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6-Azido-Galactosyl Imidate as a Building Block for Preparation of 1-(4-Aminobutyl)-, Di-, Tri- and Tetra-Saccharides

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ABSTRACT

6-azidogalactosyl imidate has been used as a donor to generate 1-(4-aminobutyl)-6-aminogalactose, 6-aminothiotolyl-glycosides of disaccharide, trisaccharide and tetrasaccharide that incorporates 6-azido group and 1-(4-tolyl)thio group. Trisaccharide and tetrasaccharide were obtained from lactosyl-based acceptor. The anomeric 1-(4-tolyl)thio group could be used to conjugate with sphingosine analogs to provide the alpha-Gal Sph analogs for library extension from the azido group.

Keywords: Glycosylation; Chemoselective; Imidate; Building Block; Lactoside

1. Introduction

Glycoconjugates have been well known for their diversified functions in molecular recognition. For example, glycolipids are involved in numerous immune-related diseases such as cancer progression [1]. Recently, alpha galactosyl ceramide (α-GalCer, KRN7000) has been intensively studied owing to their immune stimulation effects that may be useful for development of cancer vaccines [2]. Because the sugar components play crucial roles in the recognition events, structural modification on the sugar moieties might be capable of discovering more potential GalCer analogs. To broaden the diversities of saccharides, the library approach has become a promising method [3-6]. The library of oligosaccharide could be generated through combinatorial methods by varying the sugar components, modifying with diverse functional groups as well as performing parallel synthesis or mixture-based synthesis [6-8].

We recently reported a preparation and analysis of libraries of amide derived from a core amine with carboxylic acids via a parallel solution phase synthesis (psps) [9-11]. The library members could be directly analyzed for their antitumoral cytotoxicities in a cell-based assay [12]. Instead of the chromatographic purification but by using a serial dilution to 1000 fold, toxicities of the residual reagents and solvents could be leveled off. Encouraged by the success in discovering a number of potential bioactive compounds [13,14], we are interested in preparing various galactosyl-containing saccharides that had been functionalized with azido group (**Figure 1**). The azido group could be potentially reduced to amine for further elaboration to amide libraries.

2. Experimental Section

2.1. Apparatus and the General Treatment of the Reagents

All preparations were routinely conducted in dried glassware under nitrogen. CH_2Cl_2, toluene, and pyridine were dried over CaH_2. THF was treated with $FeSO_4$ to remove peroxide, followed by drying over Na. MeOH was dried over Mg and distilled. Dimethyl amino pyri-

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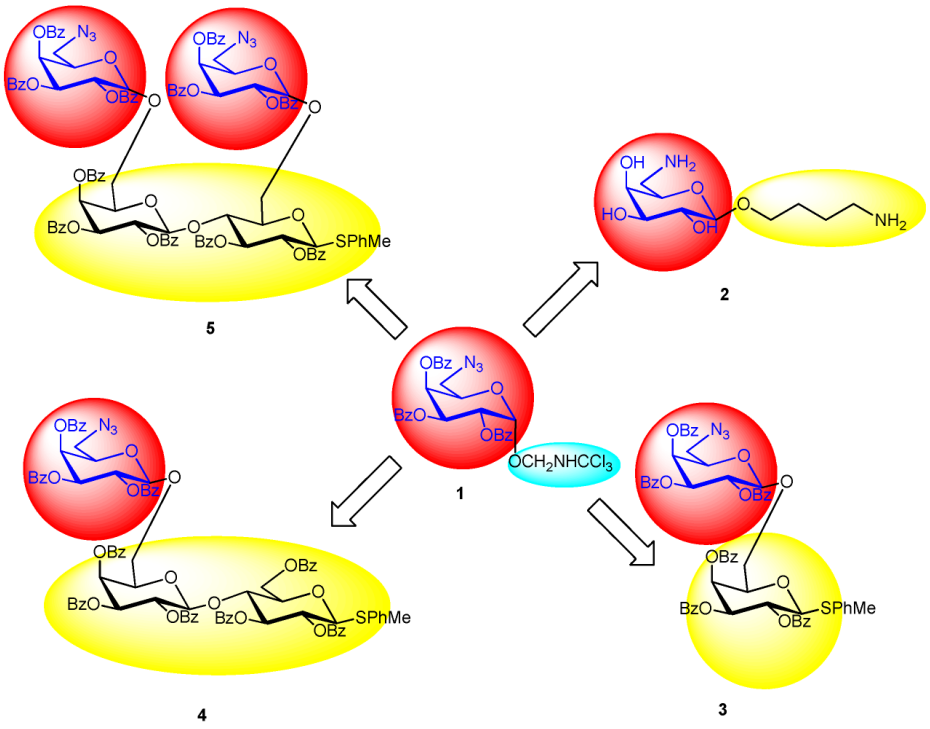
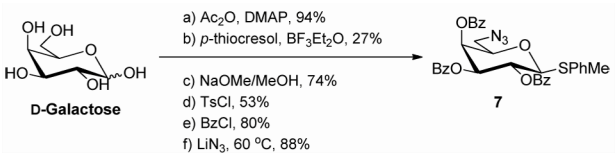


Figure 1. Illustration of the use of 6-deoxy-6-azido galactosyl imidate 1 as a building block to provide amino saccharides for preparing glycosphingolipids for library construction.

dine (DMAP) was purified through azeotropical distillation with toluene prior to use. The eluents for chromatography: EtOAc, acetone, and *n*-hexane were reagent grade and distilled prior to use; MeOH and $CHCl_3$ were reagent grade and used without further purification. NMR spectroscopy including ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz, DEPT-135) was performed by Varian Unity Inova 500 NMR spectrometer either at the department of chemistry of National Tsing-Hua University (NTHU) or the Department of Applied Chemistry of National Chiao-Tung University (NCTU). D-solvents employed for NMR, including CD_3OD, $CDCl_3$, and C_6D_6 were purchased from Cambridge Isotope Laboratories, Inc. MALDI-TOF-MS was performed by Autoflex III smartbeam LRF200-CID at the Department of Chemistry of National Tsing-Hua University (NTHU). ESI-MS spectrometry employing VARIAN 901-MS was performed at the Department of Applied Chemistry of National Chiao-Tung University (NCTU). TLC was performed with Macherey-Nagel silica gel 60 F25 precoated plates. The starting materials and products were visualized with UV (254 nm). Further visualization was carried out by using staining with 5% *p*-anisaldehyde, ninhydrin or ceric ammonium molybdate under heating. Flash chromatography was performed using Geduran Si 60 silica gel (230 - 400 mesh). Melting point was measured with MEL-TEMP and was uncorrected.

The final conjugation products were further purified and analyzed by HPLC, consisting of an Angilent 1100 pump and a linear UVIS detector (254 nm). A ZORBAX SIL column with a dimension of 250 mm × 9.4 mm and particle size of 5 μm (Si-100) was used as the stationary phase and the eluents of a combination of EtOAc and *n*-hexane with a flow rate of 3 mL/min were used as the mobile phase.

2.2. Preparation of 2,3,4-Tri-O-benzoyl-6-deoxy-6-azido-1-(4-tolyl)thio-*β*-D-galactopyranoside 7 from Commercial D-Galactose



2.2.1. Procedure (a)

Prepapration of 1,2,3,4,6-penta-*O*-acetyl-D-galactose was similar to previous reports of the 2-deoxy galactose derivative [12] and other sugars [13,14]. In practice, galactose (11.2 g, 62 mmol) was suspended in pyridine (55 mL) (780 mg, 6.38 mmol, 0.102 eq). The stirring was allowed at rt for 30 min. TLC (EtOAc/*n*-hexane = 3/7) indicated the consumption of starting material and the formation of product (1,2,3,4,6-penta-*O*-acetyl-D-galactose) (R_f = 0.3). After the solvent was distilled, the resi

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due was purified by column chromatography with eluents of EtOAc/*n*-hexane = 3/7 to give product (1,2,3,4,6-penta-*O*-acetyl-D-galactose) in 94% yield (25 g).

2.2.2. Procedure (b)

Preparation of 2,3,4,6-tetra-*O*-acetyl-1-(4-tolyl)thio-D-galactoside has been reported and was similar to previous reports of the 2-deoxy galactose derivative and other sugars [15-19]. In practice, starting material (1,2,3,4,6-penta-*O*-acetyl-D-galactose) (25 g, 0.067 mol) was dissolved in CH_2Cl_2 (50 mL) followed by cooling down to 0˚C. *p*-Thiocresol (8.7 g, 0.07 mol) and BF_3Et_2O (17 mL, 0.134 mol) were added, sequentially. The solution turned yellow. After 1.5 h, the color changed to purple. After a further stirring for 19 h, the solution turned black. TLC (EtOAc/*n*-hexane = 3/7) indicated the formation of a number of by-products. The mixture was partitioned by using 0.5 N HCl (20 mL) and saturated $NaHCO_3$ (60 mL × 3), sequentially. The organic layer was dried with $Na_2SO_{4(s)}$, followed by filtration. The filtrate was concentrated under reduced pressure. The residue obtained was recrystallized from EtOAc/*n*-hexane to give product (2,3,4,6-tetra-*O*-ace-tyl-1-(4-tolyl)thio-D-galactoside) in 27% yield (7 g).

