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THE CYCLIZATION OF 3-*O*-BENZYL-6-DEOXY-6-NITRO-D-GLUCOSE AND -L-IDOSE TO *O*-BENZYLDEOXYNITROINOSITOLS, AND EPIMERIZATIONS RELATED THERETO*

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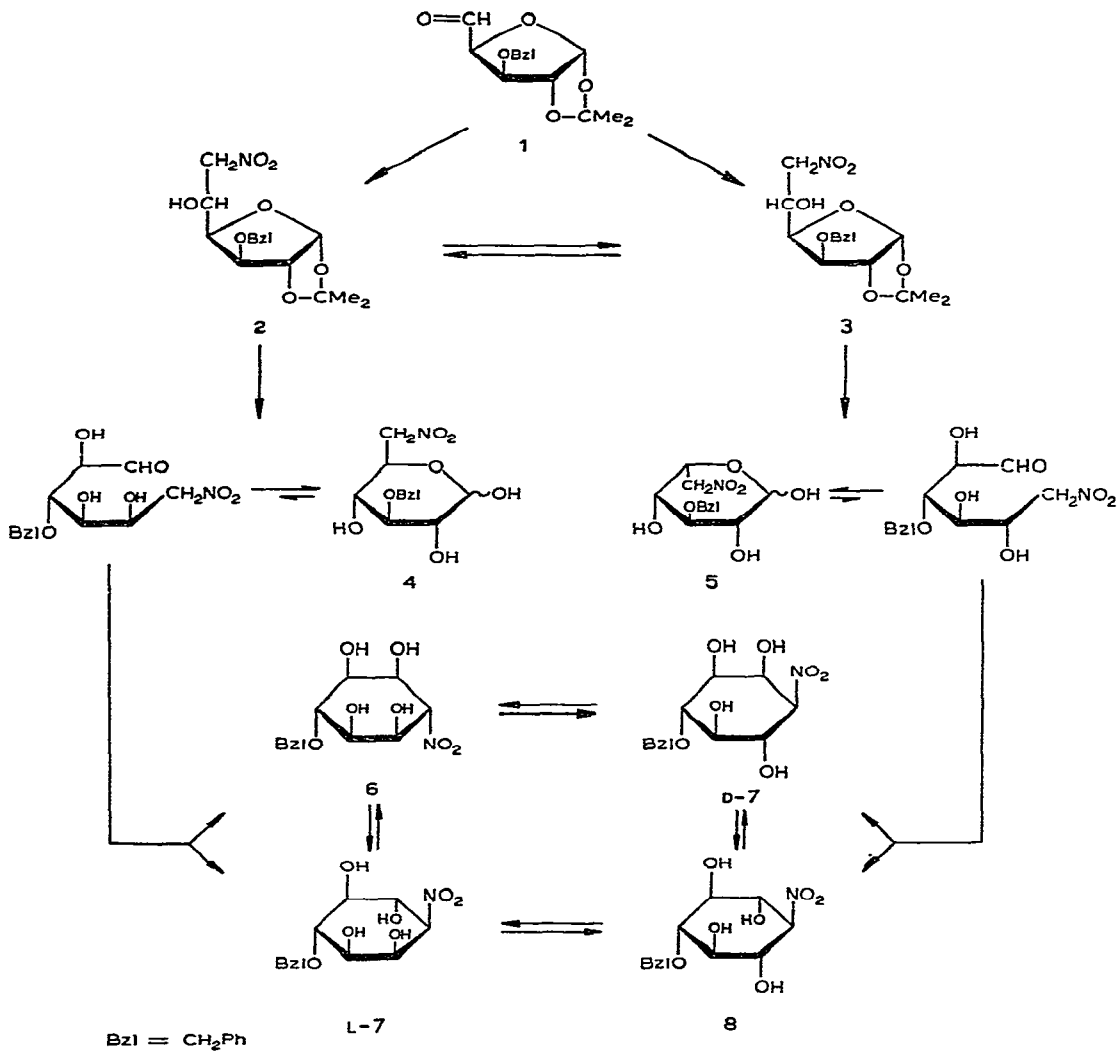
ABSTRACT

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**1**) was found to give, with nitromethane under catalysis by sodium methoxide, 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**2**) as the kinetically favored product. Subsequent, spontaneous epimerization led to a 2:1 mixture of **2** and its β-L-*ido* isomer (**3**), from which crystalline **3** was isolated. The free nitro hexoses (**4** and **5**) obtained by deacetonation of **2** and **3** were subjected to barium hydroxide-catalyzed cyclization (internal Henry reaction) to give mixtures of *O*-benzyldeoxynitroinositols. Under conditions of kinetic control, the α-D-*gluco* derivative **4** furnished 6-*O*-benzyl-3-deoxy-3-nitro-*muco*-inositol (**6**) and optically active 4-*O*-benzyl-1-deoxy-1-nitro-L-*myo*-inositol (L-**7**) in a ratio of 3:1. The β-L-*ido* derivative **5** gave the enantiomer (D-**7**) of the *myo* compound and 4-*O*-benzyl-1-deoxy-1-nitro-*scyllo*-inositol (**8**) in a similar ratio. Slow, thermodynamically controlled epimerization led from each individual nitro inositol to mixtures of the same composition, with 17–18% of **6**, 68–69% of DL-**7**, and 11–12% of **8**. All of the nitroinositol benzyl ethers were isolated crystalline and characterized further as crystalline tetraacetates (**6a–8a**). The *muco* isomer **6** gave a di-*O*-isopropylidene derivative (**6b**).

INTRODUCTION

In the framework of our synthetic[1] and mechanistic[2,3] studies on deoxynitroinositol monomethyl ethers, we investigated the corresponding benzyl ethers. It was hoped to corroborate the insights recently gained in the kinetic[2] and thermodynamic[3] aspects of the Grosheintz–Fischer synthesis and epimerization of nitroinositols[4]. Moreover, availability of nitroinositols having a hydroxyl group protected as the benzyl ether would facilitate the designing of syntheses of such biologically interesting compounds as, for example, glycosylinosamines. Consequently, the reaction sequences outlined in Scheme 1 have been performed, and we report some observations concerning the steric course of these transformations.

*Cyclizations of Dialdehydes with Nitromethane XVII. For part XVI see ref. 2. This work was supported by the National Research Council of Canada (Grant A1350 to H. H. B.).



