JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

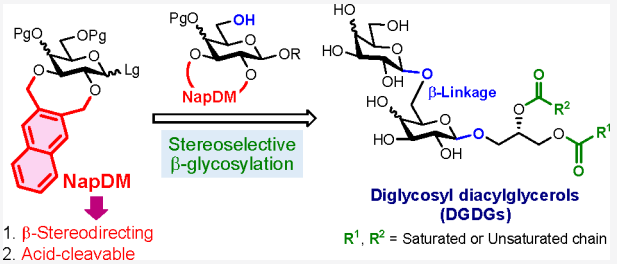
Stereoselective Synthesis of Diglycosyl Diacylglycerols with Glycosyl Donors Bearing a β-Stereodirecting 2,3-Naphthalenedimethyl Protecting Group

Nahoko Yagami,[⊥] Amol M. Vibhute,[⊥] Hide-Nori Tanaka,*[,⊥] Naoko Komura, Akihiro Imamura, Hideharu Ishida, and Hiromune Ando*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c02121 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Diglycosyl diacylglycerols (DGDGs) are major components of Gram-positive bacterial plasma membranes and are involved in the immune response systems. The chemical synthesis of DGDGs has been highly demanded, as it will allow the elucidation of their biological functions at the molecular level. In this study, we have developed a novel β-stereodirecting 2,3-naphthalenedimethyl (NapDM) protecting group that is orthogonal to protecting groups commonly used in oligosaccharide synthesis. The NapDM group can be easily cleaved under TFA-mediated acidic conditions. Futhermore, we demonstrated the application of this protecting group to an acyl protecting-group-free strategy by utilizing the NapDM group for the synthesis of DGDGs. This strategy features the use of the β-stereodirecting NapDM group as an acid-cleavable permanent protecting group and late-stage glycosylation of monoglycosyl diacylglycerol acceptors, enabling the stereoselective synthesis of three different bacterial DGDGs with unsaturated fatty acid chain(s).



INTRODUCTION

Glycoglycerolipids are abundant in plants,[1] algae,[2] and some bacteria[3] and include diglycosyl diacylglycerols (DGDGs), which are major components of Gram-positive bacterial plasma membranes. DGDGs are composed of a polar disaccharide head that is glycosidically linked to the 3-position of a nonpolar 1,2-diacyl-*sn*-glycerol tail. Over the past decade, several reports have shown that bacterial DGDGs are involved in the immune response systems.[4] Kronenberg et al. reported DGDG-containing glycolipids, from *Streptococcus pneumoniae* and group B *Streptococcus*, presented by CD1d, were recognized by human natural killer T cells.[4a] A DGDG in *Enterococcus faecalis* was recently reported to modulate lipoprotein expression and activation of the host immune system.[4c] Therefore, bacterial DGDGs have attracted increasing attention from researchers. However, the availability of DGDGs from the natural sources is limited because of their heterogeneity with respect to not only the sugar component and glycosidic linkage of the disaccharide but also the length and unsaturation of the acyl chain. To overcome this supply problem and further elucidate their biological functions at the molecular level, their chemical synthesis has been in high demand. To date, most of synthetic studies on DGDGs possessing β-glycosidic linkage(s)[5] utilize neighboring group participation by a C-2 acyl functionality on glycosyl donors, which enables a β-selective glycosylation reaction. For instance, Williams et al. have chemically synthesized *Mycobacterium tuberculosis* β-gentiobiosyl diacylglycerides and various analogues using a benzoyl protecting group at the C-2-position for β-glycosidic bond formation and showed that β-gentiobiosyl diacylglyceride signaling through macrophage-inducible Ca^{2+}-dependent lectin receptor (Mincle) varied drastically depending upon the acyl chain length.[5g] However, the C-2 acyl functionality is incompatible with the incoming fatty acyl chains. During these syntheses, the C-2 acyl functionality must be replaced with an ether-type protecting group such as a benzyl group before the introduction of fatty acid chains into the 1,2-positions of the glycerol moiety. In addition, the acyl protection at the C-2-position leads to the formation of orthoester side products during the glycosylation reaction.[6] In order to avoid these problems and improve synthetic efficiency, Nishida et al. accomplished the chemical synthesis of two different DGDGs from *Mycoplasma pneumoniae* via β-selective glycosylations using the nitrile solvent effect[7] with per-*O*-benzylated glycosyl donors having a nonmalodorous thiosalicyl leaving group.[5c] Furthermore, Fujimoto et al.

Special Issue: A New Era of Discovery in Carbohydrate Chemistry

Received: September 3, 2020

recently reported the convergent synthesis of digalactosyl diacylglycerols without the use of acyl groups; instead, they employed allyl and alloc groups as permanent protecting groups that can be easily removed under mild reaction conditions using a ruthenium catalyst.[5h]

Recently, we developed a β-selective glycosylation reaction using glycopyranosyl donors bearing 2,3-*trans*-fused cyclic protecting groups,[8] which was inspired by the β-selective glycofuranosylation method developed by Lowary and co-workers.[9] Cyclic protecting groups, such as *o*-xylylene (Xyln) and 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) group, have been proven to give excellent β-selectivity. Based on a conformational study of the oxocarbenium intermediate of a Xyln-protected donor via NMR analysis of a model derivative and DFT computational simulations, the β-selective glycosylation reaction is speculated to proceed predominantly via a $^4H_3$ conformational intermediate. The preference for a $^4H_3$ conformation can be rationalized by the presence of a rigid 2,3-*trans*-fused ring. Very recently, we achieved the chemical synthesis of diglucosyl diacylglycols with different saturated fatty acyl chains using a TIPDS-protected glucosyl donor.[5i] However, it was found that the TIPDS group was often affected during protecting group manipulations such as the acid hydrolysis of acetals and etherification under basic conditions due to its acid and base susceptibility. Moreover, this synthetic method still utilized the same late-stage introduction of fatty acyl chains into the diglycosyl glycerols as the aforementioned syntheses. Thus, these methods do not facilitate the diversity of the glycan structure, only allowing the synthesis of DGDGs with structural diversity in fatty acid chains. Herein, we report the development of (i) the 2,3-naphthalenedimethyl (NapDM) group as an acid-cleavable equivalent of the β-stereodirecting Xyln group and (ii) an acyl protecting-group-free strategy for the synthesis of DGDGs based on the NapDM group, with the aim of expanding the scope of the chemical synthesis of DGDGs (Figure 1). This strategy utilizes the NapDM group as an acid-cleavable permanent protecting group as well as late-stage glycosylation of monoglycosyl diacylglycerol (MGDG) acceptors to construct the glycan structure of DGDGs, enabling the stereoselective synthesis of three different DGDGs with unsaturated fatty acyl chain(s) (unsaturated DGDGs): 3-*O*-[6-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl]-1,2-di-*O*-oleoyl-*sn*-glycerol (**1**)[3b] found in *Mycoplasma genitalium*; a derivative of **1** with galactose at the nonreducing end, 3-*O*-[6-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosyl]-1,2-di-*O*-oleoyl-*sn*-glycerol (**2**); and 3-*O*-[6-*O*-(β-D-glucopyranosyl)-β-D-galactopyranosyl]-2-*O*-palmitoleoyl-1-*O*-stearoyl-*sn*-glycerol (**3**)[4c] found in *Mycoplasma pneumoniae* (Figure 2).

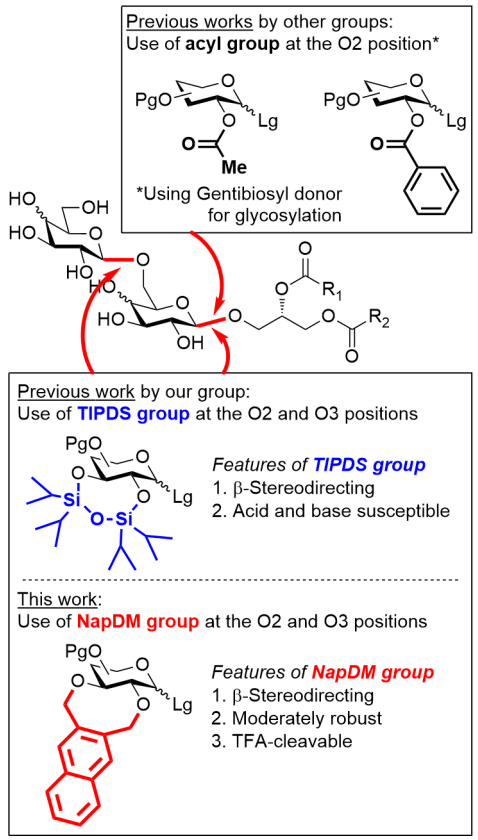


Figure 1. Background for the chemical synthesis of DGDGs.

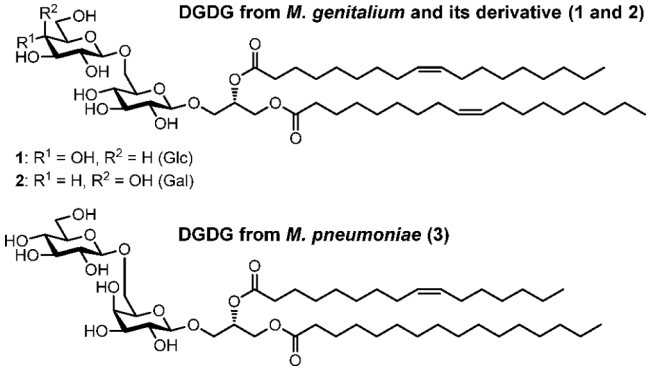


Figure 2. Structures of the targeted unsaturated DGDGs.

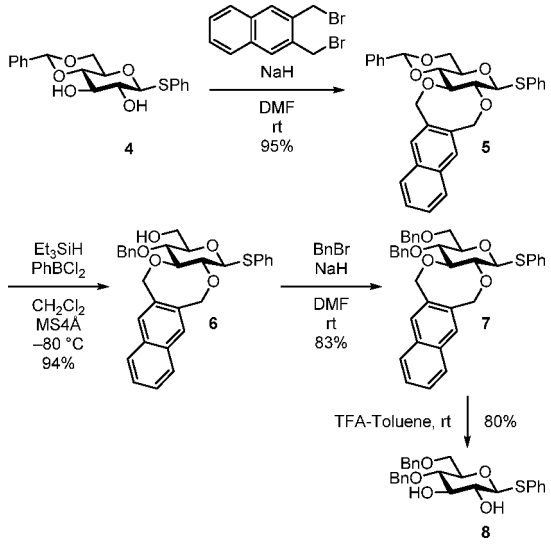
RESULTS AND DISCUSSION

In order to demonstrate the applicability of the NapDM protecting group, we initially prepared a novel glucosyl donor **7** bearing a NapDM protecting group at the 2- and 3-positions and carried out its acid cleavage (Scheme 1). 2,3-*O*-NapDM protection[10] of the known 4,6-*O*-benzylidene acetal **4**[11] was carried out using 2,3-bis(bromomethyl)naphthalene and NaH in DMF to obtain the corresponding compound **5** in 95% yield. The regioselective reductive opening of the benzylidene acetal using Et_3SiH and $PhBCl_2$ in CH_2Cl_2[12] afforded the desired product **6**, which had a free hydroxyl group at the 6-position, in 94% yield. Subsequent benzylation successfully afforded the thioglycoside donor **7** in 83% yield. Under TFA-mediated acidic conditions,[13] the NapDM group in **7** was selectively cleaved within 2 h at room temperature, giving the corresponding diol **8** in 80% yield. This encouraging result prompted us to utilize the NapDM protecting group for a TFA-cleavable protection strategy in the chemical synthesis of unsaturated DGDGs without using acyl protecting groups.

With glucosyl donor **7** in hand, we examined whether the donor gave high β-selectivity on the glycosidation reaction with the galactose acceptor **9**, similar to that of the Xyln-protected donor previously reported by our group (Scheme 2). Using the NIS-TfOH promoter system, **7** was coupled with **9** at −80 °C to provide the disaccharide **10** in 99% yield with excellent β-selectivity (β/α = >15:1). This stereoselectivity is consistent with our previous results when using the Xyln donor (93%, β/α = 11.5:1).[8] Therefore, we envisaged that the NapDM group could be used as a β-stereodirecting protecting group in glycosylation reactions.

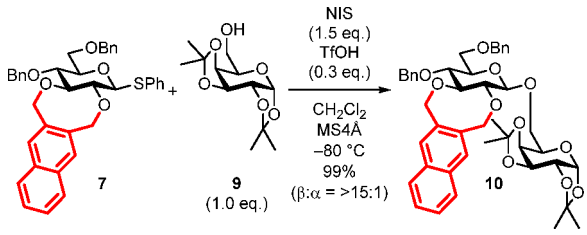
https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Preparation of Glucosyl Donor 7[a]



[a]Abbreviations: DMF, *N*,*N*-dimethylformamide; Bn, benzyl; TFA, trifluoroacetic acid.

Scheme 2. Glycosidation of Donor 7[a]

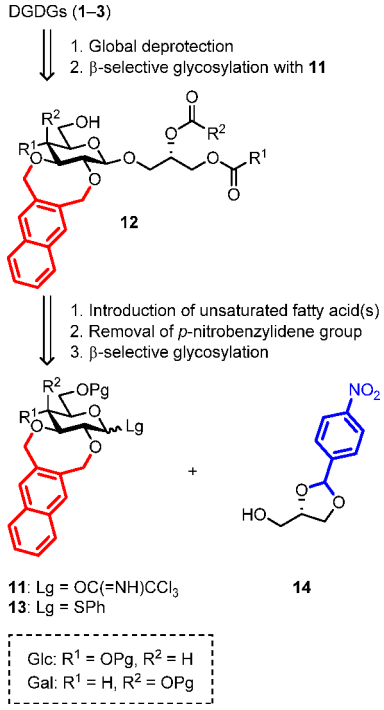


[a]Abbreviations: NIS, *N*-iodosuccinimide; TfOH, trifluoromethanesulfonic acid.

Having demonstrated the orthogonality and β-selectivity of the NapDM protecting group, we turned our attention toward the synthesis of unstaturated DGDGs without using acyl protecting groups (Scheme 3). Retrosynthetic analysis of the targeted DGDGs **1**–**3** indicated that they could be synthesized by the β-selective glycosylation reaction of MGDG **12** with the 2,3-*O*-NapDM-protected glycosyl imidate **11**, with subsequent global deprotection under acidic conditions (Scheme 3). In a recent report from Kulkarni et al., a MGDG acceptor has been used in the synthesis of the lipid-anchor-attached core trisaccharide of lipoteichoic acids of *Streptococcus pneumonia* and *Streptococcus oralis* Uo5.[14] Acceptors with the structure **12** could be accessed from glycosyl thioglycoside **13** and glycerol **14** via the following three steps: β-selective glycosylation reaction, removal of the *p*-nitrobenzylidene group on the glycerol moiety, and introduction of unsaturated fatty acyl chain(s). The use of an electron-deficient *p*-nitrobenzylidene[15] to protect the 1,2-diol of the *sn*-glycerol in **14** allows the suppression of intermolecular isomerizations when 1,2-*O*-isopropylidene-protected *sn*-glycerol was used as an acceptor.[16] Furthermore, the *p*-nitrobenzylidene protecting group allows for the chemoselective deprotection under mild conditions in the presence of other acid-labile protecting groups such as the *p*-methoxyphenylmethyl (MPM) group.

The synthesis commenced with the preparation of glucose and galactose donors with suitable protection pattern (Scheme 4). The free hydroxyl groups at the 2- and 3-positions of the

Scheme 3. Retrosynthetic Analysis of DGDGs 1–3



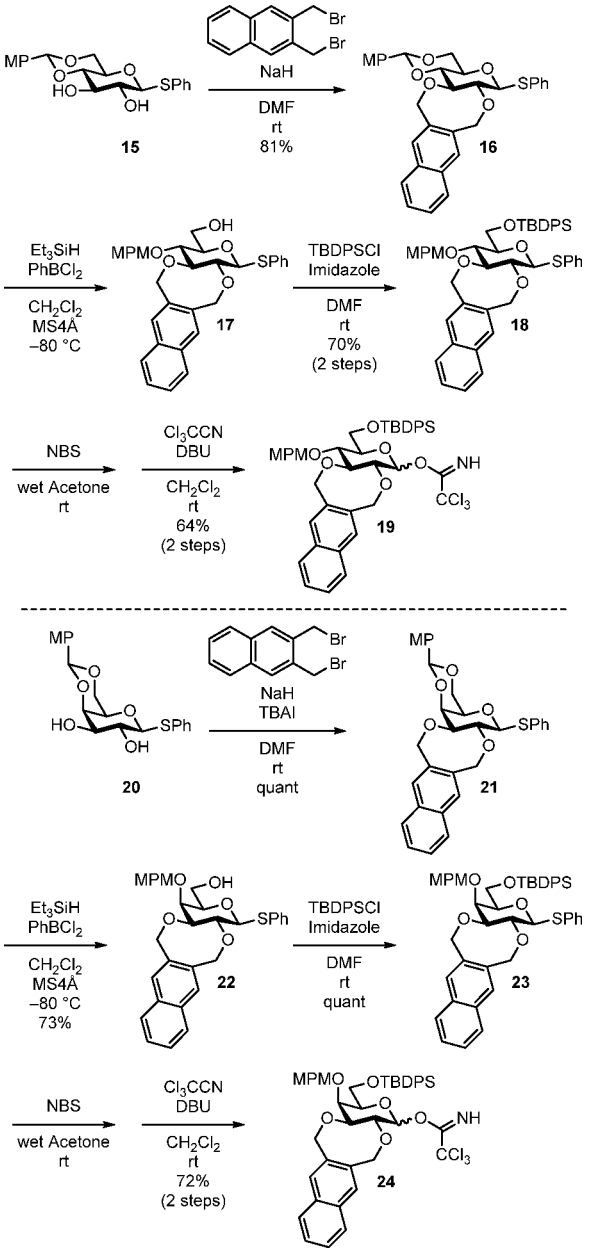
known 4,6-*O*-*p*-anisylidene acetal **15**[17] were protected with the NapDM group using 2,3-bis(bromomethyl)naphthalene and NaH under dilute conditions to give the NapDM-protected thioglucoside **16** in 81% yield. Subsequent regioselective reductive opening of the *p*-anisylidene acetal using Et_3SiH and $PhBCl_2$ afforded **17**, which was then silylated with *tert*-butyldiphenylsilyl chloride to provide the fully protected thioglycoside **18** in 70% yield over two steps. The corresponding trichloroacetimidate **19** was prepared by chemoselective hydrolysis of the anomeric phenylsulfenyl group in **18**, followed by treatment with Cl_3CCN and DBU. Similarly, the 4,6-*O*-*p*-anisilidene acetal of galactose, **20**,[18] was converted into thioglycoside **23** and trichloroacetimidate **24** by the above-mentioned reaction sequence.

