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Polystyrylboronic acid - a new polymeric protecting group for the selective functionalization of polyols

by

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for the degree of

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in
Chemistry

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Ottawa, Ontario, Canada

1977

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ABSTRACT

A regenerable polystyrylboronic acid resin has been prepared for the selective functionalization of polyols. The resin reacts with a diol group of a polyol to form a resin-bound cyclic boronate. Both the coupling and cleavage steps are performed under very mild conditions (removal or addition of water) and the resin is regenerated directly by the cleavage step.

Monoacyl derivatives of some acyclic polyols and some partially acylated carbohydrate derivatives have been prepared efficiently on the resin without the need for any purification of intermediates. In addition, the polystyrylboronic acid resin which exhibits a high selectivity for cis diol systems, can be used in the separation of cis and trans diol mixtures such as the cyclohexanediols by affinity chromatography.

INTRODUCTION

New applications of polymers in organic synthesis have resulted from the development of the solid phase method of synthesis by Merrifield[1] in the early sixties. Thus in recent years polymers have been used as supports in sequential syntheses of polypeptides[2,3], polynucleotides[4-6] and polysaccharides[7], as reagents or protecting groups in simple organic reactions and as supports for catalysts. In all these applications the advantages associated with the use of polymers are related to their insolubility in the reaction mixture.

In a reaction involving a polymeric reagent , a large excess of the polymer can be used to ensure maximum conversion without adversely affecting the separation of the desired product from the reaction mixture. The excess reagent and the polymeric by-products can be eliminated by filtration, leaving the desired product in the filtrate.

In a reaction involving a polymer as a protecting group , the starting material is attached covalently to the polymer while any unreacted material and other by-product can be washed from the polymer. The polymer-protected product then remains attached to its support through one or more synthetic steps, which can sometimes be carried out in "one pot" without intermediate purifications, until it is finally removed by action of a suitable reagent. The desired product is thus obtained in the soluble phase while

the insoluble polymer is removed by filtration.

Other advantages include the possibility of using polymers as "high dilution reagents"[8,9] and the quantitative recovery and regeneration of the polymer, via a simple reaction, after its use.

Among the protecting groups available for diols, boronates are little used due to their instability and difficulty of isolation. A brief review of the literature indicates that boronates could be useful in a number of synthetic applications as alternatives to the benzylidene and isopropylidene blocking groups. The use of boronates in such cases would be facilitated by their attachment to an insoluble polymer.

The boronate obtained by reaction of a diol with an insoluble boronic acid should be easily separated from excess reagent and by-products. In addition, reaction of a polyol with a bulky polymer may be expected to yield products different from those obtained from a low molecular weight boronic acid. This may result in additional advantages in selectivity of the reagent (choice of the site of reaction). Finally a polymeric boronic acid should be superior to its monomeric counterpart in its ease of recovery and recycling after use.

The solid phase method of synthesis developed by Merrifield[1,10,11] for polypeptides involves attachment of an amino acid to an insoluble polystyrene-type resin and the extension of the peptide chain by sequential reactions

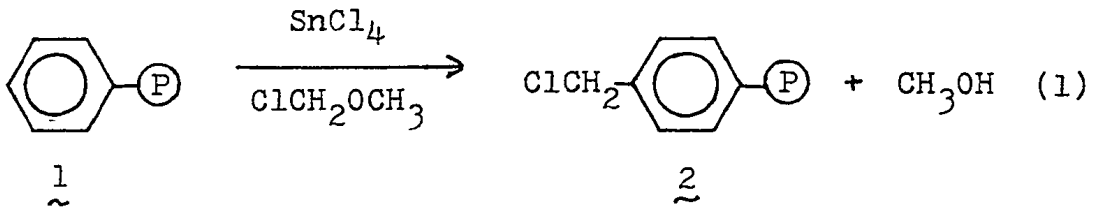
with amino acids.

The first step in such a synthesis is the attachment of the terminal amino acid to the insoluble polymer support. The link between them must be sufficiently stable to remain intact throughout the deblocking, coupling and blocking reactions but sufficiently labile to be cleaved at the end of the procedure without altering the sequence of the newly synthesized peptide. The next step involves the reaction between a monomer, with one of its reactive centers blocked and the other available for coupling, and the deblocked end of the polymer-bound substrate. After each step the resin can be washed free of unreacted monomer and by-products. The deblocking and coupling reactions are repeated until the desired product has been obtained. In order to ensure that the correct peptide has been synthesized, it is essential that all of the reactions occur in 100% yield. Finally, the peptide is cleaved from its polymer support by treatment with a suitable reagent.

The terminal amino acid can be attached to the polymer support in various ways. Usually attachment to the resin is through the carboxyl group of the C-terminal amino acid. In the original Merrifield procedure the link was in the form of a modified p-alkylbenzyl ester.

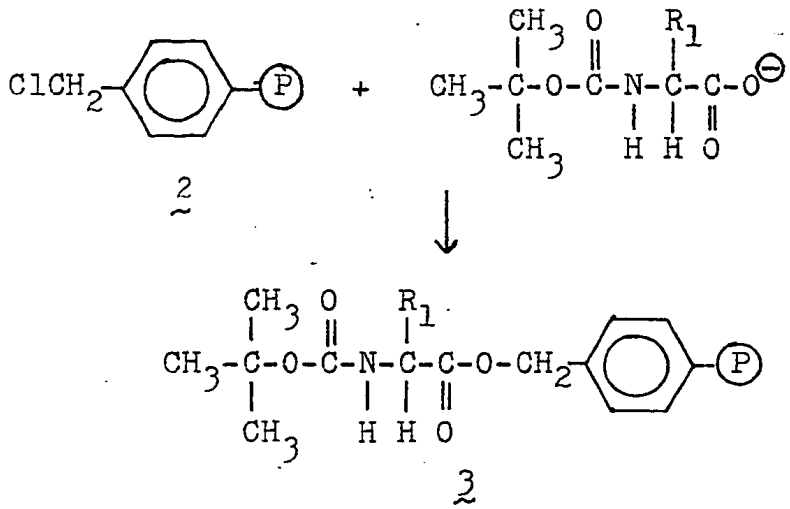
Polystyrene resins are used almost exclusively in polypeptide synthesis since they can be easily functionalized to the appropriate derivative. Also they can be cross-linked to form insoluble beads which are not degraded

by the many chemical reactions and washings required to make a long chain peptide. The resin used by Merrifield, a polystyrene cross-linked with 1 to 2% divinylbenzene, was chloromethylated with chloromethyl methyl ether to give a substitution of 1 to 2 mmoles of functional group per gram of resin, which corresponds to a degree of functionalization of 0.12 to 0.30 (1).



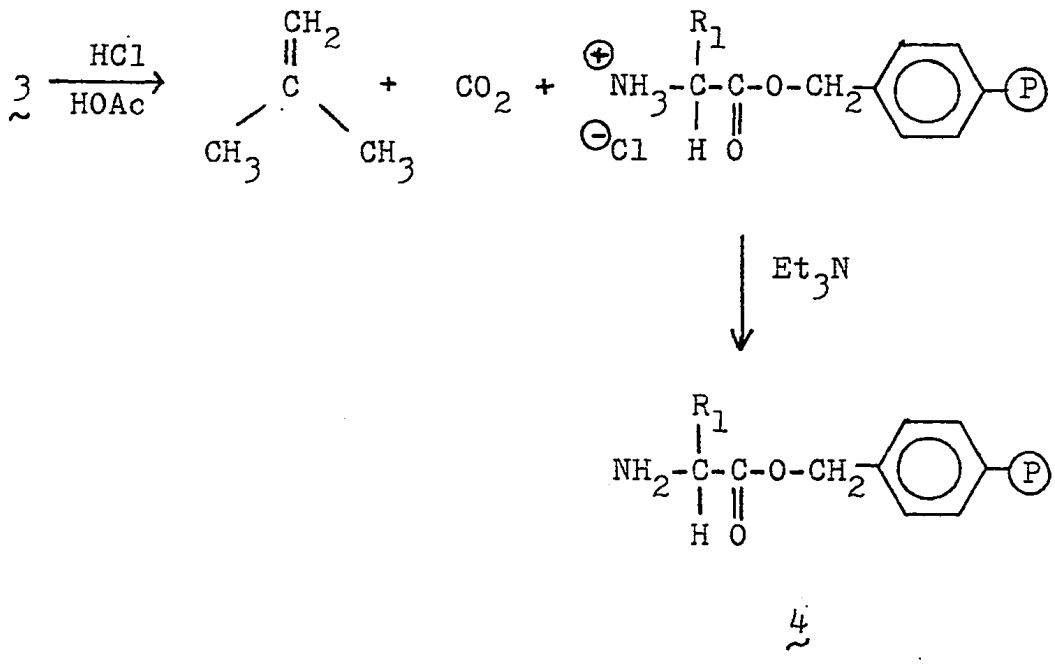
1 2 (1)

Attachment of an N-blocked amino acid to the polymer support involves a nucleophilic attack of the carboxylate anion on the chloromethylated resin (2). For solubility reasons, the cesium salt of the amino acid is generally used. The usual degree of substitution in the reaction is 0.2 to 0.6 mmoles of amino acid per gram of polymer. Tert-butyloxycarbonyl (t-Boc) groups are the most common amino blocking groups.



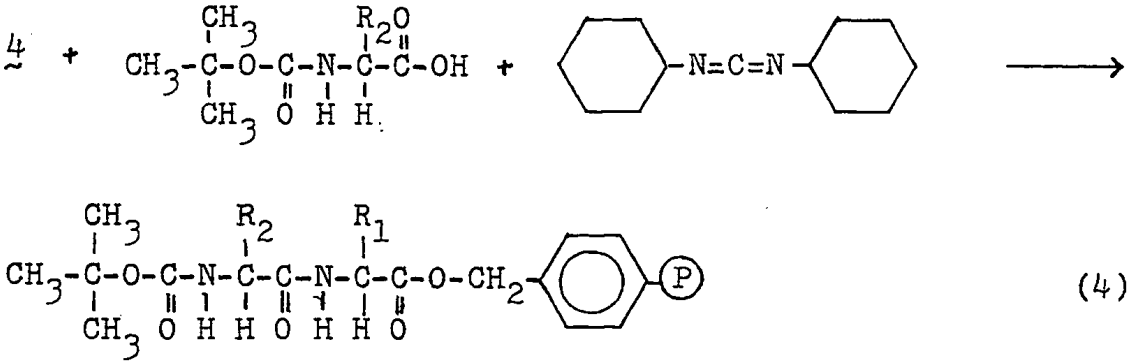
2 (2) 3

The next step involves the deblocking of the amino group by treatment with acid, followed by neutralization of the salt.



(3)

Coupling of the free amino group of 4 to the carboxylic acid end of the next amino acid can be accomplished either by using a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or by reaction with an activated acid derivative such as an acid chloride.



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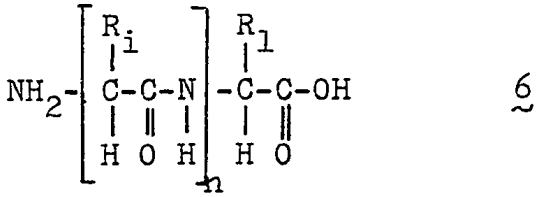
The decoupling and coupling reactions with Boc-amino acids are repeated until the desired polypeptide has been synthesized. Finally the polypeptide 6 is cleaved from its solid support by a reagent such as HBr in trifluoroacetic acid.

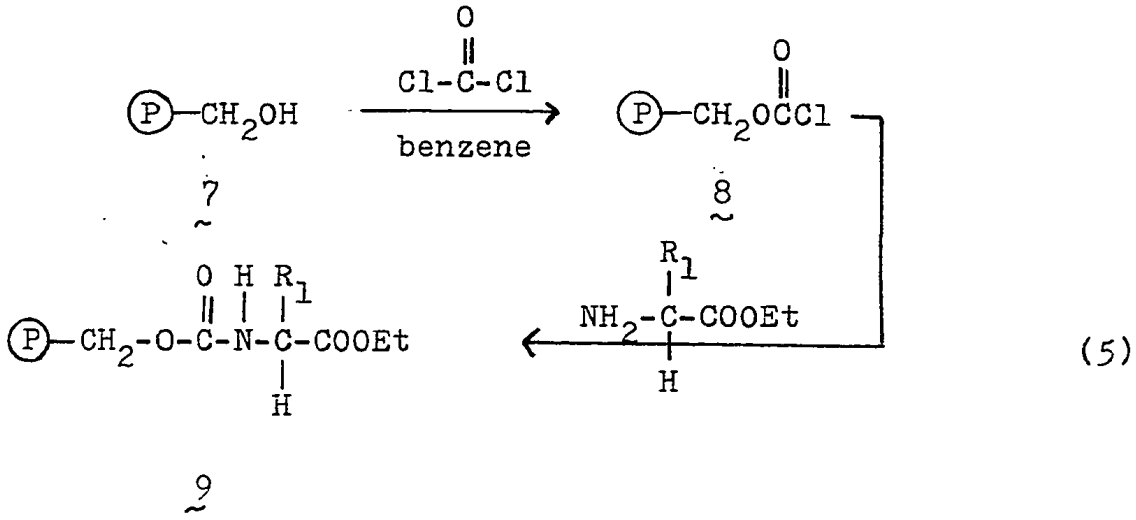


6

The first polypeptide synthesized by Merrifield in 1963 using this method was the tetrapeptide L-leucyl-L-alanylglycyl-L-valine[2]. Automation of the process by Merrifield facilitated the synthesis of longer polypeptides including, in 1969[2,11], the enzyme ribonuclease A, composed of 124 amino acids.

The apparatus designed by Merrifield for automated synthesis of polypeptides[12] is composed of two main parts: a reaction vessel designed so that reagents and solvents can be transferred from the storage area, mixed and removed by filtration; and a programmer which regulates the various operations.

There are many modifications to the basic procedure. For example, the terminal amino group (rather than the carboxyl group) could be attached to the solid support. Letsinger[13] prepared a chloroformyl derivative of polystyrene from a hydroxymethyl-substituted resin and to it attached the terminal amino group of the amino acid.



(5)

This procedure is inferior to carbonyl attachment in that the protection against racemization given by the urethane amino protecting groups (e.g t-butyloxycarbonyl groups) is lost. In addition there can be loss of peptide chains due to side reactions.

Linkage of the terminal amino acid to the resin through a side chain is also possible. There are several advantages in this procedure. Firstly, attachment of side chain functional groups to the resin could provide a specific cleavage reaction. For example, if the mercaptan group of cysteine were attached to the resin through a disulfide bond, the polypeptide could be cleaved by disulfide interchange. Also a linkage with a side chain near the center of the peptide would allow extension of the peptide at either or both the amino and carboxyl ends. The major disadvantage of the method is its specificity for a particular amino acid which restricts its general application.

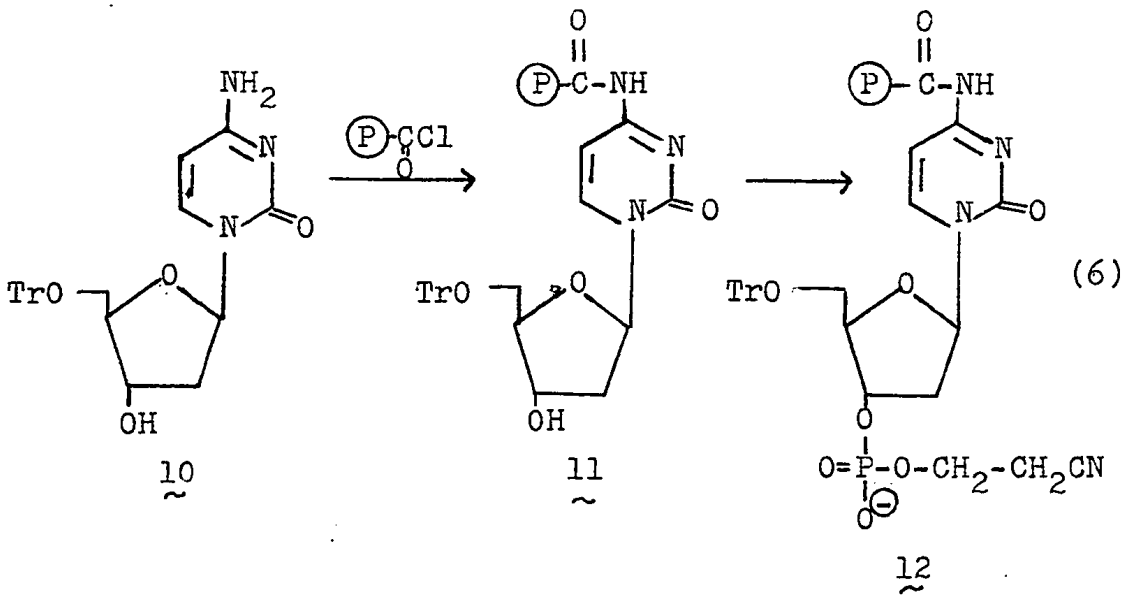
There are many advantages to the solid phase method of polypeptide synthesis. The losses of material caused by transfer from one vessel to another are eliminated. The yields are improved by the use of simple washings of the intermediates after each coupling step rather than the normal isolation and purification techniques. The use of excess reagents to force the reactions to completion results in a relatively high yield of final product. The major advantage of the solid phase method for sequential synthesis is its adaptability to automation. Syntheses normally requiring months or years to complete can be finished in weeks by an automated system.

There are several disadvantages to the solid phase method. It is difficult to determine the extent of reaction of the polymer-bound substrate. If all the reactions do not go to completion, the final polypeptide will be contaminated with many peptides having incorrect and shorter sequences. Separation of peptides differing from each other by only one residue is extremely difficult to accomplish.

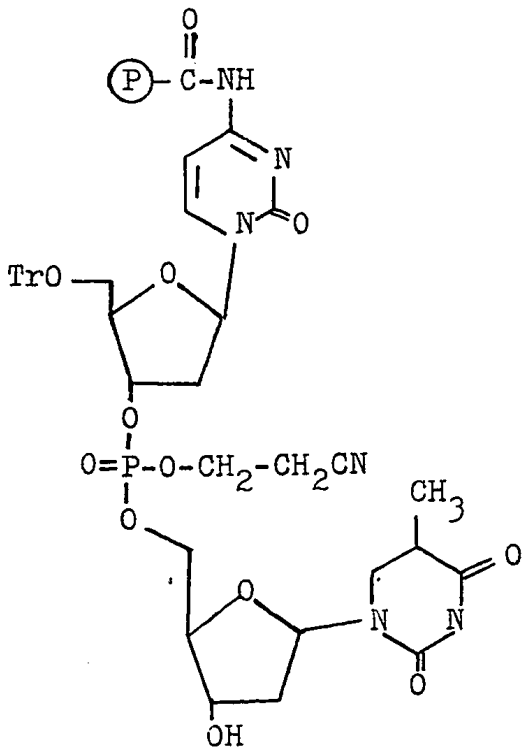
The solid phase synthesis of polynucleotides[4-6] is more complex than that of polypeptides. The functional groups in the saccharide, phosphate and base of the nucleotide must by protected during synthesis. As well, the large size and polarity of nucleotides cause problems of solubility.

The first solid phase synthesis of a poly-

nucleotide was reported by Letsinger in 1965 using a "popcorn" polymer as the support. Deoxycytidyl-(3'→5')-thymidine[11] was synthesized on a polymeric acid chloride.



Phosphorylation of the deoxyribose moiety (11) was effected with pyridinium β-cyanoethyl phosphate and DCC. The phosphodiester (12) was activated by treatment with mesitylenesulfonyl chloride and was coupled with thymidine to give the nucleotide (13).

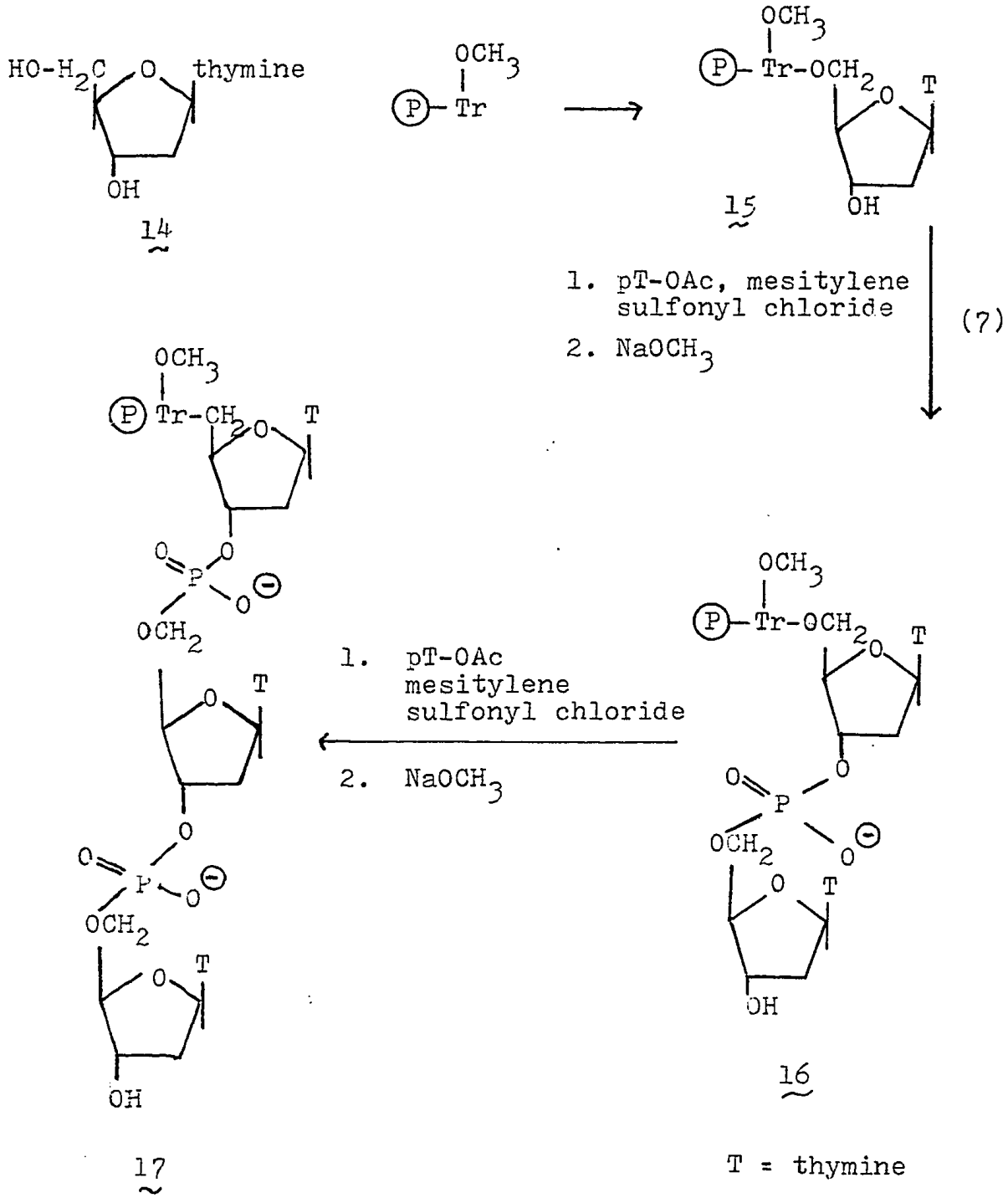


13

Cleavage with sodium hydroxide followed by purification yielded the dinucleotide. In this synthesis[4] both the 3'- and 5'- hydroxyls of the nucleoside were free, but attack of thymidine occured only at the 5'-hydroxyl. This selectivity is due to the steric bulk of the phosphorus group which favors approach of the less hindered 5'-hydroxyl in the condensation step.

Another approach to polynucleotide synthesis

developed by Khorana[6] involves the attachment of the 5'-hydroxyl of the deoxyribose moiety to a polystyrene-supported methoxytrityl chloride (7).

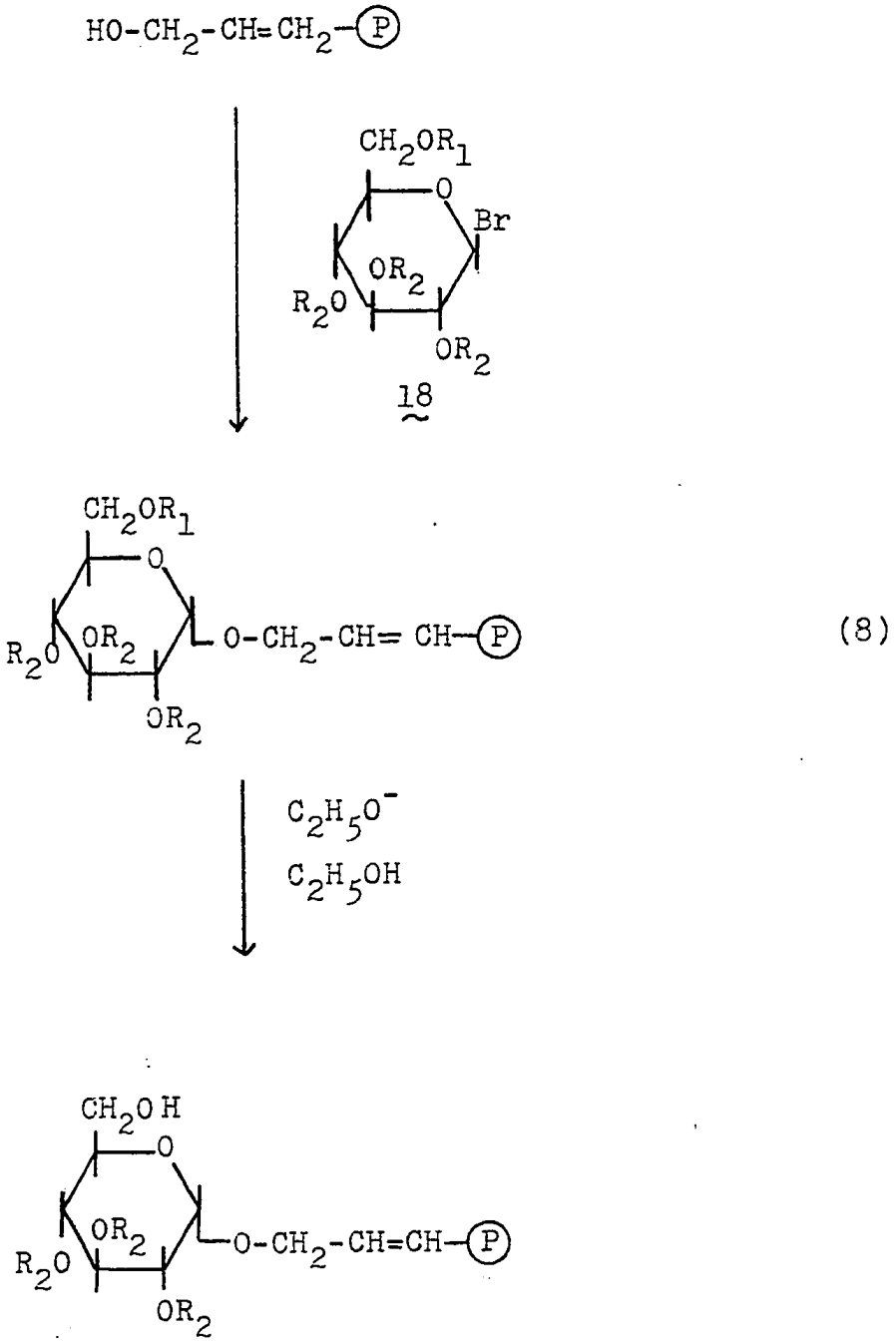


The 5'-hydroxyl of the terminal nucleoside is linked covalently to the p-methoxytrityl group of the polymer support and chain elongation occurs via the 3'-hydroxyl. A soluble polymer was used so that the reactions could be carried out in a homogeneous medium. After each step the polymer-bound material was separated from excess reagents and by-products by precipitation. The yields of each step were in the range of 88-96%.

The solid phase synthesis of polysaccharides[7] is also more difficult than that of polypeptides because of the many hydroxyl groups which must be blocked and the problem of stereochemical control. The features of the synthetic sequence outlined by Fréchet and Schuerch include the presence of a reactive leaving group at C-1, one hydroxyl protected with a readily removable blocking group R_1, the remainder of the hydroxyls protected with a stable blocking group R_2 and a resin which can be cleaved from the finished product without cleavage of the glycosidic linkages or the protecting groups. Such a procedure has the usual advantages of solid phase synthesis - purification of the intermediate steps by simple filtering and washing and an increase in reaction rate due to the large excess of reagents used.

In this synthesis the activated monomer unit, a glycosyl halide 18, was coupled to an allylic alcohol resin and the temporary blocking group, R_1, was removed. The coupling step involved the reaction of a new glycosyl halide unit with the free C-6 hydroxyl group on the polymer-

bound glycoside. The deblocking and coupling steps were repeated until the desired sequence was obtained. The oligosaccharide 19 was cleaved from its support by an oxidation reaction and, finally, the stable blocking groups R_2, benzyl, were removed.



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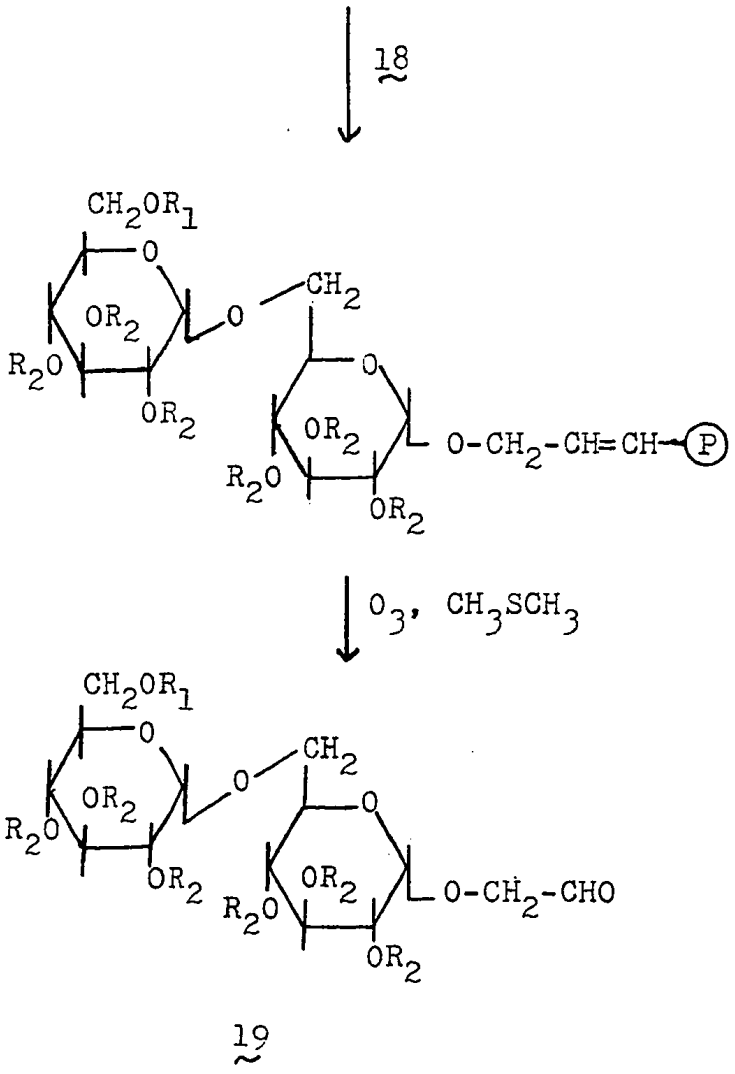


Another approach to oligosaccharide synthesis was developed by Guthrie[14] and involved the formation of a solid support by the copolymerization of 6-O-(p-vinylbenzoyl) derivatives of glucopyranoside with styrene.

