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A fluorous-assisted synthesis of oligosaccharides using a phenyl ether linker as a safety-catch linker

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ABSTRACT

We report on the fluorous-assisted synthesis of oligosaccharides using a phenyl ether linker. The phenyl ether linker is stable under both acidic and basic conditions but can be cleaved under mildly acidic conditions after reduction to a vinyl ether. The utility of the method was demonstrated by the synthesis of a trisaccharide. A protected trisaccharide with a light-fluorous tag was directly prepared by one-pot glycosylation using three building blocks that contained a building block with a light-fluorous tag though a phenyl ether. A Birch reduction of the trisaccharide provided a fully deprotected trisaccharide with the fluorous tag attached through a vinyl ether, which was easily purified by solid-phase extraction. The tag was cleaved from the sugar portion by treatment with 3% TFA in MeOH.

1. Introduction

Oligosaccharides play important roles in cell surface events via carbohydrate–protein and carbohydrate–carbohydrate interactions.[1] The chemical synthesis of structurally defined oligosaccharides would be highly desirable for use in structure–activity relationship studies, due to the fact that oligosaccharides from natural sources can be produced in only limited qualities. Recent progress in oligosaccharide synthesis has resulted in a number of new and efficient glycosidation methodologies, which are amenable to the synthesis of protected oligosaccharides by standardized and routine protocols.[2] We recently reported on the development of an efficient method for the synthesis of oligosaccharides, that is, based on one-pot glycosylation[3,4] and polymer-assisted deprotection[5] (Scheme 1). The one-pot glycosylation involved the sequential chemo- and regioselective glycosylation to provide the protected oligosaccharides **4** from several simple building blocks **1**, **2**, and **3** in one pot. This methodology was effective, not only for the synthesis of single target oligosaccharides, but also for the synthesis of an oligosaccharide library.[6] The protected oligosaccharides **4** were loaded on a solid-support via the prelinker **6** containing an activated ester and a vinyl ether and the solid-supported amine **5** to provide **7**, followed by removal of the protecting groups on the solid to afford **8**. Birch reduction was found to be effective for removing benzyl ethers on solid-supported oligosaccharides. Release from the solid-support was achieved using a volatile acid, such as TFA, to provide the fully deprotected trisaccharide **9**. The solid-support acts as a tag for ease of treating the partially and fully deprotected oligosaccharides. If the tag for purification is attached to one of the building blocks for the synthesis of oligosaccharides, the tag-installation process can be omitted. However, the solid-supported substrates would not be suitable substrate for one-pot glycosylation and the acetal linker is not sufficiently stable to survive acidic glycosidation conditions used.

Fluorous-assisted solution synthesis involving the use of perfluoroalkanes as tags for purification is an effective method for high-speed synthesis of organic compound with minium manipulations for workup and purificaiton.[7,8] The heavy-fluorous tag enables selective extraction of the tagged compounds in fluorous solvents. However, it could reduce the reactivity of the tagged compounds. On the other hand, the light-fluorous tag enables the tagged compounds to be separated by solid-phase extraction with minimum effects on their reactivity.[9]

Applications of the both heavy- and light-fluorous tag to the oligosaccharide synthesis have been reported from several research groups.[10,11] They are mainly focused on the purification after glycosylations. Herein we report on the fluorous-assisted liquid-phase synthesis of oligosaccharides using a phenyl ether linker as a safety-catch linker.

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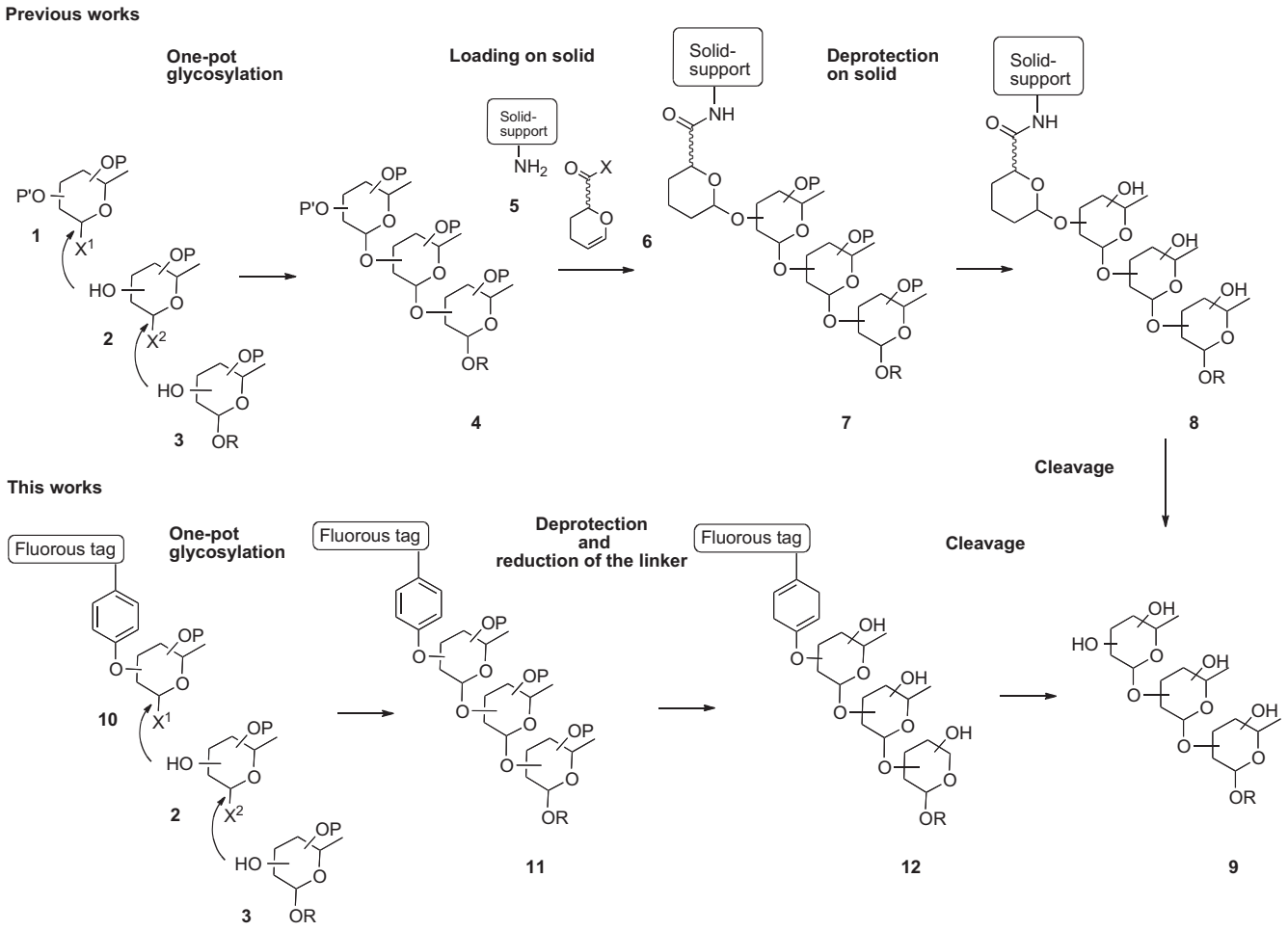


