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Rapid oligosaccharide synthesis on a fluorous support

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Abstract—The novel fluorous support **Hfb** (hexakisfluorous chain-type butanoyl) was easily prepared. The **Hfb** group was readily introduced into the anomeric hydroxyl group of a carbohydrate, and was recyclable after cleavage. The use of the **Hfb** group was applicable for the rapid oligosaccharide synthesis in which the synthetic intermediates could be purified using fluorous and normal organic solvents. Each synthetic intermediate could be monitored by TLC, NMR and mass spectrometry.

1. Introduction

Recently, it has been gradually revealed that oligosaccharides on cell surfaces play important roles in various biological processes such as cell-cell interaction, cell adhesion and immunogenic recognition.[1] In order to better understand the functions of oligosaccharides, it is necessary to rapidly and efficiently synthesize oligosaccharides. However, it is difficult to synthesize oligosaccharides because of two crucial problems. First, a multitude of hydroxyl groups have similar reactivity of each monomer, and the effective differentiation of each hydroxyl group is required to afford the glycosyl donors and acceptors. Secondly, a control of stereoselectivity at anomeric position in each glycosylation is not easy. Due to these problems, the synthesis of oligosaccharides needs a lengthy process that requires the exact optimization of the reaction conditions and chromatographic purification of the reaction mixture in each step. Therefore, there is no commercially available automatic synthesizer of an oligosaccharide. On the other hand, peptides and nucleotides are easily prepared by a commercially available automatic synthesizer using a solid-phase synthesis. The solid-phase synthesis of oligosaccharides has also been extensively studied,[2] however, the usual solid-phase method suffers from some serious disadvantages, such as the difficulty in large-scale synthesis and the inability to monitor the reaction by TLC, NMR spectroscopic analysis and mass spectrometry. The solid-phase synthesis of oligosaccharide that uses a soluble polymer support (PEG) has also been reported.[2] This strategy can overcome some of these disadvantages, however, it cannot be monitored by TLC and the intermediates cannot be purified by silica-gel column chromatography. To rapidly and efficiently synthesize oligosaccharides, we adopted another concept such as fluorous chemistry that was reported by Horváth and Rabái as the fluorous biphasic system in 1994.[3] A fluorous (highly fluorinated) solvent such as perfluorohexane and perfluoromethylcyclohexane is immiscible in most organic solvents and water, and three layers are formed. A fluorous compound exhibits a high solubility for fluorous solvents, and is readily separated from non-fluorinated compounds by a simple fluorous-organic solvent partition. Since Horváth and Rabái reported this concept, it has been developed for use in a combinatorial chemistry, a parallel synthesis and a catalytic chemistry.[4,5] In addition, since Curran and co-workers described the fluorous synthesis[5] (fluorous-tag method) as a strategic alternative to solid-phase synthesis, fluorous chemistry has become more popular in organic synthesis, such as the Baeyer–Villigar[6] or Swern[7] oxidation, Heck[8] or Suzuki[9] coupling, the Mitsunobu reaction,[10] Friedel–Crafts acylation[11] and so on.[12] Furthermore, they have also reported a fluorous mixture synthesis using a fluorous silica-gel.[13] The fluorous protecting groups are essential for the fluorous synthesis performance. Several fluorous hydroxy protecting groups such as acetal, silyl and benzyl groups have already been reported.[14,15] Other

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fluorous protecting groups for amino or carboxyl groups have also been reported.[16] Curran and co-workers adapted the fluorous-tag method to the fluorous disaccharide synthesis using the fluorous benzyl protecting group by a glycal method.[15] Unfortunately, their glycosylation method gave only the 2-deoxy disaccharides and could not synthesize the longer chain oligosaccharides in order to introduce the fluorous benzyl groups to the glycosyl donor. In addition, the yield for the reaction step to introduce the fluorous benzyl group to the hydroxyl group was not satisfactory. Recently, we reported a method for the fluorous oligosaccharide synthesis involving the novel fluorous acyl protecting group **Bfp** (bisfluorous chain-type propanoyl).[17,18] We also reported the fluorous support **Hfb** (hexakisfluorous chain-type butanoyl) in a preliminary communication.[19] Herein we describe the full details of the development of a novel fluorous support **Hfb** and its application to the rapid synthesis of oligosaccharides. Moreover, several glycosylation methods using the fluorous support **Hfb** was studied. Our concept of fluorous oligosaccharide synthesis is shown in Figure 1. We adopted the introduction of a fluorous support only at the anomeric hydroxyl group of the glycosyl acceptor in order to more efficiently synthesize the longer chain oligosaccharides. The glycosyl acceptor containing the fluorous support couples with the glycosyl donor to afford the fluorous disaccharide. After partition of the reaction mixture with fluorous and normal organic solvents, the fluorous disaccharide is extracted by the fluorous layer, and the excess amount of the glycosyl donor is extracted by the organic layer. After selective deprotection, repeating this procedure gives the fluorous oligosaccharide, which is able to be purified only by liquid–liquid extraction without column chromatography. Finally, the fluorous support is removed to give the desired oligosaccharide extracted with an organic solvent. The fluorous support is extracted by a fluorous solvent and is recyclable.

2. Results and discussion

We designed and synthesized compound **10** with six fluorous chains as a novel fluorous support. Compound **4**, which contains three fluorous chains, was prepared as a precursor (Scheme 1). The reaction of **Bfp**-OH[17] (**1**) with a fluorous amine **2**[17] provided compound **3** in 96% yield. The treatment of **3** with aqueous sodium hydroxide gave the fluorous carboxylic acid **4**, which contains three fluorous chains, in 98% yield.

We synthesized compound **10** by two methods using compound **4**, and first attempted to prepare compound **10** using route A (Scheme 2).[19]

The two primary amino groups of diethylenetriamine (**5**) were protected with the triphenylmethyl group to provide the amine **6**[20] in 95% yield. Compound **6** was coupled with methyl hydrogen glutarate to afford compound **7** in 98% yield. Removal of the triphenylmethyl groups from **7** were performed by treatment of HCl in dioxane to give compound **8**. Compound **8** was reacted with fluorous carboxylic acid **4** (2 equiv.) to afford a fluorous ester **9**, which contains six fluorous chains, in 82% yield. The treatment of **9** with aqueous sodium hydroxide gave a fluorous support **10** in 98% yield. The acyl moiety of **10** was

