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Preparation of 6-*O*-alkylcelluloses

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ABSTRACT

Cellulose derivatives specifically substituted at the primary hydroxyl groups, 6-*O*-alkylcelluloses, were prepared from 6-*O*-tritylcellulose (trityl = triphenylmethyl). In the preferred procedure, the 6-*O*-tritylcellulose was first completely allylated in dimethyl sulfoxide (Me_2SO), and subsequently detritylated with hydrogen chloride to yield 2,3-di-*O*-allylcellulose. This product was isomerized into 2,3-di-*O*-(1-propenyl)cellulose with potassium *tert*-butoxide in Me_2SO. The polymer thus prepared was then alkylated completely with methyl or ethyl iodide in Me_2SO containing a trace of water. The alkylated polymer was finally treated with 0.1 M HCl in aqueous 90% methanol at room temperature to remove the 1-propenyl groups. The products were shown by Fourier-transform infrared spectroscopy, ^{13}C nuclear magnetic resonance spectroscopy, and gas–liquid chromatographic analysis to be uniformly substituted at the 6 position.

INTRODUCTION

The distribution of substituents in cellulose derivatives is considered to be one of most influential factors determining their physical properties, such as, solubility, crystallization, gel formation, liquid crystal formation, and also resistance to enzymic degradation. In this connection, the synthesis of cellulose ethers with site-specific substitutions is important in clarifying the relationships between the chemical structure of the derivatives and their physical properties. However, methods for selective chemical modification have been available only for the 6 position (C-6) of the anhydroglucose units, where operations such as tritylation[1–3], introduction of aldehyde groups[4–6], halogenation[7], and others[8–12] have been carried out. Research activity on *O*-alkylcelluloses has been limited by the difficulty of controlling the distribution of substituents in the preparation of cellulose ethers.

