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Regioselective Synthesis of Cellulose Ester Homopolymers

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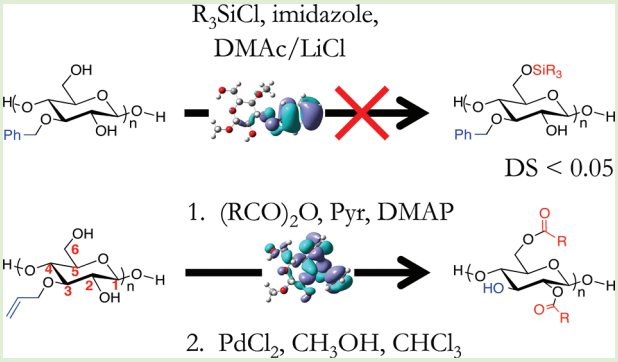
Supporting Information

ABSTRACT: Regioselective synthesis of cellulose esters is extremely difficult due to the small reactivity differences between cellulose hydroxyl groups, small differences in steric demand between acyl moieties of interest, and the difficulty of attaching and detaching many protecting groups in the presence of cellulose ester moieties without removing the ester groups. Yet the synthesis of homopolymers of particular regioselectively substituted anhydroglucose esters is of critical importance to allow us to determine the analytical characteristics of such homopolymers, their structure–property relationships, and to obtain guidance that may ultimately enable identification and synthesis of cellulose derivatives with superior properties for various applications. We report here a new, general synthesis of both cellulose-2,6-*O*-diesters and cellulose-2,6-A-*O*-3-B-*O*-triesters with a high degree of regioselectivity, employing 3-*O*-allylcellulose as a key protected precursor. 3-*O*-Allylcellulose was identified as a protected intermediate with high potential for the synthesis of these derivatives with the aid of molecular modeling of corresponding glucose analogs. We report also the first analytical and structure property studies of these regioselectively substituted cellulose esters.



INTRODUCTION

Despite the rich literature and widespread utility of the esters of renewable cellulose with carboxylic acids,[1] their regioselective synthesis is still a great challenge. Because of the extensive hydrogen and hydrophobic bonding, crystallinity, and resulting poor solubility of cellulose, it has been necessary to use forcing conditions (strong catalysts like H_2SO_4 or $HClO_4$, high temperatures, and long reaction times) to achieve high levels of substitution. Only with the discovery in recent decades of powerful solvent systems that can dissolve cellulose, especially LiCl/*N*,*N*-dimethylacetamide (DMAc),[2,3] tetrabutylammonium fluoride (TBAF)/dimethylsulfoxide (DMSO),[4,5] and several ionic liquid solvents,[6] has it been possible to use mild reaction conditions and more selective reagents, enabling the development of a few successful strategies for regioselective etherification and esterification of cellulose.[7] In particular, selective substitution at the primary OH in position 6 has become possible, using sterically bulky etherification reagents like triphenylmethyl (trityl) chloride,[8] and thexyldimethylsilyl chloride (TDMSCl).[9] Once the 6-OH has been protected as the ether, the secondary hydroxyl groups can be acylated and then the 6-*O*-protective ether group (trityl or methoxytrityl) can be deprotected using mild aqueous acid, to afford cellulose-2,3-*O*-diesters.[10] In a complementary strategy, reaction of the 6-*O*-ether with a second, orthogonal protecting group (e.g., allyl) at the secondary alcohols, followed by deprotection at *O*-6, substitution at *O*-6, and then deprotection at *O*-2 and *O*-3, has been used to prepare regioselectively substituted cellulose-6-*O*-ethers.[11] It is illustrative of the difficulties involved in regiospecific cellulose ester synthesis (in this case, presumably the issue of selective protecting group removal in the presence of the ester) that there appear to be no reports of using this strategy to prepare cellulose-6-*O*-esters.

From these few examples, we know that position of substitution has a powerful influence on key properties of cellulose esters including solubility,[12,13] crystallinity,[14] optical retardation,[15] and thermal properties.[16] Very recently, Xu and Edgar reported that direct synthesis of cellulose esters with a high proportion of ester substituents at O-6 is possible by reaction of high DS cellulose esters (e.g., cellulose triacetate, cellulose tripropionate, or cellulose acetate of DS 2.5) with tetrabutylammonium fluoride in DMSO or THF.[5] Fluoride-catalyzed deacylation occurs with remarkable facility and even more remarkable selectivity, with a high degree of deacylation at the more hindered secondary alcohol esters (2-*O*-acyl and 3-*O*-acyl) and little or no deacylation at the 6-*O*-acyl group under the proper reaction conditions. It would be extremely valuable to develop synthetic routes to the homopolymers correspond-

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ing, for example, to the 6 possible monosaccharides that comprise a cellulose ester with only one substituent type (2-, 3-, and 6-monoesters; 2,3-, 2,6-, and 3,6-diesters; the two other possible monosaccharides (unsubstituted and fully substituted) are synthetically trivial). For example, one such key target homopolymer would be poly(→4-β-D-2,6-di-*O*-acetyl-glucopyranose-1→). By synthesizing these homopolymers, we can generate critical understanding of structure property relationships in cellulose (and indeed in polysaccharide) esters that is currently simply not accessible. Of equal importance, we can create homopolymer standards that will provide the analytical data set necessary to help interpret spectra of random and other cellulose ester copolymers generated by nonregioselective synthetic methods. We report here the first regioselective synthesis of cellulose-2,6-*O*-diesters and of regioselectively substituted cellulose triesters with one ester type at O-2 and O-6, and a second type at O-3.

