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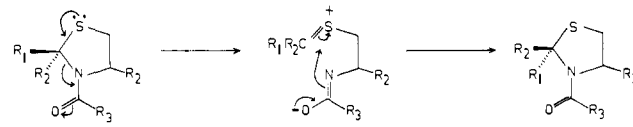

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Use of Polymers as Protecting Groups in Organic Synthesis. Application of Polystyrylboronic Acid to the One-Pot Synthesis of Acylated Carbohydrate Derivatives

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Abstract: The reactions of polystyrylboronic acid with various glycosides show that the polymer is an efficient and very selective protecting group for cis diols. Coupling of the glycosides to the polymer yields the most stable five- or six-membered ring boronate. Examples of diol protection in the formation of selectively acylated glycosides via one-pot reactions include the protection of 2,3-diols in methyl α-L-rhamnopyranoside and methyl α-D-mannopyranoside; 2,4-diols in methyl D-xylopyranosides, methyl β-D-ribopyranoside, and methyl α-D-glucopyranoside; 4,6-diols in methyl α-D-galactopyranoside and methyl α-D-glucopyranoside. In addition, the polymer can be used to protect one of the two 4,6-diol groupings of a disaccharide such as α,α-trehalose. The main advantages of the polymeric protecting group are its selectivity, its insolubility which allows all the reactions to be carried out rapidly and in one pot, and the extreme mildness of the conditions which are required for its use. In addition, the polymer is reusable without regeneration and no loss of activity is observed with repeated use.

Since Merrifield's development of the solid-phase synthesis of polypeptides,[1] functional polymers have been used as supports[2] in a number of other repetitive sequential type syntheses for the preparation of numerous peptides,[3] oligonucleotides,[4] or oligosaccharides.[5] Nonrepetitive syntheses using polymer supports and unprotected polyfunctional molecules have not been studied extensively. In such syntheses, the polymer acts as a protecting group for one of the functionalities of the starting material while reactions are carried out on the other reactive ends of the polymer-protected material. This technique has been applied successfully to the partial functionalization of glycosides[6] and to the monoprotection of other polyfunctional molecules.[7] In all of these cases, however, the polymer did not show any real selectivity. Of the advantages associated with the use of functional polymers in organic synthesis,[8] those related to enhanced purification through simple phase separations have undoubtedly been demonstrated most often and are at the basis of the solid-phase method of synthesis. Another advantage which has often been sought but seldom achieved is one which would make use of the great potential of the functional polymers to be regenerated to their former activity and recycled after use. Our approach to new polymeric protecting groups requires that the functional polymers be fully regenerable since otherwise their high cost

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might preclude their use in other than a few special cases. The regeneration of the polymer should be possible in as few steps as possible, preferably one or less.[9]

Additional features which are desirable for application of functional polymers as protecting groups in organic synthesis include a capacity sufficient for use on a practical scale, reactivity, and selectivity.

Among the protecting groups which are available for diols, boronic acids have shown remarkable selectivity in their reactions with carbohydrates[10-14] but have been little used owing to their difficult handling and the lengthy workup procedures which they require. In addition, the various alkyl- or arylboronic acids are relatively costly and usually difficult to recycle. In a preliminary communication,[15] we have shown that a polystyrylboronic acid resin can overcome these disadvantages, and, being fully regenerable, shows promise of becoming a valuable additon to the tools of the organic chemist. In earlier work,[16] 3-aminophenylboronic acid had been grafted to a carboxymethylcellulose to yield a supported boronic acid with a capacity of 0.2–0.6 mmol/g. This polymer was used effectively to form complexes of variable stabilities with numerous oligonucleotides containing free diols. Another interesting and somewhat similar application of our polystyrylboronic acid has been published recently.[17] In the present work we have examined in detail the use of this polymeric protecting group in the rapid one-pot selective acylation of various glycoside molecules possessing different stereochemical arrangements of their hydroxyls.

