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REACTIONS OF THE *p*-TOLUENESULFONATES
OF MONO- AND DISACCHARIDES WITH
LITHIUM TRIETHYLBOROHYDRIDE.

by

MIROSLAWA MEKARSKA-FALICKI

A thesis submitted to the School of Graduate Studies
in partial fulfillment of the requirements for
the degree of
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in the
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University of Ottawa

July 1985



Mirosława Mekarska-Falicki, Ottawa, Canada, 1985.

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To my research supervisor, Dr. H. H. Baer, I am grateful for his expert guidance, timeless patience and unending enthusiasm.

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TABLE OF CONTENTS

	PAGE
ACKNOWLEDGEMENTS.....	i
TABLE OF CONTENTS.....	ii
ABSTRACT.....	v
INTRODUCTION.....	1
GOALS OF RESEARCH FOR THIS THESIS.....	13
A. Application in the α,α -trehalose series.....	13
B. The action of LTBH upon tosylates in the α - <u>D</u> -manno, α - <u>D</u> -allo, and α - <u>D</u> -altro series.....	14
RESULTS AND DISCUSSION.....	16
A. Application to α,α -trehalose.....	16
B. Reaction of 4,6-O-benzylidenehexopyranoside tosylates with LTBH.....	27
1. α - <u>D</u> -Mannosides.....	27
2. α - <u>D</u> -Allosides.....	30
3. α - <u>D</u> -Altrosides.....	36
CONCLUSION.....	41
EXPERIMENTAL.....	44
General methods.....	44
A. Reaction of the α,α -trehalose p-toluenesulfonates with LTBH.....	45
1. Reaction of 4,6;4',6'-di-O-benzylidene- α,α -trehalose 2,3,2',3'-tetratosylate (32).....	45
2. Reaction of 4,6;4',6'-di-O-benzylidene- α,α -trehalose 2,2'-ditosylate (35).....	46
a) Formation and isolation of products.....	46

	PAGE
b) 4,6- <u>O</u> -Benzylidene-3-deoxy- α - <u>D</u> -arabino-hexopyranosyl 4,6- <u>O</u> -benzylidene-3-deoxy- α - <u>D</u> -arabino-hexopyranoside (37)	47
c) 4,6- <u>O</u> -Benzylidene-3-deoxy- α - <u>D</u> -arabino-hexopyranosyl 4,6- <u>O</u> -benzylidene- α - <u>D</u> -glucopyranoside (39).....	48
d) 4,6- <u>O</u> -Benzylidene- α - <u>D</u> -altropyranosyl 4,6- <u>O</u> -benzylidene- α - <u>D</u> -glucopyranoside (40)...	49
3. Reaction of 4,6;4',6'-di- <u>O</u> -benzylidene- α , α -trehalose 2-tosylate (41).....	49
4. Reaction of 4,6;4',6'-di- <u>O</u> -benzylidene-2,3,2'-tritosylate (43).....	51
a) Formation and isolation of products.....	51
b) 4,6- <u>O</u> -Benzylidene-3-deoxy- α - <u>D</u> -arabino-hexopyranosyl 4,6- <u>O</u> -benzylidene-2-deoxy- α - <u>D</u> -ribo-hexopyranoside (45)	52
c) 4,6- <u>O</u> -Benzylidene-2-deoxy- α - <u>D</u> -ribo-hexopyranosyl 4,6- <u>O</u> -benzylidene- α - <u>D</u> -glucopyranoside (47).....	53
B. Reactions of methyl 4,6- <u>O</u> -benzylidenehexopyranoside tosylates with LTBH.....	54
1. Preparation of the starting glycoside <u>p</u> -toluenesulfonates.....	54
a) Known compounds 49,52,53,55,and 62.....	55
b) Methyl 2- <u>O</u> -benzoyl-4,6- <u>O</u> -benzylidene 3- <u>O</u> - <u>p</u> -tolylsulfonyl- α - <u>D</u> -allopyranoside (58)..	55
c) Methyl 4,6- <u>O</u> -benzylidene-3- <u>O</u> - <u>p</u> -tolylsulfonyl α - <u>D</u> -allopyranoside (59).....	56
d) Methyl 4,6- <u>O</u> -benzylidene-2,3-di- <u>O</u> - <u>p</u> -tolyl-sulfonyl- α - <u>D</u> -allopyranoside (60).....	57
2. Reactions of the glycoside <u>p</u> -toluenesulfonates with LTBH.....	57
a) General procedure.....	57
b) Reaction of 49.....	58
c) Reaction of 52.....	59

	PAGE
d) Reaction of <u>53</u>	59
e) Reaction of <u>55</u>	59
f) Reaction of <u>58</u>	60
g) Reaction of <u>59</u>	60
h) Reaction of <u>60</u>	62
i) Reaction of <u>62</u>	64
3. Reaction of <u>62</u> with lithium aluminum hydride and lithium aluminum deuteride.....	65
REFERENCES.....	71

ABSTRACT

Lithium triethylborohydride reacts readily with the 2-tosylate, the 2,2'-ditosylate, the 2,3,2'-tritosylate, and the 2,3,2',3'-tetra-tosylate of 4,6;4',6'-di-O-benzylidene- α -trehalose (30), to give products resulting both from O-desulfonylation and from reductive C-desulfonyloxylation. Among the products obtained were the known, symmetrically modified, 2,2'- and 3,3'-dideoxytrehalose analogs (as bis-benzylideneacetals) having the α -D-ribo, α -D-ribo and α -D-arabino, α -D-arabino configurations, respectively, as well as three new, crystalline, unsymmetrical analogs, namely, the 2,3'-dideoxy isomer with the α -D-ribo, α -D-arabino configuration, a 2-monodeoxy analog (α -D-ribo, α -D-gluco), and a 3-monodeoxy analog (α -D-arabino, α -D-gluco). The α -D-altro, α -D-gluco isomer of 30 was isolated as a crystalline by-product in one of the reactions.

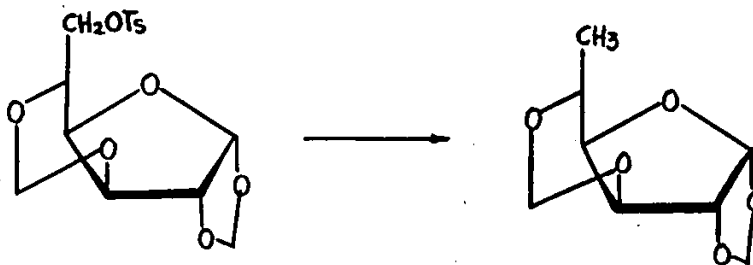
Mechanistic studies on monosaccharides were also undertaken and it was shown that lithium triethylborohydride reacted with methyl 4,6-O-benzylidene- α -D-hexopyranoside 2- and 3-tosylates, and 2,3-ditosylates, in the manno, allo, and altro configurational series both by O-S fission (O-desulfonylation), and by C-O fission (C-desulfonyloxylation), to produce carbinol and deoxy functions, respectively. The results were compared with those previously obtained with the corresponding gluco and galacto isomers, and the degree of facility of the cleavage reactions was seen to depend on the position of the sulfonic ester groups and the overall configuration of the molecules. The mechanism of reductive desulfonyloxylation also depended on configuration and was demonstrated to involve intermediary epoxide formation or displacement by internal hydride shift

as the principal paths; competing elimination and direct nucleophilic displacement was found to occur in the allo series, whereas reduction accompanied by ring contraction has thus far been encountered only in the conformationally less constrained, cis-fused acetal system of the galacto series. Like the borohydride reagent, lithium aluminum hydride was found to react (though much more slowly) with the altro 2,3-ditosylate by the epoxide-mediated mechanism, although the latter hydride is known to desulfonyloxylate the α -D-gluco isomer by a different, intramolecular reduction mechanism.

I INTRODUCTION

Lithium triethylborohydride (LTBH, Super Hydride) has first been described in 1973 as a highly efficient, nucleophilic reagent for the reduction of hindered alkyl and cycloalkyl halides (1).

It was later discovered that this powerful reducing agent was capable of reducing epoxides (2) and quaternary ammonium salts (3) rapidly and cleanly to the desired products. The hydride has also been reported (4) to react smoothly, not only with unhindered, primary tosylates but also with hindered ones as well as with secondary, cycloalkanol tosylates to form the corresponding alkanes in excellent yields. Competitive reactions such as O-desulfonylation or alkene formation by elimination are normally negligible in comparison to similar reactions with the more widely used reducing agent, lithium aluminum hydride (LAH). An early application of LTBH in carbohydrate chemistry (5) demonstrated that 1,2:3,5-di-O-methylidene-6-O-p-tolylsulfonyl- α -D-glucofuranose is readily reduced to give the desired 6-deoxy derivative in 88% yield (Scheme 1).



Scheme 1

In a synthesis recently performed in this laboratory (6), LTBH was used effectively for the reductive debromination of a bromodeoxy sugar. Thus, the unsaturated bromoglycoside, methyl-4-O-acetyl-6-bromo-2,3,6-trideoxy- α -D-erythro-hex-2-enopyranoside was converted in 93% yield into methyl 2,3,6-trideoxy- α -D-erythro-hex-2-enopyranoside (Scheme 2).



Scheme 2

In concurrent work(7) the possible use of this reagent for the reductive desulfonyloxylation of certain secondary p-toluenesulfonate esters of glycosides (which obviously are more hindered than cycloalkanol tosylates) was examined. Thus, the methyl 4,6-O-benzylidene- α - and β -D-glucopyranoside 2- and 3- tosylates (and 2,3-ditosylates) were converted with excellent yields (90%) into 2- and 3-deoxyglycosides (7). It was also noted that the action of LTBH differs in its mechanism, and consequently, with respect to the stereochemistry of the major products formed, from that of the less-efficient, if more familiar reagent, LAH. A structural requirement for facile desulfonyloxylation with LTBH appeared to be the presence of a free, or potentially free, hydroxyl group (by reduction of acetyl or S-O fission of tosyl groups) adjacent and trans to the sulfonate ester.

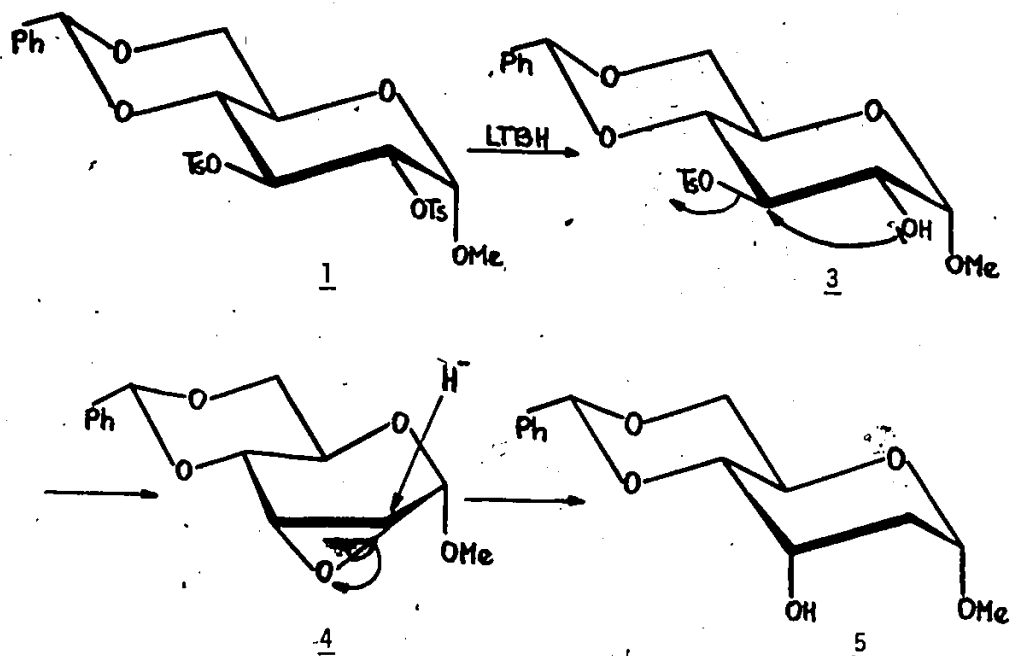
It was established that the reaction proceeds by internal displacement through intermediary epoxides, followed by subsequent reductive ring-opening in a trans-diaxial fashion, that is, according to the Fürst-Plattner rule (8), to give deoxyglycosides. This mechanism was confirmed by the isolation of such epoxides from interrupted reactions and by allowing them to react separately with LTBH, to yield the same final products. The stereochemistry of the reduction was found to be dependent on the number and location of the tosyl groups in the starting compound. Thus, treatment of methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl- α -D-glucopyranoside (1) with excess LTBH afforded in 96% yield the 2-deoxy sugar 5 (methyl 4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranoside) as shown in Scheme 3.

LTBH selectively cleaved the sulfur-oxygen bond of the tosyl group at C-2 in the 2,3-ditosylate; the resultant alkoxide intramolecularly displaced the remaining tosyloxy group to form the α -D-allo epoxide 4, which was then reductively cleaved to give the 2-deoxyglycoside 5. Similarly the 3-tosyl derivative 3 reacted through the same epoxide (4), to yield the same product (Scheme 4).

The 2-tosylate 7 reacted with LTBH to give, via the α -D-manno-epoxide 8, the desired 3-deoxyglycoside 9 (Scheme 5).

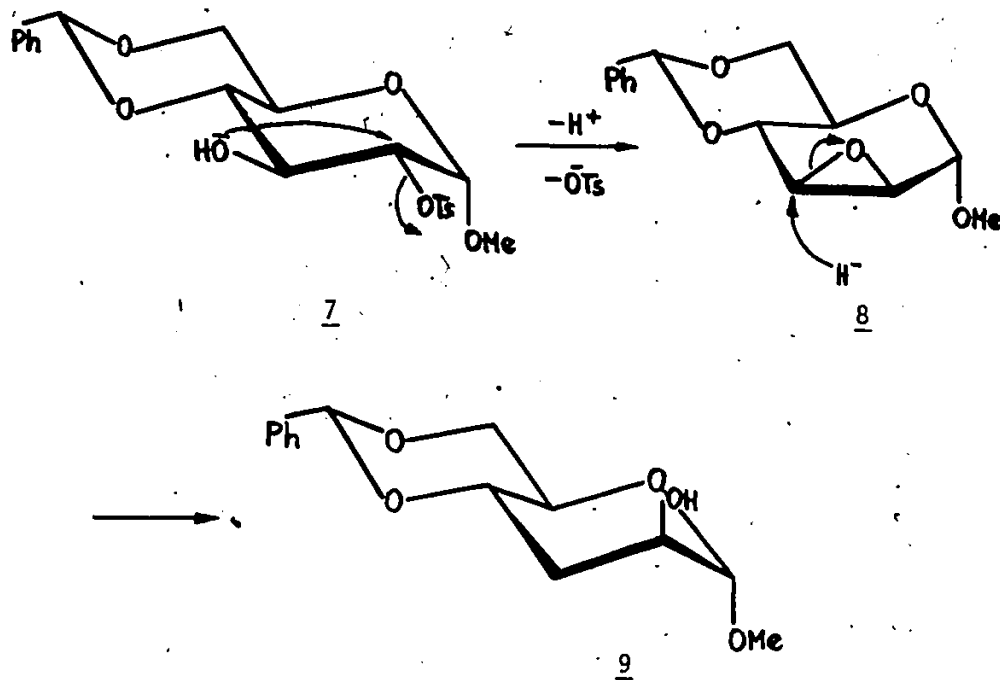
In sharp contrast to the aforescribed, facile reduction of the ditosylate 1 with LTBH, to give almost quantitatively the 2-deoxyglycoside 5, the reaction with LAH was claimed (9) to afford in 66% yield the 3-deoxyglycoside 6, together with a considerable proportion of the diol 2 (Scheme 3).

In this case, LAH also caused initial desulfonation at C-2 to give 3-tosylate 3, thus behaving like LTBH, or in fact like bases such as methoxide which are known to cause preferential hydrolytic cleavage of the sulfonic ester in the 2-position in 1 (10, 11).

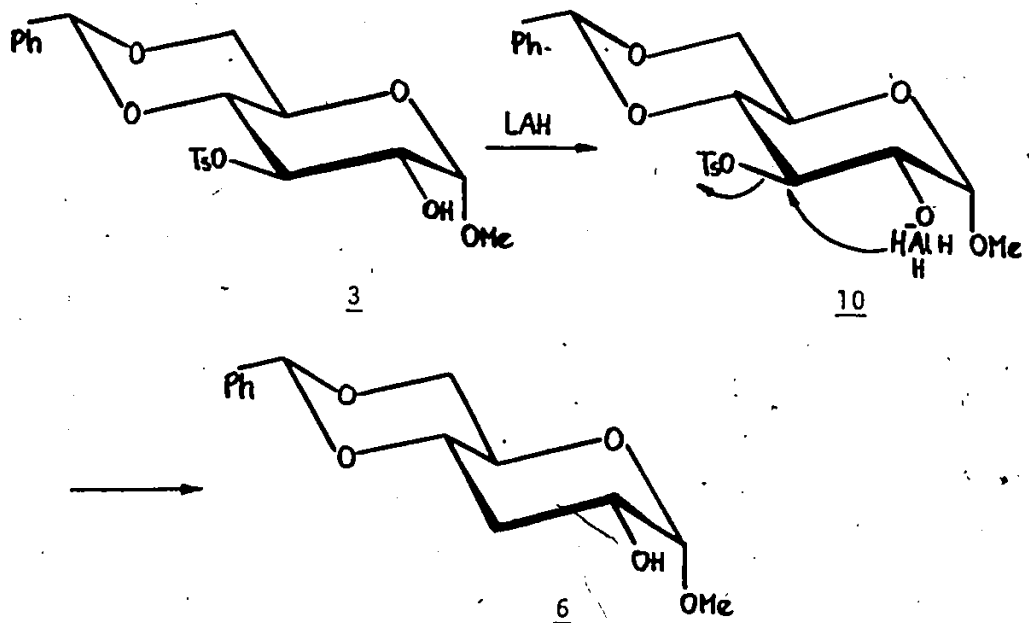


Scheme 4

However, from this point onward, the principal action of the two reductants differ. The formation of the main product 6 has been explained (12, 13) in terms of desulfonyloxylation at C-3 by an intramolecular transfer of hydride ion from an alkoxyaluminum hydride complex [R-O-AlH₃⁻] that incorporates O-2 (Scheme 6).



