Cationic Ring-Opening Polymerization of 3,6-Di-*O*-benzyl-α-D-glucose 1,2,4-Orthopivalate and the First Chemical Synthesis of Cellulose

Fumiaki Nakatsubo,* Hiroshi Kamitakahara, and Michiko Hori

Contribution from the Department of Wood Science & Technology, Faculty of Agriculture, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

Received September 25, 1995[⊗]

Abstract: Cellulose, (1→4)-β-D-glucopyranan, was for the first time synthesized by cationic ring-opening polymerization of 3,6-di-*O*-benzyl-α-D-glucose 1,2,4-orthopivalate (**5**) into 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranan (**6**) and subsequent removal of the protective groups. Polymerization of the orthoester **5** by triphenyl carbenium tetrafluoroborate gave 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranan with $[\alpha]_D$ −37.2° and a number-average molecular weight of 8.3×10^3 ($\overline{DP}_n = 19.3$). Removal of the pivaloyl and benzyl groups and subsequent acetylation gave acetylated (1→4)-β-D-glucopyranan which was completely identical with cellulose triacetate (CTA) prepared from low molecular weight cellulose. The synthesized CTA was converted by deacetylation to cellulose, which has the cellulose-II crystal structure.

Introduction

Cellulose is the most abundant natural organic polymer, existing as a main plant cell wall component, and is important as a biodegradable and renewable organic material.[1] The study for cellulose, therefore, has been continued for about 150 years, but there are still several problems which should be solved: biosynthesis and biodegradation, crystal structure, chemical synthesis, regiospecific substitution reactions and structure-function relationship of derivatives, and so on.[1,2] The synthesis of cellulose has been a very important, but extremely difficult, problem to be solved, since Schulbach first tried the synthesis.[3]

Recently, Kobayashi and his co-workers reported enzymic synthesis of cellulose. Their synthetic method with cellulase is important and interesting from the standpoint of the first *in vitro* synthesis using an enzyme.[4] Their method, however, does not satisfy the recent molecular design of cellulose derivatives having special functions, because it may not enable special functional groups to be introduced regiospecifically at the desired hydroxyl groups in the repeating pyranose units of cellulose.

There are many functional cellulose derivatives, cellulose esters and ethers having liquid crystalline properties[5] and chiral recognition ability,[6] sulfonated cellulose with anticoagulant activity with heparin,[7] branched cellulose derivatives with antitumor activity,[8] and so on. However, much remains unknown about the relationship between their structure and properties: which derivatives are more functional or active among those substituted at 2-*O*, 3-*O*, or 6-*O* positions. For these studies and for further molecular design of advanced materials from cellulose, it is imperative that we develop methods that make it possible to prepare cellulose derivatives having functional groups at the desired positions among 2,3,6-hydroxyl groups in the repeating glucopyranose unit of cellulose.

Polycondensation and ring-opening polymerization methods using a glucose derivative as the starting monomer satisfy the above requirements,[9] but all trials to synthesize cellulose by these methods, attempted since Schulbach first tried, have been unsuccessful.

Husemann and Müller[10] and Hirano[11] reported the condensation of 2,3,6-glucose tricarbanilate with phosphorus pentoxide in a mixture of chloroform/dimethyl sulfoxide to give a cellulose-like polymer that was branched and contained about 1% phosphorus. Micheel *et al.*[12] and Uryu *et al.*[13] tried cationic

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1996.

(1) See, for example: Nevell, T. P.; Zeronian, S. H. Cellulose chemistry fundamentals in *Cellulose Chemistry and its Applications*; Nevell, T. P., Zeronian, S. H., Ed.; Ellis Horwood Limited: John Wiley & Sons: New York, 1985; pp 15−29.

(2) See books on cellulose: (a) Atalla, R. H. The Structure of Cellulose. In *ACS Symposium Series 340*; Atalla, R. H., Ed.; American Chemical Society: Washington, DC, 1987; pp 1−14. (b) Symposium on the Cellulose Structure and Its Characterization, and on the Biogenesis of Cellulose. In *Cellulose and Wood−Chemistry and Technology, Proceedings of the Tenth Cellulose Conference*; Schuerch, C., Ed.; John Wiley & Sons, Inc.: New York, 1989; pp 39−322, 473−825.

(3) Schlubach, H. M.; Luhrs, *L. Ann.* **1941**, *547*, 73.

(4) Kobayashi, S.; Kashiwa, K.; Kawasaki, T.; Shoda, S. *J. Am. Chem. Soc.* **1991**, *113*, 3079.

(5) (a) Sixou, P. *et al*. Cellulose Liquid Crystals in *Cellulose-Structure, Modification and Hydrolysis*; Young, R. A., Rowell, R. M., Eds.; John Wiley & Sons: 1986; pp 203−261. (b) Siekmeyer, M. *et al*. Liquid Crystals in *Cellulose-Structure and Functional Aspects*; Kennedy, J. F., Phillips, G. O., Williams, P. A., Eds.; Ellis Horwood: New York, 1989; p 345.

(6) (a) Hesse, G.; Hagel, R. *Chromatographia* **1973**, *6*, 277. (b) Shibata, T.; Okamoto, I.; Ishii, K. *J. Liq. Chromatog.* **1986**, *9*, 313. (c) Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Am. Chem. Soc.* **1984**, *106*, 5357. (d) Shibata, T.; Sei, T.; Nishimura, H.; Deguchi, K. *Chromatographia* **1987**, *24*, 552.

