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Stereoselective synthesis of benzyl-protected β-galactosides by propionitrile-mediated glycosylation

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Abstract

β-Selective galactosylation was studied using a series of 2-*O*-benzylated phenyl 1-thio-galactosides and glycosyl acceptors in propionitrile with BSP–TTBP–Tf_2O. The glycosylation enabled us to synthesize useful precursors of *N*-acetyllactosamine and core 1 *O*-glycoserine derivatives in a highly convergent manner.

Keywords: Glycopeptide; Stereoselective synthesis of β-galactoside; Propionitrile-assisted glycosylation; Thioglycoside

1. Introduction

Synthetic oligosaccharides and their conjugates are now recognized as critical tools for chemical glycobiology or as potential therapeutic agents, because adequate quantities of homogeneous samples with a defined structure seldom occur naturally. Extensive efforts have been put into developing useful technologies and concepts for oligosaccharide synthesis. As part of our study aimed at the synthesis of complex glycopeptides of biological importance, we demonstrated that the benzyl-protected *N*- and *O*-glycoamino acids are ideal for the Fmoc-based solid-phase synthesis of glycopeptides.[1] In these studies, β-galactosides in both *N*- and *O*-glycan have been primarily synthesized by glycosylation with an acetylated galactosyl donor.[2] Transformation of the acetylated galactoside into a benzyl-protected glycoamino acid requires additional processing including deacetylation and benzylation both performed under the basic conditions. Thus, benzylated β-galactoside moieties had to be strategically constructed before attaching a base-labile Fmoc amino acid moiety. Taking into consideration the advantages of convergent synthetic processes, it is preferable to have an alternative for β-selective galactosylation without the assistance of 2-*O*-acetyl group. In this context, we have previously studied the glycosylation of a monosaccharyl-amino acid derivative with a benzylated sialyl galactosyl trichloroacetimidate, and obtained an optimum yield of the desired β-glycoside (53%), which accompanied the generation of an α-isomer (16%).[3] This limited success has prompted us to investigate a more efficient method of β-galactoside preparation. Till date, only a few papers have reported useful experiments in this context, using a benzyl-protected galactosyl donor.[4–10] Among them, the recent report by Crich and Smith,[9] who synthesized a β-galactoside by reaction with phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (**1**) in propionitrile, seemed to meet our requirements for effecting a convergent synthesis of oligosaccharides. Thus, we have investigated the versatility of this procedure for our study on the synthesis of benzyl-protected oligosaccharides and glycoamino acids. The synthesis of Gal-(β1→4)-GlcNAc and Gal-(β1→3)-GalNAc-Ser derivatives is described here.

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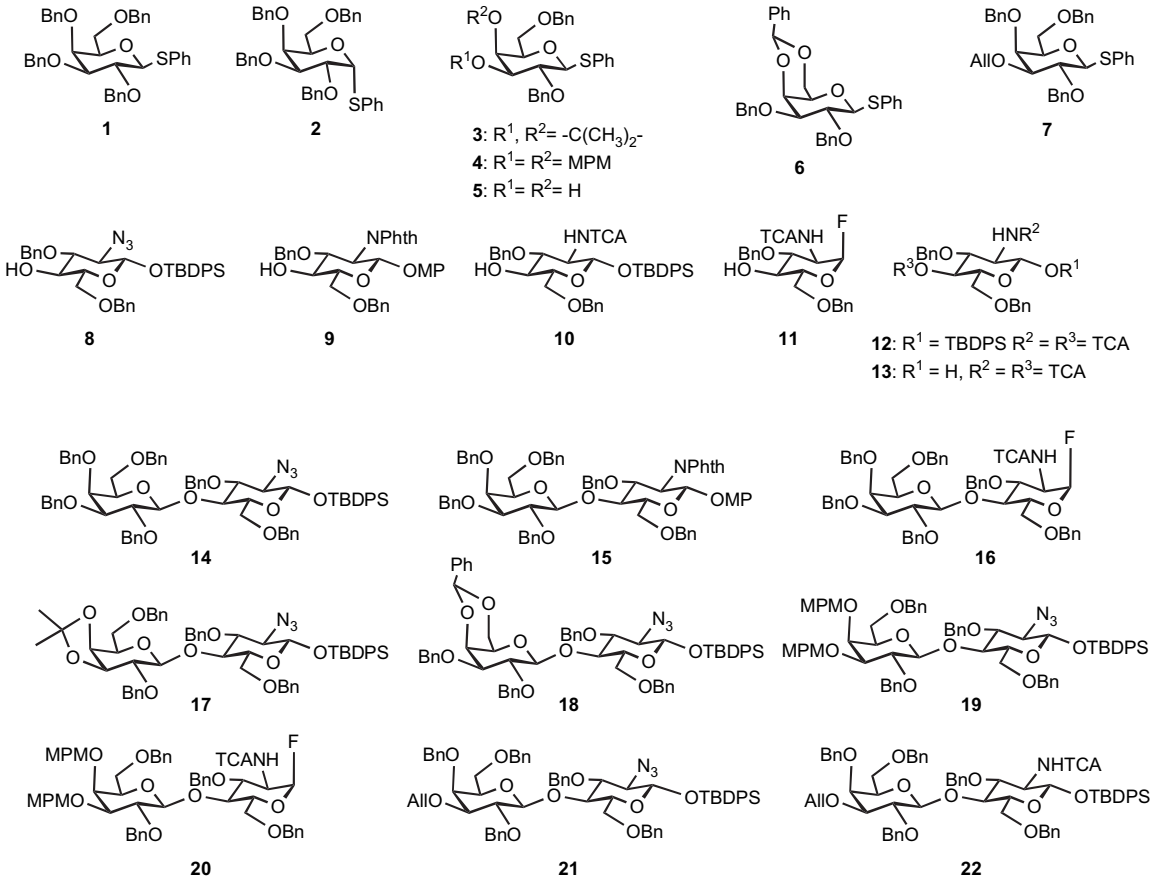


Figure 1. Glycosyl donors (**1**–**7**), glycosyl acceptors (**8**–**11**), intermediates (**12** and **13**), and disaccharides (**14**–**22**).

2. Results and discussion

In addition to thioglycoside (**1**) and its α-isomer (**2**), phenyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**3**)[11] and phenyl 2,6-di-*O*-benzyl-3,4-di-*O*-(4-methoxyphenyl)methyl-1-thio-β-D-galactopyranoside (**4**) were prepared as the comparable glycosyl donors. The latter two would enable us to elongate the sugar chain at the non-reducing end. Phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**6**)[12] and phenyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**7**) were also used as galactosyl donors in this study (Fig. 1). Compound **4** was easily obtained by 4-methoxybenzylation of the known phenyl 2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside (**5**)[11] in 75% yield. To synthesize LacNAc equivalents by reaction with **1**–**7**, the chosen glycosyl acceptors were the 3,6-di-*O*-benzyl-D-glucosamine derivatives (**8**,[13] **9**,[14] **10**, and **11**) each carrying a 2-azido, 2-*N*-phthalimido, or 2-*N*-trichloroacetamido group. Compound **10** was prepared from **8** by Zn-reduction, trichloro acetylation (→**12**), and then 4-O-deacylation. Glycosyl acceptor **11**, which would facilitate a more advanced synthesis of oligosaccharide by the orthogonal strategy,[15] was prepared by desilylation of **12** followed by fluorination and 4-O-deacylation. We first examined the reaction of **1** and **8**, where **1** (2 equiv) was preactivated for 30 min with BSP–Tf_2O–TTBP,[9] a combination of reacting agent, in EtCN at −78 °C before the addition of **8**. As shown in Table 1 (entry 1), the product was obtained as a mixture of 1:3 α/β isomers at 24% yield. However, when Tf_2O was added to the mixture of **1**, acceptor **8**, and other reagents in EtCN at −78 °C, a rapid coupling reaction occurred giving a superior yield with a similar β-selectivity (entry 2). The same reaction when performed in CH_3CN at −40 °C afforded more α-glycoside (entry 3), whereas the reaction run in dichloromethane exhibited no β-selectivity as expected[9] (entry 4). The

