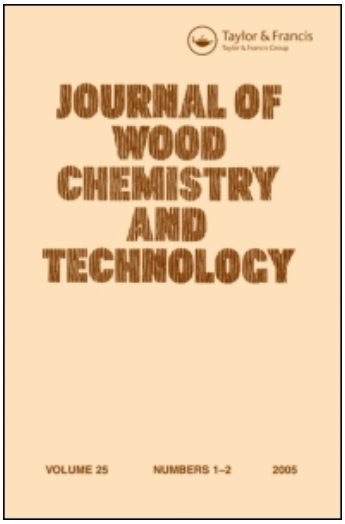

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THE SYNTHESIS AND CHARACTERIZATION OF A POLYMER-SUPPORTED CELLULOSE MODEL

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ABSTRACT

A polymer-supported cellulose model was prepared by condensing the C-4' hydroxyl group of a protected disaccharide, 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-ß-D-glucopyranosyl)-D-glucitol (**5**), with an iodomethylated polystyrene resin and removing the protecting groups. The preparation of **5** from cellobiose octaacetate (**4**) employed ten steps, utilizing allylate, acetate, and benzylidene protecting groups. The yield of **5** based on **4** was 5%.

The loading of the disaccharide on the polymer was determined by (1) measuring the resin's increase in weight after treating the allyl protected supported model with osmium tetraoxide and (2) hydrolyzing the supported model's glycosidic linkage, after removal of the allyl protecting groups, and measuring the amount of 1,5-anhydro-D-glucitol released into the liquid phase. The C-4' point of attachment was verified by exhaustive methylation, hydrolysis, and characterization of the resulting products.

The alkaline stability of the polymer-disaccharide linkage, a benzyl ether, was verified by preparing and degrading methyl 4-O-benzyl-α-D-glucopyranoside (**3**). The rate of glycosidic bond cleavage in 1,5-anhydrocellobiitol at 170°C in NaOH was about 45 times faster than the rate of disappearance of **3**.

INTRODUCTION

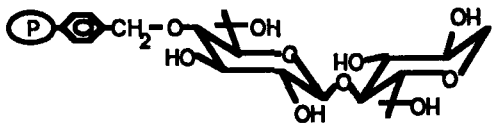
The alkaline degradation of cellulose results in both a significant loss in weight and a drastic reduction in the cellulose degree of polymerization (DP).[3] The weight loss has been attributed to the sequential peeling of

monomers from the reducing end of the cellulose chain.[4,5,6] The DP reduction has been attributed to random cleavage of the glycosidic bonds.[4]

Most of what is known about the mechanisms of glycosidic bond cleavage in cellulose has been obtained from the study of model compounds.[7,8,9,10] These compounds are generally simple glycosides or oligosaccharides which are soluble in an alkaline medium. However, cellulose is not soluble in pulping liquors and hence is subject to heterogeneous reactions. Very little is known about heterogeneous glycosidic bond cleavage.

In general, the rate of a heterogeneous reaction is slower than the analogous homogeneous reaction.[11,12] Often this is the result of mass transfer limitations.[11] However, it may also be the result of differences in the inherent reactivity of the reactants.[13,14] Hammett *et al.*[13] have shown that the losses in internal degrees of freedom in forming a transition state between an insoluble and a soluble reactant are greater than in forming a transition state between two soluble reactants. Therefore the intrinsic rate constant in the heterogeneous reaction is less.

In this paper we describe the synthesis and characterization of a polymer-supported cellulose model (**1**).



1

Ⓟ - polystyrene

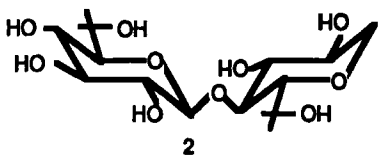
This model consists of 1,5-anhydro-4-O-β-D-glucopyranosyl-D-glucitol (1,5-anhydrocellobiitol) (**2**) coupled to a polystyrene resin through C-4' by a benzyl ether linkage. Since this model does not contain a reducing end-group, it should only undergo glycosidic bond cleavage when degraded in alkali at high temperature. Also, like cellulose, **1** is insoluble in alkaline media and should be subject to heterogeneous reactions.

RESULTS AND DISCUSSION

Design Criteria

Clearly, the polymer support and the benzyl ether linkage must be stable under the conditions to be used in the alkaline degradation studies. A macroreticular polystyrene resin, Amberlite XE-305, was selected for the support. Macroreticular resins in general contain large permanent pores which should allow the transport of reagents into and products out of the polystyrene matrix. The mean pore diameter in Amberlite XE-305 resin is 1400 Å.[15] The resin's resistance to alkaline attack was verified by treating unfunctionalized Amberlite XE-305 with 2.5 M NaOH at 170°C for five days. Gravimetric analysis showed no weight loss had occurred. In addition, the only observable differences between treated and untreated resins were minor increases in mechanical damage.

The benzyl ether linkage was selected because it should be quite stable in alkali relative to the glycosidic linkage in 1,5-anhydrocellobiitol. This assumption was verified by comparing the rate of degradation of methyl 4-O-benzyl-α-D-glucopyranoside (**3**) to the rate of glycosidic bond cleavage in 1,5-anhydrocellobiitol under pseudo-first order kinetics. Since compound **3** may degrade by either glycosidic bond cleavage or benzyl ether bond cleavage, the rate of degradation of **3** was taken as a minimum estimate of the benzyl ether's alkaline stability. The rate of degradation of **3** in 2.5 N NaOH at 170°C was 1.75×10^{-7} sec^{-1}.[16] Brandon et al.[10] reported that the rate of glycosidic bond cleavage in 1,5-anhydrocellobiitol (**2**) in 2.5 N NaOH at 170°C was 7.92×10^{-6} sec^{-1} or approximately 45 times faster than the rate of degradation of **3**.



