SOME NEW O-ETHYLBORON-ASSISTED CARBOHYDRATE TRANSFORMATIONS•

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Dedicated to Herbert C. Brown on the occasion of his 70th birthday

Abstract - New aspects and uses of O-ethylboron-carbohydrate chemistry, such as controlled glycosidations, high-yield syntheses of boron-protected halogenoses and the stereoselective, boron-assisted, glycosylations of the latter are described.

INTRODUCTION

In a previous review[1] we discussed the introduction of O-diethylboryl and O-ethylboranediyl groups in some detail. The mild conditions required for protection and deprotection with the ethylboron groups, were demonstrated by the efficient synthetic routes to some partially O-acylated monosaccharides[2,3]. Novel aspects indicated that O-ethylboron protection could possibly take on a useful role in carbohydrate chemistry. In this article we will concentrate on some new, mainly unpublished, results from our laboratory which will illustrate the protective and directive features of O-ethylboranediyl groups.

THE SUBSTRATES

The versatile nature of carbohydrates is partly due to their ability to exist in two heterocyclic forms, namely as furanoses and pyranoses. In addition to this, α- and ß-anomers of the two heterocycles can be formed.

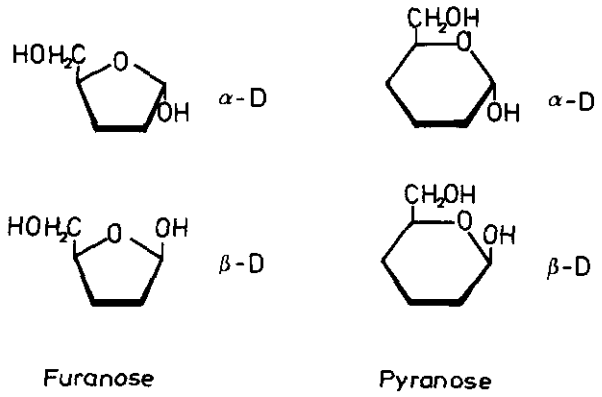


Fig. 1 Furanose and pyranose heterocycles

The acyclic aldehydo-forms can also be observed sometimes[4]. Hence a "pure" pentose or hexose, is in fact a mixture of five isomers in solution. Because of this, controlled regio- and stereoselective transformations of carbohydrates represent a particular challenge in organic chemistry.

Our contribution to this area arose from the finding that both mono-[5] and bifunctional O-ethylboron protection of saccharides is easily achieved in surprisingly good yields[1]. The ease of introduction of the groups containing electrophilic boron atoms led us to consider the possibility of using the electrophilic groupings in order to achieve stereoselective transformations of carbohydrates, by reacting these with nucleophiles. In order to realise bifunctional protection, which could possibly exert a profound influence in the stereoselectivity of further transformations at the anomeric centre, the O-ethylboron group has to be sufficiently close to the C-1 leaving group. Stereochemical considerations reveal that only 2,3- and 2,4-O-protection with a bifunctional group containing an electrophilic centre fulfil the latter prerequisite. 2,4-O-protection is, obviously, only possible with the pyranose forms of monosaccharides, whereas 2,3-O-protection is possible for both furanoses and pyranoses. The two tetraoses, four pentoses and eight hexoses can exist as 24 anomeric pyranoses and 28 anomeric furanoses, see Fig. 2.

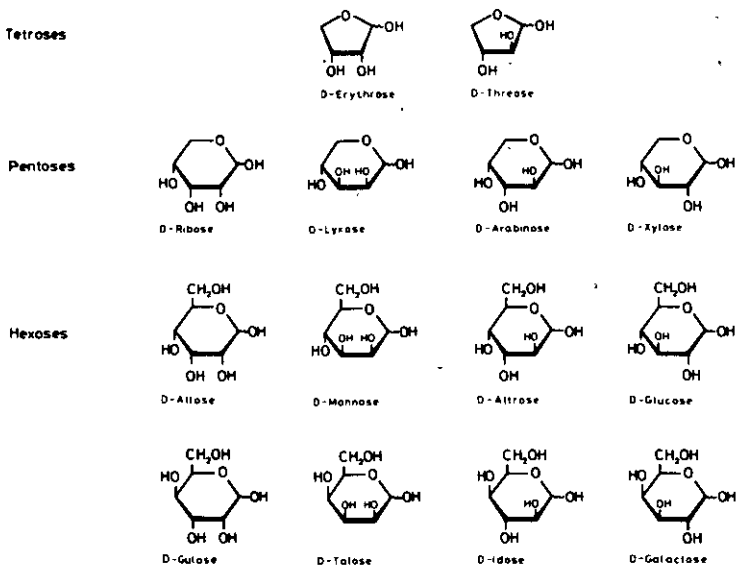


Fig. 2 The tetroses and aldopyranoses

The seven monosaccharides in the two columns on the left side of Fig. 2 have erythro 2,3-diol groups, namely erythrose, ribose, lyxose, allose, mannose, gulose and talose. An erythro-configuration is needed for the formation of 1,3,2-dioxaborolane groups, as model experiments with the c/t-1,2-diols of cyclohexane had shown[6].

Below is shown, that all of these monosaccharides react giving mainly 2,3-O-ethylboranediyl protected compounds. Notable is the exception of D-ribose, which preferentially forms the 2,4-O-protected pyranose. The reactions of the free monosaccharides to 2,3-O-protected compounds is always accompanied by pyranose to furanose ring contraction giving the thermodynamically favoured bicyclo[3.3.0]octane type systems[7].

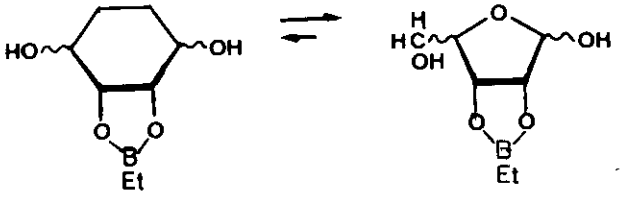


Fig. 3 Preferential formation of the cis-fused [3.3.0] ring system

Some O-ethylboron directed reactions of the seven 2,3-erythro configurated monosaccharides will be discussed. The concept of achieving stereochemical control as described above, is shown to be of particular importance in reactions of some novel bifunctional O-ethylboron protected halogenoses which allow ready access to thermodynamically unfavoured cis-1,2-derivatives.

THE O-ETHYLBORANEDIYLATION REAGENTS

The reagents which were used for achieving the various reactions described are:

1. Triethylboroxine[2] $(EtBO)_3$ reacts with alcohols to give water as the sole side-product when used stoichiometrically. The reaction course is however very complicated.
2. Ethyl-dimethoxy-borane[8] $(MeO)_2BEt$ forms methanol as the side-product on borylation.
3. 1,2:1'2'-Bis-(ethyl-pivaloyloxy)-diboroxane[1] $(tBuCO\overset{O}{\underset{|}{B}}\overset{Et}{\underset{|}{}})_2O$, (BEPDIB) liberates pivalic acid and water on reaction with the polyhydroxy substrates.

The different condensation side-products e.g. water, methanol and pivalic acid formed from these reagents, have an influence on the course of the reactions with the carbohydrates. The concentrations of the reagents also play an important role. Because of this we developed standard conditions. Normally, stoichiometric amounts of triethylboroxine of of BEPDIB are used. In general an excess of ethyl-dimethoxyborane is required for O-ethylboranediylation. Methanol forms an azeotrope with $(MeO)_2BEt$ and hence some of the boron-reagent is lost. Some applications of the three reagents for some improved transformations of monosaccharides will be given. Our results are divided into three sections. Firstly Fischer-glycosidations will be discussed. Then the syntheses of some O-ethylboranediyl protected glycosyl bromides are described. Finally some model stereoselective glycosylations are elucidated.

A. Fischer-glycosidations

The Fischer-glycosidation is the simplest method for preparing glycosides with lower alcohols[9]. An excess of alcohol is added to the monosaccharides in the presence of an acid catalyst and the glycosides are formed by elimination of water.