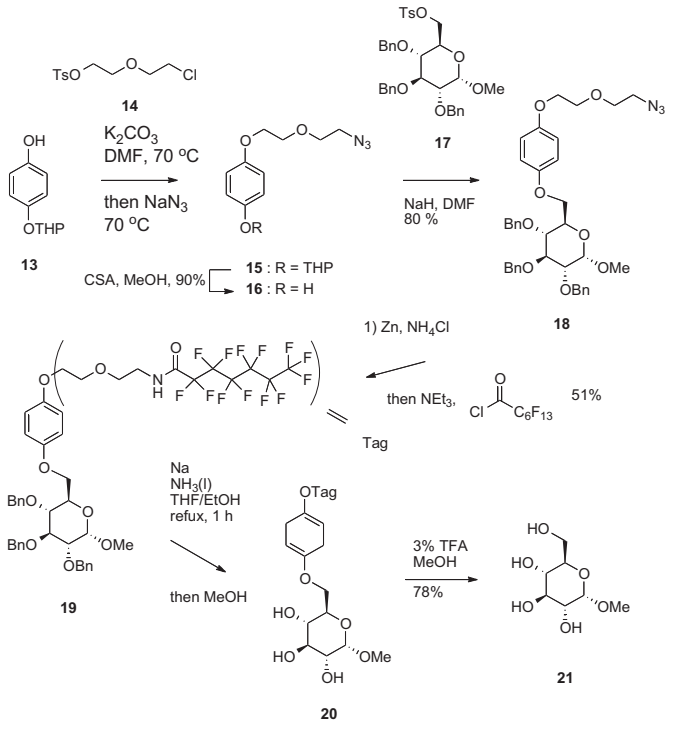
Scheme 1. Strategy for the synthesis of oligosaccharides based on a one-pot glycosylation and a tag-assisted deprotection.

2. Results and discussion

Our strategy for the light-fluorous-assisted synthesis of oligosaccharides using the phenyl ether linker is shown in Scheme 1. The first step involves the synthesis of protected oligosaccharides by a one-pot glycosylation using the sugar units **2**, **3**, and **10**, in which one of the building blocks **10** contains a light-fluorous tag attached through a phenyl ether. The phenyl ether linker is stable under the acidic and/or oxidative glycosylation conditions employed in the synthesis. This method enables the direct preparation of the tag-installed oligosaccharides. **11** The second step involves the deprotection of the protected oligosaccharides and reduction of the phenyl ether linker to a vinyl ether. Exposure of the fluorous-attached oligosaccharides **11** to Birch reduction conditions would result in, not only the removal of esters and benzyl ethers, but also the reduction of the phenyl ether to the vinyl ether **12**. Purification of the highly polar oligosaccharides was achieved by solid-phase extraction. The third step involves the cleavage of the vinyl ether linker by treatment with a volatile acid such as TFA to provide the fully deprotected oligosaccharides **9**. Although applications of the phenyl ether linker for the fluorous-assisted synthesis of oligosaccharides have been reported by Goto and Mizuno,[10a,11e,12] the use of the volatile reagents for cleaving the tag are critical for the ease of workup and purification of the fully deprotected oligosaccharides.

We first examined cleavage of the phenyl linker by reduction and hydrolysis (Scheme 2). The preparation of the substrate **19** is shown in Scheme 2. Treatment of the mono-THP protected hydroquinone **13** with tosylate **14** under basic conditions for 30 min 70 °C, followed by the addition of sodium azide to the reaction mixture provided the azido compound **15**. The subsequent removal of the THP ether under acidic conditions provided phenol **16** in 90% yield. O-Alkylation of the phenol with the tosylate **17** provided the tri-*O*-benzyl glucoside **18** in 80% yield. Attaching the light-fluorous tag to the sugar unit **18** was achieved by reduction of the azido group to an amine, followed by acylation with tridecafluoroheptanoyl chloride to provide the tri-*O*-benzyl glucoside **19** with a fluorous tag through the phenyl ether linker. Cleavage of the phenyl ether linker was examined next. The phenyl ether **19** was treated with sodium in liquid ammonia in the presence of EtOH at reflux for 1 h. After the reaction mixture was concentrated in vacuo, the residue was directly subjected to fluorous column chromatography. ^{1}H NMR analysis of the crude material indicated that the phenyl ether was reduced to a vinyl ether and all of the benzyl ether protecting groups had been removed. In addition, it should be noted that mass spectrum of **20** indicated that the alkylfluorides had been partially reduced. Treatment of the crude material under mildly acidic conditions provided α-methyl glucoside (**21**) in 78% based on **19**. The released fluorous tag was easily removed by solid-phase extraction.

