Studies in Synthetic Carbohydrate Chemistry:

Part I

Nitromethane Cyclization of Sugar Polyaldehydes with a View to the Synthesis of Nitrocyclodextrins

Part II

Approaches to the Synthesis of 2-(*R*)-Fluoro-daunosamine, a Carbohydrate Moiety for an Antitumor Drug

Youn Yuen Shu, M.Sc.

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Supervisor

Professor Hans H. Baer

Candidate

Youn Yuen Shu

Abstract

Part I.

Polyaldehydes derived by periodate oxidation from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, phenyl 4',6'-*O*-benzylidene-α-maltoside, and 6-deoxy-β-cyclodextrin incorporate nitromethine functionalities by base-catalyzed reaction with nitromethane according to the general principle of nitroalkane cyclization of sugar dialdehydes, leading to 3-deoxy-3-nitro heptoseptanosides, 3,3'-dideoxy-3,3'-dinitro-disaccharides, and "nitro 6-deoxy-β-cyclodextrin", respectively.

Chapter 1. Methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-*glycero*-D-*ido*-heptoseptanoside was debenzylidenated, and the resulting nitrotetrol was acetylated. A twofold reductive dehydroacetoxylation of the nitro tetraacetate at C-2 and C-4, and concomitant deacetylation at O-5 and O-7 then resulted in a crystalline mixture of methyl 2,3,4-trideoxy-3-nitro-α-D-*ribo*- and α-D-*arabino*-heptoseptanosides, further characterized as the corresponding 5,7-diacetates. Acetylation of methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-*glycero*-D-*ido*-heptoseptanoside with acetic anhydride and sodium acetate gave a methyl 2-*O*-acetyl-5,7-*O*-benzylidene-3,4-dideoxy-3-nitro-hept-3-enoseptanoside, reduction of which afforded a methyl 2,3,4-trideoxy-3-nitro-heptoseptanoside.

Chapter 2. Reductive cleavage of the benzylidene acetal ring of phenyl 4',6'-*O*-benzylidene-α-maltoside derivatives was attempted by several methods. One approach led to a low yield of 4'-benzyl ether of phenyl α-maltoside.

Sodium metaperiodate oxidation of phenyl 4',6'-*O*-benzylidene-α-maltoside and its 6-deoxy derivative led to di- and tetra-aldehydes.

Nitromethane condensation of the aldehydes resulted in mono- and dinitro-disaccharides, respectively. The structural analysis was done by the aid of mass spectrometry.

Chapter 3. Heptakis(6-deoxy)cyclomaltoheptaose (6-deoxy-β-CD) was obtained in high yield via 6-bromo-, 6-iodo-, and 6-phenyl-6-thio-β-CD. Periodate oxidation of the product gave 6-deoxycyclodextrin polyaldehyde, which was confirmed by sodium borohydride reduction and acetylation to give a macrocyclic polyacetal. Nitromethane condensation of the polyaldehyde resulted in "nitro 6-deoxy-β-CD".

Part II.

In an attempt to synthesize of 2(*R*)-fluorodaunosamine, a carbohydrate moiety for an antitumor antibiotic 2'-(*R*)-fluorodaunorubicin, a possible precursor compound, namely methyl 3,6-dideoxy-3-trifluoroacetamido-α-L-galactopyranoside was synthesized via periodate oxidation of L-rhamnopyranoside, nitromethane cyclization, reduction of the nitro group, and trifluoroacetylation of the resulting amino group. Selective trifluoromethanesulfonylation at 2-OH of the product gave its 2-triflate. Reaction of the latter with tetrabutylammonium fluoride, however, did not lead to displacement by fluoride but gave an epimine. Simultaneous protection of the 3-amino and 4-hydroxyl groups of methyl 3-amino-3,6-dideoxy-α-L-galactopyranoside with ethyl chloroformate gave the 3-*N*,4-*O*-carbonyl derivative which was subsequently triflated at 2-OH. Reaction of this triflate with tetrabutylammonium fluoride also failed to introduce fluorine, and resulted in a tricyclic 2,3-epimino-3-*N*,4-*O*-carbonyl compound.

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Abbreviations

Å	Angström
Ac	acetyl
AcOH	acetic acid
ADEPT	auto DEPT
aq	aqueous
Ar	aryl
Bn	benzyl
Bz	benzoyl
br	broad
°C	degrees Celsius
CI	chemical ionization
cm	centimeter
d	doublet
DEPT	distortionless enhanced polarization transfer
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate

FAB	fast atom bombardment
g	gram
h	hour(s)
Hz	Hertz
IR	infrared
L	litre
M	molar
m	multiplet
M^+	parent molecular ion
Me	methyl
min	minute(s)
mL	millilitre
mmol	millimole
mol	mole
mp	melting point
MS	mass spectrum
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
OAc	acetate
OMe	methoxy
Ph	phenyl
py	pyridine
q	quartet
Rf	retention factor

s	singlet
sept	septet
t	triplet
Tf	trifluoromethylsulfonyl
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
μL	microlitre

PART I

A Study of the Nitromethane Cyclization of Sugar Polyaldehydes with a View to the Synthesis of Nitro Cyclodextrins.

Chapter 1.

Nitromethane Cyclization of Monosaccharidic Dialdehydes.

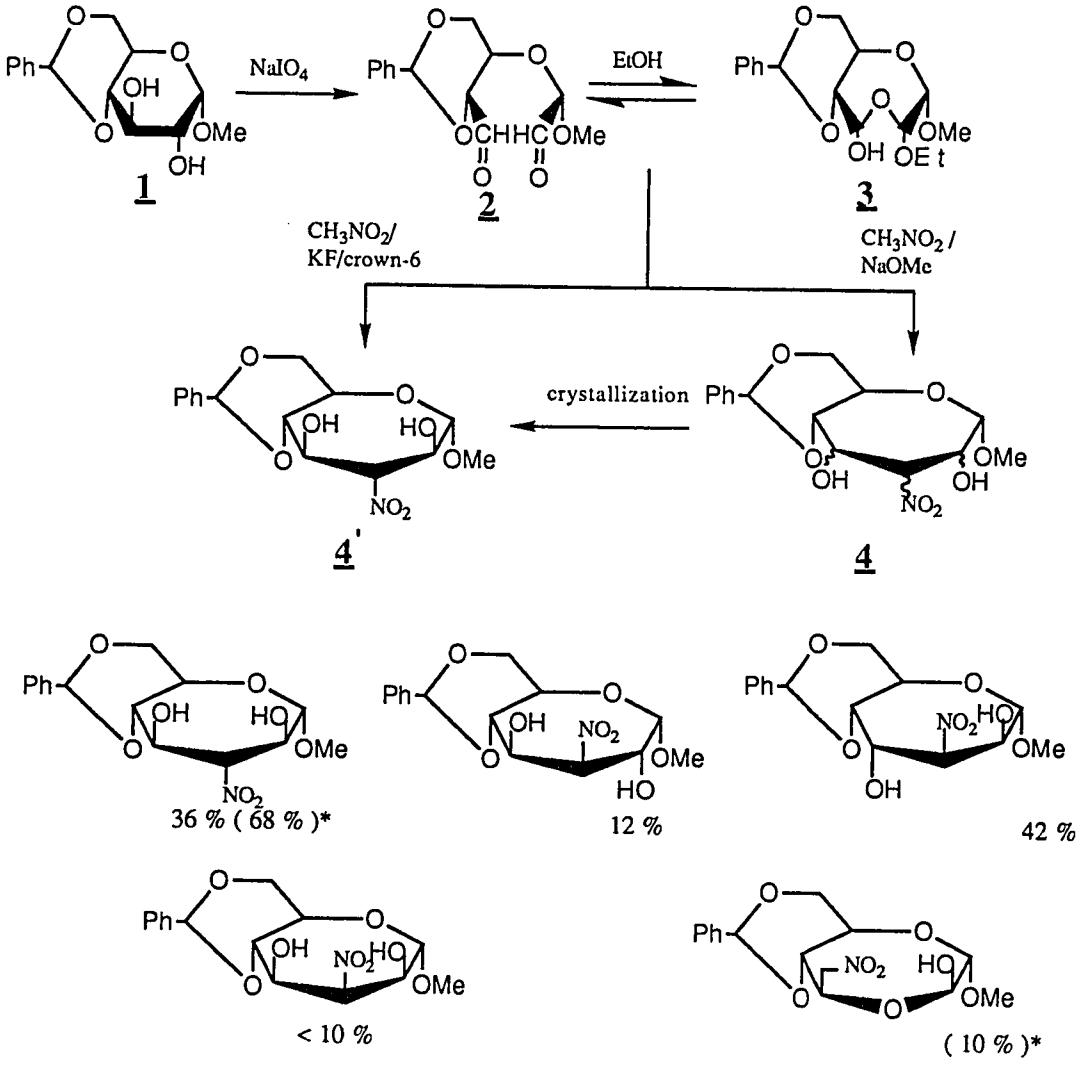
1-1. Introduction

The base-catalyzed cyclization of sugar dialdehydes with nitromethane, introduced by Baer and Fischer in 1958[1,2], has been used extensively in monosaccharides. Typically the dialdehyde is acquired by oxidation of an appropriate methyl glycoside with sodium metaperiodate. When the dialdehyde is treated with nitromethane in the presence of base, cyclization proceeds predominantly even in the presence of excess nitromethane. Independent addition of one nitromethane molecule to each aldehyde group forming an acyclic dinitro product is not observed, and neither has intermolecular polyaddition been demonstrated.

The nitromethane cyclization generates two chiral centers at the stage of the aci-nitro product and the third one upon acidification of the salt. Thus, eight possible stereoisomers may arise from such a process. Typically, however, only two or three stereoisomers are formed, with one often preponderating because of conformational factors.

Periodate oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 1 leads quantitatively to the dialdehyde 2 which from ethanolic solution forms the crystalline ethyl hemialdal 3[3]. Compound 3, under reversal of the hemialdal formation, reacts smoothly with nitromethane, whereby the dialdehyde 2 incurs cyclization to the 3-deoxy-3-nitro heptoseptanoside system 4 (Scheme 1). This particular application of the general principle of sugar dialdehyde-nitromethane cyclization[1,2,4] was first announced by Wolfrom

and colleagues[5] and recently reinvestigated in great detail by Defaye and Baer[6].



*: yields obtained from potasium fluoride method

Scheme 1.

It was found that nitromethane addition catalyzed by sodium methoxide in methanolic solution gives a mixture of diastereomeric nitrodiols 4 that have all been separated and conformationally elucidated, and among which the D-

glycero-D-*ido* isomer 4' is most easily isolated by fractional crystallization[6]. The isomers are interconvertible by epimerization in basic media, and 4' is the thermodynamically most stable one. When the nitromethane cyclization was performed in acetonitrile solution under catalysis with potassium fluoride[7-12] in the presence of dibenzo-18-crown-6, isomer 4' was the sole nitroheptoseptanoside isolated[8].

1-2. Results and Discussion

For purpose of the present thesis, both an isomer mixture 4 and the crystalline, single isomer 4' were prepared, and *O*-debenzylidenated by the action of 90 % trifluoroacetic acid as directed[6] (Scheme 2). Compound 4' gave the known[6], crystalline nitrotetrol 5', which was subsequently acetylated with acetic anhydride and boron trifluoride to furnish the new, crystalline methyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-3-nitro-α-D-*glycero*-D-*ido*-heptoseptanoside 6'. The mixture 4 was similarly debenzylidenated to the tetrol mixture 5, and acetylated to a mixture of tetracetates 6 containing at least three of the possible stereoisomers as major components, according to its ^{13}C-NMR spectrum*.

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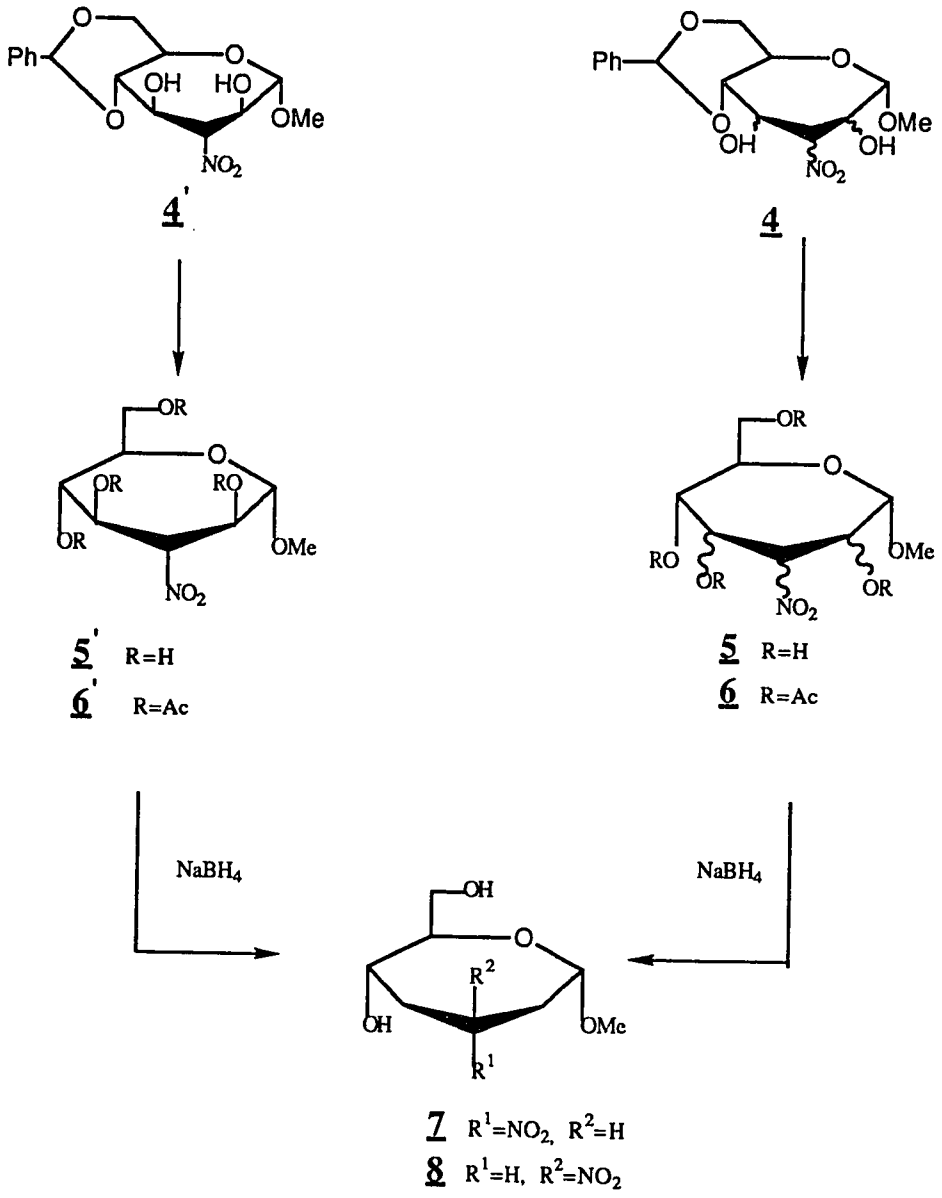
* It has been shown[6] that the D-*glycero*-D-*ido*, D-*glycero*-D-*manno*, and D-*glycero*-D-*galacto* isomers are the main components of the mixture 4 as obtained under the specified[6] conditions of cyclization, with the D-*glycero*-D-*talo* isomer being a minor component, and that the latter as well as the D-*glycero*-D-*altro* and D-*glycero*-D-*gulo* isomers arise from the former three isomers by secondary epimerization at C-3 under certain conditions of base catalysis.

1-2.1. Dideoxygenation of 2,4,5,7-tetra-*O*-acetyl-3-deoxy-3-nitro-heptoseptanosides.

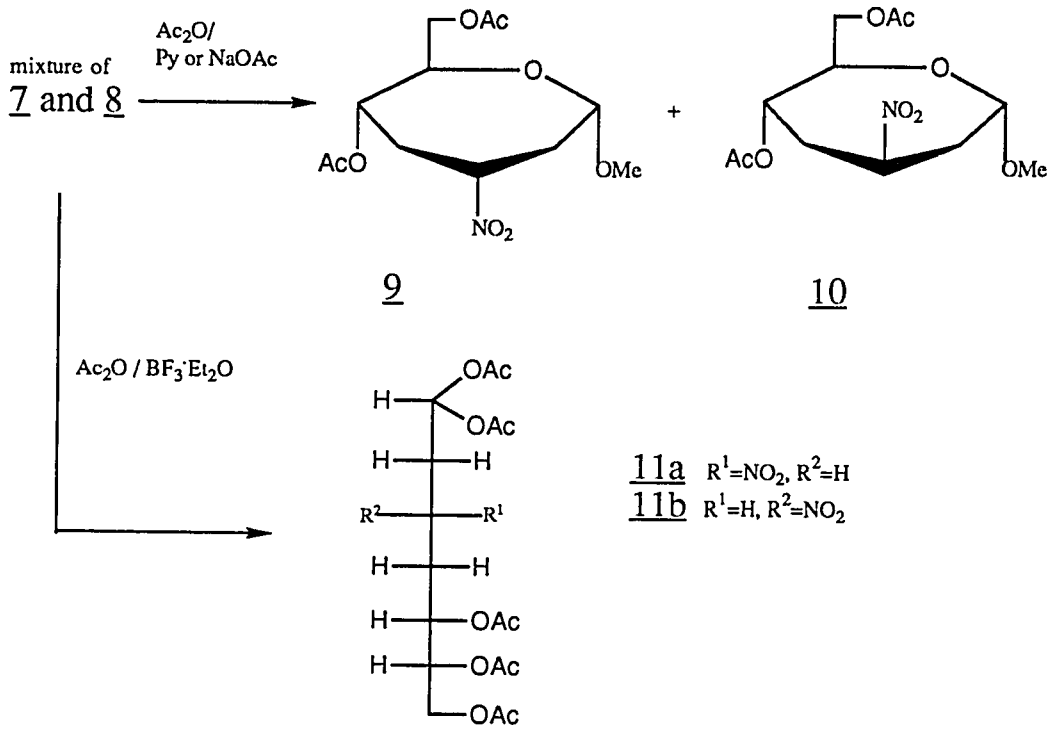


Scheme 2.

Treatment of the crystalline, homogeneous tetraacetate 6' with sodium borohydride[13] in ethanol at room temperature effected in the course of four days, a twofold reductive dehydroacetoxylation at C-2 and C-4, and concomitant deacetylation at O-5 and O-7. This led to a crystalline mixture of methyl 2,3,4-trideoxy-3-nitro-α-D-*ribo*- and α-D-*arabino*-heptoseptanosides (7 and 8) in 60 % yield after chromatographic purification. The same result was obtained when the configurationally inhomogeneous tetraacetate mixture of 6 was subjected to the same treatment. These experiments demonstrated the possibility of reducing the complexity of stereochemical situations in septanosides, predicated on the presence of three contiguous, undetermined stereogenic centers, by removing two of them through a process of deoxygenation.

Although the product of the borohydride reactions mentioned above was crystalline and well characterized by spectral and analytical data, its two 3-epimeric components (7 and 8) failed to separate in column chromatography. It was therefore decided to acetylate the mixture and attempt separation and further characterization of the corresponding 5,7-diacetates 9 and 10. Acetylation was first performed under acid-catalyzed conditions, in order to preclude any concurrent epimerization[13,14,15] at the nitromethine group as it might occur under pyridine catalysis, which would change the epimer ratio. Although such epimerization would be irrelevant from the viewpoint of characterizing the more stable epimer, it could well matter with respect to the examination of the less stable one. A mild method of acetylation using acetic anhydride and a catalytic amount of boron trifluoride was employed. This method[16-18] is a standard procedure in nitro sugar chemistry, and normally does not cause acetolysis of glycosidic bonds or acid-labile protecting groups such as cyclic acetals; as already mentioned, it has served

well in the preparation of the tetraacetates 6. However, it transpired that the 2,3,4-trideoxy-3-nitroseptanoside ring of 7 and 8 is exceptionally acid-labile. After a short reaction time (60 min) at low temperature (0°C), complete acetolysis of the glycosidic methoxy group occurred as evidenced by disappearance of the corresponding resonances from ^{1}H- and ^{13}C-NMR spectra. Surprisingly, the NMR data did not accord with the expected heptoseptanose 1,5,7-triacetate structure (nor with a heptopyranose 1,6,7-triacetate structure that could conceivably have arisen, by ring contraction) but were in agreement with a 3-epimeric mixture of open chain pentaacetates (11a and 11b) derived from the aldehyde forms (Scheme 3).



Scheme 3.

Following this experience, the diol mixture (7 and 8) was acetylated with acetic anhydride in pyridine[19,20], and the resultant mixture of diacetates (9 + 10) obtained in an almost quantitative yield was partially separated by column chromatography. This afforded pure, crystalline methyl 5,7-di-*O*-acetyl-3-deoxy-3-nitro-α-D-*ribo*-heptopyranoside 9 and a syrupy fraction consisting chiefly of the α-D-*arabino* isomer 10 but also containing a small proportion of 9. When a solution of pure 9 in pyridine-d_5 was kept at room temperature, the ^{1}H-NMR spectrum changed in the course of 3 days to that of a nearly 2:1 mixture of 9 and 10; no further change occurred after an additional two days at room temperature, nor after subsequent heating for two hours at 55°C, which indicated that epimeric equilibrium had been reached. The same equilibrium was obtained from (impure) 10 in pyridine-d_5.

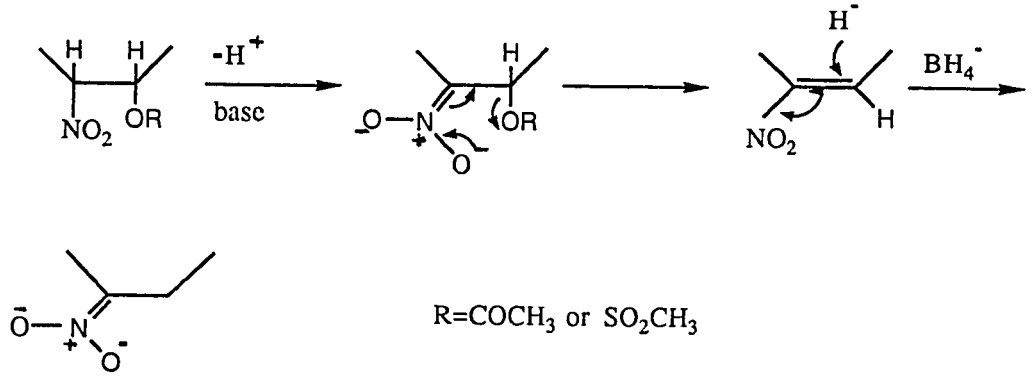


Figure 1. Mechanism of β-eliminaion of β-acyloxynitro compounds.

Mechanistically, the twofold deoxygenation of 6 by sodium borohydride is based on the well-established propensity of β-acyloxynitro compounds to undergo base-induced β-elimination of acid to give α-nitroalkenes[21,22,23] and

on the fact that nitroalkenes are readily reduced by borohydride to nitroalkanes[24-33](Figure 1).

Reduction of intermediate nitroalkene occurs in situ in the present case; and the resulting, saturated nitronate intermediate undergoes the same sequence a second time, effecting reductive elimination of the second acyloxy group. The final β,β'-dideoxynitronate upon protonation may give rise to a pair of nitromethine epimers (Figure 2).

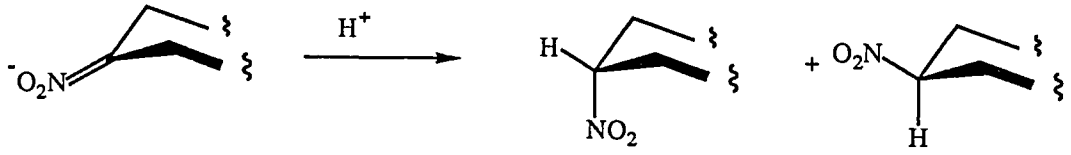
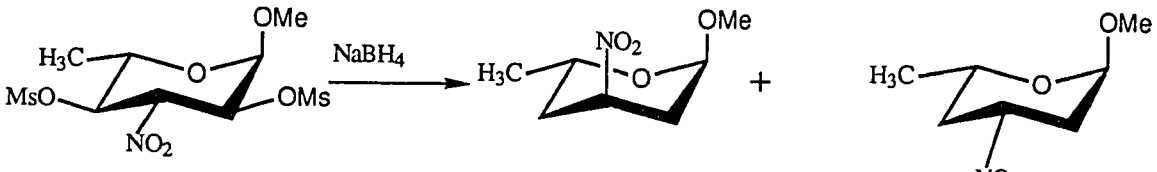


Figure 2. Protonation of β,β'–dideoxynitronate leads to nitromethine epimers.

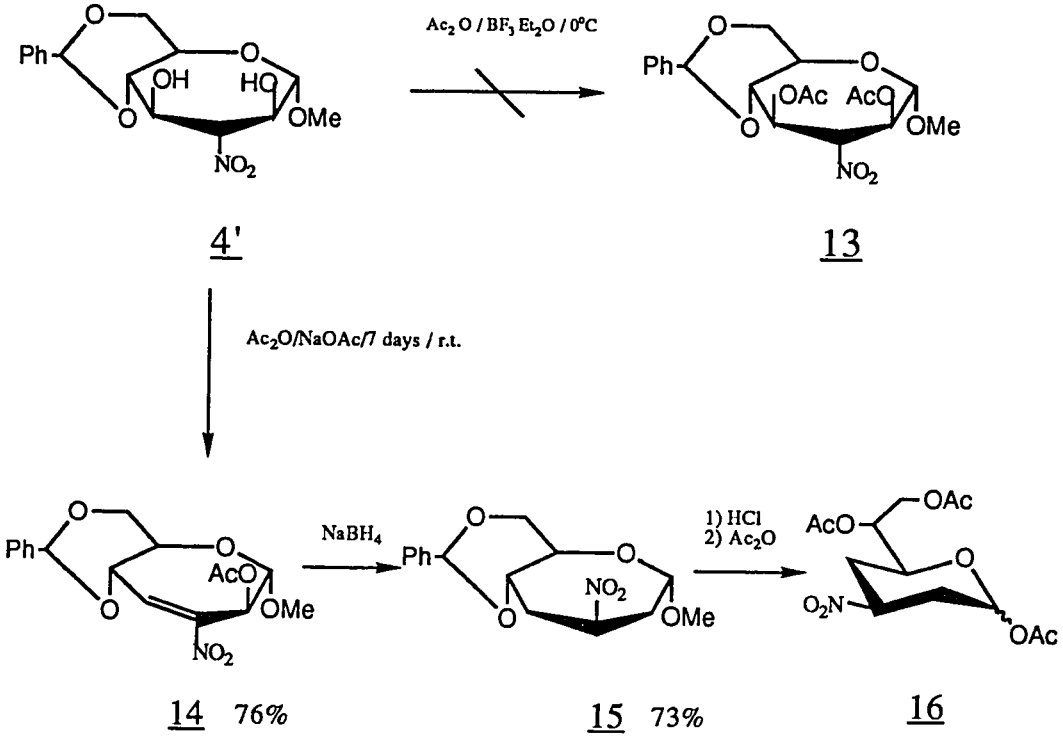
In the work on nitro sugar deoxygenation cited[27-33], the process just outlined was always performed in a stepwise fashion, i.e., nitro sugar acetates (or mesylates) were subjected to base-catalyzed elimination, and the resulting nitroolefins were isolated prior to reduction; also, most of these literature examples pertain to monodeoxygenation.



12 19 20

Scheme 4.

A precedent for the one-pot, double deoxygenation reported here was established by Baer and Hanna[13] in their synthesis of 4-deoxydaunosamine and 4-deoxyristosamine, but the substrate in that case was a dimesylate 12, not a diacetate (Scheme 4). More recently, a high-yielding one-pot monodeoxygenation involving a nitro carbohydrate acetate (1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol hexa-acetate) was reported from the same laboratory[34]. The present work complements these precedents by having demonstrated the utility of acetates in bis-deoxygenations of this type. Further observations on this topic will be discussed in subsequent paragraphs.



Scheme 5.

Next it appeared desirable to examine whether similar 2,4-bis-deoxygenation can equally well be achieved in 5,7-benzylidenated compounds such as 4. The presence of the cyclic acetal no doubt diminishes the conformational flexibility of the sugar ring in comparison to 5, and it seemed important to check for a possible influence of this on the facility of reductive eliminations. In the targeted nitrocyclodextrins, too, there will presumably be less conformational freedom than in the model monosaccharide 5. Consequently, an attempt was made to produce the 2,4-diacetate 13 from the single diol 4' by boron trifluoride-catalyzed acetylation (Scheme 5). The attempt failed because of partial loss of benzaldehyde suffered by the molecule even under carefully controlled conditions of acetylation. It was interesting to note such a sensitivity of the cyclic acetal attached to a septanoside system. Unlike the acid-sensitive 2,4-dideoxy nitro septanosides 7 / 8, the hydroxylated compound 4' should be stable under the conditions as far as its glycosidic bond is concerned, and indeed it did not lose its aglycon. The easy cleavage of its benzylidene group must be attributed to strain inherent in the *trans* fusion of a six-membered to a seven-membered ring, because analogous 4,6-*O*-benzylidene-3-deoxy-3-nitro hexopyranosides can be acetylated by this method without perceptible acetal cleavage[16].

Acetylation of 4' was therefore attempted by an alternative method, namely, with acetic anhydride in the presence of anhydrous sodium acetate. Brief heating of certain nitro sugars with this reagent has been known[19,20,35] to lead to products of dehydration (i.e.nitroalkenes) rather than acetylation, but dehydration has also been observed even after (slow) reaction at room temperature[36]. It was therefore no surprise when the main product obtained from 4', isolated in 76 % yield after a reaction of seven days at room temperature, was the 2-*O*-acetyl-3,4-dideoxy-3-nitro-hept-3-enoseptanoside 14.

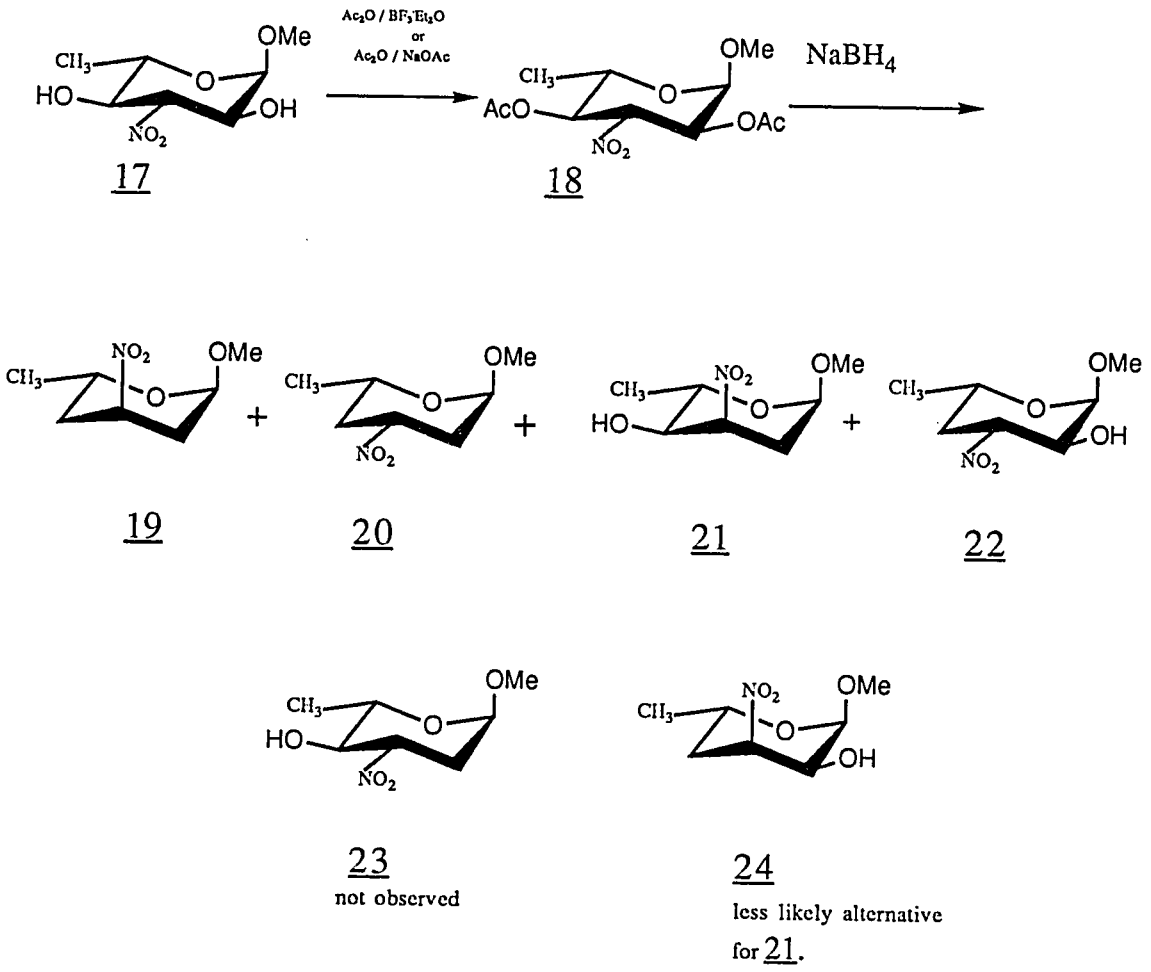
Treatment of this compound with sodium borohydride furnished a 73 % yield of crystalline methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-*arabino*-heptoseptanoside 15, proving that the reduction-elimination-reduction processes discussed above may operate also in systems that are somewhat constrained conformationally.

Compound 15 was hydrolyzed with 1M hydrochloric acid to remove the benzylidene and glycosidic groups and thus liberate the free, reducing nitro heptose which would be expected to adopt a pyranoid ring structure. The hydrolyzed material was acetylated under boron trifluoride catalysis for ^{1}H-NMR-spectroscopic examination which revealed an axially oriented H-3 proton (giving at 4.82 ppm a triplet of triplets with spacings of 12.3 and 4.3 Hz, respectively) in accord with formula 16.

For the structural studies anticipated to become necessary in connection with the planned nitrocyclodextrin work, it was desirable to collect some NMR data for a number 3-deoxy-3-nitrohexopyransides, possibly useful for purposes of comparison. Preparative work performed to that end is described in the paragraphs that follows.

As was mentioned earlier (Figure 2), the methyl 2,3,4,6-tetradeoxy-3-nitro-α-L-*erythro* and α-L-*threo* hexopyranosides (19 and 20) had been synthesized[13] from the dimesylate 12, but their ^{13}C-NMR data had not been recorded and samples were no longer available in this laboratory. In connection with the preparation of fresh samples it was considered interesting to examine, in view of the successful synthesis of the nitroseptanoside 7 and 8 from their acetate precursor 6', whether the di-*O*-acetyl analog 18 of 12 is suitable as a starting material for a twofold reductive elimination. Hence, methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside 17 was acetylated as reported[23], to give its known 2,4-diacetate 18 which was then

subjected to treatment with sodium borohydride in ethanolic solution (Scheme 6).



Scheme 6.

The reaction produced a mixture of three compounds which was fractionated by column chromatography into a 2:1 mixture (approximate ratio, according to its ^{1}H-NMR spectrum) of the bis-deoxygenated glycoside 19 (~25 %) with a 4-hydroxy compound tentatively assigned structure 21 (~12.5 %); and the

known 2-hydroxy isomer 22 (~37 %)[30] isolated as a single component. The 2,4-dideoxygenated derivative 20 was not detected among the products. However, when the reaction was repeated under slightly different conditions, namely in 10:1 methylene chloride-ethanol instead of pure ethanol, the crude product was similar as before with respect to the proportions of 19, 21, and 22 present, but it contained a fourth component (in a proportion comparable to that of 19) which was presumed to be 20, according to an evaluation of the ^{13}C-NMR spectrum. The set of 7 resonances due to this fourth component included two high-field CH_2 signals. The whole mixture was reacetylated with acetic anhydride and boron trifluoride etherate and subjected again to borohydride reduction, after which the minor hydroxy component 21 was no longer present although the major hydroxy component 22 persisted, in diminished proportion. The mixture now contained 19, 20, and 22, in that order of abundance although in roughly comparable amounts as judged from the intensity ratios of their corresponding ^{1}H- and ^{13}C- NMR signals.

The structural assignments of 19 - 22 were based on the following observations. The ^{1}H-NMR spectrum of the mixture of 19 and (presumed) 21, obtained on chromatography in the first-mentioned experiment, showed two well separated sets of signals with an intensity ratio of ~2:1.

The well resolved signals attributable to the major component were identical in every respect with those listed[13] for authentic 19. The set belonging to the minor component did not correspond to the data reported[13] for the 3-epimer 20, nor to those reported for the known[30] 2-hydroxy-α-L-*xylo* derivative 22 or the 4-hydroxy-α-L-*arabino* derivative 23 (whose D-enantiomer is known[31]). There remained, then, a choice between the 4-hydroxy-α-L-*ribo* compound 21 and its 2-hydroxy-α-L-*ribo* isomer 24, neither of which appears to have been described in the literature. A decision based on the ^{1}H-NMR

spectrum could not be made because of signal overlap (H-1 and H-3; H-5 and carbinol H-2 or H-4), but ^{13}C chemical shifts particularly for C-5(δ 66.9) and C-6 (δ 17.6) suggested that the 4-position was hydroxylated. Had formula 24 applied, these shifts should have been similar to those in 19 (δ 59.8 and 21.2, respectively), Thus, 21 was tentatively chosen as the structure of the minor product, pending definitive proof. The beautifully resolved ^{1}H spectrum of 22 was in full accord with the data reported[30] for this compound. The ^{1}H-NMR spectrum of the product mixture (19, 20, 22) obtained in the second experiment after the second borohydride treatment was complex, but the signals belonging to 19 and 22 could all be readly assigned by comparison with previously obtained spectra and published data. There were extra signals, and these corresponded to signals recorded[13] for known 20.

The results obtained in the deoxygenation experiments with the diacetate 18 warrant some discussion. The analogous dimesylate 12 in methylene chloride solution had given, upon treatment with sodium borohydride for 1 - 1.5 h, an almost quantitative yield of 19 and 20 as a mixture from which 56 % of 19 and 26 % of 20 were isolated by crystallization and chromatography[13]. By contrast, 18 reacted very slowly, requiring 3-4 days for complete consumption in either methylene chloride or ethanol medium. As previously mentioned, deoxygenation of the acetylated nitroheptoseptanosides 6 was an equally slow process. Doubtless the inferior leaving-group ability of acetate as compared to methanesulfonate ion is responsible for the observed rate differences. However, steric factors also seem to play a role, for the poor nucleofugacity of acetate appears to be of practical importance only in cyclic nitro sugar such as 6 and 18; reductive dehydroacetoxylation of the open-chain, 1-deoxy-1-nitroheptitol hexaacetate referred to on page 5 was a rapid process that gave a 85 % yield of the desired

product within 1 h[34]. At any rate, it is understandable that during the long sojourn of 18 in the reaction medium, partial ester cleavage may have ocurred in competition with β-elimination, accounting for the formation of monodeoxygenated products (21 and 22). In 6, ester cleavage at positions 5 and 7 (not relevant to the desired reduction-elimination) was complete under the same reaction conditions, but no evidence was obtained for similar cleavage at positions 2 or 4 competing with elimination. However, it cannot be excluded that a certain proportion of monodeoxygenated nitroseptanosides resulted as a consequence of such cleavage and escaped detection; the fact that the yield of crystalline 7 + 8 isolated chromatographically was only ~60 % clearly admits this possibility.

Another point to be discussed concerns the ratios of nitromethine epimers encountered in these studies, i.e., the ratios found for 7:8, 9:10, and 19:20. In the case of the reaction of the pyranosidic dimesylate 12, the axial-nitro glycoside 19 was the kinetically preferred product, but the equatorial-nitro epimer 20 which has no 1,3-diaxial substituent interaction was strongly preferred after thermodynamic equilibration[13].

In an extensive study on the stereochemistry of protonation of nitrocycloalkane nitronate ions, Bordwell[37] and Yee[38,39,40] (Figure 3) have demonstrated the importance of certain substitutent effects for the stereochemical outcome. Thus, whereas 4-*tert*-butyl-1-nitrocyclohexane preferentially (3:1) reacts by axial attack of the proton donor, to give mainly the equatorial-nitro compound (1,4-*trans*), in 2-phenyl- and 2-methyl-1-nitrocyclohexane this approach is sterically hindered and equatorial protonation favors the formation of 1,2-*cis* product in the kinetically preferred epimer.

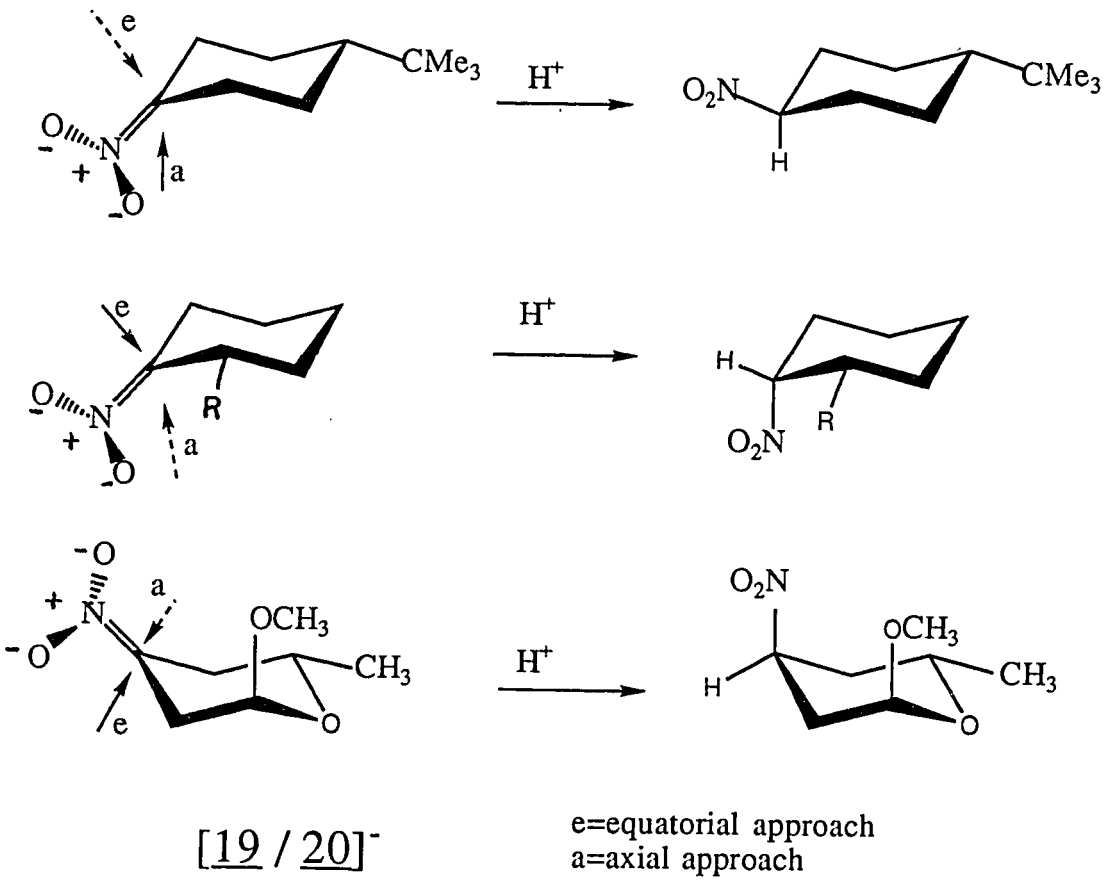


Figure 3. Protonation of nitronates.

In the common nitronate of 19 and 20 it is evidently the anomeric methoxy group which to some extent impedes axial protonation. In the present study using diacetate 18, the same kinetic preference for formation of 19 was expected and indeed observed. In the case of the formation of the nitroseptanosides 7 and 8 from 6 it was more difficult to predict the kinetic epimer distribution because of the greater conformational flexibility of the seven-membered ring which may render substituent effects less important (Figure 4). Moreover, this flexibility allows several reasonable conformations to be considered for the nitronate anion and it is not known which one

actually pertains. For example, if the anion [7,8]$^-$ adopts a conformation close to the $^0C_{3,4}$ chair depicted (A), protonation from above would appear to be favored giving 7. If on the other hand the conformation is close the $^5C_{1,2}$ chair (B), the reverse approach leading to 8 should be more favorable. Our results were that 7 and 8 arose in a ~2:1 ratio, which may suggest a kinetic preference for the former (and, by implication, a preferred conformation like A for the anion), unless the product mixture obtained in the protonation did not result from kinetic control but reflected a thermodynamic equilibration. It was demonstrated by separate epimerization experiments with the 5,7-diacetates 9 and 10 of 7 and 8, respectively, that 9 is the more stable isomer of the pair, and one may probably assume the same for 7. The 9:10 equilibrium was 2:1, and if the same ratio of 7:8 resulting from protonation of the anion was due to kinetics it must have been a remarkable coincidence.

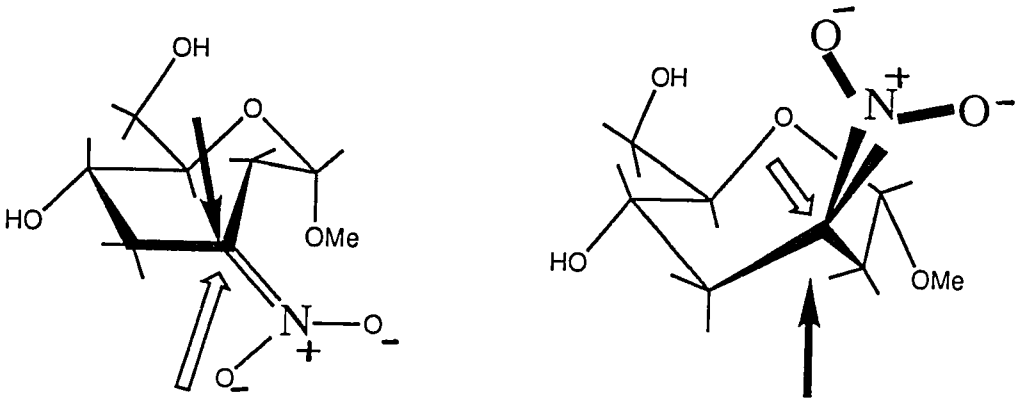


Figure 4. Protonation of nitronate [7/8]$^-$.

1-2.2. Discussion of Nuclear Magnetic Resonance Spectra and Conformations.

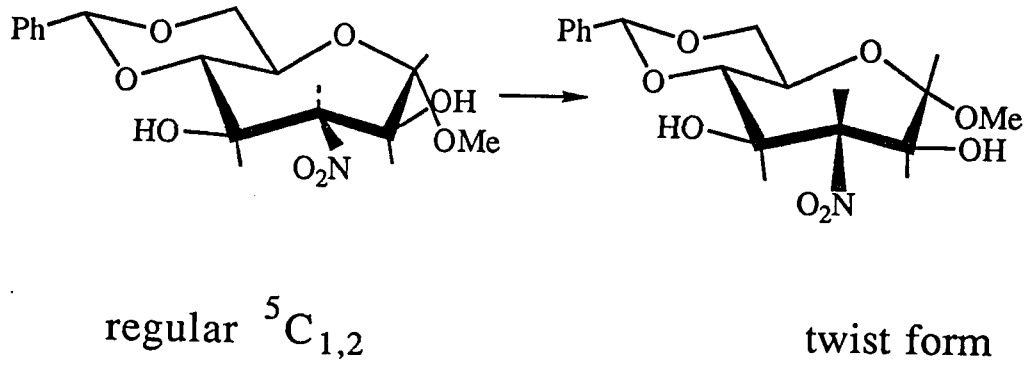


Figure 5. Conformation of compound 4'.

The ^{13}C- and ^1H- NMR data for heptoseptanoside derivatives dealt with in this thesis are listed in Tables 1 and 2, respectively. The data found for 4' and 5' agreed fully with those reported for these two known compounds, for whose conformation a twist chair basically related to the regular $^5C_{1,2}$ chair (Figure 5) has been proposed[6,8] in consideration of the ring-proton coupling constants as evaluated in light of the conformational behavior of seven-membered ring system**. The hitherto unknown tetraacetate 6' shows very similar J values and can therefore be assigned the same conformation.

** It was assumed that the detailed conformational analysis of cycloheptane[41] can be applied with fair approximation to the septanose ring. The energetically preferred conformations of cycloheptane are twist chair forms, about 2 Kcal/mol lower in energy than the regular, flexible chair form through which they are interconnected in a pseudorotational cycle. Dihedral angles (w) for consecutive *cis* bonds in the twist- chair were computed[41] as

Table 1. ^{13}C-NMR chemical shifts (ppm) for 4', 5', 6', 7, 8, 9, 10, 14, 15.

	chemical shifts(ppm)									
compound	PhCH	C-1	C-2	C-3	C-4	C-5	C-6	C-7	OMe	
4		105.1	71.3	91.9	74.0	82.9	61.5	69.7	56.3	a,1
5		104.1	70.8	92.2	76.1	72.3	71.2	62.2	56.8	b2 & a,1
6		101.8	66.8	86.2	73.3	70.1	68.9	62.9	56.4	b,4
7(or 8)		101.6	33.0	81.4	40.5	76.8	68.9	65.4	58.2	b,3
8(or 7)		101.8	40.6	81.6	44.9	76.0	69.2	64.7	58.0	b,3
9		98.6	38.4	78.0	37.9	67.4	68.8	63.7	55.7	b,4
10		98.7	36.5	78.0	34.3	68.8	68.8	64.5	55.7	b,4
14	101.1	96.6	68.9	146.7	143.1	76.3	61.0	68.9	56.1	b,4
15	100.9	98.7	36.1	77.9	35.8	63.6	76.1	69.4	55.5	b,4

a: data recorded at 125.76 MHz; b: data recorded at 50.3 MHz
1: CD_3CN, 2: D_2O, 3: 1:1 D_2O/MeOH, 4: $CDCl_3$

-42.2, 97.0, -75.8, 52.9, -75.8, 97.0, and -41.2°; for *trans* bonds, they are w±120°. Vicinal substituents can be accommodated at any angle in the ranges 0 to 97° (*cis*) and 23 to 217°(*trans*) since the various conformers are freely interconvertible by pseudorotation. In septanose 5,7-acetals such as 4, this variability is limited to the C-1 - C-4 segment of the molecule because of the *trans*-fused 1,3-dioxane ring. For the regular $^5C_{1,2}$ chair of the D-*glycero*-D-*ido* compound 4' a pseudorotational downward movement of C-2 relieves bond eclipsing by opening of the H-1,2 dihedral angle from 120 to ~150°, and a slight flattening of the ring portion C-1 to C-5 improves staggering of OH-2, NO_2-3, and OH-4, concomitant with positioning H-3 more nearly antiparallel to H-2 and H-4; the resulting conformation is a somewhat distorted twist chair as approximately depicted, having all ring protons oriented is harmony with the observed vicinal couplings of 6.5($J_{1,2}$) and 8-10Hz($J_{2,3}$ to $J_{5,6}$). Removal of the benzylidene acetal ring alters the couplings very little (by ~0.5 Hz or less), indicating that 5' has essentially the same conformation[6].

Table 2. ^{1}H-NMR spectra data of heptoseptanosides 4', 5', 6', 7, 8, 9, 10, 14, 15.

compound	4'	5'	6'	7 + 8	9	10	14	15
H-1	4.49d	4.62d	4.61d	4.96dd	4.80dd	4.92dd	4.84d	4.85dd
H-2	4.08dt	4.16dd	5.59dd	2.35-2.2m	2.65ddd	2.65ddd	6.05dd	2.94dsept
H-2'				2.0-1.85m	2.24ddd	2.21ddd		2.12ddd
H-3	4.81t	4.93t	5.04dd	4.28m	4.55tdd	4.74dddd		4.75m
H-4	4.19m	4.08dd	5.68dd	2.35-2.2m	2.75dsept	2.74ddd	7.55t	3.05dtd
H-4'				2.0-1.85m	~2.0	2.16ddd		1.91ddd
H-5	3.63dd	3.56t	5.13	4.00-3.75	4.83ddd	5.08ddd	4.89dd	3.95dt
H-6	3.77td	3.85-3.73	4.20-4.00		4.08m	4.2-4.0m	4.25-4.1m	3.87dt
H-7	4.21dd				4.18m			4.18dd
H-7'	3.60dd				4.11dd		3.80m	3.63dd
	a1	b2	c3	b2*	b3	b3	c3	b3

Protons chemical shifts in ppm.

a: recorded at 500MHz; b: recorded at 300MHz; c: recorded at 200MHz; 1:CD_3CN; 2:D_2O; 3:$CDCl_3$

* signals attributed to the major isomer.

Coupling constants in Hz.

compound	4'	5'	6'	9	10	14	15
$J_{1,2}$	6.5	6.8	6.7	5.8	4.7	3.3	7.5
$J_{1,2'}$				9.2	6.7		5.2
$J_{2,2'}$				14.7	15.5		15.6
$J_{2,3}$	10.2	10.3	10.6	1.5	7.0		1.8
$J_{2,4}$				2.2		2.3	1.2
$J_{2',4'}$							
$J_{2',3}$				11.5	3.3		7.2
$J_{3,4}$	10.2	10.3	10.4	2.8	8.3		3.8
$J_{3,4'}$				11.5	4.3		4.9
$J_{4,4'}$				12.8	14.6		14.8
$J_{4,5}$	8.1	8.5	8.4	5.4	4.3	2.3	9.6-10
$J_{4',5}$				10.4	6.5		5.0
$J_{5,6}$	10.0	9.6	9.9	9.5	7.7	9.2	9.6
$J_{6,7}$	5.8			5.2		5.2	9.6
$J_{6,7'}$	10.0			2.5			
$J_{7,7'}$	10.7			11.9		10.8	

Whereas the mixture of 2,4-dideoxy compounds (7 and 8) arising from deoxygenation of 6'(or 6) could not be separated and no conformational information could be culled from the spectrum of the mixture, the 5,7-diacetates 9 and 10 obtained from the diols were amenable to analysis. Thus, the major epimer 9 (Figure 6) showed J values (Table 1) that were compatible with a twist chair close to that just mentioned. A molecular model calculation provided the computed dihedral angles between ring protons listed in Table 3. Juxtaposition of the observed coupling constants gives good agreement. The dihedral angles computed for the C-C and C-O ring bonds are also listed in the table, and a Dreiding model built according to these parameters was used to depict, approximately, the conformational formula for 9. The orientations of the nitro and acetyl groups are also drawn according to computer-generated data for dihedral angles (not listed).

