Controlled Synthesis of Glycopolymers with Pendant D-Glucosamine Residues by Living Cationic Polymerization

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Received 8 May 1996; accepted 26 August 1996

ABSTRACT: D-Glucosamine-containing glycopolymers with well-controlled structure were synthesized by living cationic polymerization. To this end, D-glucosamine-containing vinyl ether (VE) of the type [CH_2=CH(OCH_2CH_2OR)] was prepared, where R denotes a 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimide-β-D-glucopyranoside, i.e., the hydroxyl and amino groups in D-glucosamine residues are protected by acetyl and phthaloyl groups, respectively. It was found that (1) the efficient living cationic polymerization of VE monomer is achieved by a combination of ethylaluminum dichloride ($EtAlCl_2$) with an adduct of trifluoroacetic acid (TFA) and isobutyl VE (IBVE) [$CH_3CH(OiBu)OCOCF_3$] (i.e., TFA/$EtAlCl_2$ initiating system); and (2) the polymerization in toluene at the elevated temperature (0°C) is most suitable to proceed the homogeneous polymerization over the whole conversion range. The molecular weight distribution of the resulting polymers was very narrow ($\overline{M}_w/\overline{M}_n \sim 1.1$). Quantitative deprotection of the resulting precursor polymers was successfully achieved with hydrazine monohydrate to afford the corresponding water-soluble polymers with pendant D-glucosamine residues. © 1997 John Wiley & Sons, Inc. J Polym Sci A: Polym Chem **35:** 751–757, 1997

Keywords: controlled synthesis; glycopolymer; pendant D-glucosamine residue; vinyl ether; living polymerization; cationic polymerization

INTRODUCTION

In recent years, a great attention has been paid to saccharide-containing synthetic polymers, because of their potentials as biotechnological, pharmacological, and medical materials. To date, various types of polymers bearing pendant saccharide moieties, herein referred to as "glycopolymers," have been prepared.[1–12] However, only a few studies have been reported on the preparation of glycopolymers with well-controlled molecular weight and chemical architecture.[13–17] Living polymerization is one of the useful methods for preparing the homopolymers and block copolymers with well-controlled molecular weight (MW), molecular weight distribution (MWD), and chemical architecture. In the preceding articles,[16,17] we have reported the controlled synthesis of homopolymers and block copolymers bearing pendant glucose residues by living cationic polymerization.[18]

D-Glucosamine (2-amino-2-deoxy-D-glucose where the C-2 hydroxyl group in glucose is replaced by an amino group) and its N-acetyl derivative are widely distributed in living organisms as important fragments in the oligo-saccharide sequences. They are key building units that are closely correlated with biological processes such as intercellular recognition[19] and blood group determinants.[20] Glycopolymers bearing pendant D-glucosamine or *N*-acetyl-D-glucosamine residues are of particular interest because of their unique characters in the field of biotechnological, pharmacological, and medical materials.[8–12]

In the present work, we attempted the controlled synthesis of glycopolymers having pendant D-glucosamine residues by living cationic poly-

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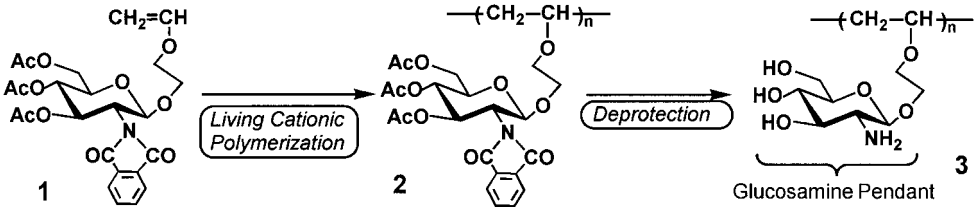
Contract grant sponsor: Grant-in-Aid for Scientific Research (Ministry of Education, Science, and Culture, Japan); contract grant no. 07455373



Scheme 1.

merization according to Scheme 1, and the results were compared with those of vinyl ether (VE) monomer with acetyl-protected glucose pendant, i.e., 1-O-(vinyloxy)ethyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside, which has been proved to undergo living cationic polymerization.[16] To this end, a D-glucosamine-containing VE monomer **1**, where the hydroxyl and amino functions are protected by acetyl and phthaloyl groups, respectively, was prepared and the living polymerization of VE monomer **1** was attempted by using cationic initiating systems. Deprotection of the resulting polymers was performed with hydrazine monohydrate to afford the corresponding glycopolymers bearing pendant D-glucosamine residues.

