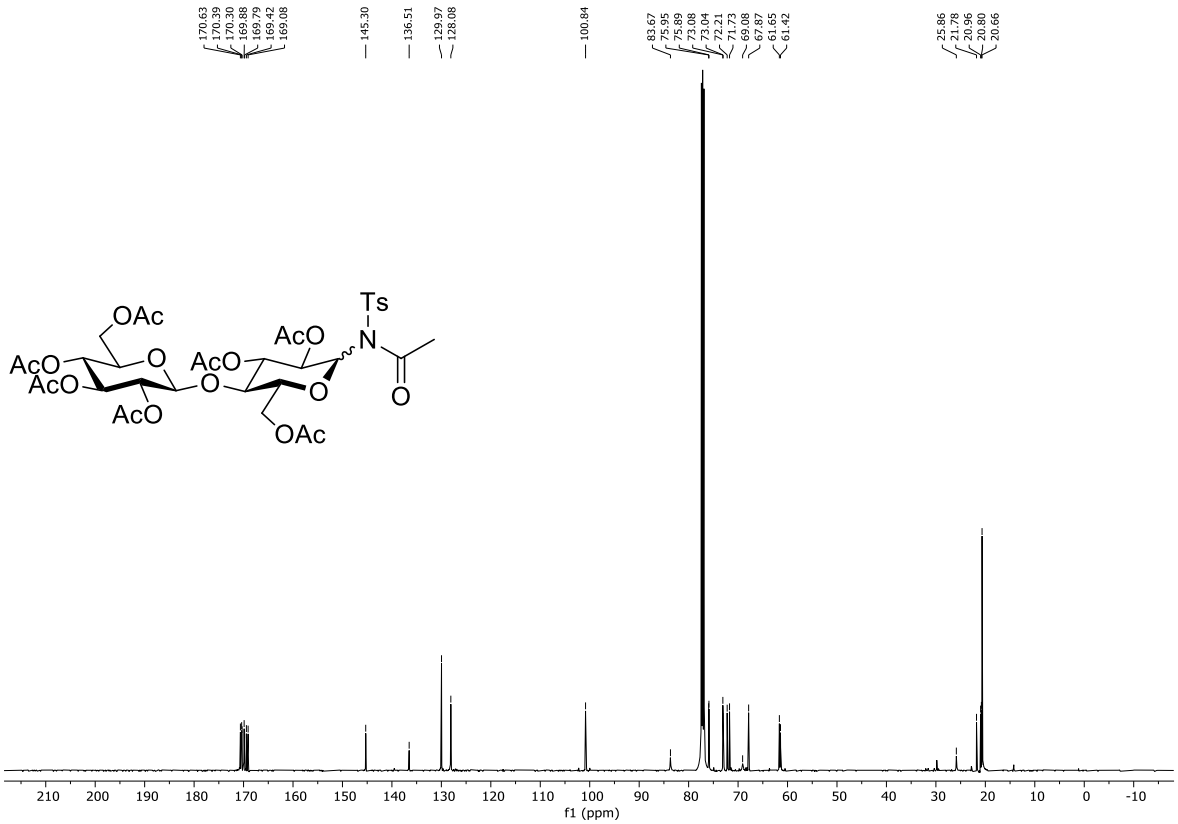
Compound 3.51



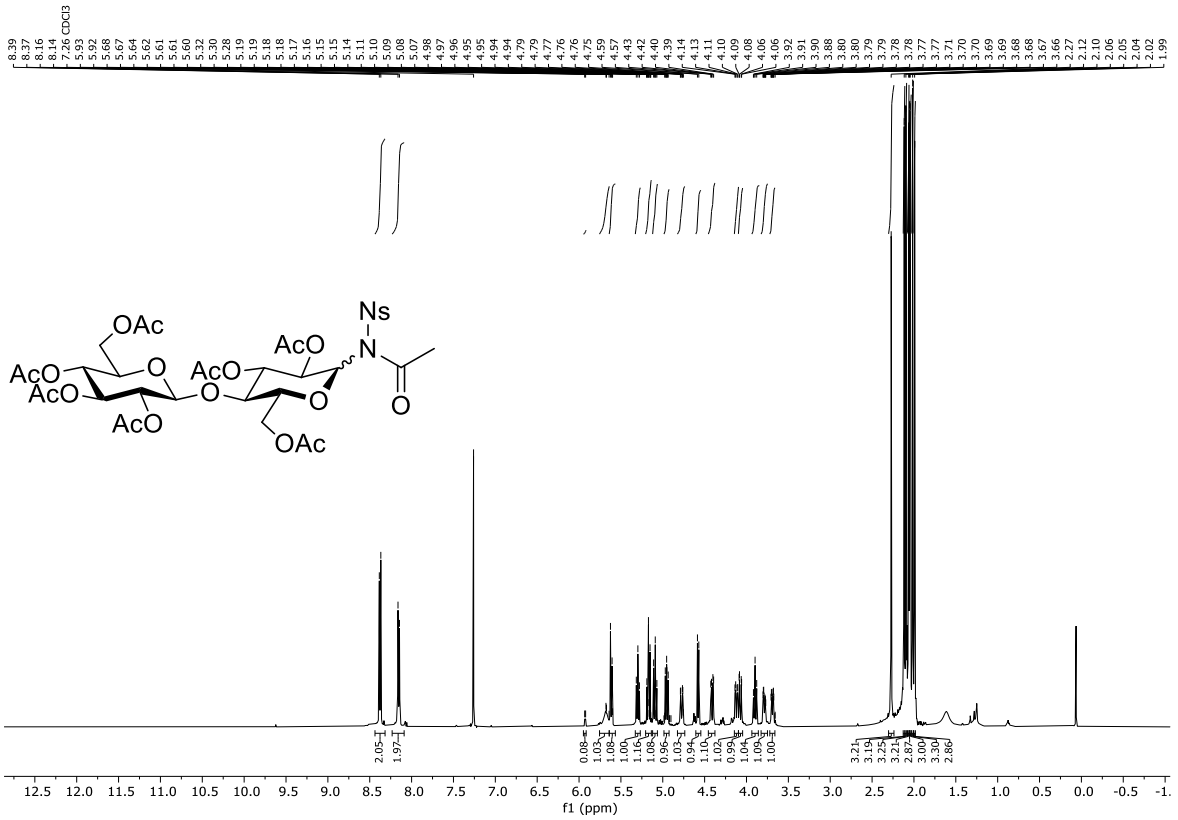


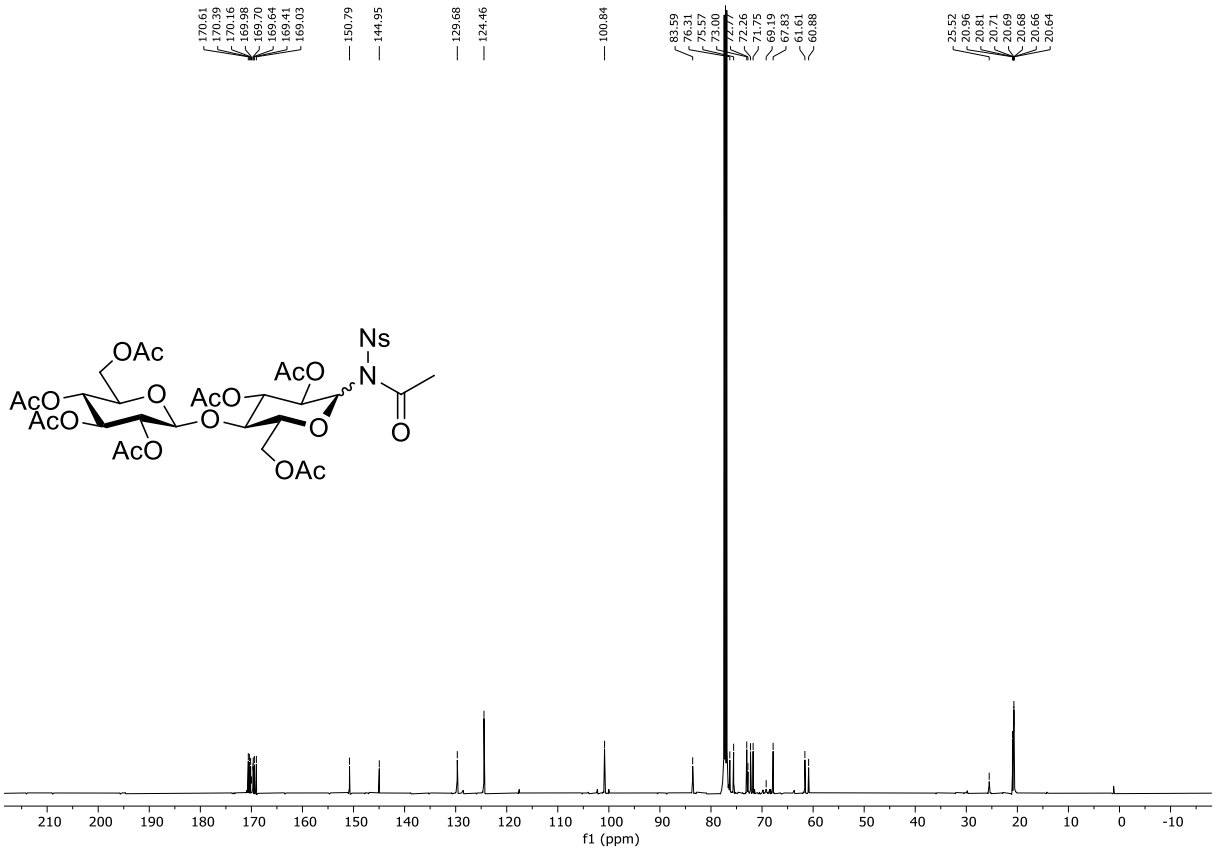
Compound 3.52



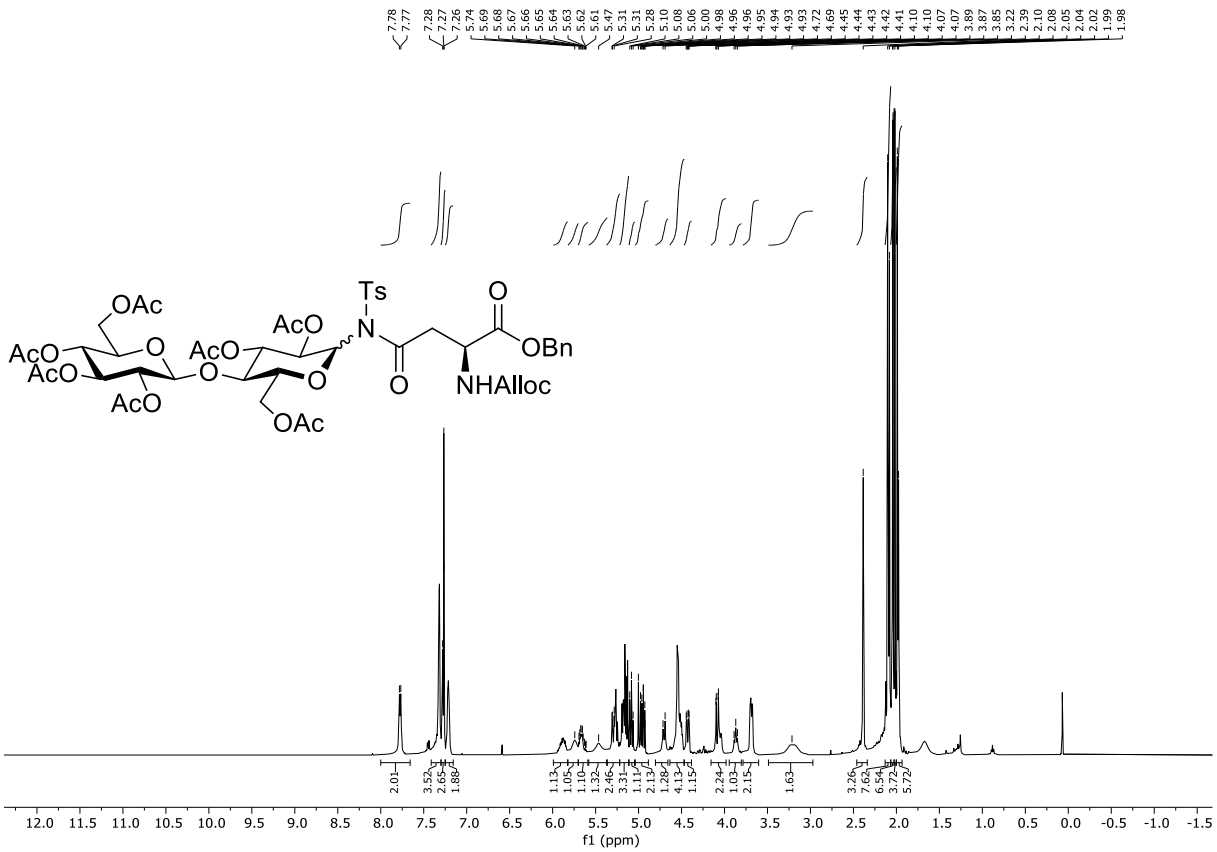