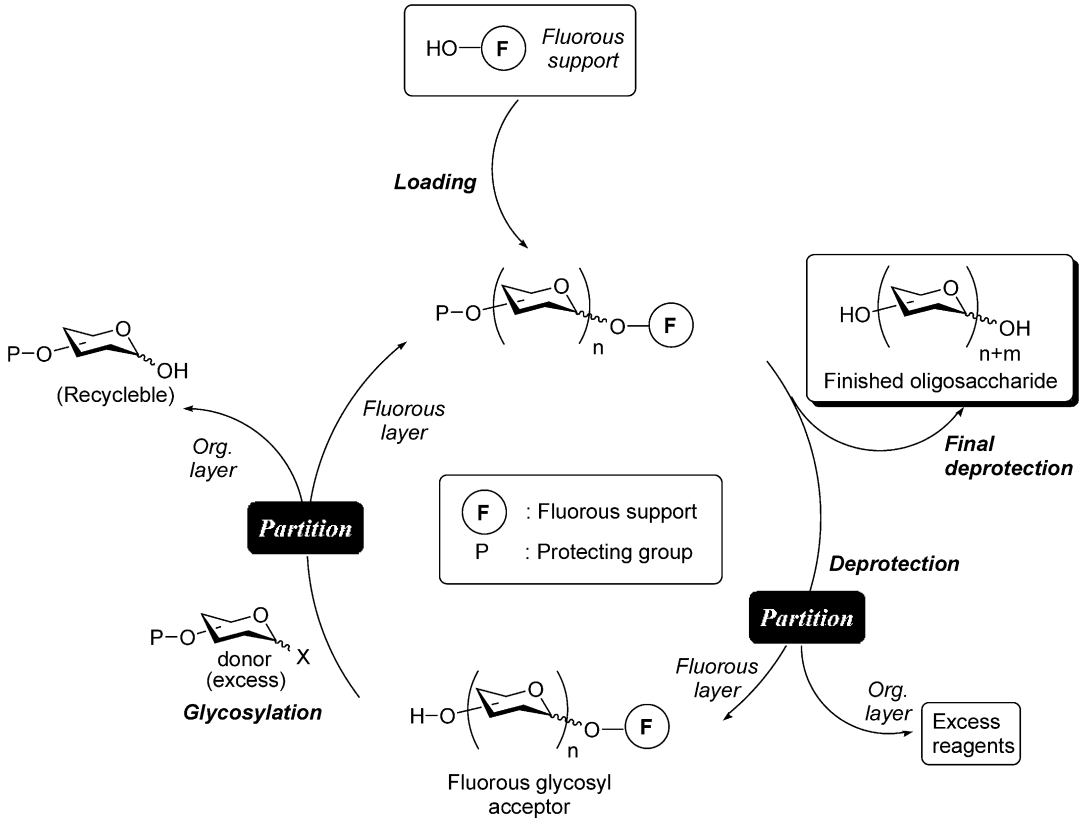
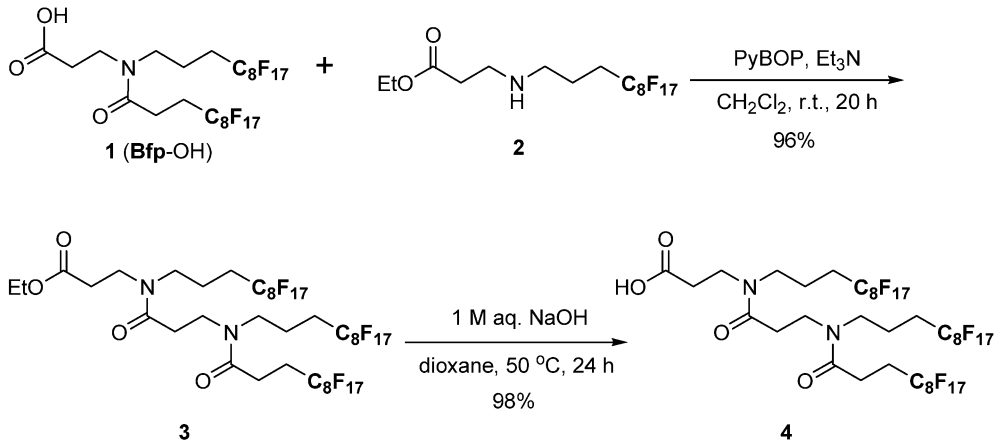


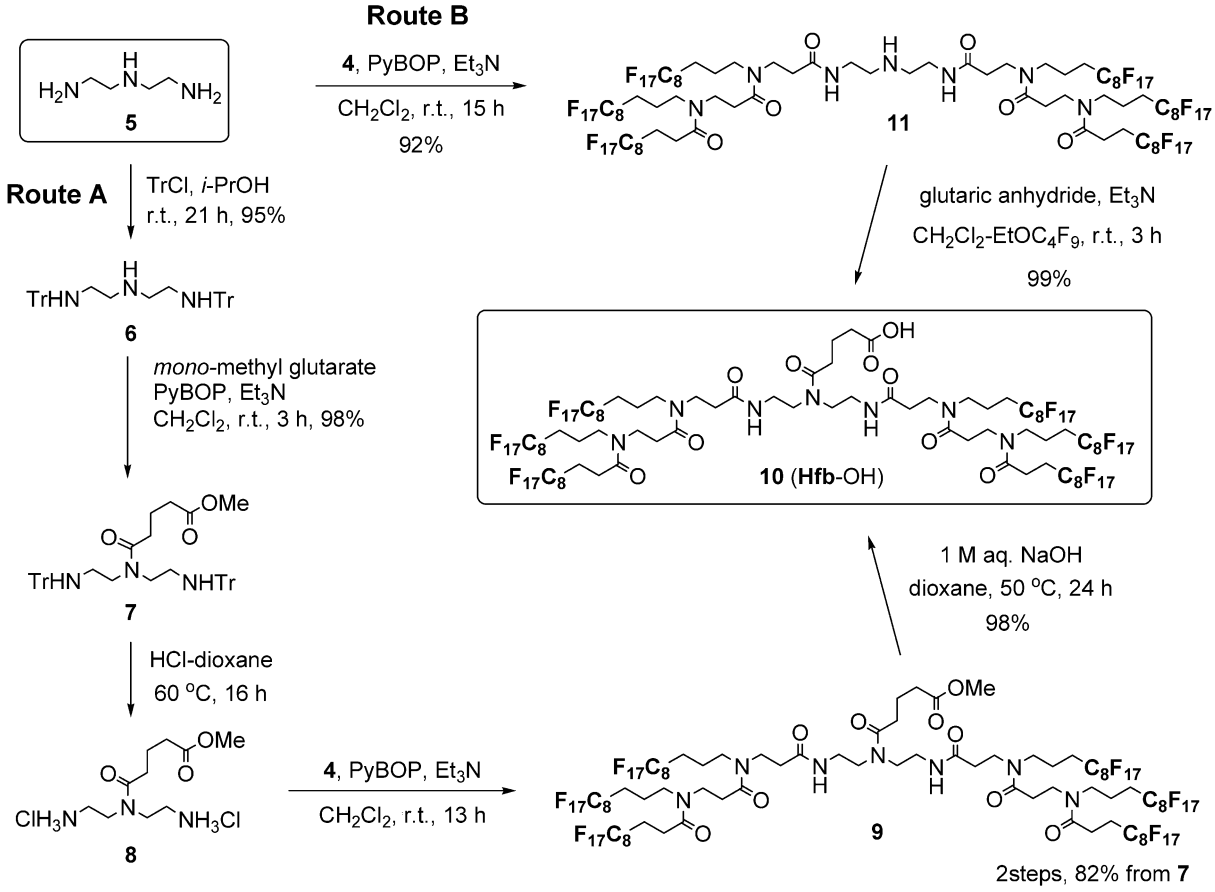
Figure 1. Concept of oligosaccharide synthesis.