Scheme 5



Scheme 6

Such complexation evidently lessens the propensity of the oxygen atom to engage in an epoxide-forming displacement.

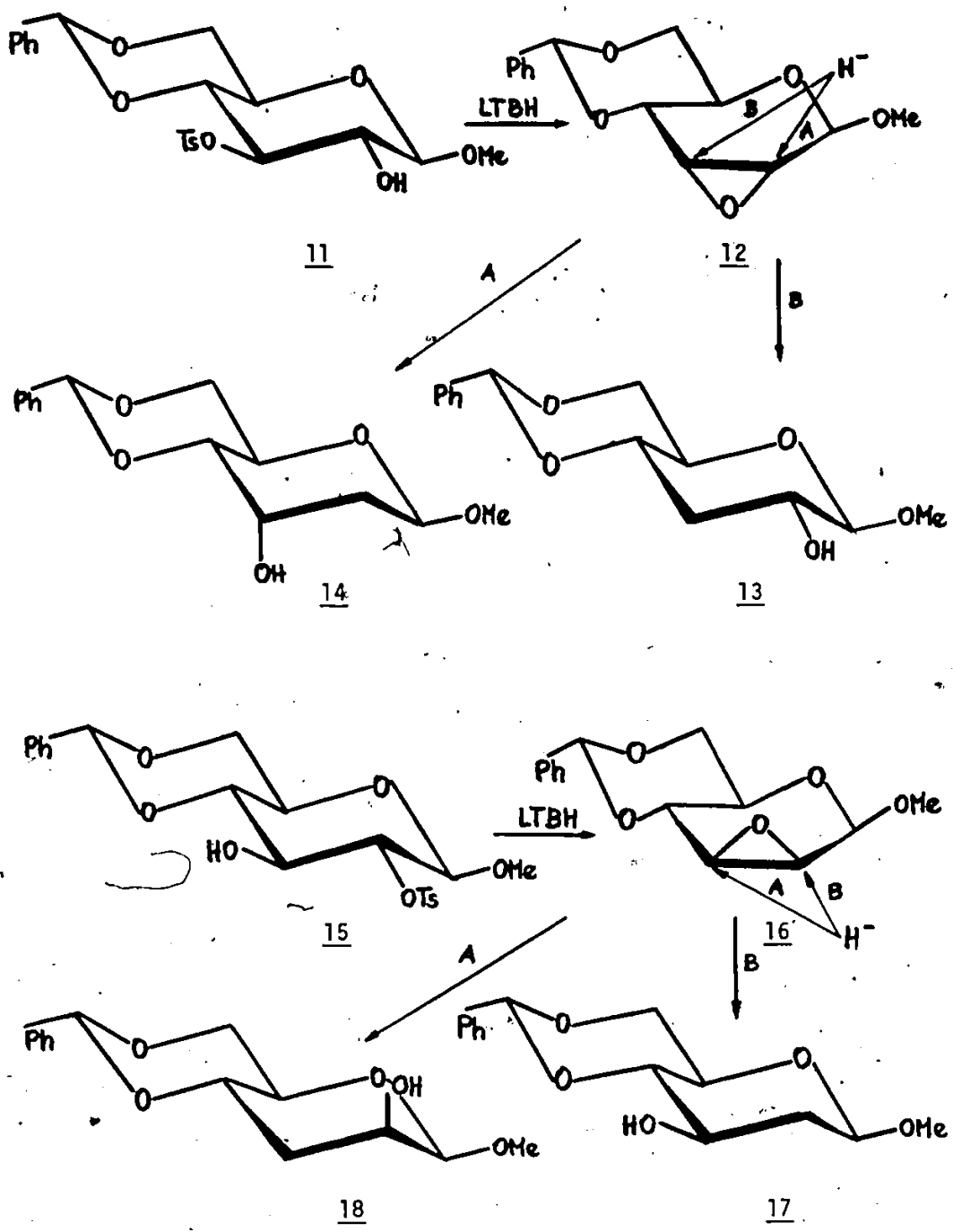
Contrary to the situation with LAH, an internal-transfer mechanism cannot operate for the monovalent hydride, LTBH, so that in its presence, 3 and 7 are freely transformed into the corresponding epoxides, wherefrom the deoxyglycosides 5 and 9 arise as single products.

The LTBH reduction was also performed in the corresponding β -anomer series (7). The 3-monotosylate 11 and the 2-monotosylate 15 were desulfonyloxyated under the same conditions that were used in the α -series. They were reduced readily, but furnished mixtures of regioisomeric deoxyglycosides, namely, the 3- and 2-deoxy- β -D-ribo derivatives 13 and 14, and the 2- and 3-deoxy- β -D-arabino derivatives 17 and 18, respectively, as shown in Scheme 7.

In contrast to their α -anomers, the intermediary β -glycosidic epoxides 12 and 16 evidently did not obey strictly the Fürst-Plattner rule of diaxial oxirane ring-opening in reduction with LTBH. However, this differential behavior was explicable on the basis of different steric and dipolar interactions in the α - and β - series during the approach of hydride (7).

One of the factors promoting high regioselectivity in the sense of the Fürst-Plattner rule doubtless was the conformational rigidity imparted to the intermediary epoxides by their trans-fused, cyclic acetal structure.

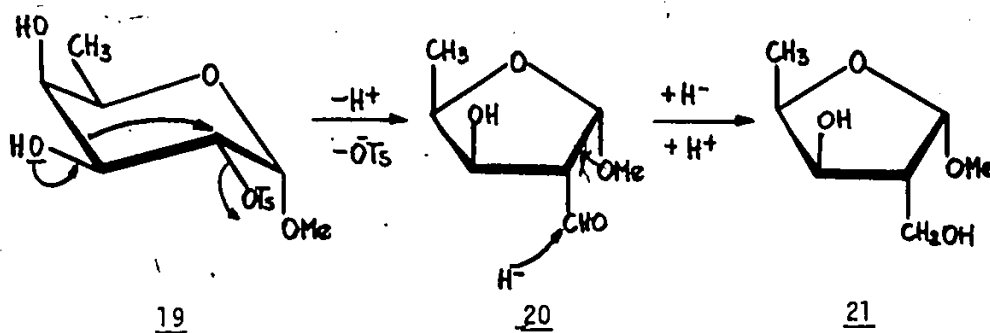
It became of interest, therefore, to examine the degree to which this structural constraint contributed to the stereochemical consequence of the reaction, and it was decided to study the action of LTBH upon a number of simple, nonacetalated hexopyranoside tosylates (16).



Scheme 7

It was rather surprising that various hexopyranoside tosylates which possessed a trans-vicinal hydroxyl group, but lacked the cyclic 4,6-acetal structure, were found to be desulfonylated by LTBH in an entirely different way: the predominant course of reaction led to ring contraction, to give deoxy-C-(hydroxymethyl)pentofuranosides.

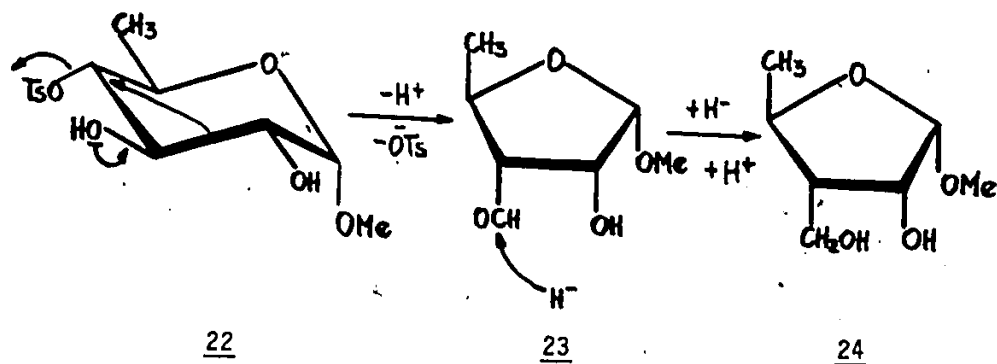
Thus, reaction of methyl 2-O-tosyl- α -D-fucopyranoside 19 with LTBH gave in 60% isolated yield the branched-chain glycoside, namely methyl 2,5-dideoxy-2-C-(hydroxymethyl)- α -D-xylo-pentofuranoside 21 (Scheme 8).



Scheme 8

Evidently, loss of the tosyloxy group was coupled with a skeletal rearrangement by migration of the C-3—C-4 bond. In corresponding hexopyranoside 4-tosylates ring contraction took place in the opposite direction, i.e., by migration of the C-2—C-3 bond, furnishing isomeric 3,5-dideoxy-3-C-(hydroxymethyl)- α -D-pentofuranosides. Thus, 22 produced the

α -D-ribo isomer 24, as shown in Scheme 9.



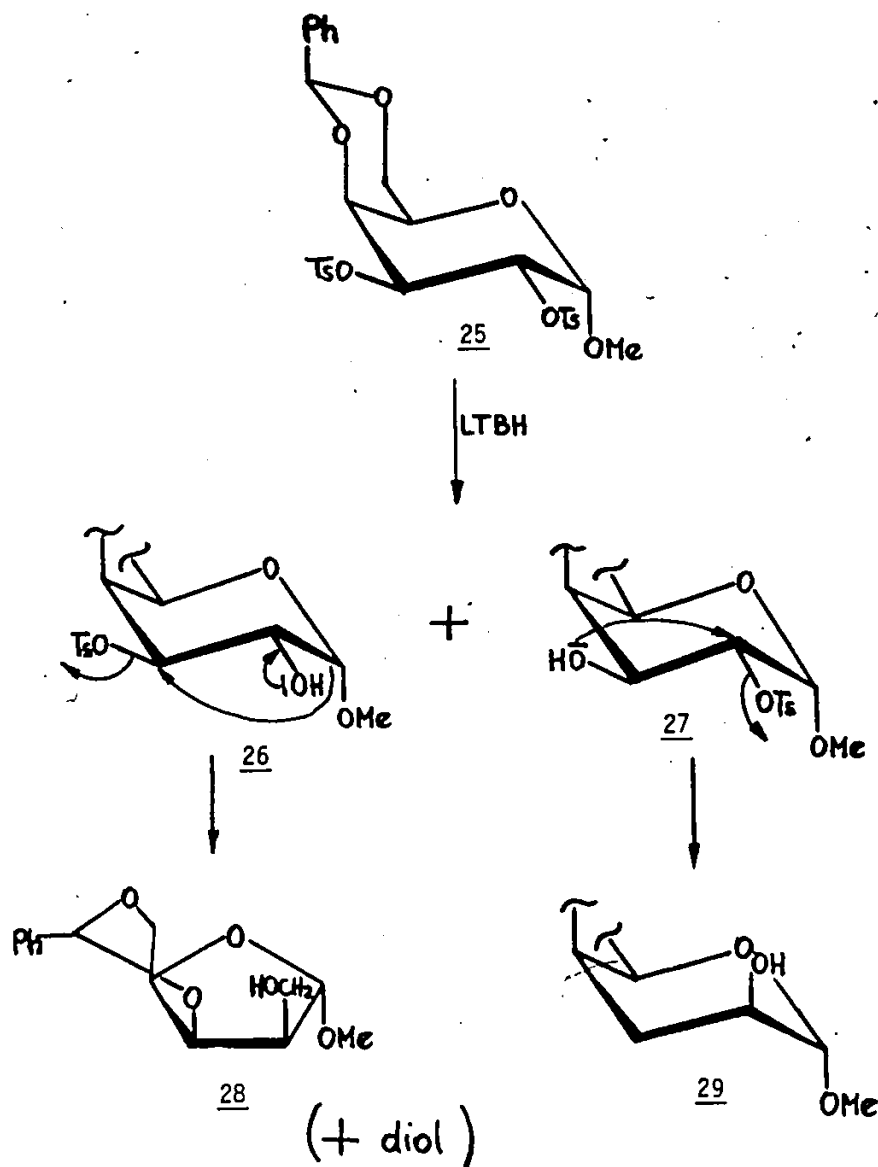
Scheme 9

Although all details of the mechanism are not clear, it was shown that epoxides were not implicated in the formation of the rearranged products, and epoxides found in some of the reaction mixtures evidently were precursors for minor products of unrearranged deoxyhexopyranosides that appeared in some instances (16, 17).

The conclusion must be drawn that, under the conditions of LTBH reduction, carbon bond migration in the nonacetalated hexopyranoside tosylates is favored over epoxide-forming internal displacement.

It appears reasonable to assume that in such a system there is no strain involved, hence ring contraction may take place. However in the case of the aforementioned glucopyranoside 4,6-acetals (Schemes 4 and 5) ring contraction did not occur probably because of the high strain that would result from the formation of six-membered ring trans-fused to a five-membered furanose ring. Consequently the alternative epoxide

formation in this system is preferred. This concept was supported when methyl 4,6-O-benzylidene- α -D-galactopyranoside 2,3-ditosylate (25), a less rigid, *cis*-fused bicyclic structure, gave with LTBH a mixture of ring contracted and an unrearranged products in the ratio of 1.7:1 (16) . (Scheme 10).



Scheme 10

The formation of such a mixture could be readily explained by initial, partial desulfonylation (with little discrimination between O-2 and O-3) to produce monosulfonates. The 3-tosylate 26 is then seen as the precursor for 28, which is formed by migration of the C-1—C-2 bond. The 2-tosylate 27, on the other hand, reacting in this instance not by ring contraction but through the talo-epoxide, is the source of the 3-deoxyhexopyranoside derivative 29.

In summary, then, we have seen LTBH-induced desulfonyloxylation to occur:

a) via intermediary epoxides in 4,6-O-benzylidenated hexopyranosides having the gluco configuration, giving 2- or 3-deoxyhexopyranosides (Schemes 3 and 4);

b) with ring contraction in nonacetalated hexopyranosides, giving deoxy-C-hydroxymethylpentofuranosides (Schemes 8 and 9); and

c) both with ring contraction and via epoxide in methyl 4,6-O-benzylidene- α -D-galactopyranoside 2,3-ditosylate (Scheme 10).

It may be noted that, in all the tosylates thus far studied, a free or potentially free (i.e., esterified) hydroxyl function trans-vicinal to the tosyl group to be reductively removed was present.

This was the state of the investigations at the outset of the present research. The aim of the work to be undertaken for this Thesis was to further elaborate the chemistry of sugar sulfonate reduction with LTBH in two directions, as stated in the following section.

II. Goals of Research for this Thesis.

There were two goals for this research, and accordingly, the thesis is divided in two sections.

The first section deals with applications of the LTBH desulfonyloxylation to derivatives of the disaccharide α,α -trehalose, and the second section deals with the study of desulfonyloxylation in 4,6-O-benzylidened hexopyranosides having the α -D-manno, α -D-allo, and α -D-altro configurations.

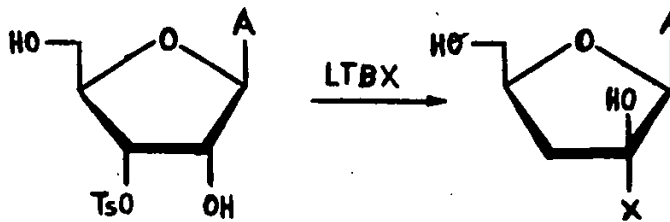
A. Applications in the α,α -trehalose series.

Deoxy derivatives of α,α -trehalose are of interest as substrate analogs for the study of the mechanism of action and specificity of the important and widespread enzyme, trehalase (14), and they may find further uses in biochemical research, as other synthetic trehalose derivatives have done, for example in studies examining structure-biological function relationships of mycobacterial cord factor (15). The synthesis of new deoxytrehaloses, or methodological improvements for the preparation of known ones, is therefore a worthwhile undertaking. It was to be examined whether the action of LTBH upon various tosylates of α,α -trehalose 4,6;4',6'-bis-benzylideneacetal can be usefully employed in this regard.

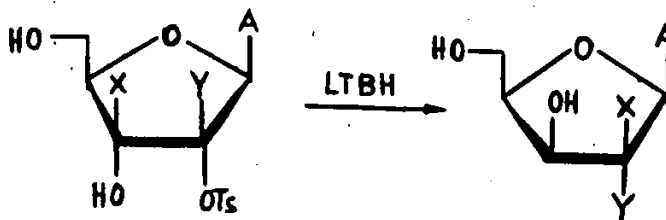
B. The action of LTBH upon tosylates in the α -D-manno, α -D-allo, and α -D-altro series.

As previously mentioned, the 4,6-O-benzylidene-glucopyranoside tosylates were reductively desulfonylated by way of intermediary epoxides (Schemes 3 and 4). The question arose how isomers which for configurational reasons cannot be transformed into epoxides would behave under the same reaction conditions. Would the manno and allo stereoisomers of 1, 3, and 7 perhaps suffer simple O-desulfonylation, to give the respective diols, or would they react by some other mechanism ? One competitive mechanism that might become operative would be S_N2 displacement of the tosyloxy group by hydride ion as reported for cycloalkanol tosylates (4).

