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Chemical approach for the syntheses of GM4 isomers with sialic acid to non-natural linkage positions on galactose

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ABSTRACT

Cell-surface glycans containing sialic acid are involved in various biological phenomena. However, the syntheses of GM4 derivatives with (2→2) and (2→4) linkages have not been investigated to date. In this study, sialylation of all of the hydroxyl groups on galactose were investigated for the syntheses of GM4 isomers. Regioselective sialylation was achieved via protection of galactosyl acceptors using electron-rich benzyl groups. These synthetic sialylated glycans will prove to be useful tools for studying unidentified carbohydrate-mediated biological roles.

1. Introduction

Cell-surface glycans, including N- and O-linked glycans, glycosphingolipids, glycosaminoglycans, glycophospholipid anchors, and lipo–oligo/polysaccharides, participate in a wide range of biological processes.[1,2] Unlike nucleic acids and proteins, oligosaccharides, which often have branched units, are rich in diversity. The combination of three different nucleotides or amino acids can only generate six trimers, while three different hexoses could theoretically generate more than 1000 trisaccharide regioisomers. Thus, by selecting a limited number of combinations from the many theoretical saccharide isomers, organisms construct sugar chain structures with specific functions.

Sialic acids are a family of naturally occurring 2-keto-3-deoxynononic acids that are involved in various functions such as cell–cell interactions, binding for bacterial toxins and viruses, and signal transduction.[3] The structural basis for the diversity of sialic acids arises from substitutions of one or more of the hydroxyl groups of *N*-acetylneuraminic acid (Neu5Ac), Neu5Gc, or KDN with acetyl, methyl, lactyl, phosphate, or sulfate groups.[4] Among the more than 50 derivatives of sialic acid, Neu5Ac is the most common and normally appears at the non-reducing ends of glycoproteins and glycolipids. Because they are generally present at the terminal ends of glycoconjugates located on cell surfaces, sialic acids act either as masks or recognition sites for ligand–receptor interactions in many important biological events.[1,4,5] Therefore, sialic acid-containing glycans have attracted attention in the fields of immunology and medicinal chemistry. In naturally occurring sialosides, Neu5Ac is observed on galactosides linked through the α(2→3) or α(2→6) bonds in glycoproteins and glycolipids.[6] The difference in the linkage to the sialic acid modulates its interaction with receptor proteins.

Influenza A viruses can be classified into subtypes depending on the types of surface glycoprotein present: hemagglutinin (HA) and neuraminidase (NA). There are 16 known HA subtypes, and 9 known NA subtypes of a total of 144 theoretically possible subtypes. Influenza virus infection is initiated by the attachment of the HA to sialic acid-containing ligands such as gangliosides and glycans on glycoproteins, which are located on host cell surfaces. Avian influenza virus HAs bind to sialic acid linked via α(2→3) glycosidic bonds, while human influenza virus HAs bind to α(2→6) receptors. Thus, the difference in the binding position of the sialic acid to the galactose is very important for species recognition. The ability of synthetic chemists to construct desired glycoside bonds has progressed and has contributed to our understanding of the recognition mechanisms for receptor proteins and the development of enzyme inhibitors.[7–10]

Sialylation is one of the most challenging reactions in carbohydrate chemistry and often proceeds with low yield and poor stereoselectivity.[11–13] In particular, the stereoselective synthesis of α-sialosides is complicated because sialic acid does not contain a neighboring C-3 functional group to direct the stereochemical outcome of the glycosylation. Moreover, the electron-withdrawing property of the carboxylic acid group at the anomeric position

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and the lack of a hydroxyl group at C-3 makes sialyl donors prone to undesired 2,3-elimination due to destabilization of the oxocarbenium ion intermediate generated from the sialyl donor.

Consequently, many synthetic sialylation methods have been developed to improve the stereoselectivity and coupling efficiency of the reaction.[11] However, these methodologies are focused on efficient α-sialoside installation with α(2→3) or α(2→6) linkages; thus, the strategies for the synthesis of non-natural sialosides with bonds to the 2- or 4-position of galactose remain undeveloped. Therefore, a synthetic method that enables the introduction of sialic acid groups at the sites of the poor reactive hydroxyl groups in galactose is required. Recently, Mine et al.[14] reported that α2,3-sialyltransferase from *Photobacterium* sp. JT-ISH-224 produced a regio-mistaken sialyl-transferred sialoside which had sialic acid at the C2 hydroxyl group of lactose. This results may indicate that some bacterial sialyltransferases have a potency to synthesize unusual sialosides in vivo. The development of chemical synthesis method for non-natural sialosides enables supply of an adequate amount of the sialoside to explore unknown biological function.

Here, we describe the comprehensive synthesis of sialyl galactoside isomers with both natural and non-natural sialic acid binding positions to galactose (Scheme 1). Access to such a range of gangliosides, including those with non-natural linkages, should lead to the discovery of novel biological functions and new aspects of the enzymatic mechanisms related to gangliosides. In this study, natural sialosides were synthesized to investigate the reactivity of galactosyl acceptors with hydroxyl group protected by acyl or alkyl groups. Based on these results, non-natural gangliosides were then efficiently synthesized by modulating the poor reactive hydroxy groups to more reactive ones.

2. Results and discussion

2.1. Design of the glycosyl acceptors and sialyl donor

Regioselective glycosylation is generally achieved when the glycosyl acceptor possesses protected hydroxyl groups with only one free hydroxyl group for reaction with the glycosyl donor. The outcomes of sialylations are known to depend primarily on the nature of the protecting groups introduced on the glycosyl donor and acceptor, which differ with respect to their electronic and steric properties. In this study, benzyl and benzoyl groups were selected as the protecting groups for the donor to investigate the reactivity of various glycosyl acceptors with different protecting groups. The allyl group was selected as a temporary protecting group for the aglycones of the glycosyl acceptors. This aglycone can be removed selectively or applied to labeling or immobilization, and so allyl glycoside was used as starting material. However, sialylation to allyl acceptor with thiophenyl sialoside as a donor decreased significantly in the yield under the NIS/TfOH activation method. Therefore, allyl group was hydrogenated using Lindlar catalyst to the corresponding propyl group. The propyl glycosides were used as acceptors to investigate sialylations. A set of selectively protected glycosyl acceptors (**1**–**6**, Fig. 1) prepared from allyl β-D-galactopyranoside **7** was then synthesized as described in Section 2.2–2.5.

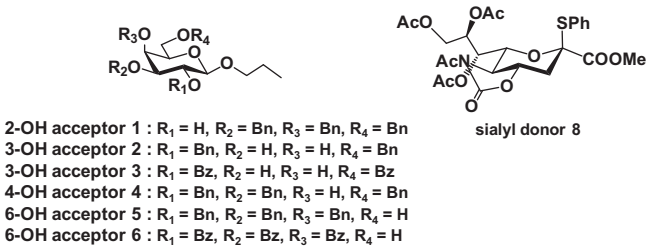


Figure 1. Six galactosyl acceptors and sialyl donor.

The nature of the 5-N-protecting group can greatly influence the efficiency and stereoselectivity of the sialylation.[12,13,15] Crich and Li achieved an elegant synthesis of (2→3) and (2→6)-linked sialosides using an *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected sialyl donor.[16] In addition, it was observed that the sialyl donor without oxazolidinone ring was low reactivity to 6-OH acceptor, whereas oxazolidinone-protected sialyl donor gave higher reactivity to the acceptor. For synthesis of non-natural linkages to axial and sterically hindered hydroxyl groups, the donor should have the high reactivity. Moreover, if β-linked sialosides are produced by sialylation, β-linked sialosides will also be attractive to investigate biological function. Thus, sialyl donor **8** (Fig. 1) bearing the *N*-acetyl-5-*N*,4-*O*-oxazolidinone moiety was employed as a donor in this study.

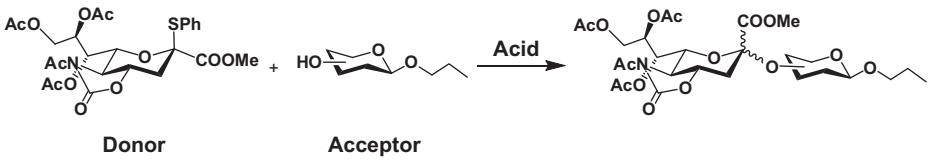
2.2. Preparation of the 6-OH acceptor

To obtain the 6-OH glycosyl acceptor, the trityl group was selected as a temporary and orthogonally functional protecting group (Scheme 2).[17] The allyl β-D-galactoside **7** was regioselectively tritylated at the 6-position, and then the remaining hydroxyl groups were protected with benzyl groups to afford **9** (74% yield, in two steps). Removal of the trityl group under acidic conditions and hydrogenolysis with Lindlar's catalyst afforded the 6-OH glycosyl acceptor **5** (77% yield, in two steps). Similarly, the 6-OH glycosyl acceptor **6** was prepared from **7** via benzoylation instead of benzylation.

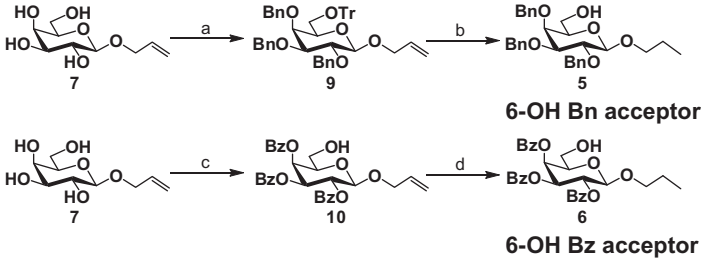
2.3. Preparation of the 3,4-OH acceptor

Regioselective sialylation of the 3,4-diol groups of galactose to synthesize naturally occurring α(2→3) linkages has been successfully achieved.[18–21] In general, glycosyl acceptors for α(2→3) sialylation have 3,4-diol structures designed for regioselective glycosylation at the more reactive C3 hydroxyl group.

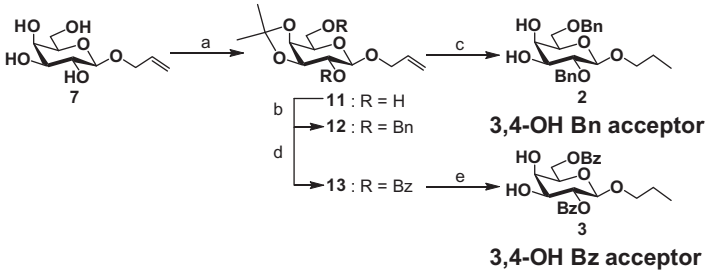
To construct the 3,4-diol structure, an isopropylidene acetal group was introduced to the 3- and 4-positions of galactose. Thus, compound **7** was treated with acetone and a catalytic amount of CSA in DMF to afford 3,4-*O*-isopropylidene protected derivative **11** in 64% yield (Scheme 3). The free OH group in **11** was then converted to the benzyl ether **12**, and the isopropylidene acetal group of **12** was selectively removed using 0.5 M aqueous HCl. Finally, the deprotected compound was hydrogenated with Lindlar's catalyst under H_2 gas in EtOAc and EtOH to afford the 3,4-OH acceptor **2**



Scheme 1. Plan for the synthesis of sialyl galactoside isomers.