The glycerol acceptor **14** was synthesized in two straightforward steps from 3-*O*-benzoylated *sn*-glycerol **25**, which was prepared from a commercially available 1,2-*O*-isopropylidene derivative following the procedure reported by Santaniello et al.[19] Compound **25** was exposed to acetalization with *p*-nitrobenzaldehyde, providing the two diastereomers **26a** and **26b** in 34 and 37% yields, respectively. The absolute configuration of the newly generated stereogenic center was determined by X-ray crystallographic analysis of **26a** (Scheme 5 and see Supporting Information). Debenzoylation under Zemplén conditions afforded the *p*-nitrobenzylidene-protected glycerol acceptors **14a** and **14b** in 92 and 89% yields, respectively.

For the construction of glycosyl glycerol fragments, acceptors **14a** and **14b** were glycosylated with thioglycoside donors **18** and **23** in CH_2Cl_2 at −80 °C by the NIS-TESOTf activation method (Table 1).[20] The use of TESOTf as an acid source rather than TfOH not only decreased the amount of acid required to 0.15 equiv due to its high solubility in organic solvents but also avoided the undesired removal of the MPM group from the glycosylated products that was observed when using 0.3 equiv of TfOH. All the glycosylations proceeded β-

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

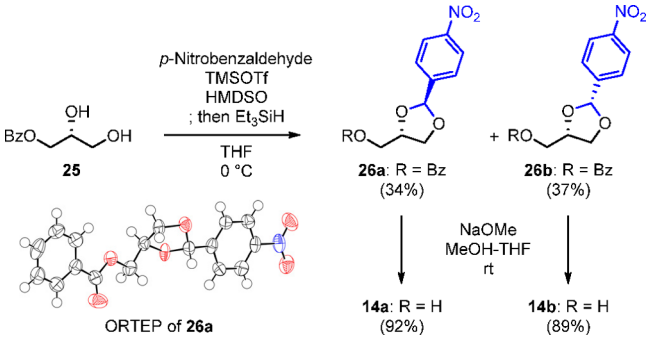
Scheme 4. Preparation of Donors 18, 19, 23, and 24[a]



[a]Abbreviations: MPM, *p*-methoxyphenylmethyl; TBDPS, *tert*-butyldiphenylsilyl; NBS, *N*-bromosuccinimide; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; TBAI, tetra-*n*-butylammonium iodide.

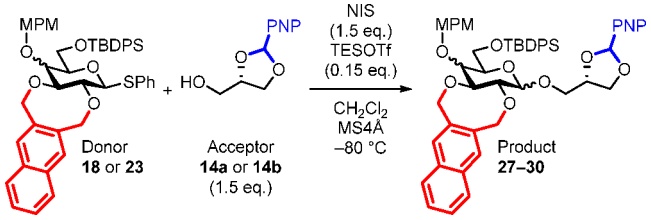
selectively without acetal isomerization to give the desired *O*-glycosides **27**–**30** in high yields (entries 1–4). The structures of the β-glycosides were confirmed by the large $J_{1,2}$ coupling constants in the ^{1}H NMR spectra (7–8 Hz), whereas smaller $J_{1,2}$ coupling constants (3–4 Hz) were observed for α-glycosides. Moreover, the anomeric carbon signals of the β-glycosides appeared at magnetic fields (approximately 103 ppm) lower than those of the α-glycosides (around 98 ppm). The β-selectivities obtained with the galactose donor **23** (β/α = 3:1, entries 3 and 4) were slightly higher than those obtained with the glucose donor **18** (β/α = 1.5–1.8:1, entries 1 and 2). These results indicated that the stereochemistry of the *p*-nitrobenzylidene acetal exerted no influence on the β-selectivity of the glycosylation with donors **18** and **23**.

Scheme 5. Synthesis of Glycerol Acceptor 14[a]



[a]Abbreviations: TMSOTf, trimethylsilyl trifluoromethanesulfonate; HMDSO, hexamethyldisiloxane; THF, tetrahydrofuran.

Table 1. Construction of Glycosyl Glycerol Framework[a]



entry	donor	acceptor	reaction time	product	isolated yield
1	18 (Glc)	**14a**	24 h	**27**	β: 61%, α: 34%
2	18 (Glc)	**14b**	24 h	**28**	β: 58%, α: 39%
3	23 (Gal)	**14a**	4 h	**29**	β: 72%, α: 24%
4	23 (Gal)	**14b**	4 h	**30**	β: 73%, α: 24%

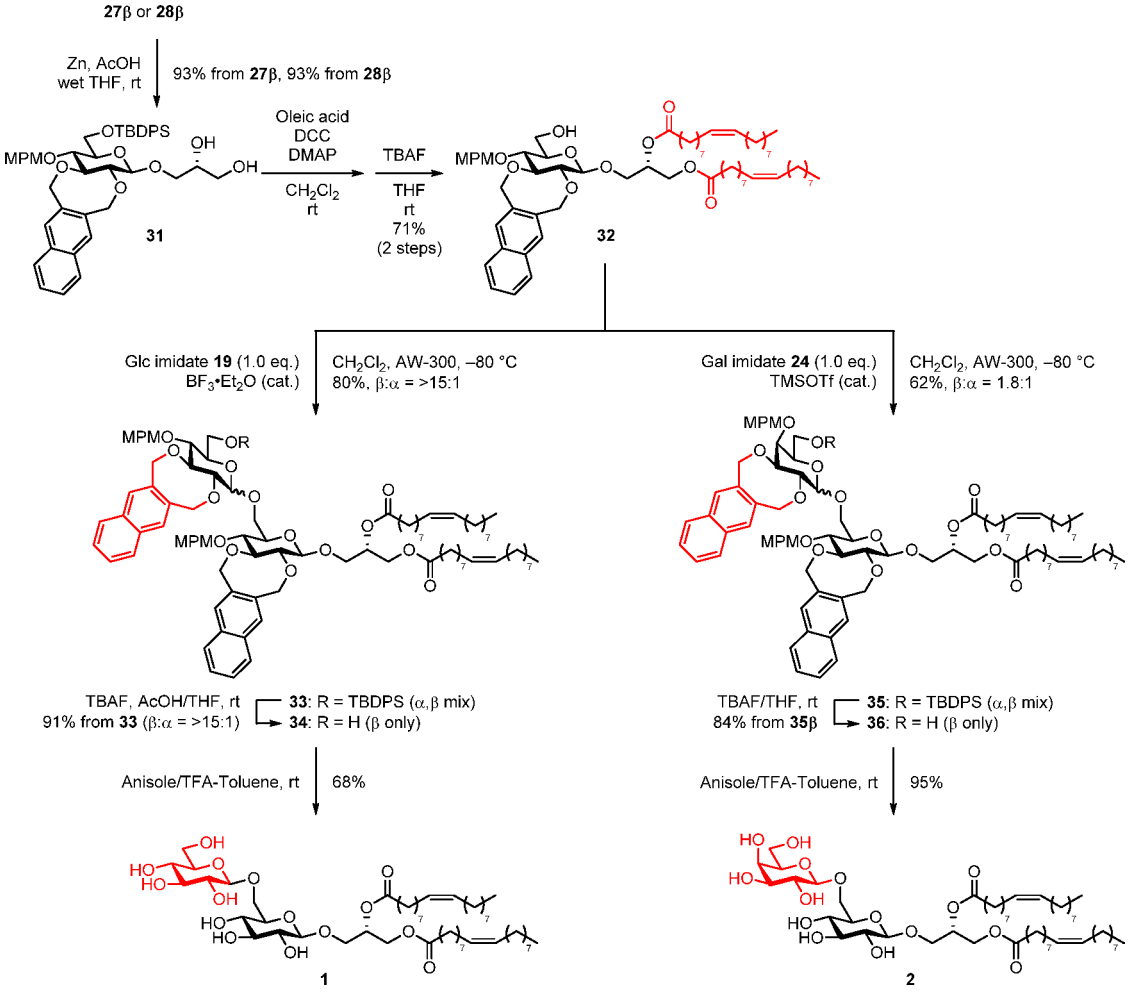
[a]Abbreviations: PNP, *p*-nitrophenyl; TESOTf, triethylsilyl trifluoromethanesulfonate.

However, we speculate that the lesser β-selectivities while using acceptors **14a,b** could be attributed with the nitrobenzylidene protecting group, making it mismatched acceptors, because the better β-selectivity (β/α = 6.7:1) was obtained during coupling of the Xyln donor with the 1,2-isopropylidene-protected glycerol acceptor.

To establish a TFA-cleavable protection strategy for the chemical synthesis of unsaturated DGDGs, we first demonstrated the synthesis of the targeted molecules **1** and **2** (Scheme 6). Chemoselective removal of the *p*-nitrobenzylidene protecting groups in **27*β*** and **28*β*** using zinc and AcOH[21] in wet THF provided the 1,2-diol compound **31**, which was subjected to acylation with oleic acid followed by desilylation using TBAF to obtain the monoglucosyl diacylglycerol acceptor **32**. For the synthesis of **1**, glucosylation of **32** with glucosyl imidate **19** was performed at −80 °C in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$, yielding the DGDG framework **33** in 80% yield with excellent β-selectivity (β/α = >15:1). After removal of the TBDPS group of **33** by treatment with TBAF and AcOH, global deprotection of **34** was conducted using a mixture of TFA and toluene as a solvent, with anisole being used as a scavenger to furnish the desired product **1** in a satisfactory yield. Turning to the next target molecule **2**, compound **32** was galactosylated with galactosyl imidate **24** under the aforementioned reaction conditions.

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 6. Synthesis of DGDGs 1 and 2[a]



[a]Abbreviations: DCC, *N*,*N*′-dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; TBAF, tetra-*n*-butylammonium fluoride.

However, the yield of the desired coupling product **35** was only 50% without β-selectivity (β/α = ~1:1). Additionally, the corresponding galactosyl fluoride was observed as a by-product,[22] which led to a change in the activator for glycosylation to TMSOTf instead of $BF_3{\cdot}Et_2O$, which improved both the yield and β-selectivity (62%, β/α = 1.8:1). Unfortunately, it seemed to be a mismatched donor–acceptor pairing between **24** and **32**. The synthesis of the non-natural DGDG **2** was then completed following the same deprotection sequence as used for natural DGDG **1**.

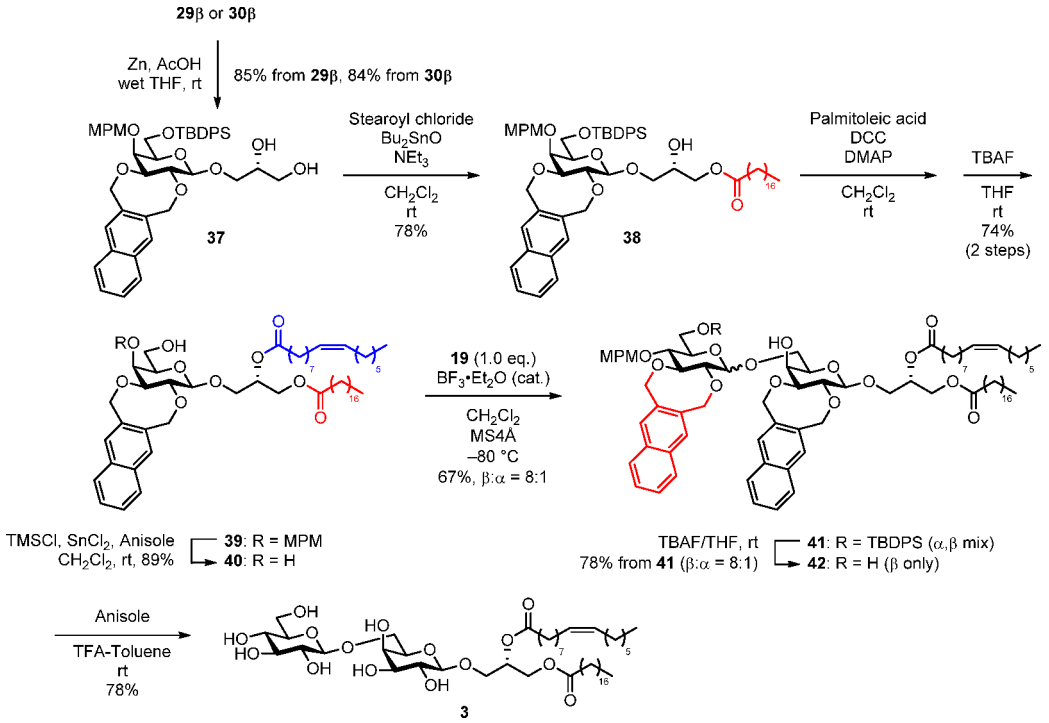
Based on the established acid-cleavable protection strategy, we addressed the preparation of the synthetically challenging DGDG **3**, which possesses two different acyl groups with saturated and unsaturated chains (Scheme 7). The 1,2-diol compound **37**, derived from **29*β*** and **30*β*** via removal of the *p*-nitrobenzylidene under reductive conditions, was exposed to tin-mediated acylation[23] with stearoyl chloride at the 1-position of the glycerol moiety to give the monoacylated compound **38** in 78% yield. Palmitoleoylation of the remaining hydroxyl group and subsequent TBDPS removal provided the diacylated product **39** in 74% yield over two steps. Since the 4-*O*-MPM protecting group in the axial direction might reduce the reactivity of a hydroxyl group at the 6-position of the galactose moiety, the acid-labile group was cleaved using the $TMSCl/SnCl_2$/anisole system[24] to obtain the galactosyl diacylglycerol acceptor **40** in 89% yield. Using a catalytic amount of $BF_3{\cdot}Et_2O$, coupling of **40** with glucosyl imidate **19** led to a good yield of the desired glucoside **41** (67%) with high β-selectivity (β/α = 8:1). A tiny amount of the corresponding regioisomer, glucosylated at the 4-position of the galactose moiety, was also observed. The glucosylated position was then confirmed by acetylation of the remaining free hydroxyl group. Finally, all the protecting groups were removed by a two-step reaction sequence to successfully afford the target DGDG **3**.

■ CONCLUSIONS

We have developed an acid-cleavable and β-stereodirecting NapDM protecting group for glycosyl donors for glycan synthesis. This group not only served as a simultaneous protecting group for the *trans*-equatorially oriented vicinal diols but also influenced the outcome of the glycosylation reaction, giving rise to the β-glycosides. The use of the NapDM protecting group prevented the formation of orthoester side products during the glycosylation reaction, which can be a problem when using the C-2 acyl functionality. The NapDM group was used to establish a TFA-cleavable protection strategy for acyl protecting-group-free synthesis of DGDGs. The key feature of this strategy was the β-stereoselective glycosylation of MGDG acceptors with NapDM-protected donors at a later stage. β-Stereoselective

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 7. Synthesis of DGDG 3[a]



[a]Abbreviation: TMSCl, trimethylsilyl chloride.

glycosylation enabled the synthesis of three different synthetically challenging unsaturated DGDGs. The strategy developed in this study would allow rapid access to not only the natural DGDGs but also functionalized derivatives, allowing for the elucidation of their biological functions.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an argon atmosphere. All reactions that required heating were performed in an oil bath. All chemicals were purchased from commercial suppliers and used without further purification. Compound **9** was purchased from Sigma-Aldrich (St. Louis, MO). Molecular sieves were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan) and predried at 300 °C for 2 h in a muffle furnace and then dried in a flask at 300 °C for 2 h in vacuo prior to use. Dry solvents for reaction media (CH_2Cl_2, toluene, THF, CH_3CN, DMF, and pyridine) were purchased from Kanto Chemical Co. Inc. (Tokyo, Japan) and used without purification. TLC analyses were performed on Merck TLC plates (silica gel 60F254 on glass plate). Compound detection on TLC was carried out either by exposure to UV light (253.6 nm) or by soaking in H_2SO_4 solution (10% in EtOH) or phosphomolybdic acid solution (20% in EtOH) followed by heating. Silica gel column chromatography separations were performed with a flash column chromatography system. Silica gel (80 mesh and 300 mesh; Fuji Silysia Co. (Aichi, Japan)) was used for flash column chromatography. The quantity of silica gel was typically 100 to 200 times the weight of the crude sample. Sephadex (Pharmacia LH-20) was used for size-exclusion chromatography. Solvent systems for chromatography are specified as v/v ratios. ^1H and ^{13}C NMR spectra were recorded on Avance III 500 spectrometers (Bruker, Billerica, MA, USA). Chemical shifts are expressed in ppm (δ) relative to the Me_4Si signal (0.00 ppm). Each of the Glc units in compounds **1**, **33**, and **34** is numbered using letters a and b: nonreducing end Glc(a), reducing end Glc(b) (see Supporting Information). Structural assignments were made with additional information from 2D NMR ($^1H-^1H$ COSY, HMBC, and HMQC) experiments. High-resolution mass spectrometry (ESI-TOF MS) data were obtained with a mass spectrometer (micrOTOF, Bruker). Optical rotations were measured with a high-sensitivity polarimeter SEPA-300 (Horiba, Kyoto, Japan).