It also appeared possible that the mannosides and allosides would be desulfonylated with involvement of an internal hydride shift such as was recently shown (18) to occur in LTBH-induced deoxygenations of ribonucleoside 2- and 3- monotosylates (Scheme 11). In these furanosidic N-glycoside sulfonates, an epoxide pathway for LTBH action is precluded because of the cis substituent arrangement, and contraction is unlikely because of the highly strained four-membered ring that would have to arise.



X = H
X = D



X = H, Y = D
X = D, Y = H

A = thymine-1-yl

Scheme 11



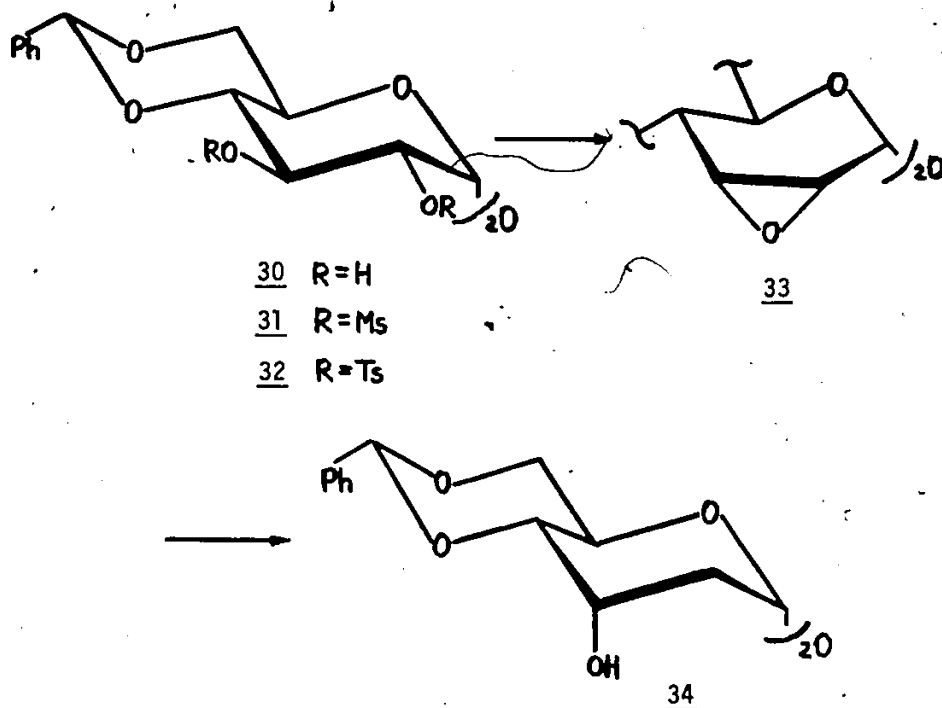
Results and Discussion.

A. Applications to α,α -trehalose.

The study of reductive desulfonyxylation by LTBH of various secondary p-toluenesulfonate esters of glycosides was extended to sulfonate esters of α,α -trehalose because of the aforementioned importance of deoxy derivatives of this disaccharide.

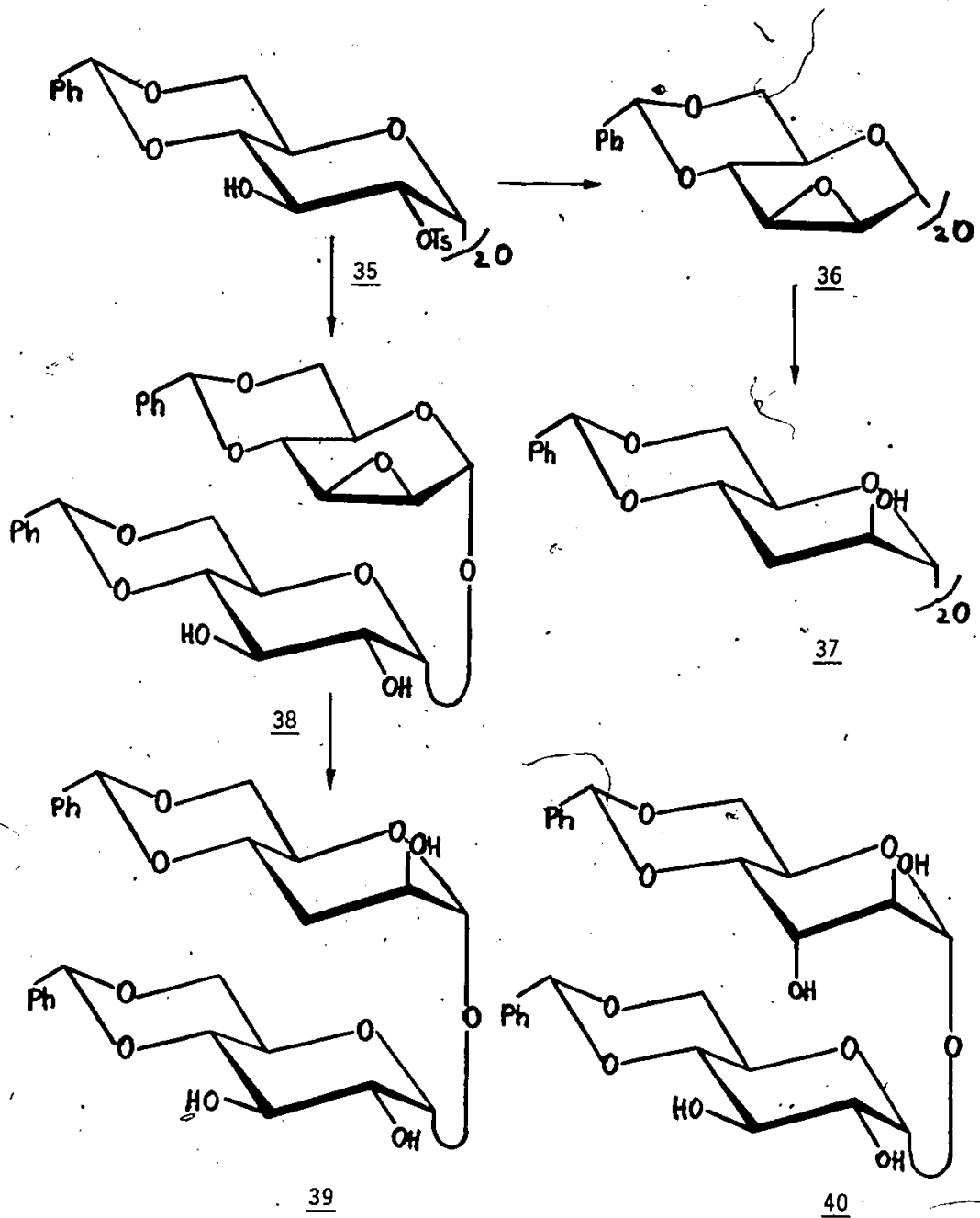
In 1971, Hough, Richardson, and co-workers reported the preparation of the symmetrical dideoxy derivative 4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranosyl 4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranoside (34), which was obtained in two steps from the tetraosylate 31 (19,20). The first step involved the conversion of the 2,3;2',3'-tetraosylate (31) of 4,6;4',6'-di-O-benzylidene- α,α -trehalose by the action of sodium ethoxide (18h) into the allo, allo-diepoxide 33 in 71% yield (19). Then the 2,2'-dideoxy functions were generated by LAH reduction for 24 hours, which gave crystalline 34 in 73% yield. The overall yield for the two consecutive steps was, therefore, 52% (Scheme 12). Employing the corresponding 2,3;2'3'-tetraosylate 32 as the starting ester, and LTBH as the reductant, compound 34 has now been obtained in a single operation. After a 3-h reaction with LTBH in boiling oxolane the yield was 65%. Although this was higher than the overall yield reported by Hough and Richardson, it should be noted that it was not as high (96%) as that for the analogous, monosaccharidic methyl glycoside 2,3-ditosylate 1 (7). More importantly, however, the example demonstrated that the method is suitable, at least in principle, for use with larger molecules. The formation of 34 was fully expected. By analogy to the

LTBH action upon 1, it is assumed that S-O fission occurred in the tosyl groups at C-2, and that the resultant alkoxides displaced the remaining tosyl groups to form the allo,allo-diepoxide 33 which was then reductively opened in trans-diaxial fashion in both moieties to give 34.



Scheme 12

A more complex course of reaction was observed in the desulfonyloxylation of the 2,2'-ditosylate 35. This is shown in Scheme 13.



Scheme 13

Thus, LTBH reduction of 35 gave a mixture of several products.

One of these was the expected, symmetrical 3,3'-dideoxy sugar, namely 4,6-O-benzylidene-3-deoxy- α -D-arabino-hexopyranosyl 4,6-O-benzylidene-3-deoxy- α -D-arabino-hexopyranoside (37), which was also the major product. The twofold desulfonyloxylation of 35 doubtless proceeded via an intermediary epoxide structure, just as the corresponding manno-epoxide 8 was (7) an intermediate in the monosaccharide reaction.

The manno,manno-diepoxide 36 is one possible intermediate which then reacted further; it is also possible that the oxirane ring formed in the first moiety is reductively opened before that in the second moiety arises. (The same consideration could be applied to the sequence 32→33→34). Hough and his co-workers prepared (19) 36 by base treatment of 35, and converted (21) it subsequently by LAH reduction into the 3,3'-dideoxy sugar 37 with an overall yield of 70%.

In our one-step procedure, 37 could be isolated in crystalline form in 45% yield only. However, in addition to 37, a small proportion of the O-desulfonylated, parent tetraol 30 likely was among the products generated from 35. That tetraol was seen in t.l.c as a slow-moving spot but not investigated further.

The formation of the corresponding diol as a by-product was also observed previously, when the analogous 2-tosylate 7 was reduced with LTBH (7). These results are not surprising because it is well known that S-O fission of the tosyloxy group in position 2 of glucopyranosides occurs more readily than in position 3 (9,10).

Furthermore, two previously unknown, crystalline products, namely 39 (11%) and 40 (7,6%) were isolated from the reaction of 35 with LTBH.

Their precursor probably was the known (19) monoepoxide 38, arising through internal displacement of tosylate in one hexoside moiety, and desulfonation in the other. The unsymmetrical structure of 4,6-O-benzylidene-3-deoxy- α -D-arabino-hexopyranosyl 4,6-O-benzylidene- α -D-glucopyranoside (39) was readily determined from the ^1H -n.m.r. spectrum. There were seen individual signals for corresponding, but non-equivalent, protons in the two moieties, for the benzylidene methine and anomeric protons. The C-3 methylene group gave the same multiplet, at δ 2.1, but with half the intensity, as that present in the spectrum of the 3,3'-dideoxy sugar 37. Upon acetylation of 39, the spectrum indicated incorporation of three O-acetyl groups. The structure of 39 was also proved chemically, by reduction with LAH of independently prepared epoxide 38, which afforded a 54% yield of 39 (with 23% of unchanged 38 being recovered).

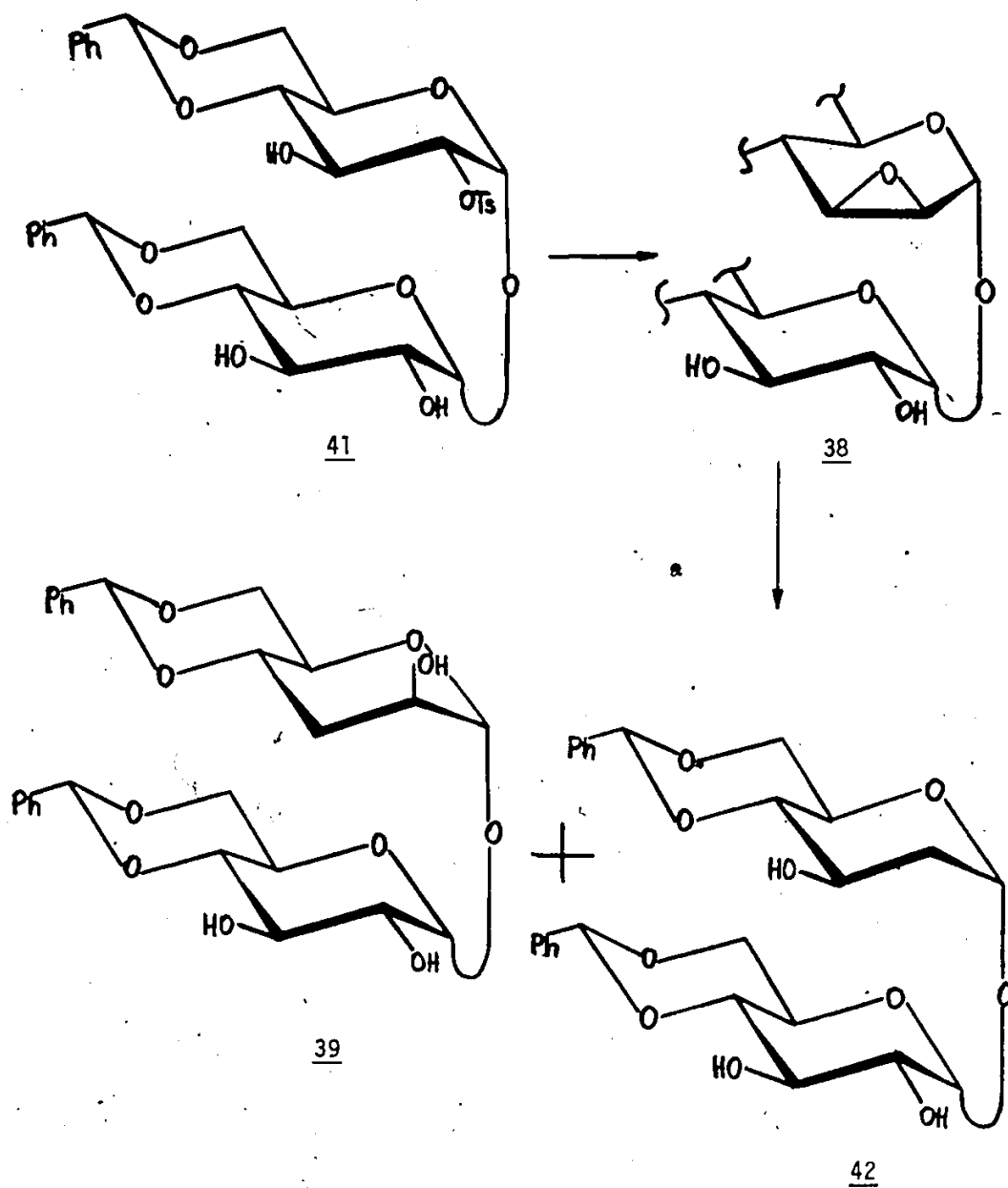
The structure of the altro,gluco tetraol 40 was deduced from elemental and spectral analysis. As for 39, separate sets of signals were observed in the ^1H -n.m.r. spectrum for the two pyranoside units. The altro moiety was characterized by two narrow multiplets for H-2 and H-3, and doublet of doublets for H-4 (J 2.4 and 11.5 Hz) and H-6e (J 5.4 and 9.7 Hz), all in the range of δ 4.1-4.5 where the corresponding signals in methyl 4,6-O-benzylidene- α -D-altro-pyranoside occur (22). The H-1 and H-5 signals, a singlet and a triplet of doublets, were deshielded by 0.35 ppm relative to those in the monosaccharide model. The gluco moiety of 40 was characterized by a doublet for H-1 (J 3.9 Hz), a doublet of doublets for H-2 (J 3.9 and 8.9 Hz), and triplets (J 9 Hz) for H-3 and H-4.

To explain the formation of 40 it may be assumed that a part of the epoxide 38 had escaped reductive ring-opening during the LTBH action and has subsequently undergone hydrolysis in the aqueous, alkaline medium of the processing operations.

The monoepoxide 38 had first been synthesized (19) in 56% yield by base treatment of 4,6-O-benzylidene-2-O-tosyl- α -D-glucopyranosyl 4,6-O-benzylidene- α -D-glucopyranoside (41). When we treated 41 with 5 molar equivalents of LTBH in boiling oxolane for 70 min, it was according to t.l.c, completely consumed, and several products were formed (Scheme 14).

It was surprising that among those products was the epoxide 38, isolated crystalline in 9% yield. The survival of a significant proportion of this intermediate under the conditions of LTBH reduction was unexpected. It did not seem to be due to any intrinsic nonreactivity toward the reagent because epoxides in general are known to react with LTBH rapidly and quantitatively (16,23). Rather, the supply of reductant (5 molar equivalents), which was presumed to be a sufficient amount according to the stoichiometry of the interaction with 41, may have been marginal, perhaps due to an inadvertent presence of some moisture or the use of an aged reagent sample. The result re-emphasizes the previous observation (7) that carbohydrate desulfonyloxylation require an adequate excess of the reagent. In the case of 41, 3 equivalents of LTBH are instantly consumed by the hydroxyl groups, which are converted into alkoxytriethylboronate groupings, with release of molecular hydrogen. Triethylborane liberated in the subsequent epoxide forming-step complexes, and thereby deactivates (23) a fourth equivalent, and a fifth is needed

to reduce the epoxide.



Scheme 14

In processing the reaction mixture from 41, protracted exposure of the products to aqueous alkali was avoided, which likely prevented the transformation of surviving 38 into the tetraol 40.

The major reaction product obtained from 41 was the 3-deoxy sugar 39, which was isolated in crystalline form in 46% yield and gave correct microanalytical data but was not isomerically homogeneous. The t.l.c. showed 39 to be contaminated by a marginally faster moving component, and separation by repeated column chromatography remained unsatisfactory.

