

Low-Concentration 1,2-*trans* β -Selective Glycosylation Strategy and Its Applications in Oligosaccharide Synthesis

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Dedicated to Professor Hak-Fun Chow

Abstract: This study develops an operationally easy, efficient, and general 1,2-*trans* β -selective glycosylation reaction that proceeds in the absence of a C2 acyl function. This process employs chemically stable thioglycosyl donors and low substrate concentrations to achieve excellent β -selectivities in glycosylation reactions. This method is widely applicable to a range of glycosyl

substrates irrespective of their structures and hydroxyl-protecting functions. This low-concentration 1,2-*trans* β -selective glycosylation in carbohy-

Keywords: carbohydrates • glycosylation • neighboring-group effects • stereoselectivity • substrate concentration

drate chemistry removes the restriction of using highly reactive thioglycosides to construct 1,2-*trans* β -glycosidic bonds. This is beneficial to the design of new strategies for oligosaccharide synthesis, as illustrated in the preparation of the biologically relevant β -(1 $\rightarrow$ 6)-glucan trisaccharide, β -linked Gb₃ and isoGb₃ derivatives.

Introduction

Though researchers developed the first glycosylation more than a century ago, the seamless union of the glycosyl donor and acceptor in *O*-glycosidic bond formation remains a formidable challenge.^[1] A point in case is the construction of 1,2-*trans* β -glycosidic bonds, which have long been dominated by the C2 neighboring-group participation strategy.^[2] Because of the participation mechanism, this strategy occasionally suffers from side effects such as orthoester formation,^[3] C2 acyl migration to the hydroxy function,^[4] and aglycon transfer reaction.^[4b,5] Under these circumstances, the glycosylation yield is reduced. These issues can be alleviated by employing benzoyl^[6] and pivaloyl functions.^[7] An alternative approach to address this problem is to use 1,2-*trans* β -selective glycosylation methods, which do not need the C2 acyl functions. Though researchers have developed various 1,2-*trans* β -selective glycosylation methods and some of these

methods exhibit excellent β -selectivities in glycosylation reactions,^[8–13] their use in oligosaccharide synthesis remains scarce.^[12c] This is not surprising because most of these methods suffer from stringent requirements for the structures and hydroxy-protecting functions of the glycosyl donors. This lack of flexibility severely limits the scope of the application of such methods. Therefore a general, high-yielding and operationally easy 1,2-*trans* β -selective glycosylation that does not invoke neighboring-group participation is highly desired.

In the light of the discussion above, this study describes, for the first time, the low-concentration 1,2-*trans* β -selective glycosylation process. This method employs easily available and stable thioglycosides as glycosyl donors for glycosylation and does not require any C2 participating groups or the use of special anomeric functions. This study also demonstrates the proposed glycosylation method in the facile preparation of β -(1 $\rightarrow$ 6)-glucan trisaccharide,^[14] Gb₃,^[15] and isoGb₃ derivatives.^[16]

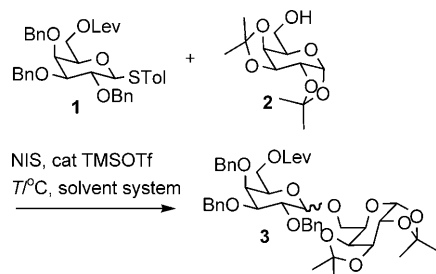
Results and Discussion

Invention of the low-concentration 1,2-*trans* β -selective glycosylation: In an experiment investigating the nitrile solvent effect on the stereochemical outcomes of glycosylation,

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commercially available galactopyranose acceptor **2** was coupled with 2,3,4-tri-*O*-benzyl-6-*O*-levulinoyl β -D-thiogalactopyranoside (**1**)^[17] in CH_2Cl_2 (solvent A), 1:3 CH_2Cl_2 – CH_3CN (solvent B) and 1:3 CH_2Cl_2 –EtCN (solvent C; Scheme 1 and Table 1). *N*-Iodosuccinimide and trimethylsilyl trifluoromethanesulfonate were employed as promoters for the activation of thioglycoside.^[18]



Scheme 1. Glycosylations of galactopyranose acceptor **2** with thiogalactopyranoside **1**.

Table 1. Glycosylations of galactopyranose acceptor **2** with thiogalactopyranosyl donor **1** under different reaction conditions.

Entry	[1] mM	[2] mM	Solvent ^[a]	<i>T</i> [°C]	Yield [%] (α/β) ^[b]
1	120	100	A	–55	75 (1:1.6)
2	240	120	B	–55	83 (1: 6)
3	120	100	B	–55	80 (1:9)
4	60	50	B	–55	84 (1:10)
5	12	10	B	–55	83 (1:13)
6	12	10	B	–70	84 (1:19)
7	120	100	A	–75	78 (1:4)
8	240	120	C	–75	75 (1: 6)
9	120	100	C	–75	81 (1:9)
10	60	50	C	–75	81 (1:12)
11	12	10	C	–75	70 (1:16)
12	12	10	D	–70	81 (1:19)
13	12	10	D ^[c]	–70	81 (1:19)

[a] Solvent system: A = CH_2Cl_2 ; B = 1:3 v/v CH_2Cl_2 – CH_3CN ; C = 1:3 v/v CH_2Cl_2 –EtCN and D = 1:2:1 v/v CH_2Cl_2 – CH_3CN –EtCN. [b] α/β Anomeric ratio was determined by HPLC analysis of crude product mixture. [c] Inverse addition of **1** and **2** to NIS and TMSOTf in 1:2:1 CH_2Cl_2 – CH_3CN –EtCN solution at -70°C . Bn = benzyl, Lev = levulinoyl, TMSOTf = trimethylsilyltriflate, Tol = toluene.

As expected, glycosylations in both the CH_2Cl_2 – CH_3CN and CH_2Cl_2 –EtCN solvent mixture afforded a 1:9 α/β -anomeric ratio of glycosylation product **3** based on the presumably nitrile solvent effect.^[12b–d] However, this level of β -selectivity in glycosylation is insufficient for state-of-the art sequential glycosylation technologies, including the automated solid phase synthesis, various one-pot glycosylation strategies, and others.^[1c,19–21] These technologies demand highly efficient couplings in each single step. A review of the literature revealed that electrochemical glycosylations in diluted solutions (10 mM of thioglycoside) yield nearly exclusive formation of β -glycosylating products.^[22] On the other hand, routine glycosylations are normally performed at a glycosyl substrate concentration between 30 and 100 mM (Table 2).^[8 d,9a,12e,23,24] Though a preliminary study concerned with the

Table 2. Concentration of glycosyl donor and acceptor used in routine glycosylations.

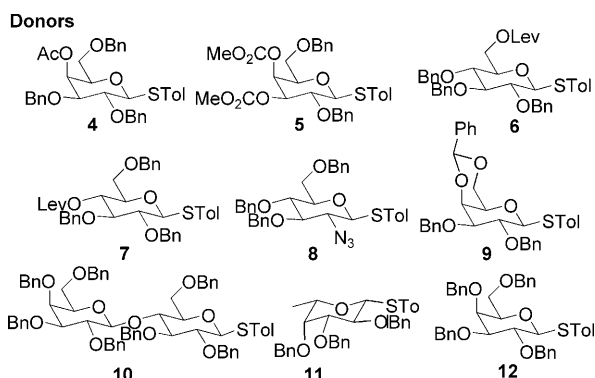
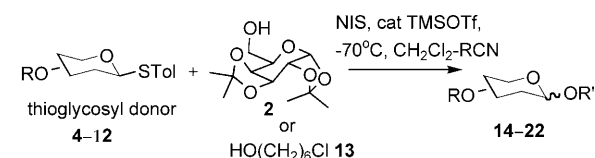
Entry	Donor [mM]	Acceptor [mM]	Solvent	Reference
1	70	75	CH_2Cl_2 or CH_3CN	[8a]
2	66	73	EtCN	[11e]
3	220	170	CH_2Cl_2 or CH_3CN	[22]
4	100	150	CH_2Cl_2	[7d]
5	27	80	CH_2Cl_2 – CH_3CN	[9b]
6	64	32	EtCN	[23]
7	150	195	CH_2Cl_2	[12]

concentration effect on α -selective glycosylation has been reported, there have been no empirical studies concerning the effect of substrate concentration on β -selective glycosylation.^[25] This lack in the literature motivated the current study to investigate this unexplored area.

Thus, this study repeated glycosylations of **2** with **1** at different substrate concentrations. All glycosylations were completed cleanly within 15–20 min. This fast glycosylation can be attributed to the absence of the disarming C2 acyl function.^[26] Interestingly, a decrease in substrate concentration accompanies an increase in the formation of the β -anomer. To be specific, when the concentrations of **1** decreased from 240 to 12 mM in 1:3 CH_2Cl_2 – CH_3CN mixture (solvent B), the α/β -anomeric ratios of **3** increased from 1:6 to 1:13 (Table 1, entries 2–5). Further improvement in the β -selectivity of glycosylation was achieved by simply lowering the reaction temperature to -70°C , which produced a 1:19 α/β -anomeric ratio (Table 1, entry 6). Considering that the eutectic temperature of the 1:3 CH_2Cl_2 – CH_3CN solvent mixture (ca. -72°C) is close to the reaction temperature (-70°C), the reaction solutions may freeze.^[27] Therefore, this study repeated the glycosylation reaction in 1:2:1 CH_2Cl_2 – CH_3CN /EtCN mixture (solvent D),^[28] which to our delight, did not erode the β selectivity observed in glycosylation (Table 1, entry 12).

In typical glycosylation reactions, reaction promoters are added to a mixture of glycosyl donor and acceptors. Schmidt and Toepfer and the others adopted an inverse addition procedure in which glycosyl donor is added to a mixture of acceptor and promoters.^[29a] It was reasoned that adding a mixture of donor and acceptor to promoters should presumably provide lower initial substrate concentrations, which may further improve the β -selectivity in glycosylation. To this end, a mixture of donor **1** and acceptor **2** was added to the promoters over 30 minutes at -70°C , however, an improvement in β -selectivity was not observed (Table 1, entry 12). This result is different from subsequent cases.

Scope and limitations of the low-concentration 1,2-*trans* β -selective glycosylation: After exploring the low-concentration 1,2-*trans* β -selective glycosylation process, this study next examined the scope and limitations of this method. Thioglycosides **4**–**12** were employed as glycosyl donors for the glycosylation of acceptors **2** and **13** (Scheme 2 and Table 3).^[17] For comparison, the glycosylation reaction was



Scheme 2. Thioglycosyl donors **4–12** for the study of low-concentration 1,2-*trans* β -selective glycosylation.

Table 3. Results of the low-concentration 1,2-*trans* β -selective glycosylations of acceptors **2** and **3** with different thioglycosyl donors **4–12**.