(7) (a) Kamide, K.; Okajima, Matsui, T.; Kobayashi, H. *Polym. J.* **1983**, *15*, 309. (b) Okajima, K. Role of molecular characteristics on some physiological properties of cellulose derivatives. In *Cellulose-Structure and Functional Aspects*; Kennedy, J. F., Phillips, G. O., William's, P. A., Eds.; Elise Horrid: New York, 1989; pp 439−446.

(8) (a) Matsuzaki, K.; Yamamoto, I.; Sato, T. *Makromol. Chem.* **1985**, *186*, 449. (b) Yamamoto, I.; Takayama, K.; Homma, K.; Gonda, T.; Matsuzaki, K.; Hatanaka, K.; Uryu, T.; Yoshida, O.; Nakashima, H.; Yamamoto, N.; Kaneko, Y.; Mimura, T. *Carbohydr. Polym.* **1991**, *14*, 53.

(9) General reviews on polysaccharides synthesis: (a) Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond-Formation and Cleavage*; Schuerch, C. trans Eds.; Pergamon Press: Oxford, 1979; pp 130−153. (b) Kochetkov, N. K. *Tetrahedron* **1987**, *43*, 2389. (c) Kochetkov, N. K. *Studies in Natural Products Chemistry, Vol. 14*, Elsevier Science B. V.: 1994; pp 201−266.

(10) Husemann, E.; Müller, G. J. M. *Makromol. Chem.* **1966**, *91*, 212.

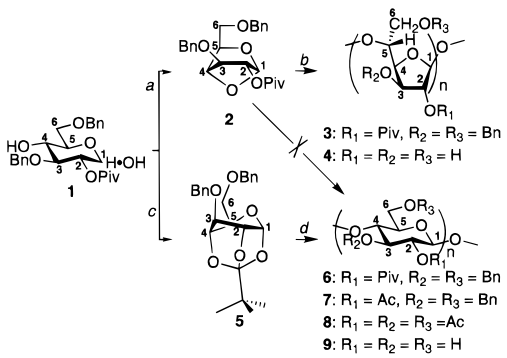
(11) Hirano, S. *Agric. Biol. Chem.* **1973**, *37*, 187.

(12) (a) Micheel, F.; Broode, O.-E.; Reinking, K. *Liebigs Ann. Chem.* **1974**, 124. (b) Micheel, F.; Bordde, O.-E. *Liebigs Ann. Chem.* **1974**, 702. (c) Micheel, F.; Bordde, O.-E. *Libigs Ann. Chem.* **1975**, 1107.

(13) Uryu, T.; Yamaguchi, C.; Morikawa, K.; Terui, K.; Kanai, T.; Matsuzaki, K. *Macromolecules* **1985**, *18*, 599.

0002-7863/96/1518-1677$12.00/0

Scheme 1



[a] *p*-TsOH/benzene/reflux/55%. [b] PF_5/toluene/−30 °C. [c] *N*,*N*′-Carbonyldiimidazole/benzene/reflux, 62.8%. [d] Ph_3CBF_4/CH_2Cl_2/room temperature.

polymerization of 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose initiated with various Lewis acids, but stereoregular (1→4)-D-glucopyranan was not obtained. Furthermore, Uryu *et al.*[14] reported the first synthesis of cellulose-type glucopyranan, (1→4)-*β*-D-ribopyranan by cationic ring-opening polymerization of 1,4-anhydro-α-D-ribopyranose derivatives. Their strategy is not applicable to the synthesis of cellulose, although it is useful for the preparation of a glucan with the same hydroxylation pattern as ribose. Very recently, Kochetkov described in his review with Malysheva had synthesized completely stereoregular (1→4)-*β*-D-glucan from a 1,2-*O*-cyanoethylidene derivative only at high pressure,[9c] but the paper described in detail has not appeared yet.

Here, we describe the first chemical synthesis of a cellulose derivative by cationic ring-opening polymerization using 3,6-di-*O*-benzyl-α-D-glucopyranose 1,2,4-orthopivalate (**5**) as a starting monomer. The derivative was converted to cellulose by removing the protective groups.

Results and Discussion

Selection of the Starting Monomer. We started, first of all, from the synthesis of cello-oligosaccharides by a stepwise synthetic method aimed at cellulose synthesis as a final goal[15] and studied the substituent effect on *β*-glycosylation.[16] We found that both ether (especially benzyl group) and ester substituents (especially pivaloyl group) at 3-*O* and 2-*O* positions, respectively, of glucose are indispensable for highly selective (1→4)-*β*-glycosidic bond formation with a high yield (protective system of the starting compound **1**[17] in Scheme 1).