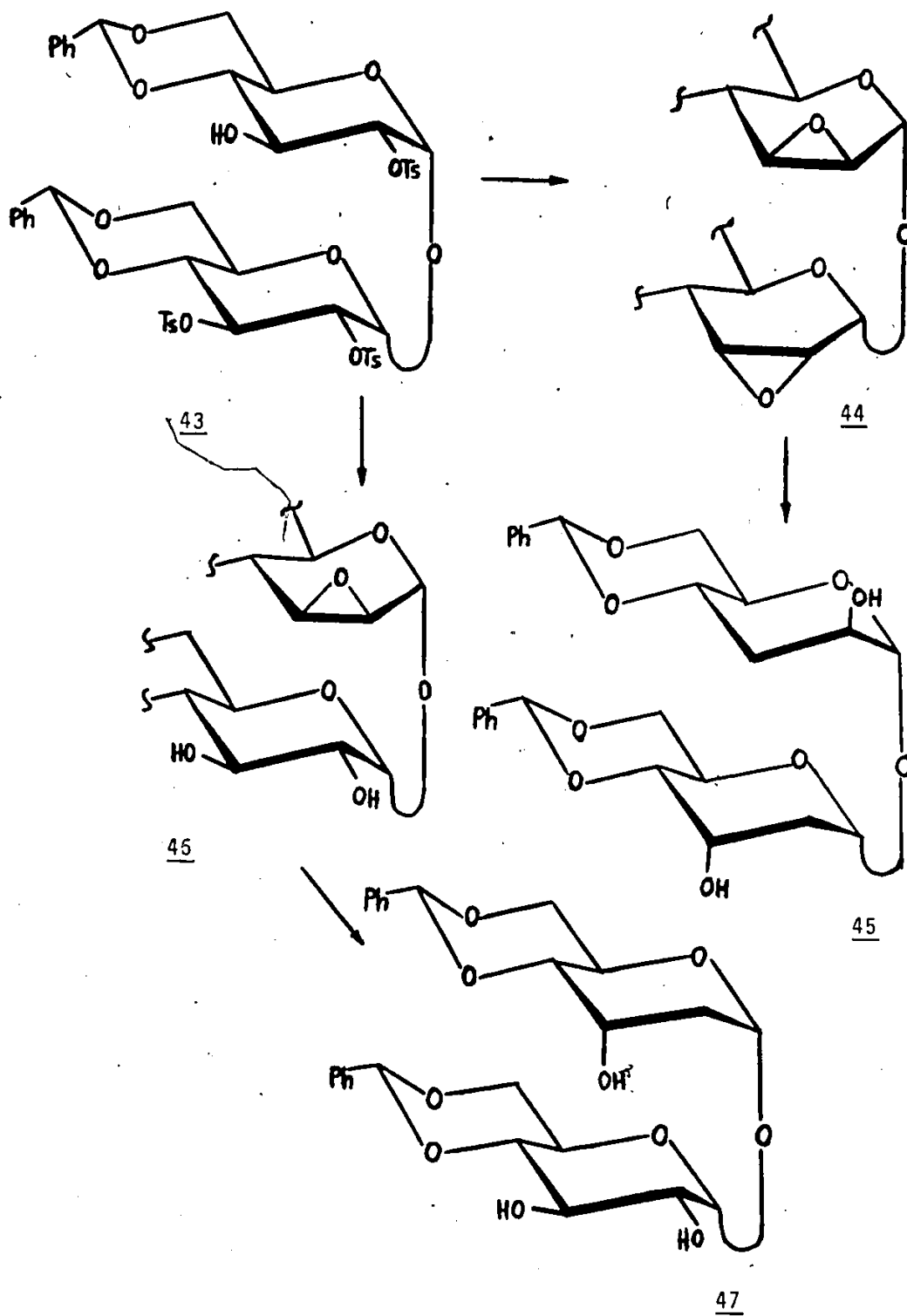
The major component, roughly three-quarters of the mixture, gave ¹H-n.m.r. signals completely matching those of pure 39. The minor component exhibited separate signals for an axial and equatorial deoxy-group proton. These were octets whose splittings closely agreed with those reported (7,22) for H-2e and H-2a in methyl 4,6-O-benzylidene-2-deoxy- α -D-arabino-hexopyranoside, and it is therefore assumed that the compound was the unsymmetrical arabino,gluco isomer 42, having arisen by anti-Fürst-Plattner opening of the epoxide 38.

This observation was noteworthy insofar as such diminished regioselectivity had in the monosaccharide series been encountered in β -glycosides only, whereas α -glycosides had obeyed the Fürst-Plattner rule strictly.

Reduction of the 2,3,2'-tritosylate 43 with LTBH gave a mixture of products which were seen in t.l.c. as 3 predominant spots, one comparatively weak but still significant spot, and four or five trace spots. By column chromatography, the most mobile of the three major components was isolated as a noncrystallizable oil whose spectral features placed it outside the category of products previously encountered in this study. Although it appeared to be a carbohydrate

derivative, it lacked benzylidene acetal groupings and showed strong proton resonances in the 2.0 region, possibly due to the presence of some organoboron moiety. The material was not investigated further. The other two, major components, each present to 30%, fitted nicely the pattern of reactivity found in the preceding experiments. One of them was shown to be the non-symmetrical dideoxy sugar (45), 4,6-O-benzylidene-3-deoxy- α -D-arabino-hexopyranosyl 4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranoside. The C-desulfonyloxylation of 43 plausibly proceeded by way of an intermediary, unsymmetrical epoxide structure-the known allo,manno-diepoxide 44, which after reductive opening afforded the hitherto unknown 45, as shown in Scheme 15.

The structure of 45 as a hybrid between 34 and 37 was established by its ^1H -n.m.r. spectrum. The other product isolated and identified was the new monodeoxy disaccharide, 4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranosyl 4,6-O-benzylidene- α -D-glucopyranoside (47). Its precursor was the monoepoxide 46, arising through internal displacement of 3-tosylate (following initial S-O fission of the 2-tosylate group) in the ditosylate moiety, and O-desulfonylation in the monotosylate moiety. The formation of 47 again reflects the differential stabilities of tosylate groups in position 2 and 3 of glucopyranose systems.



Scheme 15

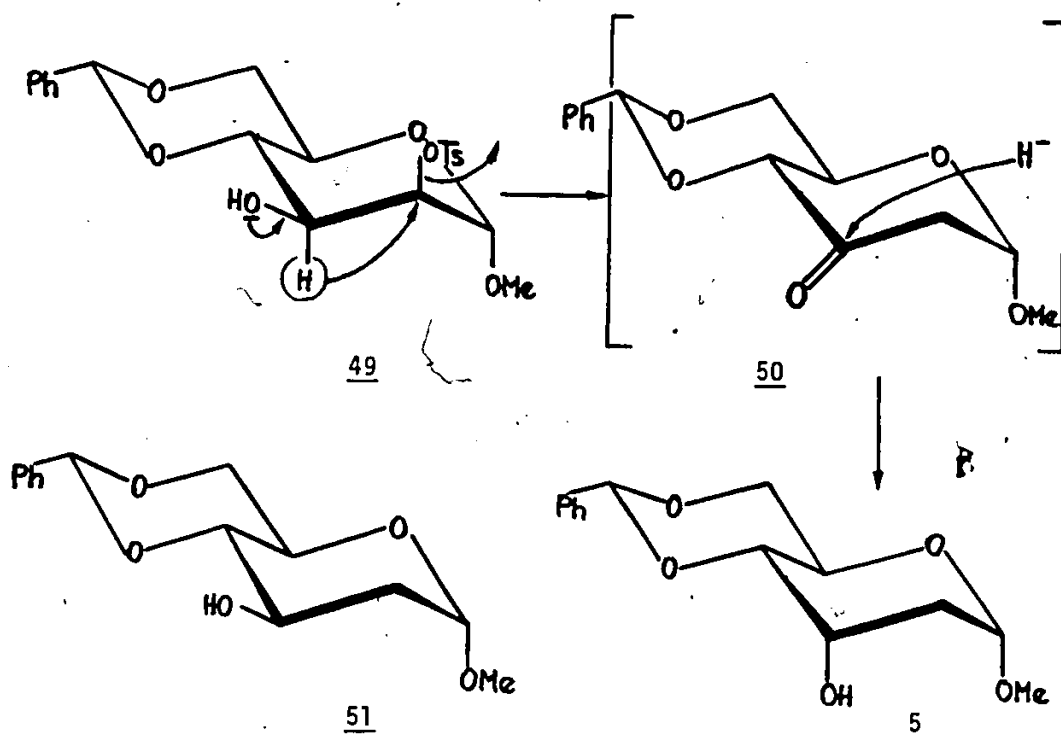
In summary, this investigation has demonstrated that deoxygenation of carbohydrate tosylates by means of LTBH can be applied to disaccharides. The known, symmetrical dideoxytrehalose analog 34 was prepared in a simplified way and with an improved yield. The known dideoxytrehalose analog 37 was obtained in a one-step procedure, in a lower yield than the published two-step procedure using LAH, but the hitherto unknown monodeoxy disaccharide 39 and the altro,gluco trehalose analog 40 were obtained and characterized in addition. Furthermore, the new monodeoxy analog 47 and the new unsymmetrical dideoxy derivative 45 were synthesized.

B. Reactions of methyl 4,6-O-benzylidenehexopyranoside tosylates with LTBH.

1. α -D-Mannosides

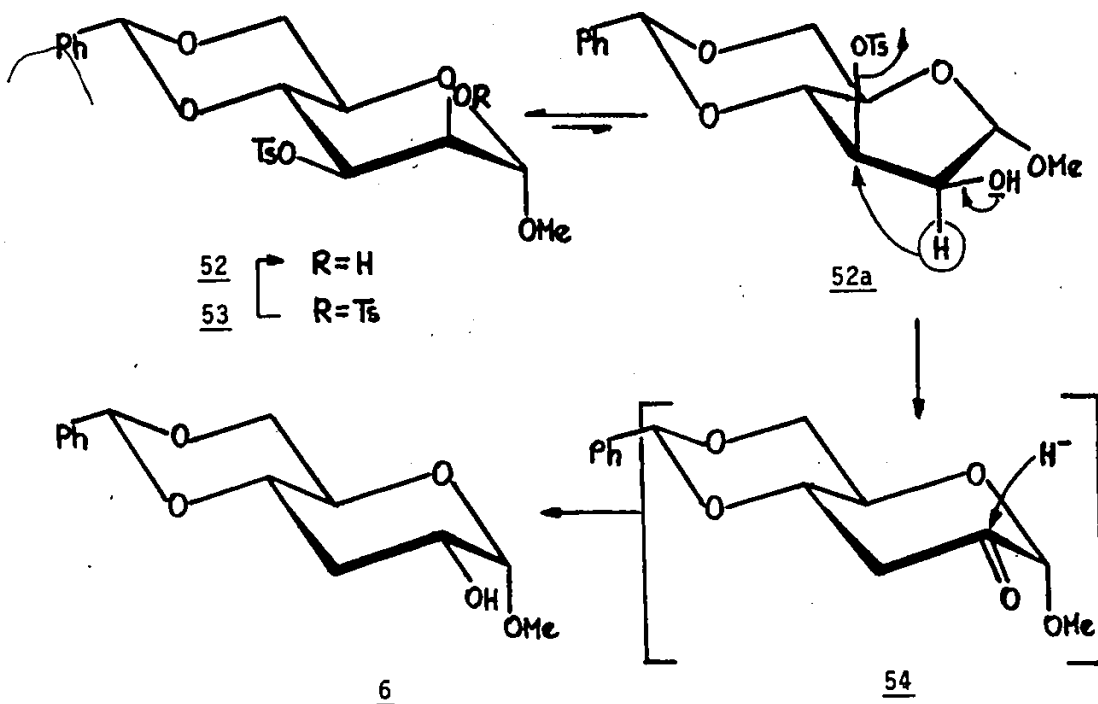
Methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl- α -D-mannopyranoside (49) reacted with excess LTBH in boiling oxolane to give, within 30 min, the known 2-deoxy- α -D-ribo-hexopyranoside 5, isolated in crystalline form in 66% yield.

If the C-desulfonyloxylation had occurred by external hydride attack, S_N2 fashion, the 2-deoxy- α -D-arabino-hexopyranoside 51 would have been formed, but not the inverted carbinol 5. S_N2 displacements at the 2- and 3- positions of α -D-mannopyranosides are known to be difficult, as has been explained (23) by consideration of dipolar and steric interactions that develop in the transition state, and it is therefore to be assumed that the tosyloxy displacement must have involved a hydride shift as shown in Scheme 16. The trans-diaxially disposed migrating hydrogen atom and leaving group in 49 are particularly conducive to such a process. Thus, hydride transfer from C-3 to C-2, accompanied by simultaneous expulsion of tosylate ion gave the 2-deoxy-3-keto intermediate 50, which after stereoselective reduction from the less-hindered side afforded 2-deoxyglycoside 5.



Scheme 16

The isomeric 3-tosylate 52 similarly gave, after 90 min, a 77% yield of the known, crystalline 3-deoxy-d-D-ribo-hexopyranoside 6. A 56% yield of the same product was obtained from the 2,3-ditosylate 53 after a reaction time of 2 hours. Evidently, the formation of the same product 6 from 52 and 53 was due the S-O fission of the 2-O-tosyl group of 53 in the first step, followed by C-desulfonyloxylation of 52 so generated. The inversion of carbinol configuration in the reaction 52→6 indicates that hydride shift must also have been involved, as shown in Scheme 17.

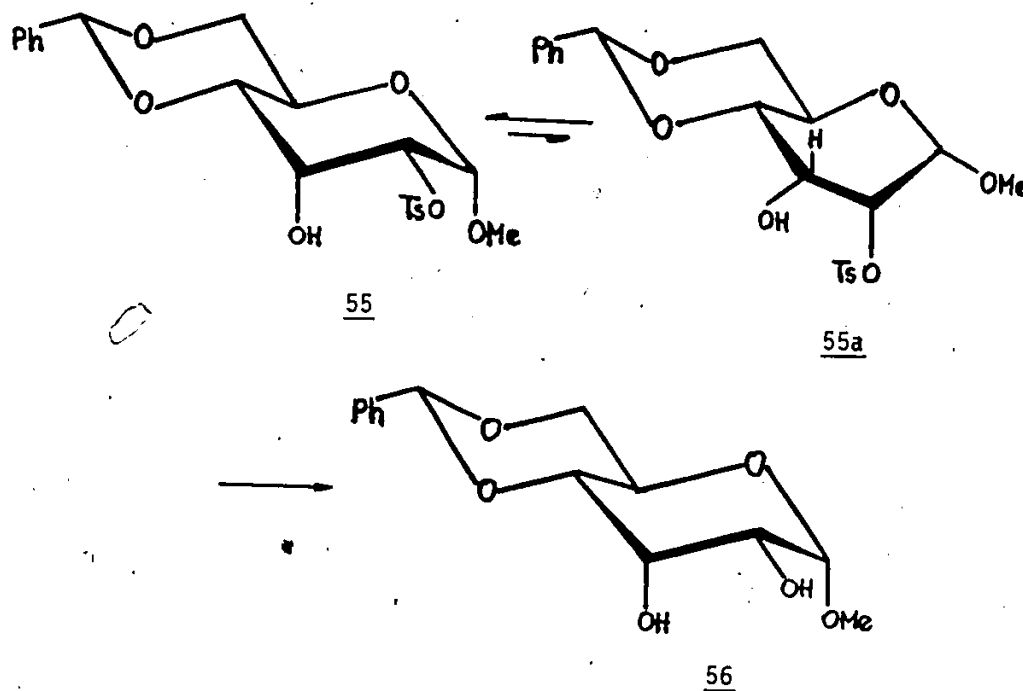


Scheme 17

In 52, the migrating hydrogen atom and the tosyl group are oriented trans-diequatorially to each other. The migration presumably requires the molecule to assume a transition state conformation close to the skew form 52a as shown in Scheme 17, where the groups are placed in the appropriate geometry.

2. α -D-Allosides.

In remarkable contrast to the α -D-mannopyranoside analogs, the α -D-allo 2-tosylate 55 under the same reaction conditions gave, within 75 min, the parent diol 56, which was isolated crystalline in 87% yield. No deoxyglycoside was detected. It is apparent that 55 underwent complete O-desulfonation as shown in Scheme 18.