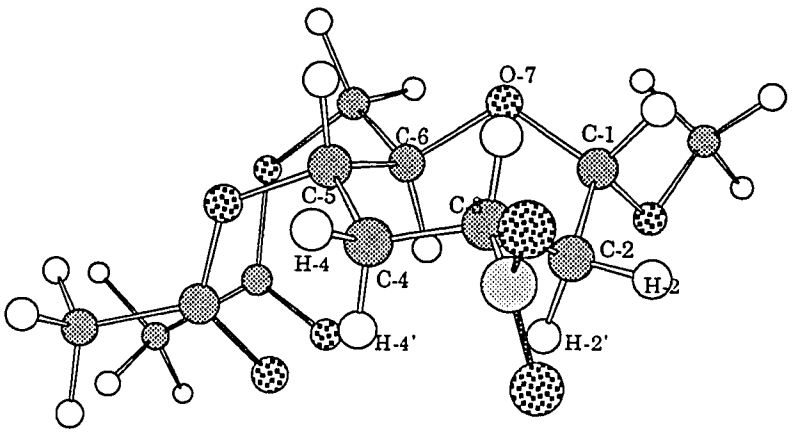
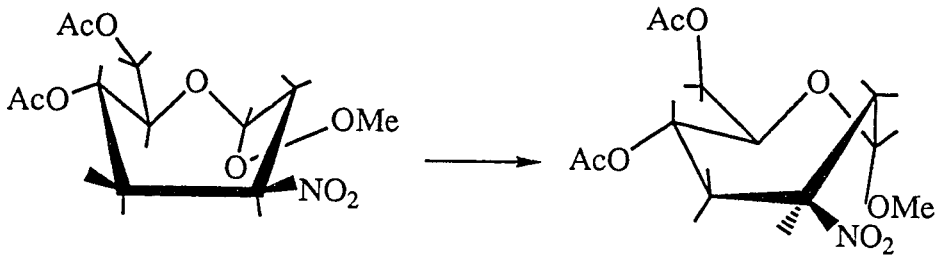


Figure 6. Lowest energy conformation of epimer 9, predicted by molecular mechanics calculation (see Table 3).

Table 3. Computed Dihedral Angles and Observed J Values of Compound 9.

Dihedral Angles	Computed (°)	J observed (Hz)
H(1)-C(1)-C(2)-H(2)	-33.3	5.8
H(1)-C(1)-C(2)-H(2')	-153.4	9.2
H(2)-C(2)-C(3)-H(3)	98.9	1.5
H(2')-C(2)-C(3)-H(3)	-21.4	11.5
H(3)-C(3)-C(4)-H(4)	-75.3	2.8
H(3)-C(3)-C(4)-H(4')	164.6	11.5
H(4)-C(4)-C(5)-H(5)	45.1	5.4
H(4')-C(4)-C(5)-H(5)	165.0	10.4
H(5)-C(5)-C(6)-H(6)	166.1	9.5
O-C(1)-C(2)-C(3)	-36.4	
C(1)-C(2)-C(3)-C(4)	98.3	
C(2)-C(3)-C(4)-C(5)	-74.8	
C(3)-C(4)-C(5)-C(6)	48.2	
C(4)-C(5)-C(6)-O	-76.0	

The conformation of the 3-epimer 10 (Figure 7) was evaluated in similar manner.



regular $^{o}C_{3,4}$ chair

twist form

(arising by an upward displacement of C-4)

Figure 7. Conformation of compound 10.

It had been found[19] that benzylidenated septanoside isomers of type 4 having a C-3 configuration opposite to 4' (i.e., D-*glycero*-D-*manno*, and D-*glycero*-D-*talo* configurations) adopt a twist-chair conformation derived by pseudorotation from the regular $^0C_{3,4}$ chair, which allows the nitro group to assume a quasi-equatorial orientation. The same appears to hold for 10. The twist conformation depicted here was obtained by molecular modeling calculations performed as for 9, and the dihedral angles computed corresponded well to the proton-proton coupling constants observed (Table 4).

Table 4. Computed Dihedral Angles and Observed J Values of Compound 10.

Dihedral Angles	Computed (°)	J observed (Hz)
H(1)-C(1)-C(2)-H(2)	82.2	4.7
H(1)-C(1)-C(2)-H(2')	-38.7	6.7
H(2)-C(2)-C(3)-H(3)	141.9	7.0
H(2')-C(2)-C(3)-H(3)	-97.2	3.3
H(3)-C(3)-C(4)-H(4)	-177.6	8.3
H(3)-C(3)-C(4)-H(4')	62.9	4.3
H(4)-C(4)-C(5)-H(5)	10.6	4.3*
H(4')-C(4)-C(5)-H(5)	130.1	6.5*
H(5)-C(5)-C(6)-H(6)	150.3	7.7
O-C(1)-C(2)-C(3)	77.1	
C(1)-C(2)-C(3)-C(4)	-96.9	
C(2)-C(3)-C(4)-C(5)	62.2	
C(3)-C(4)-C(5)-C(6)	13.4	
C(4)-C(5)-C(6)-O	-90.6	

* Values suggest that dihedral angles are actually somewhat larger than computed. A slight upward movement of C-5 in the Dreiding model widens these angles, with minimal change in other angles.

Assignment of structure to the nitroalkenic septanoside 14 (Figure 8) on the basis of its NMR spectra was straightforward. All ^1H and ^{13}C signals (Table 1 and 2) could be unambiguously identified with the aid of COSY, ADEPT, and HETCOR experiments. The proton signal appearing at lowest

field (7.55 ppm) was a triplet attributable to an olefinic proton, and this must have been H-4 as it was coupled with H-5 (a doublet of doublets at 4.89 ppm) and (long range) with H-2 (a doublet of doublets at 6.05 ppm) which in turn was coupled with H-1 (a doublet at 4.84 ppm). These features ruled out an alternative formulation of the compound as a positionally isomeric 4-*O*-acetyl 2-enoside. In constructing a Dreiding model one realizes that 14 is an extremely rigid molecule for which no conformation other than the $^{O}C_{3,4}$ chair form depicted appears reasonable. The ring-proton coupling constants were in agreement with this conformation.

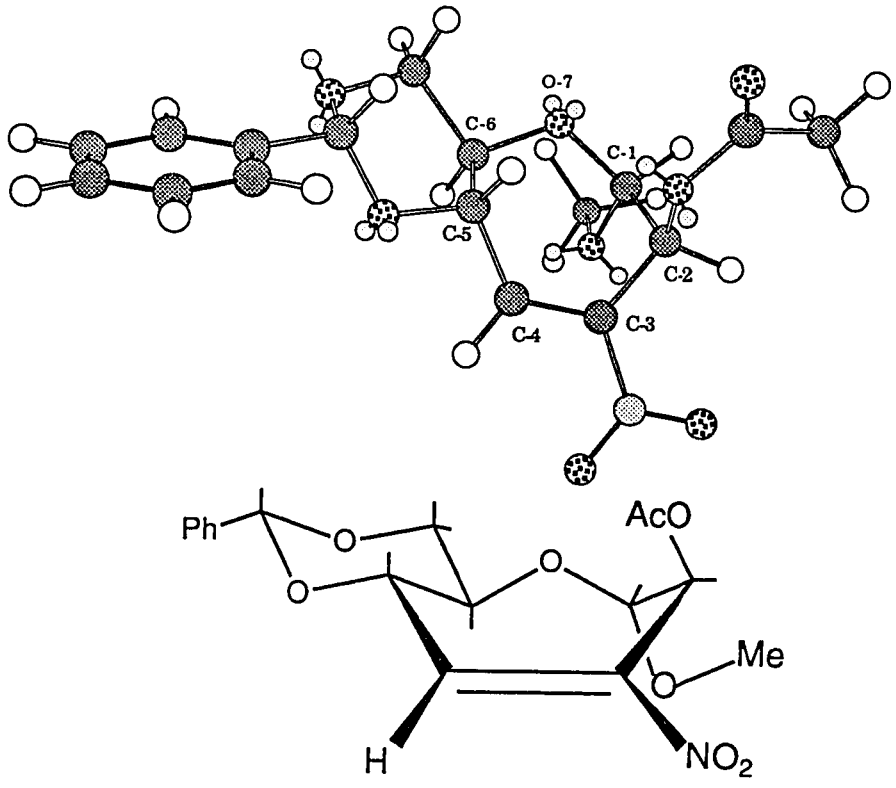


Figure 8. Lowest conformation of compound 14 (top), predicted by molecular mechanics calculation (data see Table 5).

Table 5. Computed Dihedral Angles and Observed J values of compound 14.

Dihedral Angles	Computed (°)	J observed (Hz)
H(1)-C(1)-C(2)-H(2)	-42.0	3.3
H(4)-C(4)-C(5)-H(5)	119.1	2.3~2.4
H(5)-C(5)-C(6)-H(6)	172.5	9.2
O(7)-C(1)-C(2)-C(3)	84.1	
C(1)-C(2)-C(3)-C(4)	-55.4	
C(2)-C(3)-C(4)-C(5)	-0.5	
C(3)-C(4)-C(5)-C(6)	56.2	
C(4)-C(5)-C(6)-O(7)	-81.9	

Table 6. Computed Dihedral Angles and Observed J Values of Conformers 15A, 15B, and 15C.

Dihedral Angles	15A	15B	15C	J observed (Hz)
H(1)-C(1)-C(2)-H(2)	-44.1	-17.4	76.6	5.25
H(1)-C(1)-C(2)-H(2')	-157.2	-132.4	-37.7	7.6
H(2)-C(2)-C(3)-H(3)	-41.8	178.8	-162.3	7.25
H(2')-C(2)-C(3)-H(3)	72.1	-66.1	-47.9	1.8
H(3)-C(3)-C(4)-H(4)	56.6	-159.1	87.4	4.9
H(3)-C(3)-C(4)-H(4')	-57.2	43.3	-25.8	3.8
H(4)-C(4)-C(5)-H(5)	51.8	45.8	77.6	4.9
H(4')-C(4)-C(5)-H(5)	164.9	160.8	-169.3	10.0
H(5)-C(5)-C(6)-H(6)	176.1	-177.4	176.0	9.6
O-C(1)-C(2)-C(3)	-38.7	-14.6	89.0	
C(1)-C(2)-C(3)-C(4)	85.5	-63.3	-42.4	
C(2)-C(3)-C(4)-C(5)	-66.5	37.2	-32.2	
C(3)-C(4)-C(5)-C(6)	49.5	48.1	81.2	
C(4)-C(5)-C(6)-O	-70.5	-58.0	-73.1	

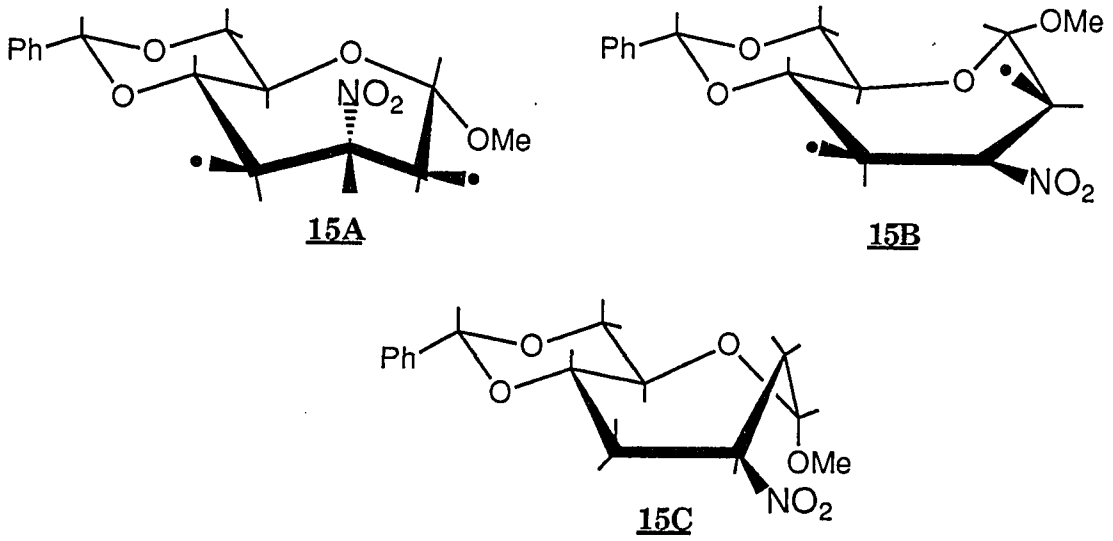


Figure 9. Possible conformations of compound 15.

A different and somewhat surprising situation pertained to the saturated, deoxygenated acetal 15. First of all, it could not be predicted with certainty whether the reductive elimination in 14 would lead to 15 or to its 3-epimer, or to a mixture of both. The experiment gave one major product isolated crystalline in 73 % yield, and two minor products that were chromatographically separated (in yields of 5-6 %) from the main product but remained unidentified. The chief product was assigned the D-*arabino* configuration (as in formula 15) because on chemical transformations that involved acid conditions throughout (and therefore precluded base-induced 3-epimerization) the pyranosidic compounds 16 were obtained whose ^{1}H-NMR spectrum indicated an axial orientation for H-3. Now as concerns the conformation of 15, the vicinal proton-proton coupling constants were compatible both with the conformation 15A (a twist-chair derived from the

regular $^5C_{1,2}$ chair by a slight pseudorotational downward shift of C-2), and with 15B (a twist-boat related to the regular $^5B^{1,2}$ boat). Molecular model calculations were performed for both species, and the results are presented in Figure 9 and Table 6.

At first sight, either form appears to violate empirical rules for conformational behavior. 15A possesses a pseudoaxial nitro group, a situation which is not normally favored when an alternative orientation is available for this group, and the situation is aggravated by the "inward" inclination of the group. In 15B the nitro group is favorably placed in an equatorial manner, but boat forms are generally of high energy and therefore avoided if possible, and in the present case the anomeric effect would also be expected to operate against it. The compound was rather anticipated to adopt a twist-chair conformation 15C analogous to 10, like some of the diols of type 4 do as discussed in Figure 7, but its J values were not consistent with the dihedral angles implied.

There were two spectral observations which may be taken as evidence in favor of 15A and against 15B. There was long-rang coupling between the protons marked (i) in position 2 and 4($^4J_{2,4}$=1.2 - 1.4Hz). In 15A these are situated in the W arrangement conducive to such coupling, whereas in 15B they are not so situated. Further, a nuclear Overhauser experiment (see Experimental part) irradiating H-3 showed strong nOe enhancement of the H-2, H-4, and H-4' signals, and medium-strong enhancement of H-2' in line with the proximity (gauche arrangements) of the protons involved. For 15B such enhancement should occur for H-2' and H-4' only, and not for H-2 and H-4 which stand anti to H-3.

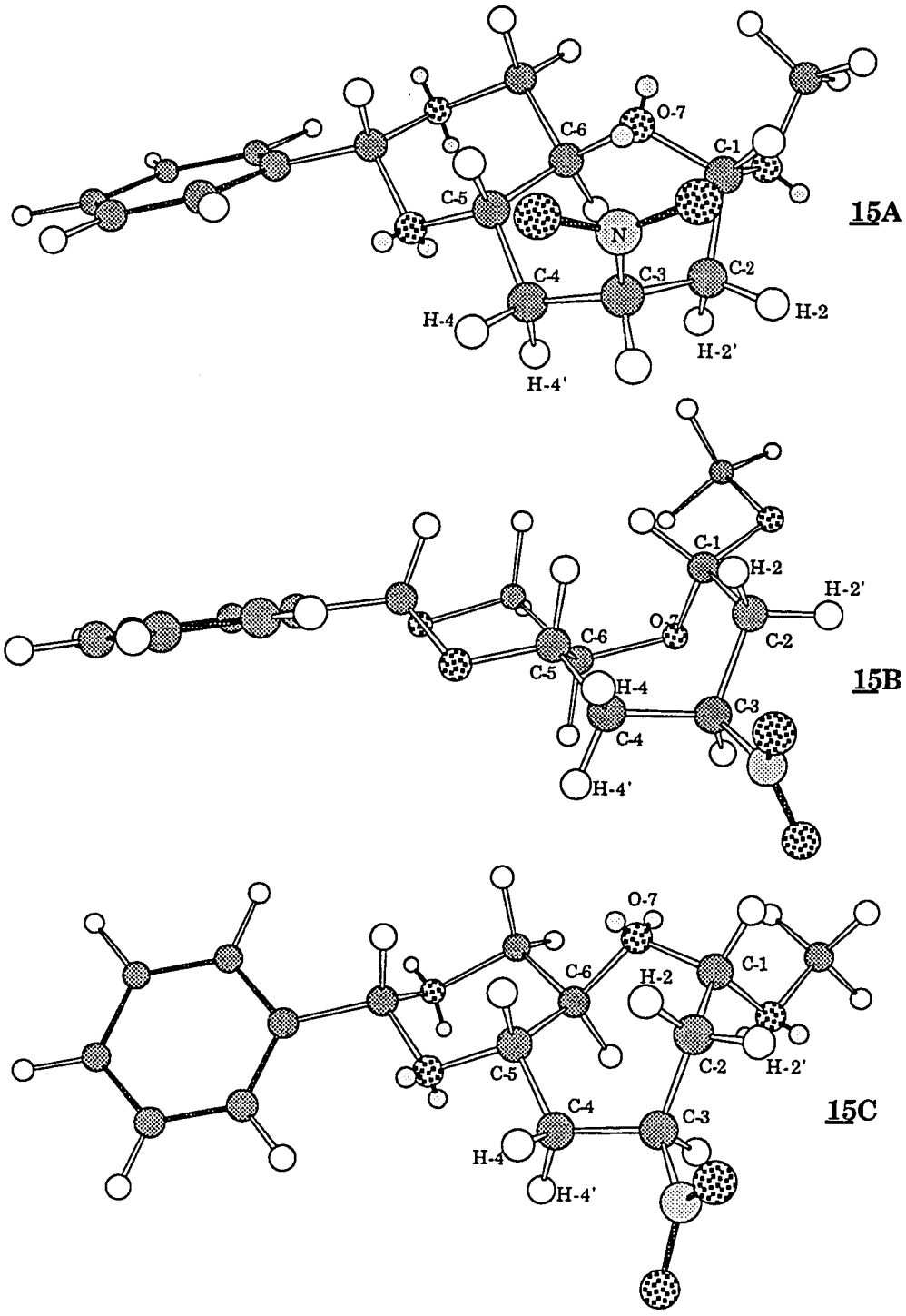
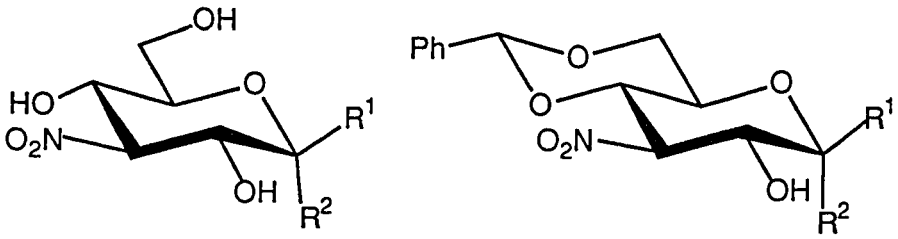


Figure 10. Computer-generated conformers of compound 15. (15A is the lowest energy conformation.)

^{1}H-NMR spectra of the nitro pyranosides encountered in this investigation need little discussion. The spectrum of the anomeric mixture 16 could not be analyzed in every detail because of overlaping signals, but fortunately the H-3 and H-4ax signals of the predominant anomer could be located with the help of a COSY experiment. These appeared, respectively, as a triplet of triplet at 4.82 ppm having two large (12.3 Hz) and two small (4.3 Hz) spacings, and as a quartet at 1.91 ppm having three equal spacings ($J_{3,4ax} \sim J_{4ax,5} \sim J_{4ax,4eq} \sim 12.3$Hz). These values clearly indicated an axial orientation of H-3 (and hence, an equatorial NO_2) and thus furnished proof for the C-3 configuration of the progenitor 15.



25, R^1=H, R^2=OMe

26, R^1=OMe, R^2=H

27, R^1=H, R^2=OMe

28, R^1=OMe, R^2=H

Figure 11. Compounds 25, 26, 27, and 28.

The pyranosides 17-20 and 22 were known, and their ^{1}H-NMR data described in the literature proved the depicted conformations. The structural problem associated with compound 21 has already been mentioned (Scheme 4). One of the reasons for preparing these pyranosidic

nitro sugars was to gather ^{13}C NMR data for them, for comparison with the corresponding septanoside data and possible use as references in the planned work on nitro cyclodextrins. The data for the 2,3,4-trideoxy-3-nitro-hexopyranosides 19, 20, 21, and 22 are given in the Experimental (page 46 and 48). Table 7 lists the data collected for four additional nitro pyranosides, namely methyl 3-deoxy-3-nitro-α- and -β-glucopyranosides 25 and 26, and their respective 4,6-*O*-benzylidene acetals 27 and 28 (Figure 10). These compounds have long been known[1], but their carbon spectra were not recorded and have now been acquired in the course of those studies.

Table 7. ^{13}C-NMR spectra data of glucopyranosides 25, 26, 27, and 28.

	chemical shifts (ppm)								
compound	PhCH	C-1	C-2	C-3	C-4	C-5	C-6	OMe	solvent
25		98.4	69.5	92.7	67.3	71.1	59.8	54.8	DMSO-d_6
26		102.8	70.6	93.8	67.1	76.1	60.4	57.6	D_2O
26		102.8	70.7	94.8	67.7	76.5	60.3	56.3	DMSO-d_6
27	101.5	98.9	70.5	88.4	77.2	62.1	68.7	55.8	$CDCl_3$
28	103.9	101.5	71.8	88.8	77.4	66.8	68.5	57.8	$CDCl_3$

1-3. Experimental

1-3.1. 7-Ethoxy-9-hydroxy-6-α-methoxy-2-phenyl-*trans*-(1,3-dioxano)[5,4-e][1:4]-dioxepan (3).

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 1 (20g) was partially dissolved in 95% ethanol (400 mL), and a solution of $NaIO_4$ (19.2 g) in water (400 mL), adjusted to pH 5 with NaOH, was added. The mixture was stirred in the dark at 25°C for 60 hours. The solid product was collected by filtration and washed thoroughly with water and then with petroleum ether (30 - 60°), to yield 17.6 g of crude product (76.5 %), which was recrystallized from hot acetone to give pure 7-ethoxy-9-hydroxy-6-α-methoxy-2-phenyl-*trans*(1,3-dioxano)[5,4-e][1:4]-dioxpan (3), m.p. 153.5 - 155°C, $[\alpha]_D$ +67.2° (c 0.5, pyridine); lit.[6] m.p. 153 - 154°C, $[\alpha]_D$ +67° (pyridine). ^{1}H-NMR data (200 MHz, DMSO-d_6): δ 7.45 (m, 5 H, Ar), 7.10 (d, 1H,OH-9), 5.60 (s, PhC<u>H</u>), 4.82 (dd, 1 H,H-9), 4.65 (d, 1 H, H-6), 4.38 (d, H-7), 4.15 (dd, H-4), 3.78 - 3.50 (m, 4H, H-4a, 9a, O<u>C</u>$H_2$$CH_3$), 3.35 (s,3H, OCH_3), 1.15 (t, 3H,CH_2CH_3). ^{13}C-NMR and ADEPT data (50.3 MHz, DMSO-d6): δ 137.8, 129.1, 128.2, 126.4 (Ph), 102.7 (C-7), 100.2 (C-2), 99.5 (C-6), 97.8 (C-9), 82.0 (C-9a), 68.4 (C-4), 63.5 (CH_3<u>CH_2</u>O), 61.3 (C-4a), 55.1 (CH_3O), 14.7 (<u>CH_3</u>CH_2O).

1-3.2. Methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-*D-glycero-D-ido*-hepto-septanoside (4').

To a cooled (0°C) mixture of the dialdehyde derivative 3 (1.45 g, 4.4 mmol) and nitromethane (0.3 ml, 5.5 mmol) in methanol (12 mL) was added a cold (0°C) solution of sodium (70 mg, 3 mmol) in methanol (10 mL). The solution was kept at 0 - 5°C for two hours, then deionized under continued

cooling with Amberlite IR-120(H^+) resin and evaporated to dryness, with evaporation of added toluene (5 mL) from the residue to give a solid mixture of diastereoisomeric cyclization products 4 (1.27 g, 84%).

A second experiment, performed on a threefold scale, afforded 3.90 g (87%) of crude product. This was dissolved in chloroform (30 mL) and stored overnight at -18°C. The precipitate was collected and recrystallized from methanol to give 0.95 g (24 %) of pure methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-*D-glycero-D-ido*-heptoseptanoside (4'), m.p. 222°C (dec.), $[\alpha]_D$ +38° (c 0.7, MeOH); lit.[6] m.p. 225°C (dec.), $[\alpha]_D$ +38° (MeOH). A ^{1}H-NMR spectrum taken at 200-MHz from a DMSO-*d6* solution was in accordance with 500-MHz data reported[6] for a CD_3CN: δ7.50 (m, 5 H's, Ph) , 6.35 (d, OH), 6.20 (d, OH), 5.62 (s, PhCH), 4.75 (t, H-3), 4.50 (d, H-1), 4.25-4.00 (m, 3H, H-2, 4, and 7), 3.90-3.55 (m, 3H, H-5, 6, and 7'), 3.35 (s, 3H, OMe).

1-3.3. Methyl 3-deoxy-3-nitro-α-*D-glycero-D-ido*-heptoseptanoside (5').

Pure benzylidene acetal derivative 4' (100 mg) was introduced into 90% trifluoroacetic acid (1.5 mL) chilled in an ice-water bath. The mixture was stirred at 0 °C and the reaction monitored by TLC (1:9 ethanol / chloroform). After 30 min, the spot for the acetal (Rf 0.77) was completely replaced by a slow-moving spot (Rf 0.08) for the tetrol. The reaction mixture was co-evaporated with added water three times to remove benzaldehyde. The residue was taken up in water and filtered to remove some undissolved material, the filtrate was then evaporated and the product dried in an oil pump vacuum to give the tetrol methyl 3-deoxy-3-nitro-α-*D-glycero-D-ido*-heptoseptanoside (5', 70 mg, 94%) as a white solid, m.p. 195 - 196.5°C (lit.[6] 194 - 195°C). ^{1}H-NMR data (200 MHz, D_2O): δ4.67 (d, H-1), 4.20 (dd, H-2), 4.99 (dd, H-3), 4.12 (dd, H-4), 3.63 (dd, H-5), 3.87 - 3.78 (m, H-6, 7, and 7'); $J_{1,2}$ 6.8 Hz,

$J_{2,3}$ 10.3 Hz, $J_{3,4}$ 10.34 Hz, $J_{4,5}$ 8.4 Hz. ^{13}C-NMR data: δ 104.1 (C-1) , 92.2 (C-3), 76.1 (C-4), 72.3 (C-5), 71.2 (C-6), 70.8 (C-2), 62.2 (C-7), 56,8 (OMe).

1-3.4 Methyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-3-nitro-α-*D-glycero-D-ido*-heptoseptanoside (6').

To a chilled mixture (0°C) of methyl 3-deoxy-3-nitro-α-*D-glycero-D-ido*-heptoseptanoside (5', 70 mg) and acetic anhydride (0.5 mL) was added a droplet of trifluoroborane etherate. The stirred suspension was removed from the ice bath and then turned clear within 10 min. TLC (1:9 ethanol-chloroform) showed the acetylated product (Rf 0.82) and no starting material (Rf 0.08). A white precipitate formed when ice-water was poured into the flask. The precipitate was filtered and crystallized from 99 % ethanol to give 102 mg of white crystals of methyl 2,4,5,7-tetra-O-acetyl-3-deoxy-3-nitro-α-*D-glycero-D-ido*-heptoseptanoside (6', 97 % yield), m.p. 154.5 - 155.5°C, $[\alpha]_D$ +112.4° (c 5.4, chloroform); MS (CI, ether) spectrum: m/z 422 (M^+ +1), 390 (M^++1-MeOH), 362 (M^++1-HOAc); ^{1}H-NMR data (200 MHz, $CDCl_3$): δ 5.68 (dd, H-4), 5.59 (dd, H-2), 5.13 (dd, H-5), 5.04 (dd, H-3), 4.61 (d, H-1), 4.22 - 4.04 (m, H-6, 7, and 7'), 3.45 (s, OMe), 2.01, 1.98, 1.96, 1.91 (s, 4 OAc); $J_{1,2}$ 6.7 Hz, $J_{2,3}$ 10.6 Hz, $J_{3,4}$ 10.4 Hz, $J_{4,5}$ 8.4Hz, $J_{5,6}$ 9.9 Hz; ^{13}C-NMR spectral data (50.3 MHz, $CDCl_3$, and ADEPT): δ 170.5, 169.6, 168.8, 167.9 (4 C=O), 101.8 (C-1), 86.2 (C-3), 73.3 (C-4), 70.1 (C-5), 68.9 (C-6), 66.8(C-2), 62.9(C - 7), 56.4 (OMe), 20.4, 20.3, 20.2, 20.1 (4 OAc); IR absorption (neat, KBr pellet): 1755 cm^{-1} (C=O), 1565 cm^{-1} (NO_2).

Anal. Calcd. for $C_{16}H_{23}NO_{12}$ (421.37): C, 45.61; H, 5.46; N, 3.33. Found C, 45.48; H, 5.31; N, 3.29.

1-3.5. Methyl 2,3,4-trideoxy-3-nitro-α-*D-ribo*- and *D-arabino*-heptoseptanoside mixture 7 and 8.

Methyl 3-deoxy-3-nitro-2,4,5,7-tetra-*O*-acetyl-α-*D-glycero-D-ido*-heptoseptanoside (6', 2.10 g) was dissolved in 99% ethanol (20 mL). Sodium borohydride (2.04 g) was added portionwise with stirring at room temperature. Another portion of sodium borohydride (3.0 g) was added after three days. Monitoring by TLC (1:9 ethanol - chloroform) indicated a slow conversion of the starting material (Rf 0.80) into the product (Rf 0.28). The reaction was nearly complete after four days. The mixture was neutralized with Amberlite IRC-50(H^+) with which it was stirred at room temperature overnight. The resin was filtered off and the filtrate concentrated and co-evaporated with several added portions of methanol. After drying at the oil pump, the product obtained (970 mg, 88 %) consisted of two isomers in a 2 : 1 ratio (by ^{13}C-NMR). The crude mixture was purified by column chromatography on silica gel with eluent 1:19 ethanol - chloroform, and then crystallized from ethanol - methylene chloride to give analytically pure material (655 mg), but the epimers could not be separated; ^{1}H-NMR data (200 MHz, D_2O, signals attributed to the major isomer): δ 4.96 (dd, J 4.5 and 8 Hz, H-1), 4.28 (m, W~17 Hz, H-3), 4.0-3.75 (m, 4H, H-5, 6, 7, and 7'), 3.50 (s, 3H, OMe), 2.35-2.2 (2 partially overlapping m, 2 H, with J 4.5, 6.7, 15, and 5.3, 5.3, 15, respectively, H-2,4), 2.00 and 1.85 (2 ddd, J 2, 9, 15 and 3, 8, 15, respectively, H-2', 4'); ^{13}C-NMR (50.3 MHz, 1:1 D_2O - MeOH): major isomer δ101.8 (C-1), 81.6 (C-3), 76.0 (C-5), 69.2 (C-6), 64.7 (C-7), 58,0 (OMe), 44.9 (C-4), 40.6 (C-2); minor isomer δ 101.6 (C-1), 81.4 (C-3), 76.8 (C-5), 68.9 (C-6), 65.4 (C-7), 58.2 (OMe), 40.5 (C-4), 38.0 (C-2).;MS (CI, ether) spectrum: m/z 296 (M^+ + 1 + ether), 264 (M^+ + 1 + ether - MeOH), 222 (M^+ + 1), 206 (M^+ + 1 - O), 190 (M^+ + 1 - MeOH); IR absorption (KBr pellet, neat): 3379 cm^{-1} (OH), 1547 cm^{-1} (NO_2).

Anal. Calcd.for $C_8H_{15}NO_6$(221.21): C, 43.44, H, 6.79; N, 6.33. Found: C, 43.39; H, 6.70; N, 6.07.

1-3.6. Mixture of epimers 7 and 8 obtained from diastereoisomers 4.

A mixture of diastereoisomers 4 (1.27 g) was debenzylidenated with 90% trifluoroacetic acid as described in the preceding experiment for compound 5' to give a diasteroisomeric mixture of nitro septanosides 5 (0.8 g). The mixture was acetylated as described in the previous experiment of synthesis of compound 6', to give a syrup of tetraacetates 6 (1.05 g, 78%) which showed at least three isomers in ^{13}C-NMR (three anomeric carbon atoms resonated at 98 ~ 102 ppm). The syrup failed to crystallize. The product was then treated with sodium borohydride as 6' to give a mixture of two epimers whose ^{13}C-NMR spectrum was the same as that of 7 and 8.

1-3.7. Methyl 5,7-di-*O*-acetyl-2,3,4-trideoxy-3-nitro-α-*D-ribo*-heptoseptanoside (9) and methyl 5,7-di-*O*-acetyl-2,3,4-trideoxy-3-nitro-α-*D-arabino*-heptoseptanoside (10).

A solution of epimers 7 and 8 mixture (170 mg) in acetic anhydride (1.5 mL) and pyridine (2.0 mL) was stirred at room temperature for one hour, after which TLC (1:19 ethanol - chloroform) showed two product spots (Rf 0.56 and 0.48) and absence of starting material (Rf 0.06). The reaction mixture was concentrated under reduced pressure at 30°C, the residue dissolved in ethyl acetate, and the solution washed with M HCl, aqueous sodium carbonate solution, and water. The organic phase was evaporated and the residue dried at the oil pump, to give 231 mg (98.5%) of a solid mixture of epimeric diacetates (9 and 10 in a ratio of 2:1) as concluded on the basis of ^{1}H- and ^{13}C-NMR spectra. The mixture was partially separated by column

chromatography on silica gel with 0-10% ethanol - chloroform as eluent, to give pure isomer 9 collected from the first fraction, and a mixture of 9 and 10 from the second fraction which showed the dominant compound 10 on the basis of NMR spectra.

Compound 9 gave IR (KBr pellet, neat): 1741 cm^{-1} (C=O), 1555 cm^{-1} (NO_2); MS (CI, ether): m/z 306 (M^+), 274 (M^+ + 1-MeOH), 288 (M^++ 1 - H_2O), 259 (M^++ 1 - HNO_2), 246 (M^++ 1 - HAc), 227 (M^++ 1 - MeOH - HNO_2); ^{1}H-NMR and COSY data (300 MHz, $CDCl_3$): δ 4.83 (ddd, $J_{4,5}$ 5.4, $J_{4',5}$ 10.4, $J_{5,6}$ 9.5 Hz, H-5), 4.80 (dd, $J_{1,2}$ 5.8, $J_{1,2'}$ 9.2 Hz, H-1), 4.55 (tdd, $J_{2,3}$ 1.5, $J_{2',3} = J_{3',4} = 11.5$, $J_{3,4}$ 2.8 Hz, H-3), 4.18 (dd, $J_{6,7}$ 5.2, $J_{7,7'}$ 11.9 Hz, H-7), 4.11 (dd, $J_{6,7'}$ 2.5, $J_{7,7'}$ 11.8 Hz, H-7'), 4.08 (m, W 17.5 Hz, H-6), 3.40 (s, 3H, OCH_3), 2.75 (d of septets, $J_{2,4}$ 2.2, $J_{3,4}$ 2.8, $J_{4,5}$ 5.4, $J_{4,4'}$ 12.8 Hz, H-4), 2.65 (dddd, $J_{1,2}$ 5.9, $J_{2,3}$ 1.5, $J_{2,4}$ 2.1, $J_{2,2'}$ 14.7 Hz, H-2), 2.24 (ddd, $J_{1,2'}$ 9.1, $J_{2',3}$ 11.5, $J_{2,2'}$ 14.8 Hz, H-2'), ~2.0 (m, H-4', obscured by OAc signals), 2.04 and 2.01 (2 s, 3H each, 2 OAc); ^{13}C-NMR, HETCOR, and ADEPT data (75.43 MHz, $CDCl_3$): δ 170.6, 169.6 (2 C=O), 98.61 (C-1), 78.0 (C-3), 68.8 (C-6), 67.4 (C-5), 63.7 (C-7), 55.7 (OMe), 38.4 (C-2), 37.9 (C-4), 20.7, 20.5 (2 OAc). The crystals obtained from absolute ethanol gave m.p. 89.3 - 91.2°C; $[\alpha]_D$ +93.1° (c 3.9, methylene chloride).

Anal. Calcd. for $C_{12}H_{19}NO_8$ (305.23): C, 47.21; H, 6.27; N, 4.59. Found: C, 47.38; H, 6.41; N, 4.42.

Compound 10 (signals attributed to the major epimer 10 of the syrupy mixture of 9 + 10) had IR (KBr pellet, neat): 1737 cm^{-1} (C=O), 1549 cm^{-1} (NO_2); MS (CI, ether): m/z 306 (M^++1), 288 (M^++ 1 - water), 274 (M^++ 1 - MeOH), 259 (M^++ 1 - HNO_2), 246 (M^++ 1 - HAc), 227 (M^++ 1 - MeOH - HNO_2); ^{1}H-NMR and COSY data (300MHz, $CDCl_3$): δ 5.075 (ddd, $J_{4,5}$ 4.3, $J_{4',5}$ 6.5, $J_{5,6}$ 7.7 Hz, H-5), 4.92 (dd, $J_{1,2}$ 4.7, $J_{1,2'}$ 6.7 Hz, H-1), 4.74 (dddd, $J_{2,3}$ 7.0, $J_{2',3}$ 3.3, $J_{3,4}$ 8.3, $J_{3,4'}$ 4.3 Hz, H-3), 4.2 - 4.0 (m, 3H, H-6,7,7'), 3.40 (s, 3H, OMe), 2.74 (ddd, $J_{3,4}$ 8.3,

$J_{4,5}$ 4.3, $J_{4,4'}$ 14.6 Hz, H-4), 2.65 (ddd, $J_{1,2}$ 4.7, $J_{2,3}$ 7.0, $J_{2,2'}$ 15.4 Hz, H-2), 2.21 (ddd, $J_{1,2'}$ 6.7, $J_{2,3}$ 3.3, $J_{2,2'}$ 15.5 Hz, H-2'), 2.16 (ddd, $J_{3,4'}$ 4.4, $J_{4',5}$ 6.3, $J_{4,4'}$ 14.5 Hz, H-4'; the downfield dd overlapping with the upfield dd of H-2'), 2.043, 2.041 (2 s, 3H each, 2 OAc); ^{13}C-NMR, ADEPT, and HETCOR data (75.43 MHz, $CDCl_3$): δ 170.8, 169.7 (C=O), 98.7 (C-1), 78.0 (C-3), 68.8 (C-5 and 6), 64.5 (C-7), 55.7 (OMe), 36.5 (C-2), 34.3 (C-4), 20.8, 20.6 (2 OAc).

Anal. found: C, 46.46; H, 6.59.

1-3.8. nOe data for 9.

	protons saturated	
	H-3	OCH3
integration enhanced		
H-1	s	m
H-2	s	
H-4	s	
H-5	s	
H-6		w

s: relatively strong enhancement; m: relatively medium enhancement; w: relatively weak enhancement.

1-3.9. nOe data for 10

	protons saturated			
	OCH3	H-1	H-3	H-5
integration enhanced				
H-1	m			
H-2'			m	
H-2		s	m	
H-3				
H-4'			m	w
H-4			m	s
H-5				
H-6	w		m	s
H-7				
H-7'				

s: relatively strong enhancement, m: relatively medium enhancement, w: relatively weak enhancement.

1-3.10. Methyl 2-*O*-acetyl-5,7-*O*-benzylidene-3,4-dideoxy-3-nitro-hept-3-enoseptanoside (14).

A mixture of 4' (600 mg), anhydrous sodium acetate (400 mg), and acetic anhydride (10 mL) was stirred at room temperature for 7 days, after which TLC (1:19 ethyl acetate - methylene chloride) showed one major spot (Rf 0.54) and one light spot (Rf 0.39) and no more starting material. The excess acetic anhydride was removed under reduced pressure below 35°C.

The residue was taken up in ethyl acetate and the solution filtered to remove the salt. Evaporation of the filtrate gave a light brown residue (650 mg) which showed one major product in ^{13}C- and ^{1}H-NMR spectra. The residue was then flash chromatographed on a silica gel column by use of 1:19 of ethyl acetate - methylene chloride to give a fast -moving product 14 (490 mg, 76 %) and slow-moving products (two components, 21 mg). The major product was a syrup that failed to crystalize from absolute ethanol but was obtained as an analytically pure, anhydrous solid upon evaporation of the alcohol: $[\alpha]_D$ +48.7° (c 2.95, methylene chloride); IR (KBr pellet, neat): 1749 cm^{-1} (C=O), 1537 cm^{-1} (nitroalkene); MS (CI, ether): m/z: 366 ($M^+ + 1$), 334 ($M^+ + 1$ - MeOH), 306 ($M^+ + 1$ - AcOH), 274 ($M^+ + 1$ - MeOH - AcOH), 260 ($M^+ + 1$ - NO_2 - AcOH); ^{1}H-NMR (200 MHz, $CDCl_3$) and COSY: δ 7.55 (t, $J_{2,4}$~$J_{4,5}$~2.3 Hz, H-4), 7.49 - 7.24 (m, 5 H, Ph), 6.06 (dd, $J_{1,2}$ 3.3, $J_{2,4}$ 2.2 Hz, H-2) , 5.52 (s, 1H, PhCH), 4.89 (dd, $J_{4,5}$ 2.4, $J_{5,6}$ 9.2 Hz, H-5), 4.84 (d, $J_{1,2}$ 3.3, H-1), 4.25 - 4.14 (m, 2 H, H-6 and H-7), 3.80 (m, H-7'), 3.45 (s, 3H, OMe), 2.15 (s, 3H, OAc); ^{13}C-NMR, ADEPT, and HETCOR data (50.3MHz, $CDCl_3$): δ 169.5 (C=O), 146.7 (C-3), 143.1 (C-4), 136.7, 129.4, 128.4, 126.1 (Ph), 101.1 (PhCH), 96.6 (C-1), 76.3 (C-5), 68.9 (C-2, and 7), 61.0 (C-6), 56.1 (OMe), 20.3 (OAc).

Anal. Calc. for $C_{17}H_{19}NO_8$(365.33): C, 55.89: H, 5.21; N, 3.84. Found: C, 56.02; H, 5.25; N, 3.76.

1-3.11. Methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-*D-arabino*-heptoseptanoside (15).

To a solution of nitroalkene 14 (155 mg) in absolute ethanol (10 mL), stirred at room temperature, was added sodium borohydride (150 mg) in portions during one hour, followed by an additional portion (60 mg) after 24 hours. Stirring was then continued for two more days. The reaction mixture

was diluted with methanol (20 mL) and neutralized by stirring it overnight with Amberlite ion exchanged resin IRC-50(H^+). The crude product (135 mg) was obtained after filtration and evaporation of the solvent. ^{13}C-NMR data of the crude showed essentially one major product. The crude product was flash chromatographed on a silica gel column by use of 20 - 10 % of hexane - methylene chloride as eluent, to give three syrup products: the fastest-moving product (7 mg, 5.3 %), the second fast-moving product 15 (96 mg, 73%), and the slow-moving product (8 mg, 6.2%). The Rf values were 0.41, 0.33, and 0.06, respectively (TLC with 1:9 methylene chloride - hexane). The major product 15 formed crystals on long standing and slow concentration of a solution in $CDCl_3$; m.p. 190.5 - 192.0°C; $[\alpha]_D$ +69.4° (c 0.5, methylene chloride); IR (KBr pellet, neat): 1540 cm^{-1} (NO_2); MS (CI, ether): m/z 310 (M^+ + 1), 278 (M^+ + 1 - MeOH), 263 (M^+ + 1 - HNO_2); ^{1}H-NMR data (300 MHz, $CDCl_3$, and COSY): δ 7.48 - 7.31 (m, 5 H, Ph), 5.46 (s, PhCH), 4.85 (dd, $J_{1,2'}$ 7.5, $J_{1,2}$ 5.2 Hz, H-1), 4.75 (narrow m, W= 17.5 Hz, H-3), 4.18 (dd, $J_{6,7}$ 5.15, $J_{7,7'}$ 10.8 Hz, H-7), 3.95 (dt, $J_{4,5}$ 5.0, $J_{4'5}$=$J_{5,6}$= 9.6 Hz, H-5), 3.87 (dt, $J_{6,7}$ 5.15, $J_{5,6}$=$J_{6,7'}$=9.6 Hz, H-6), 3.63 (dd, $J_{6,7'}$ 9.6, $J_{7,7'}$ 10.8 Hz, H-7'), 3.36 (s, 3H, OMe), 3.05 (dtd, $J_{2,4}$ 1.2, $J_{3,4}$=$J_{4,5}$=4.9, $J_{4,4'}$ 14.8 Hz, H-4), 2.94 (d of septets, $J_{1,2}$ 5.2, $J_{2,2'}$ 15.6, $J_{2,3}$ 7.25, $J_{2,4}$ 1.4 Hz, H-2), 2.12 (ddd, $J_{1,2'}$ 7.6, $J_{2,2'}$ 15.6, $J_{2',3}$ 1.8, H-2'), 1.91 (ddd, $J_{3,4'}$ 3.8, $J_{4,4'}$ 14.8, $J_{4',5}$ 10.0 Hz, H-4'); ^{13}C-NMR data (50.3MHz, $CDCl_3$, and ADEPT): δ 139.5, 137.3, 129.2, 128.4, 126.1 (Ph), 100.9 (PhCH), 98.7 (C-1), 77.9 (C-3), 76.1 (C-6), 69.4 (C-7), 63.6 (C-5), 55.5 (MeO), 36.1, 35.8 (C-2 and 4).

Anal. Calcd. for $C_{15}H_{19}NO_6$(309.31): C,58.25; H,615; N, 4.53. Found, C, 58.20, H, 6.02, N, 4.38.

1-3.12. nOe data for 15.

	protons saturated			
	OMe	H-1	H-3	H-7
integration enhanced				
H-1	s			
H-2'			m	
H-2		s	s	
H-3				
H-4'			s	
H-4			s	
H-5				m
H-6	w			m
H-7	w			
H-7'				s

s: relatively strong enhanced; m: relatively medium enhanced; w: relatively weak enhanced.

1-3.13. Compounds 16.

Starting material (15, 50 mg) in 1 M hydrochloric acid (0.5 mL) was heated in a steam bath for 3 min. The the reaction mixture was co-evaporated with several portions of water at 50°C to remove benzaldehyde. The debenzylidenated product was obtained as a brown residue (32 mg) which was dried in vacuo. The material was acetylated by treatment for 2 hours with acetic anhydride - trifluoroboron etherate at 0 to 20°C. The

mixture was stirred for two hours. After conventional work-up, 38 mg (70 %) of crude product consisting of two major components was obtained. It was purified by column chromatography to give 31 mg of a light brown syrup; no separation of the components was achieved. MS (CI, ether) gave m/z 334 (M^+ + 1), 274 (M^+ + 1 - HOAc), 227 (M^+ + 1 - HNO_2 - HOAc). ^{1}H-NMR data (300 MHz, $CDCl_3$,and COSY): δ 6.30 (m, W=9.5 Hz, H-1a,b), 5.10 (ddd, J 2.3, 3.3, 9.2 Hz, H-6a), 5.02 (~dt, J=2x3 and 9.4 Hz, H-6b), 4.82 (tt, J=2 x 4.3 and 2 x 12.3 Hz, H-3), 4.56 (dd, J 2.3, 12.3 Hz, H-7a), 4.37 (dd, J 3, 12.1 Hz, H-7b), 4.1 -3.9 (unresolved m, H-7'a,b, H-5a,b), 2.42 (2 partially overlapping m, each with W ~ 16 Hz, equate. H-4a,b), 2.2 -2.0 (m, for H-2a,b; H-2'a,b,; and H-4'a; partially obscured by OAc signals), 2.08-2.01 (multiple singlets, OAc), 1.91 (q, spacings 12.3 Hz, axial H-4'b). The product contained two major components, presumably the anomers of 16. Analysis of the ^{1}H-NMR spectrum aided by a COSY plot revealed H-3 as a triplet of triplets at δ 4.82, having two large (12.3 Hz) and 2 small (4.3 Hz) spacings, and H-4_{ax} as a quartet at δ 1.91 having 3 equal spacings of 12.3 Hz.

1-3.14. Compounds 11a and 11b.

To a mixture of epimers 7 + 8 (54 mg) in acetic anhydride (1.0 mL) was added three drops of trifluoroboron etherate under ice cooling. The reaction mixture was kept at +4°C for one hour. TLC then showed absence of starting material (Rf 0.4) and presence of two products giving spots at Rf 0.8 and 0.7 (8% ethanol - chloroform). Ice-water was poured into the reaction mixture which was then extracted with chloroform. The organic phase was washed with saturated sodium bicarbonate solution and water, dried, and evaporated to give a brown residue (75 mg). ^{13}C- and ^{1}H-NMR spectra showed multiple OAc signal but no glycosidic methoxy signals. The crude mixture was

purified through a silica gel column by use of ethyl acetate - hexane (1:1) as eluent, to give 63 mg of a product mixture that showed the same ^{13}C and ^{1}H spectra as the crude product. Signals belonging to two major isomer are listed below which gave ^{1}H-NMR data (300 MHz, $CDCl_3$, and COSY): δ 6.08 (2 superposed dd, 1H, J 3.3 and 4.2, and J 4.2 and 7.3 Hz, H-1a,b), 5.20 (m, 1 H, H-6a and H-5b), 5.08 (ddd, 0.5 H, J 4, 4.5, 6 Hz, H-6b), 4.97 (ddd, 0.5 H, J 3, 5, 9 Hz, H-5a), 4.75 (ddt, 0.5H, J 2 x 4, 8.5, 10 Hz, H-3a), 4.64 (dddd, 0.5 H, J 3, 6.7, 10 Hz, H-3b), 4.23 (dd, 0.5 H, J 4 and 12 Hz, H-7b), 4.19 (dd, 0.5 H, J 4, 11.5 Hz, H-7a), 4.08 (2 superposed dd, 1H, J 6 and 12 for both, H-7'a,b), 2.66-2.55 (2 superposed ddd, 1 H, J 4.1, 5.4, 15.2 and 3.4, 5.4, 15 Hz, H-2a,b), 2.48-2.32 (2 superposed ddd, 1 H, J 7.3, 10.5, 15.1 and 3.1, 10.0, 15.4 Hz, H-4a,b), 2.22-2.09 (complex overlapping m, 2 H, H-2'a,b and H-4'a,b), 2.07-2.00 (multiplets, OAc); ^{13}C-NMR data (75.4 MHz, $CDCl_3$): δ 170.41, 170.37, 169.94, 169.86, 169.83, 169.70, 168.47, 168.42, 168.35 (C=O), 87.1, 87.0 (C-1), 80.3, 79.3 (C-3), 71.3, 70.6, 68.7, 68.1 (C-5,6), 36.6, 36.2, 34.2, 33.8 (C-2 and 4); IR (KBr pellet, neat): 1752 cm^{-1} (C=O), 1558cm^{-1} (NO_2); MS (CI, ether): m/z 334 (M^++ 1).

1-3.15. Epimerization of compounds 9 and 10.

A solution of pure compound 9 (10 mg) in pyridine-d_5 was kept for three days at room temperature. The ^{1}H-NMR spectrum indicated partial epimerization to a 2:1 mixture of 9 and 10. After five days, the solution was heated at 55°C for two hours. The spectrum remained unchanged, indicating that epimeric equilibrium had been reached. The same result was obtained starting from the syrupy 10 that contained a small proportion of 9.

1-3.16. Methyl 2,4-di-*O*-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (18).

Compound 17 (methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside, 506 mg) was dissolved in acetic anhydride (1.0 mL), the solution was cooled in an ice-bath, and trifluoroboron etherate (3 drops) was added with stirring. After 20 min the reaction mixture was poured into briskly stirred ice water and the white solid was collected, washed, and dried (710 mg, 99 %). It melted at 108.5-110°C upon recrystallization from ethanol; lit.[23] m.p. 109 - 110°C. The Rf value of 17 was 0.31, and that of the 18 was 0.6 (TLC with 2:1 ether - hexane).

In the second experiment, the acetylation was carried out in neutral medium as follows: A suspension of starting material (214 mg) and anhydrous sodium acetate (68 mg) was stirred at room temperature for three days. Progress of the acetylation was monitored by TLC. The excess acetic anhydride was removed under reduced pressure at ~40°C. The white residue was dissolved in methylene chloride, the solution washed with water, dried over anhydrous sodium sulfate, and evaporated to give 265 mg (88 %) of product that was obtained crystalline from absolute ethanol.

^{1}H-NMR data (300 MHz, $CDCl_3$, and COSY): δ 5.26 (dd, $J_{1,2}$ 3.50, $J_{2,3}$ 10.8 Hz, H-2), 5.20 (t, $J_{3,4}$ 9.8~10.5, $J_{4,5}$ 9.5~10.0 Hz, H-4), 4.98 (d, $J_{1,2}$ 3.50 Hz, H-4), 4.95 (t, $J_{3,4}$ 9.8~10.5 Hz, $J_{2,3}$ 10.8 Hz, H-3), 3.83 (dq, $J_{4,5}$ 9.5~10.0, $J_{5,6}$ 6.3 Hz, H-5), 3.39 (s, 3H, OMe), 2.051, 2.053 (2 s, two 3H, OAc), 1.21 (d, 3H, $J_{5,6}$ 6.3 Hz, 6-Me). ^{13}C-NMR (50.3 MHz, CDCl3) and ADEPT data: δ 169.4, 168.9 (C=O), 95.6 (C-1), 85.3 (C-3), 72.0, 70.1 (C-4 and 5), 64.8 (C-2), 55.5 (OMe), 20.5, 20.4 (2 OAc), 17.1 (C-6). MS (CI, ether): m/z 291 (M^+ + 1), 260 (M^+ + 1 - MeOH), 200 (M^+ + 1 - MeOH - HOAc).

1-3.17. Sodium borohydride reduction of 18 in ethanol.

Sodium borohydride (611 mg) was added portionwise to a suspension of compound 18 (468 mg) in ethanol (30 mL), stirred in an ice-water bath. Stirring was then continued at room temperature for 4 days, and an additional portion of $NaBH_4$ (300 mg) was added during the second day. TLC (1:1 ether - hexane) indicated the conversion of starting material 18 (Rf 0.31) into products (Rf 0.4-0.33, 0.16). The solution was then neutralized with Amberlite IRC-50(H^+) resin, filtered, and coevaporated with several additions of methanol. The white residue obtained was then flash chromatographed on silica gel (230-400 mesh, 8 g) with 19:1, 9:1, and 4:1 ether - hexane as solvents, to give two fractions of products. The fast-moving fraction (110 mg) contained two components, namely 19 and 21 (provisionally assigned), and the slow-moving fraction (113 mg) contained a single component, 22. The ratio of dideoxygenated compound 19 and mono-deoxygenated compound 22 was 2:1 according to their ^1H- and ^{13}C-NMR spectra. The yields of 19, 22, and 21 were 25.3%, 36.8%, 12.6%, respectively.

Compound 19 had ^1H-NMR data (200 MHz, $CDCl_3$): δ 4.73 (d, H-1), 4.49 (m, H-3) , 4.16 (m, H-5), 3.25 (s, 3H, OMe), 2.72 (m, H-2e), 2.50 (m, H-4e), 2.09 (m, H-2a), 1.60 (dq, H-4a), 1.22 (d, 3H, C-CH_3), correspondence to lit.[2] reported; ^{13}C-NMR (50.3, MHz, $CDCl_3$) and ADEPT data: δ 96.6 (C-1), 75.9 (C-3), 59.5 (C-5), 54.6 (OMe), 33.1, 31.9 (C-2 and 4), 21.2 (Me).