Based on these results of substituent effects, we then succeeded in the synthesis of a series of cello-oligosaccharides up to cello-eicosaose derivative (DP = 20) by a convergent synthetic method.[18,19] Furthermore, we recently succeeded in the first synthesis of the stereoregular polysaccharide, 3,6-di-*O*-benzyl-2-*O*-pivaloyl-(1→5)-*β*-D-glucofuranan (**3**) from 1,4-anhydro-3,6-di-*O*-benzyl-2-*O*-pivaloyl-α-D-glucopyranose (**2**) with the same protective system as compound (**1**) by cationic ring-opening polymerization. Then, the polymer was converted to a non-natural polysaccharide, (1→5)-*β*-D-glucofuranan (**4**).[20a] Furthermore, 1,4-anhydro-α-D-glucopyranose derivatives were polymerized under various conditions to investigate the substituent effects at 2-*O*, 6-*O*, and 3-*O* positions on the ring-opening polymerization. We confirmed that the benzyl group at 3-*O* position has a special function for yielding a stereoregular polysaccharide with high molecular weight and that the pivaloyl group at 2-*O* position promotes polysaccharide *β*-configuration. Consequently, both the pivaloyl group at 2-*O* position and the benzyl group at 3-*O* position are indispensable for yielding stereoregular (1→5)-*β*-D-glucofuranan derivatives with high molecular weight.[20b] Thus, it was demonstrated that substituent effect obtained from the stepwise synthesis of cello-oligosaccharides can be also applied to the ring-opening polymerization of anhydro sugars.

For synthesizing cellulose from 1,4-anhydro-α-D-glucopyranose derivatives, however, regiospecific ring-opening, *i.e.*, 1,4-bond scission, giving 1,4-bond formation between repeating glucopyranose units have to be achieved. All trials for the regiospecific 1,4-ether bond cleavage of 1,4-anhydro-α-D-glucopyranose derivatives were unsuccessful in spite of many experiments carried out under various reaction conditions.[20] Thus, these results finally indicate that the cationic ring-opening polymerization of bicyclic 1,4-anhydro-α-D-glucopyranose derivatives such as compound **2** always afford preferentially (1→5)-D-glucofuranan rather than (1→4)-D-glucopyranan, coinciding with the results from model experiments with 2,7-dioxabicyclo[2.2.1]heptane by Hall *et al.*:[21] that is, it is impossible to synthesize stereoregular (1→4)-*β*-D-glucopyranan from the bicyclic 1,4-anhydro-α-D-glucopyranose derivatives. One strategy for yielding highly regioselective the 1,4-scission is to substitute 1,4-ether bond of 1,4-anhydro-α-D-glucopyranose derivatives for another more reactive linkage such as that of orthoester **5**. Several cationic ring-opening polymerizations of such tricyclic intramolecular orthoesters prepared from arabinose and xylose have been studied extensively by Bochkov, Kochetkov, and their co-workers:[22] they neither considered the substituent effect on polymerization nor achieved a stereoregular polymer. Finally, we selected tricyclic orthoester 3,6-di-*O*-benzyl-α-D-glucopyranose 1,2,4-orthopivalate (**5**) as a starting monomer for cationic ring-opening polymerization.

Synthesis of the Orthoester 5. Compound **1**[17] was refluxed with an equimolar amount of *N*,*N*′-carbonyldiimidazole in benzene to afford orthoester derivative **5** in about 60% yield. The structure of **5** was confirmed by elemental analysis and spectral analyses: IR (no carbonyl peak at 1740 cm^{-1}), ^{1}H-

(14) (a) Uryu, T.; Kitano, K.; Ito, K.; Yamanouchi, J.; Matsuzaki, K. *Macromolecules* **1981**, *14*, 1. (b) Uryu, T.; Yamanouchi, J.; Kato, T.; Higuchi, S.; Matsuzaki, K. *J. Am. Chem. Soc.* **1983**, *105*, 6865.

(15) Nakatsubo, F.; Takano, T.; Kawada, T.; Someya, H.; Harada, T.; Shiraki, H.; Murakami, K. *Mem. Coll. Agric. Kyoto Univ.* **1985**, *127*, 37.

(16) (a) Takano, T.; Nakatsubo, F.; Murakami, K. *Cell. Chem. Technol.* **1988**, *22*, 135. (b) Takano, T.; Harada, Y.; Nakatsubo, F.; Murakami, K. *Cell. Chem. Technol.* **1990**, *24*, 333. (c) Takano, T.; Harada, Y.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1990**, *36*, 212.

(17) Kamitakahara, H.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1994**, *40*, 302.

(18) (a) Nishimura, T.; Takano, T.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1993**, *39*, 40. (b) Nishimura, T.; Takano, T.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1994**, *40*, 44.

(19) (a) Kawada, T.; Nakatsubo, F.; Murakami, K. *Cell. Chem. Technol.* **1990**, *24*, 343. (b) Kawada, T.; Nakatsubo, F.; Murakami, K. *Mokuzai Gakkaishi* **1994**, *40*, 738. (c) Nishimura, T.; Nakatsubo, F.; Murakami, K. Abstracts of XVII Japanese Carbohydrate Symposium, 1995, 39.

(20) (a) Kamitakahara, H.; Nakatsubo, F.; Murakami, K. *Macromolecules* **1994**, *27*, 5937. (b) Kamitakahara, H.; Nakatsubo, F. *Macromolecules* **1996**, *29*, in press.

(21) Hall, H. K.; Deblauwe, F.; Carr, L. J.; Rao, V. S.; Seddy, G. S. *J. Polymer Sci.: Symposium* **1976**, *56*, 101.

