Tetrahedron 69 (2013) 1470–1475

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of a new glycosphingolipid from the marine ascidian *Microcosmus sulcatus* using a one-pot glycosylation strategy

Isao Ohtsuka [a,*], Noriyasu Hada [b], Toshiyuki Atsumi [a], Nobuko Kakiuchi [a]

[a] School of Pharmaceutical Sciences, Kyushu University of Health and Welfare, 1714-1 Yoshino-cho, Nobeoka city, Miyazaki 882-8508, Japan
[b] Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan

ARTICLE INFO

Article history:
Received 28 October 2012
Received in revised form 6 December 2012
Accepted 10 December 2012
Available online 19 December 2012

Keywords:
Microcosmus sulcatus
Glycosphingolipids
Oligosaccharide synthesis
One-pot glycosylation strategy

ABSTRACT

A novel neutral glycosphingolipid found in *Microcosmus sulcatus* containing a β-D-Gal*p*(1→4)[α-D-Fuc*p*-(1→3)]β-D-Glc*p*-(1→)Cer motif was synthesized. Trisaccharide derivatives were synthesized using trimethylsilyltrifluoromethanesulfanate (TMSOTf) and *N*-iodosuccimide (NIS)/trifluoromethane sulfonic acid (TfOH) as the promoters. Synthesis was achieved with an efficient one-pot glycosylation strategy. This is the first report of a one-pot glycosylation strategy using the procedure of Boons et al. for the synthesis of a natural product. Coupling of trisaccharide derivative **19** and ceramide derivative **20** by TMSOTf afforded the glycosphingolipid derivative **21**. The fully protected glycoside was deprotected to give the target glycosphingolipid **2**.

1. Introduction

Glycosphingolipids such as gangliosides or cerebrosides are ubiquitous in biologic systems and are involved in many important processes, such as fertilization, embryogenesis, neuronal development, hormone activity, cell proliferation, and tissue organization.[1,2] The structures and biologic functions of many gangliosides have been widely investigated and reported in various reviews.[3,4] The biologic functions of glycolipids lacking sialic acid in various invertebrate animal species, however, are unknown.[5] Elucidation of the function of glycolipids in natural products will lead to better understanding of their functional processes in animals, as well as to molecular evolution in living organisms. Gaining knowledge regarding their function will also help to uncover disease mechanisms and facilitate the development of new drugs. These complex compounds are very difficult to isolate from nature, however, and only small amounts can be obtained. Studies and structurally well-defined glycolipids provided by organic synthesis will advance the field of glycobiology.[6–9]

Recently, Fattorusso et al. isolated and characterized a novel neutral glycosphingolipid (**1**, Fig. 1) from the marine ascidian *Microcosmus sulcatus*.[10] The carbohydrate structure features a D-fucose and a D-galactose residue attached to the reducing-end of D-glucose through a β-D-Gal*p*(1→4)[α-D-Fuc*p*-(1→3)]β-D-Glc*p*-(1→)Cer configuration (**1**). Their structures are unique because oligosaccharides containing a D-fucose are not found in all mammals. Thus, these compounds and their analogues may potentially exhibit new biologic activity that will lead to better understanding of disease mechanisms and the potential development of new drugs.[11,12] The biologic activities of these compounds cannot be compared with those of glycosphingolipids from other animal species, because the molecules contain different ceramide structures. Therefore, the ceramide structures must also be controlled for functional studies of the carbohydrate moieties in glycosphingolipids. The ceramides of major natural glycosphingolipids comprise a fatty acid and a saturated or unsaturated sphingosine.[4,13] We are interested in the structure of the trisaccharide of glycosphingolipids from *M. sulcatus* and have attempted to synthesize these structures containing general ceramides (**2**, Fig. 1). Synthesis of complex glycosphingolipids requires many time- and labor-intensive reaction steps. These long synthetic routes must be decreased to enhance the efficiency of oligosaccharide synthesis, thereby providing many target compounds to biochemical researchers. One-pot multistep approaches do not require intermediate work-up and purification steps and thus expedite synthesis.[13] Glycosylation strategies using one-pot multistep approaches are highly efficient synthetic routes for complex carbohydrates.[14–17] Boons et al. recently reported the synthesis of branched trisaccharide derivatives using a one-pot glycosylation strategy[18] that combines the reductive opening of a benzylidene acetal and a trichloroacetimidate glycosylation. Their procedure had not been previously used for natural product synthesis, and here we report the first synthesis of a novel glycosphingolipid isolated from

* Corresponding author. Tel.: +81 982 23 5701; fax: +81 982 23 5702; e-mail address: ohtsuka@phoenix.ac.jp (I. Ohtsuka).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.023

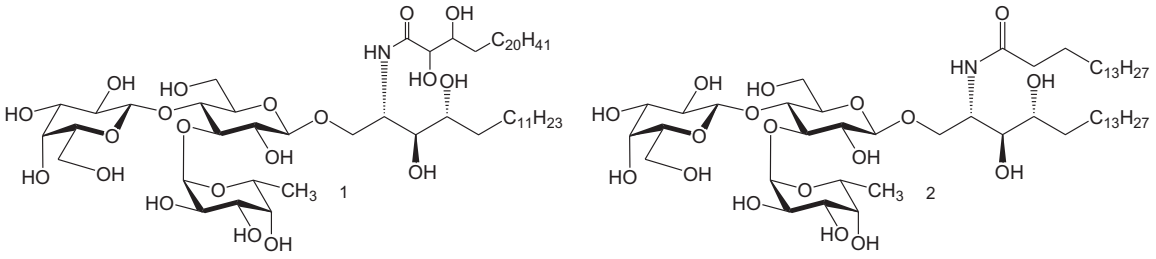


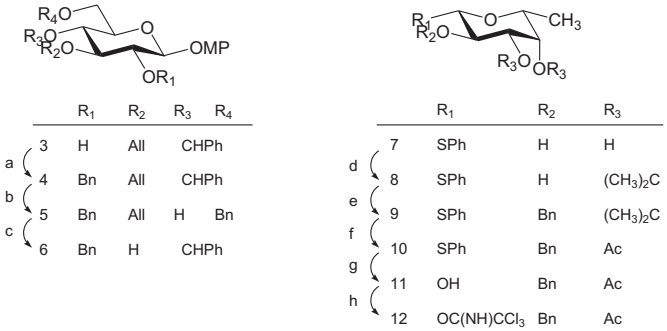
Fig. 1. Structure of glycosphingolipids **1** and **2** from *Microcosmus sulcatus*.

