

# Solid-Phase Synthesis of Oligosaccharides. I. Preparation of the Solid Support. Poly[*p*-(1-propen-3-ol-1-yl)styrene]

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**Abstract:** Solid-phase synthesis of oligosaccharides requires the use of a saccharide derivative with a reactive leaving group at C-1, one hydroxyl protected by a readily removable blocking group, the remaining hydroxyls protected by a stable blocking group, and a resin which can be separated from the formed oligosaccharide derivative without removing the alcoholic substituents. A polystyrene resin with allyl alcohol functional groups has been prepared and a procedure for the solid-phase synthesis of oligosaccharides has been tested with an appropriately substituted glycosyl halide.

The use of insoluble, functionalized polymer supports has been extensively studied for the synthesis of polypeptides<sup>1-8</sup> and polynucleotides.<sup>9-11</sup> The process of sequential synthesis on solid support has many attractive features and should be applicable to the preparation of oligosaccharides.

The main advantage of the solid-phase method is that once the growing molecule is firmly attached to a completely insoluble resin, purification is effected at each intermediate step merely by filtering and washing. Furthermore, reaction rates can be increased by using a large excess of reagent which, after the reaction has gone to completion, can be easily separated.

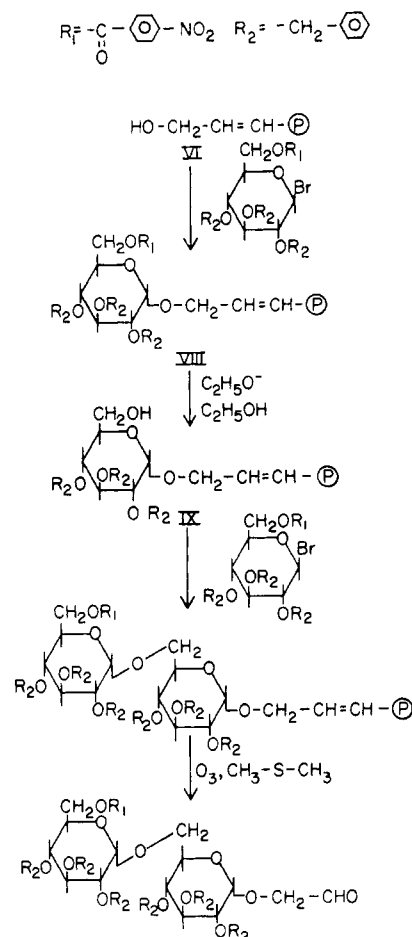
The requirements for application of this procedure to carbohydrates are the following.

1. The monomer must be a sugar derivative with a reactive leaving group at C-1, one hydroxyl group protected by an easily removable "temporary" blocking group,  $R_1$ , and the remaining hydroxyl groups protected by means of a "persistent" blocking group,  $R_2$ .

2. The solid substrate must contain an appropriate functional group to link to the glycosidic center. Separation of the solid substrate from the completed oligosaccharide must be possible under conditions which do not affect the persistent blocking groups, since their removal prior to or simultaneously with cleavage from the resin would cause formation of a hydrophilic molecule encaged in a network of hydrophobic insoluble resin.

Scheme I outlines our proposed preparation of a 1,6-linked oligomer of glucose. In the first step, the activated monomer unit (glycosyl bromide in which  $R_1 =$

Scheme I. Solid-Phase Synthesis of a Dissaccharide



*p*-nitrobenzoate and  $R_2 =$  benzyl) is coupled to a suitably functionalized allylic alcohol resin. In the next step, the temporary blocking group  $R_1$  is removed under mild conditions which leave the persistent blocking groups and the glycosidic linkage to the resin untouched. The following step involves reaction of a new monomer unit with the reactive end of the unit previously attached to the resin *via* a simple alcoholysis reaction. Further steps consist of sequential deblocking and coupling until an oligomer of the desired length is obtained. Finally, the oligomer is cleaved from the resin support by oxidation and the persistent blocking groups are removed from the soluble derivative.