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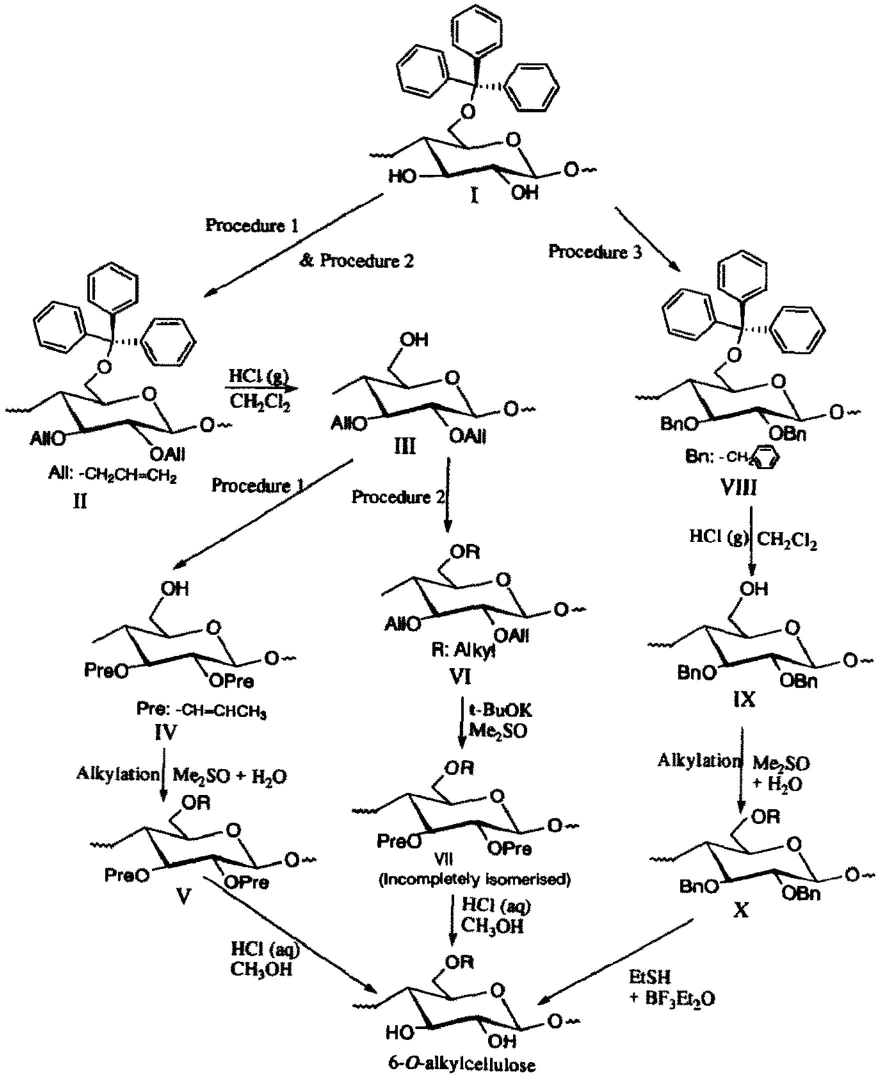
In a previous paper[13], the author reported the preparation of *O*-methyl- and *O*-ethyl-celluloses with controlled distributions of substituents. It was found that the distribution varied systematically in a series of the cellulose ethers prepared by repeated alkylation of 6-*O*-(triphenylmethyl)cellulose ("tritylcellulose"). In the present work, tritylcellulose was used as the starting material for the preparation of celluloses specifically alkylated only at the primary OH groups of the repeating anhydroglucose units (6-*O*-alkylcelluloses). For this purpose tritylcellulose was converted into 6-*O*-alkyl-2,3-di-*O*-(1-propenyl)cellulose via allylation of the OH groups at C-2 and C-3, followed by detritylation with HCl, then isomerization of the 2,3-di-*O*-allylcellulose into 2,3-di-*O*-(1-propenyl)cellulose, and finally alkylation of the polymer (Scheme 1). In this procedure, the allyl group was found to be more effective as a protective group than the benzyl group. The products were characterized by GLC of their hydrolyzates as alditol acetates, FTIR, and ^{13}C NMR. These measurements revealed that each of the final polymers has a uniform structure. Because of their uniformity, these 6-*O*-alkylcelluloses as well as 2,3-di-*O*-alkylcelluloses reported in the previous paper[13] are suggested as ideal samples for the study of correlations between physical properties and the distribution of ether substituents.

RESULTS AND DISCUSSION

To prepare 6-*O*-alkylcellulose three kinds of procedures (Procedures 1, 2, and 3) were investigated as shown in Scheme 1. Procedures 1 and 2 employed allyl groups, and Procedure 3 employed benzyl groups to protect HO-2 and HO-3 of the anhydroglucose units. Each procedure will be discussed in the following section.

6-O-Alkylcellulose with allyl protective groups.—Both Procedures 1 and 2 needed complete allylation of the HO-2 and HO-3 groups of the tritylcellulose to give 2,3-di-*O*-allylcellulose. The hydroxyl groups in the tritylcellulose were completely allylated with a method reported in our previous paper[14]. In the IR spectrum of the product (trace 1, Fig. 1) no OH absorption band was detected, while C=C absorption bands appeared at 1647 cm^{-1}. The 2,3-di-*O*-allyl-6-*O*-tritylcellulose was then subjected to treatment with HCl to remove trityl groups. The possibility of a side reaction at this step was explored as recorded in Table I, which shows a comparison of elemental analyses of allylated *O*-methylcellulose before and after HCl treatment under various conditions. This indicates that during detritylation there should be no change in the allyl groups with treatment below 0°C (compare untreated, −30°C, 1 h, and 0°C in Table I). After HCl gas was bubbled in at 0°C for 3 min, the IR spectrum of the product (trace 2, Fig. 2) confirmed the complete removal of the trityl groups[13,15] (loss of bands at 1598, 1491 and 1449 cm^{-1}, respectively) and the stability of the double bonds in the allyl groups (1647 cm^{-1}).

