Synthesis of a Regiospecifically Fluorinated Polysaccharide 3-Deoxy-3-fluoro-(1→6)-α-D-glucopyranan via Ring-Opening Polymerization

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ABSTRACT: 3-Deoxy-3-fluoro-(1→6)-α-D-glucopyranan (**4**) was synthesized via deoxyfluorination of 1,6-anhydro-2,4-di-*O*-benzyl-*β*-D-glucopyranose (**1**) and ring-opening polymerization of 1,6-anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-*β*-D-glucopyranose (**2**), followed by debenzylation of the resulting 2,4-di-*O*-benzyl-3-deoxy-3-fluoro-(1→6)-α-D-glucopyranan (**3**). Partially deoxyfluorinated (1→6)-α-D-glucopyranans were also prepared via copolymerization of **2** with 1,6-anhydro-2,3,4-tri-*O*-benzyl-*β*-D-glucopyranose (**6**). The assignments of steric arrangements of the C−F bond and stereoregularity of polymers were made from their ^{1}H- and ^{13}C-NMR spectral analysis. The deoxyfluorination at position 3 proceeded with retention of the configuration. The axial C−F orientation and *β*-anomeric configuration in the $^1C_4$ conformer of monomer **2** was converted via polymerization to the equatorial C−F orientation and α-anomeric configuration of the $^4C_1$ conformer in polymers **3** and **4**. Monomer **2** had only a little lower polymerization reactivity than that of **6**.

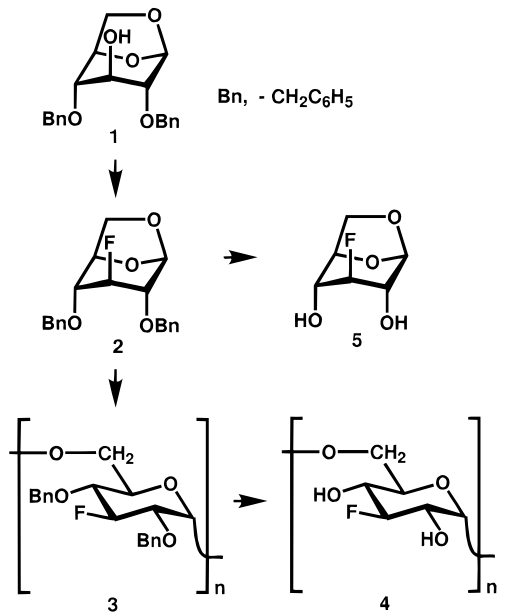
Introduction

Deoxyfluorinated mono- and oligosaccharides are useful as unique cellular and enzymatic probes to investigate carbohydrate metabolism, enzymology, antigen−antibody specificity, and carbohydrate transport and also as biomedical substances to design antiviral and antitumor agents.[1−5] Since fluorine is characteristic of relatively small atomic size and of high electronegativity, the C−F bond of deoxyfluorinated sugars can participate only as its proton acceptor in hydrogen bonding between C−F···H-O (or H−N). The unique hydrogen-bonding capability of C−F bonds may induce biological activities of deoxyfluorinated sugars via specific interactions with carbohydrate-binding proteins.

Continuing attention has been given to fluorinated polymeric materials because of their unique interfacial, electrical, and optical characteristics.[6,7] In these connections, fluorinated polysaccharides consisting of well-defined deoxyfluorinated sugar units are of interest from the viewpoints of both biologically active carbohydrates and specialty polymeric materials. However, there has been no report on well-defined deoxyfluorinated polysaccharides, except for the following related papers: preparation of highly substituted deoxyfluorocellulose acetate;[8] substitution of hydroxyl groups along cellulose with perfluorinated alkyl ether;[9] and introduction of deoxyfluorinated D-glucose residue into the nonreducing terminal of *malto*-oligosaccharide chain via the enzymatic action of phosphorylase.[10]