Synthetic Procedure. *3-O-[6-O-(β-D-Glucopyranosyl)-β-D-glucopyranosyl]-1,2-di-O-oleoyl-sn-glycerol (1).* To a solution of **34** (30 mg, 20 μmol) in TFA/toluene (10:1, 0.10 mL) was added anisole (22 μL, 0.20 mmol) at 4 °C using an ice bath. After being stirred for 24 h at the same temperature as the reaction was monitored by TLC ($CHCl_3$/MeOH = 5:1), the reaction was quenched by the addition of NEt_3 at 4 °C using an ice bath. The reaction mixture was concentrated, and the resulting residue was purified by flash column chromatography on silica gel using toluene/EtOAc (10:1) as the eluent and Sephadex LH-20 using $CHCl_3$/MeOH (1:1) as the eluent to give **1** (13 mg, 68%) as a colorless syrup: $[\alpha]_D^{25}$ −18.0 (*c* 0.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3/CD_3OD$ = 1:2) δ 5.38−5.26 (m, 5 H, 4 CH = C*H*, H-2^{Gro}), 4.43 (dd, 1 H, J_{vic} = 2.9 Hz, J_{gem} = 12.1 Hz, H-1a^{Gro}), 4.36 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1^{Glc}), 4.27 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1^{Glc}), 4.22 (dd, 1 H, J_{vic} = 6.9 Hz, H-1b^{Gro}), 4.17 (dd, 1 H, $J_{5,6a}$ = 2.0 Hz, J_{gem} = 11.5 Hz, H-6a^{Glc}), 3.98 (dd, 1 H, J_{vic} = 5.5 Hz, J_{gem} = 11.0 Hz, H-3a^{Gro}), 3.87 (dd, 1 H, $J_{5,6a}$ = 2.1 Hz, J_{gem} = 12.1 Hz, H-6a^{Glc}), 3.79−3.74 (m, 2 H, H-6b^{Glc}, H-3b^{Gro}), 3.68 (dd, 1 H, $J_{5,6b}$ = 5.3 Hz, H-6b^{Glc}), 3.46−3.17 (m, 8 H, H-2^{Glc}, H-3^{Glc}, H-4^{Glc}, H-5^{Glc}, H-2^{Glc}, H-3^{Glc}, H-4^{Glc}, H-5^{Glc}), 2.35−2.31 (m, 4 H, 2 O(CO)CH_2), 2.03−1.98 (m, 8 H, 4 CH=CHCH_2), 1.68−1.20 (m, 44 H, 22 CH_2), 0.91−0.88 (m, 6 H, 2 Me); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$/CD_3OD = 1:2) δ 175.0, 174.8, 130.9, 130.7, 104.8, 104.6, 79.4, 79.3, 79.1, 78.9, 77.9, 77.7, 77.0, 75.0, 74.8, 71.7, 71.5, 71.3, 69.9, 68.9, 62.7, 49.9, 49.6, 35.1, 34.9, 33.0, 30.8, 30.7, 30.6, 30.4, 30.3, 30.2, 28.1, 26.0, 23.7, 14.5; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{51}H_{92}O_{15}Na$ 967.6328; found $[M + Na]^+$ 967.6328.

3-O-[6-O-(β-D-Galactopyranosyl)-β-D-glucopyranosyl]-1,2-di-O-oleoyl-sn-glycerol (2). To a solution of **36** (8.1 mg, 5.4 μmol) in toluene (0.1 mL) were added anisole (5.9 μL, 54 μmol) and TFA (1.0 mL) at 4 °C using an ice bath. After being stirred for 4 h at room temperature as the reaction was monitored by TLC ($CHCl_3$/MeOH = 5:1), the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel using $CHCl_3$/MeOH (20:1→15:1→5:1) as the eluent to give **2** (5.6 mg, 95%) as a white solid: $[\alpha]_D^{25}$ −16.6 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz,

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

$CDCl_3/CD_3OD$ = 1:1) δ 5.38−5.26 (m, 5 H, 4 CH = C*H*, H-2^{Gro}), 4.41 (dd, 1 H, J_{vic} = 3.0 Hz, J_{gem} = 12.1 Hz, H-1a^{Gro}), 4.30 (d, 1 H, $J_{1,2}$ = 7.7 Hz, H-1^{Gal}), 4.27 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1^{Glc}), 4.24 (dd, 1 H, J_{vic} = 6.7 Hz, H-1b^{Gro}), 4.17 (dd, 1 H, $J_{5,6a}$ = 1.5 Hz, J_{gem} = 11.1 Hz, H-6a^{Glc}), 3.97 (dd, 1 H, J_{vic} = 5.4 Hz, J_{gem} = 11.0 Hz, H-3a^{Gro}), 3.87 (d, 1 H, $J_{3,4}$ = 3.1 Hz, H-4^{Gal}), 3.83−3.73 (m, 4 H, H-5^{Gal}, H-6a^{Gal}, H-6b^{Glc}, H-3b^{Gro}), 3.58 (dd, 1 H, $J_{2,3}$ = 9.6 Hz, H-2^{Gal}), 3.53−3.48 (m, 2 H, H-3^{Gal}, H-5^{Glc}), 3.47−3.38 (m, 3 H, H-3^{Gal}, H-6b^{Gal}, H-4^{Glc}), 3.25 (dd, 1 H, $J_{2,3}$ = 8.1 Hz, H-2^{Glc}), 2.36−2.32 (m, 4 H, 2 O(CO)CH_2), 2.04−2.00 (m, 8 H, 4 CH = CHCH_2), 1.63−1.17 (m, 44 H, 22 CH_2), 0.91−0.88 (m, 6 H, 2 Me); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$/CD_3OD = 1:1) δ 174.6, 174.3, 130.4, 130.2, 104.6, 104.1, 78.7, 78.3, 76.9, 76.1, 75.8, 74.1, 74.0, 71.9, 70.9, 70.6, 69.5, 69.2, 68.5, 63.3, 62.0, 49.6, 34.8, 34.6, 34.2, 32.4, 32.4, 32.3, 30.2, 30.1, 30.0, 29.8, 29.8, 29.7, 29.6, 29.6, 27.7, 27.6, 25.5, 25.4, 25.4, 23.1, 14.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{51}H_{92}O_{15}Na$ 967.6328; found $[M + Na]^+$ 967.6326.

3-O-[6-O-(β-D-Glucopyranosyl)-β-D-galactopyranosyl]-2-O-palmitoleoyl-1-O-stearoyl-sn-glycerol (3). To a solution of **42** (16 mg, 12 μmol) in TFA/toluene (10:1, 0.10 mL) was added anisole (6.2 μL, 58 μmol) at 4 °C using an ice bath. After being stirred for 4 h at room temperature as the reaction was monitored by TLC ($CHCl_3$/MeOH = 5:1), the reaction was quenched by the addition of NEt_3 at 4 °C using an ice bath. The reaction mixture was concentrated and the resulting residue was purified by flash column chromatography on silica gel using $CHCl_3$/MeOH (5:1) as the eluent to give **3** (8.2 mg, 78%): $[\alpha]_D^{25}$ +47.5 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$/CD_3OD = 1:2) δ 5.35−5.33 (m, 2 H, 2 CH = C*H*), 5.27 (m, 1 H, H-2^{Gro}), 4.44 (dd, 1 H, J_{vic} = 2.5 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.36 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1^{Gal}), 4.24 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.23 (m, 1 H, H-1b^{Gro}), 4.03−3.96 (m, 2 H, H-4^{Gal}, H-3a^{Gro}), 3.91−3.84 (m, 2 H, H-4^{Glc}, H-6a^{Glc}), 3.76 (dd, 1 H, $J_{2,3}$ = 5.5 Hz, J_{gem} = 11.0 Hz, H-3b^{Gro}), 3.72−3.65 (m, 2 H, H-5^{Gal}, H-6a^{Gal}), 3.53 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{Glc}), 3.52 (dd, 1 H, H-2^{Glc}), 3.47 (dd, 1 H, $J_{5,6b}$ = 3.5 Hz, J_{gem} = 10.0 Hz, H-6b^{Glc}), 3.94−3.23 (m, 3 H, H-3^{Gal}, H-6b^{Gal}, H-5^{Glc}), 3.21 (dd, 1 H, $J_{2,3}$ = 9.0 Hz, H-2^{Gal}), 2.35−2.31 (m, 4 H, 2 O(CO)CH_2), 2.03−2.02 (m, 4 H, 2 CH = CHCH_2), 1.62−1.28 (m, 46 H, 23 CH_2), 0.95−0.88 (m, 6 H, 2 Me); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$/CD_3OD = 1:2) δ 174.9, 174.6, 130.7, 130.5, 105.0, 104.4, 79.1, 78.8, 78.6, 77.7, 77.5, 74.9, 74.7, 74.4, 72.1, 71.5, 71.4, 69.5, 69.1, 68.6, 63.8, 62.5, 49.5, 48.5, 35.0, 34.9, 32.8, 32.7, 30.6, 30.5, 30.5, 30.4, 30.2, 30.1, 30.0, 29.8, 28.0, 28.0, 25.8, 23.5, 14.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{49}H_{90}O_{15}Na$ 941.6172; found $[M + Na]^+$ 941.6172.

Phenyl 4,6-O-benzylidene-2,3-O-[2,3-bis(methyl)naphthele]-1-thio-β-D-glucopyranoside (5). To a solution of **4**[25] (130 mg, 360 μmol) in DMF (7.4 mL) was added NaH [60% in oil] (72 mg, 1.8 mmol) at 4 °C using an ice bath. The mixture was stirred for 30 min at room temperature, and 2,3-bis(bromomethyl)naphthalene (72 mg, 0.40 mmol) was added at 4 °C using an ice bath. After being stirred for 5 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of MeOH. The resulting mixture was coevaporated with toluene, diluted with $CHCl_3$, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using toluene/$CHCl_3$ (7:1) as the eluent to give **5** (179 mg, 95%) as a white solid: $[\alpha]_D^{25}$ +18.9 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.55−7.14 (m, 16 H, 4 Ar), 5.50 (s, 1 H, >C*H*Ar), 5.34 (d, 1 H, J_{gem} = 14.0 Hz, ArCH_2), 5.33 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.27 (d, 1 H, ArCH_2), 5.05 (d, 1 H, J_{gem} = 10.0 Hz, ArCH_2), 4.73 (d, 1 H, $J_{1,2}$ = 10.0 Hz, H-1), 4.33 (dd, 1 H, $J_{5,6a}$ = 4.5 Hz, J_{gem} = 10.5 Hz, H-6a), 3.88 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3), 3.88 (t, 1 H, $J_{5,6b}$ = 10.5 Hz, H-6b), 3.59−3.43 (m, 3 H, H-2, H-4, H-5); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 137.1, 134.8, 134.2, 133.0, 132.9, 132.3, 130.6, 129.1, 129.0, 128.5, 128.3, 127.9, 127.6, 127.3, 126.5, 126.4, 126.4, 101.8, 87.7, 81.2, 79.5, 78.7, 77.6, 73.0, 72.5, 70.4, 68.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{31}H_{28}O_5SNa$ 535.1550; found $[M + Na]^+$ 535.1552.

Phenyl 4-O-benzyl-2,3-O-[2,3-bis(methyl)naphthele]-1-thio-β-D-glucopyranoside (6). To a solution of **5** (184 mg, 300 μmol) in CH_2Cl_2 (3.0 mL) was added 4 Å molecular sieves (184 mg). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C using a low constant temperature bath. Subsequently, Et_3SiH (112 μL, 660 μmol) and $PhBCl_2$ (87 μL, 660 μmol) were added to the reaction mixture at −80 °C. After being stirred for 30 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of NEt_3 and MeOH at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (10:1) as the eluent to give **6** (174 mg, 94%) as a white solid: $[\alpha]_D^{25}$ +28.8 (*c* 3.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86−7.05 (m, 16 H, 4 Ar), 5.34 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.30 (d, 1 H, J_{gem} = 14.0 Hz, ArCH_2), 5.24 (d, 1 H, ArCH_2), 5.09 (d, 1 H, ArCH_2), 5.00 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.67 (d, 1 H, ArCH_2), 4.64 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 3.78−3.56 (m, 2 H, H-3, H-6a), 3.64 (m, 1 H, H-6b), 3.49−3.43 (m, 2 H, H-2, H-4), 3.37 (m, 1 H, H-5), 1.83 (t, 1 H, $J_{6a,OH}$ = $J_{6b,OH}$ = 6.5 Hz, OH); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 138.3, 134.9, 134.5, 133.1, 132.9, 131.9, 130.0, 129.0, 128.5, 128.5, 128.1, 127.9, 127.7, 127.5, 127.4, 126.5, 126.4, 86.6, 85.7, 79.1, 79.0, 77.6, 75.0, 73.1, 73.0, 62.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{31}H_{30}O_5SNa$ 537.1706; found $[M + Na]^+$ 537.1703.

Phenyl 4,6-di-O-benzyl-2,3-O-[2,3-bis(methyl)naphthele]-1-thio-β-D-glucopyranoside (7). To a solution of **6** (92 mg, 0.17 mmol) in DMF (0.85 mL) was added NaH [60% in oil] (108 mg, 270 μmol) at 4 °C using an ice bath. The mixture was stirred for 30 min at the same temperature, and benzyl bromide (101 μL, 850 μmol) was added at 4 °C using an ice bath. After being stirred for 20 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of MeOH. The resulting mixture was coevaporated with toluene, diluted with $CHCl_3$, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using toluene/$CHCl_3$ (7:1) as the eluent to give **7** (85 mg, 83%) as a white foamy material: $[\alpha]_D^{25}$ +24.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.79−7.21 (m, 21 H, 5 Ar), 5.31 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.25 (d, 1 H, J_{gem} = 14.5 Hz, ArCH_2), 5.21 (d, 1 H, ArCH_2), 5.04 (d, 1 H, ArCH_2), 4.92 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.60 (s, 1 H, ArCH_2), 4.58 (s, 1 H, ArCH_2), 4.53 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 4.47 (d, 1 H, ArCH_2), 3.78−3.73 (m, 2 H, H-3, H-6a), 3.65 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, J_{gem} = 11.0 Hz, H-6b), 3.51−3.44 (m, 3 H, H-2, H-4, H-5); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 138.5, 138.3, 135.0, 134.6, 133.5, 133.0, 128.8, 128.4, 128.4, 128.3, 127.7, 127.6, 127.5, 127.5, 127.4, 126.4, 126.3, 86.6, 85.9, 78.9, 78.9, 77.6, 77.6, 75.0, 73.4, 73.1, 73.0, 69.2, 29.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{38}H_{36}O_5SNa$ 627.2176; found $[M + Na]^+$ 627.2177.

Phenyl 4,6-di-O-benzyl-1-thio-β-D-glucopyranoside (8). Compound **7** (8.1 mg, 13 μmol) was dissolved in toluene/TFA (1:10, 0.10 mL) at room temperature. After being stirred for 2 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction mixture was coevaporated with toluene. The residue was diluted with $CHCl_3$, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (3:1) as the eluent to give **8** (3.6 mg, 80%): the optical and spectroscopic data ($[\alpha]_D$, ^1H and ^{13}C NMR, MS) were identical to the reported value.[26]

4,6-Di-O-benzyl-2,3-O-[2,3-bis(methyl)naphthele]-β-D-glucopyranosyl]-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (10). To a solution of Glc thioglycoside **7** (73 mg, 0.12 mmol) and **9** (31 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) were added 4 Å molecular sieves (60 mg) and NIS (41 mg, 0.18 mmol). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

using a low constant temperature bath. Subsequently, TfOH (3.2 μL, 36 μmol) was added to the reaction mixture at −80 °C. After being stirred for 3 h at the same temperature as the reaction was monitored by TLC (toluene/EtOAc = 4:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by column chromatography on sephadex LH-20 using $CHCl_3$/MeOH (1:1) as the eluent to give the glycosylated product **10** (90 mg, 99%, β/α = >15:1). The β-isomer was partially separated by flash column chromatography on silica gel using toluene/EtOAc (20:1→10:1) as the eluent to give **10*β*** in pure form. **10*β***: $[\alpha]_D^{25}$ +28.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.21 (m, 16 H, 4 Ar), 5.58 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 5.39 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.24 (s, 2 H, 2 ArCH_2), 5.00 (d, 1 H, ArCH_2), 4.94 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.61 (dd, 1 H, $J_{4,5}$ = 2.5 Hz, $J_{3,4}$ = 8.0 Hz, H-4^{Gal}), 4.56 (d, 1 H, J_{gem} = 12.0 Hz, ArCH_2), 4.54 (d, 1 H, ArCH_2), 4.49 (d, 1 H, ArCH_2), 4.43 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.33 (m, 2 H, H-2^{Gal}, H-3^{Gal}), 4.10−4.06 (m, 2 H, H-5^{Gal}, H-6a^{Gal}), 3.80 (m, 1 H, H-6b^{Gal}), 3.76 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3^{Glc}), 3.70 (dd, 1 H, $J_{5,6a}$ = 2.0 Hz, J_{gem} = 9.0 Hz, H-6a^{Glc}), 3.64 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, H-6b^{Glc}), 3.48 (t, 1 H, $J_{4,5}$ = 8.5 Hz, H-4^{Glc}), 3.45−3.41 (m, 2 H, H-2^{Gal}, H-5^{Gal}), 1.58−1.33 (m, 12 H, 4 Me); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.6, 138.2, 135.4, 135.2, 133.0, 132.8, 130.7, 129.5, 128.3, 128.3, 127.9, 127.8, 127.6, 127.5, 127.2, 126.3, 126.0, 109.3, 108.6, 102.6, 96.4, 84.1, 80.4, 74.8, 73.4, 73.0, 72.6, 71.3, 70.7, 70.6, 69.2, 68.9, 67.7, 26.2, 26.0, 25.0, 24.4; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{50}O_{11}Na$ 777.3245; found [M + Na]$^+$ 777.3240.

*1,2-O-[(S)-p-Nitrobenzylidene)]-sn-glycerol (**14a**).* To a solution of **26a** (121 mg, 366 μmol) in MeOH/THF (2:1, 3.7 mL) was added NaOMe [28% solution in MeOH] (7.1 mg, 37 μmol) at 4 °C using an ice bath. After being stirred for 3.5 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of Muromac (H^+) at 4 °C using an ice bath. The resulting mixture was filtered through a pad of Celite, and the pad and resin were washed with EtOAc. The combined filtrate and washings were concentrated and the resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1) as the eluent to give **14a** (77 mg, 92%) as a colorless syrup: $[\alpha]_D^{25}$ +14.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, 2 H, $J_{H,H}$ = 8.7 Hz, Ar), 7.65 (d, 2 H, Ar), 6.06 (s, 1 H, >C*H*Ar), 4.36 (m, 1 H, H-2^{Gro}), 4.20 (dd, 1 H, J_{vic} = 6.4 Hz, J_{gem} = 8.3 Hz, H-1a^{Gro}), 3.93 (dd, 1 H, J_{vic} = 6.9 Hz, H-1b^{Gro}), 3.86 (dd, 1 H, J_{vic} = 3.6 Hz, J_{gem} = 12.0 Hz, H-3a^{Gro}), 3.75 (dd, 1 H, J_{vic} = 5.3 Hz, H-3b^{Gro}), 1.85 (brs, 1 H, OH); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.4, 144.9, 127.3, 123.6, 102.4, 76.8, 66.8, 62.6; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{11}NO_5Na$ 248.0529; found [M + Na]$^+$ 248.0525.