MATERIALS AND METHODS

Materials. Cellulose (Avicel PH-101, DP 280) was vacuum-dried before use. Thexyldimethylsilyl chloride, imidazole, and TBAF·3H_2O were purchased from Acros Organics; NaH, allyl chloride, acetic anhydride, propionic anhydride, and pyridine were purchased from Fisher; all reagents were used without further purification. Commercial cellulose esters were from Eastman Chemical Company.

Measurements. FTIR spectra were recorded with a Thermo Electron Nicolet 8700 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were acquired on a Varian INOVA 400 (400 MHz) spectrometer at room temperature or 50 °C. DS values were calculated from the integration ratios of acetyl or propionyl proton resonances to those of the backbone hydrogens. HMBC and COSY spectra were acquired on a 600 NMR Bruker Avance II spectrometer (600 MHz) at 50 °C. Differential scanning calorimetry (DSC) was conducted using a TA Instruments DSC Q2000. DSC data were obtained from 35 to 200 °C at heating/cooling rates of 20 °C/min under nitrogen. Glass transition temperatures were determined as the midpoint of heat capacity change in the glass transition region during the second heating cycle. Molecular weights of the synthesized polymers were determined using size exclusion chromatography (SEC) with refractive index (RI) and viscometer DP detectors vs polystyrene standards. SEC measurements were performed at 30 °C in $CHCl_3$ (compounds **9**, **11**, CTP, CA-398-30, and CAP-504-0.2) or NMP/LiBr (CA-435-75S and CA-320S), with a sample concentration 5.00 mg/mL at a flow rate of 1.00 mL/min on a Waters Alliance model 2690 chromatograph. The degree of substitution (DS) values were determined by means of ^{1}H NMR spectroscopy, according to the following equations, respectively.

Peracetylated 3-*O*-benzyl cellulose:

$$DS_{benzyl} = 7I_{phenyl}/5I_{backbone}$$

$$DS_{acetate} = 7I_{acetate-CH_3}/3I_{backbone}$$

Peracylated 3-*O*-allyl cellulose:

$$DS_{acetate} = 22I_{acetate-CH_3}/(I_{backbone} + 5I_{acetate-CH_3})$$

$$DS_{propionate} = 22I_{propionate-CH_3}/(I_{backbone} + 5I_{propionate-CH_3})$$

$$DS_{allyl} = 3 - DS_{acetate} \quad \text{or} \quad 3 - DS_{propionate}$$

3-*O*-Benzyl-2,6-di-*O*-thexyldimethylsilyl Cellulose. 2,6-Di-*O*-thexyldimethylsilyl cellulose (10 g, 22.38 mmol) was suspended in 100 mL of dry THF. To the solution, NaH (5.37 g, 228.8 mmol, 10 mol/mol modified AGU) was added. Then benzyl bromide (26.6 mL, 228.8 mmol, 10 mol/mol modified AGU) was added dropwise with vigorous stirring. The mixture was stirred at room temperature for 1 day and at 50 °C for another 3 days. The reaction was quenched by addition of isopropanol and poured into 500 mL phosphate buffer solution (pH = 7.0). The precipitate was collected, washed with 500 mL of ethanol, and dried under vacuum at 40 °C.

Characterization Data for Product. Yield: 80% (based on 2,6-di-*O*-thexyldimethylsilyl cellulose). Degree of substitution (DS): DS_{benzyl} = 0.98 (determined by ^{1}H NMR spectroscopy). FT-IR (cm^{-1}): 2866, 2954 ν(C−H), 1361, 1463 ν(C−$C_{aromatic}$), 1251 ν(C−Si), 828, 776 ν(C−$H_{aromatic}$). ^{1}H NMR (in $CDCl_3$): δ (ppm) =0.11−1.61 (thexyldimethylsilyl group), 4.97 (CH_2−C_6H_5), 7.27, 7.41 (H-aromatic), 3.28−4.73 (AGU).

3-*O*-Benzyl Cellulose. 3-*O*-Benzyl-2,6-di-*O*-thexyldimethylsilyl cellulose (20 g, 44.8 mmol) was dissolved in 100 mL of DMSO and treated with TBAF (56.6 g, 179.4 mmol, 4 mol/mol modified AGU). The mixture was stirred at 50 °C for 3 days. The mixture was poured into 1000 mL of water, then the product was collected by filtration, washed thoroughly with water, and dried under vacuum at 40 °C. The crude product (5.0 g) was suspended in 100 mL DMAc and 10 g LiCl. TBAF (10 g) was then added. The temperature was raised to 50 °C and the solution was kept at this temperature for another 3 days under stirring. The mixture was added dropwise into 500 mL of ethanol. The product was isolated by filtration, then the precipitate was washed with ethanol and dried under vacuum at 40 °C.