M. sulcatus based on the one-pot method recently reported by Boons et al.

2. Results and discussion

2.1. Synthesis of monosaccharide, disaccharide, and trisaccharide derivatives

Compound **4** was synthesized from β-D-glucopyranoside derivative **3**[19] by benzylation (90%) and converted to glycosyl acceptor **5** by ring opening of the benzylidene acetal group. The glucopyranoside derivative **6** containing a free C-3 hydroxyl group for use in the one-pot glycosylation was obtained by removing the allyl (All) group of **5** using $PdCl_2$.[20] D-Fucopyranoside derivatives were synthesized according to the preparations reported by Kiso.[21] Glycosyl donor **10** containing acetyl (Ac) groups on O-2 and O-3 and a benzyl (Bn) group on O-4 was obtained from phenyl 1-thio-β-D-fucopyranoside (**7**), which was prepared by acetylation, thioglycosylation, and deprotection of D-fucose over three steps. The thiophenyl group of **10** was converted to a trichloroacetimidate group because the one-pot glycosylation required two types of trichloroacetimidate donors: fucosylimidate and galactosylimidate derivatives. The α and β isomers of **11** (α/β=0.99:1.0) containing a free C-1 hydroxyl group were obtained by treatment with *N*-bromosuccimide (NBS),[22] and trichloroacetimide derivative **12** (α/β=1.0:0.25) for the one-pot glycosylation was synthesized by addition of trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]-7-undecane (DBU) (Scheme 1).



Scheme 1. Reagents and conditions: (a) BnCl, NaH, DMF/THF, 90%; (b) HCl/Et_2O, $NaCNBH_3$, THF, 78%; (c) $PdCl_2$, AcONa, $AcOH/H_2O$, 88%; (d) $(CH_3)_2C(OCH_3)_2$, CSA, DMF, 88%; (e) BnCl, NaH, DMF/THF, 89%; (f) (1) 90% AcOH; (2) Ac_2O, py, 89% (two steps); (g) NBS, acetone/H_2O, 90%; (h) Cl_3CCN, DBU, CH_2Cl_2, quant.

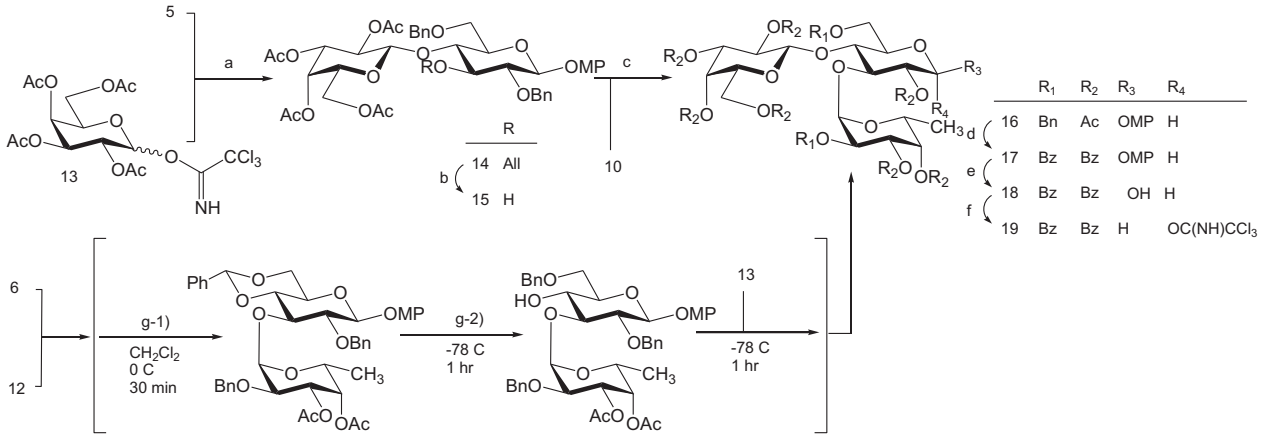
Disaccharide derivative **14** was synthesized using the trichloroacetimidate method. Glycosyl acceptor **5** was treated with donor **13**[23] using trimethylsilyltrifluoromethanesulfonate (TMSOTf)[24] as the glycosylation promoter. Thin layer chromatography (TLC) revealed that purification of the mixture by silica gel column chromatography afforded **14** (72%). The β-linkage was confirmed by ^1H NMR and ^{13}C NMR spectrometry.[25] The anomeric protons of Gal*p* appeared as a doublet with a coupling constant of 7.8 Hz (δ=4.69 ppm, d, 1H, H-1′). The All group of compound **14** was selectively removed by treatment with $PdCl_2$ to form acceptor **15**. Next, disaccharide acceptor **15** was glycosylated with donor **10**. The synthesis of trisaccharide derivative **16** using acceptor **15** and donor **10** was achieved with *N*-iodosuccimide (NIS) and trifluoromethane sulfonic acid (TfOH)[26] in 72% yield (Scheme 2). Anomeric protons of **16** were observed at δ=5.76 (br s, 1H, H-1″), 5.01 (d, 1H, $J_{1,2}$=7.4 Hz, H-1), and 4.71 (d, 1H, $J_{1,2}$=7.8 Hz, H-1′) in the ^1H NMR spectrum. Furthermore, C-1 atoms of Glc*p*, Gal*p*, and Fuc*p* were observed at δ=102.7 (C-1), 98.8 (C-1′), 95.9 (C-1″) in the ^{13}C NMR spectrum. The NMR data supported the structure of the trisaccharide. Trisaccharide derivative **16** in 37% overall yield was synthesized from monosaccharide derivative **5**.

2.2. Synthesis of trisaccharide derivatives using a one-pot glycosylation strategy

In traditional approaches of oligosaccharide synthesis, the product of a glycosylation reaction is isolated and subsequently reacted to be suitable for the next glycosylation reaction. Reducing the number of steps in this process would improve synthesis of the target compound. A one-pot multistep strategy uses the product of one glycosylation reaction directly in the next reaction, avoiding the work-up and isolation steps of the intermediate glycoside. The new glycosylation approach reported by Boons et al. combines the reductive opening of a benzylidene acetal and trichloroacetimidate glycosylation. This strategy is efficient for the synthesis of branched trisaccharide derivatives. Using this method, glycosyl acceptor **6** and donor **12** were coupled by using TfOH as the glycosylation promoter.[27] The benzylidene acetal group of the synthesized disaccharide intermediate was opened using reductive conditions with trimethylsilane and TfOH.[28] This reaction gave a disaccharide intermediate containing a free C-4 hydroxyl group on Glc*p*. Finally, donor **13** was added to the reaction mixture at −78 °C, and the reaction mixture was allowed to warm to 0 °C (Scheme 2). The reaction progress was monitored by TLC. The trisaccharide derivative was obtained in 47% yield using the one-pot glycosylation strategy in three steps and identified as compound **16** by ^1H NMR and ^{13}C NMR. This procedure proved very useful for the synthesis of a branched trisaccharide, producing a higher yield than the traditional procedure.

