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Development of Fully and Partially Protected Fucosyl Donors for Oligosaccharide Synthesis

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Supporting Information

ABSTRACT: The use of fully and partially *tert*-butyldimethylsilyl (TBDMS) protected fucose thioglycosides as glycosyl donors for oligosaccharide synthesis is described. Both the trisilyl- and disilyl-protected thioglycoside donors were prepared, and their reactivity under a range of activation conditions was investigated. Both silyl-protected donors were found to give good yields of the desired α products and the silyl protecting groups could be removed in the presence of unsaturated bonds. The disilyl-protected donor was found to behave as an efficient, partially protected glycosyl donor. The synthetic scope and limitations of these new donors is presented. Both donors were applied to the synthesis of a Lewis X trisaccharide displaying a propargyl group at the anomeric position. It was determined that the additional steric bulk of the TBDMS group inferred unusual reactivity on these fucosyl donors.

■ INTRODUCTION

Fucose is an important monosaccharide in glycobiology and is often displayed on *N*-linked glycoproteins.[1,2] In mammals, fucose-containing glycans have important roles in a diverse array of biological functions, including selectin-mediated leukocyte−endothelial adhesion, host−microbe interactions, and several ontogenic events.[3] The ABO blood group antigens are among the most well-known fucosylated glycans in mammals. To date, 13 fucosyl transferase genes have been identified in the human genome, and aberrant fucosylation patterns have been observed in several pathogenic processes including cancer,[4] chronic hepatitis,[5] and liver cirrhosis.[6] Core fucose is found exclusively α-1,6-linked to the reducing *N*-acetylglucosamine (GlcNAc) moiety of the chitobiose core.[7] The core fucosylation of the plasma protein, α-fetoprotein is a well-known tumor marker for hepatocellular carcinomas.[8] α-1,3 fucosylation is often found in plants and insects.[9] Access to synthetically pure samples of fucosylated glycans is important for understanding their biology and for the development of new therapeutics. For the synthesis of fucosylated oligosaccharides, α-fucosylation has generally been achieved either enzymatically, through the use of fucosyl transferase enzymes,[10] or else chemically, through the use of non participating protecting groups, the most commonly employed being the OBn protecting group.[11−13] These reactions work well and give the desired α-fucosylated product in good yield. However, removal of benzyl protecting groups often relies on catalytic hydrogenation or birch reduction conditions which may be unsuitable for molecules containing unsaturated bonds or sensitive functional groups. Other variants of the OBn group are known to have more facile deprotection, for example the meta-NO_2-benzyl protecting group can be removed photochemically, and the *p*-OMe-benzyl protecting group can be removed by milder hydrogenation conditions or oxidation.[14] In glycosylation reactions, the use of ether protecting groups offers enhanced reactivity due to the "arming" effect,[15] but this is offset by a reduction in stereocontrol at the newly formed glycosidic linkage. For this study, we were interested in investigating the reactivity of silyl protected fucosyl donors. The use of a per-TMS protected fucosyl donor has been reported by Hindsgaul and co-workers.[16] Activation with TMSI resulted in α-selective fucosylations via the glycosyl iodide, however the temporary nature of the TMS protecting groups, which are hydrolyzed upon workup, means that further protecting group manipulation of the glycosylated product is restricted. As part of our studies into the synthesis of biologically active glycoconjugates for therapeutic applications[17,18] we became interested in the development of a fucosylation protocol that would allow for removal of the fucosyl protecting groups in the presence of unsaturated groups such as alkynes. We envisaged that silyl protecting groups would be appropriate for the fucosyl donor due to their orthogonality to other protecting groups and relatively mild deprotection conditions.[14] In order to confer a degree of stability onto the donor, we decided to investigate the use of the more robust TBDMS protecting groups rather than the labile TMS groups reported by Hindsgaul.[16] It was determined

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that the additional steric bulk of the TBDMS group inferred unusual reactivity on these compounds. The results of these studies are reported herein.

■ RESULTS AND DISCUSSION

A number of per-silylated glycosyl donors have been successfully employed in oligosaccharide and glycoconjugate synthesis.[16,19] These compounds are readily converted into the reactive anomeric iodide on treatment with TMS-iodide. We first investigated conditions for the per-silylation of L-fucopyranose **1** on treatment with *tert*-butyl dimethylsilyl chloride (TBDMS chloride). The per-silylation of fucose with TMS chloride as reported by Hindsgaul and co-workers proceeded in good yield to furnish the desired pyranose product **2**; however, the reaction with the more bulky *tert*-butyl reagent furnished the furanose product **3** as the major isomer (Scheme 1). Marino and co-workers have recently reported the

Scheme 1. Preparation of Persilylated Derivatives from L-Fucose

furanose product under similar conditions starting from D-galactose and have successfully applied this molecule as a galactofuranose donor on treatment with TMS iodide.[20] For our synthetic targets, including the human histo blood group oligosaccharide, Lewis X, we required the pyranose form of fucose and so it was decided to employ *β*-thioglycoside **4** as a starting material for the per-silylation reaction (Scheme 2). Thioglycoside donors are robust enough to withstand protecting group manipulation and have the advantage of having several modes of activation.[21,22]

Scheme 2. Preparation of Fully and Partially Protected Fucosyl Thioglycosides

R = TBDMS

The synthesis of TBDMS-protected pyranoside thioglycoside donors has been reported by Bols and co-workers, who coined the term "super armed" by virtue of the observed increased reactivity of per-TBDMS donors over armed donors.[23] Interestingly, despite intensive research in this area, the TBDMS-protected fucose thioglycoside derivatives have not previously been reported. Fucosyl thioglycoside **4** was treated under a number of silylating conditions (Table 1), and it was found that, depending on the reagents used, both the fully protected **7** and the partially protected compound **5** could be isolated in high yields (Scheme 2).

The observation that the less reactive chloro reagent furnished mainly the partially protected donor **5** is of interest since this isomer could potentially be employed as a partially

Table 1. Optimization of Ethyl 2,3,4-Tri-TBDMS-Fuc-*α*-thioglycoside 7 Synthesis

entry	reagent	solvent/base	temp (°C)	time (h)	% yield 5	% yield 7
1	TBDMSCl[a]	DMF, imidazole	40	16	26	trace
2	TBDMSCl[a]	DMF, imidazole	50	48	86	5
3	TBDMSCl[a]	DMF, lutidine, DMAP (cat.)	100	96	22	46
4	TBDMSCl[a]	pyridine, DMAP (cat.)	0−60	24		83
5	TBDMSOTf[b]	pyridine, DMAP (cat.)	0−60	36		97

[a]5 equiv. [b]4.5 equiv.

protected donor. Following formation of **5**, further functionalization of the remaining unprotected hydroxyl group, 3-OH, is sterically hindered by the bulky neighboring TBDMS protecting groups. The regioisomer **6** displaying 2,3 di-TBDMS substitution was also isolated in a 3% yield. The fact that the 2,4 substitution pattern of **5** was the major isolated isomer requires some rationalization. Given the long reaction time required for optimum yields of **5**, it is likely that this reaction is under thermodynamic control. Kinetically, one would expect the axial 4-OH to be the least reactive so either the 2- or 3-OH should be protected first. Literature precedent for imidazole and/or alternative base-mediated intramolecular transfer of silyl protecting groups, to neighboring hydroxyls has been presented by Santos et al.[24] and Tadano et al.[25] A similar process of silyl group migration may be responsible for the observed partially protected product regioisomer **5** in high yield. A single literature example of the preparation of a di-TBDMS protected fucosyl donor has been reported by Du and co-workers.[26] They found that the use of TBDMSCl and imidazole in DMF at 40 °C for 12 h furnished the 3,4 di-TBDMS regioisomer as the major product. The reported characterization data of that product is identical to our observed characterization for the 2,4 regioisomer **5**. Through high-resolution 2D NMR, (HSQC, and HMBC experiments, see the Supporting Information), the structure of the 2,4 regioisomer **5** was unambiguously assigned. The remaining unprotected hydroxyl was found to be located in the 3-C position. Although trace amounts (3%) of the 2,3 di-TBDMS isomer **6**, were isolated none of the 3,4 di-TBDMS substituted fucose thioglycoside was observed in our studies. We anticipated that both the fully and partially protected thioglycosides **5** and **7** would be able to function as fucosyl donors.

NMR characterization of the trisilylated donor **7** suggested that some conformational change was occurring due to the steric bulk of the protecting groups. Full "ring flipping" has been observed in the "super armed" donors previously prepared by Bols and co-workers.[23] Significant line broadening in the NMR suggested that the molecule was being forced out of the usual $^1C_4$ conformation due to steric interactions between the bulky silyl protecting groups. Interestingly, an X-ray crystal structure of the donor showed that it had crystallized exclusively in the $^1C_4$ conformation (Figure 1).

In contrast to the trisilylated donor, the proton NMR spectrum of the partially protected donor **5** was completely

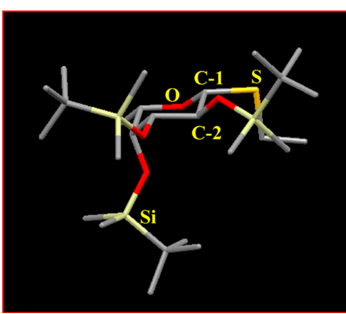

Figure 1. X-ray crystal structure of donor 7.

resolved (see the Supporting Information). The clearly resolved OH peak suggested slow proton exchange resulting from the buttressing of neighboring TBDMS groups. No ring flipping was observed by NMR and the donor existed exclusively in the $^1C_4$ conformation.

■ INVESTIGATION OF SYNTHETIC APPLICATIONS OF GLYCOSYL DONORS

With both the fully and partially protected fucosyl donors **5** and **7** in hand, we set out to investigate their application as fucopyranosyl donors. *O*-Propargyl NAc glycosamine acceptor **8** was chosen as an acceptor for optimization studies since the acceptor contains a propargyl group at the anomeric position that cannot tolerate hydrogenation conditions (Scheme 3).

Scheme 3. Investigation of Glycosylation Conditions for Donor 7

Also, the 1,6 disaccharide formed is a highly specific substrate for the fucose binding lectin isolated from *R. solanacearum*.[27,28] We first investigated glycosylation conditions for the fully protected trisilyl donor **7**. A number of common activation conditions for thioglycosides were investigated. The results of these studies are outlined in Table 2.

A recent thioglycoside activation technique reported by Fugedi and co-workers is the DMDS/Tf_2O method.[29] Entries 1−3 show our attempts at glycosylation using this activator both in the presence and absence of a hindered basic buffer. Both DTMP and TMU[30] have been used as buffers in glycosylation reactions in order to minimize the loss of acid-labile protecting groups. The addition of these buffers resulted in the isolation of the desired product **9** in 13% and 21% yields, respectively, with reasonable anomeric selectivity as determined by NMR. The absence of any basic buffer resulted in none of the disaccharide product being isolated (entry 1). A two-stage activation procedure involving formation of the anomeric bromide followed by reaction with AgOTf has been widely used for the activation of thioglycosides. Activation of donor **7** with Br_2 was performed according to literature procedure,[31] and the excess bromine was either quenched with cyclohexene or removed through evaporation (entry 4). The fucosyl bromide intermediate was not isolated but reacted directly with acceptor **8** at −40 °C, followed by silver triflate activation of the anomeric bromide. After 30 min, complete consumption of the donor **7** had occurred (by TLC), but the expected disaccharide product was only visible in trace amounts by HRMS analysis of the crude reaction mixture. NMR studies were carried out in order to monitor formation of the anomeric bromide and to ensure that no deprotection was taking place at the bromination step (see the Supporting Information for NMR studies).