The allyl ether as a protective group in carbohydrate chemistry has been well-investigated[16–18], because it is conveniently removed by isomerization[19,20] to



Scheme 1. Procedures for the preparation of 6-*O*-alkylcelluloses.

the *cis*-1-propenyl group and subsequent acid hydrolysis. In this paper, this isomerization step was crucial and the following two procedures were employed: (*i*) Procedure 1; 6-*O*-alkylcellulose from 2,3-di-*O*-allylcellulose by isomerization prior to alkylation; (*ii*) Procedure 2; 6-*O*-alkylcellulose from 2,3-di-*O*-allylcellulose by the inverse reaction sequence.

Procedure 1: III → IV → V → 6-O-alkylcellulose.—2,3-Di-*O*-allylcellulose was dissolved completely in Me_2SO, following which the prototropic rearrangement of the allyl ether groups to their propenyl analogs was effected with potassium *tert*-butoxide (*t*-BuOK) as catalyst in a homogeneous solution. IR spectra (Fig. 2) were use to monitor the process of the isomerization. As shown in traces 2, 3, and

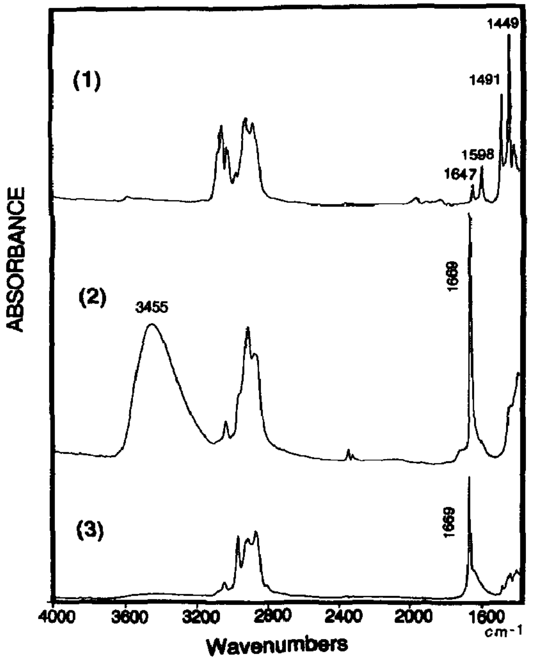


Fig. 1. IR spectra of (1) 2,3-di-*O*-allyl-6-*O*-tritylcellulose, (2) 2,3-di-*O*-(1-propenyl)cellulose, and (3) 6-*O*-ethyl-2,3-di-*O*-(1-propenyl)cellulose.

4 of Fig. 2, the absorption band at 1647 cm^{-1} due to allyl double bonds ($OCH_2CH{=}CH_2$) decreased as a function of the reaction time, being replaced by a new band at 1669 cm^{-1} due to 1-propenyl double bonds ($OCH{=}CHCH_3$). The change in the NMR spectra of the samples during the reaction corroborated these findings. The signals for the two carbons involved in the allyl double bond, which are located around δ 136 ($\mathit{C}H{=}CH_2$) and δ 116 ($CH{=}\mathit{C}H_2$)[14], decreased with the increase of 1-propenyl carbon signals around δ 99.5 ($O\mathit{C}H{=}CH$) and δ 147.5 ($OCH{=}\mathit{C}H$), respectively. The signal of C-1 in the anhydroglucose ring did not

TABLE I

Elemental analyses of allylated *O*-methylcellulose [a] treated with HCl gas under various conditions

Treatment	C (%)	H (%)	Cl (%)
Untreated	57.8	7.6	0
−30°C, 1 h	56.6	7.4	0.6
−30°C, 2 h	55.1	7.4	1.0
−30°C, 3 h	54.9	7.3	1.1
0°C, 3 min	57.6	7.7	0
0°C, 1 h	57.3	7.7	1.0
0°C, 3 h	55.8	7.4	1.0

[a] Ds by methyl 1.6, by allyl 1.4.

