Synthesis of (1→6)-2,5-Anhydro-D-glucitol through Cyclopolymerization of 3,4-Di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol and Optical Resolution Ability of Its Derivative in HPLC

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ABSTRACT: The cyclopolymerization of 3,4-di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) was carried out using $BF_3 \cdot OEt_2$ and *t*-BuOK. The polymer obtained by the polymerization with $BF_3 \cdot OEt_2$ mainly consisted of (1→6)-bonded 3,4-di-*O*-allyl-2,5-anhydro-D-glucitol as the five-membered constitutional repeating unit, though it contained a small amount of other cyclic repeating units. On the other hand, during the polymerization using *t*-BuOK, the stereoregular polymer (1→6)-linked 3,4-di-*O*-allyl-2,5-anhydro-D-glucitol (**2**) was synthesized via a regio- and stereoselective mechanism. Cleavage of the allyl ether linkage in polymer **2** occurred to produce the polymer consisting of only 2,5-anhydro-D-glucitol units, i.e., (1→6)-2,5-anhydro-D-glucitol (**3**). Chromatographic enantioseparation of chloroquine and tröger base has been performed on (3,5-dimethylphenyl)carbamate and 4-methylbenzoate derivatives of **3** as a chiral stationary phase for high-performance liquid chromatography. © 1998 John Wiley & Sons, Inc. J Polym Sci A: Polym Chem 36: 901–909, 1998

Keywords: (1→6)-2,5-anhydro-D-glucitol; HPLC; optical resolution

INTRODUCTION

Various types of polymers having carbohydrate moieties in their main chains and side chains have been synthesized. Ring-opening polymerization of a bicyclic monosaccharide is widely used as a synthetic method for producing artificial carbohydrate polymers.[1–3] Recently, we presented the cyclopolymerization of diepoxides derived from hexitols as a new method. The cationic and anionic cyclopolymerizations of 3,4-di-*O*-alkyl-1,2 : 5,6-dianhydro-D-mannitols (alkyl: methyl, ethyl, pentyl, and decyl) led to stereoregular polymers.[4–10] In particular, the polymerization using *t*-BuOK produced the highly regio- and stereospecific polymer whose structure was the (1→6)-bonded 2,5-anhydro-D-glucitol, i.e., (1→6)-3,4-di-*O*-alkyl-2,5-anhydro-D-glucitol.[6,8–10] The structural characteristic of this polymer is a lack of an anomeric linkage, thus resulting in a new type of polymeric carbohydrate. Cleavage of the protective groups from the polymer yields the mother substance, (1→6)-2,5-anhydro-D-glucitol (**3**), which should find wide application in various 3,4-di-*O*-substituted derivatives (Scheme 1).

The alkyl group for the protection of the alcoholic hydroxyl function is stable during polymerization but is difficult to remove. On the other hand, the allyl group is commonly used in carbohydrate chemistry because of its ease of removal (Scheme 2).

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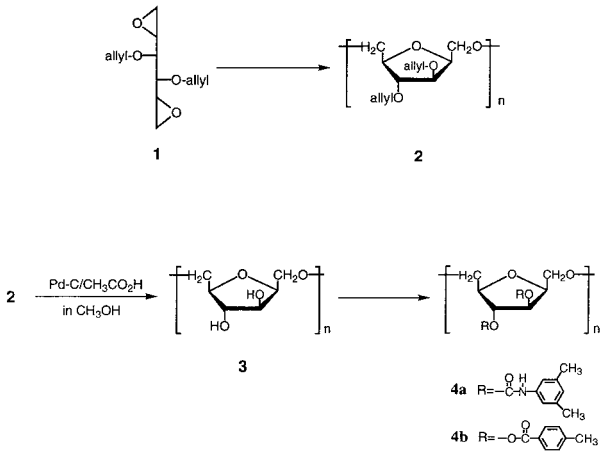


Scheme 1.

Polysaccharides derivatives, particularly phenylcarbamate derivatives of cellulose and amylose, are known to show high chiral stationary phases (CSPs) in high-performance liquid chromatography (HPLC).[11–13] It is known that the chiral discrimination ability of CSPs is highly dependent upon the polysaccharide used.[13] Therefore, it is of particular interest to utilize phenylcarbamate and benzoate derivatives of **3** as a stationary phase in a chromatographic system for the optical resolution of racemates.

In this paper, we report the cyclopolymerization of 3,4-di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) protecting the 3- and 4-hydroxy functions by allyl groups and the deallylation of the resulting polymer (**2**) to convert it into (1→6)-2,5-anhydro-D-glucitol (**3**). To confirm the structure of polymers **2** and **3,** the model compounds 3,4-di-*O*-allyl-2,5-anhydro-1, 6-di-*O*-methyl-D-glucitol (**6**), 2,5-anhydro-1,6-di-*O*-methyl-D-glucitol (**7**), and 3,4-di-*O*-allyl-2,5-anhydro-6-*O*-methyl-D-glucitol (**8**) were prepared. Furthermore, we synthesized (3,5-dimethylphenyl)-carbamate and 4-methylbenzoate derivatives of **3** and examined their chiral recognition abilities as stationary phases for HPLC.