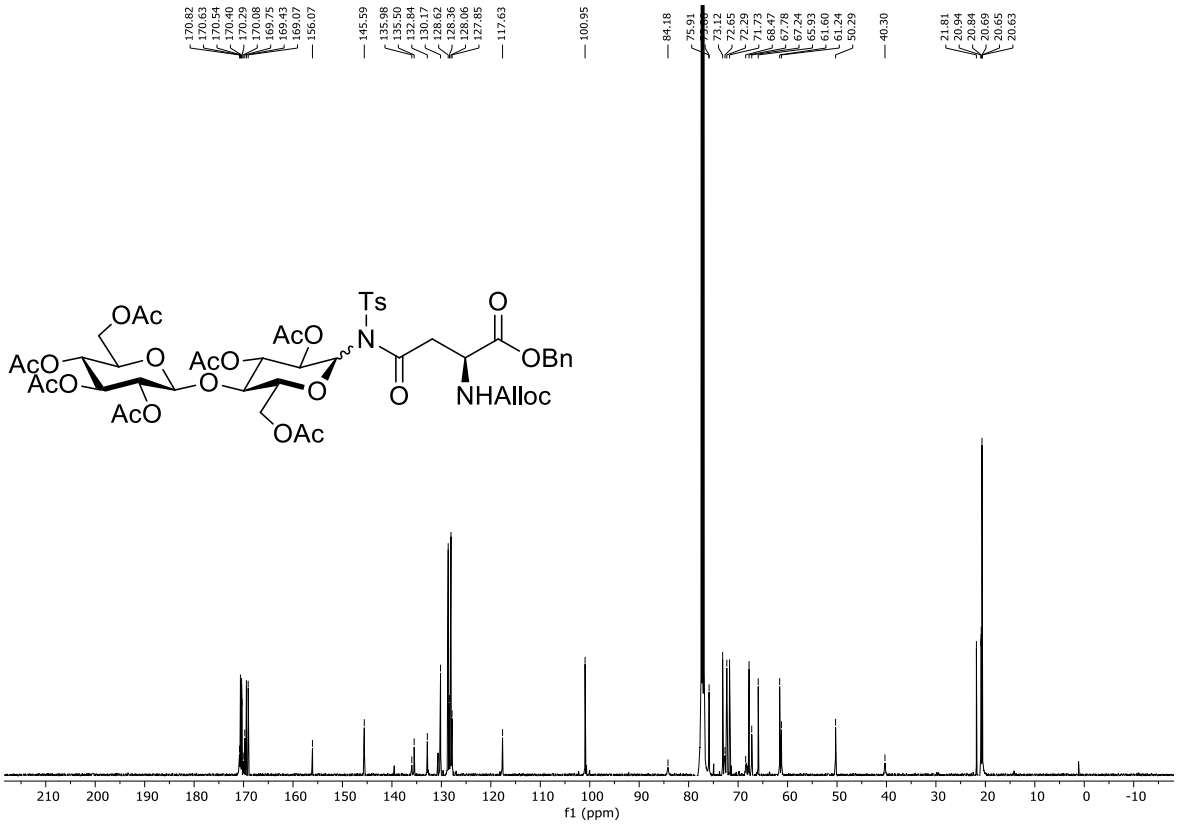
Compound 3.53



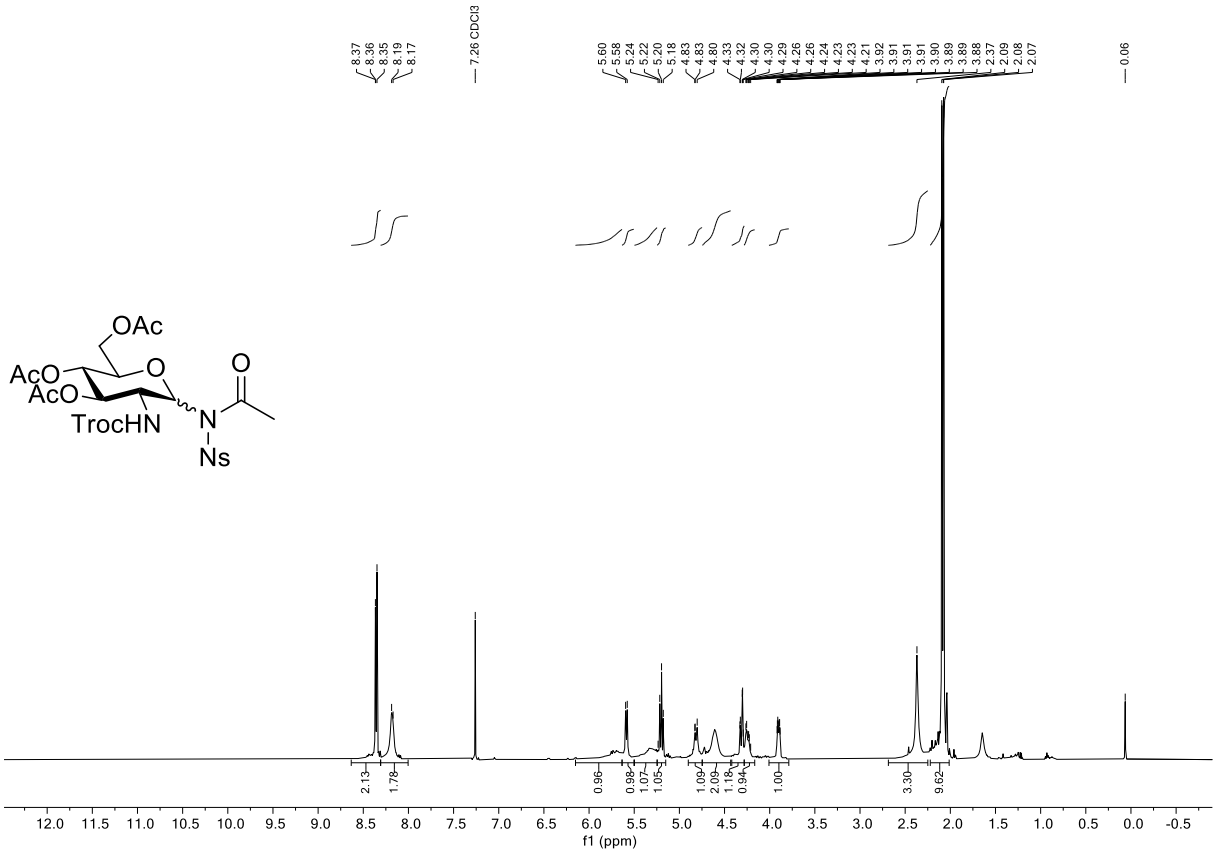


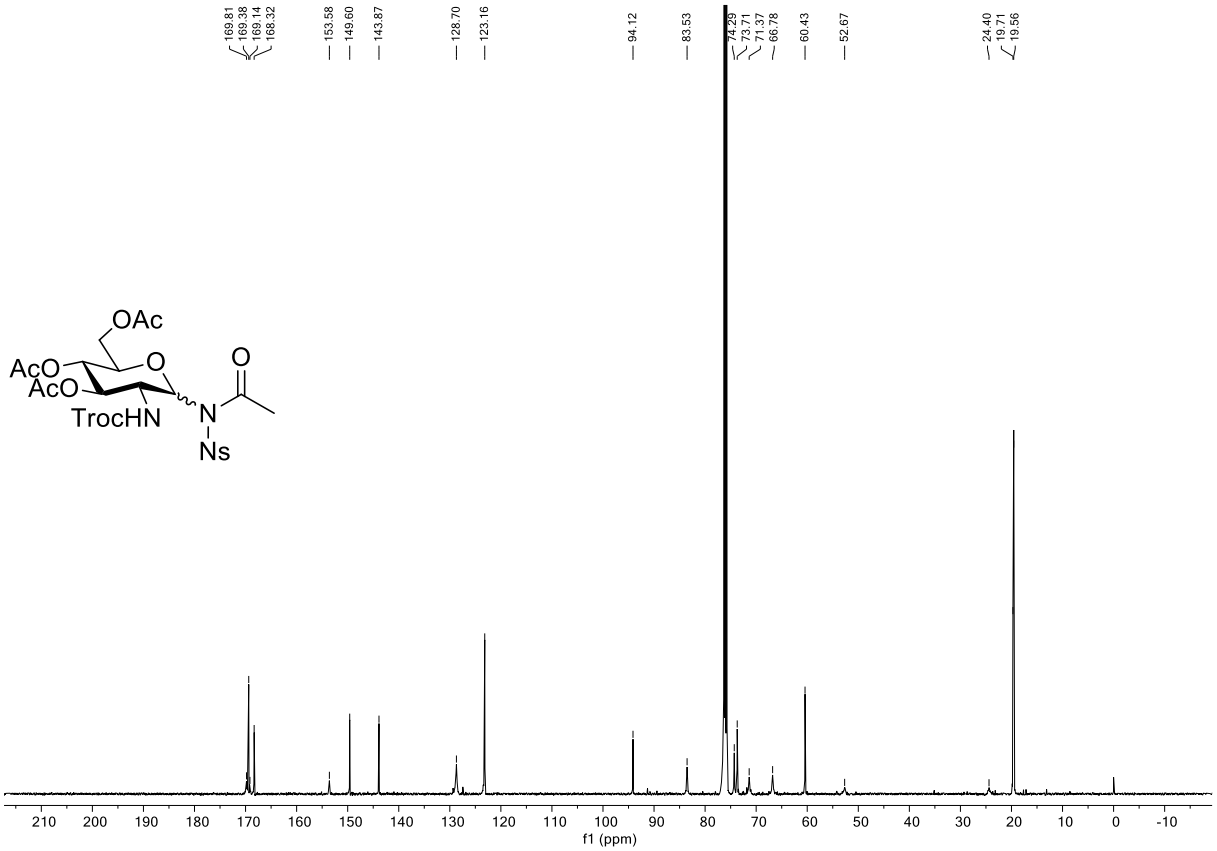
Compound 3.56





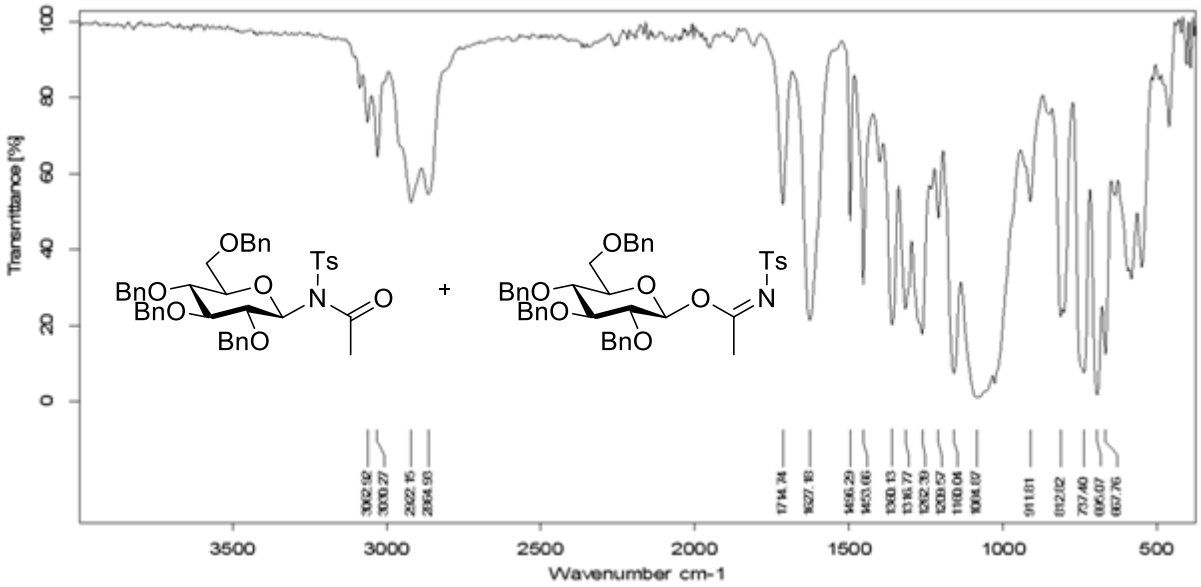
Compound 3.55




169.81
169.38
169.14
168.32
153.58
149.60
143.87
128.70
123.16
94.12
83.53
74.29
73.71
71.37
66.78
60.43
52.67
24.40
19.71
19.56
OAc
AcO
AcO
O
TrocHN
N
Ns
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