*1,2-O-[(R)-p-Nitrobenzylidene)]-sn-glycerol (**14b**).* To a solution of **26b** (77 mg, 0.23 mmol) in MeOH/THF (2:1, 2.3 mL) was added NaOMe [28% solution in MeOH] (4.4 mg, 23 μmol) at 4 °C using an ice bath. After being stirred for 3.5 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of Muromac (H^+) at 4 °C using an ice bath. The resulting mixture was filtered through a pad of Celite, and the pad and resin were washed with EtOAc. The combined filtrate and washings were concentrated and the resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1) as the eluent to give **14b** (46 mg, 89%) as a colorless syrup: $[\alpha]_D^{25}$ −13.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, 2 H, $J_{H,H}$ = 8.7 Hz, Ar), 7.68 (d, 2 H, Ar), 5.90 (s, 1 H, >C*H*Ar), 4.42 (m, 1 H, H-2^{Gro}), 4.15 (dd, 1 H, J_{vic} = 6.3 Hz, J_{gem} = 8.1 Hz, H-1a^{Gro}), 4.03 (dd, 1 H, J_{vic} = 5.8 Hz, H-1b^{Gro}), 3.83 (dd, 1 H, J_{vic} = 3.8 Hz, J_{gem} = 11.9 Hz, H-3a^{Gro}), 3.70 (dd, 1 H, J_{vic} = 5.3 Hz, H-3b^{Gro}), 1.73 (brs, 1 H, OH); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.6, 144.0, 127.5, 123.6, 102.7, 77.3, 67.0, 63.0; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{11}NO_5Na$ 248.0529; found [M + Na]$^+$ 248.0525.

*Phenyl 4,6-O-anisylidene-2,3-O-[2,3-bis(methyl)naphthele]-1-thio-β-D-glucopyranoside (**16**).* To a solution of **15**[27] (2.30 g, 5.89 mmol) in DMF (116 mL) was added NaH [60% in oil] (696 mg, 17.4 mmol) at 4 °C using an ice bath. The mixture was stirred for 30 min at room temperature, and 2,3-bis(bromomethyl)naphthalene (2.04 g, 6.48 mmol) was added at 4 °C using an ice bath. After being stirred for 12 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of MeOH. The resulting mixture was coevaporated with toluene, diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using toluene/$CHCl_3$ (1:1) as the eluent to give **16** (2.44 g, 81%) as a yellow solid: $[\alpha]_D^{25}$ +20.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−6.88 (m, 15 H, 4 Ar), 5.46 (s, 1 H, >C*H*Ar), 5.34 (d, 1 H, J_{gem} = 14.0 Hz, ArCH_2), 5.33 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.26 (d, 1 H, ArCH_2), 5.04 (d, 1 H, ArCH_2), 4.72 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.31 (dd, 1 H, $J_{5,6a}$ = 5.0 Hz, J_{gem} = 11.0 Hz, H-6a), 3.87 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3), 3.81 (s, 3 H, OMe), 3.69 (dd, 1 H, $J_{5,6b}$ = 10.0 Hz, H-6b), 3.53 (dd, 1 H, H-2), 3.51−3.46 (m, 2 H, H-4, H-5); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.2, 134.7, 134.2, 133.0, 133.0, 132.9, 132.2, 130.6, 129.7, 129.0, 129.0, 128.5, 128.2, 127.8, 127.7, 127.6, 127.3, 126.5, 126.3, 125.3, 113.6, 101.7, 87.7, 81.2, 79.4, 78.7, 73.0, 72.0, 70.4, 68.6, 55.3; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{30}O_6SNa$ 565.1655; found [M + Na]$^+$ 565.1659.

*Phenyl 2,3-O-[2,3-bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-1-thio-β-D-glucopyranoside (**18**).* To a solution of **16** (1.70 g, 3.14 mmol) in CH_2Cl_2 (31.0 mL) was added 4 Å molecular sieves (1.70 g). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C using a low constant temperature bath. Subsequently, Et_3SiH (1.20 mL, 6.90 mmol) and $PhBCl_2$ (913 μL, 6.90 mmol) were added to the reaction mixture at −80 °C. After being stirred for 2 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of NEt_3 and MeOH at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (7:1) as the eluent to give **17**. After exposure to high vacuum overnight, this compound was dissolved in DMF (31.4 mL). TBDPSCl (3.20 mL, 3.14 mmol) and imidazole (1.71 g, 25.1 mmol) were added to the reaction mixture at room temperature. After being stirred for 2 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of MeOH. The resulting mixture was coevaporated with toluene, diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by column chromatography on Sephadex LH-20 using $CHCl_3$/MeOH (1:1) as the eluent to give **18** (4.05 g, 70% over two steps) as a white foamy material: $[\alpha]_D^{25}$ −38.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−6.81 (m, 25 H, 6 Ar), 5.34 (d, 1 H, J_{gem} = 13.5 Hz, ArCH_2), 5.28 (d, 1 H, J_{gem} = 14.0 Hz, ArCH_2), 5.22 (d, 1 H, ArCH_2), 5.12 (d, 1 H, ArCH_2), 4.87 (d, 1 H, J_{gem} = 10.5 Hz, ArCH_2), 4.61 (d, 1 H, $J_{1,2}$ = 10.0 Hz, H-1), 4.57 (d, 1 H, ArCH_2), 3.93 (dd, 1 H, $J_{5,6a}$ = 1.5 Hz, J_{gem} = 11.0 Hz, H-6a), 3.84 (dd, 1 H, $J_{5,6b}$ = 4.0 Hz, H-6b), 3.81 (s, 3 H, OMe), 3.76 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.59 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4), 3.47 (dd, 1 H, H-2), 3.36 (td, 1 H, H-5), 1.06 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.2, 135.8, 135.6, 135.0, 134.8, 133.8, 133.5, 133.0, 133.0, 132.9, 131.8, 130.6, 129.7, 129.6, 129.6, 129.6, 128.8, 128.5, 127.7, 127.6, 127.5, 127.4, 127.3, 126.4, 126.3, 113.8, 86.6, 86.1, 79.8, 79.1, 77.6, 76.2, 74.8, 73.3, 73.1, 62.9, 55.3, 26.8, 19.2; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{50}O_6SSiNa$ 805.2990; found [M + Na]$^+$ 805.2991.

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

*2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-D-glucopyranosyl trichloroacetimidate (**19**).* To a solution of **18** (257 mg, 0.33 mmol) in 90% aqueous acetone (3.33 mL) was added NBS (175 mg, 0.98 mmol) at room temperature. After being stirred for 10 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 2:1), the reaction mixture was diluted with EtOAc, and washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1→2:1) as the eluent to give the corresponding hemiacetal. After exposure to high vacuum overnight, this compound was dissolved in CH_2Cl_2 (31.0 mL). CCl_3CN (0.33 mL, 3.29 mmol) and DBU (0.15 mL, 1.00 mmol) were added to the solution at room temperature. After being stirred for 30 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 2:1), the reaction mixture was evaporated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (5:1→3:1) as the eluent to give **19** (174 mg, 64% over two steps, α/β = 2.4:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1 H, NH$^{\alpha}$), 8.49 (s, 1 H, NH$^{\beta}$), 7.79−6.85 (m, 20 H, 5 Ar), 6.52 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1$^{\alpha}$), 5.76 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1$^{\beta}$), 5.42 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar$^{\beta}$), 5.31−5.23 (m, 5 H, 5 CH_2Ar), 5.09 (d, 1 H, CH_2Ar$^{\beta}$), 5.06 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar$^{\alpha}$), 4.93 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar$^{\beta}$), 4.92 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar$^{\alpha}$), 4.64 (d, 2 H, 2 CH_2Ar), 4.16 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3$^{\alpha}$), 3.91−3.70 (m, 10 H, H-2$^{\alpha}$, H-4$^{\alpha}$, H-5$^{\alpha}$, H-6a$^{\alpha}$, H-6b$^{\alpha}$, H-2$^{\beta}$, H-3$^{\beta}$, H-4$^{\beta}$, H-6a$^{\beta}$, H-6b$^{\beta}$), 3.82 (s, 3 H, OMe$^{\alpha}$), 3.81 (s, 3 H, OMe$^{\beta}$), 3.48 (td, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 2.5 Hz, $J_{4,5}$ = 7.5 Hz, H-5$^{\beta}$), 1.04 (s, 9 H, ^{t}Bu$^{\alpha}$), 0.99 (s, 9 H, ^{t}Bu$^{\beta}$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.1, 159.4, 135.8, 135.7, 135.0, 134.9, 133.6, 133.2, 132.9, 132.8, 130.5, 129.9, 129.8, 129.6, 129.6, 128.3, 127.7, 127.6, 127.4, 127.4, 126.4, 126.2, 113.9, 95.4, 91.3, 81.2, 78.5, 77.6, 76.3, 75.2, 74.3, 74.1, 71.9, 62.5, 55.3, 31.6, 26.8, 22.6, 19.3, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{46}Cl_3NO_7SiNa$ 856.2001; found [M + Na]$^+$ 856.2002.

*Phenyl 4,6-O-anisylidene-2,3-O-[2,3-bis(methyl)naphthele]-1-thio-β-D-galactopyranoside (**21**).* To a solution of **20**[28] (853 mg, 2.18 mmol) in DMF (21.8 mL) were added NaH [60% in oil] (262 mg, 6.54 mmol) and TBAI (402 mg, 1.09 mmol) at 4 °C using an ice bath. The mixture was stirred for 30 min at room temperature, and 2,3-bis(bromomethyl)naphthalene (820 mg, 2.40 mmol) was added at 4 °C using an ice bath. After being stirred for 19 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 2:1), the reaction was quenched by the addition of MeOH. The resulting mixture was coevaporated with toluene, diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1→1:2) as the eluent to give **21** (1.18 g, quant) as a white foamy material: $[\alpha]_D^{25}$ +31.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76−6.70 (m, 15 H, 4 Ar), 5.47 (s, 1 H, >C*H*Ar), 5.29 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 5.22 (d, 1 H, J_{gem} = 14.5 Hz, CH_2Ar), 5.09 (d, 1 H, CH_2Ar), 5.06 (d, 1 H, CH_2Ar), 4.60 (d, 1 H, $J_{1,2}$ = 9.0 Hz, H-1), 4.32 (dd, 1 H, $J_{5,6a}$ = 1.5 Hz, J_{gem} = 12.5 Hz, H-6a), 4.28 (d, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 4.00 (dd, 1 H, $J_{5,6b}$ = 1.5 Hz, H-6b), 3.90 (t, 1 H, $J_{2,3}$ = 9.0 Hz, H-2), 3.75 (dd, 1 H, H-3), 3.75 (s, 3 H, OMe), 3.48 (s, 1 H, H-5); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.9, 134.7, 134.7, 132.9, 132.8, 132.4, 130.3, 130.0, 128.8, 127.8, 127.8, 127.6, 127.5, 127.4, 126.3, 126.1, 113.3, 100.9, 86.1, 80.8, 77.6, 75.2, 74.6, 73.5, 72.7, 70.0, 69.2, 55.2; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{30}O_6SNa$ 565.1655; found [M + Na]$^+$ 565.1665.

*Phenyl 2,3-O-[2,3-bis(methyl)naphthele]-4-O-p-methoxybenzyl-1-thio-β-D-galactopyranoside (**22**).* To a solution of **21** (100 mg, 185 μmol) in CH_2Cl_2 (1.90 mL) was added 4 Å molecular sieves (100 mg). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C using a low constant temperature bath. Subsequently, Et_3SiH (68 μL, 407 μmol) and $PhBCl_2$ (54 μL, 407 μmol) were added to the reaction mixture at −80 °C. After being stirred for 10 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of NEt_3 and MeOH at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as the eluent to give **22** (73 mg, 73%) as a white solid: $[\alpha]_D^{25}$ +22.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−6.39 (m, 15 H, 4 Ar), 5.41 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 5.28 (d, 1 H, J_{gem} = 14.5 Hz, CH_2Ar), 5.14 (d, 1 H, CH_2Ar), 4.92 (d, 1 H, CH_2Ar), 4.69 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.62 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.40 (d, 1 H, CH_2Ar), 3.97 (t, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.67 (d, 1 H, $J_{3,4}$ = 2.5 Hz, H-4), 3.79 (dd, 1 H, $J_{5,6a}$ = 4.0 Hz, J_{gem} = 8.5 Hz, H-6a), 3.75 (dd, 1 H, H-3), 3.66 (s, 3 H, OMe), 3.54−3.49 (m, 2 H, H-5, H-6b); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 131.2, 129.9, 128.8, 127.7, 127.4, 127.0, 126.1, 113.4, 87.2, 82.7, 78.7, 77.6, 75.6, 74.3, 73.2, 62.5, 55.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{32}O_6SNa$ 567.1812; found [M + Na]$^+$ 567.1819.

*Phenyl 2,3-O-[2,3-bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-1-thio-β-D-galactopyranoside (**23**).* To a solution of **22** (58 mg, 0.11 mmol) in DMF (1.1 mL) were added TBDPSCl (137 μL, 533 μmol) and imidazole (73 mg, 533 μmol) at room temperature. After being stirred for 1 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction was quenched by the addition of MeOH. The resulting mixture was coevaporated with toluene, diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (10:1) as the eluent to give **23** (84 mg, quant) as a white solid: $[\alpha]_D^{25}$ +65.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−6.19 (m, 25 H, 6 Ar), 5.45 (d, 1 H, J_{gem} = 12.0 Hz, CH_2Ar), 5.25 (d, 1 H, J_{gem} = 14.5 Hz, CH_2Ar), 5.06 (d, 1 H, CH_2Ar), 4.89 (d, 1 H, CH_2Ar), 4.70 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.56 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.34 (d, 1 H, CH_2Ar), 4.00 (d, 1 H, $J_{3,4}$ = 2.0 Hz, H-4), 3.95 (t, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.78−3.75 (m, 3 H, H-3, H-6a, H-6b), 3.60 (s, 3 H, OMe), 3.55 (t, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 7.0 Hz, H-5), 1.07 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.6, 135.6, 135.2, 134.8, 134.7, 134.1, 133.3, 133.3, 133.1, 133.0, 131.2, 130.9, 130.9, 129.7, 129.7, 129.4, 128.7, 127.8, 127.7, 127.5, 127.4, 126.6, 126.3, 126.1, 113.0, 87.1, 82.6, 78.7, 77.6, 75.1, 74.3, 74.1, 73.1, 71.3, 62.1, 55.1, 26.9, 26.5, 19.2, 19.0; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{50}O_6SSiNa$ 805.2990; found [M + Na]$^+$ 805.2994.

*2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-D-galactopyranosyl trichloroacetimidate (**24**).* To a solution of **23** (40 mg, 51 μmol) in acetone/H_2O (2.4 mL/60 μL) was added NBS (18 mg, 0.10 mmol) at room temperature. After being stirred for 15 min at room temperature as the reaction was monitored by TLC (EtOAc/*n*-hexane = 1:3), the reaction mixture was diluted with $CHCl_3$, and washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel using EtOAc/*n*-hexane (1:4 to 1:2) as the eluent to give a hemiacetal. This compound was exposed to high vacuum overnight. The resulting residue was dissolved in CH_2Cl_2 (1.0 mL), and CCl_3CN (51 μL, 0.51 mmol) and DBU (23 μL, 0.15 mmol) were added to the solution at 0 °C. After being stirred for 40 min at room temperature as the reaction was monitored by TLC (EtOAc/*n*-hexane = 1:3), the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1) as the eluent to give **24** (31 mg, 72%, α/β = 5:1 over two steps) as a white foamy material: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1 H, NH$^{\beta}$), 8.51 (s, 1 H, NH$^{\alpha}$), 7.85−6.69 (m, 25 H, 5 Ar), 6.44 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1$^{\alpha}$), 6.40−6.20 (m, 4 H, Ar$^{\alpha}$, Ar$^{\beta}$), 5.74 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1$^{\beta}$), 5.54 (d, 1 H, J_{gem} = 12.2 Hz, ArCH_2^{β}), 5.41 (d, 1 H, J_{gem} = 12.9 Hz, ArCH_2^{α}), 5.33 (d, 1 H, J_{gem} = 15.0 Hz, ArCH_2^{β}), 5.23 (d, 1 H, J_{gem} = 14.4 Hz, ArCH_2^{α}), 5.16−5.06 (m, 3 H, 2 ArCH_2^{α}, ArCH_2^{β}), 4.92 (d, 1 H, ArCH_2^{β}), 4.79 (d, 1 H, J_{gem} = 10.3 Hz, ArCH_2^{α}), 4.70 (d, 1 H, J_{gem} = 10.2 Hz, ArCH_2^{β}), 4.49 (d, 1 H, ArCH_2^{α}), 4.36 (d, 1 H, J_{gem} = 10.2 Hz, ArCH_2^{β}), 4.30 (dd, 1

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

H, $J_{2,3}$ = 10.0 Hz, H-2$^{\alpha}$), 4.23 (dd, 1 H, $J_{3,4}$ = 2.7 Hz, H-3$^{\alpha}$), 4.18 (d, 1 H, H-4$^{\alpha}$), 4.13−4.05 (m, 4 H, H-5$^{\alpha}$, H-2$^{\beta}$, H-3$^{\beta}$, H-4$^{\beta}$), 3.86−3.56 (m, 11 H, Me$^{\alpha}$, Me$^{\beta}$, H-6a$^{\alpha}$, H-6b$^{\alpha}$, H-5$^{\beta}$, H-6a$^{\beta}$, H-6b$^{\beta}$), 1.07−1.05 (m, 18 H, ^{t}Bu$^{\alpha}$, ^{t}Bu$^{\beta}$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.2, 159.0, 135.6, 135.6, 135.5, 135.5, 135.1, 133.3, 133.1, 133.0, 130.7, 130.1, 129.8, 129.6, 128.1, 127.7, 127.7, 127.7, 127.4, 126.4, 126.2, 113.4, 113.2, 95.9, 91.5, 77.8, 76.0, 75.7, 75.3, 74.9, 73.7, 73.1, 72.7, 61.9, 55.1, 55.1, 29.7, 26.9, 26.9, 11.2; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{44}H_{46}Cl_3NO_7SiNa$ 856.2001; found [M + Na]$^{+}$ 856.2000.

