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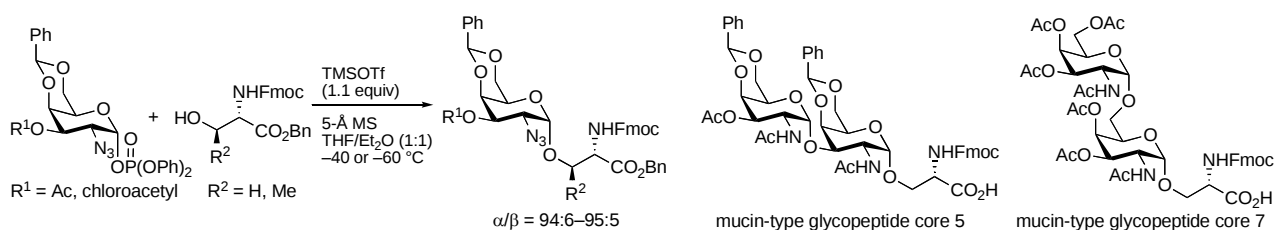
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A stereocontrolled construction of 2-azido-2-deoxy-1,2-*cis*- α -galactosidic linkages utilizing 2-azido-4,6-*O*-benzylidene-2-deoxygalactopyranosyl diphenyl phosphates: stereoselective synthesis of mucin core 5 and core 7 structures

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A stereocontrolled construction of 2-azido-2-deoxy-1,2-*cis*- α -galactosidic linkages utilizing 2-azido-4,6-*O*-benzylidene-2-deoxygalactopyranosyl diphenyl phosphates: stereoselective synthesis of mucin core 5 and core 7 structures

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ABSTRACT

TMSOTf-promoted glycosidation of 2-azido-4,6-*O*-benzylidene-2-deoxygalactosyl diphenyl phosphates with fluorenylmethoxycarbonyl (Fmoc)-protected serine and threonine derivatives in THF/Et₂O (1:1) gave glycosyl amino acids in high yields and with excellent levels of α -selectivity (α/β = 94:6–95:5). The synthetic utility of the present glycosidation method was demonstrated by a stereoselective synthesis of mucin-type glycopeptide core 5 and core 7 building blocks, which are suitable for Fmoc-based solid-phase synthesis of *O*-glycopeptides.

1. Introduction

2-Acetamido-2-deoxy-D-glycopyranosides are the structural units in glycoproteins, one of the most important classes of naturally occurring oligosaccharides and glycoconjugates.¹ Mucin-type glycoproteins, the oligosaccharide moiety of which is *O*-glycosidically linked to L-serine and L-threonine through 2-acetamido-2-deoxy- α -D-galactopyranose (GalNAc), have attracted much attention due to their major roles in numerous biological aspects.² The glycoproteins can serve as a source of antigens to the immune system. Since a variety of tumor-associated antigens are *O*-linked glycans,³ synthetic mucin-type *O*-linked glycopeptides have been pursued as anti-tumor vaccines.⁴ Eight core structures of mucin-type glycopeptides have been identified to date. The GalNAc α -1-*O*-Ser/Thr structure, commonly referred to as the T_N-antigen, forms the biosynthetic foundation for a diverse array of core structures generated by glycosylation at the C-3 and/or C-6 hydroxy groups of GalNAc (Figure 1).

The formation of the 1,2-*cis*- α -glycosidic linkage between GalNAc and serine or threonine has garnered much attention and has been extensively reviewed in the literature.^{5,6} The majority of reported approaches toward the construction of this type of linkage rely on the methodology introduced by Paulsen in 1978,⁷

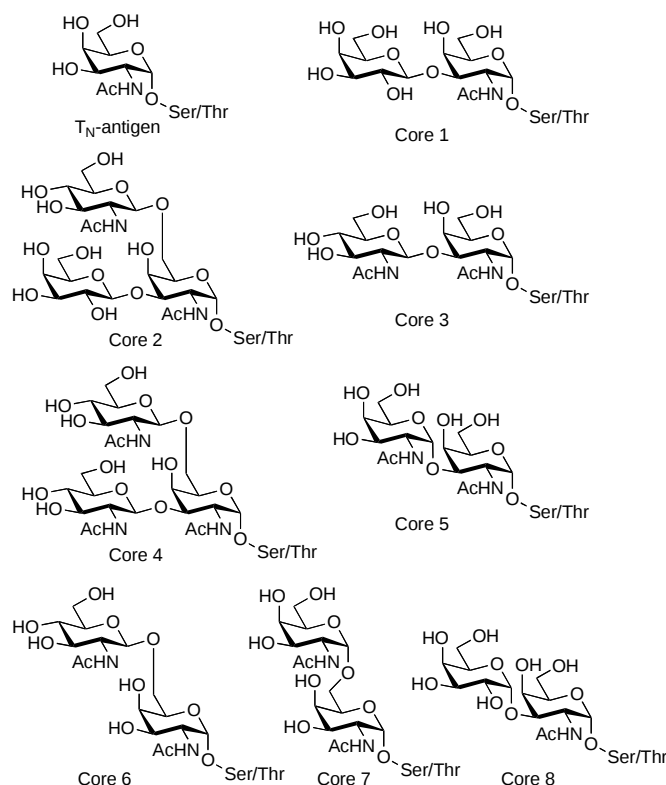
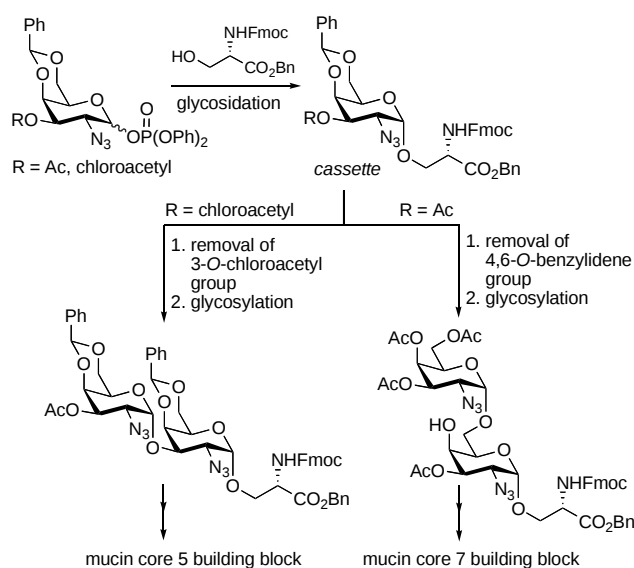


Figure 1. Structures of mucin-type glycopeptide cores.

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in which the nonparticipating azido group is selected as a latent amino functionality at C-2. 2-Azido-2-deoxygalactosyl halides,⁸ trichloroacetimidates^{8h,9–11} and thioethers¹² are the most commonly used glycosyl donors to prepare this type of linkage.^{13–15} Although the stereochemical outcome of the glycosidation with these donors often resulted in moderate to good α -selectivity,^{5f} several examples of highly stereocontrolled 1,2-*cis*- α -glycosidation reactions were reported by the Mukaiyama,¹⁴ Danishefsky,^{8h} Polt,⁸ⁱ Field,^{8j} and Boons^{12h} groups. In contrast, there are only a few reports on glycosidations using C-2 functionalities capable of neighboring group participation, such as NHAc¹⁶ and NHTroc.¹⁷ Kiso and co-workers reported that reactions of 4,6-*O*-di-*tert*-butylsilylene-protected GalNTroc donors with serine and threonine derivatives produced exclusively α -glycosides in high yields despite the presence of a participating NHTroc group at C-2.^{5g,17b,c} Conceptionally different approaches were developed by the Schmidt¹⁸ and Gin¹⁹ groups. Schmidt and co-workers reported a Michael-type addition of serine and threonine derivatives to 2-nitrogalactal to give the corresponding 2-deoxy-2-nitro- α -galactosides.¹⁸ Despite the variety of methods available, stereoselective synthesis of GalNAc-1-*O*-Ser/Thr structures continues to be a challenge because reports on high-yielding and highly stereoselective construction of this type of linkage are limited.^{8h,12h,14,17}

For the past two decades, we have been engaged in the development of novel stereocontrolled glycosidation reactions capitalizing on phosphorus-containing leaving groups.^{20,21} For stereoselective construction of 1,2-*cis*- α -glycosidic linkages,²² we recently reported that catalytic stereoselective glycosidations of glycosyl diphenyl phosphates using a commercially available HClO₄ solution (0.1 M solution in dioxane) in dioxane/Et₂O (1:1) gave glycosides in good yields and with good to high α -selectivities (up to α/β = 92:8).²³ Herein, we report a high-yielding and highly stereoselective construction of 2-azido-2-deoxy-1,2-*cis*- α -galactosidic linkages by TMSOTf-promoted glycosidation of 2-azido-4,6-*O*-benzylidene-2-deoxygalactosyl diphenyl phosphates with fluorenylmethoxycarbonyl (Fmoc)-protected serine and threonine derivatives in THF/Et₂O (1:1) and its application to the synthesis of mucin core 5 and core 7 building blocks employing the cassette approach developed by the groups of Meldal and Paulsen²⁴ and Danishefsky's group²⁵ as outlined in Scheme 1.²⁶



Scheme 1. Synthesis of mucin core 5 and core 7 building blocks by the cassette method.

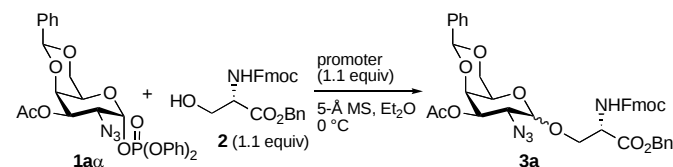
2. Results and discussion

2.1. Glycosidation of 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-D-galactosyl diphenyl phosphates **1a** with serine derivative **2**

At the outset of this work, the glycosidation of 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy- α -D-galactopyranosyl diphenyl phosphate (**1a**)²⁷ was explored using Fmoc-protected serine derivative **2** (1.1 equiv) as an acceptor alcohol. The reaction using TMSOTf (1.1 equiv) as a promoter and 5-Å molecular sieves (MS) in Et₂O proceeded at 0 °C to completion within 0.1 h, giving glycoside **3a** in 83% yield (Table 1, entry 1). The α/β ratio of **3a** was determined to be 71:29 by HPLC (Zorbax[®] Sil column). The use of a 0.5 M solution of TMSClO₄ in toluene, prepared from TMSCl and AgClO₄,²⁸ resulted in a similar level of α -selectivity (α/β = 73:27, entry 2). TMSNTf₂-promoted glycosidation provided modest yield and poor α -selectivity (59%, α/β = 55:45, entry 3). The reaction with BF₃·OEt₂ required a significantly longer time (10 h) to reach completion even at room temperature and provided **3a** in 46% yield with an α/β ratio of 69:31 (entry 4). Although HClO₄ was the optimal promoter in our previous work,²³ the use of a commercially available 0.1 M solution of anhydrous HClO₄ in dioxane gave moderate yield and α -selectivity due to partial hydrolysis of the benzylidene acetal functionality (63%, α/β = 67:33, entry 5). Since explosive AgClO₄ is necessary to prepare TMSClO₄, our efforts focused on the use of conveniently handled TMSOTf.

Table 1

Screening of promoters in the glycosidation of 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy- α -D-galactosyl diphenyl phosphate (**1a**) with serine derivative **2**



Entry	Promoter	<i>t</i> (h)	Yield (%)	α/β^a
1	TMSOTf	0.1	83	71:29
2	TMSClO ₄ ^b	0.1	83	73:27
3	TMSNTf ₂	0.1	59	55:45
4 ^c	BF ₃ ·OEt ₂	10	46	69:31
5	HClO ₄	0.5	63	67:33

^a The ratio was determined by HPLC (column, Zorbax[®] Sil, 4.6×250 mm; eluent, hexane/AcOEt 3:2; flow rate, 1.0 mL/min).

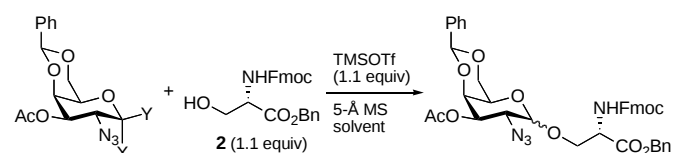
^b Prepared from TMSCl and AgClO₄.

^c The reaction was performed at 23 °C.

Using TMSOTf as a promoter, we next studied the effects of solvents on stereoselectivity (Table 2). Switching the solvent from Et₂O to CH₂Cl₂ or toluene slightly increased α -selectivities at the expense of product yields (entries 2 and 3). Good yield and α -selectivity were obtained in dioxane, although the high melting point of dioxane precluded a direct comparison with those obtained with the foregoing solvents at 0 °C (entry 4). Since the use of THF improved α -selectivity (α/β = 86:14, entry 5), we then explored a mixed solvent system of THF and Et₂O. Gratifyingly, the reaction in THF/Et₂O (1:1) gave **3a** in high yield and α -selectivity (85%, α/β = 89:11, entry 6).²⁹ An examination of the temperature profile demonstrated that lowering the reaction temperature to –20 or –40 °C increased α -selectivity (entries 7 and 8). Although the α -selectivity and yield obtained at –60 °C were the same as those at –40 °C (entries 8 vs 9), a much longer time (10 h) was necessary to complete the reaction. We next investigated the effect of the ratio of a mixed solvent system at –40 °C. Increasing the ratio of THF to Et₂O

Table 2

Effects of solvents, temperature and anomeric composition of the donor on selectivity



1aα: X = OP(O)(OPh)₂, Y = H
1aβ: X = H, Y = OP(O)(OPh)₂

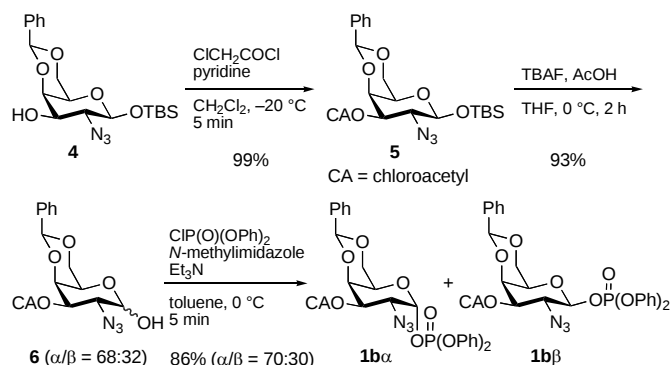
Entry	Donor	Solvent	T (°C)	t (h)	Yield (%)	α/β ^a
1	1aα	Et ₂ O	0	0.1	83	71:29
2	1aα	CH ₂ Cl ₂	0	0.1	73	75:25
3	1aα	toluene	0	0.1	64	77:23
4	1aα	dioxane	23	0.1	80	80:20
5	1aα	THF	0	0.1	76	86:14
6	1aα	THF/Et ₂ O (1:1)	0	0.1	85	89:11
7	1aα	THF/Et ₂ O (1:1)	-20	0.5	91	91:9
8	1aα	THF/Et ₂ O (1:1)	-40	1.5	93	95:5
9	1aα	THF/Et ₂ O (1:1)	-60	10	93	95:5
10	1aα	THF/Et ₂ O (2:1)	-40	1.5	63	94:6
11	1aα	THF/Et ₂ O (1:2)	-40	2	91	94:6
12	1aα	THF/Et ₂ O (1:5)	-40	2	95	93:7
13	1aβ	THF/Et ₂ O (1:1)	-40	1.5	94	94:6

^a The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, hexane/AcOEt 3:2; flow rate, 1.0 mL/min).

(2:1) resulted in lower yield due to the formation of unidentified glycosyl polytetrahydrofurans (entry 10),³⁰ while increasing the ratio of Et₂O to THF (THF/Et₂O = 1:2–1:5) had little impact on product yield and α-selectivity (entries 11 and 12). Thus, we selected THF/Et₂O (1:1) as a solvent system for further experiments.³¹ The use of β-phosphate **1aβ** gave virtually the same product yield and α-selectivity as those obtained with α-phosphate **1aα** (entries 8 vs 13), because thermodynamically less-stable β-phosphates anomerize to the corresponding α-phosphates in the presence of acids.^{27,32} Therefore, stereoselective preparation of α- or β-phosphates is not a requirement for this method. From comparison of the α/β ratios obtained with 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactosyl diphenyl phosphate and 3,4,6-tri-*O*-acetyl-protected diphenyl phosphate **19** (*vide infra*),³³ the presence of a 4,6-*O*-benzylidene acetal group proved to be crucial for high levels of α-selectivity.

2.2. TMSOTf-promoted glycosidation of diphenyl phosphates **1** with acceptor alcohols **2**, **7–9**

As mentioned above, the core structures of mucin-type glycopeptides contain additional glycosyl residues at position 3 and/or position 6 to form complex *O*-glycans (Figure 1). Therefore, regioselective deprotection of **3aα** was explored. Although hydrolysis of the 4,6-*O*-benzylidene acetal group in **3aα** could be achieved (*vide infra*), attempts at deprotection of the 3-*O*-acetyl group with various bases were unsuccessful because of the instability of the Fmoc group under these conditions. Since removal of the chloroacetyl (CA) group in glycosides under mild conditions could be easily achieved,^{13b,34} we prepared 3-*O*-CA-protected galactosyl diphenyl phosphates **1b** (Scheme 2). Treatment of the known alcohol **4**^{9a} with chloroacetyl chloride and pyridine followed by removal of the TBS-protecting group with TBAF gave 3-*O*-CA-protected lactol **6** (α/β = 68:32) in 92% yield. Although phosphorylation of **6** with diphenyl chlorophosphate using DMAP³⁵ provided diphenyl phosphate **1bα** in only 15% yield due to the formation of several by-products, the Tanabe protocol using *N*-methylimidazole and triethylamine³⁶ afforded phosphates **1bα** and **1bβ** (α/β = 70:30) in 86% yield.



