ACKNOWLEDGMENT

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ABSTRACT

SECTION I

A method of chain elongation at the non-reducing terminal of 6-deoxy-6-halo and 6-O-tosyl hexopyranosides, to give methyl (methyl-deoxyhepto-pyranosid)uronates was developed on the basis of organoiron chemistry. Thus, methyl 2,3,4-tri-O-acetyl-6-O-p-tolysulfonyl-β-D-glucopyranoside reacted almost instantly under mild conditions with sodium dicarbonyl-η^5-cyclopentadienyliron (NaFp) in tetrahydrofuran, to form an isolable, well-characterized dicarbonyl-η^5-cyclopentadienyl(methyl 2,3,4-tri-O-acetyl-6-deoxy-β-D-glucopyranosid-6-yl)iron in which the tosyloxy group was replaced by Fp. Oxidative carbonyl insertion in this sugar-iron derivative could be induced by a variety of oxidants but was best accomplished by bromine in the presence of methanol, at low temperatures. The process caused removal of the iron moiety and led in 80% overall yield to the methyl ester of the corresponding, 6-deoxyhepturonoside. Similarly, the methyl 4-O-benzoyl-6-bromo-6-deoxy-α and β-D-glucopyranosides, their 2,3-diacetates and 2,3-dimethyl ethers, as well as the methyl 6-bromo-6-deoxy-α-D-gluco-pyranoside and 6-deoxy-6-iodo-α-D-mannopyranoside 2,3,4-tribenzoates furnished high yields of 6-deoxyhepturonoside esters by application of this reaction sequence, although the intermediate sugar-iron compounds were not normally isolated.

SECTION II

Lithium triethylborohydride (LTBH) reacts readily with methyl 4,6-O-benzylidene-α-D-glucopyranoside p-toluenesulfonates to give deoxyglycosides in over 90% yield. Thus, the methyl 4,6-O-benzylidene-2,3-di- and -3-mono-

O-p-tolylsulfonyl-α-D-glucopyranosides afford methyl 4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside in regio- and stereo-selective reactions that proceed via methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside. Methyl-4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-glucopyranoside gives the corresponding 3-deoxy-α-D-arabino isomer via the corresponding 2,3-anhydro-α-D-mannopyranoside. In the series of the corresponding β-anomers, the 4,6-O-benzylidene-3- and -2-mono-O-p-tolylsulfonyl-β-D-glucopyranosides are similarly desulfonyloxylated, with equal ease, but furnish mixtures of regioisomeric deoxy glycosides, namely, the 3- and 2-deoxy-β-D-ribo derivatives, and the 2- and 3-deoxy-β-D-arabino derivatives, respectively. It could be shown that this difference is due to the failure of the intermediary, methyl 2,3-anhydro-4,6-O-benzylidene-β-D-allo- and -manno-pyranosides to obey the Fürst-Plattner rule in their reductive ring-opening with LTBH. Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-β-D-gluco-pyranoside reacts less readily and gives a mixture of 2- and 3-deoxy hexopyranosides, with the corresponding 3-deoxy-β-D-ribo-hexopyranoside predominating. The methyl 4,6-O-benzylidene-2-O-methyl-3-O-p-tolylsulfonyl-β-D-glucopyranoside is partly desulfonylated and partly desulfonyloxylated, whereas its 3-O-methyl-2-O-p-tolylsulfonyl isomer undergoes desulfonylation exclusively. The reductions, by LTBH, of the α-glycoside tosylates are compared with the reductions previously effected by lithium aluminium hydride, which are slower, involve considerable desulfonylation, and afford lower yields of deoxyglycosides, with the main products differing from those obtained by the action of LTBH. Mechanistic differences associated with the two reductants are discussed.

SECTION III

Treatment of methyl 3,6-dideoxy-2,4-di-O-methylsulfonyl-3-nitro-α-L-glucopyranoside with sodium acetate and acetic acid in acetone gave methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside as a kinetic product, and the 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-eno isomer as the thermodynamically preferred product. Treatment of these enosides or the dimesylate directly, with sodium borohydride produced a separable mixture of methyl 2,3,4,6-tetradeoxy-3-nitro-α-L-threo-hexopyranoside and its α-L-erythro epimer, the erythro isomer being converted into the threo isomer by base-catalyzed epimerization. Acid hydrolysis of the isomeric glycosides afforded the corresponding, free nitro sugars. Catalytic hydrogenation of the methyl 2,3,4,6-tetradeoxy 3-nitro-α-L-threo-hexopyranoside led to the corresponding amino glycoside, isolated as its acetate or hydrochloride; similarly, the erythro glycoside gave the epimeric amine which was isolated as acetate or picrate. N-Trifluoroacetylation of methyl 3-amino-2,3,4,6-tetradeoxy-α-L-threo-hexopyranoside acetate provided the corresponding N-trifluoroacetyl glycoside, which was hydrolyzed to give a 49% yield (overall from the dimesylate) of 2,3,4,6-tetradeoxy-3-trifluoroacetamido-L-threo-hexose (4-deoxy-N-trifluoroacetyldaunosamine). Analogously, methyl 3-amino-2,3,4,6-tetradeoxy-α-L-erythro-hexopyranoside acetate afforded the corresponding, epimeric N-trifluoroacetyl glycoside which was hydrolyzed to give a 28% overall yield of 2,3,4,6-tetradeoxy-3-trifluoroacetamido-L-erythro-hexose (4-deoxy-N-trifluoroacetylristosamine).

SECTION IV

The methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitrohex-2-enopyranosides having the β-D-erythro (1), α-D-erythro (2), β-D-threo (3), and α-D-threo (4) configuration reacted with diazomethane to give high yields of 2,3-(1'-pyrazolino-3',4') derivatives. The pyrazolines obtained from 1 and 2 were deduced on the basis of nuclear magnetic resonance and optical rotatory dispersion data to possess the β- and α-D-gluco configurations, and those obtained from 3 and 4, to have the β- and α-D-ido configurations, respectively. Thermolysis of the pyrazolines led to methyl-branched, nitroolefinic glycosides, except for the pyrazoline having the β-D-ido configuration, which afforded the corresponding 2,3-cyclopropano derivative. The pyrazoline having the α-D-ido configuration afforded a 2,3-cyclopropano derivative on treatment with silica gel.

INTRODUCTION

In this thesis, some contributions to the preparative chemistry of deoxy sugars will be presented. Deoxy sugars[1,2] are carbohydrates in which one or more hydroxyl groups are replaced by hydrogen atoms. A large number of them are known, and many are widely distributed in nature, whilst some of the theoretically possible members of the class have not yet been discovered or synthesized. Abundance and biological significance of naturally occurring deoxy sugars span an enormous range. Thus, 2-deoxy-D-*erythro*-pentose (more commonly known as 2-deoxy-D-ribose) in ubiquitous in living organisms as a component of deoxyribonucleic acids (DNA) in cell nuclei, and is therefore of major biological importance. 6-Deoxy-L-galactose (L-fucose) is a chief constituent of seaweed polysaccharides, thus occurring in huge quantities in the oceans, but it is also found in such diversified locations as microorganisms, frogspawn, and human milk. Its D enantiomer is relatively rare, although it does occur in several plant glycosides. A more frequent component of plant polysaccharides and gums, plant glycosides, and bacterial polysaccharides is 6-deoxy-L-mannose (L-rhamnose). Certain dideoxy sugars such as, for example, 2,6-dideoxy-D-*ribo*-hexose (digitoxose) play a role as components of the medicinally important cardiac glycosides obtained from *Digitalis* species, wherein the sugars are linked to steroidal aglycons and a number of stereoisomeric 3,6-dideoxy-hexoses were identified in the pyrogenic, toxic lipopolysaccharides of various strains of *Salmonella*, *Escherichia coli*, and other bacteria. Some trideoxy sugars, in addition to mono- and dideoxy sugars, have been found as constituents of antibiotics. The chemistry of carbohydrate-containing antibiotics[3] provides particular

excitement in that it is also the principal domain of unusual amino[4] and branched-chain[5] sugars, and frequently one finds deoxy, amino, and C-alkyl functionalities or modified versions combined in the same molecule. A few examples illustrating this are shown on page 3, together with the formulas of the sugars mentioned above.

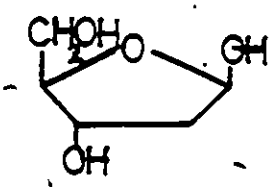
The chemical synthesis of such natural products, as well as of structural analogs or configurational isomers that may be desired, provides continuing challenges for the organic chemist. The research undertaken for this thesis was aimed, partly at making contributions to synthetic methodology in a general way, and partly, at synthesizing certain individual target molecules. Work was performed in four independent areas, the common denominator being only the involvement of deoxy functions. Consequently, the thesis is divided in four self-contained sections:

1. A new application of organometallic methodology for the synthesis, by use of an ironcarbonyl reagent, of novel, chain-extended alduronic acid derivatives.

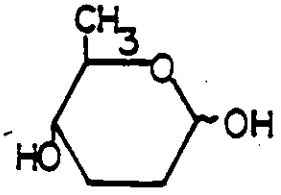
2. The utilization of lithium triethylborohydride for the synthesis of 2- and 3-deoxy sugars from secondary p-toluenesulfonates of glycosides, and a comparison of the action of this reagent with that of lithium aluminum hydride.

3. The synthesis of two aminodeoxy sugars related to the chemistry of antitumor and antibacterial drugs, specifically, the 3-amino-2,3,4,6-tetradeoxy-L-threo- and L-erythro-hexoses (4-deoxy-L-daunosamine and 4-deoxy-L-ristosamine, respectively).

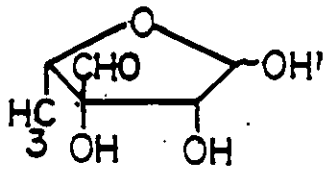
4. The determination of configuration of the branched-chain products obtainable by the action of diazomethane upon four stereoisomeric, un-



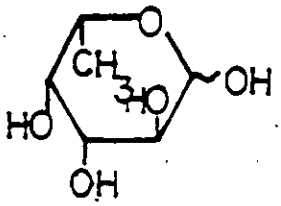
2-deoxy-D-ribose[a]



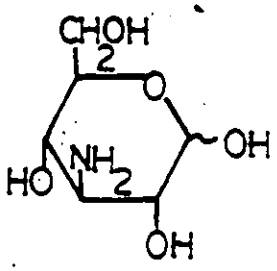
amicetose[b]



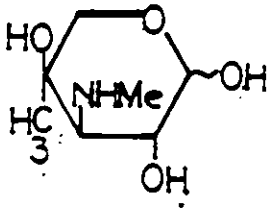
streptose[c]



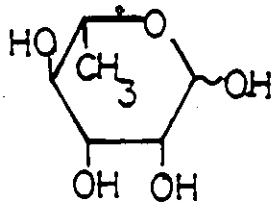
L-fucose



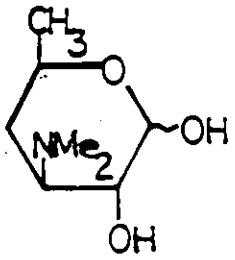
kanosamine[d]



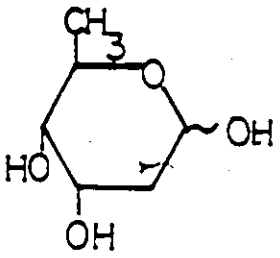
garosamine[e]



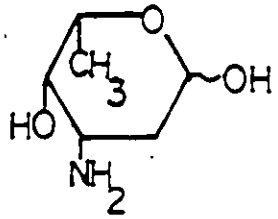
L-rhamnose



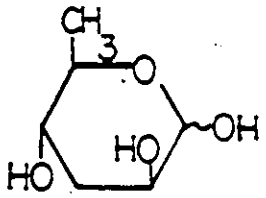
desosamine[f]



digitoxose



daunosamine[g]



tyvelose[h]

ristosamine[i]

a Written in the β-furanose form in which it is bound in DNA.
b Trideoxy sugar occurring in the antibiotic, amicetin.
c A constituent of streptomycin.
d Present in the kanamycin antibiotics.
e A component of the gentamycin group of antibiotics.
f Present in macrocyclic-lactone antibiotics.
g The sugar component of the antitumor agent adriamycin.
h An example of the 3,6-dideoxyhexoses occurring in Salmonella lipopolysaccharide endotoxins.
i A component of the antibiotic, ristomycin.

saturated nitro sugar derivatives.

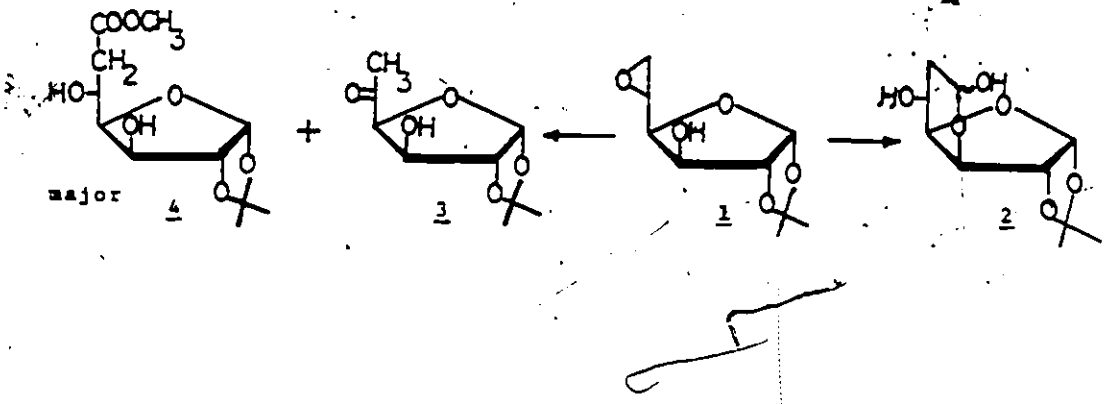
For convenience, each section has received an independent set of formula numbers, and the same applies to the numbering of schemes, figures and tables. However, references are numbered consecutively through all sections.

SECTION I

DICARBONYL-PENTAHAPTO-CYCLOPENTADIENYLIRON IN THE SYNTHESIS OF 6-DEOXYHEPTOSIDURONIC ACIDS

INTRODUCTION

Transition-metal organometallic chemistry has in recent times developed into one of the most important and exciting areas of organic synthesis [6]. One facet of this field is the utility of metal-carbonyl complexes, with the aid of which it is possible to perform a wide variety of synthetic processes,[7,8] and it was the aim of this thesis to apply such chemistry to carbohydrates. Rosenthal and his co-workers were the first to realize the great potential of transition-metal carbonyl complexes in sugar synthesis when, during the 1960's, they performed pioneering investigations of the "Oxo reaction", i.e., the hydroformylation or hydro-(hydroxymethyl)ation of alkenes and oxiranes promoted by cobalt carbonyls, as applied to appropriate sugar derivatives [9]. Among the numerous transformations elaborated were chain-lengthening processes at the nonreducing terminal of aldose derivatives [10]. Thus, 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (1) reacted with carbon monoxide and hydrogen, in the presence of dicobalt octacarbonyl, to give 6-deoxy-1,2-O-isoproplidene-α-D-gluco-heptodialdo-1,4-furanose-7,3-pyranose (2); alternatively, it reacted with carbon monoxide and sodium cobalt tetracarbonyl, followed by methanol and iodine, to afford methyl 6-deoxy-1,2-O-isopropylidene-α-D-gluco-heptofuranuronate (4) as a main product [10]. Yields were high (80%), but both reactions needed to be performed in an autoclave under pressure, one[10a] requiring an elevated temperature (100-105°), and the other[10], an extended period of time (60h). These somewhat inconvenient conditions, and also the limitation in scope that is inherent in a method predicated on the use of terminal epoxides, are avoided in a new synthesis of 6-deoxy-hepturonic acid derivatives from readily available 6-bromo-6-deoxy (or 6-



O-tosyl) -hexopyranosides, to be described in this thesis. The method makes use of oxidatively-induced carbonyl insertion by ligand transfer in a σ-bonded, sugar dicarbonylcyclopentadienyliron intermediate, the latter being produced by substitution of the bromo (or tosyloxy) substituent with sodium dicarbonyl-pentahapto-cyclopentadienyliron, $NaFe(CO)_2Cp$, (NaFp). Well established in general organic chemistry[8,11-14], the process may be represented as shown in scheme 1. After alkylation of Fp^- anion (an extremely

$$Na^+[FeCp(CO)_2]^- + Rx \xrightarrow{[1]} R - FeCp(CO)_2 + NaX$$

5

$$5 + L \xrightarrow{[2]} R\text{-}CO\text{-}FeCp(CO)L$$

6

$$5 - \bar{e} \xrightarrow{[3]} [R\text{-}FeCp(CO)_2]^+ \xrightarrow{[4]} [R\text{-}CO\text{-}FeCp(CO)]^+ \xrightarrow{[5]} + MeOH$$

7 8

R-CO-Me

9

SCHEME 1

powerful nucleophile[14]) by RX, to produce an alkyliron complex 5 (reaction [1]), a ligand-transfer reaction (carbonyl insertion) gives an acyliron complex 6 (reaction [2]) in which one carbonyl ligand is replaced by a new ligand L. This transfer may be induced thermally, or photochemically, or by reaction with other ligands or solvent. Frequently, L represent triphenylphosphine, or a fresh carbon monoxide supplied from an external source.[11] However, under conditions of oxidative insertion as applied in the present work, using an oxidant in the presence of an alcohol,[15,16] 5 is presumed to be oxidized (reaction [3]) to 7, which undergoes insertion (reaction [4]) at a greatly increased rate. The resulting, cationic acyliron complex 8 is rapidly attacked by methanol to give the ester 9 (reaction [5]).

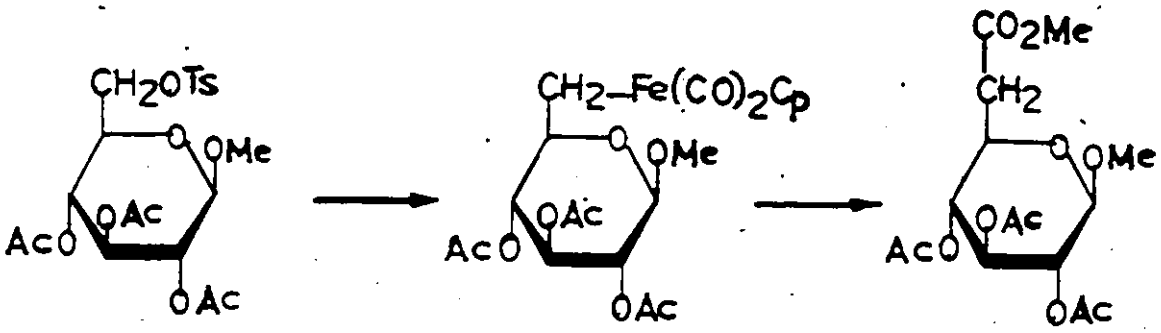
These reactions resemble, in principle, the aforementioned cobalt-promoted carbonylations,[9,10] but have the advantage of proceeding very rapidly at ordinary pressure and at room temperature or below. It therefore appeared worthwhile to examine their potential in carbohydrate syntheses, within the broader context of this laboratory's research[17] on the utility of organometallic processes in that field. As an immediate target for the present study, the development of a general route to 6-deoxy-hepturonic acid derivatives was chosen. To the best of our knowledge, such homologs of the familiar hexuronic acids have not as yet been discovered in nature, and their synthesis seems to have received very little attention. Apart from the instance cited above[10b], we were unable to find more than one other example of synthesis. The latter involved a sulfonate displacement by potassium cyanide, in 1,2-O-isopropylidene-α-D-glucofuranose 6-tosylate, which was followed by total hydrolysis of the resulting nitrile [18].

There is no shortage of general methods for lengthening the carbon chain in monosaccharides. However, most of the available methods involve extension at the reducing terminal (the anomeric center) of the sugar, the Fischer-Kiliani cyanohydrin synthesis and the nitromethane synthesis being the most widely employed ones, besides aldol condensations, malonic ester condensations, additions of acetylenic Grignard compounds, and diazomethane reactions.[19] On the other hand, ascent of the series by extending the chain at the non-reducing terminal is a far more restricted proposition which normally requires prior conversion of the chain-end into a carbonyl function, with appropriate, selective blocking of all other functionalities. The attachment of a carbon atom to readily available ω-deoxyhalogeno sugars (or ω-sulfonic esters), by way of organometallic carbonylation as outlined above, would constitute a useful addition to methodology in this regard.

Other work employing organo-iron chemistry in carbohydrates, with different reagents and objectives, has recently been reported[20,21].

RESULTS AND DISCUSSION

Sodium dicarbonyl-pentahapto-cyclopentadienyliron (NaFp) was prepared from commercially available dicarbonylcyclopentadienyliron and sodium amalgam in dry tetrahydrofuran.[11] It was found to react readily with a variety of sugar derivatives. Methyl 2,3,4-tri-O-acetyl-6-O-p-tolylsulfonyl-β-D-glucopyranoside (10) was chosen as the subject of initial trials that were intended to establish the most appropriate reaction-conditions. It reacted at room temperature to give the covalently linked, sugar-iron compound 11. The reaction was complete almost instantaneously, as evidenced by thin-layer chromatography performed



10 11 12

shortly after the mixing of the reactants; 10 had disappeared completely, and the formation of 11 was indicated by a yellow spot that was visible directly, prior to spraying the plates with sulfuric acid followed by heating. Compound 11 was isolated, in a good yield, as a chromatographically purified, yellow syrup. It tended to decompose slowly, but its structure could, nevertheless, be ascertained by spectroscopy. It showed light absorption in the visible region (λ_{max}^{MeOH} 412 nm), and displayed strong infrared bands for ligand carbonyl (2015 and 1940 cm^{-1}), as well as for

ester carbonyl groups (1745 cm^{-1}). The ^{1}H-n.m.r. spectrum of 11 showed all the signals expected for such a complex, of special significance being a 5-proton singlet at δ 4.80 for the pentahapto-cyclopentadienyl group (Cp), and the multiplets for H-6 and H-6', which had incurred a strong, upfield shift (to δ 1.62 and 1.24 respectively) from their resonance position (δ 4.12) in the parent compound 10 (see Experimental). The ^{13}C-n.m.r. data (see Experimental) also confirmed the structure of 11, with signals occurring at δ 217.4 and 216.8 (ligand CO), 170.4, 169.9, and 169.5 (ester CO) and 85.4 (Cp), in addition to the signals expected from the remaining carbon atoms. An extensive collection of spectral data for alkyl-Fp derivatives has been provided by Rosenblum et al.[22] and was consulted for comparison in making these assignments. Compound 11 was amenable to mass spectrometry, in which it gave a molecular ion peak at m/z 480, fragments signifying the progressive loss of CO and Cp ligands, and a fragment indicating loss of the entire iron moiety Fp, as is characteristic for cyclopentadienyliron complexes.[11b]

When compound 11 was dissolved, at room temperature, in methanol containing a seven-fold, molar excess of anhydrous cupric chloride[23], to effect oxidative carbonyl insertion, the heptosiduronic methyl ester 12 was formed within ~1h, and was subsequently isolated crystalline. In preparative experiments performed on a larger scale, isolation of 11 was dispensed with, as it proved both unnecessary and detrimental to the overall yield. Instead, methanol and oxidant were added to the reaction mixture of 10 and NaFp. The yields of crystalline 12 were ~60% (based on 10) when 7 molar equiv. of cupric chloride, or 4 molar equiv. of ferric chloride[13a], were employed as oxidants, with reaction times of 0.5 and 6h, respectively, being required. Yields were markedly higher (~80%) with

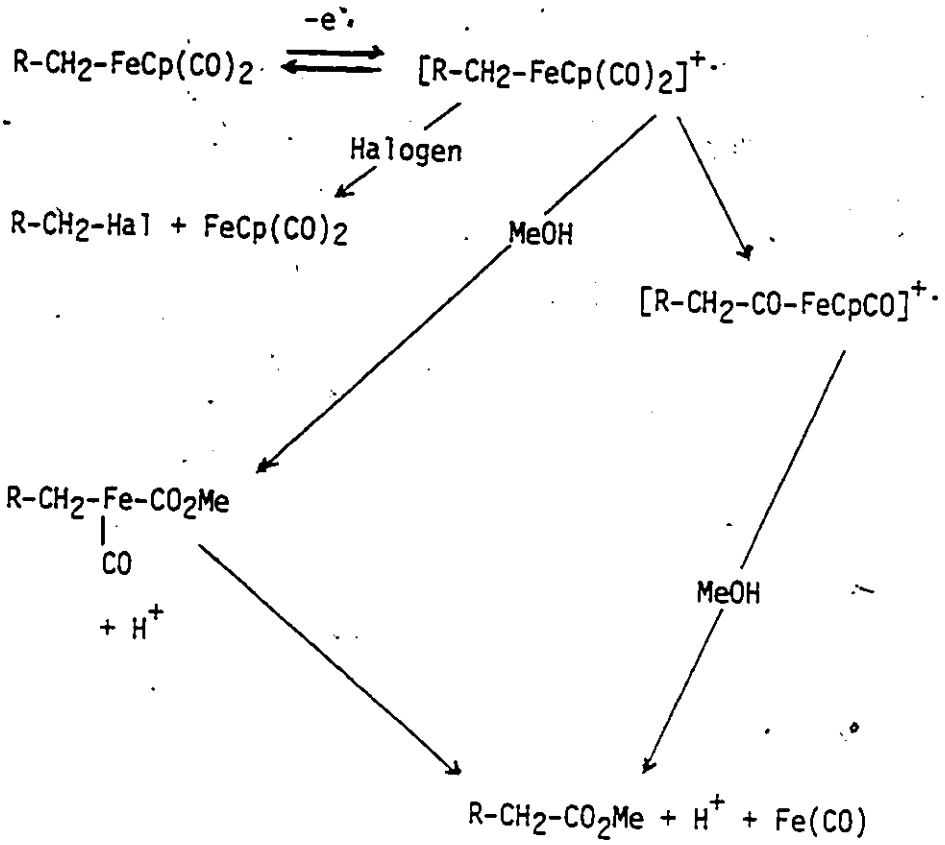
iodine[10a,15] or bromine[24]. The latter halogen became the reagent of choice for all subsequent experiments because, in these trials with 10, it effected complete consumption of the intermediate 11 at a higher rate (within a few minutes, see Table 1) than did iodine (30 min or more, depending on the amount added). Moreover, the isolation of the final product from the reaction mixture proved much easier in the reaction with bromine than in those with the other oxidants. However, the desired product 12 was accompanied by a by-

Table 1. Some trials using different oxidizing agent with compound 10 + FpNa.

Oxidizing agent[a]	Molar equivalents[b]	Temperature	Reaction time	Yield %
$CuCl_2$	7	room temp.	1h	60
$FeCl_3$	4	room temp.	6h	61
I_2	4-5	room temp.	½-1h	82
Br_2	Excess, ≈9	-50 — room temp.	5-10 min	81

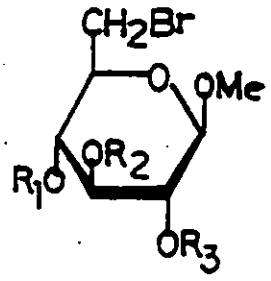
[a] In MeOH. [b] with respect to the starting tosylate.

product which was isolated chromatographically, in 15% yield, and was revealed to be the long-known methyl 6-bromo-6-deoxy-β-D-glucopyranoside triacetate 13. It has been observed that, in aprotic solvents, alkyliron carbonyls are cleaved by molecular halogen to form alkyl halides[13a,16,24]. Although oxidative carbonyl insertion dominates in methanolic solution[16,24] (scheme 2) brominolysis of 11 can evidently compete to some extent in that medium, too. A lowered reaction temperature (0 to -50°) did not seem to make any difference in this regard. However, as it was found that the reactions with bromine were still very fast, even at low temperatures, cooling was, in

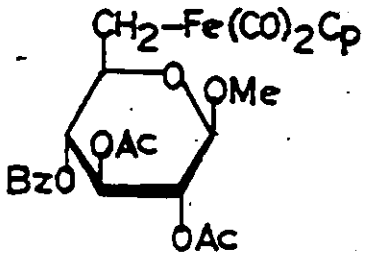


SCHEME 2

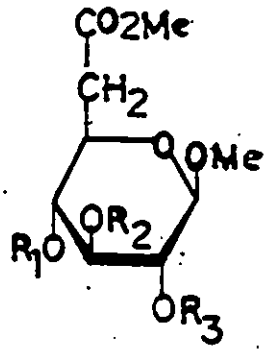
subsequent experiments, employed as a precaution against secondary reactions that could involve other functionalities in the sugar molecule. As a matter of fact, it was noticed on some occasions that partial deacylation may take place slowly at room temperature.



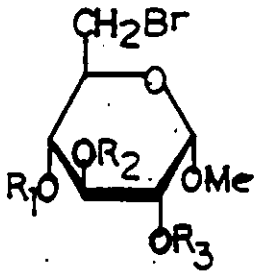
13 $R_1 = R_2 = R_3 = Ac$
14 $R_1 = Bz$, $R_2 = R_3 = Ac$
15 $R_1 = Bz$, $R_2 = R_3 = H$
16 $R_1 = Bz$, $R_2 = R_3 = Me$



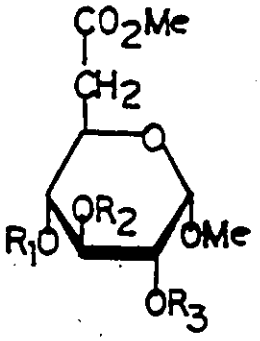
17



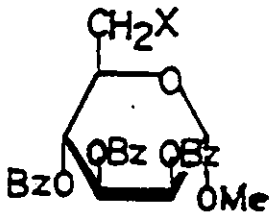
18 $R_1 = Bz$, $R_2 = R_3 = Ac$
19 $R_1 = Bz$, $R_2 = R_3 = H$
20 $R_1 = R_2 = R_3 = H$
21 $R_1 = Bz$, $R_2 = R_3 = Me$



22 $R_1 = R_2 = R_3 = Bz$
23 $R_1 = Bz$, $R_2 = R_3 = Ac$
24 $R_1 = Bz$, $R_2 = R_3 = H$
25 $R_1 = Bz$, $R_2 = R_3 = Me$



26 $R_1 = R_2 = R_3 = Bz$
27 $R_1 = R_2 = R_3 = H$
28 $R_1 = Bz$, $R_2 = R_3 = Ac$
29 $R_1 = Bz$, $R_2 = R_3 = H$
30 $R_1 = Bz$, $R_2 = R_3 = Me$



31 X = I
32 X = CO_2Me
33 X = Br

Analogous (methoxycarbonyl)ations, all using NaFp in tetrahydrofuran followed by bromine in methanol, were performed with the 6-bromo-6-deoxy-glycosides 14-16, and 22-25. The corresponding heptopyranosiduronates 18, 19, 21, 26, and 28-30 were obtained in high yields, together with

various proportions at the respective, starting bromo sugars (see Table 2). The latter were present, not as a result of incomplete conversion in the first stage (as could be demonstrated by t.l.c.), but owing to

TABLE 2 Yields of glycuronates and by-products

Starting compound	Glycuronate	Isolated yield (%)	By-product Compound	Yield(%)	Identification Method
10	12	~80[a],~60[b]	13	15[c]	d
14	18	71	14	23	d
15	19	80	15	9	e
	20[f]	92			
16	21	90	16	10	e
22	26	79	22	13	d
	27[g]	97			
23	28	88	23	trace	h
24	29	70	i		
25	30	85	i		
31	32	75	33	12	d

[a]With Br_2 or I_2. [b]With $CuCl_2$ or $FeCl_3$. [c]Observed in the case of Br_2-oxidation only. [d]By physical and spectral data of isolated compound. [e]By t.l.c. and proton n.m.r. spectrum of impure, syrupy material. [f]From 19 by debenzoylation. [g]From 26 by debenzoylation. [h]By t.l.c. only. [i]Although the crude product contained impurities, the presence of regenerated starting compound could not be established.

partial brominolysis in the second stage, just as 13 had arisen from 11. Reaction of methyl 2,3,4-tri-O-benzoyl-6-deoxy-6-iodo-α-D-mannopyranoside (31) led to the 6-deoxy-D-manno-hepturonic ester 32, demonstrating that iodo sugars may also be used as substrates. The by-product observed in this case was the 6-bromo analog (33) of 31.