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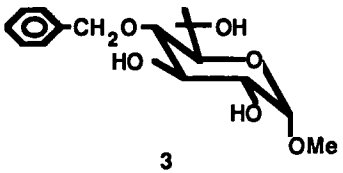

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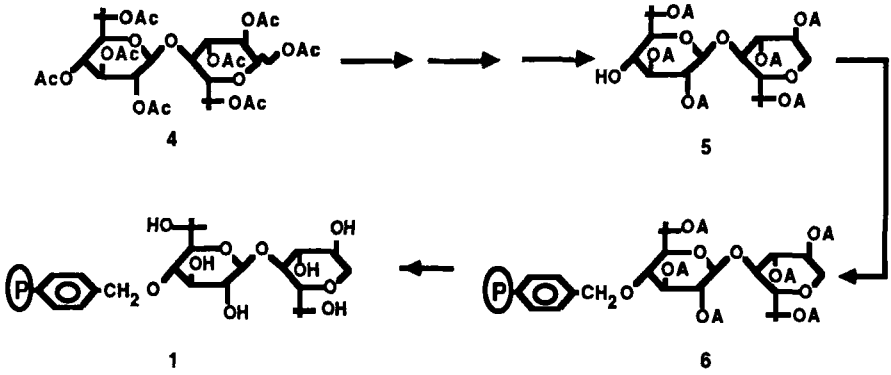

Scheme 1

Synthetic Approach

The preparation of the polymer-supported cellulose model (**1**) is illustrated in Scheme 1. First, an allyl ether protected disaccharide, 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (**5**), was prepared from cellobiose octaacetate (**4**). Next, the protected disaccharide was condensed with a functionalized polystyrene resin to yield the intermediate **6**. Finally, the allyl ether protecting groups were removed to give the polymer-supported model **1**.

Allyl ethers were selected as the protecting groups because they are stable under the conditions required for the condensation of **5** with the functionalized resin and can be removed in the presence of benzyl ethers.[17] Also, allyl ethers are sterically small and therefore should not interfere with the reaction at C-4'.

Preparation of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (5)

Compound **5** was prepared according to the scheme shown in Figure 1. The first objective was the preparation of 1,5-anhydrocellobiitol (**2**). Several syntheses of 1,5-anhydroalditols are known.[18,19] Schroeder