Scheme 2. Preparation of 3-*O*-chloroacetyl-protected galactosyl phosphate **1b**.

Under optimized reaction conditions, the TMSOTf-promoted glycosidation of diphenyl phosphates **1aα** and **1bα** with serine and threonine derivatives **2** and **7** was examined (Table 3, Figure 2). The reaction of 3-*O*-CA-protected galactosyl phosphate **1bα** with alcohol **2** (1.1 equiv) at -40 °C gave glycoside **3b** in a similar high yield and α-selectivity as those obtained with **1aα** (92%, α/β = 95:5, entry 2). When threonine derivative **7** was used as an acceptor, 1.5 equiv of **7** was required to provide good

Table 3

TMSOTf-promoted glycosidation of 2-azido-4,6-*O*-benzylidene-2-deoxy-D-galactosyl diphenyl phosphates **1** with acceptor alcohols **2**, **7–9**

Entry	Donor	R'OH	Equiv	T (°C)	t (h)	Glycoside	Yield (%)	α/β ^a
1	1aα	2	1.1	-40	1.5	3a	93	95:5
2	1bα	2	1.1	-40	6	3b	92	95:5
3	1aα	7	1.5	-40	4	10a	84	94:6
4	1bα	7	1.5	-40	10	10b	69	93:7
5	1bα	7	1.5	-60	48	10b	80	95:5
6	1aα	8	1.1	-60	1.5	11	92	82:18
7	1aα	9	1.1	-60	5	12	76	94:6

^a The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, hexane/AcOEt 2:1–3:2; flow rate, 1.0 mL/min).

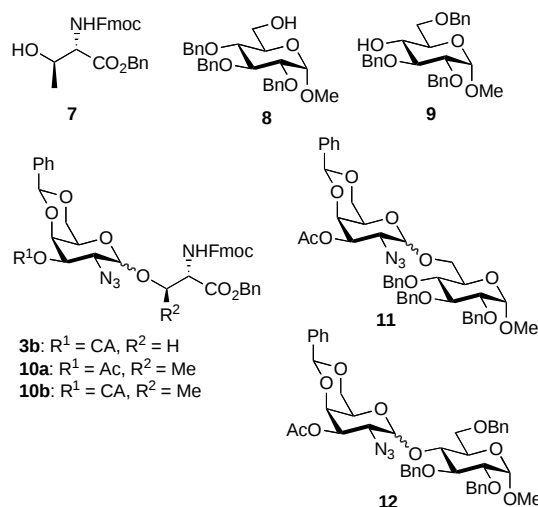


Figure 2. Acceptor alcohols and products in Table 3.

yield because of the attenuated reactivity of the acceptor. Coupling of **1a α** with **7** afforded glycoside **10a** in 84% yield with an α/β ratio of 94:6 (entry 3). The use of less reactive glycosyl donor **1b α** exhibited nearly the same stereoselectivity as that found with **1a α** but led to a marked decrease in product yield (69%, α/β = 93:7, entry 4) due to the competitive formation of glycosyl polytetrahydrofurans. When the reaction was conducted at -60 °C for 48 h, higher yield and α -selectivity were obtained (80%, α/β = 95:5, entry 5). Since the α - and β -anomers in all cases (**3a**, **3b**, **10a** and **10b**) are readily separated by column chromatography on silica gel, the present protocol provides easy access to appropriately protected T_N-antigen building blocks. The glycoside **10b α** is a key intermediate for the synthesis of antifreeze glycoproteins reported by Chen.^{13b,37}

To further evaluate this glycosidation method, we next examined the reaction of diphenyl phosphate **1a α** with 1.1 equiv of glycoside alcohols **8** and **9** (entries 6 and 7). According to the general trend of α -selectivity in this system, high α -selectivity was observed in the reaction with less-reactive 4-*O*-unprotected glycoside **9** (α/β = 94:6, entry 7), whereas the primary alcohol **8** led to moderate α -selectivity (α/β = 82:18, entry 6).

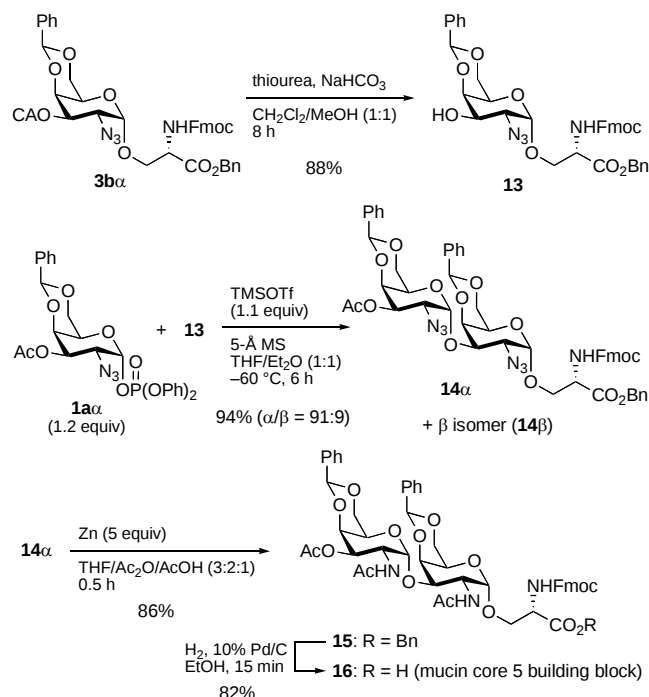
2.3. Synthesis of mucin core 5 and core 7 building blocks

With appropriately protected T_N-antigen derivatives in hand, we set out to synthesize mucin-type glycopeptide core 5 and core 7 building blocks. *O*-Glycan with core 5 was found in sialylated form of a human rectal adenocarcinoma glycoprotein³⁸ and in meconium glycoproteins.³⁹ Oligosaccharide with core 7 was detected in bovine submaxillary-gland mucin.⁴⁰

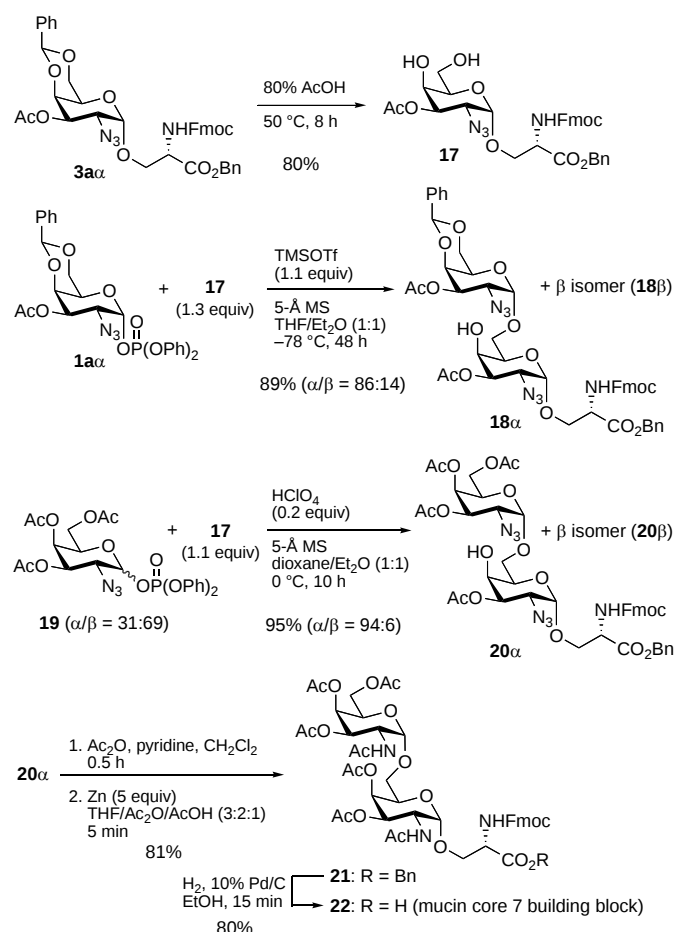
In 1995, Paulsen and co-workers reported the synthesis of core 5 and core 7 building blocks employing the Koenigs–Knorr method, in which glycosidations of disaccharide donors with a threonine acceptor gave exclusively α -glycosides in 73–74% yields.⁴¹ This protocol depends on conventional labile glycosyl bromides that must be prepared just prior to glycosidation, thus clearly diminishing synthetic flexibility. Koganty and co-workers accomplished the synthesis of a core 5 building block, although coupling of 2-acetamido-4,6-*O*-benzylidene-2-deoxygalactosyl trichloroacetimidate with 3-*O*-unprotected T_N-antigen derivatives in THF resulted in poor yields (30–35%).⁴² Recently, Schmidt and co-workers reported the synthesis of a variety of mucin core building blocks, including core 5 and core 7 building blocks, by capitalizing on the Michael-type addition described above.^{18c}

The chloroacetylated α -glycoside **3b α** was deblocked with thiourea and sodium bicarbonate⁴³ to give 3-*O*-unprotected glycoside alcohol **13** in 88% yield (Scheme 3). The present protocol was found to be applicable to the acceptor alcohol **13**, providing disaccharides **14 α** and **14 β** in 94% yield with an α/β ratio of 91:9. After chromatographic separation of the anomers, transformation of azide **14 α** to acetamide **15** with Zn in THF/Ac₂O/AcOH (3:2:1) followed by hydrogenolysis of the benzyl ester over 10% Pd/C in EtOH furnished core 5 building block **16** in 71% yield. The carboxylic acid **16** could be a key intermediate for Fmoc-based solid-phase synthesis of mucin-type *O*-linked glycopeptides.

We next explored the synthesis of mucin core 7 building block from **3a α** (Scheme 4). Removal of the benzylidene acetal group in **3a α** with 80% AcOH gave 4,6-*O*-unprotected glycoside **17** in 80% yield. TMSOTf-promoted coupling of **1a α** with diol **17** (1.3 equiv) in THF/Et₂O (1:1) at -78 °C resulted in 89% yield of disaccharides **18** with less satisfactory α -selectivity (α/β = 86:14). In an effort to enhance the α -selectivity, we were pleased to find that this goal could be achieved by our previously reported method.²³ HClO₄-catalyzed glycosidation of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxygalactosyl diphenyl phosphate (**19**)



Scheme 3. Synthesis of mucin core 5 building block.



Scheme 4. Synthesis of mucin core 7 building block.

(α/β = 31:69) with **17** (1.1 equiv) in dioxane/Et₂O (1:1) at 0 °C greatly improved the stereoselectivity, affording disaccharides **20 α** and **20 β** in 95% yield with an α/β ratio of 94:6. Protection of

the C4 hydroxy group in **20** α with Ac₂O and pyridine followed by reductive acetylation gave acetamide **21** in 86% yield. Finally, hydrogenolysis of **21** completed the synthesis of core 7 building block **22**. The present synthetic routes to these building blocks offer distinct advantages in overall yield over other methods.^{18c,41,42}

2.4. Mechanistic aspects

The beneficial effect of ethereal solvents,^{44,45} such as Et₂O,⁴⁶ dioxane⁴⁷ and THF,^{8h,16a,25b,48} on 1,2-*cis*- α -glycosidations has been well documented.⁴⁹ We previously demonstrated that HClO₄-catalyzed glycosidation with per-*O*-benzyl-protected glucosyl diphenyl phosphate in dioxane/Et₂O (1:1) would proceed via a kinetically favored α -face attack of an acceptor alcohol on a solvent-separated ion pair, leading to the preferential formation of α -glycoside.²³ Under similar conditions, the use of THF resulted in poor α -selectivity. In the TMSOTf-promoted glycosidation of 2-azido-4,6-*O*-benzylidene-2-deoxy- α -D-galactosyl diphenyl phosphate **1a**, the use of Et₂O or dioxane exhibited lower α -selectivity than that found with THF (Table 2, entries 1 and 4 vs 5). Consequently, the glycosidation mechanism is assumed to be different from the previous one. Wulff and co-workers reported that an excess of THF can compete with an acceptor alcohol to give mainly a highly reactive β -tetrahydrofuranium ion, which, in turn, reacts with the alcohol to afford the α -glycoside.^{48b} On the basis of Wulff's work, we propose the reaction pathway for the present glycosidation in THF/Et₂O as shown in Scheme 5. Diphenyl phosphate **1** is activated by silylation on the phosphoryl oxygen atom, resulting in cleavage of the phosphate group to provide glycosyl triflate **24**, along with trimethylsilyl diphenyl phosphate. Intermediate **24** is rapidly trapped by THF to form an anomeric mixture of tetrahydrofuranium ions **25** α and **25** β because of the higher donor ability of THF than those of Et₂O and dioxane.⁵⁰ In this step, the equilibrium between the β -oxonium ion **25** β and the α -oxonium ion **25** α would heavily lie to **25** β , which occupies an equatorial position due to the steric hindrance.⁵¹ Although actual glycosyl tetrahydrofuranium salts have yet to be observed, there have been some examples of the formation of THF ring-opening

products from glycosyl tetrahydrofuranium ion intermediates.⁵² The α -glycoside **28** α arises from the α -axial attack of the acceptor alcohol on the molecule-oxocarbenium ion complex **26** derived from the β -oxonium ion **25** β ,⁵³ along with generation of TfOH, while the β -glycoside **28** β results from the S_N2-like displacement by the acceptor alcohol at the anomeric carbon of the α -oxonium ion **25** α via an "exploded" transition state **27**.⁵⁴ Owing to the kinetic anomeric effect⁵⁵ and the steric hindrance of the 4,6-*O*-benzylidene acetal group,⁵⁶ the α -axial attack of the acceptor alcohol on the β -oxonium ion **25** β might have lower activation energy than the displacement of **25** α via a loose association of the acceptor alcohol with the anomeric center. The proportion of 1,2-*cis*- α -galactosides decreased with highly reactive alcohols, such as the sterically less demanding 6-*O*-unprotected glycoside alcohols **8** and **17**, compared to less reactive ones. The nucleophilic attack of highly reactive alcohols might competitively occur on **25** α and **26**, resulting in the decrease of α -selectivity. Although the reason for the enhanced α -selectivity in a mixed solvent system such as THF/Et₂O (1:1) is unclear at present, it is clear that the use of Et₂O as a co-solvent suppresses the formation of glycosyl polytetrahydrofurans from oxonium ions **25** α and **25** β .

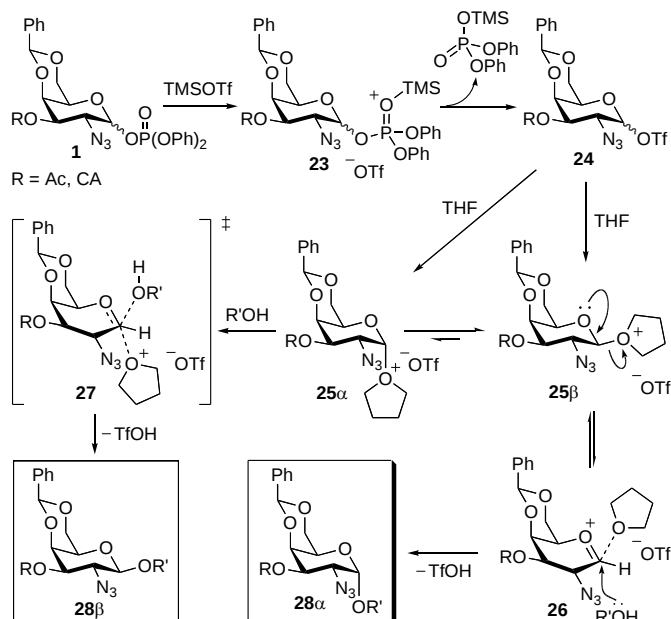
3. Conclusion

TMSOTf-promoted glycosidation of 2-azido-4,6-*O*-benzylidene-2-deoxygalactosyl diphenyl phosphates with Fmoc-protected serine and threonine derivatives in THF/Et₂O (1:1) gave glycosyl amino acids in high yields and with excellent α -selectivities (α/β = 94:6–95:5), regardless of the anomeric composition of the donor. Comparative studies with 3,4,6-tri-*O*-benzyl- and 3,4,6-tri-*O*-acetyl-protected diphenyl phosphates under the same conditions demonstrated that the presence of a 4,6-*O*-benzylidene acetal group is crucial for high levels of α -selectivity. Regioselective deprotections of the obtained 3-*O*-chloroacetyl- and 3-*O*-acetyl-4,6-*O*-benzylidene-protected T_N-antigen derivatives provided 3- and 4,6-*O*-unprotected glycosides, respectively, which were suitable acceptor alcohols to construct core structures of mucin-type glycopeptides. Using the 3-*O*-unprotected acceptor alcohol, we achieved the synthesis of core 5 building block employing the present glycosidation method. In the synthesis of core 7 building block, HClO₄-catalyzed glycosidation of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxygalactosyl diphenyl phosphate with the 4,6-*O*-unprotected glycosyl amino acid afforded the corresponding disaccharides in 95% yield with an α/β ratio of 94:6. Thus, we demonstrated efficient routes to mucin core 5 and core 7 building blocks that are useful in Fmoc-based solid-phase synthesis of *O*-linked glycopeptides. Further application of this methodology to the synthesis of biologically active mucin-type glycopeptides is currently in progress.

