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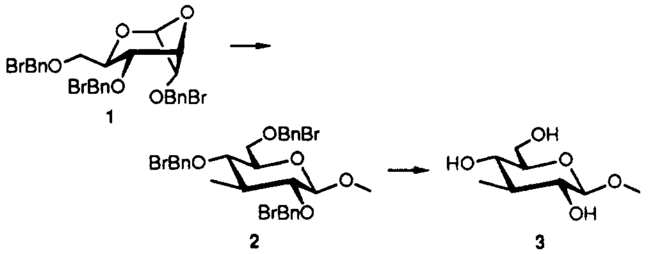
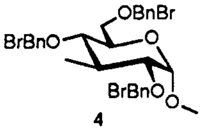
Chemical Synthesis of (1→3)-β-D-Glucopyranan by Ring-Opening Polymerization of a 1,3-Anhydro Sugar Derivative

Naturally occurring (1→3)-β-linked polysaccharides having branches at their 6-positions such as lentinan and schizophyllan exhibit excellent antitumor activities.[1-3] Curdlan, (1→3)-β-D-glucopyranan, displays an antitumor activity when D-glucose branches are introduced to some of its 6-positions.[4,5] In addition, sulfated curdlan and lentinan act as effective inhibitors against the growth of human immunodeficiency viruses (HIV).[6-9]

A variety of polysaccharides of well-defined structures have been synthesized not only from carbohydrate sources but also from noncarbohydrate sources.[10,11] Among the synthetic procedures for polysaccharides, ring-opening polymerization of anhydro sugar derivatives is most suitable for obtaining high molecular weight stereoregular homopolysaccharides.[12,13] However, no (1→3)-β-linked polysaccharide has been obtained so far by the ring-opening polymerization method, although (1→3)-α-D-glucopryanan and (1→3)-α-D-mannopyranan were successfully synthesized from the corresponding 1,3-anhydro sugar derivatives by Schuerch and his co-workers.[14-16] In this paper, we report the first chemical synthesis of (1→3)-β-D-glucopyranan (**3**) by ring-opening polymerization of 1,3-anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-glucopyranose (**1**).



Schuerch et al.[14,16] investigated the polymerization of 1,3-anhydro-2,4,6-tri-*O*-benzyl (or *p*-bromobenzyl or *p*-methylbenzyl)-β-D-glucopyranose with a variety of initiators: Cationic initiators such as phosphorus pentafluoride and trifluoromethanesulfonic acid anhydride were effective for producing polysaccharides mostly composed of the (1→3)-α-linked structural unit (**4**, α form). They found that only the triethylaluminum–water (1:1) system gave a polymer rich in the (1→3)-β-linked structural unit (**2**, β form) and speculated that the polymerization proceeded through a mechanism different from the conventional cationic mechanism.



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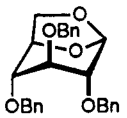
Generally, an anhydro sugar derivative (bicyclic acetal) cannot be polymerized with the complete retention of the configuration of its acetal carbon by the cationic mechanism, except in the special cases where every propagation step involves an oxonium exchange reaction[17-19] or neighboring group participation.[20] 1,3-Anhydro sugar derivatives contain a highly strained four-membered cyclic ether moiety. Since some four-membered cyclic ethers undergo ring-opening polymerization through a coordination mechanism, 1,3-anhydro sugar derivatives also may polymerize by a coordination mechanism as well as by the ordinary cationic mechanism. Therefore, we have examined the polymerization of **1** with modified organoaluminum compounds which act as effective catalysts for coordination polymerizations of epoxides, oxetanes, and β-lactones.

The anhydro sugar derivative **1** was synthesized from D-glucose by an eight-step reaction sequence according to the procedures described by Schuerch et al.[21] with slight modifications. Polymerization of **1** was carried out in toluene at 60 °C by using high-vacuum techniques. The stereoregularity of the resulting polymer was determined from the relative peak intensities of the corresponding anomeric carbon signals appearing at 95.8 and 102.4 ppm in the ^{13}C NMR spectrum. Table I summarizes the results of the polymerization of **1** by various triisobutylaluminum–water catalyst systems.

