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**LA THÈSE A ÉTÉ  
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Synthetic and Mechanistic Studies  
in the field of  
Deoxy, Branched-Chain and Amino Sugars

by

David James Astles

A thesis  
presented to the University of Ottawa  
in fulfillment of the  
thesis requirement for the degree of  
Doctor of Philosophy  
in  
Chemistry

Department of Chemistry  
University of Ottawa  
Ottawa, Ontario  
Canada



UNIVERSITÉ D'OTTAWA  
UNIVERSITY OF OTTAWA

"Mine is the nature of a scholar,  
and my branch of scholarship is science.  
And science is nothing else than a  
'strange hankering after differences'.  
Her essence could not be better defined.  
For men of science nothing is so important  
as the clear definition of differences".

Hermann Hesse

in

Narziss and Goldmund

### ACKNOWLEDGEMENT

First and foremost, I would like to thank Professor Baer for his patient guidance through all my years in his lab. I am indebted to him for my enjoyable tenure here. I would also like to thank him for enabling me to present my work in an international forum in the Netherlands.

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Technicians Lisa Siemsen and Ho-Chi Chin are thanked heartily for their skillful assistance in many aspects of the work. Summer students Cristine Lajeunesse, Fabio Zanetti, Russel Gowan, Bill Hendriks, Chinh Nguyen and Sanjay Wadhera are all thanked for their assistance, great or small, in making starting materials and the like.

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Last, but by no means least, I would like to thank Cristine for her support and tolerance of me, especially during the writing of this thesis.

## PREFACE

This thesis is divided into two sections. The first deals with studies concerning the reaction of lithium triethylborohydride with carbohydrate tosylates. The second section deals with some investigations in the area of selective functionalization of trehalose derivatives.

As both sections cover distinctly different areas of carbohydrate chemistry, they each have their own numbering systems for compounds, figures and references. Within each section these numbers should, however, be consistent. Any inconsistency that has passed the many proof readings is purely accidental and the reader has the author's sincerest apologies for any problems this may cause.

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Part 1

REACTIONS WITH LITHIUM TRIETHYLBOROHYDRIDE



## I

ABSTRACT

Desulfonyloxylations with lithium triethylborohydride were attempted with several carbohydrate sulfonates as substrates. Presumed to proceed via intermediary epoxides, the reactions were expected to furnish 2,6-dideoxy-hexopyranosides, according to the method of Baer and Hanna<sup>1</sup>. Instead, ring-contraction was found to occur and 2,5- and 3,5-dideoxy-2- or 3-C-(hydroxymethyl)-pentofuranosides were found to occur as principal reaction products.

Arguments are presented for the structures of the compounds using nmr data as well as empirical calculation of molecular rotations.

Studies with blocked model compounds are presented as are studies with other alkali metal alkylborohydrides, all in an attempt to elucidate the mechanism of the ring-contraction process. Several mechanistic possibilities are discussed and weighed in light of the experimental observations.

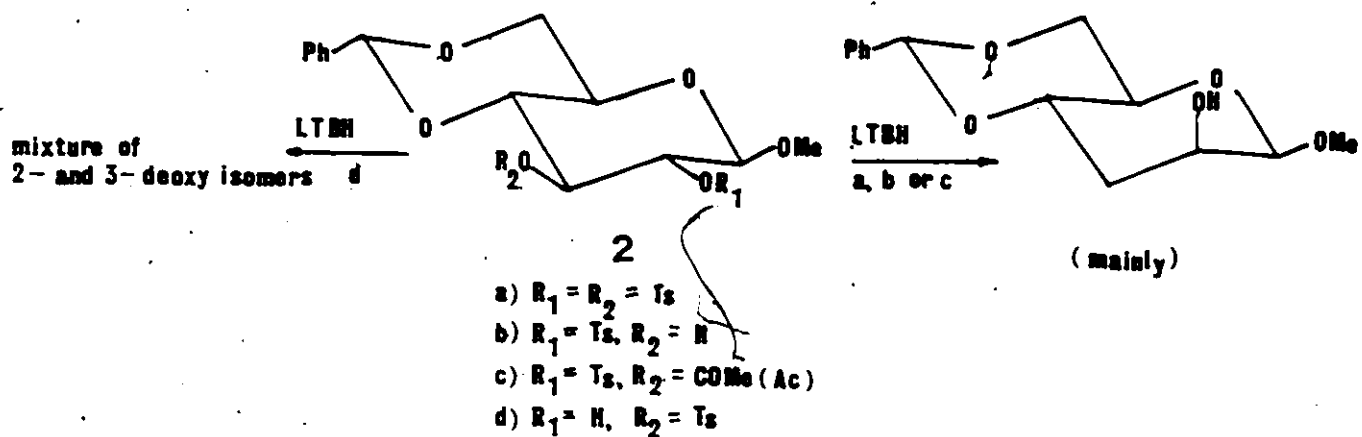
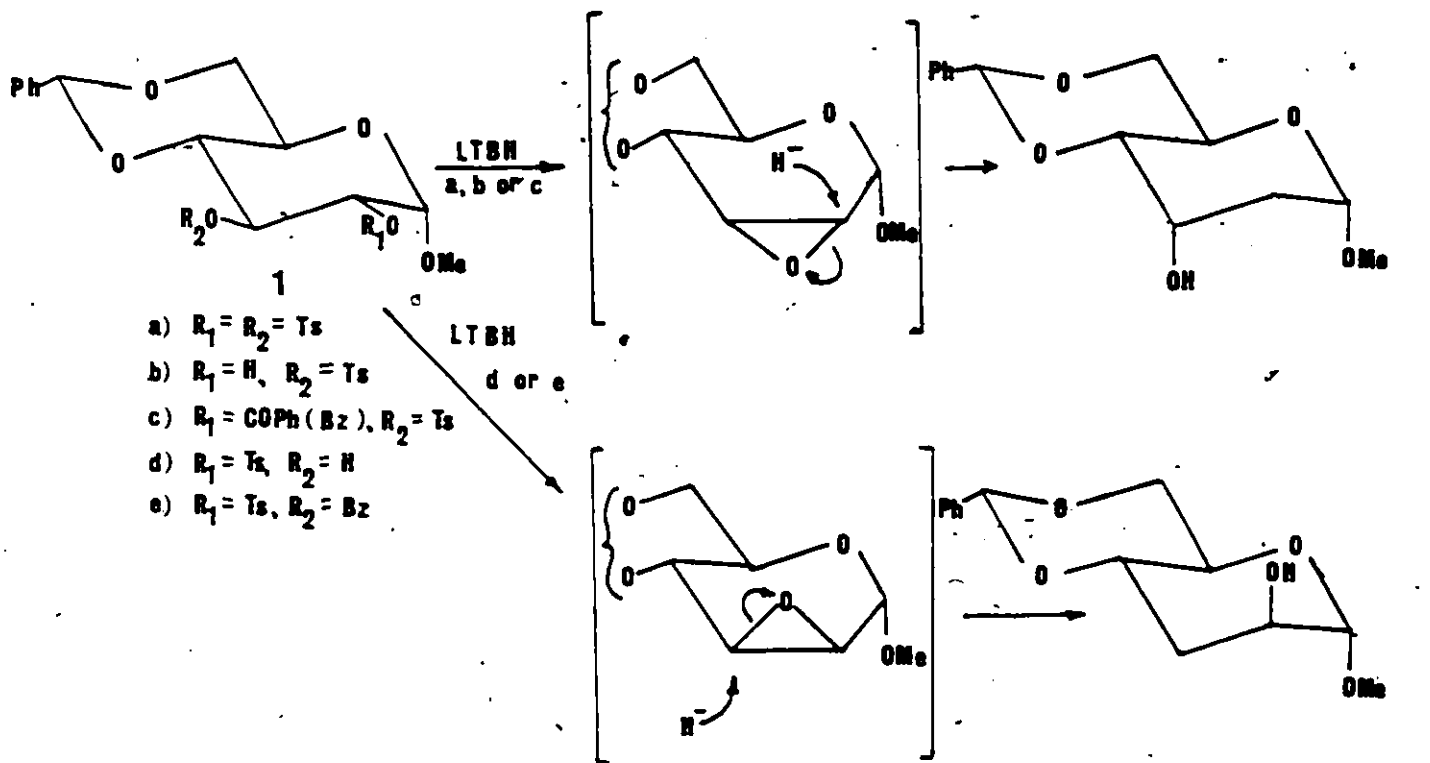
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Chapter II  
INTRODUCTION

Recent work in this laboratory focussed on the reductive desulfonyloxylation of methyl 4,6-O-benzylidene- $\alpha$ - and  $\beta$ -D-glucopyranoside p-toluenesulfonates (tosylates), (1 and 2 respectively), by the action of lithium triethylborohydride (LTBH), which permitted the convenient and efficient preparation of certain 2- and 3- deoxypranoside derivatives<sup>1</sup> (Scheme 1). The method was subsequently applied to various tosylates of the analogous bis-acetal from the disaccharide,  $\alpha,\alpha$ -trehalose<sup>2</sup>.

A structural prerequisite for the reaction appeared to be the presence of a free, or potentially free (see below), hydroxyl group adjacent and trans to the sulfonic ester. It was then established that the reaction proceeded through intermediary epoxides formed by intramolecular displacement of the tosyloxy by the vicinal hydroxyl group. The latter moiety reacts as its alkoxide which results either from deprotonation of a free hydroxyl (1b,d; 2b,d) or by nearly instantaneous O-deacylation of ester derivatives (1c,e; 2c). In the cases of ditosyl compounds (1a; 2a),

0-desulfonylation occurred first at the more reactive 2-position<sup>1,2</sup> thereby generating the alkoxide nucleophile.



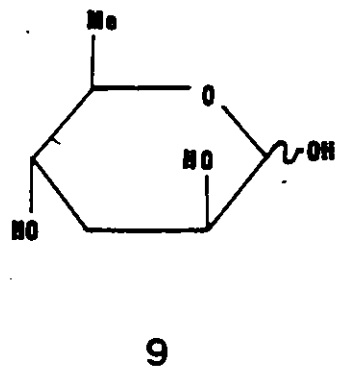
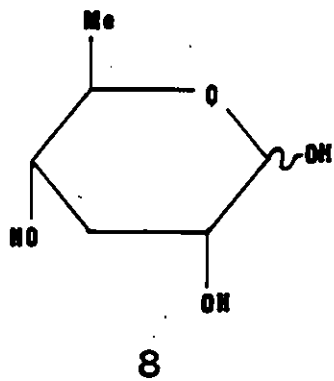
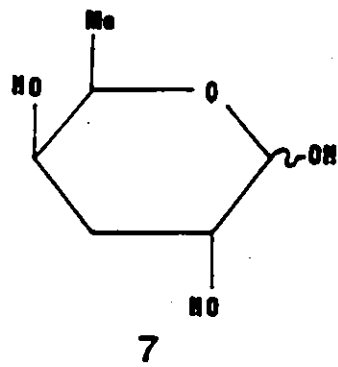
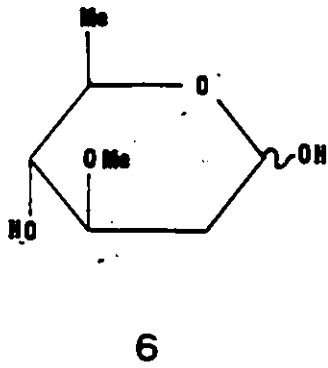
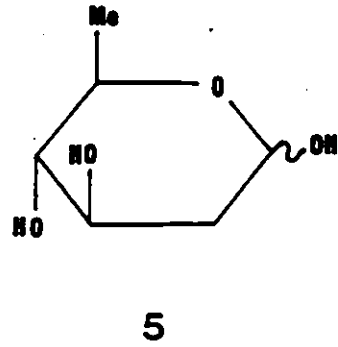
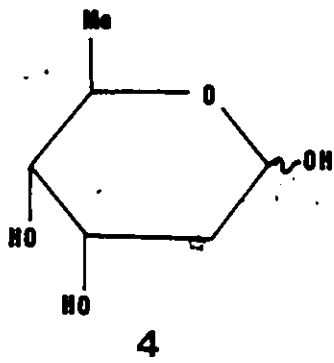
Scheme 1

The epoxides, once formed, opened in a trans -diaxial fashion according to well established stereochemical principles. Very high regioselectivity was generally observed. One of the factors promoting this selectivity, in the sense of the Frost-Plattner rule predicting diaxial ring-opening, presumably was the conformational rigidity imparted on the molecule by the trans -fused cyclic acetal structures.

The success and facility of these reactions inspired us to attempt their application to the synthesis of naturally occurring 2,6- and 3,6-dideoxy sugars, the supposition being that a suitably tosylated sugar ( or 6- deoxy sugar ) could undergo the above-mentioned reaction concurrently with reduction of a primary sulfonic at C-6 ( if applicable ).

In any case, it would be interesting to examine the degree to which the structural constraint imposed by the cyclic acetals contributed to the stereochemical outcome of the reaction.

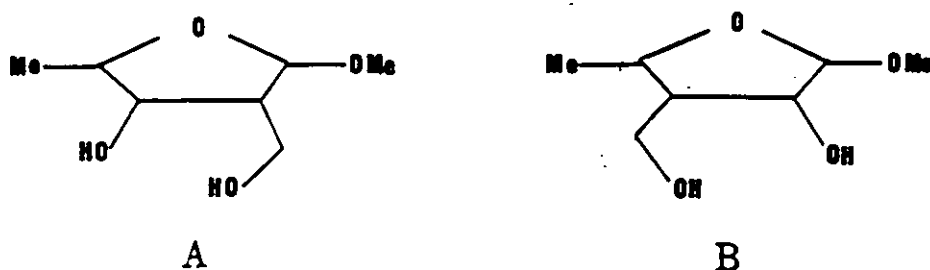
The target dideoxy sugars belong to a class of important, biologically significant compounds. These sugars are ubiquitous in Nature, being found in the form of plant glycosides ( e.g. digitoxose<sup>4</sup> in Digitalis ), as components of antibiotics ( e.g. chromose<sup>5</sup> and oleandrose<sup>6</sup> in chromomycins and oleandomycin ), and as bacterial components ( e.g. abequose<sup>7</sup>, paratose<sup>8</sup>, and tyvelose<sup>9</sup> in Salmonella polysaccharides ).



The synthesis of dideoxy sugars is well established<sup>1,2,3</sup>. A common synthetic sequence is the reduction of sugar epoxides formed from sugar tosylates<sup>4,5</sup>. It was felt that the LTBH-mediated reaction, combining both steps, might offer some practical advantages over the published procedures.

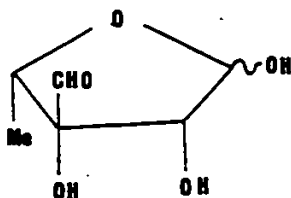
It was with the above-mentioned considerations that the work described herein was undertaken.

As will be discussed, the expected dideoxy sugars did not arise in these reactions or at least not as the major products. Instead, branched-chain sugars of the general types A and B were found to be the principal products.



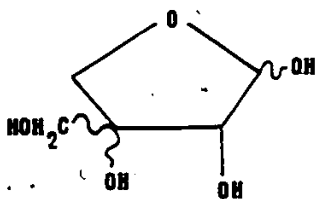
These interesting, and rather surprising, results led to a divergence from the original plan toward the mechanistic and structural investigations described in this thesis. They also provide an unusual, and perhaps synthetically useful, access to naturally occurring members of this class of compounds, the most notable of which is streptose (10)<sup>1,2</sup>.

Found in streptomycin and related antibiotics ( sometimes as its dihydro derivative ), streptose has yielded to several synthetic attempts, the first having been published in 1965<sup>12</sup>.

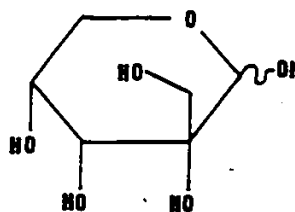


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Historically, the first branched-chain sugar structurally characterized was apiose ( 11 ). This compound was first isolated from parsley ( Apium petroselinum L. )<sup>13</sup>. Identified later<sup>14</sup>, but with a much more colorful history<sup>14</sup>, is hamamelose ( 12 ). Found in witch-hazel ( Hamamelis virginiana ), it was used by Oneida Indian Medicine-Men and later in "Snake-Oil" type patent medicines<sup>14</sup>.

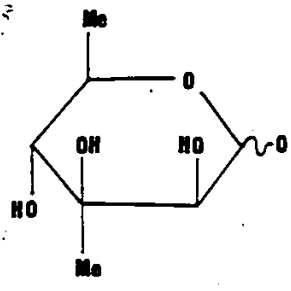


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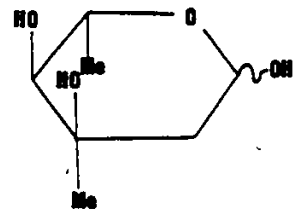


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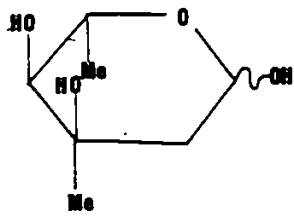
Other branched-chain sugars of natural occurrence include evalose<sup>15</sup> ( 13 ), axenose<sup>16</sup> ( 14 ), mycarose<sup>17</sup> ( 15 ), evermicose<sup>18</sup> ( 16 ), and pillarose<sup>19</sup> ( 17 ).



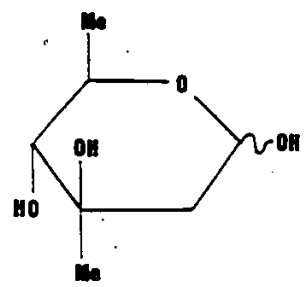
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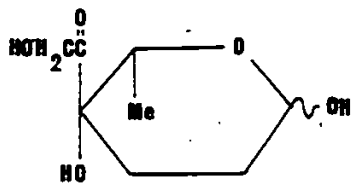
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These, and other branched-chain sugars, have been subjected to sufficient investigation to warrant a specific section in Specialist Periodical Reports in Carbohydrate Chemistry,<sup>20</sup> where the plethora of synthetic techniques is amply described.

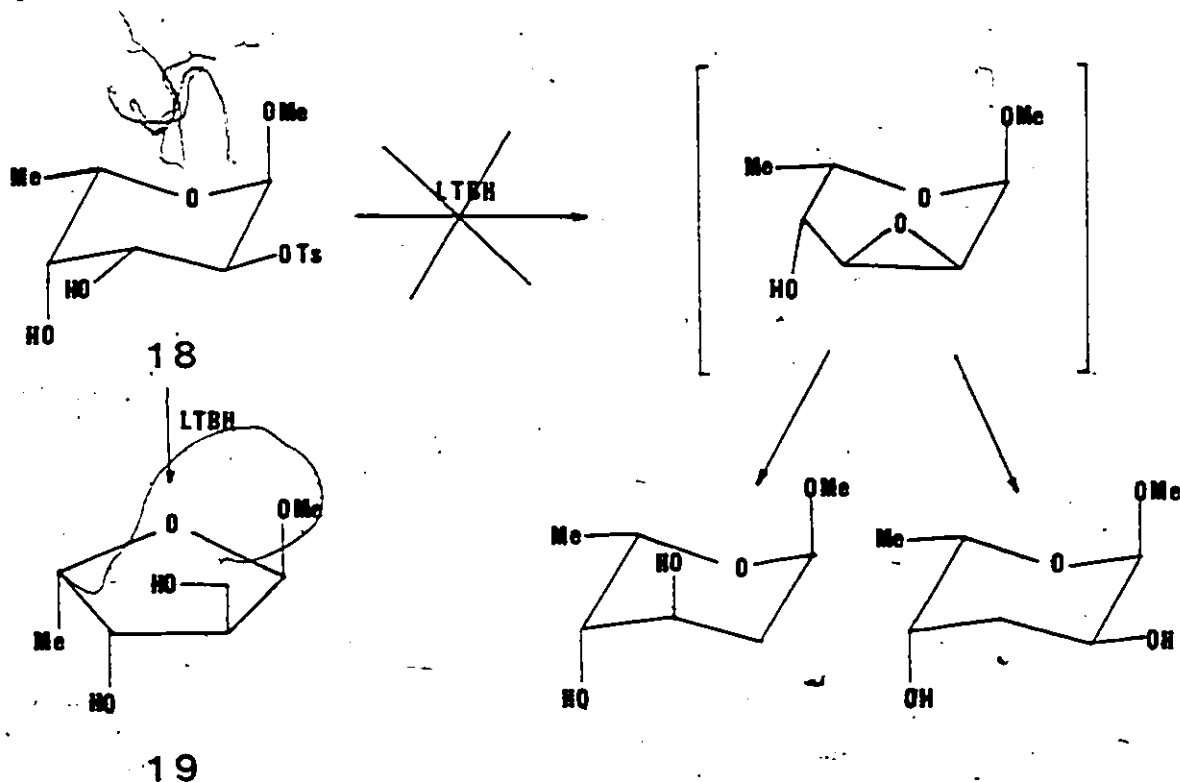
The discussion of the LTBH-mediated reactions follows. Due to the complexity of many aspects of this work, the format of the ensuing discussion will be as follows: The first section, entitled 'LTBH-Mediated Reaction Products', will present the experimental results and observations without justification of the structures presented. A second section, 'Structures of the Branched-Chain Glycosides', will deal with that particular point. Finally, a third section, 'Mechanistic Considerations', will present the various mechanistic possibilities and investigations.

It is hoped that the format chosen will facilitate the analysis of the work in question and that its interest and utility may be appreciated.

### Chapter III

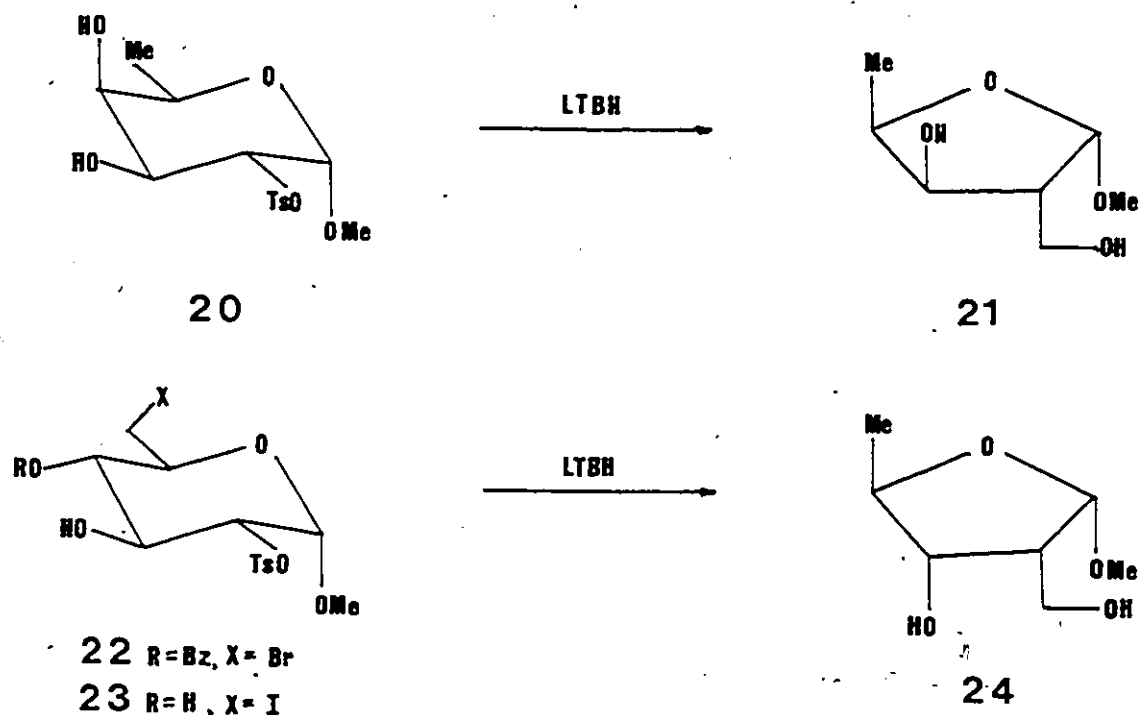
#### LTBH-MEDIATED REACTION PRODUCTS

Reaction of methyl 2-O-tosyl- $\alpha$ -L-fucopyranoside ( 18 ) with LTBH was expected to lead to internal displacement of the sulfonic ester group, followed by diaxial, reductive ring-opening of the resultant 2,3-epoxide, to give one or both ( presumably the diaxial isomer in predominance ) of the dideoxyhexopyranosides this sequence of events can provide ( Scheme 2 ).



Scheme 2 .

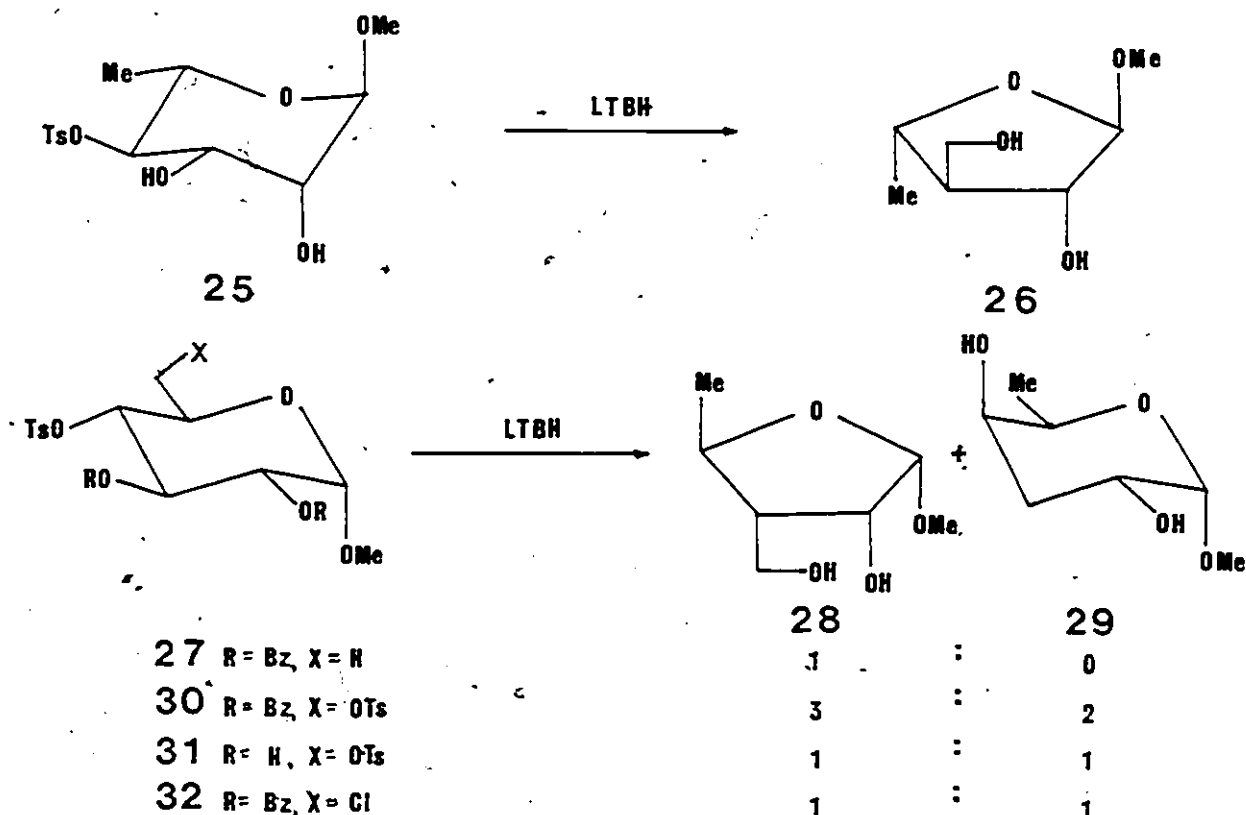
However, no such product was detected upon treatment of 18 with an excess of reductant in boiling oxolane ( THF ), although all the starting material was consumed within 30 minutes and desulfonyloxylation did indeed take place. Instead, ring contraction occurred and the branched-chain glycoside 19, methyl 2,5-dideoxy-2-C-(hydroxymethyl)- $\alpha$ -L-xylo-pentofuranoside, was isolated crystalline in approximately 60% yield. Evidently, loss of the sulfonyloxy group was coupled with a skeletal rearrangement, apparently by migration of the C-3—C-4 bond. Performance of the reaction with the D-enantiomer ( 20, Scheme 3 ) provided the corresponding D-enantiomer 21, likewise in crystalline form.



