Electronic Supplementary Material (ESI) for Polymer Chemistry

Supplementary Information

A Specific Inhibitory Effect of Multivalent Trehalose toward Aβ(1-40) Aggregation

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1. Materials, Measurements and Methods

1-1. Materials

The following reagents were used as received: amyloid β protein (human, 1-40) (Aβ (1−40)) (Peptide Institute, Inc., Osaka, Japan); D-trehalose monohydrate, lactose monohydrate, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), thioflavin T (ThT) and sodium chloride (NaCl) (Kanto Chemical Co., Inc., Tokyo, Japan); maltose monohydrate (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan); ammonium hydroxide (28-30%) (Sigma-Aldrich, USA); 2, 2‘-azobis-(2-amidinopropane)dihydrochloride (AAPD) (Wako Chemical, Osaka, Japan). Other chemicals such as multivalent saccharides were synthesized. The detailed synthetic schemes and characterization are described in the Supporting Information.

1-2. Measurements

^{1}H (300 MHz, 500 MHz) NMR spectra were recorded in D_2O, $CDCl_3$ or MeOD at room temperature with a Varian Inova 300 and 500 spectrometer (Agilent technologies, Inc., Santa Clara, CA, USA) and mass spectra were obtained with an ESI-MS LCQ-DECA XP instrument (Thermo Scientific, Waltham, MA, USA). Gel permeation chromatography (GPC) was conducted with a JASCO 800 high-performance liquid chromatograph (Jasco, Tokyo, Japan) using a Shodex SB-804HQ column (Shodex, Tokyo, Japan) with phosphate buffered saline (PBS) as eluent, and pullulan as molecular weight standard. Fluorescence intensity was measured with an LS55 instrument (Perkin-Elmer, Waltham, MA, USA).

1-3. Glycopolymers

1-*O*-(α-D-glucopyranosyl)-6-(2-propeneamido)-6-deoxy-α-D-glucopyranoside,

4-*O*-(α-D-glucopyranosyl)-1-*O*–{2-(2-propeneamido)ethyl}-β-D-glucopyranoside and 4-*O*-(β-D-galactopyranosyl)-1-*O*–{2-(2-propeneamido)ethyl}-β-D-glucopyranoside were synthesized by conventional procedures (see Supporting Information). Acrylamide derivatives of trehalose, maltose and lactose were copolymerized with acrylamide using AAPD as radical initiator.

1-4. Preparation of Aβ(1-40)

0.12 μmol Aβ40 was monomerized with 240 μl of ice-cold HFIP, and 11 μl of the solution dispensed into each of 21 tubes. The Aβ40 solution in the tubes, cooled in ice, was evaporated to dryness with a stream of nitrogen, and the Aβ40 residues preserved at -80 °C. For ThT assay, the Aβ40 stocks were dissolved in 22 μl of 0.03 % NH_3 solution to give 500 μM concentration.

1-5. ThT assay[29]

ThT assay samples were made up in 50 mM phosphate buffer with 100 mM NaCl (pH7.5), with the following concentrations of solutes: ThT, 20 μM; Aβ40, 23 μM; sugar, 10 mM. The volume of each test sample was 100 μl, which was added to a 96 well plate and the wells covered with film. The plate was incubated and shaken at 400 rpm (Incubator FMS, EYELA, Tokyo) at 37 °C. Fluorescence intensity was measured at 485 nm at 1 h intervals, with excitation at 450 nm.

1-6. Cell culture[31]

HeLa cells were suspended in DMEM with 10% FBS and 1% penicillin-streptomycin. The cells were plated at 10,000 cells/well on a tissue culture treated 24-well plate, in a humidified atmosphere (5% CO_2/95% room air) at 37°C. One day after plating, the culture medium was changed to 450 μl DMEM supplemented with 5% FBS. To generate aggregation, a sample that

was 23 μM in Aβ40 and 10 mM in sugar and glycopolymer, in 50 mM phosphate buffer with 100 mM NaCl and pH 7.5, was used. The total volume (100 μl) of each sample was added to the wells of a 96 well plate (IWAKI) together with 500 mM NaCl and 200 mM HEPES at pH 7.4, incubated at 37°C, and shaken at 400 rpm for 24 h. After the change of medium, 50 μl of pre-incubated sample was applied to the medium. The HeLa cells were further cultured for 24 h and assayed for MTT reduction.[32] MTT was dissolved in PBS at 5 mg/ml and the cell culture medium was mixed with MTT solution with DMEM supplemented with 5% FBS (in the ratio 1:9). Then 24-well plates of cell culture were charged with 300 μl of the medium and the cells cultured for 4 h, and the absorbance of solubilized MTT formazan product was measured at 570 nm (reference at 650 nm).

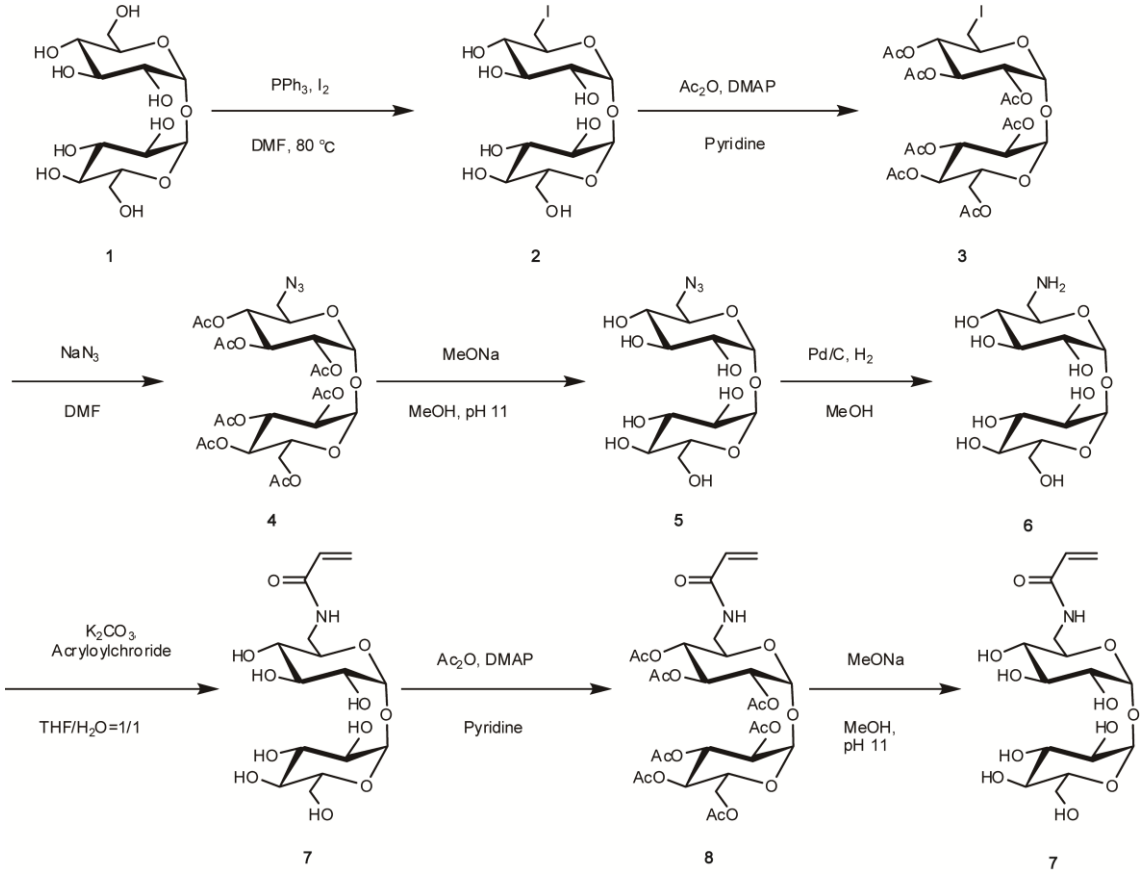
2. Syntheses

All compounds were identified by ^{1}H and ^{13}C-NMR, and mass spectroscopy (ESI-MS).

2-1. Syntheses of monomer

2-1-1. Trehalose derivatives

Scheme S1. Synthesis of acrylamide derivative of trehalose.



1-*O* -(α-D-Glucopyranosyl)-6-iode-6-deoxy-α-D-glucopyranoside (**2**)

Thermal dehydration of α-D-glucopyranosyl-(1-1)-α-D-glucopyranoside **1** (D-trehalose monohydrate) (3.5 g, 9.25 mmol) was carried out under vacuum. The subsequent trehalose and triphenyl phosphine (7.28 g, 27.8mmol) in two-necked flask were dissolved in anhydrous DMF. Iodine (5.96 g, 23.4 mmol) was added to the solution at 80°C under influx of N_2. One hour later, the completion of the reaction was confirmed by TLC (MeOH：CH_3Cl=5:1), and the solution was concentrated till the amount of one-third under reduced pressure. The solution of MeOH (150 ml) and sodium methoxide was stirred at pH 8.0 and room temperature. After 1.5 h, the solution was neutralized with ion-exchange resin and filtered. Then the filtrate was concentrated in vacuo to ginger syrup. The syrup was dissolved in H_2O again and the aqueous phase was washed with CH_3Cl, three times. The water layer was concentrated in vacuo to give a ginger residue **2** (crude product, 99 %).