(22) (a) Kochetkov, N. K.; Bochkov, A. F.; Yazlovertsky, I. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 1972. (b) Kochetkov, N. K.; Khorlin, A. Ya.; Bochkov, A. F.; Yazlovertsky, I. G. *Carbohydr. Res.* **1966**, *2*, 84. (c) Bochkov, A. F.; Yazlovertsky, I. G.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 1812. (d) Kochetkov, N. K.; Bochkov, A. F.; Yazlovertsky, I. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 1818. (e) Kochetkov, N. K.; Bochkov, A. F.; Yazlovertsky, I. G. *Carbohydr. Res.* **1969**, *9*, 49. (f) Bochkov, A. F.; Chernetsky, V. N.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 465. (g) Bochkov, A. F.; Obruchnikov, I. V.; Kochetkov, N. K. *zh. Obshch. Khim.* **1972**, *42*, 2766. (h) Bochkov, A. F.; Obruchnikov, I. V.; Kochetkov, N. K. *Zh. Obshch. Khim.* **1974**, *44*, 1197. (i) Bochkov, A. F.; Chernetsky, V. N.; Kochetkov, N. K. *Carbohydr. Res.* **1975**, *43*, 35. (j) Bochkov, A. F.; Rodionov, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 2789.

Table 1. Polymerization of 3,6-Di-*O*-benzyl-α-D-glucopyranose 1,2,4-Orthopivalate (**5**)

exp no.	initiator	monomer/solv, g/100 mL	temp, °C	time, h	yield, %	$[\alpha]_D$, deg	$10^{-3}M_{GPC}$	$\overline{DP_n}^d$
1	PF_5	25	−30	63	56[a]	−15.1	3.1	7.2
2	$BF_3{\cdot}Et_2O$	25	−30	43	100[b]	−32.8	4.5	10.6
3	Ph_3CSbCl_6	50	−30	151	90[a]	−31.4	3.0	7.0
4	Ph_3CSbCl_6	50	0	78	85[a]	−12.2	1.6	3.7
5	Ph_3CSbCl_6	50	20	14	55[a]	−12.4	1.4	3.3
6	Ph_3CBF_4	50	−30	16	50[a]	−20.1	2.9	6.9
7	Ph_3CBF_4	50	0	18	96[a]	−32.9	3.8	8.9
8	Ph_3CBF_4	50	20	14	93[a]	−35.2	4.5	10.5
9	Ph_3CBF_4	100	20	2	62[c]	−37.2	8.3	19.3

[a] Polymer was insoluble fraction in *n*-hexane. [b] No unreacted monomer was detected. [c] Polymer was insoluble fraction in chloroform/*n*-hexane (*ca.* 1/5, v/v). [d] Molecular weight was calculated from polystylene standard.

NMR (C_1-H: δ 5.79, d, J = 4.9 Hz), ^{13}C-NMR (no carbonyl peak and orthoester quaternary carbon at δ 123.1). The reagent, *N*,*N*′-carbonyldiimidazole, has been used as the dehydrating reagent for the preparation of lactones,[23] peptides,[24] glucosides,[25] and cyclic carbonates[26] from diol compounds.[27] The reagent preferentially attacks a hydroxyl group that is more acidic than 4-OH of compound **1** to give a 1-*O*-carbonylimidazole derivative, which is further converted to a dioxocarbenium ion intermediate with removal of the carbonylimidazole group and then to orthoester **5** by intramolecular attack of 4-OH.

Polymerization of the Orthoester 5. Polymerization of the orthoester **5** was carried out under several reaction conditions: at different temperatures (−30 to 20 °C), in the presence of different catalysts (PF_5, $BF_3{\cdot}Et_2O$, Ph_3CSbCl_6, Ph_3CBF_4) at 5 mol % concentration, and at different monomer concentrations (25−100 g/100 mL). Methylene chloride was the best solvent among those tried. A portion of the results is summarized in Table 1. The molecular weight of the polymer increases with an increase of monomer concentration. In the polymerization catalyzed by Ph_3CBF_4, increasing temperature tends to increase the molecular weight of the polymer, but the opposite tendency was obtained in the case of Lewis acids other than Ph_3CBF_4. The best result was obtained using Ph_3CBF_4 catalyst, that is, the highest $\overline{DP_n}$ was approximately 20 (Table 1, experiment no. 9). All polymers obtained are levorotatory, and the absolute value gradually increases with increase of molecular weight but tends to converge to approximately −40°. These large negative specific rotations clearly indicate that these polymers have β-configuration. In fact, all these polymers were proved to be stereoregular (1→4)-β-D-glucopyranan by ^{13}C-NMR analyses as described in a later section.

Structure of Polymer 6. Polymers obtained from experiment nos. 1−9 in Table 1 gave the same ^{1}H- and ^{13}C-NMR spectra, shown in Figures 1 and 2. The following data are those of the polymer **6** from experiment no. 9. The ^{1}H resonances for the polymer **6** were assigned *via* their cross-peaks in the H−H COSY spectrum (Figure 3A). The ^{13}C resonances were assigned by comparing the ^{1}H assignments with ^{1}H−^{13}C correlation data in the C−H COSY spectrum (Figure 3B).

Each ring proton appears clearly even though the substance is a polymer, which indicates high stereoregularity of the polymer **6**. This is also supported by the fact that the polymer **6** is a crystalline compound with melting point 206−217 °C.