Bzl = CH_2Ph

Scheme 1

RESULTS AND DISCUSSION

The base-catalyzed addition of nitromethane to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**1**) has been performed on two previous, independent occasions[5,6], but the stereochemical results reported seem to show a discrepancy. In the first instance[5], the reaction was conducted in methanolic solution at pH 8–9 and room temperature, and t.l.c. revealed that, within 10 min, **1** was completely converted into two products (ratio not stated) which were presumed to be the 5-epimeric nitro hexoses **2** and **3**. It was further observed[5] that, at longer times,

"one compound was gradually transformed into the other", so that, after about 1 h, "the latter product was the only one predominantly detected." Processing after 1.5 h gave a syrup that upon column chromatography gave 74% of a syrupy nitro hexose that showed one spot in t.l.c. but for which no physical data were recorded. The product was considered to be 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**2**), since upon catalytic hydrogenation it gave a high yield of a known, crystalline derivative of 6-amino-6-deoxy-D-glucose. The facts as described[5] invite the interpretation that the β-L-*ido* isomer (**3**) of **2** is formed, together with **2**, in the early kinetic phase of the nitromethane addition of **1** but is subsequently epimerized completely to what would appear to be the thermodynamically *much* more stable product, the α-D-*gluco* isomer (**2**). This view, however, is incorrect at least in part, as will be demonstrated here. In the second work[6] the reaction was performed under quite similar conditions, namely, in ethanol solution at pH 7.8–8.0, also at room temperature. After a reaction time of 5 h, the syrupy mixture of nitro sugars (of unspecified composition) was acetylated to give a crude mixture of acetates (yield, 75%) from which a pure isomer—obviously the main component—was obtained by recrystallization in 47% yield based on **1**. No attempt to isolate the other isomer, which presumably was present, was recorded. The isolated product was assigned[6] the β-L-*ido* configuration on the basis of its $[\alpha]_D$ value. Clearly this result is at variance with the earlier[5] investigation. It should be noted in this connection that the 3-*O*-methyl analog of **1** gave[1] α-D-*gluco* and β-L-*ido* adducts in a ratio of about 2:1, again under conditions similar to those mentioned above except for a longer reaction time (18 h).

In the present studies, the course of the addition of nitromethane to **1** was monitored by n.m.r. spectroscopy, which was made possible by virtue of a distinct difference (0.06 p.p.m.) in the chemical shift of H-1 in the products **2** and **3**, and by observation of the aldehydic proton signal in **1**. In agreement with Saeki and coworkers[5] we found that **1** reacts very rapidly, disappearing completely within 5 min to form **2** and **3**. However, it was established that **2** predominates strongly (>90%) even at that early stage, with almost no change in its proportion occurring during the first h of the reaction (Table I). The β-L-*ido* isomer (**3**) initially formed (<10%) does not disappear but, contrary to what might be inferred from the earlier work[5],

TABLE I

KINETIC PRODUCTS OF THE ADDITION OF NITROMETHANE TO ALDEHYDE **1** AT 25°

Time (min)	*Products* (%)	
	2	**3**
5	>90	<10
30	90	10
60	90	10
225	80	20
1240	70–75	25–30

increases gradually in its proportion to reach 25–30% after 20 h, although it never becomes the preponderant product as was implied in the paper by Iida and co-workers[6]. In a preparative run that was processed after 18 h, the ratio of **2** to **3** in the crude product was approximately 2:1 according to spectroscopic estimation, and column chromatography of the mixture furnished **2** as a pure syrup and, for the first time, crystalline **3**. Comparison of their optical rotatory dispersions with those of several sets of structurally related, 5-epimeric compounds[7] permitted an unequivocal assignment of configuration.

We then investigated the mutual interconversion of **2** and **3** by starting with the isolated compounds. In the presence of sodium methoxide and an excess of nitromethane (simulating the buffered reaction-medium of the Henry addition), practically identical mixtures of **2** and **3** in the ratio 3:2 were obtained after 96 h, with **3** epimerizing marginally faster than **2** (Table II). There was no indication for formation of side-products*. In summary, then, we have shown that formation of the α-D-*gluco*

TABLE II

EPIMERIZATION OF **2** AND **3** IN METHANOL–NITROMETHANE AT pH 8–9 AND 25°

Time (h)	*Product ratios (%)*			
	Epimerization of **2**		*Epimerization of* **3**	
	2	**3**	**2**	**3**
1	100	0	<5	>95
4	88	12	20–25	75–80
24	68–70	30–32	40	60
96	58–62	38–42	56–62	38–44

isomer is kinetically favored to a high degree, and thermodynamically favored to a lesser degree, over formation of the β-L-*ido* isomer. Kinetic control is the more important factor under the conditions that ordinarily prevail in the preparative Henry reaction, and it follows from Table I that an optimal yield of **2** could be obtained by employing a short reaction-time. A stereochemical rationale accounting for the kinetic preference of **2** has been discussed[1] in terms relating to the 3-*O*-methyl analogs. The thermodynamically controlled epimerization is relatively slow, and

*When the medium contained 1 molar equivalent of sodium methoxide but *no* added nitromethane, the semi-quantitative spectroscopic analysis of the product mixtures was rather more difficult because of an apparent complexity of the reaction, although epimerization could be seen to take place. Intermediate appearance of an aldehydic proton signal (δ 9.69, J 2 Hz) suggested liberation of a substantial amount of **1** by way of a retrograde Henry reaction (in part) of the nitro sugar. Thus, starting from **2**, the detectable amount of aldehyde was 10–20 mole percent after 30 min and continuing through the first few h of the reaction; later, the aldehyde disappeared again. Presumably the strongly alkaline, unbuffered medium promotes side reactions in **1** and probably also in the nitromethane liberated.

judging from the equilibrium position (Table II) the free-energy difference between **2** and **3** is not great. This accords with an inspection of molecular models, which do not exhibit compelling features in favor of one or the other isomer. An attempt to explain the somewhat greater stability of **2** has been made[5] by considering the steric bulk of groups in conformations assumed to be favored, but dipolar interactions that might also exist were not discussed.

Compounds **2** and **3** were deacetonated with 90% trifluoroacetic acid to give the corresponding nitro hexoses (**4** and **5**) as syrupy mixtures of anomers. N.m.r. spectra established the sucessful removal of the isopropylidene group and retention of the benzyl group, but these sensitive free sugars were not characterized further except by recording their optical rotations and the v.p.c. retention times after trimethylsilylation*.