Results and Discussion

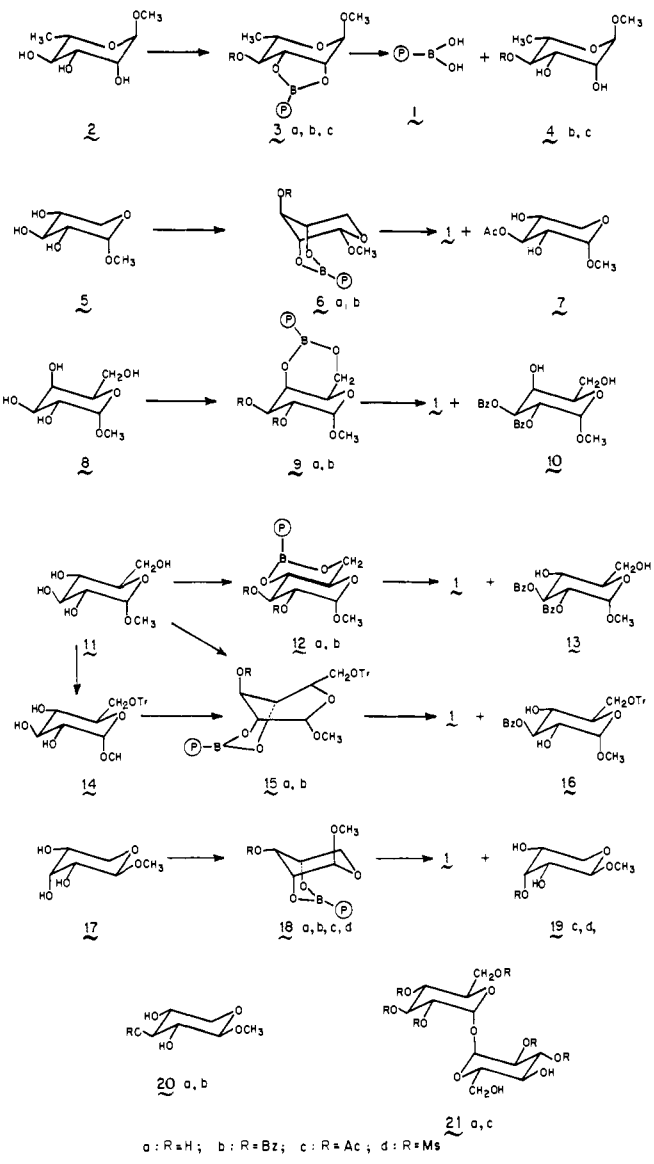
Preparation of the Polystyrylboronic Acid Resin. The functional polymer is best prepared by a simple four-step process involving first the aromatic bromination of polystyrene with bromine in the presence of a catalytic amount of a Tl(III) salt, a reaction[18] which can be controlled easily to yield the desired degree of functionalization and which produces a polymer substituted only in the para positions of the aromatic rings.[19] The remaining three steps can be carried out in one pot by a sequential addition and removal of reagents using a special flask fitted with inert gas and reagent inlets, a reflux condenser, and a fritted glass filter. The entire apparatus can be rotated from its normal upright position to effect filtrations. Thus, the brominated polymer was lithiated using *n*-BuLi in dry benzene and the resulting resin was allowed to react with an excess of trimethylborate. After removal of the liquid phase, the polymer was treated with aqueous acid to yield resin **1**.

An alternate, shorter route, involving the direct lithiation of polystyrene with tetramethylethylenediamine—*n*-BuLi, was not used extensively as the degree of functionalization was difficult to control and varied from preparation to preparation to a maximum of about 0.2.

The results which are reported here were obtained using a 1% cross-linked solvent-swellable resin with 1.1–3.2 mequiv of functional group per gram. Macroreticular resins were also tested but gave consistently lower yields than their swellable counterparts and were also more difficult to recycle owing to their mechanical fragility.

Protection of Cis Diols in Glycosides. Selectivity of the Reagent. All the reactions were carried out in one pot using a special flask. The glycosides studied were representative of cyclic polyols having one, two, or three cis 1,2- or 1,3-diol groupings. A typical reaction involving the polystyrylboronic acid resin for the preparation of **4b** from the methyl rhamnoside (**2**) is carried out as follows. The coupling reaction is effected in dry benzene or dry pyridine with azeotropic removal of the water which is liberated upon formation of the boronate. Once the reaction has taken place, any unbound **2** which remains in the soluble phase can be removed by a simple filtration and be recycled after evaporation of the solvent. The polymer-protected glycoside (**3a**) is attached to the solid support through its 2,3-cis diol grouping and has one free hydroxyl at C-4. Benzoylation of **3a** yields **3b** which can be purified through removal of the soluble phase. Finally, moist solvent is added to liberate **4b** from its solid support. The starting resin (**1**) is regenerated by the cleavage step and can be reused directly; thus, at least one batch of resin was used repeatedly in more than 12 reaction cycles without loss of activity and the only losses which were observed were mechanical. The NMR spectrum of **4b** included a doublet of doublets centered at δ 5.10 with $J_{3,4} = J_{4,5} = 9.5$ Hz for H-4, consistent with the triaxial arrangement of H-3, H-4, and H-5. Compounds **4b** and **4c** have been prepared in three steps via their isopropylidene derivative[20] but the yields in these preparations were only 30–35% vs. 83% using the polystyrylboronic acid. Similarly, the only protecting group which is presently available for the cis diol in positions 2 and 4 of methyl α-D-xylopyranoside is phenylboronic acid but this reagent only affords **7** in 42% yield[10] vs. 87% using the polymeric protecting group (Scheme I). The protection of the 4,6-diol systems of **8** and **11** can be easily achieved using **1** as well as with benzaldehyde or even a polymer-supported benzaldehyde.[6] That coupling of **1** with methyl α-D-galactopyranoside indeed occurs through the 4,6-diol can be seen easily on inspection of the NMR spectrum of the 4,6-di-*O*-*p*-tolylsulfonyl derivative of **10** in which H-2 and H-3