4. Experimental section

4.1. General

Melting points were measured on a Büchi 535 digital melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO P-1030 digital polarimeter with a sodium lamp (589 nm). Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm⁻¹). Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on JEOL JNM-AL400 (400 MHz), JNM-ECX400P (400 MHz), JNM-ECS400 (400 MHz) or JNM-ECA500 (500 MHz) spectrometers with tetramethylsilane (δ _H 0.00), CHCl₃ (δ _H 7.26), benzene (δ _H 7.16) or methanol (δ _H 3.31)



Scheme 5. Plausible mechanism of the TMSOTf-promoted glycosidation using 2-azido-4,6-*O*-benzylidene-2-deoxygalactosyl diphenyl phosphates in THF/Et₂O.

as an internal standard. Coupling constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL JNM-ECX400P (100 MHz) or JNM-ECA500 (126 MHz) spectrometers with CDCl_3 (δ_{C} 77.0) or CD_3OD (δ_{C} 49.0) as an internal standard. Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on JEOL JNM-ECX400P (160 MHz) or JNM-ECA500 (202 MHz) spectrometers with H_3PO_4 (δ_{P} 0.00) as an external standard. Electrospray ionization (ESI) mass spectra were obtained on a Thermo Scientific Exactive spectrometer. Fast atom bombardment (FAB) mass spectra were obtained on a JEOL JMS-700TZ spectrometer by the Center for Instrumental Analysis, Hokkaido University.

Column chromatography was carried out on Kanto silica gel 60 N (40–50 μm or 63–210 μm) or Wakogel C-200 (75–150 μm). Analytical and preparative thin layer chromatography (TLC) was carried out on 0.25-mm Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde or phosphomolybdic acid stain, followed by heating. Analytical high-performance liquid chromatography (HPLC) was performed on a JASCO PU-980 and UV-970 (detector, $\lambda = 254$ nm). Retention times (t_{R}) and peak ratios were determined with a JASCO-Borwin. Hexane was HPLC grade, and filtered and degassed prior to use.

Reagents and solvents were purified by standard means or used as received unless otherwise noted. Dehydrated CH_2Cl_2 , Et_2O , THF (stabilizer free) and toluene were purchased from Kanto Chemical Co., Inc. Dioxane was distilled from sodium metal/benzophenone ketyl prior to use. A 0.1 M solution of anhydrous HClO_4 in dioxane was purchased from Kishida Chemical Co., Ltd. 5-Å molecular sieves was finely ground in mortar and heated in vacuo at 200 °C for 12 h.

All reactions were conducted under an argon atmosphere. 3-*O*-Acetyl-2-azido-2-deoxy-4,6-*O*-benzylidene- β -D-galactopyranosyl diphenyl phosphate (**1a**)²⁷ and 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl diphenyl phosphate (**19**)²³ were prepared according to literature procedures.

4.2. Preparation of glycosyl donor 1b

4.2.1. tert-Butyldimethylsilyl 2-azido-4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-deoxy- β -D-galactopyranoside (5). Chloroacetyl chloride (0.23 mL, 2.83 mmol) was added to a stirred solution of **4^{9a}** (1.05 g, 2.58 mmol) and pyridine (1.4 mL, 17.2 mmol) in CH_2Cl_2 (8.0 mL) at –20 °C. After stirring for 15 min, the reaction was quenched with crushed ice followed by stirring for 15 min. The mixture was extracted with AcOEt (60 mL). The organic layer was washed with HCl (3×20 mL), water (20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel 40 g, 4:1 hexane/AcOEt) to give **5** (1.24 g, 99%) as a white amorphous solid: R_{f} 0.68 (2:1 hexane/AcOEt); $[\alpha]_{\text{D}}^{24} +31.6$ (c 1.00, CHCl_3); IR (CHCl_3) 2955, 2931, 2859, 2117, 1762, 1406, 1312, 1171, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.18 (s, 3H, SiCH_3), 0.20 (s, 3H, SiCH_3), 0.95 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 3.47 (dt, $J = 1.4, 1.1$ Hz, 1H, H-5), 3.83 (dd, $J = 7.4, 10.9$ Hz, 1H, H-2), 4.06 (dd, $J = 1.1, 12.3$ Hz, 1H, H-6a), 4.15 (s, 1H, ClCH_2), 4.16 (s, 1H, ClCH_2), 4.28 (dd, $J = 1.1, 12.3$ Hz, 1H, H-6b), 4.34 (dd, $J = 1.4, 3.4$ Hz, 1H, H-4), 4.64 (d, $J = 7.4$ Hz, 1H, H-1), 4.73 (dd, $J = 3.4, 10.9$ Hz, 1H, H-3), 5.50 (s, 1H, CHPh), 7.37–7.41 (m, 3H, Ar), 7.49–7.51 (m, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0, 25.6, 40.7, 62.4, 66.1, 69.0, 72.3, 73.4, 97.3 (C-1), 100.9 (CHPh), 126.2,

128.2, 129.2, 137.4, 166.9; ESI-HRMS m/z calcd for $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_6\text{ClNaSi}$ ($\text{M}+\text{Na}$)⁺ 506.1490, found 506.1478.

4.2.2. 2-Azido-4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-deoxy-D-galactopyranose (6). Tetrabutylammonium fluoride in THF (1.0 M, 10.0 mL, 10.0 mmol) was added to a stirred solution of **5** (3.73 g, 7.71 mmol) in THF (10 mL)–AcOH (0.90 mL) at 0 °C. After stirring for 2 h, saturated aqueous NaHCO_3 (12 mL) was added, and the whole was extracted with AcOEt (200 mL). The organic layer was successively washed with saturated aqueous NaHCO_3 (50 mL) and brine (2×50 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation in vacuo furnished the crude product (3.60 g), which was purified by column chromatography (silica gel 90 g, 4:1 hexane/AcOEt) to give lactol **6** (2.65 g, 93%, $\alpha:\beta = 68:32$) as a white amorphous solid. The anomeric $\alpha:\beta$ ratio of **6** was determined by ^1H NMR: R_{f} 0.37 (2:1 hexane/AcOEt); $[\alpha]_{\text{D}}^{23} +170.1$ (c 1.00, CHCl_3) ($\alpha:\beta = 68:32$); IR (KBr) 3450, 2952, 2918, 2871, 2116, 1760, 1408, 1313, 1167, 996, 749, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.03 (br s, 0.3H, β -OH), 3.56 (ddd, $J = 1.1, 1.7, 1.7$ Hz, 0.3H, β -H-5), 3.89 (dd, $J = 8.0, 10.9$ Hz, 0.3H, β -H-2), 4.03 (ddd, $J = 1.1, 1.7, 1.7$ Hz, 0.7H, α -H-5), 4.06 (dd, $J = 3.4, 10.9$ Hz, 0.7H, α -H-2), 4.07 (dd, $J = 1.7, 12.3$ Hz, 0.3H, β -H-6a), 4.09 (dd, $J = 1.7, 12.6$ Hz, 0.7H, α -H-6a), 4.17 (s, 1.4H, α - ClCH_2), 4.18 (s, 0.6H, β - ClCH_2), 4.26 (dd, $J = 1.7, 12.6$ Hz, 0.7H, α -H-6b), 4.34 (dd, $J = 1.7, 12.3$ Hz, 0.3H, β -H-6b), 4.39 (dd, $J = 1.1, 3.4$ Hz, 0.3H, β -H-4), 4.53 (dd, $J = 1.1, 3.4$ Hz, 0.7H, α -H-4), 4.69 (d, $J = 8.0$ Hz, 0.3H, β -H-1), 4.80 (dd, $J = 3.4, 10.9$ Hz, 0.3H, β -H-3), 5.41 (dd, $J = 3.4, 10.9$ Hz, 0.7H, α -H-3), 5.51 (d, $J = 3.4$ Hz, 0.7H, α -H-1), 5.537 (s, 0.3H, β -CHPh), 5.544 (s, 0.7H, α -CHPh), 7.37–7.42 (m, 3H, Ar), 7.48–7.51 (m, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 40.7 ($\alpha\beta$), 57.7 (α), 61.4 (β), 62.1 (α), 66.2 (β), 68.8 (β), 69.0 (α), 71.4 (α), 72.2 (β), 73.0 (α), 73.7 (β), 92.4 (α -C-1), 96.1 (β -C-1), 100.6 (α -CHPh), 100.7 (β -CHPh), 126.0, 128.19, 128.23, 129.1, 129.2, 137.0, 137.2, 166.97 (β), 167.02 (α); ESI-HRMS m/z calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_6\text{ClNa}$ ($\text{M}+\text{Na}$)⁺ 392.0625, found 392.0621.

4.2.3. 2-Azido-4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-deoxy- α -D-galactopyranosyl diphenyl phosphate (1b α). Diphenyl chlorophosphate (0.33 mL, 1.60 mmol) was added to a stirred solution of lactol **6** (492 mg, 1.33 mmol), *N*-methylimidazole (0.12 mL, 1.60 mmol) and Et_3N (0.22 mL, 1.60 mmol) in toluene (10 mL) at 0 °C. After stirring for 5 min, the reaction was quenched with crushed ice, followed by stirring for 10 min. The mixture was poured into a two-layer mixture of AcOEt (15 mL) and saturated aqueous NaHCO_3 (15 mL), and the whole mixture was extracted with AcOEt (60 mL). The organic extract was successively washed with saturated aqueous NaHCO_3 (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation in vacuo furnished the crude product (1.20 g), which was purified by column chromatography (Wakogel[®] 20 g, 15:1 toluene/AcOEt) to give diphenyl phosphate **1b α** (482 mg, 60%) and **1b β** (206 mg, 26%) as a white amorphous solid. Data for α -anomer **1b α** : R_{f} 0.54 (3:1 toluene/AcOEt); $[\alpha]_{\text{D}}^{20} +149.9$ (c 1.00, CHCl_3); IR (KBr) 3067, 2918, 2116, 1765, 1590, 1489, 1290, 1188, 958, 759 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.71 (d, $J = 1.7$ Hz, 1H, H-5), 3.88 (dd, $J = 1.7, 12.6$ Hz, 1H, H-6a), 3.99 (dd, $J = 1.7, 12.6$ Hz, 1H, H-6b), 4.17 (s, 2H, ClCH_2), 4.24 (ddd, $J = 3.2, 10.9, 3.2$ ($J_{\text{H-P}}$) Hz, 1H, H-2), 4.48 (dd, $J = 1.7, 3.4$ Hz, 1H, H-4), 5.26 (dd, $J = 3.4, 10.9$ Hz, 1H, H-3), 5.49 (s, 1H, CHPh), 6.12 (dd, $J = 3.2, 6.0$ ($J_{\text{H-P}}$) Hz, 1H, H-1), 7.21–7.46 (m, 15H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 40.5, 57.1 (d, $J_{\text{C-P}} = 8.6$ Hz, C-2), 64.2, 68.3, 71.4, 72.2, 97.5 (d, $J_{\text{C-P}} = 5.7$ Hz, C-1), 100.6 (CHPh), 120.0 (d, $J_{\text{C-P}} = 4.8$ Hz), 120.2 (d, $J_{\text{C-P}} = 4.8$ Hz), 125.6, 125.7, 126.0, 128.2, 129.3, 129.77, 129.81, 136.9, 150.17 (d, $J_{\text{C-P}} = 3.9$ Hz), 150.24 (d, $J_{\text{C-P}} = 4.8$ Hz), 166.8; ^{31}P NMR (160

MHz, CDCl₃) δ -12.9; FAB-HRMS m/z calcd for C₂₇H₂₆N₃O₉ClP (M+H)⁺ 602.1095, found 602.1094. Data for β -anomer **1b**: R_f 0.36 (3:1 toluene/AcOEt); [α]_D²³ +80.7 (c 1.00, CHCl₃); IR (KBr) 3067, 2920, 2118, 1763, 1590, 1489, 1406, 1187, 957, 766 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.61 (d, J = 1.7 Hz, 1 H, H-5), 3.99 (dd, J = 1.7, 12.6 Hz, 1 H, H-6a), 4.03 (dd, J = 8.0, 10.9 Hz, 1 H, H-2), 4.14 (s, 2 H, ClCH₂), 4.20 (dd, J = 1.7, 12.6 Hz, 1 H, H-6b), 4.40 (d, J = 3.4 Hz, 1 H, H-4), 4.80 (dd, J = 3.4, 10.9 Hz, 1 H, H-3), 5.26 (dd, J = 6.3 (J_{H-P}), 8.0 Hz, 1 H, H-1), 5.51 (s, 1 H, CHPh), 7.26–7.53 (m, 15 H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 40.5, 60.4 (d, J_{C-P} = 10.5 Hz, C-2), 66.8, 68.3, 71.7, 73.8 (d, J_{C-P} = 1.9 Hz, C-3), 98.1 (d, J_{C-P} = 4.8 Hz, C-1), 100.8 (CHPh), 120.0 (d, J_{C-P} = 4.8 Hz), 120.1 (d, J_{C-P} = 4.8 Hz), 125.6, 126.2, 128.3, 129.3, 129.6, 129.8, 137.2, 150.1 (d, J_{C-P} = 7.6 Hz), 150.3 (d, J_{C-P} = 7.6 Hz), 166.7; ³¹P NMR (160 MHz, CDCl₃) δ -13.1; FAB-HRMS m/z calcd for C₂₇H₂₅N₃O₉ClPNa (M+Na)⁺ 624.0915, found 624.0915.

4.3. Glycosidation

4.3.1. Typical procedure for glycosidation of 3-O-acetyl-2-azido-4,6-O-benzylidene-2-deoxy- α -D-galactopyranosyl diphenyl phosphate: *N*-(9-fluorenylmethoxycarbonyl)-O-(3-O-acetyl-2-azido-4,6-O-benzylidene-2-deoxy-D-galactopyranosyl)-L-serine benzyl ester (**3a**). TMSOTf in CH₂Cl₂ (1.0 M, 0.11 mL, 0.11 mmol) was added to a stirred solution of diphenyl phosphate **1a** α (56.7 mg, 0.10 mmol), alcohol **2** (46.0 mg, 0.11 mmol) and pulverized 5-Å MS (50 mg) in THF/Et₂O (1:1, 1 mL) at -40 °C. After stirring for 1.5 h, the reaction was quenched with saturated aqueous NaHCO₃ (0.1 mL), and the mixture was filtrated through a celite pad. The filtrate was poured into a two-layer mixture of AcOEt (3 mL) and saturated aqueous NaHCO₃ (6 mL), and the whole was extracted with AcOEt (30 mL). The organic extract was successively washed with saturated aqueous NaHCO₃ (10 mL) and brine (10 mL), and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo furnished the crude product (90.8 mg), from which an anomeric mixture of glycosides **3a** (68.3 mg, 93%, α : β = 95:5) was obtained as a white amorphous solid after column chromatography (silica gel 10 g, 15:1 toluene/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [column, Zorbax[®] Sil, 4.6×250 mm; eluent, 3:2 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α -anomer) = 6.4 min, t_R (β -anomer) = 14.6 min]. The α - and β -glycosides were separated by flash column chromatography with 20:1 toluene/AcOEt. Data for α -anomer **3a** α : R_f 0.59 (3:1 toluene/AcOEt); [α]_D¹⁸ +122.5 (c 1.00, CHCl₃); IR (KBr) 3356, 3036, 2947, 2112, 1743, 1728, 1514, 1452, 1336, 1240, 1145, 1043 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.17 (s, 3H, CH₃CO), 3.58 (br s, 1H, H-5), 3.86 (d, J = 11.3 Hz, 1H, H-6a), 3.89 (dd, J = 3.2, 10.9 Hz, 1H, H-2), 4.01 (dd, J = 2.5, 11.1 Hz, 1H, Ser- β -CH), 4.17 (d, J = 11.3 Hz, 1H, H-6b), 4.19 (dd, J = 3.6, 11.1 Hz, 1H, Ser- β -CH), 4.24 (t, J = 7.5 Hz, 1H, Fmoc-CH), 4.35 (dd, J = 7.5, 10.4 Hz, 1H, Fmoc-CH), 4.37 (d, J = 2.7 Hz, 1H, H-4), 4.43 (dd, J = 7.5, 10.4 Hz, 1H, Fmoc-CH), 4.60 (m, 1H, Ser- α -CH), 4.96 (d, J = 3.2 Hz, 1H, H-1), 5.19 (dd, J = 2.7, 10.9 Hz, 1H, H-3), 5.22 (d, J = 12.2 Hz, 1H, OCHPh), 5.26 (d, J = 12.2 Hz, 1H, OCHPh), 5.47 (s, 1H, CHPh), 5.97 (d, J = 8.6 Hz, 1H, NH), 7.33–7.39 (m, 12H, Ar), 7.46–7.48 (m, 2H, Ar), 7.61 (m, 2H, Ar), 7.77 (d, J = 7.7 Hz, 2H, Ar); ¹³C NMR (126 MHz, CDCl₃) δ 20.8, 46.9, 54.5, 57.0, 62.8, 67.2, 67.6, 68.7, 69.0, 69.8, 73.0, 99.6 (C-1), 100.4 (CHPh), 119.9, 124.9, 125.0, 125.9, 126.96, 126.98, 127.6, 128.0, 128.3, 128.4, 128.5, 128.9, 134.9, 137.3, 141.1, 143.5, 143.6, 155.8, 169.5, 170.2; FAB-HRMS m/z calcd for C₄₀H₃₉N₄O₁₀ (M+H)⁺ 735.2667, found 735.2667. Data for β -anomer **3a** β : R_f 0.36 (3:1 toluene/AcOEt); [α]_D¹⁹ +29.7 (c 0.50, CHCl₃); IR (KBr) 3356, 3036, 2947, 2110, 1743, 1730, 1514,