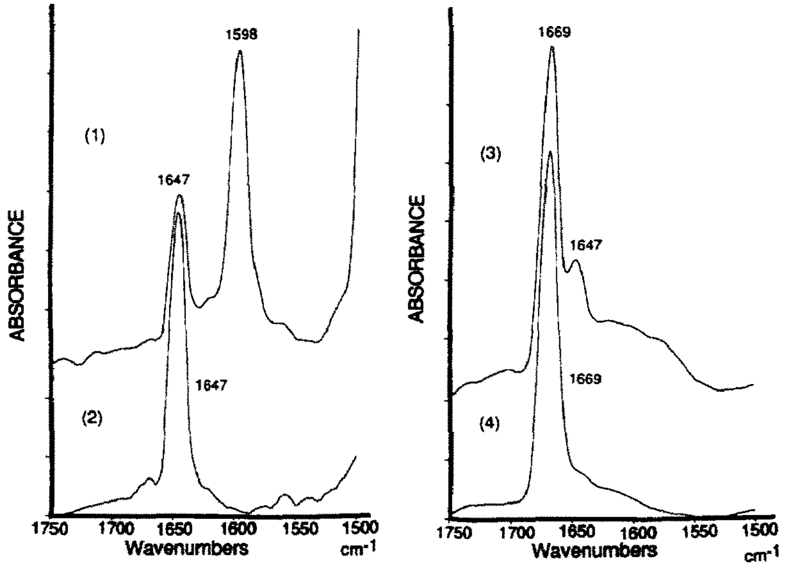


Fig. 2. Change in the IR spectrum during the isomerization of 2,3-di-*O*-allylcellulose (C=C region). (1) 2,3-di-*O*-allyl-6-*O*-tritylcellulose, (2) 2,3-di-*O*-allylcellulose, (3) 2,3-di-*O*-allylcellulose after 2 h treatment, and (4) 2,3-di-*O*-(1-propenyl)cellulose.

shift after isomerization, suggesting that there was no cleavage of the 1-propenyl ether functions at the neighbouring C-2 position.

Hydroxyl groups at position C-6 in 2,3-di-*O*-(1-propenyl)cellulose were completely alkylated with powdered NaOH and alkyl iodide in Me_2SO containing a trace amount of distilled water[13,21]. As shown in trace 3 of Fig. 1, the OH bands around 3455 cm^{-1} disappeared completely, whereas the double bonds of the 1-propenyl groups remained intact (1669 cm^{-1}).

As shown in the IR spectra of 6-*O*-methyl- and 6-*O*-ethyl-cellulose in Fig. 3, the band at 1669 cm^{-1} almost disappeared after hydrolysis with aq HCl (although a trace still remained), and a band due to hydroxyl groups appeared around 3465 cm^{-1}. This indicates that the 1-propenyl groups were removed to yield 6-*O*-alkylcelluloses. The hydroxyl bands of both 6-*O*-methyl- and 6-*O*-ethyl-cellulose were located around 3465 cm^{-1}, and 6-*O*-propylcellulose also had an OH absorption band close to the same position. That is, the frequencies of the stretching vibration bands of the OH groups at the C-2 and C-3 positions of cellulose appear to be relatively independent of the length of the alkyl side chain attached to O-6.