Scheme 3

When methyl 4-O-benzoyl-6-bromo-6-deoxy-2-O-tosyl- $\alpha$ -D-glucopyranoside 22 ) or methyl 6-deoxy-6-iodo-2-O-tosyl- $\alpha$ -D-glucopyranoside ( 23 ) were used as substrates, the crystalline  $\alpha$ -D -ribo isomer ( 24 ) of the foregoing 2,5-dideoxy-2- C -( hydroxymethyl )-pentofuranoside was obtained.

In the corresponding hexopyranoside 4-tosylates, ring contraction occurred in the opposite direction, i.e., by apparent migration of the C-2—C-3-bond, furnishing the isomeric 3,5-dideoxy-3- C -(hydroxymethyl)-pentofuranosides ( Scheme 4 ). Thus, methyl 4- O -tosyl- $\alpha$ -L-rhamnopyranoside ( 25 ) produced the crystalline  $\alpha$ -L- -arabino isomer ( 26 ), and methyl 2,3-di O -benzoyl-4- O -tosyl- $\alpha$ -D-quinovoside, 27, gave the  $\alpha$ -D -ribo isomer 28 which failed to crystallize but was isolated in chromatographically pure condition (Scheme 4).



Scheme 4

In all of these experiments, the starting tosylates reacted rapidly and completely ( provided a sufficient excess of reagent was employed ), and no unrearranged dideoxyhexopyranosides were detected although traces of unidentified by-products were sometimes seen in tlc. The crude reaction mixtures apparently contained the glycosides as alkali-stable organoboron complexes\* and because of a high ( and not altogether unexpected ) acid sensitivity of the dideoxyfuranosides, the products tended to behave somewhat capriciously during processing and isolation. Isolated yields for the pure products were in the 40-60% range.

In contrast to the 6-deoxy sugar 27, the analogous methyl 2,3-di-O-benzoyl-4,6-di-O-tosyl-  $\alpha$ -D-glucopyranoside (30) gave the ring-contracted product 28 and the unrearranged hexopyranoside 29 in a ratio of approximately 3:2. Although chromatographic separation was difficult to achieve ( and the reaction was therefore of limited preparative value )

\* The crude reaction products showed in tlc a slow-moving spot, that corresponded to that given by the pure ring-contracted glycoside, and an additional strong spot ( fast-moving but slightly slower than the starting material ) which was invisible under UV light and therefore represented tosyl-free material also. Upon chromatographic isolation, this fast-moving material showed the same proton-nmr features as the rearranged glycoside but additionally gave strong resonances near 0.9 ppm, presumably attributable to alkylboron moieties. Treatment of the alkaline reaction mixtures with hydrogen peroxide diminished the proportion of, or eliminated completely, these products which were not further characterized. It seems that the primary hydroxyl group present in the branched-chain products must be involved in the occurrence of this complication since it was not encountered in the LTBH reductions of benzylidened glycoside tosylates, previously studied<sup>1</sup>, which proceeded without rearrangement.

the isomers obtained were sufficiently pure for unambiguous spectroscopic identification. Thus compound 29 was identified as methyl 3,6-dideoxy- $\alpha$ -D- -xylo -hexopyranoside (methyl abequoside') by comparison with an independently prepared sample<sup>11</sup>.

The O -debenzoylated 4,6-ditosylate\* 31 and the 6-chloro-6-deoxy glycoside 32 both furnished, on treatment with LTBH, mixtures of 28 and 29 in approximately equal proportions ( Scheme 4 ).

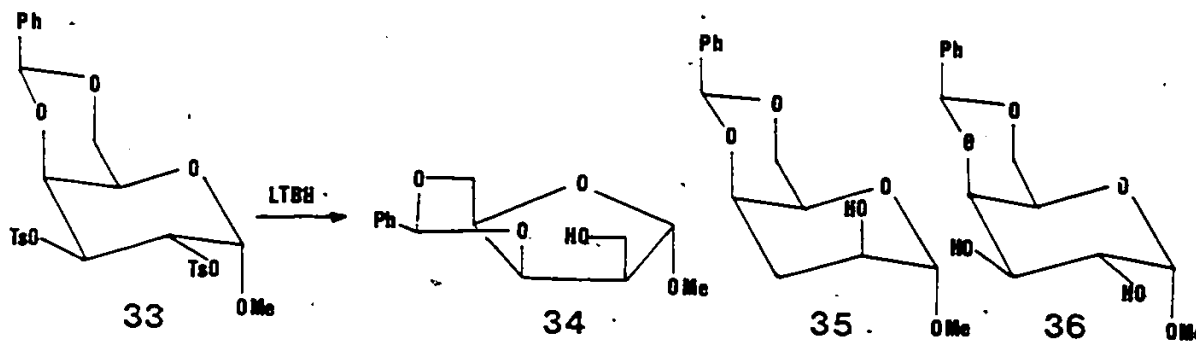
The exclusive or predominant occurrence of ring-contraction here reported stands in marked contrast to the desulfonyloxylations that have been performed on 4,6- O -benzylidenated glucopyranoside tosylates. In the latter, an analogous rearrangement would require the formation of a highly strained system comprising a six-membered acetal ring trans -fused to a five-membered furanose ring ( a 'trans bicyclo -4.3.0- system ) and is presumably disfavored for this reason<sup>12</sup>. To test this hypothesis, methyl 4,6- O -benzylidene-2,3-di O -tosyl- $\alpha$ -D-galactopyranoside ( 33 ) was subjected to reduction with LTBH, the assumption being that a cis -fused acetal might be sufficiently flexible to permit ring-contraction. Indeed, ring-contracted methyl 3,5- O -benzylidene-2-deoxy-2- C -(hydroxymethyl)- $\alpha$ -D -lyxo-

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\* Obtained from 30 by deacylation with methanolic ammonia. For a description of the complex results obtained on attempted deacylation with sodium methoxide, see the Experimental Section

<sup>12</sup>Although such a product has been observed in a deaminative ring-contraction<sup>21</sup> ( see below ).

pentofuranoside ( 34 Scheme 5 ) was isolated crystalline in 38% yield, although a second major product,



methyl 4,6-O-benzylidene-3-deoxy- $\alpha$ -D--lyxo-hexopyranoside ( 35 ) was isolated in 22% yield. As will be discussed later ( p. 47 ), 34 is thought to arise via the 3-monotosylate, and 35 via the 2-monotosylate, that originate from initial O-desulfonation of 33 at positions 2 and 3, respectively. A significant proportion ( 18% ) of the diol 36 was also isolated, evidently arising from two fold S-O cleavage. The last-mentioned side-reaction was markedly more pronounced than in the gluco series\*.

Before proceeding to a mechanistic analysis of these interesting reactions, structural proofs of the ring-contracted products will be offered in the next section.

\* A similar difference in sulfonic ester stability between 33 and its  $\alpha$ -D-gluco epimer Ia has been noted in their reaction with lithium aluminumhydride, in which 33 suffered far-reaching O-S fission at both O-2 and O-3, whereas the gluco epimer was more stable to this type of cleavage, particularly in position 3<sup>1,2,3</sup>.

## Chapter IV

### STRUCTURES OF THE BRANCHED-CHAIN GLYCOSIDES

#### NMR Analyses

The elemental analyses and 60 MHz proton nmr data for the reduction products were, at least superficially, consistent with the originally anticipated products. However, "high-field" ( 200 and 300 MHz ) nmr clearly showed that such structures were not correct.

In particular, there was in each case a single proton signal at high field, indicating a methine rather than a methylene, structure for C-2 or C-3. It was, therefore, obvious that a chain-branching was present. The position of the branch was confirmed by spin decoupling which proved the methine proton to be vicinal to the anomeric center in compounds 19, 21, 24 and 34 and vicinal to H-2 and H-4 in compounds 25 and 28. The expected, isomeric, 2- and 3-deoxy hexopyranosides, on the other hand, showed at high-field two-proton signals, often well resolved as, for example, in 29.

The carbon-13 nmr data ( Table 2 ) clearly supported the branched-chain pentofuranoside structures. The off-resonance, partially spin-decoupled spectra each contained two quartets ( for C-5 and  $\text{OCH}_3$  ), a triplet ( for hydroxymethyl ), and, significantly, a doublet at relatively high field ( 48.2-54.7 ppm ) attributed to the branch-point carbon, and three doublets for the remaining ring-carbon atoms in the usual ranges<sup>23</sup> ( c.a. 68-76 ppm ). Spectral data establishing the structures of the benzylidene acetals are listed in the Experimental Section

While gross structural determination was relatively straightforward, the question of branch-point configuration was somewhat more difficult to decide. The vicinal proton-proton coupling constants ( Table 1 ) were all in accord with the assigned configurations but, for some of the compounds, the alternative branch-point configuration could not be excluded with any certainty on this basis alone. Such difficulty was not unexpected for the conformationally flexible furanoid systems where reasonable models accommodating spectral data can often be constructed for more than one configuration. Comparisons with known conformational preferences in unbranched furanosides<sup>24,25</sup> were helpful but the possibility of bias associated with the C-hydroxymethyl had, of course, to be considered.

Table 1

<sup>1</sup>H Magnetic Resonance data for methyl dideoxy-C-  
(hydroxymethyl)pentofuranosides.

Cmpd	Chemical Shifts' ( $\delta$ )									
	H-1	H-2	H-2'a	H-2'b	H-3	H-3'a	H-3'b	H-4	C-CH <sub>3</sub>	O-CH <sub>3</sub>
<u>21</u>	5.04d	2.32m	3.86cm(2H)	4.33ddd				4.20qn	1.25d	3.37s
<u>24</u>	5.00d	2.39 cm	3.99 cm	3.86 cm	3.9			4.16qd	1.25d	3.39s
<u>26</u>	4.84d	4.10 nm			1.86 ddd	3.70(2H)		3.94dq	1.37d	3.35s.
<u>28</u>	4.96	4.43 m			1.95 tdd	3.77m (2H)		4.05 dq	1.29d	3.49s
<u>28'</u>	5.05d	5.13dd			2.29 ddd	4.28dd	4.11dd	4.06qn	1.33d	3.37s

	Coupling Constants (Hz)									
	J <sub>12</sub>	J <sub>23</sub>	J <sub>2'a</sub>	J <sub>2'b</sub>	J <sub>2gem</sub>	J <sub>3'a</sub>	J <sub>3'b</sub>	J <sub>3gem</sub>	J <sub>4,5</sub>	
<u>21</u>	5.6	5.0	4.5	5.2	11.5	6.2				6.3
<u>24</u>	4.7	6.7	6.7	5.8	11.6	2.7				6.5
<u>26</u>	1.0	4.0			8.0	6	7			6.3
<u>28</u>	4.65	8.1			8.0	7	4.6	11.4		6.1
<u>28'</u>	4.3	9.0			6.25	6.6	8.3	11.2		6.25

(For footnotes, see continuation page)

## Footnotes to Table 1

1. From 200-MHz spectra of solutions in  $\text{CDCl}_3$  containing tetramethylsilane as the standard. Spectra with spin-spin decoupling by double irradiation and spectra with  $\text{D}_2\text{O}$  exchange were additionally obtained for all compounds.
2. Signal multiplicities are indicated as cm (complex multiplet), d (doublet), nm (narrow multiplet), m (multiplet), q (quartet), gn (quintet), s (singlet), and t (triplet). Values refer to signal midpoints.
3. Apparent gn; width 20.3 Hz, compatible with dddd having splittings of 4.5, 5.0, 5.2, and 5.6 Hz; collapsing to q, width 14.7 Hz, on H-1 irradiation.
4. Giving on  $\text{D}_2\text{O}$  exchange an apparent t, width 11.2 Hz, by removal of a 3.8-Hz splitting.
5. Width 23.8 Hz; reduced to td on H-1 irradiation, with remaining splittings of 5.8, 6.7, and 6.7 Hz.
6. The signals for H-2'a, -2'b, and -3 were poorly resolved in the regular spectrum.
7. Sharp dd on  $\text{D}_2\text{O}$  exchange, and d (with broadened lines because of coupling with OH) on irradiation of H-2.
8. Upon  $\text{D}_2\text{O}$  exchange, a clearly visible dd superimposed on the H-3 multiplet; without exchange, but with irradiation of H-2, a dd due to coupling with H-2'a and OH was seen.
9. In the presence of  $\text{D}_2\text{O}$ , a singlet was observed, probably due to a slight change in the overall conformation related to hydrogen bonding.
10. Simplified to d in the presence of  $\text{D}_2\text{O}$ , due to coupling with H-3 only; see also 9.
11. Simplified to dd on  $\text{D}_2\text{O}$  exchange, and further to d upon subsequent irradiation of H-3.
12. After  $\text{D}_2\text{O}$  exchange, the signal was an AB-q, as part of an ABX system.
13. Collapsing to q on irradiation of H-3.
14. Spectrum of the di-O-acetyl derivative. The acetyl signals were at  $\delta$  2.05

Table 2

<sup>13</sup>C Chemical Shifts (ppm) for methyl dideoxy-2-C-(hydroxymethyl)pentofuranosides<sup>1</sup>

Cmpd	C-1	C-2	C-3	C-4	C-5	CH <sub>2</sub> OH <sub>2</sub>	OCH <sub>3</sub>	Sum
<u>21</u>	104.6	54.2	76.1	73.5	14.4	59.8	55.1	437.7
<u>24</u>	105.4	48.2	77.2	83.1	19.4	58.1	54.9	446.3
<u>26</u>	109.5	80.1	54.7	76.0	20.5	61.9	56.9	459.6
<u>28</u>	102.6	73.5	50.1	74.5	20.0	60.1	55.2	436.0

1. From 20-MHz spectra, obtained with a Varian FT-80 spectrometer, for solutions in CDCl<sub>3</sub> containing TMS as the internal standard.

The assignments indicated were arrived at on the basis of the discussion that follows, which considers both proton and carbon-13 nmr parameters and is based on the assumption that only the branch-point is at issue, with the other chiral centers not being involved in the reaction and having, therefore, retained their original stereochemistry. The aforementioned assumption is based on the mechanistic considerations that follow in the next section.

Beginning with C-3 branched isomers, the  $\alpha$ -L -arabino configuration of 26 can be regarded as secure. The coupling constants ( Table 1 ) demand dihedral angles of  $\Phi_{1,2} > 90^\circ < 120^\circ$ , and  $\Phi_{3,4} \approx 180^\circ$ , as for a conformation in the  $E_0 \rightleftharpoons {}^4T_0$  segment of the pseudorotational itinerary for this configuration. This is in good agreement with Angyal's<sup>22</sup> and Perlin's<sup>24</sup> deduction of  $E_0$  as the favored conformation of methyl  $\alpha$ -L-arabinofuranoside. A shift towards  ${}^4T_0$ , as suggested by the particularly large  $J_{3,4}$  value ( 8 Hz ) in 26, appears reasonable because it permits the hydroxymethyl group to become quasi-equatorial without sacrificing the quasi-axial orientation of the anomeric methoxyl group. The carbon-13 chemical shifts ( Table 2 ) indicate for 26 the largest overall deshielding (  $\Sigma = 459.6$  ppm ) among all the isomers, signifying the least amount of crowding in

\* For a discussion of the factors which govern furanoside conformation, see ref 25. The coupling constants for 26 would also be compatible with the 3-epimeric,  $\alpha$ -L-lyxo glycoside, but only for a conformation close to 'E. This is a highly unlikely form as it has three contiguous, cis-oriented substituents severely eclipsed; it is avoided by methyl  $\alpha$ -L-lyxofuranoside<sup>24,25</sup> and should be favored even less by the C-3 branched analog.

harmony with the all trans substituent pattern<sup>24</sup>.

In the stereoisomer 28, markedly increased shielding is experienced by C-1, C-2, and C-3 while C-4 and C-5 are affected little, which strongly suggests a cis, cis, trans substituent pattern, i.e., the  $\alpha$ -D ribo configuration. The coupling data fit the  ${}^0E \rightleftharpoons {}^0T_4$  conformation thereof, which has  $\Phi_{1,2} \approx 30^\circ$ ,  $\Phi_{2,3} \approx 0^\circ$ , and  $\Phi_{3,4} \approx 160^\circ$ , in which the bulky C-3 substituent occupies a somewhat more outward position than does OH-3 in methyl  $\alpha$ -D-ribofuranoside for which the adjacent segment  $E_1 \rightleftharpoons {}^0T_1 \rightleftharpoons {}^0E$  has been proposed<sup>24,25</sup>. Although the proton couplings are equally consistent with the  $\alpha$ -D- xylo ( ${}^2E \rightleftharpoons {}^2T_3$ ) arrangement, we prefer the  $\alpha$ -D- ribo assignment for 28 in view of the carbon-13 data just mentioned.

Turning now to the C-2 branched isomers 21 and 24, we note their closely similar carbon-13 shifts for C-1, upfield in comparison with 26, and therefore assume an identical 1,2- cis arrangement (the shielding effect of a cis-2-(hydroxymethyl) upon C-1 appears smaller than that of a cis-2-hydroxyl, cf. 28). This is borne out by the remaining shift data. The C-2 is shielded in 24, relative to 21, by the cis-vicinal OH-3. Conversely, C-4 in 21 is shielded, relative to 24, due to the 3,4- cis arrangement which, incidentally, has also a marked effect on C-5, moving this signal upfield by 5-6 ppm from the resonance position of the other isomers. The C-3 shifts are similar for 21 and

24, as either compound possesses one cis and one trans pattern surrounding that carbon atom. The assignments resulting from these considerations are  $\alpha$ -D -xylo for 21 and  $\alpha$ -D -ribo for 24. The  $^3J_{\text{H,H}}$  values for 24 are in excellent accord therewith, fitting the  $E_1 \rightleftharpoons {}^0T_1$  conformation ( $\Phi_{1,2} \approx 30^\circ$ ,  $\Phi_{2,3} \approx 25^\circ$ ,  $\Phi_{3,4} \approx 120^\circ$ ) that has been suggested<sup>27</sup> for methyl  $\alpha$ -D-ribofuranoside, and they are inconsistent with the 2-epimeric  $\alpha$ -D -arabino configuration. The  $^3J_{\text{H,H}}$  data for 21 allow no distinction as they agree with both the  $\alpha$ -D -xylo and  $\alpha$ -D -lyxo configuration in the respective conformations  ${}^2E$  ( $\Phi_{1,2} \approx 130^\circ$ ,  $\Phi_{2,3} \approx 150^\circ$ ,  $\Phi_{3,4} \approx 30^\circ$ ) and  ${}^3E$  ( $\Phi_{1,2} \approx 150^\circ$ ,  $\Phi_{2,3}$  and  $\Phi_{3,4} \approx 30^\circ$ ) or close pseudorotational variants. Our decision in favour of the former therefore rests solely on the foregoing interpretation of the  $^{13}\text{C}$ -nmr data. However, it receives support from molecular rotation calculations and mechanistic considerations ( see below ). Compound 19, being the enantiomer of 21, requires no extra discussion.

The acetal 34 shows  $J_{3,4} = 2.1$  Hz as expected for the gauche orientation of the protons situated at the ring junctions, and  $J_{1,2} = J_{2,3} = 4.8$  Hz. The size of  $J_{2,3}$  requires H-2 and H-3 to be cis ( $\Phi_{2,3} \leq 60^\circ$ ); if they were trans ( $\Phi_{2,3} \approx 90^\circ$ ), a very small coupling would result. Clearly, the  $\alpha$ -D -lyxo configuration is indicated. Compound

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For a series of diversely substituted, C-2 branched  $\alpha$ -L-arabino-furanosides structurally related to our compounds but obtained in a different way, Jarý and coworkers<sup>27</sup> reported  $J_{3,4}$  values in the range of 5.1-7.5 Hz ( average = 6.5 Hz ).

35 gave a two-proton multiplet at 2.13 ppm attributable to a ring methylene group. The anomeric proton signal, occurring at 4.79 ppm, was a slightly broadened singlet, as is normal in benzylidenedated hexopyranosides for a 1,2-diequatorial proton arrangement, and is indicative of absence of a 1,2-axial-equatorial proton relationship. Double irradiation at 2.13 ppm caused spin decoupling in the signal ( 3.58 ppm ) which was due to the ring proton at the hydroxylated position, and in the H-4 signal ( 4.12 ppm ). These features, whose interpretation was corroborated by comparison with data from several related isomers<sup>1</sup>, established the structure shown.

## Calculation of Molecular Rotations

Given that the  $^1\text{H}$ -nmr coupling and  $^{13}\text{C}$ -deshielding data were not entirely conclusive in all cases, it was decided to attempt empirical calculation of the molecular rotations for the proposed structures. The molecular rotation ( $[\text{M}]_D$ ) of a compound is defined as its specific rotation  $\times$  molecular weight/100.

Empirical rules for predicting optical rotation were first proposed by Whiffen<sup>24</sup> who, applying van't Hoff's principle of optical superposition<sup>25</sup>, related rotatory power to the dihedral angle between adjacent substituents. Whiffen postulated that optical rotation was related to the sine of the dihedral angle<sup>26</sup>.

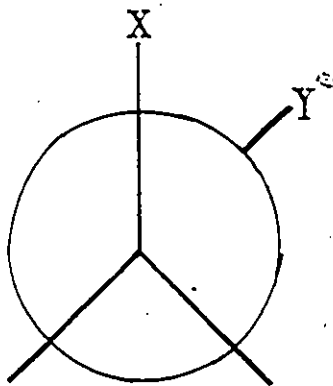
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<sup>24</sup>" In a compound with two or more asymmetric carbon atoms the optical activities of the individual atoms may be added algebraically"<sup>27</sup>. While fundamentally unsound, this postulate is used as a first-order approximation by Whiffen. van't Hoff's ideas on stereochemistry were, incidentally, questioned as early as 1877. Hermann Kolbe, one of the most eminent organic chemists of that time, wrote<sup>28</sup> " Will anyone to whom my worries may seem exaggerated please read, if he can, a recent memoir by a Herr van't Hoff on The Arrangement of Atoms in Space, a document crammed to the hilt with the outpourings of a childish fantasy. This Dr. J.H. van't Hoff, employed by the Veterinary College at Utrecht has, so it seems, no taste for accurate chemical research. He finds it more convenient to mount his Pegasus ( evidently taken from the stables of the Veterinary College ) and to announce how, on his daring flight to Mount Parnassus, he saw the atoms arranged in space".

Brewster<sup>21</sup>, in 1959, expanded on Whiffen's suggestions. Lemieux and Martin<sup>22</sup> further refined the method's application to carbohydrate pyranosides. Finally, Angyal applied the technique to carbohydrate furanosides<sup>23</sup> where complexity is increased because of the increased conformational flexibility of the 5-membered rings<sup>24</sup>.

Since Brewster and Lemieux had simplified calculations by assuming "perfect" chair conformations and dihedral angles of  $60^\circ$ , Angyal modified their empirical constants by the sine of the dihedral angles. In all the techniques H/H (see below for notation) interactions are neglected. The dihedral angles used by Angyal were those of the favored ring conformer as determined by nmr. This procedure was now applied to compounds 18-27 with some modification.

For a rotatory contributor (shown below) the following notation was used.



If, looking down the Cx-Cy bond, Y is to the right of X in the Newman projection, then the contribution is considered positive and is denoted X/Y. The dihedral angle is estimated from molecular models ( in the conformation indicated by nmr ) and the modified contributor denoted X/Y( $\theta$ ). From Angyal we see the three basic contributors are C/C, O/C and O/O with values 46°, 58°, and 52° respectively. For the purposes of these calculations, no differentiation was made for bridging atoms other than carbon ( Lémieux's O/Co and C/Co ).

Deviating from Angyal and his predecessors, no special value was chosen for the interaction of the glycosidic methyl group and the ring oxygen. Instead, conformational preferences were sometimes assumed for these and for the disposition of the hydroxyl of the branching hydroxymethyl. No further assumptions about conformation were made other than those inferred by the <sup>1</sup>H-nmr coupling data. In addition, dihedral angles were estimated only to the nearest multiple of 15°. Contributions for X/Y(0°) and X/Y(180°) were not recorded for obvious reasons. Calculations are shown below for compound 26, with the remainder being relegated to the Appendix.

Compound 26 was assumed on the basis of the <sup>1</sup>H-nmr data to be the  $\alpha$ -L-arabino isomer occupying, preferentially, the <sup>3</sup>T<sub>0</sub> form.

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\* These are Angyal's values<sup>23</sup> multiplied by sine <sup>-1</sup>(60°)

Looking down the bonds indicated in Table 3 and proceeding clockwise around the ring, the following contributions were calculated.

bond	Contributors	Contributions	Total
C-1 - O-r	-C/C(30)-O/C(90)	+23-58	-35
C-2 - C-1	-O/C(15)+C/O(105)+O/O(120)-O/O(135)	-15+56+45-37	+49
C-3 - C-2	-C/C(30)+C/O(90)-C/C(135)-C/O(135)	-23+58-33-41	-39
C-4 - C-3	-O/C(45)+O/C(165)+C/C(165)-C/C(90)	-41+15+12-46	-60
O-4 - C-4	-C/C(45)-C/C(165)	-33-12	-45
O-1 - C-1	see discussion	-50	-50
C-3' - C-3	see discussion		0

Table 3

The remarkable correlation between  $[M]_D$  calc and  $[M]_D$  obs ( $-182.1^\circ$ ) is, of course due to the arbitrary assignment of the O-1 - C-1 and C-3' - C-3 contributions. The former was assigned on the assumption that the O-CH<sub>3</sub> will adopt an orientation away from C-2 and the center of the ring. This situation is found in the pyranoses<sup>22</sup> and should apply equally in these cases. This orientation should lead to a contribution of  $-50^\circ$ . The hydroxymethyl, on the other hand, is known to rotate rather freely and its rotary contributors

should cancel unless there is bias due to solvation or intramolecular hydrogen bonding. Since the latter is not possible in this molecule and the former is minimized by the chloroform solvent, the expected contribution to the rotatory power should be near zero.

Regardless of the validity of the aforementioned assumptions, the utility of the empirical calculations is in comparison of the results obtained for both branch-point epimers of the compound in question. Although inconsistent with the proton nmr coupling data the molecular rotation of the epimeric  $\alpha$ -L -lyxo compound was calculated. The most stable conformation was estimated using Angyal's<sup>22</sup> criteria and was found to be  $^3T_2$ . This gives a result of  $-63^\circ$ , which is based on the same assumptions as those made for 26. If, however, one assumes a conformational bias due to H-bonding between OH-3' and OH-2 then a factor of up to  $-60^\circ$  would be introduced. It should be noted that, due to the inherent chirality of the  $^3T_2$  conformer, Angyal suggests a correction factor of  $-25^\circ$ . This would make the calculated rotation  $-148^\circ$ . One can see then, that the  $\alpha$ -L -lyxo configuration is inconsistent with the observed optical rotation as well as the  $^1H$ -nmr data.

As with the  $^1H$ -nmr data, the rotation calculations for 28 are not clear-cut. The  $\alpha$ -D -ribo isomer in the  $^0E$  conformation is predicted to have a molecular rotation of  $+126^\circ$  without H-bonding. With conformational bias the

maximum expected value would be  $+155^\circ$ . The  $^0T_4$  conformation would be expected to show rotations of  $+109^\circ$  and  $+138^\circ$  for the biased and unbiased forms respectively. Due to steric crowding, even without H-bonding the hydroxymethyl may suffer substantial conformational bias. If this were the case, then it would add a small positive contribution to the calculated values.

