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Total synthesis of a unique tetrasaccharide present in the human clotting factor IX and mammalian Notch 1 receptor ☆

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ABSTRACT

The synthesis of a unique tetrasaccharide linked to the serine 61 of human clotting factor IX through an α-L-fucose residue has been achieved for the first time in excellent yield. All glycosylation and protecting group manipulation steps are high yielding and reproducible for a scale-up preparation. A sequential glycosylation strategy has been used to assemble suitably protected monosaccharide synthons for the preparation of the target tetrasaccharide.

1. Introduction

Most of the proteins found in Nature are glycosylated and contain a variety of O- and N-linked oligosaccharides attached to them.[1] These oligosaccharide structures have significant roles in the physiochemical and biological functions of a particular glycoprotein.[2] Human clotting factor IX (Factor IX, Christmas factor), a vitamin K-dependent plasma glycoprotein, plays an important role in the blood coagulation process.[3] The disease called hemophilia B is the result of the deficiency of factor IX.[4] Currently, hemophilia B is being treated with the human plasma-derived factor IX. As an alternative, a recombinant factor IX has been produced in milk to avoid the potential risks associated with human blood-derived products.[5] It is a serine protease zymogen essential for the normal hemostasis.[6] In addition to the serine protease domain, human clotting factor contains γ-carboxyglutamic acid domain and two epidermal growth factor (EGF) domains, which often mediate protein–protein interactions.[7] Due to the direct *O*-glycosyl linkage of the L-fucose moiety with serine/threonine residue, several unusual post-translational modifications can be found in the EGF modules. Several glycoproteins exist in which the L-fucose moiety is directly O-glycosidically linked to serine/threonine as part of the monosaccharide or oligosaccharide structures.[8,9] The structure of a unique tetrasaccharide O-glycosidically linked to the serine 61 of human clotting factor through an α-L-fucose residue has been reported by Harris et al. and Nishimura et al. separately (Fig. 1).[10]

In another aspect, O-linked fucose has also been found in the mammalian Notch 1 cell surface receptor, which plays an essential role in a wide variety of developmental processes including somite formation, neurogenesis, angiogenesis, and lymphoid development.[11] Irregularity in the Notch signaling due to modification of its EGF domains resulted in T-cell leukemia, cerebral autosomal arteriopathy, and leukoencephalopathy.[12] Recently, Moloney et al. reported the structure of an α-L-fucose containing tetrasaccharide, O-glycosidically linked to the Notch 1 protein, which is identical to the tetrasaccharide present in the human factor IX reported earlier (Fig. 1).[13]

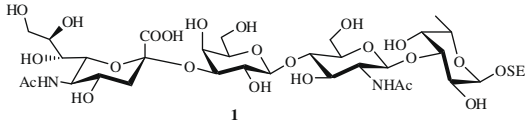

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Figure 1. Structure of the targeted tetrasaccharide as its 2-(trimethylsilyl) ethyl glycoside **1**.

Preparation of carbohydrate-derived molecules for their use in therapeutics is a thrust area in medicinal chemistry research. As mentioned earlier, treatment of hemophilia could be possible using recombinant human factor IX produced in milk.[5] However, for the successful clinical use of the recombinant factor IX, it is essential to have a thorough knowledge of the biological properties of the unique tetrasaccharide attached to it through an α-L-fucose residue. Although oligosaccharides can be isolated from natural sources, they cannot meet the desired quantity required for their biological studies. Therefore, chemical synthetic strategies are the only option left to achieve substantial amount of the oligosaccharides and their analogues. Herein, we report a concise chemical synthesis of the unique tetrasaccharide **1** found in the human clotting factor IX as its 2-trimethylsilylethyl glycoside in which α-L-fucose present at the reducing end and *N*-acetyl neuraminic acid at the non-reducing terminus. 2-(Trimethylsilyl) ethyl group (SE) can

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act as a temporary anomeric protecting group for removal whenever needed.

2. Results and discussion

In general, L-fucose can be found in the non-reducing position of the naturally occurring glycoconjugates.[14] Although a number of reports have appeared in the literature for the successful synthesis of oligosaccharides containing an α-L-fucose moiety, a practical problem of the glycosylation of L-fucose residue is the formation of the anomeric mixture.[15] Therefore, development of a glycosylation condition suitable for the stereoselective preparation of α-L-fucosides is always welcome. L-Fucose moiety present at the reducing end of the tetrasaccharide **1** in α stereochemistry poses extra challenge for its chemical synthesis. For the preparation of the tetrasaccharide **1**, suitably protected monosaccharide synthons have been prepared from commercially available reducing sugars following reported reaction conditions (Fig. 2).

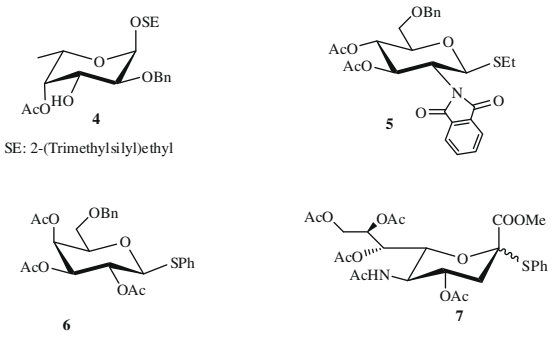
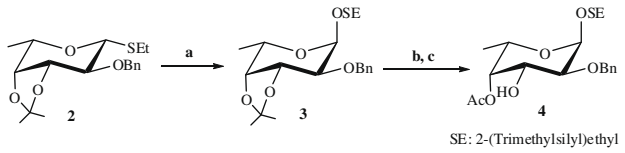


Figure 2. Suitably protected monosaccharide intermediates for the synthesis of tetrasaccharide **1**.