Scheme I



appear as a doublet of an AB quartet with coupling constants $J_{2,3}$ = 10.5 and $J_{1,2}$ = $J_{3,4}$ = 3 Hz in agreement with the proposed structure. While it is easy to protect the 4,6-diol of methyl α-D-glucopyranoside, at the present time there is no known protecting group available for the 2,4-diol grouping of **11.** Polymer **1** can be used efficiently for this purpose as shown in the one-pot synthesis of **16,** which can be prepared by successive tritylation of **11,** followed by reaction of **1** with the 2,4-diol, and benzoylation of the remaining hydroxyl on C-3. After filtration and washing of the solid phase to purify **15b,** addition of a moist solvent liberates the desired compound (**16**). The yield is low (38%) as the coupling step is made difficult by the presence of a bulky substituent on the C-6 hydroxyl, and owing to the fact that the uncoupled sugar is not recovered in this one-pot reaction. The yield of **16** can, however, be improved to over 80% if **14** is used as the starting material since most of the uncoupled material can be recovered before the benzoylation reaction.

The selective protection of the 2,4-diol grouping of methyl β-D-ribopyranoside **17** is a further example of the usefulness of polymer **1**. In this instance, the polyol possesses an all-cis 1,2,3-triol system which cannot be protected efficiently by formation of an isopropylidene derivative as the reaction yields several isopropylidene derivatives in both pyranose and furanose forms.[21] Only one example of protection of the 2,4-diol grouping of ribopyranosides can be found in the literature.[11] In this instance, phenylboronic acid was used, and **19c** was obtained in 30% yield. In contrast, we have obtained **19d** in 80% yield using polymer **1**. Polymer **1** can also be used to protect one of the two identical 4,6-diol groupings of α,α-trehalose;[22] in this synthesis, hexaacetate **21c** can be obtained in 59% yield and no product resulting from coupling to the polymer through both 4,6-diols can be found. In this reaction, as in the preparation of **16** from **11,** the loading of sugar on the support was low, presumably owing to the large bulk of the substrate which could not reach effectively all available sites of the resin.

In general, complete coupling of the sugar onto the resin was not obtained when the molar ratio of resin functional groups to glycoside was 1:1, and some uncoupled sugar usually remained in the soluble phase. This was not detrimental to the yields of the various reactions as the uncoupled sugars could easily be recovered prior to the addition of the acylating agent. Essentially complete coupling to the resin could, however, be achieved using an excess of resin as shown in the preparation of **19d** in which a 1.4:1 ratio of resin to riboside was used.

These results show clearly several of the interesting features of the polystyrylboronic acid as a diol protecting group. It is an extremely selective reagent which binds exclusively with cis diols to form five- or six-membered ring boronates. In contrast, alkyl- or arylboronic acids can sometimes bind trans diols through the formation of pyroboronates;[12] such pyroboronates are not expected to form in the case of **1** as the polymer matrix seems to be able to ensure at least some degree of isolation of the reactive sites. Another interesting feature of the polymer is the mildness of the conditions which are required for the coupling and cleavage reactions. This makes it ideal for the protection of sensitive molecules such as the ribosides or α,α-trehalose for which classical protecting groups may not be well suited.

We are presently investigating the use of polystyrylboronic acid for the rapid synthesis of several deoxy sugars and the solid-phase synthesis of some disaccharides.