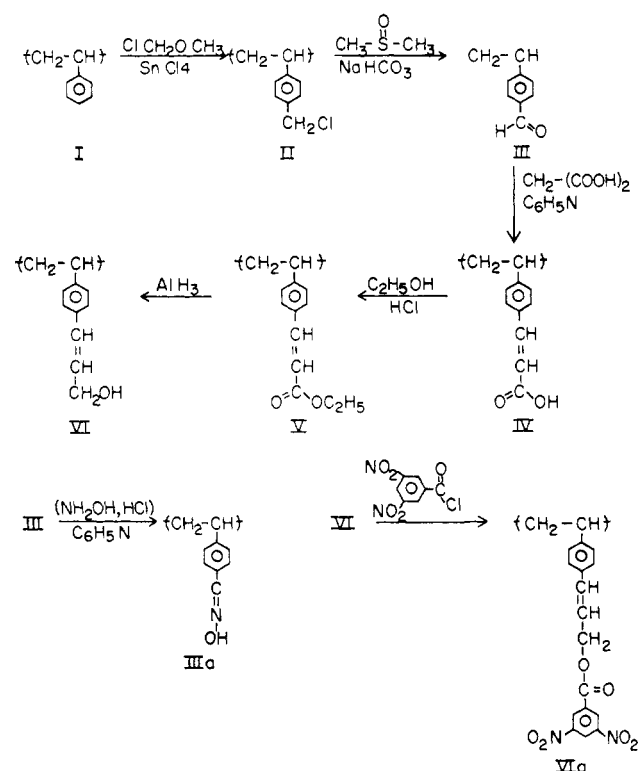
- (1) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963); **86**, 304 (1964).
- (2) R. B. Merrifield, *Biochemistry*, **3**, 1385 (1964).
- (3) R. B. Merrifield, *Science*, **150**, 178 (1965).
- (4) B. Gutte and R. B. Merrifield, *J. Amer. Chem. Soc.*, **91**, 501 (1969).
- (5) B. F. Gisin, R. B. Merrifield, and D. C. Tosteton, *ibid.*, **91**, 501 (1969).
- (6) S. Wang and R. B. Merrifield, *ibid.*, **91**, 6488 (1969).
- (7) M. Fridkin, A. Patchornik, and E. Katchalski, *ibid.*, **90**, 2953 (1968); **88**, 3164 (1966).
- (8) E. Bayer, H. Eckstein, K. Hägele, W. A. König, W. Brüning, H. Hagenmaier, and W. Parr, *ibid.*, **92**, 1735 (1970).
- (9) R. L. Letsinger and V. Mahadevan, *ibid.*, **87**, 3526 (1965); **88**, 5319 (1966).
- (10) R. L. Letsinger, M. H. Caruthers, and D. M. Jerina, *Biochemistry*, **6**, 1379 (1967).
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In the following discussion,  $\text{P-X}$  refers to a styrene-divinylbenzene copolymer in which some of the aromatic rings contain substituent X. Thus,  $\text{P-CH}_2\text{Cl}$  refers to a chloromethylated resin. It should be noted, however, that only a fraction (typically 10–15%) of the units carries the substituent X.

As is apparent above, the resin should contain a hydroxyl group for coupling with the glycosyl halide. A chloromethylated polystyrene-divinylbenzene copolymer<sup>1</sup>  $\text{P-CH}_2\text{Cl}$  has been used extensively in solid-phase peptide synthesis; from this resin,  $\text{P-CH}_2\text{OH}$  could easily be prepared. However, this resin would not be satisfactory, since cleavage of the oligomer would amount to a debenzoylation requiring the use of sodium and liquid ammonia. These conditions would cause total collapse of the resin and removal of the persistent blocking group, making cleavage and recovery of the desired product difficult.

Since other solid supports which have been prepared<sup>1,6,12</sup> for use in solid-phase peptide synthesis are not satisfactory for our purposes, we have developed a new resin prepared from commercial cross-linked polystyrene. This resin,  $\text{P-CH=CHCH}_2\text{OH}$ , contains approximately 10% allyl alcohol side chains. This type of side chain is very convenient, since it contains one site, the hydroxyl group, for coupling with the glycosyl halide and another site, the double bond, for oxidative cleavage of the finished oligomer under conditions to which the blocking groups and glycosidic linkages are resistant. The preparation of the resin  $\text{P-CH=CH-CH}_2\text{OH}$  is outlined in Scheme II.