Scheme 18

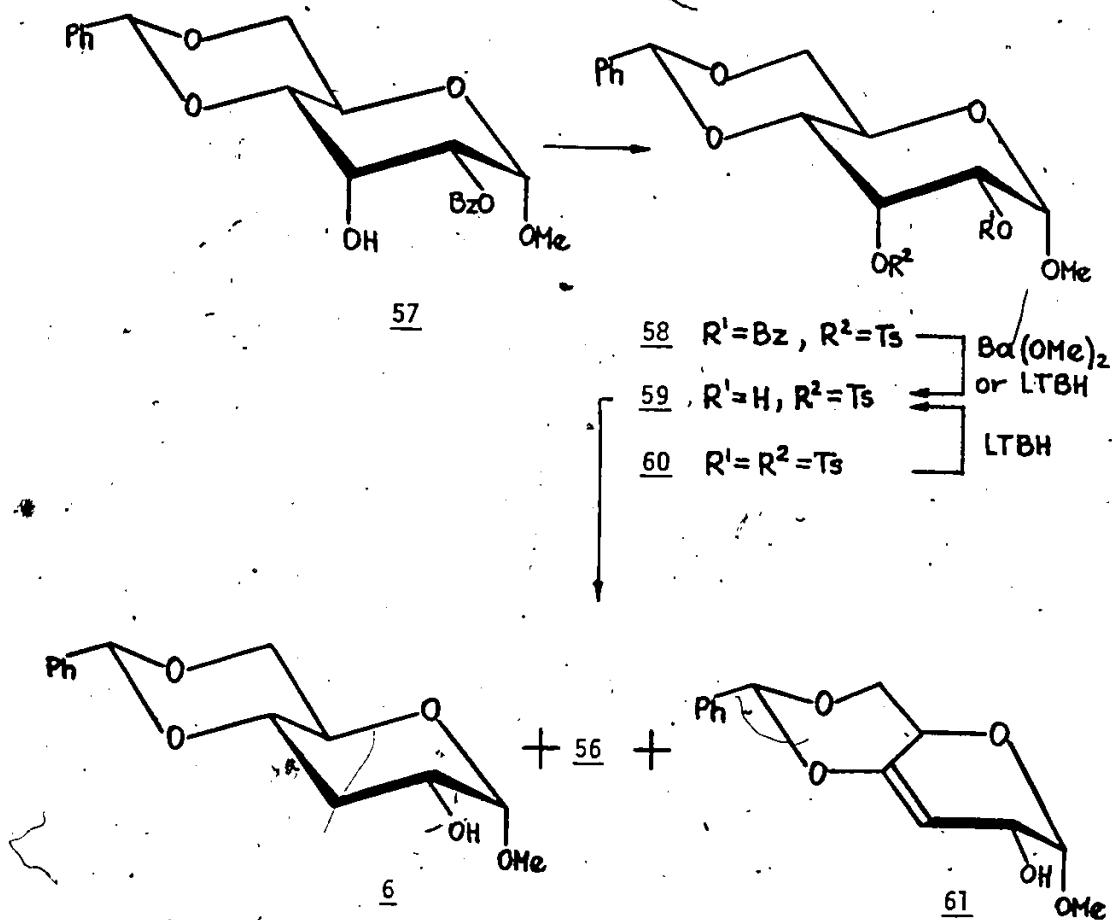
As has been previously mentioned, a facile S-O fission at position 2, promoted by the inductive effect of the adjacent anomeric center, was to be expected. However, in the glucoside and mannoside 2-tosylates,

other processes were able to compete effectively (epoxide formation and hydride shift, respectively), and it was therefore surprising that O-desulfonylation was the only result observed with 55. C-Desulfonyloxylation by hydride migration as in the mannoside isomer would presumably have to pass through the skew boat conformation 55a which is equivalent to the conformation 52a invoked for the hydride shift observed in the mannoside 52. As explanation for the failure of 55 to undergo hydride shift one may perhaps assume that 55a is too strongly disfavored (in comparison to 52a) due to the configurational disposition of the substituent at C-2, which is cis to the anomeric methoxyl and in 55a causes a " $\Delta 2$ condition". This condition is a destabilizing dipolar effect, akin to the anomeric effect; it occurs when the C \rightarrow O dipole is parallel to the resultant dipole of the anomeric O-C-OR system.

In the next phase of the studies the LTBH reduction of the isomeric 3-tosylate, methyl 4,6-O-benzylidene-3-O-p-tolylsulfonyl- α -D-allopyranoside (59), and of the 2,3-ditosylate 60 was to be examined. These derivatives had not yet been described in the literature.

In order to prepare them, methyl 2-O-benzoyl-4,6-O-benzylidene- α -D-allopyranoside (57) was tosylated to give methyl 2-O-benzoyl-3-O-p-tolylsulfonyl-4,6-O-benzylidene- α -D-allopyranoside (58). Methanolysis of 58 in the presence of barium methoxide afforded 59, which after tosylation gave 2,3-ditosylate 60 as shown in Scheme 19.

Reaction of the benzoate 58 for 20 min with an excess of LTBH in refluxing oxolane afforded the debenzoylated product 59 in 73% isolated yield. The t.l.c. showed the presence of only traces of other products.



Scheme 19

The formation of 59 was of course expected as LTBH rapidly converts carboxylic esters into alcohols. The surprising fact was that the reduction seemed to have little effect on the 3-tosylate 59 produced. However, prolonged action of LTBH on 59 under the same conditions gave increasing amounts of chromatographically visible products. After 90 min, a considerable amount of 59 could still be recovered, but the t.l.c.

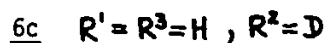
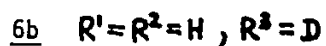
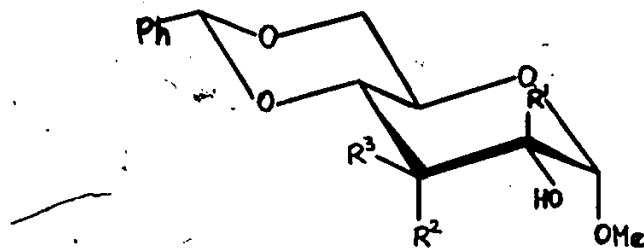
showed the presence of the slow-moving diol 56 and two faster-moving components. The same pattern was seen when the 2,3-ditosylate 60 was allowed to react with excess of LTBH in boiling oxolane for 24 hours. In contrast to the 2,3-ditosylate of α -D-mannoside 53, which was completely reduced within 2 h to 3-deoxyglycoside 6, the alloside 60 gave a mixture of several products. Among them was diol 56, isolated crystalline in 38% yield, the 3-deoxyglycoside 6 (20%) and the 3-enoside 61 (26%). The structure of 61 was proved on the basis of elemental analysis, mass spectrum, and ^1H -n.m.r. data. The 61 was characterized by a narrow multiplet at δ 5.28 for H-3 (J 4.8 Hz), doublet with broadened lines at δ 4.81 for H-1 (J 4.7 and 0.8 Hz), multiplet; quintet after D_2O exchange for H-2 (J 4.7 and 2.0 Hz), multiplet at δ 4.3 for H-5 and H-6e, doublet of doublets at δ 3.73 for H-6a (J 12.2 and 12.6 Hz), singlet at 3.5 for OMe, and broad, removed by D_2O , OH.

The formation of 3-enoside 61, as an elimination product from 59 (or 60) was not unexpected. Elimination in 4,6-O-benzylidene- α -D-hexopyranosides having an axial 3-sulfonate group, to give such 3-enosides, have been observed previously (24). A related precedent was the formation of the β -anomer of 61, which took place with 85% yield when the β -anomeric, 3-chloro-3deoxy analog of 11 was treated with sodium benzoate in boiling oxolane for 2 hours (25).

More surprising, however, were the slow rate of formation of the 3-deoxyglycoside 6 and its moderate yield, as well as the relatively high proportion of the diol 56, which appeared to be a major product. The formation of 3-deoxyglycoside 6 may have involved the hydride shift mechanism; the trans-diaxially disposed migrating hydrogen atom and

tosyloxy group in 59 should facilitate such a process. On the other hand, the slow rate of formation of 6 suggested that, unlike in the fast-reacting manno isomers, S_N2 displacement was perhaps at work.

In order to determine the mechanism operating in this case, 59 was reduced with lithium triethylborodeuteride (LTBD), under the same conditions. The isolated 3-deoxyglycoside was shown by 1H -n.m.r. to be a 7:3 mixture of the 2ax-deuterio compound 6a and the 3eq-deuterio compound 6b (Scheme 20).



Scheme 20

The 2ax-deuterio compound 6a evidently arose through a hydride shift process, and the 3eq-deuterio compound 6b must have been formed by an S_N2 displacement mechanism. There were no difficulties with the diagnosis of those two isomers, because they are readily distinguishable

from each other and from the 3ax-deuterio compound 6c for which ¹H-n.m.r. data have been recorded (13). It is worth noting that 6c had been obtained from methyl 4,6-O-benzylidene-3-O-tolylsulfonyl-α-D-glucopyranoside 3 as the major product of reduction with lithium aluminum deuteride (LAD) (13).

It is unclear at present why hydride migration in the allo 3-tosylate 59, although it does occur, is not a particularly favored process. The observed dependence of the facility of hydride shift on configuration (manno vs. allo) is remarkable.

3. α -D-Altrosides

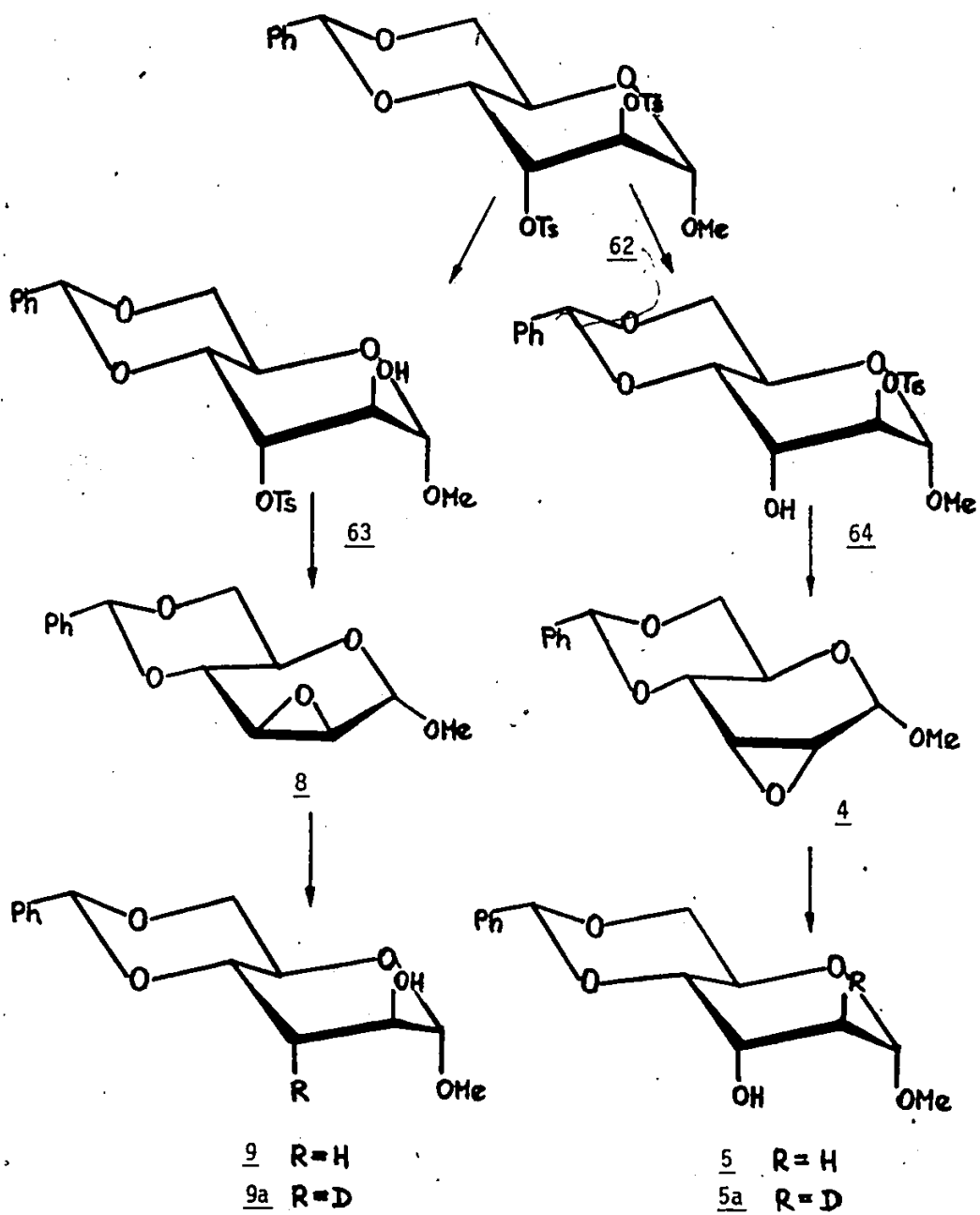
Finally, the LTBH reduction of methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl- α -D-altropyranoside (62) was examined.

The compound possesses a 2,3-trans substituent arrangement and was therefore expected to react, like its gluco isomer 1, by the epoxide mechanism. It was completely consumed within 1 hour of reaction with LTBH in boiling oxolane, to give a mixture of two products in rather comparable proportions. The slightly predominant product was methyl 4,6-O-benzylidene-3-deoxy- α -D-arabino-hexopyranoside (9), and the less abundant product proved to be the 2-deoxy- α -D-ribo isomer 5.

Unlike 60, 62 did not give its parent diol nor a product of 3,4-elimination, in detectable amounts. In this case it can be clearly seen that facile O-desulfonyloxylation takes place in 62 partly (and somewhat preferentially) on the 2-sulfonate, and partly on the 3-sulfonate group. It is assumed that the formed 3- and 2-monotosylates (63 and 64) are rapidly desulfonyloxyated via the corresponding epoxides 8 and 4 to give the deoxyglycosides, as shown in Scheme 21.

This mechanism was proved by performance of the reaction with lithium tiethylborodeuteride, which gave the expected, axially deuterated products 9a and 5a.

These results can be compared with the LTBH reduction of the α -D-gluco-pyranoside 2,3-ditosylate 1 (see Scheme 3) where desulfonyloxylation occurred also via the epoxide intermediate to afford the deoxyglycoside.



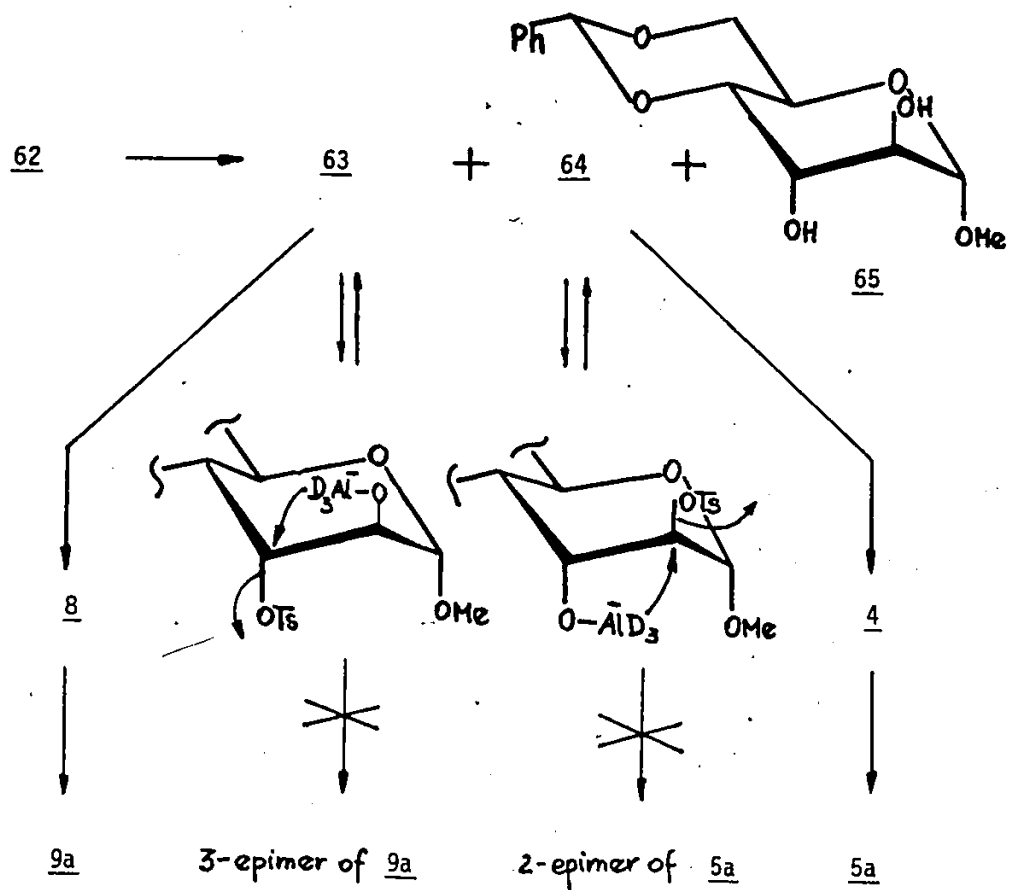
Scheme 21

However, in contrast to 1, in 62 LTBH did not exclusively cleave the S-O bond of the 2-tosyl group but showed little regioselectivity in this respect.

Jary and his coworkers (26) previously had reported the formation of 9 and 5, isolated in yields of 60 and 12%, respectively, by reaction of 62 with LAH in boiling oxolane. The reaction was incomplete after 18 hours, and produced a significant proportion (11%) of the parent diol 65. The authors concluded that S-O fission of the 2-O-tosyl group was the primary event which was followed by tosyloxy displacement to give the major product 9. However, they could not decide strictly whether this deoxy derivative was formed by intramolecular hydride transfer in the trihydridoaluminate complex of the carbinol as has been shown to occur (13,15) in the α -D-glucoside series, or alternatively through an intermediary epoxide, because both mechanisms would lead to the same products. Reduction of altroside according to the first-mentioned mechanism was considered "only probable", because epoxide could not be detected among the products of the (incomplete) reaction.

The reaction of 62 with LAH was now repeated as specified (26), and the formation of 9, 5 and 65 was confirmed. However, these were not the only products found in the reaction mixture. The monotosylate 63 and the epoxide 8 were also isolated in considerable amounts, and their identities established by $^1\text{H-n.m.r.}$ spectroscopy. (The presumptive precursors 64 and 4 for the minor product 5 were not detected).

Identification of 8 as an intermediate indicated that LAH acts—at least in part—by the same mechanism as LTBH in this instance (Scheme 21).



Scheme 22

Definitive proof was provided by performance of the reaction with lithium aluminum deuteride (LAD). It gave, besides some 63 and 8, the axially deuterated deoxyglycosides 9a and 5a, which were isolated and characterized by their ^1H -n.m.r. spectra (Scheme 22).