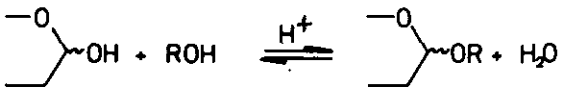


Fig. 4 Fischer-glycosidation

The formation and hydrolyses of glycosides, as shown above, is a reversible reaction which can be forced in one direction by use of a large excess of alcohol or water. This seemingly simple reaction is however very complex, as many reversible reactions occur during such an acid-catalysed alcoholysis. The reaction is thought to proceed via acyclic hemiacetals which cyclise to give furanosides as the kinetic products. These then undergo ring expansion to the thermodynamically favoured pyranosides.

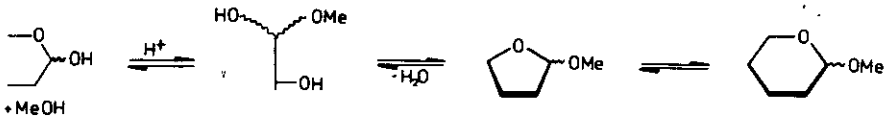


Fig. 5 Some equilibria in the Fischer-glycosidation (schematic)

Hence, it is usually easy to prepare glycoside mixtures containing mainly glycopyranosides, simply by heating the reaction mixture until the final equilibrium is achieved. The synthesis of furanosides is more difficult. The course of the reaction is monitored until a maximum furanoside content is reached at an early stage of the reaction. The reaction is then stopped by neutralisation and the furanosides can be isolated from the furanoside-rich mixture by chromatography.
Our investigations were undertaken in order to test the feasibility of using O-ethylboron protection for directing the course and stereoselectivities in some Fischer-glycosidations. Some selected results obtained with several monosaccharides are presented below.

1. Methyl D-erythrofuranosides using ethyl-dimethoxy-borane

In contrast to the pentoses and hexoses, the tetroses, erythrose and threose, which cannot form pyranoses, consist of complicated mixtures in which the dimeric forms

predominate[10-12]. This state of affairs was well-described recently by the comment, "... the simpler the sugar, the more complex is its n.m.r. spectrum and its composition in solution."[10] The complex nature of erythrose is probably the reason why the methyl D-erythrofuranosides were only obtained in ~30 % yield, by Fischer-glycosidation of the free tetrose[13]. The ß-D-glycoside constituted 75 - 80 % of the anomeric mixture obtained[13,14].

A considerable improvement in both yield and stereoselectivity is achieved by carrying out the glycosidation with dimethoxy-ethyl-borane and a small amount of methanol. Thus methyl 2,3-O-ethylboranediyl-D-erythrofuranoside was obtained directly in 80 % yield after vacuum distillation. The ß-D-glycoside strongly predominated, with an α: ß ratio of 4 : 96.

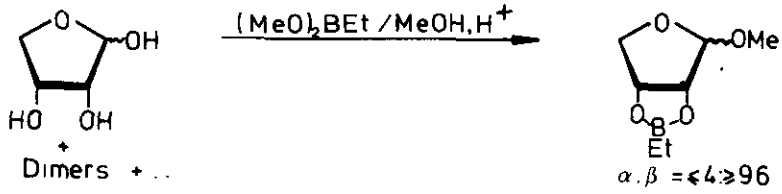


Fig. 6 Boron-directed methyl-glycosidation of D-erythrose

The reagent dimethoxy-ethyl-borane plays a number of roles in this procedure. It reacts with the erythrose mixture forcing the equilibrium in the direction of the thermodynamically favoured bicyclo[3.3.0]octane type system[7]. The methanol side product in the protection step serves as aglycon. Decomposition[13] is strongly reduced and the volatile protected glycosides are easily isolated by vacuum distillation. Further, the purities of the boron protected glycosides are readily and accurately determined by gas-liquid chromatography[15].

2. Methyl glycosidation of 2-deoxy-D-erythro-pentose (2-deoxy-D-ribose)

The acid-catalysed methyl glycosidation of 2-deoxy-D-erythropentose leads to extensive decomposition if the reaction is carried out under reflux conditions[16,17]. By carrying out the glycosidation at room temperature, decomposition is avoided and an equilibrium mixture of glycosides is obtained after 18 h. The ß-D-glycopyranoside was isolated in ~20 % yield by fractional crystallisation of the latter product mixture[17].

An efficient and quantitative separation of the pyranosides and furanosides which are formed without boron-protection is made possible by converting the glycosides to their O-ethylboranediyl derivatives. On reaction of the equilibrium mixture with triethylboroxine in benzene and subsequent vacuum distillation, the volatile methyl 2-deoxy-3,4-O-ethylboranediyl-α/ß-D-erythro-pentopyranosides, which were quantitatively separated, were obtained in 62 % yield. Gas chromatographic analysis and ^{13}C-NMR revealed that the anomeric pyranosides are formed in the ratio α : ß = 20 : 80.

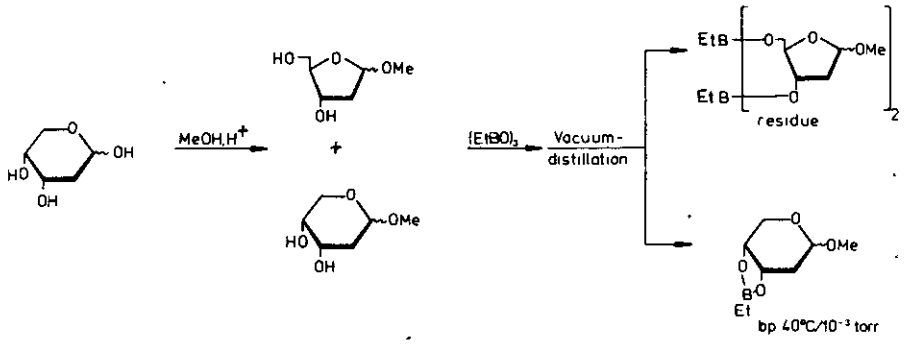


Fig. 7 Separation of the methyl furanosides and pyranosides of 2-deoxy-D-erythropentose by O-ethylboranediylation

The residue after the distillation consisted entirely of non-volatile anomeric furanosides having intermolecularly linked O-ethylboranediyl groups. Both the volatile O-ethylboron protected pyranosides and the non-volatile furanoside derivatives were quantitatively deboronated with methanol at room temperature.
When the methyl glycosidation of 2-deoxy-D-erythro-pentose was carried out at higher temperatures and the products separated as described above, two differences became apparent. Thus, after heating 2-deoxy-D-erythro-pentose for 2 h at 65° in the presence of hydrogen chloride and subsequent O-ethylboranediylation, the yield dropped and the volatile protected pyranosides were only obtained in 47 % yield after vacuum distillation. Gas chromatographic analysis revealed that the ß-glycoside content had been improved from α : ß = 20 : 80 to 13 : 87, but that this better stereoselectivity was accompanied with the formation of numerous volatile decomposition products (35 peaks, total 3 %). A higher yield and better stereoselectivity were achieved when 3,4-O-ethylboranediyl-2-deoxy-D-erythro-pentopyranose[1] was

used as an intermediate in the glycosidation.

The latter crystalline derivative can be prepared by reaction of 2-deoxy-D-ribose with 1/2 mol bis(ethyl-pivaloyloxy)-diboroxane[1,2] or with 1/3 mol triethylboroxine. It is not obtained by reaction of 2-deoxy-D-ribose with pure dimethoxy-ethyl-borane, instead quantitative formation of a novel acyclic 1,3:4,5-Di-O-ethylboranediyl methyl hemiacetal is observed. This compound is converted to the crystalline 3,4-O-ethylboranediyl derivative by addition of a small amount of methanol (see Fig. 8).

