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**LA THÈSE A ÉTÉ
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APPLICATION OF TRANSITION METAL
REAGENTS AND CATALYSTS
IN CARBOHYDRATE SYNTHESIS

by

Zaher S. Hanna

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

Ottawa, Ontario, 1981

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TO MY WIFE GAËTANE
who made writing of
this thesis a pleasure

R

During my first years in the University I was enraptured by the science and nothing but the science of chemistry. As an undergraduate, however, as the challenges of inorganic, physical and organic chemistry were overcome, I had to make a choice of specialization. I was fond of chemical substances, with their shape, color, and smell, whereas the generalizations of physical chemistry, however useful, seemed to me rather vague. But it was a difficult problem to choose between inorganic and organic chemistry, perhaps, that is why I took the essentially organometallic road. Not wishing to be Buridan's ass and die of hunger between two bundles of hay, I preferred to gather food from both bundles---As organo-element chemistry advances, the bridge between organic and inorganic is transformed into an isthmus which will unite both continents of chemistry.

A.N. Nesmayanov,
Director, Institute of
Organo-Element Compounds,
Academy of Sciences of
the USSR.

ACKNOWLEDGMENT

I should especially like to thank Professor H.H. Baer for kindly providing me with the opportunity to undertake this research work under his direction. His encouragement, guidance and valuable assistance and patience throughout the study and in the preparation of this thesis is greatly appreciated.

I also wish to express my sincere appreciation to Professor H. Alper, whose excellent graduate course on organometallic chemistry was the spark that helped to initiate this work, and for generously sharing his knowledge with me whenever difficult questions arose.

My special gratitude is also extended to Professor T. Durst for many fruitful discussions.

Finally, I wish to express my thanks to Dr. J. Krause and Mr. R. Capoor for their excellent and cooperative services in recording the mass and nuclear magnetic resonance spectra.

/kh

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ABSTRACT

PART I

Palladium-catalyzed, allylic substitution was employed in carbohydrate chemistry for the first time. It proved to be an efficient method for the synthesis of aminated and C -alkylated, unsaturated glycosides. Thus, various allylic acetates in the family of alkyl hex-2-enopyranosides were allowed to react, in the presence of triphenylphosphine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0), with an array of different amines or reactive-methylene compounds, to give high yields of new amino or branched-chain sugars. With some exceptions, the substitutions were found to be highly regio- and stereoselective, giving predominantly 4-substituted 2-enopyranosides with retention of configuration. The constitutions and configuration of the new products were established by mass spectrometry, 1H - and ^{13}C -nmr spectroscopy, and polarimetry, and in this connection, some aspects of conformation in enopyranosides were discussed.

The reaction was studied, primarily, by use of alkyl 4,6-di-O-acetyl-2,3-dideoxy-hex-2-enopyranosides as substrates for allylic substitution. Its utility having thus been established, it was then employed as a key step in a novel synthesis of the antibiotics sugar, D-forosamine (2,3,4,6-tetra-deoxy-4-dimethylamino-D-erythro-hexose). This synthesis departed from methyl 4,6-O-benzylidene- α -D-glucopyranoside, comprised several steps before and after the palladium-catalyzed amination, and moreover, addressed the question as to whether the latter is compatible with the presence of a primary halogeno substituent in the substrate.

Finally, the palladium-catalyzed substitution was applied in an approach to the synthesis of nitrogenous disaccharides, i.e., derivatives of 4-amino-trichalose.

PART II

This part describes the synthesis of branched-chain nitro sugars by use of organo-copper reagents. Various stereoisomeric methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitrohex-2-enopyranosides were C-alkylated in position 2 using lithium dimethylcuprate and lithium divinylcuprate. Moderate to high yields of saturated, C-2-branched, 3-nitro glycosides were obtained. There had been little information, in the literature, about conjugate additions of organocopper reagents to nitroalkenes; the present results indicate that it is a feasible approach to carbon-carbon bond formation in aliphatic nitro compounds.

PART III

The catalytic hydrogenation of carbohydrate α -nitroepoxides with palladium and platinum was investigated with regard to regiospecificity and stereochemistry of ring opening, and the fate of the nitro group. The methyl 2,3-anhydro-4,6-O-benzylidene-3-C-nitrohexopyranosides having the β -D-gulo, β -D-allo, α -D-manno, and β -D-manno configurations underwent facile, hydrogenolytic ring-opening in the presence of palladium to give, regardless of the orientation of the oxirane ring, methyl 4,6-O-benzylidene-3-deoxy-3-C-nitro-D-hexopyranosides having an equatorial nitro group. In addition, 3-deoxy-3-oximino derivatives arose in various proportions. It was shown that the oximes did not result from over-hydrogenation of the 3-deoxy-3-C-nitro glycosides produced, and it is suggested that they originated from intermediary nitronic acids. By catalysis with platinum,

the oxirane rings were opened in the same regiospecific sense as with palladium, but notable differences were observed otherwise. The results are compared with literature reports on the stereochemistry of hydrogenolysis of oxiranes in general, and mechanisms that may operate for the nitro derivatives are discussed.

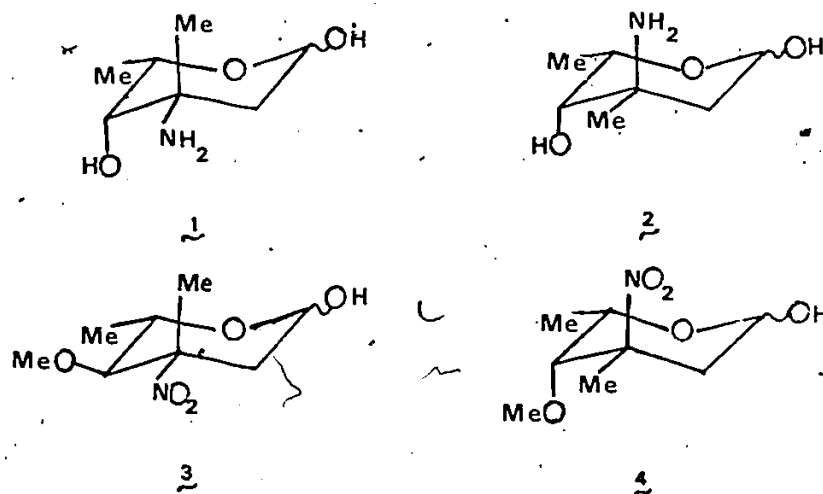
PART IV

Attempts were made to use the method of hydrozirconation for the functionalization of unsaturated carbohydrates. However, treatment of ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside with dicyclopentadienylhydrido-zirconium chloride followed by certain electrophiles did not lead to reaction at the double bond but, instead, at the C-6 ester group. A 4,6-protected(benzylidened) 2-enoside did not undergo substitution either, but suffered elimination of its glycosidic methoxyl group.

A. INTRODUCTION

The world-wide, intensive research which over the past three decades was directed at unravelling the chemical structure of antibiotics has brought to light a large number of new carbohydrates. Many antibiotics are composed entirely of sugar derivatives (including cyclitols); others contain carbohydrates attached as integral components to various types of aglycons. The chemistry of carbohydrates derived from either category of microbial metabolites is characterized by an abundance of structural and configurational features which are seldom encountered in carbohydrates that occur in higher plants or animals. Of particular interest in this regard are unusual amino sugars, polydeoxy sugars, branched-chain sugars, and sugars which possess configurations not normally found in those present in higher organisms. The chemistry and biochemistry of sugars from antibiotics has been the subject of many general reviews¹⁻¹⁰. In the following pages, some random examples of such compounds will be described in order to indicate the kinds of structural features which continue to challenge synthetic carbohydrate chemists.

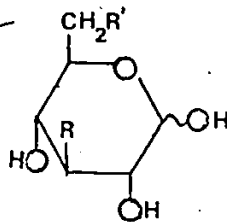
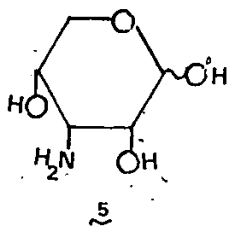
Thus, the glycopeptide antibiotic, vancomycin, contains the branched-chain amino sugar L-vancosamine (1)^{11,12}, and in another, new glycopeptide antibiotic (which has not yet been named), the 3-epimer (2) of this compound has recently been discovered¹³. Structurally related to these sugars is the branched-chain nitro compound evernitrose (3), the nitrogenous component of the everninomomycins¹⁴.



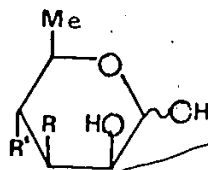
These antibiotics ("orthosomycins") belong to a class of complex oligosaccharides characterized by the presence of orthoester linkages.¹⁵ Incidentally, 3 was the only nitro sugar known to occur in nature until its stereoisomer 4, rubranitrose, was found about two years ago¹⁶.

Unbranched amino sugars are particularly frequent building blocks of antibiotics. To this family belong, among others, 3-amino-3-deoxy-D-ribose (5) in puromycin, 3-amino-3-deoxy-D-glucose (6, kanosamine) and 6-amino-6-deoxy-D-glucose (7) in the kanamycins, 3-amino-3,6-dideoxy-D-mannose (8, mycosamine) in the macrolide antibiotics nystatin and pimarcin, 4-amino-4,6-dideoxy-D-mannose (9, perosamin) in perimycin, and 5-amino-5-deoxy-D-glucose (10, nojirimycin)^{3,4}. Note the position of the amino group in these microbial products, most frequently at C-3 but also occasionally at C-4, C-5, and C-6, in striking contrast to the chief

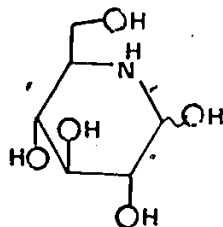
amino sugars of the animal kingdom, D-glucosamine and D-galactosamine, which bear this group at C-2. More highly deoxygenated amino sugars are exemplified by 3-amino-2,3,6-trideoxy-L-ribo-hexose (11, ristosamine) isolated from ristomycin¹⁷, its L-lyxo isomer (12, daunosamine), which is the sugar moiety of important antitumor anthracyclines (daunorubicin and adriamycin)¹⁸, and 4-amino-2,3,4,6-tetradeoxy-L-erythro-hexose (13, tolyposamine) contained in tolypomycin¹⁹.



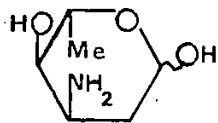
6 R = NH₂, R' = OH
7 R = OH, R' = NH₂



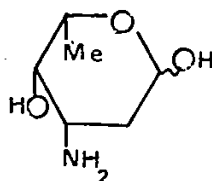
8 R = NH₂, R' = OH
9 R = OH, R' = NH₂



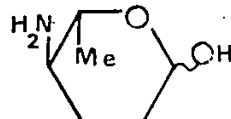
On many occasions, N,N-dimethylamino sugars were found in antibiotics, especially in macrolides; again, this is a structural feature not encountered in carbohydrates of higher organisms. Examples^{3,4} are amosamine (14), mycaminose (15), desosamine (16), angolosamine (17), forosamine (18), and ossamine (19).



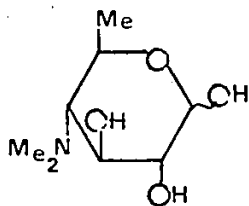
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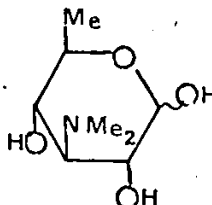
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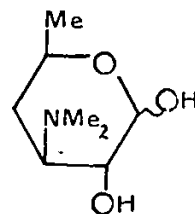
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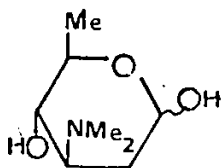
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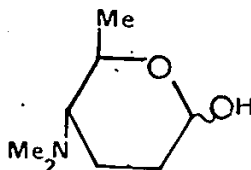
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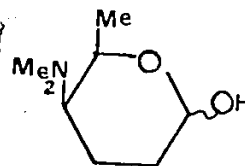
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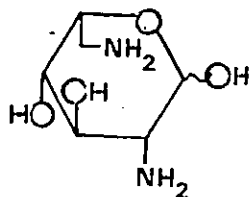
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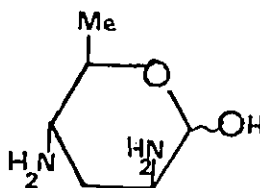
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The number of diamino sugars from antibiotics is comparatively small. As examples may be mentioned 2,6-diamino-2,6-dideoxy-L-idose (20; neosamine B or paromose) and its D-gluco isomer, which are components of the important neomycin group of aminoglycosides; and 2,4-diamino-2,3,4,6-tetradeoxy-D-arabino-hexose (21, kasugamine), which is present in kasugamycin.

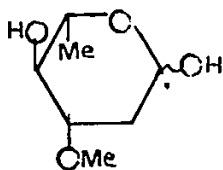
Numerous non-nitrogenous deoxy sugars (some of which have a branched chain or a methyl ether function) have also been found as constituents of antibiotics, although such structures do occur as well in glycosides present in higher plants². Typical examples are oleandrose (22), mycarose (23), cladinoses (24), and mycinose (25), all originating from macrolides. Sugars bearing an oxygenated branch are long-known streptose (26, from streptomycin) and the more recently discovered alagarose²⁰ (27, from aldagamycin E).



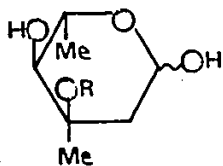
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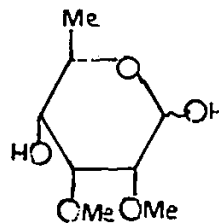
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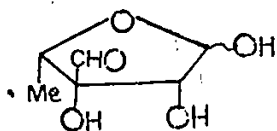
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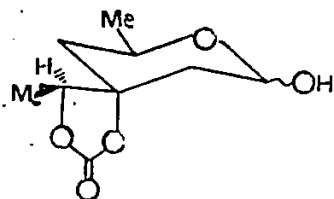
23 R = H
24 R = Me



25



26



27

B. AIMS OF THIS STUDY:

Although most of the sugar molecules listed in the foregoing introduction, and many additional similar compounds, have already been synthesized by one or more methods, there is a continuing need for methodological improvement and innovation. Shorter, more economical, and more elegant procedures for the preparation of such sugars are being sought; structural analogs are being synthesized for biochemical studies or medicinal evaluation; and newly discovered, hitherto unknown compounds call for synthesis. In many laboratories the study of semisynthetic antibiotics is actively being pursued, in order to find drugs with improved therapeutic properties. For such investigations it is necessary to make available many kinds of derivatized carbohydrates, which may be molecules derived from those occurring naturally or from synthetic analogs, to serve as synthons in total or partial chemical synthesis. One relevant example is the current quest for improved anticancer agents related to adriamycin; the natural sugar component, daunosamine (12), was removed from the anthracyclinone aglycon and replaced by an array of similar sugars (with some synthetic analogs among them), with the result that several agents showing improved characteristics were produced¹⁸. The work undertaken for the present thesis was aimed at the general target of making contributions to the methodology of synthesis for unusual nitrogenous, polydeoxy, and

branched-chain sugars. In particular, the use of transition metals in the form of organometallic reagents or catalysts was to play a major role in various approaches to regio- and stereospecific functionalization. Although in principle there appears to be no shortage of methods for the synthesis of sugars of the types mentioned, it was hoped that novel avenues would complement existing ones or overcome some of the limitations from which many of them suffer in one way or another.

The main, existing entries into the domain of amino sugars include^{3,4} cyanohydrin synthesis in the presence of amines; opening of epoxides by aminolysis or azidolysis; displacement of sulfonate esters by nitrogen nucleophiles; addition of nitrogen nucleophiles to sugars containing an activated double bond; and hydrogenation of nitro sugars (obtained²¹ by nitromethane condensation) and of oximes or phenylhydrazones (prepared from oxo sugars). Non-nitrogenous, branched-chain sugars^{4,5} are usually made from a suitable sugar carbonyl derivative which is treated with diazomethane²², Grignard reagents²³, or Wittig reagents²⁴. Alternatively, epoxides can be cleaved with organometallics²⁵ or diethyl sodiomalonate²⁶. Some branched-chain sugars were obtained by application of the "oxo reaction", i.e., the insertion of carbon monoxide in enoses, promoted by a cobaltcarbonyl catalyst²⁷, and by photochemically

induced addition of alcohols, glycols, acetals, and aldehydes to carbohydrate α -enones²⁸. Nitrogen-containing branched-chain sugars are accessible through cyclization of sugar dialdehydes with nitroalkanes^{29,30}, Michael addition of carbanions to nitroalkenic sugars³¹⁻³⁴, addition of nitroalkanes^{30,35-37} or cyanide³⁸ to glycosuloses, pyrolysis of nitro sugars bearing a fused pyrazolone ring³⁹, and photoamidation of enosides⁴⁰.

The thesis is divided into four parts. In Part I is recorded a novel, general route to amino sugars and branched-chain sugars, which consists of the first application, to carbohydrate chemistry, of the palladium-catalysed amination and alkylation of allylic esters.

In Part II, the utility of special organometallic reagents, namely, lithium dialkylcuprates, was examined, with a view to synthesizing branched-chain nitro sugar. Such reagents had not previously been employed for derivatizing nitrogenous carbohydrates.

Part III reports a study concerning the stereochemistry of palladium- and platinum-catalyzed hydrogenations of nitro sugar epoxides. These epoxides are versatile intermediates for a variety of synthetic applications; their catalytic hydrogenation had previously been investigated in this laboratory but certain

results needed clarification and further elaboration so that the course of reaction could be rationalized.

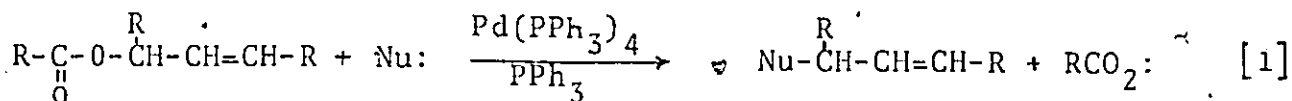
Finally, in Part IV are described some preliminary attempts to utilize the method of hydrozirconation for functionalization in carbohydrates.

PART I

PALLADIUM-CATALYZED, ALLYLIC SUBSTITUTIONS

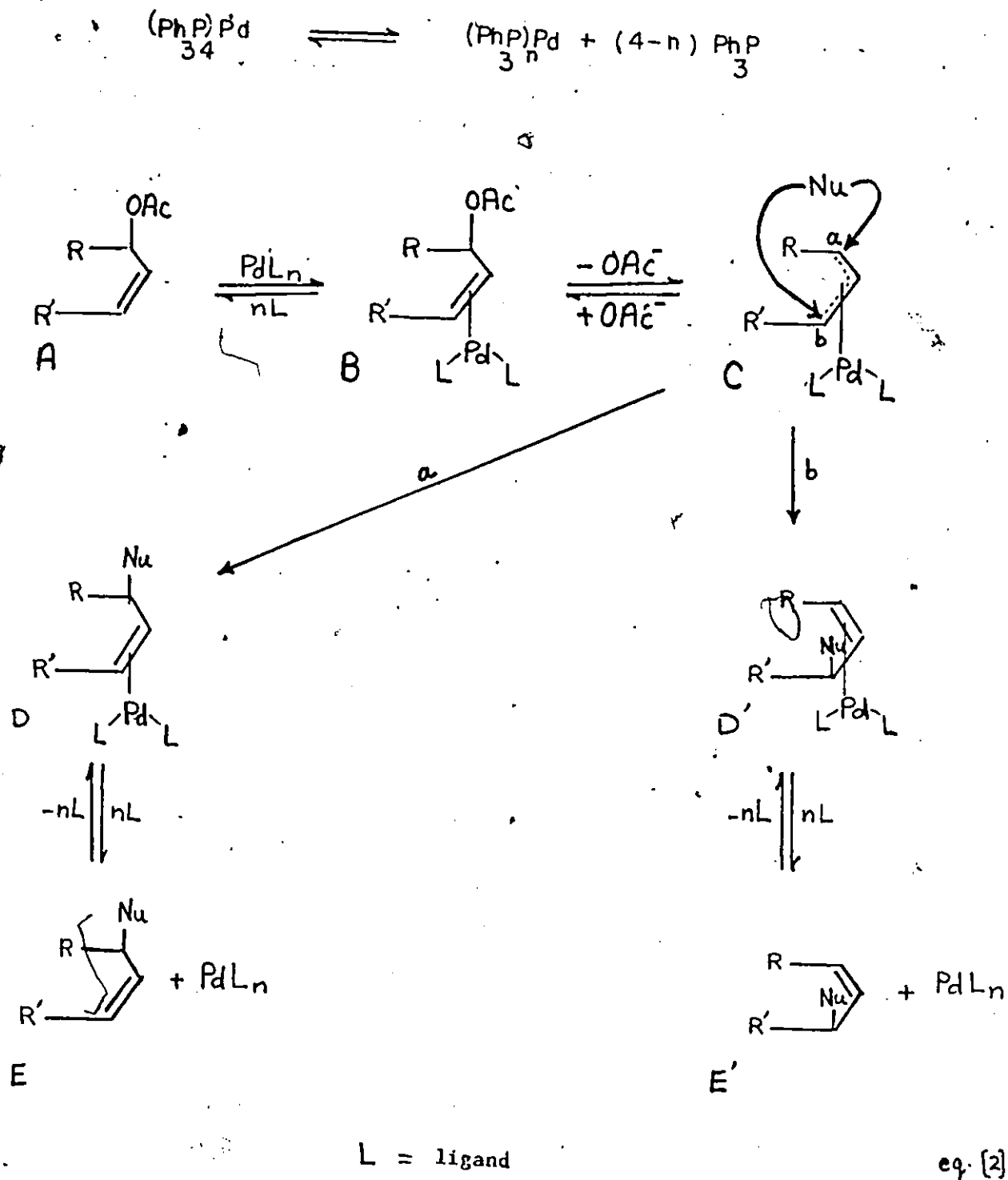
I, A. BACKGROUND

Transition metal organometallics offer an enormous range of synthetic possibilities, often affording high degrees of selectivity⁴¹. Surprisingly, such reagents have hitherto received very little attention in preparative carbohydrate chemistry. We therefore decided to examine some potential uses of organopalladium⁴² reactions in this field. The nucleophilic substitution of allylic ester groups catalyzed by tetrakis-(triphenylphosphine)-palladium(0), which was first described in 1970 by American^{43a,b} and Japanese^{43c} authors and has since been widely used and thoroughly studied primarily by Trost and his coworkers⁴⁴⁻⁴⁵, is represented schematically in eq. [1]



Since carbohydrate derivatives comprising the structural feature of allylic esters are available with little difficulty⁴⁷, it appeared attractive to employ this reaction for the introduction of amino functions or chain-branching.

Mechanistically, the reaction is considered to proceed as follows (eq. [2]).



After an initial dissociation of tetrakis(triphenylphosphine)-Palladium(0) into bis- or tris(triphenylphosphine)-palladium(0)⁸³, the Pd(0) species coordinates with the allylic ester(A) (usually

an acetate) to give a π -alkene complex (B). In the case of a chiral acetate, coordination takes place on the face of the olefin distal to the ester grouping, as shown. Palladium then donates electrons to the allylic carbon atom, thereby displacing an acetate ion. (Some groups other than acetoxy have occasionally functioned as leaving groups.) A cationic π -allyl complex (C) results. Attack by a nucleophile from the side opposite the palladium displaces the metal and leads to a substitution product (E or E'), presumably via a transitory π -alkene complex (D or D') whose dissociation regenerates the catalytic metal species. It is seen that attack at site a gives a product with retention of the original configuration⁸³ and double bond position, whereas attack at site b would furnish an allylically rearranged product. Regioselectivity presumably depends on a combination of factors: 1), the nature of the nucleophile⁹⁰, and the directing influence which unequal groups R and R' as well as the gross stereochemistry of the substrate may have on its approach; 2), different electronic effects of R and R', causing polarisation in the π -allyl system (C); and 3), unequal stabilities of D and D' conditioned by electronic or conformational features, with a possible role for non-bonded interaction between the ligand(s) L and parts of the molecule embodied in R and R'. As ligands other than PPh_3 can also be used⁴⁴ in this reaction (e.g., 2 molecules of 1,2-bis(diphenylphosphino)ethane^{93,95} instead of 4 PPh_3), one could conceivably try to alter the regiochemical outcome by means of varying L. It may be noted in this connection

9

that successful substitutions have been performed with the aid of Pd^0 catalyst immobilized on a solid support of phosphinylated polystyrene or silica gel⁴⁵.

Although the vast majority of palladium-catalyzed, allylic substitutions obey the stereochemistry just mentioned, i.e., proceed with net retention of configuration, occasional exceptions to this rule have been observed⁹⁰. It has been suggested that, in such cases, the incoming nucleophile first attaches itself to the metal atom from where it is transferred internally to an allylic carbon atom, arriving from the side of complexation to generate a substitution product of inverted configuration^{88,90}.

In the context of this laboratory's research projects it was to be examined, primarily, whether the palladium reaction here discussed may serve as a useful means for the preparation of aminated and C-alkylated sugars. If such substitutions were successful, it would, furthermore, be interesting to assess the aforementioned questions of regio- and stereochemistry with special reference to the steric differences that exist in stereoisomeric carbohydrate derivatives.

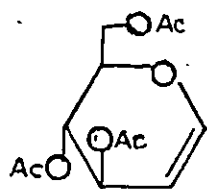
I, B. REACTIONS WITH ALKYL

4, 6-DI-O-ACETYL-2, 3-

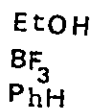
DIDEOXY-HEX-2-ENOPYRANOSIDES

I, B. 1. PREPARATIVE RESULTS

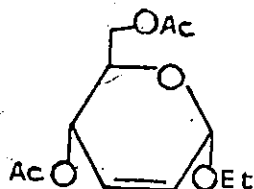
Initial investigations were focused on the crystalline allylic acetate 28, ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside. This compound is readily available



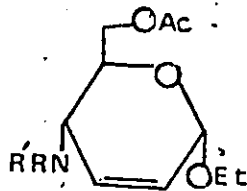
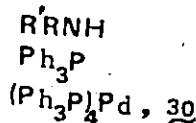
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[3]

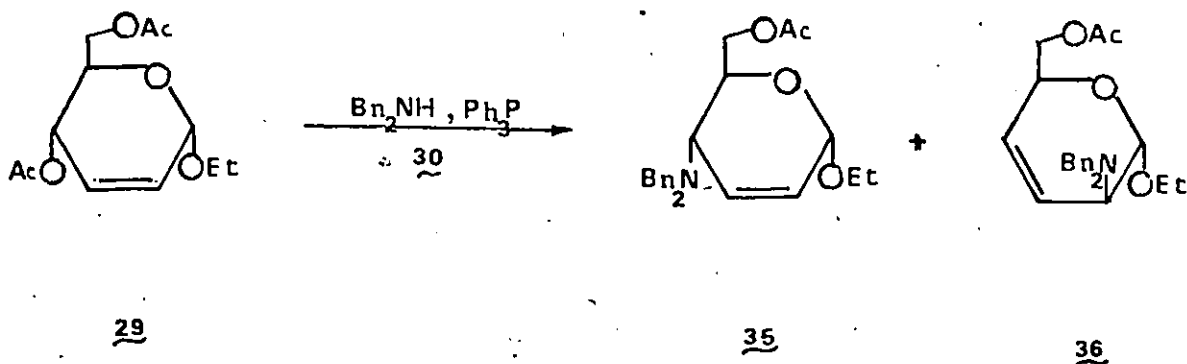


29

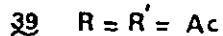
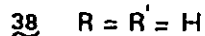
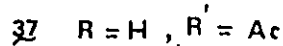
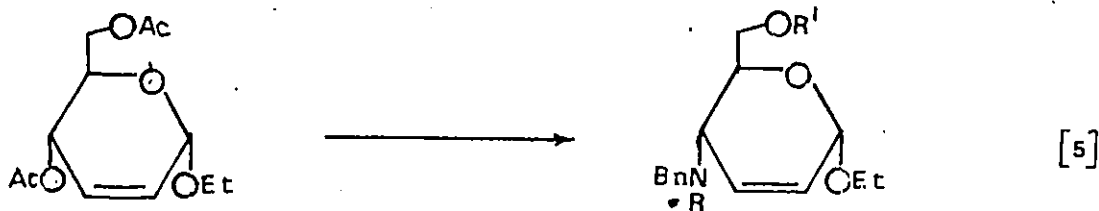


- 31 R = R' = Et
- 32 R, R' = (CH₂)₅
- 33 R = C₆H₁₁, R' = Me
- 34 R = Bn, R' = Me

from 3,4,6-tri-O-acetyl-1, 5-anhydro-2-deoxy-D-arabino-hex-1-enitol (28, tri-O-acetyl-D-glucal) by the method of Ferrier⁴⁷, eq. [3]. Treatment of the enopyranoside 29 with a variety of nucleophiles in refluxing tetrahydrofuran in the presence of a catalytic amount (0.07 molar equiv) of tetrakis-(triphenylphosphine)palladium (30) and excess triphenylphosphine readily led to allylic substitution. The use of diethylamine, piperidine, cyclohexylmethylamine and benzylmethylamine gave the 4-aminated glycosides 31-34, respectively, in yields of 70-87% after chromatographic purification. Judging from the tlc and ¹H- and ¹³C-nmr data, the compounds 31-33 were formed as single isomers accompanied, at most, by traces of slow-moving impurities. In the case of 34, a second but minor compound was seen to be present in the crude reaction mixture; it was removed by preparative tlc and could not be identified. In contrast to these highly regioselective aminations, the reaction of 29 with dibenzylamine was less selective. It produced in 83% yield a mixture of two regioisomers (35 and 36)



in a ratio of approximately 3:7 as determined by nmr spectra (eq [4]). This mixture was readily separable by ptlc; the minor component crystallized and proved to be the 4-aminated glycoside 35, whereas the major component failed to crystallize and was found to be the 2-aminated, 3,4-unsaturated isomer 36. Noteworthy is the fact that the product of substitution at C-4 had retained its stereochemistry, whereas the 2-aminated isomer 36 showed the α -D-threo configuration. (For the assignment of structure, see a subsequent Section).

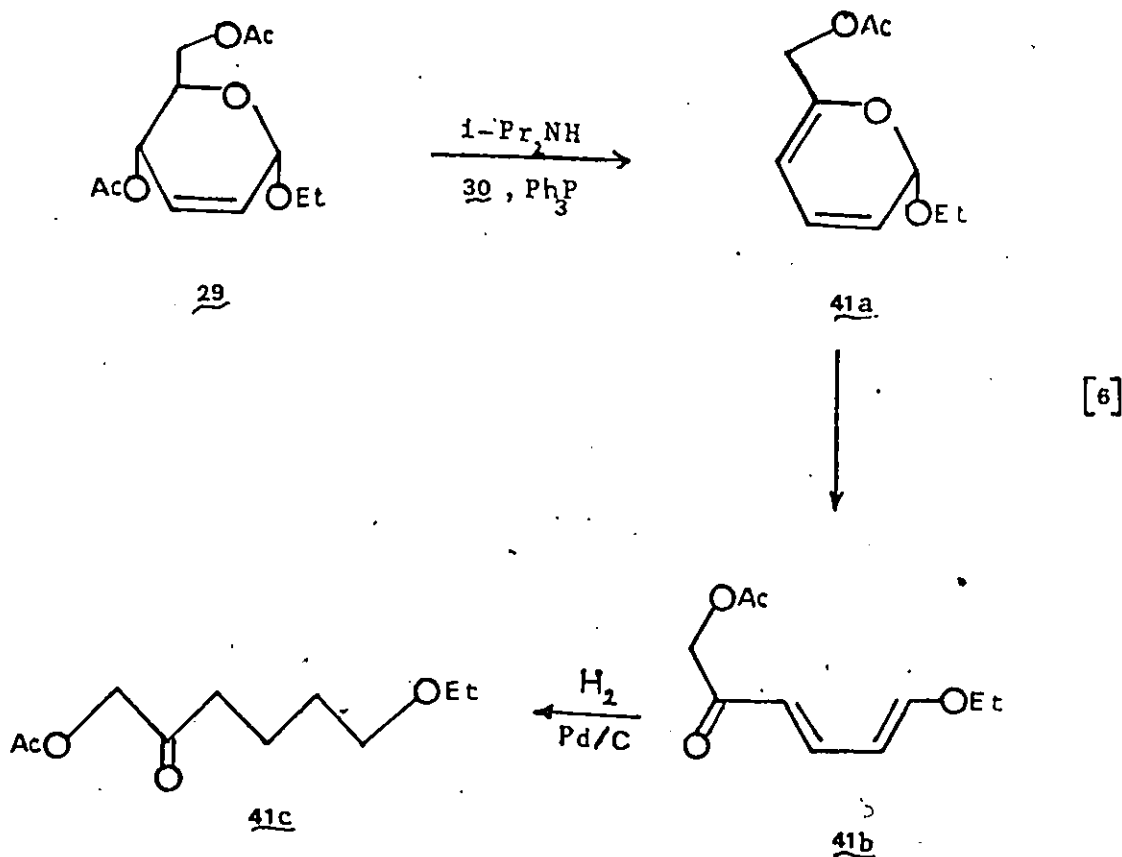


Reaction of 29 with the primary amine, benzylamine, produced a more complex result (eq. [5]). The expected 6-O-acetyl-4-benzylamino glycoside 37 could be isolated in only 31% yield, and the bulk of the reaction product was a chromatographically slow-moving mixture of two components which were difficult to separate. The nmr spectrum of this mixture suggested that the components were partially O-deacetylated starting glycoside and the O-deacetylated derivative (38) of 37. Acetylation of the mixture followed by chromatography led to the recovery of 29 (50%) and, in addition, furnished the syrupy but homogeneous N-acetyl-O-acetyl derivative 39 (15%), whereby the joint yield of isolated, aminated products (37 + 39) was raised to 46%. When syrupy 37 was stored in the refrigerator for an extended period of time, hydroxyl and amide bands developed in its ir spectrum, at the expense of the ester band. A sample stored at room temperature slowly crystallized in the course of a few weeks, and the crystals exhibited amide but no ester carbonyl bands. Although this transformation was not investigated further, it seems obvious that 37 underwent O→N acetyl migration to give 40.

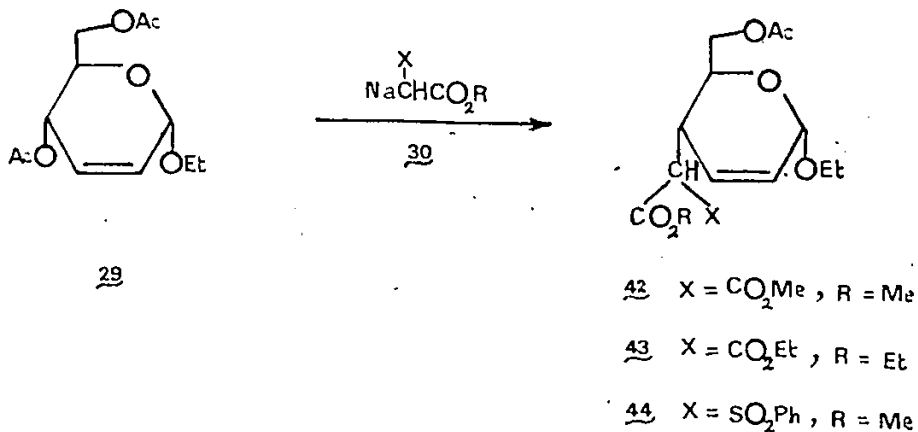
A preliminary examination of the reaction between 29 and some primary, aromatic amines, particularly p-aminobenzophenone, p-aminoacetophenone, and 2,6-dimethylaniline, led to the conclusion, based on nmr spectra of the products obtained, that these amines were also incorporated into the glycoside. However, the products have not been fully characterized as yet, and no complete investigation of these reactions was undertaken.

When allylic substitution was attempted with diisopropylamine, no amination was achieved, presumably because of the steric hindrance associated with this bulkier reagent. Instead, elimination of acetic acid occurred to give in high yield the diene 41b

(accompanied by a small proportion of what appeared to be its geometric, 3,4-cis isomer). The product most likely arose by elimination of acetic acid to give the cyclic diene 41a which then rearranged (see the discussion, section IB.3); catalytic hydrogenation of 41b over palladium on charcoal led to the saturated analog 41c as suggested by ^1H - and ^{13}C -nmr spectra (eq [6]). The same diene 41b was obtained on prolonged heating of 29 in the presence of the catalyst and triethylamine, or even without any amine.

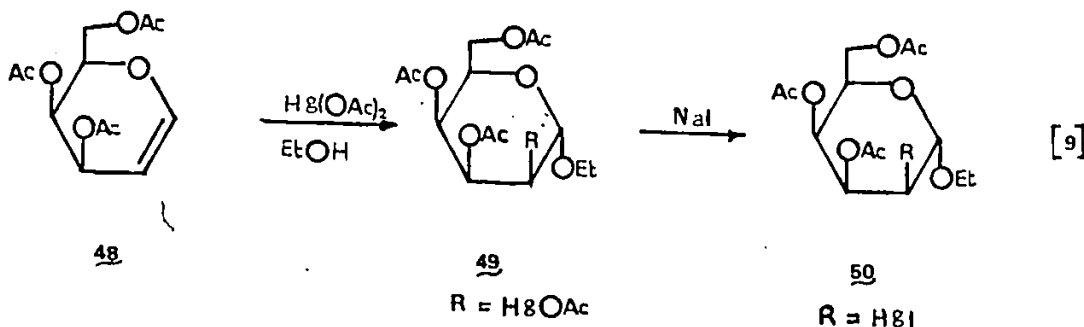
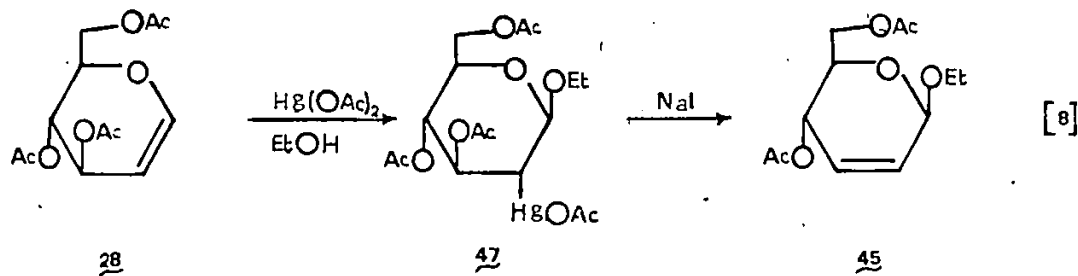


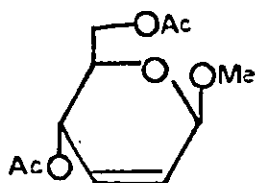
C-Alkylations of 29 were performed in full analogy to the aminations just described, by use of several reactive methylene compounds. Treatment of 29 with the sodium salts of either dimethyl or diethyl malonate in refluxing tetrahydrofuran in the presence of $(\text{Ph}_3\text{P})_4\text{Pd}$ and excess Ph_3P proceeded well and led to exclusive alkylation at C-4, giving 42 and 43 in 87 and 83% yield, respectively. Similar alkylation of 29 with the sodium derivative of methyl phenylsulfonylacetate proceeded at a somewhat slower rate, giving 44 in about 60% isolated yield (eq [7]). Whereas in the two first-mentioned instances the reactions appeared complete after 10-24h and the products (42 and 43) showed no evidence for isomeric inhomogeneity, the alkylation with methyl phenylsulfonylacetate under identical conditions required 72h for total consumption of starting material, and the crude 44 contained a small proportion of an unidentified by-product. However, 44 was obtained pure by crystallization. The configuration at C-7, the chiral centre in the side chain, was not determined. Also tested with 29 were malononitrile and ethyl cyanoacetate. They gave branched-chain glycosides according to spectroscopic evidence, but the yields were poor in these instances and the products have not been characterized definitively, nor have attempts been made to optimize the reaction conditions.



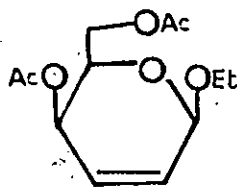
To confirm the catalytic activity of the palladium(0) complex, a control experiment involved treatment of 29 under identical conditions but in the absence of the complex. Only the starting material was recovered.

In view of the high regioselectivity which was observed in all those aminations and alkylations of 29 that proceeded with good yields, with the noteworthy exception of the reaction with dibenzylamine, it appeared interesting to supplement the findings by some comparative experiments using stereoisomers of 29 as substrates. For this purpose the β -D-erythro anomer 45 and the α -D-threo epimer 46 of the pseudoglycal 29 were desired. Although the methyl glycoside analog (45a) of 45 was known^{48,49}, and was used in the present work for a confirmatory experiment, the ethyl glycoside 45 could not be found in the literature. However, we were able to synthesize it readily, also from D-glucal triacetate 28, by way of ethoxymercuration followed by elimination of the elements of mercuric acetate with sodium iodide, in a manner analogous to that described^{49,50} for synthesis of 45a (eq. [8]).

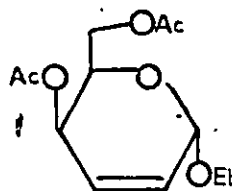




45a



51



46

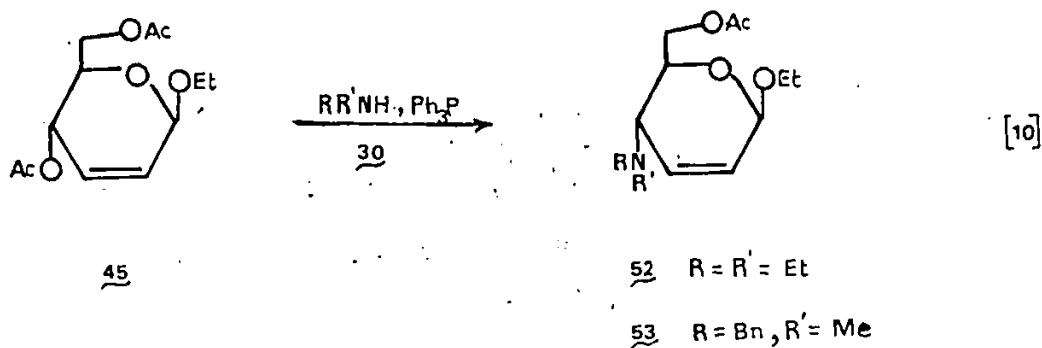
The intermediate prepared in this synthesis, namely ethyl-2-acetoxy-mercuri-3,4,6-tri-O-acetyl-2-deoxy- β -D-glucopyranoside (47), was a highly crystalline compound.

An attempt to synthesize the β -D-threo isomer 51 by analogous ethoxy-mercuration of tri-O-acetyl-D-galactal (48) did not succeed. The reaction led to the 2-acetoxymercuri α -glycoside 49, and treatment of the latter with sodium iodide gave the corresponding iodomercuri derivative 50 but no elimination product (eq. [9]).

Unlike 29, which is easily accessible from 28 (p. 17), the α -D-threo enoside diacetate 46 is difficult to prepare from 48, by the original Ferrer procedure, because of extensive formation of side-products. However, we were able to provide a sample of 46 by conventional acetylation of its parent diol*. Subsequently, a high-yielding modification of Ferrer's method, allowing to prepare 46 readily from 48, appeared in the literature⁵².

* Footnote p. 25

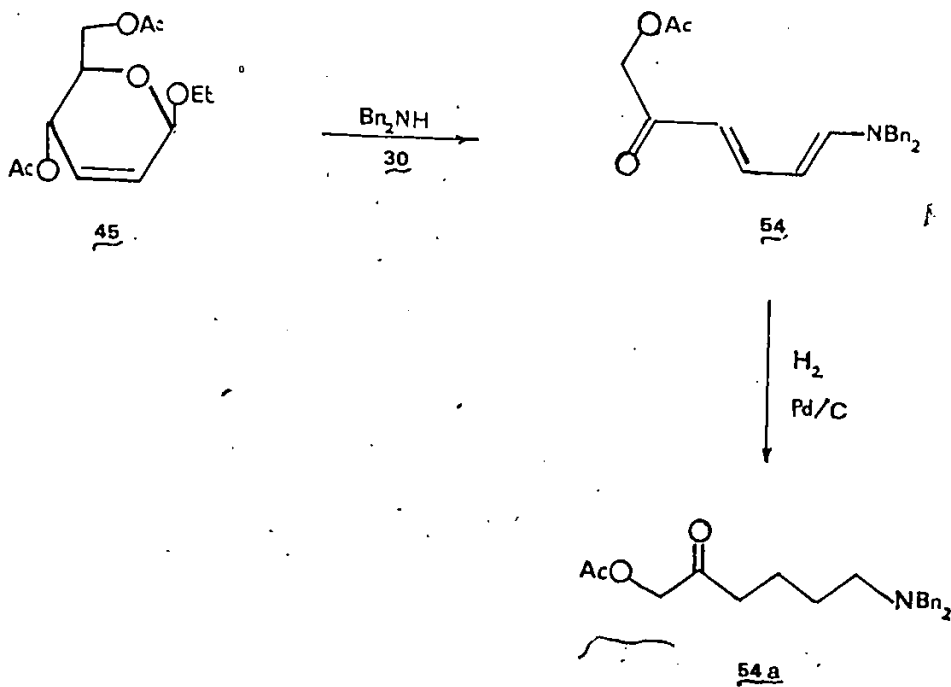
Amination of the β -enopyranoside 45 with diethylamine and benzylmethylamine under the usual conditions gave the aminated glycosides 52 and 53 in excellent yields (eq. [10]).



* Footnote

For a gift of a sample of this diol we are indebted to Professor B. Fraser-Reid who informed us privately that it was prepared from the corresponding, α -D-erythro diol by C-4 inversion through benzoylation in the presence of dialkyl azodicarboxylate and triphenylphosphine⁵¹, followed by saponification.