The synthesis of 2-(trimethylsilyl) ethyl 4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside **4** was accomplished from compound **2**[16] in three steps. The α-selective glycosylation of the thioglycoside **2** with 2-(trimethylsilyl) ethanol using methyltrifluoromethane sulfonate (MeOTf) as a thioglycoside activator[17] in dry ether furnished compound **3** in 70% yield together with its β-isomer (10%). Removal of the isopropylidene group from compound **3** using 80% aq AcOH followed by selective acetylation via orthoesterification[22] using triethyl orthoacetate and *p*-toluenesulfonic acid furnished compound **4** in 88% yield (Scheme 1). It is worth noting that a number of methods have been attempted for the preparation of compound **3**, which include: (a) the use of compound **2** and phenylthioglycoside as a glycosyl donor and NIS/TMSOTf[18] or DMTST[19] or $CuBr_2$–AgOTf–TBAB[20] as an activator; (b) the use of fucosyl trichloroacetimidate derivative instead of thioglycoside with TMSOTf as activator;[21] and (c) using a 3,4-di-*O*-acetyl-L-fucose thioglycosyl donor instead of a 3,4-*O*-isopropylidine-fucose thioglycosyl donor and the same set of activators used earlier. Unfortunately, none of them gave satisfactory α-selectivity in the glycosylation.



Scheme 1. Reagents and conditions: (a) 2-(trimethylsilyl) ethanol, MeOTf, Et_2O, 0 °C, 6 h, 70%; (b) 80% aq AcOH, 80 °C, 1 h; (c) (i) triethyl orthoacetate, *p*-TsOH, DMF, rt, 2 h; (ii) 80% aq AcOH, rt, 1 h, 88% over two steps.

Coupling of compound **4** with thioglycoside donor **5**,[23] prepared from D-glucosamine hydrochloride, in the presence of a *N*-iodosuccinimide (NIS)–trimethylsilyl trifluoromethane sulfonate (TMSOTf)[18] combination furnished disaccharide derivative **8** in 92% yield. The presence of signals at δ 5.46 (d, J = 8.3 Hz, H-1_B) and 4.71 (d, J = 3.6 Hz, H-1_A) in the ^{1}H NMR and at δ 97.7 (C-1_A) and 96.3 (C-1_B) in the ^{13}C NMR spectra confirmed the formation of compound **8**. Controlled deacetylation[24] of the compound **8** using dilute sodium methoxide gave the disaccharide acceptor **9** in quantitative yield. That the 4-*O*-acetyl group of the L-fucose moiety remained intact under deacetylation conditions may be due to the steric crowding around it. Selective glycosylation of disaccharide diol acceptor **9** with thioglycoside donor **6**[25] in the presence of NIS–TMSOTf afforded the trisaccharide derivative **10** in 92% yield. The exclusive β-selective glycosylation took place at the 4-hydroxy position of the disaccharide acceptor **9** due to the presence of the *N*-phthalimido group at the C-2 position. Signals at δ 5.22 (d, J = 8.4 Hz, H-1_B), 4.67 (d, J = 3.6 Hz, H-1_A), 4.51 (d, J = 7.9 Hz, H-1_C) in the ^{1}H NMR and at δ 101.4 (C-1_C), 97.8 (C-1_A), 96.2 (C-1_B) in the ^{13}C NMR spectra confirmed the formation of compound **10**. Removal of the *N*-phthalimido group from the trisaccharide derivative **10** using ethylenediamine[26] followed by *N*-acetylation furnished the trisaccharide acceptor **11** in 88% yield. α-Selective glycosylation of trisaccharide acceptor **11** with sialic acid thioglycoside donor **7**[27] in the presence of NIS–TfOH followed by conventional acetylation of the reaction mixture furnished tetrasaccharide derivative **12** in 42% yield (Scheme 2). Signature signals at δ 5.58–5.51 (m, 1H, H-8_D), 5.34 (dd, J = 8.7, 2.4 Hz, H-7_D), 4.79 (d, J = 10.0 Hz, H-1_B), 4.77 (d, J = 3.8 Hz, H-1_A), 4.54 (d, J = 7.9 Hz, H-1_C), 2.58 (dd, J = 12.7, 4.5 Hz, H-3_{eD}) and 1.69 (t, J = 12.3 Hz, H-3_{aD}) in the ^{1}H NMR and at δ 100.6 (C-1_A), 97.7 (C-1_B), 97.1 (C-1_C), 96.9 (C-2_D) in the ^{13}C NMR spectra confirmed the formation of compound **12**. Hydrogenolysis of the tetrasaccharide derivative **12** over 20% $Pd(OH)_2$–C[28] followed by saponification using sodium methoxide afforded pure tetrasaccharide **1** as its sodium salt of 2-(trimethylsilyl) ethyl glycoside in 74% yield. The presence of signals at δ 4.95 (d, J = 3.6 Hz, H-1_A), 4.70 (d, J = 7.0 Hz, H-1_B), 4.57 (d, J = 7.8 Hz, H-1_C) in the ^{1}H NMR and at δ 103.5 (C-1_C), 100.0 (C-2_D), 99.7 (C-1_B), 98.5 (C-1_A) in the ^{13}C NMR spectrum confirmed the presence of the required glycosyl linkages in the target tetrasaccharide **1**. Structures of all the intermediates and final tetrasaccharide **1** have been unambiguously established with the help of 1D and 2D NMR spectral analysis.