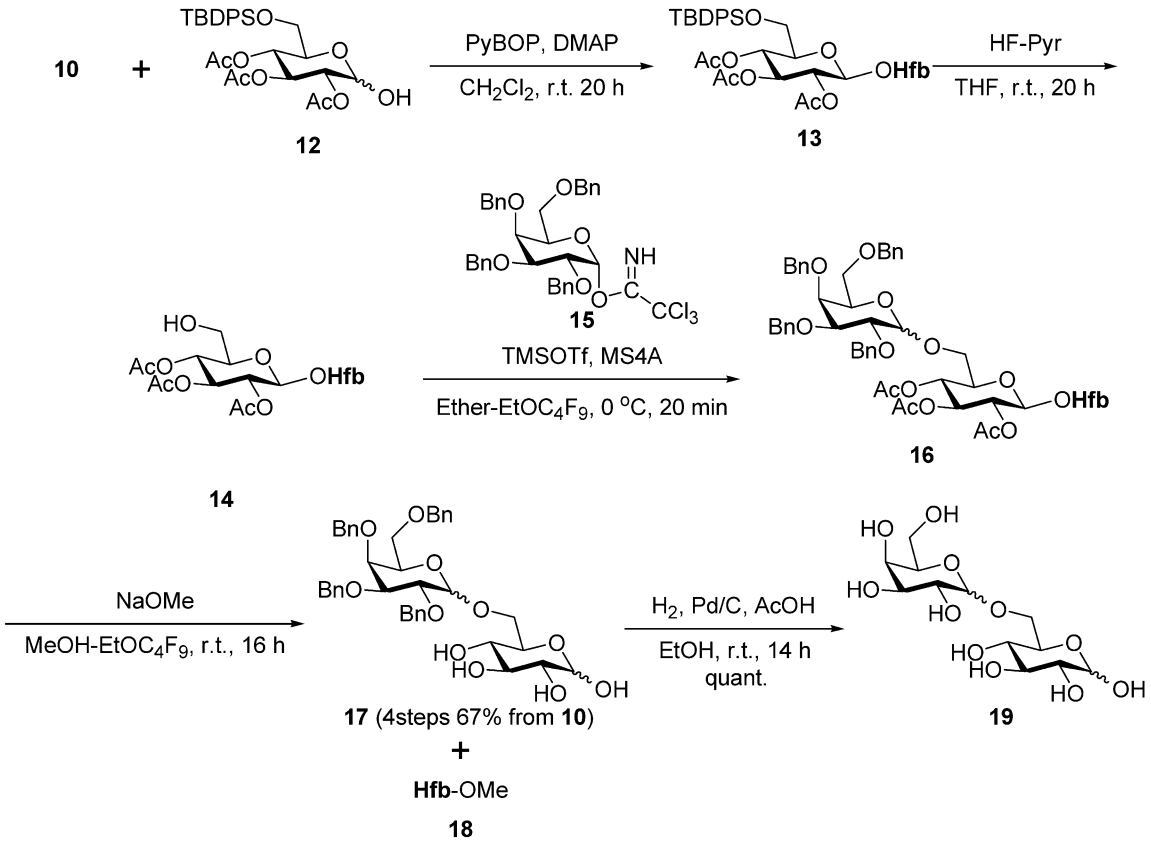
Scheme 1. Preparation of fluorous carboxylic acid **4**.

named **Hfb** (hexakisfluorous chain-type butanoyl). We thought that the six fluorous chains of **10** enhance the efficiency of the liquid–liquid extraction better than the **Bfp** group containing two fluorous chains. Thus we achieved the synthesis of **Hfb**-OH (**10**) by route A. However, route A is unsuitable for the rapid and convenient synthesis of **Hfb**-OH (**10**) due to the lengthy steps. We planned route B as shown in Scheme 2. The two primary amino group of diethylenetriamine (**5**) were directly reacted with **4** (2 equiv.) to provide a fluorous amine **11**, which contains six fluorous chains, in 92% yield. Compound **11** was coupled with glutaric anhydride to produce **Hfb**-OH (**10**) in high yield. Route A is 5 steps with a 75% overall yield from **5**, on the other hand, route B is only 2 steps with 90% yield. As a result, we improved the synthesis of **Hfb**-OH (**10**) marking it more efficient and produced a higher yield than the preliminary communication.[19]

At first, a synthesis of the disaccharide **17** was performed (Scheme 3). Among the many useful methods for glycosylation we selected Schmidt method as one of the most major synthetic methods to prepare an oligosaccharide.[21] The fluorous support **Hfb** was easily introduced into the anomeric hydroxyl group of the glucose derivative **12**



Scheme 2. Synthesis of Hfb-OH (**10**).