On the other hand, the  $\alpha$ -D -xylo epimer in the  $^2E$  conformation ( figure 1 ) gives a value of  $+267^\circ$ . This agrees very well with the observed value of  $+263^\circ$  and leads one to reconsider the -xylo configuration as a structural possibility.

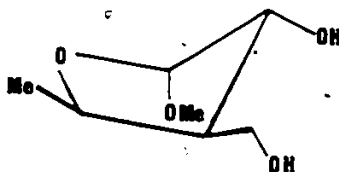


figure 1

The vicinal dihedral angles derived from the  $^1\text{H}$ -nmr data ( $\Phi_{1,2} \approx 30^\circ$ ,  $\Phi_{2,3} \approx 25^\circ$ ,  $\Phi_{3,4} \approx 120^\circ$ ) imply for 24, the  $\alpha$ -D- ribo configuration in the  ${}^3\text{T}_2 \rightleftharpoons \text{E}_2$  segment of the pseudorotational itinerary. Calculation of the rotation for the former conformer gives a value of  $+148^\circ$  if one considers that intramolecular H-bonding between OH-2' and OH-3 may be present. Free rotation of the hydroxymethyl would lower the calculated value to  $+133^\circ$ . If one considers Angyal's assumption that all values obtained for  ${}^3\text{T}_2$  conformers are too high by approximately  $25^\circ$  then the corrected values (with and without H-bonding) would be  $+123^\circ$  and  $+88^\circ$  respectively. Neither agrees very well with the observed value of  $+191^\circ$ . A non H-bonded hydroxymethyl in a staggered disposition would add a  $+C/O(60)$  contribution of  $50^\circ$  making the calculated value  $+183^\circ$  which is somewhat closer to the experimental result.

The nmr data are, however, also consistent with the  ${}^2\text{E}$  conformation and that form, with a freely rotating hydroxymethyl adopting a staggered conformation, is expected to show a rotation of  $+198^\circ$  which is in better agreement with the experimental result.

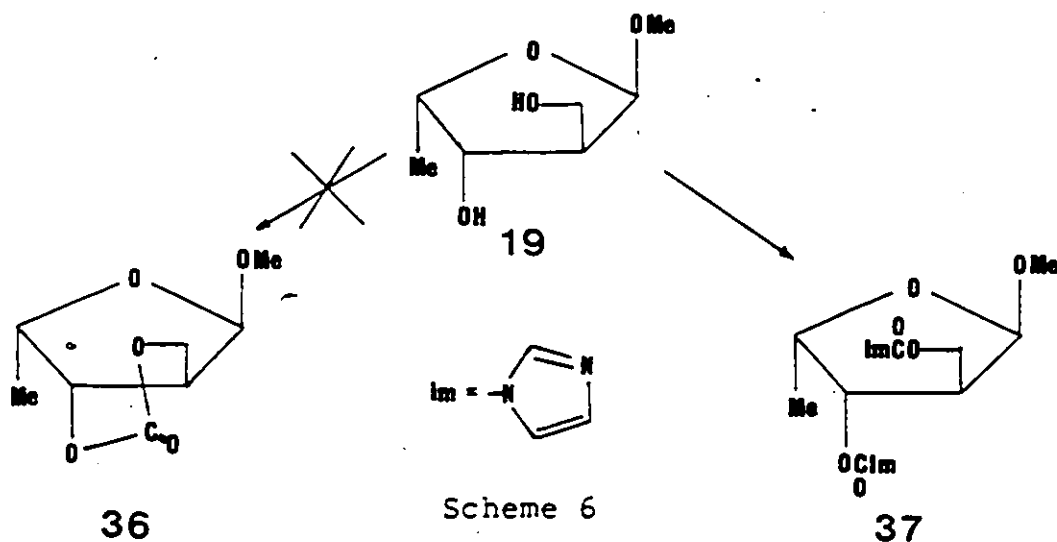
The  $\alpha$ -D -arabino epimer in the most staggered conformation ( ${}^2\text{E}$ ) has a predicted rotation of  $+106^\circ$  and, therefore, seems an unlikely possibility.

Finally, the most contentious isomer 21 is dealt with. As mentioned, the  $^3J_{\text{H,H}}$ -coupling data support equally the  $\alpha$ -D-xylo and  $\alpha$ -D-lyxo configurations in the  $^2\text{E}$  and  $^3\text{E}$  conformations respectively. Calculation of  $[\text{M}]_{\text{D}}$  for each furnishes  $+183^\circ$  for the former and  $+80^\circ$  for the latter. Neither considers the  $\text{CH}_2\text{OH}$  bias which should be minimal in the former and should contribute only a small positive contribution in the latter. If we consider the closely related  $^2\text{T}_3$  conformer for the  $\alpha$ -D-xylo configuration, we get a value for  $[\text{M}]_{\text{D}}$  calc of  $+203^\circ$ . Now, if we assume a staggered hydroxymethyl (since intramolecular H-bonding is not possible) we can add a maximum contribution of  $50^\circ$  (C/O(60)) to the calculated result. Applying Angyal's correction factor for this conformation, we get a final result of  $+278^\circ$  which is in good accord with the observed result of  $+281^\circ$  ( $-283^\circ$  for the L-enantiomer). This, in addition to the  $^{13}\text{C}$ -nmr data previously mentioned, further supports the choice of formula 21 as the correct stereochemistry.

It should be obvious to the reader that all of the above calculations contain substantial arbitrary contributions. The models are also over-simplified by the use of one conformer rather than an average (perhaps weighted) of several. The combined effects of the two factors can easily produce an uncertainty of  $\pm 50^\circ$ . In the equivocal cases 21, 24 and 28 we can only say that the calculations may add some support to the structures chosen. Because neither the nmr

nor the optical rotation analyses resolved entirely the question of configuration, especially for compound 19 it was decided to attempt derivatization of one or more of the ring-contracted products. It was felt that a six-membered cyclic derivative would offer the advantage of conformational rigidity. The acid lability of the products limited the choice of derivative to one formed under neutral or alkaline conditions. The cyclic carbonate group was felt to be a suitable choice.

Compound 19 was treated with N,N- carbonyldiimidazole in refluxing benzene according to the method of Kutney<sup>34</sup>. After three hours a slightly slower spot on tlc had replaced that of the starting material. The material isolated proved not to be the carbonate 36 but rather the bis-carbamate 37 (Scheme 6).



The proton nmr spectrum ( 200 MHz ) showed three well resolved signals in the aromatic region. These were each of twice the intensity of the signals attributed to the ring protons ( H-1 to H-4 ). The rest of the spectrum was essentially unchanged. The coupling constants ( $J_{1,2} = 6.4\text{Hz}$ ,  $J_{2,3} = 4.3\text{ Hz}$ ,  $J_{3,4} = 5.1\text{ Hz}$ ) for the ring protons indicate the  ${}^2T_3$  conformation ( $\Phi_{1,2} = 60^\circ$ ,  $\Phi_{2,3} = 75^\circ$ ,  $\Phi_{3,4} = 70^\circ$ ). The reluctance to form a cyclic carbonate was further demonstrated when the carbamate was treated with water to see if it was perhaps a kinetic product and would cyclize after partial hydrolysis. The compound proved inert under these conditions.

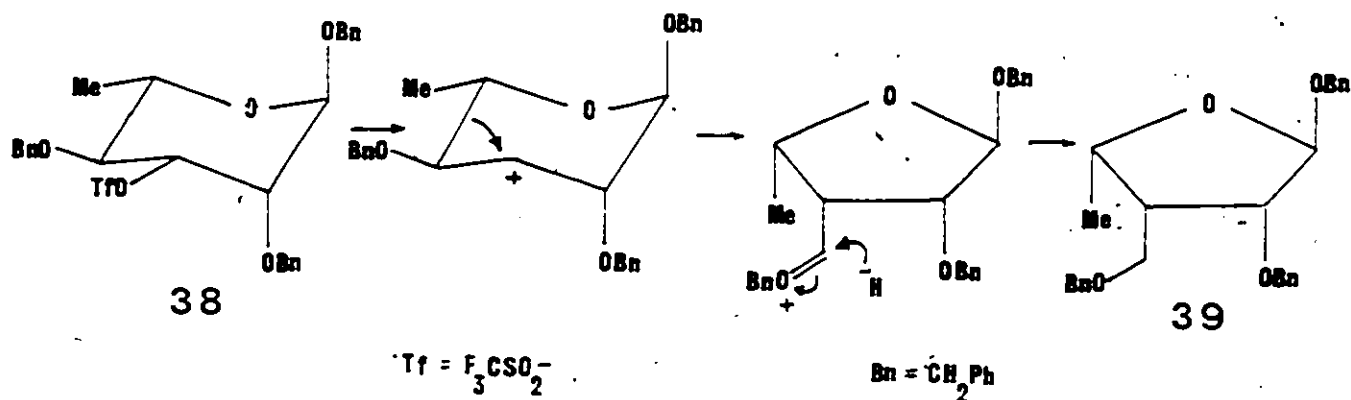
An attempt at benzylidenating a different ring-contracted derivative ( 24 ) did not prove successful.

No other derivatization experiments were undertaken. At this point, our investigations were directed towards resolution of the mechanistic questions surrounding the reaction. The results of our experimentation and of our musings are presented in the following section.

## Chapter V

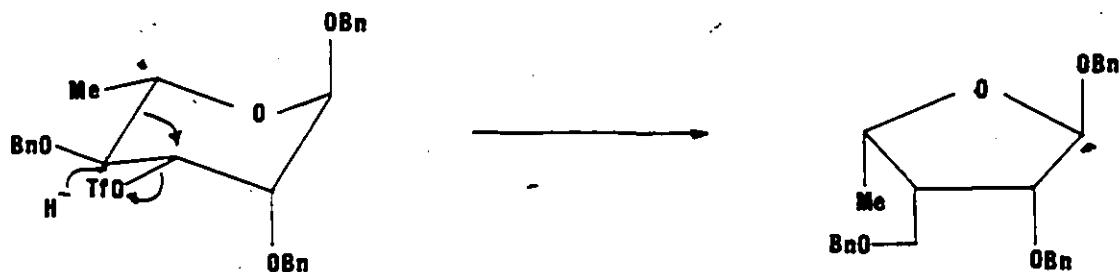
### MECHANISTIC CONSIDERATIONS

While this work was in progress, we became aware of a precedent for LTBH-mediated ring contraction in pyranosides. Pozsgay and Neszmélyi<sup>35</sup> obtained from benzyl 2,4-di-O-benzyl-3-O-trifluoromethylsulfonyl- $\alpha$ -L-rhamno-pyranoside ( 38 ) in 40% yield the ring-contracted product 39. They interpreted the reaction as being initiated by the departure of the sulfonyloxy group, to generate a pyranosid-3-yl carbocation that would rearrange by migration of the C-4 - C-5 bond ( which is antiparallel to the leaving group ), and the rearranged intermediate would then accept a hydride ion at the branch carbon atom, giving the 3-C-(benzyloxymethyl)-3-deoxypentofuranoside ( 39 ) as shown below ( Scheme 7 ).



Scheme 7

In a review article, Williams presented the following mechanism for this transformation ( Scheme 8 )<sup>26</sup> but without any explanation.

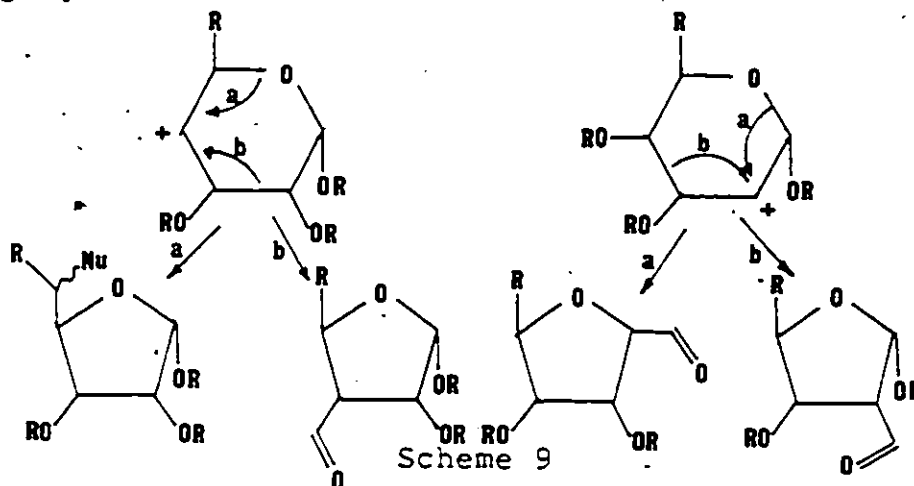


Scheme 8

Distinguishing between the two mechanisms should be easy. Lithium triethylborodeuteride ( LTBD ) should furnish a single diastereomer if the latter mechanism is at work or a mixture if the ionic mechanism occurs. This, however, is beyond the scope of this thesis.

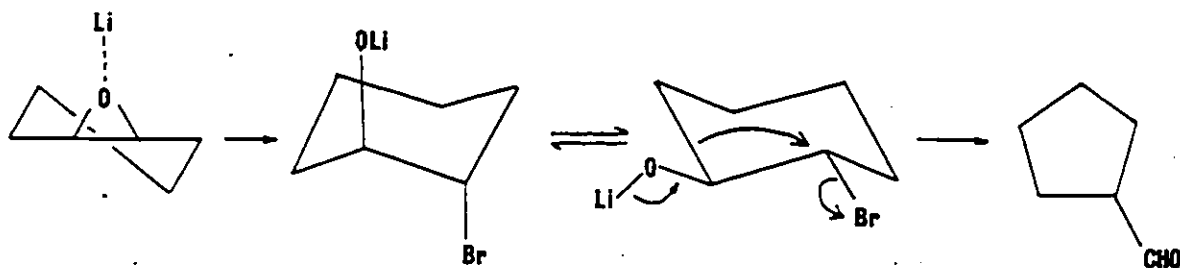
Whereas the cationic mechanism, which is supported by similar rearrangements occurring in solvolyses of pyranoside 3-O-sulfonates and in nitrous acid deamination of 3-amino sugars<sup>27</sup>, may well apply for 38, its operation in the present circumstances could not be confidently presumed, for two main reasons. First, for the 2- or 4-sulfonates studied here it would imply the development of a positive charge on C-2 or C-4, respectively. Although various examples of pyranosidic ring contraction involving incipient carbocations at those sites are indeed known, in the same domains of solvolysis and deamination<sup>27</sup>, the dominant course of rearrangement in these particular cases is by

participation of the ring oxygen atom, and alternative migrations of a  $\beta$ -carbon atom ( C-2 to  $\cdot$ C-4, or C-4 to  $\cdot$ C-2, Scheme 9 ) have been encountered only as subordinate events<sup>3,4</sup>.



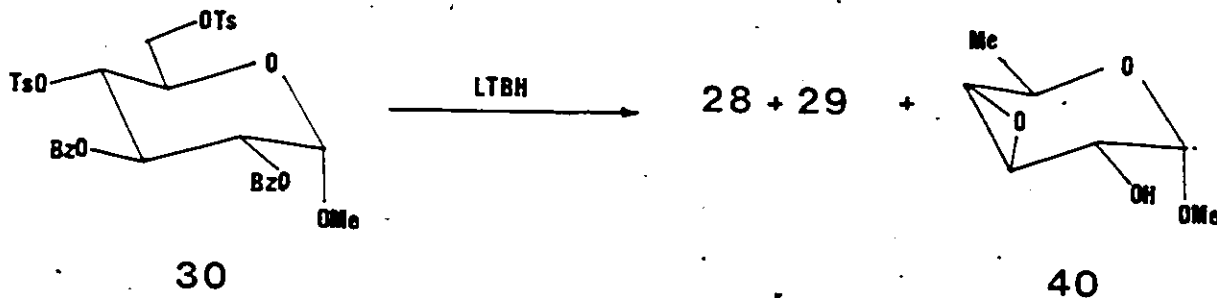
In the present study, no evidence for the formation of products originating from ring oxygen migration was found. Secondly, in contrast to 38, the glycosides considered here all contain, trans -vicinal to the sulfonate function, a free or potentially free ( i.e. esterified ) hydroxyl group which should play a key role in the observed reactions. Alcohols, including sugar hydroxyls, react instantly with alkali metal trialkylborohydrides to give hydrogen and alkoxytrialkylboronates<sup>5</sup>. As was seen earlier<sup>1,2</sup>, such boronates formed from tosylated sugars and LTBH can undergo internal displacement to produce epoxides, provided the proper geometry exists<sup>3</sup>. Although in the previous studies<sup>2</sup> the epoxides incurred ring opening with excess reductant as expected<sup>4</sup>, giving deoxyhexopyranosides, an intermediacy of epoxides in the ring contractions could not a priori be

ruled out. Epoxide-carbonyl rearrangements are known and, relevantly, are catalyzed by lithium salts<sup>41</sup>. (halides or perchlorate, Scheme 10 ).



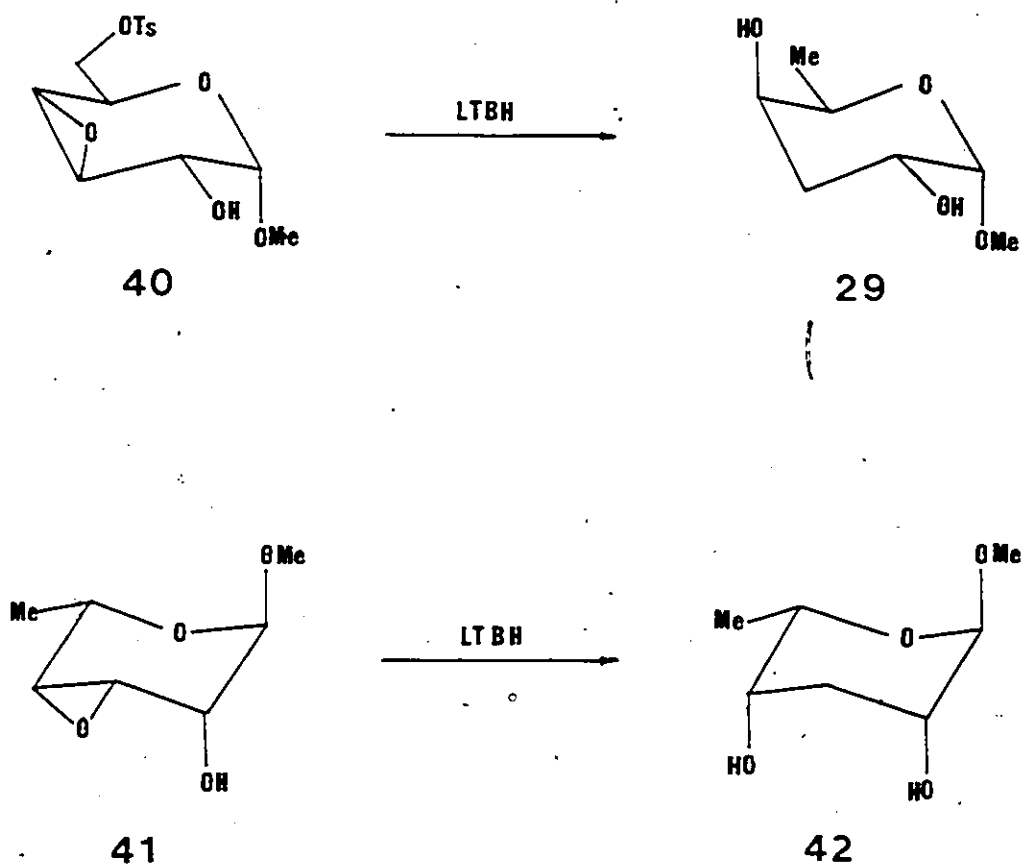
Scheme 10

Lithium tosylate produced in the epoxide-forming step ( and by C-6 reduction, where applicable ) might have induced rearrangement. In fact, when the ditosylate 30 was treated with an amount of LTBH insufficient for its complete conversion to the final products 28 and 29, the 3,4-anhydro-pyranoside 40 was isolated from the reaction mixture (Scheme 11).



Scheme 11

On the other hand, independently-synthesized 40 was rapidly ( 5 min. ) and almost quantitatively converted into 29 (isolated yield, 90% ), and no trace of 28 was detected. Similarly, the 3,4-anhydrohexopyranoside 41, obtainable from 25 by action of base, on treatment with LTBH under the same conditions gave methyl 3,6-dideoxy- $\alpha$ -L -lyxo -hexopyranoside ( 42 ), within 5 minutes and in virtually the same yield, and without formation of any 26 (Scheme 12).



Scheme 12

During the course of this work, new spectral data were obtained for compounds 29 and 42 ( Tables 4 and 5 ).

Table 4

<sup>1</sup>H Magnetic Resonance data for methyl dideoxyhexopyranosides<sup>1</sup>.

Chemical Shifts <sup>1</sup> (δ)										
Cmpd	H-1	H-2	H-3a	H-3e	H-4	H-5	C-Me	O-Me	Others	
<u>29</u>	4.68d	3.97 ddd	1.81dt	2.12 dddd'	3.73nt	3.89dq	1.21d	3.45s		
<u>29'</u>	5.07d	5.43m	2.50dt	2.32dt	5.37nt	4.24dq	1.26d	3.50s	8.34-8.19m aromatic	
<u>42</u>	4.62	3.69 nm'	2.02nm	(2H)	3.62 nm'	3.91q	1.26d	3.41s		
<u>42'</u>	4.79s	4.66 nm'	2.30dt	2.60dt	4.66 nm'	4.08m	1.33d	3.43	3.11s(Ms)	
Coupling Constants (Hz)										
	J <sub>1,2</sub>	J <sub>1,3e</sub>	J <sub>2,3a</sub>	J <sub>2,3e</sub>	J <sub>3,4gm</sub>	J <sub>3a,4</sub>	J <sub>3e,4</sub>	J <sub>4,5</sub>	J <sub>5,6</sub>	
<u>29</u>	3.7	1.3	12.2	4.6	13.0	2.9	3.5	1.4	6.6	
<u>29'</u>	3.2		12	4	13	3	4	1.4	6.6	
<u>42</u>	0				0				6.6	
<u>42'</u>	0		3.5	2.5	16.1	3.5	2.5		6.6	

(For footnotes, see continuation page)

1. From solutions in  $\text{CDCl}_3$  containing tetramethylsilane as the internal standard.
2. From 200-MHz spectra. Assignments were verified by  $sp$ -spin decoupling experiments. Signal multiplicities as in Table 1.
3. Visible after  $\text{D}_2\text{O}$  exchange.
4. di-O-(p-nitrobenzoyl)-derivative.
5. H-2 and H-4 assignments may be reverse.
6. di-O-methanesulfonyl derivative.
7. H-2 and H-4 signals coincided.
8. Small. †
9. Very small.

Table 5

<sup>13</sup>C Chemical Shifts for methyl 3,6-dideoxyhexopyranosides<sup>1</sup>

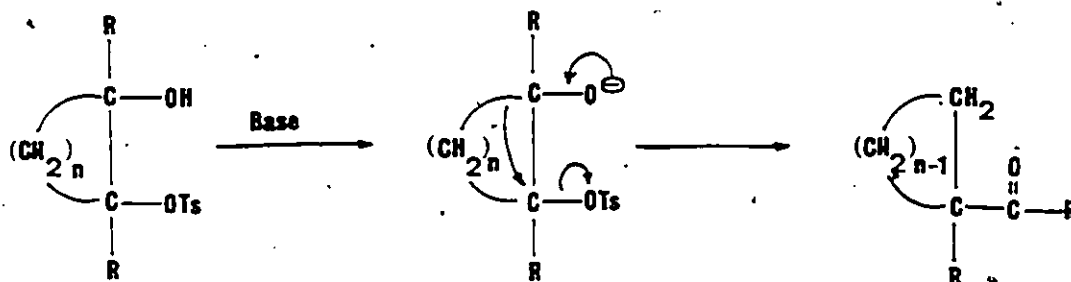
Cmpd	C-1	C-2	C-3	C-4	C-5	C-6	OCH <sub>3</sub>	Other
29	99.4	69.0	34.9	63.6	65.9	16.3	55.1	
24	96.7	72.6	28.7	68.2	64.7	16.4	55.5	164.1, 150.8, 135.2 135.1, 130.9 (2) 123.7, 123.6 (Arom.)
42	101.1	68.0	31.3	66.2	66.6	17.0	54.9	
42	98.0	74.1	29.6	71.1	64.4	16.8	55.3	38.8

1. From 20-MHz spectra, obtained with a Varian FT-80 spectrometer, for solutions in CDCl<sub>3</sub> containing TMS as the internal standard.
2. di-O-(p-nitrobenzoyl)-derivative.
3. C-4 and C-5 assignments may be reversed
4. di-O-methanesulfonyl-derivative.

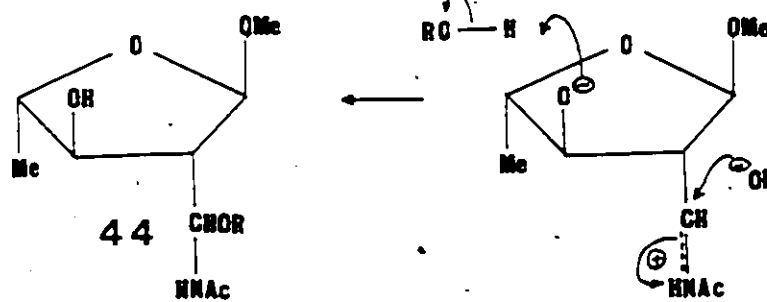
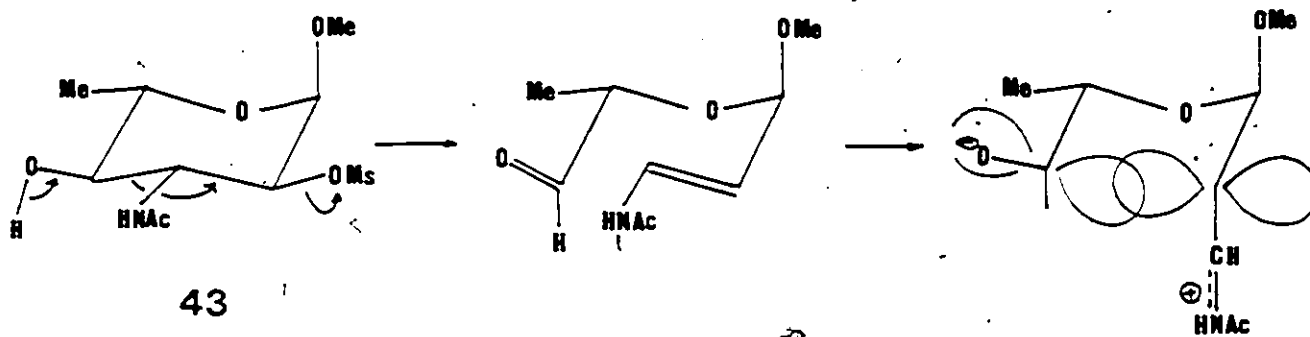
There was no discernible difference between the reactions of 40 and 41, and lithium tosylate engendered during the reaction was shown to be without influence. This was done by treating a model compound, cyclohexene oxide, with lithium tosylate<sup>42</sup> in boiling oxolane. Aliquots were frequently withdrawn and infrared spectra of them taken to try and detect aldehyde from the ring-contracted product, cyclopentane carboxaldehyde. At no time was carbonyl absorption detected.

In order to check whether or not the triethylborane, released<sup>43</sup> during the reaction with LTBH was involved, compound 41 was heated, in refluxing oxolane, with five equivalents of triethylborane in refluxing oxolane for 36 hours. No reaction was apparent. We therefore concluded, on the basis of the aforementioned experiments, that epoxides, where they do arise, are precursors for the unrearranged minor products ( 29, 35, and possibly others that escaped detection ) but not for the ring-contracted furanosides, the formation of which must occur by some other mechanism.

