

• The Synthesis of Disaccharides

Related to Heparin

by

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A thesis submitted to the

Faculty of Graduate Studies and Research

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

McGill University

Montreal Canada

© May 1986

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ISBN 0-315-34470-9

Abstract

In contrast to the general strategy employed for the synthesis of disaccharides, i.e., the linking together of monosaccharide derivatives, the approach described here entails appropriate modifications of a readily available disaccharide. Thus, maltose has been converted into the following disaccharides: 4-O-(2-amino-2-deoxy- α -D-glucopyranosyl)-L-idopyranose uronic acid, 4-O-(2-amino-2-deoxy- α -D-glucopyranosyl)-D-glucopyranose, and 4-O-(α -D-glucopyranosyl)-L-idopyranose. These disaccharides are structurally related to biose sequences found in heparin and other glycosaminoglycans. Used as starting materials were two products of the kinetic acetonation of maltose, i.e., 2,3:5,6-di-O-isopropylidene-4-O-(4,6-O-isopropylidene- α -D-glucopyranosyl) (1) and -(α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal (2), which were used in two sequences of transformations following similar synthetic strategies. These transformations included the inversion of C-5 in the reducing unit to give the L-ido configuration, the introduction of a 2'-amino-2'-deoxy function into the non-reducing end group, as well as oxidation at OH-6, and cyclization of the acyclic dimethyl acetal to give the desired pyranuronic acid. A critical factor in the formation of the latter, was the finding that the 5-O-levulinoyl substituent is less prone to acyl migration to O-6 than the more conventional acetyl ester. The conformations of some intermediates and products are discussed.

Resumé

En contraste avec la stratégie générale employée pour la synthèse de disaccharides, qui est d'assembler deux dérivés monosaccharidiques, la voie de synthèse décrite ici consiste à modifier de façon appropriée un disaccharide naturellement abondant.

Le maltose a ainsi été converti en les disaccharides suivants; l'acide (amino-2-désoxy-2- α -D-glucopyrannosyl)-O-4-L-idopyrannose glucuronique, le (amino-2-désoxy-2- α -D-glucopyrannosyl)-O-4-D-glucopyrannose, et le α -D-glucopyrannosyl-O-4-L-idopyrannose. Ces disaccharides sont de structure apparentée à celle des séquences bi-oses présentes dans l'héparine ainsi que dans d'autres sucres aminés.

Deux composés obtenus par acétonation cinétique du maltose ont été utilisés comme composés de départ. Ce sont; la diméthyl (isopropylidene-4,6- α -D-glucopyrannosyl)-O-4-bis-isopropylidene-2,3,5,6 -aldehydo-D-glucoside (1), et le diméthyl α -D-glucopyrannosyl-O-4-bis-isopropylidene-2,3,5,6-aldehydo-D-glucoside (2). Chacun des 2 composés a subi une série de transformations selon des stratégies de synthèse similaires. Ces transformations consistent en; l'inversion du C-5 de l'unité reductrice, conduisant à la configuration L-ido, l'introduction du groupe fonctionnel (amino-2'-désoxy-2') dans l'unité non réductrice, ainsi que l'oxydation du OH-6, et la cyclisation du diméthyl acétal acyclique, menant à l'acide pyranuronique désiré.

Un facteur décisif dans la formation de ce dernier fut la découverte que le substituant levulinyle-O-5 soit moins porté à subir une migration acyle sur le O-6, que le groupe ester acétyle classique.

Les conformations de certains intermédiaires et produits sont également discutées.

Acknowledgements

The author wishes to express his sincere gratitude to his research director, Professor A.S. Perlin. His generosity and insight were greatly appreciated throughout the course of the research.

Many thanks to Dr. D.N. Gupta, who helped with the early synthetic work.

The assistance with NMR by Dr. F. Sauriol and the prompt mass spectral service by Dr. O. Mamer are sincerely appreciated.

Special thanks to Ms. B. Brown for preparing the manuscript, and Ms. A.-M. Fruteau de Laclos for translating the abstract.

Among the many friends and colleagues at the Pulp and Paper Research Institute of Canada who contributed to an interesting working and social atmosphere, special acknowledgement is given to Dr. D. Argyropoulos, Dr. M.M. Abdel-Malik, Dr. V.S. Rao, and Dr. T.K. Shing for assistance and stimulating conversations, pertinent to the present work and other aspects of life.

Finally, an NSERC scholarship is gratefully acknowledged as well as financial support from the Department of Chemistry, McGill University in the form of a teaching assistantship.

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List of Terms and Abbreviations

Ac:	acetyl
AcOH:	acetic acid
Ac ₂ O:	acetic anhydride
Bn:	benzyl
t-BdMS:	<u>tert</u> -butyldimethylsilyl
t-BdPS:	<u>tert</u> -butyldiphenylsilyl
DCC:	dicyclohexylcarbodiimide
DEA:	diethanolamine
DEAD:	diethyl azodicarboxylate
DMAP:	2,2'-dimethylaminopyridine
DMSO:	dimethyl sulfoxide
D.S.:	degree of substitution
LAH:	lithium aluminium hydride
LV:	levulinoyl
MEM:	2-methoxyethoxymethyl
MMT:	4-methoxytrityl (p-anisyl-diphenylmethyl)
MOM:	methoxymethyl
PCC:	pyridinium chlorochromate
PDC:	pyridinium dichromate
pyr:	pyridine
Si:	t-BdMS or t-BdPS
Trityl:	triphenylmethyl

CHAPTER ONE

INTRODUCTION

I.1 General Remarks

A notable growth in recent years in investigations of complex carbohydrates, glycoconjugates (1-7) and polysaccharides (8,9), due to the realization of their role in cell - cell recognition, immunochemistry, transport, and other physiological processes, has led to an increase in the synthesis of oligosaccharides related to these macromolecules (10). Such model compounds are important for structure determination by spectroscopic and other physical methods, and are of value in examinations of activity-structure relationships. It also is probable that, with advances in methodology, synthetic materials of this class will come to be used as biological agents in their own right.

Because of the diversity of structures found in Nature, and the many factors affecting the reactivity and behaviour of any particular sugar derivative (11), the synthesis of each complex oligosaccharide model compound must be approached individually. The present work is an attempt to add to the repertoire of synthetic strategies based on the modification of known, plentiful, disaccharides. The strategies described here address some of the synthetic challenges encountered in the formation of specific oligosaccharides related to such glycosaminoglycans as heparin.

The conventional synthesis of an oligosaccharide from monosaccharides requires that the components to be linked must be prepared appropriately by selective blocking and deblocking procedures. The glycosyl component must be activated at the anomeric center, with all other

sites blocked. The "alcohol" donor must be a sugar with only a specific hydroxyl group (or groups) exposed. Finally, the linkage step should proceed stereospecifically in high yield, in order to avoid separation and purification problems (10). Recent advances in glycoside methodology (10,12-16), plus the large selection of blocking groups available (11,17-19) have made the synthesis of tetra- and hexasaccharides, if not common, no longer exceptional.

The situation is generally less satisfactory when the constituent sugars contain such features as an amino-deoxy group, or carboxylic acid function, for example, or must in some way be derived from available starting monosaccharides. In general, these functionalities or modifications must be introduced at appropriate stages, often extending the preparation of the monomeric components into lengthy syntheses, before a glycosidic bond is formed. The new functional groups may, themselves, alter the outcome of the glycosidic coupling step.

These problems are encountered in the synthesis of oligosaccharides related to the class of polysaccharides known as glycosaminoglycans (20-22). After a brief description of these molecules, a closer look at specific synthetic problems will follow.

I.2 Heparin and other glycosaminoglycans

The glucosaminoglycans, or mucopolysaccharides, are isolated from animal tissue, where they occur as proteoglycan macromolecules. They are alternating copolymers of an aldohexosamine and an aldohexose that, usually, is in the form of an alduronic acid (20). Notably, sulfate

groups are present at specific sites in most members of this class. A summary of the known glycosaminoglycans is listed in Table I-1 (20).

Heparin, an important member of this class of polysaccharides, has received a great deal of interest because of its use as a clinical anticoagulant. It is involved in binding to basic sites of such proteins as antithrombin, an important inhibitor of proteases in the coagulation cascade (20,23,24).

As described in Table I-1 and shown in Figure I-1, the main repeating unit of heparin is 2-O-sulfo- α -L-idopyranuronic acid (1 + 4)-2-deoxy-2-sulfamino-6-O-sulfo- α -D-glucopyranose, which constitutes approximately 80% of beef lung heparin (20). However, it is recognized that chain lengths vary, as does the degree of heterogeneity. Minor residues (Figure I-2), D-glucuronic acid, 2-acetamido-2-deoxy-D-glucose, 2-deoxy-2-sulfamino-3,6-di-O-sulfo- α -D-glucopyranose, and non-sulfated L-iduronic acid, are present as irregularities in regions of the repeating disaccharide (20). The relatively small proportion of these residues does not necessarily correspond to their relative importance, as recent evidence for an active antithrombin binding site has shown (25,26). The heterogeneity in structure and wide variation in clinical activity of various heparins (20,23) has led to a search for the necessary elements and minimum chain length needed for effective anticoagulant activity. Synthetic studies, however, have been rare until very recently (see Section I.5, p.14).

An examination of the repeating disaccharide unit reveals some specific problems associated with the synthesis of di- and oligosaccha-

Table I-1: Some Glycosaminoglycans

Name	Main Repeating Disaccharides
Keratan Sulfate	β -Gal-(1+4)- β -GlcNAC-(1+3)-
Hyaluronic acid	β -GlcA-(1+3)- β -GlcNAC-(1+4)-
Chondroitin-4-sulfate	β -GlcA-(1+3)- β -GalNAC-4S-(1+4)-
Chondroitin-6-sulfate	-GalNAC-6S-
Dermatan sulfate	α -IdoA-(1+3)- β -GalNAC-4S-(1+4)-
Heparan sulfate	β -GlcA-(1+4)- α -GlcNAC-(1+4)
	or -GlcNS, 6S-
Heparin	α -IdoA-2S-(1+4)- α -GlcNS-6S-(1+4)-

Gal = D-galactose

GlcA = D-glucuronic acid

GlcN = 2-amino-2-deoxy-D-glucose

GalN = 2-amino-2-deoxy-D-galactose

IdoA = L-iduronic acid

Ac = acetyl

S = sulfate

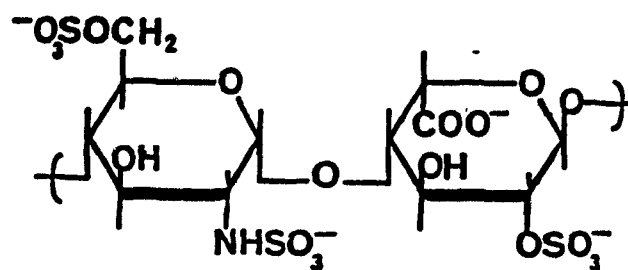


Figure I-1. The major repeating disaccharide of heparin.

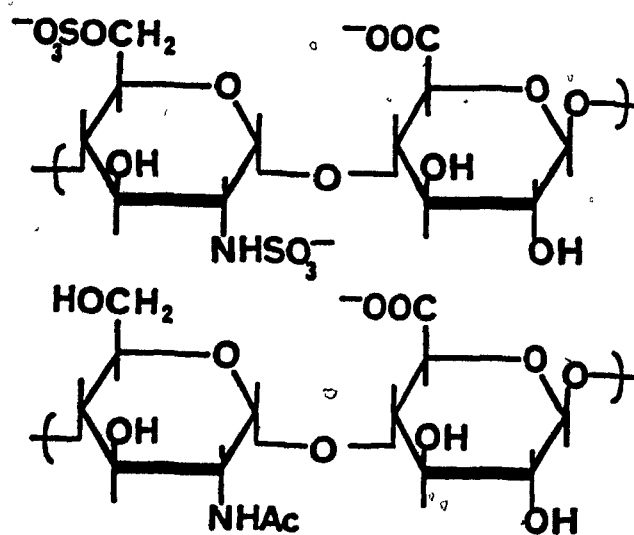


Figure I-2. Minor residues found in heparin.

rides related to heparin. The main features of the repeating unit (Figure I-1) are as follows:

- a) a 2-amino-2-deoxy-D-glucopyranosyl residue with a 1,2-cis, α -anomeric linkage,
- b) a 4-O-linked L-idopyranuronic acid,
- c) sulfate groups at several specific sites.

Clearly, the general strategy for preparing suitable component monosaccharides must consider (a) the formation of a difficult glycosidic coupling, (b) a rare sugar configuration, and (c) a complex protecting group pattern. The first two problems will be discussed in turn.

I.3 Formation of 1,2-cis-2-amino-2-deoxy- α -D-glucopyranosides

The synthesis of glycosides containing amino sugars (27-29) has been of long standing interest, since they are present in glycoproteins (7) and antibiotics (30), for example, as well as glycosaminoglycans. The 2-amino-2-deoxy- α -D-glucoside found in heparin is particularly difficult to obtain (10,12). This is because a non-participating group at C-2 is necessary to avoid formation of the trans- β -linkage. The same arguments apply to the 2-amino-2-deoxy- β -manno linkage found in some capsular polysaccharides (2). To achieve this type of linkage, either the readily available sugar, 2-amino-2-deoxy- α -D-glucose, can be used, or the amino group introduced into a suitable starting material, before or after glycosidic bond formation. Most simply, a fully protected 2-amino-2-deoxy- α -D-glucosyl halide can be used as the glucosyl donor, providing that the blocking group is non-participatory. For

example, diphenylphosphino, 2,4-dinitrophenyl, or p-methoxybenzylidene amino groups are suitable and can form the α -linkage in varying yields in the presence of mercury salts (10). The main disadvantage with this method is the often poor yields due to the bulkiness of the protecting group.

In a second, recently developed approach, an azido group is introduced into a selectively protected sugar (10, and references cited therein). This is a non-participatory neighbouring group that can be converted into the amino function by reduction at a later stage in the synthetic route. The 2-azido-2-deoxy-D-glucopyranosyl halide can be used either in a direct displacement reaction, if the β -halide is available, or with in situ anomerization using a halide salt, followed by silver salt catalysis. The choice of method depends on the reactivity of the hydroxyl and the halide components. As a rule, azido sugars need a slightly more active catalyst than the normal sugars under the same conditions (10). This method is better in terms of yield obtained in the glycosidation step, but requires synthesis of the appropriate azido compound. This may proceed either by an azide displacement of a manno-2,3-epoxide (31,32), or addition of a nitroazide (33) or halogenoazide (34) to a suitable glycal.

Another non-participating group that can be converted to an amine is an imine. Addition of nitrosyl chloride to acetylated glycals has been shown by Lemieux et al. (35) to provide alkyl 2-oximino- α -D-hexopyranosides. Reduction of the 2-oxime to the 2-aminodeoxy compound can be very efficient in some cases (36,37).

A different approach is to form the glycosidic bond with a normal sugar, then introduce the amino function later, either through an imine (39,40) or by azide displacement of a sulfonate group (38), in reactions analogous to those just described above. This method circumvents difficulties in the linkage step by using, presumably, higher-yielding conventional methodology. However, introducing the azido groups, or oxidizing OH-2 to the ketone, requires selectively protected monosaccharides. Further discussion of this latter approach will be found in Chapter III.

I.4 The synthesis of L-idopyranose derivatives

Another major synthetic problem is the formation of 4-O-linked α-L-iduronic acid derivatives. Idose and its derivatives have occupied a unique place in carbohydrate chemistry, primarily because of an inherently unstable configuration, which leads to interesting conformational behaviour (41-43). The ido configuration is rare and there are few natural sources. It is found only as the L-iduronic acid (see Table I-1, p.3) in such polysaccharides as heparin (44), heparan sulfate (47) and dermatan sulfate (45,46), and also in capsular polysaccharides (48) and fungal glycuronans (49,50). The interest in obtaining 4-O-linked L-idopyranose derivatives suitable for incorporation into oligosaccharides was central to the present work. A main problem in doing so synthetically lies in the solution composition of idose.

Aldoses exist as a mixture of tautomeric forms (51), with the pyranose ring being, in general, the most stable (41, p.160). Idose,

like altrose and talose, contains substantial amounts of furanose forms (Table I-2 and Figure I-3). In addition, the equilibrium between the two chair forms in idopyranoses, favours the formation of the stable 1,6-anhydropyranose under acidic conditions (ref. 41, p.221; and ref. 43). These features of L-idose have made the synthesis either lengthy or low yielding.

Synthetic routes toward L-idose, the C-5 epimer of D-glucose include two widely used approaches and other minor ones. The classic approach by Meyer and Reichstein (54) uses the displacement of a sulfonated O-5 by OH-6 to form the 5,6-epoxide of a 1,2-isopropylidene-D-glucofuranose derivative. Opening of the epoxide ring under basic conditions provides the corresponding L-idofuranose. This method was used by other researchers with variations (55-60), one being the replacement of sulfonate leaving groups with phosphonium salts, using triphenylphosphine/DEAD methodology (61). 6-Deoxy derivatives can be formed by lithium aluminum hydride reduction of the 5,6-epoxide (62). Starting from 1,2-O-isopropylidene-D-glucofuranurono-6,3-lactone, a similar inversion can be effected on the lactol (63) or the diol (64), obtained by reduction of appropriate derivatives. A direct displacement at O-5 of the 1,2-O-isopropylidene-D-glucofuranurono-6,3-lactone was achieved by Weidmann et al. (65) using a 5-O-triflate derivative, and inverting with sodium trifluoroacetate. The same methodology was applied by Sinay et al. (66) to obtain a methyl L-idofuranuronate from methyl 3-O-benzyl-1,2-O-isopropylidene-D-glucofuranuronate. Note that the C-5 inversion also can be achieved through epimerization of D-

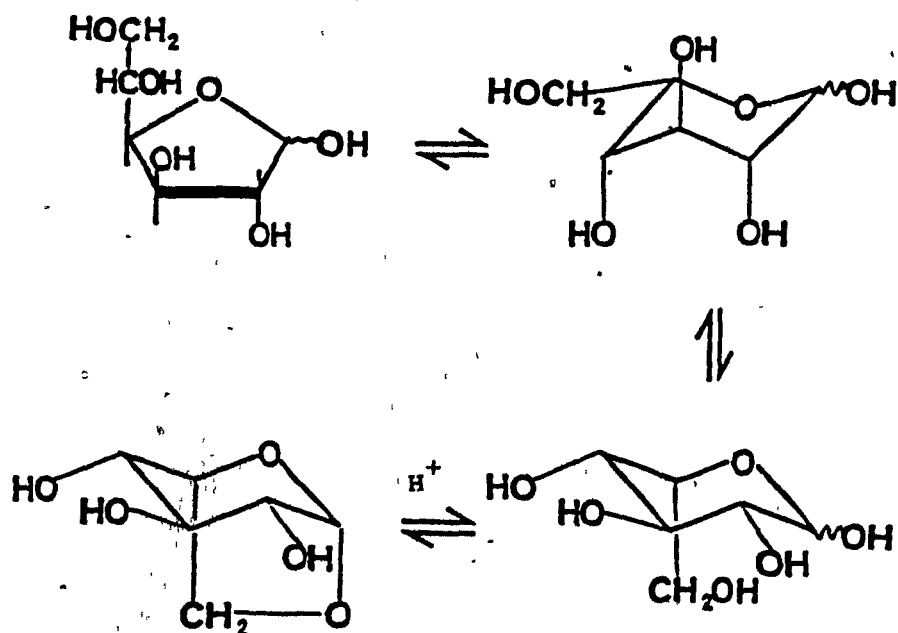


Figure I-3. Tautomeric equilibrium of L-idose in solution.

Table I-2: Percent Composition of D-Idose in D₂O

Temp.	Pyranose		Furanose		Aldehyde, Hydrate	Ref.
	α	β	α	β		
31°	38.5	36	11.5	14	0.2	51
37°	38.5	33.5	12.5	15.5	-	52
30°	35.9	33.4	13.5	16.5	0.6	53

glucofuranuronic acid derivatives (67), although this method is not synthetically useful.

A second type of synthetic route to L-iduronic acid derivatives, proceeds through the addition of a carboxyl synthon to 1,2-O-isopropylidene-D-xylo-dialdopentofuranose or related compounds, generally obtained by periodate cleavage of 1,2-O-isopropylidene-D-glucofuranose (68). The carbon fragments to be added can be cyanide (69), or ethynyl Grignard reagents (70), to give the uronic acids, or methyl Grignard reagents to give the 6-deoxy derivative (71).

Other less important methods of obtaining L-idofuranose derivatives include reduction of L-idonolactone (72) or oxidation/reduction of 1,6-anhydro-D-glucofuranose (73).

These methods, although widely used, all suffer from the complicating furanose - pyranose equilibrium discussed earlier. That is, hydrolysis or acetolysis must follow the inversion of the D-glucofuranose derivative, producing a mixture of furanoses, pyranoses and in some cases, 1,6-anhydropyranose. These products can be separated chromatographically, but the resulting yields are relatively unsatisfactory (e.g., 60,66).

To overcome this problem, several syntheses towards pyranose derivatives have been pursued. Sorkin and Reichstein (74) developed a method of obtaining D-idopyranosides from 4,6-O-benzylidene-D-galactopyranosides. To obtain L-idose, this method could be repeated with the L-galactose isomer, which can be synthesized by reduction of the more readily available L-galactono- γ -lactone (75). Perlin et al. (76) used

L-sorbose to synthesize an L-iditol derivative protected at O-4, thus preventing formation of the furanose, followed by oxidation to the aldehyde, and then cyclization. Ferrier and Tyler (77) observed the formation of α -L-idopyranoside from the hydride displacement of C-5 bromo-derivatives of penta-O-benzoyl-D-glucopyranose, obtained through photobromination. An application to L-glucose of Paulsen's (78) acetoxonium ion rearrangement used for the synthesis of D-idose from D-glucose, gave 1,2,3,4,6-penta-O-acetyl-L-idopyranose (79). Hydroboration of a double bond between C-5 and C-6 in hexopyranose derivatives (80,81), and also a cellobiose derivative (82), gave mixtures of L-ido and D-gluco isomers, separable by chromatography. L-Idopyranuronic acid derivatives also can be synthesized by C-5 inversion of diethyl dithioacetal derivatives of D-glucuronolactone. Selective protection at O-4 allows cyclization to the pyranose (83).

Although many syntheses of L-idose derivatives exist, obtaining an L-idopyranuronic acid selectively protected on O-4 appropriate for glycosidic coupling is still difficult. This problem, in addition to those discussed, for the 2-amino-2-deoxy- α -D-glucopyranosides, has hindered synthetic investigations into heparin and related glycosaminoglycans.

I.5 Synthetic work on heparin

Synthetic work on mono- or oligosaccharides related to heparin has, until recently, been restricted to the general investigation of glucosamines and L-iduronic acid derivatives, as has been discussed.

Although chemical modification of heparin has been quite extensive (20), the synthesis of model mono-, oligo- or polysaccharides has been limited. In the polysaccharide area, attempts have been made to modify polymers containing neutral, uronic acid or aminosugar components (20,84). The synthesis of small molecules designed as heparinoids was undertaken originally by Kiss and Wyss (85-90). They developed syntheses of D-glucosamine (87) and L-idose derivatives (86,89), as well as disaccharides containing D-glucosamine and D-glucuronic acid (85,88).

More recently, Sinay et al. (66,81,91-93) carried out a series of syntheses of oligosaccharides, that culminated in the pentasaccharide (Figure I-4) (92) believed to represent a minimum binding sequence of heparin (25,26). They started with D-glucose and 2-azido-~~2~~-deoxy-D-glucose derivatives, converting them into appropriately protected uronic acid and amino containing units, that then were coupled together and sulfated. Other model mono- (81), di-, and trisaccharides (81) were made in the process of this work. A second synthesis of the same pentasaccharide (Figure I-4) has been achieved by Van Boeckel et al. (60), again using such monosaccharides as penta-O-acetyl-D-glucose and 1,6-anhydro-D-glucose to form intermediate disaccharides, which, after further modifications, were linked together into a pentasaccharide.

Mori and Tejima (94) synthesized 4-O-(2-acetamido-2-deoxy- α -glucopyranosyl)-D-glucopyranose from 1,6-anhydromaltose, in order to compare its structure to disaccharides isolated from heparin hydrolysates. Also, Shing and Perlin (95) used 1,6-anhydro-cellobiose to introduce a 2-azido function via the 2,3-manno epoxide. A glycal derivative of

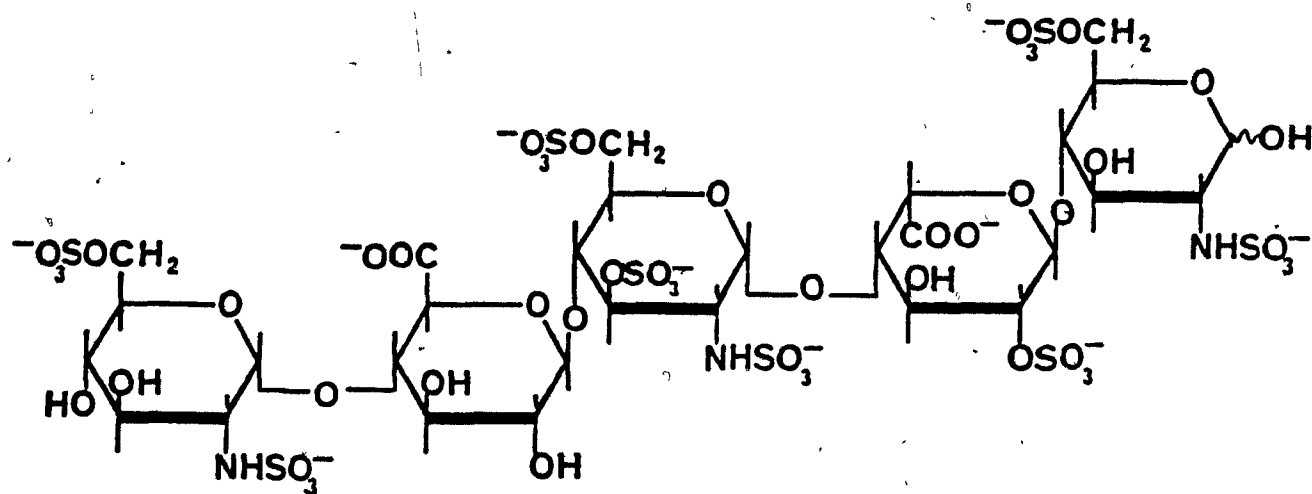


Figure I-4. The pentasaccharide segment of heparin that binds to antithrombin-III (refs. 25, 26).

cellobiose also provided the 2-azido compound by azidonitration. Kuzuhara et al. (96-98) expanded the synthetic studies based on 1,6-anhydro-cellobiose and prepared disaccharides containing D-glucuronic acid, L-iduronic acid and D-glucosamine, that were linked subsequently to form the same pentasaccharide as reported by Sinay et al. (92) (Figure I-4).

I.6 Use of disaccharides in oligosaccharide synthesis

The synthetic studies just mentioned lead into the final topic of this introduction, which is the use of disaccharides for starting materials. The latter two examples show how complex oligosaccharides can be obtained from common disaccharides, and compete with the more conventional synthetic approach adopted in the first two examples.

The use of disaccharides to form complex oligosaccharides has received relatively little attention in the development of synthetic carbohydrate methodology (99-101,12, pp. 111-115). Employing a disaccharide as a glycosyl donor is not fundamentally different from using a monosaccharide. Although the formation of the biosyl halide may be complicated by the acid-lability of its glycosidic bond (14), a number of oligosaccharides have been formed from glycosyl halides of the common disaccharides (see 12, and references cited therein). In addition, available disaccharides (e.g., sucrose, maltose, cellobiose, lactose, gentiobiose, melibiose, and chitobiose) have been modified and derivatized with many of the same reagents used for monosaccharide transformation. These reactions include esterification and etherification with

common blocking groups, the formation of glycals, anhydro sugars, and deoxy sugars, epimerization, oxidation and reduction, as well as changes in the length of the carbon chain of the constituents (99-101). For example, the glycals have been useful for introducing 2-amino-2-deoxy functions, in a manner analogous to that for monosaccharides (95,102). In summary, most of the work on disaccharides has been designed either to make a derivative or to incorporate the disaccharide directly into tri- or higher oligosaccharides.

Combining these two goals into a single strategy poses problems similar to and perhaps magnified in comparison to those found in monosaccharide chemistry. That is, to expose a single position requires selective protection or deprotection among five secondary and two primary hydroxyl groups, as well as the anomeric center. When, in addition, the sugar needs such modifications as epimerization, selective oxidation, or the introduction of an amino group for example, the complexity of preparing the required disaccharide unit increases. This situation is aggravated by the loss of convergent strategy. It is clear that only in specific cases can the modification of a disaccharide compete for efficiency with a coupling of more flexible monosaccharides. What are the situations in which the disaccharide strategy is advantageous?

The main advantage of using a disaccharide is in having a glycosidic bond of desired position and configuration already present. In the case of α -D-glucosamines (or D-galactosamines), this can be a significant advantage, as has been discussed (Section I.3, also ref. 10).

A second property of disaccharides resides in their conformations, and such intramolecular interactions as hydrogen bonding (11,103), which can, in specific cases, provide differences in hydroxyl group reactivity. Not only can this situation permit a selective protection needed for subsequent glycosidic coupling, but also may permit specific access to hydroxyl groups in a manner that is difficult to achieve with a corresponding monosaccharide derivative. For example, some well known selectivity is found between the primary hydroxyl groups of maltose (103) with respect to such bulky reagents as trityl chloride. The 3-hydroxyl group also is less reactive, presumably due to the intramolecular hydrogen bonding to O-2' (103). Differences in hydroxyl group reactivity have not been fully explored in disaccharides (11), and should extend their synthetic usefulness.

Simply, then, in a situation where two individual monosaccharides must be extensively modified, and then coupled in a low yielding step, a plentiful disaccharide may provide an alternative route, by allowing for the same modifications with perhaps less difficulty, and of course, avoiding the glycosidic coupling step. Further advantages exist in target compounds in which a disaccharide comprises the repeating unit, or where segments of different structures can be derived from the same disaccharide intermediate. This situation is found in oligosaccharides related to heparin and associated glycosaminoglycans (Figures I-1, I-2, p. 6).

As has been shown, 4,6-O-benzylidene-1,6-anhydro derivatives of cellobiose and maltose are promising substrates for the production of

"building blocks" related to heparin (94,95,98). They meet some of the criteria discussed, providing suitable built-in glycosidic linkages and, in some cases, useful regioselectivity, because the 2,3-hydroxyl groups of the 1,6-anhydro unit are diaxial. Thus, Shing and Perlin (95) found selective tosylation at OH-2 (60%) in 4,6-O-isopropylidene cellobiosan. Kuzuhara et al. (96-98) later achieved the same reaction using a derivative selectively benzylated at O-2' and -3'. This benzylation was possible because of prior, regioselective, O-silylation of O-2 and O-3 with 1,3-dichloro-1,1,3,3-tetra-isopropylidisiloxane. Interestingly, the same reagent is selective for the diequatorial O-2' and O-3' of the corresponding maltosan (104). A 1,6-anhydro maltose derivative also showed selectivity for tosylation at OH-2' under phase transfer conditions (105).

As will be shown here (see also 105a), other potentially useful disaccharide derivatives are the products of kinetic acetonation by means of 2,2-dimethoxypropane in polar solvents (e.g., dioxane). Lactose (106) laminarabiose, cellobiose, gentiobiose (107) and maltose (108) have been treated under varying conditions to give a number of products. All of these compounds have reduced numbers of exposed hydroxyl groups, and the reducing unit is a fully protected dimethyl acetal. The major products from maltose are shown in Figure I-5. Both compounds 1 and 2 are produced in different ratios, depending on the amount of catalyst, although 1 is the major product. An examination of these molecules suggested that they were appropriate starting derivatives for disaccharides related to heparin (Figure I-1, p.6).

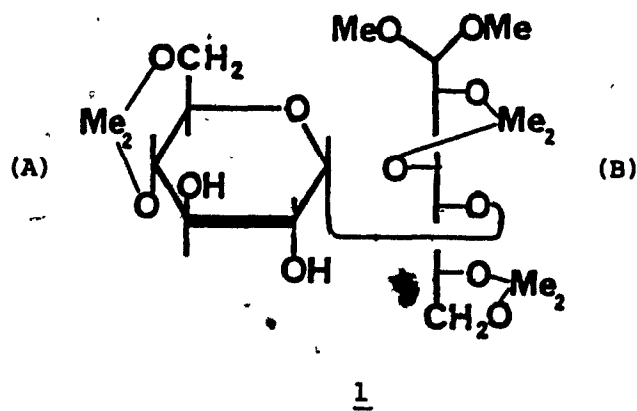
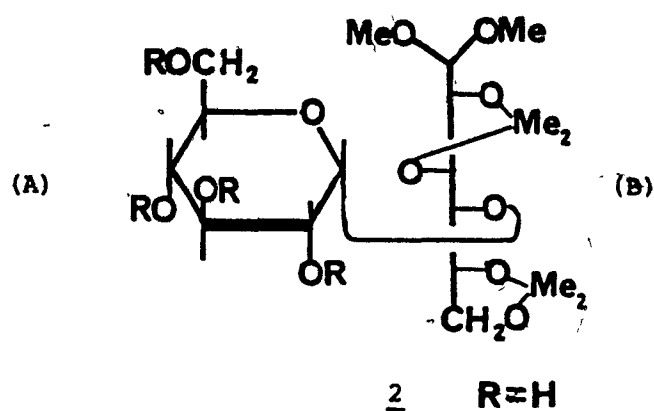


Figure I-5. Products of kinetic acetonation of D-maltose with 2,2'-dimethoxypropane (ref. 108). A - glycosyl group; B - acetal unit.

First, considering compound 1, the presence of free OH-2' and -3' suggests that introduction of an amine is possible at C-2', through well known oxidation, imine formation and reduction sequences (see discussion, Chapter III). A successful attainment of this modification would provide the 2-amino-2-deoxy- α -D-aldoside residue directly.

The hydroxyl group at C-3' then can be blocked, leaving only the relatively easy selective protection of primary OH-6' and secondary OH-4', for subsequent glycosidic coupling at the latter position. The second interesting aspect to this molecule is the acyclic dimethyl acetal unit. Selective, sequential hydrolyses of the 5,6-O-isopropylidene groups, exposing OH-5 and -6, would allow for inversion selectively at C-5 to provide the L-ido configuration. The aldehydo-L-ido dimethyl acetal so formed, is already linked at O-4, and so can only give the pyranose ring after hydrolysis of the protecting groups and subsequent cyclization.

In addition to these fundamental features, the two primary hydroxyls are differentiated by O-isopropylidene groups of differing acid-lability (see later discussion, Chapter II), allowing for oxidation only at OH-6, to give the uronic acid. Regioselective access to other hydroxyl groups for, e.g., selective sulfation can readily be envisaged.

Starting then, from maltose derivatives 1 and 2, various transformations and protecting group strategies were considered, in order to arrive at disaccharide "building blocks" related to repeating units in heparin.

CHAPTER TWO

OUTLINE OF GENERAL STRATEGIES

AND

INVESTIGATION OF STRATEGY I

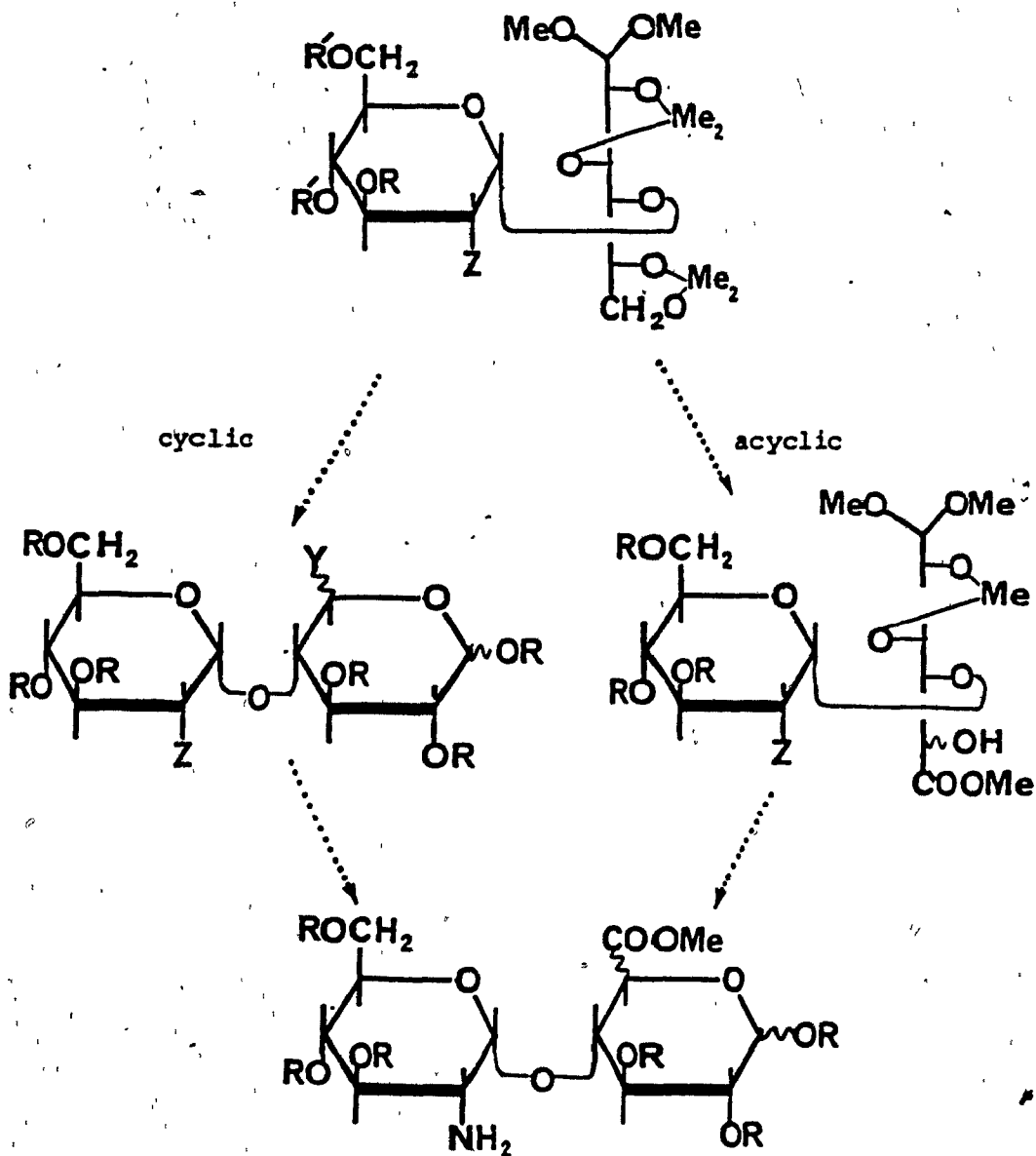
II.1 Introduction

This Chapter outlines the synthetic possibilities of using certain maltose derivatives as starting compounds, as well as routes selected for converting them into target compounds. The strategies adopted reflect various constraints imposed by their reactivities and structures, and were revised and modified as the research proceeded.

The starting compounds, 1 and 2, were modified using conventional carbohydrate methodology and reagents. The target compounds they gave are intermediates or "building blocks" that could embrace a number of possible structures.

Two general strategies were suggested by specific features of the two starting compounds (Scheme II-1). In strategy I, starting from a derivative of 2, the reducing unit is to provide the L-idose or L-iduronic acid in the first stage, followed by introduction of the 2'-amino-2'-deoxy group ~~into the non-reducing end~~. Strategy II using compound 1 is essentially the converse of I. That is, the 2'-amino-2'-deoxy group is introduced first, followed by modification of the reducing end. These two strategies were subdivided into two other general approaches: acyclic and cyclic. These terms describe the form of the reducing end during its oxidation to the uronic acid, either before or after cyclization to the pyranose form.

Two types of target compounds were considered, reflecting two stages of the project. Disaccharides resembling the main repeating units of heparin (Fig. I-1, p.6) and its biosynthetic precursor, N-acetylheparosan (Fig. I-2, p.6), served as working models for the deve-



Scheme II-1. General strategies towards target compounds.

Strategy I: $R=R' = \text{alkyl groups}$, $Z=OR$

Strategy II: $R = \text{alkyl or acyl group}$, $R' = \text{Me}_2\text{C}$,

$Z = \text{NHR}$

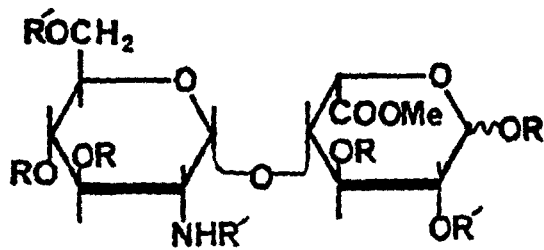
$Y = \text{CH}_2\text{OH or COOH}$

development of synthetic methods. The simple starting material was to be converted into a complex disaccharide containing as many of the features found in the repeating units as possible. The second type of target considered in the planning stages, was a more general type of building block for the synthesis of oligosaccharides. These simpler disaccharides were to be designed for subsequent condensation into tetra- and hexasaccharides. The oligomers could then be modified further with the methodology developed for the more complex disaccharides. An overall goal, of course, was to effect the synthesis of a building block that was functionalized appropriately so as to be suitable for later elaboration into oligosaccharides.

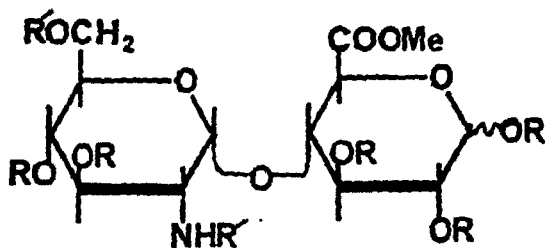
The two forms of target compounds were further subdivided into disaccharides that had either the L-ido or D-gluco configuration at the reducing end.

The four generalized targets are shown in Schemes II-2 and II-3. They were chosen as a compromise between the main disaccharide segments actually found in heparin and N-acetylheparosan, and the products accessible by reasonable routes from the maltose derivatives, 1 and 2.

Glycoside 3 contains the features found in the main repeating unit of heparin, in a non-ionic, protected form, suitable for purification and further manipulation. There are four main aspects that must be addressed within its general synthetic strategies. Carbon-5 has been inverted from the D-gluco to the L-ido configuration, and an amino group has been introduced at position C-2'. In addition, O-6 and O-6' have been differentiated to allow for oxidation and sulfation, respec-

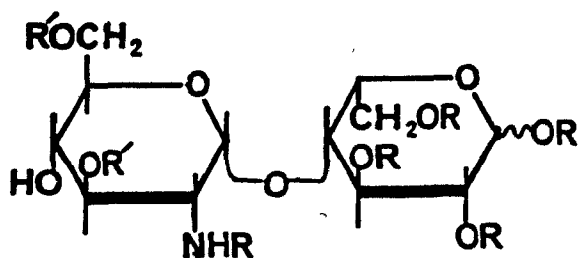


3 R' = SO₃Ph

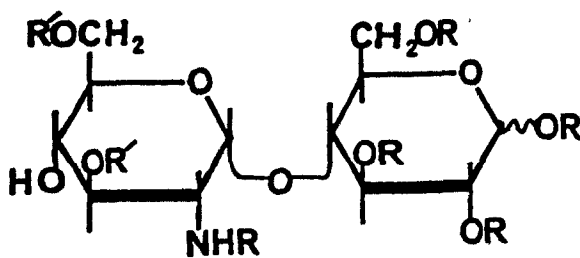


4 R' = Ac or SO₃Ph

Scheme II-2. Target model disaccharides.



5



6

R = Ac, R' = Bn

Scheme II-3. Target "building block" disaccharides.

tively. Finally, OH-2 has either been selectively sulfated or blocked in some fashion. In the early planning of this work, methodology for sulfation using chlorophenylsulfate (109,110) was considered as a means of selectively sulfating appropriate intermediates. Removal of all protecting groups would then provide a trisulfated disaccharide useful as a model in structural studies.

The second complex disaccharide, 4 (Scheme II-2) was a model for either N-acetylheparosan ($R = R' = \text{Ac}$) or a minor disaccharide sequence in heparin ($R = R' = \text{SO}_3\text{Ph}$). The synthetic demands of this compound were fewer, since the reducing unit required only oxidation at C-6.

In general, the formation of the basic glucosamine - uronic acid dimer was the most important objective. The use of disaccharides of this class as models for heparin and related glycosaminoglycans requires the availability of various analogs, differing in degree and position of sulfation. Therefore, flexibility in modifying the intermediates was also an important consideration.

The simpler, unoxidized, disaccharides 5 and 6 (Scheme II-3), which differ only in the configuration at C-5, contain features essential for glycosidic bond formation at the 1- and 4'-positions. The 1-O-acetyl derivative allows for the formation of a glycosyl halide (111). An alkyl group at O-3' is advisable for increasing reactivity at the open, OH-4' position (13). Although not necessarily the best amino-protecting group (17), the N-acetyl functionality was chosen at this stage for convenience in synthesis and characterization, in the knowledge that it can be removed by various selective or non-selective methods (17).

In compound 5, OH-2 is not selectively blocked at this stage. Preliminary evidence showed that it may be difficult to achieve selective protection there. However, little is known about the reactivities of the different hydroxyls in idose systems, and also in di- or oligosaccharides containing them (11). It would be necessary, therefore, to investigate this question of suitable intermediates with, e.g., the phenylchlorosulfate reagent mentioned earlier, or perhaps more common protecting groups.

With these four general targets in mind, the general strategies were examined more closely. The two most important modifications are the inversion at C-5 from the D-gluco to the L-ido configuration, and the introduction at C-2' of the amino function. Each of the two starting compounds is best suited for one of these steps. The diacetal, 1, requires a single selective hydrolysis necessary for the introduction of an appropriate (e.g., sulfonyl) leaving group. In using compound 2 (Fig. I-5, p.21), the 4',6'-O-isopropylidene must be removed first, owing to its greater acid lability (112), and OH-4' and -6' then reprotected before the second hydrolysis step, of the 5,6-acetal.

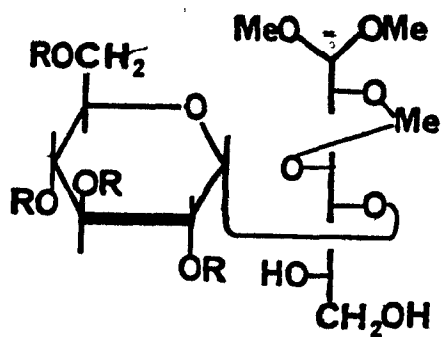
Compound 2, with only OH-2' and -3' exposed, appeared amenable to an efficient introduction of the 2'-amino groups. That is, selective oxidation, or protection of O-3' and then oxidation, would lead to the 2'-ketone; the amino group is then accessible by reduction of an appropriate 2'-imine (see Chapter II).

It appeared then, that strategy I is appropriate for the synthesis of the L-ido disaccharides, whereas strategy II is more suitable

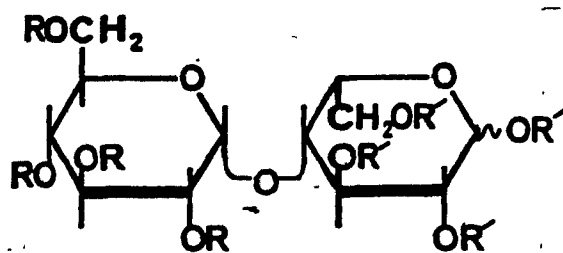
for the D-glucose disaccharides. Within each of these general strategies, the important steps were evaluated and specific routes proposed.

First, introduction of the 2'-amino group in the second stage of strategy I (Scheme II-1, p.25) entails blocking of the 4'- and 6'-OH's with a benzylidene or isopropylidene group under acidic conditions (113,114). It is possible that the 2,3-O-isopropylidene and dimethyl acetal can be cleaved or rearranged under these conditions (115). Reduction of the 2'-imine to the amine might also reduce the uronic acid or ester, if strong reagents were required. These possibilities suggested that a cyclic I scheme could be a reasonable working route towards compounds 3 and 5. However, consideration of the hydrolysis of idose suggests additional constraints, and in turn some variations in strategy, because idose readily forms the 1,6-anhydropyranose under certain acidic conditions (43). Therefore, two products might be expected in an acid-catalyzed cyclization of intermediate 7 (Scheme II-4). Nevertheless, the 1,6-anhydro pyranose (8) can be converted back into the pyranose (9) by acetolysis (116,117), or used as an intermediate in alternative schemes. As the 1,6-anhydro linkage blocks OH-6, it allows for modification of the non-reducing end. Opening of this internal ether at a suitable time can then expose OH-6 for oxidation, or other blocking strategies. The possibility of obtaining 8 also suggested such variations in strategy as protecting OH-6 before cyclization.

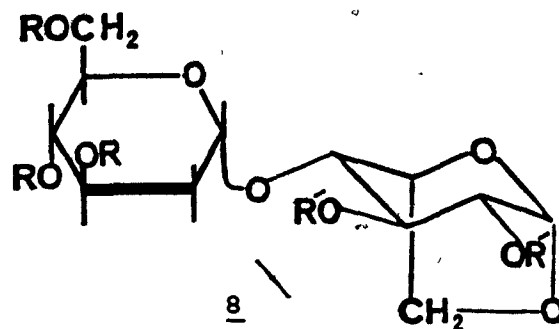
Strategy II also is applicable to the synthesis of compounds 3 and 5. As mentioned previously, exposure of OH-5 from intermediate 10 (Scheme II-5) requires two separate hydrolysis steps to give 11. Com-



7 R = alkyl or acyl group



9



8

Scheme II-4. General strategy I: expected intermediates and products of hydrolysis.

compound 11 can then be modified as outlined for the second phase of strategy II.

Since compounds 4 and 6 do not require the selective exposure of OH-5, and acidic solutions of glucopyranose are not complicated by a 1,6-anhydro form, the cyclic version of strategy II seemed applicable. After cyclization of intermediate 10 (Scheme II-5), compound 12 is accessible by acetalation of the 4'- and 6'-OH group. Then, OH-6 can be blocked or oxidized selectively, perhaps ideally, by catalytic methods.

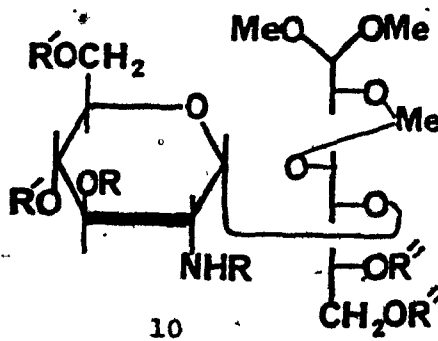
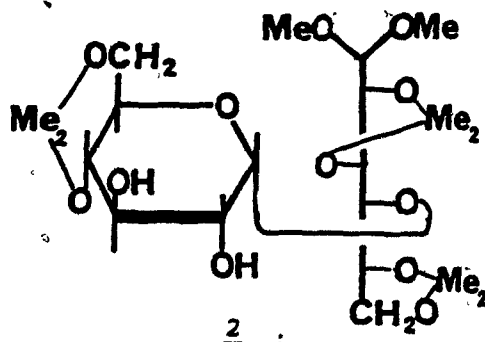
With the basic strategies now outlined, experimental investigations with compounds 1 and 2 were undertaken. The discussion is divided into three chapters (II, III, IV):

(a) The present chapter (II) continues with early investigations of the cyclic version of strategy I and its variations. The conformation of the dimethyl acetal disaccharide is discussed.

(b) The more successful strategy II is then described in Chapter III. The introduction of the 2'-amino-2'-deoxy functionality is shown with an application to a target compound of type 5, containing the L-ido configuration.

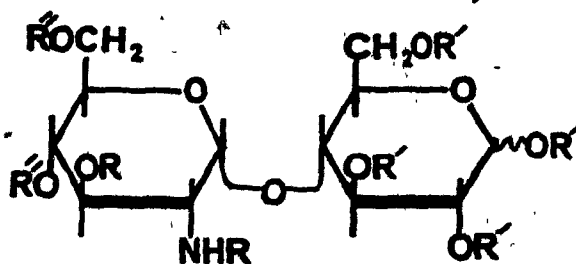
Following that, a more extensive examination of the reduction of the 2'-oxime is described. Also evaluated is the formation of intermediates in a synthesis of 3 using a type II strategy.

(c) The fourth Chapter deals with routes towards uronic acids. The presentation begins by taking up the second stage of cyclic strategy II, with a discussion on cyclization of the dimethyl acetal and subsequent routes toward oxidation of OH-6.



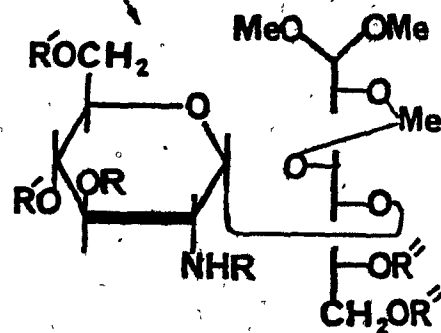
R = alkyl or acyl groups

R', R'' = R'' = Me₂C



12 R = R' = acyl group

R'', R'' = PhCH



11 R = R' = acyl or alkyl

R'' = H

Scheme II-5: General strategy II: routes towards target compounds

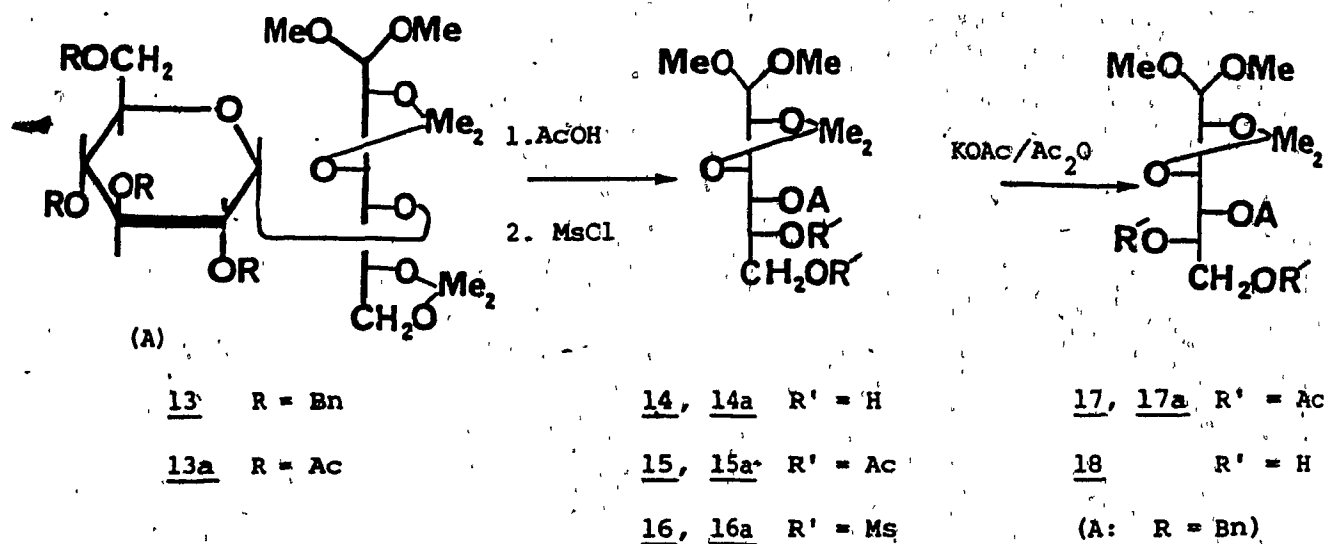
3 and 5.