Procedure 2: III → VI → VII → 6-O-alkylcellulose.—2,3-Di-*O*-allylcelluose was completely alkylated by the same method used in the previous section. However, the isomerization of the allyl groups in the resulting 6-*O*-alkyl-2,3-di-*O*-allylcelluloses did not occur completely even when either the reaction temperature or the reaction time was increased. The IR spectra of the products showed patterns similar to those of trace 3 in Fig. 2. The partial failure of the rearrangement may be due to the insolubility of 6-*O*-alkyl-2,3-di-*O*-allylcelluloses in Me_2SO. In other

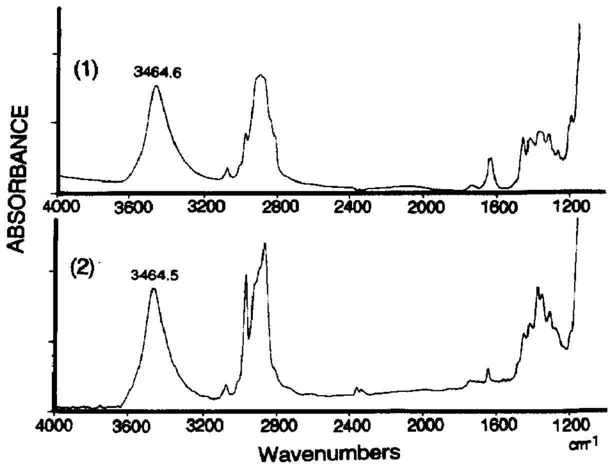


Fig. 3. IR spectra of (1) 6-*O*-methylcellulose and (2) 6-*O*-ethylcellulose.

words, a homogeneous reaction in each step of the procedure for these preparations is preferred.

*Procedure 3: Preparation of 6-*O*-alkylcellulose via 2,3-di-*O*-benzyl-6-*O*-tritylcellulose.*—6-*O*-Alkyl-2,3-di-*O*-benzylcellulose was obtained in high yield. However, in the final step, which was the removal of the benzyl groups with ethanethiol and boron trifluoride etherate[22–24], the yield was much less than 10%. Some depolymerization may have occurred. An alternative method of debenzylation would involve the use of hydrogenation catalysts such as palladium–carbon[25,26], but these might be unsuitable because of difficulty in the removal of the catalyst from the mixture after reaction. As a result, it was proved that allyl is superior to benzyl as a protective group in the preparation of 6-*O*-alkylcelluloses.

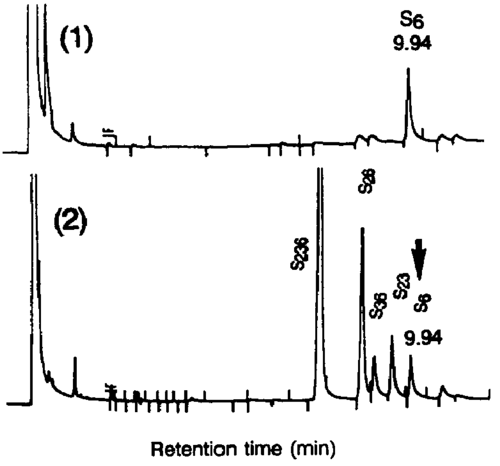
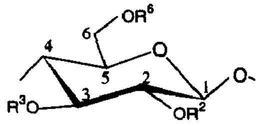


Fig. 4. GLC patterns of alditol acetates from (1) 6-*O*-ethylcellulose and (2) commercial *O*-ethylcellulose (ds 2.3). For the meaning of S_0–S_{236} see Fig. 5.



	R^2	R^3	R^6
S_0	H	H	H
S_2	Alkyl	H	H
S_3	H	Alkyl	H
S_6	H	H	Alkyl
S_{23}	Alkyl	Alkyl	H
S_{26}	Alkyl	H	Alkyl
S_{36}	H	Alkyl	Alkyl
S_{236}	Alkyl	Alkyl	Alkyl

Fig. 5. Structures of the eight possible types of glucose residues in *O*-alkylcelluloses.

Uniformity of the unit structure in 6-O-alkylcellulose.—To confirm the uniformity of the unit structure of the 6-*O*-alkylcelluloses, 6-*O*-ethylcellulose was selected for hydrolysis, and the distribution of its ethyl substituents was determined by the analysis of alditol acetates of the hydrolyzate. Fig. 4 shows the comparison of GLC pattern of 6-*O*-ethylcellulose and commercially available *O*-ethylcellulose (ds 2.3). Each peak for commercial *O*-ethylcellulose was assigned to one of the eight possible unit structures S_0–S_{236} shown in Fig. 5. 6-*O*-Ethylcellulose gave only one peak, assigned to S_6, in which only the OH groups at the C-6 position are substituted. This clearly demonstrated that this 6-*O*-alkylcellulose has a uniform structure.