As in the case of 29, the products resulting from attack at C-4 had completely retained the original stereochemistry. A very small proportion of an unidentified by-product (presumably an isomer) was present in 53 as revealed by the nmr spectrum. Amination of the β -enopyranoside 45 with dibenzylamine provided another surprise. It will be recalled that the α -anomer 29 had reacted with this amine with diminished (and reversed) regioselectivity to give two isomers (35 and 36; see p. 18). Compound 45 also gave a mixture of products. Chromatographic separation furnished a slow-moving, minor component and a fast-moving, major component. Only the former appeared to have the gross structure of an aminated, ethyl enopyranoside, according to spectral evidence. Unfortunately,

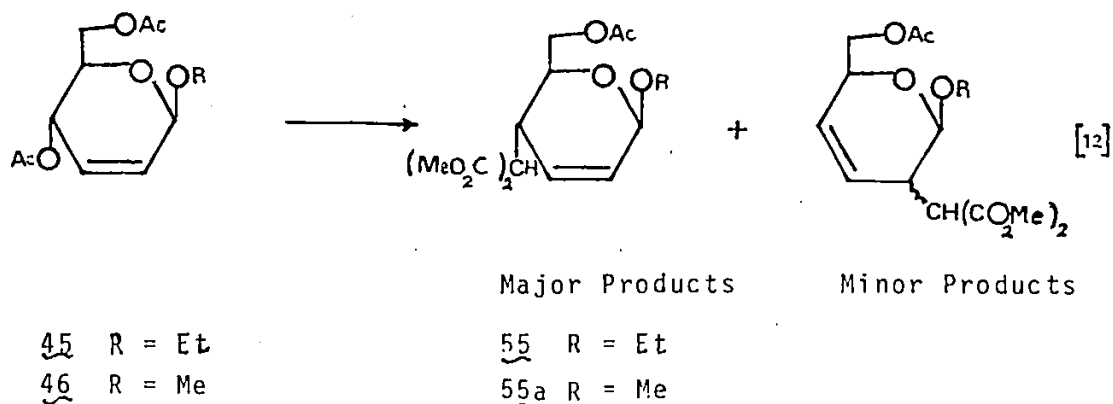


[11]

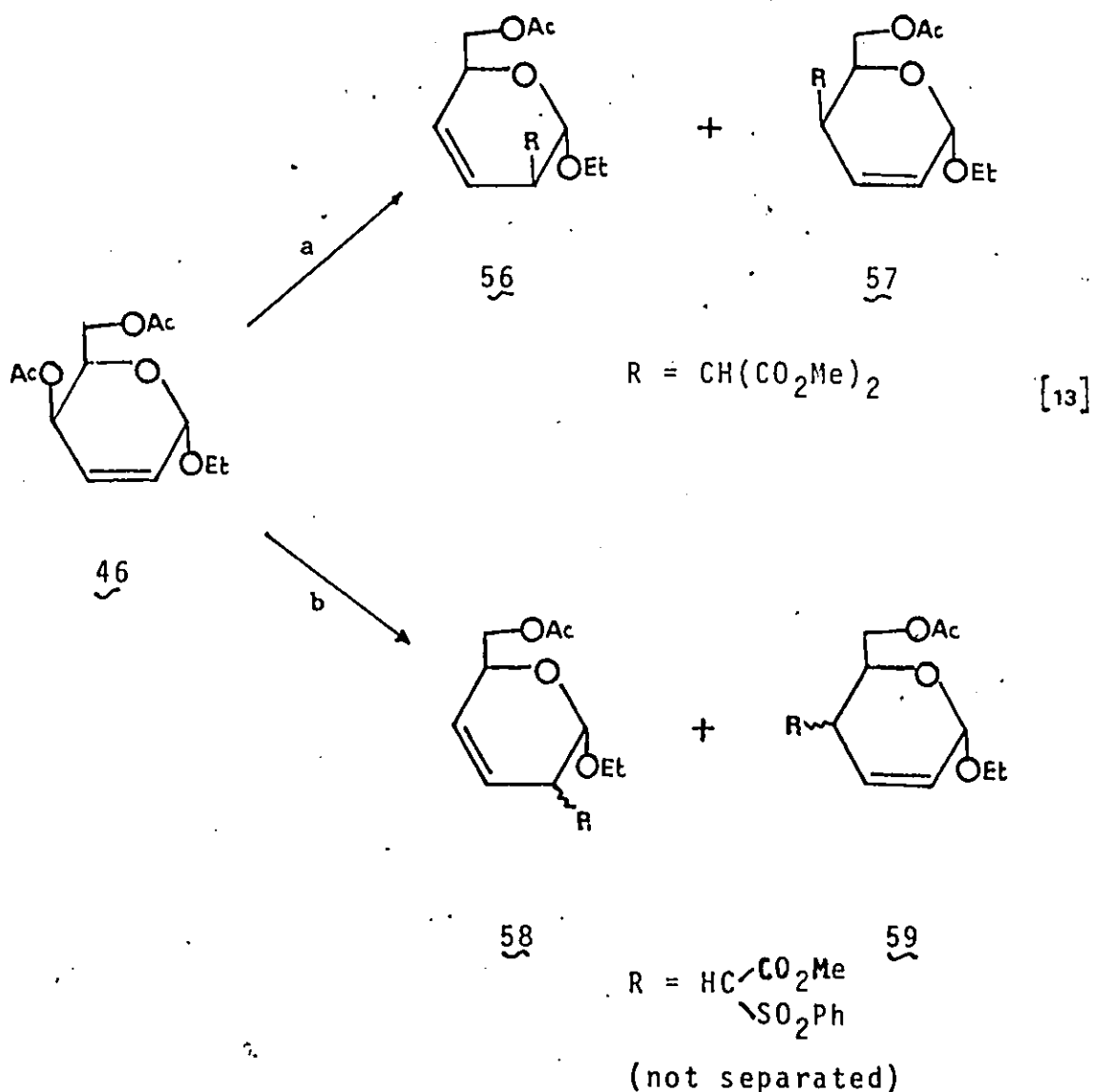
it could not be ascertained whether the product was isomerically homogeneous, nor could structural details be elucidated because of lack of material. The major component possessed a dibenzylamino group but had lost the glycosidic ethoxyl group. ^1H - and ^{13}C -nmr spectra indicated the dienic structure 54, and in agreement therewith, brief hydrogenation using a Pd/C catalyst gave the corresponding, saturated compound 54a (eq. [11]). Further studies concerning the exceptional behaviour of dibenzylamine should be worthwhile.

The β -enopyranoside 45 and, likewise, its methyl analog 45a were $\underline{\text{C}}$ -alkylated with the sodium salt of dimethyl malonate under the conditions previously stated (eq. [12]).

The products were obtained in high yields. Although they appeared as single spots in tlc, they were revealed by nmr spectroscopy to be composed of strongly preponderant, major components and minor isomers. The chief components were the 4-substituted, 2-enosides 55 and 55a, respectively, and the minor by-products were 2-substituted, 3-enosides as indicated by mass-spectral analysis (vide infra).



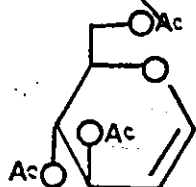
For the α -D-threo enoside 46, only two palladium-catalyzed substitutions have thus far been examined; in both instances, regioselectivity was found to be lower than in the analogous reactions with 29 or 45. With dimethylmalonate, 46 gave in 66% yield an approximately 3:1 mixture of the 2-alkylated, 3,4-unsaturated α -D-threo glycoside 56 and its 4-alkylated, 2,3-unsaturated isomer 57 (eq. [13a]). In addition, small proportions



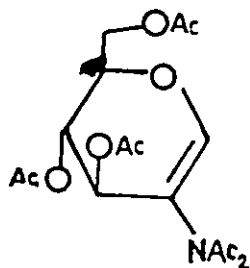
of two chromatographically slow-moving products were isolated. Both of them originated from C-alkylation as they contained methyl ester groups of an incorporated malonate residue. However, they had lost both O-acetyl groups. Reacetylation of one of these minor fractions gave 56, spectroscopically identified with the major component in the aforementioned mixture of main products. The other slow-moving by-product remained unaffected by acetylation and its ¹H-nmr spectrum suggested the presence of three methyl ester groups. Hence the product had probably arisen from O-deacetylated 56 or 57 by transesterification of OH-6 with dimethyl malonate.

Alkylation of 46 with methyl phenylsulfonylacetate gave also a mixture of two isomeric substitution products (eq. [13b]). The mixture could not be separated by chromatography, but its nmr spectrum indicated that the components were present in approximately equal proportions. Formulas 58 and 59 are tentatively suggested by analogy for these products; the configurations at C-2 and C-4, respectively, and at the asymmetric centre in the side chain (C-7) have not been determined.

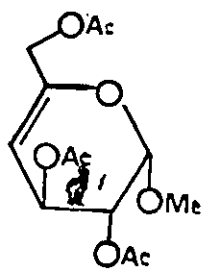
In order to explore the scope of the allylic substitution further, the glycals 28 and 72 as well as the 4-enopyranoside 73 and the 4-enopyranuronoside 74 were tried as reactants for amination using diethylamine. These trials were unsuccessful. Compound 28 gave a complex mixture of unidentifiable products, and 72 - 74 did not appear to react at all under the standard conditions.



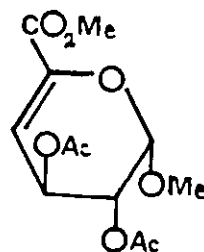
28



72



73



74

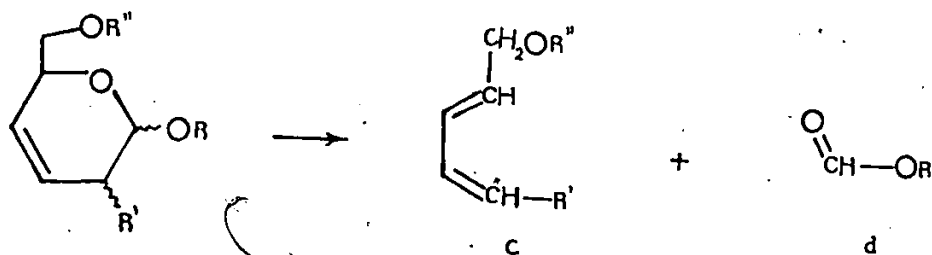
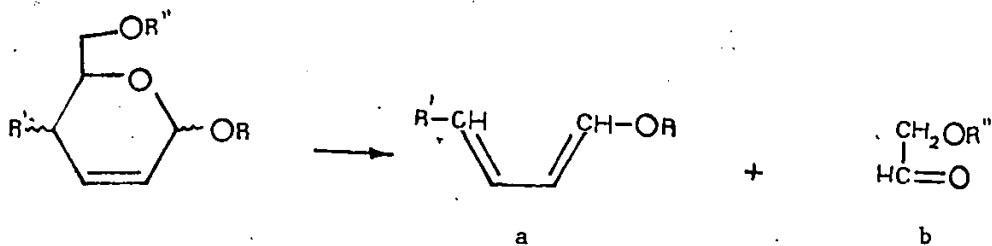
I,B.2. ASSIGNMENT OF STRUCTURE

The gross structures of the new compounds were supported by elemental analysis, fitting infrared spectra, the molecular ion peak present in the mass spectrum in most cases (Table 1), and the requisite substituent resonances displayed in the proton and carbon-13 nmr spectra.

More detailed constitutional and configurational information was derived from spectral data and from optical rotations, as follows:

I,B.2-1. MASS SPECTRA

First of all, it was necessary to ascertain the position of the olefinic double bond in the pyranoside rings. This was made



SCHEME 1

TABLE 1. Selected mass spectral data^a

Compd.	<u>m/e</u> (in parentheses, intensity in % of base peak)			
	M^+	$M^+ - 102$	$M^+ - 74$	Others [assignment]
<u>31</u>	271 (1)	169 (74)	197 (1.1)	
<u>32</u>	283 (1.1)	181 (85.5)	209 (1.3)	
<u>33</u>	311 (0.2)	209 (91.4)	237 (2)	
<u>34</u>	319 (0.1)	217 (53)	245 (1.3)	
<u>35</u>	395 (0.1)	293 (38.4)	321 (2.1)	264 (24.7) [293 - Et]
<u>36</u>	not obs.	293 (1)	321 (12)	262 (23) [321 - OAc]
<u>39</u>	347 (1.7)	245 (43)	273 (0.4)	
<u>42</u>	330 (1.2)	228 (22.8)	256 (1)	169 (53.1) [228 - OAc], 197 (6.2) [256 - OAc]
<u>43</u>	358 (0.5)	256 (10)	not obs.	183 (25) [256 - EtO ₂ C], 211 (4.2) [M - 74 - EtO ₂ C]
<u>44</u>	not obs.	not obs.	not obs.	411 (1.2) [M ⁺ - 1], 169 (49) [M ⁺ - 102 - PhSO ₂], 141 (31.8) [PhSO ₂]
<u>52</u>	271 (1.7)	169 (87.6)	197 (5.1)	
<u>53</u>	319 (0.7)	217 (46.7)	245 (2.9)	
<u>55</u>	330 (2.1)	228 (9)	256 (2)	169 (27) [228 - OAc], 197 (7.5) [256 - OAc]
<u>55a</u>	316 (0.4)	214 (12.1)	256 ^b (1.7)	155 (38.8) [214 - OAc], 197 (4) [256 - OAc]
<u>56</u>	330 (0.3)	228 (3)	256 (4)	197 (11) [256 - OAc], 169 (16) [228 - OAc]

^a The spectra were obtained with an A.E.I.-MS 902 mass spectrometer fitted with a direct-inlet probe, at an ionizing potential of 50-55 eV. ^b $M^+ - 60$ [loss of methyl formate].

possible by mass spectrometry, which permits one to distinguish between 2,3- and 3,4-unsaturated hexopyranosides on the basis of different fragmentation patterns^{53,55}. For the former type of enosides, retrodienic fragmentation leads to two fragments (a and b) according to Scheme 1.

In our compounds, since $R'' = CH_3CH_2$, $M_b = 102$ and hence $M_a = M - 102$. On the other hand, enopyranosides of the latter type are fragmented to give a diene (c) and alkyl formate (d) (Scheme 1). For ethyl glycosides, with $M_d = 74$, a fragment c having $M_c = M - 74$ is therefore diagnostic for 3,4-unsaturation. Table 1 shows that the amino glycosides 31-35, 39, 52, and 53 all gave prominent peaks of m/e $M - 102$, indicative of their 2,3-unsaturated structures. There were also peaks of m/e $M - 74$, but their intensities were only 1-6% of those of the $M - 102$ peaks. Although these minor peaks possibly may signify the presence of minute proportions of 3,4-unsaturated isomers that had escaped detection by tlc or nmr spectroscopy, they could well have resulted from thermal rearrangement of the compounds in the mass spectrometer prior to electron impact⁵⁵. On the other hand, the amine 36 gave only a feeble peak of m/e $M - 102$ but a peak 12 times as strong at m/e $M - 74$. Furthermore, 36 gave an intense daughter peak at m/e 262 believed to result from loss of OAc from the $M - 74$ fragment. By contrast, the positional isomer 35 showed only a weak peak at m/e 262 (with 12% of the intensity seen in 36), whereas it produced a strong daughter peak at m/e 264 attributable to loss of C_2H_5 from its $M - 102$ fragment. Conversely, in 36, this peak had an intensity of only 8% relative to that in 35. These features clearly permitted allocation of the double bond positions as shown.

The C-alkylated compounds 42, 43, 55 and 55a were similarly revealed to possess 2,3-unsaturated structures, on account of the strong dominance of M-102 over M-74 peaks (or the analogous M-60 peak in the case of the methyl glycoside 55a). It is noteworthy, though, that the M-102 peaks generally were markedly lower in intensity relative to the base peak than in the cases of the aminated analogs, presumably because of a high instability associated with fragments that contain a malonic ester moiety. In support of this explanation, strong daughter peaks were observed, which arose from loss of CH_3CO_2 from the M-102 fragments of 42, 55 and 55a and from loss of $\text{C}_2\text{H}_5\text{CO}_2$ in the case of 43.

As already mentioned, the β -glycosides 55 and 55a were revealed by their ^{13}C -nmr spectra to contain minor proportions of isomers that could not be isolated. The mass spectra exhibited minor peaks at m/e M-74 and M-60, respectively, whose intensities were somewhat greater (22 and 14%) relative to the major, M-102 peaks, than in the preceding compounds where these intensities ranged from 1-6% (see above). These findings corroborated the assumption that the by-products accompanying 55 and 55a were 2-substituted, 3,4-unsaturated analogs.

The mass spectrum of the phenylsulfonyl derivative 44 did not display peaks attributable to M-102 or M-74, such fragments apparently being too unstable to survive in this instance. Indeed, loss of $\text{C}_6\text{H}_5\text{SO}_2^+$ (m/e 141) was conspicuous, with concomitant formation of an intense ion peak at m/e 169 attributable to M-102-141. The spectrum thus provided at least indirect evidence for the structure of 44.

The spectrum of 56 failed to yield information to allocate the olefinic bond. Peaks for M-102 and M-74 were both weak and quite similar in intensity, and the same applied to daughter peaks expected to originate from loss of CH_3CO_2 . However, the spectrum was useful at least in so far as it established the non-identity of 56 with the α -D-erythro isomer 42. Furthermore, the spectrum of isolated 56 ($[\alpha]_D + 100^\circ$) was extremely similar to that of the mixture ($[\alpha]_D + 24^\circ$) of 56 and 57 originally obtained from 46. This observation together with the ambiguous fragmentation pattern suggests that 56 is particularly prone to sigmatropic rearrangement which may occur in the spectrometer to some considerable degree. Ferrer and coworkers⁵⁴ have found such rearrangements to be especially facile when the migrating substituent was attached quasi-axially as in 56 and 57, rather than quasi-equatorially as in 42 and most of the other compounds here considered. The mass-spectral peculiarity of 56 therefore tends to support its formulation as a threo compound. Finally, the spectrum of the mixture of phenylsulfonyl derivatives 58 and 59 furnished little structural information other than admitting that one of the components (59) may have been identical with 44.

I, B. 2-2. ^{13}C - NUCLEAR MAGNETIC RESONANCE SPECTRA

Assignments of the ^{13}C -nmr signals to individual nuclei were established on the basis of multiplicities observed in proton-coupled spectra and in accordance with known chemical shift regularities (see ref. 56 and literature cited therein). Table 2 shows the ^{13}C chemical shifts of the pyranose carbon and some selected substituent carbon atoms. Several points may be noticed from this table: (1) All of the compounds to which was assigned the 2,3-unsaturated α -D-erthyro structure (31-35, 37, 39, and 42-44) show the C-1 resonance in the narrow range of 93.8-94.3 ppm relative to tetramethylsilane. (2) No significant change was observed in C-1 chemical shift on inversion of configuration at C-4 in the starting compounds 29 and 46. The δ -effect upon C-1 is very small, both chemical shifts lie in the same range. (3) In the mixture of the two C-bis(methoxycarbonyl) methyl derivatives obtained from 46, only the minor component (57) showed a reasonably similar C-1 shift (94.6 ppm), and so did one of the components (designated 59) of the mixture of methoxycarbonyl-(phenylsulfonyl)-methyl derivatives (94.3 ppm). These data appear consistent with the assignment of a 2,3-unsaturated constitution to 57 and 59. (4) In the α -glycosides 36 and 56 for which there was positive (36) or circumstantial (56) evidence, in the mass spectrum, for 3,4-unsaturation, the C-1 chemical shift experienced a noticeable downfield shift to 97.4 ppm in contrast to the 2,3-unsaturated glycosides which showed the C-1 resonance in the range of 93.8-94.3 ppm. By analogy it may be assumed that 58, judging from its C-1 resonance at 96.5 ppm, is 3,4-unsaturated also. (5) There are further consistencies supporting the assignments above. For example: a) In each of the three pairs of positional isomers (35/36, 56/57, and 58/59), the carbon atom bearing the newly-introduced substituent resonates

TABLE 2. Selected ^{13}C chemical shifts (ppm from TMS)^a

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	Others ^b
<u>29</u> ^c	94.3	128.1	129.0	65.4	67.0	64.3	
<u>45</u>	95.0	126.2	130.7	64.5	72.9	63.7	
<u>46</u>	93.8	125.2	130.8	62.9	66.7	64.0	
<u>31</u>	94.3	127.4	130.5	54.7	67.1	64.8	44.9 (<u>N-CH₂</u>)
<u>32</u>	93.8			59.0	66.3	64.7	50.7 (<u>N-CH₂</u>)
<u>33</u>	94.2	127.3	132.9	53.8	66.9	64.9	33.6 (<u>N-CH₃</u>), 62.9 (<u>N-C-C₂</u>)
<u>34</u>	94.3	128.1	128.3	56.5	66.3	64.5	38.2 (<u>N-CH₃</u>), 58.7 (<u>N-CH₂-Ph</u>)
<u>35</u>	94.3	128.6	128.9	52.4	66.2	64.0	55.0 (<u>N-CH₂-Ph</u>)
<u>36</u>	97.4	54.6	126.2, 128.7	65.7	63.3		54.3 (<u>N-CH₂-Ph</u>)
<u>37</u>	94.2	126.1	131.7	50.8	69.1	64.3	50.4 (<u>NH-CH₂-Ph</u>)
<u>39</u>	93.9	126.1	128.9 ^d	49.9	67.0	64.1	49.0 (<u>AcN-CH₂-Ph</u>)
<u>42</u>	94.2	126.7	129.4	35.6	66.8	64.2	51.3 (C-7)
<u>43</u>	94.2	126.5	129.5	35.5	66.7	64.3	51.3 (C-7)
<u>44</u>	94.2	126.7	129.3	33.8	66.6	63.9	
<u>52</u>	95.6	129.0	129.0	53.8	72.3	65.1	44.5 (<u>N-CH₂</u>)
<u>53</u>	95.0	127.1	129.3	55.5	71.1	65.1	38.2 (<u>N-CH₃</u>), 58.3 (<u>N-CH₂-Ph</u>)
<u>55</u>	93.0	126.1	128.1	34.1	70.0	64.7	
<u>e</u>	96.1	39.8	126.3, 126.7	72.3	66.0		
<u>55a</u>	94.4	126.3	127.8	34.0	70.0	64.6	
<u>f</u>	100.7	39.7	126.3, 126.6	72.1	65.9		
<u>56</u>	97.4	38.4	124.6, 127.3	67.4	65.3		54.5 (C-7)
<u>57</u>	94.6	128.1	129.1	35.1	66.8	63.4	50.2 (C-7)
<u>58</u>	96.5	37.2					
<u>59</u>	94.3			33.7			

^aSpectra were taken from chloroform solutions with a Varian CFT-20 instrument.

^bIn addition to the resonances listed, all compounds showed resonances as expected for the carbon atoms in the various substituents.

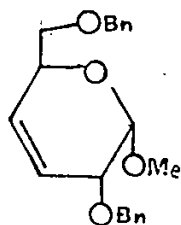
^cThe values for 29 are in good agreement with published (58) data.

^dThe signal was difficult to differentiate from nearby Ph signals; an alternative value is 129.3.

^eThe minor by-product present in 55, believed to be a 3-enoside.

^fThe minor by-product present in 53a, believed to be a 3-enoside.

at lower field by 2.2-3.5 ppm when it is in the 2-position than when it is in the 4-position. (b) The pair of epimers 42/57 shows a deshielding difference in the expected direction for a quasi-equatorially and quasi-axially substituted C-4, although the effect is small in this instance (0.5 ppm). A similar insensitivity of the C-4 shift cannot be excluded for 44 and its 4-epimer; for this reason it was not possible to decide whether the non-isolated, mixture component 59 was identical with one or the other of the α -D-erythro compounds having the structure 44 (two C-7 epimers being possible), or whether it was an α -D-threo stereoisomer. (c) The near coincidence of the C-1 shifts in 36,56 and 58 would obviously be consistent with an assumption that these compounds possess an identical configuration. However, it cannot be regarded as proof since the change from an axial C-2 substituent (α -D-threo configuration) to an equatorial one (α -D-erythro configuration) replaces one shielding factor by another one of similar magnitude, with little if any net effect upon the C-1 shift to be expected. This is exemplified in the pair methyl α -D-mannopyranoside and methyl α -D-glucopyranoside, and in other pairs of epimers having comparable features⁵⁶. On the basis of their optical rotations (vide infra), 36 and 56 were assigned the α -D-threo configuration, and it is noteworthy in this context that the constitutionally analogous, α -D-erythro glycoside 70a also shows⁷⁵ a similar C-1 resonance (97.0ppm).



70a

In ordinary methyl β -hexopyranosides, excepting the mannosides, C-1 is generally deshielded by ca. 2-5 ppm relative to the corresponding α -anomers⁵⁶. The methyl 4,6-O-benzylidene-2,3-dideoxy- α - and β -D-erythro-hex-2-enopyranosides, which are comparable to our compounds but for their rigid conformation due

to the trans-fused acetal ring, were found ⁵⁸ to obey this rule ($\Delta\delta$ -3.1ppm). Recently, Paulsen and coworkers ⁵⁹ found that the difference is somewhat smaller (-1.5 to -1.8 ppm) in the 4,6-di-O-acetyl-2,3-dideoxy-D-hex-2-enopyranosyl dimethylphosphonates (29, 45, 46 and β -D-threo isomer, with P(O)(OMe)₂ replacing the OEt group). In our case the data in Table 2 indicate that the β -glycosides 45, 52, and 53 also give C-1 resonances to slightly lower field than their α -anomers 29, 31, and 34 ($\Delta\delta$ -0.7, -1.3, and -0.7, respectively). On the other hand, the γ -effect of anomerization upon C-5 was distinctly larger in these pairs ($\Delta\delta$ -5.9, -5.2 and -4.9 ppm, respectively), exceeding the values observed ⁵⁹ in the phosphonates just mentioned (-2.5 and -3.3 ppm) and coming closer to the value (-6.6ppm) reported ⁵⁸ for the benzylidene acetals.

Summation of the chemical shifts for C-1 to C-6 in the α -glycosides 31 and 34 (\sum_{1-6} 538.8 and 538.0 ppm) and their β -anomers 52 and 53 (\sum_{1-6} 544.7 and 543.1 ppm) and juxtaposition of these values with the sums for 29 (\sum_{1-6} 548.1 ppm) and 45 (\sum_{1-6} 553.0 ppm), respectively, is taken as a good indication ⁵⁶ for structural equivalence. Surprisingly, a similar exercise comparing \sum_{1-6} for the C-alkylated α -glycoside 42 (516.7 ppm) with the values for the β -glycosidic analogs 55 (516.0 ppm) and 55a (517.1 ppm) did not yield any such difference of 5-6 ppm for anomerism. A possible explanation for this apparent discrepancy may lie in differing conformational features as will be discussed below. As regards the minor by-products that accompanied 55 and 55a, their carbon atoms showed chemical shift relations, to the structurally analogous atoms in 55 and 55a, that were qualitatively similar, to the relations seen in the pair of positional isomers

56/57. Thus, C-1 and the alkyl-substituted carbon in particular, and to a lesser degree C-5 and C-6, all were significantly deshielded relative to their counterparts in 55 and 55a. These comparisons reinforced the suggestion, already intimated by the mass spectra, that the by-products were 2-substituted, 3,4-unsaturated isomers of 55 and 55a. Unfortunately, the configuration at C-2 could not be established definitively since the optical rotations of these products are unavailable for confirmation.

I, B-2-3 ¹H-Nuclear Magnetic Resonance Spectra

Table 3 shows the ¹H-nmr parameters. The spectra of the aminated, α-glycosidic derivatives 31-35 and 37, as well as those of the C-alkylated derivatives 42-44, were sufficiently resolved to permit first-order analysis which established the D-erythro configuration of these 2-enosides. The olefinic protons resonated in the δ6.0 region and gave AB quartets showing ³J_{2,3} = 10.0-10.5 Hz; each constituent part was split further, by small vicinal and allylic couplings with H-1 and H-4. The anomeric proton produced a broadened singlet or narrow multiplet near δ5.0. Of diagnostic significance was the H-4 signal, which occurred at highest field as far as ring protons were concerned. It was a doublet (H_{4,5} = 10 Hz) of narrowly-spaced multiplets. The large coupling constant indicated that H-4 and H-5 have an anti orientation and therefore proved the D-erythro configuration. The individual multiplets composing the H-4 doublet contained small (1-2 Hz) vicinal (J_{3,4}), allylic (J_{2,4}), and homoallylic (J_{1,4}) couplings that were mirrored in the corresponding, downfield proton signals. An additional splitting of 4 Hz discernible in the H-4 signals of 42 and 43 was due to vicinal coupling with H-7, the methine proton in the side-chain.

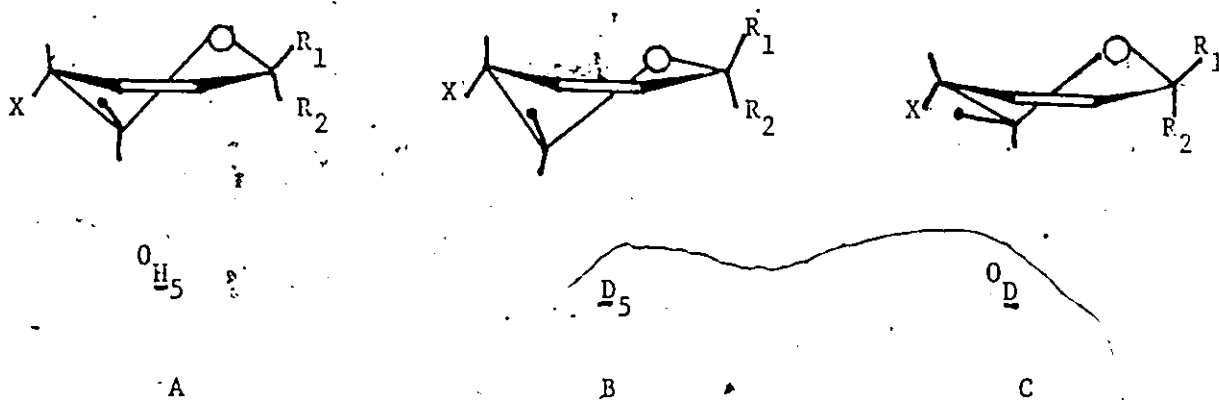
A more detailed analysis of the signal fine-structure should make possible a correlation of the various, small vicinal and allylic couplings just mentioned with the conformational shape of the molecules. It appeared reasonable to assume that the products would in this regard resemble the parent glycoside 29, for which the ⁰H₅ half-chair conformation (formula A) had been proposed⁴¹. Upon detailed spectral analysis of related molecules, Paulsen⁵⁹ and

TABLE 3. The ^1H nuclear magnetic resonance data^a

Compound	Chemical shifts ^b (δ)							Coupling constants ^c (Hz)													
	H-1	H-2	H-3	H-4	H-5	H-6,6'	H-7	$^1J_{1,2}$	$^1J_{1,3}$	$^1J_{1,4}$	$^2J_{2,3}$	$^2J_{2,4}$	$^2J_{3,4}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6}$	$^3J_{5,6'}$	$^3J_{6,7}$			
32	5.65m	5.86m	5.31d	4.09ddd	4.2m			2.7 ^d	-1 ^d	2 ^d		-2 ^d	2 ^d	9.2	~2.5, 5.0 ^e						
33	5.13q	5.94s	5.21dq	4.02dt	4.25d, 4.26d				see footnote 5 in the text					5.0	4.8	6.3					
34	5.06d	6.09dd	6.12dd	5.02dq	4.36c	4.23q		2.5	~0	~0	10.0	<0.5	4.5	2.5	6.5						
31	4.59m	5.83ddd	6.05ddd	3.31dt	3.95ddd	4.35dq		2.7	-1.2	1.8	10.5	-2.0	2.0	10.5	2.7	5.5					
32	4.55m	5.82ddd	6.11ddd	3.02cm	4.0	4.6m		2.5	-1.0	~2	10.5	-2.0	2.0	10							
33	4.97m	5.79ddd	6.03ddd	3.36cm	3.99ddd	4.30dq		2.7	-1.2	1.8	10.5	-2.0	2.0	10	3.0	5.0					
34	4.53m	5.89ddd	6.15ddd	3.26dt	4.06ddd	4.32dq		2.5	-1	1.7	10.7	-2.1	2.0	10	2.7	5.5					
35	4.97m	5.93dt	6.24ddd	3.41qm	4.0	4.4m		2.5	~-1		10.5	-2.5	~2	10							
35	5.03t	3.13m	5.87s		4.0	4.5m		<1	~-1				0								
37	4.57m	5.76ddd	6.10ddd	3.14dt	4.35d			2.5	-1	1.7	10.0	-2.0	~2	10							
32	5.00m	5.77ddd	6.07ddd	3.09cm	4.06ddd	4.16q, 4.37q	3.61d	2.8	-1	1.5	10.0	-2.4	2.0	10.5	3.0	5.0	4.0				
33	5.00m	5.76ddd	6.03ddd	3.01cm	4.11ddd	4.17q, 4.39q	3.58d	2.7	-1	1.5	10.0	-2.5	2.0	10.5	3.0	5.0	4.0				
34	5.00m	5.77dt	6.33ddd	3.27cm	4.0	4.5m		2.7	~-1		10.5	-2.5	~2	10							
32	5.09m	5.91m		3.26cm	3.92q	4.31d								5.5	5.5						
33	5.05m	5.97m		3.16cm	4.0	4.4m								4.7							
35	4.92s	5.87m		2.84ddd	4.0	4.5m								4.0				9.0			
35a	4.81s	5.87m		2.85ddd	3.9	4.5m								4.3				9.0			
35	4.52m	2.65dm	5.77m	4.36cm	4.09q, 4.27q	3.51d		<1	~0.5	10.0	<-1	5.2	0	1.5	2.0	9.5					
37	4.53d	5.83ddd	6.03ddd					2.5	-1	~0.5	10.0	<-1	5.2								

^aFrom 100-MHz spectra of solutions in CDCl_3 containing tetramethylsilane as standard. In addition to the signals listed, all compounds showed substituent resonances as required by the structures. Signal multiplicities are indicated as m (complex multiplet), d (doublet), n (narrow multiplet), m (multiplet), o (octet), q (quartet), s (singlet), and t (triplet). Measured at 250 Hz sweep width. ^bEstimated from observed splittings; see footnote page 47. ^cSplittings observed in the H-5 multiplet; these may not equal the coupling constants because of the proximity of the H-6,6' signal.

Thiem⁶⁰ recently came to the conclusion that α -D-erythro-hex-2-enopyranosides tend to adopt a noticeably flattened version of this half-chair, approaching the corresponding "sofa form" in which C-5 protrudes below the plane defined by C-1 to C-4 and the ring oxygen atom (formula B)*; this geometry has been confirmed by x-ray crystallography in three cases⁵⁹⁻⁶¹.



α - series: $R_1 = H$, $R_2 = OEt$

α - series: $R_1 = OEt$, $R_2 = H$

The spectra of our α -D-erythro products generally supported a similar molecular shape, rather than the alternate O_D sofa form (formula C) advocated by Watanabe and coworkers⁶² for some 4-amino-hex-2-enosides closely related to our derivatives, which they synthesized by different methods. Thus, the allylic couplings ${}^4J_{1,3}$ and ${}^4J_{2,4}$ of -1 to -1.2 and -2 to -2.5 Hz, respectively, implied dihedral angles $\Phi_{1,2}$ and $\Phi_{3,4}$ in the ranges of 50-55 and 67-80^o, according to Garbisch's relationship⁶³ given in eq. [14].

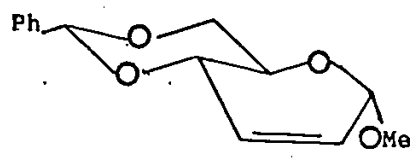
* The symbol SO has been used for sofa conformations, e.g., SO₅ for B⁶⁰.

Inasmuch as single-letter conformational symbols are now in general use and S is already reserved for skew forms, we propose the letter D (from divan) for such conformations.

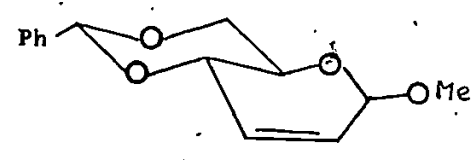
$$^4J = 1.3 \cos^2 \Phi - 2.6 \sin^2 \Phi \quad (0^\circ \leq \Phi \leq 90^\circ) \quad [14]$$

$$^3J = 6.6 \cos^2 \Phi + 2.6 \sin^2 \Phi \quad (0^\circ \leq \Phi \leq 90^\circ) \quad [15]$$

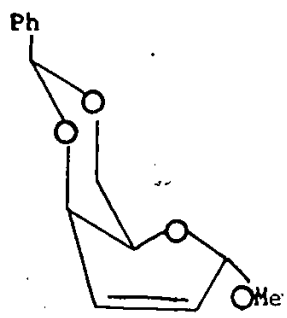
In an ideal D_5 sofa form, these angles are 60 and 90° , respectively; very small ring torsions in the direction towards a flattened 0H_5 form moves them into the indicated ranges. The homoallylic couplings, $^5J_{1,4} = 1.5-1.8$ Hz, were in accord with those found ^{60,64,65} in other 2-enosides featuring comparable, mutual dispositions of H-1 and H-4. The vicinal couplings through sp^2 hybridized carbon ($^3J_{1,2}$ and $^3J_{3,4}$) require special comment. The relationship provided by Garbisch ⁶³ for this situation (eq. [15]) fails to predict accurate values in the case of enopyranosides. It was first noted by Anet ⁶⁶ that the parameter of $+2.6$ may be too large, and couplings smaller than the minimum value derivable from eq. [15], namely 2.6 Hz for $\Phi = 90^\circ$, have since been ^{58-60,62,64,65,67,70} observed on numerous occasions. However, qualitatively the small coupling $J_{3,4} = 2$ Hz, consistently shown by our products (Table 3), certainly was in line with a large dihedral angle $\Phi_{3,4}$ as required by the conformation discussed. For an angle $\Phi_{1,2}$ of $50-55^\circ$, eq. [15] predicts $^3J_{1,2}$ values of $3.9-4.3$ Hz;



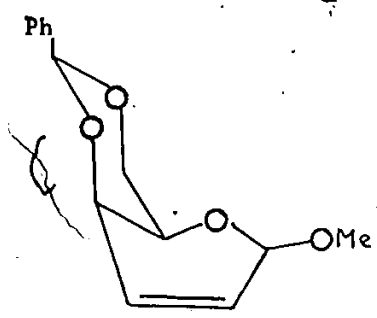
60



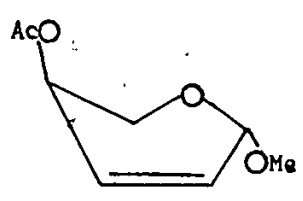
61



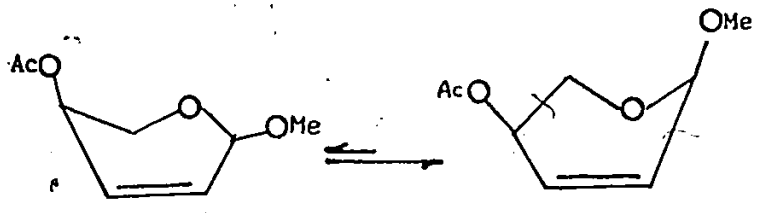
64



65



66



67'

67

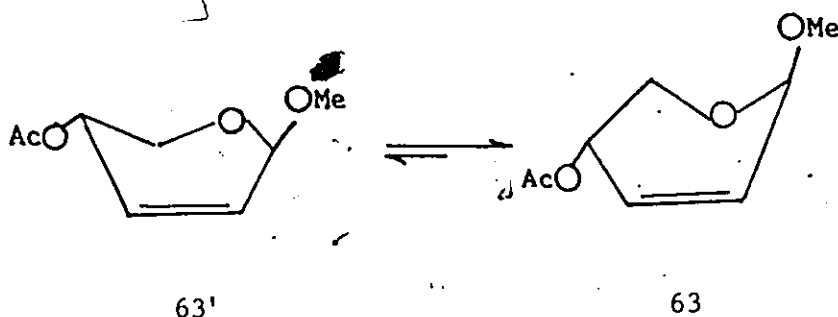
taking into account the well-known weakening of vicinal coupling at the anomeric center, in addition to an inherent inaccuracy of the equation, the observed values of 2.5-2.8 Hz do appear reasonable. Finally it may be noted that, for all of the new 4-substituted α -D-erythro-2-enopyranosides, the vinylic proton signal occurring at higher field was assigned to H-2, while that at lower field was assigned to H-3. The same chemical shift relation was observed by Lemieux and coworkers^{64,65} in the 4,6-acetals 60, 61, 64 and 65, and in the methyl pent-2-enopyranosides 66 and 67; corresponding assignments have since been made for numerous hex-2-enopyranose derivatives^{52,62,68,70}. On the other hand, the relation is the reverse in pent-2-enofuranosides⁶⁵, in some of the aforementioned enopyranosyl phosphonates⁵⁹, and in certain disaccharidic analogs of 29^{60,69,71a}. In compound 29 itself (and also in 45) the vinylic signals happen to coincide*, a phenomenon encountered not infrequently in this series (Table 3 and refs. 58 and 67), and it is therefore clear that such shift differences as may be observable are quite sensitive to structural differences. A justification for our mode of assignment derives from the fact that the signal attributed to H-2 (δ 5.8 \pm 0.1) incurred little change from the resonance position in 29 (δ 5.86), whereas a downfield shift to δ 6.15 \pm 0.15 was evident for the other signal, which could therefore be allocated to H-3, the proton vicinal to the site of chemical modification.

*See p. 47 for footnote

* Because of this coincidence in 29, the protons H-3, H-2, and H-1 constitute an AA'X system, as do H-2, H-3, and H-4. Hence, H-1 and H-4 are expected to give multiplets with splittings arising from averaging of the coupling constants involved. The two narrow parts of the wide H-4 doublet ($J_{4,5} = 9.2$ Hz) each appeared as crude quartets with a line separation of ~ 0.7 Hz. Line separation in the H-1 multiplet ($W_H = 3.6$ Hz) was ~ 1.2 Hz. Calculation shows that these patterns can arise from estimated coupling constants as given in Table 3. These constants are compatible with the geometry of a flattened 0H_5 conformation approaching the D_5 form.

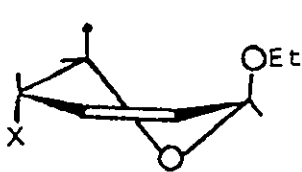
In compound 45, the vinylic protons also coincided and the situation is, therefore, analogous. The two constituent parts of the H-4 doublets were quartets with a line separation of ~ 1.2 Hz, whereas H-1 gave a quartet with a line separation of 0.8 Hz. We have calculated approximate splittings as may be expected for the six conformations A-F, using estimated coupling constants that seemed reasonable for the respective, dihedral angles; eq. (14) was used for calculating $J_{1,3}$ and $J_{2,4}$; and values reported in this paper and elsewhere (52, 60, 64, 65 and 71) were taken into account for choosing $J_{1,2}$, $J_{1,4}$, and $J_{3,4}$. The resultant splittings ranged from 0.3 to 1.7 Hz for H-1 and from 0.5 to 1.9 Hz for H-4, but none of the sets of values so derived for each individual conformation corresponded well with the actually observed pattern. However, the data were accommodated by a 1:1 equilibrium of the S_D form (calc. splittings: H-1, 0.5; H-4, 1.9 Hz) and the D_5 form (calc. splittings: H-1, 1.0 Hz; H-4, 0.5 Hz).

An evaluation of the spectra of the β -glycosides 52-55a obtained from the β -D-erythro-enoside 45 (or 45a in the case of 55a) must begin with a consideration of 45 itself. This deserves to be done in some detail as it is pertinent also to the discussion of optical rotations that will be presented in a subsequent section. For some 2-substituted analogs of 45, namely, certain β -linked D-erythro-hex-2-enopyranose derivatives bearing an acetoxy group at C-2, the inverted 5H_0 half-chair conformation ^{71b,72} or a flattened version approaching the



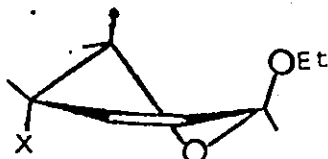
closely related 5D sofa conformation ⁶⁰ have been deduced from nmr data. No doubt the nonbonded interaction existing in such compounds, between the vinylic substituent and the neighboring, quasi-equatorial β -anomeric group [the $A^{(1,2)}$ strain ⁷³] contributes jointly with the anomeric effect to destabilization of the normal 0H_5 half-chair and favors inversion, overcoming opposition by a C-1,5 syn-diaxial-type substituent interaction (which in half-chair conformations is diminished anyway). No such opposing interaction is present in alkyl 4-O-acetyl-2,3-dideoxypent-2-enopyranosides, e.g. 63 and 67, which

on the strength of the anomeric effect alone prefer a conformation wherein the anomeric group is pseudoaxial rather than one wherein it is pseudoequatorial (63' and 67')^{65,67}. Although in 45 the anomeric effect could be anticipated to favor a similar conformation, it was more difficult to predict whether 1,5-substituent interaction would significantly counteract. The spectrum of 45 showed the H-4 signal as a doublet of narrow multiplets at δ 5.21. The largest spacing (5.0 Hz) was mirrored in the upfield multiplet given by H-5 and hence represented $J_{4,5}$. This coupling immediately revealed a substantial deviation from the 0H_5 or D_5 forms (formulas A and B) in which the α -glycosides were



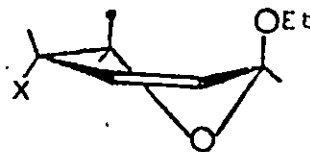
5H_0

D



5D

E



D_0

F

found to reside, and for which $J_{4,5} = 9-10.5$ Hz. On the other hand, the value appeared too large to be compatible with the inverted conformations 5H_0 , 5D , and D_0 (formulas D-F) where $\Phi_{4,5}$ is in the range $60-90^\circ$ and $J_{4,5}$ should therefore be only 1-3 Hz. A possibility is the 0D sofa form (formula C) with $\Phi_{4,5} = 150^\circ$, but, as the sole representation of 45, this is deemed unlikely for it does not have the benefit of the anomeric effect. Unfortunately, the small, additional splittings observed in the H-4 signal and those present in the H-1 signal could not be used to decide the matter. However, the data were consistent with the assumption that 45 exists as a conformational equilibrium to which an inverted form such as 5H_0 or 5D makes a large contribution[†].

[†] See page 47 for footnote

Now, the spectra of the β -glycosides 52-55a paralleled that of 45 in that they all displayed similar $J_{4,5}$ values, with those of the C-alkyl derivatives 55 and 55a being even somewhat smaller (~ 4 Hz). In view of the foregoing discussion, this feature was compatible with the β -D-erythro configuration and suggested conformational similarity to 45, with perhaps an increased preference for an inverted form in 55 and 55a. The assigned configuration was supported by the optical rotation of the products (see later), but definitive proof to exclude the β -D-threo configuration could not be obtained from the nmr data alone, mainly because the olefinic proton signals were ill resolved and pertinent J values could not be determined. However, one noteworthy observation relates to a comparison of the C-alkyl derivatives in the two anomeric series (42 and 43 vs. 55 and 55a) with regard to the vicinal $J_{4,7}$ couplings found in the H-4 and sidechain methine proton signals. The most favoured torsional orientation of the C-4^o substituent about the C-4,7 bond should place H-7 antiperiplanar to H-4, allowing the bulky alkoxycarbonyl groups to point away from the sugar ring. In 42 and 43, however, such an arrangement would imply a syn-parallel orientation of one of these groups with the acetoxymethyl group at C-5. To alleviate this, some rotation about the C-4,7 bond appears to take place, resulting in a diminished $J_{4,7}$ value (4Hz). By contrast, there is no such steric encumbrance to be expected for 55 and 55a if indeed they are D-erythro compounds residing in an inverted conformation. In keeping with this assumption, their $J_{4,7}$ values of 9.0 Hz indicated a more

nearly antiperiplanar orientation of H-4 and H-7.

The 3,4-unsaturated glycosides 36 and 56 displayed closely similar over-all patterns of their respective ring proton signals, although H-1 to H-4 were slightly more deshielded in 36. Specifically, they showed nearly identical patterns in their very narrow H-1 signals, their virtually coinciding olefinic proton signals (H-3 and H-4), and their complex multiplets for H-5. Also very similar in shape and width were the complex multiplets given by H-2, except that in 56 the multiplet was doubled by coupling with H-7. A splitting of 9.5 Hz indicated here, too, an H-2,7 anti situation. Very weak H-1,2 coupling (≤ 1 Hz) as observed in 36 and 56 is characteristic for 3-enopyranosides having the α -D-threo configuration whereas α -D-erythro epimers show values of 3.5-4 Hz ^{74,75}.

The parameters for 46 (Table 3) were in fair agreement with data recently given ⁵² for the same compound (but measured in a different solvent). They bear out a flattened ${}^0\text{H}_5$ half-chair conformation, which is in harmony with previous observations ^{71b} of similar conformational behaviour in α -D-threo and α -D-erythro-hex-2-enopyranose systems. Finally, the data for compound 57 whose H-1, H-2, and H-3 signals were clearly separated and visible in the spectrum of the crude mixture of 56 and 57, allowed allocation of the α -D-threo-2-enoside structure to this minor product.

I, B. 2-4 Optical Rotations

The configurational assignments made by spectroscopy were corroborated, and questions that remained open were settled, by the inclusion of arguments derived from comparison of optical rotations, with due consideration of conformational aspects⁷⁶ of optical superposition. Table 4 lists the molar rotations, $[M]_D = [\alpha]_D \times \text{mol. wt./100}$, for chloroform solutions unless indicated otherwise. It is seen that all of the α -D-erythro-2-enopyranosides, whose configuration is secure, are strongly dextrorotatory. This is fully in line with abundant data on analogous molecules found in the literature and conforms to a generality first stressed by Ferrier⁷⁷. As has also been noted previously, it is apparent that the magnitude of $[M]_D$ depends to a considerable degree on the nature and size of the 4-substituent (compare, for example, ref. 65). The relatively low value of the primary amine 37, as compared to the other amines, may perhaps be due to special effects of solvation or hydrogen bonding.