Finally, the application of an acyclic version of strategy II is described, illustrating oxidation strategies with model compounds as well as intermediates from section III. In addition, it contains a discussion of the conformation of the disaccharides obtained.

II.2 Introduction of L-ido configuration according to strategy I

Starting compound 2 (Fig. I-5, p.21) was prepared according to Ueno et al. (108), and was characterized by ^1H -n.m.r. spectroscopy. The O-benzyl and O-acetyl derivatives, 13 and 13a, respectively (Scheme II-6), were made by conventional methods. In the ^1H -n.m.r. spectra of both compounds, complex overlapping of ring protons was partially alleviated, and extensive assignments were possible, by using 2-D techniques. The spectrum of 13a showed five downfield signals in addition to the anomeric protons, corresponding to H-2', -3', -4' and -6a,b'. Compound 13 also produced a separation of signals in this region, including the two singlets corresponding to the dimethyl acetal. An unusual downfield shift was observed for H-2 (4.65 ppm) compared to its "normal" range (~ 4.1 ppm) found in compound 13a and other non-benzylated derivatives (Table II-1). This effect must arise from proximity to certain phenyl rings, and hinted at some appropriate conformation. A full discussion of the conformation and orientation of the acyclic moiety is presented in Section II.6, p.53.

In an early plan, it was proposed to exchange the dimethyl acetal of 2 with an alkylthio group in order to stabilize the acyclic form^{as}



Scheme II-6. Inversion of C-5 to give the L-ido configuration.

Table II-1: ^1H -Chemical shifts (δ) for Compounds

13 - 18 and 13a - 17a

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	OMe
<u>13</u>	4.32	4.65	4.16	3.80	4.21	~ 4.0		3.32, 3.43
<u>14</u>	4.29	4.71	4.07	3.85	-	-	-	-
<u>15</u>	4.36	4.47	4.18	~4.0	~5.3	4.22	4.56	-
<u>17</u>	4.31	4.63	4.04	3.83	5.38	~ 4.4		-
<u>18</u>	4.31	4.69	4.06	-	-	-	-	-
<u>13a</u>	4.33	4.16	4.05	3.93	4.25	4.02	4.09	3.45, 3.47
<u>14a</u>	4.33	4.27	4.10	3.77	3.98	~ 3.7		-
<u>15a</u>	4.35	4.18	4.11	3.86	5.27	4.52	4.33	-
<u>17a</u>	4.29	4.18	4.03	3.80	5.31	4.52	4.29	-

the dithioacetal (118). In addition to the greater hydrolytic stability expected, the reactivity of OH-2 in some cases is known to be decreased (118) which might allow for selective protection strategies. The use of dithioacetals also permits cyclization to the pyranose form under neutral conditions (118), avoiding 1,6-anhydro ring formation. Cyclization can also lead to the formation of thioglycosides (118), and so provide for mild methods of glycosidation (14). However, the reaction of 13 with ethanethiol in the presence of a catalytic amount of p-toluenesulfonic acid gave only products showing the loss of O-isopropylidene groups, and no presence of ethylthio acetals. These early experiments were not elaborated, although in the light of recent successful glycoside methodology using thioglycosides (14), additional work on this idea could be fruitful.

The resistance of the acyclic dimethyl acetal towards the ethanethiol exchange, suggested pursuing the first stages of strategy I, that is, the selective hydrolysis of the 5,6-O-isopropylidene group.

The hydrolysis of acetonates has been studied extensively (11,112). The five membered 5,6-O-isopropylidene, or α ring in 13 according to Barker and Bourne's notation (112), is expected to be less stable than the 2,3-O-isopropylidene, in an α -threo ring. In fact, by using 80% aqueous acetic acid at a controlled temperature (40 - 50°C), the 5,6-O-isopropylidene group was removed from compounds 13 and 13a with 60 - 75% yields. In the benzylated system (13), the reaction was faster (2 h) as compared to its acetylated counterpart, 13a (8 h). In both cases, the ¹H-n.m.r. spectra of the products clearly showed the

loss of one O-isopropylidene group and retention of the dimethyl acetal. The two diols, 14 and 14a, were acetylated to give 15 and 15a for characterization. Accordingly, their ¹H-n.m.r. spectra contained additional downfield signals corresponding to H-5, H-6a and H-6b (Table II-1). Other notable changes in the spectra were observed for the coupling constants of protons on the acyclic unit. For example, $J_{3,4}$ in 15 increased to 5.7 Hz from 2.8 Hz in 14, reflecting changes in rotamer populations upon cleavage of the O-isopropylidene group (see Section II-6).

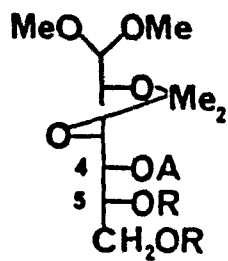
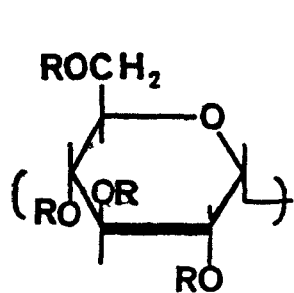
The hydroxyl at C-5 was then inverted using methodology developed for the synthesis of L-idofuranosides from glucofuranoside derivatives (89). Use of *p*-toluenesulfonyl chloride with 14 gave only a mono-tosylate compound, according to n.m.r. evidence and so methanesulfonyl chloride was used. The di-mesylate 16 was then inverted to the diacetate 17 having the expected L-ido configuration.

The latter configuration was substantiated in two ways. First, although the ¹H-n.m.r. spectrum of 17 superficially resembles that of diacetate 15, significant differences suggested that the inversion had been successful. The signals corresponding to H-5, -6a and -6b are again downfield with respect to those of 14, but chemical shifts and splitting patterns are quite different than for 15. A distinctive feature is the coupling between H-3, -4 and -5. For the D-gluco diacetate, 15 (see Table II-3, p.59), $J_{3,4}$ is 5.7 Hz, whereas the $J_{4,5}$ value, although not unequivocally determined must be "small" (~ 1 - 3 Hz). That is, by examining the patterns for H-5, -6a and -6b, the

multiplet partially buried under H-1', was found to contain one large coupling to H-6a, and one small coupling to H-6b. Hence, the remaining small coupling must be $J_{4,5}$. If these values are compared to those extracted from the corresponding signals for the L-ido diacetate (17), a similar analysis gives a "large" coupling (~ 6.3 Hz) for $J_{4,5}$ and a "small" coupling (1.1 Hz) for $J_{4,3}$.

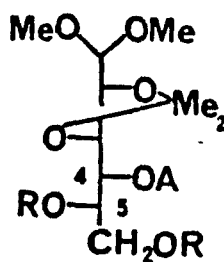
Similar results were obtained for the acetylated series, 13a - 17a. Hexaacetate 17a obtained after the same synthetic steps as for 13 to 17 showed analogous differences in its $^1\text{H-n.m.r.}$ spectrum when compared to that of the D-gluco isomer (15a). The same reversal of coupling magnitudes was found (Table II-3), and is shown in Figure II-1.

In addition to the fact that the proton n.m.r. data were compatible with the proposed structures, the L-ido configuration was confirmed chemically. A vigorous acid hydrolysis of 17 gave a mixture of products from which a compound corresponding to 1,6-anhydro-D-idose was isolated. After acetylation and purification, a product indistinguishable in its optical rotation and $^1\text{H-n.m.r.}$ spectrum from authentic 2,3,4-tri-O-acetyl-1,6-anhydro- β -L-idopyranose was obtained (see experimental, p.249).



$$J_{4,5} = 1.6 \text{ Hz}$$

(A)



R = Ac

$$J_{4,5} = 5.9 \text{ Hz}$$

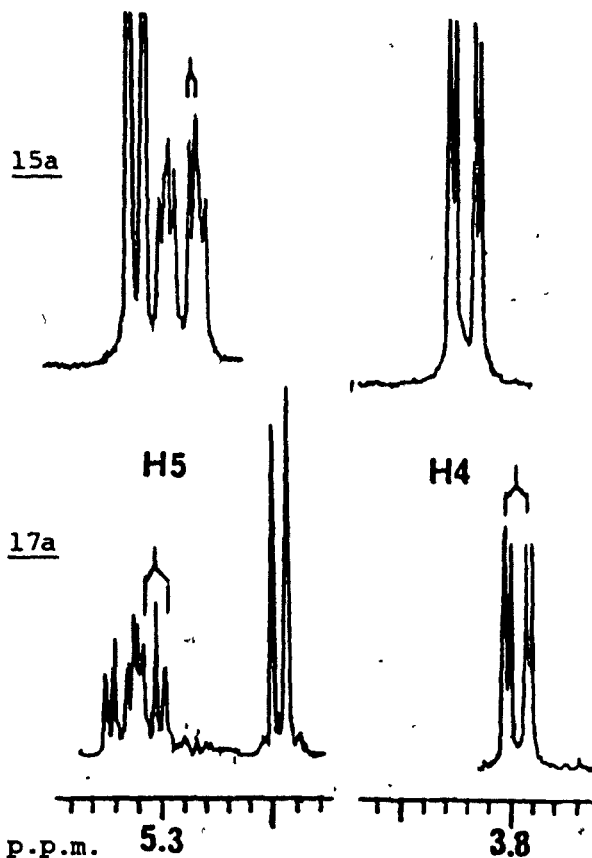


Figure II-1. Proton coupling between H-4 and H-5 in L-ido (17a) and D-gluc (15a)-acyclic dimethyl acetal compounds.

II.3 Investigations of cyclic strategy I

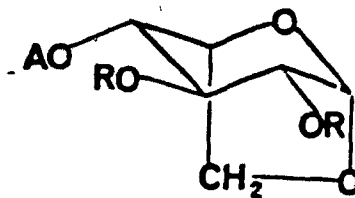
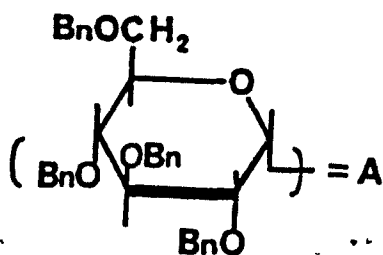
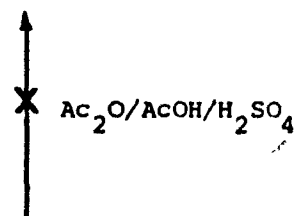
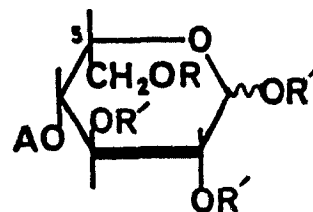
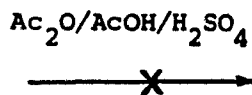
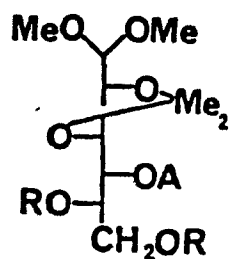
With the successful formation of the L-ido configuration, it was now possible to investigate the variations in cyclic strategy I.

The simplest approach is outlined in Scheme II-7. Acetolysis of intermediate 17 cleaves the O-isopropylidene and acetal groups (116), and permits cyclization to the fully acetylated pyranose.

Although acetolysis can cleave glycosidic linkages (116), it was anticipated that appropriately mild conditions could be found. The use of 2:1:0.03 acetic anhydride - acetic acid - sulfuric acid led to a mixture of products. ¹H-n.m.r. spectra of the crude products showed retention of the dimethyl acetal when the reaction was carried out in the cold, and glycosidic bond cleavage when the reaction mixtures were heated.

Because of these unencouraging results, the two step route through the hydrolysis of 17, for example, was re-examined. Initial plans called for the preparation of the 1,6-anhydro-β-L-idopyranose derivative, 19. Opening of a 1,6-anhydro ring is usually faster than the cleavage of a disaccharide (119,120), and use of trifluoroacetic anhydride for example (121) can lead to free sugars suitable for glycosidation with triflate methodology (122).

Analysis of the reaction mixture from the vigorous hydrolysis of 17 described on page 40 provided a compound, recovered, in low yield, believed to be 19 (Scheme II-7). The ¹H-n.m.r. spectrum showed two signals corresponding to acetyl methyl and a singlet in the anomeric

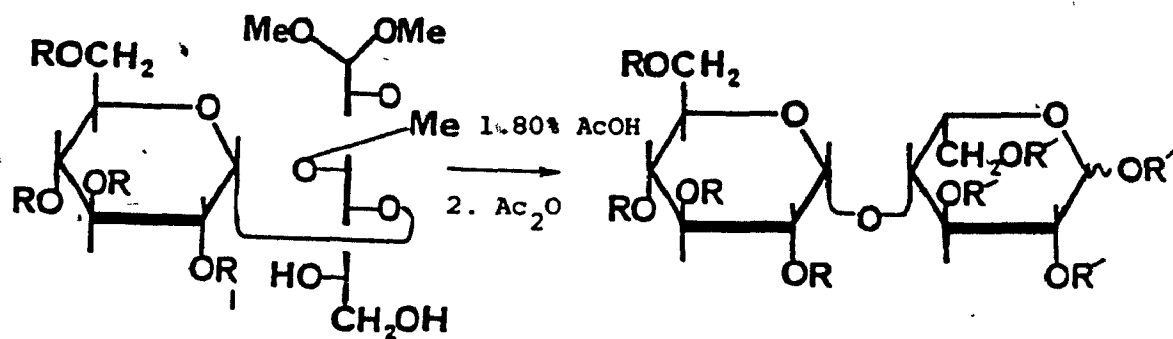


Scheme II-7: Attempts at forming L-ido-pyranoses by acetolysis.

region. A downfield triplet with couplings $J_{3,2} = J_{3,4} = 8.5$ Hz, corresponded to H-3, and was compatible with the ${}^4C_1$ conformation of the 1,6-anhydro- β -L-idopyranose disaccharide. This compound was treated with an acetolysis mixture (2:1:0.03 acetic anhydride - acetic acid - sulfuric acid) for 3 h at room temperature. The major fraction isolated by chromatography (eluant, 1:2 ethyl acetate - hexane) was a mixture of products, presumably α and β pyranoses of the general structure 20 (Scheme II-7). The ${}^1H$ -n.m.r. spectrum also showed, however, that one O-benzyl group had also been cleaved and replaced by an O-acetyl group. The cleavage of primary O-benzyl groups under acetolysis conditions has been reported elsewhere (123,124).

To avoid these complications, the hydrolyses experiments were continued with the acetylated compound 17a. Hydrolysis with 90% aqueous trifluoroacetic acid was attempted, after removing the acetyl groups with sodium methoxide (21, Scheme II-8). After 2 h, t.l.c. (20% methanol - chloroform) showed a mixture of products and heating did not change their ratio, as indicated by t.l.c. Instead, analysis of the mixture, after acetylation, showed extensive cleavage of the disaccharide. Compounds identified as penta-O-acetyl- D-glucose and penta-O-acetyl-L-idose were recovered.

The use of milder hydrolysis conditions was more encouraging. Compound 18, obtained by deacetylation of 17 with sodium methoxide, was heated under reflux in 80% aqueous acetic acid for 2 h (Scheme II-8). The major product isolated, after acetylation, corresponded to 22, with

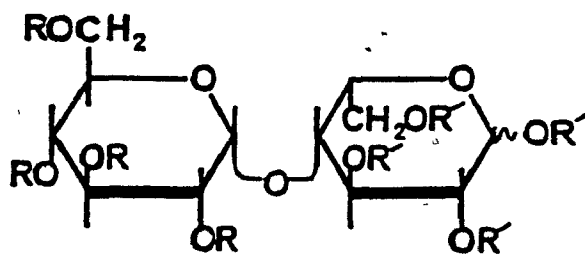


18 R = Bn

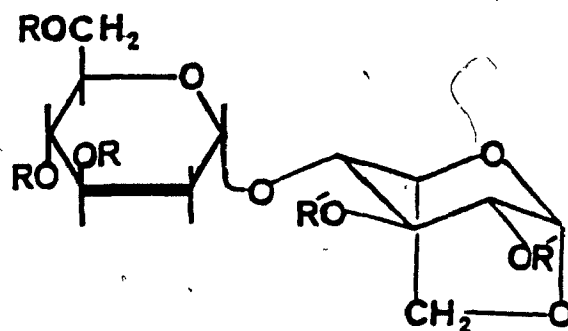
22 R = Bn, R' = Ac

21 R = H

90% TFA
50° - 70°



R = R' = H



R = R' = H

(observed formation of monosaccharides)

Scheme II-8: Cyclization of L-idose dimethyl acetals in disaccharides, by acidic hydrolyses.

no 1,6-anhydro\pyranose detected. Evidently the formation of the internal ether requires strong acidic conditions, and the possibilities of obtaining this compound without extensive glycosidic cleavage are limited.

The ^1H -n.m.r. spectrum of disaccharide 22 (Fig. II-2), though a mixture of α and β 1-acetates, was partially assigned. The two anomeric signals both had small coupling constants, consistent with an L-ido configuration. The assignment of the α and β systems was based on chemical shift values from analogous penta-O-acetyl-L-idose compounds (125), as well as the presence of long range coupling between H-1 and H-3 ($J_{1,3} = 1 \text{ Hz}$), which is possible only with the "W" arrangement in the α anomer (126). From the downfield signals corresponding to the acetylated O-2 and O-3 positions, $J_{2,3}$ and $J_{3,4}$ coupling constants were estimated. The β anomer showed larger couplings ($J_{2,3} = J_{3,4} = 5 \text{ Hz}$) than the α anomer ($J_{2,3} = J_{3,4} = 3.8 \text{ Hz}$). A discussion of these values in relation to conformation and other idose compounds will be found in Chapter IV.

II.4 Hydrolysis of 14 with OH-6 blocked

The relative ease of cyclization of compound 18 to pyranose 22 (Scheme II-8), suggested using a 6-OH protected derivative, as depicted in Scheme II-9.

The R group on O-6 would allow for selective oxidation at a later stage, such as after glycoside formation or incorporation into an oli-

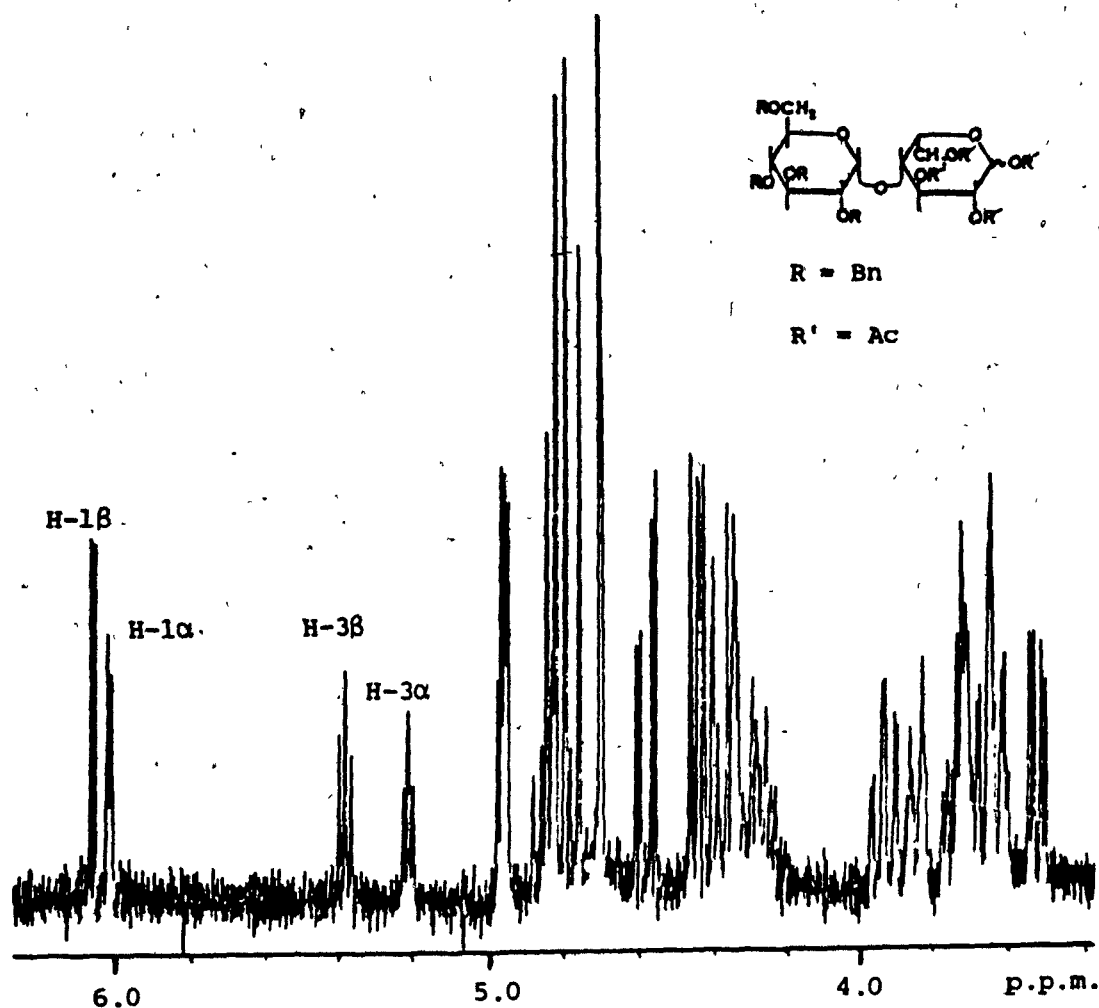
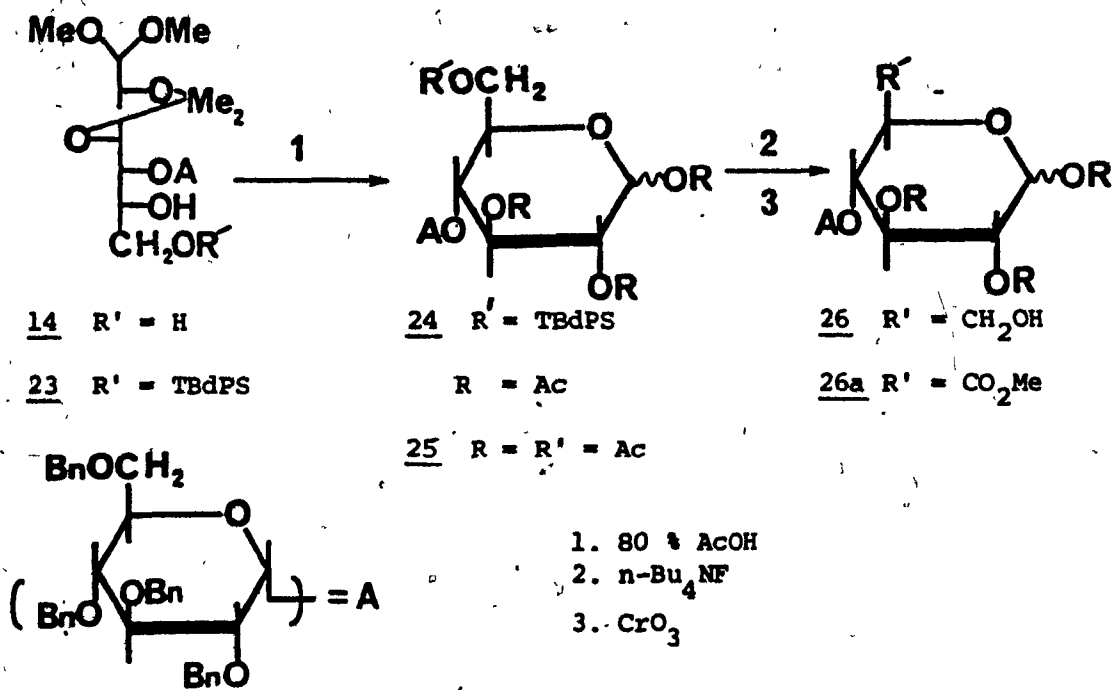


Figure II-2. ¹H-n.m.r. spectrum of 1,2,3,6-tetra-O-acetyl-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-L-idopyranose (22).



Scheme II-9: Cyclization and oxidation sequence with a model compound having OH-6 selectively blocked.

0 gosaccharide. Suitable protecting groups for this sequence are few in number, however. Most groups that are selective for primary hydroxyls are sensitive to acidic hydrolysis or prone to migration under these conditions. Though some esters can be directed selectively to primary hydroxyls, the problem of migration in this 1,2-diol system was anticipated.

As O-benzyl groups are stable to the acidic conditions used, attempts were made to selectively benzylate using benzyl chloride and barium hydroxide, barium oxide mixtures as the base, in N,N'-dimethylformamide (127). However, these resulted either in no reaction, or mixtures of products. Phase transfer (128) with alkyl tin derivatives (129) was not investigated.

0 Selective substitution of OH-6 of 14, by a tosyl group was then effected as has been observed elsewhere (11). However, acidic hydrolysis of the 6-O-tosyl derivative resulted in mixtures of compounds, presumably due to migration and hydrolysis of the p-tosyl ester.

0 The tert-butyldiphenylsilyl (TBDPS) protecting group was next considered as a candidate since its stability to mild acid is well documented (130). The formation of the 6-O-TBDPS derivative, 23 (Scheme II-9), proceeded readily. Two products were isolated after mild hydrolysis and acetylation. The major product, 24, had the silyl group intact, as the ¹H-n.m.r. spectrum showed a mixture of α and β anomers with three pairs of downfield signals corresponding to H-1, -2 and -3 (Table II- 2). However, the minor product, 25, had lost the silyl group and the spectrum was compatible with a 1,2,3,6-tetra-O-acetyl derivative.

Table II-2: ^1H -Chemical Shifts (δ) and ^1H - ^1H Coupling

Constants (Hz) for Compounds 23 - 26a

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	CO_2Me
<u>23</u>	4.33 (5.9)	4.75 (6.6)	4.38 -	3.99 -	4.17 -	-
<u>24a</u>	6.30 (3.7)	5.01 (10.2)	5.57 (10.1)	- -	- -	-
<u>24b</u>	5.60 (8.1)	5.07 (9.1)	5.35 (9.6)	- -	- -	-
<u>26a</u>	6.29 (3.7)	5.02 (10.3)	5.64 (9.4)	4.07 (9.5)	~3.9 -	-
<u>26aa</u>	6.32 (3.7)	5.09 (10.3)	5.56 (9.2)	4.19 (9.6)	4.30 -	3.65 -

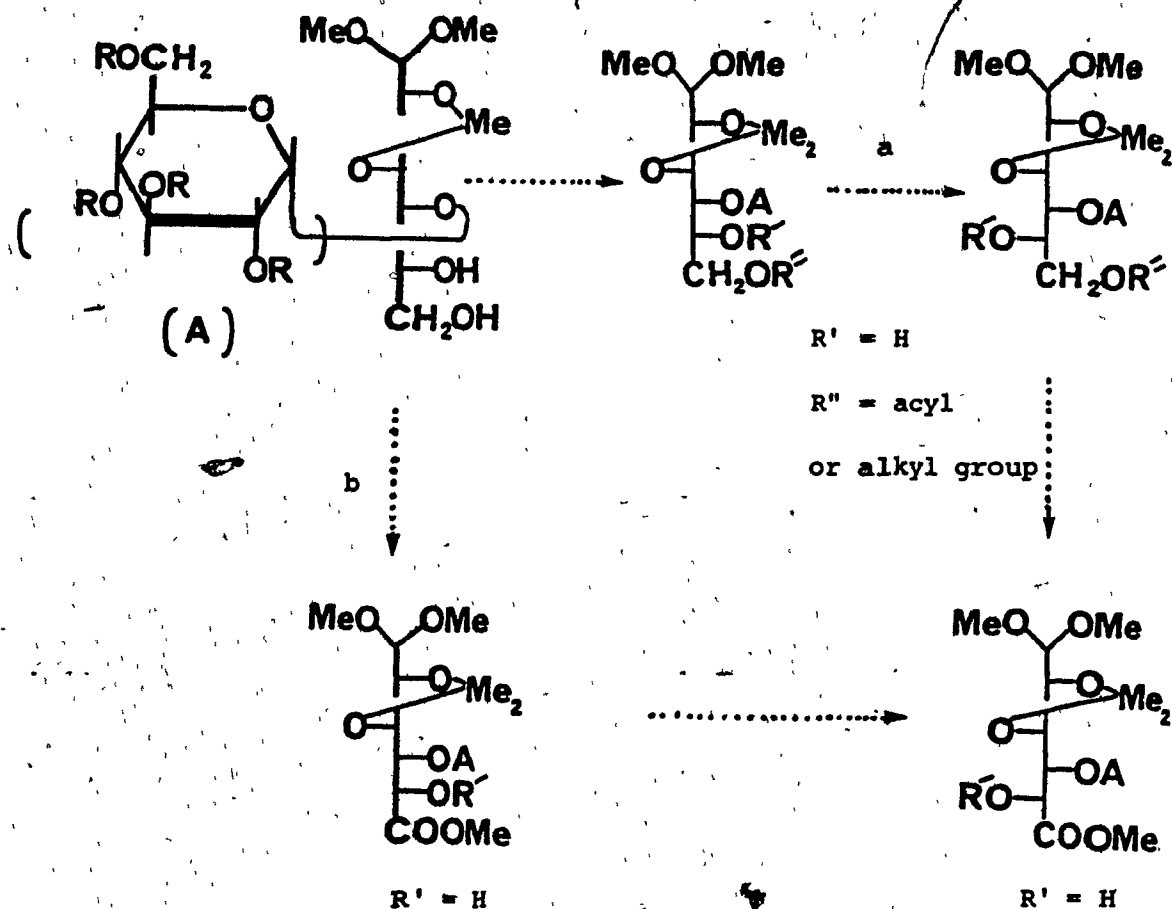
The next step, that of removing the silyl group with fluoride ion, also produced a mixture of compounds, with the desired product (26), isolated in only 36% yield as the α anomer. Other fractions appeared to contain rearrangement products, from acetyl migration (131). The free OH-6 then was oxidized by the conventional Jones reagent (132) to give uronic acid 26a. A ^1H -n.m.r. spectrum showing the methyl ester singlet, and a doublet assigned to H-5 confirmed the structure.

In view of the partial success of this route, consideration of ester and other ether blocking groups for OH-6 might be worthwhile.

Other aspects of strategy I could benefit from a successful method for blocking OH-6. For example, in Scheme II-10, the selective protection of OH-6 could allow inversion of OH-5, followed by cyclization as described above (route a), or preliminary oxidation to the uronic acid (route b) (see below).

II.5' Attempted oxidation of OH-6: An acyclic version of strategy I

Another variation within general strategy I entails catalytic oxidation of either derivatives 14, 17 (Scheme II-6) or 22 (with 6-OH) (Scheme II-8). Unfortunately, attempts to do so using Pd-C/O_2 (133) were not successful, and only starting material was recovered from the reaction mixtures. A possible factor here is the conformation of such derivatives as 17, which is considered in Section II.6. Although these experiments were not continued, recent work by Sinay et al. (66) des-



Scheme II-10: Proposed variations on oxidation schemes within general strategy I.

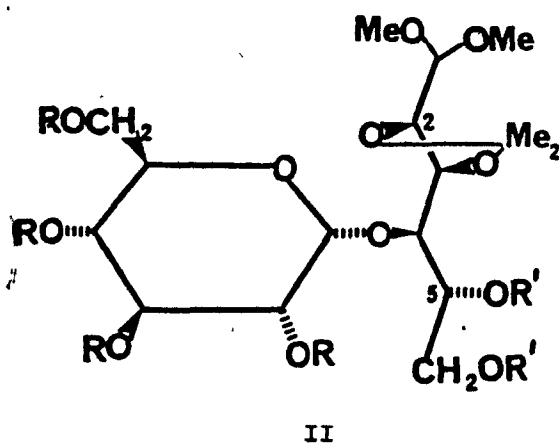
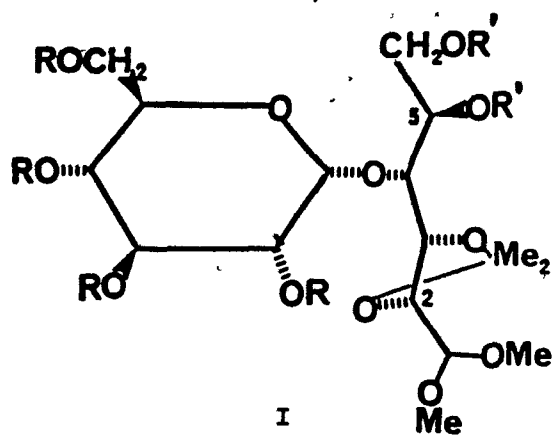
cribing the inversion of glucofuranuronic acid derivatives, suggest that a second look at catalytic oxidation might be profitable. A route such as shown in Scheme II-10(b), would reduce the number of steps needed to arrive at the L-iduronic acid functionality on the acyclic moiety.

In conclusion, the early experiments on compounds 13 and 13a, using the type I strategy were only partially successful. Concurrent investigations into strategy II (see Chapter III) were more promising at the outset. In retrospect, however, there remain some interesting possibilities for strategy I, some of which are noted above.

II.6 Conformation of the acyclic dimethyl acetal unit

The orientation and conformation of the acyclic aglycon in these derivatives, has been alluded to in the discussion of chemical shifts of certain derivatives (see Table II-1, p.37), and the pattern of coupling constants seen in the isomeric 5,6-diacetates. As will be seen here, and considered further in Chapter III, this question may have a bearing on the relative reactivities of OH-2' and -3'. Consequently, further speculation is offered about probable structural details, based on a more careful analysis of these data and an examination of models.

Figure II-3 shows a schematic representation of two feasible orientations of the acyclic moiety. The non-reducing residue lies above the plane of the paper. Either orientation could provide steric



$R = R' = \text{Ac}$
 or $R = \text{Bn}, R' = \text{Ac}$

Figure II-3. Schematic representations of disaccharides 15 and 15a showing two possible orientations of the acyclic dimethyl acetal residue.

hindrance to substitution at OH-2' although, in space-filling models, I projects a greater bulk into its vicinity.

The downfield shift of H-2 when R = benzyl, and the differences in field sensed by the protons of the two methyl groups of the dimethyl acetal (Table II-1, p.37, and Fig. II-4), must come from the proximity of these nuclei to an aromatic ring. It is possible to move either the 2'-O-benzyl or the 6'-O-benzyl in structures I and II, respectively, into plausible positions for such an effect. However, models of II show H-2 projecting either downward away from the ring or buried very close to the ring. In addition, the 6'-O-benzyl is freely rotating as shown by a singlet for the methylene protons. In I, likely rotamers (see later) for the C-3 -- C-4 bond place H-2 in suitable positions for deshielding by an aromatic ring on OH-2', and the benzylic protons at that position show an AB quartet, indicative of restricted motion. In addition, rotamer populations of the C-4,C-5 and C-3,C-4 bonds are invariant with changes of R from benzyl to acetyl, or with replacement of OH-2' with a 2'-acetamido function. This invariance favours structure I. Confirmation of these arguments was provided by the ¹H-n.m.r. spectral data for 2,3:5,6-di-O-isopropylidene-4-O-(2,3-di-O-benzyl-4,6-O-isopropylidene-α-D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (13b), a compound obtained from benzylation of 1. The same downfield shift of H-2 was observed, as in compound 13. This deshielding can only come from the benzyl group on O-2', and is thus possible in structure I, but not structure II (Fig. II-5).

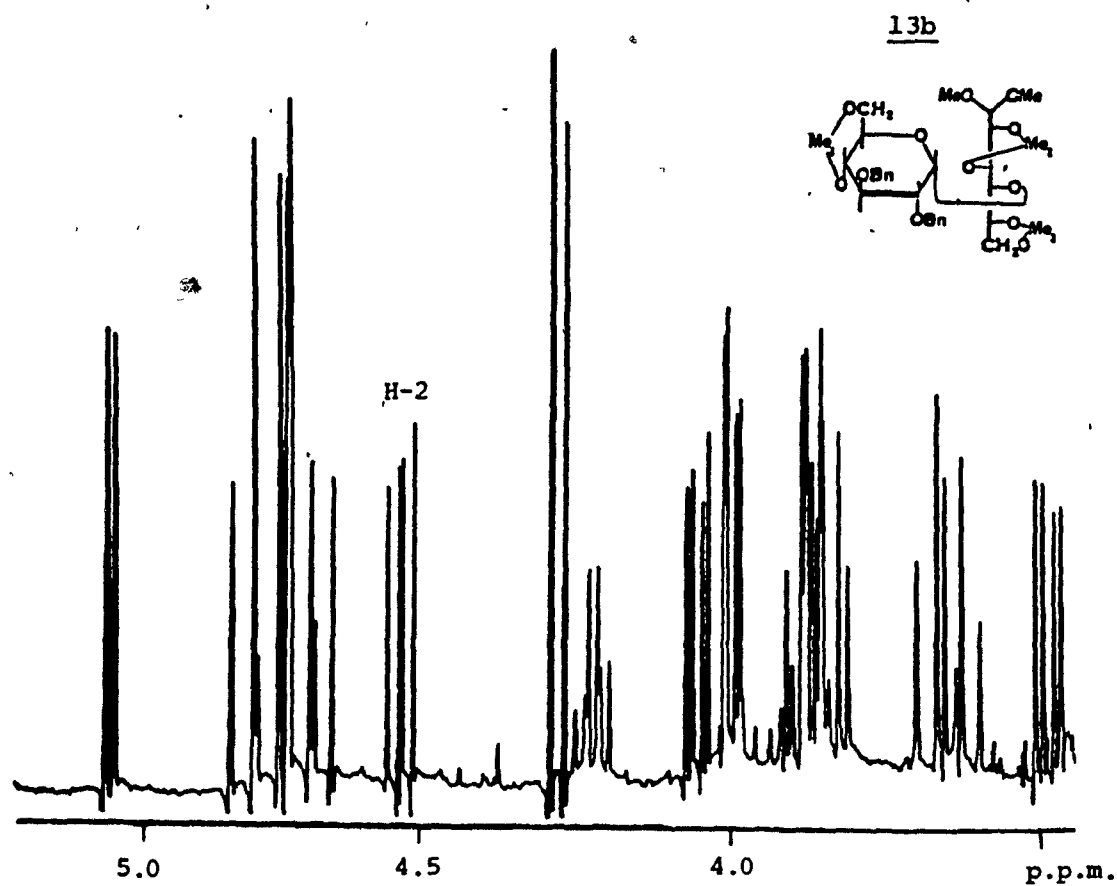
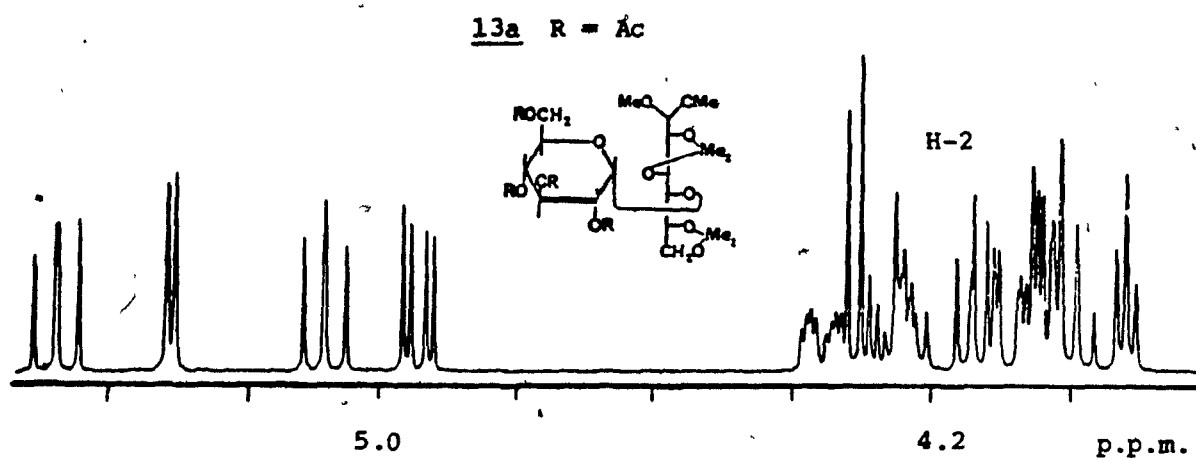


Figure II-4. ¹H-n.m.r. spectra of compounds 13a and 13b showing down-field shift of H-2 in 13b.

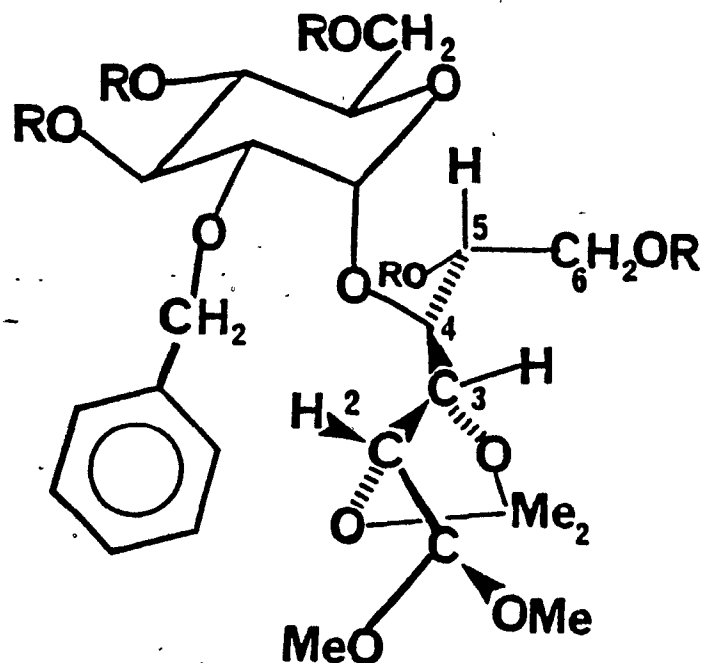


Figure II-5. Proposed preferred conformation of the acyclic moiety showing the proximity of H-2 and the dimethyl acetals to the 2'-O-benzyl group.

The coupling between H-3, -4 and -5 shows consistent patterns for the D-gluco and L-ido isomers, regardless of the structure of the non-reducing unit (Table II-3). These values, in terms of Karplus-type relationships (134,135) and established conformational concepts (41), suggest preferred rotamer populations that differ significantly from the conformations of related acyclic aldopentose and aldohexose derivatives (136,137). Proton coupling constants, measured by Horton and Wander (136) for a series of such derivatives, suggest that the usual planar zig-zag conformations allow for minimal gauche interactions along the carbon backbone. Another study, by Szarek and coworkers (137) using ^{13}C chemical shifts, confirmed the preponderance of such conformers. The Newman projections of bonds C-3 -- C-4 and C-4 -- C-5 in the monosaccharide derivatives (136,137) are shown in Figures II-6 and II-7 with the predicted range of coupling constants for H-3, -4 and -5 (rotamers I, III, V, VII). Shown as well, are the predicted major rotamers of the acyclic unit in the synthesized maltose derivatives (e.g., 15, 17, etc.) as derived from the measured coupling constants (rotamers II, IV, VI, VIII).

One would not necessarily expect, a priori, that a substituent on O-4 of an acyclic derivative, even a large glucopyranosyl ring, would change its conformation. Interestingly, however, the values found for the maltose derivatives are generally the converse of those found for the acyclic compounds. That is, a large coupling between H-4 and H-5 in one (rotamer I, for example), is small in the other (rotamer II), and vice versa.

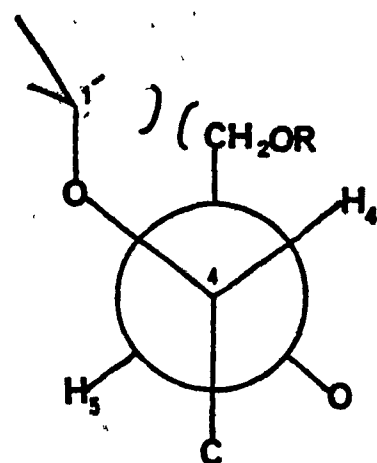
Table II-3: ^1H - ^1H Coupling Constants (Hz) for D-gluco and
L-ido Acyclic Dimethyl Acetal Intermediates

Compound	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$
<u>D-gluco</u>				
<u>15</u>	5.7	~1-2	8.8	2.2
<u>15a</u>	6.8	1.6	8.3	2.6
<u>37</u>	7.2	~1.6	8.0	3.0
<u>52</u>	6.6	1.5	-	2.4
<u>L-ido</u>				
<u>17</u>	1.1	~6.3	-	-
<u>17a</u>	1.7	5.9	7.2	2.6
<u>36</u>	2.5	5.2	7.8	2.7
<u>54</u>	2.2	5.4	7.3	2.7

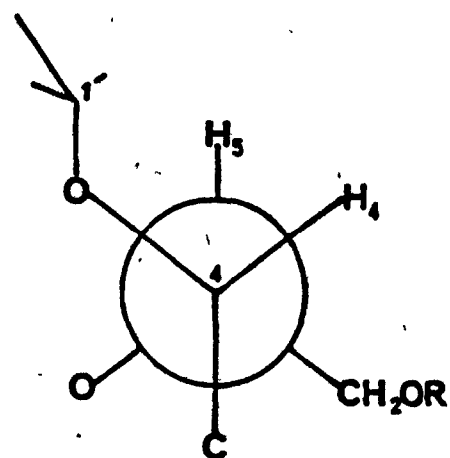
After constructing models, it is possible to rationalize these values and propose some possible conformational changes that are compatible with the data. Accordingly, it is assumed that the acyclic unit is oriented with the non-reducing unit according to Fig. II-5). This brings C-5 and C-6 close to the ring, near O-5' and C-6'. The 2,3-O-isopropylidene is not expected to cause a major change in conformation since the threo arrangement of O-2 and O-3 is the same as found in the open acyclic chain.

Projection I (Fig. II-6) shows the preferred rotamer about the C-4 -- C-5 bond of D-glucose derivatives according to the studies cited (136,137). $J_{4,5}$ should be large, and is found to be 6.2 Hz, indicating contributions from other rotamers as well. When OH-4 is substituted by the α -glucopyranosyl ring as shown, interactions are possible between the ring (O-5' -- O-6' bond, as well as the 6'-hydroxymethyl) and the 6-hydroxymethyl group, situated "above" the plane of the acyclic chain. The value of $J_{4,5}$ of the D-glucose maltose derivatives is small (1.6 Hz), and can arise from rotamers such as II. The 6-hydroxymethyl group has rotated away from the ring, bringing H-5 into a gauche arrangement with H-4, and presumably reducing unfavourable interactions with the ring.

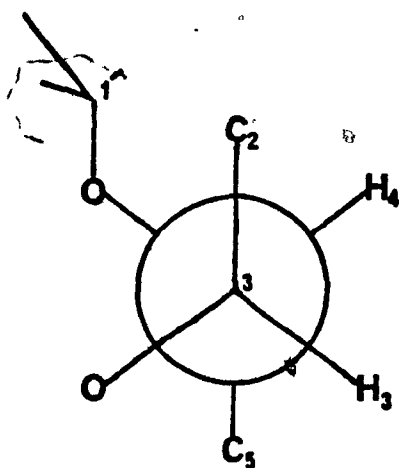
The change in values for the C-3 -- C-4 rotamers is less easily rationalized. However, examination of models shows that the rotation about C-4 -- C-5 described above can bring the 6-hydroxymethyl close to H-3. Projection III shows the rotamer derived for the conformation of the acyclic monosaccharide derivative. It permits a small coupling



I $J_{4,5} = 6 - 10 \text{ Hz}$

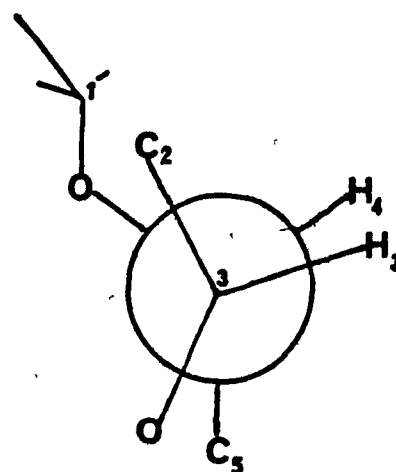


II $J_{4,5} = 1 - 5 \text{ Hz}$



III $J_{3,4} = 1 - 5 \text{ Hz}$

Left: expected major rotamers
based on acyclic monosaccharides
(refs. 136, 137)



IV $J_{3,4} = 6 - 10 \text{ Hz}$

Right: proposed major rotamers
based on measured $^1\text{H} - ^1\text{H}$
coupling (Table II-3)

Figure II-6. Comparison of expected and proposed major rotamers for the acyclic moiety with D-glucose configuration.

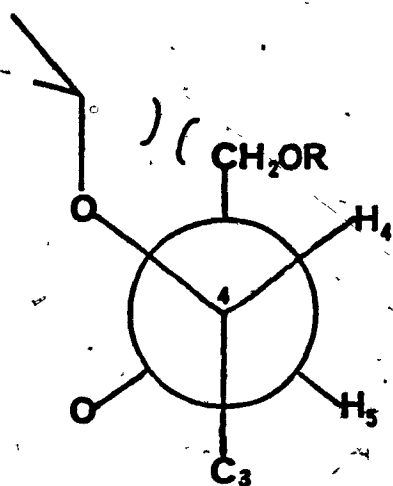
value, and as the measured value is 5 Hz, a contribution from other rotamers is likely as well.

Rotation of H-3 away from H-4 produces even greater interactions between C-2 and C-6 than found for H-3 and C-6 in rotamer III as indicated by models. It is more likely that H-3 moves closer to H-4, as shown for IV, giving rise to the large $J_{3,4} = 6 - 7$ Hz found for the maltose derivatives. In addition, IV allows H-2 to be situated within shielding influences of the 2'-O-benzyl group, as discussed earlier (Fig. II-5).

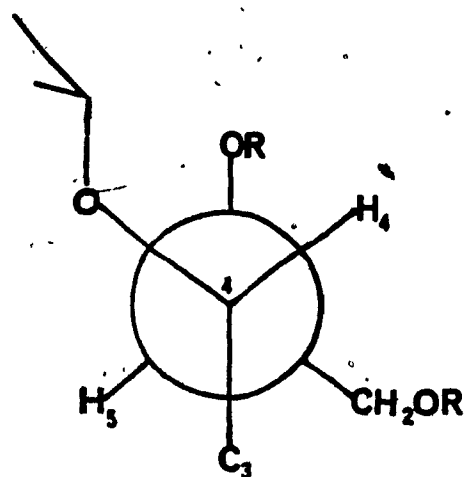
Looking at Figure II-7, the same arguments are applied to the L-ido configuration. The predicted C-4 — C-5 rotamer is shown as V, again with the 6-hydroxymethyl "above" the acyclic plane, interacting with the pyranose ring linked to O-4. The acyclic monosaccharide derivatives (136,137) give relatively small values of 4.4 Hz for $J_{4,5}$, as is predicted. In the maltose derivatives, however, the corresponding value is 6 - 7 Hz, which indicates substantial populations of rotamer VI, in which C-6 has been replaced by the less bulky O-5.

Similarly, the interactions between C-6 and C-2 arising from the combination of rotamers VI and VII might be alleviated by rotating the C-3 -- C-4 bond to give rotamer VIII.

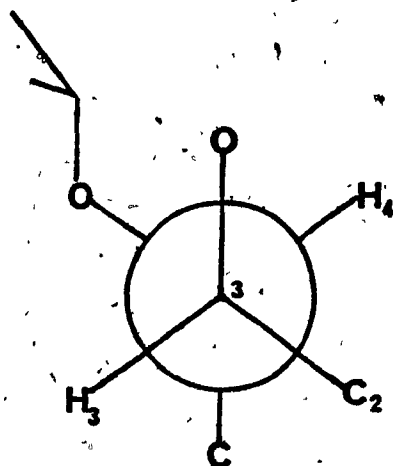
Rotamer VII, predicted from the monosaccharide acyclic derivatives (136,137), has a large (6.5 Hz) coupling for the trans-related H-3,H-4 angle. In the maltose derivative the value is only 1.6 Hz, indicating that rotamer VIII contributes. The other rotamer in which H-3 is situated between O-4 and H-4 was rejected because it brings O-2



V $J_{4,5} = 1 - 5 \text{ Hz}$

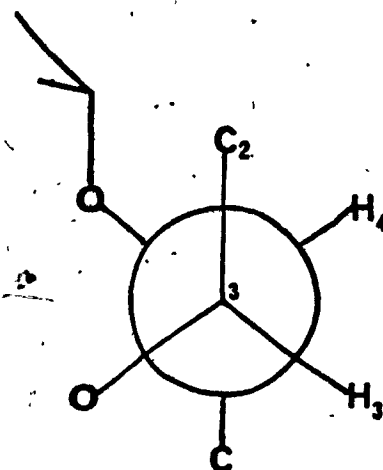


VI $J_{4,5} = 6 - 10 \text{ Hz}$



VII $J_{3,4} = 6 - 10 \text{ Hz}$

Left: expected major rotamers
based on acyclic monosaccharides



VIII $J_{3,4} = 1 - 5 \text{ Hz}$

Right: proposed major rotamers
based on measured $^1\text{H} - ^1\text{H}$
coupling data

Figure II-7. Expected and proposed major rotamers for the acyclic moiety with L-ido configuration.

and the 2,3-O-isopropylidene methyl groups into close contact with C-6, and also does not allow for sufficient exposure of H-2 to the 2'-O-benzyl group to account for the chemical shift observed, as discussed previously.

Overall, then, the data for both the D-gluco and L-ido isomers favour orientation of the cyclic unit represented by structures I, Figure II-3 (p.54) and Figure II-5 (p.57). The conformation of this unit is best represented by rotamers II and IV (gluco), and VI and VIII (ido), Figures II-6 and II-7.