2.2.3. Procedure (c)

Preparation of 1-(4-tolyl)thio-D-galactoside was similar to the previous reports of the 2-deoxy galactose derivative and other sugars [15-24]. To a mixture of starting material (2,3,4,6-tetra-*O*-acetyl-1-(4-tolyl)thio-D-galactoside) (6.8 g, 0.015 mol) and MeOH (20 mL) was added NaOMe (700 mg, 0.012 mol). The stirring was allowed for 1 h. TLC ($MeOH/CH_2Cl_2$ = 1/4) indicated the consumption of starting material (R_f = 0.83) and the formation of product (R_f = 0.55). The mixture was treated with ion exchange resin of Amberlite IR-120 (H^+ form). The resin was removed by gravitational filtration. The filtrate was concentrated under reduced pressure to generate the product in 74% yield (2.8 g).

2.2.4. Procedure (d)

Preparation of 6-*O*-(*p*-tolylsulfonyl)-1-(4-tolyl) thio-D-galactoside was similar to the previous reports [25,26]. To a mixture of the starting material (*p*-tolyl 1-thio-D-galactoside) (2.8 g, 9.7 mmol) and pyridine (3.5 mL) was added TsCl (2.05 g, 10.6 mmol, 1.1 eq). The stirring was allowed at rt for 1 h. TLC ($MeOH/CHCl_3$ = 1/19) indicated the incomplete formation of product (R_f = 0.2) and the incomplete consumption of starting material (R_f = 0.1). To the above mixture was added TsCl (1 g, 5.3 mmol, 0.54 eq). The crude product was purified using column chromatography with eluents of $MeOH/CHCl_3$ = 1/19 to afford the product in 53% yield (2.3 g).

2.2.5. Procedure (e)

To a mixture of the starting material 6-*O*-(p-tolylsulfonyl)-1-(4-tolyl)thio-D-galactoside) (1.9 g, 0.0043 mmol) and pyridine (5 mL) was added BzCl (1.3 mL, 0.014 mmol, 3.25 eq) at 0˚C [27]. The ice bath was removed and the stirring was allowed for 1.5 h. TLC indicated the consumption of starting material (R_f = 0.07, EtOAc/*n*-hexane = 1/1) and the formation of product (2, 3, 4-tri-*O*-benzoyl-6-*O*-(p-tolylsulfonyl)-1-(4-tolyl)thio-D-galactoside) (R_f = 0.61, EtOAc/*n*-hexane = 2/3). The mixture was quenched by addition of MeOH. The solvent was distilled and EtOAc (3 mL) was added to the residue. The organic layer was extracted with 1 N HCl (2 mL), $NaHCO_{3(aq)}$ (2 mL) and water (2 mL), sequentially. The organic layer was dried with $Na_2SO_{4(s)}$ followed by filtration. The filtrate was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane = 1/4 to provide product (2,3,4-tri-*O*-benzoyl-6-*O*-(p-tolylsulfonyl)-1-(4-tolyl)thio-D-galactoside) in 80% yield (2.6 g).

2.2.6. Procedure (f)

The aqueous solution of LiN_3 [25] (67 mmol, 20.3 eq) was coevaporated with toluene under reduced pressure. To a mixture of starting material (2,3,4-tri-*O*-benzoyl-6-*O*-(*p*-tolyl sulfonyl)-1-(4-tolyl)thio-D-galactoside) (2.5 g, 3.3 mmol) and DMF (4 mL) was added the above solution of LiN_3 in DMF (1 mL). The stirring was allowed at 80˚C for 17 h. TLC (EtOAc/*n*-hexane = 1/4) indicated the consumption of starting material (R_f = 0.12) and the formation of product **7** (R_f = 0.4). The mixture was concentrated under reduced pressure. Water (15 mL) and EtOAc (30 mL) were added for partition. The organic layer was dried with $Na_2SO_{4(s)}$ followed by filtration. The filtrate was concentrated under reduced pressure. The residue obtained was purified using column chromatography to provide product **7** in 88% yield (1.3 g). ^{1}H-NMR (500 MHz, C_6D_6) δ 2.03 (s, 3H, C$\underline{H}_3$, H_{SPhMe}), 2.57 (dd, 1H, $J_{6a,6b}$ = 13.0, $J_{6a,5}$ = 3.5 Hz, H_{6a}), 3.05 (dd, 1H, $J_{6b,6a}$ = 13.0, $J_{6b,5}$ = 8.5 Hz, H_{6b}), 3.26 (dd, 1H, $J_{5,6b}$ = 8.5, $J_{5,6a}$ = 3.5 Hz, H_5), 4.59 (dd, 1H, $J_{1,2}$ = 10.0, $^4J_{1,3}$ = 2.5 Hz, H_1), 5.52 (ddd, 1H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.5, $^4J_{3,1}$ = 1.5 Hz, H_3), 6.02 (d, 1H, $J_{4,3}$ = 3.5 Hz, H_4), 6.09 (dd, 1H, $J_{2,3}$ =10.0, $J_{2,1}$ = 10.0 Hz, H_2), 6.71 (t, 2H, *J* = 7.5 Hz, H_{arom}), 6.82 (t, 1H, *J* = 7.0 Hz, H_{arom}), 6.95 (t, 5H, *J* = 7.0 Hz, H_{arom}), 6.98 - 7.03 (m, 3H, H_{arom}), 7.71 (d, 2H, *J* = 8.5 Hz, H_{arom}), 7.91 - 7.98 (m, 4H, H_{arom}), 7.99 - 8.01 (m, 4H, H_{arom}), 8.09 - 8.14 (m, 2H, H_{arom}); ^{13}C-NMR (125 MHz, C_6D_6) δ 21.13 (CH_3, C_{SPhMe}), 51.12 ($N_3\underline{C}H_2$), 68.28 (CH), 69.34 (CH), 73.50 (CH), 76.50 (CH), 85.55 (CH), 125.64 (CH, C_{arom}), 127.48 (CH, C_{arom}), 128.29 (CH, C_{arom}), 128.43 (CH, C_{arom}), 128.51 (CH, C_{arom}), 128.61 (CH, C_{arom}), 128.77 (CH, C_{arom}), 129.28 (CH, C_{arom}), 129.35 (C, C_{arom}), 129.51 (C, C_{arom}), 129.84

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(CH, C_{arom}), 129.95 (CH, C_{arom}), 130.02 (CH, C_{arom}), 130.13 (C, C_{arom}), 130.23 (CH, C_{arom}), 133.17 (CH, C_{arom}), 133.21 (CH, C_{arom}), 133.41 (CH, C_{arom}), 135.66 (CH, C_{arom}), 138.81 (CH, C_{arom}), 165.39 (O<u>C</u>O), 165.42 (O<u>C</u>O), 165.65 (O<u>C</u>O).

2.3. Preparation of 2,3,4-Tri-O-benzoyl-1-(2,2,2-trichloroenthanimidate)-6-deoxy-6-azido-*α*-D-galactopyranose 1

To a solution of compound **7** (448 mg, 0.71 mmol) in acetone (5 mL) was added *N*-bromosuccinimide [14,25] (152 mg, 0.39 mmol). After 30 min, the mixture was treated with EtOAc (5 mL), followed by partition using $NaHCO_3$ (5 mL) and brine (5 mL), sequentially. The organic layer was dried with Na_2SO_4 followed by filtration. The filtrate was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane = 1/4 to afford 2,3,4-tri-*O*-benzoyl-6-deoxy-6-azido-*α*-D-galactopyranose in 78% yield (287 mg). Anal. $C_{27}H_{23}N_3O_8$, M (calcd.) = 517.2 (m/z), ESI + Q-TOF: M = 518.1 (m/z), $[M + K]^+$ = 557.1; ^{1}H-NMR (500 MHz, C_6D_6) δ 2.59 (d, 1H, $J_{6a,6b}$ = 12.0 Hz, H_{6a}), 3.09 (dd, 1H, $J_{6b,6a}$ = 13.0, $J_{6b,5}$ = 9.0 Hz, H_{6b}), 4.04 (bs, 1H, H_5), 5.46 (bs, 1H), 5.75 (bs, 1H), 5.97 (dd, 1 H, J = 10.0, J = 3.5 Hz), 6.19 (t, 1 H, J = 10.5, J = 3.0 Hz), 6.72 (t, 2H, J = 8.0, J = 8.0 Hz, H_{arom}), 6.83 - 7.12 (m, 8H, H_{arom}), 7.92-8.12 (m, 5H, H_{arom}).