The β -glycosides 52-55a are less dextrorotatory than their α -linked counterparts; in either series the rotations are lower for C-alkylated than for aminated derivatives. However, in the parent diacetates 45 and 29 the difference is very small, and in benzene solution 45 is even more dextrorotatory than 29 (+383 vs. +276⁹), an anomaly that has been suspected⁷⁸ before. Deviations from Hudson's rule of isorotation have also been recognized in (non-acetylated) pairs of anomeric alkyl 2,3-dideoxypent-2-enopyranosides^{65,67} and in 2-acetylated 3-deoxy-

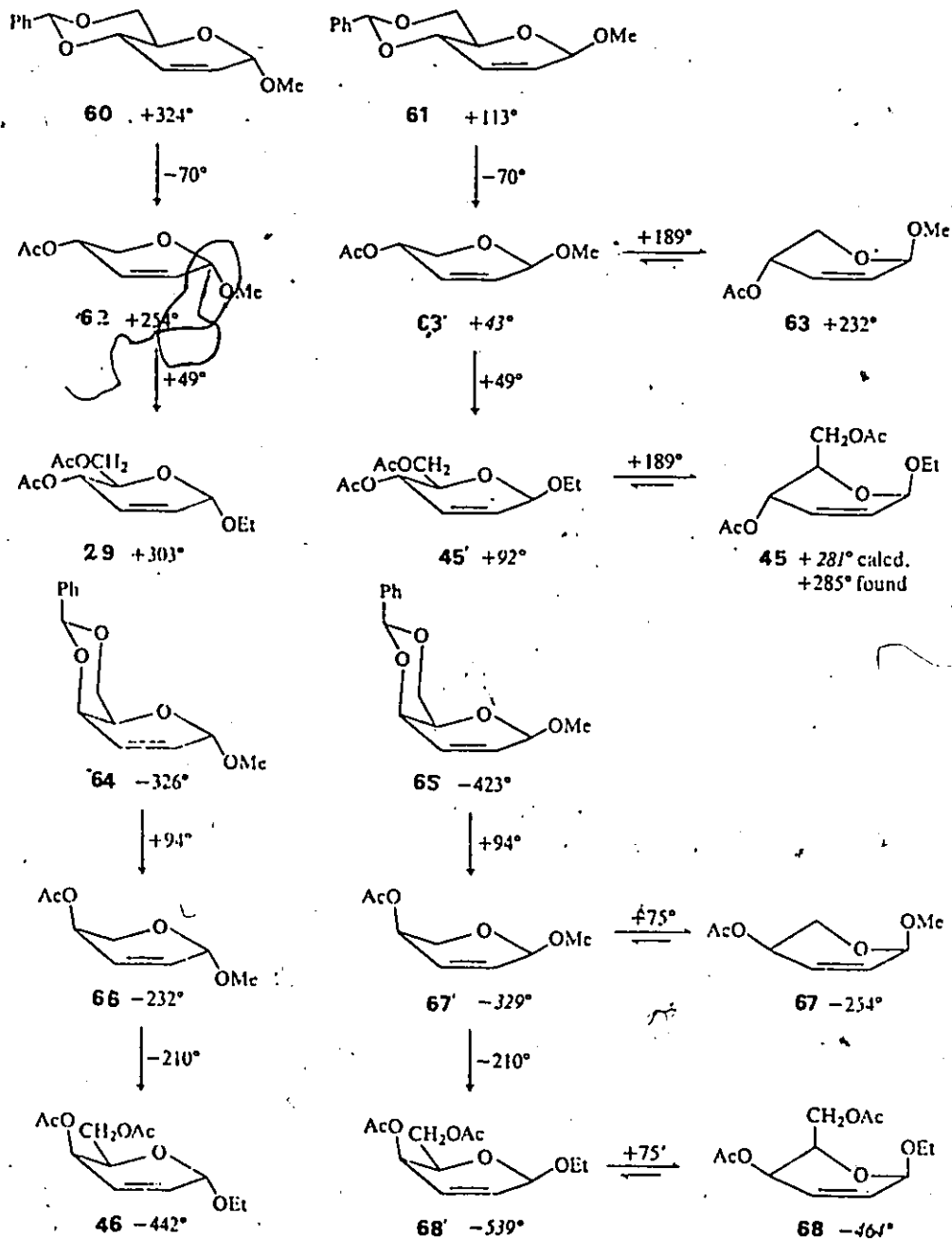
TABLE 4. Molecular rotations of enopyranosides in chloroform.

2-Enosides	Configuration	$[M]_D(^{\circ})$
<u>29</u>	α -D- <u>erythro</u>	+30.3; +276 ^a
<u>31</u>		+460
<u>32</u>		+465
<u>33</u>		+466
<u>34</u>		+527
<u>35</u>		+678
<u>37</u>		+350
<u>39</u>		+448
<u>42</u>		+309
<u>43</u>		+334
<u>44</u>		+305
<u>45</u>	β -D- <u>erythro</u>	+285; +383 ^a
<u>52</u>		+362
<u>53</u>		+376
<u>55</u> ^b		+173
<u>55a</u> ^b		+139
<u>46</u>	α -D- <u>threo</u>	-442
<u>57</u>		-600
3-Enosides	Configuration	$[M]_D(^{\circ})$
<u>36</u>	α -D- <u>threo</u>	+614
<u>56</u>		+330

^a In benzene^b Containing small proportion of isomer(see text)

hex-2-enopyranosides^{71b}. Likewise, the anomeric assignments for the aforementioned hexenopyranosyl phosphonates, originally made on the basis of optical rotations, later had to be revised^{59,79}. The anomalies doubtless are rooted in the conformational behaviour of β -D-glycosides in the enoside family (vide supra). In order to put the choice between the 4-epimeric alternatives for 52-55a on firm ground, and because there is a paucity of analogous β -D-threo derivatives for comparison, it became desirable to examine what sign and range of rotation could be predicted for each of the two configurational possibilities. Fortunately, this could be done with the aid of data, provided by Lemieux^{64,65}, on six securely characterized compounds (the benzylidene derivatives 60, 61, 64, and 65, and the pentosides 66 and 67) in conjunction with our own data on 29, 45 and 46. The argument is illustrated in Scheme 2. Compare the conformationally fixed acetal 60 with the 4-acetate 62 (the enantiomer of 67) that is known to exist in the same, or nearly the same, conformation. The structural alteration entails a rotatory shift of -70° ($[M]_D$ values). An identical structural change in the conformationally rigid, β -anomeric acetal 61 may be expected to cause the same shift, which leads to a calculated rotation of 43° for the conformer 63' of 63. However, compound 63 (the enantiomer of 66) is known to exist predominantly in the conformation having pseudoaxial substituents as depicted, and the difference to its actual rotation of $+232^\circ$, namely $+189^\circ$,

SCHEME 2



Values based on calculation are shown in italics

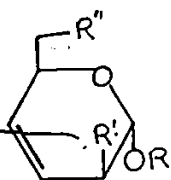
therefore represents the sum total of optical changes associated with this conformational equilibration. Now consider the structural alteration $62 \rightarrow 29$, disregarding the optically insignificant replacement of OMe by OEt. Introduction of the 5-acetoxymethyl substituent increases the rotation by 49° . Use of this increment in applying the same manoeuvre to $63'$ leads to a calculated rotation of $+92^\circ$ for $45'$, a conformer of 45 deduced by nmr spectroscopy to be unstable (vide supra). If one now makes the assumption that the equilibration $45' \rightleftharpoons 45$ is attended by a similar optical contribution as the process $63' \rightleftharpoons 63$ and consequently uses the same value ($+189^\circ$) for it, a calculated rotation of $+281^\circ$ is indicated for 45 , in remarkably good agreement⁺ with the measured value of $+285^\circ$. Performance of the same exercise starting with the D-threo acetals 64 and 65 involves the pentosides 66 and 67 as well as the hexenoside 46 and should lead to a good indication of the rotation to be expected for the latter's unknown β -anomer 68 . As the Scheme shows, different parameters apply here for the various transformations. Thus, in $64 \rightarrow 66$, replacement of the fused ring by 4-acetoxy, and in $66 \rightarrow 46$, the introduction of a 5-acetoxymethyl group, produce rotatory changes opposite in sign and different in degree compared to the preceding series. The

⁺ There may be an element of coincidence in this, since the equilibrium constants for $63' \rightleftharpoons 63$ and $45' \rightleftharpoons 45$ are not necessarily the same and, furthermore, application of the same increment ($+189^\circ$) to both equilibrations may not be entirely sound. Nevertheless, a reasonable agreement was to be expected.

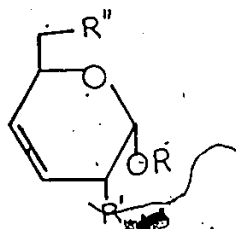
increment for conformational inversion (+75°) is also different. The final result of the exercise is the prediction that β -D-threo compounds of type 68 will be highly levorotatory regardless of conformational preference, and it is therefore evident that 52 - 55a must be β -D-erythro compounds. As an ancillary bonus, the calculations contribute to an understanding why it is inadvisable to rely on Hudson's rule of isorotation for anomeric (as opposed to epimeric) assignments in enopyranoside pairs which are not constrained in the same rigid conformation. Although the rotational differences in such pairs can be fairly large and in the expected direction (Table 4), substituent and solvent influences may cause them to become quite small (even reversed), as exemplified by 62/63, 29/45 and 46/68.

For the 3,4-unsaturated α -D-glycosides 36 and 56 the threo configuration was buttressed, and the erythro configuration rejected, by comparing their specific rotations with those of model compounds found in the literature (Table 5). The product which was formed together with 56 and judged on the basis of ^{13}C -nmr data to be a positional isomer rather than a stereoisomer, but differed from 42 and was therefore assigned formula 57, showed strong levorotation as expected for an α -D-threo-2-enoside.

TABLE 5. Specific rotations of some alkyl hex-3-enopyranosides in chloroform



69a-c
α-D-threo



70a-e
α-D-erythro

Compd.	R	R'	R''	$[\alpha]_D$	(Ref.)	Compd.	R	R'	R''	$[\alpha]_D$	(Ref.)
<u>36</u>				+155.3	(^a)	<u>70a</u>	Me	OBn	OBn	-30	(57)
<u>56</u>				+100	(^a)	<u>70b</u>	Me	pNO ₂ BzO	pNO ₂ BzO	-57.7	(80)
<u>69a</u>	Me	OBn	OBn	+44	(51b)	<u>70c</u>	Me	OH	OCH ₃	-11.3	(80)
<u>69b</u>	Me	OH	OCH ₃	+38	(80)	<u>70d</u>	Me	OMs	OCH ₃	-28.5	(80)
<u>69c</u>	Et	SCSMe O	OCSMe S	+50	(81)	<u>70e</u>	Et	SCSMe O	OCSMe S	-100	(81)

^a This work

I, B. 3. DISCUSSION

The experiments described in the preceding section have established that palladium-catalyzed, allylic substitution can be used as a convenient, high-yielding route to amino and branched-chain carbohydrates. With the pronounced regio- and stereoselectivity observed in most of the substitutions of the D-erythro 2-enoside substrates 29 and 45, the methods represent a valuable addition to the arsenal of tools for specific carbohydrate modifications. The finding that substitution normally occurred at C-4 of the pyranose ring was particularly welcome in view of the fact 4-amino sugars are far less readily accessible through other, general methods than are 2-amino sugars. The results provided encouragement to apply this reaction as a key step towards the synthesis of certain 4-amino sugars of known or potential, biological interest, as will be shown in sections I, C and I, D. Possibilities for similar applications are numerous.

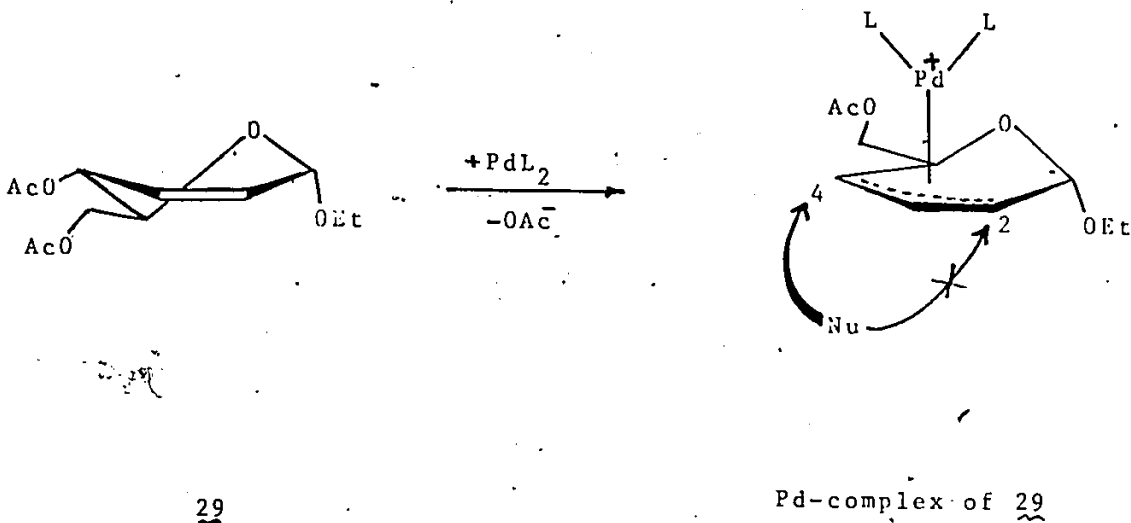
Although this investigation was focused primarily on the introduction of a new synthetic procedure into carbohydrate chemistry, and although its essential results were straightforward and in accord with expectations derived from knowledge of the reaction as developed in general organic chemistry, some questions which invite discussion emerged during the work.

First of all, it became clear that all allylic acetates are not equally suitable substrates. Thus, the reaction failed with the glycols 28 and 72, and with the 4-enosides 73 and 74, all of which have in common an enol ether structure. Enol ethers quite generally resist Pd⁰ — directed substitution under standard conditions^{43,84*}, and it is assumed that the reason is their reluctance to form the initial, requisite π -olefin complex (see eq.(2), p.13). Whereas an electron-withdrawing substituent facilitates complexation, an electron-donating one greatly hampers it because it renders more difficult the back-donation of electron density from palladium to the π -orbital⁸². (Recently, some simple enol ethers that had previously failed to react have been successfully alkylated by use of reactive-methylene compounds in the presence of diazabicycloundecane in hot toluene^{84,85}. Perhaps this variant might prove applicable to the above sugar enol ethers, too).

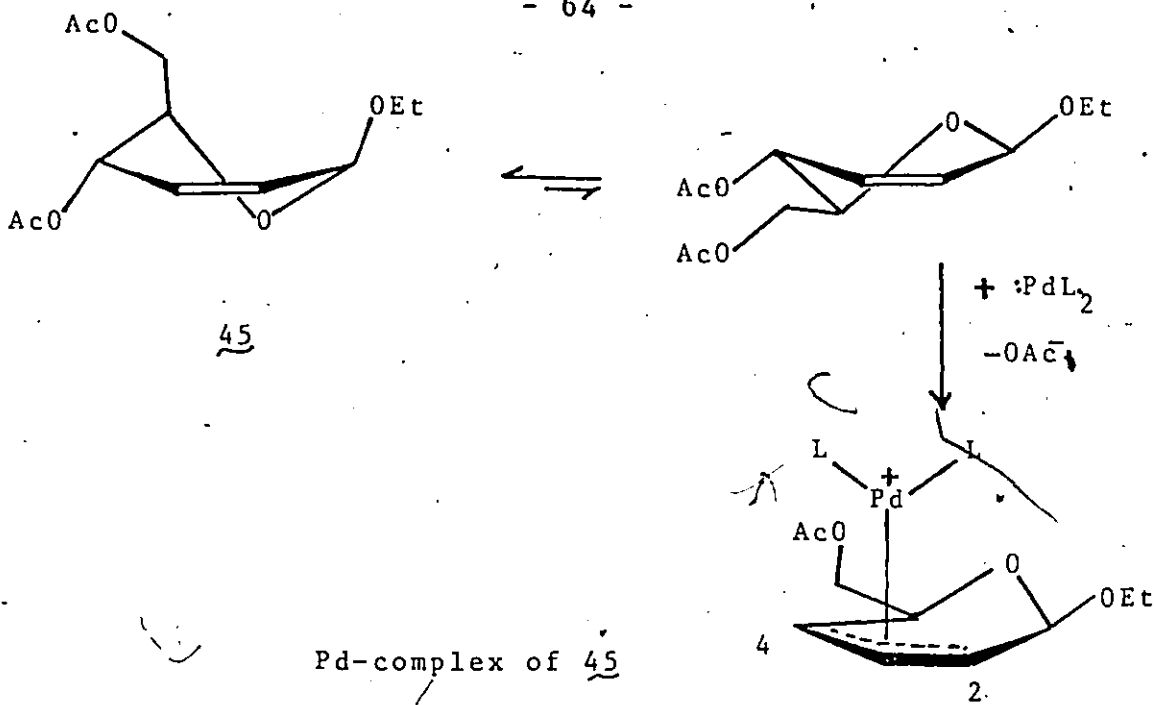
Turning now to the D-erythro 2-enosides 29 and 45, which underwent substitution smoothly, it transpired that, except for the reactions with dibenzylamine (to be discussed later), the favored products were 4-substituted 2-enosides having the original configuration. In fact, according to tlc and nmr evidence the α -glycoside 29 in almost all of its reactions gave single isomers accompanied, at most, by traces of slow-moving impurities. Only in amination with benzylmethylamine and in alkylation with

methyl phenylsulfonylacetate was a second, but minor, product detected in the crude reaction mixtures. These by-products could not be identified; they may have been isomers signalling a somewhat diminished selectivity in these particular instances, or they may have been other (unknown) transformation products. It seems evident that the palladium catalyst species, in forming the π -allyl complex of 29, places itself on the β -face of the pyranose ring, opposite the acetoxy group it is displacing. It is then in turn displaced by the nucleophile approaching C-4 from the opposite direction, with resultant net retention of configuration. This sequence of events is in accord with the general understanding of this interaction ⁴². As regards the regioselectivity of the nucleophilic attack, the clear preference for C-4 may in large measure be due to polarization of the

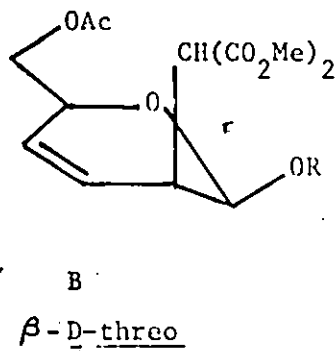
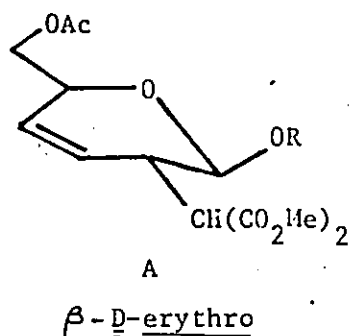
π -allyl complex by the electron-withdrawing, inductive effect of the anomeric center (C-1). Steric hindrance to nucleophile approach at C-2 by the neighboring, quasi-axial glycoside group might at first sight have been invoked as a contributory factor since selectivity was indeed most pronounced for the reactions of the α -glycoside 29. However, if this factor played a role it cannot have been a very important one since selectivity was quite similar in the β -glycoside 45, at least as far as aminations were concerned. With dimethyl malonate, 45 (and its methyl glycoside analog 45a) also gave predominantly



the corresponding 4-substituted, D-erythro 2-enoside (55 and 55a, respectively). On the whole, therefore, the β -glycoside 45 behaved like its α -anomer 29, and one has to conclude that it forms a conformationally similar palladium complex, as depicted, even though free 45 exists to a large extent as an inverted conformer in conformational equilibrium (see p.56). In this complex, nucleophilic attack from the lower side of the molecule at C-2 should encounter no steric impediment, and yet, products resulting from attack on C-4 only were clearly identified. It is true, though, that the 4-C-malonyl derivatives 55 and 55a were each accompanied by a noticeable, if small, proportion of an



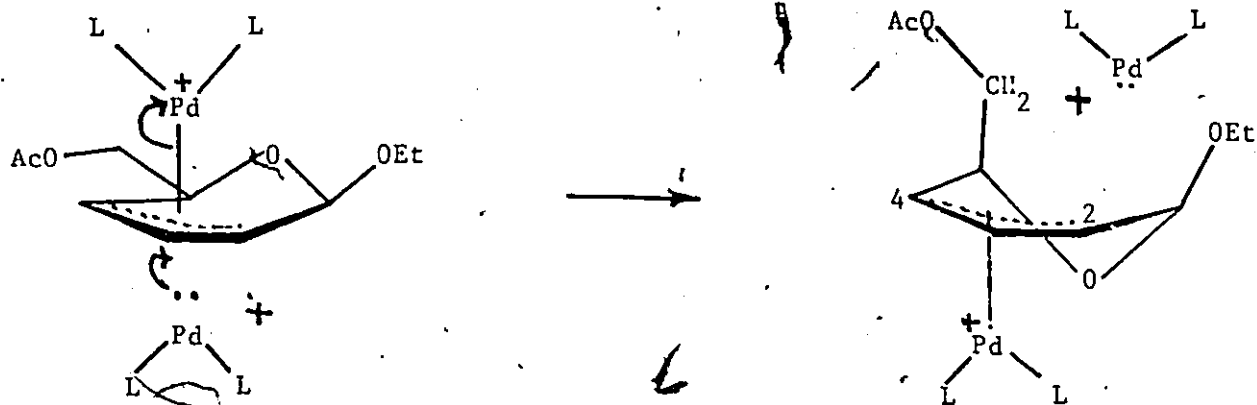
isomer that spectroscopic analysis suggested to be a 2-substituted 3-enoside (see pp.34 and 39). The configuration of these minor by-products could not be convincingly established as the compounds were not isolable, which precluded detailed analysis including the measurement of optical rotation. Based on the discussed mechanism the prediction would seem reasonable that the by-products should possess the β -D-erythro configuration (A), i.e., should have originated from lower-side attack at C-2. However, some ^{13}C -nmr data could tentatively be interpreted in favor of the β -D-threo configuration (B). How would the formation of such stereoisomers be explicable? The alternative mechanism, which proceeds via attack of the nucleophile at the metal followed by its internal transfer (see p. 15), is infrequently



Possible configurations of the minor by-products of 55 (R=Et) and 55a (R=Me)

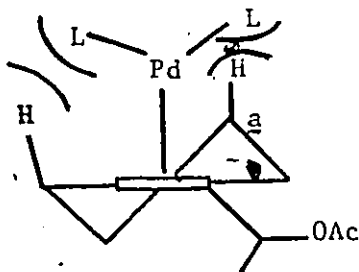
invoked and seems to apply mainly to reactions involving carbanions that are less-highly stabilized than malonate^{87,88}. Moreover, an assumption of that mechanism would beg the question why a nucleophile initially attached to the metal atom in the 45-complex should be delivered internally to C-2, in preference to C-4 which is the prevailing site for intermolecular attack. (A 4-substituted D-threo-2-enoside as would result from internal delivery to C-4 has never been detected, neither in reactions with 45 nor in those with 29.) An answer to that question is not easy to see, and it is perhaps more appropriate to consider the following possibility. It is conceivable that, in certain circumstances, an isomerization of the palladium complex competes to some degree with the normal course of events. Thus, in 45, an exchange of palladium with concomitant conformational inversion* might occur as follows:

* See footnote next page



*

It has been pointed out by Trost and coworkers^{42,86} that complexation in cyclohexene derivatives such as the one shown below is encumbered by repulsive, syn-diaxial interactions between ring hydrogen atoms and the bulky PdL₂ species. If, as in our pyranosides, the most serious of these interactions (at position a) can be avoided by adoption of the proper conformation, complex stability should be enhanced. Moreover, coordination^{86a} between palladium and a syn-oriented ring oxygen atom can then contribute to stability.

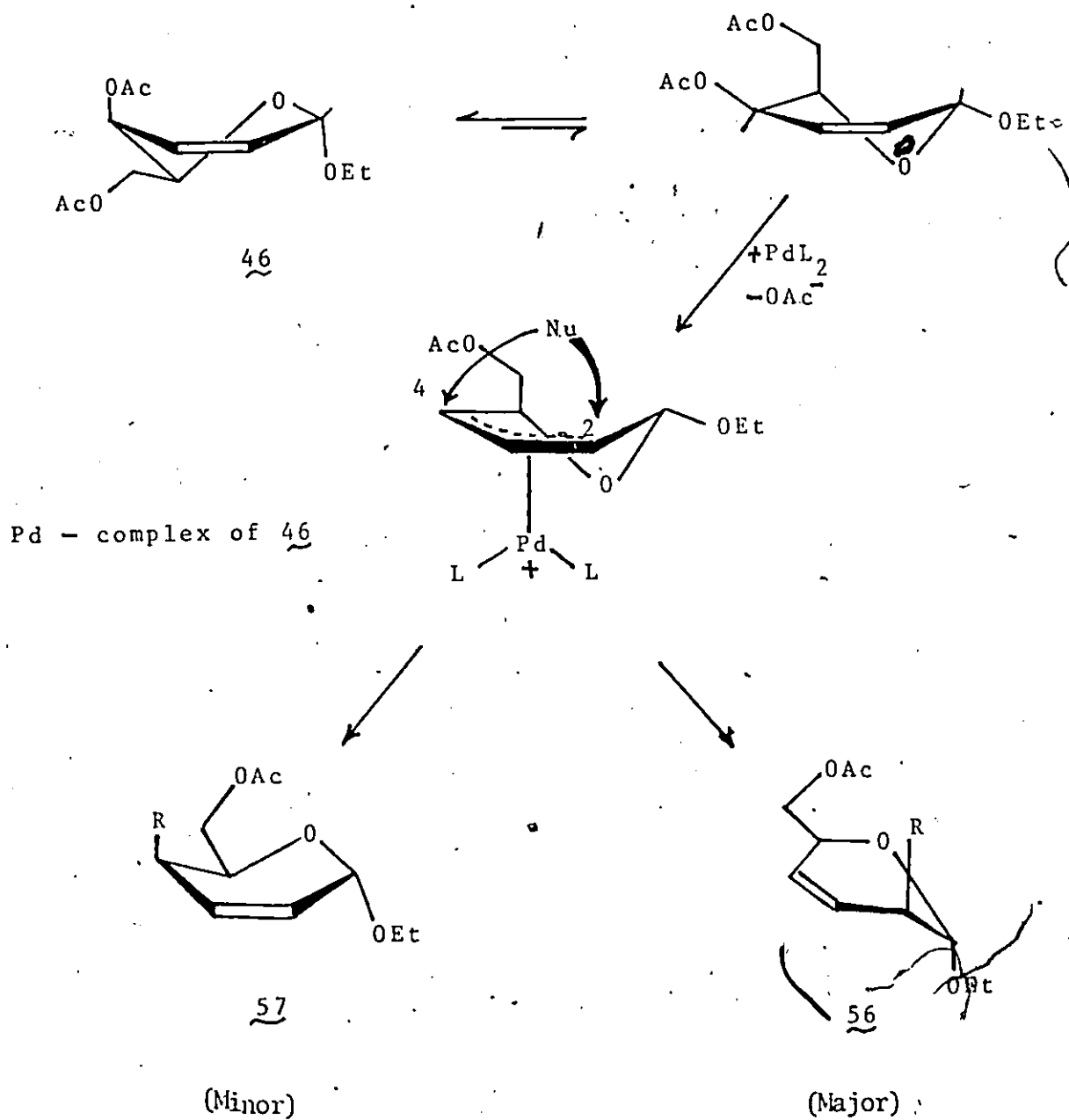


In the configurationally and conformationally isomerized complex, nucleophilic addition from the face opposite the metal should be strongly influenced by steric features which direct it towards C-2: Approach to the respective, vicinal positions 4 and 2 is expected to be hindered much more severely by the axial acetoxymethyl carbon than by the pseudoaxial oxygen atom.

The α -D-threo 2-enoside 46 provided an interesting contrast to the two foregoing isomers, in so far as regioselectivity appeared strongly reduced or even lacking completely: Unfortunately, only two substitutions could be performed because of lack of material, and of these, only the first one (with dimethyl malonate) yielded a reasonably clear picture whereas the second one (with methyl phenylsulfonylacetate) could not yet be evaluated stereochemically. Hence, the following conclusions must be regarded as preliminary and should not be generalized before further data become available.

The enoside 46 gave, with dimethyl malonate, a 66% yield of an approximately 3:1 mixture of regio-isomers (56 and 57) which both had the D-threo configuration, i.e., the nucleophile had arrived in both isomers from "above", at C-2 and C-4 respectively. This was consistent with initial palladium complexation at the lower side of the pyranose ring as required in 46 for displacement of the acetoxy group. One might have wondered whether approach of the palladium species would not be hampered, in this

instance, by the pseudoaxial, α -glycosidic ethoxyl group ⁸⁶, but any such hindrance evidently was not so severe as to prevent complexation. It is suggested that steric relief is gained by conformational inversion as shown:



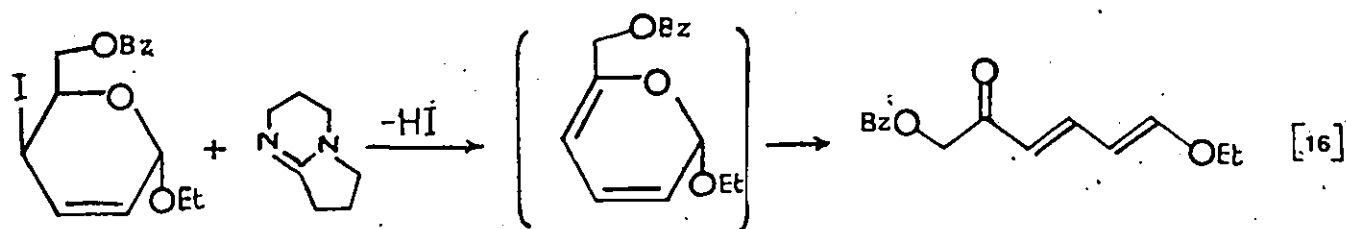
In this complex, the electronically favoured C-4 addition is strongly hindered by the axial acetoxymethyl group while C-2 addition is relatively unencumbered sterically, which would account for the observed isomer ratio.

As regards the alkylation of 46 with methyl phenylsulfonyl-acetate, the mixture of products obtained consisted no doubt of alkylated enosides, according to microanalytical and spectral data. Their ratio was approximately 1:1. It was not possible to separate the components, nor to establish firmly their double bond positions and configurations, the problem being aggravated by the possibility of diastereomerism due to chiral C-7. The products were tentatively formulated as 58 and 59 by analogy. Further work is required to prove these structures and to determine the configurations.

Now the puzzling results obtained with dibenzylamine remain to be addressed. The α -glycosidic enoside 29 afforded the "normal" product (the 4-dibenzylamino- α -~~D-erythro~~-2-enoside 35) and the unexpected 2-dibenzylamino α -~~D-threo~~-3-enoside (36) in a ratio of about 3:7. Had the latter arisen by an internal transfer mechanism⁸⁸, the 4-epimer of 35 should also have been formed, in similar if not larger proportion, as the alternate (and electronically favoured) regioisomer, but it has not been found.

Alternatively, one may consider an isomerization on the π -allyl complex stage as proposed on preceding pages. To whatever mechanism 36 owed its formation, it does not seem fruitful at the present time to speculate as to why it was just dibenzylamine that displayed an exceptional behaviour in its reaction with 29, all the more so as it behaved in a completely "normal" way towards a disaccharidic derivative of 29 (see I,D). One point of possible relevance for the phenomenon is that palladium-promoted allylic aminations (in contrast to C-alkylations) are believed to be reversible^{42,91}; an interplay of kinetic and thermodynamic control might therefore be involved.

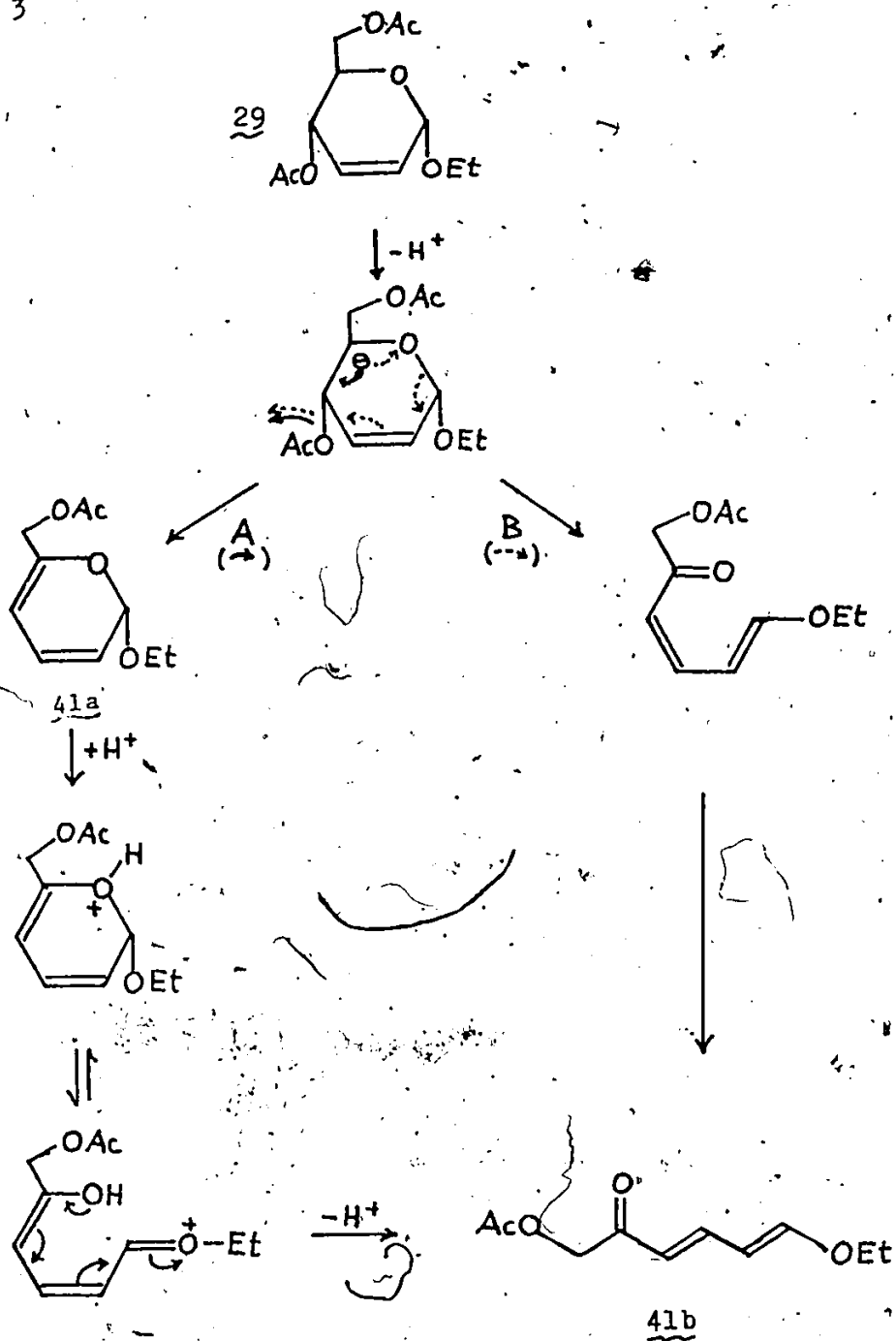
Equally remarkable was the formation of the open-chain aminodienone 54 from dibenzylamine and the β -enoside 45. Before attempting a possible mechanistic explanation, it is useful to remember that there are precedents in the literature^{89,92} for the formation of dienes from allylic acetates under conditions of palladium catalysis. Also during the present work it was noticed that use of diisopropylamine did not lead to amination of 29 (presumably because of the steric bulk of this amine) but gave, instead, the ethoxydienone 41b as a mixture of 3,4-cis,trans isomers. The same happened on prolonged heating of 29 and palladium catalyst in the presence of triethylamine or, indeed, in the absence of any amine. However, the palladium is not necessarily involved in this transformation. Yunker and Fraser-Reid⁹³ obtained the benzoate ester analog of 41b when they treated ethyl 6-O-benzoyl-2,3,4-trideoxy-4-iodo- α -D-threo-hex-2-enopyranoside with



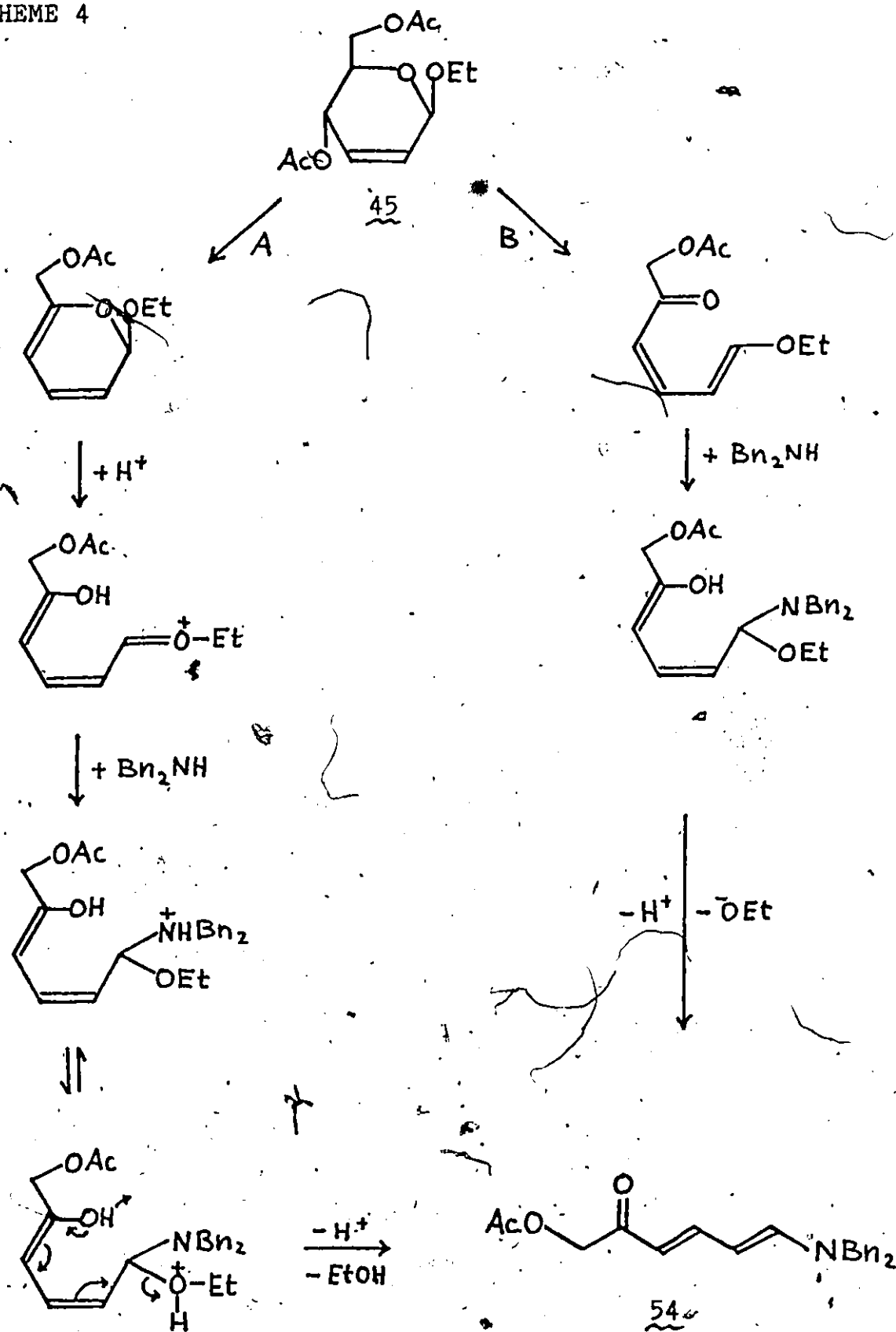
diazabicyclononene, in an attempt to synthesize by dehydroiodination the *o*-benzoyl analog of 41a (eq. [16]). One may assume that these processes are initiated by elimination of acetic acid (Scheme 3, path A), or of hydrogen iodide in the case of eq. [16], to give the pyran derivative as an intermediate which rapidly rearranges to the open-chain dienone. The rearrangement could be catalyzed by protons provided by the acid (or aminium salt) engendered in the initial elimination. An alternative proposal is a concerted process as shown in Scheme 3 (path B). Yunker and Fraser-Reid⁹³ considered both types of mechanism for their dehydroiodination without wishing to commit themselves. At any rate, the easy interconversion of 2H-pyrans and dienones is well documented in the literature⁹⁴.

Bearing in mind the transformations depicted in Scheme 3, it now becomes understandable how 54, the dibenzylamino analog of the ethoxy compound 41b, may have arisen from 45 by the action of dibenzylamine (Scheme 4). The base first causes elimination of acetic acid, which leads either to a pyran (the β -anomer of 41a) on path A, or directly to an ethoxydienone on path B. In either event it is possible to envision subsequent reactions with dibenzylamine leading to replacement of the ethoxy group as shown (Scheme 4).

SCHEME 3



SCHEME 4



I,C. SYNTHESIS OF D-FOROSAMINE

I, C SYNTHESIS OF D-FOROSAMINE

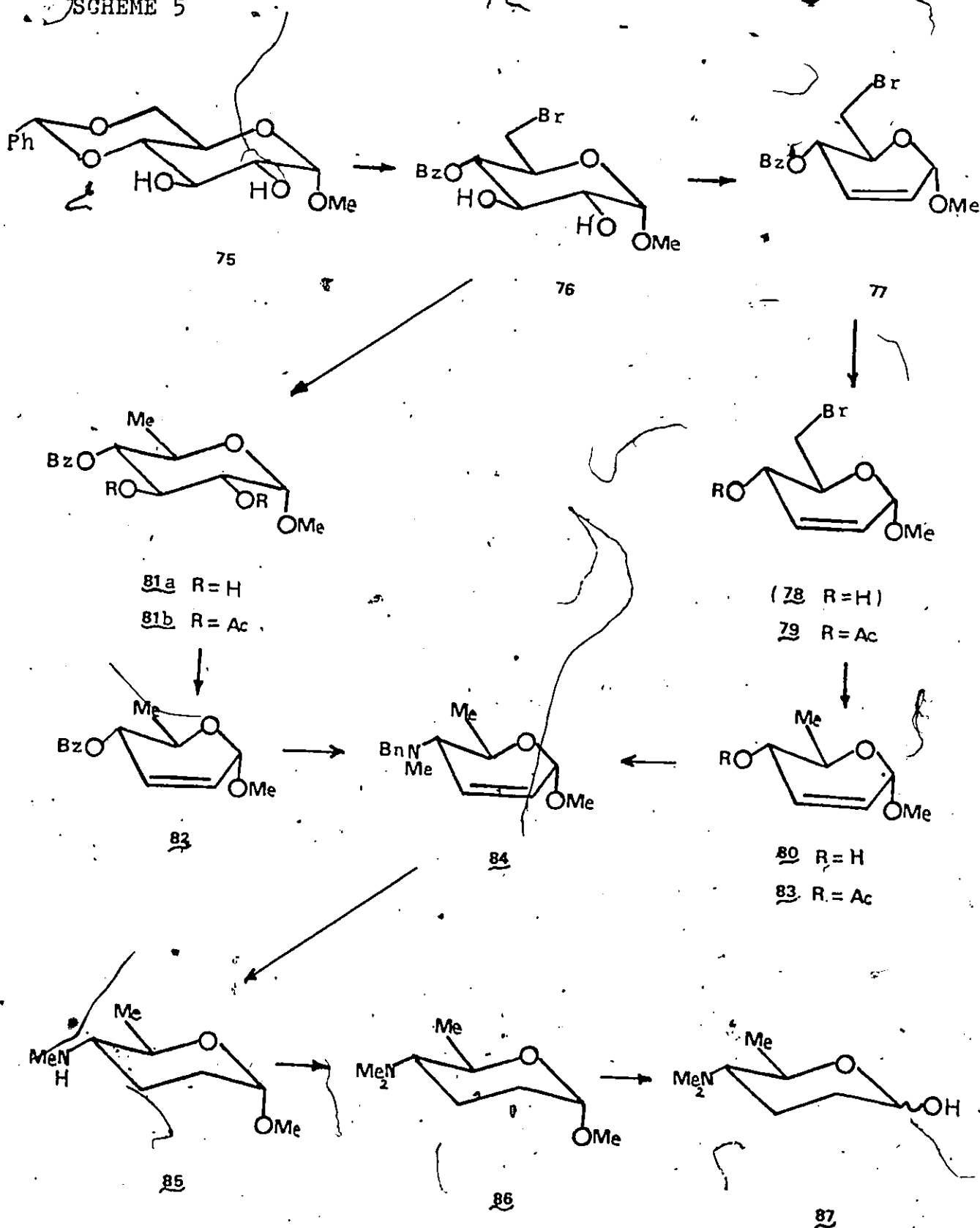
Results and Discussion

The aminopolydeoxy sugar, D-forosamine, is one of the three carbohydrate entities present in the spiramycin (foromacidin) group of macrolide antibiotics isolated from Streptomyces ambofaciens⁹⁶; it has been established^{97,98} to be 2,3,4,6-tetra-deoxy-4-(dimethylamino)-D-erythro-hexose (87). Synthesis of this amino sugar has been reported early by Stevens et al.⁹⁸ and by Albano and Horton⁹⁹. Both groups pursued multistep approaches departing formally from D-glucose, which furnished the amino sugar in very low over-all yields (1-2%). More recently, Dyong and his coworkers¹⁰⁰ accomplished an elegant, total synthesis starting from 2,4-hexadienoic acid (sorbic acid), that provided the sugar in seven steps (including a racemate resolution) with 12% over-all yield.

In the present work, the palladium-catalyzed amination was employed to synthesize the methyl glycoside 86 of D-forosamine in 24% over-all yield from readily available methyl 4,6-O-benzylidene- α -D-glucopyranoside (75). (The hydrolysis of 86 to generate the free sugar 87 has been described previously⁹⁹).

This approach not only appears to compare favourably with the previous syntheses, but it also provides facile access to analogs of forosamine structurally modified at the nitrogen atom.

SCHEME 5



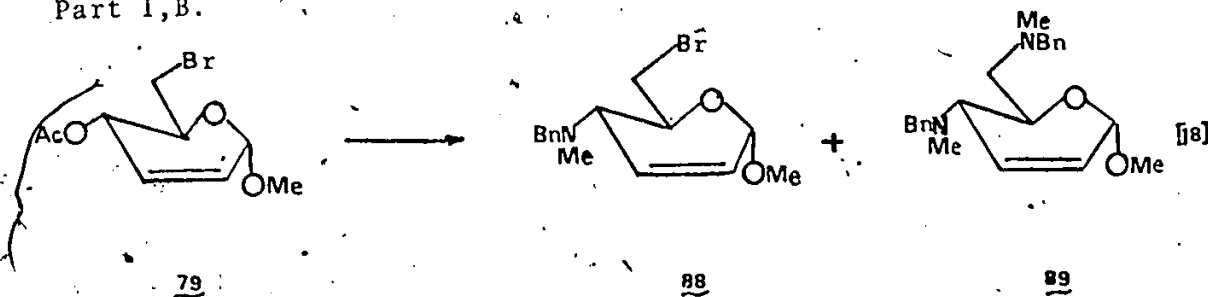
The point of departure was the known compound, methyl 4-O-benzoyl-6-bromo-6-deoxy- α -D-glucopyranoside (76), conveniently prepared¹⁰¹ from methyl 4,6-O-benzylidene- α -D-glucopyranoside (75) by the Hanessian-Hullar reaction (Scheme 5). Obviously, the plan of synthesis called for replacement of the bromine atom at C-6 by hydrogen at some stage on the route to the target molecule, and it was recognized that this could have been performed at the outset, by a reduction as described^{101a}. However, we decided for two reasons to postpone this step until later on.