Scheme II. Preparation of the Solid Support



The starting material was a commercially available polystyrene cross-linked with 1 or 2% divinylbenzene (Bio-Rad Laboratories). This resin, in the form of 200–400-mesh beads, was readily swollen by a number

(12) R. L. Letsinger, M. J. Kornet, V. Mahadevan, and D. M. Jerina, *J. Amer. Chem. Soc.*, **86**, 5163 (1964).

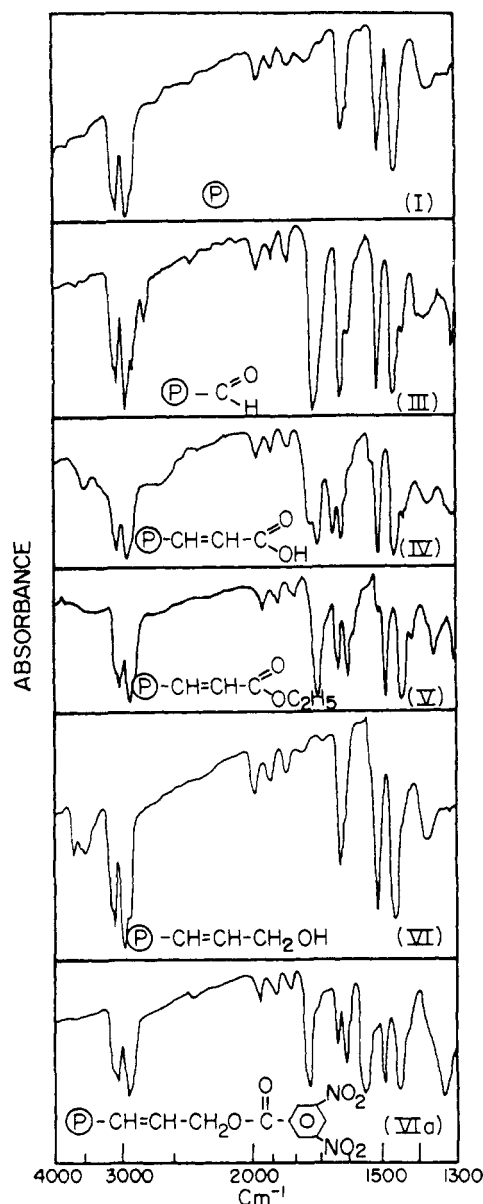


Figure 1. Infrared spectra of copolystyrene-2% divinylbenzene resin (I),  $\text{P-CHO}$  resin (III),  $\text{P-CH=CHCOOH}$  resin (IV),  $\text{P-CH=CHCOOC}_2\text{H}_5$  resin (V),  $\text{P-CH=CHCH}_2\text{OH}$  resin (VI), and  $\text{P-CH=CHCH}_2\text{O-C(=O)-C}_6\text{H}_3(\text{NO}_2)_2$  resin (VIa).

of solvents such as benzene, pyridine, dioxane, and chloroform, in which no major accessibility problems were encountered, and the resin could easily be penetrated by various reagents.

The degree of chloromethylation was kept in the range 10–15% to avoid creation of reactive end groups at more difficultly accessible sites. Oxidation of the chloromethylated material, II, with dimethyl sulfoxide<sup>13</sup> gave an aldehydic resin,  $\text{P-CHO}$ , III, which showed an intense carbonyl absorption at  $1690\text{ cm}^{-1}$  and an aldehydic CH stretching absorption at  $2700\text{ cm}^{-1}$  in the infrared spectrum (Figure 1). These values are in good agreement with those recorded by Ayres and Mann.<sup>13</sup> An estimation of the yield of the dimethyl sulfoxide oxidation was made by measuring the nitrogen content of the oxime IIIa derived from the formylstyrene polymer III. Conversion of III into its oxime

(13) J. T. Ayres and C. K. Mann, *Polym. Lett.*, **3**, 505 (1965).