Experimental Section

All the results which are reported herein were obtained using a solvent swellable 1% cross-linked styrene-divinylbenzene copolymer purchased from Bio-Rad Laboratories. The resin was washed thoroughly prior to functionalization as previously described.[18] The solvents used in the preparation of the boronic acid resin, in the coupling reactions, and in the functionalization of the polymer-bound glycosides were dried by distillation from calcium hydride (benzene, pyridine, cyclohexane) or from lithium aluminum hydride (tetrahydrofuran). All other chemicals were reagent grade and used without further purification unless specified. All the solvents used in the coupling reactions and washing steps were recovered after use and recycled. All the reactions were carried out in flasks fitted with glass filters. Infrared spectra were recorded using Beckman IR-20A or Unicam SP 1100 spectrophotometers. NMR spectra were recorded in $CDCl_3$ on a Varian HA 100 spectrometer at room temperature using a Me_4Si lock. Optical rotations were measured in a Perkin-Elmer 141 polarimeter using a 1-dm cell in the solvent indicated at 25 °C. Elemental analyses were performed by Galbraith Laboratories, Chemalytics Inc., or MHW Laboratories.

Preparation of Polystyrylboronic Acid (1). Several batches of polymer **1** were prepared by the bromination-lithiation procedure.[18] The functionalization was controlled by the bromination step and several resins with degrees of functionalization of 0.11-0.39 (1-3.2 mequiv of functional group per gram) were obtained. Alternatively resin **1** was prepared by direct lithiation of the polystyrene resin as follows. To a suspension of 10.0 g of washed 1% cross-linked resin (Bio-Beads SX-1) and 10.4 mL (7.9 g, 68 mequiv) of tetramethylethylenediamine (TMEDA) in 100 mL of dry cyclohexane, 56 mL (90 mequiv) of 1.6 M *n*-BuLi was added. The reaction was carried out under a nitrogen atmosphere in a specially designed reaction flask. The mixture was stirred at 65 °C for 4 h, and, after cooling to room temperature, the resin was filtered and washed with cyclohexane. Following the addition of 100 mL of dry THF, the stirred reaction mixture was cooled to −78°C and 15 mL (132 mequiv) of trimethylborate were added. After removal of the cooling bath the mixture was stirred at room temperature for another 30 min, then filtered, washed with THF, and treated with 25 mL of HCl, 50 mL of H_2O, and 100 mL of dioxane for 90 min at 60°C, then overnight at room temperature. The polystyrylboronic acid was then collected on filter and rinsed several times with each of the following: dioxane-water (1:1), water, THF-water (3:1), THF, acetone, and finally methanol. The infrared spectrum of the dry resin included a large hydroxyl absorption. Analysis: B, 1.88% for a degree of functionalization of 0.20 or a capacity of 1.74 mequiv/g. Other resins prepared by the same procedure contained as low as 0.8% B.

General Procedure for the Protection of Cis Diols in Glycosides. Three slightly different procedures were used in the preparation of the selectively substituted glycosides. The differences in the procedures were introduced to optimize the overall yields of the functionalization reactions. In procedure A the sugar dissolved in dry pyridine was coupled to the resin by an azeotropic distillation and the reaction mixture was acylated directly (bound and unbound sugar). The soluble impurities, which included some acylated unbound sugar, were removed by filtration followed by washing of the resin with a dry solvent such as benzene or pyridine. No efforts were made to reclaim the acylated sugar contained in the wash solvent. Cleavage was accomplished using a 4:1 acetone-water or THF-water mixture. The soluble phase was then concentrated to yield the crude product, which was purified as needed. The resin was then transferred to a tared flask and dried in vacuo. Its weight and IR spectrum were compared to those of the starting resin to ensure that the cleavage had been complete. In some instances a second cleavage was deemed necessary and was accomplished in a Soxhlet apparatus using an acetone-water or dioxane-water azeotrope. In procedure B the soluble phase was removed after the coupling step, the solvent was evaporated, and some pure uncoupled glycoside was recovered and recycled. The reaction was then continued as in A after addition of dry pyridine. This procedure gave yields superior to those obtained in procedure A but required slightly more time to carry out.

In procedure C after coupling and removal of the soluble phase as in B, dry pyridine was added and a second azeotropic distillation was carried out followed by filtration of the soluble phase. The soluble phases were concentrated to recover the unused glycosides and the reaction was then continued as above. The advantage of this procedure is that it allows for an almost complete recovery of unbound sugar and thus the yield of the overall reaction is higher.