Scheme 2. Synthesis of 6-OH acceptors **5** and **6**. (a) (i) TrCl, pyridine, 70 °C, 10 h; (ii) BnBr, NaH, DMF, rt, 13 h, 74% (2 steps); (b) (i) 4 M HCl/Dox, rt, 20 min, 79%; (ii) Lindlar's catalyst, H_2 gas, EtOAc, EtOH, rt, 6 h, 98%; (c) (i) TrCl, pyridine, 70 °C, 16 h; (ii) BzCl, pyridine, rt, 2.5 h; (iii) 4 M HCl/THF, rt, 1 h, 64% (3 steps); (d) $Pd(OH)_2$, H_2 gas, EtOAc, rt, 5 h, 98%.



Scheme 3. Synthesis of 3,4-OH acceptors **2** and **3**. (a) acetone, CSA, DMF, rt, 72 h, 64%; (b) BnBr, NaH, DMF, rt, 14 h, quant.; (c) (i) 0.5 M HCl/THF, 40 °C, 8 h, 97%; (ii) Lindlar's catalyst, H_2 gas, EtOAc, EtOH, rt, 6.5 h, 99%; (d) BzCl, pyridine, CH_2Cl_2, 0 °C, 3.5 h, quant.; (e) (i) 0.5 M HCl/THF, 40 °C, 8 h, 96%; (ii) $Pd(OH)_2$, H_2 gas, EtOAc, rt, 4 h, 96%.

(96% yield, in three steps). Similarly, treatment of compound **11** with benzoyl chloride and pyridine in CH_2Cl_2 afforded the benzoylated compound **13**; isopropylidene group removal and palladium-mediated hydrogenolysis afforded the corresponding 3,4-OH acceptor **3** (92% yield, in three steps).

2.4. Preparation of the 2-OH acceptor

Synthetic route via an orthoester[22] was initially tried to synthesize compound **1**. However, the method gave low yield in benzylation. Therefore, the synthetic route via the benzylidene after introducing aglycone was planned. Compound **7** was protected with benzylidene acetal to afford 4,6-*O*-benzylidenated glalactosides (Scheme 4). Unfortunately, the benzylidene-protected product was not soluble in many organic solvents such as EtOAc, MeOH, CH_2Cl_2, and toluene. Thus, to purify the reaction mixture using normal phase silica gel chromatography, acetylation of the 2,3-diol moiety on the benzylidene-protected product was performed to afford **14** in 83% yield (2 steps). Acetyl groups of compound **14** were removed by NaOMe in MeOH, followed by monobenzylation of the C3 hydroxyl group and acetylation of the C2 hydroxyl group to afford **15** (22%). The low yield of the desired monobenzylated product was due to the formation of byproducts, that is, the 2,3-di-*O*-benzyl derivative (29%) and the 2-*O*-benzyl derivative (2%). Prior to reduction, the allyl group of compound **15** was converted to the propyl group via hydrogenolysis because it reacted with the BH_3. Subsequently, regioselective reduction of the 4,6-*O*-benzylidene acetal derivative using $CoCl_2$ and BH_3·THF[23] afforded the corresponding 4-*O*-benzyl derivative **16** in 83% yield.

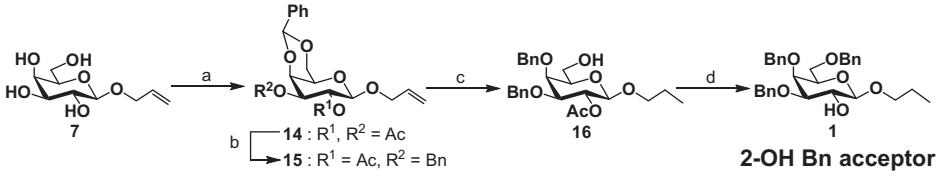
Next, compound **16** was benzylated with benzyl imidate under acidic conditions, in which the acetate esters were stable and not hydrolyzed.[24,25] Finally, the acetyl group was removed using NaOMe in MeOH and aqueous NH_3 to afford 2-OH derivative **1**, which served as the glycosyl acceptor in the synthesis of Neu(2→2)Gal.

2.5. Preparation of the 4-OH acceptor

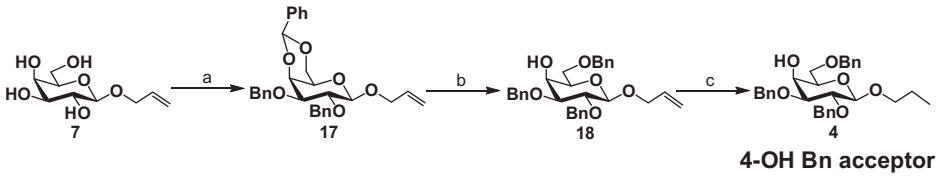
Compound **7** was first protected with benzylidene acetal at the 4- and 6-positions, and then the remaining hydroxyl group was benzylated to afford **17** (74% yield, in two steps) (Scheme 5). Regioselective ring-opening of the benzylidene acetal of **17** using $NaBH_3CN$ and 4 M HCl in dioxane afforded **18** almost exclusively in 82% yield.[26,27] Treatment of compound **18** with Lindlar's catalyst under H_2 gas in EtOAc and EtOH afforded the 4-OH propyl acceptor **4** in 98% yield.

2.6. Sialylation with galactosyl acceptors

To investigate the solvent effect on the synthesis of the α(2→6) linkage, coupling reactions of donor **8** with acceptor **5** were examined in various mixtures of MeCN and CH_2Cl_2 at −40 °C using the

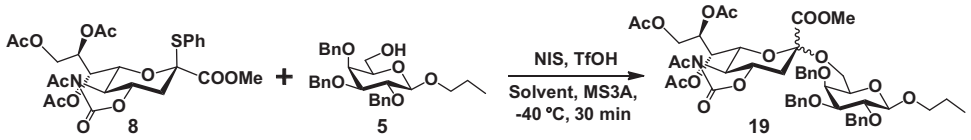


Scheme 4. Synthesis of 2-OH Bn acceptor **1**. (a) (i) $PhCH(OCH_3)_2$, CSA, DMF, rt, 17 h; (ii) Ac_2O, pyridine, 50 °C, 2 h, 83% (2 steps); (b) (i) NaOMe, MeOH, DMF, rt, 48 h; (ii) BnBr, NaH, DMF, 0 °C, 23 h; (iii) Ac_2O, pyridine, rt, 2.5 h, 22% (3 steps); (c) (i) Lindlar's catalyst, H_2 gas, EtOAc, EtOH, THF, rt, 4 h, quant.; (ii) $CoCl_2$, BH_3·THF, from 0 °C to rt, 55 min, 83%; (d) (i) benzyl imidate, TfOH, CH_2Cl_2, cHex, MS4A, from 0 °C to rt, 1.5 h; (ii) NaOMe, MeOH, NH_3 aq, 50 °C, 28 h, 44% (2 steps).



Scheme 5. Synthesis of 4-OH Bn acceptor **4**. (a) (i) $PhCH(OCH_3)_2$, CSA, DMF, rt, 24 h; (ii) BnBr, NaH, DMF, rt, 19 h, 74% (2 steps); (b) $NaBH_3CN$, 4 M HCl/Dox, THF, 0 °C, 2 h, 82%; (c) Lindlar's catalyst, H_2 gas, EtOAc, EtOH, rt, 3 h, 98%.

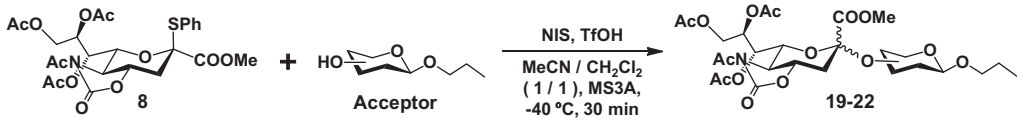
Table 1
Effect of solvent on sialylation

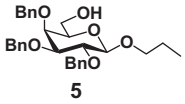
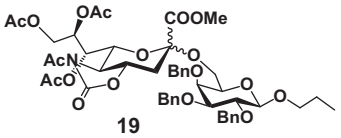
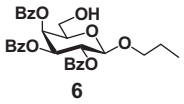
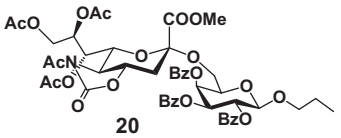
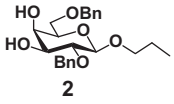
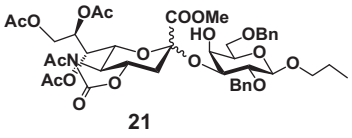
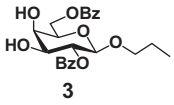
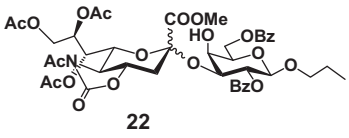


Entry	Solvent	Yield (%)	Ratio (α:β)
1	CH_2Cl_2	91.3	7.1:1
2	MeCN	94.2	6.0:1
3	MeCN/CH_2Cl_2 (1/1)	98.3	10.0:1

Anomeric ratios were determined by ^1H NMR analysis.
Donor:acceptor = 1.5:1.