Table 1
Synthesis of disaccharides

Entry	Glycosyl donor (equiv)	Glycosyl acceptor	Solvent	Time (h)	Products (%)	α/β
1	**1** (2)	**8**	EtCN	16	**14** (24)	25:75
2	**1** (2)	**8**	EtCN	0.5	**14** (94)	21:79
3	**1** (2)	**8**	MeCN	0.5	**14** (88)	39:61
4	**1** (2)	**8**	CH_2Cl_2	0.5	**14** (37)	51:49
5	**1** (1.5)	**8**	EtCN	0.5	**14** (88)	21:79
6	**1** (1.2)	**8**	EtCN	22	**14** (60)	23:77
7	**2** (2)	**8**	EtCN	0.5	**14** (88)	23:77
8	**1** (2)	**9**	EtCN	0.5	**15** (93)	30:70
9	**1** (2)	**11**	EtCN	0.5	**16** (97)	19:81
10	**3** (2)	**8**	EtCN	0.5	**17** (21)	50:50
11	**6** (2)	**8**	EtCN	0.5	**18** (96)	54:46
12	**4** (2)	**8**	EtCN	0.5	**19** (90)	15:85
13	**4** (2)	**11**	EtCN	0.5	**20** (80)	15:85
14	**7** (2)	**8**	EtCN	0.5	**21** (92)	23:77
15	**7** (2)	**10**	EtCN	0.5	**22** (91)	23:77

The reactions were performed at −78 °C, except for entry 3 (at −40 °C).

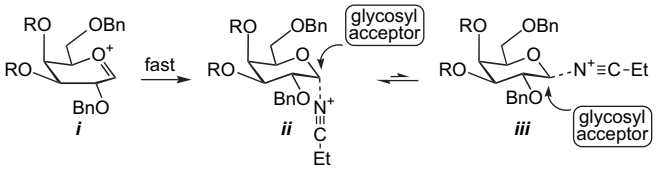


Figure 2. Plausible intermediates for propionitrile-mediated β-galactosylation.

reaction, with a reduced amount of **1** (1.5 equiv) gave a slightly lower yield (entry 5). However, a slight excess of **1** (1.2 equiv) resulted in an incomplete conversion of **8**, even after a prolonged reaction period (entry 6). The reaction with α-thioglycoside donor **2** also showed a similar result (entry 7). Therefore, β-selective glycosylation may be explained by the rapid attack of an acceptor on the α-nitrilium intermediate (**ii**) preferentially formed from oxacarbenium ion (**i**), whereas the absence of the acceptor at the generation of the intermediate (**ii**) may induce conversion into the other non-reactive species, resulting in a lower yield of the disaccharide (Fig. 2). The other glycosyl acceptors **9** and **11** were equally reactive with the intermediate to produce β-disaccharides **15** and **16**,[16] respectively, in a high yield (entries 8 and 9).

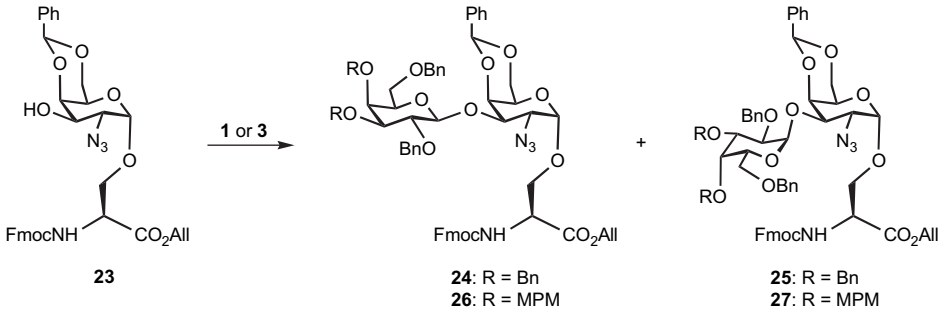
3,4-*O*-Isopropylidenated thiogalactoside **3** was a poor glycosyl donor for the β-galactosylation resulting in a low coupling yield with no stereoselectivity under identical conditions (entry 10). Since donor **3** was definitely consumed and a considerable amount of hemiacetal was generated in the ultimate products, the intermediates were distorted and/or disarmed by the isopropylidene group possibly in an unfavorable form to react with acceptor **8**. In contrast, 4,6-*O*-benzylidene analog **6** gave a high-yielding reaction but with little stereoselectivity (entry 11). The 4,6-*O*-benzylidene derivative, relatively less reactive than **1**, might easily permit an equilibrium to exist between the nitrilium intermediates, resulting in additional formation of α-galactoside via unstable **iii**. The previous related discussion has focused on the benzylidene-influenced stereochemical outcome of the glycosylation with **6** in CH_2Cl_2 medium.[12] 3,4-Di-*O*-(4-methoxybenzyl) derivative **4** smoothly reacted with **8** and **11** to β-selectively produce disaccharides **19** and **20**, respectively (entries 12 and 13). Interestingly, Crich's promoter system retained an intact allyl group during glycosylation reactions,[17] in contrast to the other thiophilic and enophilic promoters such as NIS–TfOH. Therefore, the 3-*O*-allyl-protected thioglycoside (**7**) functioned as a suitable glycosyl donor under identical conditions to selectively produce β-disaccharides **21** and **22** both at high yield (entries 14 and 15). The effectiveness of this protocol on the synthesis of glycoamino acid derivatives was demonstrated by glycosylation of known $GalN_3$-Ser derivative **23**[18] with glycosyl donor **1** or **4** (Scheme 1). By the addition of Tf_2O (2.2 equiv) to a cold mixture of **1** (2 equiv), **23**, BSP (3 equiv), and TTBP (4 equiv) in EtCN, the glycosylation completed within 30 min to afford the desired β-galactoside **24** (67%) and α-isomer **25** (15%). Compounds **24** and **25** were identical to compounds prepared as precursors of core 1 and 8 type *O*-glycoamino acids in our previous studies.[19,20] The reaction of glycosyl donor **4** and **23** also succeeded in producing a core 1 *O*-glycoamino acid analog **26** (79%) and α-isomer **27** (8%). Compound **26** should be an effective intermediate to synthesize the extended *O*-glycans of cores 1 and 2, because 4-methoxybenzyl groups are selectively removable.

In summary, we have demonstrated an efficient method for the convergent route to the benzyl-protected β-galactoside. Using phenyl 1-thio-galactoside derivatives (**1**, **2**, **4**, and **7**) as a glycosyl donor, LacNAc-related disaccharides (**14**–**16** and **19**–**22**) were all synthesized in a high yield with β-selectivity. The β-galactoside synthesis was efficient, only when Tf_2O was added to the cooled (−78 °C) mixture of all the other reactants in EtCN. However, 3,4-*O*-isopropylidene **3** and 4,6-benzylidene analog **6** were the inadequate glycosyl donors and resulted in non-stereoselective reactions in the propionitrile conditions. The method was also utilized to selectively synthesize core 1 type *O*-glycoamino acid derivatives **24** and **26**. This successful result has enhanced the usefulness of compound **23** as a crucial intermediate for a series of core structures of *O*-glycoamino acid. Further studies on this nitrile-mediated glycosylation applied to the convergent synthesis of complex oligosaccharides using disaccharyl or trisaccharyl galactosyl donors are in progress.