Compound 21 had ^1H-NMR (200 MHz, $CDCl_3$): δ 4.78 (dd,1 H), 3.80-3.60 (m, 2 H), 3.32 (s, 3H, OMe), 3.17 (d, 1 H), 2.38 (1 H), 2.20 (1 H), 1.42 (d, 3H, C-Me); ^{13}C-NMR (50.3 MHz, $CDCl_3$) and ADEPT: δ 96.6 (C-1), 84.8 (C-3), 72.8 (C-4), 66.9 (C-5), 54.7 (OMe), 34.8 (C-2), 17.6 (Me).

Compound 22 had ^1H-NMR (200 MHz, $CDCl_3$): δ 4.80 (d, H-1), 4.75 (m, H-3), 4.10 (m, becoming dd upon deuterium exchange, H-2), 3.93 (12 lines, H-

5), 3.41 (s, 3H, OMe), 2.52 (d,OH), 2.25 (ddd, H-4e), 1.88 (q, H-4a), 1.23 (d, 3H, C-Me), correspondence to the lit.[30] reported; ^{13}C-NMR (50.3 MHz, $CDCl_3$) and ADEPT data: δ 98.9 (C-1), 85.2 (C-3), 69.2 (C-2), 63.0 (C-5), 55.4 (OMe), 37.0 (C-4), 20.4 (Me).

1-3.18. Sodium borohydride reduction of 18 in ethanol-methylene chloride.

To an ice-cooled solution of compound 18 (255 mg) in methylene chloride (25 mL) and 99% ethanol (2.5 ML) was added sodium borohydride (255 mg) in small portions. The suspension was then stirred at room temperature and the reaction was monitored by TLC (1:1 ether - hexane) until all of the starting material had disappeared after 3 days. The mixture was neutralized with Amberlite IRC-50(H^+) resin and filtered. The filtrate was co-evaporated several times with methanol, to afford 205 mg of a crude product that showed in its ^{13}C-NMR spectrum four components, namely 19, 21 and 22 in similar ratios as in the preceding experiment, and additionally 20 in a proportion similar to that of 19.

Parts of the crude product mixture (135 mg) was acetylated at 0°C with acetic anhydride (2 mL) and boron trifluoride etherate (3 droplets) during 30 min. The excess acetic anhydride was removed by evaporation at reduced pressure below 40°C. The remaining acetylated residue was dissolved in methylene chloride (5 mL) and the solution washed with water (2 x 5 mL), dried over anhydrous sodium sulfate, and evaporated give 141 mg a solid. This was suspended in ethanol (15 mL) at 0°C, and sodium borohydride (200 mg) was added. The suspension was stirred at room temperature for three days and then neutralized with Amberlite IRC-50(H^+). TLC (50 % ether - hexane) showed three spots with Rf values 0.38, 0.23, and 0.17. The solution

was filtered and co-evaporated with methanol (3 x 5 mL) to give 72 mg of crude mixture which contained three major products: 19, 22, and 20 in a ratio of approximately 1:1:1. The ^{1}H-NMR data of 20 corresponded to those reported[13]; ^{13}C-NMR data (50.3 MHz, $CDCl_3$, and ADEPT): δ 97.6 (C-1), 77.9 (C-3), 62.9 (C-5), 54.9 (OMe), 37.1, 33.9 (C-2 and 4), 21.0 (Me).

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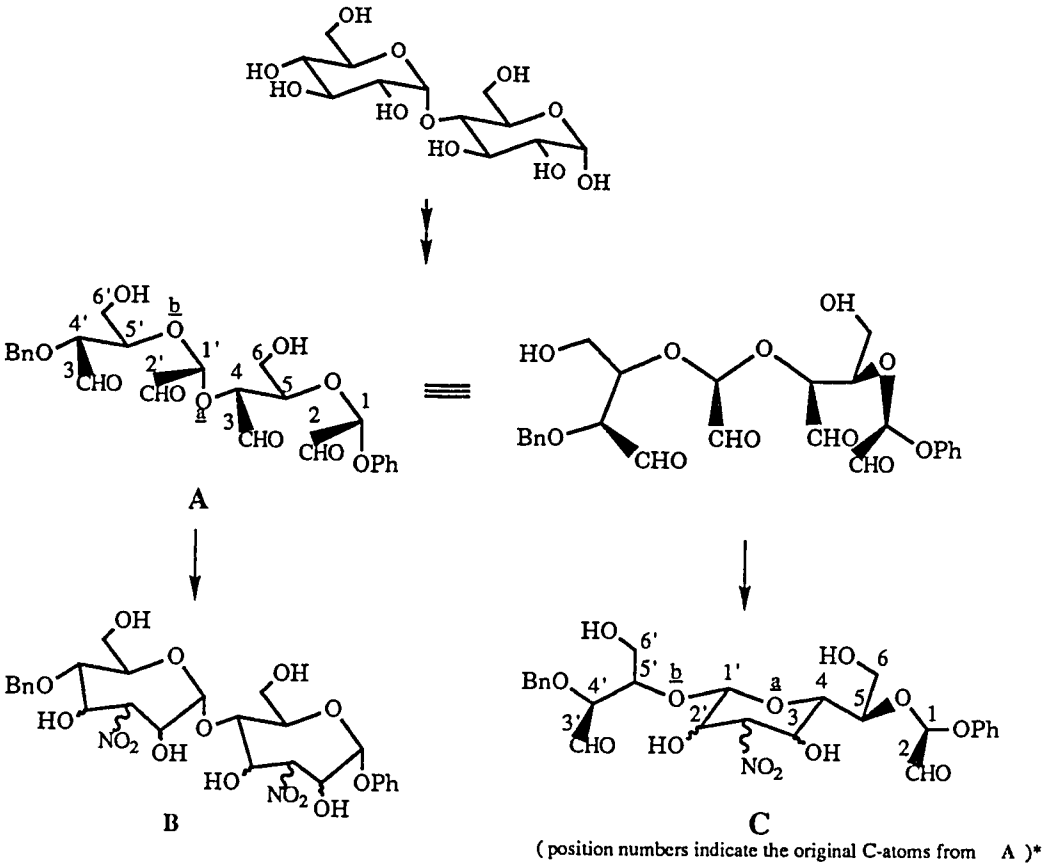
Chapter 2.
Nitromethane Cyclization of Disaccharide Tetraaldehydes.

2-1. Introduction.

In order to assess possible patterns of reaction between cyclodextrin polyaldehyde and nitromethane it was deemed useful to study this kind of addition in simpler model systems first.

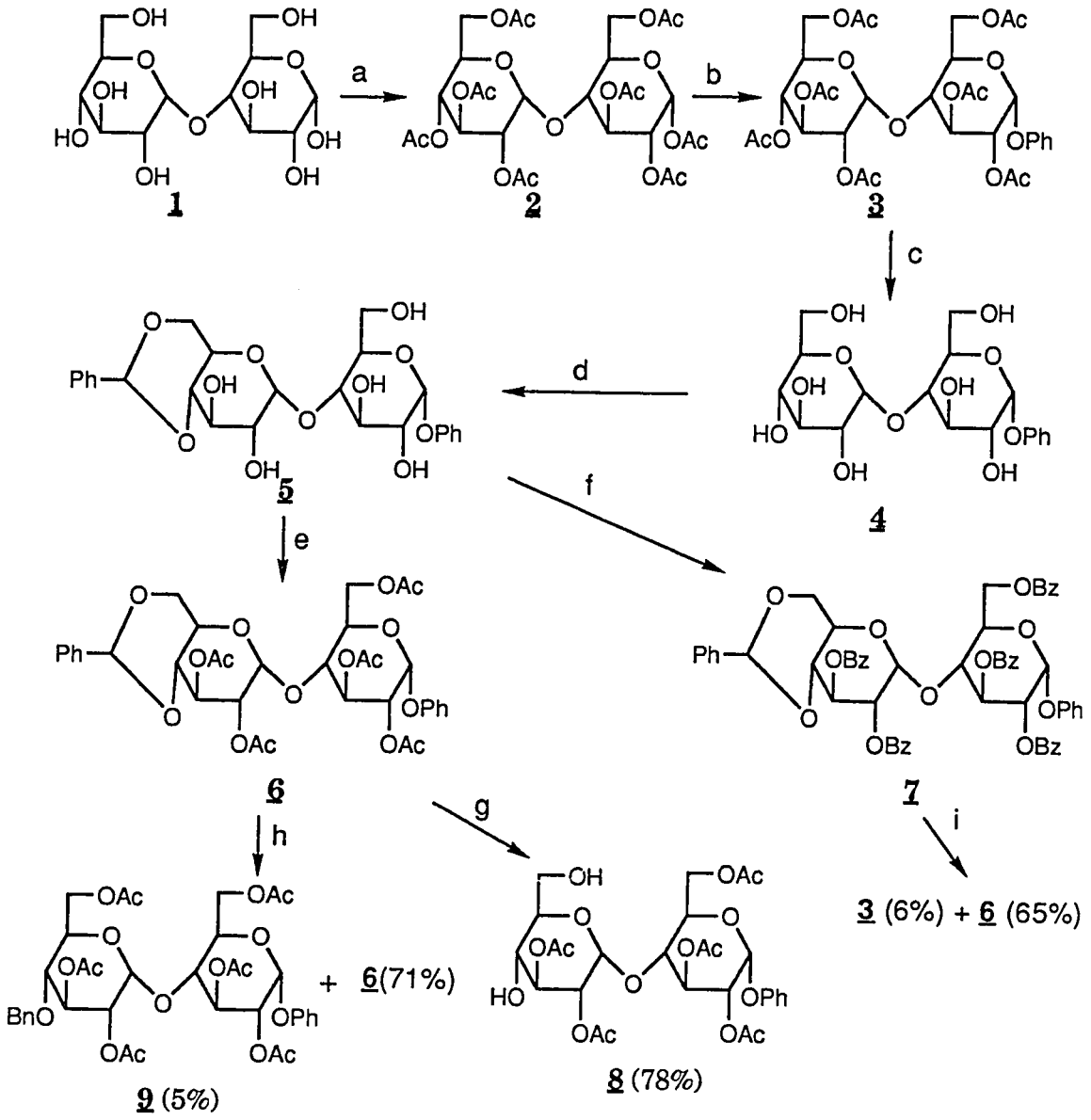


* Note that the α-anomeric C-1' of A becomes β-anomeric in C. This "anomerization" results from the fact that the glycosidic oxygen (a) of A becomes the ring oxygen in C, and the "ring" oxygen (b) of A becomes the glycosidic oxygen in C.

Figure 1. Model of nitromethane condensation of maltose-tetraaldehyde to form bis-septanosidic dinitro disaccharide and pyranosidic nitro disaccharide.

The tetraaldehyde A derived from maltose was considered as such a model mimicking a two-unit segment of cyclodextrin polyaldehyde (Figure 1). Such a 4'-blocked molecule might obviously react with two moles of nitromethane, under twofold cyclization, to give bis-septanosidic dinitro disaccharide B. This reaction path would represent an intra-unit cyclization. However, an inter-unit addition of one mole of nitromethane (by insertion between C-3 and C-2') might also occur, generating a pyranosidic structure C as the primary product. This should actually be the favored pathway because according to general principles a six-membered ring should arise in preference over a seven-membered one on kinetic grounds, and also on thermodynamic grounds as pyranoses are much more stable than septanoses. The cyclization product C is drawn in Figure 1 in a way so as to illustrate its formation from A. In reality the aldehyde and primary hydroxyl groups in each of the substituents at C-1' and C-4 will no doubt engage in cyclic hemiacetal formation. This is reversible, however, and the aldehyde groups (C-2 and C-3') may therefore add nitromethane (if an excess of the reagent is available), to be converted into primary-nitro alcohols (NO_2CH_2-CHOH-). Once the pyranoside ring in C is formed, C-2 and C-3' are too distant for a second cyclization unless the pyranoside first undergoes chair inversion in which case a 12-membered ring could be formed. This is extremely unlikely to happen because of the severe 1',4-diaxial interaction in the inverted chair and the extreme steric crowding that would exist in such a poly- substituted bicyclic structure.

2-2. Results and Discussion.*



a: Ac_2O/pyridine/DMAP; b: PhOH/$ZnCl_2$; c: NaOMe/MeOH;
d: PhCHO/$ZnCl_2$ or $PhCHBr_2$/pyridine or $PhCH(OMe)_2/(H^+)$;
e: Ac_2O/pyridine; f: PhCOCl/pyridine; g: $BH_3{\cdot}Et_3N/AlCl_3$/toluene;
h: 1)$BH_3{\cdot}Me_3N/AlCl_3$/toluene,2)Ac_2O/pyridine;
i: 1)$LiAlH_4/AlCl_3$/ether-CH_2Cl_2, 2)pyridine/Ac_2O.

Scheme 1.

* A new set of formula numbers is used.

2-2.1. Synthesis of phenyl maltoside derivatives (3 - 9).

Following these considerations we set out to prepare tetraaldehyde A derived from maltose. A phenyl and a benzyl group were chosen as substituents on *O*-1 and *O*-4', to represent adjacent glucose units in cyclodextrin. Commercial maltose (1) was converted into its octaacetate[1,2] 2 and hence into phenyl α-maltoside heptaacetate[3] 3 which was *O*-deacetylated to phenyl α-maltoside[4] 4 (Scheme 1). This glycoside was benzylidenated using several different procedures (benzaldehyde-zinc chloride[5,6], α,α-dimethoxytoluene in acetonitrile or in *N,N*-dimethylformamide[7,8] catalyzed by *p*-toluenesulfonic[9] or camphorsulfonic acids; or α,α-dibromotoluene[10,11] in pyridine[12,13]), to furnish phenyl 4',6'-*O*-benzylidene-α-maltoside (5) and, after acetylation, its pentaacetate 6 or, after benzoylation, its pentabenzoate 7. Derivatives 2 - 6 were known, and literature procedures were followed in their preparation. In the experimental section are listed the yields obtained and physical constants measured, and literature data are cited for comparison. Mass-spectral and NMR data were recorded to authenticate the products. The pentabenzoate 7 could not be found in the literature; its preparation in 67% yield from 4, by treatment with α,α-dibromotoluene followed by benzoylation of the product *in situ*, is described in greater detail.

The next objective was to open the benzylidene acetal ring in 5, 6, or 7 regioselectively by one of the methods of reductive acetal cleavage reported in the literature[14-32], with the aim of obtaining a 4'-benzyl ether. Reducing agents such as lithium aluminum hydride-aluminum trichloride[33,34], diisobutylaluminum hydride (DIBAH)[35-38], triethylamine-aluminum trichloride, and borane trimethylamine-aluminum trichloride[39,40] were applied for obtaining 4'-benzyl ethers as exemplified in Figure 2.

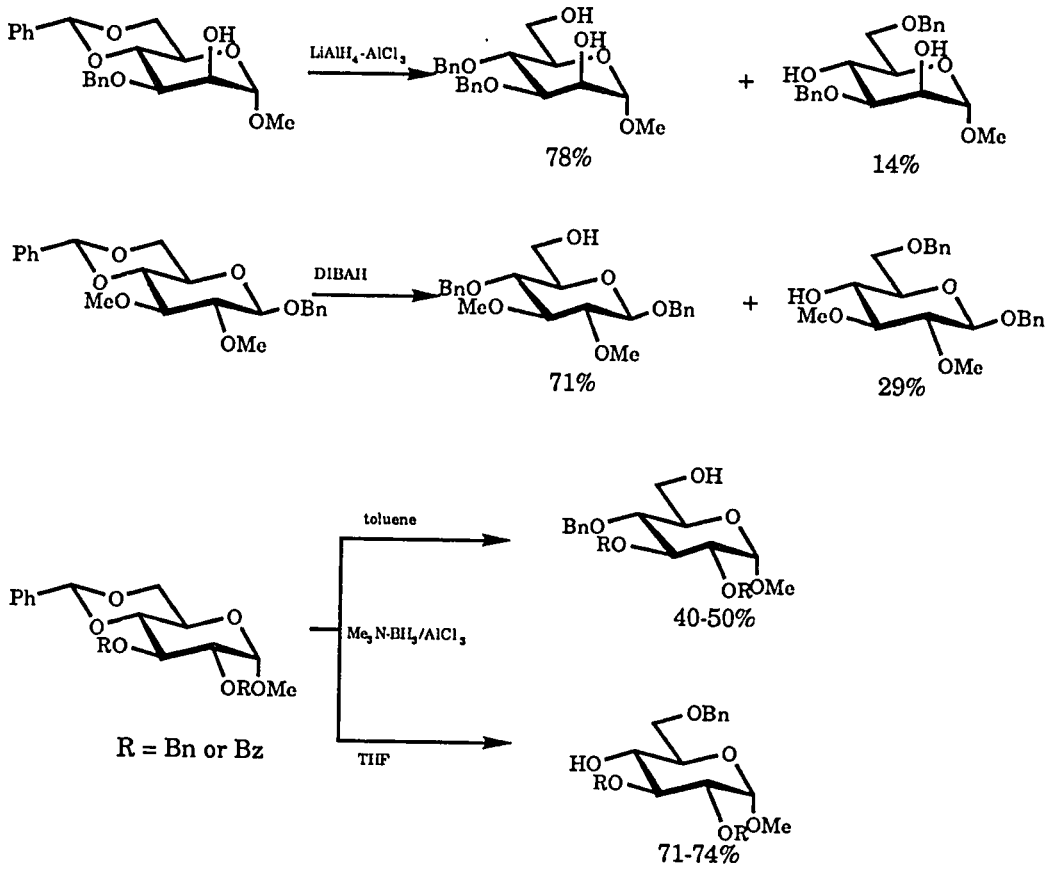


Figure 2. Literature examples for regioselective cleavage of 4,6-*O*-benzylidene ring.

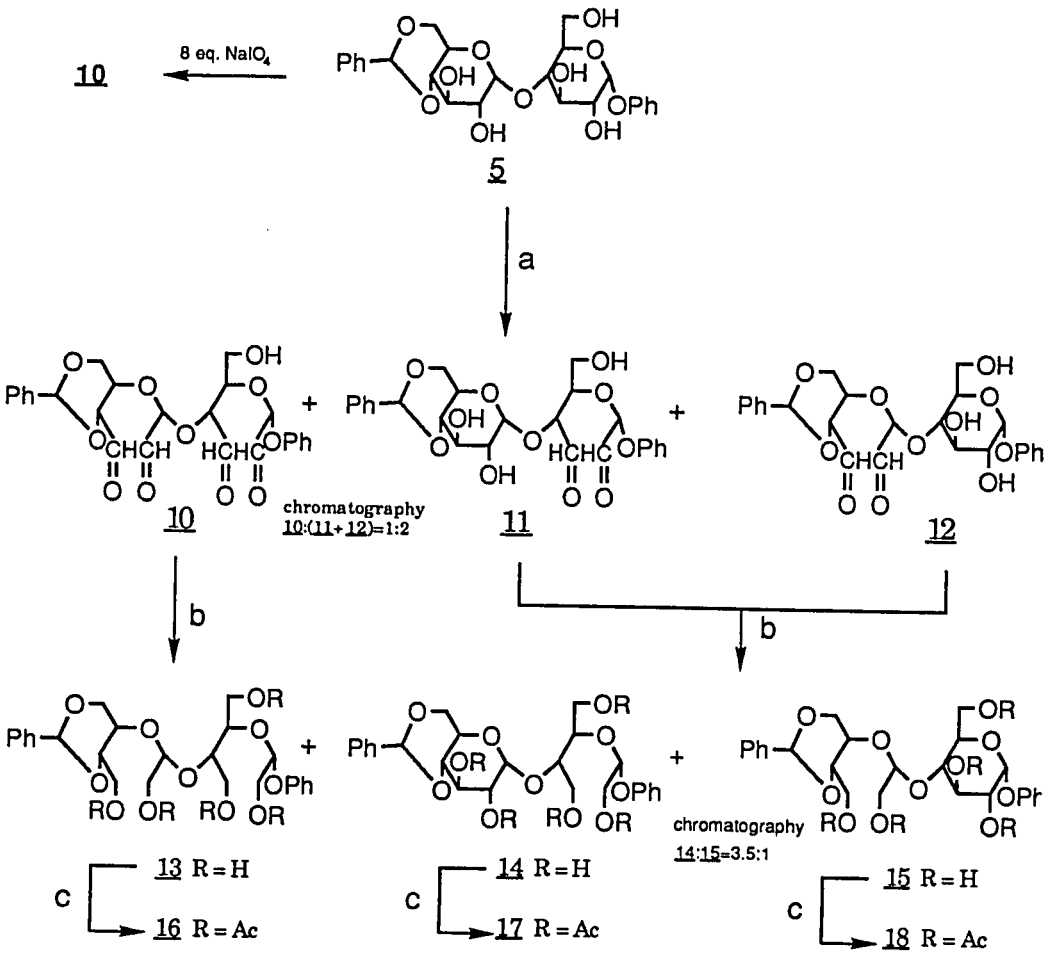
Unfortunately, all attempts at achieving such reductive acetal cleavage were fruitless. Thus, treatment of 7 with a mixture of lithium aluminum hydride and aluminum trichloride in ether-dichloromethane[41-44] failed to give any benzyl ether. It removed all the *O*-benzoyl protecting groups but cleaved the acetal only partially, and not reductively but by hydrolysis; acetylation of the reaction product gave a 1 : 10 mixture of 3 and 6 which after column chromatography yielded 6% of 3 and 65% of 6, identified by their ^{1}H-NMR spectra. Reaction of 6 with borane triethylamine complex and

aluminum trichloride in toluene also produced no benzyl ether. The product was phenyl α-maltoside 2,3,6,2',3'-pentaacetate[5] 8, isolated in 78% yield after chromatography and characterized by microanalysis and spectral data.

In a similar experiment performed with 6, but using borane trimethylamine[39,40] (instead of triethylamine) complex, the acetal ring remained largely uncleaved. Acetylation of the crude reaction mixture, and chromatography of the material so obtained, led to the recovery of 71 % of 6. In addition, however, a very small proportion (5%) of what according to the ^{1}H-NMR spectrum appeared to be the desired 4'-*O*-benzylmaltoside hexacetate 9 was isolated, but the amount obtained was insufficient for definitive characterization and for use in the experiments contemplated.

Finally, the unprotected acetal 5 was treated with diisobutylaluminum hydride[35] in methylene chloride, but no reaction occurred and 92% of unchanged 5 was chromatographically recovered. Reaction of 5 with lithium aluminum hydride / aluminum trichloride in ether-methylene chloride produced the deacetalated glycoside 4. It had to be conceded that all attempts at making a maltoside 4'-benzyl ether in a practical way were unsuccessful, and no further approach to such an ether was pursued. It was instead decided to use the 4',6'-*O*-benzylidene acetal 5 for the contemplated studies of periodate oxidation followed by nitromethane cyclization.

2-2.2. Sodium metaperiodate oxidation of phenyl 4',6'-*O*-benzylidene-α-maltoside 5.



a: $NaIO_4$ (1.3 eq.)/MeOH-H_2O; b: $NaBH_4$/EtOH; c: Ac_2O/pyridine

Scheme 2.

Although the tetraaldehyde 10 was the desired model aldehyde and was, therefore, the preparative objective of the experiments described in this section, the stepwise course of periodate oxidation of the bis-glycol 5 was

considered to be a matter of general interest; *i.e.*, we first sought to find out which of the two glycol groupings undergoes cleavage more rapidly. When compound 5 was treated with 1.4 molar equivalents of sodium metaperiodate (*i.e.*, less than the 2 molar equivalents needed for complete oxidation), a mixture of tetraaldehyde 10 and the two dialdehydes 11 and 12 was generated in quantitative yield (Scheme 2). Chromatography furnished 10 and 11 + 12 (unseparated) in a 1 : 2 ratio. Reduction of the products with sodium borohydride afforded the pentol 13 and a mixture of the pentols 14 and 15. The latter pentols could be separated by column chromatography and were obtained in a ratio of 3.5 : 1. Evidently, oxidation was faster in ring A (the phenyl-glycosidic or "reducing" terminal) of the disaccharide. This result appears understandable. The mechanism of periodate cleavage involves primary formation of a cyclic ester of periodic acid, which in a *trans*-diequatorial glycol on a six-membered ring is relatively difficult in any case because it requires the ring to become more puckered; but the difficulty is greater in ring B than in ring A, owing to the presence of the *trans*-fused 4,6-acetal structure which makes the former less flexible.

Subsequent acetylation of each alcohol furnished the compounds 16, 17, and 18. Structural assignments were made on the basis of mass spectra, NMR spectra, and microanalytical data. Thus, the ^{13}C-NMR spectrum of 16 shows six methylenic carbon atoms (CH_2 groups recognized by an ADEPT plot) whereas the spectra of 17 and 18 show only four such atoms. Hence the aldehydic precursor of 16 (namely 10) must have arisen from 5 by two glycol cleavages, whereas the precursors of 17 and 18 (namely 11 and 12) arose from single cleavages. Distinction between 17 and 18 could be drawn, unambiguously, from the mass spectral fragmentation patterns. The

discussion and comparison of mass fragmentation patterns of compound 6, 16, 17, and 18 are shown in Figure 3 to 6, and Table 1.

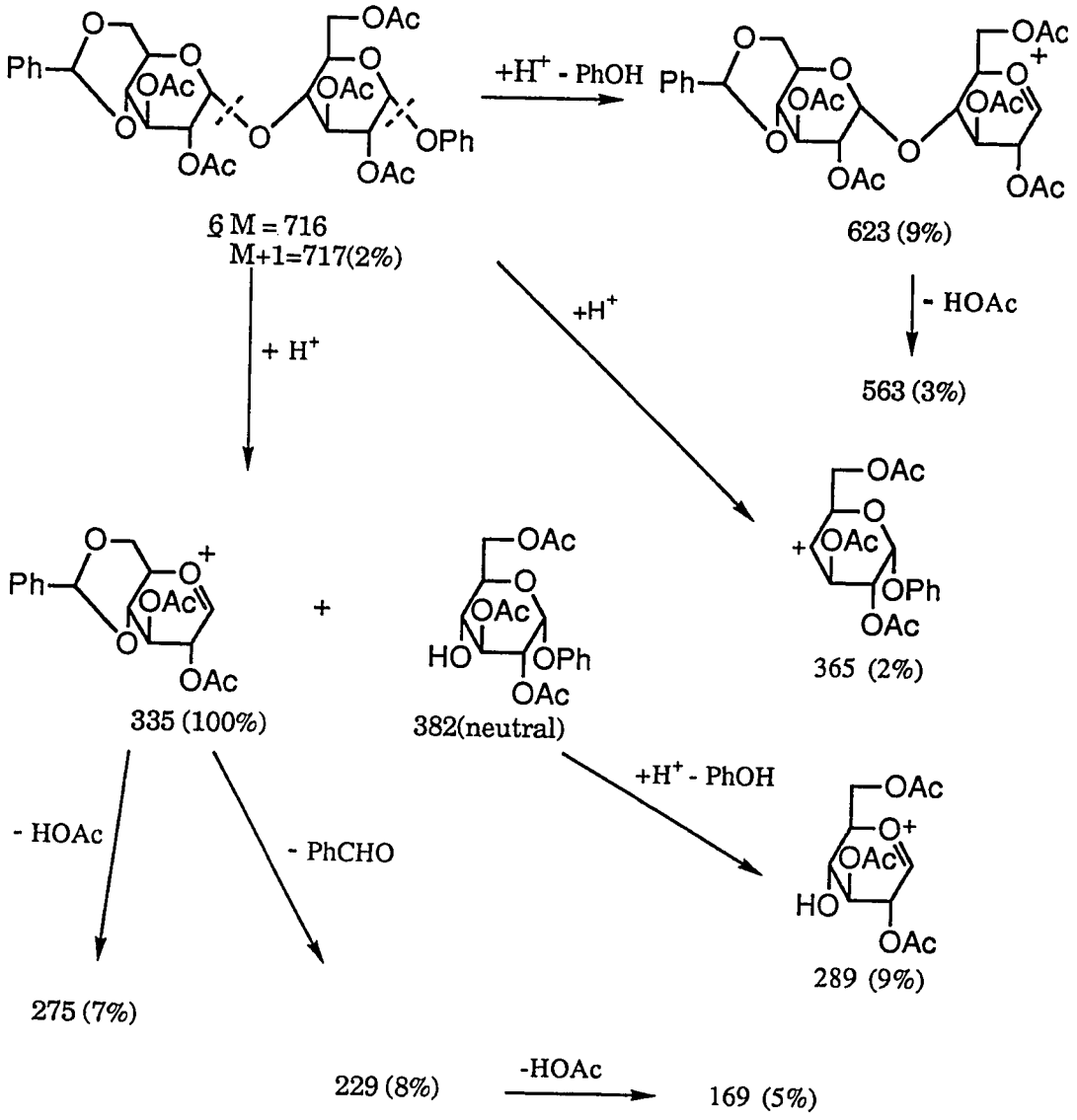


Figure 3. Fragmentation of compound 6 in chemical ionization mass spectrometry.

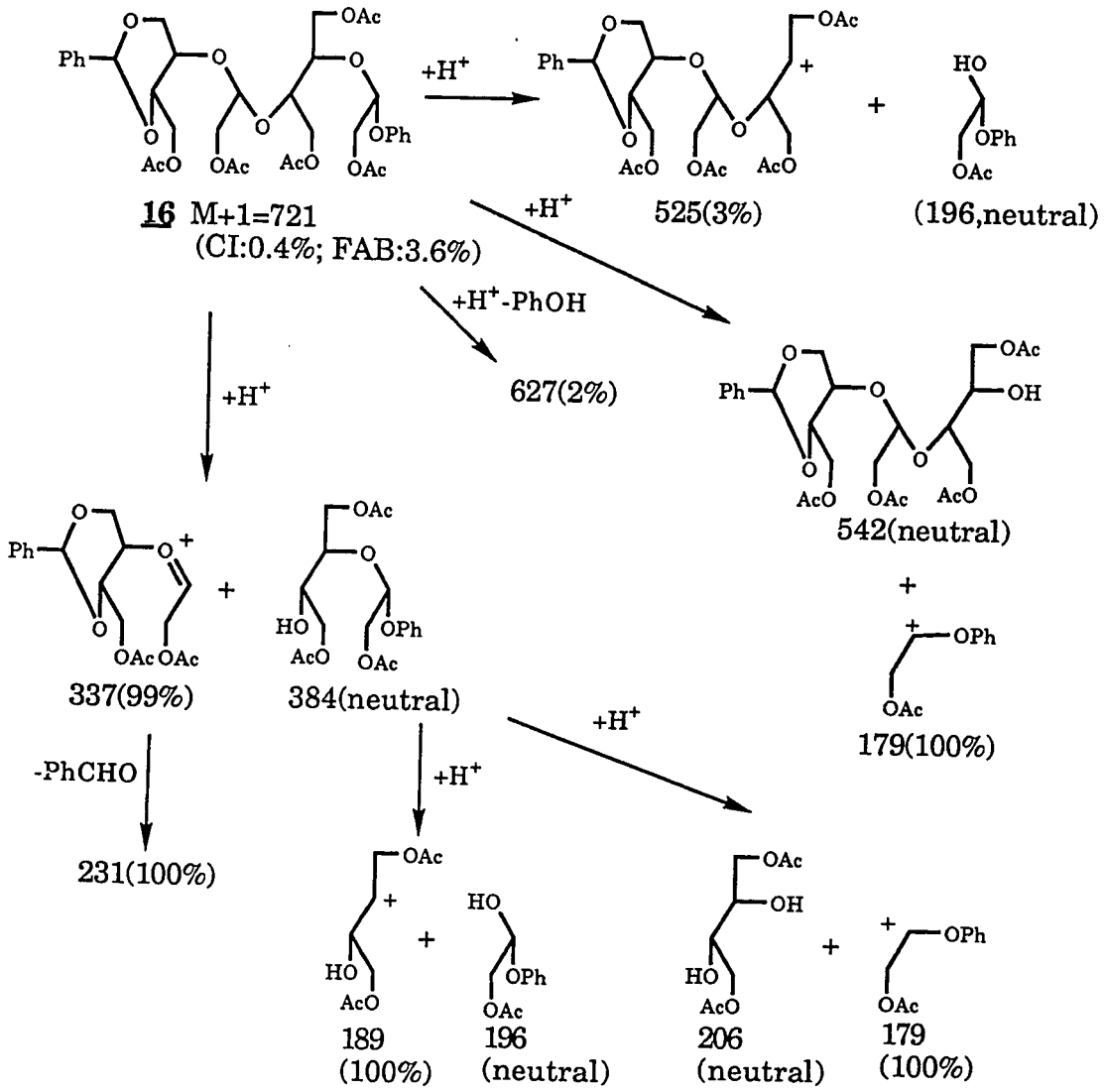


Figure 4. Fragmentation of compound 16 in chemical ionization mass spectrometry.

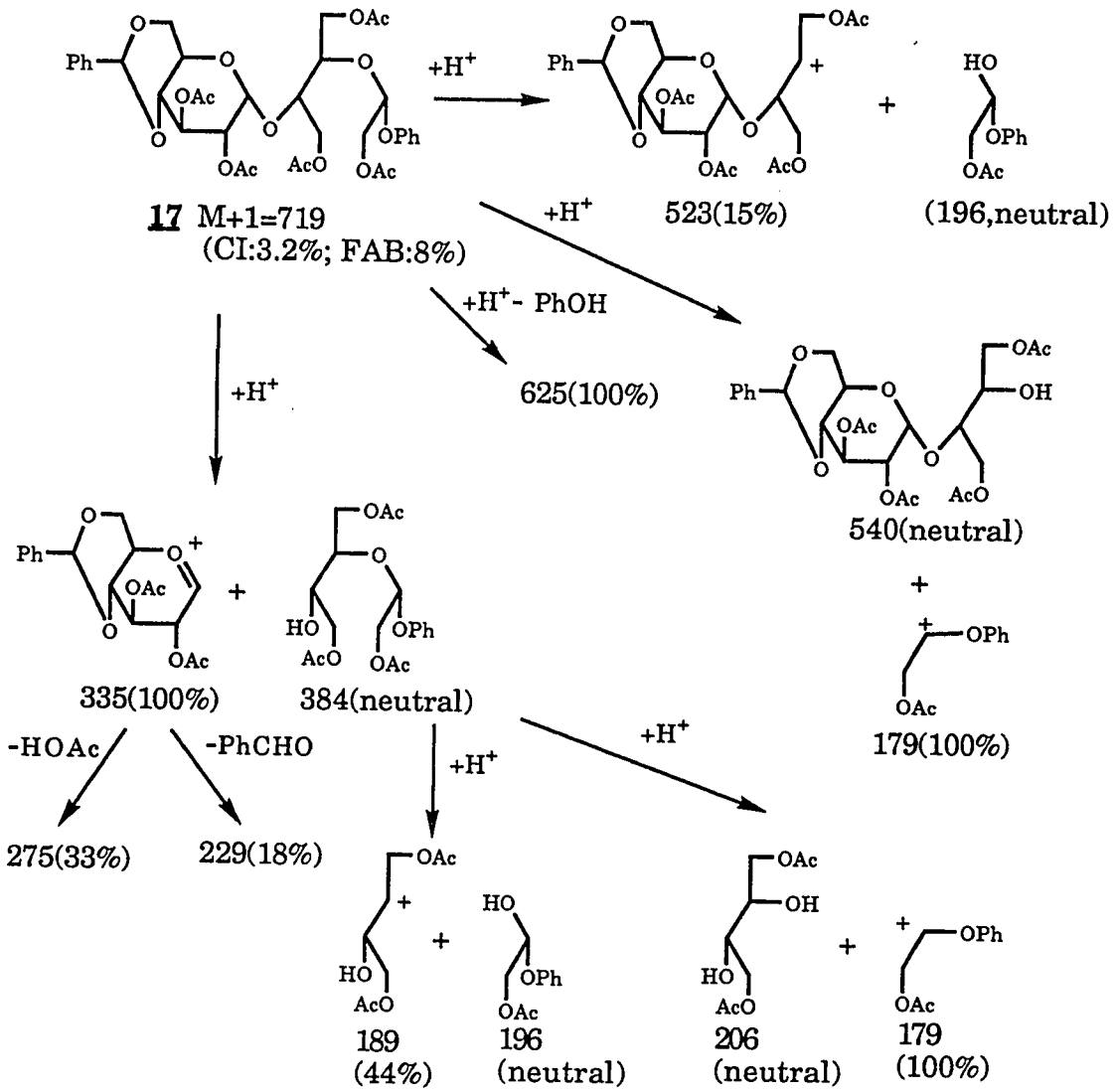


Figure 5. Fragmentation of compound 17 in chemical ionization mass spectrometry.

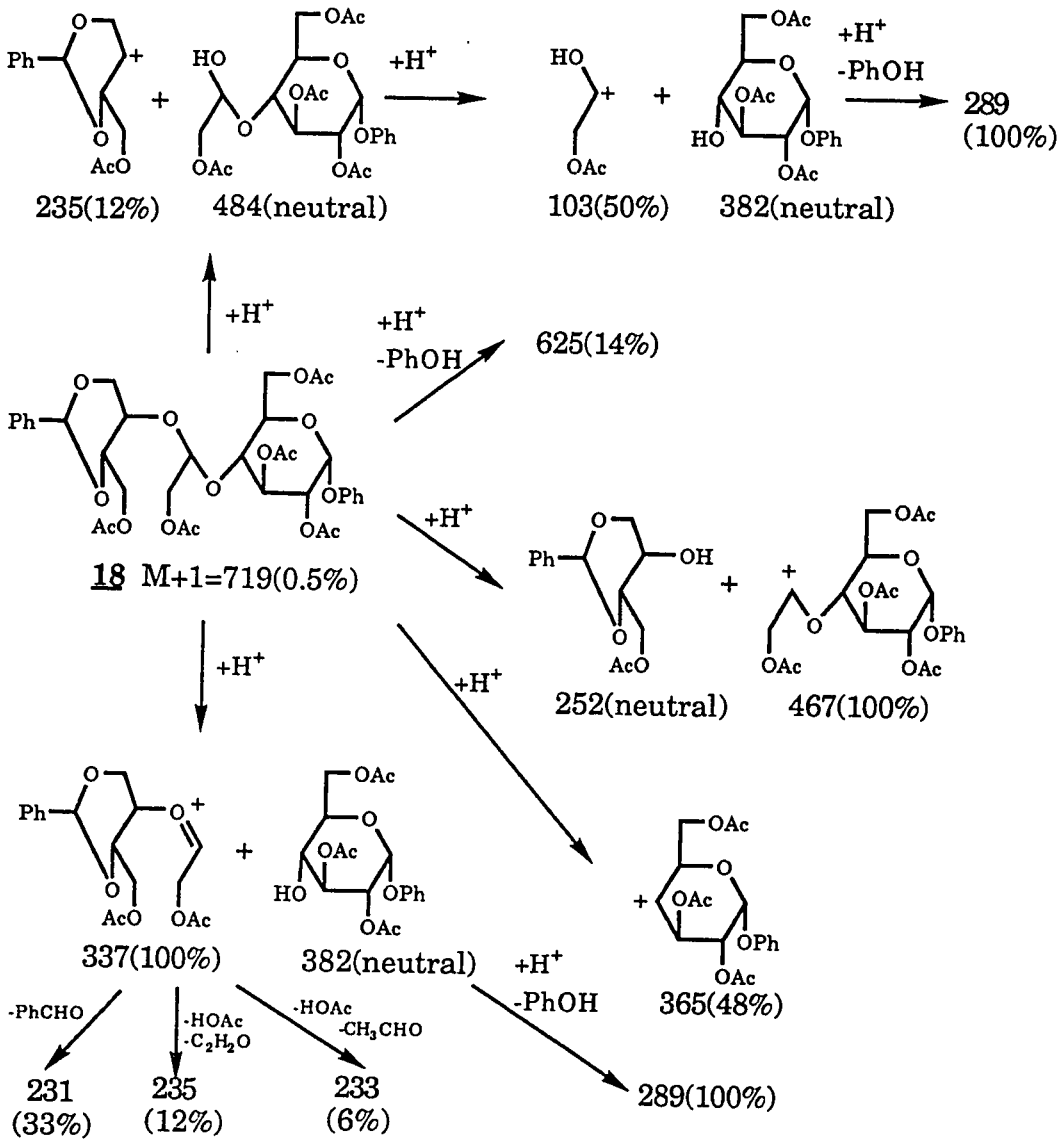


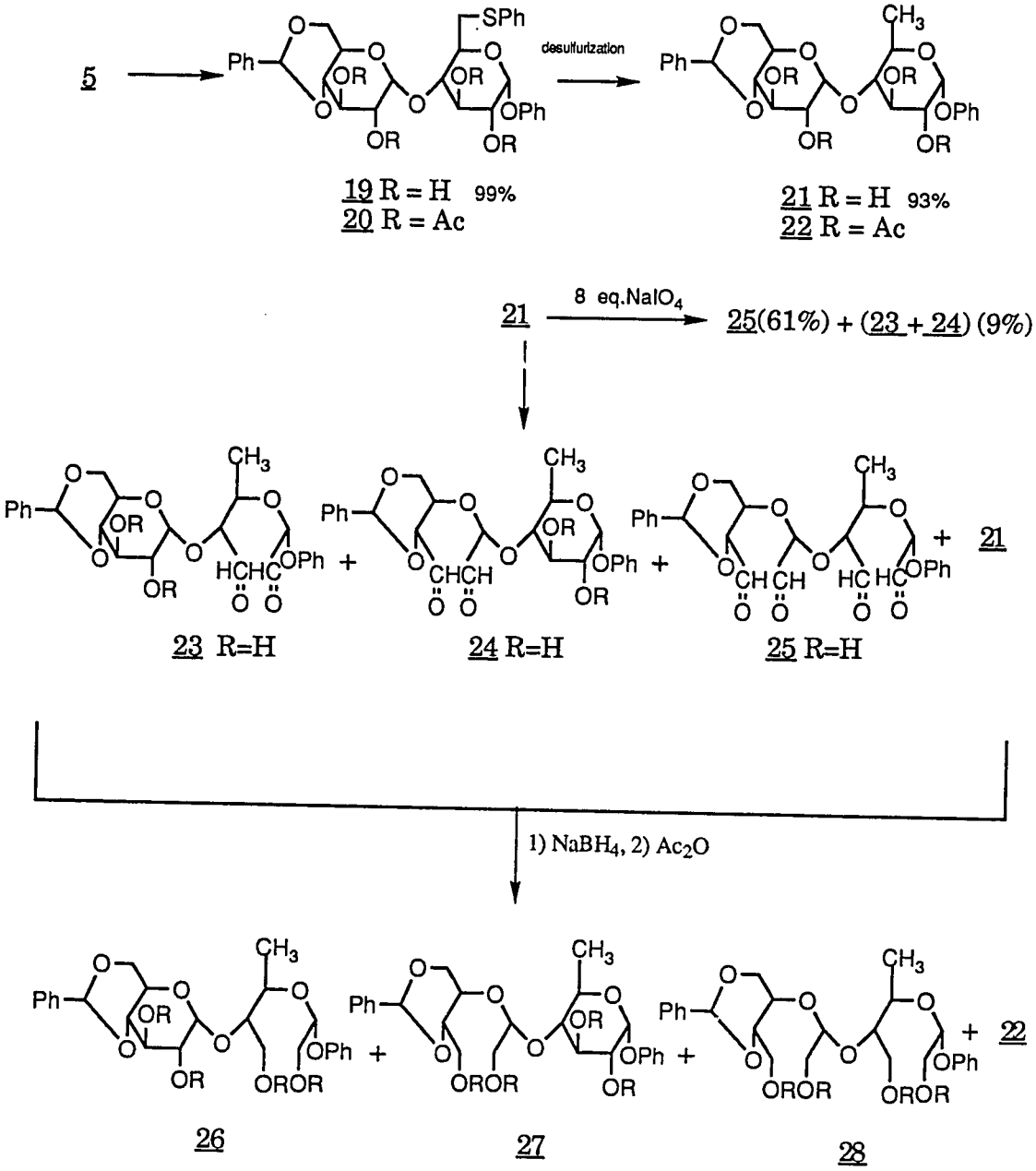
Figure 6. Fragmentation of compound 18 in chemical ionization mass spectrometry.

Table 1. Mass spectral data for compounds 6, 16, 17, and 18.

	6 M=716	16 M=720	17 M=718	18 M=718
fragments from ring A m/z (%)	365(2) 289(9)	367(12) 189(100) 179(100)	189(44) 179(100)	365(48) 289(100)
fragments from ring B m/z (%)	335(100) 275(7) 229(8) 169(5)	337(99) 235(96) 233(30) 231(100) 193(11) 175(59) 147(91) 129(10) 103(90)	335(100) 275(33) 229(18) 169(16)	337(100) 235(12) 233(6) 231(33) 193(3) 175(14) 147(18) 129(11) 103(50)
fragments from A and B m/z(%)	717(2) 623(9) 563(3)	721(0.4) 627(2) 525(3) 469(50)	719(3) 625(100) 523(15)	719(0.5) 625(14) 467(100)
ring A ring B	closed closed	open open	open closed	closed open

For the practical preparation of 10, the glycoside 5 was oxidized with an excess (8 mol. equiv.) of sodium meta periodate. This gave 421 mg of 10 from 500 mg of 5, confirmed by borohydride reduction of a sample to give the pentol 13 for spectral comparison.

2-2.3. Synthesis of phenyl 6-deoxy-α-maltoside derivatives 19 - 22.



ratio = 6 : 2 : trace : 1

R = Ac

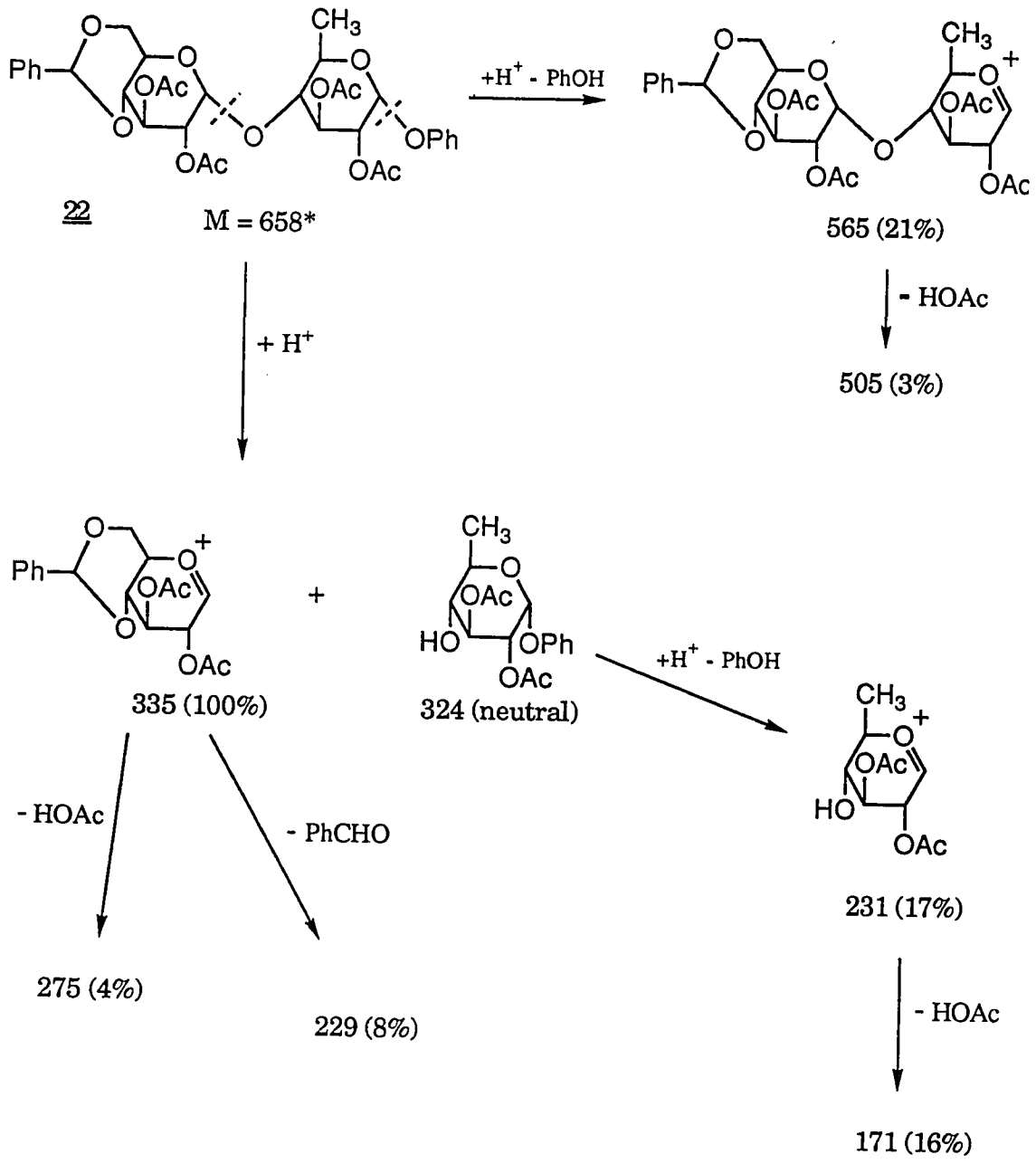
Scheme 3.

As a further polyaldehyde model the tetraaldehyde 25 derived from phenyl 4',6'-*O*-benzylidene-6-deoxy-α-maltoside (21) was synthesized (Scheme 3). Deoxygenation at the primary carbinol position in the phenyl glycoside 5 was accomplished via the 6-*S*-phenyl-6-thiomaltose derivative 19, which was prepared from 5 by reaction with diphenyl disulfide and tributylphosphine, a method[45,46] that has recently served well[47] in the corresponding functionalization of D-glucose and D-galactose. This excellent procedure gave crystalline 19 in almost quantitative yield. The compound was additionally characterized through preparation of its tetraacetate 20. Next, 19 was reductively desulfurized by sodium borohydride in the presence of nickel chloride in ethanolic solution. The reaction was complete after two hours at room temperature and gave a 92.5 % yield of crude phenyl 4-*O*-(4',6'-*O*-benzylidene-α-D-glucopyranosyl)-α-D-quinovoside (21). This method of desulfurization[48-52] appeared superior to the more-familiar one using Raney nickel[53-60]. A recently published example[61] of Raney nickel desulfurization of a phenylthio carbohydrate required treatment with a larges excess of the reductant in boiling alcohol for four hours and resulted in a modest yield. The crude glucosylquinovoside showed no organic contaminants in its ^{13}C NMR spectrum, but it did contain traces of nickel as an impurity, causing a grayish color. Purification by column chromatography afforded 21 as a white, analytically pure solid in 64 % yield. For additional characterization, a sample was acetylated to give the tetraacetate 22, also obtained in analytically pure form. The mass-spectral and NMR data for 19 - 22 agreed with the structures in every respect. Each of the compounds gave a molecular-ion peak in the mass spectrum, and integration of the phenyl protons in the ^{1}H-NMR spectra as well as the number of aromatic carbon signals in the ^{13}C-NMR spectra clearly indicated the presence of 3 phenyl groups in 19 and 20,

and of two such groups in 21 and 22; the latter compounds displayed the expected signals for a C-methyl group.

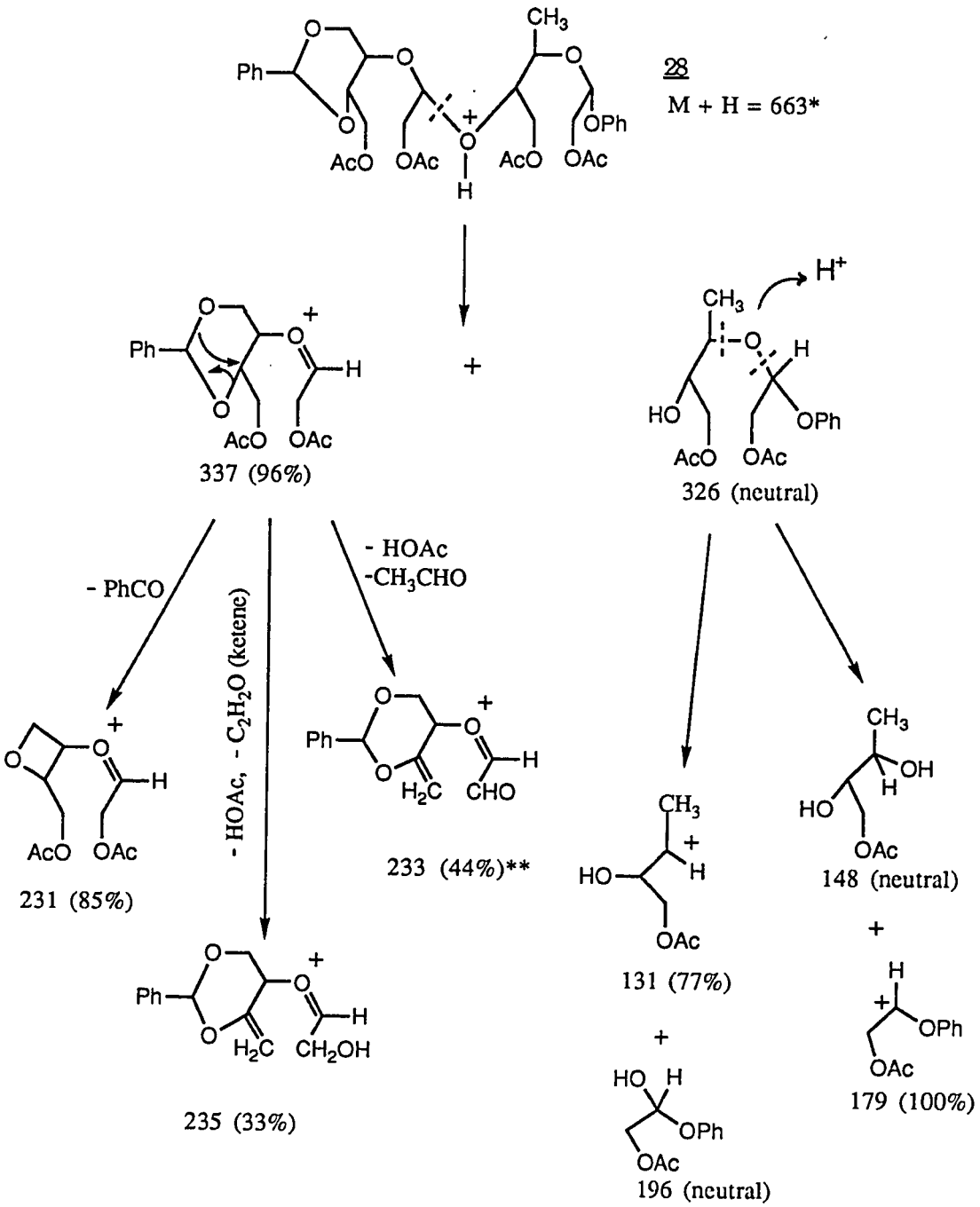
2-2.4. Sodium metaperiodate oxidation of phenyl 4',6'-*O*-benzylidene-6-deoxy-α-maltoside (21).