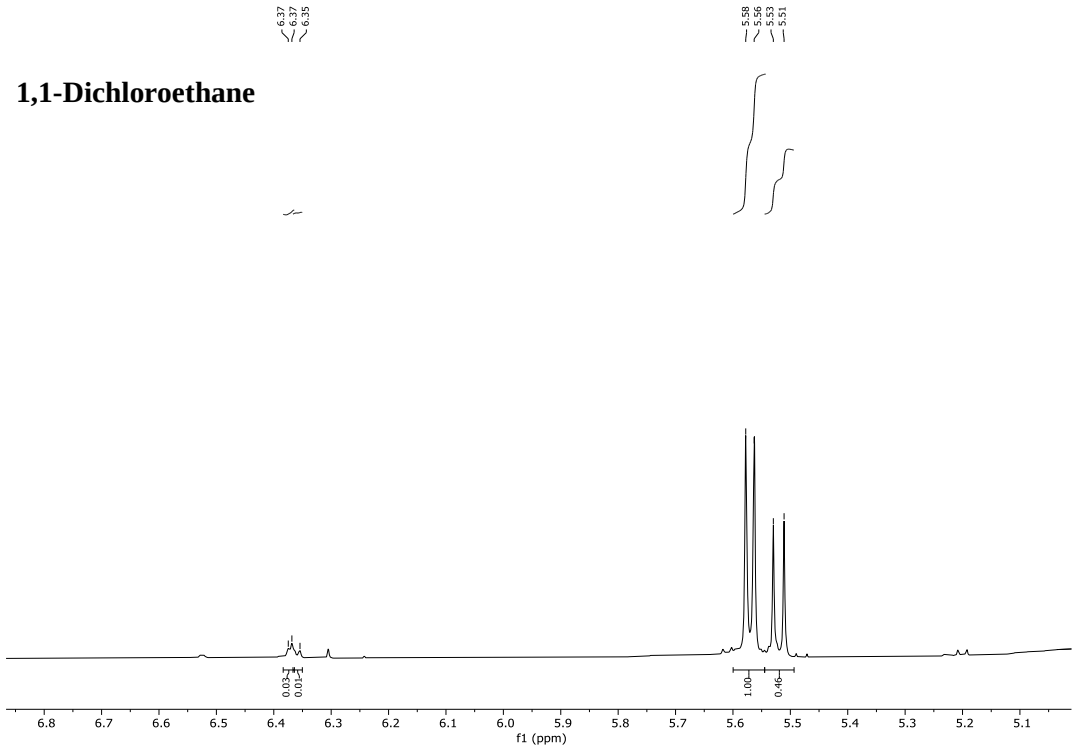
3.4.6. Appendix of IR Spectrum

Compounds 3.35β and 3.38β

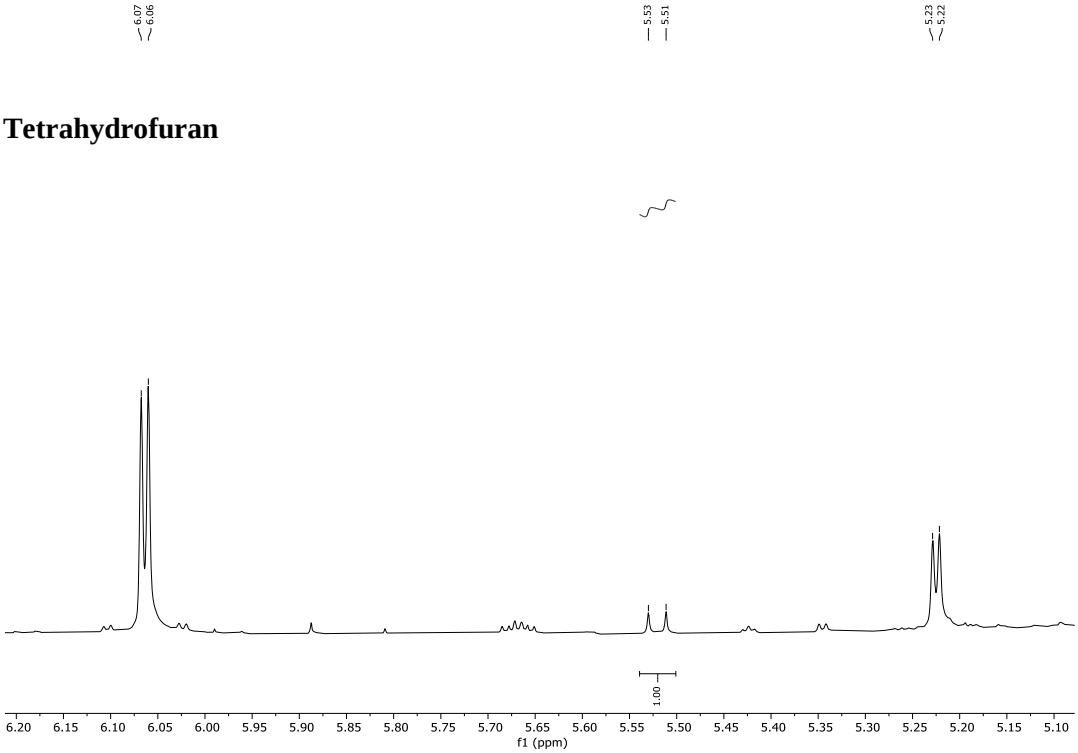


3.4.7. Appendix of Solvent Screening

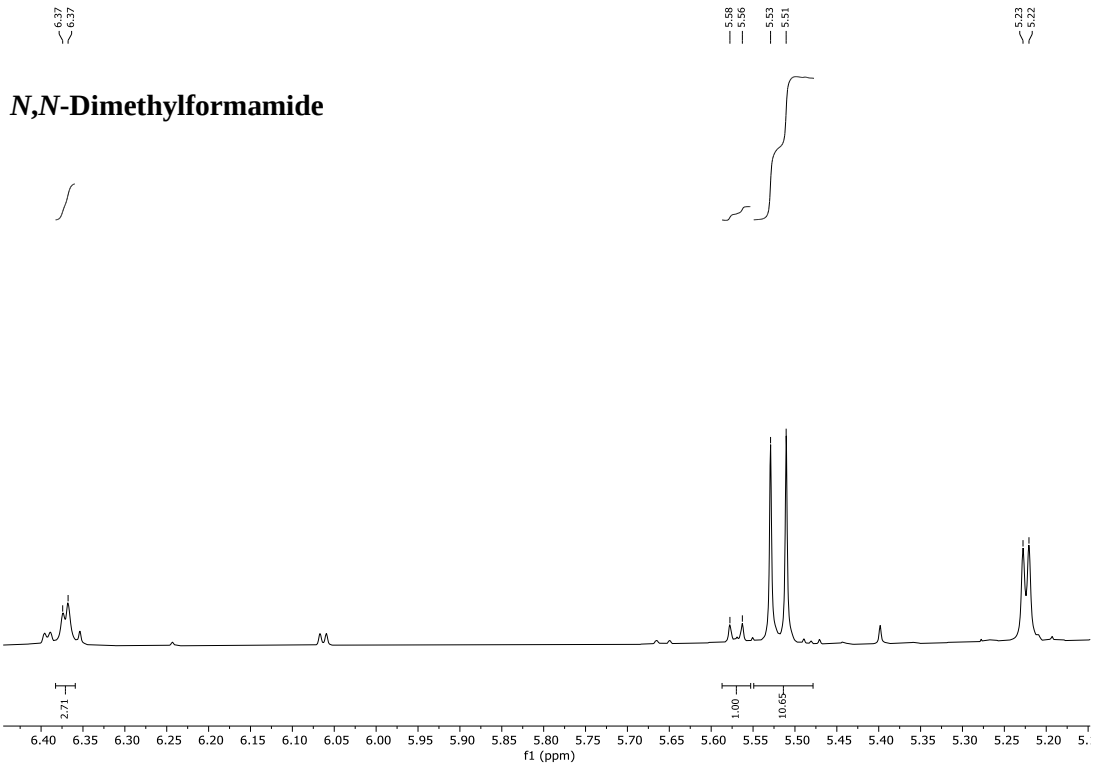