CHAPTER THREE

INVESTIGATION OF GENERAL STRATEGY II

III.1 Introduction

This chapter discusses the development of general strategy II, which comprises the introduction into compound 2 of an aminodeoxy group at C-2' of the α -D-glucosyl residue, and of an L-ido configuration into the dimethyl acetal unit.

A brief outline of aminosugar synthesis was presented in the Introduction, and a means for introducing an aminodeoxy group at C-2' of 2 by way of an imine was proposed. The methodology developed for introducing aminodeoxy functions into carbohydrates by this method is well known. In oxidation studies on polysaccharides, the ketones formed were stabilized as their oxime derivatives (138). The reduction of oximes into two epimeric amines is also well known (139). Catalytic reduction of oximes and hydrazones on six-membered rings usually gives the axial amino group (140). However, in substituted rings, the resulting amine usually is cis to nearby groups (140,141).

Lemieux and coworkers (36,37) investigated the preparative use of 2-oximino-2-deoxy sugars to provide 2-amino-2-deoxy- α -D-glycosides. They reasoned that the normal tendency towards formation of an axial, or D-manno, amine would be offset by the sterically hindering α -aglycon. The success of this method prompted its application to maltose derivative 2.

III.2 Selective protection of OH-2', and introduction of the 2'-amino-deoxy group

The first requirement was an oxidation of 2 at OH-2' to form the 2'-ketone. This step was possible from two approaches: selective oxidation, or selective protecting - deprotecting strategies that expose OH-2'.

Selective oxidation at OH-2, in addition to oxidation at primary OH-6, had been observed for some polysaccharides (138). For example, 6-O-trityl amylose was oxidized with methyl sulfoxide and acetic anhydride to give an oxidized product that was reduced, after formation of the oxime derivative, to an amino containing polysaccharide with a D.S. of 0.8, according to its nitrogen content. Hydrolyses gave exclusively D-glucose and 2-amino-2-deoxy glucose. Unfortunately, this selectivity was not reproducible when methyl 4,6-O-benzylidene- α -D-glucopyranoside was used and, instead, a mixture of amine products was isolated (138).

Better results were obtained with bromine oxidation of unprotected methyl glycosides. Methyl α -D-glucopyranoside yielded mainly the 2-keto and 4-keto derivatives (142). However, overall yields were not promising and so this reagent was not considered for the present study. A few preliminary experiments with pyridinium chlorochromate (143) with compound 1 did not show promise either, giving only complex mixtures of products.

The selective oxidation method, therefore, was not pursued. However, a recent paper by Anderson et al. (40) reports results that could be relevant to the maltose system. That is, when treated with

bromine water at pH 7, 4,6-O-ethylidene- α -D-glucopyranosides underwent selective oxidation at the 2-position, providing products in overall yields of 40 - 50%.

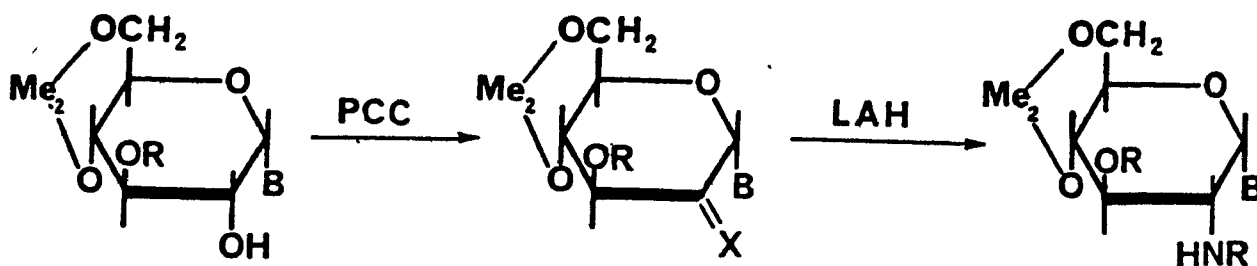
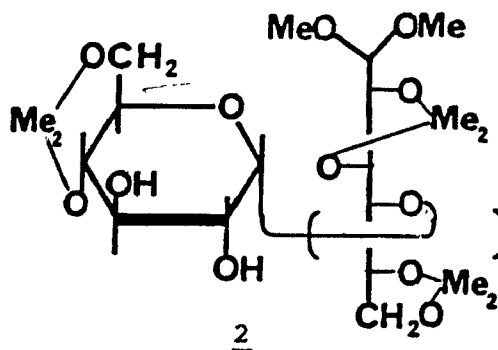
The alternative to selective oxidation was selective protection, either at OH-2 or -3, followed by the appropriate deblocking and/or oxidation step. Differences in relative reactivity between OH-2 and -3 have been extensively studied in compounds such as 4,6-O-benzylidene- α -D-glucopyranosides. Often, mixtures are obtained having major and minor monosubstituted components as well as disubstituted compounds. In general, acid chlorides tend to favour OH-2, whereas carboxylic anhydrides give O-3 esters as the major products under standard conditions (11). For example, esterification with benzoyl chloride and triethylamine in methylene chloride or tetrahydrofuran gave mainly 2-benzoates with an α -gluco derivative (144).

In studies on maltose (103), some selectivity also has been observed with the secondary hydroxyls. For example, one can prepare methyl 2,6,2',3',4',6'-hexa-O-benzoyl- β -maltoside in ~ 70% yield with benzoyl chloride in pyridine. The lack of reactivity of OH-3 is attributed to steric hindrance by the non-reducing unit that is held close to OH-3 by OH-3 -- OH-2' intramolecular hydrogen bonding. In 4',6'-O-benzylidene derivatives, the order of reactivity towards esterification is OH-6, OH-2 > OH-2', OH-3' > OH-3. In 1,6-anhydro-4',6'-O-benzylidene derivatives, reaction with benzoyl chloride gives the 2'-O-benzoate as a major product, with the 2',3'-dibenzoate as one of the minor products. In a recent paper, Mori et al. (145) have established phase

transfer conditions for selective 2'-O-tosylation of 1,6-anhydro-4',6'-O-benzylidene- β -maltose.

It was not possible, then, to predict selectivity with certainty for either hydroxyl in maltose derivative 1, although OH-2' was expected to be slightly more reactive towards esterification. Some exploratory experiments with benzoyl chloride in pyridine gave mixtures in which the 3'-O-benzoate was the major product, according to ^1H -n.m.r. spectra. Matching this result with the speculation that the conformation of the acyclic aglycon places it close to OH-2' (see previous discussion II.6, p.53), suggested that a steric factor might be important, and led to experiments using benzyl and silyl ethers.

Selective benzylation using a variety of methods (127,146) was tried, but in all cases, mixtures were obtained. The use of bulkier substituted benzyl halides was considered, but not pursued, because that very same steric repulsion might prove to be a problem in glycosidations at OH-4'. Some common silyl protecting groups were considered as temporary blocking groups, and proved to be very effective. Reactions of 2 with tert-butyldiphenyl- (130) or tert-butyl dimethylsilyl chloride under standard conditions (147) provided the 3'-O-silyl ethers 27 and 27a in yields greater than 70% (Scheme III-1). The position of the silyl ether was confirmed by acetylation of 27a, which then showed the expected downfield signal corresponding to H-2' (27b). As will be seen, subsequent reactions also confirm the position of the free hydroxyl group at C-2'. This selectivity was an unexpected advantage gained in using a disaccharide instead of a monosaccharide as a start-



27 R = TBdPS

27a R = TBdMS

27b R = TBdMS

2'-OAc

28, 28a X = O

29, 29a X = NOH

30 R = Ac

31 Manno isomer

R = Ac

Scheme III-1. Introduction of a 2'-amino-2'-deoxy group through reduction of a 2'-oxime intermediate.

ing material. The same reaction with methyl 4,6-O-benzylidene- α -D-glucopyranoside, for example, provides a mixture of tert-butyl dimethylsilyl derivatives in a 3:2 ratio of O-2:O-3 (148).

These promising results were moderated by the realization that the silyl groups are not stable to vigorous acidic hydrolysis, and their bulk would surely lower reactivity at OH-4'. Although a more durable protecting group for this position should be advantageous, the synthetic sequence outlined in Scheme III-1 was pursued further with the silyl ethers. Both groups were used, with similar results. In general, the tert-butyl diphenylsilyl group was more stable during the oxidation step, but was poorer yielding in the blocking stage, and required higher temperatures or longer reaction times.

The oxidation of OH-2' to the ketone, which is straightforward in principle, was not so on a preparative scale. Although the number of suitable oxidation reagents are many (149,150), a few criteria had to be met. Both the O-isopropylidene and the O-silyl group are sensitive to acidic conditions, and the latter group also is sensitive to basic conditions, and a possibility of migration from OH-3' to OH-2' (151). In addition, the large scale preparation of these materials early in the synthetic sequence required experimental techniques of practical utility. The chromium VI-heterocyclic base oxidants, such as pyridinium dichromate (152) and pyridinium chlorochromate (143), which have been widely effective as reagents in carbohydrate chemistry (150), were selected for examination.

Oxidation of silyl ether 27a (Scheme III-1) with PCC adsorbed on alumina (153) in refluxing benzene was moderately successful. The adsorbed reagent is not strongly acidic, and recovery of the product presumably requires only washing of the adsorbent with a suitable solvent. However, in the present study, inefficient mixing of the heterogeneous system, and difficulty in recovering all of the carbohydrate material, reduced yields in large scale runs. It was not known whether the starting material was degraded through cleavage of O-isopropylidene groups or simply adsorbed onto the alumina too strongly to resist extraction with chloroform or ethyl acetate. Use of a buffered mixture of powdered PCC in benzene (143) gave similar results. Finally, PDC with acetic anhydride in methylene chloride (154) proved to be the most convenient reagent, although yields remained at 70 - 80%. Isolation of the ketone chromatographically was complicated by the presence of a polar gem-diol form.

The ketones (28, 28a) were characterized by ^1H and ^{13}C -n.m.r (Tables III-1 and III-2). A downfield singlet corresponded to H-1' and a doublet, also shifted downfield from the starting material, was assigned to H-3'. The ^{13}C spectrum clearly showed a signal at 197.4 ppm corresponding to the C-2' carbonyl. C-1' also was shifted downfield, characteristic of protons α to a carbonyl (154a). Reaction of the ketone with hydroxylamine (155) afforded the 2'-deoxy-2'-oxime derivatives, 29 and 29a (Scheme III-1), with no loss or migration of the silyl group. The oxime was characterized by the H-1' singlet, now shifted further downfield to ~ 6 ppm, and the imine carbon (C-2') at 154 p.p.m.

Table III-1: ^1H -n.m.r. Chemical Shifts (δ) and ^1H - ^1H Coupling Constants (^3J) for Compounds 27 - 29a

Compound	27	27a	27b	28	28a	29	29a
H-1'	5.02 (3.9)	5.05 (3.7)	5.10 (3.7)	5.03 (s)	5.04 -	6.11 (s)	6.14 (s)
H-2'	3.5- 3.8	- -	4.82 (9.7)	- -	- -	- -	- -
H-3'	3.5- 3.8	- -	- -	4.50 (10.0)	4.47 (10.0)	4.60 (9.3)	4.53 (8.4)

Table III-2: ^{13}C -Chemical Shifts (δ) for Compounds 27 - 29

Compound	27	28	29
C-1'	100.95	102.12	99.37
C-2'	73.8- 74.2	197.38	153.87
C-3'		76.95	71.28

An oxime can exist as E- or Z-isomers. One can establish the orientation of its hydroxyl group in substituted six-membered rings, by examining the deshielding effect of the hydroxyl on adjacent equatorial hydrogens. That is, in the ^1H -n.m.r. spectrum of cyclohexanone oxime, two signals for the flanking equatorial hydrogens are visible (156). In derivative 29a, the only equatorial hydrogen is H-1', which is deshielded by ~ 0.8 p.p.m. upon oxidation. This large shift suggests that the oxime is in the Z-configuration, with the hydroxyl cis to C-1'. A space-filling model shows that this orientation reduces interaction with a bulky group on O-3'. If the E-configuration were present, H-1' would be expected to shift by only ~ 0.3 p.p.m. (156).

The oxime was then reduced with lithium aluminium hydride (37), giving a mixture of products, which, after acetylation and purification provided both the axial, α -D-manno 2'-acetamido-2'-deoxy isomer (31), and the desired equatorial α -D-gluco 2'-acetamido-2'-deoxy isomer (30) in approximately a 2:3 ratio. The 3'-O-silyl group had also been cleaved, and hence OH-3' had been acetylated during the subsequent processing. Although little stereoselectivity was expected with this reagent (37), its use stemmed more from lack of success with other reagents than by choice. (A more comprehensive discussion of the reduction of the oxime, and various derivatives of it, can be found later in this chapter, Section III.4).

The two diacetates were identified by ^1H -n.m.r. spectroscopy. Characteristic of both compounds were the expected singlets corresponding to the acetyl methyl groups and a doublet at ~ 6 p.p.m. attributed

to the -NH of the acetamido group. The gluco and manno assignments were based on the coupling constants of the anomeric H-1' and the downfield dd corresponding to H-3' (see Table III-3, Figure III-1).

For the gluco isomer 36, H-1' is a doublet with $J_{1',2'} = 3.7$ Hz, as found in the starting maltose compound (2), whereas the dd for H-3' has values $J_{3',2'} = J_{3',4'} = 9.5$ corresponding to the trans-diaxial proton arrangement found in the D-gluco series. By contrast, the spectrum of the manno isomer (35) shows a doublet for H-1' with a $J_{1',2'} \sim 1.6$ Hz. Also, the dd for H-3' has two coupling constants: a small $J_{3',2'} = 4.5$ Hz for the equatorial - axial arrangement of H-2' and H-3', and the expected diaxial $J_{3',4'} = 10.2$ Hz. Other differences in the spectra include the chemical shifts for H-2'; the equatorial proton of the manno derivative is ~ 0.4 p.p.m. downfield to the axial gluco H-2', consistent with general chemical shift patterns (157). An interesting aspect of the reduction was the complete loss of the 3-O-silyl ether. It is known that silyl - oxygen bonds can be reductively cleaved (158), but the silyl protecting groups used here are thought to be stable to lithium aluminium hydride reduction (17). Silyl protecting groups also can migrate under basic conditions (151), and so it is possible that the group was cleaved from the oxime, or one of its reduced intermediates, after migration (see Scheme III-2). Migration most probably occurred late in the reduction process, with formation of a silyl - amine bond. It will be seen in section III.4 that similar results were obtained with methylated oximes, so that migration to the oxygen atom, even with an intermediate hydroxyl amine, is unlikely.

Table III-3: ^1H -Chemical Shifts (δ) and ^1H - ^1H Coupling Constants (Hz) for 2'-Acetamido-2'-deoxy-glucoside (30) and mannoside (31) Derivatives

Compound	H-1'	δ		H-3'	1,2	^3J	
		H-2'	H-2'			2,3	3,4
<u>30</u>	4.98	4.35	4.35	5.12	3.7	9.5	9.5
<u>31</u>	4.97	4.72	4.72	5.20	1.6	4.5	10.2

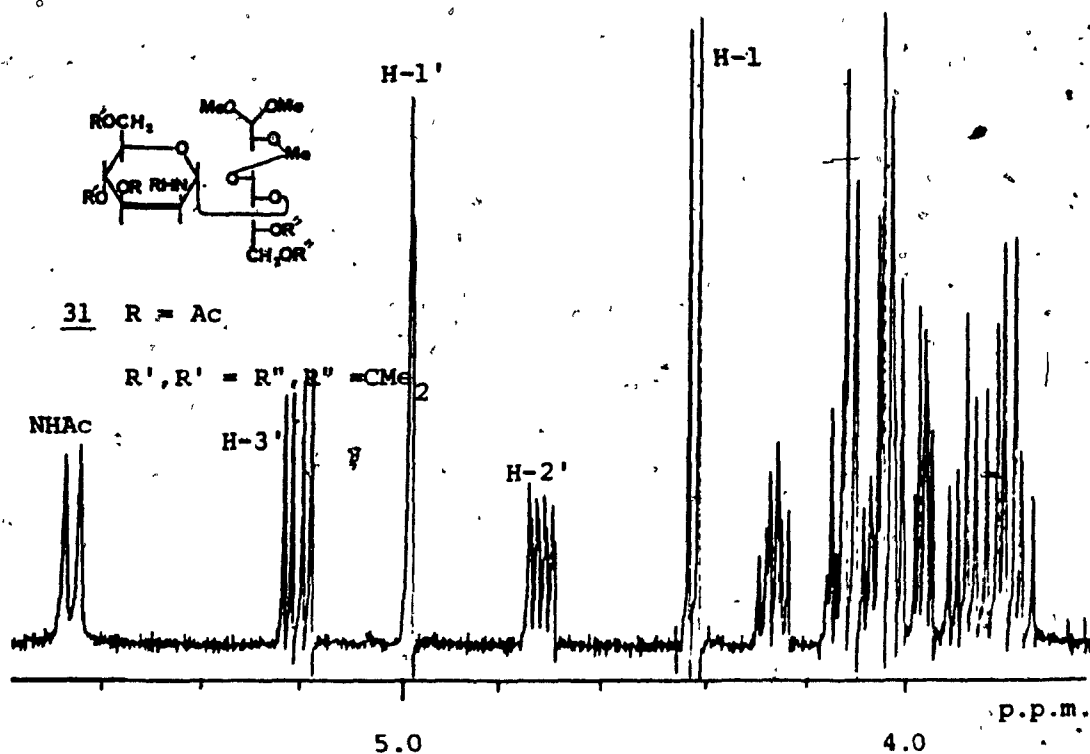
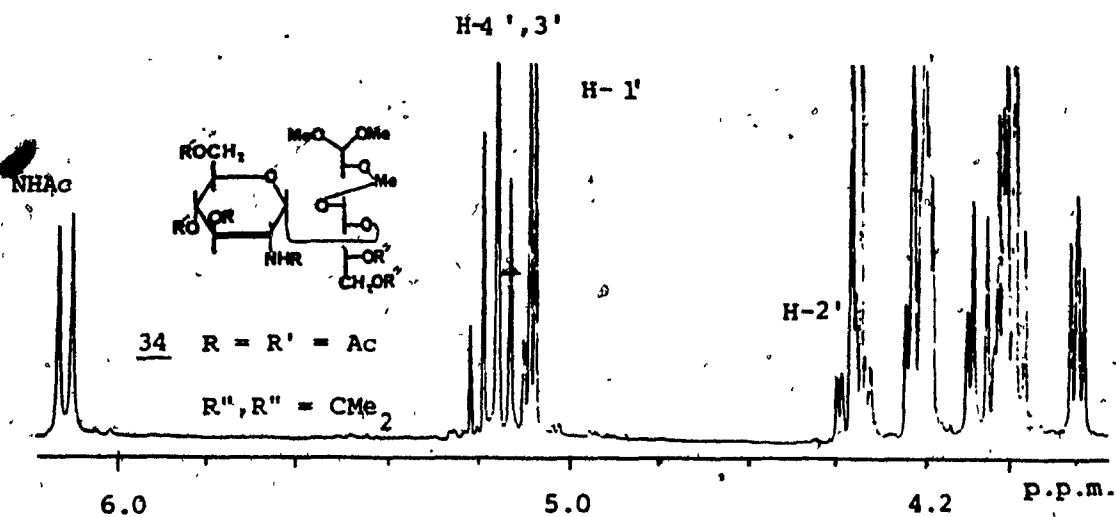
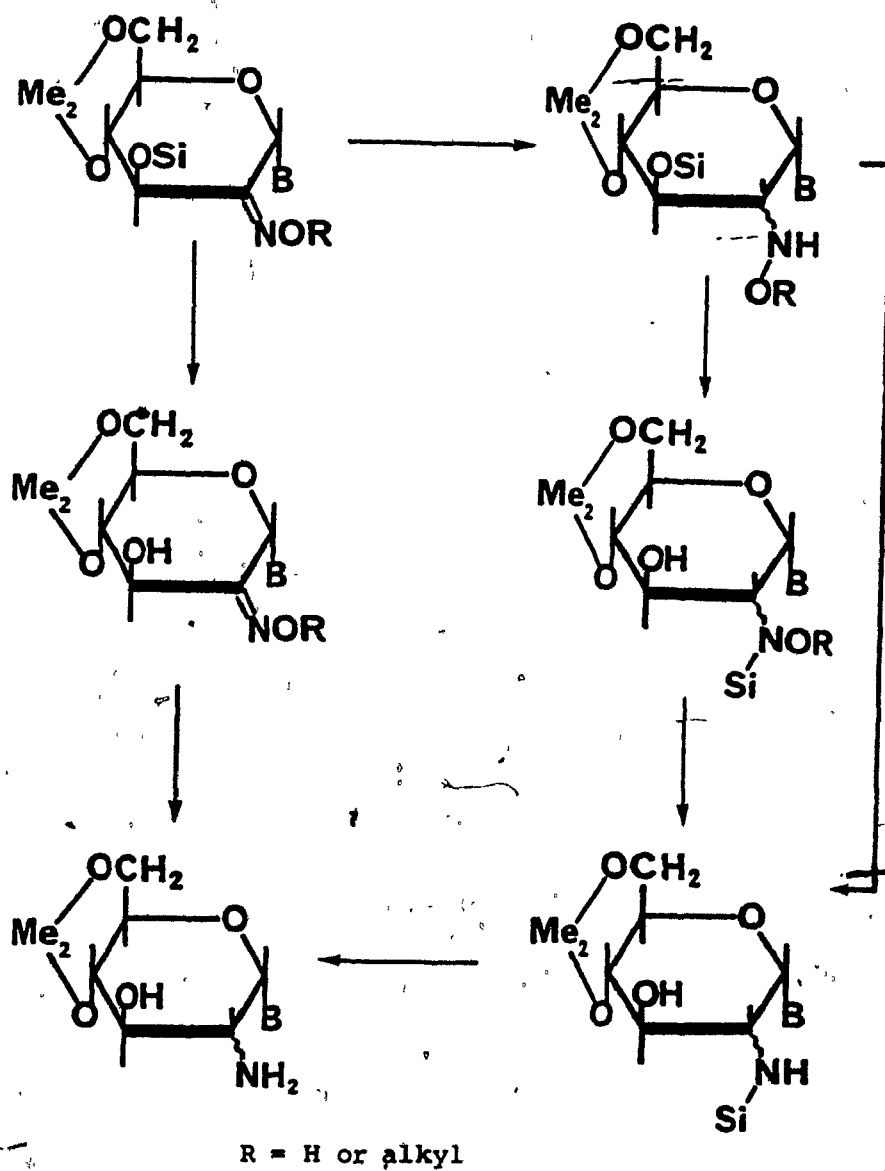


Figure III-1. ¹H-n.m.r. spectrum of 2'-acetamido-2'-deoxy-α-D-glucose (34) and -D-manno (31) derivatives.



Scheme III-2. Possible routes of silyl group cleavage during the reduction of the 2'-oxime-2'-deoxy intermediates.

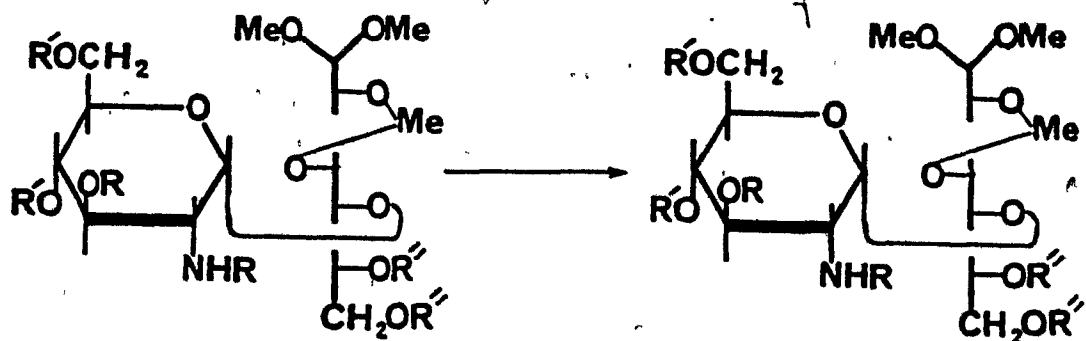
III.3 Combining the formation of the 2'-amino-2'-deoxy intermediate with conversion into the L-ido configuration

At this stage, it was thought pertinent to combine the two methods discussed here, and earlier in section II.2, in order to introduce both the 2'-amino and L-ido modifications into one disaccharide.

As mentioned in the discussion of general strategy II, the formation of target disaccharides 3 and 5 (Schemes II-2 and II-3, pp. 27, 28) containing L-ido sugars, requires selective exposure of OH-5 and -6. To do this with intermediate 30, Scheme III-3, first requires a selective hydrolysis of the 4',6'-O-isopropylidene group, followed by reprotection of OH-4' and -6'.

The 4',6'-O-isopropylidene ring is formed only under kinetic acetonation conditions (159) owing to the thermodynamic instability arising from an axial C-methyl group. The order of lability towards acid hydrolysis is reflected in the relatively greater stability of 1,3-dioxolane than of 1,3-dioxane type rings, leading to the expectation that the 4',6'-O-isopropylidene group can be removed selectively (11).

Although mild acid conditions gave mixtures of products having lost either one (32) or two (33) O-isopropylidene groups (Scheme III-3), the major product was the desired one (32). It was isolated, and acetylated to give 34, the structure of which was confirmed by its doublet of doublet resonance corresponding to H-4' having been shifted downfield into the anomeric region. The 5,6-O-isopropylidene group was then hydrolyzed under the slightly stronger acidic conditions used



30 $R', R'' = R'', R'' = Me_2C$

32 $R' = H, R'', R'' = Me_2C$

33 $R' = R'' = H$

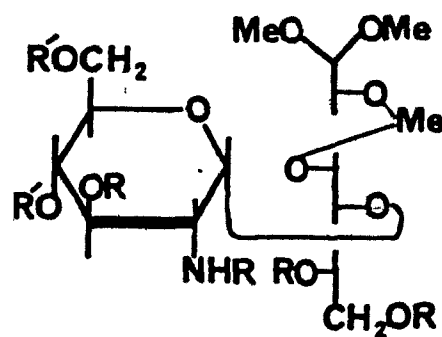
34 $R' = Ac, R'', R'' = Me_2C$

35 $R' = Ac$

$R'' = OH$

37 $R' = R'' = Ac$

$R = Ac$



36 $R = R' = Ac$

Scheme III-3. Formation of a disaccharide having both a 2'-amino-2'-deoxy function and the L-ido configuration at the reducing end.

earlier (p.35) to obtain diol 35. Its ^1H -n.m.r. spectrum clearly showed only one remaining isopropylidene group. The diol was then converted into the dimesylate, as before, and diacetate 36 was then formed by inversion with potassium acetate. The product, believed to have the L-ido configuration, was compared by ^1H -n.m.r. spectroscopy to a D-gluco diacetate (37), obtained after direct acetylation of 35. Both spectra were compatible with the assigned structures (Fig. III-2). In addition, the same pattern of coupling constants was observed for the L-ido/D-gluco pair, as already seen for compounds 15 and 17, and 15a and 17a. That is, $J_{4,3} = 7$, $J_{4,5} = 1.7$ Hz for the D-gluco isomer, whereas $J_{4,3} = 2.5$ and $J_{4,5} = 5.2$ Hz for the L-ido isomer (see also Table II-3, p.59).

III.4. Improvements in the reduction of 2'-deoxy-2'-oxime derivatives

It has been clearly shown in the earlier sections of this Chapter, that the introduction of the 2'-aminodeoxy group and the L-ido configuration were possible. However, there remained an investigation into increasing the efficiency of such reactions as the reduction of the imine. In addition, suitable blocking groups were needed to eventually obtain an intermediate capable of being oxidized at OH-6 to an uronic acid derivative. In the following sections of this chapter, the formation of this intermediate is explored.

The relatively low yield of the equatorial D-gluco epimer in the lithium aluminium hydride reduction of the 2'-deoxy-2'-oxime (29a)

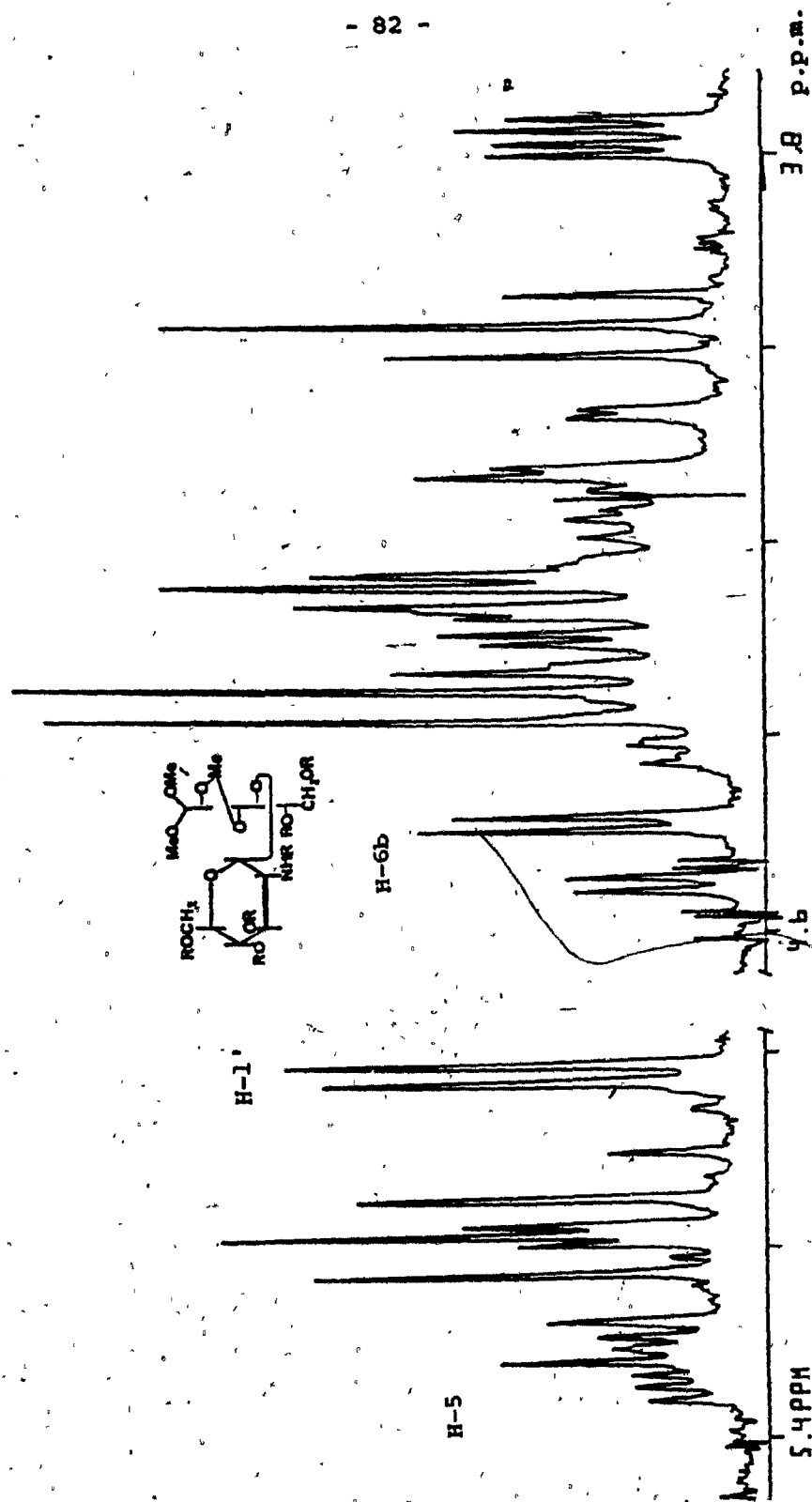


Figure III-2. $^1\text{H-NMR}$ spectrum of a 2'-acetamido-2'-deoxy-L-ribose derivative (36; R = Ac).

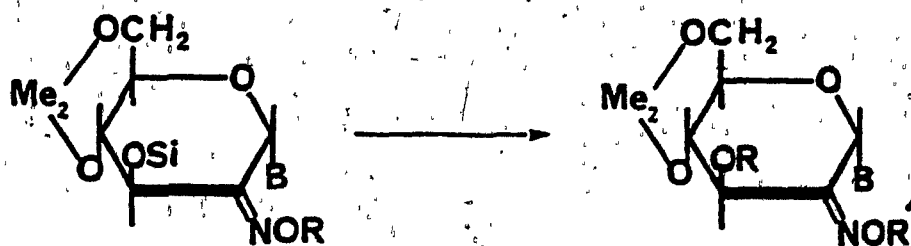
(Scheme III-1, p.70), prompted further investigation. In a series of papers on reduction of oximes and their derivatives, Lemieux and coworkers (36,37) successfully used three methods: hydrogenation over palladium in the presence of hydrazine, diborane, and lithium aluminium hydride. They found that the first two reagents showed appreciable stereoselectivity with most of the 2-deoxy-2-oximino- α -D-arabino hexopyranosides studied.

All three methods were tried with oxime 29a (Scheme III-1). Hydrogenation under the specified conditions gave no reduced products after 24 h. Probably, access to the imine double bond was restricted by both the neighbouring aglycon and the 3-O-silyl ether.

Experiments with borane - tetrahydrofuran complex also were unsuccessful: an N-O-acetylated derivative, when combined with excess reagent, showed no reaction. With more forcing conditions, using concentrated solutions and heating, mixtures of products were obtained (t.l.c. and ^1H -n.m.r. evidence).

In order to simplify the system and see if the 3-O-silyl ether was impeding the reduction, a series of derivatives was prepared, after removing the silyl group (Scheme III-4).

The 3'-O-silyl derivative (29a) gave the 3'-hydroxyl product (38) easily after treatment with fluoride ion (147), and no isomerization was detected. A similar treatment of the corresponding ketone gave mixtures of products (160). Then, acetylation provided 39, which clearly showed the two acetyl methyl signals as well as a downfield doublet corresponding to H-3'.



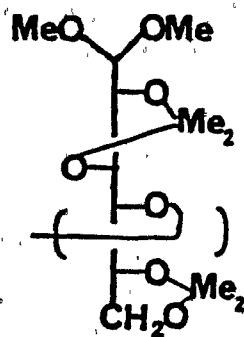
29 R = H, Si = TBdMS

38 R = R' = H

39 R = R' = Ac

40 R = H, R' = Bn

41 R = R' = Bn



(B)

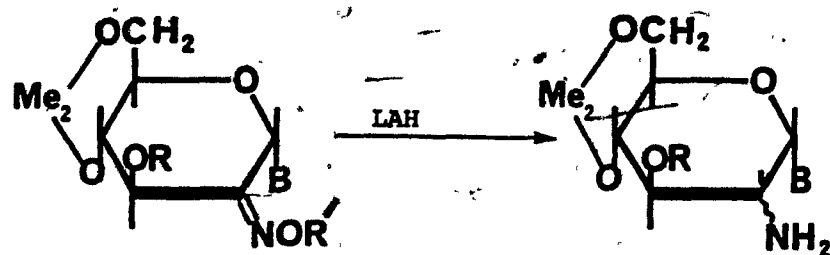
Scheme III-4. Removal of the 3'-O-TBdMS group and formation of oxime derivatives.

Benzylation of 38 also was carried out, for a number of reasons. The general strategies discussed earlier call for an alkyl group as opposed to an acyl group at OH-3' to provide sufficient reactivity at OH-4 during glycosidation at a subsequent stage. The exposure of OH-3 at this stage provided a convenient opportunity to O-benzylate without fear of alkylating the amino group at a later stage. In addition, the stability of oximes to acid hydrolysis is increased by alkylation (161), a useful property if reduction is postponed until after cyclization of the reducing end to the pyranose. The synthesis of 41 proceeded in two steps, as described in the Experimental section. First, monobenylation (40) of the oxime occurred, followed by formation of the dibenzyl compound (41) after more vigorous treatment. The =N-O-benzyl is freely rotating, as shown by a singlet in the ¹H-n.m.r. spectrum, whereas the 3'-O-benzyl has the customary AB quartet for the methylene protons.

These three compounds (38, 39, 41) were then subjected to reduction with lithium aluminium hydride (LAH), as well as borane-THF, superhydride, and sodium borohydride. The reduction of 38 and 39 with LAH gave the same results as the starting compound 29a, i.e., a ~ 3:2 ratio of gluco to manno amines in an overall yield of ~ 60%. The use of borane with 39 produced little reaction: in addition to starting material, the reaction mixture contained small amounts of polar compounds that did not correspond on t.l.c. to the amino compounds 30 and 31 prepared from the LAH reduction (Scheme III-1, p.68). Similar experiments with sodium borohydride and superhydride showed no reaction.

The dibenzyl compound 41 also was unreactive to treatment with the borane-THF complex, but gave interesting results with the LAH reduction (Scheme III-5). Although the reaction proceeded incompletely, giving a mixture of products, and the desired 2'-amino-3'-O-benzyl-2-deoxy compound (42) in low yield, it appeared that the gluco isomer was the only one formed. Another product, after acetylation, was diacetate 30 (see Scheme III-1, p.70), indicating that cleavage of the 3-O-benzyl group had occurred and, again, a preponderance of the gluco isomer of 43 was formed. It is known that LAH will cleave benzyl ethers, but generally as a complex with aluminium chloride and under vigorous conditions (158). What was most interesting, was the increase in the relative yield of the gluco isomer.

The reasons for this change are not immediately apparent, because the compound has been altered in a number of ways. The reduction was repeated with the monobenzylated compound (40), having a free OH-3', and similar results were obtained: an isolated gluco to manno 2'-amine ratio of ~ 10:1 (43). Assuming that the change in the substitution on OH-3' was less important than the alkylation of the oxime, derivatives 44 and 44a were prepared by methylation with iodomethane and sodium hydride or barium oxide as a base (Scheme III-5). They were identified by ¹H and ¹³C-n.m.r., both of which showed the added singlet corresponding to the methyl group. Reduction of this compound gave results -- similar to the reduction of benzyloxime 40. Both of the 2'-amino-2'-deoxy epimers were isolated, but with the greater gluco to manno ratio (~ 10:1) than found with the non-alkylated oxime. As before, the 3-O-



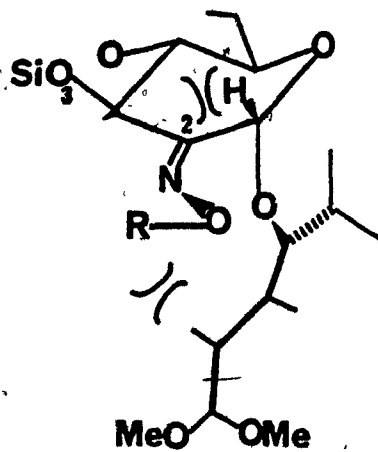
			gluco/manno
<u>41</u>	R = R' = Bn	<u>42</u>	R = Bn ~ 10
<u>40</u>	R = H, R' = Bn	<u>43</u>	R = H ~ 10
<u>44</u>	R = TBdPS, R' = Me	<u>43</u>	~ 10
<u>44a</u>	R = TBdMS, R' = Me	<u>43</u>	
<u>29</u>	R = TBdMS, R' = H		~ 1.5

Scheme III-5. Reduction of some 2-deoxy-2-amino derivatives showing increased gluco configuration.

silyl group was lost (see section III.2, p.67). That is, the type of silyl group on O-3 did not affect the outcome of the reaction.

These differences in stereoselectivity between the two compounds, 29 and 44, differing only in the presence of the methyl group, are not readily explained. As mentioned in the introduction to this chapter, reduction of the 2'-oxime in an α -glycoside naturally favours the cis amine because the approach or coordination of the reducing species is hindered by the axial aglycon (37). This stereoselectivity also applies to the reduction of the corresponding ketone (162). In the D-glucose series, the 1,2-cis amine also means the thermodynamically favoured equatorial group. Despite these factors, in Lemieux's work LAH shows very little selectivity in comparison to the borane. Presumably this is due to the greater reactivity of the LAH and also possibly the smaller size of the aluminium hydride reducing species.

If the size of the aglycon is a factor in preventing approach from the α -face, then the maltose derivatives discussed here should really exhibit greater selectivity than for a simple methyl α -glycoside. This is observed, however, only for the alkyl oxime. If one considers a model of the oxime (Fig. III-3, upper drawing), having the hydroxyl group cis to C-1', it is clear that any group R will prefer a position between H-1' and the acyclic aglycon below the plane of the pyranosyl ring. For example, the benzyl group in compound 40 (Scheme III-5, R = Bn), shows a singlet for the methylene protons, indicative of free rotation. This can occur only if the N-O bond of the oxime is rotated within this area, as shown.



$\text{R} = \text{Me or AlH}_3$

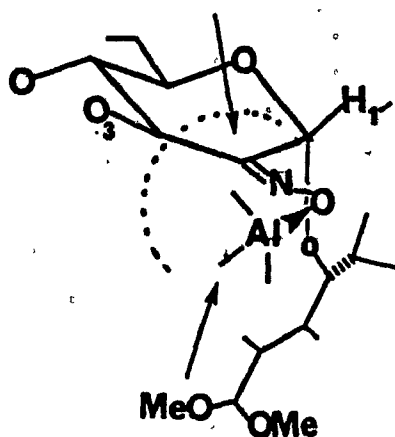


Figure III-3. The proposed effect of oxime substitution on the stereo-selective outcome of its reduction.

In the first stage of the oxime reduction, this R group would be a charged aluminum hydride species bonded to the oxygen. One might predict that the approach, or complexation, of a second reducing species would be hindered due to electrostatic, as well as, steric repulsion (lower drawing, Fig. III-3). If group R is close to H-1', for example, away from the bulky aglycon, the approach of a second aluminum hydride complex from above would be hindered, and hence the formation of the equatorial D-gluco isomer less probable. Thus, the expected interference from below by the α -aglycon is countered by an interference from above.

Another way of viewing the situation, is that a reducing species complexing from below can rotate the aluminium complex upward with less hindrance than in the converse case. In addition, the reduction to the equatorial hydroxyl amine intermediate, although normally more stable, might cause steric interactions between the large aluminium complex and the aglycon. If R is an alkyl group, however, the smaller size, which makes access to a position close to the aglycon more probable, and the lack of electrostatic repulsion towards an incoming aluminium hydride complex, makes its presence less critical. In this case, the prevention of complexation and hydride attack from below due to the α -aglycon again becomes the dominant factor.

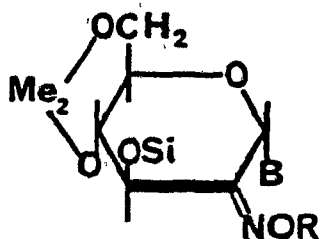
Though this rationale was not tested, with different alkyl oximes, for example, the results from Lemieux et al (37) are consistent. With free oximes, they found that the borane reduction shows only moderate selectivity; a 7:3 gluco to manno isomeric ratio, whereas with

acetoximes (although unsuitable here), the ratio of gluco isomer markedly increased to, 19:1. The O-acetyl group would prevent the formation of an O-borohydride complex, and similar arguments would then apply.

III.5 The synthesis of a 3'-O-benzyl-2'-acetamido-2'-deoxy intermediate

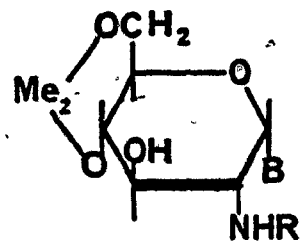
The final strategy adopted for obtaining the desired intermediate 2'-amino-2'-deoxy compound was through the reduction of a methyloxime, followed by the protecting scheme outlined in Scheme III-6. Methyloximes, (44 and 44a) are available either through methylation of an oxime (161), or directly from the ketone by reaction with methoxylamine (40).

Reduction then provided the mixture of amines (43), as described earlier. Because it was desirable to have OH-3 selectively blocked with an O-benzyl group (see previous discussion), the mixture was acetylated in an alcoholic solution in order to protect only the amino function. The two isomers were separated chromatographically at this stage. As with the diacetyl compounds (30 and 31, Scheme III-1, p.70) obtained earlier, the acetamido compounds were characterized by n.m.r. spectroscopy (Tables III-4 and III-5). The gluco isomer showed the doublet for H-1' with the characteristic value $J_{1',2'} = 3 \text{ Hz}$, whereas the equivalent signal for the manno isomer was a singlet, showing $J_{1',2'} < 1 \text{ Hz}$ for this equatorial - equatorial system. The ^{13}C spectra



44a Si = TBDMS, R = Me

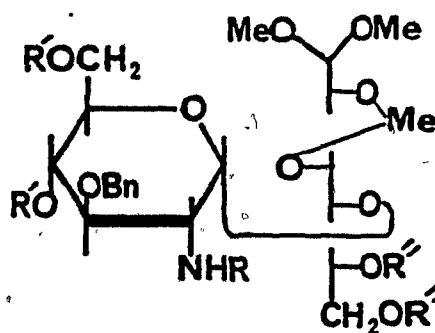
44 Si = TBDPS, R = Me



43 R = H, gluco, manno mix

45 R = Ac

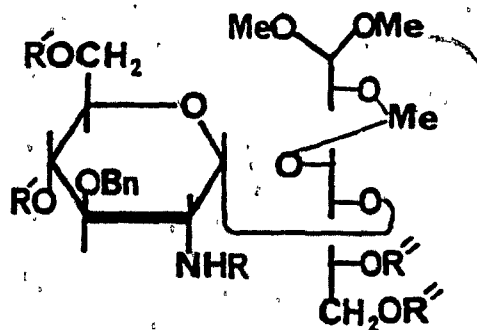
46 R = Ac, manno isomer



47 R = Ac, R', R'' = Me₂C

48 R = Ac, R' = H, R'', R''' = Me₂C

49 R = Ac, R' = R'' = H



50 R = Ac, R' = allyl, R'', R''' = Me₂C

Scheme III-6. Final strategy for reduction of oxime and protection of the 2'-amino-2'-deoxy pyranosyl residue

Table III-4: ^1H -Chemical Shifts (δ) and ^1H - ^1H Coupling

Constants (Hz) for Compounds 44 - 50

Compound	H-1' ($J_{1,2'}$)	H-2' ($J_{2,3'}$)	H-3' ($J_{3,4'}$)	H-4' ($J_{4,5'}$)	H-5'	H-6a' or 6b'
<u>44</u>	6.11s -	- -	4.55d (9.0)	3.7 - 3.95 -	-	~3.7 -
<u>47</u>	4.90 (3.9)	4.28 (7.0)	3.49 (8.3)	-	3.73-3.84 -	- -
<u>48</u>	5.01 (3.6)	~4.24 (10.7)	3.57 (8.6)	(3.67) 3.75	3.7 - 3.8 -	-
<u>50</u>	4.92 (3.7)	~4.2 (10.3)	3.58 (9.7)	~3.6* -	~3.8* -	~3.7* -

* Tentative assignment

Table III-5: ^{13}C -Chemical Shifts (δ) for Compounds 44, 47 - 50

Compound	44	47	48	49	50
C-1	105.49	105.77	105.65	105.73	105.09
C-2	74.14	76.95	-	-	76.29
C-3	76.30	78.85	78.55*	-	78.40
C-4	78.45	80.45	79.63*	82.93	80.60
C-5	76.34	75.55	-	-	75.25
C-6	65.86	66.62	65.51	63.41	66.73
C-1'	99.34	101.17	99.98	101.08	100.73
C-2'	152.13	52.70	52.37	52.87	52.52
C-3'	71.20	76.56	-	-	79.56
C-4'	75.69	75.55	-	-	78.03
C-5'	62.04*	62.53	-	-	71.55
C-6'	64.02*	64.52	62.39	62.37	68.25
CMe ₂	92.58	99.72	-	-	-
	108.42	109.09	108.76	-	108.94
	109.58	110.79	110.40	110.90	110.57
Other	61.92	73.81	73.84	73.64	74.69
	(=NOMe)	(PhCH ₂)	(PhCH ₂)	(PhCH ₂)	(PhCH ₂)
	-	-	-	-	72.47
	-	-	-	-	73.71
	-	-	-	-	(silyl)

* Tentative assignment

of these compounds also clearly showed a signal upfield, at $\sim \delta$ 52, assigned to the 2'-acetamido-2'-deoxy carbon.

Benzylation of OH-3 (47) proceeded in moderate yields. Under some conditions, other products were observed, presumably due to competitive benzylation of the acetamido nitrogen (163). The 3-O-benzyl substitution was confirmed by the characteristic aromatic singlet and AB quartet of the benzylic methylene protons at $\sim \delta$ 4.5. A broad singlet in the spectrum of 45, corresponding to the hydroxyl resonance, disappeared, and H-3' was observed at high field ($\sim \delta$ 3.5), characteristic of O-benylation. Analysis of coupling constants revealed a large $J_{4,5}$ (6.1 Hz) and a smaller $J_{4,3}$ (2.9 Hz) contrary to the results seen for the similar 5,6-diacetate derivatives discussed earlier (section II.6, p.53). The signal for H-2' also is characteristic in showing a ddd structure, due to coupling to H-1', -3' and the NHAc proton, and the value of these couplings did not seem to change with changes in OH-3 substitution.

The ^{13}C spectrum of 47 (Table III-5, Fig. III-4), also was analyzed, by 2-D heterocorrelated spectroscopy and included signals for the aromatic and methylene carbons of the benzyl group. The C-2' acetamido signal is again upfield, as is that of C-5', which resonates at a field lower than the two primary carbons, C-6 and C-6'. This upfield shift is observed for carbons α to one that is involved in a 1,3-dioxane type of ring (164). For example, C-2 of 1,3-propylene glycol is shifted upfield by ~ 9 p.p.m. when the diol is blocked with an O-isopropylidene group (154a). Other examples of 4,6-O-benzylidene pyrano-

sides also show this δ -gauche effect-(164). Signal C-4 is the farthest downfield of the ring carbons, as expected for a position involved in a glycosidic linkage. C-1', as an α -anomeric carbon in a pyranose ring (at ~ 100 p.p.m.), is upfield from C-1 (~ 105 p.p.m.), the acyclic anomeric carbon (164). The signals for the three quaternary carbons of the O-isopropylidene groups are separated, with the furthest upfield (99 p.p.m.) corresponding to the 4',6'-O-isopropylidene ring. The other two signals in the anomeric region belong to the quaternary carbons of the five-membered dioxolane acetals which show characteristically deshielded values relative to their six-membered ring counterparts (164).

III.6 Protection of the glycosyl group

The next stages in the route toward such target compounds as 5 (Scheme II-3, p.28), involved the application of methods developed in Section III.3 (p.79). That is, a sequence of selective removal of the O-isopropylidene groups would expose OH-5 for inversion to the L-ido configuration.

Selective cleavage of the 4',6'-O-isopropylidene group gave results similar to those obtained in the sequence discussed in Section III-3 (Scheme III-3, p.79), although some different conditions were tried for improving yields (see Experimental, p.205). It seems that two products (48 plus 49) are inevitable. However, stopping the reaction before completion and recycling the starting material improved overall yields of the desired diol. The major product (48) showed the loss of

one O-isopropylidene group and the presence of a broad singlet at $\sim \delta$ 2.8. corresponding to a hydroxyl resonance. Although the signals for H-4' and H-6' could not be clearly identified, a few features of the proton and carbon spectra supported the loss of the 4',6'-O-isopropylidene group. The benzyl methylene quartet seen for 47, became a singlet, indicating less restriction to rotation. (Interestingly, after a D₂O exchange, the AB pattern returned). In the ¹³C spectrum, the upfield signal of the 1,3-dioxane quaternary carbon had disappeared, and the C-5' signal, upfield in 47, had now shifted downfield by 10.2 p.p.m., as expected.

The second, more polar, product was identified as 49, as its spectra clearly showed the loss of two O-isopropylidene groups. The remaining quaternary carbon of the 2,3-O-isopropylidene group was the signal with the highest value of the three ($\sim \delta$ 110).

Some attempts to differentiate between the 4',6' and 5,6-diols in compound 49, and so recycle this material into the main synthetic route, were unsuccessful. For example, reaction with benzaldehyde and zinc chloride (165) or 2,2'-dimethoxy toluene and p-toluenesulfonic acid (166) produced material in which two O-benzylidene groups had been introduced (¹H-n.m.r. evidence). Another strategy used the property of cyclic carbonates that can only form across 1,2-diols. Heating 49 with ethylene carbonate (167) produced the desired 5,6-cyclic carbonate, although in low yields. However, further alkylations of OH-4' and -6' under basic conditions caused cleavage of the carbonate (17), and gave mixtures of products.

The major byproduct (49) of the synthesis of 48, was then directed towards the cyclic form of strategy II, and formation of gluco type disaccharides 4 and 6, where inversion at OH-5 is not required (see Section IV.2).

The final protection of 48 was achieved by using alkyl substituents as selectively-removable blocking groups. Strategy II, when applied to L-ido disaccharides, required complete blocking of the non-reducing end to allow for subsequent modification solely of the reducing end: inversion, oxidation and cyclization.

The blocking groups had to be resistant to acid hydrolysis, and stable towards such oxidation reagents as catalysts or chromium VI compounds. In addition, it was desirable for these groups to be removed selectively in order to allow for glycosidic linkage formation at OH-4. The use of simple esters was ruled out because of the need to deacylate after the inversion with potassium acetate, in order to oxidize OH-6, or cyclize. Differentiation between OH-4' and OH-3, for example, would be lost at this stage. Many common ether groups that are removable at a later stage are, unfortunately, acid-labile.

The possibility, mentioned earlier, of forming the 4',6'-O-benzylidene acetal, followed by selective reductive cleavage to give the 6-O-benzyl derivative (168) was again considered. However, the conditions needed for the cleavage step are acidic and the stability of the 2,3-O-isopropylidene and dimethyl acetal were in question. Also, a second protection step would be necessary for OH-4'.

Another possibility was to substitute with an allyl halide or form the 2,2,2-trichloroethane derivative, both amenable to selective removal methods (17). Unfortunately, the 2,2,2-trichloroethyl group is only available as the alcohol, suitable as a protecting group at the anomeric center. The allyl group has been investigated by Gigg et al. (169). Its advantage rests in its selective removal in the presence of O-benzyl groups by isomerization to an acid labile O-vinyl group. The double bond and allylic carbon are reactive, however, and can be oxidized with potassium permanganate, ozone and chromium VI reagents under certain conditions (17). Nevertheless, the oxidation conditions that were envisaged, such as catalytic (Pt-C, Pd-C), pyridinium dichromate with acetic anhydride, or Jones reagent, were believed to be compatible with both the double bond and the allylic position (17,170). At least the rates of oxidation under these conditions would be slow in comparison to oxidation of a primary hydroxyl group.