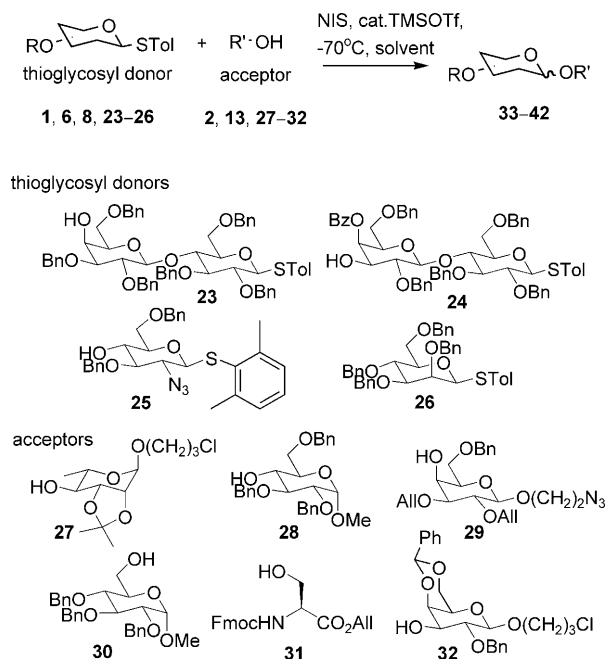
Entry	12 mm donor	10 mm acceptor	Product	Yield [%] (α/β) ^[a]	Yield [%] (α/β) ^[a,b]
1	4	2	14	85 (1:33) ^[c]	83 (1:2)
2	5	2	15	70 (1: $\geq$ 49) ^[c]	67 (1:2)
3	6	2	16	77 (1: $\geq$ 49) ^[d]	73 (1:1)
4	7	2	17	83 (1:19) ^[d]	77 (1:8)
5	8	2	18	83 (1: $\geq$ 49) ^[c]	85 (1:2.5)
6	9	2	19	75 (1:9) ^[c]	75 (1:6)
7	9	2	19	83 (1:19) ^[c,e]	not done
8	10	2	20	75 (β only) ^[c]	75 (1:6)
9	11	13	21	80 (1:49) ^[c]	80 (1:4)
10	12	13	22	85 (1: $\geq$ 49) ^[c]	88 (1:4)

[a] α/β -Anomeric ratio was determined by HPLC analysis. [b] Glycosylations in CH_2Cl_2 with 120 mm of thioglycosyl donor and 100 mm of acceptor at -55°C . [c] Glycosylations in 1:3 v/v $\text{CH}_2\text{Cl}_2\text{-CH}_3\text{CN}$ with 12 mm of thioglycosyl donor and 10 mm of acceptor at -70°C . [d] Glycosylations in 1:2:1 v/v $\text{CH}_2\text{Cl}_2\text{-CH}_3\text{CN-EtCN}$ with 12 mm of thioglycosyl donor and 10 mm of acceptor at -70°C . [e] For this particular reaction, 6 mm of thioglycosyl donor **9** and 5 mm of acceptor **2** were used.

performed under both low-concentration 1,2-*trans* β -selective and conventional glycosylation conditions.

Remarkably, the low-concentration β -selective glycosylation for thioglycosyl donors in the *D*-gluco (**6**, **7**, **8**), *D*-galacto (**4**, **5**, **9**, and **12**), *D*-lacto (**10**), and *L*-fuco (**11**) series produced excellent β -selectivities and the resulting α/β -anomeric ratios ranged from 1:9 to 1: $\geq$ 49. An additional advantage of this method is its tolerance to different hydroxy-protecting functions, as evidenced by the glycosylation reactions with thiogalactopyranosides **1**, **4**, **5**, **9**, and **12** (Table 1 and Table 3, entries 1, 2, 6–7, and 10). Although 4,6-*O*-benzylidene thiogalactopyranosyl acetal **9** is generally considered as an α -directing glycosyl donor,^[30] the glycosylation of acceptor **2** with **9** under low-concentration conditions resulted in the predominant formation of the β -anomer (Table 3, entries 6, 7).

Encouraged by these preliminary results, we extended the scope of this study to more diverse glycosyl substrates. Thus β -D-thiolactosides (**23**, **24**), 2-azido-2-deoxy- β -D-thioglucopyranoside **25**, and β -D-thiomannopyranoside **26** prepared by standard methods were used for glycosylation of acceptors (Scheme 3 and Table 4).^[17,31] With the exception of gly-



Scheme 3. Glycosyl donors **23–26** and acceptors **27–32** for the extended investigation of the low-concentration 1,2-*trans* β -selective glycosylation.

Table 4. Results of the extended investigation of low-concentration 1,2-*trans* β -selective glycosylation.

Entry	12 mm donor	10 mm acceptor	Product	Yield [%] (α/β) ^[a,c]	Yield [%] (α/β) ^[b,c]
1	1	27	33	65 (1:49)	64 (1:1)
2	1	28	34	63 (1: $\geq$ 49)	60 (1:8)
3	1	29	35	60 (β only)	not done
4	6	30	36	83 (1: $\geq$ 49)	80 (1:2)
5	1	31	37	73 (1: $\geq$ 49)	75 (19:1)
6	8	32	38	77 (1:32)	78 (1:7)
7	23	13	39	80 (β only) ^[d]	77 (1:3)
8	24	13	40	83 (1: $\geq$ 49) ^[d]	not done
9	25	13	41	60 (1: $\geq$ 49)	not done
10	26	2	42	85 (3:1)	not done

[a] Glycosylation in 1:2:1 v/v $\text{CH}_2\text{Cl}_2\text{-CH}_3\text{CN-EtCN}$ mixture at -70°C with 12 mm of thioglycosyl donor and 10 mm of acceptor. [b] Glycosylation in CH_2Cl_2 at -55°C with 120 mm of thioglycosyl donor and 100 mm of acceptor. [c] α/β -Anomeric ratio was determined by HPLC analysis. [d] Two equivalents of acceptor was used to prevent self-condensation.

cosylation with thiomannopyranoside **26**, all reactions produced excellent β -selectivities in the glycosylation reactions, with α/β -anomeric ratios ranging from 1:32 to β -exclusive. The glycosylations of acceptors **27**, **28**, **29**, and **32** are typical examples (Table 4, entries 1–3 and 6). Though all these acceptors contain the sterically hindered hydroxyl function,

the corresponding glycosylations yielded β -anomers as the sole isomeric products.^[32] These results reveal the synthetic utility of this novel method because disaccharides **36** and **38** constitute the essential components in the cell wall of *Saccharomyces cerevisiae*^[14] and the type-2 backbone in blood-group determinants, respectively.^[33]

Figure 1 presents a dramatic set of data for the glycosylations of *N*^α-Fmoc serine allyl ester **31** (Fmoc = 9-fluorenylmethoxycarbonyl) with thiogalactopyranoside **1**. The glyco-

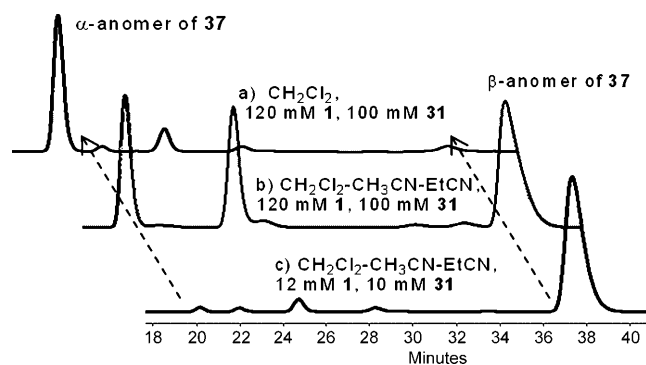


Figure 1. HPLC traces for glycosylations of *N*-Fmoc serine ester **31** with thiogalactopyranoside **1** under different conditions: a) conventional glycosylation conditions in CH_2Cl_2 and b) conventional glycosylation conditions in 1:2:1 v/v CH_2Cl_2 - CH_3CN - EtCN mixture; and c) low-concentration 1,2-*trans* β -selective glycosylation conditions in 1:2:1 v/v CH_2Cl_2 - CH_3CN - EtCN mixture.

sylation of aglycon acceptor **31** with thioglycoside **1** in CH_2Cl_2 under conventional conditions produced the α -anomer of **37** as the major isomer (Figure 1, HPLC trace a). Even when the same glycosylation was performed in a 1:2:1 CH_2Cl_2 / CH_3CN / EtCN mixture, only marginal β -selectivity in glycosylation was observed under conventional glycosylation conditions (Figure 1, HPLC trace b). In sharp contrast, the application of low-concentration 1,2-*trans* β -selective glycosylation led to nearly exclusive formation of the β -anomer (Figure 1, HPLC trace c).

Mechanistic insight of the low-concentration 1,2-*trans* β -selective glycosylation: To gain insight into the mechanisms of the present glycosylation, this study further investigates which particular substrate concentration is most closely related to the β -selectivity observed. Thus, 10 mM of acceptor **2** was glycosylated with different concentrations of thiogalactopyranoside **1** and *N*-iodosuccinimide (NIS; concentration range of 12–60 mM). Plotting the percentage of the α -anomer of **3** obtained against the concentration of donor **1** revealed a concentration-dependent relationship (Figure 2). Meanwhile, no significant change in β -selectivity was noted for glycosylation of 60 mM of acceptor **2** with 10 mM of donor **1**. This finding confirmed the substantial role of low thioglycoside concentration that is present in 1,2-*trans* β -selective glycosylation.

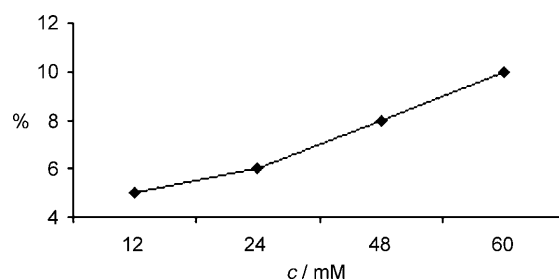
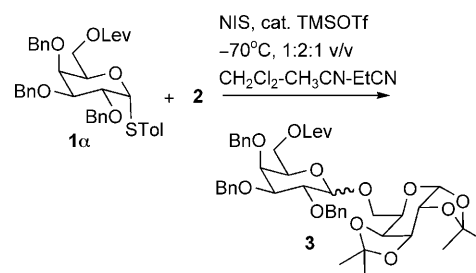


Figure 2. The plot of the percentage of α anomer of **3** against the concentrations (mM) of thiogalactopyranoside **1**.

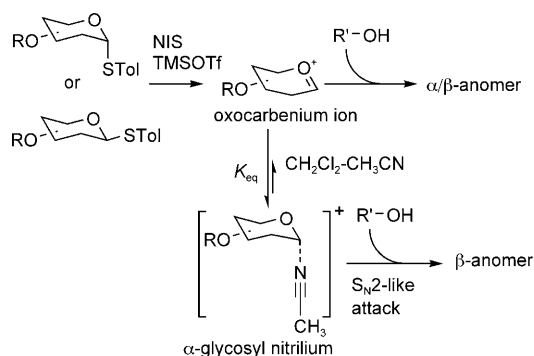
After confirming the importance of thioglycoside concentration, we next examine the effect of the anomeric configuration of the glycosyl donor on low-concentration 1,2-*trans* β -selective glycosylation. Poletti and co-workers reported that the anomeric configuration of thioglycosyl donors affects the stereoselectivities of glycosylation.^[32] However, these results differ from those observed for glycosylations with glycosyl imidate^[12d] or phosphite donors.^[12f] To clarify the role of anomeric configuration of thioglycoside, α -thiogalactopyranoside **1 α** was prepared and used for the glycosylation of **2**. No significant change in β -selectivity was observed (Scheme 4). Empirically, anomeric configuration of



Scheme 4. Low-concentration 1,2-*trans* β -selective glycosylation of galactopyranose acceptor **2** with α -thiogalactopyranoside **1 α** .

thioglycoside is immaterial to β -stereoselectivity in glycosylation, which implicates that the stereochemical course of low-concentration 1,2-*trans* β -selective glycosylation probably involves a common intermediate.

