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Hafnium(IV) Tetratriflate as a Glycosyl Fluoride Activation Reagent

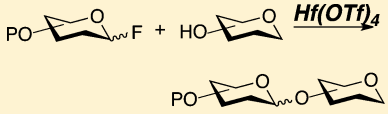
Shino Manabe*,† and Yukishige Ito*,†,‡

†RIKEN, Synthetic Cellular Chemistry Laboratory, Hirosawa Wako, Saitama 351-0198, Japan

‡ERATO, JST, Hirosawa Wako, Saitama 351-0198, Japan

Supporting Information

ABSTRACT: Hafnium(IV) tetratriflate was found to be a good activator of glycosyl fluoride. The protocol was operationally simple and was widely applicable to a variety of substrates in both solid-phase and solution-phase glycosylation reactions.



Glycosyl fluoride is one of the most frequently used glycosyl donors in glycosylation reactions. The relatively strong C−F bond imparts stability to such compounds; however, glycosyl fluorides can be activated under the appropriate reaction conditions. Several methodologies have been developed for achieving glycosyl fluoride activation. For example, Mukaiyama et al. reported for the first time that $SnCl_2$−$AgClO_4$ could efficiently activate glycosyl fluoride,[1] and Noyori and Nicolaou reported that TMSOTf and BF_3•OEt_2 work as effective mediators for armed glycosyl fluorides, respectively.[2,3] Later, Suzuki reported that a combination of Cp_2HfCl_2−$AgClO_4$ had a high efficacy for glycosyl fluoride activation,[4] which is now a protocol widely applied to the synthesis of complex oligosaccharides and glycoconjugates.[5−7] However, most glycosyl fluoride activation methodologies are not operationally simple. Multiple reagents and preactivated molecular sieves are required, in addition to preactivation/premixing of the activator prior to the addition of the glycosyl donor and acceptor. In this paper, we report an operationally simple glycosyl fluoride activation methodology.

Hafnium(IV) tetratriflate ($Hf(OTf)_4$) is a commercially available solid that is easy to handle in air. It is known to be a good Lewis acid for a variety of reactions.[8−18] It was therefore expected that it would be a good mediator for glycosyl fluoride activation.

Glycosyl fluoride **1α**/**1β** (1:4 mixture) was smoothly activated, even at −78 °C, to give disaccharides **3α**/**3β** (16:84) in 58% yield in a β-selective manner after 2 h (Table 1, entry 1). After 14 h, the yield was increased up to 70% (entry 2). At −50 °C, the reaction was completed within 1 h, and the disaccharides **3α**/**3β** (20:80) were obtained in 99% yield (entry 3). Molecular sieves 3A and 4A did not help to increase the yield (entries 6 and 7). Especially, the reaction in the presence of molecular sieves 4A was messy and the disaccharide **3α**/**3β** was not isolated in a pure form. Although activation of glycosyl fluoride using a catalytic amount of reagent has previously been reported,[19−21] the reaction did not complete, even after 10 h, if the amount of $Hf(OTf)_4$ was reduced (entry 8), with the disaccharide **3α**/**3β** being only obtained in 59% yield. Interestingly, the α:β ratio was altered, with the α-isomer obtained as the major product, although the reason was not clear. The well-known solvent effect was observed,[2,22,23] with the β-selectivity being increased in CH_3CN (entries 9 and 10) and the α-selectivity being increased in dioxane/toluene (entries 11 and 12).[24] Prolonged reaction periods completed the reaction, but did not increase the yields (entries 10 and 12), because several unidentified byproducts were formed. Both the pure α-anomer **1α** and β-anomer **1β** gave disaccharides **3α**/**3β** in a β-selective manner, with little variation in the α:β ratios (entries 13 and 14). The excess of glycosyl fluoride **1a**/**1b** was changed to its corresponding hemiacetal and glycal as main products under the conditions for entry 1.