Next, periodate oxidation studies were performed with the 6-deoxy disaccharide 21. As was the case for the 6-hydroxy analog 5, products of single and double glycol fission (23–25) were formed, in proportions depending on the amount of oxidant employed. Thus, reaction of 21 with a limited amount of sodium metaperiodate (0.85 molar equivalent), followed by borohydride reduction and peracetylation, gave a 6 : 2 : 1 mixture of the products from single cleavage (26 and 27) and 22 (from unreacted 21); a very small proportion of the product from twofold cleavage (28) was also present. The composition of this complex mixture could be evaluated on the basis of its ^{1}H-NMR spectrum at 500 MHz (including a COSY plot), in conjunction with the well-resolved spectra of pure 22 and pure 28. The 6 : 2 : 1 ratio of the main components was deduced by integration of the 3-proton doublets for the C-CH_3 group, which happened to be well separated at δ 1.215, 1.285, and 1.335. As the mass spectral fragmentation schemes (Figure 7 and 8) show, the most important fragmentation involves cleavage of the interglycosidic bond to give the oxocarbonium ion corresponding to the non-reducing terminal unit. Thus, 22 produces a base peak (100%) at m/z 335, and 28 gives a similarly strong peak (96%) at m/z 337 for the oxocarbonium ion corresponding to the nonreducing terminal unit, characteristic respectively for an uncleaved and a cleaved ring; and 28 gives prominent daughter ions at m/z 179 (100%) and 131 (77%) which characteristically arise from fragmentation of the cleaved, "reducing" unit and are not produced from the intact, "reducing" terminal



* Molecular ion peak $M^+ + 1$ very weak (0.9%).

Figure 7. Fragmentation of compound 22 in chemical ionization mass spectrometry.



*) Not observed in c.i. spectrum. In the FAB spectrum, a molecular ion peak at m/z 662 was present.
**) Peak not present in FAB spectrum.

Figure 8. Fragmentation of compound 28 in chemical ionization mass spectrometry.

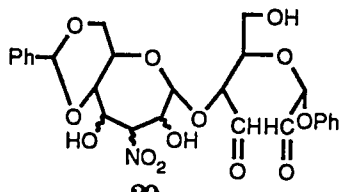
of 22. Compound 22, on the other hand, gives rise to oxocarbonium ions by loss of phenoxy, seen as moderately intense peaks at m/z 565 (21%) and 231 (17%). The spectra of the mixture 22 + 26 + 27 + 28 displayed its three most prominent peaks at m/z 335 (75%), 179 (69%), and 131 (22%), indicative of a preponderance of cleaved reducing and intact nonreducing pyranose structures, as for formula 26. Peaks representative of the inverse structure, *i.e.*, 27, were also present, but were relatively weak: m/z 567 (10%, M^+ - PhO), 337 (14%), 231 (15%), 233 (13%), and 235 (4%).

At the stage of completed oxidation of 21 with 0.85 molar equivalents of periodate as just described, but prior to borohydride reduction, the reaction mixture could be freed chromatographically from the unreacted 21, and so was obtained a mixture of the dialdehydes 23 and 24 (containing, perhaps, a trace of 25) for further study as will be mentioned below.

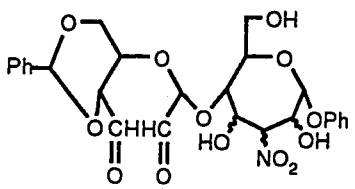
When the oxidation of 21 was performed with an excess (8 molar equivalents) of periodate, again a mixture of products resulted, but this time the tetraaldehyde 25 predominated. Column chromatography furnished pure 25 (61%) and a fraction (9%) judged to be a mixture of 23 and 24. Borohydride reduction of the minor fraction, followed by peracetylation, gave an acetate mixture which showed the same spots in t.l.c. as the previously described preparation containing mainly 26 and 27. For characterization of 25, a sample of the product was also reduced and acetylated, giving chromatographically homogeneous and analytically pure tetraacetate 28 in 78% yield.

2-2.5. Reactions of disaccharidic dialdehydes and tetraaldehydes with nitromethane.

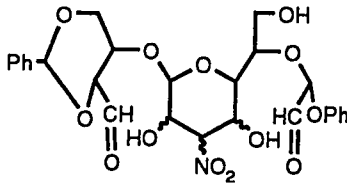
It was to be examined whether disaccharidic dialdehydes such as 11 and 12 and their 6-deoxy analogs undergo nitromethane cyclization in the normal way familiar from monosaccharidic dialdehydes, and what course of reaction will be observed with the tetraaldehyde 10 and its 6-deoxy analog 25. With the tetraaldehydes in particular, it might be expected that the proportion of nitromethane employed should have an influence on product composition. Thus, the structures 29 - 31 might be formed from 10 and one molar equivalent of nitromethane, whereas 32 and 33 could be formed with an excess of the reagent; 29, 30, and 32 would represent products of *intra*-unit cyclization, whereas 31 and 33 would be products of *inter*-unit cyclization.



29



30



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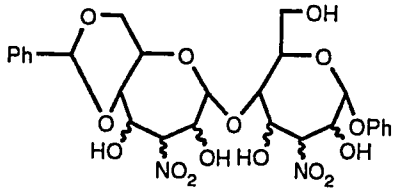

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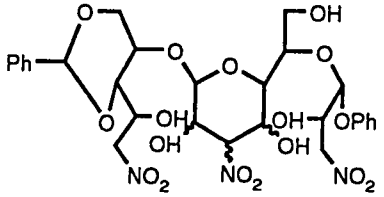


33

2-2.6. Reactions of tetraaldehyde 10 and nitromethane.

The nitromethane reactions of these disaccharidic aldehydes proved difficult to perform and unravel, far more so than the much-investigated and

facile cyclizations of monosaccharidic sugar dialdehydes. When the tetraaldehyde 10 was treated with one molar equivalent of nitromethane in the presence of potassium fluoride[62-65] and dibenzo-18-crown-6[66] in acetonitrile solution according to the procedure of Santoyo Gonzalez[67,69], very little nitrogen was incorporated. The reaction product was treated with sodium borohydride (to reduce unreacted aldehyde groups), and subsequently acetylated, but the IR spectrum of the product lacked a distinctive band in the 1550 cm^{-1} region that would have been indicative of a nitro group introduced. An elemental analysis for nitrogen showed less than 10 % of the theoretical proportion of nitrogen. A similar result was obtained when an excess of nitromethane (7.7 molar equivalents) was employed.

Cyclization of 10 was then attempted by use of nitromethane in methanolic solution in the presence of sodium methoxide, the classical procedure most often used in monosaccharide chemistry[70]. Both 1 and 5.8 molar equivalents of nitromethane were employed, and the products, whose IR spectra showed strong absorption at 1557 cm^{-1}, were subsequently treated with sodium borohydride for aldehyde group reduction. However, this time the reduced material was not acetylated but subjected instead to acid-catalyzed acetolysis (both with hydrochloric and with sulfuric acid as catalysts), to obtain acetylated, monosaccharidic fragments for which it was hoped that mass spectrometry would permit to make structural assignments.

Thus, compounds 29 - 31 possibly present upon cyclization of 10 with one equivalent of nitromethane should give the pentols 34 - 36 on reduction, and subsequently the acetylated fragments 37 - 40 on acetolysis (Figure 9). Compounds 32 or 33 (Figure 10) possibly formed from 10 with excess nitromethane should be acetolyzed to give 37 only (from 32) or 40 - 42 (from 33).

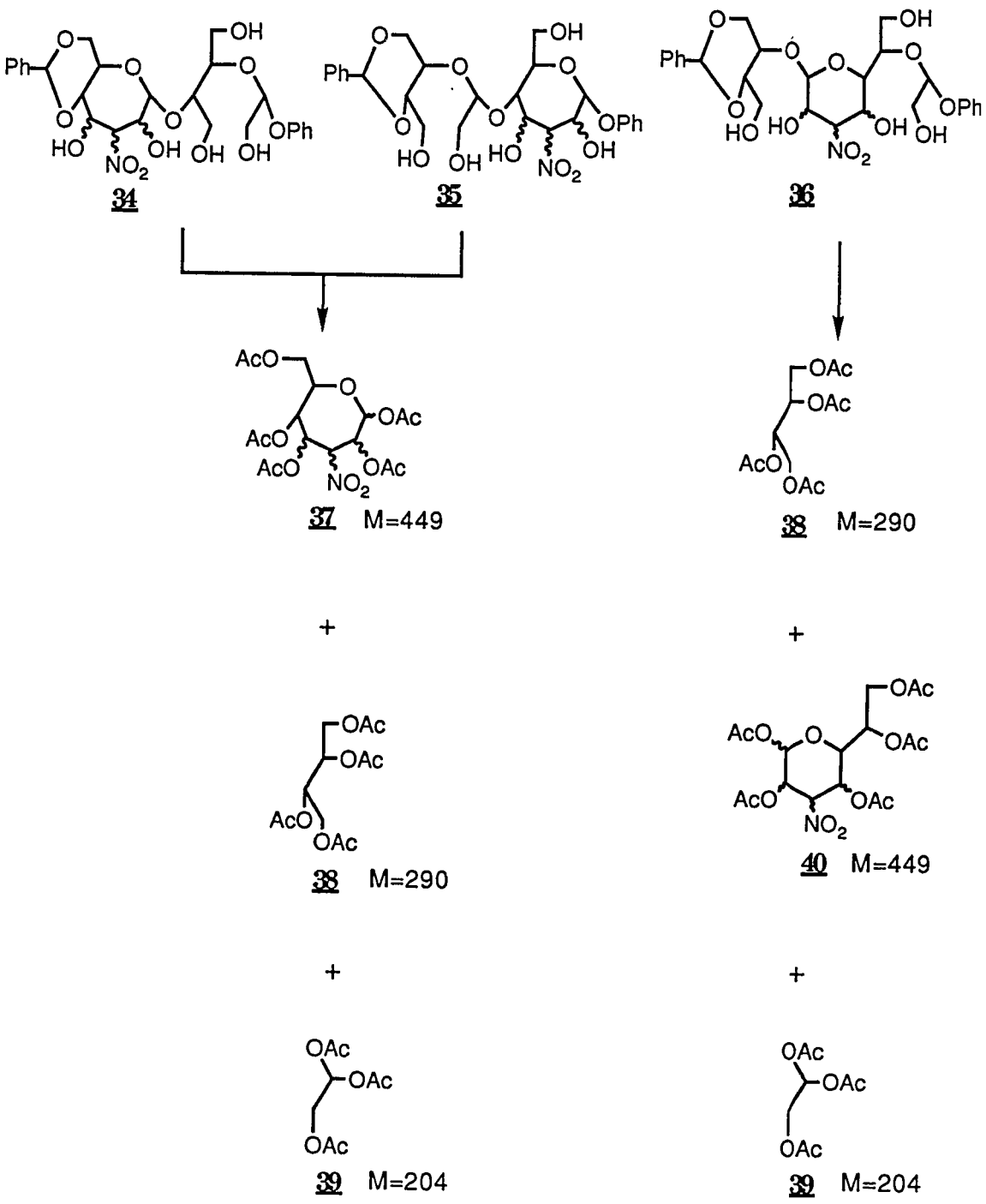


Figure 9. Acetolysis of compounds 34, 35, and 36.

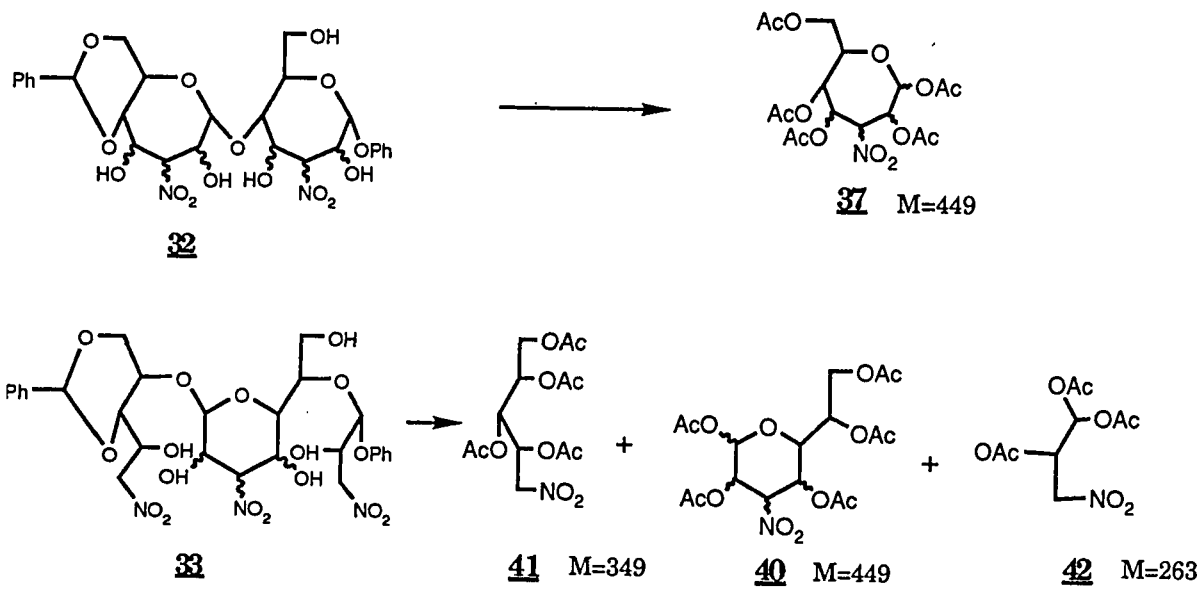


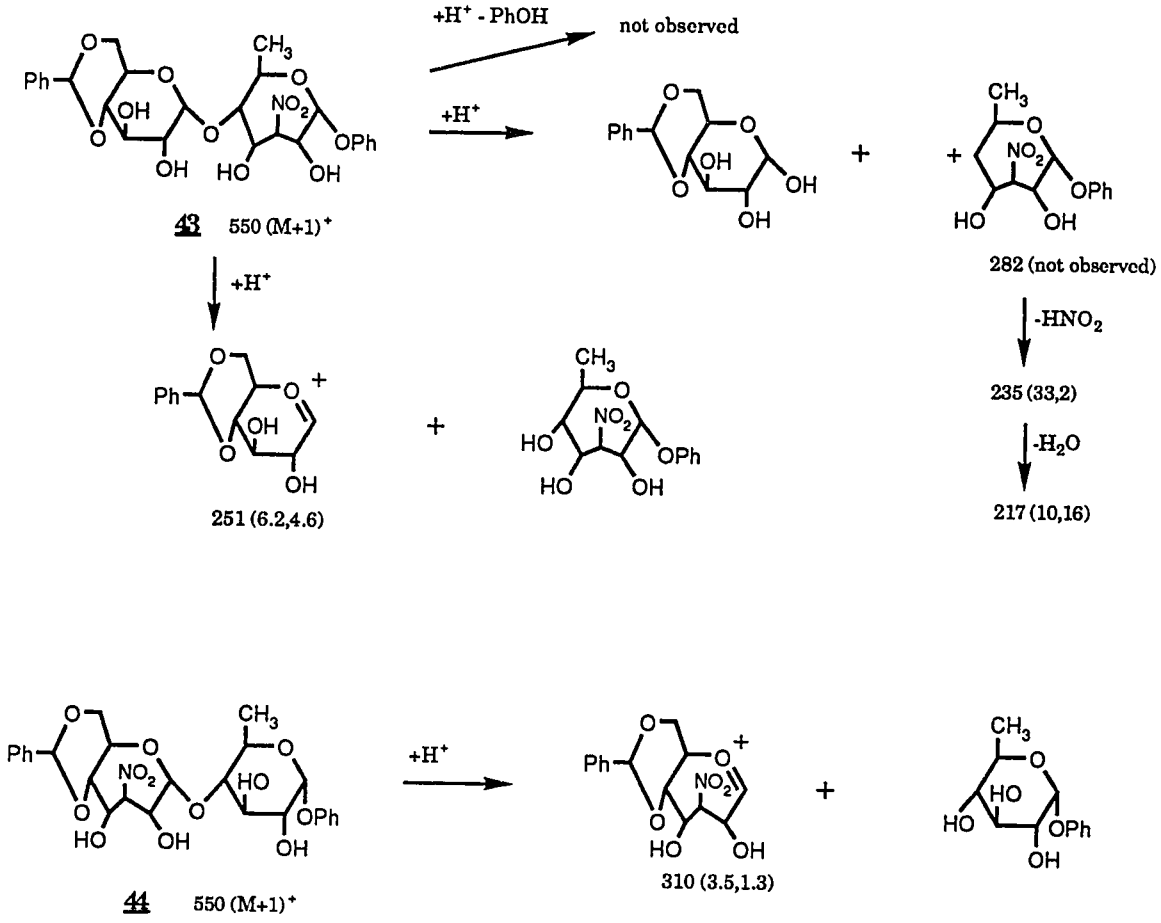
Figure 10. Acetolysis of compounds 32 and 33.

Although the nitroseptanose 37 and nitropyranose 40 have the same molecular weight, it was thought that they might differ in their fragmentation patterns in mass spectra, or that the spectra might show molecular ion peaks due to 38, 39, 41, or 42, and (or) daughter ions from these compounds, and that in this way some conclusions could be drawn as to the course of the nitromethane reactions. Unfortunatly, no conclusion could be drawn from the spectral data.

2-2.7. Reactions of 6-deoxy dialdehydes 23 + 24 and nitromethane.

In the 6-deoxy series, the following experiments were performed. The dialdehyde mixture (23 + 24) was allowed to react with a large excess of nitromethane (24 molar equiv.) in 2-propanol solution by the potassium

fluoride method. The product mixture showed very strong IR absorption at 1556 cm^{-1}. Peaks at m/z 550, 310, 251, and 217 were observed in the FAB mass spectrum and taken to indicate the presence of 43 and 44 (molecular weight 549) as shown in Figure 11.



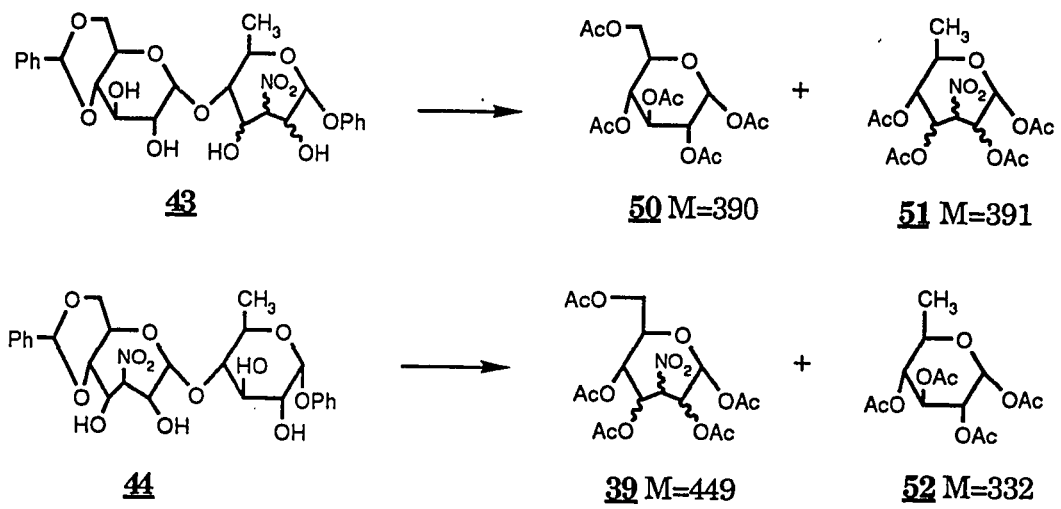
* In parentheses, % relative intensity from NaOMe method, followed by % relative intensity from KF method.

Figure 11. Fragmentation of compound 43 in FAB mass spectrometry.

Acetylation of the product with acetic anhydride catalyzed by boron trifluoride appeared to produce incompletely acetylated and partially debenzylidenated material according to IR (showing decreased, but still significant absorption at 3400 cm^{-1}) and ^{13}C-NMR (phenylic signals at δ 131 - 128 smaller than expected).

Next, reactions of 6-deoxy aldehydes with nitromethane under conditions of sodium methoxide catalysis were studied. The mixture of dialdehydes (23 + 24) gave a result similar to that of the potassium fluoride method. Mass-spectral peaks of the product at m/z 550 (M^+ + 1), 310, 251, 235, and 217 indicated fragmentions of 43 + 44 as shown in Figure 11.

Having previously experienced difficulties in the attempted, boron trifluoride-catalyzed acetylation of 43 + 44, the mixture was this time subjected to acetolysis instead, for further mass-spectral examination. The expected products were *D*-glucose pentaacetate 50 and the 6-deoxy nitroglycoside tetraacetate 51 from 43; and the nitroglycoside pentaacetate 39 and 6-deoxy-*D*-glucose tetraacetate 52 from 44. The CI mass-spectral data are given in Figure 12 and proved the presence of all four acetylated sugars. From the high intensities especially of the M^+ + 1 and M^+ + 1 - AcOH peaks for 50 and 51 relative to those for 39 and 52, it was concluded that 43 was the dominant cyclization product, which means that the dialdehyde 23 was the chief product of periodate oxidation of 21. The mass spectral data obtained from the debenzylidenation and acetylation of the mixture were also consistent with the above results.

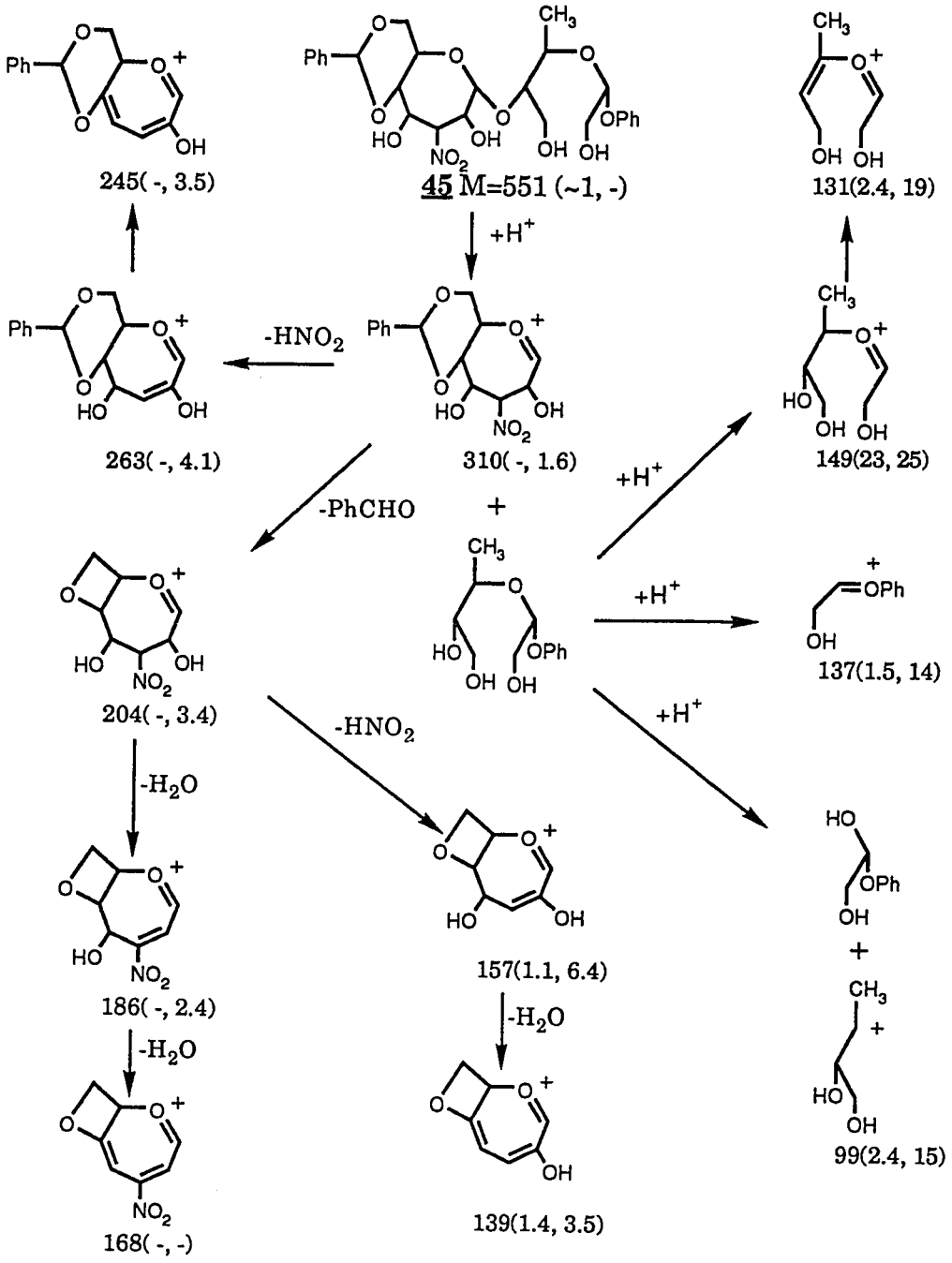


m / z (%)	39	50	51	52
$M^+ + 1$	450(0.5)	391(95)	392(26)	333(7)
$M^+ + 1$ - HOAc	390(9)	331(100)	332(33)	273(25)
$M^+ + 1$ - 2HOAc	330(7)	271(29)	272(6)	213(16)
$M^+ + 1$ - 3HOAc	270(1)	211(8)	212(3)	153(8)

Figure 12. Acetolysis of compounds 43 and 44 and fragmentation of acetylated fragments in CI mass spectrometry.

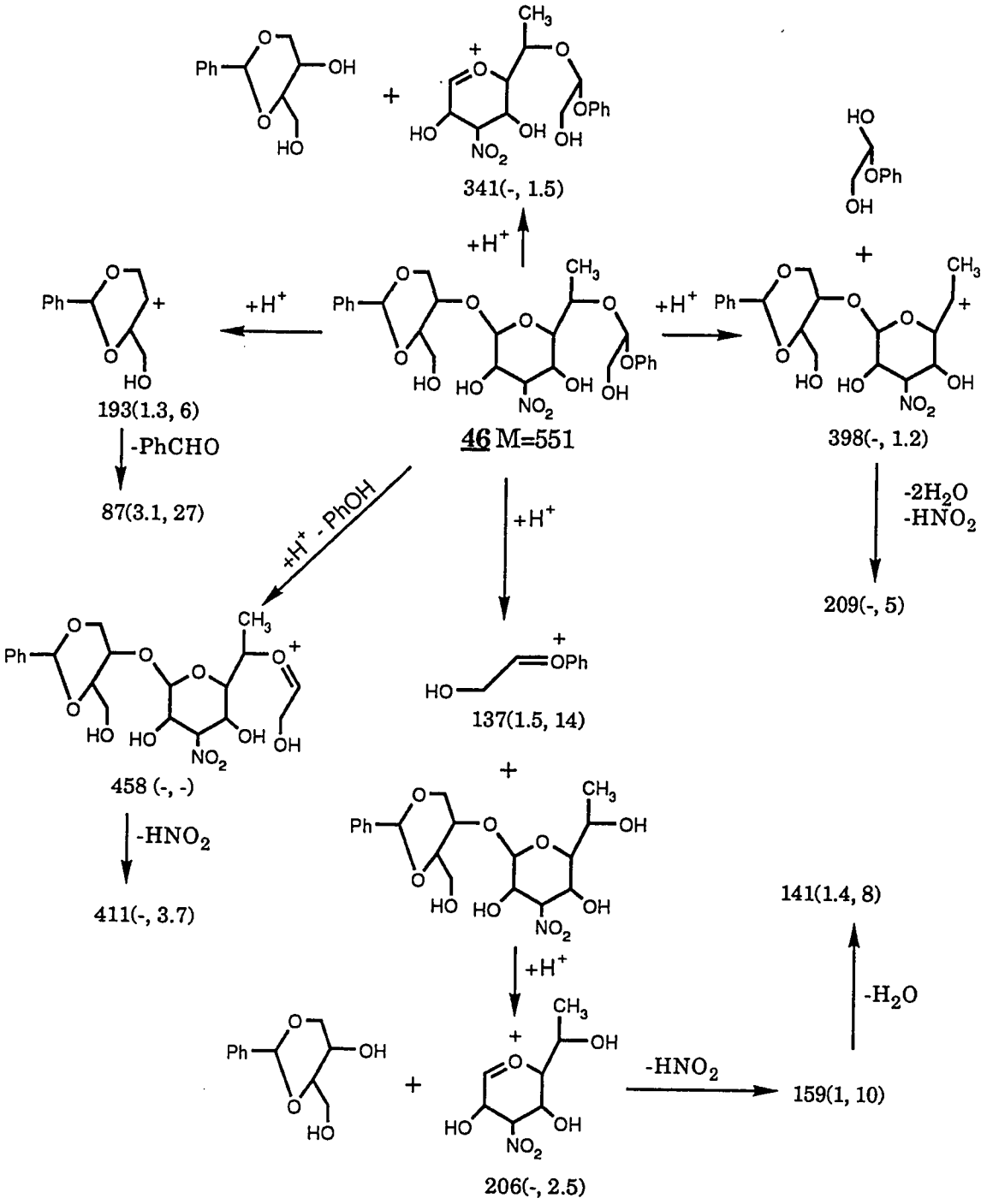
2-2.8. Reactions of 6-deoxy tetraaldehyde 25 and nitromethane in the presence of potassium fluoride.

Reaction of the tetraaldehyde 25 with approximately one molar equivalent of nitromethane under potassium fluoride catalysis, followed by borohydride reduction of the products, led to a mixture exhibiting strong nitro group absorption at 1554 cm^{-1}. The ^{13}C-NMR spectrum showed anomeric and benzylidenic carbon atoms at δ 101.4 - 98.9. The MS (FAB) fragmentation pattern suggested that the three possible reduced cyclization products 45, 46, and 47 were indeed present (see Figure 13a-13c).



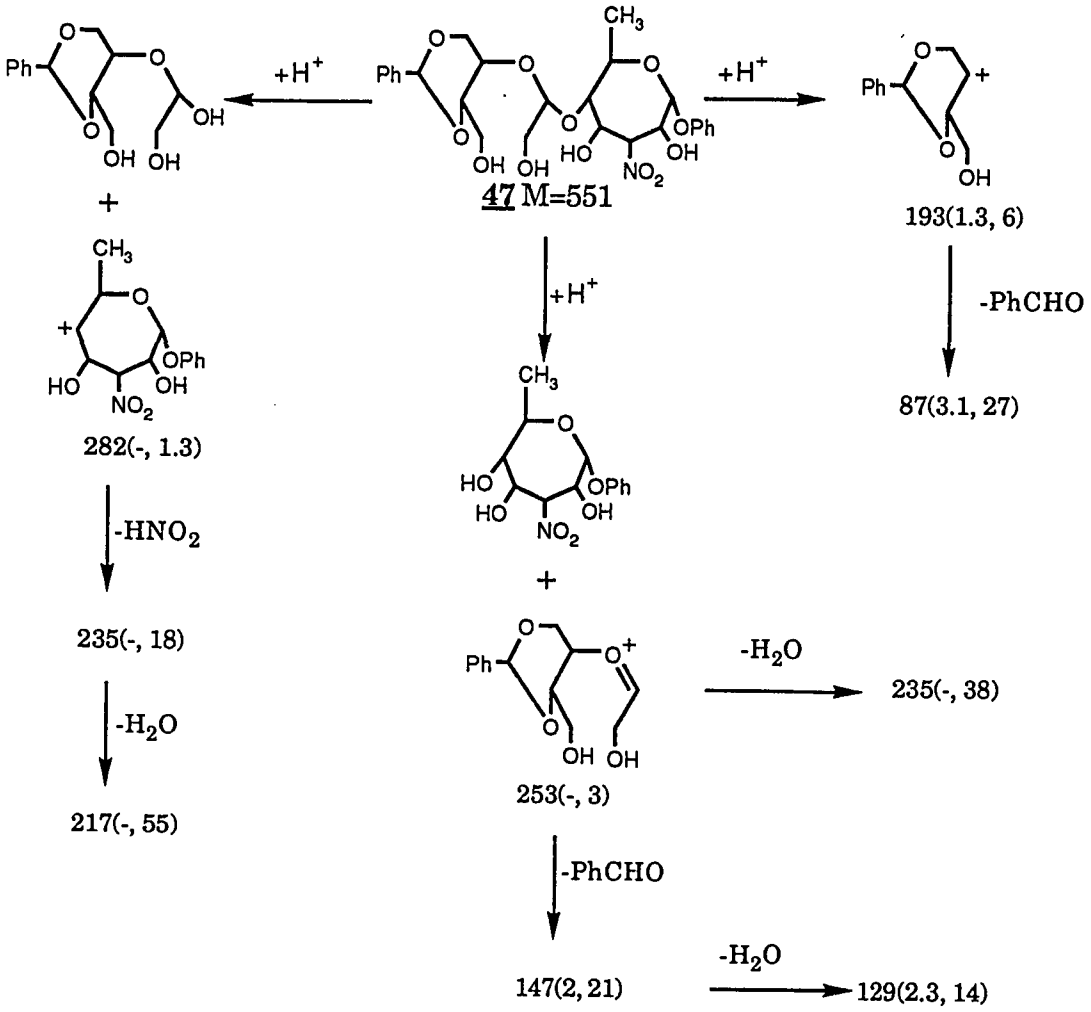
* In parentheses, % relative intensity from NaOMe method, followed by % relative intensity from KF method.
-: not observed.

Figure 13a. Fragmentation of compound 45 in FAB mass spectrometry



* In parentheses, % relative intensity from NaOMe method, followed by % relative intensity from KF method.
-: not observed.

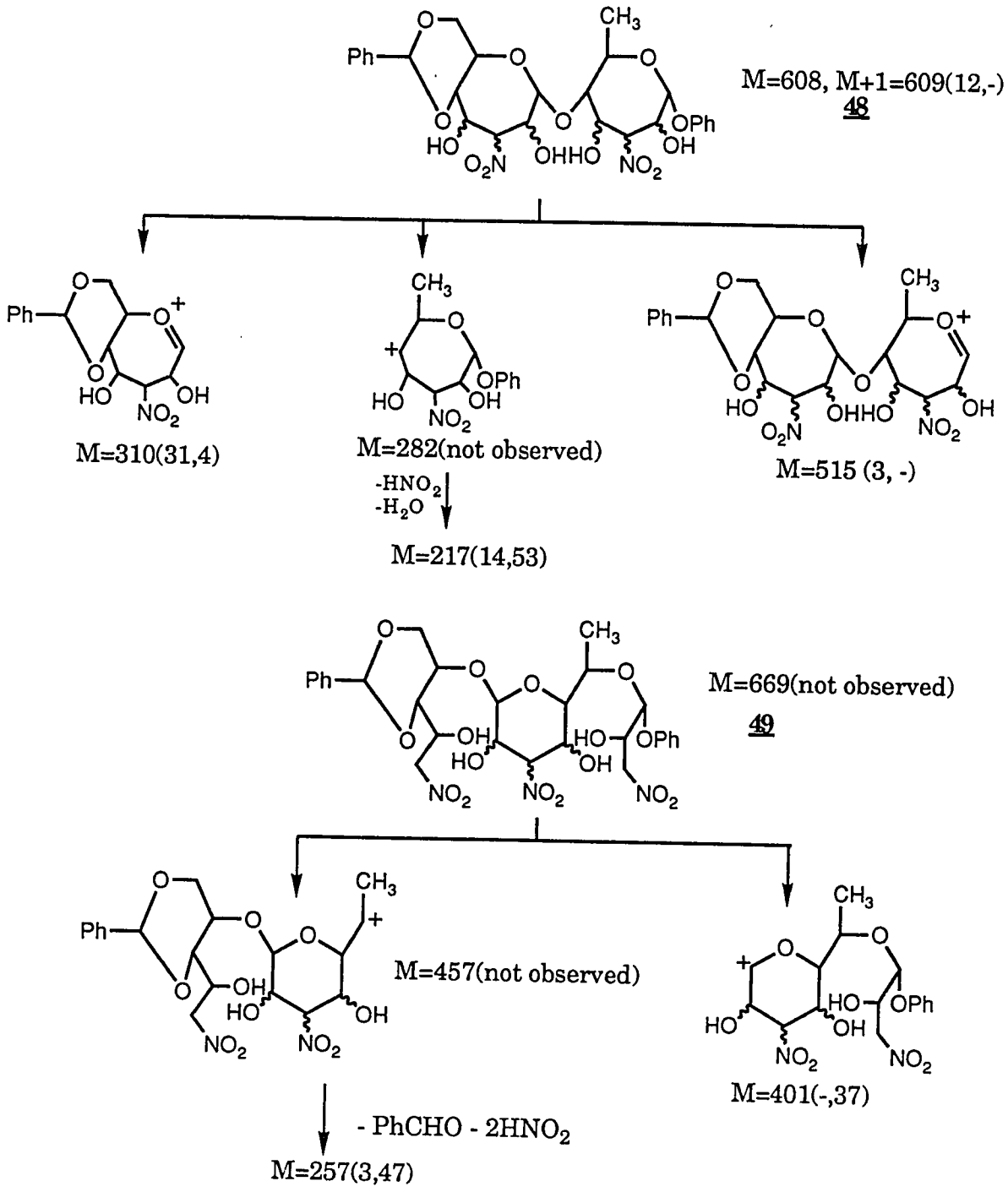
Figure 13b. Fragmentation of compound 46 in FAB mass spectrometry.



* In parentheses, % relative intensity from NaOMe method, followed by % relative intensity from KF method.
-: not observed.

Figure 13c. Fragmentation of compound 47 in FAB mass spectrometry.

With an excess of nitromethane, 25 gave a mixture of products that also showed strong IR absorption for the nitro group at 1557 cm^{-1}, and ^{13}C-NMR signals for anomeric and benzylidenic carbon atoms at δ 102 - 101. The FAB mass spectrum was interpreted as indicating the presence of 48 and 49 (Figure 14).



* In parentheses, % relative intensity frome NaOMe method, followed by relative intensity from KF method.

-: not observed.

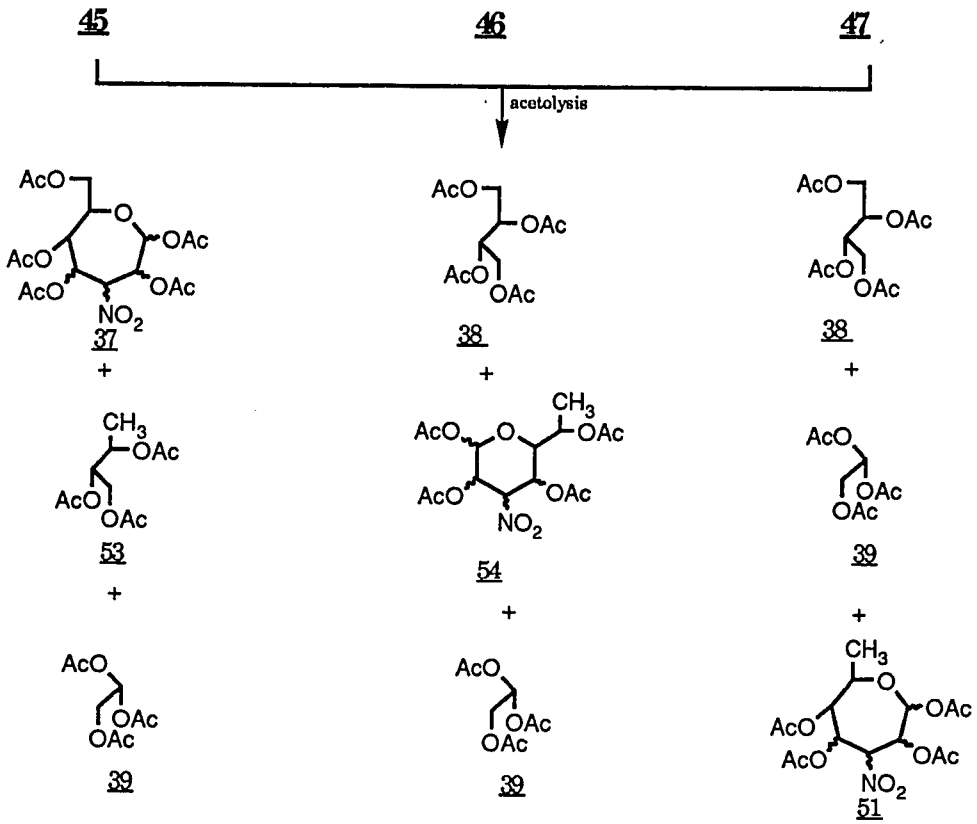
Figure 14. Fragmentation of compounds 48 and 49 from NaOMe method and KF method in FAB mass spectrometry.

2-2.9. Reaction of 6-deoxy tetraaldehyde 25 and nitromethane in the presence of sodium methoxide.

Reaction of the tetraaldehyde 25 with approximately one molar equivalent of nitromethane followed by borohydride reduction of the products led to 45, 46, and 47 as in the case of potassium fluoride catalysis. The mixture showed the corresponding nitro group IR absorption. The FAB mass spectrum (Figures 13a-13c) showed a peak at m/z at 551 corresponding to the molecular ions of the three possible products.

Acetolysis of the above mixture could lead to the following acetylated fragments (Figure 15): 37 + 53 + 39 (from 45), 38 + 54 + 39 (from 46), and 38 + 39 + 51 (from 47). The molecular ion peak at m/z 391 attributable to 51 and(or) 54 was strong (19 %), whereas the peaks assignable to 37 (m/z 449) and 53 (m/z 238) were weak (2.9 and 3.7 %), suggesting that 46 and(or) 47 represented the predominant cyclization products.

With an excess of nitromethane (3.2 molar equiv.) in the presence of sodium methoxide, the tetraaldehyde gave a product whose FAB mass spectrum showed an $M^+ + 1$ peak at m/z 609 accompanied by an M^+ - OPh peak (3 %) at m/z 515, and a very intense peak at m/z 310 (31 %) attributable to the benzylidenated moiety of the molecule 48 (refer to Figure 14). An M + 1 peak for the other possible product, 49, was not observed, and other peaks from it were very weak (*e.g.* m/z 257, 2.9 %). Curiously, in the reaction of 25 with a large excess of nitromethane under potassium fluoride catalysis the relative intensities of the m/z 257 (47 %) and 310 (4 %) peaks were reverse (see Figure 14), possibly suggesting that 48 and 49 were formed in different proportions under the two sets of conditions.



	37 M=449	38 M=290	39 M=204	51 M=391	53 M=238	54 M=391
CI($M^+ + 1$)%	1.1	11	1.4	16	1.7	16
FAB(M^+)%	2.9	7.6	4.8	19	3.7	19

Figure 15. Acetolysis of compounds 45, 46, and 47 and mass spectral data for their acetylated fragments.

In order to examine the reaction further, the mixture obtained by methoxide catalysis was debenzylidenated in 70 % acetic acid and then acetylated with acetic anhydride / boron trifluoride. If 48 and 49 were original components, then the acetylated derivatives 55 (Figure 16a) and 56 (Figure

16b) should now be present. The FAB mass spectral data given in the Figures, clearly support these structures. The data were analyzed as follows.

Compound 55 is expected to undergo primary cleavages at the glycosidic centers, to give the oxocarbonium ion fragments A and B (Figure 16a):

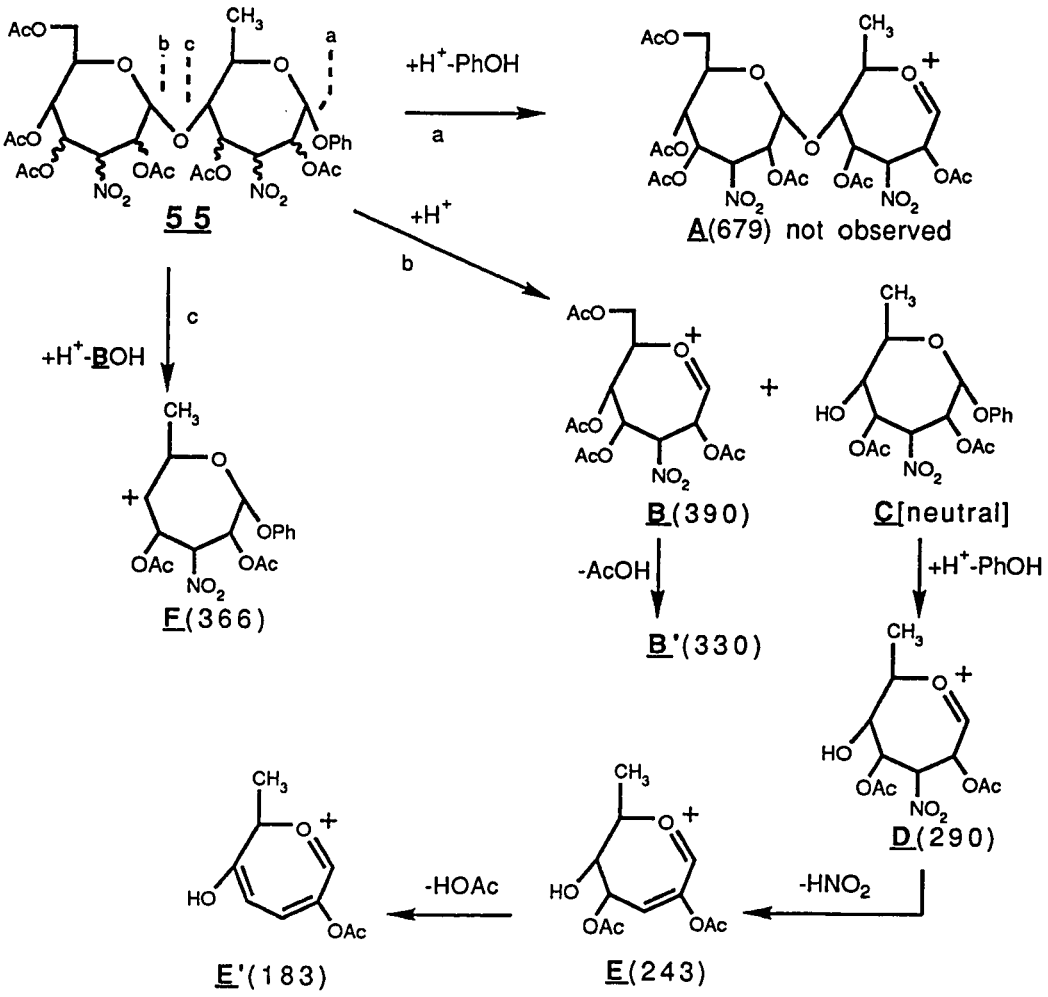


Figure 16a. Fragmentation of compound 55 in FAB mass spectrometry.

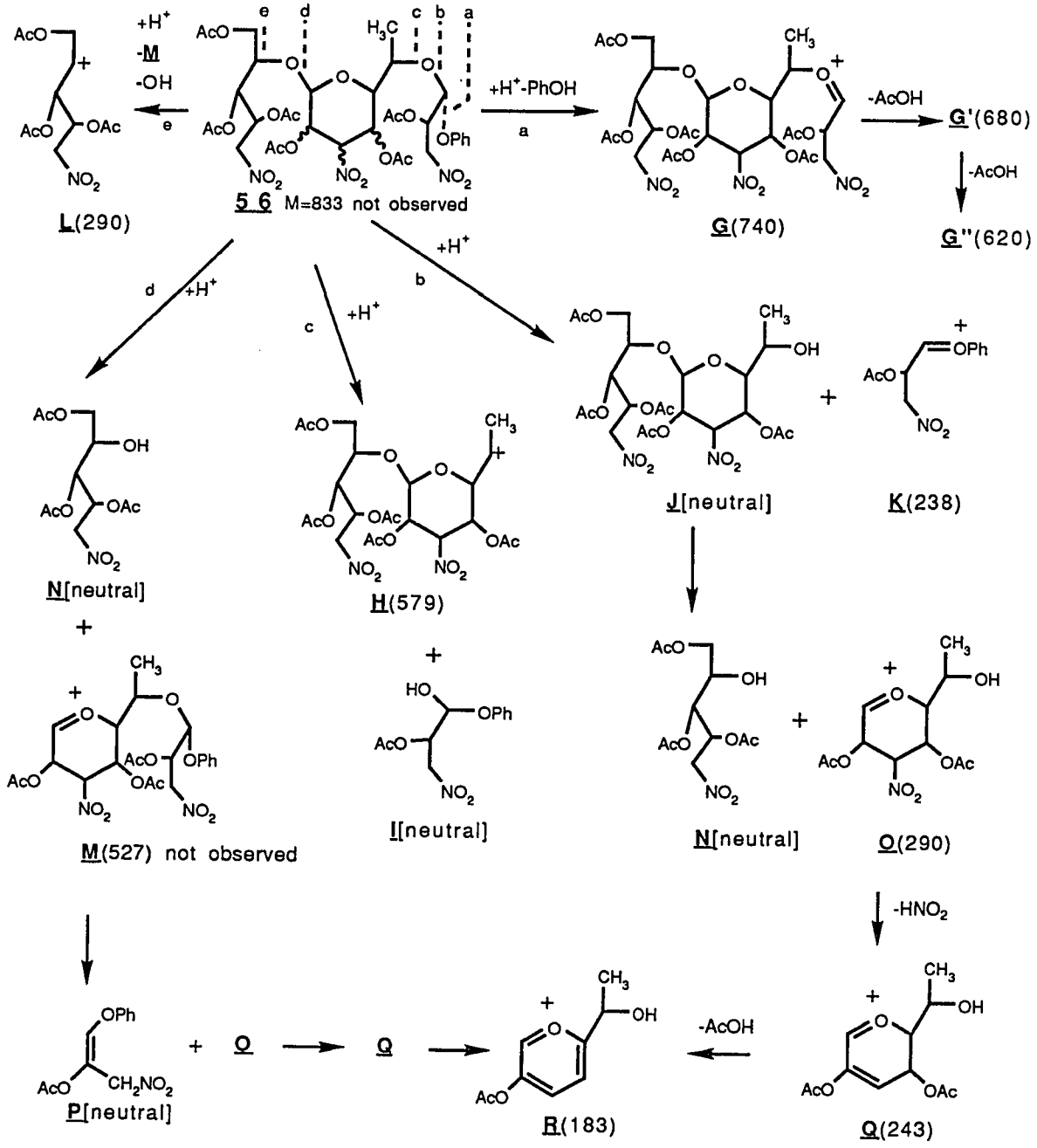


Figure 16b. Fragmentation of compound 56 in FAB mass spectrometry.

Table 2. FAB mass spectral data of acetylated fragments from acetolysis of compounds 55 and 56.

m/z	773	740	680	620	579	390	366	330	290	243	238	183
%	~1	2	3.9	6.2	2.4	42	3.8	3.5	41	10	6	16
assign-ment	M+1 of 55	G	G'	G''	H	B	F	B'	D,L,O	E,Q	K	E',R

Fragment A obtained by cleavage at a was not observed, nor were any daughter ions conceivably arising from it by elimination of one or more molecules of AcOH (loss of 60, 120, etc. mass units) or HNO_2 (loss of 47 mass units). However, fragment ion B was abundant, as were ions D, E, and E' arising from neutral fragment C, indicating that primary cleavage at b was preferred. A minor path appears to be cleavage at c, accounting for ion F.

Fragmentation in 56 could occur as shown in Figure 16b. Cleavage at a gives oxocarbonium in G, which successively eliminates acetic acid molecules to give G' and G''. Bond breakage at b produces the ion K and the neutral molecule J which in turn is cleaved at its anomeric center to form the glycopyranosyl ion Q and neutral N, with Q giving rise to the elimination products Q and R. Cleavage at c furnishes the ion H and neutral hemiacetal I. Cleavage at d was also predicted and should have produced the glycosyl ion M (together with neutral N), but M was not observed, possibly as a consequence of its immediate and complete degradation to the abundant ion Q and the neutral fragment P. Cleavage at e may be least likely; if it does occur, the ion L and the neutral, parent glycose of M + OH (mass 544) would be formed. Ion L has the same mass as Q; it probably makes only a minor contribution, if any, to the strong peak at m/z 290.

It is seen from these degradation schemes that the very strong peak at m/z 290 (Table 2) may be due to different fragments from both 55 and 56; it therefore does not indicate whether both of the compounds or only one of them was present. However, the equally prominent peak at m/z 390 can be due to fragment B only and therefore establishes 55 as a component, possibly the major one. (The M + 1 peak at m/z 773, however weak, supports this conclusion.) Conversely, fragments G and its daughter ions G' and G", as well as fragments H and K clearly prove the presence of 56. The corresponding peaks were all relatively weak, so that 56 was probably the minor component.

Finally, the mixture 55 + 56 was subjected to reductive dehydroacetoxylation with potassium borohydride in ethanol. This reaction was expected to convert structural units -CH(OAc)-$CHNO_2$-CH(OAc)- into -CH_2-$CHNO_2$-CH_2- by base catalyzed β-elimination of acetic acid and immediate reduction of the resulting nitroalkene, followed by repetion of this sequence, as discussed in Chapter 1; the remaining ester groups in the molecule are concomitantly saponified. Thus, the tetradeoxygenated bis-septanosidic derivative 57 was expected to be formed from 55, and a substituted 2,4-dideoxypyranoside should analogously arise from 56. Processing of the reaction mixture by silica gel column chromatography gave four fractions (26, 6, 2, and 4%), all of which showed a strong nitro group band in the IR spectrum. Only the major fraction (26 %) was further characterized. It appeared to contain four diastereomers, according to ^{13}C-NMR and ADEPT spectral data. Two were predominant components. The anomeric carbon atoms resonated at δ 95.3, 94.4, 93.3, and 93.7; multiple signals (at least 10) for methylenic carbon atoms (C-2, 2', 4, and 4') occurred at δ 42 - 34 ; and the signals for methyl carbons (C-6) resonated at δ 19.6, 19.0,

and 18.9 (two carbons). The FAB mass spectrum of the product, which is explained in Figure 17, was in accord with structure 57. The result of dehydroacetoxylation thus confirmed the precursor of 55, namely 48 as a major product in the cyclization of tetraaldehyde 25. No product originating from 49 could be identified.