Polymers can also be used as protecting groups in simple organic synthesis[8]. The selective blocking of one functional group of a completely symmetrical bifunctional compound is usually difficult to carry out. In a

typical reaction, the monoacyl derivative of a symmetrical diol can be prepared by reaction of an excess of diol with an acyl halide or by working under conditions of high dilution. In both cases however the desired product has to be separated from large amounts of unreacted diol and diacylated diol. This process is time-consuming and results in low yields. In contrast, the selective functionalization of one hydroxyl group of a diol can be accomplished by attaching the diol through one of its hydroxyl groups to an insoluble polymer support, acylating the remaining hydroxyl and finally cleaving the desired product from its support.

The first attempt to monofunctionalize symmetrical diols using a polymer support was carried out by Leznoff and Wong[9]. They prepared monotrityl and monotetrahydropyranyl ethers of various diols $HO(CH_2)_nOH$ (n = 2,4,6,8,10) by attachment to an acid chloride polymer Ⓟ-CH_2COCl containing 0.8 meq of functional group per gram, for a degree of functionalization of 0.1.

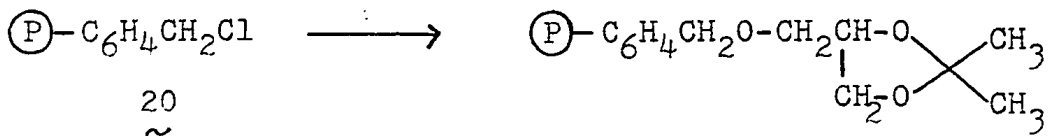
The coupling reaction was carried out in pyridine and, after filtration to remove unreacted starting material, the polymer-bound alcohol was treated with either trityl chloride (in pyridine) or dihydropyran (in dioxane). The yields of monotrityl ethers after cleavage were in the range of 37 to 51%. The inefficiency of the cleavage step was the main cause of the relatively low yields.

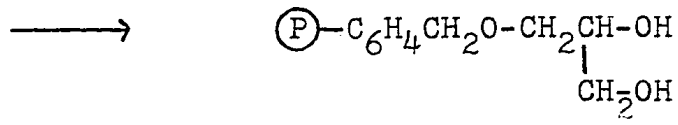
Regeneration of the used polymer after cleavage

of the product was attempted by reaction with thionyl chloride. The recycled resin was however found to be only half as effective as the fresh material and after a second regeneration the activity of the resin had seemingly dropped to 25% of its initial value.

The polymer-supported synthesis of monotetrahydropyranyl derivatives of symmetrical diols resulted in higher yields than those for the corresponding trityl derivatives. Again in recycling the resin lost 50% of its capacity. In addition the reaction of polymer-bound alcohol with dihydropyran was incomplete and cleavage from the resin afforded a mixture of monoprotected and unreacted diol. The major advantage of the Ⓟ-CH_2COCl resin is that it simulates high dilution thus giving only monoprotection of the diols.[9]

Another insoluble support designed by Leznoff[15] contains a 1,2-diol functional group suitable for acetal formation with one end of a symmetrical dialdehyde. This resin was prepared by treating a chloromethylated 2% cross-linked polystyrene resin with the sodium salt of 2,2-dimethyl-1,3-dioxolane-4-methanol. Acid hydrolysis gave a resin containing a vicinal diol functional group.

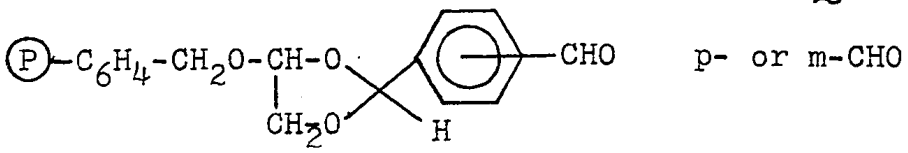




(9)

21

Treatment of the resin with excess terephthalaldehyde or isophthalaldehyde gave the monoacetal (22).



22

An estimate of the capacity of the resin was obtained from the cleavage of the aldehyde form its support. It was found that resin 22 contained 0.34 mmole of terephthalaldehyde per gram of resin indicating a degree of functionalization of about 0.04, for a functional yield of 20% in the transformation 20→22. Thus polymer 21 had a low loading capacity which limits its usefulness for laboratory scale organic synthesis.

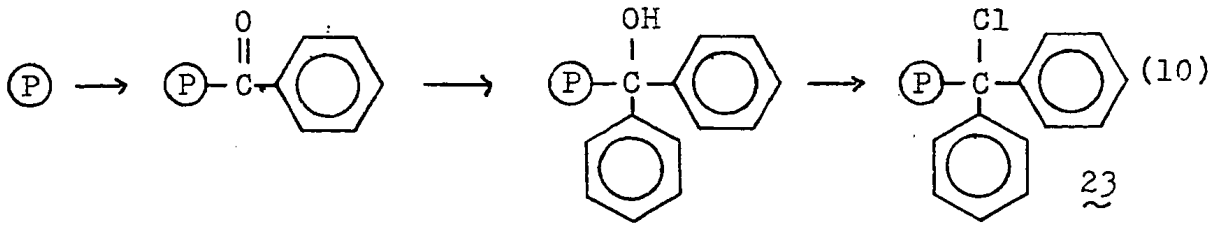
However various chemical reactions could be carried out on the monoprotected aldehyde including oxime formation, Wittig reactions, crossed aldol condensations, benzoin condensations, Grignard reactions and reductions with metal hydrides.

This resin has several advantages over classical protecting groups. First, many new monoderivatives of symmetrical aldehydes could be synthesized without the problem of mixed products. Second, the resin was completely regenerable. The main problem in the use of

resin 21 was its relatively low loading capacity (less than 0.5 mmole per gram). Another limitation is that the acetal linkage that attaches the aldehyde to the resin is cleaved in acidic media. This sensitivity to acid is the source of a problem in Grignard and metal hydride reactions where metal salts of the resin alcohols cause filtration problems in nonacid solutions.

Another example of a polymeric protecting group is the polymeric trityl chloride reagent for blocking primary alcohol functional groups[16,17,18]. The advantages of this reagent include its selectivity and reactivity for primary hydroxyls versus secondary or tertiary hydroxyls and the ease of cleavage of the trityl ethers in acidic media. The polymeric trityl chloride can act as a dilute reagent and thus react with only one hydroxyl of a molecule containing several primary hydroxyl groups. The purification by filtering and washing simplifies the isolation of the product and the steric bulk of the resin could give extra selectivity.

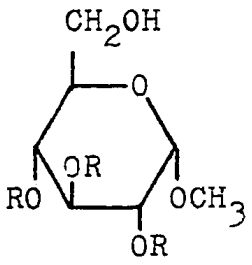
The resin was prepared by Fréchet and Haque[16] from 1% cross-linked polystyrene-divinylbenzene by treatment with benzoyl chloride and aluminum chloride in CS_2. The resulting ketone was reacted with phenylmagnesium bromide in dry THF and the resulting compound hydrolyzed to give the trityl alcohol polymer. Treatment with acetyl chloride yielded the polymeric trityl chloride containing 0.9 to 2.3 meq of chlorine per gram.



(10)

23

Coupling of methyl α-D-glucopyranoside to the resin, followed by benzoylation of the free hydroxyls and cleavage from the resin by dry hydrogen bromide gave an 86% yield of the tribenzoylated derivative (24).



24 R = $-\overset{\overset{O}{\|}}{C}C_6H_5$

The resin could be regenerated quantitatively.

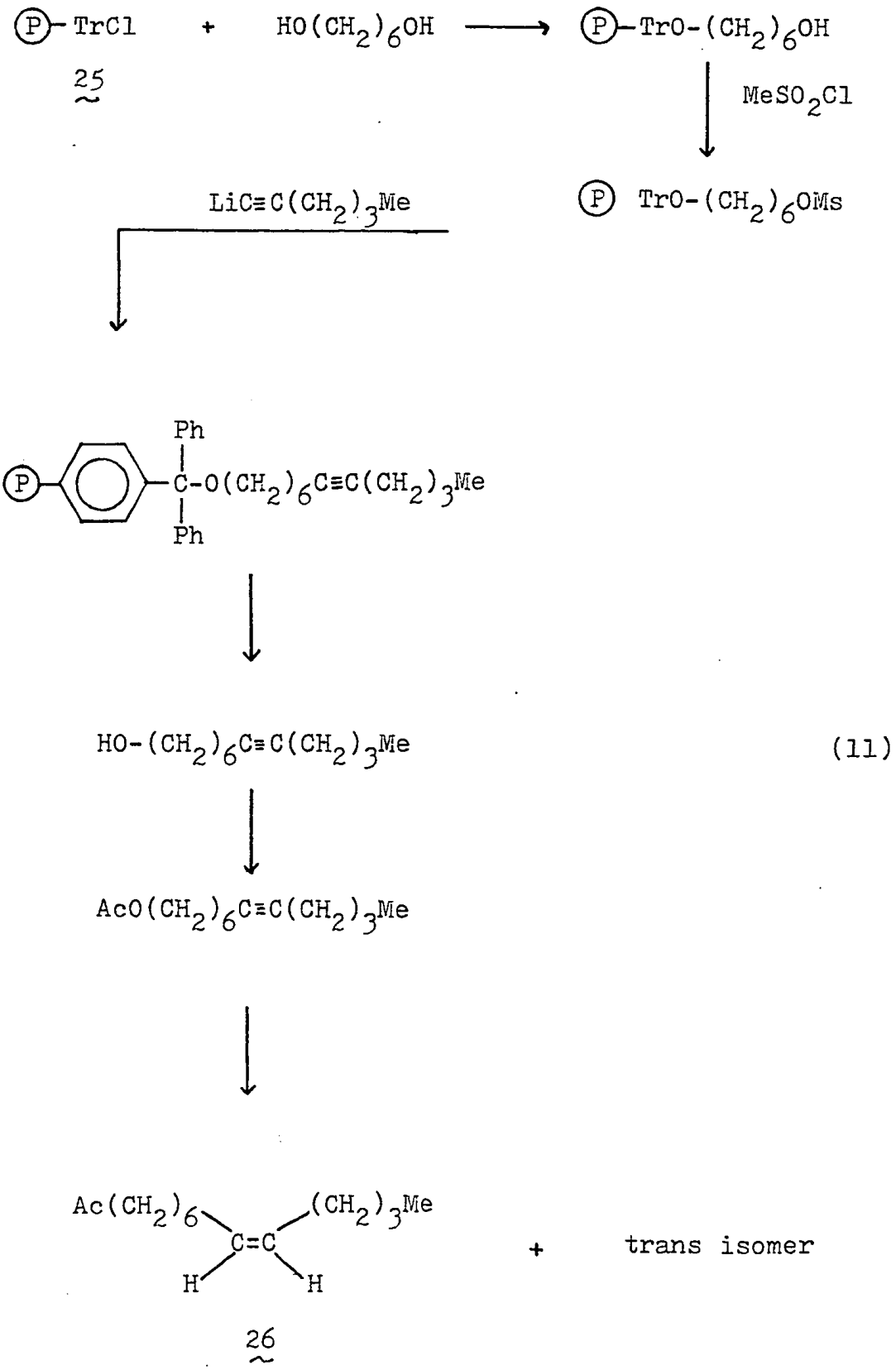
Polymeric trityl chloride reagents were used by Fréchet and Nuyens to protect one primary hydroxyl group in several polyols[17]. The alcohol, present in 50-100% excess, was coupled to the resin in dry pyridine and unreacted alcohol was recovered by filtration and recycled. The free hydroxyls were protected by benzoylation and the product cleaved from the resin. Cleavage of the product from the solid support by dry hydrogen bromide required a longer time than cleavage of ordinary trityl ethers but gave high yields. Cleavage with trifluoroacetic acid resulted in a 1:1 mixture of alcohols and trifluoroacetates (which were easily hydrolyzed to the corresponding alcohols).

Polymeric trityl chloride reagents were also

prepared by Leznoff and Fyles[18] by the direct lithiation of a divinylbenzene-styrene copolymer with n-butyl lithium in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) followed by treatment with a suitable benzophenone to give the polymeric trityl alcohol.

Reaction of symmetrical diols with the polymeric trityl chloride followed by acetylation and acid cleavage gave the monoacetylated derivatives. With 1,10-decanediol, some of the diol was thought to be attached to the resin through both ends.

A trityl chloride resin was also used as a support for the synthesis of some insect sex attractants[19,20]. For example, the sex attractant of the cabbage looper was synthesized in 27% overall yield (57% if recovered intermediates and starting material are recycled).(11)


P-TrCl
HO(CH2)6OH
P-TrO-(CH2)6OH
MeSO2Cl
P TrO-(CH2)6OMs
LiC≡C(CH2)3Me
Ph
C-O(CH2)6C≡C(CH2)3Me
Ph
HO-(CH2)6C≡C(CH2)3Me
AcO(CH2)6C≡C(CH2)3Me
Ac(CH2)6
(CH2)3Me
C=C
H
H
+ trans isomer

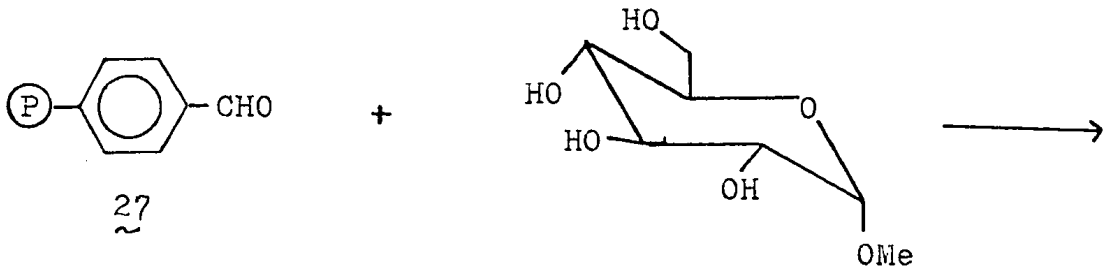
25

26

(11)

The diol was attached to the resin and the free hydroxyl group was mesylated. Treatment with lithioacetylene in THF-hexamethylphosphoric triamide gave the acetylene precursors of the insect sex attractants. Cleavage from the resin with acid gave the acetylenic alcohols and Ⓟ-TrOH. Hydrogenation and acetylation reactions in solution gave the <u>cis</u> acetate. The yield was comparable to that obtained by the classical synthesis.

An insoluble polystyrene resin containing aldehyde substituents[21] was used independently by Hanessian et al.[22] and Fréchet and Pellé[23] to form benzylidene-type acetals with carbohydrates. The resin was prepared by oxidation of a chloromethylated resin with dimethylsulfoxide and sodium bicarbonate. Hanessian and co-workers carried out the coupling step of the sugar to the resin in a dioxane solution containing p-toluenesulfonic acid monohydrate and molecular sieves to remove water. Boiling overnight in a Soxhlet apparatus gave coupling yields of 80 to 90%. Sulfonylation at 0° C, followed by cleavage with 1% methanolic hydrogen chloride yielded the monomethanesulfonylated derivative in 40% yield. No attempt to recycle the polymeric aldehyde was reported.



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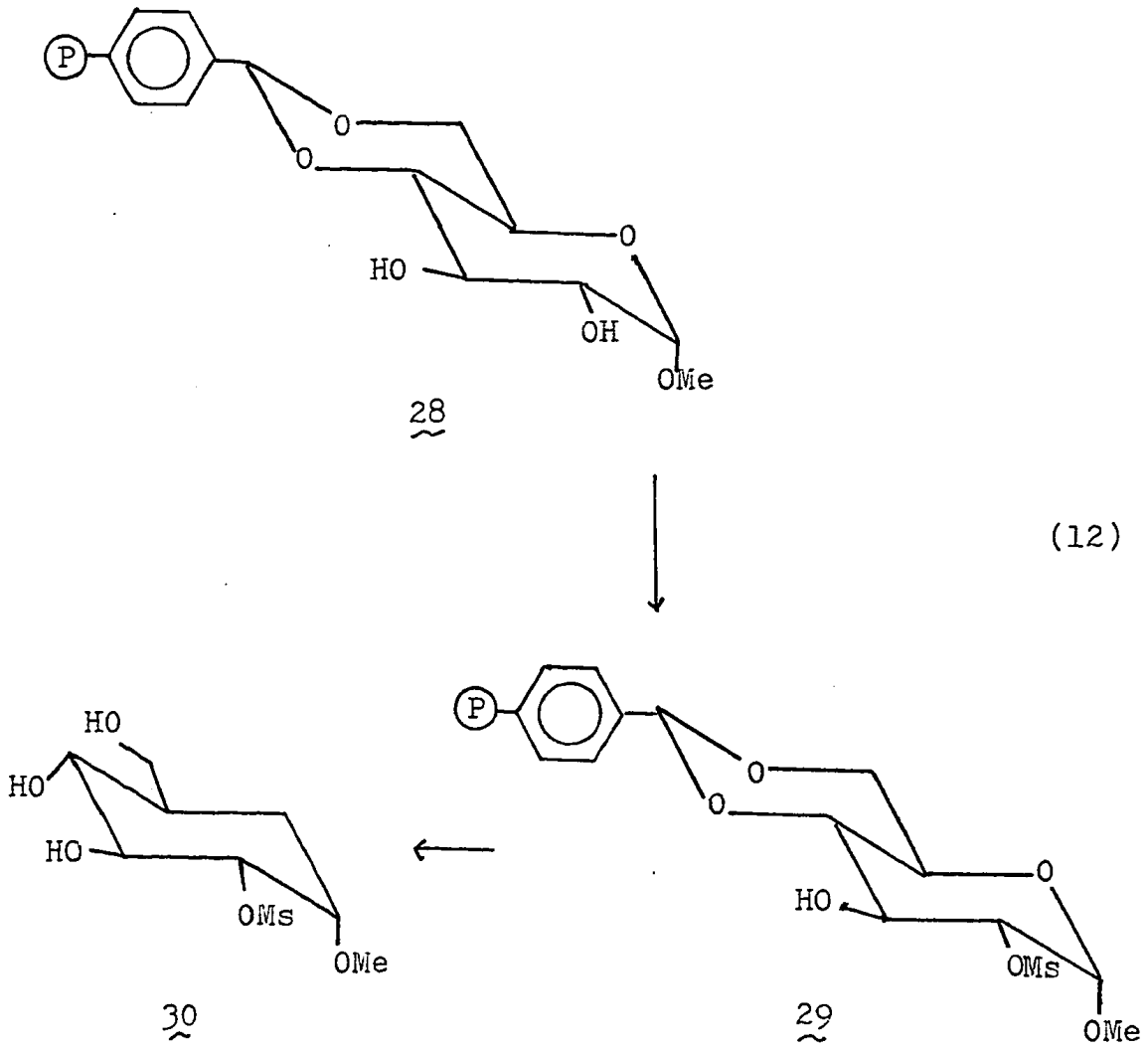
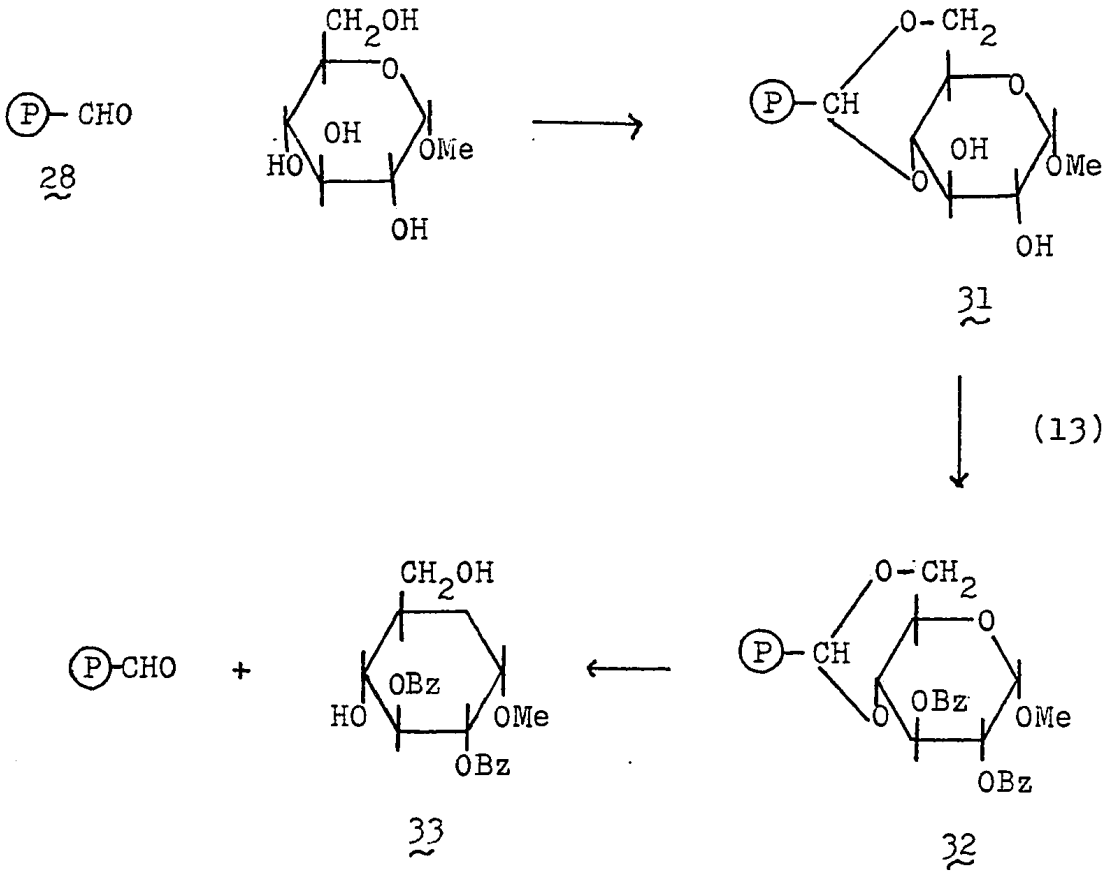


Polystyrene resins containing vinylbenzaldehyde units were also prepared by Fréchet and Pellé[23] and used in the synthesis of partially substituted derivatives of D-glucose. Coupling of methyl α-D-glucopyranoside to the resin occurred in 89% yield using a 2- to 3-fold excess of glucoside in the presence of a catalytic amount of p-toluene sulfonic acid. Treatment of the resin-bound glycoside with an excess of benzoyl chloride and cleavage with

trifluoracetic acid in dioxane gave the product in 70 to 80% yield.

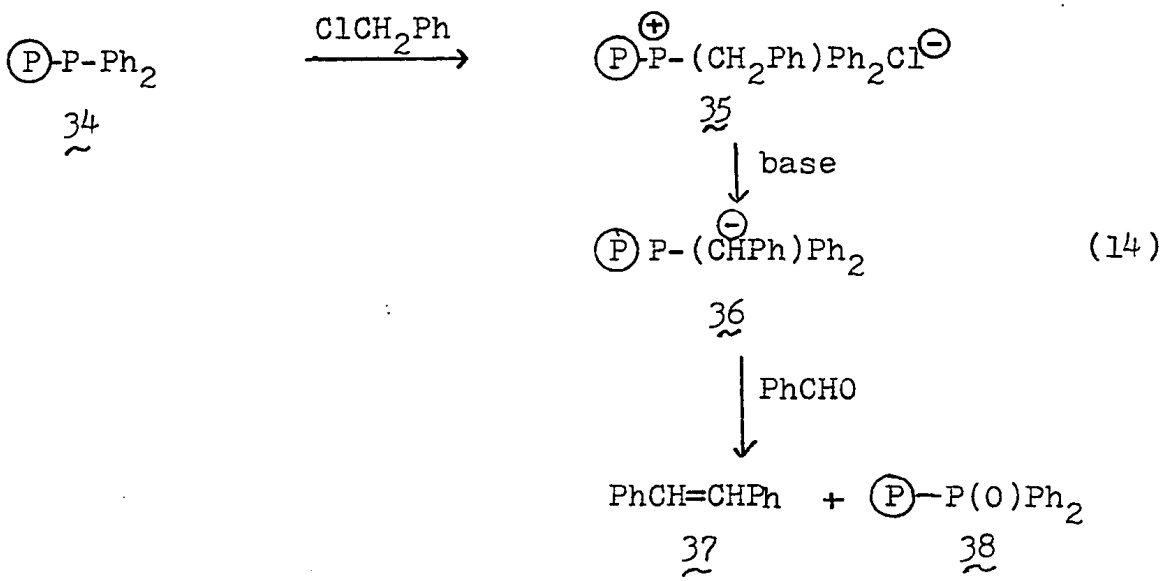


Benzylation of the polymer-bound glycoside with sodium hydride and benzyl chloride in DMSO followed by acid cleavage resulted in a mixture of products. The crystalline 2,3-di-O-benzyl-α-D-glucopyranoside was isolated from this mixture in 20% yiels and a monobenzylated glycoside that could not be crystallized was obtained in 15% yield. The polymeric vinylbenaldehyde was not recycled.

Several examples of organic reagents attached to

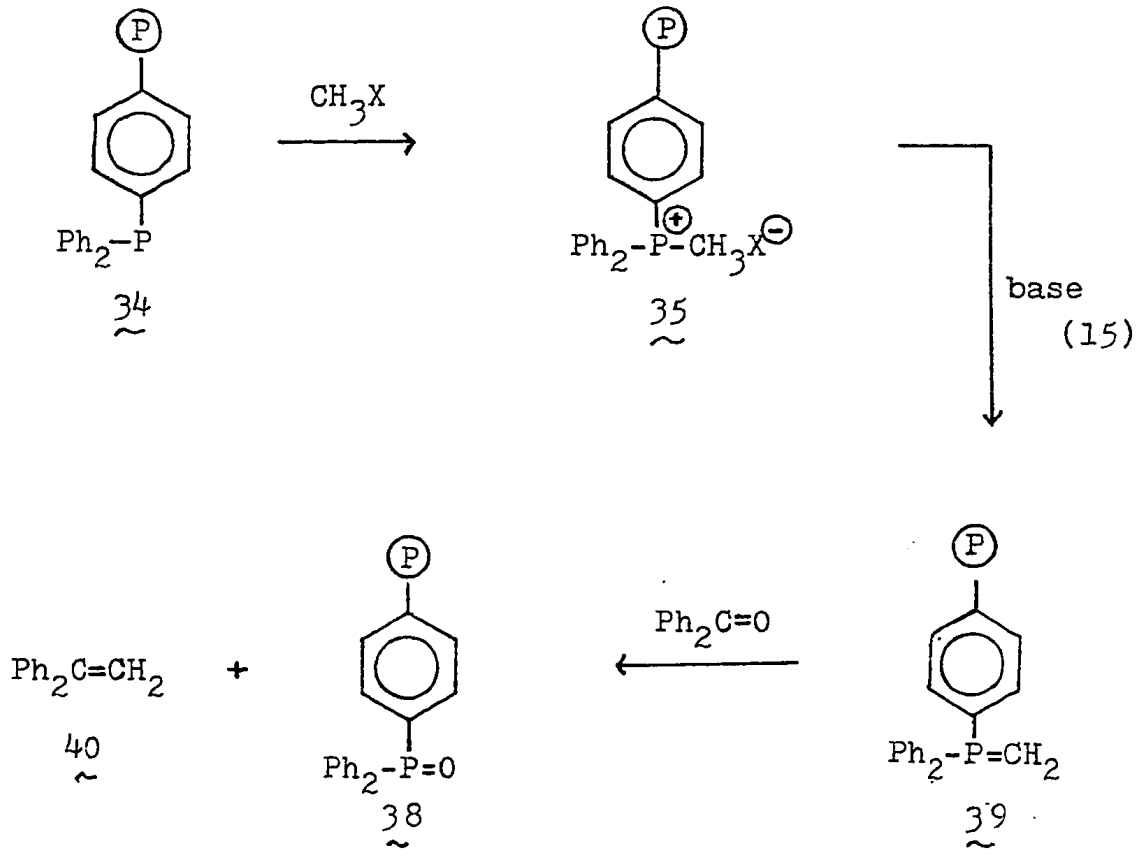
insoluble polymer supports have been reported in the literature[8,11]. The reactions involving immobilized reagents must be single step rather than multiple step processes. The advantages associated with the ability to carry out several successive steps in the solid phase without isolation are therefore lost. The possible regeneration of the reagent and the ease of separation of the resin-bound by-products from the desired product are definite advantages.

Polymer-bound Wittig reagents[24-26] have been prepared which eliminate the problem of separation of triphenylphosphine oxide, the usual by-product of the reaction. Attachment of the Wittig reagent to a resin means that the triphenylphosphine oxide will remain bound after reaction and thus can be easily separated from the product by filtration.



(14)

The yields of olefins are generally comparable to those obtained by the classical method. For example[25]:



The yield by the classical method was 52% while the solid phase method gave an overall yield of 63%, based on the initial amount of carbonyl and a 90% yield based on the amount of carbonyl reactant consumed.

Several uses of low molecular weight boronates as diol protecting groups in various types of polyols have been reported in the literature[27-37]. One of these applications is the temporary blocking of one or more diol functionalities while the remainder of the hydroxyls in the molecule undergo a reaction. Another is the separation of cis and trans diols from a mixture of isomers.