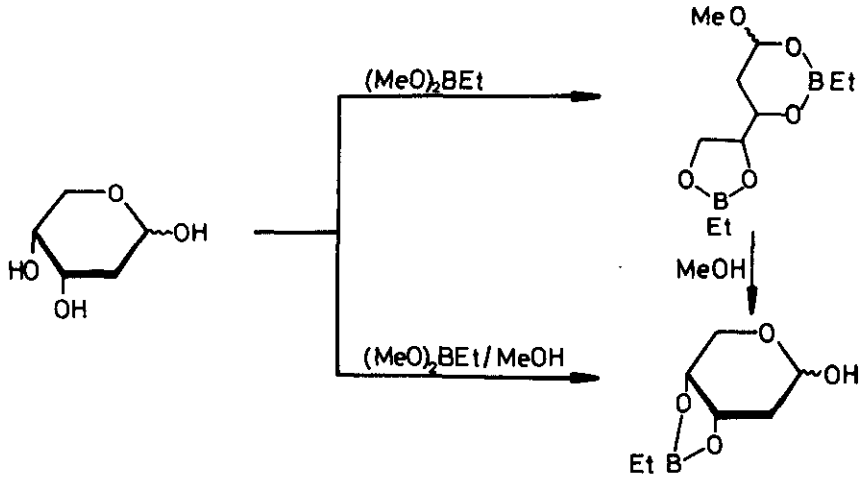


Fig. 8 Mono- and di-O-ethylboranediyl derivatives of 2-deoxy-D-ribose

An alternative procedure, which is the basis of the efficient glycosidation process, involves reaction of 2-deoxy-D-ribose with dimethoxy-ethyl-borane containing ca. 10 % of methanol. The boron directed glycosidation with $EtB(OMe)_2$ is extremely simple to carry out. An excess of dimethoxy-ethyl-borane containing small amounts of methanol is added to 2-deoxy-D-ribose in the presence of hydrogen chloride catalyst. After 18 h at room temperature, or heating for 2 h under reflux, the protected glycopyranosides were obtained in ~ 95 % yield after vacuum distillation. No furanosides were formed using this approach.

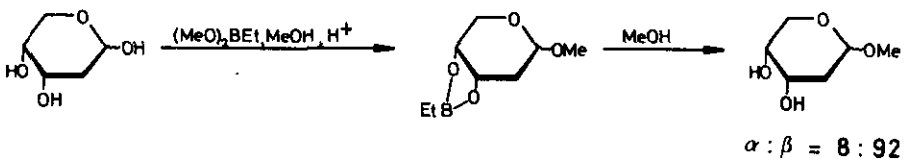


Fig. 9 Preparation of methyl 2-deoxy-D-erythro-pentopyranosides

The ß-glycoside (GC-analysis; α : ß = 8 : 92) was the predominant product and no decomposition products were observed. Deprotection with methanol gave the methyl glycopyranosides in quantitative yield.

3. Alkyl α-D-mannofuranosides

Synthetic routes to alkyl D-mannofuranosides have attracted much attention, in particular in recent years[18-21]. The newer approaches usually involve transformations, under non-acidic-conditions, of the readily available 2,3:5,6-di-O-isopropylidene-D-mannofuranose. Care must however be taken during the deprotection, as acidic conditions are required which can cause glycoside cleavage[21]. Alternative procedures involving carbonate protection[22] or acyclic dithioacetals[23] have attracted little attention as the yields are poor.

The O-ethylboranediyl group is sufficiently acid-stable for the efficient conversion of D-mannose into alkyl D-mannofuranosides. Reaction of D-mannose with 1 mol BEPDIB or 2/3 mol triethylboroxine gave 2,3:5,6-di-O-ethylboranediyl-D-mannofuranose in ~95 % yield[24].

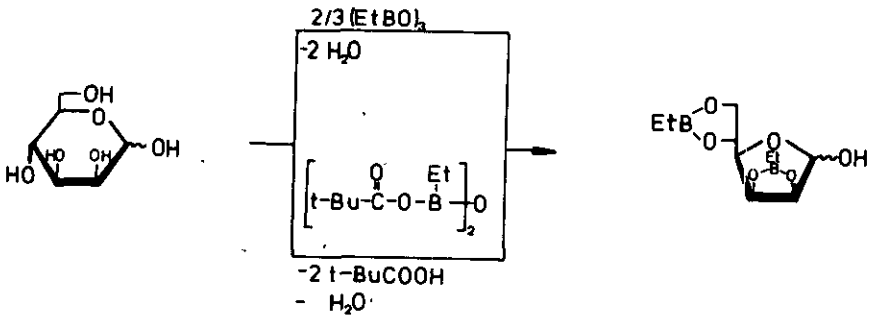
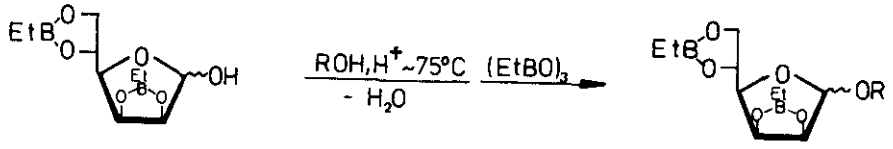


Fig. 10 Two preparations of 2,3:5,6-di-O-ethylboranediyl-D-mannofuranose

This colourless, vacuum distillable derivative is a valuable intermediate for the preparation of alkyl α-D-mannofuranosides. It reacted smoothly with aliphatic alcohols at 65 - 80° in the presence of acid catalysts to give alkyl α-D-mannofuranosides in ~80 % yield after vacuum distillation. The most convenient syntheses were carried out using acidic ion exchange resins as the catalyst was readily removed by filtration after the glycosidation. Thus 80 - 90 % yields of alkyl α-D-mannofuranosides were achieved.



R	Yield (%)	Composition (GC) α-Fur.	β-Fur.	Pyr.
Me	90	90	1	8
Et	73	~94	< 1	6
n-Pr	83	92	2	6
i-Pr	85	~97	< 1	3
s-Bu	77	~97	< 1	3

Fig. 11 Alkyl mannofuranoside syntheses

The differences in the stereoselectivities and purities of the alkyl α-D-mannofuranosides prepared in this way are readily understood. Methyl glycosidation of 2,3:5,6-di-O-ethylboranediyl-D-mannofuranose gives a crystalline product mixture containing 90 % of the α-D-mannofuranoside in ~90 % yield after vacuum distillation. GC-MS analysis revealed that the major contaminant (~7 %) was the 2,3:4,6-O-ethylboranediyl protected methyl α-D-mannopyranoside[3]. The formation of small amounts of pyranosides is not unexpected, as the glycosidation conditions are essentially those which are used for deboronation, albeit that no acid is required for the latter reaction. The problem of methyl mannopyranoside formation is particularly noticable with methanol as the aglycon, because methanol is also the best deboronating agent of the acyclic monofunctional alcohols.

The formation of pyranosides can however be suppressed by reacting D-mannose with dimethoxy-ethyl-borane in the presence of acid ion exchange resin.

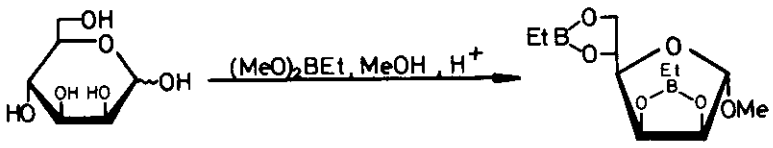


Fig. 12 One step preparation of protected methyl α-D-mannofuranoside

The crystalline, 96 % pure (GLC), methyl α-D-mannofuranoside derivative was obtained in 90 % yield after vacuum distillation.

Reactions of bis-O-ethylboranediyl-D-mannofuranose with secondary alcohols such as isopropanol and sec.-butanol were particularly advantageous, as excellent stereoselectivities were observed. The 97 % pure (by gas-chromatography) alkyl α-D-mannofuranosides were obtained in ~80 % yield, without attempting to optimise the yield. The stereoselectivity was improved in favour of the thermodynamically more stable trans-1,2-glycosides, with increasing steric demands of the aglycon.

The deboronation of the boron-protected alkyl α-D-mannofuranosides are unproblematic and do not endanger the glycoside bond. Total deprotection was achieved with alkane-diols, such as ethane-1,2-diol and propane-1,3-diol, in quantitative yield. Partial deboronation was also possible by reaction with methanol at room temperature. The exocyclic 5,6-O-ethylboranediyl group is more readily opened than the 2,3-O-located protective group and hence partially protected alkyl α-D-mannofuranosides can be prepared.

