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1,2-cis-Glycosyations:
Method Development and Synthesis of Complex Oligosaccharides

Bas Hagen
1,2-CIS-GLYCOSYLATIONS:
METHOD DEVELOPMENT AND SYNTHESIS OF COMPLEX
OLIGOSACCHARIDES

PROEFSCHRIFT

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C. J. J. M. Stolker
volgens besluit van het College voor Promoties
te verdedigen op 12 december 2016
klokke 13:45

door

Bas Hagen

geboren te Leiden in 1988
Promotiecommissie

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Dr. M. T. C. Walvoort (Rijksuniversiteit Groningen)
‘la maladie principale de l’homme est la curiosité inquiète des choses qu’il ne peut savoir’

Blaise Pascal
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<tr>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Alloc</td>
<td>Allyloxy carbonyl</td>
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<td>APT</td>
<td>Attached Proton Test</td>
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<td>aq</td>
<td>Aqueous</td>
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<td>Contact Ion Pair</td>
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<tr>
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<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
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<tr>
<td>CPS</td>
<td>Capsular Polysaccharide</td>
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<td>Cq</td>
<td>Quaternary carbon</td>
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<td>Camphorsulfonic acid</td>
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<td>dr</td>
<td>Diastereoisomeric ratio</td>
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<td>H</td>
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<td>HFIP</td>
<td>1,1,1,3,3,3-Hexafluoro-iso-propanol</td>
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<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
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<td>HSQC</td>
<td>Heteronuclear Single Quantum Coherence</td>
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<td>Infrared</td>
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<td>J</td>
<td>J-coupling</td>
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<tr>
<td>LC-MS</td>
<td>Liquid Chromatography-Mass Spectrometry</td>
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<tr>
<td>m</td>
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<td>N-Iodosuccinimide</td>
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<tr>
<td>Nu</td>
<td>Nucleophile</td>
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<td>p</td>
<td>Para</td>
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<td>PE</td>
<td>Petroleum ether</td>
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<tr>
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<tr>
<td>quant</td>
<td>Quantitative</td>
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<tr>
<td>rT</td>
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<tr>
<td>SSIP</td>
<td>Solvent-Separated Ion Pair</td>
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<tr>
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<tr>
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<td>Trifluoromethylsulfonyl</td>
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<td>Tetrahydrofuran</td>
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<td>2,4,6-Tri-tert-butylpyrimidine</td>
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<td>UV</td>
<td>Ultraviolet</td>
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<td>v</td>
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Chapter 1

General introduction

Carbohydrates represent one of the major three classes of biopolymers, and fulfill a plethora of functions, including energy storage, structural integrity, and signaling. The field of glycobiology has been expanding rapidly in the past few decades, as more and more scientists realize the profound and intricate relation between carbohydrates and many biological processes.
Carbohydrates play a significant role in immunity. Many bacteria and other pathogens possess unique and complicated polysaccharides on their cell surface. Since their structures are often completely different from human glycan structures, these polysaccharides are interesting as potential components for glycoconjugate vaccines. Several glycoconjugate vaccines already exist, aimed at pathogens causing influenza, streptococcal infections and typhoid fever. The carbohydrate portions of these vaccines are isolated from the pathogen by biotechnological methods, which, while effective, yield a complex mixture of polysaccharides, differing in composition, length and structure. In order to study the role of bacterial carbohydrates at a molecular level and to acquire structure-activity relationships, it is desirable to have access to well-defined and pure carbohydrates. Synthetic organic chemistry is able to provide these structures.

The field of synthetic carbohydrate chemistry, despite having made tremendous advances in the past few decades, still faces several obstacles. Perhaps the most significant of these problems is that of glycosidic bond formation, or glycosylation, whose exact mechanism remains poorly understood in many cases.

**The glycosylation reaction**

In a glycosylation reaction (Scheme 1), a donor (bearing a latent leaving group at its anomeric center) and an acceptor (generally another carbohydrate) react under the agency of a promoter (catalytic or stoichiometric). The latter activates the donor's leaving group, generating one or more reactive intermediates. Subsequent nucleophilic attack on the anomeric center then yields a new glycosidic bond. This creates a new stereocenter at the anomeric position, and controlling the stereoselective outcome of a glycosylation is arguably the greatest challenge in synthetic carbohydrate chemistry.

**Scheme 1**: General overview of a glycosylation reaction.

The outcome of a glycosylation depends on many factors, including but not limited to: activation conditions, solvent(s), reaction temperature, concentration of the reactants, and reactivity of both donor and acceptor. Owing to the fact that carbohydrates are often branched
and can be elongated on theoretically any hydroxyl group, both glycosyl donors and -acceptors often require elaborate protecting group manipulations. The protecting group pattern on a given carbohydrate donor significantly influences its reactivity, and this fact has been recognized for decades.\textsuperscript{16–18} The reactivity of the acceptor, however, is often disregarded and, in comparison to donor reactivity studies, the number of literature examples that examine the influence of acceptor reactivity, in a systematic matter, on glycosylations is scarce.\textsuperscript{19–21}

**Outline of this Thesis**

This thesis aims to investigate the glycosylation properties in terms of reactivity and stereoselectivity of a selection of carbohydrate donors, in the context of the synthesis of pathogen-related oligosaccharides. Chapter 2 gives an overview of studies aimed at the nature of glycosyl oxocarbenium ions and their intermediacy in glycosylation reactions. The role of these intermediates will be illustrated by examples from literature regarding oligosaccharide synthesis.

Chapter 3 presents an investigation on the glycosylating properties of 2-azidofucosyl (FucN\textsubscript{3}) donors in glycosylation reactions with selected acceptors, due to the presence of \(N\)-acetylfucosamine (FucNAc) moieties in bacterial oligosaccharides. Several factors, including the type and position of the applied protecting groups in the FucN\textsubscript{3} donor and the nature of the acceptor, will be considered to give a detailed picture of the relation between the stereochemical outcome of 2-azidofucosylations and the reactivities of both donor and acceptor. Building on the results of Chapter 3, the synthesis of the *Staphylococcus aureus* type 5 Capsular Polysaccharide repeating unit is accomplished as described in Chapter 4. This complex polysaccharide is a major virulence factor in *S. aureus* infections and is therefore an interesting component in future glycoconjugate vaccines.

Chapter 5 describes an investigation of the glycosylating properties of of differently protected 2-azidoalacturonic acid (GalN\textsubscript{3}A) donors. Special attention is directed to 3,6-lactone derivatives of GalN\textsubscript{3}A, as conformational restriction of carbohydrates has been shown to be a powerful strategy in introducing challenging glycosidic linkages. Because the glycosylations of the GalN\textsubscript{3}A donors studied did not provide the desired \(\alpha\)-glycosidic linkages with sufficient selectivity, Chapter 6 investigates the use of a non-oxidized 2-azidogalactosyl (GalN\textsubscript{3}) donor for the synthesis of the repeating unit of the *S. aureus* Strain M Capsular Polysaccharide. This polysaccharide, consisting of \(N\)-acetylgalactosaminuronic acid (GalNAcA) and FucNAc units, is a virulence factor associated with increased mortality in mouse models. Chapter 7 details the synthesis of glycan fragments related to the trematode *Schistosoma mansoni*, a major pathogen causing the
debilitating parasitic disease schistosomiasis, which has been classified a neglected tropical disease.

References
Chapter 2

Additions to oxocarbenium ions*

Introduction

Tremendous progress has been made in the construction of oligosaccharides and many impressive examples of large and complex oligosaccharide total syntheses have appeared over the years.1-3 At the same time the exact mechanism underlying the union of two carbohydrate building blocks often remains obscure and optimization of a glycosylation reaction can be a time- and labor intensive process.4,5 This can be explained by the many variables that affect the outcome of a glycosylation reaction: the nature of both the donor and acceptor building blocks, solvent,

activator and activation protocol, temperature, concentration, and even the presence and type of molecular sieves.

The large structural variety of carbohydrates leads to building blocks that differ significantly in reactivity, both with respect to the nucleophilicity of the acceptor molecule and the reactivity of the donor species. The reactivity of a donor is generally related to the capacity of the donor to accommodate developing positive charge at the anomic center, upon expulsion of the anomeric leaving group. This also determines the amount of carbocation character in the transition state leading to the products. Most glycosylation reactions will feature characteristics of both $S_N1$ and $S_N2$ type pathways in the transition states leading to the products. It is now commonly accepted that the exact mechanism through which a glycosidic linkage is formed can be found somewhere in the continuum of reaction mechanisms that spans from a completely dissociative $S_N1$ mechanism on one side to an associative $S_N2$ pathway on the other side (Figure 1).6–8 On the $S_N1$-side of the spectrum, glycosyl oxocarbenium ions are found as product forming intermediates. On this outer limit of the reaction pathway continuum, the oxocarbenium ions will be separated from their counterions by solvent molecules (solvent separated ion pairs, SSIPs) and there will be no influence of the counterion on the selectivity of the reaction. Moving towards the $S_N2$ side of the spectrum contact (or close) ion pairs (CIPs) are encountered, and in reactions of these species the counterion will have a role to play. Because glycosylation reactions generally occur in apolar solvents (dichloromethane is by far the most used one) ionic intermediates have very limited lifetimes and activated donor species will primarily be present as a pool of covalent intermediates. The stability, lifetime and reactivity of an oxocarbenium ion depends - besides the nature of the counterion - on the nature and orientation of the functional groups present on the carbohydrate ring. This chapter explores the role of oxocarbenium ions (and contact ion pairs, featuring a glycosyl cation) in chemical glycosylation reactions. Where it was previously often assumed that glycosylations, proceeding via an oxocarbenium ion intermediate, show poor stereoselectivity, it is now clear that oxocarbenium ions can be at the basis of stereoselective glycosylation events. The first part of this Chapter will deal with the stability, reactivity and conformational behavior of glycosyl oxocarbenium ions, where the second part will describe their intermediacy in the assembly of (complex) oligosaccharides.

**Stability, reactivity and conformational behavior of glycosyl oxocarbenium ions**

Amyes and Jencks have argued that glycosyl oxocarbenium ions have a short but significant lifetime in aqueous solution.9 They further argued that in the presence of properly positioned counterions (such as those derived of expulsion of an aglycon), close ion pairs will
rapidly collapse back to provide the covalent species and that the ‘first stable intermediate for a significant fraction of the reaction’ should be the solvent separated oxocarbenium ion.

**Figure 1:** Continuum of intermediates to explain the stereochemical course of glycosylation reactions.

By extrapolation of these observations to apolar organic solvents Sinnott reached the conclusion that intimate ion pairs have no real existence in an apolar environment, such as used for glycosylation reactions.¹⁰ Hosoya et al. have studied contact ion pairs by quantum mechanical calculations in dichloromethane as a solvent.¹¹ In these calculations they have included four solvent molecules to accurately mimic the real life situation. In many of the studied cases, contact ion pairs turned out to be less stable than the corresponding solvent separated ions, as will be described below.¹² Yoshida and co-workers have described that activation of thioglucoside 1 with a sulfonium salt activator, featuring the bulky non-nucleophilic tetrakis(pentafluorophenyl) borate counterion, in a continuous flow microreactor, provides a reactive species (2) that has a lifetime in the order of a second (Scheme 1).¹³ They argued that this species was a glucosyl oxocarbenium ion, ‘somewhat stabilized’ by the disulfide generated from the donor aglycon and the activator.
The stability of a glycosyl oxocarbenium ion is largely influenced by the substituents on the carbohydrate ring. The electron-negative substituents (primarily oxygen, but also nitrogen based) have an overall destabilizing effect on the carbocation, and the destabilizing effect can be further enhanced by the presence of electron withdrawing protecting groups, such as acyl functions. The exact position of the substituent on the ring and its orientation influence the stability of the anomeric cation. The combined influence of all substituents on the ring determine the reactivity of a glycosyl donor and the extensive relative reactivity value (RRV) charts, drawn up by the groups of Ley and Wong for a large panel of thioglycosides clearly illustrate these functional group effects.\textsuperscript{14–17} From these RRV-tables it is clear that the donor reactivity spectrum spans at least eight orders of magnitude. To investigate the influence of the carbohydrate ring substituents on the stereochemical outcome of a glycosylation reaction, Woerpel and co-workers have systematically studied C-glycosylation reactions of a set of furanosides and pyranosides, featuring a limited amount of ring substituents.\textsuperscript{18–21} Their studies in the furanose series are summarized in Scheme 2A.\textsuperscript{18,20} As can be seen, the alkoxy groups at C-2 and C-3 have a strong influence on the stereochemical outcome of the reaction, where the alkoxy group at C-5 appears to have less effect on the reaction. The presence of an alkoxy or alkyl group at C-3 leads to the formation of the allylglycosides 11 and 12 with opposite stereoselectivity. Woerpel and co-workers have devised a model to account for these stereodirecting substituent effects that takes into account the equilibrium between two possible envelope oxocarbenium ion conformers (13 and 14, Scheme 2B).\textsuperscript{20} Attack on these oxocarbenium ion conformers by the nucleophile occurs from the ‘inside’ of the envelopes, because this trajectory avoids unfavorable eclipsing interactions with the substituent at C-2 and it leads, upon rehybridization of the anomeric carbon to a fully staggered product (15 and 16), where attack on the ‘outside’ would provide the furanose ring with a eclipsed C-1-C-2 constellation. The spatial orientation of the alkoxy groups influences the stability of the oxocarbenium ions. An alkoxy group at C-3 can provide some stabilization of the carbocation when it takes up a \textit{pseudo}-axial position. Stabilization of the oxocarbenium ion featuring a C-2-alkoxy group is best achieved by placing the electronegative substituent in a \textit{pseudo}-equatorial position to allow for the hyperconjugative stabilization by the properly oriented C-2-H-2 bond. Alkyl substituents at C-3 prefer to adopt a \textit{pseudo}-equatorial position.
because of steric reasons. With these spatial substituent preferences, the stereochemical outcome of the C-allylation reactions in Scheme 2 can be explained. Activation of the C-3-benzyloxy furanosyl acetate with SnBr₄ can provide an oxocarbenium ion intermediate that preferentially adopts an E₃ conformation, as in 14. Nucleophilic attack on this conformer takes place from the diastereotopic face that leads to the 1,3-cis product. In a similar vein, inside nucleophilic attack on the C-2-benzyloxy furanosyl oxocarbenium ion E₃ conformer, derived from furanosyl acetate 4, accounts for the stereochemical outcome of the C-allylation leading to product 9.

Scheme 2: A) Diastereoselective C-allylations of furanosyl acetates. B) 'Inside' attack model.

To accurately gauge the combined effect of multiple substituents on a furanosyl ring, van Rijssel et al.²⁴,²⁵ used a quantum mechanical calculation method, originally developed by Rhoad and co-workers²⁶, to map the energy of furanosyl oxocarbenium ions related to the complete conformational space they can occupy. Energy maps for all four possible diastereoisomeric, fully decorated furanosyl oxocarbenium ions were generated revealing the lowest energy conformers for the ribo-, arabinо-, xylo- and lyxo-configured furanosyl oxocarbenium ions 17-21 (Scheme 3). It became apparent that the orientation of the C-5-substituent, having a gg, gt or tg relation to the substituents at C-4, was of profound influence on the stability of the oxocarbenium ions and differences up to 4 kcal/mol were observed for structures only differing in their C-4-C-5 rotation. These stereoelectronic effects have also been described in the pyranose series, where a C-4-C-6 acetal can restrict the C-6-oxygen in a tg position, for manno- and gluco-configured systems, or in
Chapter 2

a \( gg \) position for \textit{galacto}-configured constellations.\textsuperscript{27–29} The \( tg \) orientation represents the most destabilizing orientation because in this situation the O6 atom is furthest away from the electron depleted anomic center, not allowing for any electron density donation for stabilization. With the lowest energy furanosyl oxocarbenium ion conformers found by the free energy surface (FES) mapping method, the stereochemical outcome of reduction reactions at the anomic center of the four diastereoisomeric furanosyl acetates \textsuperscript{22–25} could be explained (Scheme 3). Interestingly, all four furanosides reacted in a 1,2-\textit{cis} selective fashion with the incoming nucleophile (tri-ethylsilane-\( d \)). Only xylofuranosyl acetate \textsuperscript{24} provided some of the 1,2-\textit{trans} addition product, which could be related to the stability of the \textsuperscript{3}E, \textit{gt}oxocarbenium ion intermediate \textsuperscript{20}.

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{scheme3.png}
\end{center}
\end{figure}

\textbf{Scheme 3:} Free energy surface maps of fully decorated furanosyl oxocarbenium ions and diastereoselective reductions of furanosyl acetates.

The stereoelectronic substituent effects found in the furanose series are paralleled in the pyranose system, where the following substituent effects have been delineated: The stability of pyranosyl oxocarbenium ions benefits from an equatorial orientation of the C-2-alkoxy groups (allowing for hyperconjugative stabilization by the \( \sigma_{C-2-H-2} \) bond) and an axial orientation of the C-
3 and C-4 alkoxy groups. The C-5-alkoxymethylene group has a slight preference for an equatorial position because of steric reasons. These substituent preferences have been used to explain the stereochemical outcome of a series of C-allylations, using a two-conformer model. Woerpel and co-workers reasoned that six-membered oxocarbenium ions preferentially adopt a half-chair structure to accommodate the flat [C-1=O-5]+ oxocarbenium ion moiety (Scheme 4A). These half-chair intermediates are attacked by incoming nucleophiles following a trajectory that leads to a chair-like transition state. Thus, attack of a 3H4 half chair 30 preferentially occurs form the β-face (in the case of a D-pyranoside), where attack on the opposite half chair 31 (the 4H3) leads to the α-product. With the above described spatial substituent preferences and mode of nucleophilic attack the stereoselectivities in the C-allylation reactions shown in Scheme 4B can be accounted for: the C-4-OBn is trans-directing, where the C-3 and C-2-O-Bn promote the formation of the cis-product. In the lyxopyranosyl oxocarbenium ion, these three substituent preferences can be united, and the allylation of 2,3,4-tri-O-benzyl lyxopyranosyl acetate 35 proceeds in a highly stereoselective manner to provide the 1,2-cis product 40.

Scheme 4: A) Two conformer model to explain the stereoselectivity in pyranosyl C-allylations. B) Observed diastereoselectivity in reactions of (partially) substituted pyranosyl acetates (major products are shown).

When a C-5 benzyloxymethyl group is added to this system, as in a mannosyl cation, it can be reasoned that the 3H4 oxocarbenium ion is more stable than its 4H3 counterpart (See Scheme 5): the C-2, C-3 and C-4 groups are all positioned properly to provide maximal stabilization of the
electron depleted anomeric center and only the C-5 substituent, in itself not a powerful
stereodirecting group, is not positioned favorably. However, the axial orientation of this
group does lead to a significant 1,3-di-axial interaction with the axially positioned C-3-alkoxy group. The
allylation of mannose proceeds with α-selectivity, indicating that nucleophilic attack on the β-face
of the \( {^3}H_4 \) oxocarbenium is not a favorable reaction pathway. To account for this stereochemical
outcome, Woerpel and co-workers have suggested a Curtin-Hammett kinetic scenario, in which
the two half chairs 42 and 43 are in rapid equilibrium. Attack on the \( {^3}H_4 \) conformer suffers from
unfavorable steric interactions between the incoming nucleophile and the substituents at C-3 and
C-5, in addition to the destabilizing C-3-C-5 interaction, already present in the system. Attack on
the α-face of the \( {^4}H_3 \) oxocarbenium ion on the other hand is devoid of these unfavorable steric
interactions, making this transition state overall more favorable.

**Scheme 5**: The \( {^3}H_4 \) and \( {^4}H_3 \) mannosyl oxocarbenium ions and the trajectories of incoming nucleophiles.

With strong nucleophiles, the two-conformer oxocarbenium ion model falls short and \( S_N2 \)-
type pathways come into play. In a continuation of their efforts to understand the
stereoselectivities of C-glycosylation reactions of (partially) substituted pyranosyl donors, the
Woerpel laboratory studied the addition reactions of a series of C-nucleophiles, ranging from
weak nucleophiles (such as allyl trimethylsilane) to relatively strong nucleophiles (such as silyl
ketene acetics). Table 1 tabularizes the stereoechemical outcome of the reactions of 2-deoxy
glucopyranosyl acetate donor 44 with these nucleophiles under the agency of TMSOTf as a Lewis
acid catalyst, together with their relative nucleophilicity, as established by Mayr and co-
workers. The α-selectivity in the reaction with allyl trimethylsilane can be accounted for by
invoking the \( {^4}H_3 \) oxocarbenium ion (55, Scheme 6A) as most likely product forming intermediate.
Nucleophilic attack on the alternative \( {^3}H_4 \) half chair 54 again suffers from prohibitively large steric
interactions to be a reasonable pathway. With reactive nucleophiles, such as silyl ketene acetics
48 and 49 (Table 1, entries 4 and 5), the most likely product-forming pathway proceeds with
significant \( S_N2 \)-character taking place on the α-triflate intermediate 56 (Scheme 6B). Of note, no
attempts to characterize this triflate were undertaken.
Computational studies

To better understand the conformational behavior, reactivity and stability of glycosyl oxocarbenium ions, several quantum mechanical studies have been undertaken (See Table 2).\textsuperscript{34–38,11,12} Whitfield and co-workers have reported many computational studies in which they investigated the conformational behavior of, among others, tetra-\textit{O}-methyl gluco- and manno.pyranosyl triflates as well as their 4,6-\textit{O}-benzylidene congeners upon ionization (that is, expulsion of the triflate leaving group) and the conformational behavior of the resulting oxocarbenium ions.\textsuperscript{35} To prevent collapse of the initially formed ion pair, they used lithium cations to stabilize the departing anionic leaving group. These calculations revealed that ionization of the tetra-\textit{O}-methyl gluco- and manno.pyranosyl \textit{\alpha}-triflates initially provide \textit{\textit{4}H}_3 (58 and 60, respectively) or closely related \textit{\textit{4}E}-like oxocarbenium ions 59 (See Stoddart’s hemisphere representation\textsuperscript{39} for pseudo-rotational itineraries in Figure 2A).

Table 1: Changing diastereoselectivity in the addition of \textit{C}-nucleophiles of increasing reactivity.

\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
entry & nucleophile & \textit{N}\textsubscript{e} & Product & yield (\alpha/\beta) \\
\hline
1 & MeO & 1.8 & 45 & 57\% (89:11) \\
2 & MeO & 4.4 & 46 & 73\% (50:50) \\
3 & TMS & 6.2 & 47 & 94\% (68:32) \\
4 & TMS & 8.2 & 48 & 78\% (27:73) \\
5 & TMS & 9.0 & 49 & 68\% (19:81) \\
\hline
\end{tabular}
\end{center}

Expulsion of the anomeric triflate from the \(\beta\)-isomers requires a conformational change, where the glucose and mannose pyranosyl rings distort to a \(\text{^1S}_2\)-like structure.\textsuperscript{35} In this constellation, the anomeric leaving group can be expelled by assistance of one of the ring oxygen lone pairs leading to a \(\textit{\textit{4}E}\) (for the glucose) or \(\textit{\textit{4}H}_3\) half chair (for the mannose) oxocarbenium ion.
Chapter 2

The stability of these ions is primarily governed by steric interactions, since they lack the electronic stabilization described above. Interestingly, similar itineraries have been established to be operational in glycosyl hydrolases. Rovira and co-workers have determined that the hydrolysis of β-glucosides by retaining glucosyl hydrolases, belonging to the GH-5, GH7 and GH-16 families, proceeds via a trajectory, in which the substrate is first placed in a conformation that allows expulsion of the aglycon (Figure 2B). Then, passing through 4H3 transition state 80, which is close in conformational space to the starting 1S3 geometry 79, the 4C1 product 81 (the covalent enzyme-glucose adduct) is obtained.

Scheme 6: Reactive intermediates in Sₘ₁ (A) and Sₘ₂-type (B) pathways.

This catalytic itinerary was visualized using a combination of X-ray crystallography, free energy landscape mapping (to determine the intrinsically favorable ground state conformations) and QM/MM reaction simulations. Further calculations of the Whitfield group showed that the 4,6-Ω-benzylidene glucose oxocarbenium ions preferentially takes up a 4E conformation 61, where the corresponding benzylidene-mannose structure is most stable taking up a B₂⁺E geometry (62). In the latter structure, both the through-space electron donation by the C-3-O-Me ether and hyperconjugative stabilization of the σC-2,11-2 bond contributes to the stability of the ion. Recently, Hosoya and co-workers described a method that takes into account explicit solvent molecules in the determination of the stability of contact ion pairs and solvent separated oxocarbenium ions. They first optimized the amount of solvent molecules required to get a reliable outcome while maintaining acceptable calculation costs, eventually using four dichloromethane molecules as an optimum. Using these solvent molecules, they were able to find lowest energy contact ion pairs and solvent separated ion pairs. Stabilization of the developing charge was effected by the proper positioning of the solvent molecules: the hydrogen atoms of the
dichloromethane molecules were capable of stabilizing the negative charge at the triflate leaving group, while the electron density around the chloride atoms of the dichloromethane molecules could be used to support the positive charge at the oxocarbenium ion. It was described that the stability of tetra-O-methyl glucopyranosyl oxocarbenium ions having a triflate associated at either the α- or β- face were quite similar in energy. The lowest energy oxocarbenium ion having the counterion associated on its α-face was found in a 2H3/E3 conformation (63/64) at +9.5 kcal/mol with respect to the lowest energy α-triflate. The β-CIP 65 took up a 4H3 structure at +10.6 kcal/mol. Interestingly, solvent separated ion pairs were found that are lower in energy than the CIPs. A 2H3/5S0 SSIP 71 was found to be the most stable, at +8.5 kcal/mol, where 4H3 ion 72 was found at +10.6 kcal/mol. For tetra-O-methyl mannose an α-CIP, with a 5S2/3H2 structure (66/67) was determined to be the most stable ion pair. Although this oxocarbenium does not benefit from an optimal geometry of the C=O+ moiety, it can be stabilized by the σC-2-H-2 bond and by electron donation from the pseudo-axial substituents at C-3 and C-4. These authors studied the 4,6-O-formylidene gluco- and mannopyranosyl oxocarbenium ion pairs to account for stereoselectivities obtained with benzylidene glucose and mannose donors (vide infra). For the formylidene glucose system, the lowest energy CIP turned out to be the cation 68 with a 4E/4H3 structure with the anion associated on its β-face (+13.2 kcal/mol with respect to the lowest energy covalent α-triflate). The lowest energy SSIP was found in a 4E conformation (+10.9 kcal/mol), in line with the results of the Whitfield group. Also for the formylidene mannose ion pairs, the SSIPs were found to be more stable than the lowest energy CIPs. An B2,5 α-CIP (69) was found at +11.7 kcal/mol (with respect to the lowest energy α-triflate), where the lowest β-CIP 70 had a 5S2/B2,5 structure (+14.3 kcal/mol). The lowest energy SSIP also took up an 5S/B2,5 conformation (76/77) and was significantly more stable (+9.8 kcal/mol). The latter geometry corresponds to the structure found by Whitfield and co-workers.

 Hünenberger and co-workers have computationally studied ion pairs derived from tetra-O-methyl glucosyl triflate in different solvents. Through a series of molecular dynamics and quantum mechanical calculations they came to the hypothesis that different solvents affect the stability of pairs in a different manner. Their calculations suggest that in acetonitrile, the glucopyranosyl oxocarbenium ion preferentially takes up a B2,5 structure, with the counter ion associated on the α-face. In 1,4-dioxane, a 4H3 structure proved to be most stable with the triflate ion coordinating on the β-face. The authors suggested that their calculations could provide an adequate explanation of the generally observed β- and α-directing effect of the solvents (acetonitrile and 1,4-dioxane, respectively) studied.
Table 2: A selection of oxocarbenium ions and their calculated energies (determined by DFT calculations).

<table>
<thead>
<tr>
<th></th>
<th>Whitfield</th>
<th>Hosoya CIPs</th>
<th>Hosoya SSSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>tetra-O-Me Glc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58 ($E^1$)</td>
<td><img src="image" alt="Structure 58" /></td>
<td><img src="image" alt="Structure 63" /> $^1H_3$</td>
<td><img src="image" alt="Structure 71" /> $^1E_3$</td>
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<tr>
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<td><img src="image" alt="Structure 59" /></td>
<td><img src="image" alt="Structure 65" /> $^1H_3$</td>
<td><img src="image" alt="Structure 72" /> $^1E_3$</td>
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<tr>
<td>tetra-O-Me Man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 ($E^1$)</td>
<td><img src="image" alt="Structure 60" /></td>
<td><img src="image" alt="Structure 66" /> $^1H_2$</td>
<td><img src="image" alt="Structure 73" /> $^1E_3$</td>
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<tr>
<td>61 ($E^2$)</td>
<td><img src="image" alt="Structure 61" /></td>
<td><img src="image" alt="Structure 67" /> $^1E_2$</td>
<td><img src="image" alt="Structure 74" /> $^3E_3$</td>
</tr>
<tr>
<td>benzylidene-Glc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62 ($B_{2,3}$)</td>
<td><img src="image" alt="Structure 62" /></td>
<td><img src="image" alt="Structure 69" /> $^1B_{2,3}$</td>
<td><img src="image" alt="Structure 76" /> $^1B_{2,3}$</td>
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<tr>
<td>63 ($E^1$)</td>
<td><img src="image" alt="Structure 63" /></td>
<td><img src="image" alt="Structure 65" /> $^1H_3$</td>
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<tr>
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<td><img src="image" alt="Structure 65" /> $^1H_3$</td>
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<td><img src="image" alt="Structure 67" /> $^1E_2$</td>
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<tr>
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<td><img src="image" alt="Structure 67" /> $^1E_2$</td>
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<td><img src="image" alt="Structure 71" /> $^1E_3$</td>
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<td><img src="image" alt="Structure 72" /> $^1E_3$</td>
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<td><img src="image" alt="Structure 73" /> $^1E_3$</td>
<td><img src="image" alt="Structure 72" /> $^1E_3$</td>
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<tr>
<td>74 ($E^1$)</td>
<td><img src="image" alt="Structure 74" /></td>
<td><img src="image" alt="Structure 74" /> $^3E_3$</td>
<td><img src="image" alt="Structure 72" /> $^1E_3$</td>
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<tr>
<td>75 ($E^1$)</td>
<td><img src="image" alt="Structure 75" /></td>
<td><img src="image" alt="Structure 75" /> $^1E_3$</td>
<td><img src="image" alt="Structure 72" /> $^1E_3$</td>
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<tr>
<td>76 ($E^1$)</td>
<td><img src="image" alt="Structure 76" /></td>
<td><img src="image" alt="Structure 76" /> $^1B_{2,3}$</td>
<td><img src="image" alt="Structure 76" /> $^1B_{2,3}$</td>
</tr>
<tr>
<td>77 ($E^1$)</td>
<td><img src="image" alt="Structure 77" /></td>
<td><img src="image" alt="Structure 77" /> $^1B_{2,3}$</td>
<td><img src="image" alt="Structure 76" /> $^1B_{2,3}$</td>
</tr>
</tbody>
</table>

Because of the different computational approaches, care should be taken to compare the calculation methods described above. It is apparent, however, that similarities arise and that the minimum energy conformations determined with the different methods are close in conformational space. For tetra-O-benzyl (or methyl) glucose a structure close to the $^4H_3$ half chair appears from all calculations. Here, all ring substituents take up a sterically favorable equatorial position. Stabilization of the cation is only provided by hyperconjugation of the C-2-H-2 bond. For the corresponding mannosyl cation a similar structure arises, although the method described by Hosoya and co-workers indicates that cations having a rather different structure are also possible. The introduction of a cyclic ketal restricts the conformational freedom of the cations and the different methods collectively point to an $E_3$ envelope and $B_{2,3}$ boat structure as most stable oxocarbenium ions for the benzylidene (or formylidene) glucosyl and mannosyl cation respectively.
**Figure 2:** A) Stoddart’s hemisphere representation for conformational interconversions (only the Northern hemisphere is shown). B) Conformational itinerary of the substrate as used by various β-glucosidases. The trajectory has been highlighted in the Stoddart diagram in Figure 2A and was also calculated to be the lowest energy pathway of the ionization of a β-glycosyl triflate.

**Observation of glycosyl oxocarbenium ions by NMR spectroscopy**

Where many anomeric triflates have been spectroscopically characterized, glycosyl oxocarbenium ions are too reactive to detect by straightforward NMR techniques. Very recently, Blériot and co-workers reported the use of a superacidic medium (HF/SbF₅) to generate glycosyl oxocarbenium ions and allow their spectroscopic investigation. As depicted in Scheme 7, 2-deoxyglucosyl donor 82 was transformed into the 4E oxocarbenium ion 83, that proved to be stable in the super acid medium for several hours at -40 °C. The conformation of the ion was deduced from the coupling constants of the ring protons and corroborated by DFT calculations and simulated spectra. The found structure is very close in conformational space to the fully substituted glucosyl oxocarbenium ions found in the above described DFT calculation (Table 2). Quenching of the oxocarbenium ion by cyclohexane-δ₂ led to the selective formation of the α-deuterium 2-deoxy glucoside. The formation of this product can be accounted for using the 4E oxocarbenium ion as the product forming intermediate and a favorable 4E → 4C₁ reaction trajectory. Obviously, the solvent system used in this NMR experiment differs significantly from the solvents normally used in glycosylation reactions, and therefore, care should be taken in the translation of the results obtained in the super acid medium to a “normal” glycosylation reaction. It does, however, provide valuable information on the conformation of glycosyl oxocarbenium ions.
ions. Expansion of these NMR studies to a broader pallet of carbohydrates with different functionalities will generate insight and spectroscopic proof for stereoelectronic substituent effects that determine the overall shape of the oxocarbenium ions.

Scheme 7: Generation of a 2-deoxy glucosyl oxocarbenium ion in HF/SbF₅ allowing for its characterization by NMR.

Oxocarbenium ion (β-like) intermediates as product-forming intermediates in glycosylation reactions

The best-studied glycosylation system to date is the Crich β-mannosylation reaction. In this reaction (Scheme 8) a benzylidene (or related acetal) protected mannosyl donor (such as 84) is pre-activated to provide an α-anomeric triflate 85. The corresponding β-triflate is not observed because this species lacks the stabilizing anomeric effect, present in the α-anomer, and it places the anomeric substituent in an unfavorable Δ2-position. Addition of an acceptor to the activated donor then provides the β-linked product 89β, generally with very high stereoselectivity. Where the construction of 1,2-cis mannolides used to be one of the biggest challenges in synthetic carbohydrate chemistry, this linkage can now be installed with great fidelity using this methodology. In addition the system has been a great inspiration to unravel the underlying mechanistic details to explain the observed stereoselectivity. Crich and co-workers have carried out a suite of studies to understand and learn from the mechanistic pathways operational in the system. Secondary kinetic isotope effects, established in a glycosylation reaction with a 2,3,6-tri-O-benzyl glucosyl acceptor, revealed significant oxocarbenium ion character in the transition state leading to the β-linked product. This led the authors to presume that the contact ion pair (CIP) is the actual reactive species in this glycosylation reaction. Using natural abundance ¹³C primary kinetic isotope effects, in combination with computation methods, Crich, Pratt and co-workers established the amount of carbocation character that develops in the transition state of glycosylations of iso-propanol with either a benzylidene protected glucosyl or mannosyl donor. From the established values, corroborated by computational validation, it was established that the β-mannosyl products were formed through an associative pathway, in which the mannose ring adopts a B₆₋₅-structure in the transition state 87. In contrast, the α-products
originated from a more dissociative mechanism, involving a distinct oxocarbenium cation and triflate anion. In this case, computational studies suggested a 4E/4H3 structure for the intermediate oxocarbenium ion 86. For the benzylidene glucose system, which is generally α-selective with carbohydrate acceptors, it was established that both the α- and β-isopropanol products 95α and 95β were formed through an S_n2-like mechanism.\(^\text{50}\) Notably, upon pre-activation of the benzylidene glucose donor, a single triflate is observed: the α-anomer 91.\(^\text{53}\) To account for the formation of the α-product, Crich and co-workers have proposed a Curtin-Hammett kinetic scenario in which the α- and β-triflates 91 and 92 are in rapid equilibrium.\(^\text{50}\) Substitution of the most reactive of the two, i.e. the β-triflate, then leads to the stereoselectivity observed in reactions of this donor. As described below, equatorial glycosyl triflates have been observed, lending support to this scenario.\(^\text{54}\)

**Scheme 8**: Product forming pathways for benzylidene mannosylations and glucosylations.

Using the cation clock methodology shown in Scheme 9, in which external nucleophiles (iso-propanol or allyl trimethylsilane) are made to compete with an intramolecular nucleophile
on mannosyl and glucosyl donors 96 and 97 (i.e. an allylsilane ether appended at C-2), Crich and co-workers showed the O-glycosylation reactions to be more concentration dependent than the corresponding C-glycosylation reactions.51,52 With this methodology, the finding that the formation of the O-glycosyl α- and β-benzylidene products results from different mechanistic pathways (an S_N1-like pathway for the former and an S_N2-like pathway for the latter) was corroborated. When trimethyl(methallyl)silane was employed as a nucleophile, only the β-C-allyl mannosyl and α-C-allyl glucosyl products (101 and 104, respectively) were obtained in a reaction that was relatively independent of the concentration of the nucleophile, indicating S_N1-characteristics in these reactions. Of note, formation of the trans-fused benzylidene mannosyl product 99 through intramolecular attack at the α-face, indicates the intermediacy of an oxocarbenium ion adopting a B_2,5-conformation. The alternative 4H_3-half chair would not allow the pseudo-axially appended nucleophile to reach the α-face of the oxocarbenium ion.

**Scheme 9:** Inter-intramolecular competition reactions for O- and C-mannosylations and glucosylations.

Bols and Pedersen and co-workers have studied glycosylation reactions of the closely related 4,6-O-silylindicene donor 105 as depicted in Scheme 10.55 They described that this donor provided the β-linked products with reasonable to good selectivity, regardless of the activation protocol (pre-activation with BSP/TfO or in situ activation with NIS/TfOH). Even when the in situ activation method (NIS/TfOH) was employed at room temperature, the β-product formation prevailed. This led the authors to propose the B_2,5 oxocarbenium ion as the actual reactive species.
The above described studies on the benzylidene mannose and glucose systems provide an excellent example of the continuum of mechanisms that operate during a glycosylation reaction. Clearly, the different reaction paths are energetically very close to each other making a clear-cut distinction between an S_{N}2 or S_{N}1-type mechanism impossible. In fact, the structures of the glycosyl donor in the transition state are probably very similar to each other. The analysis presented by Crich and co-workers, as illustrated in Scheme 8, shows that the benzylidene mannose ring takes up B_{2,5}-like structure 87 in the S_{N}2-displacement of the covalent triflate, where the benzylidene glucose takes up an 4H_{3} structure 94. These structures also represent the conformation of the most stable oxocarbenium ions of these donors. The exact amount of carbocation character in the transition states of these glycosylations will be determined by the difference in timing of the bond breaking and bond forming processes. This will critically depend on the nature of the nucleophile. When reactive nucleophiles (such as iso-propanol described above) are used the formation of the new glycosidic linkage will be rather synchronous to the departure of the triflate. Unreactive nucleophiles (such as allyl-TMS and unreactive secondary carbohydrate alcohols) will react through a transition state further along the reaction coordinate, with departure of the triflate preceding the formation of the glycosidic linkage. In this scenario more positive charge develops at the anomeric center and the reaction becomes more S_{N}1-like.

The C-6 oxidized analogues of mannosyl donors, mannuronic acid donors, have been found to be highly β-selective, both when pre-activation and direct activation protocols are employed. Although it was expected that this type of glycosyl donors would be relatively inreactive, by virtue of the electron withdrawing effect of the C-5-carboxylate, these donors turn out to be rather reactive. This is manifested in competition reactions in which the reactivity of mannuronic acid donor 108 was shown to be in the same order as the reactivity of tetra-O-benzyl mannose donor 109 (Scheme 11A). Another illustration of the relatively high reactivity of these species is found in the stability of the anomeric triflates that are formed upon activation of the donors. These are stable up to -40 °C, a decomposition temperature which is below that of the 4,6-O-benzylidene mannosyl triflate. Strikingly, low temperature NMR spectroscopy showed the anomeric triflate derived from mannuronic acid donor 108 to take up two conformations at low
temperature, as both the $^4$C$_1$ and $^4$C$_4$ chairs products were present at -80 °C (113 and 114, respectively, see Scheme 11B). The “inverted” chair triflate places three of the ring substituents in a sterically unfavorable axial orientation. In addition this structure places the anomeric triflate in an equatorial unfavorable position, where it does not benefit from a stabilizing anomic effect. This striking conformational behavior and the relatively high reactivity of these donors was rationalized by the hand of the structure of the oxocarbenium ion that can form from these donors (Scheme 11C). In $^3$H$_4$ half chair 116, the C-2, C-3 and C-4 substituents all take up optimal orientations to stabilize the electron depleted anomeric center (vide supra). Model studies on pyranosides, having a single C-5 carboxylate group, revealed that this substituent can provide stabilization of the oxocarbenium ion half-chair when placed in a pseudo-axial position. Thus, in the manuronic acid $^3$H$_4$ half chair oxocarbenium ion 116, all substituents collaborate to stabilize the carbocation. This carbocation can also provide an explanation for the $\beta$-selectivity observed in glycosylations of these donors. Attack on the diastereotopic face of the half chair that leads to a transition state with a chair like structure, i.e. the $\beta$-face, accounts for this selectivity. The smaller size of the carboxylate in comparison to a methyloxybenzyl appendage, present in manopyranosides, leads to diminished steric interactions of this group with the C-3-substituent and the incoming nucleophile (as in Scheme 5). Where the stereoselectivity of 4,6-$O$-benzylidene mannose donors decreased with small substituents (e.g. azides) at C-2 and C-3, the stereoselectivity of C-2-azido and C-2, C-3-diazido manuronic acid donors remained intact. We have accounted for this “robust” stereoselectivity by taking into account that both an $S_N2$-like substitution of the anomeric $\alpha$-triflates 113 and 114, and an $S_N1$-pathway involving the $^3$H-$4$ half chair oxocarbenium ion 116, lead to the $\beta$-product (Scheme 11C). To minimize steric interactions in this transition state, the manuronic acid ring may adopt a closely related $^3$E-structure. The manuronic acid donors have been successfully employed in the construction of several bacterial oligosaccharides, as well as in the automated solid-phase synthesis of $\beta$-mannuronic acid alginate fragments (Scheme 11D). In the latter synthetic endeavor, manuronic acid N-phenyltrifluoroacetimidate donor 118 was used to construct a tetra-, octa- and dodecasaccharide on a resin that was equipped with a butenediol linker system. All glycosylation reactions were executed at a temperature just below the decomposition temperature of the intermediate triflates to allow for effective glycosylation reactions. The dodecasaccharide 120 was eventually obtained, after cleavage from the resin and saponification of the methyl esters, to allow for a straightforward purification, in 11% yield (~91% per step).
Studies on the C-5 epimer of D-mannuronic acid, i.e. L-guluronic acid, revealed a marked decrease in 1,2-"cis"-selectivity of these donors. This was explained by taking into account that in the possible L-guluronic acid oxocarbenium ions, there would be conflicting "substituent interests": in the possible 3H₄ half chair, the C-2, C-3 and C-4 substituents take up a stabilizing orientation but the C-5 carboxylate is positioned in an unfavorable pseudo-equatorial orientation. This situation is reversed in the opposite 4H₃ half chair. L-Gulose donors, such as 2,3,4,6-tetra-O-benzyl-L-gulosyl donor 121, on the other hand, provide very selective glycosylation reactions also in the absence of any special stereodirecting functionalities (Scheme 12). In this case the 3H₄ half chair oxocarbenium ion 123 represents a structure that benefits from the stabilization by the
functionality at C-2, C-3 and C-4, while minimizing steric interactions between the substituents (especially the bulky C-5 substituent). "Non-oxidized" gulose synths have been successfully employed in the synthesis of L-guluronic acid alginates, as well as 'mixed' alginates, containing both β-D-mannuronic acid and α-L-guluronic acid residues.

**Scheme 12:** Stereoselective glycosylation involving L-gulosyl donors.

Another L-sugar, renowned for its high 1,2- *cis*-selectivity in glycosylation reactions, is L-fucose, an important constituent of, among others, the blood group determinants. Different methods are available for the introduction of the α-fucosyl linkage. One of the most common methods relies on the use of acyl groups at C-3 and/or C-4. Although there is ongoing debate as to the role of the acyl functions, an often forwarded explanation is that they can provide 'remote participation', generating species such as dioxolenium ion 126, thereby shielding the bottom face of oxocarbenium ion and allowing the selective formation of the α-fucosidic linkage (see Scheme 13A). This approach has been successfully employed in the synthesis of fucoidan oligosaccharides. On the other hand, there are also numerous examples of fucosylation that do not rely on the presence of acyl groups at C-3 and/or C-4. For example, the highly reactive per-O-benzylated fucosyl donor 128 has been used by Wong and co-workers to synthesize Lewis* hapten 131, using a sequential reactivity-based one-pot strategy, in 44% yield (Scheme 13B). Although the use of the ethereal solvent mixture in this case can be important to install the α-fucosyl linkage, this is most likely not the only reason underlying the excellent selectivity observed in this glycosylation. Another example is shown in Scheme 13C where two fucose moieties have been introduced to synthesize pentasaccharide 134, using perbenzylated thioethyl fucosyl donor 135, in combination with methyl triflate (MeOTf), in dichloromethane at room temperature. A possible explanation for the generally good α-selectivity observed in fucosylation reactions can
be found in oxocarbenium ion half-chair 137 (Scheme 13D). In this 3H4 half chair oxocarbenium ion, the axial C-4 alkoxy substituent and the pseudo-equatorial H-2 can stabilize the positive charge of the oxocarbenium ion. The C-5 methyl substituent is placed in a sterically favorable equatorial position. The high reactivity of per-benzylated fucosyl donors also supports the intermediary of an oxocarbenium ion intermediate.

The use of cyclic protecting groups to conformationally restrict glycosyl donors has also been employed in furanosylation reactions. Almost simultaneously, the groups of Ito, Boons and Crich reported that locked arabinoarafuranoses can be used for the stereoselective construction of the β-arabinose bond.73-75 Scheme 14A depicts the synthesis of an arabinogalactan using 3,5-O-silylidenene protected arabinose donor 138 as reported by Boons and co-workers.74 The high selectivity of donor 138 was rationalized by the intermediary of oxocarbenium ion 140 (Scheme 14B), which is locked in the E2 conformation by the cyclic protecting group. The ‘inside attack’ model, described above, explains the facial selectivity for the attack of the incoming nucleophile. Ito and co-workers used a similar 3,5-O-di-(di-iso-propyl)siloxane-protected arabinosyl donor 141 (Scheme 14C), that also exhibits a very high β-selectivity.75 The authors performed molecular modeling studies, which suggested that the total energy of β-glycosylation product 144 was about 3.7 kcal/mol lower than that of the alternative α-isomer. The β-glycosidic linkages take up a pseudo-axial orientation, thereby benefitting from a stabilizing anomeric effect and providing an explanation for the energy difference. Although the conditions used by the authors do not suggest thermodynamic control in these glycosylations, the energy difference of the products can already become somewhat apparent in the transition states leading to the products. A kinetic explanation for the observed selectivity based on the intermediate oxocarbenium ions is more likely. Analogous donor 146 was used for the introduction of terminal β-arabinofuranosidic residues in branched arabinan oligosaccharides (Scheme 14D), up to 22 monosaccharide units in length.75

As described above, C-glycosylation reactions and reductions (addition of an H-nucleophile) on ribofuranosides generally proceed with excellent stereoselectivity to provide the product, resulting from nucleophilic attack at the α-face of the E2 oxocarbenium ion.24 Also with other nucleophiles this stereoselectivity is observed as described in Scheme 15A.76 In their efforts to synthesize poly-(ADP-ribose) trisaccharide core 154 (a so-called supernucleoside), Kistemaker et al used tribenzylated ribosyl donor 148 to form diriboside 150 in high yield and complete α-selectivity.76 Further elaboration to the trisaccharide was carried out with 5-O-TIPS protected ribosyl donor 152, leading to trisaccharide 153, again with complete α-selectivity, in 57% yield.
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Scheme 14: Stereoselective arabinofuranosylations through the use of locked arabinofuranosyl donors. A) Boons’ synthesis of an arabinogalactan hexasaccharide. B) Putative oxocarbenium ion envelope involved in arabinosylation reactions. C) Ito’s conformationally locked arabinosyl donors to obtain high β-selectivities. D) Ito’s synthesis of branched oligoarabinofuranosides.
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The stereoselectivity of ribosyl donors can be reversed through the use of cyclic protecting groups to mask the bottom face the ribofuranosyl oxocarbenium ion. Ichikawa et al found that 2,3-\(O\)-(3-pentylidene) protected ribosyl fluoride 158 reacted in a very \(\beta\)-selective manner with \(G\)-nucleophiles (Scheme 15B). DFT-computations showed that the intermediate oxocarbenium ion preferably adopts an \(E_3\) conformation. Inside attack on this species is prohibited by the blocking 3-pentylidene protecting group, leading to attack on the other side of the furanosyl ring. This approach was used in the total synthesis of the antibiotic (+)-caprazol 162 (Scheme 15C), where 2,3-\(O\)-(3-pentylidene)-5-azidoribosyl donor 158 gave near-complete \(\beta\)-selectivity in the glycosylation with acceptor 159, while the less sterically demanding 2,3-\(O\)-propylidene analogue 157 only gave modest \(\beta\)-selectivity.76

Conclusions

The vast majority of glycosylation reactions takes place somewhere along the continuum of mechanisms hemmed in between \(S_N1\) and \(S_N2\)-type reactions, with product forming transitions states that have characteristics of both reaction types. Insight in and control over the place of a given glycosylation reaction in the continuum opens up ways to control the stereochemical outcome of the glycosylation reaction at hand. Over the recent years - and spurred by the initial discovery of a covalent mannosyl triflate - much insight into reactive intermediates has been gathered. NMR spectroscopy has been used to characterize a multitude of covalent reactive intermediates, such as anomeric triflates. Often only a single anomeric triflate can be observed spectroscopically, because the other anomer is too unstable to allow its detection. To study glycosyl oxocarbenium ions, sophisticated and detailed DFT computational approaches have been presented to validate experimental results. Very recently NMR was added to the toolbox available to study glycosyl oxocarbenium ions. To pin-point the location of the mechanism of a given glycosylation reaction on the continuum of mechanisms, kinetic isotope effects and cation clock methodology have been used to determine how much oxocarbenium character develops in the transition state of the glycosylation reaction. While the structure of a non-charged covalent intermediates are primarily dictated by the steric requirements of the ring substituents, the shape of positively charged oxocarbenium ion like intermediates is governed by electronic (stabilizing or destabilizing) substituent effects. These effects will also be apparent in the transition state of a glycosylation reaction in which partial oxocarbenium ion character develops. The amount of positive charge at the anomeric center that can or has to develop for a given glycosylation reaction to occur, not only depends on the nature of the donor but also on the nucleophilicity of the acceptor. Acceptors of high nucleophilicity will be able to displace covalent reactive intermediates,

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Scheme 15: Stereoselective ribosylations. A) Synthesis of the ‘supernucleoside’ 154. B) Putative oxocarbenium ion envelopes involved in ribosylation reactions. C) The installation of 1,2-trans ribofuranosyl linkages using 3-pentylidene protected ribosyl donors, applied to the synthesis of the antibiotic (+)-caprazol 162.

where poor nucleophiles require more oxocarbenium ion character. With the ever-growing insight into the reactivity of different reactive intermediates at play during a glycosylation reaction, more control over the stereoselective construction of glycosidic bonds will be gained,
reducing the time and labor-intensive trial-and-error component that has thwarted synthetic carbohydrate chemistry for so long.

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(28) Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.* **2013**.
Additions to oxocarbenium ions

78, 2191–2205.


(42) The beta-triflate was established to be only 0.8 kcal/mol higher in energy than its alpha-counterpart, translating to an 3:1 mixture of triflate anomers at equilibrium. Under experimental conditions only the alpha-anomer has been observed for the tetra.


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Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

Introduction

The rare sugar 2-acetamido-2-deoxy-fucose (FucNAc) is a constituent monosaccharide of several bacterial capsular polysaccharides (CPS), including the *Staphylococcus aureus* type 5 and type 8 CPS, the *S. aureus* Strain M type 1 CPS, as well as O-antigenic polysaccharides from *Escherichia coli* strains (Figure 1). Both D- and L-enantiomers are found in Nature and they can be connected to other carbohydrate moieties through an α- or a β-glycosidic linkage. In order to chemically synthesize α-FucNAc-containing oligosaccharides, the C2-amino functionality is generally masked as a non-participating azido group to allow the formation of the 1,2-β linkage.6

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While 2-azido-2-deoxy fucosyl (FucN₃) donors have previously been used in oligosaccharide synthesis, lack of systematic knowledge regarding their reactivity and selectivity has resulted in relatively low yields and stereoselectivity. Notably, analogous L-fucosyl (Fuc) donors, are known to give highly α-selective glycosylation reactions, under a variety of conditions (also see Chapter 2). A general paradigm to account for the α-selectivity in fucosylations (and by extension, 2-azido-2-deoxy-fucosylations) is that 3,4-di-O-acyl protecting groups provide the desired selectivity through a remote participating effect, where one of the acyl groups coordinates with a transient oxocarbenium ion from the β-face, thereby only allowing α-facial attack of the incoming nucleophile. This Chapter describes the synthesis of a panel of six 1-phenylseleno-FucN₃ donors featuring a range of protecting groups at 3-O and 4-O, and investigation of their reactivity and selectivity in glycosylation reactions. The formation and stability of potential covalent reactive intermediates is investigated by low-temperature NMR. The influence of the nucleophilicity of the acceptor on the stereochemical outcome of the glycosylations is studied in detail through the use of a series ethanol acceptors, carrying no, one, two or three β-fluoride atoms. In contrast to the numerous studies on the reactivity of donor glycosides and the effect of donor reactivity on the outcome of a glycosylation reaction, the systematic study of acceptor reactivity is minimally explored, even though it is well known that
the nature of the acceptor can be of decisive influence for the outcome of a glycosylation reaction.30–35

Results and Discussion

For this study six 1-FucN\textsubscript{3} donors 1-6, bearing either benzyl (Bn), benzyol (Bz) or tert-butyldimethylsilyl (TBS) groups on the 3-\textit{O} and 4-\textit{O} position were selected (Figure 2A). The influence of protecting groups on the reactivity of glycosyl donors has been long appreciated in carbohydrate chemistry. It has led to the ‘armed-disarmed’ concept, originally conceptualized by Fraser-Reid and co-workers,\textsuperscript{36} and to the ensuing establishment of relative reactivity values (RRVs) of glycosyl donors.\textsuperscript{22,23,37} The group of Bols has found that the use of multiple TBS protecting groups in a monosaccharide donor can ‘super-arm’ these donors, by forcing them in a more reactive conformation.\textsuperscript{29,38,39} Scanlan and co-workers have reported the synthesis and successful application of TBS-protected fucosyl donors in constructing α-fucosyl linkages.\textsuperscript{40}

The set of acceptor alcohols used is depicted in Figure 2B. The set of partially fluorinated ethanols will be used to investigate how gradually diminishing nucleophilicity of the acceptor (going from ethanol to 2-mono-, 2,2-di- and 2,2,2-trifluoroethanol) affects the stereochemical outcome of the glycosylation reactions.\textsuperscript{35} Three secondary acceptors will be used: cyclohexanol, mannosyl acceptor 7, having an axially oriented hydroxyl group\textsuperscript{41} and mannoside 8, with an equatorially oriented OH.\textsuperscript{42}

Figure 2: Donors (A) and acceptors (B) used in this study.
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Donor synthesis

Synthesis of diol building block 12 commenced with the acetylation of commercially available l-fucose, according to the procedure of Roseman and co-workers (Scheme 1). Under these conditions, the formation of furanosides is avoided. Conversion of the crude peracetate 10 to the glycal 11 was achieved by bromination of the anomeric center, followed by zinc-mediated elimination (64% yield over 3 steps). Azidophenylselenylation of the fucal, following a protocol from Nifantiev and co-workers, led to a mixture of diastereomers, with the desired α-phenylseleno fuco-configured product prevailing. Deacetylation using Zemplén conditions, followed by crystallization of the desired diol from toluene/hexane afforded central building block 12 in 56% yield over 2 steps. Dibenzyalted (1) and dibenzoylelated donors (2) were obtained using standard conditions in 85% and 90% yield, respectively. Silylation of 13 using TBSOTf and DMAP in pyridine at 70 °C proceeded uneventfully, giving 5 in 85% yield, while the use of TBSCI and imidazole in DMF only resulted in mono-silylated product. 1H-NMR analysis indicated that fucosazide 5 resides in a 'normal' 1C4 conformation, even though significant signal broadening was observed in the 13C-NMR spectrum. Donor 3 was obtained by tin-mediated regioselective benzylaion, followed by benzoylation of the 4-O position, in 47% yield over two steps. Synthesis of donors 4 and 6 required more elaborate protecting group manipulations: tin-mediated para-methoxybenzylation (81% yield), followed by benzylaion delivered intermediate 13 in 90% yield. Removal of the PMB ether was accomplished with a catalytic amount of HCl in 1,1,1,3,3,3-hexafluoro-iso-propanol (HFIP) to give 14 in 64% yield. Triethylsilane (TESH) was added as a scavenger to the reaction to prevent attack of the anomeric phenylseleno moiety on the generated para-methoxybenzyl cation. Benzylaion and silylation of 14 proceeded uneventfully to obtain donors 5 (96% yield) and 6 (92% yield).

Low-temperature NMR studies

In order to study potential reactive intermediates during glycosylation, low-temperature NMR studies were carried out. Donors 1 and 2 were selected, as they represent two 'extremes' of the four benzyl/benzoyl protected donors in terms of reactivity. As an activation method, the Ph3SO/Tf2O-mediated pre-activation protocol was selected. This method has been previously used, for the activation of selenoglycosides, and for the detection of reactive intermediates by low-temperature NMR spectroscopy on hemiacetal- and thioglycoside donors. Thus, a mixture of dibenzylated donor 1 and Ph3SO (1.3 equivalents) in deuterated dichloromethane was treated with Tf2O (1.3 equivalents) at -80 °C (Figure 3A). After recording a 1H NMR spectrum (Figure 3B), two new anomeric signals appeared (δ: 6.06 and 6.10 ppm), which were assigned as
α-triflate 15 ($J = 3.2$ Hz) and oxosulphonium triflate 17α ($J = 3.2$ Hz), respectively, based on their chemical shift.29

**Scheme 1:** Synthesis of FucN₃ donors.

Further addition of Ph₂SO (to 2.0 eq.) resulted in an increase of the signal at δ: 6.10 ppm, (Figure 3C), reinforcing the presence of oxosulphonium triflate 17α. Activation of donor 1 with 4.0 equivalents of Ph₂SO resulted in the spectrum shown in Figure 3D. In this spectrum the signal at 6.06 ppm (the anomic triflate) is not present but a new set of signals has appeared. Based on the doublet at 5.42 ppm, with a coupling coupling of 8.4 Hz, this resonance set was tentatively assigned to β-oxosulphonium triflate 17β. In order to assess the stability of the reactive intermediates, the NMR probe was warmed up gradually by increments of 10 °C. Decomposition of α-triflate 15 and α/β-oxosulphonium triflates 17 started at -20 °C. Donor 2 was also converted to two new species (δ: 6.31 ppm, and δ: 6.62 ppm, both with a coupling constant of 3.2 Hz), upon activation using the conditions described for dibenzylated donor 1 and these species were thus assigned as α-triflate 16 and α-oxosulphonium triflate 18 (Figure 3E). Incremental heating of the sample indicated that the onset of decomposition of both species started at 0 °C. It must be noted
that the observation of covalent intermediates (such as glycosyl triflates and oxosulphonium triflates) does not rule out the presence of other intermediates, such as glycosyl oxocarbenium ions or their ion pairs. Such species are much higher in energy than covalent species and are therefore so short lived in organic media, that they are not observable on the NMR timescale.

**Figure 3:** Partial of the $^1$H-NMR spectra of activated FucN$_3$ donors 1 and 2. A) The used donors and intermediates formed. B) Donor 1, 1.3 eq. Ph$_2$SO. C) Donor 1, 2.0 eq. Ph$_2$SO. D) Donor 1, 4.0 eq. Ph$_2$SO. E) Donor 2, 1.3 eq. Ph$_2$SO.

**Model glycosylations**

After establishing the presence of covalent reactive species of donors 1 and 2, and the temperature of decomposition of these species, reaction conditions for model glycosylations could be established. All glycosylations were carried out under identical conditions. The selenoglycosyl donors were activated with the Ph$_2$SO/Tf$_2$O couple at -80 °C after which the temperature was allowed to raise to -60 °C to ensure complete activation of the donor fucosides. The mixtures were then cooled to -80 °C, prior to the addition of the acceptor and slow warming of the reaction mixture to -40 °C, at which temperature the reactions were stopped.
First the series of primary ethanol acceptors was investigated and the results of these fucosaminylations are summarized in Table 1. Glycosylation of donors 1-6 with the series of ethanols (Table 1, Columns A-D) revealed a clear dependency of the stereochemical outcome of the glycosylations on the nucleophilicity of the acceptor alcohols. All donors show the same trend: with decreasing nucleophilicity (increasing amount of fluorine atoms in the acceptors) the α-selectivity increases. Where the more reactive donors (1, 5 and 6) react in a non-selective manner with the most nucleophilic acceptor, ethanol (Column A), the less reactive, benzoyl bearing fucosazide donors react with moderate β-selectivity. The glycosylations of the least reactive nucleophile, 2,2,2-trifluoroethanol all proceed with very good to excellent α-selectivity. The more reactive donors (1, 5 and 6) performed best in these glycosylation reactions, both in terms of yield and stereoselectivity.

Table 1: Glycosylations of 1-6 with model acceptors (B).

<table>
<thead>
<tr>
<th>Donor</th>
<th>Reaction Conditions</th>
<th>Et</th>
<th>FEt</th>
<th>F2Et</th>
<th>F3Et</th>
<th>Cy</th>
<th>2-O-Man</th>
<th>3-O-Man</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (R1, R2: Bn)</td>
<td>Ph3SO, THF, 3A MS, CH2Cl2</td>
<td>88% (1:1)</td>
<td>72% (1:1)</td>
<td>81% (2:1)</td>
<td>80% (19:1)</td>
<td>75% (2:1)</td>
<td>68% (19:1)</td>
<td>72% (19:1)</td>
</tr>
<tr>
<td>2 (R1, R2: Bz)</td>
<td></td>
<td>59% (1:3)</td>
<td>34% (1:2)</td>
<td>74% (3:2)</td>
<td>50% (10:1)</td>
<td>38% (1:9)</td>
<td>38% (4:1)</td>
<td>64% (19:1)</td>
</tr>
<tr>
<td>3 (R1: Bn; R2: Bz)</td>
<td></td>
<td>61% (1:3)</td>
<td>56% (1:1)</td>
<td>76% (3:1)</td>
<td>77% (7:1)</td>
<td>75% (1:4)</td>
<td>58% (10:1)</td>
<td>54% (19:1)</td>
</tr>
<tr>
<td>4 (R1: Bz; R2: Bn)</td>
<td></td>
<td>58% (1:3)</td>
<td>60% (2:3)</td>
<td>80% (1:1)</td>
<td>45% (19:1)</td>
<td>71% (1:4)</td>
<td>68% (4:1)</td>
<td>64% (10:1)</td>
</tr>
<tr>
<td>5 (R1: Bn, R2: TBS)</td>
<td></td>
<td>63% (2:5)</td>
<td>81% (2:3)</td>
<td>75% (5:2)</td>
<td>84% (19:1)</td>
<td>84% (1:3)</td>
<td>67% (19:1)</td>
<td>73% (19:1)</td>
</tr>
<tr>
<td>6 (R1: Bn, R2: TBS)</td>
<td></td>
<td>81% (1:1)</td>
<td>80% (1:1)</td>
<td>87% (2:1)</td>
<td>90% (19:1)</td>
<td>80% (1:2)</td>
<td>74% (19:1)</td>
<td>64% (9:1)</td>
</tr>
</tbody>
</table>

Next, the set of secondary alcohol acceptors was studied (Table 1, Columns E-G). Cyclohexanol reacts in a non-stereoselective manner with the reactive donor fucosides, and in a β-selective manner with the less reactive benzoylated donors (Column E). The condensations of the secondary carbohydrate acceptors 7 and 8 (Columns F and G) all proceed with good to excellent α-selectivity, again with the more reactive donors providing better α-selectivity than their less reactive counterparts.

Next, several modifications on the standard conditions were investigated. The use of additives to modulate selectivity in glycosylations has become increasingly prevalent in the past
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decade.\(^{57}\) To probe the influence of additives and solvents, the glycosylation of 1 with cyclohexanol was selected as a model system (Table 2). The use of a large excess of Ph\(_2\)SO in the activation of donor 1 led to the formation of equal amounts of both anomers of \(\text{E1}\) in the coupling reaction. The low-temperature NMR experiments described above showed that the use of a large excess of Ph\(_2\)SO leads to the formation of a mixture of \(\alpha/\beta\)-oxosulphonium triflates \((17\alpha/\beta)\) Apparently, the presence of a \(\beta\)-oxosulphonium triflate intermediate in the reaction mixture does not lead to increased \(\alpha\)-product, indicating that oxosulphonium triflate \(17\beta\) is not likely to be displaced in a direct, \(S_N\)2-like manner.

Table 2: Influence of solvents and additives on the formation of \(\text{E1}\).

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent</th>
<th>additive (eq.)</th>
<th>yield ((\alpha/\beta))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl</td>
<td>-</td>
<td>75% (2:1)</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)Cl</td>
<td>Ph(_2)SO (4)(^{a})</td>
<td>53% (1:1)</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)Cl</td>
<td>Bu(_4)N(\text{OTf}) (3)</td>
<td>84% (2:5)</td>
</tr>
<tr>
<td>4</td>
<td>CH(_2)Cl/EtCN (19:1)</td>
<td>-</td>
<td>60% (1:2)</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)Cl/EtNO(_2) (1:1)</td>
<td>-</td>
<td>56% (2:5)</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)Cl/Et(_2)O (1:1)</td>
<td>-</td>
<td>69% (1:5)</td>
</tr>
</tbody>
</table>

\(^{a}\) Instead of 1.3 equivalents.

The \emph{in situ} anomerization of anomeric leaving groups has been exploited in the synthesis of \(\alpha\)-glycosidic bonds. Lemieux and co-workers were the first to show that the use of an excess of halide anions in a glycosylation mixture can be used to promote the anomerisation of an initially formed \(\alpha\)-glycosyl halide into the more reactive \(\beta\)-halide (which does not benefit from an anomeric effect), leading to an \(\alpha\)-selective glycosylation by displacement of the reactive \(\beta\)-halide intermediate.\(^{58,59}\) To investigate whether excess triflate anion has a similar effect on the glycosylation of 1 with cyclohexanol, a glycosylation was carried out using 3 equivalents of Bu\(_4\)N\(\text{OTf}\) (entry 3). The glycosylation resulted in the formation of the \(\beta\)-product with moderate selectivity \((\alpha/\beta\) 2:5). This result shows that it is unlikely that the added Bu\(_4\)N\(\text{OTf}\) leads to an \emph{in situ} anomerisation scenario as described above. This may be due to the low nucleophilicity of the triflate anion. The increased \(\beta\)-selectivity may be attributed to a shift in the equilibrium between
the covalent triflate species and the dissociated ion pairs towards the side of the anomeric α-triflate (15, Figure 3), due to the increased amount of triflate anion in the reaction mixture.

It has been long appreciated that the nature of the solvent(s) in glycosylations can have a profound effect on the outcome of the reaction, especially in terms of stereoselectivity. For example, nitrile solvents (acetonitrile and propionitrile are the most common) have often been used to promote the formation of β-glycosidic bonds.\textsuperscript{60,61} Reversely, the use of ethereal solvents generally leads to higher α-selectivity, supposedly through the intermediate formation of a species in which solvent molecules associate with the donor oxocarbenium ion on the β-face of the donor glycoside.\textsuperscript{62,63} The use of propionitrile led to increased β-product (entry 4). The large ratio of CH\textsubscript{2}Cl\textsubscript{2} to EtCN (19:1) in this pre-activation protocol was used to prevent Ritter-type byproducts arising from attack of the acceptor on the nitrile sp\textsubscript{3}carbon, as previously observed in the synthesis of β-L-rhamnosides.\textsuperscript{61} A mixture of CH\textsubscript{2}Cl\textsubscript{2} and EtNO\textsubscript{2}, in a ratio of 1:1, also led to increased β-selectivity. This may be due to the coordinating ability of the nitro group. Interestingly, the use of a 1:1 CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{2}O mixture for the glycosylation of 1 and cyclohexanol did not lead to the formation of more α-product (entry 6). Rather, more β-product was formed, in contrast to the well-documented α-directing effect of Et\textsubscript{2}O in glycosylations. An explanation can perhaps be sought in the decreased polarity of the CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{2}O mixture compared to pure CH\textsubscript{2}Cl\textsubscript{2}.

\textit{A mechanistic picture}

From the low-temperature NMR studies and the model glycosylation reactions, a general mechanism can be formulated (Scheme 2A). Upon activation of the phenylseleno moiety, a pool of reactive intermediates can be generated,\textsuperscript{64} with α-configured anomeric (oxosulphonium)triflate 20a acting as a ‘reservoir’ from which more reactive oxocarbenium ions (\textit{e.g.} 21) can transiently form.\textsuperscript{55} As shown above, the nature of the acceptor is fundamental in the outcome of glycosylation stereoselectivity.\textsuperscript{35} A highly nucleophilic acceptor (such as ethanol, 2-fluoroethanol or cyclohexanol) is able to react with the covalent species 20, and produces mainly the β-product \textit{via} direct displacement of the triflate (or oxosulphonium triflate) leaving group. On the other side, less nucleophilic acceptors (2,2,2-trifluoroethanol, or mannosyl acceptors 7 and 8) are less prone to directly displace a covalently bound leaving group (or tightly associated anion) and react preferentially \textit{via} a more loosely associated ion pair, in an S\textsubscript{N}1-like mechanism. While the NMR studies on the reactive intermediates has revealed that β-linked oxosulphonium triflates may be formed during the reaction, they do not lead to increased α-product, diminishing the possibility that they participate in an S\textsubscript{N}2-like reaction pathway. Likewise, the increased concentration of triflate anion (see Table 3, entry 3) did not lead to more α-product. It is possible that the triflate
anion influences the equilibrium between the α-triflate and dissociated glycosyl ion pairs, shifting it towards the covalent species, leading by the higher β-selectivity observed.

Scheme 2: A) Proposed mechanism for 2-azidofucosylation based on pre-activation. B) (De)stabilizing interactions in the two possible oxocarbenium ion conformers 23 and 24.

The nature of the protecting groups on the 3- O and 4- O positions influence the stability of the reactive intermediates. Electron-withdrawing benzoyl groups stabilize covalent intermediates, reflected by the higher decomposition temperature of dibenzoylated FucN3 triflate 16 compared to dibenzylated analogue 15 (Figure 3). This increased stability leads to the superior β-selectivity of donor 2, as compared to the other donors used in this study, especially when reacted with highly reactive acceptors (see Table 2, entry 2).

It is now well established that the conformation of an intermediate oxocarbenium ion can be of decisive influence on the stereochemical outcome of a glycosylation reaction. Oxocarbenium ion 21, transiently formed from the covalent triflate or oxosulfonium triflate species, likely adopts a half-chair conformation (Scheme 2B), since this conformation best accommodates the flat oxocarbenium ion moiety.\textsuperscript{65,66} When the two possible half-chair conformers are considered, it appears that \textsuperscript{3}H\textsubscript{4} oxocarbenium ion 24 benefits from stabilization by electron donation of the lone pair electrons, of the C4-oxygen, which is placed in an axial position.\textsuperscript{67,68} In addition, the axial C-2-H-2 bond can stabilize the flanking oxocarbenium ion through hyperconjugation and the C-5 methyl group, incapable of any electronic stabilization, adopts a favored pseudo-equatorial
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

orientation. Top side attack of this oxocarbenium ion proceeds via a chair-like transition state to provide the \( \alpha \)-product. The alternative \( ^4H_3 \) half-chair 23 can benefit from stabilization by the axially placed C-3-\( O \) substituent. It lacks the hyperconjugative stabilization of the C-2-H-2 bond, and the C-6 is placed in an unfavorable pseudo-axial orientation, where it experiences unfavorable steric interactions with the C3-substituent. In addition, attack of this half chair oxocarbenium ion on the bottom face would lead to the development of extra 1,3-diaxial interactions between the incoming nucleophile and the C-3 and C-6 substituents.

Conclusion

This Chapter has described an investigation into the reactivity and selectivity of phenylseleno FucN\(_3\) donors. In total, six differentially protected FucN\(_3\) donors, bearing benzyl, benzyol or TBS groups were synthesized and subsequently investigated in glycosylation reactions with seven acceptors. Low-temperature NMR studies of dibenzylated (1) and dibenzoylated donor 2 revealed the formation of two reactive intermediates upon activation with \( \text{Ph}_2\text{SO} \) and \( \text{TF}_2\text{O} \), and the structures were assigned as the corresponding \( \alpha \)-glycosyl triflates and \( \alpha \)-oxosulfonyl triflates. The model glycosylations showed a dependency of the nature of protecting groups on stereoselectivity, with more reactive donors providing higher \( \alpha \)-selectivity. The nature of the acceptor proved to be critical to the glycosylation outcome, as more reactive acceptors generally gave more \( \beta \)-product, while less reactive acceptors (including carbohydrate acceptors) were more \( \alpha \)-selective. This has been rationalized with a mechanistic pathway in which the more nucleophilic acceptors are able to react with covalent \( \alpha \)-FucN\(_3\) triflates in a \( S_\text{N}2 \)-like fashion, giving the \( \beta \)-product, while less nucleophilic acceptors preferentially react via a \( S_\text{N}1 \)-like mechanism, through the intermediacy of a \( ^3H_4 \)-like oxocarbenium ion.
**Chapter 3**

**Experimental**

**General procedures**

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4Å molecular sieves (3Å for CH₂Cl₂, MeOH and MeCN), except pyridine and DMF. NEt₃ was stored over KOH pellets. Tf₂O used in glycosylations was dried over P₂O₅ (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (λ: 254 nm), followed by spraying with 20% H₂SO₄ in EtOH (w/v) or Hanessian’s stain ((NH₄)₆Mo₇O₄₀.4H₂O, 25 g/L; (NH₄)₄Ce(SO₄)₄.2H₂O, 10 g/L; in 10%aq. H₂SO₄). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to Me₄Si (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. ¹³C-APT spectra are ¹H decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomeric carbon atoms (J_H1,Cl) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm⁻¹. HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.

**3,4-di-O-acetyl-l-fucal (11)**

![Structure](image)

To a stirred, ice-cooled mixture of Ac₂O (120 mL, 1.27 mol, 14 eq.) and pyridine (150 mL) was added L-fucose (15 g, 91 mmol, 1 eq.), in small portions, over the course of 15-20 minutes. The mixture was stirred at 0-4 °C overnight, after which TLC analysis (PE/EtOAc, 3:2 v/v) indicated complete consumption of the starting material. The mixture was poured on ice-water and stirred until the ice had melted. The mixture was extracted with CH₂Cl₂ (2x), the combined organicss were washed with sat. aq. NH₄Cl solution (3x), water (2x), and brine (1x), dried over MgSO₄, filtered and concentrated *in vacua*. The residue was coevaporated with toluene (3x) to remove residual
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

Pyridine. The crude mixture thus obtained was dissolved in CH₂Cl₂ (360 mL, 0.25 M) and cooled to 0 °C. To this solution was added HBr (33% in AcOH, 130 mL) in a dropwise fashion and the resulting solution was stirred at 0 °C until TLC analysis (CH₂Cl₂) indicated complete conversion of the starting material. The mixture was poured on ice-water and stirred until the ice had melted. The mixture was partitioned and the aqueous extracted with CH₂Cl₂ (2x). The combined organic phases were washed with sat. aq. NaHCO₃ solution (2x), water (1x) and brine (1x), dried over MgSO₄, filtered and concentrated in vacuo. The residue was co-evaporated with toluene (1x) to remove excess acetic acid, and subsequently dissolved in EtOAc (300 mL, 0.3 M). The mixture was added to a mixture of freshly prepared Zn/Cu couple (30 g of Zn, 455 mmol, 5 eq.) and N-methylimidazole (7.3 mL, 91 mmol, 1 eq.) in EtOAc (300 mL). The mixture was heated to 70 °C and stirred until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete consumption of the anomeric bromide. The reaction mixture was cooled to room temperature, filtered over a bed of celite, and the resulting solution concentrated in vacuo. The product was obtained from the residue by column chromatography (PE/EtOAc/NEt₃, 95:5:1 → 90:10:1 v/v/v) in 64% yield (12.5 g, 58.4 mmol). ¹H NMR (400 MHz) δ: 6.47 (dd, 1H, J = 1.6 Hz, 6.4 Hz, H-1); 5.59-5.58 (m, 1H, H-3); 5.29 (d, 1H, J = 4.4 Hz, H-4); 4.66-4.63 (m, 1H, H-2); 4.22 (q, 1H, J = 6.4 Hz); 2.17 (s, 3H, CH₃Ac); 2.02 (s, 3H, CH₃), 1.28 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 170.7, 170.4 (COAc); 146.1 (C-1); 98.2 (C-2); 71.5 (C-5); 66.2 (C-4); 65.0 (C-3); 20.9, 20.7 (CH₃Ac); 16.5 (C-6).

Phenyl 2-azido-2-deoxy-1-seleno-α-L-fucopyranoside (12)

A solution of 3,4-di-O-acetyl-L-fucose 11 (12.5 g, 58.4 mmol, 1.0 eq.) and (PhSe)₂ (18.2 g, 58.4 mmol, 1.0 eq.) in CH₂Cl₂ (300 mL, 0.2 M) was degassed by sonication (30 minutes) before being cooled to -30 °C. Added were Ph(OAc)₂ (18.8 g, 58.4 mmol, 1.0 eq.) and TMSN₃ (15 mL, 116.8 mmol, 2.0 eq.). The mixture was stirred for 1 hour at -30 °C and subsequently at -20 °C overnight. To the mixture was added cyclohexene (~15 mL) and the mixture was allowed to warm to room temperature. The bright orange solution was concentrated in vacuo and the brown residual oil was subjected to column chromatography (PE/EtOAc, 1:0 → 9:1 v/v) to separate the lipophilic impurities from the carbohydrate fraction. The latter was concentrated and suspended in MeOH (190 mL, 0.3 M), after which NaOMe (0.31 g, 5.8 mmol, 0.1 eq.) was added. The mixture was stirred overnight, after which TLC analysis (PE/EtOAc, 1:1 v/v) showed complete conversion of the starting material. The reaction mixture was neutralized by addition of ion-exchange resin (Amberlite IR-120, H⁺ form). The resin was filtered and the filtrate concentrated in vacuo. The
solid thus obtained was crystallized from toluene to obtain the title compound as an amorphous solid (11.1 g, 33.8 mmol, 58%). 1H NMR (400 MHz, acetone-\(d_6\)) \(\delta\): 7.62-7.57 (m, 2H, \(\text{CH}_{\text{arom}}\)); 7.32-7.28 (m, 3H, \(\text{CH}_{\text{arom}}\)); 5.96 (d, 1H, \(J = 5.2\) Hz, H-1); 4.29 (q, 1H, \(J = 6.4\) Hz, H-5); 4.40 (dd, 1H, \(J = 5.2\) Hz, 10.4 Hz, H-2); 3.82-3.79 (m, 2H, H-3, H-4); 1.17 (d, 3H, \(J = 6.4\) Hz, H-6). 13C-APT NMR (100 MHz, acetone-\(d_6\)) 135.4 (\(\text{CH}_{\text{arom}}\)); 130.1 (\(C_{\text{q,arom}}\)); 129.8, 128.3 (\(\text{CH}_{\text{arom}}\)); 86.7 (C-1); 72.4, 72.2 (C-3, C-4); 70.2 (C-5); 62.6 (C-2); 16.5 (C-6). IR (neat) \(\nu\): 3279, 2100, 1578, 1252, 1094, 1059. HRMS: [M-N\(_2\)+H]\(^+\) calculated for \(\text{C}_{12}\text{H}_{16}\text{NO}_3\text{Se}\): 302.02899; found 302.02914.