RESULTS AND DISCUSSION

Synthesis of Glucosamine-Carrying VE Monomer

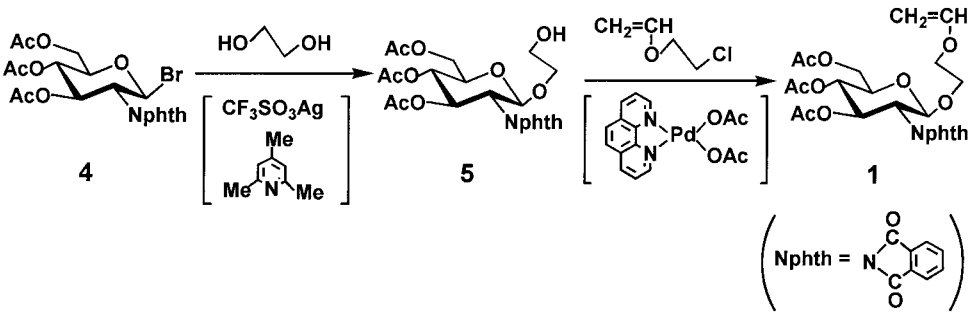
VE monomer **1** was successfully prepared via two-step reactions employing 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimide-β-D-glucopyranosyl bromide **4**[21] as the starting material.

As shown in Scheme 2, the β-bromide **4**, which was readily available from commercial D-glucosamine, was glycosylated with a large excess amount of ethylene glycol (50 equiv. to the β-bromide **4**) in the presence of silver trifluoromethanesulfonate and collidine to give **5** in 82% yield. Quantitative glycosylation was confirmed by ^{1}H- and ^{13}C-NMR analysis. The vinyl transetherification of alcohol **5** with 2-chloroethyl vinyl ether was carried out with some modifications according to the method of Mckeon et al.[22] Diacetate-(1,10-phenanthroline) palladium(II) was used as a catalyst. The crude product was purified through silica gel column to afford pure VE **1** in 43% yield with respect to the starting material **4**. The ^{1}H- and ^{13}C-NMR spectra of VE monomer **1** thus prepared were consistent with the expected structure (see the Experimental section). β-Configuration of VE monomer **1** was confirmed from the large coupling constant for H1–H2 ($J_{1,2}$ = 8.4 Hz) in the ^{1}H-NMR spectrum. VE monomer **1** was freeze-dried prior to the polymerization, because of its sensitivity to the moisture, which might seriously deteriorate the living nature in cationic polymerization.

Polymerization with HCl/ZnI_2 Initiating System

VE monomer **1** contains multiple polar groups that might induce undesirable side reactions such as chain transfer and termination. At first, the possibility of living cationic polymerization of VE **1** was examined by hydrogen chloride/zinc iodide (HCl/ZnI_2) initiating system in toluene at −15°C; HCl was herein employed in the form of the adduct of isobutyl VE (IBVE) [$CH_3CH(OiBu)Cl$]. The initiating system and reaction conditions have been proved to induce the living cationic polymerization of IBVE.[23]