Also, the alkyliron intermediate 17 was isolated, from the reaction of Fp^- with the bromide 14, for characterization by ^1H-n.m.r. spectroscopy. Like 11, it was a rather unstable syrup.

Whereas several of the uronates (12, 18, 28, 29, and 32) were obtained crystalline, compounds 19, 21, 26, and 30 failed to crystallize. Sodium methoxide–catalyzed deacylation of 19 and 26, however, furnished the corresponding, crystalline triols, namely, methyl (methyl 6-deoxy-β-D-gluco-heptopyranosid) uronate (20) and its α anomer 27, respectively. The ^1H and ^{13}C-n.m.r. data for the new compounds are given in Tables 3 and 4.

One further observation may be worth mentioning. An atmosphere of carbon monoxide (at ambient pressure) was routinely provided for the carbonyl-insertion reaction. This measure is not strictly indispensable, but has been recommended[23] for achieving improved yields. Substituting nitrogen gas for the carbon monoxide in one experiment with 10, we found a diminution in yield to 69%, from 80% (for bromine oxidation), whereas no marked effect was noticed in similar experiments with 22.

In summary, methoxycarbonylation by use of NaFp has been demonstrated to be a simple and efficient method for chain-elongation in 6-halogeno (or 6-O-tosyl) hexopyranosides, leading to homologous, 6-deoxyhepto-pyranuronoside methyl esters. The method is compatible with the presence of free hydroxyl groups, acetate and benzoate esters, and methyl ether functions on the sugar ring.

TABLE 3

Proton Magnetic Resonance Data of Methyl (methyl 6-deoxyheptopyranosid)uronates[a]

Compound	Chemical shifts (δ)								Coupling constants (Hz)					
	H-1	H-2	H-3	H-4	H-5	H-6,6'	OMe[b]	OAc[b]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$
12	4.43d	4.95dd	5.22t	4.91t	3.97o	2.57d (2 H)	3.71, 3.46	2.05, 2.01, 1.99	7.7	9.2	9.5	9.5	7	5
18	4.51d	5.02dd	5.42t	5.17t	4.12o	2.65d, 2.63d	3.59, 3.49	2.06, 1.89	7.8	9.2	9.2	9.5	7.3	4.8
19	4.25d	~3.5[c]	3.77t	4.99t	4.00dt	2.57d (2 H)	3.57, 3.50		7.5	9.0	9.0	9.0	6.5	6.5
20	4.15d	⊢——— ~3.8-3.1m (4 H) ———⊣				2.90dd, 2.42dd	3.69, 3.45		7.5				3.1	9.3[e]
21	4.32d	3.15dd	3.46t	5.06dd	3.99o	2.59d, 2.58d	3.59, 3.57, 3.53, 3.48		7.5	9.0	8.7	9.7	7	5.5
26	⊢ ~5.2m (2 H)⊣		6.16t	5.42t	4.59dt	2.67d (2 H)	3.70, 3.55			9.5	9.5	9.5	6.7	6.7
27	4.68d	⊢——— ~4.2-3.3m (4 H) ———⊣				2.95dd, 2.46dd	3.71, 3.44		3				2.5	10[f]
28	⊢ ~4.9m (2 H)⊣		5.70t[g]	5.14t	4.44dt	2.59d (2 H)	3.65, 3.49	2.09, 1.90			10	10	7	7
29	4.73d	~3.6m	3.96sx[h]	4.96dd	4.33dt	2.55d (2 H)	3.62, 3.46		3.5	9.5	9.5	10.5	6.3	6.3
30	4.85d	3.35dd	3.75t	5.03dd	4.33dt	2.55d (2 H)	3.63, 3.55, 3.51, 3.48		3.5	9.5	9.2	10.1	6.5	6.5
32	4.92d	⊢—— 5.9-5.6m (3 H) ——⊣			4.6m	2.73d, 2.72d	3.66, 3.59		1.8				7	5

[a] From 100-MHz spectra, measured at 250-Hz sweep-width, for solutions in $CDCl_3$ (unless specified otherwise) containing tetramethylsilane as the internal standard. Signal multiplicities: d, doublet; m, multiplet; sx, sextet; o, octet; and t, triplet. All compounds containing benzoate groups showed the characteristic multiplet pattern for OBz, centered near δ 7.7. [b] Three-proton singlets. [c] Obscured by OMe signals. [d] In CD_3OD solution because of poor solubility in $CDCl_3$. [e] $J_{6,6'}$, 15.6 Hz. [f] $J_{6,6'}$, 15.5 Hz. [g] Each line showed an additional, small splitting. [h] Collapsing to t after D_2O exchange; OH-2 and OH-3 gave doublets at δ 2.90 and 3.28.

TABLE 4. Selected ^{13}C chemical shifts (PPM from TMS)[a]

Compd.	C_1	C_2 —— C_5	C_6	MeO-C	MeO-C=O	Others[b]
12	101.50	70.31, 71.52, 71.64, 72.91	36.73	56.92	51.92	
18	101.64	70.63, 71.60, 72.09, 72.58	36.87	56.99	51.83	
19	103.40	70.55, 74.12, 74.24, 74.49	37.02	57.08	51.76	
21	104.29	70.41, 73.61, 83.42, 83.78	37.01	56.99	51.71	60.59, 60.70 (OMe)
27	99.33	68.10, 72.12, 73.34, 74.13	36.79	55.21	51.80	
28	96.61	65.92, 69.69, 71.11, 72.27	36.63	55.50	51.83	
29	99.00	66.20, 72.43, 72.64, 74.19	36.75	55.47	51.79	
30	97.53	66.17, 73.88, 80.93, 81.58	36.86	55.50	51.77	59.32, 61.03 (OMe)
32	98.49	52.66, 67.13, 69.87, 70.64	36.97	55.49	51.85	

[a] Spectra were taken from chloroform solutions with a Varian CFT-20 instrument,

[b] In addition to the resonances listed, all compounds showed resonance as expected for the carbon atoms in the various substituents.

SECTION II

DESULFONYLOXYLATIONS OF SOME SECONDARY p-TOLUENESULFONATES OF GLYCOSIDES BY LITHIUM TRIETHYLBOROHYDRIDE.

INTRODUCTION

Lithium triethylborohydride (Super Hydride®, LTBH) is an extremely powerful reducing agent, which acts as a hydride donor toward a variety of electrophiles. It has found numerous applications as a reagent for the reductive ring-opening of epoxides and the cleavage of alkyl halides and sulfonic esters, and it is superior in reducing power to lithium aluminum hydride or lithium borohydride while at the same time it reacts very cleanly and displays remarkable selectivity.[25,26] In carbohydrate synthesis, where reductive dehalogenation and desulfonyloxylation are on-going concerns just as in general organic chemistry, these kinds of reaction have traditionally been performed with lithium aluminum hydride (LAH), and only isolated instances of the use of LTBH have been reported. Thus, a primary p-toluenesulfonate[27] and a primary bromide of glycosides[17c] were efficiently converted into ω-deoxy glycosides. On the other hand, some secondary sugar tosylates could not be desulfonyloxylated, but suffered S-O cleavage (desulfonylation) instead,[27] although successful desulfonyloxylations had been reported[25c,d] for alicyclic tosylates including hindered, tertiary ones.

Concurrent with the work proceeding in this laboratory, on the reductive debromination just mentioned,[17c] some experiments were performed by this author with secondary sugar tosylates, and it was discovered that such compounds may well be desulfonyloxylated with LTBH, notwithstanding the reported failures[27] in previously-examined cases. It was therefore decided to investigate the behavior of LTBH towards secondary tosylates of glycosides more broadly, and to try to find out whether this reagent offers any advantages over LAH, which in carbohydrate chemistry has hither-

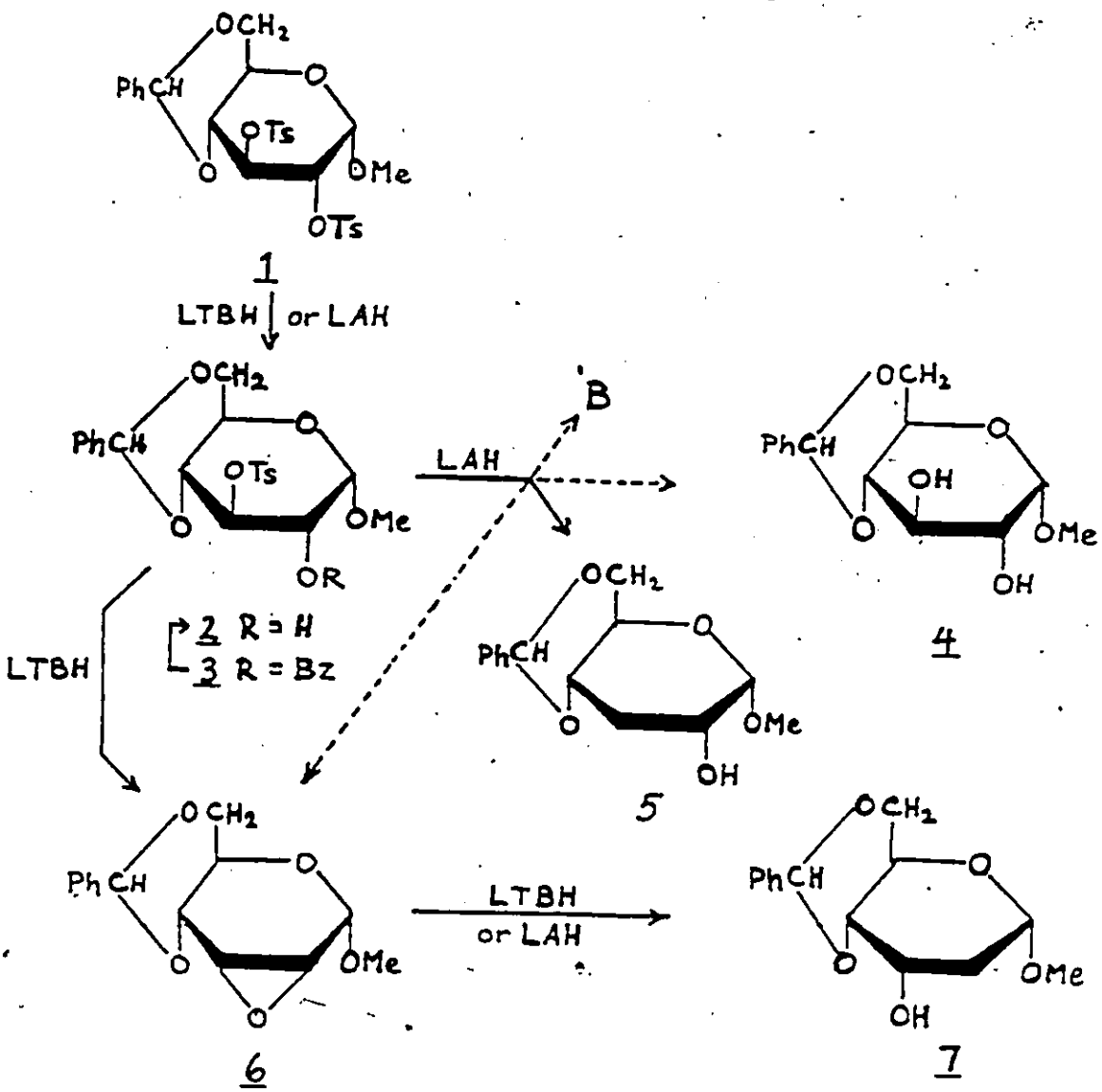
to been the reductant of choice for applications of the kind discussed.

The action of LAH on sugar sulfonic esters has been extensively studied and reviewed[28,29]. It is well established that LAH may cause either C-O fission (desulfonyloxylation) or S-O fission (desulfonylation), depending on the structure of the sulfonate. In primary sulfonates, the former type of cleavage normally prevails, whereas in secondary ones the latter type is usually observed although exceptions[30-38] have been noted. It has been determined, in this work, that, for a number of secondary tosylates derived from methyl 4,6-O-benzylidene-α and β-D-glucopyranoside, the action of LTBH does not in every respect parallel that of LAH. Firstly, with LTBH, desulfonyloxylations were found to proceed at much higher rates than with LAH, leading in the majority of cases studied to deoxyglycosides in excellent yields, and accompanied by negligible proportions of undesirable side products; and secondly, mechanistic differences cause the two reductants to give different patterns concerning the regio- and stereo-chemistry of the deoxyglycosides produced. Following their description, the results with LTBH will in subsequent paragraphs be compared with those previously obtained with LAH, and a few additional observations regarding the respective actions of the two reagents will be discussed.

RESULTS AND DISCUSSION

Reactions with Lithium Triethylborohydride

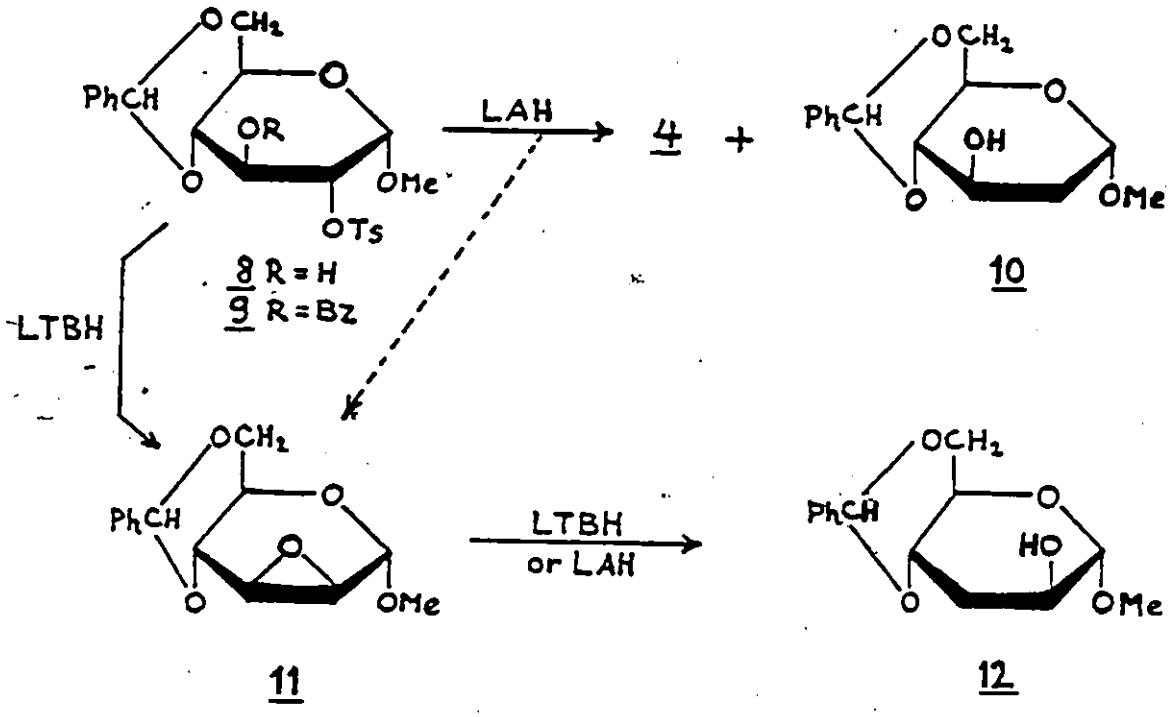
Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-α-D-gluco-pyranoside (1) was treated with LTBH (6 mol. equiv.) in boiling tetrahydrofuran for 30 min, to give a 96% yield of methyl 4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside (7), together with mere traces of the parent diol 4. The reaction was presumed to proceed via the



3-monotosylate 2 and the α-D-allo 2,3-epoxide 6, and the use of either of these intermediates as the starting compound for the process was, therefore, expected to give 7 in similar yields. When 2 was treated at room temperature with only 3 mol. equiv. of LTBH, traces of 6 and 7 were revealed by t.l.c. to have arisen after 45 min, while most of compound 2 remained unaffected. When the mixture was then boiled under reflux for 30 min, all of 2 was converted into 6, but little, if any, additional 7 was formed, and the chromatographic picture remained unchanged during a further 30 min of heating. Evidently, the proportion of reductant provided in this instance had been insufficient for complete reduction; and indeed, the introduction of an additional 1.5 mol. equiv. of LTBH at this point caused complete conversion of 6 into 7 within 15 min. The product was obtained crystalline in 92% yield. An experiment starting with crystalline 6 also gave 7, in 96% yield.

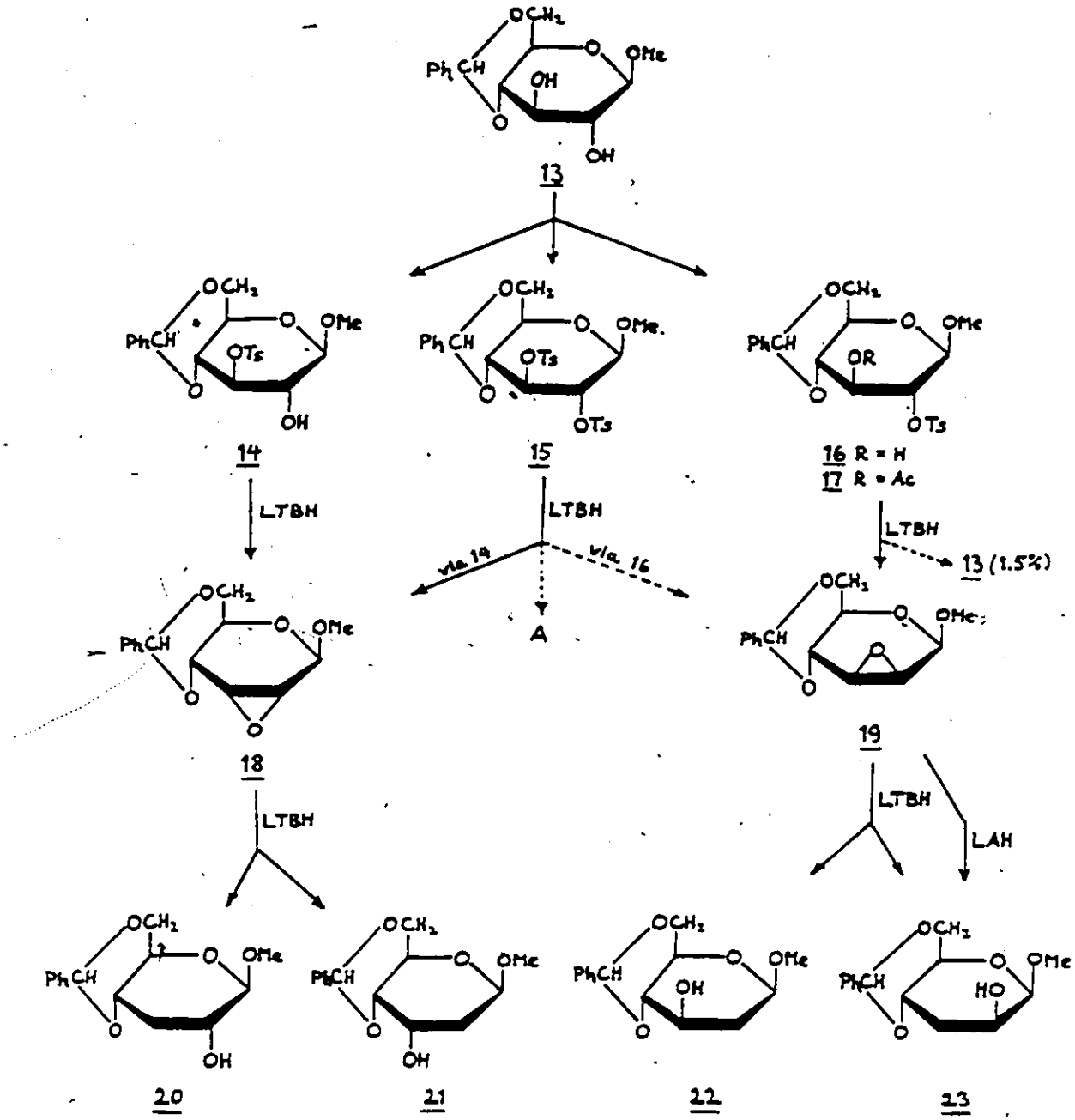
The 2-monotosylate 8 reacted with LTBH (4.3 mol. equiv.) in boiling tetrahydrofuran to furnish, after 20 min, the 3-deoxy-α-D-arabino glycoside 12, accompanied by a small amount of the diol 4, isolated in yields of 90 and 5%. An experiment performed at room temperature, and with only 3.3 mol. equiv. of hydride present, demonstrated that the reaction took its course via the α-D-manno epoxide 11, which was obtained crystalline (yield, 12%) after a reaction time of 24 h, along with 12 (82%) and 4 (4%). A reduction experiment that started with 11 likewise afforded a high yield of 12.

It has been shown previously[26] that LTBH in tetrahydrofuran possesses a remarkable ability for the rapid, regiospecific and stereospecific, reductive opening of epoxides to give alcohols in excellent isomeric



purity. These reactions are reported[26] to be very general, and applicable to epoxides with a wide range of structural features, and to be faster and cleaner than those utilizing lithium aluminium hydride for the same purpose.

For analogous studies in the β-glycosidic series, the tosylates 14, 15, and 16 were prepared from methyl 4,6-O-benzylidene-β-D-gluco-pyranoside (13). An improvement was introduced in the somewhat laborious method for obtaining the monotosylates 14 and 16 by the rather non-selective, partial tosylation[39,40] of 13. It consisted of converting the 2-monotosylate 16 into its 3-acetate 17, which is more readily separable from the ditosylate 15 that is unavoidably present and difficult to remove by chromatography alone. For the regeneration of 16 from its acetate, it was felt desirable (although perhaps not absolutely necessary) to avoid basic conditions; a high-yielding (94%) alternative was there-


13
14
15
16 R = H
17 R = Ac
LTBH
LTBH
LTBH
via 14
via 16
A
13 (1.5%)
18
19
LTBH
LTBH
LAH
20
21
22
23

fore adopted, involving acid-catalyzed methanolysis of the acetic ester group (and the benzylidene acetal), followed by re-acetalation of the glycoside with α,α -dimethoxytoluene.

The 3- and 2-monotosylates 14 and 16 were reduced by LTBH as easily as their anomers, both furnishing crystalline deoxyglycosides in approximately 95% yield. However, in contrast to the α-series, each of the tosylates gave two, positionally isomeric, products in substantial proportions. Thus, 14 yielded 59% of the 3-deoxy-β-D-ribo-hexopyranoside 20 and 36% of the 2-deoxy-β-D-ribo isomer 21; and 16 produced nearly equal proportions of the 2-deoxy-β-D-arabino (22) and 3-deoxy-β-D-arabino (23) isomers. It appeared reasonable to assume that these reactions would involve the epoxides 18 and 19, respectively, as intermediates, in analogy to the α-series, and the concomitant expectation was that the resulting products of reduction should be 21 and 23, i.e., the products of diaxial ring-opening according to the Fürst-Plattner rule.[41] For an explanation of the origin of the unexpected isomers 20 and 22, a direct displacement of the tosyloxy group by hydride ion was, at first sight, perceived as a possibility. (In at least one different tosylate, LTBH was in fact found capable of such a substitution; see later on.) Nevertheless, diequatorial opening of the oxirane rings in violation of the rule had to be considered as an alternative. Although there seem to be no precedents in the literature for abnormal hydride reductions of the conformationally quite rigid molecules 6, 11, 18, and 19, Lemieux and co-workers[42] had found that 18 does behave abnormally in ring-opening with sodium iodide, giving at least 20% of the unexpected (diequatorial) iodohydrin, whereas 6, 11, and their

α-D-gulo and β-D-talo isomers obey the rule strictly, affording almost quantitative yields of the diaxial iodohydrins. Consequently, an LTBH reduction of 18 was now performed, and its exceptional behavior was confirmed. The deviation from the rule was even more striking, for the glycosides 20 and 21 were isolated in yields of 68 and 30%, respectively. Comparison of these yields with the very similar ones (59 and 36%) obtained from the reaction of 14 suggests that desulfonyloxylation of the latter proceeds mainly through 18.

It was then established that the epoxide 19 is reduced by LTBH in a similar, abnormal way. It reacted at room temperature to give, within 10 min, a mixture of approximately equal parts of 22 and 23. While this result satisfactorily explained the course of reduction of the 2-tosylate 16, there remained an element of surprise because 19 had previously been reported[39] to furnish 23 on reduction with LAH, in what appeared to be a straightforward way; the product was isolated in good yield and no mention was made of a possible, simultaneous formation of then-unknown 22. In order to determine whether 22, whose physical constants and mobility in t.l.c. are now known to differ little from those of 23, had escaped detection in the earlier work,[39] the product of LAH reduction of 19 was examined by ^{1}H-n.m.r. and i.r. spectroscopy, but no trace of 22 was found; pure 23 was isolated in 75% yield. The differing regioselectivities of the two hydride reagents will receive further comment below.

In contrast to the facile transformation that occurred with the α-glycoside 1, reduction of the β-glycosidic 2, 3-ditosylate 15 proceeded relatively sluggishly, requiring overnight heating for completion,

and it gave several products. The principal products isolated were the deoxyglycosides 20 (57%) and 21 (11%), which in view of the foregoing discussion may be assumed to have arisen* largely via 14 and thence, 18. A fraction of mixed deoxyglycosides (~13%, free from tosyl derivatives) was judged by its n.m.r. spectrum to consist of about equal parts of the 2- and 3-deoxy-β-D-arabino isomers 22 and 23. In addition, several fast-moving, minor by-products were formed. One of these (designated A) was isolated, although impure, in an amount sufficient for a preliminary examination by ^{1}H-n.m.r. spectroscopy, which revealed it to be a benzylidenated methyl glycoside bearing a tosyloxy group at C-2, yet differing from 16. (See Table 1 for characteristic signals useful for the differentiation of deoxyglycosides and tosylates dealt with in this work. Chemical-shift differences in the resonances both for the aromatic and the methyl protons of tosyl groups, and shielding effects noticed and discussed[40] for benzylidenic methine and anomeric methoxyl signals, may serve to identify the location of tosyl groups.) The by-product A showed resonances in the region (δ1-2) associated with endocyclic methylene groups; conceivably it was the 3-deoxy analog of 16 (i.e., the tosylate of 20).**

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*There is an analogy for the somewhat lower reactivity[41] of 15, as compared to 1. The former had been found[33] to be unreactive under conditions of alkaline hydrolysis which cause the conversion[43-45] of 1 into the oxirane 6. However, a high-yielding conversion of 15 into 18 was later achieved[42] by use of slightly modified conditions.

**Hedgley et al.[33] obtained a 38% yield of 20 on treatment of 15 with LAH in boiling tetrahydrofuran, and reported no other products. In boiling dioxane, the yield was 22% and methyl 4,6-O-benzylidene-2,3-dideoxy-β-D-erythro-hexopyranoside was formed as a second product.

TABLE 1

^{1}H-CHEMICAL SHIFTS (δ) OF CHARACTERISTIC SIGNALS FOR TOSYLATES AND DEOXY DERIVATIVES OF METHYL 4,6-O-BENZYLIDENE-α- AND β-D-GLUCOPYRANOSIDE IN $CDCl_3$ SOLUTION[a]

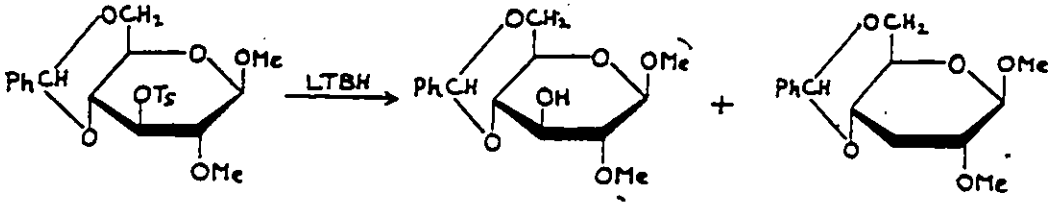
Compound	Ph-CH	OMe	TsO-2		TsO-3		Ph[c]
			Aryl[b]	C-Me	Aryl[b]	C-Me	
1	5.22	3.32,	7.79, 7.71; 7.30, 7.22	2.38	7.59, 7.51; 6.90, 6.82	2.20	7.26m
2	5.34	3.47			7.73, 7.65; 7.01, 6.93	2.30	7.28m
3	5.40	3.40			7.65, 7.57; 6.85, 6.77	2.19	7.35m
8	5.47	3.33	7.87, 7.79; 7.36, 7.28	2.43			7.36m
9	5.46	3.47	7.63, 7.55; 6.99, 6.91	2.22			7.30m
14	5.34	3.57			7.75, 7.67; 7.02, 6.94	2.30	7.32m
15	5.26	3.06	7.83, 7.75; (7.38)[d], 7.20	2.38	7.71, 7.63; 6.94, 6.86	2.22	7.29m
16	5.50	3.29	7.86, 7.78; (7.34)[d], 7.26	2.45			7.36m
17	5.46	3.29	7.78, 7.70; (7.32)[d], 7.24	2.44			7.33m
24	5.36	3.53, 3.39			7.75, 7.67; 7.05, 6.97	2.29	7.35m
27	5.51	3.35, 3.35	7.86, 7.78; (7.33)[d], 7.25	2.43			7.36m
A[e]	5.43	3.26	7.83, 7.69; (7.36)[d], 7.22	2.40			7.36m
B[f]	5.62, 5.52, 5.42	3.38, 3.33, 3.27	7.82, 7.74				7.3m
5	5.465[g]	3.435[g]					7.35m
7	5.59[h]	3.39[h]					7.36m
10	5.52[i]	3.31[i]					7.39m
12	5.54[i]	3.38					7.36m
20	5.51[i]	3.56					7.36m
21	5.555[h]	3.48[h]					7.38m
22	5.51[j]	3.48[j]					7.38
23	5.52[h]	3.53[h]					7.36m

[a] For further distinctive signals see the Experimental section and literature cited therein. [b] Line positions for the AB system of the p-tolyl group are given. [c] In the case of a multiplet, the value refers to the strongest line. [d] Calculated value for line obscured by Ph signal. [e] From 60-MHz spectrum. [f] Mixture of by-products; resonances indicated are additional to those for admixed 1. [g] Average from 10 spectra; ±0.015. [h] Average from 6 spectra; ±0.01. [i] Average from 4 spectra; ±0.02. [j] Average from 10 spectra; ±0.01.

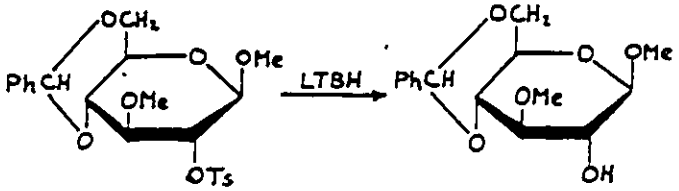
These results indicated that LTBH reacts with 15 along at least two, and possibly three, different pathways. Detosylation at O-2 initiates what appears to be the main course of reaction, which leads to 20 and 21 through an intermediary allo epoxide (18) and thus parallels the exclusive path followed for 1, the non-specific epoxide opening aside. Unlike in 1, however, detosylation at O-3 evidently competes to a noticeable, if small, extent, as must be concluded from the formation of 22 and 23, which requires the intermediacy of the 2-tosylate 16 and the manno epoxide 19. Furthermore, if the by-product A does indeed possess the structure of a 3-deoxyglycoside 2-tosylate as tentatively suggested, a third mode of reaction would be indicated for 15, namely, direct desulfonyloxylation at C-3 without the intervention of an epoxide; most of the resultant product (A) would subsequently suffer detosylation to give 20, which would account for a ratio of 20:21 greater than that produced in the reduction of 18.