seemed to be quantitative, since no carbonyl absorption could be detected in the infrared spectrum of IIIa. By this method, it was determined that the dimethyl sulfoxide oxidation proceeded in 75% yield, which is higher than the recorded yield<sup>14</sup> (~60%) for the oxidation of benzyl chloride. Condensation of the  $\oplus$ -CHO resin with malonic acid in the presence of pyridine proceeded smoothly to yield 90%  $\oplus$ -CH=CHCOOH resin, IV. The infrared spectrum of the latter resin showed a very broad hydroxyl absorption in the 2500–2800-cm<sup>-1</sup> region, an intense carbonyl absorption at 1695 cm<sup>-1</sup> which corresponds to hydrogen-bonded carboxyl groups, and a weaker band at 1725 cm<sup>-1</sup>, corresponding to free carboxyl groups. The main C=C olefin absorption was observed at 1625 cm<sup>-1</sup>, while a weaker band at 975 cm<sup>-1</sup> suggested a trans arrangement for the double bond. Other bands of interest included a CO stretching band at 1260 cm<sup>-1</sup>. The 90% conversion was estimated by titration of the carboxylic acid with butyllithium in benzene. This yield is comparable to the yield of a similar reaction run on benzaldehyde.<sup>15</sup>

The influence of the solvent medium on the availability of the functional groups is illustrated by the fact that the resin could not be titrated satisfactorily by either sodium hydroxide in 80% ethanol, sodium ethoxide in ethanol, or potassium hydroxide in diethylene glycol without requiring long refluxing periods prior to back-titration by acid. Thus, in sodium ethoxide-ethanol, only 25% of the carboxyl groups could be neutralized at room temperature.

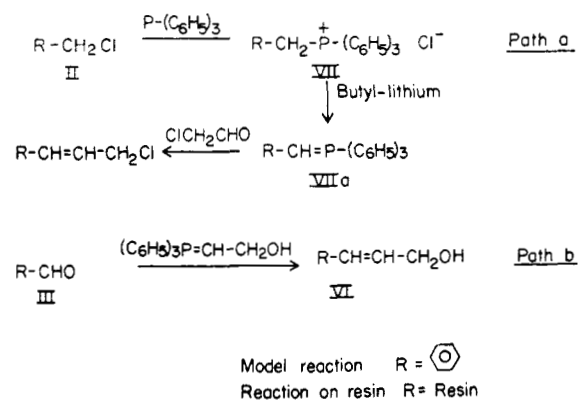
The reduction of the  $\oplus$ -CH=CHCOOH resin to the unsaturated alcohol  $\oplus$ -CH=CH<sub>2</sub>OH was first studied on model compounds. Aluminum hydride reduction<sup>16</sup> of ethyl cinnamate and cinnamic acid in anhydrous ether gave, respectively, 95 and 83% yields of cinnamyl alcohol, while very little saturated alcohol was detected by vapor phase chromatography. Since a better yield of unsaturated alcohol was obtained by reduction of the ester, IV was esterified to V, which could be characterized by its infrared spectrum featuring a strong carbonyl absorption at 1705 cm<sup>-1</sup>, a C=C stretch at 1630 cm<sup>-1</sup>, and a broad CO stretch at 1155 cm<sup>-1</sup>. Aluminum hydride reduction of V gave the desired resin,  $\oplus$ -CH=CHCH<sub>2</sub>OH, VI.

The infrared spectrum of VI showed no carbonyl absorption, indicating that the reduction was complete. The presence of a double bond in VI was confirmed by the rapid consumption of bromine when VI was shaken with a solution of bromine in carbon tetrachloride and by the formation of a black osmate ester upon addition of osmium tetroxide in pyridine. Reaction of VI with 3,5-dinitrobenzoyl chloride produced the ester VIa. Nitrogen analysis on VIa gave results confirming that all the carboxyl groups of V had been reduced.

Two other approaches toward the synthesis of similar resins are presented in Scheme III; both methods were first studied on model compounds, then applied to the resin.