2.3. Synthesis of glycosphingolipid derivatives and target compound 2

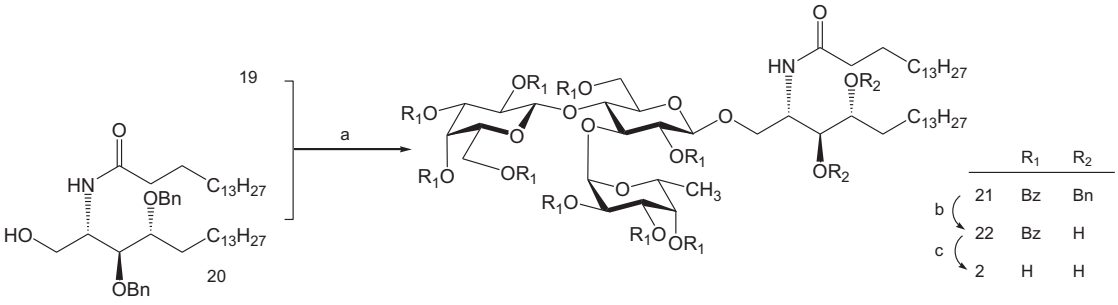
Subsequent removal of the Bn and Ac groups from **16** by catalytic hydrogenolysis over 10% Pd/C in MeOH and AcOH (1:1), treatment with NaOMe, followed by benzoylation gave **17** (58% over three steps). Selective removal of the *p*-methoxy phenyl (MP) group with ceric ammonium nitrate (CAN) in CH_3CN and H_2O (6:1),[29] and treatment with trichloroacetonitrile and DBU gave the corresponding α-trichloroacetimidate derivative **19**. Glycosylation of (2*S*,3*S*,4*R*)-3,4-di-*O*-benzyl-2-hexadecanamido-octadecane-3,4-diol (**20**)[30] with glycosyl donor **19** was carried out in the presence



Scheme 2. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 72%; (b) $PdCl_2$, AcONa, 90% AcOH, 75%; (c) NIS, TfOH, CH_2Cl_2, 72%; (d) (1) Pd/C, AcOH/MeOH; (2) NaOMe, MeOH; (3) BzCl, py, 58% (three steps); (e) CAN, CH_3CN/H_2O, 77%; Cl_3CCN, DBU, CH_2Cl_2, 81%; (g) (1) TfOH, CH_2Cl_2; (2) TfOH, Et_3SiH, 47% (three steps).

of TMSOTf and type AW-300 molecular sieves to afford trisaccharide derivative **21** (41%). Removal of the Bn group from **21** by catalytic hydrogenolysis over 10% Pd/C in CH_2Cl_2, MeOH, and AcOH (1:1:1) gave **22** (90%). Finally, removal of the benzoyl (Bz) group of **22** under Zemplén conditions and column chromatography using a Sephadex LH-20 afforded target glycosphingolipid **2** (Scheme 3.). The structure and purity of **2** were determined by ^1H NMR and ^{13}C NMR spectrometry and HR-FABMS data.

(JEOL Ltd.) in $CDCl_3$, D_2O, and CD_3OD with Me_4Si as the internal standard. High-resolution mass spectra were recorded on a JEOL JMS-700 under FAB conditions. Iontrap-LC–MS spectra were recorded on an LCO Advantage (Thermo-quest Ltd.). TLC was performed on Silica Gel 60 F_{254} (E. Merck) with detection by quenching UV fluorescence and charring with 10% H_2SO_4. Column chromatography was performed on Silica Gel 60 (E. Merck).



Scheme 3. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 41%; (b) Pd/C, CH_2Cl_2/MeOH/AcOH, 90%; (c) NaOMe, MeOH/1,4-dioxane, 50%.

3. Conclusion

In summary, we achieved the first successful synthesis of a novel glycosphingolipid from the marine ascidian *M. sulcatus*. The trisaccharide derivative was produced in good yield using both traditional procedures and a one-pot glycosylation strategy. This is the first application of the one-pot glycosylation strategy combining the reductive opening of a benzylidene acetal and a trichloroacetimidate glycosylation to the synthesis of a natural product. The development of one-pot glycosylation strategies may be a breakthrough for complex oligosaccharide synthesis.

4. Experimental

4.1. General method

Melting points (mp) of compound **2**, **5**, **11**, and **22** were obtained with a Yanaco MP-J3. Optical rotations were measured with a Jasco P-1020 digital polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded with a JMN AL 400 FT NMR spectrometer

4.2. 4-Methoxyphenyl 3-*O*-allyl-2,6-di-*O*-benzyl-β-D-glucopyranoside (5)

$NaCNBH_3$ (1.0 M) in THF (3.2 mL, 32 mmol) and 3 Å molecular sieves (5.0 g) were added to a solution of **4** (2.0 g, 3.9 mmol) in THF (15 mL), and the reaction mixture was stirred for 2 h at room temperature. HCl in diethylether (50 mL) was then added, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was filtered and extracted with $CHCl_3$. The organic solvent was washed with aqueous $NaHCO_3$, dried, and concentrated to give a clear oil. The crude product was purified by silica gel column chromatography (toluene/acetone=20:1 to 10:1) to give **5** (1.7 g, 83%) as a white solid. Mp 9699 °C; $[\alpha]_D^{25}$ −22.2 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 300K): δ 7.35–6.78 (m, 14H, Ph×3), 5.93 (m, 1H, $OCH_2CH{=}CH_2$), 5.25 (dd, 2H, $OCH_2CH{=}CH_2$), 5.02, 4.80, 4.60, 4.57 (each d, 4H, $PhCH_2O{\times}4$), 4.86 (d, 1H, $J_{1,2}$=7.8 Hz, H-1), 4.41 (dd, 1H, $OCH_2CH{=}CH_2$), 4.26 (dd, 1H, $OCH_2CH{=}CH_2$), 3.83 (dd, 1H, H-6a), 3.76 (s, 3H, $PhOCH_3$), 3.70 (dd, 1H, H-6b), 3.63 (t, 1H, H-2), 3.61 (t, 1H, H-4), 3.55 (q, 1H, H-5), 3.41 (t, 1H, H-3); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 155.1, 151.2, 138.0,

137.7, 134.8, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4, 118.3, 117.0, 102.7 (C-1), 83.7 (C-3), 84.4 (C-2), 74.8 (PhCH$_2$O), 74.3 (PhCH$_2$O), 74.2 (C-5), 73.6 (OCH$_2$CH=CH$_2$), 71.3 (C-4), 70.2 (C-6), 55.7 (PhOCH$_3$); LC–MS (ESI) calcd for $C_{30}H_{35}O_6^+$ $(M+H)^+$ m/z 507.23; measured m/z 507.23.