We next examined the fluorous-assisted synthesis of disaccharide **30** from the glycosyl donor **26** attached to a fluorous tag (Scheme 3). Treatment of thioglycoside **22** and phenol **23** with tributylphosphine and 1,1′-(azodicarbonyl) dipiperidine at 60 °C for 18 h provided the phenyl ether **24** in 72% yield. The chloride **24** was

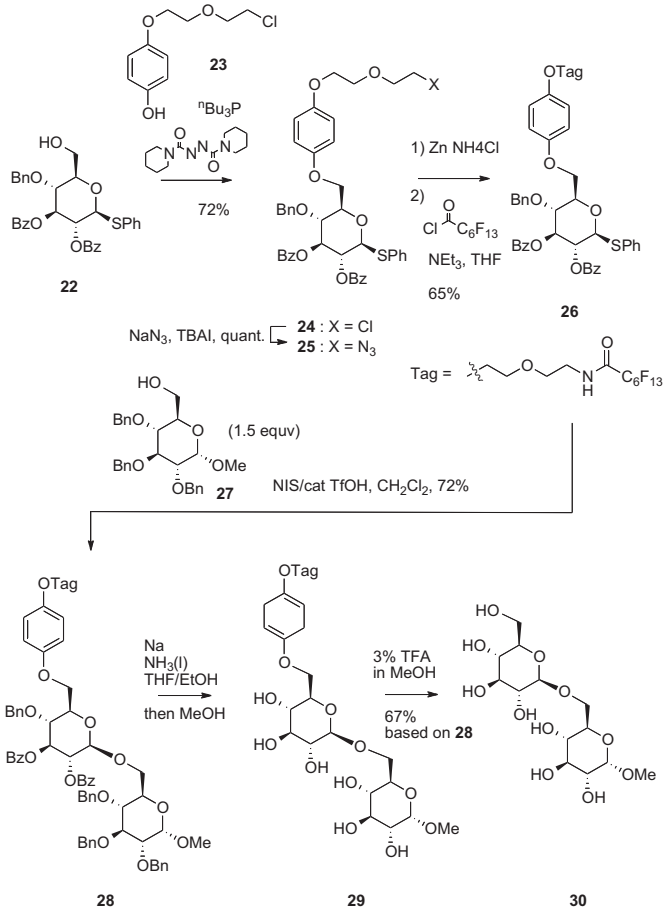


Scheme 2.

converted to the azido compound **25** in quantitative yield. Reduction of the azido **25** to an amine, followed by acylation with tridecafluoroheptanoyl chloride provided the thioglycoside **26** attached to a fluorous tag. Glycosylation of the glycoside **27** with the thioglycoside **26** was next examined. Treatment of tetra-*O*-benzyl glucoside **27** and the thioglycoside **26** with NIS/cat TfOH provided the β-linked disaccharide **28** in 72% yield as a single diastereomer. The disaccharide **28** was treated with sodium in liquid ammonia in the presence of EtOH for 1 h at reflux. The reaction mixture was quenched by the addition of MeOH. Product **29** was purified by fluorous column chromatography, followed by treatment with 3% TFA in MeOH to provide disaccharide **30** in 67% based on **28**.

We next examined the synthesis of the trisaccharide **34** by one-pot glycosylation involving the chemoselective glycosylation of thioglycoside **22** with the glycosyl bromide **31**, which was prepared from thioglycoside **26** (Scheme 4). The thioglycoside **22** and the glycosyl bromide **31** were treated with AgOTf. After TLC analysis, which indicated the generation of disaccharide **32**, the primary alcohol **27**, NIS and a catalytic amount of TfOH were added to the reaction mixture to produce trisaccharide **33**. The purification of **33** was achieved by gel permeation chromatography. Purification of the reaction mixture by gel permeation chromatography after one-pot glycosylation was one of the best ways for isolation of the desired product since it should be the largest oligosaccharide among the reaction products. On the other hand, fluorous column chromatography is difficult to separate the tagged products involving different numbers of sugar units. The yield of the trisaccharide **33** was not estimated at this stage because the products contained partially iodinated products at the linker. Reduction of the linker and removal of the protecting group was archived under Birch reduction conditions, followed by exposure of the product to acidic conditions provided the β-linked trisaccharide **34** in 59% yield based on **22** as a single diastereomer.

In conclusion, an efficient fluorous-assisted synthesis of oligosaccharides using a phenyl ether linker as a safety-catch linker is described. The phenyl ether linker was stable under the acidic glycosidation conditions and basic deprotection conditions, but can



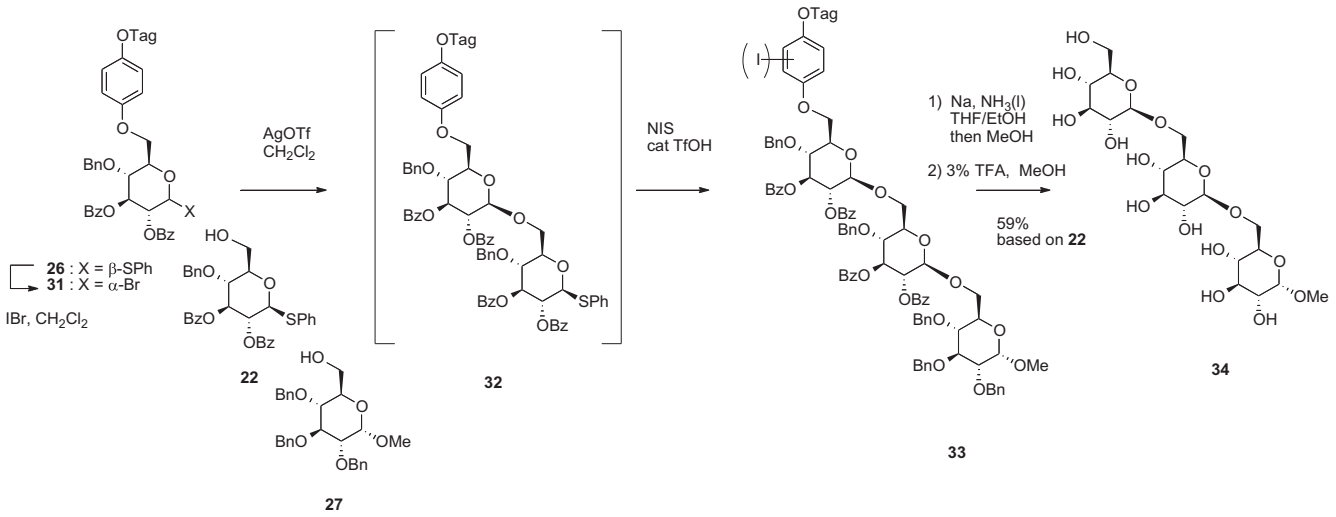
Scheme 3. Synthesis of the disaccharide **30**.

be cleaved under mildly acidic conditions after reduction to a vinyl ether by Birch reduction. The Birch reduction simultaneously removes protecting groups, such as esters and benzyl ethers. Therefore, this method enables the efficient workup and purification of the highly polar oligosaccharides by taking advantage of fluorous tags.