1450, 1336, 1240, 1145, 1043 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.17 (s, 3H, CH₃CO), 3.37 (s, 1H, H-5), 3.90 (dd, J = 8.0, 10.6 Hz, 1H, H-2), 3.93 (dd, J = 2.7, 10.3 Hz, 1H, Ser- β -CH), 4.02 (dd, J = 1.7, 12.6 Hz, 1H, H-6a), 4.23 (t, J = 7.7 Hz, 1H, Fmoc-CH), 4.29 (dd, J = 1.7, 12.6 Hz, 1H, H-6b), 4.32 (d, J = 3.4 Hz, 1H, H-4), 4.35 (dd, J = 7.7, 11.7 Hz, 1H, Fmoc-CH), 4.36 (d, J = 8.0 Hz, 1H, H-1), 4.39 (dd, J = 7.7, 11.7 Hz, 1H, Fmoc-CH), 4.50 (dd, J = 2.7, 10.3 Hz, 1H, Ser- β -CH), 4.64 (dt, J = 8.6, 2.7 Hz, 1H, Ser- α -CH), 4.69 (dd, J = 3.4, 10.6 Hz, 1H, H-3), 5.22 (d, J = 12.2 Hz, 1H, OCHPh), 5.26 (d, J = 12.2 Hz, 1H, OCHPh), 5.52 (s, 1H, CHPh), 5.94 (d, J = 8.6 Hz, 1H, NH), 7.20–7.39 (m, 12H, Ar), 7.49–7.51 (m, 2H, Ar), 7.60 (m, 2H, Ar), 7.75 (d, J = 7.6 Hz, 2H, Ar); ¹³C NMR (126 MHz, CDCl₃) δ 20.9, 47.0, 54.3, 60.2, 66.3, 67.3, 67.6, 68.7, 69.7, 72.0, 72.4, 100.8 (CHPh), 102.4 (C-1), 119.9, 125.17, 125.24, 126.2, 127.0, 127.7, 128.1, 128.2, 128.3, 128.5, 128.6, 128.9, 129.0, 129.1, 135.2, 137.5, 141.20, 141.24, 143.7, 143.9, 156.0, 169.5, 170.4; FAB-HRMS m/z calcd for C₄₀H₃₉N₄O₁₀ (M+H)⁺ 735.2667, found 735.2659.

4.3.2. *N*-(9-Fluorenylmethoxycarbonyl)-O-(3-O-acetyl-2-azido-4,6-O-benzylidene-2-deoxy-D-galactopyranosyl)-L-threonine benzyl ester (10a**).** The glycosidation was performed according to the typical procedure (1:1 THF/Et₂O 1.0 mL, -40 °C, 4 h) employing diphenyl phosphate **1a** α (56.7 mg, 0.10 mmol), alcohol **7** (69.4 mg, 0.15 mmol), TMSOTf (1.0 M in CH₂Cl₂, 0.11 mL, 0.11 mmol) and pulverized 5-Å MS (50 mg). An anomeric mixture of glycoside **10a** (62.9 mg, 84%, α : β = 94:6) was obtained as a white amorphous solid from the crude product (105.6 mg) after column chromatography (silica gel 4 g, 20:1 CH₂Cl₂/AcOEt). The anomeric ratio of **10a** was determined by HPLC analysis [eluent, 2:1 hexane/AcOEt; flow rate, 1.0 mL min⁻¹; detection, 254 nm; t_R (α -anomer) = 10.2 min, t_R (β -anomer) = 20.0 min]. The α - and β -glycosides were separated by flash chromatography with 25:1 CH₂Cl₂/AcOEt. Data for α -anomer **10a** α : R_f 0.43 (20:1 CH₂Cl₂/AcOEt); [α]_D²² +115.8 (c 1.01, CHCl₃); IR (KBr) 3427, 3358, 3065, 2980, 2112, 1755, 1730, 1514, 1452, 1375, 1240, 1043 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.34 (d, J = 6.2 Hz, 3H, Thr-CH₃), 2.18 (s, 3H, CH₃CO), 3.72 (br s, 1H, H-5), 3.94 (dd, J = 3.4, 11.1 Hz, 1H, H-2), 4.00 (br d, J = 12.4 Hz, 1H, H-6a), 4.23 (br d, J = 12.4 Hz, 1H, H-6b), 4.28 (dd, J = 6.7, 7.8 Hz, 1H, Fmoc-CH), 4.38 (dd, J = 7.8, 10.2 Hz, 1H, Fmoc-CH), 4.46–4.52 (m, 4H, H-4, Thr- α -CH, Thr- β -CH, Fmoc-CH), 5.00 (d, J = 3.4 Hz, 1H, H-1), 5.23 (d, J = 12.2 Hz, 1H, OCHPh), 5.265 (dd, J = 3.3, 11.1 Hz, 1H, H-3), 5.271 (d, J = 12.2 Hz, 1H, OCHPh), 5.51 (s, 1H, CHPh), 5.87 (d, J = 8.2 Hz, 1H, NH), 7.32–7.43 (m, 12H, Ar), 7.52–7.54 (m, 2H, Ar), 7.66 (d, J = 7.4 Hz, 2H, Ar), 7.78 (d, J = 7.5 Hz, 2H, Ar); ¹³C NMR (126 MHz, CDCl₃) δ 18.5, 20.7, 46.9, 57.4, 58.5, 62.7, 67.2, 67.5, 68.7, 69.4, 73.0, 75.9, 98.7 (C-1), 100.5 (CHPh), 119.8, 125.01, 125.04, 125.9, 126.91, 126.93, 127.5, 128.0, 128.3, 128.4, 128.5, 128.9, 134.8, 137.3, 141.06, 141.07, 143.6, 143.7, 156.6, 169.9, 170.2; FAB-HRMS m/z calcd for C₄₁H₄₁N₄O₁₀ (M+H)⁺ 749.2822, found 749.2814. Data for β -anomer **10a** β : R_f 0.29 (20:1 CH₂Cl₂/AcOEt); [α]_D²³ +9.30 (c 0.52, CHCl₃); IR (KBr) 3429, 3065, 2937, 2116, 1748, 1728, 1512, 1450, 1371, 1232, 1055 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.36 (d, J = 6.2 Hz, 3H, Thr-CH₃), 2.15 (s, 3H, CH₃CO), 3.08 (br s, 1H, H-5), 3.85 (dd, J = 8.1, 10.9 Hz, 1H, H-2), 3.90 (br d, J = 12.3 Hz, 1H, H-6a), 4.16 (br d, J = 12.3 Hz, 1H, H-6b), 4.21 (d, J = 3.5 Hz, 1H, H-4), 4.23 (dd, J = 6.4, 7.5 Hz, 1H, Fmoc-CH), 4.31–4.39 (m, 3H, H-1, Fmoc-CH $\times$ 2), 4.52 (dd, J = 1.4, 9.6 Hz, 1H, Thr- α -CH), 4.60 (dd, J = 3.5, 10.9 Hz, 1H, H-3), 4.66 (dq, J = 1.4, 6.2 Hz, 1H, Thr- β -CH), 5.18 (d, J = 12.7 Hz, 1H, OCHPh), 5.21 (d, J = 12.7 Hz, 1H, OCHPh), 5.46 (s, 1H, CHPh), 5.81 (d, J = 9.6 Hz, 1H, NH), 7.22–7.38 (m, 12H, Ar), 7.48–7.50 (m, 2H, Ar), 7.61 (m, 2H, Ar), 7.74 (d, J = 7.6 Hz, 2H, Ar); ¹³C NMR (126 MHz,

CDCl₃) δ 17.4, 20.9, 47.1, 58.6, 60.2, 66.1, 67.5, 68.6, 71.7, 72.5, 74.9, 100.1, 100.9 (C-1, CHPh), 119.9, 125.3, 126.3, 127.1, 127.60, 127.62, 128.2, 128.4, 128.6, 129.1, 135.5, 137.6, 141.20, 141.24, 143.8, 144.0, 156.8, 170.1, 170.4; FAB-HRMS m/z calcd for C₄₁H₄₁N₄O₁₀ (M+H)⁺ 749.2822, found 749.2822.

4.3.3. *N*-(9-Fluorenylmethoxycarbonyl)-O-(2-azido-4,6-O-benzylidene-3-O-chloroacetyl-2-deoxy-D-galactopyranosyl)-L-serine benzyl ester (**3b**). The glycosidation was performed according to the typical procedure (1:1 THF/Et₂O 6.0 mL, -40 °C, 6 h) employing diphenyl phosphate **1b α** (296 mg, 0.49 mmol), alcohol **2** (225 mg, 0.54 mmol), TMSOTf (1.0 M in CH₂Cl₂, 0.54 mL, 0.54 mmol) and pulverized 5-Å MS (500 mg). An anomeric mixture of glycoside **3b** (344 mg, 92%, α : β = 95:5) was obtained as a white amorphous solid from the crude product (613 mg) after column chromatography (silica gel 18 g, 10:1→6:1 toluene/AcOEt). The anomeric ratio of **3b** was determined by HPLC analysis [eluent, 2:1 hexane/AcOEt; flow rate, 1.0 mL/min; detection, 254 nm; t_R (α -anomer) = 9.2 min, t_R (β -anomer) = 23.9 min]. The α - and β -glycosides were separated by flash chromatography with 15:1 toluene/AcOEt. Data for α -anomer **3b α** : R_f 0.70 (3:1 toluene/AcOEt); [α]_D²¹ +121.1 (c 1.00, CHCl₃); IR (KBr) 3425, 3250, 3066, 2951, 2112, 1744, 1721, 1451, 1338, 1267, 1080 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.55 (br s, 1H, H-5), 3.85 (br d, J = 12.6 Hz, 1H, H-6a), 3.90 (dd, J = 3.4, 11.5 Hz, 1H, H-2), 4.02 (dd, J = 3.4, 10.9 Hz, 1H, Ser- β -CH), 4.17 (s, 2H, ClCH₂), 4.18 (br d, J = 12.6 Hz, 1H, H-6b), 4.20 (dd, J = 3.4, 10.9 Hz, 1H, Ser- β -CH), 4.24 (t, J = 7.4 Hz, 1H, Fmoc-CH), 4.33–4.39 (m, 2H, Fmoc-CH, H-4), 4.44 (dd, J = 7.4, 10.9 Hz, 1H, Fmoc-CH), 4.61 (dt, J = 8.0, 3.4 Hz, 1H, Ser- α -CH), 4.97 (d, J = 3.4 Hz, 1H, H-1), 5.216 (dd, J = 3.4, 11.5 Hz, 1H, H-3), 5.220 (d, J = 12.0 Hz, 1H, OCHPh), 5.26 (d, J = 12.0 Hz, 1H, OCHPh), 5.47 (s, 1H, CHPh), 5.94 (d, J = 8.0 Hz, 1H, NH), 7.31–7.78 (m, 18H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 40.6, 46.9, 54.5, 57.0, 62.8, 67.3, 67.8, 68.7, 70.0, 71.0, 72.7, 99.6 (C-1), 100.5 (CHPh), 120.0, 125.0, 125.1, 126.0, 127.06, 127.08, 127.7, 128.1, 128.5, 128.6, 129.1, 134.9, 137.1, 141.19, 141.21, 143.6, 143.7, 155.9, 166.8, 169.6; FAB-HRMS m/z calcd for C₄₀H₃₈N₄O₁₀Cl (M+H)⁺ 769.2276, found 769.2278. Data for β -anomer **3b β** : R_f 0.54 (3:1 toluene/AcOEt); [α]_D²⁴ +33.6 (c 1.00, CHCl₃); IR (KBr) 3327, 2949, 2112, 1750, 1732, 1538, 1453, 1283, 1056 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.36 (d, J = 1.4 Hz, 1H, H-5), 3.91 (dd, J = 8.3, 10.6 Hz, 1H, H-2), 3.95 (dd, J = 2.9, 10.0 Hz, 1H, Ser- β -CH), 4.03 (dd, J = 1.4, 12.5 Hz, 1H, H-6a), 4.177 (s, 1H, ClCH₂), 4.182 (s, 1H, ClCH₂), 4.23 (t, J = 8.3 Hz, 1H, Fmoc-CH), 4.30 (dd, J = 1.4, 12.5 Hz, 1H, H-6b), 4.34 (dd, J = 8.3, 10.6 Hz, 1H, Fmoc-CH), 4.35 (d, J = 3.7 Hz, 1H, H-4), 4.37 (d, J = 8.3 Hz, 1H, H-1), 4.40 (dd, J = 8.3, 10.6 Hz, 1H, Fmoc-CH), 4.50 (dd, J = 2.9, 10.0 Hz, 1H, Ser- β -CH), 4.64 (dt, J = 8.6, 2.9 Hz, 1H, Ser- α -CH), 4.73 (dd, J = 3.7, 10.6 Hz, 1H, H-3), 5.21 (d, J = 12.6 Hz, 1H, OCHPh), 5.26 (d, J = 12.6 Hz, 1H, OCHPh), 5.52 (s, 1H, CHPh), 5.91 (d, J = 8.6 Hz, 1H, NH), 7.27–7.77 (m, 18H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 40.6, 46.9, 54.1, 60.0, 66.1, 67.3, 67.5, 68.5, 69.7, 72.1, 73.4, 100.7 (CHPh), 102.2 (C-1), 120.0, 125.1, 125.2, 126.1, 127.0, 127.6, 128.1, 128.2, 128.3, 128.5, 129.1, 135.1, 137.2, 141.1, 141.2, 143.6, 143.8, 155.9, 166.8, 169.4; FAB-HRMS m/z calcd for C₄₀H₃₈N₄O₁₀Cl (M+H)⁺ 769.2276, found 769.2277.