Two other plausible mechanistic possibilities exist. They are the base-induced "pinacol-type"<sup>44</sup> rearrangement of 1,2-glycol monotosylates ( Scheme 13 ) and a mechanism proposed by Jary and coworkers<sup>45</sup> for similar ring contractions observed in mesylated 3-acetamidopyranosides (Scheme 14 ). We favor the former.



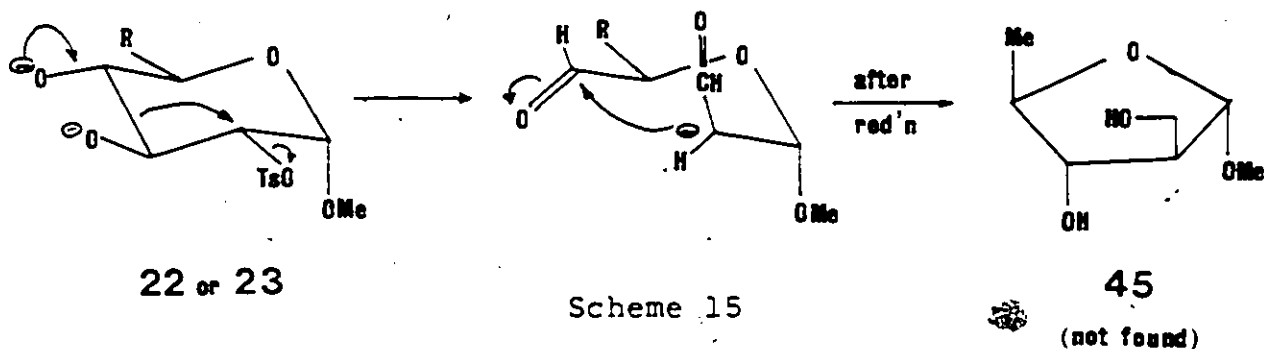
Scheme 13



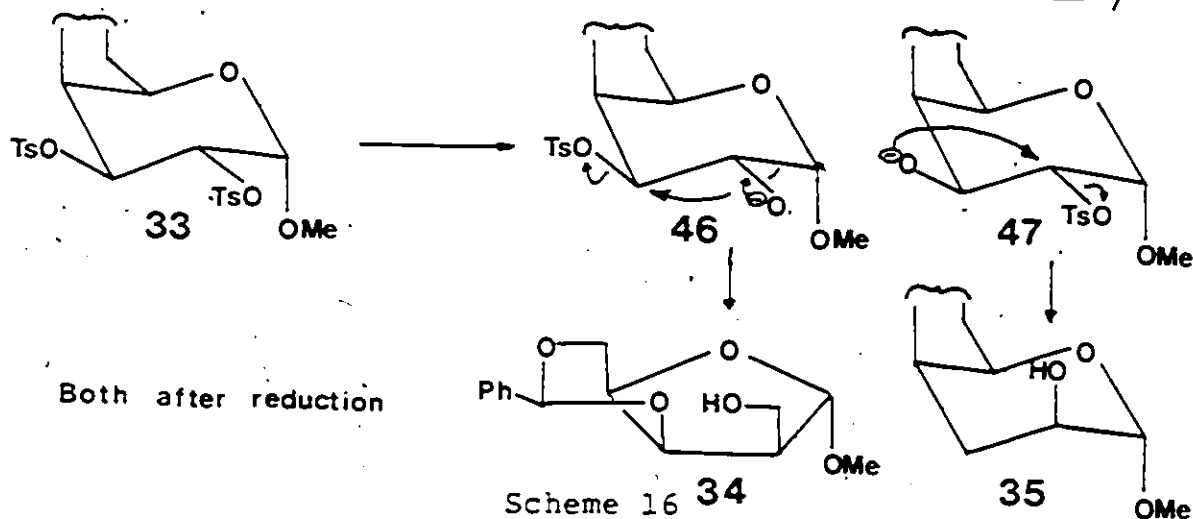
Scheme 14

Jarý's mechanism was postulated, primarily, on the basis of product and starting material stereochemistry. The authors established the necessity of a free hydroxyl at position 4 by studying blocked derivatives.

Regardless of the virtues of the mechanism in their case, it is probably not involved in the LTBH -induced ring contractions. The formation of 34 from 33 clearly defies this mechanism. The latter transformation can, however, be explained by the pinacol-type mechanism ( see below ). A second, more important , factor militating against the application of Jarý's mechanism in the LTBH case is the observed stereochemistry of the products. Were the Czechoslovak workers' mechanism at work, then 22 or 23, being in direct analogy with 43, would be expected to furnish the arabino isomer 45 ( Scheme 15<sub>g</sub> ). Likewise, in 20, 25, 27, 30 and 32, the branch -point stereochemistry would also be inverted.



It should be noted that the benzylidened furanoside 34, from the ditosyl galactopyranoside derivative 33, has branch-point stereochemistry opposite to that of the other compounds. This can, however, be rationalized in terms of a pinacol-type ring contraction in the opposite sense, that is, migration of the C-1--C-2 bond ( Scheme 16 ). Initial partial desulfonylation ( with little discrimination between O-2 and O-3 ) would furnish the monotosylates 46 and 47.



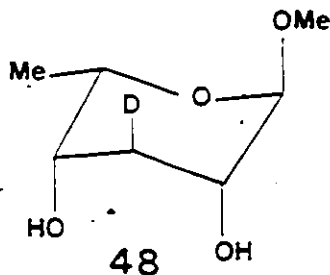
The former can then rearrange to 34, as shown, while the latter may yield, via epoxide, the 3-deoxy-hexopyranoside derivative 35. Compound 36 obviously results from two-fold desulfonylation.

One common feature of both the pinacol-type and Jarý's mechanism is the formation of an intermediate carbonyl compound. Such an intermediate was never detected by tlc or during incomplete reactions. Evidently, its reduction to hydroxymethyl must be very fast compared to the actual ring-contraction. It was felt, however, that use of LTBD

would establish the intermediacy of a carbonyl species by furnishing a product deuterated in the hydroxymethyl group.

Three separate trials were undertaken in which methyl 4-O-tosyl- $\alpha$ -L-rhamnopyranoside (25), a compound shown to give only ring-contraction product under the influence of LTBH, was treated with LTBD in refluxing oxolane. Much to our surprise, the only product isolated in all three cases was the deuterated pyranoside 48. The  $^{13}\text{C}$ -nmr spectra, both fully and partially spin-decoupled, were completely superimposable on those of the non-deuterated derivative 42 with the exception that the signal attributed to C-3 (30.88 ppm) was split into three by coupling with deuterium ( $I=1$ ).

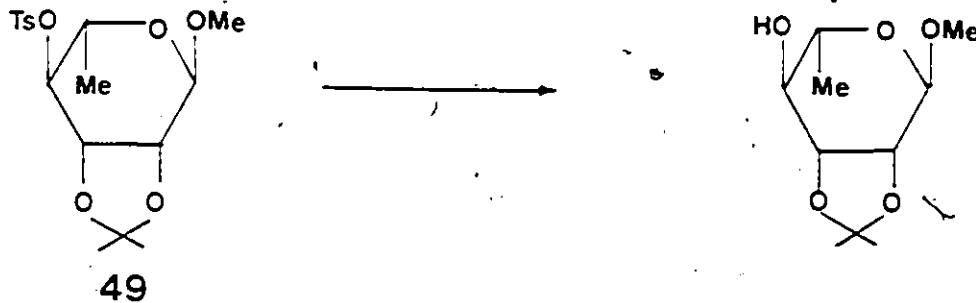
Clearly, 25 had reacted by way of epoxide 41. We can, at present, offer no explanation for the peculiar results, and we are not aware of any literature precedent for such a divergence in the action of a reagent and its deuterio analog. The matter was not further pursued.



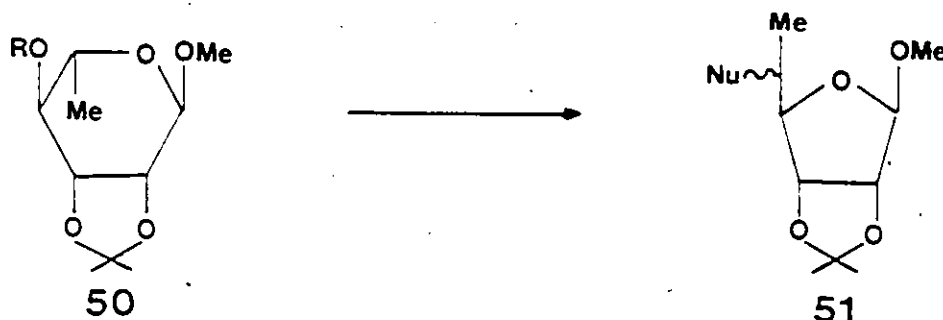
\*Dr. W. Dahlhoff, of the Max Planck Institut für Kohlenforschung, Mühlheim, Germany, informed us that similar, unexplained, phenomena with respect to LTBH vs. LTBD have occasionally been encountered in that laboratory's extensive research on organoboron chemistry. They suspect that traces of heavy metal contaminants present in the reagent batches, depending on the mode of manufacture, are responsible for catalytic effects profoundly altering reactivity. However, they do not assert to have proof for this. (Personal communication, July 1984.)

Concurrent with the aforementioned studies were a number of investigations with blocked model compounds. While not entirely conclusive, they were informative and the results are presented below.

Methyl 2,3-O-isopropylidene-4-O-tosyl- $\alpha$ -L-rhamno-pyranoside ( 49 ), a direct precursor to 25 used above, was treated with LTBH. Not surprisingly, after twenty hours of boiling the only product observed was that of O-S fission (shown below ).

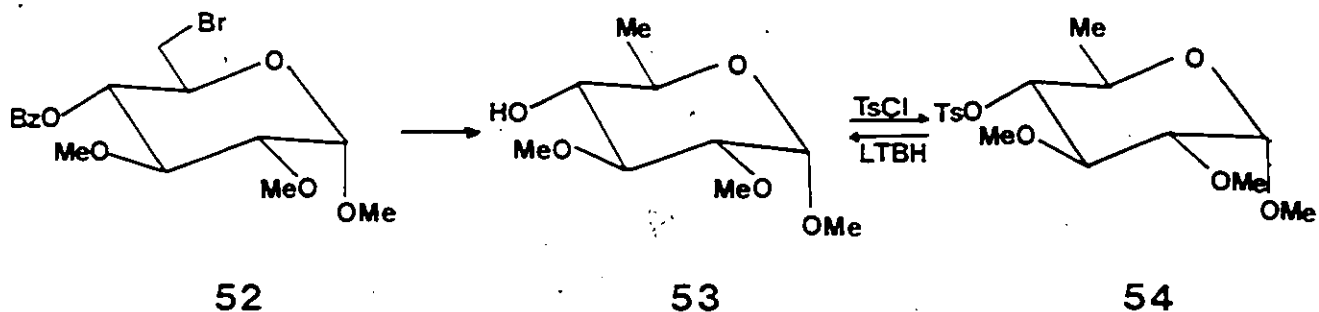


That ring contraction did not occur was further, strong evidence against the cationic ( solvolytic type ) mechanism since the solvolysis of analogue 50 has been shown to furnish a ring-contracted product ( 51 )<sup>44</sup>.



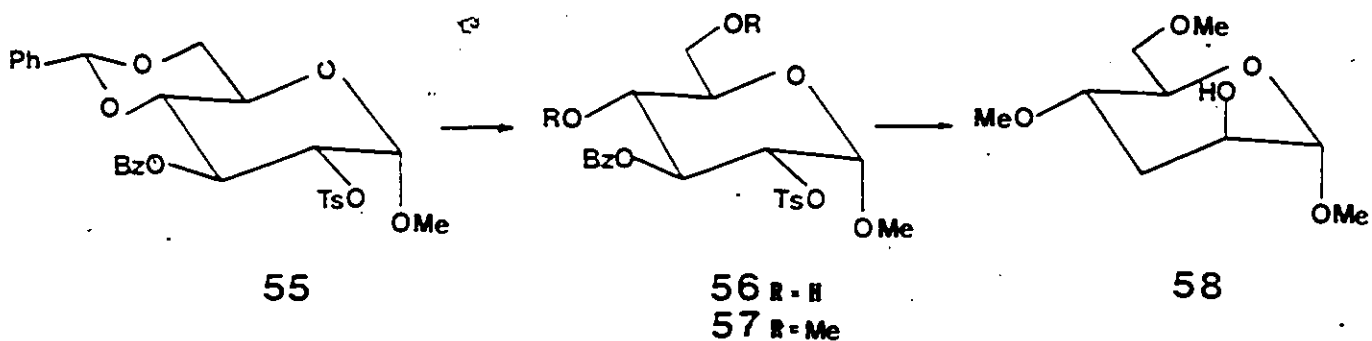
(, Actually performed in the D-series )

Furthermore, the glucoside derivative 54, prepared from 52 by the sequence shown below ( Scheme 17 ) provided only the S-O fission product 53.



Scheme 17

This clearly indicated that a free hydroxyl adjacent to the sulfonyl group is a necessary condition for ring contraction. However, it is not a sufficient condition, as the next experiment revealed ( Scheme 18 ). The partially methylated compound 57, which has a benzoylated ( *i.e.* a potentially free ) hydroxyl function trans-vicinal to a sulfonic ester group, was prepared by methylation of the diol 56 ( by use of diazomethane-boron trifluoride etherate ); the diol had been obtained by hydrolysis, with 80% acetic acid, of the known benzylidene acetal 55 .

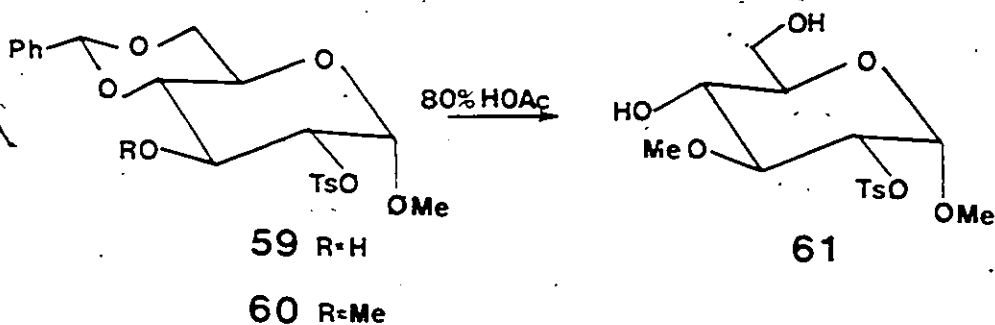


Scheme 18

Treatment of 284 mg of the methylated compound 57 gave, after processing, 30 mg of a chromatographically homogeneous colorless syrup. Other fractions (see the Experimental Section) contained principally the same product as well as others not successfully isolated even with chromatography. The proton-nmr spectrum ( 200 MHz ) of the pure fraction was sufficient to show it to be the 3-deoxy compound 58. The illuminative features of the spectrum were two, well resolved, signals at 2.26 ppm and 1.73 ppm attributed to H-3e and H-3a respectively. The former was a doublet of triplets with  $J_{2,3e} = J_{3e,4} = 3$  Hz and  $J_{2em} = 10$  Hz. The latter signal was a triplet of doublets with  $J_{3a,4} = J_{2em}$  and  $J_{2,3a} = 3$  Hz. The signal for H-1 appeared as a broad singlet at 4.58 ppm while H-2 was a narrow quartet at 3.86 ppm. The remaining signals, for H-4 and H-5, were buried under extraneous signals in the 3.4-3.7 ppm range. The three methoxyls gave rise to well resolved singlets at 3.35, 3.41 and 3.43 ppm.

According to the pinacol-type mechanism, expected to be applicable in these cases too, compound 57 should have undergone ring-contraction. Perhaps the extraneous signals in the nmr spectrum or the additional tlc spot shown by the mixed fractions were indeed due to ring-contraction product. In any case, the predominance of 58 was noteworthy and will receive comment in a subsequent section.

To see if the hydroxyl group in the 4-position of the 2-tosylates was involved in the reaction, we undertook the synthesis of 61. Methylation of the benzylidenated derivative 59 " using Kühn conditions" gave the known<sup>2</sup> compound 60 ( Scheme 19 ). Hydrolysis of the benzylidene group was effected with 80% acetic acid.

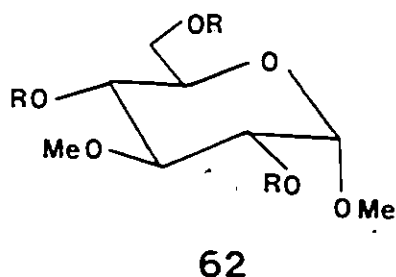


Scheme 19

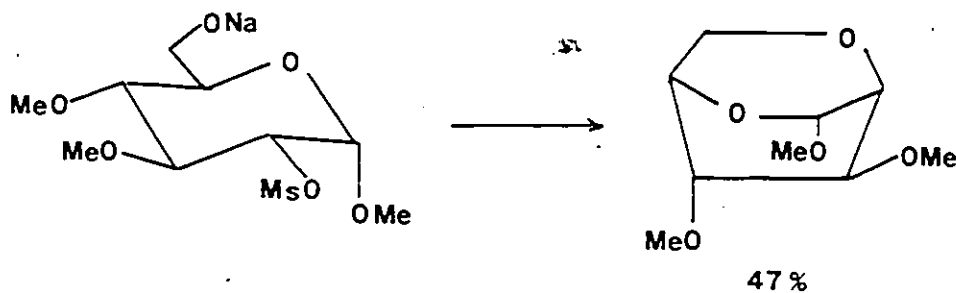
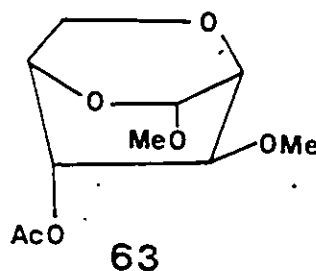
The diol ( 61 ) was then treated with LTBH in refluxing oxolane for five hours. The excess reagent was destroyed with methanol as usual ( see Experimental Section ) then acetic anhydride was added dropwise and the resultant solution allowed to stir one hour at ice-bath temperature. After extractive work-up and chromatographic purification 188 mg of material were obtained.

It was immediately evident from the nmr spectra ( both proton and carbon ), that the tosyl group was no longer present. It was also evident that only one acetyl group was present in the molecule. ( The fully decoupled  $^{13}\text{C}$ -nmr spectrum showed a single peak at 21.07 ppm ). There was absolutely no indication of the presence of a methinic center which would have arisen, as a branch-point carbon, had ring-contraction occurred. There was also no evidence for a methylenic center indicative of direct sulfonyl displacement. The remaining signals in the  $^{13}\text{C}$  spectrum fitted an acetylated, monomethylated, pyranosidic structure. The  $^1\text{H}$ -nmr spectrum, taken some days later, yielded little additional information as it was of poor quality due to heavy contamination with products of decomposition which had increased with time. No further studies could be undertaken with the product because of its deterioration. Nevertheless, the available spectral data allow the following speculation regarding the structure. If a simple O-desulfonylation had taken place, the resultant 3-O-methylglucoside should have been expected to take up more than one acetyl group, or in the case of actual monoacetylation, it should have given a regioisomeric mixture of spectroscopically differing monoacetates ( 62 where one R is Ac and the others, H ). However, the formation of a single monoacetyl derivative from the product of LTBH treatment of 61 would accord a structure ( 63 ) arising from intramolecular tosyloxy displacement by attack

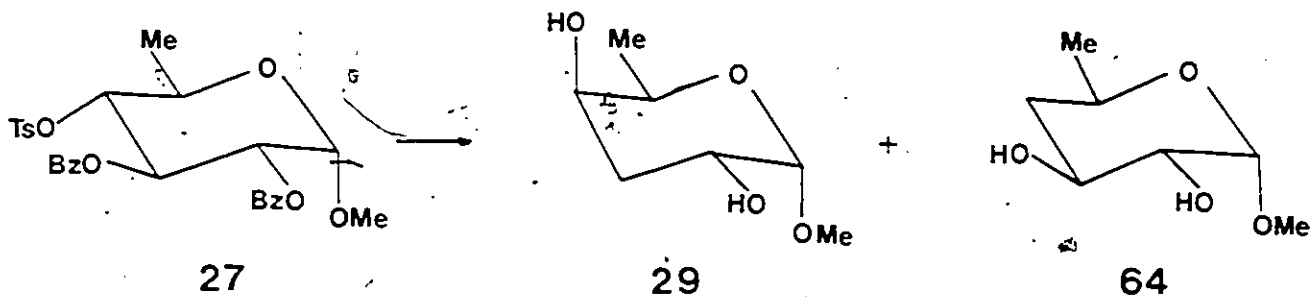
of the alkoxide ion generated from OH-6. An analogous displacement has indeed been reported<sup>33</sup> (Scheme 20). Although the complete structure of the product obtained from 61 was not secured, it was not deemed necessary to pursue its full determination, the partial structural data having revealed the absence of ring contraction in this reaction. This is a further point of evidence against Jarý's mechanism operating in the LTBH-induced ring contractions, but it is not conclusive insofar as the internal displacement (assuming it was real) could have been a more favored process, preempting possible ring contraction. The experiment should be repeated with the 6-deoxy or 6-O-methyl derivative of 61.



For R see text



The final series of experiments directly related to the elucidation of the reaction mechanism were to determine the effects, if any, of the alkali metal counteraction and of the trialkylborane structure. When compound 27 was treated with sodium triethylborohydride ( 1 M solution in oxolane ), methyl abequoside ( 29 ) was formed after 30 min. The proton-nmr and tlc of the reaction product both showed the presence of a second, apparently isomeric, carbohydrate compound. The latter disappeared on treatment of the mixture with aqueous sodium metaperiodate, thereby implying that it was the 4,6-dideoxyglycoside 64, arising from anti-Fürst-Plattner opening of the intermediary epoxide ( Scheme 21 ).



Scheme 21

\*Professor R. Köster of the Max Planck Institut für Kohlenforschung has determined the stoichiometry of the reaction of LTBH with compounds 25 and 27. The former diol was found to consume three equivalents of hydride reagent with the evolution of two equivalents of gas. The dibenzoate 27 consumed five equivalents of reagent with no gas evolution ( two equivalents each for the benzoates ). The additional equivalent of reagent in both cases presumably displaced the tosyl group ( with or without ring contraction ). No untoward reactions were noted nor did the results imply anything but normal hydride displacement reactions. We are indebted to Prof. Köster for the performance of these experiments.

No ring-contraction product was observed. Likewise, when methyl 4-O-tosyl- $\alpha$ -L-rhamnopyranoside ( 25 ) was treated with LTBH in the presence of 12-crown-4 ( to sequester the lithium ), the epoxide-derived compound 42 was the sole product. These results strongly implicated an involvement of the lithium counteraction although its direct role in the pinacol-type mechanism we favor is not immediately apparent.

Further complicating matters, it was found that L-selectride(R) ( lithium tris(sec-butyl)borohydride, 1 M solution in oxolane, (R) Aldrich Chemical Company ), acting on 25 also furnished the "epoxide product" exclusively. It seemed, therefore, that the ring contraction was specific to lithium triethylborohydride.

Several related questions now await answers. Can the experimental results just mentioned be reconciled with the pinacol-type mechanism or do they suggest a different one? Why does ring contraction occur at all, instead of the "normal" epoxide formation that had been expected at the outset? And why were mixtures of two types of products obtained in the cases of 6-substituted glycosides 30-32?

Careful consideration of the stereochemical requirements for the two reactions ( ring-contraction and epoxide formation ) sheds light on the subject. For the ensuing discussion, the two processes must be viewed as competitive events. That is to say, they are both irreversible, and the molecule has the "choice" between the two pathways. It will

prefer the route on which the rate-controlling step is of lower energy.

It is evident that epoxide formation is normally the favored pathway with trans monosulfonyl glycols as it is well established that a wide variety of bases effect this transformation. Ring contraction must then occur when epoxide formation is precluded. Lithium triethylborohydride appears to be an agent that can do this.

It is known that the ease of epoxide formation, by intramolecular displacement of a sulfonate, is related to the ease in attaining the coplanarity required in the  $S_N2$  transition state. This is influenced by the geometry of the starting material, due to "1,3-diaxial interactions in the transition state" and "passing interactions" encountered in the conformational changes necessary to the attainment of the transition state... Since all the compounds that underwent ring-contraction had a diequatorial disposition of the vicinal hydroxyl/sulfonate array in the favored chair conformation, all require significant conformational changes to undergo intramolecular tosyl displacement. The alkylboronates formed by interaction of the sugar with  $LTBH$  might, by virtue of their steric bulk, inhibit the conformational changes required owing to both the "passing" and 1,3-diaxial interactions.

Methyl 2- O -tosyl- $\alpha$ -D-fucopyranoside ( 20 ) will be presented as an example. Similar arguments would apply for the other isomers. The most stable conformer of 20 is the  ${}^4C_1$  chair conformation ( figure 2 ).

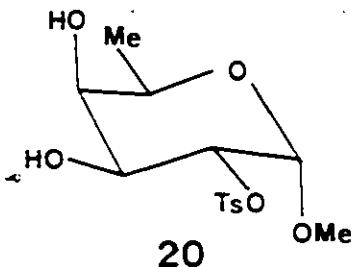


figure 2

This renders the anomeric methoxyl axial ( favorable because of the anomeric effect ) while having the majority of the remaining ring substituents equatorial. In order to achieve an antiperiplanar arrangement of the attacking oxygen atom and the departing sulfonyloxy group for forming epoxide, the molecule must invert conformationally and adopt either the  ${}^1C_4$  chair form ( Figure 3 ) or a skew form ( twist boat, Figure 4 ), at considerable expense in energy because of increased non-bonding interactions.

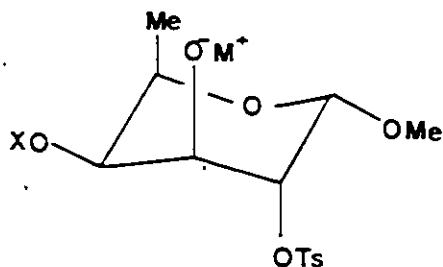


Figure 3

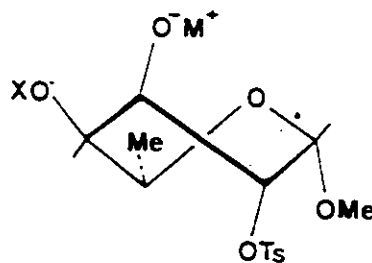


Figure 4

syn-Diaxial substituent interactions, bond eclipsing, and the anomeric and  $\Delta_2$  effects are contributing factors. Complexing of hydroxyl groups as alkoxytriethylboronates, which occurs upon reaction with LTBH, will much increase their bulk and consequently, the steric interactions. The barrier for inversion of the chair to the skew form ( 10.8 kcal/mole for cyclohexane ), which stems from the need for going through an intermediary half-chair with severe bond eclipsing, is thus increased considerably ( passing interactions ). The same considerations apply analogously to the other hexopyranoside tosylates here studied.

With conformational change greatly inhibited, the energy of activation for epoxide formation may now be higher than for an alternate pathway which involves the ground state chair conformation, that is, ring-contraction through intramolecular displacement of the tosyloxy group by migration of a carbon-carbon bond ( C-2—C-4 or C-4—C-3 ) which is antiperiplanar to the leaving group. This is the pinacol-type mechanism previously proposed. However, it appears that some unique property of the LTBH reagent further facilitates this reaction, which does not take place in the absence of lithium ion, nor when the boron bears *s*-butyl instead of ethyl groups ( see page 55/56 ).

The question of why do the 6-substituted compounds 30-32 furnish mixtures of ring-contracted and epoxide-mediated products now arises ( Scheme 4 page 13 ). Perhaps the change

from the electron-donating methyl group on C-5 in 27 to electron-withdrawing chloro- or tosyloxy-methyl groups in 30-32 is causing this retardation, by inductively rendering more difficult the development of positive charge on C-4. This holds as long as the C-6 substituents are still in place; as they are progressively removed by reduction, the ring contraction process would gain prevalence.