3. Experimental

3.1. General

Optical rotation values were determined with a Jasco DIP-370 polarimeter at 20±2 °C for solutions in $CHCl_3$. Column chromatography was performed on silica gel PSQ 100B (Fuji Silysia). TLC and HPTLC were performed on silica



Scheme 1. Synthesis of O-linked glycoamino acid derivatives by β-selective galactosylation.

gel 60 F_{254} (E. Merck). ^{1}H and ^{13}C NMR spectra were recorded with a Jeol AL400 spectrometer [^{1}H (400 MHz) and ^{13}C (100 MHz)]. For solutions in $CDCl_3$, the parts per million downfield chemical shifts are expressed from the internal Me_4Si signal. For assignment of the signals of sugar residue in oligosaccharides, the reducing terminal and the second residues are described as a and b, respectively. High resolution mass spectra were obtained with a AccuTOF (JMS-T100LC) spectrometer.

*3.1.1. Phenyl 2,6-di-O-benzyl-3,4-di-O-(4-methoxyphenyl)-methyl-1-thio-β-D-galactopyranoside **4***

To a stirred mixture of phenyl 2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside **5** (728 mg, 1.61 mmol) and 60% NaH (260 mg, 6.50 mmol) in anhydrous DMF (16 ml) was added 4-methoxybenzyl chloride (0.87 ml, 6.25 mmol) at 0 °C under Ar. Then the mixture was stirred for 2 h at room temperature, before adding a few piece of ice to quench the reaction. The mixture was extracted with EtOAc. The extract was successively washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel with toluene–EtOAc (20:1) and then crystallized from hexane–EtOAc to give pure **4** (834 mg, 75%). Mp 95.5–96.5 °C. $[\alpha]_D$ +4.9 (*c* 1.0). R_f 0.43 (2:1 hexane–EtOAc). ^{1}H NMR δ: 7.55 (m, 2H, Ar), 7.39–7.17 (m, 17H, Ar), 6.84 (d, 4H, *J*=8.3 Hz, Ar), 4.87 (d, 1H, *J*=11.2 Hz, $-CH_2Ar$), 4.78 (d, 1H, *J*=10.2 Hz, $-CH_2Ar$), 4.73 (d, 1H, *J*=10.2 Hz, $-CH_2Ar$), 4.66 (d, 1H, *J*=11.7 Hz, $-CH_2Ar$), 4.63 (d, 1H, *J*=9.7 Hz, H-1), 4.62 (d, 1H, *J*=11.2 Hz, $-CH_2Ar$), 4.54 (d, 1H, *J*=11.2 Hz, $-CH_2Ar$), 4.46 (d, 1H, *J*=11.7 Hz, $-CH_2Ar$), 4.40 (d, 1H, *J*=11.7 Hz, $-CH_2Ar$), 3.92–3.87 (m, 2H, H-2, H-6), 3.80 (s, 3H, $-OCH_3$), 3.79 (s, 3H, $-OCH_3$), 3.63–3.55 (m, 4H, H-3, H-4, H-5, H-6). Anal. Calcd for $C_{42}H_{44}O_7S$: C, 72.81; H, 6.40. Found: C, 72.80; H, 6.44.

*3.1.2. tert-Butyldiphenylsilyl 3,6-di-O-benzyl-2-deoxy-2-trichloroacetamido-4-O-trichloroacetyl-β-D-glucopyranoside **12***

A mixture of **8** (88.3 mg, 0.14 mmol), powdered Zn (354 mg, 5.41 mmol), and AcOH (0.16 ml, 2.83 mmol) in CH_2Cl_2 (5 ml) was stirred for 30 min under Ar. The mixture was diluted with $CHCl_3$ and filtered through Celite. The filtrate was concentrated in vacuo. The residue was diluted with $CHCl_3$, successively washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 ml), and stirred with trichloroacetyl chloride (79 μl, 0.71 mmol) and pyridine (0.11 ml, 1.4 mmol) at 0 °C for 30 min under Ar. The reaction was quenched with satd aq NH_4Cl and the mixture was extracted with EtOAc. The extract was successively washed with satd aq NH_4Cl, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed on silica gel with toluene–EtOAc (29:1) to afford **12** (87.4 mg, 69% in two steps). Mp 182.5–183.5 °C (recrystallized from hexane–EtOAc). $[\alpha]_D$ +3.7 (*c* 1.0). R_f 0.51 (3:1 hexane–EtOAc). ^{1}H NMR δ: 7.69 (d, 2H, *J*=6.8 Hz, Ar), 7.62 (d, 2H, *J*=6.8 Hz, Ar), 7.42–7.37 (m, 2H, Ar), 7.33–7.17 (m, 14H, Ar), 6.97 (d, 1H, *J*=7.8 Hz, $-NH$), 5.30 (t, 1H, *J*=9.3 Hz, H-4), 5.04 (d, 1H, *J*=7.8 Hz, H-1), 4.65 (d, 1H, *J*=10.2 Hz, $-CH_2Ph$), 4.61 (d, 1H, *J*=10.2 Hz, $-CH_2Ph$), 4.39 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.33 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.26 (br t, 1H, *J*=9.5 Hz, H-3), 3.78 (dt, *J*=7.8, 10.2 Hz, H-2), 4.42–3.32 (m, 3H, H-5, H-6×2). Anal. Calcd for $C_{40}H_{41}NO_7Cl_6Si$: C, 54.07; H, 4.65; N, 1.58. Found: C, 54.04; H, 4.72; N, 1.45.

*3.1.3. tert-Butyldiphenylsilyl 3,6-di-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside **10***

A solution of **12** (1.27 g, 1.43 mmol) in 80% aqueous pyridine (70 ml) was heated at 50 °C with stirring for 3 h, before being concentrated in vacuo. The residue was diluted with EtOAc, successively washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed on silica gel with toluene–EtOAc (19:1 to 9:1) to give the title compound (1.03 g, 98%). Mp 147–148 °C (recrystallized from hexane–EtOAc). $[\alpha]_D$ −9.5 (*c* 1.0). R_f 0.35 (2:1 hexane–EtOAc). ^{1}H NMR δ: 7.69–7.62 (m, 4H, Ar), 7.40–7.19 (m, 16H, Ar), 6.76 (d, 1H, *J*=8.3 Hz, $-NH$), 4.80 (d, 1H, *J*=7.8 Hz, H-1), 4.74 (d, 1H, *J*=11.2 Hz, $-CH_2Ph$), 4.71 (d, 1H, *J*=11.2 Hz, $-CH_2Ph$), 4.44 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.36 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 3.82 (dt, *J*=8.3, 10.2 Hz, H-2), 3.74 (dt, *J*=2.4, 8.8 Hz, H-4), 3.66 (dd, 1H, *J*=8.3, 10.2 Hz, H-3), 3.53 (dd, 1H, *J*=4.4, 10.2 Hz, H-6), 3.46 (dd, 1H, *J*=4.9, 10.2 Hz, H-6), 3.12 (dt, *J*=4.9, 9.3 Hz, H-5), 2.65 (d, 1H, *J*=2.4 Hz, $-OH$), 1.05 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{38}H_{42}NO_6Cl_3Si$: C, 61.41; H, 5.70; N, 1.88. Found: C, 61.34; H, 5.73; N, 1.78.