**Phenyl 2-azido-3,4-di-O-benzyl-2-deoxy-1-seleno-\(\alpha\)-L-fucopyranoside (1)**

![Structure 1](image)

To a stirred solution of 12 in DMF (8 mL, 0.25 M) were added benzyl bromide (0.71 mL, 6.0 mmol, 3.0 eq.) and Bu\(_4\)NI (0.15 g, 0.4 mmol, 0.2 eq.). The mixture was cooled in an ice-bath and NaN\(_3\) (60% w/w in oil, 0.32 g, 8.0 mmol, 4.0 eq.) was added. The mixture was stirred until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete consumption of the starting material (\(\leq 3\) hours). Excess NaN\(_3\) was quenched by slow addition of cold water until gas evolution ceased. The mixture was diluted with water and Et\(_2\)O, and the aqueous phase was washed twice with Et\(_2\)O. The combined ethereal phases were washed with brine (1x), dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The residue was purified by column chromatography (PE/Et\(_2\)O 1:0 \(\rightarrow\) 9:1) to furnish the title compound as an oil which solidified on standing, in 85% yield (0.87 g, 1.7 mmol). 1H NMR (400 MHz) \(\delta\): 7.57-7.47 (m, 2H, \(\text{CH}_{\text{arom}}\)); 7.45-7.22 (m, 13H, \(\text{CH}_{\text{arom}}\)); 5.93 (d, 1H, \(J = 5.2\) Hz, H-1); 4.92 (d, 1H, \(J = 11.2\) Hz, PhCH\(_2\)H); 4.80-4.73 (m, 2H, PhCH\(_2\)H); 4.61 (d, 1H, \(J = 11.6\) Hz, PhCH\(_2\)H); 4.35 (dd, 1H, \(J = 5.2\) Hz, 9.8 Hz, H-2); 4.22 (q, 1H, \(J = 6.4\) Hz, H-5); 3.75-3.72 (m, 2H, H-3, H-4); 1.13 (q, 3H, \(J = 6.4\) Hz, H-6). 13C-APT NMR (100 MHz) \(\delta\): 138.1, 137.4 (\(C_{\text{q,arom}}\)); 134.3, 129.0, 128.6, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6 (\(\text{CH}_{\text{arom}}\)); 85.5 (C-1); 80.6, 75.7 (C-3, C-4); 75.0, 72.5 (PhCH\(_2\)H); 69.4 (C-5); 60.9 (C-2); 16.5 (C-6). IR (neat) \(\nu\): 2882, 2112, 1474, 1298, 1101, 1063, 1047. HRMS: [M-N\(_2\)+H]\(^+\) calculated for \(\text{C}_{26}\text{H}_{28}\text{NO}_3\text{Se}\): 482.12289; found 482.12286.

**Phenyl 2-azido-3,4-di-O-benzoyl-2-deoxy-1-seleno-\(\alpha\)-L-fucopyranoside (2)**

![Structure 2](image)
To a stirred solution of 12 (0.66 g, 2.0 mmol, 1.0 eq.) in CH₂Cl₂/pyridine (3:1 v/v, 8 mL, 0.2 M) was slowly added BzCl (0.7 mL, 6.0 mmol, 3.0 eq.), followed by DMAP (0.05 g, 0.4 mmol, 0.2 eq.). The mixture was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~3 hours). The reaction was quenched with MeOH and the mixture was diluted with CH₂Cl₂, washed (1 M aq. HCl, 2x; sat. aq. NaHCO₃, 1x; brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. The residue was subjected to column chromatography (PE/EtOAc, 1:0 → 4:1) to furnish the title compound in 90% yield (0.96 g, 1.79 mmol). ¹H NMR (400 MHz) δ: 7.25-8.15 (m, 15H, CH₆arom), 6.12 (d, 1H, J = 5.2 Hz, H-1), 5.76 (d, 1H, J = 2.8 Hz, H-4), 5.51 (dd, 1H, J = 3.2 Hz, 10.8 Hz, H-3), 4.53 (dd, 1H, J = 5.6, 10.8 Hz, H-2), 4.73 (q, 1H, J = 6.4 Hz, H-5), 1.19 (d, 3H, J = 6.4 Hz, H-6); ¹³C-APT NMR (100 MHz) δ: 165.7, 165.4 (CO₂Ar), 134.9-127.2 (CH₆arom), 84.6 (C-1), 72.4 (C-3), 70.8 (C-4), 68.0 (C-5), 59.6 (C-2), 16.0 (C-6). IR (thin film) ν: 3061, 2984, 2108, 1724, 1651, 1587, 1468, 1388, 1256, 1157, 1117, 1082, 1060, 1024. HRMS: [M-N₂+H]⁺ calculated for C₂₅H₂₄NO₅Se: 510.08142; found 510.08194.

Phenyl 2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-1-seleno-α-L-fucopyranoside (5)

A 100 mL, three-necked flask was equipped with a septum, a gas inlet and a Liebig condenser fitted with a drying tube. Under a flow of N₂ gas, the flask was charged with a solution of 12 (1.31 g, 4.0 mmol, 1.0 eq.) in pyridine (20 mL, 0.2 M). At 0 °C, added was DMAP (98 mg, 0.8 mmol, 0.2 eq.) followed by TBSOTf (3.7 mL, 16.0 mmol, 4.0 eq., in a dropwise fashion). The mixture was heated to 70 °C and stirred for 16 hours, after which TLC analysis (PE/Et₂O, 19:1 v/v) showed complete conversion of the starting material. The reaction was cooled to rt, quenched with MeOH and the mixture diluted with EtOAc. The mixture was washed with 10% aq. CuSO₄ solution (2x), H₂O and brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 49:1 v/v) furnished the title compound as a light-yellow oil in 85% yield (3.4 mmol, 1.90 g). ¹H NMR (CD₂Cl₂, 193 K) δ: 7.53 (d, 2H, J = 7.6 Hz, CH₆arom); 7.27-7.25 (m, 3H, CH₆arom); 5.89 (d, 1H, J = 5.2 Hz, H-1); 4.21 (q, 1H, J = 6.4 Hz, H-5); 4.06 (dd, 1H, J = 4.8 Hz, 10.0 Hz, H-2); 3.70-3.67 (m, 2H, H-3, H-4); 1.06 (d, 3H, J = 6.0 Hz, H-6); 0.90, 0.82 (s, 9H, CH₃tBu); 0.14, 0.11, 0.09, 0.03 (s, 3H, CH₃Me). ¹³C-APT NMR (CD₂Cl₂, 193 K) δ: 134.3, 128.7 (CH₆arom); 128.0 (CH₃tBu); 127.4 (CH₆arom); 85.3 (C-1); 73.6, 72.9 (C-3, C-4); 69.5 (C-2); 61.6 (C-5); 25.5, 25.3 (CH₃tBu); 18.1, 17.8 (CH₃Me); 16.6 (C-6); -4.3, -4.7, -5.3, -5.3 (CH₃Me). IR (thin film) ν: 2953, 2930, 2856, 2106, 1472, 1252, 1115, 1067, 1022. HRMS: [M-N₂+H]⁺ calculated for C₂₅H₄ₐNO₅SeSi₂: 530.20195; found 530.20166.
Diol 12 (0.66 g, 2.0 mmol, 1.0 eq.) was suspended in toluene (7 mL, 0.3 M). Bu$_3$SnO (0.50 g, 2.0 mmol, 1.0 eq.) was added and the mixture was heated to 140 °C for 3 hours, during which a clear reaction mixture was obtained. The mixture was concentrated \textit{in vacuo} and co-evaporated once with dry toluene. The mixture was dissolved in DMF (9 mL, 0.2 M) and BnBr (0.26 mL, 2.2 mmol, 1.1 eq.) and CsF (0.33 g, 2.2 mmol, 1.1 eq.), and the mixture was stirred overnight, after which TLC analysis indicated conversion of the starting material (PE/EtOAc, 7:3 v/v). The reaction was diluted with H$_2$O, extracted (Et$_2$O, 3x), the combined ethereal phases were washed (brine, 1x), dried over MgSO$_4$, filtered and concentrated \textit{in vacuo}. The residue was passed over a small column (PE/EtOAc, 1:0 → 4:1 v/v) to obtain the 3-O-benzylated product (0.42 mmol, 1 mmol, 50%). $^1$H NMR (400 MHz) δ: 7.59-7.56 (m, 2H, $CH_{arom}$); 7.42-7.24 (m, 8H, $CH_{arom}$); 5.89 (d, 1H, $J$ = 5.2 Hz, H-1); 4.76 (d, 1H, $J$ = 11.2 Hz, PhCH$_2$H); 4.69 (d, 1H, $J$ = 11.2 Hz, PhCH$_2$); 4.30 (q, 1H, $J$ = 6.8 Hz, H-5); 4.17 (dd, 1H, $J$ = 5.2 Hz, 10.4 Hz, H-2); 3.88 (s, 1H, H-4); 3.70 (dd, 1H, $J$ = 3.2 Hz, 10.4 Hz, H-3); 2.36 (s, 1H, 3-OH); 1.26 (d, 3H, $J$ = 6.8 Hz, H-6). $^{13}$C-APT NMR (100 MHz, CDCl$_3$) δ: 137.1 ($C_{arom}$), 134.5, 129.2, 128.9, 128.5 ($CH_{arom}$), 128.2 ($C_{arom}$), 127.9 ($CH_{arom}$), 85.3 (C-1), 79.3 (C-3), 72.3 (CH$_2$ Bn), 68.7 (C-The intermediate was dissolved in CH$_2$Cl$_2$/pyridine (4:1 v/v, 5 mL, 0.2 M) and at 0 °C was added BzCl (0.14 mL, 1.2 mmol, 1.2 eq.) and DMAP (12 mg, 0.1 mmol, 0.1 eq.). After TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material (~1 hour), the mixture was quenched by the addition of water. The mixture was diluted with CH$_2$Cl$_2$ washed (1M aq. HCl, 2x; sat. aq. NaHCO$_3$ 1x; H$_2$O 1x; brine 1x), dried over MgSO$_4$ filtrated and concentrated under reduced pressure. Purification by column chromatography (PE/EtOAc, 17:3 v/v) afforded the title compound (0.49 g; 0.93 mmol; 47% over 2 steps). $^1$H NMR (400 MHz) δ: 8.09-8.04 (m, 4H, $CH_{arom}$), 7.64-7.20 (m, 11H, $CH_{arom}$), 6.00 (d, 1H, $J$ = 5.2 Hz, H-1), 5.71 (d, 1H, $J$ = 2.8 Hz, H-4), 4.85 (d, 1H, $J$ = 10.8 Hz, PhCH$_2$H), 4.57 (d, 1H, $J$ = 10.8 Hz, PhCH$_2$), 4.52 (q, 1H, $J$ = 6.4 Hz, H-5), 4.26 (dd, 1H, $J$ = 5.2 Hz, $J$ = 10.4 Hz, H-2), 3.90 (dd, 1H, $J$ = 3.2 Hz, $J$ = 10.0 Hz, H-3), 1.16 (d, 3H, $J$ = 6.4 Hz, H-6); $^{13}$C-APT NMR (100 MHz) δ: 166.0 (CO$_{arom}$), 136.9 ($C_{arom}$), 134.7-127.7 ($CH_{arom}$), 85.1 (C-1), 77.5 (C-3), 71.6 (PhCH$_2$), 69.4 (C-4), 68.1 (C-5), 60.5 (C-2), 16.2 (C-6). IR (thin film) ν: 3061, 2984, 2897, 2108, 1719, 1452, 1263, 1109, 1078, 1062, 1024. HRMS: [M-N$_2$+H]$^+$ calculated for C$_{26}$H$_{22}$NO$_3$Se: 496.10216; found 496.10233.
Phenyl 2-azido-4-O-benzyl-2-deoxy-3-O-(para-methoxybenzyl)-1-seleno-α-L-fucopyranoside (13)

In a three-necked flask, equipped with a Dean-Stark trap, a suspension of diol 12 (4.27 g, 13 mmol, 1.0 eq.) and Bu₂SnO (3.40 g, 13.7 mmol, 1.05 eq.) in toluene (65 mL, 0.2 M) was heated to 140 °C for 1 hour. The resultant clear, brown solution was cooled to 60 °C, and added were Bu₄NBr (4.42 g, 13.7 mmol, 1.05 eq.), CsF (2.08 g, 13.7 mmol, 1.05 eq.) and PMBCI (1.9 mL, 13.7 mmol, 1.05 eq.). The mixture was heated to 120 °C for ~2 hours, after which TLC analysis (PE/EtOAc, 3:2 v/v) indicated complete conversion of the starting diol. The mixture was cooled to room temperature, KF (10% in H₂O, w/v) was added and stirred vigorously for ~15 minutes. The aqueous phase was extracted (EtOAc, 2x), the combined organic fractions washed (brine 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 1:0 → 4:1) furnished the 3-O-PMB protected intermediate as a yellow oil in 81% yield (4.71 g, 10.5 mmol).

¹H NMR (400 MHz) δ: 7.58-7.56 (m, 2H, CH₃); 7.34-7.24 (m, 5H, CH₃); 6.93-6.87 (m, 2H, CH₃); 5.87 (d, 1H, J = 5.2 Hz, H-1); 4.68 (d, 1H, J = 10.8 Hz, PhCH₂); 4.62 (d, 1H, J = 10.8 Hz, PhCH₂); 4.28 (q, 1H, J = 6.4 Hz, H-5); 4.14 (dd, 1H, J = 5.2 Hz, 10.2 Hz, H-2); 3.83 (d, 1H, J = 2.4 Hz, H-4); 3.81 (s, 3H, OCH₃); 3.68 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-3); 1.25 (d, 3H, J = 6.4 Hz, H-6).

¹³C-APT NMR (100 MHz) δ: 159.6 (C₈arom); 134.4, 134.3, 129.7, 129.0 (CH₃); 129.0, 128.6 (C₈arom); 127.7, 114.0 (CH₃); 85.2 (C-1); 78.8 (C-3); 71.7 (PhCH₂); 68.5, 68.4 (C-4, C-5); 60.0 (C-2); 55.2 (OCH₃); 16.0 (C-6). IR (thin film) ν: 3441, 2987, 2106, 1612, 1512, 1246, 1088, 1063, 1031. HRMS: [M+H]+ calculated for C₂₀H₂₄N₃O₃Se: 450.09265; found 450.09232. A solution of the intermediate building block (1.56 g, 3.48 mmol, 1.0 eq.) and BnBr (0.83 mL, 6.96 mmol, 2.0 eq.) in DMF (12 mL, 0.3 M) was cooled to 0 °C. Added was NaH (60% dispersion in oil, 0.21 g, 5.22 mmol, 1.5 eq.) and the mixture was allowed to reach room temperature. After ~3 hours, TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material and the reaction was quenched by slow addition of water. After gas evolution had ceased, the mixture was partitioned between water and Et₂O. The aqueous phase was extracted (Et₂O, 2x), and the combined ethereal phases were washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 9:1) delivered the title product as a colorless oil (1.68 g, 3.12 mmol, 90%). ¹H NMR (400 MHz) δ: 7.57-7.56 (m, 2H, CH₃); 7.36-7.23 (m, 10H, CH₃); 6.92 (d, 2H, J = 8.8 Hz, CH₃); 5.91 (d, 1H, J = 5.2 Hz, H-1); 4.94 (d, 1H, J = 11.6 Hz, PhCH₂); 4.72-4.66 (m, 2H, PhCH₂); 4.60 (d, 1H, J = 11.6 Hz, PhCH₂); 4.32 (dd, 1H, J = 5.2 Hz, 10.2 Hz, H-2); 4.21 (q, 1H, J = 6.4 Hz, H-5); 3.82 (s, 3H, OCH₃); 3.73-3.68 (m, 2H, H-3, H-4). ¹³C-APT NMR (100 MHz) δ: 159.5, 138.2 (C₈arom); 134.3, 129.5, 129.0 (CH₃); 128.7 (C₈arom); 128.3,
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128.1, 127.7, 127.6, 114.0 (CH_arom); 85.6 (C-1); 80.3, 75.8 (C-3, C-4); 74.9, 72.2 (PhCH_2); 69.4 (C-5); 60.8 (C-2); 55.3 (OCH_3); 16.5 (C-6). IR (thin film) ν: 2868, 2104, 1612, 1512, 1246, 1099, 1063, 1034. HRMS: [M+H]^+ calculated for C_{26}H_{30}N_5O_4Se 540.13960; found 540.13940.

*Phenyl 2-azido-4-O-benzyl-2-deoxy-1-seleno-α-L-fucopyranoside (14)*

To a stirred solution of 13 (1.56 g, 2.9 mmol, 1.0 eq.) and Et_3SiH (0.73 mL, 8.7 mmol, 3.0 eq.) in CH_2Cl_2 (15 mL, 0.2 M) was added a solution of HCl (0.25 mL of an 37%, w/v in water) in HFIP (15 mL). After 1 minute, the mixture was poured in a solution of NaHCO_3 (sat., aq.). After separation of the layers, the aqueous phase was extracted (CH_2Cl_2, 1x), the combined organic phases were washed (brine, 1x), dried over MgSO_4, filtered and concentrated in vacuo. After column chromatography (toluene/EtOAc, 1:0 → 9:1), the title compound was obtained as an oil, in 64% yield (0.78 g, 1.9 mmol). ^1H NMR (400 MHz) δ: 7.58-7.56 (m, 2H, CH_arom); 7.38-7.25 (m, 8H, CH_arom); 5.91 (d, 1H, J = 5.2 Hz, H-1); 4.81 (d, 1H, J = 11.6 Hz, PhCHH); 4.72 (d, 1H, J = 11.6 Hz, PhCHH); 4.33 (q, 1H, J = 6.4 Hz, H-5); 4.02 (dd, 1H, J = 5.2 Hz, 10.2 Hz, H-2); 3.85-3.79 (m, 1H, H-3); 3.69 (d, 1H, J = 2.8 Hz, H-4); 2.26 (d, 1H, J = 8.8 Hz, 3-OH); 1.25 (d, 3H, J = 6.8 Hz, H-6). ^13C-APT NMR (100 MHz) δ: 137.7 (C_qarom); 134.3, 129.1, 128.7, 128.2, 128.1, 127.7 (CH_arom); 85.2 (C-1); 79.3 (C-4); 71.9 (C-3); 69.3 (C-5); 62.5 (C-2); 16.6 (C-6). IR (thin film) ν: 3468, 2882, 2106, 1263, 1094, 1057, 1022. HRMS: [M -N_2+H]^+ calculated for C_{19}H_{22}NO_3: 392.07594; found 392.07593.

*Phenyl 2-azido-3-O-benzyl-4-O-benzyl-2-deoxy-1-seleno-α-L-fucopyranoside (4)*

To a stirred solution of 14 (0.21 g, 0.5 mmol, 1.0 eq.) in CH_2Cl_2/pyridine (1.6 mL, 0.3 M, 1:1 v/v) were added BzCl (0.12 mL, 1.0 mmol, 2 eq.) and DMAP (6 mg, 0.05 mmol, 0.1 eq.) at 0 ºC. After TLC analysis indicated complete conversion of the starting material (typically, the reaction mixture was left overnight), the reaction was quenched by addition of MeOH. The mixture was diluted with CH_2Cl_2, washed with CuSO_45H_2O (in H_2O, 10% w/v, 2x), water (1x) and brine (1x), dried over MgSO_4, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtO, 1:0 → 9:1) furnished the title compound in 96% yield (0.25 g, 0.48 mmol). ^1H NMR (400 MHz)
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

\[ \delta: 8.09 \ (d, \ 2H, J = 7.6 \text{ Hz}, CH_{arom}); \ 7.63-7.58 \ (m, \ 3H, CH_{arom}); \ 7.48 \ (t, \ 2H, J = 7.6 \text{ Hz}, CH_{arom}); \ 7.41-7.23 \ (m, \ 8H, CH_{arom}); \ 6.01 \ (d, \ 1H, J= 5.2 \text{ Hz}, H-1); \ 5.29 \ (dd, \ 1H, J= 2.8 \text{ Hz}, 11.0 \text{ Hz}, H-3); \ 4.67 \ (d, \ 1H, J = 11.2 \text{ Hz}, PhCHH); \ 4.58 \ (dd, \ 1H, J = 5.2 \text{ Hz}, 11.2 \text{ Hz}, H-2); \ 4.53 \ (d, \ 1H, J = 11.6 \text{ Hz}, PhCHH); \ 4.43 \ (q, \ 1H, J = 6.4 \text{ Hz}, H-5); \ 4.01 \ (d, \ 1H, J = 2.0 \text{ Hz}, H-4); \ 1.17 \ (d, \ 3H, J = 6.4 \text{ Hz}, H-6). \]

\[^{13}\text{C}-\text{APT NMR (100 MHz)} \delta: \ 165.7 \ (CO_{\text{Bz}}); \ 137.4 \ (C_{\text{q,arom}}); \ 134.5, \ 133.7, \ 129.9, \ 129.1 \ (CH_{arom}); \ 129.0 \ (C_{\text{q,arom}}); \ 128.6 \ (CH_{arom}); \ 128.4 \ (C_{\text{q,arom}}); \ 128.3, \ 128.1, \ 127.9, \ 127.8 \ (CH_{arom}); \ 84.9 \ (C-1); \ 76.6 \ (C-4); \ 75.6 \ (PhCH_{2}); \ 75.1 \ (C-3); \ 69.1 \ (C-5); \ 59.6 \ (C-2); \ 16.3 \ (C-6). \]

IR (thin film) \(\nu: 2936, 2108, 1722, 1472, 1260, 1111, 1080, \)

Phenyl 2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-1-seleno-\(\alpha\)-L-fucopyranoside (6)

\[ \begin{array}{c}
\text{SePh} \\
\text{BuO-} \text{OTBS} \\
\end{array} \]

A 50 mL three-necked flask was equipped with a septum, a gas inlet and a Liebig condenser fitted with a drying tube. Under a flow of \(\text{N}_2\) gas, the flask was charged with a solution of 14 (0.63 g, 1.5 mmol, 1.0 eq.) in pyridine (7.5 mL, 0.2 M). At 0 °C, added was DMAP (4 mg, 0.3 mmol, 0.2 eq.) followed by TBSOTf (0.69 mL, 3.0 mmol, 2.0 eq., in a dropwise fashion). The mixture was heated to 70 °C and stirred for 16 hours, after which TLC analysis (PE/Et₂O, 19:1 v/v) showed complete conversion of the starting material. The reaction was cooled to rT, quenched with MeOH and the mixture diluted with EtOAc. The mixture was washed with 10% aq. CuSO₄ solution (2x), H₂O and brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 19:1 v/v) furnished the title compound as a light-yellow oil in 92% yield (0.73 g, 1.38 mmol). \(^1\text{H} \text{ NMR (400 MHz)} \delta: 7.57-7.55 \ (m, \ 2H, CH_{arom}); \ 7.39-7.26 \ (m, \ 8H, CH_{arom}); \ 5.96 \ (d, \ 1H, J = 4.8 \text{ Hz}, H-1); \ 5.06 \ (d, \ 1H, J = 11.2 \text{ Hz}, PhCHH); \ 4.59 \ (d, \ 1H, J = 11.2 \text{ Hz}, PhCHH); \ 4.27 \ (q, \ 1H, J = 6.4 \text{ Hz}, H-5); \ 4.22 \ (dd, \ 1H, J = 5.2 \text{ Hz}, 10.0 \text{ Hz}, H-2); \ 3.88 \ (dd, \ 1H, J = 2.4 \text{ Hz}, 10.0 \text{ Hz}, H-3); \ 3.53 \ (bs, \ 1H, H-4); \ 1.15 \ (d, \ 3H, J = 6.4 \text{ Hz}, H-6); \ 0.99 \ (s, \ 9H, (CH₃)₃CSi); \ 0.25, \ 0.22 \ (s, \ 3H, CH₂Si). \(^{13}\text{C} \text{ NMR (100 MHz)} \delta: 138.5 \ (C_{\text{q,arom}}); \ 134.3, \ 129.0, \ 128.3, \ 127.8, \ 127.7, \ 127.6 \ (CH_{arom}); \ 85.6 \ (C-1); \ 80.1 \ (C-4); \ 75.6 \ (PhCH₂); \ 74.2 \ (C-3); \ 69.4 \ (C-5); \ 62.9 \ (C-2); \ 26.0 \ (CH₂Si); \ 16.5 \ (C-6). \]

IR (thin film) \(\nu: 2953, 2930, 2886, 2857, 2106, 1472, 1260, 1111, 1080, \)

HRMS: [M+Na]⁺ calculated for C₂₅H₂₅N₃O₅SeNa: 546.09025; found 546.09021.
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*General procedure for generation of glycosyl triflates and oxosulfonyl triflates*

![Chemical reaction diagram](attachment:image.png)

A mixture of glycosyl donor (0.038 mmol, 1.0 eq.) and Ph₂SO (10 mg, 0.049 mmol, 1.3 eq.; 15 mg, 0.076 mmol, 2.0 eq.; or 31 mg, 0.152 mmol, 4.0 eq.) were dried by co-evaporation with toluene (3x), followed by three vacuum/argon purges. The mixture was dissolved in CD₂Cl₂ (0.75 mL, 0.05 M) and transferred to a dry-NMR tube, which was subsequently capped with a septum. The tube was placed in the probe of a NMR magnet and cooled to -80 °C, after which a ¹H NMR spectrum was recorded. The tube was removed from the magnet and placed in an acetone/N₂ (l) bath (temperature ≤ -80 °C). Tf₂O (8 μL, 0.049 mmol, 1.3 eq.) was added with a microliter syringe and, after rapid mixing and re-cooling, the tube was placed back in the NMR instrument. A ¹H NMR spectrum was recorded, which revealed the formation of reactive intermediate(s). After further characterization (¹³C-APT NMR, HH-COSY and HSQC) the temperature of the sample was increased by increments of 10 °C until decomposition of the intermediate(s) was observed.

*General procedure for glycosylations of 2-azido-2-deoxy-L-fucosyl donors by pre-activation.*

![Chemical reaction diagram](attachment:image.png)

To a mixture of donor (0.1 mmol, 1.0 eq.), Ph₂SO (26 mg, 0.13 mmol, 1.3 eq.) and TTBP (62 mg, 0.25 mmol, 2.5 eq.) in dry CH₂Cl₂ (2 mL, 0.05 M) were added flame-dried 3Å molecular sieves. The mixture was subsequently stirred for 30 minutes before being cooled to -80 °C. At this temperature, Tf₂O (22 μL, 0.13 mmol, 1.3 eq.) was added via syringe, and the temperature was raised to -60 °C over the course of ~30 minutes. After re-cooling to -80 °C, the acceptor (0.2 mmol, 2.0 eq., 0.4 mL of a 0.5 M stock solution in CH₂Cl₂) was added at -80 °C and the reaction mixture was allowed to warm to -40 °C, after which the reaction was quenched by addition of NEt₃ (0.1 mL) and subsequently diluted with CH₂Cl₂. The mixture was filtered through a small bed of celite, the residue washed with CH₂Cl₂ and the filtrate was washed once with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by ordinary column chromatography and/or size-exclusion chromatography afforded the corresponding O-glycoside(s).
**Ethyl 2-azido-3,4-di-O-benzyl-2-deoxy-α/β-L-fucopyranoside (A1)**

![Structure of A1](image)

The title compounds (α/β 1:1) were obtained after column chromatography (hexane/EtOAc, 1:0 → 4:1 v/v), in 39% yield (25 mg, 0.059 mmol). 1H NMR (400 MHz) δ: 8.09-8.03 (m, 10H, CH<sub>arom</sub>); 7.89-7.86 (m, 9H, CH<sub>arom</sub>); 7.64-7.59 (m, 6H, CH<sub>arom</sub>); 7.53-7.46 (m, 17H, CH<sub>arom</sub>); 7.35-7.31 (m, 10H, CH<sub>arom</sub>); 5.78 (dd, 1H, J = 3.2 Hz, 10.8 Hz, H-3α); 5.71 (dd, 1H, J = 1.2 Hz, 3.2 Hz, H-4α); 5.59 (dd, 4H, J = 0.8 Hz, 3.2 Hz, H-4β); 5.17 (dd, 4H, J = 3.6 Hz, 10.8 Hz, H-3β); 5.13 (d, 1H, J = 3.6 Hz, H-1α); 4.51 (d, 4H, J = 8.0 Hz, H-1β); 4.37 (q, 1H, J = 6.4 Hz, H-5α); 4.10 (dq, 4H, J = 7.2 Hz, 9.6 Hz, CH<sub>HCH3</sub>β); 3.98-3.90 (m, 8H, H-2β, H-5β); 3.88-3.84 (m, 2H, H-2α, CHHCH<sub>3</sub>α); 3.76-3.63 (m, 6H, CHHCH<sub>3</sub>α, CHHCH<sub>3</sub>β); 1.37-1.21 (m, 30H, H-6α, H-6β, CH<sub>2</sub>CH<sub>3</sub>α, CH<sub>2</sub>CH<sub>3</sub>β). 13C-APT NMR (100 MHz) δ: 165.8, 165.8, 165.4 (CO<sub>benz</sub>); 133.4, 133.4, 133.3, 133.2, 129.9, 129.7 (CH<sub>arom</sub>); 129.2, 129.1 (C<sub>qarom</sub>); 128.5, 128.5, 128.3, 128.3 (CH<sub>arom</sub>); 102.2 (C-1β); 98.1 (C-1α); 72.0 (C-3β); 71.4 (C-3α); 70.3 (C-4β); 69.5 (C-5β); 69.3 (C-3α); 66.2 (CH<sub>2</sub>CH<sub>3</sub>β); 65.1 (C-5α); 64.3 (CH<sub>2</sub>CH<sub>3</sub>α); 61.2 (C-2β); 57.9 (C-2α); 16.3 (C-6β); 16.1 (C-6α); 15.1 (CH<sub>2</sub>CH<sub>3</sub>β); 15.0 (CH<sub>2</sub>CH<sub>3</sub>α). IR (thin film) ν: 1980,

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**Ethyl 2-azido-3,4-di-O-benzoyl-2-deoxy-α/β-L-fucopyranoside (A2)**

![Structure of A2](image)

The title compounds (α/β 1:4) were obtained after column chromatography (hexane/EtOAc, 1:0 → 4:1 v/v), in 39% yield (25 mg, 0.059 mmol). 1H NMR (400 MHz) δ: 8.09-8.03 (m, 10H, CH<sub>arom</sub>); 7.89-7.86 (m, 9H, CH<sub>arom</sub>); 7.64-7.59 (m, 6H, CH<sub>arom</sub>); 7.53-7.46 (m, 17H, CH<sub>arom</sub>); 7.35-7.31 (m, 10H, CH<sub>arom</sub>); 5.78 (dd, 1H, J = 3.2 Hz, 10.8 Hz, H-3α); 5.71 (dd, 1H, J = 1.2 Hz, 3.2 Hz, H-4α); 5.59 (dd, 4H, J = 0.8 Hz, 3.2 Hz, H-4β); 5.17 (dd, 4H, J = 3.6 Hz, 10.8 Hz, H-3β); 5.13 (d, 1H, J = 3.6 Hz, H-1α); 4.51 (d, 4H, J = 8.0 Hz, H-1β); 4.37 (q, 1H, J = 6.4 Hz, H-5α); 4.10 (dq, 4H, J = 7.2 Hz, 9.6 Hz, CHHCH<sub>3</sub>β); 3.98-3.90 (m, 8H, H-2β, H-5β); 3.88-3.84 (m, 2H, H-2α, CHHCH<sub>3</sub>α); 3.76-3.63 (m, 6H, CHHCH<sub>3</sub>α, CHHCH<sub>3</sub>β); 1.37-1.21 (m, 30H, H-6α, H-6β, CH<sub>2</sub>CH<sub>3</sub>α, CH<sub>2</sub>CH<sub>3</sub>β). 13C-APT NMR (100 MHz) δ: 165.8, 165.8, 165.4 (CO<sub>benz</sub>); 133.4, 133.4, 133.3, 133.2, 129.9, 129.7 (CH<sub>arom</sub>); 129.2, 129.1 (C<sub>qarom</sub>); 128.5, 128.5, 128.3, 128.3 (CH<sub>arom</sub>); 102.2 (C-1β); 98.1 (C-1α); 72.0 (C-3β); 71.4 (C-3α); 70.3 (C-4β); 69.5 (C-5β); 69.3 (C-3α); 66.2 (CH<sub>2</sub>CH<sub>3</sub>β); 65.1 (C-5α); 64.3 (CH<sub>2</sub>CH<sub>3</sub>α); 61.2 (C-2β); 57.9 (C-2α); 16.3 (C-6β); 16.1 (C-6α); 15.1 (CH<sub>2</sub>CH<sub>3</sub>β); 15.0 (CH<sub>2</sub>CH<sub>3</sub>α). IR (thin film) ν: 1980,
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2927, 2110, 1724, 1450, 1261, 1175, 1109, 1094, 1067, 1026. HRMS: [M+Na]+ calculated for C_{22}H_{23}N_{3}O_{5}Na: 448.14791; found 448.14784.

Ethyl 2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-α/β-L-fucopyranoside (A3)

The title compounds (α/β 1:3) were obtained after column chromatography (hexane/Et_{2}O, 1:0 → 4:1 v/v) in 61% yield (25 mg, 0.061 mmol). {^1}H NMR (400 MHz) δ: 8.15-8.07 (m, 8H, CH_{arom}); 7.60-7.56 (m, 4H, CH_{arom}); 7.48-7.44 (m, 8H, CH_{arom}); 7.36-7.24 (m, 20H, CH_{arom}); 5.68 (d, 1H, J = 2.4 Hz, H-4α); 5.54 (dd, 3H, J = 0.8 Hz, 3.2 Hz, H-4β); 4.98 (d, 1H, J = 3.6 Hz, H-1α); 4.83 (d, 1H, J = 10.8 Hz, PhCH\(\alpha\)α); 4.79 (d, 3H, J = 11.6 Hz, PhCH\(\alpha\)β); 4.56-4.53 (m, 4H, PhCH\(\alpha\)α, PhCH\(\alpha\)β); 4.28 (d, 4H, J = 8.0 Hz, H-1β); 4.18 (q, 1H, J = 6.8 Hz, H-5α); 4.11 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-3α); 4.06-3.99 (m, 3H, CH\(\alpha\)CH\(\beta\)β); 3.78-3.60 (m, 11H, H-2α, H-2β, H-5β, CH\(\alpha\)CH\(\beta\)α, CH\(\alpha\)CH\(\beta\)β); 3.45 (dd, 3H, J = 3.2 Hz, 10.4 Hz, H-3β); 1.59-1.26 (m, 21H, H-6β, CH\(\alpha\)CH\(\beta\)α, CH\(\alpha\)CH\(\beta\)β); 1.22 (d, 3H, J = 6.8 Hz, H-6α). {^{13}}C-APT NMR (100 MHz) δ: 166.2 (\(\delta\)O\(\beta\)); 137.2, 137.1 (C\(\delta\)arom); 133.3, 133.2, 130.0, 129.8 (CH\(\alpha\)arom); 129.4 (C\(\gamma\)arom); 128.5, 128.4, 128.4, 128.4, 128.2, 128.4, 1f27.9, 127.8 (CH\(\alpha\)arom); 102.0 (C-1β); 97.9 (C-1α); 77.6 (C-3β); 74.4 (C-3α); 71.5 (PhCH\(\beta\)β); 71.5 (PhCH\(\alpha\)α); 70.0 (C-4α); 69.5 (C-5β); 68.9 (C-4β); 65.9 (CH\(\alpha\)CH\(\beta\)β); 65.1 (C-5α); 64.0 (CH\(\alpha\)CH\(\beta\)α); 62.6 (C-2β); 59.3 (C-2α); 16.5 (C-6β); 16.3 (C-6α); 15.1 (CH\(\alpha\)CH\(\beta\)β); 15.0 (CH\(\alpha\)CH\(\beta\)α). IR (thin film) ν: 2980, 2870, 2108, 1721, 1452.

Ethyl 2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-α/β-L-fucopyranoside (A4)

The title compounds (α/β 2:5) were obtained after column chromatography (hexane/Et_{2}O 1:0 → 9:1), in 58% yield (24 mg, 0.058 mmol). {^1}H NMR (400 MHz) δ: 8.10-8.06 (m, 14H, CH_{arom}); 7.62-7.58 (m, 7H, CH_{arom}); 7.49-7.45 (m, 14H, CH_{arom}); 7.26-7.19 (m, 35H, CH_{arom}); 5.57 (dd, 2H, J = 3.0 Hz, 11.0 Hz, H-3α); 5.00 (d, 2H, J = 3.6 Hz, H-1α); 4.95 (dd, 5H, J = 3.0 Hz, 11.0 Hz, H-3β); 4.72-4.68 (m, 7H, PhCH\(\alpha\)α, PhCH\(\beta\)β); 4.57-4.52 (m, 7H, PhCH\(\alpha\)α, PhCH\(\beta\)β); 4.37 (d, 5H, J = 8.0 Hz, H-1β); 4.11 (q, 2H, J = 6.8 Hz, H-5α); 4.05-3.94 (m, 14H, H-2α, H-2β, H-4α, CH\(\alpha\)CH\(\beta\)β); 3.82-3.74 (m,
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

7H, H-4β, C\(\text{HCH}_3\alpha\); 3.68-3.56 (m, 12H, H-5β, CH\(\text{HCH}_3\alpha\), CH\(\text{HCH}_3\beta\); 1.31-1.20 (m, 42H, H-6α, H-6β, CH\(\text{C}_2\text{H}_3\alpha\), CH\(\text{C}_2\text{H}_3\beta\)). \(^{13}\text{C}\)-APT NMR (100 MHz) \(δ\): 165.9 (CO Bz); 137.6, 137.5 (C\(_{\text{arom}}\)); 133.5, 133.5, 129.9 (CH\(_{\text{arom}}\)); 129.2 (C\(_{\text{arom}}\)); 128.5, 128.3, 128.2, 128.1, 127.8, 127.8, 127.6 (CH\(_{\text{arom}}\)); 101.9 (C-1β); 98.0 (C-1α); 77.4 (C-4α); 76.0 (C-4β); 75.5 (PhCH\(_3\alpha\)); 75.4 (PhCH\(_3\beta\)); 75.0 (C-3β); 72.3 (C-3α); 70.5 (C-5β); 66.2 (CH\(_2\)CH\(_3\beta\)); 63.9 (CH\(_2\)CH\(_3\alpha\)); 61.2 (C-2β); 58.0 (C-2α); 16.6, 16.4, 15.0, 15.0 (CH\(_2\)CH\(_3\), C-6α, C-6β). IR (thin film) \(ν\): 2978, 2932, 2108, 1721, 1452, 1265, 1175, 1094, 1069, 1026. HRMS: [M+NH\(_4\)]\(^+\) calculated for C\(_{22}\)H\(_{29}\)N\(_4\)O\(_5\): 429.21325; found 429.21340.

*Ethyl 2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-α/β-l-fucopyranoside (A5)*

![Structure](image)

The title compounds (α/β 2:5) were obtained after column chromatography (hexane/Et\(_2\)O, 1:0 → 19:1), along with a minor amount of inseparable, hydrolyzed donor, in 63% yield (28 mg, 0.063 mmol). \(^1\text{H}\) NMR (400 MHz) \(δ\): 4.91 (d, 2H, \(J = 3.6\) Hz, H-1α); 4.19 (d, 5H, \(J = 8.0\) Hz, H-1β); 4.01-3.95 (m, 7H, H-3α, OCH\(_2\)CH\(_3\)β); 3.88 (q, 2H, \(J = 6.4\) Hz, H-5α); 3.73-3.70 (m, 6H, H-2α, H-4α, OCH\(_2\)CH\(_3\)α); 3.62-3.52 (m, 17H, H-2β, H-4β, OCH\(_2\)CH\(_3\)α, OCH\(_2\)CH\(_3\)β); 3.45 (q, 5H, \(J = 6.4\) Hz, H-5β); 3.35 (dd, 5H, \(J = 2.4\) Hz, 10.4 Hz, H-3β); 1.29-1.18 (m, 42H, H-6α, H-6β, CH\(_2\)CH\(_3\)α, CH\(_2\)CH\(_3\)β); 0.96-0.93 (m, 126H, (CH\(_3\))\(_3\)Siα, (CH\(_3\))\(_3\)Siβ); 0.19-0.09 (m, 84H, CH\(_3\)Siα, CH\(_3\)Siβ). \(^{13}\text{C}\)-APT NMR (100 MHz) \(δ\): 102.5 (C-1β); 97.7 (C-1α); 75.2 (C-4α); 74.5 (C-3β); 74.0 (C-4β); 71.3 (C-3α); 71.2 (C-5β); 67.7 (C-5α); 65.5 (OCH\(_2\)CH\(_3\)β); 63.8 (C-2β); 63.4 (OCH\(_2\)CH\(_3\)α); 61.1 (C-2α); 26.3, 26.2, 26.1 ((CH\(_3\))\(_3\)Si); 18.6, 18.5 (C\(_3\)Si); 17.6, 17.3 (OCH\(_2\)CH\(_3\)); 15.1, 15.0 (C-6α, C-6β); -3.5, -3.6, -4.2, -4.4 (CH\(_3\)Si). IR (thin film) \(ν\): 2928, 2857, 2112, 1252, 1069. HRMS: [M+NH\(_4\)]\(^+\) calculated for C\(_{28}\)H\(_{47}\)N\(_4\)O\(_5\)Si\(_2\): 463.31304; found 463.31293.

*Ethyl 2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-α/β-l-fucopyranoside (A6)*

![Structure](image)

The title products (α/β 1:1) were obtained after column chromatography (hexane/Et\(_2\)O, 1:0 → 19:1 v/v) in 81% yield (34 mg, 0.081 mmol). \(^1\text{H}\) NMR (400 MHz) \(δ\): 7.39-7.26 (m, 10H, CH\(_{\text{arom}}\)); 5.05-5.02 (m, 2H, PhCH\(_3\)α, PhCH\(_3\)β); 4.91 (d, 1H, \(J = 3.6\) Hz, H-1α); 4.61-4.56 (m, 2H, PhCH\(_3\)α, PhCH\(_3\)β); 4.19 (d, 1H, \(J = 8.0\) Hz, H-1β); 4.12 (dd, 1H, \(J = 2.8\) Hz, 10.0 Hz, H-3α); 3.98-3.93 (m, 2H, 61
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H-5α, OCH$_2$CH$_3$); 3.74-3.50 (m, 8H, H-2α, H-2β, H-3β, H-4α, H-5β, OCH$_2$CH$_3$, 2x OCH HCH$_3$); 3.37 (d, 1H, $J = 2.4$ Hz, H-4β); 1.27-1.19 (m, 12H, H-6α, H-6β, OCH$_2$CH$_3$α, OCH$_2$CH$_3$β); 0.98, 0.96 (s, 9H, (CH$_3$)$_3$C$i$); 0.24 (s, 3H, CH$_3$i); 0.18 (m, 6H, CH$_3$i); 0.15 (s, 3H, CH$_3$i). $^{13}$C-APT NMR (100 MHz) δ: 138.6, 138.6 (C$_{q\text{arom}}$); 128.3, 128.1, 128.1, 127.9, 127.6, 127.5 (CH$_{arom}$); 102.1 (C-1β); 97.8 (C-1α); 80.9 (C-4α), 79.2 (C-4β); 75.6, 75.3 (PhCH$_2$); 74.9 (C-3β or C-5β); 71.5 (C-3α); 70.3 (C-3β or C-5β); 66.5 (C-5α); 65.4 (OCH$_2$CH$_3$); 64.6 (C-2β); 63.6 (OCH$_2$CH$_3$); 61.5 (C-2α); 25.9, 25.9 ((CH$_3$)$_3$C$i$); 18.2, 18.1 (C$i$); 16.8, 16.7 (C-6α, C-6β); 15.1, 15.0 (OCH$_2$CH$_3$α, OCH$_2$CH$_3$β); -4.0, -4.3, -4.7, -5.0 (CH$_3$i). IR (thin film) ν: 2930, 2876, 1726, 1358, 1109, 1062, 1047. HRMS: [M+NH$_4$]$^+$ calculated for C$_{22}$H$_{39}$N$_4$O$_4$Si: 439.27351; found 439.27319

2-fluoroethyl 2-azido-3,4-di-O-benzyl-2-deoxy-α/β-L-fucopyranoside (B1)

The title products (α/β 1:1) were obtained after column chromatography (hexane/EtOAc, 1:0 → 4:1), in 72% yield (30 mg, 0.072 mmol). $^1$H NMR (400 MHz) δ: 7.66-7.63 (m, 2H, CH$_{arom}$); 7.46-7.25 (m, 18H, CH$_{arom}$); 4.95-4.91 (m, 3H, H-1α, 2x PhCH$i$); 4.74-4.50 (m, CH$_3$Fα, CH$_3$Fβ, 2x PhCH$i$); 4x PhCH$_2$H); 4.26 (d, 1H, $J = 8.0$ Hz, H-1β); 4.02-3.73 (m, 9H, H-2α, H-2β, H-3α; H-4α, H-5α, CH$_2$CH$_2$Fα, CH$_2$CH$_2$Fβ); 3.54 (d, 1H, $J = 2.4$ Hz, H-4β); 3.42 (q, 1H, $J = 6.4$ Hz, H-5β); 3.31 (dd, 1H, $J = 2.8$ Hz, 10.4 Hz, H-3β); 1.20-1.17 (m, 6H, H-6α, H-6β). $^{13}$C-APT NMR (100 MHz) δ: 138.2, 137.6 (C$_{q\text{arom}}$); 131.0, 129.9, 128.5, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 124.7 (CH$_{arom}$); 102.3 (C-1β); 98.4 (C-1α); 82.7 (d, $J = 168$ Hz, CH$_2$F); 82.5 (d, $J = 168$ Hz, CH$_2$F); 80.9 (C-3β); 77.8 (C-3α); 76.1 (C-4α); 74.9 (PhCH$_2$); 74.8 (C-4β); 72.7, 72.4 (PhCH$_2$); 70.6 (C-5β); 68.3 (d, 20 Hz, CH$_2$CH$_2$F) 67.1 (d, 20 Hz, CH$_2$CH$_2$F); 66.7 (C-5α); 62.9 (C-2β); 59.5 (C-2α); 16.8, 16.7 (C-6α, C-6β). IR (thin film) ν: 2876, 2108, 1726, 1358, 1109, 1062, 1045. HRMS: [M+NH$_4$]$^+$ calculated for C$_{22}$H$_{30}$F$_2$N$_4$O$_4$: 433.2.2456; found 433.2.2418.

2-fluoroethyl 2-azido-3,4-di-O-benzyl-2-deoxy-α/β-L-fucopyranoside (B2)

The title compounds (α/β 1:2) were obtained after column chromatography (hexane/EtOAc, 1:0 → 4:1) in 34% yield (15 mg, 0.034 mmol). $^1$H NMR (400 MHz) δ: 8.08-8.03 (m, 6H, CH$_{arom}$); 7.89-
7.86 (m, 6H, $CH_{arom}$); 7.63-7.60 (m, 3H, $CH_{arom}$); 7.53-7.46 (m, 9H, $CH_{arom}$); 7.35-7.31 (m, 6H, $CH_{arom}$); 5.78 (dd, 1H, $J = 3.2$ Hz, H-3α); 5.72 (d, 1H, $J = 3.2$ Hz, H-4α); 5.59 (d, 2H, $J = 3.2$ Hz, H-4β); 5.19-5.16 (m, 3H, H-1α, H-3β); 4.77-4.60 (m, 6H, $CH_2Fα$, $CH_2Fβ$, H-1β); 4.58 (d, 2H, $J = 8.4$ Hz, H-1β); 4.42 (q, 1H, $J = 6.8$ Hz, H-5α); 4.25-3.89 (m, 11H, H-2α, H-2β, H-5β, $CH_2CH_2Fα$, $CH_2CH_2Fβ$); 1.31 (d, 6H, $J = 6.4$ Hz, H-6β); 1.25 (d, 3H, $J = 6.4$ Hz, H-6α). $^{13}$C-APT NMR (100 MHz) δ: 165.8, 165.4 ($CO_Bz$); 133.5, 133.4, 133.3, 133.3, 129.9, 129.8 ($CH_{arom}$); 129.3, 129.2, 129.0 ($C_{α/β}$); 128.6, 128.3 ($CH_{arom}$); 102.5 (C-1β); 98.6 (C-1α); 82.6 (d, $J = 169$ Hz, $CH_2CH_2Fβ$); 82.4 (d, $J = 170$ Hz, $CH_2CH_2Fα$); 72.0 (C-3β); 71.3 (C-4α); 70.2 (C-4β); 69.7 (C-5β); 69.2 (C-3α); 69.1 (d, $J = 21$ Hz, $CH_2CH_2Fβ$); 67.5 (d, $J = 20$ Hz, $CH_2CH_2Fα$); 65.4 (C-5α); 61.3 (C-2β); 58.0 (C-2α); 16.3 (C-6β); 16.1 (C-6α). IR (thin film) ν: 2984, 2924, 2110, 1721, 1450, 1260, 1169, 1107, 1094, 1067, 1026. HRMS: [M+Na]$^+$ calculated for $C_{22}H_{22}FNO_3Na$: 466.13848; found 466.13840.

2-fluoroethyl 2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-α/β-l-fucopyranoside (B3)

The products ($α/β$ 1:1) were obtained after column chromatography (hexane/EtOAc, 1:0 → 9:1) and size-exclusion chromatography ($CH_2Cl_2$/MeOH, 1:1 v/v) in 56% yield (24 mg, 0.056 mmol), accompanied by a small amount of inseparable, hydrolyzed donor. $^1$H NMR (400 MHz) δ: 8.14-8.07 (m, 4H, $CH_{arom}$); 7.60-7.56 (m, 2H, $CH_{arom}$); 7.49-4.44 (m, 4H, $CH_{arom}$); 7.35-7.25 (m, 10H, $CH_{arom}$); 5.70 (d, 1H, $J = 2.8$ Hz, H-4α); 5.55 (d, 1H, $J = 3.2$ Hz, H-4β); 5.02 (d, 1H, $J = 3.6$ Hz, H-1α); 4.85-4.53 (m, 8H, $CH_2Fα$, $CH_2Fβ$, Ph$CH_2α$, Ph$CH_2β$); 4.36 (d, 1H, $J = 8.0$ Hz, H-1β); 4.24 (q, 1H, $J = 6.4$ Hz, H-5α); 4.15-3.71 (m, 8H, H-2α, H-2β, H-3α, H-5β, $CH_2CH_2Fα$, $CH_2CH_2Fβ$); 3.47 (dd, 1H, $J = 3.2$ Hz, 10.2 Hz, H-3β); 1.28-1.21 (m, 6H, H-6α, H-6β). $^{13}$C-APT NMR (100 MHz) δ: 166.2, 166.1 ($CO_Bz$); 137.1, 137.0 ($C_{α/β}$); 133.4, 133.3, 130.2, 130.0, 129.8, 129.6 ($CH_{arom}$); 129.4 ($C_{α/β}$); 128.5, 128.4, 128.2, 128.0, 127.9, 127.8 ($CH_{arom}$); 102.3 (C-1β); 98.4 (C-1α); 82.7 (d, $J = 169$ Hz, $CH_2Fβ$); 82.5 (d, $J = 170$ Hz, $CH_2Fα$); 77.5 (C-3β); 74.3 (C-3α); 71.6 ($PhCH_2β$); 71.5 ($PhCH_2α$); 69.8 (C-4α); 69.6 (C-5β); 68.8 (d, $J = 20$ Hz, $CH_2CH_2Fβ$); 68.8 (C-4β); 67.4 (d, $J = 20$ Hz, $CH_2CH_2Fα$); 65.4 (C-5α); 62.6 (C-2β); 59.2 (C-2α); 16.5, 16.3 (C-6α, C-6β). IR (thin film) ν: 2926, 2110, 1721, 1452, 1267, 1169, 1111, 1067, 1026. HRMS: [M - N$_2$ + H]$^+$ calculated for $C_{22}H_{25}FNO_6$: 402.17113; found 402.17108.
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2-fluoroethyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-α/β-L-fucopyranoside (B4)

![Structure Image]

The products (α/β 2:3) were obtained after column chromatography (hexane/EtOAc, 1:0 → 9:1) and size-exclusion chromatography (CH$_2$Cl$_2$/MeOH, 1:1 v/v), in 60% yield (26 mg, 0.060 mmol). ¹H NMR (400 MHz) δ: 8.10-8.06 (m, 10H, CH$_2$Ar); 7.62-7.58 (m, 5H, CH$_2$Ar); 7.49-7.45 (m, 10H, CH$_2$Ar); 7.26-7.20 (m, 25H, CH$_2$Ar); 5.58 (dd, 2H, $J$ = 2.8 Hz, H-3α); 5.05 (d, 2H, $J$ = 3.6 Hz, H-1α); 4.95 (dd, 3H, $J$ = 3.2 Hz, 10.8 Hz, H-3β); 4.73-4.52 (m, 20H, CH$_2$H$_2$F, PhCH$_2$); 4.43 (d, 3H, $J$ = 8.0 Hz, H-1β); 4.17-3.78 (m, 22H, H-2α, H-2β, H-4α, H-4β, H-5α, CH$_2$CH$_2$F$_2$); 3.67 (q, 3H, $J$ = 6.4 Hz, H-5β); 1.26-1.21 (m, 15H, H-6α, H-6β). ¹³C-APT NMR (100 MHz) δ: 165.8 (CO$_2$); 137.5, 137.4 (CH$_2$Ar); 133.6, 133.5, 129.9 (CH$_2$Ar); 129.3, 129.1 (CH$_2$Ar); 128.6, 128.3, 128.1, 127.9, 127.9 (CH$_2$Ar); 102.3 (C-1β); 98.5 (C-1α); 82.6 (d, $J$ = 168 Hz, CH$_2$CH$_2$Fβ); 82.4 (d, $J$ = 169 Hz, CH$_2$CH$_2$Fα); 77.2 (C-4α); 75.9 (C-4β); 75.6 (PhCH$_2$); 75.4 (PhCH$_2$β); 74.9 (C-3β); 72.2 (C-3α); 70.6 (C-5β); 68.6 (d, $J$ = 21 Hz, CH$_2$CH$_2$Fβ); 67.3 (d, $J$ = 20 Hz, CH$_2$CH$_2$Fα); 66.5 (C-5α); 61.2 (C-2β); 58.0 (C-2α); 16.6 (C-6β). IR (thin film) ν: 2934, 2110, 1721, 1452, 1267, 1171, 1096, 1069, 1026. HRMS: [M+NH$_4$]$^+$ calculated for C$_{25}$H$_{28}$FN$_4$O$_7$: 447.20382; found 447.20380.

2-fluoroethyl 2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-α/β-L-fucopyranoside (B5)

![Structure Image]

The products (α/β 2:3) were obtained after column chromatography (hexane/Et$_2$O, 1:0 → 9:1) in 82% yield (38 mg, 0.082 mmol). ¹H NMR (400 MHz) δ: 4.94 (d, 2H, $J$ = 3.6 Hz, H-1α); 4.66-4.51 (m, 10H, CH$_2$Fa, CH$_2$Fβ); 4.26 (d, 3H, $J$ = 8.0 Hz, H-1β); 4.15-4.01 (m, 5H, H-3α, CH$_2$CH$_2$Fβ); 3.94-3.68 (m, 13H, H-2α, H-4α, H-5α, CH$_2$CH$_2$Fa, CH$_2$CH$_2$Fβ); 3.59-3.55 (m, 6H, H-2β, H-4β); 3.47 (q, 3H, $J$ = 6.4 Hz, H-5β); 3.36 (dd, 3H, $J$ = 2.4 Hz, 10.2 Hz, H-3β); 1.23 (d, 9H, $J$ = 6.4 Hz, H-6β); 1.19 (d, 6H, $J$ = 6.4 Hz, H-6α), 0.96-0.93 (m, 90H, (CH$_3$)$_3$Si); 0.19-0.08 (m, 60H, CH$_3$Si). ¹³C-APT NMR (100 MHz) δ: 102.8 (C-1β); 98.3 (C-1α); 82.8 (d, $J$ = 168 Hz, CH$_2$CH$_2$Fβ); 82.6 (d, $J$ = 168 Hz, CH$_2$CH$_2$Fa); 75.1 (C-4α); 74.4 (C-3β); 73.9 (C-4β); 71.3 (C-5β); 71.2 (C-3α); 68.3 (d, $J$ = 20 Hz, CH$_2$CH$_2$Fβ); 66.9 (d, $J$ = 20 Hz, CH$_2$CH$_2$Fa); 63.8 (C-2β); 61.1 (C-2α); 26.3, 26.1, 26.1 ((CH$_3$)$_3$Si); 18.6, 18.6, 18.5 (C$_3$Si); 17.5 (C-6β), 17.3 (C-6α); -3.5, -3.5, -3.6, -3.7, -4.3, -4.5, -4.5, -4.7 (CH$_3$Si). IR (thin film) ν: 2930, 2857, 2108, 1252, 1177, 1119, 1069, 1045, 1028. HRMS: [M+NH$_4$]$^+$ calculated for C$_{46}$H$_{62}$FN$_4$O$_7$Si$_2$: 481.30361; found 481.30338.
The title products (α/β 1:1) were isolated after column chromatography (hexane/EtO, 1:0 → 9:1) in 80% yield (35 mg, 0.080 mmol). ¹H NMR (400 MHz) δ: 7.39-7.26 (m, 10H, CH₉arom); 5.05-5.02 (m, 2H, 2x PhCHH); 4.94 (d, 1H, J = 3.6 Hz, H-1α); 4.67-5.51 (m, 6H, 2x PhCH₂, CH₂Fα, CH₂Fβ); 4.26 (d, 1H, J = 8.0 Hz, H-1β); 4.13 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-3α); 4.00-3.76 (m, 7H, H-2α, H-2β, H-5α; CH₂CH₂Fa, CH₂CH₂Fβ); 3.52-3.48 (m, 3H, H-3β, H-4α, H-5β); 3.38 (d, 1H, J = 2.8 Hz, H-4β); 1.21-1.18 (m, 6H, H-6α, H-6β); 0.98, 0.97 (s, 9H, (CH₃)₂Si); 0.24 (s, 3H, CH₃Si); 0.20 (s, 6H, 2x CH₃Si); 0.16 (s, 3H, CH₃Si). ¹³C-APT NMR (100 MHz) δ: 138.5, 138.5 (C₁arom); 128.3, 128.2, 128.1, 127.9, 127.6, 127.6 (CH₉arom); 102.5 (C-1β); 98.4 (C-1α); 82.7 (d, J = 168 Hz, CH₂F); 82.6 (d, J = 168 Hz, CH₂F); 80.7 (C-4α); 79.0 (C-4β); 75.6, 75.4 (PhCH₂); 74.8 (C-5β); 71.4 (C-3α); 70.5 (C-3β); 68.4 (d, J = 20 Hz, CH₂CH₂F); 67.1 (d, J = 20 Hz, CH₂CH₂F); 66.8 (C-5α); 64.6 (C-2β); 61.4 (C-2α); 25.9, 25.9 ((CH₃)₂Si); 18.1, 18.0 (C₂Si); 16.7, 16.6 (C-6α, C-6β); -4.0, -4.3, -4.8, -5.1 (CH₃Si).


The products (α/β 3:2) were obtained after column chromatography (toluene/EtOAc, 1:0 → 9:1 v/v), in 81% yield (35 mg, 0.081 mmol). ¹H NMR (400 MHz) δ: 7.43-7.25 (m, 50H, CH₉arom); 6.08-5.78 (m, 5H, CHF₂α, CHF₂β); 4.95-4.91 (m, 7H, H-1α, PhCH₂Hα, PhCH₂Hβ); 4.74-4.59 (m, 14H, PhCH₂); 4.24 (d, 2H, J = 8.0 Hz, H-1β); 4.01-3.73 (m, 24H, H-2α, H-2β, H-3α, H-4α, H-5α, CH₂CHF₂α, CH₂CHF₂β); 3.54 (d, 2H, J = 2.4 Hz, H-4β); 3.43 (q, 2H, J = 6.4 Hz, H-5β); 3.31 (dd, 2H, J = 2.8 Hz, 10.0 Hz, H-3β); 1.20-1.17 (m, 15H, H-6α, H-6β). ¹³C-APT NMR (100 MHz) δ: 138.1, 138.0, 137.5, 137.5 (C₂artom); 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.8, 127.8, 127.6 (CH₂arom); 114.3 (CHF₂β); 113.9 (CHF₂α); 102.4 (C-1β); 99.0 (C-1α); 80.8 (C-3β); 77.6 (C-3α or C-5α); 75.9 (C-4α); 75.0 (PhCH₂α); 74.7 (PhCH₂β); 74.6 (C-4β); 72.8 (PhCH₂β); 72.4 (PhCH₂α); 70.9 (C-5β); 68.3 (t, J = 29 Hz, CH₂CHF₂β); 67.2 (C-3α or C-5α); 67.2 (t, J = 29 Hz, CH₂CHF₂β); 62.8 (C-2β); 59.4 (C-2α); 59.1 (C-2α).
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16.7, 16.6 (C-6α, C-6β). IR (thin film) v: 2926, 2110, 1738, 1454, 1360, 1109, 1069. HRMS: [M+NH₄]⁺ calculated for C₂₂H₂⁹F₂N₄O₄: 451.21514; found 451.21500.

2,2-difluoroethyl 2-azido-3,4-di-O-benzoyl-2-deoxy-α/β-l-fucopyranoside (C₂)

The title compounds (α/β 3:2) were obtained after column chromatography (toluene/EtOAc, 1:0 → 9:1 v/v) in 74% yield (34 mg, 0.074 mmol). 8.07 α/β δ: 165.7, 165.7, 165.4 (C₆B₂; 133.5, 133.5, 133.4, 133.3, 129.9, 129.8 (CH₃arom); 129.2, 129.1, 129.0 (C₆B₂); 129.0, 128.6, 128.4, 128.3 (CH₃arom); 114.0 (t, J = 240 Hz, CHF₂β); 113.7 (t, J = 240 Hz, CHF₂α); 102.6 (C-1β); 99.1 (C-1α); 71.9 (C-3β); 71.1 (C-3α or C-4α); 70.0, 69.9 (C-4β, C-5β); 69.0 (C-3α or C-4α); 68.8 (t, J = 30 Hz, CH₂CHF₂β); 67.4 (t, J = 30 Hz, CH₂CHF₂α); 65.8 (C-5α); 61.2 (C-2β); 57.9 (C-2α); 16.2 (C-6β), 16.0 (C-6α). IR (thin film) v: 2926, 2110, 1726, 1450, 1261, 1163, 1107, 1094, 1067. HRMS: [M+Na]⁺ calculated for C₂₂H₁₂F₁₃N₃O₆Na: 484.12906; found 484.12894.

2,2-difluoroethyl 2-azido-4-O-benzyl-3-O-benzyl-2-deoxy-α/β-l-fucopyranoside (C₃)

The products (α/β 3:1) were obtained after column chromatography (toluene/EtOAc, 1:0 → 19:1) in 76% yield. (34 mg, 0.076 mmol), accompanied by a small amount of inseparable, hydrolyzed donor. ¹H NMR (400 MHz) δ: 8.12-8.07 (m, 8H, CH₃arom); 7.60-7.58 (m, 4H, CH₃arom); 7.49-7.44 (m, 10H, CH₃arom); 7.35-7.25 (m, 18H, CH₃arom); 6.12-5.82 (m, 4H, CHF₂α, CHF₂β); 5.70 (d, 3H, J = 2.8 Hz, H-4α); 5.45 (d, 1H, J = 2.8 Hz, H-4β); 5.01 (d, 3H, J = 3.6 Hz, H-1α); 4.83 (d, 3H, J = 10.8 Hz, PhCHHα); 4.79 (d, 1H, J = 11.6 Hz, PhCHβ); 4.56-4.53 (d, 4H, PhCHHα, PhCHHβ); 4.33 (d, 1H, J = 8.0 Hz, H-1β); 4.19 (q, 3H, J = 6.4 Hz, H-5α); 4.08 (dd, 3H, J = 3.2 Hz, 10.8 Hz, H-3α); 4.03-3.69 (m, 13H, H-2α, H-2β, H-5β, CH₂CHF₂α, CH₂CHF₂β); 3.47 (dd, 1H, J = 3.6 Hz, 10.8 Hz, H-3β); 1.31-
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

1.22 (m, 12H, H-6α, H-6β). 13C-APT NMR (100 MHz) δ: 166.1, 166.0 (CO2); 137.0, 136.9 (Cq-arom); 133.4, 133.3, 130.0, 129.9, 129.5, 129.4, 129.2 (CHarom); 128.6, 128.5 (Cq-arom); 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.6 (CHarom); 114.2 (t, J = 240 Hz, CHF2β); 113.8 (t, J = 240 Hz, CHF2α); 102.4 (C-1β); 99.0 (C-1α); 77.5 (C-3β); 74.1 (C-3α); 71.6 (PhCH2β); 71.5 (PhCH2α); 69.8 (C-5β); 69.6 (C-4α); 68.6 (C-4β); 64.6 (t, J = 30 Hz, CH2CHF2β); 67.4 (t, J = 28 Hz, CH2CHF2α); 65.8 (C-5α); 62.5 (C-2β); 59.1 (C-2α); 16.4, 16.3 (C-6α, C-6β). IR (thin film) ν: 2924, 2110, 1721, 1452, 1265, 1169, 1096, 1069.

2,2-difluoroethyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-α/β-L-fucopyranoside (C4)

The title compounds (α/β 1:1) were obtained after column chromatography (toluene/EtOAc, 1:0 → 9:1) in 80% yield (36 mg, 0.080 mmol). 1H NMR (400 MHz) δ: 8.10-8.06 (m, 4H, CHarom); 7.63-7.59 (m, 2H, CHarom); 7.49-7.46 (m, 4H, CHarom); 7.26-7.20 (m, 10H, CHarom); 6.11-5.82 (m, 2H, CHF2α, CHF2β); 5.54 (dd, 1H, J = 3.2 Hz, 11.2 Hz, H-3α); 5.04 (d, 1H, J = 3.6 Hz, H-1α); 4.95 (dd, 1H, J = 2.8 Hz, 10.8 Hz, H-3β); 4.72-4.69 (d, 2H, J = 11.6 Hz, 2x PhCH2); 4.57-4.52 (m, 2H, 2x PhCH2); 4.42 (d, 1H, J = 8.8 Hz, H-1β); 4.14-4.37 (m, 9H, H-2α, H-2β, H-4α, H-4β, H-5α, CH2CHF2α, CH2CHF2β); 3.68 (q, 1H, J = 6.4 Hz, H-5β); 1.30-1.20 (m, 6H, H-6α, H-6β). 13C-APT NMR (100 MHz) δ: 165.8 (CO2); 137.4, 137.3 (Cq-arom); 133.6, 133.6, 130.2, 129.9 (CHarom); 129.3 (Cq-arom); 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9 (CHarom); 114.1 (t, J = 240 Hz, CHF2); 113.8 (t, J = 240 Hz, CHF2); 102.4 (C-1β); 99.0 (C-1α); 77.0, 75.7 (C-4α, C-4β); 75.6, 75.5 (PhCH2); 74.7 (C-3β); 71.9 (C-3α); 70.9 (C-5β); 68.7-67.3 (m, 2C, CH2CHF2α, CH2CHF2β); 66.9 (C-5α); 61.1 (C-2β); 57.9 (C-2α); 16.5, 16.3 (C-6α, C-6β). IR (thin film) ν: 2924, 2110, 1721, 1452, 1265, 1169, 1096, 1069, 1026. HRMS: [M+N+H]+ calculated for C22H28F2N2O5: 420.16171; found 420.16168.

2,2-difluoroethyl 2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-α/β-L-fucopyranoside (CS)

The title products (α/β 5:2) were obtained after column chromatography (hexane/Et2O, 1:0 → 19:1 v/v) in 75% yield (36 mg, 0.075 mmol). 1H NMR (400 MHz) δ: 6.09-5.79 (m, 7H, CHF2α,
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\( \text{CHF}_2\beta \) 4.93 (d, 5H, \( J = 3.2 \text{ Hz}, H-1\alpha \)); 4.26 (d, 2H, \( J = 8.0 \text{ Hz}, H-1\beta \)); 4.01-3.73 (m, 27H, H-2\alpha, H-3\alpha, H-5\alpha, OCH\(_2\)CH\(_2\)F\alpha, OCH\(_2\)CH\(_2\)F\beta \); 3.71 (d, 5H, \( J = 2.0 \text{ Hz}, H-4\alpha \)); 3.58-3.53 (m, 4H, H-2\beta, H-4\beta \); 3.47 (q, 2H, \( J = 6.4 \text{ Hz}, H-5\beta \)); 3.36 (dd, 2H, \( J = 2.4 \text{ Hz}, 10.4 \text{ Hz}, H-3\beta \)); 1.23 (d, 6H, \( J = 6.4 \text{ Hz}, H-6\beta \)); 1.19 (d, 15H, \( J = 6.4 \text{ Hz}, H-6\alpha \)); 0.96-0.89 (m, 126H, ((CH\(_3\))\(_3\)Si); 0.18-0.09 (m, 84H, CH\(_5\)Si).

\(^{13}\text{C-APT NMR} (100 \text{ MHz}) \delta: 114.4 (t, \( J = 240 \text{ Hz}, \text{CHF}_2\beta \)); 114.1 (t, \( J = 240 \text{ Hz}, \text{CHF}_2\alpha \)); 102.8 (C-1\beta); 98.9 (C-1\alpha); 75.0 (C-4\alpha); 74.3 (C-3\beta); 73.8 (C-4\beta); 71.5 (C-5\beta); 71.1 (C-3\alpha); 68.5 (C-5\alpha); 68.2 (t, \( J = 29 \text{ Hz}, \text{CH}_2\text{CHF}_2\beta \)); 67.1 (t, \( J = 29 \text{ Hz}, \text{CH}_2\text{CHF}_2\alpha \)); 63.8 (C-2\beta); 61.0 (C-2\alpha); 26.3, 26.1 ((CH\(_3\))\(_3\)Si); 18.6, 18.5 (C\(_6\)Si); 17.4, (C-6\beta); 17.3 (C-6\alpha); -3.5, -3.5, -3.8, -4.4, -4.5, -4.7 (CH\(_2\)Si). IR (thin film) ν: 2930, 2859, 2108, 1252, 1177, 1113, 1069, 1043, 1028. HRMS: [M-N\(_2\)+H]\(^+\) calculated for C\(_{20}\)H\(_{42}\)F\(_2\)NO\(_4\)Si\(_2\): 454.26149; found 454.26129.

**2,2-difluoroethyl 2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-\( \alpha%/\beta\)-l-fucopyranoside (C6)**

The title products (\( \alpha%/\beta \) 2:1) were obtained after chromatography (hexane/Et\(_2\)O, 1:0 → 9:1 v/v) in 87% yield (40 mg, 0.087 mmol). \(^1\text{H NMR} (400 \text{ MHz}) \delta: 7.39-7.25 (m, 7.5H, \text{CH\(_{arom}\})\); 6.08-5.81 (m, 1.5H, CHF\(_2\alpha, CHF\(_2\)\beta \)); 5.05-5.02 (d, 1.5H, \( J = 11.2 \text{ Hz}, \text{PhCHH}_\alpha, \text{PhCHH}_\beta \)); 4.93 (d, 1H, \( J = 3.6 \text{ Hz}, H-1\alpha \)); 4.62-4.56 (m, 1.5H, PhCHH\(_\alpha, PhCHH\beta \)); 4.25 (d, 0.5H, \( J = 8.0 \text{ Hz}, H-1\beta \)); 4.08 (dd, 1H, \( J = 2.8 \text{ Hz}, 10.4 \text{ Hz}, H-3\alpha \)); 3.94 (q, 1H, \( J = 6.4 \text{ Hz}, H-5\alpha \)); 3.82-3.73 (m, 4H, H-2\alpha, CH\(_2\)CHF\(_2\alpha, CH\(_2\)CHF\(_2\)\beta \)); 3.66 (dd, 0.5H, \( J = 8.0 \text{ Hz}, 10.4 \text{ Hz}, H-2\beta \)); 3.52-3.50 (m, 2H, H-3\beta, H-4\alpha, H-5\beta \)); 3.39 (d, 0.5H, \( J = 2.4 \text{ Hz}, H-4\beta \)); 1.26-1.18 (m, 4.5H, H-6\alpha, H-6\beta \)); 0.98 (s, 9H, (CH\(_3\))\(_3\)Si); 0.97 (s, 4.5H, (CH\(_3\))\(_3\)Si); 0.24 (s, 3H, CH\(_3\)Si); 0.20 (s, 4.5H, CH\(_3\)Si\(_\alpha, CH\(_3\)Si\(_\beta \)); 0.16 (s, 1.5H, CH\(_3\)Si). \(^{13}\text{C-APT NMR} (100 \text{ MHz}) \delta: 138.4, 138.4 (C\(_{arom}\)\); 128.3, 128.2, 128.1, 127.9, 127.7, 127.7 (CH\(_{arom}\)); 114.3 (t, \( J = 240 \text{ Hz}, \text{CHF}_2\beta \)); 114.0 (t, \( J = 240 \text{ Hz}, \text{CHF}_2\alpha \)); 102.6 (C-1\beta); 99.0 (C-1\alpha); 80.5 (C-4\alpha); 78.9 (C-4\beta); 75.7, 75.5 (PhCH\(_2\)); 74.7 (C-3\beta or C-5\beta); 71.3 (C-3\alpha); 70.7 (C-3\beta or C-5\beta); 68.4 (t, \( J = 27 \text{ Hz}, \text{CH}_2\text{CHF}_2\beta \)); 67.3 (t, \( J = 29 \text{ Hz}, \text{CH}_2\text{CHF}_2\alpha \)); 67.3 (C-5\alpha); 64.5 (C-2\beta); 61.3 (C-2\alpha); 25.9, 25.8 ((CH\(_3\))\(_3\)Si); 18.1, 18.0 (C\(_6\)Si); 16.7, 16.6 (C-6, C-6\'); -4.1, -4.3, -4.8, -5.1 (CH\(_3\)Si). IR (thin film) ν: 2930, 2110, 1260, 1169, 1115, 1070, 1047. HRMS: [M+NH\(_4\)+ calculated for C\(_{22}\)H\(_{37}\)F\(_2\)NO\(_4\)Si\(_2\): 475.25463; found 475.25467.
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

2,2,2-trifluoroethyl 2-azido-3,4-di-O-benzyl-2-deoxy-α-L-fucopyranoside (D1)

The title compound was obtained after column chromatography (hexane/EtO 1:0 → 9:1 v/v), in 80% yield (36 mg, 0.080 mmol, 80%). 1H NMR (400 MHz) δ: 7.44-7.25 (m, 10H, CH_arom); 4.96-4.92 (m, 2H, PhCH2); 4.75 (s, 2H, PhCH2); 4.60 (d, 1H, J = 11.6 Hz, PhCH2F); 3.99-3.88 (m, 5H, H-2, H-3, H-5, CH2CF3); 3.54 (d, 1H, J = 2.4 Hz, H-4); 1.18 (d, 3H, J = 6.4 Hz, H-6). 13C APT NMR (100 MHz) δ: 138.0, 137.5 (CH_arom); 128.6, 128.3, 128.0, 127.8, 127.8 (CH_arom); 123.6 (q, J = 277 Hz, CF3); 99.0 (C-1); 77.4 (C-3 or C-5); 75.9 (C-4); 75.0, 72.5 (PhCH2); 67.5 (C-3 or C-5); 64.9 (q, J = 35 Hz, CH2CF3); 59.2 (C-2); 16.7 (C-6). 13C GATED NMR (100 MHz) δ: 99.0 (d, J = 170 Hz, C-1). IR (thin film) ν: 2927, 2108, 1454, 1356, 1279, 1163, 1082, 1051. HRMS: [M+Na]+ calculated for C22H24F3N3O4Na: 474.16111; found 474.16088.

2,2,2-trifluoroethyl 2-azido-3,4-di-O-benzoyl-2-deoxy-α/β-L-fucopyranoside (D2)

The title compounds (α/β 10:1) were isolated after column chromatography (hexane/EtOAc. 1:0 → 4:1) in 50% yield (24 mg, 0.050 mmol). NMR data is reported for the α-product only. 1H NMR (400 MHz) δ: 8.04-8.02 (m, 2H, CH_arom); 7.89-7.86 (m, 2H, CH_arom); 7.66-7.61 (m, 1H, CH_arom); 7.54-7.45 (m, 3H, CH_arom); 7.36-7.32 (m, 2H, CH_arom); 5.77-7.73 (m, 2H, H-3, H-4); 5.20 (d, 1H, J = 3.6 Hz, H-1); 4.37 (q, 1H, J = 6.4 Hz, H-5); 4.08 (q, 2H, J = 8.4 Hz, CH2CF3); 3.95 (dd, 1H, J = 3.2 Hz, 11.4 Hz, H-2); 1.26 (d, 3H, J = 6.8 Hz, H-6). 13C APT NMR (100 MHz) δ: 165.6, 165.3 (CO_Bz); 133.5, 133.4, 129.9, 129.8 (CH_arom); 129.2, 129.0 (CH_arom); 128.6, 128.3 (CH_arom); 123.4 (q, J = 276 Hz, CF3); 99.2 (C-1); 71.0 (C-3); 68.8 (C-4); 65.8 (C-5); 65.3 (q, J = 35 Hz, CH2CF3); 57.7 (C-2); 16.0 (C-6). IR (thin film) ν: 2928, 2110, 1724, 1452, 1273, 1261, 1157, 1109, 1094, 1069, 1026. HRMS: [M+Na]+ calculated for C22H26F3N3O6Na: 502.11964; found 502.11947.
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2,2,2-trifluoroethyl 2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-\(\alpha\)-l-fucopyranoside (D3)

The title compound was obtained after column chromatography (hexane/Et\(_2\)O 1:0 → 9:1 v/v) in 45% yield (21 mg, 0.045 mmol). NMR data is reported for the \(\alpha\)-isomer only. \(^1\)H NMR (400 MHz) \(\delta\): 8.08 (d, 2H, \(J = 7.2\) Hz, \(CH_{arom}\)); 7.59 (t, 1H, \(J = 7.6\) Hz, \(CH_{arom}\)); 7.46 (t, 2H, \(J = 8.0\) Hz, \(CH_{arom}\)); 7.34-7.24 (m, 5H, \(CH_{arom}\)); 5.72 (d, 1H, \(J = 2.8\) Hz, H-4); 5.05 (d, 1H, \(J = 3.6\) Hz, H-1); 4.85 (d, 1H, \(J = 10.4\) Hz, PhCH\(H\)); 4.55 (d, 1H, \(J = 10.8\) Hz, PhCH\(H\)); 4.19 (q, 1H, \(J = 6.4\) Hz, H-5); 4.11 (dd, 1H, \(J = 2.8\) Hz, 10.4 Hz, H-3); 4.01 (q, 2H, \(J = 8.4\) Hz, \(CH_2\)CF\(_3\)); 3.80 (dd, 1H, \(J = 3.6\) Hz, 10.4 Hz, H-2); 1.24 (d, 3H, \(J = 6.8\) Hz, H-6). \(^1\)C-APT NMR (100 MHz) \(\delta\): 166.0 (\(CD_3\)OD); 137.0 (\(C_{arom}\)); 133.4, 129.8 (\(CH_{arom}\)); 129.5 (\(C_{arom}\)); 128.5, 128.4, 128.3, 127.9 (\(CH_{arom}\)); 123.5 (q, \(J = 277\) Hz, CF\(_3\)); 99.1 (C-1); 74.1 (C-3); 71.6 (PhCH\(2\)); 69.6 (C-4); 66.2 (C-5); 65.3 (q, \(J = 35\) Hz, \(CH_2\)CF\(_3\)); 58.9 (C-2); 16.3 (C-6). IR (thin film) \(\nu\): 2924, 2110, 1721, 1452, 1267, 1157, 1111, 1084, 1055, 1026. HRMS: [M+H]\(^+\) calculated for \(C_{22}H_{23}F_3N_3O_5\): 466.15843; found 466.15813.