2,3,4-Tri-*O*-acetyl-1-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-iode-6-deoxy-α-D-glucopyranoside (**3**)

2 was dissolved in pyridine (250 ml), and to the solution were added acetic acide anhydride (28.0 ml, 296 mmol) and DMAP (56.5 mg, 0.46 mmol). The solution was stirred at room temperature. After 10 h, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=1:1). Following concentration, the crude product was dissolved in EtOAc and washed with 1N HCl, sat. $NaHCO_3$ and sat. $NaCl_{aq}$. The organic phase was dried over magnesium sulfate, concentrated, and then purified by silica gel-column chromatography (toluene: ethyl acetate=6:4). The solution was concentrated in vacuo to give yellowish powder **3** (2.41g, 37 %).

^{1}H-NMR (500 MHz, $CDCl_3$, 2D-COSY,ppm, r.t.): δ 5.495 (dd, 1H, $J_{2',3'}$ = 10 Hz, $J_{3',4'}$ =9.5 Hz, H-3'),

5.469 (t, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 5.371 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.334 (d, 1H, $J_{1',2'}$ =4.5Hz, H-1'), 5.184 (dd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$= 10.5 Hz, H-2), 5.040 (t, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 5.032 (dd, 1H, $J_{1',2'}$ = 3.5 Hz, $J_{2',3'}$ = 11.5 Hz, H-2'), 4.878 (t, 1H, $J_{3',4'}$ = 10.0 Hz, $J_{4',5'}$ = 10.0 Hz, H-4'), 4.205 (dd, 1H, $J_{5,6a}$ = 6.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.021 (m, 2H, H-5, H-6b), 3.925 (dt, 1H, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ =9.5 Hz, H-5'), 3.218 (dd, 1H, $J_{5',6'a}$ = 2.5 Hz, $J_{6'a,6'b}$ = 11 Hz, H-6'a), 3.057(dd, 1H, $J_{5',6'b}$ = 9 Hz, $J_{6'a,6'b}$ = 11 Hz, H-6'b), 2.140 (s, 3H, -O*Ac*), 2.110-2.062(m, 9H, -O*Ac*), 2.060-2.012(m, 9H, -O*Ac*).

2,3,4-Tri-*O*-acetyl-1-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-azide-6-deoxy-α-D-glucopyranoside (**4**)

3 (2.41 g, 3.44 mmol) and sodium azide (1.34 g, 20.6 mmol) were dissolved in anhydrous DMF. After 24 hours, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=5:5). The solution was concentrated, and the crude product was dissolved in EtOAc and washed with H_2O (two times) and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate, concentrated, and then purified by silica gel-column chromatography (toluene: ethyl acetate=7:3). The solution was concentrated in vacuo to give white powder **4** (2.06 g, 91 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 5.485 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 5.471 (dd, 1H, $J_{2',3'}$ = 9.9 Hz, $J_{3',4'}$ = 9.3 Hz, H-3'), 5.317 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 5.305 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.080 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{2,1}$ = 3.9 Hz, H-2), 5.052 (dd, 1H, $J_{4,5}$ = 11.1 Hz, $J_{3,4}$ = 9.3 Hz, H-4), 5.024 (dd, 1H, $J_{1',2'}$ = 3.6 Hz, $J_{3,4}$ = 9.9 Hz, H-2'), 4.980 (dd, 1H, $J_{3',4'}$ = 9.3 Hz, $J_{4',5'}$ = 10.2 Hz, H-4'), 4.241 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.057 (m, 1H, H-5'), 4.050 (dd, 1H, $J_{5',6'a}$ = 2.4 Hz, $J_{6'a,6'b}$ = 12.3 Hz, H-6'b), 4.045 (ddd, 1H, $J_{4,5}$ = 11.7 Hz, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 2.1 Hz , H-5), 3.351 (dd, 1H, $J_{5,6a}$ = 7.2 Hz, $J_{6a,6b}$ = 13.2 Hz, H-6a), 3.158 (dd, 1H, $J_{5,6b}$ = 2.4 Hz,

$J_{6a,6b}$ = 13.2 Hz, H-6b), 2.122 (s, 3H, -O*Ac*), 2.104-2.070 (m, 6H, -O*Ac*), 2.070-2.043 (m, 6H, -O*Ac*), 2.032 (s, 6H, -O*Ac*).

6-Azide -6-deoxy-1-*O* -(α-D-glucopyranosyl)-α-D-glucopyranoside (**5**)

To a MeOH solution of **4** (2.06 g, 3.12 mmol) was added a catalytic amount of sodium methoxide to pH 11 and stirred at room temperature. After 1.5 h, the solution was neutralized with ion-exchange resin, and filtered. Then the filtrate was concentrated in vacuo to give a white syrup **5** (1.34g, 99 %).

^{1}H-NMR (D_2O, 300 MHz, ppm, r.t.): δ 5.066 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 5.055 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1'), 4.833 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 5.7 Hz, $J_{5,6}$ = 2.7 Hz , H-5), 3.509 (m, 11H).

6-Amino -6-deoxy-1-*O* -(α-D-glucopyranosyl)-α-D-glucopyranoside (**6**)

To a MeOH solution of **5** (1.34 g, 3.34 mmol) was added a Pd/C (67 mg) stirred under hydrogen at room temperature. 12 hours later, the solution was filtered with glass fiber filter (GF-75, Advantec, Tokyo, Japan), and thw filtrate was concentrated in vacuo to give a white syrup **6** (1.15 g, 90 %).

^{1}H-NMR (D_2O, 300 MHz, ppm, r.t.): δ 5.078 (d, 1H, $J_{1,2}$ = 2.4 Hz), 5.066 (d, 1H, $J_{1','2}$ = 2.1 Hz), 3.675 (m, 6H), 3.547 (dd, 2H, $J_{1,2}$ = $J_{1',2'}$ = 2.1 Hz, $J_{2,3}$ =$J_{2',3'}$ = 9.9 Hz, H-2,H-2'), 3.263 (m, 2H), 2.786 (m, 2H).

6-(2-Propenamido) -6-deoxy-1-*O* -(α-D-glucopyranosyl)-α-D-glucopyranoside (**7**)

6 (1.15 g, 3.65 mmol) and K_2CO3 (2.05 g, 14.9 mmol) were dissolved in the mixture of THF and H_2O (THF: H_2O = 8:2) and stirred at 0℃. After 10 min, to the solution was dropwisely added acryloyl chloride (805 ml, 9.90 mmol) and stirred at 0℃ for 40 min. After 40 min, the

solution was stirred at room temperature. 17 hours later, the solution was neutralized with ion-exchange resin and filtered. The filtrate was concentrated in vacuo to give a ginger residue mixture **7**.

^{1}H-NMR (D_2O, 300 MHz, ppm, r.t.): δ 6.154 (ddd, 1H, *J* = 0.9 Hz, *J* = 9.6 Hz, *J* = 16.8Hz, -NHCOC*H*=CH_2), 6.043 (dd, 1H, *J* = 1.5 Hz, *J* = 16.8 Hz, -NHCOCH=$CH_{cis}H_{trans}$), 5.624 (dd, 1 H, *J* = 1.5 Hz, *J* = 9.6 Hz, -NHCOCH=$CH_{cis}H_{trans}$), 5.032-4.926 (2s, 2 H, *J* = 3.9 Hz, H-1, H-1'), 3.782-3.064 (m).

2,3,4-Tri-*O*-acetyl-1-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-(2-propen amido)-6-deoxy -α-D-glucopyranoside (**8**)

To pyridine solution of **7** were added acetic acid anhydride (28.0 ml, 296 mmol) and DMAP (56.5 mg, 0.46 mmol). The solution was stirred at room temperature. After 3 h, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=5:5). Following the concentration, the product was dissolved in EtOAc and washed with 1N-HCl, sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate, concentrated, and then purified by silica gel-column chromatography (toluene: ethyl acetate=3:7). At last, the solution was concentrated in vacuo to give white powder **8** (1.41 g, 56 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 6.284 (dd, 1H, *J* = 1.5 Hz, *J* = 16.8 Hz, -NHCOCH=$CH_{cis}H_{trans}$), 6.096 (dd, 1H, *J* = 10.2 Hz, *J* = 16.8 Hz, -NHCOC*H*=$CH_{cis}H_{trans}$), 5.860 (br, 1H, -N*H*COCH=$CH_{cis}H_{trans}$), 5.682 (dd, 1 H, *J* = 1.5Hz, *J* = 10.2 Hz, -NHCOCH=C$H_{cis}H_{trans}$), 5.484 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 5.474 (dd, 1H, $J_{2',3'}$ = 9.6 Hz, $J_{3',4'}$ = 9.6 Hz, H-3'), 5.320 (d, H, $J_{1,2}$ = 3.9 Hz, H-1), 5.279 (d, H, $J_{1',2'}$ = 3.9 Hz, H-1'), 5.027 (dd, 1H, $J_{3',4'}$ = 10.2 Hz, $J_{4',5'}$ = 10.5 Hz, H-4'), 4.994 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 4.947 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 9.6 Hz, H-2'), 4.899 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 9.6 Hz, H-4), 4.229 (dd, 1H, $J_{5,6a}$ = 5.7 Hz, $J_{6a,6b}$ =

9.6 Hz, H-6a), 4.016 (m, 2H, H-5, H-6b), 3.903 (ddd, 1H, $J_{5',6'a}$ = 2.4 Hz, $J_{5',6'b}$ = 6.9 Hz, $J_{4',5'}$ = 10.5Hz, H-5'), 3.694 (ddd, 1H, $J_{5',6'a}$ = 2.4 Hz, $J_{\text{-NH},6'a}$ = 6.9 Hz, $J_{6'a,6'b}$ = 14.1 Hz, H-6'a), 3.289 (ddd, 1H, $J_{\text{-NH},6'b}$ = 5.1 Hz, $J_{5'6'b}$ = 6.9 Hz, $J_{6'a,6'b}$ = 14.1 Hz, H-6'b), 2.055 (m, 21 H, -O*Ac*).

