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Structure and reactions of amino- and nitro-heptoseptanosides obtained by cyclization of dialdehydes with nitromethane

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ABSTRACT

Base-catalyzed addition of nitromethane to the 2-ethyl hemialdal **3**, resulting from the reversible addition of ethanol to the dialdehyde **2** obtained from $NaIO_4$ oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) in aqueous solution, yields four main isomeric 3-nitroheptoseptanosides having respectively the D-*glycero*-D-*manno* (**7**, 42%), D-*glycero*-D-*ido* (**5**, 36%), D-*glycero*-D-*galacto* (**6**, 12%) and D-*glycero*-D-*talo* (**9**, <10%) configurations. Compound **7** equilibrated slowly in pyridine with the D-*glycero*-D-*altro* isomer **11**, whereas, under similar conditions, **6** underwent a fast epimerization to the D-*glycero*-D-*gulo* isomer (**10**). Equilibration of **5** in the presence of an excess of sodium methoxide afforded a 3:2 mixture of **9** and **7**, whereas conversely action of a catalytic proportion of the same base on **9** produced **5**. The configuration at C-2–C-4 for the series of nitroheptoseptanosides have been assigned by conversion into the corresponding methyl 3-acetamido-3-deoxyheptopyranosides and then into known 3-amino-3-deoxyhexose derivatives. Tentative correlations have been drawn between the stereochemistry in the transition state for the addition of the nitroalkyl carbanion, the conformation of the resulting seven-membered ring and its nitronate, and the relative distribution and stability of epimeric nitroheptoseptanosides obtained in the reaction. Conformational preferences for nitroheptoseptanosides, as inferred from ^{1}H-n.m.r. data, are discussed. Comparative $NaIO_4$ oxidations were performed on methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**43**) resulting in the formation of the corresponding C-2–C-3 dialdehyde **44** isolated as its 2-ethyl hemialdal **45**. Base-catalyzed nitromethane addition to **45** resulted in the formation of at least three isomeric nitroheptoseptanosides with respective configurations D-*glycero*-D-*altro*, D-*glycero*-D-*gluco*, and D-*glycero*-D-*galacto* which were identified mostly by comparison of their ^{13}C-n.m.r. parameters with compounds obtained in the α-D series.

INTRODUCTION

Polyaldehydes derived by periodate oxidation from amylose[1], starch[1], and cellulose[2] incorporate nitromethine functionalities by base-catalyzed reaction with nitromethane, according to the general principle of nitroalkane cyclization[3] of sugar dialdehydes. The method has recently been elaborated further by us, with the aim of converting the obtainable nitrodeoxypolysaccharides into polysaccharides selectively aminated at secondary positions, a proposition that had met with difficulties in earlier studies[1] but has now been accomplished[4]. However, the problem of elucidating the probably

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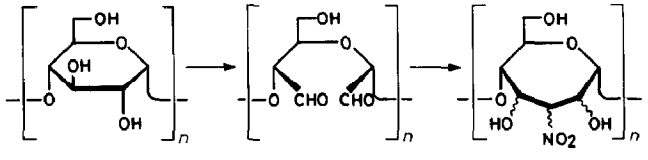
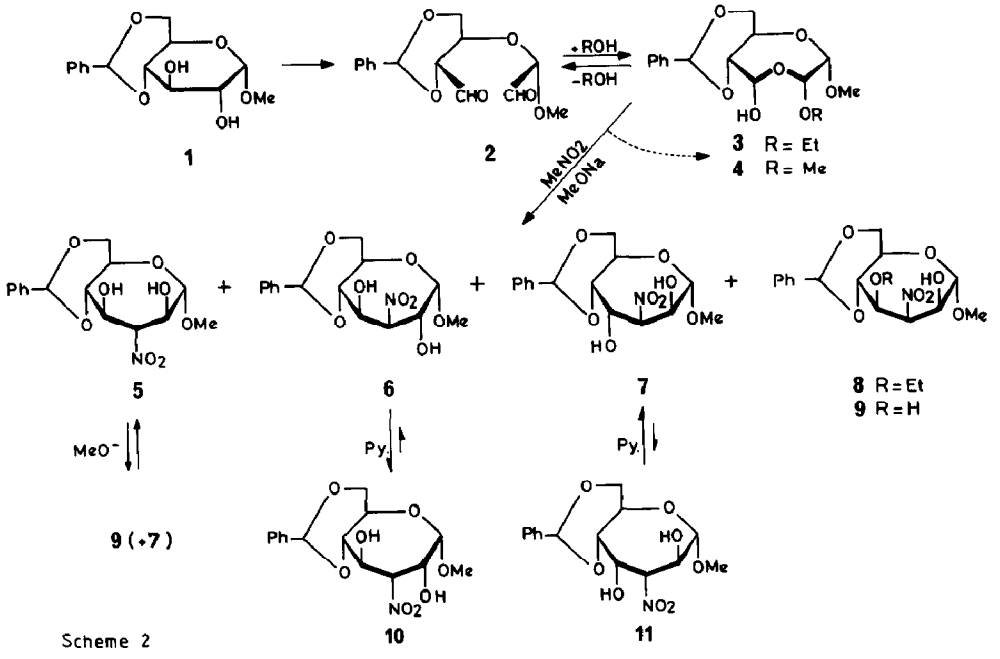
complex structures[2] of the nitrogenated materials, especially with regard to the stereochemistry of the constituent monosaccharide units, remains to be solved. In order to facilitate such structural investigations, it was desirable to prepare a set of configurationally defined, stereoisomeric 3-deoxy-3-nitroheptosides, and the corresponding aminated derivatives, which could serve as reference compounds in contemplated, spectroscopic and degradative work on the polymers. In particular, 3-nitrogenated heptose derivatives of the uncommon septanoside type were required as this structural feature is presumable involved in the polysaccharide in question. We report here the synthesis of a series of methyl 3-deoxy-3-nitro-D-heptoseptanosides and 3-acetamido-3-deoxy analogs, and the transformation of the latter into 3-acetamido-3-deoxy-D-hexose derivatives.

RESULTS

The dialdehyde moiety resulting from oxidative cleavage between C-2 and C-3 of an α-(1→4)-linked D-glucopyranoside residue in amylose may, on cyclization with nitromethane, give rise to any one of eight stereoisomeric, α-(1→5)-linked 3-deoxy-3-



Scheme 1



Scheme 2

nitroheptoseptanoside units. These are expected to vary configurationally in the C-2–C-4 sequence of the ring, but to have identical configuration at C-5 and C-6 (Scheme 1).

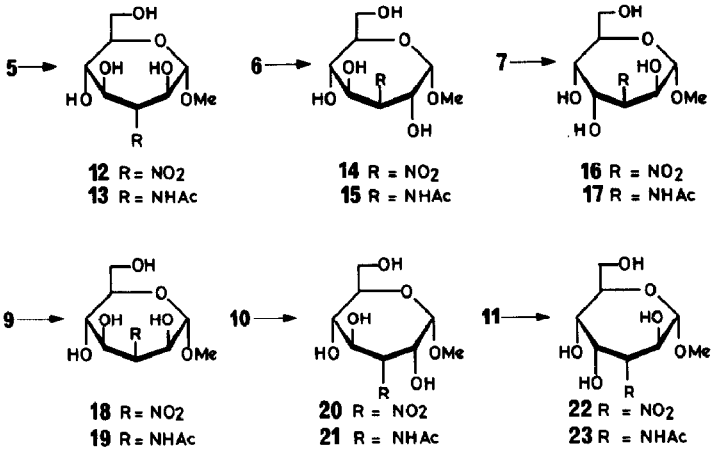
Monosaccharide model compounds for such units may be synthesized from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**, Scheme 2) by cyclization of its product (**2**) of periodate oxidation. This general approach was first used by Baschang[5] who, employing the ethylidene analog of **2**, obtained 41% of a 3-deoxy-3-nitroheptoseptanoside as the sole product, shown to have the α-D-*glycero*-D-*manno* configuration. In 1967, Wolfrom, Nayak, and Radford[6] announced that they had cyclized **2** with nitromethane, to give four isomeric 3-deoxy-3-nitroheptoseptanosides, but their configurations were not determined and experimental details have never been published. Subsequently, Butcher and Lee[7] reported on reactions of **2** with nitroalkanes; nitroethane and nitropropane gave C-3 branched septanosides, but no data characterizing the products obtained with nitromethane were provided. We then decided to reinvestigate the nitromethane cyclization* of **2**.

The dialdehyde **2**, generated from **1** by periodate oxidation in aqueous ethanol, readily and reversibly adds a molecule of ethanol to form the highly crystalline hemialdal[9,10] **3**, stable in storage and conveniently handled. It reacted smoothly with 1 molar equivalent of nitromethane in the presence of 0.6 equivalent of sodium methoxide in methanol solution (2 h at 0°), to give, after deionization of the reaction mixture, 90% of a crude glycoside mixture from which were isolated by fractional crystallization the α-D-*glycero*-D-*ido* (**5**) and α-D-*glycero*-D-*galacto* (**6**) nitroseptanosides in 36 and 12% yields respectively; the major component (42%) was the syrupy α-D-*glycero*-D-*manno* isomer **7**, probably accompanied by a small proportion of the α-D-*glycero*-D-*talo* isomer **9**. A minor by-product (< 1%), also isolated crystalline, was the methyl hemialdal **4**, resulting from **3** by alkoxy exchange. An attempt at crystallization of impure syrupy **7** from hot ethanol resulted in the formation of a small amount of crystalline 4-ethyl ether **8**, which also arises from pure **9** (see below) during prolonged storage in aqueous ethanolic solution.

When **5** was treated with 1.67 molar equivalents of sodium methoxide in methanol at 0° for 24 h, the product obtained after deionization was a 3:2 mixture of **9** and **7**, according to the ^{13}C-n.m.r. spectrum, and 60% of pure **9** could be isolated crystalline. Use of a larger excess of base (5 molar equivalents) gave the same result. Conversely, treatment of **9** with a catalytic proportion (0.1 molar equivalent) of sodium methoxide in methanol at 25°, followed by deionization, produced a 10:1 mixture of **5** and **9**.

Compound **6** underwent epimerization to the α-D-*glycero*-D-*gulo* isomer **10** by simple dissolution in pyridine at room temperature; after 5 h, a 3:2 equilibrium between **10** and **6** appeared to have been established (^{13}C-n.m.r.), and this was shifted further, in

* In a personal communication, Professor D. Horton (Ohio State University, Columbus, Ohio) has kindly made available to us an internal report from Professor Wolfrom's laboratory, authored by Dr. T. Radford and dated August 31, 1967, in which experimental details for the convenient preparation of dialdehyde **2** (isolated as ethyl hemialdal **3**) and for the isolation procedures for the four glycoside 5,7-acetals are described: regarding the crucial nitromethane addition step, the important proportions of reactants actually employed were not recorded; it was stated that "the general procedure used by Baer[8] was followed".



Scheme 3

favor of the former, during processing that furnished a 94% yield of crystalline **10**. Compound **7** was similarly epimerized to give the α-D-*glycero*-D-*altro* isomer **11**, although the equilibration was slower (55 h at room temperature, or 2 h at 60°), and **7** predominated moderately in equilibrium; **11** was isolated crystalline in 30% yield. The n.m.r. data for **5**–**11** are listed in Tables I and II.

O-Debenzylidenation of the six isomeric acetals (**5**–**7**, **9**–**11**) with trifluoroacetic acid led to the corresponding methyl 3-deoxy-3-nitroheptoseptanosides **12**, **14**, **16**, **18**, **20** and **22** (Scheme 3), all fully characterized, and subsequent reduction with Raney nickel followed by *N*-acetylation afforded the 3-acetamido-3-deoxyheptoseptanosides **13**, **15**, **17**, **19**, **21** and **23** in high yields. The n.m.r. data for **12**–**23** are given in Tables III and IV.

Because configurations could not be assigned with confidence on the basis of n.m.r. spectroscopy alone (see a subsequent section), it was necessary to correlate the new heptoseptanosides chemically with known compounds. Hydrolysis would obviously lead to the corresponding free heptoses; however, no 3-deoxy-3-nitro-heptoses appear to have been described in the literature, and of the eight stereoisomeric 3-acetamido-3-deoxy-(C-5 D)-D-heptoses relevant for comparison, only five have been described[5,11]. On the other hand, abundant literature data covering all configurational series are available for 3-amino-3-deoxy-D-hexose derivatives. We therefore decided to convert all of our methyl 3-acetamido-3-deoxyheptosides into such derivatives, by chain shortening at the non-reducing terminal[11]. This involved methanolytic transformation of the heptoseptanosides into heptopyranosides, degradation of the latter to hexopyranosides by periodate cleavage followed by borohydride reduction, and characterization of the products as appropriate* (Scheme 4).

* Performance of such a sequence with the nitro precursors of the acetamido glycosides appeared unattractive. Exploratory experiments revealed that **12** is remarkably sluggish in undergoing methanolytic ring contraction; in boiling methanol containing 5% of HCl, 60% of **12** was unchanged after 5 days, and 20% remained after 10 days in 10% methanolic HCl. For acid hydrolysis, a greater stability of nitrodeoxypyranosides as compared to ordinary pyranosides has been observed before[12].