Table 2
Effect of the acceptor protecting groups on sialylation



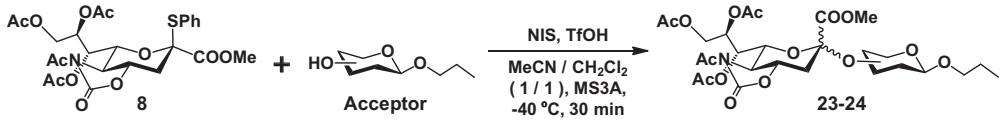
Entry	Acceptor	Product	Yield (%)	Ratio (α:β)
1			98.3	10.1:1
2			96.8	α only
3			76.7	1:1
4			56.6	1:1.9

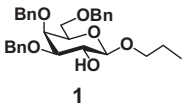
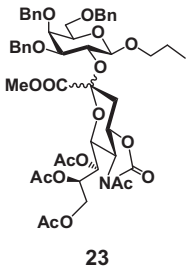
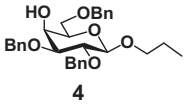
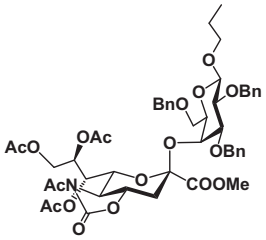
Anomeric ratios were determined by ^1H NMR analysis.
Donor:acceptor = 1.5:1.

promoter NIS/TfOH (Table 1).[16] As shown in Table 1 entry 3, the highest yield (98%) and stereoselectivity (α:β = 10:1) for the α(2→6) sialylation was obtained in a 1:1 (v/v) mixture of MeCN and CH_2Cl_2. The influence of the solvent on the sialylation was probably due to both the moderate solvent polarity and stabilization of the oxocarbenium ion due to the nitrile effect.[28–30] This same solvent-system was applied to following sialylations.

Next, the effect of acceptors with acyl and alkyl protecting groups on the sialylation was investigated using synthesized α(2→6) and α(2→3) linked GM4 derivatives (Table 2). The ano-

Table 3
Synthesis of sialyl galactose regioisomers



Entry	Acceptor	Product	Yield (%)	Ratio (α:β)
1	 1	 23	>99	2.4:1
2	 4	 24	57.7*	β only

Anomeric ratios were determined by ^{1}H NMR analysis.
Donor:acceptor = 1.5:1.
* Acceptor recovery = 11.9%.

meric configurations of all sialylated products were assigned on the basis of both the chemical shifts of *H*-3eq and the $^{3}J_{C1,H\text{-}3ax}$ coupling constants.[31] Sialylation with the 6-OH derivatives **5** and **6** afforded the corresponding sialosides in high yields (98% and 97%) with excellent stereoselectivity (10:1 and α only, entries 1 and 2, respectively). When compared to their stereoselectivity, the benzoyl acceptor 6 was suited to afford α-isomer in 6-O-sialylation. In the case of the 3,4-OH acceptors **2** and **3**, 3-O-sialylated products **21** and **22** were obtained with moderate yields (77% and 57%) and low stereoselectivity (1:1 and 1:1.9), respectively, (entries 3 and 4). Crich and Li[16] and Farris and Meo[32] observed similar β-stereoselectivity in the coupling of donor **8** with 3,4-diol acceptors. Note that, in the sialylation using 3,4-OH acceptors **2** and **3**, disialylates at both the 3 and 4-positions were obtained in 9% and 7% yield, respectively, and a small amount of sialyl lactone was also obtained. In both reactions, the (2→4)-monosialylate was not detected in the crude mixture. Due to these side reactions, the yields of the target compounds were decreased. As Table 2, the sialylation with the 6-OH acceptors **5** and **6** afforded higher yield with excellent stereoselectivity than the sialylation with the 3,4-OH acceptors **2** and **3**. Moreover, the glucosyl acceptors protected with the electron-donating benzyl group exhibited increased reactivity for sialylation.

Based on the results for the α(2→6) and α(2→3) sialylation, the benzyl group used to protect acceptors designed for the synthesis of GM4 isomers with non-natural linkages. As presented in Table 3, the synthesis of (2→2) linked GM4 derivative **23** was realized in 99% yield with moderate selectivity (entry 1, α:β = 2.4:1). Previously, a galactoside blocked at only the C6 hydroxyl group was reported to react with sialyl donors specifically at the C3 position,[33] and regioselective sialylation with a 2,3-diol galactosyl acceptor led to the formation of only the α(2→3) linkage product.[21,34] Thus, the C3 hydroxyl group is assumed to be more reactive than the C2 hydroxyl group. Nevertheless, in our case, sialylation with the 2-OH acceptor **1** afforded sialylation product in higher yield than that of the 3,4-OH acceptor **2**, which afforded the desired product in a modest yield along with sialyl lactone and disialylated byproducts. Moreover, reaction of the 2-OH acceptor **1** proceeded with higher α-stereoselectivity (α:β = 2.4:1) than 3,4-OH acceptor **2**. Based on these results, it can be concluded that sialylation of the C2 hydroxyl group can be performed using acceptor **1**, which is protected with an electron-rich benzyl group.

Sialylation with 4-OH glycosyl acceptor **4** afforded the corresponding disaccharide **24** in 58% yield. In contrast to sialylation with 2-OH acceptor, the sialylation gave lower yields of the disaccharide due to poor reactivity on axial hydroxyl group, along with only 12% recovery of the unreacted acceptor **4**. (Sialylation with other position of galactose hydroxyl groups were not isolated recovery of the unreacted acceptor.) Moreover, surprisingly, the (2→4) linked product was detected only β-isomer ($^{3}J_{C\text{-}1',H\text{-}3'ax}$ = 0 Hz). To investigate the β-selectivity, additional experiments were performed in different conditions of temperature and solvent. However, the α-isomer was not detected in the conditions, and there was no noticeable effect on the stereoselectivity. This anomeric configuration results showed that the reactivity of 4-OH on galactose with sialyl donor is clearly different from hydroxyl groups of the other position. However, the mechanism for this unique β-sialylation is not explained except for dependency on thermodynamic stability of product. Therefore, it remains interesting to investigate the mechanism and α-selective synthetic method.

3. Conclusion

In this study, comprehensive GM4 isomers with Neu5Ac residues at each hydroxyl group of galactose were synthesized for the first time. A set of selectively protected glycosyl acceptors were

prepared and their sialylations with an *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected sialyl donor were investigated. A mixture of MeCN and CH_2Cl_2 (1:1, v/v) was determined to be effective for achieving stereoselective sialylation in Neuα(2→6)Gal derivative, and GM4 isomers could be synthesized efficiently using this solvent system. Moreover, it was demonstrated that the oxazolidinone-protected sialyl donor could be utilized to efficiently sialylate the 2 and 4 positions of galactoside. All of the hydroxyl groups of galactoside were linked to sialic acid to form Neuα(2→2)Gal, Neuβ(2→2)Gal, Neuα(2→3)Gal, Neuβ(2→3)Gal, Neuβ(2→4)Gal, Neuα(2→6)Gal and Neuβ(2→6)Gal derivatives. Most importantly, sialylation was performed at the less reactive C2 and C4 hydroxyl groups of galactose acceptors to afford non-natural GM4 derivatives. Thus, this synthetic method is effective for the preparation of GM4 derivatives with Neu5Ac residues of galactoside at various linkage positions. When the glycosyl acceptors were protected by benzyl group, the reactivity of each hydroxyl group on the acceptor in sialylation got to the following order: 6-OH ≒ 2-OH > 3-OH > 4-OH. Meanwhile, (2→4) linked sialoside was given only β-anomer and further studies on the synthesis of Neuα(2→4)Gal needs to be improved the stereoselectivity and coupling efficiency.

4. Experimental section

4.1. General

All reagents were purchased from commercial sources and used without further purification whereas NIS was recrystallized by 1,4-dioxane and tetrachloromethane before use.[35] Dry solvents were dried by molecular sieves (3 or 4 Å) that activated in vacuo at 200 °C and stored over molecular sieves. TLC was performed on Merck TLC plates silica gel 60 F_{254} 0.25 mm. Compounds were detected by UV and/or by treatment with EtOH/H_2O/H_2SO_4/orcinol and subsequent heating. Column chromatography was performed with Kanto kagaku silica gel 60 N, spherical neutral, particle size 40–50 μm or 63–210 μm. Solvents for column chromatography were purchased from commercial sources and used as received. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV-400 spectrometers (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) or Bruker AV-600 spectrometers (600 MHz for ^{1}H, 150.9 MHz for ^{13}C). Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in deuterated chloroform. ^{13}C NMR spectra were also recorded on the same NMR spectrometers and were calibrated with $CDCl_3$ peak (δ = 77.00 ppm). The $^3J_{C1,H\text{-}3ax}$ coupling constants were measured by the phase-sensitive gradient-enhanced HMBC spectra.[30,36] Multiplicities are reported by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; *J* = coupling constant values in Hertz. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a JEOL JMS-S3000 mass spectrometer using 2,5-dihydroxybenzoic acid (DHBA) as the matrix.

4.2. Synthesis of 6-OH Bn acceptor

4.2.1. Allyl 2,3,4-tri-*O*-benzyl-6-*O*-triphenylmethyl-β-D-galactopyranoside (9)

A stirred solution of allyl β-D-galactopyranoside **7** (1.20 g, 5.45 mmol) in dry pyridine (20 mL) was added triphenylmethyl chloride (1.67 g, 5.99 mmol) and heated to 70 °C. After 10 h, the reaction mixture was cooled down to room temperature and quenched by addition of methanol (4 mL). Subsequently, the solvent was evaporated under reduced pressure. The residue was dissolved in dry DMF (30 mL) and added sodium hydride (60% dispersion in oil, 1.30 g, 32.5 mmol) in an ice bath. After stirring for 1 h at room temperature under reduced pressure, benzyl bromide (4.0 mL, 33.6 mmol) was added dropwise to the solution in an ice bath, and the mixture was warmed to room temperature, and stirred for 13 h. The reaction was quenched by addition of methanol (10 mL). The mixture was then diluted with H_2O and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (15:1) to give **9** (2.94 g, 4.01 mmol, 73.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.11 (m, 30H, 6×Ph), 5.94 (m, 1H, OCH_2CH=CH_2), 5.31 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.0 Hz, J_{trans} = 17.6 Hz, OCH_2CH=C*H*H), 5.17 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{cis} = 10.4 Hz, OCH_2CH=CH*H*), 4.83 (d, 2H, *J* = 10.8 Hz, PhCH_2), 4.72 (d, 2H, *J* = 12.0 Hz, PhCH_2), 4.65 (d, 2H, *J* = 11.6 Hz, PhCH_2), 4.40 (ddt, 1H, *J* = 5.2 Hz, *J* = 12.8 Hz, OC*H*HCH=CH_2), 4.36 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.12 (ddt, 1H, *J* = 6.0 Hz, *J* = 12.8 Hz, OCH*H*CH=CH_2), 3.84 (d, 1H, $J_{3,4}$ = 2.8 Hz, H-4), 3.80 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.51–3.45 (m, 2H, H-6b, H-3), 3.34 (t, 1H, $J_{5,6}$ = 6.4 Hz, H-5), 3.20 (dd, 1H, $J_{6a,6b}$ = 9.2 Hz, H-6a).

4.2.2. Propyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (5)

Compound **9** (1.14 g, 1.56 mmol) was dissolved in hydrogen chloride-dioxane (4 M, 10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 20 min. Subsequently, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give allyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (604 mg, 1.23 mmol, 79.2%).