4.3. 4-Methoxyphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (6)

AcONa (12 g) and $PdCl_2$ (5.4 g) were added to a solution of **5** (2.1 g, 2.5 mmol) in AcOH (100 mL) and H_2O (10 mL), and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was filtered, extracted with AcOEt, washed with aqueous $NaHCO_3$, dried, and concentrated. The crude product was purified by silica gel column chromatography (toluene/acetone=60:1 to 30:1) to give **6** (1.5 g, 75%) as a colorless oil. $[\alpha]_D^{25}$ −19.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 7.49–6.81 (m, 14H, Ph×3), 5.43 (s, 1H, PhC*H*), 5.05, 4.82 (each d, 2H, PhC*H*$_2$×2), 4.97 (d, 1H, H-1), 4.37 (dd, 1H, H-6a), 3.91 (t, 1H, H-2), 3.83–3.73 (m, 4H, H-4, PhOC*H*$_3$), 3.62 (t, 1H, H-3), 3.60 (dd, 1H, 6b), 3.52 (q, 1H, H-5); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 137.9, 136.8, 129.1, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 126.1, 125.9, 118.6, 114.6, 102.9 (PhCH), 101.8 (C-1), 81.6 (C-2), 80.3 (C-3), 75.0 (PhCH$_2$O), 73.3 (C-5), 68.7 (C-6), 66.3 (C-4), 55.7 (PhOCH$_3$); LC–MS (ESI) calcd for $C_{27}H_{29}O_7^+$ $(M+H)^+$ m/z 464.18; measured m/z 464.18.

4.4. Phenyl 3,4-di-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-fucopyranoside (10)

H_2O (5.0 mL) was added dropwise to a solution of **9** (3.1 g, 8.0 mmol) in AcOH (50 mL), and the reaction mixture was stirred for 4 h at 50 °C, and then concentrated with EtOH. Ac_2O (30 mL) was added to a solution of the residue in pyridine (30 mL) at 0 °C, and the reaction mixture was stirred for 16 h. The reaction was quenched by MeOH and concentrated with toluene. The crude product was purified by silica gel column chromatography (hexane/AcOEt=8:1 to 4:1) to give **10** (1.6 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ +5.2 (*c* 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 7.60–7.25 (m, 5H, Ph), 5.24 (d, 1H, H-4), 5.03 (dd, 1H, H-3), 4.85, 4.58 (each d, 2H, PhC*H*$_2$O×2), 4.72 (d, 1H, $J_{1,2}$=9.7 Hz, H-1), 3.78 (m, 1H, H-5), 3.72 (t, 1H, H-2), 2.14, 1.92 (each s, 6H, Ac×2), 1.23 (d, 3H, H-6); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 170.2, 169.2 (CH$_3$*C*=O×2), 137.7, 133.4, 131.8, 128.1, 127.6, 127.6, 87.6 (C-1), 75.3 (PhCH$_2$O), 75.1 (C-2), 74.6 (C-3), 72.8 (C-5), 70.9 (C-4), 20.8, 16.6 (C-6); LC–MS (ESI) calcd for $C_{23}H_{27}O_6S^+$ $(M+H)^+$ m/z 430.15; measured m/z 430.15.

4.5. 3,4-Di-*O*-acetyl-2-*O*-benzyl-D-fucopyranose (11)

NBS (1.27 g, 7.7 mmol) was added to a solution of **10** (2.2 g, 5.1 mmol) in acetone (45 mL) and H_2O (5.0 mL) at −10 °C, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was extracted with $CHCl_3$, washed with aqueous $NaHCO_3$, dried, and concentrated. The crude product was purified by silica gel column chromatography (hexane/AcOEt=5:1) to give the α and β isomers of **11** (1.6 g, 90%, α/β=0.99:1.0) as a white solid. Mp 100–103 °C; $[\alpha]_D^{25}$ −17.2 (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 7.36–7.22, 5.33–5.26 (m, 3H, H-3 of α, H-4 of α, H-4 of β), 5.20 (d, 1H, $J_{1,2}$=2.3 Hz, H-1 of α), 4.98 (dd, 1H, H-3 of β), 4.90, 4.70, 4.69, 4.66 (each d, 4H, PhC*H*$_2$×4), 4.73 (d, 1H, $J_{1,2}$=7.8 Hz, H-1 of β), 4.37 (q, 1H, H-5 of α), 3.83 (t, 1H, H-2 of α), 3.87 (q, 1H, H-5 of β), 3.58 (t, 1H, H-2 of β), 2.14, 2.13, 1.99, 1.96, 1.19 (d, 3H, H-6 of β), 1.10 (d, 3H, H-6 of α); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 170.3, 170.2, 169.8, 137.6, 128.3, 128.1, 127.8, 127.6, 127.5, 127.4, 97.3 (C-1 of α), 91.5 (C-1 of β), 77.5 (PhCH$_2$O), 74.7 (PhCH$_2$O), 73.8 (C-2 of β), 73.2 (C-3 of β), 72.7(C-3 of α), 71.4 (C-5 of β), 70.7(C-2 of α), 69.7 (C-5 of α), 69.0 (C-4 of β), 64.6 (C-4 of α), 20.9, 20.8, 16.3 (C-6 of β), 16.1 (C-6 of α); LC–MS (ESI) calcd for $C_{17}H_{23}O_7^+$ $(M+H)^+$ m/z 338.14; measured m/z 338.14.