4.3.4. *N*-(9-Fluorenylmethoxycarbonyl)-O-(2-azido-4,6-O-benzylidene-3-O-chloroacetyl-2-deoxy-D-galactopyranosyl)-L-threonine benzyl ester (**10b**).^{13b} The glycosidation was performed according to the typical procedure (1:1 THF/Et₂O 1.0 mL, -60 °C, 48 h) employing diphenyl phosphate **1b α** (60.8 mg, 0.10 mmol), alcohol **7** (65.4 mg, 0.15 mmol), TMSOTf (1.0 M in CH₂Cl₂, 0.11 mL, 0.11 mmol) and pulverized 5-Å MS (100 mg). An anomeric mixture of glycoside **10b** (61.4 mg, 80%, α : β = 95:5)

was obtained as a white amorphous solid from the crude product (105.6 mg) after column chromatography (silica gel 4 g, 10:1 toluene/AcOEt). The anomeric ratio of **10b** was determined by HPLC analysis [eluent, 2:1 hexane/AcOEt; flow rate, 1.0 mL/min; detection, 254 nm; t_R (α -anomer) = 6.3 min, t_R (β -anomer) = 11.1 min]. The α - and β -glycosides were separated by flash chromatography with 15:1 toluene/AcOEt. Data for α -anomer **10b α** : R_f 0.64 (3:1 toluene/AcOEt); [α]_D²² +109.1 (c 0.54, CHCl₃); IR (KBr) 3369, 3065, 3036, 2926, 2112, 1749, 1727, 1515, 1451, 1405, 1041 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.31 (d, J = 6.9 Hz, 3H, Thr-CH₃), 3.71 (d, J = 1.1 Hz, 1H, H-5), 3.92 (dd, J = 3.4, 10.9 Hz, 1H, H-2), 4.03 (dd, J = 1.1, 12.6 Hz, 1H, H-6a), 4.16 (s, 2H, ClCH₂), 4.24 (dd, J = 1.1, 12.6 Hz, 1H, H-6b), 4.26 (t, J = 7.4 Hz, 1H, Fmoc-CH), 4.35 (dd, J = 7.4, 10.9 Hz, 1H, Fmoc-CH), 4.45 (dd, J = 7.4, 10.9 Hz, 1H, Fmoc-CH), 4.46–4.50 (m, 3H, H-4, Thr- α -CH, Thr- β -CH), 4.98 (d, J = 3.4 Hz, 1H, H-1), 5.22 (s, 1H, OCHPh), 5.23 (s, 1H, OCHPh), 5.23–5.26 (m, 1H, H-3), 5.52 (s, 1H, CHPh), 5.75 (d, J = 9.7 Hz, 1H, NH), 7.30–7.41 (m, 12H, Ar), 7.47–7.49 (m, 2H, Ar), 7.62 (d, J = 7.5 Hz, 2H, Ar), 7.77 (d, J = 7.5 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 18.6, 40.6, 47.1, 57.6, 58.6, 62.7, 67.4, 67.7, 68.9, 71.6, 72.7, 76.3, 98.7 (C-1), 100.7 (CHPh), 119.9, 125.1, 125.2, 125.3, 126.0, 127.1, 127.7, 128.2, 128.5, 128.6, 128.7, 129.0, 129.2, 134.9, 137.2, 141.22, 141.24, 143.7, 143.8, 156.7, 169.9, 170.0. Data for β -anomer **10b β** : R_f 0.27 (3:1 toluene/AcOEt); [α]_D²² +11.0 (c 0.74, CHCl₃); IR (KBr) 3429, 3066, 2932, 2116, 1751, 1726, 1513, 1451, 1369, 1055 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.37 (d, J = 6.3 Hz, 3H, Thr-CH₃), 3.02 (br s, 1H, H-5), 3.87 (dd, J = 8.0, 10.9 Hz, 1H, H-2), 3.90 (dd, J = 1.1, 12.6 Hz, 1H, H-6a), 4.16 (s, 1H, ClCH₂), 4.166 (dd, J = 1.1, 12.6 Hz, 1H, H-6b), 4.167 (s, 1H, ClCH₂), 4.230 (t, J = 7.4 Hz, 1H, Fmoc-CH), 4.234 (d, J = 3.4 Hz, 1H, H-4), 4.33 (dd, J = 7.4, 10.3 Hz, 1H, Fmoc-CH), 4.34 (d, J = 8.0 Hz, 1H, H-1), 4.38 (dd, J = 7.4, 10.3 Hz, 1H, Fmoc-CH), 4.52 (dd, J = 1.7, 9.7 Hz, 1H, Thr- α -CH), 4.62 (dd, J = 3.4, 10.9 Hz, 1H, H-3), 4.67 (m, 1H, Thr- β -CH), 5.18 (d, J = 12.6 Hz, 1H, OCHPh), 5.22 (d, J = 12.6 Hz, 1H, OCHPh), 5.48 (s, 1H, CHPh), 5.81 (d, J = 9.7 Hz, 1H, NH), 7.18–7.39 (m, 12H, Ar), 7.47–7.49 (m, 2H, Ar), 7.60 (dd, J = 3.4, 7.4 Hz, 2H, Ar), 7.75 (d, J = 8.5 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 17.4, 40.7, 47.0, 58.4, 59.9, 65.9, 67.47, 67.50, 68.5, 72.1, 73.2, 75.9, 100.0 (C-1), 100.9 (CHPh), 119.9, 125.3, 126.2, 127.1, 127.62, 127.63, 128.2, 128.5, 128.6, 129.2, 135.5, 137.3, 141.19, 141.22, 143.7, 143.9, 156.9, 167.0, 170.0.

4.4. Synthesis of mucin core 5 building block

4.4.1. *N*-(9-Fluorenylmethoxycarbonyl)-O-(2-azido-4,6-O-benzylidene-2-deoxy-D-galactopyranosyl)-L-serine benzyl ester (**13**).^{18c} Thiourea (0.66 g, 8.7 mmol) and NaHCO₃ (0.73 g, 8.7 mmol) was added to a solution of glycoside **3b α** (0.67 g, 0.87 mmol) in CH₂Cl₂/MeOH (1:1, 10 mL) at room temperature. After stirring at room temperature for 8 h, saturated aqueous NaHCO₃ (60 mL) was added, and the whole was extracted with AcOEt (200 mL). The organic layer was successively washed with saturated aqueous NaHCO₃ (50 mL) and brine (2×50 mL), and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo furnished the crude product (0.88 g), which was purified by column chromatography (silica gel 25 g, 10:1 toluene/AcOEt) to give alcohol **13** (0.55 g, 88%) as a white solid: R_f 0.50 (2:1 hexane/AcOEt); mp 86.0–87.0 °C; [α]_D²⁰ +80.3 (c 1.42, CHCl₃); IR (KBr) 3500, 3303, 3065, 2914, 2100, 1750, 1725, 1693, 1549, 1063, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.38 (s, 1H, OH), 3.51 (dd, J = 3.4, 10.6 Hz, 1H, H-2), 3.58 (s, 1H, H-5), 3.89 (d, J = 12.2 Hz, 1H, H-6a), 3.97–4.03 (m, 2H, H-3, Ser- β -CH), 4.15–4.19 (m, 3H, H-4, H-6b, Ser- β -CH), 4.23 (t, J = 7.0 Hz, 1H, Fmoc-CH), 4.34 (dd, J = 7.0, 10.4 Hz, 1H, Fmoc-CH), 4.46 (dd, J = 7.0, 10.4 Hz, 1H, Fmoc-CH), 4.60 (dt, J = 8.2, 3.1 Hz, 1H,

Ser- α -CH), 4.91 (d, $J = 3.2$ Hz, 1H, H-1), 5.23 (s, 1H, OCHPh), 5.25 (s, 1H, OCHPh), 5.52 (s, 1H, CHPh), 5.90 (d, $J = 8.2$ Hz, 1H, NH), 7.31–7.43 (m, 12H, Ar), 7.46–7.49 (m, 2H, Ar), 7.60 (dd, $J = 4.3, 7.7$ Hz, 2H, Ar), 7.78 (d, $J = 7.7$ Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 47.0, 54.6, 60.4, 63.2, 67.0, 67.8, 68.9, 69.8, 75.2, 100.0 (C-1), 101.1 (CHPh), 120.0, 125.0, 125.1, 126.1, 127.07, 127.10, 127.8, 128.3, 128.62, 128.64, 129.3, 135.0, 137.2, 141.3, 143.6, 143.7, 155.9, 169.7.

4.4.2. *O*-(3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-*D*-galactopyranosyl)-(1 $\rightarrow$ 3)-(2-azido-4,6-*O*-benzylidene-2-deoxy- α -*D*-galactopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-*L*-serine benzyl ester (**14**). The glycosidation was performed according to the typical procedure (1:1 THF/Et₂O 1.0 mL, -60°C , 6 h) employing diphenyl phosphate **1a** α (56.7 mg, 0.10 mmol), alcohol **13** (76.0 mg, 0.11 mmol), TMSOTf (1.0 M in CH_2Cl_2 , 0.11 mL, 0.11 mmol) and pulverized 5-Å MS (100 mg). An anomeric mixture of disaccharide **14** (95.0 mg, 94%, $\alpha:\beta = 91:9$) was obtained as a white amorphous solid from the crude product (110 mg) after flash column chromatography (silica gel 10 g, 20:1 toluene/AcOEt). The anomeric ratio of **14** was determined by HPLC analysis [eluent, 5:1 hexane/*i*-PrOH; flow rate, 1.0 mL/min; detection, 254 nm; t_R (α -anomer) = 6.5 min, t_R (β -anomer) = 15.0 min]. The α - and β -glycosides were separated by flash chromatography with 15:1 toluene/AcOEt. Data for α -anomer **14** α : R_f 0.59 (3:1 toluene/AcOEt); $[\alpha]_D^{20} +184.1$ (c 1.00, CHCl_3); IR (KBr) 3326, 2914, 2112, 1745, 1728, 1452, 1242, 1046 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.15 (s, 3H, CH_3CO), 3.48 (s, 1H, H-5'), 3.79 (dd, $J = 3.4, 10.9$ Hz, 1H, H-2'), 3.89 (d, $J = 12.6$ Hz, 1H, H-6'a), 3.97 (dd, $J = 3.4, 11.5$ Hz, 1H, H-2), 3.98 (s, 1H, H-5), 3.99 (dd, $J = 2.7, 8.0$ Hz, 1H, Ser- β -CH), 4.07 (dd, $J = 1.1, 12.9$ Hz, 1H, H-6'a), 4.10 (dd, $J = 2.6, 10.9$ Hz, 1H, H-3'), 4.20 (d, $J = 12.6$ Hz, 1H, H-6'b), 4.21 (dd, $J = 2.7, 8.0$ Hz, 1H, Ser- β -CH), 4.23 (t, $J = 7.2$ Hz, 1H, Fmoc-CH), 4.27 (d, $J = 2.6$ Hz, 1H, H-4'), 4.32 (dd, $J = 1.1, 12.9$ Hz, 1H, H-6'b), 4.35 (dd, $J = 7.2, 10.6$ Hz, 1H, Fmoc-CH), 4.46 (dd, $J = 7.2, 10.6$ Hz, 1H, Fmoc-CH), 4.54 (d, $J = 2.9$ Hz, 1H, H-4), 4.59 (dt, $J = 8.0, 2.7$ Hz, 1H, Ser- α -CH), 4.94 (d, $J = 3.4$ Hz, 1H, H-1'), 5.21 (d, $J = 12.0$ Hz, 1H, OCHPh), 5.23 (d, $J = 12.0$ Hz, 1H, OCHPh), 5.32 (d, $J = 3.4$ Hz, 1H, H-1), 5.39 (d, $J = 2.9, 11.5$ Hz, 1H, H-3), 5.54 (s, 1H, CHPh), 5.55 (s, 1H, CHPh), 5.93 (d, $J = 8.0$ Hz, 1H, NH), 7.32–7.42 (m, 15H, Ar), 7.50–7.54 (m, 4H, Ar), 7.60 (d, $J = 7.5$ Hz, 2H, Ar), 7.77 (d, $J = 7.5$ Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 47.0, 54.6, 56.5, 58.2, 63.1, 63.2, 67.2, 67.7, 68.8, 69.0, 69.1, 70.1, 71.1, 71.4, 73.3, 95.3 (C-1'), 99.9 (C-1), 100.7 (CHPh $\times 2$), 120.0, 124.94, 125.03, 125.2, 125.9, 126.1, 127.06, 127.09, 127.8, 128.1, 128.16, 128.18, 128.5, 128.7, 128.9, 129.0, 129.1, 135.0, 137.2, 137.4, 141.1, 143.57, 143.64, 155.9, 169.7, 170.3; FAB-HRMS m/z calcd for $\text{C}_{53}\text{H}_{52}\text{N}_7\text{O}_{14}$ ($\text{M}+\text{H}$) $^+$ 1010.3572, found 1010.3569. Data for β -anomer **14** β : R_f 0.36 (3:1 toluene/AcOEt); $[\alpha]_D^{24} +95.6$ (c 0.85, CHCl_3); IR (KBr) 3424, 2904, 2116, 1746, 1728, 1509, 1452, 1235, 1048 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.16 (s, 3H, CH_3CO), 3.41 (s, 1H, H-5), 3.59 (s, 1H, H-5'), 3.87 (d, $J = 12.6$ Hz, 1H, H-6'a), 3.90 (dd, $J = 3.4, 10.9$ Hz, 1H, H-2), 3.97 (dd, $J = 7.4, 10.9$ Hz, 1H, H-2'), 4.00 (d, $J = 12.9$ Hz, 1H, H-6'a), 4.04 (dd, $J = 2.9, 8.6$ Hz, 1H, Ser- β -CH), 4.06 (dd, $J = 3.2, 10.9$ Hz, 1H, H-3), 4.16 (dd, $J = 2.9, 8.6$ Hz, 1H, Ser- β -CH), 4.17 (d, $J = 12.6$ Hz, 1H, H-6'b), 4.24 (t, $J = 7.2$ Hz, 1H, Fmoc-CH), 4.26 (d, $J = 12.9$ Hz, 1H, H-6'b), 4.31 (d, $J = 3.7$ Hz, 1H, H-4'), 4.35 (dd, $J = 7.2, 10.6$ Hz, 1H, Fmoc-CH), 4.41 (d, $J = 3.2$ Hz, 1H, H-4), 4.46 (dd, $J = 7.2, 10.6$ Hz, 1H, Fmoc-CH), 4.616 (m, 1H, Ser- α -CH), 4.618 (d, $J = 7.4$ Hz, 1H, H-1'), 4.71 (dd, $J = 3.7, 10.9$ Hz, 1H, H-3'), 4.98 (d, $J = 3.4$ Hz, 1H, H-1), 5.24 (s, 2H, OCHPh), 5.50 (s, 1H, CHPh), 5.54 (s, 1H, CHPh), 5.90 (d, $J = 8.6$ Hz, 1H, NH), 7.32–7.43 (m, 15H, Ar), 7.48–7.53 (m, 4H, Ar), 7.59–7.61 (m, 2H, Ar), 7.78 (d, $J = 7.5$ Hz,

2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 47.0, 54.6, 59.1, 60.2, 63.5, 66.2, 67.3, 67.8, 68.85, 68.90, 69.7, 72.2, 72.3, 74.1, 75.6, 100.0 (C-1), 100.5 (CHPh), 100.9 (CHPh), 102.7 (C-1'), 120.1, 125.0, 125.1, 126.1, 126.2, 127.1, 127.2, 127.8, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 129.2, 134.9, 137.5, 141.3, 143.5, 143.7, 155.9, 169.7, 170.5; FAB-HRMS m/z calcd for $\text{C}_{53}\text{H}_{51}\text{N}_7\text{O}_{14}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1032.3392, found 1032.3385.

4.4.3. *O*-(2-Acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy- α -*D*-galactopyranosyl)-(1 $\rightarrow$ 3)-(2-acetamido-4,6-*O*-benzylidene-2-deoxy- α -*D*-galactopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-*L*-serine benzyl ester (**15**). Zn powder (40 mg) was added to a solution of glycoside **14** α (46.0 mg, 0.046 mmol) in THF/Ac₂O/AcOH (3:2:1, 1 mL) at room temperature. After stirring for 5 min, the mixture was filtered through a celite pad. The filtrate was poured into a two-layer mixture of AcOEt (3 mL) and saturated aqueous NaHCO_3 (4 mL), and the whole mixture was extracted with AcOEt (12 mL). The organic extract was successively washed with saturated aqueous NaHCO_3 (2 $\times$ 4 mL) and brine (4 mL), and dried over anhydrous Na_2SO_4 . The filtrate was concentrated and purified by column chromatography (silica gel 2 g, 1:4 hexane/AcOEt) to give acetamide **15** (41.0 mg, 86%) as a white solid: R_f 0.20 (1:4 hexane/AcOEt); $[\alpha]_D^{25} +141.6$ (c 1.01, CHCl_3); mp 138.0–139.0 $^\circ\text{C}$; IR (KBr) 3414, 3065, 2923, 1740, 1727, 1667, 1522, 1244, 1050, 743 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.60 (s, 3H, CH_3CO), 2.00 (s, 6H, CH_3CO), 2.04 (s, 3H, CH_3CO), 3.51 (s, 1H, H-5'), 3.71 (s, 1H, H-5), 3.78 (dd, $J = 2.0, 10.6$ Hz, 1H, H-3'), 3.89–3.98 (m, 2H, Ser- β -CH $\times 2$), 3.93 (d, $J = 13.2$ Hz, 1H, H-6'a), 4.05 (d, $J = 11.5$ Hz, 1H, H-6'a), 4.20 (d, $J = 13.2$ Hz, 1H, H-6'b), 4.23 (t, $J = 7.2$ Hz, 1H, Fmoc-CH), 4.27 (d, $J = 11.5$ Hz, 1H, H-6'b), 4.31 (br s, 1H, H-4'), 4.33 (d, $J = 3.4$ Hz, 1H, H-4), 4.41 (dd, $J = 7.2, 10.6$ Hz, 1H, Fmoc-CH), 4.52 (dd, $J = 7.2, 10.6$ Hz, 1H, Fmoc-CH), 4.60 (br s, 1H, Ser- α -CH), 4.68 (ddd, $J = 2.9, 10.3, 10.6$ Hz, 1H, H-2'), 4.80 (ddd, $J = 4.0, 9.7, 11.5$ Hz, 1H, H-2), 4.81 (d, $J = 2.9$ Hz, 1H, H-1'), 4.97 (dd, $J = 3.4, 11.5$ Hz, 1H, H-3), 5.19 (d, $J = 12.6$ Hz, 1H, OCHPh), 5.23 (d, $J = 12.6$ Hz, 1H, OCHPh), 5.26 (d, $J = 4.0$ Hz, 1H, H-1), 5.48 (s, 1H, CHPh), 5.52 (s, 1H, CHPh), 5.81 (d, $J = 8.6$ Hz, 1H, NHFmoc), 5.83 (d, $J = 10.3$ Hz, 1H, NHAc), 6.25 (d, $J = 9.7$ Hz, 1H, NHAc), 7.31–7.59 (m, 21H, Ar), 7.77 (d, $J = 7.7$ Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 22.7, 23.3, 46.4, 47.0, 47.7, 54.6, 63.0, 63.3, 67.1, 67.8, 69.1, 69.2, 69.3, 71.0, 71.3, 73.3, 94.2 (C-1'), 99.8 (C-1), 100.7 (CHPh), 100.9 (CHPh), 120.1, 124.76, 124.81, 126.0, 126.3, 127.1, 127.8, 127.9, 128.2, 128.3, 128.4, 128.8, 129.0, 129.2, 134.5, 137.0, 137.3, 141.3, 143.4, 143.5, 156.0, 170.1, 170.4, 170.7, 171.2; FAB-HRMS m/z calcd for $\text{C}_{57}\text{H}_{59}\text{N}_3\text{O}_{16}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1064.3793, found 1064.3781.