The cyclization of **4** was performed under catalysis with barium hydroxide at pH 8 and 0°, and it led to a mixture of products consisting chiefly of 6-*O*-benzyl-3-deoxy-3-nitro-*muco*-inositol (**6**) and optically active 4-*O*-benzyl-1-deoxy-1-nitro-L-*myo*-inositol (L-**7**). Fractional crystallization gave **6** as a partly crystalline material which by acetonation afforded the 1,2;4,5-di-*O*-isopropylidene derivative (**6b**) in a yield of 40% (based on **4**). Pure **6** was subsequently obtained by hydrolysis of **6b**. The crystalline L-*myo* isomer (L-**7**) was isolated in 16.5% yield directly from the crude cyclization mixture. For further characterization, especially by n.m.r. spectroscopy, the tetraacetates **6a** and L-**7a** of these products were also prepared. Cyclization of **5** was conducted likewise and produced mainly the enantiomer (D-**7**) of the *myo* compound, together with a lesser proportion of 4-*O*-benzyl-1-deoxy-1-nitro-*scyllo*-inositol (**8**). Owing to secondary epimerization, the product mixture also contained some **6** and some L-**7**, the latter causing a minor lack of optical purity in isolated D-**7**. However, recrystallization of the acetylated product (D-**7a**) removed the racemic admixture. Isolation of **8** or its tetraacetate (**8a**) proved troublesome in these experiments. It succeeded more readily, although with poor yield, when **4** or **5** were cyclized by sodium methoxide in a medium of methanol and nitromethane, and the ensuing epimeric equilibration was allowed to continue until the solution had zero rotation. Processing then furnished 6% of **8**, which was purified via **8a**. A small proportion (1%) of racemic tetraacetate DL-**7a** was also isolated on this occasion, whereas acetonation of crude reaction product yielded pure **6b** (18%). No additional nitroinositol stereoisomers were detected in any of these experiments, in notable contrast to the studies[1–3] on *O*-methyl analogs in which the *epi*-3 configuration was encountered in addition to the configurations mentioned here.

Allocation of the *muco-3*, *myo-1*, and *scyllo* configurations to the products readily followed from analysis of their ring-proton n.m.r. signals. The enantiomeric

*Analysis by v.p.c. (see later) revealed that the L-idose derivative **5** was always contaminated by significant amounts (up to 15%) of nitroinositols which arose by spontaneous cyclization during preparation and storage. Crystals that occasionally formed in syrupy **5** were identified as such products. It is to be recalled that the non-benzylated parent compound of **5** also displayed a similar tendency to cyclize (more so than its α-D-*gluco* isomer), even at neutral or slightly acidic pH (ref. 8).

assignment of the optically active compounds D- and L-**7** was derived from consideration of the configurations at C-5 in the respective precursors **3** and **2** and application of the IUPAC/IUB 1967 Rules of Nomenclature as outlined by Anderson[9] (see also ref. 2).

With the pure nitroinositol benzyl ethers in hand for comparison, it became possible to determine product ratios, in reaction mixtures, by means of vapor-phase chromatography (v.p.c.) of trimethylsilyl derivatives. The procedure[2,3] was used to monitor the course of the cyclizations of **4** and **5** in the presence of 0.1 equiv. of barium hydroxide at 0°. The data obtained (Table III) agree roughly with the results of the preparative work already detailed. The reaction of **4** was found to be nearly complete after less than 4 h, and that of **5** was even faster. The course of epimerization of the individual nitroinositols at 25° was then examined similarly. In the presence of a catalytic amount of barium hydroxide (0.1 equiv.) the epimerizations were very slow, with 90% or more of each surviving for 48 h. Doubling the amount of base thereafter accelerated the conversion of **6** and **7** slightly but scarcely that of **8**. Epimeric equilibrium had not been reached after 5 days when observations were abandoned because of increasing deterioration of the reaction solutions. More rewarding was a similar study using an *excess* of barium hydroxide (4.6 equiv.) (Table IV). Equilibration was reasonably fast under these conditions, giving identical mixtures composed of **6** (17–18%), **7** (68–69%), and **8** (11–12%) after 24 h (starting from **7** and **8**) and 72 h (starting from **6**). The reactions were invariably accompanied by slow precipitation of solid material, which presumably was barium nitronate of one or more of the isomers; such precipitates were included in the samples withdrawn for v.p.c. analysis. For this reason, the product ratios just mentioned do not necessarily reflect the true epimeric equilibrium in solution, and free-energy differences calculated from them would be liable to error. Conformational-energy calculations and experimental data of our previous work[3] on analogous methyl ethers would entertain an expectation that the thermodynamic stabilities of the present compounds as *nitronates*

TABLE III

CYCLIZATION OF **4** AND **5** AT 0° IN THE PRESENCE OF BARIUM HYDROXIDE (0.1 EQUIV.)

Time	*Composition (%) of reaction mixture*									
	Cyclization of **4**					*Cyclization of* **5**				
	4	**6**	**7**	**8**	U[a]	**5**	**6**	**7**	**8**	U[a]
1 min	93	~1			6	75	~1	~15	~3	~6
5 min	77	16	6		1	18	1	67	12	2
1 h	37	46	17			1	4	77	17	1
3.75 h	2	74	23		1	tr	8	74	17	1
20.5 h		76	24			1	7	74	17	1
3 days		77	23				7	76	17	

[a]Unidentified products.

TABLE IV

EPIMERIZATION OF *O*-BENZYLDEOXYNITROINOSITOLS WITH EXCESS BARIUM HYDROXIDE AT 25°

Time (h)	*Composition (%) of reaction mixture*											
	Epimerization of **6**				*Epimerization of* **7**				*Epimerization of* **8**			
	6	**7**	**8**	U[a]	**6**	**7**	**8**	U[a]	**6**	**7**	**8**	U[a]
0.1	84	13		3	3	83	6	8		19	79	1
1	57	24	11	8	9	63	22	6	5	42	49	4
24	24	63	10	2	17	68	12	3	18	69	11	2
72	18	69	11	2	18	68	8	6	17	68	7	8

[a]Unidentified products.

(namely, in the presence of excess base) should follow the order **6**>**7**>**8**. The unexpectedly high proportion of **7** in the equilibrated mixtures therefore is an apparent anomaly that might well be caused by solubility factors as yet unelucidated.