Figure 1 shows the time–conversion curve for the polymerization of VE **1**, compared with that of glucose-carrying VE **6**, which has been proved to undergo living cationic polymerization initiated by a HCl/ZnI_2 initiating system.[16] The difference in chemical structure between both monomers is only the substituent groups at C-2 position in the pendant saccharide residue (**1**, phthalimide; **6**, acetate). It can be seen that the polymerization of VE monomer **1** proceeded smoothly without an induction phase similarly as that of VE monomer **6**. However, the rate of polymerization of VE monomer **1** with glucosamine pendant was much slower than that of glucose counterpart **6**. The latter result indicates that the effective concentration of ZnI_2, which determines the rate of polymerization, depends on the chemical structure of pendants. This may be considered to reflect that the interaction between pendant saccharide residue and the propagating species and/or the complexation of carbonyl groups in the pendant with Lewis acid (ZnI_2)[24,25] are much stronger in VE monomer **1** than those in VE monomer **6**, because



Scheme 2.

the former has five pendant carbonyl groups, whereas the latter four. Consequently, the rate of polymerization of VE monomer **1** becomes much slower than that of VE monomer **6**.

Figure 2 shows the number-average molecular weight ($\overline{M}_n$) of the resulting polymers as a function of monomer conversion for both monomer **1** and monomer **6**. The $\overline{M}_n$ of both polymers increased in proportion to monomer conversion in an initial and middle stage of the polymerization, but it leveled off at around 80% conversion and their MWDs became broader. Similar results have been already observed for the living cationic polymerization[16] and ring-opening metathesis polymerization[15] of saccharide-containing monomers. This phenomenon is presumably attributed to poor solubility of resulting polymers for the reaction medium. In fact, the gelation was observed under the polymerization conditions employed, when the monomer conversions became higher than 80%. To suppress the gelation, there are two available methods; one is the use of better solvent for the resulting polymer and the other the polymerization at the elevated temperature. The polymerization of monomer **1** was carried out at −40°C in dichloromethane, which is expected to be a better solvent for the resulting polymer, and in toluene at 0°C. It was found that the polymerization proceeded homogeneously without gelation for both cases mentioned above over the whole conversion range, but the MWDs of the obtained polymers became much broader ($\overline{M}_w/\overline{M}_n \sim 1.3$).

Living cationic polymerization of VEs is known to be achieved by stabilization of the growing carbocation not only with a suitably nucleophilic counteranion but also with an externally added Lewis base.[18] Next we examined the effect of the addition of Lewis base on the polymerization of VE monomer **1**.

Effect of Added Base on the Polymerization with TFA/EtAlCl$_2$ Initiating System

The combination of trifluoroacetic acid/ethylaluminum dichloride (TFA/EtAlCl$_2$) is also one of

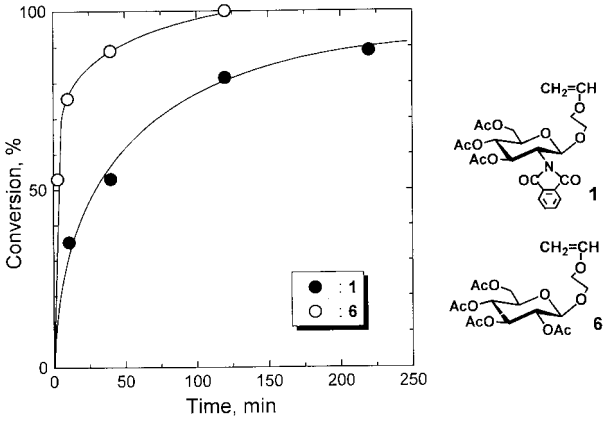


Figure 1. Time–conversion curves for the polymerization of **1** (●) and **6** (○) by HCl/ZnI$_2$ in toluene at −15°C: [**1**]$_0$ = [**6**]$_0$ = 0.20*M*, [CH$_3$CH(O*i*Bu)Cl]$_0$ = 5.0 m*M*, [ZnI$_2$]$_0$ = 2.0 m*M*.