This paper reports the first synthesis of a well-defined regiospecifically deoxyfluorinated polysaccharide. According to Scheme 1, 3-deoxy-3-fluoro-(1→6)-α-D-glucopyranan (**4**) was prepared via the following three-step procedure: (1) deoxyfluorination of 1,6-anhydro-2,4-di-*O*-benzyl-*β*-D-glucopyranose (**1**), (2) ring-opening polymerization of 1,6-anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-*β*-D-glucopyranose (**2**), and (3) debenzylation of the resulting 2,4-di-*O*-benzyl-3-deoxy-3-fluoro-(1→6)-α-D-glucopyranan (**3**). Partially deoxyfluorinated (1→6)-α-D-glucopyranans were also prepared via copolymerization of **2** with 1,6-anhydro-2,3,4-tri-*O*-benzyl-*β*-D-glucopyranose (**6**). Each fluorinated and benzyloxy (or hydroxy) unit of the copolymers is abbreviated as F and O units in this paper.

Scheme 1. Synthesis of 3-Deoxy-3-fluoro-(1→6)-α-D-glucopyranan (4)



In spite of the strong electron-attracting property of the fluorine atom, polymerization and deprotection was successful without any side reactions. Regiospecifically deoxygenated, alkylated, C-alkylated, aminated, and branched polysaccharides were previously prepared via the ring-opening polymerization method.[11−15] The scope

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Table 1. ^{13}C-NMR Chemical Shifts (δ, ppm) and Coupling Constants ($J_{C,F}$, Hz) of 1,6-Anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2), 1,6-Anhydro-3-deoxy-3-fluoro-β-D-glucopyranose (5), 2,4-Di-*O*-benzyl-3-deoxy-3-fluoro-(1→6)-α-D-glucopyranan (3), 3-Deoxy-3-fluoro-(1→6)-α-D-glucopyranan (4), and Methyl 3-Deoxy-3-fluoro-α-D-glucopyranose (7)

	C-1	C-2	C-3	C-4	C-5	C-6	benzyl CH_2	*ipso*-phenyl	*o*-, *m*-, and *p*-phenyl
2[a]	100.5 (3.7)	76.1 (25.6)	90.0 (180.5)	75.7 (23.2)	74.3 (2.4)	65.7 (0)	72.2, 71.6	137.4	128.5−127.8
5[b]	101.5 (∼0)	68.9 (25.2)	93.7 (178.1)	68.6 (22.0)	75.9 (∼0)	64.9 (0)			
3[c]	97.7 (11.0)	77.8 (17.0)	96.1 (181.6)	75.9 (17.0)	70.2 (7.3)	65.7 (0)	74.4, 72.5	138.4, 138.3	128.4−127.3
4[d]	98.2 (10.6)	69.7 (16.8)	95.5 (178.6)	67.9 (17.4)	70.1 (7.4)	65.6 (0)			
7[e]	99.3 (10.7)	69.8 (17.5)	95.1 (179.1)	67.9 (17.9)	71.0 (7.1)	60.2 (0)			

[a] 67.8 MHz; 5% in $CDCl_3$; 50 °C. [b] 100 MHz; 13% in Me_2SO-d_6; 50 °C. [c] 67.8 MHz; 8% in $CDCl_3$; 50 °C. [d] 100 MHz; 4% in Me_2SO-d_6; 50 °C. [e] Reference 21; in D_2O; 23 °C.

of regiospecifically-substituted polysaccharides via ring-opening polymerization has been extended to fluorine-containing polysaccharides. Investigation of biomedical and other functional properties of the polysaccharides is in progress. Since a variety of 1,6-anhydro sugar derivatives having one to three fluorine atoms were reported in the literature,[3,16,17] new types of fluorine-containing polysaccharides will be synthesized.

Results and Discussion

Synthesis of 1,6-Anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2). 1,6-Anhydro-2,4-di-*O*-benzyl-β-D-glucopyranose (**1**) was treated with (dimethylamino)sulfur trifluoride in refluxed benzene. The deoxyfluorination proceeded rapidly in less than 30 min to give 1,6-anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (**2**) as a colorless syrup in 95% yield. Its debenzylated product 1,6-anhydro-3-deoxy-3-fluoro-β-D-glucopyranose (**5**) was prepared by treating **2** with sodium in liquid ammonia and used as a model substance for NMR analysis.