The triisobutylaluminum–water (1:0.7) binary catalyst without heat treatment gave a polymer consisting of 25% α form and 75% β form. The same initiator system was heat-treated under high vacuum at 200 °C in a manner similar to the procedure for the preparation of ethylaluminoxane.[22] The resulting white powdery solid, which is hereafter referred to as isobutylaluminoxane, gave a polymer of a much improved stereoregularity (96% β form). A combination of isobutylaluminoxane and epichlorohydrin (1:1)[23] gave a higher molecular weight polymer entirely composed of the β form.

In order to clarify the nature of the propagation catalyzed by isobutylaluminoxane, polymerization of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**5**) was attempted with isobutylaluminoxane alone and the isobutylaluminoxane–epichlorohydrin (1:1) binary system as catalysts under similar conditions as in the polymerization of **1**.



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However, no polymerization occurred at all with either of these catalysts. Since **5** polymerizes very readily in the presence of typical cationic initiators such as phosphorus pentafluoride and antimony pentafluoride,[24] the inertness of monomer **5** to isobutylaluminoxane and its combination with epichlorohydrin suggest that polymerization of **1** by these organoaluminum catalysts does not proceed by the conventional cationic mechanism. Therefore, it is highly probable that the polymerization of **1** proceeds by a coordination mechanism. The isobutylaluminoxane–epichlorohydrin system, however, has a drawback: The activity of the catalyst is not high enough to produce the desired (1→3)-β-linked polymer in high yield. We found that a triisobutylaluminum–water–acetylacetone (1:0.4:0.7) ternary system was a more active catalyst, giving a high molecular weight polymer entirely composed of the β-form units in higher yield. In addition, the reproducibility of the polymerization was better. The trialkylaluminum–water–acetylacetone system has been successfully used for the stereospecific ring-opening polymerizations of substituted oxetanes as well as epoxides.[25-29]

The deprotection of the *p*-bromobenzyl groups of polymer **2** was achieved in liquid ammonia at −78 °C by using metallic lithium.[16] This procedure has an advantage over the conventional one using metallic sodium in that the chain cleavage during the reaction is appreciably, although not completely, suppressed. A white powdery solid polymer was obtained after workup and purification by dialysis. The number-average molecular weight of the polysaccharide estimated by gel-permeation chromatog-

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Table I
Polymerization of 1,3-Anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-glucopyranose (1) with Triisobutylaluminum–Water Catalyst Systems[a]

catalyst	mol %[b]	time, h	yield,[c] %	M_n[d] × 10^{-3}	M_w/M_n[e]	$[\alpha]^{25}_D$,[f] deg	β form,[g] %
i-Bu_3Al-H_2O (1:0.7)	5	96	74	6.7	1.6	+37.8	75
$(i\text{-}BuAlO)_n$[h]	5	48	47	6.9	3.0	+31.4	96
$(i\text{-}BuAlO)_n$-ECH[i] (1:1)	5	48	50	20.0	5.0	+42.1	~100
i-Bu_3Al-H_2O-Acac[j] (1:0.4:0.8)	5	48	86	24.0	2.8	+40.7	~100
i-Bu_3Al-H_2O-Acac (1:0.4:0.8)	2	48	96	21.0	6.9	+41.7	~100
i-Bu_3Al-H_2O-Acac (1:0.4:0.8)	5	24	82	23.0	2.3	+40.2	~100

[a] Monomer, 0.20 g (0.30 mmol); solvent, toluene; $[M]_0$, 0.4 mol/L; temp, 60 °C. [b] Mole percent of aluminum to monomer. [c] Petroleum ether insoluble fraction. [d] Determined by VPO (benzene). [e] Determined by GPC (polystyrene standard). [f] In chloroform. [g] Determined by ^{13}C NMR spectroscopy. [h] Prepared from i-Bu_3Al–H_2O (1:0.7) by heat treatment under high vacuum for 30 min at 200 °C. [i] ECH, epichlorohydrin. [j] Acac, acetylacetone.