4.6. 3,4-Di-*O*-acetyl-2-*O*-benzyl-β-D-fucopyranosyltrichloroacetimidate (12)

Cl_3CCN (537 mL, 5.3 μmol) and DBU (119 μL, 0.8 mmol) were added to a solution of **11** (180 mg, 0.53 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C, and the mixture was stirred for 1 h. After completion of the reaction, the mixture was concentrated. Column chromatography of the residue on silica gel (hexane/AcOEt=10:1, then 3:1) gave **12** (256 mg, quant.) as a colorless oil. $[\alpha]_D^{25}$ +96.3 (*c* 6.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 8.59 (s, 1H, C=NH), 7.33–7.26 (m, 5H, Ph), 6.72 (d, 1H, H-1 of β), 6.51 (d, 1H, H-1 of α), 5.37–5.36 (m, 2H, H-3 of α, H-4 of α), 5.19 (d, 1H, H-4 of β), 4.79 (dd, 1H, H-3 of β), 4.89 (d, 1H, PhC*H*$_2$), 4.68, 4.65 (each d, 2H, PhC*H*$_2$×4), 4.45 (q, 1H, H-5 of β), 4.35 (q, 1H, H-5 of α), 4.03 (d, 1H, H-2 of α), 3.77 (d, 1H, H-2 of β), 2.21, 2.14, 2.12, 1.99, 1.95, 1.19 (d, 2H, H-6 of α), 1.15 (d, 2H, H-6 of β); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 170.3, 170.1, 169.9, 169.8, 161.0, 138.3, 137.5, 129.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 103.4. 94.4 (C-1 of α), 91.0 (C-1 of β), 77.2 (PhCH$_2$O), 74.6 (C-2 of β), 72.8 (PhCH$_2$O), 72.6 (C-2 of α), 70.9 (C-3 of α), 70.7 (C-3 of β), 69.8 (C-5 of α), 68.7 (C-5 of β), 67.3 (C-4 of α), 65.8 (C-4 of β), 20.9, 20.8, 20.7, 16.0 (C-6 of α), 15.4 (C-6 of β); LC–MS (ESI) calcd for $C_{19}H_{22}Cl_3NO_7^+$ $(M+H)^+$ m/z 481.05; measured m/z 481.05.

4.7. 4-Methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-3-*O*-allyl-2,6-di-*O*-benzyl-β-D-glucopyranoside (14)

A solution of **5** (1.77 g, 3.5 mmol) and **13** (3.43 g, 7.0 mmol) containing activated type AW-300 molecular sieves (5.5 g) in dry CH_2Cl_2 (11 mL) was stirred under a nitrogen atmosphere for 2 h at room temperature. After cooling to 0 °C, TMSOTf (253 μL, 1.4 mmol) was added, and the mixture was stirred for 1.5 h at 0 °C. The reaction mixture was neutralized with Et_3N, filtered, and extracted with $CHCl_3$. The organic solvent was washed with aqueous $NaHCO_3$, dried, and concentrated to give clear oil. The crude product was purified by silica gel column chromatography (hexane/AcOEt=3:1 to 3:2) to give **14** (2.1 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ −13.2 (*c* 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 7.48–6.78 (m, 4H, ph×3), 5.98 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.40 (dd, 2H, OCH$_2$CH=C*H*$_2$), 5.30 (d, 1H, H-4′), 5.18 (t, 1H, H-2′), 4.98, 4.88, 4.80, 4.48 (each d, 4H, PhC*H*$_2$O×4), 4.95 (dd, 1H, H-3′), 4.81 (d, 1H, H-1), 4.69 (d, 1H, $J_{1,2}$=7.8 Hz, H-1′), 4.13–4.10 (m, 3H, H-6a, H-6b, OC*H*$_2$CH=CH$_2$), 3.87 (t, 1H, H-3), 3.77–3.74 (m, 5H, H-5, H-6a′, PhOC*H*$_3$), 3.71 (t, 1H, H-6b′), 3.62 (dd, 1H, OC*H*$_2$CH=CH$_2$), 3.58 (t, 1H, H-2), 3.53 (t, 1H, H-4), 3.47 (q, 1H, H-5′), 2.16, 2.13, 2.06, 2.05 (each s, 12H, Ac×4); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 171.1, 170.1, 169.9, 169.8 (CH$_3$*C*=O×4), 155.1, 151.2, 138.1, 137.8, 135.2, 128.3, 127.9, 127.7, 127.6, 127.5, 118.4, 115.7, 102.5 (C-1), 100.4 (C-1′), 82.5 (C-4), 81.5 (C-2), 77.2 (C-3), 75.0 (C-5′), 74.6 (PhCH$_2$O), 73.6 (PhCH$_2$O), 71.1 (C-5), 70.5 (C-3′), 69.7 (C-6′), 68.1 (C-2′), 67.9 (OCH$_2$CH=CH$_2$), 66.9 (C-4′), 61.0 (C-6), 55.7 (PhOCH$_3$), 20.8 (CH$_3$C=O×4); LC–MS (ESI) calcd for $C_{44}H_{53}O_{16}^+$ $(M+H)^+$ m/z 836.33; measured m/z 836.33.

4.8. 4-Methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside (15)

AcONa (12 g) and $PdCl_2$ (5.4 g) were added to a solution of **14** (2.1 g, 2.5 mmol) in AcOH (100 mL) and H_2O (10 mL), and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was filtered, extracted with AcOEt, washed with aqueous

$NaHCO_3$, dried, and concentrated. The crude product was purified by silica gel column chromatography (toluene/acetone=60:1 to 30:1) to give **15** (1.5 g, 75%) as a colorless oil. $[\alpha]_D^{25}$ −10.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ 7.41–6.78 (m, 14H, Ph×3), 5.45 (d, 1H, H-4′), 5.19 (t, 1H, H-2′), 4.97 (dd, 1H, H-3′), 4.83 (d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.92, 4.86, 4.69, 4.48 (each d, 4H, PhCH_2O×4), 4.52 (d, 1H, $J_{1,2}$=7.7 Hz, H-1′), 4.15–4.13 (m, 2H, H-6a, H-6b), 3.94 (br t, 1H, H-3), 3.81 (t, 1H, H-4), 3.77–3.62 (H-5, H-6a′, H-6b′, PhOCH_3), 3.56 (t, 1H, H-2), 3.54 (q, 1H, H-5′), 2.16, 2.13, 2.06, 2.05 (each s, 12H, Ac×4); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 170.1, 169.9, 169.8, 169.7 (CH_3C=O×4), 138.8, 137.8, 128.3, 128.1, 127.4, 127.4, 102.1 (C-1), 101.4 (C-1′), 80.7 (C-2), 75.1 (C-4), 74.8 (C-3), 73.9 (PhCH_2O), 73.6 (C-5′), 71.7 (C-3′), 70.8 (PhCH_2O), 68.9 (C-6′), 68.0 (C-2′), 67.5 (C-4′), 61.6 (C-6), 55.7 (PhOCH_3), , 20.8 (CH_3C=O×4); LC–MS (ESI) calcd for $C_{41}H_{49}O_{16}^+$ $(M+H)^+$ *m*/*z* 796.29; measured *m*/*z* 796.29.