The first approach (path a) takes advantage of the availability of the chloromethylated resin. In the model reaction benzyltriphenylphosphonium chloride was prepared in quantitative yield from benzyl chlo-

Scheme III



ride.<sup>17</sup> A Wittig reaction carried out on the phosphonium salt with inverse addition of the phosphorane to chloroacetaldehyde, freshly prepared from its trimer,<sup>18</sup> yielded cinnamyl chloride in ~50% yield. When this reaction sequence was applied to the chloromethylated resin, it was found that formation of the phosphonium salt was slow but could be forced to completion as evidenced by phosphorus analysis. Reaction of  $\oplus$ -CH<sub>2</sub>P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub> + Cl<sup>-</sup> with butyllithium produced the bright colored ylide which reacted rapidly with chloroacetaldehyde to yield the desired resin; 52% of the theoretical amount of triphenylphosphine oxide was collected, indicating that the yield of this reaction was comparable to that of the model reaction.

In the second approach (path b) benzaldehyde was used as a model for the formyl-substituted resin,  $\oplus$ -CHO. The reaction was carried out in one step by reaction of the alkoxide of hydroxyethylidenephosphorane with freshly distilled benzaldehyde. Unfortunately, the yields of cinnamyl alcohol were low (~30%) and when the reaction was applied to the resin, the product was found to contain some carbonyl groups.

The resin prepared above,  $\oplus$ -CH=CHCH<sub>2</sub>OH, was allowed to react at room temperature with an excess of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl- $\beta$ -D-glucopyranosyl bromide<sup>19</sup> in a dry solvent such as benzene or methylene chloride.

The reaction time was determined by model reaction of the glycosyl bromide with cinnamyl alcohol. The infrared spectrum of the resin-bound glycoside VIII, taken after rinsing and drying, exhibited a strong carbonyl absorption at 1720 cm<sup>-1</sup> and a CO stretching band at 1280 cm<sup>-1</sup>. Both bands are characteristic of the *p*-nitrobenzoyl ester substituent on carbon 6 of the sugar molecule. The yield of the coupling step, estimated from the gain in weight of the resin after coupling, varied from 70 to 91%, depending on the reaction conditions.

A solution of sodium ethoxide in ethanol-benzene was found to give excellent results for the removal of the temporary blocking group, as evidenced by the complete disappearance of the C=O absorption in the infrared spectrum of the resin (IX) after ester interchange.

After removal of the temporary blocking group, the resin containing a monomer unit with a free hydroxyl group on C-6 (IX) was condensed again with the protected glycosyl halide. The yield of this coupling step was found to be ~75% and the product (X) was

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(15) G. Lock and E. Bayer, *Chem. Ber.*, **72**, 1064 (1939).

(16) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

(17) K. Friedrich and H. Henning, *Chem. Ber.*, **92**, 2756 (1959).

(18) H. Gross, *J. Prakt. Chem.*, **4**, 99 (1963).

(19) T. Ishikawa and H. G. Fletcher, *J. Org. Chem.*, **34**, 563 (1969).

again characterized by the appearance of a strong carbonyl absorption.

A resin-bound protected trisaccharide was synthesized from X in comparable yield by repetition of the ester interchange and coupling reaction sequence.

These experiments demonstrate the feasibility of solid-phase oligosaccharide synthesis. The preparation of a suitable resin was an important step in this direction. In preliminary experiments, the oligosaccharides prepared by this method have been cleaved from the solid support by ozonolysis. We are now proceeding with the characterization of these products, optimization of the various yields, and preparation of longer and varied sequences.

## Experimental Section

Infrared spectra were taken on a Perkin-Elmer 137 infrared spectrophotometer in potassium bromide pellets and are shown in Figure 1. Elementary analyses were performed by Galbraith Laboratories and in this laboratory. The resin used was a copolymer of styrene-divinylbenzene in the form of 200–400 mesh resin beads containing 1 or 2% divinylbenzene and available commercially (Bio-Rad Laboratories: Bio-Beads S-X1 and S-X2). All the Wittig reactions were carried out in a drybox under nitrogen atmosphere.

**Preparation of  $\text{CH}_2\text{Cl}$  (II).** This polymer was prepared as described by Merrifield.<sup>1,2</sup> The degree of chloromethylation could be controlled by changes in temperature and reaction time. In most cases resins with a capacity of 1–1.7 mequiv/g were prepared.