As mentioned previously ( page 47 ), the ring-contraction and " epoxide " products 34 and 35, respectively, are believed to arise after partial desulfonylation of the 4,6-O-benzylidenegalactoside 33 at the 2- and 3-positions, respectively ( Scheme 22 ). It is not immediately evident why the intermediary 3-sulfonate 46 undergoes ring-contraction and not epoxide formation, and why for the 2-tosylate 47 the reverse is true.

Let us first attempt to answer the second part of this question. The geometry of the pyranoside ring of 47 is the same as that of the fucoside 20 which behaved in the

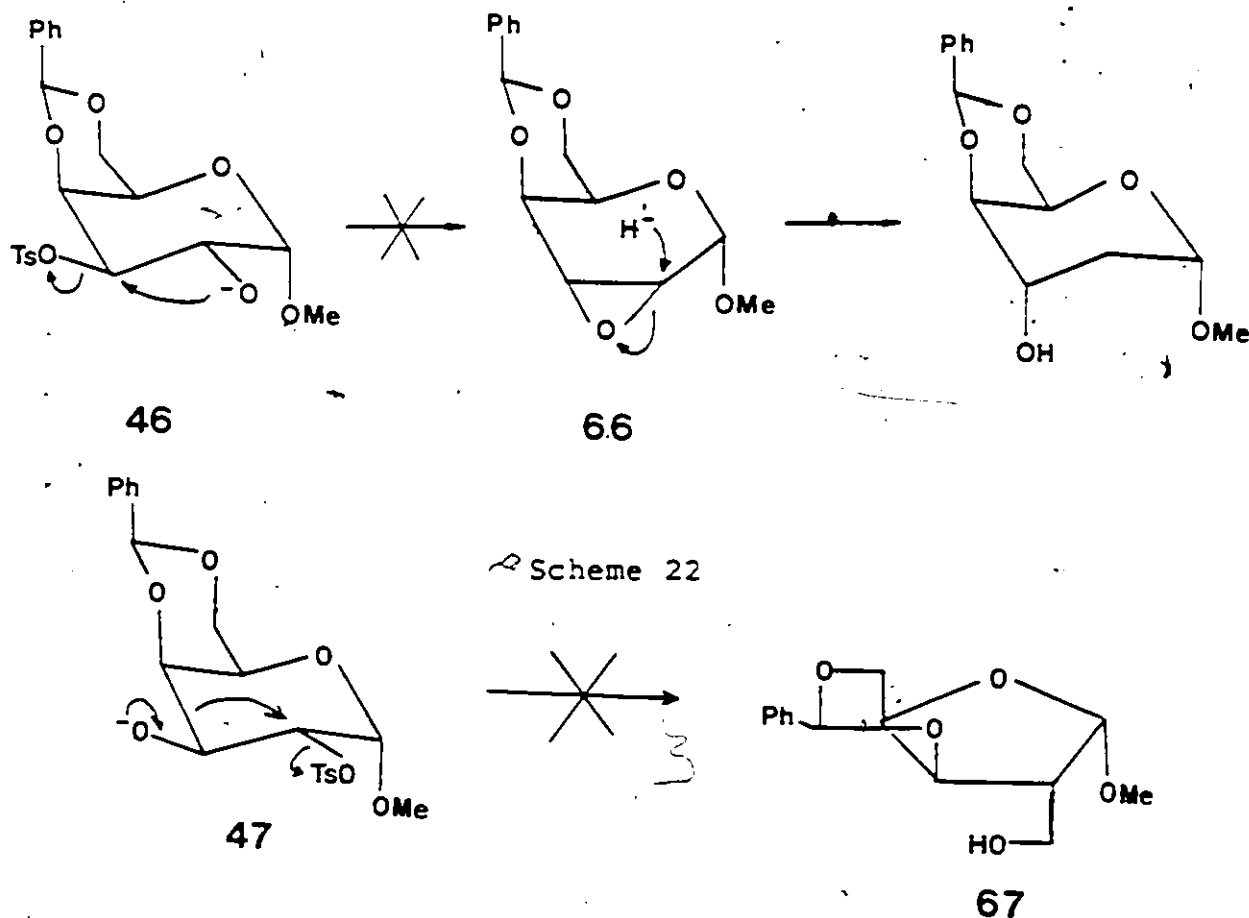
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\* A relatively greater proportion of ring-contracted product was obtained from the 2,3-di -O-benzoyl-4,6-di -O-tosyl compound 30 than from its debenzoylated derivative 31 and from its 6-chloro analog 32. The differences were not great and may not be mechanistically significant but reflect, perhaps, variations in the work-up operations. Nevertheless, it appears reasonable to expect such differences in product proportions to occur, in dependence of the pattern of substitution. Thus, the diol 31 is "ready" for immediate epoxide formation whereas its dibenzoate 30 must await prior debenzoylation which, although rapid, does require some time during which a certain amount of C-6 reduction may also occur. The differences shown by 30 and 32 may be attributable to a slower removal of chlorine atom as compared to the 6-tosyloxy group.

opposite manner, i.e., underwent rearrangement rather than epoxide formation. It was argued ( pages 58-60 ) that the behaviour of 20 ( and the other 6-deoxyglycosides that rearrange ) was due to the availability of a reaction path, leading to ring contraction out of the preferred chair conformation, that is lower in energy than the path to epoxide which requires transition through an unfavorable, higher-energy conformation. The latter route, however, is obviously taken by 46, which suggests that the "epoxide" route ( to 66 ) is unavailable, or no longer of lower energy, for this compound. For what reason? The 4,6-acetal ring, being cis-fused, must be ruled out as a steric impediment since the same structure did not prevent the regioisomer 46 from producing the furanosidic acetal 34; moreover, the non-bonded interactions in, and therefore the energy contents of, 34 and hypothetical 67 should be very nearly the same. The only structural difference on the pyranoside rings of 47 and the fucoside 20 is the ether-type blocking of O-4, versus a free OH-4 group, and this must have some significance, even though the oxygen is not directly involved in the rearrangement. At this juncture, the experiment with the partially methylated glycoside 57 must be recalled ( see pages 50-51 ). This 4,6-di -O-methylhexopyranoside 2-tosylate is a close structural analogy of 47, and indeed, it gave an unrearranged

• The <sup>2</sup> 3 -O-benzoyl group may be ignored as it will be removed by the LTBH before any other transformation occurs, and the epimeric C-4 configuration is immaterial as regards ring contraction in ( non-benzylidenated ) gluco and galacto 2-tosylates.

3-deoxyhexopyranoside ( 58 ) analogous to 35, not a pentofuranoside of the type obtained from the unmethylated gluco and galacto 2-tosylates 18, 20, 22, and 23. It appears that the negative charge in the C-4 substituent (  $C-O-Li^+ \rightleftharpoons C-O-BET_3-Li^+$  ) fosters the shift of C-4 to C-2. In the case of the rearrangement 46-34, C-1 migrates to C-3, although it does not bear an anionic substituent. However, it does carry two electronegative alkoxy groups, thus incorporating the positive terminus of a dipole much stronger than that in the monoalkoxylated C-4 of 47. One may conclude that dipolar stabilization of the migrating carbanion is what facilitates this bond shift.



Finally, the rather unusual results obtained by varying the reagent can be explained in terms of the borane complexation theory outlined above. For example, it is not unreasonable to imagine that increased steric bulk prevents efficient complexation of tri-(sec-butyl)borane with one or both of the vicinal alkoxides formed from 25. Without this complexation, epoxide formation is free to occur and hence unrearranged deoxy pyranoside 42 was produced.

The special role that lithium appears to play as counterion must lastly be addressed. Generally in hydride reductions, the cation is an important factor. For example, rates are different for  $\text{LiAlH}_4$  and  $\text{NaAlH}_4$  as a consequence of different activation parameters for the reduction of mesityl phenyl ketone in oxolane at  $25^\circ$ ; the following  $\Delta H^\ddagger$  (Kcal/mole) and  $\Delta S^\ddagger$  (cal./mole.K) were found for  $\text{LiAlH}_4$ , 9.9 and -26.2; for  $\text{NaAlH}_4$ , 17.5 and -5.4. These values indicate that the transition state is considerably more ordered with  $\text{Li}^+$  cations than with  $\text{Na}^+$ . Addition of a lithium-specific cryptand has been shown to suppress  $\text{LiAlH}_4$  reductions, and it has been postulated that  $\text{Li}^+$  (or some other electrophile) complexes with the substrate in the transition state during hydride transfer. These considerations may well be relevant to certain reactions with trialkylborohydrides too. However,  $\text{NaBHET}_3$  and crown ether- $\text{LiBHET}_3$  in our examples did effect reduction (of intermediary epoxides to deoxy sugars); what they failed to do was to induce ring contraction. A possible

explanation is that lithium ion, owing to its electrophilic character, coordinates with the tosylate, thereby facilitating its departure and thus promoting the rearrangement, perhaps in a cyclic fashion as suggested in Figure 7. In the absence of such assistance, carbon migration may be more difficult than conformational inversion followed by epoxide-forming displacement.

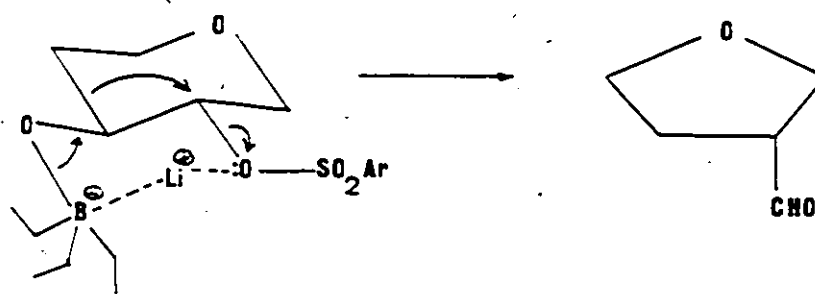
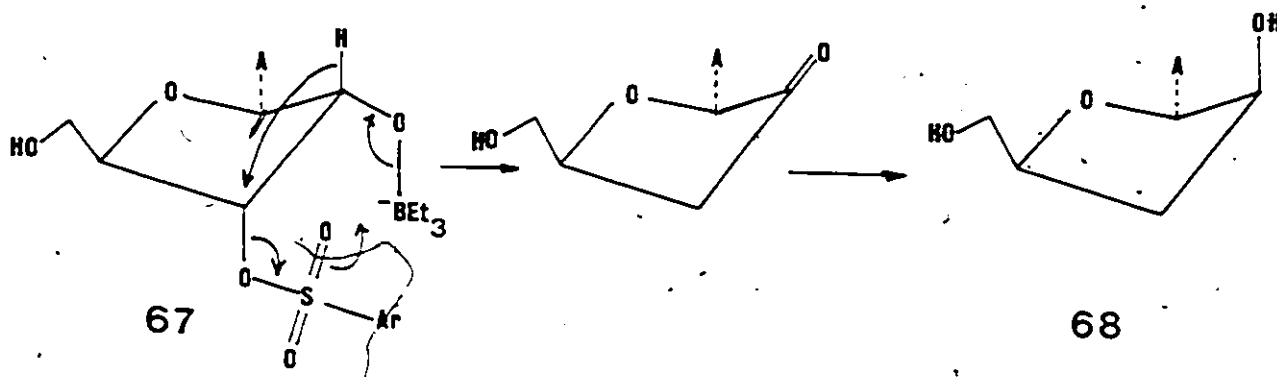


Figure 7

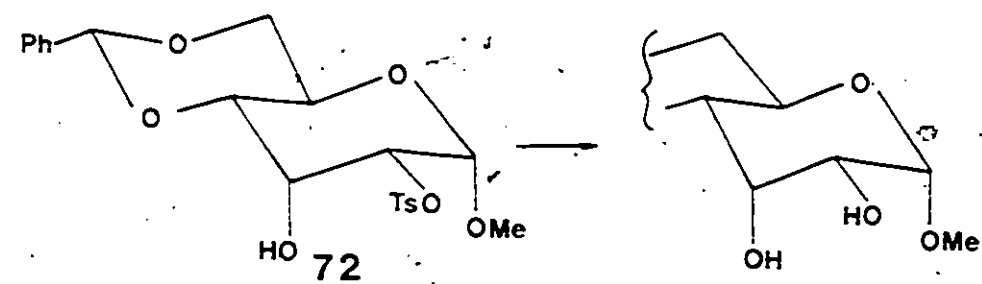
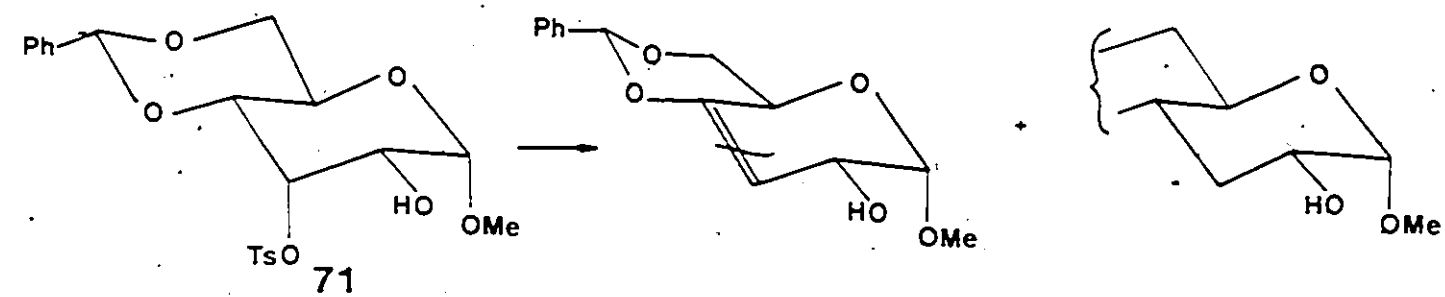
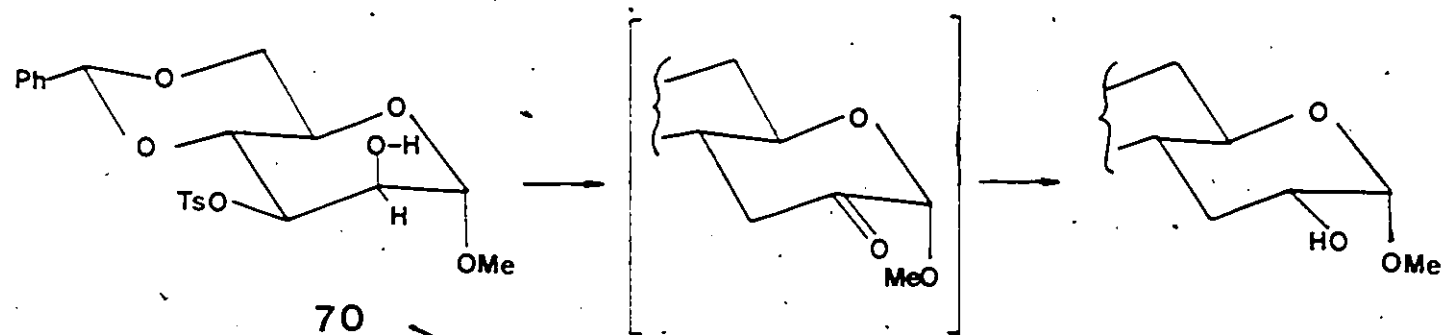
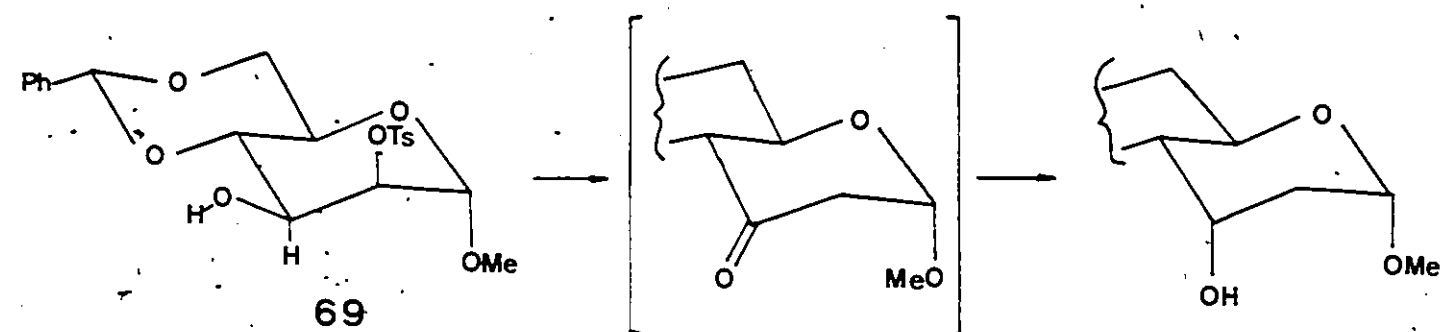
It must be noted that the arguments presented above are simply attempts to explain the experimental results. Further studies will be required to establish the mechanism definitively. That stereochemical factors are involved in LTBH-mediated reactions has, however, been demonstrated both in this laboratory<sup>10</sup> and by others<sup>11</sup>. Hansske and Robins<sup>12</sup> have observed hydride migration, analogous to our carbon migration, in attempts to desulfonyloxylate ribonucleoside monotosylates (Scheme 23).



Scheme 23

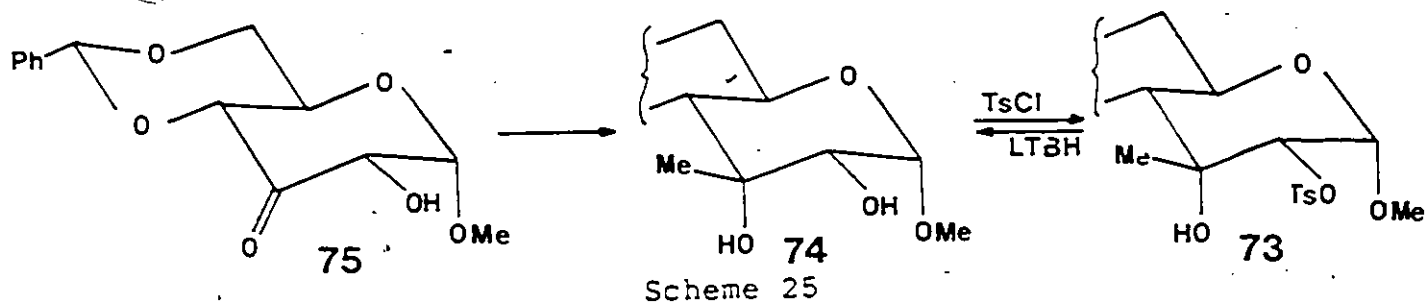
The cis configuration of the ribonucleoside precludes epoxide formation thus allowing the trans-coplanar hydride to displace the sulfonate. The authors formulated the cyclic mechanism shown ( Scheme 23 ), which may or may not be valid, but is not really relevant to the present discussion. The hydride migration was established unequivocally by means of deuterium-labelled derivatives.

These results prompted Baer and Mekarska<sup>10</sup> to investigate desulfonyloxylation in hexopyranoside tosylates having a 2,3- cis arrangement like the ribonucleosides just mentioned. The substrates, having the D -manno and D -allo configurations, possessed a trans-fused 4,6-acetal ring and were therefore not expected to incur ring contraction, because of the strained bicyclic system that would have to arise. Hydride migration was found to occur in these cases as well, but was sometimes accompanied by O-desulfonylation or elimination ( Scheme 24 ).

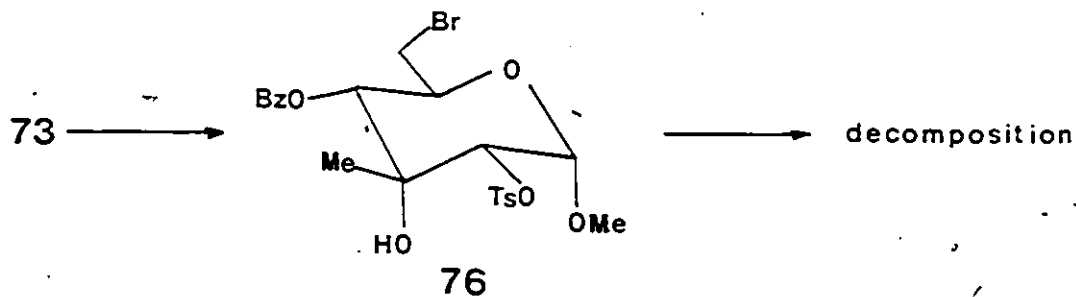


Scheme 24

While ring-contraction was theoretically possible in the 2-tosyl allo derivative ( 72 and 70 ) it presumably did not occur because of the trans -fused benzylidene ring ( vide supra ). A parallel study by this author found only desulfonation and extensive decomposition when the 3- C -methyl analogue of 72 was used ( 73 Scheme 25 ). Compound 73 was made by selective tosylation of the diol 74 which is itself made by Grignard addition to the ketone 75<sup>2</sup> as described<sup>3</sup>.



Treatment of compound 73 with N-bromosuccinimide<sup>4</sup> (Scheme 26) cleanly gave the 6-bromo compound 76 which was perhaps more amenable to ring contraction than 73 but nevertheless decomposed under the influence of LTBH.

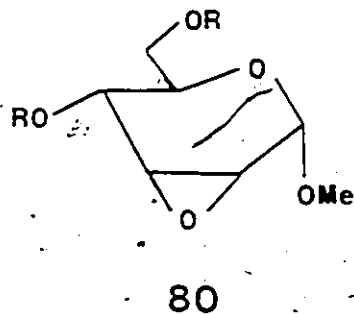
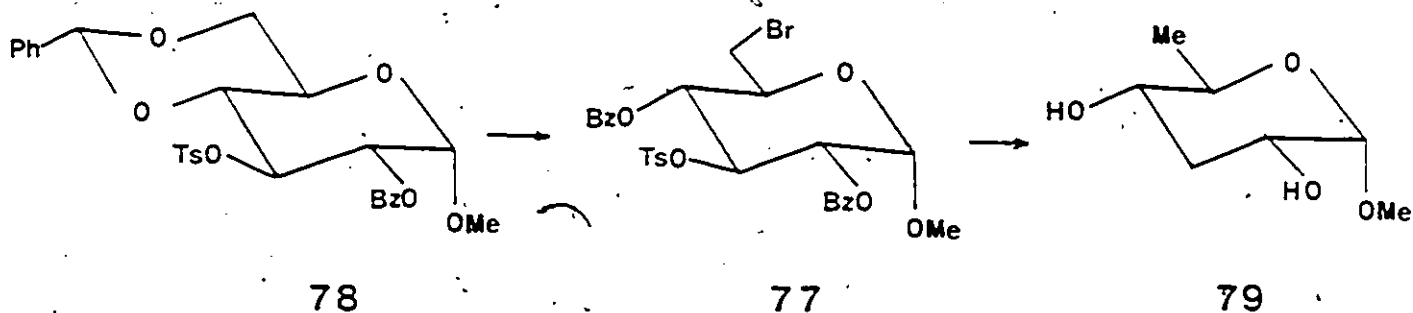


There were no further mechanistic experiments carried out.

## Ancillary reactions

With the mechanism of the LTBH-mediated ring contractions fairly well understood, or at least fairly well rationalized, a short foray into the realm of 3-tosyl sugars was made to see what kind of product they would provide. Consequently, methyl 6-deoxy-6-bromo-2,4-di-O-benzoyl-3-O-tosyl- $\alpha$ -D-glucopyranoside ( 77 ), obtained after treatment of the 4,6-O-benzylidene sugar 78 with N-bromosuccinimide<sup>44</sup>, was treated with LTBH. The product, methyl paratoside<sup>4</sup> ( 79 ) was surprising in that it appears to be the result of either direct tosyloxy displacement (  $S_N2$  reaction ) or of anti-Fürst-Plattner<sup>3</sup> ring-opening of the expected intermediary epoxide(s). This unusual behaviour<sup>3</sup> is not unlike that of epoxide 80 ( an analogue of one of two possible in the reduction of 77 ) under conditions of reduction with diborane-borohydride<sup>45</sup>. In that case, unusually high proportions of the anti-Fürst-Plattner product were attributed to the increased importance of electronic ( as opposed to steric ) factors which favor attack of nucleophile at C-3<sup>45</sup>. The authors claim that the diborane-borohydride reagent, not unlike LTBH in its combination of a Lewis acid ( borane ) and a hydride nucleophile, favors such polar direction of the reaction. It is interesting to note, as an aside, that the authors claim that "...excess diborane effectively shields the sulfonyloxy function from a nucleophilic attack by a vicinal trans -hydroxy group"<sup>45</sup>. This is similar to our

triethylborane in the ring contractions. In any case, it appeared that the product from the 3-tosyl sugar was not so unusual and did not warrant further investigation as the reactions involving intermediary epoxides are already well established<sup>1,2</sup>.



## Chapter VI

### EXPERIMENTAL SECTION

#### General Experimental

Lithium triethylborohydride ( Super Hydride(R), LTBH ) and all other trialkylborohydrides were purchased from the Aldrich Chemical Co. as M solutions in oxolane ( THF ). Other reagents used were reagent grade or better. Oxolane used was dried under a nitrogen atmosphere by means of refluxing over and distilling from sodium and benzophenone.

Optical rotations were measured at approximately 25° with a Perkin-Elmer 241 polarimeter and refer to chloroform solutions unless otherwise specified. Nuclear magnetic resonance spectra were recorded on Varian Associates FT-200 or -300 instruments ( 200 and 300 MHz respectively ) and refer to deuteriochloroform solutions unless otherwise indicated. Mass spectra were recorded on a VG Analytical model 7070E double focusing instrument. Infrared spectra were recorded on a Perkin-Elmer model 821 instrument. Melting points were determined with a Gallenkamp apparatus and are uncorrected.

Thin layer chromatography was performed on precoated plates of glass ( SIL-25UV-254, Macherey - Nagel and Co., Germany ) or aluminum ( Kieselgel 60 F254 Merck A.G. Darmstadt ). All spots, including those visible under UV light, were made visible by spraying the plates with 5% sulfuric acid in ethanol, and heating them briefly on a hot plate. Column chromatography was performed on Merck Silica Gel 60, 230-400 mesh, or on basic aluminum oxide suitable for chromatography ( Shawinigan ), as referred to by silica and alumina, respectively. Preparative thin-layer chromatography was performed on glass plates coated with 1-mm thickness of Merck Kieselgel 60 GF254. Unless otherwise indicated, the following solvent mixtures ( V/V ) were employed for chromatography: A, ethyl acetate-hexane, 1:2; B, the same solvents but 1:1; C, the same but 2:1; D ethyl acetate; and E, ethyl acetate-hexane 1:3.

## Preparation of Starting glycosides

## Known Compounds

Published procedures were employed, occasionally with minor technical modifications, for the preparation of 18, 25, 27, 30, 32, and 33. Compound 20 ( mp 156-157°C,  $[\alpha]_D^{25} +86.3^\circ$  ) was obtained from its known 3,4-O-isopropylidene derivative as described for 18 ( mp 157-158°C,  $[\alpha]_D^{25} -85^\circ$  ). The ir and nmr spectra of the enantiomers 18 and 20 were identical.