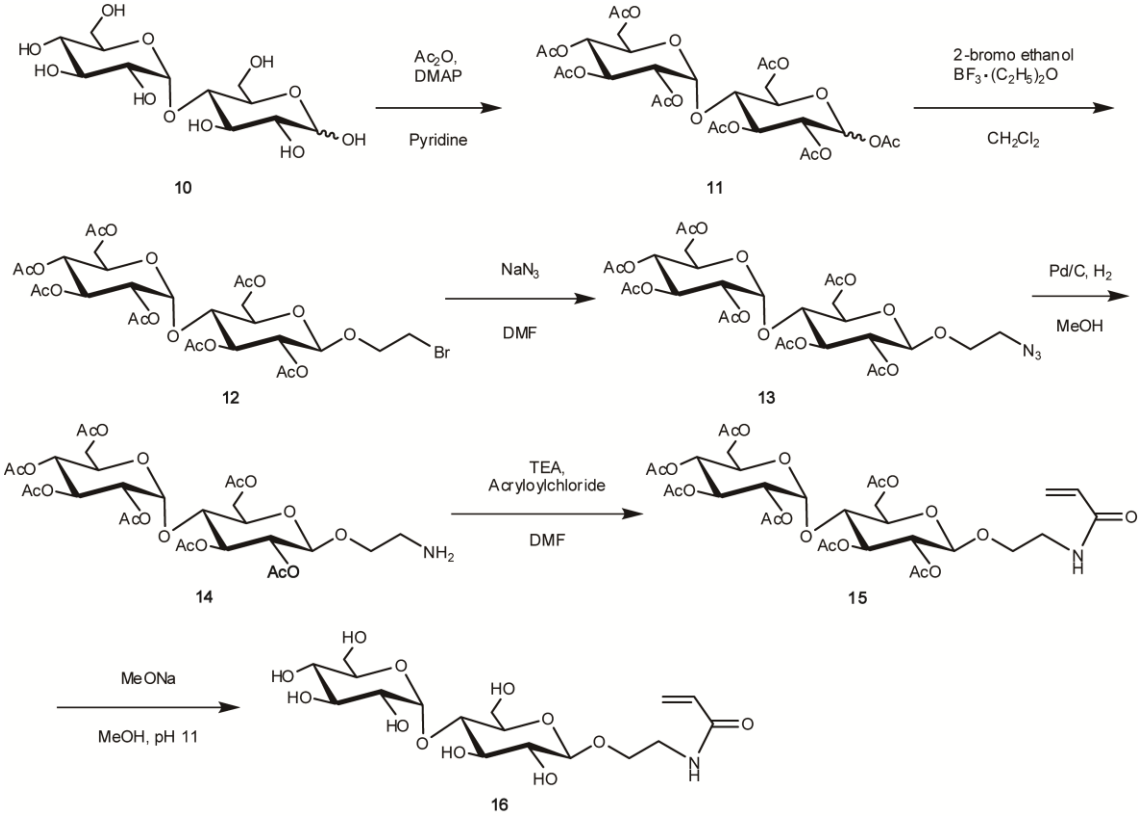
1-*O* -(α-D-Glucopyranosyl)-6-(2-propen amido)-6-deoxy-α-D-glucopyranoside (**7**)

To a MeOH solution of **8** (72 mg, 0.11 mmol) was added a catalytic amount of sodium methoxide to pH 11 and stirred at room temperature. After 1.5 h, the solution was neutralized with ion-change resin and filtered and then filtrate was concentrated in vacuo to give a white powder **7** (41.7 mg, 96 %).

^{1}H-NMR (D_2O, 300 MHz, ppm, r.t.): δ 6.134 (ddd, 1H, *J* = 9.9 Hz, *J* = 17.1 Hz, -NHCOC*H*=$CH_{cis}H_{trans}$), 6.021 (dd, 1H, *J* = 1.8 Hz, *J* = 17.1 Hz, -NHCOCH=$CH_{cis}H_{trans}$), 5.602 (dd, 1 H, *J* = 1.8 Hz, *J* = 9.9 Hz, -NHCOCH=C$H_{cis}H_{trans}$), 5.022-4.912 (2s, 2 H, *J* = 3.6 Hz, H-1, H-1'), 3.752-3.104 (m, 12H, H-2, 3, 4, 5, 6_a, 6_b, 2', 3', 4', 5', 6'a, 6'b); ^{13}C-NMR (125.7 MHz, D_2O): δ 168.9 (NH*C*OCHCH_2), 129.8 (NHCO*C*HCH_2), 127.7 (NHCOCH*C*H_2), 93.4 (C-1'), 93.3 (C-1),72.6, 72.4, 72.2, 71.2, 71.1 (C-2 and C-2'), 70.7, 69.7, 60.6 (C-6), 39.9 (C-6'); ESI-MS [positive]: 418.1 $[M+Na^+]^+$ (calculated), 418.2 $[M+Na^+]^+$ (observed).

2-1-2. Maltose derivatives

Scheme S2. Synthesis of acrylamide derivative of maltose.



1,2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-α-D-glucopyranosyl) –β-D-glucopyranoside (**11**)

Thermal dehydration of maltose monohydrate was carried out under vacuum. **10** (2.58 g, 7.16 mmol), and maltose was dissolved in pyridine (180 ml) .To the solution of **10** were added acetic acide anhydride (16.2 ml, 172 mmol) and DMAP (43.7 mg, 0.36 mmol). The solution was stirred at room temperature. After 11 h, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=5:5). Following concentration, the product was dissolved in EtOAc and washed with 1N-HCl, sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate, filtrated, and concentrated in vacuo to give yellowish powder **11** (5.70 g, 99 %).

^{1}H-NMR (500 MHz, $CDCl_3$, 2D-COSY, ppm, r.t.): δ 5.732 (d, 1H, $J_{1',2'}$ = 8.5 Hz, H-1'), 5.396 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.344 (t, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 10.0 Hz, H-3), 5.284 (t, 1H, $J_{2',3'}$ = 9.5 Hz, $J_{3',4'}$ = 9.5 Hz, H-3'), 5.048 (t, 1H, $J_{3,4}$ = 10.0 Hz, $J_{4,5}$ = 10.0Hz, H-4), 4.967 (t, 1H, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 8.5 Hz, H-2'), 4.865 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 11.0Hz, H-2), 4.445 (dd, 1H, $J_{5,6a}$ = 2.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.227 (dd, 1H, $J_{5',6'a}$ = 3.5 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'a), 4.211 (dd, 1H, $J_{5,6b}$ = 3.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 4.034 (dd, 1H, $J_{5',6'b}$ = 3.0 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'b), 4.025 (dd, 1H, $J_{3',4'}$ = 8,5 Hz, $J_{4',5'}$ = 8.5 Hz, H-4'), 3.933 (ddd, 1H, $J_{4',5'}$ = 10.0 Hz, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ = 3.5 Hz, H-5'), 3.829 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 2.5 Hz, $J_{5,6b}$ = 3.5 Hz, H-5)、2.15-1.95(m, -O*Ac*).

2,3,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-*O*-(2-bromoethyl)-β-D-glucopyranoside (**12**)

11 (4.07 mmol, 2.76 g) was dehydrated with molecular sieve (4A), degassed, and dissolved in anhydrous CH_2Cl_2. To the solution was added 2-bromo ethanol (378 μl, 5.29 mmol) and stirred at 0℃. After 10 min, to the solution was dropwisely added trifluoroboran-ethylether complex (3.54 ml, 28.2 mmol) and stirred at 0℃ for 40 min. After 40 min, the reaction solution was stirred at room temperature. 24 hours later, to the solution was dropwisely added cold H_2O, and the reaction was quenched. The solution was filtered, and then the filtrate was washed with sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$ (two times). The organic phase was dried over magnesium sulfate, concentrated, and then purified by silica gel-column chromatography (toluene: ethyl acetate=7:3). At last, the solution was concentrated in vacuo to give white powder **12** (1.68 g, 56 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 5.409 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 5.354 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{2,3}$ = 10.5 Hz, H-3), 5.256 (t, 1 H, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 9.0 Hz, H-3'), 5.046 (t, 1H, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 9.6 Hz, H-4), 4.851 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 4.841 (dd, 1H, $J_{1',2'}$ = 8.1 Hz,

$J_{2',3'}$ = 9.3 Hz, H-2'), 4.587 (d, 1H, $J_{1',2'}$ = 8.1 Hz, H-1'), 4.494 (dd, 1H, $J_{5,6a}$ = 2.7 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.248 (dd, 1H, $J_{5',6'a}$ = 4.2 Hz, $J_{6'a,6'b}$ = 12.6 Hz, H-6'a), 4.218 (dd, 1H, $J_{5,6b}$ = 4.2 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6b), 4.119 (m, 1H, -OCH_2CH$_2$Br), 4.041 (dd, 1H, $J_{5',6'b}$ = 2.4 Hz, $J_{6'a,6'b}$ = 12.3 Hz, H-6'b), 4.001 (dd, 1H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'}$ = 10.2 Hz, H-4') 3.951 (ddd, 1H, $J_{5',6'b}$ = 2.4 Hz, $J_{5',6'a}$ = 4.2 Hz, $J_{5',4'}$ = 10.2 Hz, H-5'), 3.812 (m, 1H, -OCH_2CH$_2$Br), 3.687 (ddd, 1H, $J_{5,6b}$ = 2.7 Hz, $J_{5,6a}$ = 4.2 Hz, $J_{5,4}$ = 9.6 Hz, H-5), 3.440 (m, 2H, -OCH$_2$CH_2Br), 2.07 (m, 21 H, -O*Ac*).