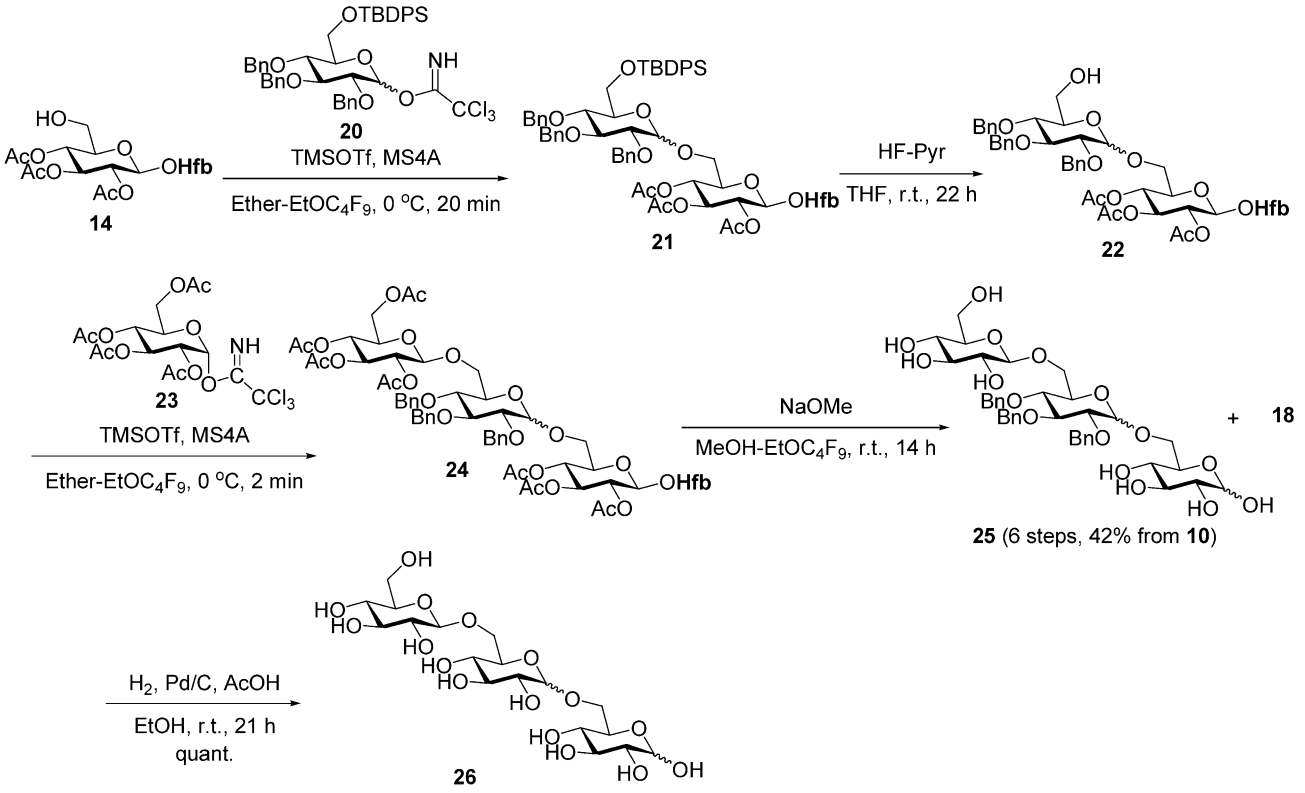
Scheme 3. Disaccharide synthesis on fluorous support **Hfb**.

using PyBOP and 4-dimethylaminopyridine (DMAP) to give the fluorous compound **13**.[22] Removal of the TBDPS group from **13** was achieved by treatment with HF-pyridine in THF to afford the flourous glycosyl acceptor **14**.[22] The fluorous disaccharide **16**[22] was obtained by the reaction of **14** with the excess glycosyl donor **15**[21] in the presence of trimethylsilyl trifluoromethanesulfonate (TMS-OTf) in ether–$EtOC_4F_9$.[23] $EtOC_4F_9$ is miscible in most organic solvents and fluorous solvents. The fluorous intermediates **13**, **14** and **16** were respectively extracted with the fluorous solvent FC-72[24] by partitioning the product mixtures between FC-72 and an organic solvent such as MeOH, MeCN and toluene. No further purification such as silica-gel column chromatography was carried out. The **Hfb** group of **16** was easily removed by treatment with NaOMe in MeOH–$EtOC_4F_9$ to afford crude **17**, which was extracted with MeOH by partitioning the mixture between FC-72 and MeOH. The methyl ester of **Hfb** (**Hfb**-OMe, **18**) was recovered from the FC-72 layer in 81% yield. Compound **18** was treated with aqueous sodium hydroxide to give **Hfb**-OH (**10**), which was reused. After a single silica-gel column chromatographic purification step, the disaccharide **17** was obtained in 67% overall yield from **12** (4 steps). The benzyl groups of compound **17** were removed by hydrogenation in the presence of Pd/C to afford compound **19**.[25,26]

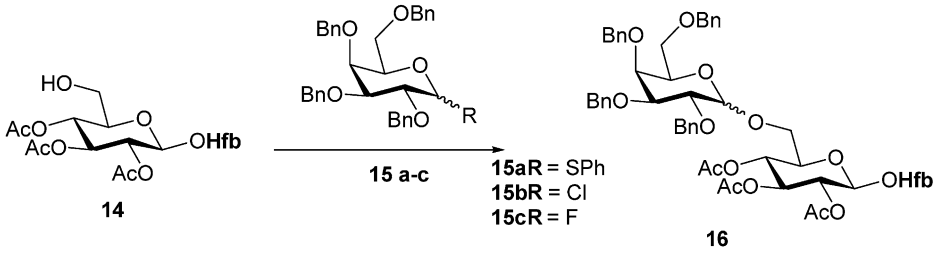
Next, we synthesized the longer chain oligosaccharide, and the fluorous glycosyl acceptor **14** was reacted with the glycosyl donor **20**[27] to afford the fluorous disaccharide **21** (Scheme 4).[22,28] Removal of the TBDPS group from **21** was achieved by treatment with HF-Pyr in THF to afford the fluorous compound **22**.[22] The reaction of the glycosyl acceptor **22** with the glycosyl donor **23**[21] under similar glycosidation conditions afforded the fluorous trisaccharide **24**.[22,28] The fluorous intermediates **21**, **22** and **24** were respectively extracted with the fluorous solvent FC-72 by partitioning the product mixtures between FC-72 and the organic solvents. No further purification such as silica-gel column chromatography was performed. The **Hfb** group of **24** was removed by the same method, as described above. After a single silica-gel column chromatographic purification step, the trisaccharide **25** was obtained in 42% overall yield from **10** (6 steps). The benzyl groups of compound **25** were removed by hydrogenation in the presence of Pd/C to afford compound **26**.[29,30]

Among the many useful methods for glycosylation, we attempted only Schmidt method as the major synthetic method to provide oligosaccharide.[21] Therefore, we applied other glycosylation methods to the fluorous acceptor **14** (Scheme 5).

We performed the thioglycoside method,[31] the Köenigs–Knorr method[32] and the Suzuki method[33] (Table 1). All these methods gave the corresponding disaccharides as a white solid in good yield. Especially, entry 5 (Suzuki method) and entries 7 and 8 (thioglycoside method) show that these methods gave the corresponding disaccharide in good yields with the use of a small excess of the glycosyl donor. As a result, it was found that the major glycosylation



Scheme 4. Trisaccharide synthesis on fluorous support **Hfb**.



Scheme 5.