First, from the viewpoint of assessing the scope and general utility of the palladium-catalyzed allylic amination in different kinds of carbohydrate derivatives we wished to examine whether the method is compatible with the presence of a 6-halogeno substituent. An encouragement in this regard was the recent paper by Trost and Verhoeven⁴² who reported that 3-acetoxy-8-bromo-1-octene can be allylically alkylated with retention of the bromine atom; on the other hand, we did not find in the literature any similar precedent for amination. Secondly, it was thought that, should such amination be successful, the required removal of the halogen atom might advantageously be combined, in a single operation, with a subsequent reductive step that would be necessary for preparing the desired aminopolydeoxy sugar.

Consequently, the bromoalkene 77 was prepared from the bromo diol 76 in 90% yield. This was accomplished by application of the excellent procedure of Garegg and Samuelsson¹⁰², which employs the reagent system triphenylphosphine/2,4,5-triodoimidazole/imidazole. Performing the reaction on a 20-g scale we found it somewhat cumbersome

to to prepare 77 in entirely pure state, i.e. free from triphenylphosphine oxide; complete removal of the contaminant from an analytical sample required preparative thin-layer chromatography. However, this difficulty was of little consequence, as thorough purification proved unnecessary for performance of the next step; actually, it was found advisable to proceed without undue delay, using partially-purified 77, because the isolated compound showed only limited stability on the shelf. Saponification of the benzoate ester 77 with triethylamine followed by acetylation of the intermediary alcohol 78 (which was not characterized) afforded the crystalline acetate 79. Although this ester 79, too, was rather unstable at room temperature, its structure and purity were confirmed spectroscopically. However, the acetate 79 could be stored for prolonged periods at -20° . The over-all yield of 79 from 75 was about 60%. This yield was increased when the crude 76 was used for the next step without purification, in which case a 92% yield of crude 77 and therefrom, an 80% crude yield of 79 was obtained. It decreased to 65% on purification by column chromatography.

The allylic acetate 79 was treated with benzylmethylamine in the presence of triphenylphosphine and a catalytic amount of tetrakis-(triphenylphosphine)palladium(0) by the method delineated in Part I, B.



Processing of the reaction mixture gave two aminated compounds that were separated by preparative thin-layer chromatography (eq. [18]). The less-polar product proved to be the desired 6-bromo-4-(N-benzyl)-methylamino glycoside 88 and was isolated in 37% yield. The more-polar product, revealed to be the bromine-free, 4,6-di[(N-benzyl)methylamino] derivative 89, was obtained in 55% yield. Two by-products having intermediate chromatographic mobility amounted to only a few milligrams of material and were not identified. In full analogy to the aminations of the 6-acetoxy derivatives reported in Part IB, this experiment indicated that a very high degree of regio- and stereoselective, allylic amination at C-4 can be achieved in the bromo glycoside 79. However, the large amount of nucleophilic substitution which concurrently took place at C-6 defeated this venue as a high-yielding approach to monoamino sugars of the forosamine type, although further work along this line might provide a useful route to certain 4,6-diamino sugars. In view of the moderate yield of 88 it was decided to perform a reductive debromination prior to amination.

Treatment of the unsaturated bromo sugar, 79 with lithium triethylborohydride in tetrahydrofuran smoothly removed the bromine¹⁰³ atom as well as the 4-O-acetyl group while leaving the alkene function intact. Known^{104,105} methyl 2,3,6-trideoxy- α -D-erythro-hex-2-enopyranoside 80 was obtained in 93% yield (or 56% over-all

yield from 75). It is noteworthy that compound 80 had previously been prepared¹⁰⁵ from 75, in 15-20% over-all yield, via the 75-dimesylate in a sequence involving the Hanessian-Hullar reaction, reduction by zinc-copper couple, and reductive elimination, employing a modified, Tipson-Cohen procedure¹⁰⁶. On the other hand, the ethyl glycoside analogous to 80 has been synthesized¹⁰⁵ in 3 steps (and 70% yield) from the corresponding 4,6-diol, but the latter needs first to be prepared by the Ferrier method, from tri-O-acetyl-D-glucal, which is considerably more expensive than 75.

The facile synthesis of 80 superseded an alternative approach which was concurrently examined in a preliminary way. Reductive hydrogenation of compound 76 with zinc-copper couple in warm acetic acid led to the 6-deoxy-D-glucoside 81a (65%), which was characterized as its 2,3-diacetate 81b by spectroscopic analysis. Side-products that tended to arise in this reaction decreased the yield significantly. Nevertheless, the diol 81a was then subjected to olefination¹⁰², producing the unsaturated 4-benzoate 82. The yield was disappointing (~30%) in the one experiment that was performed. Still, in view of the highly successful conversion 76→77 as well as the reported¹⁰² olefinations, appropriate trials might well be expected to lead to improved results. No further work was done along this line, however, as in the meantime the desired key compound 80 had become conveniently available through 77 and 79 as outlined above. A confirmatory Zemplén deacylation correlated the crystalline benzoate

82 with the liquid alcohol 80 (from which it had previously been obtained¹⁰⁵ by benzylation). Physical and spectral data for 80 and 82 were in accord with those reported for L enantiomers¹⁰⁷⁻¹⁰⁹ and racemic forms¹¹⁰.

Quantitative acetylation of the alcohol 80 afforded the 4-acetate 83, and the latter was subjected to palladium-catalyzed amination with benzyl-methylamine. The reaction readily gave the unsaturated, tertiary amine 84, essentially as a single product which, upon purification from traces of contaminants by column chromatography, was isolated in 81% yield. Amination of the benzoate 82 under identical conditions also provided 84 in 80% yield. The reaction was faster than in case of the acetate analog; this is noteworthy insofar as there seem to be few examples for the use of allylic benzoates as substrates in such substitutions⁴². Catalytic hydrogenation of 84 over palladium-on-carbon simultaneously saturated the alkenic bond and removed the N-benzyl group, affording a 72% yield of methyl-2,3,4,6-tetraoxy-4-(methylamino)- α -D-erythro-hexopyranoside (85, methyl N-monodemethyl- α -D-forosaminide). N-Methylation of this compound by use of formaldehyde and sodium borohydride¹¹¹ gave methyl 2,3,4,6-tetraoxy-4-(dimethylamino)- α -D-erythro-hexopyranoside (86, methyl α -D-forosaminide) in 74% yield. The nmr data of this liquid glycoside agreed fully with those reported by Albano and Horton^{99a} who have also described its conversion by acid hydrolysis into the free dimethylamino sugar 87.

The over-all yield of 86 from 75 was 24%.

On account of the results obtained in Part IB, it could be anticipated that the products of amination generated from 79 and 83 would possess the α -D-erythro 2-enoside structure as formulated for 88, 89, and 84. Spectral and optical rotation data provided structural proof for 88 and 89 and also corroborated the assignment of 84 which, of course, rested independently on the unambiguous transformation of the latter compound into known 86. All the data were entirely consistent with those gathered for the numerous analogs and evaluated in Part IB. The following, decisive spectral features may be noted.

The position of the olefinic double bond in the pyranoside rings was made possible by mass spectrometry, which permits one to distinguish between 2,3- and 3,4-unsaturated hexopyranosides on the basis of different fragmentation patterns (see Part IB for more detail). Thus, compound 88, suffered retrodienic fragmentation and showed a strong peak at m/e 203, resulting from loss of bromoacetaldehyde. The same prominent fragment was given by 89 (loss of benzylmethylaminoacetaldehyde) and 84 (loss of acetaldehyde). The precursors 79 as well as 80, 82 and 83 all gave the corresponding fragments due to loss of bromoacetaldehyde and acetaldehyde, respectively. On the other hand, peaks corresponding to loss of methyl formate ($m/e = M-60$), which would have signified 3,4-unsaturation, were absent or very weak. The assignment was further confirmed by the 1H -nmr data (Table 6), which were in excellent

TABLE 6 - PROTON MAGNETIC RESONANCE DATA^a

CON- TAINER	CHEMICAL SHIFTS (δ)										COUPLING CONSTANTS (Hz)									
	H-1	H-2	H-3	H-4	H-5	H-6, 6' or C-Ne	OHc	N-Mc	Others	J _{2,3}	J _{4,5}	J _{5,6}	J _{6,6'}	J _{6,6''}	Others					
27 ^b	4.97m	5.86s	5.40dm	4.07sx	3.44dd, 3.17dd	3.56s			R.00m, 7.45m (ORz)											
28	4.94m	5.82m	5.14dd	3.69dd	3.41dd, 3.16dd	3.56s			2.10s (OAc)											
29	4.87m	5.66dt	6.07dt	4.1 - 3.1m		3.51s			7.28s (Ph), ~3.5 (N-CH ₂ -Ph)	10.5	9.5	8.3	2.7	10.8						
29	4.83m	5.89dt	6.12dt	3.10dd	4.11sp	3.05dd, 2.56dd	3.49s	2.32s	7.31m, 7.24s (Ph), 3.66s (N-CH ₂ -Ph), 3.71d, 3.49d (AB-system of N-CH ₂ -Ph)	10.5	9.7	8.0	1.7	13.7						
29 ^c	4.81m	5.71dt	5.19dt	3.9-3.5m		1.31d	3.42s		2.6 (broad, exchangeable, OH)	10.0		6								
29 ^b	3.65m (H), 5.2-4.8m (M)			4.00dq	1.25d		3.42s		7.95m, 7.40m (ORz), 2.04s, 1.66s (OAc)		10	6.5								
29 ^f	4.92m	5.66dd	5.99dm	5.34dd	4.14dq	1.31d	3.43s		8.05a, 7.45m (ORz)											
29 ^g	4.87m	5.84m	5.07dm	3.92dq	1.24d		3.46s		2.10s (OAc)	10.2	9.2	6.5								
29 ^h	4.79m	5.86dt	6.12dt	2.99dd	3.95dq	1.34d	3.42s	2.24s	7.29s (Ph), 3.72d, 3.54d (AB-system of N-CH ₂ -Ph)	10.5	9.5	6.3								
29 ⁱ	4.65dd	2.3 - 1.4m		3.57dq	1.24d		3.34s	2.44s	1.57s (exchangeable, NH)		9.2	6.3								
29 ^j	4.70m	2.0 - 1.5m	~2.5m	3.80dq	1.23d		3.35s	2.26s				6.5								

^a From 100-MHz spectra, measured at 250-MHz sweep width, of solutions in CCl₄ containing tetramethylsilane, as the internal standard (unless specified otherwise). Signal multiplicities: d, doublet; m, multiplet; nm, narrow multiplet; q, quartet; s, singlet; sp, septet; sx, sextet; and t, triplet.

^b Measured at 60 MHz.

^c The small splittings present in the signals of H-1 to H-4, which represented vicinal (J_{1,2} and J_{3,4}), allylic (J_{1,3} and J_{2,4}), and homoallylic (J_{1,4}) couplings, were nearly the same as those in Part 18 for analogous α-D-erythro-2-cmopyranosides.

^d gem 14 Hz (N-CH₂-Ph).

^e Data in good agreement with those of L enantiomer 109, except for reversed assignment of H-2 and H-3; also in good agreement with those of D/L form measured in CCl₄ solution (where all J-values were lower by 0.1-0.15 ppm).

^f Data in good agreement with those of L enantiomer 107.

^g gem 13.5 Hz (N-CH₂-Ph).

^h Data in full agreement with those from reported 99 60-MHz spectrum.

accord with those of relevant analogs (Part IB). The requisite, large coupling constant $J_{4,5}$ in 89 (9.7 Hz) and 84 (9.5 Hz) proved an axial orientation of H-4 and, hence, the D-erythro configuration. (In 88, unfortunately, the H-4 and H-5 signals were insufficiently resolved to permit analysis). Compounds 88, 89 and 84 displayed the same, characteristic AB patterns for their olefinic protons H-2 and H-3 as were found typical for the 4-aminated, α -D-erythro 2-enopyranosides prepared earlier, with each signal component showing multiplicities due to vicinal ($J_{1,2}$ and $J_{3,4}$) and allylic coupling ($J_{1,3}$ and $J_{2,4}$) as described in Part IB. (In the esters 77, 79 and 83 the olefinic proton signals coincided, as did those of ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside.) Confirmation of these assignments was obtained by the ^{13}C -nmr data (Table 7) that were also fully consistent with those obtained from structural analogs (Part IB). Noteworthy in particular was the narrow range in which the C-1 chemical shifts of all the unsaturated glycosides listed in Table 7 appeared (δ 95.4-95.8). This parameter which appears to be rather sensitive, suggested equality with respect to the position of the double bond and to the overall configuration in these compounds. Finally, but not least significantly, the molecular rotations of 88 ($[\text{M}]_{\text{D}} + 584^{\circ}$), 89 ($[\text{M}]_{\text{D}} + 560^{\circ}$), and 84 ($[\text{M}]_{\text{D}} + 521^{\circ}$) agreed satisfactorily with that of ethyl 6-O-acetyl-4-(N-benzyl)-methylamino-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside ($[\text{M}]_{\text{D}} + 527^{\circ}$) (34 in Part IB). This fact alone ruled out the opposite configuration at C-4 since alkyl α -D-threo-hex-2-enopyranosides exhibit strong levorotation.

TABLE 7

¹³O-chemical shifts (ppm from tetramethylsilane)³

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OMe	NMe	NCH ₂ Ph	C=O	COMe	Ph
77	95.8	128.5	129.8	68.9	70.0	45.5	56.6			165.8		128-129, 133.5
79	95.7	127.9	128.8	68.8	69.5	5.4	56.5			170.2	21.0	
88	95.7	128.4	128.6	61.5	67.9	9.1	56.0	38.1	59.8			127-129, 139.1
89	95.4	128.1	128.6	59.1	67.5	62.5	56.0	38.0, 43.2	58.5, 59.1			127-129, 139.5
80	95.4	126.2	133.9	66.0	69.5	18.0	55.6					
82	95.5	128.4	129.7	65.0	71.3	18.1	55.8			166.0		128-130, 133.2
83	95.4	127.7	129.8	64.8	70.9	18.0	55.8			170.6	21.1	
84	95.5	128.2	128.6	62.8	64.4	18.9	55.4	33.2	58.6			127-130, 139.7
85	97.5	24.2	29.6	61.2	58.9	18.7	54.3	33.7				

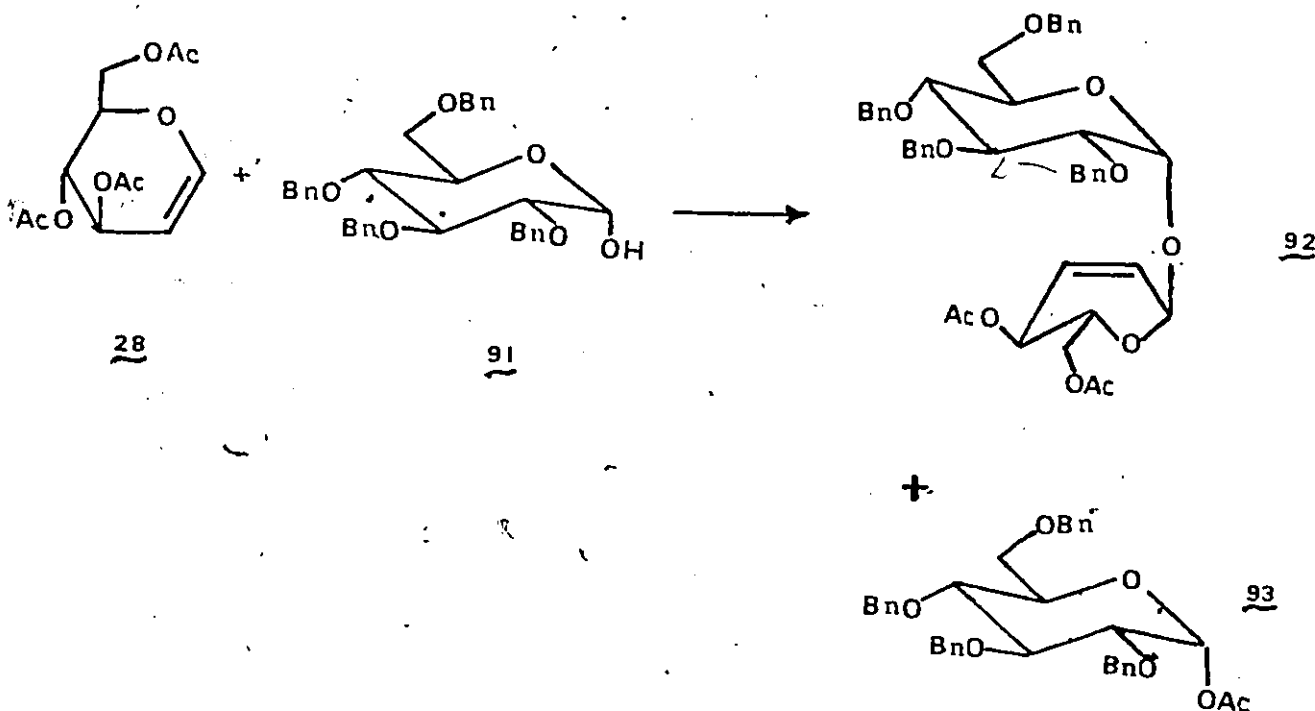
From spectra of chloroform solutions. The signal multiplicities observed in proton-coupled spectra were taken into account for making assignments. In the compounds bearing an aromatic substituent, the two signals of highest intensity in the range of 127-130 ppm were attributed to the alkenic atoms C-2 and C-3, and the remaining signals were assigned to the aromatic ring carbons. In the other compounds C-2 and C-3 gave similar, high-intensity signals.

I, D - SYNTHESIS OF NEW AMINO
DERIVATIVES OF α, α -TREHALOSE

Having established, in Parts IB and IC, the utility of the palladium-catalyzed, allylic substitution for the synthesis of various, aminated monosaccharides, we decided to examine a possible application of the method to the preparation of amino disaccharides. The field of trehalose chemistry was selected for this exercise. This choice suggested itself because of the great biological importance of α, α -trehalose (α -D-glucopyranosyl α -D-glucopyranoside) and the broad interest that exists in the synthesis and biochemical evaluation of many kinds of trehalose derivatives and analogs¹¹². Amongst the known amino derivatives of particular interest are 2-amino-2-deoxy-¹¹³ and 4-amino-4-deoxy- α, α -trehalose¹¹⁴, which are naturally occurring antibiotics. The synthetic 6-amino-6-deoxy analog proved antibiologically inactive¹¹⁵, whereas the recently synthesized 3-amino-3-deoxy analog¹¹⁶ has not yet been examined in this regard although it proved to be a substrate for insect trehalases. Furthermore, 3,3'-diamino-3,3'-dideoxy- α, α -trehalose and the corresponding D-gluco, D-manno and D-manno, D-manno stereo-isomers were recently obtained by synthesis in this laboratory¹¹⁷, and the last-mentioned isomer was found¹¹⁸ to be a potent inhibitor of Mycobacterium tuberculosis. Consequently, it was reasoned that new, modified compounds related to such amino trehaloses might be of potential biochemical or medical significance and that the new amination procedure for sugars might be able to help advance this field of research.

The first requirement for the present project was an α,α -trehalose - type disaccharide possessing an allylic ester moiety and being suitably protected at its sugar hydroxyl groups. It was decided to synthesize the hitherto unknown compound 92 which would display these features. Ferrier's synthesis of 2,3-unsaturated glycosides (see Part IB), which has previously served well in the synthesis of similar disaccharides¹¹⁹, was to be employed for this purpose.

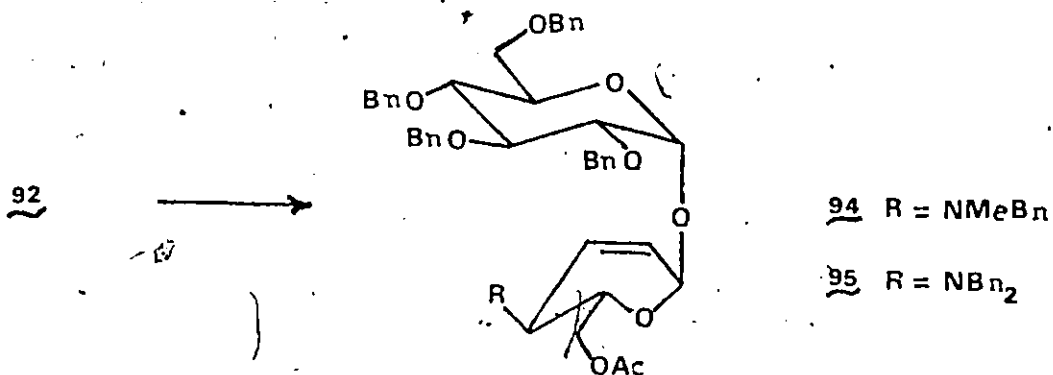
Treatment of a mixture of tri-O-acetyl-D-glucal¹²⁰ (28) and 2,3,4,6-tetra-O-benzyl- α -D-glucopyranoside¹²¹ (91) in dry benzene with boron trifluoride etherate as a catalyst^{47b,c} produced the desired disaccharide 92 in 66% yield; ¹H- and ¹³C- nmr spectra as well as thin layer chromatography gave no evidence for the formation of any other isomer. The reason for the relatively low yield was formation of the by-product 93, produced from part of the alcohol 91 by acetate transfer from 28. The identity of 93 was established on



the basis of spectroscopic analysis as well as through comparison with an authentic sample prepared by a different route. However, use of stannic chloride in dichloroethane⁵² as the catalyst diminished the proportion of this side product significantly and increased the yield of the desired product 92 up to 93%.

Addition of the allylic acetate 92 to a tetrahydrofuran solution of tetrakis(triphenylphosphine)palladium(0) and excess triphenylphosphine at room temperature followed by addition of a solution of methylbenzylamine in tetrahydrofuran led, after refluxing for 30 h, to a 90% yield of a homogeneous amination product 94. The structural assignment of 94 was based on ¹H- and ¹³C - nmr spectra (Tables 8,9) as well as elemental analysis. The stereochemical course of the allylic amination was confirmed by comparison of the spectroscopic data with those of the 6-acetoxy derivatives previously studied (part IB).

In a similar fashion, compound 95 was prepared by use of dibenzylamine as the nucleophile. Again, the structure and stereochemistry of the product was allocated on the basis of spectroscopic data and elemental analysis.



Difficulties were encountered in attempts to perform this reaction on larger scales (> 6 mmol). It was observed in such larger-scale runs that amination of the substrate remained incomplete and dibenzylamine was consumed in a competing reaction to give tetrabenzylhydrazine. Further work is required to clear up the reason for, and obviate the occurrence of, this complication. With sufficient quantities of 95 in hand, it should then be a straight-forward proposition to produce 4-amino-2,3,4-trideoxy- α , α -trehalose by removal of the 6-O-acetyl group followed by catalytic saturation of the alkenic bond and hydrogenolysis of the O- and N-benzyl protecting groups.

TABLE 8

¹H-Magnetic Resonance Data

Compd	Chemical Shifts (δ)							Coupling Constants (Hz)											
	H-1	H-2	H-3	H'-1	OAc	OBn's	Others	J _{1,2}	J _{1,3}	J _{2,3}	J _{2,4}	J _{3,4}	J _{1',2'}						
92	5.76	dt	5.95	dm	5.4	d	2.02	7.30	5.46-5.26 nm, 3H, H-1, H'-1, H-4); 5.04-4.50 (m, 17H)	2	10	1.5	3.5						
							2.06	m											
93			6.36	d	2.11	S	7.29	m	3.33-5.05 (14H)				3.5						
94	5.31	nm	5.84	dt	6.18	dm	5.45	d	1.90	S	7.26	m	3.5-5(m, 20 H) 2.22(s, N-Me)	2.5	~1	10.5	2.5	~2	3.5
95	5.28	nm	5.88	dt	6.27	ddd	5.37	d	1.71	S	7.24	m	3.32-4.92(m, 22H)	2.5	~1	10.5	2.5	2	3.5

TABLE 9
¹³C-Chemical Shifts (ppm from TMS)²

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	C'-1	C'-2	C'-3	C'-4	C'-5	C'-6	CONC	CO	N-CH ₂ -Ph	Others
92	92.89	127.94	127.61	65.04	67.12	62.81	89.71	81.84	79.18	77.57	71.01	68.36	20.96 20.76	170.67 170.19		(72.58, 73.52, 75.22, 75.66) -OCH ₂ -Ph
93							89.97	91.65	78.86	76.94	72.84	68.10	21.04	169.32		(73.15, 73.52, 75.24, 75.65) O-CH ₂ -Ph
94	92.36	127.91	127.39	55.93	66.49	64.34	89.66	81.72	79.39	77.58	70.87	68.45	20.79		58.56	(72.28, 73.17, 75.13, 75.48) O-CH ₂ -Ph; (38.17) N-CH ₂ -Ph
95	92.74	127	128	54.55	66.42	63.30	89.96	81.07	79.32	77.53	70.88	68.44	20.71			(72.31, 73.45, 75.28, 75.44) O-CH ₂ -Ph; (54.78, 53.11) N-CH ₂ -Ph

² Spectra were taken from chloroform solutions. The signal multiplicities observed in proton-coupled spectra were taken into account for making assignments.

PART II

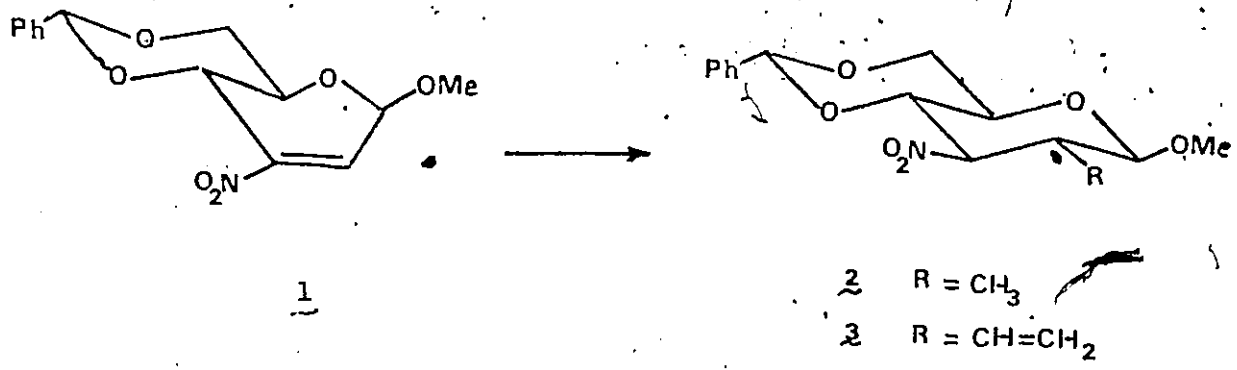
CONJUGATE ADDITION OF LITHIUM
DIALKYLcuprates TO UNSATURATED
NITRO SUGARS

IIA.- INTRODUCTION

In the second part of the thesis, we will examine the possible use of organocopper reagents¹²² as a means of introducing chain-branching in nitrogenous sugars. In recent years, reactions of various types of alkyl- and alkenyl-copper complexes with electrophilic reagents have been employed frequently, to effect C-alkylation. Among the most commonly used electrophiles are organic halides and α,β -unsaturated carbonyl compounds, the latter undergoing conjugate addition reactions to give compounds containing carbonyl groups that are useful in subsequent transformations. In the present study, addition reactions of lithium-dimethylcuprate and lithium divinylcuprate with some nitrohexenopyranosides were investigated. Whereas such reactions had been applied frequently to a large variety of reactive, unsaturated structures¹²², which included some carbohydrate α -enones¹²³, we found only one brief report¹²⁴ referring specifically to nitroalkenes, namely, some β -arylnitroethylenes. It remained to be determined whether nitroalkenes in general and nitroalkenic sugars in particular would be suitable substrates for alkylation by organocuprates. The reaction mechanism still appears to be a contentious issue¹²⁵.

IIB. RESULTS AND DISCUSSION

We decided to investigate reactions of various nitro-olefinic sugars with lithium dialkylcuprates*. The reaction of two molar equivalents of $\text{LiCu}(\text{CH}_3)_2$, prepared from two moles of CH_3Li and one mole of CuI , with methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- β -D-erythro-hex-2-enopyranoside (1) in a mixture of diethyl ether and tetrahydrofuran, initially at -50° and then for 1h at 0° , gave a single product, which was isolated by crystallization in 91% yield. It proved to be methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro- β -D-glucopyranoside (2). In a similar fashion, $\text{LiCu}(\text{CH}=\text{CH}_2)_2$ reacted with the



* These reagents have been shown to be dimeric in ether solution, but will be represented in this text by the stoichiometric composition formula LiCuR_2 where further clarification is unnecessary¹²².

enopyranoside 1 to afford the normal conjugate addition product, the crystalline 2-C-vinyl analog 3, in 68% yield.

Similarly, the β -D-threo enopyranoside 4 gave the β -D-galactopyranoside derivatives 5 and 6, respectively, also in crystalline form. Whereas the yield of 5 was 72%, that of isolated 6 was only 35-40%. These lower yields were due to the formation of a second, major product that was detected in chromatography but could not be isolated as it tended to decompose rapidly.

The reactions of the α -D-erythro hexenopyranoside 7 also were found to be less straightforward than those of the β -anomer 1. With the methylcopper reagent, 7 gave a mixture showing two spots

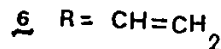
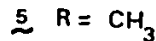
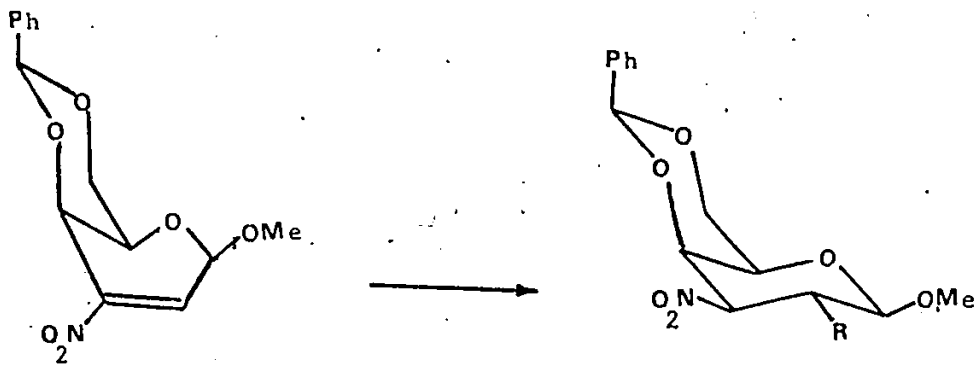


TABLE I
PROTON CHEMICAL SHIFT DATA^a

Compd.	Chemical shifts (s)											
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6e	PhCH	OMe	C-Me	-CH=C	-C=CH ₂
2	4.17d	2.31m	4.48dd	4.14dd	3.46 ^b	3.84t	4.36dd	5.54s	3.51s	1.06d	-	-
3	4.35d	2.93sx	4.69dd	4.16dd	3.52m ^b	3.86t	4.39dd	5.57s	3.51s	-	5.68o	~5.26m (2 H)
5	4.03d	2.68m	4.34dd	4.48dd	3.45m ^c	4.07dd	4.35dd	5.51s	3.50s	1.06d	-	-
6	4.15d	3.32m	4.65dd	4.52dd	3.48m ^c	4.08dd	4.35dd	5.51s	3.48s	-	5.73o	~5.26m (2 H)
8	4.58d	2.76 ^d	5.01dd	~4.3m	(2 H)	~3.9m	(2 H)	5.66s	3.36s	1.06d	-	-
9	6.52dd	4.90dd	5.26dt	~4.5m	(2 H)	~3.9m	(2 H)	5.62	-	-	-	-

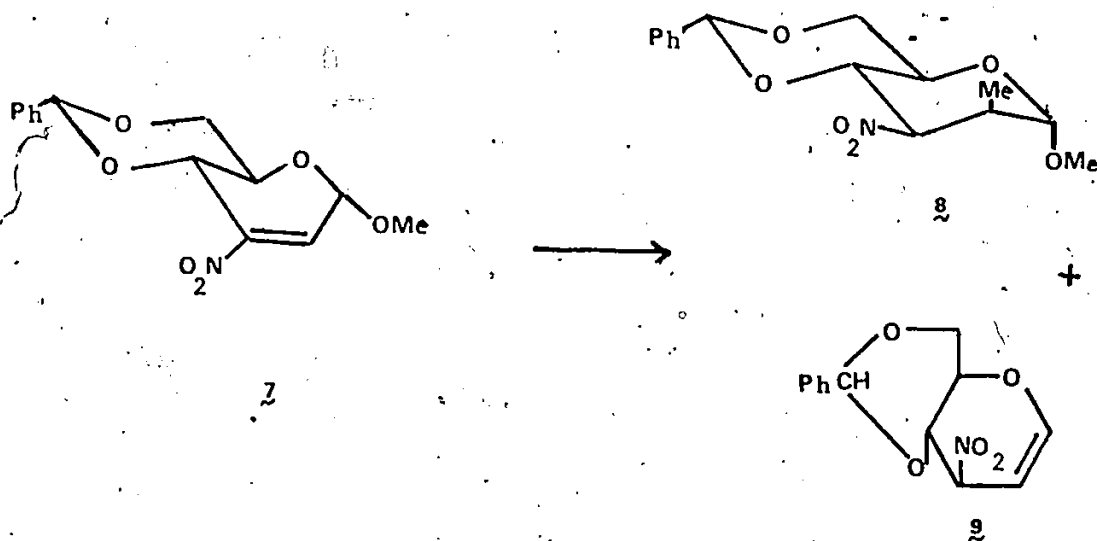
^aFrom 100-MHz spectra, measured at 250 Hz sweep width, of solutions in CDCl₃ containing tetramethylsilane as the internal standard. All spectra showed 5H-signals for the phenyl group near δ7.4. Signal multiplicities d, doublet; m, multiplet; o, octet; s, singlet; sx, sextet; and t, triplet. ^bPartially overlapped by OMe signal. ^cVery narrow. ^dQuintet, with lines broadened by a very small splitting with H-1; total width, 29 Hz.

TABLE II
PROTON-PROTON SPIN COUPLING DATA

Compd.	Splittings ^a (Hz)									
	J _{1,2}	J _{2,Me}	J _{2,Vi}	J _{2,3}	J _{3,4}	J _{4,5}	J _{5,6a}	J _{5,6e}	J _{6a,6e}	Others
1	8.5	6.5	-	11.2	10	9	10	5	10.5	
2	8.3	-	8.3	11.2	10	9	10	5	10.5	J ₁ ^b 16.5, 11.5, ~2
3	8.7	6.3	-	11.5	3.7	1.3	1.7	1.5	13	
4	8.5	-	7.5	11.7	3.8	1.3	1.8	1.6	12.7	J ₁ ^b 18, 9.5, 1.5-2
5	< 1	7.5	-	5.5	10.5					
6										
7										
8										
9					8.5					J _{1,3} ^b 2

^a See footnote a in Table I. ^b trans and cis vicinal, and geminal coupling, respectively, of the vinylic protons.

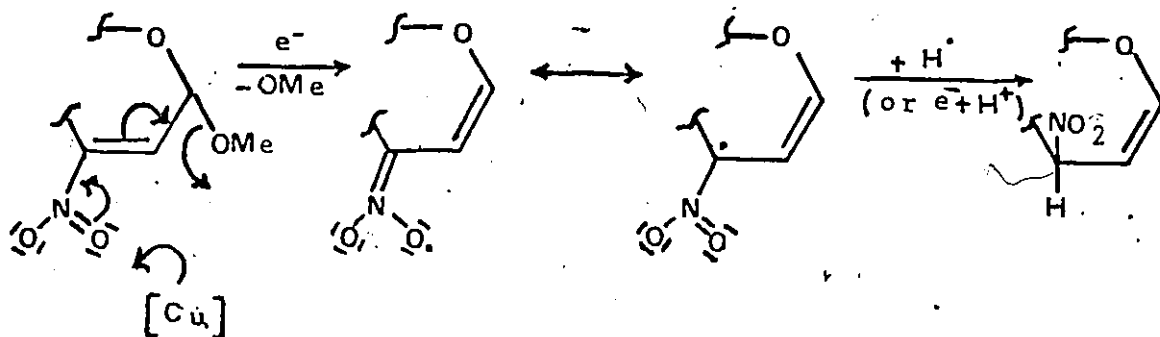
in tlc (R_F 0.7 and 0.6). During processing and preparative tlc, partial decomposition occurred and several additional spots appeared. Nevertheless, the two original products could be separated, and isolated crystalline in yields of 42 and 38%. The compound of R_F 0.6 proved to be the expected addition product, the 2-C-methyl glycoside **8** having the α -D-manno configuration. The other product (R_F 0.7) was revealed by spectral and elemental analysis to be the nitro glycal **9**. It evidently arose from a competing, reductive elimination. It seems reasonable that the process might be initiated by electron transfer^{122e} from the cuprate to an oxygen atom of the nitro group, with concomitant bond shift and departure of methoxide ion; the intermediary, nitronic radical* would upon further reduction yield the nitro



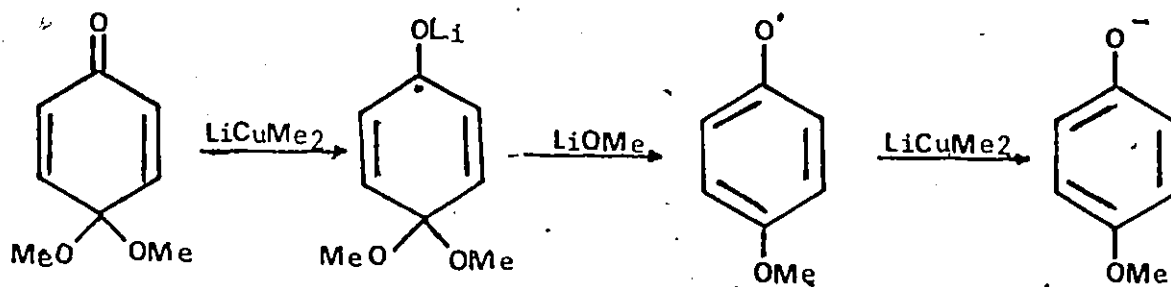
* See pages 138, 139 in Part III for similar postulated intermediates.

compound 9 (Scheme 1). At least one precedent for such an event could be seen in the conversion¹²⁶, by $\text{LiCu}(\text{CH}_3)_2$, of 4,4-dimethoxycyclohexa-2,5-dienone into p-methoxyphenol (Scheme 2) The reaction also recalls the generation of a glycol as a by-product, by the action of $\text{LiCu}(\text{CH}_3)_2$ upon a methyl 2,3-anhydroglycoside¹²⁷, and by attempted hydrozirconation of an enopyranoside*.

SCHEME 1



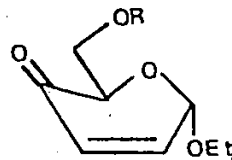
SCHEME 2



*See Part IV of this thesis for more detail

Reaction of the α -glycoside 7, with $\text{LiCu}(\text{CH}=\text{CH}_2)_2$ also gave a mixture of two products (one of which was possibly identical with 9, according to tlc), but the formation of secondary decomposition products during processing frustrated all attempts at separation.

In summary, these experiments have demonstrated that C-alkylation by conjugate addition of lithium dialkylcuprates to nitroalkenic sugars is possible and that it may in some cases be an attractive approach to branched-chain, nitrogenous sugars although formation of by-products in other cases may pose certain limitations. It is noteworthy that in all of the products encountered and characterized in this study, the substituent introduced at C-2 had entered trans to the anomeric methoxyl group, which implies stereospecific approach of the reagent from the less-hindered side of the substrate molecule. The same observation had been made by Fraser-Reid and his coworkers¹²³ in lithium dialkylcuprate additions to hex-2-enopyrano-4-ulosides (10). The stereochemical result is also in accord with earlier observations showing the same directive effect of the anomeric configuration in various, kinetically-controlled, nucleophilic addition reactions of the same and similar substrates^{32,33,128,129}. (By contrast, the stereochemistry of addition of diazomethane to 1, 4 and 7 appears to be governed³⁹ by the C-4 configuration.)



II C. ASSIGNMENT OF STRUCTURE AND CONFIGURATION

The structure of 2 was assigned on the basis of readily interpretable infrared and nmr spectra. The infrared spectrum indicated the presence of an unconjugated nitro group (ν_{\max} 1565 cm^{-1} , strong). The 100-MHz ^1H -nmr spectrum was fully consistent with the assigned structure (Tables 1 and 2). The spectrum revealed the presence of the benzylidene acetal group (5-proton multiplet centered at δ 7.4, and 1-proton singlet at δ 5.54). The disappearance of the olefinic proton signal present in compound 1, and appearance of H-2 in compound 2 as a multiplet at δ 2.31 with 8.5 and 11.2 Hz splittings indicated a 2,3-diaxial proton arrangement, i.e., the gluco configuration. A 3-proton doublet resonance at δ 1.06 confirmed the presence of CH-Me group.

The assignment of the structure of 3 was also based on infrared and nmr spectra. The infrared spectrum showed a saturated nitro group stretching frequency at 1560 cm^{-1} and of a carbon-carbon double bond absorption for the vinyl group at 1640 cm^{-1} . In the 100-MHz ^1H -nmr spectrum of 3, the vinylic proton signals appeared as multiplets in the 5.26-5.68 range. The proton attached to C-2 gave a sextet at δ 2.93 ($J_{1,2} = 8.3$; $J_{2,\text{vinyl}} = 8.3$; $J_{2,3} = 11.2\text{Hz}$), with the large vicinal couplings $J_{1,2}$ and $J_{2,3}$ confirming the β -D-gluco configuration.

Compounds 5 and 6 showed absorption bands for saturated nitro compounds at 1555 and 1560 cm^{-1} , respectively, in addition to a weak absorption at 1650 cm^{-1} for the vinyl group in the case of compound 6. The nmr spectra of 5 and 6 showed no low-field resonance for nitroalkenic protons; instead, there were the corresponding substituent resonances as required for these structures. The β -D-galacto configuration was indicated by the ring-proton coupling patterns (Tables 1 and 2).

The 2-C-methyl glycoside 8 showed a strong infrared band at 1560 cm^{-1} for its nitro group, attached to saturated carbon. The nmr spectrum displayed a resonance pattern consistent with the α -D-manno configuration. The H-2 signal showed as a quintet, with lines broadened by a very small splitting with H-1, at δ 2.76 ($J_{1,2} \leftarrow 1$; $J_{2,3} = 5.5$, $J_{2,\text{Me}} = 7.5$ Hz). The presence of the methyl group at C-2 was revealed by the resonance at δ 1.06, a 3-proton doublet.

Finally, the infrared spectrum of the nitro glycol 9 had a stretch band at 1640 cm^{-1} due to the -C=C-O- grouping and a strong band at 1560 cm^{-1} due to the nitro group. Its nmr spectrum showed H-1 as a low-field (δ 6.52) doublet of doublets, with $J_{1,2} = 6$ and $J_{1,3} = 2$ Hz; H-2 at δ 4.90 as a doublet of doublets ($J_{1,2} = 6$ and $J_{2,3} = 2$ Hz) and H-3 at δ 5.26 as a doublet of triplets with coupling constants of 2, 2, and 8.5 Hz (Table 2). There were no resonances attributable to OMe or C-Me groups.

PART III
THE CATALYTIC HYDROGENATION OF
EPOXYNITRO SUGARS

III A. INTRODUCTION

The third part of this thesis is concerned with a continuation of prior work which has been done in this laboratory¹³⁰, specifically, the catalytic hydrogenation of some α -epoxynitro sugars. Interpretation of the mechanism and stereochemistry of hydrogenolysis were made possible on the basis of these extended studies.

Most oxiranes readily undergo hydrogenolysis, affording as principal products an alcohol or mixtures of alcohols that result from cleavage of a carbon-oxygen bond. Other products may arise by cleavage of the carbon-carbon bond in the oxirane ring¹³¹ or by loss of the oxygen function¹³².

The major problem connected with hydrogenolysis of epoxides in general is control of the direction of ring opening. Epoxides having a high degree of symmetry in the vicinity of the function tend to open randomly regardless of conditions¹³³, but in unsymmetric epoxides one bond is usually cleaved preferentially. The regioselectivity of oxirane fission depends on various factors such as substrate structure, reaction conditions, and type of catalyst¹³⁴. Thus it is often difficult to predict which bond will be broken unless precedents of closely analogous situations are known for comparison. The ring may open at the weakest bond, or at the carbon atom with the fewest substituents, or at the carbon atom least sterically hindered by structural features in the vicinity, or in acidic solution, so as to afford the most

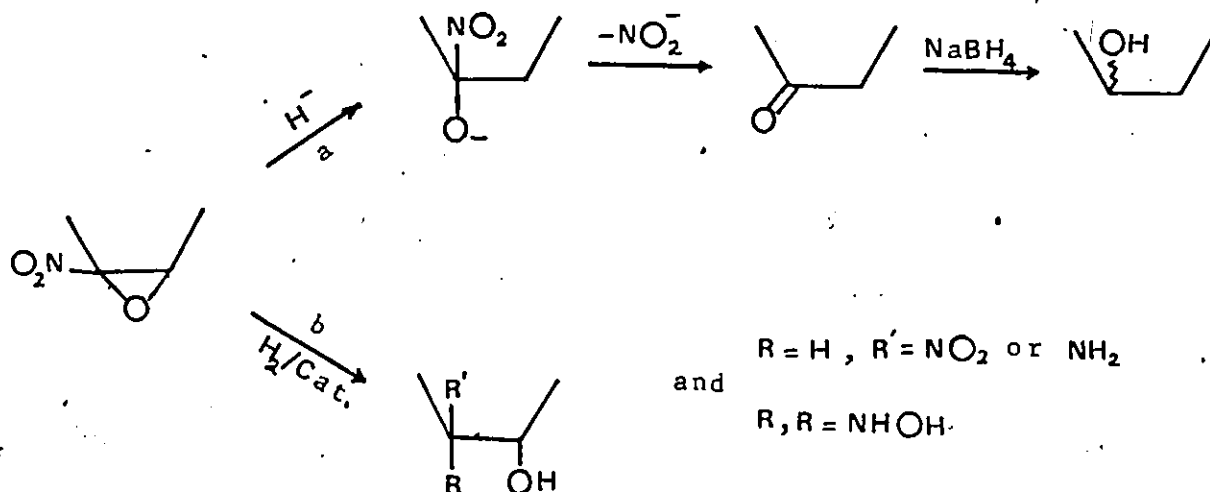
stable carbonium ion.

As far as nitro compounds are concerned, they can generally be reduced to amines by catalytic hydrogenation without undue difficulty. However, they may also give rise by accident or design, to partially reduced products containing nitroso, oximino, hydroxylamino, azo, or hydrazo functions¹³⁴. Most problems connected with their hydrogenation center around such products of partial reduction and, also, on the fate of other functional groups in the molecule that may be prone to reduction¹³⁴.