Table 2. Conditions for Glycosylation Conditions for Donor 7

entry	activation conditions	temp (°C)	time (min)	% yield (α/β) of 9
1	DMDS, Tf_2O	−40	30	not isolated
2	DMDS, Tf_2O, DTMP	−40	30	13, (5.1:1)
3	DMDS, Tf_2O, TMU	−40	30	21, (5.4:1)
4	Br_2, AgOTf, cyclohexene	−40	30	trace product
5	Br_2, AgOTf[a]	−40	25	71, (10.2:1)
6	NIS, TMSOTf	−20	80	86, (8.1:1)

[a]Inverse glycosylation.

The NMR studies on Br_2 activation of donor **7** confirmed the stability of the TBDMS groups during activation and that the expected intermediate fucosyl bromide was formed quantitatively. It was concluded that the problems observed with the two-stage glycosylation must occur after the bromination step. A number of literature examples of α-Fuc-(1−6)-GlcNAc synthesis highlight the extremely labile nature of the biologically important α-(1−6) linkage.[32,33] Kunz et al. showed that the presence of arming groups such as benzyl protection on the fucose increase the instability of the α-(1−6) glycosidic bond.[34] The highly reactive nature of the donor **7**, coupled with the sensitive glycosidic bond in the product **9**, was identified as the main reason for the low yields in the glycosylation reactions screened. Schmidt et al. pioneered the inverse glycosylation method, which provided increased glycosylation yields when using highly reactive trichloroacetimidate donors.[35] Inverse glycosylation therefore seemed an appropriate approach in our efforts to prepare α-Fuc-(1−6)-*O*-propargyl-β-GlcNAc. Inverse glycosylation maintains the acceptor and activator concentrations higher than the donor, encouraging glycosylation of the acceptor before side product formation or hydrolysis can occur. Gratifyingly, the reaction under these conditions proceeded very cleanly with the isolation of **9** in 71% yield along with high α-selectivity (10.2:1, α:β) and short reaction times (entry 5).

The successful synthesis of **9** under inverse glycosylation conditions demonstrated the synthetic application of **7** as a fucosyl donor. The use of Br_2 for donor activation is not ideal, however, due to the gradual decrease in pH of Br_2 over time on storage. Addition of wet bromine leads to partial TBDMS deprotection and reduced yields due to contamination from HBr. Therefore, NIS/TMSOTf activation of donor **7** was also investigated. Activation of **7**, with NIS, once maintained at, or below −20 °C did not result in any iodine addition across the propargyl triple bond (a side reaction observed in our earlier studies). The acceptor **8** was consumed within 80 min, and the disaccharide product **9** was isolated in a high yield of 86%, with good α anomeric selectivity (8.1:1 α/β) (entry 6). Following the screening of various activation conditions for the thioglycoside donor **7**, it was determined that NIS/TMSOTf activation was optimum for fucosyl donor **7**. Using the optimized activation conditions, the glycosylation reactions of the donor **7**

Table 3. Synthetic Scope of Fucosyl Donor 7

Entry	Acceptor	Activation Conditions	Yield (α:β) %
1	**10**	NIS, TMSOTf, 40 min, -20 °C	**11**, 86 (α only)
2	**12**	NIS, TMSOTf, 40 min, -20 °C	**13**, 83 (3.2:1, α:β)[a]
3	**8**	NIS, TMSOTf, 80 min, -20 °C	**9**, 86 (8.1:1 α:β)[a]
4	**14**	NIS, TMSOTf, 60 min, -30 °C	**15**, 66 (α only)
5	**16**	NIS, TMSOTf, 40 min, -20 °C	**17**, 31 (α only) Glycosylated at 3-OH
6	**18**	NIS, TMSOTf, 240 min, -20 °C	**19**, 24 (α only)

[a]Anomeric ratio determined by ^{1}H NMR.

with a number of acceptor molecules were investigated. The results of this study are presented in Table 3.

Glycosylation reactions with primary alcohols under NIS/TMSOTf activation proceeded in good yield with high alpha selectivity (entries 1−3). Glycosylation with a monosaccharide acceptor containing a single free secondary hydroxyl also proceeded in good yield with exclusive *α* selectivity (entry 4). This result also demonstrated how the armed thioglycoside donor **7** could be selectively activated in the presence of a less reactive thioglycoside donor **14** (Figure 2). A regioselective glycosylation on galactosyl diol acceptor **16** furnished a single product with complete alpha selectivity, albeit in a low yield of 30%. Only the 1,3-linked disaccharide was formed, none of the 1,2 regioisomer was observed. For the fucosylation of lactosamine acceptor[18] **18**, the yield of the desired trisaccharide **19** was particularly low. Increasing the reaction time and raising the donor ratio to 3 equiv did not result in any measurable increase in yield. The steric bulk of fucose donor **7** may cause difficulty in approaching the free 3-OH on the disaccharide acceptor **18**, given the close proximity of the Gal moiety. Dwek et al.[36] reported that the Lewis X trisaccharide is a very rigid molecule even when fully deprotected. The extra steric constraints imparted by the TBDMS groups in close proximity may increase the energy barriers for this glycosylation. Kondo et al. showed that the steric bulk around the 3-OH of GlcNAc in Lewis X synthesis dramatically affects glycosylation yields at that hydroxyl.[12] The use of alternative activation conditions, namely DMDS-Tf_2O and the highly reactive Br_2/AgOTf inverse glycosylation did not improve the yield of trisaccharide

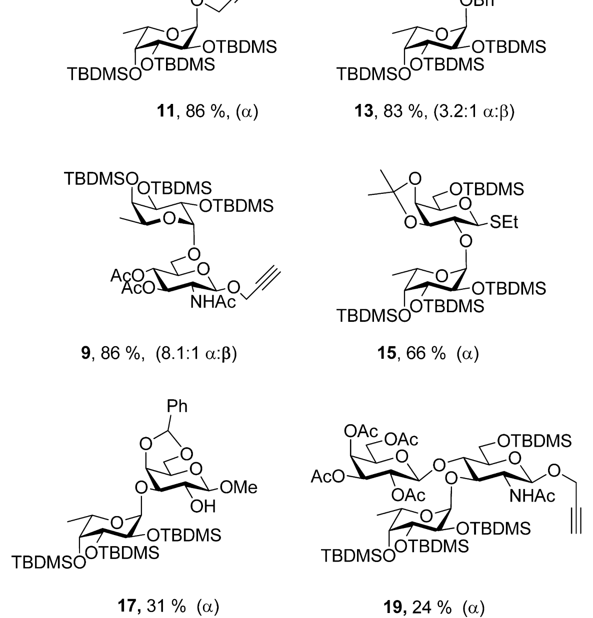

Figure 2. Products obtained from the fucosylation reactions with fucosyl donor **7**.

19. Conversion of thioglycoside donor **7** to a highly reactive trichloroacetimidate was performed in situ, after NBS-promoted hydrolysis of **7**, followed by reaction with trichloroacetonitrile and Cs_2CO_3. The trichloroacetimidate

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was extremely unstable, so the crude material was not purified but used directly in the glycosylation following removal of Cs_2CO_3 by filtration and distillation of the excess trichloroacetonitrile. The trisaccharide **19** was only isolated in reduced yields of 10−12% using the TCA donor. These studies demonstrated that the donor **7** is valuable for fucosylation of sterically accessible hydroxyl groups but that its scope may be limited for glycosylation reactions at sterically crowded centers.

Following the successful synthesis of the fucosyl-containing disaccharide **9** and trisaccharide **19**, we investigated the removal of the silyl protecting groups in order to validate the synthetic application of the TBDMS protected donor. Davis et al. have reported an efficient one pot desilylation/deacetylation procedure using BF_3OEt_2 in MeCN as a fluoride source, followed by the addition of Na_2CO_3 and MeOH.[37] Application of this procedure to disaccharide **9** unfortunately resulted only in complete hydrolysis of the α-(1−6) glycosidic bond and yielded none of the deprotected disaccharide. As a milder alternative, the route was modified to a protecting group interconversion. Following BF_3OEt_2 mediated removal of the TBDMS groups at room temperature, the Lewis acid was quenched with an excess of pyridine and the mixture acetylated overnight to furnish the peracetylated disaccharide in 52%. It was observed by TLC and mass spectroscopic analysis that the sensitive 1,6 glycosidic linkage was undergoing hydrolysis in the presence of the Lewis acid so this deprotection strategy was abandoned. TBAF deprotection is commonly used for the removal of primary hydroxyl TBDMS groups; however, an attempted deprotection of disaccharide **9** with 1.1 equiv of TBAF per TBDMS group at rt did not succeed. Bols and co-workers noted the difficulty in the deprotection of TBDMS groups on super armed donors[23] and recommended the use of 3 or more equiv of TBAF per TBDMS protecting group. Disaccharide **9** was treated with 3.3 equiv of TBAF per TBDMS group and stirred at rt for 16 h. The naked F^- ion in THF is a very strong base and promotes acetyl migration. For this reason, the reaction was quenched with the addition of pyridine and acetic anhydride to ensure per-acetylation of the final product (Scheme 4). Two products were isolated

Scheme 4. Deprotection of Disaccharide 9

1. TBAF (10 eq), 30 h, THF
2. Ac_2O, Pyr

NaOMe/MeOH: **20**, 86 %, R = Ac → **21**, 94 %, R = H

following this reaction, the starting material **9** in 71% yield and the required per-acetylated disaccharide **20** in 28% yield. The S_N2 elimination of a glycoside from a silyl protecting group proceeds via a proposed pentacoordinate Si atom. The high steric hindrance of multiple TBDMS groups may cause a comparatively high energy barrier for the first deprotection, thereby slowing down the deprotection process. Once an initial TBDMS group is removed, the steric bulk should be lowered and due to the large excess of TBAF, subsequent deprotection should occur more readily. Applying this hypothesis, TBAF deprotection was repeated for 30 h and following per-acetylation successfully furnished the desired disaccharide product **20** in 87% yield. Deacetylation with NaOMe/MeOH yielded the target disaccharide **21**, in 94% after freeze-drying.

TBAF deprotection followed by acetylation was also successfully applied to the Lewis X trisaccharide **19**, albeit with an increased reaction time of 64 h. The reaction time was reduced to 16 h without any reduction in yield by increasing the reaction temperature from rt to 50 °C. No hydrolysis of any of the glycosidic linkages was observed under these conditions. The per-acetylated trisaccharide was isolated in 77% over two steps. Quantitative deacetylation, followed by freeze-drying allowed the isolation of *O*-propargyl Lewis X trisaccharide **23** in 97% yield (Scheme 5).