3. Experimental section

3.1. General

NMR spectra were recorded on a JEOL Model EX-270 (270 MHz for ^{1}H, 67.5 MHz for ^{13}C) or a JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts are reported in units parts per million (ppm) relative to the signal (0 ppm) for internal tetramethylsilane for solutions in $CDCl_3$. ^{1}H NMR spectrum data are reported as follows: $CDCl_3$ (7.26 ppm) or CD_3OD (3.30 ppm) or D_2O (HOD (4.8654 ppm at 285 K, 4.7015 ppm at 303 K, 4.6201 ppm at 311 K, 4.3560 ppm at 339 K as internal standard using 3-(trimethylsilyl)-1-propanesulfonicacid sodium salt as external standard)). ^{13}C NMR spectrum data are reported as follows: $CDCl_3$ (77.1 ppm) or CD_3OD (49.3 ppm) or acetone-d_6 (30.3 ppm) as internal standard for D_2O. Multiplicities are reported by using the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet, br; broad, *J*; coupling constants in Hertz. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IRspectrophotometer. Only the strongest and/or structurally important peaks are reported as the IR data given in cm^{-1}. Optical rotation was measured on a JASCO model P-1020 polarimeter. All



Scheme 4. Synthesis of the disaccharide **34** by one-pot glcysoyaltion.

reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by 10% ethanolic phosphomolybdic acid, *p*-anisaldehyde solution or 0.5% ninhydrin *n*-butanol solution. Daiso silica gel or Merk silica gel was used for column chromatography. Gel permeation chromatography (GPC) for qualitative analysis were performed on Japan Analytical Industry Model LC908 (recycling preparative HPLC), on a Japan Analytical Industry Model RI-5 refractive index detector and on a Japan Analytical Industry Model 310 ultra violet detector with a polystylene gel column (JAIGEL-1H, 20×600 mm), using $CHCl_3$ as solvent (3.5 mL/min). ESI-TOF Mass spectra were measured with P. E. Biosystems TK-3500 Biospectrometry Workstation mass spectrometers and Waters LCT Premier™ XE. HRMS (ESI-TOF) were calibrated with angiotensin I (SIGMA), bradykinin (SIGMA), and neurotensin (SIGMA) as an internal standard. Dry dichloromethane, dry THF, and dry toluene were obtained from solvent purification columns. *N*-Iodosuccinimide was recrystallized from CCl_4–1,4-dioxane. Pulverized MS-4Å was activated by heating at 350 °C for 8 h. FluoroFlash SPE cartridges (2 g, 8 cc tube) were purchased from Fluorous Technologies Inc.

*3.1.1. 4-[2-(2-Azidoethoxy)-ethoxy]-phenol (**16**).* To a mixture of 2-(2-chloroethoxy)ethyl *p*-toluenesulfonate (**14**) (2.04 g, 7.34 mmol) and *p*-(tetrahydropyran-2-yloxy)phenol (**13**) (950 mg, 4.89 mmol), DMF (25.0 mL) was added K_2CO_3 (1.35 g, 9.78 mmol) at room temperature under argon. After the reaction mixture was stirred at 70 °C for 30 h, sodium azide (1.30 g, 19.6 mmol) and tetra-*n*-butylammonium iodide (1.80 g, 4.89 mmol) were added to the reaction mixture at the same temperature. After being stirred at same temperature for 30 h, the reaction mixture was poured into ice-cooled 3 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification. To a stirred solution of the above residue in methanol (10.0 mL) and THF (5.00 mL) was added a catalytic amount of 10-camphorsufonic acid at room temperature under argon. After being stirred at same temperature for 5 min, the reaction mixture was concentrated in vacuo. The residue purified by chromatography on silica gel with 75:25 ethyl acetate–hexane to give 4-[2-(2-azidoethoxy)ethoxy]phenol (**16**) (981 mg, 4.39 mmol, 90% in three steps). ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.73–6.85 (m, 4H), 4.10 (t, 2H, *J*=4.9 Hz), 3.84 (t, 2H, *J*=4.9 Hz), 3.74 (t, 2H, *J*=5.3 Hz), 3.41 (t, 2H, *J*=5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.9, 115.9, 115.7, 69.9, 69.6, 68.0, 50.4; IR (neat): 3377, 2929, 2106, 1603, 1509, 1452, 1346, 1233, 1129, 1063, 927, 829, 755, 643, 521 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{13}O_3$ $[M+H]^+$ *m*/*z*=224.1035, found: 224.1037.

*3.1.2. Methyl 2,3,4-tri-O-benzyl-6-O-{4-[2-(2-azidoethoxy)-ethoxy] phenyl}-α-D-glucopyranoside (**18**).* To a stirred solution of 4-[2-(2-azidoethoxy)ethoxy]phenol (**16**) (147 mg, 660 μmol) in DMF (1.00 mL) were added 63 wt% sodium hydride (50.0 mg, 1.32 mmol) and a solution of DMF (2.00 mL) and methyl 6-*O*-*p*-toluenesulfonyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**17**) (612 - mg, 989 μmol) at room temperature. After being stirred at 70 °C for 3 h, the reaction mixture was poured into ice-cooled 3 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with H_2O, saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with 20:80 ethyl acetate–hexane to give methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4-[2-(2-azidoethoxy)ethoxy]phenyl)-α-D-glucopyranoside (**18**) (354 mg, 528 μmol, 80%). $[\alpha]_D^{18}$ +51.7 (*c* 0.51, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.16–7.36 (m, 15H), 6.80 (d, 4H, *J*=10.6 Hz), 4.49–5.03 (m, 7H), 4.07–4.10 (m, 4H), 4.03 (dd, 1H, *J*=9.6, 9.6 Hz), 3.82–3.91 (m, 3H), 3.74 (t, 2H, *J*=5.3 Hz), 3.72 (dd, 1H, *J*=9.6, 9.6 Hz), 3.60 (dd, 1H, *J*=3.3, 9.6 Hz,), 3.39–3.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.2, 153.2, 153.0, 137.0, 133.2, 132.8, 132.4, 129.9, 129.7, 129.4, 129.3, 128.8, 128.3×2, 128.0, 127.9, 115.7×2, 86.3, 78.2, 76.4, 75.6, 74.9, 70.7, 70.2, 69.9, 68.2, 67.1, 50.7; FT-IR (neat): 3030, 2925, 2103, 1508, 1454, 1231, 1071, 915, 825, 738, 698 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{38}H_{43}N_3O_8[M+H]^+$ *m*/*z*=670.3128, found: 670.3124.