Methyl 4-O-benzoyl-6-bromo-~~6~~-deoxy-2-O-p-tolylsulfonyl- $\alpha$ -D-glucopyranoside ( 22 )

Pure methyl 4,6-O-benzylidene-2-O-tosyl- $\alpha$ -D-glucopyranoside ( 9.1g ) was heated for 2.5 h with N-bromosuccinimide ( 4.72 g ) and barium carbonate ( 10 g ) in refluxing carbon tetrachloride ( 350 mL ). Processing as for the analogous 2-O-mesyl compound gave 22 ( 5.1 g, 47.5% ) after crystallization from a small volume of carbon tetrachloride: mp 50-51°C,  $[\alpha]_D^{25} +48.7^\circ$  ( c 0.25 ); m/z ( DCI mode ): 515, 517 ( M+1 ), 483, 485 ( M+1-OMe ), 405 ( M+1-OMe-Br ). The <sup>1</sup>H-nmr data ( 200 MHz ): 8.04-7.26<sup>2</sup> ( 9H, arom. ), 5.05 ( dd,  $J_{3,4} = 9, J_{4,5} = 9.9$  Hz, H-4 ), 4.87 ( d,  $J_{1,2} = 3.7$  Hz, H-1 ), 4.34 ( dd,  $J_{2,3} = 9.5$  Hz, H-2 ), 4.19 ( dt,

$J_{3,OH} = 13.7$  Hz;  $t$  upon  $D_2O$  exchange,  $J_{2,3} = J_{3,4} = 9.5$  Hz, H-3 ) 4.06 ( ddd,  $J_{4,5} = 10$ ,  $J_{5,6} = 2.8$ ,  $J_{5,6} = 7.2$  Hz, H-5 ), 3.44 ( m, 2H, H-6,6' ), 3.42 ( s, O-Me ), and 2.44 ( s, Ar-Me ). Anal. calcd. for  $C_{21}H_{23}BrO_8S$  ( 515.4 ): C 48.93, H 4.50, Br 15.51; found: C 49.01, H 4.60, Br 15.4.

Methyl 6-deoxy-6-iodo-2-O-p-tolylsulfonyl- $\alpha$ -D-glucopyranoside ( 23 )

The crystalline ( mp 119.5-121° C, from ethyl acetate-hexane ) 3,4-di-O-acetyl derivative of 23 ( 5.42 g, 10.6 mmole ) was deacetylated by treatment with sodium methoxide ( 2 mL of a 2 M solution ) in a mixture of chloroform ( 50 mL ) and methanol ( 10 mL ), at room temperature during 1 h. Complete saponification of the diacetate (  $R_F$  0.65 ) to 23 (  $R_F$  0.5 ) was indicated by tlc ( solvent B ), and pilot-runs had shown that 23 is stable for several hours under these conditions, with only minute traces of a faster-moving product arising. The solvents were removed at low temperature, and 3 portions of added THF were evaporated from the residue which was obtained as a slightly yellowish foam and was used without purification after drying in a desiccator.

Methyl 4,6-di-O-p-tolylsulfonyl- $\alpha$ -D-glucopyranoside  
(31) by ammonolysis of 30

Methanolic ammonia ( 160 mL, saturated at 0° C ) and a solution of 30 ( 4.11 g ) in methanol ( 160 mL ) were mixed and stored in a refrigerator for 3 days. Tlc with solvent A revealed clean replacement of the fast-moving 30 by slow-moving 31. The solvent was removed at low temperature and the residue chromatographed on a short column of silica by means of solvent B. Compound 31 was obtained as a colorless syrup ( 2.37 g, 82% ),  $[\alpha]_D^{+102}$  ( c 1.1 ). A 60-MHz nmr spectrum indicated complete removal of the benzoyl and retention of the tosyl groups.

Attempted Zemplén deacylation of 30

Although 30 is known to give the anhydro sugar 40 on heating with sodium methoxide in methanol solution<sup>11</sup>, we attempted to prepare the presumed intermediate, 31, by employing milder conditions. In spite of the failure in this regard the experiment is recorded because of unexpected results concerning relative stabilities of different ester functions.

To a solution of 30 ( 3.55 g, 5 mmol ) in 1:1 chloroform-methanol ( 50 mL ) was added at 0° C an M sodium methoxide solution ( 1 mL ). After standing for 4 h at 0° C, the mixture showed a complex pattern in tlc ( solvent B ), which changed little during another hour and after addition of another 0.5 mL of methoxide. There were 5 spots,  $R_f$  0.8, 0.6, 0.35, 0.1, and 0.0. Work-up included neutralization with Dry Ice, evaporation, deionization in methanolic medium with cation and anion exchange resins, and evaporation of added toluene from the material which was obtained as a syrup. Trituration of the syrup with toluene and refrigeration ( 2 days ) caused crystallization of the immobile component (  $R_f$  0.0 ), which evidently was the major reaction product ( 1.735 g ). Recrystallized from a small amount of ethyl acetate, it had mp 103-104° C, whereas from chloroform it gave long needles of mp 122-123.5° C. From a small amount of water a hydrate ( mp 55-56° ) crystallized readily. These data, together with ir and <sup>1</sup>H-nmr data showing absence of benzoyl and the presence of only one tosyl group besides hydroxyl, identified the product as methyl 6-O -tosyl- $\alpha$ -D-glucopyranoside; reported<sup>22</sup>, mp 124°C ( anhydrous ) and 56-58° C ( hydrate ). Addition of a little hexane to the above toluene mother liquor gave a gummy deposit containing some of the same product together with the component of  $R_f$  0.1. The

latter probably was ditosylate 31, but the amount was small and it could not be isolated pure. The three faster-moving components, contained in the toluene-hexane solution that was decanted from the gum, were separated on a column ( 16 x 1 cm ) of silica ( solvent B ). There was obtained some unchanged 30,  $R_F$  0.8, mp 132° C ( from methanol ); a small amount of crystalline product  $R_F$  0.6, mp 145.5° C ( from ethanol ), whose ir and  $^1H$ -nmr spectra suggested that it was the 3-monobenzoate of 31; and methyl 3,4-anhydro-6-O-tosyl- $\alpha$ -D-galactopyranoside ( 40 ),  $R_F$  0.3, needles upon trituration with water and a few drops of ethanol on a steam bath, mp 95-96° C ( reported<sup>11a</sup>, mp 94-95° C ). The extensive de-O -sulfonylation at the 4-position, to give the major product (  $R_F$  0.0 ) under conditions where even debenzoylation was incomplete, appears rather remarkable.

General Procedure for Reactions of Glycoside Tosylates  
with LTBH

The starting sugar derivative was dissolved in THF. The M LTBH solution was introduced by syringe into the magnetically stirred and chilled ( ice-water bath ) solution of the substrate. Cooling was then discontinued and the mixture boiled under reflux, with periodic monitoring of the progress of reaction by tlc. Amounts of materials and reaction times are given for each individual experiment. For processing, the reaction mixture was chilled to 0°, and methanol was added dropwise in slight excess to ensure decomposition of the remaining hydride. The solution was then concentrated on the rotary evaporator at 35° to a small volume ( one-quarter to one-fifth ) and poured into 10 volumes of ice-water. The mixture was stirred at ambient temperature for several hours ( or overnight ). An amount of 30% hydrogen peroxide as specified was diluted with water and added cautiously and dropwise to the mixture, preferably with cooling. (Violent reaction may occur if this addition is done too rapidly.) After 1 h, the solution was carefully neutralized to pH 7 with aqueous sodium hydrogen sulfate solution unless otherwise indicated; any excess of acid being carefully avoided. The solution was then

evaporated to one-third its volume, and exhaustively extracted with chloroform or ethyl acetate as specified. Finally, the aqueous phase was evaporated to dryness, and the residue checked by tlc. If it still contained a significant amount of the organic material, it was extracted with ethyl acetate or chloroform. The combined extracts were dried (  $\text{MgSO}_4$  or  $\text{Na}_2\text{SO}_4$  ) and evaporated to give the crude reaction product.

Methyl 2,5-dideoxy-2-C-(hydroxymethyl)- $\alpha$ -L-xylo-  
pentofuranoside (19)

The reaction was performed with 18 ( 4.10 g, 12.35 mmol $\bar{e}$  ) in THF ( 100 mL ) and LTBH solution ( 100 mL, 8.1 mol. equiv. ) during 30 min, after which tlc ( solvent D ) showed absence of 18 (  $R_F$  0.7 ) and presence of a new spot,  $R_F$  0.35. Oxidative treatment was performed with 33 mL of 30% hydrogen peroxide. Extraction of the aqueous phase with ethyl acetate, and of the residue of evaporation with chloroform, gave a combined yield of 1.27 g ( 63.5 % ) of crude 19 which crystallized in part from ethyl acetate-hexane; mp 73°C.

Chromatography of the mother liquor material on alumina using solvent B followed by solvent D as eluents, furnished additional, crystalline 19. The combined crops were recrystallized from chloroform, affording 1.06 g ( 53% ) of analytically pure 19, mp 74-75°C,  $[\alpha]_D$  -174.5° ( c 2.2 ). Anal. calcd for  $C_7H_{14}O_4$  (162.2 ): C 51.84, H 8.70; found: C 51.60, H 8.67.

Methyl 2,5-dideoxy-2-C-(hydroxymethyl)- $\alpha$ -D-xylo-  
pentofuranoside (21)

Compound 21 was obtained from 20 in 60% crude yield, as described for the enantiomer 19. After purification by chromatography and crystallization, it showed mp 73-75° C, and  $[\alpha]_D +173^\circ$  ( c 0.9 ). Its ir and  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra were superimposable on those of 19.

Methyl 2,5-dideoxy-2-C-(hydroxymethyl)- $\alpha$ -D-ribo-  
pentofuranoside(24)

(a) From the 6-bromo-6-deoxyglycoside 22

Compound 22 ( 5.15 g, 10 mmole ) in THF ( 60 mL ) and LTBH solution ( 100 mL ) were allowed to react for 2 h. Processing included a peroxide treatment with 35 mL of 30% reagent and was performed as described before, except that the neutralization with  $\text{NaHSO}_4$  was dispensed with. Chloroform extraction of the partially evaporated, aqueous solution afforded crude 24 ( 868 mg, 53.6% ) as a solid after solvent evaporation. Recrystallized from 1:1 carbon tetrachloride-hexane, it had mp 41-42° C and  $[\alpha]_D +133^\circ$  ( c 2.2 ). Anal. calcd. for  $\text{C}_7\text{H}_{14}\text{O}_4$  ( 162.2 ): C 51.84, H 8.70; found: C 51.91, H 8.48.

(b) From the 6-iodo-6-deoxyglycoside 23

The crude 23 obtained in the aforementioned saponification of 5.42 g ( 10.6 mmol ) of its diacetate was dissolved in THF ( 60 mL ) and allowed to react with LTBH solution ( 80 mL ) during 1.75 h. In this instance, the treatment with 30% hydrogen peroxide ( 26 mL ) included in the work-up was followed by neutralization of the reaction mixture with  $\text{NaHSO}_4$ , and the partially evaporated solution was extracted with ethyl acetate. There was obtained crude 24 ( 1.27 g, 62% ) as a yellow syrup. Column chromatography on alumina using solvent C gave, from chromatographically homogeneous fractions, compound 24 as a colorless syrup that crystallized on refrigeration but proved difficult to recrystallize; mp 34-35° C and  $[\alpha]_D +188^\circ$  ( c 4.4 ). Although the physical constants were somewhat lower than in 24 prepared under (a), the ir,  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra of the two preparations were identical.

5  
Methyl 3,5-dideoxy-3-C-(hydroxymethyl)- $\alpha$ -L-arabino-pentofuranoside (26)

Compound 25 ( 3.40 g, 10.23 mmol ) in THF ( 80 mL ) and LTBH solution ( 82 mL ) was allowed to react for 30 min, after which all of the 25 was consumed ( tlc with solvent D ): In this and similar, preceding experiments with 25 no peroxide treatment was included

in the work-up procedure as the studies were performed at an early stage before the beneficial effect of such treatment on yields was realized. The yield of pure 26 ( 506 mg, 30.5% ) obtained upon chloroform extraction and column chromatography on alumina with solvent B followed by solvent D, and recrystallization from ether-petroleum ether ( bp 30-60° ), was therefore low, and a considerable portion of the product emerged from the column as a fast-moving organoboron conjugate. Crystalline 26 showed  $R_F$  0.35 ( solvent D ), mp 64° C,  $[\alpha]_D^{25} -112^\circ$  ( c 2.3 ). Anal. calcd. for  $C_{17}H_{14}O_4$  (162.2 ): C 51.84, H 8.70; found: C 51.67, H 8.47.

Methyl 3,5-dideoxy-3-C-(hydroxymethyl)- $\alpha$ -D-ribo-pentofuranoside (20)

(a) From the 6-deoxyglycoside 27

Compound 27 ( 4.32 g, 8.0 mmole ) in THF ( 32 mL ) was allowed to react with LTBH solution ( 64 mL, 8 mol. equiv. ) during 45 min. Normal processing, but with addition of potassium carbonate in the treatment with hydrogen peroxide ( 22 mL ), and prolongation of this treatment overnight, furnished 1.00 g ( 77 % ) of 28,  $R_F$  0.34 ( solvent D ), by chloroform extraction. Compound 29 (  $R_F$  0.40, see below ) was not detected. Compound 28 resisted all attempts at crystallization. After chromatography on silica with solvent A

recovery, 74% ) it showed  $[\alpha]_D +162.2^\circ$  ( c. 1.2 ). To corroborate the structure, a sample of 28 was acetylated in the conventional manner ( acetic anhydride-pyridene), and the 200-MHz nmr data of the diacetate are included in Table 1 (page 19).

(b) From the 4,6-ditosylate 30

A solution of compound 30 ( 3.70 g, 5.21 mmol ) in THF ( 40 mL ) and LTBH solution ( 37 mL ) was boiled for 2 h, after which time another 7 mL of LTBH was added ( for a total of 8.4 mol. equiv. ), and boiling was continued for 1 h. Work-up included oxidation with 15 mL of 30% hydrogen peroxide, and chloroform extraction. It gave a syrupy glycoside mixture ( 470 mg, 56% ) that showed two partially overlapping spots,  $R_f$  0.40 and 0.35, in tlc with solvent D. The proton nmr spectral features of 28 were superposed on those of methyl abequoside ( 29 ), as was ascertained by comparison with the spectra of pure 28 and independently-prepared ( see below ) pure 29. A ratio of 3:2 was found by signal integration for H-1, O-Me, and C-Me at  $\delta$  4.96, 3.49 and 1.29 ( for 28 ), and 4.68, 3.45 and 1.21 ( for 29 ), respectively.

Several similar experiments were carried out using 10 mol. equiv. of LTBH and reaction times of 2-6 h, and results were always similar. However, in a 30-min. reaction, desulfonyloxylation was incomplete, and from

the mixture of products a small proportion of the 3,4-epoxide 40 was chromatographically isolated crystalline ( mp 93° C ). It was identified by comparison with an authentic sample<sup>11</sup>.

Separation of 28 and 29 was difficult to achieve and required multiple chromatography. While it was possible to isolate part of the 28 in spectroscopically homogeneous form, the abequoside 29 was never obtained free from small proportions of 28. Nevertheless, its identity was established beyond doubt as the 200-MHz proton nmr matched those of independently prepared material ( see reduction of 40 below ).

(c) From the 4,6-ditosylate 31 and the 6-chloro-6-deoxyglycoside 32

A 40-min reaction performed with 31 ( 2.3 g, 4.58 mmole ) and 13.5 mol. equiv. of LTBH gave, after standard processing, a mixture of 28 and 29 ( yield not recorded ), for which the nmr spectrum indicated an approximate 1:1 ratio. A 60-min. reaction of 32 ( 1.49 g, 2.6 mmole ) with 10 mol. equiv. of LTBH gave a similar, 1:1 mixture ( 200 mg, 47% ).

Methyl 3,5-O-benzylidene-2-deoxy-2-C-(hydroxymethyl)- $\alpha$ -D-lyxo-pentofuranoside (34), methyl 4,6-O-benzylidene-3-deoxy- $\alpha$ -D-lyxo-hexopyranoside (35) and methyl 4,6-O-benzylidene- $\alpha$ -D-galactopyranoside (36)

To a solution of 33 (1.00 g, 1.75 mmol) in THF (10 mL) was added LTBH solution (10 mL), followed after 30 min of refluxing by another 10 mL of the same. After 20 h of boiling, the solution showed 3 spots, at  $R_F$  0.57, 0.22, and 0.1 (tlc with 1:4 ethyl acetate-chloroform). Processing was unproblematical and was performed as in the work with the benzylidene glucosides. It included addition of methanol to the chilled reaction mixture followed by dilution with water, evaporation to remove most of the THF, and extraction of the products by ethyl acetate. Peroxide treatment was not required. The product mixture was chromatographed on a silica gel column by use of 1:4 ethyl acetate-chloroform. The component emerging first ( $R_F$  0.57) proved to be the pyranoside 35; yield, 100 mg (21.5%); mp 88.5-89° C,  $[\alpha]_D^{20} +56.8^\circ$  (c 0.9); m/z (FAB mode) 267 (M+1) and 235 (M-OMe).  $^1\text{H-nmr}$  (200 MHz):  $\delta$  7.52-7.26 (m, 5H, Ph), 5.49 (s, Ph-CH), 5.30 (d,  $J_{1,2} = 4.8$  Hz, H-1), 4.79 (s, slightly broadened, H-1), 4.30 (dd,  $J_{5,6} = 1.6$ ,  $J_{6,6'} = 12.5$  Hz, H-6), 4.12 (nm, WH=3.2 Hz, H-4), 4.075 (dd,  $J = 1.6$  and 12.5 Hz, H-6'), 3.70 (d,  $J_{2,\text{OH}} = 11.5$  Hz, OH-2, strongly hydrogen-bonded with O-4), 3.69 (nm,  $J_{4,5} = 1.5$  Hz, H-5), 3.58 (d of nm;

on double irradiation at  $\delta$  2.13: dd,  $J_{2,OH} = 11.5$ ,  $J_{2,4} = 1.6$  Hz, H-2), 3.44 (s, 3H, OMe), and 2.13 (nm, 2H, H-3,3'). Anal. calcd. for  $C_{14}H_{18}O_5$  (266.3): C 63.14, H 6.81; found: C 63.14, H 6.73.

The second product ( $R_f$  0.22) eluted from the column was the furanoside 34; yield, 177 mg (38%); mp 121-122°C,  $[\alpha]_D +51.4^\circ$  (c 0.9);  $^1H$ -nmr (200 MHz)  $\delta$ : 7.49-7.34 (m, 5H, Ph), 5.47 (s, Ph-CH), 5.30 (d,  $J_{1,2} = 4.8$  Hz, H-1) 4.63 (dd  $J_{2,3} = 5.4$   $J_{3,4} = 2.1$  Hz, H-3), 4.46 (d,  $J_{5,5'} = 13.2$  Hz, H-5), 4.16 (dd,  $J_{4,5'} = 2.2$ ,  $J_{5,5'} = 13.2$  Hz, H-5'), 4.00 (m, 3H, H-4 and H-2,2' [ hydroxymethyl ]), 3.47 (s, 3H, OMe), and 2.46 (ddt,  $J_{1,2} = J_{2,3} = 4.8$ ,  $J_{2,2'} = 4.5$ ,  $J_{2,2''} = 6.2$  Hz, H-2). Anal. calcd. for  $C_{14}H_{18}O_5$  (266.3): C 63.14, H 6.81; found: C 63.14 H 6.73.

The third component ( $R_f$  0.1) eluted from the column amounted to 90 mg (18%) and was identified as the diol 36 by spectral comparison with an authentic sample.

Reaction of methyl 2,6-dideoxy-2-C-(hydroxymethyl)- $\alpha$ -L-xylo-pentofuranoside (19) with carbonyldiimidazole

The sugar ( 16.2 mg, 0.1 mmole ) was dissolved in 2 mL of anhydrous benzene to which 64 mg ( 2 mol. equiv. ) of N,N-carbonyldiimidazole was added. The mixture was boiled under reflux for 3 h after which tlc showed a new spot (  $R_F$  0.49, solvent D ) which ran only slightly slower than the starting material (  $R_F$  0.54 ) but which was readily distinguishable by virtue of its visibility under UV light. The benzene was then washed thrice with 2 mL of water and dried (  $MgSO_4$  ). Evaporation of the solvent furnished a material which was identified by proton-nmr as methyl 2,5-dideoxy-2-C-(hydroxymethyl)-2',3-di-imidazocarbamoyl- $\alpha$ -L-xylopentofuranoside ( 37 ). The following nmr features were observed:  $\delta$  8.117, 7.383, 7.070 ( 2H each, imidazolyl ), 5.452 ( dd,  $J_{2,3} = 4.27$ ,  $J_{3,4} = 5.06$  Hz, H-3 ), 5.168 ( d,  $J_{1,2} = 5.37$  Hz, H-1 ), 4.657 ( 2H, qd,  $J_{2a,2b} = 11.35$ ,  $J_{2,2a} = 7.12$ ,  $J_{2,2b} = 8.13$  Hz, H-2'a, 2'b ), 4.483 ( dq,  $J_{4,5} = 6.54$  Hz, H-4 ), 2.98 ( complex m, 1H, H-2 ) and 1.338 ppm ( 3H, H-5s ).

When, in one trial, water was added to the benzene solution of 37 no reaction was observed after 72 h.

Attempted benzylidenation of 24

A small amount ( unweighed, approximately 20 mg ) of 24 was dissolved in approximately 2 mL of dimethoxytoluene<sup>3</sup> to which were added a few crystals of p-toluenesulfonic acid. The reaction mixture was put on a rotary evaporator ( bath temp. approximately 40° C ), and the solvent allowed to evaporate somewhat. More dimethoxytoluene was added and the process repeated. Dilution of the reaction mixture with chloroform, followed by extraction with water and drying over magnesium sulfate, yielded no carbohydrate material. Benzoic acid was the only material isolated from the organic phase.

Methyl 3,6-dideoxy- $\alpha$ -D-xylo-hexopyranoside (29)

An ice-cooled solution of methyl 3,4-anhydro-6-O-tosyl- $\alpha$ -D-galactopyranoside<sup>11</sup> (40, 1.65 g, 5 mmol) in dry oxolane (20 mL) was magnetically stirred and LTBH solution added dropwise by syringe. The ice bath was removed and the solution boiled under reflux for 15 min after which tlc (solvent D) indicated the disappearance of all of 40 ( $R_f$  0.65) and formation of a single spot for 29 ( $R_f$  0.28). After cooling of the reaction mixture, the excess of reductant was destroyed with methanol and the mixture poured into ice-water (400 mL), with which it was stirred for 2 h. Some fresh ice was added, followed by 19 mL of 30% hydrogen peroxide which was introduced cautiously, and stirring was continued at ambient temperature for several hours (or overnight). The alkaline solution was evaporated at reduced pressure to near-dryness, and the resulting residue was taken up in saturated, aqueous potassium carbonate solution (50 mL). The organic material was extracted with chloroform (7 x 100 mL). The extract was dried ( $MgSO_4$ ), and evaporated to give 29 as a nearly colorless oil (760 mg, 94%, vacuum-dried), homogeneous in tlc;  $[\alpha]_D^{25} +139.1^\circ$  (c 0.9) and  $146.7^\circ$  (c 1, methanol); lit.<sup>11</sup>  $+143 \pm 3^\circ$  (methanol). Mass spectra (m/z, FAB mode), 131 ( $M^+-OMe$ ), 161 ( $M^+-H$ ), and 261 (dimerized fragments,  $2M^+-OMe$ ); CDI mode, 131, 163 ( $M+1$ ), and 261.

A sample of 29 was p-nitrobenzoylated<sup>11</sup> to give the crystalline diester which was recrystallized from ethanol-acetone. It had  $[\alpha]_D +155.5^\circ$  ( c 1 ) and melted at 89-90° after sintering at 80-83°; lit.<sup>11</sup> mp 80-83° C.

Methyl 3,6-dideoxy- $\alpha$ -L-lyxo-hexopyranoside (42)

Methyl 3,4-anhydro-6-deoxy- $\alpha$ -L-talopyranoside<sup>11</sup> (41, 2.0 g, 12.5 mmol ) in dry THF ( 50 mL ) was allowed to react with LTBH ( 42 mL, 3.4 mol. equiv. ), and the reaction mixture subsequently processed, as described for the preparation of 29. Compound 42 was obtained as a pale-yellow syrup ( 1.90 g, 94% ) whose tlc ( solvent B ) showed a trace of a slower-moving impurity beside the main product,  $R_f$  0.25. The material was purified by chromatography on a column of silica gel using solvent D as the eluent, and the colorless syrup then showed  $[\alpha]_D -100^\circ$  ( c 1 ); lit.<sup>11</sup>,  $-103.3 \pm 1^\circ$ . Mass spectra ( m/z FAB mode ): 131 ( M-OMe ), 161 ( M-H ), 163 ( M+1 ), 325 ( dimer, 2M+H ); DCI mode 131, 163, and 261 ( dimerized fragment, 2M-OMe-HOME ).

A sample of 42 was mesylated<sup>11</sup> to give the crystalline diester which was recrystallized from chloroform-petroleum ether; mp 153-155° C,  $[\alpha]_D -47.0^\circ$  ( c 1 ); lit.<sup>11</sup> mp 153-154° C,  $[\alpha]_D -48.5 \pm 0.6^\circ$ .

Methyl 3,6-dideoxy-3-deuterio- $\alpha$ -L-idopyranoside (48)

Methyl 4-O-tosyl- $\alpha$ -L-rhamnopyranoside ( 25, 710 mg, 2.14 mmol ) was dissolved in 20 mL of THF then treated with 9 mL Super Deuteride(R) ( 1 M solution of LTBD in THF, (R) Aldrich Chemical Co. ) and heated to reflux. The starting material disappeared after one hour ( tlc, solvent D ) whereupon the solution was processed essentially as described for 29. Exhaustive extraction of the concentrated aqueous solution with chloroform afforded a syrupy material ( R 0.36 ) contaminated with a faint trace of slower-running material ( Rf 0.2).

Chromatographic purification ( alumina, solvent D as eluent ) furnished 100 mg ( 29% ) of 48. The product was identified by its nmr spectrum ( cf. Tables 4 & 5 ):carbon-13 ( fully decoupled )  $\delta$  101.2 ( C-1 ), 67.97 ( C-2 ), 66.16, 66.29 ( C-4 and C-5, interchangeable ), 54.82 ( OCH<sub>3</sub> ), 30.876 ( triplet, C-3), 16.85 ppm ( C-6 );proton ( 300 MHz )  $\delta$  4.626 ( broad s, H-1 ), 3.915 ( qd,  $J_{4,5} = 1.4$ ,  $J_{5,6} = 6.6$  Hz, H-5), 3.690 ( broad d from coupling with H-O,  $J_{OH,2} = 5.8$  Hz, H-2 ), 3.638 ( very narrow m, H-4 ), 3.410 (s, O-CH<sub>3</sub> ), 3.261, 2.722 ( OHs ), 2.041 ( very narrow m, H-3 ) and 1.26 ppm ( 3H, H-6s ).

Treatment of Cyclohexene oxide with lithium tosylate

Lithium tosylate, prepared according to Galynker and Still<sup>12</sup>, ( 3.52 g, 19.7 mmol ) and cyclohexene oxide ( 2 mL, 19.72 mmol ) were dissolved in 50 mL of THF. Upon heating the lithium tosylate precipitated out but redissolved on subsequent cooling. No carbonyl ( from cyclopentane carboxaldehyde ) was detected ( by ir ) after 24 h at room temperature nor after 5 days of boiling the suspension. Ring-contraction was, therefore, concluded not to occur with lithium tosylate.

Treatment of 41 with triethylborane

A 1 M solution of triethylborane ( 25 mL, Aldrich Chemical Co., ) was added to 801 mg ( 5 mmol ) of 41 in 20 mL of THF. Tlc ( ethyl acetate eluent ) indicated that no reaction had occurred after stirring overnight at room temperature nor after 36 h of reflux.

Desulfonation of methyl 4-O-tosyl-2,3-O-isopropylidene- $\alpha$ -L-rhamnopyranoside (49) with LTBH

Compound 49 ( 270 mg, 0.73 mmol ) in 5 mL of THF was treated with 3 mL of LTBH. After 17 hours at reflux temperature, tlc ( solvent A ) indicated incomplete reaction. After cooling, a further 3 mL of LTBH was added and the mixture boiled for another 3 h after which time the reaction was complete. Normal work-up, with ether as the extraction solvent, furnished a syrup which proved, by tlc and 60MHz  $^1\text{H}$ -nmr comparison with an authentic sample', to be methyl 2,3-O-isopropylidene- $\alpha$ -L-rhamnopyranoside.