Boronates of acyclic polyols have been studied. McKinley and Weigel[27,28] have prepared a series of phenylboronates and investigated the relative ease of formation of five-, six- and seven-membered cyclic phenylboronates. Dahlhoff and Köster[29] prepared some per-O-diethylborylated derivatives of acyclic polyols.

Ferrier et al[30-33] have used phenylboronates extensively as temporary blocking groups in carbohydrate chemistry. For example, phenylboronic acid will react with methyl α- and β- xylopyranosides to give crystalline 2,4-cyclic esters[30]. Once the free hydroxyl group at C-3 has been esterified, the phenylboronic acid can be removed from the product by ester substitution with 1,3-propanediol. The main disadvantage of this procedure is the many purification steps required. The phenylboronate of the xyloside and the acylated derivative must be prepared and purified by crystallization. Then the phenylboronic acid must be removed and the acylated xyloside purified by crystallization. Hence the procedure is time-consuming and results in a relatively low yield.

Separation of cis and trans diols has been attempted using various boronates.[36,37] Brown et al[36] succeeded in separating cis and trans isomers of 1,3- and 1,4-cyclohexanediol mixtures. In each case, the cis isomer formed a volatile n-butylboronate that could be separated by distillation while the trans derivative remained in the nonvolatile residue and tended to polymerize. The cis isomer could be freed from its boronate ester by treatment with ethylene glycol. Cis and trans 1,2-cyclohexanediols could not be separated by this procedure since they formed volatile n-butylboronates with similar boiling points.

The process of affinity chromatography has been developed for the isolation and purification of biologically active macromolecules.[38] Selective adsorbents can be prepared which utilize specific and reversible covalent binding of ligands to proteins and polypeptides. For example, a selective adsorbent for a protein can be prepared by attaching a specific competitive inhibitor to an insoluble polymer.

When a crude solution of a protein is applied to such a column, molecules having no affinity for the ligand will pass through while the protein will be bound. If the binding is weak, the product will emerge directly behind the impurities or mixed with them. If the binding is strong, the protein will be adsorbed on the top section of the column and a change in eluent (such as a different

pH) will be required to remove it.

Thus affinity chromatography has wide applications in biochemistry in the isolation and purification of natural products due to the ease and rapidity of the method. Affinity chromatography could be extended to the purification of products in organic reactions if a suitable adsorbent could be prepared that would bind only to the desired product. An insoluble resin containing a boronic acid residue might be useful in selectively binding certain diol functionalities.

RESULTS AND DISCUSSION

There are several factors which must be considered in the design of a polymeric protecting group. A resin must be chosen that can be used in hydrophilic and hydrophobic media. The degree of cross-linking of the resin is important in that if the resin is too highly cross-linked, its pores will not have the capacity to handle large molecules. If the degree of cross-linking is too low, the resin might have partial solubility in the solvent. As well, a resin with low cross-linking has a more flexible chain which could cause problems with double binding to the substrate.

The degree of functionalization of the resin must also be decided. A resin having a low degree of functionalization has more site isolation but it is more difficult to work with on a practical scale. Crowding of reactive ends might occur in resins having a high degree of functionalization.

Since these polymers are not available commercially and their synthesis is not easy, they should be designed for repeated use. Regeneration of the used polymer should be a simple process.

Coupling of the substrate to the polymer should be a high yield reaction that can be carried out under mild conditions. The polymer-substrate bond should be stable under the conditions of the functionalization reaction on the rest of the molecule. Cleavage of the

polymer-product bond should be quantitative and should require only mild conditions.

The polymeric reagent should be selective in its reaction with certain functional groups of the molecule. Finally, its use should offer some advantages over the use of the more conventional protecting groups.

Choice and preparation of the resins

Both macroreticular 20% cross-linked resins and solvent-swellable 1% cross-linked styrene-divinylbenzene copolymers were used in this research. The 20% cross-linked resin has a rigid macroporous structure and can be used in a wide variety of solvents since no swelling is needed to ensure penetration of the reagents into the pores of the resin. In addition, separation of reactive sites is probably easier to achieve on a macroreticular resin than on a more flexible support. However site separation is not a primary consideration in this project since attachment of a polyol to more than one site is not very likely. Secondary effects from remote sites, such as coordination, may however be a factor in some reactions.

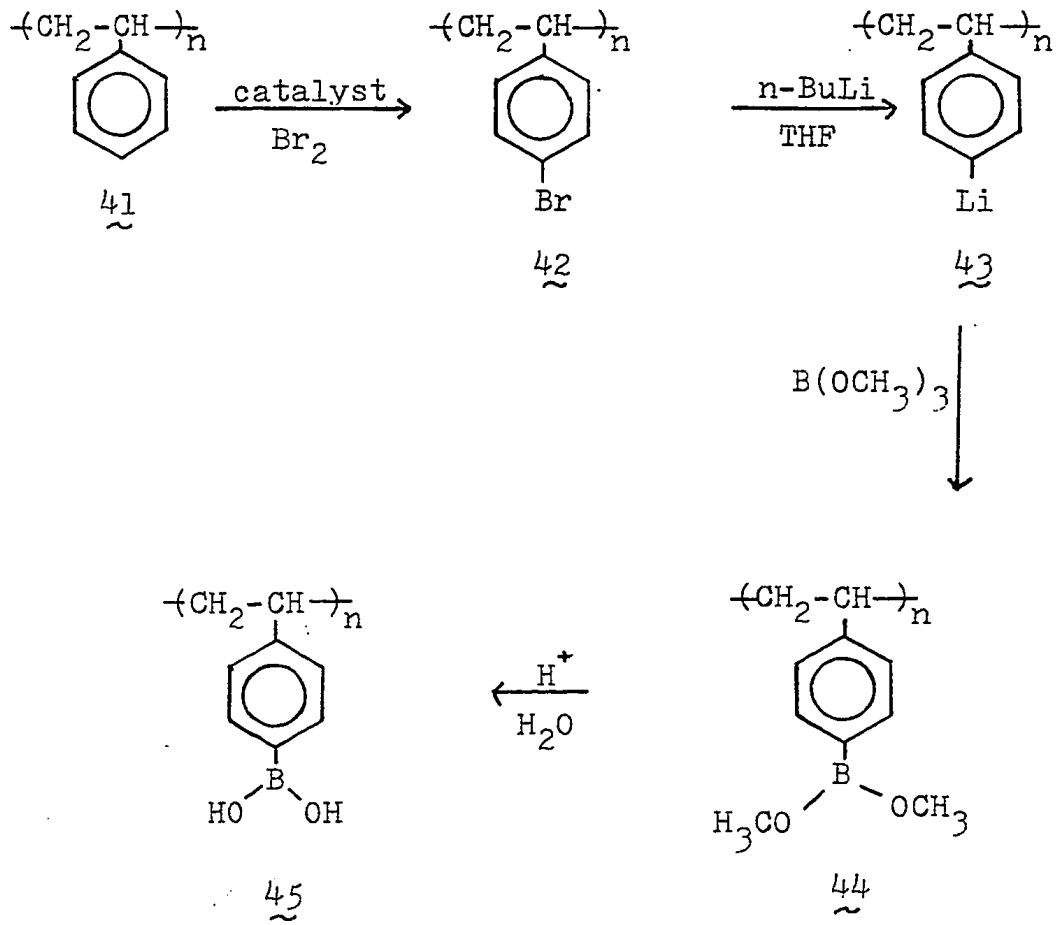
The advantages associated with the use of a macroreticular resin include a wider choice of solvents, ease of filtration and adaptability to use in column techniques. The major drawback of the macroreticular resin is the mechanical fragility of the resin beads which tend to break up on repeated use.

The 1% cross-linked resins in bead form, 200-400 mesh "research grade", must be swollen before reaction. Typically in benzene or pyridine, a 1% cross-linked resin will swell to 10 to 12 times its original size. The advantages of these resins include their ease of functionalization, high capacity and mechanical stability.

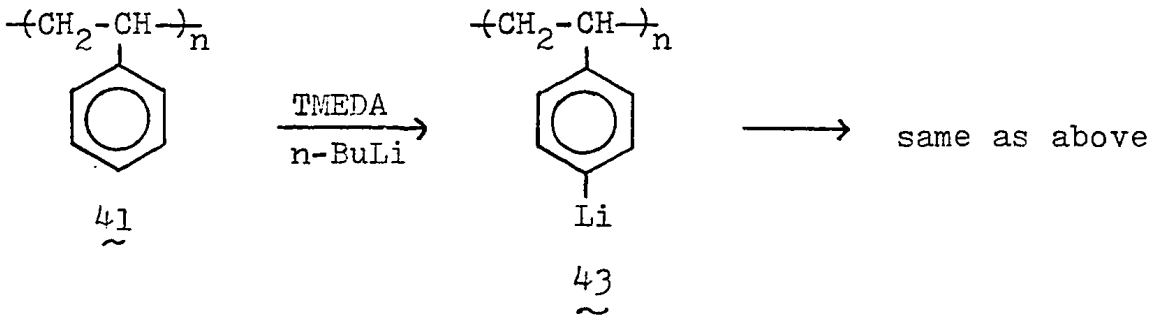
Preparation of the polystyrylboronic acid resin

Two different procedures were used in the preparation of the polystyrylboronic acid resin. These are shown in Scheme 16 below.

Scheme 16 - Method A



Method B



41 43

Method A was used in the functionalization of a macroreticular resin, Amberlite XE-305. The bromination reaction, performed in the presence of $FeCl_3$ as catalyst, gave a high degree of functionalization, 0.59. However the product obtained after lithiation and reaction with trimethylborate had only a low degree of functionalization, 0.13-0.19. Removal of bromine from polymer 42 was generally found to be complete but extensive loss of functional groups had occurred.

A similar reaction carried out on commercially available 1% cross-linked polystyrene failed to yield any of the desired resin 43. Only the first step of the reaction sequence, bromination, could be carried out. The brominated polymer was unreactive and had an infrared spectrum which did not correspond to that expected for 42. Elemental analysis of samples of research grade 1% cross-linked polystyrene resins[39] showed that the polymers were contaminated with small amounts of suspending and emulsifying agents used in the emulsion polymerization process. After extensive washing of the commercial 1%

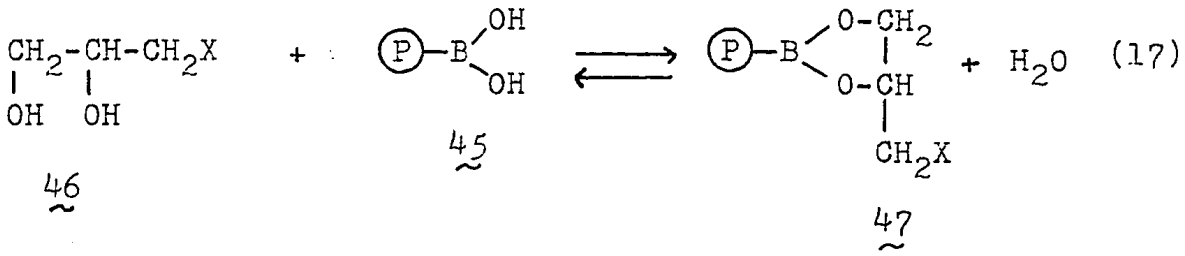
cross-linked polymer to remove these impurities, polymer 45 was obtained in excellent yield (97%) using a procedure developed in this laboratory[40] and involving catalytic bromination in the presence of thallic acetate.

A few samples of resin 45 were prepared by Method B in which the starting resin is lithiated directly by reaction with a mixture of tetramethylethylenediamine (TMEDA) and n-butyllithium. The main advantage of this procedure is its rapidity. However the method has not yet been adapted to the preparation of resins with a high degree of functionalization (greater than 0.25) and has not yielded reproducible results.

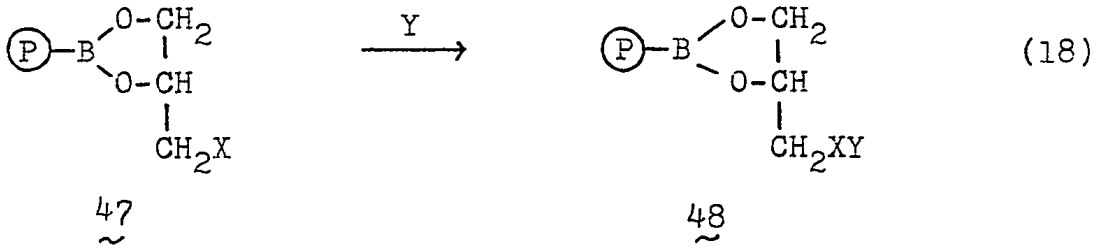
APPLICATION OF THE POLYSTYRYLBORONIC ACID RESIN AS A PROTECTING GROUP IN ORGANIC SYNTHESIS

A. General reaction scheme

In a typical experiment, an excess of a polyfunctional molecule (46) containing a diol grouping is added to a suspension of the polystyrylboronic acid resin (45) in benzene, pyridine or other suitable solvent. The following equilibrium is rapidly established.

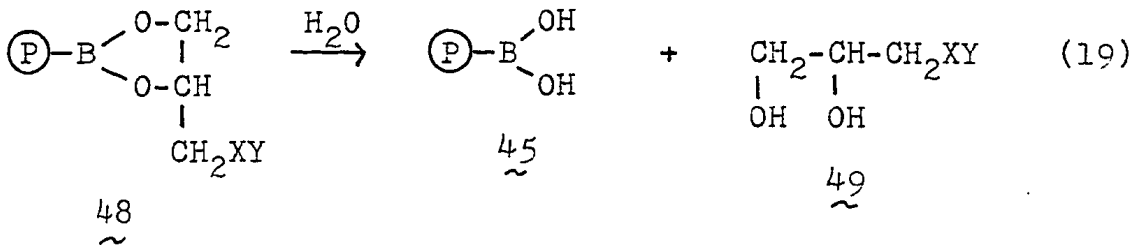


The equilibrium is displaced in favor of the cyclic boronate by removal of the water in an azeotropic distillation. At this stage, the excess of 46 can be removed by filtration and recycled if desired. Then the polymer-bound boronate is modified by addition of a suitable anhydrous reagent.



47 48 (18)

After removal of all excess reagent and soluble by-products, the modified molecule 48 can be cleaved from its support by addition of water.



48 45 49 (19)

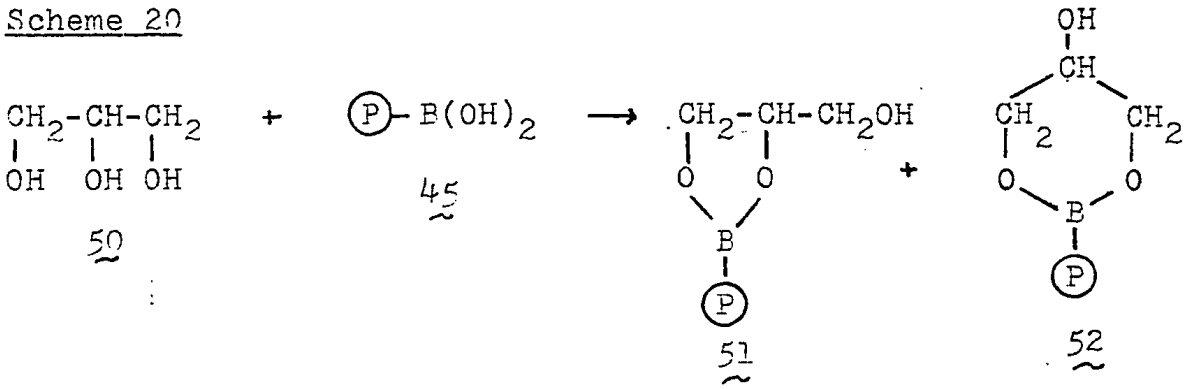
Both the coupling and cleavage steps are performed under very mild conditions (removal or addition of water) and the starting polymer is regenerated directly by the cleavage step thus eliminating the need for an additional step to recycle the resin. Depending on the choice of functionalization reaction, the entire reaction sequence can be carried out in one flask with a minimum of handling

of the resin. Purification at each intermediate step is done by a simple filtration and washing with an appropriate solvent in a specially designed flask[40] (see Figure 1).

B. Protection of acyclic polyols

The first attempt to use the polystyrylboronic acid with an acyclic polyol was carried out with glycerol in the preparation of a monoacyl derivative. Coupling of the resin with glycerol could be expected to yield two different polymer-bound cyclic boronates (51 and 52 in Scheme 20 below).

Scheme 20



Thus after acylation and cleavage from the polymer, a mixture of two isomeric monoesters could be expected. No characterization of the intermediate boronates 51 and 52 could be carried out. Therefore the stereochemical outcome of the reaction could only be evaluated by a study of the product obtained after acylation and cleavage from the resin.

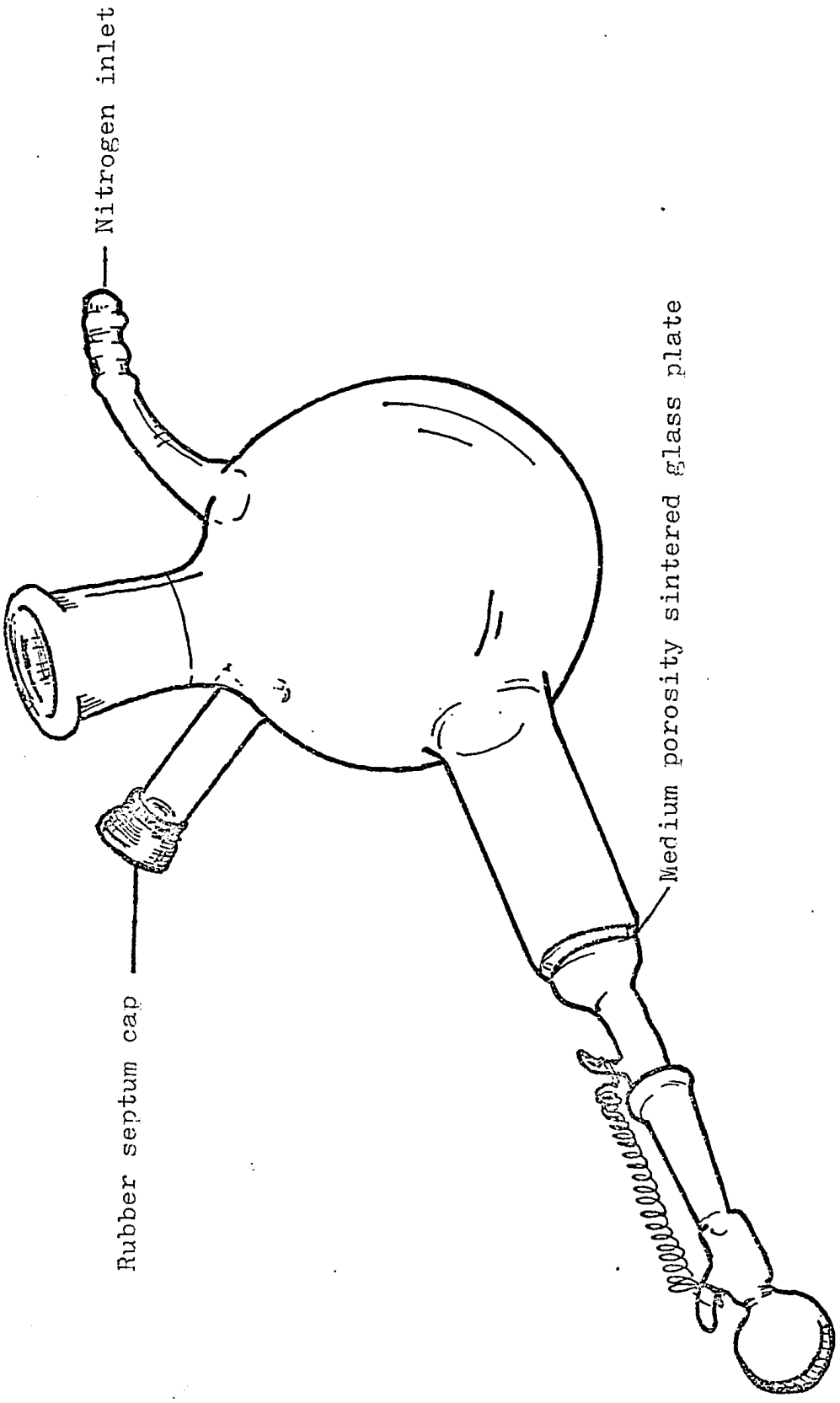
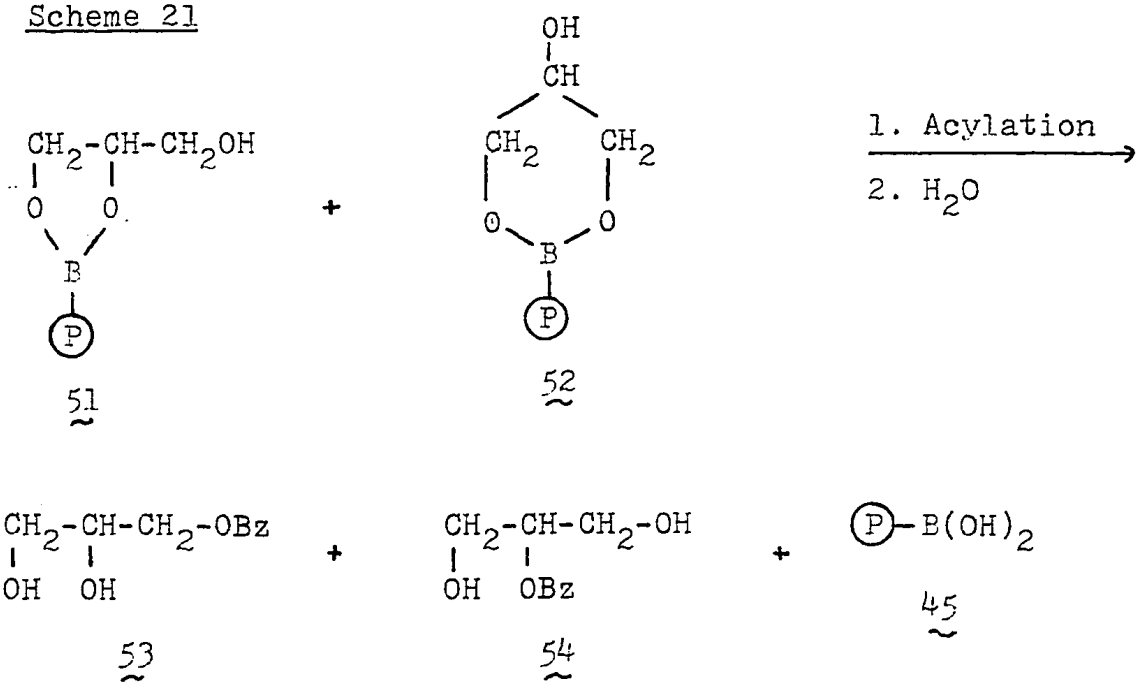


Figure 1. The specially designed reaction flask.

Scheme 21



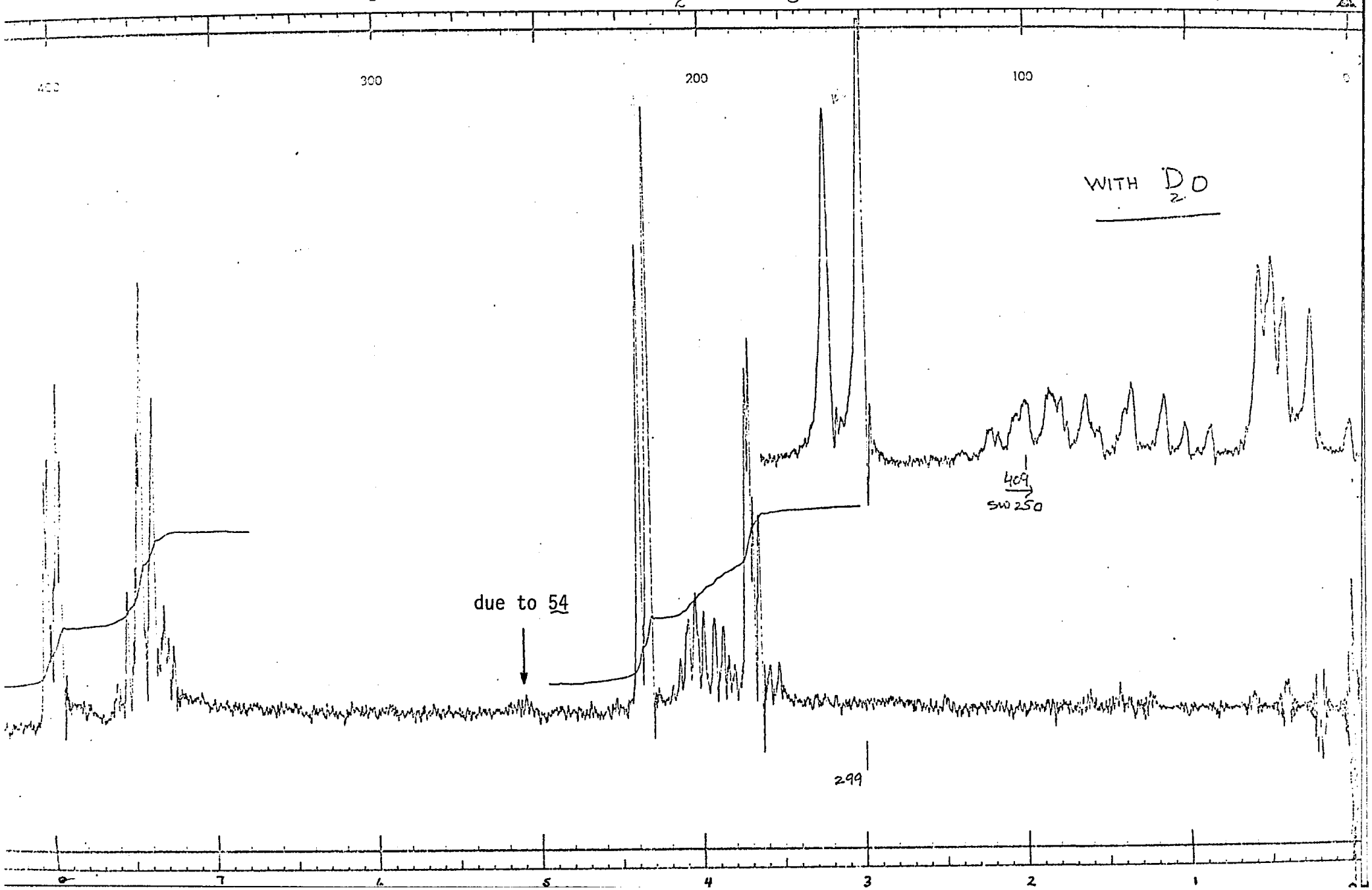
51 52

53 54 45

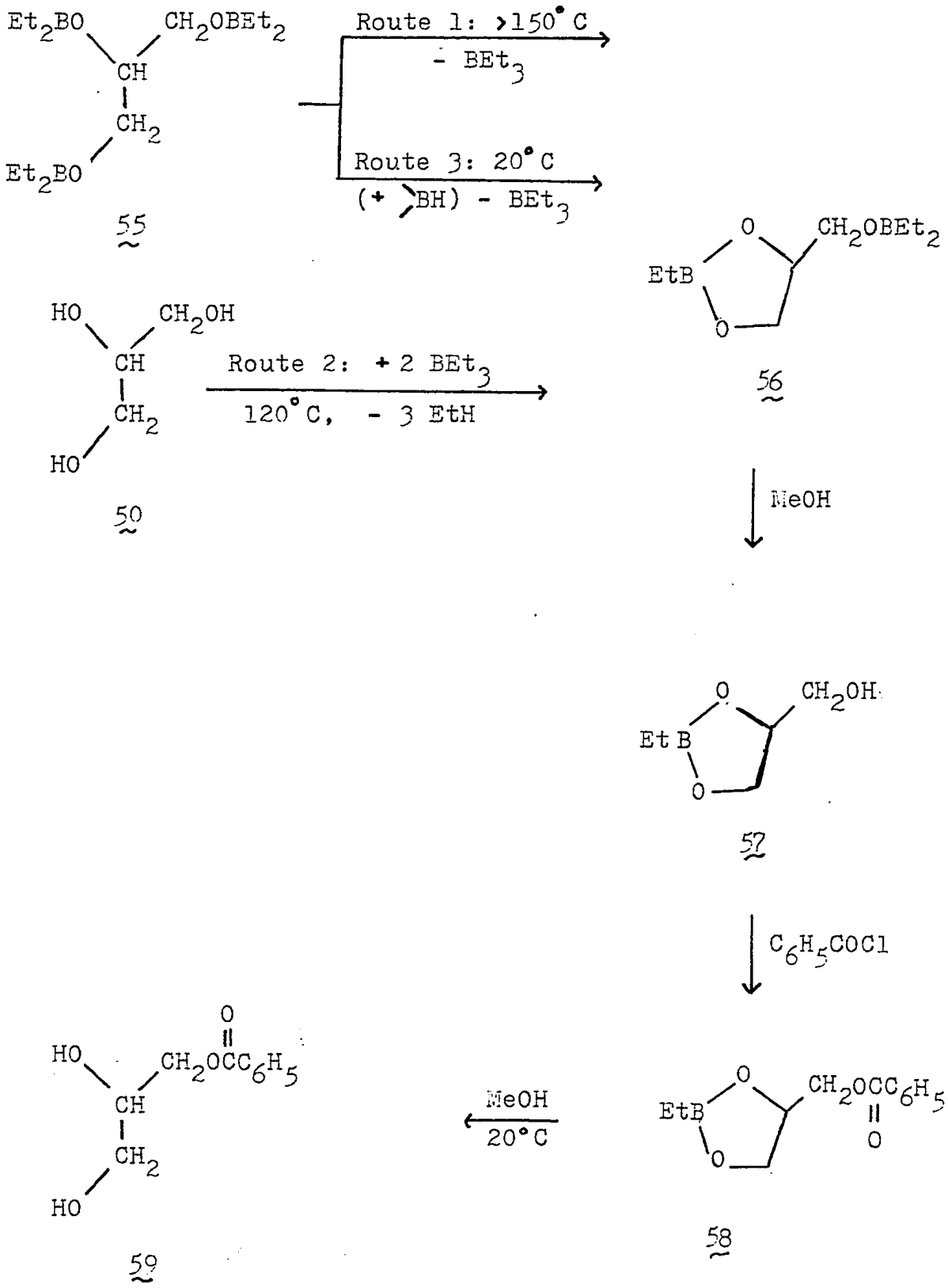
The material obtained in this reaction was found to be almost pure 53 contaminated with a very small amount of 54 (as determined from the nmr spectrum, Figure 2). This indicates that the reaction proceeded mainly through the five-membered boronate 51 since no rearrangement of 54 into 53 was likely under the very mild conditions of the reaction.