2,2,2-trifluoroethyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-\(\alpha/\beta\)-l-fucopyranoside (D4)

The title compounds (\(\alpha/\beta\) 7:1) were obtained after column chromatography (hexane/Et\(_2\)O 1:0 → 4:1 v/v), in 77% yield (36 mg, 0.077 mmol). \(^1\)H NMR (400 MHz) \(\delta\): 8.10-8.06 (m, 2.3H, \(CH_{arom}\)); 7.63-7.59 (m, 1.2H, \(CH_{arom}\)); 7.49-7.46 (m, 2.5H, \(CH_{arom}\)); 7.29-7.21 (m, 6H, \(CH_{arom}\)); 5.54 (dd, 1H, \(J = 2.8\) Hz, 11.2 Hz, H-3\(\alpha\)); 5.07 (d, 1H, \(J = 3.6\) Hz, H-1\(\alpha\)); 4.95 (dd, 0.15H, \(J = 2.8\) Hz, 11.2 Hz, H-3\(\beta\)); 4.72-4.69 (m, 1.15H, PhCH\(H\)\(\alpha\), PhCH\(H\)\(\beta\)); 4.57-4.52 (m, 1.15H, PhCH\(H\)\(\alpha\), PhCH\(H\)\(\beta\)); 4.48 (d, 0.15H, \(J = 8.0\) Hz, H-1\(\beta\)); 4.11 (q, 1H, \(J = 6.8\) Hz, H-5\(\alpha\)); 4.07-3.95 (m, 4.45H, H-2\(\alpha\), H-4\(\alpha\), \(CH_2\)CF\(_3\)\(\alpha\), H-2\(\beta\), \(CH_2\)CF\(_3\)\(\beta\)); 3.82 (d, 0.15H, \(J = 2.8\) Hz, H-4\(\beta\)); 3.68 (q, 0.15H, \(J = 6.8\) Hz, H-5\(\beta\)); 1.26-1.22 (m, 3.45H, H-6\(\alpha\), H-6\(\beta\)). \(^1^3\)C-APT NMR (100 MHz) \(\delta\): 165.8 (\(CD_3\)OD); 137.3 (\(C_{arom}\)); 133.6, 129.9 (\(CH_{arom}\)); 129.1 (\(C_{arom}\)); 128.6, 128.4, 128.3, 128.2, 128.0 (\(CH_{arom}\)); 123.5 (q, \(J = 277\) Hz, CF\(_3\)\(\alpha\)); 102.0 (C-1\(\beta\)); 99.1 (C-1\(\alpha\)); 76.9 (C-4\(\alpha\)); 75.6 (PhCH\(2\)); 75.6 (C-4\(\beta\)); 75.5 (PhCH\(H\)\(\beta\)); 74.6 (C-3\(\beta\)); 71.8 (C-3\(\alpha\)); 71.0 (C-5\(\beta\)); 67.2 (C-5\(\alpha\)); 65.0 (q, \(J = 35\) Hz, \(CH_2\)CF\(_3\)\(\alpha\)); 61.1 (C-2\(\beta\)); 57.6 (C-2\(\alpha\)); 16.4 (C-6\(\beta\)); 16.3 (C-6\(\alpha\)). IR (thin film) \(\nu\): 2924, 2110, 1721, 1452, 1267, 1155, 1105, 1096, 1070, 1045, 1026. HRMS: [M+NH\(_4\)]\(^+\) calculated for \(C_{22}H_{26}F_3N_4O_5\): 483.18498; found 483.18487.
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

2,2,2-trifluoroethyl 2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-α-L-fucopyranoside (D5)

The title compound were isolated after column chromatography (hexane/Et₂O, 1:0 → 49:1) in 84% yield (42 mg, 0.084 mmol). NMR data is reported for the α-isomer only. \(^1\)H NMR (400 MHz) δ: 4.97 (d, 1H, J = 3.2 Hz, H-1); 4.01 (dd, 1H, J = 2.0 Hz, 10.4 Hz, H-3); 3.98-3.88 (m, 3H, H-5, CH₂CF₃); 3.79 (dd, 1H, J = 3.6 Hz, 10.4 Hz, H-2); 3.72 (d, 1H, J = 1.2 Hz, H-4); 1.20 (d, 3H, J = 6.4 Hz, H-6); 0.96, 0.94 (s, 9H, (CH₃)₃ CSi); 0.19 (s, 3H, CH₂Si); 0.16-0.15 (m, 6H, CH₂Si); 0.07 (s, 3H, CH₃Si). \(^{13}\)C-APT NMR (100 MHz) δ: 123.7 (q, J = 276 Hz, CF₃); 98.8 (C-1); 74.9 (C-4); 70.9 (C-3); 68.8 (C-5); 64.7 (q, J = 35 Hz, CH₂CF₃); 60.8 (C-2); 26.2, 26.1 ((CH₃)₃ CSi); 18.6, 18.5 (C₅Si); 17.2 (C-6); -3.5, -3.8, -4.5, -4.8 (CH₃Si). IR: 2932, 2859, 2108, 1279, 1256, 1177, 1045. HRMS: [M+H-N₂]⁺ calculated for C₂₀H₂₁F₃NO₄Si₂: 472.25207; found 472.25180.

2,2,2-trifluoroethyl 2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-α-L-fucopyranoside (D6)

The title product was obtained after column chromatography (hexane/Et₂O, 1:0 → 9:1 v/v) in 90% yield (43 mg, 0.090 mmol). \(^1\)H NMR (400 MHz) δ: 7.39-7.25 (m, 5H, CH₅ arom); 5.04 (d, 1H, J = 11.2 Hz, PhCHH); 4.96 (d, 1H, J = 3.6 Hz, H-1); 4.57 (d, 1H, J = 11.2 Hz, PhCHH); 4.10 (dd, 1H, J = 2.4 Hz, 10.2 Hz, H-3); 3.97-3.91 (m, 3H, H-5, CH₂CF₃); 3.81 (dd, 1H, J = 3.6 Hz, 10.0 Hz, H-2); 3.53 (d, 1H, J = 2.0 Hz, H-4); 1.20 (d, 3H, J = 6.4 Hz, H-6); 0.98 (d, 9H, (CH₃)₃ CSi); 0.24, 0.20 (s, 3H, CH₃Si). \(^{13}\)C-APT NMR (100 MHz) δ: 138.4 (C₅ arom); 128.3, 128.1, 127.9 (CH₅ arom); 123.6 (q, J = 277 Hz, CF₃); 99.0 (C-1); 8.4 (C-4); 75.7 (PhCH₂); 71.1 (C-3); 67.7 (C-5); 64.9 (q, J = 35 Hz, CH₂CF₃); 61.1 (C-2), 25.9 ((CH₃)₃ CSi); 18.1 (C₅Si); 16.5 (C-6); -4.1, -5.1 (CH₃Si). IR (thin film) v: 2930, 2859, 2108, 1279, 1261, 1163, 1121, 1084, 1045. HRMS: [M+NH₄]⁺ calculated for C₂₁H₃₆F₃N₂O₄Si: 493.24524; found 493.24515.
The title compounds (α/β 1:2) were obtained after column chromatography (hexane/EtOAc 1:0 → 9:1 v/v), in 75% yield (34 mg, 0.075 mmol). 1H NMR (400 MHz) δ: 7.44-7.25 (m, 30H, CH\textsubscript{arom}); 5.02 (d, 1H, \(J = 3.6\) Hz, H-1\(\alpha\)); 4.94-4.91 (m, 3H, PhCH\textsubscript{2}H\(\alpha\), PhCH\textsubscript{2}H\(\beta\)); 4.77-4.60 (m, 12H, PhCH=CH\(\alpha\), PhCH=CH\(\beta\)); 4.28 (d, 2H, \(J = 8.0\) Hz, H-1\(\beta\)); 4.02-3.96 (m, 2H, H-3\(\alpha\), H-5\(\alpha\)); 3.81-3.74 (m, 4H, H-2\(\alpha\), H-2\(\beta\), H-4\(\alpha\)); 3.65 (tt, 2H, \(J = 7.6\) Hz, 9.6 Hz, CH\(\textsubscript{2}C\)); 3.58 (tt, 1H, \(J = 7.6\) Hz, 9.6 Hz, CH\(\textsubscript{2}C\)); 3.51 (d, 2H, \(J = 2.4\) Hz, H-4\(\beta\)); 3.38 (q, 2H, \(J = 6.4\) Hz, H-5\(\beta\)); 3.26 (dd, 2H, \(J = 2.8\) Hz, 10.4 Hz, H-3\(\beta\)); 1.90-1.62 (m, 12H, CH\(\textsubscript{2}C\)); 1.50-1.34 (m, 10H, CH\(\textsubscript{2}C\)); 1.25-1.15 (m, 15H, H-6\(\alpha\), H-6\(\beta\), CH\(\textsubscript{2}C\)). \(^{13}\)C-APT NMR (100 MHz) δ: 138.2, 137.8 (C\(\textsubscript{q,arom}\)); 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.6 (CH\textsubscript{arom}); 100.3 (C-1\(\beta\)); 96.6 (C-1\(\alpha\)); 80.9 (C-3\(\beta\)); 77.6 (C-3\(\alpha\)); 77.2 (CH\(\textsubscript{2}C\)); 76.2 (C-4\(\alpha\)); 76.1 (CH\(\textsubscript{2}C\)); 74.8 (C-4\(\beta\)); 74.5, 72.6, 72.2 (PhCH\textsubscript{2}H\(\beta\)); 70.4 (C-5\(\beta\)); 66.5 (C-5\(\alpha\)); 63.2 (C-2\(\beta\)); 59.4 (C-2\(\alpha\)); 33.3, 31.5, 31.4, 25.6, 25.5, 24.1, 23.9, 23.8 (CH\(\textsubscript{2}C\)); 17.0 (C-6\(\beta\)); 16.7 (C-6\(\alpha\)). IR (thin film) ν: 2932, 2855, 2106, 1454, 1359, 1107, 1067, 1038. HRMS: [M+NH\(_4\)]\(^{+}\) calculated for C\(_{26}\)H\(_{37}\)N\(_4\)O\(_4\): 469.28093; found 469.28096.

The title compounds (α/β 1:1.9) were obtained after column chromatography (hexane/EtOAc 1:0 → 9:1 v/v), in 38% yield (18 mg, 0.038 mmol). NMR data is reported only for the β-glycoside. 1H NMR (400 MHz) δ: 8.09-8.07 (m, 2H, CH\textsubscript{arom}); 7.89-7.85 (m, 2H, CH\textsubscript{arom}); 7.64-7.60 (m, 1H, CH\textsubscript{arom}); 7.52-7.45 (m, 3H, CH\textsubscript{arom}); 7.32 (t, 2H, \(J = 7.6\) Hz, CH\textsubscript{arom}); 5.56 (d, 1H, \(J = 3.6\) Hz, H-4); 5.15 (dd, 1H, \(J = 3.6\) Hz, 10.8 Hz, H-3); 4.61 (d, 1H, \(J = 8.0\) Hz, H-1); 3.95-3.88 (m, 2H, H-2, H-5); 3.79 (tt, 1H, \(J = 7.6\) Hz, 9.6 Hz, CH\(\textsubscript{2}C\)); 2.03-2.01 (m, 2H, CH\(\textsubscript{2}C\)); 1.81-1.79 (m, 2H, CH\(\textsubscript{2}C\)); 1.57-1.43 (m, 3H, CH\(\textsubscript{2}C\)); 1.37-1.22 (m, 8H, H-6, H-6, CH\(\textsubscript{2}C\)); 1.13-1.08 (m, 10H, CH\(\textsubscript{2}C\)). \(^{13}\)C-APT NMR (100 MHz) δ: 165.9, 165.4 (CO\(_{\text{Bz}}\)); 133.4, 133.3, 129.9, 129.7 (CH\textsubscript{arom}); 129.3, 129.1 (C\(_{\text{q,arom}}\)); 128.5, 128.3 (CH\textsubscript{arom}); 100.5 (C-1); 78.3 (CH\(\text{C}_2\)); 71.9 (C-3); 70.3 (C-4); 69.4 (C-5); 61.5 (C-2); 33.5, 31.6, 25.5, 24.1, 23.9 (CH\(\text{C}_2\)); 16.4 (C-6). IR (thin film) ν: 2934, 2857, 2110, 1724, 1450, 1281, 1263, 1173, 1107, 1096, 1069, 1026. HRMS: [M+Na]\(^{+}\) calculated for C\(_{26}\)H\(_{26}\)N\(_2\)NaO\(_6\): 502.19486; found 502.19479.
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

**Cyclohexyl 2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-α/β-l-fucopyranoside (E3)**

![Structure of E3](image)

The title compounds (α/β 1:4) were obtained after column chromatography (hexane/EtO 1:0 → 9:1 v/v), in 71% yield (33 mg, 0.071 mmol). 1H NMR (400 MHz) δ: 8.14-8.07 (m, 2.5H, CH_arom); 7.60-7.56 (m, 1.25H, CH_arom); 7.48-7.44 (m, 2.5H, CH_arom); 7.35-7.24 (m, 6.25H, CH_arom); 5.70 (d, 0.25H, / = 2.4 Hz, H-4α); 5.52 (dd, 1H, / = 0.8 Hz, 3.2 Hz, H-4β); 5.11 (d, 0.25H, / = 3.6 Hz, H-1α); 4.84 (d, 0.25H, / = 10.4 Hz, PhCHHα); 4.78 (d, 1H, / = 11.6 Hz, PhCHHβ); 4.56-4.52 (m, 1.25H, PhCHHβ); 4.39 (d, 1H, / = 8.4 Hz, H-1β); 4.26 (q, 0.25H, / = 7.2 Hz, H-5α); 4.13 (dd, 0.25H, / = 3.6 Hz, 10.6 Hz, H-3α); 3.74-3.60 (m, 3.5H, H-2α, H-2β, H-5β, CH3γ); 3.41 (dd, 1H, / = 3.2 Hz, 10.2 Hz, H-3β); 1.98-1.77 (m, 5H, CH2,CH3); 1.55-1.43 (m, 4H, CH2,CH3); 1.31-1.20 (m, 7.25H, H-6α, H-6β, CH2,CH3).

13C-APT (100 MHz) δ: 166.30 (CO_Bz); 137.2 (C_qarom); 133.3, 133.2, 130.1, 129.8 (CH_arom); 129.5 (C_qarom); 128.4, 128.4, 128.2, 128.1, 127.8, 127.8 (CH_arom); 100.3 (C-1β); 96.7 (C-1α); 78.0 (CHα); 77.5 (C-3β); 74.1 (C-3α); 71.5 (PhCH2β); 71.5 (PhCH2α); 70.1 (C-4α); 69.4 (C-5β); 69.0 (C-4β); 65.2 (C-5α); 62.9 (C-2β); 59.2 (C-2α); 33.5, 33.3, 31.6, 31.5, 25.5, 24.1, 23.9, 23.8 (CH2,CH3); 16.6 (C-6β); 16.3 (C-6α). IR (thin film) ν: 2922, 2110, 1720, 1446, 1265, 1107, 1068. HRMS: [M+H]+ calculated for C26H26N3O8: 466.23365, found 466.23352.

**Cyclohexyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-α/β-l-fucopyranoside (E4)**

![Structure of E4](image)

The title compounds (α/β 1:4) were obtained after column chromatography (hexane/EtO 1:0 → 9:1 v/v), in 71% yield (35 mg, 0.075 mmol). 1H NMR (400 MHz) δ: 8.10-8.06 (m, 10H, CH_arom); 7.62-7.58 (m, 5H, CH_arom); 7.48-7.45 (m, 11H, CH_arom); 7.25-7.18 (m, 28H, CH_arom); 5.59 (dd, 1H, / = 2.4 Hz, 11.2 Hz, H-3α); 5.13 (d, 1H, / = 3.2 Hz, H-1α); 4.93 (dd, 4H, / = 2.8 Hz, 10.8 Hz, H-3β); 4.71-4.69 (m, 5H, PhCHHβ); 4.57-4.52 (m, 5H, PhCHHβ); 4.47 (d, 4H, / = 8.0 Hz, H-1β); 4.19 (q, 1H, / = 6.4 Hz, H-5α); 3.98-3.93 (m, 5H, H-2β, H-4α); 3.88 (dd, 1H, / = 3.4 Hz, 11.2 Hz, H-2α); 3.76-3.70 (m, 8H, H-4β, CH3β); 3.66-3.61 (m, 5H, H-5β, CH3γα); 1.93-1.75 (m, 22H, CH2,CH3); 1.52-1.43 (m, 18H, CH2,CH3); 1.32-1.18 (m, 38H, H-6α, H-6β, CH2,CH3).

13C-APT NMR (100 MHz) δ: 165.8 (CO Bz); 137.6, 137.5 (C_qarom); 133.5, 129.9 (CH_arom); 129.2 (C_qarom); 128.5, 128.3, 128.2, 128.2, 127.8, 127.8 (CH_arom); 100.3 (H-1β); 96.7 (H-1α); 77.6 (CH3β); 77.4 (H-4α); 76.5 (CH3α); 75.9 (C-4β); 75.5
(PhCH₂α); 75.3 (PhCH₂β); 74.8 (C-3β); 72.0 (C-3α); 70.4 (C-5β); 66.2 (C-5α); 61.4 (C-2β); 57.8 (C-2α); 33.4, 33.3, 31.4, 29.7, 25.5, 23.9, 23.8 (CH₃₂₃); 16.7 (C-6β); 16.4 (C-6α). IR (thin film) ν: 2932, 2857, 2108, 1452, 1265, 1173, 1096, 1069, 1038, 1026. HRMS: [M+NH₄]⁺ calculated for C₂₆H₃₅N₄O₅: 483.26020; found 483.26018.

*Cyclohexyl 2-azido-2-deoxy-3,4-di-O-(tert-butylidemethylsilyl)-α/β-L-fucopyranoside (E5)*

![Image of cyclohexyl 2-azido-2-deoxy-3,4-di-O-(tert-butylidemethylsilyl)-α/β-L-fucopyranoside]

The products (α/β 1:3) were obtained after column chromatography (hexane/Et₂O, 1:0 → 9:1) in 80% yield (40 mg, 0.080 mmol). ¹H NMR (400 MHz) δ: 5.04 (d, 1H, J = 3.6 Hz, H-1α); 4.28 (d, 3H, J = 7.6 Hz, H-1β); 4.05 (dd, 1H, J = 2.4 Hz, 10.4 Hz, H-3α); 3.94 (q, 1H, J = 6.8 Hz, H-5α); 3.69-3.56 (m, 6H, H-2α, H-4α, OCH₃₃α, OCH₃₃β); 3.55 (d, 3H, J = 2.4 Hz, H-4β); 3.51 (dd, 3H, J = 8.0 Hz, 10.2 Hz, H-2β); 3.42 (q, 3H, J = 6.4 Hz, H-5β); 3.33 (dd, 3H, J = 2.4 Hz, 10.4 Hz, H-3β); 1.97-1.25 (m, 40H, CH₂₂₃); 1.22 (d, 9H, J = 6.4 Hz, H-6β); 1.17 (d, 3H, J = 6.4 Hz, H-6α); 0.96-0.90 (m, 72H, (CH₃)₃CSi); 0.18-0.08 (m, 48H, CH₂Si). ¹³C-APT NMR (100 MHz) δ: 100.6 (C-1β); 96.3 (C-1α); 77.4 (CH₂β); 75.6 (CH₂α); 74.5 (C-3β); 74.0 (C-4β); 71.2 (C-3α); 71.0 (C-5β); 67.8 (C-5α); 64.2 (C-2β); 60.9 (C-2α); 33.5, 33.3, 31.8, 31.4 (CH₂₂₃); 26.2, 26.1 ((CH₃)CSi); 25.7, 25.6, 24.1, 24.0, 23.9, 23.7 (CH₂₂₃); 18.6, 18.5 (C₃Si); 17.7 (C-6β); 17.3 (C-6α); -3.4, -3.6, -4.3, -4.4, -4.5, -4.7 (CH₂Si). IR (thin film) ν: 2930, 2857, 2110, 1252, 1376, 1352, 1327, 1293, 1239, 1218, 1177, 1109, 1031, 962, 853, 764, 720. HRMS: [M+Na]⁺ calculated for C₃₄H₄₉N₃O₅Si₂Na: 522.31538; found 522.31506.

*Cyclohexyl 2-azido-4-O-benzyl-3,4-di-O-(tert-butylidemethylsilyl)-2-deoxy-α/β-L-fucopyranoside (E6)*

![Image of cyclohexyl 2-azido-4-O-benzyl-3,4-di-O-(tert-butylidemethylsilyl)-2-deoxy-α/β-L-fucopyranoside]

The title compounds (α/β 1:2) were obtained after column chromatography (hexane/Et₂O, 1:0 → 19:1), in 80% yield (38 mg, 0.080 mmol). ¹H NMR (400 MHz) δ: 7.39-7.26 (m, 15H, CH₃∠ₚ); 5.03-5.01 (m, 4H, H-1α, PhCH₂α, PhCH₂β); 4.61-4.55 (m, 3H, PhCH₂α, PhCH₂β); 4.28 (d, 2H, J = 8.0 Hz, H-1β); 4.14 (broad doublet, J = 8.4 Hz, H-3α); 4.00 (q, 1H, J = 6.4 Hz, H-5α); 3.67-3.43 (m, 11H, H-2α, H-2β, H-3β, H-4α, H-5β, OCH₃₃α, OCH₃₃β); 3.36 (bs, 2H, H-4β); 1.89-1.11 (m, 39H, CH₂₂₃α/β, H-2β, H-3β, H-4α, H-5β, OCH₃₃α, OCH₃₃β); 3.36 (bs, 2H, H-4β); 1.89-1.11 (m, 39H, CH₂₂₃α/β.
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

H-6α, H-6β; 0.98 (s, 9H, (CH₂)₃CSiα, 0.96 (s, 18H, (CH₂)₃CSiβ); 0.23-0.15 (m, 18H, CH₂Siα/β).³¹C-APT NMR (100 MHz) δ: 138.7 (C₆arom); 128.2, 128.2, 128.1, 127.9, 127.5, 127.5 (CH₆arom); 100.4 (C-1β); 96.6 (C-1α); 81.0 (C-4α); 79.2 (C-4β); 77.3 (OCH₂β); 76.0 (OCH₂α); 75.6 (PhCH₂α); 75.3 (PhCH₂β); 74.9 (C-3β or C-5β); 71.3 (C-3α); 70.2 (C-3β or C-5β); 66.6 (C-5α); 64.9 (C-2β); 61.2 (C-2α); 33.4, 33.3, 31.5 (CH₂C₂); 25.9, 25.6 (CH₃)₃CSiα/β); 24.1, 23.9, 23.8 (CH₂C₂); 16.9 (C-6β); 16.7 (C-6α); -3.9, -4.3, -4.7, -5.0 (CH₃Si). IR (thin film) ν: 2930, 2857, 2108, 1250, 1160, 1059, 1040. HRMS: [M+NH₄]⁺ calculated for C₉₂H₄₅N₄O₄Si: 493.32046; found 493.32016.

Methyl 2-O-(2-azido-3,4-di-O-benzyl-2-deoxy-α/β-L-fucopyranosyl)-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (Φ₁)

The product was obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v), in 68% yield (49 mg, 0.068 mmol). NMR data is reported for the α-linked fucoside only. ¹H NMR (400 MHz) δ: 7.53-7.50 (m, 2H, CH₆arom); 7.44-7.23 (m, 18H, CH₆arom); 5.64 (s, 1H, PhCH); 4.95 (d, 1H, J = 3.6 Hz, H-1'); 4.90 (d, 1H, J = 11.2 Hz, PhCHH); 4.79-4.69 (m, 5H, H-1, PhCH₂); 4.59 (d, 1H, J = 11.6 Hz, PhCHH); 4.37 (q, 1H, J = 6.4 Hz, H-5'); 4.25 (dd, 1H, J = 4.8 Hz, 10.2 Hz, H-6); 4.19-4.13 (m, 3H, H-2, H-4, H-3'); 3.98 (dd, 1H, J = 3.6 Hz, 10.0 Hz, H-3); 3.89 (t, 1H, J = 10.4 Hz, H-6); 3.78 (dt, 1H, J = 4.8 Hz, 9.2 Hz, H-5); 3.74 (d, 1H, J = 1.2 Hz, H-4'); 3.70 (dd, 1H, J = 3.2 Hz, 10.8 Hz, H-2'); 3.36 (s, 3H, OCH₂); 1.70 (d, 3H, J = 6.8 Hz, H-6').³¹C-APT NMR (100 MHz) δ: 138.2, 137.6, 137.5 (C₆arom); 128.8, 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 127.9, 127.7, 127.6, 127.5, 126.1 (CH₆arom); 101.5 (PhCH); 98.8 (C-1); 97.3 (C-1'); 78.5 (C-4); 76.5 (C-2 or C-3'); 76.0 (C-4'); 75.0 (PhCH₂); 74.8 (C-3); 73.5 (C-2 or C-3'); 72.7, 71.9 (PhCH₂); 68.8 (C-6); 67.1 (C-5'); 64.1 (C-5); 58.9 (C-2'); 55.0 (OCH₂); 16.7 (C-6').³¹C-GATED (100 MHz) δ: 98.8 (C¹H¹J = 168 Hz, C-1); 97.3 (C²H²J = 170 Hz, C-1'). IR (thin film) ν: 2909, 2108, 1454, 1371, 1101, 1059, 1040, 1003. HRMS: [M+Na]⁺ calculated for C₄₁H₄₅N₃O₉Na: 746.30480; found 476.30475.
Chapter 3

Methyl 2-O-(2-azido-3,4-di-O-benzoyl-2-deoxy-α/β-L-fucopyranosyl)-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (F2)

The title compounds (α/β 4:1) were obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v), followed by column chromatography (toluene/acetone, 1:0 → 49:1 v/v), in 38% yield (29 mg, 0.038 mmol). ¹H NMR (400 MHz, for the α-isomer) δ: 8.12-8.09 (m, 2H, CH₅); 7.60-7.22 (m, 18H, CH₅); 5.72-5.69 (m, 2H, H-3', PhCH); 5.03 (d, 1H, J = 3.6 Hz, H-1'); 4.85 (d, 1H, J = 12.0 Hz, PhCHH); 4.77 (d, 1H, J = 1.2 Hz, H-1); 4.71-4.65 (m, 2H, PhCH₂); 4.56 (q, 1H, J = 6.4 Hz, H-5'); 4.51 (d, 1H, J = 11.2 Hz, PhCHH); 4.30-4.20 (m, H-4, H-6); 4.17 (dd, 1H, J = 1.6 Hz, 3.2 Hz, H-2); 3.98 (dd, 1H, J = 3.6 Hz, 10.2 Hz, H-3); 3.92-3.87 (m, 2H, H-4', H-6); 3.85-3.75 (m, 2H, H-2', H-5); 3.76 (s, 3H, OCH₃); 0.98 (d, 3H, J = 6.4 Hz, H-6'). Diagnostic peaks for the β-anomer: 5.62 (s, 0.25H, PhCHH); 3.54 (q, 0.25H, J = 6.4 Hz, H-5'), 1.22 (d, 0.75H, J = 6.4 Hz, H-6'). ¹³C-APT NMR 100 MHz, for the α-isomer) δ: 165.8 (CO₂); 137.7, 137.4 (C₅H₄); 135.5, 129.9 (CH₂); 129.2 (C₅H₄); 128.7, 128.5, 128.2, 128.1, 128.1, 127.8, 127.6, 127.5, 127.3, 127.1, 126.0 (CH₂); 101.4 (PhCH); 98.9 (C-1); 97.4 (C-1'); 78.8 (C-4); 77.5 (C-4'); 75.6 (PhCH₂); 74.6 (C-3); 74.3 (C-2); 73.0 (PhCH₂); 71.2 (C-3'); 68.7 (C-6); 66.7 (C-5'); 64.1 (C-5); 57.6 (C-2'); 54.9 (OCH₃); 16.1 (C-6'). IR (thin film) v: 2936, 2110, 1726, 1452, 1273, 1268, 1176, 1152, 1045, 997, 914, 883, 773, 693, 651, 585, 568, 503, 488. HRMS: [M+Na]⁺ calculated for C₄₁H₄₀N₅O₁₁Na: 774.26332; found 774.26333.

Methyl 2-O-(2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-α/β-L-fucopyranosyl)-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (F3)

The title compound (α/β 10:1) was obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v) and column chromatography (toluene/acetone, 1:0 → 49:1 v/v), in 58% yield (43 mg, 0.058 mmol). NMR data is reported for the α-isomer only. ¹H NMR (400 MHz) δ: 8.07-8.05 (m, 2H, CH₂); 7.58-7.25 (m, 18H, CH₂); 5.66 (s, 1H, PhCHH); 5.65 (d, 1H, J = 2.4 Hz, H-4'); 5.03 (d, 1H, J = 3.2 Hz, H-1'); 4.88-4.80 (m, 2H, PhCH₂); 4.72 (d, 1H, J = 12.0 Hz, PhCHH); 4.65 (q, 1H, J = 6.4 Hz, H-5'); 4.54 (d, 1H, J = 10.8 Hz, PhCHH); 4.29-4.23 (m, 2H, H-6, H-3'); 4.20-4.15 (m, 2H,
H-2, H-4); 4.02 (dd, 1H, J = 3.2 Hz, 10.0 Hz, H-3); 3.90 (t, 1H, J = 10.4 Hz, H-6); 3.80 (dt, 1H, J = 4.8 Hz, 9.6 Hz, H-5); 3.59 (dd, 1H, J = 3.6 Hz, 10.8 Hz, H-2'); 3.39 (s, 3H, OCH3); 1.04 (d, 3H, J = 6.8 Hz, H-6'). 13C-APT NMR (100 MHz) δ: 166.1 (COBz); 138.1, 137.6, 137.1 (Cαaron); 133.2, 130.0, 129.8 (CHαrom); 129.6 (Cαaron); 128.9, 128.4, 128.4, 128.3, 128.2, 128.2, 127.8, 127.8, 127.7, 127.1, 126.1 (CHαrom); 101.5 (Cαaron); 98.8 (C-1); 97.3 (C-1'); 78.7 (C-2 or C-4); 74.5 (C-3); 74.2 (C-2 or C-4); 73.2 (C-3'); 73.1 (PhCH2); 71.3 (PhCH2); 69.8 (C-4'); 68.8 (C-6); 65.7 (C-5'); 64.1 (C-5); 58.7 (C-2'); 55.0 (OCH3); 16.2 (C-6'). IR (thin film) ν: 2932, 2108, 1721, 1452, 1373, 1267, 1175, 1101, 1074, 1061, 1045, 1026, 1003. HRMS: [M+Na]+ calculated for C41H43N3O10Na: 760.28407; found 760.28375.

Methyl 2-O-(2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-α/β-L-fucopyranosyl)-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (Fed)

1H NMR (400 MHz, for the α-anomer) δ: 8.11 (d, 2H, J = 7.2 Hz, CHαrom); 7.60-7.22 (m, 18H, CHαrom); 5.72-5.69 (m, 2H, H-3', PhCH); 5.03 (d, 1H, J = 3.6 Hz, H-1'); 4.85 (d, 1H, J = 4.85 Hz, PhCHH); 4.70 (d, 1H, J = 1.2 Hz, H-1); 4.70-4.65 (m, 2H, PhCH2); 4.56 (q, 1H, J = 6.4 Hz, H-5'); 4.51 (d, 1H, J = 11.2 Hz, PhCHH); 4.30-4.20 (m, 2H, H-4, H-6); 4.17 (dd, 1H, J = 1.6 Hz, 3.2 Hz, H-2); 3.98 (dd, 1H, J = 3.2 Hz, 10.2 Hz, H-3); 3.92-3.87 (m, 2H, H-4', H-6); 3.92-3.75 (m, 2H, H-2', H-5); 3.38 (s, 3H, OCH3); 0.98 (d, 3H, J = 6.4 Hz, H-6'). Diagnostic peaks for the β-anomer: 5.62 (s, 0.25H, PhCH); 3.54 (q, 0.25H, J = 6.4 Hz, H-5'); 3.35 (s, 0.75H, OCH3); 1.22 (d, 0.75H, J = 6.4 Hz, H-6'). 13C-APT NMR (100 MHz, for the α-anomer) δ: 165.8 (COBz); 138.4, 137.7, 137.4 (Cαaron); 133.5, 129.9 (CHαrom); 129.2 (Cαaron); 128.8, 128.5, 128.2, 128.1, 127.8, 127.6, 127.5, 127.3, 127.1, 126.0 (CHαrom); 101.4 (PhCH); 98.9 (C-1); 97.4 (C-1'); 78.8 (C-4); 77.5 (C-4'); 75.6 (PhCH2); 74.6 (C-3); 74.3 (C-2); 73.0 (PhCH2); 71.2 (C-3'); 68.7 (C-6); 66.7 (C-5'); 64.1 (C-5); 57.6 (C-2'); 54.9 (OCH3); 16.1 (C-6'). IR (thin film) ν: 2934, 2909, 2110, 1722, 1452, 1373, 1269, 1103, 1074, 1043, 1028. HRMS: [M+Na]+ calculated for C41H43N3O10Na: 760.28407; found 760.28375.
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Methyl 2-O-(2-azido-2-deoxy-3,4-di-O-(tert-butylimethylsilyl)-α-L-fucopyranosyl)-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (F5)

The title compound was obtained after column chromatography (hexane/Et₂O, 1:0 → 9:1) as the sole product in 67% yield (52 mg, 0.067 mmol). ¹H NMR (400 MHz) δ: 7.50-7.49 (m, 2H, CH₃); 7.39-7.25 (m, 13H, CH₃); 5.59 (s, 1H, PhCH); 4.95 (d, 1H, J = 3.6 Hz, H-1'); 4.80 (d, 1H, J = 12.4 Hz, PhCHH); 4.74-4.70 (m, 2H, H-1, PhCHH); 4.29-4.25 (m, H-5', H-6'); 4.17 (dd, 1H, J = 2.4 Hz, 10.4 Hz, H-3'); 4.12-4.05 (m, H-2, H-4'); 3.96 (dd, 1H, J = 3.2 Hz, 9.8 Hz, H-3); 3.86-3.76 (m, 2H, H-5, H-6); 3.71 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-2'); 3.61 (d, 1H, J = 1.6 Hz, H-4'); 3.36 (s, 3H, OC₃H₃); 1.01-0.99 (m, 12H, H-6', (CH₃)₃Si); 0.91 (s, 9H, (CH₃)₃Si); 0.22, 0.16, 0.15, 0.14 (4x s, 3H, CH₂Si). ¹³C-APT NMR (100 MHz) δ: 138.4, 137.6 (C_{arom}); 128.8, 128.3, 128.1, 127.5, 127.4, 126.1 (CH_{arom}); 101.5 (PhCH); 99.1 (C-1); 97.3 (C-1'); 79.0 (C-4); 75.3 (C-4'); 74.5 (C-3); 73.6 (C-2); 72.3 (PhCH₂); 70.9 (C-3'); 69.0 (C-6); 68.4 (C-5'); 64.0 (C-5); 60.9 (C-2'); 55.0 (OCH₃); 26.2, 26.1 ((CH₃)₃Si); 18.6, 18.6 (C₂Si); 17.2 (C-6'); -3.4, -3.4, -4.6, -4.7 (CH₂Si). IR (thin film) ν: 2930, 2857, 2108, 1254, 1177, 1103, 1061, 1042, 1028, 1004. HRMS: [M+Na]⁺ calculated for C₃₉H₆₁N₃O₅Si₂Na: 794.38385; found 794.38385.

Methyl 2-O-(2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butylimethylsilyl)-α-L-fucopyranosyl)-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (F6)

The title disaccharide was isolated after column chromatography (hexane/Et₂O, 1:0 → 4:1) as the sole product in 74% yield (55 mg, 0.074 mmol). ¹H NMR (400 MHz) δ: 7.51-7.50 (m, 2H, CH₃); 7.40-7.24 (m, 13H, CH₃); 5.62 (s, 1H, PhCH); 5.00 (d, 1H, J = 11.2 Hz, PhCHH); 4.95 (d, 1H, J = 3.2 Hz, H-1'); 4.81-4.70 (m, 3H, H-1, PhCH₂); 4.53 (d, 1H, J = 11.2 Hz, PhCHH); 4.37 (q, 1H, J = 6.4 Hz, H-5'); 4.29-4.24 (m, 2H, H-3', H-6'); 4.14-4.09 (m, 2H, H-2, H-4'); 3.97 (dd, 1H, J = 3.2 Hz, 10.0 Hz, H-3); 3.86 (t, 1H, J = 10.4 Hz, H-6); 3.78 (dt, 1H, J = 4.4 Hz, 9.6 Hz, H-5); 3.64 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-2'); 3.44 (d, 1H, J = 2.4 Hz, H-4'); 3.36 (s, 3H, OC₃H₃); 1.04 (d, 3H, J = 6.4 Hz, H-6'); 0.99 (s, 9H, (CH₃)₃Si); 0.26 (s, 3H, CH₂Si); 0.21 (s, 3H, CH₂Si). ¹³C-APT NMR (100 MHz) δ: 138.6,
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

138.3, 137.6 (C_{arom}); 128.8, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.0, 126.1 (C_{arom}); 101.5 (PhCH); 98.9 (C-1); 97.4 (C-1'); 81.0 (C-4'); 78.8 (C-4); 75.6 (PhCH_{2}); 74.6 (C-3); 73.5 (C-2); 72.5 (PhCH_{2}); 70.7 (C-3'); 68.9 (C-6); 67.1 (C-5'); 64.1 (C-5); 61.0 (C-2'); 55.0 (OCH_{3}); 25.8 ((C\_3)_{3}CsSi); 18.1 (C_{Si}); 16.6 (C-6'); -3.6, -5.0 (CH_{3}Si). IR (thin film) v: 2928, 2857, 2106, 1454, 1371, 1258, 1171, 1101, 1040, 1004. HRMS: [M+Na]^+ calculated for C_{46}H_{53}N_{3}O_{8}Si: 770.34433; found 770.34412.

Methyl 3-O-(2-azido-3,4-di-O-benzyl-2-deoxy-α-L-fucopyranosyl)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (G1)

The title compound was obtained after size-exclusion chromatography (CH_{2}Cl_{2}/MeOH, 1:1 v/v) and column chromatography (toluene/acetone, 1:0 → 9:1 v/v) in 72% yield (52 mg, 0.072 mmol).

{\textsuperscript{1}}H NMR (400 MHz) δ: 7.39-7.22 (m, 20H, C_{arom}); 4.95-4.91 (m, 2H, H-1', PhCH=H); 4.86 (d, 1H, J = 11.6 Hz, PhCH=H); 4.72 (d, 1H, J = 12.0 Hz, PhCH=H); 4.69-4.63 (m, 3H, H-1, PhCH_{2}); 4.53 (d, 1H, J = 11.6 Hz, PhCH=H); 4.23 (dd, 1H, J = 4.0 Hz, 9.6 Hz, H-6); 4.16-4.09 (m, 3H, H-3, H-4, H-5'); 4.00 (m, 2H, H-2', H-3'); 3.88-3.77 (m, 3H, H-2, H-5, H-6); 3.56 (s, 1H, H-4'); 3.31 (s, 3H, OCH_{3}); 0.88 (d, 3H, J = 6.4 Hz, H-6'). {\textsuperscript{13}}C-APT NMR (100 MHz) δ: 138.3, 138.1, 137.7, 137.6 (C_{arom}); 128.9, 128.6, 128.4, 128.2, 128.1, 127.8, 127.6, 127.4, 126.2, 125.9 (C_{arom}); 101.8 (PhCH); 100.3 (C-1); 95.7 (C-1'); 78.3 (C-3'); 77.1 (C-3 or C-4); 76.3 (C-4'); 75.4 (C-2); 74.8, 73.8 (PhCH_{2}); 73.4 (C-2); 72.1 (PhCH_{2}); 68.9 (C-6); 66.6 (C-5'); 64.2 (C-5); 59.9 (C-2'); 54.8 (OCH_{3}); 16.3 (C-6'). IR (thin film) v: 2930, 2108, 1454, 1098, 1057, 1026. HRMS: [M+Na]^+ calculated for C_{41}H_{45}N_{3}O_{8}Na: 746.30480; found 746.30414.

Methyl 3-O-(2-azido-3,4-di-O-benzoyl-2-deoxy-α-L-fucopyranosyl)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (G2)

The title compound was obtained after size-exclusion chromatography (CH_{2}Cl_{2}/MeOH, 1:1 v/v) and column chromatography (toluene/acetone, 1:0 → 49:1 v/v) in 64% yield (48 mg, 0.064
mMol). \(^1\)H NMR (400 MHz) \(\delta: 8.00-7.98\) (m, 2H, \(CH_{arom}\)); \(7.90-7.87\) (m, 2H, \(CH_{arom}\)); \(7.60-7.24\) (m, 16H, \(CH_{arom}\)); 5.79 (dd, 1H, \(J = 3.2\) Hz, 10.0 Hz, H-3'); 5.64 (s, 1H, PhCH); 5.55 (d, 1H, \(J = 2.0\) Hz, H-4'); 5.14 (d, 1H, \(J = 3.6\) Hz, H-1'); 4.96 (d, 1H, \(J = 12.0\) Hz, PhCH\(H\); 4.78 (d, 1H, \(J = 12.0\) Hz, PhCH\(H\)); 4.70 (d, 1H, \(J = 1.6\) Hz, H-1); 4.57 (q, 1H, \(J = 6.4\) Hz, H-5'); 4.27 (dd, 1H, \(J = 4.4\) Hz, 9.6 Hz, H-6); 4.22-4.18 (m, 2H, H-3, H-4); 4.10 (dd, 1H, \(J = 3.6\) Hz, 11.0 Hz, H-2'); 3.93-3.88 (m, 3H, H-2, H-5, H-6); 3.35 (s, 3H, OCH\(3\)); \(\nu: 2932, 2108, 1724, 1452, 1275, 77.1\) (C\(_1\)); 138.1, 137.4 (C\(_{arom}\)); 133.3, 133.2, 129.7 (CH\(H\)) 129.5, 129.2 (C\(_{arom}\)); 129.1, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 126.3 (CH\(H\)); 102.1 (PhCH); 100.4 (C-1); 96.3 (C-1') 77.1 (C-3 or C-4); 75.8 (C-2); 74.8 (C-3 or C-4); 73.9 (PhCH\(3\); 71.4 (C-4'); 70.1 (C-3'); 68.8 (C-6); 65.2 (C-5'); 64.4 (C-5); 58.8 (C-2'); 54.9 (OCH\(3\); 15.4 (C-6'). IR (thin film) \(\nu: 2932, 2108, 1724, 1452, 1275, 1261, 1098, 1065, 1026, 1005\). HRMS: [M+Na\(^+\)] calculated for C\(_{41}\)H\(_{43}\)N\(_3\)O\(_{10}\): 774.26333; found 774.26294.

**Methyl 3-O-(2-azido-4-O-benzoyl-3-O-benzyl-2-deoxy-\(\alpha\)-I-fucopyranosyl)-2-O-benzyl-4,6-O-benzylidene-\(\alpha\)-D-mannopyranoside (G3)**

The title compound was obtained after size-exclusion chromatography (CH\(_2\)Cl\(_2\)/MeOH, 1:1 v/v) and column chromatography (toluene/acetone, 1:0 \(\rightarrow\) 49:1 v/v) in 54% yield (40 mg, 0.054 mmol). \(^1\)H NMR (400 MHz) \(\delta: 8.08-8.06\) (m, 2H, \(CH_{arom}\)); 7.61-7.59 (m, 1H, \(CH_{arom}\)); 7.47-7.19 (m, 17H, \(CH_{arom}\)); 5.59 (s, 1H, PhCH); 5.52 (d, 1H, \(J = 2.8\) Hz, H-4'); 5.02 (d, 1H, \(J = 3.6\) Hz, H-1'); 4.94 (d, 1H, \(J = 11.6\) Hz, PhCH\(H\)); 4.81-4.75 (m, 2H, PhCH\(H\)); 4.68 (d, 1H, \(J = 1.2\) Hz, H-1); 4.50 (d, 1H, \(J = 10.8\) Hz, PhCH\(H\)); 4.41 (q, 1H, \(J = 6.4\) Hz, H-5'); 4.25 (dd, 1H, \(J = 3.6\) Hz, 9.4 Hz, H-6); 4.17-4.12 (m, H-3, H-4, H-3'); 3.91-3.80 (m, 4H, H-2, H-5, H-6, H-2'); 3.33 (s, 3H, OCH\(3\)); 0.83 (d, 3H, \(J = 6.4\) Hz, H-6'). \(^1\)C-APT NMR (100 MHz) \(\delta: 166.1\) (C\(_{arom}\)); 138.1, 137.6, 137.1 (C\(_{arom}\)); 133.2, 129.8 (CH\(H\)); 129.7 (C\(_{arom}\)); 129.2, 128.4, 128.3, 128.3, 128.1, 127.8, 127.8, 26.2 (CH\(H\)); 102.1 (PhCH); 100.4 (C-1); 96.0 (C-1'); 77.1, 75.6, 75.0, 74.2 (C-2, C-3, C-4, C-3'); 73.8, 71.4 (PhCH\(3\)); 70.0 (C-4'); 68.9 (C-6); 65.2 (C-5'); 64.3 (C-5); 59.6 (C-2'); 54.9 (OCH\(3\); 15.8 (C-6'). IR (thin film) \(\nu: 2930, 2110, 1721, 1454, 1269, 1110, 1099, 1059, 1026, 1003\). HRMS: [M+Na\(^+\)] calculated for C\(_{41}\)H\(_{43}\)N\(_3\)O\(_{10}\): 760.28407; found 760.28387.
Reactivity and selectivity of 2-azido-2-deoxy-fucosyl donors

Methyl 3-O-(2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-α/β-L-fucopyranosyl)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (G4)

The products (α/β 10:1) were obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v) and column chromatography (toluene/acetone, 1:0 → 49:1 v/v) in 64% yield (47 mg, 0.064 mmol). ¹H NMR (400 MHz) δ: 8.08-8.06 (m, 2H, CH₄arom); 7.61-7.17 (m, 18H, CH₄arom); 5.61-5.57 (m, 2H, H-3', PhCH₂); 5.03 (d, 1H, J = 3.6 Hz, H-1'); 4.93 (d, 1H, J = 12.0 Hz, PhCHH); 4.73 (d, 1H, J = 12.0 Hz, PhCHH); 4.66 (d, 1H, J = 1.6 Hz, H-1); 4.58 (d, 1H, J = 11.2 Hz, PhCHH); 4.46 (d, 1H, J = 11.2 Hz, PhCHH); 3.38 (t, 1H, J = 10.0 Hz, H-6); 3.83-3.78 (m, 3H, H-2, H-5, H-4'); 3.32 (s, 3H, OCH₃); 0.82 (d, 3H, J = 6.4 Hz, H-6'). ¹³C-APT NMR (100 MHz) δ: 165.8 (CO₂H); 138.1, 137.6 (C₄arom); 133.5, 129.8 (CH₂arom); 129.3 (C₆arom); 128.9, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7 (CH₂arom); 102.0 (PhCH); 100.4 (C-1); 96.2 (C-1'); 77.5 77.1, 76.4, 74.5 (C-2, C-3, C-4, C-4'); 75.6, 73.8 (PhCH₂); 73.0 (C-3'); 68.8 (C-6); 66.4 (C-5'); 58.8 (C-2'); 54.8 (OCH₃, 15.8 (C-6'). IR (thin film) ν: 2932, 2108, 1722, 1452, 1298, 1098, 1067, 1026. [M+Na]+ calculated for C₄₁H₄₃N₃O₁₀: 760.28407; found 760.28357.

Methyl 3-O-(2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-α/β-L-fucopyranosyl)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (G5)

The title product was obtained after column chromatography (hexane/Et₂O, 1:0 → 4:1) in 73% yield (56 mg, 0.073 mmol). ¹H NMR (400 MHz) δ: 7.45-7.25 (m, 10H, CH₄arom); 5.58 (s, 1H, PhCH); 4.98-4.95 (m, 2H, H-1, PhCHH); 4.78 (d, 1H, J = 11.6 Hz, PhCHH); 4.69 (d, 1H, J = 1.6 Hz, H-1); 4.24 (dd, 1H, J = 4.0 Hz, 9.6 Hz, H-6); 4.14-4.12 (m, 2H, H-3, H-4); 4.07-4.02 (m, 2H, H-3', H-5'); 3.88-3.82 (m, H-2, H-2', H-5, H-6); 3.55 (d, 1H, J = 1.6 Hz, H-4'); 3.32 (s, 3H, OCH₂); 0.94 (s, 9H, (CH₃)₃COSi); 0.90 (s, 9H, (CH₃)₃COSi); 0.79 (d, 3H, J = 6.4 Hz, H-6'); 0.16, 0.13, 0.13, 0.03 (4x s, 3H, CH₃Si). ¹³C-APT NMR (100 MHz) δ: 138.4, 137.8 (C₄arom); 128.9, 128.3, 128.1, 127.9, 127.7, 126.2, 125.8 (CH₂arom); 101.9 (PhCH); 100.7 (C-1); 96.1 (C-1'); 77.3 (C-3, C-4); 75.7 (C-2, C-5); 75.3 (C-4'); 73.9 (C-3, C-4); 73.9 (PhCH₂); 71.4 (C-3', C-5'); 68.9 (C-6); 68.0 (C-3', C-5'); 64.4 (C-2, C-5);
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61.8 (C-2’); 54.8 (OCH₃); 26.3, 26.1 ((CH₃)₃Si); 18.6, 18.5 (C₈Si); 16.8 (C-6’); -3.4, -4.0, -4.5, -4.6 (CH₂Si). IR (thin film) ν: 2953, 2857, 2106, 1179, 1121, 1099, 1049, 1028. HRMS: [M+Na]⁺ calculated for C₃₀H₆₉N₃O₃Si₂Na: 794.38385; found 794.38385.

Methyl 3-O-(2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-α/β-L-fucopyranosyl)-2-O-benzyl-4,6-O-benzilidene-α-D-mannopyranoside (G6)

The title compounds (α/β 10:1) were obtained after column chromatography (hexane/Et₂O, 1:0 → 4:1) in 64% yield (48 mg, 0.064 mmol). NMR data is reported for the α-isomer only. ¹H NMR (400 MHz) δ: 7.46-7.24 (m, 15H, CH₂aryl); 5.58 (s, 1H, PhCH); 5.00-4.92 (m, 3H, H-1’, 2x PhCH₂H); 4.78 (d, 1H, J = 11.6 Hz, PhCH₂H); 4.70 (d, 1H, J = 1.6 Hz, H-1’); 4.50 (d, 1H, J = 10.8 Hz, PhCH₂H); 4.42 (dd, 1H, J = 4.0 Hz, 9.6 Hz, H-6’); 4.16-4.06 (m, 4H, H-3, H-3’, H-4, H-5’); 3.90 (ddd, 1H, J = 3.2 Hz, 10.2 Hz, H-2’); 3.88-3.79 (m, 3H, H-2, H-5, H-6); 3.36-3.32 (m, 4H, H-4’, OCH₂); 0.96 (s, 9H, (CH₃)₃Si); 0.80 (d, 3H, J = 6.4 Hz, H-6’); 0.21 (s, 3H, CH₂Si); 0.15 (s, 3H, CH₂Si). ¹³C-APT NMR (100 MHz) δ: 138.7, 138.3, 137.7 (C₈aryl); 128.9, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 126.2, 125.8 (CH₂aryl); 101.9 (PhCH); 100.5 (PhC); 96.5 (C-1’); 81.0 (C-4’); 77.2 (C-4); 75.8 (C-2); 75.6 (PhCH₂); 74.4 (C-3 or C-3’); 73.8 (PhCH₂); 71.8 (C-3 or C-3’); 68.9 (C-6); 66.9 (C-5’); 63.3 (C-5); 62.3 (C-2’); 54.8 (OCH₂); 25.9 ((CH₃)₃Si); 18.0 (C₈Si); 16.1 (C-6’); -4.2, -5.0 (CH₂Si). IR (thin film) ν: 2930, 2857, 2106, 1454, 1364, 1344, 1364, 1364, 1364, 1121, 1099, 1049, 1028. HRMS: [M+Na]⁺ calculated for C₄₀H₆₉N₃O₃Si: 770.34433; found 770.34424.

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Modular synthesis of the Staphylococcus aureus type 5 capsular polysaccharide trisaccharide repeating unit*

Introduction

The Gram-positive bacterium Staphylococcus aureus is a ubiquitous pathogen, causing a variety of diseases, ranging from skin infections to potentially life-threatening ones, such as meningitis, pneumonia and bacteremia. Methicillin-resistant S. aureus (MRSA)\(^1\) is a particular hazard in hospital environments, where immunocompromised patients are at an increased risk of infection. Considering the increased prevalence of antibiotic-resistant S. aureus strains, as well as a lack of novel antibiotics,\(^2\),\(^3\) immunization could be a promising alternative to combat S. aureus infections. Most S. aureus isolates have a polysaccharide capsule,\(^4\) which may be employed as an antigen in a protein-conjugate vaccine. This approach has been used in the development of vaccines, for example against Streptococcus pneumoniae\(^5\) and Haemophilus influenzae type b.\(^6\)

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Figure 1: Structures of the S. aureus type 5 and type 8 CPS repeating units.

Most clinical isolates of *S. aureus* contain one of two capsular polysaccharides (CPS), the Type 5 or Type 8, of which the repeating units are shown in Figure 1. While most vaccines that are currently used employ carbohydrate antigens that are isolated from bacterial sources, there is a growing interest in the use of well-defined (fragments) of bacterial polysaccharides, obtained through chemical synthesis.

The Type 5 and Type 8 CPS repeating units share many structural features. Both contain three rare monosaccharide constituents; *N*-acetyl mannosaminuronic acid (ManNAcA), a 2-*N*-acetyl *L*-fucosamine (*L*-FucNAc) and a 2-*N*-acetyl *D*-fucosamine (*D*-FucNAc) residue. The ManNAcA is linked to the *L*-FucNAc through a 1,2-*cis* mannosidic bond, where the *L*-FucNAc units are connected by an α-glycosidic linkage, and the *D*-FucNAc residues feature either an α- (as in Type 8) or an β-linkage (as in Type 5). Furthermore, both repeating units contain an *O*-acetyl modification; on the 3-*O* position on the *L*-FucNAc in the Type 5, and on the 4-*O* position of the ManNAcA unit in the Type 8.

Different efforts towards the synthesis of the Type 5 and Type 8 repeating units have been reported. In their synthetic route to the Type 5 CPS, Adamo and co-workers\(^8\) relied on a glucuronic acid donor with a participating 2-*O* levulinoyl ester in order to construct the β-glycosidic bond, which was followed by a substitution on the C-2 position to furnish the β-mannosamine moiety. Unfortunately, the final glycosylation between the ManN\(_3\)A-*L*-FucN\(_3\) disaccharide donor and the reducing end *D*-FucN\(_3\) acceptor proceeded with poor stereoselectivity (α/β 2:1). For the synthesis of the Type 8 CPS trisaccharide, Demchenko\(^9\) and co-workers relied on an analogous strategy, using a *gluco*-configured donor, followed by a C-2 inversion to obtain the ManNAcA moiety. Although the synthesis of the trisaccharide was successful, the trisaccharide bore no conjugation handle, preventing its use in a conjugate vaccine. Boons and co-workers used monosaccharide building blocks with the ‘native’ *fuco*- and *manno*-configurations in their synthesis of the Type 5 CPS trisaccharide.\(^10\) Also in their hands, the pivotal glycosylation between the *L*-FucN\(_3\) and *D*-FucN\(_3\) proceeded with relatively low selectivity. For the introduction of the β-ManNAcA linkage, the authors relied on the a benzylidene-protected mannosazide (ManN\(_3\)) donor, requiring a late-
stage oxidation step. This Chapter describes a modular synthesis of the *S. aureus* type 5 Capsular Polysaccharide repeating unit. It relies on the highly stereoselective glycosylations of mannosaziduronic acid (ManN₃A)¹¹ and the outcome of the glycosylation of studies on FucN₃ donors described in Chapter 3.

**Results and discussion**

The retrosynthetic analysis for linker-equipped Type 5 CPS trisaccharide 1 is shown in Scheme 1. The fully protected trisaccharide 2 contains a benzyol protecting group at the C-3- O position of the central L-FucN₃ moiety in order to discern this particular hydroxyl group, which bears an acetate in the native trisaccharide, from the other hydroxyls, which are protected as benzyl ethers. An ester protecting group was chosen to minimize deprotection- and functionalization steps at the trisaccharide stage. Disconnection along the three glycosidic bonds of trisaccharide 2 reveals the three requisite monosaccharide building blocks 4–6. D-FucN₃ donor 4 contains a benzyol ester at the 3-O position as a β-directing group in glycosylation (see Chapter 3). This donor does not possess a participating, β-directing functionality on the C-2 amino group. Instead, it is masked as an azide to minimize deprotection steps at the end of the synthesis, in which all azides are simultaneously converted into the corresponding acetamides. It was anticipated that the β-selective formation of the glycosidic bond between the d-FucN₃ and the spacer acceptor could be affected using the chemistry described in Chapter 3.

**Scheme 1:** Retrosynthetic analysis of Type 5 CPS 1.

For the introduction of the α-glycosidic linkage between the d-FucN₃ and l-FucN₃ units it was envisaged the ideal l-FucN₃ donor would bear a 3-O benzoyl protecting group. In Chapter 3,
however, it was revealed that glycosylations of FucN₃ donors bearing ester protecting groups generally proceed with diminished α-selectivity. Finally, it was planned to install the β-mannosaminuronic linkage through a selective glycosylation of 2-azido mannuronic acid imidate donor 6, since earlier studies on these C-6 oxidized donors have shown that they possess a strong electronic preference to form β-glycosidic bonds.¹¹⁻¹²


A

Reagents and conditions: a) Ac₂O, pyridine, 0-4 °C; b) HBr, AcOH, CH₂Cl₂, 0-4 °C; c) Zn/Cu, N-methylimidazole, EtOAc, 70 °C (66%, 3 steps); d) (PhSe)₂, TMSN₄, Phl(OAc)₂, CH₂Cl₂, -30 → -10 °C; e) Na, MeOH, (48%, 2 steps); f) Bu₂SnO, toluene, Dean-Stark, 140 °C; then PMBCl, Cs₂F, Bu₄NBr, 120 °C, (86%); g) BnBr, NaH, DMF, 0 °C, (87%); h) HCl, Et₂SiH, HCl, HFIP, (64% for 13, 63% for 18); i) BzCl, DMAP (cat.), CH₂Cl₂, pyridine, (94% for 4, 70% for 19, 82% for 20); j) Ph₂SO, TTBP, 3Å MS, CH₂Cl₂, Et₂O; Tf₂O, -80 → -60 °C; 3, -80 → -40 °C, (80%, α/β:1:7); k) Na, MeOH, (95%); l) NapBr, NaH (60% in oil), Bu₄NI (cat.), DMF, 0 °C (87%).

Synthesis of the d-FucN₃ building blocks commenced with commercially available d-fucose 7, in a route that is identical to the synthesis of l-FucN₃ donors (Chapter 3). Thus, acetylation of the unprotected sugar, followed by anomeric bromination and subsequent zinc-mediated elimination delivered fucal 9 in 66% yield over three steps. Azidophenylelenylation of the double bond, deacetylation and crystallization yielded key diol building block 10 in 48% yield, Tin-mediated, regioselective 4-methoxybenzylolation on the 3-O position (86% yield), followed by
benzylaition, delivered fully protected 12 in 87% yield. Removal of the PMB ether using acidic conditions (HCl in CH₂Cl₂/HFIP) liberated the C-3 hydroxyl in 64% yield, which was subsequently benzyolated to give the donor 4 in 94% yield. Introduction of linker 3 on the D-FucN₃ unit proceeded efficiently, using a Ph₃SO/TF₂O-mediated pre-activation in a mixture of CH₂Cl₂ and Et₂O to give the product 14 in 80% yield, with good stereoselectivity (α/β 1:7). The desired β-anomer could be separated from the α-anomer by column chromatography. Cleavage of the benzoyl ester using Zemplén conditions then gave monosaccharide acceptor 15 in 95% yield.

The L-FucN₃ donor was synthesized in a similar fashion (Scheme 2B); 2-naphthylmethylation of the 4-O position of 16 (see Chapter 2) was achieved to yield 17 in 87% yield. Since both Nap and PMB ethers can be cleaved using acidic conditions, care had to be exercised to selectively remove the PMB group in 17. The aforementioned conditions, using HCl in CH₂Cl₂/HFIP proved effective, yielding 18 in 63% yield. Benzoylation gave the building block 19 (70% yield). Alternative L-FucN₃ donor 20, carrying a PMB ether on the C-3-O position and a C-4-O-benzoyl moiety, was synthesized by benzoylation of 16 in 82% yield.

**Scheme 3**: Synthesis of Man₃A donor 6.

![Scheme 3](image)

Reagents and conditions: a) TtN₃, CuSO₄ (cat.), NEt₃, pyridine, H₂O; Ac₂O; b) PhSH, BF₃·OEt₂, CH₂Cl₂ (76%, 3 steps); c) Na, MeOH; d) PhCH(OH)(OMe)₂, CSA (cat.), MeCN, 50 °C, 250 mbar (99%); e) BrN, NaH (60% in oil), BuHN (cat.), DMF, 0 °C (96%); f) BH₃·THF, Bu₂BOTf, CH₂Cl₂, 0 °C (94%); g) TEMPO (cat.), Phl(OAc)₂, AcOH (cat.), CH₂Cl₂, tBuOH, H₂O; Mel, K₂CO₃, DMF (79%, 2 steps); h) NBS, acetone, H₂O, 0 °C (82%); i) FcCC(NPf)Cl, CszCO₃, acetone (88%).

For the synthesis of the 2-azidomannuronic acid donor 6 (Scheme 3), a route was developed starting frommannosamine hydrochloride 21. Diazo transfer using imidazole sulfonyl azide 30,14 followed by acetylation, gave the product 2-azidomannoside 22, accompanied by significant amounts of the corresponding gluco-configured isomer. The epimerization of the 2-position also occurred when a procedure from Wong and co-workers was employed, using TtN₃
as the diazotransfer reagent.\textsuperscript{15} It was hypothesized that the epimerization occurred during concentration of the diazotransfer reaction mixture at the elevated temperature of the rotary evaporator’s water bath (\(\sim 40^\circ C\)) normally used to remove the solvents from the crude product. The epimerization could be circumvented by concentrating the reaction mixture at ambient temperature; this, however, drastically limited the practical feasibility of this protocol. Several years ago, Ye and co-workers reported an alternative procedure for the diazo transfer on glycosylamines, employing pyridine as a solvent.\textsuperscript{16} It was therefore envisioned that a one-pot synthesis of peracetylated mannosazide \textbf{22} would be possible, in which the intermediate mannosazide was directly transformed into its peracetate. Following a procedure in which \textbf{21} was reacted with freshly prepared TfN\(_3\) in pyridine, in the presence of a catalytic amount of CuSO\(_4\),\textsuperscript{15} followed by direct addition of Ac\(_2\)O to the reaction mixture, \textbf{22} was isolated in quantitative yield, on 70 mmol scale.

The peracetylated derivative \textbf{22} was next transformed into known building block \textbf{26} using literature procedures.\textsuperscript{17} Regioselective, reductive opening\textsuperscript{18} of the 4,6-\(\beta\)-benzylidene ring using BH\(_3\)-THF and Bu\(_2\)BOTf\textsuperscript{19} liberated the primary alcohol, yielding \textbf{27} in 94\% yield.\textsuperscript{9} Oxidation of \textbf{27} using the TEMPO/Phl(OAc)\(_2\) reagent system,\textsuperscript{20,21} followed by methylation, delivered the protected methyl mannuronate building block \textbf{28} in 79\% yield over 2 steps. NMR analysis revealed that this mannosaminuronic acid adopts a ‘flipped’ \(\text{C}_4\) conformation,\textsuperscript{11} NBS-mediated hydrolysis of the anomic thiophenyl functionality\textsuperscript{22} proceeded in 84\% yield to give \textbf{29}, which was followed by introduction of the anomic imidoyl group to give final building block \textbf{6} as a mixture of anomers, in 88\% yield.\textsuperscript{23,24}

With all required building blocks in hand, the formation of the pivotal \(\alpha\)-fucosamine linkage between the \(\alpha\)- and \(\beta\)-FucN\(_3\) units was investigated next. Glycosylation of donor \textbf{19} with acceptor \textbf{15} provided disaccharide \textbf{32} in 35\% and disappointing stereoselectivity (Table 1, entry 1), and therefore alternative donor \textbf{20} was investigated (entry 2). This reactive donor gave disaccharide \textbf{32} in 65\% yield, with the \(\alpha\)-product predominating (\(\alpha/\beta\) 9:1). A drawback of this disaccharide, however, is the need for an extra deprotection step at the trisaccharide stage (\textit{i.e.} removal of the PMB ether, while a benzoyl ester can be saponified together with the methyl mannuronate ester).

\[\text{It must be noted that the quality of the Lewis acid (Bu}_2\text{BOTf) solution is essential for the success of the reaction.}\]

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Table 1: Synthesis of type 5 CPS disaccharides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Donor</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (α/β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Bz</td>
<td>Nap</td>
<td>32</td>
<td>35% (1:2)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>PMB</td>
<td>Bz</td>
<td>33</td>
<td>65% (9:1)</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>TBS</td>
<td>TBS</td>
<td>34</td>
<td>76% (&gt;19:1)</td>
</tr>
</tbody>
</table>

In Chapter 3 it was revealed that 3,4-di-O-TBS protected donor 31 generally provides very α-selective glycosylations. When 31 was reacted with acceptor 15, the target disaccharide 34 was obtained as the single anomer in good yield (76%). To install the benzoate moiety at the C-3’ position, the TBS ethers were removed using Bu₃NF (Scheme 4), followed by benzylation using Taylor’s (2-aminoethyl)diphenylborinate catalyst 36 to give the disaccharide 35 in 67% over 2 steps.

Scheme 4: Transformation of glycosylation product 34 into disaccharide acceptor 35.

Reagents and conditions: a) Bu₃NF, THF; b) BzCl, 36 (cat.), DIPEA, MeCN (67%, 2 steps).

The final glycosylation to construct the β-mannuronate linkage proved challenging (Table 2). The use of imidate donor 6 (1.5 eq.) and a catalytic amount of TMSOTf (entry 1) led, after prolonged reaction times and intermediate additions of Lewis acid (up to 1.05 eq.), to only 38% of desired trisaccharide 2. Elevated temperatures (entry 2) or the use of TBSOTf (entry 3) did not improve the yield of the reaction, and the employment of thioglycoside donor 28 (entries 4 and 5) was also unsuccessful. The low yields may be attributed to the poor reactivity of the acceptor, as it could be partially recovered from all reactions. To force the reaction to completion, it was decided to employ a large excess of donor 6. By using 4.0 equivalents of donor 6 and 0.8 equivalents of TBSOTf, trisaccharide 2 was obtained in 75% yield. The hydrolyzed donor could be partially recovered after the reaction.
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Table 2: Synthesis of protected trisaccharide 2.

<table>
<thead>
<tr>
<th>entry</th>
<th>donor (eq.)</th>
<th>activator (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (1.5)</td>
<td>TMSOTf (0.15 to 1.05)</td>
<td>-80 to -55</td>
<td>46</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>6 (2.0)</td>
<td>TMSOTf (0.4 to 0.8)</td>
<td>-80 to -25</td>
<td>50</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>6 (2.0)</td>
<td>TBSOTf (0.4 to 1.2)</td>
<td>-80 to -55</td>
<td>52</td>
<td>36%</td>
</tr>
<tr>
<td>4</td>
<td>28 (1.3)</td>
<td>Ph₃SO (1.3), TFE (1.3)</td>
<td>-80 to 0</td>
<td>6</td>
<td>33%</td>
</tr>
<tr>
<td>5</td>
<td>28 (2.0)</td>
<td>NIS (3.0), AgOTf (1.0)</td>
<td>-60 to -30</td>
<td>3</td>
<td>34%</td>
</tr>
<tr>
<td>6</td>
<td>6 (4.0)</td>
<td>TBSOTf (0.8)</td>
<td>-80 to -55</td>
<td>5</td>
<td>75%</td>
</tr>
</tbody>
</table>

Deprotection of the trisaccharide 2 commenced with KOH/H₂O₂ mediated saponification of the methyl mannuronate ester and the 3-O benzoyl functionality, giving 37 in 66% yield (Scheme 5). Zinc-mediated reduction of the azides, followed by N-acetylation led to a complex mixture of products, with 40 as the major product as observed by LC-MS. Therefore, AcSH in pyridine was employed to directly convert the azides into the corresponding acetamides. Subsequent O-acetylation of the crude reaction mixture led, after chromatography, to a product which was tentatively assigned as lactamized product 41. No evidence was found for lactamation by LC-MS during the AcSH-mediated azide conversion or the O-acetylation. It is therefore likely that the lactamation occurs during concentration after work-up of the O-acetylation. Reversing the order of the two reactions, i.e. performing the O-acetylation prior to the azide-acetamide conversion effectively circumvented lactam formation, leading to 39 in 57% yield over the two steps. Subsequent hydrogenation, using Pearlman’s catalyst, delivered the target trisaccharide 1 in quantitative yield.

Conclusion

This Chapter describes the synthesis of the Staphylococcus aureus Type 5 Capsular Polysaccharide trisaccharide repeating unit. Key features in the synthesis include the β-selective glycosylation of a D-FucN₃ donor with a reactive 5-aminopentanol. The glycosidic linkage between the L-FucN₃ and D-FucN₃ units was installed with high yield and complete selectivity by use of a reactive, di-O-TBS L-FucN₃ donor. Finally, a 2-azidomannuronate donor was used to obtain the protected trisaccharide with complete β-selectivity. Deprotection of the target trisaccharide was
achieved in a four step reaction sequence. The glycosylation properties of FucN₃ donors as established in Chapter 3 are confirmed and advantage was taken of the high α-selectivity of armed FucN₃ donors.

Scheme 5: Deprotection of 2 and synthesis of deprotected trisaccharide 1.

Reagents and conditions: a) H₂O₂, KOH, THF, H₂O, (66%); b) Ac₂O, pyridine; c) AcSH, pyridine (57%, 2 steps); d) Pd(OH)₂/C, H₂ (1 atm), AcOH, THF, tBuOH, H₂O (quant.).

Experimental

General procedures

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4Å molecular sieves (3Å for CH₂Cl₂, MeOH and MeCN), except pyridine and DMF. NEt₃ was stored over KOH pellets. Tf₂O used in glycosylations was dried over P₂O₅ (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (λ: 254 nm), followed by spraying with 20% H₂SO₄ in EtOH (w/v).
or Hanessian's stain \((\text{NH}_4)_9\text{Mo}_7\text{O}_{24}\cdot4\text{H}_2\text{O}\), 25 g/L; \((\text{NH}_4)_2\text{Ce(SO}_4)_3\cdot2\text{H}_2\text{O}\), 10 g/L; in 10% aq. \text{H}_2\text{SO}_4). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to \text{Me}_4\text{Si} (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. \(^{13}\text{C}\)-APT spectra are \(^1\text{H}\) decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomeric carbon atoms \((J_{\text{H1,Cl}})\) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm\(^{-1}\). LC-MS analyses were performed on a Thermo Finnigan Surveyor HPLC system equipped with a Gemini C-18 column (250 x 10 mm), connected to a Thermo Finnigan LCQ Advantage Max Ion-trap mass spectrometer with (ESI+). Eluents used were MeCN, \text{H}_2\text{O} with addition of TFA (0.1%). HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.

**3,4-di-O-acetyl-d-fucal (9)**

To an ice-cooled mixture of Ac₂O (85 mL) and pyridine (110 mL) was added d-fucose (10 g, 60.9 mmol, 1.0 eq.) over the course of ~25 minutes. The mixture was stirred at 4 °C overnight, after which TLC analysis (PE/EtOAc, 7:3 v/v) showed complete conversion of the starting material. The mixture was poured on sat. aq. \text{NaHCO}_3 solution and the aqueous phase was extracted (CH₂Cl₂, 3x). The combined organic phases were washed (sat. aq. NH₄Cl, 3x; \text{H}_2\text{O}, 1x; brine, 1x), dried over MgSO₄, filtered and concentrated \textit{in vacuo}. The residue was coevaporated with toluene (3x) to remove the remaining pyridine. The oil thus obtained was dissolved in CH₂Cl₂ (240 mL, 0.25 M) and cooled to 0 °C. HBr (33% in AcOH, 80 mL) was added slowly with a dropping funnel. The mixture was allowed to reach room temperature overnight, after which TLC analysis (CH₂Cl₂) indicated complete conversion of the starting material. The mixture was poured on ice-water and stirred until the ice had molten. The two layers were separated, and the aqueous phase was extracted (CH₂Cl₂, 2x). The organic phases were washed (sat. aq. NaHCO₃, 2x; \text{H}_2\text{O}, 1x; brine, 1x), dried over MgSO₄, filtered and concentrated \textit{in vacuo}. The residue was dissolved in EtOAc (200 mL, 0.3 M) and added to a suspension of freshly prepared Zn/Cu couple (20 g of Zn, 305 mmol, 5.0 eq.)²⁷ and \(N\)-methylimidazole (5.3 mL, 67 mmol, 1.1 eq.) in EtOAc (200 mL) and the mixture was heated to 75 °C until TLC analysis indicated complete conversion of the starting material (toluene/EtOAc, 7:3 v/v). The reaction mixture was cooled to ambient temperature, filtered over 96
a bed of celite, and washed (sat. aq. NaHCO₃, 1x; H₂O, 1x). The aqueous phases were extracted (EtOAc, 1x), and the combined organic phases were washed (brine, 1x), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc/NEt₃, 95:5:1 → 90:10:1) to afford the title compound as an oil (8.6 g, 40 mmol, 66% over three steps). ¹H NMR (400 MHz) δ: 6.47 (dd, 1H, J = 1.6 Hz, 6.4 Hz, H-1); 5.59-5.58 (m, 1H, H-3); 5.29 (d, 1H, J = 4.4 Hz, H-4); 4.66-4.63 (m, 1H, H-2); 4.22 (q, 1H, J = 6.4 Hz); 2.17 (s, 3H, CH₃) 13C-APT NMR (100 MHz) δ: 170.7, 170.4 (CO₂); 146.1 (C-1); 98.2 (C-2); 71.5 (C-5); 66.2 (C-4); 65.0 (C-3); 20.9, 20.7 (CH₃); 16.5 (C-6).

*Phenyl 2-azido-2-deoxy-1-seleno-α-D-fucopyranoside (10)*

![Phenyl 2-azido-2-deoxy-1-seleno-α-D-fucopyranoside (10)](image)

To a stirred solution of fucal 9 (6.4 g, 30 mmol, 1.0 eq.) in CH₂Cl₂ (150 mL, 0.2 M) was added (PhSe)₂ (9.4 g, 30 mmol, 1.0 eq.) and the resulting bright orange solution was degassed by sonication for 30 minutes. The reaction mixture was cooled to -30 °C, after which Phl(OAc)₂ (9.7 g, 30 mmol, 1.0 eq.) and Me₂SiN₃ (7.9 mL, 60 mmol, 2.0 eq.) were added. The reaction mixture was stirred overnight at -20 °C, after which TLC analysis (toluene/EtOAc, 1:1 v/v) indicated complete conversion of the starting material. Cyclohexene (6 mL) was added and after 30 minutes, the reaction mixture was concentrated *in vacuo*. The resulting dark oil was subjected to column chromatography (PE/EtOAc, 1:0 → 3:2) to remove lipophilic byproducts. The carbohydrate-containing fractions were dissolved in MeOH (150 mL, 0.2 M) and a chip of Na was added. The mixture was stirred until TLC analysis (PE/EtOAc, 1:1 v/v) indicated complete conversion of the starting material. The reaction mixture was neutralized by addition of Amberlite IR-120 (H⁺-form), filtered and concentrated *in vacuo*. The resulting solid was crystallized from toluene/hexane to obtain the title compound as a slightly tan solid, in 48% yield (4.7 g, 14.3 mmol). ¹H NMR (400 MHz, acetone-­d₆) δ: 7.62-7.57 (m, 2H, CH₆); 7.32-7.28 (m, 3H, CH₆); 5.96 (d, 1H, J = 5.2 Hz, H-1); 4.29 (q, 1H, J = 6.4 Hz, H-5); 4.40 (dd, 1H, J = 5.2 Hz, 10.4 Hz, H-2); 3.82-3.79 (m, 2H, H-3, H-4); 1.17 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz, acetone-­d₆): 135.4 (CH₆); 130.1 (C₆); 129.8, 128.3 (CH₆); 86.7 (C-1); 72.4, 72.2 (C-3, C-4); 70.2 (C-5); 62.6 (C-2); 16.5 (C-6). IR (neat) ν: 3258, 2100, 1578, 1252, 1153, 1094, 1057. HRMS: [M+NH₄]⁺ calculated for C₁₂H₁₅N₄O₄S: 347.02639; found 347.02856.
Chapter 4

Phenyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-seleno-α-D-fucopyranoside (11)

A two-necked flask was charged with diol 10 (3.94 g, 12.0 mmol, 1.0 eq.), Bu₂SnO (3.04 g, 12.2 mmol, 1.02 eq.) and toluene (60 mL, 0.2 M) was equipped with a stopcock and a Dean-Stark trap. The mixture was heated to 140 °C in an oil bath for 2 hours, after which the mixture was cooled to 60 °C. Added was Bu₂NBr (4.06 g, 12.6 mmol, 1.05 eq.), CsF (1.85 g, 12.2 mmol, 1.02 eq.) and PMBCl (1.7 mL, 12.6 mmol, 1.05 eq.) and the mixture was heated to 120 °C and stirred for ~1 hour, after which TLC (PE/EtOAc, 3:2 v/v) indicated complete conversion of the starting material. The mixture was cooled to room temperature, added was a 10% aq. KF solution and, after ~30 minutes of vigorous stirring, the layers were separated, the aqueous phase extracted with EtOAc (1x), and the combined organic fractions were washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. The residual dark brown oil was subjected to column chromatography to furnish the title compound as a yellow oil in 86% yield (4.65 g, 10.4 mmol). ¹H NMR (400 MHz) δ: 7.58-7.56 (m, 2H, CH₆om); 7.34-7.24 (m, 5H, CH₆om); 6.93-6.87 (m, 2H, CH₆om); 5.87 (d, 1H, J = 5.2 Hz, H-1); 4.68 (d, 1H, J = 10.8 Hz, PhCH₂); 4.62 (d, 1H, J = 10.8 Hz, PhCH₂); 4.28 (q, 1H, J = 6.4 Hz, H-5); 4.14 (dd, 1H, J = 5.5 Hz, 10.2 Hz, H-2); 3.83 (d, 1H, J = 2.4 Hz, H-4); 3.81 (s, 3H, OCH₃); 3.68 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-3); 1.25 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 159.6 (C₆amom); 134.4, 134.3, 129.7, 129.0 (C₆om); 129.0, 128.6 (C₆amom); 127.7, 114.0 (C₆om); 85.2 (C-1); 78.8 (C-3); 71.7 (PhCH₂); 68.5, 68.4 (C-4, C-5); 60.0 (C-2); 55.2 (OCH₃); 16.0 (C-6). IR (thin film) ν: 3421, 2900, 2106, 1610, 1510, 1246, 1173, 1061, 1032. HRMS: [M+H]⁺ calculated for C₂₀H₂₄N₃O₄Se: 450.09265; found 450.09243.