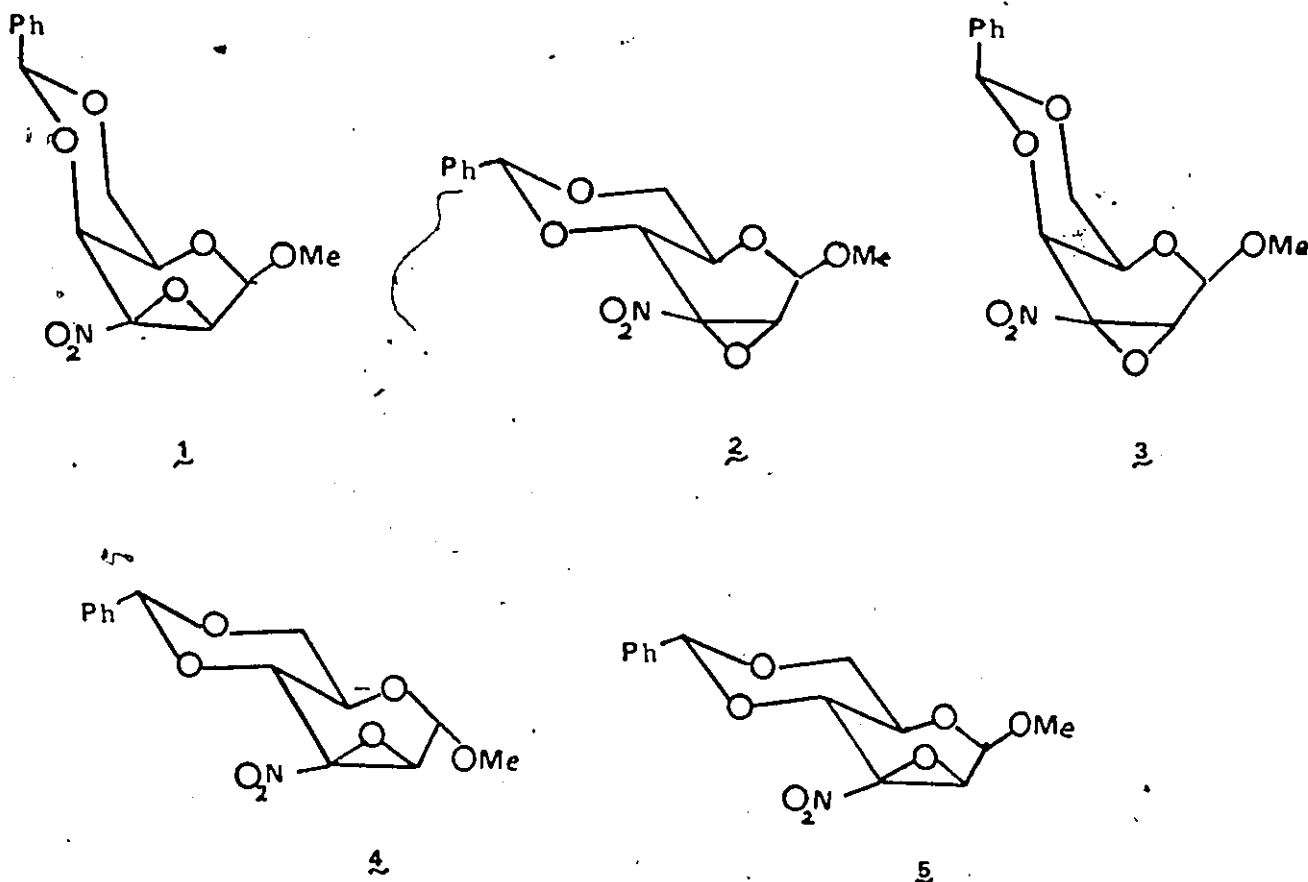
Unsaturated, nonconjugated, aliphatic nitro compounds can usually be hydrogenated with ease to the corresponding, saturated nitro compounds over either palladium or platinum catalysts¹³⁴. On the other hand, hydrogenation of conjugated nitroolefins may yield either selective saturation of the double bond with retention of the nitro group¹³⁵, or afford a variety of products through partial and complete reduction, as well as through reductive hydrolysis^{134,136}. This again depends on the type of catalyst used, the nature of the substrate, and the reaction conditions.

Baer^{130,137} and Sudoh¹³⁸ showed that treatment of carbohydrate α -nitroepoxides with sodium borohydride and lithium aluminum hydride, respectively, leads to reductive denitration producing nitrogen-free, deoxy sugars (Scheme 1a).

SCHEME 1



Attack by hydride ion occurred exclusively at the unhindered back-side of the β -position of the α -nitrooxirane moiety in a first set of stereoisomers, the methyl 2,3-anhydro-4,6-O-benzylidene-3-C-nitrohexopyranosides having the β -D-talo(1) and β -D-allo(2) configurations. The ring opening was followed by elimination of nitrite ion, to generate, presumably, an intermediary oxo derivative that underwent rapid reduction to the carbinol stage. In a second set of stereoisomers, those having the β -D-gulo(3) and α -D-manno (4) configurations, such a process would have required attack from the direction of the hindered face of the sugar ring and therefore appeared disfavoured¹³⁷.

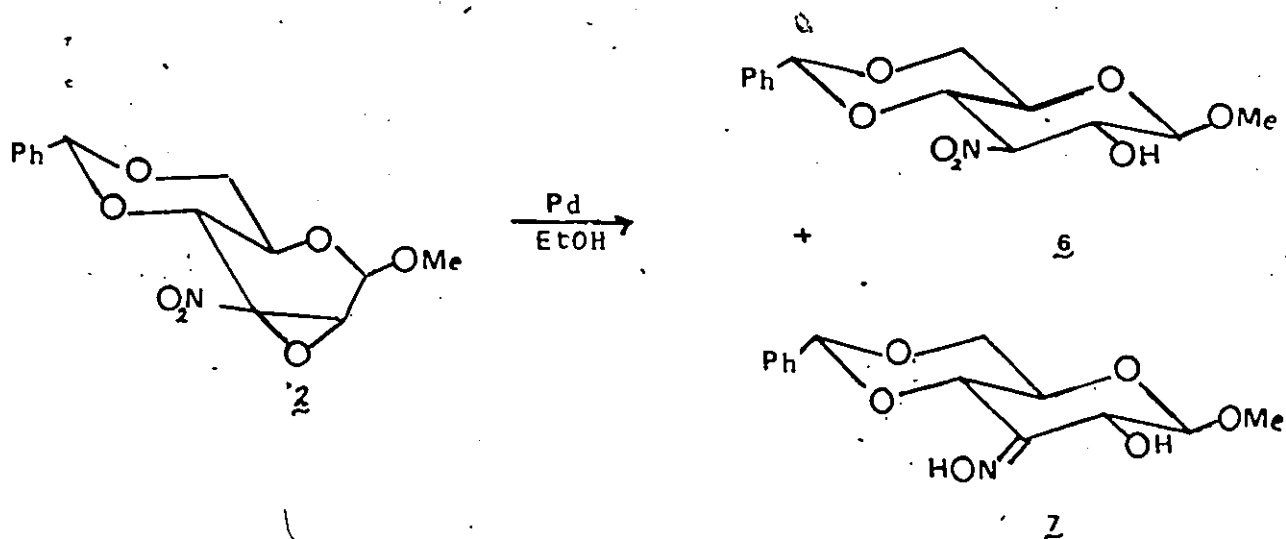


The regiospecificity of nucleophilic attack in these stereoisomeric nitro sugars epoxides by borohydride as just mentioned, as well as by some other nucleophiles¹³⁹, is independent of the steric orientation of the oxirane ring and hence, must result from the presence of the nitro group. This provided an interesting contrast to similar reactions of analogous, unsubstituted epoxides. As is well known, epoxides of six-membered rings may incur nucleophilic ring-opening at either carbon atom, with regioselectivity normally being governed by stereochemical features (Fürst-Plattner rule).

In view of these general facts and recent observations, Baer and Madumelu¹³⁰ decided to investigate the catalytic hydrogenation of carbohydrate α -nitroepoxides, feeling that it should be interesting to compare their behaviour with that of non-nitro analogs whose catalytic hydrogenation had been reported^{25a,140,141}. All the hydrogenations studied by Madumelu^{130b}, whether catalyzed by palladium-on-charcoal or by platinum (Adams catalyst), resulted in facile fission of the oxirane ring between the oxygen atom and the nitro-substituted carbon atom, with retention of a nitrogen function (Scheme 1,b). The results agreed with those mentioned in the only previous report¹⁴² on catalytic hydrogenation of (aryl-substituted) α -nitroalkenes, and they were analogous to those obtained¹⁴³ with α -epoxyketones. In the latter it was found that, barring the presence of additional activating influences¹³⁴, the oxirane bond broken by hydrogenolysis is the one adjacent to the carbonyl group¹⁴³.

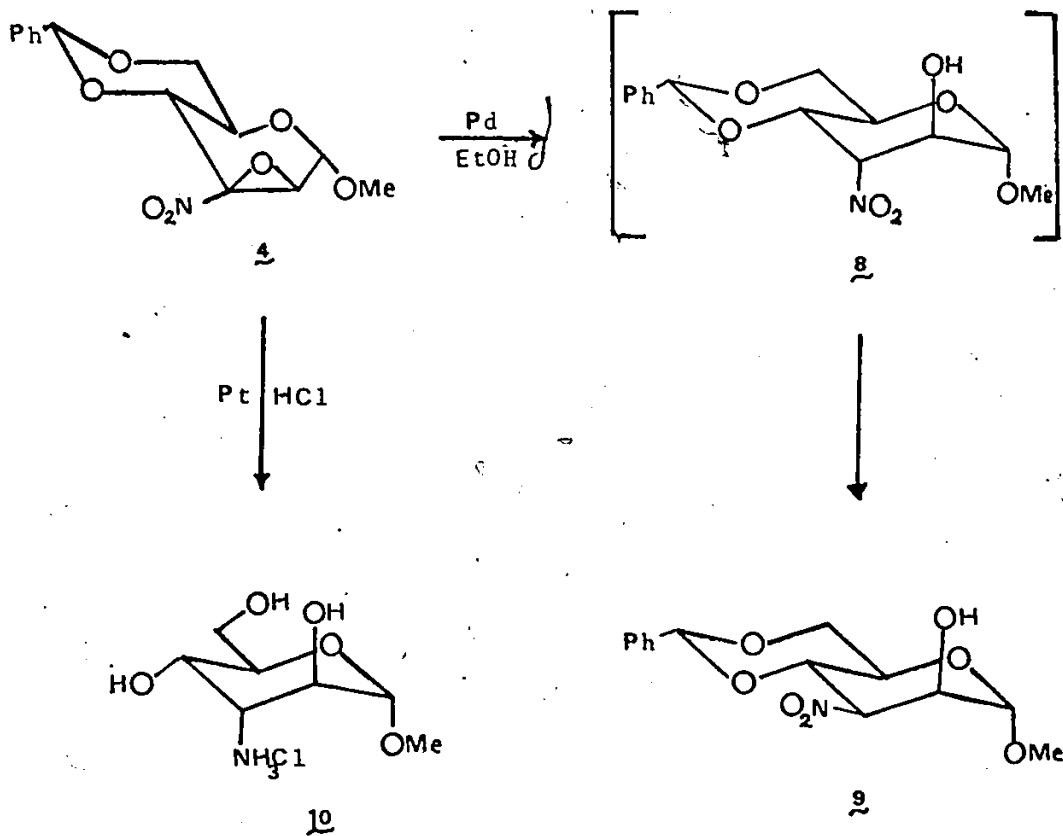
The following details were elaborated by Madumelu^{130b}:

1. The β -D-allo epoxide 2 was hydrogenated in ethanolic solution with palladium catalyst, furnishing in 90% yield the nitro glucoside 6 together with a 7% yield of a crystalline by product to which the oximino structure 7 was assigned:

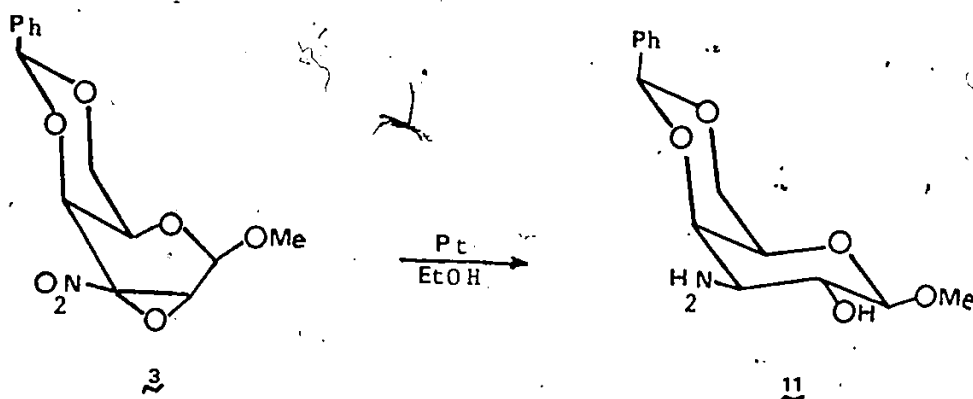


2. The same reaction performed with the α -D-manno epoxide 4 gave the corresponding nitro mannoside 9. The crude, syrupy product (yield, 98%) was stated to be chromatographically homogeneous; crystallization afforded pure 9 in 70% yield. No mention was made of formation of an oxime corresponding to 7. Considering cis-addition of hydrogen from the side of the oxirane oxygen as the most likely mechanism, it was reasoned that the nitro altroside 8 was probably the primary product; the actual isolation of 9 was ascribed to epimerization during the course of the reaction or processing, which was not taken as an unusual event since carbohydrates bearing an axial nitro group were known to be exceedingly unstable. To prove the point, 4 was hydrogenated in the presence of hydrochloric acid (to prevent such epimerization, which is catalyzed by traces of base), with the more powerful catalyst,

platinum, in order to produce the corresponding, non-epimerizing amino sugar. Indeed, the 3-amino altroside hydrochloride 10 was obtained crystalline in 54% yield, the benzylidene acetal group having been lost in the process. This result was consistent with the assumed intermediacy of the nitro altroside 8 but did not prove it since, with platinum, reduction of the nitro group could have occurred prior to hydrogenolysis of the epoxide ring.



3. Madumelu hydrogenated the β -D-gulo epoxide 3 in ethanol solution with platinum catalyst (but without added acid), which afforded the crystalline 3-amino galactoside acetal 11 (yield: 90% crude, 60% after purification). No reactions using palladium catalyst were described and no oxime was detected.

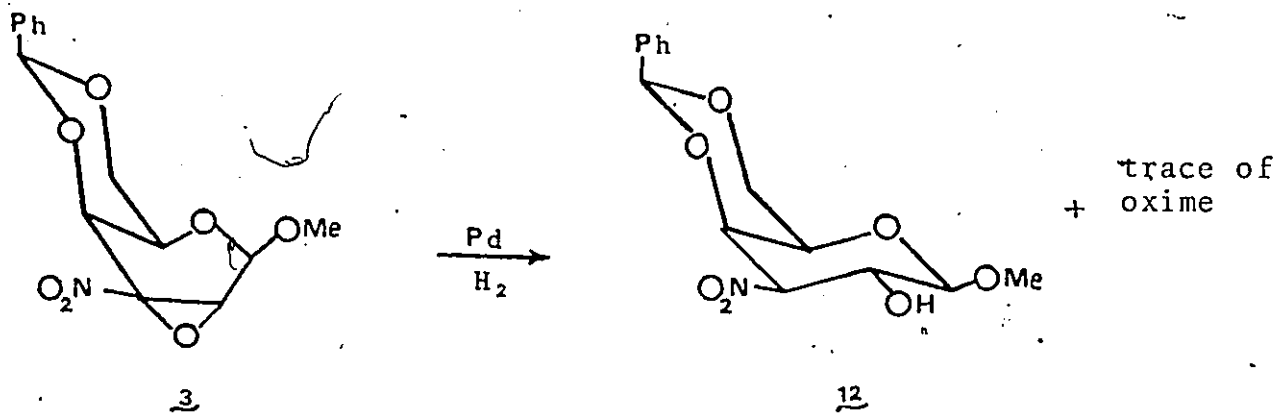


The studies just cited left some interesting questions unanswered. For example, solely the epoxide 4 had been hydrogenated (with differing results) by use of both palladium and platinum, whereas 2 and 3 had been hydrogenated only with one or the other of them. A more complete comparison seemed called for in order to assess the differential action of these catalysts upon nitro sugars. Included in such studies should also be the β -D-manno epoxide 5, which was available in the laboratory, as an additional example of an isomeric molecule bearing the oxirane ring on the upper side. It was hoped to gain in this way a clearer picture of how stereo factors influence catalytic hydrogenation in this family of compounds. Especially

intriguing in this connection was the occurrence, albeit in small proportion, of the oxime 7, which was rather unexpected since oximes are not normally generated from nitroalkanes by hydrogenation with noble-metal catalysts (see the Discussion). It was therefore necessary, first, to ascertain whether oxime formation is in fact confined to the reaction of 2 or whether it is a more general phenomenon; and secondly, it was desirable to seek an explanation for it.

III. B. RESULTS*

1. Hydrogenation of the β -D-gulo epoxide 3 with palladium.
Compound 3 was hydrogenated at 19° with Pd/C in 7:3 methanol-dioxane in the presence of a small proportion of acetic acid. The epoxide was completely consumed after 1 h and gave in 96% yield a crystalline product identified as methyl 4,6-O-benzylidene-3-deoxy-3-nitro- β -D-galactopyranoside (12) by comparison with an authentic sample. The mother liquor exhibited a faint, purple-color reaction in the Griess test (sulfanilic acid- α -naphthylamine) modified¹⁴⁴ for the detection of oximes. It was concluded that an oximino derivative (analogous to 7 obtained¹³⁰ from 2) was present, albeit as a very minor by-product only. In every other respect, the result paralleled that of the platinum-catalyzed reaction¹³⁰, which had given the corresponding amino galactoside 11.



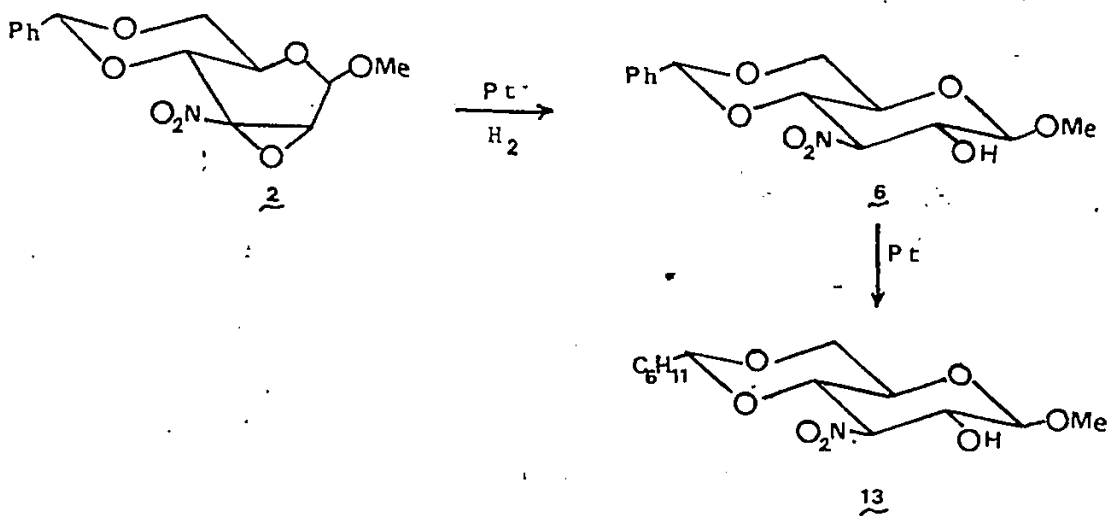
*Throughout Part III, palladium refers to 10% palladium-on-carbon (Pd/C). Unless otherwise indicated, platinum refers to prehydrogenated platinum dioxide catalyst. All catalytic hydrogenations were performed at ambient temperature (21-26°, unless otherwise specified), with hydrogen at a pressure slightly above atmospheric.

2. Hydrogenation of the β -D-allo epoxide 2 with platinum.

It had been expected that hydrogenation with platinum would convert 2 into a 2,3-diequatorial amino alcohol (i.e., a derivative of 3-amino-3-deoxy-D-glucose), just as similar hydrogenation of 5 had given¹³⁰ the 3-amino-3-deoxy-D-galactose derivative 11. Monitoring the reaction by tlc revealed that 2 (R_F 0.82) was in fact rapidly consumed (it was absent after 90 min), but only traces of slow-moving, ninhydrin-positive spots attributable to amino sugar appeared even after prolonged periods of continued hydrogenation. The main product spot (R_F 0.75) seen after 1.5 and 16 h appeared similar to that given by authentic benzylidene nitroglucoside 6 (which was the chief product obtained¹³⁰ from 2 under palladium catalysis), and it appears reasonable to assume that 6 was indeed produced under the present conditions also. However, careful tlc examination suggested that the product was not homogeneous, and the spot seen after 44 h was clearly distinct from that of 6 (see Experimental). Processing then gave a material which according to spectral and chromatographic evidence was methyl 4,6-O-(cyclohexylmethylene)-3-deoxy-3-nitro- β -D-glucopyranoside (13), identical with 13 obtained as described in the next paragraph. It had arisen by perhydrogenation of the benzylidene group, a process which, surprisingly, had occurred without simultaneous reduction of the nitro group.

In order to verify this, authentic crystalline 6 was hydrogenated for 46h, in the presence of platinum under the same conditions as 2.

Crystalline 13 was isolated in 82% yield, and only traces of slow-moving, ninhydrin-positive products (amino sugar) were seen in tlc. The new product 13 gave readily interpretable ir and nmr spectra (see Experimental section) that were consistent with the postulated structure. The nmr spectrum showed no resonances downfield from δ 5.0, but instead gave unresolved multiplets in the δ 1-2 region, indicating that the original benzylidene acetal group had incurred perhydrogenation in the phenyl ring. A symmetrical triplet for H-3 at δ 4.63, showing a 10-Hz splitting, indicated 2,3- and 3,4-diaxial proton arrangements, *i.e.*, the gluco configuration. The (cyclohexylmethylene) acetal proton resonated at δ 4.45 as a doublet with a vicinal coupling of 5Hz.



3. Hydrogenation of the α -D-manno epoxide 4

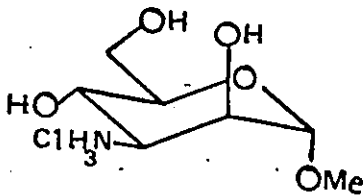
As already mentioned in the Introduction (p.110), Madumelu had isolated crystalline nitro mannoside 9, upon hydrogenation of 4 with palladium in ethanolic medium. Hydrogenation had been conducted for 25 h, without recorded inspection of its progress by tlc, and the crude product had been chromatographed on a silica gel column to give syrupy 9 in 98% yield (homogeneous according to tlc), from which 70% of crystalline 9 was then obtained. It appeared interesting to determine whether perhaps small amounts of an oxime arose in this reaction, too, but had escaped detection. Repetition of the experiment on a small scale, but with monitoring by tlc, revealed that soon after the beginning of hydrogenation (after \sim 5 min), a strong spot migrating like authentic 9 (R_F 0.8) was present together with much unreacted 4 (R_F 0.9), and with a second product spot (R_F 0.6) that slowly increased in intensity as the reaction progressed; a trace spot had R_F 0.35. A small proportion of 4 was still seen after 1 h but it disappeared within the next 30 min. The reaction mixture gave a weak purple color in the Griess test, indicating the presence of a small proportion of an oximino sugar.

Another experiment, also using palladium catalyst, was performed in a similar manner but in methanol-dioxane as the solvent and with addition of acetic acid. The latter was added in view of the possible formation of the nitro altroside 8 as the primary

product of ring opening; an acidic medium should prevent or retard its epimerization to 9 so that one might be able to ascertain its formation. However, the tlc pattern shown by the reaction mixture during the hydrogenation was similar to that of the aforescribed experiment, except that the reaction was somewhat faster. The starting epoxide 4 had completely disappeared after 15 min; and the spot having R_F 0.6 was more pronounced at that early stage. The product pattern then remained essentially unchanged during further hydrogenation which was continued for 19 h. As before, the main product migrated like authentic 9; it could not be found out whether or not some of the unknown epimer 8 was present. However, the formation of oxime was evident also in this variant of hydrogenation, as was indicated by a Griess test which was even more strongly positive than in the previous case.

In view of these results it was considered worthwhile to examine somewhat more closely also the platinum-catalyzed hydrogenation of 4. Madumelu¹³⁰ had obtained, in 54% yield, the crystalline amino-altroside 10 (p.111), and he had noticed the presence of two trace spots in tlc of the crude hydrogenation mixture, after a reaction time of 20 h. However, no record was made of an inspection of the mixture by tlc during early stages of the reaction. This has now been done. When 4 was hydrogenated with Pt-catalyst in ethanol in the presence of a molar equivalent of hydrochloric acid as described^{130b}, it was found that all of 4 had already been consumed after 1 h. At least six products

differing widely in polarity were formed: $R_F \sim 0.9, 0.8,$ and 0.5 (all weak), and $0.6, 0.2$ and 0.07 (strong), on irrigation with 1:4 methanol-chloroform. The spots of intermediate and low mobility gave a positive ninhydrin reaction signifying amino sugars. As the hydrogenation progressed, the two fastest-moving (and ninhydrin-negative) intermediates disappeared, and, after 20 h, the most-slowly moving compound(s) preponderated. This was, by and large, in agreement with Madumelu's observation although the most-slowly moving material was probably not a single compound but rather, a mixture that gave overlapping spots in the $R_F 0.07 - 0.2$ region. (The whole pattern was similar to that obtained with β -manno epoxide 5 and discussed in greater detail in a subsequent section). At any rate, it seems likely that 10 was not the only, final product arising from 4, a contention that would appear to receive support from the fact that its isolated yield was far from quantitative. It may be supposed that 10 was accompanied by its D-manno isomer 14, a known compound showing similar chromatographic behaviour.



14

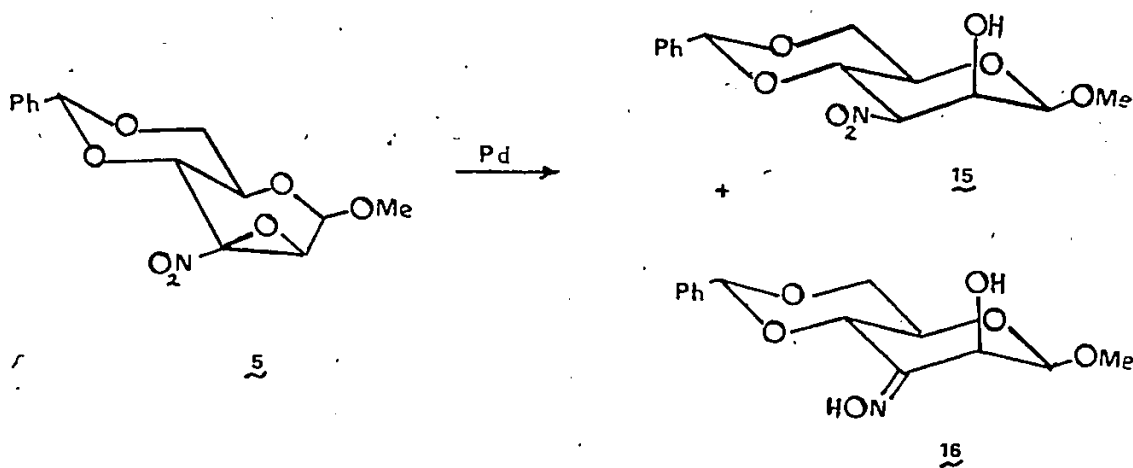
In summary, the experiments performed with 4 suggest that the hydrogenation scheme previously elaborated (p. 111) should be amended to show an oximino sugar as a minor by-product of 9, and another amino sugar (most likely 14) as a companion of 10, with a question mark still being attached to the presumed intermediate 8.

4. Hydrogenation of the β -D-manno epoxide 5 and experiments related thereto

The β -D-manno stereoisomer 5 had not been included in the earlier studies^{130b}, and it was therefore focused upon with special emphasis in the present research.

- a. Hydrogenation with palladium. - As anticipated, cleavage of the epoxide occurred exclusively between the ring oxygen atom and C-3. This fission was rapid, consuming 5 completely within 3 h in neutral, ethanolic solution and within 45 min in acidified, methanol-dioxane solution. In either case, two spots showing comparable intensities were indicated by tlc at that point. One of them had the same R_F value as authentic methyl 4,6-O-benzylidene-3-deoxy-3-nitro- β -D-mannopyranoside (15) spotted for comparison, whereas the other one was less mobile, had the shape of a double spot, and proved to be due to an oximino sugar (present as a pair of geometric isomers). The product migrating like the nitro sugar 15 appeared to be formed at a faster rate. After only a few minutes of hydrogenation in methanol-dioxane, when a considerable proportion of unchanged 5 was still visible, the nitro sugar seemed to be the main product although traces of the oxime had already arisen. After 45 min, at the time of complete consumption of 5, the oxime had attained a spot intensity not much less than that of the nitro derivative, and, after 36 h, the spot corresponding to

the latter had disappeared and the former could be isolated as the sole product, by direct crystallization. The constitution of methyl 4,6-O-benzylidene-3-deoxy-3-(oximino)- β -D-arabino-hexopyranoside (16) was allocated to it on the basis of microanalytical and spectral data. Similarly, when the hydrogenation was conducted in ethanol and extended beyond the time (3 h) when the two products showed roughly equal strength, namely, to 24 h, their ratio changed markedly in favor of 16. Preparative tlc then allowed the isolation of a large amount of 16 which, in this instance, was obtained in two crystalline forms constituting geometric isomers, and of a small amount of a crystalline benzylidene nitro sugar which in fact proved to be the known mannoside 15.

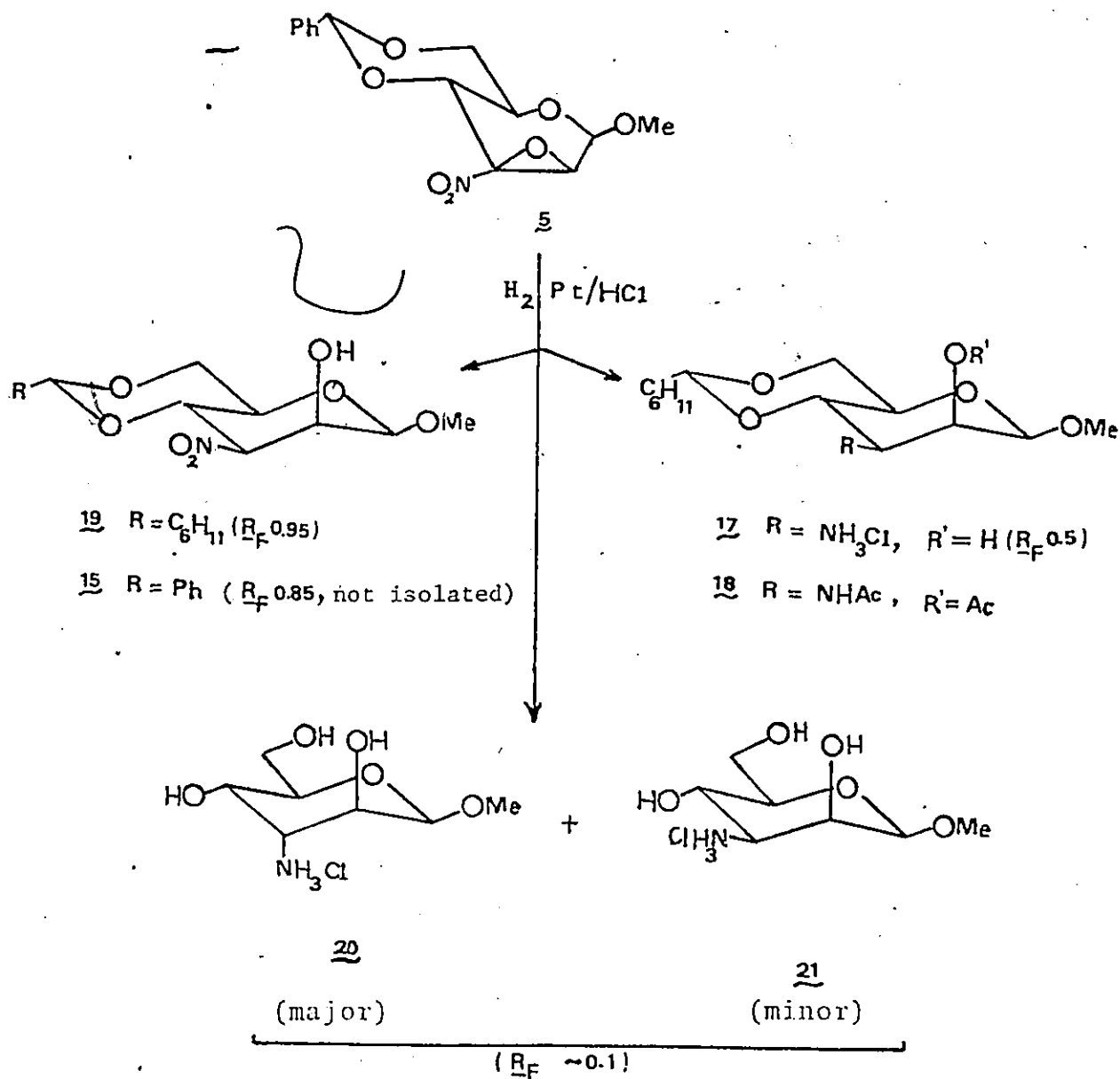


The new oximino glycoside 16 lacked the strong ir band near 1550 cm^{-1} characteristic for nitroalkanes but showed, instead, a weak band at $1570\text{-}1600\text{ cm}^{-1}$ attributable to a C=N vibration. The nmr spectrum of a $\text{CDCl}_3 - (\text{CD}_3)_2\text{SO}$ solution exhibited an off-field signal ($\delta 11.2$) removable by deuterium exchange, which was due to the oxime proton. The main part of the spectrum proved that the benzylidene group was intact and, moreover, that no hydrogen was attached to C-3, as H-2 and H-4 each gave a doublet (1.5 and 9.3 Hz, respectively) owing to coupling with one vicinal proton only. The signals for H-5, -6, and -6' were also well resolved.

b. Hydrogenation with platinum - The nitroepoxide 5 was hydrogenated in ethanolic solution containing a stoichiometric amount of hydrochloric acid. The epoxide was completely consumed within 4.5 h, at which point the reaction mixture, like that of the α -anomer 4 (section C, above), showed a complex tlc pattern of at least six spots differing greatly in intensity and R_F value (0.95 to ~ 0.1). Processing at this stage permitted the isolation of three of the products by fractional crystallization. The chief component (R_F 0.5) thus separated, in 31% yield, proved to be methyl 3-amino-4,6-O-(cyclohexylmethylene)-3-deoxy- β -D-mannopyranoside hydrochloride (17), characterized by analytical and spectral data, through preparation of its

N,O-diacetyl derivative 18, and also by total hydrolysis to give known 3-amino-3-deoxy-D-mannose. The fastest-moving component (R_F 0.95) was isolated in 5% yield, and shown to be the (cyclohexylmethylene)-nitro analog 19. Finally, a third crystalline fraction could be elaborated from mother liquors. It contained only slow-moving material giving a ninhydrin-positive double spot ($R_F \sim 0.1$). The material had ir and nmr characteristics consistent with those for a methyl aminodeoxy glycoside hydrochloride, but it was probably not isomerically homogeneous, as its specific rotation ($[\alpha]_D -127.6^\circ$) lay between the values for the β -D-altroside 20 ($[\alpha]_D -138^\circ$) and the β -D-mannoside 21 ($[\alpha]_D -68^\circ$). The optical rotations suggested, however, that 20 preponderated, and this was supported by the results of acid hydrolysis. The hydrolyzate showed, in tlc, an elongated spot that was consistent with the presence of 3-amino-3-deoxy-D-altrose and its 1,6-anhydride (with which it is known to enter into equilibrium in aqueous solution), and that differed from the somewhat slower spot of 3-amino-3-deoxy-D-mannose, as given by an authentic sample and by the product of total hydrolysis of 17. The remaining products in the hydrogenation of 5 were all minor in proportion, and could not be isolated.

They gave ninhydrin-negative spots at R_F 0.85 and 0.4 (trace), and ninhydrin-positive spots at R_F 0.75 and 0.35 (trace). The two former ones corresponded to those given by authentic samples of the nitro glycoside 15 and its debenzylidenated parent compound 22.



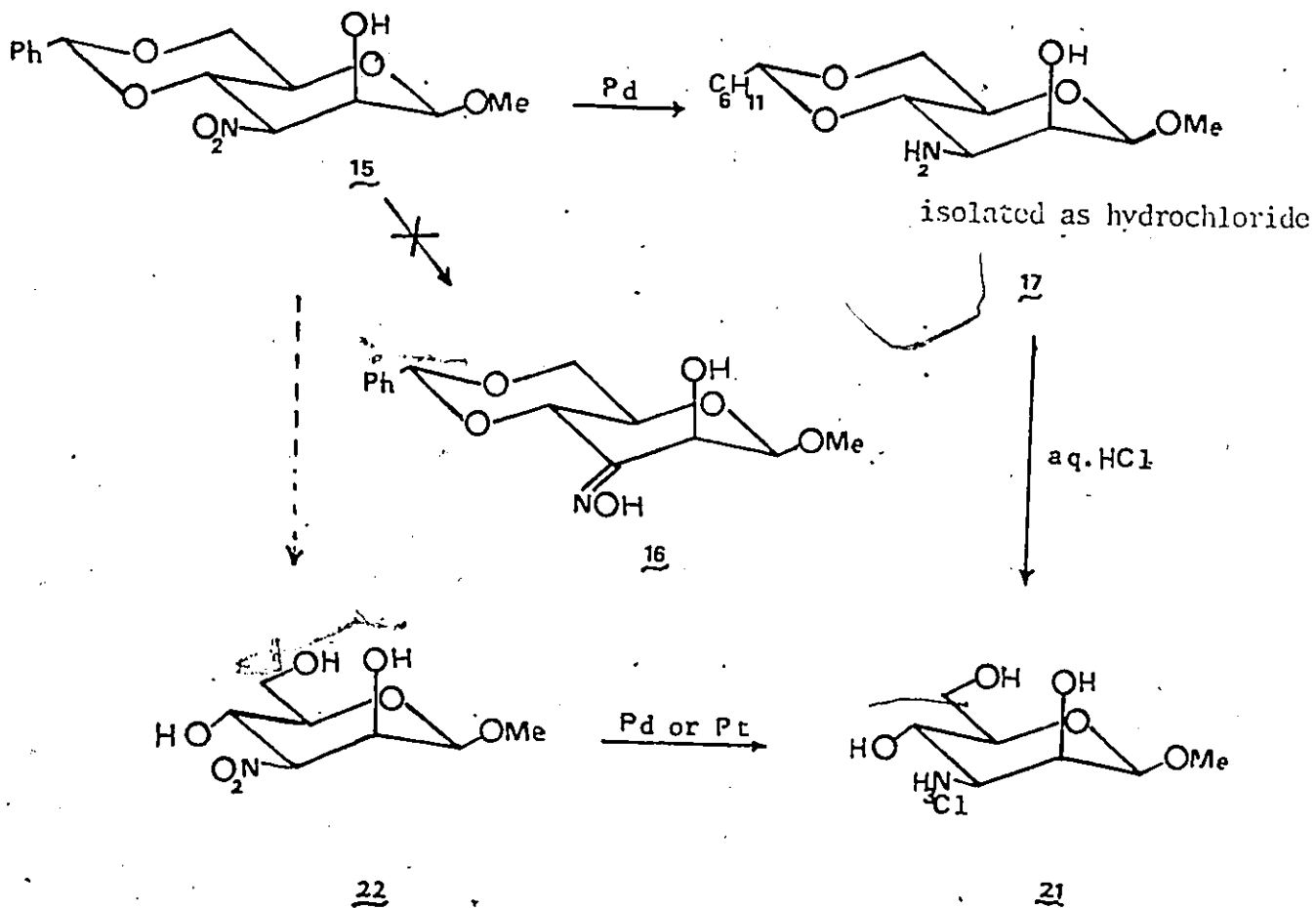
The (cyclohexylmethylene) acetal structure of the new compounds 17, 18, and 19 was readily apparent from their nmr spectra (see the Experimental section, and the discussion on p.116 for the analog 13). The H-3 signal of 19 was a quartet having 3.5- and 10.5-Hz splittings that revealed the manno configuration, and this was confirmed by the coupling constants of the remaining, well resolved, ring-proton signals. The acetalic proton resonated at δ 4.45 as a doublet showing vicinal coupling of 5 Hz. The spectrum of 17 afforded little additional information, but that of its diacetyl derivative 18 exhibited, at lowest field, a quartet for H-2 ($J_{1,2}$ 1.3 Hz and $J_{2,3}$ 3 Hz) which was followed upfield by the anomeric-proton doublet ($J_{1,2}$ 1.3 Hz) and a quartet for H-3 ($J_{2,3}$ 3 and $J_{3,4}$ 9.5 Hz), as well as an apparent triplet for H-4 ($J_{3,4} \approx J_{4,5} = 9-10$ Hz). These features established the manno configuration.

c. Hydrogenation of the benzylidenenitro glycoside 15.

The results of the palladium-catalyzed hydrogenation of the nitro epoxide 5 (Section a) invited at first sight the interpretation that the nitro glycoside 15 was a primary reaction product which in the course of time was rather smoothly converted into the oxime 16. However, this notion appeared at variance with the known, general reluctance of nitroalkanes to undergo such conversion

under the conditions here employed (see the Discussion). It was therefore important to examine whether 15 actually was a precursor of 16. To this end, crystalline 15 (previously obtained by independent synthesis) was subjected to hydrogenation for 30 h under the same conditions as the epoxide 5, (with Pd/C in methanol-dioxane). Examination of the reaction mixture by tlc in 1:4 methanol-chloroform showed that by far the major product (R_F 0.5) was a ninhydrin-positive amino sugar. (It is recalled that no amino sugar arose from 5 under these conditions). There was also a trace spot (R_F 0.75) that happened to migrate like the oxime 16 in this solvent system, but more slowly than 16 in another system (1:2 ethyl acetate-petroleum ether), which proved that it was a different product. Furthermore, there were two weak spots, R_F 0.9 and 0.4, that turned yellow (not violet) on spraying with ninhydrin and migrated like starting 15 and its debenzylidenated parent compound 22. (Compare herewith the possible occurrence of the same compounds, as minor products, in the platinum-catalyzed reaction of 5 as reported in section b). The chief product (R_F 0.5) was isolated as a crystalline hydrochloride and proved to be identical with the cyclohexylmethylene acetal 17 previously encountered; upon graded, acid hydrolysis it yielded the known methyl 3-amino-3-deoxy- β -D-mannopyranoside 21. The important result of this experiment was the absence of oxime 16 among the products. It thus became clear that the nitro glycoside 15 generated from the epoxide 5 is not the precursor of the

oxime that is a prominent product in the same reaction.



When 15 was hydrogenated in ethanol with platinum in the presence of 1 equiv. of hydrochloric acid, all of the starting material was revealed by tlc to have reacted after 4 h, although reduction of the nitro group was not necessarily complete at that stage. Although ninhydrin -positive spots attributable to 17 and 21 were evident, there was also a spot due to the (cyclohexylmethylene)-nitro derivative 19, and it took 30 h for the latter eventually to disappear. These chromatographic results were consistent with a close similarity of the Pt-catalyzed reactions of 5 (section b) and 15, as far as the final product composition is concerned, except that the former showed evidence for giving a significant proportion of a product (20) which had the D-altro configuration.

For another experiment, a mixture of 15 and 16 was prepared by hydrogenating 5 with Pd/C in methanol-dioxane for 45 min. (See section a). The mixture was isolated by solvent evaporation and then redissolved, in ethanol, to be subjected to a second hydrogenation but with platinum in the presence of hydrochloric acid. This second hydrogenation (24 h) caused 15 and 16 to disappear, and produced a small proportion of the cyclohexylmethylene nitro glycoside 19 (isolated by column chromatography and identified spectroscopically) besides three slow-moving, ninhydrin-positive compounds as the major products. The most mobile of the latter corresponded to 17 in tlc, whereas the others, giving a double spot at $R_F \sim 0.1$, evidently were deacetalated amino glycoside hydrochlorides. The three products were obtained

together as a crystalline mixture that could not be separated. A relatively low levorotation ($[\alpha]_D -51^\circ$, in water) of the mixture, and the result of paper chromatography after total acid hydrolysis suggested that the D-manno configuration predominated. If a small proportion of the D-altro amine 20 (or a 4,6-acetal thereof) was present, it could have originated from reduction of the oxime 16, through partial attack from the hindered, β -face direction. For comparison, a solution containing only 16 was hydrogenated under the same conditions; subsequent acid hydrolysis of the products gave a mixture of amino sugars showing the same pattern in paper chromatography.

It is to be noted that, as these experiments showed, 16 is hydrogenated by platinum catalysis whereas, having arisen from 5 by palladium catalysis, it resists further reduction under the latter conditions.

- d. Hydrogenation of the nitro glycoside 22. - In view of the important observation reported in section c, namely, that palladium-catalyzed hydrogenation of 15 does not lead to an oxime, we wished to ascertain that the same is true for its non-benzylidenated parent glycoside 22. The experiment did bear this out. After 10.5 h of hydrogenation, virtually all of 22 had been consumed, and the Griess test was negative. Crystalline amino mannoside hydrochloride (21) was the only product obtained

(upon addition of hydrochloric acid in processing); it proved identical with an authentic sample in every respect.

For comparison, 22 was also hydrogenated with platinum, in ethanol containing 1 equiv. of hydrochloric acid, and crystalline 21 was obtained as the sole product, in accord with previous work¹⁴⁵ in which an aqueous medium was used.

III. C. DISCUSSION

The data assembled in Section III.B., in conjunction with the experimental results previously obtained by Madumelu^{130b} and summarized in Section III.A., may be interpreted in the following way.

First of all, the facile, hydrogenolytic opening of the oxirane ring in α -nitroepoxy sugars under catalysis with palladium or platinum contrasts with the much more severe reaction conditions required to achieve such cleavage in non-nitro analogs.

Thus the unsubstituted 2,3-anhydro sugars previously studied^{140,141} underwent ring opening with hydrogen under pressure at elevated temperatures in the presence of Raney Nickel; a platinum catalyst was ineffective at 80° in one case examined^{140a}. An electronic effect of the C-3 nitro group (to be discussed in more detail later on) is undoubtedly responsible for enhanced reactivity which greatly facilitates cleavage of the bond between C-3 and the oxirane oxygen atom in the sense of the observed regio-specificity. However, there is no need to ascribe an indispensable, regiodirective role to the nitro group in the benzylidenated 2,3-anhydropyranosides under discussion, as the same selectivity was manifest in unsubstituted analogs, too. Thus, the non-nitro analogs of 1 and 4 which bear the oxirane ring on the β -face of the pyranose ring, were hydrogenolyzed to give 3-deoxy glycosides having an axial OH-2 group, and the unsubstituted (but α -anomeric)

analogs of 2 and 3, in which the oxirane ring is situated on the α -face, incurred hydrogenolysis in the same sense nevertheless, to give 3-deoxy glycosides having an equatorial OH-2 group^{140,141}. This behaviour stands in contrast to the reductive ring opening by lithium aluminum hydride in the same compounds, which obeys^{141,146} The Fürst-Plattner rule. No satisfactory explanation appears to have been offered in the literature as to why none of the catalytic ring openings should have occurred at C-2. For lack of a proper rationale, the preceding analogies could not, therefore, be meaningfully invoked to predict the behaviour of any nitro derivatives. Considering the results now available it is tempting to speculate that a nitro substituent introduced at C-2 would override other regiodirective features present in 2,3-anhydro-pyranosides, so that hydrogenolytic fission might occur at that site. Unfortunately, such a prediction cannot be tested as yet, because no 2-nitro-2,3-anhydro sugars are known:

Next, the question as to which configuration should be expected to arise at C-3 presents itself. Extensive investigations by Mitsui and co-workers^{147,148} on the mechanism and stereochemistry of catalytic hydrogenolysis of epoxides and aziridines have revealed significant differences as to types of catalyst and reaction media. The authors suggested^{147,148} that the compounds are adsorbed by Raney nickel on the side of, and through coordination with, the hetero atom and are hydrogenolyzed in a manner stereochemically analogous to an S_Ni process, whereas palladium,

showing no affinity for the hetero atom, was considered to initiate attack with SN2-like geometry from the opposite, stereoelectronically favored direction; platinum, apparently, can act by either mode. It should be noted, however, that the conclusions of Mitsui and coworkers pertain largely to α -phenyl-substituted (styrene oxide type) compounds, where anchoring on the catalyst surface through π -benzyl bonding is considered to be a prime factor. There seem to be few reports along these lines concerning purely aliphatic epoxides^{148,149}, and the antecedent findings in the area of benzylidenated^{140,141,146} and other^{25a} carbohydrate oxiranes have not been commented upon in this context so that it was uncertain how these precepts would relate to epoxynitro sugars in which other factors, both polar and steric, might come into play. Actually, no simple correlations were evident.