Dahlhoff and Köster[29] prepared the 1-O-benzoylglycerol by converting the per-O-diethylborylated derivative 55 to the 2-ethyl-4-diethylboryloxyalkyl-1,3,2-dioxaboracycloalkane (Scheme 22).

Figure 2. The nmr spectrum of 1-O-benzoyl-1,2,3-propanetriol. 53
100 MHz spectrum with TMS lock, D_2O exchange.

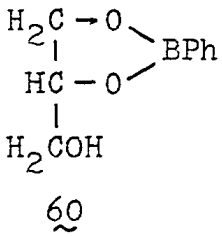


Scheme 22

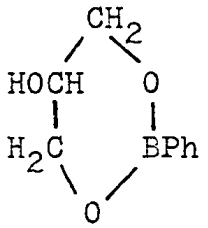

Et2BO
CH2OBEt2
CH
CH2
Et2BO
55
Route 1: >150° C
- BEt3
Route 3: 20° C
(+ >BH) - BEt3
HO
CH2OH
CH
CH2
HO
50
Route 2: + 2 BEt3
120° C, - 3 EtH
O
CH2OBEt2
EtB
O
56
MeOH
O
CH2OH
Et B
O
57
C6H5COCl
HO
O
CH2OCC6H5
CH
CH2
HO
59
MeOH
20° C
O
CH2OCC6H5
EtB
O
O
58

This reaction was found to proceed only through the five-membered cyclic intermediate 56. This would mean that five-membered cyclic boronates are more readily formed or that substituents on the secondary carbon atom are more easily removed.

In 1965, Weigel et al[41] prepared the phenylboronate of glycerol which could have either structure 60 or 61.



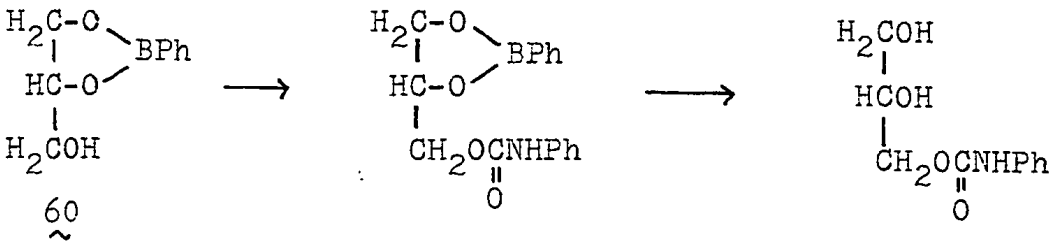
60



61

Their analysis of the product obtained involved the preparation of the O-phenylcarbamoylglycerol phenylboronate 62, hydrolysis of the boronate and direct treatment of the crude mixture with sodium periodate.

Scheme 23



60 → 62 → 63

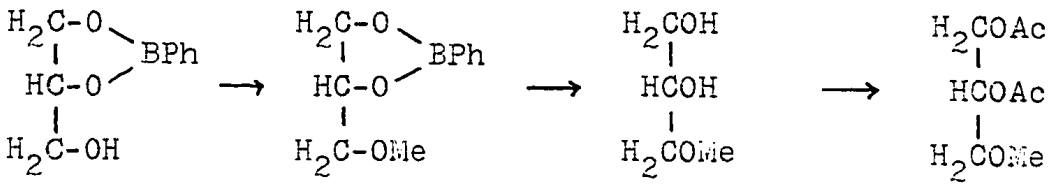
It was found that the O-phenylcarbamoylglycerol consumed 1.0 moles of periodate. Therefore the product was all

derived from the five-membered cyclic boronate 60.

In 1973, McKinley and Weigel [27] reported that slight modification of the experimental conditions gave an O-phenylcarbamoylglycerol which reduced only 0.84 moles of periodate. This indicates that the phenylboronate was a mixture of isomers 60 and 61.

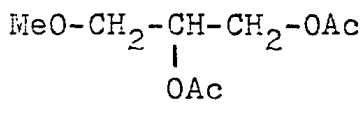
McKinley and Weigel[27] have also reported another method for determining the composition of the phenylboronates. The phenylboronates were prepared by refluxing the triol with phenylboronic anhydride, $(PhBO)_3$, in benzene or toluene for several hours. The structure of the phenylboronates was determined as described in Scheme 24, by (a) treatment of the phenylboronate with diazomethane and boron trifluoride to methylate the free hydroxyl group; (b) hydrolysis of the boronate ester and (c) acetylation of the resulting groups.

Scheme 24

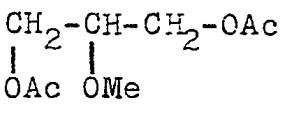


60 64 65 66

The reaction mixture was analyzed by glc-ms and it was found to consist of 31% of 66 and 69% of isomer 67 resulting from the cyclic boronates 60 and 61 respectively.



66



67

The crude product was recrystallized from benzene-hexane yielding a mixture enriched in 66 (61% of 66).

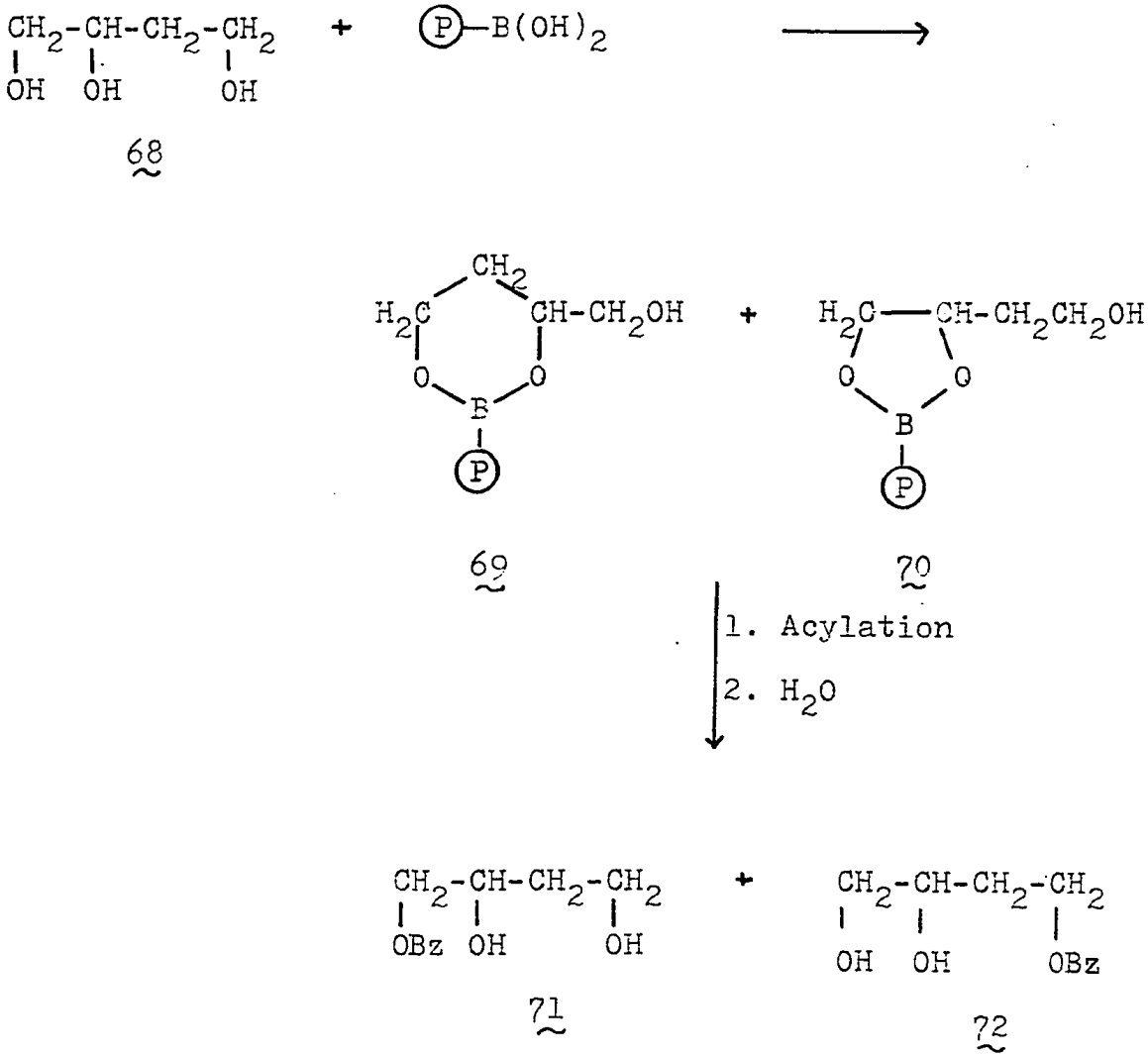
However this report lacks experimental data so that it is difficult to evaluate the reliability of the analytical technique involved. For example, although some acylated derivatives were prepared, no nmr spectra were recorded. It is difficult to determine whether the glc-ms studies were carried out on the crude product or on a "purified" fraction.

The discrepancy between our results and the most recent results of Weigel and coworkers is difficult to explain since it seems unlikely that phenylboronic acid and polystyrylboronic acid would behave so differently. It is interesting to note however that the results obtained by Weigel in 1973 are in such sharp contrast with those he obtained earlier using a different and usually reliable method of analysis of 1,2-diols. The nmr spectrum (Figure 2) of our reaction product (53 + 54) clearly indicates that the five-membered ring boronate is formed preferentially and that only a very small amount of product arising from the six-membered ring boronate is present.

If the results which were obtained in the reaction of glycerol with polystyrylboronic acid are applicable

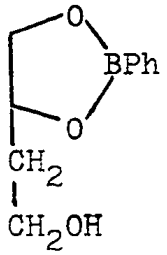
to 1,2,4-butanetriol, the reaction would be expected to proceed mainly through a five-membered boronate such as 70 and thus yield mainly 72 after acylation.

Scheme 25

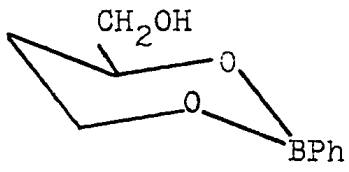


However when the reaction was carried out under conditions similar to those used earlier for glycerol the crude product was found to contain both isomers 72 and 71 (Bz = $-COC_6H_5$) in a 17% to 83% proportion, as determined from the nmr spectra. Hence the product resulting from esterification of the six-membered cyclic boronate 69 predominated.

This result, although slightly surprising, is in agreement with earlier work on 1,2,4-butanetriol using phenylboronates or ethylboronates. McKinley and Weigel[27] treated the phenylboronates of 1,2,4-butanetriol in the manner described in Scheme 24. Approximately one-half of the resulting mixture could be distilled. The nonvolatile residue contained 89% of the derivative of isomer 74 and the distillate 88% of this isomer.

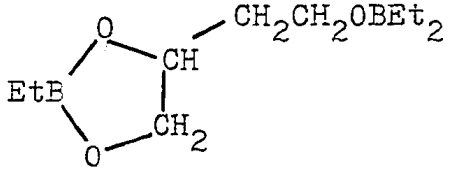


73

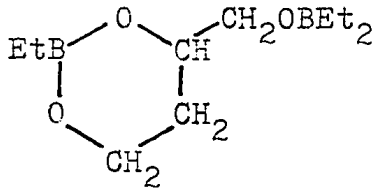


74

Dahlhoff and Köster[29] prepared the monobenzoyl and monoacetyl derivatives of 1,2,4-butanetriol according to the procedure described in Scheme 22.



75



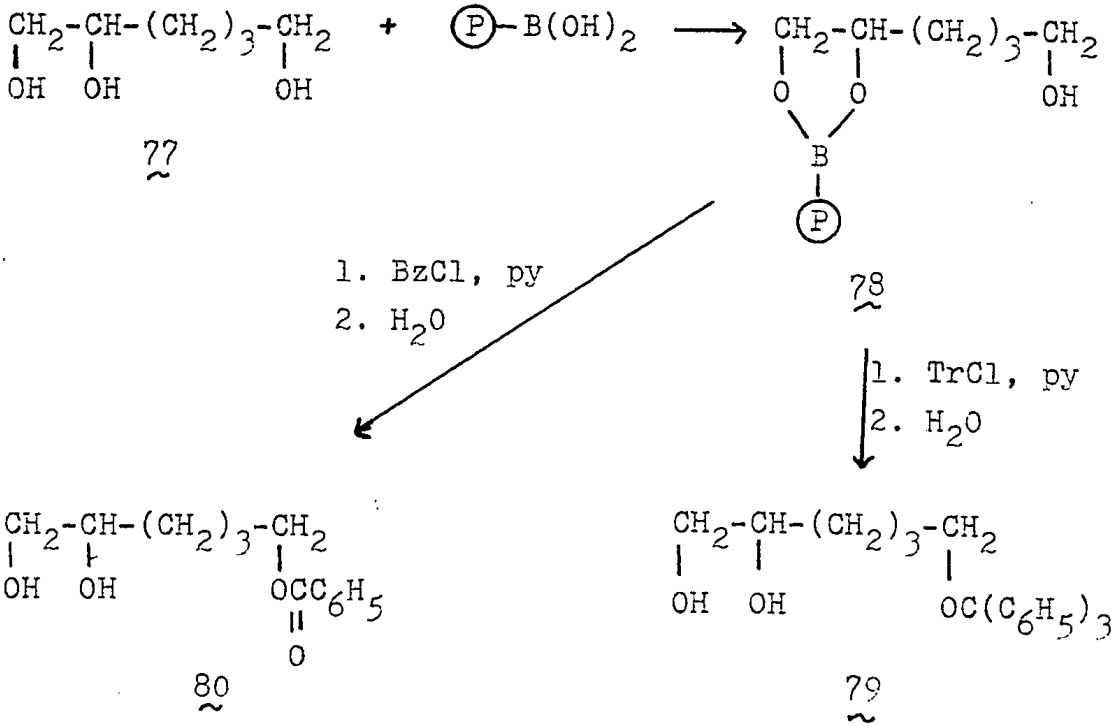
76

The derivative of intermediate 76, the six-membered cyclic boronate, composed 90% of the product.

Various blocking groups can be used to protect the free hydroxyls in the boronates. Esters of carboxylic acids, such as benzoates and acetates, have been used successfully. For example, benzoate esters of both 1,2,3-propanetriol and 1,2,4-butanetriol were prepared. Sulfonic acid esters, such as mesylates or tosylates, are also suitable protecting groups. Trityl ethers are also suitable protecting groups for free primary hydroxyls, such as the C_6-hydroxyl of many carbohydrates.

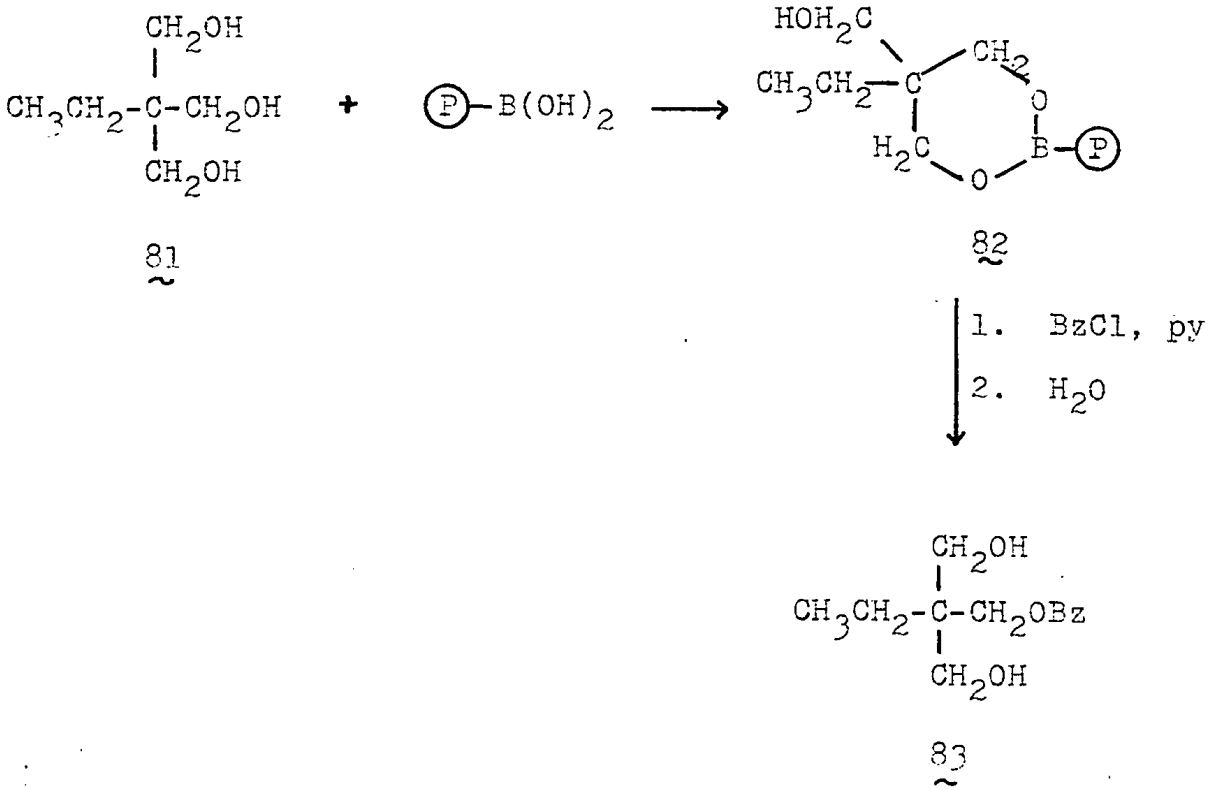
The monotrityl ether and the monobenzoyl ester of 1,2,6-hexanetriol were prepared. As was expected only one product was obtained in both of these reactions, that derived from the five-membered cyclic intermediate.

Scheme 26



Coupling of a diol functionality to the polystyrylboronic acid resin is also useful in the preparation of monoacyl derivatives of symmetrical triols such as 2-ethyl-2-(hydroxymethyl)-1,3-propanediol. Only one product is possible thus eliminating the problem of separation of mono-, di-, and tri-acylated derivatives that would result from a classical synthesis.

Scheme 27



C. Protection of carbohydrates

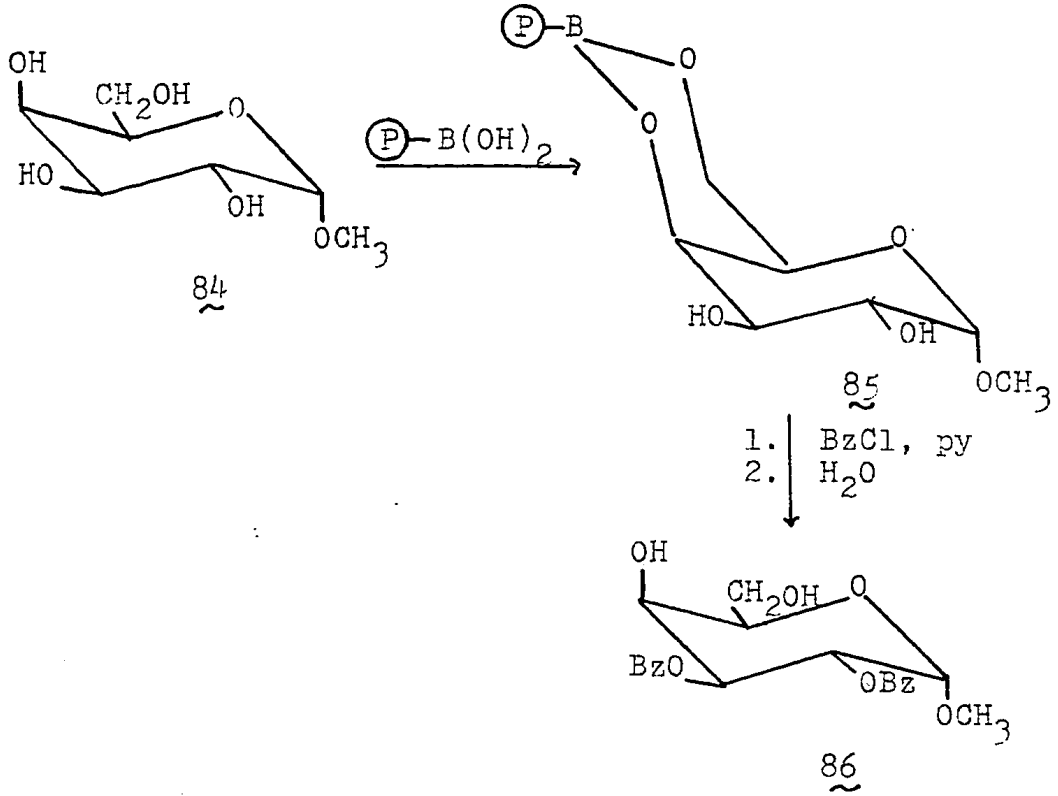
The polystyrylboronic acid resin has many applications in carbohydrate chemistry. Certain compounds which are difficult or impossible to prepare by normal routes can be made by selectively blocking two of the hydroxyl groups as resin-bound boronates. After formation of the derivative, the product is easily cleaved from the resin by treatment with water. The very mild reaction conditions make this ideal for acid-labile carbohydrates. The selectivity of the resin towards hydroxyls which are cis to each other and to those which form a six-membered ring rather than a five-membered one has been investigated as follows using a simple partial acylation of selected carbohydrates as model systems.

Methyl α-D-galactopyranoside (84)[42] contains four hydroxyl groups and thus offers the possibility of formation of four different 5- or 6-membered cyclic boronates. Two of these can be disregarded. A 6-membered ring boronate between the C_2 and C_4 trans hydroxyls is geometrically impossible. A 5-membered ring boronate cannot be formed between C_2 and C_3 since the two trans hydroxyls cannot be brought into the same plane. Of the remaining two cyclic boronates, one involves the formation of a strain-free six-membered ring between the hydroxyls at C_4 and C_6 and this is likely to be formed. The other would involve a five-membered ring between hydroxyls at C_3 and C_4. Such a cyclic boronate could be obtained if

the sugar molecule assumed a half-chair conformation, a definite possibility but less likely than the previous one in which the sugar molecule was in the preferred chair conformation.

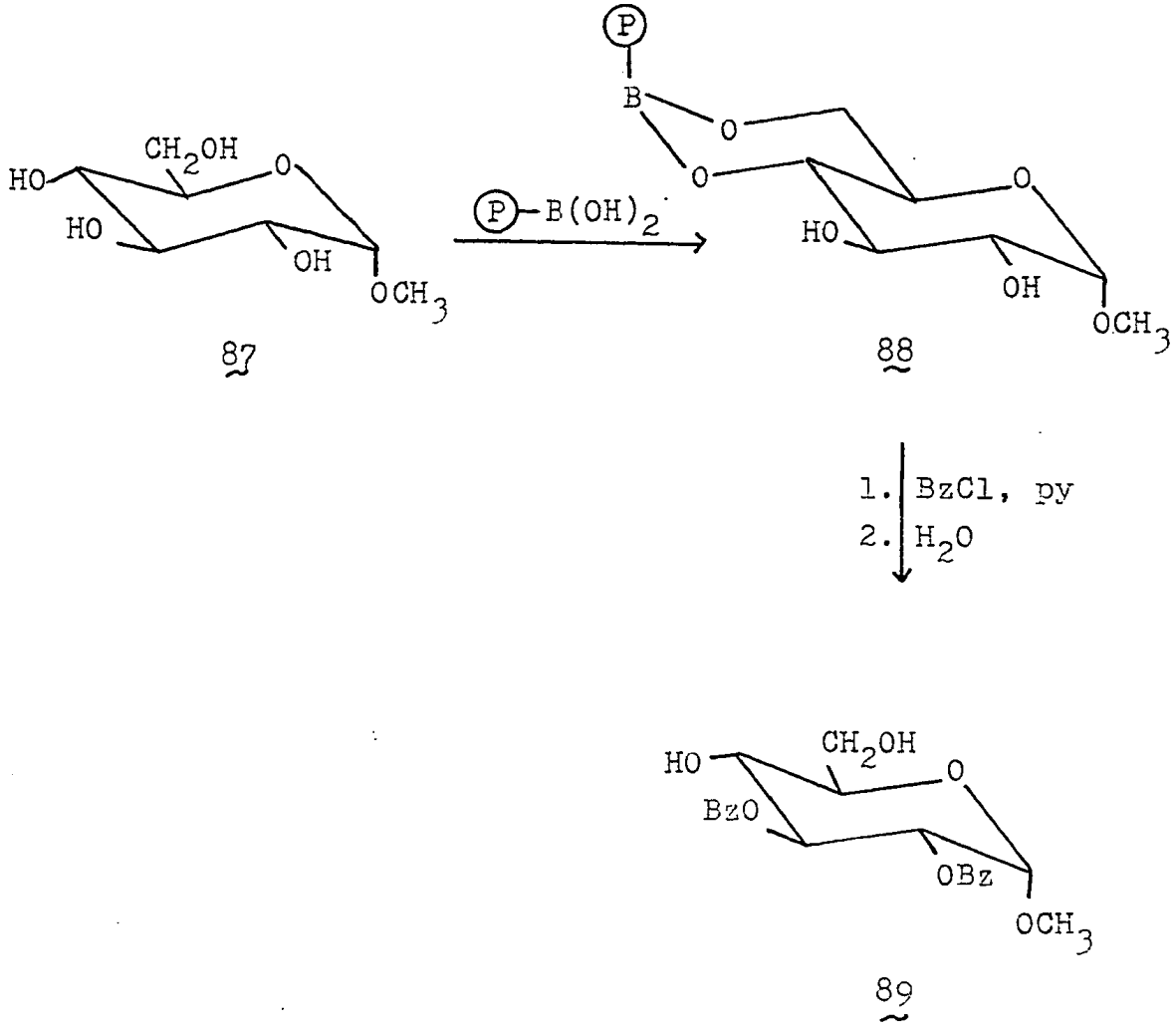
Coupling of methyl α-D-galactopyranoside to the resin followed by benzoylation of the remaining hydroxyls gave only one product, the known[43] methyl 2,3-di-O-benzoyl-α-D-galactopyranoside (86) which was further characterized by the preparation of its crystalline 4,6-di-O-(p-tolylsulfonyl) derivative.

Scheme 28



In the case of methyl α-D-glucopyranoside[42] (87) in which vicinal hydroxyls are trans to each other only two cyclic boronates between cis diols are possible. Five-membered rings formed from trans hydroxyl groups are the least likely of the possible intermediates. The cis diol formed between C_2 and C_4 would require an intermediate in which all the substituents (except C_1) would be axial. This would certainly be less favorable than the formation of a strain-free C_4-C_6 cyclic boronate.