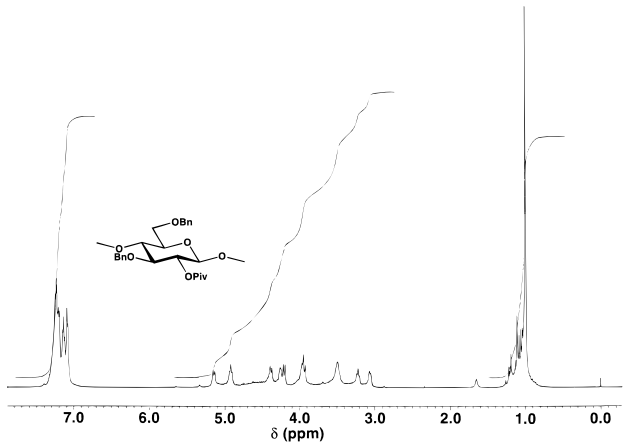


Figure 1. 500-MHz ^{1}H-NMR spectrum of 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranan (**6**) ($CDCl_3$ as solvent).

The relatively large coupling constant of the ring protons (J = approximately 9 Hz) suggests that the polymer **6** consists of glucopyranosyl repeating units with $^4C_1$-conformation, not of furanosyl units.[28] The presence of the pivaloyl group is supported by various spectral data: IR spectrum (1740 cm^{-1}), ^{1}H-NMR (δ 0.97−1.13 ppm, 9H) and ^{13}C-NMR (δ 27.2, 38.7). This group must exist at a C_2-*O*-position of the repeating glucopyranosyl units, because the C_2-proton appears at the lowest magnetic field (δ 4.95, t, J = 8.7 Hz) among the ring protons. Thus, the above spectroscopic data strongly indicate that the polymer **6** has exactly the (1→4)-D-glucopyranan skeleton with $^4C_1$-conformation, although there is a possibility of producing both (1→2)- and (1→4)-glucans on the cationic ring opening polymerization of the 1,2,4-orthoester.

The value of the coupling constant of C_1-H appearing at δ 4.23 is 8.7 Hz calculated from the $J_{1,2}$-value of C_2-H. This indicates β-glucosidic linkages between the repeating units in polymer **6**; the value would be about 3.0 Hz in the case of α-glucosidic linkages.[28] The β-glucosidic linkage is also supported by a sharp peak assigned to the C_1-carbon appearing at 99.60 ppm in ^{13}C-NMR. The chemical shift is very close to that (C_1' δ 99.50 ppm) of the cellobiose derivative, allyl 2,2′-di-*O*-pivaloyl-3,3′,6,6′-tetra-*O*-benzyl-β-D-cellobioside, obtained in our previous study.[18a] Furthermore, the high negative specific rotation of polymer **6** also supports β-glucosidic linkages in the polymer. Thus, all above results strongly indicate that the polymer **6** is a (1→4)-β-D-glucopyranan derivative.

Conversion of the Polymer 6 into Cellulose (9) *via* Cellulose Triacetate (CTA) (8). Polymer **6** was converted into its 2-*O*-acetyl derivative (**7**) by treating with $NaOCH_3$ in THF/

(23) Colvin, E. W.; Purcell, T. A.; Rahael, R. A. *J. Chem. Soc., Chem. Commun.* **1972**, 1031.
(24) Paul, R.; Aderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596.
(25) Ford, M. J.; Ley, S. V. *Synlett* **1990**, 255.
(26) (a) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, 47. (b) Kang, S.-K.; Jeon, J.-H.; Nam, K.-S.; Park, C.-H.; Lee, H.-W. *Synth. Commun.* **1994**, *24*, 305.
(27) Our initial plan was aimed at preparation of the 1,4-cyclic carbonate from compound **1**, which is also expected to be used as the starting monomer for polymerizations such as poly-α-amino acid synthesis from *N*-carboxy-α-amino acid anhydride.
(28) Hall, L. D. Nuclear Magnetic Resonance. In *Advances in Carbohydrate Chemistry Vol. 19*; Wolfrom, M. L., Tipson, R. S., Ed.; Academic Press: New York, London, 1964; pp 51−93.

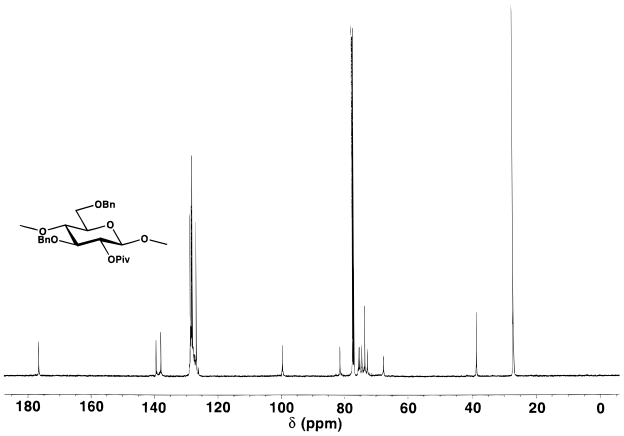


Figure 2. 125-MHz ^{13}C-NMR spectrum of 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranan (**6**) ($CDCl_3$ as solvent).