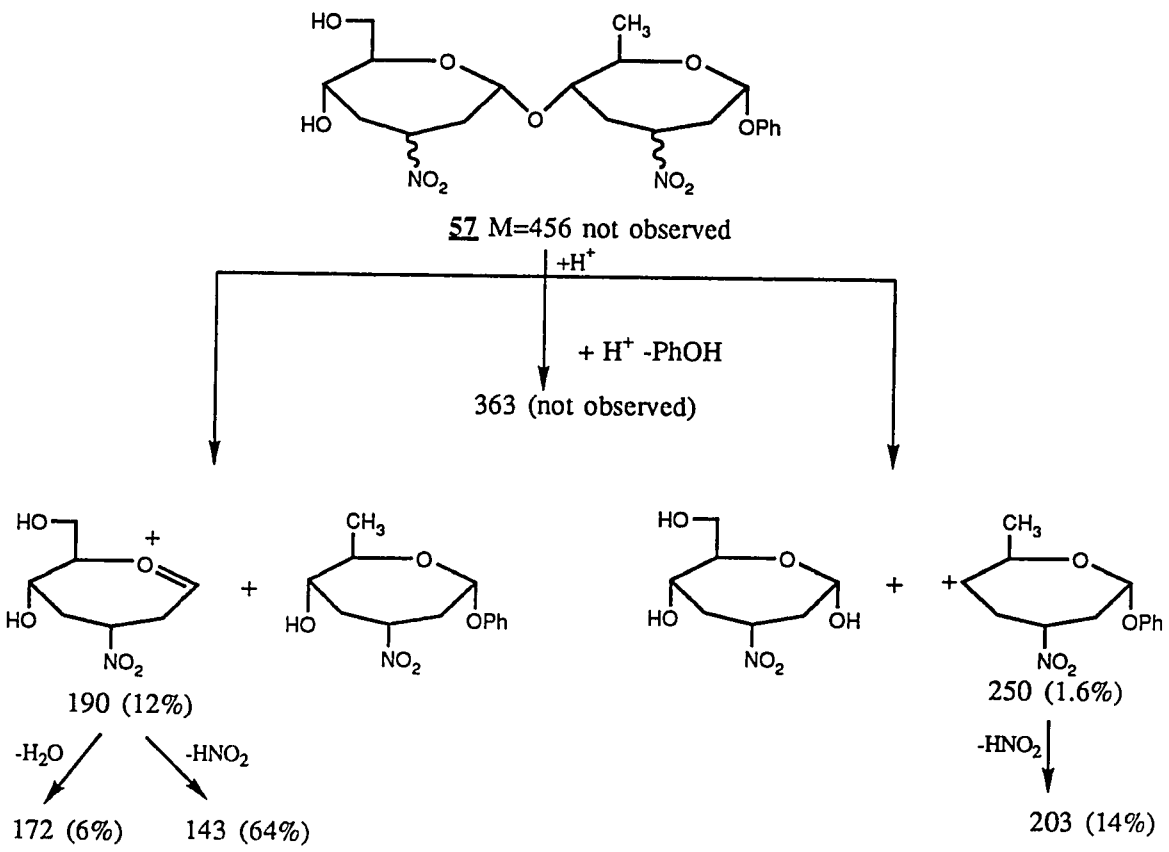


Figure 17. Fragmentation of compound 57 in FAB mass spectrometry.

In summary:

I. The reaction of tetraaldehyde 10 with nitromethane (both one equivalent and > three equivalents) by the potassium fluoride method gave products with a very low nitrogen content.

II. The reaction of tetraaldehyde 10 with nitromethane by the sodium methoxide method gave products whose attempted characterization by mass spectrometry was inconclusive.

III. The reaction of the dialdehyde mixture (23 + 24) with nitromethane by the sodium methoxide methode gave the expected product, 43 + 44 as determined on the basis of MS analysis of the product mixture itself and after acetolysis. The same reaction carried out by the potassium fluoride method gave similar results.

IV. The reaction of tetraaldehyde 25 with nitromethane (one equivalent) both by the sodium methoxide and the potassium fluoride method gave products exhibiting mass spectral data that suggested 46 and 47 to be chief components in the mixture of 45 + 46 + 47.

V. The reaction of tetraaldehyde 25 with nitromethane (more than three equivalents) by both the sodium methoxide and the potassium fluoride method furnished a mixture of 48 and 49, with the former predominating (in the sodium methoxide method), as evaluated by mass spectrometry of the debenzylidenated and acetylated derivatives 55 and 56, and by an experiment of dehydroacetoxylation leading to 57.

2-3. Experimental

2-3.1. Octaacetylmaltose (2).

A solution of 50 g of anhydrous maltose in 200 mL of acetic anhydride and 75 mL of pyridine containing a catalytic amount of 4-dimethylaminopyridine was stirred at room temperature for two days with t.l.c. monitoring (Rf 0.48 maltose, 0.79 octaacetylmaltose, in 3 : 3 : 4 water / ethanol / butanol). At the end of the reaction, the volume of the mixture was reduced to one-third by rotary evaporator at 50° C to give a brown syrup. Ice-water (300 mL) was poured into the syrup with vigorous stirring. The white precipitate formed was separated and dissolved in chloroform (750 mL), and the aqueous filtrate was extracted with chloroform (3 x 50 mL). The combined organic phase was washed with water (3 x 200 mL), 5% hydrochloric acid (3 x 300 mL), and saturated sodium bicarbonate (2 x 150 mL), and then dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure to give 90.8 g (96%) of a white solid which was crystallized from ethanol (99%), to yield crystalline 1 (81.6 g, 86%); m.p. 159.5 -161.0° C (lit[4]. 158 - 159° C); $[\alpha]_D$ + 124.5° (c 1.0, chloroform), lit.[4] +124°. MS (CI,ether): m/z 619 (M^+ + 1 - HOAc), 559 (M^+ + 1 - 2HOAc), 332 (M^+ + 1 - $C_{14}H_{19}O_{10}$), 331 (M^+ + 1 - $C_{14}H_{20}O_{10}$), 271 (M^+ + 1 - $C_{14}H_{20}O_{10}$ - HAc), 211(M^+ + 1 - $C_{14}H_{20}O_{20}$ - 2 HOAc).

2-3.2. Phenyl hepta-*O*-acetyl-α-maltoside (3).

The mixture of octaacetylmaltose (1,40 g), phenol (45g), and fused zinc chloride (7.3g) was heated under vigourous stirring for 2.5 h at 95 - 100° C, with monitoring by TLC. After the reaction completed, the mixture was cooled, and the dark brown oil was diluted with water and extracted with benzene. The extract was well washed successively with water, 1 N aqueous

sodium hydroxide, and with water until the washings were colorless, and finally dried over anhydrous sodium sulfate and decolorized with activated carbon. The solvent was then evaporated under reduced pressure, leaving a yellowish oil. The oil was crystallized from ethanol (99%) to give 11 g of white crystals which was recrystallized to give pure α-isomer 3 (10.23g); $[\alpha]_D$ +171.3° (c 1.0, chloroform) and m.p. 185.5 - 186.5 °C, lit[4]. $[\alpha]_D$ +170.2° and m.p. 185 - 186 °C. MS (CI,ether): m / z 713 (M^+ +1), 619 (M^+ +1 - PhOH - HOAc), 559 (M^+ +1 - PhOH - HOAc), 365 ($M^+ + 1 - C_{14}H_{20}O_{10}$), 331 ($M^+ + 1 - C_{18}H_{21}O_9$), 271 ($M^+ + 1 - C_{18}H_{21}O_9$ - HOAc). ^{1}H-NMR data ($CDCl_3$, 300 MHz, COSY): δ 7.03 - 7.32 (m, 5H, Ph), 5.73 (dd, $J_{2,3}$ 10.18, $J_{3,4}$ 8.62 Hz, H-3), 5.60 (d, $J_{1,2}$ 3.67 Hz, H-1), 5.41 (d, $J_{1',2'}$ 3.96 Hz, H-1'), 5.34(dd, $J_{2',3'}$ 10.45, $J_{3',4'}$ 9.62, Hz, H-3'), 5.04 (dd, $J_{3',4'}$ 9.62, $J_{4',5'}$ 9.80 Hz, H-4'), 4.90 (dd, $J_{1,2}$ 3.67, $J_{2,3}$ 10.18 Hz, H-2), 4.85 (dd, $J_{1',2'}$ 3.96, $J_{2',3'}$ 10.45, H-2'), 3.91 - 4.24 (m, 7H, H-4, 5, 6, 6a, 5', 6', 6a'), 2.08, 2.075, 2.07, 2.03, 2.01, 2.00, 1.98 (7 singlets, 21H, 7 Ac). ^{13}C-NMR data: δ 129.6, 123.1, 116.8 (Ph), 95.6 (C-1), 94.1 (C-1'), 72.6, 72.3, 70.8, 69.9, 69.2, 68.4, 68.3, 67.8 (C-2, 2', 3, 3', 4, 4', 5, 5'), 62.3, 61.3 (C-6 and 6'), 20.7, 20.68, 20.6, 20.5, 20.4, 20.3, 20.2 (Ac).

2-3.3. Phenyl α-maltoside (4).

A solution of phenyl hepta-*O*-acetyl-α-maltoside (3, 6.0 g), methanolic sodium methoxide (0.4g Na in 100 mL of MeOH), and chloroform (100 mL) was kept at overnight 4° C. The reaction mixture was then deionized with Amberlite IR-120 (H^+) ion exchange resin, filtered, and evaporated to give 3.35 g of a white solid. The white solid was dissolved in a minimum amount of methanol, and excess ether was carefully added to give crystalline phenyl α-maltoside, m.p.209 - 211° C, $[\alpha]_D$ + 213° (c 1.88, water); lit[5]. m.p. 212 - 213° C, $[\alpha]_D$ +211° (c 1.3, water) and +215.3° (c 1.86, water).MS (FAB): m / z 419 (M^+ +

1), 325 (M^+ + 1 - PhOH), 255 (M^+ - $C_6H_{11}O_5$), 163 (M^+ - $C_{12}H_{15}O_6$), 145 (M^+ - $C_6H_{11}O_5$ - PhOH). ^{1}H-NMR data (D_2O, 300 MHz): δ 7.15 - 7.46 (m, 5H, Ph), 5.69 (d, $J_{1,2}$ 3.74 Hz, H-1), 5.47 (d, $J_{1',2'}$ 3.91 Hz, H-1'), 4.26 - 3.41 (m, 12H, other ring and methylenic protons).^{13}C-NMR data (DMSO-d_6, 50.3 MHz): δ 161.9, 134.8, 127.5, 122.0 (PhO), 105.6 (C-1), 102.3 (C-1'), 83.9, 78.1, 78.1, 77.8, 77.1, 76.5, 75.8, 74.6, (C-2, 2', 3, 3', 4, 4', 5, 5'), 65.7 , 64.9 (C-6 and 6').

2-3.4. Phenyl 2,2',3,3',6-penta-*O*-acetyl-4',6'-*O*-benzylidene-α-maltoside (6).

Method A: A suspension of phenyl α-maltoside (5.93 g) and anhydrous zinc chloride (5.2 g) in freshly distilled benzaldehyde (30 mL) was stirred at room temperature for 120 h. It was then poured into a vigorously stirred mixture of ice-water and petroleum ether (600 mL) to give a precipitate which turned to an oil-like layer that stayed in the bottom of the flask. The upper layer was decanted and the lower oily layer was extracted with chloroform (3 x 50 mL). The organic phase was co-evaporated several times with water to remove excess benzaldehyde, and dried *in vacuo* to yield 5.72 g (80%) of crude phenyl 4',6'-*O*-benzylidene-α-maltoside (5). A portion (3.2 g) of the crude product was acetylated with acetic anhydride (30 mL) and pyridine (30 mL). The reaction mixture was stirred at room temperature for 24 h with TLC monitoring and then processed conventionally by dilution with chloroform (100 mL), washing the solution with water (100 mL), 1N hydrochloride acid, and saturated aqueous sodium bicarbonate (100 mL), drying (Na_2SO_4), and solvent removal under reduced pressure. The crude pentaacetate (3.43 g, 95%) was purified by chromatography on a silica gel column with 1:2 ethylacetate/hexane as eluent, to give homogenous phenyl 2,2',3,3',6-penta-*O*-acetyl-4',6'-*O*-benzylidene-α-maltoside (3.15 g), m.p. 187 - 189°C, $[\alpha]_D$ +143.1°C (c 1.83, chloroform); lit[5]. $[\alpha]_D$ + 141.9°, m.p. 188 - 189 °C; 1H-NMR data

($CDCL_3$, 300 MHz, COSY): δ 7.41 - 7.02 (m, 10 H's, Ph), 5.74 (dd, $J_{2,3}$ 10.1, $J_{3,4}$ 8.57 Hz, H-3), 5.59 (d, $J_{1,2}$ 3.7 Hz, H-1), 5.45 (s, PhCH), 5.44 (dd, $J_{2',3'}$ 10.1, $J_{3',4'}$ 9.7 Hz, H-3'), 5.37 (d, $J_{1',2'}$ 4.1 Hz, H-1'), 4.91 (dd, $J_{2,3}$ 10.1, $J_{1,2}$ 3.7 Hz, H-2), 4.88 (dd, $J_{1',2'}$ 4.1, $J_{2',3'}$ 10.1 Hz, H-2'), 4.47 - 4.11 (m, H-5,5',6,6',6a,6a'), 4.05 (dd, $J_{3,4}$ 8.6, $J_{4,5}$ 9.8, H-4), 3.61 (dd, $J_{4',5'}$ 9.5, $J_{3',4'}$ 9.7 Hz, H-4'), 2.10, 2.06, 2.04, 2.03, 2.02 (4 singlets, 15 H's, OAc); ^{13}C-NMR data ($CDCl_3$, 50.3MHz): δ 171.0, 170.4, 170.3, 169.9, 169.7 (C=O), 156.2, 136.8, 129.6, 129.1, 128.2, 126.2, 123.1, 116.8 (Ph), 101.6 (PhCH), 96.6, 94.2, 78.7, 72.8, 72.5, 70.9, 70.8, 68.4 (C-6' and two other carbon atoms), 63.6 (C-6), 62.2.

Method B: Benzal bromide (1.09 mL, 65 mmol, freshly distilled) was added to a solution of phenyl α-maltoside (2.5 g, 6 mmol) in pyridine (25 mL) which was refluxed and mointored with TLC (5 : 4 : 3 hexane / ethyl acetate / methanol). After five hours, the spot for the starting material (Rf 0.14) was completely replaced by a new spot (Rf 0.42). Acetic anhydride (20 mL) was added to the cooled mixture, which was then stirred overnight at room temperature and thereafter showed only one faster - moving spot (Rf 0.83). Most of the acetic anhydride and pyridine were removed in a rotary evaporator. The residual dark brown syrup was dissolved in chloroform (100 mL), washed with water (100 mL x 2), saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous magnesium sulfate, decolorized with activated carbon, and filtered to give a light brown solution. The solvent was then removed under reduced pressure at 60°C to give 3.69 g of a brown residue which was subjected to silica gel flash chromatography with 1:2 hexane - ethyl acetate as an eluent . Homogeneous fractions (3.42 g, 80%) of 6 gave white, crystalline phenyl 2,2',3,3',6-penta-*O*-acetyl-4',6'-*O*-benzylidene-α-maltoside from hot absolute ethanol, m.p. 189 -190.5°C, $[\alpha]_D$ + 142.5° (c 1.83, chloroform).

Method C: A solution of phenyl α-maltoside (200 mg) and α,α-dimethoxytoluene (0.3 mL) in acetonitrile (5 mL) containing Amberlite IR-120(H^+) resin was agitated under reduced temperature in a rotary evaporator at 52° C. The pressure was adjusted so as to avoid excessive evaporation of solvent. After 2h, TLC showed no more starting material (Rf 0.23) but benzylidenated product (Rf=0.67) (solvent: 3 : 3 : 4 water / ethanol / butanol). The solvents were evaporated to dryness. The residue was dissolved in methylene chloride (5 mL) and filtered. The solution was co-evaporated several times with water to give 172 mg of residue. The residue was acetylated overnight with acetic anhydride (2 mL) and pyridine (1 mL) and then worked up conventionally. Flash chromatography of crude acetylated product (202 mg, 59% overall) gave pure 6 (156 mg): $[\alpha]_D$ = +14 2° (c 1.83, chloroform).

2-3.5. Phenyl 4',6'-*O*-benzylidene-α-maltoside (5).

Phenyl α-maltoside (4) (500 mg, dried), α,α-dimethoxytoluene (300 mg), dry DMF (10 mL), and *p*-toluenesulfonic acid (10 mg) were placed in a round-bottom flask, and rotated on a rotary evaporator under reduced pressure (water aspirator) at a bath temperature of 62° C so that gentle refluxing of the DMF occurred. One hour later, the temperature of the water bath was raised to 90° C, to remove the solvents. Saturated aqueous sodium bicarbonate (5 mL) was added, and the mixture was co-evaporated three times with water to remove excess benzaldehyde at 95°C. The residue (600 mg) was dissolved in chloroform (30 mL) and washed with cold water (2 x 20 mL). The aqueous phase was extracted with chloroform (20 mL) and the extract dried over sodium sulfate, filtered, and evaporated, to give 595 mg of crude 5 which was

then flash-chromatographed (1:3 MeOH-chloroform) through silical gel to give 388 mg of pure 5, $[\alpha]_D$= +176.1° (c 1.54, chloroform); lit[5]. $[\alpha]_D$= + 173.8°.

Alternatively, camphorsulfonic acid was used as an acid catalyst, which resulted in a 55% yield of 5.

2-3.6. Deacetylation of pentaacetate 6.

Sodium methoxide (50 mg of Na in 20 mL of methanol) was added to a solution of phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-α-D-glucopyranoside (6,6.25 g) suspended in methanol (30 mL). The suspension was stirred at room temperature for one hour until it turned clear. TLC showed no more starting material. The solution was then neutralized with Amberlite IR-120(H^+), filtered, and evaporated to give 4.16 g (94%) of 5, $[\alpha]_D$= +177°; ^{1}H-NMR data (DMSO-d_6, 200 MHz): δ 7.45 - 6.95 (m, 10 H, Ph), 5.55 (s, PhCH), 5.39 (d, H-1), 5.26 (d, H-1'), 5.68, 5.50, 5.32, 5.21 (d, 2,3,2',3'-OH's), 4.60 (t, 6-OH), 3.30 - 4.12 (m, other ring and methylenic protons); ^{13}C-NMR (DMSO-d_6, 50.3 MHz): δ 156.6, 137.1, 126.6, 129.2, 128.3, 126.4, 122.7, 117.0 (two carbons), 102.3, 101.7, 97.3, (C-1,1', and PhCH), 80.5, 80.2, 73.3, 71.4, 71.7, 63.7 (ring carbons), 68.4 (C-6), 60.6 (C-6'); MS (FAB): m/z at 507 (M+1), 413 (M+1-PhOH), 251 (M-$C_{12}H_{15}O_6$), 145 (M+1-PhOH-$C_{13}H_{16}O_6$).

Anal. calc. for $C_{25}H_{30}O_{11}$ (506.49): C, 59.28; H, 5.97. Found: C, 59.12; H, 6.16.

2-3.7. Phenyl 2,2',3,3',6'-penta-*O*-benzoyl-4',6'-*O*-benzylidene-α-maltoside (7).

A solution of 2.54 g of phenyl α-maltoside (4) and 1.5 mL of benzal bromide in 30 mL of pyridine was heated under reflux temperature for 3 h with TLC monitoring (Rf 0.29 for starting material, Rf 0.48 for 5; solvent: 3 : 4 : 5 methanol–ethyl acetate–hexane). Benzoyl chloride (3.0 mL) was added to

the cooled reaction mixture when the phenyl α-maltoside was consumed. After overnight stirring, most of pyridine was removed by rotary evaporator at 55 - 60°C to give a dark brown residue. The residue was dissolved in 100 mL of chloroform and washed with water. The aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phase was then washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and water, dried over magnesium sulfate, evaporated, and purified by flash chromatography (1:5:6 methanol / ethyl acetate / hexane) to give 4.05 g (67%) of phenyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-α-D-glucopyranoside (7). The product was crystallized from ethanol, m.p. 212°C; $[\alpha]_D$ +153.6 (c 1.2, chloroform); ^{1}H-NMR data (300 MHz, $CDCl_3$, COSY): δ 6.27 (dd, $J_{2,3}$ 10.1, $J_{3,4}$ 8.6 Hz, H-3), 5.92 (t, $J_{2',3'} \sim J_{3',4'}$ = 9.8 ~ 10.1 Hz, H-3'), 5.84 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.69 (d, $J_{1',2'}$ 4.2, H-1'), 5.45 (s, 1H, PhCH), 5.26 (dd, $J_{1',2'}$ 4.2, $J_{2',3'}$ 10.1 Hz, H-2'), 5.21 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 10.1 Hz, H-2), 4.79 (dd, $J_{5,6}$ <1, $J_{6,6a}$ ~12 Hz, H-6), 4.63 (dd,$J_{4,5}$ ~12, $J_{5,6}$ <1 Hz, $J_{5,6a}$ ~11Hz, H-5), 4.50 -4.40 (m, 2H, H-4, 6a), 4.20 (dd, $J_{5',6'}$ 4.8 Hz, $J_{6',6a'}$ 10.3 Hz, H-6'),4.07 (sx, $J_{4',5'}$ 9.5, $J_{5',6'}$ 4.8, $J_{5',6a'}$ 10.1 Hz, H-5'), 3.82 (t, $J_{3',4'} \sim J_{4',5'}$ = 9.5 ~9.8 Hz, H-4'), 3.70 (t, $J_{5',6a'} \sim J_{6,6a'}$ = 10.1 ~ 10.3 Hz, H-6a'); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): δ 166.1, 166.0, 165.9, 165.6, 165.0 (C=O), 156.4 - 117.1 (Ph), 101.6 (PhCH), 98.2, 94.5, 79.1, 74.7, 72.1 (two carbon atoms), 71.3, 69.3, 69.0, 68.3 (CH_2), 64.2, 63.1 (CH_2).

Anal. calc. for $C_{60}H_{50}O_{16}$(1027.00): C, 70.12; H, 4.91. Found: C, 70.30; H, 5.00.

2-3.8. Reaction of phenyl 2,2',3,3',6-penta-*O*-benzoyl-4',6'-*O*-benzylidene-α-maltoside (7) and lithium aluminum hydride - aluminum chloride.

Compound 7 (2.4 g, 2.34 mmol) was added to a stirred suspension of lithium aluminum hydride (0.8 g, 21 mmol) in methylene chloride (20 mL) and ether (20 mL). An ethereal solution (40 mL) of alumnium chloride (anhydrous, 2.81 g, 21 mmol) was added to the reaction mixture which was stirred for 5 h at the reflux temperature under exclusion of moisture. The reaction was quenched by addition of cold water, the ether layer separated, and the aqueous suspension extracted with chloroform (3 x 20 mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated to dryness. The crude residue (1.05 g) showed two spots on TLC having the same Rf values as 4 and 5.

The crude mixture was acetylated with 1:1 acetic anhydride - pyridine (10 mL) overnight and worked up conventionally,to give 1.35 g of crude product. The crude product was separated by flash chromatography (1:4 ethyl acetate-hexane) to give acetylated phenyl α-maltoside 3 (0.11 g) and acetylated compound 6 (1.09 g).

2-3.9. Reaction of phenyl 4',6'-O-benzylidene α-maltoside (5) and diisobutyl-aluminum hydride.

Compound 5 (500 mg, 1.0 mmol) in 5 mL of dry methylene chloride was added at -30° C to a solution of diisobutylaluminum hydride (DIBAH, 2.2 mL of 1 M solution in methylene chloride, 2.2 mmol), and the mixture was stirred for 30 min under a dry nitrogen atmosphere. The temperature was allowed to raise to room temperature during the period. The solvent was evaporated after adding water to the reaction mixture. The crude mixture was flash-

chromatographed on silical gel (1:3 MeOH-chloroform) to afford 463 mg of homogeneous starting material (5).

2-3.10. Phenyl 2,2',3,3',6-penta-*O*-acetyl-α-maltoside (8).

Borane in tetrahydrofuran (10 mL, 1.0 M solution) was added to a flask containing triethylamine (8 mL) and molecular sieve (4 Å). The solution was stirred at room temperature for 10 min and co-evaporated with toluene at 50°C. The resulting white residue was dried overnight in an oil pump vacuum to constant weight, and then added to a solution of compound 6 (250 mg, 0.35 mmol) in toluene (10 mL), together with molecular sieve (4 Å). The mixture was stirred at room temperature for 30 min and then cooled to 0°C before anhydrous aluminium chloride (1.1 g) was added. TLC showed all of the 6 consumed within 10 min. The reaction mixture was filtered and washed with hydrochloric acid (5%, 2 x 50 mL), saturated sodium bicarbonate (2 x 50 mL), and saturated aqueous sodium chloride (2 x 50 mL). The organic phase was dried over magnesium sulfate, evaporated, and dried *in vacuo* at 90°Cto remove excess BH_3-Et_3N. The residue was then purified by flash chromatography on silical gel with 1:1 hexane - ethyl acetate to afford 170 mg (78%) of homogeneous, oily 8, MS(FAB): m/z 1257 ($2M^+$ - H), 629 (M^+ + 1), 535 (M^+ + 1 - PhOH), 475 (M^+ + 1 - PhOH - HOAc), 365, 289, 271; MS(CI/ether): 288 (M^+ + 1 - PhOH - $C_{10}H_{15}O_7$),247 (M^+ - $C_{18}H_{19}O_9$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32-7.02 (m, 5H, Ph), 5.72 (dd, J 8.4 and 10.2 Hz, 1H), 5.60 (d, J 3.6 Hz, 1H), 5.36 (d, J 4.0 Hz, 1H), 5.17 (m, 1H), 4.91 (dd, J 3.6 and 10.2 Hz, 1H), 4.77 (dd, J 4.0 and 10.5 Hz, 1H), 4.43 (dd, J 2.1 and 12.3 Hz, 1H), 4.20 (dd, J 3.93 and 12.2 Hz, 1H), 4.13-3.61 (m, 6H), 3.65-3.55 (broad, 1H, disappeared after D_2O exchange, OH), 3.00 (t, 1H, disappeared after D_2O exchange, OH), 2.09, 2.07, 2.06, 2.03, 2.02 (5s, 15H, 5 OAc); ^{13}C-NMR (75.6 MHz, $CDCl_3$, ADEPT): δ 171.1,

171.0, 170.9, 170.4, 170.0 (C=O), 156.1, 129.6, 123.0, 116.8 (Ph), 95.8 and 94.6 (two anomeric carbons), 72.8, 72.5, 72.1, 71.8, 70.9, 70.4, 69.0, 68.4 (ring carbons), 62.6 and 61.6 (two secondary carbons of C-6 and 6'), 21.0, 20.8, 20.79, 20.7, 20.6 (Ac).

Anal. calc. for $C_{28}H_{36}O_{16}$ (628.57): C, 53.50; H, 5.77. Found: C, 53.64; H, 6.00.

2-3.11. Phenyl 2,2',3,3',6-penta-*O*-acetyl-4'-*O*-benzyl-α-maltoside (9).

A mixture of borane trimethylamine (890 mg, 17 equiv.) and molecular sieve (4 Å, 5 g) in toluene (20 mL) was stirred at room temperature for 1 h before aluminum chloride (1.56 g, 17 equiv.) was added. Starting material 6 (dry, 500 mg) was added after 30 min and the reaction mixture was stirred at room temperature and monitored with TLC (1:1 hexane-ethyl acetate). The starting material was consumed within 3 h. The mixture was neutralized with Amberlite IR-120 (H^+), filtered, and co-evaporated with methanol (3 x 10 mL) to give a white residue that showed two spots in TLC.

The white residue was dissolved in 1:1 acetic anhydride - pyridine (24 mL) and stirred overnight. The solvent was co-evaporated with toluene and the remaining residue was worked up conventionally to give 401 mg of a white solid. Flash chromatography (2:1 hexane - ethyl acetate) gave 353 mg (71%) of starting material 6 and 30 mg (5%) of syrupy 4'-*O*-benzyl ether 9, ^{1}H-NMR data (300 MHz, $CDCl_3$, COSY): δ 5.72 (dd, $J_{2,3}$ 10.2, $J_{3,4}$ 8.5 Hz, H-3), 5.59 (d, $J_{1,2}$ 3.7, H-1), 5.41 (dd, $J_{2',3'}$ 10.6, $J_{3,4}$ 9.3 Hz, H-3'), 5.34 (d, $J_{1',2'}$ 4.1 Hz, H-1'), 4.88 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 10.2 Hz, H-2), 4.78 (dd, $J_{1',2'}$ 4.1, $J_{2',3'}$ 10.6 Hz, H-2'), 4.54 (dd, J 11.4 Hz, 2 H, $PhCH_2$), 4.40 - 4.13 (m, 4H, H-6, 6a, 6', 6a'), 4.09 (m, 1H. H-5) 4.02 (dd, $J3_{,4}$ 8.6, $J_{4,5}$ 9,8 Hz, H-4), 3.83 (m, 1H, H-5'), 3.59 (dd, $J_{3',4'}$ 9.3, $J_{4',5'}$ 10.0 Hz, H-4'); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): δ 168.3, 168.2, 168.1,

167.6, 167.4 (carbonyl carbons), 153.9, 134.8, 127.3 , 126.3, 125.8, 120.7, 114.5 (Ph), 93.5, 91.7 (C-1, 1'), 72.8 and 72.2 ($PhCH_2$), 70.2, 70.1, 68.9, 68.6, 68.0, 67.4, 65.0, 60.0 and 59.6 (C-6 and 6').

2-3.12. Periodate oxidation of 5.*

A solution of sodium metaperiodate ($NaIO_4$, 70 mg, 1.4 equiv. in 1 mL of H_2O) was poured into a solution of starting material 5 (118 mg, 0.23 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for two days and monitored by TLC (Rf 0.09 for 5, Rf 0.5 for 10, and Rf 0.23 - 0.34 for 11 + 12; solvent: 1:19 methanol - chloroform). Ethanol (10 mL) was added to the reaction mixture, precipitating sodium iodate which was filtered off. The filtrate was concentrated to give a white residue, flash chromatography of which yielded a fast-moving fraction containing tetraaldehyde 10 (40 mg) and a slow-moving fraction containing a mixture of dialdehydes 11 + 12 (76 mg); IR (KBr pellet, neat): 3400cm^{-1} and 1720cm^{-1} (weak shoulder).

Tetraaldehyde 10 (40 mg) was then dissolved in ethanol (2 mL) and reduced by adding sodium borohydride (64 mg, 4 equiv.) at 0°C. The suspension was stirred overnight at room temperature. At the end of the reaction, which was monitored by TLC, methanol (3 mL) was added to decompose excess sodium borohydride. The solution was deionized with Amberlite IR-120(H^+), and the solvent evaporated, to give compound 13 as a syrup. Acetylation of 13 with acetic anhydride (0.5 mL), pyridine (0.5 mL), and a catalytic amount of 4-dimethylaminopyridine then afforded 16 as a syrupy in 60% overall yield based on tetraaldehyde 10.

* Numbering for protons and carbons of compounds 13 - 18 as in maltoside.

The mixture of dialdehydes 11 + 12 (76 mg) was reduced with sodium borohydride (80 mg, 2.5 equiv.) in the same manner, to furnish syrupy products 15 (15 mg) and 14 (51 mg), separated by silical gel column chromatography. Both reduced compounds were acetylated as described for 13, to give 18 (11 mg, syrup, contaminated with impurities) and 17 (46 mg), respectively.

The Rf values of 13, 14, and 15 were 0.33, 0.54, 0.60, respectively in 1:2 methanol - chloroform. Those for 16, 17, and 18 were 0.25, 0.36, and 0.45, respectively in 1:12 ethyl acetate - methylene chloride.

Compound 13 gave the following ^{13}C-NMR data (50.3 MHz, acetone-d_6, ADEPT): δ 162.7, 143.8, 134.8, 133.8, 133.1, 122.8 (Ph), 102.8 (PhCH), 107.4, 106.0 (C-1 and 1'), 86.4, 85.5, 84.3, 74.2 (CH_2), 70.2 (CH_2), 69.0, 68.0, 66.8, 66.4, 66.1.

Anal. calc. for $C_{25}H_{34}O_{11}$ (510.52): C, 58.81; H, 6.72. Found: C, 58.91; H, 6.56.

Compound 14 had ^{1}H-NMR (200 MHz, acetone-d_6): δ 7.55 - 6.93 (m, 10 H's, Ph), 5.60 (d, disappeared after D_2O exchange, OH), 5.58 (s, PhCH), 5.10 (d, 1H), 4.71 (d, disappeared after D_2O exchange, OH), 4.59 (d, disappeared after D_2O exchange, OH), 4.39 (t, disappeared after D_2O exchange, OH), 4.20 (m, 2H), 4.08 (overlap with other signals, disappeared after D_2O exchange, OH), 4.25 - 3.35 (m, 13 H); ^{13}C-NMR data (50.3 MHz, acetone-d_6, APT): δ 158.6, 139.3, 130.8, 129.9, 129.1, 127.6, 123.6, and 118.7 (Ph), 104.1, 102.4, 100.7 (PhCH, C-1, and 1'), 74.0, 71.7, 69.5 (CH_2), 64.2, 63.9 (CH_2), 62.1 (CH_2) and 62.0 (CH_2).

Compound 15 had ^{1}H-NMR (200 MHz, acetone-d_6): δ 7.55 - 6.95 (m, 10 H , Ph), 5.55 (s, PhCH), 5.48 (d, 1H), 5.22 (t, 1H), 4.42 (m, 2H, became q and 1H after D_2O exchange), 4.10 - 3.40 (m, 17 H became 13 H after D_2O exchange); ^{13}C-NMR data (50.3 MHz, acetone-d_6, APT): δ 134.6, 133.7, 133.0, 131.6, 127.3,

122.1 (Ph), 107.7, 105.8, 103.1 (PhCH, C-1 and 1'), 86.4, 81.4, 79.4, 77.2, 77.1, 74.6 (CH_2), 71.1, 69.1 (CH_2), 66.3 (CH_2), 65.8 (CH).

Compound 16 had $[\alpha]_D$ -25.5 ° (c 0.54, chloroform); IR (KBr pellet, neat): 1743 and 1239 cm^{-1}; MS (CI,ether): m/z 721 ($M^+ + 1$), 719 ($M^+ - 1$), 627 ($M^+ + 1$ - PhOH), 525, 469, 367, 337, 235, 233, 231, 193, 189, 179, 175, 147, 129, and 103; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.50 - 6.90 (m, 10 H, Ph), 5.63 (dd, 1 H), 5.45 (s, PhCH), 4.93 (t, 1H), 4.60 - 3.81 (m, 15 H), 3.61 (t, 1 H), 2.05, 2.04, 2.00, 1.97, and 1.95 (5 s, 3 x 5 H, 5 OAc); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): 170.84, 170.81, 170.6, 170.54, and 170.5 (MeCO), 156.2, 137.0, 129.1, 128.3, 126.2, 122.8, 116.9 (Ph), 101.1, 99.3, 99.0, 78.0, 75.7, 74.5, 69.3 (CH_2), 65.9, 64.3 (CH_2), 63.9 (CH_2), 63.1 (CH_2), 62.9, (CH_2), 62.7 (CH_2), 20.6, 20.5, and 20.4 (COMe).

Anal. calc. for $C_{35}H_{44}O_{16}$ (720.67): C, 58.33; H, 6.14. Found: C, 58.23; H, 6.29.

Compound 17, had $[\alpha]_D$ + 90.9 (c 1.85, $CDCl_3$); MS (FAB): m/z 719 ($M^+ + 1$); MS (CI,ether): m/z 719 ($M^+ + 1$), 625 ($M^+ + 1$ - PhOH), 523, 335, 275, 229, 189, 179, and 169; ^{1}H-NMR data (300 MHz, $CDCl_3$, COSY): δ 7.43 - 6.99 (m, 10 H, Ph), 5.63 (dd, $J_{1,2a}$ 6.0, $J_{1,2b}$ 4.7 Hz, H-1), 5.49 (t, $J_{2',3'} \sim J_{3',4'}$ = 9.8 ~10.0 Hz, H-3'), 5.48 (s, 1H, PhCH), 5.29 (d, $J_{1',2'}$ 4.0 Hz, H-1'), 4.86 (dd, $J_{1',2'}$ 4.0, $J_{2',3'}$ 10.0 Hz, H-2'), 4.52 (dd, $J_{3a,3b}$ 12.0, $J_{3a,4}$ 3.0 Hz, H-3a), 4.35 - 4.27 (m, 3 H, H-2a, 6'eq, and 6a), 4.16 - 4.00 (m, 6 H, H-2b, 3b, 4, 5, 5', 6b), 3.73 (t, $J_{5',6'ax}$ = $J_{6'ax,6'eq}$ = 10.2 Hz, H-6'ax), 3.63 (t, $J_{3',4'} = J_{4',5'}$ = 9.8 Hz, H-4'), 2.04, 2.025, 2.023, 1.98, and 1.97 (5 s, 5 x 3 H, 5 OAc); ^{13}C-NMR data (75.4 MHz, $CDCl_3$, APT and HETCOR): δ, 170.6, 170.4, 170.3, 170.2, 169.6 (MeCO), 156.8, 136.9, 129.8, 128.9, 128.1, 126.1, 122.8, 117.0 (Ph), 101.5 (PhCH), 98.9 (C-1), 95.5 (C-1'), 79.0 (C-4'), 75.1 and 73.7 (C-5 and 5'), 71.2 (C-2'), 68.7 (C-3'), 68.6 (C-6'), 62.9 (C-4), 63.6, 62.7, and 62.3 (C-2, 3, and 6), 20.8 and 20.5 (OAc).

Anal. calc. for $C_{35}H_{42}O_{16}$ (718.69): C, 58.49; H, 5.89. Found: C, 58.45; H, 6.05.

Compound 18 had [α]D +90.9 ° (c 1.85, $CDCl_3$); MS (CI,ether): m/z 719 ($M^+ + 1$), 625 ($M^+ + 1$ - PhOH), 467, 365, 337, 289, 235, 233, 231, 193, 175, 147, 129, and 103; ^{1}H-NMR (200 MHz, $CDCl_3$); δ 7.50 - 6.95 (m, 10 H, Ph), 5.71 (dd, 1 H, J 8.7, 10.2 Hz), 5.62 (d, J 3.6 Hz, 1 H), 5.47 (s, 1 H, PhCH), 4.94 (t, J 5.1 ~ 5.3 Hz, 1 H), 4.91 (dd, J 3.6, 10.2 Hz, 1 H), 4.61 - 3.55 (m, 12 H), 2.14, 2.10, 2.09, 2.02, and 1.99 (5 s, 5 x 3 H, 5 OAc); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): δ 170.9, 170.8, 170.6, 170.4, 169.8 (MeCO), 156.2, 136.9, 129.6, 129.2, 128.3, 126.1, 122.9, 116.8 (Ph) 101.0, 100.0, 94.2 (PhCH, C-1, and 1'), 78.1, 73.1, 71.9, 70.6, 69.7 (CH_2), 68.7, 66.5, 64.1 (CH_2), 62.7 (CH_2), 62.2 (CH_2), 20.9, 20.7, 20.6, 20.4 (OAc).

Anal. calc. for $C_{35}H_{42}O_{16}$ (718.69): C, 58.49; H, 5.89. Found: C, 58.63; H, 6.00.

2-3.13. Phenyl 4',6'-*O*-benzylidene-6-*S*-phenyl-6-thio-α-maltoside (19).

To a solution of 5 (965 mg, 1.9 mmol, dried at 110°C over P_2O_5 for 5 h), diphenyl disulfide (2.5 g, 6 equiv.), in pyridine (15 mL, freshly distilled and dried over molecular sieve) was added tributyl phosphine (2.85 mL, 6 equiv.) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and monitored with TLC (Rf 0.4 for 5, 0.58 for 19; solvent; 1 : 5 methanol - chloroform). When the reaction was complete, methanol (50 mL) was added, the mixture which stirred for 30 min, and the solvent evaporated. This process was repeated three times. The yellowish liquid residue was dried at 100°C in an oil-pump vacuum for 2 h and then subjected to flash chromatography on silical gel column (230 - 400 mesh, 40 g). Elution was first started with ether, and then chloroform with 2.5, 5, and 10% methanol-chloroform. A yield of 1.13 g (99%) of pure 19 was obtained, m.p. 188 - 190°C;

$[\alpha]_D$ + 80.6 ° (c 1.25, chloroform); MS (FAB): m/z 599 (M^+ + 1), 505 (M^+ - PhO); ^{1}H-NMR data (200 MHz, acetone-d_6, D_2O exchange): δ 7.60 - 7.00 (m, 15 H, Ph), 5.61 (s, 1 H, PhCH), 5.50 (d, 1 H, H-1), 5.30 (d, 1 H, H-1'), 4.15 - 3.40 (m, 10 H,other ring protons), 3.12 (q, 2 H, H-6 and 6a, CH_2SPh); ^{13}C-NMR data (50.3 MHz, acetone-d_6, APT): δ 158.6, 139.4, 137.9, 131.0, 130.5, 130.1, 129.1, 127.7, 127.3, 123.4, 118.33, and 118.30 (Ph), 103.8 (PhCH), 102.6 (C-1), 98.8 (C-1'), 86.0, 82.3, 74.7, 74.6, 72.8, 71.8, 69.4 (C-6'), 64.9, 37.1 (C-6).

Anal. calc. for $C_{31}H_{34}O_{10}S$ (598.644):C, 62.19; H, 5.72; S, 5.36. Found: C, 62.03,;H, 5.91; S, 5.56.

2-3.14. Phenyl 2,2',3,3'-tetra-*O*-acetyl-4',6'-*O*-benzylidene-6-*S*-phenyl-6-thio-α-maltoside (20).

A solution of 19 (34 mg), acetic anhydride (0.5 mL), pyridine (0.5 mL), and a catalytic amount of 4-dimethylaminopyridine was stirred overnight at room temperature. TLC showed a single spot (Rf 0.67) for 20; starting material 19 (Rf 0.25) was absent (1:9 ethanol-chloroform). The reaction mixture was evaporated under reduced pressure and the remaining residue was dissolved in methylene chloride, washed with water, and dried over sodium sulfate. A crude product (42 mg, 97%) was obtained after removal of solvent *in vacuo*. It was passed through a silical gel column to afford 20 as a colorless syrup; MS (CI,ether): m/z 766 (M^+), 673 (M^+ + 1 - PhOH), and 335 (M^+ - $C_{22}H_{23}O_7S$); ^{1}H-NMR data (300 MHz, $CDCl_3$, COSY): δ 7.38 - 6.98 (m, 15 H, Ph), 5.72 (dd, $J_{2,3}$ 10.1, $J_{3,4}$ 8.8 Hz, H-3) 5.60 (d, $J_{1,2}$ 3.7 Hz, H-1), 5.45 (s, 1 H, PhCH), 5.41 (t, $J_{2',3'} = J_{3',4'}$ = 9.5 ~ 9.8 Hz, H-3'), 5.39 (d, $J_{1',2'}$ 4.2 Hz, H-1'), 4.91 (dd, $J_{2,3}$ 10.1, $J_{1,2}$ 3.7, H-2), 4.89 (dd, $J_{1',2'}$ 4.2, $J_{2',3'}$ 9.8 Hz, H-2'), 4.25 - 4.18 (m, 2 H, H-5 and 6'), 4.05 (t, $J_{3,4}$ 4.8 Hz, H-4), 3.88 (sx, $J_{4',5'}$ 6.7, H-5'), 3.69 (t, $J_{5',6a'}$ 10.0, $J_{6',6a'}$ 10.3 Hz, H-6a'), 3.62 (t, $J_{3',4'}$ 9.5, $J_{4',5'}$ 9.7 Hz, H-4'), 3.34

(dd, $J_{5,6}$ 2.9, $J_{6,6a}$ 13.5, H-6), 3.22 (dd, $J_{5,6a}$ 6.1, $J_{6,6a}$ 13.5, H-6a); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): δ 170.9, 170.3, 169.9, and 169.6 (MeCO), 156.2, 149.7 (SPh), 136.8, 135.8, 129.8, 129.6, 129.0, 128.1, 126.4, 126.2, 123.0, and 116.9 (Ph), 101.5 (PhCH), 96.6 (C-1), 94.1 (C-1'), 78.7, 75.0, 72.6, 71.2, 70.7, 69.1, 68.5, 68.4 (C-6'), 63.9, 36.5 (C-6).

Anal. calc. for $C_{39}H_{42}O_{14}S$ (766.79): C, 61.08; H, 5.52; S, 4.18. Found: C, 61.30;H, 5.66; S, 4.08.

2-3.15. Phenyl 4',6'-*O*-benzylidene-6-deoxy-α-maltoside (21).

Compound 19 (800 mg) was dissolved in hot ethanol (75 mL) and the solution was then cooled to room temperature before nickel chloride hexahydrate ($NiCl_2$. $6H_2O$, 1.6 g, 5 equiv.) was added. The solution was stirred for another 30 min until all the salt had dissolved. Sodium borohydride ($NaBH_4$, 755 mg, 15 equiv.) was added in portions and the temperature was kept at 25°C. The reaction was complete after 2 h as seen by TLC (Rf 0.66 for 19; Rf 0.61 for product; solvent, 3:17 ethanol-chloroform.). The black precipitate was filtered off and washed with ethanol (50 mL) and ethyl acetate (50 mL). The filtrate was deionized with Amberlite resin IRC-50(H^+) and concentrated to give a pale-gray solid crude product (606 mg) which showed high purity in its ^{13}C-NMR spectrum. The crude product was purified by flash chromatography on silica gel to give 420 mg (64%) of white, solid 20; MS (CI, ether): m/z 491(M^+ + 1), 397(M^+ + 1 - PhOH), 379 (M + 1 - PhOH - H_2O), 251(M^+ + 1 - $C_{12}H_{16}O_5$); ^{1}H (200 MHz, $CDCl_3$): δ 7.70 - 7.10 (m, 10 H, Ph), 5.71 (1 H), 5.63 (PhCH), 5.50 (2 H), 4.50 (1 H), 4.40 - 3.70 (9 H), 3.60 (t, 1 H), 3.30 (t, 1 H), 1.40 (d, 3 H, 6-CH_3); ^{13}C-NMR data (200 MHz, acetone-d_6, ADEPT): δ 158.6, 139.4, 130.6, 129.9, 129.3, 129.1, 127.6, 123.2, 118.0 (Ph), 103.6 (PhCH), 102.5 (C-1), 98.7 (C-1'), 88.4, 82.4, 74.8, 74.7, 73.0, 72.0 (C-6'), 69.4, 67.8,

64.6, 18.3 (6-CH3); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 156.8, 137.1, 129.6, 129.2, 128.3, 126.4, 122.7, 117.1 (Ph), 102.3, 101.8, 97.2 (PhCH, C-1, and C-1'), 87.1, 80.5, 73.7, 73.4, 71.6, 70.8, 68.6 (C-6'), 66.7, 63.3, 17.3 ($6\text{-}CH_3$).

Anal. calc. for $C_{25}H_{30}O_{10}$ (490.49): C, 61.20; H, 6.17. Found: C, 61.31, H, 6.36.

2-3.16. Phenyl 2,2',3,3'-tetra-*O*-acetyl-4',6',-*O*-benzylidene-6-deoxy-α-maltoside (22).

A solution of 21 (49 mg), acetic anhydride (1 mL), pyridine (2 mL), and a catalytic amount of 4-dimethylaminopyridine (DMAP) was stirred overnight at room temperature. The solvent was removed under reduced pressure at room temperature to give a brown oily residue. A solution of the residue in methylene chloride (5 mL) was washed with H_2O (5 mL), concentrated, and applied to preparative TLC, using 1:1 ethyl acetate - hexane as developing solvent, to give 55 mg (84%) of homogeneous, semi-solid 22, $[\alpha]_D$ + 114.1° (c 3.9, chloroform); MS (CI,ether): m/z: 659 (0.9%, $M^+ + 1$), 565 (21%, M^+ - PhO), 505 (M^+ - PhO - HOAc), 335 (100%, 2,3-di-*O*-benzylidene glucopyranosylium ion), 275 (5%, loss of HOAc from mass 335), 231 (17%, 2,3-di-*O*-acetyl-6-deoxyglucopyranosylium ion), 229 (8%, loss of PhCHO from mass 335), 171 (16%, loss of HOAc from mass 231); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40 - 7.00 (m, 10 H, 2 Ph), 5.71 (dd, $J_{2,3}$ 10.2, $J_{3,4}$ 9.1, H-3), 5.56 (d, $J_{1,2}$ 3.5, H-1), 5.48 (s, PhCH), 5.47 (t, $J_{2',3'} \sim J_{3',4'} = \sim 9.8$ Hz, H-3'), 5.37 (d, $J_{1',2'}$ 4.2 Hz, H-1'), 4.91 (dd, $J_{1',2'}$ 4.3, $J_{2',3'}$ 10.3 Hz, H-2'), 4.88 (dd, $J_{1,2}$ 3.6, $J_{2,3}$ 10.2 Hz, H-2), 4.25 (dd, $J_{5',6'eq}$ 4.6, $J_{6'eq,6'ax}$ 10.3 Hz, H-6'eq), 4.07 (dq, w = 27.5 [3 x 6.1 Hz + 9.2 Hz], H-5), 3.96 (dt, $J_{5',6'eq}$ 4.5, $J_{5',6'ax} = J_{4',5'} = 9.6$ Hz, H-5'), 3.74 (~t, $J_{5',6'ax}$ 9.4, $J_{6'eq,6'ax}$ 10.3 Hz, H-6'ax), 3.67 (t, $J_{3,4} \sim J_{4,5} = \sim 9.2$ Hz, H-4), 3.63 (t, $J_{3',4'} \sim J_{4',5'} = \sim 9.6$ Hz, H-4'), 2.10, 2.04, 2.03, 2.01 (4 s, 3 H each, 4 OAc), 1.335 (d, 3 H,

J 5,6 6.1 Hz, 6-CH_3); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): δ 171.1, 170.5, 170.1, 169.8 (C=O), 156.4, 136.7, 129.7, 129.6, 128.3, 126.1, 122.8, 116.7 (Ph), 101.4, 96.5, 94.0 (PhCH, C-1, and 1'), 78.7, 77.9, 72.6, 71.4, 70.6, 68.5, 68.2, 66.1, 63.3, 20.8, 20.6, 20.4, 18.3 (C-CH_3).

Anal. calc. for $C_{33}H_{38}O_{14}$ (658.63): C, 60.17; H, 5.82. Found: C, 59.91; H, 5.81.

2-3.17. Oxidation of 21 with a limited amount of sodium metaperiodate.

A solution of 21 (29 mg, 0.06 mmol) and sodium metaperiodate (11 mg, 0.05 mmol, 0.85 molar equiv.) in methanol (0.5 mL) and water (1.0 mL) was stirred at room temperature for 48 h, with TLC monitoring (Rf 0.27 - 0.38 for product, 0.16 for 21; solvent, 1:19 ethanol - chloroform). An excess amount of ethanol was added to the suspension, to precipitate more salts. The white salt was filtered, and the filtrate was concentrate to give 28 mg of a white residue. This was dissolved in ethanol (5 mL) and reduced by stirring with sodium borohydride (10 mg) during 24 h at room temperature, with TLC monitoring (Rf 0.34 - 0.30 for products, same solvent) The mixture was then stirred with added H_2O (1 mL) and methanol (1 mL) for another 30 min, and evaporated to give a white solid. The product was dissolved in water and extracted into chloroform (3 x 2 mL). The organic layer was filtered through silical gel and flushed with ethanol. After removal of the solvent, 23 mg of residue was obtained, which was acetylated with acetic anhydride (0.2 mL), pyridine (0.3 mL), and a catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature and worked up conventionally giving 30 mg of crude product. The crude product was passed through silical gel column by means of 1:11 ethyl acetate-methylene chloride to give 24 mg of a mixture of

26, 27, and 22 in the ratio of 6 : 2 : 1 according to their 6-CH_3 proton signals in the NMR spectrum.

MS (CI,ether):

Peaks attributed to 26: m/z 567 (10%, M^+ - PhO), 335 (75%, 2,3-di-*O*-acetyl-4,6-*O*-benzylidene glucopyranosylium ion), 179 (69%, phenyl 2-acetoxyethyl ether ion $C_{10}H_{11}O_3$), 131 (22%, 1-*O*-acetyl-1,2-butanediol ion $C_6H_{11}O_3$). Peaks attributed to 27: m/z 567 (10%, M^+ - PhO), 337 (14%, 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-2,3-*seco*-glucopyranosylium ion), 235 (4%), 233 (13%), and 231 (15%) for fragmentation ions $C_{13}H_{15}O_4$, $C_{13}H_{13}O_4$, and $C_{10}H_{15}O_6$ (see Figures 7 and 8 for structures). Unattributed peak : m/z 409 (8%).

Compound 26 had the following ^{1}H-NMR data (500 MHz, $CDCl_3$, COSY): δ 7.47 - 7.00 (m, 10 H, 2 Ph), 5.54 (t, $J_{2',3'} \sim J_{3',4'} = \sim 9.9$ Hz, H-3'), 5.50 (t, $J_{1,2a}$ 4.7, $J_{1,2b}$ 5.9 Hz, H-1), 5.48 (s, PhCH), 5.29 (d, $J_{1',2'}$ 3.9, H-1'), 4.86 (dd, $J_{1',2'}$ 3.9, $J_{2',3'}$ 10.0 Hz, H-2'), 4.32 (dd, $J_{1,2a}$ 4.7, $J_{2a,2b}$ 11.7 Hz, H-2a), 4.28 (dd, $J_{5',6'eq}$ 5.0, $J_{6'eq,6'ax}$ 10.2, H-6'eq), 4.18 (m, 2 H, H-3a, 5'), 4.13 (dd, $J_{1,2b}$ 5.9, $J_{2a,2b}$ 11.7, H-2b), 4.00 (dd, $J_{3b,4}$ 6.4, $J_{3a,3b}$ 11.7 Hz, H-3b), 3.95 - 3.88 (m, 2 H, H-4,5 superposed on signals of minor components), 3.72 (t, $J_{5',6'ax} = J_{6'eq,6'ax} =$ 10.2, H-6'ax), 3.62 (t, > 1 H, $J_{3',4'} = J_{4',5'} = 9.7$ Hz, H-4' superposed on signals of minor components), 2.05, 2.02, 2.00, 1.98 (4 s, 3 H each, 4 OAc), 1.215 (d, 3 H, $J_{5,6}$ 6.0 Hz, C-CH_3); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, ADEPT): δ 170.9, 170.7, 170.5, 169.9 (MeCO), 137.0, 129.8, 129.6, 129.0, 128.3, 128.2, 126.2, 122.7 (Ph), 101.4 (PhCH), 97.8 (C-1), 95.8 (C-1'), 79.1, 77.9, (C-4,4'), 71.9, 71.4 (C-5,5'), 68.7 (C-6'), 68.6 (C-2'), 64.0, 63.8 (C-2,3), 62.6 (C-3', 20.7, 20.5 (OAc), 15.0 (C-CH_3).

Compound 27 had ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.68 (t, $J_{2,3} + J_{3,4} = 19.4$ Hz, H-3), 5.58 (d, $J_{1,2}$ 3.7 Hz, H-1), ~5.50 (s, PhCH), 5.00 (~ t, J ~ 6 Hz, H -1'), 4.90 (dd, $J_{1,2}$ 3.8, $J_{2,3}$ 10.1 Hz, H-2), 4.61 (dd, $J_{3'a,4'}$ 1 - 2, $J_{3'a,3'b}$ 10 - 11 Hz, H-3'a), 4.39 (dd, $J_{5',6'eq}$ 4.7, $J_{6'eq,6'ax} \sim$ 10 Hz, H-6'eq), ~4.3 (H-3'b obscured by

signals of 26), ~4.15 (H-2'a,5' obscured by signals of 26), ~3.9 (H-2'b,4',4,5 in complex m together with H-4,5 of 26), 3.55 (t, splitting 9.4 Hz, H-6'ax), 1.285 (d, J 6.2 Hz, C-CH_3).

Evidence for the presence of 22 and 28 came from small signals which happened not to coincide with those of the major components 26 and 27. For 22: δ 5.70 (t, splitting 10 Hz, H-3), 5.47 (t, splitting 10 Hz, H-3'), 5.37 (d, J ~ 4 Hz, H-1'). For 28: δ 4.97 (dd, H-1'), 4.57 (dd, J ~ 2 and 12 Hz, H-6'a), 4.37 (dd, J ~ 5 and 12 Hz, H -2a), 4.24 (dd, J ~ 6 and 12 Hz, H-3'b). For 22 and 28: δ 4.10 - 4.05 (complex m), 3.62 (t for H-4' of 26 was > 1 H and contained the H-4 and H-4' signals of 22 as well as the H-6'ax signal of 28).