Based on experimental data and literature review, the aforementioned intermediate should be the free oxocarbenium ion arising from activation of thioglycoside,^[12b,c,g] and thereof a mechanism is proposed as shown in Scheme 5. Activation of thioglycoside gives rise to free oxocarbenium ion. Owing to the high dielectric constant of the CH_2Cl_2 /nitrile solvent mixture,^[34] the formation α -glycosyl triflate is unlikely.^[35] Instead, the free oxocarbenium ion reacts with the hydroxy acceptor to produce a α/β -anomeric mixture. Alternatively, it might couple with the nitrile solvent molecule to generate the kinetically favoured α -glycosyl nitrilium.^[12,36,37] Further $\text{S}_{\text{N}}2$ -like reaction of the α -glycosyl nitrilium with the acceptor leads to the formation of the β -anomer.



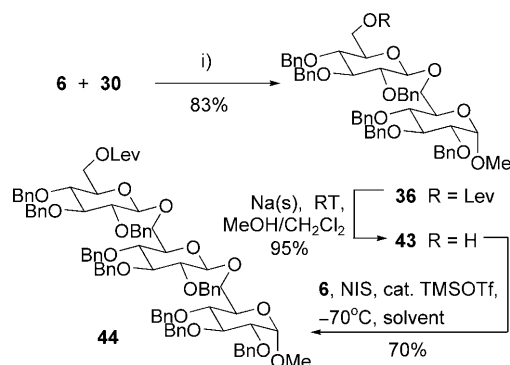
Scheme 5. Proposed mechanism of the low-concentration 1,2-*trans* β -selective glycosylation.

Apparently, low substrate concentrations, low reaction temperature, and appropriate CH_2Cl_2 /nitrile solvent mixture act synchronously to enhance α -glycosyl nitrilium formation, which depletes the free oxocarbenium ion through an equilibrium process. The argument agrees with that proposed by Crich and co-workers in β -selective rhamnosylation.^[10b] However, attempts to detect the α -glycosyl nitrilium with NMR spectroscopy have so far been unsuccessful owing to substantial peak broadening in low-temperature NMR spectroscopy (below approximately -50°C).^[38] Additional experimentations are currently underway to address this issue.

Synthetic utilities of the low-concentration 1,2-*trans* β -selective glycosylation: Regarding synthetic utility, the direct impact of low-concentration 1,2-*trans* β -selective glycosylation is to provide an alternative 1,2-*trans* β -selective glycosylation strategy. This strategy does not require a C2-participation protecting function and therefore allows the use of more-reactive thioglycosyl donors in the formation of 1,2-*trans* β -glycosidic bonds. This is useful in the design of new strategies in oligosaccharide synthesis as the following examples illustrate.

β -(1 $\rightarrow$ 6)-Glucan is the essential fungal-specific carbohydrate component found in the cell wall of *Saccharomyces cerevisiae*.^[14] Previous attempts to synthesize β -(1 $\rightarrow$ 6)-glucan trisaccharide without a C2 acyl function have been reported, resulting in a 1:9 α/β -anomeric mixture.^[13] Low-concentration 1,2-*trans* β -selective glycosylation might enable a highly stereoselective synthesis of β -(1 $\rightarrow$ 6)-glucan trisaccharide (Scheme 6). The glycosylation of methyl α -D-glucopyranoside **30** with thiogalactopyranoside **6** produced disaccharide glycoside **36** as mentioned above, and the treatment of **36** with standard Zemplén deacylation produced disaccharide acceptor **43**. The glycosylation of **43** with donor **6** afforded protected β -(1 $\rightarrow$ 6)-glucan trisaccharide **44** with a high yield and excellent β -anomeric purity.

Further to the stepwise synthesis, the low-concentration 1,2-*trans* β -selective glycosylation is useful for sequential glycosylation, as illustrated in the preparation of globotriaosylceramide (Gb_3) and iso Gb_3 derivatives. Both the trisaccharide derivatives carry the β -linked functionalizable



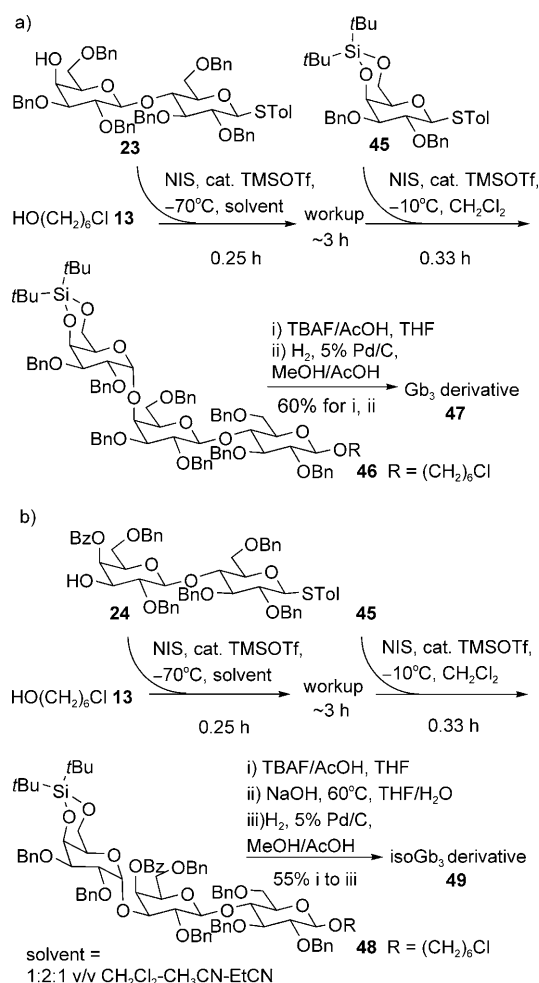
Scheme 6. Stepwise synthesis of β -(1 $\rightarrow$ 6)-glucan trisaccharide **44**. i) See Table 3, entry 4 for conditions.

spacer; with such a spacer, further chemical elaboration is possible. Conventional preparation of Gb_3 and iso Gb_3 derivatives involves construction of perbenzoyl lactoside, which undergoes further protection–deprotection reactions and additional glycosylation to furnish the target.^[39] It was envisaged that the application of low-concentration 1,2-*trans* β -selective glycosylation should enable the development of a reverse sequential glycosylation strategy for the preparation of Gb_3 and iso Gb_3 derivatives.

Acceptor **13** was chemoselectively glycosylated with thiolactosides **23** and **24** with low-concentration β -selective glycosylations to afford the corresponding β -linked lactoside acceptors (Scheme 7a and b). No traces of self-condensation products were detected, which is attributed to the higher reactivity of the hydroxy function in aglycon acceptor **13** compared with the hindered hydroxy functions in thiolactosides **23** and **24**. Without isolation of the glycosylation product and deprotection of the protected hydroxy function, the crude β -linked lactosides was used directly as acceptors for glycosylation with thiogalactopyranoside **45** in CH_2Cl_2 . This reverse sequential glycosylation strategy produces the protected Gb_3 and iso Gb_3 derivatives **46** and **48** in high overall yields (75 % for **46** and 70 % for **48** based on two glycosylation steps) with extremely good anomeric purities, as proven in the ^{13}C NMR spectra in Figure 3. Subsequent standard global deprotection reactions afforded Gb_3 and iso Gb_3 trisaccharide derivatives, **47** and **49**.

Conclusions

The study explores, for the first time, the effect of substrate concentrations on 1,2-*trans* β -selective glycosylation. This study proposes a low-concentration 1,2-*trans* β -selective glycosylation method, which is applicable to a wide range of glycosyl substrates and enables the development of new synthetic routes for biologically relevant β -(1 $\rightarrow$ 6)-glucan trisaccharide, Gb_3 and iso Gb_3 . As β -linked glycosidic bonds occur frequently in natural oligosaccharides, this new β -selective glycosylation strategy should prove useful for their preparation.



Scheme 7. a) Sequential glycosylation strategy for synthesis of Gb₃ derivative **47** and b) isoGb₃ derivative **49**. TBAF=tetrabutylammonium fluoride, TMSOTf=trimethylsilyltriflate.

Experimental Section

General: Reagent-grade chemicals were purchased and used without further purification. N,N-dimethylformamide (DMF) was distilled over calcium hydride and stocked with flame-dried molecular sieves (MS) under N₂. The progress of reactions was monitored by thin-layer chromatography on silica gel 60 F-254 plate and visualized under UV illumination and by staining with acidic ceric ammonium molybdate or *p*-anisaldehyde. Optical rotations were measured with polarimeter at 27°C. HPLC analysis was performed over Mightysil column with elution of EtOAc/hexane mixture at a 1.2 mL min⁻¹ flow rate by the gradient pump (L-2130) and UV detector (L-2400) from Hitachi. NMR spectra were recorded at 300 MHz and 75 MHz spectrometers in a Bruker console or 500 MHz and 125 MHz in a Varian console as specified. The chemical shift was calibrated against the residual proton signal and the ¹³C signal of deuterated chloroform or deuterated methanol. Coupling constants in Hz was calculated from chemical shift of ¹H NMR or spectra.

General procedure for low-concentration 1,2-*trans* β-selective glycosylation: A mixture of thioglycoside (1.2 mol equiv), acceptor (1.0 mol equiv), and flame-dried MS (AW300) were suspended in 1:3 v/v CH₂Cl₂-CH₃CN or 1:2:1 v/v CH₂Cl₂-CH₃CN-EtCN solvent mixture such that the final concentrations of thioglycoside and acceptor were 12 and 10 mM, respectively (for particular details see Table S1 in the Supporting Information). The resulting mixture was stirred at room temperature for 10 min and at -70°C for an additional 20 min under N₂, and followed by the addition of NIS (1.2 mol equiv) and trimethylsilyltriflate (TMSOTf; 0.24 mol equiv). Glycosylation coupling was monitored by TLC with either EtOAc-hexane or EtOAc-CH₂Cl₂-hexane mixture as the developing solvent. Upon completion of glycosylation, a small volume of saturated NaHCO₃ and small lumps of Na₂S₂O₃(s) were added to the mixture, followed by vigorous stirring until the deep-red color of the reaction mixture turned to pale yellow. Then the MS were removed by filtration over celite. The filtrate was dried (over MgSO₄), filtered, and concentrated for flash-chromatography purification over silica gel to furnish glycosylation products for NMR characterization. A small portion of crude reaction mixture was filtered through a short pad of silica gel (approximately 10 cm) and concentrated for determination of the α/β-anomeric ratio by HPLC analysis by using conditions as described in the general experimental section. Preparation of glycosyl substrates **1**, **4**-**12**, **23**-**32** for glycosylation studies and NMR spectra of compounds **1**, **3**-**12**, **14**-**49** are presented in the Supporting Information.

Low-temperature NMR spectroscopy for thiogalactopyranoside (1**):** Thiogalactopyranoside **1** (33 mg for 100 mm or 3.3 mg for 10 mm) in a pre-dried NMR tube was dried under vacuum overnight and then 1:3 v/v CD₂Cl₂-CD₃CN with 5 vol % EtCN (500 μL) was added under N₂. The resulting mixture was then analyzed by NMR spectroscopy at a temperature range of 25°C to -60°C (selected spectra are given in the Supporting Information).