Scheme 29

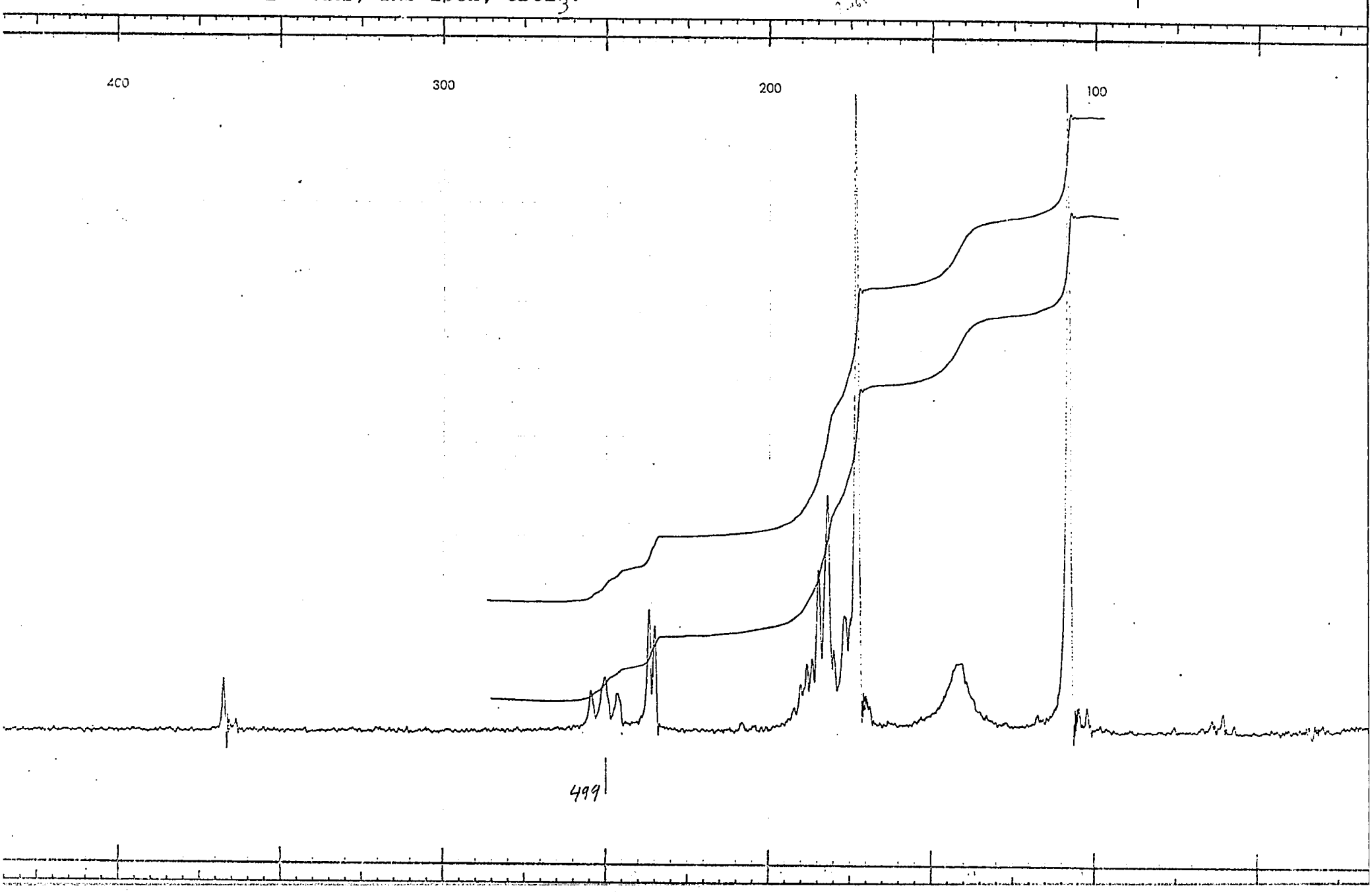


87 88 89

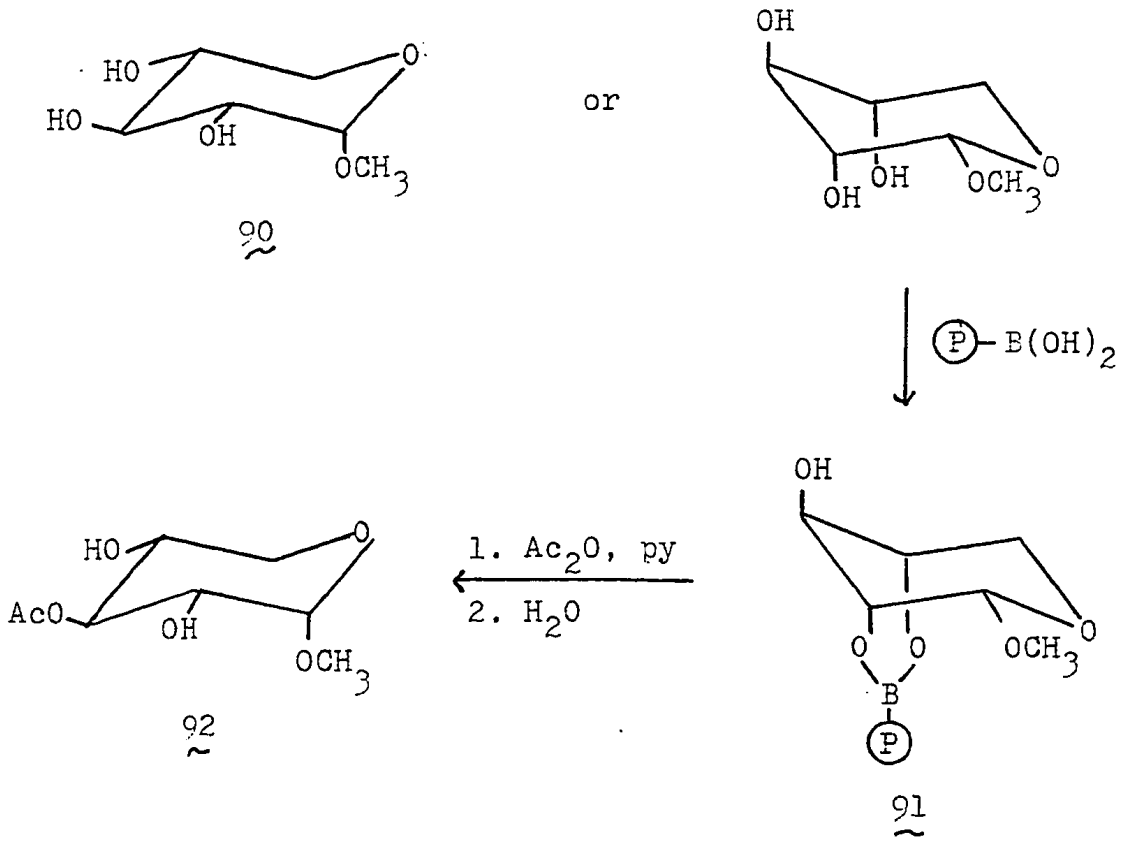
As in the previous case only one product, methyl 2,3-di-O-benzoyl-α-D-glucopyranoside (89) was obtained in the reaction. The product was characterized by its spectral and physical properties which were in agreement with those reported in the literature.[23,44]

Monoacyl derivatives of methyl α- and β-D-xylopyranosides have also been prepared. The xylosides have the same configuration as the glucosides except that they are missing the $-CH_2OH$ group at C_5. Hence the vicinal hydroxyls are <u>trans</u> to each other. Thus the C_2 and C_4 hydroxyls are <u>cis</u> to each other and can form a six-membered ring boronate if the three hydroxyl substituents come in axial positions (91). Although this axial arrangement is not normally the preferred one, the six-membered boronate which is obtained in this case is favored over any other five-membered ring boronate formed on vicinal hydroxyl groups. The vicinal <u>trans</u> diol would require twisting of the conformation to bring both hydroxyls into the same plane. Hence the only product of the reaction is methyl 3-O-acetyl-α-D-xylopyranoside (92). The nmr spectrum of this compound is shown in Figure 3.

Figure 3. The nmr spectrum of methyl 3-O-acetyl-α-D-xylopyranoside. 92.
100 MHz, TMS lock, $CDCl_3$.



Scheme 30

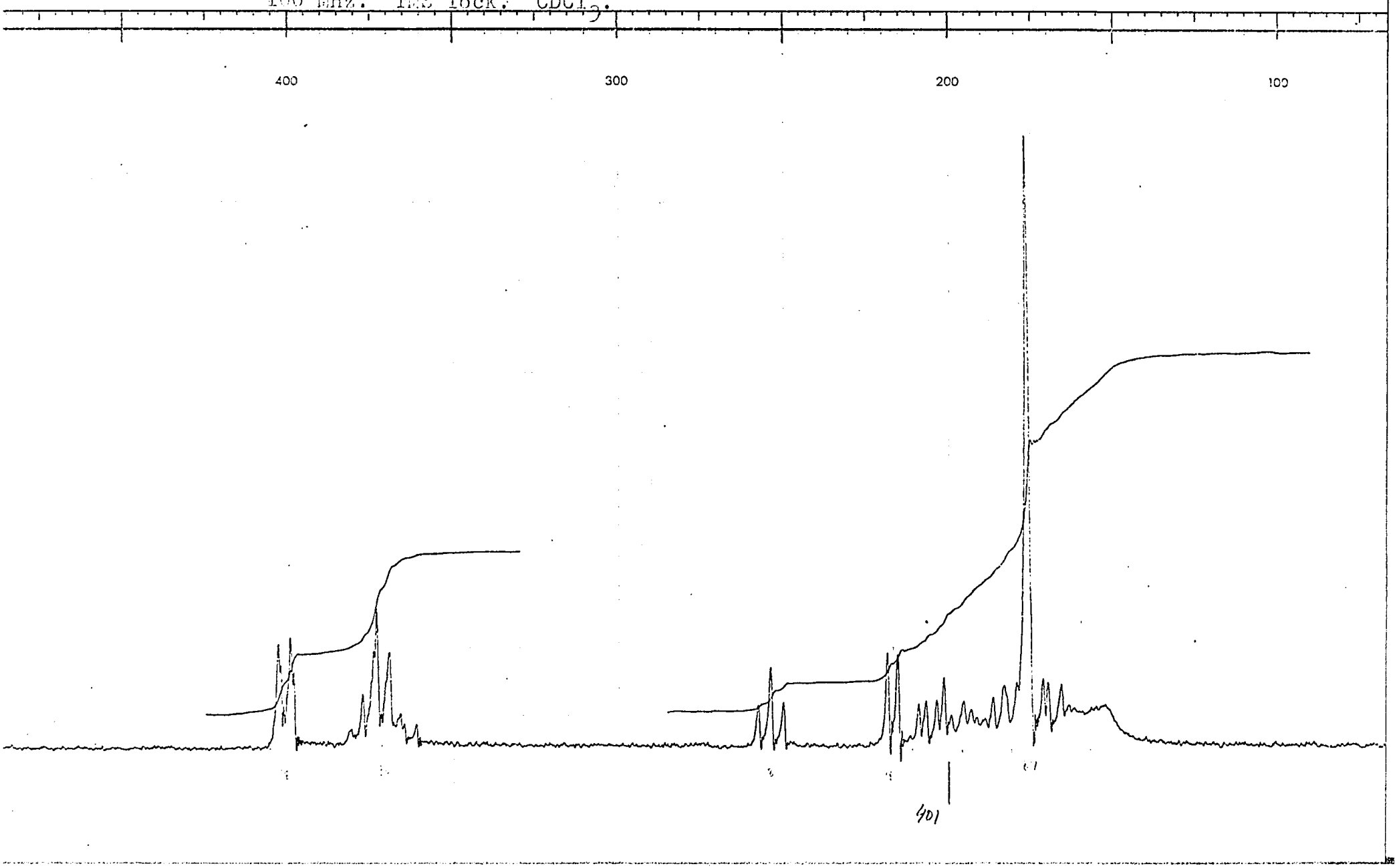


90 or 91 → 92

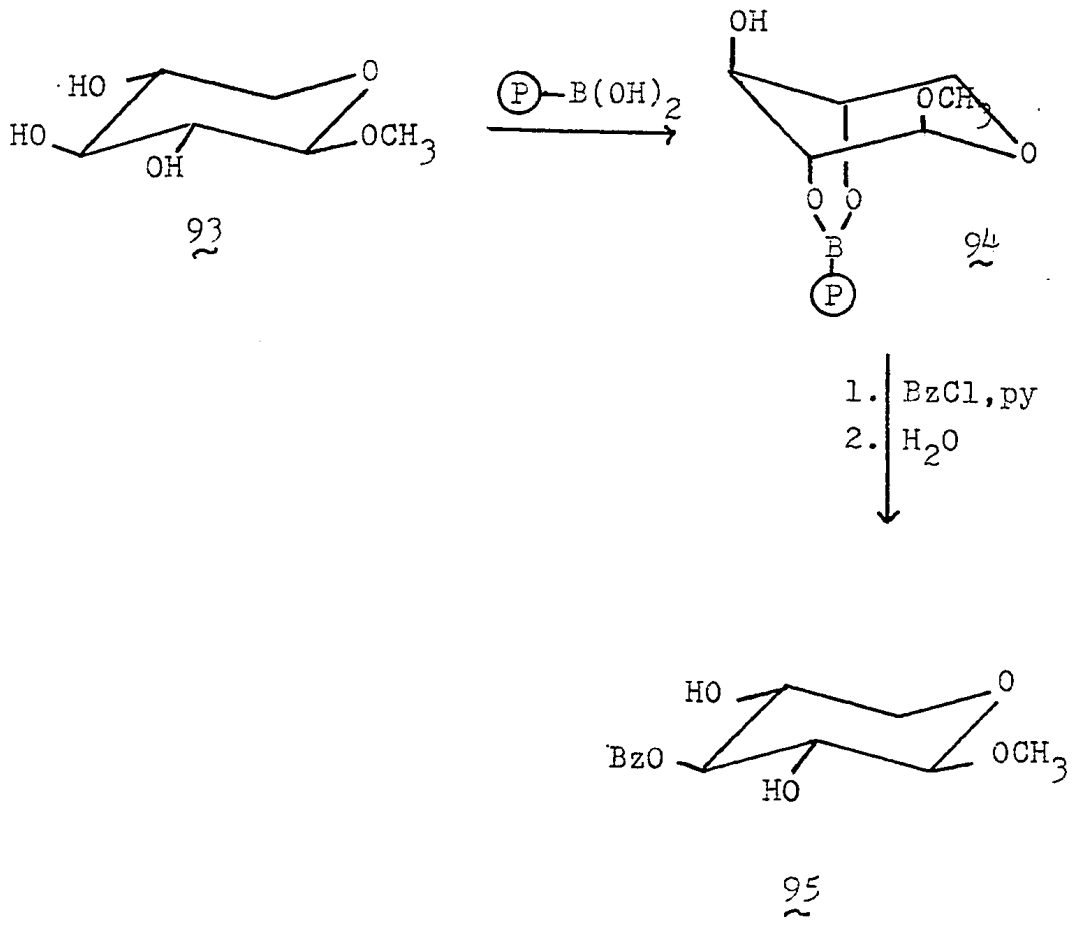
Similarly the 3-O-benzoyl derivative of methyl β-D-xylopyranoside has been prepared. The structure of the intermediate cyclic boronate is the same as above except that all substituents are in axial positions (94). The nmr spectrum of 95 is shown in Figure 4.

Figure 4. The nmr spectrum of methyl 3-O-benzoyl-β-D-xylopyranoside. 95

100 MHz. TMS lock. $CDCl_3$.



Scheme 31



93 94 95

Both of these compounds have been prepared by Ferrier et al[30] using phenylboronates as blocking groups. The work-up involved crystallization of the phenylboronate, acylation, recrystallization of the acylated phenylboronate, cleavage by exchange with 1,3-propanediol, separation from the propanediol and derivatives and finally crystallization of the acylated xyloside. Yields at each step were in the order of 80 to 90%. For example, the preparation of methyl 3-O-acetyl-α-D-xylopyranoside

by Ferrier resulted in a 64% yield after five steps while the solid phase preparation gave an 84% yield with all reactions being carried out in one flask with no intermediate purifications necessary.

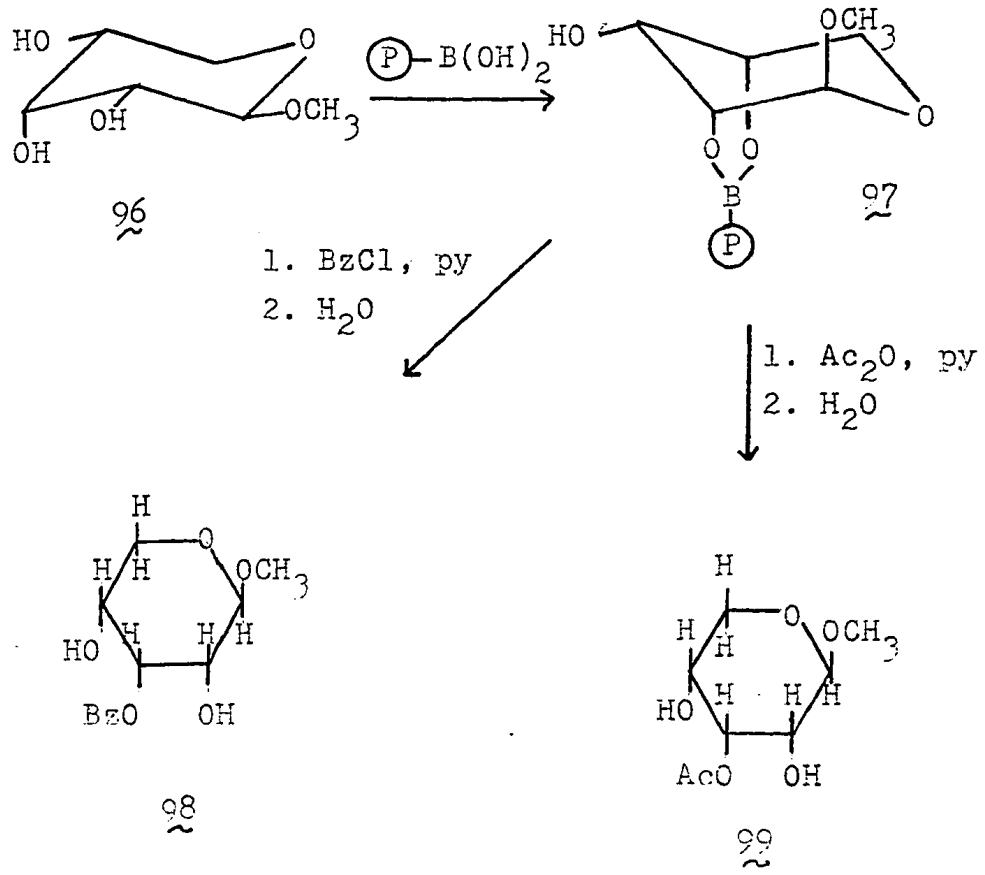
Monoacyl derivatives of methyl β-D-ribopyranoside have also been prepared. The sugar has an all cis 1,2,3-triol system. Thus the formation of two five-membered cyclic boronates between cis hydroxyls is possible. As well a six-membered boronate can be formed when most of the substituents are in axial positions.

The attempted synthesis of a monoacylated derivative of methyl β-D-ribopyranoside using an isopropylidene blocking group by Barker et al[45] resulted in a mixture of products. Treatment of methyl β-D-ribopyranoside with acetone in the presence of an acid catalyst formed isopropylidene derivatives at the C_2-C_3 and C_3-C_4 sites as well as causing ring contraction with the formation of ribofuranoside derivatives.

Ferrier and Prasad[46] prepared methyl 3-O-acetyl-β-D-ribopyranoside by using a phenylboronic acid protecting group. Although several isomers were possible only one was found. The structure of the product was identified as the 3-O-acetyl derivative since it did not undergo periodate oxidation.

Treatment of methyl β-D-ribopyranoside with the polystyrylboronic acid resin yields only one product, the 3-O-acyl derivative, as described in Scheme 32.

Scheme 32



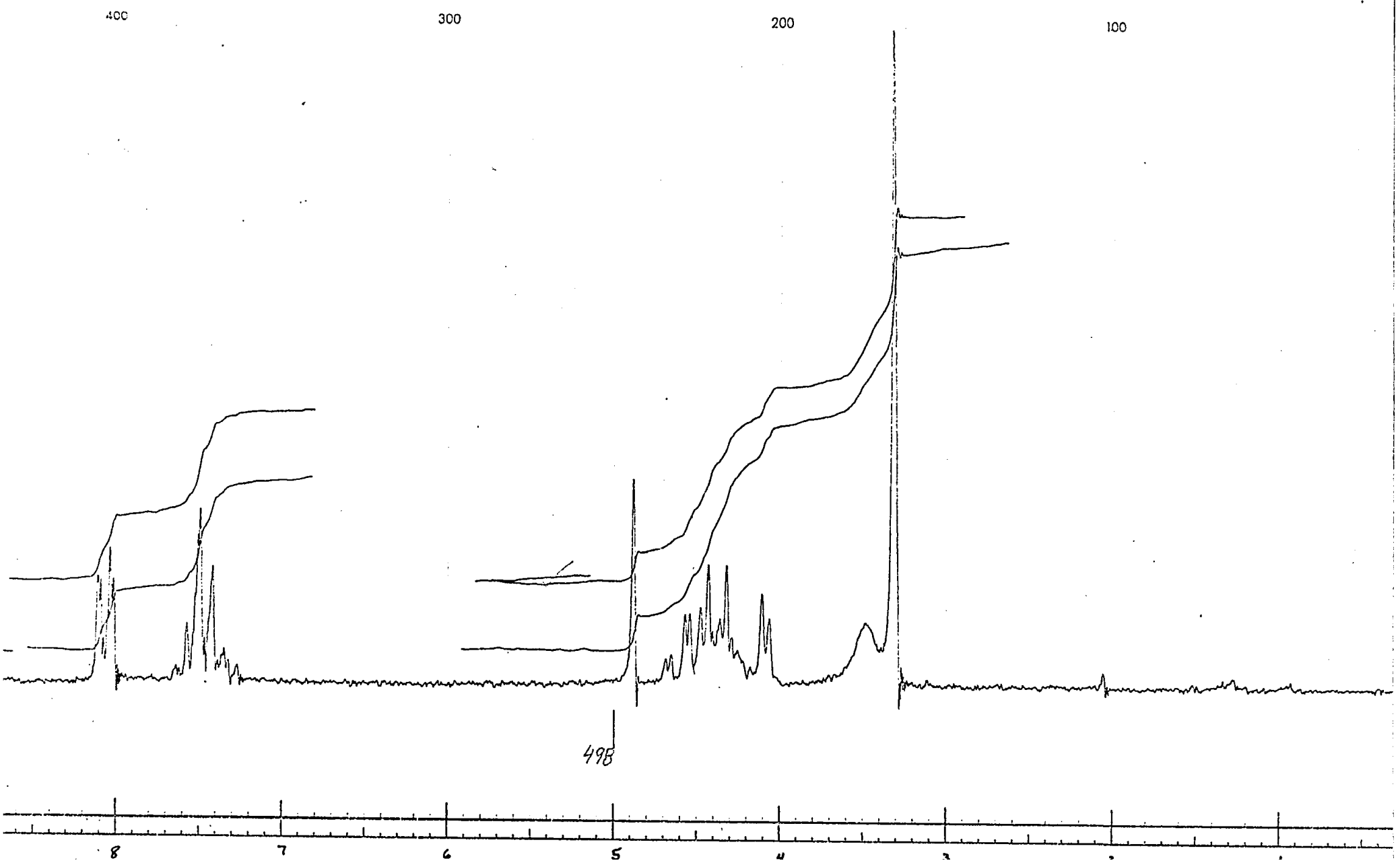
96 97 98 99

The structure of the product was determined by comparison of the properties of the acetylated derivative to those reported by Ferrier[46]. The 3-O-benzoyl derivative had not been synthesized previously. The classical synthesis, analagous to that described for the xylosides, resulted in an overall yield of 30%. The solid phase method gave higher yields (in the order of 50-60%) with much simpler reaction conditions.

The acetylation of the resin-bound ribopyranoside

Figure 5. The nmr spectrum of methyl 3-O-benzoyl-β-D-ribopyranoside. 98

100 MHz spectrum, TMS lock, $CDCl_3$ solution.



was also attempted using acetyl chloride in pyridine. This reaction gave a lower yield of the desired product since cleavage of the sugar from the resin seemed to have occurred.

The protection of the C_2 and C_4 hydroxyls as resin-bound cyclic boronates has many possible applications. It can be used for the selective acylation of a C_3 hydroxyl as described and also for the selective removal of the C_3 substituent.

The monobenzoyl and monoacetyl derivatives of methyl α-L-rhamnopyranoside (methyl 6-deoxy-α-L-manno-pyranoside) have been prepared.

Scheme 33

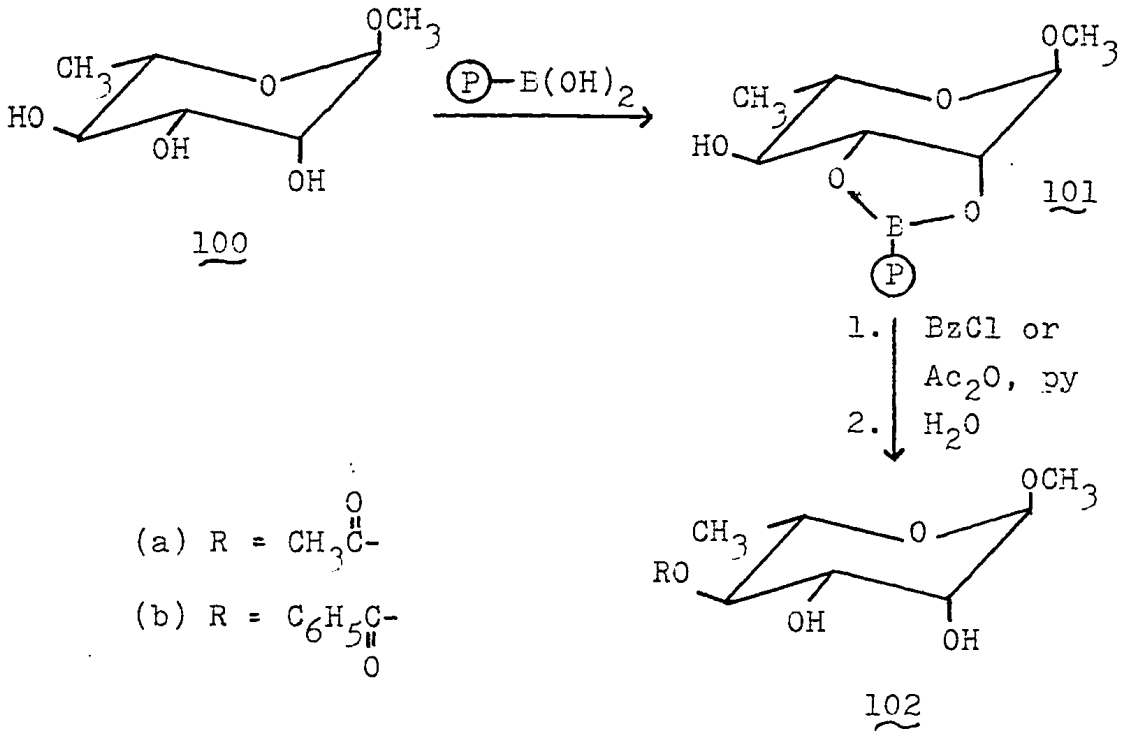
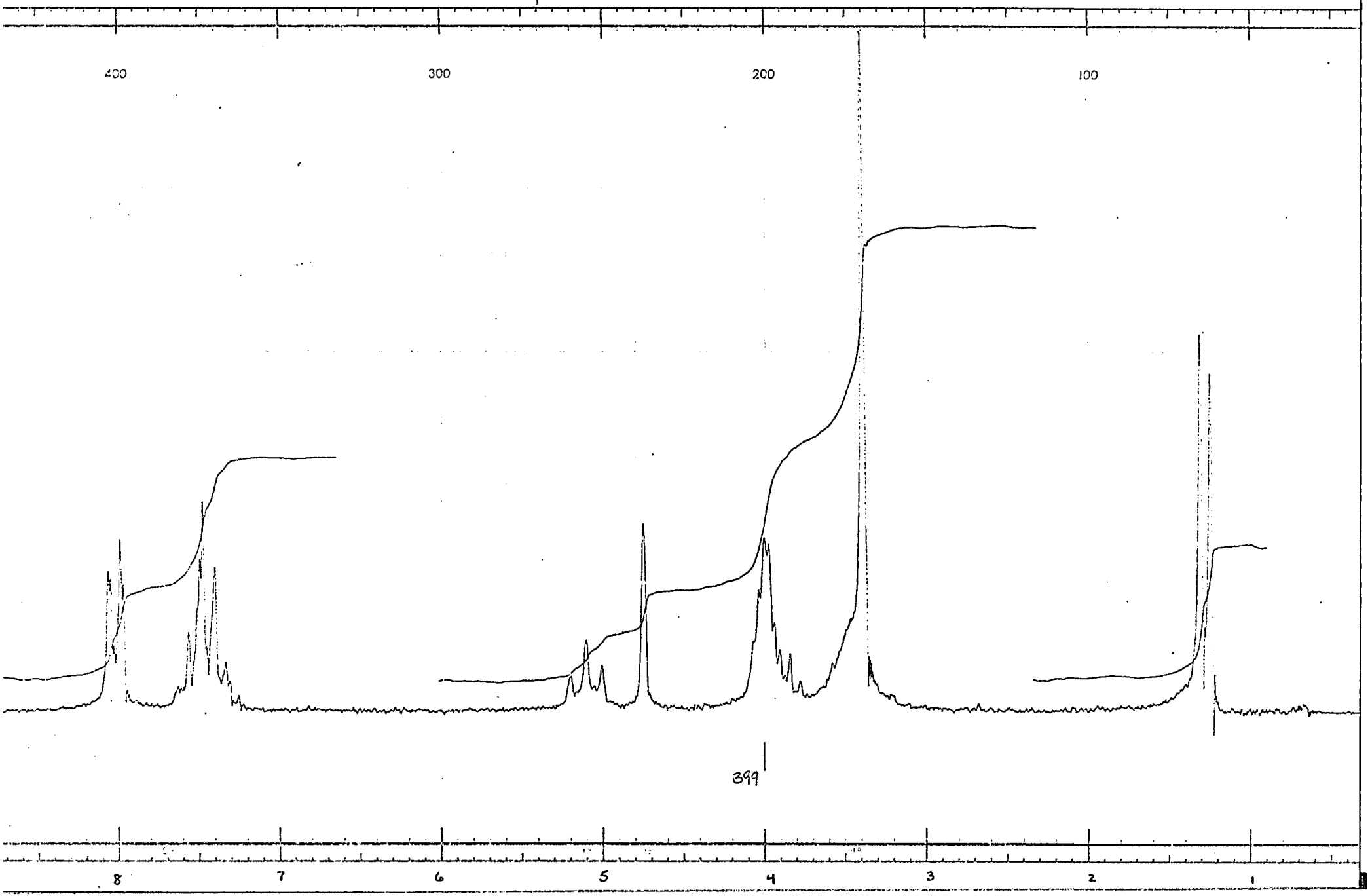


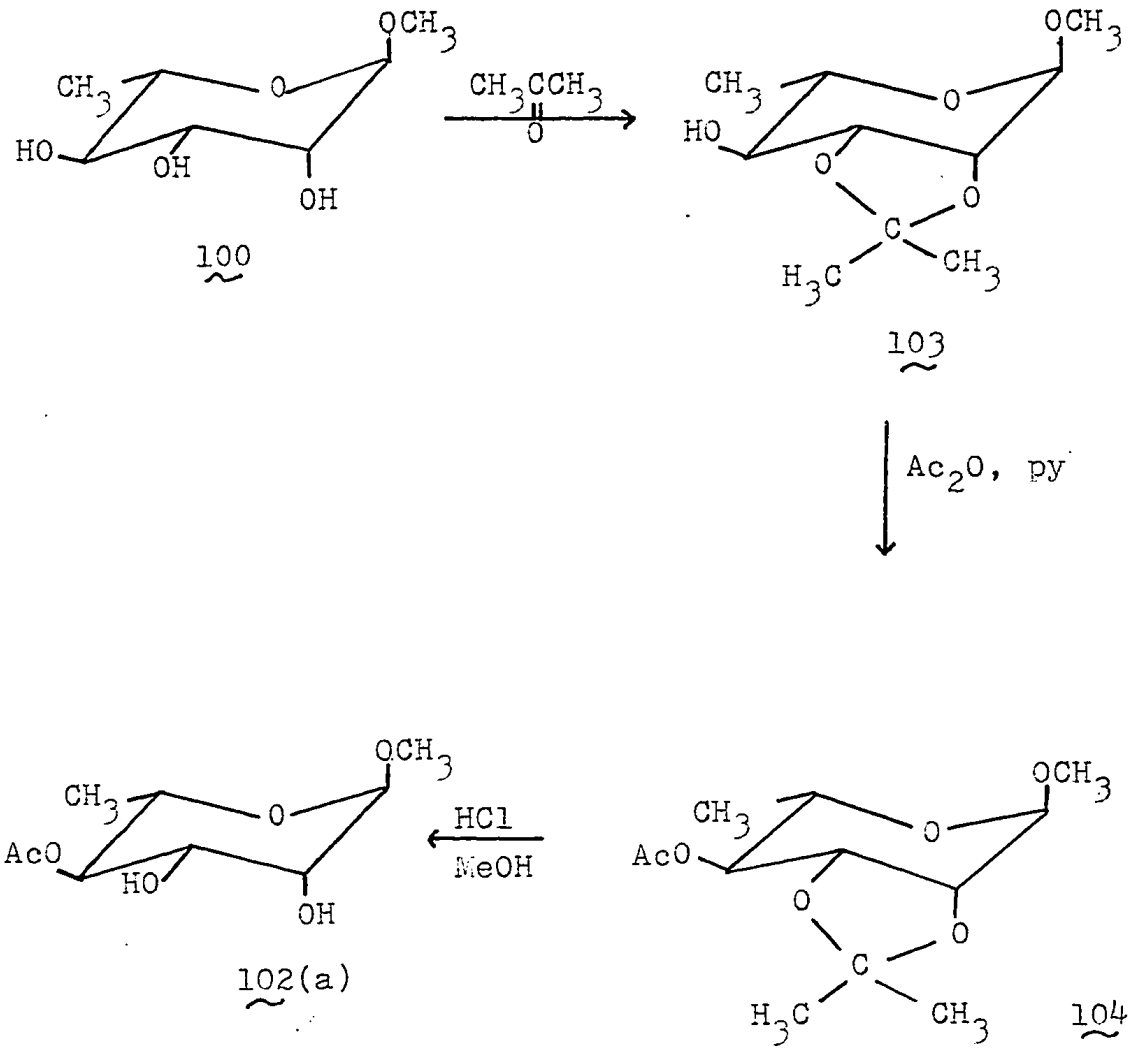
Figure 6. The nmr spectrum of methyl 4-O-benzoyl-α-L-rhamnopyranoside. 102(b)
100MHz, TMS lock, $CDCl_3$ solution.