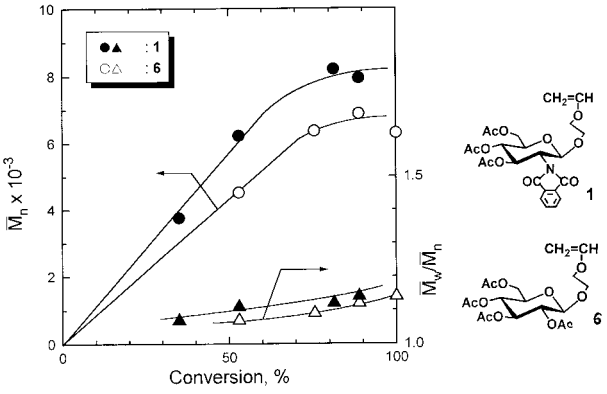


Figure 2. $\overline{M}_n$ and $\overline{M}_w/\overline{M}_n$ values of poly(**1**) (●) and poly(**6**) (○) obtained by HCl/ZnI$_2$ in toluene at −15°C: [**1**]$_0$ = [**6**]$_0$ = 0.20*M*, [CH$_3$CH(O*i*Bu)Cl]$_0$ = 5.0 m*M*, [ZnI$_2$]$_0$ = 2.0 m*M*.

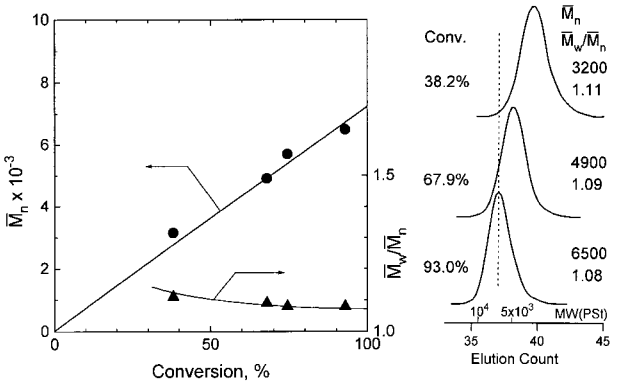


Figure 3. $\overline{M}_n$, $\overline{M}_w/\overline{M}_n$, and MWD curves of poly(**1**) obtained by TFA/$EtAlCl_2$ in the presence of 1,4-dioxane in toluene at 0°C: $[\mathbf{1}]_0 = 0.20M$, $[CH_3CH(OiBu)OCOCF_3]_0 = 5.0$ mM, $[EtAlCl_2]_0 = 10$ mM, [1,4-dioxane]$_0 = 0.6M$.

suitable initiating systems for the living cationic polymerization of VE monomers. Furthermore, the addition of the bases such as ester and ether to this initiating system is known to endow the polymerization of IBVE with living character even at high temperature (up to 70°C).[26] The polymerization of monomer **1** was carried out with the TFA/$EtAlCl_2$ initiating system in the presence of 1,4-dioxane in toluene at 0°C; TFA was herein employed in the form of the adduct of IBVE [$CH_3CH(OiBu)OCOCF_3$] (Fig. 3).

The polymerization proceeded homogeneously over the whole conversion range, this being probably due to the increase in solubility of resulting polymers at the elevated temperature. Consequently, a linear relationship was observed between $\overline{M}_n$ and monomer conversion throughout the polymerization and the polymers exhibited narrow MWDs ($\overline{M}_w/\overline{M}_n \sim 1.1$) even at high conversion. These results demonstrate that the TFA/$EtAlCl_2$-initiated polymerization of VE monomer **1** yields monodisperse living polymers with controlled molecular weight, although the monomer has four ester functions that might cause chain transfer and termination.

Aoshima and Higashimura reported that in the case of 2-benzoyloxyethyl VE monomer containing an ester group in the pendant, the addition of base to the initiating system little affects the living nature in the cationic polymerization.[27] It has also been suggested that the propagating carbocation might be stabilized by the side ester group through an intra- or intermolecular interaction, depending on the temperature.[28] Thus, it is necessary to elucidate the effect of the added base on the cationic polymerization of VE monomer **1**.