The 4',6'-di-O-allyl derivative 50 (Scheme III-6, p.92) was obtained in moderate yields. Experimental difficulties were observed for large scale reactions, and some over alkenylation, presumably of the amide, reduced yields. Product 50 was characterized by three groups of multiplets in the ¹H spectrum, corresponding to the three types of protons on the allyl group. However, these multiplets became a major drawback in the n.m.r. characterization of the complex carbohydrates, because the allylic protons resonate from δ 3.9 - 4.4 and overlap with many of the sugar ring signals. Also, the terminal protons of the double bond resonate between δ 5.1 and 5.3, often overlapping ring

protons that have been shifted downfield upon esterification, for example (see Fig. III-5).

Other features of the spectrum for 50 included the loss of the broad singlet (hydroxyl) signals and the return of the AB quartet of the benzylic protons, as compared to the singlet observed in 48.

The ^{13}C spectrum also showed the new signals belonging to the two allyl groups; a pair of signals at δ 73 for the allylic carbon, $\sim \delta$ 117 for the terminal carbon, and $\sim \delta$ 134 for the middle carbon of the double bond. In addition to these obvious changes, the C-6' signal had shifted downfield by ~ 6 p.p.m. upon alkylation (Fig. III-4).

III.7 Inversion of the non-reducing unit to the L-ido configuration

The non-reducing end was now completely blocked, allowing for a repeat of the inversion sequence described earlier in Section II.2 (p.35).

The 5,6-O-isopropylidene group was hydrolyzed as before, to the 5,6-diol 51 (Scheme III-7), loss of the acetal group being indicated by the loss of the appropriate methyl signals in the ^1H and ^{13}C spectra. Absence of the quaternary-C signal at δ 108 showed that the low field signal (δ 110) in the spectrum of 51 belonged to the 2,3-O-isopropylidene group. An acetylated derivative (52) confirmed this result, as a downfield multiplet at δ 5.2 in its ^1H spectrum corresponded to H-5 (although overlapped with allyl ^1H signals) (Tables III-6 and III-7). One of the H-6 doublet of doublets was visible, downfield by ~ 1 p.p.m.

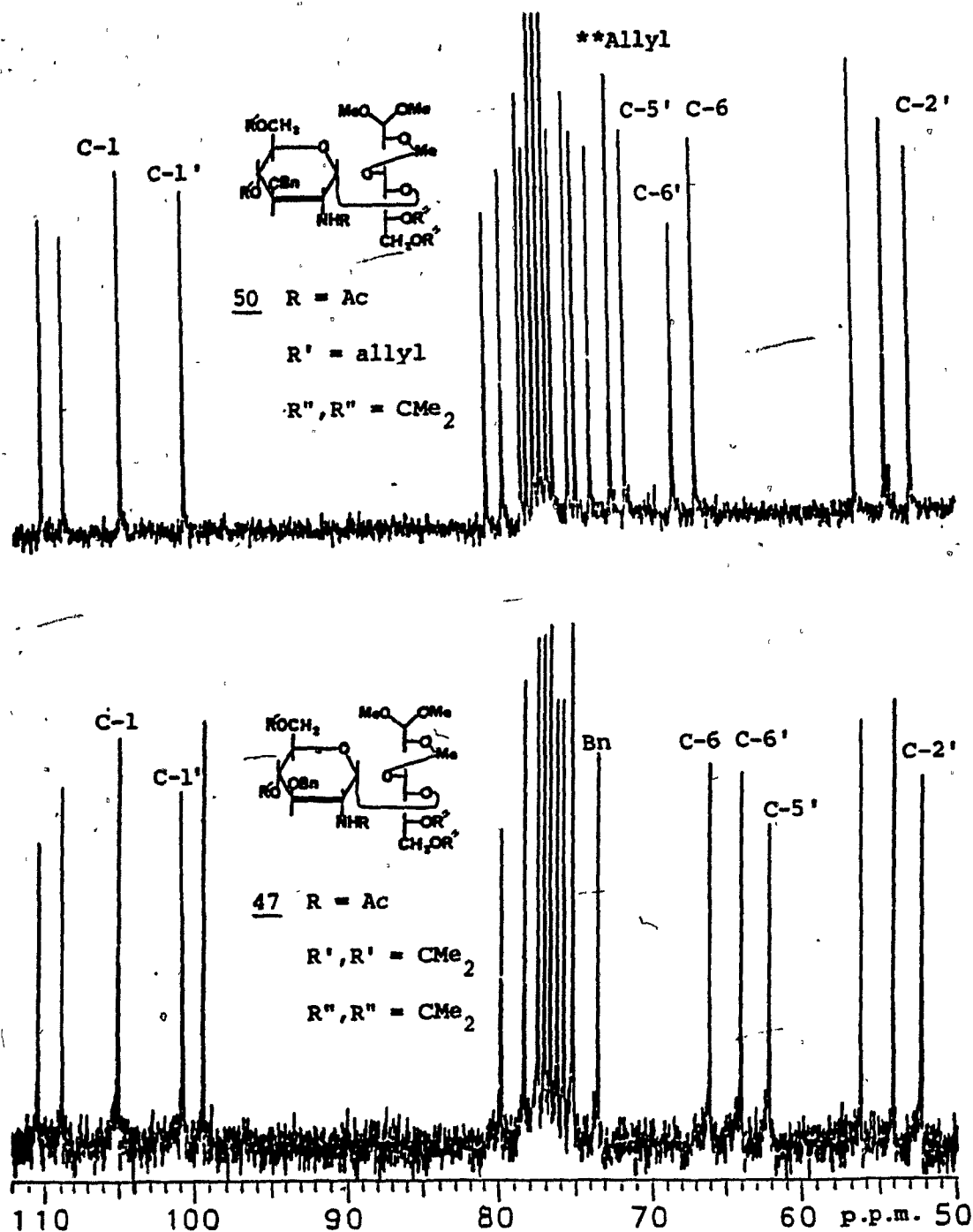
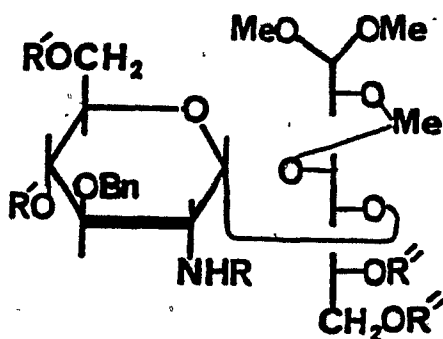


Figure III-4. ^{13}C spectra of 2'-acetamido-3-O-benzyl-2'-deoxy intermediates, 47 and 50.

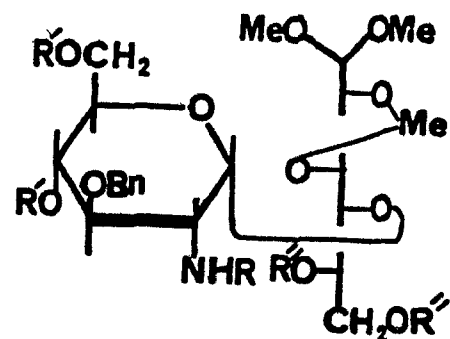
50



51 R = Ac, R' = allyl, R'' = H.

52 R = Ac, R' = allyl, R'' = Ac

53 R = Ac, R' = allyl, R'' = MS



54 R = Ac, R' = allyl, R'' = Ac

55 R = Ac, R' = allyl, R'' = H

Scheme III-7. Inversion of the acyclic moiety at C-5 to give the L-ido configuration.

Table III-6: ^1H -Chemical Shifts (δ) and ^1H - ^1H Coupling (Hz)

Constants for Compounds 51 - 55

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6b}$)	H-6a ($J_{6a,5}$)	H-6b ($J_{6a,6b}$)
<u>51</u>	4.34 (5.9)	3.98 (5.9)	4.27 (4.4)		~4.0- 4.3	~3.3 -	3.8- -
<u>52</u>	4.34 (5.5)	~4.1 -	~4.1 (1.5)*	3.85 (6.6)*	~5.2 (2.4)	~4.1 -	4.46 (12.2)
<u>54</u>	4.30 (6.4)	3.88 (6.4)	4.17 (2.3)	3.72 (5.4)	~5.3 (2.7)	4.29 (7.3)	4.39 (12.6)
<u>55</u>	4.33 (6.0)	3.95 (6.0)	4.28 (3.7)	~3.7* -	(3.8) 3.9	~3.7 (br)	- -
	H-1' ($J_{1',2'}$)	H-2' ($J_{2',3'}$)	H-3' ($J_{3',4'}$)	H-4' ($J_{4',5'}$)	H-5' ($J_{5',6b'}$)	H-6a' ($J_{6a',5'}$)	H-6b' ($J_{6a',6b'}$)
<u>51</u>	4.86 (4.2)	~4.2- 4.34	3.57 (10.3)	3.3- 3.8	3.74- 3.84	~3.3- -	3.8 -
<u>52</u>	4.97 (3.7)	~4.2 (9.3)	3.59 (9.3)	3.67 (9.5)	~3.9 (3.0)	3.6 -	3.73 (10.0)
<u>54</u>	4.94 (3.9)	4.1- 4.2	3.56 (8.8)	3.66 (9.7)	3.82 (2.7)	3.63 (2.0)	3.72 (10.7)
<u>55</u>	4.95 (3.7)	~4.2 (5.1)*	3.56 (5.1)*	~3.5 -	- -	- -	- -

* Tentative assignment

Table III-7: ^{13}C -Chemical Shifts (δ) for Compounds 51 - 55

Compound	C-1	C-2	C-3	C-4	C-5	C-6
<u>51</u>	105.07	77.45	78.51	84.37	72.09	62.98
<u>52</u>	104.79	76.58*	78.49*	80.57	71.94	62.29
<u>54</u>	105.09	76.61	76.70	77.55*	72.04	63.25
<u>55</u>	105.36	77.27	77.54	82.59	71.69	62.25

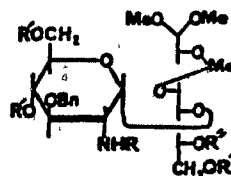
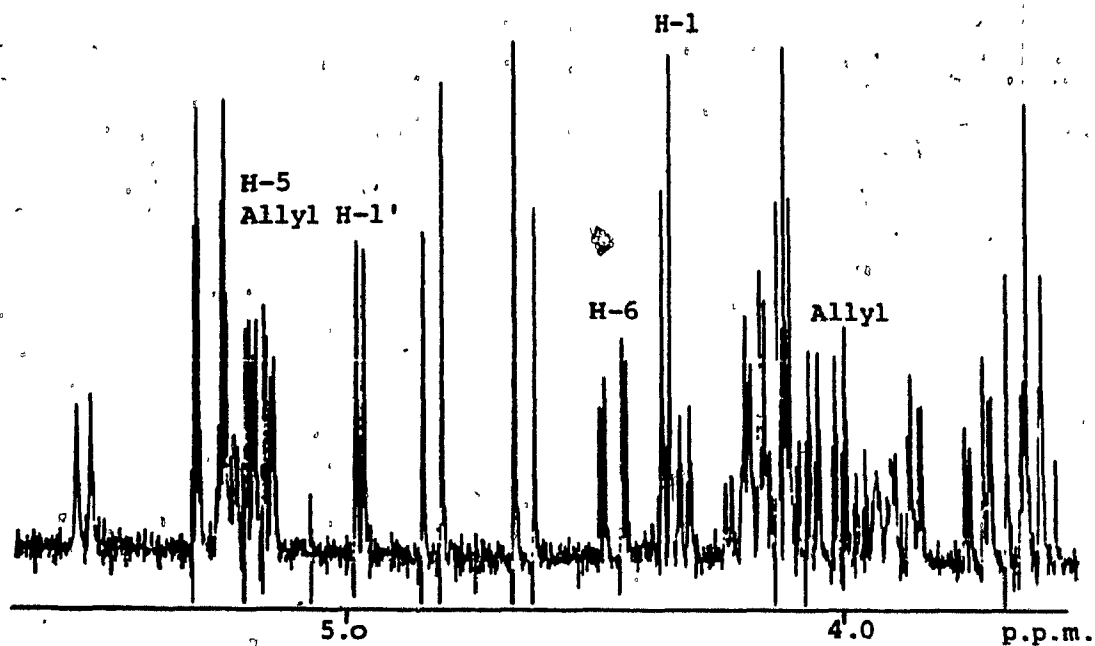
Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
<u>51</u>	101.23	52.64	80.10	78.37	72.53	68.97
<u>52</u>	99.87	52.60	79.42	77.87	72.12	68.33
<u>54</u>	100.76	52.74	79.16	77.89	72.04	68.02
<u>55</u>	100.52	52.66	79.83	78.43	71.96	68.97

* Tentative assignment

from the signal range of H-6 in the diol (51). Signal H-4 also was visible, and showed the characteristic doublet of doublets with large and small coupling constants (6.6 and 1.5 Hz). It was not possible to directly assign these coupling values, because H-5, -3 and -2 did not allow for adequate analysis. Nevertheless, based on the previous results (see discussion in Section II.6, p.53), the assignments were taken to be $J_{3,4} = 6.6$ and $J_{4,5} = 1$ Hz, for this D-gluc configuration (Fig. III-5).

The 5,6-diol (51) was then treated with methanesulfonyl chloride, as described earlier, to form the dimesylate (53). In general, this intermediate was used directly for the next step with only minimal purification. Isolation of a small amount of 53 allowed for its identification by $^1\text{H-n.m.r.}$ spectroscopy, which showed the two methyl signals at δ 3.04 and δ 3.06 and, in addition, that H-5, H-6a, and H-6b were deshielded, as with diacetate 52.

Inversion with potassium acetate under the conditions used previously provided the diacetate (54) with the L-ido configuration. The proton spectrum, when compared to that of 52, again showed significant differences in some chemical shifts and coupling constants. Values of $J_{3,4} = 2.2$ Hz and $J_{4,5} = 5.4$ Hz, correspond to data for other L-ido compounds and is consistent with the earlier analysis (Table II-1, p.37). The ^{13}C spectra also are very similar, with only a major up-field shift for C-4 in the L-ido isomer. Unfortunately, not enough ^{13}C data overall are available to see if this is a general phenomenon.

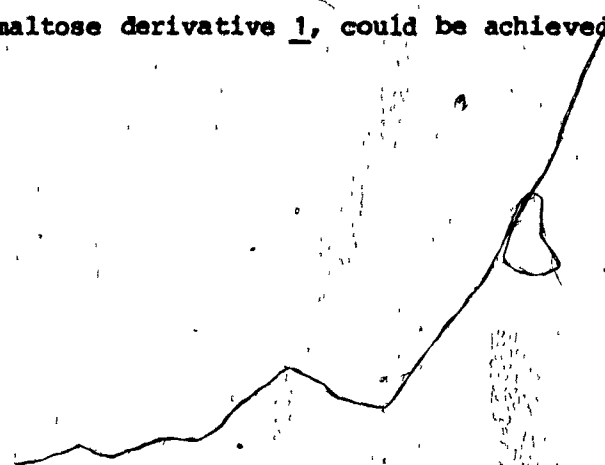


52 R = R'' = Ac, R' = Allyl

Figure III-5. ^1H -n.m.r. spectrum of 4',6'-di-O-allyl protected intermediate 52.

The deacetylation of 54 provided the 5,6-diol (55) suitable for further modification, according to either cyclic or acyclic versions of strategy II.

In conclusion, it has been shown in this Chapter that the first stages of strategy II, that is, the introduction of a 2'-aminodeoxy function into the maltose derivative 1, could be achieved with reasonable stereocontrol.



CHAPTER FOUR

OXIDATION STRATEGIES AND CYCLIZATION OF THE DIMETHYL ACETAL

IV.1 Introduction

The remaining stages in preparing a target disaccharide included the oxidation of C-6 to a carboxylic acid and cyclization of the dimethyl acetal to the pyranose form. It was necessary to assess at which stage the oxidation should be carried out and then choose the most suitable methods and reagents.

The question of whether the oxidation step might be more efficient after subsequent formation of higher oligosaccharides from the neutral disaccharides was left, in practice, until a later date. As discussed in the introduction to general strategy, oxidations were to be explored at the disaccharide level and, presumably, these methods could be applied at the appropriate time to an oligosaccharide. In fact, the strategy based on a late oxidation step has certain advantages. Thus, as Van Boeckel et al. (60) have noted, glycosidic couplings involving uronic acids are lower yielding than those of their neutral counterparts. This observation led them to build disaccharides from neutral monosaccharide units in high yielding coupling reactions, followed by oxidation at the disaccharide stage. Similar reasoning would suggest delaying the oxidation even further, if economical blocking strategies were available.

In addition to being easier to couple, a neutral disaccharide should allow for other practical advantages. For example, uronic acids are subject to β -elimination (171), which can be a problem if basic conditions are used in protection or deprotection steps. Secondly, in some cases where selective oxidation or protection of OH-6 is to be

carried out, the reactive anomeric centre would require protection as a glycoside. Making this glycosidic linkage a permanent one to another sugar unit could reduce the overall number of steps needed in adding and removing a temporary aglycon. Of course, performing only one final oxidation on an oligosaccharide, rather than two or three separate oxidations is advantageous for the general experimental procedure, if yields are adequate. A further discussion, and examples of this approach will be presented in Section IV.5.

The general literature on oxidation in carbohydrate chemistry is quite extensive (150,172), although relatively few reagents are routinely used for the synthesis of uronic acids (173). Most reagents require a single exposed hydroxyl, and therefore a selective blocking strategy. Catalytic oxidation has been very successful in some cases because its selectivity for primary hydroxyls alleviates this problem (133).

As mentioned previously, the use of catalytic oxidation was considered early in the design of synthetic routes towards the uronic acid-containing disaccharides. The main drawback to this method is the wide range of yields, which are dependent on many factors (133).

The catalytic oxidation of oligosaccharides and polysaccharides has not been explored to any great extent, though maltose (103), and an arabinogalactan (174), for example, have produced derivatives containing uronic acids. Whereas the catalytic oxidation of benzyl α -maltoside gives only the aldobiuronic acid (103), methyl α -maltoside (175) gives three products: the two mono-, and the di-carboxylic acid deri-

vatives. In general, the yields were poor, especially for the oxidation of C-6 on the reducing end.

Acyclic sugars also have been selectively oxidized by platinum catalysts with some success (133). This suggested that 5,6-diol intermediates (56, $R=R'=H$, in Scheme IV-1) would be suitable substrates for this method, if OH-6 was sufficiently accessible to the catalyst's surface. This cannot be determined unequivocally by the analysis of the conformation and orientation of the acyclic dimethyl acetal. An examination of models shows that the 6-hydroxymethyl group can assume an orientation which brings it out of the "surface" of the disaccharide. However, it is clearly not a linear acyclic compound with the same planar "zig-zag" conformation as an unsubstituted alditol, for example (see section II.6, p.53).

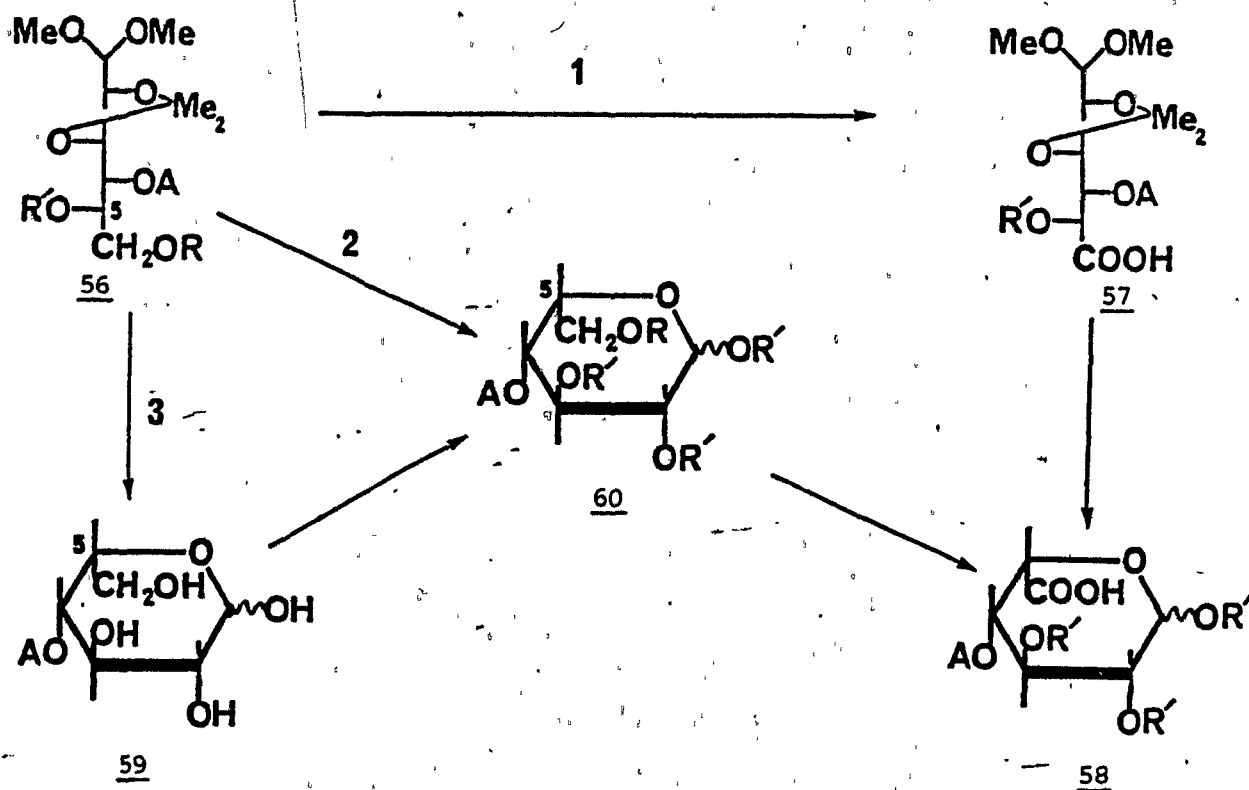
These unpromising indications from the literature led to only a cursory look at catalytic methods with some of the compounds discussed earlier. Also, unencouraging experimental results halted the investigation, perhaps prematurely, as discussed in section II.5.

More conventional oxidizing reagents require selective protection and deprotecting strategies in order to expose the primary hydroxyl group for oxidation. In practice, blocking the primary hydroxyl with a trityl group (176) (or 4-methoxytrityl (177), or 4,4'-dimethoxytrityl (177)) followed by in situ acetylation provides a compound that can be oxidized directly under acidic conditions (e.g., Jones oxidation (132)). Selective removal of the trityl group with dilute acid (178)

or by hydrogenolysis (17) allows for oxidation of the free hydroxyl with common basic or neutral reagents (e.g., potassium permanganate).

The choice of strategies for oxidation of C-6 is outlined in Scheme IV-1, which shows the "acyclic" and "cyclic" versions of general strategy II. Acyclic disaccharide derivatives with OH-5 and -6 exposed (56, R = R' = H) can be oxidized to 57, after a suitable protection scheme, and then cyclized to a pyranose (58), as in route 1. Alternatively, route 3 shows cyclization to a pyranose (59) (or pyranoside), followed by protection (60) and oxidation to the uronic acid (58). A variation is shown with route 2, where OH-6 has been selectively blocked (R) before cyclization, with a stable group that survives the acidic hydrolysis step. A preliminary investigation of route 2 has been presented in Section II.4, p.46. Routes 2 and 3 both provide, in principle, intermediates (60) that can be used in the synthesis of oligosaccharides, and oxidized at later stages. Routes 3 and 1, as methods to obtain disaccharides containing either D-glucuronic or L-iduronic acid, will be discussed in the following sections, respectively.

For the investigation of route 3, the cyclization of the dimethyl acetal is discussed first, followed by the application of conventional blocking group strategy. For the investigation of route 1, experiments on model compounds as well as disaccharides containing 2'-amino-2'-deoxy- α -D-glucosyl residues and L-idose are discussed.



Scheme IV-1. Possible oxidation strategies towards an uronic acid ("A" is an appropriately functionalized pyranosyl residue).

IV.2 Cyclic oxidation route (route 3, Scheme IV-1)

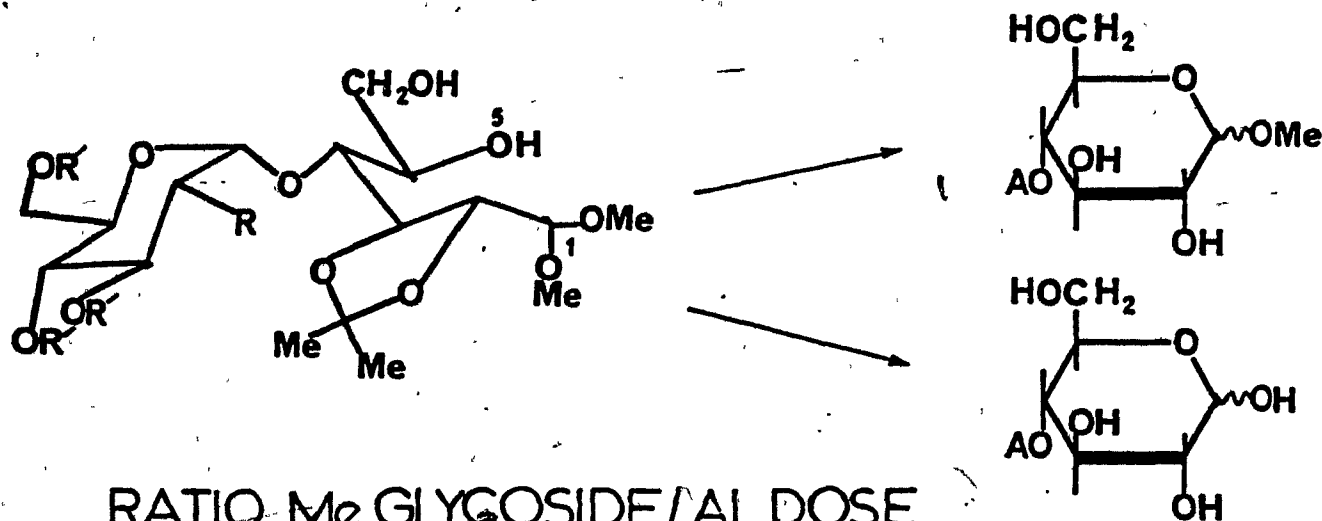
a) Cyclization of the aldose dimethyl acetal

The desired product of cyclization was the free pyranose. This would allow eventual formation of a glycosidic bond, either as a temporary measure or as part of an oligosaccharide. The alternative of forming a glycoside directly would allow for direct oxidation of C-6 by catalytic methods (see previous discussion) but might require a vigorous hydrolysis or acetolysis to remove the aglycon (116,179). It also might be necessary to have a free amino group at C-2' to provide sufficient stabilization of the $\alpha(1 \rightarrow 4)$ glycosidic linkage (179).

A variety of conditions were employed on a number of disaccharide derivatives in order to effect cyclization to the pyranose or pyranoside. The results, which were unexpectedly complicated, are summarized in Scheme IV-2.

Upon mild acid hydrolysis (80% refluxing aqueous acetic acid) of 4-O-(α -D-glucopyranosyl)-D-glucose or L-idose derivatives (61), the free pyranose was the only product isolated (see Scheme II-8, p.45). However, a similar hydrolysis of 2'-acetamido-2'-deoxy derivatives (62, for example) gave a mixture of products, containing both anomers of methyl glycosides, as well as free pyranose. Stronger acid conditions (90% aqueous trifluoroacetic acid) also provided mixtures from the maltose dimethyl acetal derivatives, either with or without 2'-amino-2'-deoxy groups.

The acid catalyzed hydrolysis of acetals is one of the most thoroughly studied reactions in organic chemistry (180). However, very



RATIO Me GLYCOSIDE / ALDOSE

80% AcOH REFLUX 90% TFA R.T.

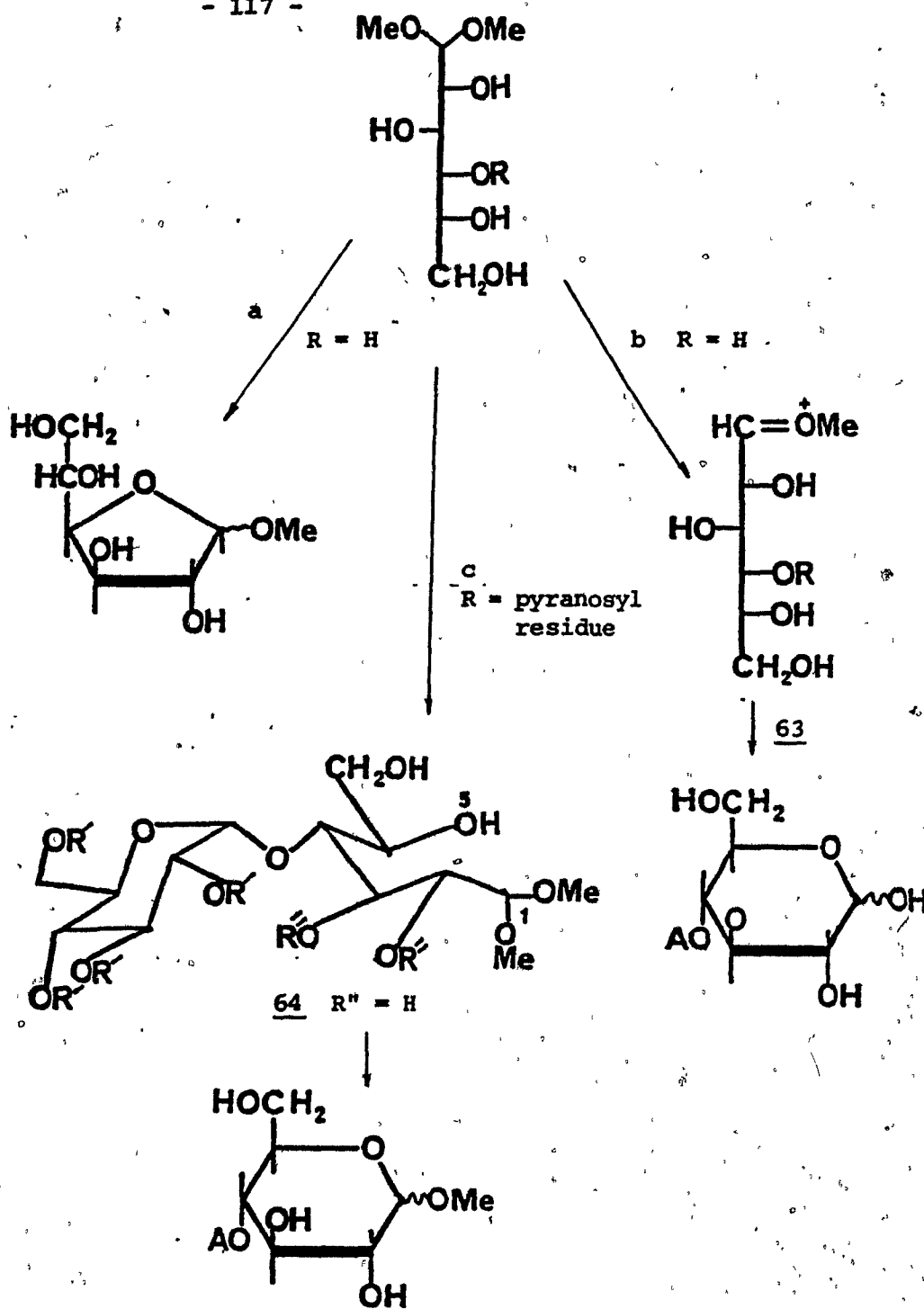
<u>61</u>	R = OBn OAc	0	2
<u>62</u>	R = NAc	1	2

Scheme IV-2. Formation of pyranosides from acid hydrolyses of dimethyl acetal intermediates.

little systematic work has been done on carbohydrates beyond establishing suitable conditions for cleaving cyclic acetals and ketals, or regenerating furanose and pyranose rings (11,112). In rationalizing the results of hydrolysis of the maltose dimethyl acetal derivatives, two main factors must be considered. First, the ratio of methyl glycoside to free pyranose will be determined by the ability of the acyclic chain to form a cyclic transition state resembling a pyranose ring, and therefore allow for nucleophilic attack by OH-5 in competition with water. Related to this factor are the relative rates of hydrolysis of the 2,3-isopropylidene group and the dimethyl acetal.

It is known that the rate of ring closure from an intermediate aldehyde (gem diol) form to a pyranose is slower than to a furanose (181). Capon (182) has studied the cyclization of dimethyl acetal derivatives, and found that methyl furanosides are formed preferentially through intramolecular nucleophilic attack by OH-4 (route a, Scheme IV-3). Pyranosides are not formed, evidently, since the rate of cyclization is slow enough, and the possibility of nucleophilic attack by OH-5 small enough, to allow for complete hydrolysis of the dimethyl acetal. Hence, route b (Scheme IV-3) was a minor contributor.

The formation of methyl pyranosides during the attempted hydrolyses of the maltose dimethyl acetal derivatives in Scheme IV-2, for example, implies that in these compounds, the rate of nucleophilic attack by OH-5 is enhanced relative to the rate of hydrolysis of the dimethyl acetal. It seems unlikely that the rate of hydrolysis of a dimethyl acetal, in effect the rate of formation of 63 (Scheme IV-3)



Scheme IV-3. Possible outcomes of the hydrolysis of aldose dimethyl acetals.

would be altered significantly by a substituent on O-4. Nevertheless, it is known that substituents on some acyclic compounds cause an increase in the rate of cyclization, presumably due to the increase in free energy of the acyclic form with respect to the cyclic transition state (64) (183). It is possible, then, that the glycosyl residue at O-4, by interacting with the acyclic dimethyl acetal (see section II.6, p.53) raises its free energy, or lowers that of 64, sufficiently to enhance the cyclization rate.

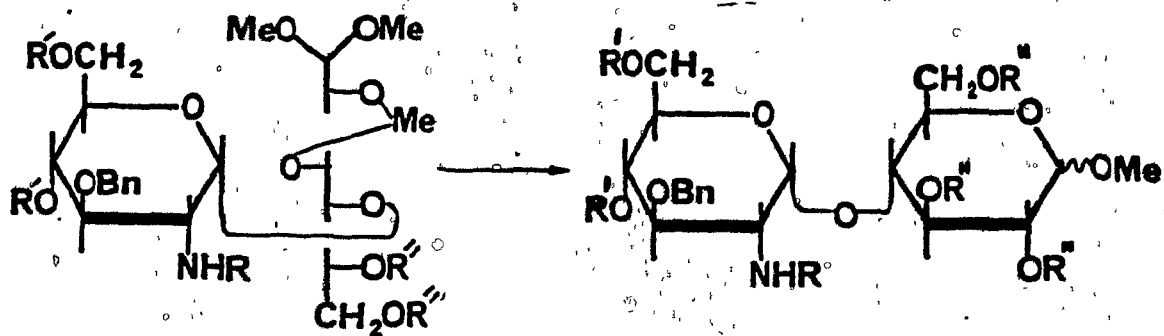
A prerequisite for the formation of a methyl pyranoside is a 6-membered cyclic transition state (e.g., 64) that would allow for nucleophilic attack by OH-5 on the anomeric center. A prior condition for the formation of 64 is cleavage of the 2,3-O-isopropylidene group shown in Scheme IV-2, because this trans-1,3-dioxolane system is too strained to permit the formation of a 6-membered chair (184).

These considerations are compatible with the production of methyl pyranosides in the hydrolysis of some of the maltose dimethyl acetal derivatives described. However, what is still lacking is an explanation as to why the ratios of pyranoside to pyranose change in different acidic media or with substrates differing only in a (seemingly) remote group (e.g., 2'-O-benzyl and 2'-acetamido-2'-deoxy groups). Clearly, the data concerning these transformations are relatively limited, and only major products have been isolated and characterized. It would be interesting to pursue the subject more systematically, and determine to what degree substitution on the glycosyl group affects the stability of the acyclic dimethyl acetal and so, alters its propensity to cyclize.

b) Investigation of a "cyclic" strategy

In the preceding discussion it was noted that complex mixtures of products were obtained by aqueous hydrolysis of the dimethyl acetal derivatives. For convenience, the preliminary investigation of a cyclic oxidation scheme was conducted on methyl pyranosides obtained by cyclization of the dimethyl acetal in methanolic solution. This reaction proceeded readily to give an anomeric mixture of methyl glycosides. The route followed, starting with the methyl maltoside derivatives, was similar to that used by Aspinall et al. (185) in the synthesis of methyl[methyl 2,3-di-O-methyl-4-O- (2,3,4,6-tetra-O-methyl- α -D-glucopyranosyl)- β -D-glucopyranosyl]uronate from methyl- β -maltoside. Scheme IV-4 outlines the steps from intermediate 49, which was a substantial byproduct of the first hydrolysis (Scheme III-6, p.92). Alternatively, the fully acetalated intermediate (47, Scheme III-6), can be used directly in this route. The mixture of methyl glycosides (65) obtained was characterized as the peracetate (66). The ^1H -n.m.r. spectrum of 66 showed the presence of both anomers ($\alpha:\beta = 2:1$), and also that signals H-3' and H-4 were clearly upfield and H-2, 3 and 4' were relatively downfield, as dictated by the respective locations of the alkyl and acyl groups. (Tables IV-1 and IV-2).

Formation of the 4,6-O-benzylidene ring of derivative 67 was effected with benzaldehyde dimethyl acetal and toluenesulfonic acid in dimethyl formamide (166), rather than with benzaldehyde and zinc chloride (167). Although the reaction proceeded well (according to t.l.c.) the yield was reduced during isolation from the high boiling medium.

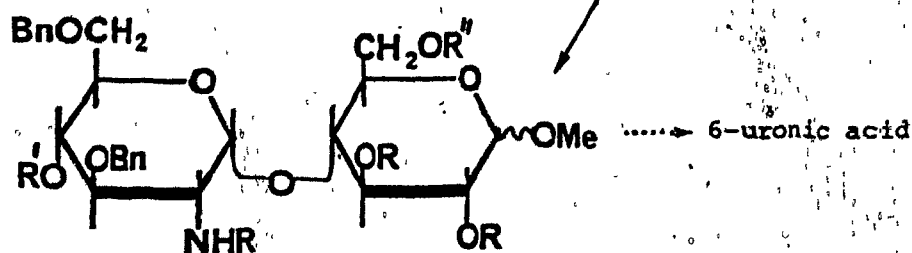


49 $R = \text{Ac}, R' = R'' = \text{OH}$

65 $R = \text{Ac}, R' = R'' = \text{H}$

66 $R = R' = R'' = \text{Ac}$

67 $R', R'' = \text{PhCH}, R = R'' = \text{Ac}$



68 $R = R'' = \text{Ac}, R' = \text{H}$

69 $R = R' = R'' = \text{Ac}$

70 $R = R' = R'' = \text{H}$

71 $R = R' = \text{Ac}, R'' = \text{MMT}$

Scheme IV-4. A cyclic route toward a 6-uronic acid.

Table IV-1: ¹H-Chemical Shifts (δ) for Compounds 66, 69 and 71

Compound	H-1'	H-2'	H-3'	H-4'	H-5'	H-6a'	H-6b'	H-6a,b
<u>66</u> (α)	5.17	~4.38*	3.62	~5.19	~3.85*	~4.0*	~4.2*	-
<u>69</u>	~5.2	4.36- 4.4	3.65	5.21	3.83	~3.5*	~3.5*	~4.5*
<u>71</u>	~5.1	~4.3	~3.3- 3.4	5.18	3.2-3.3	~3.0- 3.2	~3.0- 3.2	3.35- 3.5

* Tentative assignment

Table IV-2: ^{13}C -Chemical Shifts of 66, 67, 69 and 71 (α -anomers)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Other
<u>67</u>	97.00	71.47	72.78	74.04	68.89*	63.14*	101.50 (PhCH)
<u>69</u>	97.01	71.48	72.85	73.51	68.31	63.31	74.20 (PhCH ₂)
<u>71</u>	96.69	71.67	73.86*	73.20	69.93	64.34	55.45 (Ph-OMe) 87.02 (Ph ₃ C)

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
<u>67</u>	99.81	52.15	76.73	82.70	64.40*	68.22*
<u>69</u>	98.75	51.82	77.98	70.89	71.14	69.28
<u>71</u>	97.97	51.60	78.12	70.23	70.94	68.64

* Tentative assignment

Acetylation then provided the desired product (67), as indicated by ^1H and ^{13}C -n.m.r. spectra. The multiplet in the aromatic region, as well as the acetal proton signal, substantiated the presence of the 4,6-O-benzylidene group. Minor changes in the spectrum included a downfield shift (~ 0.2 p.p.m.) of the 3-O-benzyl methylene protons. In the ^{13}C spectrum (Table IV-2), the benzylidene carbon (δ 101.5) and the additional aromatic resonances were present. In addition, C-5' was shifted upfield to δ 64.4 and C-4' and -6' shifted downfield, as compared with such compounds as maltose octaacetate (103). A partial assignment of the α and β anomers, showed C-1 α at δ 97.0 and C-1 β at δ 101.4, as expected for methyl glycosides (164).

Recent work on the selective reductive cleavage of 4,6-O-benzylidene rings has shown (168) that one can obtain either a 4-O-benzyl or the 6-O-benzyl derivative depending on reaction conditions. The use of sodium cyanoborohydride and a proton donor (hydrogen chloride) provides the 5-O-benzyl derivative in good yield (which then would allow for glycosidic bonding to the resulting free OH-4) (186).

Accordingly, intermediate 68 (Scheme IV-4) was prepared by this method, and characterized by n.m.r. spectroscopy: the O-benzylidene methylene singlet was absent, having been replaced by the O-benzyl AB quartet. Also, when the free hydroxyl group of 68 was acetylated to give compound 69, the n.m.r. spectra (Tables IV-1 and IV-2) of the latter clearly showed that H-4' had moved downfield, to δ 5.21, as in acetylated disaccharide 66, whereas H-6a' and -6b' were upfield, at δ 3.5, in the same range as H-3'. The AB quartet at δ 4.7, from the

6-O-benzyl methylene protons, coalesced into a singlet at δ 4.52. Comparing its ^{13}C spectrum with that of the 4,6-O-benzylidene derivative (67), C-4' resonated at its expected upfield position, whereas the C-6' signal remained downfield at δ 69.3.

Because OH-6 of maltose has been reported to be less reactive than most primary hydroxyls (103), it was important to try a selective protection with a reactive group, such as 4-methoxytrityl chloride (177). When dry conditions were ensured, the tritylation of 70 proceeded readily, although subsequent in situ acetylation reduced the isolated yields in these preliminary investigations. However, compound 71 was identified as a mixture of anomers, with the appropriate aromatic and methoxyl signals in its ^1H and ^{13}C -n.m.r. spectra (Tables IV-1 and IV-2). Interesting characteristics of the ^1H spectrum, in addition to the upfield shifts expected of H-6a and -6b; were the increased shieldings of H-6a', -6b', -5' and even -3', presumably by the phenyl rings of the 6-O-(4-methoxytrityl) group. This bulky group also restricts the rotation of the 6'-O-benzyl group, as indicated by the return to an AB pattern for the benzylic protons, from the singlet for 69 (Fig. IV-1).

The proposed final oxidation step to the uronic acid then corresponds to the procedure described by Aspinall et al. (185), using a mild acid to remove the trityl group, followed by treatment with chromic acid (Jones reagent (132)). Alternatively, a one-pot oxidation with the same reagent is possible, as described, for example, by Sinay et al. (66).

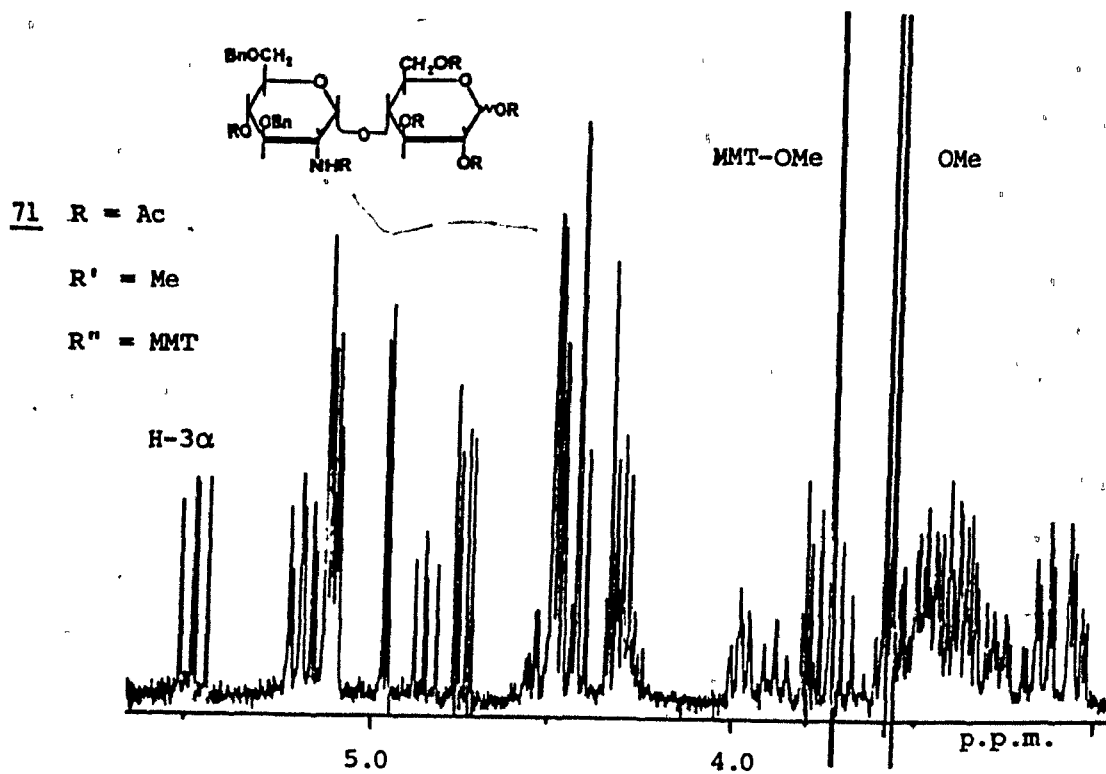
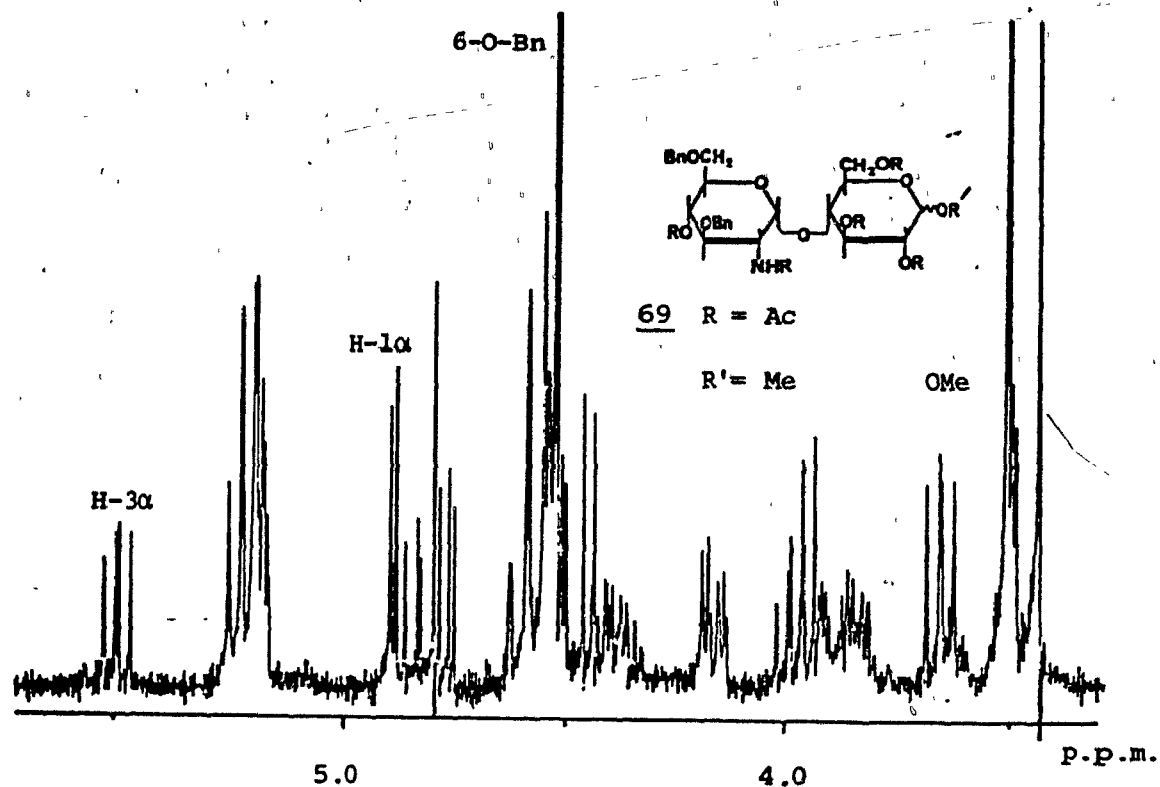


Figure IV-1. ^1H -n.m.r. spectrum of selectively protected glucopyranoside intermediates, 69 and 71.

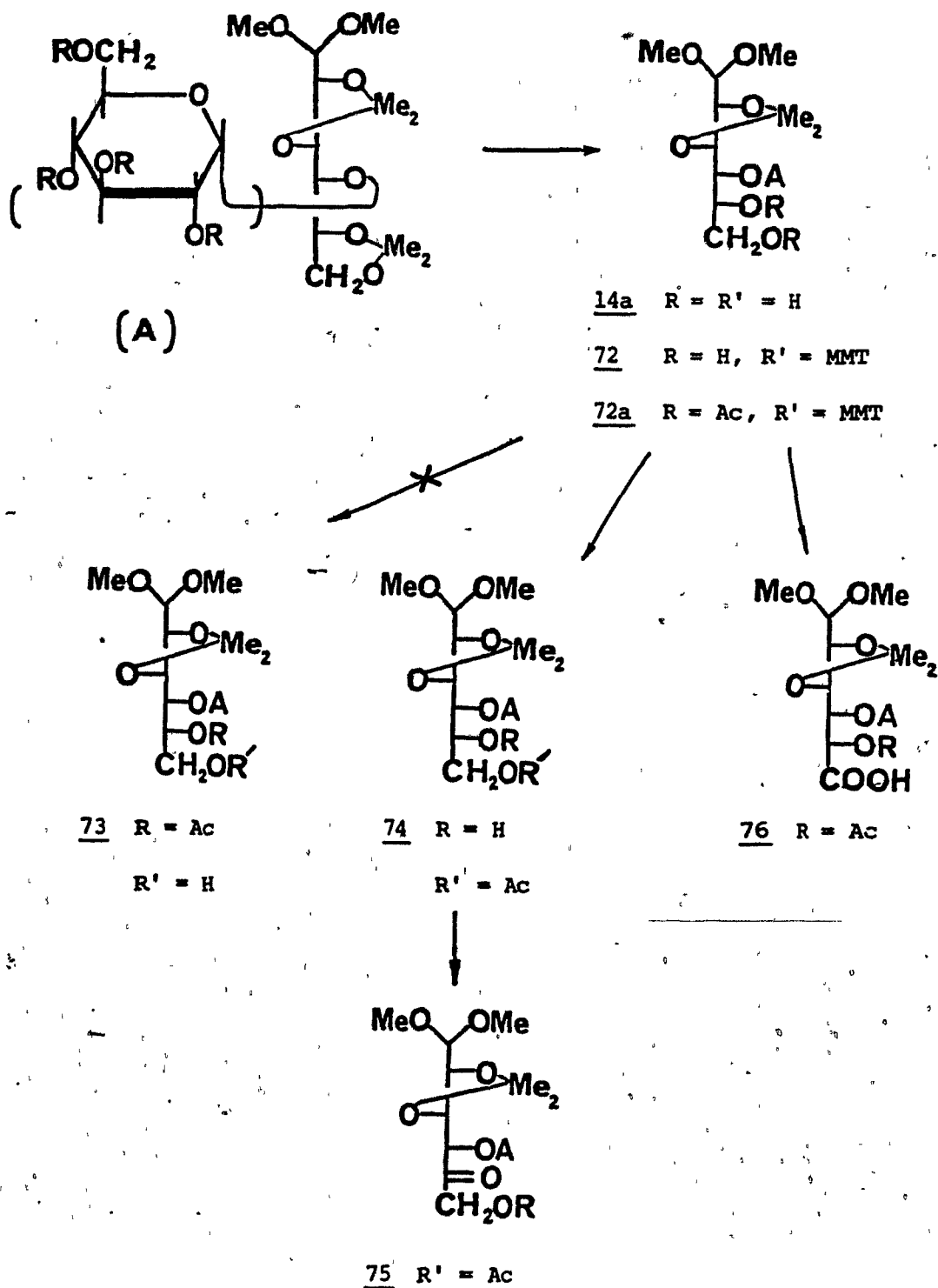
IV.3 Acyclic oxidation strategies

The third strategy to be discussed (route 1, Scheme IV-1, p.113) can be described as an acyclic version of strategy II. This route was investigated with model compounds, and then used for the derivatives containing 2'-amino-2'-deoxy-D-glucopyranosyl and L-idose dimethyl acetal components.

As mentioned in Section II.5, p.51, catalytic oxidation of the primary hydroxyl in acyclic derivatives (for example, 14a, Scheme IV-5), met with little success. Consequently, a conventional protecting-deprotecting scheme was considered. The choice of oxidation reagents was restricted at first to neutral or basic reagents, because of the remaining acetals. In addition, reagents that would react with the allyl or benzyl protecting group (potassium permanganate, ozone, silver oxide or bromine water (17)) were to be avoided, if possible.

IV.3 a) Acyl migration as a problem

Scheme IV-5 shows an attempt at exposing the primary hydroxyl group by selective deprotection. The starting diol, 14a, in this case a model compound, was alkylated at O-6 with 4-methoxytrityl chloride, followed by acetylation of OH-5 by the addition of acetic anhydride. The protected compound (72a) showed, in its ¹H spectrum, the expected aromatic, methoxyl and acetoxyl signals for these two protecting groups, and H-5 was shifted downfield as expected (Table IV-3). Values of $J_{3,4}$ (6.6 Hz) and $J_{4,5}$ (1.7 Hz) indicated the occurrence of a popula-



Scheme IV-5. Preliminary attempts at "acyclic" oxidation of a model compound.