EXPERIMENTAL

General methods. — For general preparative and instrumental techniques, see previous articles from this laboratory[1,2,10]. Unless otherwise indicated, the mobile phase in t.l.c. was 5:1 chloroform–ethyl acetate and the n.m.r. data refer to 100 MHz spectra of $CDCl_3$ solutions with tetramethylsilane as the internal standard. Optical rotations were measured at room temperature.

Preparation of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose[11–13] (**1**). — 1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranose (25 g) was benzylated with benzyl bromide in *N*,*N*-dimethylformamide as described[14], except that barium oxide was used[15] instead of silver oxide. Passage of the crude product through a 450-g column of aluminum oxide (reagent grade, for chromatography) by means of benzene gave the 3-benzyl ether (28 g) as a pure syrup; R_F 0.73, $[\alpha]_D$ −28° (*c* 1.5, chloroform). Lit.[14] $[\alpha]_D$ −25.5° and[16] −27.7°. Removal of the 5,6-*O*-isopropylidene group by the procedure[1] using 90% acetic acid (300 ml) at 40° required 2 h and gave oily but chromatographically homogeneous (R_F 0.10) 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose. N.m.r. data (60 MHz): δ 7.38 (s, 5H, Ph), 5.97 (d, H-1, $J_{1,2}$ 4 Hz), 4.65 (d, H-2), 4.75 and 4.58 (AB-q, 2H, J_{AB} 12 Hz, $-CH_2-$), 4.2–3.8 (5H, unresolved), 1.47 and 1.30 (s, 2×3H, CMe_2), 2.87 (s, broad, 2H, hydroxyl). In order to ascertain purity, the material was acetylated conventionally with acetic anhydride and pyridine. The crystalline 5,6-diacetate was obtained pure (20.4 g) after one recrystallization from methanol; m.p. 120°, $[\alpha]_D$ −50.8° (*c* 0.5, chloroform), R_F 0.68. Lit.[17] m.p. 119–120°, $[\alpha]_D$ −46.4°. Catalytic deacetylation of the diacetate[13] (20 g) regenerated the 5,6-dihydroxy compound (17 g) as a colorless oil showing $[\alpha]_D$ −45.5° (*c* 0.4, chloroform); reported[17] $[\alpha]_D$ −45.9°. The n.m.r.

spectrum was superposable on that of the substance prior to acetylation, so that inclusion of this step would appear unnecessary. Glycol cleavage of this compound leading to **1** has been performed by use of lead tetraacetate[11], periodic acid in acetic acid[12], and sodium metaperiodate in aqueous methanol[13]. We employed the last-mentioned method and obtained **1** as reported[13].

3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (**2**) *and -β-L-idofuranose* (**3**). — *A. Kinetics of formation.* A solution of **1** (100 mg) in methanol (2.0 ml) and nitromethane (1.0 ml) was rendered alkaline by the addition of 3.25M sodium methoxide solution (0.11 ml). The mixture was kept at 25° in a stoppered flask. At specified time-intervals (Table I), 0.60-ml samples were withdrawn and injected into 0.5M acetic acid in methanol (1.0 ml). The acidified solution was passed through a small column containing Rexyn 101 (H^+) resin (2 ml, prewashed with methanol), the column was rinsed with methanol (5 ml), and the combined effluent was evaporated to give a residue from which 2 ml of carbon tetrachloride was evaporated. After drying *in vacuo*, the residue (16–19 mg) was dissolved in carbon tetrachloride (0.4 ml) and its n.m.r. spectrum was recorded. Integration of peaks at δ 5.97 (**2**) and 6.03 (**3**) at a sweep width of 250 Hz gave the product ratio (Table I). The aldehydic proton signal of **1** (δ 9.68) had already disappeared in the first sample taken.

B. Preparation. A solution of **1** (15 g) in ethanol (47 ml) and nitromethane (11.7 ml) was stirred under nitrogen at 0°, and a methanolic 3.5M sodium methoxide solution (13.1 ml) was added dropwise. After the addition had been completed, the reaction mixture was kept overnight at room temperature, and then cooled with ice, acidified with glacial acetic acid (5 ml), and diluted with water (150 ml). The solution was extracted with 4 portions of chloroform, and the extract was dried (magnesium sulfate) and evaporated to give a brown syrup (19 g) which by its n.m.r. spectrum was found to consist largely of **2** and **3** in a ratio of approximately 2:1. The syrup was chromatographed in a column of Silica Gel 7734 (Merck; 570 g of the gel moistened with 10% water) by elution, first with benzene (5.7 l) and then with benzene containing 1% of ethanol. Fractions of 570 ml were collected. Fractions 1–10 (pure benzene) remained blank, 11–19 contained unidentified material (1.7 g), 20–21 gave **2** (4.8 g, pure according to n.m.r.), 22 gave a syrupy mixture of **2** and **3** (5.4 g), and **23** yielded a partly crystallized syrup (4.3 g) rich in **3**. Higher fractions contained unidentified impurities only (0.4 g).

Compound **2** (fractions 20–21) was a colorless syrup, homogeneous in t.l.c. (R_F 0.59); $[\alpha]_{578}$ −27°, $[\alpha]_{546}$ −33°, $[\alpha]_{436}$ −75°, $[\alpha]_{365}$ −218° (*c* 0.3, methanol); n.m.r. data: δ 7.42 (s, 5H, Ph), 5.97 (d, H-1, $J_{1,2}$ 4 Hz), 4.9–4.3 (6H, unresolved), 4.3–4.1 (m, narrow, 2H), 2.7 (d, 1H, hydroxyl), 1.48 and 1.33 (s, 2×3H, CMe_2).

Anal. Calc. for $C_{16}H_{21}NO_7$ (339.3): C, 56.63; H, 6.24; N, 4.13. Found: C, 56.59; H, 6.15; N, 4.21.

Compound **3** (1.31 g) was isolated from fraction 23 by trituration with and recrystallization from carbon tetrachloride. The mother liquor therefrom contained **3** and **2** in a ratio of about 3:2. Crystalline **3** showed m.p. 77–78°, $[\alpha]_{578}$ −41°, $[\alpha]_{546}$ −48°, $[\alpha]_{436}$ −71°, $[\alpha]_{365}$ −40° (*c* 0.3, methanol); R_F 0.55. The n.m.r. spectrum was

similar to that of **2** except that the H-1 doublet ($J_{1,2}$ 4 Hz) was at δ 6.03 and the shape of the unresolved multiplets (δ 4.9–4.1) was different.