Here the polymerization of VE monomer **1** was carried out by using the TFA/$EtAlCl_2$ initiating system in the absence of 1,4-dioxane, and the results were compared with those in the presence of 1,4-dioxane. For the sake of comparison, polymerization experiments by BF_3OEt_2 initiator were also carried out. BF_3OEt_2 induced almost instantaneous and extremely rapid polymerization to afford a high molecular weight polymer ($\overline{M}_w = 4.1 \times 10^4$, $\overline{M}_n = 2.4 \times 10^4$) with a broad MWD (Fig. 4, chart A). In contrast, the TFA/$EtAlCl_2$ initiating system was found to result in slower but efficient polymerization to give polymer with a narrow MWD ($\overline{M}_w/\overline{M}_n = 1.13$, at 90% conversion; Fig. 4, chart B) even in the absence of 1,4-dioxane. This polymerization behavior is somewhat different from that of VEs with acetyl- or isopropylidene-protected glucose pendant; in the case of VE monomers with acetyl- (monomer **6**) or isopropylidene-protected glucose pendant (monomer **7**), the addition of 1,4-dioxane to the TFA/$EtAlCl_2$ initiating system led to narrower MWDs ($\overline{M}_w/\overline{M}_n \sim 1.1$) for both monomers, while the MWDs of polymers obtained in the absence of 1,4-dioxane were 1.2 for monomer **6** and 1.4 for monomer **7**, respectively.[29] It is of interest to note these results, because they suggest that although the monomer **1** has five pendant carbonyl functions that might cause chain transfer and termi-

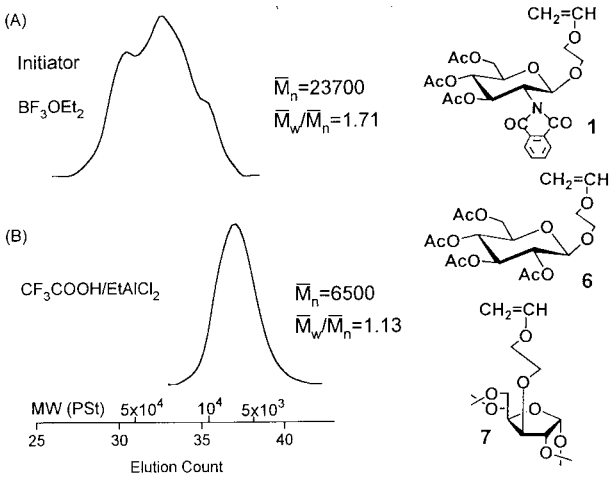


Figure 4. MWD curves of poly(**1**) obtained with (A) BF_3OEt_2, and (B) TFA/$EtAlCl_2$ in the absence of added base in toluene at 0°C: (A) $[\mathbf{1}]_0 = 0.20M$, $[BF_3OEt_2]_0 = 5.0$ mM, conversion $\sim$ 100%; (B) $[\mathbf{1}]_0 = 0.20M$, $[CH_3CH(OiBu)OCOCF_3]_0 = 5.0$ mM, $[EtAlCl_2]_0 = 10$ mM, conversion = 90%.