Table IV-3: ^1H -Chemical Shifts (δ) and ^1H - ^1H Coupling

Constants (Hz) for Compounds 72a - 76 and 79 - 81

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6b}$)	H-6a ($J_{6a,5}$)	H-6b ($J_{6a,6b}$)
<u>72a</u>	4.28 (6.2)	4.15 (6.9)	3.97 (6.6)	3.79- (1.7)	5.43 -	3.38-3.49 -	
<u>73</u>	4.34 (5.1)	4.17 (7.1)	4.12 (6.1)	3.88 (1.8)	5.07 (4.2)	3.83 (7.0)	3.97 (12.0)
<u>74</u>	4.28 (5.7)	~4.22 (7.6)	4.05 (2.8)	3.70 (2.0)	4.16 -	- -	4.2 -
<u>76</u>	4.43 (5.4)	~4.1 -	4.46 (6.7)	3.96 (< 1)	5.48 (s)	- -	- -
<u>79</u>	4.27 (5.9)	4.13 (6.4)	~3.92- 3.98	~3.3- 3.5	5.4 -	3.3-3.5 -	
<u>80</u>	4.36 (5.4)	~4.1- 4.15	~4.1 -	3.91 (2.2)	~5.1 -	3.83-4.03 -	
<u>81</u>	~4.3 -	3.99 (6.3)	4.06- 4.37	3.94 (1.5)	5.57 (d)	- -	- -

tion of rotamers similar to those found with other acyclic D-glucose derivatives (see previous discussion). However, mild acid hydrolysis of the trityl group then resulted in an efficient migration of the acetyl ester from O-5 to O-6, producing compound 74, instead of the expected 73. The structure of 74 was inferred from the absence of a downfield signal attributable to H-5, now at δ 3.7, and the fact that the signals assigned to H-6a and -6b had moved downfield by $\sim$ 0.6 p.p.m. The coupling values $J_{3,4}$ and $J_{4,5}$ were both smaller, an indication of some change in the rotamer populations of the acyclic chain. However, because of the steep slope of the Karplus curve (134) around these values, minor changes in torsion angles can lead to significant changes in J values.

The migration of the 5-O-acetyl group also was confirmed by oxidation with pyridinium dichromate and acetic anhydride to give ketone 75, and not the acid (or aldehyde) expected from a primary alcohol. In the ^1H spectrum of 75, the C-6 protons give an AB quartet downfield at $\sim$ δ 5.0, and no detectable aldehydic proton signal. The ^{13}C spectrum (Table IV-4) has a signal at δ 200.4, corresponding to a ketone carbonyl, and both the C-4 and C-6 signals are shifted downfield by $\sim$ 3 p.p.m. and 6 p.p.m., respectively.

In attempting to circumvent this migration, the same protected derivative (72a) was treated with acidic Jones reagent (132). It was hoped that the rates of acid cleavage of the trityl groups and the subsequent oxidation of the exposed primary hydroxyl, would be fast enough to compete with that of the migration of the acetate group, as well as

Table IV-4: ^{13}C -Chemical Shifts (δ) for Compounds 75, 76, 79 and 80

Compound	C-1	C-2	C-3	C-4	C-5	C-6
<u>75</u>	105.86	(76.25, 78.13)		83.48	200.43	67.24
<u>76</u>	104.77	(77.26, 78.43)*		80.62	72.88*	~170
<u>79*</u>	105.47	76.10	78.45	81.75	74.31	61.79
<u>80</u>	105.06	77.27	78.19	80.17	72.59	167.4 - 171.8

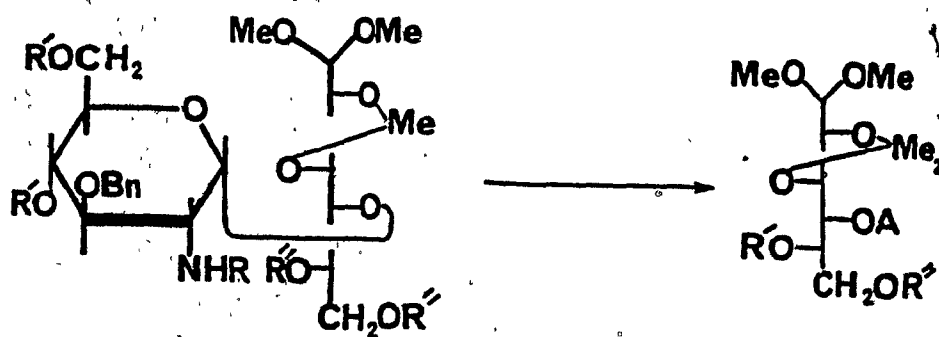
Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
<u>75</u>	98.96	68.48	-	-	70.91	62.00
<u>76</u>	97.13	70.62	69.78	68.06	67.58	61.34
<u>79</u>	97.66	70.44	69.71	67.85	67.76	61.04
<u>80</u>	96.76	70.56	69.44	67.99	67.71	61.47

* Tentative assignment

cleavage of the O-isopropylidene group. Treatment of 72a according to Sinay et al. (66) produced a mixture of products from which the desired acid 76, Scheme IV-5, p.127, was isolated in low yield (~ 30%). Compound 76 gave a ¹H-n.m.r. spectrum that integrated for the required twelve protons in the range of δ 3.9 - 5.5. The H-5 signal at δ 5.5, appeared as a singlet with $J_{4,5} < 1$ Hz. The larger coupling constant for H-4 (6.8 Hz) due to $J_{4,3}$, once again is consistent with the earlier evaluation of rotamer populations. The ¹³C spectrum showed an appropriate signal in the carbonyl range (δ 169.8 - 170.9) and the absence of a second signal in the primary hydroxyl C-6 range (δ 61 - 68).

Among the minor products of this acidic oxidation was the de-O-tritylated 5-O-acetyl compound 73, as well as the 6-O-acetyl product of migration (74). Compound 73, showed the expected downfield signal due to H-5, although it was less deshielded than that of either the 6-O-methoxytrityl (72a) or 6-carboxylic acid derivative (76).

The amount of recovered material showing retention of the 2,3-O-isopropylidene group and dimethyl acetal was enough to encourage the application of this method to the fully protected 2'-acetamido-2-deoxy- α -D-glucopyranosyl-L-idose dimethyl acetal derivative 55, Scheme IV-6. Following the same procedure, 55 was selectively protected to give 77a. As for compound 72a, H-5 was deshielded by acetylation of OH-5 (although the signal was obscured by allylic resonances), and the appropriate signals for the O-acetyl and O-trityl group were present. H-6a and -6b were both shielded to some extent by the 6-O-methoxytrityl group. Aside from the presence of additional signals due to the pro-

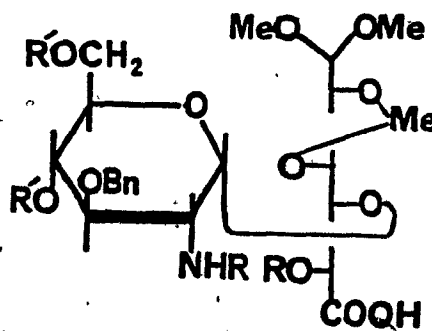


55 R = Ac, R' = allyl, R'' = H

77 R' = H

R'' = MMT

77a R' = Ac, R'' = MMT



78 R = Ac

Scheme IV-6. Attempted oxidation to an L-iduronic acid.

protecting groups, the ^{13}C spectrum showed little change as compared to that of the starting material. The downfield shift of C-6, after alkylation was only ~ 1 p.p.m. in this case.

When 77a was treated with Jones' reagent, as before, the reaction was slower than for the model compound, and produced only unidentified compounds, none corresponding to the desired acid (78). It appeared that the reaction was slow enough to allow for oxidative attack on the O-alkyl or O-benzyl protecting groups (187). It also was possible that the different substituents on the glycosyl group of 55 as compared to that of 14a altered the acid stability of the isopropylidene group or dimethyl acetal, and led to degradation. These results required a second look at this reaction and possible variations.

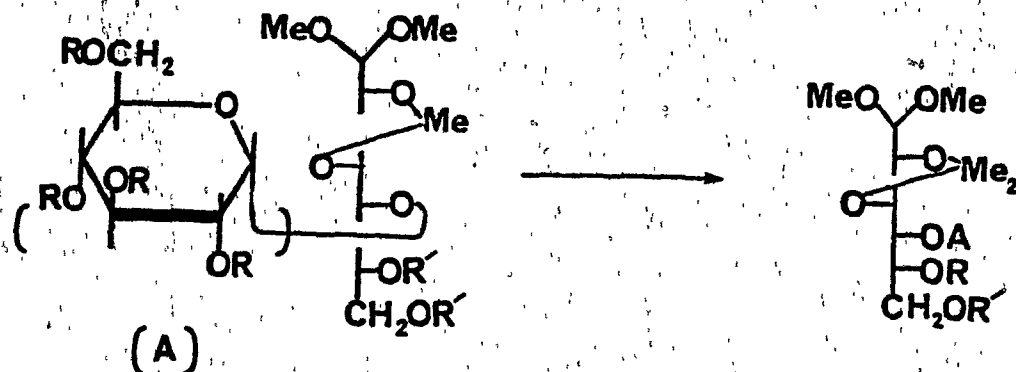
A simple consideration was that the acid was being formed, but was difficult to recover from the reaction by-products because of the polar 2'-acetamido-2'-deoxy glucosyl residue. This implied that an esterification would be necessary before isolation, and hence that the 5-O-acetyl group introduced would have to be removed subsequently from the methyl ester derivative. Under basic conditions this would most likely cause some 1,4- β -elimination (171).

A more important consideration was the need for a different oxidizing reagent, one that would deal with selectively exposed primary hydroxyl groups. Both of these prospects required a new protecting group on O-5, that is, one that was not likely to migrate from O-5 to O-6, and could be removed under mild conditions.

IV.3 b) A solution to the problem of acyl migration

Sundry groups were considered, but rejected either because of acid sensitivity (MOM or MEM (17)), or difficulty in selective deprotection (allyl or benzyl). Other esters, such as chloroacetyl groups can be removed under non-basic conditions (188), but migration is as likely as with the simple acetyl group. Instead of these, a successful choice was made of the levulinoyl group, which has been used rarely as an alternative to the more common esters. Its cleavage by hydrazine under mild conditions does not affect O-acetyl or O-benzoyl substituents (17), and its use in nucleotide chemistry has shown it to be a relatively stable protecting group (190).

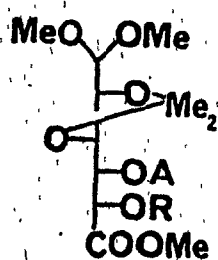
The synthesis of the 5-O-levulinate equivalent of the earlier model compound (72a) provided 79 (Scheme IV-7). One can use levulinic anhydride (189) in a manner analogous to acetic anhydride, or react the isolated 6-O-trityl derivative with levulinic acid and dicyclohexylcarbodiimide (190). The fully protected derivative, 79, showed, in addition to the aromatic and methoxyl resonances of the methoxytrityl group, the methyl and methylenic protons of the levulinyl group. The methylene signals are conveniently situated between the acyl methyl and pyranose ring protons, allowing for easy monitoring of the protection step. This is useful because the polarity of the protected derivative is too close to that of the starting material for t.l.c. analysis. Most of the other features of the spectrum, such as the downfield shift of H-5, resembled those of 72a (Scheme IV-5). The two carbonyls of the



14a R = Ac, R' = H

79 R = Lv, R' = MMT

80 R = Lv, R' = H



81 R = Lv

CrO₃

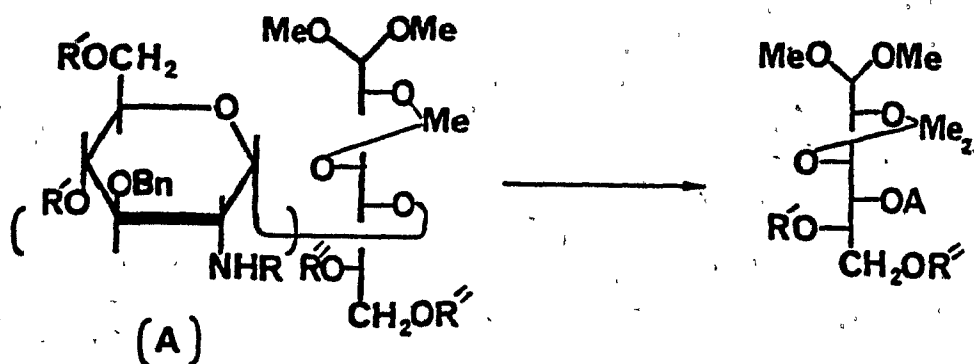
Scheme IV-7. Oxidation of a model compound using a non-migrating 5-O-levulinoyl protecting group.

levulinic ester were evident in the ^{13}C spectrum: the ketone at $\delta \sim 206$ and the ester at $\delta \sim 173$.

Removal of the O-trityl group, as before, gave a major product (80) retaining the levulinoyl group on O-5. Although now resonating at δ 5.1, slightly upfield from that of the starting material, H-5 is still deshielded by the ester group on O-5. In addition, a complex multiplet for H-6a showed coupling to a hydroxyl proton as well as to H-5 and H-6b.

This successful exposure of the primary hydroxyl group now allowed for the use of mild oxidation reagents. Pyridinium dichromate in the presence of acetic anhydride has been shown to provide carboxylic acids (154), and with 80, the desired product (81) was obtained, after esterification with diazomethane. As described for acid 76 (Scheme IV-5, p.127), the ^1H spectrum showed a narrow downfield doublet for H-5. In addition, the methyl ester gave a singlet at δ 3.82. As expected for the D-glucose acyclic series, $J_{4,5} = 1.5 \text{ Hz}$ and $J_{4,3} = 8 \text{ Hz}$.

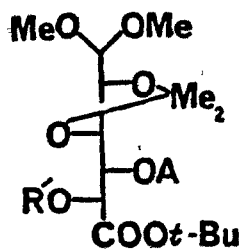
Encouraged by these results, a repeat of this protection scheme was carried out with 5,6-diol 55 (Scheme IV-8). Protection, as before, with O-methoxytrityl and O-levulinoyl groups proceeded in good yields to give 82, characterized by ^1H and ^{13}C h.m.r. spectroscopy (Tables IV-5 and IV-6, p.141). The analysis of the coupling constants for H-3, 4 and 5 was often difficult in this series of compounds, but from the limited data obtained, differences with respect to other L-ido derivatives were found (see Table II-1, p.37). As with the model compounds, the methoxytrityl group was removed to give 83, without significant mi-



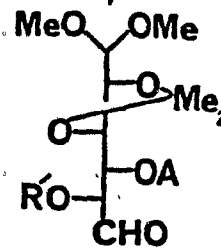
55 R = Ac, R' = allyl, R'' = H

82 R' = Lv, R'' = MMT

83 R' = Lv, R'' = H

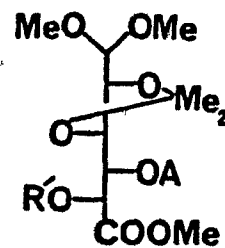


86 R' = Lv



84 R' = Lv

+



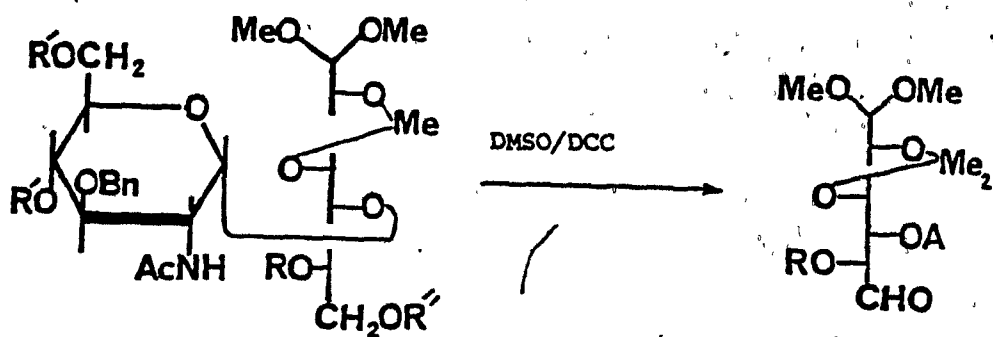
85 R' = Lv

Scheme IV-8. Oxidation attempts using chromium (VI) reagents.

gration of the levulinyl group. However, the use of pyridinium dichromate with acetic anhydride produced mixtures of products with only small amounts of aldehyde 84 or the desired acid (after esterification), 85. Concern that the free acid could not be isolated satisfactorily from the tarry oxidation by-products led to the use of a variation developed by Corey et al. (191). The addition of tert-butyl alcohol to the reaction mixture leads to the formation of the t-butyl ester in situ, facilitating recovery of the product. However, no t-butyl ester was isolated, and only small amounts of aldehyde 84 were observed (t.l.c.). Perhaps, as with Jones' reagent, the excess of pyridinium dichromate caused some degradation of the O-allyl and O-benzyl protecting groups. To avoid these complications, a two step oxidation was then tried.

Use of an equivalent amount of the pyridinium dichromate oxidant, in order to first obtain the aldehyde (84, Scheme IV-9), again produced extensive smearing on t.l.c. However, dimethyl sulfoxide with dicyclo-carbodiimide (192) gave better results, and a preparation of aldehyde 84 was obtained.

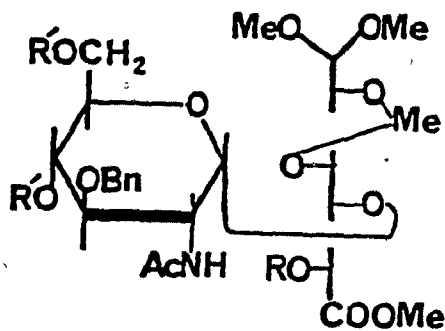
Oxidation of aldehydes to carboxylic acids can be performed with a variety of reagents in addition to the chromium compounds already mentioned. Potassium permanganate or hydrogen peroxide (149) have been used, but were not considered in this case due to the allylic double bonds present. Silver oxide (193) and such halogen oxides as chlorite (193) have been used in the carbohydrate field. The latter reagent is successful with vanillin (194) as well, and conditions were found to



83 R = Lv, R' = allyl, R'' = H

84 R = Lv

NaClO₂



85 R' = Lv

86 R' = H

Scheme IV-9. A two stage oxidation to an L-iduronic acid intermediate.

reduce by-products due to the presence of chlorine. Accordingly, treatment of aldehyde 84 with sodium chlorite in the presence of a chlorine scavenger, produced the desired acid (85) cleanly, in moderate yields, after esterification.

The characterization of 84 and 85 by ^1H - and ^{13}C n.m.r. spectroscopy confirmed their structures (Tables IV-5 and IV-6). The ^1H spectrum of aldehyde 88 contains the aldehydic proton signal, at δ 9.5, and the H-5 doublet is downfield, at δ 5.2. The pattern of rotamer populations, such as seen for previous L-ido compounds is less clear, because both $J_{4,3}$ and $J_{4,5}$ are small (2 - 4 Hz). A C-6 signal, now absent from the δ 63 region shown by the starting material (83), appears as a carbonyl at δ 196. The C-5 signal also is shifted downfield by 5 $\rightarrow$ 7 p.p.m. as compared to that of the unoxidized precursor.

The ester (85) has a ^1H spectrum similar to that of 84, with the H-5 doublet downfield at δ 5.3. The presence of a singlet at δ 3.7 identifies the methyl ester. In this compound, the rotamer populations are the converse of those of the other L-idose compounds (Table II-1, p.37) with $J_{4,3} = 6.7$ Hz and $J_{4,5} = 1.8$ Hz. The possibility of isomerization during the oxidation was ruled out, not only because of the clear formation of one product, but more so because of the analysis of subsequent products.

The ^{13}C spectrum showed the ester carbonyl signal at δ 168, and that of the methyl ester at δ 53. C-5 was assigned a resonance at δ 71.19, up from the value of δ 77 in the aldehyde, and in the range of the starting material (83).

Table IV-5: ^1H -Chemical Shift (δ) Data for Compounds 77a and 82 - 86

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
<u>77a</u>	4.18 -	3.86 -	- -	- -	5.11- 5.32	3.19 -	3.37 -
<u>82</u>	4.19 -	3.82 -	3.92 -	3.2- 3.4	~5.25 -	3.2 -	3.4 -
<u>83</u>	4.32 -	3.87 -	4.23 -	3.75- 3.8	5.10 -	3.79 -	3.8 -
<u>84</u>	4.33	3.90	4.30	3.95	5.22d	5.53(1H,S)	
<u>85</u>	4.34	3.94	4.31	4.05	5.26d	-	-
<u>86</u>	4.37	4.06	4.32	3.95	4.40d	-	-

Table IV-6: ^{13}C -Chemical Shift (δ) for 77a and 82 - 86

Compound	C-1	C-2	C-3	C-4	C-5	C-6
<u>77a</u>	105.09	75.77	76.86*	79.35*	74.68	63.16
<u>82</u>	104.99	76.02	~76.9*	79.47	74.77	63.18
<u>83</u>	105.33	-	-	79.86	70.46*	66.16
<u>84</u>	104.73	~77.2	~77.2	79.60	~77.2	195.98
<u>85</u>	104.67	77.88	~77.4	80.51	71.19	167.91
<u>86</u>	104.88	~77.4	~77.4	81.78	70.0	172.96

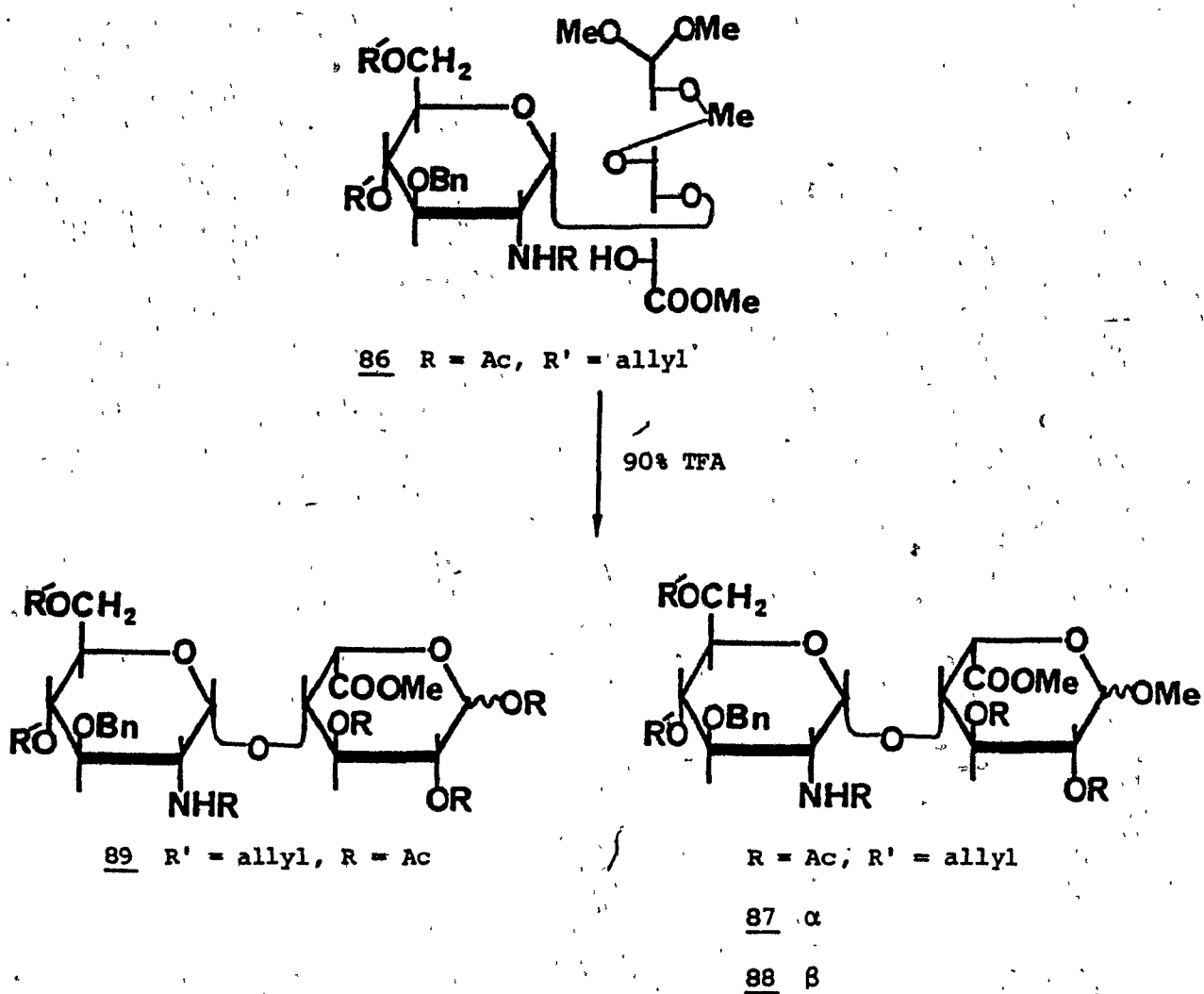
* Tentative assignment

The final step prior to cyclization of the dimethyl acetal to the pyranose form, was removal of the levulinyl group with a buffered hydrazine solution (190). The absence of the appropriate methylene and methyl signals in both ^1H and ^{13}C spectra confirmed the deprotection step to give 86 (Scheme IV-9). Signal H-5 returned to a less deshielded position at δ 4.4, although still slightly downfield due to the 6-carboxyl group (Table IV-5). Due to the rapid rate of cleavage of the O-levulinoyl group and the mild conditions, the methyl ester remained intact.

IV.4 Cyclization to methyl L-idopyranosiduronates

The cyclization of uronate 86 (Scheme IV-10) was carried out under conditions expected to produce both methyl glycoside and free aldose, in order to have specimens in both series for examination. The use of 90% trifluoroacetic acid, followed by acetylation, gave both methyl glycosides 87 and 88, as well as some of the acetylated pyranose 89. As already discussed, higher yields of either the methyl glycosides or pyranose can be obtained with methanolic solutions or acetic acid solutions, respectively. The α - and β -methyl glycosides were separated by chromatography, whereas the acetylated pyranoses were isolated as an anomeric mixture.

The general features of both ^1H and ^{13}C spectra confirmed that complete cyclization had taken place (Tables IV-7 and IV-8). The signals corresponding to the O-isopropylidene groups and the dimethyl acetal were absent, and the two O-acetyl methyl signals, as well as the



Scheme IV-10: Cyclization of an L-iduronic acid intermediate to the pyranose and pyranoside forms.

Table IV-7: ^1H -Chemical Shifts (δ) and ^1H - ^1H Coupling

Constants (Hz) for Compounds 87 - 89

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5
<u>87</u> (α)	4.99 (4.9)	4.80 (6.5)	5.33 (6.6)	4.08 (5.1)	4.72 -
<u>88</u> (β)	4.89* (~3.6)	4.88* (6.9)	5.59 (6.9)	3.98 (4.4)	4.50 -
<u>89</u> α	6.17 (2.8)	- (~7.0)	5.45 (~7.0)	- -	- -
<u>89</u> β	6.35 (~5.6)	- (~6.7)	5.68 (~6.7)	- -	- -

* Tentative assignment

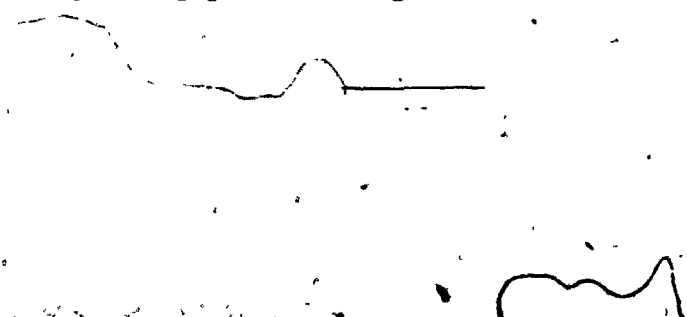
Table IV-8: ^{13}C -Chemical Shifts (δ) for Compounds 87 and 88

Compound	C-1	C-2	C-3	C-4	C-5	C-6
<u>87</u>	99.58	69.89	69.36	71.92	70.73	~169.5
<u>88</u>	98.63	70.17	68.88	72.35	71.59	~169 - 170

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
<u>87</u>	98.54	52.25	80.52	78.11	72.34	68.85
<u>88</u>	98.80	52.39	80.67	78.20	72.48	68.57

glycosidic methyl signals were present. Portions of the spectra showing the ring protons are presented in Figures IV-2 and IV-3. The coupling constants for H-5 ($J_{4,5} = 5.1$ Hz) or H-2 ($J_{3,2} = 6.5$ Hz) for example, clearly show that the reducing pyranose ring does not have the D-gluco configuration, which normally is characterized by values closer to 9 or 10 Hz (see 24 - 26, Table II-2, p.50, for example). In Figure IV-2, most of the chemical shift data and coupling constants for the methyl α -glycoside are available. The first striking feature is the relatively large coupling constants for the L-ido ring, which will be discussed more fully later. H-5, being next to the carboxylic ester, produces a doublet downfield from that of the aldose region, and the protons at the acetylated O-2 and -3 positions also are deshielded, as expected. Interestingly, H-6a' and -6b' have become accidentally equivalent, resulting in a doublet rather than the expected AB pattern. As discussed earlier (section II.6, p.53), the orientation proposed for the acyclic aglycon should bring it into close proximity with the glycosyl residue near O-5' and C-6'. Cyclization certainly would reduce this interaction.

The ^{13}C spectrum of the methyl α -glycoside shows only a few minor changes from that of its acyclic precursor, in addition to the expected absence of O-isopropylidene and dimethyl acetal signals. C-2 and C-3 resonate upfield following removal of the O-isopropylidene group, and the C-1 signal is upfield from its position when in the acyclic form (164). Signal C-4 is shifted upfield by ~ 9 p.p.m. in the pyranoside,



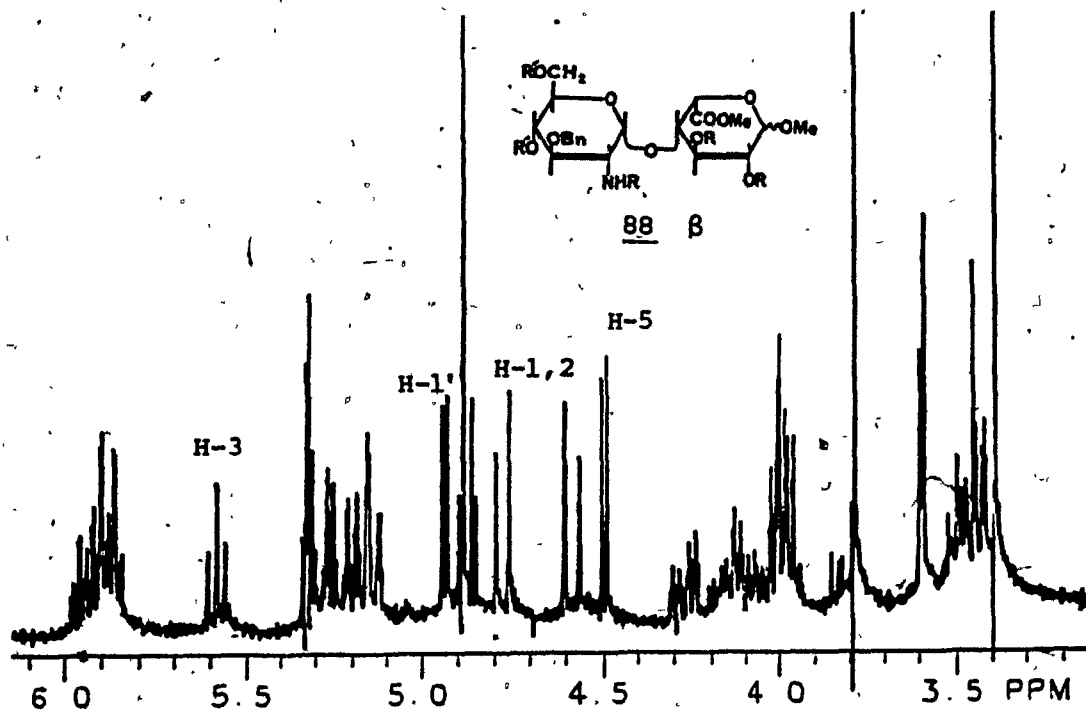
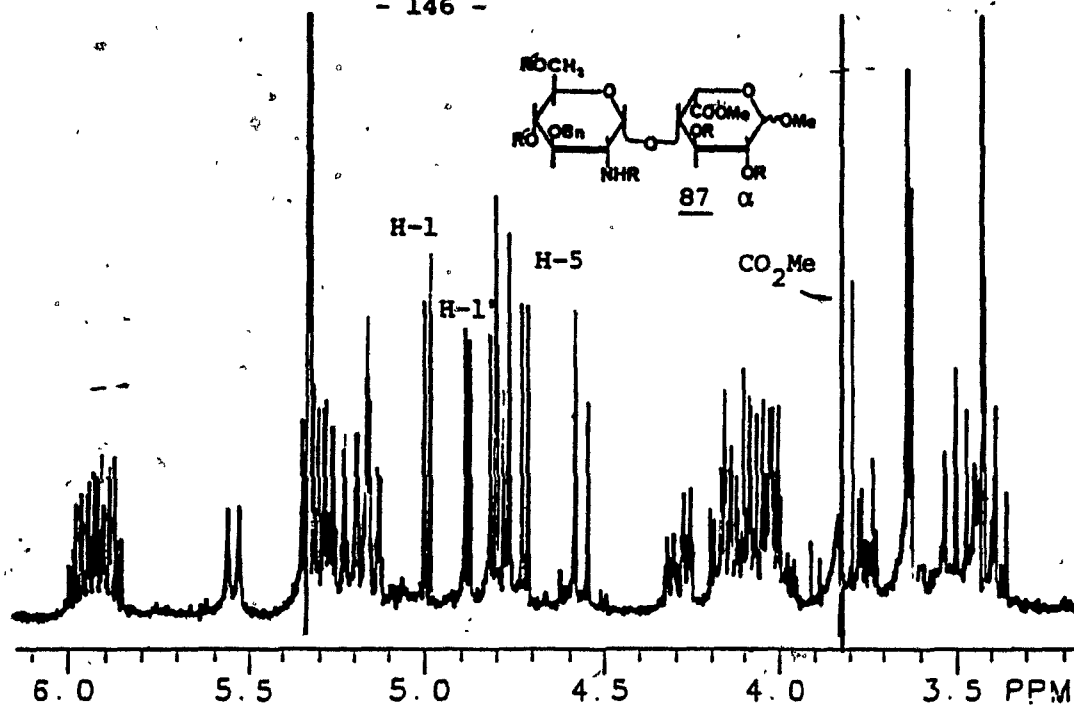


Figure IV-2. ¹H-n.m.r. spectra of methyl α -(87) and β -(88)-L-idopyranosiduronates (R = Ac, R' = allyl).

although this probably is due to the effect of the adjacent 3-acetoxy group (164).

The corresponding methyl β -glycoside (Fig. IV-2) exhibited very similar spectral characteristics, even though the overlapping of some proton resonances prevented an accurate determination of all chemical shifts and coupling constants. Overlapping signals for H-1 and H-2 were simulated by a computer program (195), to provide approximately δ 4.89 (H-1) and δ 4.88 (H-2) with $J_{1,2} = 3.6$ Hz. The ^{13}C spectrum was almost identical to that of the α -anomer, except for a small difference in the value for C-1, which was slightly upfield of that of the α -anomer.

The anomeric assignments of these glycosides was based on n.m.r. and optical rotatory data. As shown in Table IV-7 (p.144), the coupling constants for the ring protons are all quite large in comparison to values expected for an L-ido derivative in the $^1\text{C}_4$ conformation (Fig. IV-4, p.151), wherein all protons are gauche. From a simplistic analysis, this implies that a significant proportion of the $^4\text{C}_1$ also is present in equilibrium. In the α -anomer the $^1\text{C}_4$ conformer provides an equatorial - equatorial arrangement for H-1 and -2, and consequently a small $J_{1,2}$ value. The trans diaxial arrangement in the $^4\text{C}_1$ conformer would provide a large $J_{1,2}$ value (~ 8 Hz). For the β -anomer, both conformers should give relatively small values for $J_{1,2}$, as H-1 and -2 in both, have gauche arrangements. Therefore, the compound with the smaller $J_{1,2}$ (~ 3.6 Hz) is designated the β -anomer, and the larger $J_{1,2}$ (~ 4.9 Hz) is ascribed to the α -glycoside.

In L-ido systems, long range coupling is possible because of "W" arrangements between protons (195a). The 2-D contour plot of the α -anomer shows a small correlation between H-1 and H-3, although the coupling value is too small to be seen.

The ^{13}C spectrum also is compatible with the assignments made (Table IV-8, Fig. IV-3). Although the ^{13}C chemical shifts for methyl α - and β -glucopyranosides (δ 100.0 and 104.0, respectively) and their tetraacetates (δ 96.3 and 101.1, respectively) differ by 4 - 5 p.p.m., anomers of aldoses in which O-2 is axial, show, by contrast, that C-1 of the β -form is slightly more shielded (e.g., δ 101.4 and δ 100.1 for methyl α - and β -D-altropyranoside, respectively (164)). The values obtained here concur, in that they are δ 99.6 and δ 98.6 for the designated α - and β -anomers. Although ^{13}C chemical shift data for both methyl α - and β -L or D-idopyranosides or their uronate derivatives were not found, the values for C-1 in α - and β -D-idopyranose in D_2O show a similar relationship (δ 94.4 and 93.7, respectively (181)). Another characteristic of the ^{13}C spectra of aldopyranosides in the usual, $^4\text{C}_1$ (D) or $^1\text{C}_4$ (L), conformation, is the shielding of C-5 due to a gauche interaction with the α -anomeric group, resulting in a 3 - 6 p.p.m. upfield shift, as compared to the β -anomer. In the two L-idopyranosiduronates reported here, the difference between the two anomers qualitatively supported the assignment, but was much smaller (C-5 α at δ 70.7, C-5 β at 71.6), perhaps for conformational reasons.

The optical rotations as well, are consistent with the assignments, being $+31^\circ$ and $+90^\circ$ for the α - and β -anomers, respectively. A

rough estimate of expected optical rotatory values for a similar disaccharide can allow a qualitative comparison. For example, the combination of molecular rotatory data for methyl 2-acetamido-3,4,5-tri-O-acetyl-2-deoxy- α -D-glucopyranoside ($[\alpha]_D + 44^\circ$ (196), M.W. 360) and methyl (benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosid)uronate ($[\alpha]_D - 65^\circ$ (66), M.W. 420) gives an expected value for a disaccharide in the range of -10° . A similar calculation with the β -L-idopyranosiduronate ($[\alpha]_D + 70^\circ$ (66)) suggests a value for the corresponding disaccharide of approximately $+55^\circ$, and hence a difference of 65° . Considering the differences of structure between these two hypothetical disaccharides and, of course, the approximations in this type of calculation, the relative values observed ($[\alpha]_\beta > [\alpha]_\alpha$, $\Delta[\alpha] = 60^\circ$), are consistent with the anomeric designations proposed.

The question of conformation in the ido series is highly complex, as many studies using ^1H and ^{13}C have shown (197). Although in the crystalline phase, penta-O-acetyl- α -D-idopyranose is found in the "usual" ${}^4\text{C}_1$ conformation (198), the methyl α -D-glycoside in D_2O exists in substantial proportion in the "non-usual" ${}^1\text{C}_4$, or as skew forms (197). Based on more limited data, the β -D-anomer has a greater preference for the conformer wherein OH-2, -3 and -4 are axial, i.e., the "usual" ${}^4\text{C}_1$ form. For convenience and clarity in the following discussion, all conformations refer to L-sugars and hence the equivalent conformations are ${}^1\text{C}_4(\text{D}) = {}^4\text{C}_1(\text{L})$ and ${}^4\text{C}_1(\text{D}) = {}^1\text{C}_4(\text{L})$ (Fig. IV-4). As the free energies of both these ${}^1\text{C}_4$ and ${}^4\text{C}_1$ forms are not widely different, conformational equilibria in the ido series are not unexpected. More-

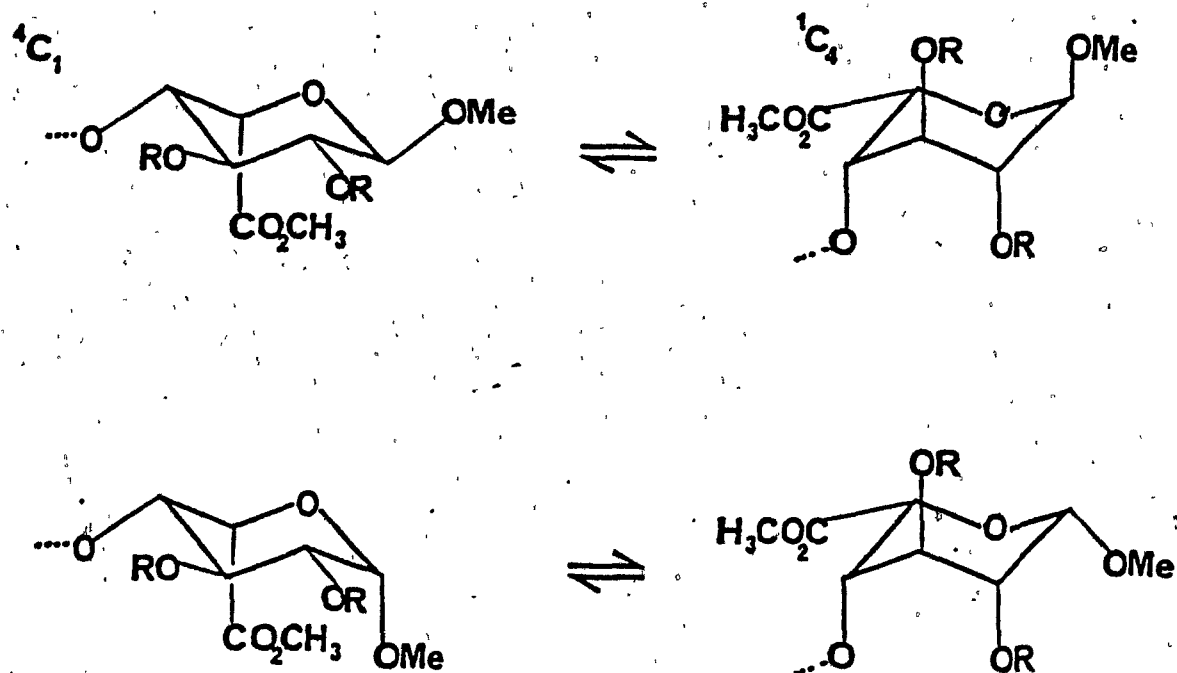


Figure IV-4: Interconversion of chair forms in α, β -L-idopyranosiduronic acids.

over, the picture is complicated by variations in substituents on the oxygen atoms, different solvents, and changes in intramolecular hydrogen bonding, which shift the equilibria (198). Further analysis of the conformational equilibria also suggests the presence of distorted chair or skew conformations (199). Recently, the importance of skew forms has been stressed. A discussion by Augé and David (197) proposes that skew forms, such as $^5S_3$, are appropriate to account for the large coupling constants observed with some idose derivatives. The skew form $^0S_2$ ($^2S_0$ for L-series) invoked for methyl 4,6-O-benzylidene-2,3-di-O-acetyl- α -D-idopyranoside derivatives by Angyal et al. (199) provides a large coupling between H-2 and -3 (~ 8 Hz) but a small one (~ 3.5 Hz) between H-3 and -4. A $^2S_0(L)$ skew form also has been proposed to account for the large $J_{2,3}$ value (7.5 Hz) in the 2-sulfated iduronic acid residue of a synthetic pentasaccharide related to the antithrombin binding site of heparin (200,201). A $^1S_3$ skew conformation for L-iduronic acid was proposed by Nieduszynski et al. (202) to fit the differing periodicities in sodium and calcium forms of solid, macromolecular, heparin.

Clearly, the number of factors involved in establishing the population of conformers for any particular L-idose derivative are many, and so it is not always profitable to compare different structures. A simple analysis of the L-iduronic acid unit in disaccharides 87 and 88 is compatible with a ratio between the $^1C_4$ and $^4C_1$ chair conformers. If values of 1.4 Hz and 7.5 Hz are taken for the $J_{1,2}$ values of equatorial - equatorial and axial - axial H-1 and H-2 protons (199), the methyl α -glycoside (87) is approximately 57% $^4C_1$ and 43% $^1C_4$. From the

$J_{2,3}$ and $J_{3,4}$ values (181), one can calculate similarly a ratio of ~ 53% ${}^4C_1$ and 47% ${}^1C_4$ for 87. This large amount of the ${}^4C_1$ conformer is not uncommon for methyl α -idoside derivatives under certain conditions, although the similar proportion for the β -anomer is unusual (197).

The ${}^1H$ coupling data acquired for these two disaccharides is not comprehensive enough to distinguish between a mixture of chair conformers with or without skew forms present. The large value for $J_{4,5}$ (4.5 - 5.0 Hz) suggests some contribution from the skew form ${}^2S_0$ is possible (199). However, large gauche coupling constants are also observed when the groups trans to the protons are polar (203), such as is found in this case.

Overall, it is clear that the conformations of the L-iduronic acid residue in both disaccharides (87 and 88) depart noticeably from the ${}^1C_4$ chair conventionally found for most aldoses - both the ${}^1C_4$ and ${}^4C_1$, as well as such skew forms as ${}^2S_0$ appear to be represented.

CHAPTER FIVE

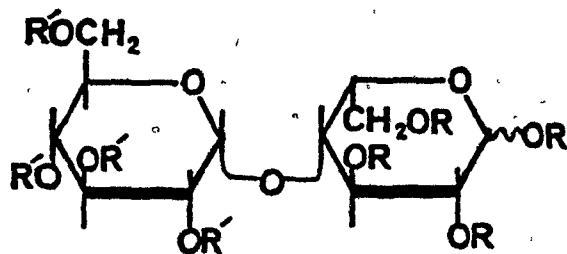
SUMMARY OF RESULTS AND SUGGESTIONS FOR FURTHER RESEARCH

V.1 Summary of Results

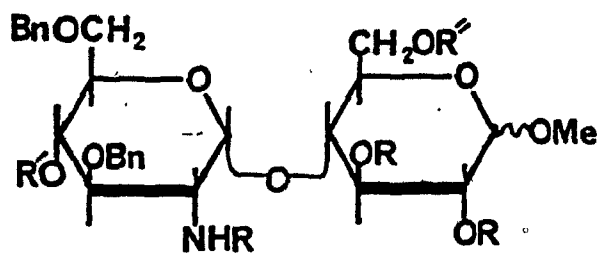
This study has shown that maltose dimethyl acetal derivatives 1 and 2 (Fig. I-5) provide suitable starting materials for the synthesis of other, specific, disaccharides. Three main disaccharides were obtained (Scheme V-1), one containing α -D-glucopyranose and L-idopyranose (22), α -D-glucosamine and D-glucose (suitably protected for oxidation to D-glucuronic acid) (71), whereas in the third, α -D-glucosamine is linked to L-iduronic acid (87,88). These intermediates are suitable for incorporation into oligosaccharides, after appropriate additional modifications.

Although, during the course of this work, other related syntheses of similar compounds have appeared, some unique features of the present strategy may merit its addition to the repertoire of oligosaccharide synthetic methods. To assess its success, it should be considered on two levels; that of the flexibility and applicability of the overall approach, and also in terms of its efficiency towards specific targets.

Certainly, there are improvements to be made at specific steps in the synthetic sequences. Some methods that received only limited attention, such as catalytic oxidation, should be pursued (see section II.5, p.51), as should the investigation of such complicating factors as methyl glycoside formation during dimethyl acetal cyclization (section IV.2). The potential of a number of these improvements has been noted already during the discussion of results. Most of these proposals will be summarized and amplified in the following section. Extensions and generalizations of the method will also be considered.

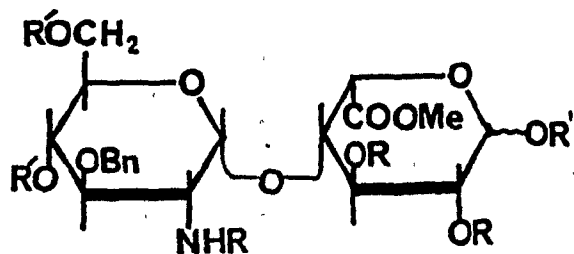


22 R = Ac, R' = Bn



68 R = R'' = Ac, R' = H

71 R = R' = Ac, R'' = MMT



87, 88 R = Ac, R' = allyl, R'' = Me

89 R = R'' = Ac, R' = allyl

Scheme V-1. Summary of disaccharides obtained from maltose.

V.2 Discussion of Concurrent Research

Before discussing these modifications, it is useful to gain some perspective on the strategy by comparing it to corresponding syntheses from other researchers, which have recently appeared. As indicated in the introduction, three other groups have obtained oligosaccharides related to heparin. Two, Sinay et al. (92) and van Boeckel et al. (60) used monosaccharides as starting materials, and the third, Kuzuhara et al. (98) started from cellobiose.

It is difficult to quantitatively compare the different routes being considered because of variations in their target compounds. In all three cases, an intermediate disaccharide containing L-iduronic acid and D-glucosamine is of the form, α -L-IdoA(1 + 4)-D-GlcN, whereas the disaccharide synthesized in the present work is of the form, α -D-GlcNAc(1 + 4)-L-IdoA. Sinay et al. (93) did synthesize the latter type of disaccharide, but experimental details were not given. It is possible, however, to estimate the number of steps and overall yields for these and related disaccharides.

In one sequence, Sinay et al. (93) obtained a methyl (methyl 2,3-di-O-benzyl- β -L-idopyranosid)uronate in seven steps from methyl 2,3-di-O-benzyl- α -D-glucopyranoside. The starting material was derived from methyl α -D-glucoside in three steps. The yields are not given, but can be estimated from similar work done by Lehmann (80) and Kuzuhara et al. (96). The critical step is in the hydroboration of a 6-deoxy-D-xylohex-5-enopyranoside intermediate, which gives both L-ido and D-gluco epimers. Lehmann obtained a 2.5/1 ratio of L-ido to D-gluco and total

yields of ~ 80%. Other steps should be high yielding, except perhaps for the oxidation of OH-6 to the uronate (96). However, an estimate of 8 - 10% is reasonable for this sequence.

An alternate synthesis of the L-iduronic acid component by Sinay et al. (66) through a methyl D-glucofuranuronate derivative, requires eight steps, in about 10% yield, from 3-O-benzyl-1,2-O-isopropylidene-D-glucofuranose, which is available from D-glucose in three steps. The D-glucosamine unit used by Sinay et al. (66) for the resulting disaccharide, was prepared according to Paulsen et al. (204) in eight steps from 1,6-anhydro-D-glucose in approximately 15% yield. The final coupling of the L-iduronic acid components with the D-glucosamine, in both cases was high yielding (80 - 90%). In summary, this convergent strategy from monosaccharides required around 16 - 20 steps with overall yields on the order of 5 - 10%.

Van Boeckel et al. (60) also used simple D-glucose starting materials, as already discussed. Their protected α -L-iduronic acid (1 + 4)-D-glucosamine disaccharide intermediate required a total of approximately twenty steps. The preliminary L-idopyranosidic halide component was made from 3-O-benzyl-1,2-O-isopropylidene- α -D-glucofuranose in six steps in high (~ 40%) yield. The 2-azido-1,6-anhydro-D-glucose component was also derived from 1,6-anhydro-D-glucose (204) in seven steps with about 15% overall yield. Coupling to give a disaccharide, achieved in moderate yield (~ 40%), was followed by seven further steps (oxidation, etc.) to give an L-iduronic acid containing disaccharide in an overall yield of 5 - 10%.

Kuzuhara et al. (98), in their synthesis of a similar disaccharide to the one above, used 1,6-anhydrocellobiose, and after seventeen steps with an overall yield of ~ 2% obtained the desired product. The hydroboration of the 5,6-ene intermediate (see above) was poor yielding in this case, giving only 19% of the desired L-ido compound.

The strategy in the present study required eighteen steps from the maltose dimethyl acetal 2 (Fig. I-5, p.21), to reach a disaccharide containing L-iduronic acid and α -D-glucosamine. It is difficult to calculate an overall yield because of the divergence of the hydrolysis step, for example (Scheme III-6, p.92) where a minor product was used for another synthetic route. However, a rough calculation gives an overall yield of approximately 1%, using 50% yields for the C-5 inversion step and 50% for the cyclization to the free pyranose. It should be stressed that this study was not overly concerned with optimizing yields, and it appears reasonable to suggest that some of the protecting and deprotecting steps that gave moderate yields (60 - 80%), can probably be improved to more acceptable levels (85 - 95%).

Thus, the present synthesis of this particular disaccharide requires approximately the same number of steps as with monosaccharide coupling, and is slightly lower in overall yield.

A similar analysis can be done for other disaccharides discussed in this work, such as α -D-glucosamine(1+4)-D-glucuronic acid derivatives. In the synthesis of Sinay et al. (92), the D-glucuronic acid component alone required thirteen steps from D-glucose. Van Boeckel et al. (60) made a "building block" containing β -D-glucuronic acid and

D-glucosamine in about sixteen steps, Kuzuhara (98) does the same in approximately 13 steps. In the present study, a disaccharide containing these components (and the α -linkage) was obtained in about ten steps.

Finally, the simple 4-O-(α -D-glucopyranosyl)-L-idose (22, Scheme V-1, p.156) was obtained in six steps from maltose, but would require about 15 steps from D-glucose.

Thus, for some particular disaccharides, and certainly for the components of the target pentasaccharide synthesized by the researchers just mentioned, the monosaccharide approach is more than competitive. However, for other cases the disaccharide approach using maltose is superior. The disadvantages of the latter method lie in a few critical low yielding steps, and in the following discussion, some of these particular problems will be addressed.

The advantages of the disaccharide method seem to lie in the formation of higher oligosaccharides. For example, the total number of steps in the synthesis of the fully protected pentasaccharide intermediate by Sinay et al. (92) was on the order of forty to fifty. Because two different disaccharides (containing either D-glucuronic or L-iduronic acid) can be obtained from the same intermediate in this synthesis from maltose, a hexasaccharide containing the same elements found in the same pentasaccharide could likely be formed with only two glycosidic coupling steps of these disaccharide condensations, in closer to 30 steps, and perhaps fewer, if improvements discussed below are incorporated. As will be seen in the last sections of this chapter, the ap-

plication of this methodology to less functionalized, longer oligosaccharides could exploit its major advantages. Before addressing the extensions of this work, some particular areas of the existing methodology will be re-evaluated and improvements proposed.

V.3 Some suggestions for improvements and modifications to the strategies

One of the first areas requiring attention is a reactivation of Strategy I, as discussed in Chapter II. Recall that the preliminary work described was superseded by the development of Strategy II. In retrospect, some aspects of strategy I could have been advantageous, as has already been mentioned briefly.