*3-O-Benzoyl-1,2-O-(p-nitrobenzylidene)-sn-glycerol (**26**).* To a solution of **25**[19] (218 mg, 1.11 mmol) and *p*-nitrobenzaldehyde (503 mg, 3.33 mmol) in THF (11.0 mL) were added HMDSO (1.40 mL, 6.59 mmol) and TMSOTf (0.11 mL, 0.61 mmol) at 0 °C. After being stirred for 10 min at the same temperature, Et_3SiH (886 μL, 5.56 mmol) was added to the reaction mixture at 0 °C. After being stirred for 30 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ at 0 °C. The resulting mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (10:1→3:1) as the eluent to give **26a** (124 mg, 34%) as a colorless syrup along with the diastereomer **26b** (135 mg, 37%) as a colorless syrup.

***26a**:* $[\alpha]_D^{25}$ −19.4 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26−7.26 (m, 9 H, Ar), 6.10 (s, 1 H, >C*H*Ar), 4.63 (m, 1 H, H-2^{Gro}), 4.52 (m, 2 H, H-3a^{Gro}, H-3b^{Gro}), 4.31 (dd, 1 H, J_{vic} = 6.5 Hz, J_{gem} = 8.5 Hz, H-1a^{Gro}), 3.99 (dd, 1 H, J_{vic} = 6.0 Hz, H-1b^{Gro}); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.3, 144.6, 133.4, 129.7, 129.6, 128.5, 127.4, 123.6, 102.6, 77.6, 74.4, 67.4, 64.3; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{17}H_{15}O_6NNa$ 352.0792; found [M + Na]$^{+}$ 352.0790.

***26b**:* $[\alpha]_D^{25}$ +25.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−7.24 (m, 9 H, Ar), 5.96 (s, 1 H, >C*H*Ar), 4.65 (m, 1 H, H-2^{Gro}), 4.55 (dd, 1 H, J_{vic} = 4.5 Hz, J_{gem} = 12.0 Hz, H-3a^{Gro}), 4.43 (dd, 1 H, J_{vic} = 5.0 Hz, H-3b^{Gro}), 4.24 (dd, 1 H, J_{vic} = 7.0 Hz, J_{gem} = 8.5 Hz, H-1a^{Gro}), 4.11 (dd, 1 H, J_{vic} = 5.5 Hz, H-1b^{Gro}); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.2, 148.5, 144.1, 133.3, 129.7, 129.5, 128.4, 127.5, 123.6, 103.0, 74.8, 67.5, 64.3; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{17}H_{15}O_6NNa$ 352.0792; found [M + Na]$^{+}$ 352.0792.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-D-glucopyranosyl}-1,2-O-[(S)-p-nitrobenzylidene]-sn-glycerol (**27**).* To a solution of Glc thioglycoside **18** (118 mg, 151 μmol) and **14a** (51 mg, 226 μmol) in CH_2Cl_2 (3.0 mL) were added 4 Å molecular sieves (0.30 g) and NIS (52 mg, 231 μmol). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C using a low constant temperature bath. Subsequently, TESOTf (5.1 μL, 23 μmol) was added to the reaction mixture at −80 °C. After being stirred for 24 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (3:1→3:2) as the eluent to give **27*β*** (83 mg, 61%) as a colorless syrup along with **27*α*** (48 mg, 34%) as a colorless syrup.

***27β**:* $[\alpha]_D^{25}$ +55.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21−6.83 (m, 24 H, 6 Ar), 6.08 (s, 1 H, >C*H*Ar), 5.33 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.30 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar), 5.17 (d, 1 H, CH_2Ar), 5.15 (d, 1 H, CH_2Ar), 4.88 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.59 (d, 1 H, CH_2Ar), 4.52 (m, 1 H, H-2^{Gro}), 4.40 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.25 (dd, 1 H, J_{vic} = 8.0 Hz, J_{gem} = 8.5 Hz, H-1a^{Gro}), 4.06 (dd, 1 H, J_{vic} = 8.0 Hz, H-1b^{Gro}), 4.00 (dd, 1 H, $J_{5,6a}$ = 4.5 Hz, J_{gem} = 11.5 Hz, H-6a^{Glc}), 3.90 (dd, 1 H, $J_{5,6b}$ = 2.0 Hz, H-6b^{Glc}), 3.86−3.79 (m, 5 H, H-3a^{Gro}, H-3b^{Gro}, OMe), 3.72 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3^{Glc}), 3.52 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4^{Glc}), 3.47 (dd, 1 H, H-2^{Glc}), 3.30 (m, 1 H, H-5^{Glc}), 1.03 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 148.5, 144.4, 135.8, 135.5, 134.9, 133.6, 133.2, 132.9, 132.9, 130.5, 129.7, 129.6, 129.6, 129.5, 128.9, 127.8, 127.7, 127.5, 127.4, 127.4, 126.4, 126.3, 123.5, 113.8, 102.8, 102.5, 84.3, 80.6, 77.6, 76.5, 75.7, 74.8, 73.3, 72.9, 69.3, 68.0, 62.8, 55.3, 26.8, 19.3; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^{+}$ 920.3437.

***27α**:* $[\alpha]_D^{25}$ +61.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04−6.84 (m, 24 H, 6 Ar), 5.65 (s, 1 H, >C*H*Ar), 5.31−5.24 (m, 3 H, 3 CH_2Ar), 5.12 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 5.01 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1^{Glc}), 4.89 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.58 (d, 1 H, CH_2Ar), 4.37 (m, 1 H, H-2^{Gro}), 4.19−4.09 (m, 2 H, H-1a^{Gro}, H-1b^{Gro}), 4.04 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{Glc}), 3.89−3.83 (m, 4 H, H-5^{Glc}, H-6a^{Glc}, H-6b^{Glc}, H-3a^{Gro}), 3.83 (s, 3 H, OMe), 3.66 (dd, 1 H, H-2^{Glc}), 3.64−3.58 (m, 2 H, H-4^{Glc}, H-3b^{Gro}), 1.05 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 148.2, 144.4, 135.8, 135.6, 135.2, 135.0, 133.5, 133.3, 132.9, 132.8, 130.5, 129.7, 129.7, 129.6, 129.5, 129.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 126.4, 126.2, 123.5, 123.4, 113.8, 102.3, 98.3, 82.6, 79.8, 77.6, 76.9, 74.9, 74.9, 74.2, 73.0, 71.9, 67.7, 67.5, 63.0, 55.3, 29.7, 26.8, 26.8, 19.3; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^{+}$ 920.3432.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-D-glucopyranosyl}-1,2-O-[(R)-p-nitrobenzylidene]-sn-glycerol (**28**).* To a solution of Glc thioglycoside **18** (83 mg, 106 μmol) and **14b** (36 mg, 160 μmol) in CH_2Cl_2 (2.1 mL) were added 4 Å molecular sieves (0.21 g) and NIS (50 mg, 156 μmol). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C using a low constant temperature bath. Subsequently, TESOTf (3.5 μL, 16 μmol) was added to the reaction mixture at −80 °C. After being stirred for 24 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (3:1→3:2) as the eluent to give **28*β*** (55 mg, 58%) as a colorless syrup along with **28*α*** (37 mg, 39%) as a colorless syrup.

***28β**:* $[\alpha]_D^{25}$ +44.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19−6.83 (m, 24 H, 6 Ar), 5.87 (s, 1 H, >C*H*Ar), 5.32 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 5.26 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 5.15 (d, 1 H, CH_2Ar), 5.14 (d, 1 H, CH_2Ar), 4.88 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.59 (d, 1 H, CH_2Ar), 4.54 (m, 1 H, H-2^{Gro}), 4.35 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.16−4.15 (m, 2 H, H-3^{Glc}, H-1a^{Gro}), 3.99 (dd, 1 H, J_{vic} = 4.5 Hz, J_{gem} = 10.5 Hz, H-1b^{Gro}), 3.89 (dd, 1 H, $J_{5,6a}$ = 1.5 Hz, J_{gem} = 11.0 Hz, H-6a^{Glc}), 3.80 (m, 4 H, H-6b^{Glc}, OMe), 3.72−3.67 (m, 2 H, H-3a^{Gro}, H-3b^{Gro}), 3.57 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4^{Glc}), 3.45 (t, 1 H, $J_{2,3}$ = 9.5 Hz, H-2^{Glc}), 3.29 (m, 1 H, H-5^{Glc}), 1.03 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 148.5, 144.4, 135.8, 135.6, 135.0, 134.9, 133.6, 133.3, 133.0, 132.9, 130.6, 129.6, 129.6, 129.6, 128.8, 127.7, 127.7, 127.6, 127.5, 127.4, 126.4, 126.3, 123.5, 113.9, 102.8, 102.5, 84.4, 80.6, 76.6, 75.7, 74.8, 73.3, 72.9, 69.3, 68.0, 62.9, 60.4, 55.3, 29.7, 26.8, 22.6, 21.0, 19.3, 14.2; HRMS (ESI) m/z [M + Na]$^{+}$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^{+}$ 920.3439.

***28α**:* $[\alpha]_D^{25}$ +92.8 (*c* 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−6.83 (m, 24 H, 6 Ar), 5.76 (s, 1 H, >C*H*Ar), 5.27−5.21 (m, 2 H, 2 CH_2Ar), 5.22 (d, 1 H, J_{gem} = 10.0 Hz, CH_2Ar), 5.15 (d, 1 H, CH_2Ar), 4.99 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1^{Glc}), 4.88 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.57 (d, 1 H, CH_2Ar), 4.41 (m, 1 H, H-2^{Gro}), 3.99 (m, 1 H, H-1a^{Gro}), 3.99 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3^{Glc}), 3.87−3.78 (m, 6 H, H-6a^{Glc}, H-6b^{Glc}, H-1b^{Gro}, OMe), 3.74 (dd, 1 H, J_{vic} = 5.5 Hz, J_{gem} = 10.5 Hz, H-3a^{Gro}), 3.70 (m, 1 H, H-5^{Glc}), 3.66−3.61 (m, 2 H, H-2^{Glc}, H-3b^{Gro}), 3.56 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4^{Glc}), 1.01 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 148.4, 144.4, 135.8, 135.6, 135.2, 134.9, 133.6, 133.3, 132.9, 132.8, 130.5, 129.7, 129.6, 129.6, 129.1, 128.0, 127.7, 127.6, 127.6, 127.5, 127.4, 127.4, 126.3, 126.2, 123.5, 123.4, 113.9, 102.6, 98.2, 82.9, 80.2, 76.9, 75.6, 74.9, 74.3, 73.4, 71.9, 67.8, 67.8, 63.0, 60.4, 55.3, 26.8, 19.3; HRMS (ESI)

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

m/z [M + Na]$^+$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^+$ 920.3435.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-D-galactopyranosyl}-1,2-O-[(S)-p-nitrobenzylidene]-sn-glycerol (**29**).* To a solution of Gal thioglycoside **23** (140 mg, 179 μmol) and **14a** (61 mg, 271 μmol) in CH_2Cl_2 (3.60 mL) were added 4 Å molecular sieves (0.36 g) and NIS (61 mg, 271 μmol). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C using a low constant temperature bath. Subsequently, TESOTf (6.1 μL, 27 μmol) was added to the reaction mixture at −80 °C. After being stirred for 4 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (3:1→3:2) as the eluent to give **29*β*** (116 mg, 72%) as a colorless syrup along with **29*α*** (38 mg, 24%) as a colorless syrup.

29β: $[\alpha]_D^{25}$ +120.1 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21−6.29 (m, 24 H, 6 Ar), 6.07 (s, 1 H, >C*H*Ar), 5.44 (d, 1 H, J_{gem} = 12.6 Hz, CH_2Ar), 5.28 (d, 1 H, J_{gem} = 14.2 Hz, CH_2Ar), 5.16 (d, 1 H, CH_2Ar), 4.97 (d, 1 H, CH_2Ar), 4.72 (d, 1 H, J_{gem} = 12.4 Hz, CH_2Ar), 4.45−4.38 (m, 3 H, H-1^{Gal}, H-2^{Gro}, CH_2Ar), 4.21 (dd, 1 H, J_{vic} = 6.7 Hz, J_{gem} = 8.2 Hz, H-1a^{Gro}), 4.07 (dd, 1 H, J_{vic} = 6.5 Hz, H-1b^{Gro}), 3.95 (m, 2 H, H-4^{Gal}, H-3a^{Gro}), 3.82 (dd, 1 H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 9.1 Hz, H-2^{Gal}), 3.79−3.70 (m, 4 H, H-3^{Gal}, H-6a^{Gal}, H-6b^{Gal}, H-3b^{Gro}), 3.59 (s, 3 H, OMe), 3.50 (t, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 6.7 Hz, H-5^{Gal}), 1.06 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.7, 148.4, 145.0, 135.5, 135.3, 135.0, 133.4, 133.3, 133.0, 133.0, 131.0, 130.7, 129.7, 129.7, 129.6, 127.7, 127.7, 127.7, 127.6, 127.4, 127.3, 126.5, 126.1, 123.5, 113.1, 103.3, 102.4, 81.1, 78.3, 77.2, 75.2, 74.9, 74.5, 74.2, 73.5, 71.7, 69.2, 67.6, 62.2, 55.0, 26.8, 19.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^+$ 920.3436.

29α: $[\alpha]_D^{25}$ +140.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15−6.40 (m, 24 H, 6 Ar), 5.81 (s, 1 H, >C*H*Ar), 5.36 (d, 1 H, J_{gem} = 13.1 Hz, CH_2Ar), 5.26 (d, 1 H, J_{gem} = 14.2 Hz, CH_2Ar), 5.13−5.08 (m, 2 H, CH_2Ar), 5.02 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1^{Gal}), 4.75 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.48−4.43 (m, 2 H, H-2^{Gro}, CH_2Ar), 4.16−4.14 (m, 2 H, H-2^{Gal}, H-1a^{Gro}), 4.10 (dd, 1 H, $J_{3,4}$ = 2.7 Hz, $J_{2,3}$ = 10.0 Hz, H-3^{Gal}), 4.03 (brs, 1 H, H-4^{Gal}), 3.91 (t, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, H-5^{Gal}), 3.83 (dd, 1 H, J_{vic} = 6.5 Hz, J_{gem} = 10.5 Hz, H-1b^{Gro}), 3.75−3.73 (m, 3 H, H-6a^{Gal}, H-3a^{Gro}, H-3b^{Gro}), 3.69 (dd, 1 H, $J_{5,6b}$ = 5.3 Hz, J_{gem} = 11.0 Hz, H-6b^{Gal}), 3.63 (s, 3 H, OMe), 1.05 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.9, 148.3, 144.6, 135.5, 135.5, 135.5, 135.1, 133.3, 133.3, 132.9, 130.6, 129.7, 129.7, 129.5, 127.9, 127.7, 127.7, 127.5, 127.4, 127.4, 126.3, 126.2, 123.4, 113.3, 102.2, 98.8, 78.4, 77.3, 77.2, 75.6, 75.2, 74.5, 73.8, 72.8, 71.6, 67.9, 67.7, 62.7, 55.1, 26.8, 19.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^+$ 920.3439.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-D-galactopyranosyl}-1,2-O-[(R)-p-nitrobenzylidene]-sn-glycerol (**30**).* To a solution of Gal thioglycoside **23** (115 mg, 147 μmol) and **14b** (51 mg, 226 μmol) in CH_2Cl_2 (2.9 mL) were added 4 Å molecular sieves (0.29 g) and NIS (50 mg, 222 μmol). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C. Subsequently, TESOTf (5.1 μL, 23 μmol) was added to the reaction mixture at −80 °C. After being stirred for 4 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (3:1→3:2) as the eluent to give **30*β*** (97 mg, 73%) as a colorless syrup along with **30*α*** (31 mg, 24%) as a colorless syrup.

30β: $[\alpha]_D^{25}$ +116.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23−6.28 (m, 24 H, 6 Ar), 5.85 (s, 1 H, >C*H*Ar), 5.43 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.22 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 5.09 (d, 1 H, CH_2Ar), 4.96 (d, 1 H, CH_2Ar), 4.72 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.44 (m, 1 H, H-2^{Gro}), 4.38 (d, 1 H, CH_2Ar), 4.33 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Gal}), 4.18−4.10 (m, 2 H, H-1a^{Gro}, H-1b^{Gro}), 3.96−3.93 (m, 2 H, H-3^{Gal}, H-3a^{Gro}), 3.82−3.68 (m, 4 H, H-2^{Gal}, H-4^{Gal}, H-6a^{Gal}, H-6b^{Gal}), 3.61 (dd, 1 H, J_{vic} = 6.5 Hz, J_{gem} = 10.5 Hz, H-3b^{Gro}), 3.59 (s, 3 H, OMe), 3.48 (t, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, H-5^{Gal}), 1.05 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.7, 148.5, 144.5, 135.5, 135.3, 135.1, 133.3, 133.0, 131.1, 130.8, 129.8, 129.7, 127.7, 127.7, 127.5, 127.4, 126.5, 126.1, 123.5, 113.1, 103.3, 102.7, 81.1, 78.2, 77.6, 75.5, 74.8, 74.5, 74.1, 73.5, 71.7, 69.4, 68.0, 62.1, 55.1, 26.9, 19.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^+$ 920.3429.