Preparation of Methyl 4-*O*-Benzoyl-α-L-rhamnopyranoside (4b). The preparation was carried out according to method C in the special flask and under a nitrogen atmosphere. Methyl α-L-rhamnopyranoside (**2**, 1.05 g, 5.9 mmol) was added to a suspension of 3.2 g (6.1 mequiv) of resin **1** in 70 mL of dry pyridine. Coupling to the resin was achieved

by an azeotropic distillation which was continued until approximately 20 mL of solvent had distilled. During the distillation, efforts were made to prevent condensation of the distillate inside the reaction vessel. After cooling to room temperature the flask was rotated to remove the soluble phase by vacuum filtration. An additional 55 mL of dry pyridine was then introduced in the flask to soak the solid phase and a second azeotropic distillation was carried out in which approximately 10 mL of distillate was collected. The soluble phase was again removed under vacuum and evaporation of the combined soluble phases led to the recovery of 0.22 g of uncoupled **2**. The solid phase was again soaked in 40 mL of dry pyridine, 4 mL of benzoyl chloride was added, and the mixture was stirred overnight at room temperature.

After filtration, the solid phase was washed with dry pyridine to remove the soluble impurities. Cleavage of the product **4b** from its support was accomplished by addition of 20 mL of acetone-water (4:1). The mixture was stirred for 30 min, then the soluble phase was filtered and the operation was repeated with several small portions of acetone-water (4:1) to complete the cleavage of **4b.** After drying, the resin, which weighed 3.18 g, was recycled. After evaporation of the acetone-water, crude **4b** was obtained as a thick oil which solidified on cooling. The crude product was purified by passing it through a short column of silica gel using ethyl acetate-petroleum ether (2:3) for elution. Pure **4b** was obtained as a white, crystalline material (1.09 g, 83%) which after recrystallization from ether-petroleum ether had mp 114–115 °C and $[\alpha]_D$ −112° (*c* 1, chloroform). Anal. C, 59.68; H, 6.45. The NMR spectrum of **4b** included signals centered at δ 8.02 (m, 2 H, benzoyl), 7.46 (m, 3 H, benzoyl), 5.10 (dd, 1 H, J = 9.5 Hz, H_4), 4.75 (s, 1 H, H_1), 4.01 (m, 3 H, H_2, H_3, H_5), 3.41 (s, 3 H, OCH_3), 1.29 (d, 3 H, J = 6 Hz, $-CH_3$).

Preparation of Methyl 4-*O*-acetyl-α-L-rhamnopyranoside (4c). The preparation was carried out according to procedure A using 1.06 g (5.95 mmol) of **2** with 2.03 g (6.4 mequiv) of **1** in 60 mL of dry pyridine. After coupling by azeotropic distillation of approximately 20 mL of solvent, the stirred mixture was treated with 5 mL (49 mmol) of acetic anhydride at room temperature for 1 h and at 50 °C for 15 min. The soluble phase was then removed by filtration and the solid phase washed with dry pyridine to remove all soluble impurities and byproducts. After cleavage with several portions of 4:1 acetone-water mixture the soluble phase was evaporated to yield an oil which was dissolved in chloroform, and resin **1** was dried and weighed 2.025 g. The chloroform solution was washed with aqueous sodium bicarbonate, then water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the product which was crystallized from ether-petroleum ether (0.86 g for 65% yield). The crystalline material had mp 106–109 °C and $[\alpha]_D$ =90 (*c* 1, chloroform). Richardson and Williams[20] report mp 112–116 °C and $[\alpha]_D$ −55 (H_2O).

Anal. C, 49.18; H, 7.41. The NMR spectrum included signals centered at δ 4.82 (dd, 1 H, J = 9.5 Hz, H_4), 4.70 (s, 1 H, H_1), 3.74 (m, 5 H, 2 -OH, H_2, H_3, H_5) 3.38 (s, 3 H, $-OCH_3$), 2.13 (s, 3 H, acetyl), 1.21 (d, 3 H, J = 6 Hz, CH_3).