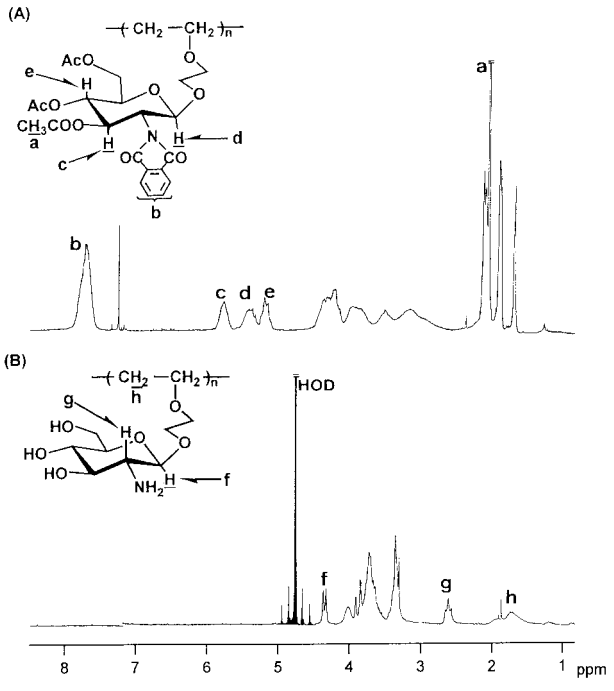


Figure 5. ^{1}H-NMR spectra of **2** and **3** in $CdCl_3$ (A) and in D_2O (B). (A) Precursor polymer **2**; (B) deprotected product **3** obatined from sample A.

nation, the degree of stabilization of the growing species of monomer **1**, in other words, the interaction of the growing species with monomer **1**, is much stronger than those of monomers **6** and **7**. In order to discuss the stability of the growing species, however, it is necessary to carry out more detailed polymerization experiments. Such a study is in progress.

Conversion of Polymer 2 into Polymer 3

Deprotection of precursor polymer **2** was achieved with hydrazine monohydrate in a 1,4-dioxane/methanol mixture to yield polymer **3** with pendant D-glucosamine residues (see the Experimental section). The polymer **2** was soluble in chloroform, toluene, and other common organic solvents but insoluble in water, whereas the resulting polymer **3** was insoluble in those organic solvents, but readily soluble in water under a neutral condition.

Figure 5 compares the ^{1}H-NMR spectra of polymer **2** (in $CDCl_3$) with its deprotected polymer **3** (in D_2O). Comparison of both spectra proved that the phthalimide and acetate groups were quantitatively converted into the corresponding primary amine and hydroxyl groups, respectively. In Figure 5B, for example, the absorptions of the pendant acetyl groups (peak a) and phthaloyl groups (peak b) disappeared completely, and new peaks assigned to H-1 and H-2 in the pyranose ring of D-glucosamine (peak f and g, respectively) were newly observed, whereas those of main chain (peak h) remained unchanged, suggesting that the side reactions had little occurred under the deprotection reaction conditions employed.

In summary, the present study has demonstrated that VE monomer having pendant D-glucosamine residues is capable of undergoing living cationic polymerization with TFA/$EtAlCl_2$ initiating system in toluene at 0°C, when the hydroxyl and amino functions in D-glucosamine residues are protected by acetyl and phthaloyl groups, respectively. These results also suggest that the amphiphilic block copolymers bearing glucosamine pendants can be prepared through the sequential living block copolymerization of monomer **1** and hydrophobic VE followed by deprotection. Such a study is now in progress.

The bioactive applications of D-glucosamine-containing glycopolymers obtained in the present work are of considerable interest, because bioactive agents or peptides could be interact with the polymers through the amino and/or hydroxyl groups of the glucosamine residues.[8–10] Investigations on the molecular recognition functions of these water-soluble glycopolymers are also in progress.

EXPERIMENTAL

Materials

D-Glucosamine (Nacalai Tesque, Inc.) was obtained as a hydrochloric acid salt and employed without further purification. Nitromethane and collidine (for glycosylation) were dried and distilled over calcium hydride prior to use. Ethylene glycol was dried over sodium sulfate. Silver trifluoromethanesulfonate (Aldrich; purity $> 99\%$) was used as received. 2-Chloroethyl vinyl ether (Nisso Maruzen Chemical, Japan) was distilled over calcium hydride. Diacetate-(1,10-phenanthroline) palladium(II) was prepared as reported.[22] Column chromatography was performed on silica gel (Wakogel C-200; Wako Chemicals). $EtAlCl_2$ (Kanto Chemicals; 0.96M solution in n-hexane) and ZnI_2 (Aldrich; purity $> 99.99\%$) were used as received. Toluene and n-hexane (polymerization solvent) were purified by the usual methods and distilled twice over calcium hydride before

use. 1,4-Dioxane as added base was distilled twice over sodium wire. Diethyl ether (Dojin; purity > 99%, anhydrous) for ZnI_2 solvent was distilled over calcium hydride before use. Boron trifluoride etherate (BF_3OEt_2) was purified by distillation of commercial products under reduced pressure. IBVE–HCl adduct[30] and IBVE–CF_3COOH adduct[31] were synthesized as reported.