EXPERIMENTAL

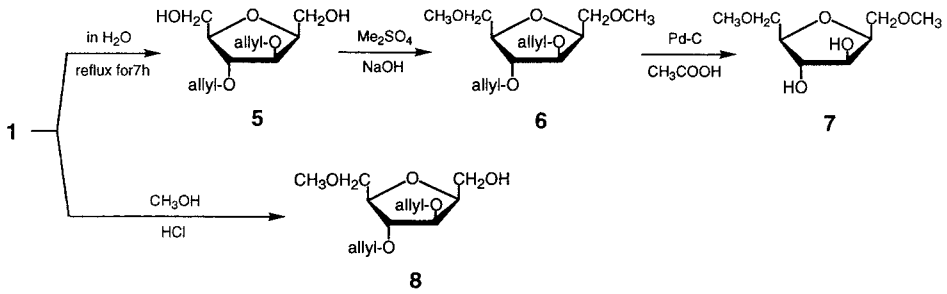
Materials

Boron trifluoride etherate ($BF_3 \cdot OEt_2$) was purified by distillation of a commercial product under reduced pressure and used as a solution in dry dichloromethane. Potassium *tert*-butoxide (*t*-BuOK) was purified by sublimation under vacuum before use. Dichloromethane and nitroethane were purified by the usual methods and distilled over calcium hydride. Toluene, tetrahydrofuran, and 1,4-dioxane were purified by the usual methods and distilled from sodium benzophenone. Column chromatography was performed on silica gel 60 (particle size 0.063–0.200 mm, Merck). 3,4-Di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) was prepared from D-mannitol according to the method reported by Kuszmann.[14] Monomer **1** was distilled over CaH_2 under reduced pressure before the polymerization runs.

Racemic compounds and (3-aminopropyl)triethoxysilane were purchased from Aldrich. 3,5-Dimethylphenyl isocyanate was obtained from Tokyo Kasei. *p*-Toluoyl chloride was obtained from Kanto Chemical.

3,4-Di-*O*-allyl-2,5-anhydro-D-glucitol (5)

A mixture of 1.75 g (10 mmol) of **1** and 40 mL of water was heated under reflux for 7 h. After cooling, the solution was evaporated under reduced pressure to obtain a syrup from which the water was removed using two azeotropic distillations of benzene and chloroform. The syrupy mixture was separated using flash column chromatography with ethyl acetate as the eluent. The fractions having R_f = 0.2 produced, upon evaporation, **5** as a syrup (1.60 g, 82%): $[\alpha]_D$ + 55.9°, $[\alpha]_{577}$ + 60.0°, $[\alpha]_{546}$ + 69.2°, $[\alpha]_{435}$ + 115.7°, and $[\alpha]_{405}$ + 138.3° (c = 1.0 in $CHCl_3$ at 23°C); ^{1}H-NMR ($CDCl_3$) δ = 5.82–5.95 (m, allyl —CH═, 2H), 5.30 (ddd, J_{trans} = 17.3 Hz,



Scheme 2.

Table I. Cationic Cyclopolymerization of 3,4-Di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) with $BF_3 \cdot OEt_2$[a]

No.	Solvent	Temp. (°C)	Yield (%)	M_n (M_w/M_n)[b]	DP	$[\alpha]_{546}^{23}$[c]
1	CH_2Cl_2	0	46.4	4220 (1.98)	18	+36.9
2	CH_2Cl_2	−10	58.9	4890 (1.60)	21	+34.0
3	$C_2H_5NO_2$	0	47.2	3570 (1.38)	15	+35.9
4	$C_2H_5NO_2$	−10	39.5	2640 (1.32)	11	+38.8

[a] [**1**] = 0.5 mol L^{-1}; [**3**]/[cat.] = 100; time, 2 h.
[b] Measured in THF by GPC using polystyrene as standard.
[c] Measured in $CHCl_3$ (c = 1.0).

J_{gem} = 4.9 Hz, $^4J_{vic}$ = 1.6 Hz, allyl trans $=CH_2$, 2H), 5.23 (ddd, J_{cis} = 10.4 Hz, J_{gem} = 4.3 Hz, $^4J_{vic}$ = 1.4 Hz, allyl cis $=CH_2$, 2H), 3.82–4.19 (m, allyl $-CH_2-$, 4H and H1–6, 7H), 3.70 (dd, J = 11.9 Hz, J = 4.1 Hz, H1, 1H), 2.23 (br s, —OH, 2H); ^{13}C-NMR ($CDCl_3$) δ = 134.11, 133.69 (allyl —CH=), 117.90, 117.55 (allyl $=CH_2$), 83.92, 83.63 (C3, 4), 82.64, 80.28 (C5, 2), 71.00, 70.76 (allyl $-CH_2-$), 62.84, and 61.77 ppm ($-CH_2OH$); FI-MS m/z (relative intensity) 243 (9.3), 244 (M^+ − 91.6), 245 (MH^+ − 100), 246 (20.9), 489 ($(2M + H)^+$ − 23.0), 490 (8.5). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00%; H, 8.25%. Found: C, 59.01%; H, 8.25%.