Scheme 5. Deprotection of Lewis X Trisaccharide 19

1. TBAF, THF, 50 °C, 16h
2. Ac_2O, Pyr

NaOMe/MeOH: **22**, 77 %, R = Ac → **23**, 97 %, R = H

The deprotection reactions of disaccharide **9** and trisaccharide **19** demonstrated that the trisilylated fucosyl donor **7** could be employed as a useful fucosyl donor for oligosaccharide synthesis, albeit with long reaction times for the deprotection reaction. The steric bulk of the protecting groups assisted formation of the alpha anomer but may have resulted in diminished yields for sterically challenging glycosylation reactions such as the formation of trisaccharide **19**. It was anticipated that both of these issues may be resolved through the use of the partially protected donor **5**, since it does not possess the steric bulk of donor **7**. Examples of partially protected glycosyl donors in oligosaccharide synthesis are rare but a small number of examples have been reported in the literature. This is due to the fact that it is extremely difficult to avoid polymerization reactions unless the hydroxyl group on the donor is particularly unreactive due to steric or electronic constraints. Using a large excess of the acceptor molecule can help avoid formation of unwanted side products but this is often impractical for oligosaccharide synthesis. Partially protected donors are extremely desirable in terms of atom efficiency and also in terms of offering reduced numbers of steps in oligosaccharide synthesis. The potential role of partially protected donors in combinatorial approaches toward accessing complex glycoconjugate libraries has been highlighted by Seeberger et al.[38] Linhardt and co-workers have reported the use of partially protected galactosyl thioglycoside donors for the efficient synthesis of saponins. The partially protected donors were found to be efficient for glycosylation of primary alcohols and unhindered secondary alcohols but when a glycosyl acceptor containing a single secondary hydroxyl was examined, low yields or complex product mixtures were observed.[39] Fraser Reid and co-workers have reported the use of a partially protected *n*-pentenyl orthoester donor with a primary alcohol.[40] Kahne and co-workers have achieved glycosylation of a secondary hydroxyl group on a glycosyl acceptor using a partially protected sulfoxide donor. Inverse glycosylation conditions were employed in order to maintain a high concentration of the acceptor sugar and to avoid polymerization reactions.[41] Despite these elegant examples, the use of

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partially protected glycosyl donors in oligosaccharide synthesis remains relatively unexplored.

In the case of the 2,4-TBDMS-protected thioglycoside **5**, the 3-OH group is sterically shielded by the presence of the bulky protecting groups on the adjacent hydroxyl groups. Before investigating the partially protected monosaccharide **5** as a potential fucosyl donor, we first investigated the reactivity of the free 3-OH group. Attempts to silyl protect, benzyl protect, and acetylate the free OH resulted in mainly starting material or decomposition products. Under one set of conditions the 3-OH group was acetylated, but this required reaction with acetic anhydride, pyridine, and DMAP at rt for 18 days. This time scale is well outside the scope of synthetic glycosylation reactions.

In order to investigate the reactivity of the free OH group toward glycosylation reactions, a trichloroacetimidate donor **24** was activated in the presence of thioglycoside donor **5**. No disaccharide product was formed, therefore confirming that the 3-OH is essentially unreactive toward glycosylation reactions. However, due to the unreactivity of the 3-OH, and the presence of a thioether group on donor **5** an unusual rearrangement reaction occurred to give compounds **25** and **26** (Scheme 6).

Scheme 6. Attempted Glycosylation of 3-OH on Donor 7

5; 24; BF_3OEt_2, DCM, 0 °C - RT, 16 h; 25, 46 %; 26, 71 %

Similar rearrangement reactions been reported previously when an unreactive thioglycoside acceptor was used in the presence of a trichloroacetimidate donor.[42−45] Boons et al. previously described the transfer of an anomeric thioether group from acceptor to donor.[46] Analyzing the products from Scheme 6, it can be assumed that upon formation of the glycosyl oxocarbenium ion resulting from activation of trichloroacetimidate **24**, the lone pair on the sulfur of fucosyl donor **5** is more accessible than the lone pair on the 3-OH. The SEt group is transferred onto the galactose donor to give thioglycoside **26** and the resulting fucosyl oxocarbenium ion reacts with trichloroacetamide to furnish **25**. This reaction, although not synthetically useful for our fucosyl donor, highlights the lack of reactivity of the 3-OH in partially protected donor **5**.

Following our investigation into the reactivity of thioglycoside **5** as an acceptor molecule, we then set about investigating its reactivity as a partially protected donor for fucosylation reactions. Activation of the fucosyl donor **5** under the conditions optimized for the fully protected fucosyl donor **7** in the presence of a benzyl alcohol acceptor furnished the *O*-benzyl product **27** in a high yield of 88% with good α selectivity (Scheme 7). None of the disaccharide or associated polymeric

Scheme 7. Glycosylation of Benzyl Alcohol with Partially Protected Donor 5

5; BnOH, NIS/TMSOTf; 27, 88% (2.6:1, α:β)

compounds were detected under these conditions. This glycosylation reaction therefore demonstrated that the partially protected fucosyl donor **5** could be employed for glycosylation reactions. This represents the first example of a partially protected fucosyl donor for glycosylation reactions.

In order to investigate the synthetic scope of the partially protected fucosyl donor **5** and in order to compare it directly with the persilylated donor **7**, we investigated the glycosylation reaction with the lactosamine disaccharide acceptor **18** (Scheme 8). We predicted that the reduced steric strain of the partially protected donor should improve the yield of the glycosylation reaction. Gratifyingly, the partially protected donor furnished the trisaccharide **28** in 53% yield, almost double the yield obtained when using the fully protected donor. This is equivalent to the literature yields reported using OBn protected fucosyl donors. We attribute the improvement in yield to the reduced steric bulk of the partially protected donor however, more complex electronic factors relating to the relative ease of formation of the oxocarbenium ion intermediate cannot be ruled out.[23]

Finally, we attempted to apply the deprotection protocol previously employed for the trisaccharide **19** to trisaccharide **28**. We expected that the TBDMS groups on the partially protected donor would be easier to remove since they should be more accessible to the fluoride ions from the TBAF reagent. It was found that the TBDMS groups could be removed under much milder conditions relative to the per-silylated fucose in compounds **9** and **19**. No heating was required for full deprotection in 24 h. TBAF deprotection followed by deacetylation furnished the desired *O*-propargyl-containing Lewis X trisaccharide **23** in good yield (Scheme 9).

■ CONCLUSION

In conclusion, we have developed both fully and partially protected fucosyl donors **5** and **7** that have general applications for the synthesis of fucose containing compounds where catalytic hydrogenation cannot be carried out. Both of the new donors could be prepared in high yield and gave good yields and high alpha selectivity in fucosylation reactions with a number of acceptors. The partially protected donor was of particular use when glycosylating sterically confined centers within an oligosaccharide. It is the first example of a partially protected glycosyl donor that can be used to efficiently glycosylate hindered secondary alcohols under “normal” glycosylation conditions without any requirement for excess acceptor or reverse activation. Deprotection reactions were carried out to prove the synthetic utility of these donors. We anticipate that these fucosyl donors will find general application within synthetic carbohydrate chemistry. The partially protected donor is particularly novel, and further investigations of other partially protected glycosyl donors are ongoing.

■ EXPERIMENTAL SECTION

General Experimental Methods. For NMR spectra, a 400 MHz spectrometer was employed for ^1H (400.13 MHz) and ^{13}C (100.61 MHz) spectra, and a 600 MHz spectrometer was employed for ^1H (600.13 MHz) and ^{13}C (150.90 MHz) spectra. Resonances δ are in ppm units downfield from an internal reference in $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.0 ppm), MeOH (δ_H = 3.31 ppm, δ_C = 49.0 ppm). For oligosaccharides, the notation a, b, c... refers to the monosaccharide from the reducing end. Mass spectrometry analysis was performed with Maldi-quadrupole time-of-flight (Q-Tof) mass spectrometer equipped with Z-spray electrospray ionization (ESI). Silica gel (200 mesh) was used for column chromatography. Analytical thin-layer

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Scheme 8. Glycosylation of Lactosamine Acceptor 18 with Fucosyl Donor 5

NIS/TMSOTf, DCM, -20 °C, 3 h

18 → **28**, 53 %

Scheme 9. Deprotection of Trisaccharide 28

1. TBAF, THF 0 - 20 °C, 24h
2. Ac_2O, Pyr

28 → **22**, 74 %, R = Ac; NaOMe MeOH → **23**, 97 %, R = H

chromatography was performed using silica gel (precoated sheets, 0.2 mm thick, 20 cm × 20 cm) and visualized by UV irradiation or molybdenum staining. DCM, MeOH, THF and toluene were dried over flame-dried 3 Å or 4 Å sieves. Dimethylformamide (DMF), triethylamine (Et_3N) and trifluoroacetic acid (TFA) were used dry from sure/seal bottles. Other reagents were purchased from an industrial supplier.

1,2,3,5-Tetra-O-TBDMS-α-L-fucofuranoside 3. To a stirred solution of L-fucopyranoside **1** (0.20 g, 3.84 mmol) in DMF (5 mL) were added 2,6-lutidine (1.20 mL, 12.10 mmol) and DMAP (0.05 g). A solution of TBDMSCl (1.47 g, 9.76 mmol) in DCE (5 mL) was added and the mixture stirred at 100 °C with condenser attached for 24 h under N_2. The mixture was quenched with the addition of deionized H_2O (40 mL) over ice and the product diluted with EtOAc (150 mL). The organic layer was collected and washed with brine, 1 M HCl, and satd aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The mixture was filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (EtOAc/Hex, 1:99 v/v) to yield the product **3**, as a clear oil (643 mg, 85%): $[\alpha]^{22}_D$ = 54 (deg cm^3 g^{-1} dm^{-1}) (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 2929 cm^{-1} (CH); ^1H NMR (600 MHz, $CDCl_3$) δ 5.16 (1H, s, H-1), 3.92 (2H, m, H-2, H-3), 3.88 (1H, m, H-5), 3.85 (1H, dd, $J_{4,5}$ = 5.5 Hz, $J_{4,3}$ = 3.5 Hz, H-4), 1.19 (3H, d, $J_{6,5}$ = 6 Hz, H-6), 0.92, 0.91, 0.90, 0.90 (9H, s, $SiC(CH_3)_3$), 0.12, 0.12, 0.10, 0.10, 0.10, 0.10, 0.09, 0.08 (3H, s, $Si(CH_3)$; ^{13}C NMR (150 MHz, $CDCl_3$) δ 103.3 (C-1) 90.3 (C-4), 85.2 (C-2), 79.8 (C-3), 69.1 (C-5), 26.0, 25.8, 25.7, 25.7 ($SiC(CH_3)_3$), −4.2, −4.2, −4.4, −4.4, −4.5, −4.6, −4.8, −5.2 ($Si(CH_3)$; *m/z* HRMS (ESI-TOF) calcd for $C_{30}H_{68}O_5NaSi_4$ 643.4042 (M + Na)$^+$, found 643.4022.