In summary, 6-*O*-alkylcelluloses composed uniformly of 6-*O*-alkylglucose residues have been prepared from allylated 6-*O*-tritylcellulose, by rearrangement of the allyl protective groups at the C-2 and C-3 positions of the anhydroglucose units, replacement of the trityl groups by alkyl at the C-6 positions, and subsequent acid hydrolysis.

EXPERIMENTAL

Materials.—Commercial cellulose acetate samples were provided by Eastman (acetyl content 39.9%, ASTM viscosity 27). The samples were completely deacetylated on standing in aq 15% NH_4OH for 14 days at room temperature. Dimethyl sulfoxide (Me_2SO) and pyridine were dried over 3A molecular sieves. Reagent-grade solvents and reagents (Aldrich Gold Label) were used without further purification. Powdered NaOH was made by grinding NaOH pellets in a domestic coffee grinder. Water was used after distillation.

General.—The distribution of alkyl groups in the alkylcelluloses was determined by acid hydrolysis of samples, conversion of the hydrolyzates into partially alkylated alditol acetates, and analysis by GLC[13,14]. The instrument used was a Hewlett-Packard Model 3392A equipped with an integrator, a flame-ionization detector, and a J.&W. Scientific DB-1 fused-silica capillary column (0.25 mm × 30 m; film thickness 0.25 μm). The temperature was increased from 190 to 210°C at 1°C/min.

IR spectra were obtained with a Nicolet type 7199 FT-IR spectrophotometer. ^{13}C NMR spectra were obtained with a Varian XL 200 spectrometer at a frequency of 50.4 MHz. Deuterated chloroform and pyridine-d_5 were used as solvents. Chemical shifts were referenced to tetramethylsilane.

Preparation of 6-O-(triphenylmethyl)cellulose ("tritylcellulose").—The tritylcellulose was prepared according to the method in a previous paper[12]. The yield of the product was 95% of the theoretical, and the degree of substitution (ds) by trityl groups was 1.07 by ^1H NMR measurements.

2,3-Di-O-allyl-6-O-tritylcellulose (II).—The preparative method followed that given in our previous paper[14], tritylcellulose (3 g) was dissolved completely in 150 mL of Me_2SO by constant stirring for 2 h at 60°C. The solution was cooled to room temperature, and 5.94 g of powdered NaOH was dispersed in it. Following 1 h stirring under an N_2 atmosphere, allyl chloride (12.1 mL) was added to the solution all at once. The amounts of powdered NaOH and allyl chloride added corresponded to 10 moles per mole of hydroxyl groups in the tritylcellulose. The mixture was stirred under N_2 at 70°C for 4 h. It was then cooled down to room temperature and precipitated by pouring into aq 95% MeOH. The precipitate was dissolved in CH_2Cl_2, the solution was extracted with water (3 ×), and evaporated under diminished pressure at 60°C to a syrup. The product was precipitated from the syrup by the addition of MeOH, filtered, and dried under vacuum at 65°C. The yield was 95% of the theoretical.

2,3-Di-O-allylcellulose (III).—The detritylation procedure followed that given in our previous paper[13]. 2,3-Di-*O*-allyl-6-*O*-tritylcelluolse (4.5 g) (II) was treated with HCl gas in 150 mL of CH_2Cl_2 for 3 min at 0°C. The mixture was then poured into acetone (500 mL). The product was isolated by centrifugation, washed with acetone, and dried under vacuum at 65°C. The yield of the detritylated product was ~85%. To test the stability of the double bonds of allyl groups during the treatment, a completely allylated *O*-methylcellulose[14] (ds by methyl 1.6 and by allyl 1.4) was subjected to HCl gas at both −30 and 0°C and the treated products were characterized by elemental analyses.