Table 1. Study of glycosylation using various glycosylation methods on fluorous support **Hfb**

Entry	Temperature (°C)	Time	Solvent	R	Donor (equiv.)	Activator	Yield (%)[a]	α/β ratio[b]
1	0	24 h	Ether–$EtOC_4F_9$	Cl	10	AgOTf–$AgCl_4$	61	2.5:1
2	0	25 h	Ether–$EtOC_4F_9$	Cl	3	AgOTf–$AgCl_4$	39	2.0:1
3	−20	2.5 h	Ether–$EtOC_4F_9$	F	10	Cp_2ZrCl_2–$AgClO_4$	93	1.3:1
4	−20	2.5 h	Ether–$EtOC_4F_9$	F	5	Cp_2ZrCl_2–$AgClO_4$	77	1.5:1
5	−20	4 h	Ether–$EtOC_4F_9$	F	3	Cp_2ZrCl_2–$AgClO_4$	70	1.6:1
6	0	20 min	CH_2Cl_2–$EtOC_4F_9$	Sph	5	NIS–TfOH	72	1.4:1
7	0	50 min	CH_2Cl_2–$EtOC_4F_9$	Sph	3	NIS–TfOH	80	1.6:1
8	0	2.5 h	CH_2Cl_2–$EtOC_4F_9$	Sph	1.5	NIS–TfOH	81	1.4:1

[a] Isolated yield.
[b] Detected by ^1H NMR spectra of products after deprotection.

methods were available for the fluorous oligosaccharide synthesis.

3. Conclusion

The use of the **Hfb** group as a fluorous support made it possible to rapidly synthesize an oligosaccharide by minimal column chromatography purification. We achieved the synthesis of **Hfb**-OH (**10**) quite efficiently and rapidly compared it with the previous method.[19] The **Hfb** group was readily introduced into the anomeric hydroxyl groups of the glycosyl acceptor, and removed in high yield by the usual procedure. Moreover, it was recyclable after cleavage. Each fluorous synthetic intermediate could be obtained in a straightforward manner by simple FC-72-organic solvent extraction. The reaction conditions for each synthetic step could be rapidly optimized, because the reactions could be

monitored by TLC and mass spectrometry in contrast to the usual solid-phase reactions. Although the fluorous intermediates could also be measured by NMR spectroscopic analysis, the peaks in the NMR of the fluorous compounds containing the **Hfb** group are somewhat broad due to the influence of the amide linkages and the fluorous groups.[15] Although the fluorous intermediates could also be subjected to silica-gel column chromatography, only the final compounds were purified by chromatography. This fluorous oligosaccharide synthesis should be applicable for a large-scale synthesis. Furthermore, it was found that major glycosylation methods were available to the fluorous oligosaccharide synthesis. Thus the oligosaccharide synthesis using the fluorous support **Hfb** is an excellent alternative strategy to solid-phase method. Further application for the synthesis of a bioactive carbohydrate and glycoconjugate is now in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded using JEOL JNM-EX-400 (400 MHz) or JEOL JNM-ECA-600 (600 MHz) spectrometers. MALDI-TOF MS. were recorded using Voyager-DE STR, and α-cyano-4-hydroxy cinnamic acid was used as a matrix. ESI-TOF MS. were recorded on Mariner™. Part of the product was isolated by column chromatography on silica-gel (Kanto Chemical, silica-gel 60 N, spherical, neutral, 40–50 μm). The fluorous solvent FC-72 and Novec HFE-7200 were purchased from 3 M Tokyo. The aqueous NH_3 was 28% aqueous solution purchased from Wako Pure Chemical Industries, Ltd.

4.1.1. Compound 3. Triethylamine (4.0 mL, 29.2 mmol) and PyBOP (6.08 g, 17.7 mmol) were added to a solution of compound **1** (**Bfp**-OH; 10.0 g, 9.77 mmol) and **2** (5.64 g, 9.77 mmol) in CH_2Cl_2 (120 mL) at room temperature. After stirring for 20 h at room temperature, the reaction mixture was added to water, and then extracted with $CHCl_3$. The $CHCl_3$ layers were washed with water, 2 M aq. HCl, saturated aq. $NaHCO_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica-gel (hexane–AcOEt, 1:1) to give compound **3** (14.9 g, 96%) as a white amorphous solid. R_f=0.56 (hexane–AcOEt, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.20–1.30 (m, 3H), 1.80–1.95 (m, 4H), 2.01–2.17 (m, 4H), 2.46–2.79 (m, 8H), 3.36–3.54 (m, 4H), 3.56–3.76 (m, 4H), 4.09–4.20 (m, 2H); MALDI-TOF MS: Calcd for $C_{41}H_{30}F_{51}N_2O_4$ *m/z* $[M+H]^+$: 1583.1, Found: 1583.7; Calcd for $C_{41}H_{29}F_{51}N_2O_4Na$ *m/z* $[M+Na]^+$: 1605.1, Found: 1606.1; Calcd for $C_{41}H_{29}F_{51}N_2O_4K$ *m/z* $[M+K]^+$: 1621.1, Found: 1622.4.

4.1.2. Compound 4. To a solution of compound **3** (22.2 g, 14.0 mmol) in 1,4-dioxane (300 mL) was added 1 M aq. NaOH (150 mL) at room temperature. After stirring for 4 h at 50 °C, 2 M aq. HCl was added and the reaction mixture was adjusted to pH 2. The reaction mixture was extracted three times with AcOEt–$EtOC_4F_9$ (2:1), dried over anhydrous Na_2SO_4, and concentrated. Compound **4** (21.5 g, 99%) was obtained as a white amorphous solid. R_f=0.56 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.81–1.96 (m, 4H), 2.01–2.17 (m, 4H), 2.47–2.79 (m, 8H), 3.39–3.55 (m, 4H), 3.57–3.75 (m, 4H); MALDI-TOF MS; Calcd for $C_{39}H_{25}F_{51}N_2O_4Na$ *m/z* $[M+Na]^+$: 1577.1, Found: 1576.5; Calcd for $C_{39}H_{25}F_{51}N_2O_4K$ *m/z* $[M+K]^+$: 1593.1, Found: 1592.3.

4.1.3. Compound 6.[20] Diethylamine (6.0 mL, 61.2 mmol) and chlorotriphenylmethane (17.0 g, 61.2 mmol) were added to a solution of compound **5** (diethylenetriamine; 3.0 mL, 27.8 mmol) in 2-propanol (60 mL) at room temperature. After stirring for 21 h at room temperature, 1 M aq. NaOH was added, and the reaction mixture was adjusted to pH 11. The reaction mixture was extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica-gel ($CHCl_3$–MeOH, 20:1) to give compound **6** (15.5 g, 95%) as a white amorphous solid.