*3.1.4. 3,6-Di-O-benzyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl fluoride **11***

To an ice-cooled mixture of **12** (107.6 mg, 0.12 mmol) and AcOH (139 μl, 2.42 mmol) in freshly distilled THF (1.5 ml) was added 1 M ^{n}Bu$_4$NF–THF (1.2 ml, 1.21 mmol) under Ar. Then the mixture was stirred at 0 °C for 2 days and concentrated in vacuo. The residue was diluted with EtOAc, successively washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. To a stirred solution of the crude mixture in freshly distilled THF (2.5 ml) was added Et_2NSF_3 (32 μl, 0.24 mmol) at 0 °C under Ar and stirred for 30 min. To the reaction mixture was added 80% aqueous pyridine (2 ml) and stirred at room temperature for 1 h before being concentrated in vacuo. The residue was diluted with EtOAc, successively washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed on silica gel with toluene–EtOAc (19:1 to 9:1) to give crystals (35.5 mg, 58% in three steps). Mp 81.0–82.0 °C (recrystallized from hexane–EtOAc). $[\alpha]_D$ +51.1 (*c* 1.0). R_f 0.41 (4:1 toluene–EtOAc). ^{1}H NMR δ: 7.39–7.26 (m, 10H, Ar), 6.69 (d, 1H, *J*=8.8 Hz, $-NH$), 5.69 (dd, 1H, *J*=2.4, 53.2 Hz, H-1), 4.82 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.79 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.63 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.56 (d, 1H, *J*=12.2 Hz, $-CH_2Ph$), 4.18 (dddd, 1H, *J*=2.4, 8.8, 10.7, 26.8 Hz, H-2), 3.99–3.89 (m, 2H, H-4, H-5), 3.80 (dd, 1H, *J*=3.9, 10.7 Hz, H-6),

3.72–3.68 (m, 2H, H-3, H-6), 2.81 (br s, 1H, –O*H*). Anal. Calcd for $C_{22}H_{23}NO_5FCl_3$: C, 52.14; H, 4.57; N, 2.76. Found: C, 52.20; H, 4.63; N, 2.69.

*3.2. Typical glycosylation procedure [synthesis of tert-butyldiphenylsilyl 2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl-(1→4)-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside **14**]*

A mixture of **1** (103 mg, 0.16 mmol), **8** (51 mg, 0.08 mmol), BSP (51 mg, 0.24 mmol), TTBP (81 mg, 0.33 mmol), and dried MS (4 Å, 300 mg) in anhydrous EtCN (2.5 ml) was cooled at −78 °C with stirring under Ar for 10 min. To the cold mixture was added Tf_2O (30 μl, 0.18 mmol). The mixture was stirred at −78 °C for 30 min before the reaction was quenched by adding satd aq $NaHCO_3$. The mixture was filtered through Celite. The filtrate was extracted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on Bio-beads S-X3 with toluene–EtOAc (3:1) and then on silica gel with toluene–EtOAc (99:1 to 49:1) to give **14** (70 mg, 74%) and α-isomer (18 mg, 20%). Compound**14**: $[\alpha]_D$ −9.1 (*c* 1.0). R_f 0.54 (19:1 toluene–EtOAc). ^{1}H NMR *δ*: 7.72–7.69 (m, 4H, Ar), 7.41–7.10 (m, 36H, Ar), 5.01 (d, 1H, *J*=10.3 Hz, –C*H*$_2$Ph), 4.96 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.74 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.69 (br s, 2H, –C*H*$_2$Ph×2), 4.65 (d, 1H, *J*=11.0 Hz, –C*H*$_2$Ph), 4.61 (d, 1H, *J*=10.3 Hz, –C*H*$_2$Ph), 4.53 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.42 (d, 1H, *J*=7.8 Hz, H-1b), 4.39–4.33 (m, 2H, –C*H*$_2$Ph×2), 4.30 (d, 1H, *J*=7.8 Hz, H-1a), 4.23 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.22 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 3.97 (t, 1H, *J*=9.5 Hz, H-4a), 3.91 (d, 1H, *J*=2.4 Hz, H-4b), 3.70 (dd, 1H, *J*=7.8, 9.5 Hz, H-2b), 3.64 (dd, 1H, *J*=3.1, 11.2 Hz, H-6a), 3.52 (br t, 1H, *J*=7.6 Hz, H-6b), 3.44–3.33 (m, 4H, H-2a, H-3b, H-5b, H-6b), 3.24–3.19 (m, 2H, H-3a, H-6a), 2.82 (br d, 1H, *J*=8.6 Hz, H-5a), 1.10 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{70}H_{75}N_3O_{10}Si$: C, 73.34; H, 6.59; N, 3.67. Found: C, 73.31; H, 6.57; N, 3.62.

α-Isomer: $[\alpha]_D$ +18.5 (*c* 1.5). R_f 0.63 (19:1 toluene–EtOAc). ^{1}H NMR *δ*: 7.72–7.67 (m, 4H, Ar), 7.41–7.12 (m, 36H, Ar), 5.60 (d, 1H, *J*=3.9 Hz, H-1b), 4.85 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.78 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.73 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.70 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.63 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.60 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.54 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.51 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.35 (d, 1H, *J*=7.8 Hz, H-1a), 4.32–4.29 (m, 3H, –C*H*$_2$Ph×3), 4.23 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.04 (dd, 1H, *J*=8.3, 9.7 Hz, H-4a), 3.97 (dd, 1H, *J*=3.9, 10.3 Hz, H-2b), 3.95 (br s, 1H, H-4b), 3.89 (br t, 1H, *J*=7.3 Hz, H-5b), 3.79 (dd, 1H, *J*=2.9, 10.3 Hz, H-3b), 3.81 (dd, 1H, *J*=3.9, 11.2 Hz, H-6a), 3.52–3.48 (m, 2H, H-2a, H-6b), 3.42–3.37 (m, 2H, H-3a, H-6b), 3.31 (dd, 1H, *J*=1.9, 11.2 Hz, H-6a), 3.03 (br d, 1H, *J*=9.7 Hz, H-5a), 1.11 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{70}H_{75}N_3O_{10}Si$: C, 73.34; H, 6.59; N, 3.67. Found: C, 73.34; H, 6.70; N, 3.66.

*3.2.1. 4-Methoxyphenyl 2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **15***

$[\alpha]_D$ +30.1 (*c* 0.9). R_f 0.53 (7:1 toluene–EtOAc). ^{1}H NMR *δ*: 7.80–7.67 (m, 4H, Ar), 7.35–7.18 (m, 24H, Ar), 6.98–6.96 (m, 2H, Ar), 6.89–6.80 (m, 6H, Ar), 6.69–6.66 (m, 2H, Ar), 5.61 (d, 1H, *J*=8.3 Hz, H-1a), 4.94 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.91 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.86 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.83 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.73 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.70 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.54–4.32 (m, 8H, –C*H*$_2$Ph×5, H-2a, H-3a, H-1b), 4.27 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.08 (dd, 1H, *J*=8.6, 9.7 Hz, H-4a), 3.90 (d, 1H, *J*=3.0 Hz, H-4b), 3.83–3.77 (m, 3H, H-6a×2, H-2b), 3.69 (s, 3H, –OC*H*$_3$), 3.68 (m, 1H, H-5a), 3.50–3.42 (m, 4H, H-3b, H-5b, H-6b×2). Anal. Calcd for $C_{69}H_{67}NO_{13}$: C, 74.11; H, 6.04; N, 1.25. Found: C, 74.12; H, 6.25; N, 1.10.

α-Isomer: $[\alpha]_D$ +74.7 (*c* 1.1). R_f 0.56 (7:1 toluene–EtOAc). ^{1}H NMR *δ*: 7.64 (m, 4H, Ar), 7.34–7.16 (m, 24H, Ar), 6.85–6.77 (m, 8H, Ar), 6.67–6.65 (m, 2H, Ar), 5.56 (d, 1H, *J*=8.3 Hz, H-1a), 5.53 (d, 1H, *J*=3.7 Hz, H-1b), 4.92 (d, 1H, *J*=11.5 Hz, –C*H*$_2$Ph), 4.78 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.73 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.72 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.68 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.64 (d, 1H, *J*=11.5 Hz, –C*H*$_2$Ph), 4.60–4.39 (m, 6H, –C*H*$_2$Ph×4, H-2a, H-3a), 4.34 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.31 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.15 (br t, 1H, *J*=9.2 Hz, H-4a), 4.08 (dd, 1H, *J*=3.9, 10.3 Hz, H-2b), 4.01–3.98 (m, 2H, H-4b, H-5b), 3.91–3.78 (m, 4H, H-5a, H-6a×2, H-3b), 3.69 (s, 3H, –OC*H*$_3$), 3.55–3.47 (m, 2H, H-6b×2). Anal. Calcd for $C_{69}H_{67}NO_{13}$: C, 74.11; H, 6.04; N, 1.25. Found: C, 74.23; H, 6.17; N, 1.10.