Phenyl 2-azido-4-O-benzyl-2-deoxy-3-O-(4-methoxybenzyl)-1-seleno-α-D-fucopyranoside (12)

To a stirred solution of 11 (6.8 g, 15.2 mmol, 1.0 eq.) in DMF (50 mL, 0.3 M) was added BnBr (2.7 mL, 22.7 mmol, 1.5 eq.). At 0 °C, added was NaH (as 60% dispersion in mineral oil, 0.91 g, 22.7 mmol, 1.5 eq.). The reaction was allowed to warm to room temperature and stirred until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material. The excess NaH was quenched by addition of cold water, and the mixture was partitioned between Et₂O and water, and the aqueous phase was extracted (Et₂O, 2x). The combined organic phases were washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column
chromatography (PE/Et₂O, 1:0 → 9:1 v/v) yielded the title product in 87% yield (7.1 g, 13.2 mmol), 7.56-7.54 (m, 2H, CH₉arom); 7.36-7.22 (m, 10H, CH₉arom); 6.93-6.90 (m, 2H, CH₉arom); 5.91 (d, 1H, / = 5.2 Hz, H-1); 4.93 (d, 1H, / = 11.2 Hz, PhCH₂H); 4.68 (s, 2H, PhCH₂); 4.59 (d, 1H, / = 11.6 Hz, PhCH₂H); 4.32 (dd, 1H, / = 5.2 Hz, 10.0 Hz, H-2); 4.20 (q, 1H, / = 6.4 Hz, H-5); 3.80 (s, 3H, OCH₃); 3.76-3.68 (m, 2H, H-3, H-4); 1.11 (d, 3H, / = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 159.4, 138.1 (C₉arom); 134.2, 129.5 (CH₉arom); 129.4 (C₉arom); 128.9 (CH₉arom); 128.6 (C₉arom); 128.2, 128.1, 127.7, 127.5, 113.9 (CH₉arom); 85.5 (C-1); 80.2 (C-3); 75.6 (C-4); 74.9, 72.1 (PhCH₂); 69.3 (C-5); 60.7 (C-2); 55.2 (OCH₃); 16.5 (C-6). IR (neat) ν: 2866, 2106, 1611, 1512, 1294, 1246, 1063, 1030. HRMS: [M+H]⁺ calculated for C₂₇H₃₀N₃O₄Se: 540.13960; found 540.13960.

Phenyl 2-azido-3-O-benzoyl-2-deoxy-1-seleno-α-D-fucopyranoside (13)

![Phenyl 2-azido-3-O-benzoyl-2-deoxy-1-seleno-α-D-fucopyranoside](image)

To a stirred solution of 12 (3.2 g, 5.9 mmol, 1.0 eq.) in CH₂Cl₂ (30 mL, 0.2 M) was added Et₃SiH (2.8 mL, 17.7 mmol, 3.0 eq.), followed by a solution of HCl (0.5 mL 37% aq. HCl in 30 mL HFIP). After 1 minute, the mixture was poured on NaHCO₃ (sat. aq.). After separation from the organic phase, the aqueous phase was extracted (CH₂Cl₂, 2x). The combined organic phases were washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc, 1:0 → 9:1) delivered the title compound in 64% yield (1.6 g, 3.8 mmol). ¹H NMR (400 MHz) δ: 7.61-7.56 (m, 2H, CH₉arom); 7.38-7.24 (m, 8H, CH₉arom); 5.91 (d, 1H, / = 5.2 Hz, H-1); 4.80 (d, 1H, / = 11.6 Hz, PhCH₂H); 4.72 (d, 1H, / = 11.6 Hz, PhCH₂H); 4.32 (q, 1H, / = 6.4 Hz, H-5); 4.03 (dd, 1H, / = 5.2 Hz, 10.4 Hz, H-2); 3.82 (dd, 1H, / = 3.2 Hz, 10.2 Hz, H-3); 3.67 (d, 1H, / = 3.2 Hz, H-4); 1.24 (d, 3H, / = 6.4 Hz, H-6).¹³C-APT NMR (100 MHz) δ: 137.7 (C₉arom); 134.3, 129.0, 128.6, 128.2, 128.0, 127.7 (CH₉arom); 85.2 (C-1); 79.3 (C-3); 76.1 (PhCH₂); 71.9 (C-4); 69.3 (C-5); 62.5 (C-2); 16.6 (C-6). IR (thin film) ν: 2880, 2108, 1578, 1098, 1059. HRMS: [M+H]⁺ calculated for C₁₉H₂₂N₃O₅Se: 420.08029; found 420.08199.

Phenyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-1-seleno-α-D-fucopyranoside (4)

![Phenyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-1-seleno-α-D-fucopyranoside](image)

To a stirred solution of 13 (2.5 g, 6.0 mmol, 1.0 eq.) in CH₂Cl₂/pyridine (20 mL, 1:1 v/v, 0.3 M) were added, at 0 °C, DMAP (73 mg, 0.6 mmol, 0.1 eq.) and BzCl (1.4 mL, 12.0 mmol, 2.0 eq.). The
reaction mixture was allowed to warm to room temperature, and stirred until TLC (PE/EtOAc, 4:1 v/v) analysis indicated complete conversion of the starting material. The reaction was quenched by addition of water and diluted with CH₂Cl₂. The organic phase was washed (1 M aq. HCl, 3x; sat. aq. NaHCO₃, 1x; H₂O, 1x; brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 9:1 v/v) furnished the title compound in 94% yield (3.0 g, 5.7 mmol). ¹H NMR (400 MHz) δ: 8.09 (d, 2H, J = 7.6 Hz, CH_arom); 7.63-7.58 (m, 3H, CH_arom); 7.48 (t, 2H, J = 7.6 Hz, CH_arom); 7.41-7.23 (m, 8H, CH_arom); 6.01 (d, 1H, J = 5.2 Hz, H-1); 5.29 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-3); 4.67 (d, 1H, J = 11.6 Hz, PhCH₂H); 4.59 (dd, 1H, J = 5.2 Hz, 10.6 Hz, H-2); 4.53 (d, 1H, J = 11.6 Hz, PhCH₂H); 4.43 (q, 1H, J = 6.4 Hz, H-5); 4.01 (d, 1H, J = 2.8 Hz, H-4); 1.17 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 165.7 (CO_Bz); 137.4 (C_q,arom); 134.5, 133.7, 129.9, 129.1 (CH_arom); 129.0 (C_q,arom); 128.6 (CH_arom); 128.4 (C_q,arom); 128.3, 128.1, 127.9, 127.8 (CH_arom); 84.9 (C-1); 76.6 (C-4); 75.6 (PhCH₂); 75.1 (C-3); 69.1 (C-5); 59.6 (C-2); 16.3 (C-6). IR (thin film) v: 2936, 2108, 1722, 1267, 1107, 1086, 1070. HRMS: [M+NH₄]⁺ calculated for C₂₉H₂₉N₄O₅Se: 541.13485; found 541.13439.

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-3-O-benzoyl-4-O-benzyl-2-deoxy-β-D-fucopyranoside (14)

5.5 mmol scale – A three-necked 250 mL flask, equipped with a thermometer, rubber septa, an argon balloon and a gas outlet, was charged with a solution of donor 4 (2.86 g, 5.5 mmol, 1.0 eq.), Ph₅SO (1.44 g, 7.1 mmol, 1.3 eq.), TTBP (3.39 g, 13.4 mmol, 2.5 eq.) in CH₂Cl₂/Et₂O (110 mL, 1:1 v/v, 0.05 M). Flame-dried 3Å MS were added and the mixture was stirred at room temperature for ~30 minutes. After cooling to -80 °C, TF₅O (1.2 mL, 7.1 mmol, 1.3 eq.) was added and the mixture was allowed to warm to -60 °C. After re-cooling to -80 °C, a solution of 5-(benzyl(benzylxoycarbonyl)amino)pentanol (3.58 g, 10.9 mmol, 2.0 eq.) in CH₂Cl₂/Et₂O (20 mL, 1:1 v/v) was added via cannula transfer (reaction mixture temperature did not exceed -70 °C during addition). The mixture was allowed to warm to -40 °C, after which the reaction was quenched by addition of NEt₃ (4 mL), filtered over a pad of Celite, diluted with CH₂Cl₂, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Column chromatography (PE/EtOAc, 49:1 → 9:1 v/v) first furnished a mixture of α/β products (0.77 g, 1.1 mmol, 20% yield, α/β 1:3); when all higher-running α-product had eluted off, further elution (PE/EtOAc, 4:1 v/v) delivered pure β-product as a colorless oil (2.43 g, 3.5 mmol, 60%). NMR data is reported for the pure β-isomer. ¹H NMR (400 MHz, 323 K) δ: 8.06 (d, 2H, J = 7.6 Hz, CH_arom); 7.59 (t, 1H, J = 7.6 Hz,
$CH_{arom}$; 7.46 (t, 2H, $J = 7.6$ Hz, $CH_{arom}$); 7.30-7.17 (m, 14H, $CH_{arom}$); 5.17 (bs, 2H, PhCH$_2$); 4.93 (dd, 1H, $J = 2.8$ Hz, 10.8 Hz, H-3); 4.68 (d, 1H, $J = 11.6$ Hz, PhCH$_2$H); 4.55 (d, 1H, $J = 11.6$ Hz, PhCH$_2$H); 4.49 (s, 2H, PhCH$_2$); 4.29 (d, 1H, $J = 8.0$ Hz, H-1); 3.96-3.91 (m, 2H, H-2, OCH$_3$H); 3.78 (d, 1H, $J = 2.0$ Hz, H-4); 3.63 (q, 1H, $J = 6.4$ Hz, H-5); 3.48 (bs, 1H, OCH$_3$H); 3.23 ($CH_2$N$_2$pentyl); 1.61 (bs, 4H, 2x $CH_2$pentyl); 1.35 (bs, 2H, 2H, $CH_2$pentyl); 1.25 (d, 3H, $J = 6.4$ Hz, H-6). $^{13}$C-APT NMR (100 MHz, 323 K) $\delta$: 165.9 (CO$_3$); 138.1, 137.7 ($C_{arom}$); 133.5, 129.9 ($CH_{arom}$); 129.4 ($C_{arom}$); 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.3 ($CH_{arom}$); 102.3 (C-1); 76.3 (C-4); 75.5 (PhCH$_2$); 75.0 (C-3); 70.6 (C-5); 69.8 (OCH$_2$pentyl); 67.2 (PhCH$_2$); 61.6 (C-2); 50.7 (PhCH$_2$); 29.2, 23.3 ($CH_2$pentyl); 16.7 (C-6). IR (thin film) $\nu$: 2937, 2110, 1719, 1695, 1452, 1421, 1265, 1096, 1069, 1026. HRMS: [M+Na]$^+$ calculated for C$_{40}$H$_{44}$Na$_2$O$_7$: 715.31022; found 715.30968.

5-(benzyl(benzyloxycarbonyl)amino)pentyl 2-azido-4-O-benzyl-2-deoxy-$\beta$-D-fucopyranoside (15)

To a stirred solution of 14 (2.43 g, 3.5 mmol, 1.0 eq.) in dry MeOH (18 mL, 0.2 M) was added a chip of Na metal. The reaction mixture was stirred at room temperature until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material. The reaction mixture was neutralized by addition of Amberlite IR-120 (H$^+$ form), filtered and concentrated in vacuo. The title compound was obtained after column chromatography (PE/EtOAc) as a colorless oil in 95% yield (1.94 g, 3.3 mmol). $^1$H NMR (400 MHz, 323 K) $\delta$: 7.36-7.22 (m, 15H, $CH_{arom}$); 5.17 (s, 2H, PhCH$_2$); 4.80 (d, 1H, $J = 11.6$ Hz, PhCH$_2$); 4.72 (d, 1H, $J = 11.6$ Hz, PhCH$_2$H); 4.48 (s, 2H, PhCH$_2$); 4.16 (d, 1H, $J = 7.2$ Hz, H-1); 3.86 (bs, 1H, OCH$_3$H); 3.53-3.43 (m, 5H, OCH$_3$H); 2.17 (d, 1H, $J = 9.2$ Hz, 3-OH); 1.57-1.53 (m, 4H, $CH_2$pentyl); 1.44-1.43 (m, 2H, $CH_2$pentyl); 1.26 (d, 3H, $J = 7.2$ Hz, H-6). $^{13}$C-APT NMR (100 MHz, 323 K) $\delta$: 138.1 ($C_{arom}$); 128.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.3 ($CH_{arom}$); 102.3 (C-1); 78.6 (C-3, C-4, or C-5); 76.0 (PhCH$_2$); 73.2, 70.9 (C-3, C-4 or C-5); 69.7 (OCH$_2$pentyl); 67.2 (PhCH$_2$); 64.8 (C-2); 29.3, 23.3 ($CH_2$pentyl); 16.9 (C-6). IR (thin film) $\nu$: 2934, 2108, 1690, 1454, 1421, 1229, 1171, 1067. HRMS: [M+Na]$^+$ calculated for C$_{33}$H$_{40}$Na$_2$O$_6$: 611.28401; found 611.28327.
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Phenyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-4-O-(2-naphthylmethyl)-1-seleno-α-L-fucopyranoside (17)

To a stirred solution of 16 (1.4 g, 3.1 mmol, 1.0 eq.) in DMF (10 mL, 0.3 M) was added (2-naphthyl)methyl bromide (1.4 g, 6.2 mmol, 2.0 eq.) and Bu$_3$NI (0.11 g, 0.3 mmol, 0.1 eq.). At 0 °C was added NaH (60% dispersion in mineral oil, 0.19 g, 4.7 mmol, 2.0 eq.), and the mixture was allowed to warm to room temperature overnight, after which TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material. The reaction was quenched by addition of H$_2$O, and the mixture was partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted (Et$_2$O, 2x), and the combined organic fractions were washed (brine, 1x), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 1:0 → 9:1 v/v) delivered the title compound in 87% yield (1.6 g, 2.7 mmol). $^1$H NMR (400 MHz) δ: 7.80-7.77 (m, 3H, CH$_{arom}$); 7.70 (s, 1H, CH$_{arom}$); 7.58-7.55 (m, 2H, CH$_{arom}$); 7.49-7.44 (m, 3H, CH$_{arom}$); 7.38-7.35 (m, 2H, CH$_{arom}$); 7.27-7.22 (m, 3H, CH$_{arom}$); 6.95-6.91 (m, 2H, CH$_{arom}$); 5.94 (d, 1H, $J =$ 5.2 Hz, H-1); 5.08 (d, 1H, $J =$ 12.0 Hz, PhCH$_2$); 4.78 (d, 1H, $J =$ 11.6 Hz, PhCH$_2$); 4.75-4.68 (m, 2H, PhCH$_2$); 4.37 (dd, 1H, $J =$ 5.2 Hz, 10.0 Hz, H-2); 4.22 (q, 1H, $J =$ 6.4 Hz, H-5); 3.83 (s, 3H, OC$_3$H$_3$); 3.75-3.72 (m, 2H, H-3, H-4); 1.13 (d, 3H, $J =$ 6.4 Hz, H-6). $^{13}$C NMR (100 MHz) δ: 159.4, 135.5 (C$_{arom}$); 134.4 (CH$_{arom}$); 133.1, 133.0 (C$_{arom}$); 129.6 (CH$_{arom}$); 129.5 (C$_{arom}$); 129.0 (CH$_{arom}$); 128.7 (C$_{arom}$); 128.1, 127.8, 127.7, 127.6, 126.9, 126.3, 126.1, 125.9, 114.0 (CH$_{arom}$); 85.6 (C-1); 80.4, 75.6 (C-3, C-4); 74.9, 72.3 (PhCH$_2$); 69.4 (C-5); 60.8 (C-2); 55.3 (OCH$_3$); 16.6 (C-6). IR (thin film) ν: 2874, 2106, 1612, 1512, 1300, 1246, 1099, 1063, 1034. HRMS: [M+H]$^+$ calculated for C$_{31}$H$_{32}$N$_3$O$_4$Se: 590.15525; found 590.15516.

Phenyl 2-azido-2-deoxy-4-O-(2-naphthylmethyl)-1-seleno-α-L-fucopyranoside (18)

To a stirred solution of 17 (1.3 g, 2.3 mmol, 1.0 eq.) and Et$_3$SiH (1.1 mL, 6.8 mmol, 3.0 eq.) in CH$_2$Cl$_2$ (11 mL, 0.2 M) was added a solution of HCl (0.17 mL 37% aq. HCl in 10 mL HFIP). After 1 minute, the mixture was poured on NaHCO$_3$ (sat. aq.) and, after separation of the layers, the aqueous phase was extracted (CH$_2$Cl$_2$, 2x), the combined organic phases were washed (brine, 1x), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc, 1:0 → 9:1 v/v) delivered the title product in 63% yield (0.67 g, 1.4 mmol). $^1$H
NMR (400 MHz) δ: 7.84-7.81 (m, 4H, CH<sub>arom</sub>); 7.60-7.56 (m, 2H, CH<sub>arom</sub>); 7.55-7.46 (m, 3H, CH<sub>arom</sub>); 7.31-7.16 (m, 3H, CH<sub>arom</sub>); 5.93 (d, 1H, J = 5.2 Hz, H-1); 4.96 (d, 1H, J = 11.6 Hz, ArCH<sub>2</sub>H); 4.88 (d, 1H, J = 11.6 Hz, ArCH<sub>2</sub>H); 4.33 (q, 1H, J = 6.4 Hz, H-5); 4.07 (dd, 1H, J = 5.2 Hz, 10.4 Hz, H-2); 3.86-3.80 (m, 1H, H-3); 3.73 (d, 1H, J = 2.4 Hz, H-4); 2.30 (d, 1H, J = 8.4 Hz, 3-OH); 1.26 (d, 3H, J = 6.4 Hz, H-6).<sup>13</sup>C-APT NMR (100 MHz) δ: 135.0 (C<sub>qarom</sub>); 134.4 (CH<sub>arom</sub>); 133.2, 133.1 (C<sub>qarom</sub>); 129.1, 128.6 (CH<sub>arom</sub>); 128.6 (C<sub>qarom</sub>); 127.9, 127.7, 127.4, 127.0, 126.3, 126.2, 125.8 (CH<sub>arom</sub>); 85.2 (C-1); 79.2 (C-4); 76.2 (ArCH<sub>2</sub>); 72.0 (C-3); 69.3 (C-5); 62.5 (C-2); 16.7 (C-6). IR (thin film) ν: 3534, 2889, 2104, 1263, 1092, 1053, 1034, 1020. HRMS: [M+H]<sup>+</sup> calculated for C<sub>23</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>Se: 470.09774; found 470.09760.

Phenyl 2-azido-3-O-benzoyl-2-deoxy-4-O-(2-naphthylmethyl)-1-seleno-α-L-fucopyranoside (19)

To a stirred solution of 18 (0.67 g, 1.4 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub>/pyridine (4:1 v/v, 7 mL, 0.2 M) were, at 0 °C, added DMAP (17 mg, 0.14 mmol, 0.1 eq.) and BzCl (0.24 mL, 2.1 mmol, 1.5 eq.). The reaction was allowed to warm to room temperature and stirred overnight, after which TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material. The reaction was quenched with H<sub>2</sub>O, the mixture diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed (1M aq. HCl, 2x; sat. aq. NaHCO<sub>3</sub>, 1x; H<sub>2</sub>O, 1x; brine, 1x), dried over MgSO<sub>4</sub>, filtered and concentrated <i>in vacuo</i>. The title product was obtained after column chromatography (PE/EtOAc, 1:0 → 19:1) in 70% yield (0.56 g, 1.0 mmol).

<sup>1</sup>H NMR (400 MHz) δ: 8.05-8.03 (m, 2H, CH<sub>arom</sub>); 7.74-7.68 (m, 3H, CH<sub>arom</sub>); 7.61-7.56 (m, 4H, CH<sub>arom</sub>); 7.47-7.36 (m, 5H, CH<sub>arom</sub>); 7.31-7.25 (m, 3H, CH<sub>arom</sub>); 6.02 (d, 1H, J = 5.2 Hz, H-1); 5.29 (dd, 1H, J = 2.8 Hz, 10.8 Hz, H-3); 4.79 (d, 1H, J = 11.6 Hz, ArCH<sub>2</sub>H); 4.72 (d, 1H, J = 11.6 Hz, ArCH<sub>2</sub>H); 4.61 (dd, 1H, J = 5.2 Hz, 10.8 Hz, H-2); 4.44 (q, 1H, J = 6.4 Hz, H-5); 4.07 (d, 1H, J = 2.4 Hz, H-4); 1.20 (d, 3H, J = 6.4 Hz, H-6).<sup>13</sup>C-APT NMR (100 MHz) δ: 165.7 (C<sub>qarom</sub>); 134.8 (C<sub>arom</sub>); 134.5, 133.6 (CH<sub>arom</sub>); 133.0, 132.9 (C<sub>qarom</sub>); 129.8, 129.1 (CH<sub>arom</sub>); 128.9, 128.6 (C<sub>qarom</sub>); 128.4, 128.2, 127.8, 127.6, 126.9, 126.1, 126.0 (CH<sub>arom</sub>); 84.9 (C-1); 76.7 (C-4); 75.8 (ArCH<sub>2</sub>); 75.1 (C-3); 69.1 (C-5); 59.6 (C-2); 16.3 (C-6). IR (thin film) ν: 3056, 2108, 1721, 1263, 1107, 1082, 1069, 1047, 1022. HRMS: [M+Na]<sup>+</sup> calculated for C<sub>30</sub>H<sub>27</sub>N<sub>3</sub>NaO<sub>3</sub>Se: 596.10590; found 596.10637.
Chapter 4

**Phenyl 2-azido-4-O-benzoyl-2-deoxy-3-O-(4-methoxybenzyl)-1-seleno-α-L-fucopyranoside (20)**

To a stirred solution of 16 (0.45 g, 1.0 mmol, 1.0 eq.) in CH₂Cl₂/pyridine (3:2 v/v, 5 mL, 0.2 M) was added DMAP (12 mg, 0.1 mmol, 0.1 eq.). At 0 °C was added BzCl (0.23 mL, 2.0 mmol, 2.0 eq.) and the mixture was stirred at this temperature until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~2 hours). The reaction was quenched by addition of MeOH, diluted with CH₂Cl₂, washed (sat. aq. NH₄Cl, 2x; H₂O, 1x; brine, 1x) dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 1:0 → 9:1 v/v) delivered the title compound in 82% yield (0.45 g, 0.82 mmol). ¹H NMR (400 MHz) δ: 8.11-8.01 (m, 2H, CH₉ arom); 7.63-7.56 (m, 3H, CH₂ arom); 7.51-7.43 (m, 2H, CH₂ arom); 7.33-7.26 (m, 5H, CH₉ arom); 6.86-6.83 (m, 2H, CH₂ arom); 5.99 (s, 1H, J = 5.2 Hz, H-1); 5.69 (d, 1H, J = 2.8 Hz, H-4); 4.78 (d, 1H, J = 10.8 Hz, ArCH(C)); 4.54 (q, 1H, J = 6.4 Hz, H-5); 4.50 (d, 1H, J = 10.4 Hz, ArCH(C)); 4.22 (dd, 1H, J = 5.2 Hz, 10.4 Hz, H-2); 3.88 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-3); 3.78 (s, 3H, OCH₃); 1.17 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 166.0 ( Cô₂); 134.6, 133.3, 130.1, 129.8 (CH₉ arom); 129.5, 129.1 (C₉ arist); 129.0, 128.5, 127.9, 113.8 (CH₂ arom); 85.1 (C-1); 77.0 (C-3); 71.2 (ArCH₂); 69.3 (C-4); 68.0 (C-5); 60.4 (C-2); 55.2 (OCH₃); 16.2 (C-6). IR (thin film) ν: 2934, 2108, 1719, 1514, 1265, 1248, 1175, 1109, 1080, 1063, 1024. HRMS: [M-N₂+H]+ calculated for C₂₉H₂₈NO₅Se: 526.11272; found 526.11254.

**1,3,4,6-tetra-O-acetyl-2-azido-2-deoxy-α/β-D-mannopyranoside (22)**

TfO (14 mL, 84 mmol, 1.2 eq.) was slowly added to an ice-cooled suspension of NaN₃ (6.8 g, 105 mmol, 1.5 eq.) in pyridine (120 mL) and the mixture was stirred at this temperature for 2 hours. Mannosamine.HCl (15 g, 70 mmol, 1.0 eq.) was suspended in pyridine (70 mL, 1M), and added was NEt₃ (19 mL, 140 mmol, 2.0 eq.) and a solution of CuSO₄.5H₂O (0.17 g, 0.7 mmol, 0.01 eq.) in a minimal amount of H₂O, and the homogeneous blue mixture thus obtained was cooled to 0 °C. To this mixture was added the TfN₃ solution via a syphon, during which the reaction mixture obtained a green color. The reaction mixture was stirred at 0 °C until TLC analysis (CH₂Cl₂/MeOH/NEt₃b, 20:75:5) indicated complete conversion of the starting material (~3 hours, color turned from green to yellow). Added was Ac₂O (73 mL, 770 mmol, 11 eq.) and the mixture was stirred overnight, after which TLC analysis (PE/EtOAc, 3:2 v/v) indicated complete conversion to the peracetylated product. The mixture was diluted with EtOAc, washed (1M aq.
HCl, 3x; sat. aq. NaHCO₃, 3x; H₂O, 1x; brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. The crude sugar (α/β 3:2) was used without further purification. ¹H NMR (400 MHz) δ: 6.12 (d, 3H, J = 2.0 Hz, H-1α); 5.85 (d, 2H, J = 1.2 Hz, H-1β); 5.43-5.36 (m, 5H, H-3α, H-4α); 5.30 (t, 2H, J = 9.6 Hz, H-4β); 5.07 (dd, 2H, J = 3.6 Hz, 9.6 Hz, H-3β); 4.30-4.23 (m, 5H, H-6α, H-6β); 4.16-4.08 (m, 13H, H-2α, H-2β, H-5α, H-6α, H-6β); 3.77-3.72 (m, 2H, H-5β); 2.20 (s, 6H, CH₃α,β); 2.17 (m, 9H, CH₃α,β); 2.13 (s, 15H, CH₃α,β); 2.10 (s, 9H, CH₃α,β); 2.06 (s, 9H, CH₃α,β); 2.05 (s, 6H, CH₃α,β).

Phenyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-thio-α-D-mannopyranoside (23)

To a stirred, ice-cooled solution of mannosazide 22 (12.4 g, 33 mmol, 1.0 eq.) in CH₂Cl₂ (165 mL, 0.2 M) were added PhSH (3.6 mL, 32.9 mmol, 0.99 eq.) and BF₃·OEt₂ (8.3 mL, 66 mmol, 2.0 eq.). After 1 hour the ice-bath was removed and the mixture was stirred until TLC analysis (PE/EtOAc, 3:2 v/v) indicated complete consumption of the starting material (~16 hours). The reaction was quenched by addition of NEt₃, diluted with CH₂Cl₂ and subsequently washed (sat. aq. NaHCO₃, 1x; 1M aq. NaOH 3x; H₂O 1x, brine 1x), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) to deliver the title compound as an oil in 76% yield (10.6 g, 25 mmol). ¹H NMR (400 MHz) δ: 7.50-7.27 (m, 5H, CH₃α,β); 5.53 (d, 1H, J = 0.8 Hz, H-1); 5.40-5.33 (m, 2H, H-6); 4.52-4.48 (m, 1H, H-5); 4.30-4.25 (m, 2H, H-2, H-4); 4.06 (dd, 1H, J = 2.4 Hz, 11.2 Hz, H-3); 2.12, 2.08, 2.06 (s, 3H, CH₃α,β).

Phenyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (25)

To a stirred solution of 23 (10.6 g, 25 mmol, 1.0 eq.) in MeOH (85 mL, 0.3 M) was added a piece of Na. After overnight stirring, TLC analysis (PE/EtOAc, 2:3 v/v) indicated complete conversion of the starting material. The reaction mixture was neutralized with Amberlite IR-120 ion-exchange resin (H⁺-form), filtered, and concentrated in vacuo. The residue was dissolved in MeCN (85 mL, 0.3 M) and added were benzaldehyde dimethyl acetal (4.5 mL, 30 mmol, 1.2 eq.) and camphorsulfonic acid (0.58 g, 2.5, mmol, 0.1 eq.). The reaction mixture was stirred on a rotary evaporator under reduced pressure (250 mbar, 50 °C) until the mixture was concentrated to ~20% of the original volume, after which TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete
conversion of the starting material. The mixture was basified with NEt₃ and concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc, 9:1 → 2:1 v/v) to deliver the title compound in 99% yield (9.6 g, 24.8 mmol). ¹H NMR (400 MHz) δ: 7.50-7.24 (m, 10H, CH₆); 5.57 (s, 1H, PhCH₃); 5.46 (s, 1H, H-1); 4.35-4.16 (m, 4H, H-3, H-5, H-6); 3.95 (t, 1H, J = 9.6 Hz, H-4); 3.81 (t, 1H, J = 10.0 Hz, H-6), 2.85 (bs, 1H, OH).

*Phenyl 2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (26)*

![Structural diagram](image)

To a stirred solution of 25 (2.05 g, 5.3 mmol, 1.0 eq.) in DMF (18 mL, 0.3 M) was added BnBr (1.3 mL, 10.6 mmol, 2.0 eq.) and Bu₂N (0.18 g, 0.5 mmol, 0.1 eq.). The reaction mixture was cooled to 0 °C, after which NaH (60% w/w in oil, 0.32 g, 8.0 mmol, 1.5 eq.) was added. The reaction mixture was stirred at 0 °C until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete consumption of the starting material (~3 hours). The excess NaH was quenched by careful addition of H₂O, the mixture was partitioned between Et₂O and H₂O, and after separation, the aqueous layer was extracted with Et₂O (2x). The combined ethereal phases were washed with brine (1x), dried over MgSO₄, filtered and concentrated in vacuo. The title compound was obtained after column chromatography (PE/Et₂O, 1:0 → 9:1 v/v) as an oil which solidified on standing, in 96% yield (2.43 g, 5.11 mmol). ¹H NMR (400 MHz) δ: 7.48-7.24 (m, 15H, CH₆); 5.63 (s, 1H, PhCH₃); 5.43 (s, 1H, H-1); 4.93 (d, 1H, J = 12.0 Hz, PhCH₂H); 4.75 (d, 1H, J = 12.0 Hz, PhCHH); 4.32 (dt, 1H, J = 4.8 Hz, 9.6 Hz, H-5); 4.23-4.11 (m, 4H, H-2, H-3, H-4, H-6); 3.85 (t, 1H, J = 10.0 Hz, H-6).

*Phenyl 2-azido-3,4-di-O-benzyl-2-deoxy-1-thio-α-D-mannopyranoside (27)*

![Structural diagram](image)

To a stirred, ice-cooled solution of benzylidene-protected mannnoside 26 (4.9 g, 10.3 mmol, 1.0 eq.) in CH₂Cl₂ (30 mL, 0.3 M) was added, under argon, BH₃·THF (as 1.0 M solution in THF, 30 mL, 3.0 eq.), followed by Bu₂BOTf (as 1.0 M solution in CH₂Cl₂, 10 mL, 1.0 eq.) and the reaction mixture was kept at 0 °C. After 1 hour, TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material, and the reaction was quenched by sequential addition of NEt₃ (4 mL) and MeOH (added dropwise until gas evolution ceased). The mixture was concentrated in vacuo and the residue was co-evaporated with MeOH (3x). Purification by column chromatography (PE/EtOAc, 19:1 → 9:1 v/v) delivered the title compound as a colorless oil (4.6 g, 9.7 mmol, 94%
yield. $^1$H NMR (400 MHz) $\delta$: 7.42-7.22 (m, 15H, $CH_{\text{arom}}$); 5.40 (s, 1H, H-1); 4.90 (d, 1H, $J= 10.8$ Hz, PhCH$_2$); 4.75 (s, 2H, PhCH$_2$); 4.66 (d, 1H, $J= 11.2$ Hz, PhCH$_2$); 4.15-4.04 (m, 3H, H-2, H-3, H-5); 3.92 (t, 1H, $J= 9.6$ Hz, H-4); 3.77 (bs, 2H, H-6); 1.88 (bs, 1H, 6-OH). $^{13}$C-APT NMR (100 MHz) $\delta$: 137.9, 137.3, 132.9 ($C_{\text{g,arom}}$); 132.1, 129.2, 128.6, 128.4, 128.1, 128.0, 127.9 ($CH_{\text{arom}}$); 86.2 (C-1); 79.8 (C-2, C-3 or C-5); 75.4 (PhCH$_2$); 74.2 (C-4); 73.2 (C-2, C-3 or C-5); 72.7 (PhCH$_2$); 62.7 (C-2, C-3 or C-5); 61.7 (C-6). IR (thin film) $\nu$: 2872, 2102, 1454, 1439, 1265, 1180, 1103, 1094, 1078, 1026. HRMS: [M+Na]$^+$ calculated for $C_{26}H_{27}N_3NaO_8S$: 500.16145; found 500.16110.

*Methyl (phenyl 2-azido-3,4-di-O-benzyl-2-deoxy-1-thio-$\alpha$-$\delta$-mannopyranosiduronate) (28)*

Primary alcohol 27 (1.17 g, 2.6 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (8 mL) and added were H$_2$O (4 mL) and tert-butanol (1 mL, final concentration 0.2 M). Under vigorous stirring were added AcOH (15 $\mu$L, 0.26 mmol, 0.1 eq.), TEMPO (81 mg, 0.52 mmol, 0.2 eq.) and Phl(OAc)$_2$ (2.09 g, 6.5 mmol, 2.5 eq.) and the resulting red mixture was stirred until TLC analysis (PE/EtOAc/AcOH, 75:20:5 v/v/v) indicated complete conversion of the starting material into a lower-running spot (~90 minutes). The reaction was quenched by addition of sat. aq. Na$_2$S$_2$O$_3$ and the resulting light yellow mixture was extracted (CH$_2$Cl$_2$, 2x). The combined organic fractions were washed (H$_2$O 1x, brine 1x), dried over MgSO$_4$, filtered and concentrated *in vacuo*. After co-evaporation with toluene (1x), the residue was dissolved in DMF (9 mL, 0.3 M) and added were MeI (0.32 mL, 5.2 mL, 2.0 eq.) and K$_2$CO$_3$ (0.72 g, 5.2 mmol, 2.0 eq.). The reaction was stirred overnight, after which TLC analysis (PE/EtOAc/AcOH, 70:30:5 v/v/v) indicated complete conversion of the starting material. The reaction mixture was partitioned between Et$_2$O and H$_2$O, and after separation, the aqueous phase was extracted with Et$_2$O (2x). The combined ethereal phases were washed (brine 1x), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc, 1:0 $\rightarrow$ 9:1 v/v) to deliver the title compound as an oil in 79% yield (1.04 g, 2.06 mmol). $^1$H NMR (400 MHz) $\delta$: 7.62-7.60 (m, 2H, $CH_{\text{arom}}$); 7.38-7.25 (m, 13H, $CH_{\text{arom}}$); 5.61 (d, 1H, $J= 7.6$ Hz, H-1); 4.69-4.59 (m, 5H, H-5, PhCH$_2$); 4.21 (dd, 1H, $J= 4.4$ Hz, 5.6 Hz, H-4); 3.93 (dd, 1H, $J= 3.2$ Hz, 5.6 Hz, H-3); 3.72 (dd, $J= 2.4$ Hz, 7.6 Hz, H-2); 3.54 (s, 3H, OCH$_3$). $^{13}$C-APT NMR (100 MHz) $\delta$: 169.3 (C-6); 137.3, 136.8 ($C_{\text{g,arom}}$); 132.4 ($CH_{\text{arom}}$); 132.0 ($C_{\text{g,arom}}$); 128.9, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7; 74.6 (C-4); 73.0 (PhCH$_2$); 72.9 (C-5); 58.7 (C-2); 52.2 (OCH$_3$).

The C-1 and C-3 were not observable at room temperature due to signal broadening. IR (thin film) $\nu$: 2870, 2102, 1749, 1454, 1439, 1265, 1119, 1094, 1078, 1024. HRMS: [M+Na]$^+$ calculated for $C_{27}H_{27}N_3NaO_8S$: 528.15636; found 528.15588.
Chapter 4

Methyl (2-azido-3,4-di-O-benzyl-2-deoxy-α/β-d-mannopyranosiduronate) (29)

To a solution of thioglycoside 28 (0.56 g, 1.12 mmol, 1.0 eq.) in acetone (8.4 mL) was added H₂O (2.8 mL, final concentration 0.1 M). At 0 °C was added NBS (0.60 g, 3.35 mmol, 3.0 eq.) and the reaction mixture assumed an orange-brown color. After ~90 minutes, a second portion of NBS (0.60 g, 3.35 mmol, 3.0 eq.) was added and the mixture was stirred for 15 more minutes, after which TLC (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material. The reaction was quenched by addition of sat. aq. Na₂S₂O₅, the mixture was extracted (EtOAc, 3x). The combined organic phases were washed (H₂O 1x, brine 1x), dried over MgSO₄, filtered and concentrated in vacuo. The title compounds were obtained after column chromatography (PE/EtOAc, 9:1 → 7:3 v/v), with the β-product predominating (α/β ~ 1:9), in 82% yield (0.38 g, 0.92 mmol). NMR data is reported for the β-isomer only. ¹H NMR (400 MHz, 323 K) δ: 7.29-7.22 (m, 10H, CH₃; 5.42 (d, 1H, J = 3.6 Hz, H-1); 4.65 (s, 2H, PhCH₂); 4.62-4.54 (m, 2H, PhCH₂); 4.49 (d, 1H, J = 5.6 Hz, H-5); 4.33 (bs, 1H, 1-OH); 4.12 (t, 1H, J = 5.6 Hz, H-4); 3.96 (bd, 1H, J = 3.2 Hz, H-3); 3.76 (bs, 1H, H-2); 3.55 (s, 3H, OCH₃).¹³C-APT NMR (100 MHz, 323 K) δ: 169.7 (C-6); 137.5, 137.3 (C₆); 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7 (CH₃); 92.1 (C-1); 77.4 (C-3); 75.2 (C-4); 73.5, 72.8 (PhCH₂); 72.3 (C-5); 61.0 (C-2); 52.1 (OCH₃). ¹³C-GATED NMR (100 MHz, 323 K) δ: 92.1 (d, J = 170 Hz, H-1). IR (thin film) 3439, 2104, 1747, 1454, 1437, 1281, 1240, 1123, 1093, 1072, 1024. HRMS: [M+Na]⁺ calculated for C₂₁H₂₅N₃O₆: 436.14791; found 436.14758.

Methyl (2-azido-3,4-di-O-benzyl-2-deoxy-1-O-(N-phenyl-2,2,2-trifluoroacetimidoyl)-α/β-d-mannopyranosiduronate) (6)

To a stirred solution of hemiacetal 29 (0.30 g, 0.73 mmol, 1.0 eq.) in acetone (2.5 mL, 0.3 M) was added N-phenyl 2,2,2-trifluoroimidoyl chloride (0.17 mL, 1.1 mmol, 1.5 eq.) and Cs₂CO₃ (0.29 g, 0.88 mmol, 1.2 eq.), and the mixture was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~2 hours). The reaction mixture was diluted with acetone, filtered and concentrated in vacuo. Purification of the residue by column chromatography (PE/EtOAc/NEt₃, 100:0:1 → 90:10:1) delivered the title compound as a mixture of anomers and/or conformers, in 88% yield (0.38 g, 0.64 mmol). ¹H NMR (major isomer, 400 MHz, 323 K) δ: 7.34-7.25 (m, 13H, CH₃; 7.11 (t, 1H, J = 7.6 Hz, CH₃; 6.80 (d, 2H, J = 8.0 Hz, 108
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(CH<sub>arom</sub>): 6.30 (bs, 1H, H-1); 4.77-4.64 (m, 4H, PhCH<sub>2</sub>); 4.38 (d, 1H, J = 7.2 Hz, H-5); 4.18 (t, 1H, J = 7.6 Hz, H-4); 4.02 (dd, 1H, J = 2.8 Hz, 7.6 Hz, H-3); 3.87 (bs, 1H, H-2); 3.66 (s, 3H, OCH<sub>3</sub>). 13C-APT NMR (100 MHz, 323 K) δ: 168.5 (C-6); 143.1, 137.5, 137.1 (C<sub>quarom</sub>); 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 124.6, 119.4 (CH<sub>arom</sub>); 94.4 (C-1); 77.8 (C-3); 74.9 (C-4); 74.6 (PhCH<sub>2</sub>); 73.8 (C-5); 73.5 (PhCH<sub>2</sub>); 59.8 (C-2); 52.4 (OCH<sub>3</sub>). Diagnostic 1H NMR signals for the minor isomer (400 MHz, 323 K) δ: 6.00 (bs, 0.2H, H-1); 4.30 (t, 0.2H, J = 6.8 Hz, H-4); 3.91 (bs, 0.2H, H-2); 3.62 (s, 0.6H, OCH<sub>3</sub>). IR (thin film) ν: 2110, 1751, 1717, 1317, 1207, 1161, 1115, 1026.

HRMS: [M+Na]<sup>+</sup> calculated for C<sub>29</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>N<sub>O</sub>: 607.17749; found 607.17767.

5-(benzyl(benzylloxycarbonyl)amino)pentyl 2-azido-3-O-(2-azido-3-O-benzoyl-2-deoxy-4-O-(2-naphthylmethyl)-α/β-l-fucopyranosyl)-4-O-benzyl-β-D-fucopyranoside (32)

To a mixture of donor 19 (57 mg, 0.10 mmol, 1.0 eq.), Ph<sub>2</sub>SO (26 mg, 0.13 mmol, 1.3 eq.) and TTBP (62 mg, 0.25 mmol, 2.5 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL, 0.05 M) were added flame-dried, rod-shaped 3Å molecular sieves. After stirring for ~30 minutes, the reaction mixture was cooled to -80 °C and treated with Tf<sub>2</sub>O (22 μL, 0.13 mmol, 1.3 eq.). The mixture was warmed to -60°C and subsequently re-cooled to -80 °C. Added was a solution of acceptor 15 (dried by triple co-evaporation with toluene, 62 mg, 0.105 mmol, 1.05 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (0.2 mL), and the temperature was slowly raised to -30 °C over the course of ~3 hours, then kept at this temperature for 1.5 hours. The reaction was quenched by addition of NEt<sub>3</sub> (0.1 mL), filtered over a pad of celite, washed with brine (1x), dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc, 1:0 → 9:1 v/v), followed by size-exclusion chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 1:1 v/v) delivered the title disaccharides as a mixture (α/β 1:2) in 35% yield (35 mg, 0.035 mmol).

1H NMR (400 MHz) δ: 8.07 (d, 2H, J = 7.6 Hz, CH<sub>arom</sub>α); 8.02 (d, 4H, J = 7.6 Hz, CH<sub>arom</sub>β); 7.76-7.56 (m, 15H, CH<sub>arom</sub>); 7.47-7.17 (m, 60H, CH<sub>arom</sub>); 5.55 (dd, 1H, J = 2.4 Hz, 11.2 Hz, H3'α); 5.43 (d, 1H, J = 3.6 Hz, H-1'α); 5.19-5.15 (m, 6H, PhCH<sub>2</sub>α, PhCH<sub>2</sub>β); 5.05-5.00 (m, 3H, H-3'β, PhCHHα); 4.96-4.68 (m, 10H, PhCH<sub>2</sub>); 4.53-4.48 (m, 8H, H-1'β, PhCH<sub>2</sub>); 4.22-4.11 (m, 5H, H-1α, H-1β, H-2β); 3.98 (dd, 1H, J = 3.2 Hz, 11.4 Hz, H-2'α); 3.91-3.68 (m, 14H, H-2α, H-2β, H-3β, H-4α, H-5α, H-4'α, H-4'β, H-5'α, OCH<sub>3</sub>pentylα, OCH<sub>3</sub>pentylβ); 3.62 (d, 2H, J = 1.6 Hz, H-4β); 3.53-3.42 (m, 8H, H-3α, H-5β, H-5'β, OCH<sub>3</sub>pentylα, OCH<sub>3</sub>pentylβ); 3.26-3.19 (m, 6H, NCH<sub>2</sub>pentylα, NCH<sub>2</sub>pentylβ); 1.56 (m, 11H, CH<sub>2</sub>pentyl); 1.34-1.25 (m, 16H, H-6α, H-6β, CH<sub>2</sub>pentyl); 1.17-1.13 (m, 9H, H-6α, H-6β). Diagnostic 13C-APT NMR signals (100 MHz) δ: 102.6 (C-1α); 102.2 (C-1β); 100.4 (C-1'β); 99.9 (C-1’α); 71.4 (C-3’α); 63.6
(C-2α); 62.7 (C-2β); 61.7 (C-2’β); 57.7 (C-2’α). 13C-GATED NMR (100 MHz) δ: 100.4 (J = 160 Hz, H-1’β); 99.9 (J = 172 Hz, C-1’α). IR (thin film) ν: 2938, 2112, 1717, 1694, 1452, 1422, 1362, 1267, 1173, 1069. HRMS: [M+NH₄]⁺ calculated for C₅₇H₆₆N₈O₁₀: 1021.48182; found 1021.48229.

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-3-O-(2-azido-4-O-benzoyl-2-deoxy-4-O-(4-methoxybenzyl)-α/β-l-fucopyranosyl)-4-O-benzyl-β-D-fucopyranoside (33)

To a stirred solution of 20 (0.11 g, 0.2 mmol, 2.0 eq.), Ph₃SO (40 mg, 0.2 mmol, 2.0 eq.) and TTBP (99 mg, 0.4 mmol, 4.0 eq.) in CH₂Cl₂ (2 mL, 0.1 M relative to donor) were added flame-dried, rod-shaped 3Å molecular sieves. After 30 minutes at room temperature, the reaction mixture was cooled to -80 °C, after which Tf₂O (34 μL, 0.2 mmol, 2.0 eq.) was added. The reaction mixture was allowed to warm to -60 °C, after which it was re-cooled to -80 °C. Added was a solution of acceptor 15 (dried by triple co-evaporation with toluene, 59 mg, 0.1 mmol, 1.0 eq.) in CH₂Cl₂ (0.2 mL) via the wall of the flask and the mixture was allowed to warm to -40 °C, after which it was stirred at this temperature for 15 minutes. The reaction was stopped by addition of NEt₃ (1 mL), the mixture filtered over a pad of celite, washed with brine (1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by size-exclusion chromatography delivered the title compounds as a mixture (α/β ~9:1) in 65% yield (64 mg, 0.065 mmol). NMR data is reported for the α-isomer only. 1H NMR (400 MHz) δ: 8.05 (d, 2H, J = 7.6 Hz, CH₅arom); 7.56 (d, 1H, J = 7.6 Hz, CH₅arom); 7.46-7.22 (m, 19H, CH₅arom); 6.67 (d, 2H, J = 7.6 Hz, CH₅arom); 5.48 (s, 1H, H-4’); 5.48 (s, 1H, H-4’); 5.38 (d, 1H, J = 3.2 Hz, H-1’); 5.17 (bs, 2H, PhCH₂); 4.76 (d, 1H, J = 11.6 Hz, PhCH₂); 4.68-4.65 (m, 2H, PhCH₂); 4.49 (bs, 2H, PhCH₂); 4.33 (d, 1H, J = 10.8 Hz, PhCH₂H); 4.19 (d, 1H, J = 8.0 Hz, H-1’); 4.01 (q, 1H, J = 6.4 Hz, H-5’); 3.91-3.70 (m, 5H, H-2, H-2’, H-3’, OCH₃penty); 3.68 (s, 3H, OCH₃); 3.53-3.43 (m, 4H, H-3, H-4, H-5’, OCH₃penty); 3.24 (bs, 2H, NCH₂penty); 1.55 (bs, 4H, CH₂penty); 1.35 (bs, 2H, CH₂penty); 1.28 (d, 3H, J = 6.4 Hz, H-6’); 1.14 (d, 3H, J = 6.4 Hz, H-6’). 13C-APT NMR (100 MHz) δ: 166.1 (CO₂Ba); 160.0, 138.3, 138.1 (Cqarom); 133.2, 130.1 (CH₅arom); 130.0, 129.9 (Cqarom); 129.8, 129.3, 128.5, 128.4, 128.2, 127.9, 127.9, 127.6, 127.3, 114.0 (CH₅arom); 102.7 (C-1); 99.8 (C-1’); 79.0, 78.9 (C-4, C-5); 75.4 (PhCH₂); 73.1 (C-3’); 71.1 (PhCH₂); 70.8 (C-3); 70.1 (C-4’); 69.8 (OCH₂penty); 67.2 (PhCH₂); 66.0 (C-3’); 63.9 (C-2); 59.3 (C-2’); 55.2 (OCH₃); 50.6 (NCH₂penty); 29.3, 23.3 (CH₂penty); 17.0, 16.4 (C-6, C-6’). IR (thin film) ν: 2936, 2112, 1719, 1694, 1452, 1422, 1362, 1173, 1099, 1067, 1026. HRMS: [M+NH₄]⁺ calculated for C₅₇H₆₅N₈O₁₀: 1001.47673; found 1001.47711.
5-(benzyl(benzyloxy carbonyl) amino)pentyl 2-azido-3-O-(2-azido-2-deoxy-3,4-di-O-(tert-butyldimethylsilyl)-α-L-fucopyranosyl)-4-O-benzyl-β-D-fucopyranoside (34)

To a stirred solution of 31 (1.22 g, 2.2 mmol, 2.0 eq.), Ph2SO (0.44 g, 2.2 mmol, 2.0 eq.) and TTBP (1.09 g, 4.4 mmol, 4.0 eq.) in CH2Cl2 (22 mL, 0.1 M relative to donor) were added flame-dried, rod-shaped 3Å molecular sieves. After 30 minutes at room temperature, the reaction mixture was cooled to -80 °C, after which Tf2O (0.37 mL, 2.2 mmol, 2.0 eq.) was added. The reaction mixture was allowed to warm to -70 °C, after which it was re-cooled to -80 °C. Added was a solution of acceptor 15 (dried by triple co-evaporation with toluene, 0.65 g, 1.1 mmol, 1.0 eq.) in CH2Cl2 (2.2 mL) via the wall of the flask and the mixture was allowed to warm to -60 °C, after which it was stirred at this temperature for 15 minutes. The reaction was stopped by addition of NEt3 (1 mL), the mixture filtered over a pad of celite, washed with brine (1x), dried over MgSO4, filtered and concentrated in vacuo. Purification of the residue by column chromatography (toluene/EtOAc, 1:0 → 9:1 v/v) and size-exclusion chromatography (CH2Cl2/MeOH, 1:1 v/v) furnished the title compound as an oil (0.83 g, 0.84 mmol, 76%). 1H NMR (400 MHz, 323 K) δ: 7.34-7.21 (m, 15H, CHarom); 5.36 (d, 1H, J = 3.6 Hz, H-1'); 5.16 (s, 2H, PhCH2); 4.97 (d, 1H, J = 11.6 Hz, PhC(CH3)2); 4.58 (d, 1H, J = 11.2 Hz, PhCH2); 4.48 (s, 2H, PhCH2); 4.17 (d, 1H, J = 8.0 Hz, H-1); 4.99 (bd, 1H, J = 10.0 Hz, H-3'); 3.94 (q, 1H, J = 6.8 Hz, H-5'); 3.85-3.80 (m, 2H, OCH2CH2OCH3); 3.77-3.71 (m, 2H, H-2', H-4'); 3.52-3.42 (m, 4H, OCH2CH2CH2OCH3); 3.23 (bs, 2H, NCH2CH2pentyl); 1.53 (bs, 4H, 2x CH2CH2pentyl); 1.34 (bs, 2H, CH2CH2CH2pentyl); 1.23 (d, 3H, J = 6.4 Hz, H-6 or H-6'); 1.19 (d, 3H, J = 6.4 Hz, H-6 or H-6'); 0.93, 0.93 (s, 9H, CH3CH2CH2Ph); 0.16, 0.14, 0.11, 0.09 (s, 3H, CH3CH2CH2CH3); 13C-APT NMR (100 MHz, 323 K) δ: 151.5 (OCH3); 138.3, 138.1 (Cq,arom); 128.5, 128.4, 128.3, 127.9, 127.9, 127.8, 127.7, 127.2 (CH2arom); 102.8 (C-1); 99.3 (C-1'); 78.8, 78.7 (C-2, C-5); 75.0 (PhCH2); 74.9 (C-4); 71.4 (C-3'); 70.8 (C-3'); 69.7 (OCH2CH2pentyl); 69.0 (C-5'); 67.2 (PhCH2); 63.8 (C-2); 61.2 (C-2'); 50.5 (PhCH2); 29.2 (CH2CH2pentyl); 26.2, 26.1 (CH3CH2CH2Ph); 23.3 (PhCH2); 18.6, 18.5 (Cq,CH2Ph); 17.3, 16.9 (C-6, C-6'); -3.4, -3.6, -4.5, -4.6 (CH3Me).IR (thin film) ν: 2930, 2857, 2114, 1697, 1252, 1177, 1105, 1067, 1042, 1026. HRMS: [M+Na]+ calculated for C51H77N7NaO9Si2: 1010.52135; found 1010.52155.
To a stirred solution of disaccharide 34 (0.83 g, 0.84 mmol, 1.0 eq.) in THF (4 mL, 0.2 M) was added Bu$_3$NF (as 1M solution in THF, 2.0 mL, 2.4 eq.) and the resulting yellow reaction mixture was stirred until TLC analysis (toluene/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~2 hours). The mixture was diluted with EtOAc, and the reaction quenched by addition of sat. aq. NaHCO$_3$. After separation of the layers, the aqueous layer was extracted with EtOAc (1x), and the combined organics were washed (H$_2$O, 1x; brine, 1x), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was co-evaporated once with dry MeCN, before dissolution in MeCN (4 mL, 0.2 M). Added were, in succession, 2-aminoethyl diphenylborinate 36 (18 mg, 0.08 mmol, 0.1 eq.), DIPEA (0.3 mL, 1.68 mmol, 2.0 eq.) and BzCl (0.2 mL, 1.68 mmol, 2.0 eq.). The reaction vessel was stirred, under exclusion of light, until TLC analysis (toluene/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~16 hours). The reaction mixture was diluted with EtOAc, washed (H$_2$O, 2x; brine, 1x), dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (toluene/EtOAc, 1:0 → 17:3 v/v) furnished the title compound as a colorless oil in 67% yield over 2 steps (0.48 g, 0.56 mmol). \(^1\)H NMR (500 MHz, 323 K) $\delta$: 8.10-8.09 (m, 2H, $CH_{arom}$); 7.59 (t, 1H, $J = 7.5$ Hz, $CH_{arom}$); 7.48-7.21 (m, 17H, $CH_{arom}$); 5.46 (dd, 1H, $J = 3.0$ Hz, 11.5 Hz, H-3'); 5.42 (d, 1H, $J = 3.5$ Hz, H-1'); 5.16 (bs, 2H, PhCH$_2$); 4.93 (d, 1H, $J = 12.0$ Hz, PhCH$_2$); 4.77 (d, 1H, $J = 11.5$ Hz, PhCH$_2$); 4.48 (bs, 2H, PhCH$_2$); 4.20 (d, 1H, $J = 7.5$ Hz, H-1); 3.99 (bs, 1H, H-4'); 3.95 (q, 1H, $J = 6.5$ Hz, H-5'); 3.90-3.86 (m, 2H, H-2, OCH$_3$pentyl); 3.82 (dd, 1H, $J = 3.5$ Hz, 11.3 Hz, H-2'); 3.55-3.45 (m, 4H, H-3, H-4, H-5, OCH$_3$pentyl); 3.22 (bs, 2H, NCH$_2$pentyl); 1.59-1.21 (m, 6H, 3x CH$_3$pentyl); 1.22 (d, 3H, $J = 6.5$ Hz, H-6); 1.14 (d, 3H, $J = 6.5$ Hz, H-6'). \(^1\)C-APT NMR (125 MHz, 323 K) $\delta$: 165.5 ($CO_{Bz}$); 138.2; 138.1 ($C_{q,arom}$); 133.5, 129.9 ($CH_{arom}$); 129.5 ($C_{q,arom}$); 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.3 ($CH_{arom}$); 102.8 (C-1); 99.8 (C-1'); 78.9, 78.3 (C-3, C-4 or C-5); 75.2 (PhCH$_2$); 71.4 (C-3'); 71.0 (C-3, C-4 or C-5); 70.2 (C-4'); 69.8 (OCH$_2$pentyl); 67.2 (PhCH$_2$); 66.5 (C-5'); 63.8 (C-2); 57.4 (C-2'); 29.3, 23.3 (CH$_2$pentyl); 17.1, 16.1 (C-6, C-6'). IR (thin film) v: 2117, 1717, 1273, 1072. HRMS: [M+Na]$^+$ calculated for C$_{46}$H$_{53}$N$_7$NaO$_{16}$: 886.37461; found 886.37430.
5-(benzyl(benzyloxy carbonyl)amino)pentyl 2-azido-3-O-(2-azido-3-O-benzoyl-2-deoxy-4-O- (methyl 2-azido-3,4-di-O-benzyl-2-deoxy-β-D-mannopyranosiduronate)-α-L-fucopyranosyl)-4- O-benzyl-2-deoxy-β-D-fucopyranoside (2)

To a stirred solution of donor 6 (1.28 mmol, 4.0 eq.) and acceptor 35 (0.32 mmol, 1.0 eq.) in CH₂Cl₂ (3.2 mL, 0.1 M) were added flame-dried, rod-shaped 3Å MS. After ~30 minutes, the mixture was cooled to -80 °C and TBSOTf (60 μL, 0.26 mmol, 0.8 eq.). The reaction mixture was allowed to warm to -55 °C and was stirred at this temperature using an immersion cooler. After stirring for ~5.5 hours, TLC analysis (toluene/acetone, 4:1 v/v) indicated complete disappearance of the acceptor and the reaction was quenched by addition of NEt₃ (0.2 mL). The mixture was diluted with CH₂Cl₂, filtered over a small bed of celite, washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1v/v), followed by column chromatography (toluene/EtOAc, 1:0 → 9:1) furnished the title trisaccharide as a colorless oil, in 65% yield (260 mg, 0.21 mmol). ¹H NMR (500 MHz, 323 K) δ: 8.11-8.09 (m, 2H, CH₃arom); 7.57 (t, 1H, J = 7.5 Hz, CH₃arom); 7.47-7.14 (m, 27H, CH₃arom); 5.41-5.39 (m, 2H, H-1’, H-3’); 5.16 (bs, 2H, PhCH₂); 4.95 (d, 1H, J = 11.5 Hz, PhCH₂); 4.76 (d, 1H, J = 11.0 Hz, PhCH₂); 4.72-4.68 (m, 3H, PhCH₂); 4.55 (d, 1H, J = 11.0 Hz, PhCH₂); 4.49-4.48 (m, 3H, H-1”, PhCH₂); 4.21 (d, 1H, J = 3.0 Hz, H-4’); 4.18 (d, 1H, J = 8.0 Hz, H-1’); 4.02-3.96 (m, 3H, H-2, H-2”, H-5’); 3.94 (t, 1H, J = 9.0 Hz, H-4’); 3.86 (bs, 1H, CH₃H₁_pentyl); 3.83 (dd, 1H, J = 8.0 Hz, 10.5 Hz, H-2); 3.55 (d, 1H, J = 10.0 Hz, H-5”); 3.52-3.46 (m, 5H, H-3”, H-4, H-5, OCH₂H₃_pentyl); 3.22 (bs, 2H, NCH₂_pentyl); 3.13 (s, 3H, OCH₃); 1.58-1.38 (m, 6H, CH₂_pentyl); 1.30 (d, 3H, J = 6.0 Hz, H-6); 1.16 (d, 3H, J = 7.0 Hz, H-6’). ¹³C-APT NMR (125 MHz, 323 K) δ: 166.9, 166.1 (C-6’’, CO₂H); 138.2, 138.1, 137.4 (C₃arom); 133.0, 130.1 (C₃arom); 129.9 (C₇arom); 128.6, 128.5, 128.4, 1283, 128.2, 128.1, 127.9, 127.9, 127.7, 127.5, 127.3 (C₃arom); 102.8 (C-1); 101.2 (C-1’’); 99.5 (C-1’’’); 79.9 (C-3’’); 79.3 (C-3’); 78.3 (C-4’); 76.5 (C-4’’); 75.3, 75.2 (PhCH₂); 75.2, 75.2 (C-4’’’, C-5’’); 72.3 (PhCH₂); 70.9 (C-5); 69.8 (OCH₂_pentyl); 69.5 (C-3”); 67.2 (PhCH₂); 66.4 (C-5’); 63.8 (C-2); 61.3 (C-2’’); 57.4 (C-2’); 51.9 (OCH₃methyl); 50.9 (NCH₂_pentyl); 29.3, 23.3 (CH₂_pentyl); 17.1 (C-6); 16.6 (C-6’). ¹³C-GATED NMR (125 MHz, 323 K) δ: 102.8 (d, J = 159 Hz, C-1); 101.2 (d, J = 160 Hz, C-1’’’); 99.5 (d, J = 173 Hz, C-1’’’’). IR (thin film) ν: 2934, 2110, 1749, 1717, 1699, 1273, 1103, 1069, 1038. HRMS: [M+Na]⁺ calculated for C₆H₇₄N₁₀NaO₁₅: 1281.52273; found 1281.52279.
Chapter 4

5-aminopentyl 2-acetamido-3-O-(2-acetamido-3-O-acetyl-4-O-(2-acetamido-2-deoxy-β-D-mannopyranosiduronyl)-2-deoxy-α-L-fucopyranosyl)-2-deoxy-β-D-fucopyranoside (I)

A solution of 2 (50 mg, 0.040 mmol, 1.0 eq.) in THF (1.6 mL, 0.025 M) was treated at 0 °C with a freshly prepared solution of KOOH (0.4 mL, prepared by adding H₂O₂ (0.56 mL, 30% aq. w/w) to 4.4 mL 0.5 M aq. KOH solution) and the slightly turbid mixture was allowed to stir for 2 days at 4 °C until TLC analysis (toluene/EtOAc/AcOH, 60:40:5 v/v/v) indicated complete conversion of the starting material. The mixture was acidified to pH 3 with 1M aq. HCl, extracted (CH₂Cl₂ 5x), and the combined organic fractions were washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc/AcOH, 90:10:5 → 70:30:5 v/v/v) gave free uronic acid 37 as a milky solid (30 mg, 0.026 mmol, 66%). ¹H NMR (500 MHz, 323 K, CD₃CN + acetic acid-d₄) δ: 7.40-7.18 (m, 25H, CH₆arom); 5.22 (d, 1H, J = 3.5 Hz, H-1’); 5.12 (s, 2H, PhCH₂); 4.85 (d, 1H, J = 11.0 Hz, PhCHH); 4.77-4.75 (m, 3H, H-1”, PhCH₂); 4.66-4.61 (m, 3H, PhCH₂); 4.46 (s, 2H, PhCH₂); 4.34 (d, 1H, J = 2.5 Hz, H-2”); 4.24 (d, 1H, J = 7.0 Hz, H-1); 4.03 (q, 1H, J = 6.5 Hz, H-5”); 3.96 (d, 1H, J = 9.0 Hz, H-5’); 3.94-3.89 (m, 2H, H-3’, H-4’); 3.87 (t, 1H, J = 9.5 Hz, H-4’); 3.78 (dd, 1H, J = 3.5 Hz, 9.0 Hz, H-3’’); 3.75-3.74 (m, 1H, OC₂H₂p entity); 3.63-3.54 (m, 4H, H-2, H-3, H-4, H-5); 3.48-3.36 (m, 1H, OCH₂p entity); 3.39 (dd, 1H, J = 3.5 Hz, 10.5 Hz, H-2’’); 3.27 (t, 2H, J = 7.5 Hz, NCH₂p entity); 1.53-1.50 (m, 4H, CH₂p entity); 1.34-1.20 (m, 8H, H-6, H-6’, CH₂p entity). HRMS: [M+H]+ calculated for C₅₉H₆₉N₁₄O₁₄: 1141.49982; found 1141.49938. The uronic acid (17 mg, 0.015 mmol, 1.0 eq.) was dissolved in pyridine (0.6 mL) and at 0 °C, Ac₂O (0.15 mL) was slowly added. The mixture was stirred until TLC analysis (toluene/EtOAc/AcOH, 60:40:5 v/v/v) indicated complete conversion of the starting material. The reaction was quenched by slow addition of water, and after ~15 minutes, the mixture was extracted (CH₂Cl₂, 5x). The organic phases were washed (brine, 1x), dried over MgSO₄ filtered and concentrated in vacuo. The residue was co-evaporated with toluene (2x) to remove excess acetic acid and pyridine. ¹H NMR (500 MHz, CD₃CN + acetic acid-d₄) δ: 7.39-7.22 (m, 25H, CH₆arom); 5.32 (d, 1H, J = 3.5 Hz, H-1’); 5.14 (dd, 1H, J = 3.0 Hz, 11.5 Hz, H-3’); 5.10 (bs, 2H, PhCH₂); 4.87 (d, 1H, J = 10.0 Hz, PhCHH); 4.79-4.74 (m, 2H, PhCH₂); 4.67 (d, 1H, J = 1.0 Hz, H-1’’); 4.65-4.60 (m, 2H, PhCH₂); 4.54 (d, 1H, J = 11.0 Hz, PhCHH); 4.44 (s, 2H, PhCH₂); 4.31 (d, 1H, J = 2.5 Hz, H-2’’); 4.24 (bs, 1H, H-1); 4.11 (d, 1H, J = 3.0 Hz, H-4’’); 4.08 (q, 1H, J = 6.5 Hz, H-5’’); 3.83-3.70 (m, 5H, H-2’, H-3’, H-4’, H-5’’, OCH₂p entity); 3.58-3.53 (m, 4H, H-2, H-3, H-4, H-5); 3.44 (bs, 2H, OCH₂p entity); 3.20 (bs, 2H, NCH₂p entity); 2.01 (s, 3H, CH₃p entity); 1.51-1.49 (m, 4H, CH₂p entity); 1.32-1.19 (m, 8H, H-6, H-6’, CH₂p entity). Crude O-acetate 38 (12 mg, 0.01 mmol, 1.0 eq.) was dissolved in pyridine (0.5 mL), degassed by
sonication before use), and added was freshly distilled AcSH (0.5 mL). The reaction was stirred for 3 days after which LC-MS analysis (MeCN/H₂O/TFA, 50:50:0.1 → 90:10:0.1 v/v/v, τₐ: 6.80 min.) indicated complete conversion of the starting material. The mixture was diluted with pyridine (~1 mL) and concentrated in vacuo. The crude mixture was subjected to size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v) to isolate the intermediate 39 in 57% yield (7 mg, 0.0057 mmol). ¹H NMR (500 MHz, 323 K, CD₃CN + acetic acid-d₄) δ: 7.42-7.21 (m, 25H, CH₃orn); 5.11 (s, 2H, PhCH₂); 4.97-4.90 (m, 4H, H-1″, H-2″, H-3′, PhCH₂); 4.79-4.77 (m, 2H, PhCH₂); 4.69-4.67 (m, 2H, H-1′, PhCH₂); 4.58 (d, 1H, J = 10.5 Hz, PhCH₂); 4.48-4.46 (m, 3H, PhCH₂); 4.41 (dd, 1H, J = 3.5 Hz, 11.5 Hz, H-2″); 4.25 (d, 1H, J = 9.0 Hz, H-1′); 4.10-4.05 (m, 3H, H-2′, H-4′, H-5′); 3.81-3.60 (m, 6H, H-3′, H-3″, H-4′, H-5, H-5′, OCH₃pentyl); 3.56 (d, 1H, J = 2.5 Hz, H-4′); 3.37-3.35 (m, 1H, OCH₃pentyl); 3.21 (t, 1H, J = 7.0 Hz, NCH₂pentyl); 2.03, 1.95, 1.91, 1.81 (CH₃₃,Ac); 1.50-1.45 (m, 4H, CH₂pentyl); 1.27-1.18 (m, 8H, H-6′, CH₂pentyl). ᵃ¹C-APT NMR (125 MHz, 323 K, CD₃CN + acetic acid-d₄) δ: 171.9 (C-6″); 129.6, 129.5, 129.4, 129.4, 129.3, 129.0, 128.9, 128.8, 128.8, 128.6, 128.3 (CH₃orn); 102.3 (C-1); 101.5 (C-1′); 100.4 (C-1″); 80.9 (C-3″, C-4″ or C-5″); 80.4 (C-4); 78.8 (C-3); 77.3, 77.0 (C-4 and C-3″, C-4″ or C-5″); 76.2, 75.8 (PhCH₂); 75.6 (C-3″, C-4″ or C-5″); 72.0 (PhCH₂); 71.5 (C-5); 71.0 (C-3′); 69.9 (OCH₂pentyl); 68.1 (C-5′); 67.9 (PhCH₂); 53.0 (C-2); 50.3 (C-2″); 47.8 (C-2″′); 30.1, 24.1 (CH₂pentyl); 23.5, 23.3, 23.3, 21.3 (CH₃₃,Ac); 17.5, 16.8 (C-6, C-6′). HRMS: [M+H]+ calculated for C₆₃H₁₃N₁₃O₁₈: 1231.56969; found 1231.57044. The trisaccharide 39 (4 mg, 0.003 mmol) was dissolved in THF, tert-butanol and H₂O (1:1.3 v/v/v, 0.002 M). Added was a drop of AcOH and the mixture was degassed (freeze-thaw, 3 cycles) and backfilled with argon. Pd(OH)₂ (20 weight% on carbon, 50% H₂O) was added and the mixture was purged with argon (balloon), followed by H₂ (balloon). After purging, the mixture was stirred under H₂ atmosphere for 2 days. The mixture was filtered over a fritted syringe filled with celite, the residue was washed with THF/H₂O (1:1 v/v) and concentrated in vacuo. After ᵃ¹H NMR analysis revealed no aromatic signals, the crude trisaccharide was purified by passing over a C18 solid-phase extraction column (MeCN/H₂O, 0:1 → 1:9) and subsequently lyophilized to obtain the product 1 in quantitative yield (2.5 mg, 0.003 mmol). ᵃ¹H NMR (500 MHz, D₂O) δ: 5.03 (dd, 1H, J = 3.0 Hz, 12.0 Hz, H-3′); 5.01 (d, 1H, J = 4.0 Hz, H-1′); 4.74 (bs, 1H, H-1″); 4.59 (d, 1H, J = 4.5 Hz, H-2″); 4.41 (d, 1H, J = 8.5 Hz, H-1); 4.38 (dd, 1H, J = 4.0 Hz, 11.5 Hz, H-2′); 4.22 (d, 1H, J = 2.5 Hz, H-4′); 4.19 (q, 1H, J = 6.5 Hz, H-5′); 3.99 (t, 1H, J = 8.5 Hz, H-2′); 3.91-3.86 (m, 1H, OCH₃pentyl); 3.82-3.77 (m, 4H, H-3′, H-3″, H-4′, H-5′); 3.65 (t, 1H, J = 9.5 Hz, H-4″); 3.60-3.56 (m, 2H, H-5″, OCH₃pentyl); 2.14, 2.09, 2.01, 1.99 (s, 3H, CH₃₃,Ac); 1.66 (t, 2H, J = 7.5 Hz, CH₂pentyl); 1.62-1.56 (m, 2H, CH₂pentyl); 1.41-1.38 (m, 2H, CH₂pentyl); 1.28 (d, 3H, J = 6.5 Hz, H-6); 1.25 (d, 3H, J = 6.5 Hz, H-6′). ᵃ¹C-APT NMR (125 MHz, D₂O) δ: 175.7, 175.6, 174.3, 174.1, 173.9 (C-6″, CO₂); 101.6 (C-1); 99.9 (C-1″); 99.1 (C-1′); 78.7 (C-5″); 71.1 (C-3, C-3″, C-4 or C-5); 71.7, 70.8, 70.5 (C-3, C-3″, C-4, C-5); 70.1 (OCH₂pentyl); 69.9 (C-3′); 69.6 (C-4″); 66.9 (C-5); 53.1 (C-2″); 51.4 (C-2); 47.2 (C-2′); 39.4 (NCH₂pentyl); 28.2, 26.5 (CH₂pentyl); 22.2, 22.2,
22.1 \((\text{CH}_3\text{Ac})\); 22.0 \((\text{CH}_2\text{penty})\); 20.4 \((\text{CH}_3\text{Ac})\); 15.4, 15.3 \((\text{C}-6, \text{C}-6')\). HRMS: [M+H]⁺ calculated for \(\text{C}_{31}\text{H}_{53}\text{NaO}_{16}\): 737.34511; found 737.34515.

References


Synthesis of Staphylococcus aureus type 5 CPS


Chapter 5

Synthesis and reactivity of 2-azido-2-deoxy-galacturonic acid-[3,6]-lactones*

Introduction

The monosaccharide $N$-acetylgalactosaminuronic acid (GalNAcA) is a C-6 oxidized sugar (an uronic acid) and a constituent of several bacterial polysaccharides, such as the *Salmonella typhi* Vi antigen (in which the 3-$O$ position is randomly acetylated, see Scheme 1A) and the *Staphylococcus aureus* Strain M Capsular Polysaccharide.\textsuperscript{2,3} In both cases, the GalNAcA units are

connected through an α-glycosidic linkage at their reducing ends and are extended at the 4-O position on their non-reducing side.

**Scheme 1:** A) Repeating unit structures of GalNAcA-containing polysaccharides. B) GalA lactone 1-2 reacts via triflate 3 to give α-selective glycosylations. C) Use of lactone donor 1 and acceptor 5 to synthesize the three frame-shifted repeating units of the S. pneumoniae Sp1 polysaccharide.

The synthesis of GalNAcA and galacturonic acid (GalA)-containing oligosaccharides is a demanding task, because of the difficulties associated with the stereoselective introduction of α-glycosidic (1,2-cis) linkages. An additional problem is the oxidized C-6 position, which is thought to hamper the reactivity of glycuronic acid donor and acceptor synthons, by virtue of its electron-withdrawing properties. Therefore, the most common approach towards the synthesis of oligosaccharides containing uronic acids involves introducing the glycosidic linkage(s), using non-oxidized carbohydrate donors. Selective deprotection and oxidation of the primary C-6 alcohol then yields the uronic acid. A drawback of this post-glycosylation oxidation strategy is the
increased number of manipulations at the oligosaccharide stage, as well as the necessity for an extra orthogonal protecting group for the C-6-OH, leading to a more elaborate and demanding protecting group strategy.

Recently, various applications have been reported for ‘pre-oxidized’ donor glycosides. Methyl mannuronates have shown to be relatively reactive and extremely β-selective glycosyl donors, and have been successfully employed in the synthesis of alginates and bacterial oligosaccharides.\textsuperscript{6–11} Likewise, glucuronic acid donors have shown to be useful building blocks in the synthesis of heparin- and hyaluronan oligomers,\textsuperscript{12–15} as well as \textit{Streptococcus pneumoniae} type 3 Capsular Polysaccharide fragments.\textsuperscript{16}

Galacturonic acid donors have been used in the synthesis of oligosaccharides, for example in the synthesis of pectin fragments.\textsuperscript{5,17–19} An extra challenge in the construction of galacturonic acid containing oligosaccharides is the low reactivity of the axial C-4-OH of GaLA units, making them poor acceptors and therefore less attractive in the synthesis of oligosaccharides. Van den Bos \textit{et al.} first reported the synthesis and reactivity of galacturonic acid derivative 1 (Scheme 1B),\textsuperscript{20} which contains a 3,6-lactone functionality. This lactone places the pyranose ring in a ‘flipped’ \(\text{C}_4\) conformation. In addition to conformational rigidity, the C-4-OH position is now placed in a more accessible, equatorial position. Lactone 1 was shown to be highly \(\alpha\)-selective with a variety of carbohydrate acceptors. A further study conducted by Christina \textit{et al.} revealed, using low-temperature NMR spectroscopy,\textsuperscript{21} that analogous donor 2 is transformed into an anomeric triflate 3 under pre-activation conditions (Ph\(_3\)SO/Tf\(_2\)O),\textsuperscript{22,23} which is subsequently displaced in an S\(_\text{N}2\)-like fashion, giving the \(\alpha\)-glycosidic bond. Interestingly, a ‘direct’ activation protocol (that is, in the presence of acceptor), using \(p\)-NO\(_2\)PhSCI/AgOTf\textsuperscript{24} gave the opposite stereoselectivity. The high reactivity and selectivity of lactone 1 has been exploited successfully in the synthesis of the three frame-shifted repeating units of the \textit{Streptococcus pneumoniae} type 1 Capsular Polysaccharide (Scheme 1C).\textsuperscript{25} Additionally, the ‘flipped’ conformation renders the C-4-OH more accessible and more nucleophilic, as evidenced by the successful use of lactone acceptor 5. This Chapter describes the synthesis of a 2-azidogalacturonic acid (GalN\(_3\)A) lactone as a GalNAcA building block. The reactivity and selectivity will be assessed by NMR studies and in a set of model glycosylations. The performance of the lactone will be compared to a conformationally non-restricted GalN\(_3\)A donor and the previously described 2,3-di-\(O\)-benzyl galacturonic acid-[3,6]-lactone donor.
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Results and Discussion

The assembly of the GalN₃ lactone requires the generation of a building block with a protecting group at C-4 and two free alcohols at C-3 and C-6. Introduction of the anomic selenophenol group and the C-2 azide can, in line with the synthesis of the fucosamine building blocks in Chapter 3 and 4, be readily accomplished from d-galacta.

Scheme 2: Attempted protection of the 4-O position of 3,6-di-O protected GalN₃ units.