4.4.4. *O*-(2-Acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy- α -*D*-galactopyranosyl)-(1 $\rightarrow$ 3)-(2-acetamido-4,6-*O*-benzylidene-2-deoxy- α -*D*-galactopyranosyl)-*N*-(9-fluorenylmethoxycarbonyl)-*L*-serine (**16**). 10% Pd/C (30.0 mg) was added to a solution of glycoside **15** (30.1 mg, 0.029 mmol) in EtOH (1.0 mL) under an argon atmosphere, and the mixture was vigorously stirred under 1 atm of hydrogen for 15 min. The catalyst was filtered through a celite pad, and the filtrate was evaporated in vacuo. Purification of the crude product (28.2 mg) by column chromatography (silica gel, 1.20 g, 19:1:0.1 $\text{CHCl}_3/\text{MeOH}/\text{AcOH}$) afforded carboxylic acid **16** (22.6 mg, 82%) as a white solid: R_f 0.21 (4:1 $\text{CHCl}_3/\text{MeOH}$); mp 180.0–181.0 $^\circ\text{C}$ (decomp.); $[\alpha]_D^{23} +163.3$ (c 0.48, CHCl_3); IR (KBr) 3407, 2924, 1721, 1662, 1523, 1243, 1050, 759, 743 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 1.45 (s, 3H, CH_3CO), 1.98 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 3.72 (s, 1H, H-5'), 3.79 (s, 1H, H-5), 3.93–3.97 (m, 2H, Ser- β -CH $\times 2$), 4.00 (dd, $J = 3.2, 11.2$ Hz, 1H, H-3'), 4.06 (d, $J = 12.6$ Hz, 1H, H-6'a), 4.12 (d, $J = 12.6$ Hz, 1H, H-6'b), 4.13 (d, $J = 12.0$ Hz, 1H, H-6'a), 4.21 (d, $J = 12.0$ Hz, 1H, H-6'b), 4.24 (t, $J = 6.6$ Hz, 1H, Fmoc-

CH), 4.37 (m, 1H, Ser- α -CH), 4.43 (dd, J = 6.6, 11.5 Hz, 1H, Fmoc-CH), 4.45 (m, 2H, H-4, H-4'), 4.49 (dd, J = 6.6, 11.5 Hz, 1H, Fmoc-CH), 4.59 (ddd, J = 4.0, 7.8, 11.2 Hz, 1H, H-2'), 4.62 (ddd, J = 3.4, 8.9, 11.5 Hz, 1H, H-2), 4.92 (d, J = 4.0 Hz, 1H, H-1'), 5.03 (dd, J = 3.4, 11.5 Hz, 1H, H-3), 5.22 (d, J = 3.4 Hz, 1H, H-1), 5.59 (s, 1H, CHPh), 5.60 (s, 1H, CHPh), 7.31–7.82 (m, 18H, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ 20.7, 23.0, 23.8, 56.5, 58.3, 64.3, 64.4, 67.8, 70.0, 70.3, 70.4, 71.1, 71.8, 74.6, 94.4 (C-1'), 100.6 (C-1), 101.9 (CHPh), 102.1 (CHPh), 121.0, 126.06, 126.13, 127.5, 127.8, 128.3, 128.9, 129.1, 129.2, 130.0, 130.1, 139.5, 139.6, 142.6, 145.2, 145.3, 158.4, 172.2, 173.46, 173.54, 174.0; ESI-HRMS m/z calcd for $\text{C}_{50}\text{H}_{52}\text{N}_3\text{O}_{16}$ (M-H) $^-$ 950.3348, found 950.3355.

4.5. Synthesis of mucin core 7 building block

4.5.1. *N*-(9-Fluorenylmethoxycarbonyl)-O-(3-O-acetyl-2-azido-2-deoxy- α -D-galactopyranosyl)-L-serine benzyl ester (17). **3a α** (515 mg, 0.70 mmol) was dissolved in 80% AcOH (14 mL) and the solution was stirred for 8 h at 50 °C. The mixture was poured into a two-layer mixture of AcOEt (15 mL) and saturated aqueous NaHCO_3 (20 mL), and the whole was extracted with AcOEt (150 mL). The organic layer was washed with saturated aqueous NaHCO_3 (35 mL) and brine (2 $\times$ 35 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation in vacuo furnished the pale yellow residue (490 mg), which was purified by column chromatography (silica gel 15 g, 1:2 hexane/AcOEt) to give diol **17** (360 mg, 80%) as a white amorphous solid. R_f 0.17 (1:2 hexane/AcOEt); $[\alpha]_D^{20}$ +83.9 (c 1.01, CHCl_3); IR (KBr) 3430, 3066, 2948, 2112, 1742, 1725, 1524, 1451, 1247, 1044 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.20 (s, 3H, CH_3CO), 2.89 (br s, 1H, OH), 3.68 (dd, 1H, J = 3.4, 10.9 Hz, H-2), 3.65–3.78 (m, 4H, OH, H-5, H-6a, H-6b), 3.94 (dd, J = 2.6, 11.2 Hz, 1H, Ser- β -CH), 4.13 (d, J = 2.9 Hz, 1H, H-4), 4.23 (t, J = 6.9 Hz, 1H, Fmoc-CH), 4.26 (dd, J = 2.6, 11.2 Hz, 1H, Ser- β -CH), 4.44 (d, J = 6.9 Hz, 2H, Fmoc-CH $\times$ 2), 4.58 (dt, J = 8.0, 2.6 Hz, 1H, Ser- α -CH), 4.83 (d, J = 3.4 Hz, 1H, H-1), 5.12 (dd, J = 2.9, 10.9 Hz, 1H, H-3), 5.22 (d, J = 12.0 Hz, 1H, OCHPh), 5.23 (d, J = 12.0 Hz, 1H, OCHPh), 6.10 (d, J = 8.0 Hz, 1H, NH), 7.31–7.42 (m, 9H, Ar), 7.62 (d, J = 7.4 Hz, 2H, Ar), 7.77 (d, J = 7.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 47.0, 54.6, 57.1, 62.9, 67.1, 67.8, 68.6, 69.7, 70.2, 70.3, 99.8 (C-1), 120.0, 125.1, 127.1, 127.7, 128.4, 128.59, 128.63, 134.9, 141.21, 141.23, 143.6, 143.7, 156.0, 169.7, 170.1; FAB-HRMS m/z calcd for $\text{C}_{33}\text{H}_{35}\text{N}_4\text{O}_{10}$ (M+H) $^+$ 647.2353, found 647.2351.

4.5.2. O-(3-O-Acetyl-2-azido-4,6-O-benzylidene-2-deoxy-D-galactopyranosyl)-(1 $\rightarrow$ 6)-(3-O-acetyl-2-azido-2-deoxy- α -D-galactopyranosyl)-N-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (18). The glycosidation was performed according to the typical procedure (1:1 THF/Et $_2$ O 1.0 mL, -78 °C, 48 h) employing diphenyl phosphate **1a α** (56.7 mg, 0.10 mmol), diol **17** (80.8 mg, 0.13 mmol), TMSOTf (1.0 M in CH_2Cl_2 , 0.11 mL, 0.11 mmol) and pulverized 5- $\text{\AA}$ MS (100 mg). An anomeric mixture of disaccharide **18** (85.8 mg, 89%, α : β = 86:14) was obtained as a white amorphous solid from the crude product (120 mg) after flash column chromatography (silica gel 12 g, 4:1 $\rightarrow$ 2:1 toluene/AcOEt). The anomeric ratio of **18** was determined by HPLC analysis [eluent, 3:1 hexane/*i*-PrOH; flow rate, 1.5 mL/min; detection, 254 nm; t_R (α -anomer) = 3.5 min, t_R (β -anomer) = 6.6 min]. The α - and β -glycosides were separated by flash chromatography with 1:2 hexane/AcOEt. Data for α -anomer **18 α** : R_f 0.54 (1:2 hexane/AcOEt); $[\alpha]_D^{20}$ +143.0 (c 1.00, CHCl_3); IR (KBr) 3434, 2938, 2111, 1742, 1726, 1517, 1452, 1374, 1236, 1036 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.13 (s, 3H, CH_3CO), 2.21 (s, 3H, CH_3CO), 2.81 (d, J = 2.3 Hz, 1H, OH), 3.70 (br s, 1H, H-5'), 3.72 (dd, J = 3.4, 11.5 Hz, 1H, H-2), 3.76

(dd, J = 7.2 12.3 Hz, 1H, H-6a), 3.85–3.89 (m, 2H, H-5, H-6b), 3.94 (br d, J = 12.6 Hz, 1H, H-6'a), 4.01 (dd, J = 3.4, 10.9 Hz, 1H, Ser- β -CH), 4.04 (dd, J = 3.4, 10.9 Hz, 1H, H-2'), 4.17 (br d, J = 12.6 Hz, 1H, H-6'b), 4.15–4.18 (m, 2H, H-4, Ser- β -CH), 4.24 (dd, J = 7.4, 10.3 Hz, 1H, Fmoc-CH), 4.34 (dd, J = 7.4, 10.3 Hz, 1H, Fmoc-CH), 4.41 (m, 2H, H-4', Fmoc-CH), 4.63 (dt, J = 8.0, 3.4 Hz, 1H, Ser- α -CH), 4.88 (d, J = 3.4 Hz, 1H, H-1), 5.11 (d, J = 3.4 Hz, 1H, H-1'), 5.188 (dd, J = 2.6, 10.9 Hz, 1H, H-3'), 5.190 (dd, J = 3.4, 11.5 Hz, 1H, H-3), 5.22 (d, J = 12.6 Hz, 1H, OCHPh), 5.28 (d, J = 12.6 Hz, 1H, OCHPh), 5.48 (s, 1H, CHPh), 5.97 (d, J = 8.0 Hz, 1H, NH), 7.26–7.42 (m, 12H, Ar), 7.46 (dd, J = 2.9, 6.9 Hz, 2H, Ar), 7.61 (dd, J = 4.0, 7.5 Hz, 2H, Ar), 7.75 (d, J = 7.5 Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 20.88, 20.90, 46.9, 54.4, 57.1, 62.6, 66.8, 67.4, 67.67, 67.70, 68.8, 68.9, 69.5, 69.8, 70.2, 73.1, 98.2 (C-1'), 99.5 (C-1), 100.6 (CHPh), 119.9, 125.1, 125.2, 126.0, 127.0, 127.1, 127.7, 128.1, 128.3, 128.4, 128.5, 129.0, 135.0, 137.3, 141.2, 143.6, 143.8, 155.9, 169.7, 169.8, 170.4; FAB-HRMS m/z calcd for $\text{C}_{48}\text{H}_{50}\text{N}_7\text{O}_{15}$ (M+H) $^+$ 964.3365, found 964.3365. Data for β -anomer **18 β** : R_f 0.27 (1:2 hexane/AcOEt); $[\alpha]_D^{24}$ +65.2 (c 1.01, CHCl_3); IR (KBr) 3430, 2948, 2117, 1747, 1726, 1508, 1451, 1371, 1236, 1052 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.14 (s, 3H, CH_3CO), 2.16 (s, 3H, CH_3CO), 2.65 (br s, 1H, OH), 3.46 (br s, 1H, H-5'), 3.67 (dd, J = 3.4, 10.9 Hz, 1H, H-2), 3.81 (dd, J = 6.0, 10.0 Hz, 1H, H-5), 3.97 (dd, J = 8.0, 10.9 Hz, 1H, H-2'), 3.98 (t, J = 6.0 Hz, 1H, H-6a), 4.02 (br d, J = 12.0 Hz, 1H, H-6'a), 4.03–4.08 (m, 3H, H-6b, Ser- β -CH $\times$ 2), 4.15 (t, J = 6.9 Hz, 1H, Fmoc-CH), 4.20 (m, 1H, H-4), 4.25 (d, J = 12.0 Hz, 1H, H-6'b), 4.33 (d, J = 3.4 Hz, 1H, H-4'), 4.35 (dd, J = 7.4, 10.9 Hz, 1H, Fmoc-CH), 4.390 (dd, J = 7.4, 10.9 Hz, 1H, Fmoc-CH), 4.394 (d, J = 8.0 Hz, 1H, H-1'), 4.58 (dt, J = 8.4, 3.2 Hz, 1H, Ser- α -CH), 4.72 (dd, J = 3.4, 10.9 Hz, 1H, H-3'), 4.88 (d, J = 3.4 Hz, 1H, H-1), 5.19 (d, J = 12.0 Hz, 1H, OCHPh), 5.21 (dd, J = 3.4, 10.9 Hz, 1H, H-3), 5.25 (d, J = 12.0 Hz, 1H, OCHPh), 5.50 (s, 1H, CHPh), 5.80 (d, J = 8.4 Hz, 1H, NH), 7.30–7.40 (m, 12H, Ar), 7.47 (dd, J = 2.9, 6.9 Hz, 2H, Ar), 7.54 (d, J = 7.4 Hz, 1H, Ar), 7.63 (d, J = 7.4 Hz, 1H, Ar), 7.75 (dd, J = 2.9, 7.7 Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 21.0, 46.9, 54.4, 57.2, 60.1, 66.4, 67.2, 67.3, 67.7, 68.7, 68.8, 69.1, 70.0, 72.2, 72.4, 99.1 (C-1), 100.8 (CHPh), 101.7 (C-1'), 119.9, 125.13, 125.15, 126.1, 126.98, 127.04, 127.6, 128.2, 128.4, 128.5, 128.6, 129.2, 135.0, 137.3, 141.2, 143.9, 155.9, 169.6, 169.8, 170.5; FAB-HRMS m/z calcd for $\text{C}_{48}\text{H}_{49}\text{N}_7\text{O}_{15}\text{Na}$ (M+Na) $^+$ 986.3184, found 986.3182.

4.5.3. O-(3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-galactopyranosyl)-(1 $\rightarrow$ 6)-(3-O-acetyl-2-azido-2-deoxy- α -D-galactopyranosyl)-N-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (20). HClO_4 in dioxane (0.1 M, 0.20 mL, 0.02 mmol) was added to a stirred solution of diphenyl phosphate **19** (56.3 mg, 0.10 mmol), diol **17** (71.1 mg, 0.11 mmol) and pulverized 5- $\text{\AA}$ MS (100 mg) in dioxane/Et $_2$ O (1:1, 1.0 mL) at 0 °C. After stirring at this temperature for 10 h, the reaction was quenched with saturated aqueous NaHCO_3 (0.1 mL), and the mixture was filtrated through a celite pad. The filtrate was poured into a two-layer mixture of AcOEt (3 mL) and NaHCO_3 (6 mL), and the whole was extracted with AcOEt (30 mL). The organic layer was successively washed with saturated aqueous NaHCO_3 (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation in vacuo furnished the crude product (121.5 mg), from which an anomeric mixture of disaccharide **20** (91.2 mg, 95%, α : β = 94:6) was obtained as a white amorphous solid after flash column chromatography (silica gel 10 g, 10:1 CH_2Cl_2 /acetone). The anomeric ratio of **20** was determined by HPLC analysis [eluent, 2:1 hexane/THF; flow rate, 1.0 mL/min; detection, 254 nm; t_R (α -anomer) = 15.3 min, t_R (β -anomer) = 19.9 min]. The α - and β -glycosides were separated by flash