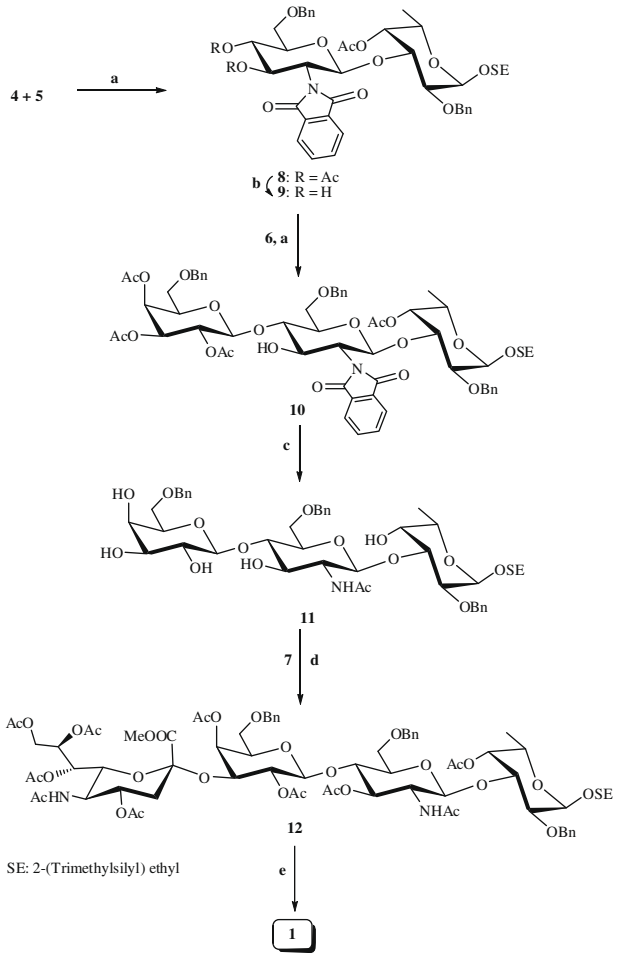
3. Conclusion

In conclusion, a unique tetrasaccharide **1** present in the human clotting factor IX and mammalian Notch 1 has been synthesized for the first time in a concise manner. In the synthetic strategy, the α-L-fucose moiety present at the reducing end has been prepared by tuning the reaction condition after a series of experimentation. Condensation of *N*-acetyl neuraminic acid derivative (sialic acid) at the non-reducing terminus was achieved in moderate yield. The target compound was achieved with the minimum number of steps using regioselective glycosylation and functional group manipulation. All intermediate steps are high yielding, reproducible, and can be used for a scale-up preparation of the target compound.

4. Experimental

4.1. General methods

All the reactions were monitored by thin layer chromatography over silica gel-coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4) sprayed plates in hot plate. Silica gel 230–400 mesh was used for column



Scheme 2. Reagents and conditions: (a) NIS, TMSOTf, MS 4 Å, CH_2Cl_2, −40 °C, 45 min, 92% for **8**, 92% for **10**; (b) CH_3ONa, CH_3OH, rt, 2 h, quantitative; (c) (i) ethylenediamine, *n*-butanol, 80 °C, 6 h; (ii) acetic anhydride, pyridine, rt, 12 h; (iii) CH_3ONa, CH_3OH, rt, 6 h, 88% in three steps; (d) (i) NIS, TfOH, CH_3CN, MS 3 Å, −30 to −20 °C, 24 h, 42%; (ii) acetic anhydride, pyridine, rt, 8 h; (e) (i) H_2, 20% $Pd(OH)_2$–C, CH_3OH, rt, 24 h; (ii) CH_3ONa, CH_3OH, rt, 8 h then few drops of H_2O, 5 h, 74%.

chromatography. ^1H and ^{13}C NMR, 2D COSY, HSQC, and NOESY spectra were recorded on Brucker Advance DPX 300 MHz using $CDCl_3$ and D_2O as solvents and TMS as internal reference unless stated otherwise. Chemical shift value is expressed in δ ppm. ESI-MS were recorded on a MICROMASS QUTTRO II triple quadrupole mass spectrometer. Elementary analysis was carried out on Carlo ERBA-1108 analyzer. Optical rotations were measured at 25 °C on a Rudolf Autopol III polarimeter. Commercially available grades of organic solvents of adequate purity are used in many reactions.

4.1.1. 2-(Trimethylsilyl) ethyl 2-*O*-benzyl-3,4-*O*-isopropylidine-α-L-fucopyranoside 3

