Synthesis of type 2 Lewis antigens via novel regioselective glycosylation of an orthogonally protected lactosamine diol derivative

Yamazaki, Yuji; Sezukuri, Kyohei; Takada, Junko; Obata, Hiroaki; Kimura, Shunsaku; Ohmae, Masashi

Citation: Yamazaki, Yuji ...[et al]. Synthesis of type 2 Lewis antigens via novel regioselective glycosylation of an orthogonally protected lactosamine diol derivative. Carbohydrate Research 2016, 422: 34-44

Issue Date: 2016-03

URL: http://hdl.handle.net/2433/216657

Right: © 2016. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/; The full-text file will be made open to the public on 1 March 2018 in accordance with publisher’s 'Terms and Conditions for Self-Archiving'; この論文は出版社版ではありません。引用の際には出版社版をご確認ご利用ください。; This is not the published version. Please cite only the published version.
Synthesis of type 2 Lewis antigens via novel regioselective glycosylation of an orthogonally protected lactosamine diol derivative

Yuji Yamazaki, Kyohei Sezukuri, Junko Takada, Hiroaki Obata, Shunsaku Kimura, Masashi Ohmae*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku-katsura, Nishikyo-ku, Kyoto 615-8510, Japan

Tel.: +81-75-383-2403; fax: +81-75-383-2401

E-mail address: ohmae@peptide.polym.kyoto-u.ac.jp

*Corresponding author
Abstract

The novel and efficient synthesis of type 2 Lewis antigens is reported in this study. The rationally designed lactosamine-3,2′-diol derivative with an orthogonal set of protecting groups is efficiently glycosylated with a benzyl protected 1-thio-1-fucoside donor in a unique regioselective manner to produce Lewis x (Le^x) and Lewis y (Le^y) derivatives in good yields. These derivatives can be prepared not only exclusively but also synchronously by choosing the appropriate reaction temperature and donor-acceptor molar ratio. The Le^x derivatives are easily converted into sulfated or non-sulfated Le^x bearing a terminal azido functionalized oligo-(ethyleneoxide) linker; the Le^y derivative having the same linker can also be prepared, all of which can be further used for the chemical modification of other compounds and materials.

**Keywords:** Type 2 Lewis antigens; Sulfated Lewis x; Lewis y; Regioselective glycosylation; The Heyns rearrangement

1. Introduction

Lewis antigens are well-known as glycan-based blood group antigens,¹ which are classified as type 1 and type 2, depending on the disaccharide core structure. Type 1 Lewis antigens, Lewis a and Lewis b, have a common backbone [→3Galβ(1→3) GlcNAcβ1→] and exist widely in the membrane of erythrocytes. The type 2 core structure [→3Galβ(1→4) GlcNAcβ1→] is also found
in numerous glycoconjugates; however, the distribution of its fucosylated derivatives, Lewis x (Le\(^x\)) and Lewis y (Le\(^y\)), classified as type 2 Lewis antigens (T2-LAs), is limited to some epithelial cells and leukocytes. Notably, T2-LAs are overexpressed in various tumor cells,\(^2\) and are thus frequently used as biomarkers for the diagnosis of cancer. Furthermore, these T2-LAs are sometimes found in their sulfated form, which includes a 6-O-sulfo-GlcNAc residue.\(^3\) The Le\(^x\) determinant also plays a critical role in various biological events such as inflammation, lymphocyte homing, and infection of pathogens.\(^4\) Thus, T2-LAs have attracted much attention as promising target compounds for cancer therapy as well as for the treatment of inflammation, infectious diseases, etc.

In order to utilize T2-LAs and their derivatives as bioactive compounds, it is essential to establish versatile, widely applicable synthetic methods. A large number of reports on the synthesis of Lewis antigens have been published to date;\(^5\) however, none of them have reported the use of common key intermediates to construct T2-LAs, including their sulfated form. In the present study, we report the successful and rapid assembly of T2-LAs (3–5) via a refined disaccharide key intermediate 2, which can be readily prepared from lactulose 1 through the Heyns rearrangement method\(^6\) (Figure 1). This method is very convenient to obtain useful 2-amino-2-deoxy sugars, particularly lactosamine derivatives.\(^7\)
Figure 1. Efficient synthesis of T2-LAs (3–5) via the refined orthogonally protected T2 disaccharide derivative 2 derived from lactulose 1.

2. Results and discussion

2.1 Refinement of the molecular design of key intermediate 2

In a previous paper,\(^8\) we reported the synthesis of T2-LAs having a set of orthogonal protecting groups via the useful disaccharide intermediate 2’ (Figure 2). Compound 2’ was found to be an excellent intermediate for the synthesis of T2-LAs, but had a major drawback concerning the
removal of the anomic 4-methoxyphenyl (PMP) group: the 6-O-tert-butyldimethylsilyl (TBDMS) group was found to be labile under oxidation conditions by cerium(IV) ammonium nitrate (CAN).

It is acceptable to produce neutral, non-sulfated T2-LAs; however, in order to synthesize structurally complicated and highly bioactive sulfated T2-LAs, the protecting group at glucosamine C6 must be stable under oxidation conditions. Thus, we refined the molecular design from 2’ to 2: the stability of the tert-butyldiphenylsilyl (TBDPS) group is several hundred times higher than that of TBDMS under acidic conditions, whereas both show similar susceptibility to tetra-n-butylationmonium fluoride (TBAF). Therefore, TBDPS was selected as a more suitable protecting group for the C6 position of the glucosamine residue. Further, the 4,6-O-benzylidene protecting group for the Gal residue was replaced with the p-methoxybenzylidene group, which is more rapidly removed by hydrogenolysis.

**Figure 2.** Refinement of the molecular design of key intermediate 2.

According to our previous report, the lactosamine derivative of 6 was readily prepared from lactulose 1 via the Heyns rearrangement (Scheme 1). After removal of the acetyl protecting groups in 6, the 4’- and 6’-hydroxy moieties were protected with a p-methoxybenzylidene group to afford 7 in 69% yield via a two-step procedure. The 6-OH moiety in 7 reacted selectively with TBDPS-Cl.
in pyridine, giving 8 in moderate yield (59%). We originally controlled the selectivity in the regioselective 3′-O-benzoylation by lowering the reaction temperature (−50 °C). However, the unfavorable 3,3′-di-O-benzoyl product was formed even under the optimized conditions designed to obtain the target 3′-mono-O-benzoyl product. In the present study, we exclusively obtained the target product 2 at ambient temperature in 73% yield by employing a metal-coordinated regio- and chemoselective nucleophilic substitution method.10

**Scheme 1.** Reagents and conditions: (a) 1) MeONa / MeOH, 2) p-anisaldehyde dimethylacetal, (±)-10-camphorsulfonic acid/DMF, 30 °C, 24 h, 69% (2 steps); (b) TBDPS-Cl/pyridine, rt, 64 h, 59%; (c) Bu_2SnCl_2, PEMP, BzCl/THF, rt, 48 h, 73%. NPhth: phthalimido, PMP: 4-methoxyphenyl, PEMP: 1,2,2,6,6-pentamethylpiperidine.
2.2 On demand synthesis of Le\(^\alpha\) and Le\(^\gamma\) derivatives by regioselective α-fucosylation of 2

Glycosylation of 2 with benzyl-protected phenyl 1-thio-L-fucopyranoside (9)\(^{11}\) is the extremely unique reaction throughout the synthesis of T2-LAs (Scheme 2). In order to obtain the Le\(^\alpha\) derivative 10, the glycosylation was carried out at lower temperature (−78 °C) with a slight excess of 9 over 2; under these conditions, 10 was isolated as the sole product in 76% yield (Table 1, entry 1). Le\(^\gamma\) derivative 11 was exclusively formed in 83% yield when more than twice the amount of 9 (2.4 eq) relative to 2 was used at a higher temperature of −40 °C (entry 2). The synchronous synthesis of 10 and 11 using 9 and 2 (entries 3 and 4) is worth mentioning. Compound 11 appeared at a higher temperatures (−40 °C or −50 °C) than that in entry 1. Furthermore, both 10 and 11 were obtained efficiently in 49% and 45% yields, respectively, using an excess amount of 9 (1.8 eq) at −40 °C (entry 4). These results indicate that the synthesis of 10 and 11 can be finely controlled by varying the reaction temperature and the feed ratio. Notably, compounds 10 and 11 can be easily separated by conventional silica gel column chromatography: the \(R_f\) values for 10 and 11 in an \(n\)-hexane–EtOAc 2:1 mixture are 0.28 and 0.44, respectively.
Scheme 2. On demand and synchronous syntheses of Le\textsuperscript{x} and Le\textsuperscript{y} derivatives via glycosylation of 2 with 9 under the reaction conditions summarized in Table 1.

Table 1. One-pot synthesis of 10 and 11 under different reaction conditions.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>path</th>
<th>2(eq)</th>
<th>9(eq)</th>
<th>NIS(eq)</th>
<th>TfOH(eq)</th>
<th>T(°C)</th>
<th>time(h)</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>1.0</td>
<td>1.2</td>
<td>2.5</td>
<td>0.2</td>
<td>−78</td>
<td>1.0</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>1.0</td>
<td>2.4</td>
<td>5.0</td>
<td>0.4</td>
<td>−40</td>
<td>3.0</td>
<td>n.d.\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>1.0</td>
<td>1.2</td>
<td>2.5</td>
<td>0.2</td>
<td>−50</td>
<td>2.0</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>c</td>
<td>1.0</td>
<td>1.8</td>
<td>2.5</td>
<td>0.2</td>
<td>−40</td>
<td>1.0</td>
<td>49</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction was carried out under the indicated conditions, in CH\textsubscript{2}Cl\textsubscript{2}–Et\textsubscript{2}O using the NIS–TfOH...
activation system. \(^b\)Time for complete consumption of 9. \(^c\)Not detected.

It is very intriguing that the reactivity of the two hydroxy groups in 2 is strictly fixed as 3-OH > 2'-OH: a mono-fucosylated product at 2'-OH, that is, a type 2H \([\text{Fuca}(1\rightarrow2)\text{Galβ}(1\rightarrow4)\text{GlcNAcβ}1\rightarrow]\) derivative is not formed at all in this series of reactions. These results are consistent with our previous report,\(^8\) although the molecular design of acceptor 2 is slightly different from that of 2'. Thus, the combination of the newly designed diol acceptor 2 and donor 9 has proved to be highly effective for not only the selective synthesis of Le\(^x\) or Le\(^y\) derivatives but also the synchronous synthesis of both derivatives in a one-pot reaction. Although there are a few reports on lactosamine diol derivatives for the synthesis of T2-LAs,\(^12\) the order of reactivity of the two hydroxy groups in these derivatives is 2'-OH > 3-OH without exception, which is opposite to that for 2 and renders the preparation of Le\(^x\) derivatives difficult. Therefore, compound 2 is the most effective acceptor capable of providing both Le\(^x\) and Le\(^y\) derivatives when using 9 as the donor.

2.3 Synthesis of 6-O-sulfo-Le\(^x\) 3 and non-sulfated Le\(^x\) 4 bearing a terminal azido functionalized oligo-ethylenoxide linker

For future applications of T2-LAs, we introduced a terminal azido functionalized aglycon moiety. A highly hydrophilic oligo-(ethylenoxide) structure is advantageous for conjugation with
all kinds of bioactive compounds such as proteins, lipids, polysaccharides, and synthetic polymers. Furthermore, azides are the first choice in current biochemical and materials sciences as they allow conjugation with a range of substances having alkyne groups via a Huisgen cycloaddition (“click chemistry”).\textsuperscript{13,14} Hence, we selected a 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl group as an efficient linker for T2-LAs, as shown in Fig. 1.