**Preparation of  $\text{CH=O}$  (III).** Chloromethylated Bio-Beads S-X2 (45 g, capacity 1.05 mequiv/g) were stirred in 300 ml of dimethyl sulfoxide with 19 g of sodium bicarbonate for 6 hr at 155°. The resin was then collected on a glass filter, washed with dimethyl sulfoxide, hot water, and a 2:1 mixture of dioxane and water, then rinsed with dioxane, acetone, ethanol, methylene chloride, and benzene. A yield of 44 g of cream colored  $\text{CH=O}$  was obtained after drying at 100° under vacuum. Microanalysis indicated that this resin contained no chlorine. III (0.5 g) was transformed into its oxime by reaction with excess hydroxylamine hydrochloride (0.3 g) in 5 ml of pyridine for 6 hr at 90–100°. After washing with pyridine and the solvents mentioned above, the oxime IIIa was dried in a vacuum oven at 50°. By microanalysis it was shown that this resin contained 1.11% nitrogen which corresponds to 0.79 mmol of functional group/g of resin, indicating a yield of 75% for the dimethyl sulfoxide oxidation.

**Preparation of  $\text{CH=CHCOOH}$  (IV).** III (40 g) was suspended in 300 ml of pyridine. After addition of 7 g of malonic acid and 5 ml of piperidine, the mixture was stirred and heated to 80–90° for 1 hr, then brought to 110–115° for 3 hr. After cooling, the resin was collected on a glass filter and washed with benzene, dioxane, a 4:1:1 mixture of dioxane–HCl–water, a 2:1 mixture of dioxane–water, acetone, benzene, and methylene chloride, then dried at 100° under vacuum.

Titration was effected by treating 0.5 g of polymer with an excess of BuLi in benzene and back-titrating with 0.1 N  $\text{H}_2\text{SO}_4$ . This method was preferred over a titration in ethanolic medium which required a refluxing period prior to back-titration. IV was found to contain 0.71 mmol of functional groups/g of resin and was, therefore, obtained from III in 90% yield.

**Preparation of  $\text{CH=CHCOOC}_2\text{H}_5$  (V).** IV (40 g) was suspended in 160 ml of absolute ethanol. The mixture was heated to reflux and a current of dry HCl passed through the suspension for 2 hr. After cooling, the resin was collected on a glass filter, rinsed, and dried in a vacuum oven.

**Preparation of  $\text{CH=CHCH}_2\text{OH}$  (VI).** The reduction of IV and V to the corresponding unsaturated alcohol VI was first studied on model compounds. To a cooled solution of 0.09 mol of lithium aluminum hydride in 50 ml of anhydrous ether was added 0.03 mol of aluminum chloride. After dissolution of the aluminum chloride, the solution was brought to room temperature and a solution of 0.1 mol of cinnamic acid in 250 ml of anhydrous ether was added slowly. Reaction was allowed to proceed at room temperature for 30 min. The reaction mixture was then treated with water and 3 N HCl, and after work-up cinnamyl alcohol was isolated in 83% yield. The same reaction was carried out on ethyl cinnamate

with a 3:1 M ratio of lithium aluminum hydride to aluminum chloride. Cinnamyl alcohol was obtained in 95% yield.

The preceding reactions were also carried out as above with a 1:1 ratio of lithium aluminum hydride to aluminum chloride. Under these conditions, the reducing agent was the hydridoaluminum halide,  $\text{AlH}_2\text{Cl}$ ,<sup>20</sup> which proved to be very satisfactory and gave cinnamyl alcohol from cinnamic acid and ethyl cinnamate in 80 and 92% yields, respectively.

The yields were measured by weight of crystalline product and by vapor phase chromatography on a 6-ft 10% Carbowax 20M column in a Hewlett-Packard 5750 research chromatograph. In the reduction of ethyl cinnamate, the only side product found in significant quantity (~5%) was 3-phenylpropanol. In the case of the reduction of cinnamic acid, 3-phenylpropanol was also found (~7%) together with another side product, possibly 1-phenyl-2-propen-1-ol (~8–10%).