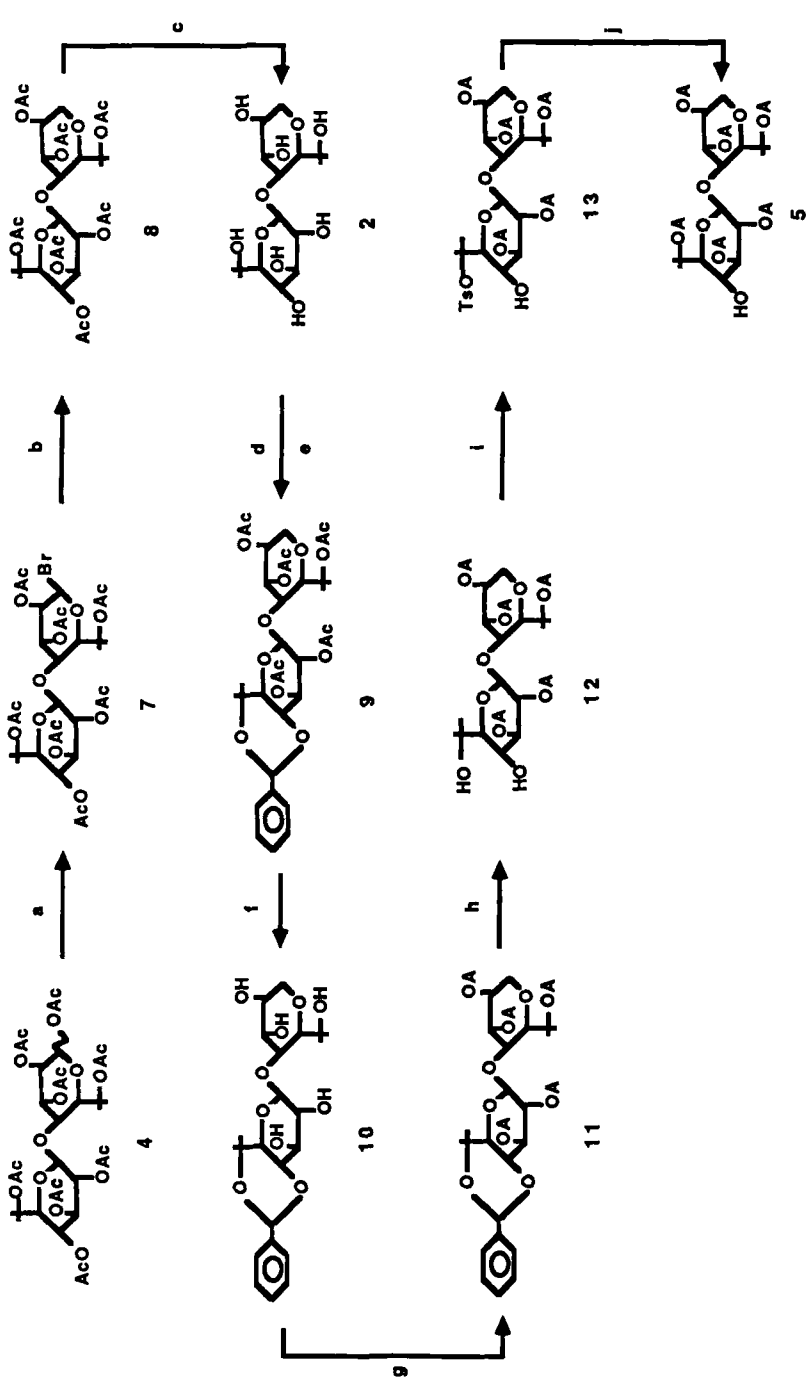

Figure 1. Synthesis of **5** from **4**: (a) HBr/AcOH, (b) Raney Nickel, (c,f) NaOMe, (d) TsOH/PhCH(OMe)$_2$, (e) Ac$_2$O/pyridine, (g) NaH/CH$_2$=CHCH$_2$Br, (h) HCl/MeOH, (i) TsCl/pyridine, and (j) NaOCH$_2$CH=CH$_2$.

and coworkers,[9,10] have prepared esterified 1,5-anhydroalditols by reductive desulfurization of esterified 1-thioglycopyranosides with Raney nickel and by palladium catalyzed hydrogenation of esterified glycopyranosyl halides in the presence of amines. The Raney nickel-desulfurization has been preferred for large scale preparations because of good yields and ease of isolation; however, large scale catalytic hydrogenations can result in complex product mixtures that require chromatographic purification. Nevertheless, since the thioglycosides are typically synthesized from glycosyl halides, direct reduction of the glycosyl halide was investigated.

Cellobiose octaacetate (**4**) was treated with hydrobromic acid in glacial acetic acid to yield α-cellobiosyl bromide heptaacetate (**7**).[20] Reductive dehalogenation of **7** with Raney nickel in the presence of triethylamine afforded 1,5-anhydrocellobiitol heptaacetate (**8**) in excellent yield (78%). The acetate esters present in **8** were removed with methanolic sodium methoxide to give **2**.

The Raney nickel reduction of the glycosyl halide provided an excellent means of preparing large quantities of **8**. The only report of a similar reduction is a brief mention of the reduction of tri-O-benzoyl-β-D-arabinopyranosyl bromide with Raney nickel as part of a study on the preparation of 2-deoxy sugars by hydrogenolysis of benzoylated glycopyranosyl bromides.[21] The yield of the deoxy sugars was only 3%, but the yield of 1,5-anhydro-tri-O-benzoyl-D-arabinitol was 52%. Although a trace amount of the deoxy analog of 1,5-anhydrocellobiitol was detected by GLC, it did not interfere with the crystallization of **8**. The physical constants of **2** were consistent with the desired product.

Treatment of **2** with α,α-dimethoxytoluene in *N,N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid gave the benzylidene derivative **10**. The conditions employed were essentially the same as those reported by Evans[22] for the preparation of methyl 4,6-O-benzylidene-α- and β-D-glucopyranoside. Formation of **10** was confirmed by ^{13}C-NMR spectroscopy, which indicated the presence of aromatic carbons at 136.0, 128.7, 127.8, and 125.8 ppm and two acetal carbons at 103.6 and 100.6 ppm. The EI mass spectrum showed fragments

corresponding to loss of the benzylidene group (265, M-149),[23] the aglycone (251, M-163), and the glycone (147, M-267).

Attempts to isolate **10** directly from **2** afforded only low yields (30%). Thus, the reaction mixture from benzylidenation of **2** was acetylated in situ and the product was isolated as its peracetate **9**. Compound **10** was obtained by catalytic deacetylation of **9** with sodium methoxide. The conversion of **2-->9-->10** increased the yield of **10** to 65%.

Next, the free hydroxyl groups in **10** were protected with allyl ethers.[24] Etherification with allyl bromide and sodium hydride in DMF gave crystalline **11** (59%). The fact that **11** was completely allylated was apparent from the ratio of vinylic to aromatic protons (3:1) observed in the ^{1}H-NMR spectrum. Also, the ^{13}C-NMR spectrum of **11** showed signals at 135.2, 134.5, and 134.1 ppm for the 2-C allyl carbon and 116.6, 116.1, and 115.4 ppm for the 3-C allyl carbon.

Removal of the benzylidene group with dilute acid and methanol gave **12**. Although direct allylation of the primary hydroxyl group in **12** is possible, it was not attempted since selective etherifications generally result in low yields.[25] Instead a two step procedure was used to etherify the primary hydroxyl group. This method[25] combines a regioselective tosylation of the C-6 hydroxyl group with a subsequent nucleophilic displacement of the tosyloxyl substituent by a sodium alkoxide.

Compound **12** was not isolated. Its primary hydroxyl group was selectively tosylated to yield **13** as an amorphous syrup. Purification by column chromatography afforded a low yield (50%) of **13** and allowed the recovery of unreacted **12**. The formation of **13** was apparent from its NMR spectra. The aromatic signals in the ^{1}H-NMR were split into an AA'BB' pattern indicative of *p*-substituted benzene rings such as a *p*-tosyl group. Also the ratio of vinylic to aromatic protons (15:4) was consistent with **13**. The ^{13}C-NMR spectrum showed signals at 21.4 ppm for the tosyl methyl carbon and 144.6 ppm for the sulfur substituted aromatic carbon.