2-3.18. Oxidation of 21 with an excess sodium metaperiodate. Preparation of 6-deoxy tetraaldehyde 25, and its characterization as tetraacetate 28.

An aqueous solution of sodium metaperiodate (350 mg, 1.6 mmol, 4 mL of water) was poured into a methanolic solution (2 mL) of 21 (100 mg, 0.2 mmol). The resulting suspension was stirred at room temperature in the dark for 48 h and the reaction was monitored by TLC (Rf 0.16 for 21, 0.53 - 0.33 for oxidized compounds 23 - 25; solvent, 1:19 ethanol - chloroform). The solvent was removed by evaporation to give a white residue which was dissolved in water (5 mL) and extracted with chloroform (3 x 3 mL). The crude oxidized product (98 mg) was obtained from the extract was chromatographed on a silica gel column using 1:19 ethanol-chloroform, to afford 23 + 24 (9 mg) and 25 (61 mg).

The mixture 23 + 24 (9 mg) was reduced with sodium borohydride (10 mg) in ethanolic solution (1 mL), and the product acetylated subsequently with acetic anhydride (0.3 mL), pyridine (0.3 mL), and a catalytic amount of

DMAP. Processing as described previously afforded a mixture of acetylated compounds 26 + 27, identified by its ^{1}H-NMR spectrum.

Similar reaction and acetylation of the 6-deoxy-tetraaldehyde 25 afforded acetylated product 28 as a semisolid material (54 mg, 78%), R_f 0.70 (1:19 ethyl acetate - methylene chloride), $[\alpha]_D$ - 26.7 (c 1.8, chloroform); MS (FAB): m/z 662 (M^+); MS (CI,ether) see Figure 8; ^{1}H-NMR data (500 MHz, $CDCl_3$): δ 7.40 - 7.00 (m, 10 H, 2 Ph), 5.51 (t, J 5 - 6 Hz, H-1, superposed at δ 5.49 by s for PhCH), 4.96 (dd, $J_{1',2'a}$ 4.5, $J_{1',2b'}$ 5.9 Hz, H-1'), 4.58 (dd, $J_{3a',4'}$ 1.9, $J_{3a',3b'}$ 12.1 Hz, H-3a'), 4.44 (dd, $J_{5',6'eq}$ 5.1, $J_{6'eq,6'ax}$ 10.8 Hz, H-6a'), 4.35 (dd, $J_{1,2a}$ 4.8, $J_{2a,2b}$ 11.7 Hz, H-2a), 4.24 (dd, $J_{3',4'}$ 6.2, $J_{3a',3b'}$ 12.1 Hz, H-3b'), 4.17 (dd, $J_{1,2b}$ 5.9, $J_{2a,2b}$ 11.7 Hz, H-2b), 4.15 - 4.05 (m, H-2a',3a,3b,5'), 3.94 (dd, $J_{1',2b'}$ 6.0, $J_{2a',2b'}$ 11.7 Hz, H-2b'), 3.91 - 3.86 (m, 3 H, H-4,4',5), 3.63 (t, $J_{5',6b'} + J_{6'eq,6'ax}$ = 20.9 [probably 10.1 + 10.8] Hz, H-6ax'), 2.08, 2.05, 2.02, 2.00, (4s, 3 H each, 4 OAc), 1.19 (d, 3 H, $J_{5,6}$ 6.2 Hz, C-CH_3); ^{13}C-NMR data (50.3 MHz, $CDCl_3$, APT): δ 171.0, 170.9, 170.7, 170.6 (MeCO), 137.8, 129.8, 129.1, 128.3, 126.2, 122.7, 117.2 (Ph), 101.1 (PhCH), 99.3 (C-1), 98.3 (C-1'), 78.02 (2 carbon atoms), 73.1, 69.2 (C-6'), 65.7, 64.4, 64.0, and 63.4 (2 carbon atoms) (C-2,3,2', and 3'), 20.7, 20.5, 20.4 (OAc), 14.6 (C-CH_3).

Anal. calc. for $C_{33}H_{42}O_{14}$ (662.67): C, 59.81; H, 6.39. Found: C, 59.82; H, 6.41.

2-3.19. Preparation of 6-deoxy dialdehydes 23 + 24.

An aqueous solution of sodium metaperiodate (65 mg, 0.3 mmol, 2 mL of water) was poured into a methanolic solution (2 mL) of 21 (150 mg, 0.3 mmol). The resulting suspension was stirred at room temperature in the dark for 36 h and the reaction was monitored by TLC (Rf 0.16 for 21, 0.46 - 0.33 for oxidized compounds 23 + 24; solvent, 1:19 ethanol - chloroform). The solvent was

removed by evaporation to give a white residue which was dissolved in water (5 mL) and extracted with chloroform (3 x 3 mL). The crude oxidized product (146 mg) obtained from the extract was chromatographed on a silica gel column using 1:19 ethanol-chloroform, to afford 23 + 24 (125 mg); IR (KBr, pellet, neat): 3400 cm^{-1} (broad) and 1720 cm^{-1} (weak shouder).

The mixture 23 + 24 (20 mg) was reduced with sodium borohydride (25 mg) in ethanolic solution (1 mL), and the product acetylated subsequently with acetic anhydride (0.5 mL), pyridine (0.5 mL), and a catalytic amount of DMAP. Processing as described previously afforded a mixture of acetylated compounds 26 + 27, identified by its ^{1}H-NMR spectrum.

2-3.20. Periodate oxidation of phenyl 4',6'-*O*-benzylidene-α-D-maltoside.

Preparation of tetraaldehyde 10.

To a solution of sodium metaperiodate (1.6 g) in water (10 mL) was added phenyl 4',6'-*O*-benzylidene-α-D-maltoside (5, 500 mg) and ethanol (10 mL). The reaction mixture was stirred at room temperature in the dark. Monitoring by TLC (1:9 ethanol-chloroform) showed a very light spot for starting material, which remain unchanged during another three days. An excess amount of ethanol was poured into the reaction mixture and the resulting salt precipitate filtered off. The filtrate was evaporated to dryness, the white solid was suspended in ethanol, and the undissolved material was removed. This process was repeated three times. The product so obtained was then purified through a silical gel column by use of 1:49 ethanol-choloroform as eluent, to give 421 mg tetraaldehyde 10 (73%, if calculated for a bis-hemialdal with ethanol); IR (KBr pellet, neat): 3400 cm^{-1}(broad) and 1710 cm^{-1} (weak shoulder). Twenty milligram of this product was subsequently reduced

by sodium borohydride. Processing as described previously afforded 13, identified by its ^{13}C-NMR spectrum.

2-3.21. Reaction of tetraaldehyde 10 and one equivalent of nitromethane in the presence of potassium fluoride.

A solution of tetraaldehyde 10 (160 mg, 0.27 mmol of bis-hemialdal), nitromethane (17 μl, 0.31 mmol), dibenzo-18-crown-6 (11 mg, 0.03 mmol), potassium fluoride (9 mg, 0.155 mequiv.) in 2-propanol (2.0 mL) was stirred at 40°C for one day and at room temperature for five days. Monitoring of the reaction by TLC failed due to long tailing of spots. The solvent was then evaporated to give a brown residue which was subjected to silical gel column filtration by elution of ethanol. The crude product (152 mg) eluted from the column was allowed to react overnight with sodium borohydride (100 mg) in ethanol (10 mL). The ethanolic solution was neutralized with Amberlite IR-120(H^+) ion exchange resin and then filtered and evaporated to give 121 mg of a brown residue after oil pump drying. The reduced crude produced was treated with acetic anhydride (0.5 mL), pyridine (0.5 mL), and a catalytic amount of DMAP. The mixture was stirred overnight and worked up conventionally to give 95 mg of acetylated crude product. After complete drying, the acetates showed no IR absorption for the nitro group in the 1550 cm^{-1} region, and elemental analysis indicated the incorporation of only 10% of the theoretically required amount of nitrogen.

2-3.22. Reaction of tetraaldehyde 10 and excess nitromethane in the presence of potassium fluoride.

A solution of tetraaldehyde 10 (140 mg, 0.24 mmol of bis-hemialdal), nitromethane (0.1 mL, 1.85 mmol, 7.7 molar equiv.), dibenzo-18-crown-6 (10

mg), and potassium fluoride (8 mg) in 2-propanol (2.0 mL) was stirred at 40 - 45 °C for one day and at room temperature for another seven days. The subsequent process of reduction and acetylation was carried out in the same manner as in the previous experiment. The IR spectrum of the final product showed no nitro group absorption; microanalysis showed less than 4% of the theoretical nitrogen content.

2-3.23. Reaction of tetraaldehyde 10 and excess nitromethane in the presence of sodium methoxide.

A solution of tetraaldehyde 10 (65 mg, 0.11 mmol of bis-hemialdal), nitromethane (46 µl), and sodium methoxide (20 mg of Na in 1.0 mL of methanol) was stirred at room temperature for five days. The methanolic solution was deionized with Amberlite IR-120(H^+), filtered, and evaporated to give a residue that weighed 51 mg after drying. The IR spectrum showed bands at 1719 and 1557 cm^{-1}. The residue was treated with sodium borohydride (50 mg) in ethanol (2 mL) by stirring overnight at room temperature. The solution was treated with Amberlite IR-120(H^+), filtered and coevaporated several times with methanol. The dried product weight 45 mg and showed an IR band at 1558 cm^{-1}. The crude product was subjected to acetolysis in two ways: a), by treatment with acetic anhydride (1 mL), glacial acetic acid (0.5 mL), and hydrochloric acid (catalytic amount); and b), by treatment with acetic anhydride (1 mL), glacial acetic acid (0.5 mL), and sulfuric acid (catalytic amount). Both reactions were allowed to proceed at room temperature for two days and the mixtures worked up by conventional processing. The brown crude products were analyzed by both FAB and CI mass spectrometry which did not show the expected fragmentation patterns.

2-3.24. Reaction of tetraaldehyde 10 and one equivalent nitromethane in the presence of sodium methoxide.

The processes were carried out in the same manner as described above. The crude cyclic product showed IR band at 1728 (strong) and 1556 cm^{-1} (medium) whereas the reduced product gave absorptions at 1729 (weak), 1643 (strong), and 1554 cm^{-1} (medium). The product of the acetolysis also did not show the expected fragmentation patterns.

2-3.25. Reaction of 6-deoxy dialdehydes 23 + 24 and nitromethane in the presence of potassium fluoride. The formation of 43 and 44.

A solution of dialdehydes 23 + 24 (77 mg, 0.153 mmol), potassium fluoride (10 mg), dibenzo-18-crown-6 (10 mg), and nitromethane (0.2 mL, 3.7 mmol) in 2-propanol (0.8 mL) was heated at 50°C for two days with stirring. The reaction mixture was filtered through silical gel and evaporated, to give 81 mg of a light brown syrupy residue; IR (neat): 1596 (medium), and 1556 (strong) cm^{-1}; MS (FAB): m/z at 550, 310, 251, 235, and 217.

The residue was acetylated in acetic anhydride containing trifluoroboron etherate. Conventional processing gave a material that appeared incompletely acetylated and partially debenzylidenated, according to its IR and ^{13}C-NMR spectra.

2-3.26. Reaction of 6-deoxy dialdehydes 23 + 24 and nitromethane in the presence of sodium methoxide.

A solution of dialdehydes 23 + 24 (246 mg, 0.49 mmol), nitromethane (0.6 mL), and sodium methoxide (24 mg of Na in 2 mL of methanol) was kept at room temperature for three days. The solution was neutralized with Amberlite IR-120 (H^+) ion exchange resin, filtered through Celite and silical

gel, and decolorized with activated carbon, to give 255 mg of a brown residue after solvent removal. IR (neat , KBr pellet): 3385 and 1557 cm^{-1}. MS (FAB): m/z at 550, 310, 251, and 217.

The cyclized product was divided into two portions. One was subjected to debenzylidenation and acetylation, and the other was subjected to acetolysis.

Debenzylidenation and Acetylation. The debenzylidenation was carried out by treating the cyclized product (50 mg) with 90% trifluoroacetic acid (1 mL) at 0 - 15°C for 30 min until the slow-moving spots remained unchanged in TLC (1:4 ethanol-methylene chloride). The trifluoroacetic acid was removed by evaporation under reduced pressure and the benzaldehyde by several co-evaporation with water. The brown residue was completely dried at 40°C (it gave peaks at 179 and 163 in CI-MS), treated with acetic anhydride (1 mL) and trifluoroboron etherate (one droplet) at 0°C. The reaction mixture was kept overnight at -18°C. The reagent was evaporated under reduced pressure at room temperature, and the remaining residue was dissolved in methylene chloride (3 mL) and washed with water, to give 68 mg of crude acetylated product after solvent removal and drying. IR (KBr pellet, neat): 1751 and 1563 cm^{-1}. MS (FAB): m/z 620 (9%, $M^+ + 1$ - PhOH), 390 (7%), and 331 (74%); MS (CI, ether): m/z 714 (1.1%, $M^+ + 1$), 620 (98%, $M^+ + 1$ - PhOH), 390 (25%), and 331 (100%).

Acetolysis (Formation of acetylated fragments 50, 51, 39, and 52). The acetolysis of the cyclied product was carried out in the same manner as described in **2-2.23.**. The mass spectral data are presented in Figure 12.

2-3.27. Reaction of 6-deoxy tetraaldehyde 25 and one equivalent nitromethane in the presence of potassium fluoride. Formation of 45 - 47.

Tetraaldehyde 25 (95 mg, 0.16 mmol of bis-hemialdal), potassium fluoride (6 mg), dibenzo-18-crown-6 (6 mg), and nitromethane (10 μl, 0.185 mmol) in 2-propanol (1.2 mL) were stirred at 50°C for five days. The solvent was evaporated to give 112 mg of residue, 80 mg of which was treated with sodium borohydride (100 mg) in 3 : 1 ethanol-methylene chloride (2 mL). The solution was stirred overnight, then neutralized with Amberlite IR-120(H^+) ion exchange resin, filtered, and evaporated with added methanol (3 x 2 mL), to give 69 mg of a yellow solid after silical gel filtration (1:19 ethanol - chloroform); IR (neat) 1554 cm^{-1}; MS (FAB): see Figures 13a - 13c.

2-3.28. Reaction of 6-deoxy tetraaldehyde 25 and one equivalent nitromethane in the presence of sodium methoxide. Formation of 45 - 47.

Sodium methoxide (20 mg of Na in 4.0 mL of methanol) was added to a solution of tetraaldehyde 25 (386 mg, 0.66 mmol of bis-hemialdal), and nitromethane (43 μl, 0.8 mmol) at 0 °C. The reaction mixture was kept at 0 - 5°C for three days, then neutralized with Amberlite IR-120(H^+) ion exchange resin at 5°C. After filtration and evaporation of the solvent, 410 mg of a brown residue was obtained. The residue was dissolved in ethanol (20 mL) and reduced by portionwise addition of sodium borohydride (300 mg) at 0°C. After stirring the mixture at room temperature for 24 h, and neutralizing it with Amberlite IR-120(H^+) ion exchange resin, the filtered solution was passed through silical gel with 1:1 ethanol - methylene chloride as an eluent. There was obtained 405 mg of a light brown residue; IR (KBr, neat): 1598 cm^{-1}; MS (FAB): m/z see Figures 13a - 13c.

Acetolysis. One drop of sulfuric (or hydrochloric) acid was added to a cooled solution of residue obtained from above (20 mg), acetic anhydride (0.3 mL), and glacial acetic acid (0.1 mL) at 0°C. The solution was gradually warmed to room temperature and allowed to stand for two days, with TLC monitoring, until fast-moving spots remained unchanged. Cold water (0.5 mL) was added and the mixture was extracted with methylene chloride (2 x 0.5 mL). The organic phase was then washed with saturated sodium bicarbonate solution (0.5 mL), 5% hydrochloric acid (0.5 mL), and water (0.5 mL), then evaporated to dryness, giving a brown oil which was subjected to MS analysis (see Figure 15).

2-3.29. Reaction of 6-deoxy tetraaldehyde 25 and excess nitromethane in the presence of potassium fluoride. Formation of 48 and 49.

Tetraaldehyde 25 (174 mg, 0.3 mmol of bis-hemialdal), potassium fluoride (11 mg), dibenzo-18-crown-6 (11 mg), and nitromethane (50 μL, 0.9 mmol) were stirred in 2-propanol (2.0 mL) at 50 °C for three days. The solvent was removed by evaporation to give a light brown residue which after silical gel chromatography (1:9 ethanol-chloroform) furnished 104 mg of a white solid, Rf 0.26 - 0.13 (same solvent); IR (KBr pellet, neat): 3419 and 1556 cm^{-1}. The FAB mass spectral data are presented in Figure 14.

2-3.30. Reaction of 6-deoxy tetraaldehyde 25 and excess nitromethane in the presence of sodium methoxide. Formation of 48 and 49.

A solution of tetraaldehyde 25 (509 mg, 0.875 mmol of bis-hemialdal), nitromethane (0.15 mL, 2.70 mmol, 3.2 molar equiv.), and sodium (61 mg) in methanol (6.0 mL) was stirred for 3 h, at a temperature of below 10°C initially and then gradually raised to room temperature. The reaction was monitored

by TLC (Rf 0.25 - 0.68 at the end of reaction; Rf 0.41 - 0.50 for starting 25; solvent, 1:19 methanol-methylene chloride). The solution was neutralized by Amberlite IR-120(H^+) in an ice-bath and filtered. The filtrate was evaporated and dried under reduced pressure (oil pump) to give a brown residue which was dissolved in methylene chloride (10 mL), decolorized by activated carbon, and filtered through silical gel. The silical gel was washed with 1:4 ethanol-methylene chloride (20 mL). The combined filtrate was evaporated to give 520 mg of a yellowish brown residue; IR (KBr pellet, neat): 1594 and 1557 cm^{-1}. The FAB mass spectral data are presented in Figure 14.

Debenzylidenation and acetylation. Formation of 55 and 56. Part of the material (400 mg) was stirred with 8 mL of 90% trifluoroacetic acid at 0-10°C for 1 h. The reaction was monitored by TLC (1:9 methanol-methylene chloride) which showed formation of products, with no change after 45 min. The reaction mixture was then coevaporated several times with water at 35 - 40°C under reduced pressure to remove the acid and benzaldehyde. After thorough drying, the brown residue (331 mg) of crude debenzylidenated product was treated with acetic anhydride (8 mL) and trifluoroboron etherate (two droplets) at a temperature between 0°C (initially) and 25°C, until the fast-moving spots produced did not change further (Rf 0.65-0.55, 1:1 hexane-ethyl acetate). Water (5 mL) was then poured into the reaction mixture, and the mixture was extracted with methylene chloride (10 mL). The organic phase was washed with saturated sodium bicarbonate solution (5 mL), 5% hydrochloric acid (5 mL), and water (10 ML), dried over sodium sulfate, decolorized with activated carbon, and evaporated to give 417 mg of a brown, oily residue, IR (KBr pellet, neat): 1755 and 1563 cm^{-1}. The FAB mass spectral data are given in Figures 16a and 16b and the accompanying Table 2.

Dehydroacetoxylation. Formation of 57. The debenzylidenated-acetylated product (270 mg) and sodium borohydride (500 mg) were suspended in 99% ethanol (15 mL) and stirred at room temperature for 36 h, with TLC monitoring (3:7 ethyl acetate-methylene chloride) until no more changes occurred. Methanol (3 x 5 mL) was added to, and evaporated from, the yellowish white residue which was then dissolved in methanol (20 mL) and neutralized with Amberlite IRC-50(H^+) ion exchange resin. The solution was filtered and evaporated to give 97 mg of a solid product which was passed through a silical gel column with ethanol-methylene chloride (1:19,gradually increased to 1:1). This resulted in 59 mg of a mixture of products that showed more than four spots in TLC (Rf 0.35, 0.22, 0.14, and 0.1 - 0.05 with 2 : 5 of ethyl acetate-methylene chloride; Rf 0.66 - 0.57, 0.50 - 0.38 with 1:19 ethanol-methylene chloride). Flash chromatography of the product gave four fractions amounting to 41, 8, 3, and 6 mg of materials, all of which showed a nitro group band in the IR spectrum (1550, 1551, 1550, and 1551 cm^{-1}, respectively). The major fraction, characterized as four disaccharidic diastereoisomers (two of them as major components) of phenyl 5-*O*-(2,3,4-trideoxy-3-nitro-α-*D*-heptoseptanosyl)-2,3,4,7-tetradeoxy-3-nitro-α-*D*-heptoseptanosides (57), crystallized from $CDCl_3$ after prolonged standing: ^{1}H-NMR data (500 MHz, $CDCl_3$, COSY): δ 7.30 - 6.95 (m, Ph), 5.70 - 5.50 (2t, H-1), 5.20 - 5.10, 4.83 - 4.62 (m, H-3 and 3'), 5.09 - 5.00, 4.62 - 4.53(m, H-1'), 4.12 - 3.50 (m, ring protons), 2.96 - 1.88 (m, H-2,2',4, and 4'), 1.03 - 1.00 (CH_3); ^{13}C-NMR (75.4 MHz, $CDCl_3$, ADEPT): δ 156.5-116.4 (Ph), 95.3-93.7 (8 anomeric carbon atoms), 78.6-78.0 (8 nitro $CHNO_2$ carbon atoms), 74.9-67.5 (primary carbon atoms), 64.0-63.7 (4 C-6' carbon atoms), 42.0-34.1 (16 C-2,2',4,4' secondary carbon atoms), 19.6-18.9 (4 CH_3 carbon atoms); MS (FAB): see Figure 17.

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Chapter 3

Nitromethane Cyclization of 6-Deoxycyclodextrin Polyaldehyde.

3-1. Introduction

Cyclodextrins are oligosaccharides consisting of at least six glucopyranose units which are joined together by α (1 → 4) linkages[1]. Although cyclodextrins with up to 12 glucose residues are known[2,3], only the first three homologs have been studied extensively. The oligosaccharide ring forms a torus with the primary hydroxyl groups of the glucose residues lying on the narrow end of the torus. The secondary hydroxyl groups are located in the wider end.

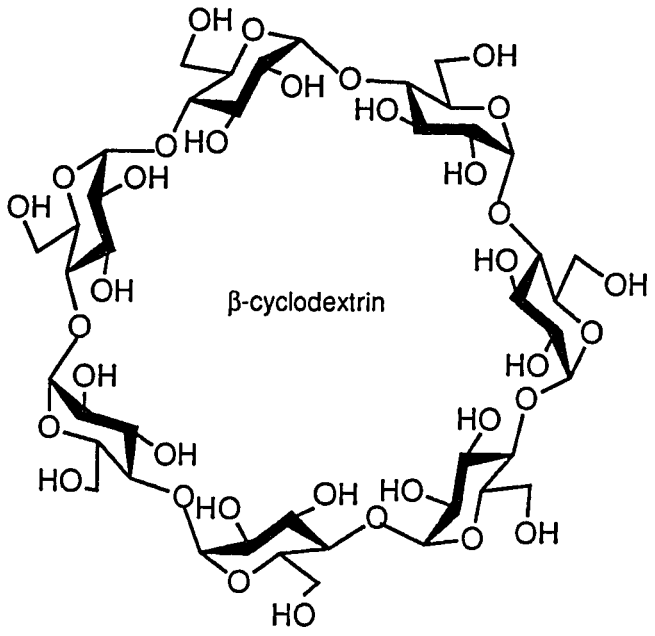


Figure 1. β-Cyclodextrin.

The initial discovery of cyclodextrins is attributed to Villiers[4], who isolated them as degradation products of starch. In 1904, Schardinger[5] demonstrated that these compounds could be obtained by the action of *Bacillus macerans* amylase upon starch. The cyclodextrins have neither a reducing nor a nonreducing end group and are therefore not degraded by yeast fermentation or the α-amylase enzyme.

β-Cyclodextrin (β-CD, Figure 1) is the second in a series of six cyclodextrins labeled α to η which consist respectively of 6 (α) to 12 (η) α-D-glucopyranose units. The 7.8 Å cavity[5], large enough to incorporate a benzene ring, is lined with the electron rich-glucosidic bridging oxygens and has a slightly hydrophobic, apolar character.

Cyclodextrins having fewer than six α-D-glucopyranosyl units are unknown, probably because of steric reasons[7]. As a consequence of the $^4C_1$ conformation of the α-D-glucopyranosyl units and the lack of free rotation about the glycosidic bonds, the compounds are not perfectly cylindrical molecules, but are somewhat cone-shaped, with all of the secondary hydroxyl groups situated at one end of the annulus and all of the primary hydroxyl groups at the other. The cavity is lined by a ring of hydrogen atoms (bonded to C-5), a ring of D-glucosidic oxygen atoms, and another ring of hydrogen atoms (bonded to C-3), thus making the cavity relatively apolar. The shape of the molecule is stabilized by hydrogen bonds between the secondary hydroxyl groups of adjacent D-glucopyranosyl units.

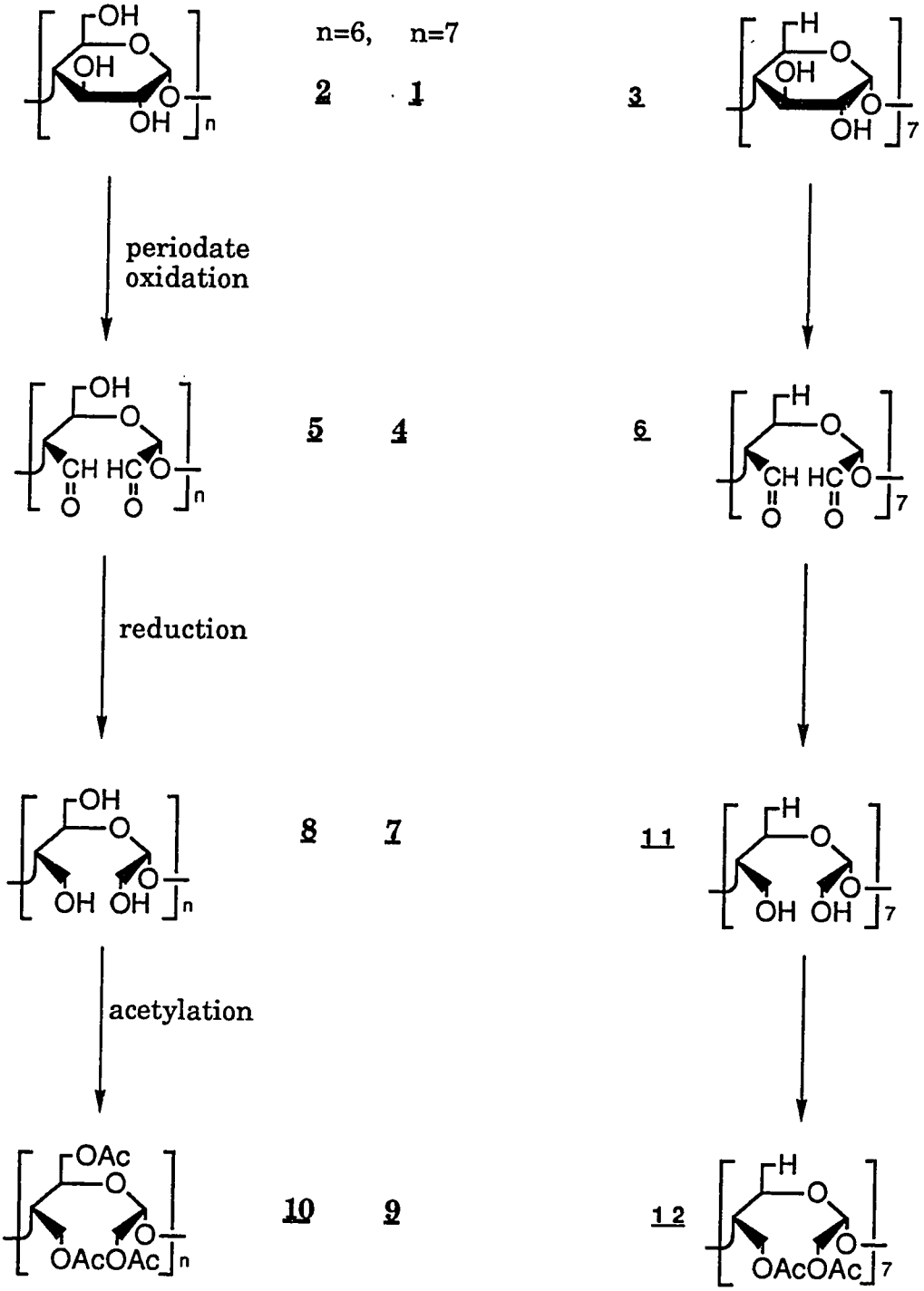
The great utility of this molecule derives from its ability to form an abundance of crystalline inclusion complexes[8,9]. For example, 2-propanol added to an aqueous solution of β-CD displaces the water from the cavity[10,11], affording an inclusion complex which may be crystallized. The potential applications of such a molecule are wide. Unstable compounds may be

encapsulated in a cyclodextrin and be protected from oxidation by atmospheric oxygen (*eg.*, vitamin A)[12]. A liquid drug may often be crystallized as a β-CD complex (i.e., nitroglycerin, used to treat angina pectoris, has been crystallized as a β-CD complex which may be rendered in tablet form and is also reported to be suitable for use as an explosive). The specific size of the cavity and the easily modified hydroxyl groups make it suitable for polymerization to produce resins of specialized properties.

Cyclodextrin stabilizes a large number of different compounds in liquid and in solid state. In some cases, however, the surrounding hydroxyl groups and the apolar cavity will exert specific catalytic effects[13,14]. This makes cyclodextrins suitable for generating enzyme models[15]. The main areas of industry where cyclodextrins are finding applications are in food, pharmaceuticals[16], organic chemical production, and cosmetics.

Many of the synthetic derivatives obtained from cyclodextrins have also found wide application in industry. Most of the synthetic derivatives are a result of substitution of the hydroxyl groups[17,18]. Thus, often, the solubility in water decreases even though the complexing ability of the molecule may be enhanced.

The synthesis of novel, modified cyclodextrins and the study of their complexing ability is therefore an ongoing concern. In this regard it appeared interesting to investigate analogs that bear nitrogenous functions, particularly nitro or amino groups, on secondary positions of the glucose units. For the purpose of this thesis, the applicability of the nitromethane cyclization process for incorporation of nitrogen into sugar molecules was to be investigated.



Scheme 1. Periodate oxidation of cyclodextrins.

Periodate oxidation of 1 is known to give the polyaldehyde 4[19]. The course of the reaction was examined by measurement of the consumption of periodate and by the change in optical rotation. The IR and ^{13}C-NMR spectra data of polyaldehyde 5 were recorded[20].

Periodate oxidation of β-CD (1) and α-CD (2), followed by borohydride reduction and acetylation, yielded the macrocycles 2s,4S,5R,7s,9S,10R,12s, 14S,15R,17s,19S,20R,22s,24S,25R,27s,29S,30R,32s,34S,35R-heneicosaacetoxy-methyl-1,3,6,8,11,13,16,18,21,23,26, 28,31,33-tetradecaoxacyclopentatriacontane (9) and 2s,4S,5R,7s,9S, 10R,12s,14S,15R,17s,19S,20R,22s,24S,25R,27s,29S, 30R-octadecaacetoxymethyl-1,3,6,8,11,13,16,18,21,23,26,28-dodecaoxacyclotriacontane (10), respectively[19]. These cyclic polyacetals were obtained crystalline (Scheme 1).

Research on the use of nitromethane chemistry in cyclodextrin was initiated some years ago jointly in the laboratories of Baer and Defaye (Grenoble, France), who published a detailed paper[21] concerning the formation, in monosaccharidic model compounds, of seven-membered nitro sugar rings such as might be expected to arise in nitromethane cyclization of 4. However, only preliminary studies were undertaken with 4 itself. Thus nitromethane cyclizations of polyaldehyde 4 to give a "nitro-β-CD" were performed by McGarry[22]. The cyclizations were carried out in the presence of sodium bicarbonate or barium hydroxide in aqueous solution. Yields of up to 70 % of nitro products were achieved, with microanalysis showing nitrogen contents of 3.9 - 5.2 % (theory: 6.3 %).

The "nitro-CD" was reduced to "amino-CD", and various experiments involving hydrolysis, methanolysis, and acetolysis of the products to give monosaccharidic fragments were performed in the hope of obtaining evidence for the structure, but no final conclusions were reached in this regard. The

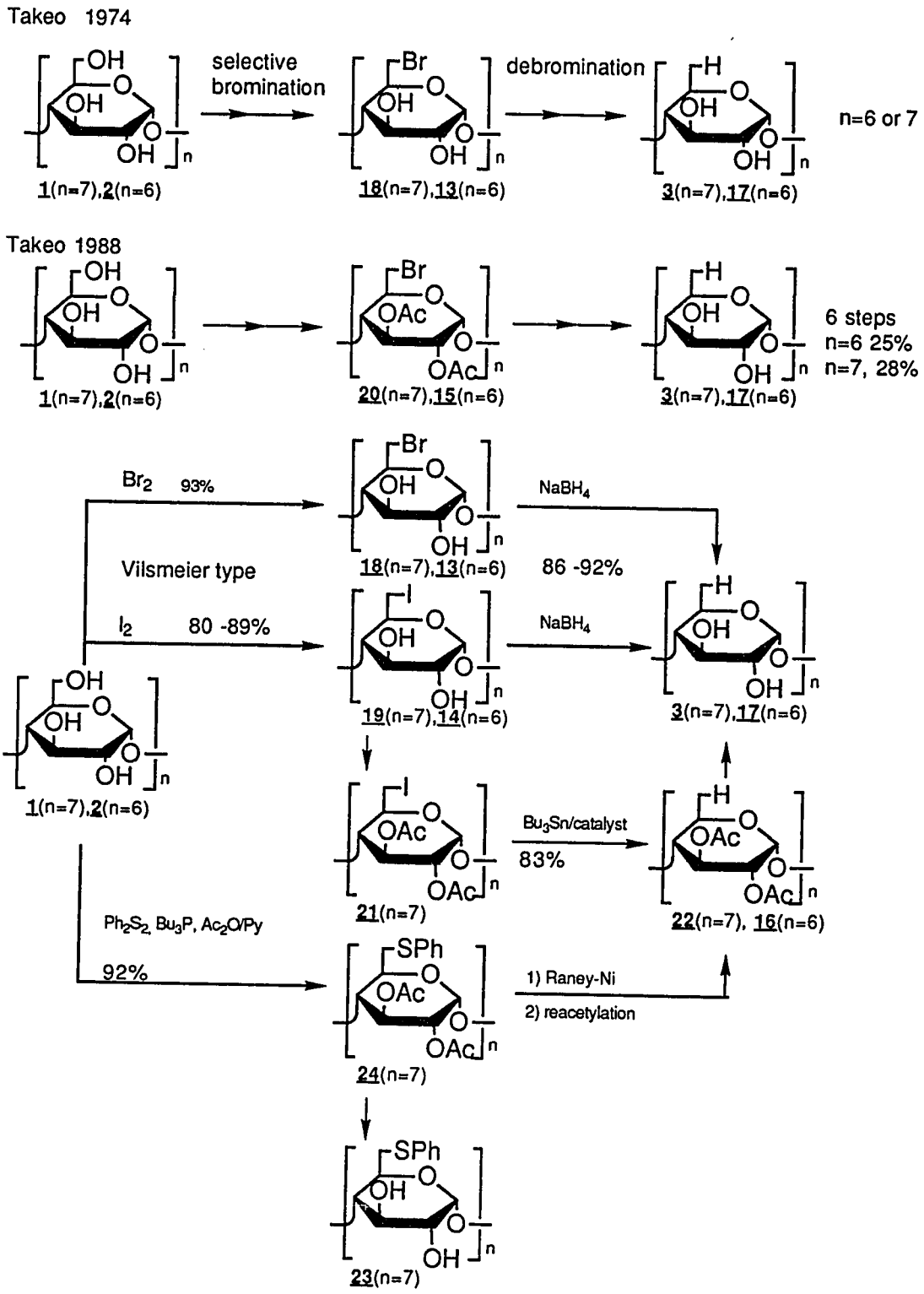
project is currently being pursued in the Grenoble laboratory, where a parallel investigation dealing with analogous introduction of nitrogen functions into starch and cellulose is also underway[23]. The aim of the present thesis was to extend the study to heptakis-6-deoxy-β-cyclodextrin (3, 6-CH_3-β-CD).

3-2. Results and Discussion

The deoxy derivative 3, officially called heptakis(6-deoxy)-cyclomaltoheptaose, has first been prepared by Takeo and coworkers[24] from β-CD 1 by selective bromination at C-6 positions with methanesulfonyl bromide in *N,N*-dimethylformamide, followed by reductive debromination of the peracetates with sodium borohydride in dimethyl sulfoxide. Yields were high, but deoxygenation was not entirely complete. More-recent approaches to 3 and its α-CD homolog 17 led[25,26] to their per-*O*-acetyl derivatives 22 and 16 in 6 steps from 2 and 1, respectively, with 25 and 28 % overall yields (Scheme 2.).

3-2.1 Preparation of 6-Deoxy Cyclodextrin Analogs.

It was found that unprotected cyclodextrins can be directly halogenated in the 6-position, with high yields, by Vilsmeier-type reagents arising from interaction of bromine or iodine with triphenylphosphine and *N,N*-dimethylformamide, used *in situ*[27]. Thus, direct bromination of 2 at 80°C during 15 h gave a 93 % yield of crystalline, analytically pure hexakis(6-bromo-6-deoxy)cyclomaltohexaose (13). The same procedure applied to 1 gave the heptakis(6-bromo-6-deoxy) analog 18 in the same yield, and the corresponding hexakis- and heptakis(6-deoxy-6-iodo) derivatives 14 and 19 were obtained in yields of 80 and 89 %, respectively, by use of iodine instead of



Scheme 2. Preparation of 6-deoxy cyclodextrins.

bromine[27]. The products were characterized by microanalysis, FAB mass spectra (in which they showed the expected molecular-ion peaks), and ^{13}C-NMR spectra (in which each displayed only one set of signals for C-1 to C-6, as required by the six- and seven-fold symmetries of uniformly hexa- and hepta-substituted α- and β- cyclodextrins).

In attempts to effect reductive debromination in 13 and 18 by means[28] of sodium borohydride in dimethyl sulfoxide, Takeo and coworkers[24] reported to have encountered practical difficulties; they therefore performed the reductions on the per-*O*-acetylated bromides, which necessitated subsequent deacetylation of the 6-deoxy products. In our hands the direct reductive dehalogenation of the both bromides 13 and 18 and the iodides 14 and 19 by treatment with the reductant mentioned proceeded very well (24 h at 100°C), furnishing the target compounds 17 and 3 in yields of 86 - 92 %.

In an alternative approach (Scheme 2), the heptakis(6-deoxy-6-iodo) compound 19 was conventionally acetylated to give the previously-described[26,29], crystalline peracetate 21 in 84 % yield. This had been converted[26] into 22 by overnight catalytic hydrogenation (83%). We performed its reduction with tributyltin hydride in refluxing toluene, which was complete within 45 min and, after chromatographic purification, afforded similar yields (81 - 89%) of 22, suitable for conversion into 3[30].

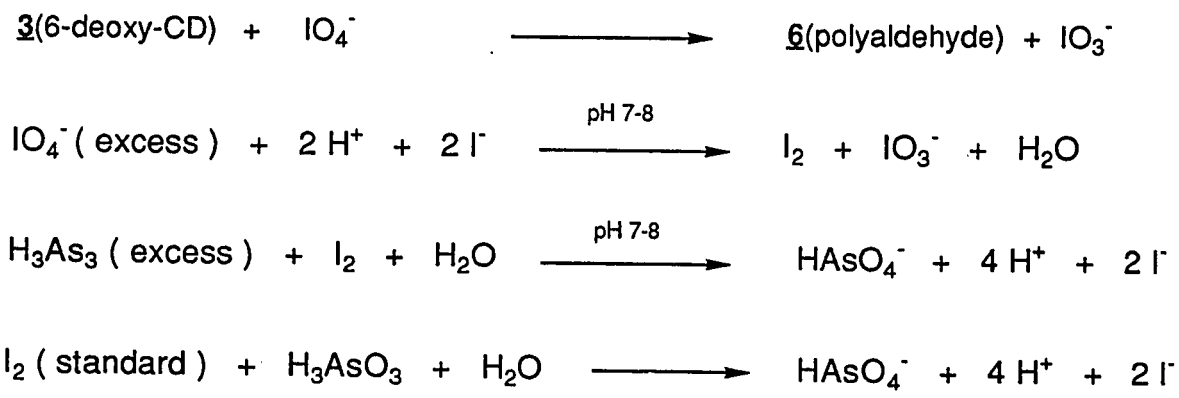
A further route to 3 was elaborated by application of a method recently used successfully in monosaccharide chemistry[31], namely, the selective phenylthio substitution of primary hydroxyl groups achievable with diphenyl disulfide in the presence of tributylphosphine and pyridine[32]. Treatment of 1 with that reagent at room temperature for 48 h gave heptakis(6-deoxy-6-*S*-phenyl-6-thio)cyclomaltoheptaose (23), isolated in 92% yield as its crystalline per-*O*-acetyl derivative 24. A sample of 24 was deacetylated (Zemplén) to

furnish crystalline 23 for analytical characterization. The ^{13}C-NMR spectra of both 23 and 24 gave no evidence of nonuniformity with respect to substitution; each showed only one set of glucopyranoside and substituent signals, in line with a seven-fold molecular symmetry. Compound 24 was then reductively desulfurized with Raney nickel. The process was slow (3 - 4 days at 30 kPa of H_2 pressure, or 8 to 9 days at ordinary pressure), but it did afford 22 in 88 % yield after reacetylation of the crude product (that had suffered some loss of acetyl), and chromatographic purification. Compound 22 was thus obtained from 1 in 81 % overall yield.

When a solution of 22 in methanol was treated with sodium methoxide for deacetylation, part of the 3 produced appeared rapidly as a precipitate, and part of it was obtained after deionization by cation exchange and evaporation of the supernatant. Whereas the latter part was analytically pure, the former contained sodium as evidenced by microanalysis and mass spectrometry. (Similar observations were made in the aforementioned deacetylation of 15). However, the sodium was readily removed by reprecipitation of the material from dimethylsulfoxide solution with aqueous hydrochloric acid, or by deionization of such a solution followed by reprecipitation with water.

3-2.2. Sodium metaperiodate oxidation of 6-CH_3-β-CD.

Oxidative cleavage of the C-2,3 bonds in the 6-deoxy-*D*-glucose units of 6-CH_3-β-CD 3, performed in aqueous solution with an excess of sodium metaperiodate, gave polyaldehyde 6 (Scheme 1). The consumption of periodate was monitored by iodometric titration[33] as shown in Equation 1.



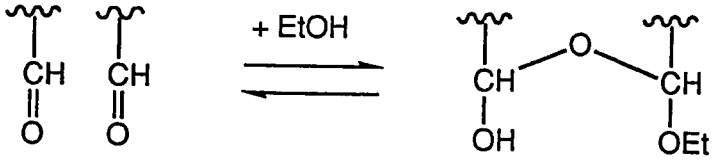
Equation 1. Iodometric titration method to monitor the consumption of 3.

Table 1. The amount of reagents used and products obtained in the periodate oxidation of 6-deoxy cyclodextrin 3 and nitromethane cyclization of 6.

	Experiment 1	Experiment 2	Experiment 3	Experiment 4
mg(mmol) of 3	372(0.36)	339(0.33)	275(0.27)	445(0.44)
mg(mmol) of 6[a]	432(0.32)	428(0.32)	353(0.26)	612(0.46)
mL(mmol) of nitromethane	0.27(5.0)	0.27(5.0)	0.20(3.7)	0.27(5.0)
mg(mmol) of Na	70(3.0)	70(3.0)	40(1.74)	100(4.35)
mL of MeOH	20	20	15	30
reaction time(day)	3	10	7	5
yield(%) of crude[b]	110	103	97	101
yield(%) of ppt	68	63	62	61
% of N found	6.71	10.98(10.88)[c]	13.34	10.24
% of N calcd.	6.8			

a: the number of mmole in parentheses is calculated on the basis of 6-7 EtOH adduct.
b: on the basis of 3.
c: residue of mother liquor.

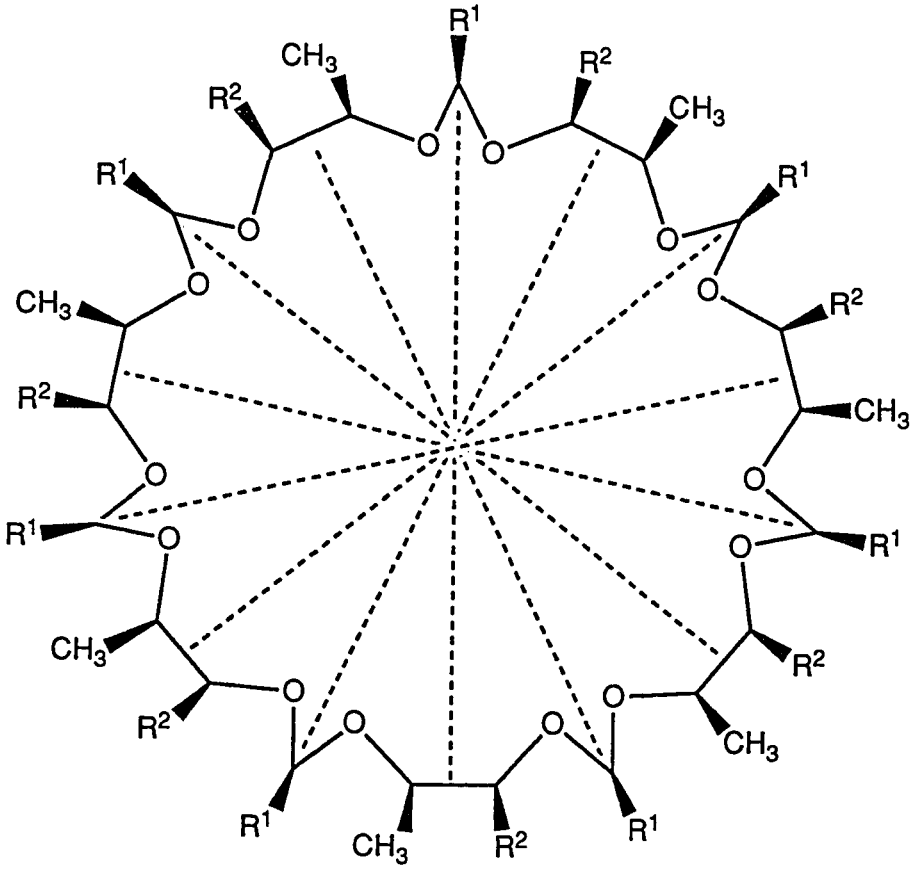
It was found that the oxidation was very slow, coming to an end after approximately 50 h (see plots in Experimental). The water was evaporated and the polyaldehyde 6 was then extracted with ethanol. For isolation of the oxidation product the water was evaporated and the polyaldehyde extracted from the salt residue with ethanol. The weight of the dried, extracted material was greater than that of the 3 used (see Table 1), although 6 has nearly the same molecular weight. However, sugar dialdehydes are known[34,35] to exist as hydrates or, when obtained from alcoholic solutions, as hemialdals such as shown below:



Indeed, the polyaldehyde 6 as isolated displayed only a very weak carbonyl absorption at 1728 cm^{-1}, but a strong hydroxyl band at 3388 cm^{-1} in its IR spectrum. It can therefore be assumed to have been obtained largely as a poly (ethyl hemialdal). This was of no concern as hemialdal formation is readily reversible under the conditions of the planned reactions.

Success of the oxidative cleavage was confirmed by reduction of 6 with sodium borohydride and subsequent acetylation, yielding 51% of the macrocyclic polyacetal 12 (Figure 2). The low yield may have been due partly to losses of substance during drying at 65°C in high vacuum where it was surprisingly volatile.

The cyclic acetal was fully characterized by IR, ^{13}C- and ^{1}H-NMR, COSY experiment, ADEPT experiment, and microanalysis.



12

$R^1 = R^2 = CH_2OAc$, with R^1 and R^2 incorporating C-2 and C-3, respectively, of the original 6-deoxyglucopyranoside units.

note: Replacement of the seven CH_3 groups by $R = CH_2OAc$ yields a representation of **9**.

Figure 2. 2R,4R,7R,9R,12R,14R,17R,19R,22R,24R,27R,29R,32R,34R-tetradeca-acetoxymethyl-5R,10R,15R,20R,25R,30R,35R-heptamethyl-1,3,6,8,11, 13,16,18,21,23,26,28,31,33-tetradecaoxacyclopentatriacontane **12**.

A: protons on C-2, 7, 12, 17, 22, 27, and 32.

B: protons on C-4, 9, 14, 19, 24, 29, and 34.

C and C': $\underline{CH_2}OAc$ of R^2.

D and D': $\underline{CH_2}OAc$ of R^1.

E: protons on C-5, 10, 15, 20, 25, 30, and 35.

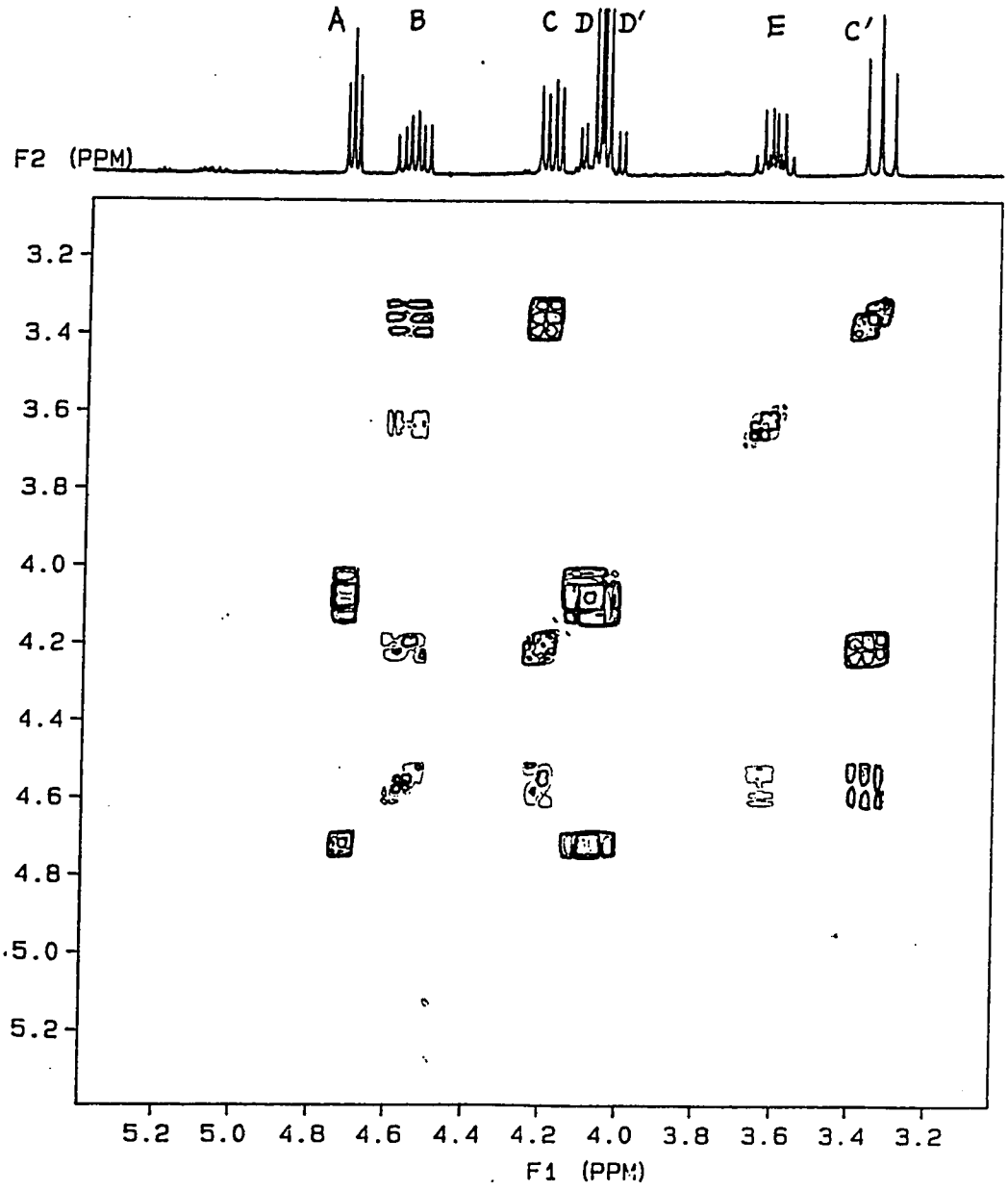


Figure 3. COSY plot of macrocyclic polyacetal 12.

The ^{1}H-NMR spectrum showed a low-field triplet at δ 4.72 (J = 4.3 and 4.9 Hz) for the equivalent acetal protons at C-2, 7, 12, 17, 22, 27, and 32. Two doublets of doublets of equal intensity at δ 4.12 (J = 4.3 and 11.7 Hz) and 4.05 (J = 4.9 and 11.7 Hz) were assigned to the acetoxymethyl protons ($\underline{CH_2}OAc$) of the R^1 groups. A multiplet at δ 4.56 (J = 10.1, 5.2, and 9.5 Hz) was due to the equivalent ring protons at C-4, 9, 14, 19, 24, 29, and 34. Two signals of equal intensity at δ 4.21 (J = 10.5 and 5.2 Hz) and 3.35 (J = 10.2 - 10.5 Hz) were assigned to the acetoxymethyl protons of the R^2 groups. A 9.5-Hz doublet of 6.2-Hz quartets at δ 3.64 belonged to the equivalent ring protons at C-5, 10, 15, 20, 25, 30, and 35. A doublet of triple intensity resonating at δ 1.23 (J = 6.2 Hz) represented the seven equivalent methyl groups, and two similar singlets at δ 2.07 and 2.03 were assigned to the acetyl groups in R^1 and R^2. The assignments were confirmed by a COSY experiment (Figure 3). Two independent sets of mutually interrelated signals were observed: δ 4.72, 4.12, and 4.05; and 4.56, 4.21, 3.64, 3.35, and 1.23. The ^{13}C-NMR and ADEPT experiment revealed that there are seven proton-bearing carbons: two primary carbon atoms ($\underline{C}$-CH_3 and $\underline{CO}$-CH_3) two secondary carbon atoms (CH_2-$\underline{OAc}$), and three tertiary carbon atoms (ring carbons).

Inspection of the symmetry properties of formula 12 revealed an interesting contrast to those of compound 9 (obtained by replacement of the CH_3 groups by CH_2OAc), the analogous macrocycle previously prepared by Stoddart, Szarek, and Jones[19] from 1. With such replacement, the compound 9 possesses seven symmetry planes which intersect at the central axis of the molecule as indicated in the drawing. It is therefore achiral, and optically inactive as found by the authors. With the CH_3 groups in place, i.e. for 12, the indicated planes are not symmetry planes and the compound is chiral: An optical rotation of $[\alpha]_D = +43.2^0$ was found.