*3.1.3. Methyl 2,3,4-tri-O-benzyl-6-O-{4-[2-(2- tridecafluorohex-anecarboxamidoethoxy)ethoxy]phenyl}-α-D-glucopyranoside (**19**).* To a stirred solution of methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4-[2-(2-azidoethoxy)ethoxy]phenyl)-α-D-glucopyranoside (**18**) (314 mg, 470 μmol) in dry THF (3.00 mL) and H_2O (1.00 mL) were added Zn (461 mg, 7.05 mmol) and NH_4OAc (361 mg, 4.70 mmol) at 0 °C. After being stirred at room temperature for 10 min, the reaction mixture was filtered through a pad of Celite with THF (6.00 mL). To the solution, triethylamine (532 μL, 3.82 mmol) and a solution of tridecafluoroheptanoyl chloride, which was freshly prepared from tridecafluoroheptanoic acid (100 mg, 275 μmol) and

dichloromethyl methyl ether (243 μL, 2.75 mmol), were added at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was poured into ice-cooled 1 M NaOH. The aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with 1 M HCl, saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel with 20:80 ethyl acetate–hexane to give methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4-[2-(2-tridecafluorohexanecarboxamidoethoxy)ethoxy]phenyl)-α-D-glucopyranoside (**19**) (38.1 mg, 38.5 μmol, 51% in two steps). $[\alpha]_D^{18}$ +10.5 (*c* 1.55, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 7.23–7.36 (m, 15H), 6.80–6.89 (m, 5H), 4.50–5.03 (m, 6H), 4.64 (d, 1H, *J*=3.9), 4.00–4.07 (m, 5H), 3.58–3.91 (m, 9H), 3.39 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 155.5, 153.2, 152.9, 141.9, 138.7, 138.1, 130.7, 128.8, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 115.5, 115.4, 102.9, 100.5, 99.9, 99.6, 99.1, 98.3, 82.1, 81.9, 80.0, 78.0, 77.6, 77.3, 77.2, 77.1, 76.9, 76.8, 75.8, 75.2, 73.4, 71.2, 69.8, 69.3, 68.9, 67.9, 67.1, 55.2, 53.5, 40.2, 39.8, 30.3, 28.9, 23.0, 21.4; FT-IR (neat): 3341, 3064, 3032, 2929, 1721, 1508, 1454, 1360, 1235, 1210, 1096, 737, 698 (cm^{-1}).

*3.1.4. Phenylthio 2,3-O-di-benzoyl-4-O-benzyl-6-O-{4-[2-(2-chloroethoxy)ethoxy]phenyl}-β-D-glucopyranoside (**24**).* To a stirred solution of 4-[2-(2-chloroethoxy)ethoxy]phenol (**23**) (819 mg, 3.78 mmol, 1.50 equiv) and phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-β-D-glucopyranoside (**22**) (1.44 g, 2.52 mmol) in dry THF (10.0 mL) were added tributylphosphine (944 mL, 3.78 mmol) and 1,1′-(azodicarbonyl) dipiperidine (954 mg, 3.78 mmol) at room temperature under argon. After being stirred at 60 °C for 18 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue purified by chromatography on silica gel with 98:2 toluene–ethyl acetate to give phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-chloroethoxy) ethoxy]phenyl)-β-D-glucopyranoside (**24**) (1.41 g, 1.83 mmol, 72%). $[\alpha]_D^{25}$ +65.3 (*c* 0.55, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 7.90–7.96 (m, 4H), 7.03–7.51 (m, 16H), 6.88 (br d, 4H), 5.76 (dd, 1H, *J*=9.2, 9.6 Hz), 5.39 (dd, 1H, *J*=9.6, 9.9 Hz), 4.95 (d, 1H, *J*=9.9 Hz), 4.57 (d, 1H, *J*=11.1 Hz), 4.50 (d, 1H, *J*=11.1 Hz), 4.26 (dd, 1H, *J*=2.3, 10.6 Hz), 4.15 (dd, 1H, *J*=4.6, 10.6 Hz), 4.12 (t, 2H, *J*=4.9 Hz), 4.06 (dd, 1H, *J*=9.2, 9.6 Hz), 3.87 (ddd, 1H, *J*=2.3, 4.6, 9.6 Hz), 3.86 (t, 2H, *J*=4.9 Hz), 3.84 (t, 2H, *J*=5.9 Hz), 3.67 (t, 2H, *J*=5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 165.2, 157.1, 145.2, 143.4, 137.0, 136.8, 133.2, 133.1, 132.7, 132.6, 132.4, 132.3, 132.2, 129.8, 129.7, 128.8, 128.3×2, 128.2, 123.4, 115.2, 86.3, 78.2, 76.4, 75.5, 75.4, 74.8, 70.7, 70.6, 66.8, 29.6, 21.6; IR (neat): 2926, 1728, 1502, 1373, 1274, 1092, 1027, 844, 750, 710 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{43}H_{41}ClO_9S$ $[M+H]^+$ *m*/*z*=769.2238, found: 769.2202.