Two types of Le\textsuperscript{x} derivatives (3 and 4) were synthesized following the reactions outlined in Scheme 3. In order to avoid damaging the α-L-fucoside linkage and azido group, hydrogenation of 10 was first carried out with Pd(OH)\textsubscript{2} on activated carbon (Pd(OH)\textsubscript{2}-C) under H\textsubscript{2} atmosphere. This reaction normally proceeds to completion within 10 h, and the reaction mixture must be immediately worked-up, as prolonged reaction accelerates the undesirable cleavage of the α-L-fucoside linkage due to the acidity of the reagents. After acetylation, compound 12 was obtained in 39\% yield, in two steps. Considering the low yield and our observations by TLC monitoring during the hydrogenation, removal of the benzyl protection in 11 without cleaving the α-L-fucoside linkage seems difficult. The anomeric PMP group of 12 was smoothly removed by CAN oxidation to produce 13 in 61\% yield. Compound 13 was converted into the activated glycosyl donor of trichloroacetimidate 14 through the reaction of trichloroacetonitrile with DBU in 83\% yield. The linker moiety was introduced through the glycosylation of 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-1-ethanol with 14, promoted by the addition of TMSOTf at −50 °C, affording 15 in a modest yield of 48\%. The acyl groups in 15 were removed successively by treatment with MeONa and hydrazine
monohydrate, followed by acetylation in pyridine and the removal of the TBDPS group with TBAF, affording 16 in 56% yield (4 steps). Sulfation at the 6-OH group in 16 was carried out by the addition of SO$_3$·NMe$_3$ to produce 17 in excellent yield (91%). Finally, all of the O-acetyl groups in 17 were removed with MeONa, which resulted in the target 6-O-sulfo-Le$^\alpha$ 3 in 63% yield. The non-sulfated Le$^\alpha$ derivative 4 was obtained from 15 through the reactions in steps e and h in 15% yield (5 steps). Thus, the sulfated and non-sulfated forms of the Le$^\alpha$ derivatives were efficiently synthesized from a common intermediate, 10, which could be readily prepared through the regioselective glycosylation described above.
Scheme 3. Reagents and conditions: (a) (1) Pd(OH)$_2$-C, H$_2$/MeOH, rt, 10 h, (2) Ac$_2$O/pyridine, rt, overnight, 39% (2 steps); (b) CAN/CH$_3$CN–H$_2$O, 0 °C, 6 h, 61%; (c) CCl$_3$CN, DBU/CH$_2$Cl$_2$, 0 °C, 5
h, 83%; (d) HO(CH₂CH₂O)₃C₂H₄N₃, TMSOTf, MS₄A/CH₂Cl₂, −50 °C, 8 h, 48%; (e) (1) MeONa/MeOH, rt, overnight, (2) NH₂NH₂·H₂O/EtOH, 90 °C, 7 h, (3) Ac₂O/pyridine, rt, 48 h, (4) TBAF–AcOH/THF, rt, 72 h, 56% (4 steps); (f) SO₃·NMe₃/DMF, 55 °C, 72 h, 91%; (g) MeONa/MeOH, rt, overnight, 63%; (h) MeONa/MeOH, rt, overnight, 15% (5 steps from 15).

2.4 Synthesis of Le⁹ bearing a terminal azido functionalized oligo-ethyleneoxide linker 5

The Le⁹ derivative bearing a terminal azido functionalized oligo-ethyleneoxide linker 5 was also prepared according to the reactions outlined in Scheme 4. Compound 11 was treated with Pd(OH)₂-C in THF–MeOH (1:1) mixture under H₂ atmosphere as described for the synthesis of 12. The obtained mixture was subjected to acetylation to provide pure 18. The anomeric PMP group in 18 was removed by CAN oxidation, followed by trichloroacetimidation to give 19. Glycosidation of 19 with 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-1-ethanol, which is the same acceptor employed in the synthesis of 15, proceeded very smoothly with the addition of a catalytic amount of TMSOTf at −50 °C and gave 20 within 30 min in a very good yield of 80%. Compound 20 was converted into 21 through a three-step reaction, i.e., removal of the acetyl and benzoyl groups by MeONa, removal of the phthaloyl group by hydrazine monohydrate and acetylation, which gave 21 in 64% yield. All the protecting groups in 21 were removed by successive treatment with TBAF in THF and MeONa in MeOH, which led to the target Le⁹ derivative 5 in 57% yield via two steps. Thus, the Le⁹ derivative can also be synthesized easily from 11, which in turn can be obtained by the glycosylation
described above.

Scheme 4. Reagents and conditions: (a) (1) Pd(OH)$_2$-C, H$_2$/THF–MeOH, rt, 10 h, (2) Ac$_2$O, DMAP/pyridine, rt, 24 h, 68% (2 steps); (b) (1) CAN/CH$_3$CN–H$_2$O, rt, 2 h, (2) CCl$_3$CN, DBU/CH$_2$Cl$_2$, 0 °C, 4 h, 56% (2 steps); (c) HO(CH$_2$CH$_2$O)$_3$C$_2$H$_4$N$_3$, TMSOTf, MS4A/CH$_2$Cl$_2$, −50 °C, 0.5 h, 80%; (d) (1) MeONa/MeOH, rt, 2 h, (2) NH$_2$NH$_2$·H$_2$O/EtOH, 90 °C, 13 h, (3) Ac$_2$O/pyridine, rt, overnight, 64% (3 steps); (e) (1) TBAF/THF, rt, 72 h, (2) MeONa/MeOH, rt, overnight, 57% (2 steps).

3. Conclusion

In the present study, we have demonstrated for the first time the feasibility of the on-demand synthesis of Le$^x$ and Le$^y$ derivatives, in addition to their synchronous synthesis in one-pot through the combined use of diol acceptor 2 and benzyl-protected thiophenyl fucoside donor 9.
selectivity was easily controlled by varying the reaction temperature and the ratio of 2 and 9. The derivatives of Le* and Le′ were further functionalized by introducing an oligo-ethyleneoxide-azide linker through glycosylation. The versatile set of orthogonal protecting groups of the obtained Le* derivative 15 enabled the facile and regioselective synthesis of both sulfated Le* 3 and non-sulfated Le* 4. Le′ derivative 5 was also easily prepared from 11. Thus, our method is highly efficient for the synthesis of T2-LAs and will be further applied to the preparation of a variety of bioactive materials.

4. Experimental

4.1 General methods

Anhydrous solvents were purchased from Wako Pure Chemical Industries, Ltd., and stored under Ar atmosphere prior to use. Other chemicals were used without further purification unless otherwise stated. Molecular sieves (MS) AW300 and 4A were powdered and activated over 100 °C under reduced pressure with P2O5 as desiccant prior to use. Silica gel flash column chromatography was performed on Silica Gel 60, spherical, neutrality (Nacalai Tesque), or with a CombiFlash Rf 75 Var (Teledyne Isco) on RediSep Rf Gold Normal Phase Silica columns. The reactions were monitored by TLC (silica gel 60 F254, Merck) visualized by sprayed with a mixture of H3(PMo12O40)· n H2O (12.5 g) and Ce(SO4)2· nH2O (5 g) in 10% H2SO4 (500 mL) and colored by heating at 140 °C. Glycosylation reactions at −50 °C or lower were performed on UCR-150
Optical rotations were measured with a P-1010 polarimeter (Jasco). $^1$H and $^{13}$C NMR were recorded on a DPX-400 spectrometer (Bruker). Assignments were based on homo- and heteronuclear correlation measurements, and DEPT measurements. High resolution mass spectrometry was carried out with JMS-HX110A spectrometer (Jeol, for FAB-MS) or Exactive spectrometer (Thermo Fisher Scientific, for ESI-MS). Melting points were determined with a MP-500P (Yanaco).

4.2. **4-Methoxyphenyl 4,6-O-(4-methoxybenzylidene)-β-D-galactopyranosyl-(1→4)-2-deoxy-2-phthalimido-β-D-glucopyranoside (7).**

Compound 6 (13.5 g, 16.2 mmol) in dry MeOH (250 mL) was treated with MeONa in MeOH (ca. 28wt%, 2.4 mL) at 0°C under dry atmosphere for 23 h. The formed precipitate was filtered through filter paper, and washed with MeOH. The filtrate was neutralized by addition of Dowex 50W-X8 (H$^+$ form), filtered through a cotton bed, and concentrated to dryness by vacuum pump overnight. The former precipitate and the latter residue were combined and dissolved in dry DMF (120 mL). To a solution of the mixture was added $p$-anisaldehyde dimethylacetal (3.16 mL, 18.6 mmol) under acidic conditions in the presence of catalytic amount of (±)-10-camphorsulfonic acid. After kept stirring at rt for 7 h, excess amount of Et$_3$N was added to neutralize the reaction system. The mixture was concentrated under diminished pressure, and coevaporated with toluene. The residue was purified by silica gel column chromatography (CHCl$_3$/MeOH, 20:1, v/v, containing 0.5% Et$_3$N) to provide 7.
(7.75 g, 11.1 mmol, 69 %) as a white solid.

$[\alpha]_D^{23} = -20.8$ (c 0.64, CHCl$_3$); mp 128–130 °C; $R_f$ 0.30 (CHCl$_3$/MeOH, 10:1); $^1$H NMR (400 MHz, CD$_3$OD, TMS): $\delta$ (ppm) 7.96–7.78 (m, 4H, NPhth), 7.47–6.72 (m, 8H, -C$_6$H$_4$-OMe×2), 5.70 (d, 1H, H-1$^I$), 5.56 (s, 1H, CH of p-methoxybenzylidene), 4.55 (d, 1H, J1,2 8.5 Hz, H-1$^II$), 4.28 (dd, 1H, J1,2 8.6, J2,3 11.0 Hz, H-2$^I$), 3.84 (t, 1H, J3,4=J4,5=9.6 Hz, H-4$^I$), 3.77 (s, 3H, OMe), 3.73–3.63 (m, 7H, H-5$^I$, H-2$^II$, H-3$^II$, H-5$^II$, OMe); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.23, 167.93 (C=O), 159.89, 155.21, 150.79, 134.03, 131.58, 130.38, 127.76, 123.32, 118.32, 114.32, 113.30 (aromatic), 103.99 (C1$^I$), 100.92 (CH of p-methoxybenzylidene), 97.45 (C1$^I$), 81.92 (C4$^I$), 75.53 (C4$^II$), 75.05 (C5$^I$), 72.08 (C3$^II$), 70.58 (C2$^II$), 69.70 (C3$^I$), 68.73 (C6$^II$), 66.82 (C5$^II$), 61.54 (C6$^I$), 56.07 (C2$^I$), 55.47, 55.17 (OMe); HRMS (FAB, positive ion mode, NBA) m/z = 718.2103 [M + Na]$^+$, calcd for C$_{35}$H$_{37}$NO$_{14}$Na, 718.2112.

4.3. 4-Methoxyphenyl 4,6-O-(4-methoxybenzylidene)-β-D-galactopyranosyl-(1→4)-6-O-tert-butyldipheylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (8).

To a solution of 7 (7.75 g, 11.1 mmol) in anhydrous pyridine (120 mL) was added tert-butyldiphenylchlorosilane (5.36 mL, 20.9 mmol) at rt under dry atmosphere. After stirring for 64 h, MeOH was added to quench excess reagent, and then the mixture was concentrated under reduced pressure. The residue was coevaporated with toluene and extracted with CHCl$_3$, washed
successively with satd aq NaHCO\(_3\) and brine. The organic layer was dried over MgSO\(_4\), filtered through a Celite bed and concentrated under diminished pressure. The residue was subjected to silica gel column chromatography eluting with CHCl\(_3\)/EtOAc (2:1, v/v, containing 0.1% Et\(_3\)N) to provide pure 8 (6.12 g, 6.55 mmol, 59%) as an amorphous powder.

\[ [\alpha]_D^{23} -20.6 (c 1.0, CHCl_3) \; ; \; R_f 0.33 (CHCl_3/EtOAc, 1:1), \; ^1H NMR (400 MHz, CDCl_3, TMS): \delta \]