Whereas the platinum-catalyzed hydrogenations of the β -D-allo (2) and β -D-gulo (3) epoxides, giving equatorial orientation of the nitrogenous substituents in 13 and 11 respectively, were consistent with hydrogen transfer from catalyst coordinated with the oxirane oxygen atom, the palladium-catalyzed reactions of these same substrates produced the same C-3 configuration (in 6 and 12) and thus gave no evidence for the latter catalyst's attacking from the opposite direction*. In the hydrogenolysis of the α -D-manno epoxide 4 platinum again acted from the side of the oxirane ring, at least mainly so, to the extent that the nitrogen atom was placed axially in the amino altroside 10, the chief product.

* See footnote on page 135

(The probable formation of a minor proportion of the D-manno isomer 14 could not be definitively ascertained.) The favored direction of attack by platinum was less clear-cut for the β -D-manno epoxide 5 from which substantial proportions of products having an equatorial nitrogen function were formed, with the derivatives 17 and 19 being isolated crystalline, and 21 considered a possible, if minor, companion of the amino altroside 20. On the other hand, palladium catalysis for both of the D-manno epoxides (4 and 5) did not give any detectable products having an axial nitrogen function.

The foregoing results would appear to constitute prima facie indications that palladium acts from the rear side of the oxirane ring (in accord with the concept of Mitsui and co-workers) only for 4 and 5, but from the oxygen side for 2 and 3, and that platinum acts from the oxygen side exclusively (for 2 and 3), predominantly (for 4), or to a considerable degree (for 5). However, the validity of such conclusions would have to rest on the premise that all of the reaction products isolated were in fact the same as those primarily engendered, and that they did not originate, in part, from a secondary epimerization of intermediates having an axial nitro group on C-3. It has been

* In a short communication that appeared while this work was in progress, Sudoh and his co-workers¹³⁸ reported, without giving experimental details, that the phenyl glycoside analog of 2 also reacts to give the D-gluco configuration, both with palladium-on-carbon and with Raney nickel.

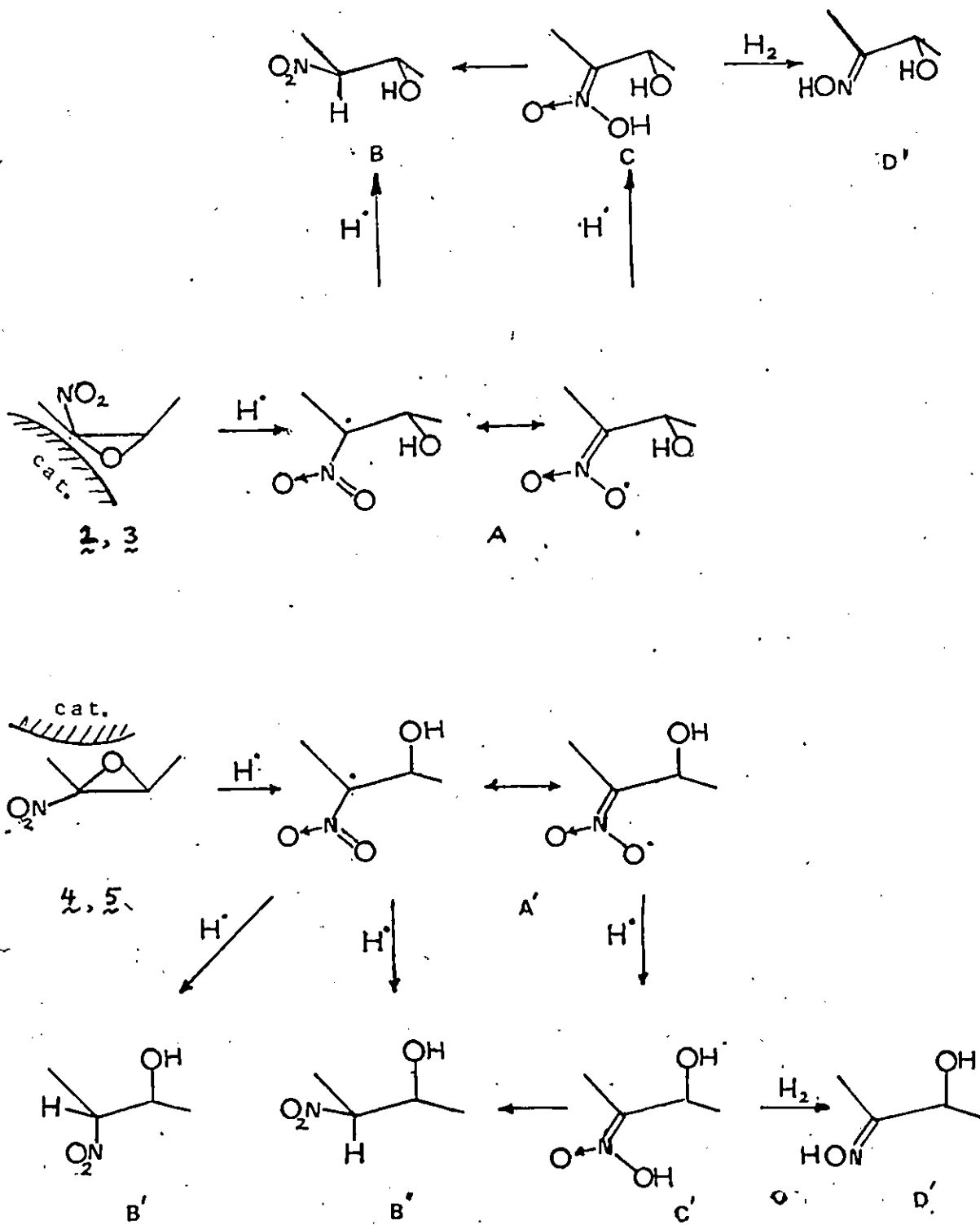
established that an axial nitro group on this atom in pyranosides, or on any ring-carbon atom in deoxynitroinositols, is thermodynamically highly disfavored; with one explicable exception, all of the numerous known compounds of these classes display an equatorial nitro group^{21,150}. Hence, it may be expected that axial-nitro glycosides, arising from epoxides by hydrogen donation to C-3 on the β -face of the pyranose ring, will be extremely prone to epimerization that might occur in the reaction medium, or during processing. This would afford the molecule a greater gain in stability than adoption of an alternative, non-chair conformation*. Assuming that possible axial-nitro intermediates would be instantly epimerized by catalytic amounts of base, we performed the platinum hydrogenations of 4 and 5 in the presence of hydrochloric acid. Formation of the amino altrosides 10 and 20 gave proof for oxirane ring-cleavage from "above", and allowed the inference to be drawn that the corresponding axial-nitro glycosides were, indeed, intermediates in these instances. The large proportion of β -D-manno products formed simultaneously from 5 may have been due to competing hydrogenolysis from "below", facilitated in this substrate by absence of steric hindrance from an axial glycosidic substituent.

* Recently, a first derivative of methyl 4,6-O-benzylidene-3-deoxy-3-nitro- α -D-altropyranoside has been described¹⁵¹. It carries a bulky 2-C-bis(methoxycarbonyl)-methyl substituent replacing OH-2, and was reported to exist in a skew conformation. It epimerized to the more stable, D-manno isomer sufficiently slowly to permit its isolation.

As concerns the palladium-catalyzed hydrogenations, we have so far been unable to find any evidence for axial-nitro intermediates, regardless of whether the reaction medium was neutral ethanol or methanol-1,4-dioxane acidified with acetic acid. Admittedly, this does not constitute proof for the absence of such intermediates, because epimerization may have been fast, even in a mildly acidic medium. Moreover, epimerizations may well have been induced by the silica gel used in tlc and in the columns used in some of the processings. However, several runs were processed without the aid of chromatography, and yet, no nitro glycosides other than those mentioned were detected. It may, therefore, be stated, at least, that the palladium-catalyzed hydrogenations of 2-5 were consistent with non-occurrence of axial-nitro intermediates, although such intermediates would necessarily have to be postulated in the case of 2 and 3 should the hypothesis of an SN2 type of geometry for hydrogenolysis at C-3 be applied. Without intending to question its validity¹⁴⁷ for benzylic epoxides and related compounds, we contend in the following discussion that the hypothesis is inapplicable for carbohydrate α -nitroepoxides.

A clue to the mechanism operative in the palladium hydrogenations was found in the formation of oximino glycosides which were isolated crystalline (7 and 16) or detected by the Griess color reaction. Hydrogenation of nitroalkanes by noble metal catalysts does not normally lead to oximes, but passes through the nitroso and hydroxylamino stages directly to the amine stage^{152,153}.

SCHEME 2



Arrest of the sequence in the nitroso oxidation-state by way of tautomerization to oximes (which are relatively resistant to further hydrogenation) is not a normal event as nitroso compounds are more rapidly reduced than tautomerized*. In fact hydrogenation of the nitro alcohol 15 under conditions that produced the oxime 16 from the epoxide 5 did not yield any 16 nor did any oxime arise from 22. However, it is well known that oximes can be readily obtained by hydrogenation of nitronic acids and nitronates, i.e., from nitroalkanes, if these are first converted into their salts^{152b}. Cyclohexanone oxime has also been obtained from 1-chloro-1-nitrocyclohexane by palladium hydrogenation that was considered to involve intermediary cyclohexanenitronic acid¹⁵⁷. In view of these facts, a mechanism is proposed for the reactions of the nitroepoxides studied (See Scheme 2).

* 2-Nitrosocyclohexanol and several 3-deoxy-3-nitroso glycosides obtained¹⁵⁴ by oxidation of the corresponding amines with m-chloroperoxy benzoic acid showed no tendency to tautomerize, but formed stable dimers. The catalytic hydrogenation of nitrocyclohexane to cyclohexanone oxime, studied¹⁵⁵ in great detail because of its industrial appeal, did not succeed with noble metals or Raney nickel, but required the development of special, metal oxide, mixed catalysts. Oxime formation by palladium-catalyzed hydrogenation of nitroalkenes, believed to take place via hydroxylaminoalkenes, is a different matter^{152c,156}.

The catalyst, either platinum or palladium, first transfers a hydrogen atom to the oxirane oxygen atom, generating a radical (A from 2 or 3; A' from 4 or 5). With platinum, a second hydrogen atom is rapidly delivered from an adjacent site, to give nitro alcohols having equatorial (B) and axial (B') nitro groups respectively. The nitro alcohols are subsequently hydrogenated, as is usual²¹ for platinum catalysis, with retention of configuration, to give the corresponding amines. (An exception is 6 which was converted into the hexahydrobenzylidene derivative 13 with negligible attack on the nitro group, even though the parent methyl 3-deoxy-3-nitro- β -D-glucopyranoside is readily hydrogenated¹⁵⁸ to the amine). With palladium, on the other hand, donation of a second hydrogen atom is comparatively slow, and the radicals being sufficiently long-lived because of resonance stabilization, may await an independent transfer-process, if that is energetically gainful. To the extent that the second transfer occurs at C-3, it will be so directed as to produce the more-favored, equatorial-nitro alcohol; i.e., the same B would arise from A, but B'' would arise from A'. It is suggested that this mode of epoxide hydrogenolysis would also compete in the case of platinum especially with the β -glycoside 5, whose lower side is unhindered, accounting for the formation of 15. However, the radicals A and A' can alternatively accept hydrogen on the nitro group, thus giving rise to nitronic acid (C and C'). The nitronic acid is then hydrogenated by palladium to the oxime (D or D'), or it tautomerizes to the equatorial-nitro alcohol (B or B''). Differing stabilities of individual nitronic acids, owing to different amounts

of A^(1,3) strain that is present¹⁵⁰, presumably influence the final product-composition. The scheme explains why 15, which was portrayed by tlc as the major product, and was, in fact, isolable upon short, palladium-catalyzed hydrogenation of 5, vanished during extended hydrogenation in favor of 16 (that eventually became the sole product isolable), whereas "genuine" 15 gave different products (mainly 17) instead, and no oxime at all. From 5, little if any 15 is directly engendered as such, but it arises as its nitronic acid tautomer, which presents itself as 15 in tlc or upon isolation, but persists in solution until it is reduced to 16.

There are precedents in the literature^{140,141} for the formation of hexahydro derivatives from carbohydrate benzylidene acetals on hydrogenation in the presence of platinum or Raney nickel, but this type of reaction seems to have been encountered infrequently, and hydrogenolytic removal of the acetal might, rather, have been expected to prevail¹⁵⁹.

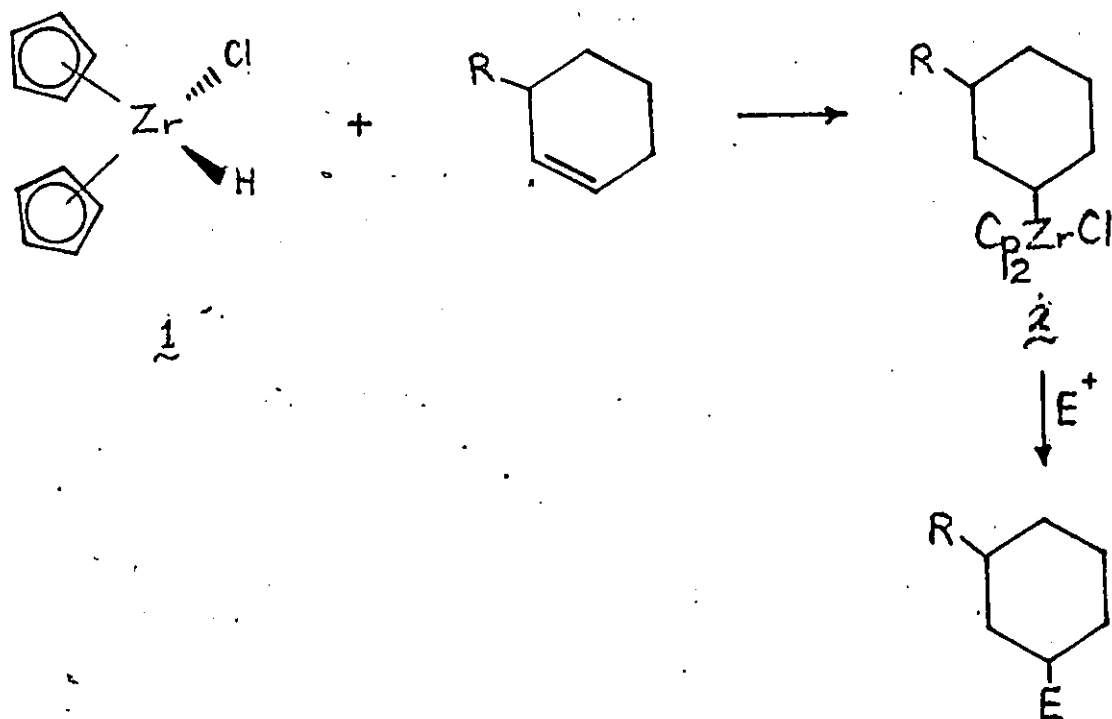
PART IV

ATTEMPTED HYDROZIRCONATION OF

UNSATURATED SUGARS

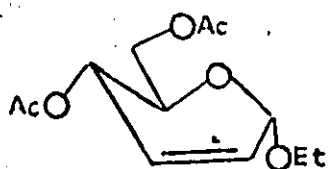
Transition metals hydrides constitute another valuable class of reagents for organic synthesis. Selective hydrometalation of such readily available starting materials as olefins and acetylenes may produce reactive, σ -bonded organometallic intermediates, which may then be converted, by appropriate cleavage of the carbon-metal bond, into a variety of organic products.

Hydrozirconation has recently^{160,161} been developed as a procedure for functionalizing alkenes, alkynes, and 1,3-dienes via organozirconium(VI) intermediates. These intermediates reacts with a variety of electrophilic reagents E^+ , (eg., Br_2 , I_2 ; N-bromo- or N-chlorosuccinimide, or iodobenzene dichloride), to give the corresponding substitution product in high yield^{161,162}. Thus,

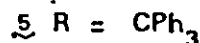
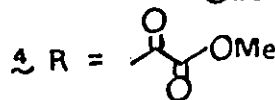
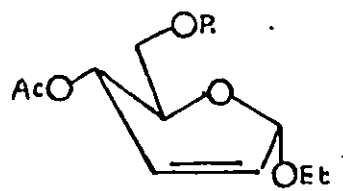
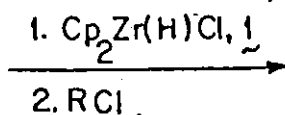


zirconiumdicyclopentadienylhydrido chloride ($\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$, 1) was found to react with alkenes under mild conditions to generate isolable alkylzirconium(IV) complexes, $\text{Cp}_2\text{Zr}(\text{R})\text{Cl}$ (2). Hydrozirconation proceeds to place the zirconium moiety at the sterically least hindered position of the olefin molecules as a whole¹⁶³.

It appeared interesting to apply this type of reaction to unsaturated carbohydrates, which had not previously been attempted. It was hoped to achieve functionalization, for example, at C-2 or C-3 in 2-enosides. However, treatment of ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (3) with the zirconium hydride 1 in benzene solution at room temperature, followed by addition of methyl oxalyl chloride as the electrophile, led to selective replacement of the primary acetyl group with the methyl oxalyl group, giving the crystalline ester 4. The structural assignment was based on elemental analysis and ^1H -nmr data. In particular, the spectrum showed a three-proton singlet at δ 3.92 due to a methoxy resonance, replacing the C-6 acetoxy resonance (δ 2.02) given by 3. The olefinic structure was unchanged as indicated by a narrow, 2-proton multiplet at δ 5.87 for H-2 and H-3 (the same as in 3).

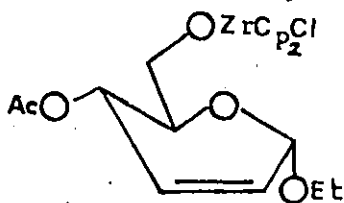


3



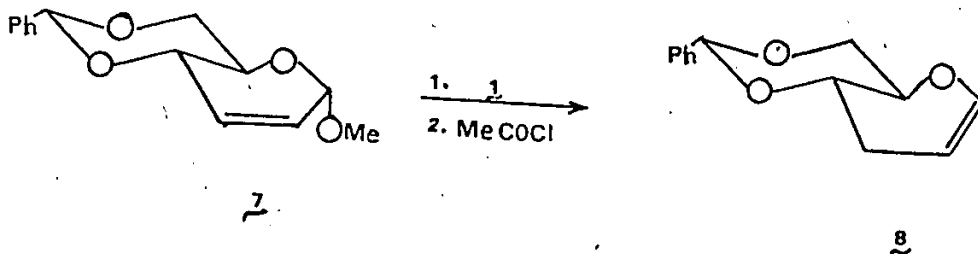
Similar treatment of 3 with another electrophile, namely triphenylmethyl chloride, proceeded at a somewhat slower rate and gave the trityl ether 5. The ^1H -nmr spectrum proved the incorporation of a trityl group. (15-proton multiplet at δ 7.2), retention of the alkenic structure (2-proton singlet at δ 5.8 due to coinciding H-2 and H-3 resonances), and presence of only one acetoxy group, whose 3-proton singlet was shifted to δ 1.84 (from δ 2.06 in 3) owing to a shielding effect that is commonly observed when aryl substituents are present in sugar acetates.

It was evident from monitoring the reaction by tlc that 3 did indeed react with 1: A reaction intermediate (presumably 6) was seen to arise and subsequently, when the electrophile was added, to disappear again. Use of acetyl chloride as the electrophile led to recovery of 3.

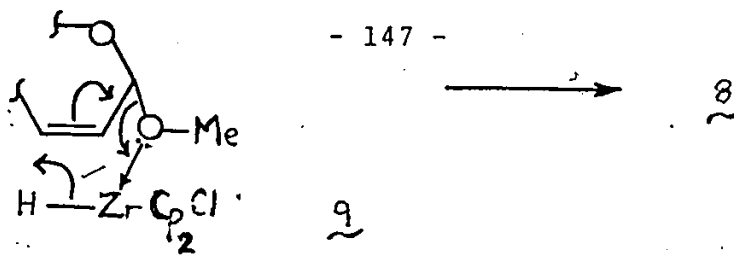


6

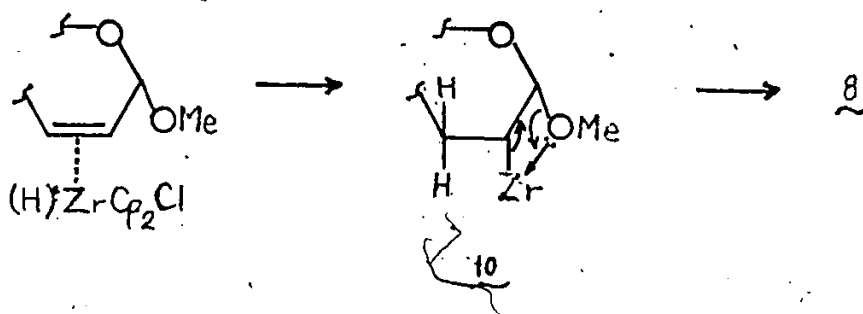
Having thus realized that a primary acetate group in the molecule interferes with the desired hydrozirconation of the alkene function, we decided to try a substrate which lacks such a group. Methyl 4,6-O-benzylidene-2,3-dideoxy- α -D-erythro-hex-2-enopyroside (7) was chosen and allowed to react with 1 and acetyl chloride under identical conditions. The result was even more surprising. Compound 7 suffered loss of its glycosidic methoxyl group, accompanied by isomerisation of the double bond to give the 3-deoxy glycal 8. This transformation is reminiscent of the reductive rearrangement of some allylic acetals to vinyl ethers by use of chloride-free LiAlH_4 in ethereal solvents¹⁶⁴. The formation of 8 can be explained by the formation of an intermediary complex 9 in analogy to the



explanation suggested for the LiAlH_4 case¹⁶⁴. This pentacoordinated complex collapses to form the vinyl ether 8. An alternative mechanism could be initial formation of the hydrozirconated intermediate 10, from which, by the assistance of the glycosidic



oxygen atom (with its lone pair of electrons coordinating with an empty orbital of the zirconium atom), elimination occurs to give the observed product 8. Similar eliminations were observed for different substrates in hydroboration reactions, and intermediates analogous to 10 were proposed¹⁶⁵.



It may perhaps be possible to avoid elimination by performing the hydrozirconation at a lower temperature, or by using a silyl instead of a methyl glycoside as the substrate. It is known that silicon has the ability to use its vacant 3d - orbitals in the formation of π -type bonds with oxygen which have considerable double-bond character¹⁶⁶. This would decrease the coordination ability of the glycosidic oxygen atom and thus discourage its interaction with the zirconium moiety.

* The author is indebted to Professor J. Schwartz for proposing this explanation.

EXPERIMENTAL SECTION

GENERAL TECHNIQUES.

A glove-bag was used as a convenient device for the handling, transfer, and preparation of moisture- or air-sensitive materials in an inert atmosphere. Where necessary for critical experiments, glassware and NMR tubes were first heated overnight in an oven at ca. 110° and then purged, while still hot, with a stream of dry nitrogen. All reactions involving organometallic reagents were carried out in an atmosphere of dry nitrogen under slightly positive pressure, in flame-dried glassware. Rubber septa and hypodermic needles were conveniently used for transferring liquids to and from vessels without introducing air.

All reactions were performed in reagent-grade solvents which were further purified as follows. Tetrahydrofuran (THF) was freshly prepared by refluxing over, and distilling from, sodium or potassium metal under nitrogen in the presence of (dark blue) benzophenone radical anion. Benzene and ether were dried over sodium wire, and ethanol was made absolute by means of magnesium. All other solvents were used as purchased, without further purification unless otherwise noted. Petroleum ether normally refers to the fraction boiling at 30-60°.

Thin layer chromatography (tlc) was routinely employed to monitor reactions and column-chromatography separations, and to check the purity of products. It was performed on precoated silica-gel plates

SIL G-25 UV₂₅₄, whereas preparative tlc was done on glass plates coated with MN-Kieselgel G/UV₂₅₄. (both products manufactured by Macherey-Nagel & Co., West Germany). Spots were made visible by inspection under UV light and (or) by spraying the plates with 5% sulfuric acid in ethanol, followed by heating. For detection of amino sugars, a spray of 0.2% ninhydrin in ethanol was also used. The R_F values given are illustrative; they may vary somewhat with minor changes in solvent composition or temperature. Starting compounds and authentic samples of products, where available, were routinely spotted alongside unknown products. Column chromatography was performed with silica gel 60 (E. Merck AG., West Germany). Systems employed for development were mixtures of the following solvents in the ratios (V/V) indicated. Ethyl acetate-petroleum ether: (A) 1:1, (B) 1:2, (C) 1:3, (D) 1:4, (D') 1:6, (E) 1:10, (F) 3:2; ethyl acetate-pentane: (G) 1:1; methanol-chloroform: (H) 1:2, (J) 1:4; ethylacetate-ether: (J) 1:1; ethyl acetate-ether-petroleum ether: (K) 1:1:1; methanol-dichloromethane: (L) 1:2. Other solvents were used where so indicated.

The $^1\text{H-NMR}$ spectra were recorded at 60 MHz with a Varian T-60 spectrometer or at 100 MHz with a Varian HA-100 spectrometer. The $^{13}\text{C-NMR}$ spectra were recorded at 20 MHz with a Varian CFT-20 spectrometer. The NMR spectra were obtained from CDCl_3 solutions containing tetramethylsilane as the internal standard. The chemical shifts are expressed in parts per million (δ) downfield from Me_4Si , and the $^1\text{H-NMR}$ peak areas are expressed as

the number of hydrogen atoms (H). Infrared spectra were recorded on a Beckman IR-20 or IR-20A infrared spectrophotometer. Spectra of syrupy compounds were obtained from neat liquid films, and those of crystalline compounds, from Nujol mulls and were calibrated with a polystyrene standard. Some absorption bands are characterized as bd (broad), ms (medium strong), s (strong), sh (shoulder), or w(weak). Mass spectra were recorded on an AE-1-MS902 mass spectrometer fitted with a direct-inlet probe at an ionizing potential of 50-55 eV. Optical rotations were performed at room temperature with Perkin-Elmer 141 automatic polarimeter and refer to chloroform solutions unless otherwise stated. Melting points were determined with a Gallenkamp capillary melting point apparatus and are uncorrected.

All catalytic hydrogenations were performed at ambient temperature (21-26°), with hydrogen at a pressure slightly above atmospheric, unless otherwise indicated, and efficient shaking of the vessel was assured. The palladium catalyst (10% Pd-on-carbon) was obtained from Matheson Coleman & Bell, and was used without pretreatment. Adams catalyst ($\text{PtO}_2 \cdot \text{H}_2\text{O}$) was purchased from Engelhard Industries, Inc., or BDH Chemicals of Canada, Ltd., and was prehydrogenated in a small volume of the reaction solvent. In experiments performed without the addition of acid, the prehydrogenated platinum catalyst was washed by several decantations with fresh solvent prior to use. For product isolation, the catalysts were filtered off and washed exhaustively with methanol or ethanol, and the filtrates were evaporated.

Evaporations were carried out at about 35° (bath temperature) in a rotatory evaporator. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona.

PART I

Preparation of the Unsaturated Glycoside Diacetates 29, 24, 46

Ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (29) was prepared from 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (28, tri-O-acetyl-D-glucal) according to the method of Ferrier⁴⁷; it showed m.p. 79° and $[\alpha]_D + 109^\circ$ (c 1, benzene) as reported; $[\alpha]_D + 117.3^\circ$ (c 2.2, chloroform).

The β -anomer 45 was prepared from the intermediate, ethyl 3,4,6-tri-O-acetyl-2-acetoxymercuri-2-deoxy- β -D-glucopyranoside in analogy to its methyl glycoside described by Inglis and coworkers⁵⁰. A solution of tri-O-acetyl-D-glucal (5.0 g, 18.4 mmol) in absolute ethanol (20 mL, dried over and distilled from magnesium) was added to a stirred suspension of mercuric acetate (6.14 g, 19.2 mmol) in absolute ethanol (70 mL), whereupon the salt dissolved rapidly. The ethoxymercurated intermediate began to crystallize after an hour and was collected after overnight storage of the reaction mixture. (It thus proved unnecessary to convert the product into the chloromercuri compound as had been done in the methoxymercuriation just cited). The crystals (3.50 g, 33%) had mp 177° after recrystallization from ethyl acetate; $[\alpha]_D - 15.5^\circ$ (c 2.3); $\nu_{\text{max}}^{\text{Nujol}} 1735$ and 1240 (OAc), 1620-1600 (AcO), 1300, 1140-1000, and 920 cm^{-1} . Two sharp, medium strong bands at 755 and 690 cm^{-1} were possibly due to Hg-O vibrations¹⁶⁷. NMR (100 MHz, CDCl_3); δ 5.17 (dd, $J_{2,3} = 11.3$, $J_{3,4} = 9.3$ Hz, H-3), 4.95 (t, $J = 9.3$ Hz, H-4), 4.71 (d, $J_{1,2} = 10$ Hz, H-1), 4.34 (dd, $J_{5,6} = 4.7$, $J_{6,6'} = 12$ Hz, H-6), 4.09 (dd, $J_{5,6} = 2.7$, $J_{6,6'} = 12$ Hz, H-6'), 3.95-3.4 (m, 3 H, Me-CH_2 and H-5), 2.62 (dd, $J = 10$ and 11.3 Hz, H-2), 2.15, 2.06, 2.02 (3 s,

total intensity 12 H, 4 OAc), 1.22 (t, $J = 7$ Hz, ethyl CH_3).

Anal. calcd. for $\text{C}_{16}\text{H}_{24}\text{HgO}_{10}$ (577): C 33.31, H 4.19; found: C 33.51, H 4.36.

A solution of this acetoxymercuri derivative (1.0g) in aqueous, 75% ethanol (25 mL) was mixed with a solution of sodium iodide (1.5 g) in 25 mL of the same solvent. Complete conversion of the mercurial (R_F 0.0) into 45 (R_F 0.6) was indicated by tlc (solvent B) after 30 min. The reaction mixture was concentrated in vacuo to one-third of its volume and then diluted with water to 50 mL. Then it was extracted several times with ether.

The organic phase was washed successively with saturated aqueous sodium thiosulfate solution and water, dried over anhydrous magnesium sulfate and the solvent removed in vacuo to give 45 as a colorless syrup (0.38, 85%); $[\alpha]_D + 148.5^\circ$ (c 3.6, benzene); ν_{max} 1750 and 1240 (OAc), 1150, 970, 910, 815, and 750 cm^{-1} .

Anal. calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_6$ (258.3): C 55.80, H 7.02; found: C 55.82, H 7.00.

The known^{50,78} methyl glycoside analog (45a) of 45 was prepared from 28 by analogous methoxymercuration⁴⁹ followed by elimination⁵⁰. NMR data (100 MHz, CDCl_3) of the intermediate methyl 3,4,6-tri-O-acetyl-2-chloromercuri-2-deoxy- β -D-glucopyranoside: δ 5.18 (dd, $J_{2,3} = 11.5$, $J_{3,4} = 9$ Hz, H-3), 4.93 (t, $J = 9$ and 9.5 Hz, H-4), 4.65 (d, $J_{1,2} = 9.7$ Hz, H-1), 4.32 (dd, $J_{5,6} = 5$, $J_{6,6'} = 12.5$ Hz, H-6), 4.09 ($J_{5,6'} = 2.5$; $J_{6,6'} = 12.5$ Hz, H-6'), 3.67 (o, H-5), 3.52 (s, 3H, OMe), 2.55 (dd, $J = 9.7$ and 11.5 Hz, H-2), 2.08 and

2.04 (s, 6 and 3H, 3 OAc)..

Ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-threo-hex-2-enopyranoside (46)⁵² was obtained by conventional acetylation with acetic anhydride in pyridine (1 h at 25°), of a crystalline sample of ethyl 2,3-dideoxy- α -D-threo-hex-2-enopyranoside kindly donated by

Professor B. Fraser-Reid. The diacetate was a colorless syrup,

R_F 0.8 (solvent B), $[\alpha]_D - 171.5^\circ$ (c 1.5, chloroform); Lit⁵² $[\alpha]_D - 171^\circ$ (dichloromethane); ν_{max} 1750 and 1240 (OAc), 1110, 1050, 1020-970, 915, 850, 760 and 600 cm^{-1} .

General Procedure for Allylic Substitution

For Amination

The catalyst employed through this Part was tetrakis(triphenylphosphine)palladium(0). It may be prepared according to Coulson¹⁶⁸ or purchased from Aldrich Chemical Company, Inc. A sample was kindly donated by Professor H. Alper. Reactions were normally performed on a 0.5 mmol scale with respect to the glycoside employed (0.13 g). Deviations from this amount of starting glycoside are specifically indicated and imply proportionate changes in the amounts of solvent and other reactants. Typically the glycoside (0.13g, 0.5 mmol), triphenylphosphine (95 mg, 0.35 mmol) and the catalyst (41 mg, 0.035 mmol) were stirred in tetrahydrofuran (10 ml) for 30 min at room temperature, under nitrogen, in a flask equipped with reflux condenser and gas inlet. An excess of the amine (3.3-3.5 mmol) was then added by syringe, and the mixture was heated at reflux until monitoring by tlc indicated absence of the starting glycoside. (See individual sections for the various reaction times.) The cooled reaction mixture was partitioned between ether and water, the aqueous phase was extracted with ether (4 x 30 mL), and the combined extracts and organic phase were dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give a yellow residue which contained the aminated sugar together with triphenylphosphine oxide, residual amine, and other impurities. Purification of this residue, via column chromatography or preparative tlc as indicated in the individual sections, furnished

the desired product in homogenous form, usually as a colorless, analytically pure oil.

For Alkylation

The mixture of glycoside, triphenylphosphine, and catalyst was prepared as described above, except that only 5 ml of tetrahydrofuran was used as the solvent. Separately and simultaneously, a solution of the sodio derivative of the reactive methylene component was prepared. For this purpose, sodium hydride (130 mg, of a 61% dispersion in mineral oil; ca. 3.3 mmol) was washed twice with hexane and once with tetrahydrofuran by decantation and was then suspended in 5 ml of tetrahydrofuran. The methylene component (3.35 mmol or slightly more) was added drop wise with stirring, which caused the hydride to dissolve completely in the course of 15 min. The resulting, clear solution was added, in one portion, to the aforementioned solution of reactants when the latter had interacted for 30 min, and the combined mixture was then heated at reflux until tlc indicated completion of the reaction. The precautions and processing modes applied were the same as those in the aminations.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-4-diethylamino- α -D-crythrohex-2-enopyranoside (31)

Compound 31 was obtained from 29 and diethylamine (0.35 mL) after a reaction time of 48 h and preparative tlc (solvent D). The colorless oil (110 mg, 80%) showed R_f 0.9 (tlc with solvent B), $[\alpha]_D +169.8^\circ$ (c 1), ν_{max} 1745 and 1260 (OAc), 1150-1000 (C-N, C-O-C),

and 730 cm^{-1} (cis alkene). Anal.: calcd. for $\text{C}_{14}\text{H}_{25}\text{NO}_4$ (271.4):
C 61.97, H 9.29, N 5.16; found C 62.11, H 9.18, N 4.97.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-4-piperidino-
 α -D-erythro-hex-2-enopyranoside (32)

Prepared exactly like the preceding compound, but with piperidine (0.33 mL), 32 was a colorless oil (100 mg, 70%), R_F 0.9 (tlc in solvent B), $[\alpha]_D +164.3^\circ$ (c 1), ν_{\max} 1745 and 1240 (OAc), 1160-1000 (C-N, C-O-C), and 730 cm^{-1} (cis alkene). Anal. calc. for $\text{C}_{15}\text{H}_{25}\text{NO}_4$ (283.4); C 63.58, H 8.89, N 4.94, found: C 63.41, H 8.97, N 4.67.

Ethyl 6-O-Acetyl-4-(N-cyclohexyl)methylamino-2,3,4-trideoxy-
 α -D-erythro-hex-2-enopyranoside (33)

From 29 (200 mg) and cyclohexylmethylamine (0.44 mL), compound 33 was obtained after a reaction time of 5 days; it was accompanied by traces of 2 slow-moving by-products (tlc with solvent B) which were readily removed by preparative tlc (solvent D). The colorless, homogeneous product (180 mg, 75%) had $[\alpha]_D +149.7^\circ$ (c 1), ν_{\max} 1745 and 1240 (OAc), 1120-1000 (C-N, C-O-C), and 730 cm^{-1} (cis alkene). Anal. calcd. for $\text{C}_{17}\text{H}_{29}\text{NO}_4$ (311.4): C 65.56, H 9.39, N 4.50; found: C 65.53, H 9.27, N 4.51.

Ethyl 6-O-Acetyl-4-(N-benzyl)methylamino-2,3,4-tri-deoxy-D-erythro-hex-2-enopyranoside (34)

Reaction of 29 with benzylmethylamine (0.5 mL) was complete after 24 h, and tlc (solvent B) showed a main spot (R_F 0.8) accompanied by a minor spot (R_F 0.7), which was presumably due to an isomer. Isolated by preparative tlc (solvent C), the major product 34 was a colorless syrup (140 mg, 87%) that tended to crystallize on strong cooling (mp below 0°); $[\alpha]_D +165.4^\circ$ (c 1), ν_{\max} 3100-3050, 1600, 1500, and 700 (Ph), 1745 and 1240 (OAc), 1120 - 970 (C-N, C-O-C), and 740 cm^{-1} (cis alkene). Anal. calcd. for $C_{18}H_{25}NO_4$ (319.4): C 67.69, H 7.89, N 4.39; found: C 67.53, H 7.83, N 4.51.

Ethyl 6-O-Acetyl-4-dibenzylamino-2,3,4-trideoxy- α -D-erythro-hex-2-enopyranoside (35) and Ethyl 6-O-Acetyl-2-dibenzylamino-2,3,4-trideoxy- α -D-threo-hex-3-enopyranoside (36)

The reaction of 29 with dibenzylamine (0.64 mL) was nearly complete after 30 h. The tlc (solvent C) indicated the presence of two main products having $R_F \sim 0.8$ (major product) and ~ 0.7 (minor product), together with traces of slow-moving by-products. Integration of the sufficiently separated acetoxy group signals in the nmr spectrum of the crude mixture (166 mg, 83%) suggested that the two main components were present in the ratio 7:3. The components were separated by preparative tlc using multiple irrigation with solvent E, which furnished either product free from the other (according to nmr spectra).

The syrupy, slower-moving, minor product proved to be the isomer 35. It crystallized on storage in the refrigerator. Collected after trituration with petroleum ether and recrystallized from that solvent, it showed mp 78-79°, $[\alpha]_D +171.4^\circ$ (c 1.4); ν_{\max} 3100-3040, 1600, 1500, and 700 (Ph); 1745 and 1240 (OAc), 1120-975 (C-N, C-O-C), and 755-735 cm^{-1} (cis alkene). Anal. calcd. for $\text{C}_{24}\text{H}_{29}\text{NO}_4$ (395.5): C 72.89, H 7.39, N 3.54; found: C 72.69, H 7.56, N 3.54.

The faster-moving, major product (36) failed to crystallize; $[\alpha]_D +155.3^\circ$ (c 1.2). Its infrared spectrum was very similar to that of 35, showing only minor differences in the fingerprint region. Anal. calcd. as for 35; found C 72.57, H 7.83, N 3.68.

Ethyl 6-O-Acetyl-4-benzylamino-2,3,4-trideoxy- α -D-erythro-hex-2-enopyranoside (37) and Ethyl 6-O-Acetyl-4-(N-benzyl-acetamido)-2,3,4-trideoxy- α -D-erythro-hex-2-enopyranoside (39)

The allylic acetate 29 was reacted with benzylamine (0.36 mL) for 24 h, after which, tlc with solvent B showed the presence of three products ($R_F \sim 0.6, 0.25, \text{ and } 0.2$) together with some remnant starting material ($R_F \sim 0.75$). An additional 10 mg of the catalyst and 0.1 mL of benzylamine were introduced and refluxing was continued for another 9 h, which caused 29 to disappear completely. Upon processing, the mixture of products was applied to a silica gel column that was irrigated with solvent D. The fast-moving product (37) was isolated as a colorless oil (48 mg, 31%), $[\alpha]_D +115.5^\circ$ (c 1.1); ν_{\max} 3200 (broad, NH), 3100-3050,

1600 and 1500 (weak), and 700 (Ph), 1740 and 1240 (OAc), 1100-1000 (C-N, C-O-C), and 730 cm^{-1} (cis alkene). On ageing of the sample, an amide band at 1650 cm^{-1} developed owing to O \rightarrow N acetyl migration.

The two slow-moving products were subsequently eluted from the column as a mixture. An attempt was made to separate this mixture by preparative tlc (solvent E), but separation was unsatisfactory in that each of the two bands isolated contained a substantial proportion of the other component ($\sim 1/3$ according to nmr spectra). The spectra suggested that the components were the O-deacetylated derivative (38, R_F 0.25) of 37, and partially O-deacetylated 29 (R_F 0.2). The fractions were individually acetylated with acetic anhydride and pyridine (16 h at room temperature), whereupon they gave similar tlc patterns showing a fast-moving spot (29) and a slow-moving spot (the N-acetyl-O-acetyl derivative 39). Preparative tlc (solvent E) of these mixtures gave a total of 65 mg (50% recovery) of 29, identified by its nmr spectrum and an undepressed mixture mp of 79-81 $^{\circ}$; and oily but homogeneous 39 (27 mg, 15%) showing $[\alpha]_D^{20}$ 129 $^{\circ}$ (c 1.1); ν_{max} 3100-3050, 1610 and 1500 (weak), and 700 (Ph), 1740 (ester CO), 1650 (amide CO), 1250-970 (multiple bands), 900, and 735 cm^{-1} . Anal. calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_5$ (347.4): C 65.69, H 7.25, N 4.03; found: C 65.53, H 7.41, N 3.83.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-4- [bis(methoxycarbonyl)-methyl] - α -D-erythro-hex-2-enopyranoside (42)

Reaction of 29 and dimethyl malonate (0.40 mL) was complete after 10 h and gave 42 as the sole product; according to tlc ($R_F \sim 0.4$, solvent B). The colorless syrup (145 mg, 87%) obtained after processing showed $[\alpha]_D +93.5^\circ$ (c 1.3); ν_{max} 1740 (ester C=O), 1250-970 (C-O-C), and 730 cm^{-1} (cis alkene). Anal. calcd. for $C_{15}H_{22}O_8$ (330.3): C 54.54, H 6.71; found: C 54.72, H 6.89.

Ethyl 6-O-Acetyl-2,3,4--trideoxy-4- [bis(ethoxycarbonyl)-methyl] - α -D-erythro-hex-2-enopyranoside (43)

Compound 29 and diethyl malonate (0.50 mL) were allowed to react for 24 h. In this instance, the product 43 had the same R_F value (0.8) as 29 and could only be distinguished by the light brown color of its spot, which differed from the black spot given by 29 (tlc with solvent B). Possibly the reaction was finished earlier. Processing gave 43 (150 mg, 83%) as a colorless syrup, $[\alpha]_D +93.4^\circ$ (c 1.1); ν_{max} 1750, 1730 (ester C=O), 1250-1000 (C-O-C), and 730 cm^{-1} (cis alkene). Anal. calcd. for $C_{17}H_{26}O_8$ (358.4): C 56.97, H 7.31; found C 56.81, H 7.57.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-4- [methoxycarbonyl(phenylsulfonyl) methyl] - α -D-erythro-hex-2-enopyranoside (44)

Compound 29 (300 mg, 1.16 mmol) was allowed to react with a 0.117 M solution (65 mL) of methyl phenylsulfonylacetate sodium in tetrahydrofuran. Incomplete consumption of 29 was noted by tlc (solvent B) after 48 h; an additional 30 mg of catalyst and 4 mL

of the solution of the sodio ester solution were introduced, whereupon 29 disappeared completely after a further 24 h of refluxing. There was formed one major product ($R_F \sim 0.45$) which was accompanied by a minor, slightly faster moving product. Column chromatography using solvent D as eluent gave 300 mg (63%) of the product as a syrup that still contained the minor by-product. Crystallization from ethyl acetate-petroleum ether furnish chromatographically pure 44, mp 100-102°, $[\alpha]_D +74^\circ$ (c 2.8); $\nu_{\text{max}}^{\text{Nujol}}$ 3100-3050, 1600, and 700 (Ph), 1750-1730 (ester CO), 1320 (S=O), 1250-950 (multiple bands, S = 0, C-O-C), and 730 cm^{-1} (cis alkene). Anal. calcd. for $\text{C}_{19}\text{H}_{24}\text{O}_8\text{S}$ (412.4), C 55.33, H 5.87, S 7.77; found: C 55.08, H 5.77, S 7.62.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-4-[bis(methoxycarbonyl)-methyl]- β -D-erythro-hex-2-enopyranoside (55)

The acetate 45 was reacted with dimethylmalonate (0.40 mL) for 10 h, after which a single spot having R_F 0.55 was seen in tlc (solvent B). Purification of the residual oil by column chromatography which was eluted, first, with petroleum ether, and then with solvent E, afforded (145 mg, 87%) of 55 as an oily product. Although it appeared chromatographically homogenous, analysis by the ^{13}C -nmr spectrum, revealed the presence of a small proportion (probably, not more than 10%) of an isomer;

$[\alpha]_D +52.5^\circ$ (c 3); ν_{max} 1750-1730 (ester CO), 1300-1010 (multiple bands), 880-800, and 735 cm^{-1} . Anal. calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_8$ (330.3): C 54.54, H 6.71; found C 54.63, H 6.76.

Methyl 6-O-Acetyl-2,3,4-trideoxy-4-[bis(methoxycarbonyl)methyl]- β -D-erythro-hex-2-enopyranoside (55a)

As for 45, acetate 45a (120 mg) was reacted with dimethylmalonate to give after 20 h and purification via column chromatography, (125 mg, 83%) of 55a as a clear, pale yellow syrup. The compound showed as a single spot in tlc (R_F 0.6, solvent B) but contained, nevertheless, a small proportion of an isomer, according to the ^{13}C -nmr spectrum; $[\alpha]_D +44$ (c 0.5); ν_{max} 1750 (ester CO), 1300-1050 (multiple bands), 970, 870-810, and 740 cm^{-1} . Anal. calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_8$ (316.3): C 53.16, H 6.37; found: C 53.16, H 6.47.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-4-diethylamino- β -D-erythro-hex-2-enopyranoside (52)

The reaction of 45 (130 mg) with diethylamine (0.85 mL) was not entirely complete after 20 h (tlc with solvent B); it was completed by adding further amounts of diethylamine (0.4 mL) and catalyst (20 mg) and continued refluxing for another 6 h. Processing included purification of the crude product via a silica gel column which was eluted, first with petroleum ether and then, with solvent E. Compound 52 was obtained as a colorless syrup (90 mg, 66%), R_F 0.3 (solvent B), $[\alpha]_D +133.6^\circ$ (c 1.1); ν_{max} 1745 and 1250 (OAc), 1200, 1120-1020 (C-N, C-O-C), 980, 900, 835, 800, 730 and 700 cm^{-1} .