A solution of compound allyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (413 mg, 841 μmol) in EtOAc, EtOH (5:2, v/v, 14 mL) was stirred vigorously with Lindlar's catalyst (57 mg) at room temperature under H_2 atmosphere for 6 h. The solid material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1) to give **5** (404 mg, 821 mmol, 97.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.25 (m, 15H, 3×Ph), 4.96 (d, 2H, *J* = 11.6 Hz, PhCH_2), 4.83–4.65 (m, 4H, 2×PhCH_2), 4.36 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.93–3.88 (m, 1H, OC*H*HCH_2CH_3), 3.84 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.79–3.73 (m, 2H, H-4, H-6b), 3.52 (dd, 1H, $J_{3,4}$ = 3.2 Hz, H-3), 3.49–3.43 (m, 2H, H-6a, OCH*H*CH_2 CH_3), 3.36 (t, 1H, $J_{5,6}$ = 6.0 Hz, H-5), 1.70–1.64 (m, 2H, OCH_2CH_2 CH_3), 1.51 (dd, 1H, OH-6), 0.96 (t, 3H, $OCH_2CH_2CH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.75, 138.48, 138.27, 128.72, 128.45, 128.31, 128.20, 127.98, 127.70, 127.64, 127.59 (arom), 104.11 (C-1), 82.31 (C-3), 79.71 (C-2), 75.24 (PhCH_2), 74.49 (C-5), 74.12 (PhCH_2), 73.45 (PhCH_2), 72.87 (C-4), 71.73 ($OCH_2CH_2CH_3$), 62.06 (C-6), 23.03 ($OCH_2CH_2CH_3$), 10.71 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{30}H_{36}O_6Na$ ($M+Na^+$): 515.2410, Found: 515.2446.

4.3. Synthesis of 6-OH Bz acceptor

4.3.1. Allyl 2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (10)

A stirred solution of allyl β-D-galactopyranoside **7** (4.00 g, 18.1 mmol) in dry pyridine (80 mL) was added triphenylmethyl chloride (6.60 g, 23.6 mmol) and heated to 70 °C. After 16 h, the reaction mixture was cooled down to 0 °C, and benzoyl chloride (2.40 mL, 20.7 mmol) was added dropwise. After stirring for 2.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, then washed with 1 M HCl aqueous, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was dissolved in hydrogen chloride–THF (4 M, 150 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2, then washed with saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1) to give **10** (6.16 g, 11.6 mmol, 63.7%). ^{1}H NMR (400 MHz,

$CDCl_3$): δ 8.13–7.23 (m, 15H, 3×Ph), 5.90–5.77 (m, 3H, H-2, OCH_2-C*H*=CH_2, H-4), 5.59 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 5.27 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.0 Hz, J_{trans} = 17.2 Hz, OCH_2-CH=C*H*H), 5.16 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{cis} = 10.4 Hz, OCH_2-CH=CH*H*), 4.86 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.41 (ddt, 1H, *J* = 4.8 Hz, *J* = 13.2 Hz, OC*H*HCH=CH_2), 4.20 (ddt, 1H, *J* = 6.0 Hz, *J* = 13.2 Hz, OCH*H*CH=CH_2), 4.03 (t, 1H, $J_{5,6}$ = 6.8 Hz, H-5), 3.87–3.63 (m, 2H, H-6), 2.66 (t, 1H, OH-6).

4.3.2. Propyl 2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (6)

A solution of compound **10** (203 mg, 380 μmol) in EtOAc (6 mL) was stirred vigorously with palladium hydroxide (100 mg) at room temperature under H_2 atmosphere for 5 h. The solid material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1 to 2:1) to give **6** (199 mg, 373 mmol, 98.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–7.23 (m, 15H, 3×Ph), 5.87–5.81 (m, 2H, H-2, H-4), 5.58 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 4.80 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.03 (m, 1H, H-5), 3.96–3.90 (m, 1H, OC*H*HCH_2CH_3), 3.88–3.81 (m, 1H, H-6b), 3.69–3.63 (m, 1H, H-6a), 3.56–3.50 (m, 1H, OCH*H*CH_2CH_3), 2.65 (t, 1H, OH-6), 1.63–1.53 (m, 2H, $OCH_2CH_2CH_3$), 0.80 (t, 3H, $OCH_2CH_2CH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 133.83, 133.34, 133.20, 130.17, 129.77, 129.68, 129.49, 128.79, 128.75, 128.65, 128.39, 128.34 (arom), 101.74 (C-1), 74.00 (C-5), 72.13 ($OCH_2CH_2CH_3$), 71.90 (C-3), 70.07 (C-2), 69.08 (C-4), 60.63 (C-6), 22.72 ($OCH_2CH_2CH_3$), 10.23 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{30}H_{30}O_9Na$ ($M+Na^+$): 557.1788, Found: 557.1788.

4.4. Synthesis of 3-OH Bn acceptor

4.4.1. Allyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (11)

A stirred solution of allyl β-D-galactopyranoside **7** (201 mg, 913 μmol) in dry DMF (1.80 mL) was added acetone (1.34 mL, 18.2 mmol) and CSA (44.0 mg, 189 μmol) at room temperature and stirred for 72 h. Subsequently, the reaction mixture was neutralized with triethylamine (0.05 mL, excess), and the solvent was evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography, eluting with Hex/EtOAc (1:1) to give **11** (150 mg, 577 mmol, 63.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (m, 1H, OCH_2C*H*=CH_2), 5.32 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.2 Hz, J_{trans} = 17.6 Hz, OCH_2CH=C*H*H), 5.23 (ddd, 1H, $J_{allylic}$ = 1.2 Hz, J_{cis} = 10.4 Hz, OCH_2CH=CH*H*), 4.39 (ddt, 1H, *J* = 5.6 Hz, *J* = 12.8 Hz, OC*H*HCH=CH_2), 4.26 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.18–4.09 (m, 3H, H-3, H-4, OCH*H*CH=CH_2), 3.99 (m, 1H, H-5), 3.85 (m, 2H, H-6), 3.59 (dt, 1H, H-2), 2.54 (s, 1H, OH-2), 2.19 (br d, 1H, OH-6), 1.53 (s, 3H, OCH_3), 1.35 (s, 3H, OCH_3).

4.4.2. Allyl 3,4-*O*-isopropylidene-2,6-di-*O*-benzyl-β-D-galactopyranoside (12)

Sodium hydride (60% dispersion in oil, 2.00 g, 50.0 mmol) washed thrice with hexane was placed in dry DMF (5 mL). The slurry was cooled in an ice bath and compound **11** (3.21 g, 12.3 mmol) dissolved in dry DMF (60 mL) was added dropwise with stirring. When the addition was completed, the stirring was continued for 1 h at room temperature under reduced pressure. Bnzyl bromide (4.4 mL, 37.0 mmol) was added dropwise to the solution in an ice bath, and the mixture was warmed to room temperature and stirred for 14 h. The reaction was quenched by addition of methanol (2 mL). The mixture was then diluted with H_2O and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (15:1 to 13:1) to give **12** (5.48 g, 12.4 mmol, quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.23 (m, 10H, 2×Ph), 5.95 (m, 1H, OCH_2C*H*=CH_2), 5.34 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.2 Hz, J_{trans} = 17.2 Hz, OCH_2-CH=C*H*H), 5.20 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{cis} = 10.8 Hz, OCH_2-CH=CH*H*), 4.82 (dd, 2H, *J* = 12.0 Hz, PhCH_2), 4.60 (dd, 2H, *J* = 12.0 Hz, PhCH_2), 4.42 (ddt, 1H, *J* = 5.2 Hz, *J* = 12.8 Hz, OC*H*HCH=CH_2), 4.37 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.16–4.11 (m, 3H, H-3, H-4, OCH*H*CH=CH_2), 3.90 (dt, 1H, $J_{4,5}$ = 1.6 Hz, $J_{5,6}$ = 6.8 Hz, H-5), 3.79 (m, 2H, H-6), 3.42 (m, 1H, H-2), 1.35 (s, 3H, OCH_3), 1.33 (s, 3H, OCH_3).

4.4.3. Propyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (2)

Compound **12** (494 mg, 1.12 mmol) was dissolved in THF (24 mL) and added 1 M HCl aqueous (40 mL) in an ice bath. Subsequently, the mixture was warmed to 40 °C and stirred for 8 h. The reaction mixture was then cooled down to room temperature and diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give allyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (435 mg, 1.09 mmol, 96.8%). A solution of compound allyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (426 mg, 1.06 mmol) in EtOAc, EtOH (10:3, v/v, 13 mL) was stirred vigorously with Lindlar's catalyst (57.2 mg) at room temperature under H_2 atmosphere for 6.5 h. The solid material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give **2** (424 mg, 1.05 mmol, 99.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.26 (m, 10H, 2×Ph), 4.82 (d, 2H, *J* = 11.2 Hz, PhCH_2), 4.59 (s, 2H, PhCH_2), 4.37 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 3.99 (t, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 3.96–3.91 (m, 1H, OC*H*HCH_2CH_3), 3.81–3.72 (m, 2H, H-6), 3.63–3.57 (m, 2H, H-3, H-5), 3.52–3.46 (m, 2H, H-2, OCH*H*CH_2CH_3), 2.56 (dd, 1H, OH-4), 2.50 (dd, 1H, OH-3), 1.71–1.63 (m, 2H, $OCH_2CH_2CH_3$), 0.97 (t, 3H, $OCH_2CH_2CH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.38, 137.87, 128.49, 128.41, 128.10, 127.84, 127.74, 127.70 (arom), 103.63 (C-1), 79.04 (C-2), 74.53 (PhCH_2), 73.63 (PhCH_2), 73.25, 73.12 (C-3, C-5), 71.55 ($OCH_2CH_2CH_3$), 69.32 (C-6), 68.91 (C-4), 22.96 ($OCH_2CH_2CH_3$), 10.67 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{23}H_{30}O_6Na$ ($M+Na^+$): 425.1940, Found: 425.1951.