3,4-Di-*O*-allyl-2,5-anhydro-1,6-di-*O*-methyl-D-glucitol (6)

To a stirred solution of 0.96 g (5 mmol) of **5** in 6.4 mL of dimethyl sulfoxide was simultaneously added a solution of 1 g of sodium hydroxide in 1 mL of water and 1.60 g (12.6 mmol) of dimethyl sulfate, and the temperature of the reaction mixture did not exceed 60°C. Stirring was continued at this temperature for 30 min. After standing overnight at room temperature, the mixture was poured into water and extracted with chloroform. The extract was dried and evaporated, and the residue was separated using column chromatography with *n*-hexane/ethyl acetate (5/1) as the eluent. The fractions having R_f = 0.2 gave, on evaporation, **6** as a colorless liquid (0.59 g, 55.6%): $[\alpha]_D$ + 46.2°, $[\alpha]_{577}$ + 48.3°, $[\alpha]_{546}$ + 54.3°, $[\alpha]_{435}$ + 90.8°, and $[\alpha]_{405}$ + 108.1° (c = 1.0 in $CHCl_3$ at 23°C); ^{1}H-NMR ($CDCl_3$) δ = 5.82–5.95 (m, allyl —CH=, 2H), 5.29 (ddd, J_{trans} = 17.2 Hz, J_{gem} = 4.7 Hz, $^4J_{vic}$ = 1.6 Hz, allyl trans $=CH_2$, 2H), 5.20 (ddd, J_{cis} = 10.4 Hz, J_{gem} = 4.7 Hz, $^4J_{vic}$ = 1.5 Hz, allyl cis $=CH_2$, 2H), 3.80–4.17 (m allyl $-CH_2-$, 4H and H2–5, 4H), 3.58–3.67 (m, H6, 2H), 3.54 (dd, J = 10.1 Hz, J = 6.1 Hz, H1, 1H), 3.47 (dd J = 10.1 Hz, J = 6.1 Hz, H1, 1H), 3.39 (s, $-OCH_3$, 6H); ^{13}C-NMR ($CDCl_3$) δ = 135.13 (allyl —CH=), 117.89, 117.64 (allyl $=CH_2$), 84.70, 83.24 (C3, 4), 83.23, 80.60 (C5, 2), 73.89, 71.40 (C1, 6), 71.39 (allyl $-CH_2-$), and 59.91 ppm ($-OCH_3$); FI-MS m/z (relative intensity) 272 (M^+ − 100), 273 (27.5), 274 (6.9), 545 ($(2M + H)^+$ − 4.1). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74%; H, 8.88%. Found: C, 61.60%; H, 9.06%.

2,5-Anhydro-1,6-di-*O*-methyl-D-glucitol (7)

A stirred solution of 200 mg (0.735 mmol) of **6** in ethanol (3 mL), acetic acid (1.0 mL), and water (3 mL) under argon was boiled in the presence of a 10% Pd–C catalyst (240 mg). After 10 h, the catalyst was filtered off, and the filtrate was evaporated. The residue was then separated using chromatography with methanol/chloroform (1/9). Evaporation of the fractions having R_f = 0.34 gave **7** as a colorless syrup (48 mg, 34%): $[\alpha]_D$ + 23.7°, $[\alpha]_{577}$ + 29.6°, $[\alpha]_{546}$ + 33.3°, $[\alpha]_{435}$ + 57.4°, and $[\alpha]_{405}$ + 68.8° (c = 1.0 in $CHCl_3$ at 23°C); ^{1}H-NMR ($CDCl_3$) δ = 4.17–4.21 (m, H2, 1H), 4.14 (s, H4, 1H), 4.03 (br s, 1H), 3.92–3.97 (m, H3, 5, 2H), 3.72 (dd, J = 10.4, 4.0 Hz, H1, 1H), 3.62–3.68 (m, H1, 6, 2H), 3.58 (dd, J = 10.3, 3.0 Hz, H6, 1H), 3.43 (s, $-OCH_3$, 3H), 3.42 (s, $-OCH_3$, 3H), 2.85–3.15 (br, 1H); ^{13}C-NMR ($CDCl_3$) δ = 84.56 (C5), 80.14 (C2), 79.49 (C4), 77.99 (C3), 72.96 (C6), 71.38 (C1), 59.45 ($-OCH_3$) and 59.39 ppm ($-OCH_3$). Anal. Calcd for $C_8H_{16}O_5$: C, 49.99%; H, 8.39%. Found: C, 49.54%; H, 8.48%. FI-MS: m/z (relative intensity) 78 (25.6), 87 (12.3), 88 (18.5), 147 (16.2), 160 (15.9), 191 (33.1), 192 (M^+ − 100), 193 (MH^+ − 94.7), 194 (13.5), 385 ($(2M + H)^+$ − 14.2).

Table II. Anionic Cyclopolymerization of 3,4-Di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) with *t*-BuOK[a]

No.	Solvent	[**1**]/[Cat.]	Yield (%)	M_n (M_w/M_n)[b]	DP	$[\alpha]_{546}^{23}$[c]
5	Toluene	10	85.0	4730 (1.35)	21	+47.2
6	THF	20	66.1	4340 (1.36)	19	+56.9
7	1,4-Dioxane	20	68.8	5240 (1.66)	23	+50.1
8	Toluene	20	92.6	6600 (1.58)	29	+54.4
9	Toluene	30	80.0	5520 (1.37)	24	+51.0
10	Toluene	50	43.7	7170 (1.49)	32	+54.4
11	Toluene[d]	50	64.6	10400 (1.52)	46	+60.8

[a] $[M]$ = 1.0 mol L^{-1}; temp., 60°C; time, 48 h.
[b] Measured in THF by GPC using polystyrene as standard.
[c] Measured in $CHCl_3$ (c = 1.0).
[d] Polymerization time, 96 h.