7.96–6.68 (m, 22H, NPth, -OSi\(_2\)CMe\(_3\), -C\(_6\)H\(_4\)OMe×2), 5.75 (d, 1H, J\(_{1,2}\) 8.0 Hz, H-1\textsuperscript{I}), 5.45 (s, 1H, CH of 4-methoxybenzylidene), 4.55 (dd, 1H, J\(_{2,3}\) 10.5, J\(_{3,4}\) 8.0 Hz, H-3\textsuperscript{I}), 4.47 (d, 1H, J\(_{1,2}\) 8.0 Hz, H-1\textsuperscript{II}), 4.44 (dd, 1H, J\(_{1,2}\) 8.5, J\(_{2,3}\) 11.0 Hz, H-2\textsuperscript{I}), 4.30–4.22 (m, 2H, H-6\textsuperscript{Ia}, 3\textsuperscript{I}-OH), 4.17 (d, 1H, J\(_{3,4}\) 8.5, J\(_{2,3}\) 11.0 Hz, H-2\textsuperscript{II}), 4.14–4.08 (m, 1H, H-6\textsuperscript{Ia}), 4.06–3.97 (m, 2H, H-6\textsuperscript{Ib}, H-6\textsuperscript{II}b), 3.96 (t, 1H, J\(_{3,4}\) 9.5 Hz, J\(_{4,5}\) 3.5 Hz, H-4\textsuperscript{I}), 3.86 (t, 1H, J\(_{3,4}\) 9.5 Hz, J\(_{4,5}\) 3.5 Hz, H-4\textsuperscript{II}), 3.79 (s, 3H, OMe), 3.76–3.67 (m, 5H, H-5\textsuperscript{I}, H-2\textsuperscript{II}, OMe), 3.59 (ddd, 1H, J\(_{3,4}\) 9.5, J\(_{3,0}\) 3.5 Hz, H-3\textsuperscript{II}), 3.49 (bs, 1H, H-5\textsuperscript{II}), 2.44 (d, 1H, J\(_{3,0}\) 9.5 Hz, 3\textsuperscript{II}-OH), 2.34 (d, 1H, J\(_{2,0}\) 2.5 Hz, 2\textsuperscript{II}-OH), 1.08 (s, 9H, Me\(_3\) of tert-Bu); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \delta 168.51, 168.04 (C=O), 160.11, 155.33, 150.98, 149.54, 136.20, 135.84, 135.65, 134.09, 133.49, 132.78, 131.70, 130.04, 129.68, 127.76, 127.66, 123.81, 118.80, 114.39, 113.49 (aromatic), 103.73 (C\(_1\)\textsuperscript{II}), 101.17 (CH of 4-methoxybenzylidene), 97.42 (C\(_1\)\textsuperscript{I}), 81.06 (C\(_4\)\textsuperscript{I}), 75.32 (C\(_3\)\textsuperscript{II}), 75.09 (C\(_4\)\textsuperscript{II}), 72.81 (C\(_5\)\textsuperscript{I}), 71.19 (C\(_2\)\textsuperscript{II}), 69.75 (C\(_3\)\textsuperscript{I}), 68.67 (C\(_6\)\textsuperscript{II}), 66.93 (C\(_5\)\textsuperscript{II}), 62.41 (C\(_6\)\textsuperscript{I}), 56.37 (C\(_2\)\textsuperscript{I}), 55.61, 55.22 (OMe), 26.81 (CMe\(_3\) of tert-Bu), 19.36 (CMe\(_3\) of tert-Bu); HRMS (FAB, positive ion mode, NBA) m/z = 956.3308 [M + Na]\(^+\), calcd for C\(_{51}\)H\(_{55}\)NO\(_{14}\)SiNa, 956.3290.
4.4. 4-Methoxyphenyl 3-O-benzoyl-4,6-O-(4-methoxybenzylidene)-β-D-galactopyranosyl-(1→4)-
6-O-\textit{tert}-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (2).

To a solution of compound 8 (2.40 g, 2.57 mmol) in dry THF (50 mL) was added Bu$_2$SnCl$_2$ (78.1 mg, 0.26 mmol) and 1,2,2,6,6-pentamethylpiperidine (0.92 mL, 5.14 mmol), followed by kept
stirring for 10 min at rt under Ar atmosphere. Benzoyl chloride (0.36 mL, 2.57 mmol) was added
dropwise to the mixture at rt under Ar atmosphere. After stirring for 48 h, MeOH was added to
quench excess reagent, and the mixture was evaporated under reduced pressure. The residue was
diluted with CHCl$_3$, and washed with satd aq NaHCO$_3$ and brine. The organic layer was dried over
MgSO$_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (CHCl$_3$/EtOAc, 1:0 to 0:1, v/v, linear gradient) to
afford 2 (1.95 g, 1.88 mmol, 73%) as colorless amorphous.

$[\alpha]_D^{23} +23.9$ (c 1.0, CHCl$_3$); R$_f$ 0.41 (n-hexane/EtOAc, 1:1); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$
8.13–6.69 (m, 27H, aromatic), 5.75 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1$^i$), 5.41 (s, 1H, CH of 4-
methoxybenzylidene), 5.01 (dd, 1H, $J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz, H-3$^ii$), 4.60 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1$^{ii}$), 4.54
(t, 1H, $J_{2,3} = J_{3,4} = 8.6$ Hz, H-3$^i$), 4.50–4.41 (m, 2H, H-2$^i$, H-4$^ii$), 4.27 (m, 1H, H-6$^{ii}$a), 4.23 (s, 1H, 3$^i$
OH), 4.14–3.98 (m, 4H, H-2$^{ii}$, H-6$^i$a, H-6$^b$b, H-6$^{ii}$b), 3.86 (t, 1H, $J_{3,4} = J_{4,5} = 8.5$ Hz, H-4$^i$) 3.82–3.70
(m, 7H, H-5$^i$, OMe×2), 3.59 (s, 1H, H-5$^{ii}$), 2.17 (d, 1H, J$_{2,OH}$ 4.0 Hz, 2$^{ii}$-OH), 1.09 (s, 9H, Me$_3$ of
\textit{tert}-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.55, 168.13, 166.45 (C=O), 160.03, 155.39, 151.03,
135.94, 135.69, 134.16, 133.48, 133.35, 132.85, 131.79, 130.16, 129.98, 129.83, 129.77, 129.65,
128.53, 127.87, 127.73, 127.53, 123.67, 123.41, 118.80, 114.44, 113.49 (aromatic), 104.03 (C1I),
100.73 (CH of 4-methoxybenzylidene), 97.48 (C1I), 81.94 (C4I), 75.40 (C5I), 74.25 (C3II), 73.31
(C4II), 69.87 (C3I), 68.69 (C2II), 68.56 (C6II), 66.81 (C5II), 62.79 (C6I), 56.24 (C2I), 55.66, 55.29
(OMe), 26.88 (CMe3 of tert-Bu), 19.38 (CMe3 of tert-Bu); HRMS (FAB, positive ion mode, NBA)

\[ m/z = 1037.3693 \ [\text{M}]^+ \text{, calcd for } C_{58}H_{59}NO_{15}Si, 1037.3654. \]

4.5. 4-Methoxyphenyl 3-O-benzoyl-4,6-O-(4-methoxybenzylidene)-\( \beta \)-D-galactopyranosyl-(1→4)-
[2,3,4-tri-O-benzyl-\( \alpha \)-L-fucopyranosyl-(1→3)]-6-O-tert-butylidiphenylsilyl-2-deoxy-2-
phthalimido-\( \beta \)-D-glucopyranoside (10).

Compound 2 (817 mg, 787 μmol) was added to a solution of 9 (497 mg, 944 μmol) in anhydrous

CH2Cl2 (10 mL), and then diluted with anhydrous Et2O (20 mL). The mixture was kept stirring at rt
for 30 min under Ar atmosphere in the presence of activated powdered molecular sieves (MS) AW
300 (1.00 g). N-Iodosuccinimide (443 mg, 1.97 mmol) was added to the mixture, followed by
cooling down to −78 °C under Ar atmosphere. Triflic acid (13.8 μL, 141 μmol) in anhydrous Et2O
(124 μL) was added dropwise to the mixture. After stirring for 1 h, excess amount of Et3N was
added to terminate the reaction. After kept stirring for 15 min, the mixture was filtered through a
bed of Celite, diluted with CHCl3, washed successively with 5 wt% aq Na2S2O3, satd aq NaHCO3
and brine. The organic layer was dried over MgSO4, filtered through a bed of Celite, and
concentrated under reduced pressure. The residue was subjected to silica gel column
chromatography (n-hexane/EtOAc, 2:1, v/v, containing 0.1% Et₃N), providing pure 10 (867 mg, 596 μmol, 76%) as a white solid.

[α]D°23 −10.2 (c 0.64, CHCl₃); mp 106–107 °C; Rf 0.28 (n-hexane/EtOAc, 2:1); ¹H NMR (400 MHz, CDCl₃, TMS): δ 8.20–6.64 (m, 42H, aromatic), 5.55 (d, 1H, J₁,₂ 8.5 Hz, H-1¹), 5.52 (s, 1H, CH of 4-methoxybenzylidene), 5.13–5.07 (m, 2H, H-1³, H-1¹II), 5.13 (s, 1H, H of 4-methoxybenzylidene), 5.07 (d, 1H, J₁,₂ 8.5 Hz, H-1¹), 5.02 (s, 2H, -CH₂Ph), 4.61 (s, 2H, -CH₂Ph), 4.53–4.25 (m, 6H, H-4³, H-6¹a, H-4³II, H-6¹a, -CH₂Ph), 4.19–4.10 (m, 2H, H-2³, H-2¹), 4.01–3.96 (m, 3H, H-6¹b, H-6¹b, H-3¹II), 3.71 (s, 3H, OMe), 3.69–3.62 (m, 2H, H-5¹, H-2¹), 3.59–3.48 (m, 4H, OMe, -CH₂Ph), 3.42 (s, 1H, H-5¹II), 3.21 (s, 1H, H-4¹II), 2.38 (d, 1H, J₂,OH 3.0 Hz, 2¹II-OH), 1.13 (s, 9H, Me₃ of tert-Bu), 1.08 (d, 3H, H-6¹II, J₅,₆ 6.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 171.28, 166.35 (C=O), 159.96, 155.37, 151.18, 139.56, 139.48, 138.16, 136.11, 135.44, 134.29, 133.88, 133.53, 132.29, 130.28, 130.00, 129.96, 129.80, 128.63, 128.57, 128.39, 128.29, 128.23, 128.17, 128.05, 127.98, 127.93, 127.85, 127.78, 127.66, 127.46, 127.39, 127.25, 127.12, 127.07, 127.02, 126.78, 123.76, 118.83, 114.44, 113.39 (aromatic), 101.78 (C₁³II), 99.72 (CH of 4-methoxybenzylidene ), 98.19 (C₁³I), 97.89 (C₁I), 79.14 (C₃³II), 78.77 (C₄³II), 76.00 (C₂³II), 74.90 (CH₂Ph), 74.61 (C₄I), 74.36 (C₃³II), 73.64 (C₄³II), 73.42 (C₅I), 73.01 (CH₂Ph), 72.41 (C₃I), 71.47 (CH₂Ph), 69.63 (C₂³III), 69.08 (C₆³III), 66.63 (C₅³III), 66.45 (C₅³II), 61.79 (C₆I), 56.81 (C₂I), 55.70, 55.06 (OMe), 26.99 (Me₃ of tert-Bu), 19.74 (CMe₃ of tert-Bu), 16.63 (C₆²II) ; HRMS (FAB, positive ion mode, NBA) m/z = 1476.5502 [M + Na]⁺, calcd for C₈₅H₈₇NO₁₉SiNa, 1476.5539.
4.6. 4-Methoxyphenyl 2,3,4-tri-O-benzyl-α-L-fucopyranosyl-(1→2)-3-O-benzoyl-4,6-O-benzylidene-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-benzyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butylidiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (11).

Compound 2 (2.01 g, 1.94 mmol) was added to a solution of 9 (2.45 g, 4.66 mmol) in anhydrous CH2Cl2 (15 mL), and then diluted with anhydrous Et2O (30 mL). The mixture was kept stirring at rt for 30 min under Ar atmosphere in the presence of activated powdered MS AW 300 (2.0 g). N-Iodosuccinimide (2.18 g, 9.70 mmol) was added to the mixture, and then it was cooled down to −40 °C under Ar atmosphere. Triflic acid (68 μL, 776 μmol) in anhydrous Et2O was injected to the mixture. After stirring for 3 h, excess amount of Et3N was added to terminate the reaction. The mixture was filtered through a bed of Celite, diluted with CHCl3, washed successively with 5 wt% aq Na2S2O3, satd aq NaHCO3 and brine. The organic layer was dried over MgSO4, filtered through a Celite bed, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (n-hexane/EtOAc, 1:0 to 0:1, v/v, linear gradient), providing pure 11 (3.03 g, 1.61 mmol, 83%) as a white solid.