4.5. Synthesis of 3-OH Bz acceptor

4.5.1. Allyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (13)

Compound **11** (503 mg, 1.93 mmol) was dissolved in dry CH_2Cl_2 (8 mL) and added dry pyridine (1 mL, 12.4 mmol) and cooled to 0 °C, after which benzoyl chloride (670 μL 5.77 mmol) was added dropwise. After 3.5 h, the reaction mixture was diluted with CH_2Cl_2, then washed with 1 M HCl aqueous, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (10:1) to give **13** (940 mg, 2.00 mmol, quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07, 7.57, 7.45 (m, 10H, 2×Ph), 5.79 (m, 1H, OCH_2C*H*=CH_2), 5.30 (dd, 1H, $J_{2,3}$ = 7.2 Hz, H-2), 5.17 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.2 Hz, J_{trans} = 17.2 Hz, OCH_2CH=C*H*H), 5.07 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{cis} = 10.8 Hz, OCH_2 CH=CH*H*), 4.67 (m, 2H, H-6), 4.57 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.38 (m, 1H, $J_{3,4}$ = 5.6 Hz, H-3), 4.33–4.28 (m, 2H, H-4, OC*H*HCH=CH_2), 4.20 (m, 1H, H-5), 4.11 (ddt, 1H, *J* = 13.6 Hz, OCH*H*CH=CH_2), 1.64 (s, 3H, OCH_3), 1.37 (s, 3H, OCH_3).

4.5.2. Propyl 2,6-di-*O*-benzoyl-β-D-galactopyranoside (3)

Compound **13** (500 mg, 1.07 mmol) was dissolved in THF (24 mL) and added 1 M HCl aqueous (40 mL) in an ice bath. Subsequently, the mixture was warmed to 40 °C and stirred for 8 h. The reaction mixture was then cooled down to room temperature, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$,

and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give allyl 2,6-di-*O*-benzoyl-β-D-galactopyranoside (438 mg, 1.02 mmol, 95.7%).

A solution of compound allyl 2,6-di-*O*-benzoyl-β-D-galactopyranoside (432 mg, 1.01 mmol) in EtOAc (13 mL) was stirred vigorously with palladium hydroxide (40 mg) at room temperature under H_2 atmosphere for 4 h. The solid material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give **3** (417 mg, 0.970 mmol, 96.2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45, 7.57, 7.44 (m, 10H, 2×Ph), 5.22 (dd, 1H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 4.70 (dd, 1H, $J_{5,6b}$ = 6.4 Hz, $J_{6a,6b}$ = 11.6 Hz, H-6b), 4.61–4.57 (m, 2H, H-6a, H-1), 4.06 (br s, 1H, H-4), 3.91–3.82 (m, 3H, H-5, H-3, OC*H*HCH$_2$CH$_3$), 3.55 (br d, 1H, OH-3), 3.50–3.45 (m, 1H, OCH*H*CH$_2$CH$_3$), 3.21 (br d, 1H, OH-4), 1.60–1.50 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.80 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.22, 166.56, 133.32, 133.29, 129.87, 129.71, 129.62, 129.57, 128.44, 128.35 (arom), 101.00 (C-1), 74.28 (C-2), 72.80 (C-3), 72.14 (C-5), 71.63 (OCH$_2$CH$_2$CH$_3$), 68.72 (C-4), 62.91 (C-6), 22.71 (OCH$_2$CH$_2$CH$_3$), 10.29 (OCH$_2$CH$_2$CH$_3$). HRMS (*m*/*z*) Calcd for $C_{23}H_{26}O_8Na$ (M+Na$^+$): 453.1525, Found: 453.1523.

4.6. Synthesis of 2-OH Bn acceptor

4.6.1. Allyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranoside (14)

A stirred solution of allyl β-D-galactopyranoside **7** (3.02 g, 13.7 mmol) in dry DMF (30 mL) was added benzaldehyde dimethyl acetal (3.1 mL, 20.6 mmol) and CSA (316 mg, 1.36 mmol) in an ice bath and then was warmed to room temperature. After 17 h, the reaction mixture was neutralized with triethylamine (1.2 mL), and the solvent was evaporated under reduced pressure. The residue was acetylated with acetic anhydride (6 mL) in dry pyridine (9 mL) at 50 °C. After 2 h, the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1) to give **14** (4.45 g, 11.3 mmol, 82.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52, 7.37 (m, 5H, Ph), 5.88 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.51 (s, 1H, PhC*H*), 5.42 (dd, 1H, $J_{2,3}$ = 10.4 Hz, H-2), 5.29–5.16 (m, 2H, OCH$_2$CH=C*H*$_2$), 4.97 (dd, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 4.56 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.41–4.32 (m, 3H, H-4, OC*H*HCH=CH$_2$, H-6b), 4.15–4.05 (m, 2H, OCH*H*CH=CH$_2$, H-6a), 3.51 (d, 1H, H-5), 2.07 (s, 3H, OCOCH$_3$), 2.06 (s, 3H, OCOCH$_3$).

4.6.2. Allyl 2-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (15)

Sodium methoxide (110 mg, 2.04 mmol) was added to the solution of compound **14** (2.27 g, 5.78 mmol) in methanol (35 mL) at room temperature. After stirring for 1 h, the reaction product was crystallized and the reaction mixture became suspension. Then DMF (5 mL) was added to the reaction mixture. After stirring for 48 h at room temperature, the reaction mixture was neutralized with Diaion SK 1B, which was removed by filtration. The filtrate was concentrated under reduced pressure.

Sodium hydride (60% dispersion in oil, 695 mg, 17 mmol) washed thrice with hexane was placed in dry DMF (1 mL). The slurry was cooled in an ice bath and the residue dissolved in dry DMF (50 mL) was added dropwise with stirring. When the addition was completed, the stirring was continued for 1 h at room temperature under reduced pressure. The mixture was then cooled down at 0 °C, benzyl bromide (800 μL, 6.8 mmol) was added dropwise to the solution and stirred for 23 h. The reaction was quenched by addition of methanol (7 mL). The mixture was then diluted with H_2O and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (8:1 to 2:1) to give mono-*O*-benzylated derivative (646 mg) and 2,3-di-*O*-benzyl derivative (820 mg, 29%).

A solution of mono-*O*-benzylated derivative (646 mg) in dry pyridine (4.5 mL) was treated with acetic anhydride (3 mL) and stirred for 2.5 h at room temperature. Then, the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give 2-*O*-acetyl-3-*O*-benzyl derivative **15** (547 mg, 1.24 mmol, 21.5%) and 2-*O*-benzyl-3-*O*-acetyl derivative (52 mg, 0.12 mmol, 2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.29 (m, 10H, 2×Ph), 5.86 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.48 (s, 1H, PhC*H*), 5.39 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 5.26 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.0 Hz, J_{trans} = 17.2 Hz, OCH$_2$CH=C*H*H), 5.15 (ddd, 1H, $J_{allylic}$ = 1.4 Hz, J_{cis} = 10.4 Hz, OCH$_2$CH=CH*H*), 4.67 (d, 2H, J = 12.6 Hz, PhC*H*$_2$), 4.47 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.39–4.30 (m, 2H, OC*H*HCH=CH$_2$, H-6b), 4.17 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 4.10 (ddt, 1H, J = 6.0 Hz, J = 13.2 Hz, OCH*H*CH=CH$_2$), 4.03 (dd, 1H, H-6a), 3.60 (dd, 1H, H-3), 3.35 (d, 1H, H-5), 2.07 (s, 3H, OCOCH$_3$).

4.6.3. Propyl 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-galactopyranoside (16)

A solution of compound **15** (393 mg, 893 μmol) in EtOAc–EtOH–THF (20:4:1, v/v, 25 mL) was stirred vigorously with Lindlar's catalyst (80 mg) at room temperature under H_2 atmosphere for 6 h. The solid material was filtered off, and the filtrate was concentrated under reduced pressure to give propyl 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-galactopyranoside (394 mg, 890 μmol, 99.7%).

To a stirred solution of propyl 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-galactopyranoside (567 mg, 1.28 mmol) in THF solution (1 M BH_3 solution in THF, 15 mL), anhydrous $CoCl_2$ (500 mg, 3.85 mmol) was added at 0 °C. After stirring for 15 min at 0 °C, 40 min at room temperature, the blue reaction mixture was diluted with an excess volume of CH_2Cl_2, and filtered through Celite. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1) to give **16** (469 mg, 1.06 mmol, 82.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37, 7.29 (m, 10H, 2×Ph), 5.38 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 4.80 (d, 2H, J = 12.0 Hz, PhC*H*$_2$), 4.64 (d, 2H, J = 12.2 Hz, PhC*H*$_2$), 4.34 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.85–3.78 (m, 3H, H-4, H-6b, OC*H*HCH$_2$CH$_3$), 3.55–3.52 (m, 2H, H-3, H-6a), 3.43–3.36 (m, 2H, H-5, OCH*H*CH$_2$CH$_3$), 2.04 (s, 3H, OCOCH$_3$), 1.63–1.51 (m, 3H, OCH$_2$C*H*$_2$CH$_3$), 0.88 (t, 3H, OCH$_2$CH$_2$C*H*$_3$).

4.6.4. Propyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranoside (1)

After a mixture of **16** (239 mg, 538 μmol) and activated molecular sieves (4 Å, 1.0 g) in dry CH_2Cl_2 (2.0 mL) and cyclohexane (1.0 mL) was stirred at room temperature for 1 h, the mixture was cooled to 0 °C, and added benzyl trichloroacetimidate (500 μL, 2.69 mmol) and TfOH (50 μL, 563 μmol). After stirring for 1.5 h, the mixture was warmed to room temperature and stirred for 10 min. The reaction mixture was diluted with an excess volume of CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (15:1 to 10:1) to give the mixture of propyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranoside and by-product (273 mg).

The mixture dissolved in MeOH (2.7 mL) was added NaOMe (6 mg, 110 μmol) at room temperature. After 3 h, an additional amount of NaOMe (6 mg, 110 μmol) was added, and the stirring was continued for 17 h at 50 °C. Then, 28% aqueous NH_3 (4 mL) was added. After 6 h, an additional amount of 28% aqueous NH_3 (10 mL) and MeOH (10 mL) was added and the stirring was continued for 2 h at 65 °C. The reaction mixture was diluted with an

excess volume of CH_2Cl_2, washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (8:1 to 6:1) to give **1** (116 mg, 235 μmol, 43.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.24 (m, 15H, 3×Ph), 4.75 (d, 2H, J = 11.6 Hz, PhCH_2), 4.70 (d, 2H, J = 12.0 Hz, PhCH_2), 4.45 (d, 2H, J = 11.8 Hz, PhCH_2), 4.23 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 3.97–3.92 (m, 2H, H-2, H-4), 3.87–3.81 (m, 1H, OC*H*HCH$_2$CH$_3$), 3.65–3.55 (m, 3H, H-5, H-6), 3.48–3.42 (m, 2H, H-3, OCH*H*CH$_2$CH$_3$), 2.35 (s, 1H, OH-2), 1.67–1.60 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.91 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.53, 138.14, 137.89, 128.48, 128.42, 128.23, 128.15, 127.88, 127.79, 127.75, 127.62, 127.53 (arom), 103.21 (C-1), 81.94 (C-3), 74.51 (PhCH$_2$), 73.73 (C-5), 73.55 (PhCH$_2$), 72.95 (C-4), 72.39 (PhCH$_2$), 71.47 (C-2), 71.43 (OCH$_2$CH$_2$CH$_3$), 68.75 (C-6), 22.78 (OCH$_2$CH$_2$CH$_3$), 10.39 (OCH$_2$CH$_2$CH$_3$). HRMS (*m*/*z*) Calcd for $C_{30}H_{36}O_6Na$ (M+Na$^+$): 515.2410, Found: 515.2448.