Anal. Calc. for $C_{16}H_{21}NO_7$ (339.3): C, 56.63; H, 6.24; N, 4.13. Found: C, 56.46; H, 6.19; N, 4.28.

C. Interconversion of **2** *and* **3**. A solution of the nitro sugar (100 mg) in methanol (2.0 ml) and nitromethane (1.0 ml) was made alkaline (pH 8–9 on wet indicator paper) with 3.25M sodium methoxide solution (0.1 ml) and kept at 25° in a stoppered flask. Samples of the solution (0.75 ml) were withdrawn at given times, processed, and analyzed as described under *A*. The results are given in Table II. None of the spectra showed an aldehyde peak. See, however, the footnote to the pertinent text of the Discussion.

*3-O-Benzyl-6-deoxy-6-nitro-*D*-glucose* (**4**). — A solution of **2** (4.12 g) and water (1.2 ml) in trifluoroacetic acid (12.2 ml) was stirred in a closed vessel for 70 min at room temperature and then evaporated under diminished pressure. Several portions of ethyl acetate and chloroform were added to, and evaporated from, the residue, which was then dried in an oil-pump vacuum. The syrupy product (3.86 g), still showing acidic reaction, was dissolved in water (5 ml) and methanol (5 ml), and the solution was filtered, in turn, through beds of Celite, Dowex-1 X8 (acetate form; 5 ml), and Rexyn 101 (H^+, 1.5 ml) which had been pre-washed and were washed with 1:1 methanol–water. The first 35 ml of effluent was evaporated to give **4** as a light-yellow, viscous oil (3.60 g, 99%); $[\alpha]_{578}$ +26°, $[\alpha]_{546}$ +28°, $[\alpha]_{436}$ +31°, $[\alpha]_{365}$ −50° (*c* 1.7, methanol). N.m.r. data: δ 7.37 (s, 5H, Ph), 5.1–3.2 (12H, unresolved); CMe signals were absent. Analysis by v.p.c. (see later) showed only two peaks (the anomers of **4**) with retention times of 1.32 and 1.61 relative to **7**.

*3-O-Benzyl-6-deoxy-6-nitro-*L*-idose* (**5**). — Prepared from **3** in the manner already described for the preparation of **4**, compound **5** was obtained as a thick syrup; $[\alpha]_{578}$ +15°, $[\alpha]_{546}$ +18°, $[\alpha]_{436}$ +42°, $[\alpha]_{365}$ +130° (*c* 0.25, methanol). An n.m.r. spectrum showed phenyl protons and absence of *C*-methyl protons. V.p.c. analysis (see later) showed a broad, main peak for **5**, with relative retention time 1.27, and minor peaks attributable to nitroinositols (total intensity, 15% of **5**). After prolonged standing the syrup deposited crystals (10% by weight) that were shown by v.p.c. to be a mixture of **6**, **7**, and **8** in the approximate proportion 1:4:6.

Cyclization of **4** *with barium hydroxide. — A. 4-O-Benzyl-1-deoxy-1-nitro-*L*-myo-inositol* (L-**7**). To an ice-cold solution of **4** (2.39 g, 8.0 mmole) in methanol (17.5 ml) was added aqueous, 22.9mM barium hydroxide solution (17.44 ml, 0.4 mmole), and the mixture (pH 8, by indicator paper) was kept for 16 h at 0°. Acetic acid (M, 2 ml) and methanol (2 ml) were then added, and the solution was filtered through columns (5 ml) of Dowex-1 X8 (acetate form) and Rexyn 101 (H^+) which had been prewashed, and were washed afterwards, with 1:1 methanol–water. Evaporation of the first 90 ml of effluent gave a crystalline mixture of products from which the less-soluble component L-**7** was isolated by systematic recrystallizations with ethanol; yield, 393 mg (16.5%); m.p. 182–182.5°, $[\alpha]_{578}$ +16°, $[\alpha]_{546}$ +20°,

$[\alpha]_{436}$ +12°, $[\alpha]_{365}$ −154° (*c* 0.2, methanol; n.m.r. data (in Me_2SO-d_6): δ 7.33 (m, 5H, Ph), 5.54, 5.40, 5.12, 5.03 (4 1H-doublets, *J* 5 Hz, exchangeable with D_2O, hydroxyl), 4.74 (s, 2H, benzylic CH_2), 4.60 (q, 1H, $J_{1,2}$ 3 Hz and $J_{1,6}$ 10 Hz, H-1), 4.4–3.9 (m, 2H, unresolved), 3.6–3.1 (m, 3H, unresolved).

Anal. Calc. for $C_{13}H_{17}NO_7$ (299.3): C, 52.17; H, 5.72; N, 4.68. Found: C, 52.12; H, 5.71; N, 4.81.

B. Crude muco *isomer* **6**. The mother liquors from the fractional crystallization of L-**7** were combined and evaporated to give a residue from which impure **6** (m.p. 132–143°) was obtained by crystallization from ethyl acetate; yield, 974 mg (40.7%). The remaining, non-crystalline material (730 mg, 30.5%) consisted to 90% of **6**, the rest being **7** and unidentified impurities, according to v.p.c. These crude products were further processed by acetonation to give **6b** (see a later section).

2,3,5,6-Tetra-O-*acetyl-4*-O-*benzyl-1-deoxy-1-nitro*-L-myo-*inositol* (L-**7a**). — A suspension of L-**7** (295 mg) in acetic anhydride (3 ml) containing 4 drops of boron trifluoride etherate was stirred at 0°, whereby the compound rapidly dissolved. After 2 h, ethanol (3 ml) was added and the mixture was kept for another 16 h at 0°. Unidentified crystals (6 mg) that had deposited were filtered off and the solution was freeze-dried to give a residue that was washed with a small amount of ethanol and dried. The colorless crystals of L-**7a** (383 mg, 83%) then had m.p. 210–211° and $[\alpha]_{587}$ +14°, $[\alpha]_{546}$ +14°, $[\alpha]_{436}$ +9°, $[\alpha]_{365}$ −57° (*c* 0.5, chloroform); n.m.r. data: δ 7.28 (m, 5H, Ph), 6.02 (t, H-2, $J_{1,2}$ and $J_{2,3}$ 3 Hz), 5.93 (q, H-6, $J_{1,6}$ 11 and $J_{5,6}$ 9.5 Hz), 5.17 (q, H-5, $J_{4,5}$ 10 Hz), 5.02 (q, H-3, $J_{3,4}$ 10 Hz), 4.80 (q, H-1), 4.66 (s, 2H, benzylic CH_2), 3.99 (t, H-4), 2.12 (s, 3H, 2-OAc), 1.99, 1.96 (s, 3 and 6H, the remaining OAc groups).