The scope and limitations of the methodology were subsequently investigated (Table 2). Reactive acceptor **4** reacted smoothly with donor **1α**/**1β** to give disaccharides **5α**/**5β** in a β-selective manner (entry 1). Using secondary hydroxyl group acceptor **6**, the disaccharides **7α**/**7β** were obtained, and a significant solvent effect was observed (entries 2−4). In CH_3CN, the β-glycoside ratio was increased up to 80%, while dioxane−toluene gave an increase in the α-glycoside ratio up to 85%. Mannose derivative **8** gave disaccharide **9** in 64% yield (entry 6), and disarmed donor **10** could also be activated under these conditions at 4 °C (entry 7). After 2 h, disaccharide **11** was obtained in 80% yield. Unfortunately, the benzylidene group was cleaved because of the Lewis acidity of $Hf(OTf)_4$, and trisaccharide **14** was obtained in 37% yield based on acceptor **12** (entry 8). However, disaccharide **15** was obtained in the presence of 3 equiv of di-*tert*-butyl-4-methylpyridine (DTBMP) (entry 9). Disaccharide **16** was also activated at −30 °C, and trisaccharide **17** and tetrasaccharide **19** were obtained in 85% and 58% yield, respectively (entries 10 and 11).

The developed methodology was applied to rapid solid-phase oligosaccharide synthesis on a polymer support. Methyl poly(ethylene glycol) (MPEG, average M_w = 750) was used to produce acid-stable linker[25] **21**, which acted as a good acceptor and enabled rapid purification by a silica gel short pad because of the high polarity of MPEG, as previously reported (Scheme 1).[26,27] After removal of the chloroacetyl temporary protecting group under basic conditions, the MPEG-glycoside was submitted to the next glycosylation reaction, where **23** was

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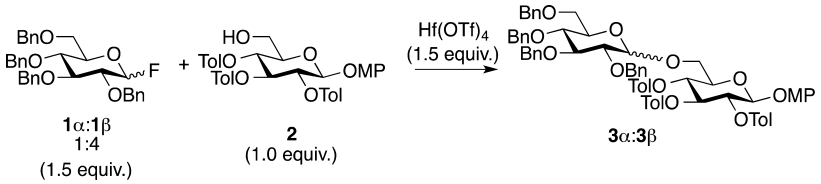
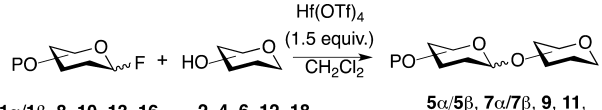
Table 1. Glycosylation Reaction with 1 and 2 under Various Conditions