3,4-Di-*O*-allyl-2,5-anhydro-6-*O*-methyl-D-glucitol (8)

To a solution of **1** (400 mg) in methanol (100 mL) was added 2 drops of concentrated hydrochloric acid. The mixture was kept for 24 h at room temperature and then evaporated to give a syrup. The residue was purified by column chromatography using ethyl acetate for elution. The fractions having R_f = 0.55 gave **8** as a colorless syrup (200 mg, 50%): $[\alpha]_D$ + 41.2°, $[\alpha]_{577}$ + 43.4°, $[\alpha]_{546}$ + 48.4°, $[\alpha]_{435}$ + 78.4°, and $[\alpha]_{405}$ + 93.1° (c = 1.0 in $CHCl_3$ at 23°C); ^{1}H-NMR ($CDCl_3$) δ = 5.82–5.95 (m, allyl —CH═, 2H), 5.29 (ddd, J_{trans} = 17.2 Hz, J_{gem} = 4.7 Hz, $^4J_{vic}$ = 1.6 Hz, allyl trans ═CH_2, 2H), 5.20 (ddd, J_{cis} = 10.4 Hz, J_{gem} = 4.7 Hz, $^4J_{vic}$ = 1.5 Hz, allyl cis ═CH_2, 2H), 3.75–4.17 (m, allyl —CH_2—, 4H and H1–5, 7H), 3.45–3.60 (m, H6, 2H), 3.39 (s, —OCH_3, 3H); ^{13}C-NMR ($CDCl_3$) δ = 134.09, 133.94 (allyl —CH═), 117.09, 116.98 (allyl ═CH_2), 83.29 (C3), 83.12 (C4), 81.31 (C5), 80.27 (C2), 72.81 (C6), 70.65, 70.53 (allyl —CH_2—), 61.20 (C1), 58.95 ppm (—OCH_3). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45%; H, 8.58%. Found: C, 59.81%; H, 8.36%.

Polymerization Using $BF_3 \cdot OEt_2$

Monomer **1** (500 mg, 2.21 mmol) was dissolved in dry dichloromethane (4.43 mL), and $BF_3 \cdot OEt_2$ in dichloromethane (30.1 mL in 0.73 mol L^{-1}, 0.0221 mmol) was added using a microsyringe. After 2 h at 0°C, the mixture was poured into a large amount of methanol containing a drop of aqueous ammonia, and the entire solution was evaporated under reduced pressure. The residue was washed several times using *n*-hexane and then dried under a vacuum to give 232 mg (yield 46.4%) of the polymer; the M_n and M_w/M_n values were 4220 and 1.98, respectively: $[\alpha]_D$ + 29.1°, $[\alpha]_{577}$ + 32.0°, $[\alpha]_{546}$ + 36.3°, $[\alpha]_{435}$ + 61.8°, and $[\alpha]_{405}$ + 73.7° (c = 1.0 in $CHCl_3$ at 23°C).

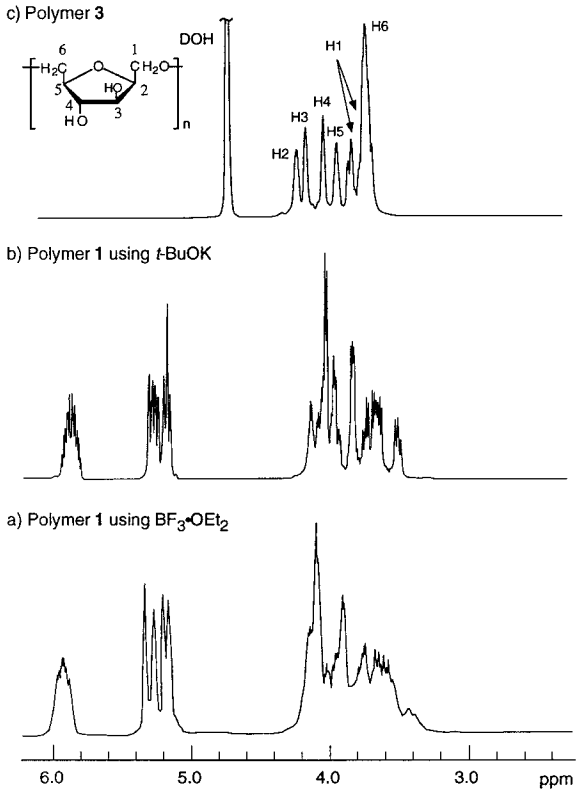


Figure 1. ^{1}H-NMR spectra of the polymers prepared from 3,4-di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) using $BF_3 \cdot OEt_2$ (a) and *t*-BuOK (b) and (1 → 6)-2,5-anhydro-D-glucitol (**3**) (c).