To a solution of 0.104 mol of aluminum hydride (made by addition of 0.078 mol of lithium aluminum hydride to 0.026 mol of aluminum chloride) in 50 ml of anhydrous ether was added a suspension of 39 g of resin V ( $\text{CH=CHCOOC}_2\text{H}_5$ ) in dry tetrahydrofuran at a rate sufficient to maintain gentle boiling. When the addition was complete, the mixture was stirred for an additional 30 min. The excess reducing agent was then destroyed by addition of an excess of 3 N HCl. The resin was then collected on a glass filter, washed, and dried.

The above reaction was also carried out on a sample of resin IV ( $\text{CH=CHCOOH}$ ). The product of the reaction had an infrared spectrum identical with that of VI.

Functional derivatives of VI were prepared as follows.

**3,5-Dinitrobenzoate Ester (VIa).** Resin VI (0.5 g) was swollen in 10 ml of pyridine and 0.5 g of dinitrobenzoyl chloride was added; the mixture was heated and stirred for 1 hr. The resin was then collected on a glass filter, rinsed, and dried. Microanalysis showed that VIa contained 1.76% nitrogen, indicating that at least 98% of the carboxyl groups of V had been reduced.

**Dibromo Derivative.** Resin VI (0.5 g) was suspended in 10 ml of a 9:1 mixture of  $\text{CCl}_4$  and  $\text{C}_2\text{H}_5\text{OH}$ . The mixture was treated with an excess of bromine in  $\text{CCl}_4$ . Bromine consumption was rapid and after 20 min the resin was collected, washed, and dried. Microanalysis showed that the reaction product contained 8.8% bromine, indicating that at least 87% of the alcohol groups in resin VI were allylic.

**Osmate Ester.** When a suspension of VI (0.25 g) in 2 ml of pyridine was treated with a solution of 50 mg of osmium tetroxide in 2 ml of pyridine, a black osmate ester was formed immediately.

**Preparation of  $\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_3 + \text{Cl}^-$  (VII).** Chloromethylated resin (32 g) containing 1.27 mmol of functional group/g was refluxed in 350 ml of dry dioxane containing 40 g of triphenylphosphine for 1 week. The resin particles were then collected on a glass filter, rinsed, and dried. Microanalysis of the resin showed that it contained 3% phosphorus, indicating that conversion of the chloromethylated resin to the phosphonium salt was quantitative.

**Preparation of Chloroacetaldehyde.** Monochloroethylene carbonate was prepared by chlorination of ethylene carbonate as described by Marder and Schuerch.<sup>21</sup> Pyrolysis of 20 g of monochloroethylene carbonate at 200° in the presence of 2 drops of triethylamine<sup>8</sup> yielded 10 g of crude chloroacetaldehyde which was collected as a green liquid. The crude material was redistilled and the fraction boiling at 82–88° was placed in the freezer compartment of a refrigerator and allowed to stand 2–3 days. The white solid (8 g) which was formed was dried under vacuum at room temperature and was identified as chloroacetaldehyde trimer (mp 85–87°). The trimer had no absorption in the 6- $\mu$  region of the infrared, attributable to a carbonyl function, and could be recrystallized from ethanol with little change in melting point. Distillation of this trimer immediately before use yielded chloroacetaldehyde, bp 85–87°.

**Preparation of  $\text{CH=CHCH}_2\text{Cl}$ .** The Wittig reaction of the phosphonium salt VII with butyllithium and chloroacetaldehyde was first studied on a model compound. To 6 g (0.0155 mol) of finely powdered benzyltriphenylphosphonium chloride,<sup>17</sup> suspended in 30 ml of dry benzene, was added 9.3 ml (0.0149 mol) of a 1.6 M butyllithium solution in hexane. The wine-colored ylide was then added slowly, with stirring, to 1.22 g (0.0156 mol) of freshly distilled chloroacetaldehyde dissolved in 10 ml of methylene chloride. The red coloration of the ylide disappeared immediately and after 3 hr

(20) E. C. Ashby and J. Prother, *J. Amer. Chem. Soc.*, **88**, 729 (1966).

(21) H. L. Marder and C. Schuerch, *J. Polym. Sci.*, **44**, 129 (1960).

of reflux the solution was concentrated on a flash evaporator. The bulk of the triphenylphosphine oxide was precipitated by addition of petroleum ether and filtered. The remaining solution was concentrated and distilled to yield 50% of the theoretical amount of cinnamyl chloride as a fraction boiling at 107–109° (12–13 mm).