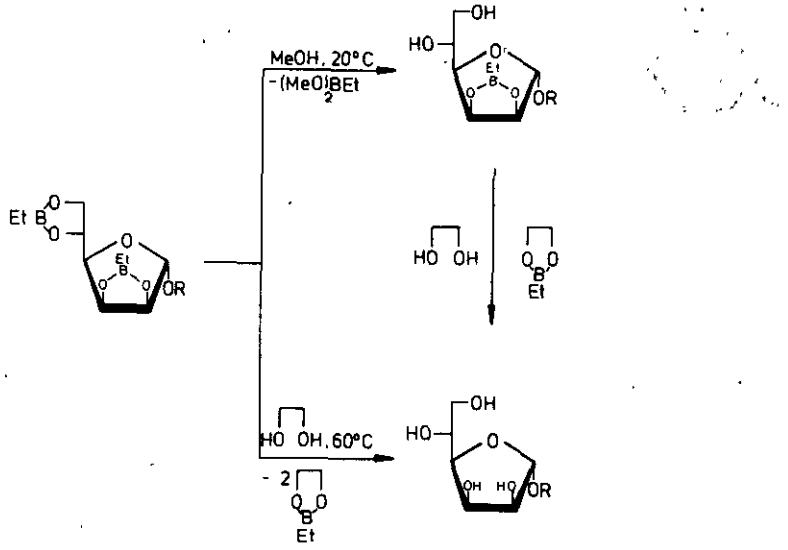


Fig. 13 Partial and total deblocking of O-ethylboron protected alkyl α-D-mannofuranoside

4. Methyl α-D-lyxofuranoside

The reaction of D-lyxose with 2/3 mol triethylboroxine gave a mixture of fully protected derivatives in quantitative yield[25]. These are converted to 2,3-O-ethylboranediyl-D-lyxofuranose[25] by addition of a small amount of methanol. The protective group in this compound was sufficiently stable under glycosidations conditions, so that 90 % methyl α-D-lyxofuranoside was formed on heating this mixture in the presence of acid catalyst.

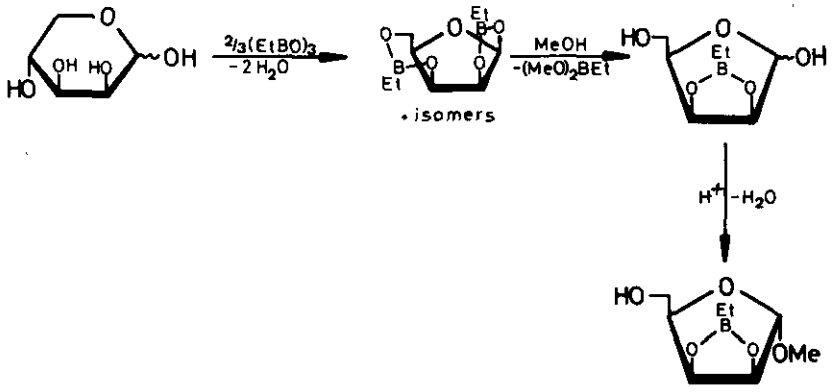


Fig. 14 Methyl 2,3-O-ethylboranediyl-α-D-lyxofuranoside from D-lyxose

A simpler route to methyl α-D-lyxofuranoside involved treatment of free D-lyxose with an excess of dimethoxy-ethyl-borane containing ~10 % methanol in the presence of acid catalyst. A quantitative yield of protected methyl lyxosides was obtained. The α-furanoside constituted 90 % of the product mixture (see Fig. 15).

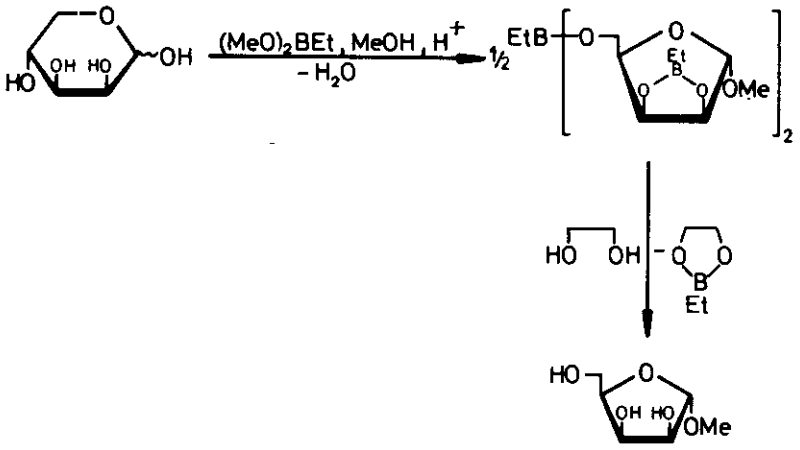


Fig. 15 Two-step preparation of methyl α-D-lyxofuranoside

Deboronation of the O-ethylboranediyl protected methyl α-D-lyxofuranoside derivatives gives the free glycoside in ≥ 95 % yield. This procedure represents a considerable improvement on the previously described approaches[26,27].

B. Preparation of O-ethylboron protected glycosyl bromides

Glycosyl halides, in particular bromides, are important intermediates in carbohydrate chemistry, as they allow the synthesis of a wide range of derivatives[28,29]. In principle, one can classify the glycosyl halides into two groups, namely into those which are monofunctionally protected and those which are bifunctionally protected. The most commonly used halogenoses have acyl groups, such as the venerable "acetobrom glucose". The O-acyl functions can, however, act as participating neighbouring groups during glycosylations, to give ortho esters[29]. A distinct trend towards using halogenoses containing nonparticipating groups has become evident during recent years[30,31], as a clearer control of the stereoselectivities during glycosylations is possible.

The first bifunctionally protected glycosyl halide was reported ca. 50 years ago, by K. Freudenberg, who prepared 2,3:5,6-di-O-isopropylidene-D-mannofuranosyl chloride[32]. Since then many methods for preparing this useful halogenose have been described[33,34]. The more reactive furanosyl bromide cannot be prepared easily due to the acid lability of the O-isopropylidene group[35]. The latter halogenose can be made by reaction of the protected D-mannofuranose with N-bromosuccinimide and triphenylphosphine, i.e. under effectively neutral conditions[36]. The product is however contaminated with triphenylphosphine oxide and the yield is lower than originally reported[37].

The acid-stability of the protective groups in 2,3:5,6-di-O-ethylboranediyl-D-mannofuranose which was demonstrated by the efficient syntheses of alkyl α-D-mannofuranosides, also allows its essentially quantitative conversion to the corresponding useful O-ethylboron protected α-D-mannofuranosyl bromide[24]. This is achieved by reaction with phosphorous tribromide at room temperature.

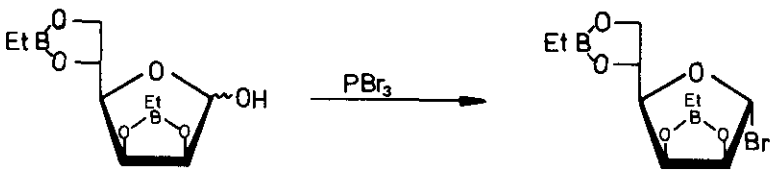


Fig. 16 Quantitative route to O-ethylboron protected α-D-mannofuranosyl bromide

A high yield preparation of a bifunctionally protected α-D-lyxofuranosyl bromide is also easily realised by O-ethylboranediylation[25]. D-Lyxose can be converted to 1,5-di-O-acetyl-2,3-O-ethylboranediyl-α-D-lyxofuranose with $(EtBO)_3$ in 95 %. This derivative reacted quantitatively with hydrogen bromide in acetic acid at room temperature to yield protected α-D-lyxofuranosyl bromide (Fig. 17).