1,1-Dichloroethane



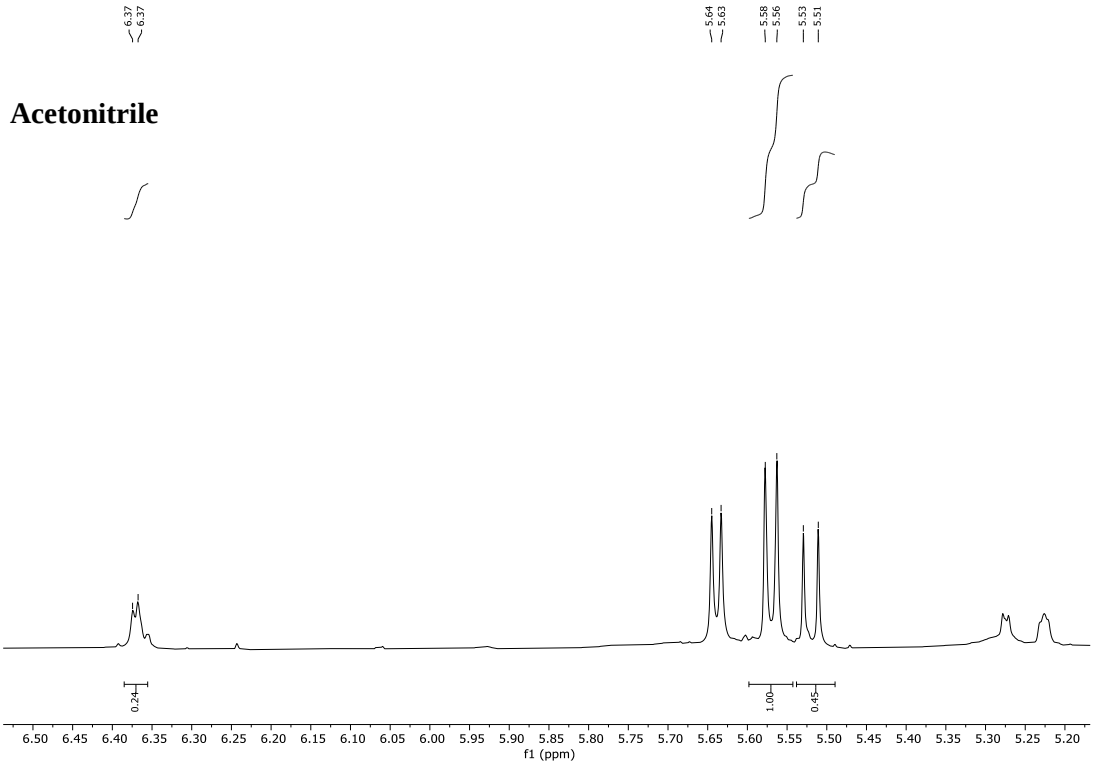
Tetrahydrofuran



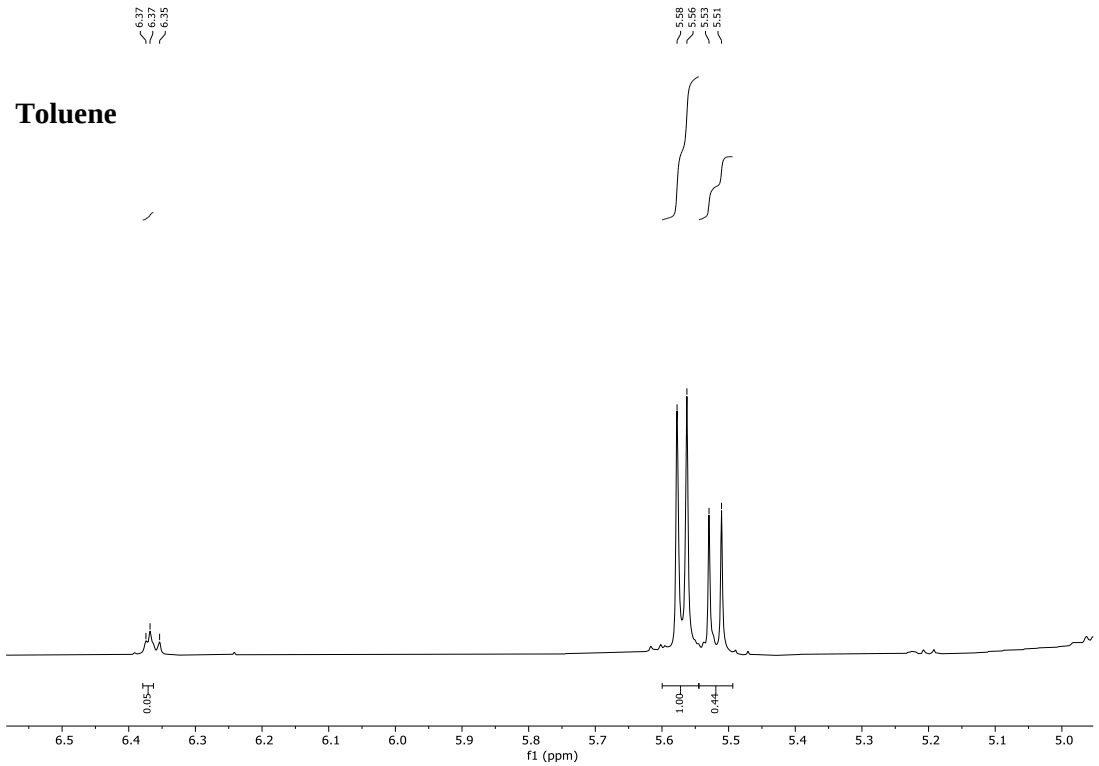
***N*,*N*-Dimethylformamide**



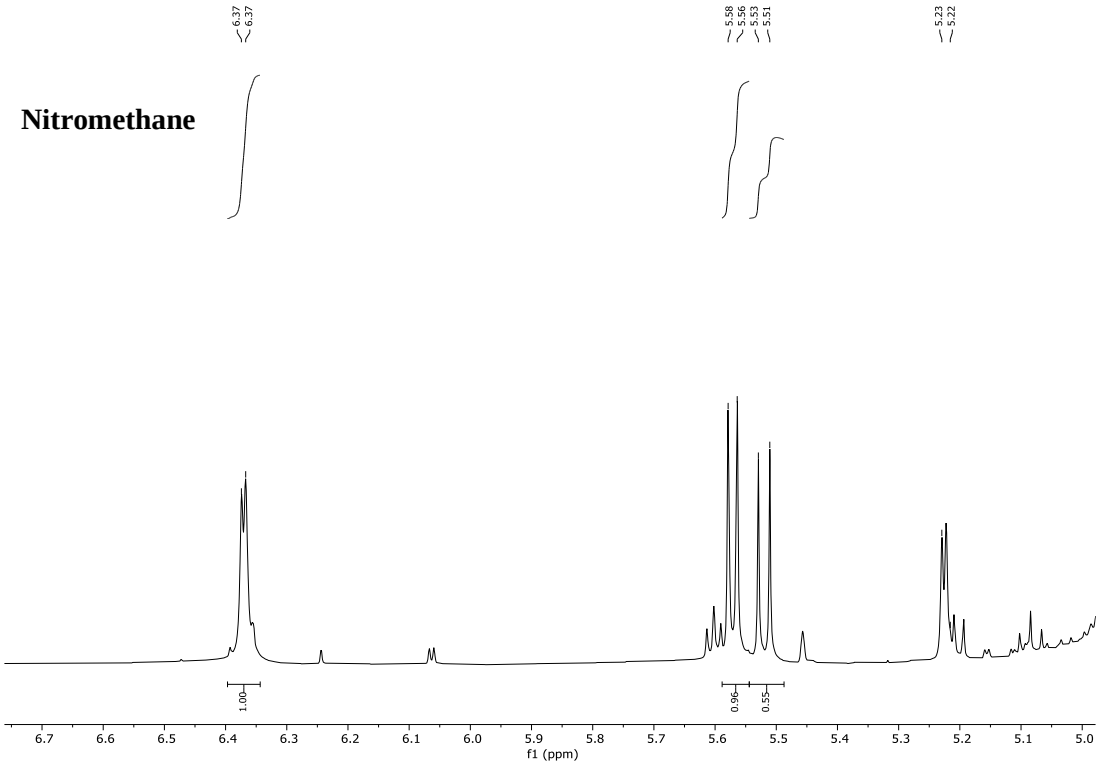