To a solution of **2** (1.3 g, 3.84 mmol), 2-(trimethylsilyl) ethanol (600 μL, 4.2 mmol), and freshly activated powdered MS 4 Å (1.5 g) in anhydrous Et_2O (60 mL) was added MeOTf (870 μL, 7.7 mmol) at 0 °C, and the reaction mixture was allowed to stir at 0 °C for 6 h. The reaction mixture was quenched by the addition of Et_3N (1 mL) and diluted with CH_2Cl_2 (40 mL). The organic layer was washed with water (2 × 40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane–EtOAc (19:1) as eluant to give compound **3** (1.05 g, 70%); $[\alpha]_D^{25} = -78$ (*c* 1.0, $CHCl_3$); IR (neat): 2361, 1454, 1379, 1247, 1216, 1080, 863, 838, 760, 698, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.22 (m, 5H, aromatic protons), 4.77 (d, *J* = 12.6 Hz, 1H, PhCH_2), 4.72 (d, *J* = 3.5 Hz, 1H, H-1), 4.67 (d, *J* = 12.6 Hz, 1H, PhCH_2), 4.29 (dd, *J* = 7.9, 5.5 Hz, 1H, H-3), 4.11–4.04 (m, 1H, H-5), 4.00 (dd, *J* = 5.5, 2.5 Hz, 1H, H-4), 3.76–3.67 (m, 1H, OCH_{2a}), 3.47 (dd, *J* = 8.0, 3.5 Hz, 1H, H-2), 3.49–3.39 (m, 1H, OCH_{2b}), 1.38, 1.32 (2s, 6H, C(CH_3)$_2$), 1.26 (d, *J* = 6.7 Hz, 3H, CCH_3), 1.07–0.83 (m, 2H, SiCH_2), 0.00 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4–127.5 (aromatic carbons), 108.6 (*C*(CH_3)$_2$), 96.4 (C-1), 76.3 (C-2), 76.2 (C-4), 75.9 (C-3), 72.1 (PhCH_2), 65.3 (OCH_2), 62.9 (C-5), 28.1 (CCH_3), 26.3 (CCH_3), 17.8 (SiCH_2), 16.2 (CCH_3), −1.5 (3C, Si(CH_3)$_3$); ESI-MS: *m/z* = 417.8 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{34}O_5Si$ (394.22): C, 63.92; H, 8.69. Found: C, 63.70; H, 8.95.

4.1.2. 2-(Trimethylsilyl) ethyl 4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside 4

A solution of compound **3** (820 mg, 2.08 mmol) in 80% aq AcOH (15 mL) was stirred at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and co-evaporated with toluene (3 × 20 mL) to give the crude diol. To the solution of the diol derivative (730 mg) in dry DMF (5 mL) were added triethyl orthoacetate (750 μL) and *p*-TsOH (50 mg), and the reaction mixture was allowed to stir at room temperature for 2 h. After complete consumption of the starting material, the reaction mixture was neutralized with triethylamine (0.5 mL), and solvents were removed under reduced pressure. A solution of the crude mass in 80% aq AcOH (10 mL) was allowed to stir at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and co-evaporated with toluene (3 × 20 mL) to give the crude product, which was purified over SiO_2 using hexane–EtOAc (3:1) as eluant to give pure compound **4** (720 mg, 88%) as syrup; $[\alpha]_D^{25} = -53$ (*c* 1.0, $CHCl_3$); IR (neat): 2924, 2360, 1736, 1246, 1219, 1096, 1038, 839, 762, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.23 (m, 5H, aromatic protons), 5.17 (d, *J* = 2.9 Hz, 1H, H-4), 4.75 (d, *J* = 3.5 Hz, 1H, H-1), 4.67 (d, *J* = 11.9 Hz, 1H, PhCH_2), 4.59 (d, *J* = 11.9 Hz, 1H, PhCH_2), 4.09 (dd, *J* = 10.0, 3.6 Hz, 1H, H-3), 4.01–3.94 (m, 1H, H-5), 3.72–3.64 (m, 1H, OCH_{2a}), 3.62 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2), 3.41–3.33 (m, 1H, OCH_{2b}), 2.12 (s, 3H, COCH_3), 1.06 (d, *J* = 6.6 Hz, 3H, CCH_3), 0.97–0.84 (m, 2H, SiCH_2), 0.00 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8 (COCH$_3$), 138.3–127.7 (aromatic carbons), 96.3 (C-1), 76.9 (C-2), 73.1 (C-4), 72.7 (PhCH_2), 67.9 (C-3), 65.1 (OCH_2), 64.6 (C-5), 20.8 (COCH_3), 18.0 (SiCH_2), 16.1 (CCH_3), −1.3 (3C, Si(CH_3)$_3$); ESI-MS: *m/z* = 414.0 $[M+NH_4^+]^+$. Anal. Calcd for $C_{20}H_{32}O_6Si$ (396.20): C, 60.58; H, 8.13. Found: C, 60.35; H, 8.37.

4.1.3. 2-(Trimethylsilyl) ethyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside 8

To a solution of compound **4** (650 mg, 1.64 mmol) and compound **5** (1.0 g, 1.90 mmol) in anhydrous CH_2Cl_2 (15 mL) was added freshly activated powdered MS 4 Å (1.0 g). The reaction mixture was allowed to stir under argon at room temperature for 1 h. After cooling the reaction mixture to −40 °C, *N*-iodosuccinimide (NIS; 530 mg, 2.36 mmol) was added to it followed by TMSOTf (5 μL), and the reaction mixture was allowed to stir at −40 °C for 45 min. The reaction mixture was quenched by the addition of triethylamine (10 μL), filtered through a Celite® bed, and washed with CH_2Cl_2 (3 × 25 mL). The organic layer was washed successively with 10% aq $Na_2S_2O_3$ and water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexane–EtOAc (7:2) as eluant to afford pure compound **8** (1.3 g, 92%) as a white solid; mp 129–30 °C; $[\alpha]_D^{25} = -37$ (*c* 1.0, $CHCl_3$); IR (KBr): 2950, 2895, 1748, 1718, 1386, 1238, 1054, 861, 836, 745, 722, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88–7.86 (m, 2H, aromatic protons), 7.76–7.72 (m, 2H, aromatic protons), 7.40–7.23 (m, 10H, aromatic protons), 5.83 (dd, *J* = 10.4,