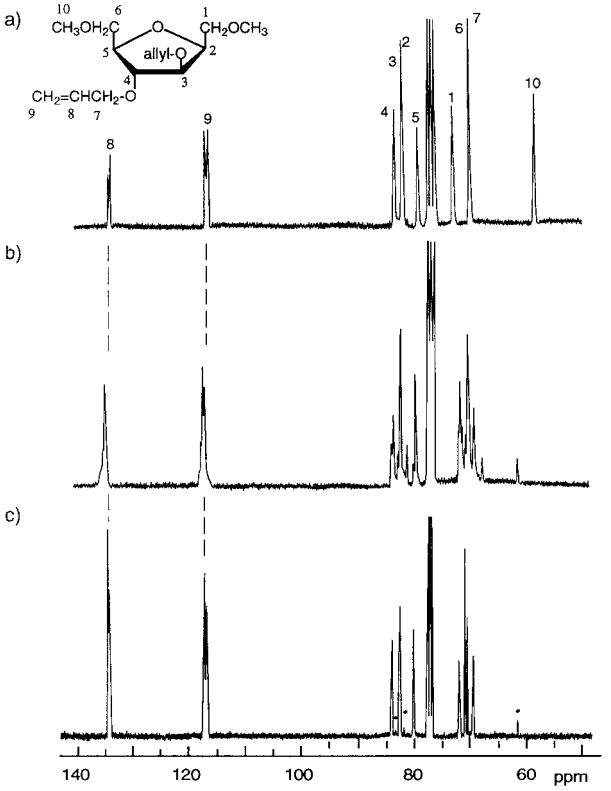


Figure 2. ^{13}C-NMR spectra of 3,4-di-*O*-allyl-2,5-anhydro-1,6-di-*O*-methyl-D-glucitol (**6**) (a) and polymers prepared from 3,4-di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) using $BF_3 \cdot OEt_2$ (b) and *t*-BuOK (c), respectively. The asterisked signals correspond to the carbons of the polymer chain ends.

Polymerization Using *t*-BuOK

The polymerization was carried out in dry toluene, tetrahydrofuran, and 1,4-dioxane in an H-shaped glass ampule. A typical polymerization procedure is as follows. *tert*-Butoxide (20.2 mg, 0.18 mmol) and dry toluene (3.6 mL) were added to the one side of the ampule, and monomer **1** (810 mg, 3.58 mmol) was added to the other side of the ampule under a nitrogen atmosphere. After sealing of the ampule, the monomer and the catalyst solution were mixed at 60°C. After 48 h, the reaction mixture was poured into a large amount of methanol and the entire solution was evaporated under reduced pressure. The residue was purified by reprecipitation from chloroform–*n*-hexane to give 750 mg (yield 92.6%) of the polymer; the M_n and M_w/M_n values were 6600 and 1.58, respectively: $[\alpha]_D$ + 48.0°, $[\alpha]_{577}$ + 53.0°, $[\alpha]_{546}$ + 59.5°, $[\alpha]_{435}$ + 97.9°, and $[\alpha]_{405}$ + 114.7° (c = 1.0 in $CHCl_3$ at 23°C); ^{13}C-NMR ($CDCl_3$) δ = 134.49 ppm (allyl —CH═), 117.12 (allyl CH_2═), 116.87 (allyl CH_2═), 83.80 (C4), 82.53 (C3), 82.49 (C2), 79.90 (C5), 71.75 (C1), 70.56 (allyl —CH_2—), 70.42 (allyl —CH_2—), and 69.37 (C6).

Deallylation

A stirred solution of polymer **2** (580 mg) in ethanol (8 mL), acetic acid (1 mL), and water (8 mL) under argon was boiled in the presence of a 10% Pd–C catalyst (500 mg). After 10 h, the catalyst was filtered off, and the filtrate was evaporated. After three evaporations using ethanol, the residue was purified by reprecipitation from methanol/tetrahydrofuran (443 mg, 76.4%): $[\alpha]_D$ + 21.0°, $[\alpha]_{577}$ + 23.1°, $[\alpha]_{546}$ + 26.0°, $[\alpha]_{435}$ + 43.5°, and $[\alpha]_{405}$ + 51.6° (c = 1.0 in H_2O at 23°C); ^{1}H-NMR ($CDCl_3$) δ = 4.22–4.30 (m, H3, 1H), 4.18 (s, H2, 1H), 4.06 (s, H4, 1H), 3.92–3.99 (m, H5, 1H), 3.82–3.90 (m, H1, 1H), 3.65–3.81 (m, H1 and H6, 3H); ^{13}C-NMR (D_2O) δ = 86.08 (C5), 82.40 (C2), 81.12 (C4), 79.81 (C3), 74.11 (C6), and 72.38 ppm (C1).

Preparation of (1→6)-2,5-Anhydro-3,4-di-*O*-((3,5-dimethylphenyl)carbamoyl)-D-glucitol (4a)

Diphenylcarbamate derivatives was synthesized by the reaction of 3,5-dimethylphenyl isocyanate (3.0 g) with polymer **3** (500 mg) dissolved in dry pyridine (50 mL) at about 100°C for 10 h and

Table III. Synthesis of (1→6)-2,5-Dianhydro-D-glucitol (**3**) by Deallylation of (1→6)-3,4-Di-*O*-Allyl-2,5-dianhydro-D-glucitol (**2**) with Pd–C

	3	
2[a]	Yield (%)	$[\alpha]_{546}^{23}$ [b]
1	47.8	+17.1
2	60.3	+18.9
3	28.7	+17.7
4	30.1	+17.3
6	59.2	+33.3
7	55.9	+31.8
8	76.4	+25.1
9	40.2	+29.8
11	63.5	+28.5

[a] 1–11 correspond to the obtained polymers for run nos. in Tables I and II.
[b] Measured in H_2O (c = 1.0).