4.1.4. Compound 7. Triethylamine (51 μL, 0.37 mmol) and PyBOP (143 mg, 0.275 mmol) were added to a solution of compound **6** (108 mg, 0.184 mmol) and methyl hydrogen glutarate (28 μL, 22 μmol) in CH_2Cl_2 (2 mL) at room temperature. After stirring for 3 h at room temperature, the reaction mixture was added to water, and then extracted with AcOEt. The AcOEt layers were washed with water, 2 M aq. HCl, saturated aq. $NaHCO_3$, and brine. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica-gel (hexane–AcOEt, 3:2) to give compound **7** (129 mg, 98%) as a white amorphous solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.64 (brs, 2H), 1.96 (t, J=7.6 Hz, 2H), 2.22 (t, J=6.2 Hz, 2H), 2.26 (t, J=6.2 Hz, 2H), 2.39 (t, J=7.6 Hz, 2H), 2.45 (t, J=7.6 Hz, 2H), 3.33 (t, J=6.2 Hz, 2H), 3.38 (t, J=6.2 Hz, 2H), 3.33 (s, 3H), 7.12–7.44 (m, 30H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=20.60, 32.28, 33.58, 42.09, 42.34, 45.91, 48.47, 51.50, 70.77, 70.94, 126.24, 126.79, 128.00, 128.41, 128.52, 145.62, 146.00, 172.61, 173.77; HRMS (ESI-TOF MS.): Calcd for $C_{48}H_{50}N_3O_3$ *m/z* $[M+H]^+$: 716.3847, Found: 716.3811.

4.1.5. Compound 8. A solution of 4 M HCl in dioxane (55 mL) was added to compound **7** (3.82 g, 5.43 mmol) at room temperature. After stirring for 16 h at 60 °C, AcOEt was added to the reaction mixture, and then filtered. The crude product of **8** (1.64 g) was obtained as a white solid, and used in the next step without further purification.

4.1.6. Compound 9. Triethylamine (3.87 mL, 27.9 mmol) and PyBOP (12.5 g, 24.0 mmol) were added to a solution of the crude compounds **8** (1.47 g) and **4** (17.2 g, 11.1 mmol) in CH_2Cl_2 (400 mL) at room temperature. After stirring for 13 h at room temperature, toluene was added to the reaction mixture and CH_2Cl_2 was concentrated. The toluene solution was partitioned three times with FC-72. The combined FC-72 layers were then concentrated. The residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH, 20:1) to give compound **9** (13.1 g, 82%) as a white amorphous solid. R_f=0.54 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.76–1.98 (m, 10H), 1.99–2.17 (m, 8H), 2.34–2.88 (m, 20H), 3.31–3.53 (m, 16H), 3.54–3.78 (m, 11H); MALDI-TOF MS: Calcd for

$C_{88}H_{68}F_{102}N_7O_9$ *m/z* $[M+H]^+$: 3304.3, Found: 3305.8; Calcd for $C_{88}H_{67}F_{102}N_7O_9Na$ *m/z* $[M+Na]^+$: 3326.3, Found: 3327.5; Calcd for $C_{88}H_{67}F_{102}N_7O_9K$ *m/z* $[M+K]^+$: 3342.3, Found: 3342.6.

4.1.7. Compound 10. *Route A*. To a solution of compound **9** (1.55 g, 0.454 mmol) in 1,4-dioxane (80 mL) was added 1 M aq. NaOH (40 mL) at room temperature. After stirring for 24 h at 50 °C, 2 M aq. HCl was added, and the reaction mixture was adjusted to pH 2. The reaction mixture was extracted three times with AcOEt–$EtOC_4F_9$ (2:1), dried over anhydrous Na_2SO_4 and concentrated. Compound **10** (1.44 g, 97%) was obtained then used in the next step without further purification. R_f=0.54 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.80–1.99 (m, 10H), 2.00–2.17 (m, 8H), 2.34–2.80 (m, 20H), 3.35–3.55 (m, 16H), 3.56–3.75 (m, 8H); MALDI-TOF MS; Calcd for $C_{87}H_{66}F_{102}N_7O_9$ *m/z* $[M+H]^+$: 3290.3, Found: 3291.5; Calcd for $C_{87}H_{65}F_{102}N_7O_9Na$ *m/z* $[M+Na]^+$: 3312.3, Found: 3315.5.

Route B. Triethylamine (197 μL, 1.42 mmol) and glutaric anhydride (81.0 mg, 0.708 mmol) were added to a solution of compound **11** (450 mg, 0.142 mmol) in $EtOC_4F_9$ (4.5 mL) and CH_2Cl_2 (4.5 mL) at room temperature. After stirring for 3 h at room temperature, 2 M aq. HCl was added and the reaction mixture was adjusted to pH 2. The reaction mixture was extracted three times with AcOEt–$EtOC_4F_9$ (2:1), dried over anhydrous Na_2SO_4 and concentrated. The crude product of **10** (464 mg, 99%) was used in the next step without further purification.

4.1.8. Compound 11. Diethylenetriamine (81 μL, 0.75 mmol) and PyBOP (935 mg, 1.80 mmol) were added to a solution of crude compound **4** (1.47 g) and triethylamine (416 μL, 3.00 mmol) in CH_2Cl_2 (25 mL) at room temperature. After stirring for 15 h at room temperature, the reaction mixture was concentrated. The residue was partitioned between MeOH and FC-72 (×3). The combined FC-72 layers were concentrated. The crude product was purified by column chromatography on silica-gel ($CHCl_3$–MeOH–aq. NH_3=85:15:0.6) to give compound **11** (2.20 g, 92%) as a white amorphous solid. R_f=0.46 ($CHCl_3$–MeOH–aq. NH_3=8:2:0.2); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.78–1.97 (m, 8H), 2.00–2.17 (m, 8H), 2.42–2.64 (m, 12H), 2.66–2.82 (m, 8H), 3.26–3.52 (m, 12H), 3.55–3.74 (m, 8H); MALDI-TOF MS: Calcd for $C_{82}H_{60}F_{102}N_7O_6$ *m/z* $[M+H]^+$: 3176.3, Found: 3177.6; Calcd for $C_{82}H_{59}F_{102}N_7O_6Na$ *m/z* $[M+Na]^+$: 3198.3, Found: 3197.1.