TABLE I

^{1}H-N.m.r. spectral data (500 MHz) for 5,7-*O*-benzylidenenitroheptoseptanosides **5**–**11** in CD_3CN

Compound[a]	*Chemical shifts (δ)*									
	PhCH	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-7'*	*OMe (s, 3 H)*
5	5.57s	4.49d	4.08dt[b]	4.81t	4.19m[b]	3.63dd	3.77td	4.21dd	3.60dd	3.40
6	5.55s	4.74d	4.38sp[b]	5.05dd	4.32m[b]	4.08t	3.72[c]	4.21m	3.72[c]	3.40
7[d]	5.59s	4.76d[e]	4.36m[b]	4.94dd	4.77m[b]	3.90dd	3.88td	4.22dd	3.59dd	3.40
8[d,f]	5.63	4.57d[e]	4.28dd	5.28dd	4.04dd	4.25dd	3.83td	~4.25m[g]	~3.7[h]	3.47
9[i]	5.56s	4.53d[e]	4.28dd	5.10dd	4.16dd	4.11dd	3.77td	4.19dd	3.64dd	3.49
10	5.54s	4.68d	4.42d[i]	4.77d	4.48m[b]	3.61dd	4.15dd	4.20dd	3.54t	3.40
11	5.56s	4.54d[e]	4.47dd[i]	4.92dd	4.46nm	3.75dd	4.02td	4.21dd	3.61t	3.44

	Coupling constants (Hz)							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{6,7'}$	$J_{7,7'}$
5	6.5	10.2	10.2	8.1	10.0	5.8	10.0	10.7
6	2.0	9.0	6.5	9.0	9.0			
7	5.9	1.8	6.2	3.5	9.6	5.8	9.7	10.7
8	5.8	1.8	4.75	7.7	9.8	~5	~10	
9	5.9	1.8	4.5	7.5	10.7	5.5	10.0	10.9
10	4.2	~0	10.5	8.3	9.8	5.6	10.0	10.0
11	5.7	10.5	1.2	3.0	10.0	6.0	10.0	11.5

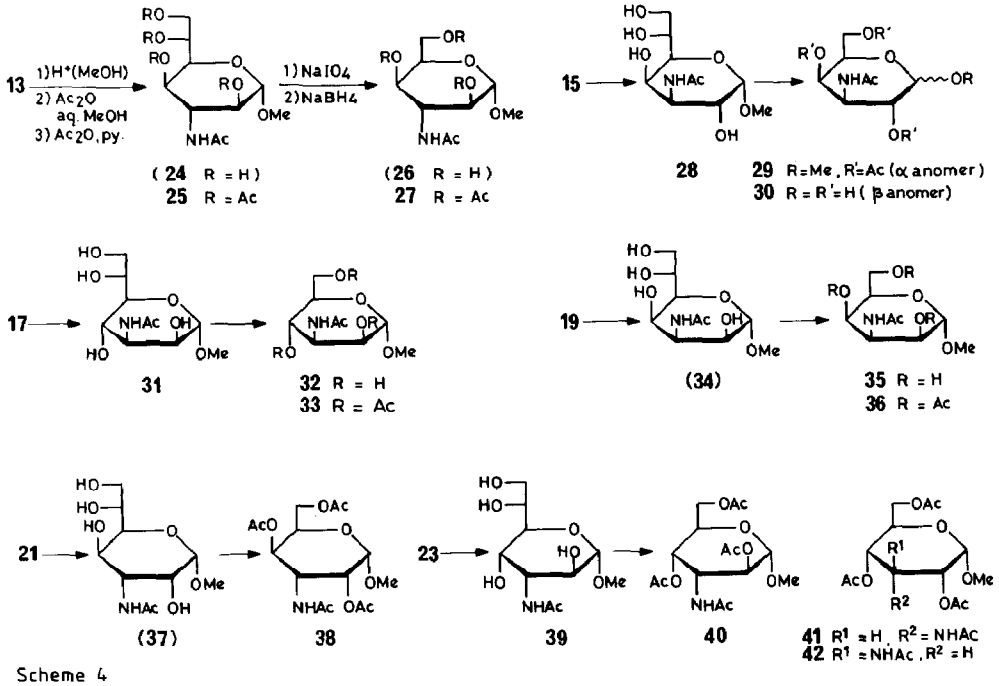
[a] All compounds showed 5-H multiplets for Ph in the δ 7.5–7.4 region. [b] Simplified to dd after D_2O exchange. [c] Part of AB-multiplet (2 H). [d] At 250 MHz. [e] Showing additional splitting of 0.5–0.7 Hz due to long-range coupling. [f] Showed a 3-H triplet at δ 1.20 for ethyl. In Me_2SO-d_6 solution, a doublet for OH coupled with H-2 occurred at δ 6.01 ($J_{2,OH}$ 5.3 Hz). [g] Overlapped by H-2 and H-5 signals. [h] Part of ill-resolved, 3-H multiplet containing the *O*-CH_2 signals of the ethyl group. [i] After D_2O exchange.

TABLE II

^{13}C-N.m.r. chemical shifts (δ) for **5**–**11** in CD_3CN (125.76 MHz)

Compound[a]	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*OMe*
5	105.1	71.3	91.9	74.0	82.9	61.5	69.7	56.3
6	103.2	73.4	91.8	70.0	80.6	64.8	69.5	57.0
7	103.2	71.2[b]	89.8	68.1[b]	78.8	59.2	69.7	56.3
8[c]	102.7	69.7[b]	91.5	68.7[b]	80.9	61.0	66.9	55.4
9	102.8	71.4	91.1	73.3	82.9	61.7	69.7	56.3
10	99.3	72.2	89.7	70.2	84.5	62.4	70.0	55.8
11	106.2	69.2	89.3	70.3	80.5	58.7	69.6	56.5

[a] All compounds except **8** showed four signals for Ph at δ 138.7 $\pm$0.2, 130.0 $\pm$0.1, 129.17 $\pm$0.08, and 127.3 $\pm$0.05, and a signal for *Ph*CH at δ 101.6 $\pm$0.1. [b] Values for C-2 and C-4 may have to be interchanged. [c] At 50.3 MHz in Me_2SO-d_6 solution; additional signals were at δ 138.3, 129.0, 128.4, and 126.6 (Ph), 99.7 (*Ph*CH), 78.1 (OCH_2Me), and 15.6 (CH_2Me).



Scheme 4

Thus, heptoseptanoside **13**, on boiling with 2.33M methanolic hydrogen chloride for 48 h underwent ring contraction and concomitant *N*-deacylation, affording after *N*-reacetylation, 75% of α-D-heptopyranoside **24**, characterized as its crystalline tetraacetate **25**; ~10% of unchanged **13** was recovered. Pure **24**, regenerated from **25** by Zemplén *O*-deacetylation, was oxidized by periodate, and the product reduced, to give 76% of an acetamido hexopyranoside (**26**) which yielded a crystalline triacetate identified as the known methyl 2,4,6-tri-*O*-acetyl-3-acetamido-3-deoxy-α-D-idopyranoside[13]

TABLE III

^{1}H-N.m.r. spectral data (300 or 400 MHz) for nitro and acetamido heptoseptanosides **12–23** in D_2O

Compound	*Chemical shifts (δ)*									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-7'*	*OMe (s, 3 H)*	*NAc (s, 3 H)*
12	4.32d	3.85dd	4.63t	3.77dd	3.26t	——3.57–3.41 (m, 3 H)——			3.20	
13	4.71d	3.82dd	4.20t	3.69dd	3.66dd	3.89ddd	4.03dd	3.94dd	3.69	2.27
14	5.15d[a]	4.83dd[a]	5.25dd[a]	4.48dd[a]	3.98dd	4.05td	3.98dd	3.87dd	3.72	
15	4.97d	4.33dd	4.73dd	4.27dd	3.84dd	4.12ddd	4.01dd	3.95dd	3.69	2.24
16	4.98d[a]	4.44dd	5.11dd	4.71dd	4.02dd	3.92td	3.82dd	3.73dd	3.56	
17	4.73d	4.42dd	4.58dd	4.14dd	3.98dd	4.05ddd	3.97dd	3.92dd	3.66	2.25
18	4.71d	4.32dd	5.22dd	4.03dd	4.06t	3.89ddd	—3.82–3.76 (m, 2H)—		3.52	
19	4.65d[a]	4.10dd	4.68dd	3.90dd	3.72dd	3.80ddd	3.99dd	3.92dd	3.65	2.20
20	4.61d	4.68d	4.40d	4.25dd	3.35dd	3.87ddd	3.63dd	3.54dd	3.30	
21	4.85d[a]	4.18dd	4.05dd	3.97dd	3.59dd	4.11ddd	3.93dd	3.84dd	3.59	2.15
22	4.83d[a]	4.65dd[a]	5.22dd	4.69dd	3.96dd	4.09ddd	4.00dd	3.93dd	3.68	
23	4.63d[a]	4.02dd[a]	4.18dd	4.11dd	3.81dd	-3.94–3.89 (m, 2 H)-		3.83dd	3.59	2.14

	Coupling constants (Hz)							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{6,7'}$	$J_{7,7'}$
12	6.8	10.3	10.3	8.5	9.6			
13	7.1	10.0	~10	8.3	~10	2.6	5.0	12.0
14	4.2	10.4	1.4	3.8	7.8	3.0	7.1	12.2
15	4.2	7.6	3.6	7.8	9.7	2.9	5.2	12.2
16	7.7	4.7	7.8	2.9	5.9	3.4	6.8	12.2
17	7.2	2.3	6.0	3.5	~9	2.8	5.0	12.2
18	6.8	1.75	3.4	8.5	~9			
19	7.0	1.5	3.7	9.0	10.2	2.9	4.3	12.2
20	4.3	~0	10.7	8.3	10.2	2.7	4.8	12.2
21	4.1	1.2	10.5	8.1	10.1	2.8	5.3	12.25
22	6.25	10.35	1.35	2.8	9.9	2.8	5.3	12.3
23	6.9	10.3	1.75	3.2	9.6		6.1	12.7

[a] Showing an additional, small splitting due to long range coupling (~0.2–0.5 Hz)

TABLE IV

^{13}C-N.m.r. chemical shifts (δ) of nitro and acetamido deoxyheptoseptanosides **12–23** in D_2O (50.32 MHz)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	O*Me*	NHCO*Me*
12	104.0	70.9	92.3	76.1	72.3	71.3	62.3	56.9	
13	104.8	71.6	53.5	77.2	73.2	71.6	62.6	56.6	23.0
14	100.6	69.6	88.4	74.6	72.1	72.9	63.9	57.6	
15	99.8	69.4	53.3	73.2	72.3	72.3	62.9	56.7	22.8
16	102.2	66.7	93.3	74.5	71.1	73.0	63.7	56.4	
17	103.8	69.9	56.1	——70.9, 70.6, 69.9——			62.9	56.7	22.8
18	102.5	72.2	91.1	74.7	71.1	71.8	62.7	56.8	
19	103.9	72.6	57.6	76.0	71.1	71.7	62.5	56.9	23.0
20	99.0	71.6	89.7	72.5	73.7	72.2	62.7	56.3	
21	99.5	73.4	53.1	73.2	74.3	72.5	62.7	56.1	22.9
22	104.6	69.3	90.0	72.5	—70.5, 70.4—		62.7	56.9	
23	105.1	68.8	52.5	73.6	70.6	70.6	62.7	56.5	22.8

(**27**, Scheme 4). The D-*glycero*-D-*ido* configuration of **13** and its precursors **12** and **5** was thereby established.

Analogous degradations were performed with the remaining five acetamido heptoseptanosides (Scheme 4). Compound **15** was methanolyzed quantitatively to an anomeric mixture of aminoheptopyranosides from which, after *N*-reacetylation, the crystalline α anomer[11] (**28**) could be isolated. Its degradation, followed by peracetylation of the product gave the known, but syrupy[14], methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-galactopyranoside (**29**). For additional confirmation, the crude mixture of **28** and its β anomer, obtained from **15**, was similarly degraded, and the anomeric mixture of methyl 3-acetamido-3-deoxyhexopyranosides (not characterized) was hydrolyzed to the free amino sugar that was *N*-acetylated and identified as the known[11,15] crystalline 3-acetamido-3-deoxy-β-D-galactose (**30**).

Septanoside **17** gave in 70% yield the crystalline α-D-pyranoside **31**, degradation of which led to the known[16] methyl 3-acetamido-3-deoxy-α-D-mannopyranoside (**32**). Although the optical rotation agreed well with the reported value[16], there was a serious discrepancy in the melting points. However the triacetate **33** proved identical by ^{1}H-n.m.r. to a reference sample prepared from authentic[17] methyl 3-amino-3-deoxy-α-D-mannopyranoside.