Treatment of **13** with sodium allylate in *N,N*-dimethylformamide and purification by column chromatography gave the hexaallyl ether protected disaccharide **5** as a syrup. Both the ^{1}H and ^{13}C-NMR spectra indicated the disappearance of the tosyl aromatic signals. The overall yield of **5** based on **4** was 5%.

Unfortunately, **5** and **11** can polymerize if not stored properly. Allyl ethers of complex carbohydrates such as starch and cellulose form infusable resins when exposed to air and light.[26] Therefore, preparations of **5** and **11** were immediately used in the next step or stored in the dark under nitrogen.

Preparation of the Supported Model (1)

Condensation of **5** with the iodomethylated resin[27] was effected in 33% yield (based on **5** consumed) by stirring a tetrahydrofuran (THF) suspension of the polymer with the glycoside and sodium hydride (Scheme 1). The IR spectrum of the product, resin **6**, indicated a strong C-O absorption between 1150 and 1000 cm^{-1} and two moderate to weak olefinic C-H absorptions at 996 and 923 cm^{-1}. Also treatment of **6** with ozone generated formaldehyde, indicating the presence of an allylated carbohydrate.

An attempt to condense the protected disaccharide **5** with the iodomethylated resin in dimethyl sulfoxide (DMSO) resulted in little reaction. The IR spectrum of the recovered resin showed only a minor increase in the C-O absorption band. In view of the enhanced reactivity normally obtained by using DMSO as a solvent in displacement reactions, this result was surprising.[28] However, the low level of reaction was probably due to the DMSO being more polar than THF and not swelling the polymer matrix to as great an extent.

The unreacted iodomethyl groups on resin **6** were converted to benzyl ethyl ethers by treatment with sodium ethoxide. The allyl ether protecting groups were then isomerized with tristriphenylphosphine-rhodium chloride and removed by acid hydrolysis to give **1**.[29] The removal was confirmed by the disappearance of the olefinic C-H absorptions at 996 and 923 cm^{-1} and the appearance of a broad OH absorption between 3600 and 3000 cm^{-1} in the IR spectrum of **1**.

Characterization of the Polymer-Supported Model

The loading was determined by measuring the increase in weight of resin **6** upon treatment with osmium tetraoxide. Resin **6** contains allyl

ethers which in the presence of pyridine react quantitatively with osmium tetraoxide to form osmylate esters.[30] Unfortunately, osmium tetraoxide also reacts with aromatic double bonds; however, the rate of this reaction is much slower.[31] To correct for this, unfunctionalized resin was also osmylated and its increase in weight was subtracted from **6**'s. The loading determined by this method was 0.25 meq. of 1,5-anhydrocellobiitol per gram of **1**.

This loading was further confirmed by hydrolyzing the supported disaccharide's glycosidic bond and monitoring the amount of the aglycone, 1,5-anhydro-D-glucitol, released into the liquid phase. The hydrolysis was performed in aqueous ethanol with hydrochloric acid. It was continued until the concentration of 1,5-anhydro-D-glucitol in the solution remained constant. The loading determined by this method was 0.22 meq. of 1,5-anhydrocellobiitol per gram of resin **1**. Although this value is slightly lower than the value determined by the osmylation method, it is considered to be a better estimate of the loading, since osmium tetraoxide may also react with the aromatic double bonds.

The point of polymer attachment to the disaccharide may be inferred from the analogous preparation of methyl 4-O-benzyl-α-D-glucopyranoside to be the C-4' position. However, based on the last crystalline material in the synthesis, **11**, the polymer could be attached through either the C-4' or C-6' position. In order to distinguish between these two possibilities and verify that the polymer was indeed covalently bound to the 1,5-anhydrocellobiitol, the supported model **1** was exhaustively methylated and the benzyl ether linkage was cleaved by an acid hydrolysis.[32] The hydrolysis also cleaved the disaccharide's glycosidic bond. The products were analyzed by GLC and GC-MS spectroscopy as their alditol acetates.

In each case the aglycone would yield 4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (**17**). Only the product from the glycone would be dependent on the point of attachment (Figure 2). The glycone from the C-6' bound disaccharide would yield 1,5,6-tri-O-acetyl-2,3,4-tri-O-methyl-D-glucitol (**14**) and the C-4' bound disaccharide would yield 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (**15**). The glycone from any nonbonded disaccharide would yield 1,5-di-O-acetyl-2,3,4,6-tetra-O-methyl-D-glucitol (**16**).

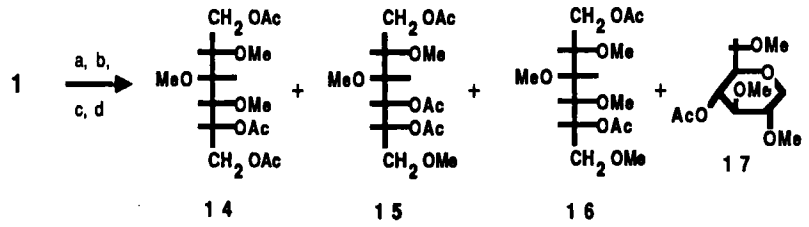

Figure 2. Potential products from methylation and hydrolysis of polymer-supported model: (a) methylation, (b) acetolysis, (c) deacetylation-reduction, (d) acetylation.