Characterization Data for 3-O-Benzyl Cellulose. Yield: 40% (based on 3-*O*-benzyl-2,6-di-*O*-thexyldimethylsilyl-cellulose). Degree of substitution (DS): DS_{benzyl} = 0.98 (determined by ^{1}H NMR spectroscopy). FT-IR (cm^{-1}): 3458 ν(OH), 2863, 2958 ν(C−H), 1371, 1450 ν(C−$C_{aromatic}$), 820, 741 ν(C−$H_{aromatic}$). ^{1}H NMR (in DMSO-d_6): δ (ppm) = 5.51 (CH_2−C_6H_5), 7.21−7.43 ($H_{aromatic}$), 3.17−4.86 (AGU).

Attempted Debenzylation of Peracetylated 3-O-Benzyl Cellulose. 3-*O*-Benzyl cellulose (0.2 g, 0.79 mmol) was dissolved in 5 mL of pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL of acetic anhydride. After stirring for 24 h at 80 °C, the product was precipitated from 100 mL of water, then washed several times with water. The crude product was collected by filtration, then was redissolved in 5 mL of $CHCl_3$. This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C to yield peracetylated 3-*O*-benzyl cellulose. To a solution of 50 mg peracetylated, 3-*O*-benzyl cellulose in 5 mL of THF/acetic acid (1:1, v/v) and 200 mg palladium hydroxide over carbon was added. The reaction mixture was kept under a hydrogen pressure of 450 kPa at 50 °C. After 1 day, the solution was filtered through Celite and concentrated to dryness. The solid product was washed with excess water and dried under vacuum at 40 °C.

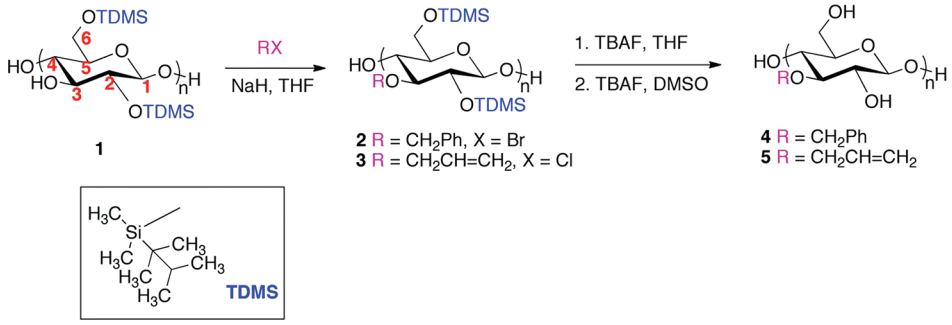
Characterization Data for Product. Yield: 80% (based on 3-*O*-benzyl-2,6-di-*O*-acetyl-cellulose). FT-IR (cm^{-1}): 3460 ν(OH), 2868, 2954 ν(C−H), 1375, 1453 ν(C−$C_{aromatic}$), 824, 776 ν($CH_{aromatic}$). Degree of substitution (DS): $DS_{acetate}$ = 1.98, DS_{benzyl} 0.46 (determined by ^{1}H NMR spectroscopy). ^{1}H NMR (in $CDCl_3$): δ (ppm) = 7.22−7.42 ($H_{aromatic}$), 5.36, 5.53 (CH_2−C_6H_5), 3.01−4.87 (AGU), 1.87, 1.77 (CH_3-acetate).

3-*O*-Allyl-2,6-di-*O*-acyl-cellulose. 3-*O*-Allyl cellulose (**5**, 200 mg, 0.99 mmol) was dissolved in 5 mL of pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL of acetic or propionic anhydride. After stirring for 24 h at 80 °C, the product was precipitated into 100 mL of water, collected by filtration, and washed several times with water. The crude product was redissolved in 5 mL of $CHCl_3$. This solution was added slowly with rapid stirring to 100 mL of ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C to yield product **6** (2,6-di-*O*-acetate) or **7** (2,6-di-*O*-propionate).

Characterization Data for 3-O-Allyl-2,6-di-O-acetyl0cellulose. FT-IR (cm^{-1}): 3088 ν(=C−H), 2884 ν(C−H), 1635 ν(C═C), 1220 ν(C−O−C_{ester}), 1739 ν(CO_{ester}). DS: $DS_{acetate}$ = 1.97, DS_{allyl} = 1.03 (determined by ^{1}H NMR spectroscopy). ^{1}H NMR (in $CDCl_3$): δ (ppm) 2.03 (CH_3-acetate), 5.04−5.73 (H_{allyl}), 3.38−4.78 (AGU).

Characterization Data for 3-O-Allyl-2,6-di-O-propionyl-cellulose. FT-IR (cm^{-1}): 3089 ν(=C−H), 2888 ν(C−H), 1636 ν(C═C), 1271 ν(C−O−C_{ester}), 1736 ν(CO_{ester}). DS: $DS_{propionate}$ = 1.96, DS_{allyl} = 1.04 (determined by ^{1}H NMR spectroscopy). ^{1}H NMR (in $CDCl_3$): δ

Scheme 1. Synthesis of 3-Protected Cellulose Ethers



(ppm) 2.31 (CH_2-propionate), 1.11 (CH_3-propionate), 5.01−5.68 (H_{allyl}), 3.34−4.79 (AGU).