4.7. Synthesis of 4-OH acceptor

4.7.1. Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (17)

A stirred solution of allyl β-D-galactopyranoside **7** (1.00 g, 4.54 mmol) in dry DMF (10 mL) was added benzaldehyde dimethyl acetal (1.05 mL, 7.01 mmol) and CSA (105 mg, 452 μmol) at room temperature and stirred for 24 h. Subsequently, the reaction mixture was neutralized with triethylamine (0.4 mL, excess), and the solvent was evaporated under reduced pressure.

Sodium hydride (60% dispersion in oil, 730 mg, 18.3 mmol) washed thrice with hexane was placed in dry DMF (6 mL). The slurry was cooled in an ice bath and the residue dissolved in dry DMF (14 mL) was added dropwise with stirring. When the addition is completed, the stirring was continued for 2 h at room temperature under reduced pressure. Benzyl bromide (1.70 mL, 14.3 mmol) was added dropwise to the solution in an ice bath, and the mixture was warmed to room temperature and stirred for 19 h. The reaction was quenched by addition of methanol (5 mL). The mixture was then diluted with H_2O and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (8:1) to give **17** (1.64 g, 3.36 mmol, 73.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.26 (m, 15H, 3×Ph), 5.97 (m, 1H, OCH$_2$-C*H*=CH$_2$), 5.50 (s, 1H, PhC*H*), 5.34 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.0 Hz, J_{trans} = 17.2 Hz, OCH$_2$CH=C*H*H), 5.19 (ddd, 1H, $J_{allylic}$ = 1.4 Hz, J_{cis} = 10.4 Hz, OCH$_2$CH=CH*H*), 4.86 (d, 2H, J = 10.8 Hz, PhCH_2), 4.77 (m, 2H, H-6), 4.48–4.36 (m, 2H, OC*H*HCH=CH$_2$, H-1), 4.30, 4.01 (m, 2H, PhCH_2), 4.17–4.10 (m, 2H, OCH*H*CH=CH$_2$, H-4), 3.88 (dd, 1H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 3.56 (dd, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 3.31 (d, 1H, H-5).

4.7.2. Allyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (18)

To a solution of compound **17** (2.22 g, 4.54 mmol) and sodium cyanoborohydride (2.43 g, 38.7 mmol) in dry THF (45 mL) was added powdered 4 Å molecular sieves (22 g), and the mixture was stirred for 30 min at room temperature, then cooled to 0 °C. Hydrogen chloride-dioxane (4 M, 10.5 mL) was added dropwise until the evolution of gas ceased. After 2 h, the reaction mixture was diluted with toluene, filtered through Celite, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (6:1) to give **18** (1.82 g, 3.71 mmol, 81.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.28 (m, 15H, 3×Ph), 5.95 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.30 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{gem} = 3.0 Hz, J_{trans} = 17.2 Hz, OCH$_2$CH=C*H*H), 5.19 (ddd, 1H, $J_{allylic}$ = 1.6 Hz, J_{cis} = 10.4 Hz, OCH$_2$CH=CH*H*), 4.83 (d, 2H, J = 10.8 Hz, PhCH_2), 4.72 (s, 2H, PhCH_2), 4.59 (s, 2H, PhCH_2), 4.45–4.40 (m, 2H, OC*H*HCH=CH$_2$, H-1), 4.14 (ddt, 1H, J = 6.0 Hz, J = 13.6 Hz, OCH*H*CH=CH$_2$), 4.02 (br t, 1H, H-4), 3.82–3.71 (m, 2H, H-6), 3.67 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.55 (t, 1H, $J_{5,6}$ = 5.8 Hz, H-5), 3.49 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 2.49 (s, 1H, OH-4).

4.7.3. Propyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (4)

A solution of compound **18** (268 mg, 546 μmol) in EtOAc, EtOH (1:1, v/v, 12 mL) was stirred vigorously with Lindlar's catalyst (60 mg) at room temperature under H_2 atmosphere for 3 h. The solid material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (6:1) to give **4** (263 mg, 533 mmol, 97.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 15H, 3×Ph), 4.83 (d, 2H, J = 10.8 Hz, PhCH_2), 4.72 (s, 2H, PhCH_2), 4.59 (s, 2H, PhCH_2), 4.36 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.02 (brt, 1H, H-4), 3.95–3.89 (m, 1H, OC*H*HCH$_2$CH$_3$), 3.80 (dd, 1H, $J_{5,6}$ = 6.0 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.72 (dd, 1H, H-6a), 3.64 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 3.55 (t, 1H, H-5), 3.51–3.45 (m, 2H, H-3, OCH*H*CH$_2$CH$_3$), 2.48 (d, 1H, OH-4), 1.70–1.65 (m, 2H, OCH$_2$C*H*$_2$-CH$_3$), 0.97 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.60, 138.00, 137.90, 128.42, 128.40, 128.28, 128.12, 127.84, 127.80, 127.76, 127.72, 127.59 (arom), 103.69 (C-1), 80.55 (C-3), 78.96 (C-2), 75.15 (PhCH$_2$), 73.69 (PhCH$_2$), 73.11 (C-5), 72.39 (PhCH$_2$), 71.56 (OCH$_2$CH$_2$CH$_3$), 69.19 (C-6), 66.89 (C-4), 22.99 (OCH$_2$CH$_2$CH$_3$), 10.67 (OCH$_2$CH$_2$CH$_3$). HRMS (*m*/*z*) Calcd for $C_{30}H_{36}O_6Na$ (M+Na$^+$): 515.2410, Found: 515.2417.

4.8. Synthesis of α(2→6) GM4 derivatives

4.8.1. Propyl-*O*-(Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate)-(2→6)-2,3,4-tri-*O*-benzyl-β-D-galactopyranoside (19)

A mixture of sialyl donor **8** (156 mg, 274 μmol, 1.5 equiv), galactosyl acceptor **5** (90 mg, 183 μmol, 1.0 equiv) and activated 3 Å molecular sieves (1 g) in dry CH_2Cl_2/MeCN (3.2 mL, 1:1, v/v) was stirred under argon atmosphere at room temperature for 1 h to remove any trace amounts of water. The reaction mixture was then cooled to −40 °C. *N*-Iodosuccinimide (148 mg, 658 μmol, 3.6 equiv) was added followed by a catalytic amount of triflic acid (24 μL, 271 μmol, 1.5 equiv) in 100 μL of dry MeCN. After being stirred at −40 °C for 30 min, the mixture was quenched with triethylamine (100 μL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The resulting filtrate was washed with 20% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1 to 2:1) to give **19** (171 mg, 180 μmol, 98.3%, α:β = 10:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.23 (m, 15H, 3×Ph), 5.53 (dd, 1H, $J_{7',8'}$ = 6.9 Hz, H-7′), 5.40 (dt, 1H, $J_{8',9a'}$ = 3.0 Hz, $J_{8',9b'}$ = 7.2 Hz, H-8′), 4.84 (d, 2H, J = 10.8 Hz, PhCH_2), 4.83 (d, 2H, J = 11.4 Hz, PhCH_2), 4.75 (d, 2H, J = 12.0 Hz PhCH_2), 4.55 (dd, 1H, $J_{6',7'}$ = 1.8 Hz, H-6′), 4.38 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.35 (dd, 1H, $J_{9a',9b'}$ = 12.0 Hz, H-9a′), 4.07 (dd, 1H, H-9b′), 4.00–3.96 (m, 1H, H-4′), 3.93–3.88 (m, 3H, H-4, H-6b, OC*H*HCH$_2$CH$_3$), 3.81 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.70 (dd, 1H, $J_{5',6'}$ = 9.6 Hz, H-5′), 3.64 (s, 3H, COOCH$_3$), 3.60–3.55 (m, 2H, H-5, H-6a), 3.53 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 3.49–3.46 (m, 1H, OCH*H*CH$_2$CH$_3$), 2.87 (dd, 1H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.0 Hz, H-3eq′), 2.49 (s, 3H, NCOCH$_3$), 2.12 (s, 3H, OCOCH$_3$), 2.10–2.08 (m, 4H, H-3ax′, OCOCH$_3$), 2.00 (s, 3H, OCOCH$_3$), 1.69–1.63 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.96 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 172.03, 170.54, 170.09, 169.92, 168.24 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 6.46 Hz), 153.65, 138.84, 138.71, 138.55, 128.29, 128.23, 128.18, 128.05, 127.70, 127.51, 127.47, 127.35, 127.26, 103.96 (C-1), 99.17, 82.09 (C-3), 79.46 (C-2), 75.80 (C-6′), 75.11 (PhCH$_2$), 74.92 (C-4′), 74.22 (PhCH$_2$), 73.42 (C-4), 73.02 (PhCH$_2$), 72.64 (C-5), 72.02 (C-7′), 71.64 (OCH$_2$CH$_2$CH$_3$), 69.56 (C-8′), 63.54 (C-6),

62.82 (C-9′), 59.06 (C-5′), 53.05 ($COOCH_3$), 36.39 (C-3′), 24.69 ($NCOCH_3$), 22.96 ($OCH_2CH_2CH_3$), 21.05, 20.86, 20.70 ($3\times OCOCH_3$), 10.69 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{49}H_{59}NO_{18}Na$ ($M+Na^+$): 972.3630, Found: 972.3639.