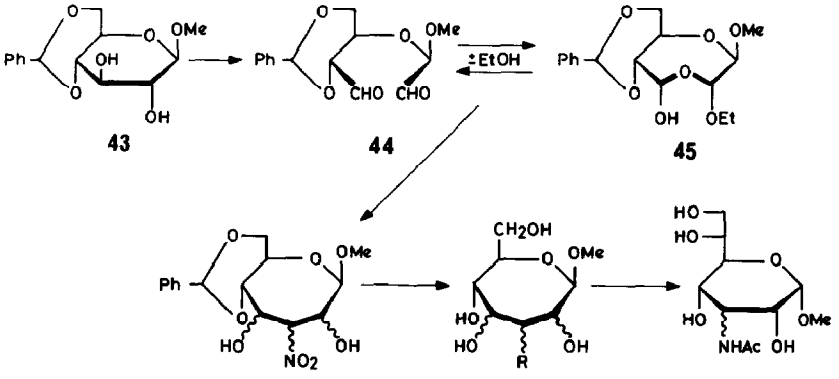
Methanolysis of the septanoside **19** produced a mixture of pyranosidic and furanosidic aminoglycoside hydrochlorides (^{13}C-n.m.r.), part of which crystallized. The crystalline fraction, consisting mainly of α-pyranoside but containing also $\sim$10% of other forms, was *N*-acetylated and the resulting, non-homogenous product (mainly **34**) was degraded to furnish in 70% yield the crystalline methyl 3-acetamido-3-deoxy-α-D-talopyranoside (**35**), not previously described. The syrupy triacetate **36**, obtained therefrom, gave a ^{13}C-n.m.r. spectrum identical with that of a reference sample prepared by peracetylation of authentic[14] methyl 3-amino-3-deoxy-α-D-talopyranoside hydrochloride.

The septanoside **21** was methanolyzed to an anomeric mixture of aminoheptopyranosides containing >90% of the α-D form, as suggested by the C-1 signal intensities at δ 99.13 (α) and δ 101.30 (β) seen in the ^{13}C-n.m.r. spectrum. *N*-Acetylation afforded 83% of the corresponding acetamide mixture, doubtless consisting chiefly of **37**, which could not be obtained crystalline for identification with known[11] **37**. However, degradation of **37**, followed by peracetylation furnished 80% of crystalline methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-gulopyranoside[13] (**38**).

Finally, methanolysis of **23** produced a mixture of pyranosidic and furanosidic amines (^{13}C-n.m.r.) from which, upon *N*-acetylation, 40% of crystalline methyl 3-acetamido-3-deoxy-D-*glycero*-α-D-*altro*-heptopyranoside (**39**) was obtained. It was converted into the known[18–20] crystalline methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-altropyranoside (**40**).

The n.m.r. data for the six peracetylated α-D-hexopyranosides obtained (**27**, **29**, **33**, **36**, **38**, and **40**) are listed in Tables V and VI. Also included, for comparison, are the data for the α-D-*allo* and α-D-*gluco* isomers (**41** and **42**, Scheme 4), not encountered in these studies.

For use in structural studies of nitrogenated products derivable from cellulose polyaldehyde[4], model monosaccharides having the β-D-glycoside anomeric configuration were needed. Moreover, it was of interest to examine the distribution of stereoisomers, produced by nitromethane cyclization, for the β-D-heptoseptanoside system in comparison with the foregoing observations in the α-series. It is well known that, in the formation of 3-deoxy-3-nitrohexopyranosides, the anomeric configuration of the starting dialdehydo glycoside has a pronounced directive effect on the stereochemistry of the products[3]. Consequently, the β-anomeric dialdehyde **44** (Scheme 5), isolated as its crystalline ethyl hemialdal **45**, was prepared from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**43**) by the procedure used for **3**, and its cyclization with nitromethane was made the object of an exploratory study by ^{13}C-n.m.r. spectroscopy. The reaction conditions previously employed for **3** led to a mixture of methyl 3-deoxy-3-nitro-β-D-



Scheme 5

TABLE V

^{1}H spectral data at 400 MHz for methyl 3-acetamido-3-deoxy-α-D-hexopyranoside 2,4,6-triacetates in $CDCl_3$

Compound	*Chemical shifts (δ)*									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*OMe (s, 3 H)*	*NH*	*Ac (4 s, 4 × 3 H)*
27	4.98ddd	5.05ddd	4.83dtd	5.30ddt	4.62sp	—4.50 (m, 2 H)—		3.49	6.3d	2.10–2.04
29	4.82d	4.98dd	4.58sp	5.31dd	4.15ddd	4.03dd	3.96dd	3.36	6.6d	2.09,2.03.1.98,1.83
33	4.68d	4.87dd	4.60sp	4.96t	3.98sp	4.26dd	4.04dd	3.35	5.7d	2.10,2.04,2.00,1.87
36	4.71 ~ s	4.87dd	4.60m	5.17dd	4.14sp	4.08dd	4.03dd	3.33	6.3d	2.1–1.9
38	4.87dnm	5.10dd	4.35m	5.02dd	4.15ddd	4.09dd	4.00dd	3.42	6.7d	2.08,2.03,2.00,1.98
40	4.65s	4.75dd	4.62m	5.02dd	4.00ddd	4.19dd	4.18dd	3.45	6.5	2.15,2.10,2.00,1.95
41[a]	4.87d	4.93dd	—4.88–4.83 (m, 2 H)—		3.99ddd	—4.22 (m, 2 H)—		3.46	6.7d	2.08,2.07,2.02,1.98
42[a]	—4.84–4.79 (m, 2 H)—		4.64ddd	4.85t	4.03ddd	4.29dd	4.07dd	3.42	5.4d	2.07,2.07,2.03,1.88
	Coupling constants (Hz)									
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{3,NH}$	*others*	
27	2.0	3.7	3.7	2.3	5.5	7.0		8.7	$J_{1,3}$ 1.3, $J_{1,4}$ 0.7, $J_{2,4}$ 0.8	
29	3.5	11.6	3.2	1.3	5.75	7.2	11.3	8.4		
33	1.5	3.25	10.35	10.35	5.1	2.3	12.2	9.2		
36	~1.5	~3	~3	~1	5.2	7.4	11.1	8.1		
38	3.6	5.0	3.5	1.4	4.9	7.6	11.5	7.9	$J_{1,3}$ 1.1, $J_{1,4}$ ~0.5	
40	<1	3.2	4.25	10.5	2.8	2.7	12.1	9.3		
41	3.6	4.5		10.0	3.7	3.7		8.0		
42		10.1	10.1	10.0	4.3	2.3	12.1	9.8		

[a] At 300 MHz.

TABLE VI

^{13}C-N.m.r. chemical shifts (δ) for methyl 3-acetamido-3-deoxy-α-D-hexopyranoside 2,4,6-triacetates in $CDCl_3$ (50.32 MHz)[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OMe*	*NAc*	*OAc*
27	98.7	67.4	46.7	66.5	64.0	62.6	55.5	23.1	20.6
29	96.2	68.9	46.7	67.7	66.1	61.6	54.6	22.0	20.2–20.0
33	97.5	71.7	48.2	66.8	68.1	62.4	55.1	23.0	20.8–20.0
36	98.1	69.0	44.8	67.0	66.8	62.3	55.0	22.8	21.0–20.5
38	97.6	64.7	48.0	68.6	63.4	62.2	55.6	23.1	20.4
40	98.7	69.9	46.7	65.0	64.7	63.0	55.8	23.4	20.8–20.7
41[b]	97.8	66.5	47.7	66.3	63.9	62.3	56.0	23.4	20.8–20.7
42[b]	96.8	70.4	49.9	68.6	67.5	61.9	55.1	23.0	20.6–20.4

[a] In some case, values given for C-2 and (or) C-4 and (or) C-5 may have to be interchanged. [b] At 75.43 MHz

heptoseptanosides (**46**). Three major components (A, B, C) present in a ratio of approximately 3:2:1 were revealed by C-1 signals at 104.2, 104.5 and 106.8 p.p.m. in the ^{13}C-n.m.r. spectrum.

Component B could be separated from A and C by flash chromatography, obtained crystalline, and assigned the *β-glycero*-D-*altro* configuration by analysis of its ^{1}H-n.m.r. spectrum in comparison with those of **5**–**11**. Thus all data were essentially the same as those for **7**, except for $J_{1,2}$, which was 2.5 instead of 5.5 Hz.

O-Debenzylidenation of the complete mixture **46** gave a mixture of nitrotetraols (**47**) showing the corresponding C-1 signals, in similar intensity ratios at 107.15, 104.3, and 104.6 p.p.m. respectively. Catalytic hydrogenation of **47** with Raney nickel, followed by *N*-acetylation, produced a mixture of acetamido septanosides (**48**) that exhibited four C-1 signals (ratio ~ 1:1.5:2:0.5), namely three major ones at 109.5, 104.9 and 106.3 p.p.m. for the compounds originating from A, B and C, and a minor one at 104.1 p.p.m. for a component whose precursors in **46** and **47** had not been clearly discernible in the spectra.

The β-heptoseptanoside mixture **48** was subjected to methanolytic ring isomerization followed by *N*-reacetylation, under the conditions employed in the α-series; it was expected that any β-septanoside present, which had its anomeric counterpart among the six α-septanosides previously investigated, should thereby give the same pyranosides and furanosides as the counterpart, in similar proportions.

The mixture of ring-contracted glycosides obtained from **48** expectedly was complex, and not every detail of its ^{13}C-n.m.r. spectrum could be unambiguously interpreted. However, its most significant features were interpretable by comparison of the C-1 signals (Fig. 1) with those of the isomerized glycosides generated from the individual α-septanosides, listed in Table VII. Therefore, knowing that the D-*glycero*-D-*altro* configuration must be represented (having been identified through isolation of component B in **46**), one could assign the peaks at 108.7, 102.5 and 102.0 p.p.m. to the furanosidic and pyranosidic forms of that configuration. The prominent peak at 99.8

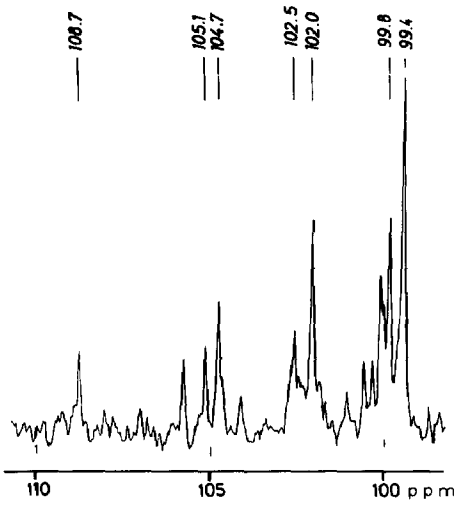


Fig. 1. Partial ^{13}C-n.m.r. spectrum (50.32 MHz, D_2O) of the mixture of glycosides obtained on methanolysis and re-*N*-acetylation of the mixture **48**.

TABLE VII

^{13}C-N.m.r. chemical shifts (δ: 50.32 MHz, D_2O) of C-1 in methyl 3-acetamido-3-deoxyheptosides formed in methanolysis of heptoseptanosides

Starting compounds	*Products after* N-*reacetylation*[a]				
	Pyranosides		*Furanosides*		*Others*
	α	β	α	β	
13	102.5 (100)				
15	99.8 (77)	105.10 (23)			
17	101.3	100.15			
19	101.9 (89)				104.7 (11)[b]
21	100.5 (88)	102.4 (12)			
23	102.0 (43)	101.6 (7)[c]	108.7 (21)[d]	102.5 (18)[e]	

[a] Intensity proportion as percentage of total C-1 signals intensities is given in parentheses. [b] Possibly 3-acetamido-1,7-anhydro-D-*glycero*-D-*talo*-heptopyranose. [c] Tentative assignment. There was an additional signal at δ 102.6 (11), possibly from an anhydro sugar, and attributions may have to be reversed. [d] With corresponding C-4 signal at δ 80.4. [e] With corresponding C-4 signal at δ 82.9.

together with the smaller one at 105.1 p.p.m. clearly represented the D-*glycero*-D-*galacto* configuration (in the form α- and β-pyranoside, respectively), which can therefore be attributed to component C in **46**. The strongest peak (99.4 p.p.m., Fig. 1) doubtless belonged to an α-pyranoside that originated from the most abundant product (A) in **46** and had not been encountered previously (compare Table VII). By exclusion, it must therefore be assigned formula **49**, representing the α-D-*glycero*-D-*gluco* or the α-D-

glycero-D-*allo* configuration, undifferentiated at present*. The remaining signals in Fig. 1 indicated additional, minor components in the mixture, but it was not possible to identify or exclude positively any of the four remaining configurations.

DISCUSSION

Structure of the heptoseptanosides. — By chemical conversion into known hexosamine derivatives, the six stereoisomeric methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-heptoseptanosides obtained from the dialdehyde **2** by nitromethane cycloaddition and, in part, by subsequent epimerization were unambiguously assigned the D-*glycero*-D-*ido* (**5**), D-*glycero*-D-*galacto* (**6**), D-*glycero*-D-*manno* (**7**), D-*glycero*-D-*talo* (**9**), D-*glycero*-D-*gulo* (**10**) and D-*glycero*-D-*altro* (**11**) configurations. From comparison of optical rotation and melting point data, it appears that **5**, **6**, and **9** correspond to the three (configurationally undetermined) products previously isolated by Wolfrom (ref. 6 and see footnote on page 131), in yields of 34, 15, and 10%, respectively. Wolfrom's fourth isomer (m.p. 188–190° dec., $[\alpha]_D$ +20° in methanol)[6] has not been encountered; it had been obtained in 8% yield after fractional crystallization of a mixture of cyclization products isolated as solid sodium nitronates (see footnote on page 131), a procedure not used in the present study. Conversely, our syrupy, major isomer **7** (yield, 42%; $[\alpha]_D$ +49° in dimethyl sulfoxide), which had the D-*glycero*-D-*manno* configuration as anticipated on the basis of Baschang's[5] closely related precedent, had not been mentioned previously. However, the 4-ethyl ether **8** of **9** was most probably identical with the monoethyl ether generated[6] by treatment of one of the isomers with aqueous ethanol†.