*3.1.5. Phenylthio 2,3-O-di-benzoyl-4-O-benzyl-6-O-{4-[2-(2-azidoethoxy)ethoxy]phenyl}-β-D-glucopyranoside (**25**).* To a stirred solution of phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-chloroethoxy)ethoxy]phenyl)-β-D-glucopyranoside (**24**) (1.74 g, 2.27 mmol) in DMF (10.0 mL) were added sodium azide (442 mg, 6.80 mmol) and tetra-*n*-butylammonium iodide (838 mg, 3.40 mmol) at room temperature under argon. After being stirred at 60 °C for 30 h, the reaction mixture was poured into ice-cooled 3 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with water, saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue purified by chromatography on silica gel with 20:80 ethyl acetate–hexane to give phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-azidoethoxy)ethoxy]phenyl)-β-D-glucopyranoside (**25**) (1.76 g, 2.27 mmol, quant.). $[\alpha]_D^{19}$ +14.4 (*c* 0.51, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 7.90–7.96 (m, 4H), 7.06–7.49 (m, 16H,), 6.88 (br d, 4H), 5.77 (dd, 1H, *J*=9.2, 9.6 Hz), 5.40 (dd, 1H, *J*=9.6, 9.9 Hz), 4.96 (d, 1H, *J*=9.9 Hz), 4.57 (d, 1H, *J*=10.9 Hz), 4.50 (d, 1H, *J*=10.9 Hz), 4.25 (d, 1H, *J*=10.2 Hz), 4.14 (dd, 1H, *J*=4.0, 10.6 Hz), 4.11 (t, 2H, *J*=4.6 Hz), 4.07 (dd, 1H, *J*=9.2, 9.6 Hz), 3.85 (m, 3H), 3.74 (t, 2H, *J*=4.9 Hz), 3.41 (t, 2H, *J*=4.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 165.6, 165.2, 153.2, 152.9, 137.0, 133.1, 132.7, 132.4, 129.8, 129.6, 129.8, 129.6, 129.3, 128.8, 128.3, 128.2, 128.0, 115.7, 115.6, 86.2, 78.2, 76.4, 75.5, 74.8, 70.7, 70.2, 69.8, 68.1, 67.0, 50.6; FT-IR (neat): 2924, 2102, 1726, 1507, 1452, 1274, 1088, 1069, 1027, 824 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{43}H_{41}N_3O_9S$ $[M+H]^+$ *m*/*z*=776.2642, found: 776.2638.

*3.1.6. Phenylthio 2,3-O-di-benzoyl-4-O-benzyl-6-O-(4-(2-(2-tridecafluorohexanecarboxamido)ethoxy)ethoxy)phenyl-β-D-glucopyranoside (**26**).* To a stirred solution of phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-azidoethoxy)ethoxy]phenyl)-β-D-glucopyranoside (**25**) (500 mg, 650 μmol) in dry THF (5.00 mL) and H_2O (2.00 mL) were added Zn (425 mg, 6.50 mmol) and NH_4Cl (348 mg, 6.50 mmol) at 0 °C. After being stirred at room temperature for 10 min, the reaction mixture was filtered through a pad of Celite with THF (10.0 mL). To the solution, triethylamine (2.26 mL, 16.2 mmol) and a solution of tridecafluoroheptanoyl chloride, which was freshly prepared from tridecafluoroheptanoic acid (473 mg, 130 mmol) and dichloromethyl was stirred at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was poured into saturated aq NH_4Cl. The aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue purified by chromatography on silica gel with 27:63 ethyl acetate–hexane to give phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-tridecafluorohexanecarboxamidoethoxy)ethoxy]phenyl)-β-D-glucopyranoside (**26**) (461 mg, 421 μmol, 65% in two steps). $[\alpha]_D^{18}$ +46.0 (*c* 1.20, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 7.90–7.96 (m, 4H, aromatic), 7.05–7.51 (m, 16H), 6.87 (m, 5H), 5.76 (dd, 1H, *J*=9.2, 9.6 Hz), 5.39 (dd, 1H, *J*=9.6, 9.9 Hz), 4.95 (d, 1H, *J*=9.9 Hz), 4.57 (d, 1H, *J*=10.9 Hz), 4.50 (d, 1H, *J*=10.9 Hz), 4.26 (d, 1H, *J*=11.8 Hz), 4.15 (dd, 1H, *J*=4.6, 11.8 Hz), 4.10 (t, 2H, *J*=4.3 Hz), 4.06 (dd, 1H, $J_{3,4}$=9.2, 9.6 Hz), 3.86 (dd, 1H, *J*=9.6, 4.6 Hz), 3.84 (t, 2H, *J*=4.3 Hz), 3.70 (t, 2H, *J*=4.6 Hz), 3.64 (t, 2H, *J*=4.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 165.7, 165.3, 158.3, 157.6, 153.1, 153.0, 144.3, 137.0, 133.2, 132.5, 129.8, 129.7, 129.3, 129.0, 128.8, 128.3, 128.2, 128.0, 127.9, 115.7, 115.6, 86.3, 78.2, 78.0, 77.2, 76.4, 75.6, 74.9, 70.7, 70.6, 69.9, 69.7, 69.1, 68.9, 67.9, 67.1, 40.0, 39.8, 29.7, 22.9; FT-IR (neat): 3336, 3063, 2931, 1724, 1508, 1452, 1274, 1088, 709 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{50}H_{42}F_{13}NO_{10}S$ $[M+H]^+$ *m*/*z*=1096.2400, found: 1096.2446.

*3.1.7. Methyl 2,3,4-tri-O-benzyl-6-O-[2,3-O-di-benzoyl-4-O-benzyl-6-O-{4-[2-(2-tridecafluorohexanecarboxamidoethoxy) ethoxy]phenyl}-β-D-glucopyranosyl]-α-D-glucopyranoside (**28**).* A mixture of phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-tridecafluorohexanecarboxamidoethoxy)ethoxy]phenyl)-β-D-glucopyranoside (**26**) (211 mg, 193 μmol), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**27**) (134 mg, 289 μmol), and pulverized activated MS4Å (193 mg) in dry CH_2Cl_2 (4.00 mL) was stirred at room temperature for 1 h under argon to remove a trace amount of water. Then the reaction mixture was cooled to −30 °C. After 5 min, *N*-iodosuccinimide (52.0 mg, 231 μmol) and a catalytic amount of trifluoro-methanesulfonic acid (8.57 μL, 96.3 μmol) were added to the reaction mixture at the same temperature. After being stirred for 1 h with being allowed to −10 °C, the reaction mixture was neutralized with triethylamine, filtered through a pad of Celite and poured into a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue purified by chromatography on silica gel with 87:13 toluene–ethyl acetate and further purified by gel permeation chromatography (GPC) to give methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-tridecafluorohexanecarboxamido