The ability of LTBH to cause such direct desulfonyloxylation was demonstrated with methyl 4,6-O-benzylidene-2-O-methyl-3-O-p-tolylsulfonyl-β-D-glucopyranoside (24). It gave the products of O-S fission (25) and C-O fission (26) in yields of 58 and 35%, respectively. Still, O-S fission was the favored event, and it could be expected to predominate even more strongly in the isomeric, 3-methyl ether 2-tosylate 27. This was borne out when 27 was found to give solely the alcohol 28, isolated in 95% yield. The reactions of the methyl ethers 24 and 27 were both rather slow, requiring 1 day at 67° for completion. On account of this slowness it may be concluded that a direct desulfonyloxylation, such as occurs in 24, makes no significant contribution to the yield of 20

produced in the fast reduction of the monotosylate 14 (that seems wholly epoxide-mediated), although it may play an appreciable role in the relatively slow transformations of 15. The non-occurrence of desulfonyloxylation in 27 reinforces the conclusion that 16 yielded 22 by way of abnormal cleavage of intermediary 19, and not by direct substitution.



24 25 26



27 28

Reactions with Lithium Aluminum Hydride

In sharp contrast to the aforedescribed, facile reduction of the ditosylate 1 with LTBH, to give almost quantitatively the 2-deoxyglycoside 7, reaction of 1 with LAH to boiling tetrahydrofuran for 16 h, first performed by Vis and Karrer,[30] was claimed to afford a 66% yield of the 3-deoxyglycoside 5; no other products except for a small amount of the diol 4 were detected at the time. The formation of 5 was difficult to explain by a mechanism involving a 2,3-anhydro glycoside intermediate, as both the α-D-allo (6) and the α-D-manno (11) epoxide had been shown[48] to give, on reduction with LAH, not 5 but the deoxyglycosides 7 and 12, respectively. The matter was reinvestigated in detail by Jary[35] and Umezawa[36] and their co-workers, who employed chromatography[35,36] and ^{1}H-n.m.r. spectroscopy[36] for the isolation and identification of products, and who included in their studies also the monotosylates 2 and 8, and some related compounds. The chemistry proved rather more complicated than had previously been presumed. Table 2 shows the pertinent results of the Czechoslovak and Japanese workers together with those of our own experiments that were performed for confirmation. Considering the variations in such parameters as reaction-times, molar excesses of reductant used, and total percentages of products accounted for after chromatographic processing, the results obtained by the three groups are, in the main, in good harmony.

In 1, LAH first causes detosylation of O-2 to give 2, thus behaving qualitatively like LTBH, or like sodium methoxide whose strong perference for hydrolytic cleavage of the 2-O-tosyl group in 1 is well established.[43,45] However, from this point onward the principal actions of the two re-

ductants differ. The formation, by LAH, of the main product (5) from 2 (or from 3 following debenzoylation) has been explained[35,36] in terms of desulfonyloxylation at C-3 by an intramolecular transfer of hydride ion from an alkoxyaluminum hydride complex ($R-O-AlH_3^-$) that incorporates O-2. (Such complexation evidently lessens the propensity of the oxygen atom to engage in an epoxide-forming displacement.) Similarly, the moderate proportion of the 2-tosylate 8 which escapes initial detosylation to 4, reacts through a C-3 alkoxyaluminum hydride complex to give the 2-deoxyglycoside 10. This mechanism, proposed earlier[34] for a similar desulfonyloxylation, was supported by studies[35,36] on secondary tosylates lacking a free, or potentially-free, adjacent trans-hydroxyl group, and analogies can be cited for some other LAH reductions in the carbohydrate field[47a-d] and elsewhere.[47e,f] However, complexation at O-2 does not completely forestall formation of the epoxide 6, as is seen from the fact that 7 (which requires 6 as a precursor) is a minor, although by no means negligible, product in the reactions of 1, 2, and 3 (see Table 2).

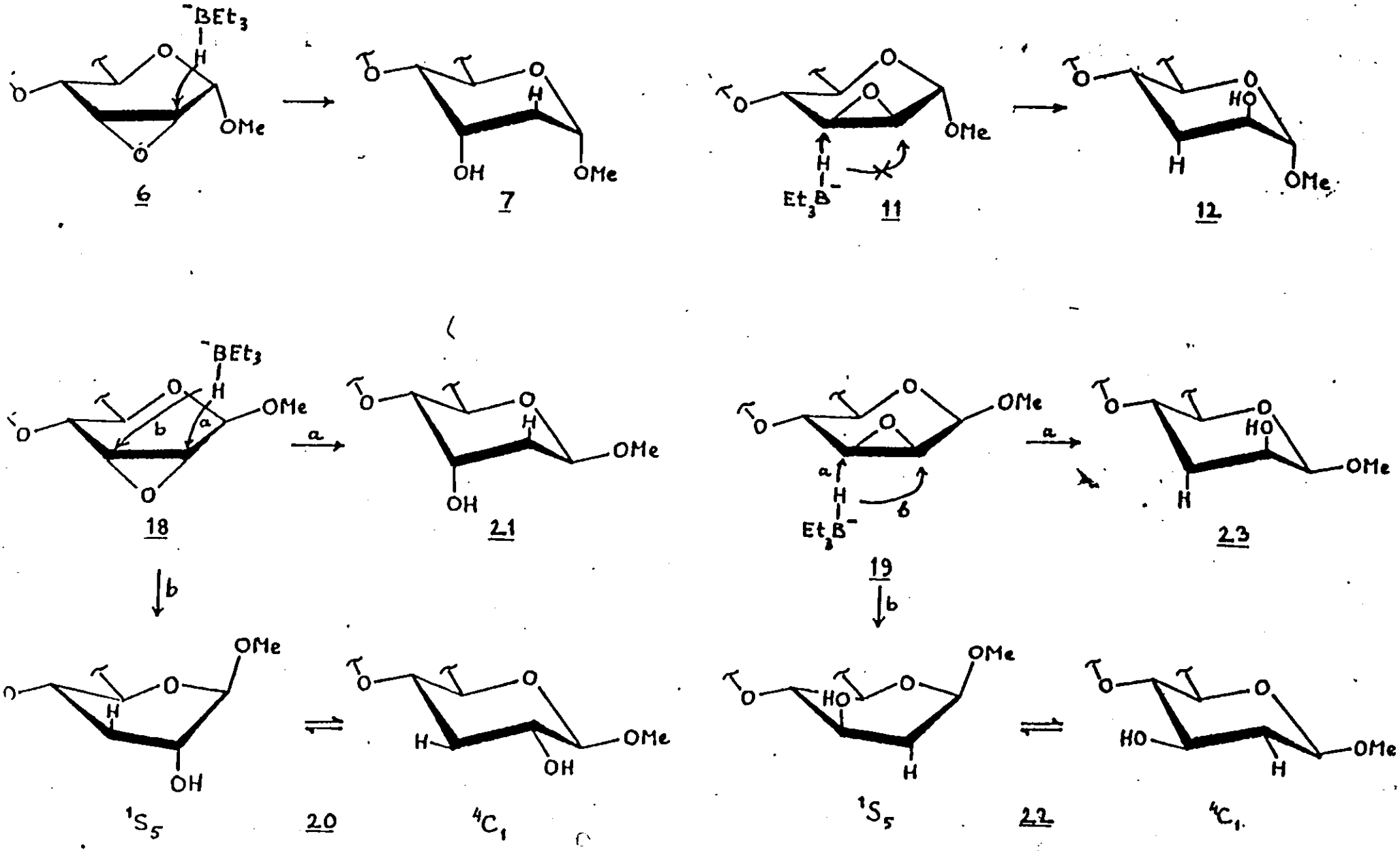
Contrary to the situation with LAH, an internal transfer mechanism cannot operate for the monovalent hydride, LTBH, so that 2 and 8 are in its presence freely transformed into the corresponding oxiranes wherefrom the deoxyglycosides 7 and 12 arise as single products. There are, in these cases, no impediments to the approach of the reductant as required for the favored, diaxial ring-opening (Scheme 1, 6→7 and 11→12). In the β-glycoside 18, on the other hand, axial approach to C-2 involves a transition state that seems sufficiently disfavored, for polar reasons, to allow for predominance of the alternative attack leading to 20. In 19, the "normal" approach (to C-3) is cis to O-4, which may imply a certain

TABLE 2

PRODUCTS OBTAINED FROM SOME GLYCOSIDE TOSYLATES BY REACTION WITH LITHIUM ALUMINUM HYDRIDE

Starting compound	LAH mol.equiv.	Reaction-time, h	Isolated Products, %									Ref.[a]
			1	2	8	4	5	7	10	Others	Total	
1	2.5	18	1.9[b]	7.1		19.5	44				91	35
1	4	18	3.2[c]	6.8		29.1	43.6				90	35
1	5.6	40	6.4[d]			15	[~46	~7.5	~7.5][e]		82.5	36
1	5.6	3.5	f	f	3.7		f					36
1	3.8	26	13.3	16.9		12.8	[~36	~9][g]		~12[h]	100	*
2	2.3	18		10.9[i]		30.1	30.3				71	35
2	4.3	20				15	71[j]				86	36
2	7.7	8		tr.		25	35[j]				60	*
3	4.9	20		3.7		6.3	[~68	~5][k]			83	36
3	7.9	9		27.5		12	[~39	~12][k]			90.5	*
8	3.2	18			tr.	50			9		59	35
8	2.3	18			6	54			1.6[l]	1.6[m]	75	35
8	7.7	19				76.5			19	tr.[n]	95.5	*
9	4.7	20				54			29	/	83	36

[a] An asterisk refers to this work. [b] Plus a fraction (18.3%) of 1 containing small proportions of four other products (t.l.c.). [c] Plus a fraction (7.3%) consisting of 1, 2, 8, and traces of 5 and 10 (t.l.c.). [d] Mixed with an unidentified substance (B? See text). [e] Mixture (61%), with component ratio determined by n.m.r.; only part of 5 was isolated. [f] Detected by t.l.c. but not isolated. [g] Mixture (45.1%), with component ratio determined by n.m.r. [h] A mixture (2:1, by n.m.r.) of by-products B and 1. [i] Mixture of 2, 5, and 6. [j] Mixture of 5 (major) and 7 (minor). [k] Ratio in mixture determined by n.m.r. [l] Plus a mixture (11.5%) of 8 and 10. [m] Compound 11. [n] Compound 12.



SCHEME 1

degree of hindrance so that the "abnormal", but unhindered, approach to C-2 becomes competitive. This alternative venue is unavailable for 11, as it is effectively blocked by the adjacent, pseudoaxial methoxyl group (Scheme 1). The very factor that may be responsible for the lack of regioselectivity in the reaction of 19 with LTBH, namely the orientation of O-4, might well contribute to the regiospecificity apparently prevailing in its reaction with LAH. Thus, prior coordination[47d] of aluminum hydride with O-4 could be of significance in this case.

One point in which our findings differed from those of Umezawa et al.[36] concerns the formation of a small proportion (~7.5%) of 10 in the reaction of 1, presumed to have arisen following a partial detosylation to 8, with the latter being isolable after a short reaction-time (Table 2, 3rd and 4th entries). We did not detect any 10 among the products from 1 (Table 2, 5th entry), although this deoxy-glycoside is readily distinguishable from 5 and 7 in n.m.r. spectra (see Table 1)*. Given the aforementioned, superior reactivity exhibited by the α-glycoside 1 at O-2, in fission by alkali or LTBH, it is considered that a noticeable, competing detosylation at O-3 in this compound would be unlikely, although a somewhat lesser selectivity exists in its β-anomer.

Further, the reaction mixture produced from 1 showed a spot in t.l.c., slightly less mobile than that of unconsumed 1, that had been ascribed to an unidentified substance.[36] Noticing this spot, too, we found it con-

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*We did observe 10 among the products obtained from a sample of 1 that was contaminated by 8. Originating from incomplete tosylation of 4, the contaminant was present in recrystallized 1. The two compounds are difficult to distinguish by melting points or t.l.c., and, in our experience, purity can only be ensured through n.m.r. spectra.

spicuous by an olive color (fading with time to brownish) that was seen after application of a sulfuric acid spray. The material giving this spot (designated B) was obtained by column chromatography as an inhomogeneous syrup that contained, in addition to some 1, three spectroscopically discernible components in roughly comparable proportions. They appeared to be benzylidenated glycoside monotosylates, as judged by the presepce, in the ^{1}H-n.m.r. spectrum, of the appropriate aromatic signals, 3 benzylidenic methine singlets, 3 methoxyl singlets, and 3 C-Me (tosyl) singlets, in addition to the signals attributable to admixed 1 (Table 1). Compounds 2 and 8 could be excluded on both spectroscopic and chromatographic grounds; and as there were no resonances for methylene groups, in the high-field region, saturated deoxyglycoside tosylates could also be ruled out. There were, however, three small (presumably one-proton) singlets at δ 6.98, 7.02, and 7.11, which were possibly due to alkenic protons. It is conceivable that these by-products were unsaturated species originating from dehydrotosyloxylations akin to those effected[48] by soda-lime in 4,6-O-benzylidene-2 (or 3)-deoxy-3 (or 2)-O-tosyl-hexopyranosides.

It has been stated that LAH reduction of 8 or 9 gives 10 as the sole deoxyglycoside,[35,36] and we, too, could isolate only 10. However, t.l.c. of the crude product clearly indicated the presence of a very small proportion of a substance which we assume was the isomer 12, and in one fraction of processed mother liquors were noticed n.m.r. signals tentatively assignable to it. Its occurrence would be in harmony with the isolation,[35] in 1.6% yield, of its epoxide precursor[46] 11, under conditions of incomplete reduction of 8. Although these observations imply that LAH does not reduce

8 exclusively by the internal-transfer mechanism, it doubtless shows a high tendency so to operate.

CONCLUSION

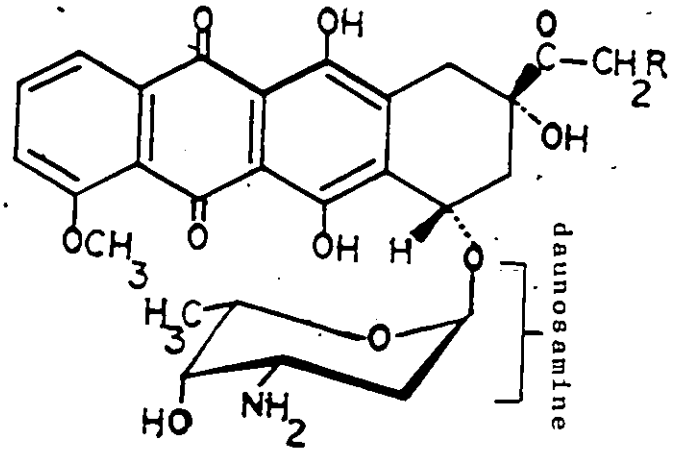
Lithium triethylborohydride proved to be an extremely effective reagent for desulfonyloxylation of some secondary tosylates of glycosides, producing certain deoxyglycosides smoothly in high yield and purity when a free, or potentially free, hydroxyl group is present trans to the sulfonic ester function. The reaction proceeds, in such a case, through an intermediary epoxide. In two of the examples studied, the reductive oxirane ring opening obeyed the Fürst-Plattner rule, whereas in two other examples the rule did not hold and regioselectivity was lacking. Desulfonyloxylation in the absence of a vicinal hydroxyl group is difficult, with desulfonylation (S-O cleavage) tending to prevail in that case. Generally speaking, though, LTBH appears to compare very favorably with lithium aluminium hydride as a reagent for the purpose of generating deoxy sugars from secondary tosylates. It should be interesting to extend future studies to further examples from among the numerous sugar tosylates that are available, and also to examine the behavior of other sulfonic esters, such as mesylates and triflates.

SECTION III

SYNTHESIS OF 4-DEOXYDAUNOSAMINE AND 4-DEOXYRISTOSAMINE

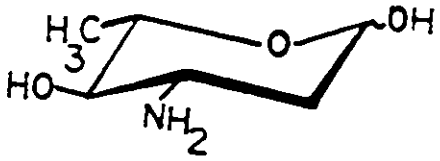
INTRODUCTION

A large number of antitumer drugs, with different origins, structures, and mechanisms of action, are nowadays in clinical use.[49] They include synthetic chemicals, antibiotics, plant products, and enzymes. Adriamycin (1), a drug which has recently become commercially available, is adding significantly to the successes achieved in cancer chemotherapy. Adriamycin is an anthracycline derivative, which contains the aminodeoxy sugar daunosamine (3-amino-2,3,6-trideoxy-L-lyxo-hexose), and is obtained by aerobic fermentation of Streptomyces peucetius.[50] Its analog daunorubicin



1, Adriamycin, R=OH

2, Daunorubicin, R=H



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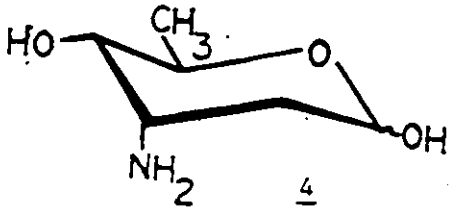

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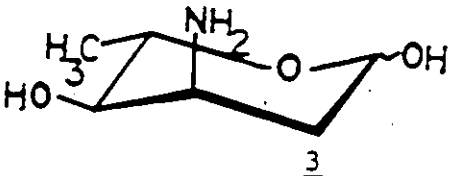
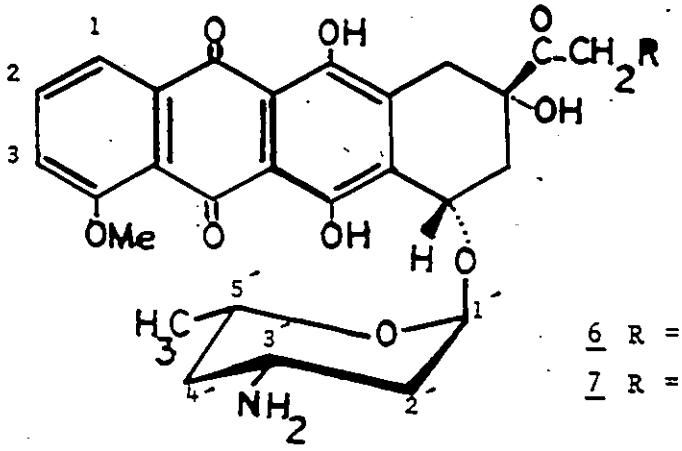


3

(2), found somewhat earlier, has also been used clincally in the treatment of leukemia[51]. The administration of these antitumor drugs is, however, accompanied by various undesirable side effects, especially a cumulative, dose-related cardiopathogenicity, which seriously limits their use[52]. Intensive, promising efforts are currently being directed in several laboratories towards the development of semisynthetic, modified analogs of daunorubicin and adriamycin which might display increased efficacy and/or lower toxicity. A large variety of analogs modified structurally or stereochemically in the aminosugar portion have been synthesized and, in part, evaluated pharmacologically[53-60]. Among the substitutes for daunosamine whose attachment to the anthracyclinone aglycons showed promise in early screening was the compound configurationally inverted at both C-3' and C-4', namely, ristosamine[53] (3; 3-amino-2,3,6-trideoxy-L-ribo-hexose). This amino sugar was originally obtained as a component of the antibiotic, ristomycin A, isolated from Proactinomyces fructifera[61]. Interestingly, attachment of the synthetic D-enantiomer (4) of ristosamine also proved effective[56]. Further, it was found, by attaching the stereoisomeric sugar acosamine (5; 3-amino-2,3,6-trideoxy-L-arabino-hexose), that inversion at C-4' alone leads to improved pharmacological properties[53b]. However, useful modification apparently need not be limited to configurational changes. Thus, replacement of the 4'-hydroxyl group by hydrogen gave the semisynthetic anthracyclines 6 and 7, containing 4'-deoxydaunosamine instead of daunosamine, and these derivatives displayed high activity against experimental tumors in mice[59]. The 4'-deoxy analogs having an axial amino group at C-3 should be worth evaluating as well, but the requisite sugar, 4-deoxy-L-ristosamine, has hitherto been unknown.



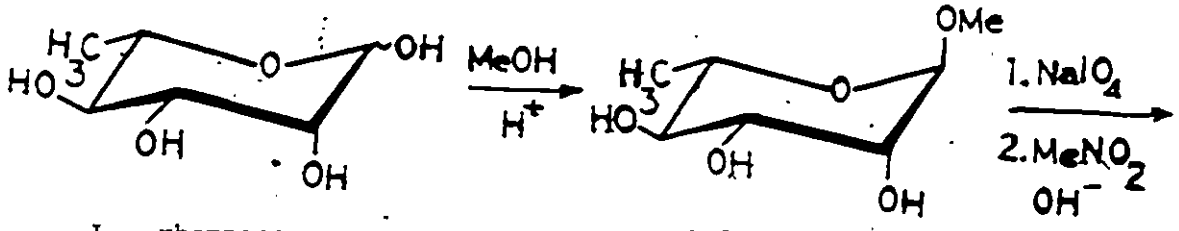
6 R = H
7 R = OH

These developments prompted the search for new and convenient, synthetic approaches to these and similar amino sugars. Of particular advantage would be designs furnishing the desired compounds in a form suitable for subsequent linking to aglycons, e.g., as N-trifluoroacetyl derivatives.

4-Deoxy-N-trifluoroacetyldaunosamine (8) had been prepared previously in a four-step reaction sequence from methyl N-trifluoroacetyldaunosaminide which, in turn, had been elaborated from natural daunorubicin[53b,59]. It would of course be possible to produce it similarly from synthetic daunosamine for which there is now available a practical method of preparation starting material from methyl α-D-mannopyranoside and comprising 9 steps[62]. A multistep, achiral synthesis of racemic, 4-deoxy-D, L-daunosamine has also been achieved[63], but this approach seems not very attractive from a practical standpoint. A short and reasonably economical synthesis of 4-

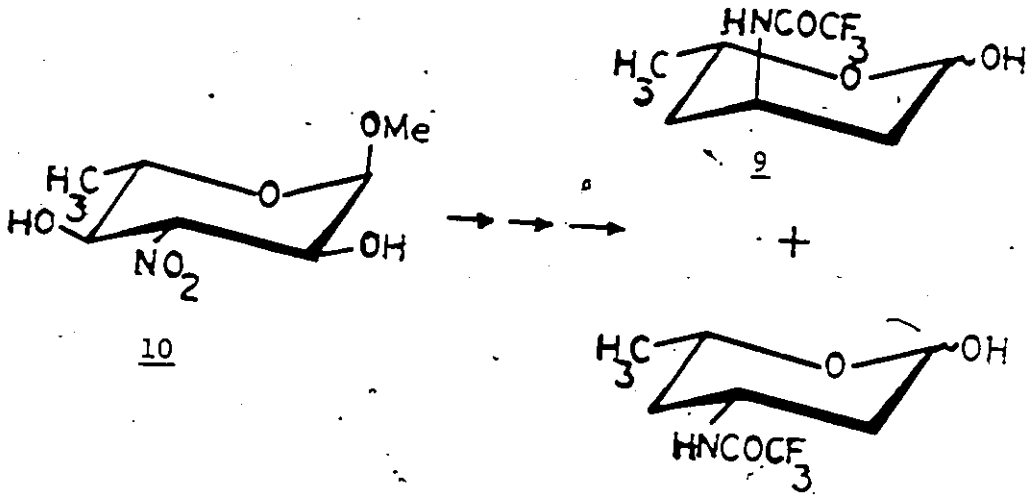
deoxy-L-daunosamine would clearly be desirable, as would be the completion of a first synthesis of 4-deoxy-L-ristosamine.

To reach these goals, it was decided to make use of the chemistry of nitro sugars. Nitro sugars are readily accessible compounds that have served well, on numerous occasions, as intermediates for amino sugars synthesis[64-69]. In the present case, the N-trifluoroacetyl derivatives 8 and 9 of 4-deoxy-L-daunosamine and 4-deoxy-L-ristosamine, respectively, were prepared by application of this methodology. The point of departure was commercial, fairly economical L-rhamnose whose readily-prepared methyl α-pyranoside yields[65,66] crystalline methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (10) on application of the nitromethane cyclization[64] method. From this known starting sugar (10) compounds 8 and 9 were jointly synthesized in acceptable overall yields, in a sequence involving five preparative steps.



L - rhamnose

methyl α-L-rhamnoside



10

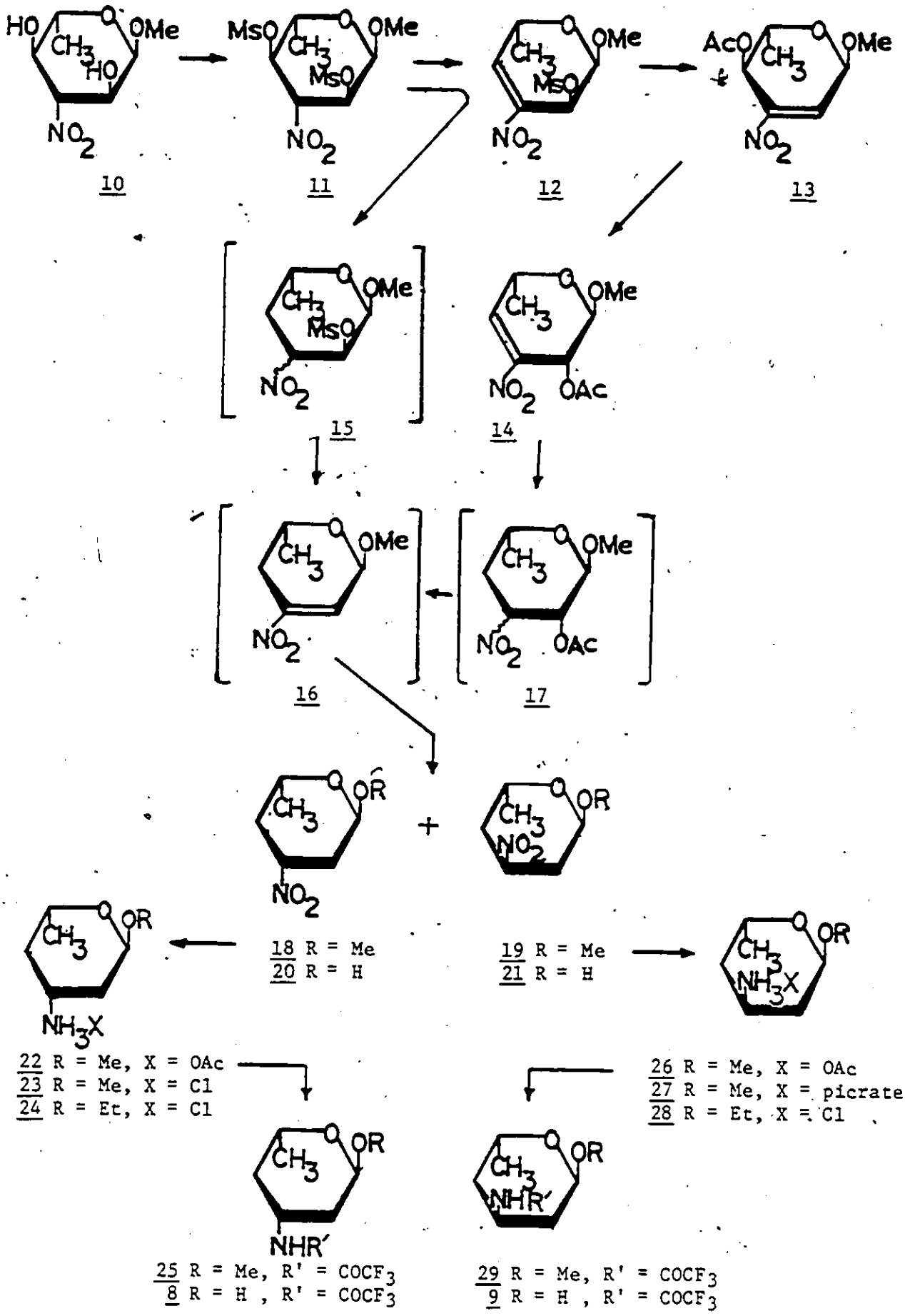
9

8

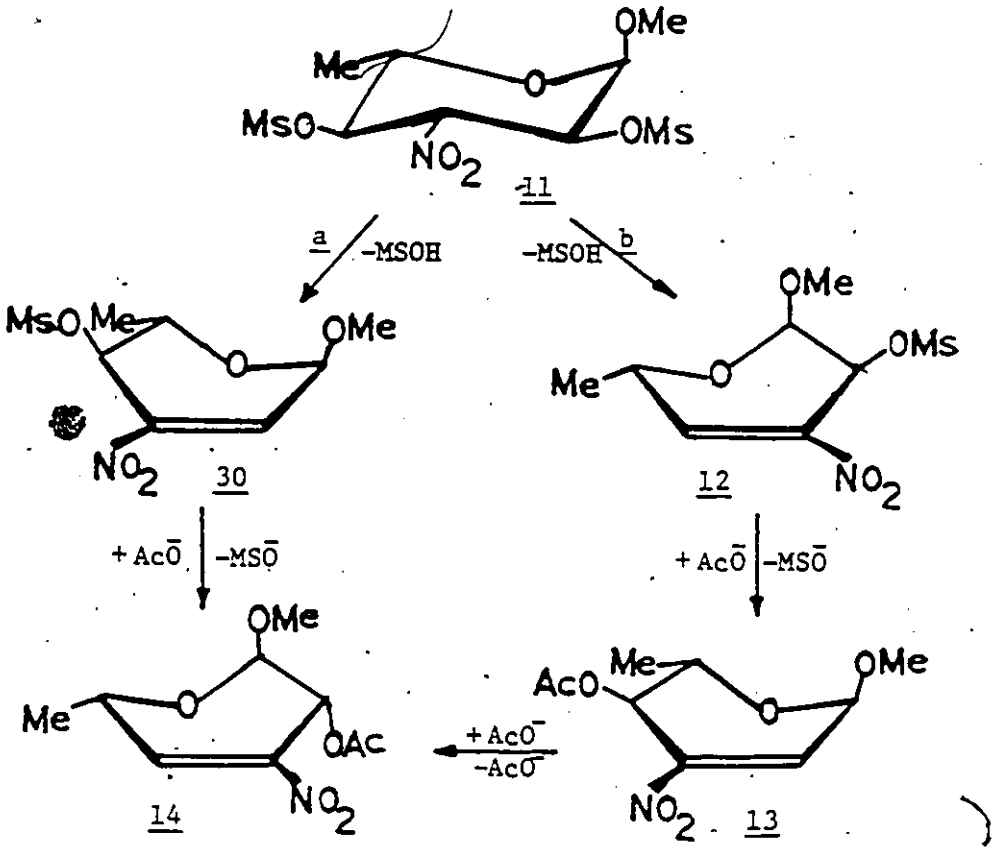
RESULTS AND DISCUSSION

The nitro glycoside 10 was first converted into its 2,4-dimesylate 11 (80% yield) by application of the procedure previously described by Baer and Georges for its D-enantiomer[68a]. Introduction of the required deoxy functions in the positions 2 and 4 was then achieved, either in a stepwise fashion or in a single operation: For the former mode, 11 was treated with sodium acetate and acetic acid in acetone solution, in order to produce the 2-O-acetyl-3-enoside 14. This procedure had previously been applied in this laboratory to the D-enantiomers[68d]; as expected, it was a successful route to compound 14. However, it was discovered during the synthesis of compound 14, through the use of a different solvent for monitoring the reaction by t.l.c., that under the previously specified conditions (namely, after 10 min of heating at the reflux temperature), an additional product was actually present in the reaction mixture. This compound disappeared when the reaction time was extended to 1h, and pure crystalline 14 was then isolated in 70% yield. To investigate the nature of the intermediary compound, the reaction was performed at room temperature, at which the rate was conveniently slow. The intermediary product was seen to arise first, and it could be isolated in crystalline form upon work-up of the reaction mixture after 2h, at the time of incipient appearance of 14. It proved to be the isomeric 4-O-acetyl-2-enoside 13, identified by comparison of its n.m.r. spectrum and optical rotation with reported data. When crystalline 13 was resubjected to the aforementioned reaction conditions, it was completely converted into 14.