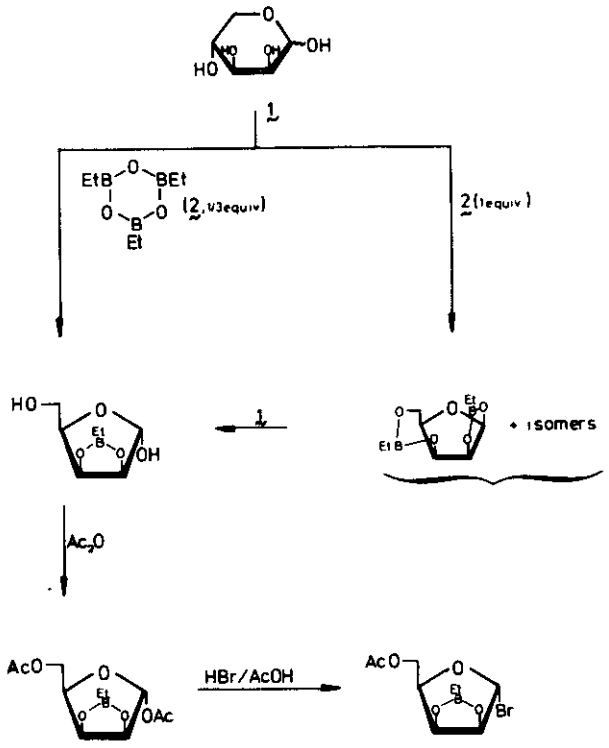


Fig. 17 Conversion of D-lyxose to the protected lyxofuranosyl bromide

Both D-[38] and L-gulose[39] are now easily available in pure form by use of ethylboron reagents. 1-O-diethylboryl-2,3:5,6-di-O-ethylboranediyl-D-gulofuranose[38] reacted smoothly with hydrogen bromide in acetic acid to give 2,3:5,6-di-O-ethylboranediyl-ß-D-gulofuranosyl bromide in excellent yield (see Fig. 18).

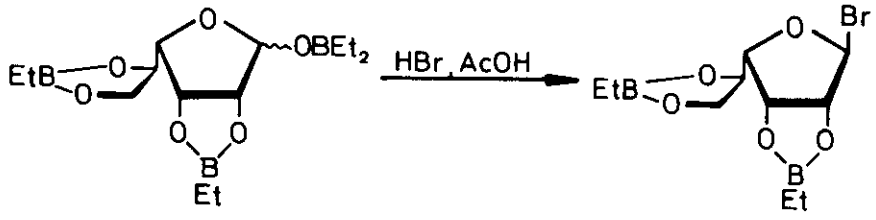


Fig. 18 Preparation of 2,3:5,6-di-O-ethylboranediyl-ß-D-gulofuranosyl bromide

The D-gulofuranosyl bromide derivative has exceptional thermal stability and can be vacuum distilled with negligable loss. This procedure is a substantial improvement on the approach described previously, which uses O-isopropylidene protection, reduction with sodium borohydride and conversion to the protected chloride with thionyl chloride in an overall yield of ~ 17 %[40]. 1-O-Diethylboryl-2,3:5,6-di-O-ethylboranediyl-L-gulofuranose[39] was also converted to the corresponding new bromide by reaction with hydrogen bromide in acetic acid.
Hence a remarkably efficient two-step conversion of D-glucurono-6,3-lactone to the useful protected L-gulofuranosyl bromide is achieved.

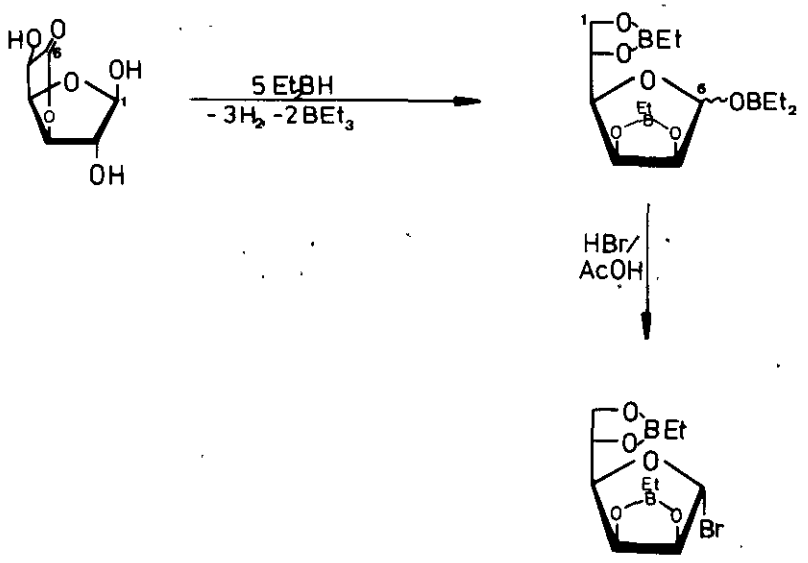


Fig. 19 Two-step conversion of D-glucurono-6,3-lactone to 2,3:5,6-di-O-ethylboranediyl-ß-L-gulofuranosyl bromide

The syntheses of boron-protected hexofuranosyl bromides are not limited to D-mannose and gulose. Allose and talose can also be converted to 2,3:5,6-di-O-ethylboranediyl-D-glycofuranosyl bromides, albeit in lower yields, by reaction with 2/3 mol triethylboroxine and subsequent bromination with phosphorous tribromide[44].

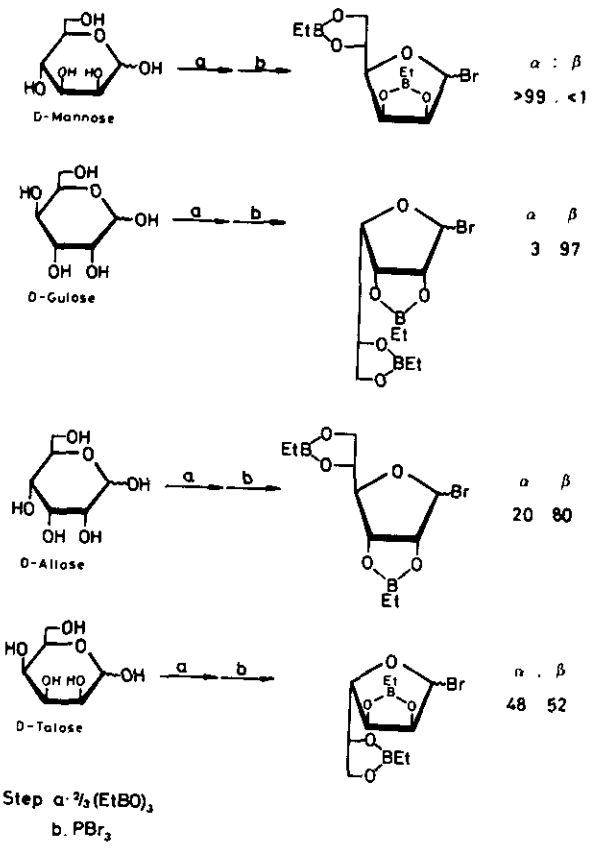


Fig. 20 New hexofuranosyl bromides

The anomeric purity of the hexose halogenoses decreases in the series mannose, gulose, allose and talose. Optimal anomeric purity, in favour of the trans-1,2-glycosyl bromide, is observed in the case of D-mannose which has the dioxaborolane rings "cis" to another and with O^4O^5-erythro orientated.

A slight increase in the formation of cis-1,2-glycosyl bromide is found in the case of gulose, which still has cis-dioxaborolane rings, but with an O^4O^5-threo-arrangement. More dramatic effects are encountered in the hexoses having the dioxaborolane rings trans to one another, in the case of D-allose, having an O^4O^5-erythro arrangement, 20 % of the cis-1,2-halide is formed. D-Talose which incorporates both destabilising features for 1,2-trans-glycosyl bromide formation, is obtained as a mixture containing approximately equal proportions of α- and ß-furanosyl bromides.