-ethoxy)ethoxy]phenyl)-β-D-glucopyranosyl)-α-D-glucopyranoside (**28**) (200 mg, 138 μmol, 72%). $[\alpha]_D^{18}$ +17.1 (*c* 1.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.85–7.93 (m, 4H), 7.02–7.52 (m, 26H), 6.83–6.86 (m, 5H, NH), 5.73 (dd, 1H, *J*=9.7, 9.7 Hz), 5.46 (dd, 1H, *J*=9.7, 9.7 Hz), 4.25–4.89 (m, 10H), 4.02–4.20 (m, 6H), 3.86 (dd, 1H, *J*=9.2, 9.2 Hz), 3.82 (t, 2H, *J*=4.8 Hz), 3.76–3.81 (m, 2H), 3.60–3.70 (m, 6H), 3.41 (dd, 1H, *J*=3.4, 9.7 Hz), 3.31 (dd, 1H, $J_{3,4}$=9.2, 9.2 Hz), 3.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.8, 165.7, 157.6, 153.1, 153.0, 147.9, 138.8, 138.2, 137.0, 133.2, 132.9, 129.7, 129.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 115.7, 115.5, 101.2, 97.9, 81.9, 79.8, 77.5, 77.2, 75.7, 75.5, 75.1, 74.8, 74.7, 74.2, 73.3, 72.0, 69.8, 69.5, 68.9, 68.2, 67.9, 67.1, 60.4, 54.9, 40.5, 39.8; FT-IR (neat): 3338, 3032, 2924, 1725, 1509, 1453, 1359, 1278, 1234, 1154, 1097, 1071, 1028, 913, 823, 738, 710, 698, 529 (cm^{-1}).

*3.1.8. Fluorous-assisted synthesis of disaccharide **30**.* Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3-*O*-di-benzoyl-4-*O*-benzyl-6-*O*-(4-[2-(2-tridecafluorohexanecarboxamidoethoxy)ethoxy]phenyl)-β-D-glucopyranosyl]-α-D-glucopyranoside (**28**) (61.0 mg, 42.1 μmol) was stirred in dry THF (1.00 mL) and EtOH (1.00 mL) at room temperature for 5 min. Then liq. NH_3 (8.00 mL) and Na (20.0 mg) were added at −50 °C. After being stirred under reflux for 1 h, the reaction mixture was quenched with MeOH. The residue was evaporated in vacuo and separated with fluorous column chromatography (Fluoro *Flash*® SPE) to give the glucopyranoside linked fluorous tag (**29**). To a stirred solution of the glucopyranoside linked fluorous tag (**29**) in dry CH_2Cl_2 (1.50 mL) and MeOH (100 μL) was added TFA (50.0 μL) at room temperature. After being stirred at room temperature for 10 min, the reaction mixture was concentrated in vacuo. The residue was evaporated in vacuo and separated with fluorous column chromatography (Fluoro *Flash*® SPE) to give methyl 6-*O*-(β-D-glucopyranosyl)-α-D-glucopyranoside (**30**) (10.0 mg, 28.1 μmol, 67%, two steps). ^1H NMR (400 MHz, D_2O): δ 4.81 (d, 1H, *J*=4.5 Hz), 4.50 (d, 1H, *J*=11.5 Hz), 4.16 (dd, 1H, *J*=1.0, 12.0 Hz), 3.91 (m, 2H), 3.80 (dd, 1H, *J*=3.0, 9.5 Hz), 3.74 (dd, 1H, *J*=5.5, 12.5 Hz), 3.68 (dd, 1H, *J*=9.5, 9.5 Hz), 3.57 (dd, 1H, *J*=4.0, 9.5 Hz), 3.39–3.53 (m, 4H), 3.44 (s, 3H), 3.33 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 103.5, 100.2, 76.7, 76.5, 74.0, 73.8, 72.0, 71.4, 70.5, 70.2, 69.3, 61.6, 56.1; HRMS (ESI-TOF) calcd for $C_{13}H_{24}O_{11}[M+H]^+$ *m*/*z*=357.1393, found: 357.1391.

*3.1.9. Methyl 2,3,4-tri-O-benzyl-6-O-[2,3-O-di-benzoyl-4-O-benzyl-6-O-(2,3-O-di-benzoyl-4-O-benzyl-6-O-{4-[2-(2-tridecafluorohexanecarboxamidoethoxy)ethoxy]phenyl}-β-D-glucopyranosyl)-β-D-glucopyranosyl]-α-D-glucopyranoside (**34**).* A mixture of the glycosyl bromide (**31**) prepared from thioglycoside **26** (100 mg, 91.2 μmol) and CH_2Cl_2 solution of IBr (137 μmL, 137 μmol), phenylthio 2,3-*O*-di-benzoyl-4-*O*-benzyl-β-D-glucopyranoside (**22**) (47.3 mg, 82.9 μmol) and pulverized activated MS4Å (83.0 mg) in dry CH_2Cl_2 (2.00 mL) was stirred at room temperature for 1 h under argon to remove a trace amount of water. Then the reaction mixture was cooled to −78 °C. After 5 min, a dry toluene (500 μL) solution of AgOTf (27.7 mg, 108 μmol) was added to the reaction mixture at the same temperature. After being stirred for 1.5 h with being allowed to −40 °C, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**27**) (54.0 mg, 116 μmol), *N*-iodosuccinimide (22.4 mg, 99.5 μmol) and a catalytic amount of trifluoromethanesulfonic acid (2.21 μL, 24.9 μmol) were added to the reaction mixture at the same temperature. After being stirred for 1 h with being allowed to −10 °C, the reaction mixture was neutralized with triethylamine, filtered through a pad of Celite and poured into a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with 84:16 toluene–ethyl acetate and further purified by gel permeation chromatography (GPC) to give the trisaccharide (**33**) (130 mg). The partial of the trisaccharide (**33**) (58.8 mg) was stirred in dry THF (1.00 mL) and EtOH (1.00 mL) at room temperature for 5 min. Then liq. NH_3 (8.00 mL) and sodium (20.0 mg) were added at −50 °C. After being stirred under reflux for 30 min, the reaction mixture was quenched with MeOH. The residue was evaporated in vacuo and separated with fluorous column chromatography (Fluoro *Flash*® SPE) to give the trisaccharide linked fluorous tag. To a stirred solution of the above trisaccharide linked fluorous tag in dry CH_2Cl_2 (1.50 mL) and MeOH (100 μL) was added TFA (50.0 μL) at room temperature. After being stirred at room temperature for 10 min, the reaction mixture was concentrated in vacuo. The residue was evaporated in vacuo and separated with fluorous column chromatography (Fluoro *Flash*® SPE) to give methyl 6-*O*-(6-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl)-α-D-glucopyranoside (**34**) (11.2 mg, 21.7 μmol, 59% based on **22**). ^1H NMR (400 MHz, D_2O): δ 4.81 (d, 1H, *J*=4.5 Hz), 4.56 (d, 1H, *J*=8.5 Hz), 4.48 (d, 1H, $J_{1,2}$=8.5 Hz), 4.22 (d, 1H, *J*=11.5 Hz), 4.19 (dd, 1H, *J*=1.0, 12.0 Hz), 3.95–3.87 (m, 3H), 3.81 (dd, 1H, *J*=3.0, 9.5 Hz), 3.74 (dd, 1H, *J*=5.5, 12.5 Hz), 3.68 (dd, 1H, *J*=9.5, 9.5 Hz), 3.65–3.62 (m, 1H), 3.57 (dd, 1H, *J*=4.0, 9.5 Hz), 3.53–3.39 (m, 6H), 3.44 (s, 3H), 3.36–3.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.6×2, 100.2, 76.7, 76.5, 76.4, 75.8, 73.9, 73.8, 72.0, 71.4, 70.4, 70.2, 70.1, 69.4, 69.3, 61.5, 56.1; HRMS (ESI-TOF) calcd for $C_{19}H_{34}O_{16}[M+H]^+$ *m*/*z*=519.1925, found: 519.1917.