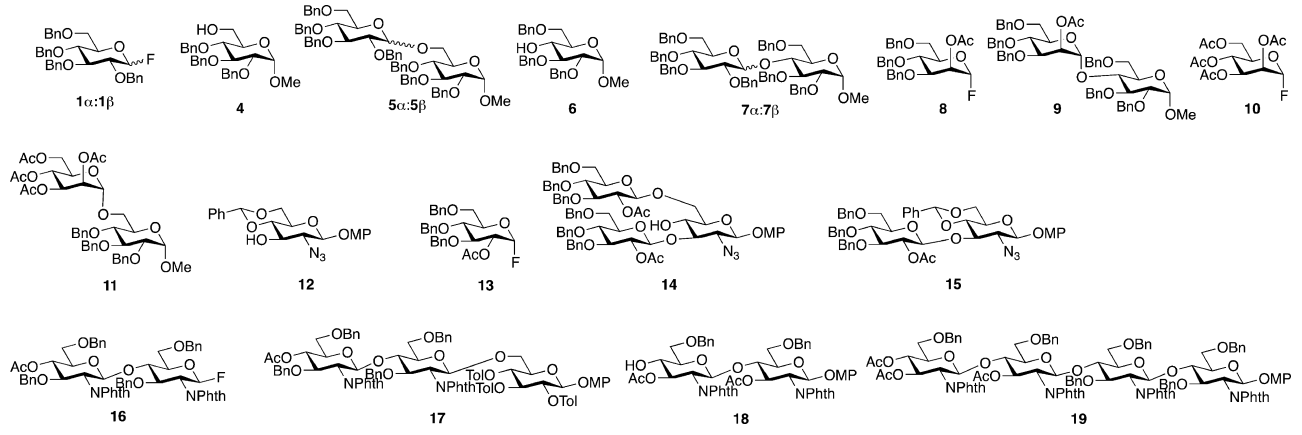
entry	donor	solvent	temp (°C)	time	yield (%)	**3α:3β**
1	**1α/1β** (1:4)	CH_2Cl_2	−78	2 h	58[a]	16:84
2	**1α/1β** (1:4)	CH_2Cl_2	−78	14 h	70	12:88
3	**1α/1β** (1:4)	CH_2Cl_2	−50	1 h	99	20:80
4	**1α/1β** (1:4)	CH_2Cl_2	−20	10 min	88[b]	31:69
5	**1α/1β** (1:4)	CH_2Cl_2	−20	0.5 h	91	30:70
6	**1α/1β** (1:4)	CH_2Cl_2, MS 3A	−20	10 min	45[c]	39:61
7	**1α/1β** (1:4)	CH_2Cl_2, MS 4A	−20	10 min	mess	_
8[d]	**1α/1β** (1:4)	CH_2Cl_2	−20	10 h	59[e]	64:36
9	**1α/1β** (1:4)	CH_3CN	−20	10 min	51[f]	11:89
10	**1α/1β** (1:4)	CH_3CN	−20	4 h	57	42:58
11	**1α/1β** (1:4)	dioxane/toluene[g] (1:1)	−20	10 min	83[h]	51:49
12	**1α/1β** (1:4)	dioxane/toluene[g] (1:1)	−20	4 h	80	66:34
13	**1α**	CH_2Cl_2	−50	1 h	82	14:86
14	**1β**	CH_2Cl_2	−50	1 h	94	18:82

[a]32% of **2** was recovered. [b]12% of **2** was recovered. [c]18% of **2** was recovered. [d]30% of **2** was recovered. 0.4 equiv of $Hf(OTf)_4$ was used. [e]40% of **2** was recovered. [f]12% of **2** was recovered. [g]Dioxane/toluene 3:1 solvent system reported in ref 23 was frozen at low temperature. The ratio of toluene was increased. [h]17% of **2** was recovered.

Table 2. Scope and Limitations of the Glycosylation Reaction Mediated by $Hf(OTf)_4$



entry	donor	acceptor	solvent	temp (°C)	time	product	yield (%)	**α:β**
1	**1α/1β** (1:4)	**4**	CH_2Cl_2	−50	1 h	**5α/5β**	94	16:84
2	**1α/1β** (1:4)	**6**	CH_2Cl_2	−50	1 h	**7α/7β**	75	44:56
3	**1α/1β** (1:4)	**6**	CH_2Cl_2	−20	0.5 h	**7α/7β**	80	45:55
4	**1α/1β** (1:4)	**6**	CH_3CN	−20	0.5 h	**7α/7β**	94	20:80
5	**1α/1β** (1:4)	**6**	dioxane/toluene (1:1)	−20	0.5 h	**7α/7β**	80	85:15
6	**8**	**6**	CH_2Cl_2	−50	1 h	**9**	64	64:0
7	**10**	**4**	CH_2Cl_2	4	2 h	**11**	80	80:0
8	**13**	**12**	CH_2Cl_2	−50	0.5 h	**14**	37	0:37
9	**13**	**12**	CH_2Cl_2, DTBMP (3 equiv)	−30	1 h	**15**	65	0:65
10	**16**	**2**	CH_2Cl_2	−30	0.5 h	**17**	85	0:85
11	**16**	**18**	CH_2Cl_2	−30	0.5 h	**19**	58	0:58