*3.2.2. 2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-O-benzyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl fluoride **16***

All physical properties of **16** were identical to those synthesized previously.[16]

α-Isomer: $[\alpha]_D$ +44.2 (*c* 1.1). R_f 0.49 (9:1 toluene–EtOAc). ^{1}H NMR *δ*: 7.35–7.15 (m, 30H, Ar), 6.63 (d, 1H, *J*=8.8 Hz, –N*H*), 5.71 (dd, 1H, *J*=2.9, 54.1 Hz, H-1a), 5.48 (d, 1H, *J*=3.9 Ha, H-1b), 4.89 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.81 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.72 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.70 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.66 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.61–4.52 (m, 4H, –C*H*$_2$Ph×4), 4.45 (d, 1H, *J*=12.2 Hz, –C*H*$_2$Ph), 4.35 (d, 1H, *J*=11.7 Hz, –C*H*$_2$Ph), 4.28 (d, 1H, *J*=11.2 Hz, –C*H*$_2$Ph), 4.23 (m, 1H, H-2a), 4.20 (t, 1H, *J*=9.3 Hz, H-4a), 4.04–4.01 (m, 2H, H-5a, H-2b), 3.95–3.87 (m, 4H, H-3a, H-6a, H-4b, H-5b), 3.83 (dd, 1H, *J*=2.9, 10.7 Hz, H-3b), 3.67 (dd, 1H, *J*=1.5, 11.2 Hz, H-6a), 3.50–3.44 (m, 2H, H-6b×2). Anal. Calcd for $C_{56}H_{57}NO_{10}Cl_3F$: C, 65.34; H, 5.58; N, 1.36. Found: C, 65.43; H, 5.83; N, 1.30.

*3.2.3. tert-Butyldiphenylsilyl 2,6-di-O-benzyl-3,4-O-isopropylidene-β-D-galactopyranosyl-(1→4)-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside **17***

$[\alpha]_D$ +2.4 (*c* 1.0). R_f 0.31 (3:1 hexane–EtOAc). ^{1}H NMR *δ*: 7.73–7.69 (m, 4H, Ar), 7.44–7.14 (m, 26H, Ar), 4.92 (d, 1H,

J=10.0 Hz, −CH_2Ph), 4.73 (d, 1H, J=11.7 Hz, −CH_2Ph), 4.65 (d, 1H, J=10.3 Hz, −CH_2Ph), 4.61 (d, 1H, J=11.7 Hz, −CH_2Ph), 4.51 (d, 1H, J=12.2 Hz, −CH_2Ph), 4.42 (d, 1H, J=12.0 Hz, −CH_2Ph), 4.40 (d, 1H, J=8.1 Hz, H-1b), 4.31 (d, 1H, J=7.6 Hz, H-1a), 4.29 (d, 1H, J=11.2 Hz, −CH_2Ph), 4.25 (d, 1H, J=12.2 Hz, −CH_2Ph), 4.11 (br d, 1H, J=3.4 Hz, H-4b), 4.05–3.97 (m, 2H, H-4a, H-3b), 3.74–3.62 (m, 3H, H-6a, H-5b, H-6b), 3.53 (dd, 1H, J=5.9, 9.3 Hz, H-6b), 3.38–3.20 (m, 4H, H-2a, H-3a, H-6a, H-2b), 2.87 (br d, 1H, J=9.8 Hz, H-5a), 1.38 (s, 3H, −CH_3), 1.34 (s, 3H, −CH_3), 1.11 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{59}H_{67}N_3O_{10}Si$: C, 70.42; H, 6.71; N, 4.18. Found: C, 70.22; H, 6.79; N, 4.08.

α-Isomer: $[\alpha]_D$ +29.7 (*c* 1.5). R_f 0.37 (3:1 hexane–EtOAc). ^{1}H NMR δ: 7.73–7.69 (m, 4H, Ar), 7.40–7.12 (m, 26H, Ar), 5.41 (d, 1H, J=3.4 Hz, H-1b), 4.78 (d, 1H, J=11.2 Hz, −CH_2Ph), 4.72 (d, 1H, J=10.7 Hz, −CH_2Ph), 4.60 (d, 1H, J=12.2 Hz, −CH_2Ph), 4.56 (d, 1H, J=11.7 Hz, −CH_2Ph), 4.49 (d, 1H, J=12.2 Hz, −CH_2Ph), 4.43 (d, 1H, J=10.7 Hz, −CH_2Ph), 4.37 (d, 1H, J=8.3 Hz, H-1a), 4.31–4.24 (m, 4H, −CH_2Ph×2, H-3b, H-5b), 4.14 (dd, 1H, J=2.4, 5.9 Hz, H-4b), 3.92 (br t, J=9.7 Hz, H-4a), 3.64–3.55 (m, 3H, H-6a, H-6b×2), 3.53–3.47 (m, 3H, H-2a, H-6a, H-2b), 3.31 (dd, 1H, J=8.8, 9.8 Hz, H-3a), 3.05 (m, 1H, H-5a), 1.30 (s, 3H, −CH_3), 1.28 (s, 3H, −CH_3), 1.12 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{59}H_{67}N_3O_{10}Si$: C, 70.42; H, 6.71; N, 4.18. Found: C, 70.29; H, 6.83; N, 4.08.

3.2.4. tert-Butyldiphenylsilyl 2,3-di-O-benzyl-4,6-O-benzylidene-β-D-galactopyranosyl-(1→4)-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside **18**

Spectral data of **18** were identical with those previously reported.[2b]

α-Isomer: $[\alpha]_D$ +32.0 (*c* 1.0). R_f 0.51 (19:1 toluene–EtOAc). ^{1}H NMR δ: 7.73–7.70 (m, 4H, Ar), 7.48–7.15 (m, 31H, Ar), 5.70 (d, 1H, J=3.4 Hz, H-1b), 5.37 [s, 1H, PhCH(O)$_2$–], 4.79–4.72 (m, 3H, −CH_2Ph×3), 4.67 (d, 1H, J=12.2 Hz, −CH_2Ph), 4.63 (d, 1H, J=12.2 Hz, −CH_2Ph), 4.54 (d, 1H, J=11.7 Hz, −CH_2Ph), 4.37 (d, 1H, J=10.7 Hz, −CH_2Ph), 4.36 (d, 1H, J=8.3 Hz, H-1a), 4.18 (d, 1H, J=11.7 Hz, −CH_2Ph), 4.13–4.04 (m, 2H, H-4a, H-4b), 4.02 (dd, 1H, J=3.4, 10.2 Hz, H-2b), 3.89 (br d, 1H, J=12.2 Hz, H-6b), 3.85 (dd, 1H, J=3.4, 10.3 Hz, H-3b), 3.66 (br d, 1H, J=12.2 Hz, H-6b), 3.54–3.50 (m, 3H, H-2a, H-6a, H-5b), 3.40 (dd, 1H, J=8.8, 9.3 Hz, H-3a), 3.23 (br d, 1H, J=10.7 Hz, H-6a), 3.01 (br d, J=9.3 Hz, H-5a), 1.11 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{63}H_{67}N_3O_{11}Si$: C, 71.77; H, 6.41; N, 3.99. Found: C, 71.84; H, 6.50; N, 3.84.