Because of the flexibility of seven-membered ring systems, it is difficult to predict conformational preferences in substituted heptoseptanoses, even when mobility is partly restricted by a *trans*-fused cyclic acetal ring. Therefore, interrelation of estimated dihedral angles deduced from proton–proton coupling constants could not *a priori* be relied on for identifying configuration positively. However, with their configurations firmly established by chemical correlations, it became possible to suggest plausible conformations for **5**–**7** and **9**–**11** on the basis of their ^{1}H-n.m.r. data (Table I). It was assumed that conformational analysis of cycloheptane[22] 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,

* In the (non-nitrogenous) methyl hexopyranoside analogs, the C-1 signals[21] for the α-D-*allo* and α-D-*gluco* isomers coincide (100.0 p.p.m.), although those for the β-anomers differ (101.9 and 104.0 p.p.m. respectively). The peak at 104.7 p.p.m. (Fig. 1) might well be due to the companion β-D-*glycero*-D-*gluco* anomer of **49**, but other signals (unidentified or obscured) might refer to the β-D-*glycero*-D-*allo* anomer, or furanoid isomers. It is also conceivable that both 3-epimers were present.

† Although no degradation studies were performed with compound **8**, this ethyl ether could be securely correlated configurationally with its parent **9**, by ^{1}H-n.m.r. (see the *J* values in Table I). The hydroxylic proton was coupled with H-2, indicating that the *O*-ethyl group was located on *O*-4. The mere fact that **8** was obtainable by treatment of **9** with ethanol might have seemed suggestive of configurational identity but constituted no proof since an elimination-addition proceeding through a 3,4-unsaturated intermediate must be involved in this alkylation.

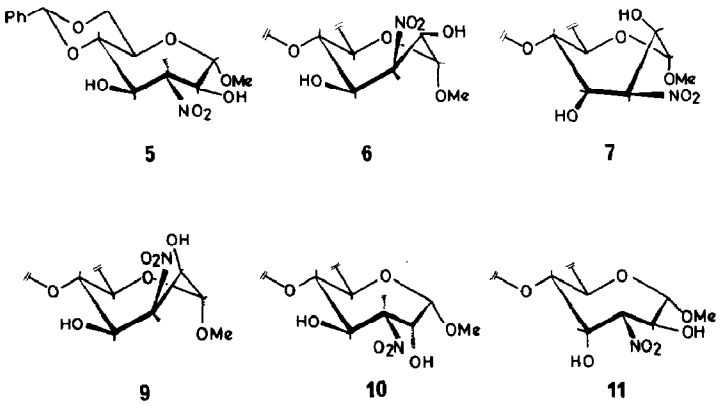


Fig. 2. Possible conformations of methyl 5,7-*O*-benzylidene-3-deoxy-3-nitroheptoseptanosides.

flexible chair form through which they are interconnected in a pseudorotational cycle. Dihedral angles (ω) for consecutive *cis* bonds in the twist-chair were computed[22] as $-41.2, 97.0, -75.8, 52.9, -75.8, 97.0$, and $-41.2°$; for *trans* bonds, they are $\omega \pm 120°$. 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 our septanose acetals, 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 D-*glycero*-D-*ido* isomer **5** a Dreiding model of the regular $^5C_{1,2}$ chair shows that pseudorotational downward movement of C-2 (to relieve eclipsing by opening the H-1,2 dihedral angle from 120° to ~150°) and some flattening of the ring portion C-1 to C-5 (to improve staggering of OH-2, NO_2-3, and OH-4, concomitant with positioning H-3 more nearly antiparallel to H-2 and H-4)*, leads to a somewhat distorted twist conformation as depicted approximatively in Fig. 2, having all ring protons oriented in harmony with the observed vicinal couplings of 6.5 ($J_{1,2}$) and 8–10 Hz ($J_{2,3}$ to $J_{5,6}$). Very similar conformational models can be constructed for the isomers **10** and **11** that have the same C-3 configuration as **5**. In the case of **10**, 1,2-eclipsing associated here with substantial non-bonded interaction between the 1-methoxy and 2-hydroxy groups in the $^5C_{1,2}$ chair requires a somewhat larger downward shift of C-2, which relieves this strain and also enhances staggering between NO_2 and OH-4, generating a twist form with dihedral angles (H-1,2 ~60°, H-2,3 ~100°, H-3,4 ~180°) that accord with the observed J values. A conformation as postulated for **5** also agrees with the n.m.r. data of **11**.

For the isomers having the opposite C-3 configuration (**6**, **7**, and **9**), no models of twist forms adjacent to the $^5C_{1,2}$ chair on the pseudorotation itinerary were found to

* This manipulation is necessary in Dreiding models with their rigid, 109.5° tetrahedral angles. In cycloheptane the C-C-C angles are[22] 112° and so the ring is naturally flatter than the models suggest. Little additional bond angle strain is probably introduced in **5**, and a net gain in energy results from this reduction in non-bonded substituent interaction.

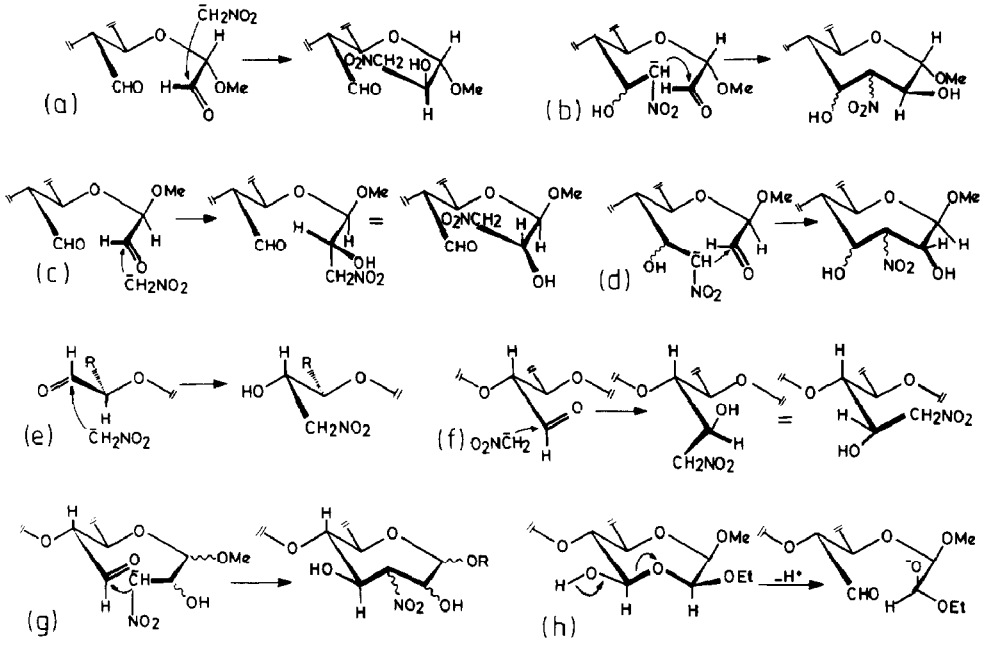
accommodate the n.m.r. parameters. Evidently, these isomers must adopt alternative conformations wherein the sterically demanding nitro group can avoid an axial orientation. (Opposition to axial placement of that group is a well-known phenomenon in deoxynitro pyranosides and cyclitols[3,23]. Thus, for **6** and **9** is suggested a twist conformation derived from the $^{O}C_{3,4}$ chair by an upward displacement of C-3; this move abolishes the eclipsing between the NO_2 and OH-4 groups and brings all H,H dihedral angles into harmony with the recorded J values. The same form would appear unfavorable for isomer **7** because of severe 1,4-transannular interaction of oxygen substituents on the lower face of the ring; indeed, $J_{3,4} = 6$ Hz argues against such a form in which the H-3,4 dihedral angle would lie between 90 and 120°. However, a form arising from the $^{O}C_{3,4}$ chair by opposite twisting (*i.e.*, an upward shift of C-4), which places MeO-1 and OH-4 farther apart, shows in the Dreiding model approximate angles of 20° (H-1,2), 90° (H-2,3), 150° (H-3,4), 60° (H-4,5), and 180° (H-5,6), compatible with the measured constants.

The foregoing analysis leads to an interesting conclusion concerning the results of base-catalyzed epimerizations at C-3. The thermodynamically more-stable epimers (**5**, **10**, and **11**) are those which can be accommodated in a twist conformation basically related to the $^{5}C_{1,2}$ chair, whereas their less-stable counterparts (**9**, **6**, and **7**, respectively) appear to adopt twist-form variants framing the $^{O}C_{3,4}$ chair. It is also to be noted that, upon removal of the benzylidene acetal ring, coupling between ring protons ($J_{1,2}$ to $J_{5,6}$) is altered very little in the cases of **5**, **10**, and **11**; the corresponding values for the unblocked derivatives **12**, **20**, and **22** differ by ~0.5 Hz or less (Table III). This indicates that no significant changes in conformation occur in the process. On the other hand, some of the J values of **6**, **7**, and **9** change quite distinctly by up to 5.1, 3.7, and 1.7 Hz, respectively (see **14**, **16**, and **18** in Table III), which suggests that debenzylidenation is here associated with relief of strain through some conformational adjustment.

Stereochemistry of the nitromethane cycloaddition reaction. Configurations at C-2 and C-4. — The regioselectivity of the cycloaddition of nitroalkanes to sugar dialdehydes with respect to the initial addition of the nucleophile to one of the carbonyl groups* is not known. In the present case however, where the initial reaction involves the relatively stable ethyl hemialdals **3** and **45**, it may appear reasonable to assume primary addition at "C-4"; however, both possibilities need to be considered.

The rotameric preference of the "C-2" aldehydo group in **2** should involve orientation of the C=O double bond between H-1 and the less hindered acetal oxygen atom at C-1 (*i.e.*, the anomeric methoxyl), and, according to Cram's rule, nucleophilic attack should occur on the less hindered, *si* face leading to the *S* configuration for C-2, regardless of whether it is an initial attack (*a*) by methanenitronate ion, or a cyclizing attack (*b*) by a pregenerated C-3 nitronate ion (Scheme 6). Therefore, *O*-1,2-*trans* stereochemistry is to be expected for products of kinetic control. Previous studies in the

* For convenience of discussion, carbohydrate numbering is applied to **2**, **3**, **44**, and **45**. Thus, "C-2" and "C-4" refer to the aldehyde or potential aldehyde groups that, upon cyclization, become C-2, and C-4 in the nitroglycosides formed.



Scheme 6

synthesis of analogous 3-deoxy- and 3,6-dideoxy-3-nitro-α-D- (or L)-hexopyranosides had shown that *O*-1,2-*trans* products are indeed favored kinetically, but that *O*-1,2-*cis* isomers nevertheless may become preponderant owing to thermodynamically controlled, secondary epimerizations[3,14,16,17,24]. With **5** and **7** and possibly some **9** accounting for 78% of the isolated products, the kinetic rule was largely obeyed and concurrent epimerization was less important than in hexopyranosides where conformational-energy differences between stereoisomers tend to be greater. In the case of the β-anomeric dialdehyde **44**, the arguments just given predict attack of the nucleophile on the *re* face of the "C-2" carbonyl group (Scheme 6, *c* and *d*), again leading to *O*-1,2-*trans* stereochemistry which does in fact predominate also in 3-deoxy-3-nitro-β-D- (and L)-hexopyranosides[3,8,15,25]. As the β-D-*glycero*-D-*gluco* (or *allo*) product was believed to be the preponderant component of the mixture of β-nitroheptoseptanosides **46** obtained from **44**, and the β-D-*glycero*-D-*galacto* isomer was a second, major component, the rule was followed.

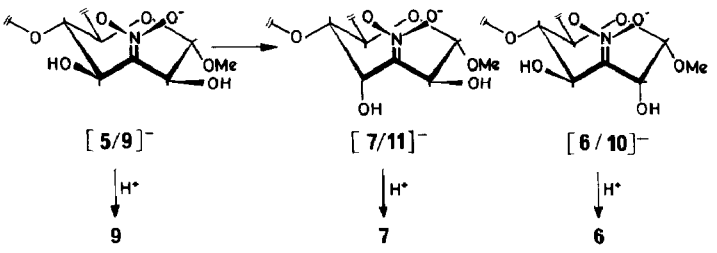
As concerns to the reaction at "C-4", experience in synthesis of nitropyranosides has shown that *O*-4–*O*-5 *anti* products (*i.e.*, O-4, C-6 bonds *trans*) are formed with high stereoselectivity under kinetic control, in either anomeric series[3,8,14,17,24,25]. Clearly, the preferred rotameric orientation of "C-4" is determined, not by the steric bulk of the substituents borne by C-5 (namely, C-6 and the heterocyclic oxygen group), but by polarity that causes the C=O bond to be placed antiparallel to the C-5–O-5 bond (Scheme 6 *e*). Attack by methanenitronate ion on the less hindered, *si* face of the carbonyl, or cyclizing attack by pregenerated C-3 nitronate (which necessarily would

occur from the same direction), leads to the observed O-4–O-5 *anti* stereochemistry. The same mechanism should operate in cyclizations of **2** and **44**, but with an important difference. In these aldehydes, the "C-4" carbonyl group in its preferred orientation offers its less-hindered face to approach by a nucleophile from the outside only, for a primary addition to give O-4–O-5-*cis* stereochemistry (Scheme 6, *f*), whereas cyclizing attack by pregenerated C-3 nitronate on the same carbonyl rotamer would give an O-4–O-5-*trans* product (Scheme 6, *g*). For production of a compound with O-4–O-5-*cis* stereochemistry, the cyclizing step would have to involve a less-favored carbonyl rotamer. In fact, the carbanionic addition with **44**⇌**45** gave O-4–O-5-*cis*, β-D-*glycero*-D-*gluco* (or *allo*) and β-D-*glycero*-D-*altro* glycosides in considerable preponderance, lending weight to the aforementioned suggestion that primary addition may take place at "C-4" rather than "C-2".