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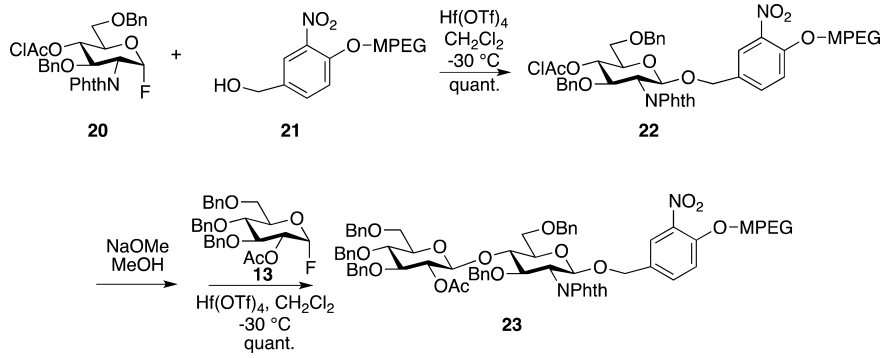
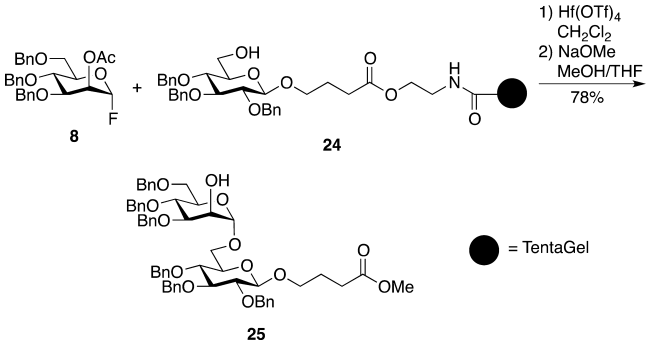
Scheme 1. Glycosylation Reaction on a Polymer Support Using Glycosyl Fluoride, Mediated by $Hf(OTf)_4$



quantitatively yielded. The acceptor immobilized on TentaGel **24**[28] also served as a good substrate for the glycosylation reaction with glycosyl fluoride **8** using the same methodology. Disaccharide **25** was obtained after cleavage from the TentaGel under basic conditions in 78% yield from **24** (Scheme 2), and the corresponding acceptor was not obtained.

Scheme 2. Solid-Phase Glycosylation Reaction Using Glycosyl Fluoride Mediated by $Hf(OTf)_4$



In conclusion, $Hf(OTf)_4$ was shown to be a good activator for glycosyl fluoride. The reagent was observed to be stable, and the procedure was simple. This methodology is widely applicable to solid-phase and polymer-supported oligosaccharide synthesis, as well as solution-phase synthesis.

EXPERIMENTAL SECTION

General Experimental Methods. All commercial reagents were used without further purification. Analytical TLC was performed on silica gel 60 F254 plates and visualized by UV fluorescence quenching and 12 Molybdo(VI) phosphoric acid acid/phosphoric acid staining. Flash column chromatography was performed on silica gel 60N (spherical, neutral, 40−100 μm). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature (23−24 °C) in $CDCl_3$ using a 400 MHz spectrometer. Chemical shifts are reported in ppm relative to internal TMS (δ = 0.00 ppm) for ^{1}H and $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR spectra. HRMS was measured by Quadrupole-TOF mass spectrometry. Novasyn TentaGel was purchased from Novabiochem.

General Procedure. $Hf(OTf)_4$ was added to a solution of donor (1.5 equiv) and acceptor (1.0 equiv) in CH_2Cl_2 (acceptor concentration, 0.1 M) at the stated temperature. After the starting material was consumed or after adequate periods, the reaction was quenched with sat. $NaHCO_3$, and the aqueous layer was extracted several times with EtOAc. The combined layers were washed with brine and dried over Na_2SO_4. After concentration, the crude product was purified by preparative TLC. The products **3a**,[22] **3b**,[22] **5a**,[29] **5b**,[29] **7a**,[30] **7b**,[30] **9**,[31] **11**,[32] **16**,[33] **18**,[34] and **20**[26] were reported.