1-Ethylthio-2,4-di-O-TBDMS-α-L-fucopyranoside, 5. To a solution of 1-ethylthio-α-L-fucopyranoside **4** (1.3 g, 1.63 mmol) and imidazole (1.47 g, 21.98 mmol) in DMF (10 mL) was added TBDMSCl (1.47 g, 9.77 mmol). The mixture was heated to 50 °C for 48 h. The reaction was cooled to rt and quenched over ice with deionized H_2O (10 mL). The mixture was diluted with EtOAc (100 mL), sequentially washed with brine (3 × 100 mL) and deionized H_2O (2 × 100 mL), and dried over $MgSO_4$. The mixture was filtered, and the solvent removed in vacuo. The crude material was purified by column chromatography (Et_2O/hexane, 1:25 v/v) to yield the product **5**, as a yellow oil (2.34 g, 86%): $[\alpha]^{20}_D$ = 78 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3602 cm^{-1} (OH), 2928 cm^{-1} (CH); ^1H NMR (600 MHz, $CDCl_3$) δ 4.24 (1H, d, $J_{1,2}$ = 9.1 Hz, H-1), 3.80 (1H, d, $J_{4,5}$ = 2.7 Hz, H-4), 3.67 (1H, app t, $J_{2,3}$ = $J_{2,1}$ = 8.9 Hz, H-2), 3.57 (1H, q, $J_{5,6}$ = 6.4 Hz, H-5), 3.46 (1H, m, H-3), 2.74 (1H, m, SC*H*(H)), 2.65 (1H, m, SCH(*H*)), 1.98 (1H, d, *J* = 6.7 Hz, OH), 1.30 (3H, t, *J* = 7.5 Hz, SCH_2CH_3), 1.35 (3H, d, $J_{6,5}$ = 6.3 Hz, H-6), 0.96 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 0.20, 0.16, 0.15, 0.11 (3H, s, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 85.7 (C-1), 76.8 (C-3), 74.9 (C-5), 73.5 (C-4), 71.9 (C-2), 26.1, 26.0 ($SiC(CH_3)_3$, 23.9 (SCH_2CH_3), 18.4, 18.4 ($SiC(CH_3)_3$), 17.7 (C-6), 14.9 (SCH_2CH_3), −3.9, −4.0, −4.1, −4.2 ($Si(CH_3)_2$); *m/z* HRMS (ESI-TOF) calcd for $C_{20}H_{44}O_4NaSSi_2$ 459.2397 (M + Na)$^+$, found 459.2401.

1-Ethylthio-2,3-di-O-TBDMS-α-L-fucopyranoside, 6. Side product from the synthesis of **5** to yield the product **6** as a clear oil (80 mg, 3% yield): $[\alpha]^{20}_D$ = 39 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3492 cm^{-1} (OH), 2929 cm^{-1} (CH); ^1H NMR (600 MHz, $CDCl_3$) δ 4.28 (1H, d, $J_{1,2}$ = 8.8 Hz, H-1), 3.69 (1H, app t, $J_{2,3}$ = $J_{2,1}$ = 8.3 Hz, H-2), 3.67 (1H, m, H-4), 3.65 (1H, dd, $J_{3,2}$ = 8.0 Hz, $J_{3,4}$ = 2.0 Hz, H-3), 3.60 (1H, q, $J_{5,6}$ = 6.5 Hz, H-5), 2.70 (2H, m, SCH_2CH_3), 2.35 (1H, d, *J* = 1.5 Hz, OH), 1.36 (3H, d, $J_{6,5}$ = 6.5 Hz, H-6), 1.29 (3H, t, *J* = 7.4 Hz, SCH_2CH_3), 0.97, (9H, s, $SiC(CH_3)_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 0.22, 0.18, 0.15, 0.11 (3H, s, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 86.4 (C-1), 77.8 (C-3), 73.9 (C-5), 72.9 (C-4), 71.4 (C-2), 26.4, 26.3 ($SiC(CH_3)_3$, 24.8 (SCH2CH3), 18.3, 18.2 ($SiC(CH_3)_3$), 16.7 (C-6), 14.8 (SCH_2CH_3), −2.1, −3.4, −3.4, −4.0 ($Si(CH_3)_2$); *m/z* HRMS (ESI-TOF) calcd for $C_{20}H_{44}O_4NaSSi_2$ 459.2397 (M + Na)$^+$, found 459.2392.

Ethyl-2,3,4-Tri-O-*tert*-butyldimethylsilyl-1-thio-α-L-fucopyranoside, 7. To a solution of 1-ethylthio-α-L-fucopyranoside **4** (0.87 g, 4.20 mmol) and DMAP (50 mg) in pyridine (10 mL) was added TBDMSOTf (5.0 g, 18.92 mmol) at 0 °C under N_2. The mixture was stirred for 5 min before being heated to 60 °C for 36 h. The reaction was cooled over ice and quenched with deionized H_2O (10 mL). The mixture was diluted with EtOAc (50 mL) and washed sequentially with brine (100 mL), 10% $CuSO_4$ (2 × 50 mL), and deionized H_2O (2 × 50 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed in vacuo. The product was purified by column chromatography (EtOAc/Hex, 1:49 v/v) and recrystallized from 2% Et_2O/Hex to yield the product **132**, as a white crystalline solid (2.2 g, 97%); $[\alpha]^{20}_D$ = 65 (*c* = 0.1 in $CHCl_3$); mp = 62−63 °C; ν_{max} (thin film) 2929 cm^{-1} (CH); ^1H NMR (400 MHz, DMSO 75 °C) δ 4.43 (1H, d, $J_{1,2}$ = 7.2 Hz, H-1), 3.90 (1H, br s, H-4), 3.85 (1H, app, t, $J_{2,3}$ = $J_{2,1}$ = 7.2 Hz, H-2), 3.81 (1H, m, H-5), 3.71 (1H, dd, $J_{3,2}$ = 7.1 Hz, $J_{3,4}$ = 1.9 Hz, H-3), 2.60 (2H, m, SCH_2CH_3), 1.23 (3H, d, $J_{6,5}$ = 4.4 Hz, H-6), 1.21 (3H, t, *J* = 7.5 Hz, SCH_2CH_3), 0.95, 0.94, 0.92 (9H, s, $SiC(CH_3)_3$), 0.15, 0.14, 0.14, 0.14, 0.10, 0.09 ($Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (Signals too broad for full characterization); *m/z* HRMS (ESI-TOF) calcd for $C_{26}H_{58}O_4NaSSi_3$ 573.3261 (M + Na)$^+$, found 573.3257 (X-ray data supplied in the Supporting Information).

2-Acetamido-3,4-di-*O*-acetyl-2-deoxy-1-*O*-propargyl-6-*O*-triphenylmethyl-α-D-glucopyranoside, 8a. To a mixture of 2-acetamido-2-deoxy-1-*O*-propargyl-α-D-glucopyranoside (300 mg, 1.16 mmol) and trityl chloride (387 mg, 1.39 mmol) was added pyridine (5 mL). The solution was heated to 90 °C for 5 h. The reaction was cooled over ice, and Ac_2O (0.43 mL, 4.64 mmol) was added. The mixture was stirred for 2 h. The reaction was quenched with H_2O (10 mL) and diluted with EtOAc (30 mL). The organic layer was washed sequentially with brine (10 mL), 10% $CuSO_4$ solution (2 × 20 mL), and H_2O (10 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed in vacuo. The crude material was purified using column chromatography (EtOAc/Hex, 8:2 v/v) to yield the product **8a** as a white amorphous solid (477 mg, 70% yield): $[\alpha]^{20}_D$ = −28 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3276 cm^{-1} (C≡CH), 3250 cm^{-1} (NH), 3091 cm^{-1} (Ar CH), 2932 cm^{-1} (CH), 1743 cm^{-1} (C═O), 1654 cm^{-1} (NHC═*O*); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (6H, d, *J* = 7.8 Hz, *o*-Ph), 7.32 (6H, t, *J* = 7.9 Hz, *m*-Ph), 7.25 (3H, t, *J* = 7.5 Hz, *p*-Ph), 5.49 (1H, d, *J* = 9.1 Hz, NH), 5.20 (2H, m, H-3, H-4), 4.84 (1H, d, $J_{1,2}$ = 8.6 Hz, H-1), 4.50 (2H, d, *J* = 2.1 Hz, OCH_2), 4.10 (1H, m, H-2), 3.61 (1H, m, H-5), 3.27 (1H, dd, $J_{6',6}$ = 10.5 Hz, $J_{6',5}$ = 1.8 Hz, H-6′), 3.13 (1H, dd, $J_{6,6'}$ = 10.4 Hz, $J_{6,5}$ = 4.8

Hz, H-6), 2.51 (1H, t, J = 2.2 Hz, C≡CH), 2.05, 2.01 (3H, s, CH_3), 1.76 (NHCOCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.3, 168.9 (C═O), 143.6, 143.6, 143.6, (Ar C), 128.7, 128.7, 128.7, 128.7, 128.7, 128.7 (Ar CH), 127.8, 127.8, 127.8, 127.8, 127.8, 127.8 (Ar CH), 127.0, 127.0, 127.0 (Ar CH), 98.3 (C-1), 86.6 ($C(Ph)_3$), 78.6 (C≡CH), 75.3 (C≡CH), 73.6 (C-5), 72.9 (C-3), 68.7 (C-4), 62.0 (C-6), 55.4 (OCH_2), 54.3 (C-2), 23.4, 20.8, 20.4 (CH_3); m/z HRMS (ESI-TOF) calcd for $C_{34}H_{35}NO_8Na$ 608.2260 (M + Na)$^+$, found 608.2253.

2-Acetamido-3,4-di-*O*-acetyl-2-deoxy-1-*O*-propargyl-α-D-glucopyranoside, 8. Et_2O/formic acid (1:1 v/v) (6 mL) was added to **8a** (470 mg, 0.8 mmol) and the mixture stirred at rt for 2 h. The solvent was removed in vacuo by coevaporation with toluene/MeOH. The crude material was loaded in DCM and purified by column chromatography (EtOAc/hexane, 4:1 v/v) to yield the product **8** as a white amorphous solid (213 mg, 77%): $[\alpha]^{20}_D$ = −60 (c = 0.1 in $CHCl_3$); ν_{max} (thin film) 3460 cm^{-1} (OH), 3268 cm^{-1} (C≡CH), 3089 cm^{-1} (NH), 2939 cm^{-1} (CH), 1745 cm^{-1} (C═O), 1650 cm^{-1} (NHC═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (1H, d, J = 9.4 Hz, NH), 5.34 (1H, app t, $J_{3,4} = J_{3,2}$ = 9.6 Hz, H-3), 5.06 (1H, app t, $J_{4,3} = J_{4,5}$ = 9.6 Hz, H-4), 4.88 (1H, d, $J_{1,2}$ = 8.7 Hz, H-1), 4.42 (2H, br s, OCH_2), 4.10 (1H, app q, $J_{2,1} = J_{2,H} = J_{2,3}$ = 9.3 Hz, H-2),, 3.78 (1H, d, $J_{6',6}$ = 12.2 Hz, H-6′), 3.63 (1H, dd, $J_{6,6'}$ = 12.1 Hz, $J_{6,5}$ = 3.9 Hz, H-6), 3.57 (1H, m, H-5), 2.50 (1H, s, C≡CH), 2.09, 2.07 (3H, s, CH_3), 1.99 (NHCOCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 169.8 (C═O), 98.1 (C-1), 78.2 (C≡CH), 74.9 (C≡CH), 73.8 (C-5), 71.8 (C-3), 68.3 (C-4), 60.8 (C-6), 55.6 (OCH_2), 53.9 (C-2), 22.9, 20.3, 20.3 (CH_3); m/z HRMS (ESI-TOF) calcd for $C_{15}H_{21}NO_8Na$ 366.1165 (M + Na)$^+$, found 366.1183.