2,6-Di-*O*-acyl-cellulose. 3-*O*-Allyl-2,6-di-*O*-acyl-cellulose (**6** or **7**, 120 mg) was dissolved in 8 mL of chloroform and 5 mL of methanol, and to this solution was added 10 mg $PdCl_2$. After stirring at room temperature for 24 h, the mixture was filtered through Celite and evaporated to afford the 2,6-di-*O*-acyl cellulose product **8** (2,6-di-*O*-acetyl-cellulose) or **10** (2,6-di-*O*-propionyl-cellulose).

Characterization Data for 2,6-Di-O-acetyl-cellulose. DS: $DS_{acetate}$ = 1.97 (determined by ^1H NMR spectroscopy). FT-IR (cm^{-1}): 3405 ν(OH), 2885 ν(C−H), 1271 ν(C−O−C_{ester}), 1730 ν(CO_{ester}). ^1H NMR (in pyridine-d_5 with 1 drop trifluoroacetic acid (TFA) added to shift water peak out of region of interest): δ (ppm) 5.66 (H-3), 5.43 (H-2), 5.31 (H-1), 5.05 (H-6), 4.81 (H-6′), 4.51 (H-4), 4.17 (H-5), 2.22, 2.09 (CH_3-acetate).

Characterization Data for 2,6-Di-O-propionyl-cellulose. DS: $DS_{propionate}$ = 1.96 (determined by ^1H NMR spectroscopy). FT-IR (cm^{-1}): 3453 ν(OH), 2958 ν(C−H), 1275 ν(C−O−C_{ester}), 1726 ν(CO_{ester}). ^1H NMR (in pyridine-d_5 with 1 drop TFA added): δ (ppm) 5.60 (H-3), 5.32 (H-2), 5.00 (H-1), 4.71 (H-6), 4.39 (H-6′), 4.05 (H-4), 3.91 (H-5), 2.44 (CH_2-propionate), 1.15 (CH_3-propionate).

2,6-Di-*O*-acyl-3-*O*-acyl′-cellulose. 2,6-Di-*O*-acyl-cellulose (100 mg) was dissolved in 5 mL of pyridine, 20 mg 4-(dimethylamino)-pyridine, and 5 mL of acetic (**11**) or propionic (**9**) anhydride. After stirring for 24 h at 80 °C, the product was precipitated into 100 mL water, collected by filtration, and then washed several times with water. The crude product was redissolved in 5 mL of $CHCl_3$. This solution was added slowly with rapid stirring to 100 mL of ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C to yield triester products **11** or **9**.

Characterization Data for 2,6-Di-O-acetyl-3-O-propionyl-cellulose, 9. FT-IR (cm^{-1}): 2945 ν(C−H), 1275 ν(C−O−C_{ester}), 1756 ν(CO_{ester}). ^1H NMR (in $CDCl_3$): δ (ppm) = 5.03 (H-3), 4.71 (H-2), 4.38 (H-1), 4.31 (H-6), 3.99 (H-6′), 3.64 (H-4), 3.47 (H-5), 2.15 (CH_2-propionate), 1.00 (CH_3-propionate), 2.04, 1.91 (CH_3-acetate). ^{13}C NMR (in $CDCl_3$): δ (ppm) = 168.95, 170.15, 173.10 (C═O), 100.31 (C-1), 72.11 (C-2), 75.95 (C-4), 72.27 (C-3), 75.75 (C-5), 62.19 (C-6), 20.61, 20.41 (CH_3-acetate), 27.09 (CH_2-propionate), 8.90 (CH_3-propionate).

Characterization Data for 3-O-Acetyl-2,6-di-O-propionyl-cellulose, 11. FT-IR (cm^{-1}): 2940 ν(C−H), 1275 ν(C−O−C_{ester}), 1750 ν(CO_{ester}). ^1H NMR (in $CDCl_3$): δ (ppm) = 5.05 (H-3), 4.80 (H-2), 4.38 (H-1), 4.38 (H-6), 4.04 (H-6′), 3.69 (H-4), 3.49 (H-5), 2.37, 2.24 (CH_2-propionate), 1.16, 1.06 (CH_3-propionate), 1.90 (CH_3-acetate). ^{13}C NMR (in $CDCl_3$): δ (ppm) = 169.38, 172.67, 173.58 (C═O), 100.36 (C-1), 71.77 (C-2), 76.08 (C-4), 72.64 (C-3), 73.31 (C-5), 62.12 (C-6), 20.36 (CH_3-acetate), 27.31, 27.26 (CH_2-propionate), 8.95, 8.80 (CH_3-propionate).

Computational Details. Density functional calculations were performed with geometry optimization at the M05−2X/6−311+G-(d,p) level with an integration grid of 70590 as implemented in Gaussian09, Revision B.01[TE1]. Frequency calculations were performed to verify the identification of an energetic minimum.