30α: $[\alpha]_D^{25}$ +106.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16−6.40 (m, 24 H, 6 Ar), 5.84 (s, 1 H, >C*H*Ar), 5.35 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.29 (d, 1 H, J_{gem} = 14.3 Hz, CH_2Ar), 5.05 (m, 2 H, CH_2Ar), 5.00 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1^{Gal}), 4.73 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.50 (m, 1 H, H-2^{Gro}), 4.42 (d, 1 H, CH_2Ar), 4.13 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, H-2^{Gal}), 4.07 (t, 1 H, J_{vic} = J_{gem} = 7.8 Hz, H-1a^{Gro}), 4.02−4.00 (m, 2 H, H-3^{Gal}, H-4^{Gal}), 3.86−3.85 (m, 2 H, H-5^{Gal}, H-1b^{Gro}), 3.74−3.66 (m, 4 H, H-6a^{Gal}, H-6b^{Gal}, H-3a^{Gro}, H-3b^{Gro}), 3.61 (s, 3 H, OMe), 1.04 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.9, 148.4, 144.5, 135.5, 135.4, 134.9, 133.3, 132.9, 132.9, 130.6, 129.8, 129.7, 129.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.3, 126.3, 126.1, 123.4, 113.3, 102.7, 98.7, 78.3, 77.5, 77.2, 75.8, 75.6, 74.5, 74.0, 72.8, 71.5, 68.4, 67.9, 62.6, 55.0, 26.8, 19.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{52}H_{55}O_{11}NSiNa$ 920.3437; found [M + Na]$^+$ 920.3431.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-β-D-glucopyranosyl}-sn-glycerol (**31**).* To a solution of **27*β*** (152 mg, 169 μmol) in 80% aqueous THF (3.40 mL) were added AcOH (1.90 mL, 33.2 mmol) and Zn (553 mg, 8.46 mmol) at room temperature. After being stirred for 10 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1→1:2) as the eluent to give **31** (120 mg, 93%) as a pale yellow foamy material: $[\alpha]_D^{25}$ + 51.8 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−6.81 (m, 20 H, 5 Ar), 5.32 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 5.29 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar), 5.18 (d, 1 H, CH_2Ar), 5.15 (d, 1 H, CH_2Ar), 4.84 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.54 (d, 1 H, CH_2Ar), 4.34 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 3.94−3.86 (m, 3 H, H-6a^{Glc}, H-2^{Gro}, H-1a^{Gro}), 3.83−3.76 (m, 2 H, H-6b^{Glc}, H-1b^{Gro}), 3.80 (s, 3 H, OMe), 3.71 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3^{Glc}), 3.71 (m, 1 H, H-3a^{Gro}), 3.62 (dd, 1 H, J_{vic} = 5.0 Hz, J_{gem} = 11.0 Hz, H-3b^{Gro}), 3.56−3.46 (m, 3 H, H-2^{Glc}, H-4^{Glc}, OH), 3.33 (m, 1 H, H-5^{Glc}), 2.47 (brs, 1 H, OH), 1.04 (s, 9 H, ^{t}Bu); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 135.8, 135.6, 134.9, 134.7, 133.4, 133.0, 133.0, 130.4, 129.7, 129.6, 129.4, 129.2, 127.7, 127.6, 127.5, 127.4, 126.4, 126.4, 113.8, 102.7, 84.1, 80.4, 76.6, 75.9, 74.7, 73.3, 72.9, 72.8, 70.7, 63.6, 63.0, 60.4, 55.3, 29.7, 26.8, 21.0, 19.2, 14.2, 14.0; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{45}H_{52}O_9SiNa$ 787.3273; found [M + Na]$^+$ 787.3274.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl}-1,2-di-O-oleoyl-sn-glycerol (**32**).* To a solution of **31** (120 mg, 157 μmol) and oleic acid (120 μL, 378 μmol) in CH_2Cl_2 (1.6 mL) were added DCC (98 mg, 475 μmol) and DMAP (3.7 mg, 30 μmol) at room temperature. After being stirred for 1 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction mixture was evaporated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1→3:1) as the eluent to give the diacylated compound. After exposure to high vacuum overnight, this compound was

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

dissolved in THF (1.6 mL). TBAF [1 M solution in THF] (0.47 mL, 470 μmol) was added to the reaction mixture at room temperature. After being stirred for 12 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 5:1), the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1→3:2) as the eluent to give **32** (118 mg, 71% over two steps) as a colorless syrup: $[\alpha]_D^{25}$ +56.8 (*c* 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81−7.23 (m, 10 H, 3 Ar), 5.36−5.27 (m, 5 H, CH_2Ar, 4 CH = C*H*), 5.25 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 5.16 (d, 1 H, CH_2Ar), 5.11 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 4.88 (d, 1 H, J_{gem} = 11.0 Hz, CH_2Ar), 4.61 (d, 1 H, CH_2Ar), 4.47 (dd, 1 H, J_{vic} = 3.0 Hz, J_{gem} = 12.0 Hz, H-2^{Gro}), 4.34 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.18 (dd, 1 H, J_{vic} = 7.0 Hz, H-1a^{Gro}), 3.84−3.75 (m, 4 H, H-4^{Glc}, H-1b^{Gro}, H-3a^{Gro}, H-3b^{Gro}), 3.82 (s, 3 H, OMe), 3.72 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 7.5 Hz, H-3^{Glc}), 3.62 (dd, 1 H, $J_{5,6a}$ = 5.5 Hz, J_{gem} = 12.5 Hz, H-6a^{Glc}), 3.41 (t, 1 H, H-2^{Glc}), 3.38 (dd, 1 H, $J_{5,6b}$ = 9.5 Hz, H-6b^{Glc}), 3.30 (m, 1 H, H-5^{Glc}), 2.50 (brs, 1 H, OH), 2.35−2.27 (m, 4 H, 2 O(CO)CH_2), 2.07−1.98 (m, 8 H, 4 CH = CHCH_2), 1.62−1.61 (m, 4 H, 2 CH_2), 1.29−1.26 (m, 40 H, 20 CH_2), 0.89−0.84 (m, 6 H, 2 Me); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.6, 173.1, 159.4, 134.9, 134.8, 133.0, 132.9, 130.3, 130.0, 129.8, 129.8, 129.7, 129.7, 128.8, 127.5, 127.4, 126.4, 126.3, 113.9, 103.1, 83.9, 80.3, 76.5, 75.2, 74.6, 72.9, 72.9, 70.2, 68.0, 62.9, 62.2, 55.3, 34.3, 34.1, 31.9, 29.7, 29.7, 29.5, 29.3, 29.2, 29.1, 29.1, 29.1, 27.2, 27.2, 24.9, 24.9, 22.7, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{65}H_{98}O_{11}Na$ 1077.7001; found [M + Na]$^+$ 1077.7000.

3-O-(6-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-β-D-glucopyranosyl}-2,3-O-[2,3-bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl)-1,2-di-O-oleoyl-sn-glycerol (**33**). To a solution of **19** (15 mg, 17 μmol) and **32** (18 mg, 17 μmol) in CH_2Cl_2 (0.70 mL) were added AW-300 molecular sieves (35 mg). After being stirred for 5 min at room temperature, the mixture was then cooled to −80 °C. Subsequently, $BF_3{\cdot}Et_2O$ (0.1 μL, 0.8 μmol) was added to the reaction mixture at −80 °C. After being stirred for 2 h at the same temperature as the reaction was monitored by TLC (toluene/EtOAc = 7:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (5:1) as the eluent to give the glycosylated product **33** (23 mg, 80%, β/α = >15:1). The stereoisomers were partially separated by flash column chromatography on silica gel using toluene/EtOAc (10:1) as the eluent to give **33*β***: $[\alpha]_D^{25}$ +59.6 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.82−6.80 (m, 30 H, 8 Ar), 5.39 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.34−5.28 (m, 6 H, CH_2Ar, H-2^{Gro}, 4 CH = C*H*), 5.23 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 5.23 (s, 2 H, 2 CH_2Ar), 5.10 (d, 1 H, CH_2Ar), 5.09 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.07 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 4.95 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.87 (d, 1 H, CH_2Ar), 4.70 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.58 (d, 1 H, CH_2Ar), 4.38 (dd, 1 H, J_{vic} = 3.5 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.37 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1^a), 4.30 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^b), 4.26 (dd, 1 H, J_{vic} = 6.5 Hz, H-1b^{Gro}), 4.18 (dd, 1 H, $J_{5,6a}$ = 1.5 Hz, J_{gem} = 11.0 Hz, H-6a^a), 4.08 (dd, 1 H, J_{vic} = 5.0 Hz, J_{gem} = 10.5 Hz, H-3a^{Gro}), 3.86−3.80 (m, 2 H, H-6a^b, H-6b^b), 3.80 (s, 3 H, OMe), 3.79−3.73 (m, 2 H, H-3^a, H-3^b), 3.75 (s, 3 H, OMe), 3.69−3.63 (m, 2 H, H-6b^a, H-3b^{Gro}), 3.62−3.56 (m, 2 H, H-4^a, H-4^b), 3.55−3.48 (m, 3 H, H-2^a, H-5^a, H-2^b), 3.24 (m, 1 H, H-5^b), 3.32−2.24 (m, 4 H, 2 O(CO)CH_2), 2.00−1.96 (m, 8 H, 4 CH = CHCH_2), 1.59−1.56 (m, 4 H, 2 CH_2), 1.36−1.20 (m, 40 H, 20 CH_2), 0.98 (s, 9 H, ^{t}Bu), 0.89−0.86 (m, 6 H, 2 Me); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.4, 172.9, 159.2, 135.8, 135.6, 135.1, 135.1, 135.0, 133.7, 133.2, 133.0, 132.9, 132.9, 132.8, 130.8, 130.7, 130.3, 130.0, 129.7, 129.6, 129.6, 129.5, 129.5, 128.6, 128.2, 127.6, 127.5, 127.4, 126.4, 126.2, 126.1, 113.8, 103.1, 102.9, 84.3, 80.7, 80.5, 77.6, 76.5, 75.6, 74.7, 74.6, 74.5, 73.2, 73.1, 72.9, 72.7, 70.0, 68.7, 67.8, 62.8, 62.7, 55.3, 55.2, 34.3, 34.1, 31.9, 29.8, 29.7, 29.5, 29.3, 29.3, 29.2, 29.2, 29.2, 29.1, 29.1, 27.2, 27.2, 26.7, 24.9, 24.9, 22.7, 19.2, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{107}H_{142}O_{17}SiNa$ 1749.9909; found [M + Na]$^+$ 1749.9906.

3-O-(6-O-{2,3-O-[2,3-Bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl}-2,3-O-[2,3-bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl)-1,2-di-O-oleoyl-sn-glycerol (**34**). To a solution of **33** [α/β = >15:1] (39 mg, 23 μmol) in THF (0.20 mL) were added TBAF [1 M solution in THF] (0.34 mL, 0.34 mmol) and AcOH (19 μL, 0.33 mmol) at room temperature. After being stirred for 1 h at the same temperature, TBAF [1 M solution in THF] (0.34 mL, 0.34 mmol) and AcOH (6.5 μL, 0.11 mmol) were added to the reaction mixture at room temperature. After being stirred for 1 h at room temperature as the reaction was monitored by TLC (toluene/EtOAc = 7:1), the mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (3:1→1:1) as the eluent to give **34** (30 mg, 91%): $[\alpha]_D^{25}$ +7.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81−6.87 (m, 20 H, 6 Ar), 5.39−5.29 (m, 8 H, 3 CH_2Ar, H-2^{Gro}, 4 CH = C*H*), 5.28−5.19 (m, 3 H, 3 CH_2Ar), 5.11 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.03 (d, 1 H, J_{gem} = 13.5 Hz, CH_2Ar), 4.95 (d, 1 H, J_{gem} = 10.0 Hz, CH_2Ar), 4.86 (d, 1 H, J_{gem} = 11.0 Hz, CH_2Ar), 4.71 (d, 1 H, CH_2Ar), 4.59 (d, 1 H, CH_2Ar), 4.40 (dd, 1 H, J_{vic} = 3.5 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.32 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^a), 4.32 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^b), 4.23 (dd, 1 H, J_{vic} = 6.0 Hz, H-1b^{Gro}), 4.01−3.96 (m, 2 H, H-6a^a, H-3a^{Gro}), 3.80 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 3.78−3.67 (m, 7 H, H-3^a, H-4^a, H-5^a, H-6b^a, H-6a^b, H-6b^b, H-3b^{Gro}), 3.59 (m, 1 H, H-6b^b), 3.53 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^b), 3.38−3.23 (m, 3 H, H-2^a, H-2^b, H-4^b), 3.25 (m, 1 H, H-5^b), 2.33−2.28 (m, 4 H, 2 O(CO)CH_2), 2.01−1.99 (m, 8 H, 4 CH = CHCH_2), 1.59 (brs, 4 H, 2 CH_2), 1.27−1.26 (m, 40 H, 20 CH_2), 0.89−0.86 (s, 6 H, 2 Me); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.4, 173.0, 159.4, 135.2, 135.0, 134.9, 134.8, 134.4, 133.0, 132.9, 132.9, 130.6, 130.5, 130.2, 130.0, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 128.8, 128.4, 127.9, 127.7, 127.5, 127.4, 126.4, 126.2, 113.9, 102.9, 84.2, 80.4, 76.4, 75.0, 74.6, 73.1, 73.0, 72.7, 70.1, 67.9, 62.7, 62.2, 55.3, 34.3, 34.1, 31.9, 29.8, 29.7, 29.5, 29.3, 29.3, 29.2, 29.1, 29.1, 27.2, 27.2, 26.5, 26.0, 24.9, 24.9, 22.7, 19.0, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{91}H_{124}O_{17}Na$ 1511.8731; found [M + Na]$^+$ 1511.8733.

3-O-(6-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-β-D-galactopyranosyl}-2,3-O-[2,3-bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl)-1,2-di-O-oleoyl-sn-glycerol (**35**). To a solution of **24** (17 mg, 20 μmol) and **32** (22 mg, 20 μmol) in CH_2Cl_2 (0.40 mL) were added AW-300 molecular sieves (40 mg). After being stirred for 15 min at room temperature, the mixture was then cooled to −80 °C. Subsequently, TMSOTf (0.2 μL, 1.1 μmol) was added to the reaction mixture at −80 °C. After being stirred for 3 h at the same temperature as the reaction was monitored by TLC (toluene/EtOAc = 10:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (5:1) as the eluent to give the glycosylated product **35** (21 mg, 62%, β/α = 1.8:1). The stereoisomers were partially separated by flash column chromatography on silica gel using toluene/EtOAc (10:1) as the eluent to give **35*α*** and **35*β*** in pure form.

35β: $[\alpha]_D^{25}$ +79.8 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.82−6.24 (m, 30 H, 8 Ar), 5.42−5.16 (m, 10 H, 5 ArCH_2, H-2^{Gro}, 4 CH = C*H*), 5.09 (d, 1 H, J_{gem} = 15.3 Hz, ArCH_2), 5.07 (d, 1 H, J_{gem} = 13.5 Hz, ArCH_2), 4.90 (d, 1 H, J_{gem} = 12.4 Hz, ArCH_2), 4.86 (d, 1 H, J_{gem} = 10.6 Hz, ArCH_2), 4.68 (d, 1 H, J_{gem} = 10.4 Hz, ArCH_2), 4.59 (d, 1 H, ArCH_2), 4.41 (dd, 1 H, J_{vic} = 3.4 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.35 (d, 1 H, $J_{1,2}$ = 7.9 Hz, H-1^{Gal}), 4.34 (d, 1 H, ArCH_2), 4.32 (d, 1 H, $J_{1,2}$ = 7.7 Hz, H-1^{Glc}), 4.27 (dd, 1 H, J_{vic} = 6.4 Hz, H-1b^{Gro}), 4.09−

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

4.05 (m, 2 H, H-6a^{Glc}, H-3a^{Gro}), 3.93 (d, 1 H, $J_{3,4}$ = 2.5 Hz, H-4^{Gal}), 3.79−3.60 (m, 9 H, H-2^{Gal}, H-3^{Gal}, H-5^{Gal}, H-6a^{Gal}, H-4^{Glc}, H-3b^{Gro}, OMe), 3.57−3.53 (m, 4 H, H-6b^{Glc}, OMe), 3.48−3.35 (m, 4 H, H-6b^{Gal}, H-2^{Glc}, H-3^{Gal}, H-5^{Glc}), 2.32−2.26 (m, 4 H, 2 O(CO)CH$_2$), 2.01−1.96 (m, 8 H, 4 CH = CHCH_2), 1.59−1.26 (m, 44 H, 22 CH$_2$), 1.04 (s, 9 H, ^{t}Bu), 0.89−0.87 (m, 6 H, 2 Me); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 173.4, 172.9, 159.3, 158.7, 135.6, 135.5, 135.3, 135.1, 135.1, 133.4, 133.1, 133.0, 132.9, 131.2, 131.0, 130.7, 130.3, 130.0, 129.8, 129.7, 129.7, 129.7, 129.5, 128.2, 127.7, 127.7, 127.5, 127.4, 126.4, 126.3, 126.2, 126.0, 113.8, 113.1, 103.5, 102.6, 84.3, 81.1, 80.6, 78.4, 77.6, 75.0, 74.6, 74.5, 74.3, 73.4, 73.1, 73.0, 71.7, 70.0, 68.7, 67.7, 62.8, 62.0, 55.3, 55.1, 34.4, 34.1, 31.9, 29.8, 29.8, 29.7, 29.5, 29.3, 29.3, 29.3, 29.2, 29.2, 29.1, 27.2, 27.2, 26.9, 25.0, 24.9, 22.7, 19.2, 14.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{107}H_{142}O_{17}SiNa$ 1749.9909; found [M + Na]$^+$ 1749.9910.