In the α-D-series emanating from **2**⇌**3**, stereoselectivity at C-4 was low and actually reversed, as O-4–O-5-*trans* nitroseptanosides (**5**, **6**, and **9**) arose in a combined proportion slightly higher than that of the O-4–O-5 *cis* isomer **7** (~5:4), although the reaction conditions were identical. One explanation for this might be a lower energy of activation for opening of the α-D-hemialdal (**3**→**2**), compared to that for the β-D-anomer **45**→**44** where the oxyanionic charge developing at "C-2" should unfavorably interact with the anomeric configuration (*Δ*2 effect, see Scheme 6, *h*). Consequently, reaction of **3** with base and nitromethane would be faster and a kinetic product formed would be exposed to the base for partial thermodynamic isomerization for a longer period of time than a more slowly generated product from **45**.

Stereochemistry of the nitromethane cycloaddition reaction. Configuration at C-3. — In syntheses of 3-deoxy-3-nitropyranosides, the C-3 configuration obtained is determined by the great tendency of the nitro group to emerge equatorially in the preferred chair conformer of the sugar; an axial nitro group would face severe nonbonded interactions[23]. This is independent of what direction might appear kinetically favored for protonation of an intermediate 3-nitronate since epimerization at that center is extremely facile. For the conformationally versatile septanoside system, however, it may be expected that both nitromethine configurations can be accommodated with little strain, at least in some of the possible permutations of stereochemistry at the other chiral centers, and pairs of isolable 3-epimers (**5**, **9**; **6**, **10** and **7**, **11**) have indeed been found.

In the presence of at least one equivalent of a strong base, nitromethine epimers are converted into a common nitronate. Thus, both **5** and **9** give the anion [**5**, **9**]$^-$. Rapid acidification at low temperature protonates C-3 from the more accessible, lower side of the molecule, to produce **9**. However, part of the salt suffers epimerization at C-4 during its sojourn in an alkaline medium, to give the anion [**7**, **11**]$^-$, which, in turn, is similarly protonated to **7** (Scheme 7). Such epimerizations at adjacent carbinol centers, referred to in the preceding section, have been explained mechanistically[26,27], by reversibility of the nitromethane addition. The driving force is the strong $A^{(1,3)}$ effect between the oxygen atoms of the nitronate group and the nearly coplanar hydroxyl groups in [**5**, **9**]$^-$, which is partly relieved in the [**7**, **11**]$^-$ anion. No such strain exists in free **5**, and the latter



Scheme 7

is more stable thermodynamically than its epimer **9**, as is shown by the 10:1 equilibrium established in the presence of only a catalytic proportion of base, *i.e.*, at relatively low pH value where the free-nitro group form prevails. The fact that much **5** and little **9** was present in the nitromethane cyclization mixture obtained from **2** is likewise explained by the use of a nonstoichiometric proportion of base in the reaction.

Like the α-D-*glycero*-D-*talo* nitroseptanoside **9**, its α-D-*glycero*-D-*galacto* isomer **6** appears to be quite strained conformationally, being forced into a form which avoids a pseudo-axial nitro group pointing inward over of the heterocycle (see Fig. 2). It epimerized readily by the action of pyridine, to give the more stable D-*glycero*-D-*gulo* isomer **10**. Similar considerations apply to the epimeric equilibrium between the α-D-*glycero*-D-*manno* and D-*glycero*-D-*altro* isomers **7** and **11** in pyridine, although this process was slower and the energy difference appeared small. The fact that the less stable isomers **6** and **7** were obtained in the cyclization, rather than **10** and **11**, must be attributed to the stability of the anions [**6**, **10**]$^-$ and [**7**, **11**]$^-$ in a moderately alkaline medium; this stability, greater than that of [**5**, **9**]$^-$ because of smaller $A^{(1,3)}$ strain, accounts for the existence of these isomers as salts rather than free nitro compounds in the presence of the limited amount of base that was provided, and protonation then proceeded as shown in Scheme 7. Related observations of steric strain, causing differential nitromethine acidities in configurationally isomeric nitro sugars, have been made before[27].

Thus the process, as performed under the given conditions, may be approximated by the following equation:

$$\mathbf{2} + CH_3NO_2 + 0.6\ RO^- \rightarrow \sim 0.4\ \mathbf{5} + \sim 0.01\ [\mathbf{5,9}]^- + \sim 0.1\ [\mathbf{6,10}]^- + \sim 0.5\ [\mathbf{7,11}]^- + 0.6\ ROH \xrightarrow{H^+} \sim 0.4\ \mathbf{5} + \sim 0.1\ \mathbf{6} + 0.5\ \mathbf{7} + 0.01\ \mathbf{9}$$

It is understandable, from the discussion, that different conditions of alkalinity, temperature, and reaction time will lead to different isomer distributions*.

* After completion of this study, Professor F. Santoyo González (Granada) informed us that **3** reacted with nitromethane in the presence of a catalytic amount of potassium fluoride and dibenzo-18-crown-6, in acetonitrile solution during 32 h at 45°, to give 68% of **5** as the sole nitroheptoseptanoside isolated (A. Vargas Berenguel, Ph.D. thesis, University of Granada, September 1989). Clearly, these were conditions for thermodynamic control, and the result confirms our own conclusion that **5** is the thermodynamicallly most favored isomer.

EXPERIMENTAL

General methods. — Conventional processing for *O*-acetylations means that the mixture containing Ac_2O and pyridine was concentrated under diminished pressure in a rotatory evaporator, then several times in the presence of added methanol and then, the residue was coevaporated with toluene. Melting points were determined with a Büchi 535 apparatus in capillary tubes, and optical rotations in a Jobin Yvon Digital micropolarimeter. ^{1}H-N.m.r. spectra were measured in Bruker instruments at 200, 300, 400, or 500 MHz. Chemical shifts are referenced to internal Me_4Si for solutions in organic solvents, or acetone for solutions in D_2O. ^{13}C-N.m.r. data were obtained with a Bruker 200 SY spectrometer at 50.32 MHz and are referenced to internal acetone (31.07 p.p.m.) for solutions in D_2O. When required, the ^{1}H and ^{13}C signals were assigned using 2D–CH correlation, obtained by using the Bruker program XHCORR AU with ^{1}H decoupling. The delay times D_3 and D_4 were set respectively to 3.3 and 2 ms. The relaxation time D_1 was set to 2 s; 64 experiments of 320 transients with a size of 2K were accumulated. Spectral values were 5000 Hz for the ^{13}C domain and 1200 Hz for the ^{1}H domain. The final data matrix was zero filled at 2048 × 512 and apodised with a sine-bell function in f_1 and a square function in f_2.

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[28] (**1**, 56.4 g, 0.2 mol) was suspended, and partially dissolved, in 95% EtOH (1 L) and a solution of $NaIO_4$ (48 g, 0.22 mol) in water (1 L), adjusted to pH 5 with M NaOH, was added. The mixture was stirred in the dark at 25° for 48 h. The product was collected by filtration, washed thoroughly with water and then with light petroleum (b.p. 30–60°) to yield crude **3** (50 g, 77%). Recrystallization from boiling acetone gave pure **3** (42 g, 64.4%), m.p. 153–154°, $[\alpha]_D$ +67° (*c* 0.5, pyridine); lit.[9] m.p. 144–145°; ^{1}H-n.m.r. [300 MHz, $(CD_3)_2SO$]: δ 7.45 (m, 5 H, Ar), 7.05 (d, $J_{9,OH}$ 6.4 Hz, OH-9), 5.60 (s, PhC*H*), 4.81 (dd, $J_{9,9a}$ 7.4 Hz, H-9), 4.65 (d, $J_{6,7}$ 6 Hz, H-6), 4.38 (d, $J_{6,7}$ 6 Hz, H-7), 4.16 (dd, $J_{4,4a}$ 5.2, $J_{4,4'}$ 10.3 Hz, H-4), 3.78 (m, 2 H, ~ddd with $J_{4a,4'} \sim J_{4a,9a} \sim 10$ and $J_{4,4a} \sim 5$ Hz for H-4a, superposed by q for CH_3CH), 3.66 (t, $J \sim 10$ Hz, H-4'), 3.50 (m, 2 H, H-9a and CH_3CH_2), 3.34 (s, 3 H, OCH_3), and 1.14 (t, 3 H, CH_2CH_3); ^{13}C-n.m.r. [$(CD_3)_2SO$]: δ 137.2, 128.8, 128.0 and 126.6 (Ph), 102.7 (C-7), 100.1 (C-2), 99.5 (C-6), 97.8 (C-9), 82.1 (C-9a), 68.4 (C-4), 63.5 (CH_3CH_2O), 61.3 (C-4a), 55.1 (CH_3O) and 14.9 (CH_3CH_2O).

Anal. Calc. for $C_{16}H_{22}O_7$ (326.3): C, 58.88; H, 6.80. Found: C, 59.15; H, 6.67.

Reaction of the hemialdal **3** *with nitromethane: isolation of methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-heptoseptanosides (***5–8***) and hemialdal byproduct* **4**. — To a cooled (0°) mixture of the crude hemialdal **3** (16.3 g, 50 mmol) and $MeNO_2$ (2.8 mL, 50 mmol) in MeOH (120 mL) was added a cold (0°) solution of Na (0.7 g, 30 mmol) in MeOH (60 mL). The mixture was kept for 2 h at 0–5°, then deionized under continued cooling with Amberlite IRN-77 (H^+) resin (70 mL, prewashed with MeOH), and evaporated to dryness, with evaporation of added toluene (50 mL) from the residue. Dissolution of the residue in $CHCl_3$ (100 mL) and storing it overnight in a refrigerator yielded a crystalline precipitate (6.0 g, 36%) which was recrystallized from hot metha-

nol, furnishing *methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-glycero-D-ido-heptoseptanoside* **5** (4.0 g, 24%), m.p. 225° dec. (from MeOH), 232–233° dec. (from 1,4-dioxane–hexane), $[\alpha]_D$ +38° (*c* 0.7, MeOH).

Anal. Calc. for $C_{15}H_{19}NO_8$ (341.3): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.75; H, 5.62; N, 4.10.

The $CHCl_3$ mother liquor of **5** was evaporated, the dry residue dissolved in ether (100 mL) and the solution stored overnight at 0°, to deposit the methyl hemialdal *9-hydroxy-6-α,7-dimethoxy-2-phenyl*-trans-m-*dioxano[5,4-e][1:4]-dioxepan* (**4**, ~100 mg after recrystallization from MeOH), m.p. 124–125°, $[\alpha]_D$ +68° (*c* 0.6, pyridine); ^{1}H-n.m.r. [300 MHz, $(CD_3)_2SO$]: δ 7.46 (m, 5 H, Ph), 7.00 (d, $J_{9,OH}$ 6.3 Hz, OH-9), 5.60 (s, H-2), 4.85 (dd, $J_{9,9a}$ 7.4 Hz, H-9), 4.60 (d, $J_{6,7}$ 6 Hz, H-6), 4.40 (d, $J_{6,7}$ 6 Hz, H-7), 4.15 (dd, $J_{4,4a}$ 5.2, $J_{4,4'}$ 10.2 Hz, H-4), 3.80 (ddd, $J_{4a,4'}$ 10.2, $J_{4a,9a}$ 9.65 Hz, $J_{4a,4}$ 5.2 Hz, H-4a), 3.65 (t, *J* 10.2 Hz, H-4'), 3.55 (dd, *J* 7.4 and 9.7 Hz, H-9a), 3.40 and 3.35 (2 s, 6 H, OCH_3); ^{13}C-n.m.r. [$(CD_3)_2SO$]: δ 137.1, 128.9, 128.1 and 126.3 (Ph), 102.6 (C-7), 100.9 (C-2), 100.1 (C-6), 97.9 (C-9), 82.0 (C-9a), 68.4 (C-4), 61.3 (C-4a), 55.6 and 55.1 (2 OCH_3).

Anal. Calc. for $C_{15}H_{20}O_7$ (312.3): C, 57.68; H, 6.46. Found: C, 57.64; H, 6.16.

The ethereal filtrate from **4** was evaporated to dryness and the residue dissolved in $CHCl_3$. Addition of petroleum ether (b.p. 30–60°) and refrigeration overnight gave crystals (2 g, 12%) which were recrystallized from the same solvent mixture to give 1.5 g (9%) of *methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-glycero-D-galacto-heptoseptanoside* (**6**), m.p. 184–185°, $[\alpha]_D$ +66.4° (*c* 0.5, MeOH).