***O*-(2,3,4-TBDMS-α-L-fucopyranoside)-(1−6)-2-acetamido-3,4-di-*O*-acetyl-2-deoxy-1-*O*-propargyl-α-D-glucopyranoside, 9.** To a stirred solution of acceptor **8** (100 mg, 0.29 mmol), donor **7** (400 mg, 0.44 mmol), and NIS (98 mg, 0.44 mmol) in DCM (15 mL) with activated 3 Å ms at −20 °C under N_2 was added a catalytic amount of TMSOTf. The solution was stirred at −20 °C for 4 h before quenching with Et_3N (0.5 mL) and diluting with DCM (20 mL). The organic layer was washed with satd aqueous $Na_2S_2O_3$ solution (2 × 10 mL) and deionized H_2O (10 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed in vacuo. The crude mixture was purified by column chromatography (EtOAc/Hex, 3:2 v/v) to yield the product **9** as an amorphous white solid (208 mg, 86%): $[\alpha]^{22}_D$ = −55 (c = 0.1 in $CHCl_3$); ν_{max} (thin film) 3286 cm^{-1} (C≡CH), 3100 cm^{-1} (NH), 2931 cm^{-1} (CH), 1754 cm^{-1} (C═O), 1661 cm^{-1} (NHC═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (1H, d, J = 8.8 Hz, NH), 5.22 (1H, app t, $J_{3,2}$ = 10.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3A), 4.96 (1H, app t, $J_{4,3} = J_{4,5}$ = 9.6 Hz, H-4A), 4.78 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1A), 4.7 (1H, d, $J_{1,2}$ = 2.8 Hz, H-1B), 4.36 (2H, d, J = 2.2 Hz, OCH_2), 4.01 (1H, br d, $J_{3,2}$ = 7.4 Hz, H-3B), 3.94 (3H, br m, H-2A, H-2B, H-5B), 3.79 (1H, br s, H-4B), 3.71 (1H, dd, $J_{6',6}$ = 11.4 Hz, $J_{6',5}$ = 1.6 Hz, H-6′A), 3.70 (1H, m, 5-A), 3.58 (1H, dd, $J_{6,6'}$ = 11.6 Hz, $J_{6,5}$ = 6.4 Hz, H-6A), 2.42 (1H, t, J = 2.2 Hz, C≡CH), 2.02, 2.00 (3H, s, CH_3), 1.96 (NHCOCH_3), 1.18 (3H, d, $J_{6,5}$ = 6.5 Hz, H-6B), 0.92, 0.91, 0.89 (9H, s, $SiC(CH_3)_3$), 0.13, 0.12, 0.09, 0.06, 0.06, 0.05 ($Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.3, 169.2 (C═O), 99.1 (C-1B), 98.0 (C-1A), 78.6 (C≡CH), 75.2 (C≡CH), 73.6 (C-5A), 73.4 (C-4B), 72.8 (C-3A), 72.4 (C-2B), 70.3 (C-3B), 69.2 (C-4A), 68.9 (C-5B), 67.2 (C-6A), 55.4 (OCH_2), 54.2 (C-2A), 26.5, 26.1, 26.1 (SiC-$(CH_3)_3$), 23.4, ($NHCOCH_3$), 20.3, 20.3 (CH_3), 18.7, 18.5, 18.3, ($SiC(CH_3)$, 16.6 (C-6B), −3.6, −4.0, −4.2, −4.3, −4.6 ($Si(CH_3)_2$); m/z HRMS (ESI-TOF) calcd for $C_{39}H_{73}NO_{12}NaSi_3$ 854.4338 (M + Na)$^+$, found 854.4331.

2,3,4-Tri-*O*-*tert*-butyldimethylsilyl-1-*O*-propargyl-α-L-fucopyranoside, 11. General procedure (from the synthesis of **9**) with propargyl alcohol **10** as an acceptor (8.16 μL, 0.14 mmol) at −20 °C for 40 min. The crude material was purified by column chromatography (EtOAc/Hex, 1:19 v/v) to yield the required product **11** as a clear oil (51 mg, 86%): $[\alpha]^{20}_D$ = −30 (c = 0.1 in $CHCl_3$); ν_{max} (thin film) 3313 cm^{-1} (C≡CH), 2886 cm^{-1} (CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, d $J_{1,2}$ = 3.2 Hz, H-1), 4.25 (2H, m, OCH_2), 4.11 (1H, dd, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 3.0 Hz, H-2), 3.95 (1H, dd, $J_{3,2}$ = 9.4 Hz, $J_{3,4}$ = 2.2 Hz), 3.89 (1H, br q, $J_{5,6}$ = 6.6 Hz, H-5), 3.77 (1H, br s, H-4), 2.37 (1H, t, J = 2.3 Hz, C≡CH), 1.20 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6), 0.94, 0.93, 0.92 (3H, s, SiC(CH_3)$_3$), 0.16, 0.14, 0.12, 0.10, 0.09. 0.08 (3H, s, Si(CH_3)$_2$; ^{13}C NMR (100 MHz, $CDCl_3$) δ (C-1−6 not visible, due to broadening) 79.7 (−C≡CH), 74.0 (−C≡CH), 54.4 (OCH_2), 26.6, 26.2, 26.1 (SiC(CH_3)$_3$, 18.8, 18.6, 18.3 (SiC(CH_3)$_3$, −3.4, −3.9, −4.1, −4.2, −4.6, −4.6 ($Si(CH_3)_2$; m/z HRMS (ESI-TOF) calcd for $C_{27}H_{56}O_5NaSi_3$ 567.3333 (M + Na)$^+$, found 567.3351.

2,3,4-Tri-*O*-*tert*-butyldimethylsilyl-1-*O*-benzyl-α-L-fucopyranoside, 13. General procedure (from the synthesis of **9**) with benzyl alcohol **12** as an acceptor (14.7 μL, 0.14 mmol) at −20 °C for 40 min. The crude material was purified by column chromatography (EtOAc/Hex, 1:19) to yield the required product **13** as a clear oil (54 mg, 86% (3:2 α/β); Data for α anomer: $[\alpha]^{20}_D$ = −38 (c = 0.1 in $CHCl_3$); ν_{max} (thin film) 2953 cm^{-1} (CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (5H, m, Ar CH), 4.86 (1H, d, $J_{1,2}$ = 2.9 Hz, H-1), 4.73 (1H, d, J = 12.4 Hz, OCHH), 4.52 (1H, d, J = 12.4 Hz, OCHH), 4.12 (1 H, dd, $J_{2,3}$ = 9.5 Hz, $J_{2,1}$ = 2.5 Hz, H-2), 4.08 (1H, dd, $J_{3,2}$ = 9.4 Hz, $J_{3,4}$ = 1.8 Hz, H-4), 3.90 (1H, q, $J_{5,6}$ = 6.6 Hz, H-5), 3.77 (1H, br s, H-4), 1.16 (3H, d, $J_{6,5}$ = 6.5 Hz, H-6), 0.95, 0.93, 0.90 (SiC(CH_3)$_3$), 0.16, 0.15, 0.12, 0.08, 0.06, 0.05 ($Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (Ar C), 138.2 127.3 (Ar CH), 99.2 (C-1), 75.8 (C-4), 72.3 (C-3), 70.1 (C-2), 69.3 (OCH_2), 68.4 (C-5), 26.6, 26.2, 26.1 ($SiC(CH_3)_3$), 18.8, 18.6, 18.3 (SiC(CH_3)$_3$), 16.9 (C-6), −3.5, −3.9, −4.1, −4.3, −4.6, 4.6 ($Si(CH_3)_2$); m/z HRMS (ESI-TOF) calcd for $C_{31}H_{60}O_5NaSi_3$ 619.3646 (M + Na)$^+$, found 619.3636.

(2,3,4-Tri-*O*-*tert*-butyldimethylsilyl-α-L-fucopyranoside)-1−2-(ethyl 6-*tert*-butyldimethylsilyl-3,4-O-isopropylidene-1-thio-β-D-galactopyranoside), 15. General procedure (from the synthesis of **9**) with acceptor **14** (130 mg, 0.34 mmol), at −30 °C for 60 min. The crude material was purified by column chromatography (EtOAc/Hex, 1:24 v/v) to yield the product **15** as a clear oil (198 mg, 66%): $[\alpha]^{20}_D$ = −25 (c = 0.1 in $CHCl_3$); ν_{max} (thin film) 2929 cm^{-1} (CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, d, $J_{1,2}$ = 1.7 Hz, H-1B), 4.39 (1H, d, $J_{1,2}$ = 9.4 Hz, H-1A), 4.19 (3H, m, H-5B, H-4A, H-3A), 4.12 (2H, br s, H-2B, H-3B), 3.89 (1H, dd, $J_{6,6'}$ = 10.1 Hz, $J_{6,5}$ = 7.1 Hz, H-6A), 3.8 (1H, dd, $J_{6',6}$ = 10.0 Hz, $J_{6',5}$ = 5.7 Hz, H-6′A), 3.79 (1H, dd, $J_{5,6}$ = 10.5 Hz, $J_{5,4}$ = 1.6 Hz, H-5A), 3.79 (1H, br s, H-4B), 3.73 (1H, dd, $J_{2,1}$ = 9.4 Hz, $J_{2,3}$ = 5.9 Hz, H-2A), 2.78 (1H, dq, J_{gem} = 12.8 Hz, J = 7.9 Hz, SCH(H)), 2.68 (1H, dq, J_{gem} = 12.8 Hz, J = 7.5 Hz, SCH(H)), 1.15, 1.30 (3H, s, C(CH_3)$_2$), 1.29 (2H, t, J = 7.3 Hz, SCH_2CH_3), 1.16 (3H, d, $J_{6,5}$ = 6.3 Hz, H-6B), 0.96, 0.95, 0.95, 0.92 (SiC(CH_3)$_3$), 0.16, 0.16, 0.13, 0.13, 0.11, 0.10. 0.10, 0.90 Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.6 ($C(CH_3)_2$), 97.1 (C-1B), 83.2 (C-1A), 79.3 (C-3A), 76.9 (C-5A, 76.8 (C-4B), 74.1 (C-2A), 73.0 (C-4A), 71.6 (C-3B), 69.5 (C-2B), 68.7 (C-5B), 62.1 (C-6A), 27.7 ($CCH_3(CH_3$), 26.5, 26.2, 26.1 ($SiC(CH_3)_3$), 25.9 ($CCH_3(CH_3$), 25.7 ($SiC(CH_3)_3$), 24.0 (SCH_2CH_3), 18.8, 18.5, 18.2, 18.1 ($SiC(CH_3)_3$), 16.8 (C-6B), 14.9 (SCH_2CH_3), −3.7, −4.2, −4.3, −4.4, −4.6, −4.6, −5.5, −5.7 ($Si(CH_3)_2$; m/z HRMS (ESI-TOF) calcd for $C_{41}H_{86}O_9SSi_4Na$ 889.4967 (M + Na)$^+$, found 889.4956.