Low-temperature NMR spectroscopy for NIS/TMSOTf-activated thiogalactopyranoside (1**):** Thiogalactopyranoside **1** (33 mg) in a pre-dried NMR tube was dried under vacuum overnight and then 500 μL of 1:3 v/v CD₂Cl₂-CD₃CN (with 25 μL of EtCN added as internal reference) was added under N₂. The resulting solution was cooled at -80°C bath for approximately 10 min, followed by the addition of TMSOTf (2 μL) in CD₂Cl₂ solution (10 μL). The resulting mixture was then analyzed by NMR spectroscopy at temperature range of -50 to -30°C (selected spectra for VT-NMR are given in the Supporting Information).

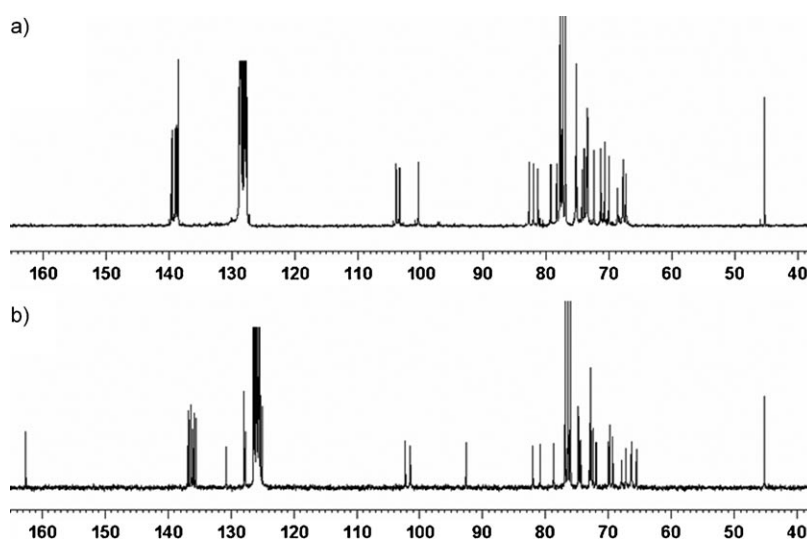


Figure 3. ¹³C NMR spectra of a) protected Gb₃ **46** and b) protected isoGb₃ **48**.

1,2,3,4-di-O-isopropylidene-6-O-(2',3',4'-tri-O-benzyl-6'-O-levulinoyl-β-D-galactopyranosyl)-1-α-D-galactopyranose (3): Synthesis of **3** was performed as per the general procedure of low-concentration 1,2-*trans* β-selective glycosylation. **3** (128 mg, 84 %) was obtained as glassy solid. $[\alpha]_D^{25} = -35.34$ ($c = 0.9$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.50\text{--}7.47$ (d, $J = 9.3$ Hz, 2H; ArH), 7.46–7.28 (m, 13H; ArH), 5.59 (d, $J = 4.95$ Hz, 1H, H-1), 5.09 (d, $J = 11.1$ Hz, 1H), 4.88 (d, $J = 12$ Hz, 1H), 4.80–4.75 (m, 2H), 4.68 (d, $J = 11.4$ Hz, 1H), 4.61 (dd, $J = 2.4$, 7.8 Hz, 1H), 4.45 (d, $J = 7.8$ Hz, 1H), 4.33 (dd, $J = 2.4$, 5.1 Hz, 1H), 4.28–4.22 (m, 2H), 4.18–4.10 (m, 3H; 3.91–3.83 (m, 2H), 3.7 (dd, $J = 6.9$, 9.9 Hz, 1H), 3.58–3.54 (m, 2H), 2.76–2.71 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.53–2.48 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.20 (s, 3H; $\text{CH}_3\text{C}=\text{O}$), 1.52 (s, 3H; CH_3C), 1.48 (s, 3H; CH_3C), 1.35 (s, 3H; CH_3C), 1.34 ppm (s, 3H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 206.9$, 172.74, 139.4, 139.0, 138.7, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 128.0, 127.8, 109.7, 109.0, 105.1, 96.8, 82.3, 79.3, 75.2, 74.8, 72.3, 71.9, 71.2, 70.9, 7.1, 67.8, 63.5, 38.3, 30.2, 28.2, 26.44, 26.41, 25.5, 24.8 ppm; HRMS (FAB): m/z : calcd for $\text{C}_{44}\text{H}_{54}\text{O}_{13}$: 790.3564 $[M]^+$; found: 790.3561.

1,2,3,4-Di-O-isopropylidene-6-O-(4'-O-acetyl-2',3',6'-tri-O-benzyl-β-D-galactopyranosyl)-1-α-D-galactopyranose (14): Synthesis of **14** was performed as per to the general procedure of low-concentration 1,2-*trans* β-selective glycosylation. **14** (120 mg, 85 %) was obtained as colorless oil. $[\alpha]_D^{25} = -6.31$ ($c = 1.2$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.50\text{--}7.48$ (m, 2H; ArH), 7.42–7.28 (m, 13H; ArH), 5.63–5.61 (m, 2H), 5.08 (d, $J = 11.1$ Hz, 1H), 4.8 (d, $J = 11.4$ Hz, 1H), 4.72 (d, $J = 11.1$ Hz, 1H), 4.64–4.49 (m, 5H), 4.36 (dd, $J = 2.4$, 5.1 Hz, 1H), 4.27 (dd, $J = 1.5$, 7.8 Hz, 1H), 4.22–4.14 (m, 2H), 3.82–3.73 (m, 2H), 3.68–3.53 (m, 4H), 2.11 (s, 3H; $\text{CH}_3\text{C}=\text{O}$), 1.54 (s, 3H; CH_3C), 1.49 (s, 3H; CH_3C), 1.36 ppm (s, 6H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 170.8$, 139.3, 138.4, 138.0, 128.91, 128.9, 128.7, 128.6, 128.52, 128.51, 128.3, 128.1, 127.8, 109.8, 109.0, 105.0, 96.8, 79.4, 79.0, 75.4, 74.1, 72.5, 72.4, 71.9, 71.2, 70.9, 70.4, 68.4, 67.8, 67.3, 26.4, 25.5, 24.9, 21.4 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{41}\text{H}_{50}\text{O}_{12}\text{Na}$: 757.3194 $[M+\text{Na}]^+$; found: 757.3194.

1,2,3,4-Di-O-isopropylidene-6-O-(2',6'-di-O-benzyl-3',4'-di-O-methoxycarbonyl-β-D-galactopyranosyl)-1-α-D-galactopyranose (15): Synthesis of **15** was performed as described in the general procedure for low-concentration 1,2-*trans* β-selective glycosylation. **15** (98 mg, 71 %) was obtained as light-yellow oily liquid. $[\alpha]_D^{25} = -8.39$ ($c = 0.53$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.39\text{--}7.26$ (m, 10H; ArH), 5.57 (d, $J = 5.1$ Hz, 1H; H-1), 5.37 (d, $J = 3.0$ Hz, 1H), 5.02 (d, $J = 11.4$ Hz, 1H), 4.85 (dd, $J = 3.3$, 10.2 Hz, 1H), 4.65–4.47 (m, 5H), 4.33 (dd, $J = 2.4$, 4.8 Hz, 1H), 4.23 (dd, $J = 1.8$, 8.1 Hz, 1H), 4.16–4.07 (m, 2H), 3.82 (s, 3H), 3.80–3.58 (m, 8H), 1.52 (s, 3H; CH_3C), 1.46 (s, 3H; CH_3C), 1.33 ppm (s, 6H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 155.9$, 155.3, 138.9, 138.1, 128.8, 128.5, 128.4, 128.22, 128.2, 127.8, 109.8, 109.0, 104.5, 96.8, 76.9, 75.1, 74.0, 72.1, 71.9, 71.8, 71.1, 70.9, 0.1, 68.0, 67.8, 55.53, 55.51, 26.43, 26.38, 25.4, 24.8 ppm; HRMS (ESI): m/z : calcd $\text{C}_{36}\text{H}_{46}\text{O}_{15}\text{Na}$: 741.2729 $[M+\text{Na}]^+$; found: 741.2729.

1,2,3,4-Di-O-isopropylidene-6-O-(2',3',4'-tri-O-benzyl-6'-O-levulinoyl-β-D-glucopyranosyl)-1-α-D-galactopyranose (16): Synthesis of **16** was prepared according to the general procedure of low-concentration 1,2-*trans* β-selective glycosylation. **16** (117 mg, 77 %) was obtained as white glassy solid. $[\alpha]_D^{25} = -14.80$ ($c = 0.84$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.46\text{--}7.42$ (m, 2H; ArH), 7.36–7.25 (m, 13H; ArH), 5.59 (d, $J = 5.1$ Hz, 1H; H-1), 5.08 (d, $J = 11.1$ Hz, 1H), 5.00 (d, $J = 10.8$ Hz, 1H), 4.88 (d, $J = 10.8$ Hz, 1H), 4.81 (d, $J = 11.1$ Hz, 1H), 4.74 (d, $J = 11.1$ Hz, 1H), 4.63–4.56 (m, 2H), 4.49 (d, $J = 7.8$ Hz, 1H), 4.35–4.25 (m, 4H), 4.15–4.10 (m, 2H), 3.77–3.65 (m, 2H), 3.54–3.44 (m, 3H), 2.78–2.72 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.62–2.58 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.20 (s, 3H; $\text{CH}_3\text{C}=\text{O}$), 1.52 (s, 3H; CH_3C), 1.48 (s, 3H; CH_3C), 1.35 (s, 3H; CH_3C), 1.33 ppm (s, 3H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 206.8$, 172.9, 139.0, 138.9, 138.2, 129.0, 128.9, 128.8, 128.6, 128.5, 128.3, 128.0, 127.9, 109.8, 108.9, 104.9, 96.8, 84.9, 81.9, 77.8, 77.6, 76.4, 75.4, 74.8, 73.2, 71.2, 71.8, 71.1, 70.8, 70.2, 67.7, 63.7, 38.3, 30.3, 28.3, 26.43, 26.4, 25.4, 24.8 ppm; HRMS (FAB): m/z : calcd for $\text{C}_{44}\text{H}_{54}\text{O}_{13}$: 790.3564 $[M]^+$; found: 790.3578.

1,2,3,4-Di-O-isopropylidene-6-O-(2',3',6'-tri-O-benzyl-4'-O-levulinoyl-β-D-glucopyranosyl)-1-α-D-galactopyranose (17): Synthesis of **17** was prepared according to the general procedure of low-concentration 1,2-*trans*

β-selective glycosylation. **17** (126 mg, 83 %) was obtained as colorless oily liquid. $[\alpha]_D^{25} = -22.42$ ($c = 0.35$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.46\text{--}7.43$ (m, 2H; ArH), 7.37–7.27 (m, 13H; ArH), 5.6 (d, $J = 5.1$ Hz, 1H), 5.09–4.99 (m, 2H), 4.86 (d, $J = 11.7$ Hz, 1H), 4.73 (d, $J = 11.1$ Hz, 1H), 4.67–4.59 (m, 2H), 4.55–4.51 (m, 3H), 4.35 (dd, $J = 2.4$, 5.1 Hz, 1H), 4.26 (dd, $J = 1.5$, 7.8 Hz, 1H), 4.21–4.12 (m, 2H), 3.78 (dd, $J = 7.2$, 10.2 Hz, 1H), 3.66–3.50 (m, 5H), 2.62–2.54 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.45–2.25 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.13 (s, 3H; $\text{CH}_3\text{C}=\text{O}$), 1.53 (s, 3H; CH_3C), 1.48 (s, 3H; CH_3C), 1.35 ppm (s, 6H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C, TMS): $\delta = 206.6$, 172.0, 139.0, 138.9, 138.5, 129.1, 128.71, 128.68, 128.64, 128.3, 128.0, 127.9, 109.8, 109.0, 104.7, 96.8, 81.9, 81.7, 75.4, 74.9, 74.0, 73.7, 71.8, 71.4, 71.2, 70.9, 69.9, 67.9, 38.2, 30.2, 28.3, 26.5, 26.4, 25.4, 24.9 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{44}\text{H}_{54}\text{O}_{13}$: 790.3564 $[M]^+$; found: 790.3568.