4.1.9. Compound 13. 4-Dimethylaminopyridine (243 mg, 1.98 mmol) and PyBOP (1.03 g, 1.98 mmol) were added to a solution of compound **12** (1.00 g, 1.84 mmol) and **Hfb**-OH (**10**, 2.17 g, 0.660 mmol) in CH_2Cl_2 (110 mL). After stirring for 20 h at room temperature, MeOH (110 mL) was added to the reaction mixture and only CH_2Cl_2 was concentrated. The reaction mixture was extracted three times with FC-72 (110 mL). The combined FC-72 layers were then concentrated. The crude product of **13** (2.45 g) was used in the next step without further purification. R_f=0.47 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.03 (s, 9H) 1.76–2.19 (m, 27H), 2.30–2.85 (m, 20H), 3.26–3.82 (m, 27H), 5.07–5.17 (m, 1H), 5.18–5.27 (m, 2H), 5.69–5.76 (m, 1H, H-1), 6.73–7.21 (m, 1H), 7.30–7.74 (m, 11H); MALDI-TOF-MS: Calcd for $C_{115}H_{99}F_{102}N_7O_{17}Na$ *m/z* $[M+Na]^+$: 3838.5, Found: 3837.1.

4.1.10. Compound 14. HF-Pyr (4.45 mL, 159 mmol) was added to a solution of crude **13** (2.45 g) in THF (38 mL). After stirring for 20 h at room temperature, the reaction mixture was added to saturated aq. $NaHCO_3$ (150 mL). Toluene (150 mL) was then added to the reaction mixture. The reaction mixture was extracted three times with FC-72 (150 mL). The FC-72 layers were washed with brine, then dried over anhydrous Na_2SO_4 and concentrated. The crude product of **14** (2.30 g) was used in the next step without further purification. R_f=0.36 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.71–2.21 (m, 28H), 2.27–2.87 (m, 20H), 3.27–3.83 (m, 27H), 5.04–5.18 (m, 2H), 5.27–5.38 (m, 1H), 5.69–5.82 (m, 1H, H-1), 6.75–7.23 (m, 1H), 7.29–7.96 (m, 1H); MALDI-TOF MS: Calcd for $C_{99}H_{82}F_{102}N_7O_{17}Na$ *m/z* $[M+Na]^+$: 3600.4, Found: 3600.9.

4.1.11. Compound 16. *Using the Schmidt method.*[21] Molecular sieves 4A powder (1.4 g) was added to a solution of the crude compound **14** (395 mg) and compound **15** (680 mg, 0.992 mmol) in ether (6.0 mL)–$EtOC_4F_9$ (3.2 mL) under an argon atmosphere. After stirring for 2 h at room temperature, TMS-OTf (140 μL, 0.773 mmol) was added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, triethylamine (0.5 mL) was added to the reaction mixture. The reaction mixture was then filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16** (372 mg), and this residue was used in the next step without further purification. R_f=0.47 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.76–2.16 (m, 27H), 2.20–2.83 (m, 20H), 3.16–4.06 (m, 33H), 4.29–5.33 (m, 12H), 5.66–5.71 (m, 1H, H-1), 6.69–7.17 (m, 2H), 7.02–7.44 (m, 20H); MALDI-TOF MS: Calcd for $C_{133}H_{115}F_{102}N_7O_{22}Na$ *m/z* $[M+Na]^+$: 4122.6, Found: 4121.4.

General procedure for disaccharide **16** *using thioglycoside method.*[30] Molecular sieves 4A powder (1.6 g) was added to a solution of compound **14** (133 mg, 37.2 μmol) and compound **15a** (70.6 mg, 0.112 mmol) in CH_2Cl_2 (2.0 mL)–$EtOC_4F_9$ (1.0 mL) under an argon atmosphere. After stirring for 2 h at room temperature, NIS (50.0 mg, 0.223 mmol) and TfOH (2 μL, 22 μmol) were added to the reaction mixture at 0 °C. After stirring for 50 min at 0 °C, the reaction mixture was filtered. The filtrate was added to saturated aq. $NaHCO_3$, and extracted three times with AcOEt. The AcOEt layers were washed with saturated aq. $NaHCO_3$, saturated aq. $Na_2S_2O_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16**, and this residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH=40:1) to give compound **16** (122 mg, 80%) as a white amorphous solid.

General procedure for disaccharide **16** *using the Köenigs–Knorr method.*[31] Molecular sieves 4A powder (1.5 g) was added to a solution of compound **14** (131 mg, 36.5 μmol) and AgOTf (204 mg, 0.365 mmol), $AgClO_4$ (188 mg, 0.365 mmol) in ether (1.0 mL)–$EtOC_4F_9$ (1.5 mL) under an argon atmosphere. After stirring for 2 h at room temperature, compound **15b** (204 mg, 0.365 mmol) in ether (2.0 mL) was added to the reaction mixture at 0 °C. After stirring for 24 h at 0 °C, the reaction mixture was filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16**, and this residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH=40:1) to give compound **16** (91.4 mg, 61%) as a white amorphous solid.

General procedure for disaccharide **16** *using the Suzuki method.*[32] A mixture of Cp_2ZrCl_2 (161 mg, 0.55 mmol), $AgClO_4$ (114 mg, 0.55 mmol) and molecular sieves 4A powder (1.0 g) in ether (2.5 mL) was stirred at −20 °C under an argon atmosphere. After stirring for 10 min at −20 °C, compound **14** (165 mg, 46.1 μmol) and compound **15c** (75.1 mg, 0.138 mmol) in ether (5.0 mL)–$EtOC_4F_9$ (2.5 mL) were added to the reaction mixture. After stirring for 4 h at −20 °C, the reaction mixture was filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16**, and this residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH=40:1) to give compound **16** (132 mg, 70%) as a white amorphous solid.

4.1.12. Compound 17. A sodium methoxide solution (28%) in methanol (10 μL) was added to a solution of the crude compound **16** (349 mg) in $EtOC_4F_9$ (8 mL)–MeOH (16 mL). After stirring for 16 h at room temperature, Amberlite IR-120 (H^+ form) was added and the reaction mixture was neutralized. After filtration, the filtrate was concentrated. The residue was partitioned between MeOH and FC-72 (×3). The MeOH layer was concentrated to give the crude product of **17**. The FC-72 layers were concentrated to afford the pure compound **18**. The crude product of **17** was purified by column chromatography on silica-gel to give pure compound **17** (50 mg, 67% in 4 steps) as a white powder. HRMS (ESI-TOF MS.): Calcd for $C_{40}H_{46}O_{11}Na$ *m/z* $[M+Na]^+$: 725.2932, Found: 725.2959.

4.1.13. Compound 19.[25,26] A solution of **17** (31.0 mg) in EtOH (9.0 mL) was added to a suspension 10% Pd/C (40.0 mg) in EtOH (1.0 mL)–AcOH (1.0 mL). After bubbling with hydrogen for 14 h at room temperature, the reaction mixture was filtered. After the filtrate was concentrated, the compound **19** (16.0 mg, quant.) was obtained as a white powder.