2,3,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-*O*-(2-azideethyl)-β-D-glucopyranoside (**13**)

12 (1.65 g, 2.23 mmol) and sodium azide (632 mg, 10.0 mmol) were dissolved in anhydrous DMF. 12 hours later, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=5:5). Following the concentration, the product was dissolved in EtOAc and washed with H_2O (two times) and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate and filtered. Then the filtrate was concentrated in vacuo to give white powder **13** (1.39 g, 90 %). ^{1}H-NMR (500 MHz, $CDCl_3$, 2D-COSY, ppm, r.t.): δ 5.406 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.348 (t, 1H, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 10.0 Hz, H-3), 5.247 (t, 1H, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 9.0 Hz, H-3'), 5.043 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 4.845 (dd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 4.842 (dd, 1H, $J_{1',2'}$ = 8.0 Hz, $J_{2',3'}$ = 9.0 Hz, H-2'), 4.604 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 4.514 (dd, 1H, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.244 (dd, 1H, $J_{5',6'a}$ = 4.0 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'a), 4.205 (dd, 1H, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 4.040 (dd, 1H, $J_{5',6'b}$ = 3.0 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'b), 4.012 (dd, 1H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'}$ = 9.5 Hz, H-4'), 3.997 (ddd, 1H, *J* = 3.5 Hz, *J* = 5.0 Hz, *J* = 11.0, -OCH_2CH$_2$N$_3$), 3.947 (ddd, 1H, $J_{5',6'b}$ = 3.0 Hz, $J_{5',6'a}$ = 4.0 Hz, $J_{4',5'}$ = 9.5, H-5'), 3.687 (ddd, 1H, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 4.5 Hz, $J_{4,5}$ = 10.0, H-5), 3.685 (ddd, 1H, *J* = 3.5 Hz, *J* = 8.0 Hz, *J* = 11.0,

-OC*H*$_2$CH$_2$N$_3$), 3.469 (ddd, 1H, *J* = 3.5 Hz, *J* = 8.0 Hz, *J* = 13.5, -OCH$_2$C*H*$_2$N$_3$), 3.255 (ddd, 1H, *J* = 3.5 Hz, *J* = 5.0 Hz, *J* = 13.5, -OCH$_2$C*H*$_2$N$_3$), 2.062 (m, 21H, -O*Ac*).

2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-α-D-glucopyranosyl) -1-*O* -(2-aminoethyl)-β-D-glucopyranoside (**14**)

To a MeOH solution of **13** (1.39 g, 1.97 mmol) was added a Pd/C (70 mg) and 35 % HCl (216 μl), and stirred under hydrogen at room temperature. 3.5 hours later, the solution was filtered with glass fiber filter and then filtrate was concentrated in vacuo to give a white syrup **14** (1.40 g, 99 %).

^{1}H-NMR (500 MHz, CD$_3$OD, 2D-COSY, ppm, r.t.): δ 5.406 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.359 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 5.323 (t, 1H, $J_{3',4'}$ = 9.0 Hz, $J_{2',3'}$ = 9.0 Hz, H-3'), 5.059(t, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.849 (dd, 1H, $J_{1',2'}$ = 8.0 Hz, $J_{2',3'}$ = 9.0 Hz, H-2), 4.846 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2'), 4.777 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 4.707 (dd, 1H, $J_{6'a,6'b}$ = 12.5 Hz, $J_{5',6'a}$ = 2.5 Hz, H-6'a), 4.245 (dd, 1H, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.230 (dd, 1H, $J_{6'a,6'b}$ = 12.5 Hz, $J_{5',6'b}$ = 4.0 Hz, H-6'b), 4.149 (dd, 1 H, $J_{5,6b}$ = 2.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 4.073 (ddd, 1H, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 2.5 Hz, $J_{4,5}$ = 9.5 Hz, H-5), 4.034 (t, 1 H, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'}$ = 9.0 Hz, H-4'), 3.972 (ddd, 1H, *J* = 4.0 Hz, *J* = 7.0 Hz, *J* = 12.0Hz, -OC*H*$_2$CH$_2$NH$_2$), 3.926 (ddd, 1H, *J* = 4.0 Hz, *J* = 6.0 Hz, *J* = 12.0 Hz, -OC*H*$_2$CH$_2$NH$_2$), 3.884 (ddd, 1 H, $J_{5',6'a}$ = 2.5Hz, $J_{5',6'b}$ = 4.0 Hz, $J_{4',5'}$ = 9.0, H-5'), 3.184 (ddd, 1H, J = 4.0 Hz, *J* = 6.0 Hz, *J* = 13.0 Hz, -OCH$_2$C*H*$_2$NH$_2$), 3.105 (ddd, 1H, *J* = 4.0 Hz, *J* = 7.0 Hz, *J* = 13.0 Hz, -OCH$_2$C*H*$_2$NH$_2$), 2.129, 2.061 (2s, 6H, -O*Ac*), 2.04-1.95 (5s, 15 H, -O*Ac*).

2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl- α-D-glucopyranosyl) -1-*O* –{2-(2-propen amido)ethyl}-β-D-glucopyranoside (**15**)

To DMF solution of **14** (1.40 g, 2.06 mmol) was added TEA (2.01 ml, 14.4 mmol) and stirred at 0℃. After 10 min, to the solution was dropwisely added acryloyl chloride (502 ml, 6.18 mmol) and stirred at 0℃ for 40 min. After 40 min, the reaction solution stirred at room temperature. 5 hours later, following concentration, the product was dissolved in CH_3Cl and washed 1N-HCl, sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate, filtered, concentrated, and then purified by silica gel-column chromatography (toluene: ethyl acetate=1.5:8.5). At last, the solution was concentrated in vacuo to give white powder **15** (936 mg, 62 %).

^{1}H-NMR (500 MHz, $CDCl_3$, 2D-COSY, ppm, r.t.): δ 6.292 (dd, 1H, J = 1.5 Hz, J = 17 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 6.128 (dd, 1H, J = 10.5 Hz, J = 17.0 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 5.644 (dd, 1H, J = 1.5 Hz, J = 10.5 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 5.408 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.351 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 10.5 Hz, H-3), 5.254 (t, $J_{3',4'}$ = 9.5 Hz, $J_{3',2'}$ = 9.5 Hz, H-3'), 5.054 (t, 1 H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.850 (dd, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 4.811 (dd, 1H, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 9.5 Hz, H-2'), 4.554 (dd, 1H, $J_{5',6'a}$ = 2.5 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'a), 4.519 (d, 1H, $J_{1',2'}$ = 8.5 Hz, H-1'), 4.255 (dd, 1H, $J_{5,6a}$ = 3.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.195 (dd, 1H, $J_{5',6'b}$ = 4.5 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'b), 4.060 (dd, 1H, $J_{5,6b}$ = 2.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 3.978 (t, 1H, $J_{3',4'}$ = 9.5 Hz, $J_{4',5'}$ = 9.5 Hz, H-4'), 3.953 (ddd, $J_{5,6b}$ = 2.5 Hz, $J_{5,6a}$ = 3.5 Hz, $J_{4,5}$ = 9.5 Hz, H-5), 3.826 (ddd, 1H, J = 4.0 Hz, J = 6.0 Hz, J = 10.5 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 3.783 (ddd, 1H, J = 4.0 Hz, J = 6.0 Hz, J = 10.5 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 3.688 (ddd, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ = 4.5 Hz, $J_{4',5'}$ = 9.5 Hz, H-5'), 3.554 (dddd, 1H, J = 4.0 Hz, J = 6.0 Hz, J = 10.5 Hz, J = 12.0 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 3.490 (dddd, 1H, J = 4.0 Hz, J = 6.0 Hz, J = 10.5 Hz, J = 12.0 Hz, -$OCH_2CH_2NHCOCH{=}CH_{cis}H_{trans}$), 2.138, 2.099 (2s, 6H, -O*Ac*), 2.05-1.95 (5s, 15 H, -O*Ac*).