In this case the preferred intermediate is the five-membered cyclic boronate formed between the <u>cis</u> hydroxyl groups on C_2 and C_3. This boronate would be more stable than those formed between the <u>trans</u> hydroxyls on C_3 and C_4 or those on C_2 and C_4.

The acetyl derivative (102a) has been prepared by a classical synthesis by Richardson and Williams[47] using an isopropylidene blocking group.

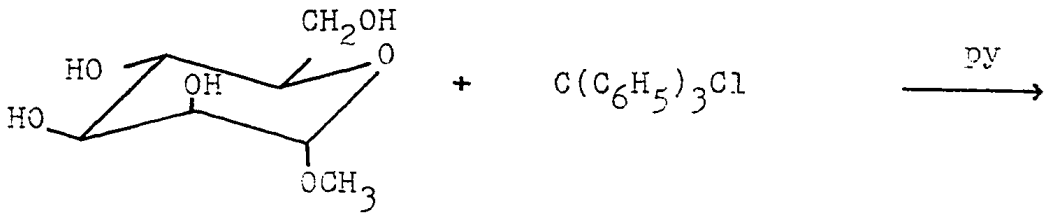
<u>Scheme 34</u>



The yield of methyl 4-O-acetyl-α-L-rhamnopyranoside prepared via the isopropylidene derivative was 40% while that from the polystyrylboronate was 65%.

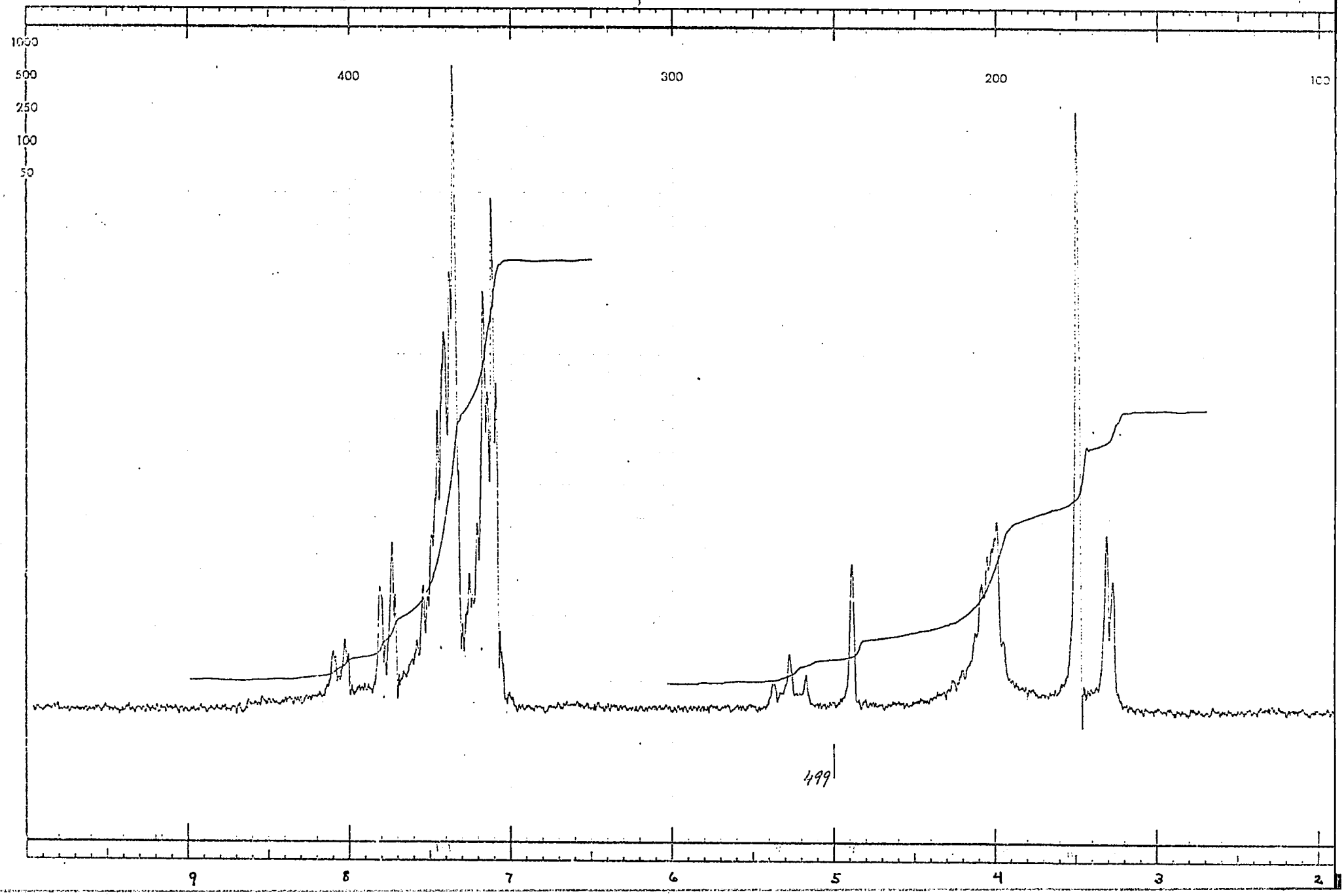
A reaction of methyl α-D-mannopyranoside with the polystyrylboronic acid resin would, by analogy with the corresponding glucoside and galactoside derivatives, be expected to yield the C_4-C_6 boronate. However the method can be used to prepare a 4-O-acyl derivative of methyl α-D-mannopyranoside through a polymer-bound 2,3-boronate after blocking of the C_6-hydroxyl group. This reaction sequence can be carried out rapidly and in one pot by tritylation of the C_6-hydroxyl, formation of the 2,3-boronate, benzoylation, removal of all impurities and unbound material by filtration, and finally cleavage from the resin.

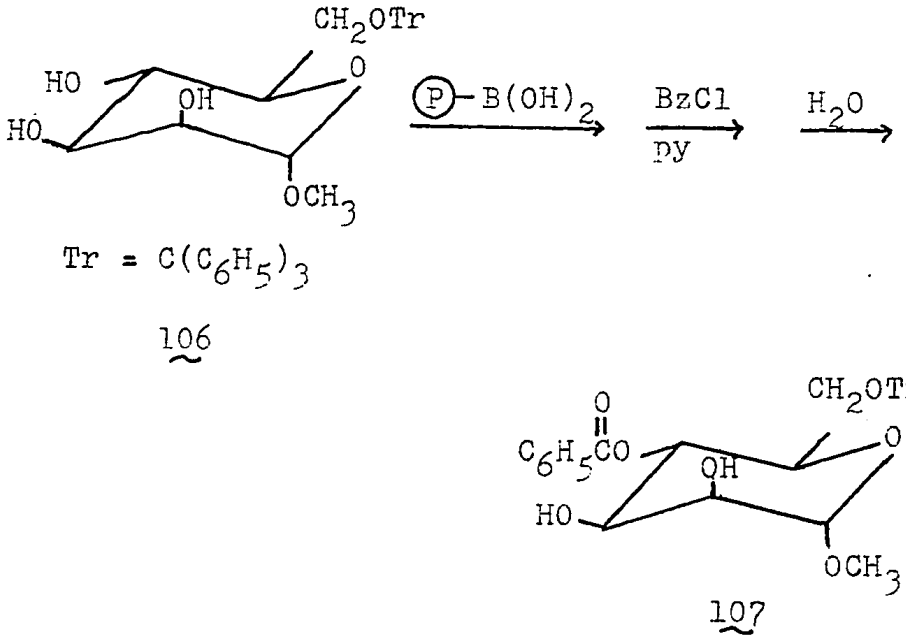
Scheme 35



105

Figure 7. The nmr spectrum of methyl 4-O-benzoyl-5-O-trityl-α-D-mannopyranoside. 107
100 MHz spectrum, TMS lock, $CDCl_3$ solution.



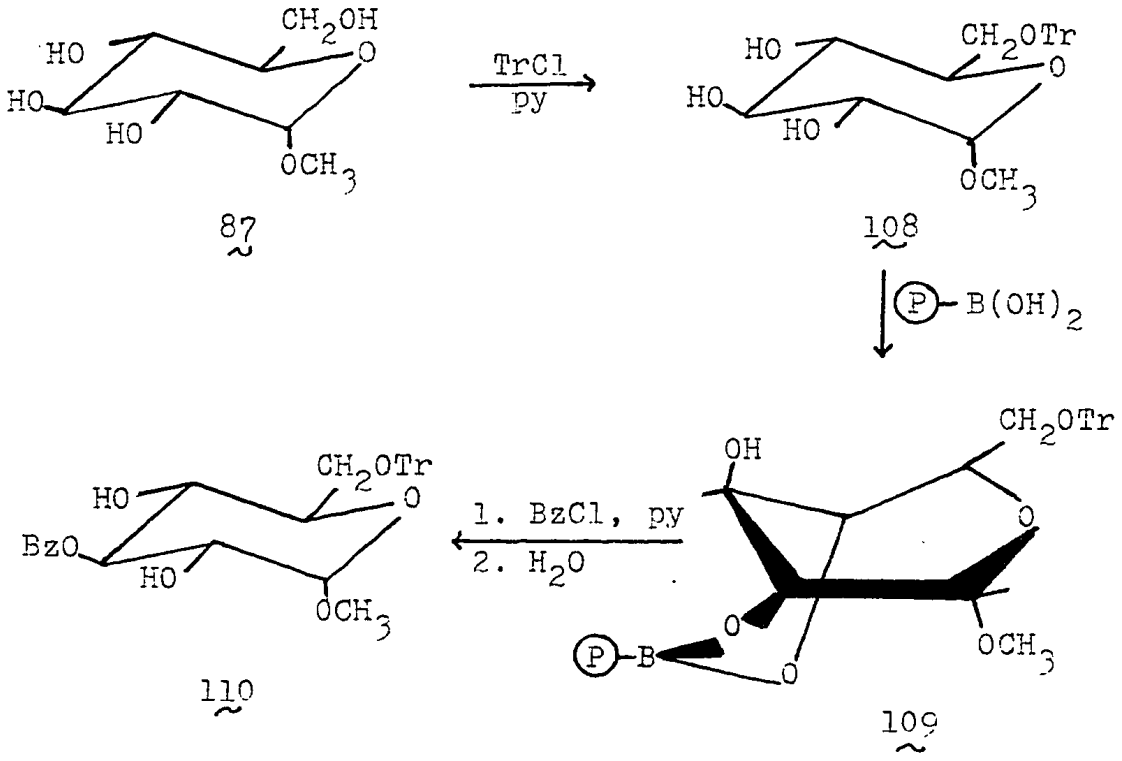


The yield of this reaction was quite low (32%) but this is not unexpected in view of the large steric requirement of the polymer-bound boronate. It is likely that the yield could be improved considerably if the unbound mannoside was recovered by filtration prior to the benzoylation and recycled. However the recovery was not attempted in this instance.

Similarly a 3-O-acyl derivative of methyl α-D-glucopyranoside could be prepared on the polystyrylboronic acid resin after protection of the C_6-hydroxyl group, for example by formation of a trityl ether. The intermediate cyclic boronate 109 is likely to be found in a twist boat conformation such as that shown in Scheme 36 since in this conformation the interaction between substituents

are minimized at least in comparison to other possible conformations.

Scheme 36



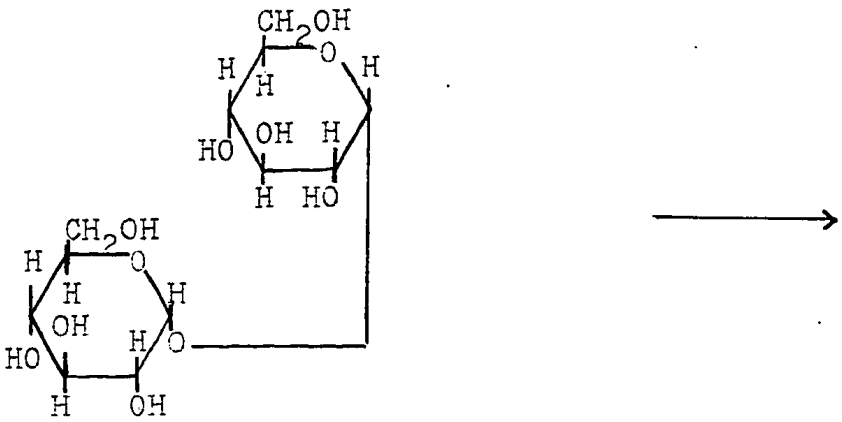
87 108 109 110

When the reaction was attempted it was found that a large proportion (56%) of the tritylated sugar remained uncoupled, presumably due to steric difficulties encountered in the formation of 109. The uncoupled sugar could however be recovered unchanged and recycled after a simple filtration. Following benzoylation of the C_3-hydroxyl and cleavage of the product form its support, methyl 3-O-benzoyl-6-O-trityl-α-D-glucopyranoside 110 was obtained in 82% yield

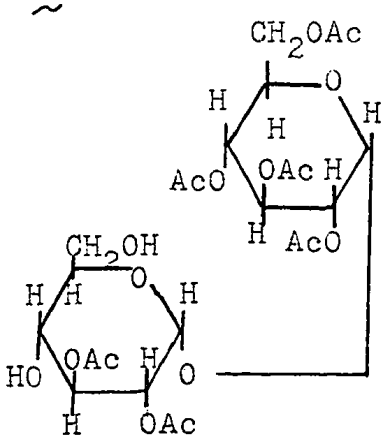
(the yield is based on the product converted after recycling).

The mild conditions of the coupling and decoupling of the resin to the polyol make it ideal for protection of acid-labile derivatives. These compounds cannot be prepared using blocking groups such as the isopropylidene group which must be removed by acid. An example of this type of reaction is the hexaacetylation of α,α-trehalose in which the glycosidic linkage would be cleaved in acidic medium should isopropylidene or benzylidene derivatives be used.

Scheme 37



111



112

Since α,α-trehalose 111 is composed of two glucose units linked through their anomeric centers, coupling to the resin could be expected to yield the 4,6-cyclic boronate as in the case of glucose. Coupling of the α,α-trehalose to the resin through both extremities is possible but unlikely as it would involve interaction of two pairs of hydroxyls of the sugar moiety with two active sites of the resin in the proper position.

Once again due to the large steric bulk of α,α-trehalose, only a small percentage of the starting material was coupled to the resin. However recovery and recycling of unreacted α,α-trehalose make this a worthwhile reaction in terms of yield. As in several other preparations the yield obtained (44%) could probably be improved considerably by the use of a better polystyrylboronic acid resin.

D. Separation of diols by affinity chromatography

The high selectivity shown by the polystyrylboronic acid resin in the protection of cis hydroxyl groups of polyols can be applied in affinity chromatography to the separation of polyols according to their stereochemistry. Cis - trans diol mixtures can be efficiently separated on the resin using a batch or a column technique.[48]

Commercially available cyclohexanediols exist as a mixture of cis and trans isomers, often present in a 1:1 ratio. These have been separated using n-butylboroxine[36] or triethylborate[37]. However these separations

which required the fractional distillation of boron-containing intermediates were relatively time-consuming and, in some instances, were not possible due to the similarity of the boiling points of the boronates of the isomeric diols.

The separation of the 1,2-cyclohexanediols by a batch technique is shown in Scheme 38. It involved the reaction of the diol mixture with a suspension of the polystyrylboronic acid resin in dry benzene or pyridine with azeotropic removal of water, followed by filtration to effect the separation of the trans diol which, being unbound, remained in solution and was obtained in 80% yield (40% of the original mixture).

The resin was then washed with a dry solvent to remove any trans diol which might have been trapped in its pores. This washing gave a mixed fraction containing both trans and cis diols indicating that some of the cis diol had leached from the resin. Finally, cleavage of the cis diol from the resin and regeneration of the polymer was accomplished in a simple step by addition of a small amount of water and an 84% yield of the pure cis diol was obtained.

Scheme 38

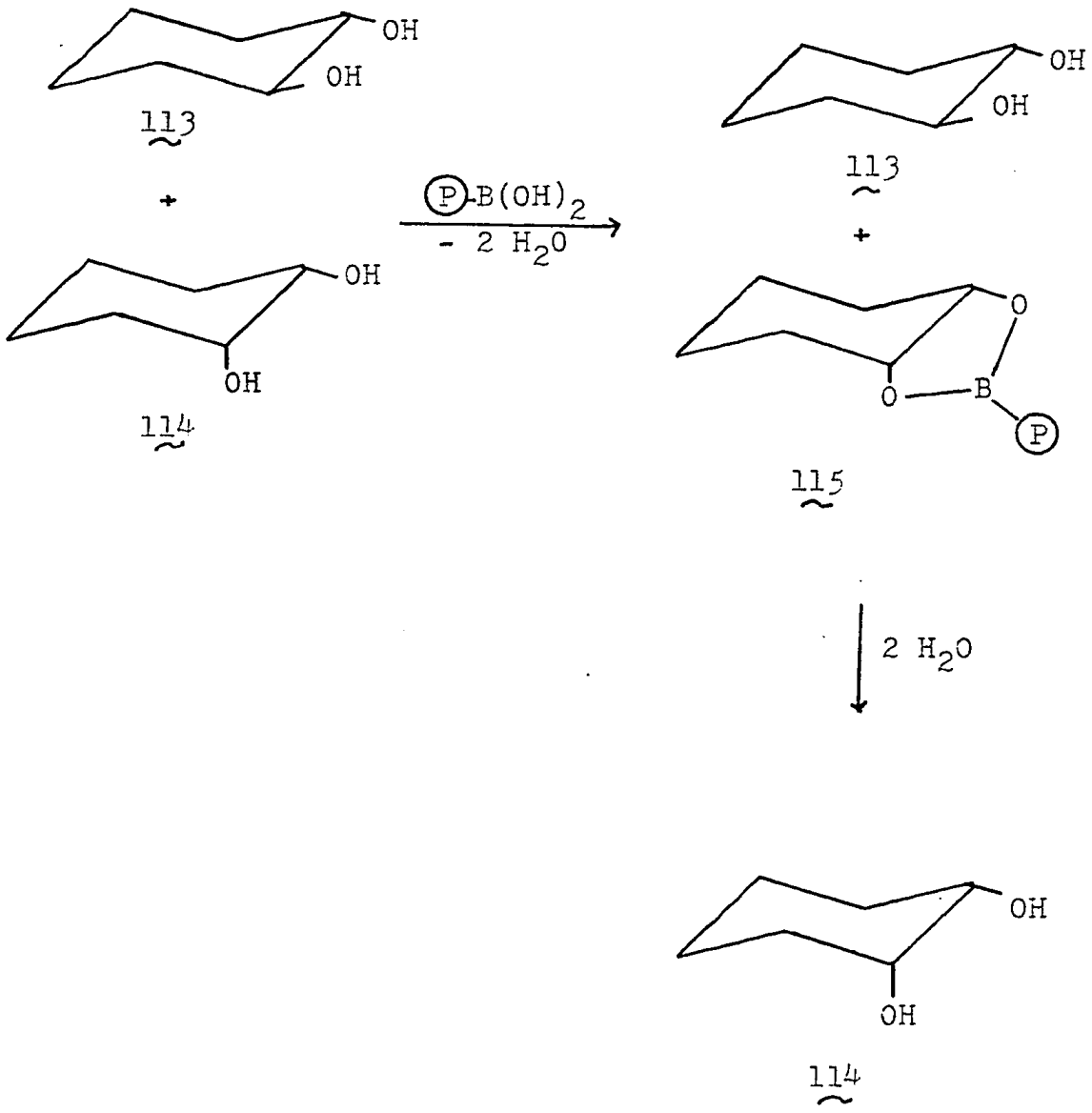


Figure 8. The nmr spectrum of <u>cis</u> 1,2-cyclohexanediol.
100 MHz, TMS lock, $CDCl_3$ solution, -35° C.

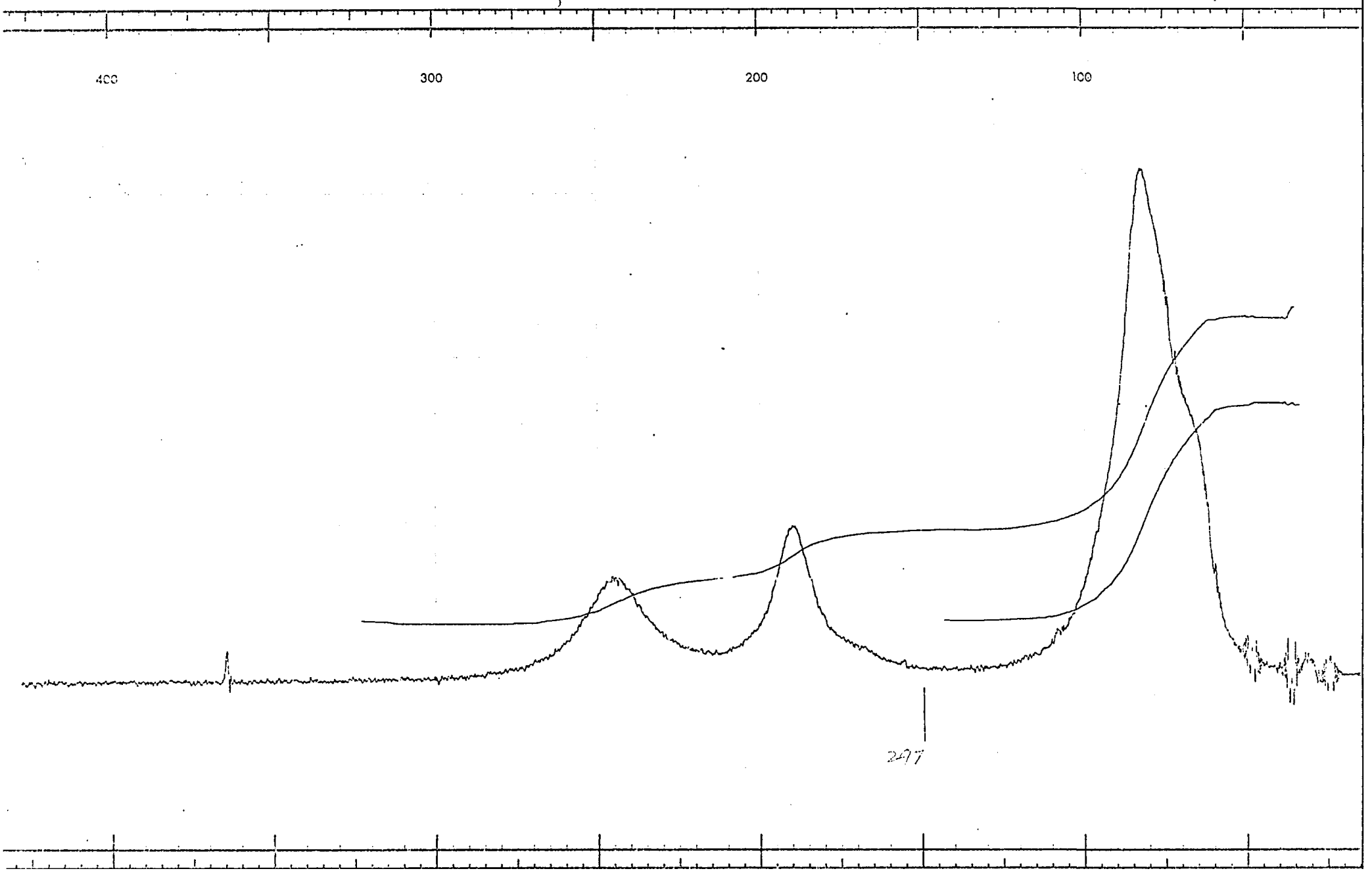
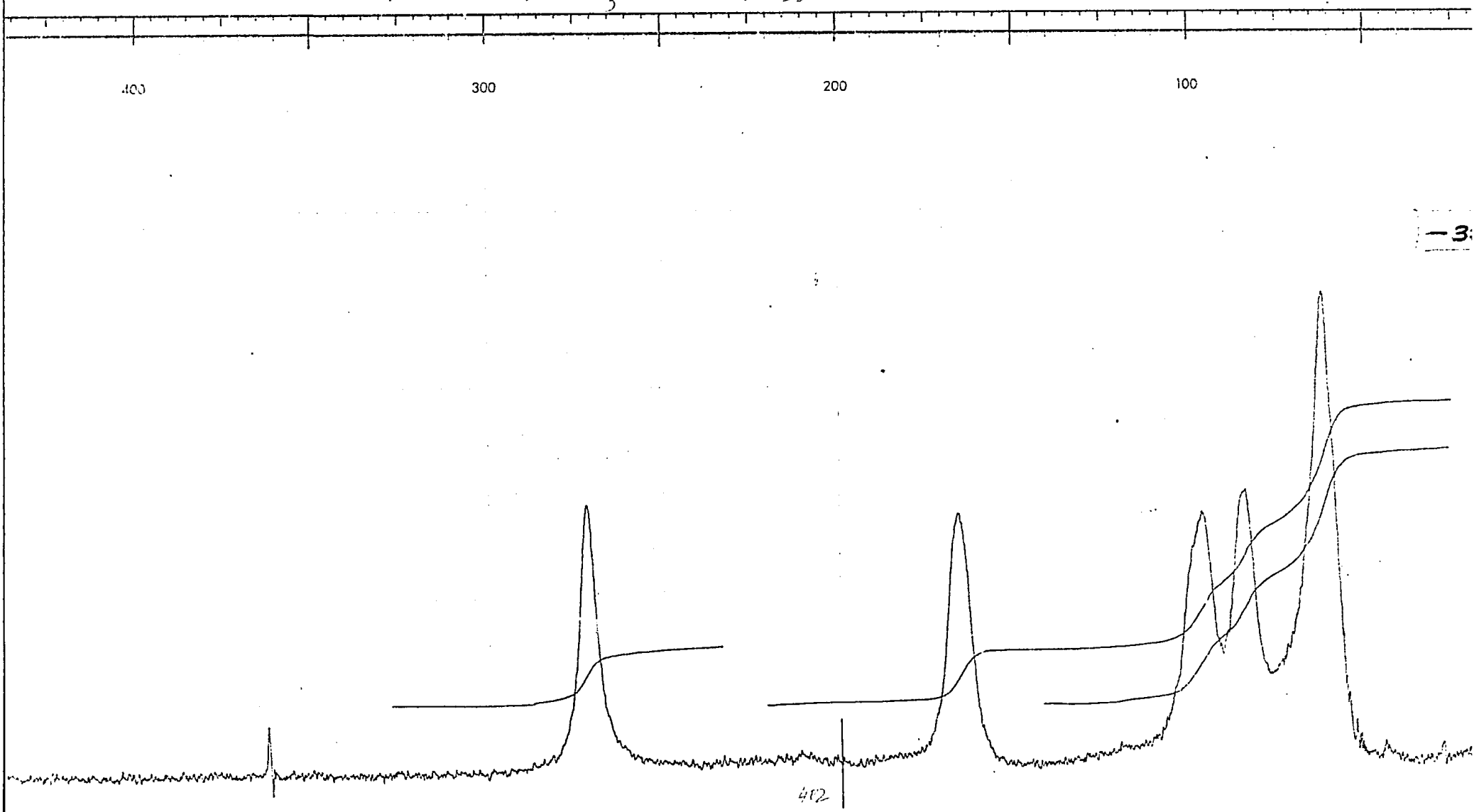


Figure 9. The nmr spectrum of <u>trans</u> 1,2-cyclohexanediol.
100 MHz, TMS lock, $CDCl_3$ solution, -35°C.



A similar reaction sequence was also used to separate and selectively deuterate the cis 1,2-cyclohexanediol of a 1:1 mixture of cis and trans isomers. The reaction was performed as described above except that deuterium oxide was used instead of water in the cleavage step.

In all cases the pure diols were characterized by their nmr spectra which included methine signals centered at δ3.78 for the cis isomer and δ3.34 for the trans isomer. (Figures 8 and 9).

The variance in reactivity of the two isomeric diols with the polystyrylboronic acid resin is explained by the ease of formation of the five-membered ring boronate with the cis isomer. For a cyclic boronate of cis 1,2-cyclohexanediol, a half-chair conformation of the carbon ring is attained. This, too, increases the ring strain, but less so than attempted forcing of trans hydroxyls into coplanarity (which would definitely not be possible).