Acetonitrile



Toluene

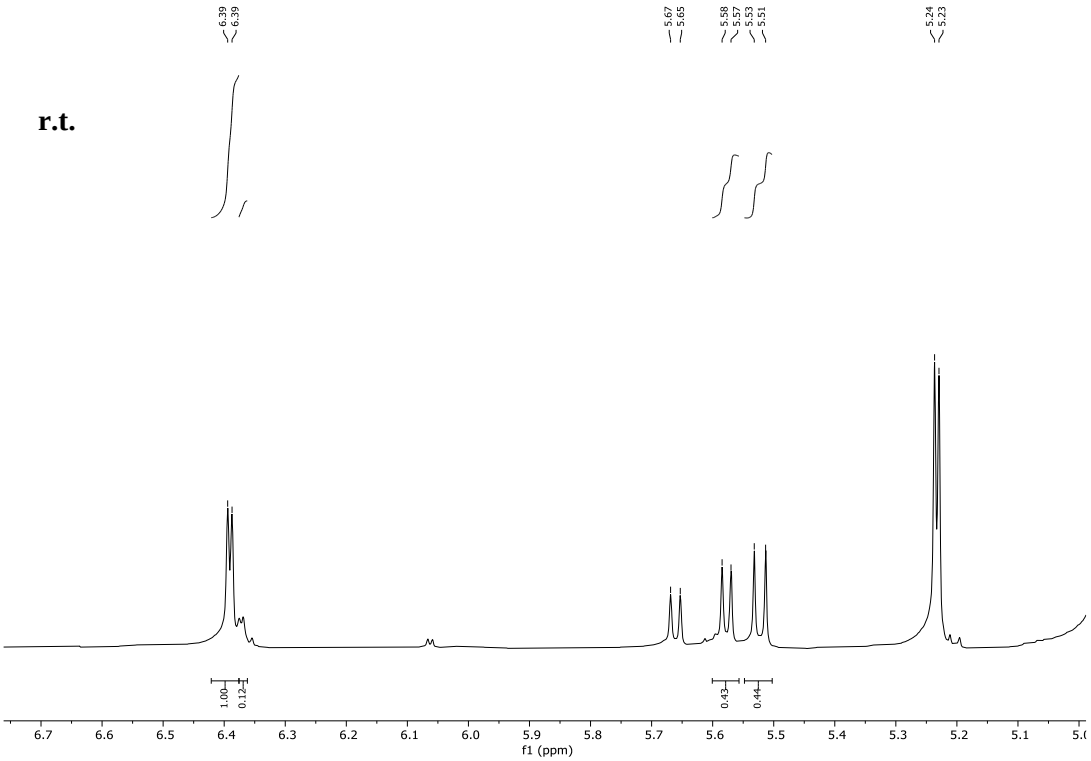


Nitromethane

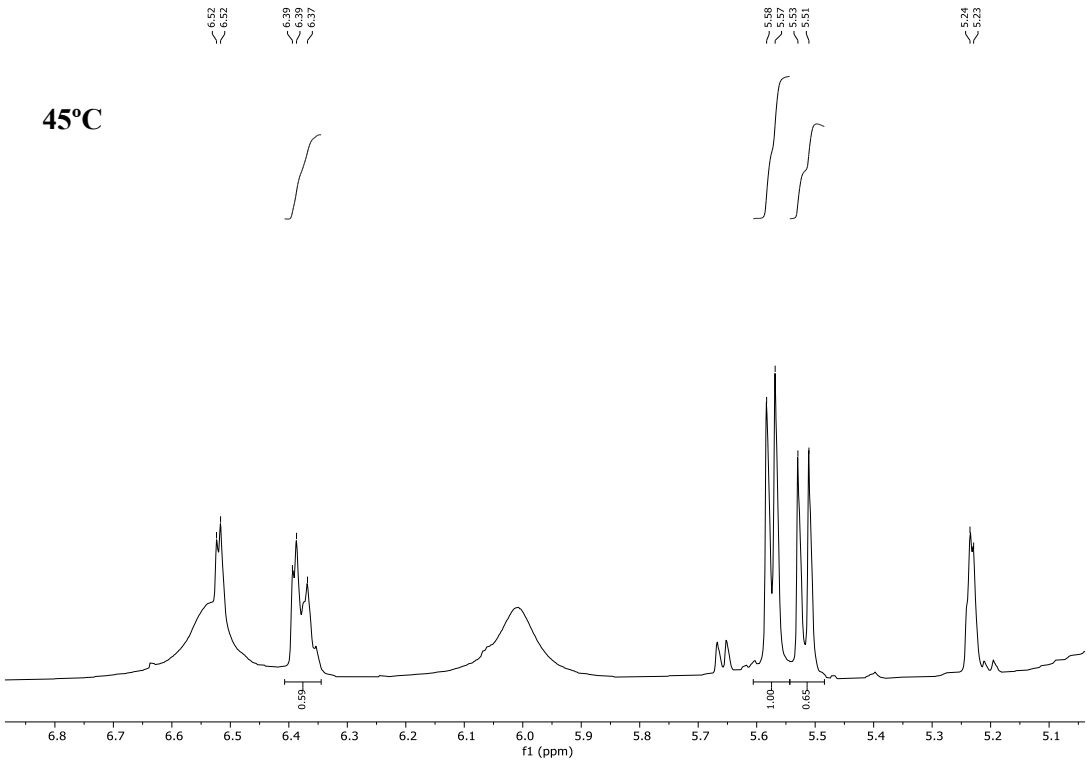


3.4.8. Appendix of Temperature Screening

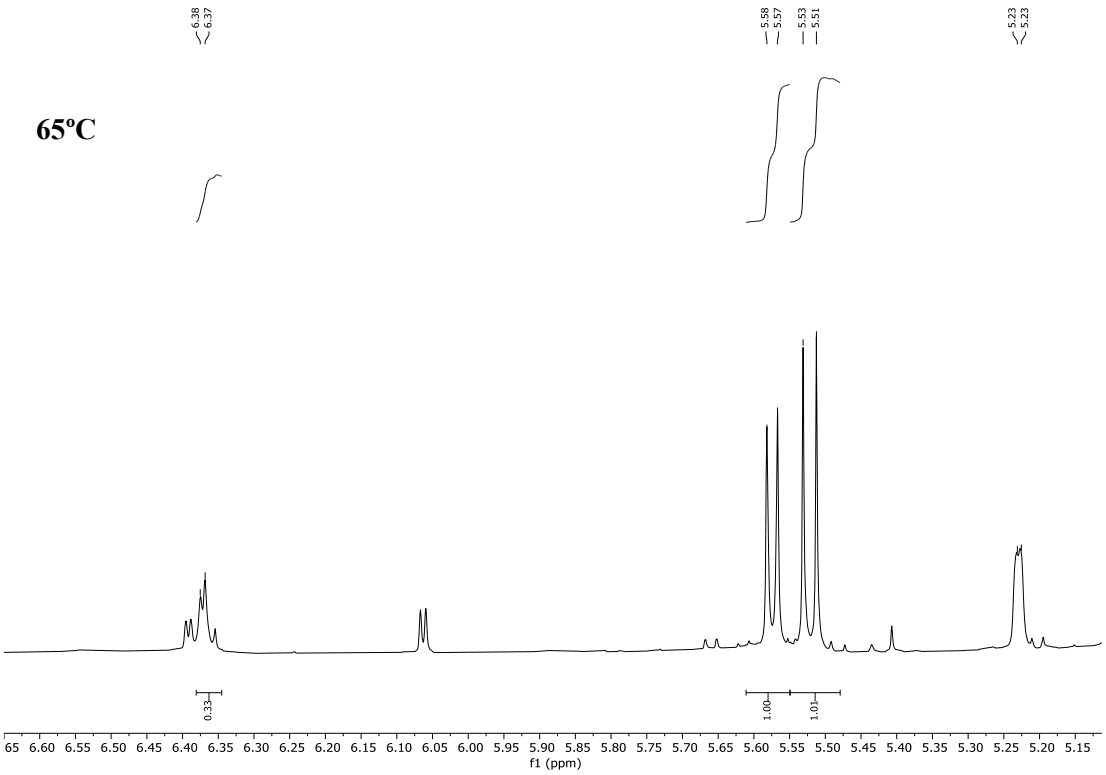
r.t.