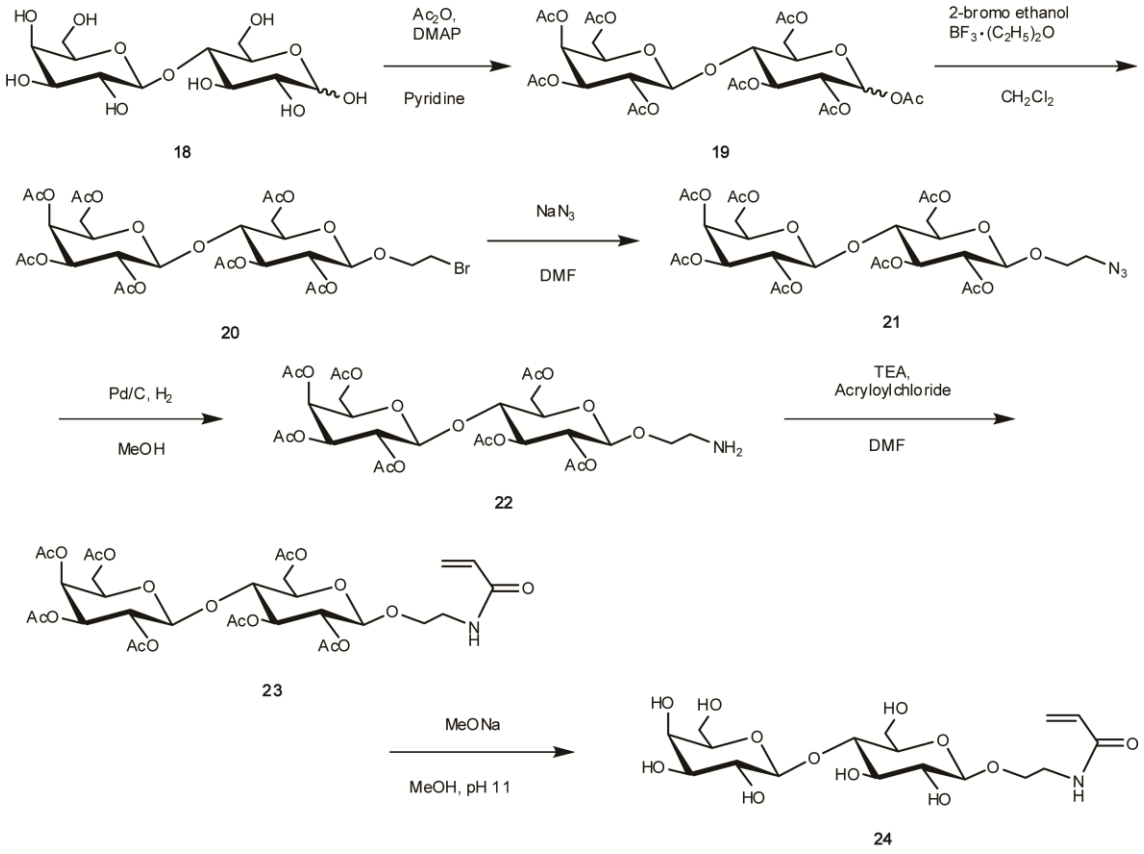
4-*O* -(α-D-glucopyranosyl) -1-*O* –{2-(2-propene amido)ethyl}-β-D-glucopyranoside (**16**)

To a MeOH solution of **15** (303 mg, 0.414 mmol) was added a catalytic amount of sodium methoxide to pH 11 and stirred at room temperature. After 4.5 h, the solution was neutralized with ion-change resin and filtered and then filtrate was concentrated in vacuo to give a white syrup **16** (211 mg, 99 %)**.**

^{1}H-NMR (500 MHz, D_2O, 2D-COSY, ppm, r.t.): δ 6.159 (dd, 1H, $J_{Hx,HA}$ = 10.5 Hz, $J_{Hx,HM}$ = 17.5 Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 6.072 (dd, 1H, $J_{HM,HA}$ = 1.5 Hz, $J_{HM,Hx}$ = 17.5 Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 5.649 (dd, 1H, $J_{HA,HM}$ = 1.5 Hz, $J_{Hx,HA}$ = 10.5 Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 5.273 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.359 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1'), 3.880 (ddd, 1H, *J* = 4.0 Hz, *J* = 6.5 Hz, *J* = 11.0, Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 3.800 (dd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 3.724 (dd, 1H, $J_{5',6'a}$ = 2.5 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'a), 3.693 (ddd, 1H, *J* = 4.0 Hz, *J* = 7.0 Hz, *J* = 11.0 Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 3.646 (t, 1H, $J_{3',4'}$ = 9.5 Hz, $J_{2',3'}$ = 9.5 Hz, H-3'), 3.639 (dd, 1H, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 3.639 (dd, 1H, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 3.629 (dd, 1H, $J_{5',6'b}$ = 5.5 Hz, $J_{6'a,6'b}$ = 12.5 Hz, H-6'b), 3.582 (m, 1H, H-6'a), 3.582 (ddd, 1H, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ = 5.5 Hz, $J_{4',5'}$ = 9.5 Hz, H-5'), 3.549 (t, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.502 (t, 1H, $J_{3',4'}$ = 9.5 Hz, $J_{4',5'}$ = 9.5, H-4'), 3.460 (ddd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 5.0 Hz, $J_{4,5}$ = 9.5 Hz, H-5), 3.448 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.427 (ddd, *J* = 4.0 Hz, *J* = 6.5 Hz, *J* = 10.5 Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 3.377 (ddd, *J* = 4.0 Hz, *J* = 7.0 Hz, J = 10.5 Hz, -$OCH_2CH_2NHCOCH$=$CH_{cis}H_{trans}$), 3.285 (t, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 9.5 Hz, H-3), 3.187 (dd, 1H, $J_{1',2'}$ = 7.5 Hz, $J_{2',3'}$ = 9.5 Hz, H-2'); ^{13}C-NMR (125.7 MHz, D_2O): δ 168.8 ($OCH_2CH_2NH\underline{C}OCHCH_2$), 129.9 ($OCH_2CH_2NHCO\underline{C}HCH_2$), 129.6 ($OCH_2CH_2NHCOCH\underline{C}H_2$), 102.3 (C-1'), 100.1 (C-1), 77.2, 76.9, 75.8, 75.0, 73.3, 73.2, 73.1, 72.9, 69.2 ($O\underline{C}H_2CH_2NHCOCHCH_2$), 60.6 (C-6 and C-6'), 39.5 ($OCH_2\underline{C}H_2NHCOCHCH_2$); ESI-MS [positive]: 462.4 $[M+Na^+]^+$ (calculated), 462.2$[M+Na^+]^+$ (observed).

2-1-3. Lactose derivatives

Scheme S3. Synthesis of acrylamide derivative of lactose.



1,2,3,6-Tetra-*O*-acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**19**)

Lactose **18** (2.21 g, 6.12 mmol) was dehydrated under vacuum and dissolved in pyridine (150 ml).To the solution was added acetic acide anhydride (20.8 ml, 220 mmol) and DMAP (74.8 mg, 0.612 mmol). The solution was stirred at room temperature. After 22 h, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=5:5). Following concentration, the product was dissolved in EtOAc and washed with 1N-HCl, sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate, filtrated, and concentrated in vacuo to give ginger powder **19** (4.44 g, 99 %).

^{1}H-NMR (500 MHz, $CDCl_3$, 2D-COSY, ppm, r.t.): δ 6.241 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1), 5.451 (dd, 1H, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 10.0 Hz, H-3'), 5.347 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.113 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 7.5 Hz, H-3), 4.995 (dd, 1H, $J_{2',3'}$ = 9.0 Hz, $J_{1',2'}$ = 3.5 Hz, H-2'), 4.951 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{1,2}$ = 3.5 Hz, H-2), 4.474 (d, 1H, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 7.5 Hz, H-4), 4.438 (dd, 1H, $J_{5,6a}$ = 2.5 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6a), 4.185-4.040 (m, 3H, H-5, H-6'a, H-6'b), 3.991 (ddd, 1H, $J_{4',5'}$=10.0Hz, H-5'), 3.872 (t, 1H, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.807 (t, 1H, $J_{3',4'}$ = 10.0 Hz, $J_{4',5'}$ = 10.0 Hz, H-4'), 2.16-1.94 (m, 24H, -O*Ac*).

2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-β-D-galactopyranosyl) -1-*O* -(2-bromoethyl)-β-D-glucopyranoside (**20**)

Thermal dehydration of **19** (2.96g, 4.36 mmol) and molecular sieve was carried out under vacuum, and under nitrogen. Then, they were dissolved in anhydrous CH_2Cl_2. To the solution was added 2-bromo ethanol (614 μl, 5.67 mmol) and stirred at 0℃. After 10min, to the solution was added gradually trifluoroboran ethylether complex (3.69 ml, 30.2 mmol) and stirred at 0℃ for 30 min. After 30 min, the reaction solution was stirred at room temperature. 16 hours later, the solution was poured into cold H_2O to quench reaction and filtered and then filtrate was washed sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$ (two times). The organic phase was dried over magnesium sulfate, filtrate, concentrated, and then purified by silica gel-column chromatography (toluene: ethyl acetate=6:4). At last, the solution was concentrated in vacuo to give white powder **20** (1.24 g, 27 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 5.478 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 5.338 (t, 1H, $J_{2',3'}$ = 9.3 Hz, $J_{3',4'}$ = 9.3 Hz, H-3'), 5.242 (dd, 1H, $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 10.5 Hz, H-3), 5.096 (dd, 1H, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 5.044 (dd, 1H, $J_{1',2'}$ = 8.1 Hz, $J_{2',3'}$ = 9.3 Hz, H-2'), 4.700-4.560 (m, 3H, H-4,

H-6a, H-1'), 4.320-4.150 (m, 4H, -OCH_2CH_2Br), 4.060-3.870 (m, 3H, H-5, 6'a,6'b), 3.748 (ddd, *J*=2.1 Hz, *J*=5.1Hz, *J*=10.2Hz, H-5'), 3.620-3.500 (m, 2H, H-6b, 4'), 2.321-2.070 (m, 21H, -OAc).