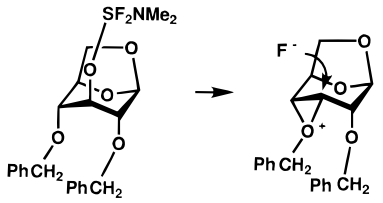
Structural analysis of **2** and **5** was made on the basis of their ^{1}H- and ^{13}C-NMR spectra, which were assigned by H−H COSY and C−H COSY techniques and by the previously reported results.[18−21] The signals due to the H-3 proton were downfield shifted and their coupling constants were large: δ 4.66 ppm ($^2J_{H-3,F}$ = 46.1) for **2** and to 4.32 ppm ($^2J_{H-3,F}$ = 45.2) for **3**. Coupling constants of the vicinal protons (H-2 and H-4) with 3-fluorine were in the range 18.2−19 Hz. Table 1 summarizes the ^{13}C-NMR chemical shifts and their coupling constants with the fluorine substituent. The carbon signal at position 3 was downfield shifted to 90.0 ppm with a large coupling constant ($^1J_{C-3,F}$ = 180.5 Hz).

The configuration of the C−F bond can be assigned as follows. The geminal coupling constants at C-2 and C-4 carbons were large: $^2J_{C-2,F}$ = 25.6 Hz and $^2J_{C-4,F}$ = 23.2 Hz. These were ascribed to trans-diaxial relationships of the fluorine substituent with the benzyloxy substituents of positions 2 and 4 of the pyranose ring.[19] In addition, the vicinal coupling constants at C-1 and C-5 carbons were small: $^3J_{C-1,F}$ = 3.7 Hz and $^3J_{C-5,F}$ = ∼0 Hz. These were ascribed to the gauche arrangement of the fluorine atom with respect to C-1 and C-5. Hence, the fluorine atom was axially oriented. In other words, the deoxyfluorination of the hydroxyl group in position 3 proceeded with retention of the configuration to give compound **2** of the gluco-type configuration.

1,6-Anhydro-3-deoxy-3-fluoro-β-D-glucopyranose (**5**) also showed the same ^{13}C-coupling features of the axially oriented C−F bond as **2** did. The gluco-type configuration was also confirmed by the NMR analysis of the polymerization products described below.

Fluorination of the hydroxyl group of carbohydrate derivatives using (dimethylamino)sulfur trifluoride is proposed to proceed through the following intermediates.[1,3,22]

Scheme 2. Proposed Mechanism of Deoxyfluorination That Gives the Gluco-Type Product 2 with Retention of the Configuration at Position 3



$$R-OH + SF_3NMe_2 \rightarrow R-O-SF_2NMe_2 + HF \rightarrow R-F$$

In many cases, the fluoride anion formed attacks the intermediate R−O−SF_2NMe_2 from the backside to cause the inversion of the configuration via an S_N2 mechanism. However, the deoxyfluorination of **2** proceeded with retention. The same stereochemistry was reported for deoxyfluorination of 1,6-anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-glucopyranose, which gave 1,6-anhydro-2-azido-4-*O*-benzyl-2,3-dideoxy-3-fluoro-β-D-glucopyranose with retention.[16]

We propose a possible mechanism as shown in Scheme 2, which involves the neighboring group participation of the axial benzyloxy substituent at position 4. The lone pair electrons of the oxygen attacked the C-3 carbon from the backside to form a three-membered oxonium intermediate, which was then replaced by the fluoride anion to cause double inversion. The retention of configuration via neighboring group participation was reported for some cases in the literature.[3,23,24]

Homo- and Copolymerization of 1,6-Anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2). Table 2 summarizes homo- and copolymerization using phosphorus pentafluoride as initiator in dichloromethane at −60 °C. The polymerization proceeded rapidly to give a powdery polymer in high yield. The copolymer composition was estimated from the ^{1}H-NMR area ratios of debenzylated copolymers. The mole fraction of **2** in copolymers was a little lower than that in the feed.