To the above intermediate (430 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) was added CCl_3CN (904 uL, 9.0 mmol, 11 eq) and 1,8-diazabicyclo[5.4.0]undec-7-ene (62 uL, 0.41 mmol, 0.5 eq), sequentially [25,28]. After 30 min, TLC (EtOAc/*n*-hexane = 1:4) indicated the consumption of the starting material (R_f = 0.35) and the formation of the product **1** (R_f = 0.46). After concentration under reduced pressure, the residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane 1:9 to provide compound **1** in 94% yield (512 mg). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.36 (dd, 1H, $J_{6a,6b\ (gem)}$ = 12.5, $J_{6a,5}$ = 5.0 Hz, H_{6a}), 3.58 (dd, 1H, $J_{6b,6a\ (gem)}$ = 13.0, $J_{6b,5}$ = 8.0 Hz, H_{6b}), 4.59 (dd, 1H, $J_{5,6b}$ = 7.5, $J_{5,6a}$ = 5.0 Hz, H_5), 5.92 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,2}$ = 9.5 Hz, H_3), 5.96-6.01 (m, 2H, H_2 and H_4), 6.87 (d, 1H, $J_{1,2}$ = 4 Hz, H_1), 7.22 - 7.51 (m, 8H, H_{arom}), 7.63 (t, 1H, J = 8.0, J = 7.0 Hz, H_{arom}), 7.77 (d, 2H, J = 7.0 Hz, H_{arom}), 7.93 (d, 2H, J = 7.0 Hz, H_{arom}), 8.07 (d, 2H, J = 7.0 Hz, H_{arom}), 8.67 (s, 1H, H_{NH}).

2.4. Preparation of 4-Azidobutan-1-ol 8

2.4.1. Preparation of TfN_3 [29]*

NaN_3 (9.7 g, 150 mmol) was dissolved in H_2O (7 mL) at 0˚C. A solution of Tf_2O (5 mL, 30 mmol) in CH_2Cl_2 (15 mL) was added. The biphasic mixture was stirred vigorously for 1 hr. The organic layer was collected and the aqueous layer was back-extracted with CH_2Cl_2 (60 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (27 mL) twice to give TfN_3. *Caution: TfN_3 should be manipulated in a solution. Explosion may occur when drying.

2.4.2. Azido Transfer Reaction

To a solution of commercial 4-aminobutan-1-ol (924 μL, 890 mg, 10 mmol) in H_2O (40 mL) was added K_2CO_3 (2 g, 15 mmol), $CuSO_4$ (16 mg, 0.1mmol) and the above solution of TfN_3, sequentially. The mixture was brought about to a homogeneous solution by addition of MeOH (100 mL). After 18 h, the mixture was partitioned between saturated $NaHCO_3$ (aq., 30 mL) and CH_2Cl_2 (80 mL). The organic layer was concentrated under reduced pressure at 30˚C to provide the crude yellow oil product **8** in 70% yield (800 mg). Anal. $C_4H_9N_3O$, M (calcd.) = 115.1 (m/z), ESI + Q-TOF:M = 115.1 (m/z), $[M + H]^+$ = 116.1; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.59 (m, 4H, H_{butyl}), 3.25 (dd, 2H, J = 6.5 Hz, $N_3C\underline{H}_2$, H_{butyl}), 3.59 (dd, 2H, J = 6.0 Hz, CH_2OH, H_{butyl}); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.92 (CH_2, C_{butyl}), 29.20 CH_2, C_{butyl}), 50.83 (CH_2N_3, C_{butyl}), 61.24 (CH_2OH, C_{butyl}). Analytic data also can be found in literature [30,31].

2.5. Preparation of 4'-Azidobutyl 2,3,4-Tri-O-benzoyl-6-deoxy-6-azido-*β*-D-galactopyranoside 9

A mixture of the donor **1** (512 mg, 0.77 mmol) and the acceptor **8** (266 mg, 2.31 mmol, 3 eq) was distilled azeotropically with toluene at 50˚C for three times followed by concentration under reduced pressure for 1 h. The mixture was transferred to a two-necked round-bottom flask charging with CH_2Cl_2 (5 mL), followed by addition of 4 Å MS (680 mg). The mixture was stirred at 0˚C under N_2 for 30 min. After addition of TMSOTf (32 μL, 0.15 mmol, 0.2 eq), the ice bath was removed and the stirring was allowed at rt for 10 min. The solution was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane = 3.5/6.5 to provide compound **9** in 86% yield (400 mg). The product was further purified using HPLC with eluents of EtOAc/*n*-hexane = 2/8 to provide compound **9**, t_R = 15.6 min. Anal. $C_{31}H_{30}N_6O_8$, M (calcd.) = 614.2 (m/z), ESI+Q-TOF: M = 614.1 (m/z), $[M + Na]^+$ = 637.1; ^{1}H-NMR (500 MHz, C_6D_6) δ 1.15 - 1.32 (m, 4H, H_{butyl}), 2.55 (t, 2H, J = 6.5 Hz, $N_3C\underline{H}_2$, $H_{4\ (butyl)}$), 2.60 (dd, 1H, $J_{6a',6b'\ (gem)}$ = 13.5, $J_{6a',5'}$ = 3.5 Hz, $H_{6a'}$), 3.18 (dd, 1H, $J_{6b',6a'\ (gem)}$ = 13.0, $J_{6b',5'}$ = 9.0 Hz, $H_{6b'}$), 3.22-3.26 (m, 1H, H_{butyl}), 3.34 (dd, 1H, $J_{5',6b'}$ = 9.0, $J_{5',6a'}$ = 3.5 Hz, $H_{5'}$), 3.83 - 3.87 (m, 1H, H_{butyl}), 4.42 (d, 1H, $J_{1',2'}$ = 8.0 Hz, $H_{1'}$), 5.63 (dd, 1H,

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$J_{3',2'}$ = 11.0, $J_{3',4'}$ = 3.5 Hz, $H_{3'}$), 5.77 (d, 1H, $J_{4',3'}$ = 3.5 Hz, $H_{4'}$), 6.23 (dd, 1H, $J_{2',3'}$ = 10.5, $J_{2',1'}$ = 8.0 Hz, $H_{2'}$), 6.71 (t, 1 H, J = 8.0, J = 7.5 Hz, 2H, H_{arom}), 6.83 (t, 1 H, J = 8.0, J = 7.0 Hz, 1H, H_{arom}), 6.90 - 7.06 (m, 6H, H_{arom}), 7.97 (d, 2H, J = 7.5 Hz, H_{arom}), 8.08 (d, 4H, J = 8.5 Hz, H_{arom}); ^{13}C-NMR (125 MHz, C_6D_6) δ 25.52 (CH_2, C_{butyl}), 26.68 (CH_2, C_{butyl}), 50.78 ($\underline{C}H_2N_3$), 51.00 ($\underline{C}H_2N_3$), 69.29 (CH_2OH, C_{butyl}), 69.38 (CH), 70.26 (CH), 72.05 (CH), 73.56 (CH), 101.65 (CH), 128.29 (CH, C_{arom}), 128.47 (CH, C_{arom}), 128.60 (CH, C_{arom}), 128.86 (CH, C_{arom}), 129.30 (CH, C_{arom}), 129.37 (CH, C_{arom}), 129.85 (CH, C_{arom}), 129.93 (CH, C_{arom}), 130.02 (CH, C_{arom}), 130.19 (CH, C_{arom}), 133.22 (CH, C_{arom}), 133.51 (CH, C_{arom}), 165.45 (O$\underline{C}$O), 165.64 (O$\underline{C}$O), 165.81 (O$\underline{C}$O).

2.6. Preparation of 4'-Azidobutyl 6-deoxy-6-azido-*β*-D-galactopyranoside 10

To a mixture of compound **9** (60 mg, 0.09 mmol) in MeOH (1 mL) was added NaOMe (4 mg, 0.07 mmol, 0.8 eq). The mixture was stirred at rt for 30 min. After the treatment with ion exchange resin (H^+), the mixture was treated with gravitational filtration. The filtrate obtained was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of MeOH/$CHCl_3$ = 1/9 to provide compound **10** in 71% yield (21 mg). ^{1}H-NMR (500 MHz, CD_3OD) δ 1.62 (m, 4H, H_{butyl}), 3.20 (dd, 1H, $J_{6a',6b'(gem)}$ = 11.6, $J_{6a',5'}$ = 3.0 Hz, $H_{6a'}$), 3.23 - 3.24 (m, 3H), 3.39 - 3.66 (m, 5H), 3.83 - 3.86 (m, 1H), 4.17 (d, 1H, $J_{1,2}$ = 6.8 Hz, H_1); ^{13}C-NMR (125 MHz, CD_3OD) δ 26.72 (CH_2, C_{butyl}), 27.91 (CH_2, C_{butyl}), 52.24 ($\underline{C}H_2N_3$), 52.57 ($\underline{C}H_2N_3$), 70.04 (O$\underline{C}H_2$, C_{butyl}), 70.85 (CH), 72.31 (CH), 74.71 (CH), 75.79 (CH), 104.82 (CH).