4.8.2. Propyl-*O*-(Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate)-(2→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (20)

A mixture of sialyl donor **8** (144 mg, 253 μmol, 1.5 equiv), galactosyl acceptor **6** (90 mg, 168 μmol, 1.0 equiv) and activated 3 Å molecular sieves (1 g) in dry CH_2Cl_2/MeCN (3.2 mL, 1:1, v/v) was stirred under argon atmosphere at room temperature for 1 h to remove any trace amounts of water. The reaction mixture was then cooled to −40 °C. *N*-Iodosuccinimide (136 mg, 604 μmol, 3.6 equiv) was added followed by a catalytic amount of triflic acid (22.4 μL, 253 μmol, 1.5 equiv) in 100 μL of dry MeCN. After being stirred at −40 °C for 30 min, the mixture was quenched with triethylamine (100 μL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The resulting filtrate was washed with 20% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1 to 2:1) to give **20** (162 mg, 163 μmol, 96.8%, α only). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08–7.23 (m, 15H, 3×Ph), 6.01 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4), 5.71 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 5.64 (dd, 1H, H-3), 5.58 (dd, 1H, $J_{7',8'}$ = 8.4 Hz, H-7′), 5.48 (dt, 1H, $J_{8',9a'}$ = 2.4 Hz, $J_{8',9b'}$ = 7.8 Hz, H-8′), 4.89 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.62 (dd, 1H, $J_{6',7'}$ = 1.8 Hz, H-6′), 4.49 (dd, 1H, $J_{9a',9b'}$ = 12.6 Hz, H-9a′), 4.27 (m, 1H, H-5), 4.06 (dd, 1H, H-9b′), 3.97–3.89 (m, 3H, H-4′, H-6b, OC*H*HCH_2CH_3), 3.73 (dd, 1H, $J_{5',6'}$ = 9.6 Hz, H-5′), 3.64–3.61 (m, 1H, H-6a), 3.57–3.53 (m, 1H, OCH*H*CH_2CH_3), 3.46 (s, 3H, $COOCH_3$), 2.73 (dd, 1H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.0 Hz, H-3eq′), 2.48 (s, 3H, $NCOCH_3$), 2.22 (s, 3H, $OCOCH_3$), 2.12 (s, 3H, $OCOCH_3$), 2.08 (t, 1H, H-3ax′), 2.04 (s, 3H, $OCOCH_3$), 1.61–1.53 (m, 2H, $OCH_2CH_2CH_3$), 0.79 (t, 3H, $OCH_2CH_2CH_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 172.04, 170.70, 170.42, 170.13, 168.20 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 6.31 Hz), 165.55, 165.30, 165.29, 153.60, 133.30, 133.09, 133.04, 129.93, 129.73, 129.66, 129.60, 129.55, 128.99, 128.52, 128.28, 128.20, 101.43 (C-1), 99.51, 75.76 (C-6′), 74.74 (C-4′), 71.96 ($OCH_2CH_2CH_3$), 71.92 (C-3), 71.62 (C-5, C-7′), 70.00 (C-2), 68.84 (C-8′), 67.79 (C-4), 63.50 (C-9′), 63.21 (C-6), 58.93 (C-5′), 52.87 ($COOCH_3$), 36.43 (C-3′), 24.70 ($NCOCH_3$), 22.67 ($OCH_2CH_2CH_3$), 21.05, 20.96, 20.76 ($3\times OCOCH_3$), 10.21 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{49}H_{53}NO_{21}Na$ ($M+Na^+$): 1014.3008, Found: 1014.3005.

4.9. Synthesis of α(2→3) GM4 derivatives

4.9.1. Propyl-*O*-(methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate)-(2→3)-2,6-di-*O*-benzyl-β-D-galactopyranoside (21)

A mixture of sialyl donor **8** (190 mg, 335 μmol, 1.5 equiv), galactosyl acceptor **2** (90 mg, 224 μmol, 1.0 equiv) and activated 3 Å molecular sieves (1 g) in dry CH_2Cl_2/MeCN (3.2 mL, 1:1, v/v) was stirred under argon atmosphere at room temperature for 1 h to remove any trace amounts of water. The reaction mixture was then cooled to −40 °C. *N*-Iodosuccinimide (181 mg, 805 μmol, 3.6 equiv) was added followed by a catalytic amount of triflic acid (30 μL, 339 μmol, 1.5 equiv) in 100 μL of dry MeCN. After being stirred at −40 °C for 30 min, the mixture was quenched with triethylamine (100 μL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The resulting filtrate was washed with 20% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1 to 3:2) to give **21** (148 mg, 172 μmol, 76.7%, α:β = 1:1). (**21α**) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.27 (m, 10H, 2×Ph), 5.57 (dd, 1H, $J_{7',8'}$ = 7.2 Hz, H-7′), 5.44 (dt, 1H, $J_{8',9a'}$ = 2.4 Hz, $J_{8',9b'}$ = 7.2 Hz, H-8′), 4.78 (d, 2H, *J* = 12.0 Hz, PhC*H*$_2$), 4.57 (s, 2H, PhC*H*$_2$), 4.48 (dd, 1H, $J_{6',7'}$ = 1.8 Hz, H-6′), 4.44–4.41 (m, 2H, $J_{1,2}$ = 7.8 Hz, H-1, H-9a′), 4.03 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 3.99–3.93 (m, 2H, H-4′, H-9b′), 3.92–3.89 (m, 1H, OC*H*HCH_2CH_3), 3.88 (br s, 1H, H-4), 3.82–3.78 (m, 4H, H-6b, $COOCH_3$), 3.72–3.70 (m, 1H, H-6a), 3.66 (dd, 1H, $J_{5',6'}$ = 9.6 Hz, H-5′), 3.61 (t, 1H, H-5), 3.56 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.52–3.49 (m, 1H, OCH*H*CH_2CH_3), 2.81–2.78 (m, 2H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.0 Hz, H-3eq′, OH-4), 2.48 (s, 3H, $NCOCH_3$), 2.22 (t, 1H, H-3ax′), 2.11 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 1.89 (s, 3H, $OCOCH_3$), 1.69–1.65 (m, 2H, $OCH_2CH_2CH_3$), 0.95 (t, 3H, $OCH_2CH_2CH_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 172.00, 170.63, 170.24, 169.69, 168.35 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 6.41 Hz), 153.56, 138.80, 138.06, 128.35, 128.13, 127.93, 127.68, 127.51, 103.76 (C-1), 98.78, 77.09 (C-2), 76.21 (C-3), 75.65 (C-6′), 75.04 (C-4′), 74.73 (PhC*H*$_2$), 73.54 (PhC*H*$_2$), 72.75 (C-5), 71.88 (C-7′), 71.59 ($OCH_2CH_2CH_3$), 69.62 (C-8′), 69.02 (C-6), 68.39 (C-4), 62.97 (C-9′), 58.85 (C-5′), 53.23 ($COOCH_3$), 34.86 (C-3′), 24.61 ($NCOCH_3$), 22.95 ($OCH_2CH_2CH_3$), 21.14, 20.77, 20.54 ($3\times OCOCH_3$), 10.63 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{42}H_{53}NO_{18}Na$ ($M+Na^+$): 882.3160, Found: 882.3127.

(**21β**) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.28 (m, 10H, 2×Ph), 5.50 (br t, 1H, H-7′), 5.40 (bs, 1H, H-8′), 4.75 (d, 2H, *J* = 11.4 Hz, PhC*H*$_2$), 4.65–4.62 (m, 1H, H-9a′), 4.60 (s, 2H, PhC*H*$_2$), 4.55 (dt, 1H, H-4′), 4.48 (dd, 1H, $J_{6',7'}$ = 2.4 Hz, H-6′), 4.37 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.03–3.99 (m, 2H, H-4, H-9b′), 3.95–3.92 (m, 1H, OC*H*HCH_2CH_3), 3.85–3.77 (m, 3H, H-3, H-6), 3.69 (t, 1H, $J_{5',6'}$ = 9.6 Hz, H-5′), 3.65–3.56 (m, 2H, H-2, H-5), 3.52 (s, 3H, $COOCH_3$), 3.51–3.47 (m, 1H, OCH*H*CH_2CH_3), 2.84 (dd, 1H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.6 Hz, H-3eq′), 2.48 (s, 3H, $NCOCH_3$), 2.18–2.06 (m, 7H, H-3ax′, 2×$OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 1.72–1.64 (m, 2H, $OCH_2CH_2CH_3$), 0.95 (t, 3H, $OCH_2CH_2CH_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 172.59, 170.78, 170.61, 169.68 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 0 Hz), 166.49, 153.73, 138.32, 137.86, 128.38, 128.37, 128.24, 127.75, 127.72, 127.68 103.99 (C-1), 99.06, 76.64 (C-3), 75.32 (C-6′), 74.88 (PhCH_2), 74.35 (C-4′), 73.71 (PhC*H*$_2$), 72.81 (C-5), 72.78 (C-7′), 71.68 ($OCH_2CH_2CH_3$), 70.95 (C-8′), 69.92 (C-6), 69.24 (C-4), 63.29 (C-9′), 59.30 (C-5′), 52.77 ($COOCH_3$), 35.63 (C-3′), 24.68 ($NCOCH_3$), 22.97 ($OCH_2CH_2CH_3$), 21.07, 20.78, 20.73 ($3\times OCOCH_3$), 10.66 ($OCH_2CH_2CH_3$). HRMS (*m*/*z*) Calcd for $C_{42}H_{53}NO_{18}Na$ ($M+Na^+$): 882.3160, Found: 882.3186.

4.9.2. Propyl-*O*-(methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate)-(2→3)-2,6-di-*O*-benzoyl-β-D-galactopyranoside (22)

A mixture of sialyl donor **8** (178 mg, 314 μmol, 1.5 equiv), galactosyl acceptor **3** (90 mg, 209 μmol, 1.0 equiv) and activated 3 Å molecular sieves (1 g) in dry CH_2Cl_2/MeCN (3.2 mL, 1:1, v/v) was stirred under argon atmosphere at room temperature for 1 h to remove any trace amounts of water. The reaction mixture was then cooled to −40 °C. *N*-iodosuccinimide (169 mg, 751 μmol, 3.6 equiv) was added followed by a catalytic amount of triflic acid (28 μL, 316 μmol, 1.5 equiv) in 100 μL of dry MeCN. After being stirred at −40 °C for 30 min, the mixture was quenched with triethylamine (100 μL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The resulting filtrate was washed with 20% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (3:1 to 3:2) to give **22** (105 mg, 118 μmol, 56.6%, α:β = 1:1.9). (**22αβ** mixture) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–7.43 (m, 10H, 2×Ph), 5.60–5.55 (m, 1H, H-8′ α), 5.49 (dd, 1H, H-7′ α), 5.41 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2 β), 5.38 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2 α), 4.68 (d, 1H, $J_{1,2}$ = 7.6 Hz,

H-1 α), 4.58 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1 β), 3.72 (m, 3H, $COOCH_3$ α), 3.58 (m, 3H, $COOCH_3$ β), 2.88 (dd, 1H, $J_{3eq',4'}$ = 3.2 Hz, $J_{3eq',3ax'}$ = 12.0 Hz, H-3eq′ α), 2.70 (dd, 1H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.8 Hz, H-3eq′ β), 2.01 (H-3ax′ α, β).