Preparation of Methyl 3-*O*-benzoyl-β-D-xylopyranoside (20b).[10] The reaction was carried out by procedure B using 1.20 g (7.3 mmol) of methyl β-D-xylopyranoside (**20a**) with 3.80 g (7.24 mequiv) of resin **1** in 70 mL of dry pyridine. After coupling by azeotropic distillation as above, the soluble phase was removed and evaporated to yield 0.24 g of uncoupled methyl β-D-xylopyranoside. The polymer-bound xyloside was then suspended into 50 mL of dry pyridine and 5 mL of benzoyl chloride was added at room temperature. After the mixture was stirred overnight, the soluble phase was removed and the resin was washed with dry pyridine. Cleavage of the monobenzoylated xyloside from its support was accomplished using several portions of acetone-water (4:1). After drying, resin **1** weighed 3.825 g. After evaporation of the solvent the product was obtained as an oil which was purified by passing it through a short column of silica gel using ethyl acetate-petroleum ether (1:1) for elution to yield **20b** which was crystallized in needles from ether-petroleum ether (1.21 g, 77%). **20b** had mp 131–133 °C and $[\alpha]_D$ −15.6° (*c* 1, dioxane). Anal. C, 58.19; H, 5.91. The NMR spectrum showed signals centered at δ 8.03 (m, 2 H, benzoyl), 7.43 (m, 3 H, benzoyl), 5.08 (t, 1 H, J = 7.6 Hz, H_3), 4.35 (d, 1 H, J = 6.5 Hz, H_1), 3.92 (m, 3 H, H_2, H_4, OH), 3.54 (s, 3 H, $-OCH_3$), 3.14 (m, 3 H, 2 H_5, OH).

Preparation of Methyl 3-*O*-acetyl-α-D-xylopyranoside (7).[10] The reaction was carried out using 1.1 g (6.2 mmol) of methyl α-D-xylopyranoside (**5**) with 2.2 g (6.3 mequiv) of resin **1** in 50 mL of dry pyridine. Following procedure C, two azeotropic distillations were carried out and 0.19 g of **5** was recovered unchanged by evaporation of the soluble phase. The solid phase (**6a**) was then acetylated using 5 mL of acetic anhydride in 30 mL of dry pyridine with overnight stirring. After the usual workup as in the preparation of **4c**, the product (0.92 g for a yield of 87%) was crystallized from ethyl acetate-heptane. After recrystallization from the same solvent system **7** was obtained as white needles with mp 120–122 °C and $[\alpha]_D$ +148 (*c* 1, chloroform).

Anal. C, 46.82; H, 7.12. The NMR spectrum of **7** included signals centered at δ 5.01 (t, 1 H, J = 8.2 Hz, H_3), 4.72 (d, 1 H, J = 3.5 Hz, H_1), 3.68 (m, 4 H, H_2, H_4, 2 H_5), 3.47 (s, 3 H, $-OCH_3$), 2.83 (s, 2 H, 2 -OH), 2.18 (s, 3 H, acetyl).

Preparation of Methyl 2,3-Di-*O*-benzoyl-α-D-galactopyranoside (10). The reaction was carried out using procedure A with 0.82 g (4.2 mmol) of methyl α-D-galactopyranoside (**8**) and 3 g (4.2 mequiv) of resin **1** in 55 mL of dry pyridine. Following the removal of 15 mL of solvent by azeotropic distillation 5 mL of benzoyl chloride was added to **9a** and the mixture was stirred at room temperature overnight. The soluble phase was then separated and resin **9b** was washed with dry pyridine. The cleavage reaction was carried out using several portions of 4:1 acetone-water but was found to be harder than usual as some glycoside remained on the resin. After an additional cleavage using a dioxane-water azeotrope in a Soxhlet apparatus the resin still weighed 3.21 g. Concentration of the soluble phases collected during the cleavage procedure gave an oil which was purified by passing it through a column of silica gel. The final product (0.88 g for a 52% yield) was a clear oil which failed to crystallize and had $[\alpha]_D$ +200° (*c* 1, chloroform).

Anal. C, 62.36; H, 5.12. The NMR spectrum of **10** included signals centered at δ 7.98 (m, 4 H, benzoyl), 7.42 (m, 6 H, benzoyl), 5.70 (m, 2 H), 5.21 (m, 1 H), 4.48 (m, 1 H), 4.02 (m, 3 H, $-CH_2-$ and H_5), 3.45 (s, 3 H, $-OCH_3$), 3.26 (s, 1 H, -OH), and 2.68 (s, 1 H, -OH). The product was further characterized by preparation of the known[23] methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-(*p*-tolylsulfonyl)-α-D-galactopyranoside.