A further example of the use of O-ethylboron protection for preparing furanosyl bromides was realised with 6-deoxy-L-mannose (L-rhamnose) which can be readily reacted to the 1,5-di-O-acetyl-2,3-O-ethylboranediyl-6-deoxy-α-L-mannofuranose[2]. This derivative was smoothly converted to the protected bromide in good yield with hydrogen bromide in acetic acid.

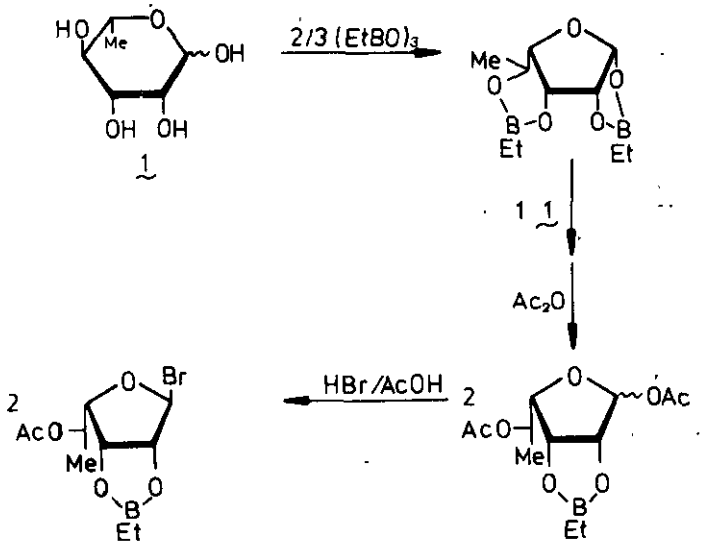


Fig. 21 Synthesis of O-ethylboron protected α-L-rhamnofuranosyl bromide

Halogenoses of 2-deoxy-saccharides are difficult to prepare. They can be synthesised by addition of hydrogen halides to the corresponding glycals[41] or by reaction of the methyl glycosides with trimethylsilyl bromide[42]. We found that 3,4-O-ethylboranediyl-ß-D-erythro-pentopyranose gave the protected 2-deoxy-ß-D-erythro-pentopyranosyl bromide by reaction with phosphorous tribromide at room temperature.

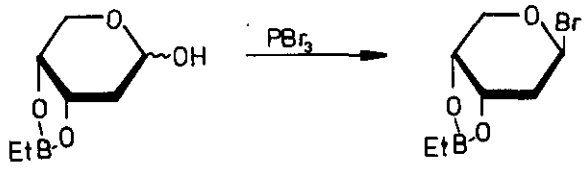


Fig. 22 Preparation of 2-deoxy-3,4-O-ethylboranediyl-ß-D-erythro-pentopyranosyl bromide

A novel crystalline 2,4-O-bridged D-ribopyranosyl bromide was obtained in ~70 % overall yield from D-ribose in a simple procedure. O-Phenylboranediyl protection[43] was used, rather than O-ethylboron protection of D-ribose[1], as an O-phenylboranediyl ribopyranose derivative fortuitously crystallised out and was therefore readily separated from the furanose components[44]. Full protection of D-ribose with dihydroxy-phenyl-borane or triphenylboroxine gave a mixture of two derivatives in quantitative yield. Partially protected compounds were then made by transesterification. This was done by dissolution of the fully protected D-riboses in pyridine and adding 1 mol equivalent of D-ribose to give a mixture of 2,4-O-phenylboranediyl-D-ribopyranoses and 2,3-O-phenylboranediyl-ribofuranoses. Following O-acetylation, addition of diethyl ether selectively precipitated the 1,3-di-O-acetyl-2,4-O-phenylboranediyl-D-ribopyranose, which was then filtered off. This crystalline derivative reacted quantitatively with hydrogen bromide in acetic acid at room temperature to give crystalline 2,4-O-phenylboranediyl-3-O-acetyl-ß-D-ribopyranosyl bromide[44].

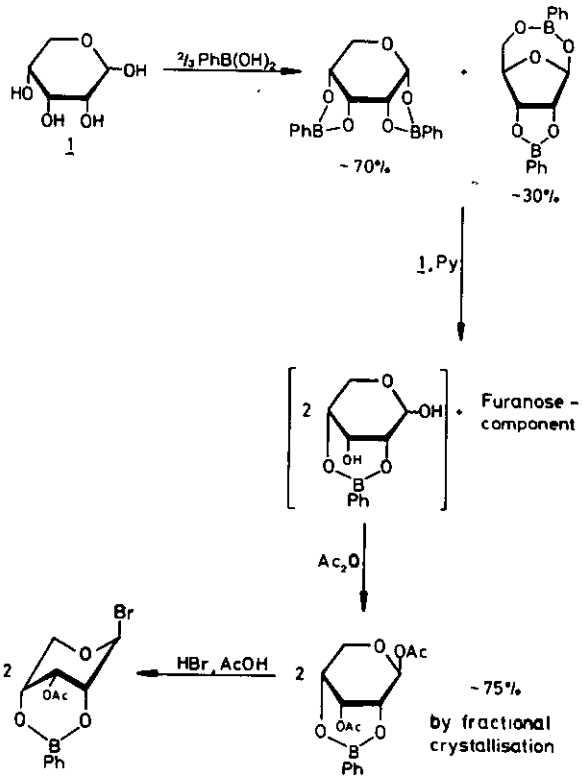
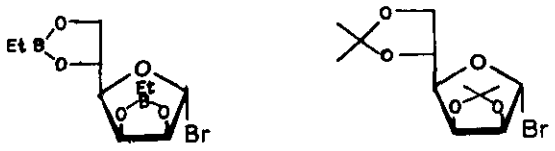


Fig. 23 Conversion of D-ribose (1) to 2,4-O-phenylboranediyl-3-O-acetyl-ß-D-ribopyranosyl bromide

C. Glycosylations of the O-organoboron-protected glycosyl bromides

The ready syntheses of a variety of O-ethylboron-protected halogenoses in good yields gave rise to various questions concerning the usefulness of these intermediates for preparing other derivatives, in particular glycosides. As it was known that the protective group can be removed under mild conditions which do not endanger the glycosidic bond[3], the main question was concerned with the stereoselectivity of glycosylations. A novel feature of the new halogenoses, is that they contain bifunctional protective groups having an electrophilic centre, so that the possibility of achieving stereoselective glycosylations by reactions with nucleophilic reagents was of interest.

In order to shed some light on the latter questions, the glycosylation of 2,3:5,6-di-O-ethylboranediyl-α-D-mannofuranosyl bromide[24] (I) under a variety of conditions was investigated in some detail and the results were compared with those found, under identical conditions, for the corresponding O-isopropylidene protected mannofuranosyl bromide (II).



I II

Fig. 24 O-Ethylboranediyl- (I) and O-isopropylidene protected (II) mannofuranosyl bromide

We found that II can be prepared in 85 % yield by reaction of di-O-isopropylidene-D-mannofuranose with phosphorous tribromide, as described for the O-ethylboron protected compound[44].

The comparison of the glycosylations of I and II proved boron assistance. The first major differences were encountered in the reactions of the two halogenoses with methanol in the absence of acid-acceptors. I reacted smoothly with methanol at room temperature and gave 96 % pure (GLC) protected methyl α-D-mannofuranoside in 90 % yield after vacuum distillation. As partial deboronation occured to a minor extent, treatment with small amounts of triethylboroxine was necessary prior to distillation.

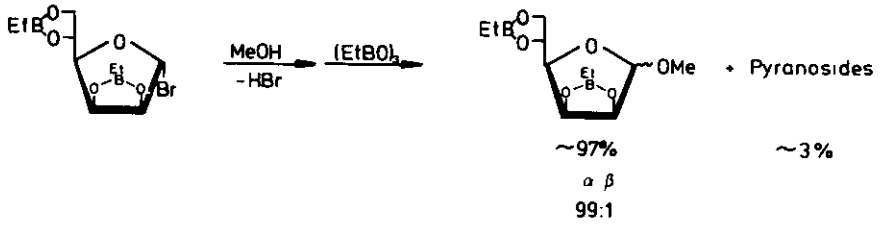


Fig. 25 Methyl glycosylation of I under acidic conditions

In contrast, extensive deprotection was observed in the reaction of II. The deprotection allowed ring expansion to the thermodynamically favoured methyl α-D-mannopyranoside to occur.