4.9. 4-Methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-[3,4-di-*O*-acetyl-2-*O*-benzyl-β-D-fucopyranosyl-(1→3)]-2,6-di-*O*-benzyl-β-D-glucopyranoside (16)

A solution of **15** (900 mg, 1.1 mmol) and **10** (995 mg, 2.2 mmol) containing activated type AW-300 molecular sieves (3.0 g) in dry CH_2Cl_2 (6.0 mL) was stirred under a nitrogen atmosphere for 2 h at room temperature. After cooling to 0 °C, NIS (1.0 g 4.4 mmol) and TfOH (42 μL, 0.44 mmol) were added sequentially, and the mixture was stirred for 1.5 h at 0 °C. The reaction mixture was neutralized with Et_3N, filtered, and extracted with $CHCl_3$. The organic solvent was washed with aqueous sodium thiosulfate, dried, and concentrated to give a clear oil. The crude product was purified by silica gel column chromatography (toluene/acetone=40:1 to 15:1) to give **16** (900 mg, 72%) as a colorless oil. $[\alpha]_D^{25}$ −20.2 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ 7.51–6.72 (m, 21H, Ph×4), 5.76 (br s, 1H, H-1″), 5.38 (dd, 1H, H-3″), 5.19 (d, 1H, H-4″), 5.14 (t, 1H, H-2′), 5.10 (dd, 1H, H-3′), 5.01 (d, 1H, $J_{1,2}$=7.4 Hz, H-1), 4.89 (d, 1H, H-4′), 4.81–4.51 (m, 6H, PhCH_2O×6), 4.71 (d, 1H, $J_{1,2}$=7.8 Hz, H-1′), 4.39 (q, 1H, H-5″), 4.29 (t, 1H, H-6a), 4.09–4.02 (m, H-6a′, H-6b), 3.88–3.78 (m, 6H, H-2, H-6b′, H-2″, PhOCH_3), 3.60 (q, 1H, H-5), 3.43 (q, 1H, H-5′), 1.70 (d, 3H, H-6″), 2.11, 2.02, 1.96, 1.95, 1.94, 1.88 (Ac×6); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 170.2, 169.9, 169.8, 169.7, 168.8, 155.1, 151.0, 137.9, 137.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 118.1, 118.0, 102.7 (C-1), 98.8 (C-1′), 95.9 (C-1″), 80.1, 77.2, 75.5, 75.2, 75.1, 73.6, 72.6, 72.0, 71.9, 71.7, 71.0, 70.9, 69.4, 69.3, 69.1, 68.7, 66.8, 64.2, 60.8, 55.7, 15.4; LC–MS (ESI) calcd for $C_{58}H_{69}O_{22}^+$ $(M+H)^+$ *m*/*z* 1116.42; measured *m*/*z* 1116.42.

4.10. Synthetic procedure of 16 using the one-pot glycosylation strategy

A solution of **6** (164 mg, 0.35 mmol) and **12** (255 mg, 0.5 mmol) in dry CH_2Cl_2 (3.0 mL) was stirred under a nitrogen atmosphere for 2 h at room temperature. After cooling to 0 °C, TfOH (3.2 μL, 35 μmol) was added, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was then cooled to −78 °C, and TfOH (49 μL, 0.5 mmol) and triethylsilane (112 μL, 0.7 mmol) were added sequentially. The reaction mixture was stirred again for 1 h at −78 °C. For the second glycosylation, **13** (312 mg, 0.64 mmol) dissolved in dry CH_2Cl_2 (1.0 mL) was added, and the mixture was allowed to warm to 0 °C while stirring for 3 h. The reaction mixture was quenched by Et_3N, filtered, and extracted with $CHCl_3$. The organic solvent was washed with aqueous $NaHCO_3$, dried, and concentrated to give a clear oil. The crude product was purified by silica gel column chromatography (toluene/acetone=40:1 to 15:1) to give **16** (165 mg, 47% over three steps).

4.11. 4-Methoxyphenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzoyl-α-D-fucopyranosyl-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranoside (17)

Pd/C (10%, 500 mg) was added to a solution of **16** (503 mg, 0.45 mmol) in MeOH (3.0 mL) and AcOH (3.0 mL), and the reaction mixture was stirred under hydrogen atmosphere for 12 h at room temperature. The mixture was filtered, concentrated, and redissolved in MeOH (10 mL). To the solution, 30% NaOMe (100 μL) in MeOH was added, and the mixture was stirred for 2 h at room temperature. The residue was protected with benzoyl chloride (313 μL, 2.7 mmol) in pyridine (10 mL) for 3 h. The reaction mixture was quenched with MeOH at 0 °C and extracted with $CHCl_3$. The extract was washed with 5% HCl and aqueous $NaHCO_3$, dried, and concentrated. The crude product was purified by silica gel column chromatography (toluene/acetone=40:1 to 15:1) to give **17** (400 mg, 58%—three steps) as a colorless oil. $[\alpha]_D^{25}$ −70.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ 8.13–6.62 (m, 45H, Ph×10), 5.94 (dd, 1H, H-3″), 5.84–5.74 (m, 4H, H-2, H-2′, H-4′, H-1″), 5.67 (d, 1H, H-4″), 5.53 (dd, 1H, H-3′), 5.23 (d, 1H, H-1), 4.86 (d, 1H, H-1′), 4.76 (q, 1H, H-5″), 4.58 (dd, 1H, H-6a), 4.52 (dd, 1H, H-6a′), 4.49 (t, 1H, H-3), 4.45–4.37 (m, 2H, H-6b, H-5), 4.28 (t, 1H, H-6b′), 4.05 (q, 1H, H-5′), 3.99 (t, 1H, H-4), 3.70 (s, 3H, PhCH_3), 1.59 (d, 3H, H-6″); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 165.7, 165.6, 165.5, 165.2, 165.1, 164.9, 164.8, 164.8, 155.1, 100.9 (C-1′), 99.2 (C-1), 96.9 (C-1″), 77.2, 76.5, 75.7, 73.5, 71.9, 71.8, 69.8, 69.1, 68.8, 67.8, 66.0, 63.5, 61.8, 55.6, 16.1; LC–MS (ESI) calcd for $C_{88}H_{75}O_{25}^+$ $(M+H)^+$ *m*/*z* 1530.45; measured *m*/*z* 1530.45.