The homopolymer **3** was soluble in benzene, toluene, carbon tetrachloride, chloroform, dichloromethane, tetrahydrofuran, pyridine, and so on. The solubility was almost the same as that of 2,3,4-tri-*O*-benzyl-(1→6)-α-D-glucopyranan.[11] These polymers showed clear endothermic peaks due to melting in differential scanning calorimeter (DSC) diagrams. The melting point was 68−70 °C for fluorinated homopolymer **3** and was lowered with the decreasing content of the F unit. Since the melting point of 2,3,4-tri-*O*-benzyl-(1→6)-α-D-glu-

Table 2. Homo- and Copolymerization of 1,6-Anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2) with 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (6)[a]

expt no.	amt of **2**, g	mol fr of **2** in feed	$[M]_0$, mol/L	PF_5, mol ratio to monomers	time, min	yield, %	mol fr of **2** in copolymer[b]	$10^{-4}M_n$[c]	$[a]_D^{25}$,[d] deg	mp,[e] °C
HP-1	0.96	1.0	1.4	10	2	67	1.0	2.1	+121.3	
HP-2	1.05	1.0	1.5	10	15	75	1.0	3.9	+130.5	
HP-3	0.78	1.0	1.5	4	25	59	1.0	3.5	+138.2	68−70
CP-3	0.72	0.70	1.2	5	95	73	0.68	12.3	+129.0	58−61
CP-1	1.00	0.49	1.5	5	7	67	0.47	8.1	+117.3	62−65
CP-2	0.31	0.30	1.2	5	30	69	0.28	7.8	+111.6	61−63

[a] Solvent, dichloromethane; temperature, −60 °C. [b] Determined by ^{1}H-NMR spectra of debenzylated copolymer. [c] Determined by SEC (polystyrene standards). [d] *c* 1, in chloroform. [e] Determined by DSC.

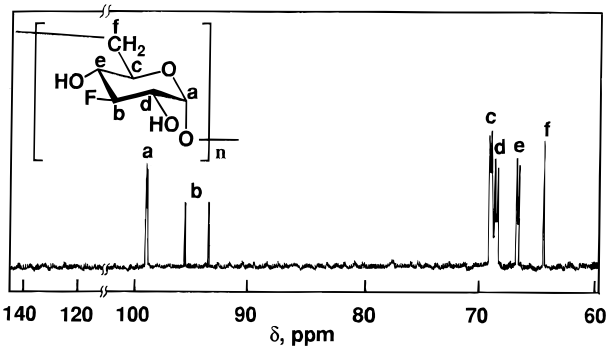


Figure 1. ^{13}C-NMR spectrum of 3-deoxy-3-fluoro-(1→6)-α-D-glucopyranan (**4**). Conditions: 4% in Me_2SO-d_6; TMS; 50 °C; 100 MHz.

copyranan was 51−54 °C,[25] introduction of fluorine substituents elevated the melting point by about 15 °C. The number-averaged molecular weights (M_n) of the homopolymers were in the range 2.0×10^4 to 3.9×10^4 ($DP_n = 60-110$), which were estimated by SEC using polystyrene standards in chloroform.

Homopolymerization of **2** was rapid, and the copolymerization reactivity of deoxyfluorinated monomer **2** was a little lower than that of the tribenzylated monomer **6**. We reported[25] that the 3-deoxygenated monomer (1,6-anhydro-2,4-di-*O*-benzyl-3-deoxy-β-D-*ribo*-hexopyranose) had a higher copolymerization reactivity than **6**. The polymerization reactivity decreased in the order H- > $C_6H_5CH_2O$- > F-substituent in position 3.