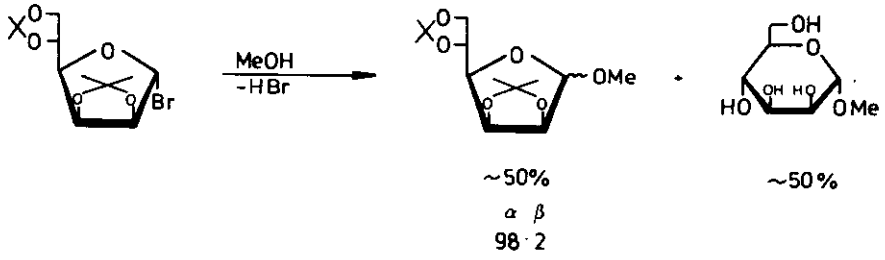
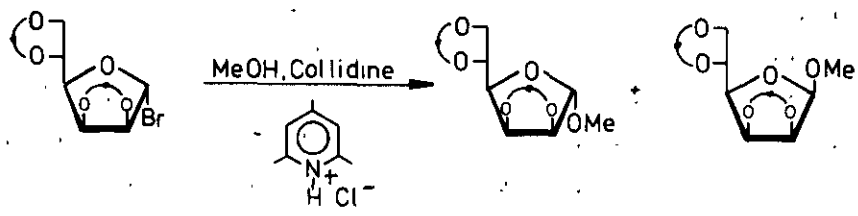


Fig. 26 Methyl glycosylation of II under acidic conditions

By carrying out the methyl glycosylation of I in the presence of an acid-acceptor such as collidine, a relatively high degree of inversion was observed. 91.4 % pure (GC) protected methyl ß-D-mannofuranoside was obtained in 70 % yield after distillation. Only 9 % of the α-glycoside had been formed under these reaction conditions.



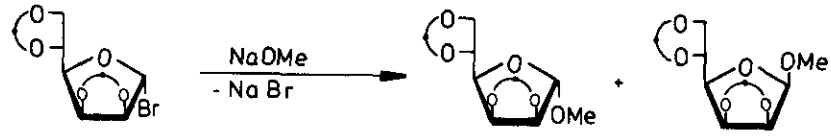
Stereoselectivity	= 82 % } = ⩾BEt,	9	91
"	= 30 % } = ⩾CMe$_2$,	35	65

Fig. 27 Reactions of I and II with methanol in the presence of an acid-acceptor

Predominant inversion was also observed in the case of II although a significantly lower proportion of the ß-glycoside was formed (see Fig. 27).

The stereoselectivities and yields in the glycosylations in the presence of silver salt promoters, such as silver oxide, were found to be strongly dependent on the experimental procedure. A quantitative yield of methyl glycosides was obtained when I was added dropwise to aglycon in the presence of silver oxide. The high yield was however linked with a poor stereoselectivity (α : ß = 45 : 55). Reversal of the mode of addition gave a greater degree of inversion with α : ß = 5 : 95, the yield however dropped to 72 %. Similar results were obtained with II.

Dramatic differences between the two halogenoses were observed in their reactions with the highly nucleophilic sodium methoxide. I reacted with extremely high stereoselectivity and the > 99 % pure (GC) ß-D-glycoside was obtained in 90 % yield. In contrast, II yielded mainly the α-glycoside (see Fig. 28).



	Stereoselectivity ⩾ 98 % } = ⩾BEt,	<1	> 99
inverse	" = 92 % } = ⩾CMe$_2$,	96	4

Fig. 28 Different stereoselectivities in the reactions of I and II with NaOMe

Different steric requirements of the two protective groups are not the reason for the drastic change in stereoselectivity observed, as is evident from inspection of molecular models. The high degree of inversion observed in the reaction of I with sodium methoxide, is however readily explained on the basis of electronic effects. The electrophilic boron in the 2,3-O-ethylboranediyl group exerts a directive effect during the glycosylation. We assume an interaction between the boron and the methoxide ion gives an intermediate borate-type species, with the alkoxy residue ideally located on the ß-side of the anomeric centre, so that a smooth boron-assisted S_N2-reaction occurs. This reaction allows the synthesis of pure methyl ß-D-mannofuranoside (see Fig. 29).

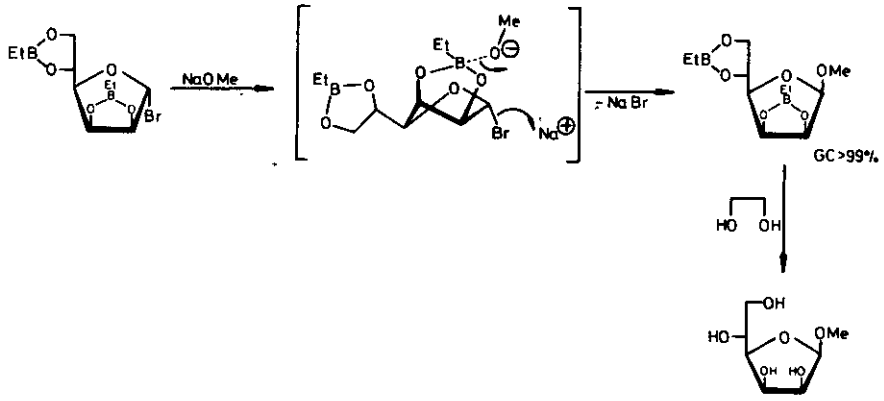


Fig. 29 Pure methyl ß-D-mannofuranoside by boron-assisted glycosylation

Previously, this glycoside could only be prepared in much lower yield and with a poorer degree of anomeric purity[21,45,46]. We found $[\alpha]_D^{20}$ -115.8 (H_2O), c. f. $[\alpha]_D^{20}$ -80.6[21] .

We verified the above interpretation for the high degree of inversion, by preparing the analogous O-phenylboranediyl-α-D-mannofuranosyl bromide[44]. This halogenose also reacted with essentially quantitative inversion with sodium methoxide.

The glycosylations of other boron-protected halogenoses such as 2,3-O-ethylboranediyl-5-O-acetyl-α-D-lyxofuranosyl bromide[25] confirm that these halogenoses are extremely useful, as they allow essentially stereospecific protective-group controlled glycosylations to be performed. Hence, a methyl α-D-lyxofuranoside derivative with 99 % anomeric purity is obtained in over 90 % yield by treatment

of the above-mentioned halogenose with methanol. The equally pure methyl ß-lyxofuranoside is obtained by reaction with sodium methoxide (see Fig. 30).

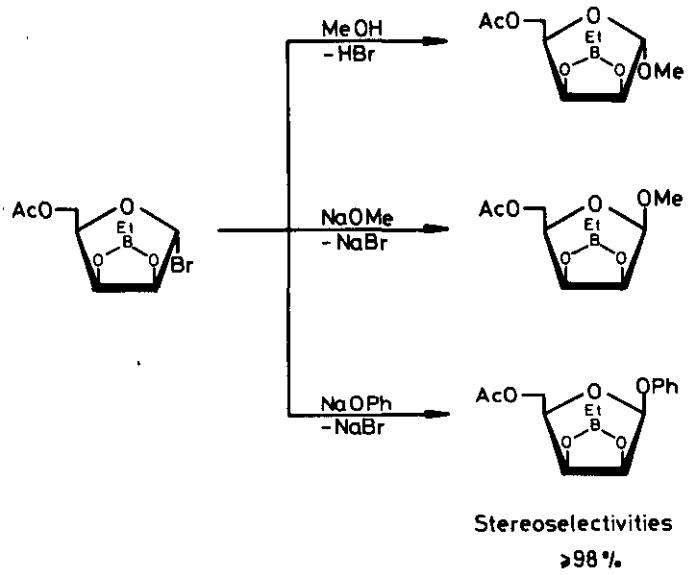


Fig. 30 Highly stereoselective glycosylations of O-ethylboron protected α-D-lyxofuranosyl bromide

That this highly stereoselective glycosylation is not limited to the reaction with sodium methoxide, is indicated by the preparation of the phenyl ß-D-lyxofuranoside derivative shown in Fig. 30. Deboronations and de-O-acetylations are quantitative and gave highly pure glycosides in good yield. The procedure gave a purer methyl ß-D-lyxoside than described previously[26,47].