2.7. Preparation of 4'-Aminobutyl 6-deoxy-6-amino-*β*-D-galactopyranoside 2

To compound **10** (21 mg, 0.07 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 50%). The mixture was charged with a ballon containing H_2. The stirring was allowed for 2 h as monitored by TLC (MeOH/$HCCl_3$/NH_3 = 5/5/2). The mixture was filtered through a celite pad. The filtrate obtained was concentrated under reduced pressure to afford compound **2** in 70% yield (12 mg). Anal. $C_{10}H_{22}N_2O_5$, M (calcd.) = 250.2 (m/z), ESI + Q-TOF: M = 250.2 (m/z), $[M + Na]^+$ = 273.2; ^{1}H-NMR (500 MHz, CD_3OD) δ 1.59 - 1.66 (m, 4H, H_{butyl}), 2.71 (t, J = 6.5 Hz, 2H, $C\underline{H}_2NH_2$, $H_{4\ (butyl)}$), 2.79 (dd, 1H, $J_{6a',6b'(gem)}$ = 13.5 Hz, $J_{6a',5'}$ = 4.0 Hz, $H_{6a'}$), 2.95 (dd, 1H, $J_{6b',6a'(gem)}$ = 13.0, $J_{6b',5'}$ = 7.5 Hz, $H_{6b'}$), 3.41 - 3.58 (m, 3H, $H_{2'}$ and $H_{3'}$ and $H_{5'}$), 3.59 (dt, J_{gem} = 10.0, J = 6.5 Hz, 1H, $H_{1a(butyl)}$), 3.77 (d, 1H, J = 3.0 Hz, $H_{4'}$), 3.90 (dt, J_{gem} = 10.0, J = 6.5 Hz, 1H, $H_{1b(butyl)}$), 4.21 (d, 1H, $J_{1,2}$ = 8.0 Hz, $H_{1'}$).

2.8. Preparation of 2,3,4-tri-O-benzoyl-1-(4-tolyl)thio-*β*-D-galactopyranoside 11

Compound **6** (700 mg, 2.45 mmol) and DMAP (189 mg, 1.6 mmol, 0.63 eq) was dissolved in pyridine (3 mL). A solution of TBDMSCl (738 mg, 4.9 mmol, 2 eq) in CH_2Cl_2 was added [24]. The stirring was allowed for 20 h. TLC (MeOH/$CHCl_3$ = 1/9) indicated the consumption of compound **6** (R_f = 0.24). The mixture was cooled down by ice bath. BzCl (1.7 mL, 2.1 g, 14.7 mmol, 6 eq) was added. The mixture was then stirred for 0.5 h. TLC (EtOAc/*n*-hexane = 1/3) indicated the formation of the intermediate compound (R_f = 0.75). The mixture was concentrated under reduced pressure. The residue was purified using column chromatography with gradients of EtOAc/*n*-hexane = 1/19 → 1/9 to provide the intermediate product, 2,3,4-tri-*O*-benzoyl-6-*O*-(tert-butyldimethylsilyl)-1(4-tolyl)-thio-*β*-D-galactopyranoside, in 56% yield (976 mg).

The obtained intermediate compound (170 mg, 0.24 mmol) was dissolved in THF (5 mL). AcOH (1 mL) and HF-pyridine (700 μL) were added, sequentially. The stirring was allowed for 10 min. TLC (EtOAc/*n*-hexane = 1/3) indicated the consumption of the intermediate compound (R_f = 0.63) and the formation of product **11** (R_f = 0.27). The reaction was quenched by washing with saturated $NaHCO_{3(aq)}$ (5 mL). The organic layer was dried with Na_2SO_4 followed by filtration with a celite pad. The filtrate was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane = 1/3 to provide product **11** in 88% yield (126 mg). ^{1}H-NMR (500 MHz, C_6D_6) δ 2.03 (s, 3H, $C\underline{H}_3$, H_{SPhMe}), 3.62 (dd, 1H, $J_{5,6b}$ = 7.0, $J_{5,6a}$ = 6.5 Hz, H_5), 4.12 (dd, 1H, $J_{6a,6b}$ = 11.0, $J_{6a,5}$ = 6.0 Hz, H_{6a}), 4.32 (dd, 1H, $J_{6b,6a}$ = 11.0, $J_{6b,5}$ = 7.0 Hz, H_{6b}), 4.64 (d, 1H, $J_{1,2}$ = 10.0 Hz, H_1), 5.62 (dd, 1H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.5 Hz, H_3), 6.01 (d, 1H, $J_{4,3}$ = 3.5 Hz, H_4), 6.11 (dd, 1H, $J_{2,3}$ = 10.0, $J_{2,1}$ = 10.0 Hz, H_2), 6.67 - 7.10 (m, 12H, H_{arom}), 7.64 - 8.15 (m, 7H, H_{arom}).

2.9. Preparation of 2,3,4-tri-O-benzoyl-6-azido-6-deoxy-*β*-D-galactopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-(4-tolyl)thio-galactopyranoside 3

A mixture of the donor **1** (13 mg, 0.02 mmol) and the acceptor **11** (17 mg, 0.028 mmol, 1.3 eq) were azeotropically distilled with toluene at 50˚C for three times, which was followed by concentration under reduced pressure for 1 h. The mixture was dissolved in a two-necked round-bottom flask charging CH_2Cl_2 (5 mL) and 4 Å MS (30 mg). The stirring was allowed at rt for 30 min, followed by cooling down with an ice bath. An aliquot of TMSOTf (100 uL, 0.006 mmol) generated from TMSOTf (17 μL) in CH_2Cl_2 (1 mL) was added [16,

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30-34]. The bath was then removed. After 10 min, TLC (EtOAc/*n*-hexane 1:3) indicated the formation of the product **3** (R_f = 0.34) and the consumption of the donor **1** (R_f = 0.62). The mixture was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane = 1/3 to provide compound **3** in 85% yield (19 mg). The sample was further purified using HPLC with eluents of EtOAc/*n*-hexane = 3/7. t_R = 15.88 min. Anal. $C_{61}H_{51}N_3O_{15}S$, M (calcd.) = 1097.3 (m/z), ESI + Q-TOF: M = 1097.3 (m/z), $[M + Na]^+$= 1120.3 (3.8%), 1121.3 (2.3%), equivalent to the calculated isotopic ratio 100:67; ^{1}H-NMR (500 MHz, C_6D_6) δ 2.06 (s, 3H, C$\underline{H}_3$, H_{SPhMe}), 2.57 (dd, 1H, $J_{6a',6b'}$ = 13.0, $J_{6a',5'}$ = 4.0 Hz, $H_{6a'(donor)}$), 2.93 (dd, 1H, $J_{6b',6a'}$ = 13.0, $J_{6b',5'}$ = 8.0 Hz, $H_{6b'(donor)}$), 3.29 (dd, 1H, $J_{5',6b'}$ = 8.0, $J_{5',6a'}$ = 4.0 Hz, $H_{5'(donor)}$), 3.67 (dd, 1H, $J_{5,6b}$ = 7.0, $J_{5,6a}$ = 5.0 Hz, $H_{5(acceptor)}$), 3.96 (dd, 1H, $J_{6b,6a}$ = 11.0, $J_{6b,5}$ = 7.0 Hz, $H_{6b(acceptor)}$), 4.01 (dd, 1H, $J_{6a,6b}$ = 11.0, $J_{6a,5}$ = 5.0 Hz, $H_{6a(acceptor)}$), 4.64 (d, 1H, $J_{1,2}$ = 10.0 Hz, $H_{1(acceptor)}$), 4.66 (d, 1H, $J_{1',2'}$ = 8.0 Hz, $H_{1'(donor)}$), 5.58 (dd, 1H, J_{AA} = 10.0, J_{AE} = 3.5 Hz, H_{Axial}), 5.63 (dd, 1H, J_{AE} = 10.0, J_{AE} = 3.5 Hz, H_{Axial}), 5.77 (d, 1H, J_{EA} = 3.5 Hz, $H_{Equatorial}$), 6.02 (d, 1H, J_{EA} = 3.5 Hz, $H_{Equatorial}$), 6.09 (dd, 1H, $J_{2,3}$ = 10.0, $J_{2,1}$ = 10.0 Hz, $H_{2(acceptor)}$), 6.26 (dd, 1H, $J_{2',3'}$ =10.0, $J_{2',1'}$ = 8.5 Hz, $H_{2'(donor)}$), 6.68 - 6.76 (m, 4H, H_{arom}), 6.80 - 6.86 (m, 2H, H_{arom}), 6.90 - 7.14 (m, 14H, H_{arom}), 7.68 (d, 2H, J = 7.5 Hz, H_{arom}), 7.92 - 7.96 (m, 2H, H_{arom}), 7.99 - 8.01 (m, 4H, H_{arom}), 8.08 - 8.10 (m, 2H, H_{arom}), 8.16 - 8.21 (m, 4H, H_{arom}); ^{13}C-NMR (125 MHz, C_6D_6) δ 21.15 (CH_3, C_{SPhMe}), 50.48 (CH_2), 67.82 (CH_2), 68.58 (CH), 69.13 (CH), 69.20 (CH), 70.35 (CH), 72.19 (CH), 73.23 (CH), 73.42 (CH), 77.06 (CH), 85.52 (CH), 101.19 (CH), 125.64 (CH, C_{arom}), 128.29 (CH, C_{arom}), 128.47 (CH, C_{arom}), 128.54 (CH, C_{arom}), 128.63 (CH, C_{arom}), 128.89 (CH, C_{arom}), 129.28 (CH, C_{arom}), 129.34 (C, C_{arom}), 129.43 (C, C_{arom}), 129.57 (C, C_{arom}), 129.86 (C, C_{arom}), 129.93 (CH, C_{arom}), 129.98 (CH, C_{arom}), 130.04 (C, C_{arom}), 130.16 (C, C_{arom}), 130.20 (C, C_{arom}), 130.31 (CH, C_{arom}), 132.98 (CH, C_{arom}), 133.09 (CH, C_{arom}), 133.20 (CH, C_{arom}), 133.54 (CH, C_{arom}), 135.17 (CH, C_{arom}), 138.61 (CH, C_{arom}), 165.35 (O$\underline{C}$O), 165.45 (O$\underline{C}$O), 165.58 (O$\underline{C}$O), 165.63 (O$\underline{C}$O), 165.74 (O$\underline{C}$O).