Reagents and conditions: a) HBr/AcOH, CH₂Cl₂, 0 °C; 2n/Cu, N-methylimidazole, EtOAc, 70 °C (74%, 2 steps); b) (PhSe)₂, Me₂SiN₃, Ph(OAc)₂, CH₂Cl₂, -30 → -20 °C (54%); c) Na, MeOH (quant.); d) TBSI, imidazole, DMF (80%); e) (ClAc)₂O, pyridine, CH₂Cl₂ 0 °C (91%); f) triphosgene, pyridine, toluene, 0 °C → rT; then AllylOH (97%); g) NEt₃-3HF, THF (64% for 16; 37% for 17); h) BnBr, NaH (60% in oil), THF, DMF, 0 °C; i) PivCl, pyridine, 0 °C → rT (92%); j) BnBr, NaH (60% in oil), Bu₄NI (cat.), THF.

Synthesis of intermediate 10 was accomplished following known procedures (Scheme 2A). Transformation of peracetylated galactoside 7 into the corresponding glycal 8, followed by azidophenylselenylation led, after crystallization, to product 9 in 54% yield. Using the homogeneous procedure using TMSN₃ (instead of NaN₃), reported by Nifantiev and co-workers,²⁶ this reaction was scalable to ~100 mmol. Zemplén deacetylation afforded 10 in quantitative yield.
Initial attempts to generate the 4-O-protected 3,6-diol entailed the selective protection of the more reactive 3-O and 6-O positions with sterically demanding protecting groups. Thus, reacting 10 with TBSCI delivered di-silylated product 11 in 80% yield. The C-4-\(\text{OH}\) was then protected with a chloroacetyl group, since this group has been shown to be compatible with the relatively labile lactone functionality. Reacting 11 with (ClAc)\textsubscript{2}O and pyridine afforded 12 91% yield. Unfortunately, removal of the TBS groups, using NE\textsubscript{t}\textsubscript{3}HF, was accompanied by migration of the chloroacetyl group, delivering the 6-O chloroacetyl ester 16 as the major product (64% yield).

The allyloxycarbonyl carbonate (Alloc) protecting group was investigated next as a protecting group for the C-4-\(\text{OH}\), as these are generally less prone to undergo migration. Attempted protection of 11 under conventional conditions (AllocCl, pyridine) did not lead to any product, owing to the low reactivity and poor accessibility of the C-4-\(\text{OH}\). However, reacting 11 with triphosgene and pyridine in toluene, followed by addition of allyl alcohol,\textsuperscript{27} gave the desired C4-O-Alloc-protected glycoside 13 in 97% yield. Removal of the TBS groups was, unfortunately, again accompanied by migration of the Alloc group to the 6-O position, giving 17 as the major product in 37% yield. Next, protection of the C-4-hydroxyl group with a benzyl ether was explored. However, when standard benzylation conditions were employed (BnBr and NaH in DMF, at 0 °C) a mixture of products was obtained. NMR analysis revealed that a mixture of the 4-O and 3-O benzylation products (18 and 19, respectively) was formed. Jacquetin reported that the C-4-alcohol of a 2-azido-3,6-di-O-TBS protected galactoside could be benzylation using a mixture of THF and DMF without migration.\textsuperscript{28} Unfortunately, application of these conditions to 11 did not prevent migration of the C-3-O-silyl group. Acid-mediated benzylation, using benzyl 2,2,2-trichloroimidate 23,\textsuperscript{29} or neutral conditions, involving phospinite 24, reported by Mukaiyama et al.,\textsuperscript{30} failed to yield any product. In an attempt to curb protecting group migration, the TBS groups were replaced by pivaloyl groups, the introduction of which on triol 10 proceeded uneventfully to yield di-pivaloate 20 in 92% yield (Scheme 2B). While Karst and Jacquetin reported the successful C-4-O-benzylation of a 3,6-di-O-pivaloyl galactose under basic conditions, using THF as the solvent and Bu\textsubscript{4}NI as an additive,\textsuperscript{31,32} application of these conditions to 20 yielded an inseparable mixture of products 21 and 22. Using benzyl 2,2,2-trichloroacetimidate 23 as a benzylating reagent or the use of the neutral N-methyl 2-benzoxypyridinium triflate 25, as reported by Poon and Dudley,\textsuperscript{33} did not lead to any product formation.

Therefore, an alternative strategy was followed, which relied on the reductive opening of a 4,6-O-benzylidene acetal (Scheme 3).\textsuperscript{34} To this end, the C4 and C-6 hydroxyls in 10 were masked with a para-methoxybenzylidene group, which was followed by acetylation of the remaining free C-3-alcohol to give 26 in 85% yield over 2 steps. The reductive opening of 26 proved to be dependent on the Lewis acid used, and it was found that an equimolar amount of Bu\textsubscript{3}BOTf and
Chapter 5

BH₃·THF gave the desired 4- O-PMB product 27 in 90% yield, after deacetylation of the crude intermediate to give 28. Protection of the C3-alcohol proved to be vital for the regioselectivity of the reductive opening. With the desired protecting group pattern in place, the TEMPO/Ph(I(OAc))₂-mediated oxidation of the primary alcohol and concomitant lactone formation was accomplished to give 29 in 80% yield. Oxidation of the C-3- O-acetyl protected 27, using the same reagent system gave, after methylation of the resulting uronic acid, methyl uronate 30 in 35% yield.

Scheme 3: Synthesis of lactone 29 and methyl uronate 30 via a reductive acetal opening strategy.

Reagents and conditions: a) para-methoxybenzaldehyde, CSA (cat.), MeCN, 50 °C, 300 mbar; b) Ac·O, pyridine (85%, 2 steps); c) Bu₂OBF₄, BH₃·THF, CH₂Cl₂, THF (90%); d) Na, MeOH (quant.); e) TEMPO (cat.), Ph(I(OAc))₂, AcOH (cat.), CH₂Cl₂, H₂O (80% for 29); f) Mel, K₂CO₃, DMF (35%, 2 steps).

NMR experiments

In order to investigate potential reactive intermediates formed upon activation of lactone 29, low-temperature NMR experiments were conducted. Previously it was found that galacturonic acid lactone thioglycosides can be transformed into the corresponding anomic β-triflates using Ph₂SO/ Tf₂O at -80 °C. Thus, donor 29 and Ph₂SO in CD₂Cl₂ were treated with Tf₂O at -80 °C, and an ¹H NMR spectrum was immediately recorded. Donor 29 was completely consumed to provide a single new compound (Figure 1A). Based on the chemical shift and coupling constant of the anomeric signals (H-1: δ: 6.11 ppm, singlet; and C-1: δ: 103.9 ppm), this new species was identified as anomic trflate 31. Next, the solution was slowly warmed to assess the stability of the reactive species. Onset of decomposition was observed at -30 °C, which is at a notably lower temperature than the decomposition temperature recorded for related lactone 2, which proved to be stable up to -10 °C. In a similar experiment, methyl uronate 30 was activated with the Ph₂SO/Tf₂O cocktail at -80 °C (Figure 1B). Again, rapid conversion of the donor into a new species occurred (H-1: δ:
6.21 ppm, $J = 3.2$ Hz), which was tentatively assigned as anomeric $\alpha$-triflate 32. Decomposition of 32 started at -30 °C.

Model glycosylations

With lactone 29 in hand, its reactivity and selectivity was assessed in a series of glycosylations with a panel of acceptors. In line with the study reported in Chapter 3, ethanol and its 2-fluorinated counterparts (2-fluoro-, 2,2-difluoro- and 2,2,2-trifluoroethanol) were used to map the influence of acceptor nucleophilicity on glycosylation outcome.39 This panel of ethanols was complemented with cyclohexanol and the two glucosides 33 and 34. Methyl galacturonate 30 and galacturonic acid lactone 2 were probed with the same set of acceptors.

The results of the glycosylation reactions are shown in Table 1. The glycosylations of GalN$_3$ lactone donor 29 all predominantly provide the $\alpha$-linked products, with the stereoselectivity ranging between 2:1 and 6:1 (products 35-41). In contrast to the clear correlation observed for the stereoselectivity in the glycosylations of the series of fluorinated ethanols with the fucosazide donors, reported in Chapter 3, no clear trend can be discerned. Mono- and difluoroethanol gave coupling products with an higher $\alpha/\beta$ ratio than ethanol ($\alpha/\beta$ 4:1). Glycosylation of 29 with 2,2,2-trifluoroethanol led less selective coupling reaction ($\alpha/\beta$ 2:1). The condensation of the secondary cyclohexanol acceptor proceeded with similar selectivity as the coupling of ethanol ($\alpha/\beta$ 3:1), while the use of the carbohydrate acceptors 33 and 34 led to $\alpha/\beta$ ratios of 6:1 and 3:1, respectively. The low yield with the latter acceptor (18%) is likely due to the poor accessibility and reactivity of the C-4-hydroxyl group. The methyl 2-azidogalacturonate donor 30 was remarkably $\beta$-selective (products 42-48). In the case of the reactive acceptors ethanol and 2-fluoroethanol, the $\beta$-product was obtained as the only product. With decreasing nucleophilicity of the acceptor, the amount of $\alpha$-product increased: 2,2-difluoroethanol and 2,2,2-trifluoroethanol were condensed with galacturonic acid donor 30 to give the coupling products 44 and 45 with an $\alpha/\beta$ ratio of 1 : 9 and 2 : 5, respectively. Cyclohexanol and the reactive, primary glucosyl acceptor 33 yielded the corresponding $\beta$-products exclusively, whereas the condensation with the poorly reactive acceptor 34 resulted in a complex mixture of products.

When lactone 2 was probed in the series of glycosylations with the panel of acceptors only formation of the $\alpha$-products 49-55 was observed, underscoring the excellent stereoselectivity of this donor.$^\dagger$

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$^\dagger$ In the glycosylations with ethanol and trifluoroethanol, some unreacted donor appeared to be left after the glycosylation reactions.
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Figure 1: Partial low-temperature NMR spectra of lactone 29 (A) and 30 (B) and their covalent reactive intermediates.
Table 1: Model glycosylations with donors 2, 29 and 30.

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The high β-selectivities observed in the glycosylations of galacturonic acid donor 30 with the nucleophilic acceptors can be explained by an Si2-like displacement of an α-triflate (Scheme 4), observed by low-temperature NMR spectroscopy (Figure 1B). This species can act as a precursor for more reactive oxocarbenium ion-like intermediates. Acceptors of lower nucleophilicity, are less effective in the direct displacement of the covalent triflate 32, and require a more reactive electrophilic species for reaction. Analysis of the $^3$H$_4$ and $^4$H$_3$ half-chair conformers, that the oxocarbenium ion 56 can adopt shows that in both conformers two out of four substituents can occupy a position that best stabilizes the positive charge at the anomeric center. In the $^3$H$_4$ conformer the axially oriented C-5 carboxylate functionality and the C3 substituent take up an pseudo-axial orientation to allow for the donation of electron density to the carbocation. The $^4$H$_3$ conformer, on the other hand, places the C4-O-PMB in an favorable
pseudo-axial position and benefits from a hyperconjugative stabilization of the C2-H2 bond. Therefore, there is no clear preference for either of the two conformers leading to reduced selectivity in the glycosylation of 30 with poorly nucleophilic 2,2,2-trifluoroethanol (Table 1).

Scheme 4: Mechanistic rationale for the observed selectivities in glycosylations.

A

Scheme 4B

The high α-selectivity of lactone 2 has been attributed before to the intermediacy of covalent triflate 3 (Scheme 1B). Notably, the reactivity of the acceptor seems to be of little influence to the stereoselectivity of the glycosylations of this donor (Table 1). While it could be expected that glycosylations with poor nucleophiles, such as trifluoroethanol, require a significant amount of Sn1-character proceeding via oxocarbenium ion 3H+ conformer 60, to give the 1,2-trans products, this appears not to be a relevant reaction pathway. The lower stereoselectivity of 2-azido lactone donor 29 indicates that for this donor, other reaction itineraries are available besides the Sn2-type displacement of anomeric triflate 31. The increased prevalence of oxocarbenium ion 60 seems to be a plausible explanation for the decreased stereoselectivity. Even though the electron-
Synthesis and reactivity of GalN\(\alpha\)A lactone

withdrawing C-2 azide would likely destabilize this species, when compared to its C-2-\(\text{O}\)-benzyl counterpart, the relatively low decomposition temperature for triflate 31 indicates that the oxocarbenium ion derived from the C-2-azido lactone forms more readily than the ion formed from triflate 3.

**Conclusion**

This Chapter describes the synthesis of a 2-azidogalacturonic acid [3,6]-lactone donor and investigation of its reactivity and selectivity. The synthesis was accomplished via an efficient reductive 4,6-\(\text{O}\)-benzylidene opening, followed by a tandem oxidation-cyclization. The corresponding methyl 2-azidogalacturonate donor was also synthesized, in order to investigate the influence of the lactone on the outcome of glycosylations. Low-temperature NMR studies revealed that both the lactone and methyl uronate form an anomic glycosyl triflate at -80 °C. Both triflates were stable up to -30 °C. Next, the performance of the lactone was assessed in glycosylations with a set of model acceptors, and the results were compared with the methyl uronate, as well as a previously described galacturonic acid lactone. The methyl 2-azidogalacturonate proved a \(\beta\)-selective glycosyl donor, especially in reactions with reactive acceptors. Conversely, the 2-azido lactone showed moderate \(\alpha\)-selectivity, but the selectivity depended on the reactivity of the acceptor. In line with previous reports, the ‘normal’ 2,3-di-\(\text{O}\)-benzyl galacturonic acid [3,6]-lactone was very \(\alpha\)-selective, regardless of the reactivity of the acceptor. A mechanistic rationale explains the stereoselectivities of the glycosylation with these donors is presented.

**Experimental**

**General procedures**

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4 Å molecular sieves (3 Å for CH\(_2\)Cl\(_2\), MeOH and MeCN), except pyridine and DMF. NEt\(_3\) was stored over KOH pellets. TF\(_2\)O used in glycosylations was dried over P\(_2\)O\(_5\) (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (\(\lambda\): 254 nm), followed by spraying with 20% H\(_2\)SO\(_4\) in EtOH (w/v) or Hanessian’s stain ((NH\(_4\))\(_6\)Mo\(_7\)O\(_{24}\).4H\(_2\)O, 25 g/L; (NH\(_4\))\(_4\)Ce(SO\(_4\))\(_3\).2H\(_2\)O, 10 g/L; in 10% aq.
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H₂SO₄). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to Me₄Si (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. ^13C-APT spectra are ^1H decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomic carbon atoms (J_H1,C1) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm⁻¹. HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.

3,4,6-tri-O-acetyl-α-D-galactal (8)

To a stirred solution of peracylated galactose 7 (57.4 g, 147 mmol, 1.0 eq.) in CH₂Cl₂ (500 mL, 0.3 M) at 0 °C was added HBr (33% w/v in AcOH, 245 mL) in a dropwise fashion. The reaction mixture was stirred until TLC analysis (CH₂Cl₂) indicated complete conversion of the starting material. The reaction mixture was poured on ice and stirred until the ice had molten. After separation of the two phases, the aqueous phase was extracted with CH₂Cl₂ (2x). The combined organic phases were carefully washed with NaHCO₃ (sat., aq., 2x), water (1x) and brine (1x), dried over MgSO₄, filtered and concentrated in vacuo The resultant bright yellow oil was dissolved in EtOAc (500 mL, 0.3 M) and slowly added, using a dropping funnel, to a suspension of freshly prepared Zn/Cu (based on 48.4 g of Zn, 750 mmol, 5.0 eq.) and N-methylimidazole (11.7 mL, 150 mmol, 1.0 eq.) in EtOAc (500 mL, 0.3 M). The reaction mixture was heated to 70 °C and stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~2 hours). The reaction mixture was cooled to room temperature, filtered over a bed of Celite, and the filtrate was concentrated in vacuo The title product was obtained after column chromatography (PE/EtOAc/NEt₃, 100:0:1 → 85:15:1) in 74% yield (30.3 g, 111 mmol).

Phenyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-seleno-α-D-galactopyranoside (9)
A solution of galactal 8 (30.3 g, 111 mmol, 1.0 eq) and (PhSe)$_2$ (34.7 g, 111 mmol, 1.0 eq) in CH$_2$Cl$_2$ (560 mL, 0.2 M) was degassed by sonication under argon. After cooling to -30 °C, Phl(OAc)$_2$ (35.8 g, 111 mmol, 1.0 eq) and Me$_2$SiN$_3$ (29 mL, 222 mmol, 2.0 eq.) were sequentially added. The reaction was warmed to -20 °C and stirred at this temperature until TLC analysis indicated complete conversion of the starting material (~18 hours). The reaction was quenched by addition of cyclohexene in the fume hood, while being warmed to room temperature. The bright orange solution was concentrated in vacuo. The residue was subjected to column chromatography (PE/EtOAc, 1:0 → 7:3 v/v) in order to remove lipophilic byproducts; after concentration of the carbohydrate-containing fractions, the title product was crystallized from EtOH in 54% yield (28.3 g, 60 mmol).

*Phenyl 2-azido-2-deoxy-1-seleno-α-D-galactopyranoside (10)*

![Structure of Phenyl 2-azido-2-deoxy-1-seleno-α-D-galactopyranoside (10)](image)

To a solution of 9 (27.3 g, 57.8 mmol, 1.0 eq.) in MeOH (200 mL, 0.3 M) was added a chip of sodium. The mixture was stirred until TLC analysis indicated complete conversion of the starting material (~18 hours). The reaction mixture was neutralized by addition of Amberlite IR-120 (H$^+$ form), filtered and concentrated in vacuo. The residue thus obtained was used without further purification.

*Phenyl 2-azido-2-deoxy-3,6-di-O-(tert-butyldimethylsilyl)-1-seleno-α-D-galactopyranoside (11)*

![Structure of Phenyl 2-azido-2-deoxy-3,6-di-O-(tert-butyldimethylsilyl)-1-seleno-α-D-galactopyranoside (11)](image)

To a solution of 10 (1.7 g, 5.0 mmol, 1.0 eq.) in DMF (20 mL, 0.25 M) was added imidazole (1.19 g, 17.5 mmol, 3.5 eq.) and TBSCI (2.26 g, 15.0 mmol, 3.0 eq.). The reaction mixture was stirred overnight at room temperature, after which TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material. The reaction was quenched by addition of MeOH, the mixture was diluted with H$_2$O and extracted (Et$_2$O, 3x). The combined ethereal layers were washed (brine, 1x), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 1:0 → 19:1) delivered the title compound in 80% yield (2.3 g, 4.0 mmol). $^1$H NMR (400 MHz) $\delta$: 7.62-7.60 (m, 2H, CH$_{arom}$); 7.29-7.25 (m, 3H, CH$_{arom}$); 5.94 (d, 1H, $J$ = 5.2 Hz, H-1); 4.24 (t,
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1H, J = 6.0 Hz, H-5); 4.10 (dd, 1H, J = 5.2 Hz, 9.6 Hz, H-2); 3.97 (d, 1H, J = 2.8 Hz, H-4); 3.86 (dd, 1H, J = 6.0 Hz, 10.2 Hz, H-6); 3.78-3.72 (m, 2H, H-3, H-6); 2.71 (s, 1H, 4-OH); 0.95, 0.89 (s, 9H, (CH$_3$)$_3$CSi); 0.23, 0.18 (s, 3H, CH$_2$Si); 0.06 (m, 6H, CH$_2$Si). $^{13}$C-APT NMR (100 MHz) δ: 134.4, 129.0 (CH$_{arom}$); 128.7 (C$_{arom}$); 127.7 (CH$_{arom}$); 85.5 (C-1); 72.8, 72.4 (C-3, C-5); 69.2 (C-4); 62.5 (C-2); 62.1 (C-6); 25.8, 25.7 ((CH$_3$)$_3$Si); 18.3, 18.0 (C$_3$Si); -4.8, -4.9, -5.4, -5.5 (CH$_2$Si). IR (thin film) ν: 2930, 2110, 1464, 1263, 1098, 1063. HRMS: [M+H]$^+$ calculated for C$_{24}$H$_{44}$N$_2$O$_2$SeSi$_2$: 574.20315; found 574.20307.

**Phenyl 2-azido-4-O-chloroacetyl-2-deoxy-3,6-di-O-(tert-butyl(dimethyl)silyl)-1-seleno-α-D-galactopyranoside (12)**

![Chemical structure of phenyl 2-azido-4-O-chloroacetyl-2-deoxy-3,6-di-O-(tert-butyl(dimethyl)silyl)-1-seleno-α-D-galactopyranoside](image)

To a solution of 11 (1.1 g, 2.0 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (7 mL, 0.3 M) was added pyridine (0.81 mL, 10.0 mmol, 5.0 eq.) and ClAc$_2$O (0.68 g, 4.0 mmol, 2.0 eq.). After TLC analysis (PE/EtOAc, 19:1 v/v) indicated complete conversion of the starting material (~1 hour), the reaction was quenched by addition of MeOH. The mixture was diluted with CH$_2$Cl$_2$, washed (sat. aq. NH$_4$Cl, 1x, brine, 1x), dried over MgSO$_4$, filtered and concentrated _in vacuo_. Purification by column chromatography (PE/Et$_2$O/NEt$_3$, 100:0:1 → 95:5:1) delivered the title compound in 91% yield (1.19 g, 1.83 mmol).

$^1$H NMR (400 MHz) δ: 7.61-7.59 (m, 2H, CH$_{arom}$); 7.31-7.26 (m, 3H, CH$_{arom}$); 5.97 (d, 1H, J = 5.2 Hz, H-1); 5.47 (d, 1H, J = 2.8 Hz, H-4); 4.38 (t, 1H, J = 6.8 Hz, H-5); 4.11 (s, 2H, CH$_2$Cl); 4.02 (dd, 1H, J = 5.2 Hz, 9.6 Hz, H-2); 3.86 (dd, 1H, J = 3.2 Hz, 10.0 Hz, H-3); 3.57-3.47 (m, 2H, H-6); 0.90, 0.87 (s, 9H, (CH$_3$)$_3$CSi); 0.21, 0.18, 0.01, 0.00 (s, 3H, CH$_2$Si). $^{13}$C-APT NMR (100 MHz) δ: 134.6, 129.1, 128.0 (CH$_{arom}$); 85.1 (C-1); 71.8, 71.4, 71.1 (C-3, C-4, C-5); 63.0 (C-2); 60.5 (C-6); 40.7 (CH$_2$Cl); 25.8, 25.7 ((CH$_3$)$_3$Si). IR (thin film) ν: 2953, 2930, 2857, 2110, 1775, 1751, 1254, 1148, 1107, 1067. HRMS: [M+H]$^+$ calculated for C$_{24}$H$_{44}$N$_2$O$_2$SeSi$_2$: 650.17460; found 650.17433.

**Phenyl 2-azido-6-O-chloroacetyl-2-deoxy-1-seleno-α-D-galactopyranoside (16)**

![Chemical structure of phenyl 2-azido-6-O-chloroacetyl-2-deoxy-1-seleno-α-D-galactopyranoside](image)

To a solution of 12 (1.07 g, 1.65 mmol, 1.0 eq.) in THF (8 mL, 0.2 M) was added NEt$_3$·3HF (0.54 mL, 3.30 mmol, 2.0 eq.) and the mixture was stirred at room temperature until TLC analysis (PE/EtOAc 4:1 v/v) indicated complete conversion of the starting material (~18 hours). The
reaction was quenched by addition of sat. aq. NaHCO₃, the mixture was extracted (CH₂Cl₂, 3x). The combined organic fractions were washed (sat. aq. NaHCO₃, brine), dried over MgSO₄, filtered and concentrated \textit{in vacuo}. Purification by column chromatography (PE/ETOAc/NET₃, 80:20:1 \rightarrow 30:70:1 v/v/v) delivered the 6-\textit{O} chloroacetyl ester in 64\% yield (0.44 g, 1.05 mmol). \textsuperscript{1}H NMR (400 MHz, CD₃CN) \(\delta\): 7.63-7.57 (m, 2H, \textit{CH}₃\text{arom}); 7.36-7.29 (m, 3H, \textit{CH}₃\text{arom}); 5.99 (d, 1H, \textit{J} = 5.2 Hz, H-1); 4.42 (t, 1H, \textit{J} = 6.0 Hz, H-5); 4.31-4.23 (m, 2H, H-6); 4.08-4.01 (m, 3H, H-2, CH₂Cl); 3.81 (s, 1H, H-4); 3.78 (bs, 1H, 3-\textit{O}H); 3.71 (dd, 1H, \textit{J} = 2.8 Hz, 10.8 Hz, H-3); 3.53 (bs, 4-\textit{O}H). \textsuperscript{13}C-APT NMR (100 MHz, CD₃CN) \(\delta\): 168.1 (C\textit{Clac}); 135.6, 130.1 (\textit{CH}₃\text{arom}); 128.9 (C₃\text{arom}); 128.8 (\textit{CH}₃\text{arom}); 85.9 (C-1); 71.7 (C-3); 71.6 (C-5); 69.5 (C-4); 65.8 (C-6); 62.3 (C-2); 42.0 (CH₂Cl). IR (neat) \textit{v}: 3360, 2104, 1751, 1730, 1254, 1194, 1171, 1086, 1051, 1030, 993. HRMS: [M+Na]⁺ calculated for \(\text{C}_{14}\text{H}_{16}\text{ClN}_3\text{NaO}_5\text{Se}: 443.98359\); found 443.98348.

\textit{Phenyl 4-O-allyloxycarbonyl-2-azido-2-deoxy-3,6-di-\textit{O}-(\textit{tert}-butyldimethylsilyl)-1-seleno-\textit{d}-galactopyranoside (13)}

To an ice-cooled solution of \textbf{11} (2.27 g, 4.0 mmol, 1.0 eq.) in toluene (40 mL, 0.1 M) was added pyridine (1.3 mL, 15.8 mmol, 4.0 eq.), followed by triphosgene (0.59 g, 2.0 mmol, 0.5 eq.). The resulting cloudy reaction mixture was allowed to warm to room temperature, and after one hour allyl alcohol (2.7 mL, 40 mmol, 10.0 eq.) was added (evolution of gas was observed). The reaction mixture gradually becomes translucent and, after \~30 minutes, TLC analysis (PE/ET₂O, 9:1 v/v) indicated complete conversion of the starting material. The reaction was quenched by addition of MeOH, the mixture was diluted with CH₂Cl₂, washed (sat. aq. NaHCO₃, water, brine), dried over MgSO₄, filtered and concentrated \textit{in vacuo}. The title compound was obtained after column chromatography (PE/ET₂O, 49:1 v/v) in 97\% yield (2.51 g, 3.9 mmol). \textsuperscript{1}H NMR (400 MHz) \(\delta\): 7.61-7.59 (m, 2H, \textit{CH}₃\text{arom}); 7.30-7.25 (m, 3H, \textit{CH}₃\text{arom}); 5.97-5.90 (m, 2H, H-1, \textit{CH}₃\text{ally}); 5.36 (dd, 1H, \textit{J} = 1.2 Hz, 17.2 Hz, C=\textit{CH}H); 5.27 (dd, 1H, \textit{J} = 1.2 Hz, 10.4 Hz, C=\textit{CH}H); 5.21 (d, 1H, \textit{J} = 3.2 Hz, H-4); 4.63-4.60 (m, 2H, \textit{CH}₂\text{ally}); 3.63 (dd, 1H, \textit{J} = 7.2 Hz, 10.0 Hz, H-6); 3.52 (dd, 1H, \textit{J} = 6.0 Hz, 10.0 Hz, H-6); 0.91, 0.87 (s, 9H, (\textit{CH}₃)₃\text{Si}); 0.21, 0.19, 0.02, 0.01 (s, 3H, \textit{CH}₂\text{Si}). \textsuperscript{13}C-APT NMR (100 MHz) \(\delta\): 154.3 (C\textit{Clac}); 134.5, 131.4, 129.1 (\textit{CH}₃\text{arom}, \textit{CH}₃\text{ally}); 128.3 (C₃\text{arom}); 127.8 (\textit{CH}₃\text{arom}); 119.1 (C=\textit{CH}₂; 85.2 (C-1); 73.6 (C-4); 71.9, 71.2 (C-3, C-5); 68.6 (\textit{CH}₂\text{ally}); 62.8 (C-2); 60.6 (C-6); 25.8, 25.7 ((\textit{CH}₃)₃\text{Si}); 18.2, 17.9 (C₃\text{Si}); -4.8, -5.3, -5.6, -5.7 (\textit{CH}₃\text{Si}). IR (thin film) \textit{v}: 2952, 2928, 2857, 2112, 1755, 1472, 1254, 1107. HRMS: [M+H]⁺ calculated for \(\text{C}_{28}\text{H}_{48}\text{N}_3\text{O}_5\text{SeSi}: 658.22414\); found 658.22431.
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**Phenyl 6-O-allyloxy carbonyl-2-azido-2-deoxy-1-seleno-a-D-galactopyranoside (17)**

![Chemical Structure of 17](image)

To a solution of 13 (0.29 g, 0.44 mmol, 1.0 eq.) in THF (2 mL, 0.2 M) was added NEt₃-3HF (0.14 mL, 0.87 mmol, 2.0 eq.). After TLC analysis (PE/EtOAc, 1:1 v/v) indicated complete conversion of the starting material (~30 hours), the reaction was quenched by addition of NaHCO₃ (sat. aq.), the mixture was extracted (CH₂Cl₂, 3x), the organic phases were washed (brine), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 9:1 → 4:1 v/v) delivered the 6-alloxy carbonyl product in 37% yield as the predominant product (69 mg, 0.16 mmol). ¹H NMR (400 MHz) δ: 7.62-7.59 (m, 2H, CH₃(Alc)); 7.36-7.26 (m, 3H, CH₃(Alc)); 5.98-5.88 (m, 2H, H-1, CH₃(silyl)); 5.38 (dd, 1H, J = 1.2 Hz, 17.2 Hz, C=CH₂H); 5.30 (dd, 1H, J = 0.8 Hz, 10.4 Hz, C=CH₂H); 4.63 (d, 2H, J = 6.0 Hz, CH₃(silyl)); 4.53 (t, 1H, J = 6.4 Hz, H-5); 4.41 (dd, 1H, J = 6.0 Hz, 11.4 Hz, H-6); 4.26 (dd, 1H, J = 6.8 Hz, 11.4 Hz, H-6); 4.10 (dd, 1H, J = 5.2 Hz, 10.4 Hz, H-2); 4.02 (d, 1H, J = 2.4 Hz, H-4); 3.80 (dd, 1H, J = 2.0 Hz, 10.5 Hz, H-2); 2.92 (bs, 1H, 4-OH); 2.79 (bs, 1H, 3-OH). ¹³CAPT NMR (100 MHz) δ: 155.1 (CH₃(Alc)); 134.9, 131.1, 129.2, 128.1 (CH₃(Alc)); 127.8 (C₆H₅(Alc)); 119.3 (C=CH₂) 84.7 (C-1); 70.8 (C-3); 70.0 (C-5); 68.9 (CH₃(silyl)); 68.2 (C-4); 65.8 (C-6); 61.6 (C-2). IR (thin film) ν: 3294, 2922, 2106, 1742, 1368, 1244, 1088, 1049. HRMS: [M+H]⁺ calculated for C₁₆H₂₀N₃O₆Se; 430.05118; found 430.05072.

**Phenyl 2-azido-4-O-benzyl-2-deoxy-3,6-di-O-(tert-butyl dimethylsilyl)-1-seleno-a-D-galactopyranoside (18) and Phenyl 2-azido-3-O-benzyl-2-deoxy-4,6-di-O-(tert-butyl dimethylsilyl)-1-seleno-a-D-galactopyranoside (19)**

![Chemical Structure of 18 and 19](image)

To a solution of 11 (0.57 g, 1.0 mmol, 1.0 eq.) in DMF (4 mL, 0.25 M) was added BnBr (0.18 mL, 1.5 mmol, 1.5 eq.). Subsequently, at 0 °C, NaH (60% dispersion in mineral oil, 60 mg, 1.5 mmol, 1.5 eq.) was added and the mixture was stirred at 0 °C until TLC analysis (PE/Et₂O, 19:1 v/v) indicated complete conversion of the starting material (~1 hour). The reaction was quenched by slow addition of cold water, and the reaction mixture was partitioned between H₂O and Et₂O. The aqueous phase was extracted (Et₂O, 2x), the combined organic fractions were washed with brine (1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 9:1 v/v) furnished a mixture of desired product 18 and its 3-O-
Bn regioisomer 19 (in a ratio of 1:0.8), in 87% yield (0.58 g, 0.87 mmol). \(^1\)H NMR (400 MHz) \(\delta\): 7.61-7.58 (m, 3.6H, \(CH_{arom}\)); 7.42-7.23 (m, 14.4H, \(CH_{arom}\)); 5.96-5.93 (m, 1.8H, H-118, H-119); 5.03 (d, 1H, \(J = 10.8\) Hz, PhCH/H18); 4.73-4.72 (m, 1.6H, PhCH/H19); 4.59 (d, 1H, \(J = 11.2\) Hz, PhCH/H18); 4.27-4.16 (m, 3.6H, H-218, H-219, H-419, H-518); 4.04 (t, 0.8H, \(J = 6.8\) Hz, H-519); 3.90-3.86 (m, 2H, H-318, H-418); 3.72-3.67 (m, 1.8H, H-618, H-619); 3.61 (dd, 0.8H, \(J = 2.4\) Hz, 10.4 Hz, H-319); 3.51-3.45 (m, 1.8H, H-618, H-619); 0.99 (s, 9H, \((CH_3)_3CSi\)); 0.85 (s, 7.2H, \((CH_3)_3CSi\)); 0.25, 0.22 (s, 6H, \(CH_2Si\)); 0.04-0.02 (s, 15.6H, \(CH_2Si\)). \(^{13}\)C-APT NMR (100 MHz) \(\delta\): 138.6, 137.2 (\(C_{arom}\)); 135.1, 135.1, 134.5, 129.0 (\(C_{arom}\)); 128.8 (\(C_{arom}\)); 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, (\(CH_{arom}\)); 85.5, 85.4 (C-118, C-119); 79.9 (C-319); 76.8 (C-318 or C-418); 75.4 (PhCH/H18); 74.1 (C-519); 74.0 (C-318 or C-418); 73.5 (C-518); 72.8 (PhCH/H19); 67.2 (C-419); 63.1, 61.1 (C-218, C-219); 61.0, 60.8 (C-618, C-619); 26.0, 25.9, 25.9, 25.8 ([CH_3]_3CSi); 18.5, 18.2, 18.1, 18.1 (\(C_{Si}\)); -4.2, -4.3, -5.0, -5.4, -5.4, -5.5 (\(CH_2Si\)). IR (thin film) \(\nu\): 2953, 2927, 2108, 1262, 1253, 1120, 1098, 1084, 1065. HRMS: [M+H] + calculated for \(C_{31}H_{50}N_3O_4SeSi_2\): 664.25020; found 664.25001.

**Phenyl 2-azido-2-deoxy-3,6-di-O-pivaloyl-1-seleno-α-D-galactopyranoside (20)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Piv} & \quad \text{O}, \quad \text{N} \\
\text{N}_{\text{Se}} & \quad \text{Ph}
\end{align*}
\]

To a solution of 10 (6.9 g, 20.0 mmol, 1.0 eq.) in pyridine (33 mL, 0.6 M) was added, at 0 °C, pivaloyl chloride (7.4 mL, 60.0 mmol, 3.0 eq.). The mixture was allowed to warm to room temperature and stirred overnight, after which TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete consumption of the starting material. The reaction mixture was quenched by slow addition of MeOH, diluted (\(CH_2Cl_2\)), washed (sat. aq. NH_4Cl, water, brine), dried over MgSO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (PE/EtO, 19:1 → 3:1 v/v) to obtain the title compound as a solid, in 92% yield (9.4 g, 18.3 mmol). \(^1\)H NMR (400 MHz) \(\delta\): 7.63-7.60 (m, 2H, \(CH_{arom}\)); 7.31-7.27 (m, 3H, \(CH_{arom}\)); 5.98 (d, 1H, \(J = 5.2\) Hz, H-1); 4.92 (dd, 1H, \(J = 2.8\) Hz, 10.8 Hz, H-3); 4.49 (t, 1H, \(J = 6.4\) Hz, H-5); 4.40-4.35 (m, 2H, H-2, H-6); 4.13-4.08 (m, 2H, H-4, H-6); 2.45 (d, 1H, \(J = 4.0\) Hz, 4-OH); 1.29, 1.18 (s, 9H, \((CH_3)_3C\)). \(^{13}\)C-APT NMR (100 MHz) \(\delta\): 178.8, 177.4 (\(CO_{Piv}\)); 134.2, 129.2 (\(CH_{arom}\)); 128.3 (\(C_{arom}\)); 127.9 (\(CH_{arom}\)); 85.6 (C-1); 73.0 (C-3); 70.4 (C-5); 66.7 (C-4); 62.6 (C-6); 59.0 (C-2); 39.0 (\(C_{Piv}\)); 27.1, 27.0 ([\(CH_3]_3C\)]. IR (neat) \(\nu\): 2972, 2934, 2116, 1730, 1715, 1479, 1285, 1157, 1138, 1084, 1053, 1034, 1022. HRMS: [M+Na] + calculated for \(C_{22}H_{31}N_3NaO_6Se\): 536.12703; found 536.12688.
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*Phenyl 2-azido-4-O-benzyl-2-deoxy-3,6-di-O-pivaloyl-1-seleno-α-D-galactopyranoside (21) and Phenyl 2-azido-3-O-benzyl-2-deoxy-4,6-di-O-pivaloyl-1-seleno-α-D-galactopyranoside (22)*

![Chemical Structures](image)

To a solution of 20 (0.51 g, 1.0 mmol, 1.0 eq.), BnBr (0.59 mL, 5.0 mmol, 5.0 eq.), Bu₄NI (74 mg, 0.2 mmol, 0.2 eq.) and imidazole (3 mg, 0.05 mmol, 0.05 eq.) in THF (3 mL, 0.3 M) was added, at 0 °C, NaH (60% dispersion in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.). The reaction was stirred at this temperature until TLC analysis (PE/Et₂O, 9:1 v/v) indicated complete consumption of the starting material (~2 hours). The reaction was quenched by slow addition of cold water, and the mixture was subsequently extracted (CH₂Cl₂, 3x). The combined organic phases were washed (brine), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 9:1 v/v) delivered 21 and 22 as an inseparable mixture (2:1) in 98% yield (0.59 g, 0.98 mmol). ¹H NMR (400 MHz) δ: 7.62 (m, 6H, CH₃); 7.38-7.26 (m, 24H, CH₃); 5.98 (d, 2H, J = 5.2 Hz, H-121); 5.94 (d, 1H, J = 5.2 Hz, H-122); 5.63 (d, 1H, J = 2.0 Hz, H-422); 4.99 (dd, 2H, J = 2.8 Hz, 10.8 Hz, H-321); 4.78-4.74 (m, 3H, PhCH₂); 4.64 (t, 1H, J = 6.8 Hz, H-522); 4.53-4.42 (m, 7H, H-221, H-521, PhCH₂); 4.18-3.99 (m, 9H, H-222, H-421, H-6); 3.75 (dd, 1H, J = 2.4 Hz, 10.4 Hz, H-322); 1.31 (s, 18H, (CH₃)₃C); 1.20-1.15 (m, 36H, (CH₃)₃C). ¹³C-APT NMR (100 MHz) δ: 178.0 (δO_piv); 137.2 (C₉arom); 134.1, 134.1, 129.2, 129.2, 128.6, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7 (CH₃); 85.7 (C-121); 85.5 (C-122); 77.0 (C-322); 75.5 (PhCH₂); 74.5 (C-421); 73.9 (C-321); 71.6 (PhCH₂); 70.8 (C-521); 69.6 (C-522); 65.2 (C-422); 62.4 (C-621); 61.7 (C-622); 60.6 (C-222); 59.9 (C-221); 38.7 (C₉piv); 27.2, 27.2, 27.1, 27.1 ((CH₃)₃C). IR (neat) ν: 2974, 2114, 1726, 1477, 1275, 1146, 1130, 1088, 1045, 1034. HRMS: [M+NH₄]⁺ calculated for C₂₉H₄₈N₄O₄Se: 621.21881; 621.21872.

**Phenyl 3-O-acetyl-2-azido-2-deoxy-4,6-O-(4-methoxybenzylidene)-1-seleno-α-D-galactopyranoside (26)**

![Chemical Structure](image)

A solution of 20 (13.9 g, 40 mmol, 1.0 eq.), p-anisaldehyde (5.8 mL, 48 mmol, 1.2 eq.) and camphorsulfonic acid (0.93 g, 4.0 mmol, 0.1 eq.) in MeCN (130 mL, 0.3 M) was concentrated on a rotary evaporator (50 °C, 300 mbar) until around 25% of the original volume, after which TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material. The reaction
was quenched by addition of NEt₃ and concentrated to a thick syrup. Crystallization from EtOH gave the product in 86% yield (16.0 g, 34.4 mmol). ¹H NMR (400 MHz) δ: 7.58-7.56 (m, 2H, CH arom); 7.42 (d, 2H, J = 8.8 Hz, CH arom); 7.31-7.25 (m, 3H, CH arom); 6.91 (d, 2H, J = 8.8 Hz, CH arom); 6.03 (d, 1H, J = 5.2 Hz, H-1); 5.56 (s, 1H, PhCH); 4.29 (d, 1H, J = 3.2 Hz, H-4); 4.17 (m, 3H, H-2, H-5, H-6); 4.07 (m, 1H, H-6); 3.92 (dd, 1H, J = 3.6 Hz, 10.4 Hz, H-3); 3.82 (s, 3H, OCH₃); ¹³C NMR (100 MHz) δ: 133.9 (CH arom); 129.7 (C q arom); 129.3 (CH arom); 128.6 (C q arom); 127.9, 127.7, 113.8 (CH arom); 101.4 (PhCH); 85.4 (C-1); 75.1 (C-4); 70.2 (C-3); 69.2 (C-6); 65.1 (C-5); 62.0 (C-2); 55.4 (OCH₃). To a solution of the intermediate (14.0 g, 30.2 mmol, 1.0 eq.) in pyridine (100 mL, 0.3 M) was added, at 0 °C, Ac₂O (11.4 mL, 120 mmol, 4.0 eq.). The mixture was allowed to warm to room temperature and stirred until TLC analysis indicated complete consumption of the starting material. The reaction was quenched by addition of sat. aq. NaHCO₃ and the mixture was extracted with CH₂Cl₂ (3x). The combined organic phases were washed with HCl (1M, aq., 1x), NaHCO₃ (sat. aq., 2x), water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The title compound was obtained as a yellow syrup in 76% yield (11.3 g, 23.0 mmol). ¹H NMR (400 MHz) δ: 7.58-7.56 (m, 2H, CH arom); 7.41 (d, 2H, J = 8.4 Hz, CH arom); 7.28-7.25 (m, 4H, CH arom); 6.90 (d, 2H, J = 8.8 Hz, CH arom); 6.03 (d, 1H, J = 5.2 Hz, H-1); 5.55 (s, 1H, PhCH); 4.28 (d, J = 3.2 Hz, H-4); 4.17-4.04 (m, 4H, H-2, H-5, H-6); 3.92 (dt, 1H, J = 3.6 Hz, 10.0 Hz, H-3); 3.80 (s, 3H, OCH₃); 2.63 (d, 1H, J = 10.4 Hz, 3-OH). ¹³C-APT NMR (100 MHz) δ: 160.4 (C q arom); 137.8 (CH arom); 129.6 (C q arom); 129.2 (CH arom); 128.5 (C q arom); 127.7, 127.6, 113.4 (CH arom); 101.3 (PhCH); 85.2 (C-1); 74.9 (C-4); 70.6 (C-3); 69.0 (C-6); 65.0 (C-5); 62.0 (C-2); 55.3 (OCH₃). IR (neat) ν: 2930, 2110, 1744, 1614, 1516, 1402, 1369, 1240, 1219, 1086, 1061, 1032. HRMS: [M+H]+ calculated for C₂₂H₂₄N₃O₆Se: 506.08263; found 506.08228.

Phenyl 3-O-acetyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-1-seleno-α-D-galactopyranoside (27)

To a solution of 26 (4.0 g, 8.0 mmol, 1.0 eq.) in CH₂Cl₂ (40 mL, 0.2 M) was added, at 0 °C, BH₃·THF (as 1M solution in THF, 16 mL, 16 mmol, 2.0 eq.), followed by Bu₃BOTf (as 1M solution in CH₂Cl₂, 8 mL, 8 mmol, 1.0 eq.). The reaction was stirred at 0 °C until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~2 hours), the reaction was quenched by addition of NEt₃ (~1 mL), followed by careful addition of MeOH until H₂ evolution had ceased. The reaction mixture was concentrated in vacuo and co-evaporated with MeOH (5x). Purification by column chromatography (PE/EtOAc, 1:0 → 4:1 v/v) delivered the 4-O-PMB product as the single product in 82% yield (3.3 g, 6.5 mmol, 82%). δ: 7.57-7.55 (m, 2H, CH arom); 7.23-7.21 (m, 5H,
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\[ \text{CH}_{26}\text{H}_{32}\text{N}_{2}\text{O}_{2}\text{Se}: \text{508.09828; found 508.09790.} \]

**Phenyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-1-seleno-\(\alpha\)-d-galactopyranoside (28)**

![Phenyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-1-seleno-\(\alpha\)-d-galactopyranoside (28)](image)

To a solution of 27 (3.3 g, 6.5 mmol, 1.0 eq.) in MeOH (35 mL, 0.2 M) was added a chip of metallic Na. The reaction was stirred until TLC analysis (PE/EtOAc, 3:2 v/v) indicated complete conversion of the starting material (~3 hours). The reaction mixture was neutralized by addition of Amberlite IR-120 (H\(^+\) form), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 1:0 → 3:2 v/v) gave the title product in 89% yield (2.6 g, 5.7 mmol).

\(^\text{1}H\) NMR (400 MHz) \(\delta\): 7.607.57 (m, 2H, \text{CH}_{26}\text{H}_{32}\text{N}_{2}\text{O}_{2}\text{Se}); 7.30-7.26 (m, 5H, \text{CH}_{26}\text{H}_{32}\text{N}_{2}\text{O}_{2}\text{Se}); 6.92-6.89 (m, 2H, \text{CH}_{26}\text{H}_{32}\text{N}_{2}\text{O}_{2}\text{Se}); 5.98 (d, 1H, \(\text{J} = 6.4 \text{ Hz}, \text{H}-1\)); 4.66 (m, 2H, Ph\text{CH}_{2}); 4.25 (t, 1H, \(\text{J} = 8.0 \text{ Hz}, \text{H}-5\)); 4.08 (dd, 1H, \(\text{J} = 10.0 \text{ Hz, 3-OH}\)); 1.43 (t, 1H, 6-OH); \(^\text{13}C\) NMR (100 MHz) \(\delta\): 135.0, 130.1, 129.3, 128.2, 114.28 (\text{CH}_{26}\text{H}_{32}\text{N}_{2}\text{O}_{2}\text{Se}); 84.5 (C-1), 76.8 (C-3), 75.2 (Ph\text{CH}_{2}), 73.6 (C-5), 71.9 (C-4), 62.8 (C-2), 62.0 (C-6); 55.4 (O\text{CH}_{3}). IR (thin film) v: 3462, 2936, 2110, 1742, 1514, 1302, 1244, 1227, 1045, 1032, 1022, 741. HRMS: [M+H]\(^+\) calculated for C\(_{26}\)H\(_{32}\)N\(_2\)O\(_2\)Se: 488.06963; found 488.06933.

**Phenyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-1-seleno-\(\alpha\)-d-galactopyranosidurono-[3,6]-lactone (29)**

![Phenyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-1-seleno-\(\alpha\)-d-galactopyranosidurono-[3,6]-lactone (29)](image)

To a solution of 28 (2.64 g, 5.7 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\)/H\(_2\)O (2:1 v/v, 28 mL, 0.2 M) were added AcOH (32 \(\mu\)L, 0.57 mmol, 0.1 eq.), TEMPO (0.18 g, 1.1 mmol, 0.2 eq.) and Phl(OAc)\(_2\) (4.57 g, 14.2 mmol, 2.5 eq.). The reaction mixture was stirred vigorously until TLC analysis (PE/EtOAc, 4:1 v/v)
indicated complete conversion of the starting material (~45 minutes). The reaction was quenched by addition of sat. aq. Na₂S₂O₅ and after separation of the layers, the aqueous phase was extracted (CH₂Cl₂, 3x). The combined organic fractions were washed (brine), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 17:3 v/v), followed by crystallization from EtOH delivered the title lactone in 80% yield (2.11 g, 4.6 mmol).

1H NMR (400 MHz) δ: 7.55-7.53 (m, 2H, CH₃); 7.32-7.23 (m, 6H, CH₂); 6.89 (m, 2H, CH₂); 5.39 (d, 1H, J = 2.8 Hz, H-1); 4.81 (d, 1H, J = 4.4 Hz, H-3); 4.55 (m, 2H, PhCH₂); 4.31 (dd, 1H, J = 3.4, 4.6 Hz, H-2); 4.29 (s, 1H, H-5); 4.21 (s, 1H, H-4); 3.79 (OCH₃,SE); 13C NMR (100 MHz) δ: 170.8 (C-6); 159.9 (C₆); 133.5, 129.8, 129.6, 128.5 (CH₃); 128.4 (C₆); 114.2 (CH₃); 81.5 (C-1); 81.1 (C-3); 75.3 (C-4); 75.2 (C-5); 71.7 (PhCH₂); 64.2 (C-2); 55.4 (OCH₃); IR (thin film) ν: 2947, 2835, 2110, 1796, 1612, 1514, 1344, 1250, 1151, 1030, 829, 743. HRMS: [M+N-N₂]⁺ calculated for C₂₀H₂₀NO₂Se: 434.05004; found 434.05028.

2-azido-2-deoxy-4-O-(4-methoxybenzyl)-1-seleono-α-D-\(\text{galactopyranosiduronate}\) (30)

To a stirred solution of 27 (1.27 g, 2.5 mmol, 1.0 eq.) in CH₂Cl₂/H₂O (2:1 v/v, 12.5 mL, 0.2 M) were added AcOH (14 µL, 0.25 mmol, 0.1 eq.), TEMPO (78 mg, 0.5 mmol, 0.2 eq.) and Ph(OAc)₂ (2.01 g, 6.25 mmol, 2.5 eq.). The mixture was stirred vigorously until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~4 hours). The reaction was quenched by addition of sat. aq. Na₂S₂O₅ and 1M aq. H₃PO₄ (10 mL) was added. After separation of the layers, the aqueous phase was extracted (CH₂Cl₂, 3x). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was co-evaporated with toluene, and subsequently dissolved in DMF (12.5 mL, 0.2 M). Added were Mel (0.31 mL, 5.0 mmol, 2.0 eq.) and K₂CO₃ (0.69 g, 5.0 mmol, 2.0 eq.) and the mixture was stirred until TLC analysis indicated complete conversion of the starting material (~2 hours). The reaction was quenched by addition of H₂O (~25 mL) and the aqueous phase was extracted (Et₂O, 3x). The combined ethereal phases were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography to provide the title methyl uronate in 35% yield (0.47 g, 0.87 mmol). 1H NMR (400 MHz) δ: 7.56-7.53 (m, 2H, CH₃); 7.28-7.24 (m, 3H, CH₃); 7.19-7.17 (m, 2H, CH₂); 6.88-6.84 (m, 2H, CH₂); 6.04 (d, 1H, J = 5.2 Hz, H-1); 5.01 (dd, 1H, J = 3.2, 10.8 Hz, H-3); 4.94 (d, 1H, J = 3.2 Hz, H-4); 4.56 (m, 1H, PhCH₂); 4.47 (m, 3H, PhCH₂H, H-2, H-5); 3.79 (s, 3H, OCH₃); 3.67 (s, 3H, CO₂CH₃); 2.12 (s, 3H, CH₃O). 13C-APT NMR (100 MHz) δ: 170.1
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(CO\textsubscript{Ac}); 168.0 (C-6); 134.1 (CH\textsubscript{arom}); 129.6 (C\textsubscript{q,arom}); 129.4, 128.1 (CH\textsubscript{arom}); 113.9 (CH\textsubscript{arom}); 85.0 (C-1); 75.0 (PhCH\textsubscript{2}); 74.9 (C-5); 73.7 (C-3); 72.4 (C-4); 58.7 (C-2); 55.4 (OCH\textsubscript{3,PMB}); 52.6 (CO\textsubscript{2}CH\textsubscript{3}); 20.9 (CH\textsubscript{3,Ac}); IR (thin film) ν: 2951, 2936, 2108, 1741, 1612, 1536 cm\textsuperscript{-1}.

**General procedure for generation of glycosyl triflates**

![Reaction scheme for glycosyl triflates](image)

A mixture of glycosyl donor (0.038 mmol, 1.0 eq.) and Ph\textsubscript{2}SO (10 mg, 0.049 mmol, 1.3 eq.; 15 mg, 0.076 mmol, 2.0 eq.; or 31 mg, 0.152 mmol, 4.0 eq.) were dried by co-evaporation with toluene (3x), followed by three vacuum/argon purges. The mixture was dissolved in CD\textsubscript{2}Cl\textsubscript{2} (0.75 mL, 0.05 M) and transferred to a dry-NMR tube, which was subsequently capped with a septum. The tube was placed in the probe of a NMR magnet and cooled to -80 °C, after which a \textsuperscript{1}H NMR spectrum was recorded. The tube was removed from the magnet and placed in a acetone/N\textsubscript{2} (I) bath (temperature ≤ -80 °C). Tf\textsubscript{2}O (8 μL, 0.049 mmol, 1.3 eq.) was added with a microliter syringe and, after rapid mixing and re-cooling, the tube was placed back in the NMR instrument. A \textsuperscript{1}H NMR spectrum was recorded, which revealed the formation of reactive intermediate(s). After further characterization (\textsuperscript{13}C-APT NMR, HH-COSY and HSQC) the temperature of the sample was increased by increments of 10 °C until decomposition of the intermediate(s) was observed.

**General procedure for glycosylations**

![Reaction scheme for glycosylations](image)

To a stirred solution of donor (0.1 mmol, 1.0 eq.), Ph\textsubscript{2}SO (26 mg, 0.13 mmol, 1.3 eq.) and TTBP (62 mg, 0.25 mmol, 2.5 eq.) in CH\textsubscript{2}Cl\textsubscript{2} were added flame-dried, rod-shaped 3Å molecular sieves. After stirring for ~30 minutes, the reaction mixture was cooled to -80 °C. Tf\textsubscript{2}O (22 μL, 0.13 mmol, 1.3 eq.) was added and the mixture was allowed to warm to -70 °C. After re-cooling to -80 °C, a solution of the acceptor (0.5 M in CH\textsubscript{2}Cl\textsubscript{2}, 0.4 mL, 2.0 eq.) was slowly added \textit{via} the wall of the flask and the mixture was warmed to -40 °C. The reaction was quenched by addition of NE\textsubscript{T}\textsubscript{3} (0.1 mL), filtered over a small bed of celite, diluted with CH\textsubscript{2}Cl\textsubscript{2}, washed with brine (1x), dried over MgSO\textsubscript{4},
filtered and concentrated \textit{in vacuo}. Purification by column chromatography and/or size-exclusion chromatography delivered the corresponding product(s).

\textit{Ethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-β-galactopyranosidurono-[3,6]-lactone (35)}

![Structure of Ethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-β-galactopyranosidurono-[3,6]-lactone (35)](image)

The title products (α/β 4:1) were obtained after column chromatography (PE/Et\textsubscript{2}O, 1:0 → 4:1 v/v) in 69\% yield (24 mg, 0.069 mmol). \textsuperscript{1}H NMR (400 MHz) δ: 7.26-7.21 (m, 10H, \textit{C}_\text{arom}); 6.92-6.87 (m, 10H, \textit{C}_\text{arom}); 4.95 (d, 4H, \textit{J} = 2.8 Hz, H-1α); 4.80 (s, 1H, H-1β); 4.73-4.71 (m, 5H, H-3α, H-3β); 4.57-4.48 (m, 10H, PhCH\textsubscript{2}); 4.22 (d, 4H, \textit{J} = 1.6 Hz, H-5α); 4.19-4.15 (m, 6H, H-2α, H-2β, H-5β); 4.10 (s, 4H, H-4α); 3.99-3.93 (m, 5H, CH\textsubscript{Et}α, H-4β); 3.86 (s, 3H, OCH\textsubscript{3,PMB}); 3.81-3.78 (m, 13H, OCH\textsubscript{3}β, OCH\textsubscript{3,PMB}); 3.66-3.58 (m, 4H, CH\textsubscript{H}α); 3.48-3.42 (m, 1H, CH\textsubscript{H}β); 1.33-1.17 (m, 16H, CH\textsubscript{3}Et); \textsuperscript{13}C-APT NMR (100 MHz) δ: 171.3 (C-6); 159.7 (C\textsubscript{q,arom}); 133.2, 132.1, 131.1, 129.6, 129.4, 129.3 (C\textsubscript{arom}); 128.5 (C\textsubscript{q,arom}); 127.7, 126.2, 124.8, 114.1, 113.9 (C\textsubscript{arom}); 99.5 (C-1β); 97.9 (C-1α); 79.7 (C-3α); 78.7 (C-3β); 75.5 (C-5β); 75.0 (C-5α); 71.9 (C-4α); 71.5, 71.4 (Ph\textsubscript{H}2); 70.5 (C-4β); 66.7 (CH\textsubscript{2,Et}α); 64.3 (CH\textsubscript{2,Et}β); 62.4 (C-2β); 60.6 (C-2α); 55.3 (OCH\textsubscript{3,PMB}); 15.1 (CH\textsubscript{3,Et}α); 14.4 (CH\textsubscript{3,Et}β); \textsuperscript{13}C-GATED NMR (100 MHz): 99.5 (d, \textit{J} = 171 Hz, C-1β); 97.8 (d, \textit{J} = 164 Hz, C-1α); IR (thin film) ν: 2936, 2924, 2126, 2110, 1802, 1612, 1514, 1250, 1153, 976, 827. HRMS: [M + NH\textsubscript{4}]\textsuperscript{+} calculated for C\textsubscript{16}H\textsubscript{10}N\textsubscript{2}O\textsubscript{6}: 367.16121; found 367.16119.

\textit{2-fluoroethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-β-galactopyranosidurono-[3,6]-lactone (36)}

![Structure of 2-fluoroethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-β-galactopyranosidurono-[3,6]-lactone (36)](image)

The title products (α/β 6:1) were obtained after column chromatography (PE/Et\textsubscript{2}O, 1:0 → 4:1) in 74\% yield (27 mg, 0.074 mmol). \textsuperscript{1}H NMR (400 MHz) δ: 7.26-7.22 (m, 14H, \textit{C}_\text{arom}); 6.91-6.88 (m, 14H, \textit{C}_\text{arom}) 5.01 (d, 6H, \textit{J} = 2.8 Hz, H-1α); 4.87 (s, 1H, H-1β); 4.77-4.48 (m, 35H, H-3α, H-3β, CH\textsubscript{3}F, PhCH\textsubscript{2}); 4.27-4.22 (m, 1H, H-2α, H-5α, H-2β); 4.19 (d, 1H, \textit{J} = 1.2 Hz, H-5β); 4.16-4.03 (m, 13H, H-4α, CH\textsubscript{CH}CF\textsubscript{3}); 3.94-3.80 (m, 29H, H-4β, CH\textsubscript{H}CF\textsubscript{3}, OCH\textsubscript{3,PMB}). \textsuperscript{13}C-APT NMR (100 MHz) δ: 171.1 (C-6); 159.8 (C\textsubscript{q,arom}); 131.1, 129.6, 129.4 (C\textsubscript{arom}); 128.5 (C\textsubscript{q,arom}); 124.8, 114.1 (C\textsubscript{arom}); 107.0 (C-1β); 98.4 (C-1α); 88.2 (d, \textit{J} = 170 Hz, CH\textsubscript{3}F); 79.6 (C-3α); 78.7 (C-3β); 75.3 (C-5β); 74.8 (C-5α);
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71.9 (C-4α); 71.6 (PhCH₂α); 71.4 (PhCH₂β); 70.6 (C-4β); 68.7 (d, J/= 20 Hz, CH₂CH₂Fα); 67.3 (d, J/= 20 Hz, CH₂CH₂Fβ); 62.0 (C-2β); 60.3 (C-2α); 55.3 (O-CH₃PMB); ¹³C-GATED NMR (100 MHz): 98.4 (d, J/= 170 Hz, C-1α). IR (thin film) ν: 2936, 2859, 2126, 2110, 1802, 1514, 1250, 1157, 1059, 826. HRMS: [M + NH₄]⁺ calculated for C₁₆H₁₆F₃N₃O₆: 385.15179; found 385.15175.

2,2-difluoroethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-D-galactopyranosidurono-[3,6]-lactone (37)

The title products (α/β 6:1) were obtained after column chromatography (PE/Et₂O, 1:0 → 4:1) in 86% yield (33 mg, 0.086 mmol). ¹H NMR (400 MHz) δ: 7.26-7.22 (m, 14H, CH₃rom); 6.91-6.88 (m, 14H, CF₂); 6.05-5.76 (m, 7H, CHF₂); 4.99 (d, 6H, J/= 2.8 Hz, H-1α); 4.86 (s, 1H, H-1β); 4.75-4.72 (m, 7H, H-3α, H-3β); 4.57-4.49 (m, 14H, PhCH₂); 4.26-4.19 (m, 14H, H-2α, H-5α, H-2β, H-5β); 4.12 (s, 6H, H-4α); 4.10-3.98 (m, 6H, CH₂CHF₂Hα); 3.96 (s, 1H, H-4β); 3.86-3.76 (m, 28H, OCH₂PMB, CH₂CHF₂Hα, CH₂CHF₂Hβ); 3.68-3.58 (m, 1H, CH₂CHF₂Hβ); ¹³C-APT NMR (100 MHz) δ: 170.8 (C-6); 159.8 (C₃,αrom); 129.7, 129.4 (CH₂rom); 128.4 (C₃,αrom); 114.2, 113.9 (CH₂rom); 113.4 (t, J/= 240 Hz, CF₂H); 100.0 (C-1β); 98.5 (C-1); 79.5 (C-3); 78.6 (C-3β); 75.1 (C-5β); 74.7 (C-5); 72.0 (C-4); 71.6 (PhCH₂α); 71.5 (PhCH₂β); 70.6 (C-4β); 69.1 (t, J/= 28 Hz, CH₂CHF₂Hα); 66.8 (t, J/= 28 Hz, CH₂CHF₂Hβ); 61.8 (C-2β); 60.2 (C-2); 55.3 (O-CH₃PMB); ¹³C-GATED NMR (100 MHz): 100.0 (d, J/= 175 Hz, C-1β); 98.5 (d, J/= 165 Hz, C-1α); IR (thin film) ν: 2936, 2928, 2113, 1802, 1748, 1612, 1514, 1250, 1070, 830, 758. HRMS: [M + NH₄]⁺ calculated for C₁₆H₁₇F₂N₃O₆: 403.14237; found 403.14233.

2,2,2-trifluoroethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-D-galactopyranosidurono-[3,6]-lactone (38)

The title products (α/β 2:1) were obtained after column chromatography (PE/Et₂O, 1:0 → 4:1) in 57% yield (23 mg, 0.057 mmol). ¹H NMR (400 MHz) δ: 7.26-7.22 (m, 6H, CH₃rom); 6.92-6.89 (m, 6H, CH₃rom); 5.03 (d, 2H, J/= 2.8 Hz, H-1α); 4.92 (s, 1H, H-1β); 4.77-4.73 (m, 3H, H-3α, H-3β); 4.61-4.49 (m, 6H, PhCH₂); 4.29-4.17 (m, 8H, H-2α, H-5α, H-2β, H-5β, CH₂CHF₂α); 4.12 (s, 1H, H-4α); 4.01-3.88 (m, 5H, H-4β, CH₂CHF₂α, CH₂CHF₂β); 3.82 (s, 9H, OCH₃PMB); ¹³C-APT NMR (100 MHz) δ: 170.6
Cyclohexyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-D-galactopyranosidurono-[3,6]-lactone (39)

The title products (α/β 3:1) were obtained after column chromatography (PE/Et₂O, 1:0 → 4:1) in 75% yield (30 mg, 0.075 mmol). ¹H NMR (400 MHz) δ: 7.26-7.21 (m, 8H, CHₐrom); 6.91-6.87 (m, 8H, CHₐrom); 5.07 (d, 3H, J = 2.8 Hz, H-1α); 4.94 (s, 1H, H-1β); 4.73-4.71 (m, 4H, H-3α, H-3β); 4.57-4.47 (m, 8H, PhCH₂); 4.24 (s, 1H, H-4α); 4.17-4.15 (m, 2H, H-2β, H-5β); 4.12-4.09 (m, 6H, H-2α, H-5α); 3.92 (s, 1H, H-4β); 3.81 (s, 12H, OCH₃,PMB); 3.75-3.63 (m, 4H, OCH₃); 1.90-1.69 (m, 16H, C₉₂O₂); 1.49-1.13 (m, 24H, CH₂O₂). ¹³C-APT NMR (100 MHz) δ: 171.5 (C-6); 159.7 (C₉₂O₂); 129.6, 129.4, (CHₐrom); 128.6 (C₉₂O₂); 114.1, 114.1 (CHₐrom); 97.0 (C-1β); 96.2 (C-1α); 79.8 (C-3α); 78.7 (C-3β); 76.0 (CH₉₂O₂); 75.6 (C-5β); 75.0 (C-4α); 71.9 (C-5α); 71.5 (PhCH₂α); 71.4 (PhCH₂β); 70.5 (C-4β); 62.8 (C-2β); 61.2 (C-2α); 55.3 (OCH₃,PMB); 33.1, 32.2, 31.5, 30.5, 29.7, 25.5, 25.4, 24.0, 23.9, 23.5, 23.4 (CH₂O₂); ¹³C-GATED NMR (100 MHz): 97.0 (d, J = 173 Hz, H-1β); 96.2 (d, J = 162 Hz, H-1α); IR (thin film) ν: 2936, 2931, 2126, 2108, 1803, 1715, 1514, 1250, 1163, 1092, 1032, 968, 829. HRMS: [M + NH₄]⁺ calculated for C₁₅H₁₆F₃N₃O₆: 421.13586; found 421.13258.

Methyl 4-O-(2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-D-galactopyranosidurono-[3,6]-lactone)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (40)
The products (α/β 6:1) were obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v) and column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) in 61% yield (41 mg, 0.061 mmol). 

¹H NMR (400 MHz, for the α-isomer) δ: 7.14 (m, 17H, CH₆₆); 6.86 (d, 2H, J = 8.8 Hz, CH₆₆); 5.13 (d, 1H, J = 2.8 Hz, H-1′); 5.04 (d, 1H, J = 12.0 Hz, PhCH₂); 4.72 (d, 1H, J = 11.6 Hz, PhCH₂); 4.62-4.39 (m, 8H, H-1, H-3′, PhCH₂); 4.00 (d, 1H, J = 0.8 Hz, H-4′); 3.92-3.87 (m, 2H, H-3, H-5′); 3.79 (s, 3H, OCH₃); 3.74-3.62 (m, 4H, H-4, H-5, H-6); 3.52 (dd, 1H, J = 3.6 Hz, 9.6 Hz, H-2); 3.38 (s, 3H, OCH₃). Diagnostic peaks for the β-anomer: 5.17 (bs, 1H, H-1′); 4.07 (bs, 1H, H-4′) ¹³C-APT NMR (100 MHz) δ: 171.0 (C-6); 159.6, 138.7, 138.2, 137.7 (C₆₆); 129.6, 129.5, 128.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 114.0 (CH₆₆); 99.3 (C-1′); 97.7 (C-1); 81.2 (C-3); 80.2 (C-2); 79.2 (C-3′); 77.5 (C-5); 75.4 (PhCH₂); 74.7 (C-4′); 73.6, 73.1 (PhCH₂); 71.8 (C-5′); 71.2 (PhCH₂); 69.3 (C-4); 68.6 (C-6); 59.9 (C-2′); 55.4, 55.3 (OCH₃, OCH₃). Diagnostic signal for the β-anomer: 101.0 (C-1′). IR (thin film) ν: 2918, 2126, 1712, 1592, 1382, 1377 (CH₂, CH₃); 1712, 1678, 1592, 1587, 1462, 1388, 1226, 1158, 1102, 1047, 972. HRMS: [M+Na]⁺ calculated for C₄₂H₄₅N₃NaO₁₁: 790.29463; found 790.29468.

*Methyl 6-O-(2-azido-2-deoxy-4-O-(4-methoxybenzyl)-α/β-D-galactopyranosidurono-[3,6]-lactone)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (41)*

The products (α/β 3:1) were obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v) and column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) in 18% yield (14 mg, 0.018 mmol). NMR data is reported for the major α-isomer only. ¹H NMR (400 MHz) δ: 7.37-7.19 (m, 17H, CH₆₆); 6.86 (d, 2H, J = 8.8 Hz, CH₆₆); 5.00 (d, 1H, J = 2.8 Hz, H-1′); 4.97 (d, 1H, J = 10.8 Hz, PhCH₂); 4.90-4.77 (m, 3H, PhCH₂); 4.70 (dd, 1H, J = 1.6 Hz, 5.0 Hz, H-3′); 4.67-4.62 (m, 2H, PhCH₂); 4.55-4.46 (m, 3H, H-1, PhCH₂); 4.23-4.20 (m, 2H, H-2′, H-6); 4.17 (d, 1H, J = 0.8 Hz, H-4′); 4.06 (bs, 1H, H-5′); 3.98 (t, 1H, J = 9.6 Hz, H-3); 3.79 (s, 3H, OCH₃); 3.75-3.68 (m, 2H, H-5, H-6); 3.59 (t, 1H, J = 9.6 Hz, H-4); 3.47 (dd, 1H, J = 3.2 Hz, 9.6 Hz, H-2); 3.34 (s, 3H, OCH₃). ¹³C-APT NMR (100 MHz) δ: 171.1 (C-6); 159.7, 138.7, 138.6 (C₂); 129.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 114.0 (CH₆₆); 98.2, 98.1 (C-1, C-1′); 81.7 (C-3); 79.9 (C-2); 79.5 (C-3′); 77.2 (C-4); 75.8, 75.2 (PhCH₂); 74.9 (C-4′); 73.5 (PhCH₂); 71.8 (C-5); 71.5 (PhCH₂); 69.7 (C-5′); 68.5 (C-6); 60.2 (C-2′); 55.3, 55.2 (OCH₃, OCH₃). IR (thin film) ν: 2913, 1226, 1803, 1612, 1514, 1250, 1155, 1092, 1047, 1030. HRMS: [M+Na]⁺ calculated for C₄₂H₄₅N₃NaO₁₁: 790.29463; found 790.29454.
The product was obtained after column chromatography (PE/EtOAc, 19:1 → 3:2) in 68% yield (29 mg, 0.068 mmol). \(^1^H\) NMR (400 MHz) \(\delta\): 7.19 (d, 2H, \(J = 8.8\) Hz, \(CH_{\text{arom}}\)); 6.85 (d, 2H, \(J = 8.4\) Hz, \(CH_{\text{arom}}\)); 4.72 (dd, 1H, \(J = 3.2\) Hz, 10.8 Hz, H-3); 4.54 (d, 1H, \(J = 11.2\) Hz, PhCH\(H\)); 4.48 (d, 1H, \(J = 11.6\) Hz, PhCH\(H\)); 4.33 (d, 1H, \(J = 8.0\) Hz, H-1); 4.28 (d, 1H, \(J = 2.0\) Hz, H-4); 4.11-4.03 (m, 2H, H-5, OCH\(H\)\(_{\text{Et}}\)); 3.87 (dd, 1H, \(J = 8.0\) Hz, 10.8 Hz, H-2); 3.80 (s, 3H, OCH\(\text{Me}_{\text{3-PMB}}\)); 3.69-3.59 (m, 4H, OCH\(\text{Me}_{\text{3,PMB}}\); CO\(\text{Me}_{\text{2}}\)); 2.07 (s, 3H, CH\(_{3,\text{Ac}}\)); 1.29 (t, 3H, \(J = 7.2\) Hz, CH\(_{3,\text{Bu}}\)). \(^1^C\)-APT NMR (100 MHz) \(\delta\): 170.0, 167.8 (C-6, \(\text{CO}_{\text{Ac}}\)); 159.4 (C\(_{\text{arom}}\)); 129.9 (CH\(_{\text{arom}}\)); 129.5 (C\(_{\text{arom}}\)); 113.7 (CH\(_{\text{arom}}\)); 101.8 (C-1); 74.5 (PhCH\(_2\)); 74.0, 73.6, 73.1 (C-3, C-4, C-5); 66.0 (CH\(_{2,\text{Me}}\)); 60.5 (C-2); 55.3 (OCH\(_{3,\text{PMB}}\)); 52.5 (CO\(_{2}\)CH\(_3\)); 20.8 (CH\(_{3,\text{Ac}}\)); 14.9 (CH\(_{3,\text{Bu}}\)). IR (thin film) \(\nu\): 2934, 2112, 1748, 1612, 1514, 1366, 1229, 1165, 1098, 1032. HRMS: [M+\(\text{NH}_4\)]\(^+\) calculated for C\(_{19}\)H\(_{20}\)N\(_4\)O\(_6\): 441.19737; found 441.19799.

Methyl (2-fluoroethyl 2-azido-2-deoxy-4-O-(4-methoxybenzyl)-\(\beta\)-\(\text{D}\)-galactopyranosiduronate) (43)

The product was obtained after column chromatography (PE/EtOAc, 19:1 → 3:2) in 79% yield (35 mg, 0.079 mmol). \(^1^H\) NMR (400 MHz) \(\delta\): 7.19 (d, 2H, \(J = 8.8\) Hz, CH\(_{\text{arom}}\)); 6.86 (d, 2H, \(J = 8.4\) Hz, CH\(_{\text{arom}}\)); 4.73 (dd, 1H, \(J = 3.2\) Hz, 10.8 Hz, H-3); 4.71-4.45 (m, 4H, CH\(_2\)F, PhCH\(_2\)); 4.41 (d, 1H, \(J = 8.0\) Hz, H-1); 4.29 (dd, 1H, \(J = 0.8\) Hz, 3.0 Hz, H-4); 4.22-4.10 (m, 2H, H-5, CH\(_{2}\)CH\(_2\)F); 3.98-3.87 (m, 2H, H-2, CH\(_2\)CH\(_2\)F); 3.80 (s, 3H, OCH\(_{3,\text{PMB}}\)); 3.67 (s, 3H, CO\(_{2}\)CH\(_3\)); 2.10 (s, 3H, CH\(_{3,\text{Ac}}\)). \(^1^C\)-APT NMR (100 MHz) \(\delta\): 170.1, 167.5 (C-6, \(\text{CO}_{\text{Ac}}\)); 159.4 (C\(_{\text{arom}}\)); 129.8 (CH\(_{\text{arom}}\)); 129.4 (C\(_{\text{arom}}\)); 113.7 (CH\(_{\text{arom}}\)); 102.1 (C-1); 82.5 (d, \(J = 169\) Hz, CH\(_2\)F); 74.6 (PhCH\(_2\)); 73.9 (C-4); 73.8 (C-5); 73.1 (C-3); 68.9 (d, \(J = 21\) Hz, CH\(_2\)CH\(_2\)F); 60.5 (C-2); 55.3 (OCH\(_{3,\text{PMB}}\)); 52.5 (CO\(_{2}\)CH\(_3\)); 20.8 (CH\(_{3,\text{Ac}}\)). IR (thin film) \(\nu\): 2938, 2114, 1748, 1612, 1514, 1364, 1229, 1163, 1096, 1034. HRMS: [M+\(\text{NH}_4\)]\(^+\) calculated for C\(_{19}\)H\(_{20}\)F\(_2\)N\(_4\)O\(_6\): 459.18857; found 459.18785.
The title products (α/β 1:9) were obtained after column chromatography (PE/EtOAc, 19:1 → 3:2) in 72% yield (33 mg, 0.072 mmol). NMR data is reported for the major β-isomer only. 1H NMR (400 MHz) δ: 7.18 (d, 2H, β H); 6.86 (d, 2H, β H); 6.13-5.84 (m, 1H, CHF₂); 4.73 (dd, 1H, J = 3.2 Hz, H-β); 4.55 (d, 1H, J = 11.6 Hz, PhCH₂); 4.48 (d, 1H, J = 11.2 Hz, PhCH₂); 4.39 (d, 1H, J = 8.0 Hz, H-1); 4.29 (dd, 1H, J = 1.2 Hz, H-4). 1H-APT NMR (100 MHz) δ: 170.0, 167.3 (C=O α); 159.5 (C₆PMβ); 129.6 (CH₃); 129.2 (C₄α); 113.9 (CH₃); 102.1 (C-1); 77.0 (t, J = 32 Hz, CHF₂); 74.6 (PhCH₂); 73.7 (C-4, C-5); 72.9 (C-3); 68.6 (t, J = 27 Hz, CH₂CHF₂); 61.4 (C-2); 55.3 (OCH₃); 52.5 (CO₂CH₃); 20.8 (CH₃). IR (thin film) ν: 2955, 2114, 1751, 1612, 1514, 1229, 1084, 1059, 1032. HRMS: [M+NH₄]⁺ calculated for C₁₉H₂₇F₃NαOβ: 477.17915; found 477.17839.

The title products (α/β 2:5) were isolated after column chromatography (PE/EtOAc, 19:1 → 3:2) in 34% yield (16 mg, 0.034 mmol). 1H NMR (400 MHz) δ: 7.20-7.17 (m, 14H, CH₃); 6.88-6.85 (m, 14H, CH₃); 5.32 (dd, 2H, J = 2.8 Hz, 11.2 Hz, H-3α); 5.18 (d, 2H, J = 3.6 Hz, H-1α); 4.73 (dd, 5H, J = 2.8 Hz, 11.0 Hz, H-3β); 4.59-4.45 (m, 23H, H-1β, H-4α, H-5α, PhCH₂α, PhCH₂β); 4.31-4.22 (m, 12H, H-4β, CH₂CF₃β); 4.13 (d, 5H, J = 1.2 Hz, H-5β); 4.09-3.90 (m, 16H, H-2α, H-2β, CH₂CF₃α, CH₂CF₃β); 3.80 (s, 21H, CH₂); 170.0, 167.7, 167.1 (C-6α, C-6β, CO₂α, CO₂β); 159.5 (C₆α); 129.9, 129.7 (CH₃); 113.8, 113.8 (CH₃); 101.8 (C-1β); 99.0 (C-1α); 75.0 (C-5α); 74.9 (PhCH₂); 74.7 (PhCH₂); 73.8, 73.7 (C-4β, C-5β); 72.8 (C-3β); 70.7 (C-4α); 70.1 (C-3α); 65.9 (q, J = 35 Hz, CH₂CF₃β); 60.4 (C-2β); 56.9 (C-2α); 55.3 (OCH₃); 52.6 (CO₂CH₂); 20.8, 20.8 (CH₃). IR (thin film) ν: 2924, 2114, 1751, 1612, 1514, 1279, 1227, 1165, 1086, 1032. HRMS: [M+NH₄]⁺ calculated for C₁₉H₂₇F₃NαOβ: 495.16972; found 495.16898.
The product was obtained after column chromatography (PE/EtOAc, 9:1 → 7:3) in 36% yield (17 mg, 0.036 mmol). $^1$H NMR (400 MHz) $\delta$: 7.19 (d, 2H, $J = 8.4$ Hz, $CH_{arom}$); 6.85 (d, 2H, $J = 8.4$ Hz, $CH_{arom}$); 4.70 (dd, 1H, $J = 3.2$ Hz, 10.8 Hz, H-3); 4.54 (d, 1H, $J = 11.2$ Hz, PhCH$I$); 4.49 (d, 1H, $J = 11.6$ Hz, PhCH$I$); 4.43 (d, 1H, $J = 8.0$ Hz, H-1); 4.25 (dd, 1H, $J = 1.2$ Hz, 3.0 Hz, H-4); 4.09 (d, 1H, $J = 1.2$ Hz, H-5); 3.86 (dd, 1H, $J = 8.0$ Hz, 10.8 Hz, H-2); 3.80-3.74 (m, 4H, OCH$_3$py, OCH$_3$$_{3,PMB}$); 3.68 (s, 3H, CO$_2$H$_3$); 2.06 (s, 3H, C$_{H,Ac}$); 1.99-1.90 (m, 2H, CH$_2$($CO$$_3$)); 1.77-1.74 (m, 2H, CH$_2$(CO$_3$)); 1.55-1.42 (m, 3H, CH$_3$(CO$_3$)); 1.32-1.22 (m, 3H, CH$_3$(CO$_3$)). $^{13}$C-APT NMR (100 MHz) $\delta$: 170.1, 167.8 (C-6, CO$_{Ac}$); 159.4 (C$_{arom}$); 130.0 (C$_{arom}$); 129.5 (C$_{arom}$); 113.7 (C$_{arom}$); 100.1 (C-1); 77.8 (OCH$_3$); 74.5 (PhCH$_2$); 73.9, 73.6 (C-4, C-5); 73.0 (C-3); 60.7 (C-2); 55.3 (OCH$_3$$_3$$_{PMB}$); 52.4 (CO$_2$CH$_3$); 33.2, 31.2, 25.5, 23.8, 23.6 (CH$_2$(CO$_3$)); 20.8 (CH$_3$(Ac)). IR (thin film) v: 2934, 2857, 2110, 1746, 1612, 1514, 1225, 1163, 1092, 1030. HRMS: [M+Na]$^+$ calculated for C$_{23}$H$_{31}$NaO$_6$: 500.20034; found 500.19953.