***p*-Methoxyphenyl 3,6-Di-*O*-(2-*O*-acetyl-3,4,6-*O*-tribenzyl-β-D-glucopyranoside)-2-azido-2-deoxy-β-D-glucopyranoside.** ^{1}H NMR δ 7.28−7.12 (m, 30H), 6.97 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.99 (t, J = 8.0 Hz, 1H), 4.98 (t, J = 8.0 Hz, 1H), 4.76−4.60 (m, 6H), 4.53−4.38 (m, 8H), 4.20 (d, J = 11.2 Hz, 1H), 3.70−3.40 (m, 17H), 3.34 (t, J = 8.8 Hz, 1H), 3.13 (t, J = 8.8 Hz, 1H), 1.99 (s, 3H), 1.77 (s, 3H); ^{13}C NMR δ 169.5, 169.4, 155.5, 151.2, 138.2, 138.0, 137.9, 137.4, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 118.0, 114.8, 102.0, 101.4, 101.1, 85.8, 83.1, 82.7, 78.0, 77.8, 75.7, 75.3, 75.1, 75.1, 75.0, 74.5, 73.5, 73.4, 73.0, 72.8, 69.1, 68.7, 68.7, 64.5, 55.6, 20.8, 20.6; [α] 13.3 (c 1.0, $CHCl_3$); HRMS (MALDI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{71}H_{77}N_3O_{18}Na$ 1282.5094; Found 1282.5103.

***p*-Methoxyphenyl (2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-azido-β-D-glucopyranoside.** ^{1}H NMR δ 7.37−7.02 (m, 20H), 6.99 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 5.45 (s, 1H), 5.04 (t, J = 8.8 Hz, 1H), 4.81−4.41 (m, 7H), 4.36 (d, J = 12.4 Hz, 1H), 4.31 (dd, J = 11.2, 5.2 Hz, 1H), 3.80−3.58 (m, 8H), 3.77 (s, 3H), 3.52−3.42 (m, 3H), 3.29 (m, 1H), 1.98 (s, 3H); ^{13}C NMR δ 170.6, 155.9, 150.8, 138.2, 138.2, 137.9, 137.0, 129.1, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 126.1, 118.6, 114.7, 102.2, 101.6, 100.0, 82.9, 70.4, 78.7, 77.8, 75.2, 75.0, 74.9, 73.5, 73.4, 68.5, 68.4, 66.5, 66.1, 55.7, 30.2, 20.9; [α] 7.0 (c 0.64, $CHCl_3$); HRMS (MALDI Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{49}H_{51}N_3O_{12}Na$ 896.3365; Found 896.3377.

***p*-Methoxyphenyl (4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-glucopyranoside)-(1→4)-(3,6-*O*-dibenzyl-2-deoxy-2-phthalimido-β-glucopyranoside)-(1→3)-2,3,4-tri-*O*-(4-methylbenzoyl)-β-D-glucoside.** ^{1}H NMR δ 7.73 (d, J = 8.4 Hz, 2H), 7.50 (s, 4H), 7.32 (d, J = 8.4 Hz, 2H), 7.80−760 (br, 8H), 7.31−6.89 (m, 21H), 6.85 (m, 3H), 6.69 (s, 4H), 5.69 (t, J = 9.2 Hz, 1H), 5.47 (t, J = 8.4 Hz, 1H), 5.27 (d, J = 8.4 Hz, 1H), 5.19 (t, J = 9.6 Hz, 1H), 5.12 (t, J = 9.2 Hz, 1H), 5.02 (d, J = 7.6 Hz, 1H), 4.94 (d, J = 7.6 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.50−4.03 (m, 11H), 3.94 (m, 1H), 3.79−3.76 (m, 1H), 3.76 (s 3H), 3.60−3.30 (m, 5H), 3.18 (m, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 1.88 (s, 3H); ^{13}C NMR δ 169.6, 165.6, 155.4, 151.3, 144.1, 143.9, 138.4, 138.3, 138.2, 137.7, 133.3, 131.6, 129.8, 129.0, 129.0, 128.3, 128.1, 127.8, 127.6, 127.4, 127.3, 127.2, 126.9, 126.5, 126.1, 125.9, 123.1, 118.2, 114.6, 100.6, 98.2, 96.9, 75.8, 74.5, 74.4, 73.8, 73.5, 73.3, 72.7, 72.6, 71.5, 69.5, 69.4, 56.2, 55.7, 55.5, 21.6, 20.9; [α] 22.3 (c 1.45, $CHCl_3$); HRMS (MALDI Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{95}H_{88}N_2O_{23}Na$ 1647.5670; Found 1647.5673.