The GLC and GC-MS analyses of the methylation-hydrolysis products showed approximately equal amounts of 4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (**17**) and 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (**15**). Neither **14** or **16** was detected in the reaction mixture. The presence of **15** and the absence of **14** and **16** confirmed that the polymer was covalently bound through the disaccharide's C-4' position.

The distribution of the disaccharide across the polymer support was determined by electron microscopy. Resin **6** was osmylated, cross sectioned, and mapped for osmium. The concentration of osmium and therefore the disaccharide was greatest at the outer surfaces and least in the center.

EXPERIMENTAL

General Methods

Melting points were determined on a calibrated Thomas-Hoover capillary apparatus. Optical rotations were obtained with a Perkin-Elmer 141MC polarimeter. The NMR spectra were determined with a JEOL FX100 Fourier transform spectrometer at normal probe temperature using TMS as an external standard. The IR spectra were obtained as KBr pellets with a Nicolet 7199 Fourier transform spectrometer.

Thin layer chromatography (TLC) was performed on microscope slides coated with silica gel G (Merck Kieselgel D-5). The solvents for development are described in the appropriate sections. Components were

detected by spraying the chromatography with H_2SO_4 in MeOH (1:4 v/v.), followed by charring.

Gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 5890 instrument equipped with a flame ionization detector and interfaced with a Hewlett-Packard 3392A integrator. Helium was used as the carrier gas at a rate of 25 mL/min. All analyses were performed on glass columns (6 ft x 1/4 in x 2 mm). Column A was an OV-17 (3%) on Supelcoport (80-100 mesh) and column B was a SP-2340 (3%) on Supelcoport (80-100 mesh). The operating conditions are described in the appropriate sections.

A Hewlett-Packard 5985 instrument was used for direct insertion (DI) and GLC mass spectroscopy (GC/MS). The GC/MS interface was maintained at 250°C. Electron impact (EI) MS used helium as the carrier gas, a source temperature of 200°C, and an ionization voltage of 70 Ev.

Polystyrene

Amberlite XE-305 polystyrene resin (150 g), purchased from Polysciences, Inc., Warrington, Pennsylvania in the form of 20 to 50 mesh beads, was refluxed for thirty minutes in each of the following solvents (1.5 L each): benzene, methanol, DMF, dioxane-2M aq. NaOH (1:1 vol.), dioxane-2M aq. HCl (1:1 vol.), and water.[15] The resin was solvent exchanged between refluxes by decantation with the next solvent. After the final water wash, the resin was extracted in a Soxhlet apparatus for four hours with diethyl ether and for twelve hours with hexane.

Chloromethylated Polystyrene

The polymer was prepared by chloromethylation of Amberlite XE-305 resin with stannic chloride and chloromethylmethyl ether as described by Hodge and Sherrington.[11,16] IR: cm^{-1} 1265 (CH_2Cl).

Anal. C, 74.08; H, 6.41; Cl, 17.83.

Iodomethylated Polystyrene

The iodomethylated resin was prepared by refluxing chloromethylated Amberlite XE-305 with sodium iodide in acetone as described by Snyder *et al.*[27,16] IR: cm^{-1} 1155 (CH_2I).

Anal. C, 44.18; H, 3.81; Cl, 9.64; I, 35.27.

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-D-glucitol (8)

Hepta-O-acetyl-α-cellobiosyl bromide[20] (7) (121 g) and triethylamine (10 mL) were dissolved in THF (800 mL) and added to a slurry of W-2 Raney nickel[33] (180 g) in THF-ethanol (350 mL, 1:1, vol.). The mixture was stirred at 30°C for 30 minutes and then overnight at room temperature. The slurry was filtered and the catalyst was rinsed with THF-ethanol. The filtrates were combined and concentrated *in vacuo* to a solid which on crystallization from absolute ethanol yielded **8** (83.5 g, 78%), m.p. 194.5-195.0°C; $[\alpha]_D$ +3.8° ($CHCl_3$). Literature: m.p. 193.5-194.0°C; $[\alpha]_D$ +4.1 ($CHCl_3$).[9]

1,5-Anhydro-4-O-β-D-glucopyranosyl-D-glucitol (2)

Compound **8** (56 g) was deacetylated with sodium methoxide[34] (1.0 N, 2.5 mL) in anhydrous methanol (400 mL) and chloroform (250 mL) at room temperature. Crystallization from 95% ethanol gave **2** (22 g, 78%): m.p. 203-205°C, $[\alpha]_D$ +28.0° (c 1.0, H_2O). Literature: m.p. 204.5-205.5°C, $[\alpha]_D$ +28.2° (c 1.5, H_2O).[10]

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (9)