The disaccharide was obtained after column chromatography (PE/EtOAc, 1:0 → 3:2), followed by size-exclusion chromatography (CH$_2$Cl$_2$/MeOH, 1:1 v/v), in 48% yield (40 mg, 0.048 mmol). $^1$H NMR (400 MHz) $\delta$: 7.36-7.26 (m, 15H, $CH_{arom}$); 7.17 (d, 2H, $J = 8.4$ Hz, $CH_{arom}$); 6.85 (m, 2H, $J = 8.4$ Hz, $CH_{arom}$); 4.98 (d, 1H, $J = 11.2$ Hz, PhCH$I$); 4.91 (d, 1H, $J = 11.2$ Hz, PhCH$I$); 4.82-4.77 (m, 2H, PhCH$_2$); 4.69 (dd, 1H, $J = 3.2$ Hz, 10.8 Hz, H-3'); 4.67-4.58 (m, 3H, H-1, PhCH$_2$); 4.51 (d, 1H, $J = 11.2$ H, PhCH$I$); 4.45 (d, 1H, $J = 11.2$ Hz, PhCH$I$); 4.26 (d, 1H, $J = 2.4$ Hz, H-4'); 4.21-4.19 (m, H-1', H-6); 4.02-3.98 (m, H-3, H-5'); 3.88 (dd, 1H, $J = 8.0$ Hz, 10.8 Hz, H-2'); 3.86-3.83 (m, 1H, H-5); 3.79 (s, 3H, OCH$_3$(CO$_3$$_{3,PMB}$); 3.70-3.64 (m, 4H, H-6, CO$_2$CH$_3$); 3.52 (dd, 1H, $J = 3.6$ Hz, 9.8 Hz, H-2); 3.46 (t, 1H, $J = 9.6$ Hz, H-4); 3.38 (s, 3H, OCH$_3$); 2.07 (s, 3H, C$_{H,Ac}$). $^{13}$C-APT NMR (100 MHz) $\delta$: 170.1, 167.6 (C-6, CO$_{Ac}$); 159.4, 138.7, 138.3, 138.1 (C$_{arom}$); 129.7 (C$_{arom}$); 129.5 (C$_{arom}$); 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 113.7 (C$_{arom}$); 102.0 (C-1'); 97.9 (C-1); 82.0 (C-3); 80.0 (C-2); 77.9 (C-4); 75.7, 74.8, 74.6 (PhCH$_2$); 74.1 (C-5'); 73.6 (C-4'); 73.4 (C-3'); 73.4 (PhCH$_2$); 69.9 (C-5); 68.6 (PhCH$_2$); 61.0 (C-2'); 55.3, 55.1 (OCH$_3$$_3$$_{PMB}$, OCH$_3$); 52.4 (CO$_2$CH$_3$); 20.8 (C$_{3,Ac}$). IR (thin

*Ethyl 2,4-di-O-benzyl-α-ᴅ-galactopyranosidurono-[3,6]-lactone (49)*

![Chemical structure](image)

The title product was obtained after column chromatography (hexane/EtOAc, 19:1 → 6:1 v/v) in 52% yield (20 mg, 0.052 mmol), along with unreacted donor. NMR data is reported for the O-glycosidic product only. ¹H NMR (400 MHz) δ: 7.40-7.26 (m, 10H, CH₉ arom); 4.93 (d, 1H, J = 12.0 Hz, PhCH/H); 4.82 (d, 1H, J = 2.4 Hz, H-1); 4.46 (dd, 1H, J = 1.6 Hz, 5.0 Hz, H-3); 4.60-4.55 (m, 3H, CH₉ arom); 4.48 (bs, 1H, H-5); 4.15 (bs, 1H, H-4); 4.03-3.94 (m, 2H, H-2, CH₂H₃); 3.62-3.56 (m, 1H, CHH₇); 1.27 (t, 3H, J = 6.8 Hz, CH₃). ¹³C-NMR (100 MHz) δ: 171.8 (C-6); 138.5, 137.5, 136.7 (Cₐ arom); 128.6, 128.5, 128.2, 128.1, 127.9, 127.8 (CH₉ arom); 98.5 (C-1); 80.4 (C-3); 75.6 (C-5); 74.6 (C-2); 74.4 (PhCH₂); 71.9 (C-4); 71.5 (PhCH₂); 66.5 (CH₂H₃); 15.2 (CH₃). IR (thin film) ν: 2924, 1798, 1454, 1364, 1155, 1103, 1076, 1059, 928. HRMS: [M+H]+ calculated for C₂₂H₂₅O₆: 385.16456; found 385.16472.

*2-fluoroethyl 2,4-di-O-benzyl-α-ᴅ-galactopyranosidurono-[3,6]-lactone (50)*

![Chemical structure](image)

The title compound was obtained after column chromatography (hexane/EtOAc, 19:1 → 6:1 v/v) in 60% yield (24 mg, 0.060 mmol). ¹H NMR (400 MHz) δ: 7.46-7.28 (m, 10H, CH₉ arom); 4.92 (d, 1H, J = 12.0 Hz, PhCH/H); 4.87 (d, 1H, J = 2.4 Hz, H-1); 4.67 (dd, 1H, J = 1.6 Hz, 5.2 Hz, H-3); 4.63-4.49 (m, 5H, H-4, 3x PhCH₂, CH₂F); 4.16 (bs, 1H, H-5); 4.13-4.03 (m, 1H, CHCH₂F); 4.02 (dd, 1H, J = 2.4 Hz, 5.2 Hz, H-2); 3.89-3.77 (m, 1H, CHHCH₂F). ¹³C-NMR (100 MHz) δ: 171.6 (C-6); 137.4, 136.7 (Cₐ arom); 128.6, 128.7, 128.3, 128.1, 128.0, 127.8 (CH₉ arom); 98.9 (C-1); 82.2 (d, J = 168 Hz, CH₂F); 80.3 (C-3); 75.5 (C-5); 74.5 (PhCH₂); 74.3 (C-2); 72.0 (C-4); 71.6 (PhCH₂); 69.6 (d, J = 20 Hz, CH₂CH₂F). ¹³C-GATED (100 MHz) δ: 98.9 (J = 160 Hz, C-1α). ¹³C-GATED NMR (100 MHz) δ: 98.9 (d, J = 160 Hz, C-1). IR (thin film) ν: 2914, 1798, 1456, 1084, 1067. HRMS: [M+H]+ calculated for C₂₂H₂₄FO₆: 403.15514; found 403.15517.
2,2-difluoroethyl 2,4-di-O-benzyl-α-D-galactopyranosidurono-[3,6]-lactone (51)

The title product were isolated after column chromatography (hexane/EtOAc, 19:1 → 6:1 v/v) in 62% yield (26 mg, 0.062 mmol). 1H NMR (400 MHz) δ: 7.39-7.26 (m, 10H, CH<sub>arom</sub>); 6.06-5.76 (m, 1H, CHF<sub>2</sub>); 4.89-4.86 (m, 2H, H-1, PhC=H); 4.67 (dd, 1H, J = 1.6 Hz, 5.0 Hz, H-3); 4.58-4.55 (m, 3H, PhCH<sub>2</sub>); 4.49 (s, 1H, H-4); 4.16 (s, 1H, H-5); 4.10-3.99 (m, 2H, H-2, CHHCHF<sub>2</sub>); 3.83-3.74 (m, 1H, CHHCHF<sub>2</sub>). 13C-APT NMR (100 MHz) δ: 171.3 (C-6); 137.2, 136.6 (C<sub>arom</sub>); 128.6, 128.4, 128.3, 128.2, 128.0, 127.8 (CH<sub>arom</sub>); 113.6 (t, J = 239 Hz, CHF<sub>2</sub>); 99.1 (C-1); 80.2 (C-3); 75.3 (C-5); 74.5 (PhCH<sub>2</sub>); 74.1 (C-2); 72.0 (C-4); 71.7 (PhCH<sub>2</sub>); 69.0 (t, J = 27 Hz, CH<sub>2</sub>CHF<sub>2</sub>). 13C-GATED NMR (100 MHz) δ: 99.1 (J = 161 Hz, H-1). IR (thin film) v: 2922, 1802, 1454, 1279, 1155, 1082, 1063, 964. HRMS: [M+H]<sup>+</sup> calculated for C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>O<sub>6</sub>: 421.14572; found 421.14576.

2,2,2-trifluoroethyl 2,4-di-O-benzyl-α/β-D-galactopyranosidurono-[3,6]-lactone (52)

The product was obtained after column chromatography (hexane/EtOAc, 19:1 → 9:1 v/v) in 41% yield (18 mg, 0.041 mmol), along with unreacted donor. 1H NMR (400 MHz) δ: 7.39-7.26 (m, 10H, CH<sub>arom</sub>); 4.91-4.87 (m, 2H, H-1, PhCH=H); 4.68 (dd, 1H, J = 1.6 Hz, 5.2 Hz, H-3); 4.59-4.55 (m, 3H, PhCH<sub>2</sub>); 4.50 (d, 1H, J = 1.2 Hz, H-5); 4.26-4.18 (m, 1H, CHHCF<sub>3</sub>); 4.16 (t, 1H, J = 1.2 Hz, H-4); 4.04 (dd, 1H, J = 2.4 Hz, 5.2 Hz, H-2); 3.96-3.89 (m, 1H, CH<sub>2</sub>CF<sub>3</sub>). 13C-APT NMR (100 MHz) δ: 171.1 (C-6); 137.0, 136.5 (C<sub>arom</sub>); 129.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9 (CH<sub>arom</sub>); 123.3 (q, J = 277 Hz, CF<sub>3</sub>); 98.9 (C-1); 80.1 (C-3); 75.2 (C-5); 74.5 (PhCH<sub>2</sub>); 73.8 (C-2); 72.0 (C-4); 71.7 (PhCH<sub>2</sub>); 66.7 (q, J = 35 Hz, CH<sub>2</sub>CF<sub>3</sub>). 13C-GATED NMR (100 MHz) δ: 98.9 (d, J = 160 Hz, C-1). IR (thin film) v: 2922, 1802, 1454, 1279, 1155, 1082, 1063, 964. HRMS: [M+H]<sup>+</sup> calculated for C<sub>22</sub>H<sub>22</sub>F<sub>3</sub>O<sub>6</sub>: 439.13630; found 439.13639.
Cyclohexyl 2,4-di-O-benzyl-α/β-D-galactopyranosidurono-[3,6]-lactone (53)

The title product was obtained after column chromatography (hexane/EtOAc, 19:1 → 9:1 v/v) in 43% yield (19 mg, 0.043 mmol). $^1$H NMR (400 MHz) $\delta$: 7.38-7.26 (m, 10H, $CH_{arom}$); 4.96-4.94 (m, 2H, H-1, PhCH$_2$); 4.80 (dd, 1H, $J = 1.6$ Hz, 5.2 Hz, H-3); 4.61-4.58 (m, 3H, PhCH$_2$); 4.50 (d, 1H, $J = 0.8$ Hz, H-5); 4.14 (bs, 1H, H-5); 3.91 (dd, 1H, $J = 2.4$ Hz, 5.2 Hz, H-2); 3.68 (m, 1H, OCH$_3$); 1.95-1.22 (m, 9H, CH$_2$CO$_2$). $^{13}$C-APT NMR (100 MHz) $\delta$: 172.0 (C-6); 137.6, 136.6 ($C_{arom}$); 128.6, 128.5, 128.2, 128.1, 127.9, 127.8 ($CH_{arom}$); 96.8 (C-1); 80.5 (C-3); 78.4 (OCH$_3$); 75.7 (C-5); 75.0 (C-2); 74.4 (PhCH$_2$); 72.0 (C-4); 71.5 (PhCH$_2$); 33.3, 31.7, 25.5, 24.0, 23.7 (CH$_2$CO$_2$). IR (thin film) v: 2855, 1802, 1456, 1364, 1153, 1117, 1076, 1057. HRMS: [M+H]$^+$ calculated for C$_{29}$H$_{33}$O$_{6}$: 439.21152; found 439.21135.

Methyl 2,3,6-tri-O-benzyl-4-O-(2,4-di-O-benzyl-α/β-D-galactopyranosidurono-[3,6]-lactone)-α-D-glucopyranoside (54)

The title disaccharide was obtained after size/exclusion chromatography (CH$_2$Cl$_2$/MeOH, 1:1 v/v) in 24% yield (19 mg, 0.024 mmol). $^1$H NMR (400 MHz) $\delta$: 7.37-7.16 (m, 25H, $CH_{arom}$); 5.14 (d, 1H, $J = 2.0$ Hz, H-1'); 5.04 (d, 1H, $J = 12.0$ Hz, PhCH$_2$); 4.73-4.69 (m, 2H, PhCH$_2$); 4.62-4.47 (m, 9H, $J = 3'$, PhCH$_2$); 4.34 (d, 1H, $J = 12.4$ Hz, PhCH$_2$); 4.30 (d, 1H, $J = 1.2$ Hz, H-4'); 3.99 (bs, 1H, H-5'); 3.87 (t, 1H, $J = 8.8$ Hz, H-3); 3.80-3.65 (m, 4H, H-4, H-5, H-6); 3.53 (dd, 1H, $J = 3.2$ Hz, 9.6 Hz, H-2); 3.44 (dd, 1H, $J = 2.4$ Hz, 5.2 Hz, H-2'); 3.39 (s, 3H, OCH$_3$). $^{13}$C-APT NMR (100 MHz) $\delta$: 171.5 (C-6'); 138.5, 138.3, 137.7, 136.7 ($C_{arom}$); 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4 (C$_{arom}$); 99.7 (C-1'); 97.7 (C-1); 81.5 (C-3); 79.9, 79.8 (C-2, C-3'); 77.2 (C-4); 75.6 (C-4'); 75.3 (PhCH$_2$); 74.7 (C-2'); 74.3, 73.5, 73.1 (PhCH$_2$); 71.9 (C-5'); 71.3 (PhCH$_2$); 69.4 (C-5); 68.8 (C-6), 55.3 (OCH$_3$). IR (thin film) v: 2912, 1800, 1454, 1364, 1188, 1155, 1111, 1053, 1028. HRMS: [M+Na]$^+$ calculated for C$_{60}$H$_{50}$NaO$_{13}$: 825.32453; found 825.32448.
Methyl 2,3,4-tri-O-benzyl-6-O-(2,4-di-O-benzyl-α/β-β-galactopyranosidurono-[3,6]-lactone)-α-β-glucopyranoside (55)

The disaccharide was obtained after size-exclusion chromatography (CH₂Cl₂/MeOH, 1:1 v/v) in 71% yield (57 mg, 0.071 mmol). 1H NMR (400 MHz) δ: 7.35-7.19 (m, 25H, CH₃), 4.97 (d, 1H, J = 10.8 Hz, PhCH₂); 4.92-4.89 (m, 2H, H-1', PhCH₂); 4.84-4.76 (m, 3H, PhCH₂); 4.69 (dd, 1H, J = 1.6 Hz, 5.2 Hz, H-3'); 4.65-4.61 (m, 2H, PhCH₂); 4.59-4.56 (m, 4H, H-1, PhCH₂); 4.44 (dd, 1H, J = 0.8 Hz, H-4'); 4.19 (dd, 1H, J = 3.6 Hz, 10.8 Hz, H-6); 4.12 (bs, 1H, H-5'); 4.01-3.95 (m, 2H, H-2', H-3); 3.75-3.67 (m, 2H, H-5, H-6); 3.54 (t, 1H, J = 9.6 Hz, H-4); 3.42 (dd, 1H, J = 3.6 Hz, 9.6 Hz, H-2); 3.32 (s, 3H, OC₃H₃). 13C-APT NMR (100 MHz) δ: 171.7 (C-6'); 138.1 (C₆,arom); 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.6, 127.6 (C₆,arom); 98.9 (C-1'); 98.0 (C-1); 81.8 (C-3); 80.3 (C-3'); 79.9 (C-2); 77.7 (C-4); 75.7 (PhCH₂); 75.7 (C-4'); 75.2 (PhCH₂); 74.3 (C-2'); 74.2, 73.4 (PhCH₂); 71.9 (C-5'); 71.6 (PhCH₂); 69.8 (C-5); 68.5 (C-6); 55.2 (OC₃H₃). IR (thin film) v: 2922, 2870, 1798, 1454, 1360, 1275, 1157, 1086, 1072, 1059, 1049. HRMS: [M+Na]+ calculated for C₄₇H₅₀NaO₁₁: 825.32453; found 825.32472.

References

Chapter 5


Chapter 6

Synthesis of the repeating unit of the Capsular Polysaccharide of \textit{Staphylococcus aureus} Strain M

Introduction

\textit{Staphylococcus aureus} is a bacterial pathogen, responsible for a wide array of infections of \textit{inter alia} the skin, lungs and joints, and it can cause life-threatening conditions like endocarditis or toxic shock syndrome. \textit{S. aureus} M is a particular strain whose polysaccharide capsule has been associated with its pathogenicity, and strain M was shown to be both more lethal and more resistant to phagocytosis in mouse models when compared to other \textit{S. aureus} strains.\textsuperscript{1}

\textsuperscript{1} Hagen, B.; Van Dijk, J. H. M.; Zhang, Q.; Overkleeft, H. S.; Van der Marel, G. A.; Codée, J. D. C.; manuscript in preparation.
Hash and co-workers discovered that the strain M Capsular Polysaccharide (CPS) consists of N-acetylgalactosaminuronic acid (GalNAcA), N-acetylfucosamine (FucNAc) and taurine, in the molar ratio of 4:2:1.2 A later study established that the repeating unit is the one shown in Scheme 1A.3 It is thought, that a taurine unit is attached to one out of four GalNAcA residues by an amide bond. The polysaccharide repeating unit structure shows that all glycosidic linkages are α (or 1,2-cis), the formation of which remains a synthetic challenge. The GalNAcA units are connected through their C-4 alcohol. This presents another synthetic hurdle, because of the low reactivity of the axially oriented C-4-OH. The vicinity to the uronic acid functionality renders it even less reactive.

**Scheme 1:** A) Trisaccharide repeating unit of S. aureus Strain M CPS and S. typhi Vi antigen. B) S. typhi Vi oligomers and the applied monosaccharide building blocks by the groups of Ye and Lay.

The synthesis of GalNAcA-containing oligosaccharides has been pursued in the context of *Salmonella typhi* Vi antigen oligosaccharides. This CPS, a homopolymer of α-(1→4) linked GalNAcA (Scheme 1B), with irregular C-3-O-acetyl groups is currently used in a conjugate vaccine against typhoid fever.4,5 Synthetic efforts towards *S. typhi* Vi antigen oligomers have been published by the groups of Ye and Lay.6,7 Ye and co-workers relied on a non-oxidized, N-acetyl oxazolidinone containing GalNAc donor 16 to selectively introduce the required α-glycosidic bonds. The C-6-alcohols were oxidized after formation of all glycosidic linkages, possibly to prevent further reduction of the nucleophilicity of the already poorly nucleophilic galactosyl C-4-OH. The group of Lay used on 4,6-O-benzylidene protected donor 2A7 to synthesize a non-O-acetylated disaccharide, and relied on disaccharide donor 2B to synthesize a trisaccharide. Again, oxidation of the C-6-OH occurred after formation of all glycosidic bonds.

This Chapter describes the synthesis of a *S. aureus* strain M Capsular Polysaccharide trisaccharide repeating unit, relying on a post-glycosylation oxidation strategy. In Chapter 5, the
synthesis and reactivity of 2-azidogalacturonate (GalN₃A) donors and their corresponding 6,3-lactones was studied. While the ‘normal’ GalN₃A donors were highly β-selective, and therefore unsuitable for the construction of 1,2-cis glycosidic linkages, the corresponding lactone was found to be α-selective. However, the glycosylation outcome proved to be dependent on the acceptor, with weakly nucleophilic acceptors showing diminished α-selectivity. Based on these findings, this Chapter describes an approach in which the C-5 carboxylic acid is introduced after each glycosylation event.

**Results and Discussion**

The retrosynthetic analysis for the assembly of *S. aureus* Strain M type 1 trisaccharide 3 is shown in Scheme 2. The two GalNAcA α-glycosidic linkages would be formed using 2-azidogalactosyl donor 5, equipped with a 4,6-di-tert-butyliisylene (DTBS) protecting group.⁸⁻⁹ Kiso and co-workers found that the use of this protecting group provides highly α-selective galactosylations,¹⁰⁻¹² even in the presence of the normally dominant C-2-*/O*-acyl neighboring group participation effect of a 2-*/O*-acyl protecting group. Furthermore, the DTBS group is easily introduced and can selectively be removed.

**Scheme 2**: Retrosynthetic analysis of target trisaccharide 1.

After formation of the glycosidic bond and removal of the silylene protecting group, the primary 6-position can be selectively oxidized,¹³⁻¹⁴ leaving the 4-position available for further glycosylation. Although this strategy may render the C-4-OH of the newly formed acceptor less nucleophilic, it circumvents the need for additional protecting group manipulations (*i.e.* introduction and removal of a protecting group on the 6-*/O*-position) and the necessity for a challenging late stage oxidation step. The third monosaccharide in the target structure is a rare, α-linked d-FucNAc moiety.¹⁵ To install the 1,2-*cis* d-FucNAc bond, a FucN₃ donor 6 would be used,
Chapter 6

the reactivity of which has been explored earlier (Chapters 3 and 4). The TBS protecting group on the 3-O position serves as both an α-directing protecting group, and as an orthogonal, temporary protecting group for the potential synthesis of higher oligomers.

The synthesis of donor 5 commenced with known 2-azido selenogalactoside 9, made available by the procedure described in Chapter 5 (Scheme 3). Introduction of the DTBS moiety proceeded to give 10 in 98% yield. Subsequent benzylation of the remaining 3-O position gave donor 5, after crystallization, in 86% yield. This reaction sequence was easily executed on multigram scale. Synthesis of d-FucN$_3$ donor 6 was achieved in only one step from previously described building block 12 (see Chapters 3 and 4) by introduction of the TBS group using TBSOTf and DMAP in pyridine at elevated temperature, to obtain 6 in 77% yield.

Scheme 3: Synthesis of building blocks 5 and 6.

Reagents and conditions: a) (tBu)$_2$Si(OTf)$_2$, DMF, -40 °C; then NEt$_3$ (98%); b) BnBr, NaH, DMF, 0 °C (86%); c) TBSOTf, DMAP (cat.), pyridine, 0 → 70 °C (77%).

In order to assess the reactivity of GalN$_3$ donor 5, low-temperature NMR experiments$^{16}$ (see also Chapters 3 and 5) were carried out to determine which reactive species could form upon activation. Reacting 5 with Ph$_2$SO and Tf$_2$O in CD$_2$Cl$_2$ at -80 °C led to total conversion of 5 (Figure 1A) into a single new species (Figure 1B), which was, based on its chemical shift and small $J$-coupling constant ($\delta$: 6.16 ppm, $J = 3.0$ Hz), identified as α-triflate 13. In order to assess the stability of the newly formed triflate, the NMR sample was warmed by incremental heating. The anomic triflate proved to be relatively stable, with decomposition starting at -10 °C.
Next, donor 5 was reacted with a set of model acceptors to determine whether acceptor reactivity influences the stereoselectivity of the glycosylations. Ethanol and its 2-fluorinated derivatives have been used as a screening panel to investigate the influence of acceptor nucleophilicity on glycosylation stereoselectivity (Chapters 3 and 5). As Table 1 shows DTBS-protected donor 5 only provides α-galactosidic linkages, in contrast to the clear dependency of the stereoselectivity of glycosylations involving 2-azidofucosyl (FucN₃) donors, as well as 2-azido-2-deoxygalacturonic acid-[3,6]-lactones, on acceptor nucleophilicity (Chapter 3 and 5). These results further demonstrate the powerful α-directing effect of the 4,6-O-di-tert-butylsilylene group on galactosylation reactions. Based on the complete absence of β-linked product, one can exclude an S₄N₂-like pathway, in which the covalent anionic triflate 13 is directly displaced by the nucleophile (Scheme 4). Although a β-triflate cannot be ruled out as a reactive intermediate, its existence is deemed unlikely due to the low nucleophilicity of the triflate anion. Kiso and coworkers reported the crystal structure of a DTBS-protected 2-aminogalactoside, noting that the ring adopted a flattened, half-chair like conformation, in which one of the tert-butyl was positioned over the anomeric center. Although crystal structures do not necessarily reflect conformational behavior of molecules in solution, it is possible that shielding of the β-face by the
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DTBS group favors α-glycosidic bond formation (Scheme 4). Also in an $^4\text{H}_2$ half-chair oxocarbenium ion-like intermediate 19, the C2- and C4-substituents are placed in an electronically favorable position$^{11,18}$ this shielding can contribute to the overall selectivity. This half chair is preferentially attacked by the incoming nucleophile from the α-face, proceeding through a chair-like transition state to give α-glycoside 20.

Table 1: Model glycosylations of donor 5 with non-carbohydrate acceptors.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (α/β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>14</td>
<td>60% (1:0)</td>
</tr>
<tr>
<td>2</td>
<td>FEt</td>
<td>15</td>
<td>79% (1:0)</td>
</tr>
<tr>
<td>3</td>
<td>F$_2$Et</td>
<td>16</td>
<td>90% (1:0)</td>
</tr>
<tr>
<td>4</td>
<td>F$_3$Et</td>
<td>17</td>
<td>81% (1:0)</td>
</tr>
<tr>
<td>5</td>
<td>Cy</td>
<td>18</td>
<td>54% (1:0)</td>
</tr>
</tbody>
</table>

Having established the highly α-selective performance of 5 in glycosylations, the synthesis of trisaccharide 3 commenced with glycosylation of 5 with 5-aminopentanol spacer 7 (Scheme 5)$^{19}$ Both Ph$_2$SO/Tf$_2$O-mediated pre-activation$^{20,21}$ and NIS/TMSOTf-mediated glycosylations$^{22}$ gave 21 as the desired α-isomer in high yield. Attempted removal of the DTBS group using Bu$_4$NF proceeded in moderate yields, while the use of HF in pyridine gave the diol 22 in quantitative yield. Oxidation of the C-6 alcohol with TEMPO/Ph$_1$(OAc)$_2$ provided the oxidized acceptor 23 in 85% yield, after methylation of the acid.

Scheme 4: Stereochemical rationale for α-glycosidic bond formation.
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Glycosylation of 5 with galacturonic acceptor 23 was effected under NIS/TMSOTf conditions (selected on the basis of the operational simplicity compared to the pre-activation protocol), yielding the disaccharide 24 as the sole product in 88% yield, in spite of the low reactivity of the acceptor due to presence of the C-5 carboxylic acid ester. Removal of the DTBS group using HF in pyridine gave diol 25 in quantitative yield.

Scheme 5: Synthesis of trisaccharide 4.

Reagents and conditions: a) 7, NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, 0 °C (82%); b) HF-pyridine, THF (quant.) c) TEMPO (cat.), PhI(OAc)₂, AcOH (cat.), CH₂Cl₂, H₂O; then MeI, K₂CO₃, DMF (85%); d) 8, NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, 0 °C (88%); e) TEMPO (cat.), PhI(OAc)₂, CH₂Cl₂, THF; NaClO₂, NaH₂PO₄, 2-methylbut-2-ene, tBuOH, H₂O (84%); f) Ph₃SO, TTBP, 3Å MS, CH₂Cl₂; Tf₂O, -80 → -70 °C; 6, -80 → -40 °C (79%, α only).

The oxidation of disaccharide 25, using TEMPO/PhI(OAc)₂ and ensuing methylation,¹⁴ resulted in 35% of dicarboxylate 26. Surprisingly, monosaccharide 23 was isolated in significant quantities, indicating cleavage of the GalA-GalA glycosidic bond. Therefore an alternative oxidation protocol was employed, involving a two-step oxidation process. First, the C-6 alcohol was selectively transformed into the corresponding aldehyde, using TEMPO and PhI(OAc)₂ under anhydrous conditions to prevent hydration of the formed aldehyde and overoxidation to the carboxylate. When this oxidation step was complete (as judged by TLC analysis), a mixture of NaClO₂, 2-methylbut-2-ene and NaH₂PO₄ in tert-butanol/water was added.²³,²⁴ This Pinnick oxidation provided the desired carboxylic acid uneventfully and after methylation of the uronic acid, disaccharide 26 was obtained in 84% yield, with no detectable glycosidic bond cleavage. The final glycosylation, using FucN₃ donor 6 in combination with the Ph₂SO/Tf₂O activation couple, as described in Chapter 3 and 4, proceeded uneventfully to give 4 with complete α-selectivity (Scheme 6). It was observed that quenching of the reaction with NEt₃ can lead to drastically lower

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yields, likely due to β-elimination on the galacturonate moieties, and therefore pyridine was used to stop the glycosylation reaction.

With the fully protected trisaccharide repeating unit in hand, attention was focused on the deprotection of the trimer (Scheme 6). First all azides in 4 were transformed into acetamides, using AcSH and pyridine. The reaction proved to be slow, but afforded product 27 in 47% yield. Next the TBS group in 27 was removed using HF, pyridine and the two carboxylic esters were saponified using a mixture of H₂O₂ and KOH. Dicarboxylate 29 was obtained in 49% over these two steps. An alternative procedure in which it was attempted to remove the TBS-ether concomitantly with the saponification of the two esters proved to be inefficient. Finally, Pd(OH)₂-catalyzed hydrogenation delivered fully deprotected target trisaccharide 3 in 69% yield.

Scheme 6: Deprotection of trimer 4 towards target 3.

Reagents and conditions: a) AcSH, pyridine (47%); b) HF, pyridine, pyridine (56%); c) H₂O₂, KOH, THF, tBuOH, H₂O (87%); d) Pd(OH)₂/C, H₂ (1 atm.), AcOH, THF, tBuOH, H₂O (69%).

Conclusion

In conclusion, the first synthesis of the repeating unit of the S. aureus strain M capsular polysaccharide has been described. A post-glycosylation oxidation strategy was employed, using a 4,6-di-tert-butyl silyldene protected 2-azidogalactosyl donor as precursor of the GalNAcA residues. The two glycosylation reactions with these donors provided the corresponding products.
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with complete α-selectivity and high yields. Desilylation, followed by selective oxidation of the primary position in 2-azidogalactosyl residues to the carboxylic acids set the stage for the next glycosylation. An unprecedented cleavage of the glycosidic bond during the TEMPO/BAIB oxidation procedure was observed in the disaccharide stage. To circumvent this side reaction, a new two-step, one-pot oxidation procedure was used to transform the primary alcohol into the carboxylic acid. The final glycosylation of a 2-azidofucosyl donor proceeded with complete stereoselectivity, underscoring the usefulness of this donor for α-fucosaminylation reactions. The orthogonal TBS protecting group in the fully protected trisaccharide repeating unit allows for the elongation of the trimer to generate higher oligomers. The assembled trimer described here can be evaluated for its capacity to act as an synthetic antigen in vaccine modalities.

**Experimental**

**General procedures**

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4Å molecular sieves (3Å for CH₂Cl₂, MeOH and MeCN), except pyridine and DMF. NET₃ was stored over KOH pellets. Tf₂O used in glycosylations was dried over P₂O₅ (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (λ: 254 nm), followed by spraying with 20% H₂SO₄ in EtOH (w/v) or Hanessian’s stain ((NH₄)₆Mo₇O₂₄·4H₂O, 25 g/L; (NH₄)₄Ce(SO₄)₂·2H₂O, 10 g/L; in 10% aq. H₂SO₄). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to Me₄Si (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. ¹³C-APT spectra are ¹H decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomic carbon atoms (J_H, C) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm⁻¹. LC-MS analyses were performed on a Thermo Finnigan Surveyor HPLC system equipped with a Gemini C-18 column (250 x 10 mm), connected to a Thermo Finnigan LCQ Advantage Max Ion-trap mass spectrometer with (ESI⁺). Eluents used
were MeCN, H₂O with addition of TFA (0.1%). HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.

**Phenyl 2-azido-2-deoxy-4,6-O-(di-tert-butylsilylene)-1-seleno-α-D-galactopyranoside (10)**

![Phenyl 2-azido-2-deoxy-4,6-O-(di-tert-butylsilylene)-1-seleno-α-D-galactopyranoside (10)](image)

To a stirred, ice-cooled solution of 9 (5.5 g, 16.0 mmol, 1.0 eq.) in DMF (160 mL, 0.1 M) was added tBu₂Si(OTf)₂ (7.8 mL, 24 mmol, 1.5 eq.). After TLC analysis (PE/Et₂O, 4:1 v/v) indicated complete conversion of the starting material (~30 min.) the mixture was neutralized with NEt₃ (4.9 mL, 35.2 mmol, 2.2 eq.) and stirred for 5 additional minutes. The mixture was then diluted with water and extracted three times with Et₂O. The combined organic fractions were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et₂O, 1:0 → 4:1 v/v) gave the title compound as a slightly yellow oil in 98% yield (7.6 g, 15.7 mmol): ³H NMR (400 MHz) δ 7.58-7.25 (m, 5H, CH₃-arom); 5.96 (d, 1H, J = 5.2 Hz, H-1); 4.49 (d, 1H, J = 2.8 Hz, H-4); 4.02-4.30 (m, 2H, H-6); 4.19 (s, 1H, H-5); 4.05 (m, 1H, H-2); 3.84 (t, 1H, J = 3.2 Hz, H-3); 1.07 (d, 18H, J = 15.2 Hz, (CH₃)₃Si); ¹³C NMR (100 MHz) δ: 134.5 (CH₃-arom); 129.3 (CH-arom); 128.5 (C₄-arom); 128.0 (CH₃-arom); 85.4 (C-1); 72.3 (C-4); 71.8 (C-3); 69.9 (C-5); 66.7 (C-6); 62.1 (C-2); 27.6, 27.4 ((CH₃)₃Si); 23.4, 20.8 (C₈Si). IR (thin film) ν: 3505, 2934, 2859, 2105, 1474, 1155, 1190, 1059. HRMS: [M+H-N₂]⁺ calculated for C₂₀H₁₂NO₄SeSi: 458.12613; found 458.12573.

**Phenyl 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-1-seleno-α-D-galactopyranoside (5)**

![Phenyl 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-1-seleno-α-D-galactopyranoside (5)](image)

To a stirred solution, ice-cooled solution of 10 (7.6 g, 15.7 mmol, 1.0 eq.) and BnBr (3.7 mL, 31.4 mmol, 2.0 eq.) in DMF (150 mL, 0.1 M) was added NaH (60% dispersion in mineral oil, 0.75 g, 1.2 eq.). After TLC analysis (PE/Et₂O, 19:1 v/v) indicated complete conversion of the starting material (~2 hours), the mixture was quenched with H₂O and extracted three times with Et₂O. The combined organic fractions were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Crystallization from EtOH gave the title compound as a white powder in 86% yield (7.82 g, 13.5 mmol): ³H NMR (400 MHz) δ 7.56-7.26 (m, 10H, CH₃-arom) 5.94 (d, 1H, J =...
5.2 Hz, H-1); 4.79-4.67 (m, 2H, PhCH$_2$); 4.58 (d, 1H, J = 2.8 Hz, H-4); 4.31 (dd, 1H, J = 5.2 Hz, 10.4 Hz, H-2); 4.26-3.98 (m, 2H, H-6); 4.04 (s, 1H, H-5); 3.64 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-3); 1.06 (s, 9H, (CH$_3$)$_3$Si); 1.03 (s, 9H, (CH$_3$)$_3$Si); $^{13}$C NMR (100 MHz) δ: 137.6 (C$_{q,\text{arom}}$); 134.5, 129.2, 128.6 (CH$_{\text{arom}}$); 128.5 (C$_{q,\text{arom}}$); 128.0, 127.9, 127.9 (CH$_{\text{arom}}$); 86.0 (C-1); 78.8 (C-3); 70.6 (PhCH$_2$); 70.0 (C-5); 69.2 (C-4); 67.0 (C-6); 59.6 (C-2) 27.6, 27.3 ((CH$_3$)$_3$Si); 23.4, 20.8 (C$_3$Si). IR (thin film) ν: 2933, 2857, 2112, 1580, 1474, 1163, 1082, 1070. HRMS: [M+H]$^+$ calculated for C$_{27}$H$_{38}$N$_4$O$_4$SeSi: 576.17908; found 576.17879.

**Phenyl 2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butylidimethylsilyl)-1-seleno-α-d-fucopyranoside (6)**

A 3-necked 50 mL flask equipped with a Liebig condenser was charged with a solution of 12 (0.84 g, 2.0 mmol, 1.0 eq.) and DMAP (49 mg, 0.4 mmol, 0.2 eq.) in pyridine (10 mL, 0.2 M). The mixture was cooled to 0 °C and, under a stream of N$_2$ gas was slowly added TBSOTf (0.92 g, 4.0 mmol, 2.0 eq.). The reaction was heated to 70 °C and stirred until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material (~2 hours). The reaction was cooled to room temperature and quenched with MeOH. The mixture was diluted with EtOAc and washed (10% aq. CuSO$_4$.5H$_2$O, 2x; H$_2$O, 2x; brine, 1x), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (PE/Et$_2$O, 1:0 → 9:1 v/v) delivered the title compound in 77% yield (0.82 g, 1.54 mmol). $^1$H NMR (400 MHz) δ: 7.58-7.55 (m, 2H, CH$_{\text{arom}}$); 7.39-7.26 (m, 8H, CH$_{\text{arom}}$); 5.96 (d, 1H, J = 5.2 Hz, H-1); 5.06 (d, 1H, J = 11.2 Hz, PhCH$_2$H); 4.59 (d, 1H, J = 11.2 Hz, PhCH$_2$H); 4.27 (q, 1H, J = 6.4 Hz, H-5); 4.22 (dd, 1H, J = 5.2 Hz, 10.0 Hz, H-2); 3.88 (dd, 1H, J = 2.8 Hz, 10.0 Hz, H-3); 3.54 (d, 1H, J = 2.0 Hz, H-4); 1.15 (d, 3H, J = 6.4 Hz, H-6); 0.99 (s, 9H, (CH$_3$)$_3$Si); 0.25, 0.22 (s, 3H, CH$_3$Si). $^{13}$C-APT NMR (100 MHz) δ: 138.4 (C$_{q,\text{arom}}$); 134.2, 129.0, 128.3, 127.8, 127.7, 127.5 (CH$_{\text{arom}}$); 85.5 (C-1); 80.1 (C-4); 75.6 (PhCH$_2$); 74.1 (C-3); 69.4 (C-5); 62.9 (C-2); 25.9 ((CH$_3$)$_3$Si); 18.1 (C$_3$Si); 16.4 (C-6); -4.2, -5.0 (CH$_2$Si). IR (thin film) ν: 2953, 2106, 1360, 1254, 1111, 1080, 1063, 1043. HRMS: [M-N$_2$+H]$^+$ calculated for C$_{27}$H$_{38}$N$_4$O$_4$SeSi: 506.16242; found 506.16223.
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A mixture of 5 (22 mg, 0.038 mmol, 1.0 eq.), Ph₂SO (10 mg, 0.049 mmol, 1.3 eq.) was dried by co-evaporation with toluene (3x), followed by 3 vacuum/argon purges. The mixture was dissolved in CD₂Cl₂ (0.75 mL, 0.05 M) and transferred to a dry NMR tube and subsequently capped with a septum. The tube was placed in the probe of a NMR magnet and cooled to -80 °C, after which a ¹H NMR spectrum was recorded. The tube was transferred to an acetone/N₂ (l) bath (temperature ≤ -80 °C), and Tf₂O (8 µL, 0.049 mmol, 1.3 eq.) was added and, after rapid mixing, was placed back in the NMR probe. Observation by ¹H NMR revealed complete consumption of 5, and after further characterization of the newly formed triflate 13, its stability was assessed by incremental (by 10 °C) heating of the probe until decomposition was observed.

General procedure for Ph₂SO/Tf₂O-mediated glycosylations with non-carbohydrate acceptors

To a solution of donor 5 (57 mg, 0.1 mmol, 1.0 eq.), Ph₂SO (26 mg, 0.13 mmol, 1.3 eq.) and TTBP (62 mg, 0.25 mmol, 2.5 eq.) in CH₂Cl₂ (2 mL, 0.05 M) were added flame-dried 3Å molecular sieves. After ~30 minutes, the mixture was cooled to -80 °C, and Tf₂O (22 µL, 0.13 mmol, 1.3 eq.) was added. The reaction mixture was allowed to warm to -70 °C over the course of ~15 minutes. The mixture was re-cooled to -80 °C, a solution of the acceptor (0.5 M in CH₂Cl₂, 0.4 mL) was slowly added via the wall of the flask. The reaction mixture was allowed to warm to -40 °C over the course of ~90 minutes, after which the reaction was quenched by addition of NEt₃ (0.1 mL). The reaction mixture was diluted with CH₂Cl₂, filtered over a bed of celite, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography yielded the corresponding O-glycoside.
Ethyl 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-α-D-galactopyranoside (14)

The product was obtained after column chromatography (PE/EtOAc, 1:0 → 9:1) in 60% yield (28 mg, 0.06 mmol). δ: 7.38-7.26 (m, 5H, CH\textsubscript{arom}); 4.94 (d, 1H, J = 3.6 Hz, H-1); 4.76 (d, 1H, J = 11.6 Hz, PhCH\textsubscript{2}H); 4.67 (d, 1H, J = 11.6 Hz, PhCH\textsubscript{2}H); 4.58 (d, 1H, J = 2.4 Hz, H-4); 4.26 (dd, 1H, J = 2.0 Hz, 12.4 Hz, H-6); 4.14 (dd, 1H, J = 2.0 Hz, 12.6 Hz, H-6); 3.88 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-3); 3.79 (dd, 1H, J = 3.6 Hz, 10.6 Hz, H-2); 3.75-3.71 (m, 1H, OCH\textsubscript{2}HCH\textsubscript{3,Et}); 3.66 (bs, 1H, H-5); 3.58-3.53 (m, 1H, CHCH\textsubscript{3}Et); 1.23 (t, 3H, J = 7.2 Hz, CH\textsubscript{3}Et); 1.07 (s, 9H, (CH\textsubscript{3})\textsubscript{3}Si); 1.05 (s, 9H, (CH\textsubscript{3})\textsubscript{3}Si).

\textsuperscript{13}C-APT NMR (100 MHz) δ: 137.9 (C\textsubscript{arom}); 128.5, 127.9, 127.8 (CH\textsubscript{arom}); 98.1 (C-1); 75.7 (C-3); 70.5 (PhCH\textsubscript{2}); 69.9 (C-4); 67.4 (C-5); 67.2 (C-6); 63.9 (OCH\textsubscript{2}CH\textsubscript{3}); 58.3 (C-2); 27.7 ((CH\textsubscript{3})\textsubscript{3}Si); 27.3 ((CH\textsubscript{3})\textsubscript{3}Si); 23.5, 20.7 (C\textsubscript{Si}); 15.0 (CH\textsubscript{3,Et}). \textsuperscript{13}C-GATED NMR (100 MHz) δ: 98.1 (d, J = 170 Hz, C-1); IR (thin film) ν: 2934, 2859, 2110, 1474, 1175, 1175, 1144, 1099, 1065. HRMS: [M+NH\textsubscript{4}]\textsuperscript{+} calculated for C\textsubscript{23}H\textsubscript{41}N\textsubscript{4}O\textsubscript{5}Si: 481.28407; found 481.28381.

2-fluoroethyl 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-α-D-galactopyranoside (15)

The product was obtained after column chromatography (PE/EtOAc, 1:0 → 9:1) in 79% (38 mg, 0.079 mmol). \textsuperscript{1}H NMR (400 MHz) δ: 7.44-7.26 (m, 5H, CH\textsubscript{arom}); 4.98 (d, 1H, J = 3.6 Hz, H-1); 4.75 (d, 1H, J = 11.6 Hz, CHBn); 4.69-4.50 (m, 2H, CH\textsubscript{2}Bn, CH\textsubscript{2}F, H-4) 4.20 (dd, 2H, J = 2.0, 12.8 Hz, H-6); 4.14 (dd, 1H, J = 1.6 Hz, 12.4 Hz, H-6); 3.98-3.69 (m, 4H, H-2, H-3, CH\textsubscript{2}CH\textsubscript{2}F); 3.73 (s, 1H, H-5); 1.06 (s, 9H, (CH\textsubscript{3})\textsubscript{3}Si); 1.04 (s, 9H, (CH\textsubscript{3})\textsubscript{3}Si); \textsuperscript{13}C-APT NMR (100 MHz) δ: 137.8 (C\textsubscript{arom}); 131.1, 129.4, 129.3, 128.6, 127.9, 127.9, 127.7, 124.8 (CH\textsubscript{arom}); 98.6 (C-1); 82.5 (d, J = 169 Hz, CH\textsubscript{2}F); 75.6 (C-3); 70.5 (PhCH\textsubscript{2}); 69.7 (C-4); 67.5 (C-5); 67.3 (d, J = 20 Hz, CH\textsubscript{2}CH\textsubscript{2}F); 67.1 (C-6); 58.3 (C-2); 27.7, 27.3 ((CH\textsubscript{3})\textsubscript{3}Si); 23.5, 20.7 (C\textsubscript{Si}). \textsuperscript{13}C-GATED NMR (100 MHz): 98.6 (d, J = 171 Hz, C-1). IR (thin film) ν: 2932, 2859, 2110, 1474, 1173, 1144, 1103, 1005. HRMS: [M + NH\textsubscript{4}]\textsuperscript{+} calculated for C\textsubscript{23}H\textsubscript{40}FN\textsubscript{4}O\textsubscript{5}Si: 499.27465; found 499.27431.
The product was obtained after column chromatography (PE/EtOAc, 1:0 → 9:1) in 90% yield (45 mg, 0.09 mmol).

\textbf{2,2-difluoroethyl} \ 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-\(\alpha\)-\(\alpha\)-galactopyranoside (16)

\begin{align*}
\text{The product was obtained after column chromatography (PE/EtOAc, 1:0 → 9:1) in 81% yield (42 mg, 0.081 mmol).} & \quad \text{\(1^H\) NMR (400 MHz) \(\delta\): 7.44-7.26 (m, 5H, \(CH_{arom}\)); 6.07-5.79 (m, 1H, \(CH_{F2}\)); 4.97 (d, 1H, \(J = 1.6 \text{ Hz, H-1}\)); 4.75 (d, 1H, \(J = 11.6 \text{ Hz, PhCHH}\)); 4.67 (d, 1H, \(J = 11.2\), PhCH\(H\)); 4.26 (dd, 1H, \(J = 2.0 \text{ Hz, 12.8 Hz, H-6}\)); 4.15 (d, 1H, \(J = 1.6 \text{ Hz, 12.8 Hz, H-6}\)); 3.86-3.76 (m, 4H, H-2, H-3, \(CH_{CF3}H\)); 3.68 (s, 1H, H-5); 1.06 (s, 9H, \((CH_{3})_3CSi\)); 1.03 (s, 9H, \((CH_{3})_3CSi\)).} \\
\text{\(13^C\)-APT NMR (100 MHz) \(\delta\): 137.7 (\(C_{arom}\)); 128.6, 128.0, 127.9 (\(CH_{arom}\)); 113.8 (t, \(J = 240 \text{ Hz, CHF_2}\)); 99.2 (C-1); 75.4 (C-3); 70.6 (PhCH_2); 69.6 (C-4); 67.9 (C-5); 67.3 (t, \(J = 28 \text{ Hz, CH_2CHF_2}\)); 67.0 (C-6); 58.1 (C-2); 27.6, 27.3 (\((CH_3)_3CSi\)); 23.4, 20.7 (C, Si); \(13^C\)-GATED NMR (100 MHz): 99.2 (d, \(J = 172 \text{ Hz, C-1}\)); IR (thin film) \(v\): 2936, 2859, 2114, 1474, 1364, 1171, 1142, 1101. HRMS: [M+H-N_2]^+ calculated for C_{23}H_{35}F_3NO_5Si: 472.23253; found 472.23239.
\end{align*}

\textbf{2,2,2-trifluoroethyl} \ 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-\(\alpha\)-\(\alpha\)-galactopyranoside (17)

\begin{align*}
\text{The product was obtained after column chromatography (PE/EtOAc, 1:0 → 9:1) in 81% yield (42 mg, 0.081 mmol).} & \quad \text{\(1^H\) NMR (400 MHz) \(\delta\): 7.44-7.26 (m, 5H, \(CH_{arom}\)); 5.01 (s, 1H, H-1); 4.76 (d, 1H, \(J = 11.6 \text{ Hz, PhCHH}\)); 4.68 (d, 1H, \(J = 12.4 \text{ Hz, PhCHH}\)); 4.61 (s, 1H, H-4); 4.26 (d, 1H, \(J = 2.0 \text{ Hz, 12.8 Hz, H-6}\)); 4.15 (d, 1H, \(J = 1.6 \text{ Hz, 12.8 Hz, H-6}\)); 4.00-3.87 (m, 4H, H-2, H-3, \(CH_{CF_3}\)); 3.68 (s, 1H, H-5); 1.07 (s, 9H, \((CH_{3})_3CSi\)); 1.04 (s, 9H, \((CH_{3})_3CSi\)).} \\
\text{\(13^C\)-APT NMR (100 MHz) \(\delta\): 137.6 (\(C_{arom}\)); 128.6, 128.0 127.9 (\(CH_{arom}\)); 123.5 (q, \(J = 277 \text{ Hz, CF_3}\)); 99.3 (C-1); 75.3 (C-3); 70.6 (PhCH_2); 69.6 (C-4); 68.2 (C-5); 66.9 (C-6); 65.2 (q, \(J = 35 \text{ Hz, CH_2CHF_2}\)); 57.9 (C-2); 27.6, 27.3 (\((CH_3)_3CSi\)); 23.4, 20.7 (C, Si); \(13^C\)-GATED NMR (100 MHz): 99.3 (d, \(J = 170 \text{ Hz, C-1}\)); IR (thin film) \(v\): 2934, 2859, 2112, 1279, 1167, 1148, 1086, 1007. HRMS: [M+H-N_2]^+ calculated for C_{23}H_{35}F_3NO_5Si: 490.22311; found 490.22291.
\end{align*}
The product was obtained after column chromatography (PE/EtOAc, 1:0 → 9:1 v/v) in 54% yield (28 mg, 0.054 mmol). $^1$H NMR (400 MHz) δ: 7.44-7.26 (m, 5H, $CH_{arom}$); 5.08 (d, 1H, $J = 3.5$ Hz, H-1); 4.76 (d, 1H, $J = 11.5$ Hz, PhCH$_2$H); 4.66 (d, 1H, $J = 11.5$ Hz, PhCH$_2$H$^\beta$); 4.61 (d, 1H, $J = 2.5$ Hz, H-4); 4.26 (dd, 1H, $J = 2.0$, 12.5 Hz, H-6); 4.13 (dd, 1H, $J = 2.0$, 12.5 Hz, H-6); 3.91 (dd, 1H, $J = 3.0$, 10.5 Hz, H-3); 3.75 (s, 1H, H-5); 3.72 (dd, 1H, $J = 3.5$, 11 Hz, H-2); 3.61 (m, 1H, OCH$_3$); 1.96-1.20 (m, 10H, $CH_{2,CO}$); 1.06 (s, 9H, (CH$_3$)$_3$Si); 1.04 (s, 9H, (CH$_3$)$_2$Si); $^{13}$CAPT NMR (100 MHz) δ: 137.9 (C$_{arom}$); 128.5, 127.9, 127.8 ($CH_{arom}$); 96.8 (C-1); 76.2 (OCH$_3$); 75.2 (C-3); 70.4 (PhCH$_2$); 69.9 (C-4); 67.4 (C-5); 67.2 (C-6); 58.1 (C-2); 33.4, 31.4 (CH$_2,CO$); 27.6, 27.3 ((CH$_3$)$_3$Si); 25.5, 24.1, 23.8 (CH$_2$C$_5$); 23.4, 20.7 (C$_6$Si); $^{13}$C-GATED NMR (100 MHz): 96.8 (d, $J = 170$ Hz, C-1); IR (thin film) ν: 2932, 2859, 2114, 1474, 1364, 1175, 1111. HRMS: [M+H-N$_2$]$^+$ calculated for C$_{27}$H$_{44}$NO$_5$Si: 490.29833; found 490.29813.

5-(benzyl(phenoxycarbonyl)amino)pentyl 2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butylsilylene)-α-ᴅ-galactopyranoside (21)

To a solution of donor 5 (3.45 g, 6.0 mmol, 1.0 eq.), N-benzoxycarbonyl-N-benzyl-5-aminopentanol 7 (3.93 g, 12.0 mmol, 2.0 eq.) in CH$_2$Cl$_2$ (30 mL, 0.2 M) were added flame-dried, rod-shaped 3Å MS. After ~30 minutes, the mixture was cooled to 0 °C and N-iodosuccinimide (1.75 g, 7.8 mmol, 1.3 eq.) and TMSOTf (0.11 mL, 0.6 mmol, 0.1 eq.) were added. After TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete consumption of the starting material (~2 hours), the reaction was quenched with NEt$_3$ (5 mL) and the mixture was diluted with CH$_2$Cl$_2$. After filtration over celite, the mixture was washed with sat. aq. Na$_2$S$_2$O$_3$ (1x), sat. aq. NaHCO$_3$ (1x) and brine, dried over MgSO$_4$, filtered and concentrated in vacuo. Column chromatography (PE/EtOAc, 9:1 → 9:1) afforded the title product as the sole isomer in 82% yield (3.67 g, 4.9 mmol): $^1$H NMR (500 MHz, 323 K) & 7.40-7.20 (m, 15H, $CH_{arom}$); 5.16 (s, 2H, PhCH$_2$); 4.85 (s, 1H, H-1); 4.73 (d, 1H, $J = 11.5$ Hz, PhCH$_2$H); 4.65 (d, 1H, $J = 11.5$ Hz, PhCH$_2$H$^\beta$); 4.57 (s, 1H, H-4); 4.48 (s, 2H, PhCH$_2$); 4.22 (d,
1H, J = 12.5 Hz, H-6); 4.11 (d, 1H, J = 12.0 Hz, H-6); 3.83 (d, 1H, J = 10.5 Hz, H-3); 3.76 (d, 1H, J = 10.5 Hz, H-2); 3.60-3.57 (m, 2H, H-5, OCH₃ (pentyl)); 3.43 (bs, 1H, OCH₃ (pentyl)); 3.23 (bs, 2H, NC₇H₅ (pentyl)); 1.54-1.53 (m, 4H, CH₂ (pentyl)); 1.43-1.40 (m, 2H, CH₂ (pentyl)); 1.06 (s, 9H, (CH₃)₃C(Si)); 1.05 (s, 9H, (CH₃)₃C(Si)). ¹³C NMR (125 MHz, 323 K) δ: 138.3, 138.2 (C₇H₅ (pentyl)); 138.2, 138.2 (C₇H₅ (pentyl)); 128.6, 128.5, 128.0, 127.9, 127.8, 127.3 (CH₃ (pentyl)); 98.8 (C-1); 75.7 (C-3); 70.5 (PhCH₂); 70.3 (C-4); 68.5 (OCH₂ (pentyl)); 67.9 (C-5); 67.4 (C-6); 67.3 (PhCH₂); 58.7 (C-2); 50.8 (PhCH₂); 29.2 (CH₂ (pentyl)); 27.7, 27.5 ((CH₃)₃C(Si)); 23.4 (CH₂ (pentyl)); 20.8 (C₆H₅). IR (thin film) ν: 2932, 2859, 2108, 1699, 1472, 1374, 1244, 1138, 1030. HRMS: [M+H]+ calculated for C₃₃H₆₀N₅O₇Si: 762.42565; found 762.42586.

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-3-O-benzyl-2-deoxy-α-D-galactopyranoside (22)

To a solution of 21 (1.68 g, 2.3 mmol, 1.0 eq.) in THF (23 mL, 0.1 M) was added HF/pyridine (70% HF, 0.47 mL, 18 mmol, 8.0 eq.). After TLC analysis (PE/EtOAc, 1:4 v/v) indicated complete conversion of the starting material (~2 hours), the reaction was quenched with NEt₃ (2 mL). The mixture was concentrated, dissolved in EtOAc and subsequently washed with sat. aq. NaHCO₃ and brine. The aqueous layers were then extracted with EtOAc combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Column chromatography (PE/EtOAc, 1:0 → 1:4) furnished the title compound in 98% yield. (1.34 g, 2.2 mmol). ¹H NMR (500 MHz, 323 K) δ: 7.35-7.20 (m, 15H, CH₃ (aromatic)); 5.16 (bs, 2H, PhCH₂); 4.87 (s, 1H, H-1); 4.72 (d, 1H, J = 11.5 Hz, PhCH₂); 4.67 (d, 1H, J = 11 Hz, PhCH₂); 4.48 (bs, 2H, PhCH₂); 4.09 (s, 1H, H-4); 3.88-3.84 (m, 2H, H-3, H-6); 3.78 (bs, 2H, H-5, H-6); 3.64-3.62 (m, 2H, H-2, OCH₃ (pentyl)); 3.43 (bs, 1H, OCH₃ (pentyl)); 3.24 (bs, 2H, NC₇H₅ (pentyl)); 1.54 (bs, 4H, CH₂ (pentyl)); 1.32-1.27 (m, 2H, CH₂ (pentyl)). ¹³C-APT NMR (125 MHz, 323 K) δ: 138.1, 137.5 (C₇H₅ (pentyl)); 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.9, 127.6, 127.3 (CH₃ (aromatic)); 98.4 (C-1); 76.1 (C-3); 72.2 (PhCH₂); 70.1 (C-5); 68.3 (OCH₂ (pentyl)); 67.6 (C-4); 67.3 (PhCH₂); 62.8 (C-6); 59.5 (C-2); 50.8 (PhCH₂); 29.1, 27.7, 23.5 (CH₂ (pentyl)). ¹³C-GATED NMR (125 MHz, 323 K) δ: 98.4 (d, J = 170 Hz, C-1). IR (thin film) ν: 3456, 3408, 2106, 1693, 1423, 1229, 1138, 1043. HRMS: [M+H]+ calculated for C₃₃H₄₁N₄O₇: 605.29698; found 605.29726.
**Synthesis of Staphylococcus aureus Strain M CPS**

*Methyl (5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-3-O-benzyl-2-deoxy-α-D-galactopyranosiduronate) (23)*

To an ice-cooled solution solution of 22 (0.16 g, 0.26 mmol, 1.0 eq.) in a mixture of CH₂Cl₂, tBuOH and H₂O (4:4:1, 1.3 mL, 0.2 M) were added TEMPO (8 mg, 0.05 mmol, 0.2 eq.), Phl(OAc)₂ (0.21 g, 0.65 mmol, 2.5 eq.) and AcOH (3 drops). The resulting mixture was stirred overnight at 4 °C, after which TLC analysis (PE/EtOAc, 1:1 v/v) indicated complete conversion of the starting material. The reaction was then quenched with sat. aq. Na₂S₂O₃ (10 mL) and aq. H₃PO₄ (1 mL, 1.0 M) was added. The mixture was extracted with CH₂Cl₂ (3x) and the combined organic layers were dried over MgSO₄, filtered, concentrated *in vacuo*, and the residue was co-evaporated with toluene. The residue was then dissolved in DMF (1.3 mL, 0.2 M) and cooled to 0 °C, after which MeI (32 µL, 0.52 mmol, 2.0 eq.) and K₂CO₃ (72 mg, 0.52 mmol, 2.0 eq.) were added. The mixture was stirred 4 °C until TLC analysis indicated complete conversion of the starting material (~16 hours). The reaction was then quenched with H₂O and the mixture was partitioned between H₂O and Et₂O. The aqueous phase was extracted with Et₂O (3x), the combined organic layers washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 1:0 → 1:1) gave the title compound as a yellow oil in 85% yield (0.14 g, 0.22 mmol):

**1H NMR (500 MHz, 323 K) & 7.37-7.20 (m, 15H, CH₃om); 5.17 (s, 2H, PhCH₂); 4.96 (s, 1H, H-1); 4.74-4.68 (m, 2H, PhCH₂); 4.48 (s, 2H, PhCH₂); 4.40 (s, 1H, H-5); 4.36 (s, 1H, H-4); 3.92 (d, 1H, J = 10.0 Hz, H-3); 3.83 (s, 3H, CO₂CH₃); 3.68-3.63 (m, 2H, H-2, OCH₄pentyl); 3.46-3.45 (m, 1H, OCH₄pentyl); 3.24 (s, 2H, NCH₂pentyl); 1.56-1.51 (m, 4H, CH₂pentyl); 1.38-1.24 (m, 2H, CH₂pentyl).**

**13C NMR (100 MHz) & 168.7 (C-6); 138.2, 137.3, 137.1 (C₆om); 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.9, 127.6, 127.3 (CH₂om); 98.5 (C-1); 75.6 (C-3); 72.3 (PhCH₂); 70.3 (C-4); 69.1 (OCH₂pentyl); 67.7 (C-5); 67.3 (PhCH₂); 59.0 (C-2); 52.3 (CO₂CH₃); 50.8 (PhCH₂); 50.2 (PhCH₂); 29.7, 29.1, 27.8, 23.4 (CH₂pentyl). IR (thin film) v: 3497, 2926, 2859, 2106, 1762, 1693, 1227, 1140, 1028.**

**13C-GATED NMR (125 MHz, 323 K) δ: 98.5 (d, J = 171 Hz, C-1). HRMS: [M+H]⁺ calculated for C₃₄H₄₁N₄O₁₂: 633.29189; found 633.29215.**
Methyl (5-((benzyl(benzylloxycarbonyl)amino)pentyl-2-azido-4-O-(2-azido-3-O-benzyl-2-deoxy-4,6-O-(di-tert-butyl-silylene)-α-D-galactopyranosyl)-3-O-benzyl-2-deoxy-α-D-galactopyranosiduronate) (24)

To a solution of 23 (1.80 g, 2.8 mmol, 1.0 eq.) and 5 (3.26 g, 5.6 mmol, 2.0 eq.) in CH₂Cl₂ (14 mL, 0.2 M) were added flame-dried, rod-shaped 3Å MS. After ~30 minutes, the solution was cooled to 0 °C, and N-iodosuccinimide (1.66 g, 7.4 mmol, 2.6 eq.) and TMSOTf (0.1 mL, 0.56 mmol, 0.2 eq.) were added respectively. After TLC analysis (PE/Et₂O, 9:1 v/v) indicated complete conversion of the starting material (~2 hours), the reaction was quenched by addition of NEt₃ (3 mL) the mixture filtered over celite, washed with sat. aq. Na₂SO₄, sat. aq. NaHCO₃ and brine, dried over MgSO₄ filtered and concentrated in vacuo. Column chromatography (PE/Et₂O, 1:0 → 9:1) afforded the product as an oil in 88% yield (2.62 g, 2.49 mmol): ¹H NMR (500 MHz, 323 K) δ: 7.39-7.19 (m, 20H, CH₆rom); 5.16 (s, 2H, PhCH₂); 5.02 (s, 1H, H-1); 4.99 (s, 1H, H-1’); 4.76-4.61 (m, 5H, H-4, PhCH₂); 4.51 (s, 1H, H-4’); 4.49-4.47 (m, 2H, PhCH₂); 4.33 (s, 1H, H-5); 3.98 (s, 1H, H-5’); 3.95 (d, 1H, J = 11.0 Hz, H-3); 3.84 (s, 3H, CO₂CH₃); 3.82-3.77 (m, 4H, H-2’, H-3’, H-6’); 3.64 (bs, 1H, OCH₃pentyl); 3.37 (m, 2H, OCH₂pentyl); 3.58 (d, 1H, J = 10.5 Hz, H-2); 3.48 (bs, 1H, OCH₃pentyl); 3.23 (m, 2H, NCH₂pentyl); 1.53-1.52 (m, 4H, CH₂pentyl); 1.28 (bs, 2H, CH₂pentyl); 1.01 (s, 9H, (CH₃)₃Si); 1.00 (s, 9H, (CH₃)₃Si); ²³C NMR (125 MHz, 323 K) δ: 168.8 (C-6); 138.2, 137.3 (C₆rom); 128.6, 128.6, 128.5, 128.4, 128.0, 127.9, 127.7, 127.5, 127.3 (C₆rom); 99.8 (C-1’); 98.4 (C-1); 75.6 (C-3’); 75.5 (C-3); 74.8 (C-4); 72.4 (PhCH₂); 70.0 (C-4’); 69.1 (OCH₂pentyl); 68.2 (C-5’); 67.3 (PhCH₂); 67.1 (C-6’); 59.7 (C-2); 58.8 (C-2’); 52.5 (CO₂CH₃); 50.5 (PhCH₂Bn); 50.3 (PhCH₂); 47.1 (NCH₃); 46.1 (CH₃N linker); 29.0 (CH₂pentyl); 27.6, 27.3 ((CH₃)₃Si); 23.3 (CH₂pentyl); 23.3, 20.7 (C₆Si). IR (thin film) ν: 2934, 2859, 2106, 1730, 1697, 1474, 1362, 1256, 1140, 1040. HRMS: [M+Na]⁺ calculated for C₅₆H₇₁N₇NaO₁₂Si: 1072.48222; found 1072.48236.
**Synthesis of Staphylococcus aureus Strain M CPS**

*Methyl (5-(benzyl(benzylexcarbonyl)amino)pentyl 2-azido-4-O-(2-azido-3-O-benzyl-2-deoxy-"α-D-galactopyranosyl)-3-O-benzyl-2-deoxy-"α-D-galactopyranosiduronate) (25)*

To a solution of compound 24 (1.26 g, 1.2 mmol, 1.0 eq.) in THF (12 mL, 0.1 M) was added HF.pyrinidine (70% HF, 0.12 mL, 4.8 mmol, 4.0 eq.). After TLC analysis (PE/EtOAc, 1:4 v/v) indicated complete conversion of the starting material (~2 hours), the reaction was quenched with NEt3 (1 mL). The mixture was concentrated, the residue dissolved in EtOAc and washed with sat. aq. NaHCO3 and brine. The aqueous layers were then extracted with EtOAc and the combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. Column chromatography (PE/EtOAc, 1:0 → 1:4) yielded the title compound as an oil in quantitative yield.

(1.08 g, 1.2 mmol): 1H NMR (500 MHz, 323 K) δ: 7.40-7.15 (m, 20H, CHarom); 5.16 (s, 2H, PhCH2); 5.05 (s, 1H, H-1); 5.01 (d, 1H, J = 3.0 Hz, H-1’); 4.82 (d, 1H, J = 11.5 Hz, PhCH3); 4.70-4.63 (m, 3H, PhCH3); 4.60 (s, 1H, H-4); 4.48 (d, 2H, PhCH2); 4.35 (s, 1H, H-5); 4.09 (s, 1H, H-4’); 4.02(bs, 1H, H-5’); 3.92 (d, 1H, J = 10.0 Hz, H-3); 3.86-3.83 (m, 4H, H-3’, CO2CH3); 3.70 (dd, 1H, J = 3.5 Hz, 10.5 Hz, H-2’);3.63 (bs, 1H, OCH3penny); 3.62 (dd, 1H, J = 3.5 Hz, 10.5 Hz, H-2); 3.52-3.48 (m, 3H, H-6’, OCH3penny); 3.22 (bs, NCH2penny); 1.53 (m, 4H, CH2penny); 1.34-1.26 (m, 2H, CH2penny). 13C-APT NMR (125 MHz, 323 K) δ: 168.5 (C-6’); 138.0, 137.2, 137.2, 136.9 (Cqarom); 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.3 (CHarom); 99.5 (C-1’); 98.2 (C-1); 76.0 (C-3’); 75.3, 75.2 (C-3, C-4); 72.4, 71.9 (PhCH2); 70.2 (C-5); 69.8 (C-5’); 69.0 (OCH2penny); 67.6 (C-4’); 67.2 (PhCH2); 62.6 (C-6’); 59.4, 59.3 (C-2, C-2’); 52.6 (CO2CH3); 50.5 (NCH2penny); 29.6, 29.0, 23.3 (CH2penny). 13C-GATED NMR (125 MHz, 323 K) δ: 99.5 (d, J = 173 Hz, C-1’); 98.2 (d, J = 173 Hz, C-1). IR (thin film) ν: 3448, 2936, 2112, 2108, 1730, 1695, 1694, 1454, 1423, 1233, 1040. HRMS: [M+H]+ calculated for C47H56N7O12: 910.39815; found 910.39941.
Chapter 6

Methyl (5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-4-O-(methyl (2-azido-3-O-benzyl-2-deoxy-α-D-galactopyranosiduronate))-3-O-benzyl-2-deoxy-α-D-galactopyranosiduronate) (26)

To an ice-cooled solution of 25 (0.42 g, 0.46 mmol, 1.0 eq.) in THF and CH₂Cl₂ (3:2 v/v, 4.5 mL, 0.1 M) were added TEMPO (14 mg, 0.09 mmol, 0.2 eq.) and Phl(OAc)₂ (147 mg, 0.46 mmol, 1.0 eq.). After stirring for 30 minutes the mixture was allowed to warm to room temperature. After stirring for an additional 90 minutes a second portion of Phl(OAc)₂ (59 mg, 0.18 mmol, 0.4 eq.) was added. After TLC analysis (PE/EtOAc, 1:1 v/v) indicated complete conversion of the starting material, tBuOH (3.6 mL) and 2-methylbut-2-ene (0.5 mL) were added. The mixture was then cooled to 0 °C again and a solution of NaClO₂ (83 mg, 0.91 mmol, 2.0 eq.) and NaH₂PO₄ (0.11 g, 0.91 mmol, 2.0 eq.) in H₂O (0.45 mL) was added. After ~30 minutes, the reaction mixture was allowed to warm to room temperature. After TLC analysis (PE/EtOAc/ACOOH, 10:10:1 v/v/v) indicated complete transformation of the intermediate aldehyde, aq. 1M H₃PO₄ (2 mL) was added to the reaction mixture, after which it was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄ filtered and concentrated in vacuo. The residue was dissolved in DMF (2.4 mL, 0.2M) and MeI (57 μL, 0.91 mmol, 2.0 eq.) and K₂CO₃ (0.13 g, 0.91 mmol, 2.0 eq.) were added. After TLC analysis (PE/EtOAc, 1:1 v/v) indicated complete conversion of the starting material (~2 hours), H₂O was added and the mixture extracted with Et₂O (4x). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 1:0 → 1:1) yielded the title compound as an oil in 84% yield (0.36 g, 0.38 mmol). 1H NMR (500 MHz, 323 K) δ: 7.35-7.19 (m, 20H, CH₃O); 5.16-5.14 (m, 3H, H-1, PhCH₂); 5.04 (d, 1H, J = 2.5 Hz, H-1’); 4.85-4.82 (m, 2H, H-5’, PhCHH); 4.71-4.68 (m, 2H, PhCH₂); 4.65 (s, 1H, H-4’); 4.55 (d, 1H, J = 12.0 Hz, PhCHH); 4.47 (s, 2H, PhCH₂); 4.39 (d, 1H, J = 1.5 Hz, H-4); 4.35 (s, 1H, H-5); 3.94-3.89 (m, 2H, H-3, H-3’); 3.84 (s, 3H, CO₂CH₃); 3.73 (dd, 1H, J = 3.5 Hz, 10.5 Hz, H-2); 3.65 (bs, 1H, OCHA₃pentylic); 3.55 (dd, 1H, J = 3.5 Hz, 11 Hz, H-2’); 3.48 (bs, 1H, OCHA₂pentylic); 3.43 (s, 3H, CO₂CH₃); 3.21 (bs, 2H, NCH₂pentylic); 1.52-1.51 (m, 4H, CH₂pentylic); 1.34-1.23 (m, 2H, CH₂pentylic). 13C-APT NMR (125 MHz, 323 K) δ: 168.4, 168.3 (C-6, C-6’); 137.9, 137.0, 136.9 (Cs, arom); 128.6, 128.5, 128.4, 128.4, 128.2, 127.9, 127.9, 127.8, 127.7, 127.3, 127.2 (CH₃); 99.6 (C-1); 98.2 (C-1’); 75.6, 75.3, 74.9 (C-3, C-3’, C-4’); 72.1, 71.9 (PhCH₃); 70.6, 70.1 (C-5, C-5’); 69.0 (OCH₂pentylic); 67.2 (PhCH₂); 67.1 (C-4); 59.0 (C-2’); 58.7 (C-2); 52.6, 52.0 (CO₂CH₃); 50.5 (PhCH₂);
29.6, 28.9, 23.2 (CH$_2$-penty1). $^{13}$C-GATED NMR (125 MHz, 323 K) δ: 99.6 (d, $J$ = 173 Hz, C-1); 98.2 (d, $J$ = 172 Hz, C-1'). IR (thin film) v: 3449, 2936, 2859, 2110, 2106, 1761, 1732, 1695, 1454, 1360, 1219, 1134, 1058. HRMS: [M+H]$^+$ calculated for C$_{46}$H$_{50}$N$_5$O$_{13}$: 938.39306; found 938.39426.

Methyl (5-(benzyl(benzoxycarbonyl)amino)penty1 2-azido-4-O-(methyl (2-azido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-α-D-lyxopyranosyl)-3-O-benzyl-2-deoxy-α-D-galactopyranosiduronate))-3-O-benzyl-2-deoxy-α-D-galactopyranosiduronate) (4)

To a solution of 6 (0.57 g, 1.1 mmol 2.0 eq.) Ph$_2$SO (0.21 g, 1.1 mmol, 2.0 eq.) and TTBP (0.53 g, 2.1 mmol, 4.0 eq.) in CH$_2$Cl$_2$ (20 mL, 0.05 M) and flame-dried, rod-shaped 3Å MS were added. After ~30 minutes, the mixture was cooled to -80 °C. Tf$_2$O (0.18 mL, 1.1 mmol, 2.0 eq.) was added and the solution was allowed to warm to -70 °C, after which TLC analysis indicated complete activation of the donor. The mixture was re-cooled to -80 °C, and a solution of acceptor 26 (0.50 g, 0.53 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (1.3 mL, 0.4M) was slowly added. The mixture was warmed to -40 °C and then kept at this temperature. After TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete consumption of the acceptor, the reaction was quenched by addition of pyridine (1 mL), and the reaction mixture was diluted with CH$_2$Cl$_2$, filtered over a small bed of celite, washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by size exclusion chromatography (CH$_2$Cl$_2$/MeOH, 1:1 v/v) and subsequent column chromatography (PE/EtOAc, 1:0 → 3:1) yielded the title trisaccharide as a single isomer, in 79% yield (0.55 g, 0.42 mmol): $^1$H NMR (500 MHz, 328 K) δ: 7.36-7.23 (m, 25H, CH$_{arom}$); 5.21 (d, 1H, $J$ = 3.5 Hz, H-1); 5.16 (s, 2H, PhCH$_2$); 5.01 (d, 1H, $J$ = 3.0 Hz, H-1'); 4.96-4.46 (m, 2H, PhCH$_2$); 4.87-4.52 (m, 2H, PhCH$_2$); 4.85 (s, 1H, H-1''); 4.82-4.52 (m, 2H, PhCH$_2$); 4.78 (s, 1H, H-5'); 4.71 (d, 1H, $J$ = 2.0 Hz, H-4); 4.54 (s, 1H, H-4''); 4.47 (s, 2H, PhCH$_2$); 4.34 (s, 1H, H-5); 4.08 (q, 1H, $J$ = 6.5 Hz, H-5''); 4.01 (dd, 1H, $J$ = 2.8, 10.3 Hz, H-3''); 3.89 (m, 1H, H-3'); 3.87 (m, 1H, H-3); 3.85 (s, 3H, CO$_2$CH$_2$); 3.69 (m, 1H, H-2''); 3.66 (m, 1H, H-2); 3.65-3.45 (m, 2H, OCH$_{2}$-penty1); 3.47 (dd, 1H, $J$ = 3.8, 10.8 Hz, H-2''); 3.39 (s, 3H, CO$_2$CH$_3$); 3.34 (d, 1H, $J$ = 1.5 Hz, H-4''); 3.21 (m, 2H, NC$_{2}$-penty1); 1.51 (m, 4H, CH$_2$-penty1); 1.25 (m, 2H, CH$_2$-penty1); 0.95 (s, 9H, (CH$_3$)$_3$CSi(CH$_3$)$_3$); 0.87 (d, 3H, $J$ = 6.5 Hz, H-6''); 0.20 (s, 3H, CH$_3$Si); 0.15 (s, 3H, CH$_3$Si). $^{13}$C-APT NMR (125 MHz, 328 K) δ: 168.5, 168.3 (C-6, C-6''); 138.7 (C$_{arom}$); 138.1 (C$_{arom}$); 138.0, 137.2,

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137.2 (C\textsubscript{q,arom}); 128.6, 128.5, 128.5, 128.3, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 126.9 (CH\textsubscript{arom}); 99.4 (C-1); 98.8 (C-1’); 98.3 (C-1’’); 81.0 (C-4’’); 75.6 (PhCH\textsubscript{2}); 75.1 (C-3); 75.1 (C-3’); 74.6 (C-4); 73.5 (C-4’); 72.1 (PhCH\textsubscript{2}); 71.9 (PhCH\textsubscript{2}); 71.2 (C-3’’); 70.8 (C-5’); 70.2 (C-5); 69.0 (OCH\textsubscript{2}penty); 67.6 (C-5’’); 67.2 (PhCH\textsubscript{2}); 62.1 (C-2’’); 59.5 (C-2); 59.2 (C-2’); 52.6, 52.0 (CO\textsubscript{2}CH\textsubscript{3}; 29.0 (CH\textsubscript{2}penty); 25.9 ((CH\textsubscript{3})\textsubscript{3}CSi); 23.3 (CH\textsubscript{2}penty); 18.1 (C\textsubscript{3}Si); 16.5 (C-6’’); -3.9 (CH\textsubscript{3}Si). IR (thin film) ν: 2924, 2859, 2110, 2117, 1713, 1693, 1506, 1474, 1211, 1045. HRMS: [M+Na]\textsuperscript{+} calculated for C\textsubscript{67}H\textsubscript{84}N\textsubscript{10}NaO\textsubscript{16}Si: 1335.57282; found 1335.57294.