1,2,3,4-Di-O-isopropylidene-6-O-(2'-azido-3',4',6'-tri-O-benzyl-2'-deoxy-β-D-glucopyranosyl)-1-α-D-galactopyranose (18): Synthesis of **18** was performed according to the general procedure of low-concentration 1,2-*trans* β-selective glycosylation. **18** (114 mg, 83 %) was obtained as a colorless oily liquid. $[\alpha]_D^{25} = -35.30$ ($c = 1.08$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.42\text{--}7.30$ (m, 13H; ArH), 7.22–7.19 (m, 2H; ArH), 5.6 (d, $J = 5.1$ Hz, 1H), 4.95 (d, $J = 10.8$ Hz, 1H), 4.84 (dd, $J = 5.7$, 10.8 Hz, 1H), 4.67–4.55 (m, 4H), 4.48–4.46 (m, 1H), 4.36 (dd, $J = 2.4$, 4.8 Hz, 1H), 4.32 (dd, $J = 1.2$, 8.1 Hz, 1H), 4.1 (m, 2H), 3.88–3.66 (m, 4H), 3.49–3.45 (m, 3H), 1.59 (s, 3H; CH_3C), 1.49 (s, 3H; CH_3C), 1.38 (s, 3H; CH_3C), 1.37 ppm (s, 3H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 138.49$, 138.46, 138.39, 128.88, 128.85, 128.81, 128.47, 128.3, 128.1, 109.7, 109.1, 102.9, 96.7, 83.5, 78.1, 75.9, 75.4, 74.0, 71.7, 71.1, 70.9, 69.2, 68.9, 68.0, 66.8, 26.5, 26.4, 25.4, 24.8 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{39}\text{H}_{47}\text{N}_3\text{O}_{10}\text{Na}$: 740.3159 $[M+\text{Na}]^+$; found: 740.3154.

1,2,3,4-Di-O-isopropylidene-6-O-(2',3'-di-O-benzyl-4',6'-O-benzylidene-β-D-galactopyranosyl)-1-α-D-galactopyranose (19): Synthesis of **19** was generally based on the general procedure of low-concentration 1,2-*trans* β-selective glycosylation, but lower substrate concentrations (5 mm of glycosyl acceptor **2** and 6 mm of glycosyl donor **9**) were used to obtain a 1:19 α/β anoeimeric ratio of **19**. Disaccharide **19** (110 mg, 83 %) was obtained as white amorphous solid. $[\alpha]_D^{25} = -12.59$ ($c = 1.4$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.62\text{--}7.58$ (m, 2H, ArH), 7.55–7.52 (m, 2H, ArH), 7.45–7.28 (m, 11H, ArH), 5.62 (d, $J = 5.1$ Hz, 1H; H-1), 5.54 (s, 1H; PhCH), 5.13 (d, $J = 11.1$ Hz, 1H), 4.84–4.77 (m, 3H), 4.63 (dd, $J = 2.4$, 7.8 Hz, 1H), 4.49 (d, $J = 7.8$ Hz, 1H), 4.36 (dd, $J = 2.4$, 5.1 Hz, 1H), 4.34–4.21 (m, 3H), 4.17–4.13 (m, 2H), 4.04 (dd, $J = 1.2$, 12.3 Hz, 1H), 3.91 (dd, $J = 7.5$, 9.6 Hz, 1H), 3.77 (dd, $J = 7.2$, 10.5 Hz, 1H), 3.60 (dd, $J = 3.6$, 9.6 Hz, 1H), 3.32 (s, 1H), 1.55 (s, 3H; CH_3C), 1.50 (s, 3H; CH_3C), 1.37 ppm (s, 6H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C, TMS): $\delta = 139.6$, 138.9, 138.3, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.8, 126.9, 109.7, 109.1, 104.8, 101.6, 96.8, 79.3, 78.6, 75.4, 74.6, 72.5, 71.9, 71.2, 70.9, 69.9, 69.6, 67.8, 66.9, 26.5, 26.4, 25.5, 24.9 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{39}\text{H}_{46}\text{O}_{11}\text{Na}$: 713.2932 $[M+\text{Na}]^+$; found: 713.2933.

1,2,3,4-Di-O-isopropylidene-6-O-[2',3',6'-tri-O-benzyl-4'-O-(2'',3'',4'',6''-tetra-O-benzyl-β-D-galactopyranosyl)-β-D-glucopyranosyl]-1-α-D-galactopyranose (20): Synthesis of **20** was performed according to the general procedure of low-concentration 1,2-*trans* β-selective glycosylation. **20** (175 mg, 75 %) was obtained as a colorless oily liquid. $[\alpha]_D^{25} = -15.38$ ($c = 2.07$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.49\text{--}7.18$ (m, 35H; ArH), 5.62 (d, $J = 5.1$ Hz, 1H), 5.08–5.00 (m, 3H), 4.84–4.74 (m, 7H), 4.64–4.57 (m, 3H), 4.50–4.44 (m, 2H), 4.41–4.35 (m, 2H), 4.31–4.27 (m, 2H), 4.21–4.17 (m, 2H), 4.03–3.96 (m, 2H), 3.88–3.72 (m, 4H), 3.63–3.56 (m, 2H), 3.49–3.37 (m, 5H), 1.55 (s, 3H; CH_3C), 1.51 (s, 3H; CH_3C), 1.37 ppm (s, 6H; CH_3C); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 139.6$, 139.5, 139.4, 139.2, 139.0, 138.8, 138.5, 128.9, 128.81, 128.79, 128.68, 128.66, 128.52, 128.38, 128.30, 128.17, 128.11, 127.96, 127.86, 127.80, 127.46, 109.76, 109.02, 104.80, 103.17, 83.18, 82.98, 81.68, 80.40, 77.71, 75.79, 75.70, 75.51, 75.13, 74.97, 74.02, 73.83, 73.52, 73.36, 72.97, 71.83, 71.18, 70.93, 69.91, 68.62, 68.51, 67.74, 26.50, 26.45, 25.49, 24.88 ppm; HRMS (FAB): m/z : calcd for $\text{C}_{73}\text{H}_{82}\text{O}_{16}$: 1214.5603 $[M]^+$; found: 1214.5608.

6-Chlorohexyl 2,3,4-tri-*O*-benzyl-1- β -L-fucopyranoside (21): Synthesis of **21** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **21** (93 mg, 80%) was obtained as colorless oily liquid. $[\alpha]_D^{27} = +5.52$ ($c = 0.32$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.41\text{--}7.27$ (m, 15H; ArH), 5.01 (d, $J = 11.7$ Hz, 1H), 4.96 (d, $J = 11.1$ Hz, 1H), 4.85–4.47 (m, 4H), 4.34 (d, $J = 7.5$ Hz, 1H), 3.97 (dt, $J = 6.3$, 9.6 Hz, 1H), 3.83 (dd, $J = 7.8$, 9.6 Hz, 1H), 3.59–3.44 (m, 6H), 1.81–1.64 (m, 4H; CH_2), 1.51–1.37 (m, 4H; CH_2), 1.20 ppm (d, $J = 6.3$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 139.33$, 139.08, 139.02, 128.95, 128.79, 128.68, 128.53, 128.43, 127.97, 127.91, 104.2, 82.97, 79.89, 77.69, 76.66, 75.49, 74.34, 73.58, 70.69, 69.99, 45.5, 32.95, 30.0, 27.1, 25.9 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{33}\text{H}_{41}\text{ClO}_5\text{Na}$: 575.2540 $[M+\text{Na}]^+$; found: 575.2535.

6-Chlorohexyl 2,3,4,6-tetra-*O*-benzyl- β -D-galactopyranoside (22): Synthesis of **22** was referred to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **22** (140 mg, 85%) was obtained as colourless oily liquid. $[\alpha]_D^{27} = -4.24$ ($c = 1.90$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.46\text{--}7.31$ (m, 20H; ArH), 5.05–4.99 (m, 2H), 4.88–4.77 (m, 3H), 4.71 (d, $J = 11.7$ Hz, 1H), 4.56–4.47 (m, 2H), 4.44 (d, $J = 7.5$ Hz, 1H), 4.06–4.03 (m, 1H), 3.98 (m, 1H), 3.90 (t, $J = 9$ Hz, 1H), 3.69–3.53 (m, 7H), 1.85–1.72 (m, 4H; CH_2), 1.52–1.45 ppm (m, 4H; CH_2); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 139.3$, 139.1, 139.0, 138.4, 128.9, 128.84, 128.75, 128.64, 128.50, 128.36, 128.01, 127.93, 104.4, 82.7, 80.1, 75.6, 74.96, 74.01, 73.98, 73.50, 70.22, 69.38, 45.50, 32.99, 30.06, 27.17, 25.96 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{40}\text{H}_{47}\text{ClO}_6\text{Na}$: 681.2953 $[M+\text{Na}]^+$; found: 681.2953.

3-Chloropropyl 2,3-*O*-isopropylidene-4-*O*-(2',3',4'-tri-*O*-benzyl-6'-*O*-levulinoyl- β -D-galactopyranosyl)- α -L-rhamnopyranoside (33): Synthesis of **33** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **33** (114 mg, 65%) was obtained as yellow oily liquid. $[\alpha]_D^{27} = -16.32$ ($c = 1.16$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.46\text{--}7.29$ (m, 15H; ArH), 5.03–4.95 (m, 3H), 4.87–4.75 (m, 4H), 4.69 (d, $J = 11.7$ Hz, 1H), 4.29–4.23 (m, 2H), 4.18–4.09 (m, 2H), 3.93–3.77 (m, 3H), 3.6–3.55 (m, 7H), 2.76–2.71 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.51–2.47 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.20 (s, 3H; $\text{CH}_3\text{C}=\text{O}$), 2.11–2.03 (m, 2H; CH_2), 1.55 (s, 6H; CH_3C), 1.39–1.29 ppm (m, 7H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 206.9$, 172.8, 139.4, 139.0, 138.8, 128.8, 128.72, 128.66, 128.62, 128.5, 128.1, 128.0, 127.9, 127.8, 109.6, 102.6, 97.4, 82.7, 79.99, 79.3, 18.6, 76.3, 75.5, 74.8, 73.94, 73.87, 72.43, 42.1, 38.3, 32.7, 30.3, 28.3, 28.1, 26.8, 18.3 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{44}\text{H}_{53}\text{ClO}_{12}\text{Na}$: 833.3274 $[M+\text{Na}]^+$; found: 833.3274.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2',3',4'-tri-*O*-benzyl-6'-*O*-levulinoyl- β -D-galactopyranosyl)-1- α -D-glucopyranoside (34): Synthesis of **34** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **34** (122 mg, 63%) was obtained as white solid. $[\alpha]_D^{27} = +2.49$ ($c = 0.98$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.47\text{--}7.22$ (m, 30H; ArH), 5.06 (m, 2H), 4.88–4.77 (m, 5H), 4.75–4.59 (m, 5H), 4.37 (d, $J = 12$ Hz, 1H), 4.31 (d, $J = 7.8$ Hz, 1H), 4.12 (d, $J = 6.6$ Hz, 1H), 3.99–3.70 (m, 6H), 3.65–3.52 (m, 3H), 3.47–3.32 (m, 5H), 2.73 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.53–2.47 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.19 ppm (s, 3H; $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 206.9$, 172.6, 139.7, 139.3, 139.1, 138.94, 138.93, 138.5, 128.92, 128.82, 128.81, 128.78, 128.67, 128.59, 128.52, 128.45, 128.41, 128.36, 128.20, 128.16, 128.06, 128.02, 127.91, 127.88, 127.82, 127.55, 103.05, 98.85, 82.79, 80.6, 80.3, 77.7, 76.9, 75.9, 75.6, 75.0, 73.7, 73.6, 73.2, 72.0, 70.4, 68.3, 63.1, 55.7, 38.3, 30.3, 28.3 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{60}\text{H}_{66}\text{O}_{13}$: 994.4503 $[M]^+$; found: 994.4506.