(2,3,4-Tri-*O*-*tert*-butyldimethylsilyl-α-L-fucopyranoside)-1−3-(4,6-*O*-benzylidene-1-methyl-β-D-galactopyranoside), 17. General procedure (from the synthesis of **9**) with acceptor **16** (130 mg, 0.34 mmol) at −20 °C for 40 min. The crude material was purified by column chromatography (EtOAc/Hex, 2:3 v/v) to yield the product **17**, as a clear oil (104 mg, 31%): $[\alpha]^{20}_D$ = −18 (c = 0.01 in $CHCl_3$); ν_{max} (thin film) 3574 cm^{-1} (OH), 2931 cm^{-1} (CH); ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.50 (2H, m, Ar CH), 7.37 (3H, m, Ar CH), 5.55 (1H, s, PhC$H$$O_2$), 4.96 (1H, d, $J_{1,2}$ = 2.8 Hz, H-1b), 4.38 (2H, m, H-1a, H-6′a), 4.35 (1H, d, $J_{4,3}$ = 3.3 Hz, H-4a), 4.19 (1H, m, H-5b), 4.16 (1H, m, H-2b), 4.13 (1H, dd, $J_{3,2}$ = 8.1 Hz, $J_{3,4}$ = 1.7 Hz, H-3b), 4.10 (1H, dd, $J_{6,6'}$ 10.7 Hz, $J_{6,5}$ = 1.7 Hz, H-6a), 4.00 (1H, dd, $J_{2,3}$ = 9.5 Hz, $J_{2,1}$ = 7.9 Hz, H-2a), 3.69 (1H, br s, H-4b), 3.61 (3H, s, OCH_3), 3.49 (2H, m, H-5a, H-3a) 1.06 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6b), 0.95, 0.94, 0.93 (9H, s, $SiC(CH_3)_3$), 0.16, 0.14, 0.13, 0.13, 0.12, 0.06 (3H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (Ar C), 128.8, 128.1, 128.1, 125.9, 125.9 (Ar CH), 103.3 (C-1a), 103.1 (C-1b), 100.7 (PhCHO_2), 83.0 (C-3a), 75.9 (C-4b), 75.2 (C-4a), 71.8 (C-3b), 70.2 (C-5b), 69.4 (C-6a), 69.4 (C-2a), 69.0 (C-2b), 64.5 (C-5a), 56.7

(OCH_3), 26.7, 26.4, 26.1 ($SiC(CH_3)_3$), 19.0, 18.6, 18.5 ($SiC(CH_3)_3$, 17.2 (C-6), −3.2, −3.9, −3.9, −4.3, −4.4, −4.8 ($Si(CH_3)_2$); *m/z* HRMS (ESI-TOF) Calcd. for $C_{38}H_{70}O_{10}Si_3Na$ 793.4175, $(M + Na)^+$, found 793.4193.

(*O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl)-(1−4))-((2,3,4-tri-*O*-*tert*-butyl-dimethylsilyl-*α*-L-fuco-pyranoside)-(1−3))-2-acetamido-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-1-*O*-propargyl-*β*-D-glucopyranoside, 19. General procedure (from the synthesis of **9**) with acceptor **18** (90 mg, 0.128 mmol) at −20 °C for 4 h. The crude material was purified by column chromatography (EtOAc/Hex, 1:1 v/v) to yield the product **19** as a white solid (41 mg, 24%): $[\alpha]^{20}_D = -67$ (c = 0.01 in $CHCl_3$); ν_{max} (thin film) 3407 cm^{-1} (NH), 3296 cm^{-1} (C≡*CH*), 2930 cm^{-1} (CH), 1751 cm^{-1} (C═O), 1678 cm^{-1} (*C*═ONH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (1H, d, J = 9.9 Hz, NH), 5.41 (1H, d, $J_{4,3}$ = 3.2 Hz, H-4b), 5.16 (1H, dd, $J_{2,3}$ = 10.3 Hz, $J_{2,1}$ = 7.7 Hz, H-2b), 5.03 (1H, dd, $J_{3,2}$ = 10.6 Hz, $J_{3,4}$ = 3.5 Hz, H-3b), 4.90 (1H, br s, H-1c), 4.67 (1H, d, $J_{1,2}$ = 2.0 Hz, H-1a), 4.41 (1H, d, $J_{1,2}$ = 7.8 Hz, H-1b), 4.32 (1H, br d, J = 10 Hz, H-2a), 4.25 (2H, m, OCH_2), 4.20 (1H, m, H-6b), 4.08 (4H, m, H-6′b, H-6a, H-5c, H-5b), 3.94 (1H, m, H-4c), 3.89 (3H, m, H-2c, H-3c, H-5a), 3.84 (1H, app t, $J_{3,2} = J_{3,4}$ = 6.1 Hz, H-3a), 3.76 (1H, dd, $J_{6',6}$ = 10.1 Hz, $J_{6',5}$ = 5.2 Hz, H-6′a), 3.64 (1H, dd, $J_{4,5}$ = 9.8 Hz, $J_{4,3}$ = 5.8 Hz, H-4a), 2.36 (1H, t, J = 2.3 Hz, C≡*CH*), 2.18, 2.12, 2.07, 2.04, 2.01 (3H, s, CH_3), 1.17 (3H, br s, H-6c), 0.95, 0.93, 0.93, 0.92 (9H, s, $SiC(CH_3)_3$), 0.14, 0.13, 0.13, 0.12, 0.11, 0.10, 0.08, 0.06 ($Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (C-1c-6c not visible, due to broadening), 99.2 (C-1b), 98.0 (C-1a), 79.1 (-*C*≡CH), 76.2 (C-4a), 74.9 (C-5a), 74.3 (C≡CH), 72.3 (C-4c), 71.0 (C-3a), 70.2 (C-3b), 68.8 (C-2b), 66.7 (C-4b), 62.7 (C-6a), 61.0 (C-6b), 54.8 (OCH_2), 48.3 (C-2a), 26.6, 26.4, 26.1, 25.8 ($SiC(CH_3)_3$), 22.9 ($NHCOCH_3$), 21.0, 20.7, 20.6, 20.6 (CH_3), 18.7, 18.6, 18.2, 18.0 ($SiC(CH_3)_3$), −4.0, −4.0, −4.2, −4.7, −5.0, −5.2, −5.2 ($Si(CH_3)_2$), (a = GlcNAc, b = Gal, c = Fuc); *m/z* HRMS (ESI-TOF) calcd for $C_{55}H_{101}NO_{19}NaSi_4$ = 1214.5943 $(M + Na)^+$, found 1214.5894.

2-Acetamido-3,4-di-*O*-acetyl-2-deoxy-6-(2,3,4-tri-*O*-acetyl-*α*-L-fucopyranosyl)-1-*O*-propargyl-*β*-D-glucopyranoside, 20. To a solution of **9** (450 mg, 0.54 mmol) in THF (10 mL) was added TBAF (1 M in THF) (5.4 mL, 5.4 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred for 30 h. The solvent volume was reduced in vacuo and the residue dissolved in pyridine (3 mL). Ac_2O (1.5 mL) was added at 0 °C, and the mixture was stirred for 16 h, warming to rt. The reaction was quenched by the addition of MeOH (1 mL) followed by dilution with EtOAc (30 mL). The organic layer was washed with H_2O, 10% $CuSO_4$ solution, and H_2O, dried over $MgSO_4$, and filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (EtOAc/Hex, 9:1 v/v) to yield the product **20** as a white foam (285 mg, 86%): $[\alpha]^{20}_D = -120$ (c = 0.1 in $CHCl_3$); ν_{max} (thin film) 3276 cm^{-1} (C≡*CH*), 3083 cm^{-1}, (NH), 2927 cm^{-1} (CH), 2115 cm^{-1} (*C*≡CH), 1741 (C═O), 1655 (*C*═ONH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.50 (1H, d, J = 8.9 Hz, NH), 5.36 (1H, dd, $J_{3,2}$ = 10.6 Hz, $J_{3,4}$ =3.3 Hz, H-3B), 5.32 (1H, d, $J_{4,3}$ = 3.4 Hz, H-4B), 5.31 (1H, app t, $J_{3,2} = J_{3,4}$ = 9.9 Hz, H-3A), 5.13 (1H, dd, $J_{2,3}$ = 10.5 Hz, $J_{2,1}$ = 3.5 Hz, H-2B), 5.09 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1B), 5.07 (1H, app t, $J_{4,3} = J_{4,5}$ = 9.5 Hz, H-4A), 4.87 (1H, d, $J_{1,2}$ = 8.3 Hz, H-1), 4.40 (2H, m, OCH_2), 4.18 (1H, m, H-5B), 3.93 (1H, m, H-2A), 3.76 (1H, $J_{6',6}$ = 11.4 Hz, $J_{6,5}$ = 2.2 Hz, H-6′A), 3.70 (1H, m, H-5A), 3.59 (1H, dd, $J_{6,6'}$ = 11.6 Hz, $J_{6,5}$ = 5.1 Hz, H-6A), 2.50 (1H, t, J = 1.9 Hz, -C≡*CH*), 2.18, 2.13, 2.05, 2.05, 2.01, 1.99 (3H, s, CH_3), 1.16 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6B); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 170.6, 170.6, 170.2, 169.9, 169.3 (C═OCH_3), 98.2 (C-1A), 96.7 (C-1B), 78.6 (*C*≡CH), 75.3 (C≡*CH*), 73.2 (C-5A), 72.5 (C-3A), 71.0 (C-4B), 69.0 (C-4A), 68.0 (C-2B), 67.9 (C-3B), 66.5 (C-6A), 64.5 (C-5B), 55.7 (*CH*$_2$C≡CH), 54.3 (C-2A), 23.3 (NHCO*CH*$_3$), 20.8, 20.7, 20.7, 20.6, 20.6 ($COCH_3$), 15.9 (C-6B); *m/z* HRMS (ESI-TOF) calcd for $C_{27}H_{37}NO_{15}Na$ 638.2061 (M + $Na)^+$, found 638.2051.