Compound **2** (4.8 g), α,α-dimethoxytoluene (2.5 g), and *p*-toluenesulfonic acid (0.2 g) were dissolved in dry DMF.[22] The mixture was heated to 60°C under reduced pressure (75 mm Hg) on a rotary evaporator for four hours. The reaction solution was then cooled to room temperature, neutralized with pyridine (10 mL), concentrated *in vacuo* to a syrup, and acetylated[35] for ease of isolation. Seed crystals were obtained by column chromatography (Merck Kieselgel 60, 70-230 mesh; eluent petroleum ether (30-60°C)-acetone, 10:3, vol.). Crystallization of the product mixture from isopropyl alcohol-pyridine (50:1, vol.) gave **9** (5.3 g, 73%): m.p. 222-225°C; $[\alpha]_D$ -15.8° (c 1.107, $CHCl_3$); MS (EI) *m/e* 624 (M^+), 475 (M-149), 335 (glycone), and 273 (aglycone); ^{1}H-NMR ($CDCl_3$) δ 1.80-2.10 (15 H, m, -COC**H**$_3$), 5.44 (1 H, s, ArC**H**$(OR)_2$), 7.00-7.50 (5 H, m, C_6**H**$_5$-); ^{13}C-NMR ($CDCl_3$) *ppm* 19.3, 20.5, 20.6, 20.7, 20.9 (-CO**C**H_3), 61.8, 66.0, 66.8, 68.2, 71.6, 72.3, 73.6, 75.5, 75.9, 76.8, 78.2, 81.3 (C-2',C-

3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6, $CDCl_3$), 101.2 (Ar<u>C</u>H$(OR)_2$ and C-1'), 125.7, 127.8, 128.8 (aryl), 136.1 (C-1 aryl), 168.8, 169.0, 169.4, 169.6, 169.8 (-<u>C</u>OCH_3).

Anal. Calc. for $C_{29}H_{35}O_{15}$: C, 55.86; H, 5.65. Found: C, 55.63; H, 5.93.

1,5-Anhydro-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (10)

Compound **9** (11.4 g) was deacetylated with sodium methoxide[34] (1.0 N, 2.5 mL) in anhydrous methanol (400 mL) and chloroform (250 mL) at room temperature. Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave crude **10** (4.4 g, 58%): m.p. 95-115°C; $[\alpha]_D$+3.10° (<u>c</u> 0.803, DMF); MS (EI) *m/e* 265 (M-149), 251 (glycone), and 147 (aglycone); ^{1}H-NMR (CD_3SOCD_3) δ 5.66 (1 H, s, C_6H_5C<u>H</u>$(OR)_2$), 7.00-7.50 (5 H, m, C_6<u>H_5</u>-); ^{13}C-NMR (CD_3SOCD_3) *ppm* 60.4, 65.9, 67.6, 69.2, 69.7, 72.7, 74.3, 76.2, 79.4, 80.2 (C-2', C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6), 100.5, 100.6 (Ar<u>C</u>H$(OR)_2$), 103.0 (C-1'), 126.1, 127.7, 128.7 (aryl C), 137.4 (C-1 aryl).

Anal. Calc. for $C_{19}H_{26}O_{10}$: C, 55.06; H, 6.34. Found: C, 54.71; H, 6.35.

2,3,6-Tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (11)

Powdered sodium hydride (6.2 g, 2.5 eq) was added to a solution of **10** (8.6 g) in dry DMF (200 mL) under a nitrogen atmosphere.[24] The suspension was stirred for fifteen minutes at 0°C before the dropwise addition of allyl bromide (15 mL). The reaction was then stirred overnight at room temperature. Dry methanol was added until effervescence ceased. The reaction solution was then diluted with chloroform (500 mL) and pyridine (10 mL), washed with water (5 x 500 mL), dried over anhydrous potassium carbonate, and evaporated under reduced pressure. Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave **11** (7.5 g, 59%): m.p. 118-119°C; $[\alpha]_D$ +4.23 (<u>c</u> 0.763, $CHCl_3$); MS (EI) *m/e* 331 (glycone) and 267 (aglycone); ^{1}H-NMR (CCl_4) δ 5.00-5.40 (10 H, m, -CH=C<u>H_2</u>), 5.52 (1 H, s, ArC<u>H</u>$(OR)_2$), 5.60-6.10 (5 H, m, -C<u>H</u>=CH_2), 7.30-7.70 (5 H ,

m, $C_6\underline{H}_5$-); ^{13}C-NMR ($CDCl_3$) *ppm* 65.5, 68.0, 68.6, 71.8, 72.0, 73.4, 73.6, 73.8, 77.0, 77.4, 79.1, 80.6, 81.2, 81.6, 83.8 (C-2',C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6 and -$\underline{C}H_2$-CH=CH_2), 100.6, 100.7 (Ar$\underline{C}$H$(OR)_2$), 102.8 (d, C-1'), 115.4, 116.1, 116.6 (t, -CH=$\underline{C}H_2$), 125.1, 127.4, 128.0 (d, aryl), 134.1, 134.5, 135.2 (d, -$\underline{C}$H=CH_2), 136.9 (s, C-1 aryl).

2,3,6-Tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-6-O-tosyl-β-D-glucopyranosyl)-D-glucitol (13)

Compound **11** (5.8 g), reagent grade methanol (150 mL), and HCl (1N, 4 mL) were refluxed for approximately one hour. The reaction was monitored by TLC (silica, ethyl acetate). The solution was cooled to room temperature, neutralized with pyridine (20 mL), concentrated under reduced pressure, and purified by column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 50 cm; eluent chloroform-ethyl acetate, 10:1, vol.) to yield a syrup (4.9 g).