10.4 Hz, 1H, H-3_B), 5.46 (d, J = 8.3 Hz, 1H, H-1_B), 5.16 (t, J = 9.6 Hz, 1H, H-4_B), 5.03 (d, J = 2.6 Hz, 1H, H-4_A), 4.88 (d, J = 12.4 Hz, 1H, PhCH_2), 4.71 (d, J = 3.6 Hz, 1H, H-1_A), 4.62 (d, J = 12.4 Hz, 1H, PhCH_2), 4.51 (br s, 2H, PhCH_2), 4.38–4.28 (m, 2H, H-3_A, H-2_B), 3.97–3.81 (m, 2H, H-5_A, H-5_B), 3.74–3.41 (m, 5H, H-2_A, H-6_{abB}, OCH_{2ab}), 1.91, 1.85, 1.53 (3s, 9H, 3 COCH_3), 0.94 (d, J = 6.6 Hz, 3H, CCH_3), 1.02–0.79 (m, 2H, SiCH_2), 0.00 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 169.9 (2 C, *C*OCH$_3$), 169.4 (*C*OCH$_3$), 167.6 (2 *C*OPhth), 139.1–123.3 (aromatic carbons), 97.7 (C-1_A), 96.3 (C-1_B), 75.5 (C-3_A), 74.0 (C-2_A), 73.6 (2 C, 2 PhCH$_2$), 73.2 (C-5_B), 71.1 (C-4_A), 70.9 (C-3_B), 70.1 (C-4_B), 70.0 (C-6_B), 65.5 (OCH$_2$), 64.5 (C-5_A), 55.1 (C-2_B), 20.6, 20.4, 19.8 (3C, 3 *C*OCH$_3$), 17.9 (SiCH$_2$), 15.9 (*C*CH$_3$), −1.3 (3C, Si(CH$_3$)$_3$); ESI-MS: m/z = 880.2 [M+NH$_4$]$^+$. Anal. Calcd for $C_{45}H_{55}NO_{14}Si$ (861.34): C, 62.70; H, 6.43. Found: C, 62.52; H, 6.68.

4.1.4. 2-(Trimethylsilyl) ethyl 6-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside 9

A solution of **8** (1.0 g, 1.16 mmol) in 0.1 M CH$_3$ONa in CH$_3$OH (25 mL) was allowed to stir at room temperature for 2 h and neutralized with Dowex-50W X8 (H$^+$). The reaction mixture was filtered and evaporated to dryness to give compound **9** (900 mg, quantitative) as a white solid; mp 58–60 °C; $[\alpha]_D^{25} = -70$ (c 1.0, CHCl$_3$); IR (KBr): 2361, 1714, 1389, 1216, 1077, 761, 670 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.86 (dd, J = 5.5, 3.1 Hz, 2H, aromatic protons), 7.71 (dd, J = 5.4, 3.1 Hz, 2H, aromatic protons), 7.37–7.19 (m, 10H, aromatic protons), 5.26 (d, J = 8.2 Hz, 1H, H-1_B), 5.04 (d, J = 2.6 Hz, 1H, H-4_A), 4.86 (d, J = 12.4 Hz, 1H, PhCH_2), 4.68 (d, J = 3.6 Hz, 1H, H-1_A), 4.60 (d, J = 12.5 Hz, 1H, PhCH_2), 4.56 (br s, 2H, PhCH_2), 4.43 (dd, J = 10.5, 7.9 Hz, 1H, H-3_B), 4.32 (dd, J = 10.1, 3.3 Hz, 1H, H-3_A), 4.13 (dd, J = 10.8, 8.3 Hz, 1H, H-2_B), 3.91 (dd, J = 12.9, 6.3 Hz, 1H, H-5_A), 3.79–3.53 (m, 5H, H-2A, H-4_B, H-6_{abB}, OCH_{2a}), 3.52–3.42 (m, 2H, H-5_B, OCH_{2b}), 1.46 (s, 3H, COCH_3), 1.04–0.81 (m, 2H, SiCH_2), 0.92 (d, J = 6.4 Hz, 3H, CCH_3), 0.00 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 170.1 (*C*OCH$_3$), 168.2 (2C, 2*C*OPhth), 139.2–123.3 (aromatic carbons), 97.7 (C-1_A), 96.0 (C-1_B), 74.5 (C-3_A), 73.9 (C-2_A), 73.8 (C-4_B), 73.7 (2 C, C-5_B, PhCH_2), 73.4 (PhCH_2), 71.0 (2C, C-4_A, C-3_B), 70.3 (C-6_B), 65.4 (OCH_2), 64.5 (C-5_A), 56.6 (C-2_B), 19.7 (COCH$_3$), 17.8 (SiCH$_2$), 16.0 (CCH$_3$), −1.3 (3C, Si(CH$_3$)$_3$); ESI-MS: m/z = 796.3 [M+NH$_4$]$^+$. Anal. Calcd for $C_{41}H_{51}NO_{12}Si$ (777.32): C, 63.30; H, 6.61. Found: C, 63.10; H, 6.86.