The polymerization reactivity of **2** can be explained on the basis of electronic and steric effects of the fluoro substituent. Fluorine is an electron-attracting substituent, which reduces the nucleophilicity of the acetal oxygen atom of the monomer toward the growing trialkyloxonium ion. Fluorine is small in size, on the other hand, which causes less interference when the monomer approaches the growing trialkyloxonium ion.[11] The reactivity of monomer **2** was reduced by the former factor and accelerated by the latter factor. A balance of these two factors caused the relatively high reactivity of monomer **2**.

Completely and Partially Deoxyfluorinated (1→6)-α-D-Glucopyranan. Debenzylation of **3** with sodium in liquid ammonia gave polysaccharide **4** as a clear colorless powder in quantitative yield. The ^{13}C-NMR spectrum of **4** was quite simple as shown in Figure 1. Any signals indicating the cleavage of the C−F bond were not detected: for instance, no CH_2 signals appeared around 30 ppm. The C−F bond of polysaccharides **3** and **4** was stable under the reaction conditions. This is in contrast to the instability of the C−F bond of poly(tetrafluoroethylene). If we used a Teflon-stirred chip instead of a glass-coated chip during the debenzylation, the Teflon surface became dark tatters owing to the corrosion.

Partially deoxyfluorinated (1→6)-α-D-glucopyranans were prepared by debenzylation of the copolymer. There appeared anomeric H-1 signals at δ 4.88 of the F unit and at 4.82 ppm of the O unit and an H-3 signal at δ 4.47 ppm of the F unit separately. The copolymer compositions listed in Table 2 were estimated from the ^{1}H-NMR area ratios.

Homopolysaccharide **4** was partially soluble in Me_2SO and insoluble in water, methanol, and other solvents. The low solubility of **4** in water was attributable to the presence of highly electron-attractive and small fluorine substituents. The solubility was increased with a decrease of the mole fraction of the F unit. The copolysaccharide of F content 0.68 was partially soluble in Me_2SO and water, that of 0.47 was soluble in Me_2SO and partially soluble in water, and that of 0.28 was soluble in Me_2SO and water. On the other hand, the benzylated polymer **3** showed a solubility similar to that of the corresponding tribenzylglucopyranan.

Structural Features of Homopolysaccharide Derivatives 3 and 4. The following two structural features of **3** and **4** were derived from the ^{13}C-NMR chemical shifts and coupling constants summarized in Table 1. First is the assignment of the α-anomeric configuration of these polymers. The C-1 carbon signal of **3** at 99.1 ppm was downfield shifted from that of **2** at 96.5 ppm. The heteronuclear coupling constant ($J_{C-1,H-1} = 167.3$ Hz) of **3** was decreased by 11.3 Hz from $J_{C-1,H-1} = 178.6$ Hz of **2**. No signals due to β-anomeric structures were detectable in **3** and **4**. The positively high rotations in chloroform were also suggestive of (1→6)-α-anomeric configuration.

The second is concerned with the gluco-type configuration of the fluorine substituent.[19,20] Polymer **4** had chemical shifts and coupling constants comparable with those of methyl 3-deoxy-3-fluoro-α-D-glucopyranose (**7**).[21] Polymers **3** and **4** showed smaller geminal coupling constants of both C-2 and C-4 carbons and larger vicinal coupling constants of both C-1 and C-5 carbons, compared respectively with the corresponding ones of the anhydro sugars **2** and **5**. These coupling constants were reflected on the equatorial orientation of the fluorine substituent, which is gauche to the benzyloxy (or hydroxy) substituents in positions 2 and 4 and is anti to the C-1 and C-5 carbons.[19,20]

In conclusion, the $^1C_4$ conformer with β-anomeric configuration and axial C−F orientation in the monomer **2** was converted to the $^4C_1$ conformer with α-anomeric configuration and equatorial C−F orientation in polymers **3**.