The exceedingly simple and well-resolved character of the NMR spectra indicated a remarkable conformational simplicity of the macrocycle; there was no sign of any magnetic nonequivalence in constitutionally corresponding atoms (both hydrogen and carbon) of the seven ring segments. Apparently the macrocycle 12 exists in a highly ordered form, or it undergoes rapid pseudorotational randomization if spatial orientations in one part of the macrocycle deviate from those in others.

A Dreiding model of 12 was built and the diameter of the cavity was measured to be approximately 9.8 Å.

3-2.3. Nitromethane Cycloaddition of Polyaldehyde 6.

The nitromethane cycloaddition of polyaldehyde 6 was carried out by both the potassium fluoride and the sodium methoxide method. One of the experiments using the former method was performed at 50°C during two weeks and provided a 61% yield of nitro products. The IR spectrum showed a strong nitro group band at 1558 cm^{-1}, and a broad shoulder around 1600 - 1800 cm^{-1} probably due to unreacted carbonyl groups. Microanalysis showed only 46 % of the theoretical nitrogen content. Obviously, this result was not satisfactory.

The data relating to the performance of the cycloaddition in presence of sodium methoxide at room temperature are listed in Table 1. Four experiments were performed, with 1.6 - 2.2 molar equivalents of nitromethane and 0.93 - 1.65 equivalents of sodium methoxide per dialdehyde moiety, and with reaction times between 3 and 10 days. Experiment 1 (3 days) gave a product containing 6.71 % of nitrogen, practically the theoretical value of 6.8 %. The IR spectrum exhibited strong absorption at 1607 and 1558 cm^{-1}.

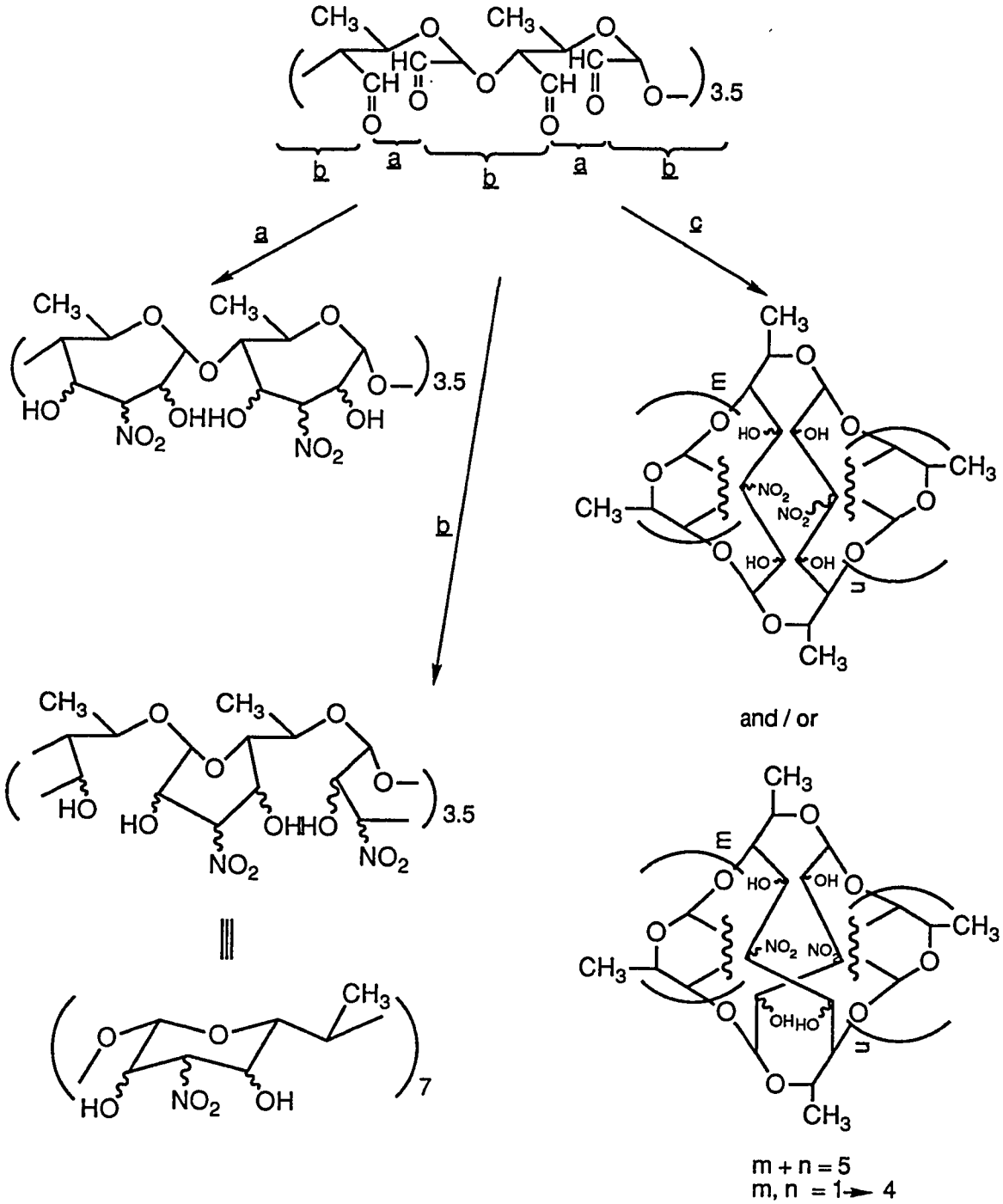


Figure 4. Nitromethane cyclization pathways.
a: intra-unit cyclization,
b: adjacent inter-unit cyclization,
c: transannular inter-unit cyclization.

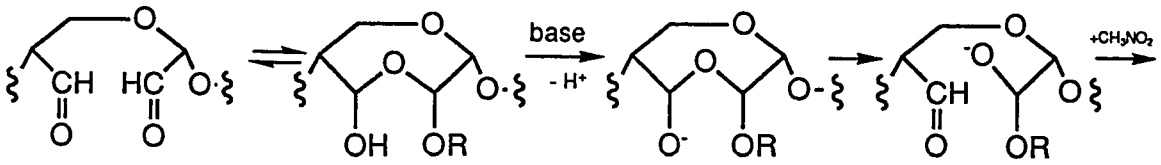
A weak shoulder at 1727 cm^{-1} suggested a small amount of unreacted carbonyl groups. The ^{13}C-NMR spectrum (50.3 MHz) was not very informative, even though it was taken from a concentrated solution (100 mg/mL) with 30720 scans. Signals were weak, broadened and numerous, no doubt because the product consisted of a large number of stereoisomers and constitutional isomers. Nevertheless, signals attributable to anomeric carbons were found in the range of δ 104 - 100 (broad) and 95.5 - 94.5 (narrow, possibly attributable to C-$\underline{NO_2}$), and this may be some of significance as will be discussed below.

Prolongation of the reaction time (Experiments 2 - 4) led to incorporation of considerably more nitrogen (10 - 13 %) than required for simple cyclization of all dialdehyde moieties. The ^{13}C-NMR spectra obtained were of similar quality as that from Experiment 1 but different from the latter in that they showed additional signals, at low field (δ 162 - 130), which were possibly attributable to nitroalkenic carbons. It may perhaps be speculated that primarily-formed nitrodiol structures incurred dehydration to nitroolefins, and that part of these then underwent Michael addition of a second nitromethane molecule. Both of these reaction types are well-documented in nitro sugar chemistry[36].

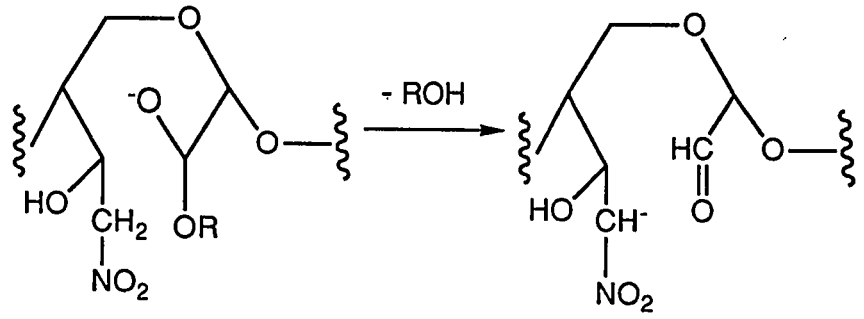
Regarding the possible course of the nitromethane cycloaddition, three pathways must be considered (Figure 4): a, intra-unit cyclization; b, adjacent inter-unit cyclization; and c, transannular inter-unit cyclization**. Path a involves reaction of the two carbonyl groups in the same dial segment and

** Non-cyclizing additions to the individual aldehyde groups of the same unit may be possible but have never been demonstrated in sugar aldehydes. The same is true for cross-linking between individual molecules, although products of such side-reactions may have arisen but escaped characterization in past studies.

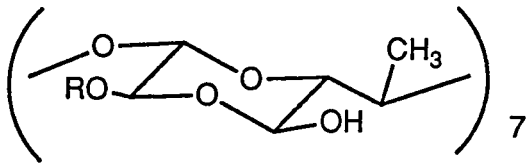
leads to α-1→5 linked 3-nitro heptoseptanosides. Path b involves cyclization between neighboring carbonyls of adjacent segments. It leads to β-1→6 linked 3-nitro heptopyranosides. Reactions of type c may lead to bicyclic or possibly tricyclic or more complex structures, presumably in an irregular way due to the multiple choices that exist for such crosslinking. The periodate-oxidized macrocycle 6 may have greater conformational freedom than the rigid torus of the parent cyclodextrin, so that crosslinking may be sterically possible; on the other hand, hemialdal formation would preempt that freedom. At any rate, the assumption is probably justified that formation of small rings (paths a and b) should be favored. The general tenet of organic chemistry that 6-membered rings are formed more readily than 7-membered ones at first glance prompts a predication that path b should be preferred for cyclization of 6.



One must, however, consider implications arising from the fact that sugar dialdehydes (and also 6) in alcoholic or aqueous solution exist as cyclic hemialdals. The nitromethane addition starts with base-induced liberation of an aldehyde group to which the nitromethane molecule attaches itself.

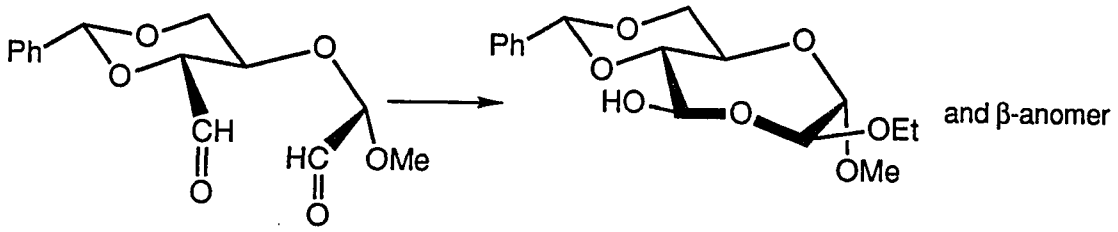


Concomitantly the second, potential aldehyde group becomes prediposed for liberation and hence, cyclizing nucleophilic attack while the neighboring carbonyl in the adjacent unit still rests in a "protected" hemialdal form. This argument for a kinetic preference of intra-unit cyclization (path a) is of course based on the premise that the hemialdal (or hydrate) structures existing prior to the reaction are of the intra-unit type as shown above. The same argumentation can be made to postulate a preference for path b, namely, if an inter-unit hemialdal structure is assumed:



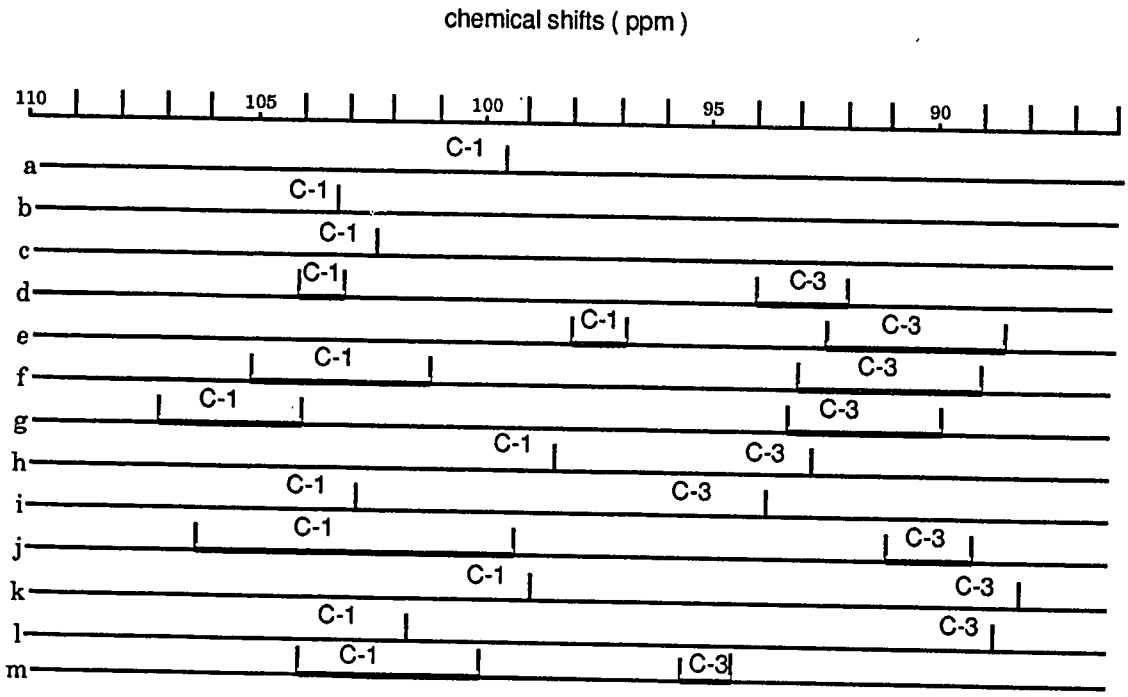
Such a 1,4-dioxane structure looks resonable indeed, but it is not known what kind of cyclic hemialdal or hydrate structures the cyclodextrin polyaldehydes actually prefer to form. We do know that the dialdehydes produced by periodate oxidation of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides give very stable, highly crystalline ethyl hemialdals[21], and although these particular dialdehydes have no other choice, their great stability suggests that such 1,4-dioxepan rings may well arise in 6. It may be

assumed that this kind of structure, rather than an inter-unit 1,4-dioxane structure,



also applies to the aforedescribed, disaccharidic model tetraaldehyde (25, Chapter 2), and this may explain why the septanosidic cyclization product (48, Chapter 2) appeared to preponderate over the pyranosidic product (49, Chapter 2) in the case of sodium methoxide-catalyzed cyclization. The latter product may have resulted from slow, thermodynamically controlled isomerization of the former, due to reversibility of the nitroaldol addition; a stable pyranoside, if formed as a primary kinetic product, should hardly be expected to isomerize to any noticeable extent.

With this consideration in mind we can now return to an evaluation of the cyclization product obtained from 6, with the correct nitrogen content for a heptakis-nitro cyclodextrin analog embodying 7-deoxyheptoses. Even if pathway c is disregarded, pathways a and b will yield mixtures of isomers which may contain an almost astronomical number of components, and it therefore appears hopeless to unravel the structures by spectroscopy alone. Still, the position of anomeric carbon signals discerned in the range δ 104 - 100 may afford some structural clue.



a: amylose
b: cellulose
c: 6-deoxy-β-cyclodextrin
d: nitro amylose
e: nitro cellulose
f: methyl 3-deoxy-3-nitro-α-heptoseptanosides
g: methyl 3-deoxy-3-nitro-β-heptoseptanosides
h: methyl 3-deoxy-3-nitro-α-glucopyranoside
i: methyl 3-deoxy-3-nitro-β-glucopyranoside
j: methyl 5,6-*O*-benzylidene-3-deoxy-3-nitro-α-heptoseptanosides
k: methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-α-glucopyranoside
l: methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-glucopyranoside
m: nitro 6-deoxy β-CD

Figure 5. ^{13}C-NMR data of 3-deoxy-3-nitro glycosides.

With the comparison of the ^{13}C-NMR spectral data of known 3-nitro monosaccharides (Figure 5), we may conclude that both pathways are possible.

For a definitive answer to the structure problem it will be necessary to resort to further chemical work. As a first measure it is proposed to attempt per-*O*-acetylation of the material, followed by reductive dehydroacetoxylation, as exercised in the model compound (5, Chapter 1). If successful, this will simplify the problem since by abolition of chirality in the positions 2 and 4 the number of stereoisomers present will be reduced and the material will, perhaps, become more amenable to NMR-spectroscopic analysis. With luck, one may also obtain some crystalline derivative suitable for X-ray crystallographic determination of the structure.

3-3. EXPERIMENTAL

3-3.1. Heptakis(6-bromo-6-deoxy)cyclomaltoheptaose (18).

To a stirred solution of Ph_3P (21 g, 80 mmol; dried *in vacuo)* and bromine (4.1 mL, 80 mmol) in dry *N,N*-dimethylformamide (80 mL) was added cyclomaltoheptaose (1, 4.32 g, 3.81 mmol = 26.7 mequiv; dried to constant weight *in vacuo* at 100°C over P_2O_5). The mixture was stirred for 15 h at 80°C, concentrated at reduced pressure to half its volume, and its pH was adjusted to 9-10 by the addition of 3 M NaOMe in MeOH (30 mL), with external cooling. The solution was then stirred for 30 min at room temperature, in order to decompose the formate esters formed in the reaction, after which it was poured into ice water (1.5 L). The precipitate was collected by filtration, washed with water (0.5 L) followed by CH_2Cl_2 (1 L), redissolved in DMF, reprecipitated by addition of MeOH, collected, and washed with MeOH, to give pure 18 (5.57 g, 92.8%)[27] , m.p. 214°C (dec.), $[\alpha]_D$ +78.1° (*c* 1.8, DMF), lit[24]. m.p. 205-206°C (dec.), $[\alpha]_D$ +98° (*c* 1, pyridine). ^{13}C-NMR (50 MHz, Me_2SO-d_6): δ 102.3 (C-1), 84.8 (C-4), 72.4, 72.2, 71.2 (C-2,3,5), 33.5 (C-6). FAB mass spectrum: m/z 1598.7, 1596.7 (87, 100, most abundant peaks of isotope cluster, $[M + Na]^+$), 1518.8, 1516.8 (59, 58, $[M + Na - HBr]^+$, 1438.9, 1436.9 (37, 33, $[M + Na - 2\ HBr]^+$).

Anal Calc. for $C_{42}H_{63}Br_7O_{28}$ (1575.29): C, 32.02; H, 4.03; Br, 35.51. Found: C, 32.03; H, 3.93; Br, 35.71.

3-3.2. Heptakis(6-deoxy-6-iodo)cylcomaltoheptaose (19).

To a stirred solution of desiccator-dried Ph_3P (21 g) in dry dimethylformamide (80 mL) was added I_2 (20.5 g) in small portions, followed after 30 min by 1 (4.32 g, dried *in vacuo* at 100°C over P_2O_5). The mixture was

stirred for 18 h at 80°C under exclusion of atmospheric moisture, then concentrated at reduced pressure to half its volume, cooled to + 5°C, basified with 3 M NaOMe in MeOH to pH 9-10, and kept at room temperature for 30 min for formate ester solvolysis. The solution was then poured into vigorously stirred ice water (1.5 L) and the beige-colored precipitate was collected by filtration, if necessary after adding a liberal quantity of NaH_2PO_3 to partially coagulate the fine suspension. The product was washed well with water, dried in the air, and suspended in CH_2Cl_2 (or $CHCl_3$, 1 L). After thorough agitation of the suspension, the undissolved material 19 was filtered off, washed several times with CH_2Cl_2, dissolved in DMF (100 mL), and reprecipitated by pouring the solution into stirred ice water. The dried product was freed from some remnant, discoloring impurity by trituration with a small amount of MeOH, to give colorless 19 (6.49 g, 89.5%), m.p. 224-224.5°C (dec.), $[\alpha]_D$ +73° (*c* 1, pyridine) and +79.6° (*c* 1, DMF); a different sample showed[27] m.p. 235°C (dec.), $[\alpha]_D$ +66.1° (*c* 1.15, DMF). ^{13}C-NMR (50 MHz, Me_2SO-d_6): δ 102.5 (C-1), 86.3 (C-4), 72.5, 72.3, 71.4 (C-2,3,5), 9.8 (C-6). Mass spectrum (glycerol-thioglycerol-NaI): m/z 1926.7 (100, $[M + Na]^+$), 1904.7 (21, $[M + H]^+$), 1800.9 (71, $[M + H + Na - I]^+$).

Anal. Calc. for $C_{42}H_{63}I_7O_{28}$ (1904.22): C, 26.49; H, 3.33; I, 46.65. Found: C, 26.68; H, 3.48; I, 46.55.

3-3.3. Heptakis(2,3-di-*O*-acetyl-6-deoxy-6-iodo)cyclomaltoheptaose (21).

A solution of 19 (2.0 g) in Ac_2O (15 mL) and pyridine (10 mL) containing a catalytic amount of 4-dimethylaminopyridine was kept for 48 h at room temperature. The mixture was processed by addition of MeOH (30 mL), and coevaporation of the solvent with additional MeOH and several portions of toluene. The crude product was purified by passage through a column of SiO_2

with 1:1 EtOAc-hexane as the eluant, to give 21 (2.2 g, 84 %) that crystallized on trituration with ether, m.p. 176-178°C (dec.), raised to 180°C (dec.) by recrystallization from Me_2CO-EtOH; $[\alpha]_D$ +82.5° (*c* 1, $CHCl_3$). Lit.[29] m.p. 172-177 °C, $[\alpha]_D$ +84±2°C (MeOH) and amorphous, $[\alpha]_D$ +78°C ($CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.31 (dd, $J_{3,4}$ 8.3, $J_{2,3}$ 9.9 Hz, H-3), 5.17 (d,$J_{1,2}$ 3.8 Hz, H-1), 4.80 (dd, J 3.8 and 9.9 Hz, H-2), 3.8-3.5 (complex m, 4 H, H-4,5,6,6'), 2.06 and 2.03 (2 s, 3 H each, 2 OAc). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 170.7, 169.5 (2 CO), 96.4 (C-1), 80.4 (C-4), 70.3, 70.1, 69.9 (C-2,3,5), 20.5 (2 CO$\underline{C}H_3$), and 7.7 (C-6). These values are in fair agreement with reported[26] 90-MHz (^{1}H) and 22.6-MHz (^{13}C) data.

Anal. Calc. for $C_{70}H_{91}I_7O_{42}$ (2492.73), C, 33.72; H, 3.68; I, 35.65. Found C, 33.87; H, 3.87; I, 35.49.

3-3.4. Heptakis(6-deoxy-6-S-phenyl-6-thio)cyclomaltoheptaose (23) and its heptakis(2,3-diacetate) 24.

A mixture of 1 (dried at 100°C over P_2O_5), diphenyl disulfide (16.2 g) and Bu_3P (19 mL) in dry pyridine (60 mL) was stirred for 48 h at room temperature, after which Ac_2O (35 mL) and a catalytic amount of 4-dimethylaminopyridine were added. After a further 6 h the mixture was diluted with $CHCl_3$ (100 mL), extracted with 5 % HCl (3 x 100 mL), aqueous $NaHCO_3$ (3 x 100 mL), and water (100 mL), then dried (Na_2SO_4) and evaporated. The syrupy residue was introduced dropwise by pipet into stirred ether (400 mL), whereby it solidified. The solid 24 was collected, washed with ether, and dried *in vacuo*; yield, 7.8 g (92.5 %). It showed Rf 0.6 (TLC with EtOAc), and although a trace of slower-moving impurity was present (not observable in the ^{1}H-NMR spectrum), it was sufficiently pure for further use. An analytical sample was purified by chromatography (SiO_2 column, 3:1

EtOAc-hexane) and crystallized from EtOH or ether; m.p. 123-125°C, $[\alpha]_D$ +147° (*c* 1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.3-7.05 (m, 5 H, Ph), 5.30 (dd, $J_{3,4}$ 8.0,$J_{2,3}$ 9.6 Hz, H-3) , 5.05 (d, $J_{1,2}$ 3.9 Hz, H-l), 4.78 (dd, $J_{1,2}$ 3.9 and 9.6 Hz, H-2), 4.15 (m, H-5), 3.80 (t, $J_{3,4}$ 8.6, $J_{4,5}$ 9.2 Hz, H-4), 3.31 (AB-m, 2 H, H-6,6'), 2.05, 2.03 (2 s, 3 H each, 2 OAc); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 170.6, 169.4 (2 CO, 155.1, 129.6, 129.1, 126.4 (Ph), 96.9(C-l), 78.9 (C-4), 70.9, 70.8, 70.3 (C-2,3,5), 36.2 (C-6), 20.84, 20.80 (2 $COCH_3$).

Anal. Calc. for $C_{112}H_{126}O_{42}S_7$ (2368.58): C, 56.79; H, 5.36; S, 9.47. Found: C, 56.50; H, 5.47; S, 9.32.

A solution of 24 (0.50 g) in MeOH (15 mL) and $CHCl_3$ (5 mL) was basified to pH 8-9 (moist indicator paper) with NaOMe solution. A white precipitate of 23 appeared within minutes. Isolated after 30 min by filtration and washing with MeOH, the air-dried product (0.36 g) decomposed above 230°C and had $[\alpha]_D$ +162° (*c* 1.6, pyridine). Although its NMR spectra conformed to structure 23, the microanalytical data suggested the presence of 1 equiv. of Na (presumably as Na_2CO_3) per molecule. Sodium-free 23 was obtained by dissolving the product in a minimum amount of dimethyl sulfoxide and reprecipitating it with a large volume of lM HCl; or alternatively, by evaporating the alkaline reaction mixture to dryness, deionizing the residue dissolved in 1:1 dimethyl sulfoxide - water (20 mL) with Amberlite IR-120(H^+) resin, and precipitating 23 with water (250 mL); yield, 0.35 g (93%), m.p. 253-255°C (dec.), $[\alpha]_D$ +164° (*c* 1.5, pyridine). ^{1}H-NMR (300 MHz, Me_2SO-d_6): δ 7.3-7.0 (m, 5 H, Ph), 4.95 (d, $J_{1,2}$ 2.8 Hz, H-l), 3.87 (t), 3.63 (t), and 3.4 (complex m) for the remaining protons; ^{13}C-NMR (75.4 MHz, Me_2SO-d_6): δ 136.6, 128.5, 128.1, 125.3 (Ph), 101.9 (C-l), 84.6 (C-4), 72.5, 72.1, 70.0 (C-2,3,5), and 34.8 (C-6).

Anal. Calc. for $C_{84}H_{98}O_{28}S_7$ (1780.07): C, 56.68; H, 5.55; S, 12.61. Found: C, 56.51; H, 5.81; S, 12.44.

3-3.5. Heptakis(6-deoxy)cyclomaltoheptaose (3).

A. From 18 or 19. The bromo compound 18 (4.5 g, 2.85 mmol, 20 mequiv) was treated with $NaBH_4$ as described for 2[30], to give 3 (2.70 g, 92.5 %), m.p. 269.5-271°C (dec.), $[\alpha]_D$ + 112° (*c* 0.9, pyridine), lit[24]. $[\alpha]_D$ + 112° (pyridine ; ^{13}C-NMR (50 MHz, Me_2SO-d_6): δ 102.3 (C-1), 88.1 (C-4), 73.2 (C-3), 72.6 (C-2), 66.7 (C-S), 17.4 (C-6). FAB mass spectrum: m/z 1045.3 (42, $[M + Na]^+$).

Dehalogenation of 19 by the same procedure gave 3 in similar yield.

B. From 22. A solution of 22 (4.80 g) in dry MeOH (300 mL) was basified to pH 8-9 (indicator paper) with NaOMe solution. The white precipitate isolated after 15 min, washed with MeOH, and dried weighed 1.61 g and was 3 containing 1.5 % of Na (determined as Na_2SO_4 ash in microanalysis); FAB mass spectrum: m/z 1045 (49, $[M + Na]^+$), 1046 (21, $[M + Na]^+$, isotope peak), 1023 (3, $[M + H]^+$), 1024 (1.6, $[M + H]^+$, isotope peak). The ^{13}C-data were identical with those given in section A; $[\alpha]_D$ + 110° (*c* 1, pyridine).

The methanolic mother liquor was deionized with Amberlite IR-120(H^+) resin, and evaporated, to give sodium-free 3 (1.07 g), m.p. 270°C (dec.), $[\alpha]_D$ + 116° (*c* 1, pyridine), also obtained by precipitation of the Na-containing product from a concentrated solution in dimethy sulfoxide with aqueous, 1 M HCl. ^1H-NMR (300 MHz, Me_2SO-d_6): δ 5.7 (br, 2OH), 4.80 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.71 (dq, $J_{4,5}$ 9.4, $J_{5,Me}$ 6.2 Hz, H-S), 3.55 (t, $J_{2,3} + J_{3,4}$ = 18.3 Hz, H-3), 3.22 (dd, $J_{1,2}$ 3 5, $J_{2,3}$ 9.5 Hz, H-2), 2.99 (t, $J_{3,4} + J_{4,5}$ = 18.3 Hz, H-4), 1.8 (d, 3 H, J 6.2 Hz, CH_3). FAB mass spectrum (glycerol): m/z 1023 (5, $[M + H]^+$), 585 (10, $[M + H - 3\ C_6H_{10}O_4]^+$,439 (40, $[M + H - 4\ C_6H_{10}O_4]^+$), 295 (51, $[M + H - 5\ C_6H_{10}O_4]^+$), 147 (70, $[M^+ + H - 6\ C_6H_{10}O_4]^+$). Each peak was accompanied by an isotope peak at m/z + 1, with a relative intensity close to that calculated.

Anal. Calc. for $C_{42}H_{70}O_{28}$ (1022.98): C, 49.31; H, 6.90. Found: C, 49.20 ; H, 6.82.

3-3.6. Heptakis(2,3-di-*O*-acetyl-6-deoxy)cyclomaltoheptaose (22).

A. From 21. A solution of 21 (2.29 g), Bu_3SnH (6 mL) and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) in toluene (100 mL) was boiled under reflux for 45 min in an N_2 atmosphere. The solvent was evaporated, and the residue dissolved in CH_2C1_2 (100 mL) was washed with water (2 x 60 mL). The dried (Na_2S0_4) organic phase was concentrated and the product purified by column chromatography on SiO_2, with ether (200 mL) followed by 3:1 EtOAc-hexane as eluants, to give 22 (1.20 g, 81 %), m.p. 168-170°C (from 2-propanol). An experiment performed on a 120-mg scale gave an 89% yield. The ^1H- and ^{13}C-NMR spectra were identical with those recorded in section B.

B. From 24. A solution of 24 (8.0 g) in oxolane (200 mL) and freshly prepared Raney nickel W-4 (40 g, administered as a slurry in EtOH) was shaken for several days under H_2, with fresh portions of nickel being added daily. Progress of the reaction was monitored by TLC (EtOAc), which indicated the transformation of 24 (Rf 0.5, u.v.-active) into 22 (Rf 0.4, u.v.-inactive). The reaction normally required 8-9 days at ordinary pressure, or 3-4 days at 25-30 kPa. The mixture was filtered, the filter residue washed well with oxolane, and the filtrate evaporated to dryness. The crude product was treated overnight at room temperature with Ac_2O (15 mL), dry pyridine (8 mL), and a catalytic amount of 4-dimethylaminopyridine. Conventional processing involving distribution of the mixture between water and $CHC1_3$ gave 22 that was purified by chromatography (SiO_2, 4:1 EtOAc-hexane), to give pure 22 (4.80 g, 88 %), m.p. 169-170°C (from 2-propanol), $[\alpha]_D$ + 109° (*c* 1,

$CHC1_3$); lit[26]. m.p. 162-165°C, $[\alpha]_D$ +111° ($CHC1_3$); ^{1}H-NMR (300 MHz, $CDC1_3$): δ 5.25 (dd, $J_{3\,4}$ 8.4, $J_{2,3}$ 9.7 Hz, H-3), 4.96 (d, $J_{1,2}$ 3 9 Hz, H-l), 4.74 (dd, $J_{1,2}$ 3-9,$J_{2,3}$ 9.9 Hz, H-2), 4.04 (m, H-S), 3.31 (t, $J_{3,4}$ 8.4, $J_{4,5}$ 9.3 Hz, H-4), 2.04, 2.01 (2 s, 3 H each, 2 OAc), and 1.35 (d, 3 H, 6.2 Hz, CH_3); ^{13}C-NMR (75.4 MHz, $CDC1_3$): δ 170.7, 169.3 (2 CO), 96.4 (C-l), 82.4 (C-4), 71.01, 70.97 (C-2,3), 67.0 (C-S), 20.7 (2 CO$\underline{CH_3}$), and 17.8 (C-6), in excellent agreement with reported[26] 22.6-MHz data.

Anal. Calc. for $C_{70}H_{98}O_{42}$ (1611.48): C, 52.17; H, 6.13. Found: C, 51.75; H, 6.18.

3-3.7. Preparation of primary-standard arsenic(III) oxide solution and standardization of iodine solution.

Primary-standard arsenic(III) oxide solution. Arsenic trioxide was dried in the oven at 110°C for one hour. A standard solution was prepared as directed[33], by dissolving 2.580 g of As_2O_3 and 5 g of NaOH pellets in 20 mL of water, followed by adding water (50 mL), 12 M HCl (10 mL), $NaHCO_3$ (3 g), and NaI (4 g). The mixture was diluted to exactly 500 mL, to give a 5.22 x 10^{-2} M arsenic solution.

Standardization of iodine solution. Reagent grade iodine (2.54 g) and potassium iodide (4 g) were dissolved in water (25 mL), and the solution was diluted to 1 L and stored in an amber bottle. Titration with standard arsenic solution indicated it to be 9.99 x 10^{-3}M.

3-3.8. Blank test of $NaIO_4$ solution.

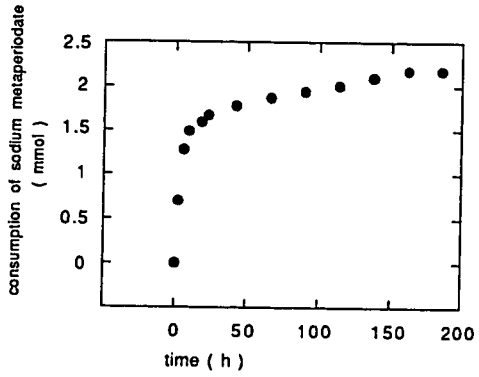
An exactly weighed amount of $NaIO_4$ (~210-220 mg, ~1mmol) was placed into each of five flasks, together with $NaHCO_3$ (0.7 g) and water (20 mL). After the salts were dissolved, 25.00 mL of 5.22 x 10^{-2}M arsenic solution was pipeted

into each flask. The mixture was allowed to react for 5-6 min, after which the excess of remaining arsenic was titrated with the standardized iodine solution, with several drops of starch solution as indicator.

3-3.9. Oxidative cleavage of the C-2,3 bonds in 6-deoxy-β-cyclodextrin.

6-Deoxy-β-cyclodextrin (292 mg)** was added to an aqueous solution of sodium metaperiodate (642 mg, 3 mmol) in 200 mL (exact amount) of water. The reaction mixture was mixed thoroughly and kept in the dark at 25°C, and periodate consumption was monitored by the method described above. The data are shown in the table and graph below.

time (h)	consumption of $NaIO_4$ (mmol)	time (h)	consumption of $NaIO_4$ (mmol)
0	0.00	66	1.87
2	0.70	90	1.94
5.5	1.28	114	2.00
9	1.49	137.5	2.10
18	1.59	162	2.18
22.5	1.67	185.5	2.18
42	1.78		

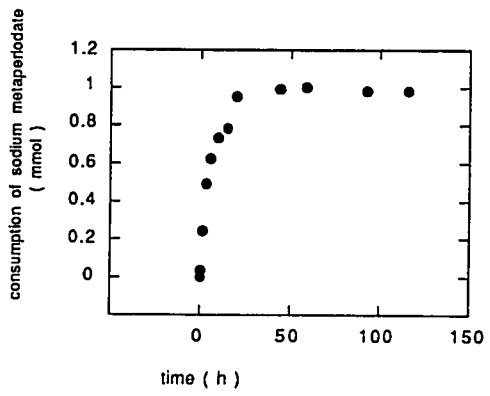


** Corresponding to 2 mmol of cleavable $C_6H_{10}O_4$ units, expected to react with 2 mmol of $NaIO_4$.

When the oxidation was complete, an excess amount of ethanol was poured into the aquous solution, the salt precipitate was filtered off, and the filtrate was evaporated to give a white solid. The white solid was suspended and partially dissolved in ethanol, undissolved material was removed, and the filtrate evaporated. This procedure was repeated three times, to give eventually the 6-deoxy-β-cyclodextrin polyaldehyde as a colorless syrup (195 mg).

A second experiment was carried out with 146 mg of 6-deoxy-β-CD (1 mmol of cleavable $C_6H_{10}O_4$ units) and 335 mg (1.57 mmol) of $NaIO_4$.

time (h)	consumption of NaIO4 (mmol)	time (h)	consumption of NaIO4 (mmol)
0	0.00	15	0.78
0.25	0.03	20	0.95
1.5	0.24	44	0.99
3.3	0.49	93	1.00
5.7	0.62	116	0.98
10	0.73	140	0.98



3-3.10. 2R,4R,7R,9R,12R,14R,17R,19R,22R,24R,27R,29R,32R,34R-tetradeca-acetoxymethyl-5R,10R,15R,20R,25R,30R,35R-heptamethyl-1,3,6,8,11,-13,16,18, 21,23,26,28,31,33-tetradecaoxacyclopentatriacontane (12).

β-Cyclodextrin-polyaldehyde (100 mg) 6 was treated with sodium borohydride (200 mg) in ethanol (10 mL). The ethanolic solution was stirred at room temperature for three days and then neutralized with Amberlite IR-120(H^+), filtered, and evaporated to give 11 (87 mg) as an oil.

11 (35 mg) was acetylated with acetic anhydride (0.5 mL), pyridine (0.5 mL), and a catalytic amount of 4-dimethylaminopyridine at room temperature for two days. Conventional processing gave 40 mg (74 %) of crude product 12. The crude product showed only one spot in TLC (Rf 0.67, 1:1 hexane - ethyl acetate); it was subjected to flash chromatography on silica gel to give 25 mg of colorless oil, $[\alpha]_D$ +43.2° (c 1.9, chloroform); IR (KBr, neat): 1745 cm^{-1} (carbonyl); ^{1}H-NMR data (300 MHz, $CDCl_3$, COSY): δ 4.72 (t, J 4.3 and 4.9 Hz), 4.56 (ddd, J 10.1, 5.2, and 9.5 Hz), 4.21 (dd, J 10.5 and 5.2 Hz), 4.12 (dd, J 4.3 and 11.7 Hz), 4.05 (dd, J 4.9 and 11.7 Hz), 3.64 (dq, J 9.5 and 6.2 Hz), 3.35 (t, J 10.2 - 10.5 Hz), 2.07, 2.03 (2s, OAc), 1.23 (d, J 6.2 Hz, CH_3); ^{13}C-NMR and ADEPT experiment (50.3 MHz, $CDCl_3$): δ 170.5, 169.8, (C=O), 99.1 (C-2, 7, 12, 17, 22, 27, and 32), 75.1 (C - 5, 10, 15, 20, 25, 30, and 35), 68.1 (C - 4, 9, 14, 19, 24, 29, 24, 29, and 34), 67.5 ($\underline{CH_2}$OAc of R^2, see Figure 2), 64.3 ($\underline{CH_2}$OAc of R^1, see Figure 2), 20.8 (OAc), 17.8 (CH_3).

Anal. Calcd. for $C_{70}H_{112}O_{42}$ (1625.60): C, 51.72; H, 6.95. Found: C, 51.63; H, 6.71.

3-3.11. General method of nitromethane cycloaddition in sodium methoxide medium.

6-Deoxy-β-cyclodextrin polyaldehyde (6) was treated with nitromethane and sodium methoxide in methanol. The mixture was kept in the dark at room temperature for several days. The methanolic solution was then neutralized with Amberlite IR-120(H^+) ion-exchange resin, filtered, and evaporated to give a brown, oily residue. The residue was dissolved in a minimum amount of methanol and precipitated by addition of ether to give a brown solid, and brown oil from the mother liquor. The amount of reagents used, the reaction periods, the yields of crude products and precipitates, and the microanalysis data are presented in the Table 1.

3-3.12. Nitromethane cycloaddition in potassium fluoride and crown ether medium.

6-Deoxy-β-cyclodextrin polyaldehyde (411 mg) was treated with nitromethane (0.3 ml) in 2-propanol. The solution was heated at 45 - 50°C for 14 days with stirring. Solvent evaporation resulted in a brown residue which was subjected to silical gel chromatography, to give 351 mg of yellowish brown solid (IR showed NO_2 strong absorption at 1559 cm^{-1} and medium-strong absorption between 1600 - 1700 cm^{-1}). The residue was dissolved in a minimum amount of methanol and precipitated by an excess amount of ether. The precipitated yellow-brown material weighed 151 mg, and the mother liquor gave 196 mg of a brown-yellow residue. The microanalysis showed only 46 % of the theoretical nitrogen content for both precipitate and residue.

Anal.Calcd for $C_{49}H_{77}N_7O_{42}$ (1436.17): C,40.98, H, 5.41, N, 6.83. Found in precipitate: C, 44.73; H, 6.36; N, 3.14. Found in residue: C,44.53; H, 6.21; N, 3.16.

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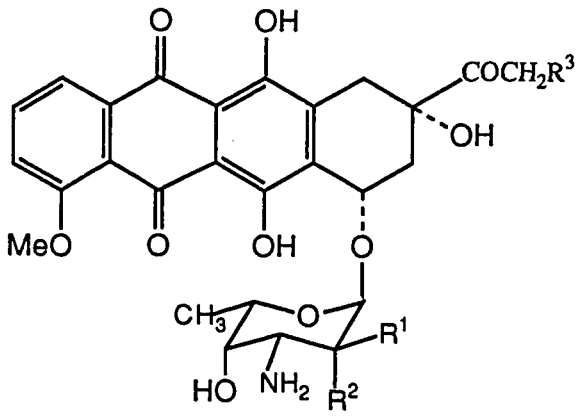
Part III

Approaches to the Synthesis of 2(*R*)-Fluorodaunosamine, a Carbohydrate Moiety for An Antitumor Drug

1. Introduction.

An initial assigment of this thesis research was to make a contribution to the synthesis of modified anthracycline antitumor antibotics, which was being pursued as a team effort in the laboratory.

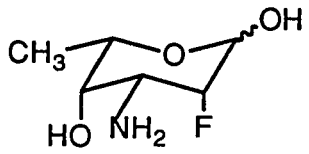


1 $R^1 = R^2 = R^3 = H$
daunorubicin

2 $R^1 = R^2 = H, R^3 = OH$
adriamycin

3 $R^1 = F, R^2 = R^3 = H$
2'-(*S*)-fluorodaunorubicin

4 $R^1 = R^3 = H, R^2 = F$
2'-(*R*)-fluorodaunorubicin

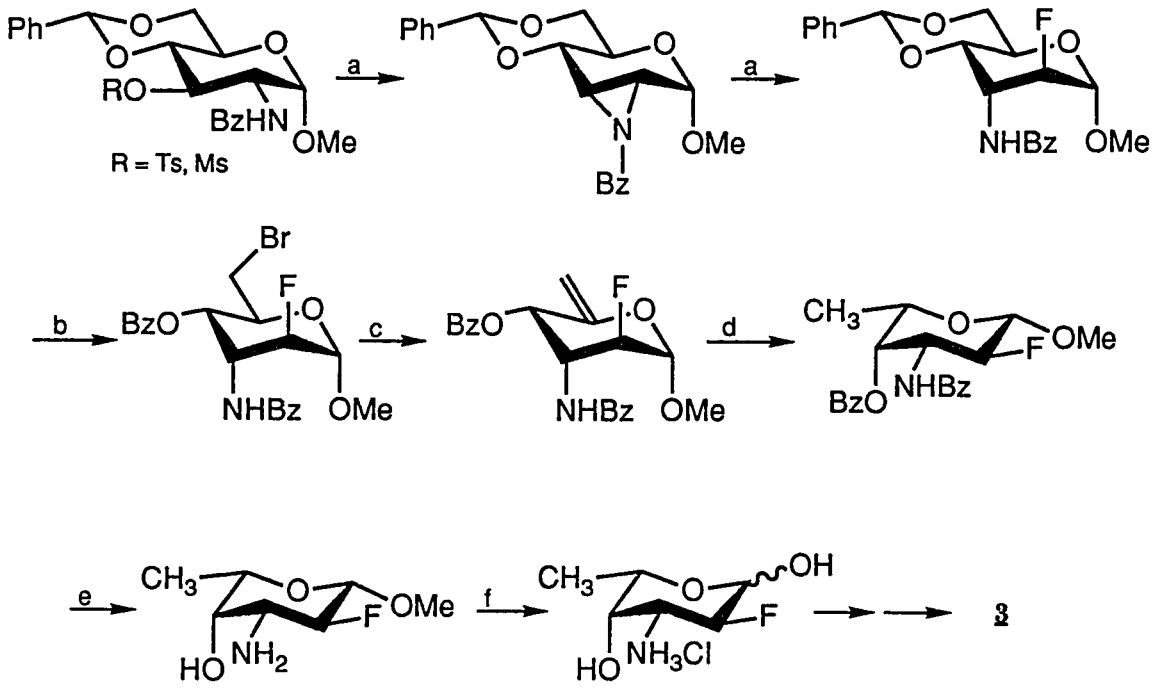


5 2-(*R*)-fluorodaunosamine

Figure 1. Adriamycin analogs and target compound.

The rational for this work was the idea that fluorine substitution at C-2 of the carbohydrate moiety daunosamine of such chemically important anticancer drugs as daunorubicin 1 or adriamycin 2 (Figure 1) might enhance their potency or lessen their serious cardiotoxicity, by retarding their cleavage into the sugar and the (toxic) aglycon in the body. Both of these compounds manifest the adverse side-effects characteristic of most

antineoplastic drugs, associated with selective toxicity towards cells in rapid turnover, as well as a cumulative, dose-related cardiotoxicity; they are also readily hydrolyzed *in vivo* to afford the sugar component and the aglycon, which display no antitumor activity. For this reasons, there is much interest in the development of active analogs in which these drawbacks are overcome or minimized.

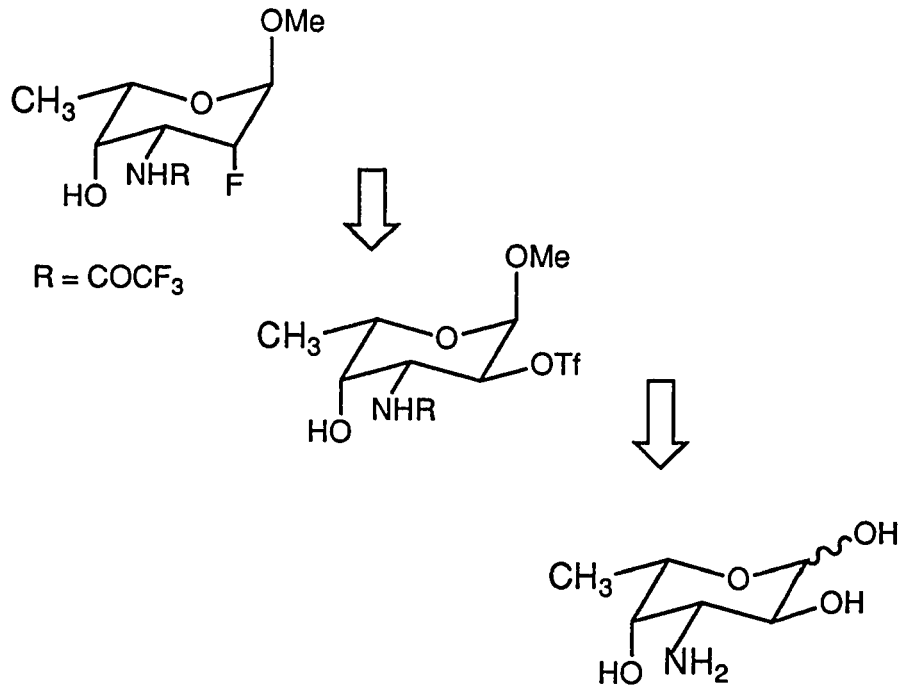


a: TBAF / CH_3CN; b: NBS, $BaCO_3$ / CCl_4; c: AgF/ pyridine / DMAP
d: H_2 / PdO_2 ; e: NaOH / $CH_3OCH_2CH_2OH$ / H_2O; f: HCl.

Scheme 1.

The synthesis of (*S*)-2'-fluorodaunorubicin 3 had already been accomplished (Scheme 1)[1,2], and its biological evaluation had shown that it was less toxic than the nonfluorinated parent drug, but also less antitumor-active, although considerable activity against various tumor cell lines *in vitro* and against L1210 murine leukemia *in vivo* was present. The activity, although too low for a potential development as an improved drug, was nevertheless quite interesting because Horton[3-7] had observed that chloro, bromo, and iodo analogs of the new fluoro derivative, all having the 2'-*S* configuration (*i.e.*, the halogen atom in equatorial disposition), were inactive whereas their 2'-*R* epimers (with axial halogen) displayed high antitumor activity. It therefore appeared highly worthwhile to synthesize and test the 2'-*R*-fluoro analog 4. Of all the halogen atoms, fluorine appeared most promising as a substituent because of its small size, which would least disturb the steric fit of the drug, and because of its high electronegativity, which would stablize the glycosidic bond most efficiently against hydrolysis. The requisite sugar for this undertaking, namely 2-(*R*)-fluorodaunosamine 5 (3-amino-2,3,6-trideoxy-2-fluoro-L-talose, Figure 1) was unknown and thus became a target of synthesis.

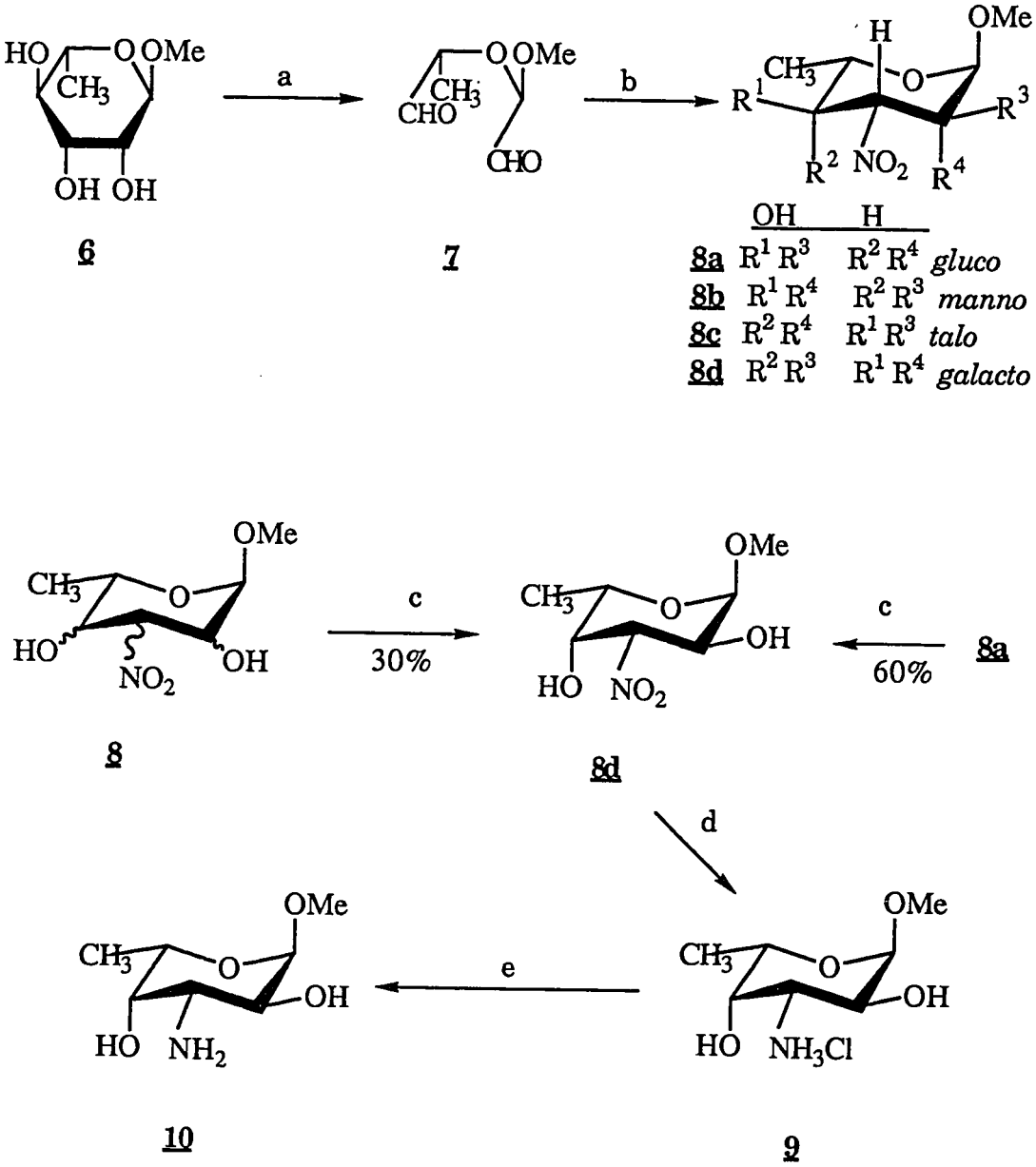
2. Results and Discussion.



3-amino-3,6-dideoxy-L-galactose

Figure 2. Proposed route to synthesize target compound 5.

One possible approach to the target sugar, it seemed, was to try to effect nucleophilic fluoride substitution, with configurational inversion at C-2 , in a suitably derivatized 3-amino-3,6-dideoxy-L-galactose (Figure 2). The approach appeared attractive because the methyl α-pyranoside 10 of this amino sugar is fairly readily available[8] by synthesis from economical methyl α-L-rhamnopyranoside 6 (Scheme 2). Application of the nitromethane cyclization method to the dialdehyde 7 derived from 6 by periodate oxidation gives a mixture 8 of four isomeric methyl 3,6-dideoxy-3-nitro-α-L-hexopyranosides which can be separated into the components, namely, the α-L-*gluco* (8a), α-L-*manno* (8b), α-L-*talo* (8c), and α-L-*galacto* (8d) isomers.



a: $NaIO_4$; b: CH_3NO_2 / NaOMe; c: epimerization in presence of NaOH

d: H_2 / PtO_2 / HCl; e: Et_3N / ether or $NaHCO_3$(aq)

Scheme 2.

Although 8a and 8b are the major components of the mixture as obtained by kinetically controlled cyclization and the desired L-*galacto* (8d) isomer is isolated in only 4.3% yield, its available proportion can be considerably increased by subsquent, base-induced epimerization[9,10] of 8a (see Figure 3).