3.2.5. tert-Butyldiphenylsilyl 2,6-di-O-benzyl-3,4-di-O-(4-methoxyphenyl)methyl-β-D-galactopyranosyl-(1→4)-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside **19**

$[\alpha]_D$ −4.7 (*c* 1.0). R_f 0.25 (3:1 hexane–EtOAc). ^{1}H NMR δ: 7.72–7.69 (m, 4H, Ar), 7.42–7.10 (m, 30H, Ar), 6.84–6.77 (m, 4H, Ar), 5.00 (d, 1H, J=10.7 Hz, −CH_2Ar), 4.86 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.73 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.64 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.63–4.57 (m, 3H, −CH_2Ar×3), 4.48 (d, 1H, J=10.7 Hz, −CH_2Ar), 4.41 (d, 1H, J=7.8 Hz, H-1b), 4.37 (d, 1H, J=12.2 Hz, −CH_2Ar), 4.35 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.29 (d, 1H, J=7.8 Hz, H-1a), 4.23 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.22 (d, 1H, J=11.7 Hz, −CH_2Ar), 3.96 (t, 1H, J=9.3 Hz, H-4a), 3.86 (d, 1H, J=2.9 Hz, H-4b), 3.79 (s, 3H, −OCH_3), 3.75 (s, 3H, −OCH_3), 3.69–3.62 (m, 2H, H-6a, H-2b), 3.50 (br t, 1H, J=7.3 Hz, H-6b), 3.43–3.32 (m, 4H, H-2a, H-3b, H-5b, H-6b), 3.24–3.18 (m, 2H, H-3a, H-6a), 2.83 (br d, 1H, J=8.3 Hz, H-5a), 1.10 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{72}H_{79}N_3O_{12}Si$: C, 71.68; H, 6.60; N, 3.48. Found: C, 71.66; H, 6.70; N, 3.40.

α-Isomer: $[\alpha]_D$ +12.9 (*c* 0.6). R_f 0.29 (3:1 hexane–EtOAc). ^{1}H NMR δ: 7.70–7.68 (m, 4H, Ar), 7.40–7.12 (m, 30H, Ar), 6.81–6.76 (m, 4H, Ar), 5.59 (d, 1H, J=3.9 Hz, H-1b), 4.78–4.69 (m, 4H, −CH_2Ar×4), 4.54 (br s, 2H, −CH_2Ar×2), 4.53 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.45 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.34 (d, 1H, J=7.8 Hz, H-1a), 4.32–4.27 (m, 3H, −CH_2Ar×3), 4.22 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.03 (dd, 1H, J=8.7, 9.7 Hz, H-4a), 3.95 (dd, 1H, J=3.9, 10.2 Hz, H-2b), 3.91 (br s, 1H, H-4b), 3.86 (br t, 1H, J=7.3 Hz, H-5b), 3.78–3.75 (1H, H-3b), 3.77 (s, 3H, −OCH_3), 3.75 (s, 3H, −OCH_3), 3.55 (dd, 1H, J=3.9, 11.2 Hz, H-6a), 3.50 (dd, 1H, J=7.8, 9.8 Hz, H-2a), 3.47 (br t, 1H, J=8.3 Hz, H-6b), 3.41–3.35 (m, 2H, H-3a, H-6b), 3.31 (dd, 1H, J=2.0, 11.2 Hz, H-6a), 3.03 (br d, 1H, J=9.3 Hz, H-5a), 1.11 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{72}H_{79}N_3O_{12}Si$: C, 71.68; H, 6.60; N, 3.48. Found: C, 71.68; H, 6.76; N, 3.40.

3.2.6. 2,6-Di-O-benzyl-3,4-di-O-(4-methoxyphenyl)methyl-β-D-galactopyranosyl-(1→4)-3,6-di-O-benzyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl fluoride **20**

$[\alpha]_D$ +29.1 (*c* 1.2). R_f 0.50 (19:1 $CHCl_3$–EtOAc). ^{1}H NMR δ: 7.33–7.16 (m, 24H, Ar), 6.85 (d, 2H, J=8.3 Hz, Ar), 6.76 (d, 2H, J=8.3 Hz, Ar), 6.64 (d, 1H, J=7.8 Hz, −NH), 5.75 (dd, 1H, J=2.4, 54.2 Hz, H-1a), 5.02 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.86 (d, 1H, J=10.7 Hz, −CH_2Ar), 4.83 (d, 1H, J=10.2 Hz, −CH_2Ar), 4.74 (d, 1H, J=10.7 Hz, −CH_2Ar), 4.65–4.58 (m, 3H, −CH_2Ar×3), 4.55 (d, 1H, J=12.2 Hz, −CH_2Ar), 4.47 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.39–4.32 (m, 3H, −CH_2Ar×2, H-1b), 4.24 (d, 1H, J=12.2 Hz, −CH_2Ar), 4.16–4.05 (m, 2H, H-2a, H-4a), 3.91–3.69 (m, 5H, H-3a, H-5a, H-6a, H-2b, H-4b), 3.79 (s, 3H, −OCH_3), 3.74 (s, 3H, −OCH_3), 3.56 (br d, J=9.8 Hz, H-6a), 3.44 (dd, 1H, J=10.2, 10.7 Hz, H-6b), 3.37–3.29 (m, 3H, H-3b, H-5b, H-6b). Anal. Calcd for $C_{58}H_{61}NO_{12}Cl_3F$: C, 63.94; H, 5.64; N, 1.29. Found: C, 64.03; H, 5.75; N, 1.19.

α-Isomer: $[\alpha]_D$ +40.0 (*c* 0.9). R_f 0.55 (19:1 $CHCl_3$–EtOAc). ^{1}H NMR δ: 7.34–7.13 (m, 24H, Ar), 6.82–6.79 (m, 4H, Ar), 6.64 (d, 1H, J=8.8 Hz, −NH), 5.70 (dd, 1H, J=2.4, 53.7 Hz, H-1a), 5.47 (d, 1H, J=3.9 Hz, H-1b), 4.81 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.80 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.72 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.63–4.56 (m, 5H, −CH_2Ar×5), 4.49 (d, 1H, J=11.2 Hz, −CH_2Ar), 4.44 (d, 1H, J=12.2 Hz, −CH_2Ar), 4.35 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.29 (d, 1H, J=11.7 Hz, −CH_2Ar), 4.21 (m, 1H, H-2a), 4.19 (t, 1H, J=9.3 Hz, H-4a), 4.02 (m, 1H, H-5a), 3.99 (dd, 1H, J=3.9, 10.3 Hz, H-2b), 3.94–3.87 (m, 4H,

H-3a, H-6a, H-4b, H-5b), 3.81 (dd, 1H, J=2.4, 10.3 Hz, H-3b), 3.77 (s, 3H, −OCH_3), 3.76 (s, 3H, −OCH_3), 3.66 (dd, 1H, J=1.5, 10.7 Hz, H-6a), 3.44 (br d, 2H, J=6.3 Hz, H-6b×2). Anal. Calcd for $C_{58}H_{61}NO_{12}Cl_3F$: C, 63.94; H, 5.64; N, 1.29. Found: C, 63.84; H, 5.87; N, 1.23.