2.10. Preparation of 2,2',6,6'-tetra-O-benzoyl-3',4'-O-isopropylidene-1-(4-tolyl)thio-*β*-D-lactoside 13 and 2,2',3,6,6'-penta-O-benzoyl-3',4'-O-isopropylidene-1-(4-tolyl)thio-*β*-D-lactoside 14

To a mixture of **12** (1.2 g, 2.46 mmol), pyridine (17 mL) and toluene (22.9 mL) was added BzCl (2.4 mL, 19.7 mmol, 8 eq) at 0˚C. After removal of the ice bath, the mixture was stirred at rt for 30 min. TLC (MeOH/$CHCl_3$ = 1/9) indicated the consumption of **12** (R_f = 0.5) and the formation of a product mixture (R_f = 0.96). The reaction was quenched by addition of MeOH. TLC (EtOAc/*n*-hexane = 1/9) indicated that the mixture consists of two products *i.e.* product **13** (R_f = 0.19) and product **14** (R_f = 0.24). The mixture was concentrated under reduced pressure. The residue obtained was purified using column chromatography with gradients of EtOAc/*n*-hexane = 1/4 → EtOAc/*n*-hexane = 1/3 to afford product **13** in 38% yield (358 mg) and product **14** in 2% yield (47.1 mg) and a mixture of **13** and **14** (642 mg). The crude yield to compound **13** and **14** was 60% and 30%, respectively. Compound **13**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H, CH_3, $H_{isopropylidene}$), 1.58 (bs, 1H, H_{OH}), 1.61 (s, 3H, CH_3, $H_{isopropylidene}$), 2.16 (s, 3H, CH_3, H_{SPhMe}), 3.60 - 3.70 (m, 2H), 3.96 (dd, 1H, $J_{3,2}$ = 9.0, $J_{3,4}$ = 8.0 Hz, H_3), 4.16 (dd, 1H, J = 12.0, J = 4.5 Hz), 4.20 - 4.28 (m, 2H), 4.35 - 4.45 (m, 3H), 4.62 (d, 1H, $J_{1',2'}$ = 8.5 Hz, $H_{1'}$), 4.65 (d, 1H, $J_{1,2}$ = 10.5 Hz, H_1), 4.83 (dd, 2H, J = 12.5, J = 2.5 Hz), 5.12 (dd, 1H, $J_{2,3}$ = 9.0, $J_{2,1}$ = 10.5 Hz, H_2), 5.32 (dd, 1H, $J_{2',3'}$ = 7.5, $J_{2',1'}$ = 8.5 Hz, $H_{2'}$), 6.78 (d, 2H, J = 8.5 Hz), 7.11 - 7.47 (m, 12H), 7.52 - 7.61 (m, 2H), 7.85 (d, 2H, J = 7.0 Hz), 7.95 (d, 2H, J = 7.0 Hz), 8.02 (d, 2H, J = 8.5 Hz), 8.06 (d, 2H, J = 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.04 (CH_3), 26.27 (CH_3), 27.61 (CH_3), 62.59 (CH_2), 63.67 (CH_2), 71.47 (CH), 72.11 (CH), 73.07 (CH), 73.43 (CH), 74.92 (CH), 75.77 (CH), 77.00 (CH), 82.17 (CH), 85.63 (CH), 101.52 (CH), 111.29 (C, $C_{isopropylidene}$), 125.29 (CH, C_{arom}), 127.78 (C, C_{arom}), 128.21 (CH, C_{arom}), 128.32 (CH, C_{arom}), 128.33 (CH, C_{arom}), 128.84 (C, C_{arom}), 129.03 (C, C_{arom}), 129.06 (CH, C_{arom}), 129.39 (CH, C_{arom}), 129.69 (CH, C_{arom}), 129.75 (CH, C_{arom}), 129.80 (CH, C_{arom}), 129.95 (CH, C_{arom}), 130.04 (C, C_{arom}), 133.06 (CH, C_{arom}), 133.08 (CH, C_{arom}), 133.22 (CH, C_{arom}), 133.41 (CH, C_{arom}), 133.79 (CH, C_{arom}), 138.16 (C, C_{arom}), 165.19 (O$\underline{C}$O, C_{Bz}), 165.26 (O$\underline{C}$O, C_{Bz}), 165.44 (O$\underline{C}$O, C_{Bz}), 165.54 (O$\underline{C}$O, C_{Bz}). Compound **14**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 3H, CH_3, $H_{isopropylidene}$), 1.50 (s, 3H, CH_3, $H_{isopropylidene}$), 2.21 (s, 3H, CH_3, H_{SPhMe}), 3.62 (dd, 1H, J = 11.5, J = 7.5 Hz), 3.75 - 3.87 (m, 2H), 4.03 - 4.13 (m, 2H), 4.16 - 4.25 (m, 2H), 4.43 (dd, 1H, J = 12.0, J = 5.0 Hz), 4.55 (d, 1H, $J_{1',2'}$ = 8.0 Hz, $H_{1'}$), 4.62 (d, 1H, J = 10.5 Hz), 4.77 (d, 1H, $J_{1,2}$ = 9.5 Hz, H_1), 5.10 (dd, 1H, $J_{2',3'}$ = 7.5, $J_{2',1'}$ = 8.0 Hz, $H_{2'}$), 5.34 (dd, 1H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 10.0 Hz, H_3), 5.69 (dd, 1H, $J_{2,3}$ = 10.0, $J_{2,1}$ = 9.5 Hz, H_2), 6.78 (d, 2H, J = 7.5 Hz), 7.22 - 7.61 (m, 17H), 7.88 - 7.95 (m, 6H), 7.97 (d, 2H, J = 7.5 Hz), 8.04 (d, 2H, J = 7.0 Hz); ^{13}C-NMR (125 MHz, C_6D_6) δ 20.97 (CH_3), 26.33 (CH_3), 27.61 (CH_3), 62.94 (CH_2), 63.19 (CH_2), 71.00 (CH), 71.54 (CH), 73.49 (CH), 74.30 (CH), 74.35 (CH), 75.86 (CH), 76.98 (CH), 77.52 (CH), 85.78 (CH), 100.89 (CH), 110.84 (C, $C_{isopropylidene}$), 127.91 (CH, C_{arom}), 128.12 (CH, C_{arom}), 128.24 (CH, C_{arom}), 128.29 (CH, C_{arom}), 128.59 (CH, C_{arom}), 128.67 (CH, C_{arom}), 128.75 (CH, C_{arom}), 128.99 (CH, C_{arom}), 129.69 (CH, C_{arom}), 129.87 (CH, C_{arom}), 129.91 (CH, C_{arom}), 130.09 (CH,

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C_{arom}), 130.20 (CH, C_{arom}), 130.26 (C, C_{arom}), 133.43 (C, C_{arom}), 130.73 (C, C_{arom}), 130.76 (C, C_{arom}), 132.85 (CH, C_{arom}), 133.17 (CH, C_{arom}), 133.44 (CH, C_{arom}), 134.23 (CH, C_{arom}), 138.08 (C, C_{arom}), 164.96 (O$\underline{C}$O, C_{Bz}), 165.50 (O$\underline{C}$O, C_{Bz}), 165.87 (O$\underline{C}$O, C_{Bz}), 165.98 (O$\underline{C}$O, C_{Bz}).

2.11. 2,3,4,-tri-O-benzoyl-6-O-(tert-butyldimethylsilyl)-*β*-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-1-(4-tolyl)thio-*β*-D-glucopyranoside 16 and 2,3,4,-tri-O-benzoyl-6-O-(tert-butyldimethylsilyl)-*β*-D-galactopyranosyl-(1→4)-2,3-di-O-benzoyl-6-O-(tert-butyldimethylsilyl)-1-(4-tolyl)thio-*β*-D-glucopyranoside 17