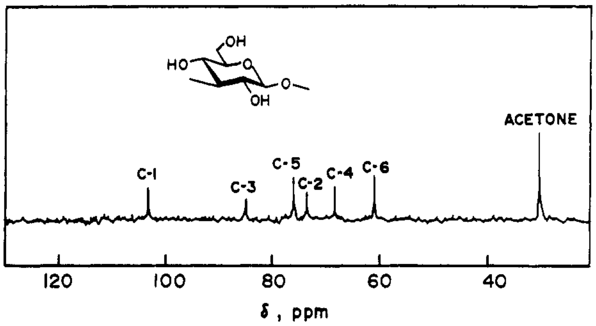

Figure 1. ^{13}C NMR spectrum of (1→3)-β-D-glucopyranan. Solvent, D_2O; concn, 1%; temp, 50 °C; internal reference, acetone; 50 MHz.

raphy (pullulan standard) was 1.2 × 10^3, which was lower than the predicted value (5.5 × 10^3) based on the molecular weight of the original *p*-bromobenzylated polymer (2.3 × 10^4; GPC, polystyrene standard). Figure 1 shows the ^{13}C NMR spectrum of the polysaccharide thus obtained.

There are six signals which are assigned as indicated in the figure. The chemical shifts of these signals are in agreement with the reported values for naturally occurring (1→3)-β-D-glucopyranan.[30] The polysaccharide 2 was hydrolyzed in refluxing 2 N aqueous trifluoroacetic acid to give D-glucose only. This is a clear indication that the polysaccharide entirely consists of D-glucose units and that it does not contain allose units which might be produced by the S_N2-type cleavage of the C(3)–O bond of the 1,3-anhydro ring of 1 during polymerization.

The present work opens a promising way to design bioactive 1,3-β-linked polysaccharides by ring-opening polymerization of 1,3-anhydro sugar derivatives. Further work is in progress to clarify the polymerization mechanism of 1 and its related monomers catalyzed by the modified organoaluminum compounds leading to the formation of 1,3-β-linked polysaccharides.

Experimental Section. General Procedures. ^1H and ^{13}C NMR spectra were recorded with a JEOL JNM-FX-200 Fourier transform NMR spectrometer operating at 200 and 50 MHz, respectively. Optical rotations were determined by a Jasco DIP-181 digital polarimeter, using a water-jacketed 1-dm cell. Number-average molecular weights of *p*-bromobenzylated polysaccharides were determined by a Corona Electric 117 vapor-pressure osmometer on solutions in benzene at 60 °C. Number-average molecular weights of deprotected polysaccharides were estimated with a Jasco 880-PU GPC instrument by using water and pullulan as the eluent and standard, respectively.

1,3-Anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-glucopyranose (1). The 1,3-anhydro sugar derivative 1 was prepared from D-glucose as a starting material through an eight-step reaction sequence as described by Schuerch et al.[21] with slight modifications. It was purified by repeated recrystallization from a mixture of ethyl acetate and *n*-hexane (1:2, v/v).

Preparation of Catalysts. (a) Triisobutylaluminum–Water (1:0.7). In a drybox filled with dry nitrogen, 5 mL of 15% triisobutylaluminum solution in *n*-hexane was taken in a flask. The solution was cooled and stirred well at 0 °C, to which 32 μL of water was slowly added with a microsyringe. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The flask was connected to a vacuum line, and, after freezing in liquid nitrogen and thawing twice, toluene was added to the solution to adjust the volume of the solution to 10 mL. A required volume of the solution was transferred to a glass tube and used for the polymerization.