Diad Sequence in Copolymers. Figure 2 is the enlarged spectra of debenzylated copolymers in D_2O, where the C-6 carbon signals were split into four peaks. By considering the copolymer composition and peak area, each peak was assignable to the crossover diad

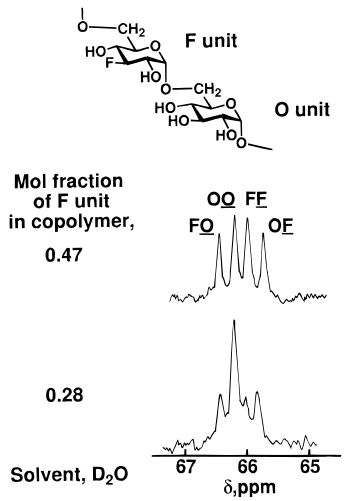


Figure 2. Enlarged ^{13}C-NMR spectra of C-6 carbon signals of debenzylated copolymers. Conditions: 50 °C; 100 MHz.

sequences between the F and O units. The upfield two peaks at δ 65.8 and 66.0 ppm were assigned to the O***F*** and F***F*** diad of the F unit and the downfield two peaks at δ 66.2 and 66.4 ppm were assigned to the O***O*** and F***O*** diad of the O unit, respectively. When Me_2SO-d_6 was used as the solvent, the C-6 carbon signals appeared as only two singlets at δ 65.6 ppm due to the F unit and at δ 66.3 ppm due to the O unit. The C-6 carbon signals of the benzylated copolymers in deuterated chloroform were also split into four peaks at δ 65.3, 65.5, 65.7, and 66.0 ppm, which were respectively assignable to O***F***, F***F***, O***O***, and F***O*** diads similarly. Other signals of the F and O units of benzylated and debenzylated copolymers were superimposed in the ^{13}C-NMR spectra.

Experimental Section

Characterization. NMR spectra were recorded with a JEOL JNM-FX-270 and a Bruker ART400 NMR spectrometer. IR spectra were taken with a Japan Spectroscopic Co. (JASCO) A-3 grating infrared spectrophotometer. Optical rotations were determined with a JASCO DIP-181 digital polarimeter using a water-jacketed 1 dm cell at 25 °C. Size exclusion chromatography (SEC) was conducted with a Toso HLC-8020 high-speed liquid chromatograph using TSKgel MHDXK7001C (30 cm) + 7002C (30 cm) columns (solvent, chloroform; polystyrene standards). Thin layer chromatography (TLC) was carried out with Merck TLC plates precoated with silica gel 60. Preparative chromatography was carried out using a Yamazen preparative liquid chromatograph. Microanalysis was made on a Perkin-Elmer 240C elemental analyzer. Thermal analysis of polymers was made with a Perkin-Elmer DSC-2 differential scanning calorimeter.

1,6-Anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2). 1,6-Anhydro-2,4-di-*O*-β-D-glucopyranose (**1**) was prepared via pyrolysis of cellulose[26] and subsequent selective dibenzylation.[13,25,27] (Dimethylamino)sulfur trifluoride (2.7 mL, 28.1 mmol) was added to a solution of **1** (5.0 g, 14 mmol) in benzene (130 mL), and the solution was refluxed with magnetic stirring for 80 min. TLC (*n*-hexane:ethyl acetate = 1:1 in volume): R_f of **1** = 0.36 and of **2** = 0.64. The solution was treated with 10% aqueous sodium hydrogen carbonate, washed with water, dried on sodium sulfate, concentrated, and chromatographed over silica gel. A colorless syrup was obtained (4.8 g, 95%).