2-Acetamido-2-deoxy-6-(*α*-L-fucopyranosyl)-1-*O*-propargyl-*β*-D-glucopyranoside, 21. General deacetylation using Zemplén conditions with **20** (108 mg, 0.16 mmol, followed by freeze-drying to yield the product **21** as a white solid (67 mg, 94%): $[\alpha]^{20}_D = -83$ (c = 0.1 in MeOH); ν_{max} (thin film) 3284 cm^{-1} (OH), 3924 cm^{-1} (CH), cm^{-1}, 1648 cm^{-1} (*C*═ONH); ^{1}H NMR (600 MHz, MeOD) δ 4.86 (1H, d, $J_{1,2}$ = 2.9 Hz, H-1B), 4.62 (1H, d, $J_{1,2}$ = 8.5 Hz, H-1A), 4.35 (2H, d, J = 2.0 Hz, OCH_2), 4.11 (1H, q, $J_{5,6}$ = 6.5 Hz, H-5B), 3.96 (1H, d, $J_{6',6}$ = 11.3 Hz, H-6′A), 3.77 (3H, m, H-6A, H-3B, H-2B), 3.69 (1H, br s, H-4B), 3.68 (1H, app t, $J_{2,3} = J_{2,1}$ = 9.0 Hz, H-2A), 3.51 (1H, m, H-3A), 3.43 (2H, m, H-4A, H-5A), 2.88 (1H, t, J = 2.0 Hz, −C≡*CH*), 2.00 (3H, s, CH_3), 1.24 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6B); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8 (C═O), 99.9 (C-1B), 99.5 (C-1A), 78.99 (−*C*≡CH), 75.9 (C-5A),75.2 (C≡CH), 74.6 (C-3A), 72.7 (C-4B), 70.8 (C-4A), 70.7 (C-3B), 69.1 (C-2B), 67.1 (C-6A), 66.6 (C-5B), 56.2 (C-2A), 55.4 (OCH_2), 21.9 (CH_3), 15.7 (C-6B); *m/z* HRMS (ESI-TOF) calcd for $C_{17}H_{27}NO_{10}Na$ = 428.1533 $(M + Na)^+$, found 428.1532.

(*O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl)-(1−4))-((2,3,4-tri-*O*-acetyl-*α*-L-fucopyranoside)-(1−3))-2-acetamido-2-deoxy-6-*O*-acetyl-1-*O*-propargyl-*β*-D-glucopyranoside, 22. To a solution of **19** (24 mg, 0.02 mmol) in THF (2.5 mL) was added TBAF (1 M in THF) (0.3 mL, 0.30 mmol) at 0 °C. The mixture was heated to 50 °C and stirred for 16 h. The solvent volume was reduced in vacuo and the residue dissolved in pyridine (1 mL). Ac_2O (1 mL) was added at 0 °C, and the mixture was stirred for 16 h, warming to rt. The reaction was quenched by the addition of MeOH (1 mL) followed by dilution with EtOAc (30 mL). The organic layer was washed with H_2O, 10% $CuSO_4$ solution, and H_2O, dried over $MgSO_4$, and filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (EtOAc/Hex, 4:1 v/v) to yield the product **22** as a white solid (14 mg, 77%): $[\alpha]^{20}_D = 77$ (c = 0.01 in $CHCl_3$); ν_{max} (thin film) 3300 cm^{-1} (NH), 3281 cm^{-1} (C≡*CH*), 2927 cm^{-1} (CH), 1740 cm^{-1} (C═O), 1672 cm^{-1} (*C*═ONH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.52 (1H, d, J = 8.8 Hz, NH), 5.46 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1c), 5.44 (1H, d, $J_{4,3}$ = 3.3 Hz, H-4b), 5.39 (1H, d, $J_{4,3}$ = 3.0 Hz, H-4c), 5.23 (1H, dd, $J_{3,2}$ = 10.9 Hz, $J_{3,4}$ = 3.1 Hz, H-3c), 5.12 (1H, d, $J_{2,3}$ = 10.4 Hz, $J_{2,1}$ = 8.2 Hz, H-2b), 5.05 (1H, dd, $J_{2,3}$ = 10.8 Hz, $J_{2,1}$ = 3.8 Hz, H-2c), 5.01 (1H, dd, $J_{3,2}$ = 10.4 Hz, $J_{3,4}$ = 3.5 Hz, H-3b) 4.82 (1H, m, H-5c), 4.81 (1H, d, $J_{1,2}$ = 7.3 Hz, H-1a), 4.63 (1H, dd, $J_{6',6}$ = 12.1 Hz, $J_{6',5}$ = 2.8 Hz, H-6′a), 4.49 (1H, dd, $J_{6',6}$ = 11.9 Hz, $J_{6',5}$ = 5.6 Hz, H-6′b), 4.49 (1H, d, $J_{1,2}$ = 8.0 Hz, H-1b), 4.33 (2H, m, OCH_2), 4.30 (1H, $J_{6,6'}$ = 7.5 Hz, $J_{6,5}$ = 11.8 Hz, H-6b), 4.19 (1H, dd, $J_{6,6'}$ = 11.9 Hz, $J_{6,5}$ = 4.9 Hz, H-6a), 4.13 (1H, m, H-3a), 3.90 (1H, t, $J_{5,6}$ = 6.8 Hz, H-5b), 3.87 (1H, m, H-5a), 3.83 (1H, m, H-2a), 3.62 (1H, m, H-4a), 2.45 (1H, J = 2.2 Hz, C≡*CH*), 2.22, 2.17, 2.16, 2.13, 2.10, 2.19, 2.02, 2.00, 1.99 (3H, s, CH_3), 1.23 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6b), (a = GlcNAc, b = Gal, c = Fuc); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 170.8, 170.7, 170.6, 170,4, 170.3, 170.03, 169.87, 169.3 (C═O), 100.4 (C-1b), 97.8 (C-1a), 95.1 (C-1c), 78.6 (−*C*≡CH), 75.2 (−C≡*CH*), 74.2 (C-5a), 72.9 (C-4a), 72.9 (C-3a), 71.3 (C-4c), 71.0 (C-5b), 70.8 (C-3b), 68.9 (C-2b), 68.1 (C-2c), 68.0 (C-3c), 66.6 (C-4b), 64.2 (C-5c), 61.9 (C-6a), 60.7 (C-6b), 55.8 (C-6b), 55.0 (C-2a), 23.5 (NHCO*CH*$_3$), 21.0, 20.9, 20.8, 20.8, 20.7, 20.7, 20.6, 20.6 (CH_3), 15.8 (C-6c); *m/z* HRMS (ESI-TOF) calcd for $C_{39}H_{53}NO_{23}Na$ 926.2906 $(M + Na)^+$, found 926.2895.

2-Acetamido-2-deoxy-(*β*-D-galactopyranosyl-(1−4))-((-*α*-L-fucopyranosyl)-(1−3))-1-*O*-propargyl-*β*-D-glucopyranoside, 23. General deacetylation method with **22** (132 mg, 0.15 mmol), followed by freeze-drying to yield the product **23**, as a white solid (78 mg, 87%) after freeze-drying: $[\alpha]^{20}_D = 35$ (c = 0.01 in CH_2Cl_2/MeOH 1:1); ν_{max} (thin film) 3274 cm^{-1} (OH), 2924 cm^{-1} (CH), 1646 cm^{-1} (*C*═ONH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.05 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1c), 4.86 (1H, m, H-5c), 4.69 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1a), 4.46 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1b), 4.37 (2H, s, OCH_2), 3.95 (2H, br s, C-6a), 3.92 (3H, m, H-2a, H-5b, H-4a), 3.88 (1H, dd, $J_{3,2}$ = 10.5 Hz, $J_{3,4}$ = 3.3 Hz, H-3c), 3.82 (1H, d, $J_{4,3}$ = 2.5 Hz, H-4b), 3.79 (1H, dd, $J_{6,6'}$ = 11.2 Hz, $J_{6,5}$ = 6.9 Hz, H-6b), 3.74 (1H, d, $J_{4,3}$ = 3.0 Hz, H-4c), 3.69 (1H, dd, $J_{6',6}$ = 11.5 Hz, $J_{6',5}$ = 5.1 Hz, H-6′b), 3.65 (1H, dd, $J_{2,3}$ = 10.2 Hz, $J_{2,1}$ = 3.5 Hz, H-2c), 3.53 (1H, $J_{2,3}$ = 9.6 Hz, $J_{2,1}$ = 7,3 Hz, H-2b), 3.48 (1H, dd, $J_{3,2}$ = 9.7 Hz, $J_{3,4}$ = 2.8 Hz, H-3b), 3.46 (2H, m, H-5a, H-3a), 2.88 (1H, br s, −C≡*CH*), 1.99 (3H, s, CH_3), 1.20 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6c); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9 (C═O), 102.9 (C-1b), 99.3 (C-1c), 99.0 (C-1c), 78.9 (-*C*≡CH), 76.5 (C-3a), 75.6 (C-5a),

75.5 (-C≡CH), 75.2 (C-4a), 74.2 (C-5b), 73.9 (C-3b), 72.7 (C-4c), 71.7 (C-2b), 70.2 (C-3c), 69.0 (C-2c), 68.9 (C-4b), 66.7 (C-5c), 61.8 (C-6b), 60.3 (C-6a), 56.2 (C-2a), 55.4 (OCH_2), 22.0 (CH_3), 15.6 (C-6c), (a = GlcNAc, b = Gal, c = Fuc); *m/z* HRMS (ESI-TOF) calcd for $C_{23}H_{37}NO_{15}Na$ = 590.2061 $(M + Na)^+$, found 590.2055.

1-*N*-Trichloroacetamido-2,4-di-*O*-TBDMS-*α*-L-fucopyranoside, 25. To a stirred solution of acceptor **5** (100 mg, 0.22 mmol) and donor **24** (135 mg, 0.27 mmol) in DCM (3 mL) with preactivated 3 Å MS at 0 °C was added $BF_3{\cdot}OEt_2$ (37 μL, 0.27 mmol). The reaction was stirred for 16 h with warming to rt before quenching with satd aqueous $NaHCO_3$ solution (5 mL). The reaction was diluted with DCM (10 mL) and filtered through a plug of Celite. The solvent was removed in vacuo and purified using column chromatography (EtOAc/hexane, 1:49 v/v) to yield the product **25**, as an off white amorphous solid (57 mg, 46% yield): $[\alpha]^{20}_D$ = 49 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3501 cm^{-1} (OH), 3389 cm^{-1} (NH), 2929 cm^{-1} (CH), 1708 cm^{-1} (C═O);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 6.4 Hz, NH), 5.54 (1H, d, $J_{1,2}$ = 4.2 Hz, H-1), 4.10 (1H, dd, $J_{2,3}$ = 7.3 Hz, $J_{2,1}$ = 4.2 Hz, H-2), 3.95 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 2.9 Hz, H-5), 3.91 (1H, dq, $J_{5,6}$ = 6.5 Hz, $J_{5,4}$ = 2.8 Hz, H-5), 3.69 (1H, dd, $J_{3,2}$ = 7.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 1.33 (3H, d, $J_{6,5}$ = 6.4 Hz, H-6), 0.96, 0.94 (9H, s, $SiC(CH_3)_3$), 0.17, 0.15, 0.14, 0.13 (3H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (C═O), 98.2 ($COCCl_3$), 76.6 (C-1), 72.2 (C-3), 70.6 (C-4), 69.8 (C-5), 69.1 (C-2), 25.9, 25.7 ($SiC(CH_3)_3$), 18.0, 17.7 ($SiC(CH_3)_3$, 16.0 (C-6), −4.3, −4.6, −4.7, −4.7 ($Si(CH_3)_2$; *m/z* HRMS (ESI-TOF) calcd for $C_{20}H_{40}NO_5NaSi_2Cl_3$ 558.1408 $(M + Na)^+$, found 558.1414.