column chromatography with 20:1 CH₂Cl₂/acetone. Data for α -anomer **20 α** : *R*_f 0.35 (10:1 CH₂Cl₂/acetone); [α]_D²⁰ +103.8 (c 1.00, CHCl₃); IR (KBr) 3424, 3066, 2945, 2112, 1749, 1727, 1520, 1451, 1230, 1050, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.99 (s, 3H, CH₃CO), 2.03 (s, 3H, CH₃CO), 2.10 (s, 3H, CH₃CO), 2.20 (s, 3H, CH₃CO), 2.66 (d, *J* = 3.4 Hz, 1H, OH), 3.70 (dd, *J* = 4.0, 10.9 Hz, 1H, H-2), 3.74 (dd, *J* = 2.3, 8.0 Hz, 1H, H-6a), 3.76 (dd, *J* = 3.4, 10.9 Hz, 1H, H-2'), 3.83–3.88 (m, 2H, H-5, H-6b), 3.98–4.08 (m, 3H, Ser- β -CH, H-5', H-6'a), 4.13–4.20 (m, 2H, Ser- β -CH, H-6'b), 4.14 (m, 1H, H-4), 4.25 (t, *J* = 7.7 Hz, 1H, Fmoc-CH), 4.33 (dd, *J* = 7.7, 10.6 Hz, 1H, Fmoc-CH), 4.41 (dd, *J* = 7.7, 10.6 Hz, 1H, Fmoc-CH), 4.65 (dt, *J* = 8.6, 3.4 Hz, 1H, Ser- α -CH), 4.90 (d, *J* = 4.0 Hz, 1H, H-1), 5.05 (d, *J* = 3.4 Hz, 1H, H-1'), 5.19 (dd, *J* = 4.0, 10.9 Hz, 1H, H-3), 5.22 (d, *J* = 12.5 Hz, 1H, OCHPh), 5.27 (dd, *J* = 2.9, 10.9 Hz, 1H, H-3'), 5.28 (d, *J* = 12.5 Hz, 1H, OCHPh), 5.41 (d, *J* = 2.9 Hz, 1H, H-4'), 5.99 (d, *J* = 8.6 Hz, 1H, NH), 7.26–7.42 (m, 9H, Ar), 7.61–7.63 (m, 2H, Ar), 7.77 (d, *J* = 7.5 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 20.5, 20.6, 20.9, 21.0, 46.9, 54.3, 57.1, 57.6, 60.4, 61.4, 66.7, 67.3, 67.4, 67.7, 68.56, 68.61, 69.5, 70.2, 97.6 (C-1'), 99.3 (C-1), 119.9, 125.1, 125.2, 127.1, 127.7, 128.4, 128.5, 128.6, 135.1, 141.15, 141.17, 143.7, 143.8, 155.9, 169.70, 169.72, 169.8, 169.9, 170.4; FAB-HRMS *m/z* calcd for C₄₅H₅₀N₇O₁₇ (M+H)⁺ 960.3263, found 960.3260. Data for β -anomer **20 β** : *R*_f 0.30 (10:1 CH₂Cl₂/acetone); [α]_D²⁴ +34.8 (c 0.40, CHCl₃); IR (KBr) 3370, 2944, 2115, 1750, 1736, 1523, 1236, 1039 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.037 (s, 3H, CH₃CO), 2.042 (s, 3H, CH₃CO), 2.08 (s, 3H, CH₃CO), 2.20 (s, 3H, CH₃CO), 2.49 (d, *J* = 3.4 Hz, 1H, OH), 3.67 (dd, *J* = 7.7, 10.6 Hz, 1H, H-2'), 3.68 (dd, *J* = 4.0, 10.9 Hz, 1H, H-2), 3.80 (dd, *J* = 6.0, 6.6 Hz, 1H, H-5'), 3.84 (dd, *J* = 6.0, 10.0 Hz, 1H, H-6'a), 3.96–4.02 (m, 3H, H-5, H-6a, H-6b), 4.05 (dd, *J* = 6.6, 10.0 Hz, 1H, H-6'b), 4.08–4.09 (m, 2H, Ser- β -CH $\times$ 2), 4.21–4.26 (m, 2H, H-4, Fmoc-CH), 4.33 (dd, *J* = 7.2, 10.6 Hz, 1H, Fmoc-CH), 4.34 (d, *J* = 7.7 Hz, 1H, H-1'), 4.44 (dd, *J* = 7.2, 10.6 Hz, 1H, Fmoc-CH), 4.62 (dt, *J* = 8.4, 3.2 Hz, 1H, Ser- α -CH), 4.76 (dd, *J* = 3.4, 10.9 Hz, 1H, H-3'), 4.86 (d, *J* = 3.4 Hz, 1H, H-1), 5.22 (d, *J* = 12.4 Hz, 1H, OCHPh), 5.23 (dd, *J* = 3.2, 10.9 Hz, 1H, H-3), 5.27 (d, *J* = 12.5 Hz, 1H, OCHPh), 5.30 (d, *J* = 3.4 Hz, 1H, H-4'), 5.86 (d, *J* = 8.4 Hz, 1H, NH), 7.26–7.42 (m, 9H, Ar), 7.62 (d, *J* = 7.5 Hz, 2H, Ar), 7.77 (d, *J* = 7.5 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 20.5, 20.58, 20.64, 21.0, 47.0, 54.4, 57.2, 60.5, 61.4, 66.2, 67.1, 67.4, 67.8, 68.9, 69.1, 70.2, 70.9, 71.1, 99.1 (C-1), 102.4 (C-1'), 120.0, 125.17, 125.24, 127.1, 127.7, 128.3, 128.5, 128.6, 128.7, 135.0, 141.2, 143.7, 143.9, 155.9, 169.6, 169.8, 169.9, 170.0, 170.4; FAB-HRMS *m/z* calcd for C₄₅H₄₉N₇O₁₇Na (M+Na)⁺ 982.3083, found 982.3084.

4.5.4. *O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- α -D-galactopyranosyl)-(1 $\rightarrow$ 6)-(2-acetamido-3,4-di-*O*-acetyl-2-deoxy- α -D-galactopyranosyl)-N-(9-fluorenylmethoxycarbonyl)-L-serine benzyl ester (**21**). Pyridine (0.039 mL, 0.48 mmol) was added to a solution of disaccharide **20 α** (46.0 mg, 0.048 mmol) in CH₂Cl₂ (1 mL) at room temperature followed by addition of acetic anhydride (0.009 mL, 0.10 mmol). After stirring at room temperature for 30 min, the reaction was quenched with crushed ice, followed by stirring for 15 min. The mixture was extracted with AcOEt (15 mL). The organic layer was washed with 10% HCl (3 $\times$ 4 mL) and brine (4 mL), and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo furnished the crude product (55.0 mg). The crude mixture thus obtained was suspended in THF/Ac₂O/AcOH (3:2:1, 1 mL), and Zn powder (50 mg) was added. After stirring at room temperature for 5 min, the mixture was filtered through a celite pad. The filtrate was poured into a two-layer mixture of AcOEt (3 mL) and saturated aqueous NaHCO₃ (4 mL), and the whole mixture was extracted with AcOEt (12 mL). The organic extract was successively

washed with saturated aqueous NaHCO₃ (2 $\times$ 4 mL) and brine (4 mL), and dried over anhydrous Na₂SO₄. The filtrate was concentrated and purified by column chromatography (silica gel 2 g, 40:1 CHCl₃/MeOH) to give acetamide **21** (40.0 mg, 81%) as a colorless film: *R*_f 0.65 (9:1 CHCl₃/MeOH); [α]_D²² +93.8 (c 0.93, CHCl₃); IR (KBr) 3372, 3066, 2955, 1748, 1676, 1529, 1373, 1242, 1048 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.94 (s, 3H, CH₃CO), 1.96 (s, 6H, CH₃CO), 2.01 (s, 3H, CH₃CO), 2.03 (s, 3H, CH₃CO), 2.16 (s, 6H, CH₃CO), 3.19 (dd, *J* = 2.7, 8.6 Hz, 1H, H-5), 3.71–3.78 (m, 2H, H-6a, H-6b), 3.902 (dd, *J* = 2.3 Hz, 1H, H-5'), 3.904 (dd, *J* = 7.7, 10.4 Hz, 1H, Ser- β -CH), 3.99 (dd, *J* = 7.7, 10.4 Hz, 1H, Ser- β -CH), 4.16–4.25 (m, 3H, Fmoc-CH, H-6'a, H-6'b), 4.34 (dd, *J* = 7.0, 10.6 Hz, 1H, Fmoc-CH), 4.49 (dd, *J* = 7.0, 10.6 Hz, 1H, Fmoc-CH), 4.55 (ddd, *J* = 3.6, 9.5, 11.3 Hz, 1H, H-2), 4.66 (ddd, *J* = 3.6, 10.0, 10.8 Hz, 1H, H-2'), 4.76 (m, 1H, Ser- α -CH), 4.81 (d, *J* = 3.6 Hz, 1H, H-1'), 4.82 (d, *J* = 3.6 Hz, 1H, H-1), 4.93 (dd, *J* = 3.0, 11.3 Hz, 1H, H-3), 5.12 (d, *J* = 3.0 Hz, 1H, H-4), 5.18 (d, *J* = 11.8 Hz, 1H, OCHPh), 5.27 (dd, *J* = 2.8, 10.8 Hz, 1H, H-3'), 5.30 (d, *J* = 11.8 Hz, 1H, OCHPh), 5.37 (d, *J* = 2.8 Hz, 1H, H-4'), 5.60 (d, *J* = 9.5 Hz, 1H, NHAc), 6.48 (d, *J* = 9.1 Hz, 1H, NHFmoc), 6.59 (d, *J* = 10.0 Hz, 1H, NHAc'), 7.28–7.43 (m, 9H, Ar), 7.63 (d, *J* = 7.2 Hz, 2H, Ar), 7.77 (d, *J* = 7.7 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 20.5, 20.7, 20.8, 23.0, 23.3, 29.6, 47.0, 47.2, 47.8, 53.7, 60.4, 61.2, 65.7, 66.8, 67.3, 67.7, 67.8, 68.0, 68.26, 68.29, 69.1, 97.4 (C-1'), 98.3 (C-1), 120.0, 125.0, 125.1, 127.0, 127.1, 127.79, 127.81, 128.5, 128.8, 128.9, 134.6, 141.2, 141.3, 143.6, 155.8, 170.1, 170.30, 170.34, 170.5, 170.7, 171.2, 171.5; FAB-HRMS *m/z* calcd for C₅₁H₆₀N₃O₂₀ (M+H)⁺ 1034.3770, found 1034.3750.

4.5.5. *O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- α -D-galactopyranosyl)-(1 $\rightarrow$ 6)-(2-acetamido-3,4-di-*O*-acetyl-2-deoxy- α -D-galactopyranosyl)-N-(9-fluorenylmethoxycarbonyl)-L-serine (**22**). 10% Pd/C (30.0 mg) was added to a solution of glycoside **21** (32.0 mg, 0.031 mmol) in EtOH (1.0 mL) under an argon atmosphere, and the mixture was vigorously stirred under 1 atm of hydrogen for 15 min. The catalyst was filtered through a celite pad, and the filtrate was evaporated in vacuo. Purification of the crude product (29.5 mg) by column chromatography (silica gel, 1.20 g, 19:1:0.1 CHCl₃/MeOH/AcOH) afforded carboxylic acid **22** (23.4 mg, 80%) as a white solid: *R*_f 0.23 (4:1 CHCl₃/MeOH); mp 146.0–147.2 °C; [α]_D²² +89.4 (c 0.90, CHCl₃); IR (KBr) 3372, 2933, 1748, 1664, 1533, 1373, 1242, 1048, 762, 742 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 1.95 (s, 3H, CH₃CO), 1.98 (s, 3H, CH₃CO), 2.00 (s, 3H, CH₃CO), 2.01 (s, 3H, CH₃CO), 2.02 (s, 3H, CH₃CO), 2.16 (s, 3H, CH₃CO), 2.22 (s, 3H, CH₃CO), 3.46 (dd, *J* = 5.2, 9.5 Hz, 1H, H-6'a), 3.86 (dd, *J* = 7.7, 9.5 Hz, 1H, H-6'b), 3.93 (dd, *J* = 6.9, 10.9 Hz, 1H, H-6a), 4.02–4.10 (m, 2H, Ser- β -CH $\times$ 2), 4.14 (dd, *J* = 6.0, 9.5 Hz, 1H, H-6b), 4.34 (t, *J* = 6.9 Hz, 1H, Fmoc-CH), 4.35–4.39 (m, 2H, H-5, H-5'), 4.41 (dd, *J* = 6.9, 10.3 Hz, 1H, Fmoc-CH), 4.49–4.55 (m, 3H, H-2, H-2', Ser- α -CH), 4.57 (dd, *J* = 6.9, 10.3 Hz, 1H, Fmoc-CH), 4.88 (d, *J* = 3.4 Hz, 1H, H-1), 5.00 (d, *J* = 4.0 Hz, 1H, H-1'), 5.24 (dd, *J* = 2.9, 11.5 Hz, 2H, H-3, H-3'), 5.42 (d, *J* = 2.9 Hz, 1H, H-4), 5.55 (d, *J* = 2.9 Hz, 1H, H-4'), 7.39–7.43 (m, 2H, Ar), 7.47 (t, *J* = 7.4 Hz, 2H, Ar), 7.78 (t, *J* = 6.6 Hz, 2H, Ar), 7.88 (d, *J* = 7.4 Hz, 2H, Ar); ¹³C NMR (100 MHz, CD₃OD) δ 20.5, 20.57, 20.60, 20.66, 20.68, 22.6, 22.7, 55.9, 63.0, 67.2, 68.0, 68.1, 68.7, 69.0, 69.7, 70.8, 99.0 (C-1'), 100.5 (C-1), 121.0, 126.2, 126.3, 126.4, 128.2, 128.3, 128.9, 129.2, 129.9, 142.6, 145.2, 145.2, 158.3, 171.9, 172.0, 172.08, 172.10, 173.4, 173.6, 173.8.