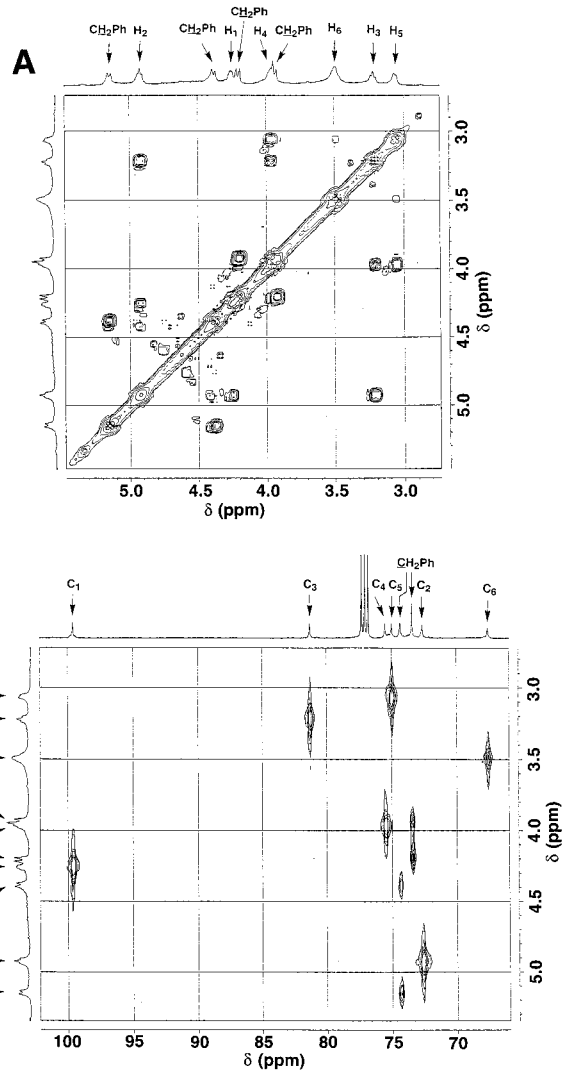


Figure 3. 2D-NMR spectra of 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranan (**6**): (A) plot from H−H COSY experiment and (B) plot from C−H COSY experiment ($CDCl_3$ as solvent).

methanol (10/1, v/v) at reflux and then with acetic anhydride and pyridine. The ^{1}H-NMR spectra of polymers **6** and **7** were completely identical except for the peaks from pivaloyl and acetyl groups. Polymer **7** was then transformed into CTA (**8**) by debenzylation with H_2 in the presence of palladium hydroxide on carbon under 4.5 kgf/cm^2 pressure and then acetylation with acetic anhydride and pyridine. The degree of polymerization

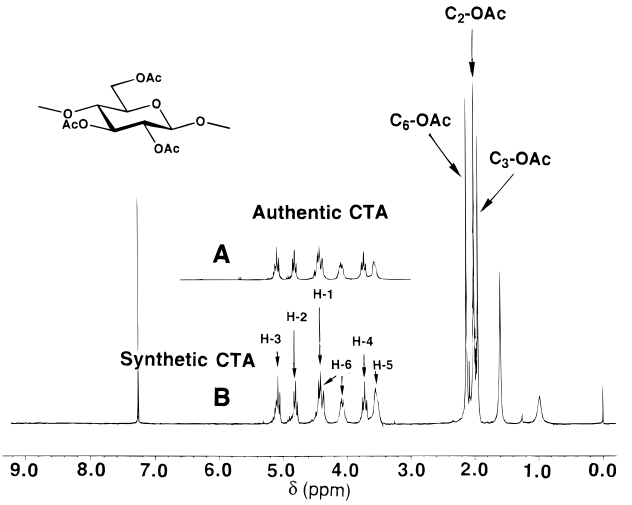


Figure 4. 300-MHz ^{1}H-NMR spectra of (A) authentic cellulose triacetate and (B) synthetic cellulose triacetate (**9**) ($CDCl_3$) as solvent).

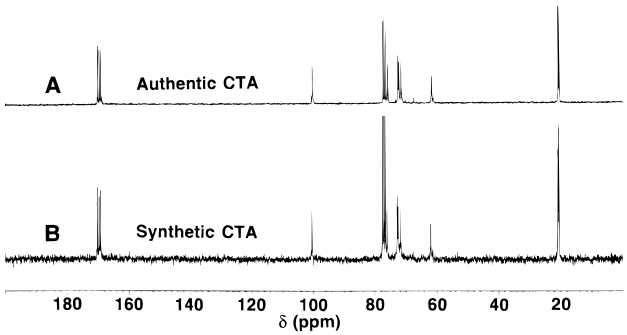


Figure 5. 75-MHz ^{13}C-NMR spectra of (A) authentic cellulose triacetate and (B) synthetic cellulose triacetate (**9**) ($CDCl_3$) as solvent).

of the CTA (**8**) was almost in agreement with that of polymer **6**: depolymerization did not occur during the deprotection processes. The ^{1}H- and ^{13}C-NMR spectra of polymer **8** were completely identical with those of authentic CTA prepared from cellulose with low molecular weight (Figures 4 and 5, respectively);[29] acetyl protons were completely identical with each other, but only ring protons are shown in Figure 4 for comparison.

Finally, the cellulose triacetate thus obtained was converted to cellulose by deacetylation with $NaOCH_3$ in THF/methanol (10/1, v/v). The X-ray diagram of cellulose prepared in this way was completely identical with that of regenerated cellulose with the cellulose-II crystal structure[30] (Figure 6).

Hence, we conclude that the chemical synthesis of (1→4)-β-D-glucopyranan cellulose was for the first time achieved *via* cationic ring-opening polymerization of tricyclic intramolecular orthoester derivative (**5**).

Conclusion

Selection of the best combination of protective groups for hydroxyl groups of sugars is very important for yielding highly selective glycosylation. Especially, the 3-*O*-benzyl group has been demonstrated to be indispensable to obtain (1→4)-β-glucosidic linkages with high stereoselectivity and in high yield from the stepwise synthesis of a series of cello-oligosaccha-

(29) (a) Atalla, R. H.; Ellis, J. D.; Schroeder, L. R. *J. Wood Chem. Technol.* **1984**, *4*, 465. (b) Isogai, A.; Usuda, M. *Mokuzai Gakkaishi* **1991**, *37*, 339.