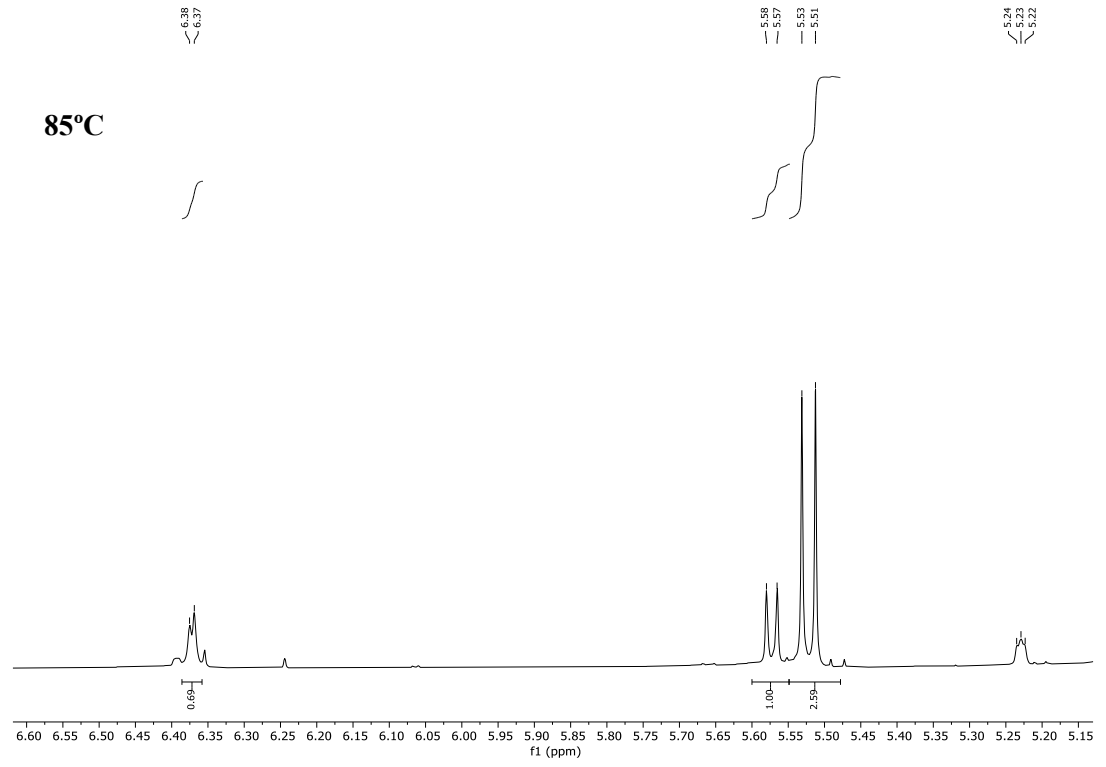
45ºC



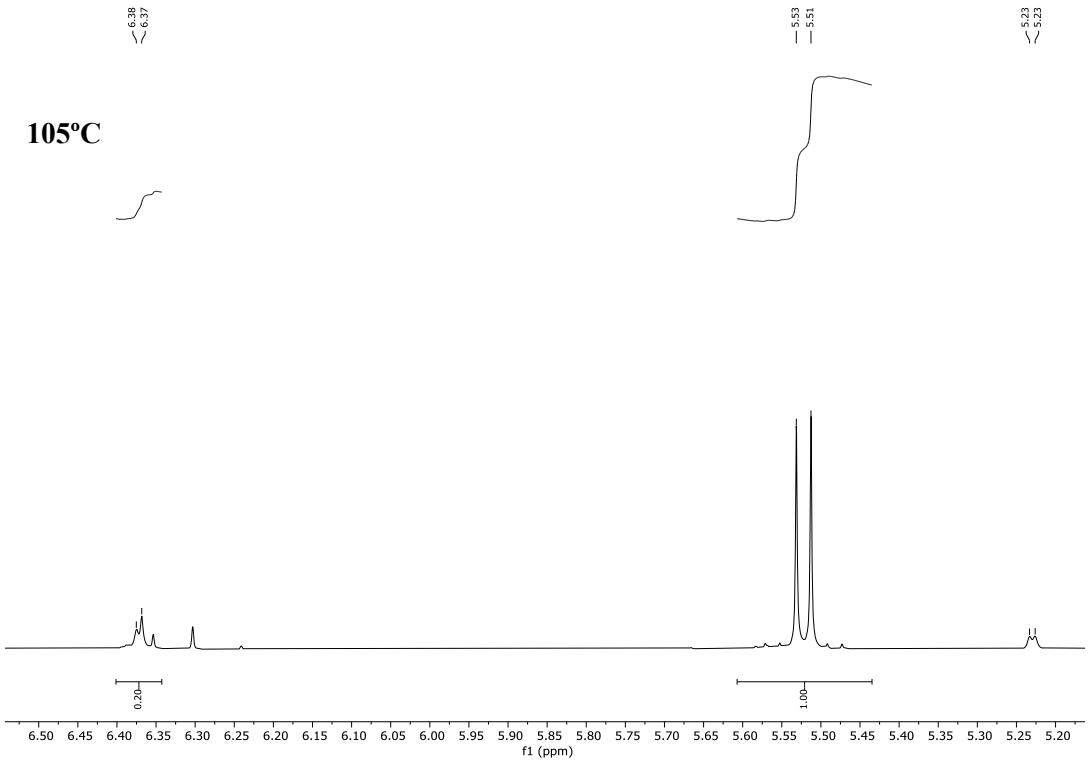
65ºC


6.38
6.37
5.58
5.57
5.53
5.51
5.23
5.23
0.33
1.00
1.01
65 6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 5.25 5.20 5.15
f1 (ppm)

85ºC

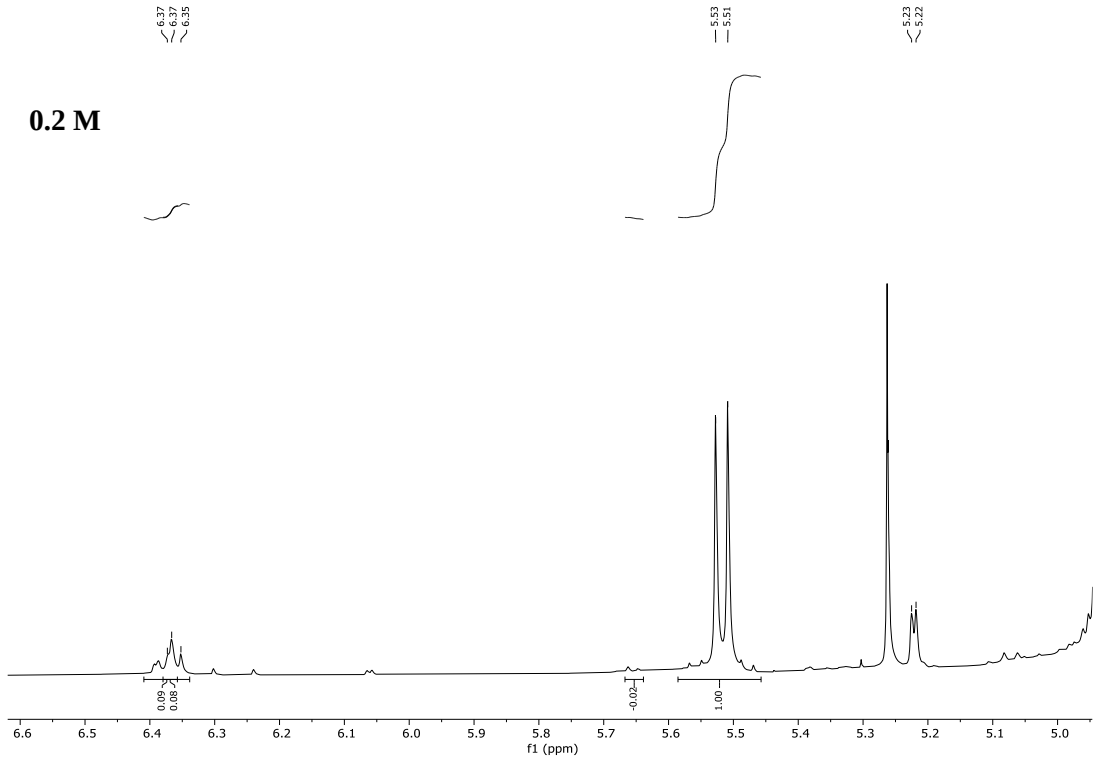

6.38
6.37
5.58
5.57
5.53
5.51
5.24
5.23
5.22
0.69
1.00
2.59
6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 5.25 5.20 5.15
f1 (ppm)