4.1.5. 2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-6-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside 10

To a solution of compound **9** (720 mg, 0.93 mmol) and compound **6** (540 mg, 1.10 mmol) in anhydrous CH$_2$Cl$_2$ (15 mL) was added freshly activated powdered MS 4 Å (1.0 g), and the reaction mixture was allowed to stir under argon at room temperature for 1 h. After cooling the reaction mixture to −40 °C, NIS (300 mg, 1.33 mmol) was added to it followed by TMSOTf (5 μL), and the reaction mixture was allowed to stir at −40 °C for 45 min. The reaction mixture was quenched by the addition of triethylamine (10 μL), filtered through a Celite® bed, and washed with CH$_2$Cl$_2$ (50 mL). The organic layer was washed successively with 10% aq Na$_2$S$_2$O$_3$ and water, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified over SiO$_2$ using hexane–EtOAc (3:2) as eluant to afford pure compound **10** (980 mg, 92%) as a white solid; mp 150–52 °C; $[\alpha]_D^{25} = -37$ (c 1.0, CHCl$_3$); IR (KBr): 3021, 2360, 1745, 1384, 1216, 1086, 761, 670 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.86 (dd, J = 5.0, 3.4 Hz, 2H, aromatic protons), 7.70 (dd, J = 5.4, 3.0 Hz, 2H, aromatic protons), 7.37–7.12 (m, 15H, aromatic protons), 5.33 (d, J = 3.1 Hz, 1H, H-4_C), 5.22 (d, J = 8.4 Hz, 1H, H-1_B), 5.13 (dd, J = 10.4, 8.0 Hz, 1H, H-2_C), 5.04 (d, J = 2.7 Hz, 1H, H-4_A), 4.91 (dd, J = 10.3, 3.3 Hz, 1H, H-3_C), 4.88 (d, J = 12.5 Hz, 1H, PhCH_2), 4.67 (d, J = 3.6 Hz, 1H, H-1_A), 4.65–4.48 (m, 4H, H-3_B, PhCH_2), 4.51 (d, J = 7.9 Hz, 1H, H-1_C), 4.45–4.25 (m, 3H, H-3_A, PhCH_2), 4.20 (dd, J = 10.7, 8.4 Hz, 1H, H-2_B), 3.95–3.87 (m, 1H, H-5_A), 3.84–3.57 (m, 7H, H-2_A, H-4_B, H-5_B, H-6_{abB}, H-5_C, OCH_{2a}), 3.51–3.42 (m, 2H, H-6_{aC}, OCH_{2b}), 3.38–3.32 (m, 1H, H-6_{bC}), 2.02, 1.98, 1.95, 1.43 (4s, 12H, 4 COCH_3), 0.92 (d, J = 6.4 Hz, 3H, CCH_3), 1.05–0.80 (m, 2H, SiCH_2), 0.00 (br s, 9H, Si(CH_3)$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 170.0, 169.9, 169.7, 169.1 (4 *C*OCH$_3$), 167.8 (2C, 2*C*OPhth), 139.2–123.1 (aromatic carbons), 101.4 (C-1_C), 97.8 (C-1_A), 96.2 (C-1_B), 81.7 (C-2_A), 74.9 (C-5_C), 74.4 (C-3_A), 73.7 (C-5_B), 73.6 (PhCH$_2$), 73.5 (PhCH$_2$), 73.4 (PhCH_2), 72.2 (C-4_B), 71.0 (C-3_C), 70.9 (C-4_A), 69.3 (C-3_B), 68.9 (C-2_C), 67.5 (C-6_C), 67.4 (C-6_B), 67.2 (C-4_C), 65.4 (OCH$_2$), 64.5 (C-5_A), 56.4 (C-2_B), 20.7, 20.6, 20.5, 19.7 (4C, 4COCH$_3$), 17.9 (SiCH$_2$), 16.0 (CCH$_3$), −1.3 (3C, Si(CH$_3$)$_3$); ESI-MS: m/z = 1178.6 [M+Na]$^+$. Anal. Calcd for $C_{60}H_{73}NO_{20}Si$ (1155.45): C, 62.32; H, 6.36. Found: C, 62.10; H, 6.60.

4.1.6. 2-(Trimethylsilyl) ethyl 6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2-*O*-benzyl-α-L-fucopyranoside 11

To a solution of compound **10** (760 mg, 0.66 mmol) in *n*-butanol (15 mL) was added ethylene diamine (1 mL), and the reaction mixture was allowed to stir at 80 °C for 6 h. The solvents were evaporated off under reduced pressure and co-evaporated with toluene (3 × 10 mL). A solution of the crude product in Ac$_2$O and pyridine (5 mL, 1:1, v/v) was stirred at room temperature for 12 h. The solvents were removed under reduced pressure and co-evaporated with toluene (3 × 10 mL). A solution of the acetylated product in 0.1 M CH$_3$ONa in CH$_3$OH (10 mL) was allowed to stir at room temperature for 6 h and neutralized with Dowex 50W-X8 (H$^+$) and filtered. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified over SiO$_2$ using EtOAc–methanol (19:1) as eluant to give pure compound **11** (520 mg, 88%) as a white solid; mp 136 °C; $[\alpha]_D^{25} = -38$ (c 1.0, CHCl$_3$); IR (KBr): 2924, 2360, 1644, 1216, 1057, 766, 670 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.34–7.19 (m, 15H, aromatic protons), 4.78–4.71 (m, 3H, H-1_A, H-1_B, PhCH_2), 4.59 (d, J = 12.3 Hz, 1H, PhCH_2), 4.55–4.44 (m, 4H, PhCH_2), 4.29 (d, J = 7.7 Hz, 1H, H-1_C), 4.13 (dd, J = 10.1, 3.3 Hz, 1H, H-3_A), 3.98–3.79 (m, 5H, H-2_A, H-5_A, H-3_B, H-4_C, H-6_{aC}), 3.77–3.53 (m, 10H, H-4_A, H-2_B, H-4_B, H-5_B, H-6_{abB}, H-2_C, H-3_C, H-6_{bC}, OCH_{2a}), 3.49–3.38 (m, 2H, H-5_C, OCH_{2b}), 1.83 (s, 3H, COCH_3), 1.19 (d, J = 6.4 Hz, 3H, CCH_3), 1.04–0.95 (m, 1H, SiCH_{2a}), 0.92–0.82 (m, 1H, SiCH_{2b}), 0.00 (br s, 9H, Si(CH_3)$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 172.7 (NH*C*OCH$_3$), 138.6–127.6 (aromatic carbons), 103.0 (C-1_C), 98.4 (C-1_A), 96.7 (C-1_B), 79.1 (C-4_B), 77.5 (C-3_A), 74.4 (C-3_C), 73.8 (C-3_B), 73.6 (C-5_B), 73.5 (PhCH$_2$), 73.5 (C-5_C), 73.4 (PhCH$_2$), 72.7 (PhCH$_2$), 72.4 (C-2_A), 70.5 (C-2_C), 70.2 (C-4_A), 69.3 (C-6_C), 69.1 (C-6_B), 68.8 (C-4_C), 65.5 (C-5_A), 65.2 (OCH$_2$), 57.5 (C-2_B), 23.2 (NHCOCH$_3$), 18.0 (SiCH$_2$), 16.2 (CCH$_3$), −1.5 (3 C, Si(CH$_3$)$_3$); ESI-MS: m/z = 899.9 [M+1]$^+$. Anal. Calcd for $C_{46}H_{65}NO_{15}Si$ (899.41): C, 61.38; H, 7.28. Found: C, 61.20; H, 7.52.