This reaction was carried out on resin VII using 0.98 molar equiv of butyllithium and 1.1 molar equiv of chloroacetaldehyde for each molar equivalent of resin. To a stirred suspension of the phosphonium salt VII (0.016 equiv) in 100 ml of dry benzene was added 9.8 ml (0.0157 mol) of a 1.6 *M* solution of butyllithium in hexane. A deep red coloration developed immediately, indicating formation of the phosphorane VIIa. After 20 min, the suspension of VIIa was added slowly, with stirring, to 1.4 g (0.0178 mol) of freshly prepared chloroacetaldehyde in 10 ml of methylene chloride. The red coloration of the resin vanished immediately and the reaction mixture was refluxed for 3 hr, then allowed to stand overnight. The cream-colored resin was then collected on a glass filter and rinsed several times with benzene and ethanol to remove the triphenylphosphine oxide. The yield of the reaction, estimated from the weight of triphenylphosphine oxide recovered from the filtrate, was about 50% and, therefore, comparable to that of the model reaction.

**Preparation of  $\text{C}^{\ominus}\text{-CH=CHCH}_2\text{OH}$  by Wittig Reaction.** The model reaction was performed on benzaldehyde as follows. To a stirred suspension of 10 g (0.029 mol) of finely powdered 2-hydroxyethyltriphenylphosphonium chloride<sup>22</sup> in 200 ml of tetrahydrofuran was added 40 ml (0.056 mol) of a 1.4 *M* butyllithium solution in hexane. After the solution became homogeneous, 3 ml of freshly distilled benzaldehyde was added. The deep red coloration changed to orange immediately, and the reaction mixture was refluxed for 2 hr, then stirred overnight at room temperature. After the usual work-up, the product was distilled under reduced pressure to yield ~30% cinnamyl alcohol.

An identical procedure was used for the reaction of hydroxyethylidenephosphorane with  $\text{C}^{\ominus}\text{-CHO}$  (II). However, the reaction product, after washing and drying, was found to contain some residual carbonyl groups.

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**Preparation of 2,3,4-Tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl- $\beta$ -D-glucopyranosyl Bromide.** This monomer was obtained in 35% yield from 2,3,4-tri-*O*-benzyl-D-glucopyranose as described by Ishikawa and Fletcher.<sup>19</sup> The slightly colored material, as crystallized from ether, had mp 94–97° and was, therefore, used without further purification.

**Formation of the Glycosidic Linkage to the Resin.** To 1 g of resin VI was added a solution of 2 g of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl- $\beta$ -D-glucopyranosyl bromide in 9 ml of dry benzene containing 0.07 ml of pyridine (molar ratio of 1:4:1 for resin-monomer-pyridine). The mixture was then stirred slowly at room temperature and the reaction allowed to proceed for 60 hr in the dark. The resin (VIII) was collected on a glass filter, washed, dried, and weighed. The weight gain of 370 mg indicated a conversion of 90% based on the number of allylic alcohol groups available for reaction on the resin. Nitrogen microanalysis gave results indicating that the actual yield might be somewhat higher than 90%. Lower yields were obtained when either lower monomer concentrations or shorter reaction times were used.

**Preparation of a Disaccharide.** To 1.2 g of resin VIII, suspended in 10 ml of benzene, was added 5 ml of an 0.21 *N* solution of sodium ethoxide in ethanol. After stirring the mixture for 30 min, resin IX was collected on a glass filter, rinsed, and dried.

IX (1 g) was allowed to react with a solution of 1.5 g of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl- $\beta$ -D-glucopyranosyl bromide in 9 ml of dry benzene (molar ratio of 1:4 resin-monomer). The reaction was allowed to proceed in the dark with stirring for 60 hr. The resin X was then collected on a glass filter, washed, and dried. The yield of the coupling step, as estimated from the gain in weight of the resin (235 mg), was 75%. The presence of a new acyl group on the resin-bound disaccharide was again confirmed by the presence of a strong carbonyl absorption at 1720  $\text{cm}^{-1}$ .

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