RESULTS AND DISCUSSION

Initially we intended to synthesize the cellulose-2,6-*O*-esters by starting with 3-*O*-benzyl-cellulose, available by benzylation and subsequent desilylation of Klemm's bis(2,6-*O*-TDMS)-cellulose[17] (Scheme 1).

Preparation of 3-*O*-benzylcellulose went smoothly, and subsequent acylation with acetic anhydride afforded the desired 3-*O*-benzylcellulose-2,6-di-*O*-acetate (or, in the case of propionic anhydride, the 2,6-di-*O*-propionate); 80 °C, 24 h, 54 equiv acetic anhydride in pyridine/4-dimethylaminopyridine. Debenzylation was carried out by means of catalytic hydrogenation. However, hydrogenation of 3-*O*-benzylcellulose-2,6-di-*O*-acetate proved surprisingly difficult. Hydrogenation using Pd/C at atmospheric H_2 pressure and ambient temperature in THF and acetic acid (1:1 volume ratio) for one day gave unexpected results. ^1H NMR analysis of the product showed almost no debenzylation (DS (benzyl) = 0.98). Hydrogenation using the stronger catalyst $Pd(OH)_2/C$ at room temperature and atmospheric pressure of H_2 (24 h) still gave incomplete debenzylation (DS (benzyl) 0.56). Harsh conditions were then applied. Using $Pd(OH)_2/C$ at 80 °C under 450 kPa H_2 for 36 h afforded a black powder with no solubility in common organic solvents, indicating profound degradation of the cellulose chain (at the same pressure and 50 °C, only partial debenzylation again was observed; DS (benzyl) 0.46). The unexpectedly poor reactivity of 3-*O*-benzylcellulose was further revealed when we attempted to react it with silyl chlorides. Because Klemm and co-workers have shown that unsubstituted cellulose reacts with 1 equiv of TDMS chloride to afford greater than 95% selective O-6 etherification, we had reasoned that the added bulky benzyl ether substituent at O-3 of **4** should virtually eliminate any O-2 substitution, leading to orthogonally protected 3-*O*-benzyl-6-*O*-silylcellulose ethers with very high regioselectivity. These protected cellulose ethers could be gateway intermediates to a variety of cellulose ether and ester homopolymers of regiospecifically substituted glucosyl units. In the event, we found that 3-*O*-benzylcellulose was quite resistant to silylation under standard or even forcing conditions. For example, reaction with 4 equiv TDMSCl at 100 °C (24 h, DMAc solvent, imidazole catalyst) gave a product with DS (TDMS) only 0.04! Similar results were obtained even when using the less bulky trimethylsilyl chloride.

At a loss to explain the poor reactivity of 3-*O*-benzylcellulose and its 2,6-di-*O*-acetate derivative, we carried out computational studies using density functional calculations on appropriate model compounds: in particular, methyl 4-*O*-methyl-*β*-glucopyranoside (**M1**) and analogues of **4** (methyl 3-*O*-allyl-4-*O*-methyl-*β*-glucopyranoside, **M2**) and **5** (methyl 3-*O*-benzyl-4-*O*-methyl-*β*-glucopyranoside, **M3**). Plots of the high-

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est occupied molecular orbital clearly indicate the presence of substantial orbital density at the C-6 position for methyl 4-*O*-methyl-*β*-glucopyranoside and the 3-*O*-allylcellulose model **M2** (Figures 1 and 2), which is completely absent from the 3-*O*-benzylcellulose model **M3** (Figure 3).[18]

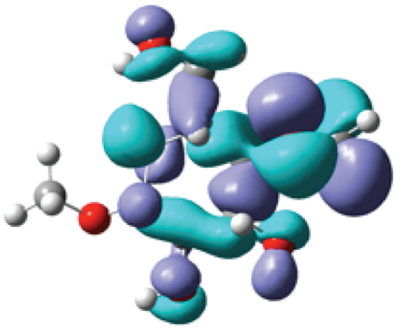


Figure 1. HOMO plot of methyl 4-*O*-methyl-*β*-D-glucopyranoside, **M1**.

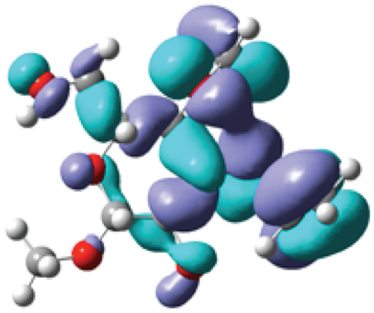


Figure 2. HOMO plot of methyl 3-*O*-allyl-4-*O*-methyl-*β*-D-glucopyranoside, **M2**.