Evidently, the reaction does take place along the epoxide paths; the alternative mechanism tentatively advocated by Jary' and coworkers (26), involving internal hydride delivery from intermediary alkoxytrihydroaluminates as shown in Scheme 22, would have produced the equatorially deuterated epimers of 9a and 5a, and these were not encountered.

IV. Conclusion


The action of LTBH upon various, bis-benzylidenated α,α -trehalose tosylates constitutes a simple way for the synthesis of certain deoxygenated trehalose analogs. In addition to the previously-described, symmetrical 2,2'- and 3,3'-dideoxy disaccharides 34 and 37, the unsymmetrical unknown 2- and 3-monodeoxy analogs 47 and 39, as well as the unsymmetrical 2,3'-dideoxy sugar 45 have been obtained. The products were predicted on basis of a course of reaction analogous to that established for methyl 4,6-O-benzylidene- α -D-glucopyranoside tosylates. The present study supports the idea that a trans-fused 4,6-acetal ring, if present in the hexopyranoside, is an important factor in permitting LTBH to generate unrearranged deoxypyranosides.

The observation made in the studies of reactions of 2- and 3-tosylates of methyl 4,6-O-benzylidenehexopyranosides with LTBH can be summarized as follows. Reduction by LTBH to a deoxy compound, more precisely C-desulfonyloxylation, can take place via epoxide, by hydride shift, by direct displacement, or with ring contraction, depending on the configuration of the glycoside. Moreover, O-desulfonylation may be observed, and one instance of nonreductive elimination of p-toluenesulfonic acid has been encountered. Clearly, the reductive desulfonyloxylation is very sensitive to steric arrangements of the molecule. For example, as was seen in Schemes 4 and 7 the α - and β -anomers of the same hexoside gave different results with respect to the regioselectivity of intermediary epoxide cleavage (7). A change of configuration at C-4, implying a change from a trans-fused,

six-membered acetal ring to cis-fused one (compare Schemes 4 and 10), entails diminished regioselectivity in O-desulfonylation and implicates a change in reaction mechanism to the extent that partial ring contraction is observed (16). It is also evident that hydroxy-tosyloxy arrangement in the molecule is an important factor in governing the mode of C-desulfonyloxylation. As was seen in gluco (Schemes 4 and 7) and altro (Scheme 21) series, a trans-vicinal hydroxy-tosyloxy relationship leads to reduction exclusively by internal displacement via intermediary epoxides. By contrast, a cis-vicinal arrangement may lead to reductive desulfonyloxylation involving, exclusively, a hydride shift mechanism as in the manno series (Schemes 16 and 17), although such an arrangement may also give rise to a more complicated reaction pattern, involving additionally direct substitution and elimination as observed in the allo series (Schemes 18 and 19).

The behavior of various methyl 4,6-O-benzylidenehexopyranoside 2,3-ditosylates toward LTBH also invites comment upon the regioselectivity of S-O fission which precedes C-desulfonyloxylation. The manno 2,3-ditosylate 53 (Scheme 17) and its gluco isomer (7) were O-desulfonylated almost exclusively at position 2, whereas selectivity was lower in the other series. Thus, the allo ditosylate 60 gave a large proportion (38%) of diol 56. Similarly, the altro isomer 62 must have suffered partial S-O fission in both positions at fairly similar rates, accounting for the observed products 9 and 5 which arose in roughly comparable proportions. The tendency for a tosyl ester group to be more prone to S-O fission when situated in position 2, which is found in all the series, can be explained by an electron-withdrawing inductive effect

of the anomeric center. The decreased stability of the 3-O-tosyl group in the allo and altro isomers (60 and 62) as compared to that in the gluco and manno isomers (1 and 53) cannot be solely due to the axial disposition of this group since the galacto isomer 25 also exhibited diminished selectivity. Rather, there appears to be a correlation between the reactivity at O-3 and the total, non-bonded interactions in the molecules. The conformational free energies in -D-hexopyranosides increase in the order: gluco < manno < galacto < allo < altro, and are known to affect the rate of such reactions as, for example, acid hydrolysis (27). They may similarly account for the reactivity differences here discussed.



V EXPERIMENTAL

General methods.

Oxolane refers to a reagent-grade product that was dried, immediately before use, by refluxing it, under nitrogen, over potassium metal in the presence of benzophenone. Lithium triethylborohydride (LTBH) was purchased from Aldrich Chemical Co. as an M solution in oxolane. Melting points were determined in capillaries in an electrically heated, aluminum-block apparatus (Gallenkamp). Optical rotations were measured at $\sim 25^\circ$ with a Perkin-Elmer 241 polarimeter, and refer to chloroform solutions unless otherwise specified. $^1\text{H-n.m.r.}$ spectra were recorded at 200 or 300 MHz with a Varian XL-200 or XL-300 instrument. Column chromatography was performed on Silica Gel (E. Merck AG, Germany), and, for t.l.c., precoated glass plates of Silica Gel Si 250F UV (J.T. Baker Chemical Co.) were used. Spots were made visible by spraying the plates with 5% sulfuric acid in ethanol, and heating them briefly on a hot plate. The following solvent combinations (v/v) were normally used for chromatography: (A) ethyl acetate - hexane, 1:2; (B) the same, but 1:1; (C) the same, but 3:2; (D) the same, but 2:1; (E) the same, but 2:3; (F) the same, but 4:1; (G) the same, but 1:5; (H) ethyl acetate - chloroform, 1:9; (I) the same, but 1:19; and (J) the same, but 1:49.

A. Reactions of the α,α -trehalose p-toluenesulfonates with LTBH.

The starting tosylates 32, 35, 41, and 43 were prepared essentially as reported (19), although some procedural improvements (28) were employed.

1. Reaction of 4,6;4',6'-di-O-benzylidene- α,α -trehalose 2,3,2',3'-tetra-
-tosylate (32).

To a magnetically stirred suspension of 32 (2.0 g, 1.76 mmol) in oxolane (20 ml), contained in a reflux apparatus under nitrogen, was added LTBH solution (20 ml) by syringe, and the mixture was then boiled for 3 h, with further portions of LTBH solution (10 and 5 ml) being added after 2 and 2.5 h, respectively. After that period, 32 (R_F 0.70) was no longer visible in t.l.c. (solvent B), and product spots were seen at R_F 0.2-0.4 (strong, elongated), 0.55 and 0.65 (both weak). The mixture was allowed to cool, poured into ice water (200 ml), and stirred with it for 1 h. It was then evaporated on a rotary evaporator until most of the oxolane had been removed, and the remaining, largely aqueous solution was extracted with dichloromethane (3 x 50 ml), together with the organic material that had gradually precipitated during the evaporation. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated, with added portions of ethanol towards the end, to give a white solid (0.84 g). Recrystallization from hot ethanol, with addition of hexane after cooling, gave a first crop (460 mg) of the 2,2'-dideoxy compound 34 (R_F 0.27). A second crop (96 mg) was obtained from the mother liquor after chromatographic purification on a short column of silica gel (10 g) with solvent A as the eluent, followed by similar

recrystallization, for a total yield of 556 mg (65%); m/z (CI mode) 487, 486, 485 (mol. wt. calcd. 486.5); m.p. 177-179° and $[\alpha]_D +126.3^\circ$ (c.0.6). lit.(20) m.p. 179-180° and $[\alpha]_D +127^\circ$. The 1H -n.m.r. data (300 MHz) were in essential agreement with the 100-MHz data reported (20). ^{13}C -n.m.r. data ($CDCl_3$): ppm (from TMS) 137.4, 129.0, 128.2, and 126.3 (arom.), 102.0 (Ph-c), 93.9 (C-1,1'), 79.8, 64.6, and 59.2 (C-3,3',4,4', 5,5'), 69.2 (C-6,6'), and 35.6 (C-2,2').

2. Reaction of 4,6;4',6'-di-O-benzylidene- α,α -trehalose 2,2'-ditosylate (35).

a) Formation and isolation of products.

The ditosylate 35 (ethanol solvate; 2.36 g, 2.7 mmol) in oxolane (20 ml) was allowed to react with LTBH solution (25 ml) at the reflux temperature for 2 h, after which a further 10 ml of reductant was added and refluxing continued for 1 h. The t.l.c. (solvent D) indicated the complete consumption of 35 (R_F 0.8) and the formation of several, slow-moving products. Processing of the cooled reaction mixture by stirring it with ice water (150 ml) for 2 h, followed by evaporation of the solution, and extraction of the residue with dichloromethane gave, from the washed (water) and dried ($MgSO_4$) extract, a white, solid mixture of products (1.332 g). It showed in t.l.c. (solvent D) three main spots corresponding to 37 (R_F 0.6), 40 (R_F 0.4), and 39 (R_F 0.3), and a weak spot migrated like 30 (R_F 0.2). The mixture was applied to a column of silica gel (40 g) and chromatographed by means of solvent B, 5-ml fractions being collected. The fractions contained the following: fr. 10-24, fast-moving, unidentified material (42 mg) that was discarded;

fr. 25-37, compound 37 (555 mg); fr. 38-53, compound 37 and 40 (176 mg); fr. 54-61, compound 40 (19 mg); fr. 62-65, compound 40 and 39 (13 mg); fr. 66-78, compound 39 (150 mg); fr. 79-83, compound 39 and 30 (?) (18 mg); fr. 84-95, compound 30 (?) mainly (75 mg); fr. 96-105, unidentified material (50 mg), discarded. The material from fractions 35-53 gave, on fractional crystallization from 2-propanol, 100 mg of pure, sparingly soluble 40 and, from the mother liquor, 70 mg of 37. No attempts were made to separate the products in the other mixture-fractions. Hence, the following totals were isolated pure: 37, 625 mg (45%); 39, 150 mg (11%); and 40, 119 mg as monosolvate with 2-propanol (7.6%).

b) 4,6-O-Benzylidene-3-deoxy- α -D-arabino-hexopyranosyl 4,6-O-benzylidene-3-deoxy- α -D-arabino-hexopyranoside (37).

Compound 37 was recrystallized from 2-propanol-petroleum ether, which removed a very small proportion of a faster-moving impurity, and was obtained as what according to combustion analysis appeared to be a hydrate; m.p. 200-202°; $[\alpha]_D + 95^\circ$ (c 0.7); lit. (21) m.p. 209-210° (anhydrous compound), $[\alpha]_D + 95^\circ$. The $^1\text{H-n.m.r.}$ spectrum was identical with that of a sample (m.p. 203-205°, $[\alpha]_D + 93.6^\circ$) prepared by LAH reduction of the diepoxide ~~as~~ described (21), and agreed with the reported (21) data.

Anal. Calc. for $\text{C}_{26}\text{H}_{30}\text{O}_9 \times 1.5 \text{H}_2\text{O}$: C, 60.82; H, 6.48; for $\text{C}_{26}\text{H}_{30}\text{O}_9 \times 2 \text{H}_2\text{O}$: C, 59.76; H, 6.56. Found: C, 60.21; H, 6.06.

A sample of 37 was acetylated with acetic anhydride and pyridine, to give the diacetate, m.p. 162-164°, $[\alpha]_D + 88.6^\circ$ (c 0.35); lit. (21) m.p. 167-168°, $[\alpha]_D + 90^\circ$.

c) 4,6-O-Benzylidene-3-deoxy- α -D-arabino-hexopyranosyl 4,6-O-benzylidene-D-glucopyranoside (39).

Crystallized from 2-propanol-petroleum ether, 39 had $[\alpha]_D +80.7^\circ$ (c 0.7). It did not show a distinct melting point but foamed at $\sim 90^\circ$, possibly because of loss of solvent of crystallization, and melted with decomposition at $115-130^\circ$. $^1\text{H-n.m.r.}$ data (200 MHz): δ 7.4 (m, 10 H, 2 Ph), 5.58 (s, PhCH), 5.51 (s, PhCH'), 5.21 (d, $J_{1,2}$, 3.9 Hz, H-1'), 4.97 (t, $J_{1,2} = J_{1,3} = 0.4$ Hz, H-1), 4.30-4.25 (m, 2 H, H-2, H-4), 3.95 (t, $J_{2',3'} = J_{3',4'} = 9.3$ Hz, H-3', partially overlapped by unresolved, 3-H m adjoining downfield), 3.8 (m, 3 H, unresolved), 3.70 (dd, J 3.8 and 9.3 Hz, H-2'), 3.50 (t, J 9.3 Hz, H-4'), and 2.17 (m, 2 H, H-3a,3e). Exchangeable, broad OH signals were at δ 3.0, 2.5, and 1.65. After D_2O exchange, the H-1 signal was recorded as a 1.0-Hz doublet. A small proportion of 2-propanol present in the sample was revealed by a 6.1-Hz doublet at δ 1.20.

For microanalysis, a sample was dried at 56° in a high vacuum. Anal. Calc. for $\text{C}_{26}\text{H}_{30}\text{O}_{10}$ (502.5): C, 62.14; H, 6.02. Found: C, 62.01; H, 6.24.

A sample of monoepoxide (19) 38 (200 mg) was reduced with LAH (150 mg) in refluxing oxolane (10 ml) during 1 h. Customary processing followed by chromatography gave 111 mg (54%) of 39, $[\alpha]_D +80.7^\circ$ (c 0.5), identical with the compound obtained from 35 according to their i.r. spectra, R_F values, and melting behavior.

A sample of 39 was acetylated with acetic anhydride and pyridine. The crystalline product, m.p. ~~123~~ 125° , $[\alpha]_D +78^\circ$, was confirmed to be a triacetate by the occurrence of 3 singlets (3 H each), at δ 2.20, 2.18,

and 2.12 (superposed on the methylenic multiplet), in the ^1H -n.m.r. spectrum.

d) 4,6-O-Benzylidene- α -D-altropyranosyl 4,6-O-benzylidene- α -D-glucopyranoside (40).

The tetraol 40 crystallized from 2-propanol as a monosolvate, m.p. 247-251° (dec.), $[\alpha]_D^{20} + 67.6^\circ$ (c 0.8). The nonsolvated compound was obtained by repeated evaporation with carbon tetrachloride.

^1H -n.m.r. data (acetone- d_6): δ 7.4 (m, 10 H, arom.), 5.68 and 5.57 (2 s, Ph-CH), 5.46 (d, $J_{1,2}$ 3.9 Hz, H-1'), 5.01 (s, H-1), 4.83 (dt, $J_{5,6e}$ 5.4, $J_{4,5} = J_{5,6a} = 10.2$ Hz, H-5), 4.73 (d, J 4.4 Hz, OH-3'), 4.62 (d, J 4.3 Hz, OH-3), 4.42 (dd, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 9.9 Hz, H-6e), 4.28 (nm, H-2), 4.23 (nm, H-3), 4.12 (dd, $J_{3,4}$ 2 Hz, H-4), 4.04 (dt, $J_{2,3} = J_{3,4} = 9$ Hz, $J_{3,OH}$ 4.4 Hz, H-3'), 3.70 (m, 3 H, unresolved), 3.61 (dd, $J_{1,2}$ 3.9, $J_{2,3}$ 8.9 Hz, H-2'), 3.44 (t, J 9 Hz, H-4'), and 2.90 (s, 2 OH). The spectrum of the 2-propanolate additionally showed a 6-proton doublet (J 6.1 Hz) at δ 1.11, a sharp OH doublet (J 4.4 Hz) at δ 3.46 superposed on the H-4' signal, and a doublet of quintets at δ 3.90, collapsing to a quintet on D_2O exchange. The assignments were made with the aid of detailed spin-decoupling experiments.

Anal. Calc. for $\text{C}_{26}\text{H}_{30}\text{O}_{11}$ (518.5): C, 60.22; H, 5.83. Found: C, 60.17, H, 5.52.

2. Reaction of 4,6;4',6'-di-O-benzylidene- α , α -trehalose 2-tosylate (41).

The monotosylate 41 (2.00 g, 3 mmol) in oxolane (20 ml) and LTBH (15 ml) were boiled under reflux for 70 min, after which time t.l.c.

(solvent D) showed two product spots, R_f 0.50 (major) and 0.70 (minor), whereas 41 (R_f 0.63) was absent. The reaction mixture was poured into, and stirred with, ice water (200 ml) for 20 min, and the solution was then carefully neutralized to pH 7-8 by sodium hydrogen sulfate. Stirring was continued for 1 h, and, after evaporation to a volume of 100 ml, the solution was extracted with dichloromethane (3×100 ml), which was subsequently washed, dried, and evaporated to give a colorless, solid foam (1.38 g). Crystallization from ethanol afforded the monoepoxide 38 (130 mg, 8.7%), R_f 0.70, slightly contaminated by the slower-moving product(s). Compound 38 showed m.p. 148-150°, $[\alpha]_D +90.3^\circ$ (c 0.9); lit. (19) m.p. 152-155°, $[\alpha]_D +88.5^\circ$. The i.r. spectrum was identical with that of an authentic sample (28). The $^1\text{H-n.m.r.}$ data agreed essentially with those reported (19).

The ethanolic mother liquor of crystallization was evaporated, and the residue applied to a column of silica gel (40 g). Elution with solvent C, and collection of the fractions that contained chiefly the substrate(s) of R_f 0.5, yielded a material that crystallized on trituration with carbon tetrachloride. The product (695 mg, 46%) showed m.p. 97-98°, $[\alpha]_D +59^\circ$ (c 0.5). Although the microanalysis agreed with structure 39, the product was not homogeneous, as was revealed by t.l.c. with solvent B, showing a double spot in the region of R_f 0.2 (with the lower part being stronger). The i.r. spectrum was virtually identical with those of 39 obtained from 35 (with LTBH) or 38 (with LAH), and the 200-MHz $^1\text{H-n.m.r.}$ spectrum showed a major component whose signals matched those of 39 in every respect. The minor component visible in the spectrum gave an H-1 doublet (J 3.9 Hz) at δ 5.15, and two methylenic

octets suggested a 2-deoxy-d-D-arabino-hexopyranose structure, namely, at δ 2.22 ($J_{1,2e} \sim 1$, $J_{2e,3} \sim 5$, $J_{2a,2e} \sim 13$ Hz, H-2e) and 1.90 ($J_{1,2a} 3.9$, $J_{2a,3} 11$, $J_{2a,2e} 13$ Hz, H-2a). The Ph-CH signal (5.52) coincided with one of Ph-CH signals of the major component 39.