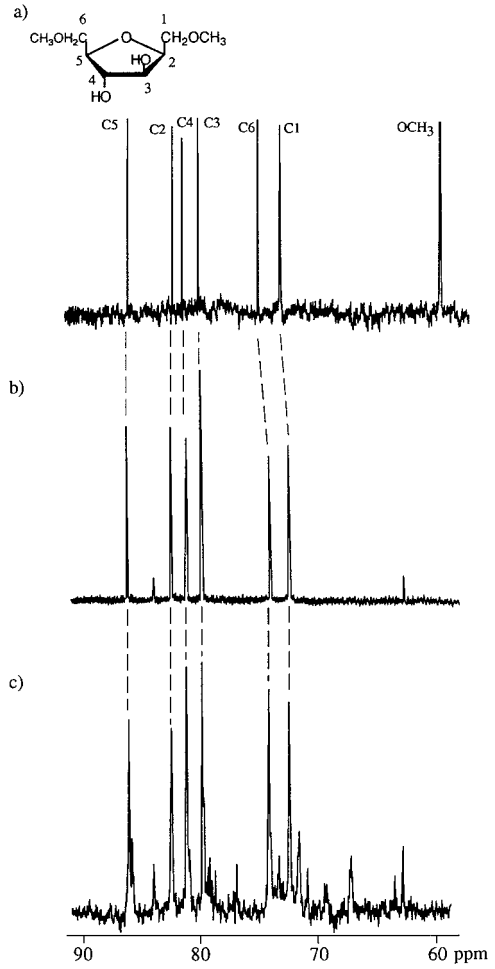


Figure 3. ^{13}C-NMR spectra of 2,5-anhydro-1,6-di-*O*-methyl-D-glucitol (**7**) (a) and polymer **3** derived from polymer **2** using *t*-BuOK (b) and $BF_3 \cdot OEt_2$ (c), respectively.

isolated as the fraction insoluble in methanol; yields were 77%. Anal. Calcd for $(C_{24}H_{28}O_6N_2)_n$: C, 65.44%; H, 6.41%; N, 6.36%. Found: C, 65.67%; H, 6.09%; N, 6.59%.

Preparation of (1→6)-2,5-Anhydro-3,4-di-*O*-(4-methylbenzoyl)-D-glucitol (4b)

Dibenzoate derivatives were synthesized by the reaction of *p*-toluoyl chloride (3.0 g) with polymer **3** (500 mg) dissolved in dry pyridine (50 mL) at about 100°C for 10 h and isolated as the fraction insoluble in methanol; yields were 70%. Anal. Calcd for $(C_{22}H_{22}O_6)_n$: C, 69.10%; H, 5.80%. Found: C, 68.63%; H, 5.83%.

Preparation of Chiral Stationary Phases

Macroporous silica gel (Merck, LiChrospher SI 1000) was treated with a large excess of (3-aminopropyl)triethoxysilane in toluene. Carbamate and benzoate derivatives (700 mg) were dissolved in tetrahydrofuran (20 mL), and the solution (10 mL) was added to the silanized macroporous silica gel (3.0 g). Then the wet silica gel was evaporated under reduced pressure. The remaining polymer solution was absorbed on the silica gel using the same procedure. The materials thus obtained were packed in a stainless-steel tube (25 × 0.6 cm i.d.) at 200 kg/cm^2 by the slurry method.

Instruments

^{1}H- and ^{13}C-NMR spectra were recorded using a JEOL A400II. Optical rotation was determined using a Jasco DIP-140 digital polarimeter. The molecular weights of the polymers were measured by gel permeation chromatography (GPC) in tetrahydrofuran on a Jasco HPLC equipped with three polystyrene gel columns (Shodex KF-804L). The number-average molecular weight (M_n) and the molecular weight distribution (M_w/M_n) were based on polystyrene calibration. FI-MS was obtained with a JEOL JMS-SX102A mass spectrometer. Chromatographic resolution was accomplished on a Jasco HPLC system equipped with a Jasco 830-RI and a Shodex OR-1 polarimetric detectors at room temperature.

RESULTS AND DISCUSSION

Cyclopolymerization of 3,4-Di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (1)

Table I lists the results of the polymerization of 3,4-di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**)

Table IV. Elemental Analyses of Diphenylcarbamate and Benzoate Derivatives

	Calculated (%)			Found (%)		
Polymer	C	H	N	C	H	N
4a	65.44	6.40	6.35	65.67	6.09	6.59
4b	69.08	5.80		68.63	5.83	

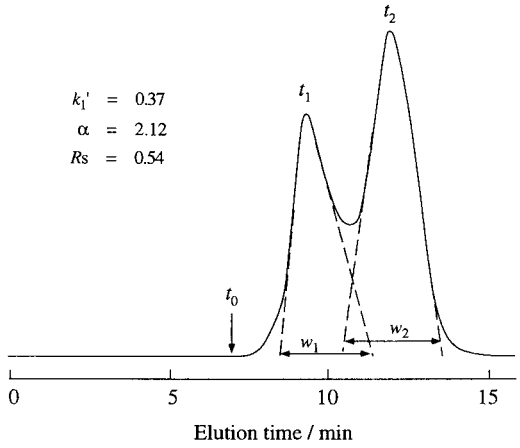


Figure 4. Chromatographic resolution of chloroquine (**9**) on polymer **4b**: Eluent, ethanol/water (20/80 v/v); flow rate, 0.5 mL/min.