References and notes

1. (a) Varki, A. *Glycobiology* **1993**, *3*, 97–130; (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720; (c) Hakomori, S. *Arch. Biochem. Biophys.* **2004**, *426*, 173–181; (d) Bucior, I.; Burger, M. M. *Curr. Opin. Struct.* **2004**, *14*, 631–637.
2. (a) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349–4393; (b) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934; (c) Wu, C. Y.; Wong, C.-H. *Chem. Commun.* **2011**, 6201–6207.
3. Review for the one-pot glycosylationsee: (a) Tanaka, H.; Yamada, H.; Takahashi, T. *Trends Glycosci. Glycotechnol.* **2007**, *19*, 183–193; (b) Wang, Y.; Ye, X.-S.; Zhang, L.-H. *Org. Biomol. Chem.* **2007**, *5*, 2189–2200.
4. (a) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919–7920; (b) Tanaka, H.; Adachi, M.; Takahashi, T. *Chem.—Eur. J.* **2005**, *11*, 849–862.
5. (a) Tanaka, H.; Ishida, T.; Matoba, N.; Tsukamoto, H.; Yamada, H.; Takahashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6349–6352; (b) Tanaka, H.; Tateno, Y.; Nishiura, Y.; Takahashi, T. *Org. Lett.* **2008**, *10*, 5597–5600.
6. (a) Takahashi, T.; Adachi, M.; Matsuda, A.; Doi, T. *Tetrahedron Lett.* **2000**, *41*, 2599–2603; (b) Tanaka, H.; Matoba, N.; Tsukamoto, H.; Takimoto, H.; Yamada, H.; Takahashi, T. *Synlett* **2005**, 824–828.
7. Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826.
8. (a) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865; (b) Zhang, W. *Chem. Rev.* **2009**, *109*, 749–795.
9. (a) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714–6715; (b) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069–9072.
10. Selected results of applications of heavy fluorous-tag assisted synthesis of oligosaccharide. (a) Goto, K.; Mizuno, M. *Tetrahedron Lett.* **2010**, *51*, 6539–6541; (b) Miura, T.; Goto, K.; Hosaka, D.; Inazu, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2047–2051; (c) Miura, T.; Hirose, Y.; Ohmae, M.; Inazu, T. *Org. Lett.* **2001**, *3*, 3947–3950; (d) Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937–4940.
11. Selected results of applications of light fluorous-tag assisted synthesis of oligosaccharide. (a) Ali, A.; van den Berg, R. J. B. H. N.; Overkleeft, H. S.; Filippov, D. V.; van der Marel, G. A.; Codee, J. D. C. *Tetrahedron Lett.* **2009**, *50*, 2185–2188; (b) Zhang, F.; Zhang, W.; Zhang, Y.; Curran, D. P.; Liu, G. *J. Org. Chem.* **2009**, *74*, 2594–2597; (c) Kim, S.; Tsuruyama, A.; Ohmori, A.; Chiba, K. *Chem. Commun.* **2008**, 1816–1818; (d) Ko, K.-S.; Park, G.; Yu, Y.; Pohl, N. L. *Org. Lett.* **2008**, *10*, 5381–5384; (e) Tojino, M.; Mizuno, M. *Tetrahedron Lett.* **2008**, *49*, 5920–5923; (f) Park, G.; Ko, K.-S.; Zakharova, A.; Pohl, N. L. *J. Fluorine Chem.* **2008**, *129*, 978–982; (g) Jaipuri, F. A.; Pohl, N. L. *Org. Biomol. Chem.* **2008**, *6*, 2686–2691; (h) Chen, G.-S.; Pohl, N. L. *Org. Lett.* **2008**, *10*, 785–788; (i) Jaipuri, F. A.; Collet, B. Y. M.; Pohl, N. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1707–1710; (j) Kojima, M.; Nakamura, Y.; Takeuchi, S. *Tetrahedron Lett.* **2007**, *48*, 4431–4436; (k) Carrel, F. R.; Geyer, K.; Codée, J. D. C.; Seeberger, P. H. *Org. Lett.* **2007**, *9*, 2285–2288; (l) Manzoni, L.; Castelli, R. *Org. Lett.* **2006**, *8*, 955–957; (m) Kasuya, M. C. Z.; Ito, A.; Cusi, R.; Sato, T.; Hatanaka, K. *Chem. Lett.* **2005**, *34*, 856–857; (n) Manzoni, L.; Castelli, R. *Org. Lett.* **2004**, *6*, 4195–4198; (o) Jing, Y.; Huang, X. *Tetrahedron Lett.* **2004**, *45*, 4615–4618; (p) Kasuya, M. C. Z.; Cusi, R.; Ishihara, O.; Miyagawa, A.; Hashimoto, K.; Sato, T.; Hatanaka, K. *Biochem. Biophys. Res. Commun.* **2004**, *316*, 599–604; (q) Manzoni, L. *Chem. Commun.* **2003**, 2930–2931.
12. (a) Goto, K.; Mizuno, M. *Tetrahedron Lett.* **2007**, *48*, 5605–5608; (b) Mizuno, M.; Kitazawa, S.; Goto, K. *J. Fluorine Chem.* **2008**, *129*, 955–960.