To a mixture of *p*-tolyl-1-thio-*β*-D-lactose **15** (300 mg, 0.67 mmol), DMAP (59 mg, 0.42 mmol) and pyridine (3 mL) was added a solution of TBDMSCl (222 mg, 1.48 mmol) in CH_2Cl_2 (2 mL). The stirring was allowed for 20 h. Followed by cooling down with an ice bath, BzCl (3 mL, 5.36 mmol, 8 eq) was added. After 10 min, the ice bath was removed and the mixture was stirred for 30 min. The mixture was concentrated under reduced pressure. The residue obtained was purified using column chromatography with eluents of EtOAc/*n*-hexane = 1/9 to provide a mixture of compound **16** and compound **17** in 56% yield (448 mg) with a ratio of 2:1. Compound **16**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 6H, Si-(C$\underline{H}_3$)$_2$, H_{TBDMS}), 0.91 (s, 9H, C(C$\underline{H}_3$)$_3$, H_{TBDMS}), 2.31 (s, 3H, CH_3, H_{SPhCH3}), 3.39 (dd, 1H, $J_{6a,6b(gem)}$ = 10.0 Hz, H_{6a}), 3.54 (dd, 1H, $J_{6b',6a'(gem)}$ = 11.5, $J_{6b',5'}$ = 7.0 Hz, $H_{6b'}$), 3.72 - 3.82 (m, 2H, H_{6b} and H_5), 3.83 (dd, 1H, $J_{6a',6b(gem)}$ = 11.5, $J_{6a',5'}$ = 6.0 Hz, $H_{6a'}$), 3.97 (dd, 1H, $J_{5',6a'}$ = 6.0, $J_{5',6b'}$ = 7.0 Hz, $H_{5'}$), 4.22 (dd, 1H, $J_{4,3}$ = 9.5, $J_{4,5}$ = 9.5 Hz, H_4), 4.74 (d, 1H, $J_{1',2'}$ = 10.0 Hz, $H_{1'}$), 5.04 (d, 1H, $J_{1,2}$ = 8.0 Hz, H_1), 5.31 (dd, 1H, $J_{2',1'}$ = 10.0, $J_{2',3'}$ = 10.0 Hz, $H_{2'}$), 5.37 (dd, $J_{3',2'}$ = 10.0, $J_{3',4'}$ = 3.0 Hz, $H_{3'}$), 5.64 (dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.0 Hz, H_2), 5.69 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 9.5 Hz, H_3), 5.73 (d, 1H, $J_{4',3'}$ = 3.0 Hz, $H_{4'}$), 7.02 - 7.09 (m, 4H, H_{arom}), 7.24 - 8.08 (m, 30H, H_{arom}). Compound **17**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ −0.29 (s, 3H, Si-C$\underline{H}_3$, H_{TBDMS}), −0.20 (s, 3H, Si-C$\underline{H}_3$, H_{TBDMS}), 0.13 (s, 3H, Si-C$\underline{H}_3$, H_{TBDMS}), 0.14 (s, 3H, Si-C$\underline{H}_3$, H_{TBDMS}), 0.74 (s, 9H, C(C$\underline{H}_3$)$_3$, H_{TBDMS}), 0.99 (s, 9H, C(C$\underline{H}_3$)$_3$, H_{TBDMS}), 2.30 (s, 3H, CH_3, H_{SPhCH3}), 2.74 (dd, 1H, $J_{6b,6a(gem)}$ = 10.0, $J_{6b,5}$ = 9.5 Hz, H_{6b}), 3.21 (dd, 1H, $J_{6a,6b}$ = 10.0, $J_{6a,5}$ = 5.0 Hz, H_{6a}), 3.37 (d, 1H, J = 10.0 Hz) , 3.64 (ddd, 1H, J = 5.0, J = 9.5, J = 9.5 Hz, H_{5a}), 3.81 - 3.71 (m, 2H), 4.13 (dd, 1H, $J_{4,3}$ = 9.5, $J_{4,5}$ = 9.5 Hz, H_4), 4.73 (d, 1H, $J_{1',2'}$ = 10.0 Hz, $H_{1'}$), 4.94 (d, 1H, $J_{1,2}$ = 8.0 Hz, H_1), 5.29 (dd, 1H, $J_{2',1'}$ = 10.0, $J_{2',3'}$ = 10.0 Hz, $H_{2'}$), 5.37 (dd, $J_{3',2'}$ = 10.0, $J_{3',4'}$ = 3.0 Hz, $H_{3'}$), 5.57 (dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.0 Hz, H_2), 5.62 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 9.5 Hz, H_3), 5.73 (d, 1H, $J_{4',3'}$ = 3.0 Hz, $H_{4'}$), 7.02 - 8.08 (m, 29H, H_{arom}).

2.12. Preparation of 2,3,4,-tri-O-benzoyl-*β*-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-1-(4-tolyl)thio-*β*-D-glucopyranoside 18 and 2,3,4,-tri-O-benzoyl-*β*-D-galactopyranosyl-(1→4)-2,3-di-O-benzoyl-1-(4-tolyl)thio-*β*-D-glucopyranoside 19

To a mixture of **16** and **17** (448 mg, 0.37 mmol) and THF (5 mL) was added HF-pyridine (2.5 mL) and AcOH (3.5 mL), sequentially. The mixture was stirred for 30 min. The mixture was then partitioned between CH_2Cl_2 (25 mL) and saturated aqueous $NaHCO_3$ (7 mL). The organic layer was filtered through a celite pad. The filtrate was concentrated under reduced pressure. The residue obtained was purified using column chromatography with gradients of EtOAc/*n*-hexane = 1/9 → 1/4 to provide compound **18** and compound **19** in total 79% yield (286 mg). Compound **19**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.85 (bs, 2H, OH), 2.30 (s, 3H, CH_3, H_{SPhCH3}), 2.67 (dd, 1H, J = 12.5, J = 7.0 Hz), 2.84 (dd, 1 H, J = 12.0, J = 6.5 Hz), 3.68 - 3.74 (m, 2H), 3.80 (dd, 1 H, J = 12.5, J = 2.0 Hz), 4.16 (dd, 1H, $J_{4,3}$ = 9.5, $J_{4,5}$ = 9.5 Hz, H_4), 4.80 (d, 1H, $J_{1',2'}$ = 10.0 Hz, $H_{1'}$), 4.88 (d, 1H, $J_{1,2}$ = 8.0 Hz, H_1), 5.36 (dd, 1H, $J_{2',1'}$ = 10.0, $J_{2',3'}$ = 10.0 Hz, $H_{2'}$), 5.40 (dd, $J_{3',2'}$ = 10.0, $J_{3',4'}$ = 3.0 Hz, $H_{3'}$), 5.54 (d, 1H, $J_{4',3'}$ = 3.0 Hz, $H_{4'}$), 5.63 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 9.5 Hz, H_3), 5.71 (dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.0 Hz, H_2), 7.01 - 8.20 (m, 29H, H_{arom}). Structure of compound **18** was indirectly confirmed from the following trisaccharide **3**.

2.13. 2,3,4-tri-O-benzoyl-6-deoxy-6-azido-*β*-D-galactopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-*β*-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-1-(4-tolyl)thio-*β*-D-glucopyranoside 4 and 2,3,4-tri-O-benzoyl-6-deoxy-6-azido-*β*-D-galactopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-*β*-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-benzoyl-6-deoxy-6-azido-*β*-D-galactopyranosyl]-(1→6)-2,3-di-O-benzoyl-1-(4-tolyl)thio-*β*-D-glucopyranoside 4

A mixture of crude compounds **18** and **19** (50 mg, 0.046 mmol, 0.6 eq) and the donor **1** (50 mg, 0.075 mmol) were distilled azeotropically using toluene at 50˚C for three times, which was followed by concentration under reduced pressure for 1 h. The mixture was transferred to a two-necked round-bottom flask charging with CH_2Cl_2 (5 mL), followed by a stirring at rt for 30 min. After cooling down with an ice bath, an aliquot of TMSOTf (100 μL, equivalent to 0.015 mmol), generated from TMSOTf (30