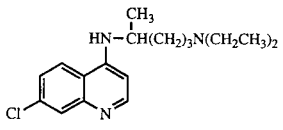
using $BF_3 \cdot OEt_2$. The cationic polymerization using $BF_3 \cdot OEt_2$ proceeded homogeneously, and the obtained polymers were sticky semisolids, soluble in methanol, chloroform, and tetrahydrofuran and insoluble in water and *n*-hexane. The number-average molecular weights (M_n) and yield were higher in dichloromethane than in nitroethane regardless of temperature. For the polymerization in dichloromethane at −10°C, the maximum yield and M_n were obtained as 58.9% and 4890, respectively. The specific rotations ($[\alpha]_{546}^{23}$) of the polymers were +34.0° to +38.8° (c = 1.0 in $CHCl_3$).

For the anionic polymerization using *t*-BuOK (Table II), the catalyst gradually dissolved into the polymerization solution after several hours and the solution slowly turned dark brown. The resulting polymers showed a solubility similar to those using $BF_3 \cdot OEt_2$. The M_ns of the polymers were 4340–9540, corresponding to the degree of polymerization (DP) of 19–32. The yields and M_ns for the polymers obtained in toluene were higher than those in tetrahydrofuran and 1,4-dioxane. For the polymerization with [**1**]/[*t*-BuOK] = 50 in toluene, the yield and M_n increased with increasing polymerization time. The molecular weight distributions (M_w/M_n) were relatively narrow with values in the range 1.35–1.66. The specific rotations ($[\alpha]_{546}^{23}$) of the polymers in the range +47.2° to +56.9° (c = 1.0 in $CHCl_3$) tended to increase with M_n.

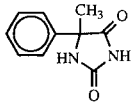
Figure 1 shows the ^{1}H-NMR spectra of the polymers obtained from **1** using $BF_3 \cdot OEt_2$ and *t*-BuOK. In the spectra, the signals of the latter polymer were sharper than those of the former polymer. Because the characteristic absorptions at 2.75–2.87 and 3.15–3.20 ppm due to the epoxy groups completely disappeared, the polymerizations proceeded according to a cyclopolymerization mechanism leading to the polymers consisting of cyclic constitutional repeating units; i.e., the extent of cyclization was 100%.

To confirm the cyclic units in the obtained polymer, 3,4-di-*O*-allyl-2,5-anhydro-1,6-di-*O*-methyl-D-glucitol (**6**) was prepared from **1.** Figure 2 shows the ^{13}C-NMR spectra of **6** and the polymers obtained using $BF_3 \cdot OEt_2$ and *t*-BuOK. The sharp signals were observed in the spectrum of the latter polymer, and this apparently differs from the observation of the former polymer. The signals at 79.90, 82.49, 82.53, and 83.80 ppm for the polymer were very close to those at 80.60, 83.23, 83.24, and 84.70 ppm which were assigned to the carbons of C5, C2, C3, and C4, respectively, for **6.** In addition, small signals in the spectrum of the polymer using *t*-BuOK should be due to the polymer end groups by comparison with the model compound, 3,4-di-*O*-allyl-2,5-anhydro-6-*O*-methyl-D-glucitol (**8**). Therefore, the polymer using *t*-BuOK was essentially (1→6)-3,4-di-*O*-allyl-2,5-anhydro-D-glucitol (**2**). The polymer using *t*-BuOK was more regio- and stereoselective than that using $BF_3 \cdot OEt_2$.

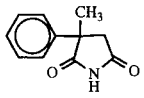
For the cyclopolymerization of **1,** there was a little difference in the cyclic structural units between the polymers using cationic and anionic catalysts, which can be explained by the general rules for ring closure on the basis of the stereoelectronic effect.[15,16] In general, the cyclization of 1,2 : 5,6-diepoxyhexane is supposed to form a five-membered cyclic product under anionic conditions, but five- and six-membered ones are formed under the cationic conditions.[17] Thus, the cationic cyclopolymerization of **1** produced a polymer with



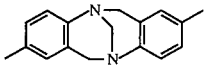
Chloroquine (**9**)



5-Methyl-5-phenylhydantoin (**10**)



α-Methyl-α
-phenylsuccinimide (**11**)



Tröger base (**12**)

Scheme 3.

Table V. Optical Resolution of Enantiomers Using Polymers **4a,b**

	Polymer **4a**				Polymer **4b**			
Racemate	Eluent[a]	k_1'[b]	α[c]	Rs[d]	Eluent[a]	k_1'[b]	α[c]	Rs[d]
9	MeOH/H_2O (20/80)	0.57 (−)	1.35		EtOH/H_2O (20/80)	0.37 (−)	2.12	0.54
	MeOH/H_2O (10/90)	0.77 (−)	1.77	0.45	EtOH/H_2O (10/90)	0.39 (−)	2.76	0.52
	MeOH/H_2O (6/94)	1.76 (−)	ca. 1		EtOH/H_2O (3/97)	0.45 (−)	2.20	0.45
10	2-propanol/*n*-hexane (7/93)	1.07 (−)	ca. 1		2-propanol/*n*-hexane (10/90)	0.34 (−)	ca. 1	
11	2-propanol/*n*-hexane (10/90)	1.83 (−)	ca. 1		2-propanol/*n*-hexane (10/90)	0.82 (−)	ca. 1	
12	2-propanol/*n*-hexane (2/98)	0.56 (+)	ca. 1		2-propanol/*n*-hexane (10/90)	0.11 (−)	ca. 1	
	n-hexane	2.67 (+)	1.17	0.57	*n*-hexane	0.30 (−)	ca. 1	

[a] Flow rate, 1.0 mL/min; temperature, ambient.
[b] Capacity factor; $k_1' = (t_1 - t_0)/t_0$.
[c] Separation factor; $\alpha = k_2'/k_1'$.
[d] Resolution factor; $Rs = 2(t_2 - t_1)/(w_1 - w_2)$.

irregularities in the structure, in contrast to the anionic one being regio- and stereoselective.