To a solution of 0.45 g (1.12 mmol) of methyl 2,3-di-*O*-benzoyl-α-D-galactopyranoside in 6 mL of dry pyridine was added 0.55 g (2.9 mmol) of 4-toluenesulfonyl chloride. The mixture was stirred at 50 °C for 2 days, cooled to room temperature, then poured over 15 mL of saturated aqueous Na_2CO_3. The oil which formed was dissolved in $CHCl_3$, and the solution was decolorized with charcoal after washing with H_2O. After drying over magnesium sulfate, the solvent was evaporated to yield 0.59 g (70%) of crude material which was recrystallized from chloroform-ether-methanol to give fine crystals melting at 128.5–130 °C with $[\alpha]_D$ +149° (*c* 0.75, $CHCl_3$). NMR spectrum: δ 7–8 (m, 18 H, benzoyl and aromatic tosyl), 5.72–5.40 (d of quartet, 2 H; H-3 centered at 5.63, H-2 centered at 5.49; $J_{2,3}$ = 10.5, $J_{1,2}$ = $J_{3,4}$ = 3 Hz), 5.3 (d with fine structure suggesting dd, 1 H, H-4, $J_{4,5}$ = $J_{4,3}$ = 3 Hz), 5.1 (d, 1 H, H-1, $J_{1,2}$ = 3 Hz), 4.43–4.03 (m from ABCX system with apparent d of 2 H at 4.08, and apparent q of 1 H at 4.32, H-6, H-6, H-5), 3.38 (s, 3 H, OCH_3), 2.48 and 2.24 (s, 3 H each, CH_3 on C-6 and C-4).

Preparation of Methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside[6] (13). The coupling reaction was carried out with procedure C using 1.522 g (7.84 mmol) of methyl α-D-glucopyranoside (**11**) with 4.1 g (7.8 mequiv) of resin **1** in 75 mL of dry pyridine. The uncoupled sugar recovered after two azeotropic distillations weighed 0.41 g indicating that 1.112 g (5.73 mmol) of **11** had become attached to the resin. After benzoylation of the remaining hydroxyls of **12a** using 4 mL of freshly distilled benzoyl chloride in 50 mL of dry pyridine, the soluble phase was removed and **12b** was washed with dry pyridine. Cleavage of **13** from its support was carried out as usual with several portions of 4:1 acetone-water to yield **13** as an oil which was purified by passing it through a short column of silica gel. Resin **1** was dried and weighed 4.18 g. Pure **13** (2.027 g for an 88% yield) was obtained as a thick, clear oil which could not be crystallized and had $[\alpha]_D$ +162.7° (*c* 1, chloroform). Anal. C, 62.41; H, 5.36. The NMR spectrum of **13** included signals centered at δ 7.96 (m, 4 H, benzoyl), 7.36 (m, 6 H, benzoyl), 5.74 (t, 1 H, J = 8.5 Hz, H_3), 5.20 (m, 2 H, H_1, H_2), 3.95 (m, 4 H, $-CH_2-$, H_4, H_5), 3.46 (s, 3 H, $-OCH_3$), 3.26 (s, 1 H, OH), 2.22 (s, 1 H, -OH).

Preparation of Methyl 3-*O*-Benzoyl-6-*O*-trityl-α-D-glucopyranoside (16). A. One-Pot Synthesis from 11. To a stirred solution of 0.8 g (4.12 mmol) of methyl α-D-glucopyranoside in 55 mL of dry pyridine was added 2 g (7.2 mmol) of trityl chloride. The reaction mixture was refluxed for 2 h and the disappearance of **11** was followed by TLC.

Once no starting glucoside seemed to remain, 2.2 g (4.18 mequiv) of resin **1** was added and approximately 20 mL of solvent was removed by azeotropic distillation. After addition of 5 mL of freshly distilled benzoyl chloride the mixture was stirred at room temperature overnight. The soluble phase was then removed and the solid phase **15b** was washed with dry pyridine. Cleavage of the desired product (**16**) from the resin was carried out using several portions of 4:1 acetone-water. The resin after drying weighed 2.19 g. After evaporation of the acetone-water an oil was obtained which was dissolved in chloroform and washed with 5% aqueous bicarbonate, rinsed with water, and dried over anhydrous magnesium sulfate. After filtration and evaporation of the chloroform, **16** was crystallized from ethyl acetate-petroleum ether. The product (0.85 g for a yield of 38%) had mp 128–130 °C and $[\alpha]_D$ +55.7° (*c* 1, chlorofrom). Anal. C, 72.98; H, 6.21.

NMR spectrum: δ 8.2–7.1 (m, 20 H, trityl and benzoyl), 5.07 (dd, 1 H, $J_{2,3} = J_{3,4} = 8.5$ Hz, H_3), 4.32–3.0 (bm, 11 H, with OCH_3 at 3.50).