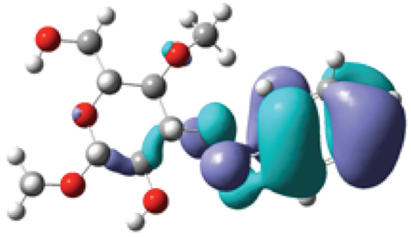
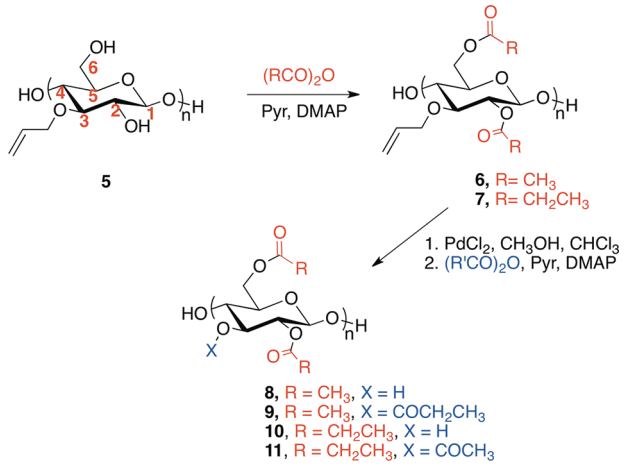


Figure 3. HOMO plot of methyl 3-*O*-benzyl-4-*O*-methyl-*β*-D-glucopyranoside, **M3**.

These computational results clearly predicted higher nucleophilicity for the hydroxyl groups of 3-*O*-allylcellulose than those of 3-*O*-benzylcellulose. In addition, previous investigators had shown[19] that hydrogenolysis of benzyl groups is retarded by electron withdrawing substituents in the benzene ring, and enhanced by electron-donating substituents. They attributed this effect to the partial positive charge on the benzylic carbon during the rate-determining step of hydrogenolysis. If low electron density at the benzylic carbon (perhaps in combination with steric issues created by the bulk of the cellulose chain and the heterogeneous nature of Pd-catalyzed hydrogenolysis[20]) were the cause of the low reactivity observed, perhaps homogeneously catalyzed removal of the allyl group would be more facile.

We tested these predictions by synthesizing 3-*O*-allylcellulose by the methods of Heinze et al.[9] (Scheme 1), then reacting the protected intermediate with carboxylic anhydrides (Scheme 2). Complete desilylation of **3** required sequential treatments with

Scheme 2. Synthesis of Cellulose-2,6-*O*-diesters



TBAF in THF and then in DMSO but was successful after this two-step process. Subsequent acylation was smooth and complete, affording, for example, 3-*O*-allylcellulose-2,6-di-*O*-acetate **6** and the corresponding 2,6-di-*O*-propionate **7** that were completely and regioselectively substituted as indicated by proton NMR spectroscopy. *The key deallylation step proceeded readily under mild conditions* (room temperature, 24 h, $PdCl_2$ in $CHCl_3$/MeOH) to afford cellulose-2,6-*O*-diacetate **8** and cellulose-2,6-di-*O*-propionate **10**. By ^1H NMR, the DS in each case was 2.0, confirming the chemoselectivity of the Pd-catalyzed deallylation (due at least in part to the mild conditions that in this case were effective in allyl removal; we have observed in related systems that $PdCl_2$/MeOH/$CHCl_3$ treatment can result in partial deacylation of other cellulose esters).

This methodology was very useful, as shown above, for the regioselective synthesis of cellulose-2,6-di-*O*-esters, for example, cellulose-2,6-di-*O*-acetate and cellulose-2,6-di-*O*-propionate, both of which are homopolymers of monosaccharides that are components of important commercial cellulose esters including cellulose diacetate and cellulose acetate propionate. It was also straightforward to convert these cellulose-2,6-di-*O*-esters into cellulose triester homopolymers in which one type of acyl group was attached to O-2 and O-6, and a second type of acyl group was attached to O-3. Acylation of cellulose-2,6-di-*O*-acetate with propionic anhydride (pyridine, DMAP, 80 °C, 24 h) cleanly afforded the desired cellulose-2,6-di-*O*-acetate-3-*O*-propionate **9**. Similarly, treatment of cellulose-2,6-di-*O*-propionate with acetic anhydride cleanly afforded cellulose-2,6-di-*O*-propionate-3-*O*-acetate **11**. No ester group migration was evident from the NMR spectra of these derivatives (e.g., Figure 4, ^{13}C spectrum of cellulose-2,6-di-*O*-acetate-3-*O*-propionate (**9**)).

Analysis of the bulk position of substitution was accomplished by NMR spectroscopy, with heteronuclear multibond correlation spectroscopy (HMBC) being particularly useful.[21] The fully substituted esters had good organic solubility, permitting NMR analysis in $CDCl_3$ solution. The ^1H and ^{13}C NMR spectra were fully assigned by the methods of Heinze,[22] Azuma,[23] and co-workers.

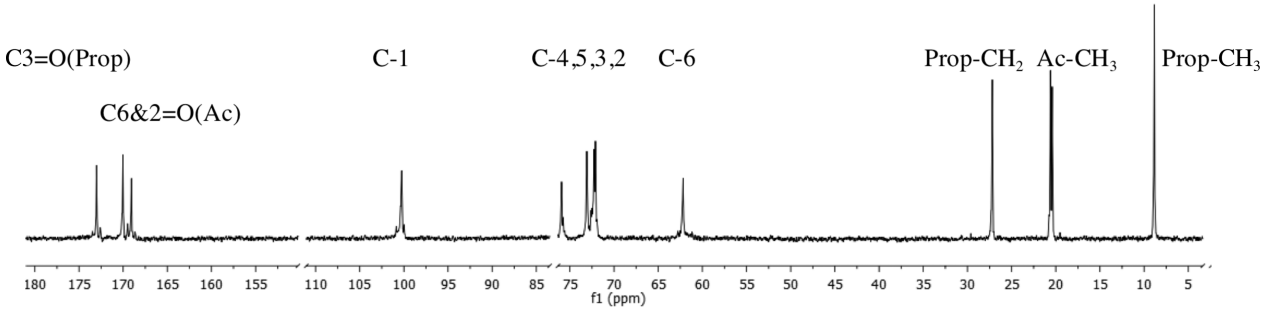


Figure 4. ^{13}C NMR spectrum of cellulose-2,6-di-*O*-acetate-3-*O*-propionate.