The discovery of 13 as a kinetic intermediate between 11 and 14 provides an interesting clarification to the elimination-addition mechanism


HO
OMe
CH3
HO
NO2
10
MsO
OMe
CH3
MsO
NO2
11
OMe
CH3
MsO
NO2
12
AcO
OMe
CH3
NO2
13
OMe
CH3
MsO
NO2
15
OMe
CH3
NO2
OAc
14
OMe
CH3
NO2
16
OMe
CH3
NO2
OAc
17
OR
CH3
NO2
+
OR
CH3
NO2
18 R = Me
20 R = H
19 R = Me
21 R = H
OR
CH3
NH3X
22 R = Me, X = OAc
23 R = Me, X = Cl
24 R = Et, X = Cl
OR
CH3
NH3X
26 R = Me, X = OAc
27 R = Me, X = picrate
28 R = Et, X = Cl
OR
CH3
NHR'
25 R = Me, R' = COCF3
8 R = H , R' = COCF3
OR
CH3
NHR'
29 R = Me, R' = COCF3
9 R = H , R' = COCF3

proposed by Baer and Georges[68d,64c], for this reaction (in the D-series). Two possible pathways had been considered, but no preference was expressed. One of them, path a, was assumed to lead, via the 4-O-mesyl-2-enoside 30, to 14 directly, while the other one, path b, was formulated to give, via the isomeric 2-O-mesyl-3-enoside 12, an intermediary 4-O-acetyl-2-enoside (13) which would then rearrange to 14. The actual occurrence of 13 as such intermediate can now be taken as evidence for the second pathway b. It is thought that this pathway is favored for electronic reason. An



initial elimination of mesylate anion from 11 should preferentially occur from position 4, rather than from position 2 where the inductive effect of the neighboring anomeric center renders anion departure more difficult.[67b] Moreover, compound 13 cannot have arisen from an initially-formed 4-O-mesyl-2-enoside 30 by an SN2 displacement, in view of the retention of the C-4 configuration. The facile isomerization of 13 to thermodynamically more-stable 14 can be ascribed to relief of $A^{(1,2)}$ allylic strain. This condition exists in six-membered, endo-cyclic olefins, substituted at the double bond, when a neighboring allylic substituent is present in pseudoequatorial orientation.

Reduction of 14 with sodium borohydride followed by acidification gave in up to 90% yield a mixture of methyl 2,3,4,6-tetradeoxy-3-nitro-α-L-threo-hexopyranoside (18) and its α-L-erythro isomer (19). The ratio of 18 to 19, visually estimated by t.l.c. as approximately 1:2 or 2:3, did not appear to change materially with variations in reaction temperature (-30 to +25°) or solvent (ethanol, methanol, or t-butanol).

A similar mixture was obtained, more conveniently and in nearly quantitative yield, by treatment of the dimesylate 11 with sodium borohydride in dichloromethane-ethanol (1.5 h at 25°). In other words, it was not necessary for preparative purposes to isolate any of the intermediates (12 - 17) in this reductive, double deacylation procedure. Whereas part of the preponderant isomer 19 crystallized directly from the acidified reaction mixture, the bulk of the products had to be separated by column chromatography on silica gel, whereby it was essential to maintain the medium slightly acidic throughout the operation. Pure 18 and crystalline 19 were thus isolated in yields of 26 and 56%, respectively. Compound 19 was thermodynamically unstable and tended to epimerize

to 18 in neutral to slightly basic medium. This conversion, occurring for example in methanolic solution in the presence of silica gel and a trace of triethylamine, could be readily monitored by t.l.c.; after 6 h, only a trace of 19 was left. By making preparative use of this epimerization, pure 18 could be isolated, after chromatography, in a yield of 71% based on 11.

The formation and interconversion of 18 and 19 must involve the nitronate anion common to the two epimers. Evidently, protonation leads to 19 as the kinetically favored product. The n.m.r. spectrum of 19 is consistent with the normal chair conformation having an axial nitro group. Although a limited distortion cannot be ruled out, any significant deviation (e.g., adoption of a skew form) should have manifested itself clearly in the ring-proton coupling pattern. Since axial-nitro epimers are rarely encountered in sugar nitronate protonation (see refs. 68 for discussions), 19 provided a surprise, not so much in that it was formed in the present case but in that it was sufficiently stable for isolation.

Although not required for the planned amino sugar synthesis, the free nitro sugars 20 and 21 were prepared from their respective glycosides 18 and 19. Whereas the hydrolysis of 18 was performed under customary conditions using hot, 0.5 M aqueous sulfuric acid (1.5 h), that of 19 was achieved best at room temperature by treating the compound for 2 h with moist chloroform saturated with hydrogen chloride. Hydrolyses with hot, aqueous sulfuric or acetic acids resulted in considerable degrees of decomposition and gave poor yields of 21. The 2,3,4,6-tetradeoxy-3-nitro-L-hexoses crystallized in the form of upward-mutarotating α-anomers.

Apart from the fact that reduction of 18 followed by N-acylation and hydrolysis led to the known amino sugar 8 (see below), the configurational assignment of 18 and 19 was readily derived from n.m.r. spectra (100 MHz in $CDCl_3$). Thus, the nitromethine proton (H-3) in the equatorial-nitro glycoside 18 gave a low-field, symmetrical triplet of triplets whose spacings of 12 and 4.5 Hz indicated diaxial relations with H-2a and H-4a and axial-equatorial relations with H-2e and H-4e. These splittings were mirrored in the well-separated, highfield signals of H-2a (a symmetrical triplet of doublets) and H-4a (a quartet) showing, respectively, additional coupling with H-1 (3-5 Hz) and H-5 (12 Hz) as well as geminal coupling (12-13 Hz). Spacings found in the well-separated multiplets for H-5 (a sextet of doublets) and H-2e and H-4e (partially overlapping) accorded therewith. The spectrum of the free sugar 20 showed almost the same features except for some reasonably expected differences in chemical shifts and, of course, for the absence of a methoxyl resonance. By contrast, the glycoside 19 displayed for its (equatorial) H-3 proton a narrow multiplet containing only small vicinal couplings. Deshielding of H-3 was somewhat weaker, and that of H-5 was slightly stronger, than in the epimer 18. The clearly separated signals for H-2a (an octet) and H-4a (a septet) reflected the small vicinal couplings with H-3 (5.5 and 4.5 Hz) in addition to 14.5 - 15 Hz geminal couplings and 3.7 and 11.5 Hz couplings with H-1 and H-5, respectively. The free sugar 21 gave a less well-resolved spectrum (taken in dimethyl sulfoxide-d_6 because of insufficient solubility in chloroform). However, the character of the clear signals for H-3 (a narrow multiplet) and H-4a (a septet as in 19) corroborated the assignment.

Platinum-catalyzed hydrogenation of the nitro glycoside 18 furnished methyl 3-amino-2,3,4,6-tetradeoxy-α-L-threo-hexopyranoside, isolated in >90% yields either as the acetate salt 22 or the hydrochloride 23 (both crystalline). When 22 was treated for 5 min at room temperature, with chloroform saturated with hydrogen chloride and containing 0.75% of ethanol*, it was converted in high yield into the corresponding ethyl glycoside hydrochloride 24. Next, the salt 22 was quantitatively N-trifluoroacetylated in the presence of triethylamine, to give crystalline methyl 4-deoxy-N-trifluoroacetyl-α-daunosaminide (25) which was hydrolyzed with 3.5 M acetic acid, affording in 94% yield the crystalline 2,3,4,6-tetradeoxy-3-trifluoroacetamido-α-L-threo-hexose (8). The overall yield in the sequence 10→11→18→22→25→8 was 49% based on isolated, pure intermediates.

An analogous sequence of reactions was performed in the 3-epimeric, L-erythro series. Thus, catalytic hydrogenation of 19 in the presence of acetic acid gave methyl 3-amino-2,3,4,6-tetradeoxy-α-L-erythro-hexopyranoside acetate (26) in virtually quantitative yield. Although crystallizable, 26 was both hygroscopic and rather volatile, subliming in vacuo; it was characterized by its n.m.r. spectrum but, for elemental analysis, it was first converted into the highly crystalline picrate 27. The ethyl aminoglycoside hydrochloride 28 was obtained from 26 exactly like 24 from 22. N-Trifluoroacetylation of 26 provided in 92% yield methyl 4-deoxy-N-trifluoroacetyl-α-ristosaminide (29) as a chromatographically pure, volatile syrup that was characterized spectroscopically and hydrolyzed with acetic acid to afford crystalline 2,3,4,6-tetradeoxy-3-

*Ordinary, ethanol-stablized chloroform was used.

trifluoroacetamido-α-L-erythro-hexose (9). The overall yield in the sequence 10→11→19→26→29→9 was 28%.

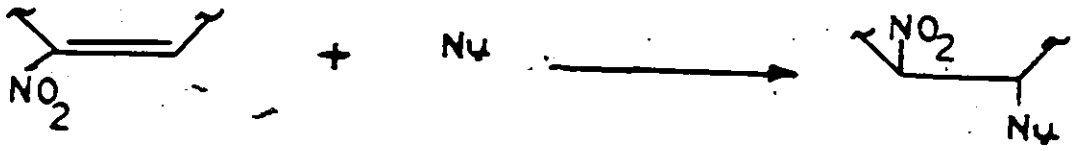
In summary, a convenient synthesis of 4-deoxydaunosamine starting from a readily available nitro sugar was elaborated. In the course of this synthesis, the hitherto unknown isomer, 4-deoxyristosamine, was also obtained. Both amino sugars were prepared in the form of their N-trifluoroacetyl derivatives, suitable for attachment, if desired, to anthracyclinones (or other aglycons) so as to generate modified antibiotics of potential, medicinal value.

SECTION IV

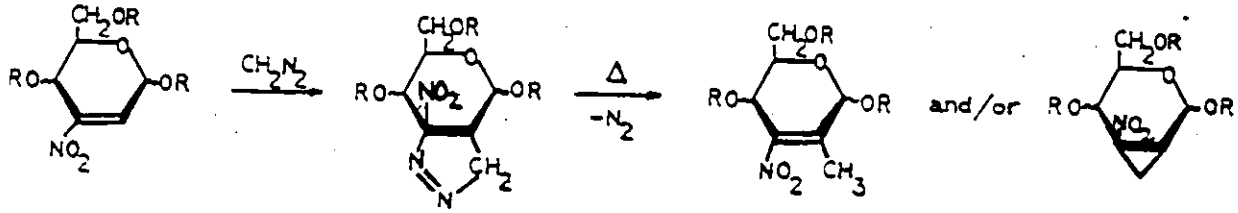
2,3-(1'-PYRAZOLINO-3',4') HEXOPYRANOSIDES AND THEIR PRODUCTS OF THERMAL DECOMPOSITION

INTRODUCTION

By the end of the 1960's numerous nitroalkenic sugar derivatives had been subjected to functionalization by way of Michael additions:[64]



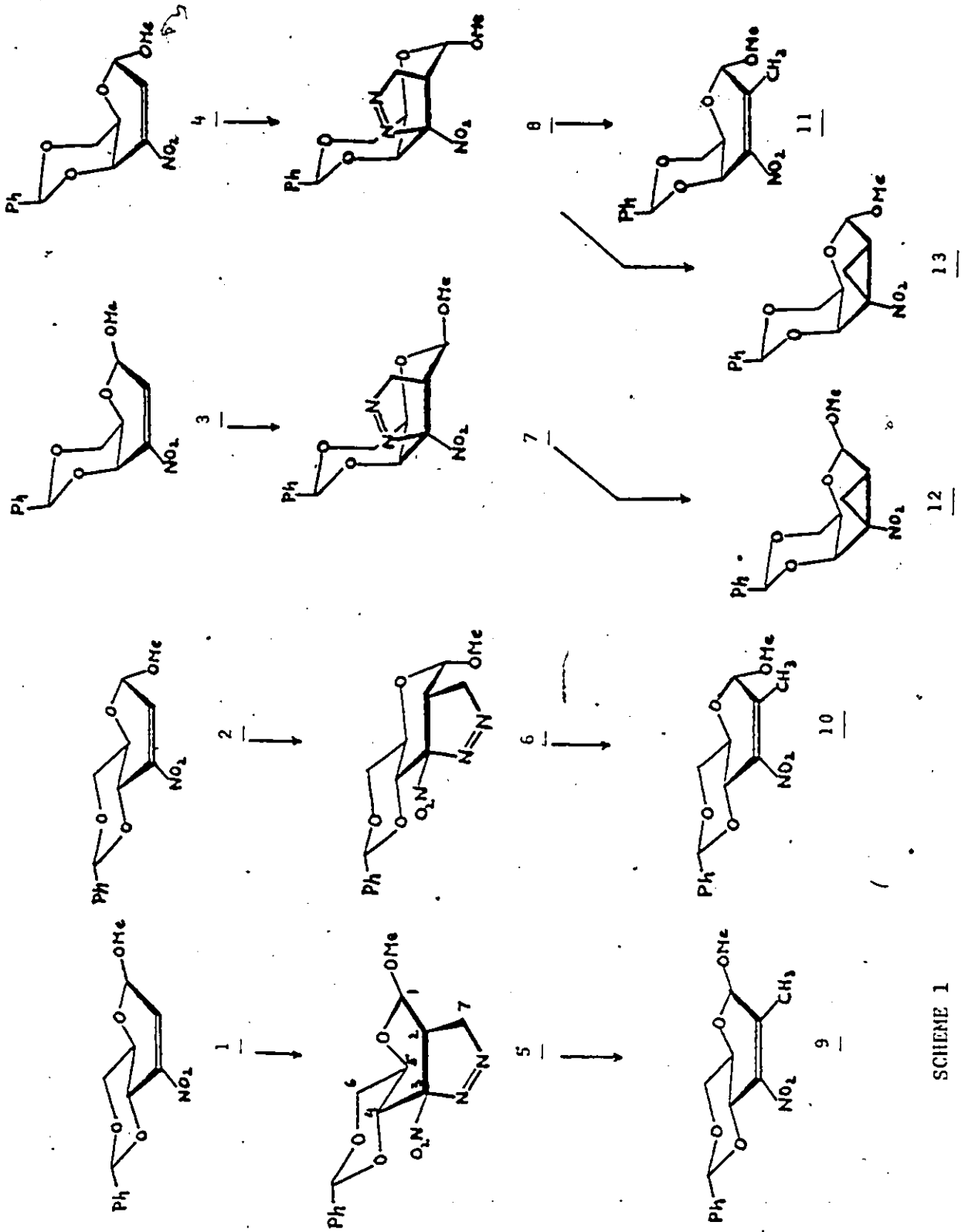
It seemed logical to extend these studies to 1,3-dipolar additions, which would lead to compounds having a five-membered hetero-ring annellated to the sugar ring. Nitroalkenes are known to be good dipolarophiles,[70-72] and the use of diazoalkanes as dipolar addends constitutes one of the classical ways of pyrazoline synthesis.[73,71] Thus, a 2,3-unsaturated, 3-nitro sugar should give a 2,3-pyrazolino derivative:



Such pyrazolino sugars would be expected to be degradable, by thermolysis according to well-established principles of pyrazoline chemistry, to yield C-methyl branched nitroalkenic and/or nitrocyclopropano sugars as novel types of carbohydrate derivatives. Although a number of sugars bearing various annellated hetero-rings were known by 1970, pyrazolino pyranosides were not among them.[74]

These considerations prompted Dr. F. Linhard, who served as a postdoctoral fellow in this laboratory 1970/1971, to undertake research along these lines.

He employed the four known, stereoisomeric methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitrohex-2-enopyranosides 1 - 4 and obtained, by reaction with diazomethane, four pyrazolino derivatives which he was able to convert, by heating them in an inert solvent, into products of thermal decomposition, as schematically indicated in the foregoing equation. The gross structures of his products were ascertained by elemental analysis and ^{1}H-n.m.r. spectra, and the results were included in a conference communication[75] in 1972. Unfortunately, Dr. Linhart's sojourn ended before he was able to unravel the stereochemistry of the products, which could not be deduced definitively from available data, and full publication of the work had therefore to be held in abeyance. Upon commencement of his Ph.D. studies, this candidate was charged with the task of repeating Linhart's experiments, optimizing conditions where desirable, gathering additional and more detailed spectral data, and settling the unresolved questions of configurational assignment.



SCHEME 1

RESULTS AND DISCUSSION

The nitroolefinic glycosides 1 - 4 reacted smoothly with a moderate excess of diazomethane in ether-tetrahydrofuran solution, giving high yields (80 - 95%) of the pyrazolines 5 - 8. The reactions of the D-erythro glycosides 1 and 2 were performed at an initial temperature of 0° for 1 h and went to completion at room temperature during an additional 30 min. The D-threo glycosides 3 and 4 (especially the latter) proved even more reactive and under the conditions just mentioned gave rise to by-products. However, good results were obtained by treating the β-glycoside 3 with diazomethane at -5° for 20 min, and the α-glycoside 4, at -20° for 5 min. (Compound 4 can literally be titrated with diazomethane solution.) The products 5, 6 and 7 crystallized readily whereas 8 was obtained as a colorless, amorphous solid. They displayed limited stability and tended to decompose on storage but could be kept under refrigeration for some weeks or months. Although progress of the reactions and purification procedures could be monitored by t.l.c., 7 and 8 in particular exhibited a certain sensitivity towards silica gel which caused in some instances the appearance of a minor spot due to a degradation product. This point will be referred to again in a subsequent paragraph.

The constitution of the pyrazolines was revealed by elemental analysis and spectral evidence. There was no infrared absorption above 3000 cm^{-1}, which indicated absence of N-H. Strong nitro bands were present at 1555-1560 cm^{-1}, and these showed shoulders around 1530-1540 cm^{-1} presumably due to N=N vibrations of the 1-pyrazoline structure.[76,77] The typical benzylidene acetal bands occurred in the 700-800 cm^{-1} region. The compounds showed low-intensity ultraviolet absorption near 325 nm as do 1-pyrazolines

generally.[76,77] The ^{1}H-n.m.r. spectrum of each product contained a 1-proton, highfield multiplet attributable to H-2 of the pyranose ring. The multiplet showed splittings due to coupling with H-1 and the two methylene protons of the fused ring. These methylene protons were deshielded by the adjacent azo group, giving well-separated AB signals of an ABX system at medium field (δ 5-6 region). The spectral features thus established the heterocycles to be 1-pyrazolines as expected, rather than 2-pyrazolines as might have resulted from tautomerization, and indicated the orientation of ring fusion, i.e., attachment of the azomethylene bridge to C-2 and C-3 of the pyranose ring through CH_2 and N, respectively. This mode of 1,3-dipolar addition of diazomethane to α-nitroalkenes was in line with expectations based on previous findings and general considerations.[70-73] All the remaining ^{1}H-n.m.r. signals could also be accounted for in terms of the constitution depicted (Tables 1 and 2). The discussion of configuration is reserved for later paragraphs.

When 5, 6, and 8 were heated at 130° in refluxing chlorobenzene, they incurred pyrolysis yielding mainly methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitrohex-2-enopyranosides (9, 10, and 11, respectively), isolated crystalline in 51 - 67% yields. By contrast, the pyrazoline 7 on similar treatment afforded in 71% yield the crystalline cyclopropano sugar 12. According to the n.m.r. spectrum the crude 12 seemed to contain a minor proportion of what may have been the corresponding 2-C-methyl olefin (i.e., the β-anomer of 11), but this could not be verified by isolation. Conversely, in the pyrolysis of 8 the corresponding cyclopropane 13 apparently was a minor by-product. The cyclopropanes 12 and 13 were also formed slowly on exposure of 7 and 8, respectively, to silica gel. This observation, first made during chromatographic tests, could be utilized

TABLE 1. The 100-MHz ^{1}H nuclear magnetic resonance data for compounds 5 - 13 in chloroform-d

Compound[b]	Chemical Shifts (δ)[a]											
	H-1	H-2	H-4	H-5	H-6$_e$	H-6$_a$	H-7$_{exo}$	H-7$_{endo}$	PhC-H	1-OMe	2-Me	Ph
5	4.40d	2.79sp	5.45d	3.24sx	4.33q	3.74t	4.98q	4.71q	5.71s	3.42s	--	7.3-7.6m
6	4.76d	2.97sx	5.04d	3.64sx	4.35q	3.85t	4.13q	5.23q	5.73s	3.28s	--	7.3-7.6m
7	4.92d	2.65m	4.88d	3.73m	4.37q	4.12q	5.02q	4.50q	5.53s	3.55s	--	7.3s
8	5.03d	2.74sx	5.20m	4.03	4.39q	4.21q	5.11q	4.40q	5.57s	3.38s	--	7.3s
9	5.22d	--	4.50oc	←4.35q, 3.7-4.1m(2H)→			--	--	5.64s	3.47s	1.92d	7.3-7.6m
10	4.85s	--	4.68q	←4.34q, 3.75-4.2m(2H)→			--	--	5.62s	3.48s	1.92d	7.25-7.50m
11	5.07s	--	4.99d	3.88m	← 4.34dq(2H) →		--	--	5.63s	3.49s	2.13s	7.3-7.6m
12	4.76d	2.54sp	5.48d	3.19m	← 4.3m(2H) →		←1.99d (2H)[c]→		5.66s	3.53s	--	7.3-7.6m
13	4.90s	2.44q	5.59d	3.68m	←4.24d(2H)→		1.74q	2.01q	5.68s	3.35s	--	7.3-7.6m

[a] Multiplicities are indicated as s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; sp, septet; oc, octet; m, multiplet.

[b] Note that, in 5 - 8 and 12 and 13, H-7$_{exo}$ is situated *cis* to H-2 and H-7$_{endo}$ is *trans* to H-2.

[c] By coincidence the H-7 protons are magetically equivalent; the give rise to a doublet (A_2 part of an A_2B system) due to coupling with H-2, and no geminal coupling is observed.

TABLE 2. The observed splittings (Hz) of compounds 5 - 13

Compounds	$J_{1,2}$	$J_{2,7exo}$	$J_{2,7endo}$	$J_{4,5}$	$J_{5,6e}$	$J_{5,6a}$	$J_{6e,6a}$	$J_{8exo,7endo}$	Others
5	3.4	8.3	5.3	10.5	5.0	10.0	10.5	18.7	
6	6.0	6.7	1.3	9.7	4.8	9.8	10.0	17.7	
7	3.7	8.5	10.5	1.3	1.7	1.7	12.8	17.5	
8	~1.5	9	10.5	~2	1.8	1.7	12.5	16.5	$J_{2,4}$ ~1
9	--	--	--	10.5			~10	--	$^5J_{4,Me}$ 2; $^5J_{1,4}$ 2.5
10	--	--	--	9			~ 9	--	$^5J_{4,Me}$ 2
11	--	--	--	~1	2.5	2.5	~13	--	
12	2	8	8	2.3				0[a]	
13	0	8.3	10.3	2.3				5.5	

[a] see footnote c of Table 1.

to produce crystalline 13 on a preparative scale in high yield.

The structure of the unsaturated glycosides 9 - 11 was proved by their ^{1}H-n.m.r. spectra which contained a 3-proton signal near δ2 owing to the 2-C-methyl group. In 9 and 10, this signal was a narrow doublet because of long-range coupling with H-4 ($^5J_{4,Me}$ = .2 Hz). The H-4 signal occurred near δ4.7 and, in the case of 9, showed long-range coupling also with H-1 ($^5J_{1,4}$ = 2.5 Hz). No long-range coupling was evident in the corresponding signals of 11. These findings were consistent with the geometry of the protons involved, in relation to the olefinic double bond.[78] The three products gave infrared bands at 1530 cm^{-1} as expected for nitroalkenes.

The cyclopropano derivatives 12 and 13 were characterized by high-field signals (δ 1.7 - 2.5) for the two methylene protons of the cyclopropane ring and H-2 of the pyranose ring, in addition to well-separated signals at lower field that accounted for the remaining protons required of these structures. Assignment of configuration was possible on the basis of chemical shift and coupling parameters in comparison with the various, structurally analogous 2,3-anhydro-3-nitro glycoside stereoisomers obtained earlier in this laboratory[79], and with the 2,3-cyclopropano glycosides described by Horton[80] and Fraser-Reid[81]. Thus, the H-4 signals of 12 and 13 were found at quite similar, conspicuously low field (δ 5.48 and 5.59, respectively). Considering that pyranose ring protons are noticeably deshielded by vicinal, trans disposed oxirane[79,82] or cyclopropane[81] rings but shielded by such rings in cis orientation, one may conclude that 12 and 13 bear their cyclopropane rings on the same side, most likely trans to H-4. In the 2,3-anhydro-3-nitro glycoside of α-D-talo configuration (the analog of 13), the H-4 resonance is at δ5.63 whereas in all its

stereoisomers studied[79] the range was δ 4.0 - 5.05. Furthermore, the H-1 signals of 12 and 13 also showed very similar chemical shifts (δ 4.76 and 4.90); the difference of only 0.14 ppm is unusually small for a pair of anomeric protons but is readily explained on the same basis. Thus, a cyclopropane ring located on the upper face of the pyranose will deshield the axial, β-anomeric proton situated trans to it but shield the equatorial, α-anomeric proton and thereby diminish the shift difference normally characteristic for the two. The configuration shown was strongly supported in the α-glycoside 13 by zero coupling between H-1 and H-2 as had previously been observed in analogous, benzylidenated 2,3-anhydro[79,80,83] and (non-nitro) cyclopropano[81] structures having an H-1,2 trans arrangement (i.e., the α-D-talo or α-D-manno configuration). In conformity with $J_{1,2}$ = 0 Hz, the H-2 signal of 13 was a quartet, split only by $H\text{-}7_{exo}$ and $H\text{-}7_{endo}$. In the event of an opposite, downward orientation of the cyclopropane ring (H-1,2 cis) one would expect a large $J_{1,2}$ value as indeed was found[80,81] for a non-nitro analog having the α-D-allo configuration ($J_{1,2}$ = 5 - 6 Hz). That the 3-C-nitro substituent does not have much influence can be seen from the value of 6.3 Hz observed in methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-C-methylene-3-nitro-α-D-"allopyranoside"*, a stereoisomer of these compounds recently obtained[84] in a different way by Sakakibara and Sudoh*. Hence the designation of 13 as methyl 4,6-O-benzylidene-2,3-

*The authors based their assignment, correctly no doubt, on the similarity of their $J_{1,2}$ value with that of the non-nitro analog[80,81] having the α-D-allo configuration. However, their adoption of the same configurational prefix allo is unfortunate since substitution of H-3 by the nitro group implies, in terms of nomenclature, an inverted configuration so that the gluco designation should be applied. Compare the usage in other branched-chain sugars containing quaternary centers; see also footnotes 2 in refs. 85a,b.

dideoxy-2,3-C-methylene-3-nitro-α-D-idopyranoside appears to be secure. The β-glycoside 12 showed $J_{1,2}$ = 2 Hz, and the H-2 signal at δ2.54 was a septet reflecting that splitting. This coupling constant compares well with those in 2,3-anhydro and cyclopropano analogs having an H-1,2 cis structure as in the β-D-manno configuration, for which was found[79] 0.8 Hz and[81] 3.5 Hz. For β-glycosidic 2,3-anhydro analogs possessing the D-allo and D-gulo configurations, $J_{1,2} \simeq 0$ Hz was found[79]; and $J_{1,2}$ = 1 Hz was reported[81] for the β-D-allo cyclopropano analog. Despite some ambiguity present in these comparisons it is believed that the data support the view of 12 being the anomer of 13, i.e., it bears the ring in like disposition and is to be designated as a β-D-ido compound. As will be seen from the following discussion, the anomeric relationship is borne out by a consideration of the strucutre of the pyrazoline precursors from which 12 and 13 arose by extrusion of nitrogen, most certainly without inversion at C-2.

To begin with, some problems were encountered in the allocation of configurations to the pyrazolino derivatives 5 - 8. From the origin of the compounds by 1,3-dipolar cycloaddition, cis fusion of the heterocycle to the pyranose ring could be inferred with certitude, but its upward or downward orientation in each individual case was difficult to establish. Although all the required ^{1}H-n.m.r. data were available (Tables 1 and 2), they did not yield unambigous information right away in this regard. This is so because, for each of the products, a reasonable conformation (distorted chair, half-chair, or skew form) that is consistent with the data can be constructed for either configuration. Nevertheless, some of the parameters were helpful in corroborating the configurations determined by other means, as will be mentioned below. Next, ^{13}C-n.m.r. spectra of 5 - 8 were evaluated. The ^{13}C chemical shifts obtained from proton-decoupled spectra (Table 3)

TABLE 3. The ^{13}C chemical shifts (ppm from tetramethylsilane) for compounds 5 - 8 in chloroform.[a]

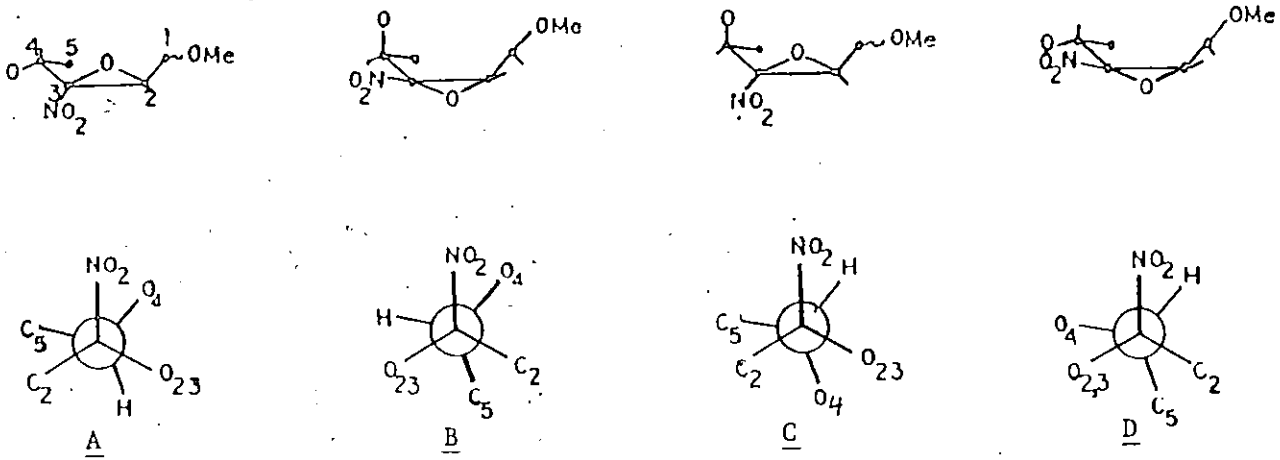
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Ph-CHO_2	O-CH_3
5	99.3	44.1	119.8	75.0	63.8	69.7	81.1	102.4	56.0
6	96.0	43.2	118.1	76.7	58.6	69.1	77.1	102.7	55.5
7	99.3	40.5	119.3	70.9	67.2	68.8	77.2	101.1	57.1
8	95.6	41.3	116.4	69.2	59.2	69.0	78.9	100.9	55.4

[a]In addition to the resonances listed, all compounds showed the appropriate signals for the phenyl ring carbon atoms in the range of 123-136 ppm.

clearly confirmed the constitution of the products and suggested at least a partial answer to the question of configuration. In the latter regard, inspection of the data reveals certain significant trends when the compounds are compared with each other, even though the over-all spectra are very similar. Thus, the normally expected increases in shielding of C-1 and C-5, and to a lesser degree of C-2 and C-4, are observed on going from a β-glycoside (5 or 7) to the respective α-glycoside (6 or 8). There are few conspicuous differences otherwise. It has been pointed out by Perlin[86-88] that the sums of all ^{13}C chemical shifts occurring in each member of a set of diastereomers mirror the total steric interactions and should therefore bear relation to the overall configurations. For compounds 5 and 6 such summation (leaving out the phenyl group) gives Σ_5 = 711.0 and Σ_6 = 697.9 ppm, and the difference of 13.1 ppm is very nearly the same as that (13.6 ppm) derived from the reported[89] shifts of the anomeric methyl 4,6-O-benzylidene-D-glucopyranosides. This fact suggests that the steric influences exerted upon the molecules 5 and 6 by the structural features surrounding C-2 and C-3 must be quite similar, which in turn justifies the conclusion that the pyrazoline rings are attached in like orientations, causing the two compounds to be a pair of anomers. Similarly for 7 and 8, the difference of the sums Σ_7 = 701.4 and Σ_8 = 685.9 ppm is 15.5 ppm. Although data of comparison for the corresponding methyl 4,6-O-benzylidene-D-galactopyranoside anomeric pair were unavailable, the difference is close to that (14.4 ppm) of the methyl β- and -α-D-galactopyranosides[86], which supports the assumption of 7 and 8 being anomers also. This result fits the aforementioned indication that the degradation products 12 and 13 represent an anomeric pair. It should be noted, however, that the deductions based on the ^{13}C chemical shifts do not interrelate the pairs 5/6 and 7/8 configurationally; they

merely advocate anomerism and leave open the C-2,3 configuration of either pair. Additional evidence was needed, and this was provided by optical rotatory dispersion measurements.