4.10. Synthesis of α(2→2) GM4 derivatives

4.10.1. Propyl-*O*-(methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate)-(2→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranoside (23)

A mixture of sialyl donor **8** (156 mg, 274 μmol, 1.5 equiv), galactosyl acceptor **1** (90 mg, 183 μmol, 1.0 equiv) and activated 3 Å molecular sieves (1 g) in dry CH_2Cl_2/MeCN (3.2 mL, 1:1, v/v) was stirred under argon atmosphere at room temperature for 1 h to remove any trace amounts of water. The reaction mixture was then cooled to −40 °C. *N*-iodosuccinimide (148 mg, 658 μmol, 3.6 equiv) was added followed by a catalytic amount of triflic acid (24 μL, 271 μmol, 1.5 equiv) in 100 μL of dry MeCN. After being stirred at −40 °C for 30 min, the mixture was quenched with triethylamine (100 μL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The resulting filtrate was washed with 20% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (4:1 to 2:1) to give **23** (174 mg, 183 μmol, >99%, α:β = 2.4:1). (**23α**) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.20 (m, 15H, 3×Ph), 5.55 (dd, 1H, $J_{7',8'}$ = 6.0 Hz, H-7′), 5.54–5.52 (m, 1H, H-8′), 4.76 (d, 2H, *J* = 12.0 Hz, PhC*H*$_2$), 4.69 (d, 2H, *J* = 13.2 Hz, PhC*H*$_2$), 4.57 (dd, 1H, $J_{8',9a'}$ = 3.0 Hz, $J_{9a',9b'}$ = 12.0 Hz, H-9a′), 4.40 (m, 1H, H-9b′), 4.37 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.33 (m, 2H, PhC*H*$_2$), 4.23 (dd, 1H, $J_{6',7'}$ = 1.8 Hz, H-6′), 4.16 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 4.01–3.96 (m, 1H, H-4′), 3.77–3.75 (m, 4H, H-4, $COOCH_3$), 3.71 (dd, 1H, $J_{5',6'}$ = 9.6 Hz, H-5′), 3.69–3.63 (m, 1H, OC*H*HCH$_2$CH$_3$), 3.52–3.50 (m, 1H, H-6b), 3.45–3.39 (m, 3H, H-5, H-6a, OCH*H*CH$_2$CH$_3$), 3.34 (dd, 1H, $J_{3,4}$ = 2.4 Hz, H-3), 3.14 (dd, 1H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.0 Hz, H-3eq′), 2.48 (s, 3H, $NCOCH_3$), 2.18–2.08 (m, 4H, H-3ax′, $OCOCH_3$), 1.93 (s, 3H, $OCOCH_3$), 1.88 (s, 3H, $OCOCH_3$), 1.64–1.58 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.86 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 171.93, 170.67, 170.35, 169.91, 167.07 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 6.58 Hz), 153.90, 138.45, 138.32, 137.81, 128.47, 128.35, 128.33, 128.18, 127.94, 127.79, 127.72, 127.62, 102.40 (C-1), 99.93, 80.69 (C-3), 75.86 (C-6′), 75.84 (C-4′), 74.34 (C-2), 74.15 (PhC*H*$_2$), 73.57 (C-5), 73.40 (PhC*H*$_2$), 73.21 (C-4), 72.77 (C-7′), 72.43 (PhC*H*$_2$), 72.03 (OC*H*$_2$CH$_2$CH$_3$), 70.97 (C-8′), 68.89 (C-6), 62.13 (C-9′), 59.24 (C-5′), 53.02 ($COOCH_3$), 36.62 (C-3′), 24.70 ($NCOCH_3$), 22.51 (OCH$_2$CH$_2$CH$_3$), 21.09, 20.70, 20.57 (3×OCO*C*H$_3$), 10.23 (OCH$_2$CH$_2$*C*H$_3$). HRMS (*m*/*z*) Calcd for $C_{49}H_{59}NO_{18}Na$ (M+Na$^+$): 972.3630, Found: 972.3628.

(**23β**) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.26 (m, 15H, 3×Ph), 5.59 (s, 1H, H-7′), 5.30 (bt, 1H, H-8′), 5.00 (d, 1H, $J_{5',6'}$ = 9.6 Hz, H-6′), 4.66 (d, 2H, *J* = 12.0 Hz, PhC*H*$_2$), 4.63 (dd, 1H, $J_{8',9a'}$ = 1.8 Hz, $J_{9a',9b'}$ = 12.0 Hz, H-9a′), 4.56–4.51 (m, 3H, H-4′, PhC*H*$_2$), 4.43 (m, 2H, *J* = 11.4 Hz, PhC*H*$_2$), 4.22 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 4.16 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.10 (m, 1H, H-9b′), 3.84 (bd, 1H, $J_{3,4}$ = 1.8 Hz, H-4), 3.82–3.78 (m, 1H, OC*H*HCH$_2$CH$_3$), 3.64–3.61 (m, 4H, H-5′, $COOCH_3$), 3.55 (d, 2H, H-6), 3.50 (t, 1H, H-5), 3.44–3.40 (m, 2H, H-3, OCH*H*CH$_2$CH$_3$), 2.85 (dd, 1H, $J_{3eq',4'}$ = 3.0 Hz, $J_{3eq',3ax'}$ = 12.6 Hz, H-3eq′), 2.42 (s, 3H, $NCOCH_3$), 2.25 (t, 1H, H-3ax′), 2.08 (s, 3H, 2×$OCOCH_3$), 1.90 (s, 3H, $OCOCH_3$), 1.64–1.56 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.86 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 171.96, 170.88, 170.58, 169.74, 166.99 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 0 Hz), 154.00, 138.40, 137.74, 137.06, 128.63, 128.45, 128.41, 128.27, 128.14, 127.82, 127.78, 127.63, 101.75 (C-1), 98.91, 81.45 (C-3), 75.14 (C-6′), 74.60 (PhC*H*$_2$), 74.45 (C-4′), 73.49 (C-5), 73.47 (PhC*H*$_2$), 73.20 (C-4), 72.94 (C-7′), 72.61 (C-8′), 72.54 (C-2), 72.45 (PhC*H*$_2$), 70.87 (OC*H*$_2$CH$_2$CH$_3$), 68.47 (C-6), 63.40 (C-9′), 59.27 (C-5′), 52.53 ($COOCH_3$), 34.96 (C-3′), 24.65 ($NCOCH_3$), 22.34 (OCH$_2$C*H*$_2$CH$_3$), 21.09, 20.83, 20.67 (3×$OCOCH_3$), 10.32 (OCH$_2$CH$_2$*C*H$_3$). HRMS (*m*/*z*) Calcd for $C_{49}H_{59}NO_{18}Na$ (M+Na$^+$): 972.3630, Found: 972.3669.

4.11. Synthesis of β(2→4) GM4 derivatives

4.11.1. Propyl-*O*-(methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-β-D-galacto-non-2-ulopyranosylonate)-(2→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (24)

A mixture of sialyl donor **8** (157 mg, 277 μmol, 1.5 equiv), galactosyl acceptor **4** (90 mg, 183 μmol, 1.0 equiv) and activated 3 Å molecular sieves (1 g) in dry CH_2Cl_2/MeCN (3.2 mL, 1:1, v/v) was stirred under argon atmosphere at room temperature for 1 h to remove any trace amounts of water. The reaction mixture was then cooled to −40 °C. *N*-Iodosuccinimide (148 mg, 658 μmol, 3.6 equiv) was added followed by a catalytic amount of triflic acid (24 μL, 271 μmol, 1.5 equiv) in 100 μL of dry MeCN. After being stirred at −40 °C for 30 min, the mixture was quenched with triethylamine (100 μL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The resulting filtrate was washed with 20% aqueous $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with Hex/EtOAc (6:1 to 2:1) to give **24** (100 mg, 105 μmol, 58%, β only).

(**24β**) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.25 (m, 15H, 3×Ph), 5.75 (d, 1H, $J_{7',8'}$ = 6.0 Hz, H-7′), 5.68 (bs, 1H, H-8′), 4.75–4.73 (m, 1H, H-6′), 4.73 (d, 2H, *J* = 10.8 Hz, PhC*H*$_2$), 4.65 (d, 2H, *J* = 12.3 Hz, PhC*H*$_2$), 4.52 (d, 2H, *J* = 12.6 Hz PhC*H*$_2$), 4.52–4.47 (m, 2H, H-4′, H-9a′), 4.31–4.30 (m, 2H, $J_{1,2}$ = 7.8 Hz, H-1, H-4), 4.27–4.24 (m, 1H, H-9b′), 3.88–3.85 (m, 1H, OC*H*HCH$_2$CH$_3$), 3.78 (bt, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.71 (t, 1H, $J_{5',6'}$ = 10.6 Hz, H-5′), 3.66 (t, 1H, H-6b), 3.59–3.53 (m, 2H, H-5, H-6a), 3.50 (s, 3H, $COOCH_3$), 3.46–3.39 (m, 2H, H-3, OCH*H*CH$_2$CH$_3$), 2.93 (dd, 1H, $J_{3eq',4'}$ = 3.6 Hz, $J_{3eq',3ax'}$ = 12.0 Hz, H-3eq′), 2.49 (s, 3H, $NCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.06 (s, 3H, $OCOCH_3$), 1.95–1.91 (m, 4H, H-3ax′, $OCOCH_3$), 1.68–1.62 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.93 (t, 3H, OCH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 171.86, 170.65, 170.53, 170.08, 167.11 (C-1′, $^3J_{C\text{-}1',H\text{-}3'ax}$ = 0 Hz), 153.80, 138.49, 137.84, 137.28, 128.59, 128.50, 128.20, 128.12, 128.07, 127.99, 127.70, 127.61, 127.51, 104.19 (C-1), 98.36, 81.31 (C-3), 78.46 (C-2), 74.97 (PhC*H*$_2$), 74.82 (C-6′), 74.72 (C-4′), 73.43 (PhC*H*$_2$), 73.28 (PhC*H*$_2$), 72.55 (C-5), 72.21 (C-7′), 71.96 (OC*H*$_2$CH$_2$CH$_3$), 70.22 (C-8′), 68.17 (C-4), 67.78 (C-6), 62.90 (C-9′), 59.33 (C-5′), 52.25 ($COOCH_3$), 37.62 (C-3′), 24.73 ($NCOCH_3$), 22.88 (OCH$_2$C*H*$_2$CH$_3$), 21.10, 20.81, 20.62 (3×$OCOCH_3$), 10.58 (OCH$_2$CH$_2$*C*H$_3$). HRMS (*m*/*z*) Calcd for $C_{49}H_{59}NO_{18}Na$ (M+Na$^+$): 972.3630, Found: 972.3632.

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