Anal. Calc. for $C_{15}H_{19}NO_8$ (341.3): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.10; H, 5.60; N, 4.11.

The mother liquor remaining after collection of **6** was concentrated and, to the residue dissolved in ether, was added petroleum ether (b.p. 30–60°) to yield, after overnight refrigeration, small amounts of unidentified, impure crystalline material (consisting possibly of **9**). The process was repeated three times in order to remove most of this crystallizable product. The bulk of the mother liquor contents (7.2 g, 42%) remained syrupy and was mainly composed of *methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-glycero-D-manno-heptoseptanoside* (**7**), $[\alpha]_D$ +49° (*c* 9.7, Me_2SO).

Anal. Calc. for $C_{15}H_{19}NO_8$ (341.3): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.54; H, 5.66; N, 4.49.

When a solution of crude **7** (1.0 g) in hot, 75% EtOH was cooled and stored for several days at room temperature, crystals were deposited. Isolated and rapidly recrystallized from hot MeOH, the product (0.11 g) proved to be *methyl 5,7-O-benzylidene-3-deoxy-4-O-ethyl-3-nitro-D-glycero-D-talo-heptoseptanoside* (**8**), m.p. 192–193°, $[\alpha]_D$ +80° (*c* 2.3, Me_2SO) and +75° (*c* 2, MeOH).

Anal. Calc. for $C_{17}H_{23}NO_8$ (369.4): C, 55.28; H, 6.28; N, 3.79. Found: C, 55.48; H, 6.25; N, 3.75.

Storage for 4 months of a solution prepared from the crystalline *D-glycero-D-talo* isomer **9** (150 mg) in 75% EtOH followed by evaporation and recrystallization of the residue from MeOH also gave the 4-ethyl ether **8** (57 mg, 35%, m.p. 192–193°, $[\alpha]_D$ +80° (*c* 1, Me_2SO).

Methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-heptoseptanosides (**9–11**) *by epimerization of* **5–7**. — A chilled (0°) solution of Na (450 mg, 19.6 mmol) in MeOH (45 mL) was added to a solution of the D-*glycero*-D-*ido* isomer **5** (4.0 g, 11.7 mmol) in cold MeOH (200 mL). The mixture was kept for 24 h at 0°, deionized under continued cooling with Amberlite IRN-77 (H^+) resin and concentrated with evaporation of added toluene. The ^{13}C-n.m.r. spectrum of the residue indicated the presence of **9** and **7** in the ratio ~3:2 as estimated by integration of their characteristic C-1 and C-3 signals (Table II). No other signals were present in the respective spectral regions.

From a cooled (0°) solution of the residue in $CHCl_3$ (80 mL), 2.4 g (60%) of *methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-glycero-D-talo-heptoseptanoside* (**9**) crystallized overnight, m.p. 186°, $[\alpha]_D$ +73° (*c* 0.8, MeOH).

Anal. Calc. for $C_{15}H_{19}NO_8$ (341.3): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.71; H, 5.75; N, 3.95.

A solution of **9** (200 mg, 0.6 mmol) and $MeNO_2$ (0.5 mL) in methanolic NaOMe (12 mL, 5 mM), was kept for 24 h at 23°, then deionized and concentrated. The ^{13}C-n.m.r. spectrum of the residue showed **5** and **9** present in ~10:1 ratio, and revealed no other isomers.

The D-*glycero*-D-*galacto* (**6**) and D-*glycero*-D-*manno* (**7**) isomers were epimerized by treatment with pyridine. To determine appropriate conditions for equilibration, pilot experiments using pyridine-d_6 were monitored by ^{13}C-n.m.r. spectroscopy. The D-*glycero*-D-*ido* isomer **5** could not be so epimerized; it was only sparingly soluble at room temperature and, at 60°, remained unchanged during 24 h.

A solution of **6** (800 mg) in pyridine (3 mL) was kept at room temperature for 5 h, after which a ~2:3 equilibrium between **6** and the D-*glycero*-D-*gulo* isomer **10** had been established (^{13}C-n.m.r. monitoring). The solution was diluted with MeOH (20 mL) and concentrated with repeated addition of MeOH. The solid residue was recrystallized from hot MeOH to give *methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-glycero-D-gulo-heptoseptanoside* (**10**), m.p. 181–182°, $[\alpha]_D$ +60° (*c* 1, Me_2SO) in a yield (750 mg, 94%) evidently enhanced by a further shift in the epimeric equilibrium occuring during the processing.

Anal. Calc. for $C_{15}H_{19}NO_8$ (341.3): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.71; H, 5.70; N, 3.95.

The D-*glycero*-D-*manno* isomer **7** (1.0 g) was epimerized in pyridine (5 mL) by the same procedure as just given, but a reaction time of 55 h at room temperature, or of 2 h at 60°, was required to establish an equilibrium between **7** and the D-*glycero*-D-*altro* isomer **11**, in which the former predominated. Processing with methanol as described for **10** gave *methyl 5,7-O-benzylidene-3-deoxy-3-nitro-α-D-glycero-D-altro-heptoseptanoside* (**11**, 300 mg, 30%), m.p. 160.5–161.5°, $[\alpha]_D$ +15° (*c* 0.4, Me_2SO).

Anal. Calc. for $C_{15}H_{19}NO_8$ (341.3): C, 52.78; H, 5.61; N, 4.10. Found: C, 52.00; H, 5.50; N, 4.05.

Methyl 3-deoxy-3-nitro-α-D-heptoseptanosides **12**, **14**, **16**, **18**, **20**, and **22**. — *A. General procedure.* The corresponding benzylidene derivative **5–7** and **9–11** (200 mg) was agitated at 25° with 90% CF_3CO_2H (1.9 mL) until it dissolved (5–10 min). The acid

and resulting benzaldehyde were then removed by evaporation with 4–5 portions of added water, under diminished pressure. The crude products that crystallized from MeOH (**12**) or EtOH (**14**, **20**, **22**) were all obtained in amounts of ~ 100 mg (70%) after crystallization; those that failed to crystallize (**16**, **18**) were analyzed as the crude syrups. The $[\alpha]_D$ values refer to solutions in water.

B. Characterization of individual isomers. The D-*glycero*-D-*ido* isomer **12** had m.p. 194–195°, $[\alpha]_D$ +61° (*c* 1); the D-*glycero*-D-*galacto* isomer **14**, m.p. 142–143°, $[\alpha]_D$ +131° (*c* 1); the syrupy D-*glycero*-D-*manno* isomer **16**, $[\alpha]_D$ +76° (*c* 2); the syrupy D-*glycero*-D-*talo* isomer **18**, $[\alpha]_D$ +111° (*c* 1.8); the D-*glycero*-D-*gulo* isomer **20**, m.p. 159–160°, $[\alpha]_D$ +112° (*c* 0.6); the D-*glycero*-D-*altro* isomer **22**, m.p. 152.5–153.5°, $[\alpha]_D$ +33.5° (*c* 1.1).

Anal. Calc. for $C_8H_{15}NO_8$ (253.2): C, 37.94; H, 5.97; N, 5.53. Found for **12**: C, 37.92; H, 6.00; N, 5.45; for **14**: C, 37.94; H, 5.91; N, 5.48; for **16**: C, 39.00; H, 6.07; N, 5.66; for **18**: C, 37.47; H, 6.10; N, 5.40; for **20**: C, 37.97; H, 5.91; N, 5.48; for **22**: C, 38.20; H, 5.88; N, 5.67.

When the *mixture* of nitro sugar acetals, obtained by reaction of **3** with nitromethane, was *O*-debenzylidenated in the same fashion, the ^{13}C-n.m.r. spectrum of the product showed clearly separated C-1 signals for **12**, **14** and **16** at 104.6, 100.6, and 102.2 p.p.m. respectively, as expected from the previously-achieved isolation of **5**–**7**, and also a small C-1 signal for **18** (102.5 p.p.m.), indicating that **9** was a minor component of the mixture of acetals. The estimated ratio of **12**:**14**:**16**:**18** was approximately 3:2:4:1.

*Methyl 3-acetamido-3-deoxy-α-*D*-heptoseptanosides* **13**, **15**, **17**, **19**, **21**, and **23**. —*A. General procedure.* The corresponding nitro glycoside (5 g, 20 mmol), dissolved in 1:1 MeOH–water (150 mL) containing AcOH (3.5 mL), was hydrogenated during 2 h at 25° under 4000–5000 kPa of H_2 pressure, in the presence of Raney nickel[29] W-2 (1–2 g). The catalyst was removed by filtration and washed well with water, and the filtrate was concentrated to give crude amino glycoside showing a positive ninhydrin reaction. The product was treated at 25° with Ac_2O (3 mL) and Et_3N (3.3 mL) in a mixture of water (30 mL) and MeOH (75 mL). After 24 h, the solution was concentrated under diminished pressure with several additions of MeOH and water, and finally deionized by passage through a mixed-bed, ion-exchange column (Amberlite MB-3, 16–50 mesh). Evaporation of the aqueous eluate gave the crude acetamido compound in 80–85% yield. With the exception of **19**, which failed to crystallize, the products were obtained crystalline from EtOH (yields, 65–80%). The $[\alpha]_D$ values refer to solutions in water.

B. Characterization of individual isomers. The D-*glycero*-D-*ido* isomer **13** had m.p. 231–232° (from aq. EtOH), $[\alpha]_D$ +68° (*c* 0.6); the D-*glycero*-D-*galacto* isomer **15**, m.p. 105–106°, $[\alpha]_D$ +90° (*c* 1.0); the D-*glycero*-D-*manno* isomer **17**, m.p. 239.5–240.5, $[\alpha]_D$ +72.5° (*c* 1.0); the syrupy D-*glycero*-D-*talo* isomer **19**, $[\alpha]_D$ +87° (*c* 0.7); the D-*glycero*-D-*gulo* isomer **21**, m.p. 205–206°, $[\alpha]_D$ +132° (*c* 1.1); the D-*glycero*-D-*altro* isomer **23**, m.p. 190–191°, $[\alpha]_D$ +23° (*c* 1.0).

Anal. Calc. for $C_{10}H_{19}NO_7$ (265.3): C, 45.28; H, 7.22; N, 5.28. Found for **13**: C, 45.15; H, 7.35; N, 5.18; for **15**: C, 44.34; H, 7.50; N, 4.92; for **17**: C, 45.33; H, 7.27; N, 4.79; for **19**: C, 43.44; H, 7.13; N, 6.00; for **21**: C, 45.50; H, 7.29; N, 5.20; for **23**: C, 44.68; H, 7.10; N, 5.12.

*Methyl 3-acetamido-3-deoxy-α-*D*-glycero-*D*-ido-heptopyranoside* (**24**) *and its 2,4,-6,7-tetraacetate* **25**. A 2.33M solution of HCl in anhydrous MeOH was prepared by mixing AcCl (20 mL, 0.28 mol) with abs. MeOH (100 mL). Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*ido*-heptoseptanoside (**13**, 5.0 g) was dissolved in the reagent, the mixture heated under reflux (bath temperature, 80°) for 48 h, and then concentrated under diminished pressure with several additions of MeOH. The resultant product was *N*-acetylated, as described in the general procedure for the preparation of **13** and its isomers, yielding **24** as a syrup (4.25 g, 85%) that contained ~10% of unreacted or regenerated **13** (^{13}C-n.m.r.). Repeated crystallizations of crude **24** removed most of this impurity and left behind purified **24** (3.75 g, 75%) as a syrup, which was not further characterized at this step.

The product was peracetylated with acetic anhydride and pyridine (1:1, v/v, 150 mL) during 16 h at 25°. Conventional processing gave **25** (3.72 g, 61%) which crystallized from chloroform by addition of ether–pentane, m.p. 89°, $[\alpha]_D$ +47° (*c* 0.5, $CHCl_3$); ^{1}H-n.m.r. (500 MHz, $CDCl_3$): δ 6.3 (d, $J_{3,NH}$ 9 Hz, NH), 5.23 (ddd, $J_{5,6}$ 9.8, $J_{6,7}$ 2.3, $J_{6,7'}$ 4.5 Hz, H-6), 4.90 (dd, $J_{3,4}$ 3, $J_{4,5}$ 1.9 Hz, H-4), 4.77 (nm, $J_{1,2}$ 1 Hz, H-1), 4.65 (m, $J_{2,3}$ 3, $J_{2,4}$ 1 Hz, H-2), 4.55 (dd, $J_{6,7}$ 2.3, $J_{7,7}$ 12.3 Hz, H-7), 4.34 (m, H-3), 4.20 (dd, $J_{6,7'}$ 4.5, $J_{7,7'}$ 12.3 Hz, H-7'), 4.17 (dd, $J_{4,5}$ 1.9, $J_{5,6}$ 9.8 Hz, H-5), 3.45 (s, 3 H, OCH_3), 2.1–2.0, (5 s, 3 H each, Ac); ^{13}C-n.m.r. ($CDCl_3$): δ 98.8 (C-1), 67.6 (C-6), 67.1 (C-2), 64.8 (C-4), 63.1 (C-5), 62.2 (C-7), 55.7 (OCH_3), 46.45 (C-3), 23.3 (NHAc), 20.6 (OAc).