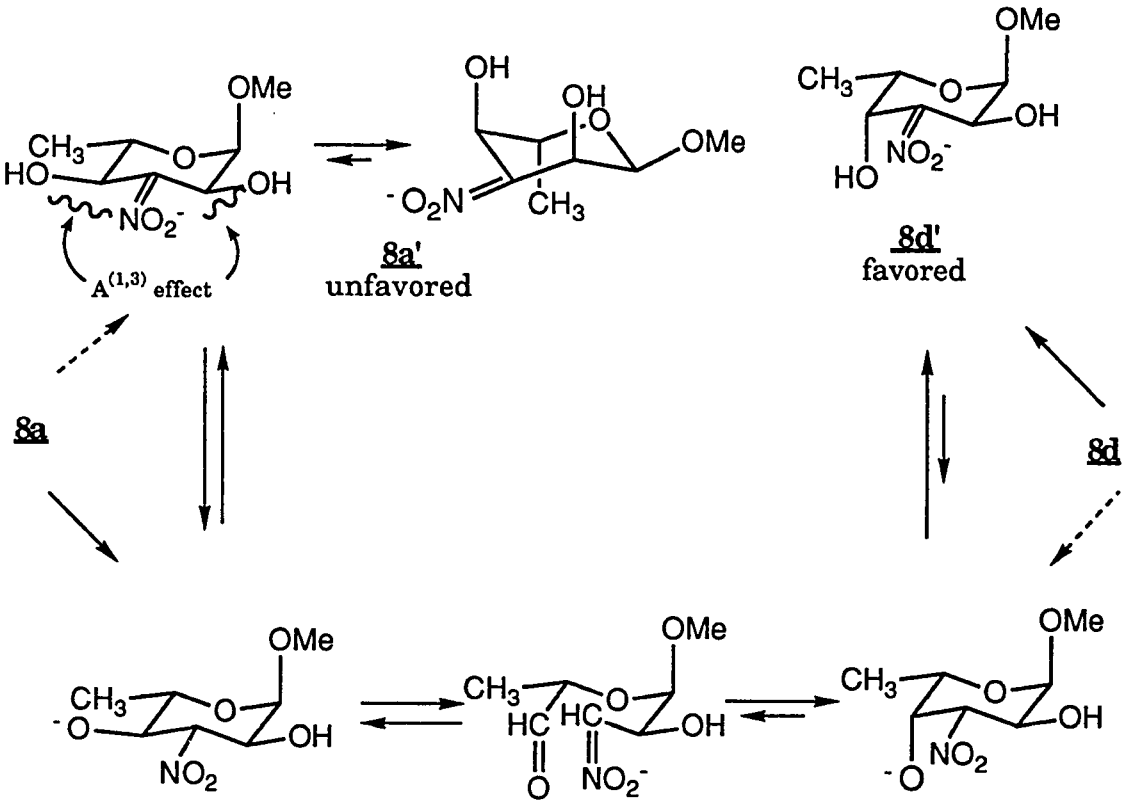


Figure 3. The configurational equilibria of nitro hexopyranosides 8.

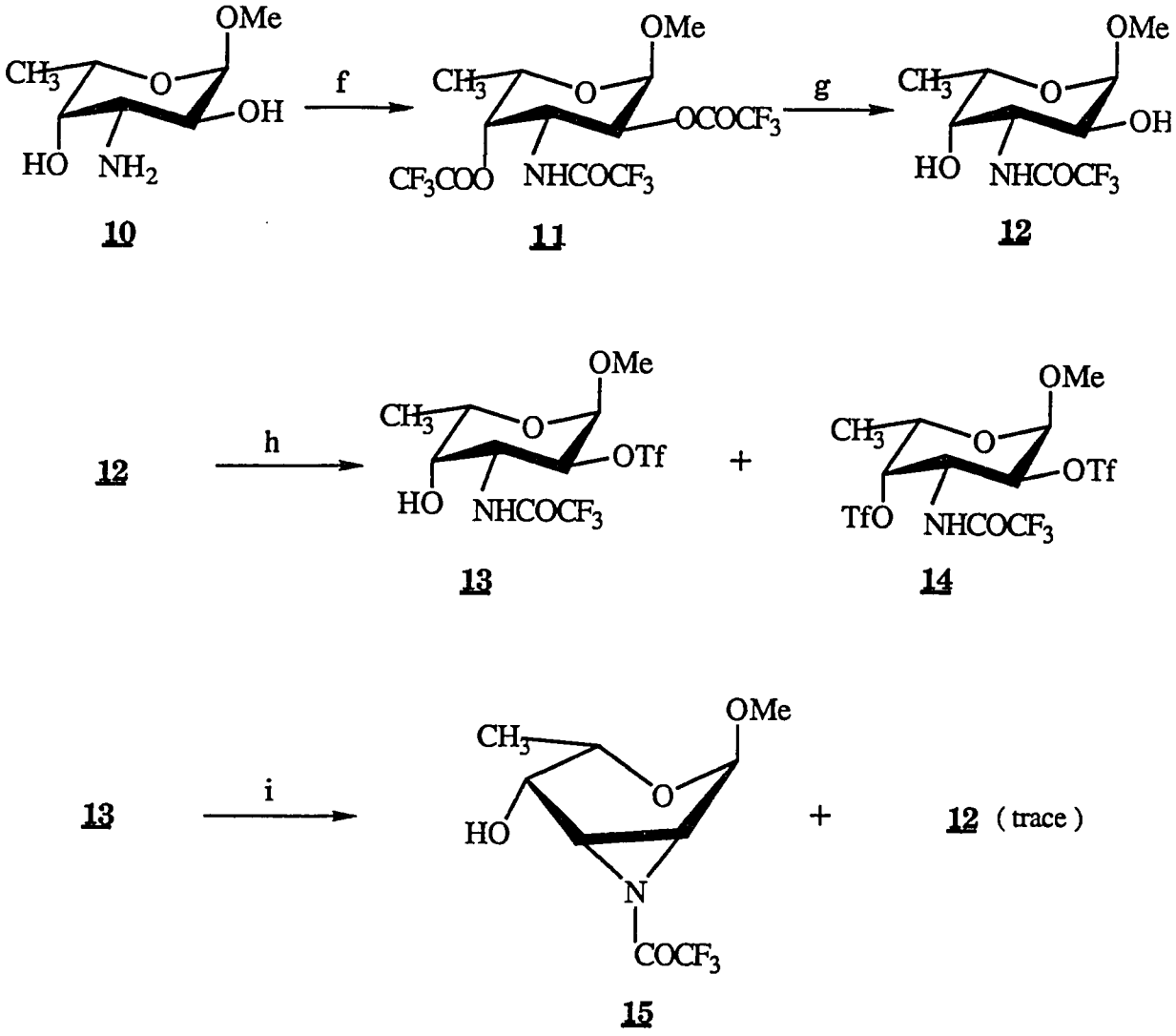
The configurational equilibria of nitro hexopyranosides 8 in basic medium have been thoroughly studied[9] (Figure 3). The reaction may be explained by assuming that proton abstraction from 8a involves the C-4 hydroxyl function, in significant competition with the nitro methine group, because of the unfavorable $A^{(1,3)}$ interactions present in the nitronate 8a'. The intermediate

alkoxide ion undergoes rapid epimerization, which takes place by reversible ring opening between C-3 and C-4, with the epimerized alkoxide being trapped, by proton transfer, to give the nitronate ion 8d' as the thermodynamically favored product. Conversely, in the isomer 8d proton abstraction is more facile at the nitromethylene group so that 8d' is readily formed and, because of paucity of the corresponding alkoxide ions in equilbrium, epimerization in the opposition direction is slow. In practice, treatment of 8a with aqueous sodium hydroxide for 1 min, followed by quenching with excess acetic acid, furnishes 8d in 30% isolated yield; in this way a sufficient supply of the desired starting material was procured.

Conversion of the nitro glycosides 8a - 8d into the corresponding amines by platinum-catalyzed hydrogenation has been described[8,11] and proceeds with practically quantitative yields. In the case of the L-*galacto* isomer, the methyl 3-acetamido-3,6-dideoxy-α-L-galactopyranoside was obtained from the hydrogenation of nitro galactoside 8d in methanol in the presence of platinum oxide and acetic anhydride, at ordinary temperature and pressure. For the present work, the hydrogenation of 8d was performed in the presence of one equivalent of hydrochloric acid, and the reduction product was isolated in 93 % yield as the crystalline amine hydrochloride 9, not previously characterized.

The strategy now contemplated was to protect the amino group in some appropriate way and to introduce in the 2-position a good leaving group, capable of nucleophilic dispacement by fluoride ion (Figure 2). Displacement of the classical sulfonate groups, namely mesylates and tosylates, from C-2 of pyranosides is reputed to be difficult[12], but there is ample precedent in the literature for such displacement of the much more nucleofugal

trifluoromethanesulfonate group[13], and this includes displacements by fluoride[14].



10 11 12

12 h → 13 + 14

13 i → 15 + 12 (trace)

f: trifluoroacetic anhydride / ether; g: methanol;
h: 1.1 e.q. triflic anhydride/ pyridine / methylene chloride;
i: tetrabutylammonium floride / acetonitrile / -35 - +10 °C

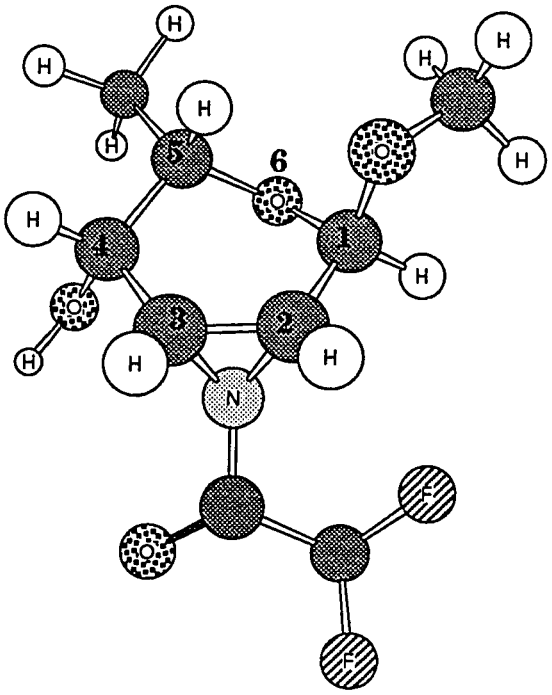
Scheme 3.

It was recognized that for fluoride to enter axially at C-2 of a *galacto* 2-triflate, there must be no neighboring group participation by the C-3 substituent, and this had to be borne in mind in choosing the protecting group for the amino function. It was thought that an *N*-trifluoroacetyl substituent might serve the purpose, on the assumption that the powerful electron-withdrawing effect of the CF_3 group would inhibit participation by the carbonyl oxygen. Consequently, the trifluoroacetamide 12 was prepared (Scheme 3). This was achieved by treating the amino sugar hydrochloride 9 with triethylamine in ether, to generate the free base 10, which was not isolated but allowed to react *in situ* with trifluoroacetic anhydride, to give the 3-*N*-trifluoroacetyl-2,4-di-*O*-trifluoroacetyl derivative 11. Compound 11 was not isolated either, but immediately treated with methanol at room temperature, to remove the labile *O*-trifluoroacetyl groups. A 82 % yield (based on 11) of crystalline methyl 3,6-dideoxy-3-trifluoroacetamido-α-L-galactopyranoside 12 was obtained.

The trifluoroacetamide 12 was then triflated by use of 1.1 mol. equivalent of trifluoromethanesulfonic anhydride in the presence of pyridine, in methylene chloride solution. It was expected that the equatorial OH-2 group would be esterified with adequate selectivity, and indeed, from the crude reaction product was obtained the crystalline 2-monotriflate 13 in 80% yield after recrystallization. The mother liquor contained besides 13 the 2,4-ditriflate 14, according to the mass spectrum.

Disappointingly, reaction of 13 with tetrabutylammonium fluoride[15], performed in acetonitrile solution at -35°C, did not afford the desired product. Although the triflate was in fact displaced completely within 1.5 hours, no fluorine was introduced. Thin-layer chromatography indicated the formation of a major product (Rf 0.55) and a minor one (Rf 0.15), whereas all of the starting 13 (Rf 0.65) was consumed. Isolated by column chromatography, the

major product (yield, 61 %) proved to be the epimine 15. This was concluded from the mass spectrum showing a strong molecular ion peak $M^+ + 1$ at m/z 256 (and fragment peaks at m/z 224 and 206 resulting from loss of OMe and OMe + H_2O, respectively), and from the ^{1}H-NMR spectrum, which was in full accord with this structure and, notably, lacked the features[1,2,16] associated with a 2-fluoro glycoside, *i.e.*, splitting of the H-2 signal due to a 45 - 50 Hz geminal coupling with F-2, and additional splitting of the H-1 and H-3 signals due to vicinal coupling with F-2. The lowest energy conformation, predicted by molecular mechanics calculation, is presented in Figure 4.

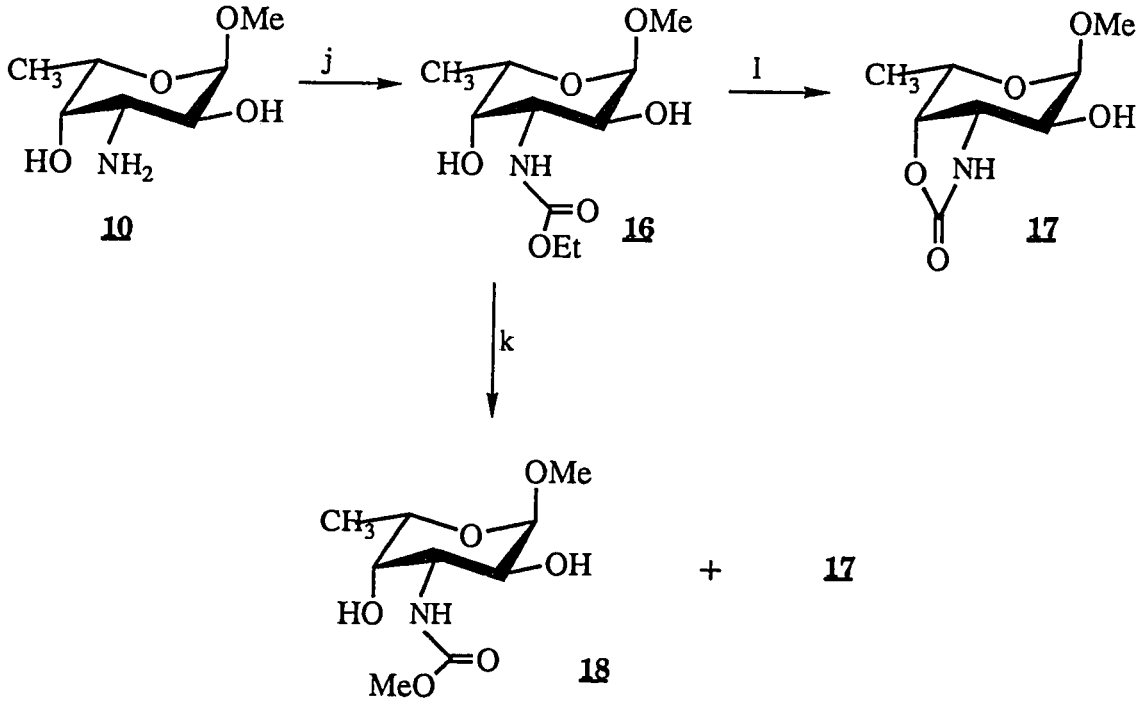


	dihedral angles (°)
H(1)-C(1)-C(2)-H(2)	71.5
H(2)-C(2)-C(3)-H(3)	0.5
H(3)-C(3)-C(4)-H(4)	9.7
H(4)-C(4)-C(5)-H(5)	54.4
O(6)-C(1)-C(2)-C(3)	-20.1
C(1)-C(2)-C(3)-C(4)	0.7
C(2)-C(3)-C(4)-C(5)	-14.9
C(3)-C(4)-C(5)-O(6)	50.1
C(4)-C(5)-O(6)-C(1)	-76.5

Figure 4. The lowest energy conformation of compound 15.

Evidently the *N*-trifluoroacetyl group was unable to prevent the amine nitrogen atom from engaging in internal displacement. The more-polar, minor product was not obtained pure; it constituted an admixture to 15 in

chromatographic end-fractions. The mass spectrum of these showed strong peaks (in addition to those attributable to 15) at m/z 274 and 242, suggesting that the minor component was the dihydroxy glycoside 12 originating from hydrolysis of the triflic ester 13.

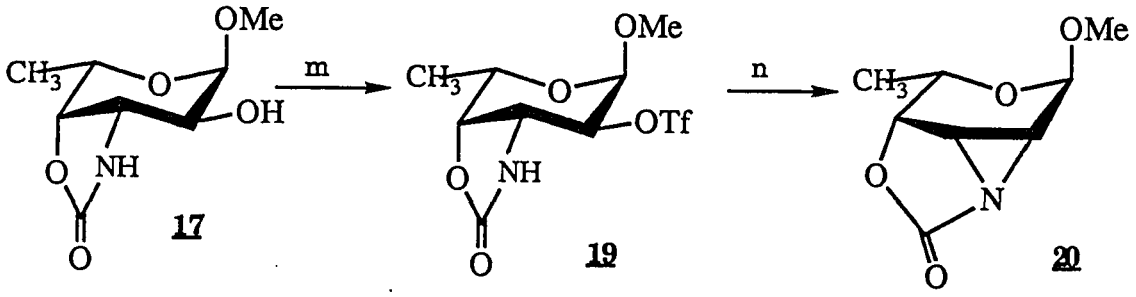


j: ClCOOEt / sodium bicarbonate (aq.); k: NaOMe / MeOH; l: NaOEt / EtOH

Scheme 4.

To circumvent the problem of epimine formation it was thought that incorporation of the amine fuction into a fused-ring system might be effective (Scheme 4). Simultaneous protection of amino and hydroxy groups has been performed in case of *cis* amino and hydroxy groups in cyclic compounds in the form of carbamate[17]. Therefore, the cyclic urethane triflate 19 (Scheme 5) was synthesized as a candidate for fluoride displacement; the steric

constraints inherent in this structure were hoped to prevent epimine formation and thus enable the desired S_N2 process to go forward.

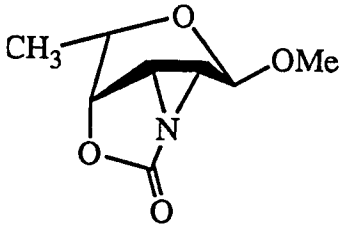


m: triflic anhydride / pyridine / methylene chloride / -30 – +10°C;
n: TBAF / acetonitrile.

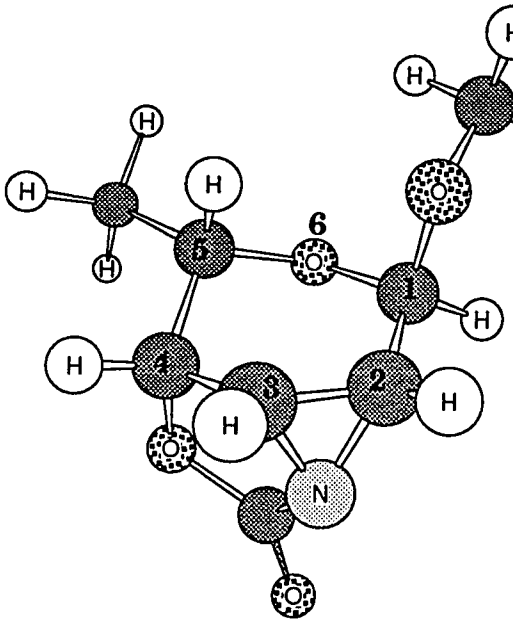
Scheme 5.

Reaction of the amino glycoside 10 (liberated from its hydrochloride 9 by sodium hydrogen carbonate) with ethyl chloroformate gave a 83 % yield of crystalline methyl 3,6-dideoxy-3-ethoxycarbonylamido-α-L-galactopyranoside (16), fully characterized by analytical and spectral data. In a first attempt to convert the product into the cyclic carbamate 17 by internal transesterification, 16 was treated with sodium methoxide in methanol at room temperature, whereby its TLC spot (Rf 0.5) was replaced slowly in the course of 5 days by a new spot having Rf 0.42. However, the ^{1}H-NMR spectrum revealed the product to consist of two components in a ratio of 4 : 3. The slightly preponderant component was the desired cyclic carbamate 17 (δ_{OMe} 3.45 in deuterated chloroform), whereas the other component apparently was the methoxycarbonylamide 18 since it exhibited two methoxy signals (δ_{OMe} 3.42 and 3.66) The chemical ionization mass spectrum of the mixture showed strong peaks at m/z 236 and 204. The former clearly was the $M^+ + 1$ peak for 18 (mol. wt. 235) whereas the latter signified either $M^+ + 1$ for 17 or loss of methoxy from 18, or both. Peaks attributable to the starting ethyl carbamate 16 (m/z 250 [$M^+ + 1$] and 218 [M^+ - OMe]) were very weak,

indicating the survival of traces only that were not detected in the NMR spectrum. No attempts were made to separate the products since it was found in concurrent experiments that use of sodium ethoxide in ethanol, acting upon 16 for 3 days at room temperature and another 2 days at 50°C, gives 17 in high yield (84 % after chromatographic purification), free from 16 according to the mass spectrum and ^{1}H-NMR spectrum. The cyclic carbamate was then triflated to afford crystalline 19 in 85 % yield.



20'



	dihedral angles (°)
H(1)-C(1)-C(2)-H(2)	67.1
H(2)-C(2)-C(3)-H(3)	6.0
H(3)-C(3)-C(4)-H(4)	-4.9
H(4)-C(4)-C(5)-H(5)	70.7
O(6)-C(1)-C(2)-C(3)	-27.4
C(1)-C(2)-C(3)-C(4)	27.2
C(2)-C(3)-C(4)-C(5)	-44.9
C(3)-C(4)-C(5)-O(6)	63.5
C(4)-C(5)-O(6)-C(1)	-65.9
C(5)-O(6)-C(1)-C(2)	48.1

Figure 5. The lowest energy conformation of compound 20.

When the triflate 19 was allowed to react with tetrabutylammonium fluoride in acetonitrile solution, the reasoning that had inspired its preparation was, unfornatuately, not borne out. As in the case of 13, the nitrogen effected internal displacement[18] of the triflyloxy group, and no fluorine entered the 2-position. The product, isolated as an analytically pure syrup in 91 % yield, was the tricyclic compound 20.

The epimine structure of compound 20 was confirmed by MS (CI, ether) spectral data: m/z 186 represents $M^+ + H$ and m/z 154 represents $M^+ + H$ - MeOH. Elemental analysis corresponded to this formula. This structure might have an alternative conformation, i.e., 20'. The lowest energy conformation of this compound, predicted by molecular mechanics calculation, seems more like conformer 20 which is presented in Figure 5.

In the meantime, some other approaches were also performed in this laboratory[15(a),12(a)]. A successful synthesis of the target compound 2-(*R*)-fluorodaunosamine (5) was achieved[19,20], and therefore, no further work along the lines indicated was performed.

3. Experimental

3-1. Methyl 3,6-dideoxy-3-nitro-α-L-galactopyranoside (8d).

The crystalline nitro glycoside 8d was prepared from methyl α-L-rhamnopyranoside 6 as described[8]. Nitromethane cyclization of the dialdehyde 7 obtained from 6 furnished the α-L-*gluco* isomer 8a in > 60 % yield, and 4-5 % of 8d. The bulk of 8d required was then obtained by epimerization of 8a in 30 % yield of pure product, m.p. 156 -157°C (lit.[8] m.p. 155-158°C).

^{1}H-NMR data (300 MHz, $CDCl_3$), not previously recorded:

For 8a: δ 4.75 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.60 (dd, $J_{2,3}$ 10, $J_{3,4}$ 7 Hz, H-3), 4.10 (ddd, $J_{1,2}$ 4, $J_{2,3}$ 10 Hz, H-2), 3.75 (sx, $J_{3,4}$ 7, $J_{4,5}$ 9-11 Hz, H-4), 3.70 (dq, $J_{4,5}$ 9-11, $J_{5,6}$ 6 Hz, H-5), 3.45 (s, 3H, OMe), 2.27 (d, OH-2), 2.16 (d, OH-4), 1.32 (d,3H, $J_{5,6}$ 6 Hz,CH3).

For 8d: d4.88 (d, $J_{1,2}$ 4.1 Hz, H-1), 4.69 (dd, $J_{2,3}$ 10.5, $J_{3,4}$ 2.9 Hz, H-3), 4.56 (ddd, $J_{1,2}$ 4.1, $J_{2,3}$ 10.5, $J_{2,OH}$ 8.7 Hz, H-2), 4.28 (ddd, $J_{3,4}$ 2.9, $J_{4,5}$ 1.1, $J_{4,OH}$ 6.2, Hz H-4), 4.03 (dq, $J_{4,5}$ 1.1, $J_{5,6}$ 6.6 Hz, H-5), 3.48 (s, 3H, OMe), 2.44 (d, $J_{2,OH}$ 8.7 Hz ,OH-2), 2.32 (d, $J_{4,OH}$ 6.2 Hz, OH-4), 1.33 (d, $J_{5,6}$ 6.6 Hz, Me-C).

3-2. Methyl 3-amino-3,6-di-deoxy-α-L-galactopyranoside hydrochloride (9)

Compound 8d (1.005g, 4.9 mmol) in water (50 mL) was added to a platinum dioxide catalyst (450 mg) that had been prehydrogenated in a mixture of water (20 mL) and 1N hydrochloric acid (5 mL). The heterogeneous reaction mixture was shaken at room temperature under hydrogen at ordinary presure. Complete hydrogenation required 4 hours, with 334 mL of hydrogen gas being consumed. Removal of the catalyst and evaporation of the

solvent gave a solid residue which was washed with ethyl acetate and then dried *in vacuo* to afford pure 9 (964 mg, 93 %), m.p. 195 °C (dec.). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.84 (broad, disappeared after D_2O exchange, 3H, $^+NH_3$), 5.48 (d, disappeared after D_2O exchange, OH), 5.34 (d, disappeared after D_2O exchange, OH), 4.53 (d, $J_{1,2}$ ~3.5 Hz, H-1), 3.74 (dq, $J_{5,6}$ ~6.5 Hz, $J_{4,5}$ very small, H-5), 3.68 (broad, becoming dd after D_2O exchange, $J_{2,3}$ ~11 Hz, $J_{3,4}$ ~3.5, H-3), 3.66 (broad, becoming dd after D_2O exchange, $J_{2,3}$ ~11Hz, $J_{3,4}$ ~3.5 Hz, H-4), 3.34 (s, 3H, OMe), 3.16 (m, becoming dd after D_2O exchange, $J_{1,2}$ ~3.5, $J_{2,3}$ ~11 Hz, H-2), 1.07 (d, $J_{5,6}$ ~6.5 Hz, C-CH3). ^{13}C-NMR (50.3 MHz, 1:1 DMSO-d_6 - acetone-d_6) : δ 99.2 (C-1), 67.8 (C-5), 65.4 and 64.9 (C-2 and 4), 54.6 (C-3), 52.5 (OCH_3), 16.1 (CH_3).

Anal. Calcd. for $C_9H_{16}ClNO_5$ (253.68): C,39.35; H, 7.55; N, 6.56. Found: C, 39.16; H, 7.35; N, 6.29.

3-3. Methyl 3,6-dideoxy-3-trifluoroacetamido-α-L-galactopyranoside (12).

A solution of 9 (943 mg) and triethylamine (2 mL, freshly distilled) in dry ether (20 mL, distilled) was stirred at room temperature, and the reaction was monitored by TLC (1:1 ethanol–hexane) which showed the formation of free amino glycoside 10 (Rf 0.27) from its hydrochloride 9 (Rf 0.71, tailing). Trifluoroacetic anhydride (2.06 mL) in dry ether (5 mL) was introduced dropwise, and the mixture was stirred for 3 hours. TLC (10% acetone-methylene chloride) showed that the amino sugar 10 (Rf 0.38) was completely converted into fast-moving ester 11 (Rf 0.62). Removal of some minor precipitate by filtration, and evaporation of the solvent gave 4.86 g of a yellow syrup. The syrup was dissolved in ethyl acetate (15 mL) and washed with cold water (2 x 5 mL). After drying (Na_2SO_4), the organic solvent was evaporated

from rotary evaporator to give a yellowish-white crude product 11 (1.79 g, 82 %).

The crude 11 was dissolved in methanol (30 mL) and stirred at room temperature. After 66 hours, *O*-deacylation was complete (TLC with 1:9 acetone-methylene chloride; a new spot of Rf 0.17 replaced Rf 0.62). Removal of the methanol under reduced pressure gave a pale yellow solid which afforded a crystalline 12 (985 mg, 82% overall yield) by crystallization from ethyl acetate-hexane, m.p. 230 - 232°C; I.R. (nujol): 1685 cm^{-1} and 1725 cm^{-1} (amide); M.S. (CI, ether): m/z 274 (M^+ + 1) and 242 (M^+ + 1 - MeOH) ^{1}H-NMR data (300 MHz, acetone-d_6, and COSY): δ 8.2 - 8.1 (broad, disappeared after D_2O exchange, NH), 4.62 (d, $J_{1,2}$ 3.4 Hz, H-1), 4.33 (d, disappeared after D_2O exchange, OH), 4.18 (septet, becoming dd on D_2O exchange, $J_{2,3}$ 11, $J_{3,4}$ 3 Hz, H-3), 3.93 (dq, $J_{4,5}$ ~1, $J_{5,6}$ 6.6 Hz, H-5), 3.87 (m, becoming dd on D_2O exchange, $J_{1,2}$ 3.5, $J_{2,3}$ 11 Hz, H-2), 3.71 (narrow m, becoming dd on D_2O exchange, $J_{3,4}$ ~3, $J_{4,5}$ ~1 Hz, H-4), 3.36 (s, 3H, OCH_3), 1.16 (d, $J_{5,6}$ 6.6 Hz, CH_3) ^{13}C-NMR spectral data (50.3 MHz, acetone-d_6): δ 100.9 (C-1), 71.2 (C-5), 67.1 (2 carbon atoms, C-2 and 4), 55.6 (C-3), 54.4 (OCH_3), 16.7 (CH_3).

Anal. Calcd. for $C_9H_{14}F_3NO_5$(273.21): C, 39.56; H, 5.16; F,20.86. Found: C,39.48; H, 5.15; F, 20.79.

3-4. Methyl 3,6-dideoxy-3-trifluoroacetamido-2-*O*-trifluoromethylsulfonyl-α-L-galactopyranoside (13) and methyl 3,6-dideoxy-3-trifluoroacetamindo-2,4-di-*O*-trifluoromethylsulfonyl-α-L-galactopyranoside (14).

Trifluoromethanesulfonic anhydride (0.1 mL, 1.1 equiv., in 5 mL of dry methylene chloride) was added dropwise by syringe at -20°C to a dry methylene chloride solution (10 mL) containing pyridine (0.08 mL, 1 equiv) and 12 (146 mg). The temperature was raised to +10°C during the reaction

interval, and after standing for 30 min with stirring, the mixture was diluted with methylene chloride (20 mL), washed successively with saturated aquous sodium bicarbonate (2 x 10 mL) and water (10 mL), dried over Na_2SO_4, and evaporated, to give a crude yellowish product (192 mg, 88%) from which 172 mg (80 %) of pure monotriflate 13 was obtained by crystallization from hexane-methylene chloride; m.p. 119 - 120°C; I.R. (nujol): 3580 cm^{-1} (NH), 3270 cm^{-1} (OH), 1710 cm^{-1} (amide C=O), 1555 cm^{-1} (amide NH), 1165 cm^{-1} and 1140 cm^{-1} (sulfone) MS (CI, ether): m/z 406 (M^+ + 1), 374 (M^+ + 1 - CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.78 (broad, disappeared on D_2O exchange, $J_{3,NH}$ 9 Hz, NH), 4.92 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.86 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, H-2), 4.75 (sx, becoming dd on D_2O exchange, $J_{2,3}$ 10, $J_{3,4}$ 3, $J_{3,NH}$ 9 Hz, H-3), 4.10 (dq, $J_{4,5}$ 1.0, $J_{5,6}$ 6.5 Hz, H-5), 3.85 (m,becoming dd on D_2O exchange, $J_{3,4}$ 3.0, $J_{4,5}$ 1.0, $J_{4,OH}$ 5.6 Hz, H-4), 3.47 (s, 3H, OCH_3), 2.01(d, $J_{4,OH}$ 5.6 Hz, OH-4), 1.26 (d, $J_{5,6}$ 6.6 Hz, C-CH_3) ^{1}H-NMR (200 MHz, acetone-d_6): δ 5.14 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 11 Hz, H-2), 4.96 (d, $J_{2,3}$ 11, $J_{3,4}$ 3.2 Hz, H-3), 4.08 (dq, $J_{4,5}$ ~1.0, $J_{5,6}$ 6.5 Hz, H-5), 3.88 (dd, $J_{3,4}$ 3.2, $J_{4,5}$ ~1.0 Hz, H-4), 3.44 (s, 3H, OCH_3), 1.20 (d, $J_{5,6}$ 6.5 Hz, C-CH_3). ^{13}C-NMR data (50.3 MHz, acetone-d_6): δ 97.4 (C-1), 83.7 (C-2), 72.3 (C-5), 67.4 (C-4), 55.8 (C-3), 50.6 (OCH_3), 16.4 (CH_3).

Anal. Calcd. for $C_{10}H_{13}F_6NO_7S$ (405.27): C, 29.63; H, 3.23; F, 28.13. Found: C,29.71; H, 3.21; F, 28.27.

The mother liquor was found to be a mixture of 13 and ditriflate 14 by proton NMR and MS spectral data: MS (CI, ether): m/z 538 (M^+ + 1), 506 (M^+ + 1 - CH_3OH); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.58 (broad, NH), 5.10 - 4.78 (other ring protons), 4.26 (q, H-5), 3.51 (s, OCH_3).

3-5. Methyl 2,3,6-trideoxy-2,3-(trifluoroacetylepimino)-α-L-talopyranoside (15).

Tetrabutylammonium fluoride (0.7 mL, 1.0 M in THF) was added to a solution of 13 (50 mg) in acetonitrile (5 mL, freshly distilled) which had been chilled to -35°C under nitrogen. The reaction was monitored with TLC until no more starting material was present (1.5 hours). Two product spots (Rf 0.55 and 0.11, 1:9 acetone-methylene chloride) were observed. The reaction mixture was evaporated to give a brown residue which was dissolved in methylene chloride (5mL). The solution was washed with water (2 x 3 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to give a light brown residue. The residue was subjected to flash chromatography with 1:19 → 1:9 acetone-methylene chloride as eluents to give a fast-moving fraction of 15 (19 mg, 61 %) as an amorphous solid, and a slow-moving fraction of by-product (~5 mg) as an oil which apparently contained 12 and 15 according to the mass spectrum (CI, ether) but not observed in the ^{1}H-NMR spectrum: m/z 274 (27 %, $M^+ + 1$, from 12), 256 (67 %, $M^+ + 1$, from 15), 242 ($M^+ + 1$ - MeOH, from 12), 224 (40 %, $M^+ + 1$ - MeOH, from 15), 206 (16 %, $M^+ + 1$ - MeOH - H_2O, from 15). Compound 15 gave ^{1}H-NMR data (300 MHz, acetone-d_6, COSY): δ 4.68 (d, $J_{1,2}$ 1.8 Hz, H-1), 4.15 (t, $J_{2,3}$~$J_{3,4}$~2.9 Hz, H-3), 3.96 (dq, $J_{5,6}$ 6.5 Hz, $J_{4,5}$ ~1Hz, H-5), 3.72 (narrow m, $\underline{w}$ = 4.7 Hz, H-2), 3.67 (narrow m, $\underline{w}$ = 4 Hz after D_2O exchange, H-4), 3.37 (s, 3H, OCH_3), 2.83 (s, exchangeable, OH-4), 1.23 (d, $J_{5,6}$ 6.5 Hz, C-CH_3); ^{13}C-NMR spectral data: δ 101.9, 70.7, 68.8, 67.1, 54.9, 49.2, and 16.8.

3-6. Methyl 3,6-dideoxy-3-(*N*-ethoxycarbonyl)amino-α-L-galactopyranoside (16).

An aqueous solution of 9 (384 mg) and sodium bicarbonate (840 mg) in water (20 mL) was stirred at room temperature for 1.5 hours, and the reaction was monitored by TLC until 9 was converted completely to 10. The aqueous solution was cooled to 0°C and ethyl chloroformate (0.6 mL) was introduced dropwise while the temperature was allowed to rise to room temperature. After 3 hours, the reaction mixture turned into two phases and TLC indicated the consumption of 10. Removal of solvent afforded a white solid which was dissolved in ethyl acetate. Some undissolved material was removed by filtration through a small amount of silical gel. The filtrate was evaporated, and the resulting residue was dried *in vacuo* to afford homogeneous compound 16 (335 mg, 83% overall, Rf 0.79, 2 : 1 ethanol-hexane), m.p. 159 - 160°C; MS (CI, ether): m/z 250 ($M^+ + 1$), 218 ($M^+ + 1 - CH_3OH$), 204 ($M^+ + 1 - C_2H_5OH$) I.R. (nujol): 3500 - 3300 cm^{-1} (broad, NH and OH), 1775 cm^{-1}, 1710 cm^{-1}, 1680 cm^{-1}, 1675 cm^{-1} (amide); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.22 (broad, disappeared on D_2O exchange, NH), 4.71 (d, $J_{1,2}$ 3.9Hz, H-1), 4.12 (q, J 7.2,Hz, 2H, O$\underline{C}H_2CH_3$), 4.00 (dq, $J_{4,5}$ ~0.5Hz, $J_{5,6}$ 6.6 Hz, H-5), 3.86 (m, becoming dd after D_2O exchange, $J_{2,3}$ 10.6, $J_{3,4}$ 2.6 Hz, H-3),3.73 (m, becoming dd after D_2O exchange, $J_{3,4}$ 2.6, $J_{4,5}$ ~0.5 Hz, H-4), 3.63 (sx, becoming dd after D_2O exchange, $J_{1,2}$ 3.9, $J_{2,3}$ 10.6 Hz, H-2), 3.43 (s, 3H, OCH_3), 2.15 (d, disappeared on D_2O exchange, J ~12 Hz, OH), 1.93 (d, disappeared on D_2O exchange, J ~8Hz, OH), 1.23 (t, J 7.15 Hz, 3H, $OCH_2\underline{C}H_3$), 1.22 (d, $J_{5,6}$ 6.6 Hz, C-CH_3) ^{13}C-NMR spectral data (75.5 MHz, acetone-d_6, ADEPT): δ 157.7 (C=O), 100.8 (C-1), 71.7 (C-5), 67.8, 67.0 (C-2 and 4), 60.9 (O$\underline{C}H_2CH_3$), 55.3 (OCH_3), 54.3 (C-3), 16.6, 14.9 (C-6 and $OCH_2\underline{C}H_3$).

Anal. Calcd. for $C_{10}H_{19}NO_6$ (249.26): C, 48.18; H, 7.68; N, 5.62. Found: C, 48.38; H, 7.51; N, 5.64.

3-7. Methyl 3,6-dideoxy-3-*N*,4-*O*-carbonyl-α-L-galactopyranoside (17) and methyl 3,6-dideoxy-3-(*N*-methoxycarbonyl)amino-α-L-galactopyranoside (18).

A solution of 16 (195 mg) and sodium methoxide (0.25 g of Na in 10 mL of methanol) was stirred at room temperature with TLC monitoring (Rf 0.50 for 16, 1 : 5 methanol-ethyl acetate). After 5 days, a slowly formed spot (Rf 0.42) became dominant. The reaction mixture was deionized under continued cooling with Amberlite IR-120(H+) resin (prewashed with methanol), and evaporated under reduced pressure to dryness, to afford 148 mg of a syrup which appeared to be a mixture of 17 and 18 at the ratio of 3 : 4 on the basis of ^{1}H-NMR and mass spectral data; I.R.(nujol): 3600 - 3100 cm-1 (broad, NH and OH), 1775 - 1680 cm-1 (C=O, amide), 1550 cm-1 (amide NH); MS (CI, ether): m/z 236 (M^+ + 1, from 18), 204 (M^+ + 1 from 17 or M^+ + 1 - CH_3OH from 18); 1H-NMR (300 MHz, $CDCl_3$): δ 3.66 and 3.42 (2s, 6H, 2 OCH_3 of 18), 3.45 (s, 3H, OCH_3 of 17), 1.33 (d, 3H, C-CH_3 of 17), 1.22 (d, 3H, C-CH_3 of 18).

3-8. Methyl 3,6-dideoxy-3-*N*,4-*O*-carbonyl-α-L-galactopyranoside (17).

A solution of 16 (941 mg) and sodium ethoxide (2.1 g of Na in 80 mL of 99% ethanol) was stirred at room temperature for 72 hours and at 50°C for another 48 hours. TLC (1 : 5 methanol-ethyl acetate) indicated the consumption of 12 (Rf 0.70) and showed a new spot of 17 (Rf 0.62). The reaction mixture was deionized under continued cooling with Amberlite IR-120(H^+) resin. The resin was filtered off and the filtrate was evaporated under reduced pressure to give 724 mg of an oily residue. The residue was purified

by silica gel flash chromatography to yield 17 as a homogeneous colorless syrup (646 mg, 84 %), I.R.(nujol): 3320 cm^{-1} (broad, NH and OH), 1750 cm^{-1} (C=O, amide); MS (CI, ether): m/z 204 (M^+ + 1), 172 (M^+ + 1 - CH_3OH) ^{1}H-NMR (300 MHz, acetone-d_6): δ 4.62 (d, $J_{1,2}$ 3.6 Hz, H-1), 4.47 (dd, $J_{3,4}$ 7.0, $J_{4,5}$ 2.4 Hz, H-4), 4.11 (dq, $J_{4,5}$ 2.4, $J_{5,6}$ 6.7 Hz, H-5), 3.75 (t, $J_{2,3}$ ~ $J_{3,4}$ ~ 7.0 ~ 7.4 Hz, H-3, simplified on D_2O exchange), 3.57 (m, becoming dd on D_2O exchange, $J_{1,2}$ 3.6, $J_{2,3}$ 7.4 Hz, H-2), 3.36 (s, 3 H, OCH_3), 1.23 (d, $J_{5,6}$ 6.7 Hz, C-CH_3) ^{13}C-NMR (75.4 MHz, acetone-d_6): δ 99.4, 77.9, 70.9, 63.4, 55.6, 54.9, 16.1.

3-9. Methyl 3-*N*,4-*O*-carbonyl-3,6-dideoxy-2-trifluoromethylsulfonyl-α-L-galactopyranoside (19).

Trifluoromethanesulfonic anhydride solution (0.15 mL of Tf_2O in 2 mL of dry methylene chloride) was introduced dropwise by syringe into a flask containing 17 (40 mg), pyridine (0.15 mL), and methylene chloride (2 mL), chilled to -30°C under nitrogen atomosphere. After 25 min, the triflation was nearly complete (TLC with 1 : 13 : 26 methanol-ethyl acetate-hexane; Rf 0.04 for 17 and 0.37 for 19). The reaction mixture was stirred at +10°C for another 2 hours, then poured into cold water (5 mL), which was extracted with methylene chloride (2 x 3mL). The organic phase was washed with 1N HCl (3 mL), saturated aqueous sodium bicarbonate (3 mL), and water (3 mL). After drying (Na_2SO_4) and treatment with activated carbon, the solvent was evaporated to give crude 19 (61 mg). The crude product was purified by preparative thin-layer-chromatography with methanol-ethyl acetate-hexane (ratio same as above) as developing solvent, to give homogeneous 19 (56 mg, 85 %) which crystallized from hexane-ethyl acetate as colorless, square platelets, m.p. 175 - 176°C; I.R. (neat, KBr): 3266 cm^{-1} (NH), 1765 cm^{-1}, 1725 cm^{-1} (C=O, amide), 1416 cm^{-1} (sulfone), 1202 cm^{-1}, 1146 cm^{-1}, 1058 cm^{-1} (C-F); ^{1}H-NMR

(300 MHz, $CDCl_3$): δ 5.53 (broad , NH), 4.93 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.74 (dd, $J_{1,2}$ 3.6, $J_{2,3}$ 7.8 Hz, H-2), 4.56 (dd, $J_{4,5}$ 2.5, $J_{5,6}$ 6.6 Hz, H-5), 4.13 (dd, overlap with H-3, $J_{4,5}$ 2.5, $J_{3,4}$ 6.7 Hz, H-4), 4.08 (ddd, overlap with H-4, $J_{2,3}$ 7.8, $J_{3,4}$ 6.7, $J_{3,NH}$ ~ 1.0 Hz, H-3), 3.45 (s, 3 H, OCH_3), 1.39 (d, $J_{5,6}$ 6.7 Hz, C-CH_3).

Anal. calcd. for $C_9H_{12}F_3NO_7S$ (335.26): C, 32.24; H, 3.61; S, 9.56. Found: C, 32.31; H, 3.76; S, 9.55.

3-10. Methyl 2,3,6-trideoxy-2,3-epimino-3-*N*,4-*O*-carbonyl-α-L-talopyranoside (20).

Tetrabutylammonium fluoride (TBAF) dihydrate (Aldrich) was co-evaporated with benzene several times under reduced pressure and then heated at 45 - 50°C for 5 days under high vacuum until the sample had lost 42% of its original weight and kept a constant weight. The acetonitrile used in the reaction was dried over P_2O_5, distilled, and stored over molecular sieves.

TBAF (92 mg) was added to a solution of 19 (22 mg) and molecular sieves (4Å) in acetonitrile (1.5 mL) at –30°C under nitrogen. After 5 min, TLC (1:15 acetone-methylene chloride) indicated the disappearance of 19 (Rf 0.27) and the presence of a new spot of 20 (Rf 0.45). Removal of the solvent under reduced pressure gave a brown oil which was then purified by preparative thin-layer-chromatography to give pure 20 (11mg, 91%); MS (CI, ether): m/z 186 (M^+ + 1), 154 (M^+ + 1 - CH_3OH); ^{1}H-NMR data (300 MHz, $CDCl_3$, COSY): δ 5.07 (t, $J_{2,4}$ ~1, $J_{3,4}$ ~0.8 Hz, H-4), 4.51 (d, $J_{1,2}$ 6.4 Hz, H-1), 3.92 (q, $J_{5,6}$ 6.6 Hz, H-5), 3.48 (s, 3H, OCH_3), 3.46 (ddd, $J_{1,2}$ 6.4, $J_{2,3}$ 4.7, $J_{2,4}$ ~1 Hz, H-2), 2.79 (dd, $J_{2,3}$ 4.7, $J_{3,4}$ 0.8 Hz, H-3), 1.2 (d, $J_{5,6}$ 6.6 Hz, C-CH_3) ^{13}C-NMR and ADEPT experiment (75.5 MHz, $CDCl_3$): δ 163.8 (C=O), 94.0 (C-1), 72.8 (C-5), 62.7 (C-4), 56.0 (OCH_3), 43.3, 42.3 (C-2 and 3), 16.5 (C-CH_3).

Anal. Calcd. for $C_8H_{11}NO_4$ (185.18): C, 51.88; H, 5.99; N, 7.56. Found: C, 51.82; H, 5.99; N, 7.26.

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General Methods.

Melting points were determined by use of a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured at ~25°C using a Perkin Elmer 241 polarimeter. Infrared (IR) spectra were taken from films on sodium bromide plates for oils, and from pellets of sodium bromide for crystals, using a Perkin Elmer 783 or Bomem MB-100 spectrometer. Mass spectra were recorded on a VG-7070E instrument by the CI mode (ether) and by FAB mode using glycerol as the matrix. The peak intensities are given as a percent of the base peak (100%) intensity. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

Unless otherwise indicated all proton NMR spectra (^{1}H-NMR) were taken at 200 MHz on a Varian Gemini 200 spectrometer, 300 MHz on a Varian XL-300 spectrometer, or 500 MHz on a Brucker Aspec 3000 spectrometer (as indicated). The chemical shifts are reported in ppm downfield relative to the internal standard tetramethylsilane (delta scale). The coupling patterns are noted as singlets (s), doublets (d), triplets (t), quartets (q), doublets of doublets (dd), doublets of doublets of doublets (ddd), doublets of doublets of doublets of doublets (dddd), doublets of triplets (dt), doublets of septets (dsept), broad (br), and multiplets (m). Spectral assignments were aided by COSY and nOe experiments. Unless otherwise indicated all carbon NMR (^{13}C-NMR) spectra were recorded at 50.3 MHz on a Varian Gemini 200 spectrometer or at 75.4 MHz on a Varian XL-300 spectrometer (as indicated). The number of protons attached to each carbon was determined by APT, ADEPT, or HETCOR spectra.

Column chromatography was performed using silical gel (60-230 mesh; E. Merck, Darmstadt, Germany). Flash chromatography was accomplished using silica gel (230-400 mesh; E. Merck, Darmstadt, Germany). Thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} precoated silica gel plates of 0.25 mm thickness and visualized by means of UV, I_2, or by charring, after application of a spray with 5% H_2SO_4 in ethanol.

Molecular mechanics calculations were carried out on a Mitac 386 microcomputer (Dr. J. Molina Molina, Departmento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain) or Macintosh Mac II ci computer, using the programs PCMODEL, Chem3D Plus, and MM2 [Serena Software, N. L. Allinger and J. T. Sprague, J. Am. Chem. Soc., 95 (1973) 3893; J. Kao and N. L. Allinger, J. Am. Chem. Soc., 99 (1977) 975.]. The program PCDISPLAY and Chem3D Plus were used for molecular graphics display.

Claims to Original Research

Part I

Chapter 1

1. Deoxygenation of nitro heptoseptanosides 6 to give dideoxy compounds 7 and 8 and their diacetates 9 and 10.
2. Spectral characterization of open-chain nitro sugar acetates 11a and 11b.
3. Formation of nitroalkene 14 and dideoxy nitro glycoside 15.
4. Deoxygenation of nitro 6-deoxyglucopyranoside 2,4-diacetate 18 to give deoxy hexopyranosides 19 - 22.
5. Conformational analysis of compounds 9, 10, 14, and 15.
6. Collection of ^{13}C-NMR data for 19 - 22 and the known compounds 25 - 28 for comparsion.

Chapter2

7. Study of the periodate oxidation of phenyl 4',6'-*O*-benzylidene-α-maltoside (5), and preparation of its previously unknown pentabenzoate 7.
8. Isolation of the products of periodate oxidation of 5 after borohydride reduction and acetylation (13 - 18).
9. Analysis of mass-spectral fragmentation of 16 - 18.
10. Synthesis of phenyl 4',6'-*O*-benzylidene-6-*S*-phenyl-6-thio-α-maltoside (19), its tetraacetate 20, and conversion into phenyl 4'.6'-*O*-benzylidene-6-deoxy-α-maltoside (21) and tetraacetate 22.
11. Study of periodate oxidation of 21, to give tetraaldehyde 25 and a mixture of dialdehydes (23 + 24).

12. Analysis of mass spectral fragmentation of 22 and of acetylated reduction product (28) of 25.
13. Study of nitromethane cyclization of tetraaldehyde 10 and 6-deoxy tetraaldehyde 25, including use of mass spectrometry for analysis of the results.
14. Deoxygenation of cyclization products (48) obtained from 25, after deacetalation and peracetylation (*i.e.*, diseptanosidic dinitro disaccharides 55), to give pentadeoxy disaccharides 57.

Chapter 3

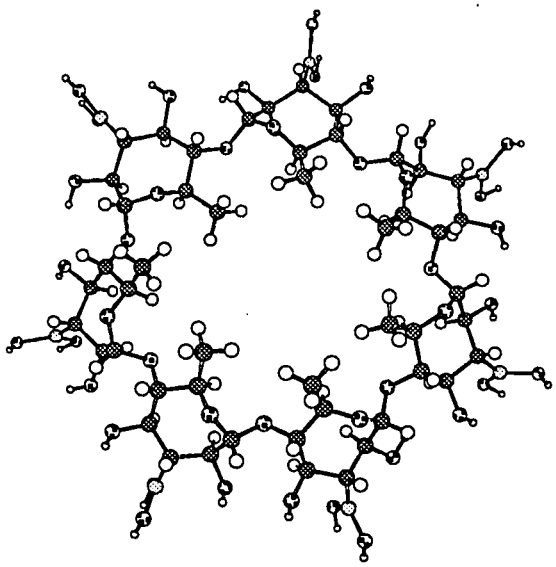
15. Synthesis of heptakis-6-deoxy-β-cyclodextrin derivatives 23 and 24, and conversion into 6-deoxy-β-CD 3.
16. Periodate oxidation of 3 and reduction of polyaldehyde 6 to macrocyclic polyacetal 12.
17. Nitromethane cyclization of polyaldehyde 6.

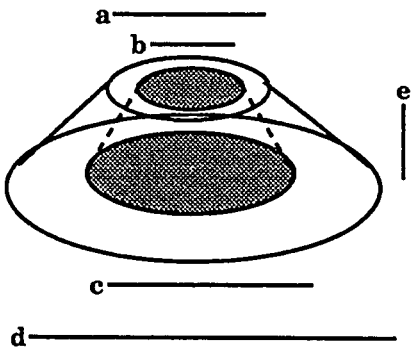
Part II

18. Synthesis of methyl 3,6-dideoxy-3-amino-α-D-galactopyranoside hydrochloride 9, the corresponding trifluoroacetamide 12, its 2-triflate 13, and the epimine 15.
19. Preparation of the *N*-ethoxycarbonyl and *N*-methoxycarbonyl derivatives (16 and 18) of 9, the cyclic urethane 17, its 2-triflate 19, and the tricyclic derivative 20.

Appendix. Computer-generated nitro 6-deoxy β-cyclodextrins.

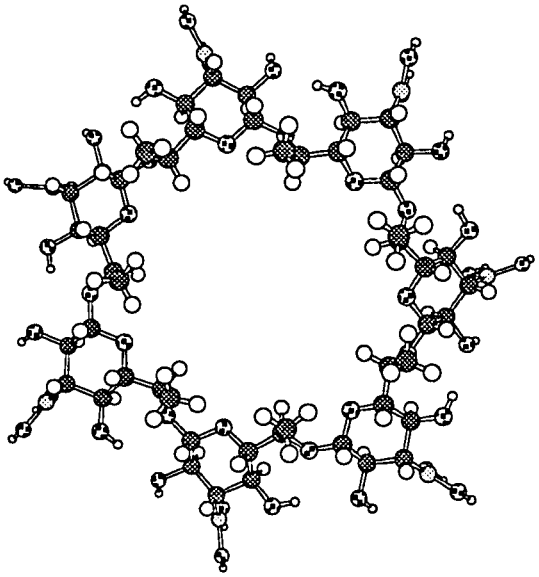
A

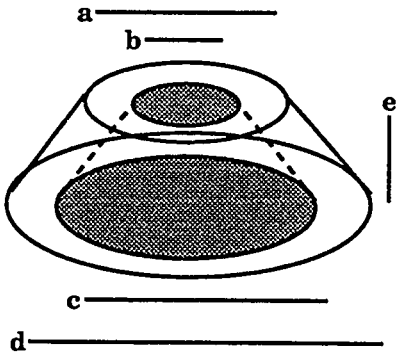




a=11.0, b=7.4, c=12.4, d=19.8, e=6.9 (in Å)

B





a=13.2, b=10.3, c=14.8, d=21.8, e=7.7 (in Å)

A: possible product of nitromethane cyclization via path a (Figure 4, Chapter 3, page 139); B: possible product via path b.