Ethyl 6-O-Acetyl-4-(N-benzyl)methylamino-2,3,4-trideoxy- β -D-erythro-hex-2-enopyranoside (53)

The reaction between 45 (195 mg) and benzylmethylamine (0.75 mL) showed, after 24 h, a product that differed from 45 only in the

color (light brown vs. black) of its tlc spot, but not in the R_F value (0.6 in solvent A). Refluxing was continued for another 24 h, which caused no change in the tlc picture. After processing (with use of dichloromethane instead of ether for extraction of the aqueous phase) and column chromatographic purification (elution with petroleum ether followed by solvent E), compound 53 was obtained as a clear, colorless syrup (220 mg, 91%) $[\alpha]_D + 118.2^\circ$ (c 1.3); ν_{\max} 3100-3050, 1600, 1500, and 700 (Ph), 1745 and 1240 (OAc), 1120-970 (C-N, C-O-C), 900 and 810, and 755-730 cm^{-1} . (cis alkene). Anal. calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_4$ (319.4): C 67.69, H 7.89, N 4.39; found: C 67.47, H 8.13, N 4.26.

Ethyl 6-O-Acetyl-2,3,4-trideoxy-2- [bis(methoxycarbonyl)methyl] - α -D-threo-hex-3-enopyranoside (56) and Ethyl 6-O-Acetyl-2,3,4-trideoxy-4- [bis(methoxycarbonyl)methyl]-hex-2-enopyranoside (57)

The acetate 46 (347 mg), triphenylphosphine (246 mg) and palladium catalyst (108 mg) in tetrahydrofuran (15 mL) were treated with dimethyl sodiomalonate, prepared from dimethyl malonate (1.32 mL) and sodium hydride (61%; 343 mg) in tetrahydrofuran (10 mL). All of 46 had disappeared after 15 h of heating at reflux temperature. Tlc with solvent B showed a strong spot (R_F 0.6) together with a second, fairly strong, double spot ($R_F \sim 0.1$) and an intermediate trace spot. Column chromatography produced the fast-moving material (295 mg, 66%) which, although homogeneous in tlc, proved to be a $\sim 3:1$ mixture of 56 and 57, according to ^1H - and ^{13}C -nmr spectra. This mixture of isomers showed $[\alpha]_D + 24^\circ$

(c 1.3) and an infrared spectrum that agreed with expectations.

Anal. calcd. for $C_{15}H_{22}O_8$ (330.3): C 54.54, H 6.71; found:
C 54.37, H 6.65..

The slow-moving material emerged from the column on continued elution with solvent E. There were obtained 2 fractions (55 and 65 mg), both of which showed methylester but lacked acetyl group resonances in the nmr spectrum. Acetylation with acetic anhydride and pyridine at room temperature left the first fraction unchanged whereas it converted the second fraction into a syrupy monacetate, $[\alpha]_D + 100^\circ$ (c 0.24), whose 1H -nmr spectrum matched the

signals belonging to the major component (56), in the spectrum of the aforementioned mixture of 56 and 57. The infrared spectrum was also closely similar to that of the mixture: ν_{max} 1750 and 1250 (ester), 1200-1000 (C-O-C), 930, 820, and 730 cm^{-1} .

Mixture of Ethyl 6-O-Acetyl-2,3,4-trideoxy-2- [methoxycarbonyl-(phenylsulfonyl)methyl] - α -D-hex-3-enopyranoside (58) and Ethyl 6-O-Acetyl-2,3,4-trideoxy-4- [methoxycarbonyl(phenylsulfonyl)-methyl] - α -D-hex-2-enopyranoside (59)

As described above, compound 46 (200 mg) was allowed to react with a 0.117 M solution (40 mL) of methyl phenylsulfonylacetate sodium in tetrahydrofuran. All of 46 was consumed after 5 days, and two product spots of comparable strength and similar mobilities (R_F 0.4 - 0.5) were seen in tlc (solvent B). The products could not be separated; their presence in a ratio of ~ 1:1 was indicated by 1H - and ^{13}C -nmr spectra. The mixture of 58

and 59 showed $[\alpha]_D +39^{\circ}.4$ (c 2.8). Anal. calcd. for $C_{19}H_{24}O_8S$ (412.4): C 55.33, H 5.87, S 7.77; found: C 55.25, H 5.83, S 7.74

Methyl 4-O-Benzoyl-6-bromo-2,3,6-trideoxy- α -D-erythrohex-2-enopyranoside (77)

A mixture of methyl 4-O-benzoyl-6-bromo-6-deoxy- α -D-glucopyranoside¹⁰¹ (76) (6.3 g, 17.5 mmol), triphenylphosphine (19.8 g, 75 mmol), 2,4,5-triiodoimidazole (18.0 g, 40 mmol), and imidazole (3.43 g, 50 mmol), in toluene (360 mL) was boiled under reflux for 2 h, after which time the slow-moving 76 was replaced by fast-moving 77, $R_F \sim 0.8$ (tlc with solvent B). After the mixture had been cooled, the solution was decanted from a gummy residue which was washed well with several portions of ether. The organic solutions were combined, washed once with a saturated, aqueous sodium hydrogencarbonate solution, twice with saturated sodium thiosulfate solution, and finally once with water, and then dried with anhydrous magnesium sulfate, filtered, and evaporated to give a brownish mixture of products that was triturated with ether. Evaporation of the extract gave a syrup from which some crystalline triphenylphosphine oxide was separated by renewed trituration with ether. The ethereal solution was evaporated to a syrup which was chromatographed on a column of silica gel (30 g per g of syrup). Elution was started with 1:20 ethyl acetate-petroleum ether (50 mL). When most of the remaining triphenylphosphine had been eluted, the eluting solvent ratio was changed to 1:10 (50 mL) and then to 1:5 (250 mL). After evaporation of the eluate, compound 77 (3.5 g, 61.4%) was obtained as a syrup

which was suitable for use in the subsequent step, although it still contained a small amount of triphenylphosphine oxide.

A higher yield of 77 was obtained when crude 76 (24 g, as produced from 20 g of the benzylidene derivative 75 before crystallization and processing of mother liquors^{101a}) was dehydroxylated as just described, with proportionate quantities of the reagents, and a reflux time of 2.5 h. Processing was performed in the foregoing manner, except that the aqueous washings of the organic layer were subsequently combined (650 mL) and, as they were revealed by tlc to contain a considerable amount of 77, extracted with dichloromethane (3 x 100 mL) followed by ether (2 x 100 mL). All extracts were combined with the original toluene-ether phase before proceeding as described, and there was obtained 21.3 g (91.8%) of crude 77.

Preparative tlc on silica gel (solvent E) was used for preparing a sample for spectral analysis. The band visible under UV light was eluted with ethyl acetate, and evaporation of the eluate afforded colorless, syrupy 77 whose nmr spectra (Tables 6 and 7, p. 83) taken immediately, established its structure and purity. Elemental analysis of 77 had to be dispensed with, since the isolated compound tended to decompose rather rapidly at room temperature.

Methyl 4-O-Acetyl-6-bromo-2,3,6-trideoxy- α -D-erythro-
hex-2-enopyranoside (79)

Crude 77 (21.0 g) was stirred at room temperature in a mixture of methanol (150 mL), water (65 mL), and triethylamine (30 mL). The debenzoylation was surprisingly slow; according to tlc (solvent B), complete replacement of the benzoate 77 (R_F 0.8) by the alcohol 78 (R_F 0.6) was required 3 days. A small amount of triphenylphosphine oxide precipitated in the course of time. The precipitate was filtered off and the filtrate was evaporated, with several portions of ethanol being added and evaporated. Finally the residue was freed from remnant ethanol by evaporation with ethyl acetate followed by dichloromethane. The vacuum-dried, syrupy 78 (13.3 g, 93%) was dissolved in acetic anhydride (10 mL), and to the cooled (-5°) solution was added pyridine (12 mL). The acetylation, allowed to proceed at room temperature, was complete after 2 h. Evaporation of the reaction mixture at 40° (bath temperature) in an oil-pump vacuum, followed by evaporation from the syrupy product, of 2 added portions of toluene, afforded the crude acetate 79 (13.65 g). It appeared relatively unstable on storage; it was immediately passed through a column of silica gel (175 g) by means of ethyl acetate-petroleum ether in the ratio 1:20 (420 mL) and, subsequently, 1:15 (1.2L). The fractions containing pure 79 yielded 0.9 g (64 %) as crystals, mp $70-71^\circ$, $[\alpha]_D + 136.8^\circ$ (c 3.5); $\nu_{\text{max}}^{\text{Nujol}}$ 1740 (OAc) and 735 cm^{-1} (cis alkene); ms: m/e 235, 233 ($M^+ - \text{OMe}$), 175, 173 ($M^+ - \text{OMe} - \text{HOAc}$), and 142 ($M^+ - \text{BrCH}_2\text{CHO}$). The compound could be stored only at -20° or below.

Methyl 4-[(N-Benzyl)methylamino]-6-bromo-2,3,4,6-tetra-deoxy- α -D-erythro-hex-2-enopyranoside (88) and Methyl 4,6-Bis[(N-benzyl)methylamino]-2,3,4,6-tetra-deoxy- α -D-erythro-hex-2-enopyranoside (89)

A solution of the crystalline acetate 79 (265 mg, 1 mmol), triphenylphosphine (185 mg, 0.7 mmol), and tetrakis(triphenylphosphine)palladium (82 mg, 0.07 mmol) in tetrahydrofuran (20 mL) was stirred for 30 min at room temperature, under nitrogen. Benzylmethylamine (1 mL) was then added by syringe, and the mixture was boiled under reflux for 36 h. Tlc with solvent C showed 2 major spots (R_F 0.5 and 0.8) and 2 minor ones ($R_F \sim 0.55$ and ~ 0.7), and no change was observed after an additional 6 h of heating. The cooled reaction mixture was then partitioned between ether and water, the aqueous phase was extracted with dichloromethane (4 x 30 mL), and the combined organic phases were dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil (0.8 g). The oil was subjected to preparative tlc (17% of ethyl acetate in petroleum ether), which gave 88 (R_F 0.8 in solvent C; 120 mg, 36.8%) and 89 (R_F 0.5 in solvent C; 200 mg, 54.6%) as colorless syrups. The intermediate fractions that contained the minor products yielded only negligible amounts of material. (unidentified).

Compound 88 showed $[\alpha]_D + 179.1^\circ$ (c 1); m.s.: m/e 327, 325 (M^+), 296, 294 ($M^+ - OMe$), 246 ($M^+ - Br$), and 203 ($M^+ - BrCH_2CHO$).

Compound 89 showed $[\alpha]_D +153.1^\circ$ (c 1), ms: m/e 366(M^+), 335 ($M^+ - OMe$), 306 (weak), 275($M^+ - Bn$), 246($M^+ - BnNMe$), and 203 (strong; $M^+ - BnMeNCH_2CHO$).

The ir spectra (liquid films) of 88 and 89, which were very similar, agreed with the proposed constitutions. Noticeable differences were seen below 800 cm^{-1} where 88 exhibited strong bands at 790, 765(with shoulder at 750), and 700 cm^{-1} , whereas 89 had strong bands at 735 (broadened) and 695 cm^{-1} (sharp).

Methyl 2,3,6-Trideoxy- α -D-erythro-hex-2-enopyranoside(80).

The bromo sugar 79 (200 mg) was dissolved in tetrahydrofuran (5 mL), and a 1 M solution of lithium triethylborohydride in tetrahydrofuran (3 mL) was added dropwise at room temperature. After 24 h, tlc with solvent C showed 79 (R_F 0.55) to be absent and indicated a strong spot of the reduction product 80 (R_F ~0.2), accompanied by a very faint, marginally faster moving spot of an unidentified by-product. The reaction mixture was cooled to 0° for 30 min, then a small amount of methanol was added dropwise in order to destroy the excess of hydride. Evaporation of the solvents afforded a white residue, which was placed onto a short column of silica gel by means of a little ethyl acetate. Elution with solvent C produced 80 (101 mg, 93%) as a colorless syrup, $[\alpha]_D +110^\circ$ (c 2.4). A similar value, $[\alpha]_D +107^\circ$, was obtained when a sample of the benzoate 82 in chloroform was catalytically saponified with a drop of sodium methoxide solution, with subsequent neutralization

by ion exchange; Lit¹⁰⁴ + 75°; for the L-enantiomer¹⁰⁸, -94° and¹⁰⁹
- 115°. Compound 80 showed $\gamma_{\text{max}}^{\text{film}}$ 3400 (OH), 1660 (weak)
and 725 (strong) for cis-alkene, 1200-970 (multiple bands), 890,
and 830 cm^{-1} ; m.s: m/e 143 (weak, $M^+ - H$), 127 (weak, $M^+ - OH$),
113 (strong, $M^+ - OMe$), and 100 (very strong, $M^+ - CH_3CHO$). The
¹H-NMR spectrum of 80 (Table 7) and that of a sample prepared by
a different route⁽¹⁰⁵⁾ proved their identity.

Methyl 4-O-Benzoyl-2,3,6-trideoxy- α -D-erythro-hex-2-
enopyranoside (82)

A mixture of the bromo sugar 76 (8.0 g) and zinc-copper couple
(10 g) in glacial acetic acid (100 mL) was stirred well by means
of a mechanical stirrer. The reductive debromination of 76
($R_F \approx 0.5$) to give 81a ($R_F \approx 0.4$) was monitored by tlc (solvent J)
and was promoted by gentle to moderate heating of the mixture
in such a manner that the spots of two fast-moving side-products
(R_F 0.8 and 0.9) did not become prominent. (These were the chief
products when, in a pilot experiment, the reaction was performed at
reflux temperature). The debromination was almost half completed
after 1 h. At this stage, additional reductant (10 g) was
introduced, and all of 76 had reacted after about 2 h. Filtration
of the warm mixture through sintered glass, followed by evaporation
of the filtrate (oil-pump vacuum, 40° bath temperature), gave a
thick syrup which was subsequently passed through a short column
of silica (10 cm x 5 cm) by flash chromatography, with ether as
the eluant. The fast-moving by-products were thereby removed, and

crude 81a was obtained as a pale yellow syrup (~4 g). For identification, a small sample of 81a was acetylated with acetic anhydride and pyridine (1 h at 25°) to give the 2,3-diacetate 81b; tlc with solvent K: R_F 0.2 (81a) and 0.8 (81b). 1H -NMR data (60 MHz) of 81b in $CDCl_3$: δ 7.95 (m, 2H) and 7.4 (m, 3H) (OBz), 5.65 (m, 1H) and 5.2 - 4.8 (m, 3 H, H-1 to H-4), 4.00 (o, 1H, H-5), 3.42 (s, 3H, OMe), 2.04 and 1.86 (s; 2 x 3H, OAc) and 1.25 (d, 3H, C-Me).

A mixture of crude 81a (2.2 g), triphenylphosphine (5.2 g), 2,4,5-triiodoimidazole (4.7 g), and imidazole (0.9 g) in dry toluene (100 mL) and dry tetrahydrofuran (20 mL) was boiled under reflux for 1.5 h. At the end of this time, tlc (solvent C) showed that the starting material was replaced by product 82 (R_F 0.9) and a slow-moving by-product (R_F 0.1-0.4). The reaction mixture was processed as described for 77, and separation of 82 from the by-product that was present in major proportion was achieved by flash chromatography on a short column of silica gel by use of petroleum ether as the eluant. The eluate was evaporated to give 0.6 g (31%) of 82 as a colorless syrup that crystallized rapidly upon refrigeration. Recrystallized from moist methanol, the long needles showed mp 50 - 50.5°, whereas, from petroleum ether containing a small proportion of ether, crystals of mp 52 - 53° were obtained on strong cooling; $[\alpha]_D + 214^\circ$ (c 0.5); lit¹⁰⁵ mp 47 - 48°, $[\alpha]_D + 104.8^\circ$; for the L enantiomer¹⁰⁷, mp 43 - 45°, $[\alpha]_D - 215^\circ$ and¹⁰⁸ mp 53-54°, $[\alpha]_D - 225^\circ$. The mass spectrum showed peaks at m/e 217 ($M^+ - OMe$) and 204 (strong, $M^+ - CH_3CHO$).

Methyl 4-O-Acetyl-2,3,6-trideoxy- α -D-erythro-hex-2-enopyranoside (83)

The alcohol 80 (600 mg) was dissolved in dichloromethane (6 mL) containing triethylamine (0.7 mL), and the solution was cooled to 0°. Acetic anhydride (0.44 mL) was added, and the solution was stored overnight at room temperature, whereafter tlc (solvent C) indicated complete conversion of 80 (R_F 0.2) into the acetate 83 (R_F 0.7). Evaporation of the mixture and passage of the residue through a small column of silica gel by means of ethyl acetate produced 83, free from triethylammonium salt. The effluent was evaporated (30° bath temperature) to give 83 as a colorless liquid weighing 0.75 g after brief drying at room temperature and 1 torr; $[\alpha]_D + 165$ (c 1.6); reported¹⁰⁸ for a distilled sample of the L enantiomer, -187°. For spectral analysis, samples were freed of traces of solvent by prolonged drying in vacuo, although this led to some loss of the compound owing to its volatility. The mass spectrum had peaks at m/e 185 (weak, $M^+ - H$), 155 (strong, $M^+ - OMe$), 142 (strong, $M^+ - CH_3CHO$), and 100 (very strong, $M^+ - CH_3CHO - CH_2CO$).

Methyl 4-[(N-Benzyl)methylamino]-2,3,4,6-tetradecoxy- α -D-erythro-hex-2-enopyranoside (84)

A. From 83: A mixture of the allylic acetate 83 (600 mg), triphenylphosphine (570 mg), tetrakis(triphenylphosphine)palladium (200 mg) and dry tetrahydrofuran was stirred for 30 min under nitrogen at room temperature. Benzylmethylamine (3 mL) was then

added in one portion, and the mixture was stirred at reflux temperature until 83 (R_F 0.7) had disappeared (tlc with solvent C). The reaction time required varied (24 - 48 h), possibly owing to variations in catalyst quality. The aminated product 84 (R_F 0.85) was accompanied only by traces of slow-moving by-products.

Processing as usual afforded 84 as a colorless syrup (645 mg, 81% yield), after chromatographic purification; $[\alpha]_D^{25} + 211^\circ$ (c 3.8); ms: m/e 247 (weak, M^+), 232 (weak, $M^+ - Me$), 216 (weak, $M^+ - OMe$), 203 (very strong, $M^+ - CH_3CHO$), and 188 (strong, $M^+ - CH_3CHO - Me$). The ir spectrum closely resembled that of 89. Anal calc. for $C_{15}H_{21}NO_2$ (247.3): C 72.84, H 8.56; N 5.66; found: C 72.60, H 8.55, N 5.45.

B. From 82: Following the same procedure as above, the benzoate 82 (200 mg) was allowed to react for 20 h with triphenylphosphine (186 mg), tetrakis(triphenylphosphine)palladium (82 mg), and benzylmethylamine (1 ml) in tetrahydrofuran (20 ml). Although 82 and 84 have almost identical R_F values (0.85 - 0.9 in solvent C; 0.7 in solvent D), they are readily distinguished by the color of the spots produced on heating the tlc plates after spraying with 5% ethanolic sulfuric acid, namely, light yellowish-brown (84) and nearly black (82). The crude reaction product showed one major spot (84), together with several, slow-moving trace spots. Processing and chromatographic purification gave 160 mg (80 %) of 84, whose 1H -NMR spectrum was identical with that of the product prepared from 83.

Methyl 2,3,4,6-Tetradecoxy-4-methylamino- α -D-erythro-hexopyranoside (85)

Catalytic hydrogenation of compound 84 (260 mg) over 10% palladium-on-carbon (200 mg) in 99% ethanol (10 mL), for 24 h at ambient temperature and pressure, effected complete conversion of 84 into a material that was immobile in tlc with solvent C but gave an elongated spot ($R_F \sim 0.4$) with solvent L. Evaporation of the filtered solution gave 85 as a colorless oil that crystallized on refrigeration; mp 161° after recrystallization from methanol-ether-petroleum ether. The yield, 121 mg (72%), was low possibly because of the considerable volatility shown by the compound in vacuo; m/e 159 (M^+) and 128 ($M^+ - OMe$); $\nu_{\text{max}}^{\text{Nujol}}$ 3400 (broad) and 1600 (weak, N-H), 1125, 1065, 1020, 983, 900, 860, 840, and 810 cm^{-1} .

Methyl 2,3,4,6-Tetradecoxy-4-dimethylamino- α -D-erythro-hexopyranoside (86):

A mixture of the methylamino derivative 85 (100 mg) and 37% aqueous formaldehyde solution (1 mL) in methanol (3 mL) was boiled for 1 h under reflux. This effected replacement of 85 by an almost immobile material (tlc with solvent L). Sodium borohydride (135 mg) was then added, which caused within 1 h the conversion of the immobile product into 86, R_F 0.3 - 0.4 (not readily distinguishable from 85). The reaction mixture was diluted with water, and extracted with dichloromethane (3 x 15 mL). The extract was dried ($Mg SO_4$), and evaporated at 25° (bath) to afford 86 (80 mg, 74%) as a colorless, rather volatile liquid. The nmr spectrum (Table 7) was in agreement with published⁹⁹ data..

4,6-Di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl 2,3,4,6-Tetra-O-benzyl- α -D-glucopyranoside (92)

A. Boron trifluoride method:

3,4,6-Tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose¹²⁰ (28, tri-O-acetyl-D-glucal) (1.36 g) and 2,3,4,6-tetra-O-benzyl- α -D-glucopyranose¹²¹ (91) (2.70 g) were dissolved in dry benzene (50 mL), and freshly distilled boron trifluoride etherate (0.5 mL) was added^{47b,c}. The solution was kept at room temperature for 2 h, during which time its color turned to dark red. Tlc with solvent C showed that the starting materials 28 (R_F 0.55) and 91 (R_F 0.5) had largely disappeared and two new products were formed. The major product (92) had R_F 0.6, and the minor one (93), R_F 0.8. The catalyst was neutralized with solid sodium carbonate which, after filtration, was washed several times with dichloromethane. The faintly pink solution was evaporated to dryness, affording a yellow syrup (4.1 g) which was chromatographed on a silica gel column. Mixtures of ethyl acetate and petroleum ether in the ratios 1:19, 1:9, and 1:4 (500 mL of each) were used successively for elution. The fast-moving product (R_F 0.8) eluted from the column (0.5 g) was 1-O-acetyl-2,3,4,6-tetra-O-benzyl- α -D-glucopyranose (93), identified by comparison of its ¹H-NMR spectrum with that of an authentic sample.

The fractions containing solely the slow-moving product yielded 2.5 g (66%) of 92 as a colorless syrup; $[\alpha]_D + 76.5^\circ$ (c 1.4),

ν_{\max} 1745 and 1240 (OAc), 3100-3040, 1600, 1500, 700 (Ph), 1120-970 (C-O-C), and 740 cm^{-1} (cis alkene). Anal. calcd. for $\text{C}_{44}\text{H}_{48}\text{O}_{11}$

(752,8): C 70.19, H 6.43; found: C 69.93, H 6.67

B. Stannic chloride method:

A higher yield of 92 was obtained when stannic chloride was used as a catalyst⁵². Typically, compound 28 (3 g) and compound 91 (5.4 g) were dissolved in 1,2-dichloroethane (100 mL, dried over P_2O_5). The solution was cooled to -5° ; and 3 mL of 1,2-dichloroethane containing 200 mg of anhydrous stannic chloride was added dropwise, with stirring. The reaction was allowed to proceed at 0° for 15 min and then at 15° for another 45 min. Tlc (solvent D) of the dark brown reaction mixture showed the disappearance of the starting materials and the formation of mainly one product; side products were seen as trace spots. The mixture was washed with a saturated solution of sodium hydrogencarbonate and then with water, and dried over anhydrous magnesium sulfate. Evaporation of the clear, colorless dichloroethane solution produced 8.5 g of a syrup which was purified by flash chromatography with petroleum ether, to afford 92 in high yield (7 g, 93%). The 1H -nmr and ir spectra were identical with those of the product prepared by the boron trifluoride method. The by-product 93 obtained from the column amounted to only 0.2 g (3.5%).

6-O-Acetyl-4-(Benzylmethylamino)-2,3,4-trideoxy- α -D-erythro-hex-2-enopyranosyl 2,3,4,6-Tetra-O-Benzyl- α -D-glucopyranoside (94)

Following the general procedure for allylic amination, a mixture of the disaccharide 92 (1.3 g), triphenylphosphine (280 mg), Pd-catalyst (123 mg), and tetrahydrofuran (30 mL) was prepared. After 30 min, 1.5 mL of benzylmethylamine in 2 mL of tetrahydrofuran was added, and the mixture was boiled under reflux for 30 h. Tlc with solvent C then indicated absence of the starting material 92 (R_F 0.6) and formation of compound 94 (R_F 0.7). Processing the reaction mixture as described before gave 94 as a colorless syrup, weighing 1.3 g (92.5%), after chromatography; $[\alpha]_D + 85^\circ$ (c 2); ν_{max} 3100-3050, 1600, 1500, and 700 (Ph), 1740 and 1250 (OAc), 1120-970 (C-N, C-O-C), and 740 cm^{-1} (cis alkene) Anal. calcd. for $C_{50}H_{55}NO_9$ (813.95); C 73.78, H 6.81, N 1.72; found: C 73.88, H 6.68, N 1.79.

6-O-Acetyl-4-(dibenzylamino)-2,3,4-trideoxy- α -D-erythro-hex-2-enopyranosyl-2,3,4,6-Tetra-O-benzyl- α -D-glucopyranoside (95)

Compound 92 (550 mg) was allowed to react with dibenzylamine (0.7 mL) in the manner described for the synthesis of 94. After a reaction time of 24 h, only traces of 92 were left, and a major product (R_F 0.7) was seen in tlc (solvent C). Processing and purification by column chromatography furnished 400 mg (67%) of colorless syrup identified as compound 95; $[\alpha]_D + 80.5^\circ$ (c 3.3); ν_{max} 3100-3040, 1610, 1500, and 700 (Ph), 1745 and 1250 (OAc), 1120-965 (C-N, C-O-C),

and 750-735 cm^{-1} (cis alkene). Anal. calcd. for $\text{C}_{56}\text{H}_{59}\text{NO}_9$ (890.0); C 75.57, H 6.68, N 1.57; found: C 75.40, H 6.80, N 1.50.

Attempts to repeat this reaction on a larger scale (>6 mmol) failed. All the dibenzylamine was precipitated as tetrabenzylhydrazine in a competing reaction. The white, crystalline material, mp 276-278 $^{\circ}$, was rather insoluble in various organic solvents except methanol; ms; m/e 97 (HNBN_2), 196 ($\text{M}^+ - \text{NBN}_2$), 120 (BnNMe), 106 (BnNH), 91 (PhCH_2), 77 (Ph); NMR (60MHz; MeOH d_4); δ 4.20 (s, $\text{N-CH}_2\text{-Ph}$) and 7.36 (s, Ph), in the intensity ratio 2:5.

PART II

The unsaturated nitro glycosides 1, 4 and 7 were prepared as described previously¹⁶⁹. The lithium dialkylcuprates were made following general prescriptions¹²². The required reagents, methyl-lithium and vinyl-lithium, were obtained from Alfa Products.

General Procedure for the Reaction of Lithium Dialkylcuprates with Nitro-olefins

Reaction of 1 with $\text{LiCu}(\text{CH}_3)_2$; Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-methyl-3-nitro- β -D-glucopyranoside (2): A solution of lithium-dimethylcuprate was prepared as follows. Into a 50-ml reaction flask, equipped with an inlet for N_2 and a side-arm capped with a rubber septum, was placed solid cuprous iodide (380 mg, 2 mmol). The flask was gently heated over a Bunsen burner while being purged with nitrogen, to ensure complete drying. The buff color of the iodide changed to a light green, and then to buff again when heating was discontinued and the material allowed to cool to room temperature. Ether (10 mL) was added, and the resulting suspension was cooled to -50°C and stirred magnetically. A 1.6 M solution of methyl-lithium in ether (2.5 mL, 4 mmol) was added dropwise through the septum by syringe over a period of 3 minutes. A bright yellow precipitate of CuCH_3 formed and redissolved gradually at the end of the addition, and on allowing the mixture to warm to 0° . The resulting clear solution of $\text{LiCu}(\text{CH}_3)_2$ was cooled again to -50° , and kept at this temperature for 15 minutes. A solution of compound 1 (293 mg, 1 mmol) in THF (3 mL) was then added drop-

wise by means of a syringe, producing a yellow precipitate. The reaction mixture was warmed to 0° and stirred for 1 hour, then poured into 15 mL of a saturated aqueous ammonium chloride solution. The mixture was stirred for 15 minutes, the layers were separated and the blue, aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried over anhydrous magnesium sulfate and evaporated to leave 280 mg (91%) of 2 as a white solid that was homogeneous in tlc, migrating slightly faster than 1 (solvent B). Recrystallized from chloroform-petroleum ether, it showed a melting point of 198-199°, $[\alpha]_D - 87.7^\circ$ (c 1.1), and $\nu_{\text{max}}^{\text{nujol}}$ 1565 cm^{-1} (NO_2). See Tables 1 and 2 for the nmr data. Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_6$ (309.3): C, 58.24; H, 6.19; N, 4.53. Found: C, 58.09; H, 6.14 and N, 4.43.

Reaction of 1 with $\text{LiCu}(\text{CH}=\text{CH}_2)_2$: Methyl 4,6-O-Benzylidene-2,3-nitro-2-C-vinyl- β -D-glucopyranoside (3)

The procedure was essentially the same as described above for 2. A 2.05 M solution (6 mL, 12.3 mmol) of vinyl lithium in ether was added to the cooled suspension of cuprous iodide (1.14 g, 6 mmol) in ether (30 mL) at -70°. A white precipitate which occurred in this case turned black towards the end of the addition; and did not dissolve completely in the pale-yellow solution that resulted on warming the mixture to 0°. Compound 1 (880 mg, 3 mmol) in THF (6 mL) was added as described before, but at -78°. Working up the reaction mixture produced a white solid (1.17 g) which showed one major spot in tlc (solvent B), with a mobility slightly greater

than that of 1, together with one still-faster and two slow-moving trace spots. Crystallization from ether-petroleum ether furnished pure 3 as cube-like, beautiful crystals (0.65 g, 68%), melting point 198-199°; $[\alpha]_D - 90^\circ$ (c 1.2), $\nu_{\text{max}}^{\text{nujol}}$ 1640 (weak, C=C) and 1560 cm^{-1} (strong, NO_2). The similarity of the physical data to those of 2 is noteworthy.

Anal. Calc. for $\text{C}_{16}\text{H}_{19}\text{NO}_6$ (321.3): C, 59.80; H, 5.96; N, 4.36.
Found: C, 59.90; H, 5.85; N, 4.31.

Reaction of 4 with $\text{LiCu}(\text{CH}_3)_2$: Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-methyl-3-nitro- β -D-galactopyranoside (5)

Using the same procedure as that described for conversion of 1 to 2, the nitroglycoside 4 (293 mg, 1 mmol) was reacted with lithium dimethylcuprate (2 mmol). Tlc of the crude product with solvent B showed one major spot which was due to 5 although the R_F value (0.25) was similar to that of 4. There were traces of slow-moving impurities which were removed by purification of the material by preparative thin layer chromatography (solvent D). Crystallization of the product from dichloromethane-ether then afforded 210 mg (72%) of pure 5 as colorless crystals, melting point 200-202°; $[\alpha]_D +63.6^\circ$ (c 0.5); $\nu_{\text{max}}^{\text{nujol}}$ 1555 cm^{-1} (NO_2).

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_6$ (309.3): C, 58.24; H, 6.19; N, 4.53.
Found: C, 58.13; H, 6.19; N, 4.29.

Reaction of 4 with $\text{LiCu}(\text{CH}=\text{CH}_2)_2$: Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-C-vinyl- β -D-galactopyranoside (6)

The procedure for the preparation of 3 was applied to the nitro

glycoside 4 except for the use of 1 mmol of 4 and correspondingly smaller proportions of the reagents and solvents. Five minutes after completion of the addition of glycoside solution at -70° (or, in some experiments, at -50°) tlc indicated (solvent A) that all of the starting material 4 (R_F about 0.6) had disappeared, and stirring at 0° was therefore omitted. Two spots of comparable intensity were seen, one moving just slightly more slowly than 4, and the other having R_F about 0.5. The product corresponding to the former was 6, and was obtained pure by recrystallization of the crude mixture from warm, anhydrous ether. The yields were 35-40% in several experiments; melting point $180.5-181.5^{\circ}$; $[\alpha]_D + 64.3^{\circ}$ (c 3.1); $\nu_{\text{max}}^{\text{nujol}}$ 1650 (weak, C=C) and 1560 cm^{-1} (strong, NO_2).
Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_6$ (321.3); C, 59.80; H, 5.96; N, 4.36.
Found: C, 59.66; H, 5.90; N, 4.28.

Several attempts to isolate and characterize the second product (R_F 0.5), either by processing of the ethereal mother liquor of 6, or by preparative tlc, were unsuccessful. Invariably, decomposition to give a large number of tlc spots occurred.

Reaction of 7 with $\text{LiCu}(\text{CH}_3)_2$: Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-methyl-3-nitro- α -D-mannopyranoside (8) and 1,5-Anhydro-4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-arabino-hex-1-enitol (9)

The procedure was identical with the synthesis of compound 2 except for the use of the nitro glycoside 7 instead of 1. Tlc (solvent B) indicated absence of the starting material 7 (R_F 0.5) and the presence of two new products (R_F 0.6 and R_F 0.7) after a 1-hour

reaction at 0°. However, the crude product isolated was shown to contain small proportions of several, more-slowly moving contaminants which apparently arose during the processing. Separation by preparative tlc using solvent E resulted in 4 bands (A-D, in order of decreasing mobility). Elution of band A gave 9 (R_F 0.7) contaminated by a small proportion of 8 (R_F 0.6), and elution of band B gave 8 contaminated by a trace of 9. Elution of bands C and D gave by-products (20 and 40 mg) that were not investigated further.

Recrystallization of the eluate A from ether-petroleum ether furnished pure 9 (111 mg, 42%), melting point 92-93°, $[\alpha]_D -152.1^\circ$ (c 3); $\nu_{\text{max}}^{\text{nujol}}$ 1640 (medium strong, C=C) and 1560 cm^{-1} (strong, NO_2).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}_5$ (263.2): C, 59.31; H, 4.98; N, 5.32.
Found: C, 59.22; H, 4.93; N, 5.19.

Recrystallization of the eluate B from ether-petroleum ether yielded pure 8 (118 mg, 38%), melting point 124-125°; $[\alpha]_D +55.0^\circ$ (c 1.7); $\nu_{\text{max}}^{\text{neat}}$ 1560 cm^{-1} (NO_2).

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_6$ (309.3): C, 58.24; H, 6.19; N, 4.53.
Found: C, 58.44; H, 6.37; N, 4.30.

PART III

The methyl 2,3-anhydro-4,6-O-benzylidene-3-deoxy-3-nitro-hex-2-enopyranosides 2, 3, and 5 were prepared by methods previously described^{170,171}.

Hydrogenation of β -D-gulo Nitroepoxide 3

The crystalline epoxide 3 (60 mg) was hydrogenated at 19° with Pd/C (30 mg) in 7:3 methanol-1,4-dioxane (6 ml.), with addition of M acetic acid (0.3 mL). Monitoring the reaction by tlc with solvent F showed, after 8 and 15 minutes, a strong spot (R_F 0.33) corresponding to that of authentic¹⁷² β -D-galactoside 12, together with a small proportion of starting material 3 (R_F 0.76); after 30 minutes, the latter was diminished to a mere trace seen only upon heavy spotting of the reaction mixture, and after 60 minutes, 3 had completely disappeared. The catalyst was filtered off and washed several times with methanol. The filtrate showed $[\alpha]_D +0.51^\circ$ (1-dm tube), which implied a specific rotation close to that reported¹⁷² for methyl 4,6-O-benzylidene-3-deoxy-3-nitro- β -D-galactopyranoside (12) in N,N-dimethylformamide, $[\alpha]_D + 24.8^\circ$. The combined filtrate and washings were evaporated to dryness. There was obtained a crystalline residue (58 mg) that, after recrystallizing from absolute ethanol and washing with ether-petroleum ether, melted at about 230° C (dec.) and had an ir spectrum identical with that of authentic 12; lit.¹⁷² melting point 230-231° (dec.). The mother liquor showed a faintly positive Griess test¹⁴⁴.

Hydrogenation of β -D-allo Nitroepoxide¹⁷⁰ 2

Compound 2 (30 mg) was dissolved in hot, 99% ethanol (5 mL) with addition of a few drops of 1,4-dioxane. The warm solution was introduced into the hydrogenation vessel containing prehydrogenated, ethanol-washed, platinum catalyst (30 mg). The starting material partly crystallized on cooling the solution to room temperature, but redissolved within the first 20 minutes of hydrogenation. After 90 minutes, the epoxide 2 (R_F 0.82, solvent F) was absent, and a single, strong spot at R_F 0.75 in tlc was indicated by the sulfuric acid spray. An additional, but weak, spot at R_F about 0.38 was revealed by ninhydrin (on a separate plate). No significant change in the pattern seemed to occur within the next 16 hours. However, at this point, it was ascertained by repeated, careful comparisons with authentic 6 that the main spot had a marginally greater R_F value. Presumably, it was a combination spot caused by 6 and a new product 13. Hydrogenation was continued, with addition of a further 20 mg of PtO_2 (not prehydrogenated), and, after a total reaction time of 44 hours, the preponderant spot, detected by sulfuric acid spray, appeared unchanged (in solvent F), whereas ninhydrin now indicated only a trace spot at R_F 0.62, and none of the spot previously seen at R_F 0.38. By use of the somewhat less-polar solvent G it was found that, at this stage, the fast-moving spot (R_F 0.77) was clearly distinct from that of authentic 16 (R_F 0.70) which was applied for comparison.

Filtration of the suspension, and evaporation of the filtrate gave a colorless, partially crystalline syrup whose ir spectrum displayed a strong, sharp nitro band at 1560 and broad hydroxyl absorption at 3300 cm^{-1} ; nmr data (60 MHz; CDCl_3): δ 4.67 (t, 1H, J 10 Hz, H-3), 3.57 (s, OMe), and 1.9-0.9 (broad m, about 11 H, cyclohexyl); the remaining protons gave unresolved multiplets in mid-field, and there was no trace of phenyl resonances. According to all of the spectra and chromatographic evidence available, the product was identical with 13 (described in the following section)...

Methyl 4,6-O-(Cyclohexylmethylene)-3-deoxy-3-nitro- β -D-glucopyranoside (13):

Methyl 4,6-O-benzylidene-3-deoxy-3-nitro- β -D-glucopyranoside¹⁷³ (6, 150 mg) was hydrogenated in 99% ethanol (15 mL) in the presence of platinum catalyst (75 mg, washed after prehydrogenation), the reaction being monitored by tlc with solvent G. A trace of 13 (R_F 0.75) appeared above 6 (R_F 0.67) after 30 minutes, and considerably increased after 5 hours; after 26 hours the product ratio, visually estimated, was 1:2 in favor of 6. A further 35 mg of catalyst (not prehydrogenated) was added, and the hydrogenation was continued for a total of 46 hours. After this period, all of the 6 had disappeared, and 13 was the only fast-moving (and major) product. (There were some trace spots of intermediate and low mobility, the latter being ninhydrin-positive). Processing gave a colorless syrup which, upon dissolution in a small volume of ethylacetate, addition of pentane to incipient opalescence, and storage for several days at -15° , yielded a

deposit of hard crystals. Isolated by decantation, and washed with pentane, they weighed only 20 mg, and proved to be a mixture of 13 and the slow-moving by-product. The mother liquor, containing the bulk of the reaction product, was allowed to evaporate in the air (with eventual addition of hexane to displace ethyl acetate) to give syrupy 13 that was only very slightly contaminated by slow-moving impurities. Dried in a desiccator, the glassy film (125 mg) showed an ir spectrum identical with that of 13 from 2, and, upon trituration with water and methanol, it readily crystallized as microscopic needles, melting point 115-116.5°, $[\alpha]_D -40.4^\circ$ (c 1.4); ν_{\max} 3450 (bd, OH) and 1555 cm^{-1} (s, NO_2), and, in the fingerprint region, obvious differences from the benzylidene analog 6; nmr data (100 MHz, CDCl_3): δ 4.63 (t, $J_{2,3} = J_{3,4} = 10$ Hz, H-3), 4.32 (d, $J_{1,2} 7.5$ Hz, H-1), 4.24 (d, $J 5$ Hz, with an additional, very small splitting, cyclohexyl- CHO_2), 4.23 (dd, $J_{5,6e} 4.3$, $J_{6a,6e} 10$ Hz, H-6e), 3.98 (dd, $J 7.5$ and 10 Hz, H-2), 3.82 (dd, $J_{3,4} 10$, $J_{4,5} 9$ Hz, H-4), 3.56 (s, 3H, OMe), 3.57 (t, $J 10$ Hz, H-6a), 3.33 (o, $J 4.3$, 9 and 10 Hz, H-5), 2.9 (broad, 1 H, exchangeable with D_2O , OH-2), and 1.9-0.9 (m, 11 H, cyclohexyl).

Anal. Calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_7$ (317.3): C, 52.99; H, 7.31; N, 4.41.

Found: C, 52.96; H, 7.35; N, 4.24.

Hydrogenation of α -D-manno Nitroepoxide¹⁷⁰ 4

A) With palladium in methanol-1,4-dioxane:

A solution of 4 (30 mg) and M acetic acid (0.2 mL) in 7:3 methanol-

1,4-dioxane (5.5 mL) was hydrogenated in the presence of Pd/C (30 mg). After 5 minutes, the reaction mixture showed a strong spot migrating like authentic nitro mannoside 9 (R_F 0.8) and a spot of similar strength attributed to the corresponding oximino glycoside (R_F 0.6); a trace spot had R_F 0.35 (tlc in solvent F). After 15 minutes, the epoxide 4 (R_F 0.9) had completely disappeared and the product pattern was essentially unchanged, remaining so for 19 hours. Solvent evaporation then gave a syrup having $[\alpha]_D + 50^\circ$ (c 2.3) and showing a positive Griess test¹⁴⁴.

B) With palladium in ethanol:

Hydrogenation of 4 (20 mg) with Pd/C (5 mg) in 99% ethanol (5 mL) gave a result similar to that in A, except that the oxime spot was produced more slowly and was weaker (relative to the spot attributed to 9). A smaller proportion of 4 was still present after 1 hour, but on addition of another 5 mg of catalyst, it disappeared within the next 30 minutes. The syrup obtained on evaporation had $[\alpha]_D + 48^\circ$ (c 1) and responded weakly to the Griess reaction.

A similar hydrogenation had been performed previously^{130 b}, but on a larger scale (200 mg of 4), with a relatively smaller proportion of Pd/C (20 mg). The reaction apparently was not monitored by tlc, and oxime was not detected. Processing after 26 hours afforded crystalline 9 in 70% yield.

Hydrogenation of β -D-manno Nitroepoxide¹⁷¹ 5

A) With palladium in ethanol:

A pilot experiment of hydrogenation of 5 (25 mg) with Pd/C (5 mg) in 99% ethanol (5 mL) showed that 5 was replaced after 3 hours by two products in the ratio of 1:1 (tlc in solvent F). One of these migrated like authentic nitro mannoside 15 (somewhat more slowly than 5), and the other appeared as a slow-moving, double spot attributable to the oximino glycoside 16 (possibly a mixture of geometric isomers). After 24 hours, the spot corresponding to 15 had largely, but not entirely, disappeared. A similar experiment, performed on a larger scale (100 mg of 5), was interrupted after 3 hours, and the products were separated by preparative tlc (solvent F). Isolated crystalline, the fast-moving product melted at 199°, and had ir and nmr spectra identical with those of authentic methyl 4,6-O-benzylidene-3-deoxy-3-nitro- β -mannopyranoside (15), lit.¹⁷² melting point 198-199° and¹⁷⁴ 202°; nmr data (100 MHz, Me₂CO-d₆): δ 7.4 (m, 5H, Ph), 5.75 (s, 1H, PhCH), 4.99 (o, 1H, $J_{2,3}$ 3.8, $J_{3,4}$ 10.8, $J_{3,OH}$ 1 Hz, H-3), 4.75 (d, 1H, $J_{1,2}$ 1 Hz, H-1), 4.66 (dd, 1 H, $J_{2,OH}$ 4.5; signal removed by D₂O exchange, OH-2), 4.57 (dd, 1 H, $J_{3,4}$ 10.8, $J_{4,5}$ 9.3 Hz, H-4), 4.50 (septet, 1 H, $J_{2,OH}$ 4.5, $J_{2,3}$ 3.8, $J_{1,2}$ 1 Hz; collapsing to narrow q on D₂O exchange, H-2), 4.52 (dd, 1 H, $J_{5,6e}$ 5, $J_{6a,6e}$ 10 Hz, H-6e), 3.93 (t, 1 H, J 10 Hz, H-6a), 3.55 (o, H-5, partially overlapped by OMe signal), and 3.51 (s, 3 H, O

The slow-moving material from the preparative tlc was obtained as two fractions (A and B), both crystallizing from chloroform and giving

a positive Griess reaction¹⁴⁴. They were methyl-4,6-O-benzylidene-3-deoxy-3-oximino- β -D-arabinohexopyranoside (16) melting with decomposition at 179-180° (A) and 165-166° (B), and showing virtually identical 60-MHz nmr spectra, as well as very similar ir spectra: ν_{\max} for A, 3360 (sharp, with broad shoulder at 3200), and, for B, 3540 (sharp) and 3350 cm^{-1} (bd, with sh at 3200); there were very slight differences in the well resolved fingerprint-patterns. The 100-MHz nmr data for A in $\text{Me}_2\text{CO-d}_6$: δ 7.4 (m, 5 H, Ph), 5.70 (s, 1 H, PhCH), 5.30 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.64 (d, 1 H, $J_{3,4}$ 9.5 Hz, H-4), 4.49 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-2), 4.30 (dd, 1 H, $J_{5,6e}$ 5, $J_{6a,6e}$ 10 Hz, H-6e), 3.88 (t, 1 H, J 10 Hz, H-6a) and 3.51 (s, 3 H, OMe, superposed on m, H-5). The =N-OH proton was seen as a peak at δ 11.2 (removeable by D_2O exchange) in a separate spectrum of a CDCl_3 solution containing $\text{Me}_2\text{SO-d}_6$.

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_6$ (295.3): C, 56.94; H, 5.80; N, 4.74.
Found: C, 57.12; H, 6.00; N, 4.63.

B) With palladium in methanol-1,4-dioxane:

A mixture of 5 (100 mg) and palladium-on-carbon (50 mg) in 7:3 methanol-1,4-dioxane (10 mL) and 0.1 N acetic acid (2 mL) was hydrogenated. After 8 minutes, tlc with solvent G indicated spots of 15 (R_F 0.45) and 16 (R_F 0.25); after 45 minutes, all of the starting material 5 (R_F 0.6) had disappeared, and the products were present in comparable proportions, as estimated visually. (Some runs were processed at this stage, attempts being made to separate the products, without recourse to chromatography, by trituration of the

solid mixture with ether, and fractional recrystallization therefrom. However, it was not possible to obtain 15 and 16 in pure form in this way, and only crystalline fractions enriched in one or the other compound could be elaborated.) When hydrogenation was continued without interruption for 36 hours, 16 remained as the sole product detectable, and it was subsequently isolated crystalline (from ethyl acetate-petroleum ether) in high yield; melting point 167-168°, ir and nmr spectra as in section A; the 60-MHz nmr spectrum (CDCl_3) showed a small satellite slightly upfield of the main PHCH signal, which possibly was due to syn-anti isomerism.