Synthesis of (1→6)-2,5-anhydro-D-glucitol (3)

The cleavage of the allyl ether linkage in polymer **2** was carried out with the Pd–C catalyst in ethanol/acetic acid/water under an argon atmosphere. After the deallylation, the polymer was purified by reprecipitation from methanol using tetrahydrofuran. The polymers were white solids, soluble in methanol and water but insoluble in chloroform, tetrahydrofuran, and *n*-hexane, which significantly differed from polymer **2** in solubility.

The results are listed in Table III. The yields for the polymers initiated by *t*-BuOK were higher than those using $BF_3 \cdot OEt_2$. The yield was lower due to reprecipitation by which the soluble parts were excluded.

In the ^{1}H-NMR spectrum of polymer **3** deallylated from **2** initiated by *t*-BuOK (Fig. 1c), the characteristic signals at 5.8–5.9 and 5.2–5.3 ppm due to the allylic protons of $=CH$ and $=CH_2$, respectively, completely disappeared. The cleavage of the allyl ether linkage occurred perfectly to form polymer **3** consisting of 2,5-anhydro-D-glucitol units. Each of the proton signals of the cyclic units were satisfactorily resolved and assigned by comparison with the chemical shift values of 2,5-anhydro-1,6-di-*O*-methyl-D-glucitol (**7**).

Figure 3 shows the ^{13}C-NMR spectra of polymer **3** and the model compound **7.** For polymer **3** derived from polymer **2** using *t*-BuOK, the signals at 86.11, 82.45, 81.12, and 79.80 ppm were very close to those at 85.59, 83.97, 81.20, and 79.68 ppm due to the carbons of C5, C2, C4, and C3, respectively, in model compound **7.** Conclusively, the polymer was (1→6)-bonded 2,5-anhydro-D-glucitol composed of a five-membered constitutional repeating unit, i.e., (1→6)-2,5-anhydro-D-glucitol. On the other hand, having many small signals in the spectrum, polymer **3** derived from the $BF_3 \cdot OEt_2$ system evidently contains a small amount of other cyclic repeating units except for the 2,5-anhydro-D-glucitol unit.

Chromatographic Enantioseparation

(3,5-Dimethylphenyl)carbamate and 4-methylbenzoate derivatives were synthesized by the reaction of polymer **3** with the corresponding phenyl isocyanate and benzoyl chloride; the polymers dissolved in dry pyridine at about 100°C and were isolated as the fraction insoluble in methanol. Elemental analysis showed complete substitutions of hydroxy groups (Table IV).

Figure 4 shows the chromatogram for the resolution of chloroquine (**9**) on a column of **4b.** Since the (−)- and (+)-isomers eluted at 9.5 (t_1) and 12.2 (t_2), respectively, the capacity factor k_1' ($=(t_1 - t_0)/t_0$, where $t_0 = 7.2$ min) was 0.37. The separation factor α ($=k_2'/k_1'$) and the resolution factor Rs ($=2(t_2 - t_1)/(w_1 + w_2)$) were 2.12 and 0.54, respectively (Scheme 3).

Table V shows the results of optical resolution of **9,** 5-methyl-5-phenylhydantoin (**10**), α-methyl-

α-phenylsuccinimide (**11**), and tröger base (**12**) on polymers **4a,b,** respectively.

The compounds **9** and **12** were resolved by the CSP **4a,** with separation factors (α) 1.17 and 1.77, when methanol/water (10 : 90 v/v) and *n*-hexane were used as eluents, respectively. For **10** and **11,** no separation was observed with a RI detector, although partial separation was found with a polarimetric detector. The CSP **4b** showed resolution ($\alpha = 2.12$) for **9** using ethanol/water (20 : 80 v/v) as eluent. However, for **10–12,** only partial separation was found with a polarimetric detector.

CONCLUSIONS

Cyclopolymerization of 3,4-di-*O*-allyl-1,2 : 5,6-dianhydro-D-mannitol (**1**) was achieved using $BF_3 \cdot OEt_2$ and *t*-BuOK. The polymerization using *t*-BuOK was more regio- and stereoselective than that using $BF_3 \cdot OEt_2$ and produced the highly stereoregulated polymer, i.e., (1→6)-3,4-di-*O*-allyl-2,5-anhydro-D-glucitol (**2**). The highly selective cyclopolymerization of 1,2 : 5,6-dianhydrohexitol using an anionic initiator is a new method for producing an artificial polymeric carbohydrate. Cleavage of the allyl ether linkage in polymer **2** occurred perfectly, and the resulting polymer was (1→6)-2,5-anhydro-D-glucitol (**3**). (3,5-Dimethylphenyl)carbamate and 4-methylbenzoate derivatives of **3** had optical resolution ability toward chloroquine.

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