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References and notes

- For reviews, see: (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720; (b) Zachara, N. E.; Hart, G. W. *Chem. Rev.* **2002**, *102*, 431–438.
- For reviews, see: (a) Kim, Y. S.; Gum, J., Jr.; Brockhausen, I. *Glycoconjugate J.* **1996**, *13*, 693–707; (b) Hang, H. C.; Bertozzi, C. R. *Bioorg. Med. Chem.* **2005**, *13*, 5021–5034; (c) Ju, T.; Otto, V. I.; Cummings, R. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 1770–1791.
- Brockhausen, I. *Biochim. Biophys. Acta* **1999**, *1473*, 67–95.
- (a) Sames, D.; Chen, X.-T.; Danishefsky, S. J. *Nature* **1997**, *389*, 587–591; (b) Danishefsky, S. J.; Allen, J. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 836–863; (c) Dziadek, S.; Kunz, H. *Chem. Rev.* **2004**, *3*, 308–321.
- (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195; (b) Arsequell, G.; Valencia, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2839–2876; (c) Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317–11362; (d) Seitz, O. *ChemBioChem* **2000**, *1*, 214–246; (e) Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495–4537; (f) Marcaurelle, L. A.; Bertozzi, C. R. *Glycobiology* **2002**, *12*, 69R–77R; (g) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Heterocycles* **2008**, *76*, 883–908.
- The chemical synthesis of T_N-antigen structure was first described by Kaifu and Osawa, in which glycosidation of 3,4,6-tri-O-acetyl-2-deoxy-2-(2,4-dinitroanilino)- α -D-galactopyranosyl bromide with N-tosyl-L-serine methyl ester provided the corresponding α - and β -galactosides in 53% and 11% yields, respectively. Kaifu, R.; Osawa, T. *Carbohydr. Res.* **1977**, *58*, 235–239.
- (a) Paulsen, H.; Kolar, C.; Stenzel, W. *Chem. Ber.* **1978**, *111*, 2358–2369; (a) Paulsen, H.; Kolar, C.; Stenzel, W. *Chem. Ber.* **1978**, *111*, 2370–2375.
- (a) Ferrari, B.; Pavia, A. A. *Carbohydr. Res.* **1980**, *79*, C1–C7; (b) Paulsen, H.; Adermann, K. *Liebigs Ann. Chem.* **1989**, 751–769; (c) Friedrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751–756; (d) Nakahara, Y.; Iijima, H.; Sibayama, S.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 6897–6900; (e) Iijima, H.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1992**, *33*, 7907–7910; (f) Macindoe, W. M.; Iijima, H.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1994**, *35*, 1735–1738; (g) Szabó, L.; Ramza, J.; Langdon, C.; Polt, R. *Carbohydr. Res.* **1995**, *274*, 11–28; (h) Wang, Z.-G.; Zhang, X.-F.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Bioorg. Med. Chem.* **1996**, *4*, 1901–1908; (i) Chen, X.-T.; Sames, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 7760–7769; (j) Mitchell, S. A.; Pratt, M. R.; Hruby, V. J.; Polt, R. *J. Org. Chem.* **2001**, *66*, 2327–2342; (k) van Well, R. M.; Kartha, K. P. R.; Field, R. A. *J. Carbohydr. Chem.* **2005**, *24*, 463–474.
- (a) Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826–1847; (b) Toyokuni, T.; Dean, B.; Hakomori, S.-I. *Tetrahedron Lett.* **1990**, *31*, 2673–2676; (c) Paulsen, H.; Schleyer, A.; Mathieux, N.; Meldal, M.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 281–293; (d) Gambert, U.; Thiem, J. *Carbohydr. Res.* **1997**, *299*, 85–89; (e) Singh, L.; Nakahara, Y.; Ito, Y.; Nakahara, Y. *Carbohydr. Res.* **2000**, *325*, 132–142; (f) Koeller, K. M.; Smith, M. E. B.; Wong, C.-H. *Bioorg. Med. Chem.* **2000**, *8*, 1017–1025; (g) Götze, S.; Fitzner, R.; Kunz, H. *Synlett* **2009**, 3346–3348; (h) Ludek, O. R.; Gu, W.; Gildersleeve, J. C. *Carbohydr. Res.* **2010**, *345*, 2074–2078.
- For the use of 2-azido-2-deoxygalactosyl (N-phenyl)trifluoroacetimidate as a glycosyl donor, see: Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Valerio, S. *Tetrahedron Lett.* **2006**, *47*, 2595–2599.
- Nguyen and co-workers reported Ni-catalyzed stereoselective glycosylation with C(2)-N-substituted benzylidene galactosamine trichloroacetimidates. (a) Mensah, E. A.; Nguyen, H. M. *J. Am. Chem. Soc.* **2009**, *131*, 8778–8780; (b) Mensah, E. A.; Yu, F.; Nguyen, H. M. *J. Am. Chem. Soc.* **2010**, *132*, 14288–14302.
- (a) Paulsen, H.; Rauwald, W.; Weichert, U. *Liebigs Ann. Chem.* **1988**, 75–86; (b) Braun, P.; Waldmann, H.; Kunz, H. *Bioorg. Med. Chem.* **1993**, *1*, 197–207; (c) Eberling, J.; Braun, P.; Kowalczyk, D.; Schultz, M.; Kunz, H. *J. Org. Chem.* **1996**, *61*, 2638–2646; (d) Eloffsson, M.; Salvador, L. A.; Kihlberg, J. *Tetrahedron* **1997**, *53*, 369–390; (e) Miyajima, K.; Nekado, T.; Ikeda, K.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 1676–1682; (f) George, S. K.; Schwientek, T.; Holm, B.; Reis, C. A.; Clausen, H.; Kihlberg, J. *J. Am. Chem. Soc.* **2001**, *123*, 11117–11125; (g) Hashihayata, T.; Ikegai, K.; Takeuchi, K.; Jona, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1829–1848; (h) Cato, D.; Buskas, T.; Boons, G.-J. *J. Carbohydr. Chem.* **2005**, *24*, 503–516.
- For the use of phenyl 2-azido-2-deoxy-1-seleno- α -D-galactosides as glycosyl donors, see: (a) Jiaang, W.-T.; Chang, M.-Y.; Tseng, P.-H.; Chen, S.-T. *Tetrahedron Lett.* **2000**, *41*, 3127–3130; (b) Tseng, P.-H.; Jiaang, W.-T.; Chang, M.-Y.; Chen, S.-T. *Chem. Eur. J.* **2001**, *7*, 585–590; (c) Kärkkäinen, T. S.; Kartha, K. P. R.; MacMillan, D.; Field, R. A. *Carbohydr. Res.* **2008**, *343*, 1830–1834.
- Mukaiyama and Matsubara reported that glycosidation of 1-O-acetyl-2-azido-2-deoxy-3,4,6-tri-O-benzylgalactoside with Troc-protected L-threonine 2,2,2-trichloroethyl ester trimethylsilyl ether provided exclusively α -galactoside in 95% yield. Matsubara, K.; Mukaiyama, T. *Chem. Lett.* **1993**, 581–584.
- For recent examples of the synthesis of Gal β 1-3GalNAc α 1-O-Ser/Thr structures (T-antigens) employing glycosidations of disaccharide donors bearing an azido group at C-2 with Ser/Thr acceptors, see: (a) Shao, N.; Guo, Z. *Org. Lett.* **2005**, *7*, 3589–3592; (b) Rauvolfova, J.; Venot, A.; Boons, G.-J. *Carbohydr. Res.* **2008**, *343*, 1605–1611; (c) Vohra, Y.; Buskas, T.; Boons, G.-J. *J. Org. Chem.* **2009**, *74*, 6064–6071.
- (a) Yule, J. E.; Wong, T. C.; Gandhi, S. S.; Qiu, D.; Riopel, M. A.; Koganty, R. R. *Tetrahedron Lett.* **1995**, *36*, 6839–6842; (b) Wei, G.; Lv, X.; Du, Y. *Carbohydr. Res.* **2008**, *343*, 3096–3099.
- (a) Matsubara, K.; Mukaiyama, T. *Chem. Lett.* **1993**, 2145–2148; (b) Imamura, A.; Ando, H.; Korogi, S.; Tanabe, G.; Muraoka, O.; Ishida, H.; Kiso, M. *Tetrahedron Lett.* **2003**, *44*, 6725–6728; (c) Imamura, A.; Kimura, A.; Ando, H.; Ishida, H.; Kiso, M. *Chem. Eur. J.* **2006**, *12*, 8862–8870.
- (a) Winterfeld, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 1167–1171; (b) Winterfeld, G. A.; Khodair, A. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, 1009–1021; (c) Geiger, J.; Reddy, B. G.; Winterfeld, G. A.; Weber, R.; Przybylski, M.; Schmidt, R. R. *J. Org. Chem.* **2007**, *72*, 4367–4377.
- Recently, Gin and Ryan reported the ring-opening of aziridine-2-carboxamides with C1-O-hemiacetal nucleophiles to form α -O-glycosyl serine conjugates in high diastereoselectivity. Ryan, D. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2008**, *130*, 15228–15229.
- Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685–687.
- For reviews on glycosidations of glycosyl phosphates, phosphites and other O-P derivatives, see: (a) Zhang, Z.; Wong, C.-H. In *Carbohydrates in Chemistry and Biology*; Ernst, B.; Hart, G. W.; Sinaÿ, P., Eds.; VCH: Weinheim, 2000; Part I, pp 117–134; (b) Vankayalapati, H.; Jiang, S.; Singh, G. *Synlett* **2002**, 16–25; (c) Palmacci, E. R.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 595–606; (d) Nakamura, S.; Nambu, H.; Hashimoto, S. In *Handbook of Chemical Glycosylation: Advances in Stereochemistry and Therapeutic Relevance*; Demchenko, A. V., Ed.; VCH: Weinheim, 2008; pp 223–259.
- (a) Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769–4772; (b) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259–1260.
- (a) Koshiha, M.; Suzuki, N.; Arihara, R.; Tsuda, T.; Nambu, H.; Nakamura, S.; Hashimoto, S. *Chem. Asian J.* **2008**, *3*, 1664–1677; (b) Nambu, H.; Nakamura, S.; Suzuki, N.; Hashimoto, S. *Trends Glycosci. Glycotechnol.* **2010**, *22*, 26–40.
- The groups of Meldal and Paulsen first used the cassette methodology for the synthesis of core 1, core 2, core 3, core 4 and core 6 building blocks. (a) Meinjohanns, E.; Meldal, M.; Schleyer, A.; Paulsen, H.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 985–993; (b) Mathieux, N.; Paulsen, H.; Meldal, M.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2359–2368.
- Danishefsky and co-workers reported a cassette-based approach for the synthesis of a variety of complex building blocks bearing tumor-related antigens. (a) Kuduk, S. D.; Schwarz, J. B.; Chen, X.-T.; Glunz, P. W.; Sames, D.; Ragupathi, G.; Livingston, P. O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12474–12485; (b) Schwarz, J. B.; Kuduk, S. D.; Chen, X.-T.; Sames, D.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 2662–2673; (c) Glunz, P. W.; Hintermann, S.; Williams, L. J.; Schwarz, J. B.; Kuduk, S. D.; Kudryashov, V.; Lloyd, K. O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 7273–7279.

26. For examples of a cassette approach for the synthesis of glycosphingolipid and gangliosides using glucosylceramide building blocks, see: (a) Hashimoto, S.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969–8972; (b) Sakamoto, H.; Nakamura, S.; Tsuda, T.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 7691–7695; (c) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *J. Org. Chem.* **2009**, *74*, 3009–3023; (d) Tamai, H.; Ando, H.; Tanaka, H.-N.; Hosoda-Yabe, R.; Yabe, T.; Ishida, H.; Kiso, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2330–2333; (e) Fujiwara, K.; Nakashima, S.; Konishi, M.; Fuse, T.; Komura, N.; Ando, T.; Ando, H.; Yuki, N.; Ishida, H.; Kiso, M. *Chem. Eur. J.* **2011**, *17*, 5641–5651.
27. Tsuda, T.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2004**, *60*, 10711–10737.
28. Saitoh, T.; Yoshida, S.; Ichikawa, J. *J. Org. Chem.* **2006**, *71*, 6414–6419.
29. Ito and co-workers recently reported a synergistic solvent effect in 1,2-*cis*- α -glycoside formation. Ishiwata, A.; Munemura, Y.; Ito, Y. *Tetrahedron* **2008**, *64*, 92–102.
30. (a) Hrkach, J. S.; Matyjaszewski, K. *Macromolecules* **1990**, *23*, 4042–4046; (b) Li, Y.; Yu, B. *Chem. Commun.* **2010**, *46*, 6060–6062.
31. TMSClO₄-promoted glycosidation of **1a** with **2** in THF/Et₂O (1:1) at –40 °C for 4 h gave virtually the same product yield and α -selectivity (93%, α/β = 94:6) as those obtained with TMSOTf.
32. (a) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1984**, 680–691; (b) Schmidt, R. R.; Gaden, H.; Jatzke, H. *Tetrahedron Lett.* **1990**, *31*, 327–330; (c) Schmidt, R. R. In *Carbohydrates – Synthetic Methods and Applications in Medicinal Chemistry*: Ogura, H.; Hasegawa, A.; Suami, T., Eds.; VCH: Weinheim, 1992; pp 66–88; (d) Garcia, B. A.; Gin, D. Y. *Org. Lett.* **2000**, *2*, 2135–2138.
33. The results obtained with these donors and serine derivative **2** under the optimized conditions (TMSOTf, THF/Et₂O 1:1, –40 °C) are as follows: 3,4,6-tri-*O*-benzyl-protected diphenyl phosphate, 1 h, 84% yield, α/β = 85:15; 3,4,6-tri-*O*-acetyl-protected diphenyl phosphate **19** (α/β = 31:69), 24 h, 49% yield, α/β = 72:28.
34. (a) Bertolini, M.; Glaudemans, C. P. J. *Carbohydr. Res.* **1970**, *15*, 263–270; (b) Ziegler, T. *Liebigs Ann. Chem.* **1990**, 1125–1131.
35. Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169–185.
36. (a) Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett.* **2009**, *11*, 4258–4261; (b) Nakatsuji, H.; Ueno, K.; Nishikado, H.; Hori, H.; Tanabe, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2010**, *52*, 463–467.
37. For examples of the synthesis of antifreeze glycoproteins, see: (a) Tsuda, T.; Nishimura, S.-I. *Chem. Commun.* **1996**, 2779–2780; (b) Tachibana, Y.; Matsubara, N.; Nakajima, F.; Tsuda, T.; Tsuda, S.; Monde, K.; Nishimura, S.-I. *Tetrahedron* **2002**, *58*, 10213–10224; (c) Wojnar, J. M.; Evans, C. W.; DeVries, A. L.; Brimble, M. A. *Aust. J. Chem.* **2011**, *64*, 723–731; (d) Nagel, L.; Plattner, C.; Budke, C.; Majer, Z.; DeVries, A. L.; Berkemeier, T.; Koop, T.; Sewald, N. *Amino Acids* **2011**, *41*, 719–732.
38. Kurosaka, A.; Nakajima, H.; Funakoshi, I.; Matsuyama, M.; Nagayo, T.; Yamashina, I. *J. Biol. Chem.* **1983**, *258*, 11594–11598.
39. (a) Hounsell, E. F.; Lawson, A. M.; Feeney, J.; Gooi, H. C.; Pickering, N. J.; Stoll, M. S.; Lui, S. C.; Feizi, T. *Eur. J. Biochem.* **1985**, *148*, 367–377; (b) Capon, C.; Leroy, Y.; Wieruszkeski, J.-M.; Ricart, G.; Strecker, G.; Montreuil, J.; Fournet, B. *Eur. J. Biochem.* **1989**, *182*, 139–152; (c) Hounsell, E. F.; Lawson, A. M.; Stoll, M. S.; Kane, D. P.; Cashmore, G. C.; Carruthers, R. A.; Feeney, J.; Feizi, T. *Eur. J. Biochem.* **1989**, *186*, 597–610.
40. Chai, W.; Hounsell, E. F.; Cashmore, G. C.; Rosankiewicz, J. R.; Bauer, C. J.; Feeney, J.; Feizi, T.; Lawson, A. M. *Eur. J. Biochem.* **1992**, *203*, 257–268.
41. Rio-Anneheim, S.; Paulsen, H.; Meldal, M.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1071–1080.
42. Qui, D.; Koganty, R. R. *Tetrahedron Lett.* **1997**, *38*, 961–964.
43. (a) Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251–254; (b) Campbell, A. S.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 10387–10388.
44. For reviews that include discussions regarding the effect of ethereal solvents, see: (a) Wulff, G.; Röhle, G. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 157–170; (b) Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35–79; (c) Demchenko, A. V. *Synlett* **2003**, 1225–1240.
45. The group of Satoh and Hünenberger recently reported a theoretical investigation of solvent effects on glycosylation reactions. Satoh, H.; Hansen, H. S.; Manabe, S.; van Gunsteren, W. F.; Hünenberger, P. H. *J. Chem. Theory Comput.* **2010**, *6*, 1783–1797.
46. For representative examples of the use of ether, see: (a) Igarashi, K.; Honma, T.; Irisawa, J. *Carbohydr. Res.* **1970**, *15*, 329–337; (b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382; (c) Kreuzer, M.; Thiem, J. *Carbohydr. Res.* **1986**, *149*, 347–361; (d) Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301–306; (e) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 4701–4704.
47. (a) Demchenko, A. V.; Stauch, T.; Boons, G.-J. *Synlett* **1997**, 818–820; (b) Demchenko, A. V.; Rousson, E.; Boons, G.-J. *Tetrahedron Lett.* **1999**, *40*, 6523–6526; (c) Manabe, S.; Ishii, K.; Ito, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10666–10667; (d) Manabe, S.; Ishii, K.; Ito, Y. *Eur. J. Org. Chem.* **2011**, 497–516.
48. (a) Szarek, W. A.; Jarrell, H. C.; Jones, J. K. N. *Carbohydr. Res.* **1977**, *57*, C13–C16; (b) Wulff, G.; Schröder, U.; Wichelhaus, J. *Carbohydr. Res.* **1979**, *72*, 280–284; (c) Prakash, C.; Cheng, T.; Vijay, I. K. *Carbohydr. Res.* **1980**, *84*, C9–C11; (d) Figueroa-Pérez, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95–102; (e) Plettenburg, O.; Bodmer-Narkevitch, V.; Wong, C.-H. *J. Org. Chem.* **2004**, *67*, 4559–4564; (f) Lucas, R.; Hamza, D.; Lubineau, A.; Bonnafe, D. *Eur. J. Org. Chem.* **2004**, 2107–2117; (g) Wallner, F. K.; Norberg, H. A.; Johansson, A. I.; Mogemark, M.; Elofsson, M. *Org. Biomol. Chem.* **2005**, *3*, 309–315; (h) Rauter, A. P.; Almeida, T.; Vicente, A. I.; Ribeiro, V.; Bordado, J. C.; Marques, J. P.; Ribeiro, F. R.; Ferreira, M. J.; Oliveira, C.; Guisnet, M. *Eur. J. Org. Chem.* **2006**, 2429–2439; (i) Ding, N.; Li, C.; Liu, Y.; Zhang, Z.; Li, Y. *Carbohydr. Res.* **2007**, *342*, 2003–2013.
49. Fukase and co-workers reported the favorable solvent effect of cyclopentyl methyl ether on 1,2-*cis*- α -glycosidations. Tokimoto, H.; Fujimoto, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron: Asymmetry* **2005**, *16*, 441–447.
50. As measured by the Gutmann donor number (heat of complexation with SbCl₅, kcal·mol^{–1}) or the Maria–Gal scale (based on complex formation with BF₃, kJ·mol^{–1}): (a) Gutmann, V. *The Donor–Acceptor Approach to Molecular Interactions*; Plenum: New York, 1978 (1,2-dichloroethane: 0.0; dioxane: 14.8; Et₂O: 19.2; THF: 20.0; pyridine: 33.1; triethylamine: 61.0); (b) Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296–1304 (dichloromethane: 10.0; dioxane: 74.09; Et₂O: 78.77; THF: 90.40; pyridine: 128.08; triethylamine: 135.87). Reichardt suggested that the Maria–Gal scale is more comprehensive and seems to be more reliable than the donor number scale. (c) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003.
51. It was believed as the reverse anomeric effect (RAE) that cationic substituents on a pyranose ring have the tendency to take an equatorial position. However, Perrin and co-workers reexamined this and their observations are the exact opposite to what is expected from RAE (i.e., consistent with an enhancement of the normal anomeric effect) and suggest that previous evidence for this effect is unreliable. (a) Perrin, C. L. *Tetrahedron* **1995**, *51*, 11901–11935; (b) Perrin, C. L.; Fabian, M. A.; Brunckova, J.; Ohta, B. K. *J. Am. Chem. Soc.* **1999**, *121*, 6911–6918; (c) Perrin, C. L.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 8846–8851.
52. (a) Helferich, B.; Zimer, J. *Chem. Ber.* **1963**, *96*, 374; (b) Wulff, G.; Schmidt, W. *Carbohydr. Res.* **1977**, *53*, 33–46; (c) Tamura, J.; Horito, S.; Yoshimura, J.; Hashimoto, H. *Carbohydr. Res.* **1990**, *207*, 153–165; (d) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 621–637; (e) Dabideen, D. R.; Gervay-Hague, J. *Org. Lett.* **2004**, *6*, 973–975.
53. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.
54. (a) Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11–18; (b) Crich, D.; Chandrasekera, N. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5386–5389; (c) El-Badri, M. H.; Willenbring, D.; Tantillo, D. J.; Gervay-Hague, J. *J. Org. Chem.* **2007**, *72*, 4663–4672; (d) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144–1153; (e) Li, Z. *Carbohydr. Res.* **2010**, *345*, 1952–1957; (f) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193–9209.
55. Tvaroška, I.; Bleha, T. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 45–123.
56. Chen, L.; Shi, S.-D.; Liu, Y.-Q.; Gao, Q.-J.; Yi, X.; Liu, K.-K.; Liu, H. *Carbohydr. Res.* **2011**, *346*, 1250–1256.