[α]D −28.2 (c 0.54, CHCl3); mp 90–91 °C; Rf 0.79 (n-hexane/EtOAc, 1:1); 1H NMR (400 MHz, CDCl3, TMS): δ 8.10–6.68 (57H, m, aromatic), 5.57 (1H, d, J1,2 3.6 Hz, H-1III), 5.46 (1H, s, -CH of p-methoxybenzylidene), 5.42 (1H, d, J1,2 8.0 Hz, H-1I), 5.18 (1H, d, J1,2 8.0 Hz, H-1II), 5.13 (1H, dd, J2,3 10.0, J3,4 3.8 Hz, H-3II), 4.98 (1H, d, Jgem 11.8 Hz, -CH2Ph), 4.91 (1H, m, H-5IV), 4.75–4.73 (2H, m, H-2I, H-3I), 4.67 (1H, d, J1,2 4.0 Hz, H-1IV), 4.62 (1H, d, Jgem 11.6 Hz, -CH2Ph), 4.57–4.49 (5H,
m, -CH$_2$Ph×4, H-4$^I$), 4.45–4.29 (7H, m, H-4$^II$, H-2$^II$, H-6$^III$b, -CH$_2$Ph×4), 4.21 (1H, m, H-5$^III$), 4.16 (1H, m, H-6$I$a), 4.05–3.98 (4H, m, H-6$^II$a, H-2$^III$, H-3$^IV$, -CH$_2$Ph), 3.76 (3H, s, OMe), 3.71–3.65 (2H, m, H-6$b$, H-2$^IV$), 3.55–3.52 (4H, m, OMe, H-3$^III$), 3.45 (1H, d, $J_{3,4}$ 3.2 Hz, H-4$^III$), 3.43 (1H, d, $J_{gem}$ 12.4 Hz, -CH$_2$Ph), 3.33 (1H, m, H-5$^II$), 3.20 (1H, m, H-5$^I$), 3.09 (1H, s, H-4$^IV$), 1.30 (1H, d, $J_{5,6}$ 7.2 Hz, H-6$^III$), 1.19 (1H, d, $J_{5,6}$ 6.4 Hz, H-6$^IV$), 1.11 (9H, s, Me$_3$ of tert-Bu); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.61, 159.97, 155.59, 151.32, 139.74, 139.57, 138.95, 138.78, 138.45, 138.19, 136.06, 135.15, 133.093, 133.71, 132.32, 130.18, 130.09, 129.94, 129.89, 129.70, 128.88, 128.46, 128.39, 128.33, 128.30, 128.27, 128.21, 128.18, 128.11, 128.04, 127.93, 127.82, 127.71, 127.57, 127.44, 127.37, 127.34, 127.10, 127.08, 127.05, 126.97, 126.65, 119.18, 114.45, 113.43 (C=O, aromatic), 99.86 (C1$^II$), 99.83 (CH of p-methoxybenzylidene ), 98.75 (C1$^IV$), 98.41 (C1$^I$), 98.36 (C1$^III$), 79.48 (C4$^III$), 79.38 (C3$^IV$), 78.73 (C4$^IV$), 77.96 (C3$^III$), 77.55 (C4$^I$), 76.61 (C2$^III$), 75.99 (C5$^I$), 75.07, 74.73 (CH$_2$Ph), 73.30 (C4$^II$), 73.28 (CH$_2$Ph), 73.09 (CH$_2$Ph), 72.94 (C3$^I$, CH$_2$Ph), 72.83 (C2$^IV$), 72.31 (C2$^II$), 71.38 (CH$_2$Ph), 69.14 (C6$^II$), 67.51 (C5$^III$), 66.84 (C5$^IV$), 66.33 (C5$^II$), 61.47 (C6$^I$), 56.92 (C2$^I$), 55.84, 55.10 (OMe), 26.87 (Me$_3$ of tert-Bu), 19.74 (CMe$_3$ of tert-Bu), 16.39 (C6$^III$), 16.31 (C6$^IV$); HRMS (FAB, positive ion mode, NBA) $m/z$ = 1892.7506 [M + Na]$^+$, calcd for C$_{112}$H$_{115}$NO$_{23}$SiNa, 1892.7527.

4.7. 4-Methoxyphenyl 2,4,6-tri-O-acetyl-3-O-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-
glucopyranoside (12).

Compound 10 (0.43 g, 294 μmol) was dissolved in the mixture of dry MeOH (4.0 mL) and dry THF (4.0 mL) followed by addition of Pd(OH)$_2$ on activated carbon (20%, 200 mg). After stirring at rt under H$_2$ atmosphere for 10 h, the mixture was filtered through filter paper, followed by concentration under reduced pressure. To a solution of the residue in pyridine (8 mL) was added Ac$_2$O (350 μL, 3.70 mmol) under dry atmosphere at rt overnight, and methanol was added to quench excess reagents. The mixture was concentrated and coevaporated with toluene under reduced pressure. The residue was dissolved in CHCl$_3$, and washed with satd aq NaHCO$_3$ and brine. The organic layer was dried over MgSO$_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Rf 75 system, n-hexane/EtOAc, 1:0 to 0:1, v/v, linear gradient) to afford 12 (153 mg, 116 μmol, 39%) as colorless amorphous.

$[\alpha]_{D}^{30}$ = −42.7 (c 0.05, CHCl$_3$); $R_l$ 0.32 (n-hexane/EtOAc, 1:1); $^1$H NMR (CDCl$_3$, 400 MHz, TMS): δ 7.95–6.69 (23H, m, aromatic), 5.60 (d, 1H, $J_{3.4}$ 3.2 Hz, H-4$_{III}$), 5.55 (d, 1H, $J_{1.2}$ 8.4 Hz, H-1$_I$), 5.42 (s, 1H, H-4$_{III}$), 5.29–5.02 (m, 5H, H-5$_{II}$, H-1$_{III}$, H-2$_{III}$, H-3$_{III}$), 4.98 (d, 1H, $J_{1.2}$ 4.0 Hz, H-1$_{II}$), 4.87–4.82 (m, 2H, H-3$_I$, H-2$_{II}$), 4.58–4.51 (m, 2H, H-2$_I$, H-6$_{IIIa}$), 4.37–4.30 (m, 2H, H-4$_I$, H-6$_{IIIb}$), 3.91–3.84 (m, 1H, H-5$_I$), 3.73 (s, 3H, OMe), 3.53 (bd, 1H, $J_{5.6}$ 10.0 Hz, H-5$_{III}$), 2.14–1.80 (m, 18H, Ac), 1.27 (d, 3H, $J_{5.6}$ 6.0 Hz, H-6$_{II}$), 1.12 (s, 9H, $Me_3$ of tert-Bu); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 170.87, 170.73, 170.48, 170.42, 169.80, 169.05, 165.32 (C=O), 155.57, 150.98, 136.13, 135.89, 134.56, 133.60, 130.25, 130.04, 129.94, 128.70, 128.23, 128.15, 127.84, 123.81, 118.83, 114.54
(aromatic), 99.92 (C_{1^{III}}), 97.74 (C_1), 95.45 (C_{1^{II}}), 75.56 (C_5), 74.17 (C_4), 72.00 (C_{3^{III}}), 71.60 (C_{4^{II}}), 71.48 (C_3), 71.36 (C_{5^{III}}), 69.35 (C_{2^{III}}), 68.30 (C_{3^{II}}), 67.94 (C_{2^{II}}), 67.07 (C_{4^{II}}), 64.37 (C_{5^{II}}), 61.19 (C_6), 61.10 (C_{6^{II}}), 56.60 (C_2), 55.74 (OMe), 27.01 (Me_3 of tert-Bu), 20.95, 20.87, 20.81, 20.67, 20.62 (Ac), 19.46 (CMe_3 of tert-Bu), 16.10 (C_{6^{II}}); HRMS (ESI, positive ion mode) m/z = 1340.4334 [M + Na]^+, calcd for C_{68}H_{75}NO_{24}SiNa, 1340.4360.

4.8. 2,4,6-Tri-O-acetyl-3-O-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-D-glucopyranose (13). Compound 12 (153 mg, 116 μmol) was dissolved in a mixed solution of CH_3CN-H_2O (8.0 mL – 2.0 mL) followed by addition of cerium(IV) ammonium nitrate (CAN) (190 mg, 348μmol). After stirring at rt for 6 h, the mixture was concentrated under reduced pressure to remove CH_3CN. The residue was dissolved in CHCl_3, washed successively with satd aq NaHCO_3 and brine. The organic layer was dried over MgSO_4, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with CH_3Cl/EtOAc (1:0 to 0:1, v/v, linear gradient, Rf 75 system) to afford 13 (86 mg, 70.9 μmol, 61%) as a yellowish amorphous powder. [α]D^{28} = -22.2 (c 0.1, CHCl_3); Rf 0.56 (CH_3Cl/EtOAc, 2:1); ^1H NMR (CDCl_3, 400 MHz, TMS): δ 7.94–7.41 (19H, m, aromatic), 5.58 (d, 1H, J_{3,4} 3.2 Hz, H-4_{III}), 5.39 (d, 1H, J_{3,4} 3.2 Hz, H-4_{II}), 5.29–5.16 (m, 3H, H-1_{I}, H-3_{II}, H-2_{III}), 5.13–5.00 (m, 3H, H-1_{III}, H-5_{II}, ), 5.03 (dd, 1H, J_{2,3} 10.0, J_{3,4} 10.0 Hz, H-3_{III}), 4.95 (d, 1H, J_{1,2} 4.0 Hz, H-1_{II}), 4.84–4.77 (m, 2H, H-3_{I}, H-2_{II}), 4.54 (dd, 1H, J_{5,6a} 6.5,
$J_{6a,6b} 11.2 \text{ Hz}, H-6^{III}a), 4.33-4.10 (m, 3H, H-4^I, H-6^{III}b, H-2^I), 4.04 (m, 2H, H-6^Ia, H-6^Ib), 3.84-3.79 (m, 1H, H-5^{III}), 3.47 (m, 1H, H-5^I), 2.66 (d, 1H, $J_{1,OH} 8.2 \text{ Hz}, 1$-OH), 2.13-1.85 (m, 18H, Ac), 1.25 (d, 3H, $J_{5,6} 6.0 \text{ Hz}, H-6^{II})$, 11.5 (s, 9H, CMe$_3$ of tert-Bu); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 170.89, 170.77, 170.48, 170.27, 169.82, 169.12, 165.35 (C=O), 136.26, 135.61, 134.55, 133.62, 133.45, 132.46, 130.34, 130.12, 129.77, 128.73, 128.21, 127.89, 123.77 (aromatic), 99.66 (C1$^{III}$), 95.30 (C1$^I$), 92.86 (C1$^I$), 75.79 (C5$^I$), 74.19 (C4$^I$), 72.04 (C3$^{III}$), 71.64 (C4$^I$), 71.26 (C5$^{III}$, C3$^I$), 69.36 (C2$^{III}$), 68.28 (C3$^I$), 68.05 (C2$^{II}$), 67.02 (C4$^{III}$), 64.37 (C5$^{II}$), 61.37 (C6$^I$), 61.09 (C6$^{III}$), 58.58 (C2$^I$), 27.12 (CMe$_3$ of tert-Bu), 20.99, 20.92, 20.84, 20.73, 20.71, 20.65 (Ac), 19.55 (CMe$_3$ of tert-Bu), 16.12 (C6$^{II}$); HRMS (ESI, positive ion mode) $m/z = 1234.3911$ [M + Na]$^+$, calcd for C$_{61}$H$_{69}$NO$_{23}$SiNa, 1234.3927.

4.9. 2,4,6-Tri-O-acetyl-3-O-benzoyl-β-D-galactopyranosyl-(1→4)[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate (14).

To a solution of compound 13 (32 mg, 26.4 μmol) in dry CH$_2$Cl$_2$ (5.0 mL) was added trichloroacetonitrile (53 μL, 527 μmol). After stirring at 0 °C under Ar atmosphere for 30 min, DBU (1 μL, 7.9 μmol) was added, then the reaction mixture was kept stirring at 0 °C under Ar atmosphere for 5 h. The mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($n$-hexane-ethyl acetate containing 0.5% Et$_3$N, 1:0 to 0:1, v/v, linear gradient,
Rf 75 system) to afford 14 (30 mg, 22.1 μmol, 83%) as colorless amorphous. 