2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-β-D-galactopyranosyl) -1-*O* -(2-azideethyl)-β-D-glucopyranoside (**21**)

20 (1.24 g, 1.66 mmol) and sodium azide (648 mg, 9.96 mmol) were dissolved in anhydrous DMF. 5 hours later, the completion of the reaction was confirmed by TLC (toluene: ethyl acetate=5:5). Following concentration, the product was dissolved in EtOAc and washed H_2O (two times) and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to give white powder **21** (1.02 g, 93 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 5.343 (dd, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 5.201 (t, $J_{2',3'}$ = 9.3 Hz, $J_{3',4'}$ = 9.3 Hz, H-3') , 5.110 (dd, $J_{2,3}$ = 7,8 Hz, $J_{3,4}$ = 10.2, H-3), 4.953 (dd, $J_{1,2}$=3.3 Hz, $J_{2,3}$=10.5 Hz, H-2), 4.920 (dd, $J_{1',2'}$ = 7.8 Hz, $J_{2',3'}$ = 9.3 Hz, H-2'), 4.554 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.527 (dd, 1 H, $J_{5',6'a}$ = 2.4 Hz, $J_{6'a,6'b}$ = 11.1 Hz, H-6'a), 4.491 (d, 1H, *J* = 7.8 Hz, H-4), 4.18-4.03 (m, 3H, H-6a, 6b, 6'b), 3.988 (ddd, 1H, *J* = 3.3Hz, *J* = 5.1 Hz, *J* = 10.8 Hz, -OCH_2CH_2Br), 3.870 (t, 1H, $J_{5,6a}$ = 6.9 Hz, $J_{5,6b}$ = 6.9 Hz, H-5), 3.819 (t, 1H, $J_{3',4'}$=9.0 Hz, $J_{4',5'}$ = 9.0 Hz, H-4'), 3.700 (ddd, 1H, *J* = 3.3 Hz, *J* = 8.4 Hz, *J* = 10.8 Hz, -OCH_2CH_2Br), 3.618 (ddd, 1H, *J* = 2.1 Hz, *J* = 5.1 Hz, *J* = 9.9 Hz, H-5'), 3.471 (ddd, 1H, *J* = 3.3 Hz, *J* = 8.4 Hz, *J* = 13.5 Hz, -OCH_2CH_2Br), 3.264 (ddd, 1H, *J* = 3.3 Hz, *J* = 5.1 Hz, *J* = 13.5 Hz, -OCH_2CH_2Br), 2.151, 2.122, 2.060, 1.964 (4S, 12H, -O*Ac*), 2.044 (s, 9H, -O*Ac*).

2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-β-D-galactopyranosyl) -1-*O* -(2-aminoethyl)-β-D-glucopyranoside (**22**)

To a MeOH solution of **21** (1.02 g, 1.53 mmol) was added Pd/C (50 mg) and 35 % HCl (180 μl),

and stirred under hydrogen at room temperature. 4 hours later, the solution was filtered with GALASS FIBER FILTER and then filtrate was concentrated in vacuo to give white syrup **22** (1.05 g, 99 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 5.355 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 5.195 (t, 1H, $J_{2',3'}$ = 9.6 Hz, $J_{3',4'}$ = 9.6 Hz, H-3'), 5.116 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{1,2}$ = 3.3 Hz, H-2), 5.009 (dd, 1H, $J_{3,4}$ = 7.8 Hz, $J_{2,3}$ = 10.2 Hz, H-3), 4.894 (dd, 1H, $J_{1',2'}$ = 8.1 Hz, $J_{2',3'}$ = 9.6 Hz, H-2'), 4.732 (d, 1H, $J_{1',2'}$ = 8.1 Hz, H-1'), 4.720 (d, 1H, $J_{3,4}$ = 7.8 Hz, H-4), 4.634 (dd, 1H, $J_{5,6a}$ = 1.5 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.18-4.05 (m, 4H, H-5, H-6a, H-6'a, H-6'b), 4.04-3.83 (m, 3H, H-4', H-5',-OC*H*$_2$CH$_2$NH$_2$), 3.83-3.73 (m, 1H, -OC*H*$_2$CH$_2$NH$_2$), 3.20-3.05 (m, 1H, -OCH$_2$C*H*$_2$NH$_2$), 2.130-1.924 (7s, 21H, -O*Ac*).

2,3,6-Tetra-*O* -acetyl-4-*O* -(2,3,4,6-tetra-*O* -acetyl-β-D-galactopyranosyl) -1-*O* –{2-(2-propene amido)ethyl}-β-D-glucopyranoside (**23**)

To DMF solution of **22** (1.05 g, 1.54 mmol) was added TEA (1.27 ml, 10.0 mmol) and stirred at 0℃. After 10 min, to the solution was dropwisely added acryloyl chloride (313 μl, 3.85 mmol) and stirred at 0℃ for 40 min. After 40 min, the solution was stirred at room temperature. 17 hours later, following concentration, the product was dissolved in CH_3Cl and washed with 1N-HCl, sat.$NaHCO_{3aq}$ and sat.$NaCl_{aq}$. The organic phase was dried over magnesium sulfate, filtered, concentrated, and then purified by silica gel-column chromatography (ethyl acetate). At last, the solution was concentrated in vacuo to give white powder **23** (769 mg, 68 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, r.t.): δ 6.285 (dd, 1H, *J* = 1.5 Hz, *J* = 17.0, -OCH$_2$CH$_2$NHCOCH=CH$_{cis}$*H*$_{trans}$), 6.116 (dd, *J* = 10.5 Hz, *J* = 17.0 Hz, -OCH$_2$CH$_2$NHCOC*H*=CH$_{cis}$H$_{trans}$), 6.116 (br, 1H, -OCH$_2$CH$_2$N*H*COCH=CH$_{cis}$H$_{trans}$), 5.639 (dd, 1H,

J = 1.5 Hz, *J* = 10.5 Hz, -OCH$_2$CH$_2$NHCOCH=C*H*$_{cis}$H$_{trans}$), 5.340 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.188 (t, 1H, $J_{2',3'}$ = 9.5 Hz, $J_{3',4'}$ = 9.5 Hz, H-3'), 5.100 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 8.5 Hz, H-3), 4.953 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 3.5 Hz, H-2), 4.627 (dd, 1H, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 9.5 Hz, H-2'), 4.529 (dd, 1H, $J_{5',6'a}$ = 2.0 Hz, $J_{6'a,6'b}$ = 12.0 Hz, H-6'a), 4.487 (d, 1H, $J_{3,4}$ = 7.5 Hz, H-4), 4.459 (d, 1H, $J_{1',2'}$ = 8.5 Hz, H-1'), 4.133 (dd, 1H, $J_{5,6a}$ = 6.5 Hz, $J_{6a,\,6b}$ = 11.0 Hz, H-6a), 4.083 (dd, 1H, $J_{5',6'b}$ = 5.0 Hz, $J_{6'a,6'b}$ = 12.0 Hz, H-6'b), 4.063 (dd, 1H, $J_{5,6b}$ = 7.5 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6b), 3.868 (brdd, 1H, $J_{5,6a}$ = 6.5 Hz, $J_{5,6b}$ = 7.5 Hz, H-5), 3.807 (ddd, 1H, *J* = 3.5 Hz, *J* = 6.0 Hz, *J* = 10.5 Hz, -OC*H*$_2$CH$_2$NHCOCH=CH$_{cis}$H$_{trans}$), 3.771 (t, 1H, $J_{3',4'}$ = 9.5 Hz, $J_{4',5'}$ = 9.5 Hz, H-4'), 3.763 (ddd, 1H, *J* = 3.5 Hz, *J* = 6.0 Hz, *J* = 10.5 Hz, -OC*H*$_2$CH$_2$NHCOCH=CH$_{cis}$H$_{trans}$), 3.606 (ddd, 1H, $J_{5',6'a}$ = 2.0 Hz, $J_{5',6'b}$ = 5.0 Hz, $J_{5',4'}$ = 9.5 Hz, H-5'), 3.557 (dddd, 1 H, *J* = 4.0 Hz, *J* = 5.5Hz, *J* = 6.0 Hz, *J* = 10.5 Hz, -OCH$_2$C*H*$_2$NHCOCH=CH$_{cis}$H$_{trans}$), 3.470 (brdddd, 1H, *J* = 4.0 Hz, *J* = 5.5Hz, *J* = 6.0 Hz, *J* = 10.5 Hz, -OCH$_2$C*H*$_2$NHCOCH=CH$_{cis}$H$_{trans}$), 2.145, 2.113, 2.054, 2.028, 1.959 (5s, 15H, -O*Ac*), 2.039 (2s, 6H, -O*Ac*).

4-*O* -(β-D-Galactopyranosyl) -1-*O* –{2-(2-propene amido)ethyl}-β-D-glucopyranoside (**24**)

To a MeOH solution of **23** (303 mg, 0.413 mmol) was added a catalytic amount of sodium methoxide to pH 11 and stirred at room temperature. After 4.5 h, the solution was neutralized with ion-change resin and filtered and then filtrate was concentrated in vacuo to give a white syrup **24** (198 mg, 99 %).