It was found that the absorption band near 325 nm is associated with a negative Cotton effect in 5 and 6, and with a positive one in 7 and 8. In order to assess the significance of this, let us consider some analogies. It is known that the Cotton effect is determined largely by chirality in the immediate environment of the chromophore. Thus, in the structurally related methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-D-hexopyranosides, which also display an effect in that region[79], the sign is independent of the anomeric configuration and determined only by the configurations at C-3 and C-4. (The configuration of C-2, being by necessity linked to that of C-3, need not be considered separately here.) Figure 1 shows Newman projections of these nitroepoxides viewed along the C-3,4 bond. (Absence of perfect staggering is a consequence of the half-chair conformation in which these compounds must exist.) The Cotton effect appears to obey the following empirical rule: When the C-3 nitro group is written at the top of the projection and O-4 then appears on its righthand side, the sign is positive (cases A, B, and C); if O-4 appears on the lefthand side, the sign is negative (case D). The same was found to hold for the nitroalkenes 1 - 4 and 9 - 11, although in these unsaturated sugars (λ_{max} 325-330 nm) C-3 is achiral and the sole determinant for the sign of the Cotton effect is C-4. The sign is negative in the α- and β-D-erythro compounds (Fig. 1, case E) and positive in the α- and β-D-threo compounds (case F). On the grounds of these observations the pyrazolino sugars 5 and 6, if indeed they are anomers as indicated by the ^{13}C-n.m.r. data, may be ascribed the configuration represented by D (with -N=N-CH_2 replacing $O_{2,3}$). The alternate



	Configuration		
α-and β-D manno	β-D-gulo	α-and β-D-talo	β-D-allo
	Cotton Effect		
positive	positive	positive	negative

	Configuration	
α-and β-D-erythro		α-and β-D-threo
	Cotton Effect	
negative		positive

Figure 1: Partial formulas, and Newman projections along the C-3-C-4 bond, of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-D-hexopyranosides (top) and methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides (R=H) and 2-C-methyl derivative (R=Me), (bottom).

possibility, corresponding to A, should be associated with a positive Cotton effect. Compounds 5 and 6 are therefore designated as β- and α-D-gluco isomers, respectively.* As for the isomers 7 and 8, which would correspond to B or C (Fig. 1), their positive effect is in accord with the rule elaborated above but evidently cannot afford a distinction between these possibilities. (The nitro epoxy and nitroolefinic glycosides just mentioned exhibit a second cotton effect at short wavelengths (approximately 275 and 285-290 nm, respectively). The same appears to apply to 5 - 8 although technical difficulties precluded accurate determination. At any rate, it has not yet been possible to correlate these second effects with configuration.) However, since, the configuration of the cyclopropano derivative 13 is well supported by the n.m.r. spectrum, the same α-D-ido configuration follows for its progenitor 8, and with the additional evidence for an anomeric relationship, 7 can be accorded the β-D-ido configuration.

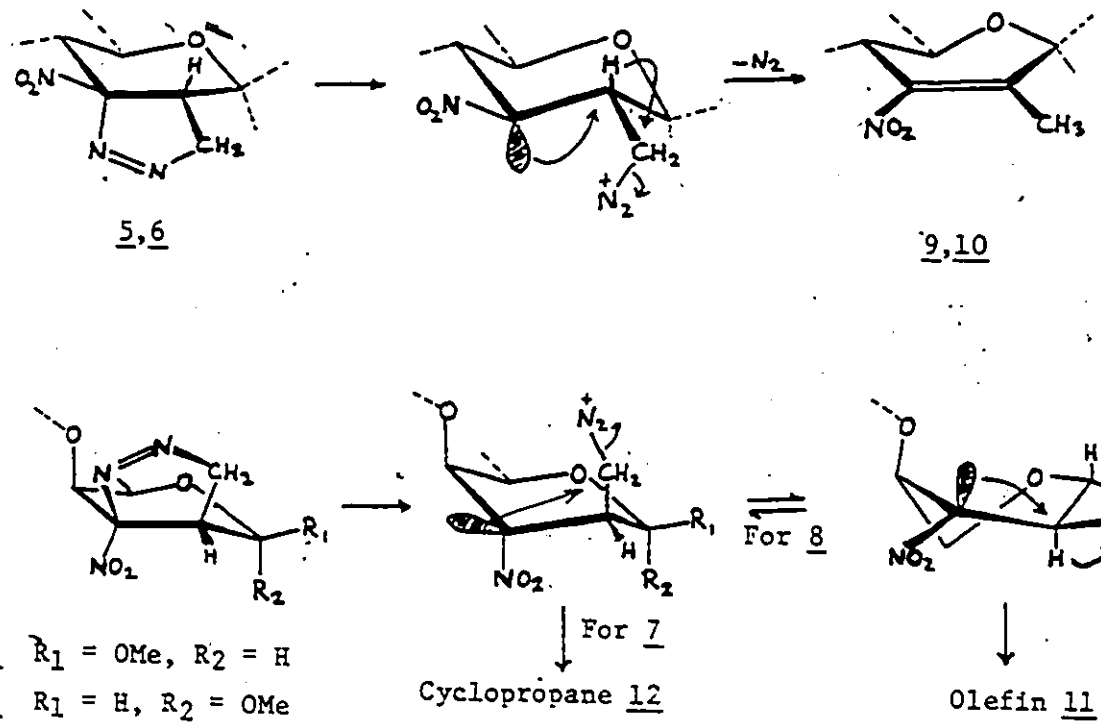
Given the configurations of 5 - 8 so assigned, one may now review the ^{1}H-n.m.r. data of Table 1 and 2 and be satisfied that these are consistent with a conformation close to the $_5H^4$ half-chair for 5, and with distorted $_1C^4$ chair conformations for 6, 7, and 8, as is best visualized with the aid of molecular models. It is worth noting, in particular, that the splitting values of 16.5 - 17.7 Hz for the geminally coupled pyrazoline protons at C-7 in 6 - 8, and also the large vicinal couplings between both of these protons and H-2 in 7 and 8, are in good agreement with corresponding data reported[77] for simple pyrazolines. The smaller $J_{2,7}$ couplings present in

*The nitro group, as the substituent of highest configurational priority at the geminally disubstituted C-3, is thought of as replacing the hydroxyl group in the parent sugar, D-glucose. Note that the analogous epoxide having like orientations of the nitro group and fused hetero ring is termed a D-allo compound.

5 and 6 likewise accord with the dihedral angles occurring in models of the conformations mentioned. The slightly increased $J_{7,7'}$ value (18.7 Hz) for 5 could be a consequence of change in the pyrazoline ring shape caused by its fusion to a pyranose half-chair. That 5 appears to stand apart conformationally from its three isomers is also suggested by the chemical shifts of the C-7 protons. These protons are influenced primarily by the anisotropy of the N=N double bond[77,90]. Thus, groups pseudoaxially oriented with respect to the plane of the double bond are placed in the shielding cone and are shifted to higher field[90]. This applies to H_{7exo} in 6 and to H_{7endo} in 7 and 8, which are shielded quite strongly relative to their geminal partners (Table 1). The difference is small in 5, implying a more nearly equal space arrangement of the C-7 protons with respect to the double bond, and this accords with a more planar 5-membered ring as would result from fusion to a half-chair. In the latter situation there is little puckering possible, contrary to the case of fusion to a (distorted) chair.

The highly stereoselective nature of diazomethane addition to each of the nitroolefins 1 - 4 invites comment. One might perhaps have anticipated at first sight that the orientation of the anomeric methoxyl group would influence the approach of the reagent to C-2; this is normally observed in kinetically controlled, nucleophilic additions[79,85b,91,92]. However, such is evidently not the case. Instead, a directing effect is associated with the orientation of O-4, and it seems possible that coordination of the diazomethane molecule precedes, and facilitates, addition which then produces the pyrazoline ring cis to this acetal oxygen. This might also explain why in 3 and 4, wherein O-4 is in a better geometric position for this purpose, the reaction proceeds faster than in 1 and 2.

Concerning the differential behavior of the pyrazolines in thermal decomposition, one may suggest that in 5 and 6 the geometry emerging concomitant with the loss of N_2 favors hydrogen migration from C-2 to C-7, leading exclusively to olefins as depicted in partial formulas in Scheme 2 (upper sequence). (See ref. 93 for ionic mechanism in activated pyrazolines.)



SCHEME 2

On the other hand, in 7 and 8 the same process may require, for a facile hydrogen shift, transition through a skew conformation. In the case of 8 such conformational change could be attained relatively easily; indeed, it would be promoted by relief of a severe 1,3-diaxial interaction between the nitro and methoxy groups present in the normal chair. Hence, the olefin 11

is favored as the main product (Scheme 2, lower sequence). The same driving force for conformational change does not exist in 7; moreover, attainment of the skew form would likely be opposed by the β-glycosidic methoxyl coming into interaction with O-4. Ring closure to give the cyclopropane 12 thus appears to be a reasonable alternative. Finally, it should be noted in this context that the decomposition of pyrazolines to cyclopropanes - a much-investigated subject* - frequently involves configurational inversion at the carbon atoms adjacent to the azo bridge. However, the central pyrazoline carbon (C-2 in our derivatives) is not affected by this complication and consequently, the orientation of ring fusion in the cyclopropano sugars must remain the same as in the parent pyrazolines.

CONCLUSION

The work described in this Section elucidated the steric course of the 1,3-dipolar addition of diazomethane to the stereoisomeric, nitro-olefinic sugars 1 - 4 to give the pyrazolines 5 - 8, and established the configuration of the cyclopropane derivatives 12 and 13 obtained by pyrolysis. These cyclopropanes, as well as the C-methylnitroalkenes 9, 10 and 11, which were also produced from the pyrazolines, should be useful intermediates for further syntheses of nitrogenous deoxy sugars.

*References 76, 81, 90, 93-95

EXPERIMENTAL

GENERAL TECHNIQUES

Solvents. - Solvents were reagent grade and were used without further purification, except where indicated otherwise. Petroleum ether normally refers to the fraction boiling at 30-60°. The solvent systems used for chromatography are listed at the beginning of each of the four individual Sections. Solvent evaporation during processing of reaction mixtures and chromatographic fractions was performed in a rotary evaporator, normally at 30-35° (bath temperature).

Handling of moisture- and air-sensitive materials. - Glassware used in the experiments with organometallic reagents (Section I) was dried by heating it overnight in an oven at ca. 120° and was then purged, while still hot, with a stream of dry nitrogen. An atmosphere of dry nitrogen (or carbon monoxide, as required) under slightly positive pressure was maintained in the apparatus during reactions. Reactant solutions were transferred, and test samples withdrawn, by means of syringes, rubber septa, and Teflon tubing.

Similar precautions were observed for the reactions with lithium triethylborohydride (Section II).

The tetrahydrofuran employed as reaction medium in Sections I and II was freshly dried immediately before each experiment by refluxing it over, and distilling it from, potassium metal in the presence of benzophenone radical anion.

Chromatography. - Analytical thin-layer chromatography (t.l.c.) was routinely employed to monitor reactions and column-chromatographic separations, and to check the purity of products. It was performed on precoated silica gel plates SIL G-25 UV_{254}, whereas preparative thin

layer chromatography (p.t.l.c.) was done on glass plates coated with MN-Kieselgel G/UV$_{254}$ (both products manufactured by Macherey-Nagel & Co., West Germany). Spots were made visible by UV light and (or) by spraying the plates with 5% sulfuric acid in ethanol and heating them briefly on a hot-plate. Silica gel 60 (E. Merck A.G., West Germany) was used as support for column chromatography, and a Prep. LC/System 500A (Waters Scientific, Ltd.) was used to perform some large-scale separations.

N.M.R. spectroscopy. - ^{1}H-n.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer, or at 60 MHz with a Varian T-60 or a Varian EM-360A spectrometer. The ^{13}C-n.m.r. spectra were recorded at 20 MHz with a Varian CFT-20 spectrometer. Unless otherwise indicated, all n.m.r. data refer to spectra obtained from $CDCl_3$ solutions containing tetramethylsilane as an internal standard, and chemical shifts are expressed as parts per million downfield from the Me_4Si signal (δ values). Proton-proton couplings (J values) given for new compounds were in most cases determined from expanded 100-MHz spectra (250 Hz sweep width).

Other spectroscopic techniques. - Infrared spectra were obtained from Nujol mulls unless otherwise specified, by use of a Beckman IR-20 or IR-20A, or a Unicam SP 1100 infrared spectrometer. Ultraviolet and visible absorptions were recorded on a Perkin Elmer spectrophotometer, model 202. Mass spectra were obtained with an AE-1-MS902 mass spectrometer fitted with a direct-inlet probe and operating at an ionizing potential of 50-55 eV.

Optical rotations. - Optical rotations ([α] values) were determined at ambient temperature (usually about 25°) in a Perkin Elmer automatic polarimeter, model 141, and refer to chloroform solutions unless otherwise stated. A Jasco ORD/UV-5 instrument served for the measurement of Cotton

effects.

Melting points were determined by use of capillaries in an electrically-heated aluminum block apparatus (Gallenkamp).

Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona.

SECTION I

Experimental. Section I

Solvent systems: - The chromatographic solvent systems (v/v) used in this section were: (A) 1 : 1 ethyl acetate–hexanes, (B) 1 : 2 ethyl acetate–hexanes, (C) 1 : 1 ether–petroleum ether, (D) the same solvents, but 1 : 2, (E) the same, but 1, 10; (F) the same, but 10 : 1, and (G) 9 : 1 methanol–ether.

Preparation of the starting glycosides. A. Methyl 2,3,4-tri-O-acetyl-6-O-(p-tolylsulfonyl)-β-D-glucopyranoside (10). — The procedure of Compton[96] was modified, for an improved yield and a simpler mode of processing, as follows. To a chilled (-20°) solution of methyl β-D-glucopyranoside (10.0 g) in dry pyridine (50 ml) was added dropwise a solution of p-tolylsulfonyl chloride (17.7 g, 1.8 mol. equiv.) in dry dichloromethane (18 ml). The mixture was kept overnight at room temperature, and acetic anhydride (15 ml) was then added and allowed to react for 24 h. The mixture was processed with crushed ice and water, to give a crystalline solid which was isolated and then dissolved in ethyl acetate. After washing with water, aqueous sodium hydrogencarbonate, and water, the solution was dried ($MgSO_4$) and evaporated. The residue of evaporation was recrystallized once from hot ethyl acetate, to give 10 (12 g, 50%), m.p. 170-171°, $[\alpha]_D$ +5.7° (c 3); lit.[96] m.p. 169-170° (after 3 recrystallizations from ethanol) and $[\alpha]_D$ +7.4° (c 3.7). The mother liquor of recrystallization contained additional 10 together with a (very slightly) faster-moving, second product (t.l.c. by triple irrigation with 1 : 3 ethyl acetate–hexanes), which presumably was a ditosylate. N.m.r. data (100 MHz) of 10 : δ7.3 (q, 4 H, arom.), 5.19 (t, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), 4.92 (~t, $J_{3,4}$ 9, $J_{4,5}$ 10 Hz, H-4), 4.89 (dd, $J_{1,2}$ 7.8, $J_{3,4}$ 9 Hz, H-2),

4.38 (d, $J_{1,2}$ 7.8 Hz, H-1), 4.12 (d, 2 H, J 4.2 Hz, H-6,6'), 3.75 (m, J 4.2 and 10 Hz, H-5), 3.44 (s, 3 H, OMe), 2.46 (s, 3H, tosyl-Me), 2.04 (s, 3 H) and 2.00 (s, 6 H) for 3 OAc.

B. Methyl 2,3-di-O-acetyl-4-O-benzoyl-6-bromo-6-deoxy-β-D-glucopyranoside (14). — Compound 14 was obtained in 74% yield from methyl 2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranoside[97,98] by application of the Hanessian-Hullar reaction[99]. Recrystallized from ethyl acetate–ether, 14 showed m.p. 169–170°, $[\alpha]_D$ -57° (c 0.65); ^{1}H-n.m.r. data (100 MHz) : δ7.7 (m, 5 H, OBz), 5.43 and 5.20 (two symmetrical one-proton triplets, J 9.3, H-3 and -4), 5.05 (dd, $J_{1,2}$ 7.8, $J_{2,3}$ 9.3 Hz, H-2), 4.54 (d, $J_{1,2}$ 7.8 Hz, H-1), 3.84 (o, H-5), 3.58 (s, 3 H, OMe), 3.5 (m, 2 H, H-6,6'), 2.07 and 2.00 (s, 3 H each, OAc).

C. The glycosides 15, 22 and 24. — Prepared according to the literature[99,100], compound 15 showed m.p. 123–124.5° and $[\alpha]_D$ -11.4° (c 3); reported[100], m.p. 120–121°, $[\alpha]_D$ -9°. Compound[101] 22 had m.p. 126.5–128°, $[\alpha]_D$ +45.7° (c 2.6, chloroform) and +91.8° (c 2, pyridine); lit.[101] m.p. 125–126° and[102] $[\alpha]_D$ +90.9° (pyridine). Compound[100] 24 exhibited m.p. 129–130° and $[\alpha]_D$ +116° (c 0.5); lit.[100] m.p. 130–131°, $[\alpha]_D$ +118°.

D. Methyl 4-O-benzoyl-6-bromo-6-deoxy-2,3-di-O-methyl-β-D-glucopyranoside (16) and its α-anomer 25. — Methyl 4,6-O-benzylidene-2,3-di-O-methyl-β-D-glucopyranoside[103] and its α-anomer[104] were conveniently prepared by Kuhn methylation[105] of the corresponding diols, with the procedure following a recent example[106], and then subjected to the Hanessian-Hullar reaction[99]. — The β-anomeric acetal gave 16 as a syrup in 79% yield after flash chromatography on a short column of silica gel (eluant, petroleum ether followed by solvent E); $[\alpha]_D$ -47° (c 2.5). ^{1}H-n.m.r. data (100 MHz) δ 7.7 (m, 5 H, OBz), 5.06 (t, $J_{3,4} = J_{4,5}$ = 9.3 Hz, H-4), 4.31 (d, $J_{1,2}$ 7.5 Hz,

H-1), 3.69 (o, H-5), 3.60 (s, 6 H) and 3.48 (s, 3 H) for 3 OMe groups. The protons H-2, -3, -6, and -6' gave ill-resolved multiplets, partially overlapped by the OMe signals, in the δ3.6-3.1 region.

The α-anomeric acetal gave syrupy 25 in 88% yield after column-chromatographic purification; $[\alpha]_D$ +56.1°, $[\alpha]_{578}$ +58.3° (c 4.1); lit.[107] $[\alpha]_{578}$ +68 and +71°. ^{1}H-n.m.r. data (100 MHz) : δ7.7 (center of m, 5 H, OBz), 5.07 (dd, $J_{3,4}$ 9, $J_{4,5}$ 10 Hz, H-4), 4.93 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.03 (m, H-5), 3.75 (t, J 9.3 Hz, H-3), 3.6-3.3 (unresolved multiplets for H-2, -6, and -6', superposed by 3 singlets for OMe). Assignment[107] of the H-4 signal as an 8-Hz doublet at δ5.13 (60-MHz spectrum) appears to be in error.

E. Methyl 2,3-di-O-acetyl-4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (23). — Compound 23 was prepared from methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-glucopyranoside[98,103a,108] by application of the Hanessian-Hullar reaction[99,107]. It was obtained in 95% yield as a slightly impure syrup which crystallized from ether-petroleum ether after purification by flash chromatography (eluant, petroleum ether followed by solvent E); m.p. 106-107°, $[\alpha]_D$ +57.2°, $[\alpha]_{578}$ +59.0° (c 2.5); lit.[107] oil, $[\alpha]_{578}$ +61°. ^{1}H-n.m.r. data (100 MHz) : δ7.7 (center of 2m, 5 H, OBz), 5.69 (t, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 5.19 (t, $J_{3,4} \sim J_{4,5} \sim$ 9.5 Hz, H-4), 5.04 (d, $J_{1,2}$ ~3.6 Hz, H-1), 4.95 (dd, $J_{1,2}$ ~3.6, $J_{2,3}$ 9.2 Hz, H-2), 4.13 (sp, H-5), 3.50 (s for OMe superposed on m for H-6 and -6'; total intensity, 5 H), 2.09 and 1.90 (s, 3 H each, 2 OAc). Recorded[107] 60-MHz data were incomplete and contained some obvious errors in assignments.

F. Methyl 2,3,4-tri-O-benzoyl-6-deoxy-6-iodo-α-D-mannopyranoside (31). — Methyl α-D-mannopyranoside (3.0 g) was converted into its 6-deoxy-6-iodo derivative by treatment with triphenylphosphine, iodine, and imidazole,

essentially as described by Garegg and Samuelsson[109], except that the reaction was performed in tetrahydrofuran solution at 70° (oil bath temperature) for 4 h, rather than in boiling toluene for 5 h. The crude product was benzoylated by treatment with benzoyl chloride and pyridine for 90 min at room temperature. Upon customary processing the material was crystallized by trituration with ether, and recrystallized from ethyl acetate–petroleum ether, to give pure 31 (4.2 g, 44%; the isolated yield was low because of losses incurred during an unsuccessful attempt at purifying, by column chromatography, the crude iodination product prior to benzoylation). Compound 31 showed m.p. 207–208.5°, $[\alpha]_D$ -110° (c 0.65); lit.[110] m.p. 202–203°, $[\alpha]_D$ -101.6°, and[111] m.p. 199–201°, $[\alpha]_D$ -106°; m.s.: m/z 616 (M^+), 585 (M^+ - OMe), and 495 (M^+ - OBz); ^{1}H-n.m.r. data (100 MHz) : δ7.7 (m, 15 H, 3 OBz), 5.65–6.0 (overlapping m, 3 H, H-2, -3, and -4), 5.00 (d, W_H 3 Hz, H-1), 4.06 (sx, H-5), 3.60 (s, 3 H, OMe), and 3.30–3.55 (m, 2 H, H-6,6').

Dicarbonyl-η^5-cyclopentadienyl (methyl 2,3,4-tri-O-acetyl-β-D-gluco-pyranoside-6-yl)iron (11). — For generation of sodium dicarbonyl -η^5-cyclopentadienyliron[11c] (NaFp), the procedure described by Bock and Whitesides[112] for the analogous molybdenum complex was used. A flame-dried, 25-ml vessel equipped with a magnetic stirring bar, nitrogen inlet, and outlet was charged with mercury (2 ml), and sodium (200 mg) was added to form an amalgam, with rapid stirring under nitrogen. After cooling of the amalgam to room temperature, dry tetrahydrofuran (20 ml) was introduced, and nitrogen gas was passed through it for a few minutes. Commercial dicarbonylcyclopentadienyliron dimer (355 mg, 2 mequiv. of Fe) was then added and the mixture stirred vigorously for 1 h, during which period the color of the solution turned from dark-red to an orange

or olive shade. Stirring was discontinued, the amalgam allowed to settle, and the supernatant transferred by means of N_2-pressure, through Teflon tubing, into a second reaction flask (also flame-dried) that contained the crystalline sugar 10 (0.71 g, 1.5 mmol). The sugar dissolved in the reagent upon stirring, and, after 10 min, was completely converted into 11 (t.l.c. with solvent A; the slow-moving spot of 10, visible after spraying the plate with 5% ethanolic sulfuric acid followed by heating, was absent, and a strong, faster-moving, yellow spot of 11 was seen prior to spraying; some unidentified trace spots were also present). In general, the solution of 11 so obtained was used directly for the preparation of 12, and similarly, the solutions of analogous iron derivatives made in the same way from other sugars were employed, without isolation of intermediates, for the syntheses of hepturonates described in subsequent sections.

For the isolation of 11, the aforementioned tetrahydrofuran solution was evaporated to give a thick, dark syrup which by means of solvent B was passed quickly through a short column of silica gel. Salts and other contaminants were retained, and the effluent yielded a yellow syrup that was purified further, without delay, by preparative t.l.c. (solvent A). The yellow band was extracted with ethyl acetate, furnishing 0.56 g (78%) of 11. In another experiment, 300 mg of 10 gave 280 mg of 11 (92%); apparently, the yield of this rather unstable compound is influenced by the speed of work-up operations. Compound 11 showed λ_{max}^{MeOH} 412 nm; ν_{max}^{neat} 2015 and 1940 (strong; ligand CO), and 1745 cm^{-1} (strong; acetyl CO); ^1H-n.m.r. data (100 MHz) : δ5.13 (t, J 9.3, H-3), 4.95 (m, H-4), 4.80 (s, 5 H, for Cp, superposed on m, 1 H, for H-2), 4.35 (d, $J_{1,2}$ 7.4 Hz, H-1), 3.53 (s, 3 H, OMe), 3.27 (o, H-5), 2.07, 2.04, and 2.00 (3 s, 9 H, 3 OAc),

1.62 (dd, $J_{5,6}$ 2.7, $J_{6,6'}$ 11 Hz, H-6), and 1.24 (m, H-6'). ^{13}C-n.m.r. data : δ217.4 and 216.8 (ligand CO), 170.4, 169.9, and 169.5 (acetyl CO), 101.9 (C-1), 85.4 (Cp), 79.4-71.9 (5 C, C-2 to C-6), 57.1 (OMe), 20.9 and 20.7 (acetyl Me). M.s.: m/z (in parentheses, relative intensities) 480 (10), M^+ for $C_{20}H_{24}O_{10}Fe$; 452 (15), M^+ - CO; 424 (70), M^+ - 2 CO; 359 (100), M^+ - 2 CO - Cp; 350 (30), M^+ - 2 CO - $C_3H_6O_2$; 304 (50), M^+ - Fp + H).

Methyl (methyl 2,3,4-tri-O-acetyl-6-deoxy-β-D-gluco-heptopyranosid-uronate (12). — A solution of 11 was prepared as just described, from 10 (400 mg) and a 1.3-molar excess of NaFp in tetrahydrofuran (40 ml). The solution was cooled (0 to -5°), a stream of carbon monoxide was passed through, and absolute methanol (20 ml) was added, followed by bromine (0.4 ml). The reaction was revealed by t.l.c. (solvent A) to be complete after a few minutes: The yellow spot of 11 (R_F 0.4, visible without spraying) was replaced by a strong spot of 12 (R_F 0.3) accompanied by a very weak spot of 13 (R_F 0.4, visible after spraying and heating). The mixture was concentrated to a small volume by evaporation, diluted with ethyl acetate (or ether), and the solution washed sequentially with sodium thiosulfate solution, sodium hydrogencarbonate solution, and water, and dried ($MgSO_4$). Removal of the solvent gave a dark syrup, which was passed through a short column of silica gel by flash chromatography with solvents A or C. The effluent furnished a syrup that was subjected to p.t.l.c. (solvent A), giving pure 12 (247 mg, 81%). Crystallized from ethyl acetate-petroleum ether, it had m.p. 149-150°, $[\alpha]_D$ -9.6° (c 0.7).

Anal. Calc. for $C_{15}H_{22}O_{10}$ (362.3): C, 49.72; H, 6.12. Found: C, 49.52; H, 6.17.

The faster-moving by-product (13) was isolated by p.t.l.c. as crystals

(~50 mg, 15%), m.p. 124.5-125.5°, $[\alpha]_D$ -2.4° (c 0.9); lit.[113] m.p. 125-126°, $[\alpha]_D$ -1.4°. The n.m.r. spectrum was in accord with the structure of methyl 2,3,4-tri-O-acetyl-6-bromo-6-deoxy-β-D-glucopyranoside.

In a similar experiment, iodine (1.0 g) in methanol (20 ml) was substituted for the bromine, and the reaction was performed at room temperature; it was complete after ~0.5 h (t.l.c. with solvent A). Processing as described before, and column chromatography with solvent E, yielded crystalline 12 (250 mg from 400 mg of 10, 82%), identified with the previous product by n.m.r. spectra.

A solution of 11 prepared from 10 (1.00 g) and NaFp (made from 0.75 g of dicarbonylcyclopentadienyliron dimer) in tetrahydrofuran (30 ml) was cooled to +5°, methanol (10 ml) as added, and carbon monoxide was bubbled through the mixture to which was then added anhydrous cupric chloride (2 g). The reaction was nearly complete after 20 min; it was allowed to go to completion by stirring at room temperature of another 15 min, with some additional cupric chloride (0.5 g). The mixture was filtered, and the filtrate was evaporated to give a syrupy product that was dissolved in ethyl acetate, washed several times with water, and recovered by solvent evaporation. After purification by flash chromatography as previously described, 12 (0.45 g, 59%) was obtained crystalline, m.p. 149-150°.

A solution of 11 (prepared from 500 mg of 10 and 1.3 molar equiv. of NaFp) in tetrahydrofuran (40 ml) was treated with methanol as just described, but in the presence of anhydrous ferric chloride (720 mg) at an initial temperature of ~+12°. The reaction was then allowed to proceed at room temperature and required 6 h for completion (t.l.c. with solvent A). Solvent removal then gave a syrupy product which was dissolved in ether,

washed several times with water, recovered by evaporation, and finally, purified by p.t.l.c. (solvent A). The yield of crystalline 12 was 239 mg (62%).

Methyl (methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-β-D-gluco-heptopyranosid)uronate (18). — In a preliminary experiment designed to demonstrate the formation of the sugar-iron intermediate 17, the bromo sugar 14 (450 mg) was treated with NaFp (1.3 molar equiv.), exactly as described for the preparation of 11 from 10. The t.l.c. showed complete consumption of 14 (R_F 0.45, prior to spraying; compare 11) together with traces of slow-moving impurities. The reaction mixture was filtered through a bed of silica gel, the solvent evaporated, and the syrupy residue dissolved in ether and purified by p.t.l.c. (solvent C). Compound 17 was isolated as a yellow syrup (228 mg) that was homogeneous initially but tended to decompose with time. (Progressive darkening was observed, within a day, on storage in a refrigerator.) The ^{1}H-n.m.r. data (100 MHz) : δ7.7 (center of m, 5 H, OBz), 5.34 and 5.06 (two t, J ~9 Hz, H-3 and -4, or reverse), 5.03 (dd, $J_{1,2}$ 7.8, $J_{2,3}$ 9 Hz, H-2), 4.74 (s, f H, Cp), 4.43 (d, $J_{1,2}$ 7.8 Hz, H-1), 3.55 (s, 3 H, OMe), 3.43 (m, H-5), 2.04 and 1.86 (s, 3 H each, 2 OAc), 1.68 and 1.34 (centers of two m, 1 H each, H-6 and 6').