B. Preparation from 14. The coupling reaction was carried out with procedure B using 1.53 g (3.51 mmol) of methyl 6-*O*-trityl-α-D-glucopyranoside[24] (**14**) and 1.88 g (4.90 mequiv) of resin **1** in 80 mL of dry pyridine. After removal of water by azeotropic distillation 0.87 g (1.98 mmol) of uncoupled **14** was recovered. After addition of 5 mL of benzoyl chloride in dry pyridine (40 mL) the mixture was stirred overnight at room temperature. The soluble phase was then removed and the solid phase (**15b**) was washed with dry pyridine. After cleavage of the product (**16**) from the resin by reaction with 4:1 acetone-water, the solvent was evaporated and the oil taken up in chloroform. The chloroform solution was then washed with 5% aqueous bicarbonate, rinsed with water, and finally dried over magnesium sulfate. After evaporation of the solvent 0.68 g of **16** was obtained for a yield of 82%. The product was identical with that obtained above.

Preparation of Methyl 3-*O*-Methanesulfonyl-β-D-ribopyranoside (19d). The reaction was carried out using procedure C with 1.84 g (11.2 mmol) of methyl β-D-ribopyranoside (**17**) and 9.65 g (15.6 mmol) of resin **1** in 130 mL of dry pyridine. After azeotropic distillation of 30 mL of pyridine the resin was filtered and 110 mL of dry pyridine was added. A second azeotropic distillation was carried out to remove another 20 mL of pyridine and resin **18a** was again separated from the liquid phase. Concentration of the pyridine phases gave 0.055 g of unchanged **17.** Mesylation of **18a** was achieved by addition of 1.3 mL of methanesulfonyl chloride to the stirred suspension of **19a** in 75 mL of dry methylene chloride and 2.9 mL of triethylamine at 0 °C. After stirring for 30 min the liquid phase was removed and discarded. The resin was then washed with dry methylene chloride. Cleavage of the product from the resin was carried out as usual by soaking **18d** in several portions of a mixture of THF-water (7:1), then in acetone-water (4:1). After cleavage the dry resin weighed 9.86 g and had an infrared spectrum which showed no new absorption. Concentration of the soluble phase after cleavage gave an oil which showed several spots on thin layer chromatography including one corresponding to the starting sugar (**17**). Purification of the crude product was accomplished on a column of 90 g of silica gel using ethyl acetate-petroleum ether for elution. The main fraction which was collected contained 1.84 g of the desired product (**19d**). In addition 0.29 g of starting material (**17**) was recovered for an overall yield of 80% of **19d**. The product crystallized from chloroform in long needles with mp 116–117 °C dec, $[\alpha]_D$ −87° (*c* 1, chloroform).

Anal. C, 34.61; H, 5.75; S, 13.34. The NMR spectrum of **19d** recorded in D_2O at 60 °C with an acetone lock included signals centered at δ 3.15 (s, 3 H, OSO_2CH_3), 3.34 (s, 3 H, OCH_3), 3.67 and 3.97 (m, 4 H), 4.54 (d, 1 H, $J_{1,2} = 6$ Hz, H-1), 4.89 (dd, 1 H, $J_{2,3} = J_{3,4} = 3$ Hz, H-3). The values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ are not surprising since it is known that methyl β-D-ribopyranoside is a mixture of about equal amounts of the two chair forms,[25] and it can be expected that the spectrum of **9d** will also reflect this type of equilibrium.

Preparation of 2,3,4,6,2′,3′-Hexaacetyl-α,α-trehalose (21c).[22] The reaction was carried out with procedure C using 1.5 g (3.97 mmol) of α,α-trehalose dihydrate and 2.10 g (4.0 mequiv) of resin **1** in 70 mL of dry pyridine. Following coupling and washing of the resin as usual, 0.884 g (2.34 mmol) of α,α-trehalose was recovered unchanged in the soluble phase. After acetylation of the resin-bound trehalose using 6 g of acetic anhydride in 30 mL of dry pyridine the mixture was worked up as usual with cleavage using 4:1 acetone-water. The resin after cleavage weighed 2.07 g. The soluble phase was evaporated to yield an oil which was dissolved in acetone and washed rapidly with aqueous sodium bicarbonate, then water, and dried over anhydrous magnesium sulfate. After evaporation of the solvent the product (0.57 g for a 59% yield) was crystallized from ethanol. Compound **21c** had mp 105–106 °C and $[\alpha]_D$ +132.6° (*c* 0.5, chloroform). Anal. C, 48.44; H, 5.91. The NMR spectrum of **21** included signals centered at δ 5.18 (m, 7 H), 3.83 (m, 7 H), 2.96 (s, 2 H, hydroxyls), 2.13 (m, 18 H, 6 acetyls).

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