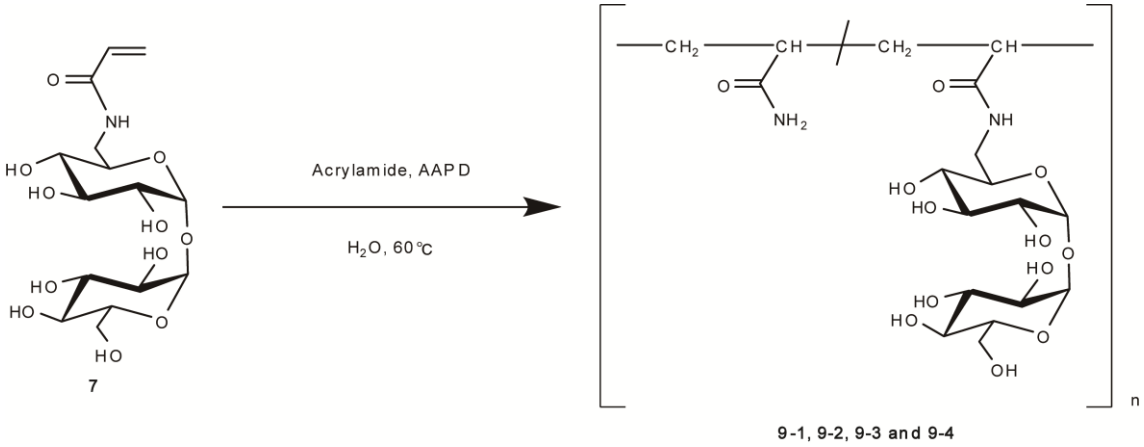
^{1}H-NMR (D_2O, 300 MHz, ppm, r.t.): δ 6.177 (dd, 1H, *J* = 9.6 Hz, *J* = 17.1 Hz, -OCH$_2$CH$_2$NHCOC*H*=CH$_{cis}$H$_{trans}$), 6.078 (dd, 1H, *J* = 1.8 Hz, *J* = 17.1 Hz, -OCH$_2$CH$_2$NHCOCH=CH$_{cis}$*H*$_{trans}$), 5.653 (dd, 1H, *J* = 1.8 Hz, *J* = 9.6 Hz, -OCH$_2$CH$_2$NHCOCH=C*H*$_{cis}$H$_{trans}$), 4.387 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.330 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1'), 3.95-3.15 (m, 16 H, H-2, H-3, H-4, H-5, H-6a, H-6b, H-2', H-3', H-4', H-5', H-6'a, H-6'b,

-OCH_2CH_2NHCOCH=C$H_{cis}$$H_{trans}$); ^{13}C-NMR (125.7 MHz, D_2O): δ 168.7 ($OCH_2CH_2NHCOCHCH_2$), 129.9 ($OCH_2CH_2NHCOCHCH_2$), 102.9 (C-1'), 102.3 (C-1), 78.9, 75.9, 74.9, 74.3, 72.9, 72.9, 72.1, 70.5, 68.0 ($OCH_2CH_2NHCOCHCH_2$), 61.1 (C-6 and C-6'), 39.5 ($OCH_2CH_2NHCOCHCH_2$); ESI-MS [positive]: 462.4 $[M+Na^+]^+$ (calculated), 462.2$[M+Na^+]^+$ (observed).

2-2. Polymerization

2-2-1. Polyvalent trehalose

Scheme S4. Synthesis of polyvalent trehalose.



Poly [2-propen amido-co-(1-*O* -(α-D-glucopyranosyl)-6-(2-propen amido)-6-deoxy-α-D-glucopyranoside].

7 (18 mg, 0.046 mmol), acrylamide (29.4 mg. 0.41 mmol) and AAPD (3.73 mg, 0.014 mmol) were dissolved in H_2O (410 ml). The solution in Pyrextube was degassed by three freeze-thaw cycles. The tube was sealed under vacuum and heated at 60℃ with 100 min^{-1} shaking. Polymerization was stopped by cooling the tube and the precipitation in acetone. The product was separated by centrifugation with 300 rpm for 60 min.. After removed of supernatant, the deposits dried in vacuo to give a white solid, and then purified by dialysis, the solid was lyophilized to afford **9** as white solid.

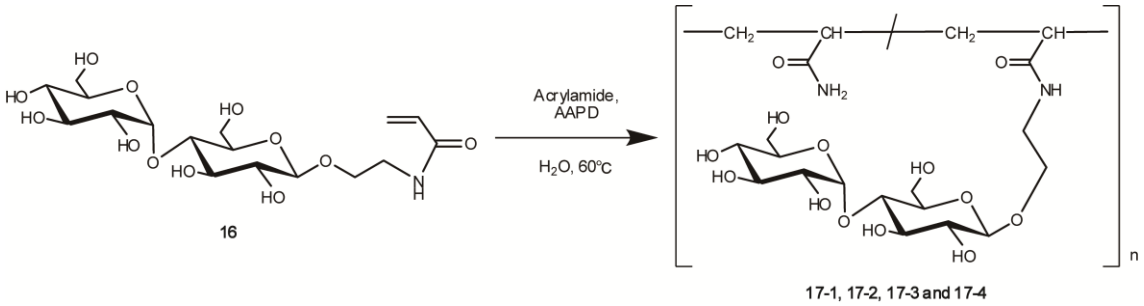
Table S1. Polymerization of poly(trehalose/acrylamide).

No	Mn[a] ($\times 10^5$)	Mw[a] ($\times 10^5$)	Mw/Mn[a]	Yield	Sugar content rates[b]
9-1	1.09	1.62	1.58	80	9.7
9-2	1.03	1.62	1.57	67	20
9-3	1.03	1.48	1.44	80	63
9-4	1.13	1.59	1.4	41	100

[a] by pullulan standard, and [b] by ^{1}H NMR.

2-2-2. Polyvalent maltose

Scheme S4. Synthesis of polyvalent maltose.



Poly[(2-propenamido)-*co*-(4-*O* -(α-D-glucopyranosyl) -1-*O* –{2-(2-propene amido)ethyl}-β-D-glucopyranoside)]

16 (20 mg, 0.046 mmol), acrylamide (29.4 mg. 0.41 mmol) and AAPD (3.73 mg, 0.014 mmol) were dissolved in H_2O (455 μl). The solution in Pyrextube was degassed by three freeze-thaw cycles. The tube was sealed under vacuum and heated at 60℃ with 100 min^{-1} shaking. Polymerization was stopped by cooling the tube and the precipitation in acetone. The product was separated by centrifugation with 300 rpm for 60 min. After removed of supernatant, the deposits dried in vacuo to give a white solid, and then purified by dialysis, the solid was

lyophilized to afford **17** as white solid.

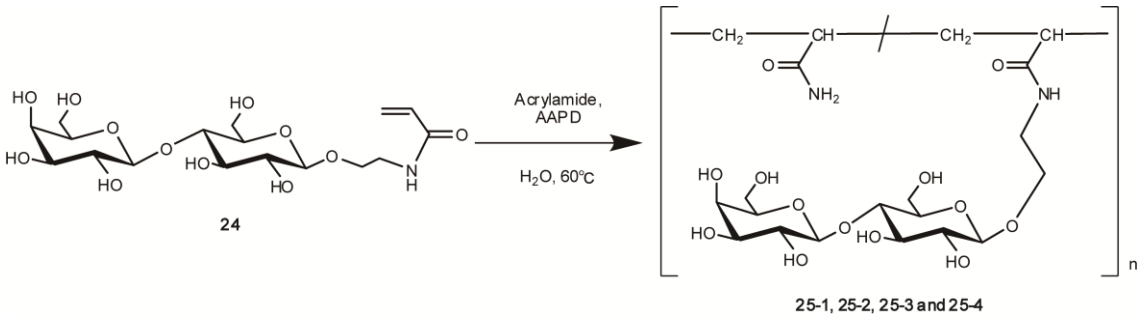
Table S2. Polymerization of poly(maltose/acrylamide).

No	Mn[a] ($\times 10^4$)	Mw[a] ($\times 10^5$)	Mw/Mn[a]	Yield	Sugar content rates[b]
17-1	6.7	1.27	1.90	72	9.7
17-2	2.6	0.62	2.37	60	30
17-3	1.8	0.48	2.73	60	51
17-4	1.6	0.39	2.44	55	100

[a] by pullulan standard, and [b] by ^{1}H NMR.

2-2-3. Polyvalent Lactose

Scheme S4. Synthesis of polyvalent maltose.



Poly[(2-propenamido)-co-(4-*O* -(α-D-glucopyranosyl) -1-*O* –{2-(2-propene amido)ethyl}-β-D-glucopyranoside)]

24 (20 mg, 0.046 mmol), acrylamide (29.4 mg. 0.41 mmol) and AAPD (3.73 mg, 0.014 mmol) were dissolved in H_2O (455 μl). The solution in Pyrextube was degassed by three freeze-thaw cycles. The tube was sealed under vacuum and heated at 60℃ with 100 min^{-1} shaking. Polymerization was stopped by cooling the tube and the precipitation in acetone. The product

was separated by centrifugation with 300 rpm for 60 min. After removed of supernatant, the deposits dried in vacuo to give a white solid, and then purified by dialysis, the solid was lyophilized to afford **25** as white solid.

Table S3. Polymerization of poly(lactose/acrylamide).

No	Mn[a] ($\times 10^4$)	Mw[a] ($\times 10^5$)	Mw/Mn[a]	Yield	Sugar content rates[b]
25-1	5.3	1.14	2.15	77	7.8
25-2	4.7	1.14	2.45	62	17
25-3	2.6	0.68	2.64	64	52
25-4	1.8	0.45	2.52	60	100

[a] by pullulan standard, and [b] by ^{1}H NMR.

3. Analysis

3-1. *Inhibitory effect caused by alteration in trehalose concentration*

The inhibitory effect of trehalose (**1**) was investigated with the various concentration of 1 mM, 10 mM, 50 mM, 100 mM, 250 mM and 500 mM with ThT fluorescence assay (Figure S1). We observe subtle dependence of the time-course of ThT fluorescence on the trehalose concentration of the additives. However all results suggested that trehalose did not inhibit Aβ aggregation even with addition of high concentration of trehalose.