Anal. Calc. for $C_{18}H_{27}NO_{11}$ (433.35): C, 49.89; H, 6.27; N, 3.23. Found: C, 49.69; H, 5.79; N, 2.97.

*Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-*D*-idopyranoside* (**27**). — Methyl 3-acetamido-2,4,6,7-tetra-*O*-acetyl-3-deoxy-α-D-*glycero*-D-*ido*-heptopyranoside (**25**, 2.72 g, 6.28 mmol) was *O*-deacetylated (1 h, 25°) in MeOH (33 mL) containing a catalytic amount of NaOMe (from 15 mg of Na). The deionized solution was evaporated to dryness, furnishing **24** (1.4 g, 85%) which was dissolved in water (12 mL). Sodium metaperiodate (1.15 g, 5.3 mol. equiv.) was added in small portions and the solution was kept for 2 h at 25° in the dark. The solution was then concentrated with successive additions of several portions of MeOH. Ethanol was added to the residue and the remnant insoluble salts removed by filtration. The ethanolic filtrate was concentrated and the residue was dissolved in MeOH (25 mL). Sodium borohydride (0.43 g, 11.5 mmol) was added in small portions and the solution was kept at 25° for 3 h, then deionized by passing it through a column of Amberlite IRN-77 (H^+) resin and the effluent was treated with Amberlite IRA-45 (OH^-) resin to adjust its pH to 4.5. Concentration to dryness yielded **26** as a solid (1.12 g, 90%) which was not further characterized.

O-Acetylation of **26** (0.5 g, 2.1 mmol) was performed by dissolution in 1:1 Ac_2O–pyridine (25 mL) and keeping the acetylation mixture for 16 h at 25°. The crude product obtained after conventional processing was crystallized from a small amount of EtOH yielding **27** (0.5 g, 65%), m.p. 135.5–136°, $[\alpha]_D$ +49° (*c* 1.1, $CHCl_3$); lit.[13], m.p. 134–135°, $[\alpha]_D$ +48 ±1° (*c* 1.6, $CHCl_3$).

*Methyl 3-acetamido-3-deoxy-α-*D*-glycero-*D*-galacto-heptopyranoside* (**28**). — Me-

thyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*galacto*-heptoseptanoside (**15**, 1 g) was treated with methanolic HCl (24.5 mL), as described for the methanolysis of the D-*glycero*-D-*ido* isomer **13**, to give a crude mixture (0.98 g, 100%) containing both anomers of the corresponding pyranosidic amine hydrochloride, part of which (0.5 g, 50%) precipitated from MeOH at 0° (^{13}C-n.m.r. in D_2O: δ 99.4 for C-1 α, and 104.5 for C-1 β, in ~3:1 ratio). *N*-Acetylation of it, as described for **13**, furnished a product (0.31 g, 60%) containing **28** (C-1 α: δ 99.8) and its β-anomer (C-1 β: δ 105.1). The former was obtained pure by crystallization from aq. EtOH (0.15 g, 30%), m.p. 238.5–239.5°, $[\alpha]_D$ +213° (*c* 4.1, water); lit.[11], m.p. 233–236°, $[\alpha]_D$ +207°; ^{1}H-n.m.r. (400 MHz, D_2O): δ 4.91 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.20 (m, 2 H, $J_{2,3}$ ~8.5, $J_{3,4}$ ~3.5, $J_{4,5}$ ~1.3 Hz, H-3, H-4), 3.96 (m, H-5), 3.94 (dd, $J_{6,7}$ 6, $J_{7,7'}$ 11.5 Hz, H-7), 3.91 (dd, $J_{6,7}$ 2.5 Hz, H-6), 3.88 (dd, H-2), 3.73 (dd, H-7'), 3.52 (s, 3 H, OCH_3), 2.16 (s, 3 H, *N*-Ac); ^{13}C-n.m.r. (D_2O): δ 99.8 (C-1), 70.0 (C-5,C-6), 67.6 (C-4), 66.9 (C-2), 63.9 (C-7), 56.0 (OMe), 52.2 (C-3), 22.8 (Ac).

Anal. Calc. for $C_{10}H_{19}NO_7$ (265.3): C, 45.28; H, 7.22; N, 5.28. Found: C, 45.34; H, 7.18; N, 5.13.

Methyl 3-acetamido-2,4,6-tri-O-*acetyl-3-deoxy*-α-D-*galactopyranoside* (**29**). — Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*galacto*-heptopyranoside (**28**, 1.4 g) was subjected to periodate oxidation followed by borohydride reduction, as described for the preparation of the isomeric 3-acetamido-D-idopyranoside **27** from the heptopyranoside **24**. The resulting noncrystalline 3-acetamido-3-deoxy-hexopyranoside (0.99 g, 80%) was not characterized at this step but immediately peracetylated (1:1 Ac_2O–pyridine, 18 h at 25°) to give, after conventional processing, syrupy **29** (1.4 g, 92%), $[\alpha]_D$ +104° (*c* 0.6, $CHCl_3$); lit.[14] $[\alpha]_D$ +91° ±3° ($CHCl_3$) for a syrupy preparation, subsequently characterized[30] by 60-MHz n.m.r. data ($CDCl_3$), which agreed reasonably with the more complete 400-MHz data ($CDCl_3$) now recorded in Table V.

3-Acetamido-3-deoxy-β-D-*galactose* (**30**). — A crude preparation of methyl-3-acetamido-3-deoxy-D-*glycero*-D-*galacto*-heptopyranoside (1.0 g), containing **28** and its β anomer, was oxidized ($NaIO_4$) and reduced ($NaBH_4$), as described for the preparation of **26** from **24**, resulting in syrupy 3-acetamido-3-deoxy-hexopyranoside (0.71 g, 80%). An aliquot of this syrup (0.5 g, 1.88 mmol), was boiled in 2M HCl (100 mL) for 18 h. Removal of the acid by evaporation of water, decolorization of the aqueous solution by activated charcoal, and evaporation of the water gave a partly *N*-deacetylated amino sugar (0.32 g, 85%) which was *N*-reacetylated as described for **13**. The product was recrystallized from MeOH to give **30** (220 mg, 55%), m.p. 173–174°, $[\alpha]_D$ +120 ±1° (*c* 1, water, 24 h, equil.); lit.[11] m.p. 170–172°, $[\alpha]_D$ +99° → +119° (2.5 h, equil.); lit.[15] m.p. 173°, $[\alpha]_D$ +92.5° → +118°; ^{1}H-n.m.r. [400 MHz, $(CD_3)_2SO$]: δ 7.66 (d, $J_{3,NH}$ 7.9 Hz, NH), 6.60 (d, $J_{1,OH}$ 6.9 Hz, OH-1), 4.67 (d, $J_{4,OH}$ 5.7 Hz, OH-4), 4.64 (d, $J_{2,OH}$ 5.3 Hz, OH-2), 4.55 (t, $J_{6,OH}$ 5.4 Hz, OH-6), 4.28 (t, $J_{1,2}$ 6.9 Hz, H-1), 3.65 (m, $J_{3,4}$ 3, $J_{4,5}$ ~0.5 Hz, H-4), 3.58 (m, $J_{2,3}$ ~10.5 Hz, H-3), 3.48 (m, $J_{5,6}$ 5.9, $J_{6,6'}$ ~10.5 Hz, H-6), 3.42 (m, $J_{5,6'}$ 6.5 Hz, H-6'), 3.35 (~t, H-5), 3.27 (m, H-2), 1.84 (s, 3 H, *N*-Ac); ^{13}C-n.m.r. [$(CD_3)_2SO$]: δ 169.5 (*C*O, *N*-Ac), 98.3 (C-1), 75.9 (C-5), 69.5 (C-2), 66.5 (C-4), 60.6 (C-6), 55.2 (C-3), 22.9 (Ac).

Methyl 3-acetamido-3-deoxy-α-D-glycero-D-manno-*heptopyranoside* (**31**). — Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*manno*-heptoseptanoside (**17**, 1 g) was treated

with methanolic HCl (24.5 mL), as described for the methanolysis of the D-*glycero*-D-*ido* isomer **13**, to give a crude mixture (0.98 g, 100%) containing both anomers of the corresponding pyranosidic, *N*-deacylated, amine (^{13}C-n.m.r. in D_2O: δ 99.35 p.p.m. for C-1α, 104.45 p.p.m. for C-1β). Following *N*-reacetylation (compare the preparation of **13**), crystalline **31** (0.7 g, 70%) was obtained, m.p. 139–140° (from EtOH–acetone), $[\alpha]_D$ +25° (*c* 1, water); ^{1}H-n.m.r. (400 MHz, D_2O–CD_3OD): δ 4.78 (d, $J_{1,2}$ 1.7 Hz, H-1), 4.17 (dd, $J_{2,3}$ 3.2, $J_{3,4}$ 9.8 Hz, H-3), 4.11 (quint. $J_{5,6} = J_{6,7}$ 3.6, $J_{6,7'}$ 7.25 Hz, H-6), 3.91 (dd, $J_{6,7}$ 3.6, $J_{7,7'}$ 12.2 Hz, H-7), 3.89 (m, H-2), 3.88 (t, *J* 9.8 Hz, H-4), 3.83 (dd, $J_{4,5}$ 9.8 Hz, H-5), 3.81 (dd, H-7'), 3.54 (s, 3 H, OCH_3), 2.15 (s, 3 H, *N*-Ac); ^{13}C-n.m.r. (D_2O): δ 101.4 (C-1), 74.1 (C-5), 73.2 (C-6), 69.7 (C-2), 66.4 (C-4), 63.0 (C-7), 55.5 (OCH_3), 53.4 (C-3), 22.9 (*N*-Ac).

Anal. Calc. for $C_{10}H_{19}NO_7$ (265.3): C, 45.28; H, 7.22; N, 5.28. Found: C, 46.33; H, 8.18; N, 6.57.

*Methyl 3-acetamido-3-deoxy-α-*D*-mannopyranoside* (**32**) *and its 2,4,6-triacetate* **33**. — Periodate oxidation followed by borohydride reduction was performed with methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*manno*-heptopyranoside (**31**, 1.4 g), as described for the preparation of **27** from **24**, to give **32** as a syrup (1.12 g, 90%) which crystallized from EtOH (0.75 g, 60%); m.p. 192–193° (dec.), $[\alpha]_D$ +43° (*c* 1.2, water); lit.[16] m.p. 241–243°, $[\alpha]_D$ +44° (*c* 1.66, water).

Anal. Calc. for $C_9H_{17}NO_6$ (235.2): C, 45.95; H, 7.29; N, 5.95. Found: C, 45.87; H, 7.17; N, 5.70.

Compound **32** (0.5 g, 2.1 mmol) was peracetylated with Ac_2O–pyridine (1:1, v/v 25 mL) during 16 h at 25°. Conventional processing, followed by passage of the crude product through a column of silica gel, with $CHCl_3$ as the eluent gave **33** (0.54 g, 70%), m.p. 142–143° (from acetone–ether), $[\alpha]_D$ +28° (*c* 0.7, water). A comparison sample prepared[20] from authentic methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride[17] showed m.p. 153°, $[\alpha]_D$ +24.6° (*c* 2, $CHCl_3$); lit.[16] m.p. 153°, $[\alpha]_D$ +41° (*c* 1.8, water); a mixture m.p. was 151–152°, and the ^{1}H-n.m.r. spectra were identical.

*Methyl 3-acetamido-3-deoxy-α-*D*-talopyranoside* (**35**) *and its 2,4,6-triacetate* **36** *from heptoseptanoside* **19**. — Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*talo*-heptoseptanoside (**19**, 1 g) was treated with methanolic HCl as described for **13**, yielding a mixture of *N*-deacylated pyranosidic and furanosidic aminoglycosides (^{13}C-n.m.r.), part of which crystallized from cold MeOH. The crystalline material (0.29 g, 30%) was composed chiefly of the α-pyranoside (δ 101.3 p.p.m. for C-1), but also contained a minor proportion (~10%) of other forms. It was *N*-reacetylated (compare the preparation of **13**) to give a syrupy mixture (0.25 g, 82%) consisting mainly of **34**, not characterized at this step.

The crude acetamide **34** (0.25 g) was oxidized ($NaIO_4$) and reduced ($NaBH_4$) as described for the preparation of **27** from **24**, furnishing crystalline **35** (0.15 g, 70%), m.p. 200–201° (from EtOH), $[\alpha]_D$ +99° (*c* 1.6, water); ^{1}H-n.m.r. (500 MHz, D_2O): δ 4.71 (d, $J_{1,2}$ 1.5 Hz, H-1), 3.97 (t, $J_{2,3} = J_{3,4}$ = 3 Hz, H-3), 3.83 (ddd, $J_{4,5}$ 1, $J_{5,6'}$ 4.2, $J_{5,6}$ 7.8 Hz, H-5), 3.72 (m, $J_{2,4}$ ~1.5 Hz, H-4), 3.68 (dd, $J_{5,6}$ 7.8, $J_{6,6'}$ 11.8 Hz, H-6), 3.65 (quin, $J_{1,2} = J_{2,4}$ = 1.5, $J_{2,3}$ 3 Hz, H-2), 3.63 (dd, H-6'), 3.32 (s, 3 H, OCH_3), 1.94 (s, 3 H, *N*-Ac).