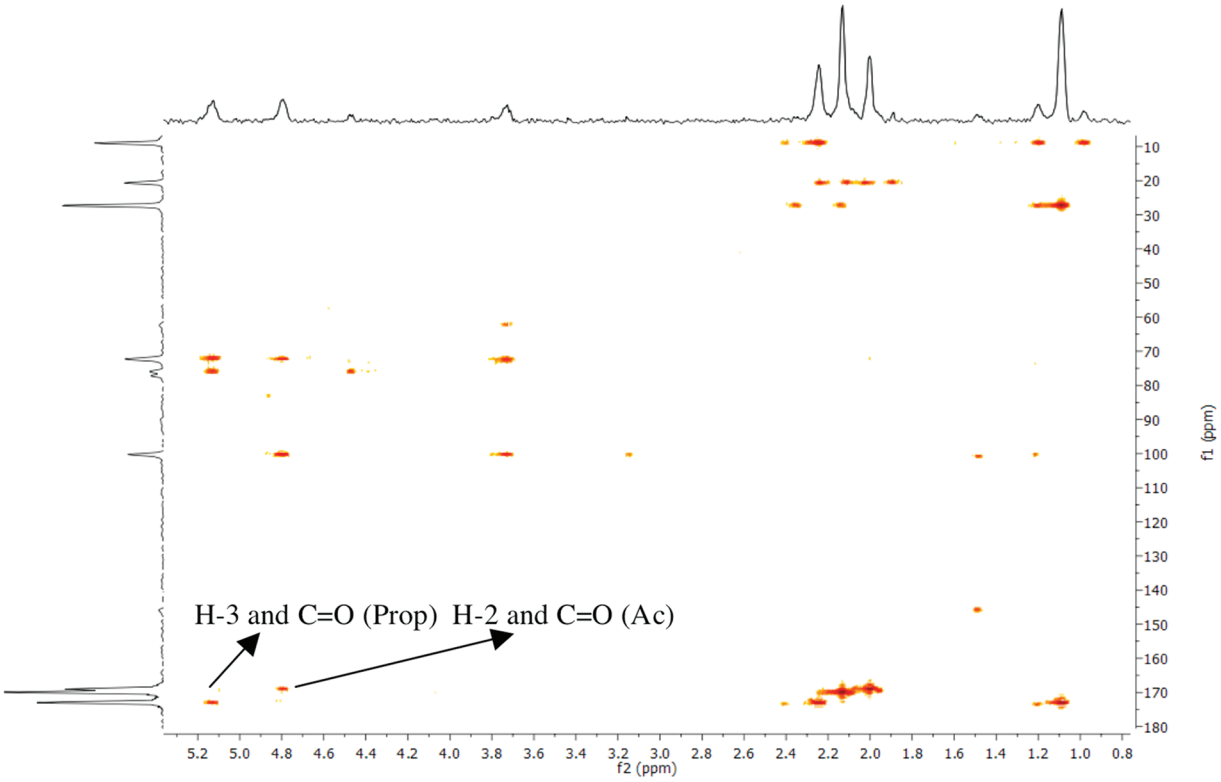


Figure 5. HMBC NMR spectrum of cellulose-2,6-di-*O*-acetate-3-*O*-propionate.

The HMBC spectrum (Figure 5) showed a correlation between the acetyl carbonyl carbon signal at 168.95 ppm and the H-2 proton signal at 4.71 ppm, confirming esterification at O-2. The propionyl carbonyl carbon (173.10 ppm) at position 3 was correlated with the H-3 proton signal (5.03 ppm), confirming propionylation at O-3. Correlation peaks between the C-6 acetyl carbonyl and the C-6 anhydroglucose (AGU) protons were not observed; our experience is that these C-6 correlation peaks are always weaker and often not observed. In contrast to the triesters, the 2,6-*O*-diesters had generally poor organic solubility, with pyridine-*d*-5 being the only convenient NMR solvent. The diester and triester products are summarized in Table 1, along with brief descriptions of their physical characteristics. We include for comparison the commercial cellulose esters that are closest in composition to these regioselectively substituted cellulose esters. While quantitative measurement of the monosaccharide composition of cellulose esters has been quite difficult to date, the best data available (from careful analysis of the ^{1}H and ^{13}C NMR spectra of cellulose acetate,[24,25] which is one of the simplest possible cases, containing only one ester type) indicate that commercial cellulose esters are indeed statistical mixtures of all possible monosaccharides. It is interesting therefore to note the different and generally inferior solubility of the regioselectively substituted diesters. Thermal properties[16] are also strongly impacted by regiochemistry; for example, the T_g of cellulose-2,6-di-*O*-propionate is much lower (146 °C) than that of commercial CAP-504−0.1 (T_g 161 °C), which has a similar DS and a presumably random substituent pattern.