The separation of a mixture of cis and trans 1,3-cyclohexanediols was also carried out by this method. The polymer reacted rapidly with the cis isomer in its cis diaxial conformation to yield the cyclic boronate, while the trans isomer, which remained in the soluble phase, could be separated by a simple filtration. The nmr spectra (Figures 10, 11) of the 1,3-cyclohexanediols in pyridine-d_5 included signals for the methine protons

Scheme 39

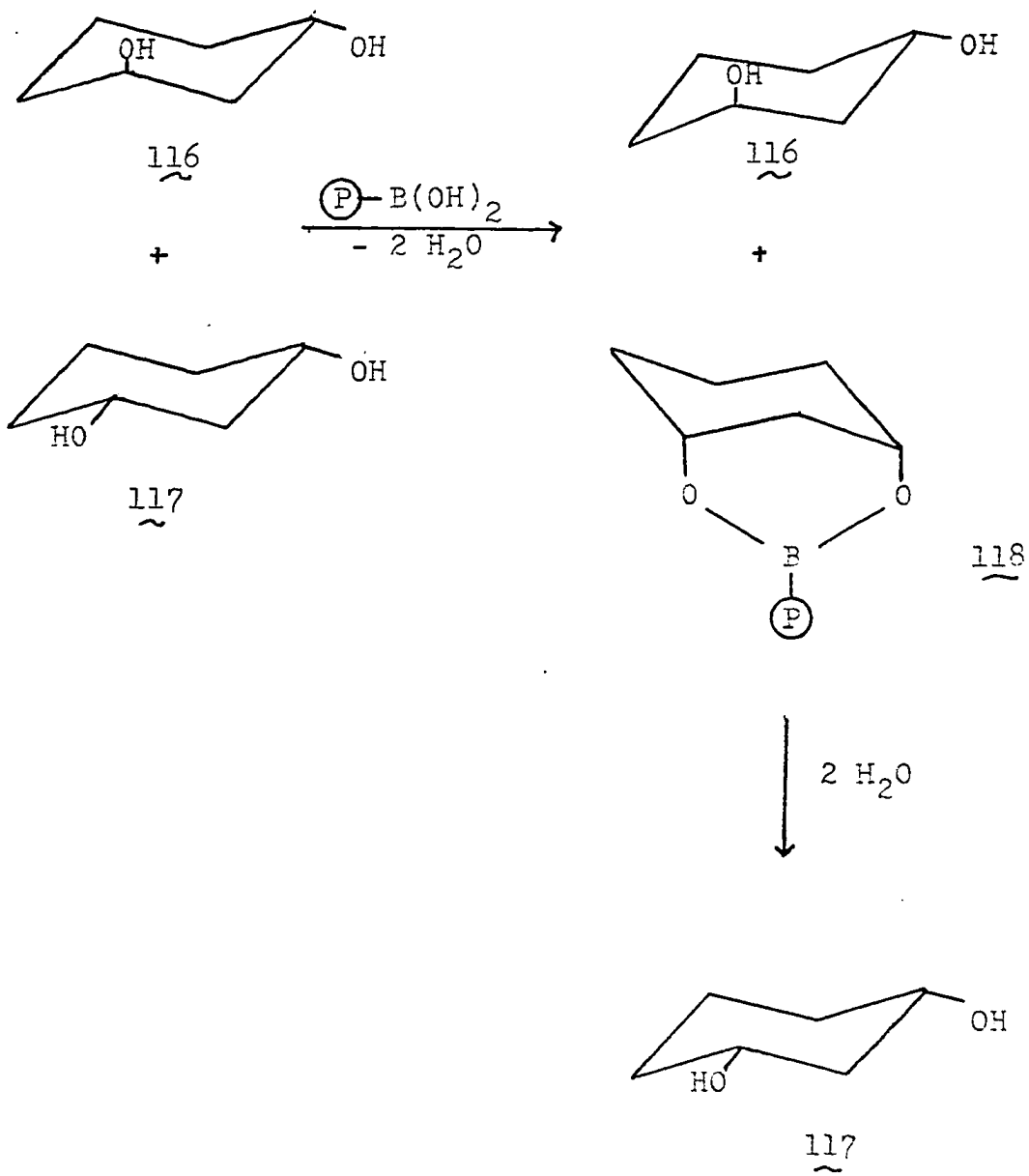


Figure 10. The nmr spectrum of <u>cis</u> 1,3-cyclohexanediol.
100 MHz spectrum, TMS lock, d_5-pyridine solution.

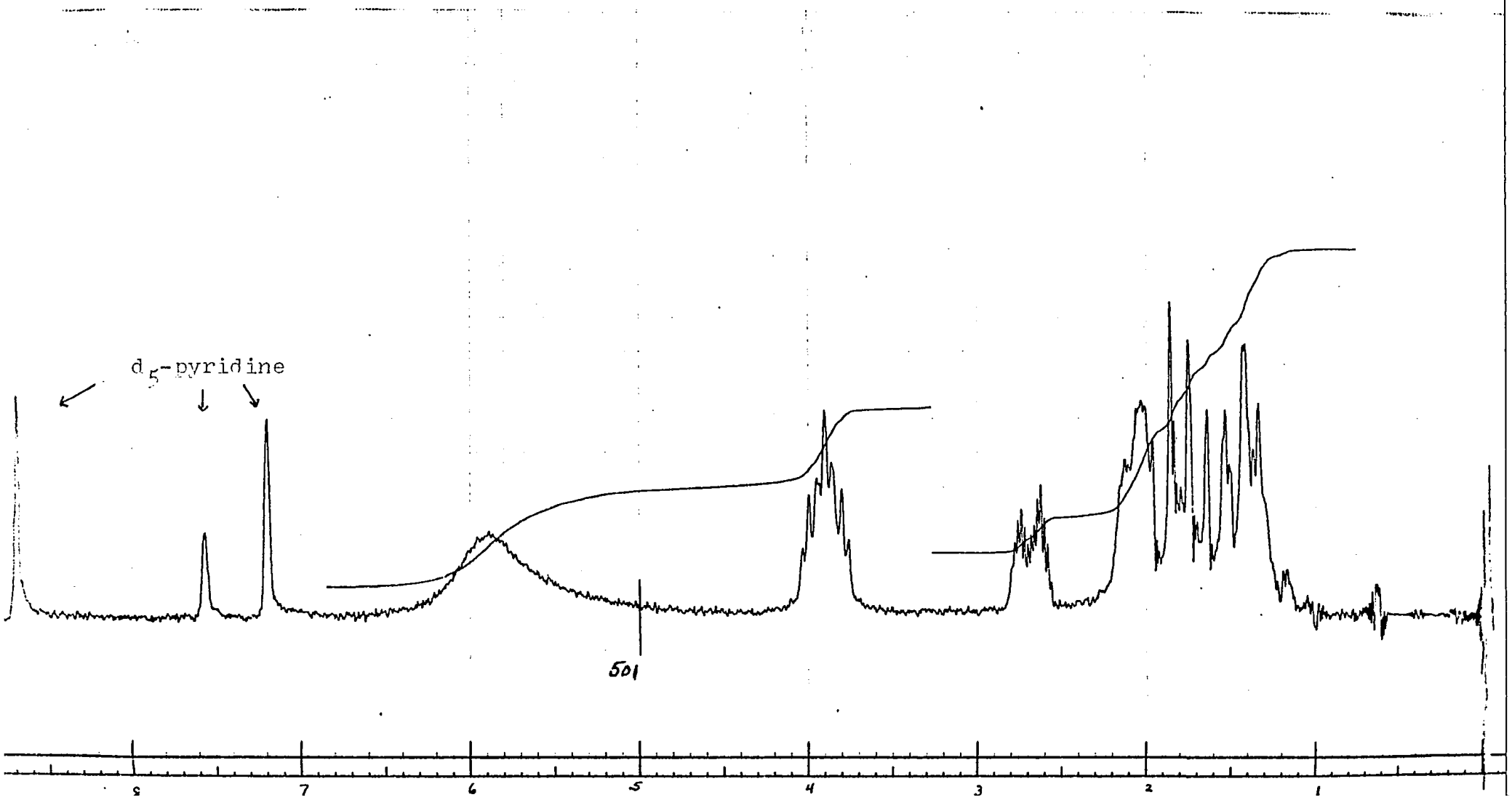
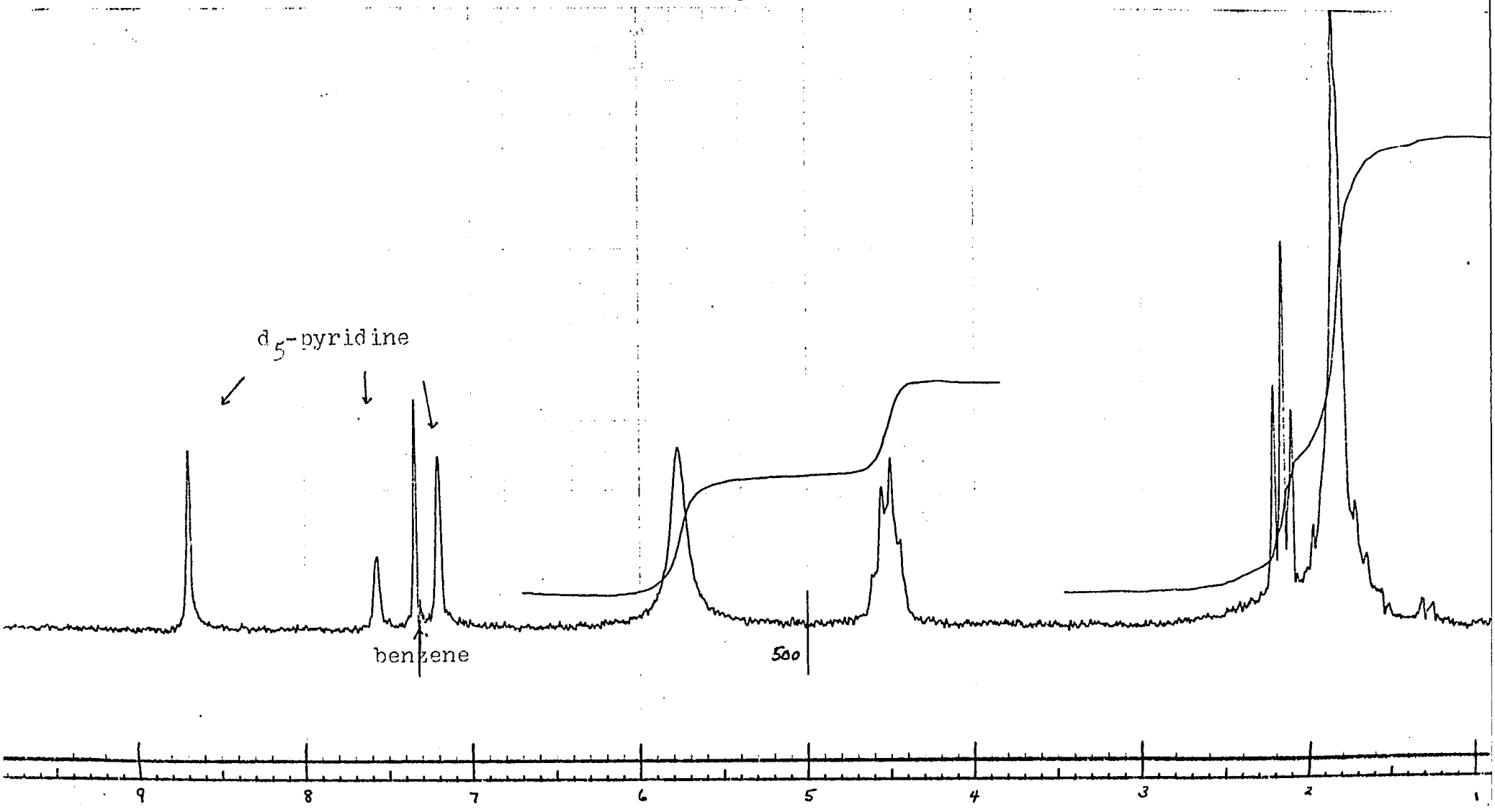


Figure 11. The nmr spectrum of <u>trans</u> 1,3-cyclohexanediol.
100 MHz spectrum, TMS lock, d_5-pyridine.



centered at δ3.90 for the cis isomer and δ4.50 for the trans isomer. Pure cis 1,3-cyclohexanediol could be cleaved from the polymer by addition of water.

In the separations of both the 1,2- and 1,3-cyclohexanediols, some binding of the trans diols to the polymer seemed to occur in cases where a large excess of the resin, with respect to the cis diol, was used. This binding could conceivably involve linkage of the diol to more than one boron atom on the polymer backbone since the formation of a six-membered ring boronate with trans 1,3-cyclohexanediol is highly unlikely.

The separation of cis and trans cyclohexanediols by affinity chromatography using the polystyrylboronic acid resin can be adapted to column techniques. For example, a solution of cis and trans 1,2-cyclohexanediols was applied to a column containing the resin. The uncoupled diol was eluted with benzene and found to be the pure trans isomer. The cis isomer was removed from the column by elution with a 3% methanolic solution of benzene. Recovery was essentially quantitative.

Similarly a mixture of 1,3-cyclohexanediols was separated on a polystyrylboronic acid column with the trans isomer being eluted with benzene and the cis isomer requiring a 5% methanolic solution for cleavage.

An attempt was also made to separate a 1:1 mixture of cis and trans 1,4-cyclohexanediols. The batch method failed to give any separation of the isomers.

When the mixture was passed through a column of the polystyrylboronic acid resin with elution with benzene, some separation was observed. The last fraction contained a mixture composed of 90% cis and 10% trans, as determined from the nmr spectrum. However complete separation could not be attained on the amount of resin available.

E. Recovery and recycling of the used resin

As was mentioned earlier, cleavage of a diol from the polymeric boronate with water results in the regeneration of the polymer which is then ready for reuse without requiring any further manipulation. Although several different batches of resin were used in this research (e.g. macroreticular, solvent swellable) at least on batch of resin was used repeatedly in a dozen reaction cycles. The recycled resin performed satisfactorily in all of these reactions and no significant loss of activity was observed.

EXPERIMENTAL

The resins were a solvent-swellable 1% divinylbenzene-styrene copolymer, Bio-Beads SX 1, purchased from Bio-Rad Laboratories, and a macroreticular resin, Amberlite XE-305, purchased from British Drug House. Tetrahydrofuran (THF) used in the experiments was purified by distillation from lithium aluminum hydride. Benzene, cyclohexane, toluene and pyridine were dried over calcium hydride. All other chemicals were reagent grade and used without further purification unless specified. All the lithiation reactions and the reactions involving lithiated resin intermediates were carried out under inert atmosphere in a specially designed flask fitted with a coarse porosity fritted glass filter. This one-piece reaction vessel allowed the addition or removal of solvents and excess reagents or by-products, the washing of the resin, etc. without transfer or exposure to the atmosphere.

Infrared spectra were recorded on a Beckman IR-20A spectrophotometer using potassium bromide pellets. Nuclear magnetic resonance spectra were measured on a Varian T-60 or a Varian HA-100 instrument using tetramethylsilane as the internal standard (δ = 0 ppm). Unless otherwise indicated, the solvent was $CDCl_3$. The data reported refer to 100 MHz spectra with a TMS lock at room temperature unless otherwise stated. The nmr data are reported with the shape of the signals (s = singlet, d= doublet, t = triplet, m = multiplet), the integration, coupling

constant and assignment whenever possible. Unresolved signals are reported with a δ corresponding to the center of the signal. The nmr spectra of compounds having benzoyl protons always showed two distinct groups of signals. The lower field signals correspond to the protons ortho to the carboxyl functionality and the higher field signals correspond to the meta and para protons.

Optical rotations were measured in a Perkin Elmer 141 polarimeter using a 1 dm cell; all rotations were measured at approximately 25°C. Elemental analyses were performed by Chemalytics Inc., Galbraith Laboratories or M-H-W Laboratories. Halogen analyses were done in this laboratory using a Parr peroxide bomb with 200-300 mg samples of the halogenated resins.

Thin layer chromatography was performed on 0.25 mm pre-coated silica gel plates from Macherey-Nagel and Co. using benzene-ether or ethyl acetate-petroleum ether for elution. Column chromatography was carried out on E. M. Laboratories' silica gel (70-325 mesh). Column chromatography was monitored by thin layer chromatography. All solvents used for elution were distilled prior to use to remove all nonvolatile impurities.

The workup of the acetone-water solutions obtained after cleavage of the desired products was carried out as follows. The solvent was evaporated to dryness and the residue extracted with chloroform. The chloroform phase was washed with water then dried with magnesium sulfate.

After filtration and decolorization with charcoal where necessary, the chloroform was evaporated to give the crude products, the yields of which are reported. In most instances the crude products contained a small amount of an impurity, such as benzoic acid for products which had been benzoylated. This was removed by passing the product through a column of silica gel. The faster moving impurity was eluted first and the slower moving desired product was eluted next.

Washing of cross-linked polystyrene resins

The resins were washed routinely to remove surface impurities[39,40]. The following solutions were used at 60-80°C with, in each case, a contact time of 30-60 min. with the resin: 1N NaOH, 1N HCl, 2N NaOH - dioxane (1:2), 2N HCl-dioxane(1:2), H_2O, methanol, methanol-dichloromethane(1:3), methanol-dichloromethane (1:10). The resins were dried under reduced pressure at 50-70°C.

Bromination of a macroreticular resin with excess bromine

One hundred grams of dry Amberlite XE-305 resin were suspended in 1 liter of dry carbon tetrachloride and 1 g of anhydrous ferric chloride was added. The reaction mixture was stirred in the dark while a solution of 60 ml (175.7 g) of bromine in 250 ml of carbon tetrachloride was added slowly. The reaction mixture was then stirred

overnight at room temperature. The resulting mixture, which still contained free bromine, was filtered and the resin washed with acetone until all the bromine coloration had disappeared. Further washings were made with dioxane-water (2:1) and butanone. After drying in vacuo at 60° C the cream-colored polymer weighed 145.1 g and contained 3.93 meq. of bromine per gram The resin obtained by this procedure was, however, not very homogeneous.

A duplicate experiment carried out under the same conditions yielded a colored product containing 3.3 meq of bromine per gram.

Bromination of a 1% cross-linked polystyrene resin

To a suspension of 40 g of washed resin (Bio-Beads SX-1) in 400 ml of dry carbon tetrachloride, 2.0 g of thallic acetate were added. Over a period of 30 min., 9.0 ml (26.4 g) of bromine were added dropwise to the mixture in the dark. After stirring 2 hours, the resin was filtered and washed with carbon tetrachloride, acetone, acetone-water (1:1), acetone, benzene and methanol. After drying under vacuum, 50.1 g of this resin containing 3.0 meq per gram were obtained.

Preparation of polymeric boronic acid -Ⓟ-$B(OH)_2$ (macro-reticular resin)

n-Butyl lithium (45 ml of a 1.6 M solution, 72 meq) was added to a suspension of 20.10 g of brominated

macroreticular polystyrene (2.8 meq Br per gram, 56.3 meq) in 125 ml of dry tetrahydrofuran under a nitrogen atmosphere and stirred for 30 min. Following removal of the solvent (by use of a syringe or by filtration), the procedure was repeated. After 1 hour at room temperature the solvent was again removed and 45 ml of tBuLi (1.6 M, 72 meq) was added and stirred for 4½ hours. Following removal of the solvent and addition of dry tetrahydrofuran, the mixture was cooled to -78°C and, after addition of 16 g (154 meq) of trimethylborate, stirred at room temperature overnight.

The resin was filtered and suspended in 140 ml dioxane/ 15 ml HCl/ 35 ml H_2O for 1 hr. at 50°C. Following filtration, it was washed with water, acetone and methylene chloride and dried under vacuum at 60°C. This yielded 19.10 g of resin containing 1.90 meq B per gram (2.05% B). The infrared spectrum showed a large hydroxyl absorption centered at 1450 cm^{-1}.

Other macroreticular boronic acid resins prepared in the same way contained from 0.4 to 1.9 meq of B per gram.

Preparation of polymeric boronic acid Ⓟ-$B(OH)_2$ (swellable)

A suspension of 15.01 g of brominated polystyrene containing 2.96 meq Br per gram and 64 ml of n-butyl lithium (1.6 M, 0.102 moles) in 120 ml of dry benzene was refluxed for 2.5 hours under a nitrogen atmosphere. The resin was filtered, washed twice with benzene and suspended in 150 ml of THF to which 18 ml (0.158 moles) of trimethyl-

borate were added. After stirring at room temperature overnight, the liquid phase was removed and the resin washed with THF. After addition of 140 ml of dioxane, 12 ml of water and 36 ml of HCl, the mixture was heated to 60°C with stirring for 1.5 hours. The resin was then collected on a filter and washed repeatedly with dioxane-water (3:1), dioxane, acetone, and finally methanol. The dry resin weighed 12.96 g and its infrared spectrum included a large hydroxyl absorption. The analysis showed 3.4% B or 3.15 meq per gram.

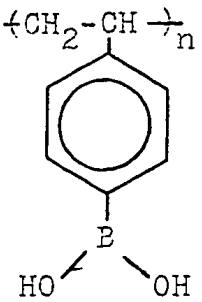
Preparation of Ⓟ-$B(OH)_2$ from a swellable resin by direct lithiation of polystyrene

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 meq) of tetramethylethylenediamine (TMEDA) in 100 ml of dry cyclohexane, 56 ml (90 meq) of 1.6 M n-BuLi were added. The reaction was carried out under a nitrogen atmosphere in the specially designed reaction flask. The mixture was stirred at 65°C for 4 hr, and, after cooling to room temperature, the resin was filtered and washed with cyclohexane. Following the addition of 100 ml of dry THF, the reaction mixture was cooled to -78°C and 15 ml (132 meq) of trimethylborate were added. After stirring at room temperature for 30 min., the resin was filtered, washed with THF and treated with 25 ml of HCl, 50 ml of H_2O and 100 ml of dioxane overnight.

The mixture was stirred at 60°C for 90 min. After cooling, the resin was filtered and washed with dioxane-water (1:1), water, THF-water (3:1), THF, acetone and methanol. The resin was washed with each solvent system several times. The dried resin weighed 9.23 g and its infrared spectrum included a large hydroxyl absorption. The elemental analysis indicated that the resin contained 1.88% boron or 1.74 meq of B per gram. Other resins prepared in this manner contained form 0.76 to 1.06 meq of B per gram.

Estimation of the degree of functionalization of a polymer

The degree of functionalization of a polystyrene resin is the fraction of the styrene units which carry the functional groups. For example, in a polystyryl-boronic acid resin containing 3.4% boron or 3.15 meq of B per gram, the molecular weight of the repeating unit is: $\frac{1000}{3.15} = 317.5$, assuming that all boron is present as a polystyrylboronic acid.



The molecular weight of one unit of polystyrylboronic acid is 147.8 while that of unsubstituted polystyrene is 104. Therefore the relative number of units without functional groups is: $\frac{317.5 - 147.8}{104} = 1.6$.

Hence the degree of functionalization is: $\frac{1}{1 + 1.6} = 0.38$

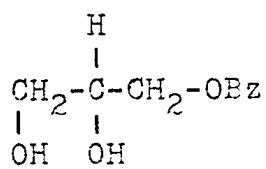
so that 38% of the aromatic rings in the resin contain $-B\begin{matrix}OH\\OH\end{matrix}$ substituents.

Preparation of monobenzoylated 1,2,3-propanetriol

A mixture of 4.14 g of macroreticular Ⓟ$-B(OH)_2$ (0.37 meq/g or 1.53 meq) and 1.2 g (13.0 meq) of 1,2,3-propanetriol was suspended in 50 ml of dry toluene. Following a one hour reflux, 30 ml of solvent were removed in an azeotropic distillation. The mixture was refluxed for another hour after the addition of 30 ml of dry pyridine and again 5 ml were distilled off. Five ml (6.05 g, 43 meq) of benzoyl chloride were added and the mixture was stirred at room temperature overnight.

The solvent was removed from the reaction mixture with a syringe and the resin was washed twice with dry benzene. Following filtration, the resin was treated twice with 50 ml of a 4:1 acetone-water mixture to cleave the resin-bound diol. The filtrate was concentrated and the product extracted in chloroform. Evaporation of the

solvent and drying under vacuum yielded 0.29 g of an oil (96% yield based on the resin). Chromatography of the reaction mixture on 50 g of silica gel with ethyl ether as eluent gave 53 which was contaminated by a small proportion of the isomer 54.



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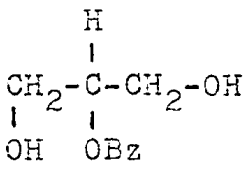

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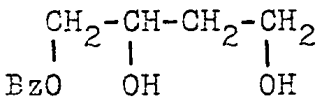
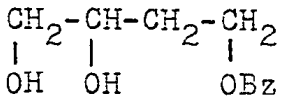
The nmr spectra included signals centered at δ7.04 (m, 2H, two aromatic H), δ7.38 (m, 3H, three aromatic H), δ5.07 (m, ~0.1 H, central H of isomer 54), δ4.31 (d, 2H, $-C\underline{H}_2-OBz$), δ3.92 (m, 1H, $-\underset{|}{C}-\underline{H}$ of 53) and δ3.60 (m, 4H, $-CH_2OH$ + 2 -OH).

Preparation of monobenzoylated 1,2,4-trihydroxybutane

The reaction was carried out as above using 5.61 g of macroreticular resin (1.2 meq B/g or 6.56 meq), 1.40 g (13.19 meq) of 1,2,4-trihydroxybutane and 50 ml of dry toluene. Following two azeotropic distillations, 5 ml (43 meq) of benzoyl chloride were added. A work-up as before yielded 1.19 g (87% based on the resin) of an oil which after fractionation on 50 g of silica gel gave only one isomer (71) in isolated form, plus a mixture of 71 and 72 in the ratio of 4:1 as estimated by nmr spectroscopy.



71



72

Compound 71, crystallized from ether-petroleum ether and recrystallized from the same solvent, had a melting point of 53-55° C. Analysis: Calc. for $C_{11}H_{15}O_4$ (MW 211.26): C 62.83 , H 6.73%. Found: C 62.58%, H 6.69%. Compound 72 could not be crystallized and was characterized by its nmr spectrum. The nmr spectra included peaks centered at δ8.04 (m, 2H, two benzoyl H), δ7.44 (m, 3H, three benzoyl H), δ4.30 (m, 3H, $OC\underline{H}_2OBz$ of each isomer), δ3.94 (m, 4H, $-CH_2OH$ of 71), δ3.55 (d, 0.4H, minor isomer 72), δ3.40 (m, 0.2 H, minor isomer 72), δ1.77 (t, 2H, $C-C\underline{H}_2-C$ (central)). Expansion of sweep width to 500 cps on the D_2O exchanged sample of the mixture gave two triplets- (a): centered at δ4.38 and (b): centered at δ3.77 corresponding to the $-CH_2OBz$ of isomer 72 and the $-CH_2OH$ of isomer 71. These peaks were cut out and weighed giving the ratio (a)/(b) 23% to 77%. Spin decoupling at δ1.77 ($C-C\underline{H}_2-C-$) on the same sample gave singlet peaks (c): δ4.40 and (d):δ3.70. Cutting out and weighing of these peaks gave the ratio (c)/(d) 20% to 80%. Therefore the product is composed of approximately 78% of isomer 71 and 22% of isomer 72.

Preparation of monobenzoylated 1,2,4-butanetriol on a 1% cross-linked resin

A 1% cross-linked Ⓟ-$B(OH)_2$ resin (2.87 g, 6.53 meq) was added to a solution of 0.70 g (6.60 meq) of 1,2,4-butanetriol in 70 ml of dry benzene. After refluxing for 1 hour, 10 ml of solvent were removed by an azeotropic distillation. This procedure was repeated and the reaction mixture was cooled to room temperature. The resin was filtered to recover uncoupled triol (0.035 g, 0.3 meq) and then stirred with a solution of 5 ml (43 meq) of benzoyl chloride in 60 ml of dry pyridine overnight. Following filtration to remove soluble by-products, the monobenzoylated derivative was cleaved from the resin by treatment with 100 ml of a 4:1 mixture of acetone-water. This yielded 0.68 g of monobenzoylated 1,2,4-butanetriol (51% yield considering recycling of recovered uncoupled triol). The nmr spectra were identical to those described for products 71 and 72 . The ratio of isomers in this crude mixture was again determined by the ratio of the areas of the peaks at δ4.38 (t) and δ3.77(t). The ratio of isomer 72 to 71 was 17% to 83% in the crude mixture.

Preparation of 6-O-trityl-1,2-dihydroxyhexane (79)

1,2,6-Hexanetriol (0.80 g, 5.96 meq) was coupled to a swellable Ⓟ-$B(OH)_2$ resin (2.82 g, 2.17 meq) in 70

ml of dry pyridine. After the usual azeotropic distillations the solvent was removed and 40 ml of dry pyridine and 2.5 g (9.0 meq) of trityl chloride were added and stirred overnight at room temperature. Following cleavage with 4:1 acetone-water and the usual work-up, 0.34 g of tritylated triol was isolated as an oil. The uncoupled triol (0.36 g, 2.7 meq) was recovered and the yield of product was 42%. The nmr spectrum showed signals at δ7.30 (m, 15 H, trityl group), δ3.56 (m, 3H, $\underset{\text{OH}}{\text{CH}_2}\text{-}\underset{\text{OH}}{\text{C}}\text{-}\underline{\text{H}}$), δ3.08 (t, 2H, -$\underline{\text{CH}}_2$-OTr), δ2.61 (s, 2H, 2 -OH), δ1.58 (m, 6H, -$(\underline{\text{CH}}_2)_3$.

Preparation of 6-O-benzoyl-1,2-dihydroxyhexane (80)

Following the same general procedure 4.98 g of macroreticular resin (1.2 meq B/g or 5.73 meq) and 1.30 g (9.69 meq) of 1,2,6-hexanetriol were suspended in 50 ml of dry toluene. After the azeotropic distillations, 5 ml (43 meq) of benzoyl chloride were added. After cleavage with 4:1 acetone-water and the usual work-up, 0.74 g (55% yield with respect to the resin) of product were isolated. The oil was purified by passing it through a column packed with 50 g of silica gel (eluent - ethyl ether) and characterized by its nmr spectrum, which included signals at δ8.08 (m, 2H, benzoyl), δ7.48 (m, 3H, benzoyl), δ4.36 (t, 2H, -$\underline{\text{CH}}_2$-OBz), δ3.62 (m, 3H, $\underset{\text{OH}}{\underline{\text{CH}}}\text{-}\underline{\text{CH}}_2\text{-OH}$), δ3.20 (s, 2H, 2 -OH), δ1.74 (m, 6H, -$(\underline{\text{CH}}_2)_3$).