Anal. Calc. for $C_{26}H_{30}O_{10}$ (502.5): C, 62.14; H, 6.02. Found: C, 62.13; H, 6.09.

3. Reaction of 4,6;4'6'-di-O-benzylidene-d,d-trehalose
2,3,2'-tritosylate (43).

a) Formation and isolation of products.

The tritosylate 43 (1.54 g, 1.57 mmol) in oxolane (15 ml) was allowed to react with LTBH solution (15 ml) at the reflux temperature for 2 h and, after addition of another 15 ml of reductant, for a further 2 h. The consumption of 43 (R_F 0.83) was monitored by t.l.c. with solvent D. To the cooled mixture was added dropwise a small amount of methanol, until gas evolution ceased. The mixture was then boiled again, and processed by stirring with ice water (200 ml) for 1 h, followed by evaporation, and extraction of the residue with dichloromethane (3×50 ml). The washed and dried extract gave a yellow syrup upon evaporation, showing 3 strong spots for major reaction-products designated A, B, and C (R_F 0.70, 0.57, and 0.23), a weak spot (R_F 0.38), and several trace spots (R_F 0.91, 0.76, 0.65, and 0.27). The material was chromatographed on silica gel (50 g) with hexane-ethyl acetate mixtures of increasing polarity (19:1, 9:1, 4:1, and 1:1), sequentially employed. Partial separation was achieved. The fractions containing A and the faster-moving trace-products yielded an oily material that was

not investigated further, as its n.m.r. spectrum lacked the features characteristic for a benzylidenated sugar. (A similar reduction of 43, performed with a reaction-time of only 1.5 h, had given a similar product mixture, but containing very little, if any, of A.) The fractions containing chiefly B (0.24 g) and C (0.22 g) were purified further by flash chromatography on small columns, by use of hexane-ethyl acetate mixtures in the proportions 7:3 followed by 1:1 (for B), and 2:3 (for C). This afforded chromatographically homogeneous B (130 mg) and C (180 mg).

- b) 4,6-O-Benzylidene-3-deoxy- α -D-arabino-hexopyranosyl
4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranoside (45).

The foregoing product B proved to be 45; double m.p. 84-86° and 100-105° (dec.), possibly due to the presence of solvent of crystallization; $[\alpha]_D^{20} +119.0$ (c 0.7); m/z (FAB mode), 487 (M+1); $^1\text{H-n.m.r.}$ data: δ 7.4 (m, 10 H, Ph), 5.63 (s, Ph-CH'), 5.57 (s, Ph-CH), 5.25 (nm, width ~ 4 Hz, H-1'), 5.00 (s, H-1), 4.32 (dd, $J_{5',6e'} 5.1$, $J_{6a',6e'} 10.0$ Hz, H-6e'), 4.23 (m, 3 H, consisting of dd with $J_{5,6a} 10$ and $J_{6a,6e} 15$ Hz, for H-6a, superposed on H-3',5'), 4.0 [m, unresolved, 2 H, H-2,4 (or -5)], 3.9-3.7 [m, 3 H, consisting of t with $J_{5',6a'} = J_{6a',6e'} = 10$ Hz for H-6a', superposed on H-5 (or -4) and -6e], 3.64 (dd, $J_{3',4'} 2.7$, $J_{4',5'} 9.5$ Hz, H-4'), 2.20 [d of narrow (~ 4 Hz) multiplets, $J_{2a',2e'} 15$ Hz, H-2e'], and 2.1-2.0 (m, 3 H, H-2a',3a 3e). The assignments were made by comparison with the spectra of 34 and 37, and corroborated by the chemical-shift and coupling data (7) of the methyl glycosides corresponding to the two deoxyhexopyranosyl moieties.

The analytical sample was dried in a high vacuum at 56°.

Anal. Calc. for $C_{26}H_{30}O_9$ (486.5): C, 64.18; H, 6.22. Found: C, 64.03; H, 6.32.

c) 4,6-O-Benzylidene-2-deoxy- α -D-ribo-hexopyranosyl
4,6-O-benzylidene- α -D-glucopyranoside (47).

The foregoing product C proved to be 47. It was a monohydrate, and the water of crystallization was retained even after recrystallizing a sample from chloroform-petroleum ether and drying it in vacuo at 65° ; double m.p. $106-107^\circ$ and $126-127^\circ$; $[\alpha]_D^{+100.7^\circ}$ (c 0.9); m/z (FAB mode), 503 (M+1); 1H -n.m.r. data: δ 7.4 (10 H, Ph), 5.62 (s, Ph-CH), 5.46 (s, Ph-CH'), 5.19 (nm, 2 H, H-1,1'), 4.40-4.30 (m, 2 H, unresolved, H-3,5), 4.23 (dd, $J_{5,6e}$ 4.4, $J_{6a,6e}$ 9.9 Hz, H-6e), 4.16 (s, broad, OH), 4.00 (t with broadened lines, $J_{2',3'} \approx J_{3',4'} \approx 9$ Hz, H-3'), 3.79 (dt, $J_{5',6'}$ 5, $J_{4',5'} = J_{5',6a'} = 10$ Hz, H-5'), 3.75-3.55 (2 t and 2 d, partially overlapping; H-4, 6a, 2', 6a'), 3.48 (t, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4'), 3.13 (s, broad, OH), 2.14 (d of narrow m, $J_{2a,2e}$ 15, H-2e), and 1.98 (dt, H-2a). The H-2a,2e signal pattern was exactly the same as in the spectrum of 34 and in that of the corresponding (7). monosaccharidic methyl glycoside.

Anal. Calc. for $C_{26}H_{30}O_{10} \cdot H_2O$ (520.5): C, 59.99; H, 6.20. Found: C, 59.93; H, 6.21.

B. Reactions of methyl 4,6-O-benzylidenehexopyranosides
tosylates with LTBH.

1. Preparation of the starting glycoside p-toluenesulfonates

Authenticity and purity of the starting compounds were ascertained by n.m.r. spectroscopy; see the data in Table 1.

a) Known compounds 49, 52, 53, 55, and 62.

Methyl 4,6-O-benzylidene- α -D-mannopyranoside (29) was monotosylated by the phase-transfer method (30) to give the 2-tosylate 49 as a white, amorphous substance showing $[\alpha]_D +1.9^\circ$ (c 1.1) in agreement with ref. (30) ($+2^\circ$), but at variance with the value (-25°) recorded earlier (31).

Monotosylation of the above benzylidenemannoside in homogeneous phase at 0-20°C as directed (32) furnished the 3-tosylate 52, m.p. 149-150°, $[\alpha]_D +19.0^\circ$ (c 5.9); lit. (32) m.p. 151-153°, $[\alpha]_D +21^\circ$.

Complete tosylation (32) of the same acetal provided the 2,3-ditosylate 53, m.p. 166-168°, $[\alpha]_D -5.7^\circ$ (c 1.8); lit.(32) m.p. 163-164°, $[\alpha]_D -5.3^\circ$.

The α -D-allo 2-tosylate 55 was prepared from the parent methyl 4,6-O-benzylidene- α -D-allopyranoside 56 which, in turn, was obtained by reduction and deacylation, with sodium borohydride, of known (33) methyl 2-O-benzoyl-4,6-O-benzylidene- α -D-ribo-hexopyranosid-3-ulose according to the published procedure (34,35). Compound 56, obtained as anhydrous crystals from hot absolute ethanol, had m.p. 176-178°, $[\alpha]_D +126.3^\circ$ (c 1.0); lit.(35) m.p. 173-177°, $[\alpha]_D +117^\circ$ and (36) m.p. 167-168° (from benzene), $[\alpha]_D +128^\circ$; and (37) m.p. 175-177°,

$[\alpha]_D +117^\circ$ (in DMF). Compound 56 is also known as a dihydrate (34,36). A solution of anhydrous 56 (400 mg), *p*-toluenesulfonyl chloride (300 mg) and *p*-dimethylaminopyridine (12 mg) in dry pyridine (2 ml) was allowed to stand at 0° for 24 h and for 3 days at 25° , with further tosyl chloride (500 mg) being added after the second day. Almost complete consumption of 56 (R_F 0.1) and the presence of 55 (R_F 0.5) and 60 (R_F 0.7) was then revealed by t.l.c. (solvent E). The crude material (558 mg) obtained after conventional processing was dissolved in hot ethyl acetate-hexane 1:1, from which the 2-tosylate 55 (385 mg) crystallized on cooling and addition of some hexane; yield, 59%; m.p. $164-165^\circ$, $[\alpha]_D +59^\circ$ (c 0.8); lit. (37) m.p. $166-167^\circ$, $[\alpha]_D +35.6^\circ$ (in DMF), for 55 prepared in a different way. We also obtained 55, albeit in lower yield (39%), by applying the phase transfer procedure for tosylation (30).

The α -D-altro 2,3-ditosylate 62 was prepared (38) from its parent diol by conventional tosylation. Recrystallized from ethyl acetate, it showed m.p. $182-183^\circ$, $[\alpha]_D +44^\circ$ (c 0.8); lit. (38) m.p. 179° , $[\alpha]_D +46.9^\circ$.

b) Methyl 2-O-benzoyl-4,6-O-benzylidene-3-O-p-tolylsulfonyl-
 α -D-allopyranoside (58).

Methyl 2-O-benzoyl-4,6-O-benzylidene- α -D-ribo-hexopyranosid-3-ulose (33) was reduced with sodium borohydride at pH 6-7, to provide (35) methyl 2-O-benzoyl-4,6-O-benzylidene- α -D-allopyranoside (57), m.p. $105-107^\circ$, $[\alpha]_D +73.3^\circ$ (c 0.7); lit. (35) m.p. $110-115^\circ$, $[\alpha]_D +74^\circ$.

A solution of 57 (1.40 g) and *p*-toluenesulfonyl chloride (1.60 g) in chilled pyridine (7.5 ml) was stored at 0° for 24h and then at room

temperature for 5 days, after which a strong spot for 58 (R_F 0.78) and a weak spot of remnant 57 (R_F 0.67) were seen in t. l. c. (solvent H). Conventional processing of the mixture by treatment with ice water and extraction of the product with chloroform, followed by washing (water), drying, and evaporation of the extract, gave the crude reaction product (1.84 g). This was dissolved in hot ethanol, and the solution cooled, whereby a semicrystalline gel separated. Trituration of the gel with ethanol-benzene, and processing of the mother liquors, gave chromatographically pure 58 (1.45 g, 74%) in several crops which were washed with small amounts of cold ethanol followed by methanol; m.p. 165-166°, $[\alpha]_D +67.8^\circ$ (c 0.9). Anal. calc. for $C_{28}H_{28}O_9S$ (540.6): C, 62.21; H, 5.22; S, 5.93. Found: C, 62.07; H, 5.36; S, 5.74.

c) Methyl 4,6-O-benzylidene-3-O-p-tolylsulfonyl-
-D-allopyranoside (59).

A suspension of 58 (2.6 g) and barium oxide (0.35 g) in dry methanol (130 ml) was boiled under reflux for 30 min, which converted 58 (R_F 0.75) into 59 (R_F 0.45, t.l.c. with solvent B). The solvent was evaporated and the dry residue distributed between water and chloroform, with addition of brine to destabilize the emulsion that tended to form. The organic phase was dried (Na_2SO_4), and concentrated, and the product was recrystallized from methanol or ethanol, to give long needles (1.43 g, 68%), m.p. 198-199° (dec.), $[\alpha]_D +110.8^\circ$ (c 1). Anal. calc. for $C_{21}H_{24}O_8S$ (436.5): C, 57.79; H, 5.53; S, 7.53. Found: C, 57.71; H, 5.69; S, 7.53.

d) Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-
- α -D-allopyranoside (60).

The monotosylate 59 (0.95 g) in pyridine (11 ml) was treated with p-toluenesulfonyl chloride (0.45 g), first at 0°C overnight and then at room temperature for 2 days. Processing with ice water, extraction of the product with chloroform, and evaporation of the washed and dried extract gave crude, crystalline 60 (1.50 g), from which pure 60 (1.05 g, 82%) was obtained by recrystallization from chloroform-ethanol; m.p. 195-197°, $[\alpha]_D^{20}$ +48.7° (c 1.5). Anal. calc. for $C_{28}H_{30}O_{10}S_2$ (590.6): C, 56.93; H, 5.12; S, 10.86. Found: C, 56.87; H, 5.14; S, 11.02.

2. Reactions of the glycoside p-toluenesulfonates with LTBH.

a) General procedure

The glycoside tosylate (0.5-2.5 mmol) was dissolved in dry (7, 16) oxolane (1 ml per 100 mg of substrate), and M LTBH solution was added by syringe, with exclusion of moisture in a reflux apparatus containing an atmosphere of dry nitrogen. The mixture was gently boiled under reflux and progress of the reaction was monitored by t.l.c. on silica plates. Amounts of reactants and reaction times are stated in the individual sections. After completion of the reaction the mixture was allowed to cool, a few milliliters of methanol were carefully introduced to decompose the excess of hydride (until hydrogen evolution ceased), and refluxing was resumed for 10 min. The solution was cooled again, poured with stirring into ice water (50-150 ml), and neutralized

against indicator paper with a solution of sodium hydrogensulfate. (It was carefully avoided to render the solution acidic). The mixture was stirred at ambient temperature for several hours (or overnight) and then concentrated under reduced pressure to a small volume, to remove the organic solvent and a large part of the water. The residue was extracted with dichloromethane (3x50 ml) or occasionally with chloroform, and the extract washed with water, dried (Na_2SO_4), and evaporated to give the product which was then purified by crystallization or chromatography as indicated.

b) Reaction of 49

The 2-tosylate 49 (200mg, 0.46 mmol; R_f 0.7 with solvent B) was converted by LTBH (2 ml) into 4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranoside (5) (R_f 0.4) during a reaction period of 30 min. The white solid (120 mg) obtained upon work-up was recrystallized from ethyl acetate to give 5 (98 mg, 80.3%), m.p. 126-128°, raised to 128-130° by another recrystallization; $[\alpha]_D +140^\circ$ (c 0.5); lit.(7) m.p. 130-131°, $[\alpha]_D +140^\circ$. $^1\text{H-n.m.r.}$, δ : 7.5 (m, 5H, Ph), 5.61 (s, Ph-CH), 4.77 (nm, H-1), 4.31 (dd, $J_{5,6e} = 5.0$, $J_{6a,6e} = 10.1$ Hz, H-6e), 4.22 (sx, H-5), 4.17 (m, narrowed after D_2O exchange, H-3), 3.76 (t, $J_{5,6a} = J_{6a,6e} = 10.1$ Hz, H-6a), 3.59 (dd, $J_{3,4} = 2.8$, $J_{4,5} = 9.5$ Hz, H-4), 3.40 (s, 3H, OMe), 3.01 (d, $J = 6.7$ Hz, removed by D_2O , OH-3), 2.18 (ddd, $J_{1,2e} = 1$, $J_{2e,3} = 3.1$, $J_{2a,2e} = 15$ Hz, H-2e), and 1.98 (dt, $J_{1,2a} = J_{2a,3} = 3.7$, $J_{2a,2e} = 15$ Hz, H-2a).

c) Reaction of 52



The 3-tosylate 52 (1.13 g, 2.59 mmol; R_F 0.6 with solvent B) was allowed to react with LTBH (12 ml) for 45 min, and for a further 45 min after addition of another 3 ml of reductant. Crude methyl 4,6-O-benzylidene-3-deoxy- α -D-ribo-hexopyranoside (6) (R_F 0.45) was obtained as a white solid (0.70 g) which by recrystallization from ethyl acetate gave pure 6 (531 mg, 77%), m.p. 189-190°, $[\alpha]_D +121.6^\circ$ (c 0.7); lit. (7) m.p. 187°C, $[\alpha]_D +119.5^\circ$, and closely similar values (13, 26, 39). The 1H -n.m.r. spectrum confirmed the identity with 6 obtained previously (7); see also section (g).

d) Reaction of 53

The 2,3-ditosylate 53 (1.44 g, 2.44 mmol) was allowed to react with LTBH (20 ml) for 1 h, after which traces of 53 (R_F 0.57, solvent A) were still visible in t.l.c. Boiling was continued for 50 min with added LTBH (5 ml), and processing then gave 6 (341 mg, 52.5%, after recrystallization from ethyl acetate) whose 1H -n.m.r. spectrum was identical with that mentioned under (C); m.p. 172-173°, raised to 185-186° by further recrystallization; $[\alpha]_D + 119.2^\circ$ (c 0.75). The identity was confirmed, moreover, by ir spectra.

e) Reaction of 55

The 2-tosylate 55 (250 mg, 0.57 mmol; R_F 0.85 with solvent F) was completely consumed after 75 min by reaction with LTBH (3 ml).