4.12. 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzoyl-α-D-fucopyranosyl-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranose (18)

CAN (722 mg, 1.3 mmol) was added to a solution of **17** (400 mg, 0.26 mmol) in CH_3CN (6.0 mL) and H_2O (1.0 mL), and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was extracted with AcOEt, washed with aqueous $NaHCO_3$, dried, and concentrated. The crude product was purified by silica gel column chromatography (toluene/acetone=40:1 to 10:1) to give **18** (260 mg, 77%) as a yellow oil. $[\alpha]_D^{25}$ −23.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ 5.58 (d, 1H, $J_{1,2}$=2.9 Hz, H-1″), 5.00 (d, 1H, $J_{1,2}$=7.8 Hz, H-1′), 4.64 (d, 1H, $J_{1,2}$=7.3 Hz, H-1); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 165.9, 165.7, 165.6, 165.5, 165.4, 165.3, 165.1, 164.8, 133.3, 133.2, 133.1, 132.5, 129.9, 129.8, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 101.3 (C-1′), 96.2 (C-1″), 89.9 (C-1), 77.2, 74.4, 72.1, 71.9, 71.9, 70.1, 69.0, 68.9, 67.8, 68.8, 61.8, 29.8, 15.9; LC–MS (ESI) calcd for $C_{81}H_{59}O_{24}^+$ $(M+H)^+$ *m*/*z* 1424.21; measured *m*/*z* 1424.41.

4.13. 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzoyl-α-D-fucopyranosyl-(1→3)]-2,6-di-*O*-benzoyl-D-glucopyranosyltrichloroacetoimidate (19)

Cl_3CCN (183 μL, 1.8 mmol) and DBU (36 μL, 0.27 mmol) were added to a solution of **18** (260 mg, 0.18 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C, and the reaction mixture was stirred for 1 h. After completion of the reaction, the mixture was concentrated. Column chromatography of the residue on silica gel (toluene/acetone=100:1, then 10:1) gave **19** (234 mg, 81%) as a colorless oil. $[\alpha]_D^{25}$ +88.6 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ 8.55, 8.54 (each s, 2H, NHCCl_3×2), 6.70 (d, 1H, $J_{1,2}$=3.2 Hz, H-1 of α), 6.58 (d, 1H, $J_{1,2}$=7.0 Hz, H-1 of β); LC–MS (ESI) calcd for $C_{83}H_{69}Cl_3NO_{24}^+$ $(M+H)^+$ *m*/*z* 1567.32; measured *m*/*z* 1567.32.

4.14. 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzoyl-α-D-fucopyranosyl-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranosyl-(1→3)-(1→1)-(2*S*,3*S*,4*R*)-3,4-di-*O*-benzyl-2-hexadecanamido-octadecane-3,4-di-ol (21)

A solution of **19** (234 mg, 0.15 mmol) and (2*S*,3*S*,4*R*)-3,4-di-*O*-benzyl-2-hexadecanamido-octadecane-3,4-diol **20** (220 mg, 0.29 mmol) containing activated type AW-300 molecular sieves (2.0 g) in dry CH_2Cl_2 (4.0 mL) was stirred under nitrogen atmosphere for 2 h at room temperature. After cooling to 0 °C, TMSOTf (22 μL, 1.2 mmol) was added, and the solution was stirred for 1.5 h at 0 °C. The mixture was neutralized with Et_3N, filtered, and extracted with $CHCl_3$. The organic solvent was washed with aqueous $NaHCO_3$, dried, and concentrated to give a clear oil. The crude product was purified by silica gel column chromatography (hexane/AcOEt=4:1 to 2.5:1) to give **21** (130 mg, 41%) as a colorless oil. $[\alpha]_D^{25}$ −20.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 8.11–6.99 (m, 77H, Ph×11), 5.85 (d, 1H, $J_{1,2}$=2.9 Hz, H-1″), 5.81 (t, 1H, H-2′), 5.76 (dd, 1H, H-3″), 5.57 (d, 1H, H-4′), 5.45 (t, 1H, H-2″), 5.44 (dd, 1H, H-3′), 5.32 (d, 1H, H-4″), 4.94 (d, 1H, $J_{1,2}$=8.1 Hz, H-1′), 4.79 (d, 1H, PhCH_2O), 4.62–4.43 (m, 11H, PhCH_2O×3, H-1, H-2, H-3, H-6a, H-6b, H-6a′, H-6b′, H-5″), 4.33 (t, 1H, H-4), 4.19 (dd, 1H, OCH_2), 4.01 (q, 1H, H-5′), 3.95 (t, 1H, C*H*OH), 3.81 (m, 2H, H-5, OCH_2C*H*N), 3.33 (d, 1H, C*H*OH), 3.14 (dd, 1H, OCH_2), 1.59 (d, 3H, H-6″); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 101.1 (C-1′), 100.1 (C-1), 96.1 (C-1″), 79.7, 77.1, 74.1, 73.3, 71.8, 71.7, 71.2, 69.8, 68.8, 67.6, 65.8, 62.9, 61.5, 36.1, 31.9, 22.6, 14.1; LC–MS (ESI) calcd for $C_{129}H_{148}NO_{27}^+$ $(M+H)^+$ *m*/*z* 2142.02; measured *m*/*z* 2142.02.

4.15. 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzoyl-α-D-fucopyranosyl-(1→3)]-2,6-di-*O*-benzoyl-β-D-glucopyranosyl-(1→3)-(1→1)-(2*S*,3*S*,4*R*)-2-hexadecanamido-octadecane-3,4-di-ol (22)

Pd/C (10%, 60 mg) was added to a solution of **21** (56 mg, 26 μmol) in CH_2Cl_2 (2.0 mL), MeOH (2.0 mL), and AcOH (2.0 mL), and the reaction mixture was stirred under hydrogen atmosphere for 12 h at room temperature. The solution was then filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/AcOEt=3:1 to 1:1) to give **22** (46 mg, 90%) as a white solid. Mp 123–126 °C; $[\alpha]_D^{25}$ −15.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 8.08–7.04 (m, 45H, Ph×9), 6.08 (d, 1H, H-4′), 5.91 (d, 1H, $J_{1,2}$=3.2 Hz, H-1″), 5.88–5.76 (m, 3H, H-2′, H-2″, H-3″), 5.51 (dd, 1H, H-3′), 5.34 (d, 1H, H-4″), 4.97 (d, 1H, $J_{1,2}$=8.0 Hz, H-1′), 4.61 (m, 1H, H-5″), 4.52 (d, 1H, $J_{1,2}$=7.0 Hz, H-1), 4.61–4.46 (m, 4H, H-6a, H-6b, H-6a′, H-6b′), 4.39 (t, 1H, H-3), 4.20 (t, 1H, H-4), 4.16 (dd, 1H, OCH_2), 4.09 (q, 1H, H-5′), 3.88 (q, 1H, H-5), 3.53 (m, 2H, OCH_2C*H*N, C*H*OH), 3.43 (dd, 1H, OCH_2), 3.25 (d, 1H, C*H*OH), 1.59 (d, 3H, H-6″); ^{13}C NMR (400 MHz, $CDCl_3$, 300 K): δ 172.9, 165.8, 165.6, 165.5, 165.4, 165.2, 165.1, 165.0, 164.6, 101.1 (C-1′), 100.7 (C-1), 96.3 (C-1″), 77.2, 75.6, 74.5, 73.7, 72.9, 72.8, 72.0, 71.8, 69.9, 69.7, 68.9, 68.7, 67.7, 66.0, 62.9, 61.7, 36.5, 32.9, 25.9, 14.3; LC–MS (ESI) calcd for $C_{115}H_{135}NO_{27}^+$ $(M+H)^+$ *m*/*z* 1961.92; measured *m*/*z* 1961.92.