35α: $[\alpha]_D^{25}$ +114.5 (c 0.5, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79−6.35 (m, 30 H, 8 Ar), 5.37−5.18 (m, 9 H, 4 ArCH_2, H-2^{Gro}, 4 CH = CH), 5.15 (d, 1 H, J_{gem} = 14.4 Hz, ArCH_2), 5.05 (d, 1 H, J_{gem} = 13.2 Hz, ArCH_2), 5.01 (d, 1 H, ArCH_2), 4.99 (d, 1 H, $J_{1,2}$ = 2.7 Hz, H-1^{Gal}), 4.98 (d, 1 H, ArCH_2), 4.73 (d, 1 H, J_{gem} = 10.8 Hz, ArCH_2), 4.72 (d, 1 H, J_{gem} = 10.5 Hz, ArCH_2), 4.46 (d, 1 H, ArCH_2), 4.40−4.36 (m, 2 H, ArCH_2, H-1a^{Gro}), 4.27 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1^{Glc}), 4.25 (dd, 1 H, J_{vic} = 6.3 Hz, J_{gem} = 12.2 Hz, H-1b^{Gro}), 4.08−4.02 (m, 3 H, H-2^{Gal}, H-3^{Gal}, H-4^{Gal}), 3.94−3.89 (m, 2 H, H-5^{Gal}, H-3a^{Gro}), 3.76 (s, 3 H, OMe), 3.74−3.62 (m, 6 H, H-6a^{Gal}, H-6b^{Gal}, H-3^{Glc}, H-6a^{Glc}, H-6b^{Glc}, H-3b^{Gro}), 3.61 (s, 3 H, OMe), 3.48−3.38 (m, 3 H, H-4^{Gal}, H-2^{Glc}, H-5^{Glc}), 2.29−2.26 (m, 4 H, 2 O(CO)CH$_2$), 2.01−1.97 (m, 8 H, 4 CH = CHCH_2), 1.61−1.13 (m, 44 H, 22 CH$_2$), 1.01 (s, 9 H, ^{t}Bu), 0.89−0.83 (m, 6 H, 2 Me); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 173.4, 172.9, 159.2, 158.8, 135.8, 135.5, 135.5, 135.2, 135.1, 133.5, 133.4, 133.0, 132.9, 131.0, 130.8, 130.1, 130.0, 129.8, 129.7, 129.6, 129.6, 129.6, 129.6, 128.5, 127.7, 127.7, 127.6, 127.5, 127.4, 126.4, 126.2, 126.2, 126.0, 113.8, 113.3, 102.4, 98.3, 84.1, 80.4, 78.2, 77.6, 77.5, 76.0, 74.7, 74.6, 74.4, 73.4, 73.0, 72.8, 72.7, 71.2, 70.1, 67.4, 66.5, 62.7, 62.5, 55.3, 55.1, 34.3, 34.1, 31.9, 29.8, 29.7, 29.5, 29.3, 29.3, 29.3, 29.3, 29.2, 29.2, 29.2, 27.2, 27.2, 26.9, 25.0, 24.9, 22.7, 19.2, 14.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{107}H_{142}O_{17}SiNa$ 1749.9909; found [M + Na]$^+$ 1749.9909.

*3-O-(6-O-{2,3-O-[2,3-Bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-galactopyranosyl}-2,3-O-[2,3-bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl)-1,2-di-O-oleoyl-sn-glycerol (**36**).* To a solution of **35β** (2.3 mg, 1.3 μmol) in THF (0.10 mL) was added TBAF [1 M solution in THF] (3.9 μL, 3.9 μmol) at 4 °C using an ice bath. After being stirred for 10 h at room temperature as the reaction was monitored by TLC (n-hexane/EtOAc = 3:1), the mixture was diluted with EtOAc and washed with H$_2$O and brine. The organic layer was dried over Na$_2$SO$_4$, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using n-hexane/EtOAc (3:1) as the eluent to give **36** (1.6 mg, 84%) as a colorless syrup: $[\alpha]_D^{25}$ +81.3 (c 0.16, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82−6.49 (m, 20 H, 6 Ar), 5.38−5.29 (m, 7 H, 2 ArCH_2, H-2^{Gro}, 4 CH = CH), 5.21−5.07 (m, 5 H, 5 ArCH_2), 4.95 (d, 1 H, J_{gem} = 12.6 Hz, ArCH_2), 4.91 (d, 1 H, J_{gem} = 10.8 Hz, ArCH_2), 4.67 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.65 (d, 1 H, ArCH_2), 4.43 (d, 1 H, ArCH_2), 4.40 (dd, 1 H, J_{vic} = 3.3 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.34 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Gal}), 4.33 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.26 (dd, 1 H, J_{vic} = 6.4 Hz, H-1b^{Gro}), 4.05−4.00 (m, 2 H, H-5^{Gal}, H-3a^{Gro}), 3.80−3.62 (m, 13 H, H-5^{Glc}, H-6a^{Glc}, H-6b^{Glc}, H-2^{Gal}, H-4^{Gal}, H-6a^{Gal}, H-3b^{Gro}, 2 Me), 3.49−3.35 (m, 5 H, H-2^{Glc}, H-3^{Glc}, H-4^{Glc}, H-3^{Gal}, H-6b^{Gal}), 2.33−2.27 (m, 4 H, 2 O(CO)CH$_2$), 2.00−1.96 (m, 9 H, OH-6^{Gal}, 4 CH = CHCH_2), 1.59−1.26 (m, 44 H, 22 CH$_2$), 0.89−0.86 (m, 6 H, 2 Me); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 173.5, 173.0, 159.4, 159.1, 135.3, 135.2135.1, 133.1, 132.9, 130.8, 130.6, 130.4, 130.2, 130.1, 130.0, 129.9, 129.8, 129.7, 128.3, 127.7, 127.6, 127.5, 127.4, 127.4, 126.4, 126.4, 126.2, 126.1, 113.9, 113.5, 103.7, 102.6, 84.3, 81.4, 80.5, 78.5, 77.6, 75.2, 74.8, 74.5, 74.0, 73.4, 73.1, 73.0, 71.9, 70.1, 69.3, 67.8, 62.8, 62.4, 55.3, 55.1, 34.4, 34.2, 31.9, 29.8, 29.8, 29.5, 29.3, 29.3, 29.3, 29.3, 29.2, 29.2, 27.2, 27.2, 25.0, 24.9, 22.7, 14.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{91}H_{124}O_{17}Na$ 1511.8731; found [M + Na]$^+$ 1511.8734.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-β-D-galactopyranosyl}-sn-glycerol (**37**).* To a solution of **29β** (116 mg, 129 μmol) in 80% aqueous THF (2.60 mL) were added AcOH (1.50 mL, 26.3 mmol) and Zn (422 mg, 6.45 mmol) at room temperature. After being stirred for 10 min at the same temperature as the reaction was monitored by TLC (n-hexane/EtOAc = 1:1), the reaction mixture was filtered through a pad of Celite, and the pad was washed with CHCl$_3$. The combined filtrate and washings were successively washed with saturated aqueous NaHCO$_3$, H$_2$O, and brine. The organic layer was dried over Na$_2$SO$_4$, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using n-hexane/EtOAc (1:1→1:2) as the eluent to give **37** (84 mg, 85%) as a pale yellow syrup: $[\alpha]_D^{25}$ +57.8 (c 0.2, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ7.84−6.32 (m, 20 H, 5 Ar), 5.39 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar), 5.26 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 5.18 (d, 1 H, CH_2Ar), 5.00 (d, 1 H, CH_2Ar), 4.72 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.38 (d, 1 H, CH_2Ar), 4.31 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Gal}), 3.91−3.63 (m, 9 H, H-2^{Gal}, H-4^{Gal}, H-6a^{Gal}, H-6b^{Gal}, H-1a^{Gro}, H-1b^{Gro}, H-2^{Gro}, H-3a^{Gro}, H-3b^{Gro}), 3.61 (s, 3 H, OMe), 3.58 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3^{Gal}), 3.48 (t, 1 H, H-5^{Gal}), 3.43 (brs, 1 H, OH), 2.41 (brs, 1 H, OH), 1.09 (s, 9 H, ^{t}Bu);^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 158.8, 135.5, 135.2, 134.9, 133.2, 133.1, 133.0, 130.6, 129.8, 129.6, 128.1, 127.7, 127.6, 127.5, 126.5, 126.2, 113.2, 103.7, 81.0, 78.3, 77.5, 75.0, 74.5, 74.0, 73.4, 73.2, 71.7, 70.6, 63.7, 62.2, 55.0, 29.7, 26.8, 22.7, 19.2, 14.1;HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{45}H_{52}O_9SiNa$ 787.3273; found [M + Na]$^+$ 787.3271.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-6-O-tert-butyldiphenylsilyl-4-O-p-methoxybenzyl-β-D-galactopyranosyl}-1-O-stearoyl-sn-glycerol (**38**).* To a solution of **37** (84 mg, 110 μmol) and stearoyl acid (45 μL, 133 μmol) in CH$_2$Cl$_2$ (1.6 mL) were added dibutyltin oxide (5.5 mg, 22 μmol) and NEt$_3$ (18 μL, 30 μmol) at room temperature. After being stirred for 30 min at the same temperature as the reaction was monitored by TLC (n-hexane/EtOAc = 2:1), the reaction mixture was diluted with EtOAc and washed with H$_2$O and brine. The organic layer was dried over Na$_2$SO$_4$, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using n-hexane/EtOAc (4:1→3:1) as the eluent to give **38** (88 mg, 78%) as a colorless syrup along with starting material **37** (10 mg, 11%) as a pale yellow syrup: $[\alpha]_D^{25}$ +92.8 (c 0.3, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83−6.30 (m, 20 H, 5 Ar), 5.40 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar), 5.27 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 5.18 (d, 1 H, CH_2Ar), 4.99 (d, 1 H, CH_2Ar), 4.72 (d, 1 H, J_{gem} = 10.5 Hz, CH_2Ar), 4.38 (d, 1 H, CH_2Ar), 4.32 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Gal}), 4.16 (dd, 1 H, J_{vic} = 6.5 Hz, J_{gem} = 11.5 Hz, H-1a^{Gro}), 4.11 (dd, 1 H, J_{vic} = 5.0 Hz, H-1b^{Gro}), 4.00 (m, 1 H, H-2^{Gro}), 3.93 (d, 1 H, $J_{3,4}$ = 2.5 Hz, H-4^{Gal}), 3.85−3.68 (m, 6 H, H-2^{Gal}, H-3^{Gal}, H-6a^{Gal}, H-6b^{Gal}, H-3a^{Gro}, H-3b^{Gro}), 3.60 (s, 3 H, OMe), 3.49 (m, 1 H, H-5^{Gal}), 2.31 (m, 2 H, O(CO)CH$_2$), 1.61 (m, 2 H, CH$_2$), 1.29−1.20 (m, 28 H, 14 CH$_2$), 1.05 (s, 9 H, ^{t}Bu), 0.88 (t, 3 H, Me); ^{13}C{^{1}H} NMR{^{1}H} (125 MHz, CDCl$_3$) δ 173.9, 158.8, 135.6, 135.3, 134.9, 133.3, 133.2, 133.0, 130.7, 129.8, 129.6, 128.0, 127.8, 127.6, 127.5, 126.5, 126.2, 113.2, 103.8, 81.0, 78.4, 77.6, 75.0, 74.5, 74.0, 73.5, 72.4, 71.7, 68.9, 65.0, 62.0, 55.1, 34.2, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 26.9, 24.9, 22.7, 19.2, 14.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{63}H_{86}O_{10}SiNa$ 1053.5882; found [M + Na]$^+$ 1053.5882.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-galactopyranosyl}-2-O-palmitoleoyl-1-O-stearoyl-sn-glycerol (**39**).* To a solution of **38** (61 mg, 59 μmol) and palmitoleic acid (20 μL, 70 μmol) in CH$_2$Cl$_2$ (1.2 mL) were added DCC (36 mg, 174 μmol) and DMAP (1.4 mg, 11 μmol) at room temperature. After being stirred for 2 h at the same temperature as the reaction was monitored by TLC (n-hexane/EtOAc = 5:1), the reaction mixture was evaporated. The resulting residue was purified by flash column chromatography on silica gel using n-hexane/EtOAc (4:1→3:1) as the eluent to give the diacylated compound. After exposure to high vacuum overnight, this compound was dissolved in THF (1.2 mL). TBAF [1 M solution in THF] (0.18 mL, 180 μmol) was added to the

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

reaction mixture at room temperature. After being stirred for 12 h at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 3:1), the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1→3:2) as the eluent to give **39** (45 mg, 74% over two steps) as a colorless syrup: $[\alpha]_D^{25}$ +35.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−6.52 (m, 10 H, 3 Ar), 5.40 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar), 5.35−5.29 (m, 3 H, 2 CH = C*H*, H-2^{Gro}), 5.27 (d, 1 H, J_{gem} = 14.5 Hz, CH_2Ar), 5.16 (d, 1 H, CH_2Ar), 4.97 (d, 1 H, CH_2Ar), 4.69 (d, 1 H, J_{gem} = 11.0 Hz, CH_2Ar), 4.46 (d, 1 H, CH_2Ar), 4.41 (dd, 1 H, J_{vic} = 3.0 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.33 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Gal}), 4.26 (dd, 1 H, J_{vic} = 6.5 Hz, H-1b^{Gro}), 3.80−3.72 (m, 4 H, H-2^{Gal}, H-3^{Gal}, H-4^{Gal}, H-6a^{Gal}), 3.69−3.66 (m, 5 H, H-3a^{Gro}, H-3b^{Gro}, OMe), 3.44−3.43 (m, 2 H, H-5^{Gal}, H-6b^{Gal}), 2.33−2.31 (m, 4 H, 2 O(CO)CH_2), 2.01−1.98 (m, 4 H, 2 CH = CHCH_2), 1.63−1.58 (m, 4 H, 2 CH_2), 1.30−1.25 (m, 44 H, 22 CH_2), 0.89−0.86 (m, 6 H, 2 Me); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.5, 173.1, 159.1, 135.2, 135.1, 133.1, 132.9, 130.9, 130.2, 130.0, 129.7, 127.7, 127.6, 127.4, 126.4, 126.1, 113.5, 103.9, 81.1, 78.2, 77.6, 75.2, 74.0, 73.7, 73.4, 71.8, 70.3, 68.0, 62.9, 62.4, 55.1, 34.3, 34.2, 31.9, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 29.1, 29.0, 27.2, 27.2, 24.9, 22.7, 22.6, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{63}H_{96}O_{11}Na$ 1051.6845; found [M + Na]$^+$ 1051.6847.

*3-O-{2,3-O-[2,3-Bis(methyl)naphthele]-β-D-galactopyranosyl}-2-O-palmitoleoyl-1-O-stearoyl-sn-glycerol (**40**).* To a solution of **39** (5.6 mg, 5.4 μmol) and anisole (0.9 μL, 8.3 μmol) in CH_2Cl_2 (0.20 mL) were added TMSCl (2.0 μL, 16 μmol) and DMAP (0.6 mg, 3 μmol) at 4 °C using an ice bath. After being stirred for 1 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction mixture was evaporated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1) as the eluent to give **40** (4.4 mg, 89%); $[\alpha]_D^{25}$ +47.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81−7.26 (m, 6 H, 2 Ar), 5.42 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.35−5.30 (m, 3 H, 2 CH = C*H*, H-2^{Gro}), 5.25 (d, 1 H, J_{gem} = 14.0 Hz, CH_2Ar), 5.15 (d, 1 H, CH_2Ar), 4.94 (d, 1 H, CH_2Ar), 4.44 (dd, 1 H, J_{vic} = 3.0 Hz, J_{gem} = 12.0 Hz, H-1a^{Gro}), 4.37 (d, 1 H, $J_{1,2}$ = 7.0 Hz, H-1^{Gal}), 4.25 (dd, 1 H, J_{vic} = 6.5 Hz, H-1b^{Gro}), 4.02−4.00 (m, 2 H, H-3^{Gal}, H-4^{Gal}), 3.88 (dd, 1 H, J_{vic} = 5.0 Hz, J_{gem} = 11.0 Hz, H-3a^{Gro}), 3.81 (dd, 1 H, J_{vic} = 3.5 Hz, H-3b^{Gro}), 3.77 (m, 1 H, H-6a^{Gal}), 3.67 (t, 1 H, $J_{2,3}$ = 7.5 Hz, H-2^{Gal}), 3.62 (dd, 1 H, $J_{5,6b}$ = 7.5 Hz, J_{gem} = 9.0 Hz, H-6b^{Gal}), 3.52 (m, 1 H, H-5^{Gal}), 2.69 (d, 1 H, $J_{6,OH}$ = 6.5 Hz, OH^{Gal}), 2.48 (s, 1 H, OH), 2.40−2.30 (m, 4 H, 2 O(CO)CH_2), 2.08−1.98 (m, 4 H, 2 CH = CHCH_2), 1.65−1.59 (m, 4 H, 2 CH_2), 1.30−1.25 (m, 44 H, 22 CH_2), 0.89−0.83 (m, 6 H, 2 Me); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.6, 173.2, 134.7, 134.3, 133.2, 132.9, 131.3, 130.0, 129.7, 128.0, 127.6, 127.4, 126.7, 126.3, 103.6, 79.0, 77.6, 77.3, 77.0, 76.8, 74.7, 73.1, 71.8, 70.3, 68.6, 68.0, 62.9, 62.7, 34.3, 34.2, 31.9, 31.8, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 29.1, 29.0, 27.2, 27.2, 24.9, 22.7, 22.7, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{55}H_{88}O_{10}Na$ 931.6270; found [M + Na]$^+$ 931.6272.