The main advantage to this strategy was suggested by the relatively poor yielding hydrolysis of the 4',6'-O-isopropylidene acetal necessary for Strategy II (e.g., 48, 49, Scheme III-6, p.92). Even though the minor product (49) can be used, the significant loss of material at this stage can be detrimental to a lengthy synthesis of oligosaccharides. In strategy I, OH-4' and -6' can be selectively blocked after modification of the L-ido reducing end, presumably in a high yielding step, or alternatively, complete protection could be accomplished before manipulation of the reducing end.

The introduction of the 2'-aminodeoxy group, either at later stages of Strategy I or in Strategy II, as shown in Chapter III, could benefit from some modifications, despite improvements already described. Selective oxidation of 1 (Fig. I-5, p.21) with bromine - water

and subsequent reaction of the 2'-ketone with methoxylamine hydrochloride, as has been proposed earlier, would reduce the number of steps to the 2'-axial form to two. A reinvestigation of the reduction of the methyloxime with diborane or a systematic evaluation of reaction conditions with other reagents could possibly increase the yields for this step.

Other modifications to the sequences described include (i) protecting schemes, (ii) inversion at C-5 to the L-ido configuration and also in (iii) cyclization of the acyclic dimethyl acetal moiety, as well as in (iv) oxidation strategies.

For example, the use of the allyl group as a temporary blocking group on OH-4' and -6' posed some problems in synthesis (p.96) and also in ¹H n.m.r. spectroscopy (see Fig. III-5, p.106, for example). Alternatives might increase yields and handling of the intermediates. The inversion step (Scheme II-6, p.36) was not thoroughly explored since acceptable yields were obtained with the conventional methods used. Leaving the inversion of C-5 until after formation of the carboxylic acid as has been done by Sinay et al. (66) using triflate methodology, might facilitate this critical step.

The cyclization of the dimethyl acetal to the pyranose was unexpectedly complicated by the formation of mixtures of products, and consequent poor yields (Scheme IV-2, p.115). Dimethyl boron bromide, which has been developed and explored by Guindon et al. (205), can selectively cleave a variety of acetals and ketals under different conditions. Some examples, such as the more rapid cleavage of a dime-

thyl acetal with respect to an O-isopropylidene acetal, and formation of glycosyl halides from methyl glycosides could find useful application to the cyclization of such intermediates as 49 (Scheme IV-4, p.120). More conventional means of obtaining higher yields of pyranoses such as acetolysis and hydrolysis of a disaccharide intermediate having an unprotected 2'-aminodeoxy group were mentioned earlier. Another alternative for ring closure and glycoside formation mentioned, was in the use of analogous dialkyldithioacetals of these disaccharides (ref. 118, p.36).

A most critical area in the synthetic routes followed, was the oxidation to the uronic acid derivatives. As it turned out, lengthy blocking - deblocking schemes and the need for a two step oxidation reduced the efficiency and yields for this seemingly straightforward step. In the light of the six steps that it took to provide a methyl L-iduronate derivative (Schemes IV-8, p.137 and IV-9, p.139) a second look at catalytic oxidation (133), could be fruitful. The advantages in avoiding blocking and deblocking schemes for both cyclic and acyclic intermediates could outweigh the generally low yields of selective catalytic oxidations of primary hydroxy groups. A simple one step oxidation can always allow for recycling of starting material.

In addition, other modifications were considered that could increase the flexibility of this general approach. The acyclic dimethyl acetal can be useful for introducing labelled (^{14}C or ^{13}C) carbons into these biologically interesting disaccharides, for example. It has been shown in some preliminary studies that the 5,6-diol of such compounds

as 33 (Scheme III-3, p.80) can be cleaved selectively by periodate (68), to give the D-xylo-pentadialdose, 90 (Scheme V-2). Addition of cyano or ethynyl groups would be expected to give a mixture of D-glucose and L-ido epimers (91), and further hydrolysis (69) or oxidation (70) would provide the desired uronic acids.

V.4 Extensions of the methods

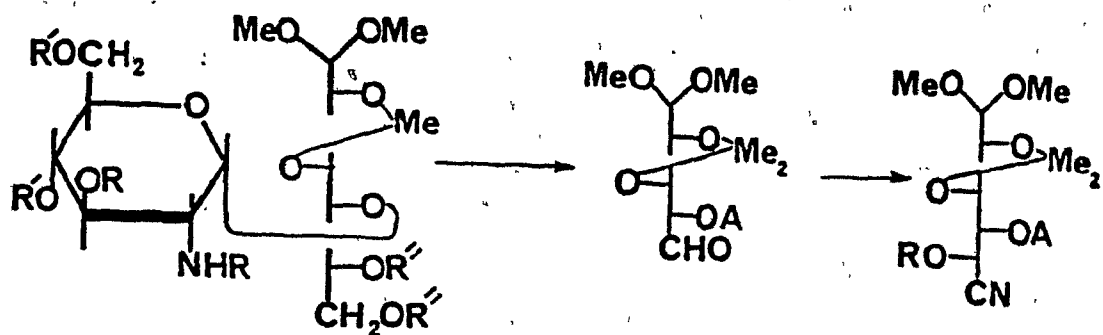
Beyond these possible improvements to the synthetic steps, and modifications in starting materials and intermediates, is the question of suitable targets. The aspect of making longer complex oligosaccharides by modifying longer, less functionalized oligosaccharides was raised in the discussion on general strategy, and alluded to earlier in this discussion.

The synthetic work of three other groups evaluated at the beginning of this chapter, was targeted toward a pentasaccharide that was highly functionalized and complex in its structure. It was shown that most synthetic strategies would require many steps to obtain the desired amino, carboxylic acid and sulfate functions. Another aspect of heparin and glycosaminoglycan research is the synthesis of simpler analogs having similar physical and biological properties, and yet accessible by efficient synthetic procedures. It is towards the goal of less functionalized hexa- and octasaccharides that the disaccharide methodology could be best directed.

Making longer chains with these maltose derivatives would best proceed with the two intermediates 5 and 6 (Scheme II-3, p.28). Start-

ing from the 3-O-benzyl-2-amino-2-deoxy intermediate 47 (Scheme III-6, p.92), and following the outline of Scheme IV-4 (p.120), the disaccharide 6a (Scheme V-2) could be coupled into tetra- and higher oligosaccharides containing this repeating unit. Further modifications could then be explored, such as catalytic oxidation, or other oxidation strategies. The resulting non-sulfated glucuronic acid containing intermediate could be used as a model for N-acetyl heparosan, the biosynthetic precursor to heparin, and perhaps modified further enzymatically (20).

The same approach could be applied to the analogous disaccharide as proposed for Strategy I or II, containing both α -D-glucosamine and L-idopyranose (6, Scheme II-3, p.28). Sinay et al. (66) have shown that the 1,2-orthoester of methyl L-iduronate can be formed, allowing for selective blocking of O-2, as well as glycosidic coupling to give the desired α -anomer. The same methods could be applied to this disaccharide intermediate, allowing access to oligosaccharides of alternating α -D-glucosamine and α -L-idose components. An even simpler disaccharide, 4-O-(α -D-glucopyranosyl)-L-idopyranose was obtained from compound 2 in Strategy I (22, Scheme II-8, p.45). This derivative could be further modified and prepared, with a 4',6'-O-benzylidene group for example, according to the general route in Scheme IV-4 (p.120), allowing condensation into oligosaccharides (186). These molecules, besides being interesting in their own right, could undergo oxidations and regioselective protection to introduce uronic acid and amino functions, and sulfate groups, following methods similar to those developed for the disaccharides.



$\text{R} = \text{Ac}$

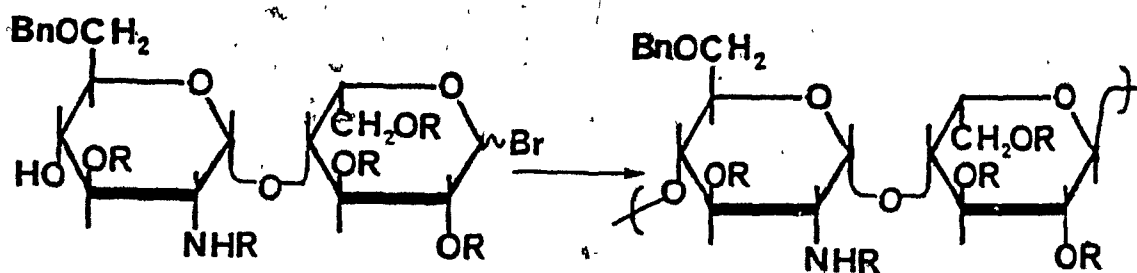
$\text{R}' = \text{R}'' = \text{H}$

90

91

+

D-gluco epimer



6a

hexa- or octasaccharide

Scheme V-2. °Some proposals for extending the present work.

Regardless of the level of complexity that can be reached, these proposed, less-functionalized, oligosaccharides are suitable targets for efficient use of the methodology developed here. Finally, most aspects of this work can be extended to other dimethyl acetals formed from the kinetic acetonation of cellobiose (107) and lactose (106), for example. Introduction of the L-ido configuration at the reducing end would be analogous to the maltose series, giving the respective β -linked disaccharides. Polysaccharides from some fungi have been found to contain α -L-iduronic- β -D-glucuronic repeating units (49,50). Because of the β -linkage and, in the lactose series, the axial OH-4, introduction of the 2-amino-2-deoxy group with the D-gluco-(D-galacto) configuration in high yields would not be expected (37). However, oligosaccharides containing 2-acetamido-2-deoxy- β -D-mannose units are important in bacterial capsular polysaccharides, potentially useful as vaccines (2).

In summary, it is believed that the basic methodology described here can find useful application in a wider range of synthetic work on oligosaccharides. It should be emphasized once again that interest in the synthesis of oligosaccharides related to heparin is not confined to the antithrombin pentasaccharide sequenceⁿ. Only some features of the latter are necessary (206), for example, in the inhibition of tumour angiogenesis (by a combination of heparin and cortisone), and also may not be essential for the lipolytic activity (20) of heparin. Consequently, the synthesis of low molecular weight oligosaccharides as potential anti-tumour or anti-atherosclerosis drugs, remains a worthwhile activity.

EXPERIMENTAL

General Methods

Instruments and analysis

Melting points (uncorrected) were determined with a Fischer - Johns hot plate apparatus.

Optical rotations were measured with a Jasco-DIP 140 Digital Polarimeter at Na/589 nm.

¹H-n.m.r. spectra were taken with either a Varian XL-200 FT-NMR spectrometer at 4.75 T and with a frequency of 200.058 MHz or a Varian XL-300 FT NMR spectrometer at 7.05 T, and 299.945 MHz.

¹³C-n.m.r. spectra were taken with either a Bruker WH-90 FT-NMR spectrometer or a Varian XL-300 FT-NMR spectrometer at 75.43 MHz.

Solvents for all samples were CDCl_3 or CD_2Cl_2 with TMS as the internal standard.

Mass spectrometry was performed by the Biomedical Mass Spectrometry Unit using an HP 5980A at 70 eV; 210° for the EI mode; or a ZAB-HS at 7 kV, 1 mA, with either diethanolamine or glycerol matrix for the FAB/MS mode.

Micro analyses were provided by Guelph Chemical Laboratories, Guelph, Ontario.

Experimental Procedures

Solvents were dried as follows::

Tetrahydrofuran: distilled over potassium

1,4-Dioxane: distilled over potassium

N,N'-Dimethylformamide: fractionated to constant boiling, in vacuo.

Methylene chloride: distilled from P_2O_5

Methanol: fractionated spectral grade quality

Pyridine: distilled from CaO.

Chromatography:

T.l.c. plates were Merck aluminium sheets, silica gel 60 F₂₅₄ coated.

Columns contained Merck silica gel 60, 400 mesh, and generally were eluted by the "flash" method.

Reagents were from Aldrich Chemicals.

Procedures

Acetylation was performed either with 1:1 acetic anhydride - pyridine, or with acetic anhydride in ether with DMAP as catalyst.

Deacetylation was performed with sodium methoxide in dry methanol.

Organic solvent extracts were washed with a saturated sodium bicarbonate solution, and water, as indicated. Drying was done with sodium or magnesium sulfate. Solutions were evaporated under water vapour pressure at $< 40^\circ C$ or with high vacuum, as indicated.

2,3:5,6-Di-O-isopropylidene-4-O-(4,6-O-isopropylidene- α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal (1)

Compound 1 was prepared by the method of Ueno et al. (108). Commercial maltose monohydrate was dried azeotropically with toluene, followed by heating at 45 - 60° C under vacuum. To a solution of the dried maltose (11.5 g, 36 mmol) in 1,4-dioxane (100 mL) were added 2,2'-dimethoxypropane (40 mL, 0.33 mol) and p-toluenesulfonic acid (100 mg) and the mixture was stirred at 80° for 20 h. Concentrated ammonium hydroxide was added dropwise until the solution was neutral (pH paper) and the solvents were evaporated. The residue was chromatographed (eluant, 1:1 ethyl acetate - hexane) to give 1 as oily crystals (9 g, 18 mmol, 51%).

¹H-n.m.r.: δ 1.35, 1.43, 1.46, 1.51 (4 s, 18 H, CMe₂), 3.44, 3.46 (2 s, 6 H, OMe), 3.19 - 4.28 (m, 13 H, H-2, 3, 4, 5, 6a, 6b, 2', 3', 4', 5', 6a', 6b', OH), 4.42 (d, 1 H, J_{1,2} 5.9 Hz, H-1), 5.08 (d, 1 H, J_{1',2'} 3.9 Hz, H-1').

¹³C-n.m.r.: δ 19.4, 25.2, 26.6, 27.3, 27.5, 29.3 (CMe₂), 54.2, 56.8 (OMe), 62.5 (C-5'), 64.4 (C-6'), 66.5 (C-6), 99.9 (4',6'-O-CMe₂), 101.4 (C-1'), 105.8 (C-1), 109.1, 110.2 (CMe₂).

4-O- α -D-Glucopyranosyl-2,3:5,6-di-O-isopropylidene-aldehydo-D-glucose dimethyl acetal (2)

Further elution of the silica gel column described above for compound 1, with ethyl acetate as the eluant, provided the second major product 2 (3 g, 6 mmol, 17%) as oily crystals.

¹H-n.m.r.: δ 1.30, 1.39, 1.42, 1.44 (4 s, 12 H, CMe₂), 2.2 (b, 1 H, OH), ~ 3.3 (b, 1 H, OH), 3.43, 3.46 (2 s, 6 H, OMe), 3.4 - 4.4 (m, 13 H, H-1, 2, 3, 4, 5, 6a, 6b, 2', 3', 4', 5', 6a', 6b'), 5.1 (d, 1 H, J_{1',2'} ~ 4 Hz, H-1').

2,3:5,6-Di-O-isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (13)

A solution of compound 2 (2.35 g, 5.0 mmol) in tetrahydrofuran (10 mL) was added to a stirred suspension of sodium hydride (0.6 g, 25 mmol) in tetrahydrofuran (25 mL) cooled to 0°. Benzyl bromide (3.5 mL, 3.0 mmol) and tetrabutylammonium iodide (10 mg) were added and the mixture was heated under reflux for 3 h. Excess sodium hydride was destroyed by the addition of wet tetrahydrofuran, then the mixture was poured into 5% hydrogen chloride - ice water and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, and water, dried, and concentrated. The residue was chromatographed (eluant, 1:4 ethyl acetate - hexane) to give a clear oil, 13 (3.06 g, 3.7 mmol, 74%); $[\alpha]_D^{20} + 41.8$ (c 1.1, chloroform).

¹H-n.m.r.: δ 1.32, 1.40, 1.43, 1.47 (4 s, 12 H, CMe₂), 3.32, 3.43 (2 s, 6 H, OMe), 3.53 (dd, 1 H, J_{2',1'} 3.4, J_{2',3'} 10.4 Hz, H-2'), 3.61 (dd, 1 H, J_{6a',5'} 2.1, J_{6a',6b'} 10.4 Hz, H-6a'), 3.67 (dd, 1 H, J_{4',3'} 10.0, J_{4',5'} 9.4 Hz, H-4'), 3.72 (dd, 1 H, J_{6b',5'} 3.1, J_{6b',6a'} 10.3 Hz, H-6b'), 3.80 (dd, 1 H, J_{4,3} 2.4, J_{4,5} 6.5 Hz, H-4), ~ 3.9 (m, 1 H, J_{5',4'} ~ 9.3 Hz, H-5'), 3.99 - 4.10 (m, 3 H, H-3', 6a, 6b), 4.16 (dd, 1 H, J_{3,2} 7.9, J_{3,4} 2.6 Hz, H-3), 4.21 (dd, 1 H, J_{5,4} = J_{5,6a} =

$J_{5,6b} = 6.1$ Hz, H-5), 4.32 (d, 1 H, $J_{1,2} = 6.6$ Hz, H-1), 4.40, 4.44, 4.58, 4.63 (AB, 2 H, PhCH_2), 4.44, 4.75, 4.80, 4.84 (AB, 2 H, PhCH_2), 4.65 (dd, 1 H, $J_{2,1} = 6.8$, $J_{2,3} = 7.8$ Hz, H-2), 4.74, 4.79, 4.87, 4.91 (AB, 2 H, PhCH_2), 4.75 (s, 2 H, PhCH_2), 5.11 (d, 1 H, $J_{1,2} = 3.3$ Hz, H-1'), 7.26 - 7.30 (m, 20 H, Ph).

2,3-O-Isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (14)

Water (7.5 mL) was added to a solution of compound 13 (2.8 g, 3.4 mmol) in glacial acetic acid (30 mL), and the milky suspension was heated at 40° for 3 h, when most of the starting material was gone (t.l.c. 1:1 ethyl acetate - hexane). The solvent volume was reduced by evaporation under high vacuum, water was added to the residue, and the mixture extracted with chloroform (3 $\times$ 70 mL). The extract was washed with sodium hydrogen carbonate solution, and water, dried, and concentrated. Chromatography of the residue (eluant, 1:1 ethyl acetate - hexane) gave a clear syrup, 14 (1.8 g, 2.3 mmol, 68%); $[\alpha]_D^{20} + 17.5$ (c 1.6, chloroform).

$^1\text{H-n.m.r.}$: δ 1.42, 1.51 (2 s, 6 H, CMe_2), 3.30, 3.45 (2 s, 6 H, OMe), 3.54 (dd, 1 H, $J_{2,1} = 3.8$, $J_{2,3} = 10.2$ Hz, H-2'), 3.41 - 3.51, 3.57 - 3.82, 4.11, 4.13 (m, 8 H, H-5, 6, 6a, 4', 5', 6a', 6b', OH), 3.85 (1 H, H-4), 3.99 (dd, 1 H, $J_{3,2} = 9.8$, $J_{3,4} = 9.1$ Hz, H-3'), 4.07 (dd, 1 H, $J_{3,2} = 8.0$, $J_{3,4} = 1.2$ Hz, H-3), 4.29 (d, 1 H, $J_{1,2} = 5.5$ Hz, H-1), 4.43, 4.47, 4.55, 4.59 (AB, 2 H, PhCH_2), 4.41, 4.48, 4.80, 4.83 (AB, 2 H, PhCH_2), 4.71 (dd, 1 H, $J_{2,1} = 5.5$, $J_{2,3} = 8.0$ Hz, H-2), 4.75 (s, 2 H,

PhCH₂), 4.77, 4.80, 4.88, 4.91 (AB, 2 H, PhCH₂), 4.95 (d, 1 H, J_{1',2'}, 3.9 Hz, H-1'), 7.26 - 7.32 (m, 2H, Ph).

Anal. calcd. for C₄₅H₅₆O₁₂: MW 788. Found: m/z 773 (M⁺-CH₃, 66), (EI).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (15)

A sample of compound 14 was acetylated to give 15, as a syrup, purified by chromatography (eluant, 1:3 ethyl acetate - hexane), [α]_D²⁰ + 52.2 (c 1, chloroform).

¹H-n.m.r.: δ 1.39, 1.43 (2 s, 6 H, CMe₂), 1.99, 2.02 (2 s, 6 H, OAc), 3.38, 3.43 (2 s, 6 H, OMe), 3.55 (dd, 1 H, J_{2',1'}, 3.4, J_{2',3'}, 9.8 Hz, H-2'), 3.61 (dd, 1 H, J_{6a',5'}, 2.0 Hz, H-6a'), 3.72 (dd, 1 H, J_{4',3'}, 9.0, J_{4',5'}, ~ 9 Hz, H-4'), 3.79 (dd, 1 H, J_{6b',5'}, 2.8 Hz, H-6b'), 3.95 - 4.0 (m, 3 H, H-4, 3', 5'), 4.18 (dd, 1 H, J_{3,2}, 7.0, J_{3,4}, 5.7 Hz, H-3), 4.22 (dd, 1 H, J_{6a,5}, 8.8, J_{6a,6b}, 12.2 Hz, H-6a), 4.36 (d, J_{1,2}, 6.0 Hz, H-1), 4.47 (dd, 1 H, J_{2,1}, 5.8, J_{2,3}, 6.9 Hz, H-2), 4.56 (dd, 1 H, J_{6b,5}, 2.2, J_{6b,6a}, 12.2 Hz, H-6b), 4.44, 4.48, 4.57, 4.62 (AB, 2 H, PhCH₂), 4.66, 4.70, 4.78, 4.82 (AB, 2 H, PhCH₂), 4.47, 4.50, 4.84, 4.88 (AB, 2 H, PhCH₂), 4.80, 4.83, 4.94, 4.97 (AB, 2 H, PhCH₂), 5.26 (d, 1 H, J_{1',2'}, 3.7 Hz, H-1'), ~ 5.27 (m, 1 H, H-5).

Anal. calcd. for C₄₉H₆₀O₁₄: MW 872. Found: m/z 857 (M⁺-CH₃, 100), (EI).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-aldehydo-L-idose dimethyl acetal (17)

Methanesulfonylchloride (0.5 mL, 6.5 mmol) was added dropwise to a solution of compound 14 (1.8 g, 2.3 mmol) in pyridine (10 mL) at 0°, and the reaction was stirred for 2 h. Ice-water was added, and the mixture extracted into chloroform (3 x 30 mL), the extract was then washed with sodium hydrogen carbonate solution and water, dried and concentrated. The residue was dissolved in acetic anhydride (10 mL), potassium acetate (2 g) was added and the mixture heated under reflux for 8 h. The dark brown mixture was diluted with ethyl ether (50 mL), water was added, the organic layer was separated, and the aqueous phase was extracted into diethyl ether. The combined ether extracts were filtered through silica gel, the solvent was evaporated, and the residue chromatographed (eluant, 1:3 ethyl acetate - hexane), which provided an inadequately pure oil. Further purification, by a second chromatographic processing under the same conditions gave 17 (1.5 g, 1.7 mmol, 74%); $[\alpha]_D^{20} + 26$ (c 1.1, chloroform).

$^1\text{H-N.M.R.}$: δ 1.41, 1.47 (2 s, 6 H, CMe_2), 1.99, 2.06 (2 s, 6 H, OAc), 3.25, 3.41 (2 s, 6 H, OMe), 3.54 (dd, 1 H, $J_{2',1'} 3.4$, $J_{2',3'} 9.8$ Hz, H-2'), 3.60 (dd, 1 H, $J_{6a',5'} 1.8$, $J_{6a',6b'} 10.6$ Hz, H-6a'), 3.71 (dd, 1 H, $J_{4',3'} 9.1$, $J_{4',5'} 9.9$ Hz, H-4'), 3.77 (dd, 1 H, $J_{6b',5'} 2.5$, $J_{6b',6a'} 10.8$ Hz, H-6b'), 3.83 (dd, 1 H, $J_{4,3} 1.2$, $J_{4,5} 5.8$ Hz, H-4), 3.86 (ddd, 1 H, $J_{5',4'} 9.7$, $J_{5',6a'} 1.7$, $J_{5',6b'} 2.2$ Hz, H-5'), 3.97 (dd, 1 H, $J_{3',2'} 9.8$, $J_{3',4'} 9.0$ Hz, H-3'), 4.04 (dd, 1 H, $J_{3,2} 7.7$, $J_{3,4} 1.1$ Hz, H-3), 4.31 (d, 1 H, $J_{1,2} 6.4$ Hz, H-1), 4.39 (m, 2 H, H-6a,

6b), 4.41, 4.45, 4.59, 4.63 (AB, 2 H, PhCH₂), 4.46, 4.50, 4.80, 4.83 (AB, 2 H, PhCH₂), 4.63 (dd, 1 H, J_{2,1} 6.6, J_{2,3} 7.6 Hz, H-2), 4.72 (s, 2 H, PhCH₂), 4.77, 4.80, 4.86, 4.90 (AB, 2 H, PhCH₂), 5.02 (d, 1 H, J_{1',2'} 3.4 Hz, H-1'), 5.38 (ddd, 1 H, J_{5,4} ~ 6, J_{5,6} ~ 3.4 Hz, H-5).

Anal. calcd. for C₄₉H₆₀O₁₄: MW 872. Found: m/z 857 (M⁺-CH₃, 100), (EI). Calcd. for C₄₉H₆₀O₁₄·H₂O: C, 66.05; H, 7.01. Found: C, 65.92; H, 7.11.

2,3-O-Isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-aldehyde-L-idose dimethyl acetal (18)

A portion of compound 17 was deacetylated with sodium methoxide and the product purified by chromatography (eluant, 1:1 ethyl acetate - hexane) to give a syrup, 18; [α]_D²⁰ + 33.5 (c 1, chloroform).

¹H-n.m.r.: δ 1.42, 1.50 (2 s, 6 H, CMe₂), ~ 2.7 (bs, OH), 3.32, 3.46 (2 s, 6 H, OMe), 3.54 (dd, 1 H, J_{2',1'} 3.9, J_{2',3'} 9.8 Hz, H-2'), 4.04 - 4.56 (m, H-4, 5, 6a, 6b, 3', 4', 5', 6a', 6b'), 4.06 (dd, 1 H, J_{3,2} 7.7, J_{3,4} 1.4 Hz, H-3), 4.31 (d, 1 H, J_{1,2} 6.1 Hz, H-1), 4.43, 4.48, 4.54, 4.58 (AB, 2 H, PhCH₂), 4.45, 4.49, 4.81, 4.85 (AB, 2 H, PhCH₂), 4.69 (dd, 1 H, J_{2,1} 6.0, J_{2,3} 8.2 Hz, H-2), 4.74 (s, 2 H, 6'-O-PhCH₂), 4.77, 4.81, 4.90, 4.93 (AB, 2 H, PhCH₂), 4.99 (d, 1 H, J_{1',2'} 4.0 Hz, H-1'), 7.29 - 7.35 (20 H, Ph).

Anal. calcd. for C₄₅H₅₆O₁₂: MW 788. Found: m/z 773 (M⁺-CH₃, 100), (EI). Calcd for C₄₅H₅₆O₁₂·H₂O: C, 66.98; H, 7.24. Found: C, 67.49, H, 7.73.

2,3:5,6-Di-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (13a)

Compound 2 was acetylated with acetic anhydride in pyridine. The residue was chromatographed (eluant 1:2 ethyl acetate - hexane) to give 13a as oily crystals.

$^1\text{H-n.m.r.}$: δ 1.36, 1.42, 1.43, 1.46 (4 s, each 3 H, CMe_2), 2.02, 2.03, 2.10, 2.12 (4 s, 12 H, OAc), 3.45, 3.47 (2 s, 6 H, OMe), 3.93 (dd, 1 H, $J_{3,4} = J_{4,5} = 4.3$ Hz, H-4), 3.98 - 4.09 (m, 3 H, H-3, 6a, 6b), 4.10 (dd, 1 H, $J_{6a',5'} = 2.3$, $J_{6a',6b'} = 12.2$ Hz, H-6a'), 4.16 (dd, 1 H, $J_{2,1} = 6.0$, $J_{2,3} = 7.3$ Hz, H-2), ~ 4.25 (m, 1 H, H-5), 4.29 (dd, 1 H, $J_{6b',5'} = 4.0$, $J_{6b',6a'} = 12.2$ Hz, H-6b'), 4.33 (d, 1 H, $J_{1,2} = 5.9$ Hz, H-1), 4.38 (ddd, 1 H, $J_{5',4'} = 10.2$, $J_{5',6a'} = 2.4$, $J_{5',6b'} = 4.1$ Hz, H-5'), 4.97 (dd, 1 H, $J_{2',1'} = 3.7$, $J_{2',3'} = 10.5$ Hz, H-2'), 5.10 (dd, 1 H, $J_{4',3'} = 9.4$, $J_{4',5'} = 10.1$ Hz, H-4'), 5.34 (d, 1 H, $J_{1',2'} = 3.7$ Hz, H-1'), 5.50 (dd, 1 H, $J_{3',2'} = 10.4$, $J_{3',4'} = 9.4$ Hz, H-3').

$^{13}\text{C-n.m.r.}$: δ 20.3, 20.4, 20.5 (OAc), 25.0, 26.3, 26.7, 27.1 (CMe_2), 54.5, 56.6 (OMe), 61.7 (C-6'), 65.6 (C-6), 67.5 (C-5'), 68.3 (C-4'), 69.8 (C-3'), 70.6 (C-2'), 75.6 (C-2), 75.9 (C-5), 78.7 (C-3, C-4), 97.0 (C-1'), 105.8 (C-1), 108.3, 110.0 (CMe_2), 169.4, 169.7, 169.9, 170.4 (OCOCH_3).

2,3-O-Isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-
aldehydo-D-glucose dimethyl acetal (14a)

As described in the procedure for compound 14, a solution of 13a (200 mg, 0.31 mmol) in 80% acetic acid - water (5 mL) was heated to 40° for 8 h, until t.l.c. (ethyl acetate) showed that most of the starting material had reacted. The aqueous acetic acid was removed by evaporation under high vacuum at room temperature, with toluene as a cosolvent. The syrupy residue was chromatographed (eluant, 1:1 ethyl acetate - hexane), providing 14a (148 mg, 0.25 mmol, 80%) as a syrup; $[\alpha]_D^{20} + 75$ (c 1.6, chloroform).

$^1\text{H-NMR}$: δ 1.43, 1.51 (2 s, 6 H, CMe_2), 2.01, 2.04, 2.09, 2.11 (4 s, 12 H, OAc), 3.46 (2 s, 6 H, OMe), 3.66 - 3.80 (m, 2 H, H-6a, 6b), 3.77 (dd, 1 H, $J_{4,3} = J_{4,5} = 3.2$ Hz, H-4), ~ 4.0 (m, 1 H, H-5), 4.10 (dd, 1 H, $J_{3,2} = 7.4$, $J_{3,4} = 3.0$ Hz, H-3), 4.14 (dd, 1 H, $J_{6a',5'} = 2.5$, $J_{6a',6b'} = 11.6$ Hz, H-6a'), 4.19 (dd, 1 H, $J_{6b',5'} = 6$, $J_{6b',6a'} = 11.4$ Hz, H-6b'), 4.27 (dd, 1 H, $J_{2,1} = 5.7$, $J_{2,3} = 7.5$ Hz, H-2), 4.33 (d, 1 H, $J_{1,2} = 6.0$ Hz, H-1), 4.42 (ddd, 1 H, $J_{5',4'} = 10.3$, $J_{5',6a'} = 2.4$, $J_{5',6b'} = 5$ Hz, H-5'), 4.95 (dd, 1 H, $J_{2',1'} = 3.8$, $J_{2',3'} = 10.4$ Hz, H-2'), 5.05 (dd, 1 H, $J_{4',3'} = 9.4$, $J_{4',5'} = 10.3$ Hz, H-4'), 5.20 (d, 1 H, $J_{1',2'} = 3.8$ Hz, H-1'), 5.52 (dd, 1 H, $J_{3',2'} = 10.4$, $J_{3',4'} = 9.4$ Hz, H-3').

Anal. Calcd. for $\text{C}_{25}\text{H}_{40}\text{O}_{16}$: MW 596. Found: m/z (M + DEAH, 65), (FABS, DEA).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (15a)

A sample of compound 14a was acetylated in the usual manner to provide a syrup that was chromatographed (eluant 1:1 ethyl acetate - hexane) giving 15a, also a syrup, $[\alpha]_D^{20} + 85$ (c 1.9, chloroform).

$^1\text{H-n.m.r.}$: δ 1.39 (s, 6 H, CMe_2), 2.02, 2.05, 2.07, 2.10, 2.107, 2.114 (6 s, 18 H, OAc), 3.43, 3.44 (2 s, 6 H, OMe), 3.86 (dd, 1 H, $J_{4,3} 6.9$, $J_{4,5} 1.6$ Hz, H-4), 4.09 (dd, 1 H, $J_{6a',5'} 2.2$, $J_{6a',6b'} 14.7$ Hz, H-6a'), 4.11 (dd, 1 H, $J_{3,2} = J_{3,4} = 6.8$ Hz, H-3), 4.18 (dd, 1 H, $J_{2,1} 5.7$, $J_{2,3} 6.7$, H-2), 4.28 (ddd, 1 H, $J_{5',4'} 10.1$, H-5'), 4.33 (dd, 1 H, $J_{6a,5} 8.3$, $J_{6a,6b} 12.2$ Hz, H-6a), 4.35 (d, 1 H, $J_{1,2} 5.6$ Hz, H-1), 4.37 (dd, 1 H, $J_{6b',5'} 2.8$, $J_{6b',6a'} 15$ Hz, H-6b'), 4.52 (dd, 1 H, $J_{6b,5} 2.6$, $J_{6b,6a} 12.3$ Hz, H-6b), 4.89 (dd, 1 H, $J_{2',1'} 3.8$, $J_{2',3'} 10.4$ Hz, H-2'), 5.15 (dd, 1 H, $J_{4',3'} 9.5$, $J_{4',5'} 10.3$ Hz, H-4'), 5.27 (ddd, 1 H, $J_{5,4} 1.7$, $J_{5,6a} 8.5$, $J_{5,6b} 2.5$ Hz, H-5), 5.32 (d, 1 H, $J_{1',2'} 3.8$ Hz, H-1'), 5.45 (dd, 1 H, $J_{3',2'} 10.4$, $J_{3',4'} 9.4$ Hz, H-3').

Anal. calcd. for $\text{C}_{29}\text{H}_{44}\text{O}_{18}$: MW 680. Found: m/z 773 (M + Glycine + H^+ , 3), m/z 681 (M + H^+ , 4), (FABS, Glycine), m/z 755 (M + H^+ + ether, 20), (CI, ether).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-L-idose dimethyl acetal (17a)

As described in the procedure for compound 17, methane sulfonyl chloride (0.4 mL, 5.1 mmol) was added dropwise to a solution of compound 55 (1.4 g, 2.3 mmol) in pyridine (20 mL) at 0°. After 2 h, water

was added and the mixture extracted into^ochloroform (3 x 50 mL), and the extract washed with water, dried, and concentrated. The crude residue was dissolved in acetic anhydride (10 mL) containing potassium acetate (1 g) and the mixture heated under reflux for 20 h. After cooling, the mixture was diluted with diethyl ether, and filtered. The filtrate was washed with water and the aqueous phase re-extracted with ether. The combined ether fractions were washed with sodium hydrogen carbonate solution and water, dried and concentrated. The residue was chromatographed (eluant, 1:1 ethyl acetate - hexane) to give 17a, a syrup (813 mg, 1.2 mmol, 52%); $[\alpha]_D^{20} + 53.3$ (c 1.2, chloroform).

¹H-n.m.r.: δ 1.41, 1.48 (2 s, 6 H, CMe₂), 1.99, 2.02, 2.04, 2.07, 2.08, 2.09 (6 s, 18 H, OAc), 3.42, 3.43 (2 s, 6 H, OMe), 3.80 (dd, 1 H, J_{3,2} 7.8, J_{3,4} 1.7 Hz, H-3), 4.08 (dd, 1 H, J_{6a',5'} 2.1, J_{6a',6b'} 12.5 Hz, H-6a'), 4.18 (dd, 1 H, J_{2,1} 6.2, J_{2,3} 7.8 Hz, H-2), 4.19 (ddd, 1 H, J_{5',4'} 10.3, J_{5',6a'} 2.1, J_{5',6b'} 3.7 Hz, H-5'), 4.29 (dd, 1 H, J_{6b',5'} 4.0 Hz, H-6b'), 4.29 (dd, 1 H, J_{6a,5} 7.2, J_{6a,6b} 12.7 Hz, H-6a), 4.29 (d, 1 H, J_{1,2} 6.2 Hz, H-1), 4.52 (dd, 1 H, J_{6b,5} 2.6, J_{6b,6a} 12.7 Hz, H-6b), 4.93 (dd, 1 H, J_{2',1'} 4.8, J_{2',3'} 10.6 Hz, H-2'), 5.09 (dd, 1 H, J_{4',3'} 9.5, J_{4',5'} 10.3 Hz, H-4'), 5.19 (d, 1 H, J_{1',2'} 4.8 Hz, H-1'), 5.31 (ddd, 1 H, J_{5,4} 5.9, J_{5,6a} 7.2, J_{5,6b} 2.5 Hz, H-5), 5.48 (dd, 1 H, J_{3',2'} 10.5, J_{3',4'} 9.5 Hz, H-3').

Anal. calcd. for C₂₉H₄₄O₁₈: MW 680. Found: m/z 755 (M + H⁺ + ether, 56), m/z 665 (M⁺-CH₃, 24), (CI, ether).

1,2,3,6-Tetra-O-acetyl-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-L-idopyranose (22)

A solution of 18 (2.0 g, 2.5 mmol) in 80% aqueous acetic acid (30 mL) was heated under reflux for 2 h. The solvents were removed by evaporation under high vacuum and the residue was chromatographed (eluant, 3% methanol in chloroform). The combined fractions containing the major product were concentrated and the residue acetylated. The resulting product was chromatographed (eluant, 1:2 ethyl acetate - hexane) to give 22 (1.6 g, 1.8 mmol, 72%).

¹H-n.m.r.: δ 1.99, 2.04, 2.05, 2.054, 2.06, 2.115, 2.123 (8 s, 12 H, OAc), 3.55 (dd, 1 H, $J_{2',1'} = 3.5$, $J_{2',3'} = 9.9$ Hz, H-2'), 3.62 - 4.41 (m, 9 H, H-4, 5, 6a, 6b, 3', 4', 5', 6a', 6b'), 4.42 - 4.9 (3 AB, 1 s, 8 H, PhCH₂), ~ 4.8 ($\frac{1}{2}$ H, H-2 α), 4.99 (d overlapping a dd, $\frac{1}{2}$ H, H-2 β , H-1'), 5.24 (ddd, $\frac{1}{2}$ H, $J_{3\alpha,2\alpha} = J_{3\alpha,4\alpha} = 3.8$, $J_{3\alpha,1\alpha} = 1$ Hz, H-3 α), 5.41 (dd, $\frac{1}{2}$ H, $J_{3\beta,2\beta} = J_{3\beta,4\beta} = 5.1$ Hz, H-3 β), 6.05 (d, $\frac{1}{2}$ H, $J_{1\alpha,2\alpha} = 2.4$ Hz, H-1 α), 6.10 (d, $\frac{1}{2}$ H, $J_{1\beta,2\beta} = 2.9$ Hz, H-1 β), 7.12 - 7.35 (m, 20 H, Ph).

6-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal (23)

To a stirred solution of 14 (900 mg, 1.14 mmol) and imidazole (153 mg, 2.3 mmol) in N,N'-dimethylformamide (5 mL) was added tert-butyldiphenylsilyl chloride (0.3 mL, 1.16 mmol). After 1 h, water was added and the mixture extracted with diethyl ether (3 x 20 mL). The extract was washed with water, dried and concentrated. The residue was

chromatographed (eluant, 1:5 ethyl acetate - hexane) to give a syrup, 23 (976 mg, 0.95 mmol, 83%); $[\alpha]_D^{20} + 13.4$ (c 3.1, chloroform).

$^1\text{H-n.m.r.}$: δ 1.07 (s, 9 H, t-butyl), 1.42, 1.52 (2 s, 6 H, CMe_2), 3.29, 3.40 (2 s, 6 H, OMe), 3.27 - 3.59 (m, 7 H, H-2', 4', 5, 6a, 6b, 6a', 6b'), 3.99 (m, 1 H, H-4), 4.05 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 9$ Hz, H-3'), ~ 4.17 (m, H-5), 4.33 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.38 (d, 1 H, $J_{3,2}$ 6.6, $J_{3,4}$ 1 Hz, H-3), 4.39, 4.43, 4.62, 4.66 (AB, 2 H, PhCH_2), 4.46, 4.50, 4.81, 4.85 (AB, 2 H, PhCH_2), ~ 4.75 (m, 1 H, H-2), 4.77 (s, 2 H, PhCH_2), 4.78, 4.82, 4.88, 4.92 (AB, 2 H, PhCH_2), 5.75 (d, 1 H, J 3 Hz, H-1'), 7.26 - 7.39 (m, 30 H, Ph).

1,2,3-Tri-O-acetyl-6-O-tert-butyl-diphenylsilyl-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-D-glucopyranose (24)

A solution of 23 (520 mg, 0.51 mmol) in 80% aqueous acetic acid (20 mL) was heated under reflux for 1 h, then the solvents were evaporated under high vacuum. The residue was acetylated with acetic anhydride and dimethylaminopyridine as the catalyst. After removal of solvents, the residue was chromatographed (eluant, 1:4 ethyl acetate - hexane) to provide two fractions, 24 (343 mg, 0.32 mmol, 62%) and 25 (121 mg, 0.14 mmol, 27%).

$^1\text{H-n.m.r.}$: δ 1.05 (s, 9 H, t-butyl), 1.55, 1.83, 2.01, 2.03, 2.11, 2.12 (6 s, 9 H, OAc), 5.01 (dd, $J_{2,1}$ 3.7, $J_{2,3}$ 10.2 Hz, H-2 α), 5.07 (dd, $J_{2,1}$ 8.0, $J_{2,3}$ 9.1 Hz, H-2 β), 5.21 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1' α,β), 5.35 (dd, $J_{3,2} = J_{3,4} = 9.6$ Hz, H-3 β), 5.57 (dd, $J_{3,2} = J_{3,4} = 10.1$ Hz, H-3 α), 5.60 (d, $J_{1,2}$ 8.1 Hz, H-1 β), 6.30 (d, $J_{1,2}$ 3.7 Hz, H-1 α), 7.21 - 7.67 (m, 30 H, Ph).

1,2,3-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)- α -D-glucopyranose (26)

Tetra-n-butylammonium fluoride in tetrahydrofuran (1 M, 2 mL) was added to a stirred solution of 24 (812 mg, 0.75 mmol) in tetrahydrofuran (20 mL) at 0°. After 5 h, the solvent was removed, chloroform was added to the residue, and the resulting solution washed with 5% aqueous hydrochloric acid, sodium hydrogen carbonate solution, and water. After drying, the solution was concentrated and the residue chromatographed (eluant, 1:2 ethyl acetate - hexane) to give 26 (226 mg, 0.27 mmol, 36%), and a second fraction containing a mixture of 26 and products derived from acetyl migration, as shown by ^1H -n.m.r. evidence; $[\alpha]_{\text{D}}^{20} + 48$ (c 1.8, chloroform).

^1H -n.m.r.: δ 1.90, 2.01, 2.17 (3 s, 9 H, OAc), ~ 2.3 (bs, 1 H, OH), 3.52 (dd, 1 H, $J_{2',1'}$ 3.5, $J_{2',3'}$ 9.9 Hz, H-2'), 3.53 (dd, 1 H, $J_{4',3'}$ 8.6, $J_{4',5'}$ 9.9 Hz, H-4'), 3.62 (m, 2 H, H-6a, 6b), 3.80 - 4.00 (m, 4 H, H-5, 5', 6a', 6b'), 3.92 (dd, 1 H, $J_{3',2'}$ 9.8, $J_{3',4'}$ 9 Hz, H-3'), 4.07 (dd, 1 H, $J_{4,3}$ 9.5, $J_{4,5}$ 9.5 Hz, H-4), 4.46, 4.49, 4.56, 4.60 (AB, 2 H, PhCH_2), 4.19, 4.45, 4.78, 4.82 (AB, 2 H, PhCH_2), 4.68 (s, 2 H, PhCH_2), 4.78, 4.82, 4.86, 4.90 (AB, 2 H, PhCH_2), 5.02 (dd, 1 H, $J_{2,1}$ 3.7, $J_{2,3}$ 10.3 Hz, H-2), 5.10 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), 5.64 (dd, 1 H, $J_{3,2}$ 10.3, $J_{3,4}$ 9.4 Hz, H-3), 6.29 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1).

Anal. Calcd. for $\text{C}_{46}\text{H}_{52}\text{O}_{14}$: MW 828. Found: m/z 934 (M + DEAH; 30), (FABS, DEA).

Methyl 1,2,3-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)- α -D-glucopyranuronate (26a)

A 50% solution of chromium trioxide in 3.5 M sulfuric acid (0.3 mL) was added to a solution of 26 (100 mg, 0.12 mmol) in acetone (10 mL) at 0°. After 3 h, the mixture was diluted with acetone and methanol, and filtered through silica gel. The solvents were removed and the oil esterified with diazomethane in ether. After evaporation of the ether, the residue was chromatographed (eluant, 1:2 ethyl acetate - hexane) to give 26a (56 mg, 0.07 mmol, 58%); $[\alpha]_D^{20} + 38$ (c 2.3, chloroform).

$^1\text{H-NMR}$: δ 1.84, 1.98, 2.16 (3 s, 9 H, OAc), 3.46 (dd, 1 H, $J_{2',1'} 3.3$, $J_{2',3'} 9.8$ Hz, H-2'), 3.52 (dd, 1 H, $J_{6a',5'} 1.7$, $J_{6a',6b'} 10.6$ Hz, H-6a'), 3.61 - 3.74 (m, 3 H, H-4', 5', 6b'), 3.65 (s, 3 H, CO_2Me), 3.90 (dd, 1 H, $J_{3',2'} 9.8$, $J_{3',4'} 8.4$ Hz, H-3'), 4.12 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.5$ Hz, H-4), 4.31 (d, 1 H, $J_{5,4} 9.7$ Hz, H-5), 4.41, 4.44, 4.78, 4.82 (AB, 2 H, PhCH_2), 4.42, 4.46, 4.54, 4.58 (AB, 2 H, PhCH_2), 4.60, 4.64, 4.67, 4.71 (AB, 2 H, PhCH_2), 4.79, 4.83, 4.88, 4.92 (AB, 2 H, PhCH_2), 4.93 (d, 1 H, $J_{1',2'} 3.3$ Hz, H-1'), 5.09 (dd, 1 H, $J_{2,1} 3.7$, $J_{2,3} 10.3$ Hz, H-2), 5.56 (dd, 1 H, $J_{3,2} 10.3$, $J_{3,4} 9.2$ Hz, H-3), 6.32 (d, 1 H, $J_{1,2} 3.7$ Hz, H-1), 6.9 - 7.27 (20 H, Ph).

Anal. Calcd. for $\text{C}_{47}\text{H}_{52}\text{O}_{15}$: MW 856. Found: m/z 962 (M + DEAH^+ , 5), (FABS, DEA).

2,3:5,6-di-O-isopropylidene-4-O-(3-O-tert-butyl-diphenylsilyl-4,6-O-isopropylidene- α -D-glucopyranosyl)-aldehyde- α -D-glucose dimethyl acetal
(27)

A solution of compound 1 (39 g, 77 mmol) in N,N'-dimethylformamide (150 mL) was added to a stirred solution of imidazole (20 g, 0.3 mol) and t-butyldiphenylsilyl chloride (27 g, 26 mL, 0.1 mol) in N,N'-dimethylformamide (100 mL). After 24 h, ice water (~ 300 mL) was added and the mixture extracted with diethyl ether (3 x 300 mL). A portion (5 g) of the residue after evaporation (66 g) was chromatographed (eluant, 1:5 ethyl acetate - hexane) to give 27 (3.2 g, 4.3 mmol, 72%). The crude residue was used directly for oxidation to 28, $[\alpha]_D^{20} + 43.9$ (c 4.1, chloroform).

$^1\text{H-n.m.r.}$: δ 1.07 (s, 9 H, SiCMe_3), 1.14, 1.20, 1.31, 1.37 (4 s, 18 H, CMe_2), 2.29 (d, 1 H, $J_{2',\text{OH}}$ 8.8 Hz, 2'-OH), 3.36, 3.40 (2 s, 6 H, OMe), 3.55 - 3.82 (6 H, H-2', 3', 4', 5', 6'), ~ 3.8 (2 H, H-4, 6a), 3.93 (dd, 1 H, J 6.3, J 8.3 Hz, H-6b), 4.01 (dd, 1 H, $J_{3,2}$ 7.1, $J_{3,4}$ 2.9 Hz, H-3), 4.12 (q, 1 H, J 5.9, J 6.4 Hz, H-5), 4.22 (dd, 1 H, $J_{2,1}$ 6.4, $J_{2,3}$ 6.8 Hz, H-2), 4.34 (d, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 5.02 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 7.3 - 7.75 (10 H, arom. H).

$^{13}\text{C-n.m.r.}$: δ 18.62, 19.71, 25.20, 26.40, 27.06, 27.26, 27.32, 28.74 (SiCMe_3 , CMe_2), 53.27, 56.27 (OMe), 62.16 (C-5'), 63.90 (C-6'), 65.82 (C-6), 73.83, 73.99, 74.22 (C-2', 3', 4'), 75.06 (C-2), 99.18 (4', 6'-O-CMe₂), 100.95 (C-1'), 104.91 (C-1), 108.61, 109.79 (CMe_2), 127 - 136 (arom. C).

Anal. calcd. for $\text{C}_{39}\text{H}_{58}\text{O}_{12}\text{Si}$: MW 746. Found: m/z 852 (M + DEAH⁺, 9.5), (FABS⁺, DEA).

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butyldiphenylsilyl-4,6-O-isopropylidene- α -D-arabino-hexopyranos-2-ulosyl)-aldehyde-D-glucose dimethyl acetal (28)

To a solution of compound 27 (3.2 g, 4.1 mmol) in methylene chloride (100 mL) was added pyridinium dichromate (2.5 g, 6.7 mmol) and acetic anhydride (3.1 g, 2.8 mL, 30 mmol) and the mixture was stirred and refluxed for 20 h. The solvents were removed by repeated evaporations using toluene, the residue was dissolved in ethyl acetate and the solution was filtered through silica gel on celite, and concentrated. Chromatography (eluant, 1:5 ethyl acetate - hexane) gave 28 as an oil (2.2 g, 3.0 mmol, 73%); $[\alpha]_D^{20} + 47.4$ (c 4.3, chloroform).

$^1\text{H-n.m.r.}$: δ 1.08 (s, 9 H, SiCMe_3), 1.05, 1.22, 1.32, 1.36, 1.38, 1.43 (6 s, each 3 H, CMe_2), 3.408, 3.413 (2 s, each 3 H, OMe), 3.7 - 4.15 (10 H, H-2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 4.39 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 4.50 (dd, 1 H, $J_{3',4'}$ 10.0 Hz, H-3'), 5.03 (s, 1 H, H-1').

$^{13}\text{C-n.m.r.}$: δ 19.67, 25.17, 26.38, 26.50, 27.02, 27.15, 28.66 (SiCMe_3 , CMe_2), 52.27, 56.29 (OMe), 61.96 (C-5'), 64.35 (C-6'), 65.71 (C-6), 73.74 (C-2), 75.42 (C-5), 76.00 (C-4'), 76.95 (C-3'), 78.01, 78.36 (C-3, C-4), 99.26 (4',6'-O- CMe_2), 102.12 (C-1'), 104.48 (C-1), 108.70, 109.45 (CMe_2), 127 - 136 (arom. C), 197.38 (C-2').

Anal. calcd. for $\text{C}_{39}\text{H}_{56}\text{O}_{12}\text{Si}$: MW 744. Found: m/z 850 (M + DEAH, 5.7), (FABS⁺, DEA).

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butyl-diphenylsilyl-2-deoxy-4,6-O-isopropylidene-2-oximin- α -D-arabino-hexopyranosyl)-aldehydo-D-glucose dimethyl acetal (29)

To a solution of compound 28 (4.5 g, 6.1 mmol) in methanol (50 mL) was added a solution of 1:2:10 hydroxylamine hydrochloride, sodium acetate and water (30 mL, buffered to pH 4.5 with acetic acid) and a further 20 mL of methanol. After stirring at room temperature for 4 h, the methanol was removed, more water added and the mixture extracted with chloroform (4 x 50 mL). The organic extract was washed with sodium hydrogen carbonate solution and water, dried and concentrated to give a syrup, 29 (4.7 g, 6.1 mmol, 100%) suitably pure for methylation to 44. A small amount was purified further by chromatography (eluant, 1:4 ethyl acetate - hexane).

¹H-n.m.r.: δ 1.08, 1.11, 1.13, 1.31, 1.35, 1.37, 1.38 (7 s, 27 H, SiCMe₃, CMe₂), ~ 1.6 (bs, NOH), 3.39, 3.41 (2 s, each 3 H, OMe), 3.3 - 4.3 (11 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 4.60 (d, 1 H, J_{3',4'} 9.3 Hz, H-3'), 6.11 (s, 1 H, H-1'), 7.26 - 7.72 (10 H, SiPh₂).

¹³C-n.m.r.: δ 18.70, 19.74, 25.33, 26.23, 26.42, 27.02, 27.27, 28.66 (SiCMe₃, CMe₂), 53.11, 56.34 (OMe), 61.88 (C-5'), 64.15 (C-6'), 65.90 (C-6), 71.28 (C-3'), 74.13 (C-2), 75.80 (C-4'), 76.22 (C-3), 78.48 (C-4), 92.15 (4',6'-O-CMe₂), 99.36 (C-1'), 105.45 (C-1), 108.49, 109.66 (CMe₂), 127 - 136 (SiPh₂), 153.87 (C-2').

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butyldimethylsilyl-4,6-O-isopropylidene- α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal (27a)

To a solution of compound 1 (12 g, 24 mmol) and imidazole (4.0 g, 60 mmol) in N,N-dimethylformamide (25 mL) at 0° C was added tert-butyldimethylsilyl chloride (4.1 g, 2.7 mmol) and the mixture left for 5 h with gradual warming to room temperature. An ice water mixture was added, followed by extraction with diethyl ether (3 x 70 mL), the extract was dried, filtered and concentrated, and the residue was chromatographed (eluant, 1:4 ethyl acetate - hexane) to give syrupy 27a (12 g, 19 mmol, 80%).

In repeat preparations, the crude residue was suitable for oxidation after a solution in 1:4 ethyl acetate - hexane was filtered through silica gel; $[\alpha]_D^{20} + 75.5$ (c 2, chloroform).