4.16. β-D-Galactopyranosyl-(1→4)-[β-α-fucopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→3)-(1→1)-(2*S*,3*S*,4*R*)-2-hexadecanamido-octadecane-3,4-di-ol (2)

NaOMe (30%) in MeOH (50 μL) was added to a solution of **22** (46 mg, 23 μmol) in MeOH (4.0 mL) and 1,4-dioxane (4.0 mL) at 40 °C, and the mixture was stirred for 8 h. The reaction mixture was neutralized with Amberlite IR-120 (H^+ form), filtered, and concentrated. The product was purified by Sephadex LH-20 column chromatography (100% MeOH) to give **16** (12 mg, 50%) as a white solid. Mp 99–101 °C; $[\alpha]_D^{25}$ −16.0 (*c* 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 4.99 (d, 1H, $J_{1,2}$=3.5 Hz, H-1″), 4.43 (d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.35 (d, 1H, $J_{1,2}$=7.8 Hz, H-1′); ^{13}C NMR (400 MHz, CD_3OD:$CDCl_3$=1:1, 300 K): δ 174.9, 103.9 (C-1′), 103.3 (C-1), 102.5 (C-1″), 77.8, 76.2, 75.4, 74.6, 74.0, 73.9, 72.8, 72.6, 71.8, 71.0, 70.8, 70.3, 69.7, 69.5, 68.7, 62.6, 60.3, 37.0, 32.6, 26.6, 14.4; HRMS (FAB) calcd for $C_{52}H_{99}NO_{18}Na^+$ $(M+Na)^+$ *m*/*z* 1048.6760; measured *m*/*z* 1048.6722.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by the Otsuka Pharmaceutical Award in Synthetic Organic Chemistry Japan Fund. The authors are grateful to Ms. J. Hada for providing HRMS data.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.023. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Kobata, A. *Eur. J. Biochem.* **1992**, *209*, 483–501.
2. Varki, A. *Cell* **2006**, *126*, 841–845.
3. Angata, T.; Varki, A. *Chem. Rev.* **2002**, *102*, 439–469.
4. Varki, A. *Glycobiology* **1992**, *2*, 25–40.
5. Itonori, S.; Sugita, M. In *Comprehensive Glycoscience*; Kamerling, J. P., Ed.; Elsevier: Amsterdam, The Netherlands, 2007; Vol. 3, pp 253–284.
6. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215–3237.
7. Demchenko, A. V. *Synlett* **2003**, 1225–1240.
8. Boons, G. J. *Contemp. Org. Synth.* **1996**, *3*, 173–200.
9. Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046–1051.
10. Aiell, A.; Fattorusso, E.; Mangoni, A.; Menna, M. *Eur. J. Org. Chem.* **2003**, 734–739.
11. Ziche, M.; Alessandri, G.; Gullino, P. M. *Lab. Invest.* **1989**, *61*, 629–634.
12. Ziche, M.; Alessandri, G.; Gullino, P. M. *Lab. Invest.* **1992**, *67*, 711–715.
13. (a) Francais, A.; Urban, D.; Beau, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665; (b) Wang, C. C.; Lee, J. C.; Luo, S. Y.; Kulkarni, S. S.; Huang, Y. W.; Lee, C. C.; Chang, S. C. *Nature* **2007**, *446*, 896–899.
14. Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580–1581.
15. Lahmann, M.; Oscarson, S. *Org. Lett.* **2000**, *2*, 3881–3882.
16. (a) Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3979–3982; (b) Yamada, H.; Kato, T.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 4581–4584; (c) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213–4216.
17. Mong, K.-K. T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4087–4090.
18. Vohra, Y.; Vasan, M.; Venot, A.; Boons, G.-J. *Org. Lett.* **2008**, *10*, 3247–3250.
19. Jiansong, S.; Xiuwen, H.; Biao, Y. *Synlett* **2005**, 437–440.
20. (a) Olvoot, J. J.; Boeckel, C. A. A. V.; Koning, J. H. D.; Van Boom, J. H. *Synthesis* **1981**, 305–308; (b) Ogawa, T.; Nakabayashi, S.; Kitajima, T. *Carbohydr. Res.* **1983**, *114*, 225–236; (c) Liu, X.; Stocker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638–3648.
21. Kiyoi, T.; Nakai, Y.; Kondo, H.; Ishida, H.; Kiso, M.; Hasegawa, A. *Bioorg. Med. Chem.* **1996**, *4*, 1167–1176.
22. (a) Lin, C.-C.; Huang, K. T.; Lin, C.-C. *Org. Lett.* **2005**, *7*, 4169–4172; (b) Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 6123–6126; (c) Tanaka, H.; Nishida, Y.; Adachi, M.; Takahashi, T. *Heterocycles* **2006**, *67*, 107–112; (d) Kondo, H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 8748–8750.
23. Pozsgay, V.; Kubler-Kielb, J.; Coxon, B.; Marques, A.; Robbins, J. B.; Schneerson, R. *Carbohydr. Res.* **2011**, *346*, 1551–1563.
24. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 213–236.
25. Matsuoka, K.; Terabatake, M.; Umino, A.; Esumi, Y.; Hatano, K.; Terunuma, D.; Kazuhara, H. *Biomolecules* **2006**, *7*, 2274–2283.
26. Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.
27. (a) Fügedi, P. *J. Carbohydr. Chem.* **1987**, *6*, 377–398; (b) Fügedi, P.; Nánási, P.; Szejtli, J. *Carbohydr. Res.* **1988**, *175*, 173–181.
28. (a) Wang, C. C.; Lee, J. C.; Luo, S.; Fan, H. F.; Pai, C. L.; Yang, W. C.; Lu, L. D.; Huang, S. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2360–2362; (b) Sakagami, M.; Hanashima, H. *Tetrahedron Lett.* **2000**, *41*, 5547–5551.
29. Hanashima, S.; Seeberger, P. H. *Chem. Asian J.* **2007**, *2*, 1447–1459.
30. Kanaya, T.; Yagi, S.; Schweizer, F.; Takeda, T.; Kiuchi, F.; Hada, N. *Chem. Pharm. Bull.* **2010**, *58*, 811–817.