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μL) in CH_2Cl_2 (1 mL), was added. After removal of the bath, the mixture was stirred at rt for 10 min. TLC (EtOAc/*n*-hexane 1:1) indicated the formation of product **3** (R_f = 0.70) and product **4** (R_f = 0.80) and the consumption of the donor **1** (R_f = 0.82). After concentration under reduced pressure, the residue was purified using column chromatography with eluents of EtOAc/*n*-hexane = 3.5/6.5 to provide compound **3** (35 mg) and compound **4** (22 mg) in a total yield of 70%. The samples were further purified using HPLC with eluents of EtOAc/*n*-hexane = 3/7 to afford compound **4** at t_R of 15.2 min and compound **3** at t_R of 18.0 min, respectively. Compound **3**: ^{1}H-NMR (500 MHz, C_6D_6) δ 1.98 (s, 3H, C$\underline{H}_3$, H_{SPhMe}), 2.66 (dt, 1H, J = 11.5, J = 7.0 Hz), 2.82 - 2.94 (m, 2H), 3.06 (dd, 1H, J = 10.0, J = 3.5 Hz), 3.31 - 3.42 (m, 3H), 3.95 (dd, 1H, $J_{(gem)}$ = 12.0, J = 4.0 Hz, CHC$\underline{H}_2$), 4.03 (d, 1H, $J_{(gem)}$ = 11.0 Hz, CHC$\underline{H}_2$), 4.30 (dd, 1H, $J_{4,3}$ = 9.0, $J_{4,2}$ = 9.0 Hz, $H_{4(Glc)}$), 4.49 (d, 1H, J = 10.0 Hz, $H_{anomeric}$), 4.80 (d, 1H, J = 8.0 Hz, $H_{anomeric}$), 4.97 (d, 1H, J = 8.0 Hz, $H_{anomeric}$), 5.56 (dd, 1H, J = 10.5, J = 3.5 Hz, $H_{3(Gal)}$), 5.72 (dd, 1 H, J = 10.0, J = 3.5 Hz, $H_{3(Gal)}$), 5.77 (dd, 1 H, J = 10.0, J = 9.5 Hz, $H_{2(Gal)}$), 5.78 (d, 1H, J = 3.5 Hz, $H_{4(Gal)}$), 5.82 (dd, 1 H, J = 9.0, J = 8.5 Hz, $H_{3(Glc)}$), 5.85 (d, 1 H, J = 3.5 Hz, $H_{4(Gal)}$), 6.22 (dd, 1H, J = 10.0, J = 8.5 Hz), 6.29 (dd, 1H, J = 10.5, J = 8.0 Hz), 6.68 - 7.19 (m, 31H, H_{arom}), 7.55 (d, 2H, J = 8.0 Hz, H_{arom}), 7.92 - 8.03 (m, 6H, H_{arom}), 8.08 - 8.28 (m, 10H, H_{arom}); ^{13}C-NMR (500 MHz, C_6D_6) δ 20.93 (CH_3), 51.02 ($N_3\underline{C}H_2$), 60.04 (CH_2), 68.81 (CH), 68.98 (CH_2), 69.35 (CH), 70.81 (CH), 70.89 (CH), 71.40 (CH), 72.16 (CH), 72.65 (CH), 73.55 (CH), 74.10 (CH), 75.23 (CH), 75.85 (CH), 78.65 (CH), 86.07 (CH), 101.07 (CH), 102.39 (CH), 125.64 (CH, C_{arom}), 127.80 (CH, C_{arom}), 127.91 (C, C_{arom}), 128.09 (C, C_{arom}), 128.29 (CH, C_{arom}), 128.43 (CH, C_{arom}), 128.52 (CH, C_{arom}), 128.69 (CH, C_{arom}), 128.85 (CH, C_{arom}), 128.99 (CH, C_{arom}), 129.13 (CH, C_{arom}), 129.25 (CH, C_{arom}), 129.36 (C, C_{arom}), 129.44 (C, C_{arom}), 129.78 (C, C_{arom}), 129.89 (CH, C_{arom}), 129.94 (CH, C_{arom}), 129.96 (CH, C_{arom}), 130.01 (CH, C_{arom}), 130.07 (CH, C_{arom}), 130.12 (CH, C_{arom}), 130.15 (CH, C_{arom}), 130.29 (CH, C_{arom}), 130.31 (CH, C_{arom}), 130.67 (C, C_{arom}), 132.74 (CH, C_{arom}), 133.02 (CH, C_{arom}), 133.11 (CH, C_{arom}), 133.31 (CH, C_{arom}), 133.41 (CH, C_{arom}), 133.44 (CH, C_{arom}), 133.63 (CH, C_{arom}), 133.69 (CH, C_{arom}), 134.14 (CH, C_{arom}), 138.40 (C, C_{arom}), 165.27 (O$\underline{C}$O), 165.57 (O$\underline{C}$O), 165.71 (O$\underline{C}$O), 165.69 (O$\underline{C}$O), 165.78 (O$\underline{C}$O), 165.85 (O$\underline{C}$O), 166.33 (O$\underline{C}$O). Compound **4**: Anal. $C_{108}H_{90}N_6O_{29}S$, M (calcd.) = 1967.55065 (100.0%), 1966.54730 (83.2%), 1968.55401 (59.5%), 1969.55736 (23.4%), 1970.56072 (6.8%), 1969.55490 (5.8%), 1968.55154 (4.8%), 1969.54645 (4.4%), 1968.54309 (3.7%), 1970.55825 (3.5%), 1970.54980 (2.6%), 1968.54769 (2.2%), 1967.54433 (1.9%), 1971.56407 (1.6%), 1971.56161 (1.4%), 1968.55683 (1.4%), 1969.55104 (1.3%), 1968.55487 (1.2%), 1967.55347 (1.1%), 1971.55316 (1.0%) (m/z), MALDI-Tof: M = 1966.5 (m/z), $[M + Na]^+$= 1989.3; ^{1}H-NMR (500 MHz, C_6D_6) δ 1.98 (s, 3H, C$\underline{H}_3$, H_{SPhCH3}), 2.66 (dd, 1H, $J_{(gem)}$ = 13.0, J = 7.0 Hz), 2.72 - 2.79 (m, 2H), 2.83 (dd, 1 H, J = 10.0 J = 4.5 Hz), 3.05 - 3.12 (m, 1H), 3.16 (t, 1H, J = 9.0 Hz), 3.21 (t, 1H, J = 6.0 Hz), 3.25 - 3.35 (m, 2H), 3.39 (dd, 1H, J = 8.5, 5.0 Hz), 3.90 (dd, 1H, $J_{(gem)}$ = 11.0, J= 4.0 Hz), 4.06 (d, 1H, J = 10.5 Hz), 4.12 (d, 1H, J = 8.0 Hz, $H_{anomeric}$), 4.13 (t, 1H, J = 10.0, 10.0 Hz, $H_{4(Glc)}$), 4.50 (d, 1H, J = 9.5 Hz, $H_{anomeric}$), 4.71 - 4.79 (m, 2H, $H_{anomeric}$), 5.52 (dd, 1H, J_{AA} = 10.5, J_{AE} = 3.5 Hz, H_{Axial}), 5.61 (dd, 1H, J_{AA} = 10.5, J_{AE} = 4.0 Hz, H_{Axial}), 5.69 (t, 1H, J_{AA} = 9.5, J_{AA} = 9.5 Hz, H_{Axial}), 5.69 (dd, 1H, J_{AA} = 10.5, J_{AE} = 4.0 Hz, H_{Axial}), 5.82 (d, 1H, J_{EA} = 3.0 Hz, $H_{Equatorial}$), 5.86 (t, 1H, J_{AA} = 9.0, J_{AA} = 9.0 Hz, H_{Axial}), 5.87 (d, 1H, J_{EA} = 3.0 Hz, $H_{Equatorial}$), 6.06 (dd, 1 H, J_{AA} = 10.0, J_{AA} = 7.5 Hz, H_{Axial}), 6.10 (d, 1 H, J_{EA} = 3.0 Hz, $H_{Equatorial}$), 6.11 (dd, 1H, J_{AA} = 10.5, J_{AA} = 8.0 Hz, H_{Axial}), 6.27 (dd, 1H, J_{AA} =10.5, J_{AA} =8.0 Hz, H_{Axial}), 6.68 - 7.14 (m, 37H, H_{arom}), 7.57 (d, 2H, J = 8.0 Hz, H_{arom}), 7.96 - 8.26 (m, 20H, H_{arom}); ^{13}C-NMR (125 MHz, C_6D_6) δ 20.94 (CH_3), 49.89 ($N_3\underline{C}H_2$), 50.97 ($N_3\underline{C}H_2$), 66.12 (CH_2), 67.87 (CH), 68.25 (CH_2), 68.53 (CH), 69.40 (CH), 70.46 (CH), 70.58 (CH), 71.05 (CH), 71.35 (CH), 71.69 (CH), 72.13 (CH), 72.23 (CH), 72.37 (CH), 73.58 (CH), 75.27 (CH), 76.66 (CH), 78.43 (CH), 85.94 (CH), 100.98 (CH), 101.54 (CH), 102.12 (CH), 125.64 (C, C_{arom}), 128.45 (CH, C_{arom}), 128.50 (CH, C_{arom}), 128.63 (CH, C_{arom}), 128.68 (CH, C_{arom}), 128.86 (CH, C_{arom}), 128.90 (CH, C_{arom}), 129.12 (CH, C_{arom}), 129.28 (CH, C_{arom}), 129.32 (C, C_{arom}), 129.41 (C, C_{arom}), 129.68 (C, C_{arom}), 129.74 (C, C_{arom}), 129.96 (CH, C_{arom}), 130.06 (CH, C_{arom}), 130.19 (CH, C_{arom}), 130.26 (CH, C_{arom}), 130.41 (CH, C_{arom}), 130.98 (C, C_{arom}), 132.52 (CH, C_{arom}), 133.02 (CH, C_{arom}), 133.19 (CH, C_{arom}), 133.26 (CH, C_{arom}), 133.31 (CH, C_{arom}), 133.55 (CH, C_{arom}), 133.94 (CH, C_{arom}), 134.22 (CH, C_{arom}), 138.37 (C, C_{arom}), 165.24 (O$\underline{C}$O), 165.28 (O$\underline{C}$O), 165.36 (O$\underline{C}$O), 165.47 (O$\underline{C}$O), 165.54 (O$\underline{C}$O), 165.61 (O$\underline{C}$O), 165.77 (O$\underline{C}$O), 165.81 (O$\underline{C}$O).