The syrup (4.0 g) was dissolved in anhydrous pyridine (150 mL), cooled to 0°C, and vigorously stirred while a solution of *p*-toluenesulfonyl chloride (2.2 g, 1.5 eq) in pyridine (50 mL) was added.[25] The reaction solution was allowed to come to room temperature, stirred for 24 hours, diluted with chloroform (200 mL), and poured into ice-water (200 mL). The chloroform and ice-water mixture was stirred for twenty minutes and separated. The chloroform phase was extracted with dilute acid (1.0 N HCl, 5 x 200 mL), washed with water (2 x 200 mL), dried over potassium carbonate, and concentrated *in vacuo* to a syrup. Column chromatography (Merck Kieselgel 60, 70- 230 mesh; 2.5 x 80 cm; eluent chloroform-ethyl acetate, 10:1, vol.) gave **13** (3.0 g, 56%) as a syrup: ^{1}H-NMR ($CDCl_3$) δ 2.43 (3 H, s, C$\underline{H}_3$Ar), 5.00-5.30 (m, -CH=C$\underline{H}_2$), 5.50-6.10 (5 H, m, -C$\underline{H}$=CH_2), 7.32 (2 H, d, J = 8.3 Hz, -$C_6\underline{H}_4$-), 7.78 (2 H, d, J = 8.2 Hz, -$C_6\underline{H}_4$-); ^{13}C-NMR ($CDCl_3$) *ppm* 21.4 (q, $\underline{C}H_3C_6H_4SO_3$-), 68.0, 68.9, 71.9, 72.0, 72.8, 73.3, 73.5, 73.8, 76.9, 77.3, 79.1, 81.2, 83.4 (C-2',C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6 and -$\underline{C}H_2$-CH=CH_2), 102.4 (d, C-1), 115.4, 116.0, 116.4 (t, -CH=$\underline{C}H_2$), 127.5, 127.7, 129.5 (d, aryl), 132.5 (s, **C**-4 aryl), 134.2, 134.5, 135.6 (d, -$\underline{C}$H=CH_2), 144.6 (s, $\underline{C}$-1 Ts).

2,3,6-Tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (5)

A solution of **13** (3.0 g) in freshly distilled DMF (50 mL) containing sodium allylate in allyl alcohol (0.5 N, 20 mL) was stirred at 75°C under a nitrogen atmosphere for four hours.[25] The reaction mixture was cooled to room temperature and concentrated *in vacuo* to dryness. The concentrate was taken up in chloroform (300 mL), washed with water (7 x 400 mL), dried over anhydrous potassium carbonate, and reconcentrated to a syrup. Column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 80 cm; eluent petroleum ether (b.p. 30-60°C)-acetone, 9:1, vol.) gave **5** (1.6 g, 64%) as a syrup: ^{1}H-NMR ($CDCl_3$) δ 4.90-5.30 (12H, m, =C$\underline{H}_2$), 5.50-6.10 (6 H, m, -C$\underline{H}$=CH_2); ^{13}C-NMR ($CDCl_3$) *ppm* 68.0, 70.2, 71.6, 71.9, 72.0, 72.3, 73.2, 73.6, 76.9, 77.1, 79.2, 81.3, 83.7 (C-2',C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, and C-6),102.4 (d, C-1'), 115.2, 115.8, 116.2, 116.5 (t, CH=$\underline{C}H_2$), 134.1, 134.6, 134.8, 135.7 (d, -$\underline{C}$H=CH_2).

Preparation of the Polymer-Supported 1,5-Anhydro-4-O-β-D-glucopyranosyl-D-glucitol (1)

Powdered sodium hydride (0.032 g, 1.33 mmol) was added to a solution of **5** (0.47 g) in freshly distilled THF (10 mL) under a nitrogen atmosphere. Iodomethylated polystyrene (1.0 g, 2.79 meq CH_2I/g) was added after twenty minutes and the suspension was stirred at room temperature for three days. The resin was isolated by filtration and washed with THF (2 x 200 mL), transferred to a soxhlet apparatus and extracted with THF and hexane, and dried *in vacuo* at 40°C.

Resin **6** (1.0 g) in freshly distilled DMF (10 mL), containing sodium ethoxide in ethyl alcohol (0.8 N, 50 mL), was stirred at room temperature for 48 hours to convert the unreacted iodomethyl and chloromethyl groups to methyl ethyl ethers. The resin was washed with methanol (4 x 100 mL), acetone (4 x 100 mL), THF (3 x 100 mL), and hexane (3 x 100 mL) and dried under vacuum at 40°C: IR cm^{-1} 1091 (C-O), 996, 923 (olefinic C-H).

Next, a slurry of **6** (2.12 g), tristriphenylphosphinerhodium chloride (0.45 g), and 1,4-diazabicyclo-[2,2,2]-octane (0.20 g) in a mixture of ethanol-benzene-water (75 mL, 7:3:1, vol.) was refluxed under a nitrogen atmosphere for eight hours.[29] The reaction was cooled to room tempera-

ture. The resin was washed with chloroform (3 x 50 mL), THF (3 x 50 mL), and hexane (2 x 50 mL), dried under reduced pressure, suspended in a mixture of dilute HCl (1.2 M, 10 mL) and acetone (50 mL), and refluxed for thirty minutes. The slurry was cooled to room temperature and filtered. The beads were washed with acetone (4 x 50 mL), THF (3 x 100 mL), and hexane (2 x 100 mL), and dried *in vacuo* at 50°C. IR: cm^{-1} 3600-3200 (O-H).