3.2.7. *tert*-Butyldiphenylsilyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside **21**

$[\alpha]_D$ −13.7 (*c* 1.1). R_f 0.54 (19:1 toluene−EtOAc). ^{1}H NMR δ: 7.72−7.70 (m, 4H, Ar), 7.42−7.11 (m, 31H, Ar), 5.91 (m, 1H, −C*H*=CH$_2$), 5.31 (dd, 1H, J=1.5, 17.1 Hz, −CH=C*H*$_2$), 5.16 (dd, 1H, J=1.5, 10.7 Hz, −CH=C*H*$_2$), 5.01 (d, 1H, J=10.2 Hz, −C*H*$_2$Ph), 4.95 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.73 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.62 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.61 (d, 1H, J=10.2 Hz, −C*H*$_2$Ph), 4.53 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.41 (d, 1H, J=7.8 Hz, H-1b), 4.37 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.35 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.30 (d, 1H, J=7.8 Hz, H-1a), 4.23 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.22 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.15 (br d, 2H, J=5.4 Hz, −C*H*$_2$CH=CH$_2$), 3.96 (t, 1H, J=9.8 Hz, H-4a), 3.86 (d, 1H, J=2.9 Hz, H-4b), 3.67−3.62 (m, 2H, H-6a, H-2b), 3.53 (t, 1H, J=7.8 Hz, H-6b), 3.44−3.34 (m, 3H, H-2a, H-6b, H-5b), 3.31 (dd, 1H, J=2.9, 9.8 Hz, H-3b), 3.25−3.19 (m, 2H, H-3a, H-6a), 2.83 (br d, J=9.8 Hz, H-5a), 1.11 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{66}H_{73}N_3O_{10}$: C, 72.30; H, 6.71; N, 3.83. Found: C, 72.34; H, 6.71; N, 3.74.

α-Isomer: $[\alpha]_D$ +17.7 (*c* 0.6). R_f 0.62 (19:1 toluene−EtOAc). ^{1}H NMR δ: 7.71−7.68 (m, 4H, Ar), 7.40−7.13 (m, 31H, Ar), 5.87 (m, 1H, −C*H*=CH$_2$), 5.59 (d, 1H J=3.9 Hz, H-1b), 5.25 (dd, 1H, J=1.5, 17.5 Hz, −CH=C*H*$_2$), 5.11 (dd, 1H, J=1.5, 10.2 Hz, −CH=C*H*$_2$), 4.84 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.76 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.73 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.72 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.53 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.50 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.34 (d, 1H, J=7.8 Hz, H-1a), 4.32−4.26 (m, 3H, −C*H*$_2$Ph×3), 4.23 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.08 (br d, 2H, J=5.4 Hz, −C*H*$_2$CH=CH$_2$), 4.02 (t, 1H, J=9.8 Hz, H-4a), 3.93 (dd, 1H, J=3.9, 10.2 Hz, H-2b), 3.90−3.85 (m, 2H, H-4b, H-5b), 3.66 (dd, 1H, J=2.4, 10.2 Hz, H-3b), 3.56−3.47 (m, 3H, H-2a, H-6a, H-6b), 3.40−3.36 (m, 2H, H-3a, H-6b), 3.31 (dd, 1H, J=1.9, 11.2 Hz, H-6a), 3.02 (br d, 1H, J=8.8 Hz, H-5a), 1.11 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{66}H_{73}N_3O_{10}$: C, 72.30; H, 6.71; N, 3.83. Found: C, 72.42; H, 6.72; N, 3.74.

3.2.8. *tert*-Butyldiphenylsilyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside **22**

Mp 115.5−116.5 °C (recrystallized from hexane−EtOAc). $[\alpha]_D$ −7.8 (*c* 1.0). R_f 0.37 (19:1 toluene−EtOAc). ^{1}H NMR δ: 7.70−7.63 (m, 4H, Ar), 7.40−7.11 (m, 31H, Ar), 6.89 (d, 1H, J=7.8 Hz, −N*H*), 5.91 (m, 1H, −C*H*=CH$_2$), 5.31 (m, 1H, −CH=C*H*$_2$), 5.16 (dd, 1H, J=1.5, 10.3 Hz, −CH=C*H*$_2$), 4.94 (d, 1H, J=10.7 Hz, −C*H*$_2$Ph), 4.93 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.99 (d, 1H, J=7.3 Hz, H-1a), 4.72 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.64 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.53 (d, 1H, J=10.7 Hz, −C*H*$_2$Ph), 4.51 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.43 (d, 1H, J=7.8 Hz, H-1b), 4.37 (d, 1H, J=12.2 Hz, −C*H*$_2$Ph), 4.33 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.23 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.22 (d, 1H, J=12,2 Hz, −C*H*$_2$Ph), 4.15 (dt, 2H, J=1.5, 5.3 Hz, −C*H*$_2$CH=CH$_2$), 4.03 (br t, 1H, J=8.5 Hz, H-4a), 3.85 (br d, 1H, J=3.4 Hz, H-4b), 3.81 (br t, 1H, J=7.8 Hz, H-3a), 3.75 (dd, 1H, J=7.8, 9.8 Hz, H-2a), 3.67−3.63 (m, 2H, H-6a, H-2b), 3.47 (dd, 1H, J=7.8, 8.3 Hz, H-6b), 3.40 (dd, 1H, J=4.9, 7.8 Hz, H-5b), 3.34−3.29 (m, 3H, H-6a, H-3b, H-6b), 3.07 (m, 1H, H-5a), 1.05 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{68}H_{74}NO_{11}Cl_3Si$: C, 67.18; H, 6.14; N, 1.15. Found: C, 67.08; H, 6.26; N, 1.13.

α-Isomer: $[\alpha]_D$ +14.0 (*c* 1.1). R_f 0.46 (19:1 toluene−EtOAc). ^{1}H NMR δ: 7.70−7.63 (m, 4H, Ar), 7.38−7.14 (m, 31H, Ar), 6.85 (d, 1H, J=6.9 Hz, −N*H*), 5.88 (m, 1H, −C*H*=CH$_2$), 5.32 (d, 1H, J=3.9 Hz, H-1b), 5.26 (dd, 1H, J=1.5, 17.1 Hz, −CH=C*H*$_2$), 5.12 (dd, 1H, J=1.5, 10.7 Hz, −CH=C*H*$_2$), 4.84 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.79 (d, 1H, J=6.8 Hz, H-1a), 4.71 (d, 1H, J=10.7 Hz, −C*H*$_2$Ph), 4.65 (d, 1H, J=12.2 Hz, −C*H*$_2$Ph), 4.57 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.51 (d, 1H, J=12.2 Hz, −C*H*$_2$Ph), 4.50 (d, 1H, J=11.2 Hz, −C*H*$_2$Ph), 4.34 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.31 (br s, 2H, −C*H*$_2$Ph×2), 4.26 (d, 1H, J=11.7 Hz, −C*H*$_2$Ph), 4.14−4.07 (m, 4H, H-2a, H-4a, −C*H*$_2$CH=CH$_2$), 3.90−3.81 (m, 4H, H-3a, H-2b, H-4b, H-5b), 3.62−3.57 (m, 2H, H-6a, H-3b), 3.50−3.43 (m, 2H, H-6b×2), 3.40 (dd, 1H, J=5.8, 8.8 Hz, H-6a), 3.30 (m, 1H, H-5a). Anal. Calcd for $C_{68}H_{74}NO_{11}Cl_3Si$: C, 67.18; H, 6.14; N, 1.15. Found: C, 67.00; H, 6.23; N, 1.16.

3.2.9. *N*-(9-Fluorenylmethoxycarbonyl)-*O*-[2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl-(1→3)-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl]-L-serine allyl ester **24** and *N*-(9-fluorenylmethoxycarbonyl)-*O*-[2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→3)-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl]-L-serine allyl ester **25**

According to the typical procedure, to a stirred mixture of **1** (66 mg, 0.10 mmol), **23** (34 mg, 0.05 mmol), BSP (33 mg, 0.16 mmol), TTBP (52 mg, 0.21 mmol), and dried MS (4 Å, 100 mg) in anhydrous EtCN (1.5 ml) was added Tf_2O (19 μl, 0.11 mmol) at −78 °C. The reaction mixture was stirred for 30 min and quenched with satd aq $NaHCO_3$. After work-up, the crude product was chromatographed on silica gel with toluene−EtOAc (7:1) to give known **24**[19] (41 mg, 67%) and then **25**[20] (16 mg, 15%).