^{13}C-n.m.r. (D_2O): δ 101.7 (C-1), 72.2 (C-5), 69.2 (C-2), 68.5 (C-4), 62.2 (C-6), 55.5 (OCH_3), 47.8 (C-3), 22.8 (*N*-Ac).

Anal. Calc. for $C_9H_{17}NO_6$ (235.2): C, 45.95; H, 7.29; N, 5.95. Found: C, 45.72; H, 7.02; N, 5.65.

A sample of **35** (0.1 g) was peracetylated in pyridine–Ac_2O (1:1, v/v, 10 mL) during 16 h at 25° to give **36** (0.14 g, 92%) which failed to crystallize, but gave ^{1}H- and ^{13}C-n.m.r. spectra (Tables V and VI) identical with those of a sample prepared by peracetylation of methyl 3-amino-3-deoxy-α-D-talopyranoside hydrochloride[14].

*Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-*D*-gulopyranoside* (**38**) *from heptoseptanoside* **21**. — Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*gulo*-heptoseptanoside (**21**, 1 g) was treated with methanolic HCl as described for **13**, yielding a syrupy mixture (0.98 g, 100%) of partly *N*-acylated anomeric aminoheptopyranosides containing >90% of the α anomer and <10% of the β anomer, as suggested by the intensity ratio of the C-1 signals (δ 99.13 and 101.30, respectively) present in the ^{13}C-n.m.r. spectrum (D_2O). The mixture was *N*-reacetylated in the usual manner (compare the preparation of **13**) to afford the corresponding acetamide mixture (0.83 g, 83%) containing chiefly the α anomer **37**, which could not be crystallized for comparison with known[11] **37**. Periodate oxidation of the crude product, followed by borohydride reduction and peracetylation of the resulting hexoside, by the methods described for the preparation of **27** from **24**, gave **38** (0.9 g, 89%) that crystallized from EtOH and was recrystallized from acetone–ether (0.72 g, 71%), m.p. 156–157°, $[\alpha]_D$ +84° (*c* 1, $CHCl_3$); lit.[13] m.p. 158–159°; $[\alpha]_D$ +86° ±1° ($CHCl_3$).

Anal. Calc. for $C_{15}H_{23}NO_{10}$ (361.3): C, 49.86; H, 6.42; N, 3.87. Found: C, 50.10; H

*Methyl 3-acetamido-3-deoxy-α-*D*-*glycero*-D-altro-heptopyranoside* (**39**). — Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*altro*-heptoseptanoside (**23**, 1 g) was treated with methanolic HCl as described for **13**, yielding a syrupy mixture (0.98 g, 100%) of *N*-deacylated aminoheptosides composed of α-pyranoside (C-1, δ 101.37), β-pyranoside (C-1, δ 102.4) and a furanoside (C-1, δ 108.45, C-4, 81.5) according to ^{13}C-n.m.r. (D_2O). The mixture was *N*-reacetylated as described for the preparation of **13**, to give **39** (0.65 g, 65%) which crystallized from a minimal amount of EtOH (0.4 g, 40%), m.p. 116–117°, $[\alpha]_D$ +28° (*c* 0.7, water); ^{1}H-n.m.r. (500 MHz, D_2O); δ 4.49 (d, $J_{1,2}$ 4.5 Hz, H-1); 4.07 (dd, $J_{2,3}$ 7.5, $J_{3,4}$ 4.5 Hz, H-3), 4.00 (dd, $J_{3,4}$ 4.5, $J_{4,5}$ 6.2 Hz, H-4), 3.91 (sext, $J_{5,6}$ 6.5, $J_{6,7}$ 3.5, $J_{6,7'}$ 7.0 Hz, H-6), 3.71 (t, $J_{4,5} \approx J_{5,6} \approx$6.4 Hz, H-5), 3.69 (dd, $J_{7,7'}$ 12 Hz, H-7), 3.58 (dd, H-2), 3.56 (dd, H-7'), 3.34 (s, 3 H, OCH_3), 1.94 (s, 3 H, *N*-Ac); ^{13}C-n.m.r. (D_2O): δ 102.0 (C-1), 74.2 (C-5), 70.95 (C-6), 69.1 (C-2), 65.6 (C-4), 62.9 (C-7), 56.65 (OCH_3), 52.3 (C-3), 22.9 (*N*-Ac).

Anal. Calc. for $C_{10}H_{19}NO_7$ (265.3): C, 45.28; H, 7.22; N, 5.28. Found: C, 44.58; H, 7.65; N, 5.29.

*Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-*D*-altropyranoside* (**40**). — Methyl 3-acetamido-3-deoxy-α-D-*glycero*-D-*altro*-heptopyranoside (**39**, 0.2 g) was oxidized ($NaIO_4$) and subsequently reduced ($NaBH_4$) as described for the preparation of **27** from **24**, yielding syrupy methyl 3-acetamido-3-deoxy-α-D-altropyranoside (0.16 g, 92%). It

was characterized by peracetylation in Ac_2O–pyridine (1:1, v:v) yielding crystalline **40** (from EtOH) (0.15 g, 60%), m.p. 176°, $[\alpha]_D$ +35.5° (*c* 2.6, $CHCl_3$); lit.[18] m.p. 177°, $[\alpha]_D$ +34.1° (*c* 1.2, $CHCl_3$); lit.[19] m.p. 175–177°, $[\alpha]_D$ +36.2° (*c* 1.0, $CHCl_3$); lit.[20] m.p. 176–177°, $[\alpha]_D$ +34° (*c* 2.7, $CHCl_3$).

7-Ethoxy-9-hydroxy-6-β-methoxy-2-phenyl-trans-*(1,3-dioxano) [5,4-e][1:4]-dioxepan* (**45**). — Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[28] (**43**, 56 g, 0.2 mol) was suspended in 95% EtOH (1 L) and a solution of $NaIO_4$ (48 g, 0.22 mol) in water (1 L) adjusted to pH 5 with M NaOH was added. The mixture was stored in the dark at 25° for 48 h and concentrated to dryness. The residue was extracted with abs. EtOH, the filtered extract concentrated to dryness and the product dissolved in boiling acetone and allowed to crystallize at 0°. Ethyl hemialdal **45** (38.8 g, 59.5%) showed m.p. 130°, $[\alpha]_D$ −105° (*c* 1, pyridine); ^{1}H-n.m.r. [400 MHz, $(CD_3)_2SO$]: δ 7.4 (m, 5 H, Ar), 6.9 ($J_{9,OH}$ 9.0 Hz, OH-9), 5.55 (s, PhC*H*), 4.90 (dd, $J_{9,9a}$ 6.5 Hz, $J_{9,OH}$ 9 Hz, H-9), 4.45 (dd, $J_{6,7}$ 6.0 Hz, H-6), 4.3 (d, H-7), 4.18 (m, $J_{4,4a}$ 3.8, $J_{4,4'}$ ~9 Hz, H-4), 3.75 (q, 1 H, CH_3CH), 3.65 (m, $J_{4a,9a}$ 9.5, $J_{4a,4}$ 4.8, $J_{4a,4'}$ 6.5 Hz, H-4a), 3.55 (m, H-4'), 3.45 (dd, $J_{4a,9a}$ 9.5, $J_{9,9a}$ 6.5 Hz, H-9a), 3.35 (s, 3 H for OCH_3, superposed by q for CH_3CH_2), 1.15 (t, 3 H, CH_2CH_3); ^{13}C-n.m.r. [$(CD_3)_2SO$]: δ 137.8, 129.0, 128.2 and 126.4 (Ph), 105.4 (C-7), 100.25 (C-2), 97.4 (C-6), 92.7 (C-9), 84.0 (C-9a), 68.25 (C-4), 67.7 (C-4a), 62.7 (CH_3CH_2O), 55.8 (OCH_3) and 14.95 (CH_3-CH_2O).

Reaction of the hemialdal **45** *with nitromethane: preparation of methyl 5,7-O-benzylidene-3-deoxy-3-nitro-β-*D*-heptoseptanosides* (**46**) *and isolation of the* D-glycero-D-altro *isomer*. — To a cooled (0°) solution of **45** (2.0 g, 6.13 mmol) and $MeNO_2$ (0.56 mL, 10 mmol) in MeOH (24 mL) was added a solution of Na (141 mg, 6.13 mmol) in MeOH (12 mL). After 2 h at 0°, the cold solution was deionized (Amberlite IRN-77, H^+) and evaporated to give a syrup (2.1 g) that showed a trace of unreacted **45** (R_F ~0.6) and a strong double spot (R_F 0.5) for products **46**, in t.l.c. with 3:1 CH_2Cl_2–ether; ^{13}C-n.m.r. (50.32 MHz, [$(CD_3)_2SO$]: δ 106.8, 104.5 and 104.2 (ratio ~1:2:3.3; C-1 of 3 major isomers), 91.8, 92.8 and 94.7 (the corresponding C-3 signals). Column chromatography (silica gel, 1:1 ether–hexane) of a sample yielded part of the fastest-moving component in pure form which crystallized from MeOH (156 mg), m.p., 180.6°, $[\alpha]_D$ −59.4° (*c* 0.8, Me_2SO). It was identified as methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-β-D-*glycero*-D-*altro*-heptoseptanoside; ^{1}H-n.m.r. [400 MHz, [$(CD_3)_2SO$]: δ 7.45–7.35 (m, 5 H, Ph), 6.24 (d, *J* 6.0 Hz, OH-4), 5.60 (s, PhC*H*), 5.54 (d, *J* 5.4 Hz, OH-2), 4.81 (d, $J_{1,2}$ 2.6 Hz, H-1), 4.72 (dd, $J_{3,4}$ 1.0, $J_{2,3}$ 8.0 Hz, H-3), 4.48 (sext, $J_{1,2}$ 2.6, $J_{2,OH}$ 5.4, $J_{2,3}$ 8.0 Hz, H-3), 4.42 (dt, $J_{4,OH}$ 6.0, $J_{3,4}$ ~$J_{4,5}$ ~1 Hz, H-4), 4.30 (dd, $J_{6,7}$ 4.8, $J_{7,7'}$ 10 Hz, H-7), 3.99 (dd, $J_{4,5}$ 1.0, $J_{5,6}$ 9.6 Hz, H-5), 3.92 (~td, $J_{6,7}$ 4.8, $J_{5,6}$ ≈$J_{6,7'}$ ≈9.8 Hz, H-6), 3.70 (t, $J_{6,7}$ = $J_{7,7'}$ 10.2 Hz, H-7), 3.42 (s, 3 H, OCH_3); ^{13}C-n.m.r. [$(CD_3)_2SO$]: δ ~138, 128.9, 128.0 and 126.4 (Ph), 104.4 (C-1), 100.6 (PhCH), 92.7 (C-3), 80.8 (C-4), 71.9, 69.9, 68.4, 67.6 (C-2,5,6,7), 55.8 (OCH_3).

*Methyl 3-deoxy-3-nitro-β-*D*-heptoseptanosides* (**47**). — Aq. CF_3CO_2H (90%, 10 mL) was added to the isomeric mixture of methyl *O*-benzylidene-nitroheptoseptanosides **46** (1.13 g) and the suspension was agitated for 20 min at 25°. The resulting solution was evaporated with several additions of water in order to remove the acid and

benzaldehyde, yielding syrupy **47** (830 mg, 99%); ^{13}C-n.m.r. (D_2O): δ 104.6, 104.3 and 107.15 (ratio ~3:2:1, C-1 of isomeric nitroheptoseptanosides).

*Methyl 3-acetamido-3-deoxy-β-*D*-heptoseptanosides* (**48**). — The mixture of isomeric nitroseptanosides **47** (2.5 g), dissolved in 1:1 MeOH–water (75 mL) containing AcOH (1.7 mL), was hydrogenated during 2 h at 25° under 4000–5000 kPa of H_2 pressure, in the presence of Raney nickel[29] W-2 (1 g) as described in the general procedure for the α series. After removal of the catalyst, the methanolic filtrate was concentrated to give the mixture of crude aminodeoxyheptoseptanosides (1.9 g, 90%). It was then dissolved in water (13.6 mL), and MeOH (32 mL), and Et_3N (1.31 mL), and Ac_2O (1.18 mL) were added. The mixture was kept for 24 h at 25° and then concentrated under diminished pressure, with several additions of MeOH and water, to give a mixture of *N*-acetylated aminoheptoseptanosides **48** (1.73 g, 78%); ^{13}C-n.m.r. (D_2O): δ 109.5, 106.3, 104.9, and 104.1 (ratio 1:2:1.5:0.5, C-1 of 4 isomers).

*Methyl 3-acetamido-3-deoxy-α-*D*-heptosides* (**49**) *from the mixture of methyl 3-acetamido-3-deoxy-β-*D*-heptoseptanosides* (**48**). — The crude mixture of 3-acetamido-3-deoxy-heptoseptanosides **48** (1 g, 3.8 mmol) was dissolved in cooled MeOH (20.4 mL) containing AcCl (4.03 mL, 56.8 mmol) and the solution was refluxed (80°) for 8 h and then concentrated under diminished pressure with several additions of MeOH. The resultant product (0.98 g, 100%) was *N*-acetylated, following the procedure described in the general procedure for the preparation of **13** and its isomers, yielding a complex mixture of 3-acetamido-3-deoxy heptofuranosides and heptopyranosides **49**, (0.85 g, 85%); see Fig. 1 for the C-1 region of the ^{13}C-n.m.r. spectrum.

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