C) With platinum:

A suspension of platinum dioxide (1.0 g) in 95% ethanol (50 mL) was prehydrogenated in the presence of M hydrochloric acid (4 mL). Then a partial suspension of epoxide 5 (1.0 g, 3.24 mmol) in ethanol (40 ml) was added and the hydrogenation was continued for 4.5 hours. According to tlc (solvent H), compound 5 had been replaced by at least six products, as described in the Results section. The catalyst was filtered off and washed several times with ethanol. Evaporation of the solvent gave a solid residue from which, by crystallization from hot ethanol and a small proportion of ethyl acetate, the product corresponding to the strongest spot (R_f 0.5) was obtained in pure form. It was the monohydrate of methyl 3-amino-4,6-O-(cyclohexylmethylene)-3-deoxy- β -D-mannopyranoside hydrochloride (17); yield, 340 mg (31%), melting point 210-212°, $[\alpha]_D -77.6^\circ$ (c 0.7, 90% ethanol); ν_{max} 3400 (s, with sh at 3100), several weak bands in the 2600 cm^{-1} region, 1590 and

1530 cm^{-1} (ms); nmr ($\text{Me}_2\text{SO}-d_6$): no low-field, phenyl signals, but intense multiplets at δ 1.9-0.9, attributable to cyclohexyl.

Anal. Calcd. for $\text{C}_{14}\text{H}_{26}\text{ClNO}_5 \cdot \text{H}_2\text{O}$ (341.8): C, 49.19; H, 8.25; N, 4.10. Found: C, 48.87; H, 8.53, N, 4.05.

A sample of the amino alcohol was quantitatively acetylated with acetic anhydride in pyridine during 90 minutes at 25° , to give chromatographically homogeneous N-acetyl-O-acetyl derivative 18, crystallized from chloroform-petroleum ether; melting point $210-211^\circ$, $[\alpha]_D -78.3^\circ$, (c 1); nmr (100 MHz, CDCl_3): δ 5.52 (dd, $J_{1,2}$ 1.3, $J_{2,3}$ 3.3 Hz, H-2), 5.42 (broad signal, NH), 4.54 (d, J 1.3 Hz, H-1), 4.38 (dd, $J_{2,3}$ 3.3, $J_{3,4}$ 10.4 Hz, with lines broadened by coupling with NH, H-3), 4.3-4.1 (m, 2 H), 3.7-3.2 (two superposed t, J 10 Hz, for H-4 and H-6a, with upfield line obscured by OMe; and adjoining m for H-5), 3.48 (s, 3 H, OMe), 2.16 (s, 3 H, OAc), 1.97 (s, 3 H, NAc), and 1.9-0.8 (m, 11 H, cyclohexyl).

Anal. Calcd. for $\text{C}_{18}\text{H}_{29}\text{NO}_7$ (371.4): C, 58.20; H, 7.87; N, 3.77. Found: C, 57.96, H, 7.99, N, 3.64.

Fractional recrystallization from ethanol-ethyl acetate was repeated with the evaporated mother liquors of crystallization of 17, to afford a mixed fraction consisting of 17 and more-polar material, not investigated further. Another repetition of the process afforded crystals (50 mg) of the fastest-moving hydrogenation product (R_f 0.95) characterized by insolubility in water, and a

negative ninhydrin reaction. It was methyl 4,6-O-(cyclohexylmethylene)-3-deoxy-3-nitro- β -D-mannopyranoside (19), melting point 212-214° after recrystallization from methanol-water; $[\alpha]_D - 77.4^\circ$ (c 0.9); ν_{\max} 3400 (s, OH) and 1560 cm^{-1} (s, NO_2), with a fingerprint pattern clearly distinct from that of the benzylidene analog 15; nmr (100 MHz, $\text{Me}_2\text{CO-d}_6$): δ 4.85 (dd, 1 H, $J_{2,3}$ 3.5, $J_{3,4}$ 10.5 Hz, H-3), 4.71 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 4.46 (2 H, dd for H-2 superposed on d, J 5 Hz, for cyclohexyl- CHO_2), 4.28 (dd, 1 H, $J_{3,4}$ 10.5, $J_{4,5}$ 9.3 Hz, H-4), 4.17 (dd, 1 H, $J_{5,6}$ 4.7, $J_{6a,6e}$ 10 Hz, H-6e), 3.66 (t, 1 H, J 10 Hz, H-6a), 3.50 (s, 3 H, OMe), 3.36 (o, H-5) and 1.9-0.8 (m, cyclohexyl).

Anal. Calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_7$ (317.3): C, 52.99; H, 7.31; N, 4.41. Found: C, 52.97; H, 7.47; N, 4.24.

Finally, a crystalline fraction that contained only slow-moving (R_F about 0.1), ninhydrin-positive material could be elaborated from the hydrogenated product mixture; it showed $[\alpha]_D -127.6^\circ$ (c 1.2, water); reported for methyl 3-amino-3-deoxy- β -D-altropyranoside hydrochloride¹⁷ (20), -138° , and for its β -D-manno isomer¹⁴⁵ (21), -68.5° . The product, judged to be mainly 20 on the basis of these data, gave an ir spectrum quite different from that of authentic¹⁴⁵ 21. Its R_F value (0.4) was also different from that of 21 (R_F 0.25), although both samples showed considerable trailing (in solvent, H). After hydrolysis in refluxing,

M hydrochloric acid for 2 hours, the corresponding R_F values were 0.3 (elongated spot) and 0.25.

B) With palladium followed by platinum:

Compound 5 (50 mg) was hydrogenated for 45 minutes in the presence of palladium, as described under B.. The catalyst was filtered off, and the filtrate was evaporated to dryness; the residue was dissolved in 95% ethanol (4 mL) and hydrogenated for 24 hours in the presence of platinum catalyst (50 mg) and M hydrochloric acid (0.15 mL). Tlc indicated the absence of 15 and 16, which were replaced by a small proportion of a faster-moving, ninhydrin-negative product (subsequently identified as 19) and three slow-moving, ninhydrin-positive compounds as the major products. The most mobile of the latter corresponded to 17, and the others were, evidently, deacetylated amino glycosides. Processing of the reaction mixture gave a crystalline mixture of amino sugar hydrochlorides (from ethyl acetate-petroleum ether) that could not be separated. Because of the relatively low levorotation ($[\alpha]_D -51^\circ$, water) and the results of paper chromatography after total acid hydrolysis, it was concluded that the D-manno configuration predominated. The nitro glycoside 19 was isolated from the mother liquor by chromatography on a small column of silica gel, with 1:2 ethyl acetate-petroleum ether as the eluant; yield 10 mg from two combined runs. It was identified by its ir and nmr spectra.

No differences in the results were detected when, in an identical

experiment, the palladium-catalyzed hydrogenation solution was stirred with silica gel for 24 hours prior to the platinum-catalyzed hydrogenation.

Another palladium-catalyzed hydrogenation of 5 was performed on the same scale, but for 36 hours in order to effect complete conversion into oxime 16 (see method B). Subsequent hydrogenation (24 hours) in the presence of platinum as just described, followed by acid hydrolysis of the products, gave a mixture of amino sugars showing the same pattern as the preceding in paper chromatography.

Hydrogenation of Benzylidenenitro- β -D-mannoside¹⁷¹ 15

A mixture of compound 15 (400 mg) and Pd/C (200 mg) in 7:3 methanol-1,4-dioxane (40 mL) was hydrogenated for 30 hours. The ninhydrin-positive, strongly preponderant product (R_F 0.5, in tlc with solvent I) was the (cyclohexylmethylene) acetal 17 (as the free base); see the Results section concerning 3 minor, tlc spots. Part of the reaction mixture was slightly acidified with acetic acid, evaporated to dryness, and the residue further hydrogenated, in the presence of platinum, in ethanol containing a small proportion of hydrochloric acid. No visible change occurred as far as 17 was concerned, although the ninhydrin-negative, minor by-products disappeared, and a slow-moving, small spot of deacetalated amino glycoside appeared (9 hours, unchanged after 24 hours). Processing then gave 17 as fine needles from ethanol-ethyl acetate, melting point 210-212°, identical with 17 obtained from 5 (ir

spectra). Another part of the original hydrogenation solution was briefly warmed after addition of aqueous hydrochloric acid (about 0.7 molar excess) and then evaporated to dryness, whereby deacetylation occurred. The white, crystalline product had $[\alpha]_D -66^\circ$ (c 0.5, water) and R_F 0.1 (solvent I); its ir spectrum confirmed the identity with known ¹⁴⁵ 21.

Hydrogenation of 15 (25 mg) with platinum (25 mg) in ethanol (5 ml) containing M hydrochloric acid (0.1 ml) was examined by tlc with solvent H.

Hydrogenation of Nitro- β -D-mannoside¹⁴⁵ 22

Compound 22 (100 mg) in 7:3 methanol-1,4-dioxane (10 mL) was hydrogenated in the presence of Pd/C (50. mg) and 0.1 M acetic acid (2 mL). After 1 and 3 hours, tlc (solvent H) indicated the presence of remaining starting material 22 (R_F 0.7). However, virtually all of it was consumed after 10.5 hours, and a strong, ninhydrin-positive spot (R_F 0.1) was produced, accompanied by trace spots having intermediate mobilities. The Griess test¹⁴⁴ was negative. Addition of an equivalent amount of hydrochloric acid to the solution, and evaporation followed by successive additions of ethanol to the residue and re-evaporation, gave a colorless syrup that yielded crystalline 21 on treatment with ethanol and ethyl acetate; melting point 202-203°, $[\alpha]_D -62.5^\circ$ (c 0.7, water). The ir spectrum was superposable on that of an authentic sample, although the crystal shape and melting point were different.

Recrystallization from absolute methanol raised the melting point to 230-231° as reported¹⁴⁵; the product was obtained as fine, rectangular prisms.

A hydrogenation of 22 in the presence of platinum and ethanol (as described for 5) was slow, with a visually estimated 50 and 25% of starting compound remaining after 4.5 and 21 hours, respectively. The only reaction-product detected chromatographically, and isolated crystalline, was 21. (The same reaction had been previously performed¹⁴⁵ in aqueous solution, wherein it was noticeably faster, requiring only 2 to 3 hours for completion (private communication by Professor H.H. Baer).

PART IV .

The zirconium hydride, $\text{Cp}_2\text{Zr(H)Cl}$, was first prepared by Wailes et al.¹⁶¹ from Cp_2ZrCl_2 and LiAlH_4 . It is also easily prepared by treatment of the dichloride in THF with a stoichiometric amount of $\text{NaAlH}_2(\text{OR})_2$. Both procedures result in the high yields of the hydride¹⁶³. The samples used in this work were kindly donated by Professor H. Alper.

Ethyl 6-O-(Methyl oxalyl)-4-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (4):

A solution of the olefin 3 (258 mg, 1 mmol) in dry benzene (2 mL) was added to a stirred suspension of dicyclopentadienylhydrido-zirconium chloride (1) (358 mg, 1 mmol) in dry benzene (10 mL), whereupon the salt dissolved partially. The mixture was stirred under N_2 at room temperature for 1 hour, after which tlc (solvent B) indicated the conversion of almost half of the starting glycoside 3 (R_F 0.6) into a new compound A, which moved more slowly (R_F 0.3). Stirring was continued for another 2 hours, which caused no change in the tlc picture; however, all the suspended zirconium hydride had disappeared to afford a colorless, clear solution. At this stage, one equivalent of methyl oxalyl chloride (about 0.1 mL) was added, and stirring was continued for one hour after which tlc (solvent B) showed disappearance of compound A and formation of a new product (4, R_F 0.5). Processing of the colorless solution by adding water caused precipitation of a white solid that was insoluble in organic solvents and was removed. The aqueous phase was then extracted with methylene chloride, and the combined organic phases were dried over anhydrous magnesium sulfate. Crude

white crystals (330 mg) were obtained on evaporation of the solvent. Recrystallization from a hot mixture of ether and petroleum ether (b.p. 30-60°) afforded beautiful crystals of compound 4 (80 mg, 26%), melting point 128-129°. The mother liquor contained additional 4 together with unchanged 3, but no efforts were made to separate these or to optimize the yield.

NMR (100 MHz, CDCl₃): δ 5.87 (narrow multiplet, 2 H, H-2 and H-3), 5.33 (d of m, J_{4,5} = 9.3 Hz, H-4), 5.04 (narrow multiplet, H-1), 4.41 (m, 2 H, H-6,6'), 4.21 (m, H-5), 3.92 (s, 3 H, OMe), 3.71 (m, 2 H, OCH₂-CH₃), 2.09 (s, 3 H, OAc), 1.26 (t, J = 7 Hz, ethyl CH₃).

Anal. Calcd. for C₁₃H₁₈O₈ (302.3): C, 51.66; H, 6.00.

Found: C, 51.41 ; H, 5.73.

Ethyl 6-O-Triphenylmethyl-4-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (5)

Compound 3 (258 mg, 1 mmol) was treated with 1 (358 mg, 1 mmol) as described above. Triphenylchloromethane (278 mg, 1 mmol) in dry benzene (2 mL) was then added, and the mixture was stirred for one hour. Processing as described for 4 afforded 0.10 g (56%) of 5 as white crystals, melting point 35-137°. NMR (60 MHz, CDCl₃): δ 7.23 (m, 15 H, 3Ph), ~5.8 (s, 2 H, H-2, H-3), 5.28 (d, J ≈ 9.3, H-4), 5.03 (bs, H-1), ~3.9 (m, 3 H, H-5 and OCH₂-CH₃), 3.15 (m, 2 H, H-6,-6'), 1.84 (s, 3 H, OAc), 1.27 (t, J = 7 Hz, ethyl CH₃).

1,5-Anhydro-4,6-O-Benzylidene-2,3-dideoxy-D-erythro-hex-1-enitol (8)
Methyl 4,6-O-benzylidene-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (7), (250 mg) was added to a suspension of the zirconium hydride 1 (286 mg) in dry benzene (10 mL). Stirring of the reaction mixture at room temperature for 2 hours caused the zirconium salt to disappear, and a yellow solution resulted. Tlc with solvent B showed no significant change in the spot intensity of the starting material (R_F about 0.7); however, on continued stirring a new spot (R_F about 0.9) appeared overnight and increased in intensity with time. After 20 hours, one equivalent of acetyl chloride (0.3 mL) was added and the reaction mixture was stirred for another hour. Work-up as described previously, extraction with methylene chloride, and evaporation of the extract afforded 300 mg of crude material. Tlc with solvent B showed the same pattern as before, in addition to some impurities which migrated more slowly (R_F 0.1-0.4). Separation by preparative tlc using solvent E yielded starting material 7 (90 mg); nmr and ir spectrum and melting point (117-119°) proved its identity. It also afforded 0.10 g (45%) of the fast-moving material (R_F about 0.9) as white crystals, melting point 112-113° (after sublimation in vacuo at 56°). The ir and nmr data of the product were in full agreement with the literature¹⁶⁴ data given for the glycal 8.

The slow-moving impurities (R_F 0.1-0.4), at least 4 compounds, were eluted from the tlc plates and amounted to a total of 40 mg. The material was not investigated further.

REFERENCES

- (1) J.D. Dutcher, Adv. Carbohydr. Chem., 18,259 (1963).
- (2) H. Grisebach, " Biosynthetic Patterns in Microorganisms and Higher Plants ", Wiley, New York, pp. 66-101 (1967).
- (3) D. Horton, in " The Amino Sugars ", R.W. Jeanloz, Edit., Academic Press, New York (1969), Vol. IA, Chapt. 1.
- (4) a) S. Hanessian and T.H. Haskell, in " The Carbohydrates ", W. Pigman and D. Horton, Edit., Academic Press, New York, Vol. IIA (1970), Chapt. 31;
b) D. Horton and J.D. Wander, ibid., Vol. IB (1980), Chapt. 16;
c) N.R. Williams and J.D. Wander, ibid., Vol. IB (1980), Chapt. 17.
- ◇ (5) J.S. Brimacombe, Angew. Chem. Int. Ed. Engl., 10,236 (1971).
- (6) H. Grisebach and R. Schmid, Angew. Chem. Int. Ed. Engl., 11,159 (1972).
- (7) W. Kessler-Schierlein, Fortschr. Chem. Org. Naturst., 30,314 (1973).
- (8) a) S. Umezawa, Adv. Carbohydr. Chem. Biochem., 30,111 (1974);
b) H. Umezawa, ibid., 30,183 (1974).
- (9) a) S. Umezawa, MTP Int. Rev. Sci. Org. Chem. Ser. Two, 7,149 (1976);
b) W.A. Szarek and D.M. Vyas, ibid., 7,105 (1976).
- (10) H. Grisebach, Adv. Carbohydr. Chem. Biochem., 35,81 (1978).
- (11) A.W. Johnson, R.M. Smith and R.D. Guthrie, J. Chem. Soc., Perkin Trans. I, 2153 (1972).
- (12) W.D. Weringa, D.H. Williams, J. Feency, J.P. Brown and R.W. King, J. Chem. Soc., Perkin Trans. I, 443 (1972).
- (13) M. Debono and R.M. Molloy, J. Org. Chem., 45,4685 (1980).
- (14) a) A.K. Ganguly, O.Z. Sarre and H. Reimann, J. Am. Chem. Soc., 90,7129 (1968);
b) For the revised structure, see A.K. Ganguly, O.Z. Sarre, A.T. McPhail and K.D. Onan, J. Chem. Soc. Chem. Commun., 313 (1977).
- (15) O.E. Wright, Tetrahedron, 35,1207 (1979).
- (16) S.A. Mizak, H. Hoeksema and L.M. Pschigoda, J. Antibiot., 32,771 (1979).
- (17) a) R. Bognar, E. Sztaricskai, M.E. Munk and J. Tames, J. Org. Chem., 39,2971 (1974);

- b) N.N. Lomakina, I.A. Spiridonova, Y.N. Sheinker and T.F. Vlasova, *Khim. Prir. Soedim.*, 9, 101 (1973); *Chem. Abstr.*, 78, 148170 (1973).
- (18) F. Arcamone, "Anticancer Agents Based on Natural Product Models", Academic Press, New York, pp. 1-41 (1980).
- (19) T. Kishi, S. Harada, M. Asai, M. Muroi and K. Mizuno, *Tetrahedron Lett.*, 97 (1969).
- (20) a) J.E. Lancaster, L.A. Milscher and G. Morton, *Tetrahedron*, 23, 3893 (1967);
b) H. Paulsen and H. Redlich, *Chem. Ber.*, 107, 1992 (1974).
- (21) H.H. Baer, *Adv. Carbohydr. Chem. Biochem.*, 24, 67 (1969).
- (22) a) W.G. Overend and N.R. Williams, *J. Chem. Soc.*, 3446 (1965);
b) J.S. Burton, W.G. Overend and N.R. Williams, *ibid.*, 3433 (1965);
c) B. Flaherty, S. Nahar, W.G. Overend and N.R. Williams, *J. Chem. Soc. Perkin Trans. I*, 632 (1973).
- (23) a) J.S. Brimacombe, A.J. Rollins and S.W. Thompson, *Carbohydr. Res.*, 31, 108 (1973);
b) D.C. Baker, D.K. Brown, D. Horton and R.G. Nickol, *ibid.*, 32, 299 (1974).
- (24) a) A. Rosenthal and L. Benzing-Nguyen, *Tetrahedron Lett.*, 2393 (1967); *J. Org. Chem.*, 34, 1029 (1969);
b) A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, 47, 3941, 4477 (1969);
c) E.H. Williams, W.A. Szarek and J.K.N. Jones, *Can. J. Chem.*, 47, 4467 (1969);
d) J.M.J. Tronchet and J.M. Chalet, *Carbohydr. Res.*, 24, 263, 283 (1972);
e) A. Rosenthal and C.M. Richards, *ibid.*, 29, 413 (1973).
- (25) a) N.R. Williams, *Adv. Carbohydr. Chem. Biochem.*, 25, 109 (1970);
b) T.D. Inch and G.J. Lewis, *Carbohydr. Res.*, 22, 91 (1972);
c) S.R. Jenkins and E. Walton, *ibid.*, 26, 71 (1973).

- (26) a) S. Hanessian, P. Dextraze and R. Masse, Carbohydr. Res., 26,264 (1973);
b) S. Hanessian and P. Dextraze, Can. J. Chem., 50,226 (1972).
- (27) A. Rosenthal, Adv. Carbohydr. Chem., 23,59 (1968).
- (28) a) B. Fraser-Reid, N.C. Holder, D.R. Hicks and D.L. Walker, Can. J. Chem., 55,3986 (1977);
b) B. Fraser-Reid, R.C. Anderson, D.R. Hicks and D.L. Walker, ibid., 55,3986 (1977);
For the photoaddition of dioxolane to alkenes, see:
c) A. Rosenthal and D. Elad, J. Org. Chem., 33,805 (1968);
d) J.S. Jewell and W.A. Szarek, Tetrahedron Lett., 43 (1969);
e) K. Matsuura, K. Nishiyama, K. Yamada, Y. Araki and Y. Ishido, Bull. Chem. Soc. Japan, 46,2538 (1973).
- (29) a) S.W. Gunner, W.G. Overend and N.R. Williams; Chem. Ind. (London), 1523 (1964);
b) H.H. Baer and G.V. Rao, Liebigs Ann. Chem., 686,210 (1965);
c) F.W. Lichtenthaler and H.K. Yahya, Carbohydr. Res., 5,482 (1967);
d) J.S. Brimacombe and L.W. Doner, J. Chem. Soc.; Perkin Trans. I, 62 (1974).
- (30) S.W. Gunner, R.F. King, W.G. Overend and N.R. Williams, J. Chem. Soc. (C) 1954 (1970).
- (31) H.H. Baer and K.S. Ong, Can. J. Chem., 46,2911 (1968).
- (32) H. Paulsen and W. Greve, Chem. Ber., 107,3013 (1974).
- (33) a) T. Sakakibara and R. Sudoh, J. Org. Chem., 40,2823 (1975);
b) T. Sakakibara and R. Sudoh, ibid., 42,1746 (1977).
- (34) a) M. Funabashi and J. Yoshimura, J. Chem. Soc. Perkin Trans. I, 1425 (1979);
b) M. Funabashi, K. Kobayashi and J. Yoshimura, J. Org. Chem., 44,1618 (1979).
- (35) G.L. Lourens, Tetrahedron Lett., 3733 (1969); Carbohydr. Res., 17,35 (1971).

- (36) a) A. Rosenthal and K.S. Ong, *Tetrahedron Lett.*, 3981 (1969);
b) A. Rosenthal and K.S. Ong, *Can. J. Chem.*, 48,3034 (1970);
c) A. Rosenthal, M. Sprinzl and D.A. Baker, *Tetrahedron Lett.*,
4233 (1970);
d) A. Rosenthal and B. Cliff, *J. Carbohydr. Nucleos. Nucleot.*,
2,263 (1975).
- (37) H.P. Albrecht and J.G. Moffat, *Tetrahedron Lett.*, 1063 (1970).
- (38) a) H. Yanagisawa, M. Kinoshita, S. Nakada and S. Umezawa,
Bull. Chem. Soc. Japan, 43,246 (1970);
b) J.M. Bourgeois, *Helv. Chim. Acta*, 57,2553 (1974); 59,2114 (1976);
c) J. Yoshimura, M. Matsuzawa, K. Sato and Y. Nagasawa,
Carbohydr. Res., 76,67 (1979).
- (39) H.H. Baer, F. Linhart and H.R. Hanna, *Can. J. Chem.*, 56,3087 (1978).
- (40) a) A. Rosenthal and K. Shudo, *J. Org. Chem.*, 37,1608 (1972);
b) A. Rosenthal and M. Ratcliffe, *Carbohydr. Res.*, 59,79 (1975);
c) *ibid.*, 54,61 (1977).
- (41) H. Alper, Edit., "Transition Metal Organometallics in Organic
Synthesis", Academic Press, New York, 1976.
- (42) a) R. Hüttel, *Synthesis*, 228 (1970);
b) B.M. Trost, *Tetrahedron*, 33,2615 (1977);
c) B.M. Trost, *Pure Appl. Chem.*, 51,787 (1979);
d) B.M. Trost, *Acc. Chem. Res.*, 13,385 (1980);
e) R.F. Heck, *Acc. Chem. Res.*, 12,146 (1979);
f) J. Tsuji, "Organic Synthesis with Palladium Compounds",
Springer-Verlag, New York (1980).
- (43) a) T.S. Shryne, E.J. Smutny and D.P. Stevenson, U.S. Pat. No.
3,493,617 (1970);
b) W.E. Walker, R.M. Manyk, K.E. Atkins and M.L. Farmer,
Tetrahedron Lett., 3817 (1970);
c) K.E. Atkins, W.E. Walker and R.M. Manyk, *Tetrahedron Lett.*,
3821 (1970);

- d) G. Hata, K. Takahashi and A. Miyako, Chem. Commun., 1392 (1970);
e) K. Takahashi, A. Miyako and G. Hata, Bull. Chem. Soc. Japan, 45, 230 (1972).
- (44) B.M. Trost, N.R. Schmuff and M.J. Miller, J. Am. Chem. Soc., 102, 5979 (1980).
- (45) a) B.M. Trost and E. Keinan, *ibid.*, 101, 7779 (1978);
b) C.U. Pittman Jr. and Q. Ng, J. Organomet. Chem., 153, 85 (1978).
- (46) B.M. Trost and T.R. Verhoeven, J. Am. Chem. Soc., 100, 3435 (1978).
- (47) a) B. Fraser-Reid, Acc. Chem. Res., 192 (1975);
b) R.J. Ferrier, Methods Carbohydr. Chem., 6, 307 (1972);
c) R.J. Ferrier and N. Prasad, J. Chem. Soc. (C), 57 (1969).
- (48) A. Rosenthal and J.N.C. Whyte, Can. J. Chem., 46, 2245 (1968).
- (49) A. DeBoer, C.J. Thanel and G.A. Wilson, Tetrahedron Lett., 5137 (1972).
- (50) G.L. Inglis, J.C.P. Schwarz and L. McLaren, J. Chem. Soc., 1014 (1962).
- (51) a) D. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Japan, 44, 3427 (1971);
b) G. Alfredsson and P.J. Garegg, Acta Chem. Scand., 27, 724 (1973);
c) G. Gryniewicz and H. Burzynska, Tetrahedron, 32, 2109 (1976).
- (52) G. Gryniewicz, W. Priche and A. Zamojski, Carbohydr. Res. 68, 33 (1979).
- (53) A. Rosenthal, Carbohydr. Res., 8, 61 (1968).
- (54) R.J. Ferrier, N. Vethaviasar, O.S. Chizhov, V.I. Kadentsev and R.M. Zolotarev, Carbohydr. Res., 13, 269 (1970).
- (55) G. Descotes, P. Boullanger, Tachi-Dung, and J.C. Martin, Carbohydr. Res., 71, 305 (1979).
- (56) a) A.S. Perlin, Internat. Rev. Sci. Org. Chem. Ser. 2, 7, 1 (1975);
b) R.G.S. Ritchie, N. Cyr and A.S. Perlin, Can. J. Chem., 54, 2301 (1976);

- c) H. Paulsen, V. Sinnwell and W. Greve, Carbohydr. Res., 49,27 (1976).
- (57) P.J. Garegg and B. Samuelsson, Synthesis, 813 (1979).
- (58) D.E. Iley and B. Fraser-Reid, Can. J. Chem., 57,653 (1979).
- (59) G. Adiwidjaja, B. Meyer, H. Paulsen and J. Thiem, Tetrahedron, 35,373 (1979).
- (60) J. Thiem, J. Schwentner, E. Schüttpelz and J. Kopf, Chem. Ber., 112,1023 (1979).
- (61) R. Stokhuyzen and C. Chieh, J. Chem. Soc., Perkin Trans. II, 481 (1976).
- (62) K.A. Watanabe, R.S. Goody and J.J. Fox, Tetrahedron, 26,3885 (1970).
- (63) E.W. Garbisch, Jr., J. Am. Chem. Soc., 86,5561 (1964).
- (64) R.U. Lemieux, E. Fraga and K.A. Watanabe, Can. J. Chem., 46,61 (1968).
- (65) R.U. Lemieux, K.A. Watanabe and A.A. Pavia, Can. J. Chem., 47,4413 (1969).
- (66) E.F.L.J. Anet, Carbohydr. Res., 1,348 (1966).
- (67) B. Fraser-Reid, B.J. Carthy, N.L. Holder and M. Yunker, Can. J. Chem., 49,3038 (1971).
- (68) B. Fraser-Reid, S.Y.K. Tam and B. Radatus, Can. J. Chem., 53,2005 (1975).
- (69) K. Heyns and J.P. Park, Chem. Ber., 109,3262 (1976).
- (70) R.R. Schmidt and R. Angerbauer, Carbohydr. Res., 72,272 (1979).
- (71) a) R.J. Ferrier and N. Prasad, J. Chem. Soc. (C), 581 (1969);
b) R.J. Ferrier and C.H. Sankey, J. Chem. Soc. 2339,2345 (1966).
- (72) R.U. Lemieux and R.J. Bose, Can. J. Chem., 44,1855 (1966).
- (73) F. Johnson and S.K. Malhotra, J. Am. Chem. Soc., 87,5492 (1965).
- (74) R.J. Ferrier and N. Vethaviasar, J. Chem. Soc. (C), 1907 (1971).

- (75) J.C. Florent, C. Monneret and Q. Khuong-Huu, Carbohydr. Res., 56,301 (1977).
- (76) a) D.H. Whiffen, Chem. and Ind. (London), 964 (1956);
b) J.H. Brewster, J. Am. Chem. Soc., 81,5483,5493 (1959);
c) R.U. Lemieux and J.C. Martin, Carbohydr. Res., 13,139 (1970).
- (77) a) D.M. Ciment and R.J. Ferrier, J. Chem. Soc.(C), 441 (1966);
b) D.M. Ciment, R.J. Ferrier and W.G. Overend, J. Chem. Soc. (C), 447 (1966).
- (78) R.J. Ferrier, J. Chem. Soc., 5443 (1964).
- (79) a) H. Paulsen and J. Thiem, Chem. Ber., 106,3850 (1973);
b) J. Thiem, B. Meyer and H. Paulsen, ibid., 111,3325 (1978).
- (80) N.L. Holder and B. Fraser-Reid, Can. J. Chem., 51,3357 (1973).
- (81) R.J. Ferrier and N. Vethaviasar, Carbohydr. Res., 58,481 (1977).
- (82) a) F. Ozawa, T. Ito, Y. Nakamura and A. Yamamoto, J. Organomet. Chem., 168,375 (1979);
b) S. Otsuka, A. Nakamura, T. Yoshida, M. Naruto and K. Ataka, J. Am. Chem. Soc., 94,2669 (1972);
c) C.A. Tolman, W.C. Sedil and D.H. Gerlach, J. Am. Chem. Soc., 94,2662 (1972);
d) F.R. Hartly, Chem. Rev., 69,799 (1969).
- (83) a) K.S.Y. Law, R.W. Friess and J.K. Stille, J. Am. Chem. Soc., 96,4985 (1974);
b) P.K. Wong, K.S.Y. Law and J.K. Stille, ibid., 96,5956 (1974);
c) K.J. Klabunde, J.S. Roberts, J. Organomet. Chem., 157,113 (1977).
- (84) B.M. Trost and F.W. Gowland, J. Org. Chem., 44,3448 (1979).
- (85) B.M. Trost and D.P. Curran, J. Am. Chem. Soc., 102,5699 (1980).
- (86) B.M. Trost and T.R. Verhoeven, J. Am. Chem. Soc., 102,4730 (1980).
- (86) a) Y. Takahashi, K. Tsukiyama, S. Sakai and Y. Ishii, Tetrahedron Lett., 1913 (1970).
- (87) a) J.C. Fiaud, A. Hibon de Gournay, M. Larcheveque and H.B. Kagan, J. Organomet. Chem., 154,175 (1978);

- b) B.M. Trost, T.J. Dietsche and T.J. Fullerton, *J. Org. Chem.*, 39,737 (1974);
- c) B.M. Trost and L. Weber, *J. Org. Chem.*, 40,3617 (1975);
- d) B.M. Trost and L. Weber *J. Am. Chem. Soc.*, 97,1611 (1975)
- e) B.M. Trost, L. Weber, P.E. Strege, T.J. Fullerton, T.J. Dietsche, *ibid.*, 100,3416,3426 (1978).
- (88) a) R. Heck, *J. Am. Chem. Soc.*, 90,5542 (1968);
- b) S. Numata, H. Kurosawa, *J. Organomet. Chem.* 131,301 (1977);
- c) S. Numata, H. Kurosawa, R. Okawara, *J. Organomet. Chem.*, 102,259 (1975).
- (89) J. Tsujii, T. Yamakawa, M. Kait and T. Mandai, *Tetrahedron Lett.*, 2075 (1978).
- (90) a) B.M. Trost, E. Keinan, *J. Org. Chem.*, 44,3451 (1979);
- b) Y. Tezuka, T. Ogura, S. Kawagushi, *Bull. Chem. Soc. Japan*, 42,443 (1969).
- (91) a) B.M. Trost, J.P. Genet, *J. Am. Chem. Soc.*, 98,8516 (1976);
- b) G.R. Wiger, M.F. Rettig, *ibid.*, 98,4168 (1976).
- (92) a) B.M. Trost, T.R. Verhoeven and J. Fortunak, *Tetrahedron Lett.*, 2301 (1979);
- b) B.M. Trost and J.M. Fortunak, *J. Am. Chem. Soc.*, 102,2841 (1980).
- (93) M.B. Yunker and B. Fraser-Reid, *Can. J. Chem.* 54, 3986 (1976).
- (94) A. Duperrier and J. Dreux, *Tetrahedron Lett.*, 3127 (1970);
- J. Rover and J. Dreux, *Bull. Soc. Chim. Fr.*, 707 (1972)
- (95) J.C. Fiaud and J.L. Malleran, *Tetrahedron Lett.*, 4437 (1980).
- (96) a) S. Pinnert-Sindico, L. Ninet, J. Preud'homme and C. Cosar, *Antibiotics Ann.*, 724 (1954);
- b) R. Corbaz, L. Ettliger, E. Gäumann, W. Keller-Schierlein, F. Kradolfer, E. Kyburz, L. Neipp, V. Prelog, W. Wettstein, and H. Zähler, *Helv. Chim. Acta*, 39,304 (1956).
- (97) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 734 (1957).

- (98) C.L. Stevens, G. Gutowski, K.G. Taylor and C.P. Bryant, Tetrahedron Lett., 5717 (1966).
- (99) a) E.L. Albano and D. Horton, Carbohydr. Res., 11,485 (1969);
b) E.L. Albano and D. Horton, J. Org. Chem., 34,3519 (1969).
- (100) a) I. Dyong, R. Knollmann and N. Jersch, Angew. Chem., 88,301 (1976);
b) I. Dyong, R. Knollmann, N. Jersch and H. Luftmann, Chem. Ber., 111,559 (1978).
- (101) a) S. Hanessian and N.R. Plessas, J. Org. Chem., 34,1035 (1969);
b) S. Hanessian and N.R. Plessas, *ibid.*, 34,1045 (1969);
c) S. Hanessian, Methods Carbohydr. Chem., 6,183 (1972).
- (102) P.J. Garegg and B. Samuelsson, Synthesis, 813 (1979).
- (103) H.C. Brown and S. Krishnamurthy, J. Am. Chem. Soc., 95,1669 (1973).
- (104) T.D. Inch, Carbohydr. Res., 21,37 (1972).
- (105) M.B. Yunker, S.Y.-K. Tam, D.R. Hicks and B. Fraser-Reid, Can. J. Chem., 54,2411 (1976).
- (106) R.S. Tipson and A. Cohen, Carbohydr. Res., 1,338 (1965).
- (107) K. Bock, J.K. Christiansen and C. Pedersen, Carbohydr. Res., 20,73 (1971).
- (108) J.S. Brimacombe, L.W. Doner and A.J. Rollins, J. Chem. Soc. Soc. Perkin Trans. I, 2977 (1972).
- (109) D.M. Clode, D. Horton and W. Weckerle, Carbohydr. Res., 49,305 (1976).
- (110) O. Achmatowicz Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, Tetrahedron, 27,1973 (1971).
- (111) B.L. Sondengam, J. Hentchoya Héno, and G. Charles, Tetrahedron Lett. 261 (1973)
- (112) a) G.G. Birch, Adv. Carbohydr. Chem: Biochem.; 18,201 (1963)
b) A.D. Elbein, *ibid.*, 30,227 (1974);

- (113) a) F. Arcamone and F. Bizioli, *Gazz. Chim. Ital.*, 87,1499 (1957);
b) M. Ghione, A. Minghetti and A. Sanfilippo, *Giorn. Microbiol.*
7,94 (1959).
- (114) H. Naganawa, N. Usui, T. Takita, M. Hanada, K. Maeda and
H. Umezawa, *J. Antibiot. Ser. A*, 27,145 (1974).
- (115) S. Hanessian and P. Lavallée, *J. Antibiot. (Tokyo)*, 25,683 (1972).
- (116) H.H. Baer and A.J. Bell, *Carbohydr. Res.*, 75,175 (1979).
- (117) H.H. Baer and A.J. Bell, *Can. J. Chem.*, 56,2872 (1978).
- (118) J. Defaye, Private communication to Dr. H.H. Baer.
- (119) a) Alfredsson and Garegg, *Acta. Chem. Scand.* (1973);
b) J. Thiem and J. Schwentner, *Tetrahedron Lett.*, 2117 (1976);
c) J. Thiem, J. Schwentner, E. Schüttpelz and J. Kopf,
Chem. Ber., 112,1023 (1979).
- (120) W. Roth and W. Pioman, *Methods. Carbohydr. Chem.*, 2,405 (1963).
- (121) C.P.J. Glaudemans and H.G. Fletcher Jr., *Methods Carbohydr.*
Chem., 6,373 (1972).
- (122) For reviews of organocopper chemistry see;
a) J.F. Normant, *Synthesis*, 63 (1972);
b) A.E. Jukes, *Adv. Organomet. Chem.*, 12,215 (1974);
c) G.H. Posner, *Org. Reaction*, 19,1 (1972);
d) *ibid.*, 22,253 (1975);
e) H.O. House, *Acc. Chem. Res.*, 9,59 (1976);
f) For the latest development see; A. Marfat, R.R. McGuirk and
P. Helquist, *J. Org. Chem.*, 44,3888 (1979).
- (123) M.B. Yunker, D.E. Plaumann and B. Fraser-Reid, *Can. J. Chem.*,
55, 4002 (1977).
- (124) S.B. Bowlus, *Tetrahedron Lett.*, 3591 (1975).
- (125) C.P. Casey and M.C. Cesa, *J. Am. Chem. Soc.*, 101,4236 (1979).
- (126) A. Nilsson, A. Ronlán, and V.D. Parker, *Tetrahedron Lett.*,
1107 (1975).
- (127) R.D. Hicks and B. Fraser-Reid, *Can. J. Chem.*, 53,2017 (1975).

- (128) a) H.H. Baer and W. Rank, *Can. J. Chem.*, 53, 2017 (1975);
b) H.H. Baer and W. Rank, *ibid.*, 52, 2257 (1974).
- (129) a) P.M. Collins, D. Gardiner, S. Kumar and W.G. Overend,
J. Chem. Soc. Perkin Trans. I, 2596 (1972);
b) P.M. Collins, W.G. Overend and V.M. Racz, *Carbohydr. Res.*,
45, 127 (1975).
- (130) a) H.H. Baer and C.B. Madumelu, *Carbohydr. Res.*, 39, C8 (1975);
b) C.B. Madumelu, Ph.D. thesis, University of Ottawa (1976).
- (131) O. Gawron, T.P. Fondy and D.J. Parker, *J. Org. Chem.*, 28, 700 (1963).
- (132) S. Mitsui, S. Imaizumi, M. Hischige and Y. Sugi, *Tetrahedron Lett.*, 29, 4093 (1973).
- (133) a) S.P. Fore and W.G. Bickford, *J. Org. Chem.*, 24, 620 (1959);
b) S.P. Fore and W.G. Bickford, *ibid.*, 26, 2104 (1961);
c) D.R. Horuton and R.W. Kaiser Jr., *J. Org. Chem.*,
29, 2420 (1964).
- (134) a) P.N. Rylander, "Catalytic Hydrogenation in Organic Synthesis",
Academic Press, Inc., New York, 1979;
b) P.N. Rylander, "Catalytic Hydrogenation over Platinum Metals",
Academic Press, Inc., New York, 1967.
- (135) H.H. Baer and F. Kienzle, *Can. J. Chem.*, 43, 3074 (1965).
- (136) H.H. Baer and F. Kienzle, *ibid.*, 45, 983 (1967).
- (138) a) S. Kumazawa, T. Sakakibara, R. Sudoh and T. Nagagawa,
Angew. Chem., 85, 992 (1973);
- (137) H.H. Baer and C.B. Madumelu, *Can. J. Chem.*, 56, 1177 (1978).
- (139) H.H. Baer and C.B. Madumelu, *Carbohydr. Res.*, 67, 329 (1978).
- (140) a) D.A. Prins, *Helv. Chim. Acta*, 29, 1 (1946);
b) H.R. Bolliger and D.A. Prins, *Helv. Chim. Acta*, 29, 1061 (1946);
c) E. Huber and T. Reichstein, *Helv. Chim. Acta*, 31, 1645 (1948).
- (141) a) D.A. Prins, *J. Am. Chem. Soc.*, 70, 3955 (1948);

- b) F.J. Hedgley, W.G. Overend and R.A.C. Rennie, *J. Chem. Soc.*, 4701 (1963)
- (142) H. Newman and R.B. Angier, *Tetrahedron*, 26,825 (1970).
- (143) P.M. McCurry Jr., and R.K. Singh, *J. Org. Chem.*, 39,2316 (1974).
- (144) F. Feigl, and V. Anger, *Spot Tests in Inorganic Analysis*, Elsevier, New York, pp. 345-346 (1972)..
- (145) H.H. Baer and F. Kienzle, *Can. J. Chem.*, 41,1606 (1963).
- (146) a) H. Hauenstein and T. Reichstein, *Helv. Chim. Acta*, 32,22 (1949);
b) T. Golab and T. Reichstein, *ibid.*, 44,616 (1961).
- (147) a) S. Mitsui, Y. Senda and K. Konno, *Chem. Ind. (London)*, 1354 (1963);
b) S. Mitsui and Y. Sugi, *Tetrahedron Lett.*, 1287,1291 (1969);
c) Y. Sugi and S. Mitsui, *Bull. Chem. Soc. Japan*, 42,2984 (1969),
43,1489 (1970);
d) S. Mitsui, Y. Kudo and M. Kobayashi, *Tetrahedron*,25,1921 (1969);
e) S. Mitsui, Y. Sugi, M. Fujimoto and K. Yokoö, *ibid.*,
30,31 (1974).
- (148) Y. Sugi, M. Nagata and S. Mitsui, *Bull. Chem. Soc. Japan*,
48,1663 (1975).
- (149) A. Suzuki, M. Miki and M. Itoh, *Tetrahedron*, 23,5621 (1967).
- (150) a) H.H. Baer and J. Kovář, *Can. J. Chem.*, 49,1940 (1971);
b) H.H. Baer and W. Rank, *ibid.*, 49,3197 (1971);
c) J. Kovář, K. Čapek and H.H. Baer, *ibid.*, 49,3960 (1971);
d) J. Kovář and H.H. Baer, *ibid.*, 51,3373 (1973);
e) J. Kovář and H.H. Baer, *Carbohydr. Res.*, 45,161 (1975);
f) H.H. Baer and J. Kovář, *Can. J. Chem.*,54,2058 (1975)
g) H.H. Baer, in "Asymmetry in Carbohydrates", R. Harmon,
Edit., Marcel Dekker. Inc., New York, pp. 51-81 (1979).
- (151) T. Sakakibara, A. Setá, Y. Tachimori, T. Takamoto and R. Sudoh,
Chem. Lett.,1365 (1977).

- (152) Houben-Weyl, Methoden der Organischen Chemie, E. Müller (Ed.), Vol. 10/4, Georg Thieme Verlag, Stuttgart 1968; (a) pp. 132-155, (b) pp. 142-144, (c) pp. 151-155.
- (153) H. Meister, Ann., 679, 83 (1964).
- (154) H.H. Baer and S.H.L. Chiu, Can. J. Chem., 51, 1801 (1973).
- (155) a) J.F. Knifton in "Catalysis in Organic Synthesis, 1976", P.N. Rylander and H. Greenfield, Eds., Academic Press, New York, p. 257 (1976);
b) J.F. Knifton, J. Org. Chem., 38, 3296 (1973);
c) C. Grundmann, Angew. Chem., 62, 558 (1950).
- (156) a) W.K. Seifert and P.C. Condit, J. Org. Chem., 28, 265 (1963);
b) H.H. Baer and F. Kienzle, Can. J. Chem., 45, 983 (1967).
- (157) J.A. Robertson, J. Org. Chem., 13, 395 (1948).
- (158) a) H.H. Baer, Chem. Ber., 93, 2865 (1960);
b) H.H. Baer, J. Am. Chem. Soc., 83, 1882 (1960).
- (159) A.N. deBelder, Adv. Carbohydr. Chem., 20, 219 (1965).
- (160) a) J. Schwartz and J.A. Labinger, Angew. Chem. Int. Ed., 15, 333 (1976);
b) J. Schwartz in "New Applications of Organometallic Reagents in Organic Synthesis", De Seyferth, Ed., Elsevier, Amsterdam, 1976;
c) M.L. Loots, J. Schwartz, J. Am. Chem. Soc., 99, 8045 (1977);
d) M.L. Loots, J. Schwartz, Tetrahedron Lett., 4581 (1978).
- (161) a) P.C. Wailes and H. Weigold, J. Organomet. Chem., 24, 405 (1970);
b) P.C. Wailes, H. Weigold and A.P. Bell, *ibid.*, 43, C32 (1972).
- (162) C.A. Bertelo and J. Schwartz, J. Am. Chem. Soc., 98, 262 (1976)
- (163) D.W. Hart and J. Schwartz, *ibid.*, 96, 8115 (1974).
- (164) B. Fraser-Reid and B. Radatus *ibid.*, 92, 6661 (1970).
- (165) H.O. House, "Modern Synthetic Reactions", 2nd Ed., pp. 116-122 (1972).

- (166) Z.S. Hanna, MSc. Thesis, Brock University, (1977).
- (167) E. Maslowsky Jr., "Vibrational Spectra of Organometallic Compounds", John Wiley and Sons, New York (1977).
- (168) D.R. Coulson, Inorganic Synthesis, 13,121 (1974).
- (169) a) H.H. Baer, Methods Carbohydr. Chem., 6,302 (1972).
b) H.H. Baer and F.F.Z. Georges, J. Org. Chem., 41,3474 (1976).
- (170) H.H. Baer and W. Rank, Can. J. Chem., 49,3192 (1971).
- (171) H.H. Baer and W. Rank, ibid., 51, 2001 (1973).
- (172) H.H. Baer, F. Kienzle and T. Neilson, ibid., 43,1829 (1965).
- (173) H.H. Baer and T. Neilson, ibid., 43,840 (1965).
- (174) H.H. Baer and W. Rank, ibid., 50,12126 (1972).
- (175) P.A. Levene and G.M. Meyer, J. Biol. Chem., 55,221 (1923).