Degree of Polymer Loading: Method A, Ethanolysis

Samples of resin **1** were sealed in screw cap vials (4 mL) with HCl (3 N, 1.5 mL) and ethanol (1.5 mL) and heated to 100°C for 15, 30, and 48 hours. The mixtures were cooled to room temperature at the desired time and an aqueous solution of D-glucitol (5.39 mg/mL) was added gravimetrically as an internal standard. The solution was decanted and the resin was washed with water (2 x 4 mL) and methanol (3 x 4 mL). The washes were combined and concentrated to dryness under reduced pressure. The residue was diluted with distilled water and reconcentrated (5 x 1 mL), and acetylated with acetic anhydride (1.5 mL) and pyridine (1.5 mL). The acetylated products were diluted with ethyl acetate (10 drops) and analyzed by quantitative GLC employing D-glucitol as an internal standard (conditions: injector, 275°C; detector, 300°C; column A; 190°C for 20 min, 10°/min to 275°C, and held at 275°C).

Degree of Polymer Loading: Method B, Osmylation

A solution of osmium tetraoxide (0.0118 g) in THF (1.0 mL) was added to a suspension of **5** (≈0.035 g) in pyridine (1 mL).[30,31] The mixture was allowed to stand at room temperature for four hours. The solution was then removed by aspiration through a syringe needle. The beads were washed with THF (3 x 5 mL), benzene (3 x 5 mL), and hexane (3 x 5 mL), and dried under reduced pressure at 40°C. The procedure was repeated on unfunctionalized polystyrene. The loading was calculated according to equation:

$$\text{Osmylation loading} = \frac{\left(\frac{\text{Weight gain of resin 5}}{\text{g resin 5}}\right) - \left(\frac{\text{Weight gain unfunctionalized resin}}{\text{g unfunctionalized resin}}\right)}{\text{(Mw of osmylate ester)*(No. allyl ethers per supported model)}}$$

Point of Attachment

The point of attachment of the polymer to the disaccharide was determined by methylation-hydrolysis of the supported model. The hydrolysis products were analyzed as their alditol acetates. Freshly prepared sodium methylsulfinyl carbanion (1.25 N, 1.0 mL) was added to a slurry of **1** (0.025 g) in dry dimethyl sulfoxide (2 mL) under a nitrogen atmosphere.[36] The mixture was allowed to stand at room temperature for thirty minutes before the addition of a solution of methyl iodide (0.1 mL) in DMSO (1 mL). The slurry was sealed and allowed to stand at room temperature for six hours. The DMSO was removed by aspiration through a hypodermic needle (25G). The resin was washed with ethanol (3 x 15 mL) and hexane (2 x 10 mL), and dried *in vacuo* at 50°C. This procedure was repeated a total of six times, until IR analysis showed no OH stretch between 3700 and 3200 cm^{-1}.

The partially methylated carbohydrate was cleaved from the support by treatment with glacial acetic acid (0.5 mL), acetic anhydride (0.5 mL), and concentrated sulfuric acid (0.04 mL) at 20°C for 12 hours.[32] The slurry was filtered and the beads were washed with chloroform (2 x 4 mL). The filtrate and chloroform washes were poured into ice water and shaken for five minutes. The products were extracted with chloroform (2 x 5 mL). The chloroform extracts were washed with saturated aqueous sodium bicarbonate (2 x 10 mL) and water (2 x 10 mL), concentrated to dryness, deacetylated with sodium methoxide[34] (2.0 mL, 0.02 M), cooled to 0°C, and reduced with sodium borohydride[37] (0.025 g). The reduction mixture was acidified with acetic acid (3 drops), repeatedly concentrated to dryness under reduced pressure with methanol (5 x 5 mL) and acetylated with acetic anhydride[35] (2 mL). The acetylation solution was poured into ice water and extracted with chloroform (2 x 5 mL). The chloroform extracts were washed with saturated sodium bicarbonate (2 x 10 mL), evaporated to dryness, and the residue was dissolved in ethyl acetate (10 drops). The acetylated alditols were analyzed by GLC and GC/MS (conditions: 1. injector, 275°C; detector, 300°C; column A; 170°C for 15 min, 10°/min to 220°C, and held at 220°C; 2. injector, 200°C.; detector, 225°C; column B; 170°C for 40 min).

Authentic samples of the products expected from the glycosyl portion of the supported model, 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (**15**) and 1,5,6-tri-O-acetyl-2,3,4-tri-O-methyl- D-glucitol (**14**), were prepared in a similar manner from the known compounds methyl 4-O-benzyl-α-D-glucopyranoside (**3**) and methyl 6-O-trityl-α-D-glucopyranoside.

Benzyl Ether Stability

The degradation of methyl 4-O-benzyl-α-D-glucopyranoside (**3**)[16,17] was investigated using equipment and procedures described previously.[9,10] The degradation was monitored by quantitative GLC analysis of deionized, acetylated samples of the reaction (conditions: injector, 250°C; detector, 300°C; column A, 210°C for 20 min, 5°/min to 250°C, and held at 250°C).

Polystyrene Stability

The reactor system used consisted of five 4 mL capacity pipe bombs, a controlled temperature oil bath, and a rotating sample rack.[16] The bombs were washed with soap and water, rinsed with water and acetone, and dried at 101°C prior to use. Purified polystyrene beads (≈ 0.050 g) were added gravimetrically to each bomb and the bombs were heated to 101°C under vacuum for four hours, transferred to a nitrogen atmosphere, loaded with sodium hydroxide solution (3.6 g, 2.78 N), and sealed. The bombs were then placed in the sample rack and lowered into the oil bath at 170°C. At the reaction time of interest the contents of one reactor were analyzed.

The beads were isolated by filtration, washed with water until the filtrate remained neutral, and dried *in vacuo*. The recovered yields for five bombs ranged from 95 to 102%.

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