¹H-n.m.r.: δ 0.07, 0.08 (2 s, 6 H, SiMe₂), 0.89 (s, 9 H, SiCMe₃), 1.35, 1.38, 1.43, 1.45 (4 s, 18 H, CMe₂), 3.43, 3.44, 3.4 - 4.4 (2 s and m, 19 H, OMe, H-1, 2, 3, 4, 5, 6a, 6b, 2', 3', 4', 5', 6a', 6b'), 5.05 (d, 1 H, J_{1',2'} 3.7 Hz, H-1').

2,3:5,6-Di-O-isopropylidene-4-O-(2-O-acetyl-3-O-tert-butyldiphenylsilyl-4,6-O-isopropylidene- α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal (27b)

Compound 27a (50 mg, 0.1 mmol) was acetylated, and chromatographed (eluant, 1:4 ethyl acetate - hexane) to give syrupy 27b (60 mg, 0.09 mmol); $[\alpha]_D^{20} + 42.3$ (c 6.4, chloroform).

^1H -n.m.r.: δ 0.03, 0.04 (2 s, 6 H, SiMe_2), 0.85 (s, 9 H, SiCMe_3), 1.35, 1.38, 1.43, 1.46 (4 s, 18 H, CMe_2), 2.13 (s, 3 H, OAc), 3.44 (s, 6 H, OMe), 3.4 - 4.25 (11 H, H-2, 3, 4, 5, 6a, 6b, 3', 4', 5', 6a', 6b'), 4.31 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1), 4.82 (dd, 1 H, $J_{2',1'}$ 3.8, $J_{2',3'}$ 9.7 Hz, H-2'), 5.10 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1').

Anal. calcd. for $\text{C}_{31}\text{H}_{56}\text{O}_{13}\text{Si}$: MW 664. Found: m/z 649 ($\text{M}^+ - \text{CH}_3$, 100), m/z 607 ($\text{M}^+ - \text{t-Bu}$, 15). Calc.: C, 56.00; H, 8.49. Found: C, 55.62; H, 8.16.

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butyltrimethylsilyl-4,6-O-isopropylidene- α -D-arabino-hexopyranos-2-ulosyl)-aldehyde-D-glucose dimethyl acetal (28a)

Method A: A mixture of compound 27a (1.2 g, 1.9 mmol) and pyridinium chlorochromate adsorbed on alumina (1.2 g) was vigorously stirred in refluxing benzene (30 mL) for 2 h. After cooling and filtering, the dark brown benzene solution was recharged with the oxidant (1.2 g) and heated under reflux for a further 4 h. After a second filtration the filtrate was concentrated, and the residue chromatographed (eluant, 1:4 ethyl acetate - hexane), to give oily 28a (0.71 g, 1.1 mmol, 58%).

Method B: To a solution of compound 27a (5 g, 7.5 mmol) in benzene (200 mL) was added finely ground pyridinium chlorochromate (3 g, 14 mmol) and potassium acetate (1 g), and the mixture was heated under reflux for 2 h. As in method A, the mixture was recharged with oxidant until no change was observed on T.l.c. (1:2 ethyl acetate - hexane).

After the final filtration, the filtrate was concentrated and the residue chromatographed (eluant, 1:4 ethyl acetate - hexane) to give 28a (3.2 g, 5.1 mmol, 68%); $[\alpha]_D^{20} + 26.5$ (c 2.5, chloroform).

$^1\text{H-n.m.r.}$: δ 0.04, 0.12 (2 s, 6 H, SiMe_2), 0.90 (s, 9 H, SiCMe_3), 1.26, 1.37, 1.41, 1.47 (18 H, CMe_2), 3.426, 3.432 (2 s, 6 H, OMe), 4.43 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.65 (d, 1 H, $J_{3',4'}$ 10 Hz, H-3'), 5.04 (s, 1 H, H-1').

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butyldimethylsilyl-2-deoxy-4,6-isopropylidene-2-oximino- α -D-arabino-hexopyranosyl)-aldehyde-D-glucose dimethyl acetal (29a)

Compound 28a (240 mg, 0.39 mmol) was treated with hydroxylamine as described for 28. The residue was chromatographed (eluant, 1:4 ethyl acetate - hexane) to give 29a (243 mg, 0.38 mmol, 97%), a clear syrup; $[\alpha]_D^{20} + 44.0$ (c 3.1, chloroform).

$^1\text{H-n.m.r.}$: δ 0.07, 0.10 (2 s, 6 H, SiMe_2), 0.90 (s, 12 H, SiCMe_3), 1.31, 1.37, 1.39, 1.42, 1.46, 1.47 (6 s, 18 H, CMe_2), 3.41, 3.43 (2 s, 6 H, OMe), 3.6 - 4.5 (m, 11 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 4.53 (d, 1 H, $J_{3',4'}$ 8.4 Hz, H-3'), 6.14 (s, 1 H, H-1').

Anal. calcd. for $\text{C}_{29}\text{H}_{53}\text{O}_{12}\text{NSi}$: MW 635. Found: m/z 636 ($\text{M} + \text{H}^+$, 100), m/z 620 ($\text{M} - \text{Me}$, 98), m/z 578 ($\text{M} - \text{t-Bu}$, 43), (FAB^+ , glycerol).

2,3:5,6-Di-O-isopropylidene-4-O-(2-O-acetoximino-3-O-tert-butylidimethylsilyl-2-deoxy-4,6-O-isopropylidene- α -D-arabino-hexopyranosyl)-aldehyde-D-glucose dimethyl acetal (29b)

Oxime 29a (240 mg, 0.38 mmol) was acetylated, and chromatographed (eluant, 1:4 ethyl acetate - hexane) to give an oil, 29b (250 mg, 0.37 mmol, 97%).

$^1\text{H-N.M.R.}$: δ 0.08, 0.16 (2 s, 6 H, SiMe_2), 0.92 (s, 9 H, SiCMe_3), 1.31, 1.36, 1.40, 1.46, 1.48 (5 s, 18 H, CMe_2), 2.24 (s, 3 H, OAc), 3.46, 3.47 (2 s, 6 H, OMe), 3.7 - 4.32 (m, 11 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 4.63 (d, 1 H, $J_{3',4}$, 9.7 Hz, H-3'), 6.10 (s, 1 H, H-1').

2,3:5,6-Di-O-isopropylidene-4-O-(2-acetamido-3-O-acetyl-2-deoxy-4,6-O-isopropylidene- α -D-glucopyranosyl) and α -D-mannopyranosyl)-aldehyde-D-glucose dimethyl acetal (31)

A solution of oxime 29a (18 g, 28 mmol) in tetrahydrofuran (100 mL) was slowly added to a stirred suspension of lithium aluminium hydride (3.8 g) in tetrahydrofuran (150 mL) at 0°. After 3 h, wet ether and then water were added slowly to decompose unreacted hydride. The resulting slurry was filtered and the filtrate concentrated. The mixture was extracted with ethyl acetate, and the organic solution evaporated to dryness with repeated additions of toluene. The crude residue was acetylated with acetic anhydride and pyridine. The solvents were removed under high vacuum and chloroform added to the residue. This solution was washed with sodium hydrogen carbonate solution and water,

then dried and concentrated. The residue was chromatographed (eluant, 2:1 ethyl acetate - hexane) to provide two major products, the gluco-isomer, 30 (6.5 g, 11 mmol, 39%) and the manno-isomer, 31 (4.5 g, 8 mmol, 29%); $[\alpha]_D^{20} + 40$ (c 1.0, chloroform).

Data for 30: $^1\text{H-n.m.r.}$: δ 1.36, 1.37, 1.43, 1.46, 1.47, 1.52 (6 s, 18 H, CMe_2), 1.97, 2.06 (2 s, 6 H, NHAc, OAc), 3.42, 3.44 (2 s, 6 H, OMe), 4.37 (d, 1 H, $J_{1,2}$ 6.5 Hz, H-1), 4.98 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1'), 5.12 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 9.4$ Hz, H-3'), 6.27 (d, 1 H, $J_{\text{NH},2'}$ 9.6 Hz, NHAc).

Data for 31: $^1\text{H-n.m.r.}$: δ 1.35, 1.38, 1.41, 1.44, 1.47, 1.51 (6 s, 18 H, CMe_2), 2.02, 2.04 (2 s, 6 H, NHAc, OAc), 3.40, 3.44 (2 s, 6 H, OMe), 4.42 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1), 4.97 (s, 1 H, H-1'), 5.20 (dd, 1 H, $J_{3',2'}$ 4.6, $J_{3',4'}$ 10 Hz, H-3'), 5.62 (d, 1 H, $J_{\text{NH},2'}$ 9 Hz, NHAc).

Anal. Calcd. for $\text{C}_{27}\text{H}_{45}\text{O}_{13}\text{N}$: MW 591. Found: m/z ($\text{M} + \text{DEAH}^+$, 25), (FABS, DEA). Calcd.: C, 54.81; H, 7.67; N, 2.37. Found: C, 54.55; H, 7.48; N, 2.21.

2,3:5,6-Di-O-isopropylidene-4-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (34)

A solution of 30 (400 mg, 0.68 mmol) in 0.004% hydrochloric acid in methanol (35 mL) was stirred for 12 h. After neutralization with basic resin, the solvents were removed by evaporation and the residue chromatographed (eluant, 1:9 methanol - ethyl acetate) to give the major product, showing loss of one isopropylidene group. This compound was acetylated and the product chromatographed (eluant, 4:1 ethyl ace-

tate - hexane) to give 34 (200 mg, 0.31 mmol, 46%); $[\alpha]_D^{20} + 64$ (c 1.4, chloroform).

$^1\text{H-n.m.r.}$: δ 1.35, 1.42, 1.43, 1.50 (4 s, 12 H, CMe_2), 1.97, 2.02, 2.021, 2.11 (4 s, 12 H, OAc, NHAc), 3.44, 3.46 (2 s, 6 H, OMe), 4.38 (d, 1 H, $J_{1,2}$ 6.1 Hz, H-1), 4.38 (ddd, 1 H, $J_{2,1}$ 3.6 Hz, H-2'), 5.11 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1'), 5.19 (dd, 1 H, $J_{4',3'} = J_{4',5'} = 9.5$ Hz, H-4'), 5.23 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 10$ Hz, H-3').

Anal. calcd. for $\text{C}_{28}\text{H}_{45}\text{O}_{15}\text{N}$: MW 635. Found: m/z 636 ($\text{M} + \text{H}^+$, 68), 620 ($\text{M} - \text{CH}_3$, 100), (FABS, Thioglycerol).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal
(37)

As described in the procedure for compound 14, 34 (200 mg, 0.31 mmol) was hydrolyzed with 80% aqueous acetic acid at 50° . The product 35 (123 mg, 0.21 mmol, 68%), obtained after chromatography (eluant, ethyl acetate), was acetylated to give 37, also purified by chromatography (eluant, 3:1 ethyl acetate - hexane); $[\alpha]_D^{20} + 36$ (c 6.5, chloroform).

$^1\text{H-n.m.r.}$: δ 1.41 (s, 6 H, CMe_2), 1.96, 2.03, 2.05, 2.09, 2.10, 2.12 (6 s, 18 H, OAc, NHAc), 3.43, 3.46 (2 s, 6 H, OMe), 3.88 (dd, 1 H, $J_{4,3}$ 7.2, $J_{4,5}$ 1.7 Hz, H-4), 4.40 (d, 1 H, $J_{1,2}$ 5.2 Hz, H-1), 4.46 (d, 1 H, $J_{6b,5}$ 3, $J_{6b,6a}$ 12.2 Hz, H-6b), 5.05 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1'), 5.28 (ddd, 1 H, $J_{5,4} \sim 1.6$, $J_{5,6a}$ 8, $J_{5,6b}$ 3 Hz, H-5), 6.05 (d, 1 H, $J_{\text{NH},2}$ 9.5 Hz, NHAc).

Anal. calcd. for $C_{29}H_{45}O_{17}N$: MW 679. Found: m/z 664 (M^+-CH_3 , 30), (EI).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-L-idose dimethyl acetal
(36)

As described in the procedure for compound 17, diol 35 (85 mg, 0.14 mmol) was converted to the 5,6-dimesylate and then reacted with potassium acetate in refluxing acetic anhydride to provide 36 (60 mg, 57%). Purification required two successive chromatographic steps (eluant, 3:1 ethyl acetate - hexane); $[\alpha]_D^{20} + 29$ (c 1.0, chloroform).

^1H -n.m.r.: δ 1.44, 1.53 (2 s, 6 H, CMe_2), 1.97, 2.02, 2.045, 2.05, 2.09, 2.10 (6 s, 18 H, OAc), 3.43, 3.44 (2 s, 6 H, OMe), 3.79 (dd, 1 H, $J_{4,3}$ 2.5, $J_{4,5}$ 5.2 Hz, H-4), 3.98 (dd, 1 H, $J_{2,1} = J_{2,3} = 6.2$ Hz, H-2), 4.10 (dd, 1 H, $J_{6a',5'}$ 2, $J_{6a',6b'}$ 12 Hz, H-6a'), 4.37 (d, 1 H, $J_{1,2}$ 6.3 Hz, H-1), 4.52 (dd, 1 H, $J_{6b,5}$ 2.8, $J_{6b,6a}$ 12.5 Hz, H-6b), 5.02 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 5.32 (ddd, 1 H, $J_{5,4}$ 5.2, $J_{5,6a}$ 7.8, $J_{5,6b}$ 2.7 Hz, H-5), 6.14 (d, 1 H, NHAc).

Anal. calcd. for $C_{29}H_{45}O_{17}N$: MW 679. Found: m/z 664 (M^+-CH_3 , 100), (EI).

2,3:5,6-Di-O-isopropylidene-4-O-(2-deoxy-4,6-O-isopropylidene-2-oxi-
mino- α -D-arabino-hexopyranosyl)-aldehydo-D-glucose dimethyl acetal
(38)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (0.8 M, 16 mL, 15 mmol) was added to a solution of compound 29a (7.0 g, 11 mmol) in tetrahydrofuran (50 mL) at room temperature. After heating at 70° for 9 h, the solvent was removed, and the residue chromatographed (eluant, 1:1 ethyl acetate - hexane) to give a syrup, 38 (4.9 g, 9.4 mmol, 94%); $[\alpha]_D^{25} + 61.8$ (c 2.7, chloroform).

$^1\text{H-n.m.r.}$: δ 1.31, 1.37, 1.40, 1.44, 1.48, 1.52 (6 s, 18 H, CMe_2), 3.42, 3.44 (2 s, 6 H, OMe), 3.64 - 4.47 (m, 13 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b', OH, NOH), 4.53 (dd, 1 H, $J_{3',4'} 9.4$, $J_{3',\text{OH}} \sim 3.4$ Hz, H-3'), 6.10 (s, 1 H, H-1').

$^{13}\text{C-n.m.r.}$: δ 19.10, 25.19, 26.38, 27.19, 28.96 (CMe_2), 53.46, 56.43 (OMe), 61.82 (C-5'), 63.55 (C-6'), 65.92 (C-6), 69.11 (C-3'), 74.23 (C-2), 75.88 (C-3, 5, 4'), 78.55 (C-4), 91.98 (4', 6'-OCMe₂), 99.96 (C-1'), 105.63 (C-1), 108.65, 109.73 (CMe_2), 152.18 (C-2').

Anal. calcd. for $\text{C}_{23}\text{H}_{39}\text{O}_{12}\text{N}$: MW 521. Found: m/z 522 ($\text{M}^+ + \text{H}^+$, 20), m/z 506 (M-Me, 50), (FABS⁺, thioglycerol).

2,3:5,6-Di-O-isopropylidene-4-O-(2-O-acetoximino-3-O-acetyl-2-deoxy-4,6-O-isopropylidene- α -D-arabino-hexopyranosyl)-aldehydo-D-glucose dimethyl acetal (39)

Compound 38 (580 mg, 1.1 mmol) was acetylated in the usual manner. The residue was purified by chromatography (eluant, 1:2 ethyl acetate - hexane) to give a syrup, 39 (520 mg, 0.86 mmol, 77%); $[\alpha]_D^{20} + 60$ (c 2, chloroform).

$^1\text{H-n.m.r.}$: δ 1.35, 1.36, 1.401, 1.403, 1.49 (5 s, 18 H, CMe_2), 2.17, 2.21 (2 s, 6 H, OAc), 3.46, 3.47 (2 s, 6 H, OMe), 3.68 (dd, 1 H, $J_{6a',5'} \sim 10.5$, $J_{6a',6b'} \sim 10.5$ Hz, H-6a'), 3.87 (dd, 1 H, $J_{6b',5'} \sim 5.2$, $J_{6b',6a'} \sim 10.5$ Hz, H-6b'), 3.87 (dd, 1 H, $J_{4',3'} 10.2$, $J_{4',5'} 10.2$ Hz, H-4'), 3.91 - 4.02 (m, H-2, 3, 4, 6a, 6b), 4.13 (ddd, 1 H, $J_{5',4'} \sim 10$, $J_{5',6a'} \sim 10$, $J_{5',6b'} \sim 5.2$ Hz, H-5'), 4.25 (d, 1 H, $J_{1,2} 5.1$ Hz, H-1), 5.66 (d, 1 H, $J_{3',4'} 10.25$ Hz, H-3'), 6.03 (s, 1 H, H-1').

$^{13}\text{C-n.m.r.}$: δ 18.99 (CMe_2), 19.37, 20.61 (OAc), 25.09, 26.38, 27.19, 28.92 (CMe_2), 55.51, 57.13 (OMe), 61.88 (C-5'), 64.4 (C-6'), 65.55 (C-6), 69.43 (C-3'), 72.88 (C-2), 76.12, 77.79 (C-3, 5, 4'), 78.17 (C-4), 93.06 (4',6'-O- CMe_2), 100.02 (C-1'), 106.49 (C-1), 108.65, 110.05 (CMe_2), 155.47 (C-2'), 167.67, 169.61 (OAc).

2,3:5,6-Di-O-isopropylidene-4-O-(2-benzyloximino-2-deoxy-4,6-O-isopropylidene- α -D-arabino-hexopyranosyl)-aldehyde-D-glucose dimethyl acetal
(40)

Compound 38 (640 mg, 1.2 mmol) in tetrahydrofuran (5 mL) was added to a stirred suspension of sodium hydride (75 mg, 3 mmol) in tetrahydrofuran (5 mL) at 0°. After 10 min benzyl bromide (0.36 mL, 3 mmol) and tetrabutylammonium iodide (< 5 mg) were added, and the mixture was stirred at room temperature for 6 h. After the excess sodium hydride was decomposed with wet tetrahydrofuran, a 5% hydrochloric acid solution was added, the mixture diluted with water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and water, dried, and concentrated. The residue was chromatographed (eluant, 2:3 ethyl acetate - hexane) to give two products, first a dibenzylated compound, 41 (60 mg, 90 μ mol, 7%) (see following procedure), and 40 (640 mg, 1.05 mmol, 85%) a monobenzylated compound; $[\alpha]_D^{20} + 79.2$ (c 1.1, chloroform).

$^1\text{H-N.M.R.}$: δ 1.27, 1.35, 1.37, 1.45, 1.48, 1.51 (6 s, 18 H, CMe_2), 3.22 (d, 1 H, $J_{\text{OH},3'}$ 3.6 Hz, H-3', OH), 3.25, 3.39 (2 s, 6 H, OMe), 3.60 - 4.25 (m, 11 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 4.55 (dd, 1 H, $J_{3',4'}$ 9.5, $J_{3',\text{OH}}$ ~ 3.5 Hz, H-3'), 5.14 (s, 2 H, PhCH_2), 6.05 (s, 1 H, H-1'), 7.36 (s, 2 H, Ph).

Anal. calcd. for $\text{C}_{30}\text{H}_{45}\text{NO}_{12}$: MW 611. Found: m/z 612 ($\text{M} + \text{H}^+$, 55), m/z 596 (M-Me , 62), (FAB $^+$, thioglycerol).

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-benzyl-2-benzyloximino-2-deoxy-4,6-O-isopropylidene-D-arabino-hexopyranosyl)-aldehyde-D-glucose dimethyl acetal (41)

Compound 41 was prepared by a method similar to that described for 40. Compound 38 (980 mg, 1.9 mmol) in tetrahydrofuran (10 mL) was added to a suspension of sodium hydride (125 mg, 5 mmol) in tetrahydrofuran (5 mL) at 0°. Benzyl bromide (0.5 mL, 4.1 mmol) and tetrabutylammonium iodide (< 5 mg) were added and the mixture was heated at 60° for 8 h. After the workup and purification described previously for 40, syrupy 41 (1.03 g, 1.5 mmol, 78%) was recovered; $[\alpha]_D^{20} + 36.4$ (c 2.2, chloroform).

¹H-n.m.r.: δ 1.20, 1.34, 1.37, 1.42, 1.45, 1.48 (6 s, 18 H, CMe₂), 3.28, 3.38 (2 s, 6 H, OMe), 3.67 - 4.27 (m, 11 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 4.36 (d, 1 H, J_{3',4'}, 9.7 Hz, H-3'), 4.59, 4.65, 4.76, 4.82 (AB, 2 H, PhCH₂), 5.16 (s, 2 H, PhCH₂-ON=), 6.09 (s, 1 H, H-1'), 7.26 - 7.39 (m, 10 H, Ph).

¹³C-n.m.r.: δ 19.20, 25.25, 26.54, 27.24, 29.19 (CMe₂), 54.81, 56.97 (OMe), 62.15 (C-5'), 64.68 (C-6'), 66.25 (C-6), 72.67 (C-3'), 75.09, 75.58, 76.33, 77.04, 77.79, 78.06 (C-2, 3, 4, 5, 4', PhCH₂), 93.00 (4',6'-OCMe₂), 99.80 (C-1'), 106.06 (C-1'), 108.70, 109.62 (CMe₂), 127.75 - 138.80 (Ph), 151.97 (C-2').

Anal. Calcd. for C₃₇H₅₁NO₁₂: C, 63.32; H, 7.32; N, 2.00. Found: C, 62.91; H, 7.16; N, 2.33.

2,3:5,6-Di-O-isopropylidene-4-O-(2-amino-2-deoxy-4,6-isopropylidene- α -D-glucopyranosyl)- β -D-mannopyranosyl)-aldehyde-D-glucose dimethyl acetal (43)

A solution of 44 (4.2 g, 6.5 mmol) in tetrahydrofuran (50 mL) was slowly added to a cooled (0°) suspension of lithium aluminum hydride (1.2 g) in tetrahydrofuran (100 mL), and the mixture was then slowly heated to 65°. After 18 h, unreacted hydride was decomposed by addition of ethyl acetate, ethanol and water in succession, and the white slurry filtered. The filtrate was concentrated and the aqueous mixture extracted with chloroform (5 x 100 mL). The extract was washed with water, dried and concentrated to a syrup which gave, after chromatography (eluant, 2.5% methanol in chloroform), a foam, 43 (2.0 g, 3.9 mmol, 60%).

$^1\text{H-n.m.r.}$: δ 1.36, 1.41, 1.43, 1.48, 1.51 (5 s, 18 H, CMe_2), ~ 2 (bs, OH), 3.45, 3.46 (2 s, 6 H, OMe), 5.05 (d, $J_{1',2'}$, 3.8 Hz, glucosyl H-1'), ~ 5.12 (d, $J_{1',2'}$, < 1 Hz, mannosyl H-1').

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butylidiphenylsilyl-2-deoxy-4,6-O-isopropylidene-2-methyloximino- α -D-arabino-hexopyranosyl)-aldehyde-D-glucose dimethyl acetal (44)

Methyl iodide (0.8 mL, 1.8 g, 12.9 mmol) was added to a stirred mixture of compound 29 (4.7 g, 6.1 mmol), barium oxide (1.6 g, 10 mmol) and barium hydroxide octahydrate (1.6 g, 5 mmol), the suspension was heated under reflux for 24 h, and filtered. The filtrate was concen-

trated, and the residue chromatographed (eluant, 1:5 ethyl acetate - hexane) to give a syrup, 44 (4.4 g, 5.7 mmol, 93%).

^1H -n.m.r.: δ 1.09, 1.10, 1.18, 1.31, 1.36, 1.42 (6 s, 27 H, SiCMe_3 , CMe_2), 3.39, 3.41 (2 s, 6 H, OMe), ~ 3.67 (2 H, H-6a', 6b'), ~ 3.7 - 3.95 (6 H, H-3, 4, 6a, 6b, 4', 5'), 3.81 (s, 3 H, NOME), 4.12 (ddd, 1 H, $J_{5,4}$ 6.8, $J_{5,6a}$ 6.8, $J_{5,6b}$ 4.9 Hz, H-5), 4.21 (dd, 1 H, $J_{2,1}$ 6.6, $J_{2,3}$ 7.8 Hz, H-2), 4.32 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.55 (d, 1 H, $J_{3,4}$ 9.0 Hz, H-3'), 6.11 (s, H-1'), 7.3 - 7.7 (m, 10 H, SiPh_2).

^{13}C -n.m.r.: δ 18.79, 19.74, 25.31, 26.07, 26.39, 27.24, 28.74 (CMe_2), 27.03 (SiCMe_3), 53.08, 56.38 (OMe), 61.92 (NOME), 62.04 (C-5'), 64.02 (C-6'), 65.86 (C-6), 71.20 (C-3'), 74.14 (C-2), 75.69 (C-4'), 76.30 (C-3), 76.34 (C-5), 78.45 (C-4), 92.58 (4',6'- OCMe_2), 99.34 (C-1'), 105.49 (C-1), 108.42, 109.58 (CMe_2), 127 - 136 (SiPh_2), 152.13 (C-2').

Anal. Calcd. for $\text{C}_{40}\text{H}_{59}\text{O}_{12}\text{NSi}$: MW 774. Found: m/z 879 ($\text{M} + \text{DEAH}^+$, 10), (FABS, DEA).

2,3:5,6-Di-O-isopropylidene-4-O-(3-O-tert-butyltrimethylsilyl-2-deoxy-4,6-O-isopropylidene-2-methyloximino- α -D-arabino-hexopyranosyl)-aldehyde-D-glucose dimethyl acetal (44a)

A solution of compound 29a (506 mg, 0.8 mmol) in tetrahydrofuran (5 mL) was added to a suspension of sodium hydride (50 mg, 2 mmol) in tetrahydrofuran (5 mL) at 0°. After 10 min, methyl iodide was added, the mixture was then held at room temperature for a total reaction time of 4 h. Wet tetrahydrofuran was added to destroy the excess of sodium

hydride, followed by the addition of water and extraction of the mixture with chloroform. The extract was washed with water, dried and concentrated. The residue was chromatographed (eluant, 1:6 ethyl acetate - hexane) to give a clear syrup, 44a (440 mg, 0.68 mmol, 85%); $[\alpha]_D^{20} + 46.5$ (c 2.1, chloroform).

$^1\text{H-n.m.r.}$: δ 0.07, 0.13 (2 s, 6 H, SiMe_2), 0.91 (s, 9 H, SiCMe_3), 1.30, 1.36, 1.39, 1.42, 1.457, 1.462 (6 s, 18 H, CMe_2), 3.44 (s, 6 H, OMe), 3.45 - 4.38 (m, 11 H, H-1, 2, 3, 4, 5, 6a, 6b, 4', 5', 6a', 6b'), 3.89 (s, 3 H, NOME), 4.49 (d, 1 H, $J_{3',4'} 9.4$ Hz, H-3'), 5.92 (s, 1 H, H-1').

Anal. calcd. for $\text{C}_{30}\text{H}_{55}\text{O}_{12}\text{NSi}$: MW 649. Found: m/z 650 ($\text{M} + \text{H}^+$, 100), m/z 592 ($m\text{-t-Bu}$, 88), (FAB S^+ , thioglycerol).

2,3:5,6-Di-O-isopropylidene-4-O-(2-acetamido-2-deoxy-4,6-O-isopropylidene- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (45) and -mannopyranosyl)-aldehyde-D-glucose dimethyl acetal (46)

Acetic anhydride (0.5 mL, 4.9 mmol) was added to a stirred solution of 43 (1.8 g, 3.5 mmol) in methanol (100 mL). After 2 h, the solvents were removed and the residue chromatographed (eluant, 2.5% methanol in chloroform) to give two products, first the gluco isomer, 45 (1.66 g, 3.0 mmol, 86%) followed by the manno isomer, 46 (200 mg, 0.36 mmol, 10%).

Data for 45: $^1\text{H-n.m.r.}$: δ 1.35, 1.42, 1.45, 1.46, 1.48, 1.52 (6 s, 18 H, CMe_2), ~ 1.8 (bs, OH), 2.07 (s, 3 H, NHAc), 3.44, 3.46 (2 s, 6

H, OMe), ~ 4.15 (m, H-2'), 4.38 (d, 1 H, $J_{1,2}$ 6.1 Hz, H-1), 4.97 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1').

^{13}C -n.m.r.: δ 19.07, 24.92, 26.29, 27.42, 28.98 (CMe_2), 22.90 (HNAC), 54.49 (C-2'), 54.67, 56.64 (OMe), 61.89 (C-5'), 63.75 (C-6'), 65.72 (C-6), 71.01 (C-3'), 74.66, 74.90, 76.81 (C-2, 5, 4'), 78.58 (C-3), 79.88 (C-4), 98.44 (CMe_2), 99.74 (C-1'), 105.03 (C-1), 108.89, 110.60 (CMe_2), 172.17 (NAC).

Anal. calcd. for $\text{C}_{25}\text{H}_{43}\text{O}_{12}\text{N}$: MW 549. Found: m/z 550 ($\text{M} + \text{H}^+$, 44), (FABS, glycerol). Calcd. for $\text{C}_{25}\text{H}_{43}\text{O}_{12}\text{N} \cdot \text{H}_2\text{O}$: C, 52.90; H, 7.99; N, 2.47. Found: C, 52.76; H, 8.08; N, 2.35.

Data for 46: ^1H -n.m.r.: δ 1.36, 1.43, 1.49, 1.55, 1.64 (5 s, 18 H, CMe_2), 2.08 (s, 3 H, HNAC), 2.77 (bs, 1 H, OH), 3.44, 3.46 (2 s, 6 H, OMe), 4.42 (d, 1 H, $J_{1,2}$ 6.2 Hz, H-1), 5.13 (s, 1 H, H-1').

2,3:5,6-Di-O-isopropylidene-4-O-(2-acetamido-3-O-benzyl-2-deoxy-4,6-O-isopropylidene- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal
(47)

Method A: A solution of 41 (190 mg, 0.78 mmol) in tetrahydrofuran (10 mL) was added to a stirred suspension of lithium aluminum hydride (30 mg) in tetrahydrofuran (10 mL) at 0°. After 10 h at room temperature, the mixture was processed as described for 30 to provide a syrup, which, after chromatography (eluant, 2:1 ethyl acetate - hexane) gave 47 (84 mg, 0.13 mmol, 46%). A second, minor fraction was identified as 30 (11 mg, 0.02 mmol, 7%).

Method B: A solution of 45 (1.25 g, 2.3 mmol) in tetrahydrofuran (20 mL) was added to a stirred suspension of sodium hydride (125 mg) in

tetrahydrofuran (20 mL) at 0°. After 10 min, benzyl bromide (0.4 mL, 3.4 mmol) and tetrabutylammonium bromide (~ 10 mg) were added, and the mixture was stirred for 12 h. After addition of ethanol, the solvents were removed and the residue dissolved in chloroform. The solution was washed with water, dried and concentrated to give a syrup, which after chromatography (eluant, 2:1 ethyl acetate - hexane) provided 47 (1.15 g, 1.8 mmol, 78%); $[\alpha]_D^{20} + 79$ (c 2.1, chloroform).

¹H-n.m.r.: δ 1.30, 1.35, 1.40, 1.43, 1.46, 1.50 (6 s, 18 H, CMe₂), 1.94 (s, 3 H, NAc), 3.38, 3.41 (2 s, 6 H, OMe), 3.49 (dd, 1 H, J_{3',2'} 8.3, J_{3',4'} 10.5 Hz, H-3'), 3.68 (dd, 1 H, J_{4,3} 2.9, J_{4,5} 6.1 Hz, H-4), 3.73 - 3.84 (m, 4 H, H-4', 5', 6a', 6b'), 3.93 (dd, 1 H, J_{2,1} = J_{2,3} = 6.1 Hz, H-2), 3.96 (dd, 1 H, J_{6a,5} 6.1 Hz, H-6a), 4.04 (dd, 1 H, J_{6b,5} 6.1 Hz, H-6b), 4.19 (ddd, 1 H, J_{5,4} = J_{5,6a} = J_{5,6b} = 6.1 Hz, H-5), 4.23 (dd, 1 H, J_{3,2} 5.9, J_{3,4} 2.7 Hz, H-3), 4.28 (ddd, 1 H, J_{2',1'} 3.7, J_{2',3'} 7, J_{2',NH} 10 Hz, H-2'), 4.32 (d, 1 H, J_{1,2} 6.6 Hz, H-1), 4.55, 4.61, 4.81, 4.87 (AB, 2 H, PhCH₂), 4.90 (d, 1 H, J_{1',2'} 3.9 Hz, H-1'), 5.84 (d, 1 H, J_{NH,2'} 9.7 Hz, NHAc), 7.31 (s, 5 H, Ph).

¹³C-n.m.r.: δ 19.33, 25.18, 26.62, 27.56, 27.60, 29.36 (CMe₂), 23.32 (NAc), 52.70 (C-2'), 54.70, 56.68 (OMe), 62.53 (C-5'), 64.52 (C-6'), 66.62 (C-6), 73.81 (PhCH₂), 75.55 (C-4', C-5), 76.56 (C-3'), 76.95 (C-2), 78.85 (C-3), 80.45 (C-4), 99.72 (CMe₂), 101.17 (C-1'), 105.77 (C-1), 109.09, 110.79 (CMe₂), 128 - 139.4 (Ph), 170.08 (OAc).

Anal. calcd. for C₃₂H₄₉O₁₂N: MW 639. Found: m/z 640 (M + H⁺, 100), m/z 624 (M⁺-CH₃, -23), (FABS, glycerol). Calcd.: C, 60.08; H, 7.72. Found: C, 59.85; H, 7.74.

2,3-O-Isopropylidene- (49) and 2,3:5,6-di-O-isopropylidene-4-O-(2-acetamido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (48)

A solution of 47 (10.5 g, 16.4 mmol) and pyridinium *p*-toluenesulfonate (25 mg) in methanol (125 mL) was stirred for 8 h. A few drops of ammonium hydroxide were added to neutralize the solution, the solvent was removed, and the residue chromatographed eluant, 3% methanol in chloroform) to give 48 (7.0 g, 12 mmol, 73%). Further elution (10% methanol in chloroform) provided 49 (1.3 g, 2.3 mmol, 14%).

Data for 48: $[\alpha]_D^{20} + 88$ (c 0.7, chloroform); $^1\text{H-n.m.r.}$: δ 1.33, 1.40, 1.42, 1.45 (4 s, 12 H, CMe_2), 1.92 (s, 3 H, NAc), ~ 2.8 (bs, OH), 3.44, 3.45 (2 s, 6 H, OMe), 3.565 (dd, 1 H, $J_{3',2'}$ 10.7, $J_{3',4'}$ 8.6 Hz, H-3'), 3.67 - 3.8 (m, 4 H, H-4', 5', 6a', 6b'), 3.79 (dd, 1 H, $J_{4,3}$ 3, $J_{4,5}$ 4.9 Hz, H-4), 4.0 (dd, 1 H, $J_{2,1} = J_{2,3} = 6.4$ Hz, H-2), ~ 4.0 (2 H, H-6a, 6b), 4.17 (dd, 1 H, $J_{3,2}$ 6.4, $J_{3,4}$ 2.9 Hz, H-3), ~ 4.24 (m, 2 H, H-2', H-5), 4.34 (d, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 4.71 (s, 2 H, PhCH_2), 5.01 (d, 1 H, $J_{1',2'}$ 3.6 Hz, H-1'), 5.94 (d, 1 H, $J_{\text{NH},2}$ 9.3 Hz, NHAc), 7.33 (s, 5 H, Ph).

$^{13}\text{C-n.m.r.}$: δ 23.19 (NAc), 24.47, 26.01, 27.24, 27.30 (CMe_2), 52.37 (C-2'), 54.72, 56.92 (OMe), 62.39 (C-6'), 65.51 (C-6), 70.74, 72.73 (C-5, 5'), 73.8 (PhCH_2), 78.55 (C-3), 79.63 (C-4), 99.98 (C-1'), 105.65 (C-1), 108.76, 110.40 (CMe_2), 128.0 - 138.2 (Ph).

Anal. calcd. for $\text{C}_{29}\text{H}_{45}\text{O}_{12}\text{N}$: MW 599. Found: m/z 600 ($\text{M} + \text{H}^+$, 40), (FABS, glycerol).

Data for 49: $[\alpha]_D^{20} + 57.2$ (c 3.2, chloroform); $^1\text{H-n.m.r.}$: δ 1.35, 1.39 (2 s, 6 H, CMe_2), 1.86 (s, 3 H, NHAc), 3.40, 3.42 (2 s, 6 H, OMe), 4.315 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.63, 4.69, 4.80, 4.86 (AB, 2 H, PhCH_2), 4.93 (d, 1 H, $J_{1',2}$ 3.5 Hz, H-1'), 6.05 (d, 1 H, NHAc), 7.30 (s, 5 H, Ph).

$^{13}\text{C-n.m.r.}$: δ 23.29 (NAC), 27.58 (CMe_2), 52.87 (C-2'), 55.17, 56.91 (OMe), 62.37 (C-6'), 63.41 (C-6), 71.45, 73.60, 73.64, 74.55, 77.89, 78.93, 80.24 (C-2, 3, 5, 3', 4', 5', PhCH_2), 82.93 (C-4), 101.08 (C-1'), 105.73 (C-1), 110.90 (CMe_2), 128.11 - 139.03 (Ph), 170.65 (NAC).

Anal. Calcd. for $\text{C}_{26}\text{H}_{41}\text{O}_{12}\text{N}$: MW^1 559. Found: m/z 665 ($\text{M} + \text{DEAH}^+$, 60), (FABS, DEA).

2,3:5,6-Di-O-isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (50)

Compound 48 (1.24 g, 2.07 mmol) in tetrahydrofuran (10 mL) was added to a stirred suspension of sodium hydride (200 mg) in tetrahydrofuran (20 mL). After 10 min, allyl bromide (0.43 mL, 5 mmol) was added and the mixture was heated at 60° for 18 h. Ethanol was added and the mixture neutralized with 5% aqueous hydrogen chloride. After removal of the solvents by evaporation, chloroform was added to the residue and the solution then washed with sodium hydrogen carbonate and water, dried, and concentrated. Chromatography (eluant, 1% methanol in chloroform) gave 50 (1.07 g, 1.6 mmol, 76%); $[\alpha]_D^{20} + 66$ (c 0.9, chloroform).

$^1\text{H-n.m.r.}$: δ 1.35, 1.41 (2 s, 6 H, CMe_2), 1.88 (s, 3 H, NAc), 3.41, 3.83 (2 s, 6 H, OMe), 3.58 - 3.71 (m, 5 H, H-4, 3', 4', 6a', 6b'), 3.76 - 3.80 (m, 1 H, H-5'), 3.95 (dd, 1 H, $J_{2,1}$ 6.6, $J_{2,3}$ 6 Hz, H-2), 3.96 - 4.31 (m, 9 H, H-3, 5, 6a, 6b, 2', $\text{CH}_2\text{CHCH}_2\text{O-}$), 4.33 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.58, 4.67, 4.80, 4.83 (AB, 2 H, PhCH_2), 4.92 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 5.1 - 5.3, 5.8 - 6.0 (m, 7 H, $\text{CH}_2\text{CHCH}_2\text{O}$, NHAc), 7.3 (Ph).

$^{13}\text{C-n.m.r.}$: δ 23.18 (HNAc), 25.07, 26.58, 27.47 (CMe_2), 52.52 (C-2'), 54.11, 56.30 (OMe), 66.73 (C-6), 68.25 (C-6'), 71.55 (C-5'), 72.47, 73.71 ($\text{CH}_2=\text{CHCH}_2\text{O}$), 74.69 (PhCH_2), 75.25 (C-5), 76.29 (C-2), 78.03 (C-4'), 78.40 (C-3), 79.58 (C-3'), 80.60 (C-4), 100.73 (C-1'), 105.09 (C-1), 108.94, 110.57 (CMe_2), 116.91, 117.09 ($\text{CH}_2=\text{CHCH}_2\text{O}$), 127.13 (Ph), 134.45, 134.70 ($\text{CH}_2=\text{CHCH}_2\text{O}$), 170.13 (NAC).

Anal. calcd. for $\text{C}_{35}\text{H}_{53}\text{O}_{12}\text{N}$: MW 679. Found: m/z 786 (M + DEAH^+ , 13.7), m/z 680 (M + H^+ , 4.7), (FABS, DEA).

2,3-O-Isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehydo-D-glucose dimethyl acetal (51)

As described in the procedure for compound 14, 50 (170 mg, 0.25 mmol) was hydrolyzed with 80% aqueous acetic acid at 40° for 5 h. Purification of the product by chromatography (eluant, ethyl acetate) gave 51 (106 mg, 0.17 mmol, 68%); $[\alpha]_D^{20} + 57$ (c 1.3, chloroform).

$^1\text{H-n.m.r.}$: δ 1.36, 1.41 (2 s, 6 H, CMe_2), 1.87 (s, 3 H, NHAc), 3.3 - 3.8 (m, 7 H, H-4, 6a, 6b, 4', 5', 6a', 6b'), 3.41, 3.44 (2 s, 6 H, OMe), 3.57 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 10.3$ Hz, H-3'), 3.96 - 4.34

(m, 4 H, H-5 and $\text{CH}_2=\text{CHCH}_2\text{O}$), 3.98 (dd, 1 H, $J_{2,1} = J_{2,3} = 5.9$ Hz, H-2), 4.23 - 4.34 (m, 2 H, H-2' and $\text{CH}_2=\text{CHCH}_2\text{O}$), 4.27 (dd, 1 H, $J_{3,2} = 5.9$, $J_{3,4} = 4.4$ Hz, H-3), 4.34 (d, 1 H, $J_{1,2} = 5.9$ Hz, H-1), 4.60, 4.64, 4.80, 4.83 (AB, 2 H, PhCH_2), 4.86 (d, 1 H, $J_{1',2'} = 4.2$ Hz, H-1'), 5.16 - 5.33, 5.84 - 5.98 (m, 7 H, NHAc and $\text{CH}_2=\text{CHCH}_2\text{O}$), 7.26 - 7.32 (Ph).

^{13}C -n.m.r.: δ 23.24 (HNAc), 27.44 (CMe_2), 52.64 (C-2'), 54.68, 56.68 (OMe), 62.98 (C-6), 68.97 (C-6'), 72.09 (C-5), 72.53 (C-5'), 73.08, 73.83 ($\text{CH}_2=\text{CHCH}_2\text{O}$), 74.87 (PhCH_2), 77.45 (C-2), 78.37 (C-4'), 78.51 (C-3), 80.10 (C-3'), 84.38 (C-4), 101.23 (C-1'), 105.07 (C-1), 110.72 (CMe_2), 117.39, 117.68 ($\text{CH}_2\text{CHCH}_2\text{O}$), 127.8 - 138.28 (Ph, $\text{CH}_2\text{CHCH}_2\text{O}$), 170.05 (HNAc).

Anal. Calcd. for $\text{C}_{32}\text{H}_{49}\text{O}_{12}\text{N}\cdot\text{H}_2\text{O}$: C, 58.43; H, 8.04; N, 2.13.
Found: C, 58.30; H, 7.95; N, 2.10.

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal
(52)

A portion of 51 was acetylated to give, after chromatography (eluant, 2:1 ethyl acetate - hexane), 52; $[\alpha]_D^{20} + 75$ (c 0.5, chloroform).

^1H -n.m.r.: δ 1.31, 1.35 (2 s, 6 H, CMe_2), 1.84 (s, 3 H, NHAc), 2.07, 2.08 (2 s, 6 H, OAc), 3.37, 3.41 (2 s, 6 H, OMe), 3.59 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 9.3$ Hz, H-3'), 3.6 (dd, 1 H, $J_{6a',6b'} = 10$ Hz, H-6a'), 3.67 (dd, 1 H, $J_{4',3'} = J_{4',5'} = 9.5$ Hz, H-4'), 3.73 (dd, 1 H, $J_{6b',5'} = 3$, $J_{6b',6a'} = 10.5$ Hz, H-6b'), 3.85 (dd, 1 H, $J = 1.5, 6.6$ Hz, H-4), ~ 3.92

(m, 1 H, H-5'), 3.96 - 4.24 (m, 8 H, H-2, 3, 6a, 2', CH₂CHCH₂O), 4.34 (d, 1 H, J_{1,2} 5.5 Hz, H-1) 4.46 (dd, 1 H, J_{6b,5} 2.4, J_{6b,6a} 12.2 Hz, H-6b), 4.63, 4.66, 4.81, 4.84 (AB, 2 H, PhCH₂), 4.97 (d, 1 H, J_{1',2'} 3.7 Hz, H-1'), ~ 5.2 (m, 1 H, H-5), 5.2 - 5.4 (m, 4 H, CH₂CHCH₂O), 5.52 (d, 1 H, J_{NH,2'} 9.7 Hz, NHAc), ~ 6 (m, 2 H, CH₂CHCH₂O), 7.3 (m, 5 H, Ph).

¹³C-n.m.r.: δ 20.84, 21.21, 23.32 (NHAc, OAc), 27.10, 27.37 (CMe₂), 52.60 (C-2'), 53.62, 56.90 (OMe), 62.29 (C-6), 68.33 (C-6'), 71.94 (C-5), 72.12 (C-5'), 72.52, 73.91 (CH₂CHCH₂O-), 74.80 (PhCH₂), 76.66, 78.49, C-2, 3, 77.87 (C-4'), 79.42 (C-3'), 80.57 (C-4), 99.87 (C-1), 104.79 (C-1'), 110.66 (CMe₂), 117.09, 117.19 (CH₂CHCH₂O-), 130 - 135 (PhCH₂ and CH₂CHCH₂O-), 170 (Ac).

Anal. calcd. for C₃₆H₅₃O₁₄N: MW 723. Found: m/z 829 (M + DEAH⁺, 3.8), m/z 724 (M + H⁺, 1.1), (FABS, DEA). Calcd.: C, 59.74; H, 7.38; N, 1.94. Found: C, 59.34; H, 7.58; N, 1.83.

2,3-O-Isopropylidene-5,6-di-O-methanesulfonyl-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (53)

A solution of 52 (300 mg, 0.47 mmol) in methylene chloride (5 mL) was added to a stirred solution of methanesulfonyl chloride (0.1 mL, 1.3 mmol) and pyridine (1 mL) in methylene chloride (10 mL). After 3 h, the solution was poured onto an ice-water mixture and the product extracted into chloroform. After washing with sodium hydrogen carbonate and water, the chloroform solution was dried and concentrated.

Chromatography (eluant, 2:1 ethyl acetate - hexane) of the residue gave a syrup, 53 (277 mg, 0.35 mmol, 74%).

¹H-n.m.r.: δ 1.29, 1.33 (2 s, 6 H, CMe₂), 1.80 (s, 3 H, NHAc), 3.04, 3.06 (2 s, 6 H, SO₃Me), 3.37, 3.44 (2 s, 6 H, OMe), 4.3 - 4.36 (H-6a), 4.34 (d, 1 H, J_{1,2} 4.9 Hz, H-1), 4.57 (dd, 1 H, J_{6b,5} 2.4, J_{6b,6a} 11.7 Hz, H-6b), 4.58, 4.62, 4.77, 4.81 (AB, 2 H, PhCH₂), 5.03 (d, 1 H, J_{1',2'} 3.4 Hz, H-1'), ~ 5.03 (m, 1 H, H-5), 5.52 (d, 1 H, J_{NH,2'} 9 Hz, NHAc), 5.1 - 5.28, 5.8 - 6.0 (m, 6 H, CH₂CHCH₂O-), 7.30 (Ph).

5,6-Di-O-acetyl-2,3-O-isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-aldehyde-L-idose dimethyl acetal (54)

A solution of 53 (230 mg, 0.28 mmol) and potassium acetate (200 mg) in acetic anhydride (8 mL) was heated at 120° for 20 h. The acetic anhydride was removed by evaporation under high vacuum, the black residue dissolved in ethyl acetate, the solution was washed with sodium hydrogen carbonate and water, dried, and concentrated to give a crude syrup. After repeated chromatography (eluant, 1:1 ethyl acetate - hexane), 54 was obtained as an impure oil. An authentic sample was prepared by acetylation of 55; [α]_D²⁰ + 49 (c 1.5, chloroform).

¹H-n.m.r.: δ 1.33, 1.38 (2 s, 6 H, CMe₂), 1.81, 2.03, 2.07 (3 s, 9 H, NHAc, OAc), 3.36, 3.39 (2 s, 6 H, OMe), 3.56 (dd, 1 H, J_{3',2'} 10.5, J_{3',4'} 8.8 Hz, H-3'), 3.63 (dd, 1 H, J_{6a',5'} 2, J_{6a',6b'} 11 Hz, H-6a'), 3.66 (dd, 1 H, J_{4',3'} 9, J_{4',5'} 9.7 Hz, H-4'), 3.72 (dd, 1 H,

$J_{4,3}$ 2.2, $J_{4,5}$ 5.4 Hz, H-4), 3.72 (dd, 1 H, $J_{6b',5'}$ 3.2, $J_{6b',6a'}$ 10.7 Hz, H-6b'), 3.82 (ddd, 1 H, $J_{5',4'}$ 10, $J_{5',6a'}$ 2.2, $J_{5',6b'}$ 2.7 Hz, H-5'), 3.88 (dd, 1 H, $J_{2,1} = J_{2,3} = 6.4$ Hz, H-2), 3.94 - 4.36 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 4.12 - 4.2 (m, 1 H, H-2'), 4.17 (dd, 1 H, $J_{3,2}$ 6.3, $J_{3,4}$ 2.3 Hz, H-3), 4.29 (dd, 1 H, $J_{6a,5}$ 7.3, $J_{6a,6b}$ 12.7 Hz, H-6a), 4.30 (d, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 4.39 (dd, 1 H, $J_{6b,5}$ 2.7, $J_{6b,6a}$ 12.5 Hz, H-6b), 4.59, 4.63, 4.82, 4.86 (AB, 2 H, PhCH_2), 4.94 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 5.14 - 5.32 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), ~ 5.28 (m, 1 H, H-5), 5.52 (d, 1 H, $J_{\text{NH},2'}$ 9.0 Hz, NHAc), 5.85 - 6.0 (m, 2 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 7.33 (Ph).

^{13}C -n.m.r.: δ 20.79, 20.96, 23.08^o (OAc, NAc), 27.30, 27.38 (CMe_2), 52.74 (C-2'), 54.21, 56.43 (OMe), 63.25 (C-6), 68.02 (C-6'), 72.04 (C-5, 5'), 73.71, 74.51 ($\text{CH}_2\text{CHCH}_2\text{O}$), 74.51 (PhCH_2), 76.61 (C-2), 76.70 (C-3), 77.55 (C-4), 77.89 (C-4'), 79.16 (C-3'), 100.76 (C-1'), 105.09 (C-1), 110.71 (CMe_2), 116.88, 116.96 ($\text{CH}_2\text{CHCH}_2\text{O}$), 128 - 134.6 (PhCH_2 , $\text{CH}_2\text{CHCH}_2\text{O}$).

Anal. calcd. for $\text{C}_{36}\text{H}_{53}\text{O}_{14}\text{N}$: MW 723. Found: m/z 829 (M + DEAH^+ , 4.3), (FABS, DEA).

2,3-O-Isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-L-idose (55)

Compound 54 was deacetylated with sodium methoxide in methanol to provide, after chromatography (eluant, ethyl acetate), syrupy 55; $[\alpha]_{\text{D}}^{20} + 56$ (c 2.4, chloroform).

¹H-n.m.r.: δ 1.35, 1.40 (2 s, 6 H, CMe₂), 1.84 (s, 3 H, NHAc), 3.36, 3.40 (2 s, 6 H, OMe), 3.95 (dd, 1 H, J_{2,1} = J_{2,3} = 6.0 Hz, H-2), 4.28 (dd, 1 H, J_{3,2} 6.0, J_{3,4} 3.7 Hz, H-3), 4.33 (d, 1 H, J_{1,2} 6.0 Hz, H-1), 4.58, 4.62, 4.78, 4.82 (AB, 2 H, PhCH₂), 4.95 (d, 1 H, J_{1',2'} 3.7 Hz, H-1'), 5.1 - 5.3, 5.8 - 6.1 (m, 6 H, CH₂CHCH₂O-), 5.64 (d, NHAc), 7.3 (Ph).

¹³C-n.m.r.: δ 23.15 (NAC), 27.34, 27.41 (CMe₂), 52.66 (C-2'), 54.95, 56.68 (OMe), 62.25 (C-6), 68.97 (C-6'), 71.69 (C-5), 71.96 (C-5'), 72.51, 73.83 (CH₂CHCH₂O-), 74.79 (PhCH₂), 77.27 (C-2), 77.54 (C-3), 78.43 (C-4'), 79.84 (C-3'), 82.59 (C-4), 100.52 (C-1'), 105.36 (C-1), 110.59 (CMe₂), 117.33, 117.55, 127.79 - 138.78 (CH₂CHCH₂O-, Ph).

Anal. calcd. for C₃₂H₄₉O₁₂N: MW 639. Found: m/z 745 (M + DEAH⁺, 11.8), m/z 640 (M + H⁺, 3.5), (FABS, DEA).

Methyl 2,3,6-tri-O-acetyl-4-O-(2-acetamido-4,6-di-O-acetyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl-α and -β-D-glucopyranoside (66)

Acetyl chloride (0.05 mL) was added to a solution of 49 (60 mg, 0.9 mmol) in methanol (30 mL). After 23 h, basic resin (IRA 400) was added, the solution was filtered and the filtrate evaporated to dryness. The residue was used directly for further reactions (see 67). For the purpose of characterization, the residue was chromatographed (eluant, 10% methanol in chloroform) to give 65 (36.6 mg, 83%); 65 was acetylated and chromatographed (eluant, 1:1 ethyl acetate - hexane) to give the title compounds 66 (49 mg, 0.7 mmol, 78%) as an anomeric mixture (α:β ~ 2:1).

¹H-n.m.r.: δ 1.68 - 2.14 (10 s, 15 H, OAc and NAc), 3.41 (s, α -OMe), 3.48 (s, β -OMe), 3.62 (dd, 1 H, J = 9.4, 10.7 Hz, H-3 α'), 4.38 (m, H-2 α'), 4.44 (d, $J_{1,2}$ 7.9 Hz, H-1 β), 4.76 (dd, $J_{2,1}$ 3.7, $J_{2,3}$ 10.4 Hz, H-2 α), 4.81 (dd, $J_{2,1}$ 7.9, $J_{2,3}$ 9.6 Hz, H-2 β), 4.87 (d, $J_{1,2}$ 3.7 Hz, H-1 α).