Melibiose. ^{1}H NMR (600 MHz, D_2O): δ=4.53 (d, J=7.6 Hz), 4.84 (d, J=4.1 Hz), 4.85 (d, J=3.4 Hz), 5.09 (d, J=3.4 Hz); ^{13}C NMR (150 MHz, D_2O): δ=61.06, 61.08, 65.82, 65.92, 68.41, 68.44, 69.20, 69.42, 69.45, 69.57, 70.06, 70.90, 71.39, 72.92, 74.03, 74.31, 75.85, 92.10, 96.03, 98.13, 98.17.

Arolactose. ^{1}H NMR (600 MHz, D_2O): δ=4.29 (d, J=9.6 Hz), 4.31 (d, J=8.3 Hz), 4.52 (d, J=8.3 Hz), 5.10 (d, J=4.1 Hz); ^{13}C NMR (150 MHz, D_2O): δ=60.97, 68.57, 68.63, 68.65, 68.68, 69.42, 69.48, 70.44, 70.74, 71.39, 72.64, 74.01, 74.86, 75.11, 75.14, 75.62, 92.10, 95.94, 103.25.

4.1.14. Compound 21. Molecular sieves 4A powder (3.3 g) was added to a solution of the crude compound **14** (953 mg) and compound **20** (1.86 g, 2.23 mmol) in ether (14 mL)–$EtOC_4F_9$ (8 mL) under an argon atmosphere. After stirring for 2 h at room temperature, TMS-OTf (338 μL, 1.86 mmol) was added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, triethylamine (0.8 mL) was added to the reaction mixture. The reaction mixture was then filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeCN and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **21** (1.07 g), and was used in the next step without further purification.

4.1.15. Compound 22. HF-Pyr (1.75 mL, 62.4 mmol) was added to a solution of the crude **21** (1.07 g) in THF (15 mL). After stirring for 22 h at room temperature, the reaction mixture was added to saturated aq. $NaHCO_3$ (200 mL), then toluene (200 mL) was added to the reaction mixture. The reaction mixture was extracted three times with FC-72 (200 mL). The FC-72 layers were washed with brine, then dried over anhydrous Na_2SO_4 and concentrated. The crude product of **22** (952 mg) was used in the next step without further purification.

4.1.16. Compound 24. Molecular sieves 4A powder (6.0 g) was added to a solution of the crude compound **22** (360 mg) and compound **23** (884 mg, 1.79 mmol) in ether (29 mL)–$EtOC_4F_9$ (3 mL) under an argon atmosphere. After stirring for 2 h at room temperature, TMS-OTf (163 μL, 0.898 mmol) was added to the reaction mixture at 0 °C. After stirring for 2 min at 0 °C, triethylamine (0.5 mL) was added to the reaction mixture. The reaction mixture was then filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **24** (360 mg), and this residue was used in the next step without further purification.

4.1.17. Compound 25. A sodium methoxide solution (28%) in MeOH (10 μL) was added to a solution of the crude compound **24** (360 mg) in $EtOC_4F_9$ (8 mL)–MeOH (16 mL). After stirring for 14 h at room temperature, Amberlite IR-120 (H^+ form) was added and the reaction mixture was neutralized. After filtration, the filtrate was concentrated. The residue was partitioned between MeOH

and FC-72. The methanol layer was concentrated to give the crude compound **25**. The FC-72 layer was concentrated to afford pure compound **18**. The crude compound **25** was purified by column chromatography on silica-gel to give pure compound **25** (34.0 mg, 43% in 6 steps) as a white powder. HRMS (ESI-TOF MS.): Calcd for $C_{39}H_{50}O_{16}Na$ *m/z* $[M+Na]^+$: 797.2991, Found: 797.2969.

4.1.18. Compound 26.[29,30] A solution of **25** (15.0 mg) in EtOH (4.0 mL) was added to a suspension 10% Pd/C (20.0 mg) in EtOH (1.0 mL)–AcOH (1.0 mL). After bubbling with hydrogen for 21 h at room temperature, the reaction mixture was filtered. After the filtrate was concentrated, the compound **26** (10.0 mg, quant.) was obtained as a white powder.

O-(β-D-Glucopyranosyl)-(1→6)-*O*-(α-D-glucopyranosyl)-(1→6)-D-glucopyranose. ^{1}H NMR (600 MHz, D_2O): δ= 4.34 (d, J=8.3 Hz), 4.51 (d, J=7.6 Hz), 4.79 (d, J= 3.4 Hz), 4.80 (d, J=4.1 Hz), 5.08 (d, J=3.4 Hz); ^{13}C NMR (150 MHz, D_2O): δ=92.14, 96.03, 97.96, 98.00, 102.57.

O-(β-D-Glucopyranosyl)-(1→6)-*O*-(β-D-glucopyranosyl)-(1→6)-D-glucopyranose. ^{1}H NMR (600 MHz, D_2O): δ= 4.34 (d, J=8.3 Hz), 4.35 (d, J=5.5 Hz), 4.36 (d, J= 8.3 Hz), 4.38 (d, J=6.9 Hz), 4.50 (d, J=10.3 Hz), 5.07 (d, J=3.4 Hz); ^{13}C NMR (150 MHz, D_2O): δ=92.07, 95.90, 102.65, 102.70, 102.77, 102.79.

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22. The product mixtures containing the fluorous compounds **13**,

16 and **24** were partitioned between FC-72 and MeOH. Those containing the fluorous compound **14** and **22** were partitioned FC-72, toluene and water. The product containing the fluorous compound **21** was partitioned between FC-72 and acetonitrile. None of the fluorous compounds were detected by TLC of the organic layer after three times extraction with FC-72, which shows that these compounds were quantitatively extracted with FC-72.

23. $EtOC_4F_9$ is a commercially available fluorocarbon solvent (3 M, Tokyo), which is called Novec™ HFE-7200.
24. FC-72 is a commercially available fluorocarbon solvent (3M, Tokyo), which consists of perfluorohexane (C_6F_{14}) isomers and is called Fluorinert™ FC-72.
25. The anomer ratio of compound **19** (the newly formed anomeric position) was determined to be $\alpha/\beta=60{:}40$ by NMR spectroscopic analysis. Moreover, the correlation between anomeric protons of galactose residue and 6-position carbons of glucose residue of the compound **19** was observed by HMQC and HMBC of NMR spectroscopic analysis.
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28. The starting materials **14** and **22** were not observed by TLC after the glycosylation.
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