It was also important to quantify the degree of regioselectivity of these transformations. Unfortunately there are no general, quantitative methods for determining the monosaccharide composition (e.g., X% *β*-D-2-*O*-acetyl-6-*O*-propionyl-Glc-*p*) of cellulose esters, as there are for cellulose ethers.[26] While cellulose ether linkages are stable during hydrolysis of the polysaccharide to monosaccharides, ester linkages are cleaved and also do not survive the alkaline conditions of permethylation. Mild methylation procedures have been investigated, but are not generally applicable.[27,28] Acyl groups can in principle be preserved under conditions of

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Table 1. Cellulose Ester Homopolymer Properties Compared with Those of Random Copolymers of Similar DP

cellulose ester[a]	DS[b]	DP[c]	T_g (°C)[d]	solubility[e]
2,6-Pr-3-Ac	Ac 1.0, Pr 2.0	193	139	THF, $CHCl_3$, DMSO, Pyr
CTP	Pr 3.0	180	165	THF, $CHCl_3$, DMSO, Pyr
2,6-Ac-3-Pr	Ac 2.0, Pr 1.0	151	137	THF, $CHCl_3$, DMSO, Pyr
CA-435-75S[f]	Ac 2.9	426	186	DMSO
CTA	Ac 3.0	n/a	185	DMSO (swollen)
2,6-Ac	Ac 2.0	n/a	143	Pyr
CA-320S[f]	Ac 1.8	159	184	DMSO, Pyr
CA-398−30[f]	Ac 2.4	189	185	THF, $CHCl_3$, DMSO, Pyr
2,6-Pr	Pr 2.0	n/a	146	Pyr
CAP-504-0.1[f]	Ac 0.1, Pr 2.1	53	161	THF, $CHCl_3$, DMSO, Pyr

[a]Ac = acetyl, Pr = propionyl, CTA = cellulose triacetate (CTA was made by peracylation of cellulose with acetyl chloride in DMAc/LiCl), CTP = cellulose tripropionate (CTP was made by peracylation of cellulose with propionic anhydride in DMAc/LiCl). [b]By ^{1}H NMR. [c]By SEC in $CHCl_3$ or NMP/LiBr; 2,6-Ac and 2,6-Pr not soluble so not measured. [d]DSC second heating scan. [e]Tested in tetrahydrofuran (THF), $CHCl_3$, dimethylsulfoxide (DMSO), pyridine (Pyr), ethanol. Insoluble in each solvent except those listed in table. [f]Commercial esters (Eastman Chemical Co.).

reductive depolymerization[29] but the method is prone to incompleteness and side reactions. Because cellulose ethers are key intermediates in our syntheses, it was possible and useful to determine their monosaccharide compositions, after permethylation of free hydroxyl groups, to provide upper limits on the regioselectivity of our synthetic methods. The latest cellulose ether intermediate in the synthesis is 3-*O*-allylcellulose (**5**). Therefore, we analyzed this ether quantitatively with respect to monosaccharide composition. Permethylation (CH_3I, DMSO, NaH, room temperature for 24 h, then 50 °C, 72 h) followed by deallylation ($PdCl_2$, $CHCl_3$, CH_3OH, room temperature, 24 h) afforded the substrate for analysis. Analysis by hydrolysis to monosaccharides, reduction to alditols, acetylation, and chromatography showed that the permethylated product was composed of 84−85%[30] 2,6-di-*O*-methyl-substituted glucose, containing small amounts of other methylated AGUs including 6-*O*-methyl (5%), 3,6-di-*O*-methyl (3.5%), 2-*O*-methyl (3%), and 2,3,6-tri-*O*-methyl (2%) glucose ethers. The 6- and 2-monomethyl ethers could have arisen from slightly incomplete desilylation, and the 3,6-dimethyl ether could have arisen from slightly incomplete allylation. However, the 2,3,6-tri-*O*-methylcellulose byproduct is a clear indication of incomplete allylation, partial deallylation during TBAF-catalyzed desilylation, or both. We tend to favor the TBAF mechanism (isomerization to the vinyl ether which is hydrolyzed off during workup) because we know that TBAF is a strong base and capable of such catalysis.[5] Thus, the actual regioselectivity at intermediate **5** is at least 85%.

CONCLUSIONS

In summary, we have developed general synthetic methods, based on computational studies of models of potential synthetic intermediates, for the successful regioselective synthesis of cellulose-2,6-di-*O*-esters and cellulose-2,6-di-*O*-(ester A)-3-*O*-(ester B) derivatives. The methods should be broadly applicable to other cellulose ester types. These syntheses of cellulose ester homopolymers are an important step toward broader and deeper understanding of cellulose ester structure−property relationships, the relationships of analytical characteristics to substitution regiochemistry, and toward learning how to more finely control the properties of these important sustainable-based derivatives.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR and FTIR spectra of all products not included in the body of the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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