Anal. Calc. for $C_{21}H_{25}NO_{11}$ (467.4): C, 53.96; H, 5.39; N, 3.00. Found: C, 54.04; H, 5.51; N, 3.18.

Repeated recrystallization of a sample of L-**7a** from ethanol lowered the m.p. to 173–176° without changing the n.m.r. spectrum and optical rotation. From the mother liquors of such recrystallizations a compound was obtained whose n.m.r. spectrum indicated the loss of one acetyl group and generation of a nitro-olefinic grouping: δ 7.17 (d, *J* 3 Hz, nitrovinylic H), 6.40 (d, *J* 4.5 Hz, allylic H), 5.63 (q, *J* 3 and 8 Hz, allylic H), 2.08, 2.06, 2.03 (s, 3 × 3H, OAc). These characteristics were not present prior to recrystallization which, therefore, appears to cause partial dehydro-acetoxylation. A similar phenomenon was noted earlier[1].

6-O-*Benzyl-3-deoxy-1,2;4,5-di*-O-*isopropylidene-3-nitro*-muco-*inositol* (**6b**). — Crude, crystalline **6** (974 mg) was dissolved at −70° in acetone (20 ml) containing conc. sulfuric acid (0.4 ml), and the mixture was then stirred at room temperature with anhydrous cupric sulfate (0.2 g). After 20 h it was cooled to −70° again, neutralized to pH 8 by addition of conc. ammonia (1 ml), the precipitate was filtered off and washed with acetone, and the filtrate was evaporated to give crystalline **6b** (1.175 g, 95%) which was quite pure according to an n.m.r. spectrum but melted at 166–174°. Minor impurities (slow-moving) were removed by a small column of silica

gel (20 g; 10% water added) which was irrigated with chloroform. The product was finally recrystallized from 1:5 benzene–ligroin; yield, 880 mg (71%); m.p. 184–184.5°. In the same way, the major part (702 mg) of the non-crystalline, impure **6** (see a preceding section) was acetonated to give pure **6b** (325 mg, 37%) so that the total yield of **6b** (based on **4**) was 40%. N.m.r. data: δ 7.31 (m, 5H, Ph), 4.80 (s, 2H, benzylic CH_2), 4.7–4.4 (m, 3H, H-2, -3, -4), 4.4–4.2 (m, 2H, H-1, -5), 3.60 (t, H-6, $J_{1,6}$ and $J_{5,6}$ 8.2 Hz), 1.48 and 1.32 (s, 2×6H, 2 CMe_2).

Anal. Calc. for $C_{19}H_{25}NO_7$ (379.4): C, 60.15; H, 6.64; N, 3.69. Found: C, 60.35; H, 6.72; N, 3.84.

6-O-Benzyl-3-deoxy-3-nitro-muco-*inositol* (**6**). — Compound **6b** (883 mg) was stirred at room temperature in 90% trifluoroacetic acid (2.5 ml). After 40 min the acid was evaporated off, and ethyl acetate was first evaporated from the residue which was then dried *in vacuo* and recrystallized from the same solvent to give **6** (605 mg, 87%) as hard, white crystals, m.p. 151–152°; n.m.r. data (in Me_2SO-d_6; Me_4Si lock signal): δ 7.32 (s, 5H, Ph), 4.41 and 4.10 (2 2H-d, J 7 and 5 Hz, respectively, 4 hydroxyl groups), 4.73 (t, H-3, $J_{2,3}$ and $J_{3,4}$ 10 Hz), 4.58 (s, 2H, benzylic CH_2), 4.1–3.9 (m, 4H, unresolved, H-1, -2, -4, -5), 3.75 (t, H-6, $J_{1,6}$ and $J_{5,6}$ 3 Hz); in 2M CF_3CO_2D with acetone as internal standard: δ 5.77 (s, 5H, Ph), 2.79 (t, H-3, $J_{2,3}$ and $J_{3,4}$ 10 Hz), 2.43 (s, 2H, benzylic CH_2), 2.14 (q, 2H, H-2 and -4, $J_{1,2(4,5)}$ 3.5 and $J_{2,3(3,4)}$ 10 Hz), 2.01 (t, 2H, H-1 and -5, $J_{1,2(4,5)}$ and $J_{1,6(5,6)}$ 3–3.5 Hz), 1.76 (t, H-6, J 3 Hz).

Anal. Calc. for $C_{13}H_{17}NO_7$ (299.3): C, 52.17; H, 5.72; N, 4.68. Found: C, 52.32; H, 5.82; N, 4.78.

1,2,4,5-Tetra-O-acetyl-6-O-benzyl-3-deoxy-3-nitro-muco-*inositol* (**6a**). — Pure **6** (181 mg) was treated overnight with acetic anhydride (1.8 ml) containing boron trifluoride etherate (2 drops), at 0°. Excess anhydride was decomposed by the addition of ethanol, and the residue of subsequent evaporation was crystallized from ethanol giving **6a** as colorless prisms (203 mg, 72%), m.p. 129–130°; n.m.r. data: δ 7.34 (s, 5H, Ph), 5.73 (q, 2H, H-2 and -4 $J_{1,2(4,5)}$ 3 and $J_{2,3(3,4)}$ 11 Hz), 5.49 (t, 2H, H-1 and -5, $J_{1,6(5,6)}$ 3 Hz), 5.17 (t, H-3, $J_{2,3}$ 11 Hz), 4.70 (s, 2H, benzylic CH_2), 3.83 (t, H-6), 2.14 (s, 6H, 1- and 5-OAc), 1.98 (s, 6H, 2- and 4-OAc).

Anal. Calc. for $C_{21}H_{25}NO_{11}$ (467.4): C, 53.96; H, 5.39; N, 3.00. Found: C, 54.08; H, 5.37; N, 3.12.