Partial reduction of methyl 4-O-benzoyl-6-6-bromo-6-deoxy-2,3-di-O-methyl- $\alpha$ -D-glucopyranoside

When only 4 equiv. of  $\text{LiAlH}_4$  were used, debenzoylation was the principal reaction, even after 72 h of boiling, affording after chromatography ( silica, solvent E ), the hitherto unknown compound methyl 6-bromo-6-deoxy-2,3-di-O-methyl- $\alpha$ -D-glucopyranoside in 44% yield. Very little 53 was isolated ( ca. 10% ). The 6-bromo compound showed the following data: Mass spectrum ( DCI/ether ): m/z 285/287 ( M+1 ), 253/255 ( M-OMe ), 221/223

(253/255-OMe ), 203/205 ( 221/223-H<sub>2</sub>O ), 173 ( M-OMe-Br);

<sup>13</sup>C-nmr ( partially spin-decoupled ):  $\delta$  97.445 ( d, C-1 ), 82.555 ( d, C-4 ), 81.811 ( d, C-5 ), 71.826 ( d, C-2 ), 69.859 ( d, C-3 ), 61.298, 58.490, 55.431 ( t, OCH<sub>3</sub>s ), 33.356 ( t, C-6 ). <sup>1</sup>H-nmr ( 300 MHz ):  $\delta$  4.92 ( d,  $J$  = 3.6 Hz, H-1 ), 3.78 ( very narrow m,  $J$  < 1 Hz, H-A ), 3.75 ( t,  $J$  = 2.4 Hz, H-B ), 3.66 ( s, 3H, OCH<sub>3</sub> ), 3.60 ( dd,  $J_{5,6e}$  = 6 Hz,  $J_{gem.}$  = 11.4 Hz, H-6e ), 3.52, 3.50 ( 2s, 3H each, OCH<sub>3</sub>s ), 3.47, 3.44 ( 2 very narrow m, 1H each, H-C, H-D ), 3.28 ( dd,  $J_{1,2}$  = 9 Hz, H-2 ).  
-2,3

#### Tosylation of 53

Compound 53 ( 1.687 g ) was stirred for 10 days at room temperature in 10 mL of pyridine containing 1.57 g of *p*-toluenesulfonyl chloride and 0.1 g of *N,N*-dimethylaminopyridine, for 10 days. Three further days in a refrigerator, repeated additions of tosyl chloride, pyridine and dimethylaminopyridine, and an additional week of reaction did not cause complete consumption of the starting material. In spite of this, the reaction mixture was poured into 200 mL of stirred ice-water and the resultant light-brown precipitate was filtered off. The tosylate 54, weighing 1.66 g ( 56% ) showed M.S. ( C.I./ether ) m/z 157 ( M+1-OCH<sub>3</sub>-OTs ), 329 ( M-OCH<sub>3</sub> ), 361 ( M+1 ); <sup>1</sup>H-nmr ( 300 MHz )  $\delta$  7.797, 7.302 ( 2d, 4H, Arom. ), 4.728

( d,  $\underline{J}_{1,2} = 3.66$  Hz, H-1 ), 4.206 ( t,  $\underline{J}_{3,4} = \underline{J}_{4,5} = 9.52$  Hz, H-4 ), 3.774 ( dd,  $\underline{J}_{4,5}, \underline{J}_{5,6} = 6.60$  Hz, H-5), 3.447, 3.377, 2.961 ( 3s, 3H each, OCH<sub>3</sub>s ), 3.369 ( t,  $\underline{J}_{2,3} = \underline{J}_{3,4} = 9.40$  Hz, H-3 ), 3.185 ( dd,  $\underline{J}_{1,2}, \underline{J}_{2,3}$ , H-2 ), 2.415 ( s, 3H, ArCH<sub>3</sub> ), 1.294 ( d,  $\underline{J}_{5,6} = 6.35$  Hz, H-6s ); <sup>13</sup>C- ( partially decoupled )  $\delta$  144.27, 134.84 129.36, 127.82 ( Arom. ), 96.868 ( d, C-1 ), 83.64 ( d, C-4 ), 82.29 ( d, C-5 ), 80.16 ( d, C-3 ), 65.13 ( d, C-2 ), 60.33, 58.85, 55.21 ( 3q, OCH<sub>3</sub>s ), 21.55 ( q, CH<sub>3</sub>-Ar ), 17.50 ( q, C-6 ) and was used without further purification.

Reduction of 54 with LTBH

The tosylate ( 54, 1.00 g, 2.78 mmol ) was dissolved in 20 mL of THF and chilled in an ice-water bath. To the solution was added 10 mL of LTBH. The reaction mixture was allowed to warm to ambient temperature and remain thus overnight. Little reaction had occurred so the solution was boiled 3 h whereupon another 10 mL of LTBH were added. Reflux was continued another 19 h at which time tlc ( solvent B ) showed virtually complete disappearance of starting material (  $R_F$  0.5 ). Methanol was added until gas evolution ceased and the reaction mixture was partitioned between ether and water ( 50 mL each ). The aqueous phase was washed 5 times with chloroform ( 40 mL ) which, after drying, furnished pure material ( 296 mg, 52 % ) in every way identical to 53. The ethereal solution contained 53 contaminated with starting material and was ignored.

Debenzylidenation of methyl 4,6-O-benzylidene-3-O-benzyl-2-O-p-tolylsulfonyl- $\alpha$ -D-glucopyranoside

The sugar ( 55, 1.00 g, 1.85 mmol ) was suspended in 50 mL of 80% ( v/v ) aqueous acetic acid and heated on a steam bath for 1.5 h. After cooling, the acetic acid was evaporated with repeated addition of toluene under reduced pressure on a rotary evaporator. After drying the solid residue thus obtained for 1 h under high-vacuum ( <1 torr ), it no longer smelled of acetic acid but slightly of benzaldehyde, and was then recrystallized from ethanol-ethyl acetate. The first crop of 56 collected weighed 611 mg ( 73% ) and showed a melting of 196-199° C. Subsequent crops yielded another 91 mg and concentration of the mother liquor gave another 50 mg, for a total yield of 90%. The nmr data are:  $^{13}\text{C}$  ( partially decoupled )  $\delta$  145.04, 133.77, 129.73, 127.94 ( s,s,d,d respectively, Arom. ), 97.68 ( d, C-1 ), 80.84, 79.46 ( dd, C-2, C-5, interchangeable ), 70.79, 70.00 ( d,d, C-3, C-5, interchangeable ), 61.55 ( t, C-6 ), 61.19, 55.48 ( 2q,  $\text{OCH}_3$ s ), 21.67 ( q,  $\text{CH}_3$  );  $^1\text{H}$ - ( 300 MHz )  $\delta$  7.832, 7.355 ( 2d, Arom. ), 4.762 ( d,  $J_{1,2} = 3.57$  Hz, H-1 ), 4.293 ( dd,  $J_{1,2} = 3.57$  Hz,  $J_{2,3} = 9.5$  Hz, collapses to d on irradiation at 4.762 ppm, H-2 ), 3.813, 3.800 (overlapping triplets, non-first order,  $J_{2,3} = J_{3,4} = J_{4,5}$ , H-3, H-4 ), 3.633 ( m, H-5 ), 3.513 ( complex m, 2H, H-6s ), 1.558 ppm ( s, 2H,  $\text{CH}_3$ -Ar ).

Methylation of 56

The diol ( 56 752 mg, 1.6 mmol ) was suspended in 30 mL of dry dichloromethane and chilled in an ice bath. Boron trifluoride etherate ( 0.1 mL, freshly distilled under nitrogen ) was added, followed by a solution of diazomethane ( 0.6 M in dichloromethane ) in portions until a persistent yellow color remained. The solution was allowed to warm to, and stir at, room temperature for two hours. The flocculent precipitate ( polymethylene ) that formed was filtered and the filtrate washed with 1 M aqueous sodium bicarbonate solution followed by water. Tlc indicated incomplete reaction so the solvent was evaporated and replaced with fresh dichloromethane and the above procedure repeated. This furnished material showing  $^1\text{H-NMR}$  ( 300 MHz )  $\delta$ : 6.97-7.85 ( 10H, Arom. ), 5.656 ( dd,  $J_{2,3} = 10.4$ ,  $J_{3,4} = 9.6$  Hz, H-3 ), 4.965 ( d,  $J_{1,2} = 3.63$  Hz, H-1 ), 4.497 ( dd,  $J_{1,2}$ ,  $J_{2,3}$ , H-2 ), 3.772 ( dt, H-5 ), 3.643 ( dd,  $J_{6a,6b} = 10.8$ ,  $J_{5,6a} = 3.8$  Hz, H-6a ), 3.600 ( dd,  $J_{6a,6b}$ ,  $J_{5,6b} = 3$  Hz, H-6b ), 3.519 ( t,  $J_{3,4} = J_{4,5}$ , H-4 ), 3.431, 3.424, 3.312 ( 3s, 3H each,  $\text{OCH}_3$  ), 2.21 ( s, 3H,  $\text{Ar-CH}_3$  );  $^{13}\text{C}$ - (partially decoupled )  $\delta$  : 164.707 ( s, CO ), 144.534-127.444 ( Arom. ), 97.698 ( d, C-1 ), 77.006 ( d, C-2 ), 76.901 ( d, C-4 ), 71.658 ( d, C-3 ), 70.225 ( t, C-6 ), 69.335 ( d, C-5 ), 60.183, 59.147, 55.595 ( 3q,  $\text{OCH}_3$  ), 21.447 ( q,  $\text{Ar-CH}_3$  ). thereby

establishing the structure as methyl 4,6-di-O-methyl-3-O-benzoyl -2-O-tosyl- $\alpha$ -D-glucopyranoside (57).

#### Reduction of 57 with LTBH

An ice-chilled solution of 284 mg ( 0.59 mmol ) of 57 in 5 mL of THF was treated with 6 mL of LTBH ( 6 mol. equiv. ) and heated to reflux. The reaction appeared complete ( tlc, solvent B ) after 15 min. The solution was cooled after a further 15 min. and the excess reagent destroyed with methanol. The resultant solution was partitioned between ether ( 20 mL ) and water ( 10 mL ) after which the aqueous solution was washed twice with 25 mL of chloroform. The two organic solutions were dried (  $MgSO_4$  ) separately and the chloroform solution showed one spot (  $R_F$  0.27, solvent D ) while the ether solution showed three spots including that mentioned above and starting material (  $R_F$  0.63 ). Concentration of the chloroform solution yielded 30 mg of a colorless syrup which gave the following  $^1H$ -nmr ( 300 MHz ) data: 4.58 ( s, H-1 ), 3.85 ( very narrow m, H-2 ), 3.7-3.3 ( unresolved signals with contamination, H-4,5 ), 3.43, 3.41, 3.35 (3s,  $OCH_3$  ), 2.24 ( dt,  $J_{2,3e} = J_{3e,4} = 3$ ,  $J_{gem} = 8$  Hz, H-3e ), 1.73 ( td,  $J_{gem} = J_{3a,4}$ ,  $J_{2,3a} = 3$  Hz, H-3a ) which are consistent with the methyl 4,6-di-O-methyl -3-deoxy- $\alpha$ -D- arabino hexopyranoside structure shown ( 58 ).

Methylation of methyl 4,6-O-benzylidene-2-O-tosyl- $\alpha$ -D-glucopyranoside (59)

The starting material ( 59, 10 g, 23 mmol ) was dissolved in 50 mL of N,N-dimethylformamide ( DMF ) containing, suspended, 10 g each of Ba(OH)<sub>2</sub> and BaO. Iodomethane ( 10 mL, 160 mmole ) was added slowly and the suspension stirred 1 h at room-temperature whereupon tlc ( solvent E ) indicated complete disappearance of the starting material ( R<sub>F</sub> 0.26 ) and formation of a single new spot ( R<sub>F</sub> 0.40 ). The reaction mixture was diluted with chloroform and filtered. The filtrate was diluted with benzene (total solvent volume 400 mL ) and washed 5 times with water. The organic solution was dried with magnesium sulfate. Crystallization of the product occurred during concentration of the solution on a rotary evaporator to afford ( after recrystallization from boiling ethyl acetate ) 8.08 g ( 78% ) of 60 mp 159-162° C, lit.<sup>33</sup> mp 156-157°. A subsequent crop of crystals weighed 1.13 g for a total yield of 89%.

Debenzylidenation of 60

A suspension of 1.00 g ( 2.22 mmol ) of 60 in 80% aqueous acetic acid was heated on a steam bath 1 h. The acetic acid was removed by repeated evaporation from toluene. Column chromatography ( silica, solvent B ) of the material thus obtained gave 545 mg ( 88% ) of ( 61 ) which were used directly in the next experiment.

Reduction of 61 with LTBH

The 545 mg of 61 obtained above were dissolved in 10 mL of THF, chilled, and treated with LTBH ( 10 mL, 6.66 mol. equiv. ). After 5 h of boiling, tlc ( solvent D ) of the reaction mixture showed virtually complete disappearance of the starting material (  $R_F$  0.58 ) and formation of a new spot (  $R_F$  0.23 ). The reaction mixture was chilled and methanol added dropwise until the cessation of gas evolution. Acetic anhydride ( approximately 1 mL ) was added dropwise to the stirred solution which was then allowed to stir 1 h at ice-temperature. Ether ( 50 mL ) was added to the reaction mixture which was subsequently washed with water then with saturated brine. The combined aqueous washings were themselves washed with ether followed by chloroform ( 5x90 mL ). The charring spot on tlc (  $R_F$  0.23 ) was found solely in the chloroform solution

which, after drying and removal of solvent, represented 280 mg of material. Preparative tlc ( solvent D ) furnished 188 mg of material which gave the following nmr spectra:  $^1\text{H}$ - ( 300 MHz ) 4.93 ( d,  $J_{1,2} = 4$  Hz, H-1 ), 4.75 ( dd,  $J_{1,2}$ ,  $J_{2,3} = 10$  Hz, H-2 ), 3.8-3.6 ( obscured by contamination, H-3 to H-6s ), 3.61, 3.42 ( 2s,  $\text{OCH}_3$ s ), 2.18 ppm ( s,  $\text{CH}_3\text{CO}$  );  $^{13}\text{C}$ - ( partially decoupled ) 170.423 ( s, CO ), 97.051 ( d, C-1 ), 81.003 ( d, C-2 ), 73.526, 70.891, 69.888 ( 3d, C-3 to C-5 ), 61.796 ( t, C-6 ), 61.013, 55.160 ( 2d,  $\text{OCH}_3$ s ) 21.071 ppm ( q,  $\text{CH}_3\text{CO}$  ).

#### Reduction of 27 with sodium triethylborohydride

Sodium triethylborohydride ( 3.2 mL, 1 M solution in THF ( Aldrich ), 8 mol. equiv. ) was added dropwise to a chilled solution of THF ( 2 mL ) containing 220 mg ( 0.4 mmole ) of 27. The reaction mixture was heated to boiling whereupon it became turbid. Tlc ( solvent B ) indicated complete reaction after 30 min. The reaction was then processed essentially as described for the reduction of 27 with LTBH. After exhaustive extraction of the resultant aqueous solution with chloroform, the material thus obtained showed an nmr ( 60 MHz ) superimposable on that of methyl abequoside ( 29 ) but with additional signals of an apparently isomeric compound. The signal areas of the two "anomeric" signals were in the ratio 1.7:1 of 29 to the isomer.

When an aqueous solution of the mixture was treated with sodium metaperiodate the tlc spot (  $R_F$  0.34, solvent B ) corresponding to the isomer disappeared while that of 29 remained unchanged. This result implies that the isomer had a 1,2 dihydroxyl array and was probably the anti-Fürst-Plattner ring-opening product.

Reduction of 25 with LTBH in the presence of 12-crown-4

The sugar sulfonate ( 25, 1.321 g, 3.97 mmole ) was dissolved in 20 mL of THF and 2.6 mL ( 4.4 mmole ) of 12-crown-4 were added followed by 16 mL ( 4 mol. equiv.)

of LTBH. No reaction occurred after 1 h at room temperature but the starting material disappeared after 30 min. at reflux temperature. After destroying the excess reagent with methanol, the reaction mixture was partitioned between chloroform and water. The aqueous phase was extracted repeatedly with chloroform ( total volume 200 mL ) but still contained most of the product and was therefore concentrated in the presence of potassium carbonate. Complete evaporation of the solvent gave a solid residue which, after exhaustive extraction with ethyl acetate, yielded 200 mg ( 30% ) of material which, after chromatographic purification, proved identical to the 42 previously prepared.

### Reduction of 25 with L-Selectride

The sugar ( 25, 1.907 g, 5.7 mmole ) was dissolved in 25 mL of THF and 23 mL ( 4 mol. equiv. ) of L-Selectride ( lithium tris(sec-butyl)borohydride, 1 M solution in THF, (R) Aldrich Chemical Co. ) were added. One hour and 15 min. of boiling caused complete consumption of starting material. Methanol was added to the solution ( which contained a flocculent white suspension ), after chilling, and it was subsequently extracted with chloroform. The contents of the organic solution seemed to have decomposed during drying overnight with  $MgSO_4$  but more of the material was isolated from the aqueous solution after concentration to a dry residue and extraction of the compound with ethanol and ethyl acetate. The product thus isolated (987 mg, heavily contaminated with salts ) proved identical to that obtained from the reduction of 25 with LTBH in the presence of 12-crown-4.

### Methyl 4,6-O-benzylidene-3-C-methyl-2-O-p-tolylsulfonyl- $\alpha$ -D-allopyranoside

A solution of methyl 4,6-O-benzylidene-3-C-methyl- $\alpha$ -D-allopyranoside, prepared according to the method of Carey and Hodgson<sup>2</sup> ( 3.52 g, 11.88 mmole ), p-tolylsulfonylchloride ( 2.72 g, 1.2 mol. equiv. ) and 100 mg of N,N-dimethylaminopyridine in 25 mL of

pyridine was stirred 51 h at room temperature after which time tlc ( solvent B ) indicated complete reaction. The reaction mixture was poured into 60 mL of ice-water to which was added 40 mL of chloroform. The two layers were separated and the organic solution washed with 50 mL of 0.1 HCl followed by 50 mL of water. Drying (  $\text{MgSO}_4$  ) and removal of solvent furnished a material (  $R_F$  0.54, solvent B ) which, after successive recrystallizations from ethyl acetate-hexane, was isolated in 82% yield. the product showed mp 140-142° C,  $[\alpha]_D^{25} +42.9^\circ$  ( c 1.4 );  $^1\text{H-nmr}$  ( 300 MHz )  $\delta$  7.28-7.89 ( 9H, Arom. ), 5.519 ( s, PhCH ), 4.822 ( d,  $J_{1,2} = 3.63$  Hz, H-1 ), 4.343 ( dd,  $J_{\text{gem}} = 10.25$ ,  $J_{5,6e} = 5.13$  Hz, H-6e ), 4.332 ( d,  $J_{1,2}$ , H-2 ), 4.060 ( td,  $J_{4,5} = J_{\text{gem}}$ ,  $J_{5,6}$ , H-5 ), 3.724 ( t,  $J_{\text{gem}} = J_{5,6a}$ , H-6a ), 3.379 ( s, 3H,  $\text{OCH}_3$  ), 3.309 ( d,  $J_{4,5}$ , H-4 ), 2.463 ( s, 3H,  $\text{ArCH}_3$  ), 1.198 ppm ( s, 3H,  $\text{CH}_3$  );  $^{13}\text{C-nmr}$  ( partially decoupled )  $\delta$  145.416-126.190 ( 8 signals, Arom. ), 101.829 ( d, PhCH ) 98.748, ( d, C-1 ), 81.709 ( d, C-2 ), 77.735 ( d, C-4 ), 71.941 ( s, C-3 ), 68.762 ( t, C-6 ), 59.149 ( s, 3H,  $\text{OCH}_3$  ), 56.294 ( d, C-5 ), 21.693 ( q,  $\text{ArCH}_3$  ), 20.612 ppm ( q,  $\text{CH}_3$  ); mass spectrum ( DCI ether ) m/z 451 ( M+1 ), 419 ( M-OMe ), 297 ( M-1-HOTs ). Anal. (for  $\text{C}_{22}\text{H}_{26}\text{O}_8\text{S}$  ) calcd. C 58.65, H 5.82, S 7.12: found C 58.58, H 6.02, S 6.91. These data indicate the 2-mono-p-tolylsulfonate derivative 69

Reduction of 69 with LTBH

Compound 69 ( 450 mg, 1 mmole ), dissolved in 10 mL of THF was chilled in an ice-bath and treated with 5 mL of LTBH ( 5 mol. equiv. ). After 20 h of boiling, the reaction mixture was cooled and more LTBH was added. A further 72 h at reflux temperature had not effected complete disappearance of the starting material ( tlc, solvent B ) although there was extensive decomposition ( heavy streaking in tlc ). The reaction was not continued further.

Methyl 6-deoxy-6-bromo-4-O-benzoyl-3-C-methyl-2-O-p-tolylsulfonyl- $\alpha$ -D-glucopyranoside

Compound 69 ( 1.351 g, 3 mmole ) was dissolved in 20 mL of carbon tetrachloride containing 5 mL of 1,2-dichloroethane. N-bromosuccinimide ( 0.641 g, 1.2 mol. equiv. ) and barium carbonate ( 0.710 g, 1.2 mol. equiv. ) were added and the mixture boiled 24 h. The reaction mixture was then cooled, diluted with chloroform, washed with a saturated solution of sodium carbonate, and dried with magnesium sulfate. Removal of the solvent and drying under vacuum gave 1.40 g (88% ) of a dry foam identified as the title compound (70 ) by mass spectrum ( DCI, ether )  $m/z$  529/531 (  $M+1$  ) 497/499 (  $M-OCH_3$  ), 451 (  $M+2-Br$  ), 343 (  $M+2-OTs$  );  $ir$ :  $\nu$  (  $cm^{-1}$  ) 3505 ( OH ), 1725 ( CO ), 1600 ( Ph ), 1375/1180 (  $OSO_2R$  ), 1100-1150 ( C-O );  $^1H$ -nmr (300 MHz)

$\delta$  8.085-8.053 ( 2d, 4H, Ph-SO<sub>2</sub> ), 7.864-7.363 ( m, 5H, Ph-CO ), 4.937 ( d,  $J_{4.5} = 10.15$  Hz, H-4 ), 4.914 ( d,  $J_{1,2} = 3.63$  Hz, H-1 ), 4.301 ( d,  $J_{1,2}$ , H-2 ), 4.279 ( ddd,  $J_{4.5}$ ,  $J_{5.6a} = 2.47$ ,  $J_{5.6b} = 7.46$  Hz, H-5 ), 3.482 ( dd,  $J_{5.6a}$ ,  $J_{gem} = 11.05$  Hz, H-6a ), 3.399 ( dd,  $J_{5.6b}$ ,  $J_{gem}$ , H-6b ), 3.465 ( s, 3H, OCH<sub>3</sub> ), 2.462 ( s, 3H, ArCH<sub>3</sub> ), and 0.994 ppm ( s, 3H, CH<sub>3</sub> ); Anal. ( for C<sub>22</sub>H<sub>25</sub>BrO<sub>8</sub>S ) calcd. C 49.9, H 4.76, Br 15.1 S 6.06; found C 47.86, H 4.75, S 5.69.

Chapter VII

APPENDIX

Calculation of Molecular Rotations

3-(hydroxymethyl)- $\alpha$ -L-lyxo  $^3T_2$ 

bond	Contributors	Contributions	Total
C-1 - O-r	+C/C(30)-O/C(90)	+23-58	-35
C-2 - C-1	-C/O(30)+C/O(90)+O/O(105)-O/O(165)	-29+58+50-13	+66
C-3 - C-2	+C/C(45)+C/O(30)+C/C(150)-C/O(75)	+32+29+23-56	+28
C-4 - C-3	-O/C(45)-O/C(165)-C/C(45)+C/C(60)	-41-15-33+40	-49
O-r - C-4	+C/C(30)-C/C(90)	+23-46	-23
O-1 - C-1	-O/C(60) see discussion	-50	-50
C-3' - C-3	see discussion	0	0

Table 1

3-(hydroxymethyl)- $\alpha$ -D-ribo  $^0E$ 

bond	Contributors	Contributions	Total
C-1 - O-r	-C/C(45)+O/C(75)	-32.5 + 56	+23.5
C-2 - C-1	+O/C(30)-O/C(90)+O/O(30)+O/O(120)	29-58+26+45	+42
C-3 - C-2	C/O(180)-O/C(120)+O/C(120)+C/C(180)	0-50+50+0	0
C-4 - C-3	-O/C(30)-O/C(150)-C/C(150)+C/C(90)	-29-29-23+46	-35
O-r - C-4	+C/C(45)+C/C(165)	32.5+12	+44.5
O-1 - C-1	+O/C(60)	+50	+50
C-3' - C-3	0 or +O/C(90)-O/C(30)	0 or 58-29	0, +29

Table 2

3-(hydroxymethyl)- $\alpha$ -D-ribo  $O_T^4$ 

bond	Contributors	Contributions	Total
C-1 - O-r	-C/C(45)+C/O(75)	-32.5 + 56	+23.5
C-2 - C-1	+C/O(30)-C/O(90)+O/O(30)+C/O(150)	+29-58+26+29	+26
C-3 - C-2	+C/C(15)-C/O(105)+C/C(90)+C/O(15)	+12-56+46+15	+17
C-4 - C-3	-O/C(45)-C/C(150)+C/C(90)-C/C(150)	-41-23+46-23	-41
O-r - C-4	+C/C(45)+C/C(180)	+32.5	+32.5
O-1 - C-1	+C/O(60)	+50	+50
C-3' - C-3	0. or +C/O(60)	0 or +50	0,50

Table 3

3-(hydroxymethyl)  $\alpha$ -D-xylo  $E^2$ 

bond	Contributors	Contributions	Total
C-1 - O-r	-C/C(30)+O/C(90)	-23+58	+35
C-2 - C-1	-C/O(30)+C/O(45)+O/O(45)+O/O(165)	-29+41+37+13	+62
C-3 - C-2	-C/C(45)-C/O(165)-C/O(150)+C/O(75)	33-15-29+56	+45
C-4 - C-3	+O/C(30)+O/C(150)-C/C(90)+C/C(30)	+29+29-46+23	+35
O-r - C-4	+C/C(0)+C/C(120)	+40	+40
O-1 - C-1	+C/O(60)	+50	+50
C-3' - C-3	0		

Table 4

2-(hydroxymethyl)- $\alpha$ -D-ribo  $^3T_2$ 

bond	Contributors	Contributions	Total
C-1 - O-r	+C/C(15)+O/C(135)	+12+41	+53
C-2 - C-1	-C/O(45)-C/O(150)+C/O(90)-C/O(45)	-41-29+58-41	-53
C-3' - C-2	+C/C(45)+O/C(45)+O/C(165)-C/C(75)	+33+41+15-44	+45
C-4 - C-3	-O/C(45)-O/O(165)-C/C(165)+C/O(75)	-41-13-12+58	-8
O-r - C-4	+C/C(30)+C/C(150)	+23+23	+46
O-1 - C-1	+C/O(60)	+50	+50
C-2' - C-2	0, +O/C(15) or +O/C(60) (see text)	0, +15 or +50	---

Table 5

2-(hydroxymethyl)- $\alpha$ -D-ribo  $^2E$ 

bond	Contributors	Contributions	Total
C-1 - O-r	+O/C(90)	+58	+58
C-2 - C-1	+C/O(45)-C/O(90)+C/O(150)+C/O(30)	+41-58+29+29	+41
C-3 - C-2	-C/C(30)-C/C(150)-O/C(30)+O/C(90)	-23-23-29+58	-17
C-4 - C-3	+O/C(30)-O/O(105)-C/C(105)+C/O(135)	+29-50-44+41	-24
O-r - C-4	+C/C(120)	+40	+40
O-1 - C-1	+C/O(60)	+50	+50
C-2' - C-2	+C/O(60) (if staggered)	+50	+50

Table 6

2-(hydroxymethyl)- $\alpha$ -D-arabino <sup>2</sup>E

bond	Contributors	Contributions	Total
C-1 - O-r	+O/C(120)	+29	+29
C-2 - C-1	-C/O(30)+C/O(90)-C/O(150)-C/O(135)	-29+58-29-41	-41
C-3 - C-2	+C/C(30)+C/C(135)-C/O(105)+C/O(135)	+23+33-56+41	+41
C-4 - C-3	-C/C(30)-C/O(150)+C/O(105)-C/C(135)	-23-29+56-33	-29
O-r - C-4	+C/C(30)+C/C(135)	+23+33	+56
O-1 - C-1	+C/O(60)	+50	+50
C-2' - C-2	0 (if freely rotating, - if stagg'd)	0	0

Table 7

2-(hydroxymethyl)- $\alpha$ -D-xylo <sup>2</sup>E

bond	Contributors	Contributions	Total
C-1 - O-r	-C/C(30)+O/C(90)	-23+58	+35
C-2 - C-1	+C/O(30)+C/O(30)-C/O(90)+C/O(150)	+29+29-58+29	+29
C-3 - C-2	-C/C(30)-C/C(150)+O/C(90)-O/C(135)	-23-23+58-41	-29
C-4 - C-3	+O/C(30)+C/O(30)+O/O(105)-C/C(135)	+29+29+50-33	+75
O-r - C-4	+C/C(120)	+23	+23
O-1 - C-1	+C/O(60)	+50	+50
C-2' - C-2	0 ( see text )	0	0

Table 8

2-(hydroxymethyl)- $\alpha$ -D-lyxo <sup>3</sup>E

bond	Contributors	Contributions	Total
C-1 - O-r	+O/C(135)	+41	+41
C-2 - C-1	-C/O(30)+C/O(105)-C/O(135)-C/O(135)	-29+56-41-41	-55
C-3 - C-2	+C/C(30)+O/C(30)+O/C(135)-O/C(90)	+23+29+41-58	+35
C-4 - C-3	-O/C(30)+O/O(90)-O/C(30)-O/C(135)	-29+52-29-41	-47
O-4 - C-4	+C/C(30)+C/C(135)	+23+33	+56
O-1 - C-1	+C/O(60)	+50	+50
C-2' - C-2	0 ( see text )	0	0

Table 9

2-(hydroxymethyl)- $\alpha$ -D-xylo <sup>2</sup>T<sub>3</sub>

bond	Contributors	Contributions	Total
C-1 - O-r	-C/C(15)+O/C(105)	-12+56	+44
C-2 - C-1	+C/O(45)+C/O(45)+C/O(165)-C/O(75)	+41+41+15-56	+41
C-3 - C-2	-C/C(45)-C/C(165)+O/C(75)-O/C(165)	-33-12+56-15	-4
C-4 - C-3	+O/C(45)+C/O(45)+O/O(165)-C/C(75)	+41+41+13-44	+51
O-r - C-4	-C/C(30)+C/C(105)	-23+44	+21
O-1 - C-1	+C/O(60)	+50	+50
C-2' - C-2	0 or +C/O(60) ( see text )	0 or +50	0,+50

Table 10

## Chapter VIII

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Part 2

STUDIES OF TREHALOSE DERIVATIVES

## Chapter IX

### ABSTRACT

Deprotection of 4-( N,N-dibenzyl )amino-2,3,4-trideoxy- $\alpha$ -D-hex-2-enopyranosyl- $\alpha$ -D-glucopyranoside 9 ) was attempted via catalytic hydrogenolysis and transfer hydrogenolysis. The deprotected material 11 was never positively identified as a product in these reactions although slightly encouraging nmr data were obtained.