4.1.7. 2-(Trimethylsilyl) ethyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-2,4-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranoside 12

To a solution of compound **11** (500 mg, 0.55 mmol) and compound **7** (650 mg, 1.11 mmol) in anhydrous CH$_3$CN (10 mL) was added freshly activated powdered MS 3 Å (500 mg), and the reaction mixture was allowed to stir under argon at room temperature for 1 h. After cooling the reaction mixture to −30 °C, NIS (300 mg, 1.33 mmol) was added to it followed by TfOH (5 μL), and the reaction mixture was allowed to stir at −20 °C for 24 h. The reaction mixture was quenched by the addition of triethylamine (10 μL), filtered through a Celite® bed, and washed with CH$_2$Cl$_2$ (50 mL). The

organic layer was washed successively with 10% aq $Na_2S_2O_3$ and water, dried (Na_2SO_4), and concentrated under reduced pressure. A solution of the crude product in Ac_2O and pyridine (5 mL, 1:1, v/v) was stirred at room temperature for 8 h. The solvents were removed under reduced pressure and co-evaporated with toluene (3 × 15 mL), and the crude product was purified over SiO_2 using $CHCl_3$–CH_3OH (49:1) as eluant to afford pure compound **12** (360 g, 42%) as a white solid; mp 94–95 °C; $[\alpha]_D^{25} = -64$ (*c* 1.0, $CHCl_3$); IR (KBr): 3020, 2361, 1740, 1651, 1217, 766, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.19 (m, 15H, aromatic protons), 5.69 (d, *J* = 9.6 Hz, 1H, N*H*COCH$_{3D}$), 5.58–5.51 (m, 1H, H-8$_D$), 5.34 (dd, *J* = 8.7, 2.4 Hz, 1H, H-7$_D$), 5.21–5.14 (m, 2H, H-4$_C$, N*H*COCH$_{3B}$), 5.07–4.99 (m, 2H, H-4$_A$, H-3$_B$), 4.96–4.77 (m, 3H, H-2$_C$, H-4$_D$, PhC*H*$_2$), 4.79 (d, *J* = 10.0 Hz, 1H, H-1$_B$), 4.77 (d, *J* = 3.8 Hz, 1H, H-1$_A$), 4.54 (d, *J* = 7.9 Hz, 1H, H-1$_C$), 4.64–4.35 (m, 7H, H-3$_A$, H-9$_{aD}$, PhC*H*$_2$), 4.17–4.10 (m, 1H, H-5$_D$), 4.08–3.90 (m, 4H, H-5$_A$, H-2$_B$, H-4$_B$, H-9$_{bD}$), 3.84 (br s, 3H, COOC*H*$_3$), 3.81–3.55 (m, 8H, H-2$_A$, H-5$_B$, H-3$_C$, H-5$_C$, H-6$_{abC}$, H-6$_D$, OC*H*$_{2a}$), 3.52–3.42 (m, 2H, H-6$_{aB}$, OC*H*$_{2b}$), 3.37–3.31 (m, 1H, H-6$_{bB}$), 2.58 (dd, *J* = 12.7, 4.5 Hz, 1H, H-3$_{eD}$), 2.12, 2.11, 2.10, 2.01, 1.99, 1.95, 1.84 (7s, 30H, 10 COC*H*$_3$), 1.69 (t, *J* = 12.3 Hz, 1H, H-3$_{aD}$), 1.10 (d, *J* = 6.4 Hz, 3H, CC*H*$_3$), 0.90–0.82 (m, 2H, SiC*H*$_2$), 0.00 (br s, 9H, Si(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.7, 170.8, 170.5, 170.3, 170.0, 169.9, 169.8, 169.6 (10 *C*OCH$_3$), 167.8 (*C*OOCH$_3$), 139.0–127.2 (aromatic carbons), 100.6 (C-1$_A$), 97.7 (C-1$_B$), 97.1 (C-1$_C$), 96.9 (C-2$_D$), 75.6 (C-4$_A$), 75.2 (C-3$_B$), 75.1 (C-4$_B$), 73.6 (C-2$_A$), 73.5 (C-4$_D$), 73.4 (PhCH$_2$), 73.3 (PhCH$_2$), 73.2 (PhCH$_2$), 72.1 (C-3$_C$), 71.7 (C-5$_C$), 71.5 (C-6$_D$), 70.6 (C-4$_C$), 70.5 (C-3$_A$), 69.3 (C-2$_C$), 68.0 (2 C, C-5$_B$, C-8$_D$), 67.6 (C-6$_C$), 67.3 (2 C, C-6$_B$, C-7$_D$), 65.5 (OCH$_2$), 64.1 (C-5$_A$), 62.4 (C-9$_D$), 53.9 (C-5$_D$), 53.1 (COOCH$_3$), 49.1 (C-2$_B$), 37.5 (C-3$_D$), 23.3, 23.1, 21.4, 21.0, 20.9, 20.7, 20.6 (10C, 10COCH$_3$), 17.9 (SiCH$_2$), 16.0 (CCH$_3$), −1.4 (3 C, Si(CH$_3$)$_3$); ESI-MS: *m/z* = 1540.9 $[M]^+$. Anal. Calcd for $C_{74}H_{100}N_2O_{31}Si$ (1540.61): C, 57.65; H, 6.54. Found: C, 57.42; H, 6.80.