2-Azidoethyl 2,3-di-*O*-allyl-4-*O*-(2',3',4'-tri-*O*-benzyl-6'-*O*-levulinoyl- β -D-galactopyranosyl)-1- β -D-galactopyranoside (35): Synthesis of **35** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **35** (117 mg, 60%) was obtained as a yellow oily liquid. $[\alpha]_D^{27} = -1.98$ ($c = 0.74$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.50\text{--}7.48$ (m, 2H; ArH), 7.38–7.28 (m, 18H; ArH), 5.97–5.86 (m, 2H), 5.39 (d, $J = 1.2$ Hz, 1H), 5.24–5.02 (m, 5H), 4.88–4.85 (m, 2H), 4.78–4.74 (m, 2H), 4.65–4.53 (m, 3H), 4.37 (d, $J = 7.8$ Hz, 1H), 4.25–3.99 (m, 8H), 3.87–3.67 (m, 5H), 3.64–3.37 (m, 7H), 2.75–2.70 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.51–2.47 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.19 ppm (s, 3H; $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 206.8$, 172.8, 139.5, 139.1,

138.8, 135.6, 135.5, 128.77, 128.76, 128.67, 128.6, 128.4, 128.2, 128.0, 127.7, 116.91, 116.88, 104.17, 103.4, 82.4, 81.6, 80.1, 79.6, 77.7, 75.3, 74.8, 74.5, 74.4, 74.3, 74.1, 73.9, 72.3, 72.1, 71.8, 70.7, 68.6, 63.7, 51.4, 38.2, 30.2, 28.1 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{53}\text{H}_{63}\text{N}_3\text{O}_{13}\text{Na}$: 972.4253 $[M+\text{Na}]^+$; found: 972.4253.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2',3',4'-tri-*O*-benzyl-6'-*O*-levulinoyl- β -D-glucopyranosyl)-1- α -D-glucopyranoside (36): Synthesis of **36** was referred to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **36** (162 mg, 83%) was obtained as white solid. $[\alpha]_D^{27} = +20.57$ ($c = 1.03$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.41\text{--}7.32$ (m, 25H; ArH), 7.28–7.24 (m, 5H; ArH), 5.06–4.77 (m, 9H), 4.74–4.56 (m, 4H), 4.43–4.39 (m, 2H), 4.30 (dd, $J = 4.2$, 12 Hz, 1H), 4.22 (d, $J = 10.5$ Hz, 1H), 4.07 (t, $J = 9.3$ Hz, 1H), 3.90 (dd, $J = 3$, 9.9 Hz, 1H), 3.77–3.69 (m, 2H), 3.63–3.51 (m, 5H), 3.41 (s, 3H), 2.78–2.73 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.63–2.58 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.21 ppm (s, 3H; $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 206.8$, 173.0, 139.3, 138.8, 138.7, 138.6, 138.2, 128.95, 128.93, 128.88, 128.84, 128.81, 128.63, 128.58, 128.44, 128.40, 128.36, 128.32, 128.17, 128.10, 128.04, 104.2, 98.5, 85.2, 82.4, 80.2, 78.4, 77.9, 76.2, 76.1, 75.5, 75.4, 75.3, 73.8, 73.3, 70.2, 69.1, 63.7, 55.7, 38.3, 30.3, 30.2, 28.3 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{55}\text{H}_{60}\text{O}_{11}\text{Na}$: 994.4503 $[M+\text{Na}]^+$; found: 994.4506.

2',3',4'-Tri-*O*-benzyl-6'-*O*-levulinoyl- α -D-galactopyranosyl *N*'-fluoren-9-yl methoxycarbonyl-L-serine allyl ester (37a): Synthesis of **37a** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation, but use only CH_2Cl_2 as reaction solvent. **37a** (128 mg, 75%) was obtained as colorless oil. $[\alpha]_D^{27} = +8.63$ ($c = 0.90$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.80\text{--}7.78$ (m, 2H; ArH), 7.68–7.56 (m, 3H; ArH), 7.44–7.28 (m, 18H; ArH), 5.96–5.84 (m, 1H), 5.40–5.22 (m, 2H), 5.05–4.80 (m, 7H), 4.74–4.59 (m, 4H), 4.51–4.39 (m, 2H), 4.34–4.04 (m, 5H), 4.02–3.81 (m, 3H), 2.79–2.64 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.60–2.45 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.16 ppm (s, 3H; $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 207.1$, 172.95, 170.2, 156.5, 144.3, 141.7, 139.0, 138.8, 138.6, 132.0, 128.89, 128.82, 128.74, 128.3, 128.2, 128.14, 128.09, 127.95, 127.87, 127.52, 125.62, 125.59, 125.29, 120.41, 119.21, 99.8, 78.99, 77.67, 76.70, 75.09, 73.79, 73.73, 70.53, 69.73, 67.57, 66.70, 66.63, 64.22, 55.1, 47.5, 38.25, 38.19, 30.29, 30.23, 28.1 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{53}\text{H}_{55}\text{NO}_{12}\text{Na}$: 920.3616 $[M+\text{Na}]^+$; found: 920.3609.

2',3',4'-Tri-*O*-benzyl-6'-*O*-levulinoyl- β -D-galactopyranosyl *N*'-fluoren-9-yl methoxycarbonyl-L-serine allyl ester (37b): Synthesis of **37b** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **37b** (124 mg, 73%) was obtained as white solid. $[\alpha]_D^{27} = +1.37$ ($c = 0.85$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.80\text{--}7.77$ (m, 2H; ArH), 7.62–7.57 (m, 2H; ArH), 7.47–7.25 (m, 19H; ArH), 5.99–5.87 (m, 2H), 5.37 (d, $J = 17.1$ Hz, 1H), 5.25 (d, $J = 10.5$ Hz, 1H), 5.01 (d, $J = 11.7$ Hz, 1H), 4.93 (d, $J = 10.8$ Hz, 1H), 4.87–4.78 (m, 3H), 4.73–4.57 (m, 4H), 4.49–4.11 (m, 7H), 3.95–3.85 (m, 3H), 3.61–3.54 (m, 3H), 2.77–2.73 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.54–2.41 (m, 2H; $\text{CH}_2\text{C}=\text{O}$), 2.2 ppm (s, 3H; $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 206.97$, 172.9, 170.1, 156.5, 144.36, 144.21, 141.66, 138.74, 138.62, 138.59, 131.94, 128.90, 128.86, 128.82, 128.77, 128.66, 128.22, 128.19, 128.13, 128.04, 127.55, 127.50, 125.74, 125.64, 120.36, 119.19, 104.8, 82.6, 79.3, 77.7, 75.8, 74.9, 73.61, 73.37, 72.6, 70.4, 67.7, 66.7, 63.4, 55.1, 47.5, 38.3, 30.3, 28.2 ppm; HRMS (ESI): m/z : calcd for $\text{C}_{53}\text{H}_{55}\text{NO}_{12}\text{Na}$: 920.3616 $[M+\text{Na}]^+$; found: 920.3619.

3-Chloropropyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2'-azido-3',4',6'-tri-*O*-benzyl-2'-deoxy- β -D-glucopyranosyl)-1- β -D-galactopyranoside (38): Synthesis of **38** was referred to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **38** (126 mg, 77%) was obtained as a colorless oily liquid. $[\alpha]_D^{27} = +7.42$ ($c = 1.22$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C, TMS): $\delta = 7.64\text{--}7.61$ (m, 2H; ArH), 7.53–7.51 (m, 2H; ArH), 7.46–7.35 (m, 19H; ArH), 7.28–7.21 (m, 2H; ArH), 5.60 (s, 1H; PhCH), 5.00–4.96 (m, 2H; vinyl-CH), 4.93–4.81 (m, 4H), 4.67–4.53 (m, 3H), 4.47 (d, $J = 7.5$ Hz, 1H), 4.36–4.33 (m, 2H), 4.17–3.98 (m, 3H), 3.9 (dd, $J = 3.3$, 9.9 Hz, 1H), 3.82–3.57 (m, 7H), 3.48–3.40 (m, 3H), 2.18–2.09 ppm (m, 2H; CH_2); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 138.9$, 138.40, 138.38, 138.23, 129.13, 128.93, 128.88, 128.82, 128.78, 128.53, 128.47, 128.45, 128.39, 128.35, 128.25, 128.20, 126.7, 104.2, 103.2, 100.98,

83.6, 78.96, 78.33, 38.21, 76.52, 75.94, 75.59, 75.56, 75.14, 73.88, 69.43, 69.30, 66.96, 66.77, 66.70, 42.35, 33.2 ppm; HRMS (ESI): m/z : calcd for $C_{50}H_{52}ClN_3O_{10}Na$: 914.3395 [$M+Na$] $^+$; found: 914.3390.

6-Chlorohexyl 2,3,6-tri-*O*-benzyl-4-*O*-(2',3',6'-tri-*O*-benzyl- β -D-galactopyranosyl)-1- β -D-glucopyranoside (39): Synthesis of **39** was prepared according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **39** (168 mg, 80%) was obtained as white glassy solid. [α] $_D^{27}$ = +15.23 (c = 0.52, in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.26–7.13 (m, 30H; ArH), 4.90 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 11.1 Hz, 1H), 4.70–4.55 (m, 6H), 4.47 (d, J = 12.3 Hz, 1H), 4.39–4.27 (m, 5H), 3.94–3.81 (m, 3H), 3.74–3.22 (m, 14H), 2.36 (br, 1H), 1.70–1.55 (m, 4H; CH_2), 1.37–1.30 ppm (m, 4H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 139.44, 139.00, 138.95, 138.65, 138.48, 138.25, 128.80, 128.71, 128.63, 128.61, 128.40, 128.27, 128.20, 128.13, 128.11, 128.01, 127.96, 127.89, 127.87, 127.81, 127.58, 103.93, 102.89, 83.22, 82.11, 81.43, 79.70, 77.60, 75.67, 75.57, 75.42, 75.25, 73.83, 73.45, 73.06, 72.33, 70.09, 68.76, 68.63, 66.46, 45.38, 32.84, 29.93, 27.01, 25.81 ppm; HRMS (FAB): m/z : calcd for $C_{60}H_{69}ClO_{11}$: 1000.4528 [M] $^+$; found: 1000.4529.