Cyclization of **5** *with barium hydroxide.* — *A. Isolation of crude products.* A solution of **5** (480 mg, 1.60 mmole) in methanol (3.5 ml) was stirred at 0° under nitrogen, and aqueous 22.9mM barium hydroxide (1.75 ml, 0.04 mmole) was added dropwise. After 20 h, the resulting thick slurry was acidified with 0.5M acetic acid (1 ml, in methanol–water) and filtered with suction, the filter cake being washed with a small amount of ethanol. There was obtained 163 mg of a crystalline material, m.p. 156–167°, shown by v.p.c. to contain at least 95% of *myo* isomer (**7**). The content of D-enantiomer (D-**7**) was estimated to be 88% by comparison of the $[\alpha]_{365}$ value with that of the pure compound. Concentration of the mother liquor furnished a second crop of crystalline product (326 mg), shown by v.p.c. to be a mixture of **7**

(67%), **8** (27%), and **6** (5%). [After acetylation of this crop, some **7a** (120 mg) and **8a** (47 mg) could be isolated, whereas the rest of the mixture could not be separated].

B. 4-O-Benzyl-1-deoxy-1-nitro-D-myo-*inositol* (D-**7**) *and its 2,3,5,6-tetraacetate* (D-**7a**). Recrystallization of crude **7** (from the first crop in A) from ethanol gave D-**7**, m.p. 180–182°, $[\alpha]_{578}$ −24°, $[\alpha]_{546}$ −23°, $[\alpha]_{436}$ −16°, $[\alpha]_{365}$ +146° (*c* 0.2, methanol).

Acetylation of crude D-**7** as described for L-**7** afforded crystalline, optically pure D-**7a** in 90% yield, m.p. 210–211° (lowered by recrystallization from ethanol without noticeable spectral or polarimetric change; see also L-**7a**); $[\alpha]_{578}$ −12°, $[\alpha]_{546}$ −13°, $[\alpha]_{436}$ −9°, $[\alpha]_{365}$ +58° (*c* 0.3, chloroform). The n.m.r. spectrum was identical with that of L-**7a**.

Cyclization of **4** *and* **5** *with sodium methoxide. Preparation of 2,3,5,6-tetra*-O-*acetyl-4*-O-*benzyl-1-deoxy-1-nitro*-scyllo-*inositol* (**8a**). — A mixture of **4** and **5** (4.36 g, 14.6 mmole), obtained by deacetonation of a 2:1 mixture of **2** and **3**, was dissolved in nitromethane (14.6 ml) and methanol (11 ml), and 4.0M sodium methoxide solution (3.65 ml, 14.6 mmole) was added dropwise with stirring and ice cooling, in a nitrogen atmosphere. After the end of the addition, the solution was brought to room temperature and stirring was continued until the optical rotation became zero (20 h). To monitor the rotational change, small samples of the reaction mixture (0.1 ml) were withdrawn from time to time, acidified with 0.5M aqueous-methanolic acetic acid (1 ml), made up to a volume of 5 ml with 1:1 methanol–water, and measured at 578, 546, 436, and 365 nm. The reaction mixture (a suspension) was then cooled with ice and slowly introduced into a cold mixture of M acetic acid (20 ml) and methanol (20 ml). The resulting solution was clarified by filtration with added charcoal and Celite, passed successively through prewashed (1:1 methanol–water), ion-exchange resins Dowex-1 X8 (acetate form, 10 ml) and Rexyn 101 (H^+, 15 ml), and evaporated after the resins had been rinsed with methanol–water. The brownish syrup obtained (4.4 g) was dissolved in boiling ethanol (10 ml) from which, on cooling, a crystalline product separated (0.18 g, m.p. 220–225° dec.). Evaporation of the mother liquor and repetition of the process gave a second crop of crystals (0.12 g, m.p. 209–215° dec.). There remained a non-crystallizable, brown syrup (4.1 g) which was acetonated as described previously for **6**, giving 984 mg (17.8% based on **4**+**5**) of chromatographically and n.m.r. spectroscopically pure **6b**, m.p. 182–184°. The aforementioned crystalline crops (0.30 g) were treated with acetic anhydride (3 ml) and boron trifluoride etherate (3 drops) for 3 h at 0° and overnight at 25°. The acetylation mixture was then cooled with ice, diluted with ethanol (3 ml), and filtered for isolation of a crystalline deposit (**8a**), which was washed with cold ethanol. The dried product (388 mg, 5.7% based on **4**+**5**) gave a single spot, R_F 0.48, in t.l.c. (11:1 chloroform–ethyl acetate) and was pure **8a** according to its n.m.r. spectrum. Its melting behavior was erratic, with melting points as high as 249–250° being occasionally observed whereas a sample recrystallized from 1:1 chloroform–ethanol melted at 220–221° (no spectral change). The n.m.r. data were: δ 7.27 (m, 5H, Ph), 5.59 (q, 2H, H-2 and -6, $J_{1,2(1,6)}$ 10.5 and $J_{2,3(5,6)}$ 9.5 Hz), 5.22 (t, 2H, H-3 and -5, $J_{3,4(4,5)}$ 9.5 Hz),

4.83 (t, H-1), 4.63 (s, 2H, benzylic CH_2), 3.81 (t, H-4, $J_{3,4}$ 9.5 Hz), 1.98 and 1.91 (s, 2 × 6H, 4 OAc).

Anal. Calc. for $C_{21}H_{25}NO_{11}$ (467.4): C, 53.96; H, 5.39; N, 3.00. Found: C, 53.92; H, 5.44; N, 3.05.

*2,3,5,6-Tetra-*O*-acetyl-4-*O*-benzyl-3-deoxy-3-nitro-*DL*-myo-inositol* (DL-**7a**). — The filtrate from **8a** (see the preceding section), which contained DL-**7a**, R_F 0.40 (11:1 chloroform–ethyl acetate), was evaporated and the residue triturated with ice–water. Recrystallization of the dried product from ethanol gave DL-**7a** (82 mg, 1.2% based on **4**+**5**); m.p. 174–176° (variable). The n.m.r. spectrum was identical with those of the optically active isomers.

Anal. Calc. for $C_{21}H_{25}NO_{11}$ (467.4): C, 53.96; H, 5.39; N, 3.00. Found: C, 53.87; H, 5.25; N, 3.14.