(30) Jones, D. W. X-ray and electron diffraction in *Cellulose and Cellulose Derivatives Part IV*; Bikales, N. M., Segal, L., Ed.; Wiley-Interscience: New York, 1971; pp 117−180.

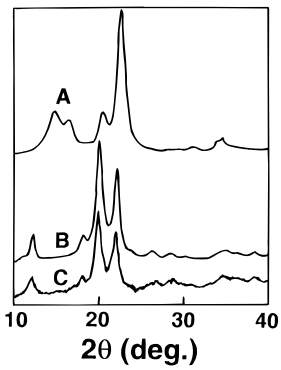


Figure 6. X-ray diffractograms of (A) Whatman cellulose CF11, (B) regenerated cellulose, and (C) synthetic cellulose.

rides.[16] Furthermore, these substituent effects were also found to be applicable to the synthesis of a stereoregular (1→5)-*β*-D-glucofuranan by ring-opening polymerization.[20]

Taking into account such substituent effects, we have now succeeded in the first syntheses of cellulose derivatives from 3,6-di-*O*-benzyl-α-D-glucopyranose 1,2,4-orthopivalate by cationic ring-opening polymerization, with conversion to cellulose by removal of the protective groups.

Experimental Section

Synthesis of 3,6-Di-*O*-benzyl-α-D-glucopyranose 1,2,4-Orthopivalate (5). 3,6-Di-*O*-benzyl-2-*O*-pivaloyl-D-glucopyranose (**1**)[17] (298.7 mg, 0.67 mM) was dissolved in benzene (40 mL), and then, *N*,*N*′-carbonyldiimidazole (116.9 mg, 1.05 equiv) was added. The solution was stirred at reflux temperature for 31 h. The reaction mixture was concentrated *in vacuo*. Compound **5** was purified on silica gel column (Wakogel C-200) eluted with ethyl acetate/*n*-hexane (1/4, v/v) to give colorless crystals (180 mg, 62.8%): mp 58.7−59.2 °C (recrystallized from methanol); $[\alpha]_D$ +22.1° (*c* 1, chloroform); ^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, piv-H), 3.75 (dd, 1H, J_{gem} = 9.6, $J_{5,6a}$ = 7.1, C_6-H_a), 3.83 (dd, 1H, J_{gem} = 9.6, $J_{5,6b}$ = 7.1, C_6-H_b), 3.95 (collapsed dt, 1H, $J_{2,4}$ = 2.0, $J_{3,4}$ = 4.6, $J_{4,5}$ = 1.4, C_4-H), 4.31 (dd, 1H, $J_{2,3}$ = 2.0, $J_{3,4}$ = 4.6, C_3-H), 4.42 (dt, 1H, $J_{1,2}$ = 4.9, $J_{2,3}$ = $J_{2,4}$ = 2.0, C_2-H), 4.60 (collapsed t, 1H, $J_{4,5}$ = 1.4, $J_{5,6a}$ = $J_{5,6b}$ = 7.1, C_5-H), 5.79 (d, 1H, $J_{1,2}$ = 4.9, C_1-H), 4.50, 4.55, 5.65 (d, s, d, 1H, 2H, 1H, respectively, *J* = 12.0, C*H*$_2$$C_6H_5$), 7.09−7.36 (10H, aromatic); ^{13}C-NMR δ 97.6 (C-1), 75.8, 73.4, 72.3, 71.9, 71.7, 71.2, 70.1 (C-2, C-3, C-3, C-4, C-5, C-6, *C*H$_2$$C_6H_5$), 123.1 (*C*(CH$_3$)$_3$), 24.9 (C(*C*H$_3$)$_3$). Anal. ($C_{25}H_{30}O_6$) Calcd: C, 70.40; H, 7.09. Found: C, 70.27; H, 7.06.

Polymerization of Compound 5. All polymerizations were carried out using a high-vacuum line capable of maintaining a vacuum of 1×10^{-3} Torr. Monomer was dried in a polymerization ampule by evacuating for *ca*. a day. Methylene chloride was distilled from CaH_2 and degassed by freezing and thawing three times in a high-vacuum line. The solvent was transferred under high vacuum. Phosphorus pentafluoride was generated from *p*-chlorobenzenediazonium hexafluorophosphate by decomposition at 160 °C and transferred to a reaction ampule. BF_3·Et_2O was added into the reaction ampule through a rubber septum by syringe. Triphenylcarbenium tetrafluoroborate was placed on a small glass plate in the reaction ampule with compound **5**. The reaction apparatus was then separated from the vacuum line by melting off and placed in a bath of the appropriate temperature. The reaction mixture was diluted with toluene/chloroform (1/1, v/v), washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The polymer mixture was dissolved in a small amount of chloroform. To the solution, *n*-hexane was added, and then precipitated polymer 3,6-di-*O*-benzyl-2-*O*-pivaloyl-(1→4)-*β*-D-glucopyranan (**6**) was collected by filtration and finally dried *in vacuo*: mp 206−217 °C; $[\alpha]_D$ −37.2° (*c* 0.65, chloroform); ^{1}H-NMR ($CDCl_3$) δ 0.97−1.13 (9H, piv-H), 3.04 (m, 1H, C_5-H), 3.16 (broad t, 1H, $J_{2,3}$ = 8.7, $J_{3,4}$ = 8.5, C_3-H), 3.48 (m, 2H, C_6-H), 3.97 (broad t, 1H, $J_{3,4}$ = 8.5, $J_{4,5}$ = 9.2, C_4-H), 4.23 (d, 1H, $J_{1,2}$ = 8.7, C_1-H), 4.95 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.7, C_2-H), 3.85, 4.16−4.20, 4.35, 5.17 (d, 1H, *J* = 12.0, respectively, C*H*$_2$$C_6H_5$), 7.07−7.24 (10H, aromatic); ^{13}C-NMR δ 99.6 (C-1), 81.1 (C-4), 67.4 (C-6), 75.4, 74.8, 74.2, 73.3, 72.4 (C-2, C-3, C-3, C-5, *C*H$_2$$C_6H_5$), 128.5, 128.2, 127.8, 126.5, 139.2, 137.7 (aromatic), 27.2 (C(*C*H$_3$)$_3$), 38.7 (*C*(CH$_3$)$_3$), 176.5 (C═O).