[α]b\textsuperscript{27} \textsuperscript{1} \textsuperscript{1} \textsuperscript{1} −42.7 (C 0.1, CHCl\textsubscript{3}); \textit{Rf} 0.41 (\textit{n}-hexane/EtOAc 1:1 containing with Et\textsubscript{3}N); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz, TMS): \textit{δ} 8.55 (s, 1H, -CNHCCl\textsubscript{3}), 7.96−7.30 (m, 19H, aromatic), 6.36 (d, 1H, J\textsubscript{1,2} 8.8 Hz, H-1\textsuperscript{b}), 5.60 (d, 1H, J\textsubscript{3,4} 3.2 Hz, H-4\textsuperscript{III}), 5.42 (d, 1H, J\textsubscript{3,4} 2.8 Hz, H-4\textsuperscript{II}), 5.31 (dd, 1H, J\textsubscript{1,2} 10, J\textsubscript{2,3} 10 Hz, H-2\textsuperscript{III}), 5.24−5.19 (m, 2H, H-1\textsuperscript{III}, H-3\textsuperscript{II}), 5.16−5.12 (m, 2H, H-3\textsuperscript{III}, H-5\textsuperscript{II}), 5.01 (d, 1H, J\textsubscript{1,2} 4.0 Hz, H-1\textsuperscript{II}), 4.91 (t, 1H, J\textsubscript{2,3} = J\textsubscript{3,4} = 8.7 Hz, H-3\textsuperscript{I}), 4.82 (dd, 1H, J\textsubscript{1,2} 3.9, J\textsubscript{2,3} 10.9 Hz, H-2\textsuperscript{II}), 4.65−4.52 (m, 2H, H-2\textsuperscript{I}, H-6\textsuperscript{II}), 4.40−4.31 (m, 2H, H-4\textsuperscript{I}, H-6\textsuperscript{II}), 4.08 (bs, 2H, H-6\textsuperscript{Ia}, H-6\textsuperscript{Ib}), 3.86 (m, 1H, H-5\textsuperscript{III}), 3.66−3.60 (m, 1H, H-5\textsuperscript{I}), 2.13, 2.12, 2.09, 2.08, 1.93, 1.84 (s×6, 18H, Ac), 1.28 (d, 3H J\textsubscript{5,6} 6.4 Hz, H-6\textsuperscript{II}), 1.15 (s, 9H, Me\textsubscript{3} of tert-Bu); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \textit{δ} 170.86, 170.82, 170.42, 170.21, 169.77, 169.03, 165.30, 160.73 (C=O, -CNHCCl\textsubscript{3}), 136.14, 135.38, 134.59, 133.60, 133.47, 131.95, 130.24, 130.02, 129.75, 128.69, 128.20, 127.80, 123.71 (aromatic), 99.95 (C1\textsuperscript{III}), 95.39 (C1\textsuperscript{II}), 93.62 (C1\textsuperscript{I}), 90.47 (-CCl\textsubscript{3}), 76.06 (C5\textsuperscript{I}), 73.95 (C4\textsuperscript{I}), 71.98 (C3\textsuperscript{III}), 71.56 (C4\textsuperscript{II}), 71.43 (C5\textsuperscript{II}), 71.20 (C3\textsuperscript{I}), 69.31 (C2\textsuperscript{III}), 68.22 (C3\textsuperscript{II}), 68.09 (C2\textsuperscript{II}), 67.10 (C4\textsuperscript{III}), 64.38 (C5\textsuperscript{II}), 61.18 (C6\textsuperscript{III}), 60.09 (C6\textsuperscript{I}), 55.58 (C2\textsuperscript{I}), 26.98 (C(CH\textsubscript{3})\textsubscript{3} of tert-Bu), 20.95, 20.89, 20.81, 20.65, 20.61 (Ac), 19.55 (C(CH\textsubscript{3})\textsubscript{3} of tert-Bu), 16.09 (C6\textsuperscript{II}); HRMS (ESI, positive ion mode) \textit{m/z} = 1377.2974 [M + Na]\textsuperscript{+}, calcd for C\textsubscript{63}H\textsubscript{69}N\textsubscript{2}O\textsubscript{23}SiCl\textsubscript{3}Na, 1377.3024.

4.10. 2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethyl 2,4,6-tri-O-acetyl-3-O-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-
butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (15).

To a solution of compound 14 (40 mg, 29.8 μmol) in dry CH₂Cl₂ (5.0 mL) was added 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethanol (19 mg, 88.5 μmol) and activated 4Å molecular sieves (MS4A, 80 mg). After stirring at −50 °C under Ar atmosphere for 30 min, TMSOTf (2 μL, 8.85 μmol) was added to the mixture, followed by stirring at −50 °C under Ar atmosphere for 8 h. After the reaction was completed, the reaction mixture was neutralized by addition of Et₃N, filtered through a Celite bed, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CHCl₃, and washed with satd aq NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/EtOAc 1:0 to 0:1, v/v, Rf 75 system, linear gradient) to afford 15 (20 mg, 14.2 μmol, 48%) as colorless amorphous.

[α]D²⁹ −44.4 (c 0.1, CHCl₃); Rf 0.31 (n-hexane/EtOAc 2:3); ¹H NMR (CDCl₃, 400 MHz, TMS): δ 7.95–7.36 (m, 19H, aromatic), 5.58 (d, 1H, J₃,4 3.2 Hz, H-4III), 5.40 (d, 1H, J₃,4 2.4 Hz, H-4II), 5.28 (dd, 1H, J₁,₂ 8.4, J₂,₂ 10.0 Hz, H-2III), 5.22–5.17 (m, 2H, H-1III, H-3II), 5.13–5.07 (m, 3H, H-1I, H-3III, H-5III), 4.95 (d, 1H, J₁,₂ 4.0 Hz, H-1II), 4.82 (dd, 1H, J₁,₂ 4.0, J₂,₂ 10.9 Hz, H-2II), 4.77 (t, 1H, J₂,₂ =J₁,₄ 9.9 Hz, H-3I), 4.55 (dd, 1H, J₅,₆a 6.7, J₆a,₆b 11.6 Hz, H-6IIIa), 4.35–4.22 (m, 3H, H-2I, H-4I, H-6IIIb), 4.07–3.98 (m, 2H, H-6Ia, H-6Ib), 3.89–3.83 (m, 2H, H-5III, PEG), 3.65–3.25 (m, 16H, H-5I, PEG), 2.12, 2.10, 2.06, 1.91, 1.82 (s×6, 18H, Ac), 1.25 (d, 3H, J₅,₆ 6.4 Hz, H-6II), 1.15 (s, 9H, Me₃ of tert-Bu); ¹³C NMR (CDCl₃, 100 MHz): δ 170.91, 170.89, 170.51, 170.29, 169.83, 169.12, 165.36
(C=O), 136.23, 135.50, 134.48, 133.62, 133.46, 132.25, 130.29, 129.79, 129.16, 128.73, 128.24, 127.85, 123.68 (aromatic), 99.93 (C11111), 98.18 (C1111), 95.36 (C111), 75.44 (C511), 74.38 (C41), 72.06 (C31111), 71.68 (C4111), 71.54 (C311), 71.31 (C51111), 70.72, 70.64, 70.62, 70.54, 70.20, 70.16 (PEG), 69.45 (C21111), 68.53 (PEG), 68.32 (C3111), 68.04 (C2111), 67.11 (C41111), 64.33 (C5111), 61.18 (C61, C61111), 56.71 (C211), 50.79 (PEG), 27.07 (CMe3 of tert-Bu), 20.98, 20.95, 20.85, 20.71, 20.67 (Ac), 19.54 (CMe3 of tert-Bu), 16.14 (C6111); HRMS (ESI, positive ion mode) m/z = 1435.5026 [M + Na]⁺, calcd for C69H84N4O26SiNa, 1435.5041

4.11. 2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-β-D-glucopyranoside (16).

Compound 15 (51 mg, 36.8 μmol) was suspended in dry MeOH (5.0 mL) followed by the addition of ca. 28 wt-% MeONa in MeOH (3 μL, 19.7 μmol). After stirring at rt under dry atmosphere overnight, the reaction mixture was neutralized by the addition of Dowex 50W-X4 (H⁺ form), filtered through cotton, and concentrated under reduced pressure. The residue dissolved in EtOH (5.0 mL) was added NH₂NH₂·H₂O (10 μL, 205.8 μmol). After stirring at 90 °C for 7 h, reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in pyridine (5.0 mL) followed by addition of Ac₂O (65 μL, 687.6 μmol) and DMAP (3 mg, 24.6 μmol). After stirring at rt under dry atmosphere for 36 h, MeOH was added to quench excess reagents, followed by
concentration under reduced pressure. The residue was dissolved in CHCl₃, and washed with satd aq NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered through a Celite bed, and concentrated under reduced pressure. The residue was dissolved in CHCl₃, and washes with satd aq NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered through a Celite bed, and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography eluting with CH₂Cl/MeOH (1:0 to 6:1, v/v, Rf 75 system, linear gradient). The obtained compound was dissolved in dry THF (3.0 mL) followed by the addition of AcOH (5 μl, 91.8 μmol) and 1M TBAF in THF (207 μl, 207 μmol). After stirring at rt under Ar atmosphere for 72 h, the reaction mixture was concentrated under reduced pressure and extracted with CHCl₃, washed with satd aq NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with CHCl₃/MeOH (1:0 to 6:1, v/v, linear gradient, Rf 75 system) to afford the compound 16 (21 mg, 20.5 μmol, 56%, 4 steps) as colorless amorphous.

[α]D²⁶ −71.4 (c 0.2, CHCl₃); Rf 0.24 (CHCl₃/MeOH, 10:1); ¹H NMR (CDCl₃, 400 MHz, TMS): δ

6.31 (d, 1H, J₂,NHAc 9.4 Hz, NHAc), 5.42–5.38 (m, 3H, H-1″, H-4″, H-4‴″), 5.22 (dd, 1H J₂,₃ 11.0, J₃,₄ 3.4 Hz, H-3‴″), 5.10–4.98 (m, 4H, H-2″, H-5″, H-2‴″, H-3‴″), 4.73 (d, 1H, J₁,₂ 7.28 Hz, H-1‴″), 4.67 (d, 1H, J₁,₁ 8.40 Hz, H-1′), 4.50 (dd, 1H, J₅,₆a 6.2, J₆a,₆b 11.4 Hz, H-6a‴″), 4.32 (dd, 1H, J₅,₆b 7.9, J₆a,₆b 11.4 Hz, H-6b‴″), 4.03–3.90 (m, 4H, H-2′, H-4′, H-6′a, H-5‴″), 3.85–3.54 (m, 16H, H-3′, H-6′b, PEG), 3.45–3.39 (m, 2H, PEG), 3.28–3.24 (m, 1H, H-5′), 2.30 (dd, 1H, J₆a,OH 3.96, J₆b,OH 9.6 Hz, ⁶-OH), 2.19, 2.14, 2.13, 2.08, 2.05, 1.98, 1.97, 1.95 (s×8, 24H, Ac), 1.19 (d, 3H J₅,₆ 6.5 Hz, H-6″), ¹³C NMR (CDCl₃, 100 MHz): δ 171.70, 171.15, 170.87, 170.67, 170.64, 170.14, 169.79, 169.26 (C=O),
102.11 (C1), 100.40 (C1), 95.58 (C1), 75.45 (C5), 74.55 (C5), 71.73 (C4, PEG), 71.09, 71.05 (C3, C3), 70.99, 70.69, 70.67, 70.52, 70.10 (PEG), 69.47 (C2, III), 68.59 (PEG), 68.11 (C2, II), 67.05 (C4, II), 64.14 (C5, II), 60.87 (C6, I), 60.59 (C6, III), 55.97 (C2, I), 50.76 (PEG), 23.35, 21.26, 20.96, 20.86, 20.83, 20.81, 20.76, 20.70 (Ac), 15.97 (C6, II);

HRMS (ESI, positive ion mode) 

\[ m/z = 1047.3740 \ [M+Na]^+ \text{, calcld for } C_{42}H_{64}N_{4}O_{25}Na, 1047.3757. \]

4.12. Triethylammonium \{2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl \ 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-6-O-sulfonato-β-D-glucopyranoside\} (17).