***p*-Methoxyphenyl (3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside)-(1→4)-(3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside) (1→4)-(3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside) (1→4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside.** ^{1}H NMR δ 7.76−7.72 (m, 16H), 7.18−7.6.82 (m, 20H), 6.72 (d, J = 9.2 Hz, 2H), 6.60 (d, J = 9.2 Hz, 2H), 5.63 (d, J = 8.0 Hz, 1H), 5.61 (t, J = 10.0 Hz, 1H), 5.41 (t, J = 9.2 Hz, 1H), 5.20 (t.d, J = 8.0 Hz, 1H), 5.07 (t, J = 9.2 Hz, 1H), 4.93 (d, J = 7.6 Hz, 1H),

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4.79 (d, J = 12.4 Hz, 1H), 4.54 (t, J = 12.8 Hz, 1H), 4.48−3.92 (m, 30H), 3.62 (s, 3H), 3.49 (m, 3H), 3.38−3.36 (m, 5H), 3.13 (m, 2H), 2.94 (d, J = 9.6 Hz, 1H), 2.69 (d, J = 9.6 Hz, 1H), 1.72 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 170.3, 170.2, 169.6, 167.3, 155.4, 150.6, 138.5, 138.2, 137.7, 134.2, 131.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 127.1, 126.9, 126.8, 123.5, 123.3, 118.8, 114.3, 97.3, 96.5, 96.3, 76.7, 76.4, 75.2, 74.4, 73.9, 73.7, 73.3, 72.7, 72.5, 72.4, 72.1, 72.1, 70.9, 70.7, 69.3, 67.6, 67.5, 56.2, 56.0, 55.5, 55.2, 54.8, 20.9, 20.5, 20.3; [α] 10.4 (c 0.95, $CHCl_3$); HRMS (MALDI Q-TOF) m/z: $[M + Na]^+$ Calcd for $[C_{111}H_{102}N_4O_{29} + Na]^+$ 1977.6522, Found 1977.6520.

Poly(ethylene glycol) Bound 4-Hydroxy-3-nitro-benzyloxy-3,6-*O*-benzyl-4-*O*-chloroacetyl-2-azido-2-phthalimide-*β*-D-glucopyranoside. To a solution of glycosyl fluoride **20** (211 mg, 0.705 mmol) and MPEG bound linker **21** (211 mg, 0.235 mmol) in CH_2Cl_2 (5 mL), $Hf(OTf)_4$ (546 mg, 0.705 mmol) was added at −30 °C. After 1 h, the reaction was quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$. The combined layers were extracted with $CHCl_3$ and then washed with brine. After drying the extract over Na_2SO_4, the solvent was removed *in vacuo*. The residue was passed through a short silica gel pad (AcOEt only−MeOH/AcOEt 1:1) to give compound **22** (340 mg, quant.). Representative peaks of ^{1}H NMR δ 5.18 (d, J = 8.0 Hz, 1H), 4.76−4.50 (m, 8H), 4.45 (d, J = 12.4 Hz, 1H), 4.27−4.12 (m, 5H).