Synthesis of 1-O-(Hydroxy)ethyl-3,4,6-tri-O-acetyl-2-deoxy-2-phthalimide-β-D-glucopyranoside (5)

A solution of the β-bromide **4** (13.8 g, 27.7 mmol) in nitromethane (30 mL) was added dropwise to a cooled (−30°C) solution of ethylene glycol (80 mL, 1.4 mol), silver trifluoromethanesulfonate (7.71 g, 30.0 mmol), and collidine (4.0 mL, 30.3 mmol) in nitromethane (30 mL). The reaction mixture was allowed to warm up to 0°C. After stirring at 0°C for 2 h, the solution was diluted with chloroform, and the solid was removed by centrifugation and filtration. The combined filtrates were successively washed with cold water, 3% hydrochloric acid and water twice, and then dried over anhydrous sodium sulfate. Filtration and concentration of the solution in vacuo yielded **5** containing a small amount of dimeric by-product. Yield: 10.85 g, 82%. $[\alpha]_D$ + 29.2° (*c* 5.0 g/dL, chloroform). ^{1}H-NMR ($CDCl_3$): δ 1.82, 2.00, 2.08 (each s, 9H, $3COCH_3$), 2.45 (br, 1H, —OH), 3.59–3.75 (m, 4H, $—OCH_2CH_2O—$), 3.90 (m, 1H, H-5), 4.20–4.35 (overlapping, 3H, H-2, H-6, H-6′), 5.11 (t, 1H, H-4), 5.41 (d, 1H, H-1, $J_{1,2}$ = 8.4 Hz), 5.74 (dd, 1H, H-3), and 7.71–7.83 (m, 4H, —phH—). ^{13}C-NMR ($CDCl_3$): δ 20.33, 20.53, 20.61 (CH_3), 54.52 (C-2), 61.81, 62.06, 68.93, 70.63, 71.90, 72.89 (C-3, C-4, C-5, C-6, $—OCH_2CH_2O—$), 98.65 (C-1), 123.59, 131.26, 134.33 (aromatic), 167.55, 169.40, 170.03, and 170.59 (C=O).

ANAL. Calcd for $C_{22}H_{25}O_{11}N_1$: C, 55.11; H, 5.26; N, 2.92. Found: C, 53.28; H, 4.94; N, 2.96.

Synthesis of 1-O-(Vinyloxy)ethyl-3,4,6-tri-O-acetyl-2-deoxy-2-phthalimide-β-D-glucopyranoside (1)

Diacetate-(1,10-phenanthroline) palladium(II) (0.70 g, 1.73 mmol) was added to a solution of **5** (10.3 g, 21.5 mmol) in 2-chloroethyl vinyl ether (30 mL, 295 mmol). After stirring at 60°C for 2 h, the reaction mixture was diluted with chloroform, filtered, and washed with water three times. Solvent removal after drying yielded a crude product, which was chromatographed on silica gel (eluent: benzene/ethyl acetate, 1/1) to afford pure **1** (Rf: 0.70). Yield: 5.40 g, 52.4% (based on **5**). $[\alpha]_D$ + 23.4° (*c* 5.0 g/dL, chloroform). ^{1}H-NMR ($CDCl_3$): δ 1.87, 2.05, 2.12 (each s, 9H, $3COCH_3$), 3.68–4.34 (overlapping, 10H), 5.18 (t, 1H, H-4), 5.44 (d, 1H, H-1, $J_{1,2}$ = 8.4 Hz), 5.82 (dd, 1H, H-3), 6.40 (q, 1H, OCH=), and 7.72–7.86 (m, 4H, —phH—). ^{13}C-NMR ($CDCl_3$): δ 20.34, 20.52, 20.65 (CH_3), 54.54 (C-2), 62.02 (C-6), 66.81, 68.37, 69.08, 70.70, 71.92 (C-3, C-4, C-5, $—OCH_2CH_2O—$), 86.57 (CH_2=), 98.48 (C-1), 123.47, 131.54, 134.08 (aromatic), 151.26 (OCH=), 167.59, 169.36, 169.99, and 170.54 (C=O).