For the preparation of 18, the bromo sugar 14 (500 mg) was converted into 17 by the aforedescribed method, except that the reaction temperature was -16°. (Cooling at that stage, also employed in some of the subsequent syntheses, did not appear to have any marked effect; it was probably not essential.) For the following, oxidative insertion (compare the reaction 11→12), the mixture was cooled to -50°, methanol (20 ml) was added, and bromine (0.5 ml) was administered dropwise as a solution in methanol (10 ml), at a fairly rapid rate. After a few minutes, t.l.c. was performed to

ascertain that the reaction was complete; it showed 18 (R_F 0.2) as the main product and 14 (R_F 0.3) as a minor by-product, the yellow spot of 17 having completely disappeared (solvent D, double irrigation). Cooling of the reaction mixture was discontinued while the t.l.c. was performed, and the mixture, having attained a temperature near 0° during this period, was immediately thereafter processed as described for 12, except that the solvents were evaporated completely (bath temperature, 35°), and the residue was dissolved in dichloromethane for performance of the aforementioned (cf. 12) washing operations. It was found advisable to process with utmost dispatch in order to minimize losses in yield due to secondary reactions. Solvent removal than gave a dark syrup containing 18 and 14, which were separated by p.t.l.c. (solvent B). Compound 18 (340 mg, 71%) crystallized from ether-petroleum ether and showed m.p. 131.5°, $[\alpha]_D$ -69° (c 0.75).

Anal. Calc. for $C_{20}H_{24}O_{10}$ (424.4): C, 56.60; H, 5.70. Found: C, 56.36; H, 5.64.

Compound 14 (114 mg, 23%) was identified by its m.p., R_F value, and ^{1}H-n.m.r. spectrum.

Methyl (methyl 4-O-benzoyl-6-deoxy-β-D-gluco-heptopyranosid)uronate (19). — For preparation of 19, the procedure just described for 18 was applied to 15 (700 mg), with appropriately adjusted quantities of reagents and solvents. T.l.c. (ether) indicated formation of slow-moving 19 and a small proportion of the faster-moving by-product 15. The products were separated by p.t.l.c. (solvent F), giving 19 (530 mg, 80%) as a syrup, $[\alpha]_D$ -13.2° (c 1.5).

Anal. Calc. for $C_{16}H_{20}O_8$ (340.3): C, 56.46; H, 5.92. Found: C, 56.31; H, 5.97.

The faster-moving material was isolated as a slightly impure syrup (63 mg), shown by its ^{1}H-n.m.r. spectrum to consist mainly of 15.

Methyl (methyl 6-deoxy-β-D-gluco-heptopyranosid)uronate (20). — The benzoate 19 (400 mg) in absolute methanol (20 ml) was treated with a catalytic amount of sodium methoxide (16 h, 25°). It was seen by t.l.c. (solvent G) that 19 (R_F 0.5) was completely debenzoylated to 20 (R_F 0.2). Deionization, treatment with activated charcoal, and evaporation of the solution gave 20 (257 mg, 92.5%) as colorless crystals (from methanol-ether), m.p. 186-187°, $[\alpha]_D$ -13.6° (c 0.5, methanol).

Anal. Calc. for $C_9H_{16}O_7$ (236.2): C, 45.76; H, 6.83. Found: C, 45.56; H, 6.73.

Methyl (methyl 4-O-benzoyl-2,3-di-O-methyl-β-D-gluco-heptopyranosid)uronate (21). — The procedure detailed for preparation of 12 and 16 was applied to 16 (0.57 g), except that the reaction temperature during the bromine oxidation was -25° initially and allowed to rise to +15° in the course of 1 h. Ether was used as the medium for the washing operations. T.l.c. and p.t.l.c. were performed with 1 : 1 : 6 ethyl acetate-ether-petroleum ether. Compound 21 (R_F 0.25) was isolated as a syrup (485 mg, 90%) showing $[\alpha]_D$ -48.9° (c 1.5).

Anal. Calc. for $C_{18}H_{24}O_8$ (368.4): C, 58.69; H, 6.57. Found: C, 58.94; H, 6.53.

The faster-moving band eluted from the p.t.l.c. plates gave a syrup (~0.1 g) that contained 16, identified by its R_F value of 0.4 and its n.m.r. spectrum, together with some 21 and unidentified impurities.

Methyl (methyl 2,3,4-tri-O-benzoyl-6-deoxy-α-D-gluco-heptopyranosid)uronate (26). — Compound 26 was prepared from 22 (600 mg) as described for 16. In t.l.c. (solvent D), 22 had R_F 0.4, and 26, R_F 0.3. In one

experiment, no 22 was detected in the product, and 26 (462 mg, 80%) was obtained as a homogeneous syrup, $[\alpha]_D$ +37.5° (c 1.6), after the removal of minor impurities by flash chromatography. In another experiment (which yielded 78% of 26) the formation of 22 could be observed; it amounted to 13% and was identified by its n.m.r. spectrum upon isolation by p.t.l.c. (solvent D). All attempts at crystallizing 26 failed.

Methyl (methyl 6-deoxy-α-D-gluco-heptopyranosid)uronate (27). — Treatment of 26 (1.00 g) in methanol (25 ml) with a catalytic amount of sodium methoxide effected complete debenzoylation within 3 h at 25° (t.l.c. with solvent A). Processing included deionozation, treatment with charcoal, and passage of the crude material through a short column of silica gel by sequential elutions with petroleum ether and ether (to elute benzoic acid) followed by ethyl acetate (to obtain 27). Crystallized from ethyl acetate (or warm ether) and petroleum ether, 27 (420 mg, 97%) showed m.p. 92-93°, $[\alpha]_D$ +146° (c 0.5).

Anal. Calc. for $C_9H_{16}O_7$ (236.2): C, 45.76; H, 6.83. Found: C, 45.84; H, 6.84.

Methyl (methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-α-D-gluco-heptopyranosid)uronate (28). — Compound 28 was prepared from 25 (700 mg) as described for 16. The medium for the washing operations was ether. T.l.c. with solvent C showed 28 (R_F 0.6) as the major product, and traces of 25 (R_F 0.7) as well as several, slow-moving impurities. Separation by p.t.l.c. was accomplished by double irrigation, first with solvent C and then with solvent A, giving 590 mg (88%) of 28 after crystallization from 99% ethanol; m.p. 99-101°, $[\alpha]_D$ +56.3° (c 0.9).

Anal. Calc. for $C_{20}H_{24}O_{10}$ (424.4): C, 56.60; H, 5.70. Found: C, 56.39; H, 5.75.

Only a very small amount of by-product 23 could be isolated; it was identified by t.l.c. only.

Methyl (methyl 4-O-benzoyl-6-deoxy-α- D-gluco-heptopyranosid)uronate (29). — The procedure for preparation of 16 was applied to 24 (700 mg). For processing, the procedure for 12 was first followed and then a second, identical washing sequence was applied to the product in dichloromethane solution. The product showed a stong spot of 29 (R_F 0.4) together with traces of more- or less-polar impurities, but little if any 24 (R_F 0.5) was seen (t.l.c. with ether). The crude, yellow syrup of processed reaction product crystallized in part from ether-petroleum ether to give pure 29, and additional, crystalline 29 was obtained by p.t.l.c. of the mother liquor (solvent F), for a total of 461 mg (70%); m.p. 154-155.5°, $[\alpha]_D$ +124.9° (c 3.5).

Anal. Calc. for $C_{16}H_{20}O_8$ (340.3): C, 56.46; H, 5,92. Found: C, 56.00; H, 5.87.

Methyl (methyl 4-O-benzoyl-6-deoxy-2,3-di-O-methyl-α-D-gluco-hepto-pyranosid)uronate (30). — Compound 25 (1.00 g) was converted into 30 at an initial reaction temperature of -20° (compare the preparation of 21). Solvent B was used to monitor the reaction by t.l.c. and to purify the product by p.t.l.c.; 30 was obtained as a syrup (0.80 g, 84.5%), $[\alpha]_D$ +62.1° (c 0.7). No by-product was isolated.

Anal. Calc. for $C_{18}H_{24}O_8$ (368.4): C, 58.69; H, 6.57. Found: C, 58.59; H, 6.83.

Methyl (methyl 2,3,4-tri-O-benzoyl-6-deoxy-α-D-manno-heptopyrano-sid)uronate (32). — Compound 32 was obtained from the mannoside 31 (0.60 g) as described for 16. T.l.c. with solvent B showed 32 (R_F 0.5) as the main product; also present was a weak spot which migrated slightly faster, like

starting 31, but was due to its bromo analog 33. P.t.l.c. with solvent B gave 32 (0.40 g, 75%), crystallized from ether-petroleum ether; m.p. 136.5-138°, $[\alpha]_D$ -135.6° (c 0.7).

Anal. Calc. for $C_{30}H_{28}O_{10}$ (548.5): C, 65.69; H, 5.14. Found: C, 65.74; H, 5.24.

A small amount of crystalline 33 (70 mg) was isolated, and recrystallized from methanol; m.p. 178-180°, lit.[100] m.p. 180-182°. The mass spectrum showed the characteristic pattern of twin peaks due to bromine isotopes: m/z 570, 568 (M^+ for $C_{28}H_{25}BrO$); 539, 537 (M^+ - OMe); 510, 508 (M^+ - HCO_2Me); 448, 446 (M^+ - BzOH); 447, 445 (M^+ - BzOH - H); 417, 415 (M^+ - OMe - BzOH); 489 (M^+ - OMe - Br); and 429 (M^+ - HCO_2Me - Br).

SECTION II

Experimental. Section II

Solvent systems: The chromatographic solvent systems (V/V) used in this section were: (A) 2:1 ethyl acetate–hexane, (B) the sames solvents, but 1:1, (C) the same, but 1:2, (D) the same, but 1:3, (E) the same, but 1:4, (F) 1:2 ethyl acetate–petroleum ether (b.p. 30–60°), (G) the same, but 1:3, and (H) the same, but 1:4.

Preparation of the starting sulfonate esters. -- A. Methyl 4,6-O-benzylidene-2,3-di-O-p-tolysulfonyl-α-D-glucopyranoside (1). Compound 1 was prepared[114] from methyl 4,6-O-benzylidene-α-D-glucopyranoside (4). The stout prisms, $[\alpha]_D$ +13.0° (c 3), melted at 154–155° as reported[114], but a chromatographically purified sample had m.p. 159–160° and showed small differences in the fingerprint region of the i.r. spectrum (Nujol mull). The dimorphous form[114] (needles of m.p. 147–148°) was not encountered. The ^{1}H-n.m.r. data agreed with those reported[40] for the 6,6'-d compound; additional data : δ4.18 (dd, $J_{5,6e}$ 3.6, $J_{6a,6e}$ 9 Hz, H-6e), 3.58 (t, H-6a, $J_{5,6a}$ 9 Hz), and data in Table 1.

B. Methyl 4,6-O-benzylidene-3-O-p-tolylsulfonyl-α-D-glucopyranoside (2) and its benzoate (3). The diol 4 was selectively benzoylated[115,116] to give its 2-monobenzoate, m.p. 169–170°. If the product was judged by its n.m.r. spectrum[36] to be not entirely pure, it was purified by h.p.l.c. using solvent D. The benzoate was p-toluenesulfonylated[117] to give 3, m.p. 187.5°, $[\alpha]_D$ +89.8° (c 1); lit.[117] m.p. 188–189°, $[\alpha]_D$ +88.5°; ^{1}H-n.m.r. data : δ8.09 and 7.45 (m, OBz), 5.40 (s for PhCH superposed on t for H-3), 5.2–5.1 (m, 2 H, H-1, 2), 4.32 (dd, $J_{5,6e}$ 3.8, $J_{6a,6e}$ 9 Hz, H-6e), 3.97 (dt, H-5), 3.75 (t, $J_{5,6a} = J_{6a,6e}$ = 9Hz, H-6a), 3.71 (t, $J_{3,4} = J_{4,5}$ = 9 Hz, H-4), and data in Table 1.

To generate 2, a partial suspension of LAH (50 mg) in a small amount of ether was introduced with swirling, into an ice-cold solution of 3 (600 mg) in tetrahydrofuran (10 ml) and ether (20 ml). Inspection by t.l.c. (solvent B) showed that, although most of 3 (R_F 0.75) had reacted within 5 min, some of it still remained after 15 min. An additional 10 mg of LAH was added and the mixture was processed after a further 5 min by pouring it into ice-water containing some sulfuric acid. The aqueous phase was extracted twice with ether and twice with ethyl acetate, and the combined organic phases were dried (K_2CO_3), and evaporated, to give crude 2 (R_F 0.40) as a dry, crystalline mass. Chromatography on silica gel (15 ml in a 15-cm column) using solvent B as eluant removed traces of contaminants (3 and 6, R_F 0.75 and 0.5) and gave pure 2 (431 mg, 89%), m.p. 167°, $[\alpha]_D$ +33° (c 1); lit.[36] m.p. 165°, $[\alpha]_D$ +33° (for 2 prepared similarly, but in boiling tetrahydrofuran, and[21] m.p. 164°, $[\alpha]_D$ +32.5° (for 2 obtained from 1, in 17% yield, by partial, alkaline hydrolysis).

Alternatively, sodium methoxide (10 drops of a freshly-prepared, saturated solution in methanol) was added during 1 h to a chilled (-15°) solution of 3 (100 mg) in 1:1 methanol-chloroform (5 ml). The mixture was kept at 0-2° for 5 h, after which time the conversion into 2 was complete; only a trace of 6 was seen (t.l.c. with solvent B). De-ionization and evaporation of the solution gave 2 (79 mg, 98%; dried in high vacuum), m.p. 163-165°, unchanged after recrystallization from dichloromethane-petroleum ether. The i.r. spectrum was identical with that of 2 from the preceding procedure. Similar methanolyses had given[36] 83 and[118] 52% yields. ^{1}H-n.m.r. data : δ4.85 (t, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), 4.84 (d, $J_{1,2}$ 3.5Hz, H-1), 4.26 (dd, $J_{5,6e}$ 3.5, $J_{6a,6e}$ 9 Hz, H-6e), 4.0-3.5 (m, 4 H, H-2, -4, -5, -6a), 2.66 (d, J 9.8 Hz, OH), and data in Table 1.

C. Methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-glucopyranoside (8) and its benzoate 9. Compound 8 was prepared from 4 by selective p-toluenesulfonylation[43,45,119]. Recrystallized first from 99% ethanol and then from ethyl acetate, it had m.p. 154-155° and $[\alpha]_D$ +62° (c 1.5); lit.[45] m.p. 155° $[\alpha]_D$ +63.5°. (A modification melting[40] at 136-138° was not observed.) Crude 8 tends to contain some ditosylate 1 which is not revealed in t.l.c. as it migrates at almost the same rate. However, it can be readily detected in the ^{1}H-n.m.r. spectrum. For effective retention of the contaminant in the mother liquor during recrystallization of 8, it is important to allow the hot solution to cool slowly to room temperature, and to avoid refrigeration. The ^{1}H-n.m.r. data : δ4.82 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.36 (dd, $J_{2,3}$ 9.3 Hz, H-2), 4.30-3.30 (m, 5 H, H-3, 4, 5, 6,6'), 2.57 (d, J 2.5 Hz, OH), and data in Table 1.

A sample of the benzoate 9 was desired for purposes of spectral comparison. It was obtained in 87% yield by customary p-toluenesulfonylation[117,119] of methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside, and showed m.p. 221-222°, $[\alpha]_D$ +52.6° (c 1.1) after recrystallization from ethyl acetate-hexane; lit.[43] m.p. 212-213°, $[\alpha]_D$ +51.6°. The ^{1}H-n.m.r. data were in full agreement with those reported[120]; see Table 1 for selected signals. Additional data: δ4.33 (dd, $J_{5,6e}$ 3.6, $J_{6a,6e}$ 9 Hz, H-6e), 4.01 (dt, H-5), 3.76 (t, $J_{5,6a}$ 9.5 Hz, H-6a), and 3.72 (t, $J_{3,4}$ 9.5, $J_{4,5}$ 9 Hz, H-4).

D. Methyl 4,6-O-benzylidene-3-O-p-tolylsulfonyl-β-D-glucopyranoside (14), methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-β-D-glucopyranoside (16), and its 3-acetate 17. Partial p-toluenesulfonylation of methyl 4,6-O-benzylidene-β-D-glucopyranoside (13) proceeds with less selectivity than for the α-anomeric diol 4; invariably, substantial proportions of the ditosylate

15 are produced together with small to moderate proportions of the monotosylates 14 and 16, but the latter can nevertheless be isolated, if somewhat laboriously. The following modification of published procedures[39,40] proved fairly satisfactory. A solution of 13 (5.0 g) in dichloromethane (30 ml) and pyridine (20 ml) was stored in a refrigerator, and p-toluenesulfonyl chloride (7.0 g, 2 mol. equiv.) was added in several, small portions during the course of 7 days. Monitoring by t.l.c. (solvent B) indicated after 10 days that only a small amount of starting 13 (R_F < 0.1) remained beside the tosylated products (R_F 0.3 and 0.5). Treatment of the mixture with crushed ice and water precipitated a solid product which, after thorough washing with water, followed by drying, was chromatographed on a column of silica gel (200 g) by use of solvent E, to give a mixture of 15 and 16 (R_F 0.48 in t.l.c. with solvent B; ratio 5.6:1, by n.m.r.), followed by chromatographically pure 14 (R_F 0.30; 1.64 g, 21.4%), and unchanged 13 (R_F <0.1; 0.36 g, 7.2%).

Recrystallized from ethanol, the 3-tosylate 14 had m.p. 159.5–160°, $[\alpha]_D$ -78.5° and $[\alpha]_{546}$ -94.3° (c 2); lit.[40] m.p. 155–156°, $[\alpha]_D$ -81.4° and[39] m.p. 162–163°, $[\alpha]_{546}$ -86.5 ± 5°. The ^{1}H-n.m.r. data agreed in essence with those reported[40], except that all resonances were found at slightly lower field (by 0.06–0.09 ppm). The H-3 signal was at δ 4.75 (t, $J_{2,3} = J_{3,4}$ = 8.7 Hz), and the H-6e signal, at 4.33 (dd, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 10 Hz); see also Table 1.

Chromatographic separation of 15 and 16, though reportedly possible[39,40] is rather difficult and inconvenient on larger scales. It was much facilitated by first converting 16 into its acetate 17. To this end, a mixture of the two esters (9.0 g, obtained from several experiments as just described, but not necessarily with exactly the same component ratio) was

treated overnight, at room temperature, with acetic anhydride (5 ml) and pyridine (20 ml). Customary processing gave a material (10 g) which was chromatographed on a column of silica gel (275 g). Elution was started with 1% ethyl acetate in hexane, and the proportion of the former was gradually increased to 10%, at which point the acetate 17 began to emerge. After recrystallization from ethanol, the long needles of 17 (3.6 g) had m.p. 160-161°, $[\alpha]_D$ -39.3° and $[\alpha]_{546}$ -46.6° (c 0.65); lit.[39] m.p. 158-160°, $[\alpha]_{546}$ -41 ± 2°. ^{1}H-n.m.r. data: δ5.39 (t, J 9 Hz, H-3), 4.59 (dd, $J_{1,2}$ 7.7, $J_{2,3}$ 9 Hz, H-2), 4.38 (d, J 7 Hz, H-1), 4.34 (dd, $J_{5,6e}$ 10 Hz, H-6e), 3.9-3.4 (m, H-4, -5, 6a); 2.06 (s, 3 H, OAc), and data in Table 1.

For regeneration of 16, the acetate 17 (1.80 g) was stirred overnight in absolute methanol (40 ml) to which acetyl chloride (2 ml) had previously been added. T.l.c. with ethyl acetate indicated the eventual replacement of all of 17 (R_F ~0.5) by a slow-moving product (R_F ~0.3) that resulted from deacetylation and debenzylidenation. The mixture was stirred for 5 min with added α,α-dimethoxytoluene (2 ml) and then evaporated at 35° to give a dark syrup. This was passed through a short column of silica gel by means of hexane to which were added increasing proportions (1-10%) of ethyl acetate. Compound 16 (1.55 g, 94%) crystallized from the chromatographic solvent as long needles, m.p. 122-122.5°, $[\alpha]_D$ -44.8° and $[\alpha]_{546}$ -54.4° (c 0.55); lit.[40] m.p. 122-123° $[\alpha]_D$ -54.1°, and[39] m.p. 123-124°, $[\alpha]_{546}$ -51.5 ± 2°. The ^{1}H-n.m.r. data were in accord with those given[40], except that all signals were found at somewhat lower field (by 0.08-0.1 ppm); see also Table 1.

E. Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-β-D-glucopyranoside (15). Compound 15 was prepared by treatment of the diol 13 with p-toluenesulfonyl chloride (3 mol. equiv.) in pyridine[121,122]. For an improved

yield (80%) and a shortened reaction-time (3–4 days at room temperature), we found it useful to add to the reaction mixture a small amount (15 mg per g of 13) of 4-(N,N-dimethylamino) pyridine as a catalyst[123]. Recrystallized from 99% ethanol and then from ethyl acetate (without refrigerating the solution), 15 had m.p. 187–188°, $[\alpha]_D$ -60.0° (c 1.2); lit.[122] m.p. 182–183°, $[\alpha]_D$ -62.8° and[40] -60.7°. The lower-melting, unstable crystal modification[40,121,122] was not encountered. The ^{1}H-n.m.r. spectrum was essentially in accord with the reported[40] data; H-6e resonated at δ4.25 (dd, $J_{5,6e}$ 4, $J_{6a,6e}$ 9.5 Hz), and H-4, -5, and -6a resonated at δ3.75–3.25 (m, 3H). See also Table 1.

F. Methyl 4,6-O-benzylidene-2-O-methyl-3-O-p-tolylsulfonyl-β-D-glucopyranoside (24). Compound 24 was prepared from 14 by Kuhn methylation[124], with the procedure following a recent example[125]. A single methylation for 3 h afforded crystalline 24 in 95% yield, without the need for chromatographic purification. The long prisms obtained from 99% ethanol had m.p. 139–139.5°, $[\alpha]_D$ -84.3° (c 2); lit.[126] m.p. 135–136°. The ^{1}H-n.m.r. data: δ4.80 (t, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), 4.40–4.25 (m, 2 H), 3.80–3.05 (m, 4 H, overlapping two 3-proton singlets for 2 OMe groups), and data in Table 1.

G. Methyl 4,6-O-benzylidene-3-O-methyl-2-O-p-tolylsulfonyl-β-D-glucopyranoside (27). A mixture of 15 and 16 (see reaction D) was methylated (compare reaction F), and the fast-moving 27 thereby formed was separated from 15 by column chromatography on silica gel (solvent H). It crystallized from ethanol as beautiful prisms, m.p. 137.5–138°, $[\alpha]_D$ -32.7° (c 3.3); lit.[127a] m.p. 125–126°, $[\alpha]_D$ -34.1 ± 3° (solvent not given). ^{1}H-n.m.r. data: δ4.60–4.45 (m, 3 H), and 3.9–3.4 (m, 4 H), and data in Table 1.

Reductions with lithium triethylborohydride (LTBH). - A. General procedure, exemplified on the reaction of 1. To a solution of 1 (3.0 g, 5.08

mmol) in tetrahydrofuran (30 ml) was added LTBH (30 ml, M solution in tetrahydrofuran), and the mixture was boiled under reflux in a nitrogen atmosphere. After 30 min, when t.l.c. (solvent B) indicated the complete replacement of 1 (R_F 0.75) by a product (R_F 0.4), the excess of hydride was decomposed by careful addition of water (200 ml) to the cooled mixture, and most of the tetrahydrofuran was removed by evaporation. The remaining, largely aqueous phase and semisolid residue were extracted three times with dichloromethane, and the extract was washed with a small amount of water (with the addition of sodium or ammonium chloride, if necessary, to destabilize persistent emulsions), dried ($MgSO_4$), and evaporated to give a white, solid product. As t.l.c. revealed a minor contamination by 4 (R_F 0.1), the material was passed through a short column of silica gel by means of solvent F, whereby 4 was completely retained and pure 7 (1.30 g, 96%) was obtained. Recrystallized from ethyl acetate-petroleum ether, it was isomerically pure according to its n.m.r. spectrum, and had m.p. 130-131°, $[\alpha]_D$ +141.0° (c 2.2), in good agreement with 7 prepared from 2 and 6 (see the following reactions); lit.[36] m.p. 129-131°, $[\alpha]_D$ +140°, and[128] m.p. 125-126°, $[\alpha]_D$ +140.3°; ^{1}H-n.m.r. data: δ7.6-7.2 (m, 5 H, Ph), 5.60 (s, PhCH), 4.77 (dd, J 1.3 and 3.7 Hz, H-1), 4.40-4.05 and 3.90-3.50 (m, 3 and 2 H, for H-3, -4, -5, -6, and -6'), 3.39 (s, 3 H, OMe), 3.02 (d, J 6.5 Hz, exchangeable, OH), 2.19 (ddd, $J_{1,2e}$ 1.3, $J_{2e,3}$ 3.2, $J_{2e,2a}$ 15.0 Hz, H-2e), and 1.95 (dt, $J_{1,2a} = J_{2a,3}$ = 3.6, $J_{2a,2e}$ 15.0 Hz, H-2a). The J values agreed well with those measured[39] for 7 in C_6D_6.

A sample of 7 was acetylated with acetic anhydride in pyridine. The ^{1}H-n.m.r. data of the acetate were: δ7.55-7.25 (m, 5 H, Ph), 5.58 (s, PhCH), 4.27 (q, $J_{2a,3} = J_{2e,3} = J_{3,4}$ = 3 Hz, H-3), 4.71 (dd, J ~1 and 4 Hz, H-1), 4.45-4.0 (m, 2 H, H-5, 6e), 3.71 (t, $J_{5,6a} = J_{6a,6e}$ = 12 Hz, H-6a), 3.67

(dd, $J_{3,4}$ 3, $J_{4,5}$ 9.2 Hz, H-4), 3.37 (s, 3 H, OMe), 2.30 (ddd, $J_{1,2e}$ 1, $J_{2e,3}$ 3, $J_{2a,2e}$ = 15 Hz, H-2e), 2.12 (s, 3 H, OAc), and 1.97 (center of m for H-2a, partly obscured by OAc signal).

A sample of 7 was converted into its tosylate[129]; ^{1}H-n.m.r. data: δ7.78, 7.70, 7.08, and 7.00 (lines of AB quartet, 4 H, Ts), 7.34 (s, 5 H, Ph), 5.45 (s, PhCH), 4.85 (q, $J_{2a,3} = J_{2e,3} = J_{3,4}$ = 3 Hz, H-3), 4.73 (dd, J ~0.8 and 4.5 Hz, H-1), 4.4-4.15 (m, 2 H, H-5, 6e), 3.63 (t, $J_{5,6a} = J_{6a,6e}$ = 12 Hz, H-6a), 3.56 (dd, $J_{3,4}$ 3, $J_{4,5}$ 9 Hz, H-4), 3.37 (s, 3 H, OMe), 2.45 (ddd, $J_{1,2e}$ 0.8, $J_{2e,3}$ 3, $J_{2a,2e}$ 15 Hz, H-2e), 2.32 (s, 3 H, C-Me), and 2.02 (ddd, J 3, 4.5, and 15 Hz, H-2a).

B. Reaction of 2. The reaction of 2 (140 mg, 0.32 mmol) with LTBH solution (1.0 ml) in tetrahydrofuran (5 ml), was initially monitored at room temperature (t.l.c. with solvent A). Only traces of 6 (R_F 0.66) and 7 (R_F 0.55) were seen besides unchanged 2 (R_F 0.61) after 45 min. When the mixture was then boiled under reflux, all of 2 disappeared within 30 min, and 6 appeared to be the main product, with little additional 7 to be seen. There was no change in t.l.c. after continued refluxing for 30 min, but, upon addition of further LTBH (0.5 ml), all of 6 was converted into 7 within 15 min. Processing gave a colorless oil, homogeneous in t.l.c. Crystallization occurred spontaneously, and 7 (79 mg, 92.5%) was isolated after trituration with a small amount of ether; m.p. 128-129°, $[\alpha]_D$ +139.8° (c 2.1).

C. Reaction of 6. The epoxide[114] 6 (300 mg) in tetrahydrofuran (3 ml) was allowed to react with LTBH (3 ml) at room temperature for 30 min, affording 7 (290 mg, 96%), m.p. 130°, $[\alpha]_D$ +141.7° (c 1.2). With LAH, the same conversion required prolonged heating at reflux temperature[46,130]

D. Reaction of 8. Compound 8 (400 mg, 0.42 mmol) in tetrahydrofuran (3 ml), and LTBH (4 ml, 4.3 mol. equiv.), were boiled under reflux for 30 min. T.l.c. with solvent B showed that all of 8 was consumed after 20 min. The crude product obtained after processing contained a small amount of diol 4 and was therefore purified by passage through a short column of silica gel. Elution was started with 1:10 ethyl acetate-petroleum ether and continued with increasing proportions of ethyl acetate being added to the eluant. There was isolated the deoxy glycoside 12 (220 mg, 90%) and the diol 4, m.p. 166-167 (12 mg, 4.6%). Recrystallized from ethyl acetate-petroleum either, 12 had m.p. 112-113°, $[\alpha]_D$ +94° (c 1.5); lit.[127b] m.p. 110-111°, $[\alpha]_D$ +95 ± 1°, and[121] m.p. 111.5-113°, $[\alpha]_D$ +95.5°; ^{1}H-n.m.r. data: δ7.5-7.2 (m, 5 H, Ph), 5.54 (s, PhCH), 4.49 (d, $J_{1,2}$ 1.1 Hz, H-1), 4.23 (dd, $J_{5,6a}$ 10, $J_{6a,6e}$ 16 Hz, H-6a), 4.0-3.7 (m, 4 H, H-2,-4,-5,-6e), 3.38 (s, 3 H, OMe), 2.75 (s, broad, exchangeable, OH), and 2.10-1.95 (m, 2 H, H-3,3').

Reduction of 8 as just described, but with only 3 ml (3.3 mol. equiv.) of LTBH solution, and performed at room temperature for 24 h, furnished a reaction product in which was present an additional component, identified as the epoxide 11. Separation by p.t.l.c. (solvent B) gave 11 (29 mg), 12 (200 mg), and 4 (11 mg). Compound 11 had m.p. 149-150°, $[\alpha]_D$ +101° (c 0.5); lit.[117] m.p. 145-146°, $[\alpha]_D$ +103.2°. The identity of the compound was confirmed by its ^{1}H-n.m.r. spectrum.

E. Reaction of 11. Independently-prepared[119] 11 (1.00 g) in tetrahydrofuran (10 ml) and LTBH (8 ml, 0.95 M solution in tetrahydrofuran) were allowed to react for 30 min at reflux temperature. The reaction was not quite complete then (t.l.c. with solvent B), but was finished after continued heating (30 min) with additional LTBH (1 ml). Addition of a

little water to the cooled mixture, and evaporation of the solvent together with several added portions of dichloromethane gave a residue which was extracted with fresh dichloromethane (50 ml). The extract was washed with water (4 x 20 ml), dried (K_2CO_3), and partially evaporated, to give a concentrated solution of 12. On addition of petroleum ether to incipient cloudiness, and overnight storage at -20°, 12 crystallized as stout prisms (708 mg), m.p. 113°, $[\alpha]_D$ +94.6° (c 2.3); further crops (m.p. 110-111°) from the mother liquor raised the yield to 882 mg (87.5%). Similar yields were obtained[46,132] by reduction of 11 with LAH.