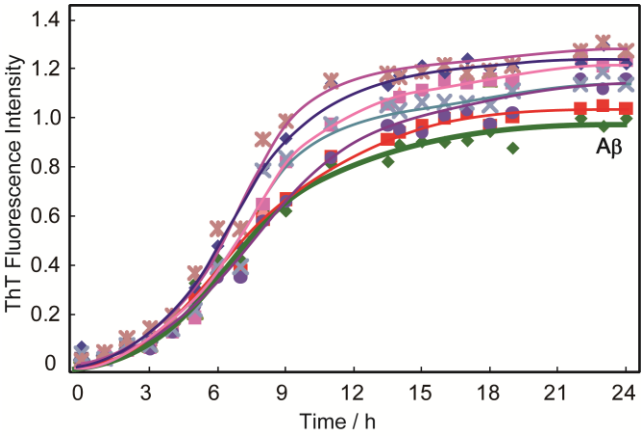


Figure S1. Time course of Aβ(1-40) aggregation at pH 7.4 and 37℃ with 400 rpm shaking monitored by ThT fluorescence. The concentration of Aβ was 23 μM. And concentrations of trehalose were 1mM (red squares), 10mM (pink squares), 50 mM (purple circles), 100mM (blue diamonds), 250 mM (apua ×) and 500 mM (pink ∗).

3-2. *Sugar content effect of polyvalent maltose*

The inhibitory effect of polyvalent maltose was investigated with the various sugar ratios of 9.8 % (**17-1**), 30% (**17-2**), 51% (**17-3**) and 100 % (**17-4**) with ThT fluorescence assay (Figure S2). The time-course of ThT was dependant on the sugar ratio of the additives. In a similar case of polyvalent trehalose, the inhibitory effect of polyvalent maltose with higher sugar content (30 %, 51 % and 100 %) was weak, instead, the addition of their polyvalent maltose didn't inhibit the Aβ aggregation, but increased the ThT fluorescence 115 %, 122 % and 140 %, respectively. On the other hand, the polyvalent maltose with modest sugar content (9.8 %) showed the inhibition effect from ThT time-course and the final fluorescence intensity. But the inhibition effect was not much more than monomeric maltose.

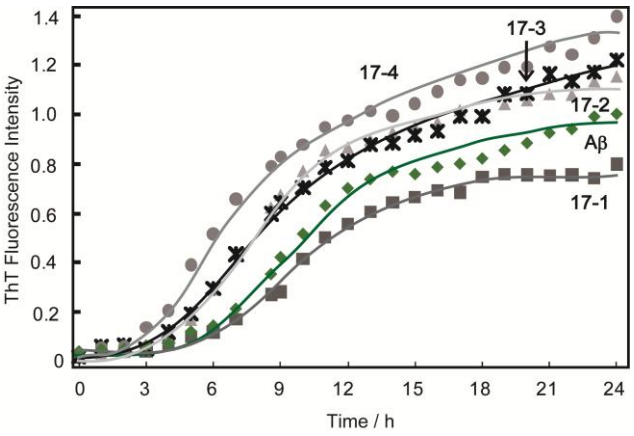


Figure S2. Time course of Aβ(1-40) aggregation at pH 7.4 and 37℃ with 400 rpm shaking monitored by ThT fluorescence. The concentration of Aβ and sugar additives (**17-1**, **17-2**, **17-3**, **17-4**) were 23 μM and 10 mM, respectively.

3-2. *Sugar content effect of polyvalent lactose*

The inhibitory effect of polyvalent lactose was investigated with the various sugar ratios of 7.8 % (**25-1**), 17 % (**25-2**), 52 % (**25-3**) and 100 % (**25-4**) with ThT fluorescence assay (Figure S3). The time-course of ThT was dependant on the sugar ratio of the additives. In a similar case of polyvalent trehalose and polyvalent maltose, the inhibitory effect of polyvalent lactose with higher sugar content (**25-3** and **25-4**) was weak. The addition of **25-3** and **25-4** didn't inhibit the Aβ aggregation, but increased the ThT fluorescence 105 % and 136 %, respectively. On the other hand, the **25-1** and **25-2** with modest sugar content (7.8 % and 17 %) showed the inhibition effect from ThT time-course and the final fluorescence intensity. **25-1** showed the best inhibitory effect against the final fluorescence intensity. This result suggested that **25-1** inhibited fibrils elongation process of Aβ aggregation. On the other hand, **25-2** showed the best inhibitory effect against lag phase. This result suggested that **25-2** inhibited nucleus process of Aβ aggregation.

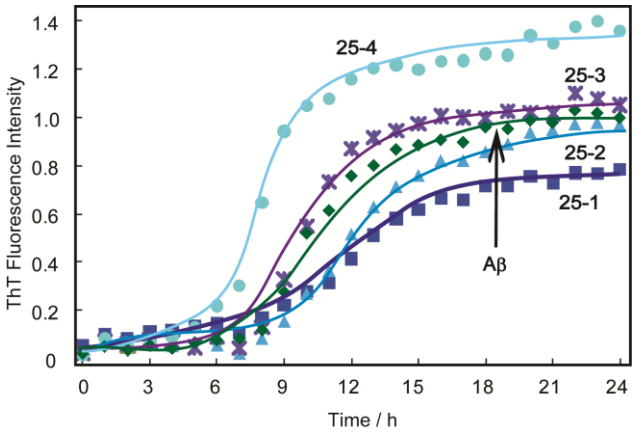


Figure S3. Time course of Aβ(1-40) aggregation at pH 7.4 and 37℃ with 400 rpm shaking monitored by ThT fluorescence. The concentration of Aβ and sugar additives (**25-1**, **25-2**, **25-3**, **25-4**) were 23 μM and 10 mM, respectively.

3-4. *MTT assay of Aβ toxicity with trehalose (1) and polyvalent trehalose (9-1)*

Addition of Ab reduced HeLa cell viability to 66 % due to the cytotoxity of Ab. The addition of trehalose (**1**) either did not reduce the cytotoxity of Ab or slightly reduced cell viability to 55 %. This result was opposite effect compared to effect of polyvalebt trehalose (**9-1**).

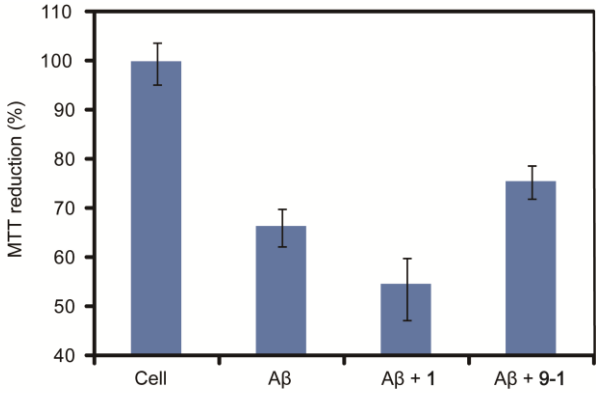


Figure S4. Toxicity of Aβ(1-40) aggregates formed preincubation temperature of 37 ℃ for 24 h in the absence, in the presence of 23 μM Aβ and addition of trehalose (**1**) (100 mM) and polyvalent trehalose (**9-1**) (1 mM). These concentrations of polyvalent compounds indicated sugar unit concentration.

3-5. *Error bar of ThT assay results after 24 hours*

We indicated error bar of ThT assay results after 24 hours. These results suggested that inhibitory effect of polyvalent trehalose was the real thing.

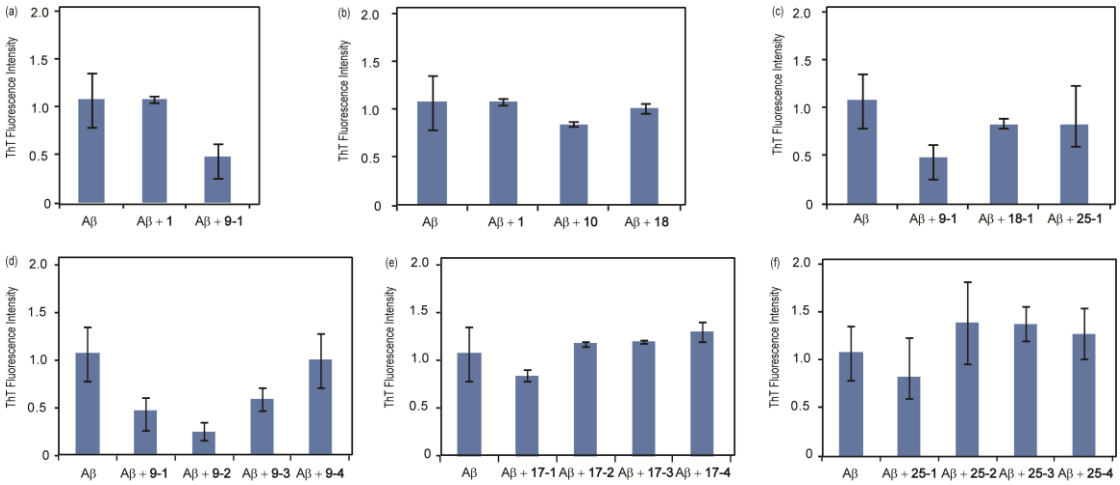


Figure S5. Error bar of ThT assay results after 24 hours.