Poly(ethylene glycol) Bound 4-Hydroxy-3-nitro-benzyloxy-(3,4,6-tri-*O*-benzyl-2-*O*-acetyl-*β*-D-glucopuranosy)3,6-*O*-benzyl-2-azido-2-phthalimide-*β*-D-glucopyranoside. To a solution of compound **22** (150 mg, 0.10 mmol) in MeOH (1 mL), 1 drop of NaOMe (28% MeOH solution) was added by Pasteur pipet, in the presence of phenolphthalein. The progress of the reaction was monitored using a *p*-nitrobenzyl pyridine color test.[26] The mixture was then neutralized by Amberlyst 15E and filtered, and the resin was washed with MeOH. After concentration, the crude product was passed though a short silica gel pad (AcOEt only−MeOH/AcOEt 1:1) to give the acceptor (141 mg, quant.). The PEG-bound acceptor was dried *in vacuo* overnight and then dissolved in CH_2Cl_2 (2 mL). Glycosyl fluoride **13** (141 mg, 0.285 mmol) and $Hf(OTf)_4$ (221 mg, 0.285 mmol) were added at −30 °C. After 1 h, the reaction was quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$. The combined layers were extracted with $CHCl_3$ and then washed with brine. After drying the extract over Na_2SO_4, the solvent was removed *in vacuo*. The residue was passed through a short silica gel pad (AcOEt only−MeOH/AcOEt 1:1) to give compound **23** (177 mg, quant.). Representative peaks of ^{1}H NMR δ 5.10 (d, J = 6.4 Hz, 1H), 5.00 (t, J = 8.4 Hz, 1H), 1.98 (s, 3H).

1-Methoxycarbonylbutyl-(3,4,6-tri-*O*-benzyl-*α*-D-mannopyranoside)(1→6)-2,3,4-tri-*O*-benzyl-*β*-D-glycopyranoside. To a suspension of acceptor-immobilized TentaGel **24** (0.30 mmol/g as OH, 313 mg, 0.09 mmol; 0.23 mmol/g as **24**, the content rate was determined after cleavage from resin), glycosyl fluoride **13** (133 mg, 0.32 mmol) and $Hf(OTf)_4$ (250 mg, 0.32 mmol) were added at −30 °C. The mixture was gently stirred for 3 h, then neutralized by Et_3N, and filtered. The resin was washed with CH_2Cl_2, MeOH, and H_2O. After the resin was dried *in vacuo* overnight, it was suspended in MeOH (2 mL) and THF (2 mL). A NaOMe solution (0.50 mL) was added, and the mixture was stirred at 60 °C overnight. AcOH (0.1 mL) was then added, and the resin was filtered and washed with THF. After concentration, disaccharide **25** (46 mg, 50% based on 0.30 mmol/g as OH; 78% from **24**) was obtained.

^{1}H NMR δ 7.30−7.16 (m, 30H), 4.89−4.78 (m, 5H), 4.46 (d, J = 11.2 Hz, 1H), 4.28 (d, J = 8.0 Hz, 1H), 4.01 (s, 1H), 3.83−4.49 (m, 11H), 3.58 (s, 3H), 3.41 (t, J = 9.2 Hz, 1H), 3.35−3.31 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H), 1.88−1.84 (m, 2H); ^{13}C NMR δ 173.8, 138.4, 138.3, 137.9, 137.7, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 103.4, 99.5, 84.7, 79.6, 77.7, 75.7. 75.1. 75.0, 74.9, 74.2, 74.0, 71.9, 71.5, 68.8, 68.1, 65.8, 62.0, 51.6, 30.7, 25.1; [α] 30.9 (c 1.0, $CHCl_3$); HRMS (MALD Q-TOF) m/z: $[M + Na]^+$ Calcd for $[C_{59}H_{66}O_{13} + Na]^+$ 1005.4396, Found 1005.4390.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: smanabe@riken.jp; yukito@riken.jp.

Notes

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