3. Results and Discussion

Preparation of the imidate **1** was accomplished by using a common protocol via first deprotection of the anomeric hydroxy group of the thioglycoside **7** followed by introduction of the trichloroacetamide (**Scheme 1**) [28]. Acceptor **8** was obtained from 4-amino-1-butanol via a diazo transfer reaction [29]. The subsequent glycosylation for the donor **1** and acceptor **8**, deprotection of the hydroxy groups and reduction of both amino groups of glycosylated product **9** proceeded effortlessly. The desired amino sugar **2** could be prepared in an acceptable

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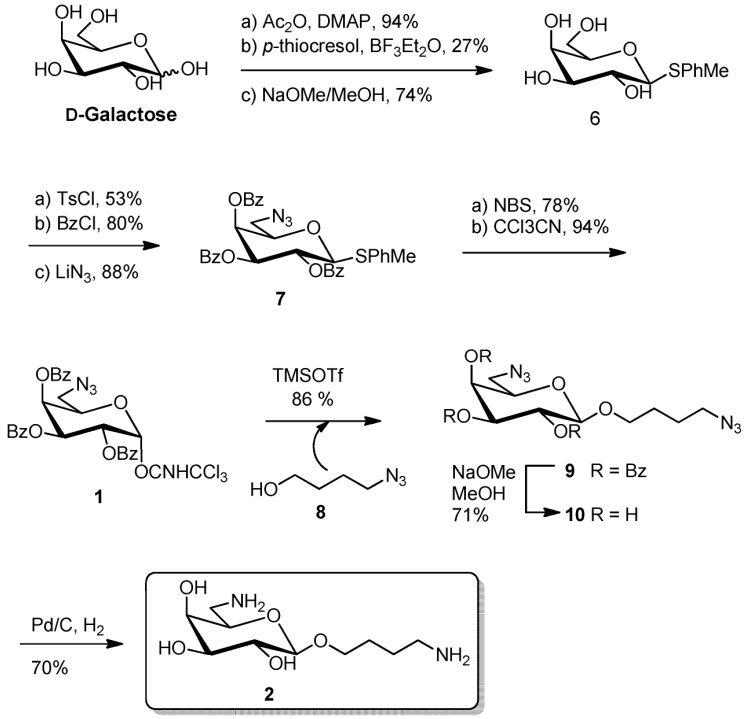
yield.

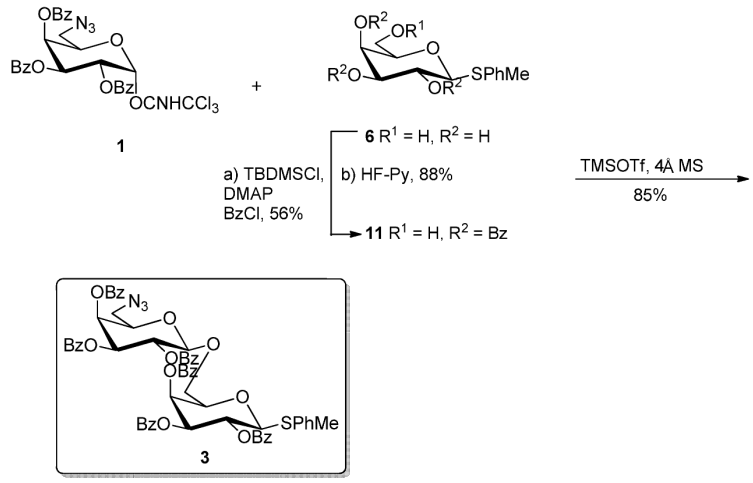
Encouraged by the success of the glycosylation of employing the primary hydroxy acceptor **8** (**Scheme 1**), the benzoyl protected thioglycoside **11** with a free primary 6-OH group was prepared (**Scheme 2**). Glycosylation proceeded smoothly.

The disaccharide **3**, however, would not be suitable as a donor for subsequent glycosylation due to the presence of fully ester-protected electronwithdrawing groups. It has been recently reported that a donor needs to be activated by substitution with at least two ether-type protecting groups to ensure a chemoselective glycosylation [35]. Hence, preparation of a trisaccharide by employing current disaccharide **3** as a donor would encounter the same problem. Using the disaccharide **13** as an acceptor and the imidate **1** as the donor might be an alternative solution (**Scheme 3**). Preparation of acceptor **13** starting from lactose could be performed uneventfully (**Scheme 3**). The spectroscopic data of compound **14** matched the reported data [41]. However, either the imidate **1** or the thiosugar **7** failed to glycosylate with the lactosyl acceptor **13** (**Scheme 4**).

This might be caused by both less reactivity and steric hindrance of the secondary hydroxy group. Therefore, a



Scheme 1. Use of the building block 1 to generate diamino galactose analog 2.



Scheme 2. Disaccharide 3 derived from core compound 1.

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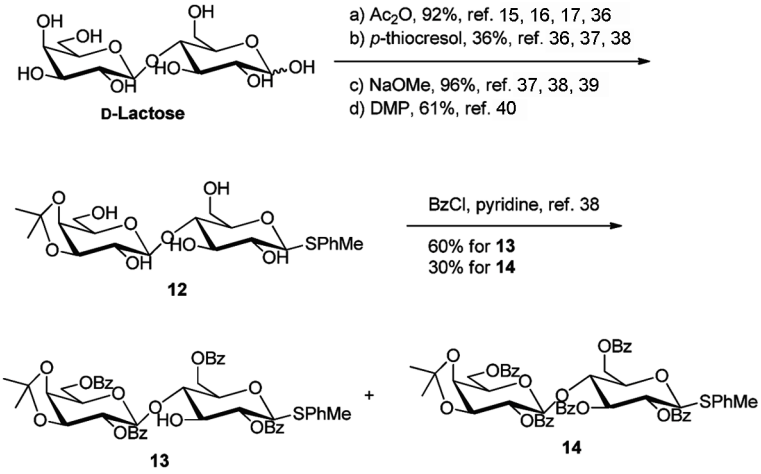
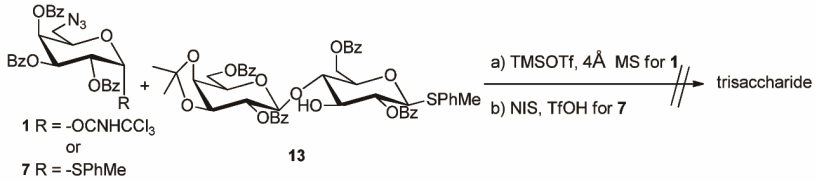
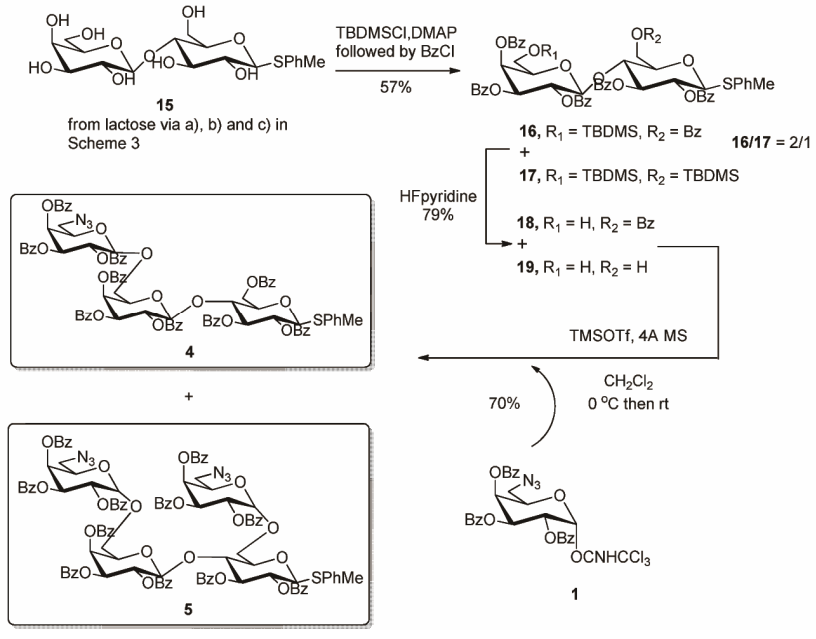
more reactive and less steric hindered acceptor needs to be generated to match the reactivity of the imidate **1** (**Scheme 5**). The lactosyl thioglycoside **15** was chosen as the starting material. The 6-OH group (s) of compound **15** was firstly protected by using TBDMS group, followed by benzoylation of the rest secondary hydroxy groups in a one-pot manner. The mixture of mono TBDMS-protected product **16** and di-TBDMS protected product **17** were not intended to isolate. Followed by subsequent deprotection using HF-pyridine, a mixture of the monohydroxy product **18** and dihydroxy product **19** were obtained. To our purpose, instead of the isolation of



Scheme 3. Preparation of the lactosyl analog 13 that bears a secondary OH can act as an acceptor.



Scheme 4. Unmatched reactivity between the disaccharide 13 and the two azido donors 1 and 7.



Scheme 5. Trisaccharide 4 and tetrasaccharide 5 were obtained from a glycosylation of a mixture of disaccharides containing mono- and di-hydroxy groups, 18, 19.

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the two acceptors, the mixture as a whole was glycosylated with the imidate **1**. The desired tri- and tetrasaccharides could then be prepared and the subsequent isolation using HPLC proceeded uneventfully.

The stereochemistry of glycosidic bonds of monosaccharide **2**, disaccharide **3** and trisaccharide **4** was identified as β-conformation as evidenced from the coupling constant ranging from J = 8.0 to 10.0 Hz by ^{1}H-NMR spectroscopy. The data matched the literature [30-34].

4. Conclusion

In brief, the current glycosylation strategy by using 6-azido galactosyl imidate **1** as a donor and the 6-OH bearing saccharides as acceptors were capable of generating the azido-bearing oligosaccharides for subsequent elaboration to glycoconjugates. When obtaining the conjugates, the amino groups will be reduced. The subsequent amide conjugation and the bioactivity screening could then be forwarded.

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