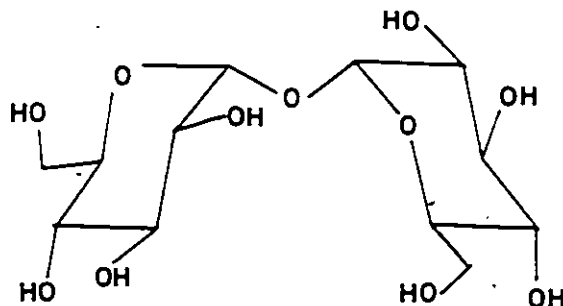
Oxyamination of the unsaturated sugar 8 was attempted. This reaction furnished a substance that was apparently a mixture of isomers and was therefore subjected to an attempted deprotection using sodium in liquid ammonia. The latter reaction was only attempted once and did not furnish anything resembling the desired products.

## Chapter X

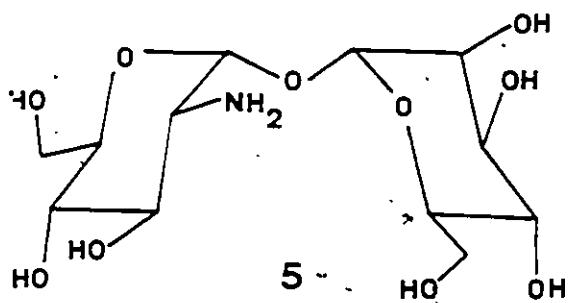
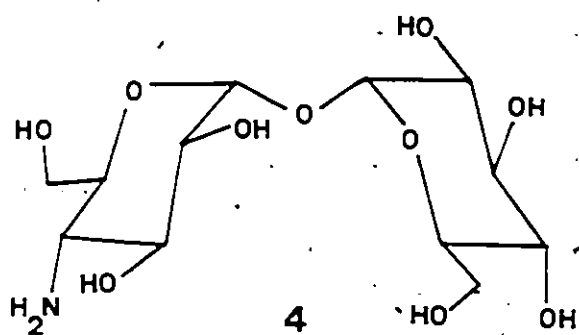
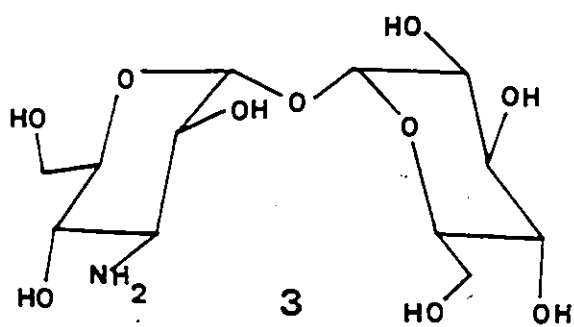
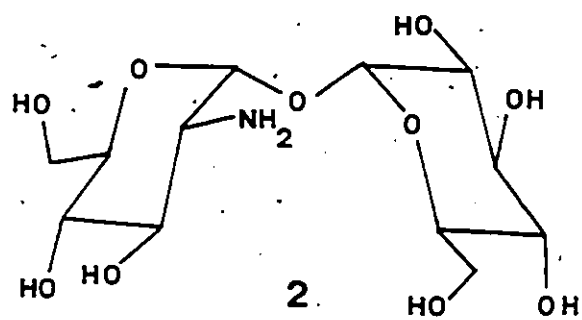
### INTRODUCTION

Ongoing research in this laboratory has focussed on the synthesis of symmetric<sup>1</sup> and unsymmetric<sup>2</sup> amino derivatives of the disaccharide  $\alpha$ -D-glucopyranosyl  $\alpha$ -D-glucopyranoside ( $\alpha,\alpha$ -trehalose, 1).

Trehalose abounds in Nature and is especially important in the insect world, in mushrooms and in mycobacteria. Its chemistry<sup>3</sup> and biochemistry<sup>4</sup> have been reviewed. The synthesis of aminated derivatives is of interest because of the discovery that 2-amino-2-deoxy- $\alpha$ -D-glucopyranosyl  $\alpha$ -D-glucopyranoside (trehalosamine, 2)<sup>5</sup>, its 3- (3)<sup>6</sup> and 4-amino (4)<sup>7</sup> isomers as well as 2-amino-2-deoxy- $\alpha$ -D-glucopyranosyl  $\alpha$ -D-mannopyranoside (5)<sup>8</sup>, isolated from Streptomyces<sup>9,10,11</sup> and Norcardiopsis<sup>12</sup> species, display antibiotic activity.



1



An additional use of derivatives of trehalose has been in the study of the hydrolytic enzyme trehalase (  $\alpha,\alpha$ -trehalose glucohydrolase, EC 3.2.1.28 ), which cleaves the disaccharide's glycosidic linkage. The study of binding and inhibitory properties of the derivatives have led to an understanding of the mechanism of hydrolysis by this enzyme' that is perhaps unparalleled for any similar enzyme. To this end, additions to the family of trehalose derivatives are always welcome.

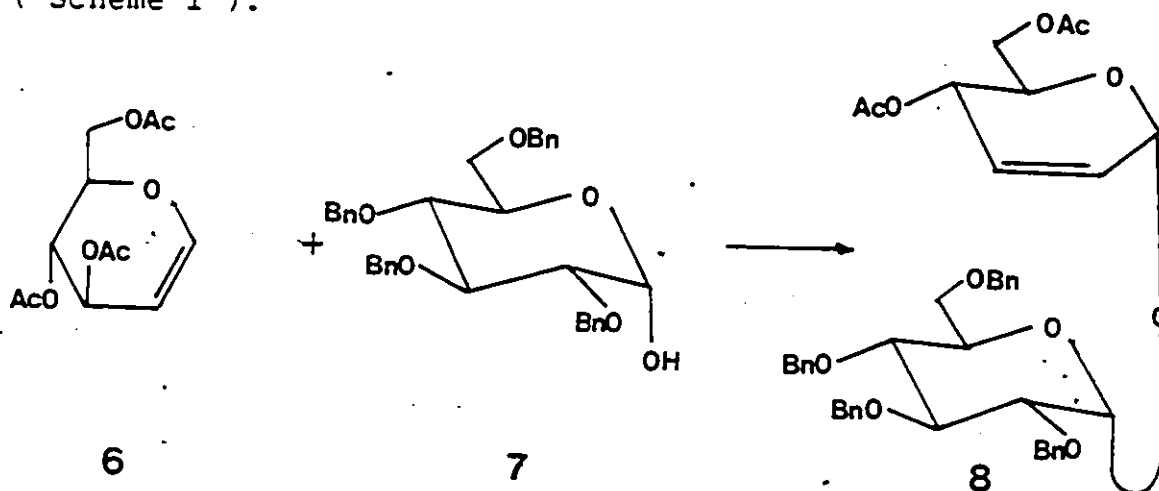
The studies of enzyme specificity have, so far, shown that a requirement for substrate recognition is one intact glucopyranosyl moiety while for the catalytic step an equatorial 2-hydroxyl group is required. Derivatives having a structure suitable for recognition but lacking this particular hydroxyl group are competitive inhibitors of the enzyme'.

Inhibition of the trehalase enzyme has, in addition to its academic interest, potential clinical significance in that trehalose ( and therefore, trehalase ) plays a crucial role in the metabolism of mycobacteria ( e.g. Mycobacterium tuberculosis and M. leprae, the organisms which cause human tuberculosis and leprosy (Hansen's disease) respectively ), where it is found as mycolic ester in the toxic cord factor of these bacilli'.

While the synthesis of symmetric trehalose derivatives is well established<sup>10</sup>, unsymmetric derivatives are not so

readily available. Selective functionalization of one ring of trehalose itself is difficult due to the chemical equivalence of the two halves. An alternate approach of forming two halves separately, then joining them by glycosidation is hampered by the difficulty in achieving anomeric specificity. A recent development in this laboratory<sup>11</sup> has enabled us to approach the synthesis of derivatives by the latter route but with virtually exclusive formation of a product with the correct anomeric configurations.

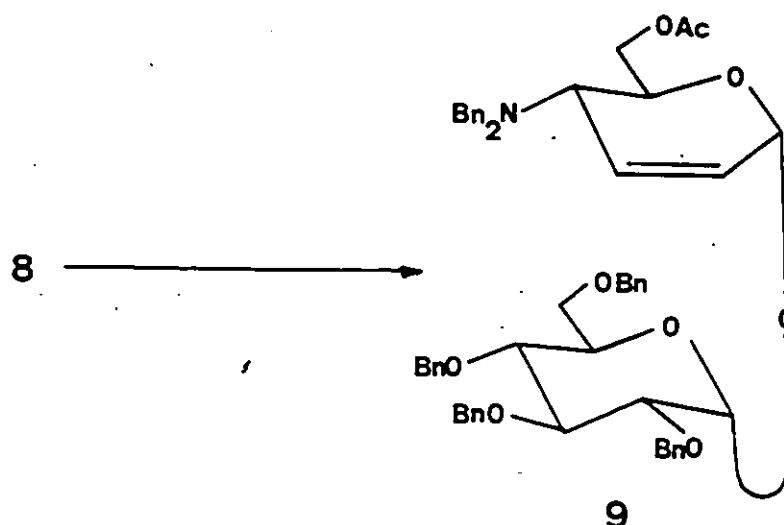
Baer and Hanna<sup>1,1</sup> have noted that Lewis acid mediated condensation of tri-O-acetyl-D-glucal ( 6 ) and 2,3,4,6-tetra-O-benzyl-glucopyranose ( 7 ) leads to the formation of the functionalized trehalose derivative ( 8 ), in high yield ( Scheme 1 ).



Scheme 1

The unsaturated half of the molecule is obviously well suited for functionalization that may lead to a variety of derivatives hard to obtain otherwise. The focus of this work was to exploit this "handle" and prepare unsymmetric amino derivatives of trehalose.

The first step toward such unsymmetric derivatives was taken during the previous<sup>1,1</sup> study. Allylic amination, mediated by zero-valent palladium, was effected following a procedure previously published<sup>1,2</sup> by the authors. This led to formation of the unsaturated N,N-dibenzylamino derivative 9 in good yield<sup>1,1</sup> ( Scheme 2 ).



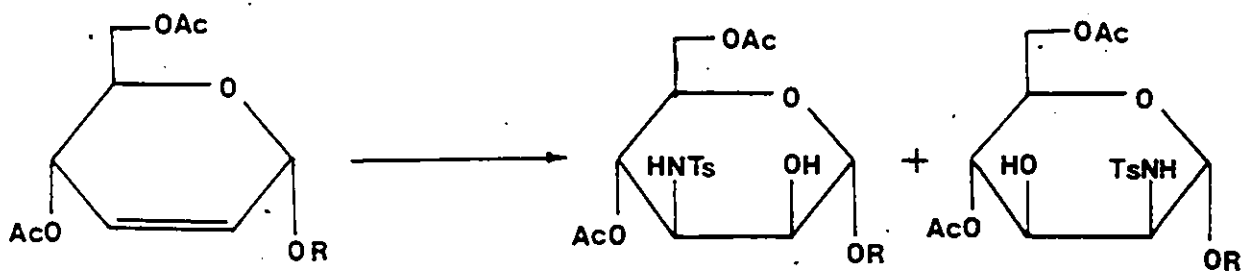
Scheme 2

However, deprotection of 9 to afford the free sugar was not successful and led to complicated mixtures of products<sup>11</sup>. The amination itself was also somewhat problematic in that it could not be performed on larger scales ( *i.e.* >6 mmole ) without extensive formation of tetrabenzyl hydrazine<sup>11</sup>. It was the purpose of this author's investigations to determine the conditions for a successful deprotection and, if possible, to improve the preparative procedure originally described<sup>11</sup>.

In addition, the unsaturation present in 8 seemed well suited for oxyamination using Chloramine-T and osmium tetroxide, after the method of Sharpless<sup>12</sup>. This procedure has been applied to the analogous ethyl glycoside 10 (Scheme 3 ), with the resultant formation of a mixture of 2- and 3-amino mannopyranosides<sup>14</sup>. Such derivatives were as yet unknown in the trehalose series and appeared of interest for the reasons outlined above. Given the success of the

method<sup>14</sup> in monosaccharides; we undertook its application to compound 8.

Unfortunately, neither project was particularly successful. Described herein are some of our efforts in this area which, despite their failure, may assist future workers in attempting to complete these projects.



**10** R=Et

**8** R=tetra benzyl glucosyl  
(tbg)

**11** R= tbg

Chapter XI  
ATTEMPTED SYNTHESIS OF  
4-AMINO-2,3,4-TRIDEOXY- $\alpha,\alpha$ -TREHALOSE

Initial attempts at catalytic hydrogenation of the double bond and simultaneous hydrogenolysis of the benzyl protecting groups in compound 9 were not successful, even when performed under pressure<sup>11</sup>. The materials isolated from these reactions generally were unresolvable mixtures of many compounds, presumably partially deprotected species. In one instance, however, chromatography of such a reaction mixture furnished a material with <sup>13</sup>C- spectral characteristics not unlike those expected for the deprotected compound 12. The spectrum contained three high-field signals ( 27-20 ppm ) consistent with the acetyl-methyl and the two deoxy carbons. Two doublets at 91.0 and 93.0 ppm were indicative of anomeric carbons. There was also a cluster of signals between 74 and 45 ppm which could be attributed to the remaining pyranosidic carbons. A singlet at 173.6 ppm spoke for a carbonyl carbon ( i.e., from the acetyl group ). In addition, however, there were a number of other signals which may or may not have been genuine and which, naturally, prevented accurate assignment of the spectrum. Unfortunately, no other data were obtained for this compound and a similar material was not isolated again.

The afore mentioned results were not entirely unexpected given the reported sluggishness of N-debenzylations in the absence of acid<sup>13</sup>. However, addition of acid to aid in deprotection was precluded because of the known, extreme sensitivity of 2,3-dideoxyglycosides to hydrolysis. This lability may also explain the untoward behaviour of the compound during work-up.

An alternate technique for deprotection that held some promise was transfer hydrogenation<sup>14</sup>. This technique employs, for example, cyclohexadiene as the hydrogen source and a transition metal ( usually palladium ) as the catalyst, and it has been used to efficiently hydrogenolyse benzyl ethers that were difficult to cleave otherwise.

Indeed, when 320 mg of 9 was treated with 25% (by weight) of palladium hydroxide on carbon and cyclohexene in boiling ethanol for 7 days, 118 mg of material was isolated which gave a <sup>13</sup>C-nmr spectrum that lacked any signals indicative of benzyl groups, thereby implying successful deprotection. However, no high-field signals attributable to the deoxy carbons were present. Unfortunately, no useful <sup>1</sup>H-nmr spectrum was obtained to aid in elucidation of the structure of the compound.

The successful completion of this investigation was frustrated by the fact that compound 9 was difficult to prepare in quantities that would allow for additional experiments on a scale adequate for proper purification and

unambiguous characterization of the products. All attempts to scale up the allylic amination of 8 were thwarted by extensive, oxidative amine coupling (to give tetrabenzyl hydrazine, as previously observed<sup>12</sup>), and this author was unable to circumvent that problem. The simultaneously pursued studies on ring contractions in sugar tosylates were gaining priority at this juncture, and the present project was therefore shelved.

## Chapter XII

### ATTEMPTED SYNTHESIS OF TREHALOSE ANALOGUES BY OXYAMINATION

As mentioned in the introduction, the unsaturated half of compound 8 appeared amenable to oxyamination with Chloramine-T and osmium tetroxide. Several attempts were, in fact, made to effect such a transformation. The results of these investigations are presented below.

Treatment of 8 with Chloramine-T and osmium tetroxide in t-butyl alcohol at 50° resulted in apparently complete consumption of starting material after 40 hours. In tlc there appeared a charring spot ( $R_F$  0.44) that ran somewhat faster than the starting material ( $R_F$  0.38) as well as a non-burning, UV-visible spot ( $R_F$  0.2) and a charring spot near the baseline. Work-up furnished a material which crystallized spontaneously and whose nmr spectrum appeared to indicate the presence of the desired products 11. There were acetyl singlets at ca. 2 ppm, ring-proton signals at 5.5-3.5 and abundant aromatic signals at 7-8 ppm. However, upon further purification it was found that the material had consisted largely of tosylamide. The encouraging nmr signals shown by the crude product were doubtless due to

admixed carbohydrate material, possibly the starting compound. Subsequent investigations indicated that the desired compound was the very slow-moving tlc spot. A small amount of material (ca. 23%) was thus obtained which displayed the expected spectral properties but was apparently a mixture of isomers.

As the material gave a homogeneous spot on tlc, separation of the isomers did not appear feasible and deprotection was therefore attempted without further characterization, in the hope that the free compounds, or simple derivatives, would be more amenable to separation. Thus the product was treated with sodium in liquid ammonia for the purpose of simultaneous N-desulfonylation and O-debenzoylation, and O-deacetylation. Processing of the reaction mixture with ammonium chloride and attempted isolation of the amino sugar by means of ion exchange resins gave a material which did not prove to be the desired products as it exhibited only three signals in its  $^{13}\text{C}$ -nmr spectrum. It could not be identified, and the fate of the sugar in this operation remained unclear.

Again, plagued by the difficulty of obtaining sufficient quantities of starting material and the pressing nature of the other work being pursued, this project was abandoned. As with the deprotection investigations mentioned previously, a concerted effort to synthesize large amounts of the starting material and some patience with these

capricious reactions should reward subsequent investigators wishing to complete this work.

## Chapter XIII

### EXPERIMENTAL

#### General Considerations

For general considerations not explicitly stated here, please see the previous section. Palladium hydroxide on carbon was prepared from palladium chloride (Aldrich) by the method of Pearlman<sup>17</sup>. Chloramine-T was freshly prepared from p-toluenesulfonamide by oxidation with 6% NaOCl (laundry bleach) followed by treatment with NaOH as described<sup>18</sup>. Osmium tetroxide (Aldrich) was used as a 0.8M solution in olefin-free hexane.

Attempted Hydrogenolysis of 9

A suspension of 10% palladium on carbon ( 700 mg ) in 99% ethanol (10 mL) containing 9 (700 mg) was stirred under an atmosphere of hydrogen overnight, whereupon a further 300mg of catalyst was added and the reaction allowed to continue for 3 days. The reaction mixture was then filtered and the catalyst washed well with 99% ethanol. The filtrate and washings were concentrated on a rotary evaporator and passed through a Waters Associates "SEP-PAK"<sup>C</sup>-18 reversed-phase column ( methanol eluant ) to afford 220 mg of a syrupy mixture. This material was passed through a short column of silica gel, with methanol as the eluant. The product obtained (190 mg) showed the following <sup>13</sup>C-nmr signals (water solvent without internal reference):  $\delta$  173.63 (singlet), 128.51, 92.95, 91.16 ( three doublets ), 72.74-69.63 ( five signals, multiplicity unresolved ), 61.18, 60.47 ( apparent triplets ), 45.24 (doublet), 27.87, 23.23, 21.87 (three signals, indeterminant multiplicities). No further data were obtained.

Attempted Transfer Hydrogenolysis of 9

To a suspension of 32 mg of 10% Pd(OH)<sub>2</sub> on carbon in 1.5 mL of cyclohexene and 5 mL of 99% ethanol was added 320 mg of 9. The mixture was stirred under reflux for six days following which another 80 mg of catalyst, 5 mL of 99% ethanol, and 2 mL of cyclohexene were added. Continued

boiling for another 24 hours, followed by filtration, washing of the catalyst with ethanol, and evaporation of the filtrate yielded a dry foam weighing 118mg whose  $^{13}\text{C}$ -nmr. spectrum showed the following signals in water solvent with no internal reference. The low signal to noise ratio prevented definitive multiplicity assignment from the off-resonance partially decoupled spectrum. The fully decoupled signals appeared at 178.1, 98.2, 94.5, 78.3, 78.1, 76.5, 75.1, 73.8, 72.0, 63.1, and 63.0 ppm. The signals at 98.2 and 94.5 ppm appeared to be doublets while the highest field signal(s) at 63 ppm seemed to be a triplet.

#### Attempted Oxyamination of B

A solution of B ( 2.366g, 3.143 mmole ) in 40 mL of tertiary butyl alcohol containing 2.66g of Chloramine-T and 1.988g of silver nitrate was stirred at 50° for three hours. Osmium tetroxide solution ( 0.795 mL, 0.8M ) was added and the mixture stirred overnight. After addition of sodium bisulfite ( 0.696g ) in water ( 23 mL ) the mixture was allowed to stir for another 24 hours and then filtered, and the solids were washed with ethyl acetate. The filtrate and washings were concentrated on a rotary evaporator to yield a light foam which was taken up in ethyl acetate. The solution was washed with saturated brine followed by water, dried (  $\text{MgSO}_4$  ), and then concentrated. Spontaneous crystallization occurred upon removal of the solvent. In

preliminary trials this was thought to be the desired material and its  $^1\text{H-NMR}$  did lend some support to this thought, as described in the previous section. However, after recrystallization of the material from ethyl acetate, the melting point of the crystals showed them to be simply tosylamide. The material was, therefore, taken up again in minimal ethyl acetate and was then chromatographed on silica gel (ethyl acetate-hexane, 1:4) to yield 696 mg of syrup. In preliminary trials, with similar proportions of reactants and times, spontaneous crystallization from the ethyl acetate solution occurred on standing. When the material thus obtained was analyzed by  $^1\text{H-NMR}$  it had the features described in the previous section. After recrystallization the material proved, by melting point, to be simply tosylamide. Chromatography was therefore undertaken immediately in the case here described, to remove the undesired by-product. The proton nmr spectrum (300 MHz) in  $\text{CDCl}_3$  had the following general features which, although compatible with the expected structure 11, could not be definitively analyzed. Aromatic signals occurred from 8.1-7.2 ppm, with the most intense being at 7.33-7.30. Numerous multiplets along with spurious signals were found from 5.5-4.5 ppm and similarly at 4.3-4.1 and 3.9-3.5 ppm. There were several sharp singlets upfield from 2.5 ppm with two notable pairs occurring at 1.98 and 1.94, and 1.25 and 1.22 ppm, respectively. The lowest-field pair could be construed as being due to the two acetyl groups while the

other pair might have been caused by solvent. Given the above assignments, no signals indicative of tosyl-methyl were seen. The multiplets in the range 5.5-3.5 ppm were in the region where the ring-proton signals of the desired compound would be expected. The presence of a multiplet at 8.1 ppm, relatively weak in comparison to the bulk of the aromatic resonances caused by the benzyl groups did, however, speak for the introduction of tosyl into the molecule. The integration offered no useful information. As the product appeared chromatographically homogeneous ( $R_F$  0.15, Ethyl acetate-hexane, 1:1) but was evidently a mixture, it was decided to proceed immediately to the next step.

#### Attempted Birch reduction of 10

All the material from the previously described experiment was suspended in approximately 100 mL of ammonia at  $-50^\circ$ . To the mixture was added about 100 mg of sodium with extensive swirling. Addition of a further 100 mg of Na caused a blue color which persisted for nearly 15 minutes and which returned for another hour upon addition of a third 100 mg portion of sodium. Ammonium chloride (1.1g) was added to quench the reaction and the remaining ammonia was evaporated by a stream of nitrogen in the fume hood. The solid material thus obtained was left on a rotary evaporator in a  $30^\circ\text{C}$  bath for one hour to remove any occluded ammonia.

It was then dissolved in water and stirred with a weak-acid cation exchange resin (Amberlite IRC-50(H<sup>+</sup>) ) until it showed ca. pH 6, whereupon the resin was filtered off and washed exhaustively with water. The resultant filtrate was similarly treated but with a strong-base anion-exchange resin (Dowex-1 X8 (OH<sup>-</sup>) ). The filtrate from this operation was then twice subjected to this sequential treatment with weak-acid and strong-base resin, after which, silver nitrate did not precipitate chloride from the solution. The combined batches of cation-exchange resin thus obtained were then washed thrice with 15% aqueous ammonia. The water and ammonia were removed on a rotary evaporator to furnish a brown, glassy expected to be the deblocked amino sugar. However, the <sup>13</sup>C-nmr spectrum of an aqueous solution of the material ( with no internal reference ) showed but three signals. One signal was at very low field while the others were a moderately high field. No shifts were reported and no further analyses were done on the compound.

Chapter XIV

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