The product was less polar (R_F 0.2 with solvent B) than the deoxyglycosides 5 and 6; it was obtained as a white solid (158 mg) following its extraction with chloroform, and was recrystallized from ethanol to give the diol 56 (140 mg, 87%), m.p. 175-177°, $[\alpha]_D +125.7^\circ$ (c 0.8), with an ir spectrum superposable on that of 56 described in a preceding section.

f) Reaction of 58

The 2-O-benzoyl 3-tosylate 58 (500 mg, 0.93 mmol) was treated with LTBH (6 ml) for 20 min, after which t.l.c. (solvent B) indicated complete absence of 58 (R_F 0.8) and showed a strong spot for the 3-tosylate 59 (R_F 0.45), accompanied by weak spots for other products (R_F 0.7 and 0.2). Processing furnished 296 mg (73.3%) of 59 (recrystallized from ethanol), m.p. 195-196° (dec.), $[\alpha]_D +106^\circ$ (c 0.5). Its ir and 1H -n.m.r. spectra were identical with those of the product obtained from 58 by methanolysis.

g) Reaction of 59

The 3-tosylate 59 (400 mg, 0.92 mmol) was allowed to react with LTBH (7 ml) during the course of 1.5 h. The t.l.c. pattern then was similar as under (f). Processing gave a first crop of crystals, m.p. 195-196° (dec.), that proved identical (ir) with starting 59 (109 mg, 27%). A second crop of crystals was a mixture of 59 and the deoxyglycosides 6 and 61, as judged by comparison of its ir spectrum with the spectra of the pure components. (It was noted that 6 and 59 have similar R_F values of ~ 0.5 in t.l.c. with solvent B.) The mother

liquor showed a spot having R_F 0.2 (56).

In a similar experiment, 59 (307 mg, 0.7 mmol) was treated with an M solution of lithium triethylborodeuteride (5.6 ml) in oxolane for an extended period of time (8 h). The crude product showed 3 well-separated spots in t.l.c. (solvent B), having R_F 0.6, 0.45, and 0.2, and the components of the mixture were isolated by column chromatography (10 g of silica gel) using 1:5 ethyl acetate-hexane as the eluent. The fast-moving product was identified by its ir and 300-MHz ^1H -n.m.r. spectra as 61 (38 mg); compare section (h). The material (47 mg) of intermediate mobility was a mixture of the deuterated analogs 6a and 6b of 6 (approximate ratio, 7:3), as was revealed by the following data.

The 500-MHz ^1H -n.m.r. data for 6 (in CDCl_3), δ : 7.47-7.45 and 7.34-7.32 (m, 2 + 3H, Ph), 5.50 (s, Ph-CH), 4.67 (d, $J_{1,2} = 3.7$ Hz, H-1), 4.25 (dd, splittings 10.3 and 15.9 Hz, H-6e), 3.77 (tdd, collapsing to ddd on D_2O exchange, $J_{1,2} = 3.8$, $J_{2,3e} = 4.8$, $J_{2,3a} \approx J_{2,OH} = 11.5$ Hz, H-2), 3.70-3.66 (m, 2H, H-5, 6a), 3.52 (m, H-4), 3.46 (s, 3H, OMe), 2.29 (dt, $J_{2,3e} = J_{3e,4} = 4.6$, $J_{3a,3e} = 11$ Hz, H-3e), 2.03 (d, removed by D_2O , $J_{2,OH} = 11.3$ Hz, OH), and 1.84 (t, $J_{2,3a} = J_{3a,3e} = 11.6$ Hz, H-3a). For the mixture of 6a and 6b (500 MHz, CDCl_3), δ : 4.67 (s for 6a, superposed on d, $J = 3.5$ Hz, for 6b, intensity ratio 7:3, H-1), 3.77 (m, $\sim 0.3\text{H}$, H-2 of 6b), 2.28 (dd, $\sim 0.7\text{H}$, $J_{3e,4} = 4.1$, $J_{3a,3e} = 11.2$ Hz, H-3e of 6a), 1.84 (t, $\sim 0.7\text{H}$, $J_{3a,3e} = J_{3a,4} = 11.4$ Hz, H-3a of 6a), and 1.83 (t, $\sim 0.3\text{H}$, $J_{2,3a} = J_{3a,4} = 11.7$ Hz, H-3a of 6b). The remaining signals were as for 6.

The 125-MHz ^{13}C -n.m.r. data for 6 (in CDCl_3), δ : 128.97, 128.19,

126.05 (Ph), 101.64 (Ph-C), 98.96 (C-1), 76.19 (C-4), 69.21 (C-6), 67.53 (C-2), 63.81 (C-5), 55.15 (O-Me), and 33.68 (C-3). The mixture 6a + 6b showed the same, single peaks for the substituent carbon atoms and C-6, and two sets of signals in 7:3 ratios for the sugar-ring carbons. Signals for 6a : 98.93 (C-1), 76.19 (C-4), 63.80 (C-5), and 33.57 (C-3), with the C-2 signal being absent; note the isotope effects of $^2\text{H-2}$ on C-1 and C-3 (-0.03 and -0.09 ppm). Signals for 6b : 98.95 (C-1), 76.12 (C-4), 67.45 (C-2), and 63.78 (C-5); a C-3 signal was not observed. Note the isotope effects of $^2\text{H-3}$ on C-2 and C-4 (-0.08 and -0.07 ppm).

h) Reaction of 60

LTBH (15 ml) was added to a suspension of the 2,3-ditosylate 60 (0.99 g, 1.68 mmol) in oxolane (10 ml), and the mixture was heated to reflux, with magnetic stirring, for 24 h. It then showed 3 strong spots in t.l.c. (solvent B), representing 56 (R_F 0.2), 6 (R_F 0.5), and 61 (R_F 0.65). The latter was a double spot having a violet front part; very faint, more-mobile traces were seen additionally. The product mixture obtained upon processing was chromatographed on a column of silica gel (25 g) by use of solvent G as the eluant. The following fractions (10 ml) were collected: 4-5 (impurities, 3 mg, discarded), 6-13 (61 with satellite, 110 mg), 14-28 (pure 61, 30 mg), 29-53 (pure 6, 89 mg), and, by elution with pure ethyl acetate, a final fraction (large) that contained pure 56 (170 mg).

Fraction 6-13 was recrystallized from ethyl acetate-hexane to

to give pure 61 (92 mg, free from the satellite component), for a total yield of 122 mg (27.5%); m.p. 150-151° (151-153° after recrystallization from ethanol), $[\alpha]_D +137.4^\circ$ (c 0.8). The spectral data agreed with the structure of methyl 4,6-O-benzylidene-3-deoxy- α -D-erythro-hex-3-enopyranoside:

$\nu_{\text{max}}^{\text{Nujol}}$ 3300 (broad, OH) and 1700 cm^{-1} (C=C fused to acetal ring);

$^1\text{H-n.m.r.}, \delta$: 7.5 and 7.4 (m, 2 + 3H, Ph), 5.56 (s, Ph-CH), 5.28 (nm, W_H 4.8 Hz, H-3), 4.81 (d with broadened lines, $J_{1,2} = 4.7$, $J_{1,3} \approx 0.8$ Hz, H-1), 4.43 (broad m; quintet after D_2O exchange, $J_{1,2} = 4.7$, $J_{2,3} \approx J_{2,5} \approx 2$ Hz, H-2), 4.31 (m, 2H, H-5,6e), 3.73 (dd, $J = 12.2$ and 12.6 Hz, H-6a), 3.53 (s, 3H, OMe), and 2.23 (broad, removed by D_2O , OH); m/z (CI, ether): 265 ($\text{M}^+ + 1$), 247 ($\text{M}^+ + 1 - \text{H}_2\text{O}$), 233 ($\text{M}^+ - \text{MeOH}$).

Anal. calc. for $\text{C}_{14}\text{H}_{16}\text{O}_5$ (264.3): C, 63.62; H, 6.10. Found: C, 63.62; H, 6.07.

The aforementioned, chromatographically homogeneous fractions 29-53 gave crystalline 6 (89 mg, 19.9%) showing m.p. 191-192° after recrystallization from ethanol; the ir spectrum was congruent with those of the products obtained from 52 and 53 (sections C and D). The crystalline diol 56 (170 mg, 35.9%) gave an ir spectrum superposable on those of an authentic sample and of the product obtained from 55 (section E). It is to be noted that the glycosides 5, 6, 56, and 61 are readily distinguishable by the shape of their hydroxyl absorption bands and by very detailed and characteristic band patterns in the region of $600\text{-}900 \text{ cm}^{-1}$.

i) Reaction of 62

The 2,3-ditosylate 62 (1.06 g, 1.8 mmol) was allowed to react with LTBH (16 ml). After 30 min, a small proportion of 62 (R_F 0.68) had remained, but the reaction was complete after 1 h, having given two products, R_F 0.37 (black spot) and R_F 0.47 (brown spot) in t.l.c. with solvent B. With solvent I, the relative mobilities were reversed (R_F 0.33 and 0.23), and in that order, too, the products were eluted by solvent J in column chromatography (15 g of SiO_2) to which the processed, crude mixture (0.45 g, 94%; syrup) was subjected. The first few, chromatographically homogeneous fractions yielded crystals (120 mg, m.p. 126°), identified as the 2-deoxyglycoside 5 by comparison with 5 previously obtained from 49 (ir and 300-MHz n.m.r. spectra, and t.l.c.)

Subsequent, mixed fractions contained mainly the second product, and these were followed by nearly pure fractions (170 mg) of the same. After a further, chromatographic purification the material (130 mg) was identified as methyl 4,6-O-benzylidene-3-deoxy-~~4~~-D-arabino-hexopyranoside (9) by its 300-MHz 1H -n.m.r. spectrum (in $CDCl_3$): δ 7.5 and 7.35 (m, 2 and 3H, Ph), 5.55 (s, Ph-CH), 4.55 (broadened s, H-1), 4.23 (distorted dd, H-6e), 3.99 (narrow m, H-2), 3.95 (td, partially overlapped by the H-2 signal, H-4), 3.8 (m, 2H, consisting of a dt for H-5 and a t with 10-Hz splitting for H-6a), 3.40 (s, 3H, OMe), 2.09 (narrow m, H-3e), and 2.05 (dd, $J_{2,3a} = 3.2$, $J_{3a,4} \sim 11$ Hz, H-3a; geminal coupling was not observed). The data agreed with the 100-MHz data recorded (7) for 9.

Performance of the same reaction, but with lithium triethyl-

=borodeuteride, gave the 2-deoxy-2-deuterio- and 3-deoxy-3-deuterio- α -D-altro analogs 5a and 9a, which were isolated chromatographically in the same way. In comparison with the $^1\text{H-n.m.r.}$ spectrum of 5 (section B), that of 5a lacked the H-2a signal, the H-2e signal was reduced to a narrow dd, H-3 gave a t with $J_{2e,3} = J_{3,4} = 2.8$ Hz (after D_2O exchange), and H-1 gave a slightly broadened s, whereas the resonances for H-4,5,6a,6e and the substituents were identical in 5 and 5a. The spectrum of 9a was identical with that of 9 except that the characteristic dd for H-3a was lacking and the H-4 and partially overlapping H-2 signals were reduced in multiplicity.

3. Reaction of 62 with lithium aluminum hydride and lithium aluminum deuteride.

Altroside ditosylate 62 (300 mg) was reduced with LAH (80 mg) in dry, boiling oxolane (4 ml) according to Jary's procedure (12), but with a reaction time of 25 instead of 18 h. A small proportion of 62 (R_F 0.63) remained unconsumed even then; the main product gave a single spot having R_F 0.43 and an elongated double spot, R_F 0.37-0.17, that was colored reddish-brown in the front and brownish-black in the rear part. In addition, a trace product having R_F 0.75 was detected, migrating like an authentic sample (39) of the manno 2,3-epoxide 8 (t.l.c. with solvent E). Processing of the reaction mixture as described (12), followed by multiple chromatography on silica gel using solvent G and similar solvent combinations (1:4 and 1:6), resulted in partial separation of the products. Part of the most abundant product (R_F 0.37;

brown spot) was isolated pure and identified as 9 by its 300-MHz ^1H -n.m.r. spectrum. The minor product 5 (R_F 0.27, blackish spot) was obtained in a 2:3 mixture with 9, but its presence was clearly indicated by its distinctive n.m.r. signals. The compound having R_F 0.43 was isolated pure in a small amount and determined to be the 3-monotosylate 63 on account of its n.m.r. spectrum (see Table 1).

When an identical experiment was performed, but with LAD, the chromatographic pattern was similar except that a somewhat larger proportion of starting 62 appeared to have remained (after 28 h), and the fast-moving spot attributed to 8 was slightly stronger than previously. Isolated chromatographically, 8 gave a 300-MHz ^1H -n.m.r. spectrum (CDCl_3) identical in every respect with that of an authentic sample and essentially agreeing with reported (40) data: δ 7.46 and 7.37 (m, 2 and 3H, Ph), 5.54 (s, Ph-CH), 4.87 (s, $J_{1,2} = 0$ Hz, H-1), 4.23 (q, splittings of 10 and 16 Hz, H-6e; misassigned as H-4 in ref. (40), 3.7-3.6 (m, 3H, H-4,5,6a), 3.45 (d, H-2 or H-3), 3.44 (s, 3H, OMe), and 3.14 (d, $J_{2,3} = 3.7$ Hz, H-3 or H-2; note that $J_{3,4} = 0$ Hz).

In an attempt to effect more complete reaction, 62 (300 mg) in oxolane (7 ml) was reduced with LAD (80 mg) as before, and further LAD (80 mg) was added after 22 h and boiling continued for another 24 h, whereafter 62 was no longer detectable by t.l.c. However, it was found upon processing (12) that the reaction had still not been entirely complete. The syrupy mixture of products (120 mg) was subjected to a single chromatography on a silica gel column (6 g) with 1:3 ethyl acetate-hexane. Various pure and mixed fractions of products totalling 70 mg

were eluted. One small, mixed fraction (8 mg) contained mainly 62, and another small fraction (12 mg, crystalline) consisted of 63 (n.m.r.). The fractions which contained the main product in more or less pure form amounted to 30 mg, and the 300-MHz ¹H-n.m.r. spectrum of a pure fraction was superposable on that of 9a obtained in the LTBD reduction. Slow-moving material eluted from the column represented mixtures in which diol 65 appeared to be present.

TABLE 1. Proton magnetic resonance parameters, at 300 MHz, for glycosides used as starting compounds

Compound	2-tosyl ^c	3-tosyl ^c	Ph-CH	H-1	Chemical shifts (δ) ^b						H-6e	O-Me	aryl-M3	OH
					H-2	H-3	H-4	H-5	H-6a	H-6e				
49	7.81, 7.31		5.50	4.77d	4.71dd	4.07m	3.76m (3H)	4.19m	3.36	2.40			2.06d	
52		7.70, 7.03	5.37	4.76d	4.30dt	4.74dd	4.04m	3.8m(2H)	4.19dd	3.35	2.18		2.61d	
53 d	7.93, 7.41	7.66, 7.21	5.63	4.94m(2H)	4.76dd	3.99dd	3.71sx	3.86t	4.21dd	3.44	2.50, 236			
55	7.83, 7.33		5.50	4.80d	4.49t	4.16m	3.44dd	4.11sx	3.69t	4.32dd	3.37	2.40	2.97d	
56 e			5.64	4.62d	3.59m	4.01m ^f	3.56dd	3.95sx	3.68t	4.26dd	3.32		4.62d, 4.43d	
57			5.61	5.02dd	5.07t	4.46dt ^f	3.64dd	4.21sx	3.79t	4.39dd	3.44		3.20d	
58		7.67, 6.90	5.44	4.95d	5.13t	5.43t	3.70dd	4.18sx	3.66t	4.28dd	3.40	2.20		
59		7.72, 7.01	5.45	4.72d	3.82dt ^f	5.28t	3.60dd	4.00sx	3.63t	4.27dd	3.42	2.31	2.89d	
60	7.79, 7.32	7.71, 7.02	5.44	4.73d	4.53t	5.25t	3.57dd	4.10sx	3.63t	4.25dd	3.29	2.43, 2.31		
62	7.85, 7.49	7.58, 7.01	5.38	4.54 ^h	4.71dd	4.48t	3.80dd	4.14sx	3.65t	4.22dd	3.31	2.47, 2.29		
63		7.42, 6.98	5.60	4.61 ^h	3.67t	4.32mm	4.25m(2H)	3.80m	4.25m	3.43	2.26		1.7 broad	

(Table continued on next page)

(Table 1, continued)

Coupling constants (Hz)

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$	$J_{H,OH}$
<u>49</u>	1.5	3.5	9	i	i	i	i	6
<u>52</u>	1.8	3.4	10	9	i	i	i	3.4
<u>53</u>	i	3.2	10.3	9.2	10	4.8	10	
<u>55</u>	4	3.5	2.5	10	10.5	5	10.5	7.5
<u>56</u>	4.8	2.7	2.7	9.6	10.4	5	10.4	9.6, 5.0
<u>57</u>	4	2.5	3	10	10	5	10	7
<u>58</u>	4.3	2.9	2.9	9.6	10.2	5.2	10.2	
<u>59</u>	4.3	3.5	4.7	9.6	10.5	5.2	10.3	12
<u>60</u>	4.2	3.3	2.8	9.6	10.5	5.2	10.3	
<u>62</u>	1.2	3.2	2.9	9.6	10	5	10	
<u>63</u>	1	3	small	i	i	i	i	3

- a In CDCl_3 solution unless otherwise indicated.
- b Signal multiplicities are indicated as d (doublet), m (multiplet), sx (dt or ddd, appearing as a sextet), and t (triplet). The data refer to first-order analysis. The signals for Ph-CH, O-Me, and aryl-Me were singlets.
- c Mid-points of the A and B parts (2 protons each) of the aromatic AB system.
- d In acetone- d_6 .
- e In dimethyl sulfoxide- d_6 .
- f Triplet after D_2O exchange.
- g Not determined accurately because of crowding with phenyl signals.
- h Slightly broadened singlet representing a very narrow doublet.
- i Not determined because of second-order effects.
- j $J_{1,3}$ 1 Hz.

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