Ethyl 2,3,4,6-Tetra-O-acetyl-1-thio-*β*-D-glucopyranoside, 26. As the synthesis of **25** and purified using column chromatography (EtOAc/hexane, 1:49 v/v) to yield the product **26** as an off-white amorphous solid (64 mg, 71% yield): $[\alpha]^{20}_D$ = −22 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 2964 cm^{-1} (CH), 1737 cm^{-1} (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, app t, $J_{3,2}$ = $J_{3,4}$ = 9.5 Hz, H-3), 5.10 (1H app t, $J_{4,3}$ = $J_{4,5}$ = 9.8 Hz, H-4), 5.05 (1H, app t, $J_{2,3}$ = $J_{2,1}$ = 9.5 Hz, H-2), 4.51 (1H, d, $J_{1,2}$ = 9.8 Hz, H-1), 4.26 (1H, dd, $J_{6,6'}$ = 12.4 Hz, $J_{6,5}$ = 4.9 Hz, H-6), 4.15 (1H, dd, $J_{6'6}$ = 12.3 Hz, $J_{6',5}$ = 2.2 Hz, H-6′), 3.73 (1H, ddd, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 4.8 Hz, $J_{5,6'}$ = 2.3 Hz, H-5), 2.72 (2H, m, SCH_2CH_3), 2.09, 2.08, 2.04, 2.03 (3H, s, CH_3), 1.29 (3H, t, *J* = 7.4 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.9, 169.0, 169.0 (C═O), 83.1 (C-1), 75.4 (C-5), 73.4 (C-3), 69.3 (C-2), 67.8 (C-4), 61.7 (C-6), 23.7 (SCH_2CH_3), 20.3, 20.3, 20.2, 20.1 (CH_3), 14.4 (SCH_2CH_3); *m/z* HRMS (ESI-TOF) calcd for $C_{16}H_{24}O_9SNa$ 415.1039 $(M + Na)^+$, found 415.1054.

2,4-Di-*O*-*tert*-butyldimethylsilyl-1-*O*-benzyl-*α*-L-fucopyranoside, 27a, and 2,4-Di-*O*-*tert*-butyldimethylsilyl-1-*O*-benzyl-*β*-L-fucopyranoside, 27b. General procedure (for the synthesis of **9**) with donor **7** (150 mg, 0.32 mmol) and benzyl alcohol **12** (0.1 mL, 0.96 mmol) for 150 min at −30 °C before purification by column chromatography (DCM/hexane, 3:2 v/v) to yield the product **27a** and **27b** as clear oils (145 mg, 88% (2.6:1, *α*/*β*). Data for *α* anomer, **27a**: $[\alpha]_D^{20}$ = 37 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3599 cm^{-1} (OH), 2929 cm^{-1} (CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 7.8 Hz, *o*-Ph), 7.35−7.32 (3H, m, *m*,*p*-Ph), 4.83 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 4.71 (1H, d, *J* = 12.1 Hz, $PhCH_2$), 4.57 (1H, d, *J* = 12.1 Hz, $PhCH_2$), 3.98 (1H, dd, $J_{2,3}$ = 9.7 Hz, $J_{2,1}$ = 3.4 Hz, H-2), 3.97 (1H, q, $J_{5,6}$ = 6.5 Hz, H-5), 3.92 (1H, m, H-3), 3.88 (1H, dd, $J_{4,3}$ = 2.6 Hz, $J_{4,5}$ = 0.8 Hz, H-4), 1.98 (1H, br s, OH), 1.20 (3H, d, $J_{6,5}$ = 6.6 Hz, H-6), 0.96, 0.92 (Si $C(CH_3)_3$), 0.16, 0.12, 0.08, 0.01 (3H, s, $Si(CH_3)_2$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (Ar C), 128.4 (Ar CH), 128.3 (Ar CH), 127.7 (Ar CH), 97.9 (C-1), 73.5 (C-4), 70.6 (C-3), 70.7 (C-2), 69.2 (OCH_2Ph), 67.2 (C-5), 26.1, 25.8 ($SiC(CH_3)_3$), 18.5, 18.2 ($SiC(CH_3)$), 17.2 (C-6), −4.0, −4.5, −4.5, −4.7 ($Si(CH_3)$); *m/z* HRMS (ESI-TOF) calcd for $C_{25}H_{46}O_5NaSi_2$ 505.2782, $(M + Na)^+$, found =505.2777. Data for *β* anomer, **27b**: $[\alpha]^{20}_D$ = 20 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3595 cm^{-1} (OH), 2929 cm^{-1} (CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 7.3 Hz, *o*-Ph), 7.35 (2H, t, *J* = 7.2 Hz, *m*-Ph), 7.31 (1H, t, *J* = 7.1 Hz, *p*-Ph), 4.93 d, *J* = 11.8 Hz, OC*H*(H)Ph), 4.61 (1H, d, *J* = 11.8 Hz, PhCH(*H*)), 4.25 (1H, $J_{1,2}$ = 7.5 Hz, H-1), 3.79 (1H, dd, $J_{4,3}$ = 2.7 Hz, H-4), 3.68 (1H, dd, $J_{2,3}$ = 9.4 Hz, $J_{2,1}$ = 7.3 Hz, H-2), 3.56 (1H, q, $J_{5,6}$ = 6.5 Hz, H-5), 3.46 (1H, m, H-3), 2.02 (1H, d, *J* = 4.7 Hz, OH), 1.29 (3H, d, $J_{6,5}$ = 6.4 Hz, H-6), 0.98, 0.90 (9H, s, Si $C(CH_3)_3$), 0.16, 0.13, 0.12, 0.06 (3H, s, $Si(CH_3)_2$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (Ar C), 128.3 (Ar CH), 128.1 (Ar CH), 127.5 (Ar CH), 102.0 (C-1), 75.5 (C-3), 73.0 (C-4), 72.7 (C-2), 71.2 (C-5), 70.5 (OCH_2Ph), 26.1, 25.9 ($SiC(CH_3)_3$), 18.6, 18.2 ($SiC(CH_3)$), 17.3 (C-6), −4.1, −4.1, −4.2, −4.7 ($Si(CH_3)$); *m/z* HRMS (ESI-TOF) calcd for $C_{25}H_{46}O_5NaSi_2$ 505.2782 $(M + Na)^+$, found 505.2786.

((2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl)-(1−4))-((2,4-di-*O*-*tert*-butyldimethylsilyl-*α*-L-fucopyranoside)-(1−3))-2-acetamido-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-1-*O*-propargyl-*β*-D-glucopyranoside, 28. To a stirred solution of acceptor **18** (225 mg, 0.32 mmol), donor **5** (251 mg, 0.57 mmol), and NIS (108 mg, 0.57 mmol) in DCM (5 mL) at −20 °C under argon was added TMSOTf (cat.). The mixture was stirred at −20 °C for 3 h. The reaction was quenched with the addition of Et_3N (0.5 mL) and diluted with DCM (10 mL). The organic layer was washed with satd aqueous $Na_2S_2O_3$ solution (10 mL) and deionized H_2O (10 mL), dried over $MgSO_4$, and filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (EtOAc/Hex, 25−50%) to yield the product **28** as a white solid (182 mg, 53%): $[\alpha]^{20}_D$ = −54 (*c* = 0.1 in $CHCl_3$); ν_{max} (thin film) 3598 cm^{-1} (OH), 3335 (NH), 3328 (C≡*CH*), 2930 cm^{-1} (CH), 1754 cm^{-1} (C═O), 1663 cm^{-1} (*C*═ONH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.04 (1H, *J* = 8.6 Hz, NH), 5.38 (1H, d, $J_{4,3}$ = 3.0 Hz, H-4b), 5.10 (1H, dd, $J_{2,3}$ = 10.6 Hz, $J_{2,1}$ = 7.7 Hz, H-2b), 5.05 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1c), 5.00 (1H, dd, $J_{3,2}$ = 10.6 Hz, $J_{3,4}$ = 3.3 Hz, H-3b), 4.69 (1H, d, $J_{1,2}$ = 6.0 Hz, H-1a), 4.61 (1H, d, $J_{1,2}$ = 8.0 Hz, H-1b), 4.26 (2H, d, *J* = 2.0 Hz, OCH_2), 4.14 (1H, dd, $J_{6,6'}$ = 11.4 Hz, $J_{6,5}$ = 7.5 Hz, H-6b), 4.13 (1H, m, H-5c), 4.10 (1H, dd, $J_{6',6}$ = 11.4 Hz, $J_{6',5}$ = 6.4 Hz, H-6′b), 4.04 (1H, app t, $J_{3,4}$ = $J_{3,2}$ = 6.0 Hz, H-3a), 3.95 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 5.7 Hz, H-4a), 3.92 (2H, m, H-6a, H-2c), 3.89 (1H, m, H-2a), 3.82 (2H, m, H-5b, H-4c), 3.78 (2H, m, H-6′a, H-3c), 3.45 (1H, m, H-5a), 2.36 (1H, br s, −C≡*CH*), 2.17, 2.07, 2.02, 2.01, 1.98 (3H, s, CH_3), 1.91 (1H, d, *J* = 4.2 Hz, OH), 1.16 (3H, d, $J_{6,5}$ = 6.2 Hz, H-6c), 0.92, 0.92, 0.90 (9H, s, $SiC(CH_3)_3$), 0.13, 0.11, 0.11, 0.09, 0.08, 0.07 ($Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 170.0, 169.9, 169.7, 169.7 (C═O), 99.12 (C-1b), 98.0 (C-1a), 97.8 (C-1c), 78.9 (−*C*≡CH), 75.7 (C-5a), 74.4 (−C≡CH), 73.8 (C-3c), 73.0, 73.0 (C-3a, C-4a), 70.7 (C-4c), 70.4 (C-3b), 70.3 (C-2c), 69.9 (C-5b), 68.9 (C-2b), 67.3 (C-5c), 66.8 (C-4b), 61.6 (C-6a), 60.9 (C-6b), 54.7 (OCH_2), 52.5 (C-2a), 25.9, 25.8, 25.7 ($SiC(CH_3)_3$), 23.3 ($NHCOCH_3$), 20.7, 20.6, 20.5, 20.4 (CH_3), 18.4, 18.0, 18.0 ($SiC(CH_3)_3$), 17.1 (C-6c), −4.0, −4.4, −4.7, −4.9, −5.3, −5.4 ($Si(CH_3)_2$), (a = GlcNAc, b = Gal, c = Fuc); *m/z* HRMS (ESI-TOF) calcd for $C_{49}H_{87}NO_{19}NaSi_3$ 1100.5078 $(M + Na)^+$, found 1100.5076.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds. X-ray data for compound 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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