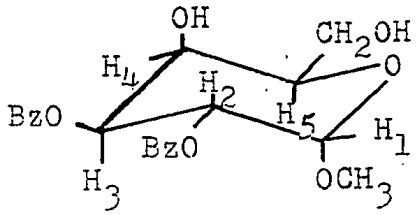
Preparation of monobenzoylated 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (81)

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (2.00 g, 15 meq) and 4.05 g of Ⓟ-$B(OH)_2$ resin (1.90 meq/g or 7.96 meq) were suspended in 50 ml of dry toluene and refluxed for 1 hr. Following the usual azeotropic distillations, 6 ml, (51 meq) of benzoyl chloride were added and stirred overnight at room temperature. The yield of monobenzoylated product after cleavage and work-up was 1.09 g or 60% based on the resin. Purification on 50 g of silica gel (eluent: 1:1 ethyl acetate - petroleum ether, b.p. 30-60°) gave the desired product with m.p. 57-60°. The nmr spectrum included signals at δ8.02 (m, 2H, benzoyl), δ7.44 (m, 3H, benzoyl), δ4.42 (s, 2H, $-C\underline{H}_2-O-\overset{\overset{O}{\|}}{C}-Ph$), δ3.68 (m, 6H, two $-C\underline{H}_2O\underline{H}$ groups), δ1.44 (q, 2H, $-C\underline{H}_2-$ of $-CH_2CH_3$), δ0.95 (t, 3H, $C\underline{H}_3CH_2$).

Preparation of 2,3-di-O-benzoyl-α-D-galactopyranoside (86)[43]

Methyl α-D-galactopyranoside (3.15 g, 4.48 meq) and macroreticular Ⓟ-$B(OH)_2$ (2.56 g, 4.48 meq) were suspended in 55 ml of dry pyridine. Following two azeotropic distillations, 13 g (88 meq) of benzoyl chloride were added and stirred at room temperature overnight. After filtration, the resin was washed several times with dry benzene and the boronate ester was cleaved by treatment with 50 ml of a 4:1 mixture of acetone and water.

Following filtration and removal of the solvent, the product was extracted in $CHCl_3$, concentrated and dried. This yielded 0.61 g of the product for a 34% yield based on the resin. Purification on 60 g of silica gel with an ethyl acetate-petroleum ether (3:1) eluent, the product, which failed to crystallize, had a specific rotation $[\alpha]_D$ (c=1, $CHCl_3$)= +200.1°. Analysis: Calc. for $C_{21}H_{22}O_8$ (MW 402.43): C 62.67%, H 5.52%. Found: C 62.36%, H 5.12%. The nmr spectrum included signals at δ7.98 (m, 4H, benzoyl), δ7.42 (m, 6H, benzoyl), δ5.70 (m, 2H), δ5.21 (m, 1H), δ4.48 (m, 1H) for H_1, H_2, H_3, H_4; δ4.02 (m, 3H, $-C\underline{H}_2-$ and H_5), δ3.45 (s, 3H, $-OC\underline{H}_3$), δ3.26 (s, 1H, -OH) and δ2.68 (s, 1H, -OH).



86

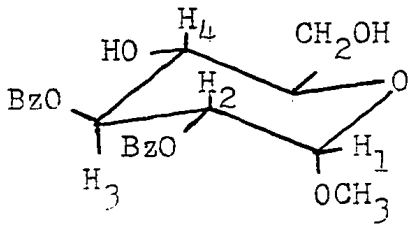
Preparation of methyl 2,3-di-O-benzoyl-4,6-di-O-(p-tolylsulfonyl)-α-D-galactopyranoside[43]

To a solution of 0.37 g (0.93 meq) of methyl 2,3-di-O-benzoyl-α-D-galactopyranoside in 5 ml of dry pyridine were added 0.44 g (2.34 meq) of 4-toluenesulfonic acid. The mixture was stirred at 50°C for two days, cooled to room temperature and poured over 12 ml of saturated aqueous Na_2CO_3. The oil was extracted in

three 6 ml portions of $CHCl_3$, washed with H_2O, concentrated and dried to yield 0.49 g (71%) of tan-colored crystals. Two recrystallizations from 3 ml of 1:1 methanol-ether gave white crystals melting at 122-123°C and having $[\alpha]_D$ (c=1, $CHCl_3$)= +145°. Lit. m.p. 128-129°, $[\alpha]_D$ = +150°.[43]

Preparation of methyl 2,3-di-O-benzoyl-α-D-glucopyranoside (89)[23,44]

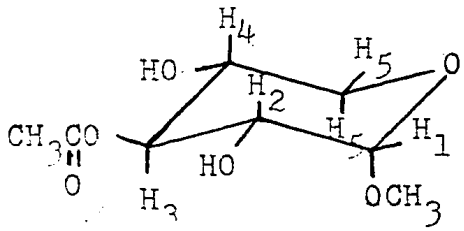
Methyl α-D-glucopyranoside (3.5 g, 18 meq) was added to a suspension of macroreticular Ⓟ-$B(OH)_2$ (3.00 g, 5.3 meq) in 55 ml of dry pyridine. The water formed in the coupling reaction was removed by two azeotropic distillations (15 ml total). Benzoyl chloride (15 g, 107 meq) was added to the mixture and was stirred overnight at room temperature. Following the usual work-up, the yield was 1.12 g (53%). Fractionation on a column of 100 g of activated silica gel using ethyl acetate as eluent gave the product as an oil which failed to crystallize and had an $[\alpha]_D$ (c=1, $CHCl_3$) = +162.7°. Analysis: Calc. for $C_{21}H_{22}O_8$ (MW 402.43): C 62.67%, H 5.52%. Found: C 62.41%, H 5.36%. The nmr spectrum included signals at δ8.00(m, 4H, benzoyl), δ7.44 (m, 6H, benzoyl), δ5.75 (m, 1H), δ5.20 (m, 2H), for H_1, H_2 and H_3; δ3.96 (m, 5H, $-CH_2-$, H_4, H_5), δ3.47 (s, 3H, $-OCH_3$), δ2.22 (b.s, 2H, -OH).



89

Preparation of methyl 3-O-acetyl-α-D-xylopyranoside (91)[30]

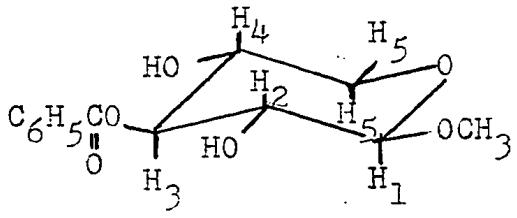
Coupling was accomplished as before using 1.87 g of 1% cross-linked resin (3.15 meq/g or 5.95 meq) and 0.81 g (4.4 meq) of methyl α-D-xylopyranoside in 35 ml of dry pyridine. Following the azeotropic distillations, addition of 5 ml (49 meq) of acetic anhydride and cleavage with 4:1 acetone-water, the crude product was extracted in $CHCl_3$ and worked-up as usual with an additional wash with aqueous Na_2CO_3. This yielded 0.91 g (84%) of the syrupy product containing a trace of impurity. Crystallization from ethyl acetate-petroleum ether yielded white needle-like crystals melting at 110-112°C and having an $[\alpha]_D$ (c=1, $CHCl_3$) = +148°. Analysis: Calc. for $C_8H_{14}O_6$ (MW 206.22): C 46.59%, H 6.86%. Found: C 46.82%, H 7.12%. The nmr spectrum included signals centered at δ5.05 (t, 1H, J = 8.2, H_3), δ4.72 (d, 1H, $J_{1,2}$ = 3.5, H_1), δ3.68 (m, 4H, H_2, H_4, $2H_5$), δ3.46 (s, 3H, $-OCH_3$), δ2.83 (b.s., 2H, 2 -OH), δ2.18 (s, 3H, CH_3-CO-). The nmr spectrum of this compound is shown in Figure 3.



91

Preparation of methyl 3-O-benzoyl-β-D-xylopyranoside (95)[30]

Methyl β-D-xylopyranoside (1.30 g, 7.73 meq) and Ⓟ-$B(OH)_2$ (4.05 g, 1.01 meq/g or 4.09 meq) in 50 ml of toluene was coupled as before with azeotropic distillations followed by treatment with 6 ml (43 meq) of benzoyl chloride in pyridine. After cleavage and work-up 0.51 g or 47 % of an oil were obtained which was crystallized from ethyl acetate-petroleum ether yielding white crystals melting at 131-133° C and having $[\alpha]_D$ (c=1, dioxane) -15.6°. Analysis: Calc. for $C_{13}H_{16}O_6$ (mw 268.29): C 58.19%, H 6.02%. Found: C 58.19%, H 5.91%. The nmr spectrum showed signals at δ 8.04 (m, 2H, benzoyl), δ 7.43 (m, 3H, benzoyl), δ 5.08 (t, 1H, $J_{2,3}$ = 7.6 Hz, H_3), δ 4.35 (d, 1H, $J_{1,2}$ = 6 Hz, H_1), δ 3.92 (m, 3H, H_2, H_4, OH), δ 3.54 (s, 3H, $-OCH_3$), δ 3.14 (m, 3H, $2H_5$, OH). (See Figure 4).



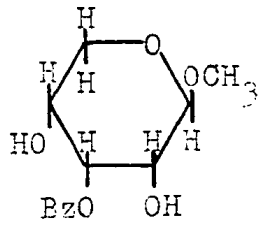
95

Preparation of methyl β-D-ribopyranoside (96)

A mixture of 5 g (33.3 meq) of D-ribose and 0.5 ml of acetyl chloride in 40 ml of spectrograde methanol was refluxed overnight. The completion of the reaction was determined by tlc (benzene, ether, methanol 7:2:1 as eluent). After cooling and neutralization with $CaCO_3$, the solid was filtered, washed with 10 ml of methanol and the filtrate concentrated to a thick oil containing both anomers of methyl-D-ribopyranoside. Separation of 3.3 g of the mixture of α- and β- anomers was accomplished on a column of anion exchange resin (Bio-Rad analytical grade AG1-X2, 200-400 mesh, hydroxide form), measuring 49 x 2 cm. The resin was packed in the column, treated with 100 ml of 2N NaOH and washed with boiled, distilled water until the eluent was neutral. 2.07 g of the β-anomer was obtained as white crystals having a melting point of 82-83°C and $[\alpha]_D$ (c=1, MeOH)= -107°. Literature value: m.p. 83°C[52] and $[\alpha]_D$ (c=0.47,H_2O) = -105.0°[53]. Other fractions which were dextrorotatory and were eluted first (presumably containing some of the α-anomer) were dicarded without characterization. The nmr spectrum of the β-anomer in D_2O contained signals at δ4.78 (m, 4H, H_1, H_2, H_3, H_4), δ 3.86 (m, 2H, $2H_5$), δ 3.40 (s, 3H, $-OCH_3$).

Preparation of methyl 3-O-benzoyl-β-D-ribopyranoside (98)

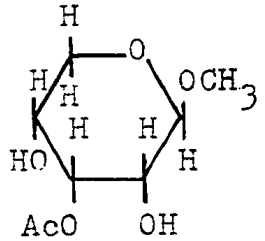
A mixture of 0.54 g (3.30 meq) of methyl β-D-ribopyranoside and 2.00 g (5.22 meq) of 1% cross-linked Ⓟ-$B(OH)_2$ in 90 ml of dry pyridine was reacted in the usual way. After three azeotropic distillations, 5 ml (36 meq) of benzoyl chloride were added. Following work-up, 0.96 g of an oil was isolated. Fractionation on a column containing 40 g of silica gel using ether-benzene 1:4 as eluent yielded 0.49 g (51%) of white powdery crystals. Recrystallization from ethyl acetate-petroleum ether gave white needle-like crystals having a melting point of 107-108°C and an $[\alpha]_D$ (c=1, $CHCl_3$)= -47°. Analysis: Calc. for $C_{13}H_{16}O_6$ (MW 268.29): C 58.19%, H 6.02%. Found: C 57.99 , H 6.10 . The nmr spectrum included signals at δ8.06 (m, 2H, 2 benzoyl), δ7.46 (m, 3H, 3 benzoyl), δ4.84 (s, 1H, H_3), δ4.36 (m, 5H, H_2, H_1, H_4, 2 H_5), δ3.48 (b.s., 2H, 2 -OH), δ3.33 (s, 3H, $-OCH_3$). The nmr spectrum is shown in Figure 5.



98

Preparation of methyl 3-O-acetyl-β-D-ribopyranoside (99)[46]

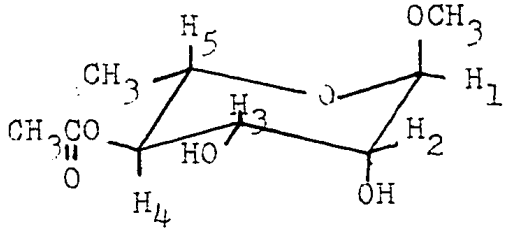
To a solution of 0.70 g (4.29 meq) of methyl β-D-ribopyranoside in 90 ml of pyridine were added 4.04 g (3.39 meq) of 1% cross-linked Ⓟ–$B(OH)_2$ resin. Following two azeotropic distillations and removal of the uncoupled sugar (0.21 g, 1.28 meq), 5 ml (49 meq) of acetic anhydride in 50 ml of dry pyridine were added. After stirring at room temperature overnight and the usual work-up, 0.90 g of an oil was obtained. Fractionation on 10 g of silica gel, with eluent changing from 1% ether-benzene to 20% ethanol-benzene when the fast-moving impurity was removed, gave 0.37 g (60%) of the 3-O-acetyl derivative. Crystallization from ethyl acetate-petroleum ether gave white crystals melting at 112°C and having an $[\alpha]_D$ (c=1, $CHCl_3$) = -141.5°. Literature value: m.p. 112-113°C and $[\alpha]_D$ = -143° ($CHCl_3$).[46] Analysis: Calc. for $C_8H_{14}O_6$ (MW 206.22): C 46.59%, H 6.86%. Found: C 46.52%, H 6.92%.



99

Preparation of methyl 4-O-acetyl-α-L-rhamnopyranoside (102a)[47]

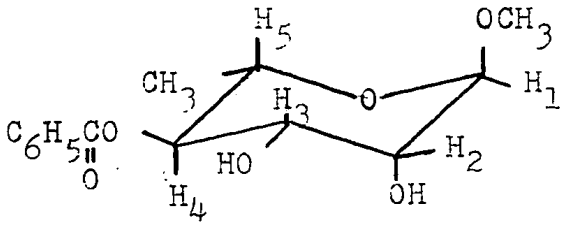
Methyl α-L-rhamnopyranoside (1.06 g, 5.98 meq) was coupled to 2.03 g of Ⓟ-$B(OH)_2$ (6.40 meq) in 60 ml of dry pyridine by two azeotropic distillations. Treatment with 5 ml (49 meq) of acetic anhydride at room temperature for 1 hour and at 50°C for 15 min. followed by cleavage with 50 ml of 4:1 acetone-water gave an oil which was extracted in $CHCl_3$ and washed with aqueous Na_2CO_3. This yielded 0.86 g (65%) of crude product which showed only one spot on tlc (ether-petroleum ether 1:1). Crystallization from ether-petroleum ether gave white crystals with melting point 105-109°C and $[\alpha]_D$ (c=1, $CHCl_3$) = -90°, Lit. value: m.p. 106°C. $[\alpha]_D$ (c=1.8, $CHCl_3$) = -55[47]. Analysis: Calc. for $C_9H_{16}O_6$ (MW 220.25): C 49.08, H 7.34. Found: C 49.18, H 7.41. The nmr spectrum included signals at δ4.82 (t, 1H, J = 10 Hz, H_4), δ4.70 (s, 1H, H_1), δ3.74 (m, 5H, 2 -OH, H_2, H_3, H_5) δ3.38 (s, 3H, $-OCH_3$), δ2.13 (s, 3H, CH_3COO), δ1.21 (d, 3H, $-OCH_3$).



102a

Preparation of methyl 4-O-benzoyl-α-L-rhamnopyranoside (102b)

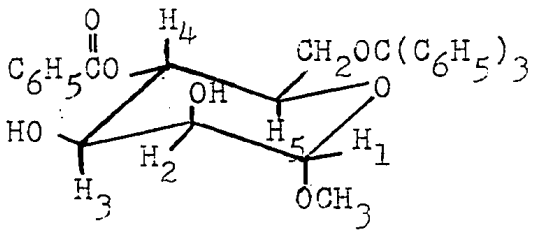
Methyl α-L-rhanmopyranoside (1.07 g, 6.00 meq) was coupled to the resin (2.03 g, 6.37 meq) in 55 ml of dry pyridine in the usual way , followed by treatment with 6 ml (43 meq) of benzoyl chloride overnight at room temperature. After work-up, 1.18 g (70%) of the product was recovered. Purification on 60 g of activated silica gel using 40% ethyl acetate-petroleum ether as eluent yielded a white solid showing only one spot on tlc. Crystallization form ether-petroleum ether gave white crystals melting at 114-115°C with an $[\alpha]_D$ (c=1, $CHCl_3$) = -111.5°. Analysis: Calc. for $C_{14}H_{18}O_6$ (MW 282.32): C 59.56%, H 6.44%. Found: C 59.68, H 6.45. The nmr spectrum included signals at δ8.04 (m, 2H, benzoyl), δ7.46 (m, 3H, benzoyl), δ5.10 (t, 1H, J=9.5 Hz, H_4), δ4.75 (s, 1H, H_1), δ4.01 (m, 3H, H_2, H_3, H_5), δ3.41 (s, 5H, OCH_3, 2 -OH), δ1,29 (d. 3H, J=6 Hz, $-CH_3$). The nmr spectrum is shown in Figure 6.



102b

Preparation of methyl 4-O-benzoyl-5-O-trityl-α-D-manno-pyranoside (107)

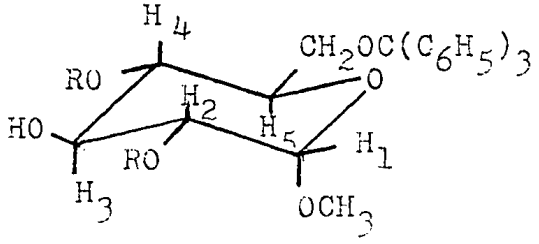
The water of hydration was removed from a solution of methyl α-D-mannopyranoside (1.02 g, 4.80 meq) in 50 ml of dry pyridine by an azeotropic distillation. Trityl chloride (1.75 g, 6.26 meq) was added and refluxed for 1 hr. Coupling took place as usual with 2.03 g (6.40 meq) of the 1% crosslinked resin, followed by treatment overnight with 4 ml (29 meq) of benzoyl chloride. Purification on 40 g of activated silica gel (eluent: 15% ether, 85% benzene) yielded a white amorphous solid having $[\alpha]_D$ (c=1, $CHCl_3$) = + 91.8°, m.p. 63-65°. Analysis: Calc. for $C_{33}H_{32}O_7$(MW 540.65): C 73.31%, H 5.98%. Found: c 73.18%, H 5.82%. The nmr spectrum included signals at δ8.08 - δ7.78, δ7.43, δ7.18; these signals are multiplets and represent a total of 20 protons - 5 benzoyl and 15 trityl, δ5.27 (t, 1H, J=10 Hz, H_4), δ4.89 (s, 1H, H_1), δ4.00(m, 5H, H_2, H_3, H_5, 2 -OH), δ3.51 (s, 3H, $-OCH_3$), δ3.30 (d, 2H, J=4 Hz, $-CH_2OTr$). The nmr spectrum is shown in Figure 7.



107

Preparation of methyl 6-O-trityl-α-D-glucopyranoside (108)[49,50]

A solution of 10.0 g (0.05 moles) of methyl α-D-glucopyranoside and 21.4 g (0.08 moles) of trityl chloride in 125 ml of dry pyridine was stirred at room temperature for 3 days. The solution was concentrated and poured over 300 ml of ice-water. After decanting the water, the semi-solid mass was extracted in 150 ml of $CHCl_3$ and washed with ice water. The concentrated solution was treated with petroleum ether to remove any trityl alcohol present. The crude product was crystallized and recrystallized from methanol, yielding 15.7 g (70%) of the product melting at 151-152°C and with $[\alpha]_D$ (c=1, $CHCl_3$) = +63.2°. The nmr spectrum included signals at 7.32 (m, 15 H, 15 aromatic protons), δ4.70 (m, 1H, H_1), δ4.49 (b.s., 1H, -OH), δ3.50 (m, 11-H, 2 -OH, H_2, H_3, H_4, H_5, $-CH_2-$, $-OCH_3$).



108 R = H

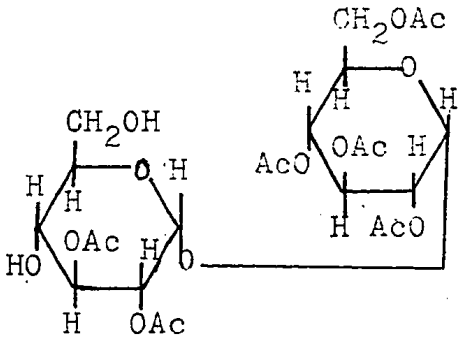
110 R = $-\overset{\overset{O}{\|}}{C}C_6H_5$

Preparation of methyl 3-O-benzoyl-6-O-trityl-α-D-gluco-pyranoside (110)

To a suspension of 1.88 g (4.90 meq) of Ⓟ-$B(OH)_2$ in 80 ml of dry pyridine were added 1.53 g (3.51 meq) of methyl 6-O-trityl-α-D-glucopyranoside. After three azeotropic distillations the uncoupled sugar was recovered by filtration (0.87 g, 1.98 meq) and 5 ml of dry pyridine were stirred with the resin overnight at room temperature. Following cleavage with a 4:1 acetone-water mixture, the solution was concentrated and extracted in $CHCl_3$. After several washings with saturated $NaHCO_3$ solution, the solvent was evaporated to give 0.68 g of an oil. This represents a conversion of 36% based on the starting material or a yield of 82% if the recovery and recycling of the uncoupled sugar are considered. The oil was crystallized from ethyl acetate-petroleum ether giving a product with m.p. 128-130° and $[\alpha]_D$ (c=1, $CHCl_3$) = +55.7°. Analysis: Calc. for $C_{33}H_{32}O_7$ (MW 540.65): C 73.31%, H 5.98%. Found: C 72.93, H 6.21. The nmr spectrum included aromatic proton signals between δ8.2 and δ7.1 (20 H) representing the 5 benzoyl and 15 trityl hydrogens, δ5.07 (m, 1H, H_3), δ4,75 (broad s, 1H, H_1), δ4.32-δ3.00 (m, 11 H, H_2, H_3, H_4, H_5, $-CH_2-$, 2 -OH, $-OCH_3$).

Preparation of 2,3,4,6,2',3'-hexaacetyl-α,α-trehalose (112)

Swellable Ⓟ-$B(OH)_2$ resin (1.95 g, 1.50 meq) was added to a solution of 1.33 g (3.51 meq) of α,α-trehalose in 100 ml of dry pyridine. Following two azeotropic distillations, the uncoupled sugar (1.13 g, 2.96 meq) was removed by filtration. The resin was treated with 6 g (43 meq) of acetic anhydride in 70 ml of dry pyridine overnight at room temperature. After the usual work-up, 0.14 g of product were obtained and recrystallized from ethyl acetate-petroleum ether. This corresponds to a conversion of 7% and a yield of 44% after recycling of the uncoupled α,α-trehalose. The white crystals had a melting point of 83-84°C and $[\alpha]_D$ (c = 0.5, $CHCl_3$) = +58°. Analysis: Calc. for $C_{24}H_{34}O_{17}$: C 48.48%, H 5.78%. Found: 48.44, H 5.91. The nmr spectrum included signals at δ5.18 (m, 6H), δ3.82 (m, 8H), δ2.95 (s, 2H, two -OH), δ2.13 (m, 18 H, six $CH_3\overset{\overset{O}{\|}}{C}O$-).



112

Separation of cis and trans 1,3-cyclohexanediols-batch technique

1. Separation of pure cis from the mixture (116)

A 1% cross-linked Ⓟ-$B(OH)_2$ resin (2.04 g, 6.42 meq) was suspended in a solution of 1.01 g (8.67 meq) of a 2:1 mixture of cis and trans 1,3-cyclohexanediols in 125 ml of dry benzene. After stirring for 30 min., 15 ml of solvent were removed in an azeotropic distillation. The resin was filtered and washed with dry benzene. Both the filtrate and washings contained a mixture of cis and trans diols (0.50 g, 0.06 g). Treatment of the resin with 50 ml of 4:1 THF/H_2O yielded 0.38 g of the cis isomer (m.p. 85-86°) which represents a 56% recovery of the cis isomer. (The overall recovery of both diols was 93%).

2. Separation of pure trans from the enriched mixture (115)

The coupling reaction was repeated on 0.57 g (4.87 meq) of the recovered cis-trans mixture and 1.56 g (4.90 meq) of the resin. Evaporation of the filtrate yielded 0.18 g of the trans isomer or 54% of the expected trans 1,3-cyclohexanediol (m.p. 114-115°C). The cleavage product yielded 0.19 g of mixed product and the washings 0.05 g. (The overall recovery was 74%).

The nmr spectrum in d_5-pyridine of the cis 1,3-cyclohexanediol included signals at δ5.89 (b.s., 2H, 2 hydroxyls), δ3.90 (m, 2H, 2 -$\underset{OH}{\underset{|}{C}}$-H), δ2.70 (m, 1H) and δ1.68 (m, 7H) are the eight -CH_2- protons.

The nmr spectrum in d_5-pyridine of the trans 1,3-cyclohexanediol included signals at δ5.77 (s, 2H, 2 hydroxyls), δ4.50 (m, 2H, -C(OH)-H), δ2.17 (t, 2H) and δ1.85 (m, 6H) remainder of $-CH_2-$ protons. The nmr spectra agree with those reported by Finegold and Kwart[51] for the two diols in pyridine solutions.

Separation of cis and trans 1,2-cyclohexanediols -- batch technique

A 1:1 mixture of cis and trans 1,2-cyclohexanediols (1 g, 8.6 meq) was added to a suspension of 1% cross-linked Ⓟ-$B(OH)_2$ resin (2 g, 6.3 meq) in 50 ml of dry benzene. After removal of 15 ml of solvent by azeotropic distillation, the resin was filtered and the filtrate evaporated to yield 0.4 g (80%) of trans 1,2-cyclohexanediol (m.p. 102-103°). The resin was washed several times with dry benzene and following evaporation this gave a fraction containing both diols. Cleavage of the cis diol from the resin with 20 ml of 4:1 acetone-water, followed by filtration of the resin and evaporation of the solvents gave 0.42 g (84%) of cis 1,2-cyclohexanediol (m.p. 98-99°C).

The nmr spectra of the isomers in $CDCl_3$ solution were recorded at -35°C. The nmr of the cis isomer included signals centered at δ4.90 (b.s., 2H, 2 -OH), δ3.80 (b.s., 2H, two -C(OH)-H), δ1.62 (m, 8H, four $-CH_2-$). The nmr spectrum of the trans isomer showed signals

centered at δ5.39 (b.s., 2H, 2 -OH), δ3.34 (b.s., 2H, two -C(OH)-H), δ1.60 (m, 8H, four $-CH_2-$).

Separation of cis and trans 1,2-cyclohexanediols-column technique

A solution of 0.42 g of a mixture of cis and trans 1,2-cyclohexanediols (3.60 meq) in 1 ml of pyridine was applied to a column (10.5 x 2.4 cm) containing 6.85 (15 meq) of Ⓟ-$B(OH)_2$ resin. The uncoupled trans diol, 0.3 g, was eluted with benzene and the cis isomer, 0.1 g, was cleaved from its support with benzene/ 3% methanol. The nmr spectra were identical to those of pure trans and cis 1,2-cyclohexanediols, respectively.

Separation of cis and trans 1,3-cyclohexanediols-column technique.

A mixture of cis and trans 1,3-cyclohexanediols was separated on a column similar to that described above. The 0.37 g sample dissolved in 1 ml of pyridine was applied to the column and the trans isomer, 0.10 g, was eluted with benzene. The cis isomer, 0.12 g, was eluted with 5% methanol/ benzene. The nmr spectra of these compounds corresponded to those of pure trans and cis 1,3-cyclohexanediols.

Separation of cis and trans 1,4-cyclohexanediols - column technique

A column (6.7 x 2.4 cm) was packed with 7.48 g (16.5 meq) of 1% crosslinked Ⓟ-$B(OH)_2$. 0.91 g (7.83 meq) of a 1:1 mixture of cis and trans 1,4-cyclohexanediol dissolved in 2 ml of pyridine were applied to the column and eluted with benzene. 0.79 g of diol (87%) were recovered in fractions containing various amounts of each isomer. The last fraction contained 90% of one isomer (cis) and 10% of the other. The nmr spectrum in d_6-DMSO included signals at δ4.46 (d, 1.8 H, -C(OH)-H), δ4.33 (d, 0.2 H, -C(OH)-H), δ3.46 (m, 2H, two -OH), δ2.54 (m, DMSO), δ1.48 (m, 8H, $-CH_2-$).

CONCLUSION

The purpose of this project was to prepare a polystyrylboronic acid resin and to study its selectivity as a diol protecting group. By synthesizing several partially acylated carbohydrate derivatives, it was found that the resin was highly selective. Intermediate resin-bound cyclic boronates were formed with hydroxyl groups *cis* to each other. As well six-membered rings were formed in preference to five-membered rings. The resin was also used successfully as a selective "adsorbent" for the separation of *cis* and *trans* cyclohexanediols by affinity chromatography.

Since the resin plays a critical role in the coupling reaction, the preparation of the resin should be studied further to make its degree of functionalization more predictable. Some of the resins used in this work gave consistently lower yields than other resins and the cause of the problem could not be located. It is likely that the yields reported for several of the compounds which were prepared would have been higher had a different batch of resin been used in the reaction.

CLAIMS TO ORIGINAL RESEARCH

1. The design of a fully regenerable polymeric reagent.
2. The preparation of a polystyrylboronic acid resin by partial functionalization of cross-linked polystyrene resins.
3. The use of the polystyrylboronic acid as a diol protecting group and the study of its addition and removal under very mild conditions.
4. The study of the selectivity of the resin in reactions with polyols containing more than one potential reaction site.
5. The application of the polystyrylboronic acid to the selective functionalization of polyols in "one-pot" systems.
6. The use of the polystyrylboronic acid in the separation of cis-trans diol mixtures on the basis of their stereochemistry by affinity chromatography.
7. The preparation of the previously unknown compounds:
   (a) Methyl 6-O-trityl-4-O-benzoyl-α-D-mannopyranoside
   (b) Methyl 6-O-trityl-3-O-benzoyl-α-D-glucopyranoside.
   (c) Methyl 3-O-benzoyl-β-D-ribopyranoside
   (d) Methyl 2,3,4,6,2',3'-hexaacetyl-α,α-trehalose
   (e) Methyl 4-O-benzoyl-α-L-rhamnopyranoside
   (f) 1-O-Benzoyl-3,4-dihydroxybutane

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