105°C

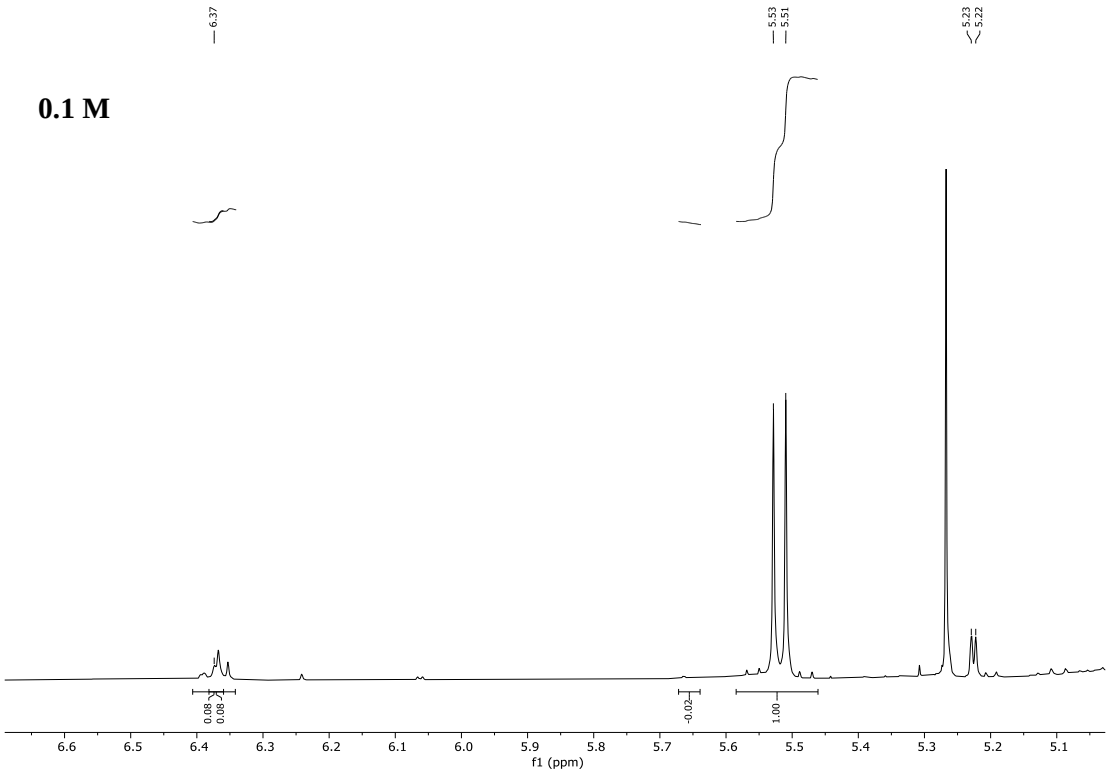

6.38
6.37
5.53
5.51
5.23
5.23
0.20
1.00
6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 5.25 5.20
f1 (ppm)

3.4.9. Appendix of Concentration Screening

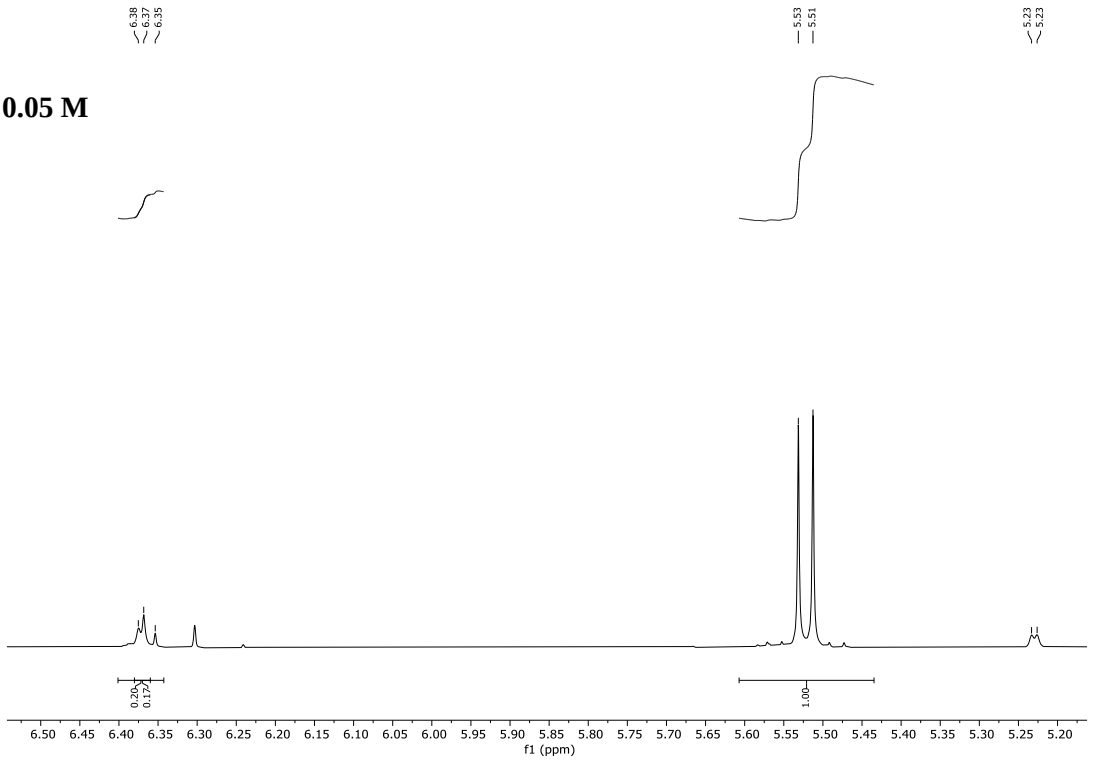
0.2 M



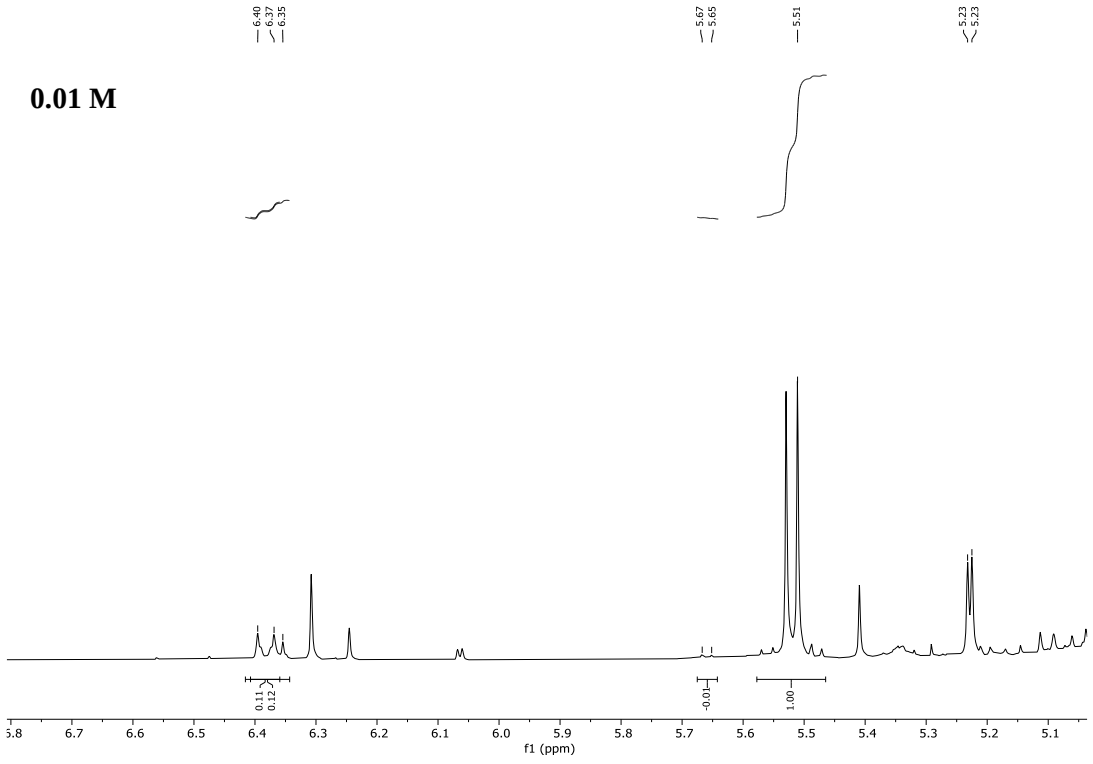
0.1 M



0.05 M


6.38
6.37
6.35
5.53
5.51
5.23
5.23
0.20
0.17
1.00
6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 5.25 5.20
f1 (ppm)

0.01 M


6.40
6.37
6.35
5.67
5.65
5.51
5.23
5.23
0.11
0.12
-0.01
1.00
5.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1
f1 (ppm)

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