2,3-Di-O-(1-propenyl)cellulose (IV).—2,3-Di-*O*-allylcellulose (3 g) was completely dissolved in Me_2SO (150 mL) by stirring for 2 h at 50°C. With the temperature kept at 50°C, potassium *tert*-butoxide (7.73 g) was added and the solution was stirred for 4 h under an N_2 atmosphere. The mixture was then poured into acetone. The precipitated product, isolated by centrifugation, was washed with acetone and dried under vacuum at 65°C (yield, 80%).

Alkylation of 2,3-di-O-(1-propenyl)cellulose (IV).—Our method[13,21] for the preparation of completely alkylated cellulose derivatives was applied to 2,3-di-*O*-(1-propenyl)cellulose. The addition of a trace amount of water to the Me_2SO solution was needed. Powdered NaOH (3.1 g) was dispersed in a solution of 2,3-di-*O*-(1-propenyl)cellulose (1.5 g) in Me_2SO (90 mL) containing water (1.5 mL), and after 1 h of stirring under an N_2 atmosphere, two thirds of the total amount of alkyl iodide (e.g., 3.5 mL of ethyl iodide) was added dropwise to the solution. The remaining alkyl iodide was added dropwise in equal portions 2, 3, and 4 h after the first addition of reagent. Following the last addition of alkyl iodide, the solution was kept under an N_2 atmosphere for 20 h at 70°C. The mixture was then cooled to room temperature. The isolation and purification of the product was accomplished as described above. The yields of products were ~ 90%.

Removal of 1-propenyl groups from 6-O-alkyl-2,3-di-O-(1-propenyl)cellulose (V). — 6-*O*-Alkyl-2,3-di-*O*-(1-propenyl)cellulose (1 g) was hydrolyzed with 0.1 M HCl in aq MeOH at room temperature[20] for 3 h. The product was isolated by pouring the mixture into a large amount of cooled water, filtered, and washing the solid several times with distilled water. The final product was dried under vacuum at 65°C and characterized by FTIR, ^{13}C NMR, and GLC of the alditol acetates of the hydrolysis products. The yields of products were 75–80%.

Alkylation of 2,3-di-O-allylcellulose (III).—The procedure employed was the same as that described above for the alkylation of 2,3-di-*O*-(1-propenyl)cellulose.

Isomerization of 6-O-alkyl-2,3-di-O-allylcelluloses (VI).—Alkyldiallylcellulose (1 g) was dispersed in Me_2SO (60 mL) and then *t*-BuOK (3 g) was added at room temperature with constant stirring. The reaction time was varied in an effort to achieve completion of the isomerization of the allyl groups, as monitored by FTIR. After base treatment, the mixture was poured into 1:1 $CHCl_3$–water and the $CHCl_3$ layer was separated. It was washed with distilled water three times, then evaporated under diminished pressure at 60°C to a syrup. The product (VII) was precipitated from the syrup by the addition of MeOH, and purified as described for product V.

Removal of 1-propenyl groups from incompletely isomerized 6-O-alkyl-2,3-di-O-(1-propenyl)celluloses (VII).—Treatment and characterization were as described above.

Preparation of 6-O-alkylcelluloses via 2,3-di-O-benzyl-6-O-tritylcellulose.—The benzylation of tritylcellulose followed the procedure reported by Kageyama et al.[27]. Trityl groups were removed as described above to give 2,3-di-*O*-benzylcellulose. After the polymer was alkylated as detailed above, the product was isolated and a portion (3 g) was debenzylated by treatment with a mixture of ethanethiol and boron trifluoride etherate[22–24]. The solution was evaporated, poured into aq $NaHCO_3$, and dialyzed for a week against distilled water. The product was freeze-dried, the yield was < 10%.

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