F. Reaction of 14. A mixture of 14 (500 mg), tetrahydrofuran (5 ml), and LTBH solution (4 ml) was examined by t.l.c. (solvent C) after it had been kept at 25° for 5 min. It showed a spot attributable to the epoxide 18 (R_F 0.5) besides that of 14 (R_F 0.2). The mixture was then boiled under reflux, whereupon a third spot (R_F 0.3) began to appear shortly. After 30 min, the spot at R_F 0.5 had vanished and only those at R_F 0.2 and 0.3 remained. Of these, the former showed a somewhat different shade of color than was produced by starting 14, and it represented in fact a reduction product (20) that had the same mobility, whereas the faster spot represented the isomer 21. Heating was stopped, the mixture was processed, and the products were separated by p.t.l.c. (solvent C), to give 20 (181 mg, 59%) and 21 (110 mg, 36%), both as long needles crystallizing from ethyl acetate-hexane.

The 3-deoxy isomer 20 showed m.p. 176-176.5°, $[\alpha]_D$ -58.7° (c 1.2); lit.[33,133-135] m.p. 165, 168-169, 174, and 173-174.5°, and $[\alpha]_D$ +59.5 (inadvertent reversal of sign?), -60.5, -61, and -61.5°. The ^{1}H-n.m.r. data were in complete agreement with those published[135]; additional data: δ4.33 (dd, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 10.3 Hz, H-6e), 3.56 (s, 3 H, OMe), and 2.56

(broad s, exchangeable, OH).

The 2-deoxy isomer 21 had m.p. 103-104°, $[\alpha]_D$ -32.3° (c 0.85); lit.[128] m.p. 96-97°, $[\alpha]_D$ -34°; ^{1}H-n.m.r. data: δ7.5-7.2 (m, 5 H, Ph), 5.56 (s, PhCH), 4.82 (dd, $J_{1,2e}$ 2.4, $J_{1,2a}$ 9.5 Hz, H-1), 4.34 (dd, $J_{5,6e}$ 4, $J_{6a,6e}$ 9.5 Hz, H-6e), 4.17 (narrow m, H-3), 3.97 (sx, $J_{4,5}$ ~9 Hz, H-5), 3.73 (t, $J_{5,6a}$ 9.5 Hz, H-6a), 3.53 (dd, partially overlapped by OMe signal, $J_{3,4}$ 2.7 Hz, H-4), 3.49 (s, 3 H, OMe), 2.57 (broad s, exchangeable, OH), 2.15 (dt with broadened lines, $J_{1,2e}$ 2.4, $J_{2e,3}$ 3.6, $J_{2a,2e}$ 14.5 Hz, H-2e), and 1.70 (ddd, $J_{1,2a}$ 9.5, $J_{2a,3}$ 3.0, $J_{2a,2e}$ 14.5 Hz, H-2a). The J values agreed well with those given[128] for 21 in C_6D_6.

G. Preparation and reduction of 18. For the preparation[42,136] of 18, a sample of pure 14 was at hand, and was used instead of its benzoate[136] or[42] 15. The sample (1.05 g) in chloroform (5 ml) was treated with M sodium methoxide in methanol (7 ml) for 2 h at room temperature. The solvent was evaporated and the residue dissolved in dichloromethane (100 ml), which was then washed several times with water, dried ($MgSO_4$), and evaporated to give a white solid (0.63 g). Recrystallization from methanol afforded 18 (588 mg, 97%), m.p. 140-141°, $[\alpha]_D$ -14° (c 0.9); lit.[42] m.p. 133-135°, $[\alpha]_D$ -15°, and[136] m.p. 138°, $[\alpha]_D$ -15.6°. The identity of the product was confirmed by its ^{1}H-n.m.r. spectrum.

To a solution of 18 (200 mg) in tetrahydrofuran (3 ml) were added, at room temperature, three 1-ml portions of LTBH solution in the course of 90 min. All of 18 had disappeared after 2 h, and only two slow-moving spots migrating like authentic 20 and 21 were seen in t.l.c. (solvent C). Processing of the reaction mixture, and separation of the products by p.t.l.c. (solvent C) gave 20 (137 mg, 68%) and 21 (61 mg, 30%), identified by their i.r. and n.m.r. spectra with the products described under F.

H. Reaction of 16. A mixture of 16 (800 mg), tetrahydrofuran (8 ml), and LTBH solution (7 ml) was heated under reflux for 25 min. Processing, followed by passage of the crude product over a short column by means of solvent B, gave a fraction of deoxy-glycosides (470 mg, 96%) that appeared homogeneous in t.l.c. but contained two components (22 and 23), as judged by the presence of two methoxyl signals (δ3.48 and 3.53) in the n.m.r. spectrum. Further elution gave the diol 13 (8 mg, 1.5%), m.p. 206°, identified by its i.r. spectrum. - Crystallization of the mixture of deoxy-glycosides from ethyl acetate–hexane furnished 22, m.p. 155–156°, raised to 158–159° by recrystallization, and undepressed in admixture with an authentic sample; $[\alpha]_D$ -73.8° and $[\alpha]_{546}$ -89.4° (c 1.7); lit.[137] m.p. 155–156° to 159–160° and $[\alpha]_D$ -66.2 to -69° for samples of various origins. The i.r. spectra of 22 and a previous sample were superposable, and the ^{1}H-n.m.r. data were as reported[137].

The mother liquor of crystallization gave 23 (slightly contaminated by 22), m.p. 161–162°, raised to 167–167.5° by one recrystallization from chloroform–hexane, and 169–170° in admixture with an authentic sample having m.p. 173°; $[\alpha]_D$ -65.6° and $[\alpha]_{546}$ -78.2° (c 3.65); lit.[39] m.p. 172–174°, $[\alpha]_{546}$ -75 ± 2°, and[134] m.p. 171–172°, $[\alpha]_D$ -66.3°. The i.r. spectrum was identical with that of authentic 23 (reaction H), as was also the ^{1}H-n.m.r. spectrum except for the presence of weak signals due to traces of admixed 22.

I. Reactions of 19. The epoxide 19 was prepared from 16 as described[39], in 87% yield; m.p. 192–193°, $[\alpha]_D$ -29.3° and $[\alpha]_{546}$ -35.5° (c 2.6); lit.[39] m.p. 185–187°, $[\alpha]_{546}$ -28.5 ± 3° and[40] m.p. 188°, $[\alpha]_D$ -29°. A sample of 19 (80 mg) in tetrahydrofuran (1 ml) was allowed to react with LTBH solution (0.5 ml) for 10 min at room temperature. Processing gave a syrup (80 mg)

from which crystals (55 mg, m.p. ~ 137°) were subsequently obtained. The ^{1}H-n.m.r. spectra of the syrup and of the crystalls were essentially identical with each other and with the spectrum of the mixture of 22 and 23 obtained from 16 (reaction H), indicating the presence of approximately equal proportions of the isomers.

A sample of 19 (75 mg) was reduced with LAH in boiling ether during 1 h, exactly as described[39], to give pure 23 (56 mg after recrystallization; 74%), m.p. 173°. The ^{1}H-n.m.r. data: δ7.4 (m, 5 H, Ph), 5.52)s, PhCH), 4.43 (d, $J_{1,2}$ 1.5 Hz, H-1), 4.30 (dd, $J_{5,6e}$ 4.3, $J_{6a,6e}$ 10 Hz, H-6e), 4.1-3.2 (m, unresolved, H-2,-4,-5,-6a), 3.53 (s, 3 H, OMe), 2.50 (s, OH), 2.40 (dt, $J_{2,3e} \sim J_{3e,4} \sim 4$ Hz, $J_{3a,3e}$ 14 Hz, H-3e), and 1.77 (m, $J_{3a,4}$ 12 Hz, H-3a).

J. Reaction of 15. A mixture of ditosylate 15 (1.0 g), tetrahydrofuran (5 ml), and LTBH solution (10 ml) was boiled overnight under reflux. (In a pilot experiment, 3 strong spots for reaction products were already indicated by t.l.c. after 45 min, but processing had shown that much unreacted 15 was still present at that point.) From the processed, crude mixture was then obtained pure 20 (205 mg) by crystallization with hot carbon tetrachloride. The mother liquor was subjected to p.t.l.c. (solvent G). There was obtained, in order of decreasing mobility: a) Unidentified material (~15 mg); b) by-product A (25 mg; see the discussion); c) compound 21 (50 mg, 11%); and d) a mixture (140 mg) of 20 and other deoxy-glycosides. The last-mentioned mixture was rechromatographed to give pure 20 (51 mg, thus raising its yield to 256 mg, 56.8%) and a mixture (60 mg, 13%) of deoxy-glycosides whose n.m.r. spectrum showed the same characteristic features as those of the mixtures of 22 and 23 obtained from 16 and 19 (reactions H and I).

K. Reaction of 24. A mixture of 24 (200 mg), tetrahydrofuran (3 ml), and LTBH solution (4 ml) was allowed to react at reflux temperature for 24 h. Monitoring by t.l.c. (solvent G) indicated conversion of 24 (R_F 0.2) into 25 (R_F 0.1) and 26 (R_F 0.3) which, after the usual processing, were separated by p.t.l.c. (solvent F). This yielded 25 (76.5 mg, 58%) and 26 (44 mg, 35%) in crystalline form.

Compound 25 had m.p. 175-176°, $[\alpha]_D$ -68.7° (c 0.5); lit.[126] m.p. 170-171°, $[\alpha]_D$ -69.2°; ^{1}H-n.m.r. data: δ7.6-7.2 (m, 5 H, Ph), 5.52 (s, PhCH), 4.35 (dd, $J_{5,6e}$ 4.3, $J_{6a,6e}$ 10.5 Hz, H-6e), 4.33 (d, $J_{1,2}$ 7.6 Hz, H-1), 3.8-3.2 (m, 10 H, H-3,-4,-5,-6a, and 2 OMe signals at δ3.63 and 3.57), 3.06 (dd, $J_{2,3}$ 8.6 Hz, H-2), and 2.74 (d, J 2 Hz, exchangeable, OH).

Compound 26 had m.p. 150-152°, $[\alpha]_D$ -73.6° (c 0.6), and no literature reference was found; ^{1}H-n.m.r. data: δ7.6-7.2 (m, 5 H, Ph), 5.50 (s, PhCH), 4.34 (dd, $J_{5,6e}$ ~4, $J_{6a,6e}$ 10 Hz, H-6e), 4.32 (d, $J_{1,2}$ 7.5 Hz, H-1), 3.75 (t, $J_{5,6a}$ 10 Hz, H-6a), 3.56 and 3.47 (s, 3 H each, 2 OMe, superposed on unresolved m for H-4 and -5), 3.21 (ddd, $J_{2,3e}$ 5.2, $J_{1,2}$ 7.5, $J_{2,3a}$ 11.2 Hz, H-2), 2.51 (m, $J_{3e,4}$ 3.8, $J_{3a,3e}$ ~12 Hz, H-3e) and 1.63 (q, $J_{3a,4}$ ~11.7 Hz, H-3a). Minor signals were attributable to a contamination by starting 24, amounting to ~6% (estimated from the intensity of a C-Me signal at δ2.30).

L. Reaction of 27. A mixture of 27 (300 mg), tetrahydrofuran (6 ml), and LTBH solution (6 ml) was boiled under reflux for 22 h, after which time all of 27 (R_F 0.4) had been replaced by a single spot (R_F 0.1) for 28 (t.l.c. with solvent F). Processing required no chromatography; the crude product (187 mg, 94.7%) was recrystallized from ethyl acetate-hexane to afford pure 28, m.p. 171.5-172°, $[\alpha]_D$ -47.0° (c 1.1); lit.[127a] m.p. 174°, $[\alpha]_D$ -50 ± 2°. ^{1}H-n.m.r. data (60 MHz): δ7.4 (m, 5 H, Ph), 5.52 (s, PhCH), 3.67 and 3.58 (s, 2 OMe, superposed on ring-proton signals that were all

unresolved in the regions δ4.5–4.1 and 3.9–3.6), and 2.85 (d, J~2 Hz, OH).

Reductions with lithium aluminum hydride. — A. Reaction of 1. To a partial suspension of LAH (0.50 g, 13.2 mmol) in dry tetrahydrofuran (8 ml) was added dropwise a solution of 1 (3.10 g, 5.25 mmol) in tetrahydrofuran (12 ml). The mixture was boiled at reflux for 22 h, and for a further 4 h following the addition of another 0.25 g (6.60 mmol) of LAH. After cooling of the mixture, it was carefully poured into chilled ethyl acetate (50 ml) and then agitated with ice-water (150 ml) that contained sulfuric acid (3 g) or, in similar experiments, sodium hydrogen sulfate (8 g). Subsequent extraction with ethyl acetate (4 x 74 ml) and ether (50 ml) gave an organic solution, which was washed with a small volume of sodium hydrogen carbonate solution, passed through dry filter paper, and evaporated without prior application of a drying agent. The partially crystalline residue of evaporation showed, in t.l.c. with solvent B, a brown spot of 4 (R_F 0.1), a strong double spot having a black front and a dark brown rear part and comprising 2, 5, and 7 (R_F 0.37–0.45), an olive-green spot due to by-products designated B (R_F 0.68), a dark brown spot of residual 1 (R_F 0.75), and faster-moving trace spots. Separation was performed on a column of silica gel (25 ml) by use of solvent B, with 10-ml fractions being collected. Compound 1 began to emerge after a forerun (20 ml) that contained odorous, non-carbohydrate material and other impurities. Mixed fractions were appropriately pooled and rechromatographed. Early fractions containing mainly 1 and B deposited, on standing of the solutions, pure 1 as large prisms which were collected before the mother liquor was evaporated for rechromatography. All fractions, except those containing appreciable proportions of B, gave dry, crystalline materials on solvent evaporation. The following substances were elaborated: a) Unchanged 1 (13.3%) in cry-

stalline crops (177 mg, m.p. 159-160°, $[\alpha]_D$ +13.7° [c 2]; and 125 mg, m.p. 153-154°) and as a partly crystalline mixture (330 mg) composed of 1 (~110 mg) and B (~220 mg) as indicated by a 100-MHz ^{1}H-n.m.r. spectrum (see Table 1 and the Discussion); b) a 4:3 mixture (98 mg, ratio estimated by n.m.r.) of B and 2, corresponding to ~56 and 42 mg, respectively; c) the diol 4 (190 mg, 12.8%) whose elution was completed by use of solvent A; m.p. 163-164°, raised to 167-168° by recrystallization from ethyl acetate-cyclohexane (lit.[114] m.p. 163-164° and[35] 168-169°).

In the combined mixture fractions c, the molar ratio 2 : (5 + 7) was determined (n.m.r.) as 1:3, corresponding to calculated amounts of 345 mg (15.1%) for 2 and 630 mg (45.1%) for 5 + 7. The deoxy-glycosides were present in a ratio of ~4:1. Repeated chromatography of the mixture furnished 2, m.p. 160-162°, R_F 0.63 or 0.45 (t.l.c. with solvents A or B), free from 5 and 7. The latter glycosides virtually coincided in t.l.c. (R_F 0.5 with solvent A, and 0.4 with B), as was verified with authentic samples, and they were not satisfactorily separable on columns. On one occasion, a small amount (25 mg) of 7 crystallized fortuitously in fairly pure form (m.p. 122-124°); its ^{1}H-n.m.r. and i.r. spectra agreed with those of pure 7 obtained by LTBH reduction. Fractions of fairly pure 5 melting as high as 180-182° were isolated, but they still contained some 7, visible in their spectra. A vacuum-sublimed[30] sample of 5 appeared free from 7 and had m.p. 187°, $[\alpha]_D$ +119.5° (c 1.4); lit.[30] m.p. 186.5-187.5°, $[\alpha]_D$ +126.9°, and[35] m.p. 186-187° to 190-191°, $[\alpha]_D$ +123° and +124°, and[46,138] m.p. 190-191°, $[\alpha]_D$ +115.8 ± 3°. Elevated $[\alpha]_D$ values may signify a contamination by 7, which is more highly dextrorotatory (+140°). The ^{1}H-n.m.r. data agreed with those reported[36].

B. Reactions of 3 and 2. Compound 3 (590 mg, 1.1 mmol) and LAH (330 mg, 7.9 mol. equiv.) were allowed to react in boiling tetrahydrofuran (30 ml) as described for 1, but for 9 h only. The crude product obtained on processing, as described, showed spots at R_F 0.15 (4), 0.5 (5 + 7), and 0.63 (2), as well as faster-moving trace spots (t.l.c. with solvent A). Column chromatography on silica gel (16 ml) with solvent A gave pure 2 (69 mg), m.p. 163°; a mixture fraction (176 mg) containing 2 and the deoxy-glycosides (5 and 7) in the molar ratio 10:30 (by n.m.r.), which corresponded to 62 mg of 2 and 114 mg of 5 + 7; a mixture (35 mg) of 5 and 7; and finally 4 (37 mg), m.p. 167-168°. The ratio of 5:7 was ~3.25 (by n.m.r.). The percentage yields are listed in Table 2.

An analogous experiment using compound 2 (200 mg) gave the results shown in Table 2.

C. Reaction of 8. Reduction of 8 (1.00 g, 2.29 mmol) with LAH (670 mg, 7.7 mol. equiv.) in boiling tetrahydrofuran during 19 h, followed by processing as described in reaction A, gave a crystalline, crude product which showed spots attributable to 4 (R_F 0.1) and deoxy-glycosides (R_F 0.42, almost black, due to 10, with a faint, brown satellite spot at R_F 0.37, presumably due to 12), and fast-moving traces of impurities (solvent B). Chromatography on silica gel (12 ml) with solvent B gave fractions showing only the aforementioned, black spot together with its weak companion spot. (These were more clearly separated in t.l.c. with solvent A: R_F 0.57 and 0.47.) Therefrom was obtained 10 (114 mg, 19%) as long needles having m.p. 144-147°, 146-147° after recrystallization from ethyl acetate-cyclohexane or 95% ethanol, and 148-149°, from pure ethyl acetate; $[\alpha]_D$ +97.5° (c 1.3, acetone); lit.[139] m.p. 151-152°, $[\alpha]_D$ +90° (acetone). The i.r. spectrum was distinctly different from those of 5, 7, and 12. The ^{1}H-n.m.r. data

(60 MHz): δ7.4 (m, 5 H, Ph), 5.52 (s, PhCH), 4.73 (dd, $J \sim 1$ and 4 Hz, H-1), 4.3-3.3 (unresolved m, 5 H), 3.30 (s, 3 H, OMe), 2.83 (broad s, OH), 2.18 (ddd, $J_{1,2e} \sim 1$, $J_{2e,3}$ 5, $J_{2a,2e}$ 13 Hz, H-2e), and 1.68 (o, $J_{1,2a} \sim 4$, $J_{2a,3}$ 35, $J_{2a,2e}$ 13 Hz, H-2e).

The bulk of the slow-moving product was eluted with solvent B, and additional amounts were eluted with solvent A followed by pure ethyl acetate. A total of 495 mg (76.5%) of crystalline 4 was thus obtained.

SECTION III

Experimental. Section III

Solvent systems: The chromatographic solvent systems (v/v) used in this section were: 1:2 ethyl acetate–chloroform (A), 1:2 methanol–chloroform (B), ethyl acetate–petroleum ether in the proportions 1:1 (C), 1:2 (D), 1:3 (E), and 1:4 (F), and 1:6 ethyl acetate–hexanes (G).

Methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (10). The preparation of 10 from methyl α-L-rhamnopyranoside as originally performed by Baer and Čapek[66] yielded 26% of the product by direct crystallization plus ca. 14% by column chromatography of the mother liquor. A minor modification of the procedure, employed later on[68c] in the D-series, gave 35% of product by crystallization, processing of the mother liquor being dispensed with. For the present work, we routinely prepared the mixture of stereoisomeric nitro glycosides as previously described and applied the whole, crude mixture (from 25 g of methyl α-L-rhamnopyranoside) to a column containing 800 g of silica gel (packed by suspending the gel in chloroform). Elution with 4:1 chloroform–ethyl acetate produced syrupy L-manno isomer followed by a mixture of the L-gluco and L-galacto isomers. This mixture was passed through a second column of the same size, which was eluted with 1:1 ethyl acetate–hexane to give pure 10 (11.9 g, 41%) melting at 141–143° as recorded[66], followed by a small amount of the L-galacto isomer, m.p. 155–156° (reported, m.p. 154–157°C[66]). A procedural variant involved omission of the first-mentioned column. The slow-moving L-galacto isomer was separated, by one chromatography using 1:1 ethyl acetate–hexane, from jointly emerging L-manno isomer and 10, and the latter was then obtained pure in good yield by crystallization from chloroform.

Methyl 3,6-dideoxy-2,4-di-O-methylsulfonyl-3-nitro-α-L-glucopyranoside (11). A solution of 10 (2.0 g) in dichloromethane (100 ml; dried over molecular sieve) containing freshly distilled methanesulfonyl chloride (2.6 ml) was cooled to -40°C, and a solution of triethylamine (3.4 ml; dried over and distilled from CaH_2) in dry dichloromethane (20 ml) was then added dropwise over a period of 10 min. [Pilot experiments had shown that, at this point, all of 10 (R_F ~0.2) had disappeared and a strong spot of 11 (R_F ~0.6) was visible together with a weak, faster spot (R_F ~0.8; t.l.c. with solvent A) which presumably represented an elimination product.] The reaction was immediately quenched by the addition of methanol (40 ml) at -40°C before the mixture was allowed to assume room temperature. Solvent evaporation gave a residue that was taken up in a small amount of ethyl acetate whereby the main part of crystalline triethylammonium chloride remained undissolved. The solution was filtered by suction through a 2-cm layer of silica gel (pre-washed with ethyl acetate) which removed remnant salt; the filter cake was washed with ethyl acetate followed by petroleum ether. The filtrate was evaporated and coevaporated with several portions of added 1-propanol. Finally, the residue was dissolved in a minimal amount of hot 1-propanol from which 11 crystallized upon slow cooling to room temperature. The yield was 2.82 g (80%); m.p. 133-134°C, $[\alpha]_D$ -122.9° (c 1, chloroform). The i.r. and n.m.r. spectra were identical with those of the D-enantiomer for which was found[68a] m.p. 132-132.5°C and $[\alpha]_D$ +110.5°.

Methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside (13) and Methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (14). The dimesylate 11 (1.0 g) and anhydrous sodium acetate (0.5 g) were stirred at room temperature in acetone (25 ml) containing

glacial acetic acid (0.5 ml). Monitoring by t.l.c. (solvent E) revealed the concurrent consumption of 11 (R_F 0.15) and appearance of 13 (R_F 0.5) as a single product.. After 2 h, traces of a second product, namely 14 (R_F 0.45) began to appear. (The spots of 13 and 14 were clearly separated provided the quantity of mixture applied to the plate was not too large.) The reaction was stopped at this point by the addition of ether (10 ml), which precipitated sodium acetate, and evaporation of the filtrate therefrom, followed by azeotropic removal of acetic acid with added toluene. The residue was extracted three times with boiling hexane. The extracts were evaporated giving a material that yielded nearly pure 13 (210 mg, 33%) by crystallization from absolute ethanol at -70°C. Recrystallized once from hot hexane (with slow cooling and storage of the solution at room temperature), 13 formed long needles (180 mg), m.p. 87°C and $[\alpha]_D$ +97.3° (c 1.3, chloroform). The data recorded[67b] for 13 obtained in a different way were m.p. 81-81.5°C and $[\alpha]_D$ +99.3° (chloroform); the ^{1}H-n.m.r. spectrum of the present sample agreed with the published one[67b] in every detail.

For the preparation of 14, a solution of 11 (1.0 g) and anhydrous sodium acetate (1.0 g) in acetone (25 ml) containing glacial acetic acid (1 ml) was boiled under reflux. T.l.c. with solvent E indicated the disappearance of 11 and the occurrence of 13 and 14 early on; the intensity of 13 (R_F 0.5) subsequently diminished and, after 1 h, 14 (R_F 0.45) remained as the sole, detectable product. The reaction mixture was processed as described above except that the residue obtained after removal of the acetic acid was passed through a small tube (disposable pipet) filled with silica gel, by means of solvent C. After solvent evaporation, 14 crystallized from a minimal amount of absolute ethanol on storage at -27°C; yield, 0.45 g

(70%), m.p. 81-82°C, $[\alpha]_D$ -162.6° (c 1.5, chloroform). Reported[67b] m.p. 81-81.5° and $[\alpha]_D$ -165°, and for the D-enantiomer[68d], m.p. 81-82°C and $[\alpha]_D$ +163°. The n.m.r. spectrum was identical with the published[67b] spectrum of 14

Methyl 2,3,4,6-tetradeoxy-3-nitro-α-L-threo-hexopyranoside (18) and L-erythro isomer 19. Preparation from 14. Sodium borohydride (500 mg) was added to a solution of 14 (500 mg) in absolute ethanol (50 ml) which was stirred at +5°C. After 15 min, methanol (15 ml) and an acidic cation exchange resin were added. The deionized solution was evaporated to give a residue from which several portions of methanol were evaporated to remove boric acid. The syrupy product was dissolved in ethyl acetate, treated with activated charcoal, and recovered after filtration through Celite and solvent removal. The dried syrup (350 mg, 92%) was a mixture of 18 (R_F 0.42) and 19 (R_F 0.28), with the latter predominating (t.l.c. with solvent F; droplets of acetic acid were applied with the sample spots at the starting line of the plates).

Preparation from 11. Sodium borohydride (1.0 g) followed by absolute ethanol (30 ml) was added at room temperature to a stirred solution of 11 (1.0 g) in dichloromethane (100 ml). An exothermic reaction ensued, causing some refluxing of solvent. Monitoring by t.l.c. as just described indicated complete consumption of 11 after 1 — 1.5 h and the formation of 18 and 19 in proportions similar as above. The reaction mixture was then cooled (5 — 10°C), acidified to pH 4 by slow addition of glacial acetic acid, and filtered through a layer of Celite (pre-washed with acetic acid followed by dichloromethane). Evaporation of the filtrate gave a white residue which was extracted several times with warm petroleum ether. The combined extracts were freed from acetic acid by coevaporation with toluene,

and the remaining syrup was freed from residual toluene by short drying in an oil-pump vacuum at room temperature. The product was then redissolved in petroleum ether, a small amount of insoluble material being filtered off. It was determined in one experiment that 470 mg (97.5%) of 18 + 19 was present at that stage.

Separation. The mixture of 18 and 19 (from 1.0 g of 11) contained in a minimum volume of petroleum ether deposited long needles of 19 (153 mg) upon storage overnight at -27°C. The mother liquor therefrom was chromatographed on silica gel (20 g). The column was prepared by first soaking the gel in a mixture of acetic acid and dichloromethane for 2 h and then washing the packed column with hexane (50 ml). Irrigation with a mixture of petroleum ether (400 parts), benzene (100 parts), ethyl acetate (50 parts), and acetic acid (1.2 parts) gave homogeneous but syrupy 18 (126 mg, 26%) and crystalline 19 (115 mg, 56% when added to the previous crystals). The two isomers gave well-resolved i.r. spectra (ν_{max} 1550 cm^{-1}, strong, NO_2) which were very similar in character but showed significant differences in band positions and intensities in the fingerprint region.

Compound 18 showed $[\alpha]_D$ -139° (c 1.3, chloroform); n.m.r. (100 MHz): δ 4.90 (dd, $J_{1,2e}$ = 2, $J_{1,2a}$ = 3.5 Hz, H-1), 4.84 (tt, partially overlapping H-1, $J_{2a,3} = J_{3,4a}$ = 12 Hz, $J_{2e,3} = J_{3,4e}$ = 4.5 Hz, H-3), 3.90 (12 lines, $J_{4e,5}$ = 2, $J_{4a,5}$ = 12, $J_{5,6}$ = 6.3 Hz, H-5), 3.34 (s, 3H, OMe), 2.43-2.18 (m, 2H, H-2e and H-4e), 2.01 (octet, $J_{1,2a}$ = 3.5, $J_{2a,3}$ = 12, $J_{2a,e}$ = 13 Hz, H-2a), 1.70 (q, $J_{3,4a} = J_{4a,5} = J_{4a,e}$ = 12 Hz, H-4a), 1.23 (d, 3H, J = 6.3 Hz, H-6).

Compound 19 showed m.p. 43°C, $[\alpha]_D$ -145° (c 1.1, chloroform); n.m.r. (100 MHz): δ 4.73 (narrow m, $J_{1,2a}$ = 3.5, $J_{1,2e}$ = 2, $J_{1,4e}$ = 0.8 Hz, H-1), 4.49 (m, 16 lines; $J_{2e,3}$ = 2.7, $J_{2a,3}$ = 5.5, $J_{3,4e}$ = 3.3, $J_{3,4a}$ = 4.5 Hz, H-3),

4.19 (m, 16 lines; $J_{4e,5}$ = 2.5, $J_{4a,5}$ = 11.5, $J_{5,6}$ = 6.5 Hz, H-5), 3.27 (s, 3 H, OMe), 2.72 (d, sx, $J_{2a,e}$ = 15, $J_{1,2e}$ = 2, $J_{2e,3}$ = 2.7, $J_{2e,4e}$ = 1.2 Hz, H-2e), 2.52 (dm, with low-field m partially overlapping upfield sx of H-2e; $J_{4a,e}$ = 14.5, and J = 0.8, 1.2, 2.5, and 3.3 Hz, H-4e), 2.09 (dq, $J_{2a,e}$ = 15, $J_{1,2a}$ = 3.5, $J_{2a,3}$ = 5.5 Hz, H-2a), 1.61(dq, $J_{4a,e}$ = 14.5, $J_{3,4a}$ = 4.5, $J_{4a,5}$ = 11.5, H-4a), 1.22 (d, 3 H, J = 6.5 Hz, C-Me). Anal. calc. for $C_7H_{13}NO_4$ (175.2): C 47.99, H 7.48, N 8.00; Found: C 48.00, H 7.32, N 8.10. The crystals are volatile; they sublimed when being kept overnight in an oil-pump vacuum at room temperature.

Similar yields of 18 and 19 could be obtained by chromatography of their whole mixture (without prior, partial crystallization of 19), in which case a correspondingly larger proportion of silica gel (30 — 35 g) had to be used. However, when a mixture of 18 and 19 (350 mg) was chromatographed on silica gel (35 g) which had not been pretreated with acetic acid, and elution was performed with solvent G instead of the aforementioned, slightly acidic solvent, there was obtained pure 18 (202 mg) followed by mixed fractions totalling 103 mg, and no pure 19 emerged. It appeared that the slower-moving 19 was continuously being isomerized on the way through the column. To verify this, a sample of such a mixture (from 50 mg of 11) was dissolved in methanol (5 ml) and stirred with silica gel (1 g) in the presence of a few drops of triethylamine. The isomerization was monitored by t.l.c. (solvent F). After 10 min, the spot intensities were reversed, and after 6 h, only a trace of 19 remained visible.

Accordingly, for the preparation of 18 in optimum yield the dimesylate 11 (500 mg) was treated with sodium borohydride as described before. After acidification and filtration through Celite, the reaction mixture was evaporated and an ethereal solution (50 ml) of the crude product was washed

with cold, saturated $NaHCO_3$ solution (3 x) and water (2 x), dried over $MgSO_4$ and evaporated to give a ~2 : 3 mixture of 18 and 19 (214 mg, 89%). This was stirred for 3 h at room temperature with silica gel (1 g) in methanol (5 ml) containing triethylamine (10 drops). Upon removal of the gel and solvent, the isomerized material was purified by passage through a column of silica gel (15 g) by means of solvent G. There was obtained 170 mg (70.5%) of pure 18 followed by a small fraction (27 mg) containing 18 and 19.