Compound 16 (28 mg, 27.3 μmol) was dissolved in dry DMF (3.0 mL) and Et3N (600 μL). After stirring at 55 °C under Ar atmosphere for 20 min, the reaction mixture was added to SO3·NMe3 (145 mg, 934 μmol). After stirring at 55 °C for 72 h, MeOH (1 mL) was added to quench excess reagents, and evaporated under reduced pressure. The residue was purified by LH-20 size exclusion column chromatography eluting with MeOH to afford 17 (30 mg, 24.9 μmol, 91%) as colorless amorphous.

\[ [\alpha]_D^{23} = -83.8 \ (c \ 0.07, \ MeOH); \ \beta \ 0.17 (\text{CHCl}_3/MeOH 10:1); \] 

1H NMR (400 MHz, CDCl3, TMS): 9.46 (1H, bs, SO3H), 6.43 (d, 1H, J2,NHAc 9.6 Hz, NHAc), 5.45 (bs, 1H, H-4II), 5.39 (d, 1H, J1,2 3.8 Hz, H-1I), 5.36 (bd, 1H, J3,4 3.0 Hz, H-4II), 5.26 (d, 1H, J2,3 10.9, J3,4 3.3 Hz, H-3II), 5.10–4.97 (m, 5H, H-2II, H-3III, H-5II, H-1III, H-2III), 4.60 (d, 1H, J1,2 8.40 Hz, H-1I), 4.44 (dd, 1H, J5,6a 5.8, J6a,6b 11.2 Hz, H-6IIIa), 4.32 (bs, 2H, H-6a, H-6b), 4.26 (dd, 1H, J5,6b 8.7, J6a,6b 11.1 Hz, H-6IIIb), 4.05–
3.93 (m, 3H, H-2I, H-5III, PEG), 3.80–3.54 (m, 14H, PEG), 3.47–3.42 (m, 4H, H-3I, H-4I, H-5I, PEG), 3.20 (6H, m, N(CH$_2$CH$_3$)$_3$), 2.17, 2.14, 2.12, 2.08, 2.06, 1.96, 1.95, 1.94 (s×8, 24H, Ac), 1.40 (t, 9H, J 7.3 Hz, N(CH$_2$C$_3$)$_3$), 1.20 (d, 3H, J 5,6 6.5 Hz, H-6II);

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 171.60, 171.26, 170.83, 170.61, 170.61, 169.83, 169.80, 169.79, 169.76 (C=O), 102.04 (C1I), 99.66 (C1III), 95.53 (C1II), 74.63 (PEG), 73.79 (C3I, C5I), 73.43 (C5III), 71.83 (C4II), 71.65 (PEG), 71.29 (C3III), 70.88 (PEG), 70.72 (C4I), 70.65, 70.61, 70.46, 70.06 (PEG), 69.44 (C2III), 68.47 (PEG), 68.20 (C2II), 67.94 (C3II), 67.25 (C4III), 64.91 (C6I), 64.30 (C5II), 60.64 (C6III), 55.46 (C2I), 50.78 (PEG), 46.71 (N(CH$_2$CH$_3$)$_3$), 23.30, 21.22, 21.02×2, 20.88, 20.83, 20.77, 20.69 (Ac), 15.97 (C6II), 8.83 (N(CH$_2$CH$_3$)$_3$): HRMS (ESI, negative ion mode) $m/z$ = 1103.3360 [M – HNEt$_3^-$], calcd for C$_{48}$H$_{63}$N$_4$O$_{28}$S, 1103.3350.

4.13. 4-Methoxyphenyl 2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→2)-4,6-di-O-acetyl-3-O-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (18).

To a solution of compound 11 (1.00 g, 0.53 mmol) in 20.0 mL of THF–MeOH (1:1, v/v) was added Pd(OH)$_2$-C (20%, 0.25 g, 1.78 mmol). After stirring at rt under H$_2$ for 10 h, the reaction mixture was filtered through a Celite bed, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry pyridine (10.0 mL), followed by addition of DMAP (64 mg 0.53 mmol) and Ac$_2$O (1.0 mL, 10.6 mmol). After stirring at rt under dry atmosphere for 24 h, MeOH was added to quench
excess reagents, and then concentrated and coevaporated with toluene under reduced pressure. The residue was dissolved in CHCl$_3$, and washed with satd aq NaHCO$_3$ and brine. The organic layer was dried over MgSO$_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography eluting with n-hexane/EtOAc (1:2, v/v, containing 0.5% Et$_3$N) to afford 18 (562 mg, 0.36 mmol, 68%) as colorless amorphous. 

$[\alpha]_D^{27} = -110.1$ (c 0.03, CHCl$_3$); $R_t$ 0.63 (n-hexane/EtOAc, 1:2); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ 7.89–7.32, 7.23–6.74 (23H, m, aromatic), 5.51 (bd, 1H, $J_{3,4}$ 3.4 Hz, H-4$^{I\text{II}}$), 5.45 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1$^{I}$), 5.40 (bd, 1H, $J_{3,4}$ 2.7 Hz, H-4$^{I\text{III}}$), 5.26–5.09 (7H, m, H-1$^{I\text{IV}}$, H-4$^{I\text{IV}}$, H-3$^{I\text{II}}$, H-1$^{I\text{II}}$, H-2$^{I\text{IV}}$, H-5$^{I\text{II}}$), 4.97–4.81 (m, 4H, H-1$^{I\text{III}}$, H-3$^{I\text{IV}}$, H-2$^{I\text{III}}$, H-3$^{I}$), 4.59 (dd, 1H, $J_{1,2}$ 8.6, $J_{2,3}$ 10.0 Hz, H-2$^{I}$), 4.53–4.40 (m, 3H, H-4$^{I}$, H-6$^{I\text{a}}$, H-5$^{I\text{IV}}$), 4.30 (dd, 1H, $J_{3,5}$ 7.4, $J_{6a,6b}$ 11.4 Hz, H-6$^{I\text{b}}$), 4.23–4.15 (m, 2H, H-6$^{I\text{a}}$, H-6$^{I\text{b}}$), 3.92 (bt, 1H, $J_{1,2\text{a}}$=$J_{2,3\text{a}}$=9.0 Hz, H-2$^{I\text{II}}$), 3.85–3.80 (m, 1H, H-5$^{I\text{II}}$), 3.75 (s, 3H, OMe), 3.47–3.43 (m, 1H, H-5$^{I\text{I}}$), 2.15, 2.11, 2.09, 2.08, 2.07, 1.92, 1.86, 1.72 (s×8, 24H, Ac), 1.27–1.24 (m, 6H, H-6$^{I\text{II}}$, H-6$^{I\text{IV}}$), 1.16 (s, 9H, Me$_3$ of tert-Bu); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 171.00, 170.88, 170.67, 170.40, 170.15, 169.88, 169.85, 169.61, 169.15 (C=O), 155.69, 1150.94, 135.99, 135.41, 134.55, 133.90, 133.46, 132.04, 130.04, 129.99, 129.93, 129.96, 128.90, 128.27, 128.15, 127.89, 127.86 (aromatic), 99.86 (C1$^{I\text{II}}$), 98.16 (C1$^{I}$), 97.72 (C1$^{I\text{IV}}$), 95.92 (C1$^{I\text{III}}$), 75.42 (C5$^{I}$), 74.21 (C2$^{I\text{II}}$), 74.07 (C3$^{I\text{II}}$), 73.04 (C4$^{I}$), 72.47 (C3$^{I}$), 71.70 (C4$^{I\text{III}}$), 71.20 (C5$^{I\text{II}}$), 71.06 (C4$^{I\text{IV}}$), 68.23 (C3$^{I\text{III}}$), 67.98 (C3$^{I\text{IV}}$), 67.67 (C2$^{I\text{III}}$), 67.27(C4$^{I\text{II}}$), 66.88 (C2$^{I\text{IV}}$), 65.41 (C5$^{I\text{V}}$), 64.41 (C5$^{I\text{III}}$), 61.14, 61.08 (C6$^{I}$, C6$^{I\text{II}}$), 56.83 (C2$^{I}$), 55.80 (OMe), 27.16 (Me$_3$ of tert-Bu), 21.06, 20.97, 20.82, 20.73, 20.69×2, 20.67, 20.34 (Ac), 20.20 (Ac).
19.43 (CMe$_3$ of tert-Bu), 15.59, 15.52 (C$_6$H$_3$, C$_6$H$_4$); HRMS (ESI, positive ion mode) $m/z =$ 1570.5151 [M + Na]$^+$, calcd for C$_{78}$H$_{89}$NO$_{30}$SiNa, 1570.5136.

4.14.  2,3,4-Tri-O-acetyl-$\alpha$-$L$-fucopyranosyl-(1$\rightarrow$2)-4,6-di-O-acetyl-3-O-benzoyl-$\beta$-$D$-galactopyranosyl-(1$\rightarrow$4)[$2,3,4$-tri-O-acetyl-$\alpha$-$L$-fucopyranosyl-(1$\rightarrow$3)]-6-O-tert-butyl diphenylsilyl-2-deoxy-2-phthalimido-$\beta$-$D$-glucopyranosyl trichloroacetimidate (19).

Compound 18 (562 mg, 0.36 mmol) was dissolved in a mixed solution of CH$_3$CN (8.0 mL)–H$_2$O (2.0 mL) followed by addition of CAN (592 mg, 1.08 mmol). After stirring at rt for 2 h, the reaction mixture was extracted with CHCl$_3$, washed successively with satd aq NaHCO$_3$ and brine. The organic layer was dried over MgSO$_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl$_3$/MeOH, 30:1, containing 0.5% Et$_3$N) to afford the corresponding anomer-free compound (440 mg). To a solution of this compound (440 mg) in dry CH$_2$Cl$_2$ (10 mL) was added CCl$_3$CN (290 μL, 2.90 mmol). After stirring at 0 °C under Ar for 15 min, DBU (13 μL, 87 μmol) was added to the mixture. After kept stirring for 4 h, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl$_3$/EtOAc, 3:1, containing 0.5% Et$_3$N ) to afford 19 (314 mg, 0.20 mmol, 2 steps, 56%) as colorless amorphous.

$[\alpha]_D^{27} = -77.4$ (c 0.5, CHCl$_3$); $R_f$ 0.57 (CHCl$_3$/EtOAc 2:1); $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ 8.58 (s, 1H, NH), 7.90–7.32 (19H, m, aromatic), 6.32 (d, 1H, $J_{1,2}$ 8.8 Hz, H-1$^1$), 5.51 (bd, 1H, $J_{3,4}$ 3.6 Hz, 34
H-4\textsuperscript{II}), 5.39 (bd, 1H, J\textsubscript{3,4} 2.8 Hz, H-4\textsuperscript{III}), 5.26–5.24 (m, 2H, H-1\textsuperscript{IV}, H-4\textsuperscript{IV}), 5.23–5.16 (m, 2H, H-3\textsuperscript{II}, H-3\textsuperscript{III}), 5.14-5.07 (m, 3H, H-5\textsuperscript{III}, H-1\textsuperscript{II}, H-2\textsuperscript{IV}), 5.02–4.95 (m, 2H, H-3\textsuperscript{IV}, H-1\textsuperscript{III}), 4.94–4.84 (m, 2H, H-3\textsuperscript{I}, H-2\textsuperscript{III}), 4.63 (dd, 1H, J\textsubscript{1,2} 8.9, J\textsubscript{2,3} 10.2 Hz, H-2\textsuperscript{I}), 4.53–4.44 (m, 2H, H-4\textsuperscript{I}, H-6\textsuperscript{II}a), 4.42–4.36 (m, 1H, H-5\textsuperscript{IV}), 4.33–4.18 (m, 3H, H-6\textsuperscript{Ia}, H-6\textsuperscript{Ib}, H-6\textsuperscript{II}b), 3.92 (dd, 1H, J\textsubscript{1,2} 8.1, J\textsubscript{2,3} 9.9 Hz, H-2\textsuperscript{II}), 3.80–3.75 (m, 1H, H-5\textsuperscript{II}), 3.62–3.58 (m, 1H, H-5\textsuperscript{I}), 2.12, 2.11, 2.09, 2.08, 2.07, 1.93, 1.86, 1.71 (s×8, 24H, Ac), 1.28–1.24 (m, 6H, H-6\textsuperscript{III}, H-6\textsuperscript{IV}), 1.16 (s, 9H, CMe\textsubscript{3} of tert-Bu); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): δ 170.97, 170.86, 170.53, 170.38, 170.13, 169.86, 169.61, 168.05, 165.23, 160.74 (C=O), 136.03, 135.40, 134.65, 133.87, 133.57, 132.19, 131.45, 130.09, 130.01, 129.57, 128.95, 128.72, 128.20, 127.88, 123.72 (aromatic, C=NH), 100.01 (C1\textsuperscript{II}), 97.80 (C1\textsuperscript{IV}), 95.89 (C1\textsuperscript{III}), 94.08 (C1\textsuperscript{I}), 90.48 (CCl\textsubscript{3}), 76.03 (C5\textsuperscript{I}), 74.39 (C2\textsuperscript{II}), 73.97 (C3\textsuperscript{II}), 72.99 (C4\textsuperscript{I}), 72.12 (C3\textsuperscript{I}), 71.65 (C4\textsuperscript{III}), 71.25 (C5\textsuperscript{II}), 71.15 (C4\textsuperscript{IV}), 68.14 (C3\textsuperscript{III}), 67.86 (C3\textsuperscript{IV}), 67.83 (C2\textsuperscript{III}), 67.33 (C4\textsuperscript{II}), 67.02 (C2\textsuperscript{IV}), 65.57 (C5\textsuperscript{IV}), 64.42 (C5\textsuperscript{III}), 61.14, 61.08 (C6\textsuperscript{I}, C6\textsuperscript{III}), 55.73 (C2\textsuperscript{I}), 27.14 (CMe\textsubscript{3} of tert-Bu), 21.00, 20.98, 20.82, 20.70, 20.68, 20.65, 20.64, 20.34 (Ac), 19.66 (CMe\textsubscript{3} of tert-Bu), 16.14, 15.73 (C6\textsuperscript{III}, C6\textsuperscript{IV}); HRMS (ESI) m/z = 1340.4334 [M + Na]\textsuperscript{+}, calcd for C\textsubscript{68}H\textsubscript{75}NO\textsubscript{23}SiNa, 1340.4360.