Methyl (5-(benzyl(benzylloxycarbonyl)amino)pentyl 2-acetamido-4-O-(methyl (2-acetamido-4-O-(2-acetamido-4-O-benzyl-2-deoxy-3-O-(tert-butyldimethylsilyl)-a-D-fucopyranosyl)-3-O-benzyl-2-deoxy-a-D-galactopyranosiduronate))-3-O-benzyl-2-deoxy-a-D-galactopyranosidurionate) (27)

To a solution of 4 (0.28 g, 0.21 mmol, 1.0 eq.) in pyridine (10 mL, 0.02M) was added freshly distilled Ac\textsubscript{2}SH (10 mL). The mixture was stirred until LC-MS analysis (MeCN/H\textsubscript{2}O/TFA, 50:50:0.1 → 90:10:0.1 v/v/v, t\textsubscript{R}: 9.50 min.) indicated completion of the reaction (~9 days). The reaction mixture was concentrated in vacuo and purification by means of size exclusion chromatography (CH\textsubscript{3}Cl\textsubscript{2}/MeOH, 1:1 v/v) and column chromatography (DCM/MeOH, 1:0 → 19:1) gave the title compound as a white solid in 47% yield (0.14 g, 0.11 mmol): \textsuperscript{1}H NMR (500 MHz, methanol-\textit{d}4, 330 K) δ: 7.37-7.22 (m, 25H, CH\textsubscript{arom}); 5.14 (s, 2H, PhCH\textsubscript{2}); 5.03 (d, 1H, J = 3.5 Hz, H-1); 4.98-4.55 (m, 2H, PhCH\textsubscript{2}); 4.95 (m, 1H, H-5); 4.92 (d, 1H, J = 3.5 Hz, H-1’); 4.87-4.58 (m, 2H, PhCH\textsubscript{2}); 4.83-4.46 (m, 2H, PhCH\textsubscript{2}); 4.68 (d, 1H, J = 2.0 Hz, H-4’); 4.58-4.46 (m, 5H, H-1”, H-2”, H-2’”, H-5’, PhCH\textsubscript{2}); 4.31 (q, 1H, J = 6.5 Hz, H-5’’); 4.06 (dd, 1H, J = 2.8, 10.2 Hz, H-3’’); 3.98 (dd, 1H, J = 2.5, 11.5 Hz, H-3); 3.84-3.82 (m, 1H, H-3’); 3.76 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}); 3.67-3.42 (m, 2H, OC\textsubscript{2}penty); 3.46 (d, 1H, J = 1.5 Hz, H-4’’); 3.27 (m, 2H, NCH\textsubscript{2}penty); 3.18 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}); 2.02 (s, 3H, CH\textsubscript{3,NHAc}); 2.02 (s, 3H, CH\textsubscript{3,NHAc}); 1.96 (s, 3H, CH\textsubscript{3,NHAc}); 1.54 (m, 4H, CH\textsubscript{2}penty); 1.30 (m, 2H, CH\textsubscript{2}penty); 0.90 (s, 9H, (CH\textsubscript{3})\textsubscript{3}Cs); 0.80 (d, 3H, J = 6.5 Hz, H-6’’); 0.19 (s, 6H, CH\textsubscript{3}Si); \textsuperscript{13}C NMR (125 MHz, methanol-\textit{d}4, 330 K) δ: 172.5; 172.3, 172.1 (\textit{d}\textsubscript{NHAc}; 169.2, 168.8 (C-6, C-6’); 139.0, 138.6, 138.4, 138.0 (C\textsubscript{q,arom}); 128.3, 128.2, 128.0, 128.0, 127.8, 127.6, 127.5, 127.2, 127.1, 127.0, 127.0, 126.9, 126.1, (CH\textsubscript{arom}); 99.2 (C-1’’); 176
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99.2 (C-1); 98.1 (C-1'); 81.0 (C-4''); 76.4 (C-3'); 75.4 (PhCH$_2$); 75.2 (C-3); 74.6 (C-4'); 73.9 (C-4); 72.0, 71.8 (PhCH$_2$); 71.0 (C-5); 70.8 (C-3''); 69.8 (C-5'); 68.7 (OCH$_2$-pentyI); 67.7 (C-5''); 67.1 (PhCH$_2$); 51.5, 51.0 (CO$_2$H$_3$); 50.3 (PhCH$_2$); 48.9 (C-2'); 48.6 (C-2''); 48.6 (C-2); 28.6 (CH$_2$-pentyI); 25.0 ((CH$_3$)$_2$CSi); 23.1 (CH$_2$-linker); 22.4, 22.0, 21.5 (CH$_3$-NH$_2$); 17.4 (C$_q$Si); 15.7 (H-6''); -5.0 (CH$_3$Si).

IR (thin film) ν: 2947, 2835, 1763, 1684, 1676, 1663, 1518, 1454, 1364, 1213, 1128, 1038.

To a plastic tube, containing a solution of 27 (35 mg, 26 μmol, 1.0 eq.) in pyridine (5 mL, 0.005 M) was added HF-pyridine (70% HF, 0.1 mL, 3.8 mmol, 150 eq.). The mixture stirred until LC-MS analysis (MeCN/H$_2$O/TFA, 50:50:0.1 → 90:10:0.1 v/v/v, t$_r$: 6.10 min.) indicated that the reaction was complete. The reaction was quenched with H$_2$O (5 mL) and the mixture was extracted CH$_2$Cl$_2$ (10x). The combined organic layers were dried over MgSO$_4$ filtered and concentrated in vacuo.

Purification by column chromatography (DCM/MeOH, 1:0 → 19:1) gave compound 28 as a white solid in 56% yield (18 mg, 14 μmol): $^1$H NMR (500 MHz) δ: 7.38-7.07 (m, 25H, CH$_{arom}$); 5.17 (s, 2H, PhCH$_2$); 5.01 (d, 1H, J = 3.5 Hz, H-1); 4.95 (s, 1H, H-1'); 4.94 (s, 1H, H-5); 4.90-4.56 (m, 2H, PhCH$_2$); 4.89-4.63 (m, 2H, PhCH$_2$); 4.86-4.47 (m, 2H, PhCH$_2$); 4.70 (s, 1H, H-4'); 4.66 (d, 1H, J = 3.5 Hz, H-1''); 4.55 (m, 1H, H-2); 4.55 (m, 1H, H-2'); 4.53 (s, 2H, PhCH$_2$Bn); 4.51 (m, 1H, H-4); 4.51 (m, 1H, H-5); 4.31 (m, 1H, H-5''); 4.30 (m, 1H, H-2''); 3.99 (m, 1H, H-3); 3.97 (m, 1H, H-3''); 3.84 (m, 1H, H-3'); 3.78 (s, 3H, CO$_2$CH$_3$); 3.67-3.44 (m, 2H, OCH$_2$-pentyI); 3.52 (d, 1H, J = 1.5 Hz, H-4''); 3.30 (t, 2H, J = 7.0 Hz, NC$_2$-pentyI); 2.05 (s, 3H, CH$_3$-NH$_2$); 2.04 (s, 3H, CH$_3$-NH$_2$); 1.97 (s, 3H, CH$_3$-NH$_2$); 1.58 (m, 4H, CH$_2$-pentyI); 1.33 (m, 2H, CH$_2$-pentyI); 0.79 (d, 3H, J = 6.5 Hz, H-6''). $^{13}$C NMR (125 MHz) δ: 172.8, 172.6, 172.3 (CO$_{arom}$); 169.0, 168.8 (C-6, C-6''); 138.9, 138.6, 138.4, 138.0, (C$_q$ arom); 128.3, 128.2, 128.0, 128.0, 127.8, 127.8, 127.6, 127.1, 127.1, 127.1, 127.0, 126.8, 126.1 (CH$_{arom}$); 98.9 (C-1); 98.6 (C-1''); 98.1 (C-1'); 80.1 (C-4''); 76.4 (C-3'); 75.4 (PhCH$_2$); 75.3 (C-3); 74.3 (C-4'); 73.8 (C-4); 71.9 (PhCH$_2$); 71.8 (PhCH$_2$); 70.9 (C-5); 69.8 (C-5''); 69.0 (C-3''); 68.7 (OCH$_2$-pentyI); 67.4
(C-5’); 67.1 (PhCH$_2$); 51.5, 51.0 (CO$_2$CH$_2$); 50.3 (PhCH$_2$); 50.3 (C-2’'); 48.9 (C-2’); 48.7 (C-2); 28.6, 23.1 (CH$_2$-pentyl); 22.0, 21.9, 21.5 (CH$_3$NHAc); 15.7 (C-6’). IR (thin film) $\nu$: 3422, 3333, 2924, 2855, 1742, 1663, 1653, 1454, 1228, 1043, 1028. HRMS: [M+H]$^+$ calculated for C$_{67}$H$_{83}$N$_4$O$_{19}$: 1247.56460; found 1247.56524.

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-acetamido-4-O-(2-acetamido-4-O-benzyl-2-deoxy-\(\alpha\)-D-fucopyranosyl)-3-O-benzyl-2-deoxy-\(\alpha\)-D-galactopyranosiduronate)-3-O-benzyl-2-deoxy-\(\alpha\)-D-galactopyranosiduronic acid (29)

Compound 28 (39 mg, 31 $\mu$mol, 1.0 eq.) was dissolved in THF (1.6 mL, 0.02M) after which 0.6 mL of a solution of 0.5 M KOH and 30% wt. H$_2$O$_2$ (22:3, v:v) was added to the solution together with t-BuOH (0.6 mL). The resulting mixture was allowed to stir for 2 days after which LC-MS analysis (MeCN/H$_2$O/TFA, 50:50:0.1 → 90:10:0.1 v/v/v, $t_r$: 4.70 min.) indicated that the reaction was complete. The reaction mixture was neutralized with 1M aq. HCl and subsequently extracted CH$_2$Cl$_2$ (10x). Evaporation of the combined organic phases gave the product as a white solid in 87% yield (33 mg, 27 $\mu$mol). $^1$H NMR (500 MHz, CD$_3$OD) $\delta$: 7.36-7.21 (m, 25H, C$_{\text{H arom}}$); 5.15 (s, 2H, PhCH$_2$); 5.14 (s, 1H, H-1); 4.93 (s, 1H, H-5); 4.88-4.83 (m, 4H, H-1’, H-1”, PhCH$_3$); 4.75 (d, 1H, $J$ = 12.5 Hz, PhCH$_2$); 4.64 (s, 1H, H-4’); 4.59-4.45 (m, 7H, H-2, H-2’, H-4, PhCH$_3$); 4.37 (s, 1H, H-5’); 4.35-4.31 (m, 2H, H-2”, H-5’); 3.98-3.93 (m, 2H, H-3, H-3’); 3.77 (m, 1H, H-3’); 3.66-3.55 (m, 1H, OCH$_2$-pentyl); 3.51 (d, 1H, $J$ = 2.0 Hz, H-4’); 3.46-3.38 (m, 1H, OCH$_2$H$_{2\text{ linker}}$) 3.26 (t, 2H, $J$ = 6.8 Hz, NCH$_2$-pentyl); 2.03, 1.99, 1.91 (s, 3H, C$_3$NHAc); 1.54-1.51 (m, 4H, CH$_2$-pentyl); 1.40 (s, 2H, CH$_2$-pentyl); 0.77 (d, 3H, $J$ = 6.5 Hz, H-6’); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$: 174.5, 173.8, 173.5 (C-6, C-6’, C$_{\text{NHAc}}$); 140.2, 140.0, 139.5 (C$_{\text{H arom}}$); 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 128.5, 128.4, 128.2 (CH$_{\text{arom}}$); 100.5 (C-1); 100.4 (C-1’); 99.4 (C-1’); 81.5 (C-4’); 77.0 (C-3’); 77.0 (C-3’); 75.8 (C-4’); 75.6 (C-4); 73.2, 73.2 (PhCH$_2$); 72.1 (C-5); 71.2 (C-5’); 70.7 (C-3’); 69.8 (OCH$_2$-linker); 68.8 (C-5’); 68.5 (PhCH$_3$); 51.7 (C-2’); 51.6 (PhCH$_2$); 50.2 (C-2’); 49.9 (C-2); 29.9, 24.4 (CH$_2$-pentyl); 23.2, 23.2, 22.8 (CH$_3$NHAc); 17.0 (C-6’). IR (thin film) $\nu$: 3422, 3333, 2924, 2855, 1742, 1663, 1653, 1454, 1228, 1043, 1028. HRMS: [M+H]$^+$ calculated for C$_{65}$H$_{79}$N$_4$O$_{19}$: 1219.53330; found 1219.53503.
5-amino-pentyl 2-acetamido-4-O-(2-acetamido-4-O-(2-acetamido-2-deoxy-α-D-fucopyranosyl)-2-deoxy-α-D-galactopyranosiduronate)-2-deoxy-α-D-galactopyranosiduronic acid (3)

To a mixture of 29 (34 mg, 28 μmol, 1.0 eq.), was dissolved in mixture of water, t-BuOH, and THF (3:1:1, 0.56 mL, 0.005M) was added AcOH until pH 3 was reached. Pd(OH)_{2}/C (78 mg, 56 μmol, 2.0 eq.) was then added to the solution, after which H₂ was bubbled through the solution. The mixture was then allowed to stir for 3 days under H₂ atmosphere, after which the solution was filtered over a Whatman filter, the residue was rinsed with THF/H₂O, co-evaporated with H₂O and then filtered again. After lyophilization, the product was obtained as a white solid in 69% yield (14 mg, 19 μmol). \(^{1}H\) NMR (500 MHz, D₂O) \(\delta\): 5.01 (d, 1H, \(H-1\)); 4.93 (d, 1H, \(J = 3.5\) Hz, \(H-1\’\)); 4.85 (d, 1H, \(J = 3.5\) Hz, \(H-1\’\’\)); 4.72 (s, 1H, \(H-5\)); 4.39 (m, 2H, \(H-4\’, H-5\’\’\)); 4.29 (s, 1H, \(H-4\)); 4.21 (m, 2H, \(H-2\’, H-5\’\’\)); 4.11 (m, 4H, \(H-2\’, H-2\’’, H-3\’, H-3\’’\)); 3.93 (dd, 1H, \(J = 3.0\), 11.0 Hz, \(H-3\’\’\)); 3.80 (d, 1H, \(J = 3.0\) Hz, \(H-4\’’\)); 3.65 (d, 1H, \(J = 7.0\) Hz, OCHH \(_{\text{pentyt}}\)); 2.95 (t, 1H, \(J = 7.8\) Hz, CHN \(_{\text{pentyt}}\)); 2.06 (s, 6H, CH\(_{3}\)N\(_{\text{Hac}}\)); 2.00 (s, 3H, CH\(_{3}\)N\(_{\text{Hac}}\)); 1.69-1.61 (m, 4H, CH\(_{2}\) \(_{\text{pentyt}}\)); 1.41-1.38 (m, 2H, CH\(_{2}\) \(_{\text{pentyt}}\)); 1.13 (d, 3H, \(J = 6.5\) Hz, \(H-6\’\’\)); \(^{13}C\) NMR (125 MHz, D₂O) \(\delta\): 174.9, 174.6, 174.5 (CO\(_{\text{Hag}}\) C-6, C-6’); 99.4 (C-1’’); 98.4 (C-1’); 96.8 (C-1’’); 79.9 (C-4’); 77.4 (C-4’’); 72.0 (C-5); 71.2 (C-4’’’); 70.6 (C-5’); 68.0 (OCH\(_{2}\) \(_{\text{pentyt}}\)); 67.9 (C-3’’); 67.7 (C-5’’); 67.2 (C-3); 67.0 (C-3’); 49.8 (C-2’); 49.5 (C-2’’); 49.5 (C-2’’’); 39.4 (NCH\(_{2}\) \(_{\text{pentyt}}\)); 28.0, 26.3, 22.4 (CH\(_{2}\) \(_{\text{pentyt}}\)); 22.3, 22.3, 21.9 (CH\(_{3}\) \(_{\text{Hac}}\)); 15.4 (C-6’’’). IR (thin film) ν: 3352, 3269, 3237, 2918, 1639, 1595, 1377, 1109, 1026. HRMS: [M+H]\(^{+}\) calculated for C\(_{29}\)H\(_{49}\)N\(_{4}\)O\(_{17}\): 725.30872; found 725.30846.

References

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Chapter 7

Synthesis of *Schistosoma mansoni* glycan fragments

Introduction

Schistosomiasis is an infection caused by schistosomes, a genus of parasitic helminths, and it is classified as a neglected tropical disease. Schistosomiasis affects an estimated 200 million people worldwide, mainly in (sub)tropical areas with poor hygienic standards. Schistosoma mansoni is the major causative agent of schistosomiasis. This parasite has a complex life cycle, including an ‘aquatic’ phase and a human phase. Sporocysts in freshwater snails mature into cercariae, which can infect humans when they come in contact with infected water. The cercariae then mature in the host’s intestine. A pair of worms reproduces sexually, laying up to 300 eggs per day. The eggs are excreted in the host’s feces, thereby closing the cycle. The eggs can survive for a long time in the host and are deposited throughout the body. In severe cases, these eggs can cause liver and kidney failure.

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Current treatment of schistosomiasis consists of administration of Praziquantel. While effective, this drug does not prevent re-infection of the host. Additionally, depending on the severity of the infection, strong side-effects can occur, caused by release of cell contents of the parasites as they are killed. An alternative strategy, one that could lead to eradication of the disease, is vaccination. \textit{S. mansoni} expresses a complex array of glycans that have been shown to be targeted by both the innate as well as the adaptive arm of the immune system.\textsuperscript{2,3} Most antibodies raised against \textit{S. mansoni} upon infection are directed at glycan epitopes of the parasite. A prominent feature in many of the \textit{S. mansoni} glycans is the presence of multi-fucosylated elements.\textsuperscript{4-6} These multi-fucosylated fragments have been shown to be a prime target for the generated antibodies.\textsuperscript{7-9} Scheme 1A depicts a heptasaccharide fragment 1, that is found in the larval stages of \textit{S. mansoni}. This carbohydrate features a backbone consisting of \textit{N}-acetylgalactosamine (GalNAc) and \textit{N}-acetylglucosamine (GlcNAc) units, decorated on the terminal GalNAc and GlcNAc units with a difucosyl chain. The fucosyl units are connected by \textalpha-(1→2)-glycosidic bonds, which are unique to \textit{S. mansoni}.\textsuperscript{5,6}

Although it is clear that the multi-fucosylated structures are important in shaping the immune response against \textit{S. mansoni}, it remains unclear which fragments are most effective as antigens. Synthetic chemistry can provide well-defined glycan fragments to study these for their antigenicity and for their ability to modulate the innate immune response. This Chapter describes preliminary studies towards the synthesis of \textit{S. mansoni} glycan fragments. The research described can be applied in the synthesis of a library of \textit{S. mansoni}-related glycan structures, to establish detailed structure-activity relationships for this class of complex glycans.

\textbf{Results & Discussion}

The target structures of four \textit{S. mansoni} glycans are shown in Scheme 1B. The glycan consists of a ‘backbone’,\textsuperscript{10} comprising \textit{N}-acetylgalactosamine (GlcNAc) and \textit{N}-acetylglucosamine (GalNAc) units, which are decorated with \textalpha-(1,2)-linked fucosyl chains. The synthesis of the GlcNAc-containing structures 2 and 3 have been reported by Van Roon, Aguilera \textit{et al.}\textsuperscript{8} The authors’ approach was to use 3,4-\textit{O}-iso-propyldiened protected fucosyl donors, with a 2-\textit{O}-\textit{tert}-butyldimethylsilyl (TBS) ether as a temporary, non-participating protecting group, which allows \textalpha-fucosylation. While this approach was effective in the synthesis of disaccharide 2, the yield dropped significantly as the fucosyl chain grew, possibly due to the large size of the TBS group. In addition, attempted deprotection of the \textit{iso}-propyldiene group on larger fragments led to decomposition.
Fucosyl donor 12 contains a non-participating 2-O-naphthylmethyl (Nap) ether, which can be selectively removed and is sterically less demanding than the TBS group. The remote 3-O and 4-O position are masked as pivaloyl esters. Additionally, the 2,2,2-trifluoro(N-phenyl)-acetimidoyl analogue 13 was also investigated as a donor. The GlcNAc donor 10 and GalNAc donors 11 N-acetyl groups are masked as trichloroacetyl groups during the synthesis, as the glycosylation of underivatized N-acetyl containing donors is often accompanied by formation of oxazoline byproducts. It is projected that these can be removed at the end of the synthesis, together with the pivaloyl esters, present on the fucosyl residues, by nucleophilic cleavage or concomitantly with the other protecting groups, the benzylidene acetal, the azide of the spacer and the Nap ether, through hydrogenation. Scheme 2 depicts the assembly of the required building blocks. The synthesis of the reducing end glucosamine unit 10 commenced with known glucosamine thioglycoside 14 (Scheme 2A). Introduction of a benzylidene acetal yielded building block 15 in 85% yield. Protection of the C-3-OH with a Nap group gave 16 in 82% yield. Purification of this building block proved to be challenging, due to the poor solubility of 16 in most organic solvents. For the same reason, the glycosylation of 16 with 6-azidohexanol, using NIS and a catalytic amount of TMSOTf, did not give any product 17. Due to the difference in reactivity
between 6-azidohexan-1-ol and the C-3-OH of 15, the possibility to install the linker in the presence of the unprotected C-3-alcohol was explored. Fortunately, NIS/TMSOTf-mediated glycosylation of 15 with the spacer alcohol gave 10 in 76% yield. The synthesis of the analogously protected galactosamine unit 11 proceeded via the same sequence of events (Scheme 2B) from galactosamine thioglycoside 18. Introduction of the 4,6-benzylidene acetal gave 19 in 76% yield. The glycosylation of 3-O unprotected donor 19 with 6-azidohexan-1-ol, proved successful, giving 11 in 68% yield.

The synthesis of fucosyl building block 12 commenced from L-fucosyl thioglycoside 20 (Scheme 2C), following a known sequence to advanced intermediate 23. Thus, introduction of an iso-propylidene acetal over the C-3 and C-4-alcohols yielded 21 in 92% yield. The remaining C-2-OH was protected as a 2-O Nap ether, giving 22 in 89% yield. Acidic removal of the iso-propylidene group furnished the 3,4-diol 23 in 92% yield. Pivaloylation using pivaloyl anhydride in a Bi(OTf)3-catalyzed protocol gave 12 in 87% yield. Next to thiofucoside 12, a imidate fucosyl donor was also generated. (N-phenyl)trifluoroacetimidate 13 was synthesized in 2 steps from thioglycoside 12 by NBS-mediated hydrolysis, and subsequent introduction of the imidoyl group to give 13 in 69% over 2 steps.

Attention was directed next to the construction of the fucosylated glucosamine disaccharide 6 (Table 1). The use of imidate donor 13 in a glycosylation with 10 led to 6 in 61% yield, with complete ω-selectivity (entry 1). Glycosylation of thioglycoside 12 with the Ph3SO/Tf2O pre-activation system successfully employed in the synthesis of ω-glycosidic linkages in the analogous 2-azidofucosyl (FuCN3) donors (see Chapters 3, 4 and 6) yielded disaccharide 6 in 15% yield (entry 2). The main product isolated was C-fucoside 27a (Scheme 3), which results from an electrophilic aromatic substitution on the naphthyl moiety. The conditions employed actually favor this intramolecular pathway, since the activation of the anomeric phenylthio moiety occurs in the absence of an external nucleophile. Interestingly, only the ω-isomer was isolated (δ: 5.55 ppm, J = 3.6 Hz), which implies the involvement of a transient oxocarbenium ion 26. Attack of the aromatic moiety likely occurs from the top (that is, ω) face of the favored 3H4 conformer 26, since this leads to a favored, chair-like transition state.
Scheme 2: A) Synthesis of reducing end glucosamine acceptor 10; B) synthesis of reducing end galactosamine acceptor 11; C) synthesis of fucosyl donors 12 and 13.

Reagents and conditions: a) PhCH(O Me)$_2$, TsOH (cat.), MeCN, 50 °C, 350 mbar (85% for 15, 76% for 19); b) NapBr, NaH (60% in oil), DMF, 0 °C (82% for 16, 89% for 22); c) 6-azidoheptan-1-ol, NIS, TMSOTf (cat.), 3Å MS, CH$_2$Cl$_2$ -20 to 0 °C (76% for 10, 68% for 11); d) (MeO)$_2$C(Me)$_2$, TsOH (cat.), MeCN, 50 °C, 350 mbar (92%); e) HCl (aq.), MeOH, 92%; f) Piv$_2$O, Bi(OTf)$_3$ (cat.), CH$_2$Cl$_2$ (87%); g) NBS, acetone, H$_2$O (90%); h) F$_3$CC(NPh)Cl, Cs$_2$CO$_3$, acetone (77%).

To prevent this intramolecular side reaction, glycosylation conditions that do not rely on a pre-activation protocol were explored. Fortunately, NIS/TMSOTf-mediated glycosylation of 12 yielded disaccharide 6 in 86% yield as a single anomer. Succinimidyl fucoside 28 was isolated as a side-product in minor amounts.
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Table 1: Synthesis of GlcNAc-Fuc disaccharide 6.

<table>
<thead>
<tr>
<th>entry</th>
<th>donor</th>
<th>activator</th>
<th>temperature (°C)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>TFOH (cat.)</td>
<td>-40 → 20</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>Ph₂SO, TTBP, Tf₂O</td>
<td>-80 → -60</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>NIS, Me₃SiOTf (cat.)</td>
<td>-40 → 20</td>
<td>86%</td>
</tr>
</tbody>
</table>

Next, the fucosyl C-2-OH in disaccharide 6 was unmasked using oxidative conditions (Scheme 4). Using DDQ in a mixture of CH₂Cl₂ and water resulted in irreproducible results, providing the desired product 29 along with varying amounts of a side product in which the benzylidene acetal was removed. The oxidative cleavage of the Nap ether could be improved by carrying out the reaction in the presence an aqueous phosphate buffer (pH 7.2), giving 29 in 74% yield.¹⁹ The important Fuc-α-(1→2)Fuc linkage was introduced using the same NIS/TMSOTf-mediated glycosylation conditions used to synthesize disaccharide 6 (see Table 1). Unfortunately, the desired trisaccharide 7 was isolated in a moderate 33% yield.

Scheme 3: Byproducts arising from glycosylations with 12.

A

B

27β

δ 5.55 ppm
J = 3.6 Hz

27α
**Scheme 4**: Synthesis of trisaccharide 7.

![Scheme 4](image)

Reagents and conditions: a) DDQ, CH₂Cl₂, aqueous phosphate buffer (pH 7.2; 74%); b) NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, -40 → -20 °C (33%).

The synthesis of the fucosylated galactosamine disaccharide 8 is shown in Scheme 5. Again using a NIS/TMSOTf-mediated glycosylation, fucosyl donor 12 and reducing end galactosamine acceptor 11 were unified to give disaccharide 8 in 68% yield. Removal of the Nap ether using the buffered oxidative conditions gave acceptor 30 in 83% yield. Trisaccharide 9 was constructed by NIS/TMSOTf-mediated glycosylation between donor 12 and 30 in 54% yield.

**Scheme 5**: Synthesis of fucosylated galactosamine di- and trisaccharide 8 and 9.

![Scheme 5](image)

Reagents and conditions: a) 11, NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, -20 to 0 °C (68%); b) DDQ, CH₂Cl₂, aqueous phosphate buffer (pH 7, 83%); c) 12, NIS, TMSOTf (cat.), 3Å MS, CH₂Cl₂, -40 → -20 °C (54%).

The deprotection sequence for the disaccharides is shown in Scheme 6. Removal of the pivaloyl esters was initially attempted using a mixture of KOH and H₂O₂, since these conditions were successfully employed in the deprotection of *Staphylococcus aureus* trisaccharides (Chapters 4 and 6). However in this case the application of these conditions led to incomplete removal of the protecting groups. A mixture of aqueous KOH, THF and methanol proved to be effective for the removal of the pivaloyl esters giving diols 31 and 32 in 57% and 61% yield, respectively. In both cases, a minor byproduct was observed in which the amide was cleaved.
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Removal of the benzylidene acetal, the Nap ether, the conversion of the TCA into the acetyl group, and reduction of the azide was achieved in a one-pot operation by palladium-catalyzed hydrogenation. The use of an aqueous phosphate buffer prevented deactivation of the palladium catalyst. The disaccharides 2 and 4 were obtained in 34% and 67% yield, respectively. Curiously, employing a similar sequence on the trisaccharides 7 and 9 were fruitless. This, combined with the modest yields obtained in the installation of the terminal fucosyl unit, prompts a revision of the building blocks. In the synthesis of the trisaccharides, the bulky pivaloyl groups on the fucosyl units complicate approach of the incoming acceptor on the anomeric center of the donor. Additionally, the steric bulk of the groups may force the trisaccharide in unfavorable conformations, imposing an energetic penalty on glycosidic bond formation. In order to avoid the steric bulk and increase yield of the glycosylation reactions, the Piv groups can be replaced by benzyl ethers. The reactivity study of the analogous 2-azidofucosyl (FucN₃) donors in Chapter 3 showed that benzyl ethers are generally more α-selective than benzoyl-containing counterparts. An additional benefit is that by using benzyl ethers, the fully protected oligosaccharides can be deprotected in one step, using catalytic hydrogenation.

Scheme 6: Deprotection of disaccharides 6 and 8.

![Scheme 6: Deprotection of disaccharides 6 and 8.](image)

Reagents and conditions: a) KOH, THF, MeOH, H₂O (57% for 31; 61% for 32); b) Pd/C, H₂ (4 bar), MeOH, aqueous phosphate buffer (pH 7.0; 34% for 2, 67% for 4).

Conclusion

The synthesis of fucosylated glycan fragments related to *Schistosoma mansoni* has been described. The synthesis of the GlcNAc- and GalNAc reducing end acceptors was achieved by efficient selective condensations of C-3-OH deprotected thioglycoside donors with the spacer alcohol. The success of the first fucosylations the depended on the activation conditions; a
NIS/TMSOTf-mediated protocol proved to be the most effective, while pre-activation conditions resulted mainly in an intramolecular annulation involving the C-2-O naphthylmethyl ether. Removal of the Nap group, using DDQ, was more effective under buffered conditions. Synthesis of the two trisaccharides proceeded in moderate yields. The unprotected disaccharides were obtained after a saponification-hydrogenation sequence. The deprotection of the trisaccharides was unsuccessful. A revision of the fucosyl building blocks is suggested, in which the pivaloyl groups are replaced by benzyl ethers to reduce steric bulk, increase reactivity of the donor, and facilitate deprotection.

**Experimental**

**General procedures**

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4Å molecular sieves (3Å for CH₂Cl₂, MeOH and MeCN), except pyridine and DMF. NET₃ was stored over KOH pellets. Tf₂O used in glycosylations was dried over P₂O₅ (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (λ: 254 nm), followed by spraying with 20% H₂SO₄ in EtOH (w/v) or Hanessian’s stain ((NH₄)₆Mo₇O₂₄·4H₂O, 25 g/L; (NH₄)₄Ce(SO₄)₂·2H₂O, 10 g/L; in 10% aq. H₂SO₄). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to Me₄Si (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. ¹³C-APT spectra are ¹H decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomic carbon atoms (J₁H,₁C) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm⁻¹. HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.
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**Phenyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside (15)**

![Structural formula](image)

To a solution of 14 (10.4 g, 25.0 mmol, 1.0 eq.) in MeCN (150 mL, 0.15M) were added benzaldehyde dimethylacetal (60.0 mmol, 9.0 mL, 2.4 eq.) and p-TsOH (0.47 g, 2.5 mmol, 0.1 eq.). The solution was heated to 50 °C and stirred on a rotary evaporator at reduced pressure (350 mbar) until TLC analysis (toluene/ EtOAc, 4:1) indicated completed conversion of the starting material (~3 hours). The reaction was quenched by addition of NEt₃ until a basic pH was obtained, and the reaction mixture was poured onto a mixture of cold Et₂O/heptane (1:1). The brown solids were collected and purified by silica gel chromatography (PE:EtOAc, 9:1 → 7:3 v/v), to give the title product as a white solid in 87% yield. (11.0 g, 21.8 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ: 7.73 (d, 1H, J = 9.2 Hz, NH); 7.50-7.31 (m, 10H, CH_arom); 5.60 (s, 1H, PhCH); 5.07 (d, 1H, J = 10.4 Hz, H-1); 4.28 (dd, 1H, J = 4.8 Hz, 6.0 Hz, H-6); 3.92-3.80 (m, 2H, H-2, H-4); 3.76 (t, 1H, 10.0 Hz, H-6); 3.60-3.50 (m, 2H, H-3, H-5). ¹³C-APT NMR (100 MHz, DMSO-d₆) δ: 164.1 (CD_TCA); 138.7, 134.5 (C_arom); 132.1, 129.9, 129.7, 129.5, 129.0, 128.7, 128.3, 127.0 (CH_arom); 102.1 (PhCH); 87.6 (C-1); 81.6 (C-5); 72.6 (C-4); 71.3 (C-3); 68.9 (C-6); 57.9 (C-2).

**Phenyl 4,6-O-benzylidene-2-deoxy-3-O-(2-napththymethyl)-2-trichloroacetamido-1-thio-β-D-glucopyranoside (16)**

![Structural formula](image)

To a stirred solution of 15 (0.96 g, 1.90 mmol, 1.0 eq.) in DMF (10 mL, 0.2M) was added NaH (60% in oil, 0.23 g, 5.7 mmol, 3 eq.) portionwise over the course of ~10 minutes. The reaction mixture was left to stir until gas evolution ceased, at which point 2-(bromomethyl)naphthalene (0.46 g, 2.10 mmol, 1.1 eq.) was added. The reaction mixture was stirred at 0 °C until TLC analysis (toluene/ EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~4 hours), after which the reaction was quenched by slow addition of MeOH. Added was H₂O (~100 mL). The resulting precipitate was collected and purified by column chromatography (toluene: EtOAc, 1:0 → 4:1 v/v), yielding the title compound in 82% yield (1.00 g, 1.55 mmol). ¹H NMR (400 MHz, acetone-d₆) δ: 8.59 (d, 1H, J = 8.4 Hz, NH); 7.87-7.76 (m, 4H, CH_arom); 7.54-7.29 (m, 13H, CH_arom); 5.78 (s, 1H, PhCH); 5.23 (d, 1H, J = 10.0 Hz, H-1); 5.05 (d, 1H, J = 12.0 Hz, PhCH); 4.95 (d, 1H, J = 12.0 Hz, PhCH); 4.33 (dd, 1H, J = 4.8 Hz, 10.4 Hz, H-6); 4.19-4.10 (m, 2H, H-2, H-3); 3.93-3.85 (m, 2H, H-4, H-6); 3.60 (dt, 1H, J = 4.8 Hz, 10.4 Hz, H-5). ¹³C-APT NMR (100 MHz, acetone-d₆) δ: 162.4 (CD_TCA); 138.9, 137.0, 134.5 (C_arom); 132.6, 129.9, 129.6, 128.9, 128.7, 128.5, 128.5, 127.2, 127.1, 126.9, 126.8, 126.6 (CH_arom); 101.8 (PhCH); 88.1 (C-1); 82.6 (C-3); 80.1 (C-4); 75.0 (PhCH);
71.3 (C-5); 69.0 (C-6); 56.8 (C-2). IR (thin film) v: 2910, 1689, 1539, 1367, 1111, 1074, 1012, 964, 823, 748, 688, 661. HRMS: [M+NH₄]⁺ calculated for C₃₂H₃₂Cl₃N₃O₇S: 661.10920; found 661.11008.

6-azido hexyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (10)

To a solution of 15 (2.53 g, 5.0 mmol, 1.0 eq.) and 6-azido-hexan-1-ol (1.08 g, 7.5 mmol, 1.5 eq.) in CH₂Cl₂ (50 mL, 0.1M) were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (1.69 g, 7.5 mmol, 1.5 eq.) was added and the reaction mixture was cooled to -40 °C. TMSOTf (0.18 mL, 0.5 mmol, 0.1 eq.) was added and the reaction mixture was allowed to warm to -20 °C, and subsequently stirred at this temperature until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~2 hours). The reaction was quenched with NEt₃ and the mixture was diluted with EtOAc, washed with Na₂S₂O₅ (sat., aq., 1x), NaHCO₃ (sat., aq., 1x) and brine (1x), dried over MgSO₄, filtered and concentrated in vacuo. The title compound was obtained after column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) in 57% yield (1.52 g, 2.84 mmol). 1H NMR (400 MHz) δ: 7.52-7.49 (m, 2H, CH₆arom); 7.43-7.29 (m, 3H, CH₆arom); 7.08 (d, 1H, J = 7.2 Hz, NH); 5.55 (s, 1H, PhCH); 4.90 (d, 1H, J = 8.4 Hz, H-1); 4.37-4.30 (m, 2H, H-3, H-6); 3.90 (m, 1H, OCH₆hexyl); 3.79 (t, 1H, J = 10.0 Hz, H-6); 3.56-3.49 (m, 4H, H-2, H-4, H-5, OCH₂hexyl); 3.27 (t, 2H, J = 4.8 Hz, N₃CH₂hexyl); 3.16 (s, 1H, 3-0H); 1.59-1.57 (m, 4H, CH₂hexyl); 1.27 -1.25 (m, 4H, CH₂hexyl). ¹³C-APT NMR (100 MHz) δ: 162.3 (CO₂C₆); 137.0 (C₆arom); 129.5, 128.5, 126.4 (CH₂arom); 101.9 (PhCH); 100.1 (C-1); 92.6 (δCl); 81.7 (C-4); 70.3 (OCH₂hexyl); 69.6 (C-3); 68.6 (C-6); 66.2 (C-5); 59.6 (C-2); 51.4 (N₃CH₂hexyl); 29.5, 28.8, 26.6, 25.6 (CH₂hexyl). IR (thin film) v: 3325, 2937, 2872, 2096, 1691, 1531, 1373, 1111, 1028, 823. HRMS: [M+H]⁺ calculated for C₂₁H₂₂Cl₃N₃O₇S: 537.10689; found 537.10681.

Phenyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-1-thio-β-D-galactopyranoside (19)

To a solution of 18 (6.60 g, 15.9 mmol, 1.0 eq.) in MeCN (120 mL, 0.15M) were added benzaldehyde dimethylacetal (2.63 mL, 17.6 mmol, 1.1 eq.) and p-TsOH (0.30 g, 1.6 mmol, 0.1 eq.). The solution was heated to 50 °C and stirred on a rotary evaporator under reduced pressure (350 mbar), until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting
material (~2 hours). The reaction was quenched by addition of \( \text{NEt}_3 \) and the mixture was poured onto an ice-cold mixture of \( \text{EtO}/\text{heptane} \) (1:1 \( v/v \)). The solids were collected and purified by silica gel chromatography (PE: EtOAc, 9:1 \( \rightarrow \) 7:3) to give the title compound as a white solid in 76 \% yield. (6.08 g, 12.05 mmol). \(^1\)H NMR (CDCl\( _3 \), 400 MHz) \( \delta \): 7.69-7.67 (m, 2H, \( \text{CH}_{\text{arom}} \)); 7.45-7.26 (m, 8H, \( \text{CH}_{\text{arom}} \)); 6.75 (d, 1H, \( J = 7.6 \), \( \text{NH} \)); 5.57 (s, 1H, Ph\( \text{CH} \)); 5.10 (d, 1H, \( J = 10.0 \) Hz, H-1); 4.42 (dd, 1H, \( J = 1.6 \) Hz, 10.8 Hz, H-6); 4.26 (d, 1H, \( J = 2.8 \) Hz, H-4); 4.18 (dd, 1H, \( J = 3.2 \) Hz, 7.2 Hz, H-3); 4.06 (dd, 1H, \( J = 1.6 \) Hz, 11.6 Hz, H-6); 3.76 (dt, 1H, \( J = 7.6 \) Hz, 2.4 Hz, H-2); 3.61 (m, 1H, H-5); 2.60 (s, 1H, 3-OH). \(^{13}\)C-APT NMR (100 MHz) \( \delta \): 161.9 (\( \text{OD}_{\text{Cl}} \)); 139.4 (\( \text{CH}_{\text{arom}} \)); 132.6 (\( \text{C}_{\text{arom}} \)); 129.6, 129.2, 128.7, 128.0 (\( \text{CH}_{\text{arom}} \)); 127.3 (\( \text{C}_{\text{arom}} \)); 126.6 (\( \text{CH}_{\text{arom}} \)); 101.5 (Ph\( \text{CH} \)); 86.4 (C-1); 75.1 (C-4); 70.6 (C-3); 70.3 (C-5); 69.4 (C-6).

\( 6\text{-azidohexyl 4,6-O-benzylidene-2-deoxy-2-trichloroacetamido-}\beta\text{-D-galactopyranoside (11) } \)

To a solution of \( 19 \) (2.52 g, 5.0 mmol, 1.0 eq.) and 6-azidohexan-1-ol (1.08 g, 1.0 mmol, 1.5 eq.) in CH\(_2\)Cl\(_2\) (40 mL, 0.13 M) were added flame-dried 3Å MS. After ~30 minutes, NIS was added (1.68 g, 7.50 mmol, 1.5 eq.) and the mixture was cooled to -40 °C. Added was TMSOTf (0.18 mL, 1 mmol, 0.2 eq.) and the mixture was allowed to warm to -20 °C, after which it was stirred until TLC analysis (PE/EtOAc, 1:1 \( v/v \)) indicated complete conversion of the starting material (~2 hours). The reaction was quenched by addition of \( \text{NEt}_3 \) and the mixture was washed with Na\( \text{SO}_4 \) (sat, aq.), NaHCO\(_3\) (sat, aq.) and brine, dried over MgSO\(_4\) filtered and concentrated in \( \text{vacuo} \). Purification by column chromatography (PE/EtOAc, 9:1 \( \rightarrow \) 2:3 \( v/v \)) furnished the title compound in 67% yield (1.79 g, 3.3 mmol). \(^1\)H NMR (400 MHz) \( \delta \): 7.50-7.48 (m, 2H, \( \text{CH}_{\text{arom}} \)); 7.42-7.32 (m, 3H, \( \text{CH}_{\text{arom}} \)); 7.00 (d, 1H, \( J = 8.0 \) Hz, \( \text{NH} \)); 5.48 (s, 1H, Ph\( \text{CH} \)); 4.60 (d, 1H, \( J = 8.4 \) Hz, H-1); 4.27 (d, \( J = 12.4 \) Hz, H-6); 4.15 (d, 1H, \( J = 3.6 \) Hz, H-4); 4.12-4.04 (m, 2H, H-3, H-6); 3.91-3.80 (m, 2H, H-2, O\( \text{CH}\text{H}_\text{hexyl} \)); 3.50-3.36 (m, 2H, H-5, O\( \text{CH}\text{H}_\text{hexyl} \)); 3.22 (t, 2H, \( J = 7.2 \) Hz, \( \text{N}_3\text{CH}_2 \)); 2.94 (d, 1H, \( J = 9.6 \) Hz, \( \text{O} \text{H} \)); 1.57-1.51 (m, 4H, \( \text{CH}_2\text{H}_\text{hexyl} \)); 1.42-1.26 (m, 4H, \( \text{CH}_2\text{H}_\text{hexyl} \)). \(^{13}\)C-APT NMR (100 MHz) \( \delta \): 162.6 (\( \text{CO}_{\text{Cl}} \)); 137.5 (\( \text{C}_{\text{arom}} \)); 129.3, 128.3, 126.4 (\( \text{CH}_{\text{arom}} \)); 101.1 (Ph\( \text{CH} \)); 100.1 (C-1); 75.0 (C-4); 69.6 (O\( \text{CH}_2\text{H}_\text{hexyl} \)); 69.4 (C-3); 66.7 (C-6); 66.7 (C-5); 56.3 (C-2); 51.4 (N\(_3\)CH\(_2\text{H}_\text{hexyl} \)); 29.4, 28.8, 26.5, 25.6 (CH\(_2\text{H}_\text{hexyl} \)). IR (thin film) \( v \): 3325, 2937, 2859, 2094, 1689, 1528, 1168, 1053, 819. HRMS: \([\text{M}\text{Na}]^+\) calculated for C\(_{22}\)H\(_{27}\)Cl\(_3\)N\(_4\)NaO\(_6\) : 559.08884; found 559.08849.
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Phenyl 3,4-O-(2-propylidene)-1-thio-β-L-fucopyranoside (21)

To a mixture of 20 (1.0 g, 5.8 mmol, 1.0 eq.) in 2,2- dimethoxypropane (20 mL, 0.3M) was added p-TsOH (0.05 g, 0.26 mmol, 0.05 eq.). The mixture was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~24 hours). The solution was neutralized by addition of NEt₃ and concentrated in vacuo. The residue was purified by column chromatography (PE:EtOAc, 7:3) to give the title compound in 88% yield (1.51 g, 5.1 mmol). ¹H NMR (400 MHz) δ: 7.56-7.54 (m, 2H, CH₆); 7.32-7.26 (m, 3H, CH₆); 4.42 (d, 1H, J = 10.2 Hz, H-1); 4.06-4.03 (m, 2H, H-3, H-4); 3.85 (dd, 1H, J = 2.1 Hz, 6.4 Hz, H-5); 3.54 (dd, 1H, J = 6.8 Hz, 10.2 Hz, H-2); 2.82 (s, 1H, OMe); 1.41 (s, 6H, C(CH₃)₂); 1.34 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 132.5 (C_q,arom); 131.7, 128.5, 127.2 (CH₆); 109.3 (C(CH₃)₂); 86.8 (C-1); 79.1 (C-3); 75.8 (C-4); 72.0 (C-5); 70.7 (C-2); 27.7, 26.0 (C(CH₃)₂); 16.5 (C-6).

Phenyl 2-O-(2-naphthylmethyl)-3,4-O-(2-propylidene)-1-thio-β-L-fucopyranoside (22)

To a solution of 21 (0.9 g, 3.0 mmol, 1.0 eq.) in DMF (10 mL, 0.3M) was added, at 0 °C, NaH (60% in oil, 0.14 g, 3.6 mmol, 1.2 eq.) was slowly added and, after ~30 minutes, 2-(bromomethyl)naphthalene (3.6 mmol, 0.80 g, 1.2 eq.). After TLC analysis (toluene/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~5 hours). The reaction was quenched by addition of MeOH. The mixture was diluted with Et₂O (30 mL) and washed three times with H₂O, dried over MgSO₄, and concentrated in vacuo. The title compound was isolated after column chromatography (PE/EtOAc, 19:1 → 17:3 v/v) in 87% yield. (1.14 g, 2.6 mmol). ¹H NMR (400 MHz) δ: 7.83-7.79 (m, 4H, CH₆); 7.60-7.53 (m, 3H, CH₆); 7.48-7.44 (m, 2H, CH₆); 7.28-7.21 (m, 3H, CH₆); 4.97 (d, 1H, J= 11.6 Hz, PhCHH); 4.82 (d, 1H, J= 11.6 Hz, PhCHH); 4.60 (d, 1H, J= 9.6 Hz, H-1); 4.24 (t, 1H, J= 6.0 Hz, H-3); 4.02 (dd, 1H, J= 1.6 Hz, 5.6 Hz, H-4); 3.80 (q, 1H, J= 6.4 Hz, H-5); 3.54 (dd, 1H, J= 6.8 Hz, 10.0 Hz, H-2); 1.39-1.35 (m, 9H, H-6, C(CH₃)₂). ¹³C-APT NMR (100 MHz) δ: 135.5, 133.8, 133.3, 133.2 (C_q,arom); 132.2, 128.9, 128.1, 128.0, 127.8, 127.5, 127.2, 126.5, 126.1, 125.9 (CH₆); 109.8 (C(CH₃)₂); 86.2 (C-1); 80.0 (C-4); 78.0 (C-5); 76.5 (C-2); 73.6 (PhCH₂); 72.5 (C-3); 28.0, 26.5 (C_q(CH₃)₂); 17.0 (C-6).
**Phenyl 2-O-(2-naphthylmethyl)-1-thio-β-L-fucopyranoside (23)**

To a suspension of 22 in (1.70 g, 4.0 mmol, 1.0 eq.) in MeOH (20 mL, 0.2M) was added HCl (4M, 4.5 mL, aq.), turning the suspension into a clear solution. The reaction was stirred until TLC analysis (toluene/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~5 hours). The reaction was quenched with NET₃ (2 mL) and the mixture was concentrated *in vacuo*, during which a precipitate formed. The yellow mother liquor was purified using column chromatography (PE/EtOAc, 9:1 → 0:1). The combined purified fractions gave the title compound in 92% yield (1.44 g, 3.64 mmol, 92%). 1H NMR (400 MHz) δ: 7.80-7.74 (m, 4H, CH₉); 7.58-7.52 (m, 3H, CH₉); 7.48-7.44 (m, 2H, CH₉); 7.33-7.24 (m, 3H, CH₉); 5.06 (d, 1H, J = 11.2 Hz. PhCHH); 4.84 (d, 1H, J = 11.2 Hz, PhCHH); 4.60 (d, 1H, J = 9.2 Hz, H-1); 3.62-3.56 (m, 3H, H-2, H-3, H-4); 3.49 (q, 1H, J = 6.4 Hz, H-5); 2.81 (bs, 1H, O), 2.03 (bs, 1H, O); 1.27 (d, 3H, J = 6.4 Hz, H-6). ¹³C-APT NMR (100 MHz) δ: 135.6, 134.2, 133.4, 133.2 (C₉); 131.7, 129.1, 128.5, 128.1, 127.8, 127.5, 127.2, 126.3, 126.2, 126.2 (CH₉); 87.5 (C-1); 78.0 (C-3); 75.3 (ArCH2); 75.2 (C-2); 74.4 (C-5); 71.8 (C-4); 16.7 (C-6).

**Phenyl 2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-1-thio-β-L-fucopyranoside (12)**

To a solution of 23 (5.0 g, 12.6 mmol, 1.0 eq.) in DCM (40 mL, 0.3M) was added Piv₂O (7.7 mL, 37.8 mmol, 3 eq.), followed by Bi(O Tf)₃ (0.25 g, 0.38 mmol, 0.03 eq.) and the mixture was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~8 hours). The mixture was diluted with EtOAc and washed with NaHCO₃ (sat., aq., 2x) and brine (1x). The organic layers was filtered over Celite and dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was crystallized from iPrOH. The mother liquor was concentrated *in vacuo* and subjected to column chromatography (PE/Et₂O, 9:1 → 7:3 v/v) to give the product in a combined yield of 87% yield (6.19 g, 11.0 mmol). ¹H NMR (400 MHz) δ: 7.82-7.78 (m, 3H, CH₉); 7.72 (s, 1H, CH₉); 7.65-7.63, (m, 2H, CH₉); 7.47-7.44 (m, 3H, CH₉); 7.32-7.29 (m, 3H, CH₉); 5.30 (d, 1H, J = 3.2 Hz, H-4); 5.13 (dd, 1H, J = 3.2, 9.8 Hz, H-3); 4.95 (d, 1H, J = 10.4 Hz, PhCHH); 4.73-4.70 (m, 2H, H-1, PhCHH); 3.88 (q, 1H, J = 6.4 Hz, H-5); 3.78 (t, 1H, J = 9.6 Hz, H-2); 1.25 (s, 9H, C(CH₃)₃,Piv); 1.22 (d, 3H, J = 6.4 Hz, H-6); 1.11 (s, 9H, C(CH₃)₃). ¹³C-APT NMR (100 MHz) δ: 177.5 (C₉); 135.4, 133.4, 133.1, 132. (C₉); 132.5, 129.1, 128.2, 128.0, 127.8, 126.4, 126.2, 126.0, 125.7 (CH₉); 87.0 (C-1); 75.2 (C-3); 75.2 (PhCH₂); 74.8 (C-2); 73.5 (C-5); 70.6 (C-4); 39.2, 38.9 (C(CH₃)₃,Piv); 27.3, 27.1 (C(CH₃)₃,Piv); 16.5 (C-6). IR (thin film): 2976,
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1782, 1477, 1396, 1276, 1220, 1153, 1124, 1101, 1056, 1028, 900, 864, 812, 794, 769. HRMS: [M+H]^+ calculated for C_{33}H_{41}O_{6}S: 565.26184; found 565.26199.

*N-phenyl 2,2,2-trifluoroacetimidoyl 2-O(2-naphthylmethyl)-3,4-di-O-pivaloyl-α/β-L-fucopyranoside (13)*

![Structure of 13](image)

To a solution of 12 (0.36 g, 0.64 mmol, 1.0 eq.) in acetone/water (4:1 v/v, 10 mL, 0.06 M) was added N-bromosuccinimide (0.32 g, 1.5 mmol, 3.0 eq.) and the solution was stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material (~15 minutes). The reaction mixture was diluted with EtOAc and washed with Na_2S_2O_3 (sat., aq., 1x), NaHCO_3 (sat., aq., 1x) and brine (1x), dried over MgSO_4 filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc, 4:1 → 7:3 v/v) to give the title products (α/β 5:4) in 93% yield (0.22 g, 0.47 mmol). 1H NMR (400 MHz) δ: 7.83-7.73 (m, 30H, C_{H_{arom}}); 7.49-7.40 (m, 25H, C_{H_{arom}}); 5.41 (dd, 5H, J = 3.2 Hz, 7.6 Hz, H-3α); 5.27 (m, 10H, H-1α, H-4α); 5.22 (d, 4H, J = 3.2 Hz, H-4β); 5.07-5.02 (m, 8H, H-3β, PhCH(H)); 4.87-4.76 (m, 18H, H-1β, PhCH_2α, PhCH(H)); 4.36 (q, 5H, J = 6.4 Hz, H-5α); 3.90 (m, 9H, H-2α, OHβ); 3.79 (q, 4H, J = 6.8 Hz, H-5β); 3.63 (dd, 4H, J = 2.8 Hz, 7.6 Hz, H-2β); 3.32 (bs, 5H, OHA); 1.28 (s, 36H, C(CHR)_3,3,Pivβ); 1.24 (s, 45H, C(CHR)_3,3,Pivα); 1.20 (s, 45H, C(CHR)_3,3,Pivα); 1.14 (d, 12H, J = 6.8 Hz, H-6β); 1.08 (s, 36H, C(CHR)_3,3,Pivβ); 1.06 (d, 15H, J = 6.8 Hz, H-6α). 13C-APT NMR (100 MHz, CDCl3) δ: 177.7, 177.5 (CO\_\text{riv}); 135.6, 134.9, 133.3, 133.2, 133.1 (C_{arom}); 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 126.5, 126.4, 126.3, 126.2, 126.0, 125.8 (CH\_arom); 97.5 (C-1β); 91.8 (C-1α); 77.7 (C-2β); 74.8 (ar\_CH2); 73.6 (C-2a); 73.3 (PhCH2); 73.0 (C-3β); 71.2 (C-4a); 70.4 (C-4β); 70.3 (C-3a); 69.1 (C-5β); 65.2 (C-5a); 39.2 (\_q, Piv α/β); 27.3 (Me, Piv α/β); 16.2 (C-6β); 16.0 (C-6a). To a solution of 24 (0.21 g, 0.45 mmol, 1.0 eq.) in acetone (5 mL, 0.1M) were added Cs_2CO_3 (0.18 g, 0.55 mmol, 1.25 eq.), and *N*-phenyl 2,2,2-trifluoroacetimidoyl chloride (0.14 mL, 0.90 mmol, 2.0 eq.) and the suspension was stirred until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material (~4 hours). The mixture was diluted with EtOAc and washed with H_2O (1x), brine (2x), dried over MgSO_4 filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 19:1 → 17:3 v/v) furnished the title compounds (α/β 3:2) in 77% yield (0.23 g, 0.35 mmol). 1H NMR for the α-anomer (400 MHz) δ: 7.79-7.16 (m, 11H, CH\_arom); 6.68 (d, 1H, J = 8.0 Hz, CH\_arom); 6.52 (bs, 1H, H-1); 3.46 (dd, 1H, J = 3.2 Hz, 7.6 Hz, H-3); 5.36 (d, 1H, J = 2.0 Hz, H-4); 4.83 (d, 2H, J = 7.2 Hz, PhCH(H)); 4.28 (q, 1H, J = 6.4 Hz, H-5); 4.06 (dd, 1H, J = 3.6 Hz, 7.6 Hz).
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Hz, 7.2 Hz, H-2); 1.28 (s, 9H, C(CH$_3$)$_3$); 1.15 (s, 9H, C(CH$_3$)$_3$); 1.10 (d, 3H, J = 6.8 Hz, H-6). $^{13}$C-APT NMR (100 MHz) δ: 177.4, 177.2 (C$_{3n}$); 143.8, 135.2 (C$_{4n}$); 128.5, 128.3, 127.8, 126.8, 126.7, 126.4, 126.2, 125.8, 124.4, 120.8, 119.5 (CH$_{arom}$); 94.2 (C-1); 73.5 (PhCH$_2$); 73.1 (C-2); 72.9 (C-4); 70.6 (C-3); 68.2 (C-5). 39.8 (C(CH$_3$)$_3$); 27.4 (C(CH$_3$)$_3$); 16.0 (C-6). $^1$H NMR data for the β-anomer (400 MHz, 323 K) δ: 7.82-7.77 (m, 3H, CH$_{arom}$); 7.73 (s, 1H, CH$_{arom}$); 7.47-7.45 (m, 2H, CH$_{arom}$); 7.40 (m, 1H, arom); 7.28-7.24 (m, 2H, CH$_{arom}$); 7.09-7.07 (m, 2H, CH$_{arom}$); 6.81 (d, 1H, J = 8.0 Hz, CH$_{arom}$); 5.66 (bs, 1H, H-1); 5.23 (d, 1H, J = 2.4 Hz, H-4); 5.06 (bd, 1H, J = 8.8 Hz, H-3); 4.95 (d, 1H, J = 11.6 Hz, PhCH$_2$); 4.83 (d, 2H, J = 11.6, PhCH$_2$); 3.90 (t, 1H, J = 8.8 Hz, H-2); 3.71 (bs, 1H, H-5); 1.26 (s, 9H, C(CH$_3$)$_3$); 1.16 (d, 3H, J = 6.4 Hz, H-6); 1.13 (s, 9H, C(CH$_3$)$_3$). $^{13}$C-APT NMR (100 MHz) δ: 189.5 (CNP); 177.5 (COP); 143.8, 135.2 (C$_{3n}$); 128.5, 128.3, 127.8, 126.8, 126.7, 126.4, 126.2, 125.8, 124.4, 120.8, 119.5 (CH$_{arom}$); 97.7 (C-1); 75.9 (C-2); 75.2 (PhCH$_2$); 73.0 (C-3); 70.6 (C-5); 70.2 (C-4); 39.3 (C(CH$_3$)$_3$); 38.9 (C(CH$_3$)$_3$); 27.4 (C(CH$_3$)$_3$); 27.3 (C(CH$_3$)$_3$); 16.1 (C-6). IR (neat): 2974, 1734, 1598, 1479, 1458, 1323, 1282, 1207, 1138, 1120, 1029, 1001, 910, 694.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-(2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-a-L-fucopyranosyl)-2-trichloroacetamido-f-b-glucopyranoside (6)

To a solution of acceptor 10 (0.16 g, 0.31 mmol, 1.0 eq.) and donor 12 (0.26 g, 0.46 mmol, 1.5 eq.) in CH$_2$Cl$_2$ (5 mL, 0.06 M) were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (0.14 g, 0.61 mmol, 2.4 eq.) was added and the mixture was cooled to -40 °C, after which TMSOTf (6 µL, 0.03 mmol, 0.1 eq.) was added. The reaction mixture was allowed to warm to -20 °C and stirred until TLC analysis (PE/EtOAc, 4:1 v/v) indicated complete conversion of the starting material. The reaction was quenched by addition of NET$_3$ (0.1 mL), the mixture was diluted with EtOAc, washed with Na$_2$SO$_3$ (sat,aq.), NaHCO$_3$ (sat,aq.) and brine, dried over MgSO$_4$, filtered and concentrated in vacuo. After column chromatography (PE/EtOAc, 19:1 → 4:1 v/v), the title product was obtained in 86% yield (0.28 g, 0.28 mmol). $^1$H NMR (400 MHz) δ: 7.83-7.79 (m, 3H, CH$_{arom}$); 7.72 (s, 1H, CH$_{arom}$); 7.49-7.46 (m, 4H, CH$_{arom}$); 7.40-7.34 (m, 4H, CH$_{arom}$); 6.92 (d, 1H, J = 7.2 Hz, N=H); 5.53 (s, 1H, PhCH$_2$); 5.44 (dd, 1H, J = 3.2 Hz, 10.8 Hz, H-3'); 5.16-5.14 (m, 2H, H-1', H-4'); 5.06 (d, 1H, J = 8.4 Hz, H-1); 4.85 (d, 1H, J = 12.0 Hz, PhCH$_2$); 4.79 (d, 1H, J = 12.0 Hz, PhCH$_2$); 4.53 (t, 1H, J = 9.2 Hz, H-3); 4.40-4.32 (m, 2H, H-5', H-6); 3.91 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-2'); 3.85-3.78 (m, 2H, H-6, OCH$_3$hexyl); 3.68 (t, 1H, J = 9.2 Hz, H-4); 3.59-3.57 (m, 1H, H-5); 3.47-3.43
(m, 2H, H-2, OCH\textsubscript{hexyl}); 3.20 (t, 2H, \(J = 7.2\) Hz, N\textsubscript{3}CH\textsubscript{2,hexyl}); 1.58 (m, 4H, CH\textsubscript{2,hexyl}); 1.32-1.26 (m, 4H, CH\textsubscript{2,hexyl}); 1.14 (s, 9H, C(CH\textsubscript{3})\textsubscript{3,Piv}); 1.09 (s, 9H, C(CH\textsubscript{3})\textsubscript{3,Piv}); 0.50 (d, 3H, 6.4 Hz, H-6). \(^{13}\)C-APT NMR (100 MHz) \(\delta\): 177.7, 177.5 (\(\delta_{\text{D}}\)piv); 161.9 (\(\delta_{\text{D}}\)TCA); 137.1, 135.5, 133.3, 133.1 (C\textsubscript{arom}); 129.5, 128.5, 128.0, 127.8, 126.6, 126.5, 126.2, 125.9, 125.4 (CH\textsubscript{arom}); 102.4 (PhCH); 99.4 (C-1); 98.1 (C-1'); 80.6 (C-3); 74.1 (C-4); 73.9 (C-2'); 73.4 (PhCH\textsubscript{2}); 71.3 (C-4'); 70.8 (C-3'); 70.5 (OCH\textsubscript{2,hexyl}); 68.9 (C-6); 66.3 (C-5); 65.5 (C-5'); 60.5 (C-2); 51.5 (N\textsubscript{3}CH\textsubscript{2}), 39.1, 38.9 (C(CH\textsubscript{3})\textsubscript{3,Piv}); 29.5, 28.8, (CH\textsubscript{2,hexyl}), 27.3 (C(CH\textsubscript{3})\textsubscript{3,Piv}), 27.1, 25.7 (CH\textsubscript{2,hexyl}), 15.1 (C-6'). IR (thin film) \(\nu\): 2972, 2934, 2870, 2093, 1730, 1521, 1479, 1283, 1163, 1092, 1028, 910, 820. HRMS: [M+NH\textsubscript{4}]\textsuperscript{+} calculated for C\textsubscript{48}H\textsubscript{65}Cl\textsubscript{3}N\textsubscript{5}O\textsubscript{12}: 1010.36741; found 1010.36776.

**Byproduct 27a**

\(\text{\textsuperscript{1}H NMR (400 MHz) \(\delta\): 8.39 (d, 1H, \(J = 8.4\) Hz, CH\textsubscript{arom}); 7.82 (d, 1H, \(J = 7.6\) Hz, CH\textsubscript{arom}); 7.78 (d, 1H, \(J = 8.4\) Hz, CH\textsubscript{arom}); 7.54 (t, 1H, \(J = 1.6\) Hz, CH\textsubscript{arom}); 7.50 (t, 1H, \(J = 7.6\) Hz, CH\textsubscript{arom}); 7.70 (d, 1H, \(J = 8.4\) Hz, CH\textsubscript{arom}); 5.55 (d, 1H, \(J = 3.6\) Hz, H-1); 5.50 (dd, 1H, \(J = 3.2\) Hz, 3.6 Hz, H-3); 3.56 (t, 1H, \(J = 3.6\) Hz, H-4); 4.82 (d, 1H, \(J = 16.0\) Hz, CH\textsubscript{2}Nap); 4.20 (d, 1H, \(J = 16.0\) Hz, CH\textsubscript{2}Nap); 4.19 (dd, 2.8 Hz, 4.0 Hz, H-2); 4.00 (m, 1H, H-5); 1.40 (d, 3H, \(J = 6.4\) Hz, H-6); 1.28 (s, 9H, C(CH\textsubscript{3})\textsubscript{3,Piv}); 1.26 (s, 9H, C(CH\textsubscript{3})\textsubscript{3,Piv}). \(\text{\textsuperscript{13}C-APT NMR (100 MHz) \(\delta\): 177.6, 177.4 (\(\delta_{\text{D}}\)piv); 133.9, 133.0, 132.2 (C\textsubscript{arom}); 129.2, 128.2, 128.8, 128.4, 126.9, 126.2, 125.8, 125.4, 124.1, 122.2 (CH\textsubscript{arom}); 72.5 (C-2); 69.0 (C-4); 68.7 (C-5); 68.6 (C-3); 66.0 (PhCH\textsubscript{2}); 64.3 (C-1); 39.2 (C(CH\textsubscript{3})\textsubscript{3,Piv}); 39.0 (C(CH\textsubscript{3})\textsubscript{3,Piv}); 27.4 (C(CH\textsubscript{3})\textsubscript{3,Piv}); 27.3 (C(CH\textsubscript{3})\textsubscript{3,Piv}); 15.2 (C-6). IR (thin film) \(\nu\): 1734, 1598, 1282, 1207, 1120, 910, 694. HRMS: [M+H]\textsuperscript{+} calculated for C\textsubscript{72}H\textsubscript{75}O\textsubscript{16}: 555.24282; found 555.24254.**
To a solution of disaccharide 6 (67 mg, 0.068 mmol, 1.0 eq.) in CH₂Cl₂ (0.8 mL, 0.1 M) was added an aqueous phosphate buffer (pH 7, 0.1 M, 0.2 mL). Under vigorous stirring, DDQ (36 mg, 0.16 mmol, 2.3 eq.) was added and the mixture was stirred until TLC analysis (toluene/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~3 hours). The reaction mixture was diluted with EtOAc, washed with Na₂S₂O₃ (sat., aq.) and a 1:1 mixture of NaHCO₃ (sat., aq.) and Na₂CO₃ (sat., aq.) until a clear aqueous phase was obtained. The organic phase was dried over MgSO₄ filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 4:1 → 3:2 v/v) yielded the title compound in 83% yield (48 mg, 0.056 mmol). ¹H NMR (400 MHz) δ: 7.47-7.44 (m, 2H, CH₁arom); 7.36-7.33 (m, 3H, CH₂arom); 6.91 (d, 1H, J = 8.0 Hz, NH); 5.50 (s, 1H, PhCH); 5.16 (dd, 1H, J = 3.2 Hz, 7.2 Hz, H-3’); 5.04 (d, 1H, J = 2.0 Hz, H-4’); 4.98 (d, 1H, J = 4.0 Hz, H-1’); 4.95 (d, 1H, J = 8.4 Hz, H-1); 4.38 (dd, J = 4.8 Hz, 6 Hz, H-6); 4.33 (t, 1H, J = 9.2 Hz, H-4); 4.20 (q, 1H, J = 7.2 Hz, H-5’); 3.89-3.85 (m, 2H, H-2’, OCH₂hexyl); 3.81 (t, 1H, J = 10.0 Hz, H-6) 3.66-3.57 (m, 3H, H-2, H-3, H-5); 3.51-3.49 (m, 1H, OCH₃hexyl); 3.25 (t, 2H, J = 6.8 Hz, N₃CH₂); 1.59-1.57 (m, 4H, CH₂hexyl); 1.37-1.35 (m, 4H, CH₂hexyl); 1.15, 1.13 (s, 9H, C(CH₃)₃); 0.41 (d, 3H, J = 6.8 Hz, H-6’). ¹³C-APT NMR (100 MHz) δ: 178.7 177.6 (CO_Piv); 162.2 (CO_TCA); 137.0 (C₆arom): 129.6, 128.5, 126.6 (CH_arom), 102.7 (PhCH); 100.0 (C-1’); 99.8 (C-1); 80.2 (C-3); 75.5 (C-4); 71.1 (C-3’, C-4’); 70.4 (OCH₂hexyl); 68.8 (C-6); 67.6 (C-2’); 66.5 (C-5); 65.8 (C-5’); 59.8 (C-2); 51.5 (N₃CH₂hexyl); 39.2, 38.9 (C(CH₃)₃; 29.5, 28.8 (CH₂hexyl); 27.4, 27.2 (C(CH₃)₃; Piv); 26.6, 25.7 (CH₂hexyl); 15.0 (C-6’). IR (film) v: 3516, 3385, 2931, 2863, 2096, 1735, 1714, 1687, 1535, 1288, 1170, 1159, 1099, 1082, 1058. HRMS: [M+NH₄]⁺ calculated for C₃₇H₅₇Cl₃N₅O₁₂: 870.30437; found 870.30486.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-((2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-α-L-fucopyranosyl)-3,4-di-O-pivaloyl-α-L-fucopyranosyl)-2-trichloroacetamido-β-D-glucopyranoside (7)

To a solution of acceptor 29 (77 mg, 0.090 mmol, 1.0 eq.) and donor 12 (68 mg, 0.120 mmol, 1.3 eq.) in CH₂Cl₂ (1 mL, 0.1M), were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (0.027 g, 0.130 mmol, 1.4 eq.) and, after cooling to ~40 °C, TMSOTf (1.8 µL, 0.01 mmol, 0.1 eq.) and the mixture was allowed warm to ~20 °C and stirred at this temperature (~6 hours). The reaction was quenched by addition of NEt₃ (0.15 mL), the mixture diluted with EtOAc (20 mL), washed with Na₂S₂O₃ (sat., aq.), NaHCO₃ (sat., aq.) and brine, dried over MgSO₄, filtered and concentrated
in vacuo. The residue was purified by column chromatography (PE/EtOAc, 19:1 → 4:1) to afford the title compound in 33% yield (39 mg, 0.029 mmol). $^1$H NMR (400 MHz, 333 K) $\delta$: 7.82-7.32 (m, 13H, $CH_{arom}$ N$_H$); 5.54 (s, 1H, PhCH$_2$); 5.50 (dd, 1H, $J = 3.2$ Hz, 7.6 Hz, H-3''); 5.47 (d, 1H, $J = 2.8$ Hz, H-1'); 5.21 (dd, 1H, $J = 3.2$ Hz, 7.2 Hz, H-3'); 5.19-5.17 (m, 2H, H-4', H-4''); 4.81 (d, 1H, $J = 12.0$ Hz, PhCH$_2$H); 4.78 (d, 1H, $J = 3.2$ Hz, H-1''); 4.62 (d, 1H, $J = 12.0$ Hz, PhCH$_2$H); 4.54-4.48 (m, 2H, H-1, H-3); 4.37 (q, 1H, $J = 6.8$ Hz, H-5''); 4.30-4.27 (m, 2H, H-5'', H-6); 3.96 (dd, 1H, $J = 3.6$ Hz, 6.8 Hz, H-2''); 3.90 (dd, 1H, $J = 3.2$ Hz, 7.2 Hz, H-2''); 3.73-3.69 (m, 3H, H-2, H-6, OCH$_3$); 3.60 (m, 1H, $J = 9.2$ Hz, H-4); 3.38-3.35 (m, 1H, H-5); 3.26-3.24 (m, 3H, OCH$_3$, N$_3$CH$_2$H$_{b}$); 1.58-1.54 (m, 4H, $CH_2$); 1.35-1.32 (m, 4H, $CH_2$); 1.14 (s, 18H, C(CH$_3$)$_3$); 1.12 (s, 9H, C(CH$_3$)$_3$); 1.02 (s, 9H, C(CH$_3$)$_3$); 0.98 (d, 3H, $J = 6.4$ Hz, H-6''); 0.78 (d, 3H, $J = 6.0$ Hz, H-6'). $^{13}$C-APT NMR (100 MHz, 333 K) $\delta$: 177.9, 177.4, 177.3, 177.2 (C$_{O}$); 162.6 (C$_{O_{CA}}$); 137.4, 135.0, 133.3, 129.2 (C$_{arom}$); 128.9, 128.4, 128.0, 127.9, 127.2, 126.7, 126.5, 126.4, 125.7 (C$_{arom}$); 101.8 (PhCH); 100.6 (C-1'); 97.2 (C-1''); 96.3 (C-1''); 92.7 (C$_{Cl}$); 81.4 (C-4'); 74.1 (C-2', C-3); 73.8 (PhCH$_3$); 73.0 (C-2'); 71.5 (C-4''); 71.2 (C-4''); 70.2 (OCH$_2$); 69.8 (C-3', C-3''); 68.8 (C-6); 66.0 (C-5, C-5''); 65.4 (C-5'); 56.5 (C-2); 51.5 (N$_3$CH$_2$); 39.2, 39.1, 39.0, 38.8 (C(CH$_3$)$_3$); 29.8, 29.6 (CH$_2$); 28.8 (C(CH$_3$)$_3$); 27.4, 27.3 (CH$_2$); 15.7 (C-6', C-6''). IR (thin film) $\nu$: 2974, 2933, 2872, 2094, 1734, 1479, 1367, 1280, 1161, 1128, 1055, 964, 910. HRMS: [M+NH$_4$]$^+$ calculated for C$_{64}$H$_{91}$Cl$_3$N$_5$O$_{18}$: 1324.54114; found 1324.54131.

6-azidoxyethyl 4,6-O-benzylidene-2-deoxy-3-O-(2-O-(2-naphthylmethyl))-3,4-di-O-pivaloyl-α-L-fucopyranosyl)-2-trichloracetamido-β-D-galactopyranoside (8)

![Structure](image)

To a solution of acceptor 11 (0.16 g, 0.33 mmol, 1.0 eq.), donor 12 (0.20 g, 0.36 mmol, 1.2 eq.) in CH$_2$Cl$_2$ (3 mL, 0.1 M) were added 3Å molecular sieves. After ~30 minutes, NIS (90 mg, 0.39 mmol, 1.3 eq.) was added and the mixture was cooled to -40 °C. TMSOTf (5µL, 0.03 mmol, 0.1 eq.) was added and the reaction mixture was allowed to warm to -20 °C, and was stirred at this temperature until TLC analysis (PE/EtOAc, 7.3 v/v) indicated complete conversion of the starting material (~3 hours). The reaction was quenched by addition of NEt$_3$, the mixture was diluted with EtOAc, washed with Na$_2$S$_2$O$_3$ (sat., aq.), NaHCO$_3$ (sat., aq.) and brine, dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 9:1 → 3:1 v/v) furnished the title compound in 68% yield (0.20 g, 0.20 mmol). $^1$H NMR (400 MHz) $\delta$: 7.84-7.80
Chapter 7

(3H, CH<sub>arom</sub>); 7.72 (s, 1H, CH<sub>arom</sub>); 7.50-7.47 (m, 4H, CH<sub>arom</sub>); 7.39-7.35 (m, 3H, CH<sub>arom</sub>); 7.08 (d, 1H, J = 6.8 Hz, NH); 5.48 (s, 1H, PhCH); 5.37 (dd, 1H, J = 2.8 Hz, 10.8 Hz, H-3'); 5.15-5.13 (m, 2H, H-1, H-4'); 4.87 (d, 1H, J = 3.6 Hz, H-1'); 4.80 (d, 1H, J = 12.4 Hz, PhCH<sub>2</sub>); 4.70 (d, 1H, J = 12.4 Hz, PhCH<sub>2</sub>); 4.53 (dd, 1H, J = 3.6 Hz, 11.2 Hz, H-3); 4.35-4.30 (m, 3H, H-4, H-5', H-6); 4.04 (d, 1H, J = 11.2 Hz, H-6); 3.96-3.92 (m, 1H, OC<sub>H1b</sub>); 3.83-3.76 (m, 2H, H-2, H-2'); 3.51-3.48 (m, 2H, H-5, OCH<sub>H</sub>); 3.24 (t, 2H, J = 6.8 Hz, N<sub>3</sub>CH<sub>2</sub>); 1.61-1.56 (m, 4H, CH<sub>2</sub>b); 1.38-1.14 (m, 22H, CH<sub>2</sub>b); 0.79 (d, 3H, J = 6.4 Hz, H-6'). <sup>13</sup>C-APT NMR (100 MHz) δ: 177.6, 177.3 (CO<sub>aryl</sub>); 162.2 (CO<sub>TCA</sub>); 137.5, 135.5, 133.2, 133.2 (C<sub>aryl</sub>); 129.3, 128.5, 128.4, 127.9, 127.8, 127.3, 126.8, 126.4, 126.2 (CH<sub>aryl</sub>); 101.3 (PhCH); 98.6 (C-1); 92.7 (Cl<sub>3,TCA</sub>); 76.8 (C-3); 75.1 (C-4); 73.1 (PhCH<sub>2</sub>); 72.2 (C-2'); 71.1 (C-4'); 70.6 (C-3'); 69.9 (OCH<sub>2</sub>b); 69.4 (C-6); 66.4, 66.0 (C-5, C-5'); 55.4 (C-2); 51.5 (N<sub>3</sub>CH); 39.1, 38.9 (CH<sub>2</sub>b); 29.5, 28.9 (CH<sub>2</sub>b); 27.3, 27.2 (CH<sub>3</sub>); 26.6, 25.7 (CH<sub>2</sub>b); 16.0 (C-6'). IR (thin film) ν: 2972, 2936, 2870, 2093, 1732, 1695, 1531, 1479, 1368, 1283, 1161, 1128, 1088, 1051, 908, 822. HRMS: [M+Na]<sup>+</sup> calculated for C<sub>48</sub>H<sub>61</sub>Cl<sub>3</sub>N<sub>4</sub>NaO<sub>12</sub>: 1015.32280; found 1015.32229.