2,3,4,6-tetradeoxy-3-nitro-α-L-threo-hexose (20). A solution of 18 (200 mg) in tetrahydrofuran (2 ml) and 0.5 M sulfuric acid (20 ml) were heated on a steam bath for 90 min. The t.l.c. (solvent E) then indicated 18 to be absent and showed a single, mobile spot (R_f 0.2) together with an immobile spot. The cooled hydrolyzate was extracted several times with ethyl acetate, and the combined extracts were washed several times with small volumes of aqueous $NaHCO_3$ solution and once with water. Drying ($MgSO_4$) and evaporation of the organic solution gave a yellow syrup that was purified by redissolution in ethyl acetate and treatment with activated charcoal followed by filtration through a small quantity of silica gel. The product was then recovered as a chromatographically homogeneous solid (112 mg, 61%) which formed colorless crystals from ethyl acetate-petroleum ether; m.p. 117-118°C, $[\alpha]_D$ -96° (3 min) → -76.3° (21 h, final; c 1, chloroform) and -39.8° (8 min) → -36.0° (20 and 120 min; c 1, water). N.m.r. (100 MHz): δ5.48 (narrow m; d after D_2O exchange; $J_{1,2e}$ = 2, $J_{1,2a}$ = 3.5 Hz, H-1), 4.94 (tt, $J_{2a,3}$ = $J_{3,4a}$ = 12, $J_{2e,3}$ = 4.5, $J_{3,4e}$ = 4 Hz, H-3), 4.19 (m, 16 lines; $J_{4a,5}$ = 11.5, $J_{5,6}$ = 6.5, $J_{4e,5}$ = 2 Hz, H-5), 2.95 (t, J 2.7 Hz, removable by D_2O exchange, OH), 2.42 (d sx, $J_{2a,e}$ = 13, $J_{1,2e}$ = $J_{2e,4e}$ = 2, $J_{2e,3}$ = 4.5 Hz, H-2e), 2.35 (d of quintets partially

overlapping the H-2e multiplet, $J_{4a,e}$ = 13, $J_{4e,5}$ = $J_{2e,4e}$ = 2, $J_{3,4e}$ = 4 Hz, H-4e), 2.03, (o, $J_{2a,e}$ = 13, $J_{2a,e}$ = 12, $J_{1,2a}$ = 3.5 Hz, H-2a), 1.74 (q, with center lines broadened; $J_{4a,5}$ = 11.5, $J_{3,4a}$ = 12, $J_{4a,e}$ = 13 Hz, H-4a), 1.25 (d, 3H, J = 6.5 Hz, C-Me). Anal. calc. for $C_6H_{11}NO_4$ (161.2): C 44.72, H 6.88, N 8.69; Found: C 44.75, H 6.93, N 8.54.

2,3,4,6-tetradeoxy-3-nitro-α-L-erythro-hexose (21). A mixture of glycoside 19 (100 mg) and ethanol-free chloroform (10 ml) saturated with gaseous hydrogen chloride was stirred at room temperature for 2 h, with the addition of a few drops of water. Evaporation then gave a solid (89 mg, 97%) which was recrystallized from hot ethanol with addition of ethyl acetate, to give colorless 21 (70 mg, 76%), m.p. 141.5-142°C; $[\alpha]_D$ -59.6° (5 min) ⟶ -46.2° (15 min) ⟶ -23.0° (45 min) ⟶ +3.2° (17 h, const; c 1, methanol). The sugar was sparingly soluble in cold water. N.m.r. (100 MHz) in $(CD_3)_2SO$: δ6.07 (m, removable with D_2O, OH), 5.06 (narrow m, H-1), 4.70 (narrow m, H-3), 4.27 (broad m, H-5), 2.5-1.9 (unresolved m, 3 H), 1.55 (septet, J = 4.5, 11, and 15 Hz, H-4a), 1.12 (d, J = 6.5 Hz, C-Me). Anal. calc. for $C_6H_{11}NO_4$ (161.2): C 44.72, H 6.88, N 8.69; Found: C 44.49, H 7.01, N 8.55.

Methyl 3-amino-2,3,4,6-tetradeoxy-α-L-threo-hexopyranoside acetate (22). Platinum dioxide catalyst (500 mg) was prehydrogenated in glacial acetic acid (30 ml), and a solution of 18 (500 mg) in absolute ethanol (20 ml) was added. The hydrogenation was performed for 10 h at ambient temperature and pressure. Thereafter, t.l.c. indicated complete reaction of 18 (R_F 0.5 in solvent F or ~0.8 in solvent B) and the presence of 22 (R_F 0 and 0.2, respectively). The filtered solution was evaporated, with azeotropic removal of acetic acid by addition of toluene. The remaining syrup gave crystals, m.p. 108 C° (with prior sintering), from dichloromethane-ethyl

acetate-petroleum ether, but these were found to contain 5% of ash (by combustion analysis). An ethyl acetate solution of the product was treated with charcoal, filtered through a layer of Celite, and evaporated to give pure 22 (540 mg, 92%), m.p. 115-116°, $[\alpha]_D$ -115° (c 1.3, chloroform). N.m.r. (100 MHz): δ8.20 (s, 3 H, $\overset{+}{N}H_3$), 4.79 (narrow m, H-1), 3.85 (broad m, H-3), 3.45 (broad m, H-5), 3.31 (s, 3 H, OCH_3), 1.95 (s, 3 H, AcO^-, superposed on unresolved m for H-2e and H-4e in the 2.2-1.9 region), 1.61 (sx containing 1 small and 2 large splittings, H-2a), 1.31 (q, J =12 Hz, H-4a), 1.20 (d, 3 H, J = 6.5, C-Me). Anal. calc. for $C_9H_{19}NO_4$ (205.3): C 52.66, H 9.33, N 6.82; Found: C 52.81, H 9.28, N 6.76.

Methyl 3-amino-2,3,4,6-tetradeoxy-α-L-threo-hexopyranoside hydrochloride (23). Compound 18 (100 mg, 0.57 mmole) in 95% ethanol (7 ml) was added to platinum dioxide catalyst (100) that had been prehydrogenated in a mixture of ethanol (2 ml), water (0.4 ml) and N hydrochloric acid (0.6 ml). Complete hydrogenation at ambient temperature and pressure required 24 h. Removal of the catalyst and solvent gave a solid which was dried in vacuo and then washed with ethyl acetate, dissolved in ethanol, treated with charcoal, and recovered by evaporation of the solution. The colorless material then crystallized from ethanol-ethyl acetate and showed m.p. 175°C (dec.), raised to 182-183°C by recrystallization from methanol-ethyl acetate. The yield of pure 23 was 98 mg (94.5%), R_F 0.5 (t.l.c. with solvent B), $[\alpha]_D$ -108.3° (c 1, water). N.m.r. (100 MHz) in $(CD_3)_2SO$: δ8.43 (s, 3 H, $\overset{+}{N}H_3$), 4.79 (narrow m, H-1), 3.74 (broad m, H-3), ~3.4 (broad m, H-5), 3.24 (s, 3 H, OCH_3), 2.2-1.9 (unresolved m, 2 H, H-2e and H-4e), 1.63 (sx, J 3.5 and 2 x 12.5 Hz, H-2a), 1.31 (q, J = 3 x 12 Hz, H-4a), 1.13 (d, 3 H, J = 6.5, C-Me). Anal. calc. for $C_7H_{16}C_1NO_2$ (181.7): C 46.28, H 8.88, N 7.71; Found: C 46.36, H 9.06, N 7.53.

A sample of the acetate 22 (27 mg) was dissolved in 1% methanolic hyrdogen chloride (10 ml). Evaporation gave crystalline 23 (23 mg, 96%), m.p. 182-183°C after recrystallization from methanol-ethyl acetate.

Ethyl 3-amino-2,3,4,6-tetradoexy-α-L-threo-hexopyranoside hydrochloride (24). Compound 22 (100 mg) was dissolved in chloroform (10 ml) that contained 0.75% of ethanol as a stabilizer and that had been saturated with hydrogen chloride. After 5 min the solution was evaporated and the residue was recrystallized from chloroform and a few drops of ethanol by slow addition of ethyl acetate. The yield of 24 was 80 mg (84%); m.p. 190-192°C (dec.), $[\alpha]_D$ -94° (c 0.7, water). N.m.r. (100 MHz) in ($CDCl_3$ + CD_3OD): δ4.94 (narrow m, H-1), 4.0-3.4 (unresolved m, 4 H, H-3, H-5, and ethyl CH_2), 2.35-2.0 (unresolved m, 2 H, H-2e and H-4e), 1.80 (sx, J = 3.5 and 2 x 12 Hz, H-2a), 1.50 (q, J = 3 x 12 Hz, H-4a), 1.21 (d, J = 6.5 Hz, C-Me), 1.18 (t, 3 H, J = 7 Hz, ethyl CH_3). Anal. calc. for $C_8H_{18}ClNO_2$ (195.7): C 49.10, H 9.27, N 7.16: Found: C 48.84, H 9.56, N 6.91.

Methyl 2,3,4,6-tetradeoxy-3-trifluoroacetamido-α-L-threo-hexopyranoside (25). To a cooled (-30°C) solution of 22 (300 mg) in spectroscopy-grade chloroform (14 ml) was added dry triethylamine (1 ml) followed by trifluoroacetic anhydride (1.5 ml) which was introduced dropwise while the temperature was allowed to rise to -20°C. Shortly thereafter, t.l.c. (solvent D) indicated 25 (R_F 0.4) as the sole product. Water (10 ml) was added at -20°C and, after some stirring, the separated aqueous phase was extracted three times with chloroform. The combined organic phase and extract was washed with sodium bicarbonate solution followed by water, dried ($MgSO_4$), and evaporated to give a solid residue (365 mg). Recrystallization from ethyl acetate-petroleum ether gave long, colorless needles of

25 (350 mg, 99%), m.p. 123-123.5°C, $[\alpha]_D$ -128.8° (c 0.7, chloroform). N.m.r. (100 MHz): δ 6.26 (broad signal, NH), 4.83 (narrow m, H-1), 4.37 (11 peaks, sx of overlapping t; $J_{2e,3} = J_{3,4e} = 4$, $J_{3,NH} = 8$, $J_{2a,3} = J_{3,4a} = 12$ Hz, H-3), 3.94 (16 lines, q of dd; $J_{4e,5} = 2$, $J_{4a,5} = 12$, $J_{5,6} = 6.3$ Hz, H-5), 3.34 (s, 3 H, OCH_3), 2.2-1.9 (m, 2 H, ill resolved), 1.52 (sx with broadened center peaks; $J_{1,2a} = 3.5$, $J_{2a,3} = 12$, $J_{2a,e} = 13$ Hz, H-2a), 1.195 (d, 3H, J = 6.3 Hz for C-Me, superposed on q, 1 H, J = 3 x 12 Hz, H-4a). Anal. calc. for $C_9H_{14}F_3NO_3$ (241.2): C 44.82, H 5.85, N 5.81; Found: C 44.59, H 5.94, N 5.68.

2,3,4,6-tetradeoxy-3-trifluoroacetamido-L-threo-hexose (8). The glycoside 25 (160 mg) was hydrolyzed with 3.5 M acetic acid (16 ml) at 90°C for 2.5 h, after which t.l.c. (solvent D) indicated complete conversion of 25 (R_F 0.4) into 8 (R_F 0.15). The hydrolyzate was diluted with water and extracted five times with chloroform. The extract was washed five times with small amounts of cold sodium bicarbonate solution and then once with water, dried ($MgSO_4$), and evaporated. The solid residue was crystallized from ethyl acetate-petroleum ether to give 8 (141 mg, 94%), m.p. 166-167°C; ms: m/z 227 (M^+), 210 (weak, $M^+ - OH$), and 209 (strong, $M^+ - H_2O$); $[\alpha]_D$ -85° (initial, extrapolated) → -80° (5 min) → -74° (15 min) → -57° (80 min) → -48° (4 h) → -47° (20 h, c 0.18, chloroform), and -26.4° (4 min) → -24.6° (2 h, final, c 0.5, water); lit.[59] : m.p. 159-160°C, $[\alpha]_D$ -80° (c 0.1 in chloroform; no mutarotation recorded). N.m.r. (100 MHz) in $(CD_3)_2SO$: δ 9.2 (broad, NH), 6.49 (d, 0.15 H, J = 6.5 Hz, OHβ), 6.12 (dd, 0.85 H, J = 1 and 4 Hz, OHα), 5.18 (broad s, W_H 6 Hz, H-1e; intensity slightly less than 1 H but supplemented by a weak signal for H-1a at 4.60), 4.4-3.8 (m, 2 H, H-3 and H-5), 1.9-1.4 (m, 3 H, H-2e, -4e, and -2a), 1.20 (q, J = 3 x 12 Hz, H-4a), 1.06 (d, 3H, J = 6 Hz, C-Me),

in good agreement with the reported[59] data. Upon addition of D_2O, the NH and OH signals disappeared and, because of progressive mutarotation, the signal for H-1a (dd, J = 2 and 8.5 Hz) grew in intensity and a second C-Me doublet became visible at δ1.12. Anal. calc. for $C_8H_{12}F_3NO_3$ (227.2); C 42.29, H 5.32, N 6.17; Found: C 42.42, H 5.17, N 5.97.

Methyl 3-amino-2,3,4,6-tetradeoxy-α-L-erythro-hexopyranoside acetate (26) and Picrate (27). The nitro glycoside 19 (430 mg) was hydrogenated catalytically in acetic acid-ethanol as described for 18. The reaction was complete after 6 h as indicated by t.l.c. (solvents F and F), and processing was performed as for 22. The crude product was briefly dried in vacuo at 25°C (prolonged drying results in losses owing to sublimation), then dissolved in ethyl acetate and filtered through Celite. Careful addition of petroleum ether to the concentrated solution followed by storage at -27° produced colorless, hygroscopic crystals (26) which were rapidly dried in vacuo after decanting the mother liquor; yield, 500 mg (99%). Thorough drying for analysis was impractical because of the volatility of the compound. N.m.r. (100 MHz): δ7.28 (broad signal, $\overset{+}{N}H_3$, removable by D_2O exchange), 4.82 (narrow m, H-1), 4.06 (broad m, H-5), 3.52 (narrower m, H-3), 3.32 (s, 3 H, OCH_3), 1.96 (s, 3 H, AcO^-), 2.1-1.4 (unresolved m), 1.21 (d, 3 H, J = 6 Hz, C-Me).

Concentrated solutions of 26 and picric acid, both in benzene, were mixed and cooled to ~+6°C. Yellow, crystalline 27 precipitated in nearly quantitative yield. Isolated and washed with ether, it had m.p. 163-164°C (dec.), raised to 164-164°C (dec.) by recrystallization from benzene-ether; $[\alpha]_D$ -59.2° (c 1.4, methanol); n.m.r. (100 MHz) in $(CD_3)_2CO$: δ8.67 (s, 2 H, arom.), 4.89 (narrow m, H-1), 4.24 (broad m, 12 lines, H-5), 3.94 (narrow m, H-3), 3.35 (s, 3 H, OCH_3), 1.75 (o, $J_{3,4a}$ = 4.5, $J_{4a,5}$ = 12,

$J_{4a,e}$ = 15 Hz, H-4a), 1.20 (d, 3 H, J = 6.3 Hz, C-Me). The remaining ring proton signals were obscured by solvent signals. Anal. calc. for $C_{13}H_{18}N_4O_9$ (374.3): C 41.71, H 4.85, N 14.97; Found: C 41.74, H 4.75, N 14.86.

Ethyl 3-amino-2,3,4,6-tetradeoxy-α-L-erythro-hexopyranoside hydrochloride (28). Obtained from the acetate 26 (150 mg) exactly as described for the preparation of 24 from 22, compound 28 (122 mg, 86%) was recrystallized from chloroform–ethyl acetate; m.p. 141-142°C (dec.), $[\alpha]_D$ -84.6° (c 0.7, water); n.m.r. (100 MHz): δ 8.47 (broad, removed by D_2O exchange, $\overset{+}{N}H_3$), 4.96 (narrow m, H-1), 4.11 (broad m, H-5), 3.85 (m, H-3), 3.5 (m, 2 H, ethyl CH_2), 2.4-2.0 (m, 2 H, unresolved, H-2e and H-4e), 1.86 (dt, $J = J'$ = 3.5, J_{gem} = 15 Hz, H-2a), 1.63 (septet, J = 4, J' = 12, J_{gem} = 15.5 Hz, H-4a), 1.27 (t, 3 H, J = 7 Hz, ethyl CH_3), 1.21 (d, 2 H, J = 6.3 Hz, C-Me). Anal. calc. for $C_8H_{18}ClNO_2$ (195.7): C 49.10, H 9.27, N 7.16; Found: C 48.88, H 9.56, N 6.91.

Methyl 2,3,4,6-tetradeoxy-3-trifluoroacetamido-α-L-erythro-hexopyranoside (29). The glycoside acetate 26 (120 mg) in chloroform (7 ml) was treated with triethylamine (1 ml) and trifluoroacetic anhydride (0.5 ml) as described for the preparation of 25 from 22, at an initial temperature of -30°C, rising to 0°C by the end of the addition. Completion of the reaction was verified by t.l.c. (solvent E). The mixture was cooled again (-10°C) before the rection was quenched by the addition of water (10 ml). Work-up as described for 25 gave 29 as a yellow syrup that was purified by passage through a small column of silica gel (8 g), with 1:5 ethyl acetate–petroleum ether as the eluent. There was obtained 29 (130 mg, 92%) as a colorless, chromatographically homogeneous syrup, R_f 0.3 (t.l.c. with solvent E), $[\alpha]_D$ -4.3° (c 2.1, chloroform); n.m.r. (100 MHz): δ 8.0 (broad

NH), 4.84 (broad s, W_H = 6 Hz, H-1), 4.29 (m, H-3), 3.94 (broad m, H-5), 3.40 (s, 3 H, OCH_3), 2.1-1.8 (m, 3 H, unresolved), 1.50 (septet, J 3.5, J' = 11.5, J_{gem} = 15 Hz, H-4a), 1.19 (d, 3 H, J = 6.5 Hz, C-Me). The compound was volatile *in vacuo* so as to render drying for analysis impractical.

2,3,4,6-tetradeoxy-3-trifluoroacetamido-L-erythro-hexose (9). Glycoside 29 (300 mg) was hydrolyzed for 2.5 h with 3.5 M acetic acid (40 ml) at 90°C. Complete hydrolysis of 29 (R_F 0.6) to 9 (R_F 0.5) was indicated by t.l.c. (solvent D). Processing as described for 8 gave 9 (200 mg, 70%) as colorless crystals from ethyl acetate-petroleum ether; m.p. 112-113°, $[\alpha]_D$ +28.9° (c 1.5, chloroform) and +10° (c 1.3, water); ms: m/z 227 (M^+), 210 (weak, $M^+ - OH$), and 209 (strong, $M^+ - H_2O$). N.m.r. (100 MHz): δ 8.3 (broad, removable by D_2O exchange, NH), 5.43 (narrow m, W_H = 7 Hz, contracting to t with W_H = 5 Hz after D_2O exchange, H-1), 4.3 (m, 2 H, H-3 and -5), 3.82 (narrow t, J 2 Hz, removable by D_2O exchange, OH), 2.1-1.7 (m, 3 H, unresolved), 1.52 (septet, $J_{3,4a}$ = 3.5, $J_{4a,5}$ = 11.5, $J_{4a,e}$ = 14.5 Hz, H-4a), 1.20 (d, 3 H, J = 6.5 Hz, C-Me). Anal. calc. for $C_8H_{12}F_3NO_3$ (227.2): C 42.29, H 5.32, N 6.17; Found: C 41.98, H 5.58, N 5.95.

SECTION IV

Experimental. Section IV

The methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitrohex-2-enopyranosides 1 - 4 were prepared[68a,140-143] as previously described. Diazomethane was generated from N-methyl-N-nitroso-p-toluenesulfonamide (Diazald ®).

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-methyleneazo-3-nitro-β-D-glucopyranoside (5). To a solution of potassium hydroxide (3 g) in water (5 ml) and 95% ethanol (15 ml), contained in a distillation flask immersed in a water bath of 65°C, was added dropwise a solution of Diazald (3 g) in ether (30 ml). The emerging mixture of diazomethane and ether vapor was passed through a condenser and the yellow condensate was allowed to react, in the receiver, with a solution of 1 (1.0 g) in dry tetrahydrofuran (10 ml, spectroscopy grade) and dry ether (17 ml) which was maintained at 0°C in an ice-water bath. After completion of the diazomethane production the reaction mixture was kept at 0°C (for a total of 1 h) and then at room temperature for another 0.5 h. The solution was evaporated *in vacuo* to give a yellow syrup which solidified upon trituration with a few drops of fresh, anhydrous ether. The material was chilled under ether (5 ml) for 3 h and then isolated as nearly colorless crystals (1.1 g), m.p. 115-116°C with decomp. Recrystallized twice from anhydrous either, the colorless product (0.8 g, 71%) showed an unchanged melting point; $[\alpha]_D$ -157.8°, $[\alpha]_{578}$ -163.9°, $[\alpha]_{546}$ -194.2°, $[\alpha]_{436}$ -429.6°, $[\alpha]_{365}$ -1307° (c 0.7, chloroform); ν_{max}^{Nujol} 1563, with shoulder at 1535-1540 cm^{-1} (NO_2, N=N); λ_{max}^{MeOH} 325 nm (ε160); ord (c 0.4, methanol): $[\phi]_{337}$ -8400°. Anal. calc. for $C_{15}H_{17}N_3O_6$ (335.3): C 53.73, H 5.11, N 12.53. Found: C 53.66, H 5.06, N 12.52.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-methyleneazo-3-nitro-α-D-glucopyranoside (6). The reaction was carried out as described above for 1, on approximately 1/3 scale, using 300 mg of 2 dissolved in tetrahydrofuran (20 ml). Complete conversion of 2 into a single, faster-moving product was indicated by t.l.c. with 1:2 ethyl acetate - petroleum ether (bp 30-60°C). Processing as described furnished colorless, crystalline 6 that was recrystallized once from ethyl acetate–anhydrous ether; yield 328 mg (95%), m.p. 179°C with decomp.; $[\alpha]_D$ -2.2°, $[\alpha]_{578}$ -1.7°, $[\alpha]_{546}$ -5.8°, $[\alpha]_{436}$ -56°, $[\alpha]_{365}$ -400° (c 2.7, chloroform); ν_{max}^{Nujol} 1560, with shoulder at about 1530 cm^{-1} (NO_2, N=N), ord (c 0.14, methanol): $[\phi]_{352}$ -720°. Anal. calc. for $C_{15}H_{17}N_3O_6$ (335.3): C 53.73, H 5.11, N12.53. Found: C 53.73, H 5.06, N 12.55.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-methyleneazo-3-nitro-β-D-idopyranoside (7). Diazomethane from 0.3 g of Diazald in ether (3 ml) was allowed to react with a solution of 3 (100 mg) in tetrahydrofuran (5 ml) maintained at -5°C. The reaction was complete within 20 min after the end of the diazomethane distillation, according to t.l.c. (1:2 ethyl acetate-petroleum ether, bp 30-60°C). The solution was immediately evaporated to give a yellowish oil which solidified upon trituration with a little anhydrous ether. The crude product (92 mg, 81%) contained a very minor contaminant that moved slightly more slowly than the main product (t.l.c.). Whereas recrystallization from ethyl acetate-petroleum ether or tetrahydrofuran-ether failed to remove the impurity, a pure sample of 7 was obtained by slow recrystallization from ethyl acetate-chlorocyclohexane at -15°C. The white needles had m.p. 115°C (with decomp.); $[\alpha]_D$ +34.3°, $[\alpha]_{578}$ +40°, $[\alpha]_{546}$ +56.7°, $[\alpha]_{436}$ +265°, $[\alpha]_{365}$ +1548° (c 1.2, chloroform); ν_{max}^{Nujol} 1563, with shoulder at 1540 cm^{-1} (NO_2, N=N); λ_{max}^{MeOH}

323 nm (ε 260); ord (c 0.12, methanol): $[\phi]_{333}$ +14000°. Anal. calc. for $C_{15}H_{17}N_3O_6$ (335.3): C 53.73, H 5.11, N 12.53. Found: C 53.65, H 5.20, N 12.39.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-methyleneazo-3-nitro-α-D-idopyranoside (8). A distilled, ethereal solution of diazomethane was prepared from Diazald (0.5 g) and ether (5 ml). This was added from a buret to a solution of 4 (100 mg) in tetrahydrofuran (5 ml), chilled by swirling in a bath of -20°C. The diazomethane was consumed rapidly and visibly. Within 5 min a yellow coloration began to persist in the reaction mixture, and the solvent was then immediately removed by evaporation at low temperature in an oil-pump vacuum. The residue was co-evaporated once with a portion of added ether, and the resulting, colorless foam was dried in vacuo; yield 114 mg. Attempts at crystallization from various common solvents failed. $[\alpha]_D$ +158.7°, $[\alpha]_{578}$ +168.2°, $[\alpha]_{546}$ +202.5°, $[\alpha]_{436}$ +516.6°, $[\alpha]_{365}$ +1820° (c 2.2, chloroform); ν_{max}^{Nujol} 1560, with shoulder at about 1535 cm^{-1} (NO_2; N=N); λ_{max}^{MeOH} 323 nm (ε 225); ord (c 0.2, methanol): $[\phi]_{330}$ +15000°. In order to obtain a pure product it is important to observe the above reaction conditions carefully. Prolonged exposure of 4 to excess diazomethane, or a higher reaction temperature, tends to lead to side products whereas an insufficient exposure may cause some 4 to remain unreacted as seen by the occurrence of minor n.m.r. peaks due to it.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro-β-D-erythro-hex-2-enopyranoside (9). The pyrazolino sugar 5 (582 mg) was boiled under reflux in chlorobenzene (15 ml) for 6 h, after which it was largely replaced by a faster-moving product (t.l.c.). The solvent was evaporated and the residue chromatographed on a column of silica gel (20 g) by means of 4:1

carbon tetrachloride - ethyl acetate. The main fractions containing 9 together with some impurities were collected and evaporated to give 270 mg (51%) of 9, m.p. 180-183°, raised to 185-187°C by recrystallization from ether at low temperature. The colorless needles showed $[\alpha]_D$ -248.5° (c 1.06, chloroform); ν_{max}^{Nujol} 1530 cm^{-1} (nitroalkene); cd: $[\theta]_{327}$ -16500 (0.0017 M in dioxane). Anal. calc. for $C_{15}H_{17}NO_6$ (307.3): C 58.63, H 5.58, N 4.56. Found: C 58.53, H 5.66, N 4.50.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro-α-D-erythro-hex-2-enopyranoside (10). The pyrazolino sugar 6 (330 mg) was boiled under reflux in chlorobenzene (10 ml) for 6 h, after which time no 9 left, according to t.l.c. The solvent was evaporated and the dry residue (304 mg) was recrystallized from ethyl acetate-petroleum ether to give 197 ml (65%) of colorless needles, m.p. 181-182°C, unchanged on a further recrystallization from ether at low temperature; $[\alpha]_D$ -117.8° (c 1.1, chloroform); ν_{max}^{Nujol} 1525 cm^{-1} (nitroalkene); cd $[\theta]_{328}$ -18600 (0.0025 M in dioxane). Anal. calc. for $C_{15}H_{17}NO_6$ (307.3): C 58.63, H 5.58, N 4.56. Found: C 58.67, H 5.63, N 4.70.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro-α-D-threo-hex 2-enopyranoside (11). A solution of the pyrazolino sugar 8 (122 mg) in chlorobenzene (5 ml) was boiled under reflux for 1 h and then evaporated to dryness. The t.l.c. (1:2 ethyl acetate-petroleum ether) indicated that the residue contained a major product (11) together with a slightly faster-migrating, minor product (the cyclopropano derivative 13). The n.m.r. spectrum of the crude product was also consistent with this. The material was recrystallized twice from ether and then weighed 75 mg (67%) and had m.p. 212-213°C but was not completely pure. It was further purified by chromatography on a column of silica gel (15 g) by use of 4:1 carbon

tetrachloride - ethyl acetate as the eluent, and by another recrystallization from ethyl acetate - ether, after which it showed m.p. 214-215°C; $[\alpha]_D$ +109° (c 1.04, chloroform); ν_{max}^{Nujol} 1520 cm^{-1} (NO_2); cd: $[\theta]_{330}$ +11500 (0.0048 M in dioxane). Anal. calc. for $C_{15}H_{17}NO_6$ (307.3): C 58.63, H 5.58, N 4.56. Found: C 58.48, H 5.66, N. 4.68.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-C-methylene-3-nitro-β-D-idopyranoside (12). A solution of the pyrazolino sugar 7 (200 mg) in toluene (10 ml) was refluxed for 16 h. Completion of the reaction was checked by t.l.c. The crystalline residue resulting from evaporation of the solvent was recrystallized from methylcyclohexane to yield 130 mg (71%) of 12, m.p. 115-116°C; $[\alpha]_D$ -40°, $[\alpha]_{578}$ -43°, $[\alpha]_{546}$ -46.8°, $[\alpha]_{436}$ -43.6°, $[\alpha]_{365}$ -43.6° (c 2.3, chloroform); ν_{max}^{Nujol} 1545 cm^{-1} (NO_2); mass spectrum: m/z 307. Anal. calc. for $C_{15}H_{17}NO_6$ (307.3): C 58.63, H 5.58, N 4.56. Found: C 58.50, H 5.46, N 4.46.

Methyl 4.6-O-benzylidene-2,3-dideoxy-2,3-C-methylene-3-nitro-α-D-idopyranoside (13). In the preparation of 11 (see a preceding reaction), the formation of a minor by-product that moved slightly faster in t.l.c. was noted. The same spot, attributed to 13, was sometimes observed on t.l.c. of the starting pyrazoline 8. Its strength was variable and seemed to depend on incidental conditions of manipulation, one of which appeared to be the time elapsed between sample spotting and irrigation. This led us to consider that action of silica gel upon 8 was responsible for an accelerated formation of 13, which was borne out by the following preparative experiment.

A sample of 8 (520 mg) dissolved in a small amount of 4:1 carbon tetrachloride-ethyl acetate was allowed to drain into the top of a column (diameter, 1 cm) of silica gel (20 g) moistened with the same solvent

mixture. The sample was kept stationary in the top of the column overnight, during which period a slow evolution of gas took place. Trapped bubbles were released by careful stirring of the upper layer with a rod, and elution of the column using the above solvent mixture was then commenced. The main fractions containing 13 were evaporated to give 348 mg (75%) of white crystals of 13 contaminated by a small proportion of 11 (t.l.c. and n.m.r.). The material was recrystallized twice from ether to give pure 13 as colorless needles, m.p. 169-171°C; $[\alpha]_D$ +87°, $[\alpha]_{578}$ +91°, $[\alpha]_{546}$ +104.5°, $[\alpha]_{436}$ +200°, $[\alpha]_{365}$ +395° (c 2.0, chloroform); ν_{max}^{Nujol} doublet 1550-1530 cm^{-1}, $\nu_{max}^{Chlf.}$ singlet 1540 cm^{-1}. Anal. calc. for $C_{15}H_{17}NO_6$ (307.3): C 58.63, H 5.58, N 4.56. Found: C 58.52, H 5.56, N 4.62.

Circular Dichroism Data of 1 - 4. Ellipticities are given for the first extremum in dioxane solution, with molar concentrations in parentheses: 1, $[\theta]_{330}$ -11700 (0.0026); 2, $[\theta]_{330}$ -12100 (0.0023); 3, $[\theta]_{325}$ +2120 (0.0036); 4, $[\theta]_{330}$ +3370 (0.005).

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