4.15. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→2)-4,6-di-O-acetyl-3-O-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (20).
To a solution of compound 19 (314 mg, 200 μmol) and 2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethanol (65 mg, 0.30 mmol) in dry CH$_2$Cl$_2$ (5.0 mL) was added activated MS4A. The mixture was kept stirring at −50 °C for 15 min under Ar atmosphere, followed by addition of TMSOTf (11 μL, 59 μmol). After stirring at −50 °C for 30 min, Et$_3$N was added to terminate the reaction. The mixture was filtered through a Celite bed, and the filtrate was washed successively with satd aq NaHCO$_3$ and brine. The organic layer was dried over MgSO$_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (n-hexane/EtOAc 1:2, v/v, containing 0.5% Et$_3$N) to afford 20 (262 mg, 159 μmol, 80%) as colorless amorphous.

$[\alpha]_{D}^{25} -73.6$ (c 0.1, CHCl$_3$); $R_{f}$ 0.39 (n-hexane/EtOAc 2:3); $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ 7.90–7.36 (19H, m, aromatic), 5.50 (bd, 1H, $J_{3,4}$ 3.8 Hz, H-4$^{{II}}$), 5.38 (bd, 1H, $J_{3,4}$ 3.0 Hz, H-4$^{{III}}$), 5.26–5.08 (m, 7H, H-1$^{{IV}}$, H-4$^{{IV}}$, H-3$^{{III}}$, H-3$^{{II}$, H-1$^{{I}}$, H-5$^{{III}}$, H-3$^{{IV}}$), 5.02 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1$^{{I}}$), 4.98–4.93 (m, 2H, H-2$^{{IV}}$, H-1$^{{III}}$), 4.87 (dd, 1H, $J_{1,2}$ 4.0, $J_{2,3}$ 11.0 Hz, H-2$^{{III}}$), 4.78 (t, 1H, $J_{2,3}=J_{3,4}$=9.7 Hz, H-3$^{{I}}$), 4.50–4.38 (m, 3H, H-5$^{{IV}}$, H-6$^{{II}$a, H-4$^{{I}}$), 4.36–4.26 (m, 2H, H-2$^{{I}$, H-6$^{{II}$b), 4.20 (bs, 2H, H-6$^{{II}$a, H-6$^{{II}$b), 3.95–3.88 (m, 2H, H-2$^{{II}$, PEG), 3.82–3.78 (m, 1H, H-5$^{{II}$), 3.70–3.23 (m, 16H, H-5$^{{I}$, PEG), 2.11, 2.10, 2.08×2, 2.07, 1.92, 1.87, 1.73 (s×8, 24H, Ac), 1.27–1.24 (m, 6H, C$^{{6}$III, C$^{{6}$IV), 1.16 (s, 9H, Me$_3$ of tert-Bu); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 170.96×2, 170.88, 170.67, 170.38, 170.13, 169.86×2, 169.63, 165.22×2 (C=O), 136.06, 135.47, 134.46, 133.88, 133.52, 132.40, 130.06, 130.01, 129.56, 128.94, 128.73, 128.22, 127.87, 123.61 (aromatic), 99.88 (C$^{{1}$II), 98.50 (C$^{{1}$), 97.63 (C$^{{1}$IV), 95.81 (C$^{{1}$III), 75.30
(C5\textsuperscript{i}), 74.07 (C2\textsuperscript{ii}, C3\textsuperscript{ii}), 73.28 (C4\textsuperscript{i}), 72.51 (C3\textsuperscript{i}), 71.72 (C4\textsuperscript{iii}), 71.14 (C5\textsuperscript{ii}), 70.77 (C4\textsuperscript{iv}), 70.87, 70.83, 70.76, 70.72, 70.66, 70.61, 70.55, 70.15, 70.10, 68.88 (PEG), 68.19 (C3\textsuperscript{iii}), 68.03 (C2\textsuperscript{iv}), 67.75 (C2\textsuperscript{iii}), 67.30 (C4\textsuperscript{ii}), 66.93 (C3\textsuperscript{iv}), 65.41 (C5\textsuperscript{iv}), 64.34 (C5\textsuperscript{iii}), 61.27 (C6\textsuperscript{i}), 61.04 (C6\textsuperscript{ii}), 56.87 (C2\textsuperscript{i}), 50.80 (PEG), 27.15 (CMe\textsubscript{3} of tert-Bu), 21.01, 20.96, 20.83, 20.70\times 2, 20.68\times 2, 20.37 (Ac), 19.61 (CMe\textsubscript{3} of tert-Bu), 16.14, 15.65 (C6\textsuperscript{iii}, C6\textsuperscript{iv}); HRMS (ESI) m/z = 1665.5807 [M + Na]\textsuperscript{+}, calcd for C\textsubscript{79}H\textsubscript{98}N\textsubscript{4}O\textsubscript{32}SiNa, 1665.5831.

4.16. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-O-acetyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-O-acetyl-α-L-fucopyranosyl-(1→3)]-6-O-tert-butyldiphenylsilyl-2-acetamido-2-deoxy-β-D-glucopyranoside (21).

To a solution of compound 20 (262 mg, 159 μmol) in MeOH (5.0 mL) was added MeONa in MeOH solution (ca. 28 wt%; 32 μL, 159 μmol). After stirring at rt for 2 h, DOWEX 50W-X8 (H\textsuperscript{+} form) was added to neutralize the reaction system, and then filtered through cotton, concentrated under reduced pressure to obtain the crude mixture (203 mg). To a solution of the mixture (164 mg, 136 μmol) in EtOH (4.0 ml) was added NH\textsubscript{2}NH\textsubscript{2}·H\textsubscript{2}O (33 μL, 681 μmol). After stirring at 90 °C for 13 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in pyridine (5.0 mL), followed by addition of Ac\textsubscript{2}O (192 μL, 2.04 mmol) and DMAP (8 mg, 68.0 μmol). After stirring at rt under dry atmosphere overnight, MeOH (1 mL) was added to quench excess reagents, and the mixture was concentrated with toluene under reduced pressure. The
residue was dissolved in CHCl₃, washed with satd aq NaHCO₃ and brine. The organic layer was
dried over MgSO₄, filtered through a Celite bed, and concentrated under reduced pressure. The
residue was purified by silica gel chromatography (MeOH/EtOAc, 1:30, v/v, containing 1% Et₃N) to
afford 21 (151 mg, 101 μmol, 64%) as colorless amorphous.

[α]D²⁵ −115.5 (c 0.24, CHCl₃); Rt 0.51 (CHCl₃/MeOH, 10:1); ¹H NMR (400 MHz, CDCl₃, TMS): δ
7.76–7.70, 7.42–7.32 (m, 10H, aromatic), 6.11 (d, 1H, J2,3 8.6 Hz, NH), 5.39–5.37 (m, 2H, H-1IV,
H-4III), 5.33–5.28 (m, 2H, H-4I, H-1III), 5.24 (dd, 1H, J2,3 11.0, J3,4 3.0 Hz, H-3III), 5.17 (bs, 1H, H-
4IV), 5.07–4.95 (m, 5H, H-1I, H-2III, H-3IV, H-2IV, H-5III), 4.92 (dd, 1H, J2,3 10.0, J3,4 3.5 Hz, H-
3II), 4.61 (d, 1H, J1,2 7.4 Hz, H-1I), 4.45 (dd, 1H, J5,6a 6.4, J6a,6b 11.5 Hz, H-6Ia), 4.32–4.20 (m, 3H,
H-4I, H-6Ib, H-5IV), 4.15–4.04 (m, 2H, H-6Ia, H-6Ib), 3.93–3.86 (m, 4H, H-2I, H-3I, PEG×1), 3.78–
3.59 (m, 14H, H-2II, H-5II, PEG×6), 3.42–3.39 (m, 2H, PEG×1), 3.16–3.12 (m, 1H, H-5I), 2.18, 2.14,
2.13, 2.11, 2.05×2, 1.99, 1.96, 1.95, 1.91 (sx10, 3H×10, Ac×10), 1.17–1.06 (m, 15H, H-6IV, H-6III,
Me₃ of tert-Bu); ¹³C NMR (100 MHz, CDCl₃): δ 171.64, 171.37, 170.90, 170.66, 170.60×2, 170.39,
170.24, 169.86, 169.80 (C=O), 136.05, 135.46, 133.61, 132.47, 129.89, 128.07, 127.81 (aromatic),
101.48 (C1I), 100.56 (C1II), 96.64 (C1III), 96.09 (C1IV), 75.37 (C5I), 73.61 (C2II), 73.40 (C3II), 73.08
(C4I), 71.79 (C4III), 71.36, 71.07 (PEG), 70.97 (C4IV), 70.94 (C5II), 70.68, 70.67, 70.55, 70.07
(PEG), 68.19 (C3III), 68.10 (C3I, C2IV), 68.04 (C2I), 67.96 (C2III), 67.72 (C3IV), 67.33 (C4II), 65.03
(C5IV), 64.06 (C5III), 61.36 (C6I), 61.04 (C6II), 50.78 (PEG), 27.10 (Me₃ of tert-Bu), 23.48, 21.33,
20.96, 20.84×2, 20.83×3, 20.76, 20.71, (Ac), 19.57 (CMe₃ of tert-Bu) 16.14, 15.71 (C6III, C6IV);
HRMS (ESI, positive ion mode) m/z = 1510.6196 [M + NH₄]⁺, calcd for C₆₈H₁₀₀N₅O₃₁Si₁, 1510.6172.

4.17. Sodium {2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl β-D-galactopyranosyl-(1→4)-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-6-O-sulfonato-β-D-glucopyranoside} (3).

To a solution of the compound 17 (30 mg, 24.9 μmol) in MeOH (3.0 mL) was added MeONa (ca. 28 wt-%) in MeOH (2 μL, 12.4 μmol). After stirring at rt overnight, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biogel P-2 gel column eluting with H₂O to afford 3 (13 mg, 15.6 μmol, 63%) as colorless amorphous.