*4-*O*-Benzyl-1-deoxy-1-nitro-*scyllo*-inositol* (**8**). — A suspension of **8a** (314 mg) in anhydrous methanol (20 ml, dried according to Lund and Bjerrum) containing methyl *p*-toluenesulfonate[18] (0.5 ml) was gently refluxed whereby the solid gradually dissolved. The progress of deacetylation was monitored by t.l.c. After 20 h, the solution was evaporated and the residue crystallized from 90% ethanol to give colorless **8** (150 mg, 75%), m.p. 238–242° (dec.); n.m.r. data in Me_2SO-d_6: δ 7.35 (m, 5H, Ph), 5.63 (d, 2H, *J* 6 Hz, removable with D_2O, 2 hydroxyl groups), 5.26 (d, 2H, *J* 5 Hz, removable with D_2O, 2 hydroxyl groups), 4.78 (s, 2H, benzylic CH_2), 4.38 (t, H-1, $J_{1,2}$ and $J_{1,6}$ 10 Hz, unchanged on addition of D_2O), 3.71 (2H sextet, changing to quartet, H-2 and -6, $J_{1,2(1,6)}$ 10, $J_{2,3(5,6)}$ 8, and $J_{2,OH(6,OH)}$ 6 Hz), 3.4–3.1 (m, 3H, H-3, -4, -5).

Anal. Calc. for $C_{13}H_{17}NO_7$ (299.3): C, 52.17; H, 5.72; N, 4.68. Found: C, 52.35; H, 5.71; N, 4.71.

Study by v.p.c. of formation and epimerization of nitroinositols. — A. Analytical procedure[2]. V.p.c. was performed in a Varian Aerograph, Series 1200, instrument with a hydrogen-flame detector and a recorder equipped with a 224 Disc. Mod. integrator. The aluminum coil (5 ft, diameter 1/8 in.) was packed with 10% Carbowax 20M on Chromosorb W 60/80. Operation was isothermal at 200 ±5°, with helium as carrier gas (pressure 50 lb.in^{-2}., flow rate 40 ml min^{-1}). The reagent for trimethylsilylation was a solution of trimethylsilyl chloride (2 ml) and hexamethyldisilazane (1 ml) in dry pyridine (17 ml). The samples to be analyzed were treated with this reagent (0.2–0.3 ml) for 20 h at 25° prior to injection. Retention times of **7** ranged from 12–16 min, and relative retention times (**7** = 1.00) and detector-response factors were determined[2,19] by analysis of the individual, isolated compounds. The inositols gave single peaks having the following T_R values (detector-response factors in parentheses): **6**, 0.73 (1); **8**, 0.82 (1.2); **7**, 1.00 (2.5). Compound **4** gave 2 peaks (anomers), with T_R 1.32 and 1.62 (2). Compound **5** showed a broad peak, with T_R 1.25–1.31 (2) and minor peaks arising through contamination (see earlier).

B. Cyclization of **4** *and* **5**. A solution that was 0.025M in **4** (or **5**) and 1.25mM in barium hydroxide was made, at 0°, with 19:1 methanol–water as the solvent. Samples (0.6 ml) were withdrawn at specified times (Table III), introduced into 0.1M

acetic acid (1 ml) and, upon evaporation followed by trimethylsilylation, analyzed by v.p.c.

C. Epimerization of **6**, **7**, *and* **8**. To a 10mM solution of a given nitroinositol in methanol was added an equal volume of aqueous 22.9mM barium hydroxide. The reaction mixture was kept in a closed vial at room temperature, and samples (1.0 ml) were withdrawn periodically, introduced into a mixture of M acetic acid (1.0 ml) and methanol (1.0 ml), filtered successively through Dowex-1 X8 (acetate form, 0.2 ml) and Rexyn 101 (H^+, 0.5 ml) resins, and evaporated. The dried residue was trimethylsilylated and analyzed by v.p.c. (Table IV). When a precipitate was present in the reaction mixture (after 24 h), the samples were withdrawn after swirling rather than from the supernatant alone. Epimerizations using a catalytic amount of base, described in the Discussion section but not tabulated, were performed analogously.

REFERENCES

1 J. KOVÁŘ AND H. H. BAER, *Can. J. Chem.*, 51 (1973) 1801.
2 J. KOVÁŘ AND H. H. BAER, *Can. J. Chem.*, 51 (1973) 2836.
3 J. KOVÁŘ AND H. H. BAER, *Can. J. Chem.*, 51 (1973) 3373.
4 J. M. GROSHEINTZ AND H. O. L. FISCHER, *J. Amer. Chem. Soc.*, 70 (1948) 1476; *ibid.*, 70 (1948) 1749; For a recent application to the synthesis of nitrocycloheptanehexols, see I. DYONG and R. BONN, *Chem. Ber.*, 106 (1973) 944.
5 H. SAEKI, T. IWASHIGE, AND E. OHKI, *Chem. Pharm. Bull.* (Tokyo), 16 (1968) 2410.
6 T. IIDA, M. FUNABASHI, AND J. YOSHIMURA, *Bull. Chem. Soc. Japan*, 46 (1973) 3203.
7 W. RANK AND H. H. BAER, *Carbohyd. Res.*, 35 (1974) 65.
8 H. H. BAER AND W. RANK, *Can. J. Chem.*, 43 (1965) 3462.
9 L. ANDERSON, in W. PIGMAN AND D. HORTON, (Eds.), *The Carbohydrates*, Academic Press, 1972, Vol. IA, p. 519.
10 H. H. BAER AND C. W. CHIU, *Carbohyd. Res.*, 31 (1973) 347.
11 M. L. WOLFROM AND S. HANESSIAN, *J. Org. Chem.*, 27 (1962) 1800.
12 R. U. LEMIEUX AND J. HOWARD, *Can. J. Chem.*, 41 (1963) 308.
13 D. HORTON AND F. O. SWANSON, *Carbohyd. Res.*, 14 (1970) 159.
14 R. KUHN, I. LÖW, AND H. TRISCHMANN, *Chem. Ber.*, 90 (1957) 203.
15 R. KUHN, H. H. BAER, AND A. SEELIGER, *Ann.*, 611 (1958) 236.
16 T. IWASHIGE AND H. SAEKI, *Chem. Pharm. Bull.* (Tokyo), 15 (1967) 1803.
17 A. S. MEYER AND T. REICHSTEIN, *Helv. Chim. Acta*, 29 (1946) 152.
18 Z. ECKSTEIN, E. GROCHOWSKI, R. KOVALIK, AND T. URBAŃSKI, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 11 (1963) 687; H. H. BAER AND I. FURIĆ, *J. Org. Chem.*, 33 (1968) 3731; H. H. BAER AND M. BAYER, *Can. J. Chem.*, 49 (1971) 568; H. H. BAER, S.-H. L. CHIU, AND D. C. SHIELDS, *ibid.*, 51 (1973) 2828.
19 K. M. BROBST, *Methods Carbohyd. Chem.*, 6 (1972) 3.