4.1.8. 2-(Trimethylsilyl) ethyl (sodium 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-β-D-galacto-pyranosyl-(1→4)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-α-L-fucopyranoside 12

To the solution of compound **12** (300 mg, 0.19 mmol) in CH_3OH (10 mL) was added 20% $Pd(OH)_2/C$ (100 mg), and the reaction mixture was allowed to stir at room temperature under a positive pressure of hydrogen for 24 h. The reaction mixture was filtered through a Celite® bed and evaporated to dryness. A solution of the crude product in 0.1 M CH_3ONa in CH_3OH (5 mL) was allowed to stir at room temperature for 8 h, then few drops of water was added to the reaction mixture and it was stirred for another 5 h. The reaction mixture was neutralized with Dowex 50W-X8 (H^+), filtered, and treated with Dowex 50W-X8 (Na^+). The reaction mixture was filtered, concentrated, and purified through a column of Sephadex LH-20 using CH_3OH–H_2O (4:1) as eluant to give pure **1** (130 mg, 74%) as a white powder; $[\alpha]_D^{25} = -49$ (*c* 1.0, H_2O); IR (KBr): 2935, 2362, 2340, 1725, 1641, 1565, 1378, 1316, 1249, 1074, 861, 838, 771, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.95 (d, *J* = 3.6 Hz, 1H, H-1$_A$), 4.70 (d, *J* = 7.0 Hz, 1H, H-1$_B$), 4.57 (d, *J* = 7.8 Hz, 1H, H-1$_C$), 4.21–4.15 (m, 1H, H-3$_A$), 4.09–3.97 (m, 4H, H-5$_A$, H-6$_{aB}$, H-4$_C$, H-8$_D$), 3.98–3.84 (m, 6H, H-2$_A$, H-6$_{bB}$, H-5$_C$, H-6$_{aC}$, H-5$_D$, H-7$_D$), 3.83–3.71 (m, 9H, H-4$_A$, H-2$_B$, H-3$_B$, H-4$_B$, H-3$_C$, H-4$_D$, H-9$_{abD}$, OC*H*$_{2a}$), 3.70–3.56 (m, 5H, H-5$_B$, H-2$_C$, H-6$_{bC}$, H-6$_D$, OC*H*$_{2b}$), 2.78 (dd, *J* = 12.4, 3.8 Hz, 1H, H-3$_{eD}$), 2.07 (br s, 6H, 2 NHCOC*H*$_3$), 1.90 (t, *J* = 12.0 Hz, 1H, H-3$_{aD}$), 1.24 (d, *J* = 6.4 Hz, 3H, CC*H*$_3$), 1.10–0.94 (m, 2H, SiC*H*$_2$), 0.07 (s, 9H, Si(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.9 (NHCOCH$_3$), 175.8 (NHCOCH$_3$), 173.5 (*C*OONa), 103.5 (C-1$_C$), 100.0 (C-2$_D$), 99.7 (C-1$_B$), 98.5 (C-1$_A$), 79.2 (C-4$_A$), 78.1 (C-4$_C$) 76.4 (C-3$_A$), 76.0 (C-4$_B$), 75.7 (C-2$_C$), 74.0 (C-3$_C$), 73.3 (C-4$_D$), 72.2 (C-2$_A$), 70.3 (C-6$_D$), 70.0 (C-7$_D$), 69.1 (C-5$_B$), 68.8 (C-3$_B$), 68.5 (C-8$_D$), 67.5 (C-5$_A$), 67.1 (2 C, C-5$_C$, OCH$_2$), 63.7 (C-6$_C$), 61.9 (C-9$_D$), 60.9 (C-6$_B$), 56.2 (C-2$_B$), 52.6 (C-5$_D$), 40.1 (C-3$_D$), 23.2 (NHCOCH$_3$), 23.0 (NHCOCH$_3$), 18.2 (SiCH$_2$), 16.2 (CCH$_3$), −1.4 (3C, Si(CH$_3$)$_3$); ESI-MS: *m/z* = 943.1 $[M+1]^+$. Anal. Calcd for $C_{36}H_{63}N_2NaO_{23}Si$ (942.35): C, 45.85; H, 6.73. Found: C, 45.63; H, 6.98.

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