[α]D²⁵ −37.5 (c 0.2, MeOH); Rf 0.51 (CHCl₃/MeOH/H₂O, 5:4:1); ¹H NMR (400 MHz, CD₃OD): δ 5.04 (d, 1H, J₁,₂ 3.9 Hz, H-1Ⅱ), 4.83–4.76 (m, 1H, H-5Ⅱ), 4.59 (d, 1H, J₁,₂ 7.6 Hz, H-1Ⅲ), 4.55 (d, 1H, J₁,₂ 7.7 Hz, H-1Ⅰ), 4.44 (dd, 1H, J₅,₆a 3.4, J₆a,₆b 10.8 Hz, H-6Ⅲa), 4.31 (dd, 1H, J₅,₆b 2.5, J₆a,₆b 10.9 Hz, H-6Ⅲb), 3.98–3.84 (m, 5H, H-2Ⅰ, H-3Ⅱ, H-4Ⅰ, PEG×1), 3.82 (d, 1H, J₃,₄ 2.9 Hz, H-4Ⅲ), 3.79–3.61 (m, 18H, H-6Ⅰa, H-6Ⅰb, H-2Ⅱ, H-3Ⅰ, H-4Ⅱ, H-5Ⅲ, PEG×6), 3.56–3.1 (m, 2H, H-3Ⅲ, H-5Ⅰ), 3.47 (dd, 1H, J₁,₂ 7.6, J₂,₃ 9.6 Hz, H-2Ⅲ), 3.42–3.38 (m, 2H, PEG×1), 1.97 (s, 3H, Ac), 1.17 (d, 3H, J₅,₆ 6.5 Hz, H-6Ⅱ); ¹³C NMR (CD₃OD, 100 MHz) δ 173.83 (C=O), 103.61 (C1Ⅲ), 102.40 (C1Ⅰ), 100.15 (C1Ⅱ), 76.40 (C5Ⅰ), 76.27, 75.17, 75.07, 74.80, 73.72 (C4Ⅱ, C3Ⅲ, C5Ⅲ, C3Ⅰ, C4Ⅰ), 72.97 (C2Ⅲ), 71.51, 71.48, 71.44, 71.40, 71.35 (PEG), 71.15 (C3Ⅰ), 71.04 (PEG), 70.11 (C4Ⅲ), 69.98 (C2Ⅱ), 69.94 (PEG), 67.72 (C5Ⅰ), 66.96 (C6Ⅲ), 62.66 (C6Ⅰ), 56.71 (C2Ⅰ), 51.77 (PEG), 23.08 (Ac), 16.61 (C6Ⅱ); HRMS (ESI,
negative ion mode) $m/z = 809.2626 \ [M - Na]^-$, calcd for $C_{28}H_{49}N_{4}O_{21}S$, 809.2610.

4.18. 2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl $\beta$-D-galactopyranosyl-(1→4)-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-$\beta$-D-glucopyranoside (4).

Compound 15 (51 mg, 36.1 $\mu$mol) was suspended in dry MeOH (3.0 mL) followed by the addition of ca. 28 wt-% MeONa in MeOH (5 $\mu$L, 32.9 $\mu$mol). After stirring at rt under dry atmosphere overnight, the reaction mixture was neutralized by the addition of Dowex 50W-X4 (H$^+$ form), filtered through cotton, and concentrated under reduced pressure. The residue dissolved in EtOH (4.0 mL) was added NH$_2$NH$_2$·H$_2$O (10 $\mu$L, 212.8 $\mu$mol). After stirring at 90 °C overnight, the reaction mixture was concentrated under reduced pressure. To a solution of the residue in pyridine (3.0 mL) was added Ac$_2$O (50 $\mu$L, 530.7 $\mu$mol). After stirring at rt under dry atmosphere for 36 h, MeOH (1 mL) was added to quench excess reagents, then concentrated with toluene under reduced pressure. The residue was purified by silica gel column chromatography (CH$_3$Cl/MeOH, 1:0 to 6:1, v/v, linear gradient, Rf 75 system). The obtained compound was dissolved in dry THF (3.0 mL) followed by the addition of AcOH (3 $\mu$L, 58.6 $\mu$mol) and 1M TBAF in THF (550 $\mu$L, 550 $\mu$mol). After stirring at rt under Ar atmosphere for 3 days, the reaction mixture was concentrated under reduced pressure and extracted with CHCl$_3$, washed with satd aq NaHCO$_3$ and brine. The organic layer was dried over MgSO$_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography (CHCl$_3$/Methanol, 1:0 to 6:1, v/v, linear gradient, Rf 75
system) to afford 16. To a solution of 16 in MeOH (4.0 mL) was added MeONa in MeOH (ca. 28 wt-%, 6 μL, 40.9 μmol). After stirring at rt overnight, the reaction mixture was concentrated under reduced pressure. The residue was subjected to LH-20 size-exclusion column chromatography eluting with H₂O, and then to reversed phase column chromatography eluting with H₂O/MeOH (1:0 to 0:100, v/v, linear gradient, Rf 75 system) to afford 4 (4 mg, 5.47 μmol, 15%, 5 steps) as colorless amorphous.

\[ [\alpha]_{D}^{24} = -56.0 \ (c\ 0.04, \text{MeOH}) \]

\[ R_{f} = 0.58 \ (\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}, 5:4:1) \]

\[ ^1\text{H} \text{NMR (400 MHz, CD}_3\text{OD):} \delta \]

- 5.03 (d, 1H, \text{J}_{1,2} 3.9 \text{ Hz, H-1}\text{II}), 4.86–4.81 (m, 1H, H-5\text{II}), 4.54 (d, 1H, \text{J}_{1,2} 7.5 \text{ Hz, H-1}\text{I}), 4.44 (d, 1H, \text{J}_{1,2} 7.3 \text{ Hz, H-1}\text{III}), 3.95–3.84 (m, 6H, H-6\text{IIIa}, H-4\text{I}, H-2\text{I}, H-3\text{II}, PEG\times1), 3.82–3.60 (m, 19H, H-4\text{III}, H-6\text{a}, H-4\text{II}, H-6\text{IIIb}, H-6\text{b}, H-5\text{III}, H-2\text{II}, PEG\times6), 3.54–3.35 (m, 6H, H-2\text{III}, H-3\text{III}, H-3\text{I}, H-5\text{I}, PEG\times1), 1.97 (s, 3H, Ac), 1.18 (d, 3H, J_{5,6} 6.6 \text{ Hz, H-6}\text{II})

\[ ^{13}\text{C} \text{NMR (CD}_3\text{OD, 100 MHz):} \delta \]

- 173.90 (C=O), 103.89 (C1\text{III}), 102.40 (C1\text{I}), 100.35 (C1\text{II}), 77.42 (C5\text{I}), 76.66 (C3\text{I}, C5\text{III}), 75.17 (C3\text{II}), 74.90 (C3\text{III}), 73.69 (C4\text{II}), 72.75 (C2\text{III}), 71.69, 71.62, 71.54, 71.51 (PEG), 71.22 (C4\text{I}), 71.13 (PEG), 70.00 (C4\text{III}), 69.94 (C2\text{II}), 69.90 (PEG), 67.67 (C5\text{II}), 62.77 (C6\text{I}), 61.39 (C6\text{III}), 57.38 (C2\text{I}), 51.77 (PEG), 23.12 (Ac), 16.61 (C6\text{II}); HRMS (ESI, positive ion mode) \text{m/z} = 753.3000 [M + Na]^+, calcd for C_{28}H_{50}N_{18}O_{18}Na, 753.3018.

4.19. \textit{2-((2-azidoethoxy)ethoxy)ethoxy)ethyl} \ \alpha\text{-L-fucopyranosyl-(1\rightarrow2)}-\beta\text{-D-galactopyranosyl-(1\rightarrow4)}-\{\alpha\text{-L-fucopyranosyl-(1\rightarrow3)}\}-2\text{-acetamido-2-deoxy-}\beta\text{-D-glucopyranoside}
Compound 21 (24 mg, 16.1 μmol) was dissolved in THF (3 mL) followed by addition of AcOH (3 μl, 64.3 μmol) and TBAF (156 μL, 156 μmol). After stirring at rt under Ar atmosphere for 72 h, the reaction mixture was concentrated under reduced pressure and extracted with CHCl₃, washed successively with satd aq NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered through a Celite bed, and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography eluting with CH₃Cl/MeOH (1:0 to 6:1, v/v, linear gradient, Rf 75 system). To a solution of the obtained product in dry MeOH (3 mL) was added MeONa in MeOH (ca. 28 wt-%, 10 μL, 56.8 μmol). After stirring at rt overnight, the reaction mixture was added DOWEX 50W-X4 (H⁺ form) to neutralize the reaction system, and then filtered and concentrated under reduced pressure. The residue was purified by LH20 column chromatography eluting with MeOH to afford 5 (8 mg, 9.1 μmol, 57%, 2 steps) as colorless amorphous.

[α]D²² −104.4 (c 0.01, MeOH); Rf 0.53 (CHCl₃/MeOH/water, 5:4:1); ¹H NMR (400 MHz, CD₃OD): δ 5.17 (d, 1H, J₁,₂ 3.2 Hz, H-I⁴), 5.03 (d, 1H, J₁,₂ 3.9 Hz, H-I⁵), 4.88–4.79 (m, 1H, H-5⁴), 4.54–4.51 (m, 2H, H-I¹, H-I¹), 4.22–4.16 (m, 1H, H-5³), 3.95–3.61 (m, 29H, PEG×6, H-2¹, H-3¹, H-4¹, H-6¹a, H-6¹b, H-2², H-3², H-4², H-5², H-6²a, H-6²b, H-2³, H-3³, H-4³, H-5³, H-6³a, H-6³b, H-2⁴, H-3⁴, H-4⁴, H-5⁴, H-6⁴), 3.47–3.43 (m, 1H, H-5¹), 3.39–3.35 (m, 2H, PEG×1), 1.97 (s, 3H, Ac), 1.26–1.21 (m, 6H, H-6³, H-6⁴); ¹³C NMR (CDCl₃, 100 MHz): δ 173.89 (C=O), 102.53, 102.21 (C-I¹, C-I¹), 102.14 (C-I⁴), 100.36 (C-I³), 79.45, 77.45, 76.72, 76.64, 76.52, 75.30, 74.46, 73.71, 73.67, 71.87, 71.68, 71.60, 71.53,
71.25, 71.13, 70.79, 70.13, 69.96, 69.93 (C5\textsuperscript{I}, C4\textsuperscript{I}, C5\textsuperscript{II}, C3\textsuperscript{I}, C4\textsuperscript{II}, C2\textsuperscript{II}, C3\textsuperscript{II}, C4\textsuperscript{II}, C2\textsuperscript{III}, C3\textsuperscript{III}, C2\textsuperscript{IV}, C3\textsuperscript{IV}, C4\textsuperscript{IV}, PEG), 68.28 (C5\textsuperscript{III}), 67.65 (C5\textsuperscript{IV}), 62.94, 62.71 (C6\textsuperscript{I}, C6\textsuperscript{II}), 57.32 (C2\textsuperscript{I}), 51.78 (PEG), 23.12 (Ac), 16.86, 16.80 (C6\textsuperscript{III}, C6\textsuperscript{IV}); HRMS (ESI, positive ion mode) \(\textit{m/z} = 899.3592\) [M + Na]\textsuperscript{+}, calcd for C\textsubscript{34}H\textsubscript{60}N\textsubscript{4}O\textsubscript{22}Na, 899.3597.

4.20. A typical procedure for synchronous synthesis of 10 and 11.

Compound 2 (100 mg, 96.3 \(\mu\text{mol}\)) was added to a solution of 9 (90 mg, 170.9 \(\mu\text{mol}\)) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL), and then diluted with anhydrous Et\textsubscript{2}O (2.0 mL). The mixture was kept stirring at rt for 30 min under Ar atmosphere in the presence of activated MSAW 300 (100 mg). \(\textit{N}\)-Iodosuccinimide (55 mg, 244.5 \(\mu\text{mol}\)) was added to the mixture, and then it was cooled down to \(-40\) °C under Ar atmosphere. Triflic acid (1.7 \(\mu\text{L}, 19.3 \mu\text{mol}\)) in anhydrous Et\textsubscript{2}O (100 \(\mu\text{L}\)) was injected to the mixture. After stirring for 1 h, excess amount of Et\textsubscript{3}N was added to terminate the reaction. The mixture was filtered through a Celite bed, diluted with CHCl\textsubscript{3}, washed successively with 5\% aq Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}, satd aq NaHCO\textsubscript{3} and brine. The organic layer was dried over MgSO\textsubscript{4}, filtered through a Celite bed, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (\(n\)-hexane/EtOAc, 1:0 to 0:1, v/v, linear gradient, Rf75 system), providing 10 (69 mg, 48.4 \(\mu\text{mol}, 49\%\)) and 11 (73 mg, 43.3 \(\mu\text{mol}, 45\%\)).

Acknowledgments
This work was partially supported by JSPS KAKENHI Grant Number 24550134.

Supplementary data

$^1$H, H,H-COSY and $^{13}$C NMR spectra of compounds 2–5, 7–8, 10–21 are provided as Supplementary data online version.

References