6-Chlorohexyl 2,3,6-tri-*O*-benzyl-4-*O*-(3'-*O*-benzoyl-2',6'-di-*O*-benzyl- β -D-galactopyranosyl)-1- β -D-glucopyranoside (40): Synthesis of **40** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **40** (235 mg, 83%) was obtained as glassy solid. [α] $_D^{27}$ = –17.10 (c = 0.74, in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.90 (m, 2H; ArH), 7.44 (m, 3H; ArH), 7.30–7.18 (m, 19H; ArH), 7.09–6.96 (m, 8H; ArH), 5.50 (d, J = 3.0 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H), 4.83–4.45 (m, 8H), 4.38–4.30 (m, 3H), 4.13 (d, J = 12.0 Hz, 1H), 3.96 (t, J = 9.3 Hz, 1H), 3.88–3.85 (m, 1H), 3.76 (dd, J = 3.6, 11.1 Hz, 1H), 3.69–3.64 (m, 2H), 3.58–3.32 (m, 10H), 2.45 (br, 1H), 1.66–1.56 (m, 4H; CH_2), 1.36–1.31 ppm (m, 4H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 166.79, 139.36, 138.98, 138.54, 138.49, 138.11, 133.50, 130.19, 130.00, 128.78, 128.71, 128.63, 128.60, 128.37, 128.29, 128.23, 128.18, 128.15, 128.01, 127.98, 127.92, 127.87, 127.60, 103.99, 102.85, 83.14, 81.97, 80.49, 77.60, 77.04, 73.78, 73.51, 73.02, 72.65, 70.61, 70.12, 68.48, 67.75, 63.06, 45.36, 32.84, 30.03, 29.92, 27.00, 25.81, 25.39 ppm; HRMS (FAB): m/z : calcd for $C_{60}H_{68}ClO_{12}$: 1015.4399 [$M+H$] $^{++}$; found: 1015.4394.

6-Chlorohexyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-1- β -D-glucopyranoside (41): Synthesis of **41** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **41** (44 mg, 60%) was obtained as colorless oil. [α] $_D^{27}$ = –32.28 (c = 0.3, in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.43–7.29 (m, 10H; ArH), 4.96 (d, J = 11.4 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.65 (dd, J = 12.0, 4.8 Hz, 1H), 4.31 (d, J = 7.8 Hz, 1H), 3.98–3.90 (m, 1H), 3.76 (d, J = 6.6 Hz, 1H), 3.68–3.52 (m, 4H), 3.46–3.29 (m, 2H), 3.26 (t, J = 9.0 Hz, 1H), 2.72 (br, 1H), 1.83–1.76 (m, 2H; CH_2), 1.72–1.64 (m, 2H; CH_2), 1.51–1.43 ppm (m, 4H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 138.5, 138.0, 129.0, 128.8, 128.5, 128.4, 128.2, 128.1, 102.6, 82.8, 75.4, 74.3, 74.1, 72.4, 70., 70.4, 66.1, 45.4, 32.9, 29.7, 27.0, 25.6 ppm; HRMS (FAB): m/z : calcd for $C_{26}H_{35}N_3O_5ClNa$: 504.2260 [$M+H$] $^+$; found: 504.2260.

1,2,3,4-Di-*O*-isopropylidene-6-*O*-(2',3',4',6'-tetra-*O*-benzyl- α -D-mannopyranosyl)-1- α -D-galactopyranose (42): Synthesis of **42** was performed according to the general procedure of low-concentration 1,2-*trans* β -selective glycosylation. **42** (128 mg, 85%) was obtained as colorless oily liquid. [α] $_D^{27}$ = –46.11 (c = 0.75, in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.42–7.25 (m, 18H; ArH), 7.19–7.16 (m, 2H; ArH), 5.55 (d, J = 5.1 Hz, 1H; H-1), 5.05 (d, J = 1.8 Hz, 1H), 4.90 (d, J = 10.5 Hz, 1H), 4.75–4.69 (m, 3H), 4.63–4.51 (m, 5H), 4.35 (dd, J = 7.5, 5.1 Hz, 1H), 4.19 (dd, J = 1.8, 8.1 Hz, 1H), 4.08–3.91 (m, 3H), 3.86–3.69 (m, 6H), 1.52 (s, 3H; CH_3C), 1.45 (s, 3H; CH_3C), 1.35 ppm (s, 6H; CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 138.9, 138.88, 138.82, 138.75, 128.7, 128.4, 128.2, 128.0, 127.98, 127.94, 127.88, 127.84, 109.7, 108.9, 97.6, 96.7, 80.4, 77.6, 75.5, 75.2, 74.9, 73.7, 72.7, 72.4, 71.3, 71.0, 70.9, 69.4, 65.7, 65.6, 26.5, 26.3, 25.3, 24.9 ppm; HRMS (ESI): m/z : calcd for $C_{46}H_{54}O_{11}Na$: 805.3564 [$M+Na$] $^+$; found: = 805.3558.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2',3',4'-tri-*O*-benzyl- β -D-glucopyranosyl)-1- α -D-glucopyranoside (43): Disaccharide **36** (410 mg, 0.4 mmol) in 1:2 v/v CH_2Cl_2 –MeOH solution (8 mL) was treated with a piece of freshly cut sodium (approximately 10 mg) at room temperature. Upon completion of

deacetylation, the mixture was neutralized with resin IR-120H $^+$, filtered, and concentrated for purification with column chromatography over silica gel (elution: hexane/EtOAc/toluene = 1/1/1) to furnish the disaccharide **43** as white glassy solid (350 mg, 95%). [α] $_D^{27}$ = +17.13 (c = 0.78, in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.41–7.34 (m, 25H; ArH), 7.28–7.22 (m, 5H; ArH), 5.06–4.93 (m, 4H), 4.90–4.80 (m, 5H), 4.76–4.67 (m, 4H), 4.57 (d, J = 11.4 Hz, 1H), 4.45 (d, J = 7.8 Hz, 1H), 4.17 (d, J = 10.5 Hz, 1H), 4.06 (t, J = 9.3 Hz, 1H), 3.92–3.85 (m, 2H), 3.79–3.50 (m, 8H), 3.42–3.40 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 139.2, 138.84, 138.76, 138.65, 138.54, 138.39, 128.96, 128.93, 128.86, 128.83, 128.62, 128.51, 128.46, 128.41, 128.35, 128.27, 128.10, 128.05, 104.2, 98.6, 85.0, 82.43, 82.41, 80.2, 78.2, 76.2, 75.56, 75.54, 75.42, 75.36, 73.84, 70.2, 69.1, 62.4, 55.7 ppm; HRMS (ESI): m/z : calcd for $C_{55}H_{60}O_{11}Na$: 919.4033 [$M+Na$] $^+$; found: = 919.4030.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2',3',4'-tri-*O*-benzyl-6'-*O*-(2'',3'',4''-tri-*O*-benzyl-6-*O*-levulinoyl- β -D-glucopyranosyl)- β -D-glucopyranosyl)-1- β -D-glucopyranoside (44): Disaccharide acceptor **43** (derived from **36** by Zemplén deacylation, 120 mg, 0.13 mmol), thioglucopyranoside **6** (105 mg, 0.16 mmol) and flame-dried MS (AW300, 300 mg) were suspended in a 1:2:1 v/v CH_2Cl_2 – CH_3CN –EtCN (13 mL) solution under N_2 . The resulting mixture was stirred at room temperature for 5 min and at –70°C for an additional 20 min, followed by addition of NIS (38 mg, 0.17 mmol) and TMSOTf (6 μ L, 0.032 mmol). Upon completion of glycosylation as monitored by TLC, saturated $NaHCO_3$ (0.1 mL) and pieces of $Na_2S_2O_3$ (s) were added to the mixture, followed by vigorously stirring at room temperature until the deep-red color of the solution changed to pale yellow. MS was then removed by filtration over celite, and the filtrate was dried (over $MgSO_4$), filtered, and concentrated for flash-chromatography purification over silica gel (elution: hexane/ CH_2Cl_2 /EtOAc = 6:3:1) to furnish the desired trisaccharide **41** as colorless oily liquid (134 mg, 70%). [α] $_D^{27}$ = +16.92 (c = 2.84, in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.38–7.21 (m, 43H; ArH), 7.19–7.16 (m, 2H; ArH), 5.08–4.75 (m, 16H), 4.74–4.45 (m, 9H), 4.39–4.12 (m, 6H), 4.00 (t, J = 9 Hz, 1H), 3.80–3.35 (m, 17H), 3.2 (s, 3H; OCH_3), 2.75–2.70 (m, 2H; $CH_2C=O$), 2.62–2.56 (m, 2H; $CH_2C=O$), 2.19 ppm (s, 3H; $CH_3C=O$); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 206.7, 172.96, 139.3, 138.86, 138.84, 138.77, 138.70, 138.57, 138.42, 138.27, 128.90, 128.86, 128.84, 128.80, 128.76, 128.58, 128.52, 128.44, 128.38, 128.34, 128.27, 128.14, 128.10, 128.08, 127.99, 127.96, 104.3, 103.9, 98.5, 85.2, 85.1, 82.4, 82.3, 80.0, 78.6, 78.2, 77.8, 77.7, 76.14, 76.09, 75.6, 75.42, 75.37, 75.23, 75.11, 73.75, 73.26, 70.1, 69.0, 68.6, 63.7, 55.7, 38.2, 30.3, 28.3 ppm. HRMS (ESI): m/z : calcd for $C_{87}H_{94}O_{18}Na$: 1449.6332 [$M+Na$] $^+$; found: = 1449.6332.

6-Chlorohexyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4,6-*-O*-di-*tert*-butylsilylidene- α -D-galactopyranosyl)- β -D-galactopyranosyl)-1- β -D-glucopyranoside (46): Thiolaetoside **23** (330 mg, 0.33 mmol), 6-chlorohexanol **13** (90 mg, 0.66 mmol), and flame-dried MS (AW300, 400 mg) were suspended in a 1:2:1 v/v CH_2Cl_2 – CH_3CN –EtCN (32 mL) solution at room temperature. The resulting mixture was stirred at room temperature for 10 min and at –70°C for additional 20 min, followed by addition of NIS (77 mg, 0.34 mmol) and TMSOTf (12 μ L, 0.066 mmol). Upon completion of glycosylation as judged by TLC, saturated $NaHCO_3$ (1 v/v % of reaction volume) and pieces of $Na_2S_2O_3$ (s) were added to the reaction mixture, followed by vigorously stirring at room temperature until the red color of the solution turned to pale yellow. The resulting crude mixture was filtered over celite and diluted with CH_2Cl_2 (40 mL). The CH_2Cl_2 solution was washed with H_2O (15 mL), brine (15 mL), dried (over $MgSO_4$), filtered, concentrated, and dried under vacuum for approximately 2 h. The resulting residue was dissolved in CH_2Cl_2 (5 mL), followed by addition of thiogalactopyranoside **45** (500 mg, 0.82 mmol) and flame-dried MS (AW300, 900 mg). The mixture was stirred at room temperature for 15 min and at –10°C for an additional 20 min, followed by addition of NIS (1.88 mg, 0.83 mmol) and TMSOTf (30 μ L, 0.17 mmol). The mixture was stirred at –10°C under N_2 and the glycosylation reaction was monitored by TLC. Upon completion of glycosylation as judged by TLC, saturated $NaHCO_3$ (1 v/v % of reaction volume) and small lumps of $Na_2S_2O_3$ (s) were added, followed by the workup procedure described in the preparation of compound **44**. The resulting CH_2Cl_2 solution was concentrated for flash column chromatography over silica gel (elution: hexane/ CH_2Cl_2 /EtOAc = 7:2:1) to furnish

target trisaccharide **46** as yellow oily liquid (248 mg, 75% from **23**). $[\alpha]_D^{27} = +46.47$ ($c = 1.06$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C , TMS): $\delta = 7.11\text{--}7.03$ (m, 4H; ArH), 4.97 (d, $J = 11.4$ Hz, 1H), 4.86 (d, $J = 3.0$ Hz, 1H), 4.80–4.14 (m, 19H), 4.02–3.62 (m, 11H), 3.54–3.14 (m, 10H), 1.64–1.53 (m, 4H; CH_2), 1.33–1.32 (m, 4H; CH_2), 0.91 (s, 9H; $t\text{Bu}$), 0.88 ppm (s, 9H; $t\text{Bu}$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 139.60$, 139.43, 139.01, 138.98, 138.88, 138.83, 138.69, 138.54, 128.80, 128.72, 128.67, 128.63, 128.58, 128.49, 128.16, 128.07, 128.03, 127.97, 127.94, 127.85, 127.78, 127.66, 127.61, 127.56, 103.86, 100.33, 82.75, 82.05, 81.35, 79.31, 78.36, 77.60, 75.39, 75.22, 74.34, 73.98, 73.59, 73.51, 73.45, 73.40, 72.45, 71.33, 70.75, 70.06, 68.70, 67.88, 67.78, 67.40, 45.36, 32.83, 30.03, 29.91, 28.06, 27.96, 27.86, 27.75, 26.85, 26.99, 25.80, 23.66, 21.00 ppm; HRMS (ESI): m/z : calcd $\text{C}_{88}\text{H}_{105}\text{ClNaO}_{17}\text{Si}$: 1483.7095 $[M+\text{H}]^+$; found: = 1483.7090.