Preparation of Cellulose (9). 2,3,6-Tri-*O*-acetyl-(1→4)-*β*-D-glucopyranan (8). To a solution of 3,6-di-*O*-benzyl-2-*O*-pivaloyl-(1→4)-*β*-D-glucopyranan (**6**) (150.4 mg) in THF/methanol (10/1, v/v) (40 mL) was added 28% sodium methoxide in methanol (1.5 mL). The reaction mixture was kept at reflux temperature overnight, treated with Amberlyst 15 ion-exchange resin for neutralization, and then filtered off. The resin was washed with chloroform. The combined washings and filtrate were concentrated to dryness. The product was treated with acetic anhydride and pyridine at 50 °C overnight to give 3,6-di-*O*-benzyl-2-*O*-acetyl-(1→4)-*β*-D-glucopyranan (**7**). To a solution of the compound **7** in THF/acetic acid (1/1, v/v) (5 mL) was added palladium hydroxide on carbon (180 mg). The reaction mixture was kept under 4.5 kgf/cm^2 at room temperature for an hour. The reaction mixture was concentrated, treated with acetic anhydride and pyridine at 50 °C overnight, and concentrated to dryness. The product was washed with methanol, collected by filtration, and dried *in vacuo* to give 2,3,6-tri-*O*-acetyl-(1→4)-*β*-D-glucopyranan (**8**) (69 mg, 68% overall yield from compound **6**): mp 299−306 °C dec; $[\alpha]_D$ −24.8° (*c* 1.3, chloroform); ^{1}H-NMR ($CDCl_3$) δ 1.95, 2.03, 2.13 (C_3-Ac, C_2-Ac, C_6-Ac, 3H, 3H, 3H, respectively), 3.55 (m, 1H, C_5-H), 3.71 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.3, C_4-H), 4.06 (d, 1H, *J* = 7.4, C_6-H_a), 4.36−4.43 (2H, C_1-H, C_6-H_b), 4.79 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.0, C_2-H), 5.07 (t, 1H, $J_{2,3}$ = 9.0, $J_{3,4}$ = 9.3, C_3-H); ^{13}C-NMR δ 100.5 (C-1), 72.0 (C-2), 72.6 (C-3), 76.2 (C-4), 73.0 (C-5), 62.1 (C-6), 20.8, 20.5 (Ac-C), 169.2, 169.7, 170.2 (C_2-C═O, C_3-C═O, C_6-C═O, respectively).

(1→4)-*β*-D-Glucopyranan, Cellulose (9). To a solution of compound **8** (14.8 mg) in THF/methanol (10/1, v/v) (4.4 mL) was added 28% sodium methoxide in methanol (0.15 mL). The reaction mixture was kept at room temperature for 48 h and neutralized with 1 N HCl. The precipitated polymer was centrifuged, washed with methanol, collected by filtration, and dried *in vacuo* to give (1→4)-*β*-D-glucopyranan, cellulose (**9**) (6.3 mg, 73%).

Measurements. ^{1}H- and ^{13}C-NMR spectra were measured in chloroform-*d* with tetramethylsilane (TMS) as an internal standard using a Bruker ARX500 FT-NMR and a Bruker AC300 FT-NMR. Chemical shifts (δ) and coupling constants (*J*) are given in δ-values (ppm) and Hz, respectively. Optical rotations were measured using a JASCO Dip-1000 digital polarimeter. Infrared spectra were recorded with a Shimadzu FTIR-4000 spectrophotometer. X-ray diagrams were recorded with a Rigaku RINT 2200V. Molecular weight distributions of the substituted polymers were analyzed by gel permeation chromatography (GPC) in tetrahydrofuran. Calibration curves were obtained by using polystyrene standards (Shodex). A Waters universal liquid chromatograph injector (model U6K), a Waters solvent delivery system (model 6000A), a Waters refractive index detector (series R-400), a Waters absorbance detector (model 440), and Shodex columns (KF802 and KF803) were used. The flow rate was 1.0 mL/min.

Acknowledgment. The authors are indebted to Dr. James L. Davis, Assistant Professor of the College of Engineering, University of Wisconsin−Madison, for his critical reading of the manuscript. This investigation was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan (No. 07456080).

JA953286U