6-azidohexyl 4,6-O-benzylidene-2-deoxy-3-O-(3,4-di-O-pivaloyl-α-L-fucopyranosyl)-2-trichloroacetamido-β-D-galactopyranoside (30)

![Structure](image)

To a solution of 8 (90 mg, 0.091 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL, 0.1 M) was added aqueous phosphate buffer (pH 7, 0.1 M, 0.2 mL). Under vigorous stirring, DDQ (62 mg, 0.27 mmol, 3.0 eq.) was added and the mixture was stirred until TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~2.5 hours). The reaction mixture was diluted with EtOAc and washed with Na<sub>2</sub>SO<sub>4</sub> (sat.,aq.) and Na<sub>2</sub>CO<sub>3</sub> (sat.,aq.) until the water layer had become clear, dried over MgSO<sub>4</sub>, filtered and concentrated <em>in vacuo</em>. Purification by column chromatography (PE/EtOAc, 9:1 → 7:3 v/v) furnished the title compound in 81% yield (62 mg, 0.073 mmol). <sup>1</sup>H NMR (400 MHz) δ: 7.49-4.48 (m, 2H, CH<sub>aryl</sub>); 7.39-7.37 (m, 3H, CH<sub>aryl</sub>); 7.06 (d, 1H, J = 6.8 Hz, NH); 5.53 (s, 1H, PhCH); 5.18-5.03 (m, 4H, H-1, H-1', H-3', H-4'); 4.59 (dd, 1H, J = 3.2 Hz, 8.0 Hz, H-3); 4.42 (d, 1H, J = 3.2 Hz, H-4); 4.36-4.31 (m, 2H, H-5', H-6); 4.09 (d, 1H, J = 12.0 Hz, H-6); 3.97-3.81 (m, 3H, H-2, H-2', OCH<sub>H1b</sub>); 3.54-3.47 (m, 2H, H-5, OCH<sub>H</sub>); 3.25 (t, 2H, J = 6.8 Hz, N<sub>3</sub>CH<sub>2</sub>b); 1.92 (d, 1H, J = 11.2 Hz, O<sub>H</sub>); 1.60-1.56 (m, 4H, CH<sub>2</sub>b); 1.43-1.14 (m, 22H, CH<sub>2</sub>b); 0.97 (d, 3H, J = 6.4 Hz, H-6'). <sup>13</sup>C-APT NMR (100 MHz) δ: 178.6, 177.5 (CO<sub>aryl</sub>); 162.3
(CO<sub>TCA</sub>); 137.4 (C<sub>a</sub>); 129.4, 128.7, 128.5, 126.2 (CH<sub>a</sub>); 101.8 (C-1’); 101.4 (PhCH); 98.7 (C-1); 92.4 (CH<sub>2</sub>TCA); 77.0 (C-3); 75.3 (C-4); 71.0, 70.8 (C-3’, C-4’); 69.9 (OCH<sub>2</sub>); 69.4 (C-6); 68.0 (C-2’); 66.4, 66.3 (C-5, C-5’); 55.4 (C-2’); 51.5 (N<sub>4</sub>CH<sub>2</sub>); 39.2, 38.9 (C(CH)<sub>3</sub>Piv); 29.8, 29.5 (CH<sub>2</sub>); 27.4, 27.2 (CC<sub>3</sub>); 26.6, 25.7 (CH<sub>2</sub>); 16.2 (C-6’). IR (thin film) ν: 3524, 3329, 2972, 2936, 2349, 2326, 2095, 1736, 1713, 1694, 1539, 1479, 1369, 1287, 1157, 1126, 1086, 1059, 1009, 822. HRMS: [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>37</sub>H<sub>57</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>12</sub>: 870.30415; found 870.30471.

6-azidoethyl 4,6-O-benzylidene-2-deoxy-3-O-((2-O-(2-naphthylmethyl)-3,4-di-O-pivaloyl-α-L-fucopyranosyl)-3,4-di-O-pivaloyl-α-L-fucopyranosyl)-2-trichloroacetamido-β-D-galactopyranoside (9)

![Diagram of the molecule](attachment:image.png)

To a solution of acceptor 30 (40 mg, 0.047 mmol, 1.0 eq.), donor 12 (53 mg, 0.093 mmol, 2.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub>(0.25 mL, 0.2 M) were added flame-dried 3Å molecular sieves. After ~30 minutes, NIS (23 mg, 0.10 mmol, 2.2 eq.) were added and the mixture was cooled to -40 °C. TMSOTf (1.7 µL, 0.009 mmol, 0.2 eq.) was added and the mixture was allowed to warm to -20 °C and kept at this temperature (~5.5 hours). The reaction was quenched with NEt<sub>3</sub> (0.1 mL), diluted with EtOAc, washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq), NaHCO<sub>3</sub> (aq) and brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 19:1 → 3:1 v/v) furnished the title trisaccharide in 54% yield (33 mg, 0.025 mmol). 1H NMR (400 MHz) δ: 7.91-7.84 (m, 3H, CH<sub>a</sub>); 7.76-7.73 (m, 2H, CH<sub>a</sub>); 7.60-7.57 (m, 2H, CH<sub>a</sub>); 7.42-7.40 (m, 3H, CH<sub>a</sub>); 7.29-7.28 (m, 3H, NH, CH<sub>a</sub>); 5.63 (dd, 1H, J = 3.2 Hz, 10.4 Hz, H-3’); 5.24-5.16 (m, 4H, H-1’, H-3’, H-4’, H-4’’); 5.03 (s, 2H, H-1’’, PhCH); 4.78-4.70 (m, 2H, PhCH<sub>2</sub>); 4.48-4.41 (m, 2H, H-1, H-2); 4.32 (q, 1H, J = 6.4 Hz, H-5’); 4.23 (q, 1H, J = 6.8 Hz, H-5’); 3.93 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-2’); 3.88-3.81 (m, 3H, H-2’, H-6, OCH<sub>H</sub>); 3.64 (dd, 1H, J = 2.8 Hz, 10.4 Hz, H-3); 3.42-3.40 (m, 1H, OCH<sub>H</sub>); 3.29 (d, 1H, J = 2.4 Hz, H-4); 3.22 (t, 2H, J = 6.8 Hz, N<sub>2</sub>CH<sub>2</sub>); 2.99 (d, 1H, J = 11.2 Hz, H-6); 2.37 (s, 1H, H-5); 1.58-1.53 (m, 4H, CH<sub>2</sub>); 1.37-1.11 (m, 40H, CH<sub>2</sub>); 1.05 (d, 3H, J = 6.8 Hz, H-6’); 0.54 (d, 3H, J = 6.4 Hz, H-6’). 13C-FAPT NMR (100 MHz) δ: 178.6, 177.3, 177.1, 176.7 (CO<sub>Piv</sub>); 162.2 (CO<sub>TCA</sub>); 137.7, 134.3, 133.3, 133.2 (C<sub>a</sub>); 129.1, 128.8, 128.2, 128.1, 127.9, 127.9, 127.1, 126.4, 126.4 (CH<sub>a</sub>); 101.7 (C-1’); 101.1 (C-1’’); 100.9
(PhCH); 96.9 (C-1’); 93.1 (Cl_{3,TA}); 79.1 (C-2’); 78.1 (C-3); 76.0 (C-2’’); 74.3 (PhCH_{2}); 73.1 (C-4); 71.6, 71.5 (C-4’, C-4’’); 69.9 (C-3’); 68.9 (C-6, OCH_{2,hexyl}); 66.7 (C-5’); 66.2 (C-5); 65.6 (C-5’’); 51.8 (C-2); 51.5 (N_{3}CH_{2,hexyl}); 39.3, 39.2, 39.2, 38.7 (α(CH_{3})_{3,Ph}); 29.5, 28.9 (CH_{2,hexyl}); 27.5, 27.4, 27.4, 27.2 (C(CH_{3})_{3,Ph}); 26.6, 25.7 (CH_{2,hexyl}); 15.9, 15.5 (C-6’, C-6’’). IR (thin film) ν: 3366, 2974, 2935, 2096, 1736, 1283, 1163, 1129, 1076, 1054, 822. HRMS: [M+NH_{4}]^{+} calculated for C_{65}H_{97}Cl_{3}N_{5}O_{18}: 1324.54114; found 1324.54132.

6-aminohexyl 2-deoxy-3-O-(α-L-fucopyranosyl)-2-acetamido-β-D-glucopyranoside (2)

To a solution of disaccharide 6 (82 mg, 0.082 mmol, 1.0 eq.) in THF (1 mL, 0.1 M) was added KOH (1M, aq., 1.2 mL) and the mixture was stirred until TLC analysis (toluene/EtOAc, 4:1 v/v) indicated complete consumption of the starting material (~2 days). The mixture was neutralized by addition of HCl (1M, aq.), washed with NaHCO_{3} (sat, aq.) and brine, dried over MgSO_{4}, filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc, 4:1 → 3:2 v/v) yielded the saponified intermediate 31 in 57% yield (39 mg, 0.046 mmol). ^{1}H NMR (400 MHz) δ: 7.85-7.78 (m, 4H, CH_{arom}); 7.51-7.40 (m, 5H, CH_{arom}); 7.36-7.35 (m, 3H, CH_{arom}); 6.84 (d, 1H, J = 8.0 Hz, NH); 5.53 (s, 1H, PhCH); 5.30 (d, 1H, J = 3.6 Hz, H-1’); 4.86 (d, 1H, J = 12.0 Hz, PhCH=H); 4.74 (d, J = 11.6 Hz, PhCH\'-H); 4.68 (d, 1H, J = 8.0 Hz, H-1’); 4.38-4.23 (m, 2H, H-4, H-6); 4.20 (q, 1H, J = 6.4 Hz, H-5’); 4.00 (dd, 1H, J = 2.8 Hz, 6.8 Hz, H-3’); 3.86-3.67 (m, 5H, H-2, H-3, H-6, H-2’, OCH\_1,hexyl); 3.63 (1H, d, J = 2.4 Hz, H-4’); 3.50-3.44 (m, 1H, H-5’); 3.42-3.38 (m, 1H, OCH_{2,hexyl}); 3.22 (t, 2H, J = 6.8 Hz, N\_3CH_{2,hexyl}); 2.34 (s, 1H, O\_H); 2.19 (s, 1H, OH); 1.55-1.52 (m, 4H, CH\_2,hexyl); 1.33-1.30 (m, 4H, CH\_2,hexyl); 0.92 (d, 3H, J = 6.8 Hz, H-6’). ^{13}C-APT NMR (100 MHz) δ: 161.9 (CH_{TLC}); 137.2, 135.4, 133.3, 133.2, 129.4, 128.8, 128.1, 127.9, 127.0, 126.4, 126.4, 126.2, 125.8 (CH_{arom}); 101.9 (PhCH); 100.7 (C-1’); 96.6 (C-1’’); 92.6 (Cl_{3}); 80.7 (C-3); 77.1 (C-2’); 73.6 (C-4); 73.3 PhCH\_2); 71.8 (C-4’); 70.4 (CH\_2,hexyl); 69.5 (C-3’); 68.8 (C-6); 66.5 (C-5); 68.8 (C-5’’); 59.3 (C-2); 51.5 (N\_3CH_{2,hexyl}); 29.5, 28.8, 26.6, 25.7 (CH\_2,hexyl) 15.8 (C-6’). To a mixture of 31 (34 mg, 0.041 mmol, 1.0 eq.) in MeOH (4 mL, 0.01M) was added an aqueous phosphate buffer (pH 7, 0.1 M, 0.2 mL). The mixture was degassed with argon before addition of palladium on carbon (10% w/w Pd, 0.017 g). The black suspension was shaken for 24h in a Parr apparatus under H\_2 atmosphere (4 bar). The solution was filtered over a Whatman filter to remove the catalyst, and subsequently purified by gel-filtration (Sephadex LH-20, eluted with H\_2O). After lyophilization, the title compound was obtained in 34% yield (8.2 mg, 0.014 mmol). ^{1}H NMR (850 MHz, D\_2O) δ:
4.97 (d, 1H, $J = 4.3$ Hz, H-1’); 4.49 (d, 1H, $J = 8.5$ Hz, H-1); 4.30 (q, 1H, $J = 6.8$ Hz, H-5’); 3.91 (dd, 1H, $J = 1.7$ Hz, 10.2 Hz, H-6); 3.88 (dt, 1H, $J = 5.6$ Hz, 4.3 Hz, 1.7 Hz, OC$H_{Me}$); 3.79 (m, 3H, H-2, H-3’, H-4’); 3.73 (dd, 1H, $J = 5.9$ Hz, H-6); 3.67, (dd, 1H, $J = 3.4$ Hz, 6.8 Hz, H-2’); 3.61 (t, 1H, $J = 9.4$ Hz, H-3); 3.56 (dt, 1H, $J = 5.6$ Hz, 4.3 Hz, 1.7 Hz, OCH$H_{Me}$); 3.49 (t, 1H, $J = 10.2$ Hz, H-4); 3.44 (m, 1H, H-5); 2.97 (t, 2H, $J = 7.7$ Hz, NCH$_2$); 2.0 (s, 3H, CH$_3$); 1.63 (m, 2H, CH$_2$); 1.55 (m, 2H, CH$_2$); 1.35 (m, 4H, CH$_2$); 1.14 (d, 3H, $J = 5.9$ Hz, H-6’). $^{13}$C-APT NMR (D$_2$O, 212 MHz) δ: 175.4 (CO$_{Na}$); 101.9 (C-1’); 100.9 (C-1’); 81.3 (C-3); 76.8 (C-5); 72.8 (C-4’); 71.4 (OCH$_2$); 70.5 (C-3’); 69.5 (C-4); 68.9 (C-2’); 67.8 (C-5’); 61.7 (C-2); 29.3, 27.6, 26.2, 25.6 (CH$_2$); 23.2 (CH$_3$); 16.1 (C-6’). HRMS: [M+H]$^+$ calculated for C$_{20}$H$_{39}$N$_2$O$_{10}$: 467.25992; found 467.25987.

6-aminoethoxy-2-deoxy-3-O-(α-L-fucopyranosyl)-2-acetamido-β-D-galactopyranoside (4)

To a solution of 8 (0.112 g, 0.114 mmol, 1.0 eq.) in THF (0.7 mL, 0.15 M) was added KOH (1M, aq., 0.3 mL) and the mixture was stirred until TLC analysis (toluene/EtOAc, 7:3 v/v) indicated complete conversion of the starting material (~18 hours). The reaction was neutralized with HCl (1M, aq.), the mixture was diluted with EtOAc, washed with Na$_2$CO$_3$ (sat., aq.) and brine, dried over MgSO$_4$ filtered and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc, 7:3 → 1:1 v/v) furnished the saponified intermediate 32 in 61% yield (57 mg, 0.069 mmol). $^1$H NMR (400 MHz) δ: 7.85-7.81 (m, 3H, CH$_{arom}$); 7.75 (s, 1H, CH$_{arom}$); 7.51-7.44 (m, 5H, CH$_{arom}$); 7.38-7.34 (m, 3H, CH$_{arom}$); 7.05 (d, 1H, $J = 6.8$ Hz, NH); 5.52 (s, 1H, PhCH); 5.05 (d, 1H, $J = 3.6$ Hz, H-1’); 4.98 (d, 1H, $J = 8.4$ Hz, H-1); 4.88 (d, 1H, $J = 12.8$ Hz, PhCH); 4.64 (d, 1H, $J = 12.8$ Hz, PhCH); 4.41-4.30 (m, 3H, H-3, H-4, H-6); 4.17 (q, 1H, $J = 6.8$ Hz, H-5’); 4.06 (d, 1H, $J = 11.6$ Hz, H-6); 4.00-3.80 (m, 3H, H-2, H-3’, OCH$_3$); 3.66-3.63 (m, 2H, H-2’, H-4’); 3.53-3.45 (m, H-5, OCH$_3$); 3.24 (t, 2H, N$_2$CH$_2$); 2.38 (bs, 1H, OH); 2.23 (bs, 1H, OH); 1.59-1.56 (m, 4H, CH$_2$); 1.38-1.31 (m, 4H, CH$_2$); 1.10 (d, 3H, $J = 6.4$ Hz, H-6’). $^{13}$C-APT NMR (100 MHz) δ: 162.2 (C$_{TCA}$); 137.8, 135.4, 133.3, 133.2 (C$_{arom}$); 129.2, 128.8, 128.7, 128.4, 128.1, 127.9, 127.3, 126.6, 126.4, 126.2, 125.9 (CH$_{arom}$); 101.1 (PHCH); 99.2 (C-1’); 98.9 (C-1); 92.7 (C$_{Cl, TCA}$); 76.9 (C-3); 75.6 (C-2’); 75.2 (C-4); 72.8 (PhCH$_2$); 71.5 (C-4’); 69.9 (OCH$_2$); 69.4 (C-6); 69.4 (C-3’); 66.5, 66.4 (C-5, C-5’); 55.2 (C-2’); 51.5 (N$_2$CH$_2$); 29.5, 28.9, 26.7, 25.7 (CH$_2$); 16.4 (C-6’). To a solution of 32 (57 mg, 0.069 mmol, 1.0 eq.) in THF and tBuOH (3:1 v/v, 0.4 mL) was added an aqueous phosphate buffer (pH 7, 0.1 M, 0.3 mL). The mixture was degassed by sparging with argon before addition of palladium on carbon (10% w/w, 11 g). The mixture was purged with H$_2$.
and subsequently stirred under a H₂ atmosphere at 4 bar for 2 days in a Parr apparatus, after which it was filtered over a Whatmann filter and concentrated in vacuo. The residue was purified by gel filtration (Sephadex LH-20, MeOH/H₂O 9:1 v/v) and lyophilized to furnish the disaccharide in 67% yield (12.7 mg, 0.046 mmol). ¹H NMR (600 MHz, D₂O) δ: 4.95 (d, 1H, J = 4.2 Hz, H-1’); 4.46 (d, 1H, J = 8.4 Hz, H-1); 4.09 (q, 1H, J = 6.6 Hz, H-5’); 3.97-3.85 (m, 4H, H-2, H-4’, H-5, OCH₂hexyl); 3.78-3.70 (m, 4H, H-3, H-4’, H-6); 3.66-3.64 (m, 2H, H-2’, H-5); 3.59-3.55 (1H, OCH₂hexyl); 2.95 (t, 2H, J = 7.8 Hz, NCH₂hexyl); 1.98 (s, 3H, CH₃NH₂); 1.64-1.52 (m, 4H, CH₂hexyl); 1.38-1.24 (m, 4H, CH₂hexyl); 1.16 (d, 3H, J = 6.6 Hz, H-6’). ¹³C-APT NMR (151 MHz) δ: 175.8 (C₂H₂N₂O₄); 126.4, 126.3 (C-1, C-1’); 79.6 (C-3); 75.9 (C-2’ or C-4); 72.6 (C-4’); 71.3 (OCH₂hexyl); 70.3 (C-3’); 69.4 (C-2’ or C-4); 68.9 (C-5); 68.4 (C-5’); 52.5 (C-2); 40.6 (NCH₂hexyl); 30.5, 27.7, 26.3, 25.5 (CH₂hexyl); 23.2 (CH₃NH₂); 16.2 (C-6’). IR (thin film) ν: 3363, 2939, 1651, 1542, 1512, 1072, 1033, 917. HRMS: [M+Na]⁺ calculated for C₂₀H₂₈N₂NaO₁₀: 489.24187; found 489.24180.
References


Chapter 8

Summary and future directions

The glycosylation reaction is the central reaction in carbohydrate chemistry and despite the big advancements made in the past few decades, it remains relatively poorly understood, in terms of yield and stereoselectivity. Understanding the glycosylation reaction necessitates investigation of its reactive species. While covalent intermediates, such as anomeric triflates, are readily observable using low-temperature NMR, the nature of the oxocarbenium ion is elusive, owing to its highly ephemeral nature. Chapter 2 provides an overview of research into the nature and reactivity of oxocarbenium ions, from model glycosylation studies to computational methods.
Also provided are literature examples of oligosaccharide syntheses, which (likely) involve oxocarbenium ion intermediates.

**Chapter 3** describes a detailed mechanistic study of the reactivity and selectivity of 2-azido-2-deoxyfucosyl (FucN₃) donors in glycosylations. Whereas a lot is known on glycosylations with 1-fucosyl donors, the behavior of FucN₃ donors is relatively unexplored. Six donors, protected with benzyl (Bn), benzyol (Bz) or tert-butylidemethoxysilyl groups were synthesized and reacted with a panel of acceptors, varying in nucleophilicity by virtue of electronic and/or steric effects. The results showed that Bn or TBS protecting groups on the FucN₃ donor increased the α-selectivity of glycosylations compared to Bz groups. The nature of the acceptor was shown to be of decisive influence on glycosylation outcome; weakly nucleophilic acceptors, including secondary carbohydrate acceptors, led to α-selective glycosylations, while highly nucleophilic acceptors, such as ethanol, preferentially gave the β-products. Low-temperature NMR studies were carried out on Bn- and Bz-protected FucN₃ donors to identify reactive intermediates. Activation at -80 °C led to formation of two species in each case, which were identified as glycosyl triflates and -oxosulphonium triflates.

Based on the results of the NMR experiments and the model glycosylations, a mechanistic picture was drawn. Reactive acceptors can react with the detected covalent species, which predominantly have an α-anomeric configuration, in a Sn2-like fashion to lead to the β-glycosides. The covalent intermediates are in equilibrium with dissociated intermediates, i.e. oxocarbenium ion-like species. Less reactive acceptors react preferentially with these transient, but more reactive species. The conformation of the oxocarbenium ion and the trajectory of the incoming acceptor determine the stereoselectivity (or lack thereof) of the addition reaction. For the FucN₃ oxocarbenium ion nucleophilic attack of the acceptor on a 4H₃-oxocarbenium ion-like species can account for the formation of the α-linked products. The nature of the protecting groups influences the stability of the reactive intermediates, and thus the outcome of the glycosylations; electron-withdrawing Bz groups destabilize the electron-depleted oxocarbenium ions, shifting the equilibrium between the covalent intermediates and the oxocarbenium ion like species to the side of the former reactive species. This leads to enhanced β-selectivity for reactions involving the benzyolated FucN₃ donors. The higher stability of the covalent triflates and oxosulphonium triflates of the Bz-protected FucN₃ donors compared to their Bn-protected counterparts is reflected by the increased temperature of decomposition of these species.

The equilibrium between the covalent (i.e. anomic triflates) and ionic (i.e. oxocarbenium ions) species is influenced by the nature of the counterion.¹ To investigate whether non-nucleophilic anions can influence the selectivity of glycosylations of dibenzylated FucN₃ donor 1 with cyclohexanol (CyOH), a set of glycosylations was performed using N-iodosuccinimide (NIS).

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in combination with different silver(I) salts (Table 1). While TfOH (entry 1) and AgOTf (entry 2) gave moderately β-selective glycosylations, activation of 1 with the hexafluorophosphate (PF$_6^-$, entry 3) and hexafluoroantimoniate (SbF$_6^-$, entry 4) salts of Ag(I) resulted in highly β-selective glycosylations (α/β 1:10). This indicates that under these conditions the generation of oxocarbenium ions is less likely. Possibly, direct substitution of the activated selenodonor (charged with the relatively weak activating systems) can account for the observed selectivity. Conversely, the glycosylation of 1 with 2,2,2-trifluoroethanol (F$_3$EtOH) gave adduct 3 with a strong preference for the α-anomer (entries 5-7). These results are in line with the results obtained in Chapter 3 and point to the involvement of an oxocarbenium ion like reactive intermediate as the product forming species.

**Table 1:** Glycosylations of 1 with NIS/Ag(I) conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>activator</th>
<th>product</th>
<th>yield (α/β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cy</td>
<td>TfOH</td>
<td>2</td>
<td>82% (1:4)</td>
</tr>
<tr>
<td>2</td>
<td>Cy</td>
<td>AgOTf</td>
<td>2</td>
<td>73% (1:6)</td>
</tr>
<tr>
<td>3</td>
<td>Cy</td>
<td>AgPF$_6^-$</td>
<td>2</td>
<td>73% (1:10)</td>
</tr>
<tr>
<td>4</td>
<td>Cy</td>
<td>AgSbF$_6$</td>
<td>2</td>
<td>71% (1:10)</td>
</tr>
<tr>
<td>5</td>
<td>F$_3$Et</td>
<td>TfOH</td>
<td>3</td>
<td>33% (19:1)</td>
</tr>
<tr>
<td>6</td>
<td>F$_3$Et</td>
<td>AgOTf</td>
<td>3</td>
<td>60% (13:1)</td>
</tr>
<tr>
<td>7</td>
<td>F$_3$Et</td>
<td>AgSbF$_6$</td>
<td>3</td>
<td>31% (19:1)</td>
</tr>
</tbody>
</table>

In Chapter 4, the synthesis of the *Staphylococcus aureus* type 5 Capsular Polysaccharide repeating unit is described. This complex trisaccharide contains two $\alpha$-acetyl fucosamine units and an $\beta$-$\alpha$-acetyl mannosonic acid residue. The repeating unit was built up using FucN$_3$ donors, building upon the reactivity study described in the previous Chapter. The $\beta$-glycosidic linkage between the first $\alpha$-FucN$_3$ and a 5-aminopentyl spacer was installed using a FucN$_3$ donor bearing electron-withdrawing Bz group and the use of Et$_2$O as a solvent. These conditions led to increased $\beta$-selectivity, likely due to the decreased polarity of the medium, which disfavors formation of charged intermediates such as oxocarbenium ions. The stereoselectivity of the formation of the
linkage between the two FucN₃ units strongly depended on the protecting groups on the donor, in agreement with the results in Chapter 3. The best result was obtained with a di-TBS protected FucN₃ donor, which gave the disaccharide in 76% yield and with complete α-selectivity. Installation of the final β-mannuronic acid linkage bond was achieved using a large excess of donor (4.0 eq.) and led to the protected trisaccharide in 75% yield and complete β-selectivity. During deprotection of the trisaccharide, an undesired lactamization occurred between the mannuronic acid’s C-5 carboxylate and C-2 amine, during a two-step reduction/acetylation of the azides. This side-reaction could be circumvented by a one-step transformation of the azides into acetamides, using thioacetic acid (AcSH).

The *S. aureus* type 8 Capsular Polysaccharide is structurally very similar to the type 5 Capsular Polysaccharide, also containing two *N*-acetylfucosamine and one *N*-acetylmannosaminuronic acid units.²,³ Preliminary synthetic studies towards the repeating unit trisaccharide are shown in Scheme 1. The first synthetic challenge was the glycosylation of the d-FucN₃ unit 4 with 5-aminopentanol linker 13, to install the desired α-linkage. The use of additives was explored to modulate the outcome of the glycosylation reaction.⁴ Bennett and co-workers reported that the use of excess Bu₄NI in Ph₂SO/Tf₂O-mediated glycosylations dramatically increases the α-selectivity in comparison to unmodified conditions.⁵ The addition of excess iodide anion to the reaction mixture leads to establishment of an equilibrium between anomic α- and a β-iodides, with the latter being displaced in an S₄N₂-like fashion by the acceptor.⁶,⁷ Applying these conditions to the coupling of 4 and 13 provided the desired α-linked d-FucN₃ unit 5 in high yield with an α/β ratio of 7:1.¹ Removal of the TBS group allowed separation of the two anomers, yielding acceptor 6 in 63% yield. Synthesis of the disaccharide, using L-4 as the donor and unmodified Ph₂SO/Tf₂O conditions, gave the disaccharide 7 in 73% yield with an α/β ratio of 7:1. Again, removal of the temporary TBS protecting group allowed separation of the anomers, yielding the disaccharide acceptor 8 in 71% yield. The final glycosylation between 8 and known ManN₃A donor 14 proceeded slowly. This was unexpected because of the perceived higher reactivity of acceptor 8 compared to the acceptor used in the synthesis of the *S. aureus* type 5 CPS trisaccharide. Even when an excess of donor was used, the trisaccharide 9 was obtained in modest yield (but complete β-selectivity). Further studies are needed to elucidate the origin of the poor performance of this donor/acceptor couple.

Initial studies towards the deprotection of 9 were also conducted. Saponification using H₂O₂ and KOH in THF/H₂O proceeded uneventfully to give the free uronic acid 10. Acetylation of the non-reducing end C-4-OH using Ac₂O/pyridine did not lead to desired product 11. Instead, α,β-unsaturated carboxylic acid 12 was isolated as the main product. This byproduct likely arises

¹The addition of *N*-methylmaleimide was necessary to scavenge nucleophilic byproducts. See ref. (5).
from the transient formation of a mixed anhydride at the uronic acid functionality, which renders the proton at C-5 sufficiently acidic for a β-elimination to occur. Other acetylation methods using metal triflate catalysts, such as Sc(OTf)₃ or Bi(OTf)₃, were unsuccessful. To circumvent this elimination reaction an alternative protecting group for the mannuronic carboxylic acid should be used, that does not require the use of basic deprotection conditions. The use of an allyl or tert-butyl ester could be explored. Another way to circumvent this problem would be to use a non-oxidized mannosazide donor, although this represents a significant revision of the synthetic route.

**Scheme 1:** Synthesis of the protected S. aureus type 8 CPS trisaccharide.

Reagents and conditions: a) PhSO₂, TTBP, N-methylmaleimide, 3Å MS, CH₂Cl₂, Ti₂O -80 → -70 °C; Bu₄NI, -80 °C; 13, 1,4-dioxane, -80 °C → rT (85%, α/β 7:1); b) Bu₄NF, THF (63% for 6; 71% for 8); c) Ph₂SO, TTBP, 3Å MS, CH₂Cl₂, Ti₂O, -80 °C → -70 °C; 1-4, -80 → -50 °C (73%, α/β 7:1); d) 14 TBSOTf, 3Å MS, CH₂Cl₂, -80 → -55 °C (34%); e) H₂O₂, KOH, THF, H₂O (74%); f) Ac₂O, pyridine.

**Chapter 5** describes a study into the reactivity and selectivity of 2-azidogalacturonic acid (GalNAc) donors. The α-selective glycosylation of galacturonic acid (GalA) donors can be effected by use of galacturonic acid-3,6-lactone donors. This lactone has been successfully used in the synthesis of oligosaccharides related to *Streptococcus pneumoniae*. Further studies have shown
Chapter 3. The ‘normal’ GalN

that the high α-selectivity of the GalA lactone arises from a covalent, axial triflate, which is
displaced in a S$_\text{N}2$-like fashion to give the α-product. In order to allow α-glycosylation of the
analogous 2-azidogalacturonic acid (GalN$_3$A) donors, the corresponding lactone has been
synthesized. This donor was generated after regioselective protection of the C-4-OH, which was
achieved by a reductive opening of a suitably protected 4,6-O-para-methoxybenzylidene masked
selenophenyl galactosazide synthon. An ensuing tandem oxidation/cyclization provided the
lactone donor. Its performance as a glycosylating agent was assessed by comparing it with a
conformationally non-restricted GalN$_3$A donor, using a range of acceptors, similar to that in
Chapter 3. The ‘normal’ GalN$_3$A donor gave highly β-selective condensation reactions with most
acceptors. The corresponding lactone was moderately α-selective, but the selectivity strongly
depended on the reactivity of the acceptor, with more reactive acceptors providing better α-selectivity.
The moderate selectivity obtained with carbohydrate acceptors unfortunately limits it use in
oligosaccharide synthesis. The GalA lactone was also assessed with the set of acceptors. In accordance
with previous reports, this lactone donor provided highly α-selective glycosylation reactions. Activation
of the GalN$_3$A lactone donor led to the formation of an axial triflate as indicated by low temperature
NMR experiments. The triflate derived from the GalN$_3$A lactone donor proved to be less stable than the
anomeric triflate formed from the GalA lactone, which provides an explanation for the diminished
stereoselectivity observed with the GalN$_3$A lactone donors.

The choice of solvent can be critical in a glycosylation reaction. Some solvents, such as nitrile
or ether solvents, have well-known ‘participating’ effects which affect the stereoselective outcome of
glycosylations.$^{4,13,14}$ A solvent’s polarity can also influence the reaction outcome - more polar solvents
can better accommodate charge separation, and thus an S$_\text{N}1$-like reaction, than nonpolar solvents. In
order to promote an S$_\text{N}2$-like pathway in glycosylations with GalN$_3$A lactones, the use of nonpolar
solvents, such as toluene and 1,1,2-trichloroethylene, should be investigated. The latter was shown by
Woerpel and co-workers to be superior in promoting S$_\text{N}2$-like reactions.$^{15}$

In Chapter 6, the synthesis of the *Staphylococcus aureus* Strain M Capsular Polysaccharide
repeating unit is described. This trisaccharide consists of two α-linked N-acetyl galactosaminuronic acid
(GalNAcA) and an α-linked N-acetylfucosamine unit. The α-GalNAcA glycosidic linkages were
installed using a non-oxidized 4,6-O-di-tert-butylsilylene (DTBS)-protected 2-azidogalactosyl donor
(GalN$_3$). This donor was shown to be completely α-selective using a variety of acceptors. Post-
glycosylation removal of the DTBS group, followed by selective oxidation of the primary position to
the corresponding uronic acids gave the GalNAcA mono- and disaccharides. Installation of the final α-
FucN$_3$ linkage, using an α-directing protecting group pattern (Chapter 3), gave the protected
trisaccharide in good yield. The orthogonal TBS group on the FucN$_3$ 3-O position makes this approach
amenable to higher oligosaccharides. Stepwise deprotection gave the target trisaccharide repeating unit.

The proposed synthesis of a taurine-bearing hexasaccharide is shown in Scheme 2A, as Hash and co-workers have determined that the Strain M CPS bears a taurine residue for every 4th GalNAcA.\(^1\) Elongation of trisaccharide 15 by glycosylation with donor 16, followed by desilylation, oxidation and methylation leads to tetrasaccharide 17. Elongation to the pentamer can be achieved following another glycosylation-deprotection-oxidation sequence to give uronic acid 18. The installation of the taurine residue, which is likely affixed to a GalNAcA residue by an amide bond,\(^1\) can be accomplished with protected taurine 19, bearing a trichloroethyl protecting group on the sulfonate moiety,\(^1\) using carbodiimide coupling chemistry.\(^1\) Installation of the second FucN\(_3\) unit using donor 4, followed by deprotection then yields the hexasaccharide 22. A more convergent approach to the synthesize higher oligosaccharides may involve block glycosylations involving di- or trisaccharide donors. To allow for the installation of the required glycosidic linkages the donor building blocks cannot be equipped with a GalNAcA donor moiety, and therefore the use of GalN\(_3\)A-FucN\(_3\) disaccharide 23 in combination with the highly \(\alpha\)-selective GalN\(_3\) building block 16, or the use of the GalN\(_3\)A-GalN\(_3\)A-FucN\(_3\) trisaccharide 24 is projected.

Chapter 7 describes the synthesis of glycan fragments related to the parasite *Schistosoma mansoni*, the causative pathogen of schistosomiasis. This parasite expresses a complex array of glycans, and antibodies raised against *S. mansoni* are glycan-specific. The general structure of these glycans possess a backbone consisting of \(N\)-acetylglucosamine (GlcNAc) and \(N\)-acetylgalactosamine (GalNAc) units, decorated with fucosyl chains. The fucose units are interconnected by \(\alpha-(1,2)\)-glycosidic linkages, and the fucosyl chains are thought to be a major epitope in anti-glycan antibodies against *S. mansoni*. In order to explore the chemistry to synthesize a library of *S. mansoni* glycan fragments, spacer-equipped Fuc-GlcNAc and Fuc-GalNAc disaccharides were synthesized. The GlcNAc and GalNAc acceptors were synthesized by glycosylations of the corresponding C-3-O unprotected donors with a spacer alcohol. The disaccharides were synthesized with a 2-O-naphthylmethyl-protected fucosyl donor, using NIS/TMSOTf-mediated glycosylations. A two-step deprotection, consisting of a saponification, followed by hydrogenation, delivered the conjugation-ready disaccharides. Additionally, the two corresponding protected difucosyl trisaccharides were synthesized, albeit in modest yield. Applying the same deprotection sequence of the Fuc-Fuc-GlcNAc trisaccharide was unsuccessful, implying that a revision of the protecting group strategy may be necessary.
Scheme 2: A) Proposed synthesis of a S. aureus Strain M CPS hexasaccharide bearing a taurine unit. B) Possible disaccharide (23) and trisaccharide (24) building blocks for synthesis of S. aureus Strain M oligosaccharides.
The synthesized described in Chapter 7 can be elaborated upon in order to synthesize a large library of *S. mansoni* glycan fragments (Figure 1A). The length and composition of the GlcNAc/GalNAc backbone can be varied, as well as the number and length of fucosyl branches. The library can be assembled with a limited set of appropriately protected monosaccharide building blocks (Figure 1B). The sites of elongation on the GlcNAc and GalNAc monosaccharides are protected with temporary protecting groups; Fmoc groups in 25, 26, 28 and 30 for the backbone sequence, and Lev groups on 26, 29 and 30 on the branching sites. The fucosyl donor can be modified, so that the sterically bulky pivaloyl esters on the C-3-O- and C-4-O-positions are replaced by benzyl ethers, giving donor 31. Due to the decreased size and electron-depleted nature of the donor, the efficiency of constructing the fucosyl chains may be enhanced. It has been shown that fucosyl donors, bearing only benzyl protecting groups are strongly α-selective.\(^\text{19,20}\) This was corroborated by the results obtained in Chapter 3, in which benzyl-protected 2-azidofucosyl donors were more α-selective than their benzoyl-protected analogs. Additionally, the presence of the benzyl ethers eliminates the need for a saponification step, meaning that the oligosaccharides can be deprotected in one step by catalytic hydrogenation.
Chapter 8

**Experimental**

**General procedures**

All reactions were carried out in oven-dried glassware (85 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under an atmosphere of argon (balloon). Solvents for reactions were of reagent grade and stored over 4Å molecular sieves (3Å for CH₂Cl₂, MeOH and MeCN), except pyridine and DMF. NET₃ was stored over KOH pellets. TF₂O used in glycosylations was dried over P₂O₅ (~3 hours), followed by distillation, and stored in a Schlenk flask at -20 °C. All other chemicals were used as received. Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, with fluorescent indicator); visualization was carried out by irradiation with UV light (λ: 254 nm), followed by spraying with 20% H₂SO₄ in EtOH (w/v) or Hanessian’s stain ((NH₄)₆Mo₇O₂₄.4H₂O, 25 g/L; (NH₄)₄Ce(SO₄)₄.2H₂O, 10 g/L; in 10% acq. H₂SO₄). Column chromatography was carried out using silica gel (Screening Devices, 0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20 (GE Healthcare). NMR spectra were recorded on Bruker AV-400, DMX-400 or AV-500 instruments. Chemical shifts (δ) are reported in ppm relative to Me₄Si (δ: 0.00 ppm) or residual solvent signals. NMR spectra were recorded at ambient temperature, and samples were prepared in CDCl₃ unless noted otherwise. ¹³CAPT spectra are ¹H decoupled. Structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants of anomeric carbon atoms (JH1,C1) were determined using HMBC-GATED experiments. Infrared spectra were recorded with a Shimadzu FTIR 8300 instrument. Wavenumbers (ν) are reported in cm⁻¹. LC-MS analyses were performed on a Thermo Finnigan Surveyor HPLC system equipped with a Gemini C-18 column (250 x 10 mm), connected to a Thermo Finnigan LCQ Advantage Max Ion-trap mass spectrometer with (ESI⁺). Eluents used were MeCN, H₂O with addition of TFA (0.1%). HRMS spectra were recorded on a Thermo Finnigan LCQ Orbitrap instrument.

**General procedure for the glycosylation of 1 with CyOH or F₂EtOH using NIS/Ag(I) salts**

To a solution of donor 1 (51 mg, 0.10 mmol, 1.0 eq.) in CH₂Cl₂ (5 mL, 0.02 M) were added a solution of CyOH or 2,2,2-trifluoroethanol (0.3 mL of a 0.5 M solution in CH₂Cl₂, 1.5 eq.) and flame-dried 3Å molecular sieves. After ~30 minutes, the reaction mixture was cooled to -50 °C, and under a stream of N₂ gas, were added NIS (38 mg, 0.15 mmol, 1.5 eq.) and the activator (0.15 mmol, 1.5 eq.) and the maroon reaction mixture was stirred at -50 °C until TLC analysis (PE/EtOAc, 9:1 v/v) indicated complete conversion of the starting material (~20 minutes). The reaction was quenched by addition of NEt₃ (0.1 mL), filtered over a pad of celite, washed with Na₂S₂O₅ (sat.,aq.) and brine,
Summary and future directions

dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography delivered the corresponding O-glycoside(s).

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-4-O-benzyl-2-deoxy-α-D-fucopyranoside (6)

To a stirred solution of donor 4 (0.80 g, 1.5 mmol, 1.0 eq.), Ph₂SO (0.39 g, 1.95 mmol, 1.3 eq.), N-methylmaleimide (0.25 g, 2.25 mmol, 1.5 eq.) and TTBP (0.93 g, 3.75 mmol, 2.5 eq.) in CH₂Cl₂ (30 mL, 0.05 M) were added, flame-dried, rod-shaped 3Å MS. After cooling to -80 °C, Tf₂O (0.33 mL, 1.95 mmol, 1.3 eq.) was added and the mixture was warmed to -70 °C, after which TLC analysis (toluene/EtOAc, 9:1 v/v) indicated complete activation of the donor. The mixture was re-cooled to -80 °C, after which Bu₄NI (as a 1M solution in CH₂Cl₂, 7.5 mL, 7.5 mmol, 5.0 eq.) was added, upon which the reaction mixture assumed a maroon color. After 5 minutes at -80 °C, a solution of acceptor 13 (as a 0.5 M solution in CH₂Cl₂/1,4-dioxane (1:1 v/v), 3.0 mmol, 2.0 eq.) and the mixture was allowed to warm to room temperature. After stirring for ~18 hours, TLC analysis (toluene/EtOAc, 9:1 v/v) indicated complete conversion of the starting material. The reaction was quenched by addition of NEt₃, diluted with CH₂Cl₂, filtered over a pad of celite, washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (toluene/Et₂O, 1:0 → 9:1) delivered the products (α/β ~7:1) as an inseparable mixture in 85% yield (0.90 g, 1.27 mmol). To a stirred solution of 5 (0.90 g, 1.27 mmol, 1.0 eq.) in THF (4 mL, 0.3 M) was added Bu₄NF (as a 1M solution in THF, 2.5 mL, 2.5 mmol, 2.0 eq.). After TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete consumption of the starting material (~2 hours) the reaction was quenched by addition of NaHCO₃ (s,S), and extracted with EtOAc (3x). The combined organic phases were washed (H₂O 1x, brine 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 19:1 → 4:1 v/v) delivered the title compound as an oil in 63% yield (0.47 g, 0.80 mmol). ¹H NMR (500 MHz, 323 K) δ: 7.36-7.20 (m, 15H, CH₃arom); 5.17 (s, 2H, PhCH₂); 4.82 (d, 1H, J = 3.0 Hz, H-1); 4.77 (d, 1H, J = 11.5 Hz, PhCHH); 4.70 (d, 1H, J = 11.5 Hz, PhCHH); 4.48 (s, 2H, PhCH₂); 4.03 (bd, 1H, J = 8.0 Hz, H-3); 3.92 (q, 1H, J = 6.0 Hz, H-5); 3.62-3.56 (m, 2H, H-4, OCHH₃pentyl); 3.15-3.39 (m, H-2, OCHH₃pentyl); 3.24 (bs, NC₃H₅pentyl); 1.54 (bs, 4H, CH₂pentyl); 1.31 (bs, 2H, CH₂pentyl); 1.24 (d, 3H, J = 6.5 Hz, H-6). ¹³C APT NMR (125 MHz, 323 K) δ: 139.0, 136.9 (C₃arom); 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 127.2, 126.9 (CH₃arom); 98.2 (C-1); 80.3 (C-4); 76.1 (PhCH₂); 68.5 (C-3); 68.1 (OCH₂pentyl); 67.2 (PhCH₂); 66.5 (C-5); 61.0 (C-2); 50.5 (NCH₂pentyl); 29.1, 23.4 (CH₂pentyl); 16.7 (C-
6). $^{13}$C-GATED NMR (125 MHz, 323 K) δ: 98.2 (d, $J = 170$ Hz, C-1). IR (thin film) v: 2934, 2108, 1690, 1454, 1421, 1229, 1171, 1067. HRMS: [M+H]$^+$ calculated for C$_{33}$H$_{41}$N$_4$O$_6$: 589.30206; found 589.30218.

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-3-O-(2-azido-4-O-benzyl-2-deoxy-α-L-fucopyranosyl)-4-O-benzyl-2-deoxy-α-D-fucopyranoside (8)

![Chemical Structure](image)

To a stirred solution of donor L-4 (0.43 g, 0.80 mmol, 2.0 eq.), Ph$_2$SO (0.16 g, 0.80 mmol, 2.0 eq.) and TTBP (0.40 g, 1.60 mmol, 4.0 eq.) in CH$_2$Cl$_2$ (8 mL, 0.1 M relative to donor) were added flame-dried, rod-shaped 3Å MS. After stirring for ~30 minutes, the mixture was cooled to -80 °C and Tf$_2$O (0.13 mL, 0.80 mmol, 2.0 eq.) was added. After allowing the mixture to warm to -70 °C, the mixture was re-cooled to -80 °C and a solution of acceptor 6 (0.40 mmol, 1.0 eq., in 0.8 mL CH$_2$Cl$_2$, dried by triple co-evaporation with toluene) was added via the wall of the flask. The mixture was warmed to -60 °C, left at this temperature for 15 minutes, and the reaction was quenched by addition of NEt$_3$. The bright yellow solution was filtered over celite, washed (brine, 1x), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by size-exclusion chromatography (CH$_2$Cl$_2$/MeOH, 1:1 v/v) yielded a mixture of disaccharides 7 (α/β ~ 7:1) in 73% yield (0.27 g, 0.28 mmol). The disaccharides 7 was dissolved in dry THF (1.4 mL, 0.2 M), and Bu$_4$N$^+$ (as 1M solution in THF, 0.34 mL, 0.34 mmol, 1.2 eq.) was added. After 4 hours, TLC analysis (PE/EtOAc, 7:3 v/v) indicated complete consumption of the starting material and the appearance of two more polar products. The reaction was quenched by addition of sat. aq. NaHCO$_3$, the mixture was extracted (CH$_2$Cl$_2$, 3x), the combined organics were washed (H$_2$O, 1x; brine, 1x), dried over MgSO$_4$ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc, 19:1 → 4:1 v/v) furnished the title disaccharide in 71% yield (0.17 g, 0.20 mmol). $^1$H NMR (500 MHz, 323 K) δ: 7.36-7.19 (m, 20H, CH$_{arom}$); 5.20 (d, 1H, $J = 4.0$ Hz, H-1'); 5.17 (bs, 2H, PhCH$_2$); 4.89 (d, 1H, $J = 3.0$ Hz, H-1); 4.79 (d, 1H, $J = 11.5$ Hz, PhCH$_2$H); 4.75 (d, 1H, $J = 11.5$ Hz, PhCH$_2$H); 4.72-4.67 (m, 2H, 2x PhCH$_2$H); 4.49 (bs, 2H, PhCH$_3$); 4.04 (dd, 1H, $J = 3.0$ Hz, 10.8 Hz, H-3); 3.93-3.90 (m, 3H, H-3', H-5, H-5'); 3.84 (dd, 1H, $J = 3.5$ Hz, 10.5 Hz, H-2); 3.59 (bs, 1H, OCH$_{pentyl}$); 3.55 (d, 1H, $J = 2.5$ Hz, H-4'); 3.54 5(dd, 1H, $J = 3.5$ Hz, 10.8 Hz, H-2'); 3.41 (bs, 1H, OCH$_{pentyl}$); 3.24 (bs, 2H, NCH$_2$$_{pentyl}$); 1.55 (bs, 4H, 2x CH$_2$$_{pentyl}$); 1.31 (bs, 2H, CH$_2$$_{pentyl}$); 1.23-1.20 (m, 6H, H-6, H-6'). $^{13}$C-APT NMR (125 MHz, 323 K) δ: 138.4, 138.0, 137.9, 136.9 (CH$_{arom}$); 128.6, 128.5, 128.4, 128.4, 128.1, 128.1, 127.9, 127.6, 127.7, 127.6, 127.3 (CH$_{arom}$); 99.8 (C-1'); 98.2 (C-1); 80.4 (C-4); 79.8 (C-4'); 218
76.2 (C-3); 76.0, 75.5 (PhCH₂); 68.7 (C-3', C-5 or C-5'); 68.2 (OCH₂penty1); 67.4 (C-3’, C-5 or C-5’); 67.2 (PhCH₂); 67.0 (C-3’, C-5 or C-5’); 61.0 (C-2’); 60.4 (C-2’); 29.1 (2x CH₂penty1); 23.4 (CH₂penty1); 16.8, 16.8 (C-6, C-6’). ¹³C-GATED NMR (125 Hz) δ: 99.8 (d, J = 170 Hz, C-1’); 98.2 (d, J = 168 Hz, C-1). IR (thin film) ν: 2936, 2106, 1694, 1454, 1422, 1092, 1036, 1028. HRMS: [M+NH₄]⁺ calculated for C₄₆H₅₅N₆O₉: 867.43995; found 867.44027.

5-(benzyl(benzyloxy carbonyl) amino) penty1 2-azido-3-O-(2-azido-4-O-benzyl-2-deoxy-3-O-(methyl 4-O-acetyl-2-azido-3-O-benzyl-2-deoxy-β-D mannopyranosiduronate)-α-L-fucopyranosyl)-4-O-benzyl-2-deoxy-α-D-fucopyranoside (9)

To a solution of acceptor 8 (0.144 g, 0.17 mmol, 1.0 eq.), donor 14 (0.364 g, 0.68 mmol, 4.0 eq.) in CH₂Cl₂ (1.7 mL, 0.1 M) were added flame-dried, rod-shaped 3Å molecular sieves. After ~30 minutes, the mixture was cooled to -80 °C and TBSOTf (32 μL, 0.14 mmol, 0.8 eq.) was added. The reaction mixture was allowed to warm to -55 °C and stirred at this temperature for 6 hours. The reaction was quenched by addition of NEt₃ (0.1 mL), filtered over a bed of celite, washed (brine, 1x), dried over MgSO₄, filtered and concentrated in vacuo. Purification by size-exclusion chromatography (CH₂Cl₂/Methanol, 1:1 v/v) and column chromatography (toluene/EtOAc, 1:0 → 9:1 v/v) delivered the title trisaccharide in 34% yield (70 mg, 0.058 mmol). ¹H NMR (500 MHz, 323 K) δ: 7.37-7.21 (m, 25H, CH₆arom); 5.39 (t, 1H, J = 9.0 Hz, H₄’’); 5.32 (d, 1H, J = 3.5 Hz, H-1’); 5.16 (bs, 2H, PhCH₂); 4.88 (d, 1H, 2.5 Hz, H-1); 4.82 (d, 1H, J = 11.5 Hz, PhCHH); 4.70-4.60 (m, 5H, PhCH₂); 4.58 (s, 1H, H-1’’); 4.84 (bs, 2H, PhCH₂); 4.20 (dd, 1H, J = 2.5 Hz, 10.5 Hz, H-3’); 4.04 (dd, 1H, J = 2.0 Hz, 10.5 Hz, H-3); 3.92-3.89 (m, 2H, H-5, H-5’); 3.85-3.78 (m, 3H, H-2, H-2’, H-5’’); 3.62 (s, 3H, OCH₃); 3.61-3.54 (m, 5H, H-2”, H-3’’); H-4, H-4’, OCH₃penty1; 3.41 (bs, 1H, OCH₃penty1); 3.23 (bs, 2H, NCH₂penty1); 2.00 (s, 3H, CH₂Ac); 1.55-1.27 (m, 6H, CH₂penty1); 1.23-1.16 (m, 6H, H-6, H-6’). ¹³C-APT NMR (125 MHz, 323 K) δ: 169.1, 167.1 (C-6”, COAc); 138.6, 138.1, 138.0, 137.3, 136.9 (Cₙarom); 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.6, 127.6, 127.2 (CH₆arom); 99.7 (C-1’); 98.1 (C-1’); 97.5 (C-1’’); 30.0 (C-3’’); 77.2, 77.2 (C-4, C-4’); 76.7 (C-3); 75.5 (C-3’); 75.4, 75.2 (PhCH₂); 73.8 (C-5’’); 72.4 (PhCH₂); 68.2 (C-4’); 68.2 (OCH₂penty1); 67.5 (C-5 or C-5’); 67.1 (PhCH₂); 66.9 (C-5 or C-5’); 61.5 (C-2’’); 60.2, 58.9 (C-2, C-2’); 52.5 (OCH₃); 50.5 (PhCH₂); 29.6, 29.1, 23.4 (CH₂penty1); 20.6 (CH₃Ac); 16.8, 16.6 (C-6, C-6’). IR (thin film) ν: 2924,
Chapter 8

2110, 1751, 1697, 1231, 1094, 1047. HRMS: [M+\text{NH}_4]^+ calculated for C_{62}H_{76}N_{11}O_{15}: 1214.55169; found 1214.55237.

5-(benzyl(benzylxoycarbonyl)amino)pentyl 2-azido-3-O-(2-azido-4-O-benzyl-2-deoxy-3-O-(2-azido-3-O-benzyl-2-deoxy-\beta-D-mannopyranosiduronate)-\alpha-L-fucopyranosyl)-4-O-benzyl-2-deoxy-\alpha-D-fucopyranoside (10)

![Chemical Structure Image]

To a solution of 9 (40 mg, 0.033 mmol, 1.0 eq.) in THF (1.4 mL, 0.02 M) was added a freshly prepared solution of KOOH (0.3 mL, prepared by adding H$_2$O$_2$ (0.56 mL, 30% aq. w/w) to 4.4 mL 0.5 M aq. KOH solution) and the mixture was stirred overnight at room temperature, after which TLC analysis (toluene/EtOAc/AcOH, 10:10:1 v/v/v) indicated complete conversion of the starting material. The reaction mixture was acidified to pH 3 with HCl (1M, aq.) and subsequently extracted with CH$_2$Cl$_2$ (5x). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. Purification by column chromatography (toluene/EtOAc/AcOH, 16:4:1 → 10:10:1 v/v/v) furnished the title compound in 74% yield (29 mg, 0.025 mmol).

$^1$H NMR (500 MHz, CD$_3$CN + acetic acid-d$_4$) δ: 7.39-7.23 (m, 25H, CH$_{\text{arom}}$); 5.17 (d, 1H, $J = 4.0$ Hz, H-1'); 5.12 (s, 2H, PhCH$_2$); 4.90-4.84 (m, 3H, H-1', H-1'', PhCH$_{\text{H}}$); 4.75 (d, 1H, $J = 11.5$ Hz, PhCH$_{\text{H}}$); 4.69 (s, 2H, PhCH$_2$); 4.60 (d, 1H, $J = 11.5$ Hz, PhCH$_{\text{H}}$); 4.47 (s, 2H, PhCH$_2$); 4.23 (dd, 1H, $J = 3.0$ Hz, 11.0 Hz, H-3'); 4.02-3.93 (m, 3H, H-3, H-5, H-5'''); 3.90 (d, 1H, $J = 3.0$ Hz, H-2'''); 3.85 (t, 1H, $J = 9.5$ Hz, H-4'''); 3.79 (d, $J = 2.0$ Hz, H-4''); 3.76-3.73 (m, 2H, H-2, H-5'''); 3.66 (d, 1H, $J = 2.0$ Hz, H-4'); 3.60-3.56 (m, 3H, H-2', H-3'', OC\text{CH}_2\text{pen})$; 3.39 (bs, 1H, OC\text{CH}_2\text{pen}); 3.24 (t, 2H, $J = 7.5$ Hz, NCH$_2$\text{pen}); 1.53-1.50 (m, 4H, CH$_2$\text{pen}); 1.31-1.27 (m, 2H, CH$_2$\text{pen}); 1.19-1.16 (m, 6H, H-6, H-6'). $^{13}$C-APT NMR (125 MHz, CD$_3$CN + acetic acid-d$_4$) δ: 174.4 (C-6''); 140.1, 139.7, 139.5, 139.2 (C$_{\text{arom}}$); 129.6, 129.6, 129.5, 129.3, 129.3, 129.1, 129.0, 128.9, 128.9, 128.8, 128.3 (CH$_{\text{arom}}$); 101.0 (C-1'); 99.0, 98.2 (C-1, C-1''); 81.2 (C-3''); 80.9 (C-4'); 78.5 (C-4'); 76.9 (C-3); 76.8 (PhCH$_2$); 76.6 (C-5'''); 76.5 (PhCH$_2$); 76.1 (C-3''); 73.3 (PhCH$_2$); 68.9 (C-4'''); 68.9 (PhCH$_2$); 68.4, 68.0 (C-5, C-5''); 68.0 (OC\text{CH}_2\text{pen}); 63.0 (C-2'''); 61.8 (C-2); 59.6 (C-2'); 30.0, 24.3 (CH$_2$\text{pen}); 17.2, 17.1 (C-6, C-6').
**Summary and future directions**

*a,β*-unsaturated uronic acid 12

![Structure](attachment:image.png)

To a solution of 10 (29 mg, 0.025 mmol, 1.0 eq.) in pyridine (1 mL, 0.025 M) was added Ac₂O (0.2 mL, 2.1 mmol, 84 eq.) and the mixture was stirred until TLC analysis (toluene/EtOAc/AcOH, 12:8:1 v/v/v) indicated complete conversion of the starting material (several days). The reaction was quenched by slow addition of H₂O (~0.5 mL) and after ~1 hour, the reaction mixture was extracted with CH₂Cl₂ (6x). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to furnish 13 as the main product. ¹H NMR (500 MHz, 323 K, CD₃CN + acetic acid-d₄) δ: 7.38-7.23 (m, 25H, CH₇aron); 6.02 (d, 1H, J = 2.5 Hz, H-4’); 5.19 (d, 1H, J = 3.5 Hz, H-1’); 5.11 (s, 2H, PhCH₂); 4.89-4.82 (m, 3H, H-1, H-1”, PhCH₃H); 4.65 (s, 2H, PhCH₂); 4.63-4.60 (m, 2H, PhCH₂); 4.52 (dd, 1H, J = 3.0 Hz, 5.0 Hz, H-3”); 4.47 (s, 3H, PhCH₃); 4.28 (dd, 1H, J = 3.0 Hz, 11.0 Hz, H-3’); 4.00-3.93 (m, 3H, H-3, H-5, H-5’); 3.80 (d, 1H, J = 5.0 Hz, H-2”); 3.81 (d, 1H, J = 2.5 Hz, H-4’); 3.75-3.70 (m, 2H, H-2, H-2’); 3.66 (d, 1H, J = 2.5 Hz, H-4); 3.58 (bs, 1H, OC₇H₃pently); 3.39 (bs, 1H, OCH₇pently); 3.24 (t, 2H, J = 7.5 Hz, NCH₂pently); 1.55-1.51 (m, 4H, CH₇pently); 1.34-1.27 (m, 2H, CH₂pently); 1.18-1.15 (m, 6H, H-6, H-6’).

**References**

Chapter 8


Samenvatting

De glycosylering, de reactie waarbij een binding wordt gevormd tussen twee suikermoleculen, is de centrale reactie in de koolhydraatchemie. Ondanks de grote vorderingen die in het veld gemaakt zijn in de afgelopen decennia, is deze reactie nog altijd relatief slecht begrepen, en de opbrengst en selectiviteit is vaak slecht in de hand te houden. Om het mechanisme van de glycosyleringsreactie te kunnen begrijpen, is het identificeren van reactieve intermediairen essentieel. Covalente intermediairen, zoals glycosyl triflaten, zijn relatief stabiel en kunnen onderzocht worden met behulp van kernspinresonantie (NMR) experimenten bij lage temperatures. Het oxocarbenium ion, waarvan het bestaan al decennia verondersteld wordt, is echter nog nooit in organische media aangetoond, vanwege de zeer korte levensduur. In Hoofdstuk 2 wordt een overzicht gegeven van het onderzoek naar oxocarbenium ionen. Computationele en experimentele studies worden besproken, evenals literatuurvoorbeelden van syntheses van oligosacchariden, waarbij oxocarbenium ionen (waarschijnlijk) bij betrokken zijn.

In Hoofdstuk 3 wordt de reactiviteit en selectiviteit van 2-azido-2-deoxyfucosyl (FucN₃) donoren beschreven. Er is gekeken naar de invloed van beschermgroepen (benzyl, benzoïl en tert-butyl(dimethyl)silyl) op de 3-O en 4-O posities, en naar de invloed van de reactiviteit van de acceptor. Het onderzoek wees uit dat acceptoren een doorslaggevende rol spelen in de selectiviteit van de glycosyleringen. Acceptoren met een lage nucleofiliciteit (zoals 2,2,2-trifluorethanol, maar ook secundaire mannosides) gaven hoge α-selectiviteiten, terwijl reactieve acceptoren (ethanol, 2-fluorethanol, cyclohexanol) overwegend lage selectiviteit gaven. De beschermgroepen op de donoren zijn eveneens van invloed op de uitkomst van de glycosyleringen. NMR experimenten bij lage temperatuur gaven de vorming aan van twee reactieve intermediairen; glycosyl α-triflaten en -oxosulfoniumtriflaten. Acceptoren met hoge reactiviteit kunnen direct reageren met deze covalente deeltjes in een substitutie op het anomere centrum (dat wil zeggen, met een hoog S₉₂-karakter). De hoge α-selectiviteiten kunnen worden verklaard door de aanwezigheid van oxocarbeniumionen; deze deeltjes zijn in evenwicht met de covalente deeltjes (die dienen als een ‘reservoir’); door hun zeer hoge reactiviteit is hun levensduur echter zo kort dat ze niet waarneembaar zijn op de NMR tijdschaal. Acceptoren van lage reactiviteit reageren liever met deze oxocarbeniumionen, die het α-product geven door te reageren met de meest gunstige conformatie van het oxocarbenium via de energetisch meest gunstige overgangstoestand. De rol van de beschermgroepen op de donoren beïnvloedt de stabilititeit van de reactieve intermediairen; elektron-zuigende benzylofgroepen destabiliseren de extra ladingsscheiding die ontstaat als een covalent deeltje dissociërt, hierdoor zijn benzyolbeschermde FucN₃ donoren over het algemeen minder α-selectief dan donoren die beschermd
zijn met benzyl- of TBS-groepen. Dit gegeven wordt ondersteund door de hogere ontledingstemperatuur van benzoil-beschermde FucN₃ triflaten, gevolgd met NMR.

In Hoofdstuk 4 wordt de synthese van de repeterende eenheid van de *Staphylococcus aureus* type 5 Capsulaire Polysaccharide beschreven. Dit complexe trisaccharide bestaat uit twee *N*-acetylfucosamine (FucNAc) eenheden, die met elkaar verbonden kunnen worden door gebruik te maken van de hierboven beschreven FucN₃ donoren, en een zeldzame *N*-acetylmannosaminuronzuur (ManNAcA) die met een β-glycosidische binding verbonden is met de centrale FucNAc, die een zeldzame *O*-acetyl modificatie bevat. Er werd gekozen voor een strategie waarbij de ManNAcA donor, met de *N*-acetyl groep bechermd als een azide, vooraf geoxideerd was. Hiervoor werd gekozen vanwege de sterk β-richtende eigenschappen van deze urenzuuren. De eerste glycosidische binding, die van een D-FucN₃ donor met een linkergroep (die latere conjugatie mogelijk maakt voor immunologische evaluatie) werd bewerkstelligd in hoge β-selectiviteit door het gebruik van een mengsel van dichloormethaan (CH₂Cl₂) en diethylether (Et₂O). De essentiële verbinding tussen de twee FucN₃ eenheden kon met complete α-selectiviteit en hoge opbrengst geïntroduceerd worden door het kiezen van een TBS-beschermde FucN₃ donor. Andere donoren gaven inferieure selectiviteit en opbrengst. Het disaccharide kon verlengd worden na afsluiting van de twee TBS-groepen, gevolgd door een regioselectieve bescherming van de 3-*O*-positie (die in het natuurlijke trisaccharide geacetyleerd is). De glycasylering met de mannuronzuur donor verliep problematisch, vermoedelijk door de lage reactiviteit van de disaccharide acceptor. Echter, door een overmaat donor en activator te gebruiken kon het beschermde trisaccharide in hoge opbrengst worden gevormd. De ontscherming, met name het transformeren van de azides naar de *N*-acetyl groepen, verliep problematisch; stapsgewijze reductie van de azides en acetylering van de vrije amines gaf een complex mengsel van producten, met als hoofdproduct een lactam, waarbij het vrije amine op de mannosaminuronzuur-eenheid reageerde met het vrije zuur. Dit werd voorkomen door een één-staps procedure, waarbij thioazijnzuur (AcSH) reageert met de azides en via een cyclisch intermediair, direct het acetamide vormt. Globale hydrogenering gaf uiteindelijk het ontschermde trisaccharide.

In Hoofdstuk 5 wordt de reactiviteit en selectiviteit van 2-azido-2-deoxy-galacturonzuur (GalN₃A) donoren bestudeerd. Eerder onderzoek heeft aangetoond dat zeer α-selectieve glycasyleringen van gerelateerde galacturonzuur (GalA) donoren bereikt kunnen worden door het vormen van een lacton over de 3- en 6-posities. Pre-activatie NMR-experimenten toonden aan dat het GalA lacton een axiaal (β-)triflaat vormt, waarna deze door een alcohol in een S_N1-achtige reactie gesubsitueerd wordt, wat leidt tot een α-glycosidische binding. In Hoofdstuk 5 is de succesvolle synthese van een GalN₃A 3,6-lacton beschreven. De synthese kwam tot stand na een regioselectieve bescherming van de C-4-OH positie, door de reductieve opening van een 4,6-*O*-
methoxybenzylideen acetaal op een phenylseleno-galactosazide. Een oxidatie van de C-6 positie, gevolgd door een ringsluiting, leverde het gewenste lacton. Vervolgens werden de glycosylrende eigenschappen van het lacton bestudeerd, onder andere door vergelijking met een ‘normale’ (dat wil zeggen, zonder het lacton) GalN₃A donor, in een serie van glycosyleringen met modelacceptoren, zoals in Hoofdstuk 3. De normale GalN₃A donor was zeer β-selectief in de meeste glycosyleringen. Het lacton was vertoonde redelijke α-selectiviteit, maar deze selectiviteit was sterk afhankelijk van de reactiviteit van de acceptor, waardoor het nut van het GalN₃A lacton in de synthese van oligosacchariden beperkt wordt. Ook is er opnieuw gekeken naar de glycosylrende eigenschappen van het eerder genoemde GaA lacton, door dezelfde serie glycosyleringen uit te voeren als voor de GalN₃A donoren. De resultaten bevestigden de uitzonderlijke α-selectiviteit van de donor, onafhankelijk van de reactiviteit van de acceptor. NMR experimenten toonden aan dat het GalN₃A lacton, net als het GaA lacton, een axiaal triflaat vormt na activatie. De ontledingstemperatuur van het GalN₃A triflaat lag echter lager dan die van het GaA triflaat, wat erop wijst dat de eerste donor minder stabiel is. Dit zou een verklaring kunnen zijn voor de lagere stereoselectiviteit ten opzichte van het GaA lacton.

Hoofdstuk 6 beschrijft de synthese van de repeterende eenheid van het Capsulaire Polysaccharide van de zogenaamde Stam M van Staphylococcus aureus. Dit trisaccharide bestaat uit twee N-acetylgalactosaminuronzuur (GalNAcA) eenheden en één N-acetylfucosamine (FucNAc) eenheid, die allen α-glycosidische banden bevatten. De twee glycosidische banden op de galacturonzuur-eenheden werden gevormd met een 2-azidogalactosyl (GalN₃) donor, die beschermd was op de C-4-O en C-6-O posities met de di-(tert-butyl)silylene (DTBS) groep, een zeer sterk α-richtende beschermpatroon voor galactosyl donoren. Verwijdering van de DTBS-groep, gevolgd door een selectieve oxidatie en verstering van de vrijgekomen C-6 positie gaf de overeenkomende GalN₃A mono- en disacchariden. De FucNAc-eenheid werd geïnstalleerd door middel van een 2-azidofucosyl (FucN₃) donor voorzien van een α-richtend beschermpatroon (Hoofdstuk 3). Stapsgewijze ontscherming leverde het gewenste trisaccharide.

In Hoofdstuk 7 wordt de synthese beschreven van suikerfragmenten gerelateerd aan de parasitaire worm Schistosoma mansoni. De eitjes van deze parasiet brengen een grote hoeveelheid suikers tot expressie die immunologische reacties opwekken. Deze suikers bestaan onder andere uit N-acetylglucosamine (GlcNAc) en N-acetylgalactosamine (GalNAc), die vertakt zijn met fucosyl (Fuc) ketens van verschillende lengte. De fucose-eenheden zijn onderling verbonden met 1,2-α-glycosidische bindingen, een eigenschap die uniek is aan S. mansoni en belangrijke epitopen zouden kunnen zijn in antilichamen gericht tegen S. mansoni. Om de chemie te onderzoeken en te ontwikkelen, met als uiteindelijk doel het synthetiseren van een bibliotheek
Résumé

La réaction de glycosylation, créant la liaison entre deux glucides, est la réaction fondamentale de la chimie des glucides. Cependant, malgré les impressionantes avancées dans cette discipline au cours des dernières décennies, cette réaction est encore peu comprise, et il est encore souvent difficile de contrôler la stéréosélectivité et le rendement de la réaction. Afin de mieux comprendre cette réaction, l'identification des espèces réactives est primordiale. Les espèces covalentes, comme les triflates glycosidiques, peuvent être détectées grâce à la résonance magnétique nucléaire (RMN). En ce qui concerne l'ion oxycarbenium, dont l'existence est supposée pour des décennies, il n'a jamais été observé dans les milieux organiques, en raison de sa très courte durée de vie. Le Chapitre 2 est consacré à la recherche de l'ion oxycarbenium. Après avoir présenté les études computationnelles et expérimentales, des exemples de la littérature impliquant les ions oxycarbenium dans des synthèses d'oligosaccharides sont discutés.

Le Chapitre 3 décrit la réactivité et la sélectivité des 2-azoture-2-déoxyfucosides (FucN₃). L'influence des groupements protecteurs (groupes benzyle, benzoyle et tert-butyldiméthylsilyle (TBS)) en position C-3-O et C-4-O, ainsi que la nature des accepteurs et de leur nucleophilité, ont été étudiés. La nucleophilité des accepteurs influencent grandement la sélectivité des glycosylations. Les accepteurs les moins réactifs (2,2,2-trifluoroéthanol, glucides) conduisent à de hautes sélectivités α, tandis que les accepteurs les plus réactifs (éthanol, cyclohexanol) donnent de moins bonnes sélectivités, ou une sélectivité principalement β. Il a aussi été montré que les groupements protecteurs influencent les sélectivités. Les groupements benzyle et TBS donnent de meilleurs sélectivités que les groupements benzoyle. Grâce aux expériences de RMN à basses températures, les intermédiaires réactifs (triflates et triflates d'oxysulfonium des 2-azidofucosidiques) ont été identifiés. Les accepteurs plus réactifs peuvent réagir avec ces intermédiaires covalents, pour donner des produits principalement β. Les accepteurs moins réactifs ne peuvent pas réagir avec ces espèces. Ils réagissent avec les ions oxycarbenium suivant la dissociation des triflates anomériques pour donner les produits principalement α. Les groupements protecteurs influencent la stabilité des espèces réactives. Les groupements benzyle déstabilisent les ions oxycarbenium et stabilisent les espèces covalentes plus fortement que les groupements benzyle ou TBS.

Le Chapitre 4 décrit la synthèse du motif trisaccharide composant le polysaccharide capsulaire type 5 de Staphylococcus aureus. Ce trisaccharide complexe est un facteur de virulence majeur et pourrait être utilisé dans le développement d’un futur vaccin contre les infections de S. aureus. Le trisaccharide contient une unité D-N-acétylfucosamine (FucNAc), une unité L-FucNAc O-acétylé, et une unité acide N-acétylmannuronique (ManNAcA). La stratégie a reposé sur
l'utilisation d'un donneur acide 2-azoture-2-deoxymannuronique (ManN₂A), qui donne de fortes 
β-sélectivités, en raison de la fonctionnalité uronique. L'utilisation d'un mélange de CH₂Cl₂ et Et₂O 
a permis la construction de la première liaison β-glycosidique entre le donneur D-FucN₃ et un 5-
aminopentanol protégé (permettant une éventuelle conjugaison, pour des évaluations 
biologiques). La liaison α-glycosidique entre les unités FucN₃ à quant à elle été créée grâce au 
donneur L-FucN₂₉ protégé avec des groupements TBS. Après la déprotection et benzoylation du 
disaccharide, la dernière glycosylation avec le donneur ManN₂A a donné le trisaccharide avec une 
totale β-sélectivité. La déprotection du trisaccharide a commencé avec saponification, suivi de 
l'acétylation de l'alcool libre sur l'unité FucN₃ centrale. L'utilisation de l'acide thioacétique a permis 
la transformation des azotures en leur acétamides correspondants. Enfin, le produit final a été 
obtenu après une hydrogénation catalytique.

Le Chapitre 5 est consacré à l'étude de la réactivité et de la sélectivité des donneurs acide 
2-azoturegalacturonique (GalN₃A). Des études antérieures ont montré que les acides 
galacturoniques (GalA) peuvent être préparés de manière α-sélective en utilisant les galacturono-
3,6-lactones. Des études RMN ont démontré qu'après activation le donneur est transformé en 
triflate axiale. Une substitution nucléophile bimoléculaire (S₂N₂) du triflate par un accepteur donne 
ensuite le produit avec une configuration α. Dans le Chapitre 5, la synthèse d'une 3,6-lactone de 
GalN₃A est accompli. Un donneur 'normal' de GalN₃A a aussi été synthétisé pour évaluer l'effet de 
la lactone sur la sélectivité des glycosylations. La série d'accepteurs utilisée est similaire à celle 
décrite dans le Chapitre 3. Les réactions avec le donneur GalN₃A ont été assez β-sélectives. Par 
contre, les réactions avec la 3,6-lactone de GalN₃A ont été modérément α-sélectives. Dans ce cas, 
il a montré que la sélectivité dépendait plus de la réactivité des accepteurs. Du fait du manque de 
sélectivité α de la lactone GalN₃A la synthèse d' oligosaccharides complexes n'a pas pu être 
accompli. La sélectivité de la lactone de GalA à quant à elle été réévalué avec la même série des 
accepteurs que précédemment utilisé. Les résultats confirme que ce donneur permet d'avoir des 
réactions exceptionnellement α-sélectives et indépendantes de la réactivité de l'accepteur. Des 
expériences RMN ont démontré que la température de décomposition de la lactone GalN₃A est 
plus basse que celle de la lactone GalA. Ceci indique que la dernière est plus stable que la première 
et peut expliquer la sélectivité plus basse de la lactone GalN₃A.

Le Chapitre 6 décrit la synthèse d'un trisaccharide composant le polysaccharide capsulaire 
de la Souche M de Staphylococcus aureus. Ce trisaccharide contient deux unités acide 2-
acetamidogalacturonique (GalNAcA) et une unité 2-acetamidofucosamine (FucNAc). Toutes les 
liaisons sont des liaisons α-glycosidiques. Pour la formation de ces liaisons entre les unités 
GalNAcA, les donneurs 2-azidogalactose (GalN₂), protégés avec un groupement 4,6-O-di-(tert-
butyl)silylène (DTBS), ont été utilisés ce qui a permis d'obtenir des α-sélectivités totales. La
déprotection du groupement DTBS, suivi de l’oxydation sélective et de la méthylation de la position C-6 ont ensuite permis d’obtenir l’accepteur GalN₃A désiré. La dernière réaction de glycosylation a été effectuée avec un donneur FucN₃ portant des groupes qui favorisent la sélectivité α. Le trisaccharide a finalement été obtenu après plusieurs étapes de déprotection successives.

Le Chapitre 7 décrit la synthèse des fragments de glycanes du parasite Schistosoma mansoni, un organisme responsable de la schistosomiase. Les œufs de ce parasite présentent une gamme de glycanes sur leurs surfaces ce qui provoque des réponses immunologiques. Les glycanes contiennent en particulier un squelette N-acétylglicosamine (GlcNAc) et N-acétylgalactosamine (GalNAc) décoré avec des branches composées d’unités fucose de longueur variable. Les unités fucose sont connectées par des liaisons α(1→2)-glycosidiques. Ceci est une particularité des glycanes des schistosomes et ses unités peuvent peut-être être des épitopes importants pour les anticorps contre les schistosomes. Pour explorer et développer une stratégie efficace pour construire une gamme de fragments de glycanes associée au parasite deux disaccharides et deux trisaccharides, composés d’une unité GlcNAc ou GalNAc, et d’une ou deux unités fucose, ont été synthétisés. Les accepteurs GlcNAc et GalNAc ont été construits par glycosylations entre le 6-azoture-hexan-1-ol et le donneur GlcNAc ou GalNAc, sans protection sur la position C-3-OH. Ensuite, la première fucosylation a été effectué avec un donneur fucosyle, protégé sur la position C-2-OH par un éther 2-méthylnaphthalènique, qui a pu être éliminé dans des conditions oxydantes. La deuxième fucosylation a été réalisée avec le même donneur, mais les trisaccharides ont été obtenus avec des rendements modérés. Les deux disaccharides ont été obtenus grâce à un protocole en deux étapes (saponification, suivi d’une hydrogénation). Ce protocole n’a pas pu être utilisé pour la déprotection des disaccharides. Ce fait, combiné aux rendements modérés des glycosylations finales a donné lieu à la modification des groupements protecteurs du donneur fucosyle.
List of publications

Synthesis and reactivity of 2-azido-2-deoxy-galacturonic acid [3,6]-lactones

Synthesis of the repeating unit of the S. aureus Strain M Capsular Polysaccharide
Hagen, B.; Van Dijk, J. H. M.; Zhang, Q.; Overkleeft, H. S.; Van der Marel, G. A.; Codée, J. D. C.; manuscript in preparation.

Mapping the reactivity and selectivity of 2-azidofucosyl donors for the assembly of N-acetyl fucosamine containing bacterial oligosaccharides

Additions to Oxocarbenium Cations

Highly Diastereoselective Construction of L-Heptosides by a Sequential Grignard Addition/Fleming-Tamao Oxidation

Hydrolysis of Thioglycosides using Anhydrous NIS and TFA

A Second-Generation Tandem Ring-Closing Metathesis Cleavable Linker for Solid-Phase Oligosaccharide Synthesis

On the Reactivity and Selectivity of Galacturonic Acid Lactones
Exploring and Exploiting the Reactivity of Glucuronic Acid Donors

**Curriculum vitae**

**English**

Bas Hagen was born on the 7th of July 1988 in Leiden. After finishing his secondary education at College Hageveld in Heemstede in 2006, he commenced his studies in Bio-Pharmaceutical Sciences at Leiden University, which he successfully completed in 2009. In that year, a research internship was carried out in the Bio-Organic Synthesis group at the Leiden Institute of Chemistry, under the supervision of dr. P. van Delft, dr. D. V. Filippov and prof. dr. G. A. van der Marel, during which he conducted synthetic studies towards cyclic dinucleotides. In 2009, he commenced his M.Sc. studies in Chemistry (Research track, focus on Design & Synthesis) at Leiden University. A research internship was carried out at the Bio-Organic Synthesis group, under supervision of dr. A. R. de Jong, dr. J. D. C. Codée and prof. dr. G. A. van der Marel, and concerned the automated solid-phase synthesis of β-(1→3)-glucan oligomers. He finished his studies in December 2011.

He commenced his Ph.D. studies, described in this thesis, in January 2012 in the same group, under the supervision of prof. dr. G. A. van der Marel and dr. J. D. C. Codée. He presented parts of the research described in this thesis on posters at the NWO Design & Synthesis section meeting in Lunteren, the Netherlands (2013) and the Chemistry As Innovating Science (ChAINS) conference in Veldhoven, the Netherlands (2014). In August 2015, an oral presentation was given at the 18th European Carbohydrate Symposium in Moscow, Russian Federation. In July 2013, he attended the Holland Research School for Molecular Chemistry (HRSMC) Summer School ‘New Vistas in Organic Synthesis in Maastricht, the Netherlands.

**Nederlands**

met als onderwerp de geautomatiseerde vaste-dragersynthese van β-(1→3)-glucanen. Het M.Sc. diploma werd in december 2011 behaald.


**Français**


1,2-cis-Glycosylations: Method Development and Synthesis of Complex Oligosaccharides

Bas Hagen

Uitnodiging

N.B. Er dient rekening gehouden te worden met beperkte parkeermogelijkheden in de omgeving van het Academiegebouw.

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