3.2.10. *N*-(9-Fluorenylmethoxycarbonyl)-*O*-[2,6-di-*O*-benzyl-3,4-di-*O*-(4-methoxyphenyl)methyl-β-D-galactopyranosyl-(1→3)-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl]-L-serine allyl ester **26** and *N*-(9-fluorenylmethoxycarbonyl)-*O*-[2,6-di-*O*-benzyl-3,4-di-*O*-(4-methoxyphenyl)methyl-α-D-galactopyranosyl-(1→3)-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl]-L-serine allyl ester **27**

According to the typical procedure, to a stirred mixture of **4** (216 mg, 0.31 mmol), **23** (100 mg, 0.16 mmol), BSP (98 mg, 0.47 mmol), TTBP (155 mg, 0.62 mmol), and dried MS

(4 Å, 300 mg) in anhydrous EtCN (4.5 ml) was added Tf_2O (58 μl, 0.34 mmol) at −78 °C. The reaction mixture was stirred for 30 min and quenched with satd aq $NaHCO_3$. After work-up, the crude product was chromatographed on silica gel with toluene–EtOAc (10:1 to 7:1) to give **26** (152 mg, 79%) and **27** (6 mg, 8%). Compound **26**: $[\alpha]_D$ +91.1 (*c* 1.1). R_f 0.58 (3:1 toluene–EtOAc). ^{1}H NMR δ: 7.76 (d, 2H, *J*=7.3 Hz, Ar), 7.59 (d, 2H, *J*=7.3 Hz, Ar), 7.52–7.49 (m, 2H, Ar), 7.41–7.18 (m, 21H, Ar), 6.86–6.79 (m, 4H, Ar), 5.96–5.86 (m, 2H, −N*H*, −C*H*=CH$_2$), 5.46 [s, 1H, PhC*H*(O−)$_2$], 5.34 (br d, 1H, *J*=17.6 Hz, −CH=C*H*$_2$), 5.26 (br d, 1H, *J*=10.2 Hz, −CH=C*H*$_2$), 5.03 (d, 1H, *J*=3.4 Hz, H-1a), 4.99 (d, 1H, *J*=10.7 Hz, −C*H*$_2$Ar), 4.86 (d, 1H, *J*=11.2 Hz, −C*H*$_2$Ar), 4.75 (d, 1H, *J*=11.2 Hz, −C*H*$_2$Ar), 4.71–4.56 (m, 5H, −C*H*$_2$CH=CH$_2$, −C*H*$_2$Ar, H-1b, Ser−αH), 4.51 (d, 1H, *J*=11.2 Hz, −C*H*$_2$Ar), 4.46–4.29 (m, 5H, −C*H*$_2$Ar×3, −OC*H*$_2$CHAr$_2$), 4.24–4.00 (m, 4H, Ser−βH×2, H-3a, −OCH$_2$C*H*Ar$_2$), 3.87–3.50 (m, 11H, H-2a, H-4a, H-5a, H-6a×2, H-2b, H-3b, H-4b, H-5b, H-6b×2), 3.80 (s, 3H, −OC*H*$_3$), 3.77 (s, 3H, −OC*H*$_3$). Anal. Calcd for $C_{70}H_{72}N_4O_{16}$: C, 68.61; H, 5.92; N, 4.57. Found: C, 68.74; H, 6.04; N, 3.98. (Because of unstable **26** by drying at 80 °C, a lower value was obtained for N analysis.) HRMS calcd for $^{12}C_{70}{}^{1}H_{72}{}^{14}N_4{}^{23}Na_1{}^{16}O_{16}$ *m/z* 1247.48410. Found 1247.46996.

Compound **27**: $[\alpha]_D$ +92.3 (*c* 1.0). R_f 0.53 (3:1 toluene–EtOAc). ^{1}H NMR δ: 7.76 (d, 2H, *J*=7.3 Hz, Ar), 7.57 (d, 2H, *J*=7.3 Hz, Ar), 7.48–7.09 (m, 23H, Ar), 6.85–6.77 (m, 4H, Ar), 5.94–5.84 (m, 2H, −C*H*=CH$_2$, −N*H*), 5.38 [s, 1H, PhC*H*(O−)$_2$], 5.32 (br d, 1H, *J*=17.6 Hz, −CH=C*H*$_2$), 5.25–5.23 (m, 2H, −CH=C*H*$_2$, H-1b), 4.99 (d, 1H, *J*=2.9 Hz, H-1a), 4.84 (d, 1H, *J*=10.7 Hz, −C*H*$_2$Ar), 4.73 (d, 1H, *J*=11.2 Hz, −C*H*$_2$Ar), 4.66–4.28 (m, 12H, −C*H*$_2$CH=CH$_2$, −C*H*$_2$Ar×6, Ser−αH, −OC*H*$_2$C*H*Ar$_2$), 4.21–4.03 (m, 7H, Ser−βH, H-3a, H-4a, H-6a, H-2b, H-3b, H-5b), 3.97–3.93 (m, 3H, H-2a, H-4b, Ser−βH), 3.86 (br d, 1H, *J*=12.7 Hz, H-6a), 3.79 (s, 3H, −OC*H*$_3$), 3.75 (s, 3H, −OC*H*$_3$), 3.59 (br s, 1H, H-5a), 3.57–3.47 (m, 2H, H-6b×2). Anal. Calcd for $C_{70}H_{72}N_4O_{16}$: C, 68.61; H, 5.92; N, 4.57. Found: C, 68.89; H, 6.15; N, 3.64. (Because of unstable **27** by drying at 80 °C, a lower value was obtained for N analysis.) HRMS calcd for $^{12}C_{70}{}^{1}H_{72}{}^{14}N_4{}^{23}Na_1{}^{16}O_{16}$ *m/z* 1247.48410. Found 1247.47154.

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References and notes

1. Nakahara, Y. *Trends Glycosci. Glycotechnol.* **2003**, *15*, 257–273.
2. For example: (a) Nakahara, Y.; Iijima, H.; Ogawa, T. *Carbohydr. Lett.* **1994**, *1*, 99–106; (b) Takano, Y.; Kojima, N.; Nakahara, Y.; Hojo, H.; Nakahara, Y. *Tetrahedron* **2003**, *59*, 8415–8427.
3. Nakahara, Y.; Nakahara, Y.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1998**, *308*, 287–296.
4. Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685–687.
5. Hashimoto, S.; Honda, T.; Ikegami, S. *Chem. Pharm. Bull.* **1990**, *38*, 2323–2325.
6. Hashimoto, S.; Yanagiya, Y.; Honda, T.; Harada, H.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 3523–3526.
7. Hashimoto, S.; Umeo, K.; Sano, A.; Watanabe, N.; Nakajima, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 2251–2254.
8. Watanabe, Y.; Nakamoto, C.; Yamamoto, T.; Ozaki, S. *Tetrahedron* **1994**, *50*, 6523–6536.
9. Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.
10. Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922–10928.
11. Janczuk, A. J.; Zang, W.; Andreana, P. R.; Warrick, P. G.; Wang, P. G. *Carbohydr. Res.* **2002**, *337*, 1247–1259.
12. Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142–8148.
13. Murakata, C.; Ogawa, T. *Carbohydr. Res.* **1992**, *234*, 75–91.
14. Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 1597–1600.
15. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074.
16. Ueki, A.; Nakahara, Y.; Hojo, H.; Nakahara, Y. *Tetrahedron* **2007**, *63*, 2170–2181.
17. Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277–2280.
18. Macindoe, W. M.; Iijima, H.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1995**, *269*, 227–257.
19. Nakahara, Y.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1996**, *292*, 71–81.
20. Maemura, M.; Ohgaki, A.; Nakahara, Y.; Hojo, H.; Nakahara, Y. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 1575–1583.