6-Chlorohexyl 4-O-[4-O-(α -D-galactopyranosyl)- β -D-galactopyranosyl]-1- β -D-glucopyranoside, Gb₃ derivative (47): Protected Gb₃ **46** (270 mg, 1.82 mmol) dissolved in a mixture of AcOH (95%, 0.25 mL) and THF (5 mL) was treated with tetrabutylammonium fluoride (TBAF; 1 M in THF, 1.8 mL).^[40] After stirring at room temperature for 13 h, the reaction was diluted with CH_2Cl_2 (40 mL), which was washed with H_2O (2×15 mL), dried (over MgSO_4), filtered, and concentrated for the next hydrogenolysis. The resulting residue from desilylation (approximately 200 mg) was dissolved in a mixture of formic acid (0.35 mL) and MeOH (7 mL) and treated with 5% Pd/C (100 mg). The reaction mixture was stirred at room temperature under H_2 for 14 h. Upon completion of hydrogenolysis as judged by TLC, Pd/C was removed by filtration over celite, and the filtrate was concentrated for column chromatography purification on C18 coated reverse-phase gel (Cosmosil 75C18-OPN) (elution: $\text{H}_2\text{O}/\text{MeOH}$ gradient from 1:0 to 4:1) to furnish desired trisaccharide **47** as white glassy solid (67 mg, 60% from **46**). $[\alpha]_D^{27} = +33.5$ ($c = 0.20$, in MeOH); $^1\text{H NMR}$ (300 MHz, CD_3OD , 25°C): $\delta = 4.90$ (d, $J = 3.9$ Hz, 1H), 4.45 (t, $J = 8.3$ Hz, 2H), 4.32 (t, $J = 6.5$ Hz, 1H), 3.99–3.50 (m, 20H), 3.25 (t, $J = 8.4$ Hz, 1H), 1.79–1.70 (m, 2H; CH_2), 1.65–1.56 (m, 2H; CH_2), 1.46–1.35 ppm (m, 4H; CH_2); $^{13}\text{C NMR}$ (75 MHz, CD_3OD , 25°C): $\delta = 103.56$, 102.28, 100.60, 78.89, 77.62, 75.73, 75.10, 74.23, 72.43, 71.19, 71.09, 70.84, 69.62, 69.20, 68.85, 60.76, 60.67, 60.32, 45.93, 32.07, 28.87, 26.09, 24.62 ppm; HRMS (ESI): m/z : calcd $\text{C}_{24}\text{H}_{43}\text{ClNaO}_{16}$: 645.2132 $[M+\text{Na}]^+$; found: = 645.2132.

6-Chlorohexyl 2,3,6-tri-O-benzyl-4-O-[2,6-di-O-benzyl-4-O-benzoyl-3-O-(2,3-di-O-benzyl-4,6-O-di-tert-butylsilylidene- α -D-galactopyranosyl)- β -D-galactopyranosyl]-1- β -D-glucopyranoside (48): A mixture of thiolactoside **24** (280 mg, 0.28 mmol), 6-chlorohexanol **13** (76 mg, 0.56 mmol) and flame-dried MS (AW300, 330 mg) were suspended in 1:2:1 $\text{CH}_2\text{Cl}_2\text{--MeCN--EtCN}$ (28 mL) at room temperature under N_2 . The mixture was stirred at room temperature for 10 min under N_2 and at -70°C for additional 20 min, followed by addition of NIS (67 mg, 0.29 mmol) and TMSOTf (10 μL , 0.056 mmol). Upon completion of glycosylation, saturated NaHCO_3 (1 v/v% of reaction volume) and small lumps of $\text{Na}_2\text{S}_2\text{O}_3(\text{s})$ were added to the reaction mixture, followed by the workup procedure as described in the preparation of compound **44**. The crude residue obtained was dried under vacuum for approximately 2 h and made ready for next glycosylation. The crude residue from the previous step was then dissolved in CH_2Cl_2 (4 mL), to which thiogalactopyranoside **45** (436 mg, 0.72 mmol) and flame-dried MS (AW300, 700 mg) were added under N_2 . The resulting mixture was stirred at -10°C for 20 min, and then followed by addition of NIS (180 mg, 0.79 mmol) and TMSOTf (29 μL , 0.16 mmol). Upon completion of glycosylation as judged by TLC, saturated NaHCO_3 and small lumps of $\text{Na}_2\text{S}_2\text{O}_3(\text{s})$ were added and then the workup procedure as described in the preparation of compound **44** was performed. The crude residue was purified by flash column chromatography over silica gel (elution: hexane/ $\text{CH}_2\text{Cl}_2/\text{EtOAc} = 15:5:1$) to furnish expected trisaccharide **48** as yellow oily liquid (292 mg, 70%). $[\alpha]_D^{27} = +56.13$ ($c = 0.62$, in CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25°C , TMS): $\delta = 7.95$ (d, $J = 7.2$ Hz, 2H; ArH), 7.46 (t, $J = 7.5$ Hz, 1H; ArH), 7.35–7.19 (m, 29H; ArH), 7.14–7.08 (m, 6H; ArH), 7.04–7.00 (m, 2H; ArH), 5.81 (d, $J = 2.7$ Hz, 1H), 5.28 (d, $J = 3.3$ Hz, 1H), 5.09 (d, $J = 10.8$ Hz, 1H), 4.93–4.60 (m, 8H), 4.55–4.36 (m, 8H), 4.24 (d, $J = 12.0$ Hz, 1H), 4.11–4.07 (m, 1H), 3.97–3.83 (m, 6H), 3.73–3.59 (m, 6H), 3.49–3.37 (m, 6H), 1.74–1.65 (m, 4H; CH_2), 1.43–1.41 (m, 4H; CH_2), 0.95 (s, 9H;

$t\text{Bu}$), 0.92 ppm (s, 9H; $t\text{Bu}$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3 , 25°C): $\delta = 165.90$, 139.41, 139.24, 138.95, 138.90, 138.66, 138.44, 138.12, 133.18, 130.25, 130.09, 128.73, 128.63, 128.58, 128.49, 128.34, 128.33, 128.25, 128.24, 128.17, 128.07, 128.01, 127.91, 127.87, 127.81, 127.80, 127.75, 127.61, 127.57, 127.33, 103.94, 103.10, 94.00, 83.11, 81.91, 79.71, 77.60, 77.31, 75.67, 75.49, 75.27, 73.85, 73.63, 73.58, 73.26, 72.79, 70.74, 70.51, 70.06, 68.62, 67.91, 67.09, 66.97, 66.19, 45.30, 32.80, 29.89, 27.91, 27.53, 26.96, 25.77, 23.62, 20.87 ppm; HRMS (ESI): m/z : calcd $\text{C}_{88}\text{H}_{105}\text{ClNaO}_{17}\text{Si}$: 1519.6707 $[M+\text{Na}]^+$; found: 1519.6702.

6-Chlorohexyl 4-O-[3-O-(α -D-galactopyranosyl)- β -D-galactopyranosyl-1- β -D-glucopyranoside, isoGb₃ derivative (49): Protected isoGb₃ **48** (280 mg, 1.87 mmol) in a mixture of AcOH (95%, 0.25 mL) and THF (5 mL) was treated with TBAF (1 M in THF, 1.8 mL).^[40] After stirring at room temperature for 13 h, the mixture was diluted with CH_2Cl_2 (40 mL), washed with H_2O (2×15 mL), dried over MgSO_4 , filtered, and concentrated for the next debenzoylation. The resulting crude product from desilylation (approximately 200 mg) was dissolved in 1:2 v/v MeOH/THF (3 mL) and treated with 2 N NaOH (2 mL), followed by stirring at 60°C for 36 h. Upon completion of benzoyl ester removal, the mixture was diluted with CH_2Cl_2 (40 mL), and the solution was then washed with 1 N HCl (15 mL), H_2O (15 mL), brine (15 mL), dried over MgSO_4 , filtered, and concentrated for next hydrogenolysis. The crude residue from debenzoylation step was dissolved in a mixture of formic acid (0.35 mL) and MeOH (7 mL), followed by addition of 5% Pd/C (100 mg). The mixture was stirred at room temperature under H_2 for 16 h. Upon completion of hydrogenolysis as judged by TLC, Pd/C was removed by filtration over celite, and the filtrate was concentrated for column chromatography purification on C18 coated reverse phase silica gel (Cosmosil 75C18-OPN; elution: $\text{H}_2\text{O}/\text{MeOH}$ gradient from 1:0 to 4:1) to furnish desired trisaccharide **49** as a colorless glassy solid (64 mg, 55% from **48**). $[\alpha]_D^{27} = +53.00$ ($c = 0.80$, in MeOH); $^1\text{H NMR}$ (300 MHz, CD_3OD , 25°C): $\delta = 5.07$ (s, 1H), 4.45 (d, $J = 6.6$ Hz, 1H), 4.32 (d, $J = 7.8$ Hz, 1H), 4.24 (t, $J = 6.3$ Hz, 1H), 4.07 (s, 1H), 3.96–3.53 (m, 18H), 3.44–3.42 (m, 1H), 3.34–3.32 (m, 1H), 3.27 (t, $J = 8.1$ Hz, 1H), 1.84–1.75 (m, 2H; CH_2), 1.71–1.62 (m, 2H; CH_2), 1.48–1.43 ppm (m, 4H; CH_2); $^{13}\text{C NMR}$ (75 MHz, CD_3OD , 25°C): $\delta = 105.03$, 104.16, 97.66, 80.99, 79.83, 76.57, 76.42, 76.35, 74.67, 72.22, 71.30, 71.08, 70.98, 70.73, 70.11, 66.60, 62.71, 62.42, 61.96, 45.71, 33.71, 30.56, 27.69, 26.32 ppm; HRMS (ESI): m/z : calcd $\text{C}_{24}\text{H}_{43}\text{ClO}_{16}\text{Na}$: 645.2132 $[M+\text{Na}]^+$; found: 645.2132.

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