$[\alpha]_D^{25} = -35.6°$ (*c* 1.0 in chloroform). Anal. Calcd for $C_{20}H_{21}O_4F$: C, 69.74; H, 6.16. Found: C, 69.72; H, 6.37. ^{1}H-NMR (400 MHz, 7% in $CDCl_3$, 50 °C): δ 7.30 (10H, m, phenyl), 5.42 (1H, s, H-1), 4.66 (1H, ddd, $J_{3,F} = 46.1$, $J_{2,3} = J_{3,4} = 3.2$ Hz, H-3), 4.70−4.56 (4H, m, CH_2Ph), 4.55 (1H, m, $J_{5,6exo} = 5.6$ Hz, H-5), 3.74 (1H, $J_{6endo,6exo} = 7.5$ Hz, H-6_{endo}), 3.64 (1H, t, $J_{5,6exo} = J_{6exo,6endo} = 6.6$ Hz, H-6_{exo}), 3.44 (1H, dd, $J_{2,F} = 18.2$, $J_{2,3} = 3.2$ Hz, H-2), 3.42 (1H, dd, $J_{4,F} = 18.4$, $J_{3,4} = 3.2$, H-4).

1,6-Anhydro-3-deoxy-3-fluoro-β-D-glucopyranose (5). 1,6-Anhydro-2,4-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranose (2) (0.31 g) was dissolved in a mixture of toluene (15 mL) and 1,2-dimethoxyethane (5 mL), and the solution was added dropwise to liquid ammonia (30 mL) in a three-necked flask equipped with a cold finger trap. Small pieces of sodium metal (0.27 g) were added until the blue-color of the solution was maintained, and reaction was continued at −33 °C for 105 min. The reaction was terminated with ammonium chloride and water. Ammonia was evaporated and organic substances were extracted with dichloromethane. The water layer was concentrated and freeze-dried.

^{1}H-NMR (400 MHz, 13% in Me_2SO-d_6, 50 °C): δ 5.25 (1H, s, H-1), 4.47 (1H, d, $J_{5,6exo} = 5.3$ Hz, H-5), 4.32 (1H, ddd, $J_{3,F} = 45.2$, $J_{2,3} = J_{3,4} = 1.2$ Hz, H-3), 3.78 (1H, d, $J_{6endo,6exo} = 7.6$ Hz, H-6_{endo}), ~3.6 (1H, d, $J_{4,F} =$ ~19 Hz, H-4), 3.59 (1H, t, $J_{5,6exo} = J_{6exo,6endo} = 6.7$ Hz, H-6_{exo}), 3.42 (1H, dd, $J_{2,F} = 18.5$, $J_{2,3} = 1.2$ Hz, H-2).

Polymerization of 2. Polymerization of viscous liquid monomer **2** was carried out by a high-vacuum technique using a vessel previously reported.[13] Anal. Calcd for $(C_{20}H_{21}O_4F)_n$: C, 69.74; H, 6.16. Found: C, 69.81; H, 6.08. ^{1}H-NMR (270 MHz, 7% in $CDCl_3$, 50 °C): δ 7.27 (10H, m, phenyl), 4.90 (1H, s, H-1), 4.88 (1H, ddd, $J_{3,F} = 54.0$, $J_{2,3} = J_{3,4} = 8.6$ Hz, H-3), 4.82, 4.56, 4.55, 4.42 (4H, 4d, $J_{gem} = 11.5$, CH_2Ph), 3.82−3.65 (3H, m, H-4, H-5, and H-6), 3.56 (1H, d, $J = 11.1$, H-6), 3.34 (1H, dd, $J_{2,F} = 10.3$, $J_{2,3} = 8.8$ Hz, H-2).

Debenzylation. Debenzylation of polymer **3** (0.30 g) was performed as described.[11,25] The yield was 0.12 g (87%). ^{1}H-NMR (400 MHz, 4% in Me_2SO-d_6, 50 °C): δ 5.32, 4.91 (broad, OH), 4.79 (1H, s, H-1), 4.38 (1H, ddd, $J_{3,F} = 54.5$, $J_{2,3} = J_{3,4} =$ 8.8Hz, H-3), 3.79 (1H, dd, $J_{6a,6b} = 10.8$, $J_{5,6b} = 4.6$ Hz, H-6_b), 3.70 (1H, br, H-5), 3.61 (1H, d, $J_{6a,6b} = 10.6$, H-6_a), 3.54 (2H, br, H-2 and H-4).

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