The exceptional stereoselectivities in the glycosylations of the boron-protected halogenoses is also found in reactions of 2,3:5,6-di-O-ethylboranediyl-gulofuranosyl bromide. Thus, for example, the L-gulofuranosyl bromide gives 98 % pure protected methyl α-L-gulofuranoside on reaction with sodium methoxide.

The boron-directive influence is not restricted to furanosyl halides having 2,3-O-organoboranediyl groups. It is also effective in the case of 2,4-O-organoboron-protected pyranoses, such as 2,4-O-phenylboranediyl-3-O-acetyl-ß-D-ribopyranosyl bromide, which is a valuable intermediate for the stereoselective syntheses of both α- and ß-D-ribopyranosides. The reaction of this halogenose with methanol in

the absence of an acid-acceptor gave the ß-glycoside in 90 % yield with an anomeric purity of 96 % (GC). In contrast, the protected methyl α-D-glycoside was obtained in 90 % yield with anomeric purity of ~99 % by reaction with sodium methoxide (see Fig. 31).

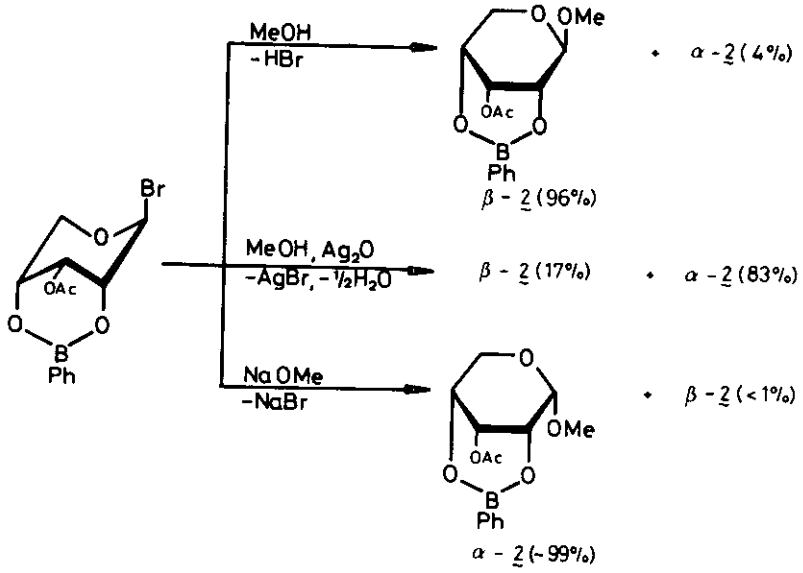


Fig. 31 Syntheses of protected methyl α- and ß-D-ribopyranosides

After deboronation and deacetylation methyl α-D-ribopyranoside was obtained pure for the first time. The optical rotation value of $[\alpha]_D^{20}$ +118 (c 0.5, MeOH) found is higher than previously reported values of $[\alpha]_D^{20}$ +86[48] and +103[49,50].

The smooth inversion observed is probably due to boron-assisted inversion at the anomeric centre, as described above for other boron-protected halogenoses.

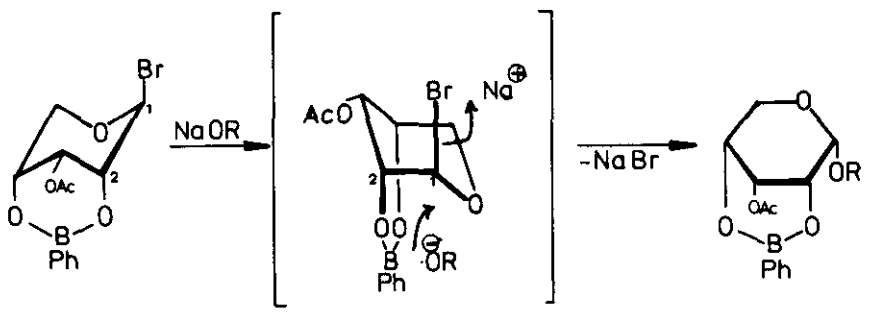


Fig. 32 Boron-assisted synthesis of alkyl α-D-ribopyranosides

In order to achieve effective inversions, the boron-protective group in the halogenoses must be located sufficiently near to the anomeric centre, so that the interaction of the boron with nucleophilic reagents leads to a borate-type intermediate species having the nucleophile in proximity of the C^1-leaving group linkage, hence enabling the inversion to occur.

It is therefore confirmatory that such highly-stereoselective glycosylations, as described above, were not observed with 3,4-O-ethylboranediyl-2-deoxy-ß-D-erythro-pentopyranosyl bromide. Its reaction with methanol gave mainly the methyl ß-D-glycopyranoside with 90 % anomeric purity, as was found in the boron-directed glycosidation of 2-deoxy-D-erythro-pentose.

The reaction of this halogenose with sodium methoxide was not stereoselective and an approximately equimolar mixture of both methyl α- and ß-2-deoxy-D-erythro-pyranosides was obtained (see Fig. 33).

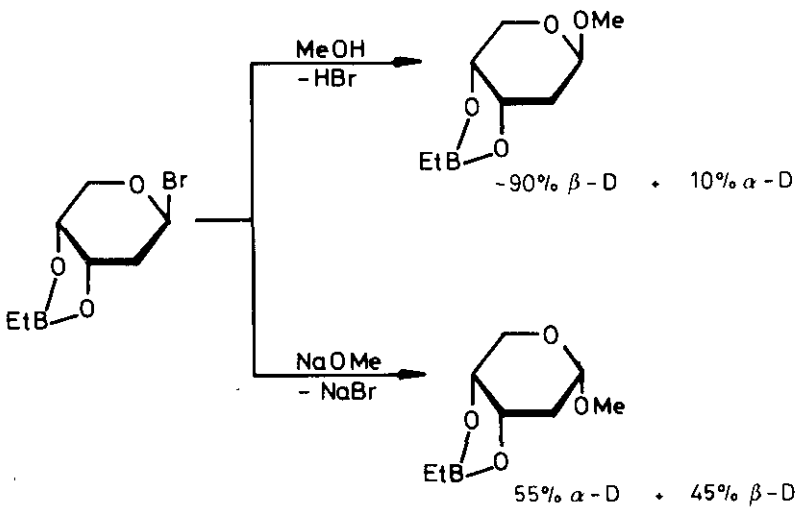


Fig. 33 Methyl glycosylation of 2-deoxy-3,4-O-ethylboranediyl-β-D-erythro-pentopyranosyl bromide

SUMMARY

The combination of two factors, namely the ease of introduction and the acid-stability of the O-ethylboranediyl groups, allows some efficient Fischer-glycosidations to be realised. The aforementioned factors are also of importance in the syntheses of the new protected "bromoses". A notable feature of these halogenoses is that they react with nucleophiles in an extraordinary stereoselective manner. The stereoselectivities of ⩾98 % permit good yield preparations of cis-1,2-glycosides, which obviate chromatographic separations.

By comparison of the methyl glycosylation of O-ethylboranediyl- and O-isopropylidene protected α-D-mannofuranosyl bromides, under a variety of conditions, it was shown that the electrophilic boron atom in the 2,3-O-ethylboranediyl group plays a vital role, as it can control the inversion at the anomeric centre. The smooth inversions observed in the reactions of the boron-protected bromoses with nucleophiles are considered to be due to the intermediate formation of highly reactive borate-type species which immediately give the cis-1,2-products. This general concept of achieving stereochemical control is currently being extented to the syntheses of more complex glycosides, nucleosides and other derivatives.

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