*3-O-(6-O-{2,3-O-[2,3-Bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-glucopyranosyl}-2,3-O-[2,3-bis(methyl)naphthele]-4-O-p-methoxybenzyl-β-D-galactopyranosyl)-2-O-palmitoleoyl-1-O-stearoyl-sn-glycerol (**42**).* To a solution of **19** (44 mg, 48 μmol) and **40** (40 mg, 48 μmol) in CH_2Cl_2 (0.50 mL) was added 4 Å molecular sieves (25 mg). After being stirred for 30 min at room temperature, the mixture was then cooled to −80 °C. Subsequently, $BF_3{\cdot}Et_2O$ (0.3 μL, 2.4 μmol) was added to the reaction mixture at −80 °C. After being stirred for 15 min at the same temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the reaction was quenched by the addition of NEt_3 at −80 °C. The resulting mixture was filtered through a pad of Celite, and the pad was washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (5:1) as the eluent to give the glycosylated product **41** (46 mg, 67%, β/α = 8:1). After exposure to high vacuum overnight, this compound [β/α = 8:1] (24 mg, 15 μmol) was dissolved in THF (0.20 mL). TBAF [1 M solution in THF] (47 μL, 47 μmol) was added to the reaction mixture at room temperature. After being stirred for 3 h at room temperature as the reaction was monitored by TLC (*n*-hexane/EtOAc = 1:1), the mixture was diluted with $CHCl_3$ and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered off, and concentrated. The resulting residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1) as the eluent to give **42** (16 mg, 78%): $[\alpha]_D^{25}$ +51.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81−6.90 (m, 16 H, 5 Ar), 5.46 (d, 1 H, J_{gem} = 12.5 Hz, CH_2Ar), 5.37−5.28 (m, 5 H, 2 CH_2Ar, H-2^{Gro}, 2 CH = C*H*), 5.24 (d, 1 H, J_{gem} = 13.0 Hz, CH_2Ar), 5.14 (d, 1 H, CH_2Ar), 5.13 (d, 1 H, CH_2Ar), 5.12 (d, 1 H, CH_2Ar), 4.93 (d, 1 H, CH_2Ar), 4.86 (d, 1 H, J_{gem} = 11.0 Hz, CH_2Ar), 4.59 (d, 1 H, CH_2Ar), 4.40−4.35 (m, 3 H, H-1^{Glc}, H-1^{Gal}, H-1a^{Gro}), 4.24 (dd, 1 H, J_{vic} = 6.5 Hz, J_{gem} = 12.0 Hz, H-1b^{Gro}), 4.06 (s, 1 H, H-4^{Gal}), 4.03−3.99 (m, 2 H, H-3^{Glc}, H-3a^{Gro}), 3.85 (dd, 1 H, $J_{5,6a}$ = 6.0 Hz, J_{gem} = 10.5 Hz, H-6a^{Glc}), 3.82 (s, 3 H, OMe), 3.80−3.73 (m, 4 H, H-4^{Glc}, H-6b^{Glc}, H-3^{Gal}, H-3b^{Gro}), 3.66−3.62 (m, 2 H, H-2^{Glc}, H-5^{Glc}), 3.56 (dd, 1 H, $J_{5,6b}$ = 5.5 Hz, J_{gem} = 12.0 Hz, H-6a^{Gal}), 3.40−3.36 (m, 2 H, H-2^{Gal}, H-6b^{Gal}), 3.28 (m, 1 H, H-5^{Gal}), 2.33−2.28 (m, 4 H, 2 O(CO)CH_2), 2.02−1.99 (m, 4 H, 2 CH = CHCH_2), 1.75−1.59 (m, 4 H, 2 CH_2), 1.37−1.25 (m, 44 H, 22 CH_2), 0.89−0.83 (m, 6 H, 2 Me); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 175.3, 173.6, 134.7, 132.9, 130.0, 129.8, 129.7, 129.5, 127.4, 126.6, 126.4, 113.9, 103.1, 102.3, 80.4, 79.0, 77.6, 74.8, 74.6, 73.2, 73.0, 67.7, 67.3, 55.3, 34.3, 34.1, 31.9, 31.8, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 29.0, 27.2, 27.2, 24.9, 24.9, 22.7, 22.6, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{81}H_{114}O_{16}Na$ 1365.7999; found [M + Na]$^+$ 1365.7997.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02121.

X-ray crystallographic data and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 2040938 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Hide-Nori Tanaka − *Institute for Glyco-core Research (iGCORE) and Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, Gifu 501-1193, Japan;* orcid.org/0000-0001-5307-4909; Email: htanaka@gifu-u.ac.jp

Hiromune Ando − *Institute for Glyco-core Research (iGCORE) and Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, Gifu 501-1193, Japan;* orcid.org/0000-0002-0551-0830; Email: hando@gifu-u.ac.jp

Authors

Nahoko Yagami − *Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, Gifu 501-1193, Japan*

Amol M. Vibhute − *Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, Gifu 501-1193, Japan*

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX

Naoko Komura − *Institute for Glyco-core Research (iGCORE) and Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, Gifu 501-1193, Japan;* orcid.org/0000-0002-8104-750X

Akihiro Imamura − *Department of Applied Bioorganic Chemistry, Gifu University, Gifu 501-1193, Japan;* orcid.org/0000-0002-7860-992X

Hideharu Ishida − *Institute for Glyco-core Research (iGCORE), Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), and Department of Applied Bioorganic Chemistry, Gifu University, Gifu 501-1193, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02121

Author Contributions

⊥N.Y., A.M.V., and H.-N.T. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful of Dr. Hiromi Ota at Division of Instrumental Analysis for the X-ray single crystal structural analyses and thank Ms. Eriko Yamaguchi for NMR data collections. This work was supported in part by JSPS KAKENHI Grant Numbers JP19F01098 (H.A.), JP18H03942 (H.A.), and JP18K05461 (H.T.) and JST CREST Grant Number JPMJCR18H2 (H.A.).

■ REFERENCES

(1) (a) Hölzl, G.; Dörmann, P. Structure and Function of Glycoglycerolipids in Plants and Bacteria. *Prog. Lipid Res.* **2007**, *46*, 225−243. (b) Michaud, M.; Jouhet, J. Lipid Trafficking at Membrane Contact Sites During Plant Development and Stress Response. *Front. Plant Sci.* **2019**, *10*, 2.

(2) Zhang, J.; Li, C.; Yu, G.; Guan, H. Total Synthesis and Structure-Activity Relationship of Glycoglycerolipids from Marine Organisms. *Mar. Drugs* **2014**, *12*, 3634−3659.

(3) (a) Shaw, N. Bacterial Glycolipid. *Bacteriol. Rev.* **1970**, *34*, 365−377. (b) Andres, E.; Martinez, N.; Planas, A. Expression and Characterization of a *Mycoplasma genitalium* Glycosyltransferase in Membrane Glycolipid Biosynthesis. *J. Biol. Chem.* **2011**, *286*, 35367−35379.

(4) (a) Kinjo, Y.; Illarionov, P.; Vela, J. L.; Pei, B.; Girardi, E.; Li, X.; Li, Y.; Imamura, M.; Kaneko, Y.; Okawara, A.; Miyazaki, Y.; Gómez-Velasco, A.; Rogers, P.; Dahesh, S.; Uchiyama, S.; Khurana, A.; Kawahara, K.; Yesilkaya, H.; Andrew, P. W.; Wong, C.-H.; Kawakami, K.; Nizet, V.; Besra, G. S.; Tsuji, M.; Zajonc, D. M.; Kronenberg, M. Invariant Natural Killer T Cells Recognize Glycolipids from Pathogenic Gram-positive Bacteria. *Nat. Immunol.* **2011**, *12*, 966−974. (b) Theilacker, C.; Sanchez-Carballo, P.; Toma, I.; Fabretti, F.; Sava, I.; Kropec, A.; Holst, O.; Huebner, J. Glycolipids Are Involved in Biofilm Accumulation and Prolonged Bacteraemia in *Enterococcus faecalis*. *Mol. Microbiol.* **2009**, *71*, 1055−1069. (c) Theilacker, C.; Diederich, A.-K.; Otto, A.; Sava, I. G.; Wobser, D.; Bao, Y.; Hese, K.; Broszat, M.; Henneke, P.; Becher, D.; Huebner, J. *Enterococcus faecalis* Glycolipids Modulate Lipoprotein-Content of the Bacterial Cell Membrane and Host Immune Response. *PLoS One* **2015**, *10*, No. e0132949.

(5) (a) von Minden, H. M.; Morr, M.; Milkereit, G.; Heinz, E.; Vill, V. Synthesis and Mesogenic Properties of Glycosyl Diacylglycerols. *Chem. Phys. Lipids* **2002**, *114*, 55−80. (b) Tanaka, R.; Sakano, Y.; Nagatsu, A.; Shibuya, M.; Ebizuka, Y.; Goda, Y. Synthesis of Digalactosyl Diacylglycerols and Their Structure-Inhibitory Activity on Human Lanosterol Synthase. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 159−162. (c) Miyachi, A.; Miyazaki, A.; Shingu, Y.; Matsuda, K.; Dohi, H.; Nishida, Y. Synthesis and Absolute Structures of *Mycoplasma pneumoniae* β-Glyceroglycolipid Antigens. *Carbohydr. Res.* **2009**, *344*, 36−43. (d) Fukuda, K.; Matsuda, K.; Matsuda, S.; Kado, S.; Masu, H.; Dohi, H.; Nishida, Y. Chemosynthetic Homologues of *Mycoplasma pneumoniae* β-Glycolipid Antigens for the Diagnosis of Mycoplasma Infectious Diseases. *Bioorg. Med. Chem.* **2018**, *26*, 824−832. (e) Amara, S.; Barouh, N.; Lecomte, J.; Lafont, D.; Robert, S.; Villeneuve, P.; De Caro, A.; Carrière, F. Lipolysis of Natural Long Chain and Synthetic Medium Chain Galactolipids by Pancreatic Lipase-related Protein 2. *Biochim. Biophys. Acta, Mol. Cell Biol. Lipids* **2010**, *1801*, 508−516. (f) Hogendorf, W. F. J.; Jagalski, V.; Pomorski, T. G.; Bols, M.; Cárdenas, M.; Pedersen, C. M. Synthesis and Thermotropic Phase Behavior of Four Glycoglycerolipids. *Molecules* **2013**, *18*, 13546−13573. (g) Richardson, M. B.; Torigoe, S.; Yamasaki, S.; Williams, S. J. *Mycobacterium tuberculosis* β-Gentiobiosyldiacylglycerides Signal through the Pattern Recognition Receptor Mincle: Total Synthesis and Structure Activity Relationships. *Chem. Commun.* **2015**, *51*, 15027−15030. (h) Inuki, S.; Kishi, J.; Kashiwabara, E.; Aiba, T.; Fujimoto, Y. Convergent Synthesis of Digalactosyl Diacylglycerols. *Org. Lett.* **2017**, *19*, 6482−6485. (i) Takato, K.; Kurita, M.; Yagami, N.; Tanaka, H.-N.; Ando, H.; Imamura, A.; Ishida, H. Chemical Synthesis of Diglucosyl Diacylglycerols Utilizing Glycosyl Donors with Stereodirecting Cyclic Silyl Protective Groups. *Carbohydr. Res.* **2019**, *483*, 107748.

(6) Hanessian, S.; Banoub, J. 1,2-Orthoester Formation and Glycosidation with Amide Acetals. *Methods Carbohydr. Chem.* **1980**, *8*, 237−242.

(7) (a) Hashimoto, S.; Hayashi, M.; Noyori, R. Glycosylation Using Glucopyranosyl Fluorides and Silicon-based Catalysts. Solvent Dependency of the Stereoselection. *Tetrahedron Lett.* **1984**, *25*, 1379−1382. (b) Schmidt, R. R.; Behrendt, M.; Toepfer, A. Nitriles as Solvents in Glycosylation Reactions: Highly Selective β-Glycoside Synthesis. *Synlett* **1990**, *1990*, 694−696.

(8) Yagami, N.; Tamai, H.; Udagawa, T.; Ueki, A.; Konishi, M.; Imamura, A.; Ishida, H.; Kiso, M.; Ando, H. A 1,2-*trans*-Selective Glycosyl Donor Bearing Cyclic Protection at the C-2 and C-3 Hydroxy Groups. *Eur. J. Org. Chem.* **2017**, *2017*, 4778−4785.

(9) (a) Imamura, A.; Lowary, T. L. β-Selective Arabinofuranosylation Using a 2,3-*O*-Xylylene-Protected Donor. *Org. Lett.* **2010**, *12*, 3686−3689. (b) Zhang, L.; Shen, K.; Taha, H. A.; Lowary, T. L. Stereocontrolled Synthesis of α-Xylofuranosides Using a Conformationally Restricted Donor. *J. Org. Chem.* **2018**, *83*, 7659−7671.

(10) Neva, T.; Carmona, T.; Benito, J. M.; Przybylski, C.; Ortiz Mellet, C.; Mendicuti, F.; Garcia Fernandez, J. M. Dynamic Control of the Self-Assembling Properties of Cyclodextrins by the Interplay of Aromatic and Host-Guest Interactions. *Front. Chem.* **2019**, *7*, 72.

(11) (a) Liptak, A.; Jodal, I.; Harangi, J.; Nanasi, P. Hydrogenolysis of the Benzylidene Acetals of Thioglycosides with the Lithium Aluminum Hydride-Aluminum Chloride Reagent. Synthesis of Partially Benzylated Thioglycoside Derivatives. *Acta Chim. Hung.* **1983**, *113*, 415−422. (b) Zhou, F.-Y.; Huang, J.-Y.; Yuan, Q.; Wang, Y.-G. Regioselective Glycosylations of 4,6-*O*-Benzylidene Glucopyranosides with Glycosyl Trichloroacetimidates. *Chem. Lett.* **2005**, *34*, 878−879. (c) Blom, P.; Ruttens, B.; Van Hoof, S.; Hubrecht, I.; Van der Eycken, J.; Sas, B.; Van hemel, J.; Vandenkerckhove, J. A Convergent Ring-Closing Metathesis Approach to Carbohydrate-Based Macrolides with Potential Antibiotic Activity. *J. Org. Chem.* **2005**, *70*, 10109−10112.

(12) Sakagami, M.; Hamana, H. A Selective Ring Opening Reaction of 4,6-*O*-Benzylidene Acetals in Carbohydrates Using Trialkylsilane Derivatives. *Tetrahedron Lett.* **2000**, *41*, 5547−5551.

(13) Li, Y.; Liu, X. Tunable Acid-sensitive Ester Protecting Groups in Oligosaccharide Synthesis. *Chem. Commun.* **2014**, *50*, 3155−3158.

(14) Ghotekar, B. K.; Podilapu, A. R.; Kulkarni, S. S. Total Synthesis of the Lipid-Anchor-Attached Core Trisaccharides of Lipoteichoic Acids of *Streptococcus pneumoniae* and *Streptococcus oralis* Uo5. *Org. Lett.* **2020**, *22*, 537−541.

(15) (a) Günther, W.; Kunz, H. Synthesis of β-D-Mannosides from β-D-Glucosides *via* an Intramolecular S_N2 Reaction at C-2.

Carbohydr. Res. **1992**, *228*, 217−241. (b) Morihiro, K.; Kodama, T.; Obika, S. Benzylidene Acetal Type Bridged Nucleic Acids: Changes in Properties Upon Cleavage of the Bridge Triggered by External Stimuli. *Chem. - Eur. J.* **2011**, *17*, 7918−7926.
(16) (a) Imai, H.; Oishi, T.; Kikuchi, T.; Hirama, M. Concise Synthesis of 3-*O*-(2-*O*-α-D-Glucopyranosyl-6-*O*-acyl-α-D-glucopyranosyl)-1,2-di-*O*-acyl-*sn*-glycerols. *Tetrahedron* **2000**, *56*, 8451−8459. (b) Shingu, Y.; Nishida, Y.; Dohi, H.; Kobayashi, K. An Easy Access to Halide Ion-catalytic α-Glycosylation Using Carbon Tetrabromide and Triphenylphosphine as Multifunctional Reagents. *Org. Biomol. Chem.* **2003**, *1*, 2518−2521.
(17) Yeung, B. K. S.; Hill, D. C.; Janicka, M.; Petillo, P. A. Synthesis of Two Hyaluronan Trisaccharides. *Org. Lett.* **2000**, *2*, 1279−1282.
(18) Roy, S.; Chakraborty, A.; Ghosh, R. Aryl 4,6-*O*-Arylidene-1-thio-β-D-glycopyranoside-based New Organogelators and Their Gels. *Carbohydr. Res.* **2008**, *343*, 2523−2529.
(19) Casati, S.; Ciuffreda, P.; Santaniello, E. Synthesis of Enantiomerically Pure (*R*)-and (*S*)-1-Benzoyloxypropane-2,3-diol and Revision of the Stereochemical Outcome of the *Candida antarctica* Lipase-catalyzed Benzoylation of Glycerol. *Tetrahedron: Asymmetry* **2011**, *22*, 658−661.
(20) Goto, K.; Tamai, H.; Takeda, Y.; Tanaka, H.-N.; Mizuno, T.; Imamura, A.; Ishida, H.; Kiso, M.; Ando, H. Total Synthesis of Sialyl Inositol Phosphosphingolipids CJP-2, CJP-3, and CJP-4 Isolated from Feather Star *Comanthus japonica*. *Org. Lett.* **2019**, *21*, 4054−4057.
(21) (a) Abiko, T.; Sekino, H. Synthesis of a Thymosin β_4-Like Peptide, Thymosin β_9^{Met}, and Its Effect on Low E-Rossette-Forming Lymphocytes of Lupus Nephritis Patients. *Chem. Pharm. Bull.* **1990**, *38*, 2301−2304. (b) Muttenthaler, M.; Ramos, Y. G.; Feytens, D.; de Araujo, A. D.; Alewood, P. F. *p*-Nitrobenzyl Protection for Cysteine and Selenocysteine: A More Stable Alternative to the Acetamidomethyl Group. *Biopolymers* **2010**, *94*, 423−432.
(22) Nielsen, M. M.; Stougaard, B. A.; Bols, M.; Glibstrup, E.; Pedersen, C. M. Glycosyl Fluorides as Intermediates in $BF_3{\cdot}OEt_2$-Promoted Glycosylation with Trichloroacetimidates. *Eur. J. Org. Chem.* **2017**, *2017*, 1281−1284.
(23) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. Dibutyltin Oxide Catalyzed Selective Sulfonylation of α-Chelatable Primary Alcohols. *Org. Lett.* **1999**, *1*, 447−450.
(24) Akiyama, T.; Shima, H.; Ozaki, S. Trimethylsilyl Chloride-Tin(II) Chloride-Anisole: A Novel Selective *p*-Methoxybenzyl Ether Cleavage Reagent. *Synlett* **1992**, *1992*, 415−416.
(25) Janczuk, A. J.; Zhang, W.; Andreana, P. R.; Warrick, J.; Wang, P. G. The Synthesis of Deoxy-α-Gal Epitope Derivatives for the Evaluation of an Anti-α-Gal Antibody Binding. *Carbohydr. Res.* **2002**, *337*, 1247−1259.
(26) Crich, D.; Jayalath, P. Stereocontrolled Formation of β-Glucosides and Related Linkages in the Absence of Neighboring Group Participation: Influence of a *trans*-Fused 2,3-*O*-Carbonate Group. *J. Org. Chem.* **2005**, *70*, 7252−7259.
(27) Yeung, B. K. S.; Hill, D. C.; Janicka, M.; Petillo, P. A. Synthesis of Two Hyaluronan Trisaccharides. *Org. Lett.* **2000**, *2*, 1279−1282.
(28) Yamamoto, K.; Sato, Y.; Ishimori, A.; Miyairi, K.; Okuno, T.; Nemoto, N.; Shimizu, H.; Kidokoro, S.; Hashimoto, M. Synthesis of D-Trigalacturonic Acid Methylglycoside and Conformational Comparison with its Sulfur Analogue. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 2039−2048.

https://dx.doi.org/10.1021/acs.joc.0c02121
J. Org. Chem. XXXX, XXX, XXX−XXX