(b) Isobutylaluminoxane. This compound was prepared in a manner similar to the procedure for the preparation of ethylaluminoxane.[19] In a drybox, 5 mL of 15% triisobutylaluminum solution in *n*-hexane was taken in a flask. The solution was cooled and stirred at 0 °C, to which 33 μL of water was added slowly. The resulting solution was stirred at 0 °C for 1 h and subsequently at room temperature for 1 h. The solution was transferred to a glass vessel, and, after freezing and thawing twice, 5 mL of decalin was added to the solution by vacuum distillation. *n*-Hexane and decalin were distilled, and the residue was heated at 200 °C under high vacuum (1 × 10^{-5} mmHg) for $^1/_2$ h. Decalin was again added to dissolve the residue, and, after removal of the solvent, the residue was heated at 200 °C under high vacuum for $^1/_2$ h. This procedure was repeated three more times (in total five times) to yield a colorless powder. A portion (15 mg) of the powder was weighed into a glass vessel and dried in a high-vacuum line. Addition of 1 mL of toluene gave a clear solution, from which a desired volume of the solution was used for the polymerization.

(c) Isobutylaluminoxane–Epichlorohydrin. A required volume of a solution of epichlorohydrin in toluene was added to the isobutylaluminoxane solution described above. The mixture was stirred at room temperature for 1 h and used for polymerization.

(d) Triisobutylaluminum–Water–Acetylacetone (1:0.4:0.7). In a drybox, 7 mL of 15% triisobutylaluminum solution in *n*-hexane was taken in a flask and was cooled to 0 °C. To this solution was cautiously added with a microsyringe 26 μL of water. The resulting solution was stirred at 0 °C for $^1/_2$ hour. Then 0.28 mL of acetylacetone was slowly added to the solution, and the mixture was stirred at 0 °C for $^1/_2$ h and subsequently at room temperature for 1 h. The resulting white turbid solution (3.75 mL) was taken in a glass vessel. After freezing in liquid nitrogen and thawing, toluene was added to the solution to adjust the volume of the solution to 10 mL. A required volume of the clear solution thus obtained was used for the polymerization.

Polymerization. Polymerization of 1 was carried out in toluene at 60 °C by using high-vacuum techniques. The reaction mixture was poured into petroleum ether to precipitate a white solid. It was purified by reprecipitation using chloroform and petroleum ether as a pair of solvent and precipitant and finally freeze-dried from a solution in benzene. Mp: 199–210 °C. ^{13}C NMR (CDCl$_3$): δ 137.29, 136.95, 136.85 (phenyl, ipso), 131.34, 131.19, 131.05 (phenyl, ortho), 129.37, 128.99, 128.89 (phenyl, meta), 121.39, 121.27 (phenyl, para), 102.35 (C-1), 83.73 (C-3), 80.60 (C-2), 76.62 (C-4), 74.85 (C-5), 73.78, 72.61 (benzyl), 69.09 (C-6). Anal. Calcd for $(C_{27}H_{25}O_5Br_3)_n$: C, 48.46; H, 3.77. Found: C, 48.13; H, 3.62.

Deprotection. A sample (721 mg) of *p*-bromobenzylated polymer was placed in a round-bottomed flask equipped with a finger trap. Dry toluene (4 mL) was added to dissolve the sample. After the flask was purged with dry nitrogen, it was cooled in a dry ice–methanol bath. Liquid nitrogen (27 mL) was introduced into the flask. Small pieces of lithium (600 mg) were added to the solution until green persisted. The reaction mixture was stirred for 3 h at −78 °C. Ammonium chloride was carefully added to the solution until the green disappeared. Then water and dichloromethane were added in this order. The resulting aqueous and organic phases were separated, and the aqueous phase was eluted through a column containing Amberlite IR 120. The eluent was dialyzed from water and finally freeze-dried. ^{13}C NMR (D$_2$O, acetone): δ 102.38 (C-1), 84.39 (C-3), 75.58 (C-5), 73.15 (C-2), 68.15 (C-4), 60.77 (C-6).

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