ANAL. Calcd for $C_{24}H_{27}O_{11}N_1$: C, 57.03; H, 5.38; N, 2.77. Found: C, 57.01; H, 5.26; N, 2.81.

Polymerization Procedures

Polymerization was carried out under dry nitrogen in a baked glass tube equipped with a three-way stopcock. The reaction was initiated by sequential addition of $CH_3CH(OiBu)Cl$ (in hexane; 0.20 mL)/ZnI_2 (in diethyl ether; 0.20 mL) or $CH_3CH(OiBu)OCOCF_3$ (in hexane; 0.20 mL)/$EtAlCl_2$ (in toluene; 0.20 mL) into a monomer solution (in toluene; 1.60 mL) containing **1** (202 mg). For the polymerization in the presence of 1,4-dioxane (0.10 mL, 0.6*M*), it was added to the monomer solution prior to initiation. After proper interval, the polymerization mixture was quenched with prechilled ammonical methanol. The quenched reaction mixture was washed with a 10% aqueous sodium thiosulfate solution (for $CH_3CH(OiBu)Cl/ZnI_2$) or with dilute hydrochloric acid (for $CH_3CH(OiBu)OCOCF_3/EtAlCl_2$) and then with water to remove the initiator residue, evaporated to dryness under reduced pressure, and vacuum dried to give a polymer in a quantitative yield. $[\alpha]_D$ +16.8° (*c* 5.0 g/dL, chloroform).

Deprotection of Polymer 2

Polymer **2** (150 mg) was dissolved in a 1,4-dioxane (10 mL)/methanol (5 mL) mixture, and hydrazine monohydrate (10 equiv. to the protection groups in the polymer) was added. The solution was magnetically stirred at 65°C for 3 h, during

which period a white precipitate appeared. The solvents and unreacted hydrazine were removed by evaporation. The residue was dissolved in a small amount of water, and the insoluble by-product, presumably phthalyl hydrazide, was removed by filtration. The filtrate was subjected to a column of Sephadex G-15 (20 × 200 mm) with water–methanol (1/1, v/v) as eluent to give pure product **3**. Yield: 45–52 mg, 60–70%. $[\alpha]_D$ − 28.5° (*c* 4.7 g/dL, water).

Measurements

^{1}H-NMR spectra were recorded in $CDCl_3$ or D_2O on a Varian VXR-200 (200 MHz) instrument. ^{13}C-NMR spectra were obtained with a JEOL GSX-400 (100 MHz) spectrometer. Optical rotations were recorded with a JASCO J-600 at 22°C in chloroform or water. Size exclusion chromatography (SEC) was carried out in tetrahydrofuran on a TOSOH HLC-802UR chromatograph equipped with polystyrene gel columns (TOSOH G2500H6 + G3000H6 + G4000H6 and G2000H6 + G5000H6 + G6000H6; exclusion limit = 1.0×10^6 and 1.0×10^7, respectively; 8.0 mm i.d. × 60 cm each) and refractive index/ultraviolet dual-mode detectors. The number-average molecular weight ($\overline{M}_n$) and polydispersity ratio ($\overline{M}_w/\overline{M}_n$) were estimated on the basis of a polystyrene calibration.

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 07455373) from the Ministry of Education, Science and Culture, Japan. We are grateful to Nisso Maruzen Chemical, Japan, for supplying 2-chloroethyl vinyl ether.

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