Anal. Calcd. for $C_{32}H_{43}O_{16}N \cdot H_2O$: C, 53.70; H, 6.34. Found: C, 53.21; H, 6.33.

Methyl - 2,3,6-tri-O-acetyl-4-O-(2-acetamido-3-O-benzyl-4,6-O-benzylidene-2-deoxy- α -D-glucopyranosyl)- α and - β -D-glucopyranoside (67)

Toluenesulfonic acid (6 mg) was added to a solution of 65 (1.76 g, 3.61 mmol) and dimethyl acetal benzaldehyde (1.2 mL, 7.9 mmol) in N,N'-dimethylformamide (10 mL). After 2 h heating at 70 - 80° under vacuum (rotaty evaporator at water vapour pressure), pyridine (3 mL) was added. The solvents were evaporated under high vacuum and the residue chromatographed (eluant, 2% followed by 6% methanol in chloroform). The major fraction was acetylated to give, after chromatography (eluant, 3:2 ethyl acetate - hexane) an anomeric mixture, 67 (851 mg, 1.2 mmol, 34%).

¹H-n.m.r.: δ 1.90 - 2.11 (7 s, 12 H, NAc, OAc), 3.40, 3.46 (2 s, OMe), 4.59, 4.63, 4.89, 4.93 (AB, 2 H, PhCH₂), 4.76 (dd, $J_{2,1}$ 3.5, $J_{2,3}$ 10.1 Hz, H-2 α), 4.84 (d, $J_{1,2}$ 3.7 Hz, H-1 α), 5.07 (d, $J_{1,2}$ 4.1 Hz, H-1 α'), 5.49 (dd, $J_{3,4}$ = $J_{3,2}$ = 10.1 Hz, H-3 α), 5.57 (s, PhCH), 7.25 - 7.38 (m, Ph).

¹³C-n.m.r.: δ 20.79 - 23.50 (OAc, NAc), 52.15 (C-2 α'), 55.68 (OMe α), 57.16 (OMe β), 63.14 (C-6 α)*, 64.40 (C-5 α')*, 68.22 (C-6 α')*, 68.89

(C-5 α), 71.47 (C-2 α), 72.32 (C-2 β), 72.78 (C-3 α), 74.04 (C-4 α), 74.45 (PhCH₂ β), 74.52 (PhCH₂ α), 75.68 (C-3 β), 76.10 (C-3 β'), 76.73 (C-3 α'), 82.70 (C-4 α'), 97.00 (C-1 α), 99.75 (C-1 β'), 99.81 (C-1 α'), 101.43 (C-1 β), 101.50 (PhCH), 126.40 - 138.93 (Ph), 170.34 - 170.83 (CO).

Methyl 2,3,6-tri-O-acetyl-4-O-(2-acetamido-4-O-acetyl-3,6-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)- α and - β -D-glucopyranoside (69)

Diethyl ether saturated with hydrogen chloride (4 mL) was added to a stirred solution of 67 (450 mg, 0.64 mmol) and sodium cyanoborohydride (600 mg, 10 mmol) in tetrahydrofuran (20 mL) at 0° containing 3 Å molecular sieves. Addition was stopped after evolution of gas had ceased and the solution remained acidic (pH paper). Chloroform (60 mL) was added after 3 h and the mixture filtered. The filtrate was washed with sodium hydrogen carbonate solution and water, dried and evaporated. The residue (68) was deacylated to give a product 70 (360 mg, 95%) suitable for subsequent reactions (see 71). A portion of the intermediate 68 was acetylated and purified by chromatography (eluant, 1:1 ethyl acetate - hexane) to give the title compounds, 69, as an anomeric mixture.

¹H-n.m.r.: δ 1.88 - 2.06 (9 s, 15 H, OAc and NAc), 3.49 (s, OMe α), 3.43 (s, OMe β), 3.65 (dd, J_{3',2'} 10.9, J_{3',4'} 9.3 Hz, H-3 α'), 3.96 (dd, J_{4,3} = J_{4,5} = 8.4 Hz, H-4 α), ~ 4.16 (m, H-6 $\alpha\alpha$, H-6 $\alpha\beta$), ~ 4.4 (m, H-2 α'), 4.45 (d, J_{1,2} 7.8 Hz, H-1 β), 4.52 (s, PhCH₂), 4.77 (dd, J_{2,1} 3.2, J_{2,3} 10 Hz, H-2 α), 4.83 (dd, J_{2,1} 7.8, J_{2,3} 9.4 Hz, H-2 β), 4.83 (d, J_{1,2} 3.3 Hz, H-1 α), ~ 5.2 (H-1 α' and H-4 α'), 5.52 (dd, J_{3,2} 10.5, J_{3,4} 8.5 Hz, H-3 α), 7.29 - 7.36 (m, 10 H, Ph).

^{13}C -n.m.r.: δ 20.83 - 23.49 (OAc and NAc), 51.82 (C-2 α'), 55.66 (OMe α), 57.15 (OMe β), 63.31 (C-6 α), 68.31 (C-5 α), 69.28 (C-6 α'), 70.89 (C-4 α'), 71.14 (C-5 α'), 71.48 (C-2 α), 72.85 (C-3 α), 73.51 (C-4 α), 74.20 (PhCH $_2$), 75.70 (C-3 β), 77.98 (C-3 α'), 97.01 (C-1 α), 98.60 (C-1 β'), 98.75 (C-1 α'), 101.58 (C-1 β), 127.96 - 138.54 (Ph), 169.7 - 170.83 (CO).

Anal. Calcd. for C $_{37}$ H $_{47}$ O $_{15}$ N: C, 59.59; H, 6.35. Found: C, 59.10; H, 6.39.

Methyl 2,3-di-O-acetyl-6-O-p-anisyldiphenyl methyl-4-O-(2-acetamido-4-O-acetyl-3,6-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)- α and - β -D-glucopyranoside (71)

A solution of 70 (187 mg, 0.32 mmol) in pyridine (5 mL) was dried and reduced in volume by azeotropic distillation with carbon tetrachloride. After cooling, p-anisylchlorodiphenylmethane (200 mg, 0.65 mmol) was added to the stirred solution, which was then heated at 35° for 18 h, until the starting material was no longer present (t.l.c., 10% methanol in chloroform). The intermediate was not isolated but acetylated by the addition of acetic anhydride (0.2 mL). After 6 h the mixture was diluted with chloroform, and then washed with sodium hydrogen carbonate solution and water, dried and evaporated. The residue contained a number of products (t.l.c., 2:1 ethyl acetate - hexane) and a small amount of 71 (55 mg, 0.06 mmol, 20%) was isolated by chromatography (eluant, 3:2 ethyl acetate - hexane).

^1H -n.m.r.: δ 1.84 - 2.04 (7 s, 12 H, OAc and NAc), ~ 3.1 (m, H-6'), 3.22 - 3.54 (m, includes H-6, 5'), 3.55 (s, OMe α), 3.57 (s,

OMe β), ~ 3.7 (H-4 α), 3.71 (s, PhOMe α), 3.72 (s, PhOMe β), ~ 4.3 (m, H-2 α'), 4.29, 4.33, 4.43, 4.46 (AB, PhCH $_2$), 4.44, 4.48, 4.49, 4.53 (AB, PhCH $_2$), 4.74 (dd, $J_{2,1}$ 3.6, $J_{2,3}$ 10.3 Hz, H-2 α), 4.84 (dd, $J_{2,1}$ 7.8, $J_{2,3}$ 9.9 Hz, H-2 β), 4.95 (d, $J_{1,2}$ 3.6 Hz, H-1 α), ~ 5.1 (H-1 α'), 5.18 (dd, J = 9.7, 11.4 Hz, H-4 α'), 5.48 (dd, $J_{3,2}$ 10.3, $J_{3,4}$ 9.1 Hz, H-3 α), 6.76 - 7.44 (m, 20 H, Ph).

^{13}C -n.m.r.: δ 20.8 - 23.45 (OAc and NAc), 51.60 (C-2 α'), 55.45, 55.50 (PhOMe, OMe α), 64.34 (C-6 α), 68.64 (C-6 α'), 69.93 (C-5 α), 70.23 (C-4 α'), 70.94 (C-5 α'), 71.67 (C-2 α), 73.20, 73.86, 73.96 (C-3 α , C-4 α , PhCH $_2$), 78.12 (C-3 α'), 87.02 (CPh $_3$), 96.69 (C-1 α), 97.80 (C-1 β'), 97.97 (C-1 α'), 101.65 (C-1 β), 113.44 - 159.07 (Ph).

Anal. Calcd. for C $_{55}$ H $_{61}$ O $_{15}$ N: MW 975. Found: m/z 1081 (M + DEAH, 30), (FABS, DEA).

5-O-acetyl-6-O-p-anisyldiphenylmethyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (72a)

p-Anisyldiphenylchloromethane (112 mg, 0.36 mmol) was added to a solution of 14a (200 mg, 0.34 mmol) in pyridine (2 mL) at 0°. The formation of 72 appeared to be complete in 16 h at room temperature. Acetic anhydride (0.5 mL) was then added to the solution, and after a further 5 h, the solvents were removed by evaporation. Chloroform was added to the residue and the resulting solution washed with sodium hydrogen carbonate solution and water, then dried, and concentrated. The residue was chromatographed (eluant, 1:2 ethyl acetate - hexane) to give 72a (280 mg, 0.31 mmol, 90%).

¹H-n.m.r.: δ 1.24, 1.30 (2 s, 6 H, CMe₂), 2.00, 2.01, 2.014, 2.09, 2.15 (5 s, 15 H, OAc), 3.36, 3.43 (2 s, 6 H, OMe), 3.38 - 3.49 (m, 2 H, H-6a, 6b), 3.79 (dd, 1 H, J_{4,3} 6.6, J_{4,5} 1.7 Hz, H-4), 3.80 (s, 3 H, PhOMe), 3.84 (ddd, 1 H, J_{5,4} 10.3 Hz, H-5'), 3.91 (dd, 1 H, J_{6a',5'} 2, J_{6a',6b'} 12.4 Hz, H-6a'), 3.97 (dd, 1 H, J_{3,2} = J_{3,4} = 6.6 Hz, H-3), 4.15 (dd, 1 H, J_{2,1} = J_{2,3} = 6.6 Hz, H-2), 4.18 (dd, 1 H, J_{6b',5'} 2.2, J_{6b',6a'} 12.7 Hz, H-6b'), 4.28 (d, 1 H, J_{1,2} 6.2 Hz, H-1), 4.80 (dd, 1 H, J_{2',1'} 3.6, J_{2',3'} 10.6 Hz, H-2'), 5.04 (dd, 1 H, J_{4',3'} = J_{4',5'} = 10 Hz, H-4'), 5.13 (d, 1 H, J_{1',2'} 3.3 Hz, H-1'), 5.23 (dd, 1 H, J_{3,2} 10.6, J_{3,4} 9.1 Hz, H-3'), 5.43 (ddd, 1 H, J_{5,4} 1.1, J_{5,6a} 2.8, J_{5,6} 8.8 Hz, H-5), 6.85 - 7.47 (m, 14 H, Ph).

Anal. Calcd. for C₄₇H₅₈O₁₈: C, 61.97; H, 6.42. Found: C, 61.48; H, 6.81.

5-O-Acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (73)

Compound 73 was obtained as a minor product in the reaction described for 76.

¹H-n.m.r.: δ 1.37, 1.38 (2 s, 6 H, CMe₂), 2.00, 2.02, 2.04, 2.08, 2.10 (5 s, 15 H, OAc), 3.43, 3.46 (2 s, 6 H, OMe), 3.83 (dd, 1 H, J_{6a,5} 7, J_{6a,6b} 11.5 Hz, H-6a), 3.88 (dd, 1 H, J_{4,3} 6, J_{4,5} 1.8 Hz, H-4), 3.97 (dd, 1 H, J_{6b,5} 4.2, J_{6b,6a} 12 Hz, H-6b), 4.12 (dd, 1 H, J_{3,2} 7, J_{3,4} 6.1 Hz, H-3), 5.07 (ddd, 1 H, J_{5,4} 1.8, J_{5,6b} 4.4 Hz, H-5).

6-O-Acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (74)

A solution of 72a (610 mg, 0.67 mmol) in 80% aqueous acetic acid (5 mL) was stirred for 10 h, until t.l.c. (ethyl acetate) showed the complete loss of starting material. The solvent was removed under high vacuum, and the residue chromatographed (eluant, 1:1 ethyl acetate - hexane) to give 74 (330 mg, 0.52 mmol, 78%), rather than the expected 5-O-acetyl product (see 73); $[\alpha]_D^{20} + 54$ (c 4.4, chloroform).

$^1\text{H-n.m.r.}$: δ 1.43, 1.51 (2 s, 6 H, CMe_2), 2.01, 2.04, 2.09, 2.10 (4 s, 15 H, OAc), 3.44, 3.46 (2 s, 6 H, OMe), 3.70 (dd, 1 H, $J_{4,3}$ 2.8, $J_{4,5}$ 2 Hz, H-4), 4.05 (dd, 1 H, $J_{3,2}$ 7.6, $J_{3,4}$ 2.8 Hz, H-3), 4.12 (dd, 1 H, $J_{6a',5'}$ 2.3, $J_{6a',6b'}$ 12.5 Hz, H-6a'), 4.13 - 4.25 (m, 6 H, H-2, 5, 6a, 6b, 6b'), 4.28 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.45 (ddd, 1 H, $J_{5',4'}$ 10.3, $J_{5',6a'}$ 2.2, $J_{5',6b'}$ 4.6 Hz, H-5'), 4.91 (dd, 1 H, $J_{2',1'}$ 3.7, $J_{2',3'}$ 10.5 Hz, H-2'), 5.03 (dd, 1 H, $J_{4',3'}$ 9.5, $J_{4',5'}$ 10.5 Hz, H-4'), 5.15 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 5.50 (dd, 1 H, $J_{3',2'}$ 10.5, $J_{3',4'}$ 9.5 Hz, H-3').

$^{13}\text{C-n.m.r.}$: δ 60.96, 61.55 (C-6, C-6').

Anal. Calcd. for $\text{C}_{27}\text{H}_{42}\text{O}_{17}$: MW 638. Found: m/z 744 (M + DEAH, 50), (FABS, DEA).

6-O-Acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-xylo-hexos-5-ulose dimethyl acetal (75)

To a stirred suspension of 74 (133 mg, 0.2 mmol) in acetone (5 mL) at -10° was added Jones reagent (0.4 mL). After 18 h, ethyl acetate was added, and the mixture washed with sodium hydrogen carbonate solution and water, dried and concentrated. The clear residue was chromatographed (eluant, 1:1 ethyl acetate - hexane) to give 75 (76 mg, 70%); $[\alpha]_D^{20} + 54$ (c 1.9, chloroform).

$^1\text{H-n.m.r.}$: δ 1.40, 1.47 (2 s, 6 H, CMe_2), 2.02, 2.04, 2.08, 2.10, 2.17 (5 s, 15 H, OAc), 3.44, 3.47 (2 s, 6 H, OMe), 4.0 - 4.46 (m, 7 H, H-1, 2, 3, 4, 5', 6a', 6b'), 4.83 (d, 1 H, $J_{6a,6b}$ 17.2 Hz, H-6a), 4.99 (dd, 1 H, $J_{2',1'} - 4$, $J_{2',3'}$ 10.3 Hz, H-2'), 5.05 (d, 1 H, $J_{6b,6a}$ 17.2 Hz, H-6b), 5.10 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.5$ Hz, H-4'), 5.13 (d, 1 H, $J_{1',2'}$ 4.1 Hz, H-1'), 5.56 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 10$ Hz, H-3').

$^{13}\text{C-n.m.r.}$: δ 20.57, 20.79 (OAc), 26.62, 27.10 (CMe_2), 55.37, 57.15 (OMe), 62.00 (C-6'), 67.24 (C-6), 68.48, 69.13, 70.10, 70.91 (C-2', 3', 4', 5'), 76.25, 78.13 (C-2, 3), 83.48 (C-4), 98.96 (C-1'), 105.86 (C-1), 111.10 (CMe_2), 169.90, 170.17, 170.33, 170.81 (OAc), 200.43 (C-5).

Anal. Calcd. for $\text{C}_{27}\text{H}_{40}\text{O}_{17}$: MW 636. Found: m/z 742 (M + DEAH, 30), (FABS, DEA).

5-O-Acetyl-2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucuronic acid dimethyl acetal (76)

To a stirred solution of 72a (420 mg, 0.46 mmol) in acetone (20 mL) at 0°, was added Jones' reagent (77% chromium trioxide in 3.5 M aqueous sulfuric acid). After 16 h, ethyl acetate was added and the mixture filtered. The filtrate was concentrated, dissolved in chloroform, and the resulting solution washed with water, dried and re-evaporated. The final residue was chromatographed (eluant, 2% methanol in chloroform) to give 76 (96 mg, 0.15 mmol, 33%) and a small amount of 73; $[\alpha]_D^{20} + 73$ (c 1.4, chloroform).

$^1\text{H-n.m.r.}$: δ 1.98 (s, 6 H, CMe_2), 1.98, 2.01, 2.04, 2.08, 2.14 (5 s, 15 H, -OAc), 3.44, 3.46 (2 s, 6 H, OMe), 3.96 (d, 1 H, $J_{4,3}$ 6.8 Hz, H-4), 4.0 - 4.12 (m, 2 H, H-2, 6a'), 4.29 - 4.35 (m, 2 H, H-5', 6'), 4.43 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1), 4.46 (dd, 1 H, $J_{3,4}$ 6.7 Hz, H-3), 4.82 (dd, 1 H, $J_{2',1'}$ 3.8, $J_{2',3'}$ 10.3 Hz, H-2'), 5.36 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1'), 5.36 (dd, 1 H, $J_{3',2'}$ 10.2, $J_{3',4'}$ 9.8 Hz, H-3'), 5.48 (s, 1 H, H-5).

$^{13}\text{C-n.m.r.}$: δ 20.55, 20.61, 20.68, 20.73, 20.83 (OAc), 26.77, 27.04 (CMe_2), 54.24, 56.88 (OMe), 61.34 (C-6'), 67.58 (C-5'), 68.06 (C-4'), 69.78 (C-3'), 70.62 (C-2'), 72.88, 77.26, 78.43 (C-2, 3, 5), 80.62 (C-4), 97.12 (C-1'), 104.77 (C-1), 110.51 (CMe_2), 169.79, 169.97, 170.07, 170.13, 170.36, 170.89 (OAc, COOH).

Anal. Calcd. for $\text{C}_{27}\text{H}_{40}\text{O}_{18}$: MW 652. Found: m/z 758 (M + DEA, 70), (FABS, DEA).

6-O-p-Anisyldiphenylmethyl-2,3-O-isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehydo-L-idose dimethyl acetal (77)

p-Anisyldiphenylchloromethane (463 mg, 1.5 mmol) was added to a solution of compound 55 (770 mg, 1.2 mmol) and 2,2'-dimethylaminopyridine (10 mg) in pyridine (3 mL) and methylene chloride (20 mL). After 8 h, the solvents were removed, and a solution of the residue in chloroform (20 mL) was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The residue was chromatographed (eluant 2:1 ethyl acetate - hexane) to give syrupy 77 (1.04 g, 1.14 mmol, 95%).

$^1\text{H-n.m.r.}$: δ 1.27, 1.38 (2 s, 6 H, CMe_2), 1.85 (s, 3 H, HNAC), 3.23, 3.33 (2 s, 6 H, OMe), 3.79 (s, 3 H, PhOMe), 4.58, 4.62, 4.80, 4.84 (AB, 2 H, PhCH_2), 4.95 (d, 1 H, $J_{1',2}$, 3.2 Hz, H-1'), 5.15 - 5.35 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O-}$), 5.80 (d, 1 H, $J_{\text{NH},2}$, 9 Hz, NHAc), 5.89 - 5.94 (m, 2 H, $\text{CH}_2\text{CHCH}_2\text{O-}$), 6.83 - 7.48 (Ph).

5-O-Acetyl-6-O-p-anisyldiphenylmethyl-2,3-O-isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehydo-L-idose dimethyl acetal (77a)

Acetic anhydride (1 mL) was added to a portion of the reaction mixture described above for compound 77, at a stage when t.l.c. (ethyl acetate) showed complete loss of the starting material and formation of compound 77. Stirring was continued for 18 h, then solvents were removed, the residue dissolved in chloroform, and washed with sodium

hydrogen carbonate and water, dried and evaporated. The residue was chromatographed (eluant, 3:2 ethyl acetate - hexane) to give a syrup, 77a; $[\alpha]_D^{20} + 51.5$ (c 1.5, chloroform).

$^1\text{H-n.m.r.}$: δ 1.07, 1.17 (2 s, 6 H, CMe_2), 1.79, 2.17 (2 s, 6 H, OAc), 3.19 (dd, 1 H, $J_{6a,5}$ 4.3, $J_{6a,6b}$ 11.3 Hz, H-6a), 3.31, 3.32 (2 s, 6 H, OMe), 3.37 (dd, 1 H, $J_{6b,5} \sim 2.1$, $J_{6b,6a} \sim 11.1$ Hz, H-6b), 3.45 (dd, 1 H, $J_{4',3'} \sim 10.4$, $J_{4',5'} 8.2$ Hz, H-4'), 3.62 - 3.77 (m, 4 H, H-3', 5', 6a', 6b'), 3.78 (s, 3 H, MMT-OMe), 3.86 (dd, 1 H, $J_{2,1}$ 6.3, $J_{2,3}$ 6.7 Hz, H-2), 3.90 - 4.337 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 4.13 - 4.19 (m, 1 H, H-2'), 4.18 (d, 1 H, $J_{1,2}$ 6.3 Hz, H-1), 4.55, 4.59, 4.80, 4.84 (AB, 2 H, PhCH_2), 5.00 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 5.11 - 5.32 (m, 5 H, H-5 and $\text{CH}_2\text{CHCH}_2\text{O}$), 5.43 (d, 1 H, $J_{\text{NH},2}$ 9.0 Hz, H-2', NHAc), 6.85 - 7.43 (m, 5 H, Ph).

$^{13}\text{C-n.m.r.}$: δ 21.27, 23.14 (OAc), 26.86, 27.12 (CMe_2), 52.79 (C-2'), 53.78, 56.45 (OMe), 55.19 (PhOMe), 63.16 (C-6), 68.05 (C-6'), 71.81 (C-5'), 72.46, 73.56 ($\text{CH}_2\text{CHCH}_2\text{O}$), 74.48 (PhCH_2), 74.68 (C-5), 79.35 (C-4'), 82.01 (Ph_3C), 99.66 (C-1'), 105.09 (C-1), 109.81 (CMe_2), 113.1 - 158.59 (Ph, $\text{CH}_2\text{CHCH}_2\text{O}$), 169.95, 170.35 (OAc, NHAc).

Anal. Calcd. for $\text{C}_{54}\text{H}_{67}\text{O}_{14}\text{N}$: MW 953. Found: m/z 1059 (M + DEAH, 20), (FABS, DEA).

6-O-p-Anisyldiphenylmethyl-2,3-O-isopropylidene-5-O-levulinyl-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucose dimethyl acetal (79)

As described in the procedure for 72a, the 6-O-p-anisyldiphenylmethyl derivative 72 was prepared, and purified by the same chromatographic process. The recovered syrup (450 mg, 0.5 mmol) was dissolved in tetrahydrofuran (15 mL) containing N,N'-dimethylaminopyridine (~ 10 mg), dicyclohexylcarbodiimide (200 mg, 0.97 mmol) and levulinic acid (0.3 mL, 2.9 mmol) were added, and the mixture was stirred for 1 h. The tetrahydrofuran was removed by evaporation, the residue dissolved in chloroform and the resulting mixture washed with sodium hydrogen carbonate and water, dried and concentrated. Chromatography (eluant, 2:3 ethyl acetate - hexane) provided 79 (420 mg, 0.43 mmol, 86%).

¹H-n.m.r.: δ 1.25, 1.30 (2 s, 6 H, CMe₂), 1.99, 2.01, 2.07, 2.18 (4 s, 15 H, OAc, Lv-CH₃), ~ 2.6, 2.8 (m, 4 H, Lv-CH₂), 3.35, 3.41 (2 s, 6 H, OMe), 3.3 - 3.5 (m, 3 H, H-4, 6a, 6b), 3.79 (s, 3 H, PhOMe), 3.85 (m, 1 H, H-5'), 3.5 - 3.92 (m, 2 H, H-3, 6a'), 4.13 (dd, 1 H, J_{2,1} = J_{2,3} = 6.4 Hz, H-2), 4.19 (dd, 1 H, J_{6b',5'} = 2.4, J_{6b',6a'} = 12.5 Hz, H-6b'), 4.27 (dd, 1 H, J_{1,2} = 5.9 Hz, H-1), 4.81 (dd, 1 H, J_{2',1'} = 3.6, J_{2',3'} = 10 Hz, H-2'), 5.04 (dd, 1 H, J_{4',3'} = J_{4',5'} = 10 Hz, H-4'), 5.13 (d, 1 H, J_{1',2'} = 3.9 Hz, H-1'), 5.22 (dd, 1 H, J_{3',2'} = J_{3',4'} = 10 Hz, H-3'), 5.4 (m, 1 H, H-5), 6.8 - 7.4 (Ph).

¹³C-n.m.r.: δ 20.57 - 37.52 (OAc, Lv-CH₃, CMe₂), 54.27, 56.91 (OMe), 55.15 (PhOMe), 61.04 (C-6'), 61.79 (C-6), 67.76, 67.85 (C-4',

5'), 69.71 (C-3'), 70.44 (C-2'), 74.31, 76.10, 78.45 (C-2, 3, 5), 81.75 (C-4), 86.30 (MMT-C), 97.66 (C-1'), 105.47 (C-1), 110.142 (CMe₂), 113.08 - 158.52 (Ph), 169.58 - 172.60 (OAc, Lv-CO₂⁻).

Anal. Calcd. for C₅₀H₆₂O₁₉: C, 62.10; H, 6.46. Found: C, 61.56; H, 6.60.

2,3-O-Isopropylidene-5-O-levulinyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-aldehyde-D-glucose (80)

A solution of 79 (290 mg, 0.3 mmol) in 80% aqueous acetic acid (3 mL) was stirred for 18 h. Removal of the solvents under high vacuum, followed by chromatography (eluant, 2:1 ethyl acetate - hexane) of the residue, gave 80 (123 mg, 0.18 mmol, 60%) as an oil; [α]_D²⁰ + 86 (c 1.2, chloroform).

¹H-n.m.r.: δ 1.40, 1.42 (2 s, 6 H, CMe₂), 2.02, 2.06, 2.08, 2.11, 2.20 (5 s, OAc, Lv-CH₃), ~ 2.6, 2.8 (m, 4 H, Lv-CH₂), 3.46, 3.49 (2 s, 6 H, OMe), 3.83 - 4.03 (m, 2 H, H-6a, 6b), 3.91 (dd, 1 H, J_{4,3} 5.7, J_{4,5} 2.2 Hz, H-4), 4.10 - 4.20 (m, 3 H, H-2, 3, 6a'), 4.265 (ddd, 1 H, J_{5',4'} 7.6, J_{5',6a'} 2.7, J_{5',6b'} 2.7 Hz, H-5'), 4.33 (dd, 1 H, J_{6b',5'} 2.8, H-6b'), 4.36 (d, 1 H, J_{1,2} 5.4 Hz, H-1), 4.91 (dd, 1 H, J_{2',1'} 3.6, J_{2',3'} 10.5 Hz, H-2'), ~ 5.1 (m, H-5), 5.14 (dd, 1 H, J_{4',3'} = J_{4',5'} = 9.2 Hz, H-4'), 5.32 (d, 1 H, J_{1',2'} 3.9 Hz, H-1'), 5.47 (dd, 1 H, J_{3',2'} 10.5, J_{3',4'} 9.2 Hz, H-3').

Anal. Calcd. for C₃₀H₄₆O₁₈: MW 694. Found: m/z 800 (M + DEAH⁺, 60), (FABS, DEA).

Methyl 2,3-O-isopropylidene-5-O-levulinyl-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-aldehyde-D-glucuronate dimethyl acetal (81)

To a stirred solution of 80 (1.15 g, 1.66 mmol) in methylene chloride (75 mL) was added pyridinium dichromate (2.82 g) and acetic anhydride (0.7 mL). After 16 h, the solvents were removed by evaporation, and the residue chromatographed (10% methanol in chloroform) to give a crude brown product (800 mg), presumably the acid. A small portion (120 mg) in methylene chloride (2 mL) was treated with ethereal diazomethane. After removal of the solvents, the residue was chromatographed (eluant, 2:1 ethyl acetate - hexane) to give 81 (100 mg, approx. yield 78% from 80); $[\alpha]_D^{20} + 66$ (c 3.9, chloroform).

$^1\text{H-n.m.r.}$: δ 1.36 (s, 6 H, CMe_2), 1.98, 2.01, 2.02, 2.08, 2.17 (5 s, 15 H, OAc, Lv-CH_3), ~ 2.6, 2.8 (m, 4 H, Lv-CH_2), 3.41, 3.45 (OMe), 3.82 (CO_2Me), 3.94 (dd, 1 H, $J_{4,3}$ 8.0, $J_{4,5}$ 1.5 Hz, H-4), 3.99 (dd, 1 H, $J_{2,1} = J_{2,3} = 6.3$ Hz, H-2), 4.08 (dd, 1 H, $J_{6a',5'}$ 2, $J_{6a',6b'}$ 12 Hz, H-6a'), 4.06 - 4.37 (m, 5 H, H-1, 3, 5', 6'), 4.75 (dd, 1 H, $J_{2',1'} = 3.7$, $J_{2',3'} = 10.5$ Hz, H-2'), 5.08 (dd, 1 H, $J_{4',3'} = J_{4',5'} = 9.8$ Hz, H-4'), 5.36 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 10$ Hz, H-3'), 5.40 (d, 1 H, $J_{1',2'} = 3.9$ Hz, H-1'), 5.57 (d, 1 H, $J_{5',4'} = 1.5$ Hz, H-5).

$^{13}\text{C-n.m.r.}$: δ 20.63 - 37.59 (OAc, Lv-CH_3 , Lv-CH_2 , CMe_2), 52.54 (CO_2Me), 53.73, 56.96 (OMe), 61.47 (C-6'), 67.71 (C-5'), 67.99 (C-4'), 69.44 (C-3'), 70.56 (C-2'), 72.59 (C-5), 77.27 (C-2), 78.19 (C-3), 80.17 (C-4), 96.76 (C-1'), 105.06 (C-1), 110.40 (CMe_2), 167.43 - 171.80 (OAc, Lv-CO_2 , CO_2Me).

6-O-p-Anisyldiphenylmethyl-2,3-O-isopropylidene-5-O-levulinyl-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-L-idose dimethyl acetal (82)

To a stirred solution of compound 77 (1.02 g, 1.2 mmol) and 2,2'-dimethylaminopyridine (10 mg) in tetrahydrofuran (30 mL) were added dicyclohexylcarbodiimide (412 mg, 2 mmol) and levulinic acid (0.16 mL, 175 mg, 1.5 mmol). After 4 h, the solution was removed, the residue was dissolved in chloroform, and the solution was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The residue was chromatographed (eluant, 2:1 ethyl acetate - hexane) to give 82 (1.16 g, 1.1 mmol, 92%); $[\alpha]_D^{20} + 40.1$ (c 2.0, chloroform).

$^1\text{H-n.m.r.}$: δ 1.10, 1.14 (2 s, 6 H, CMe_2), 1.78 (s, 3 H, NAc), 2.19 (s, 3 H, Lv-CH_3), $\sim$ 2.6 (6 m, 4 H, Lv-CH_2), 3.31, 3.33 (2 s, OMe), 3.2 - 3.4 (m, 10 H including OMe, H-4, 6a, 6b, 4'), 3.59 - 3.66 (m, 4 H, H-3', 5', 6a', 6b'), 3.78 (s, 3 H, MMT-OMe), 3.82 (dd, 1 H, $J_{2,1} = J_{2,3} = 6.4$ Hz, H-2), 3.92 (dd, $J_{3,2} = J_{3,4} = 5.8$ Hz, H-3), 3.9 - 4.16 (m, $\text{CH}_2\text{CHCH}_2\text{O}$), 4.12 - 4.14 (m, H-2'), 4.19 (d, 1 H, $J_{1,2} = 6.6$ Hz, H-1), 4.54, 4.58, 4.79, 4.83 (AB, 2 H, PhCH_2), 4.95 (d, 1 H, $J_{1,2} = 3.9$ Hz, H-1'), $\sim$ 5.25 (m, 1 H, H-5), 5.10 - 5.32, 5.83 - 6.01 (m, 6 H, $\text{CH}_2\text{CHCH}_2\text{O-}$), 5.46 (d, 1 H, $J_{\text{NH},2} = 9$ Hz, NHAc), 7.26 - 7.43 (Ph).

$^{13}\text{C-n.m.r.}$: δ 23.08, 24.88 (NHAc, Lv-CH_3), 28.22 (CMe_2), 52.75 (C-2'), 53.76, 56.38 (OMe), 55.19 (PhOMe), 63.18 (C-6), 68.08 (C-6'), 71.80 (C-5'), 72.38, 73.55 ($\text{CH}_2\text{CHCH}_2\text{O}$), 74.47 (PhCH_2), 74.77 (C-5), 76.02 (C-2), 76.92, 76.95 (C-3, 4'), 77.81 (C-3'), 79.47 (C-4), 86.01 (Ph_3C), 99.83 (C-1'), 104.99 (C-1), 110.00 (CMe_2), 113.19 - 158.58 (Ph, $\text{CH}_2\text{CHCH}_2\text{O-}$), 170.09, 172.09 (NAC, Lv-CO_2 -), 206.15 (Lv-CO-).

2,3-O-Isopropylidene-5-O-levulinyl-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-L-idose dimethyl acetal
(83)

A solution of compound 82 (1.07 g, 1.06 mmol) in 80% acic (5 mL) was stirred at room temperature for 10 h. The solvents were evaporated and the residue chromatographed (eluant, 4:1 ethyl acetate - hexane) to give 83 (750 mg, 1.02 mmol, 96%); $[\alpha]_D^{20} + 64.0$ (c 2.3, chloroform).

$^1\text{H-n.m.r.}$: δ 1.33, 1.39 (2 s, 6 H, CMe_2), 1.83 (s, 3 H, NACCH_3), 2.17 (s, 3 H, Lv-CH_3), ~ 2.7 (m, 4 H, Lv-CH_2 -), 3.36, 3.40 (2 s, 6 H, OMe), 3.45 (dd, 1 H, $J_{4',3'} = J_{4',5'} = 8.9$ Hz, H-4'), 3.55 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 8.9$ Hz, H-3'), 3.59 (dd, 1 H, $J_{6a',5'} \sim 2$; $J_{6a',6b'} = 10.8$ Hz, H-6a'), 3.61 (dd, 1 H, $J_{6b',5'} \sim 5.5$, $J_{6b',6a'} = 10.8$ Hz, H-6b'), 3.75 - 3.8 (m, 4 H, H-4, 6a, 6b, 5'), 3.87 (dd, 1 H, $J_{2,1} = J_{2,3} = 6.4$ Hz, H-2), 4.0 - 4.2 (m, H-2'), 4.0 - 4.3 (m, 6 H including H-2' and H-3, $\text{CH}_2\text{CHCH}_2\text{O}$), 4.23 (dd, $J_{3,2} = 6.4$, $J_{3,4} = 2.9$ Hz, H-3), 4.32 (d, 1 H, $J_{1,2} = 6.4$ Hz, H-1), 4.59, 4.62, 4.79, 4.83 (AB, 2 H, PhCH_2), 4.95 (d, 1 H, $J_{1',2'} = 3.9$ Hz, H-1'), 5.10 (d, 1 H, $J_{5,4} = 4.4$ Hz, H-5), 5.15 - 5.64 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 5.63 (d, 1 H, 2'-NHAc), 5.78 - 6.0 (m, 2 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 7.31 (m, 5 H, Ph).

$^{13}\text{C-n.m.r.}$: δ 23.17 (NAC), 27.40 (CMe_2), 27.92, 29.81, 37.98 (Lv), 52.67 (C-2'), 56.46, 56.62 (OMe), 66.16 (C-6), 68.52 (C-6'), 70.46 (C-5), 71.99 (C-5'), 72.61, 73.79 ($\text{CH}_2\text{CHCH}_2\text{O}$), 74.16 (PhCH_2), 75.1 - 78.8 (C-2, 3, 3', 4'), 79.86 (C-4), 82.62 (Ph_3C), 100.86 (C-1'), 105.33 (C-1), 110.64 (CMe_2), 117.07, 117.62 ($\text{CH}_2\text{CHCH}_2\text{O}$), 127.8 - 134.6 (Ph and $\text{CH}_2\text{CHCH}_2\text{O}$), ~ 170 (NAC), 172.9 (Lv-CO_2^-).

Anal. calcd. for $\text{C}_{37}\text{H}_{55}\text{O}_{14}\text{N}$: MW 737. Found: m/z 843 ($\text{M} + \text{DEAH}^+$, 14.7), m/z 738 ($\text{M} + \text{H}^+$, 2.8), (FABS^+ , DEA).

Methyl 2,3-O-isopropylidene-5-O-levuliny-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-L-iduronate dimethyl acetal (85)

To a solution of the alcohol 83 (90 mg, 0.12 mmol) in dimethyl sulfoxide (1.5 mL) were added dicyclohexylcarbodiimide (130 mg, 0.63 mmol) and pyridinium trifluoroacetate (10 mg) and the reaction stirred for 6 h until t.l.c. (ethyl acetate) showed complete loss of starting material and the formation of a less polar compound. Water (5 mL) was added, the mixture extracted into chloroform (5 x 20 mL), and the extract was washed with sodium hydrogen carbonate solution and water, dried and concentrated to give a syrupy residue, 84 (see below for further purification). The crude syrupy aldehyde 84 was dissolved in 1,4-dioxane (5 mL) and aqueous sulfamic acid (2 M, 0.15 mL, buffered with potassium acetate to pH 3) followed by aqueous sodium chlorite (2 M, 0.1 mL), were added. After 2 h, the solution was evaporated to dryness repeatedly with toluene, followed by the addition of methylene chloride (2 mL) and ethereal diazomethane (3 mL). Two hours later, the solvent was removed and the residue was dissolved in chloroform, washed successively with sodium hydrogen carbonate solution and water, dried and evaporated. The syrupy residue was chromatographed (eluant, 3:1 ethyl acetate - hexane) to give 85 (58 mg, 0.8 mmol, 67% from 83); $[\alpha]_D^{20} + 41.5$ (c 1.9, chloroform).

$^1\text{H-n.m.r.}$: δ 1.35, 1.40 (2 s, 6 H, CMe_2), 1.90 (s, 3 H, NAc), 2.20 (s, 3 H, Lv-CH_3), 2.7 - 2.8 (m, 4 H, Lv-CH_2), 3.37, 3.41 (2 s, 6 H, OMe), 3.59 (dd, 1 H, $J_{3',2'} = J_{3',4'} = 9.5$ Hz, H-3'), 3.63 - 3.83

(m, 4 H, H-4', 5', 6a', 6b'), 3.74 (s, 3 H, CO₂Me), 3.94 (dd, 1 H, J_{2,1} = J_{2,3} = 5.5 Hz, H-2), 4.05 (dd, 1 H, J_{4,3} 6.7, J_{4,5} 1.8 Hz, H-4), 4.18 - 4.29 (m, 1 H, H-2'), 4.31 (dd, 1 H, J_{3,2} 5.4, J_{3,4} 6.3 Hz, H-3), 4.34 (d, 1 H, J_{1,2} 5.1 Hz, H-1), 4.63, 4.67, 4.81, 4.85 (AB, 2 H, PhCH₂), 4.94 (d, 1 H, J_{1,2} 3.7 Hz, H-1'), 5.26 (d, J_{5,4} ~ 2.0 Hz, H-5), 5.09 - 5.32 (m, 5 H including H-5, CH₂CHCH₂O), 5.82 - 5.97 (m, 2 H, CH₂CHCH₂O), 6.15 (d, 1 H, J_{NH,2} 9.3 Hz, NHAc), 7.26 - 7.33 (m, Ph).

¹³C-n.m.r.: δ 23.37 (NAC), 27.47 (CMe₂), 27.84, 29.79, 37.87 (Lv-CH₂, CH₃), 52.59 (CO₂Me), 52.74 (C-2'), 54.58, 56.83 (OMe), 71.19 (C-5), 72.02 (C-5'), 72.39, 73.7 (CH₂CHCH₂O), 74.77 (PhCH₂), ~ 77.4 (C-3), 77.61 (C-4'), 77.88 (C-2), 80.23 (C-3'), 80.51 (C-4), 101.29 (C-1'), 104.67 (C-1), 116.74, 116.99 (CH₂CHCH₂O), 127.58 - 138.63 (Ph, CH₂CHCH₂O), 167.91 (CO₂Me), 169.90 (NAC), 171.34 (Lv-CO₂-), 206.15 (Lv-CO-).

Anal. calcd. for C₃₈H₅₅O₁₅N: MW 765. Found: m/z 871 (M + DEAH⁺, 3), (FABS⁺, DEA).

2,3-O-Isopropylidene-5-O-levulinyl-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-aldehyde-L-ido-hexodialdose 1,1'-dimethyl acetal (84)

A portion of the residue containing the aldehyde 84, from the procedure for 85, was chromatographed (eluant, 3:2 ethyl acetate - hexane) to give a syrup, 84; [α]_D²⁰ + 51.8 (c 1.3, chloroform).

¹H-n.m.r.: δ 1.30, 1.38 (CMe₂), 1.84 (NAC), 2.20 (Lv-CH₃), ~ 2.7 (Lv-CH₂), 3.37, 3.42 (OMe), 3.54 - 3.57 (m, 2 H, H-3', 4'), 3.62 - 3.64

(m, 2 H, H-6a', 6b'), 3.90 (dd, 1 H, $J_{1,2}$ 5.9, $J_{2,3}$ 5.8 Hz, H-2), 3.95 (dd, $J_{4,3}$ 1.6, $J_{4,5}$ 3.9 Hz, H-4), 3.92 - 3.98 (m, 2 H including H-4, H-5), 3.97 - 4.18 (m, 5 H including H-2', $\text{CH}_2\text{CHCH}_2\text{O}$), 4.21 (m, H-2'), 4.30 (dd, 1 H, $J_{3,2}$ 6.0, $J_{3,4}$ 1.8 Hz, H-3), 4.33 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.61, 4.65, 4.82, 4.86 (AB, 2 H, PhCH_2), 4.92 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 5.1 - 5.3 (m, 5 H including H-5, $\text{CH}_2\text{CHCH}_2\text{O}$), 5.22 (d, $J_{5,4}$ 3.7 Hz, H-5), 5.74 (d, 1 H, $J_{\text{NH},2'}$ 8.0 Hz, 2'-NHAc), 5.81 - 5.99 (m, $\text{CH}_2\text{CHCH}_2\text{O}$), 7.26 - 7.34 (m, Ph).

^{13}C n.m.r.: δ 23.20 (Nac), 27.56, 27.66 (CMe_2), 29.81, 33.92, 37.82 (Lv), 52.55 (C-2'), 54.51, 56.62 (OMe), 68.29 (C-6'), 72.04 (C-5'), 72.45, 73.82 ($\text{CH}_2\text{CHCH}_2\text{O}$), 74.68 (PhCH_2), 76 - 78 (C-2, 3, 5), 78.03 (C-4'), 79.46 (C-3'), 79.60 (C-4), 101.33 (C-1'), 104.73 (C-1), 111.22 (CMe_2), 117.18, 117.25 ($\text{CH}_2\text{CHCH}_2\text{O}$), 127.81 - 138.34 (Ph, $\text{CH}_2\text{CrCH}_2\text{O}$), 169.97 (Nac), 171.53 (Lv- CO_2^-), 195.98 (C-6), 206.15 (Lv-CO).

Anal. calcd. for $\text{C}_{37}\text{H}_{53}\text{O}_{14}\text{N}$: MW 735. Found: m/z 736 ($\text{M} + \text{H}^+$, 0.1), (FABS⁺, DEA).

Methyl 2,3-O-isopropylidene-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-aldehyde-L-iduronate dimethyl acetal (86)

To a solution of the ester 85 (500 mg, 0.67 mmol) in 2:1 pyridine - acetic acid (5 mL) was added hydrazine hydrate (0.03 mL in 1 mL 2:1 pyridine - acetic acid, 0.9 mmol) and the mixture stirred for 10 min at room temperature. Acetone (15 mL) was added, stirring was continued for 20 min, then the solution was evaporated. An extract of the resi-

due in ethyl acetate was filtered through a thin bed of silica gel, and evaporated. The syrup recovered was chromatographed (eluant, 2:1 ethyl acetate - hexane) to give 86 (345 mg, 0.52 mmol, 77%); $[\alpha]_D^{20} + 48.4$ (c 1.8, chloroform).

^1H -n.m.r.: δ 3.43, 3.45 (2 s, 6 H, OMe), 3.5 - 3.76 (m, 5 H, H-3', 4', 5', 6a', 6b'), 3.79 (s, 3 H, CO_2Me), 3.95 (dd, 1 H, $J_{4,3}$ 6.3, $J_{4,5}$ 2.2 Hz, H-4), 3.97 - ~ 4.3 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 4.06 (dd, 1 H, $J_{2,1}$ ~ 5.7, $J_{2,3}$ ~ 5.8 Hz, H-2'), 4.21 (ddd, 1 H, $J_{2',1}$ 3.7, $J_{2',3}$ 9.5, $J_{2',\text{NH}}$ ~ 9.8 Hz, H-2'), 4.32 (dd, 1 H, $J_{3,2} = J_{3,4} = 6.1$ Hz, H-3), 4.37 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1'), 4.40 (bd, 1 H, $J_{5,4}$ ~ 2.0 Hz, H-5), 4.60, 4.64, 4.79, 4.83 (AB, 2 H, PhCH_2), 4.91 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1').

^{13}C -n.m.r.: δ 23.29 (OAc), 27.32 (CMe_2), 52.59 (CO_2Me), 52.74 (C-2'), 54.70, 56.75 (OMe), 68.07 (C-6'), 70.00 (C-5), 71.99 (C-5'), 72.39, 73.65 ($\text{CH}_2\text{CHCH}_2\text{O}$), 74.69 (PhCH_2), ~ 77.4 (C-2, 3, 4'), 80.11 (C-3'), 81.78 (C-4), 100.95 (C-1'), 104.88 (C-1), 110.49 (CMe_2), 116.70, 116.99 ($\text{CH}_2\text{CHCH}_2\text{O}$), 127.55 - 138.53 (Ph, $\text{CH}_2\text{CHCH}_2\text{O}$), 169.87 (NAC), 172.96 (CO_2Me).

Anal. calcd. for $\text{C}_{33}\text{H}_{49}\text{O}_{13}\text{N}$: MW 667. Found: m/z 668 ($\text{M} + \text{H}^+$, 20), (FABS⁺, DEA).

Methyl-[methyl 2,3-di-O-acetyl-4-O-(2-acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)- α - (87) and β -L-idopyranosid] uronate (88)

90% Aqueous trifluoroacetic acid (5 mL) was added to compound 86 (345 mg, 0.52 mmol). After 40 min, the solvent was removed by evaporation under high vacuum. The residue was chromatographed (eluant, 2% then 4% methanol in chloroform) to give two fractions. The more polar fraction I (60 mg, 0.1 mmol, 20%) contained the free pyranose, and the less polar fraction II (120 mg, 0.2 mmol, 40%) contained a mixture of methyl glycosides. A portion of fraction I was acetylated to provide, after purification by chromatography (eluant, 1:1 ethyl acetate - hexane), an anomeric mixture of 1-acetates (89). Fraction II was acetylated and the anomers separated by chromatography (eluant, 1:1 ethyl acetate - hexane), providing the methyl α -glycoside, 87, and the methyl β -glycoside, 88.

Data for 87: $[\alpha]_D^{20} + 32$ (c 1.5, chloroform). $^1\text{H-n.m.r.}$: δ 1.88, 2.02, 2.03 (3 s, 9 H, OAc, NAc), 3.40 (dd, 1 H, $J_{3',2'} 10$, $J_{3',4'} 9$ Hz, H-3'), 3.42 (s, 3 H, OMe), 3.49 (dd, 1 H, $J_{4',3'} = J_{4',5'} = 9.8$ Hz, H-4'), 3.63 (d, 2 H, $J_{6',5'} 3.2$ Hz, H-6a', 6b'), 3.75 (ddd, 1 H, $J_{5',4'} 9.8$, $J_{5',6a'} = J_{5',6b'} = 3.2$ Hz, H-5'), 3.82 (s, 3 H, CO_2Me), 3.87 - 4.3 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 4.08 (dd, $J_{4,3} 6.7$ Hz, H-4), 4.16 (ddd, 1 H, $J_{2',1'} 3.6$, $J_{2',3'} = J_{2',\text{NH}} = 10$ Hz, H-2'), 4.55, 4.58, 4.76, 4.80 (AB, 2 H, PhCH_2), 4.72 (d, 1 H, $J_{5,4} 5.1$ Hz, H-5), 4.80 (dd, 1 H, $J_{2,1} 5$, $J_{2,3} 6.5$ Hz, H-2), 4.88 (d, 1 H, $J_{1',2'} 3.7$ Hz, H-1'), 4.99 (d, 1 H, $J_{1,2} 4.9$ Hz, H-1), 5.1 - 5.4 (m, 4 H, $\text{CH}_2\text{CHCH}_2\text{O}$), 5.32 (dd, 1 H, $J_{3,2} =$

$J_{3,4} = 6.6$ Hz, H-3), 5.53 (d, 1 H, $J_{NH,2}$, 9.5 Hz, HNAC), 5.8 - 6.0 (m, 2 H, CH_2CHCH_2O), 7.3 (m, 5 H, Ph).

^{13}C -n.m.r.: δ 20.88, 23.38 (OAc, NAc), 52.25 (C-2'), 52.48 (CO_2Me), 56.67 (OMe), 68.85 (C-6'), 69.36 (C-3), 69.89 (C-2), 70.73 (C-5), 71.92 (C-4), 72.34 (C-5'), 72.46, 73.75 (CH_2CHCH_2O), 75.25 ($PhCH_2$), 78.11 (C-4'), 80.52 (C-3'), 98.54 (C-1'), 97.58 (C-1), 116.3 - 138.8 (Ph, CH_2CHCH_2O), 169.43, 169.53 (CO_2Me , OAc, NAc).

Data for 88: $[\alpha]_D^{20} + 92$ (c 2.2, chloroform). ^1H -n.m.r.: δ 1.87, 2.01, 2.03 (3 s, 9 H, OAc, NAc), 3.39 (s, 3 H, OMe), 3.4 - 3.58 (m, 3 H, H-3', 4', 5'), 3.60 (d, 2 H, $J_{6',5'}$, 3 Hz, H-6a', 6b'), 3.98 (dd, 1 H, $J_{4,3}$ 6.9, $J_{4,5}$ 4.2 Hz, H-4), 3.96 - 4.31 (m, 4 H, CH_2CHCH_2O), ~ 4.17 (m, 1 H, H-2'), 4.50 (d, 1 H, $J_{5,4}$ 4.6 Hz, H-5), 4.57, 4.61, 4.76, 4.80 (AB, 2 H, $PhCH_2$), ~ 4.89 (m, 2 H, H-1, 2), 4.94 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 5.12 - 5.34 (m, 4 H, CH_2CHCH_2O), 5.59 (dd, 1 H, $J_{3,2} = J_{3,4} = 6.9$ Hz, H-3), 5.85 - 5.96 (m, 3 H, NHAc, CH_2CHCH_2O), 7.3 (m, 5 H, Ph).

^{13}C -n.m.r.: δ 20.79, 20.99, 23.29 (OAc, NAc), 52.35, 52.39 (C-2', CO_2Me), 57.11 (OMe), 68.57 (C-6'), 68.88 (C-3), 70.17 (C-2), 71.59 (C-5), 72.35 (C-4), 72.48 (C-5'), 73.69, 73.94 (CH_2CHCH_2O), 75.31 ($PhCH_2$), 78.20 (C-4'), 80.67 (C-3'), 98.63 (C-1), 98.80 (C-1'), 115.91 - 138.85 (Ph, CH_2CHCH_2O), 168.88, 169.95, 170.11, 170.23 (CO_2Me , OAc, NAc).

Anal. Calcd. for $C_{31}H_{45}O_{14}N$: MW 679.2848 + $DEAH^+$ (106.0869): 785.3717. Found: m/z 785.3625 (M + $DEAH^+$), (FABS, DEA).

Isolation of 2,3,4-tri-O-acetyl-1,6-anhydro- β -L-idopyranose

To a solution of 17 in n-propanol was added 2 N sulfuric acid until cloudy, and the mixture then heated under reflux for 14 h. A fraction corresponding to 1,6-anhydro-L-idopyranose (t.l.c.) was separated and acetylated. The resulting compound had a ¹H-n.m.r. spectrum identical to that of an authentic sample of 2,3,4-tri-O-acetyl-1,6-anhydro- β -D-idopyranose. $[\alpha]_D^{20} + 70$ (c 2.6, chloroform), lit. (207) +74.

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Claims to Original Research

- 1) A method was developed for the conversion of maltose into disaccharides containing a 2-amino-2-deoxy- α -D-glucopyranosyl group and/or L-idopyranuronic acid, as constituents. Thus, starting from an acetalated α -D-glucopyranosyl(1+4)-aldehydo-D-glucose dimethyl acetal, a series of α (1+4) linked disaccharides were prepared, and characterized.
- 2) These modifications included a unique synthesis of L-idopyranose derivatives, suitably linked at O-4 so as to prevent tautomerization to furanose forms.
- 3) The ratio of the D-gluco over the D-manno isomer, in the conversion of an α -D-glucopyranosyl group into a 2-amino-2-deoxy- α -D-glucopyranosyl group, was improved by modification of the oxidation - amination step.
- 4) A critical problem of acyl migration was overcome by using the levulinoyl ester as a temporary protecting group.
- 5) Observations on atypical hydroxyl group reactivity ($\text{OH-3'} > \text{OH-2'}$) and $^1\text{H-n.m.r.}$ characteristics in some dimethyl acetal derivatives, were rationalized by a proposal as to favoured conformations for these compounds.