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CONVERSION OF 2-HEXULOSES INTO 3-HEPTULOSES: SYNTHESIS OF D-*manno*-3-HEPTULOSE*

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ABSTRACT

A general protocol for the conversion of 2-hexuloses into 3-heptuloses is illustrated by the synthesis of D-*manno*-3-heptulose (**9**) from D-fructose (**1**). Oxidation of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2**) with the Pfitzner–Moffatt reagent gave, in high yield, 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexosulo-2,6-pyranose (**3**), which was converted into the unsaturated sugar **4** by reaction with methylenetriphenylphosphorane. Addition of iodine trifluoroacetate to **4**, followed by deacylation of the resultant adduct(s) **5**, afforded crystalline 2-deoxy-2-iodo-3,4:5,6-di-*O*-isopropylidene-β-D-*gluco*-3-heptulos-3,7-pyranose (**6**). Treatment of the iodohydrin **6** with sodium hydroxide gave the epoxide **7**, which, by a further treatment with sodium hydroxide, was converted into 3,4:5,6-di-*O*-isopropylidene-β-D-*manno*-3-heptulos-3,7-pyranose (**8**). Acid-catalyzed hydrolysis of the diol **8** furnished D-*manno*-3-heptulose (**9**).

INTRODUCTION

The 3-heptuloses have been found only rarely in Nature. The first clearly characterized 3-heptulose found in a natural product is D-*altro*-3-heptulose. It was obtained, in crystalline form, as one of the minor products from the extracts of the roots of *Primula officinalis* Jacq.[1], and has also been isolated from the leaves, fruit, stem, and root of *Coriaria japonica* A. Gray[2]; the trivial name coriose has been given to this compound. It is interesting that coriose has been found[3], by X-ray analysis, to have the α-furanose structure in the crystalline state. Coriose has been prepared by isomerization of sedoheptulose (D-*altro*-heptulose) in pyridine[1], or by way of an aldol condensation of 2,4-*O*-ethylidene-D-erythrose[4]. An incompletely identified 3-heptulose phosphate has been isolated from a rat-liver digest[5].

D-Glucoascorbic acid has been converted into a mixture of 2-*O*-methyl-3-heptuloses, from which a (2,5-dichlorophenyl)hydrazone of unknown configuration was isolated[6]. Presumably, the parent 3-heptuloses could be obtained from 2-*O*-benzyl-3-*O*-methyl-D-glucoascorbic acid[7] by the procedure described by Jackson and Jones[8] for the synthesis of 3-hexuloses by way of 2-*O*-benzyl-3-*O*-methyl-L-xyloascorbic acid as an intermediate. Schaffer[9] prepared D-*manno*-3-heptulose by way

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*Dedicated to Dr. Louis Long, Jr., in honor of his 70th birthday.

of an aldol reaction. In calcium hydroxide solution, 2,4-*O*-ethylidene-D-erythrose gave a crystalline, branched-chain octose derivative, namely, 2,2′:4,6-di-*O*-ethylidene-2-(D-*glycero*-1,2-dihydroxyethyl)-D-glucopyranose; after removal of the ethylidene groups from the condensation product, oxidation with lead tetraacetate furnished syrupy D-*manno*-3-heptulose. A hydrate of this 3-heptulose was subsequently obtained[10] in crystalline form. The present report describes a convenient synthesis of D-*manno*-3-heptulose (**9**) from a 2-hexulose, namely, D-fructose (**1**).

RESULTS AND DISCUSSION

Treatment of D-fructose (**1**) with acetone in the presence of sulfuric acid, by the procedure described by Pacsu *et al.*[11b], afforded 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[11] (**2**). Oxidation of compound **2** with the Pfitzner–Moffatt reagent[12] (methyl sulfoxide-*N*,*N*′-dicyclohexylcarbodiimide, with pyridine hydrochloride as the proton source) gave 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexosulo-2,6-pyranose (**3**), which was obtained, after two vacuum distillations, as an analytically pure syrup in 84% yield. The aldehyde **3** was readily converted into a crystalline oxime and (2,4-dinitrophenyl)hydrazone. The i.r. spectrum of **3** showed characteristic absorptions for the aldehyde group, and its n.m.r. spectrum in chloroform-*d* shows the signal of the aldehyde proton (H-1) as a singlet at τ 0.52; in deuterium oxide, the n.m.r. spectrum shows the H-1 signal at τ 5.07 as a one-proton singlet, but no aldehyde-proton signal is observed, indicating that, in aqueous solution, the aldehyde **3** exists entirely as the aldehydrol (compare Ref. 13). During the course of the present study, the preparation of aldehyde **3**, by oxidation of **2** with methyl sulfoxide–acetic anhydride, was reported by other workers[14]; however, this procedure also gave two other products, presumably the 1-acetate and 1-(methylthio)methyl ether of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose. These workers noted also that the aldehyde group in **3** is readily susceptible to oxidation when **3** is heated in air; thus, on distillation, with a capillary bleeding air, it gave a viscous syrup that appeared to be 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexulo-2,6-pyranosonic acid*.

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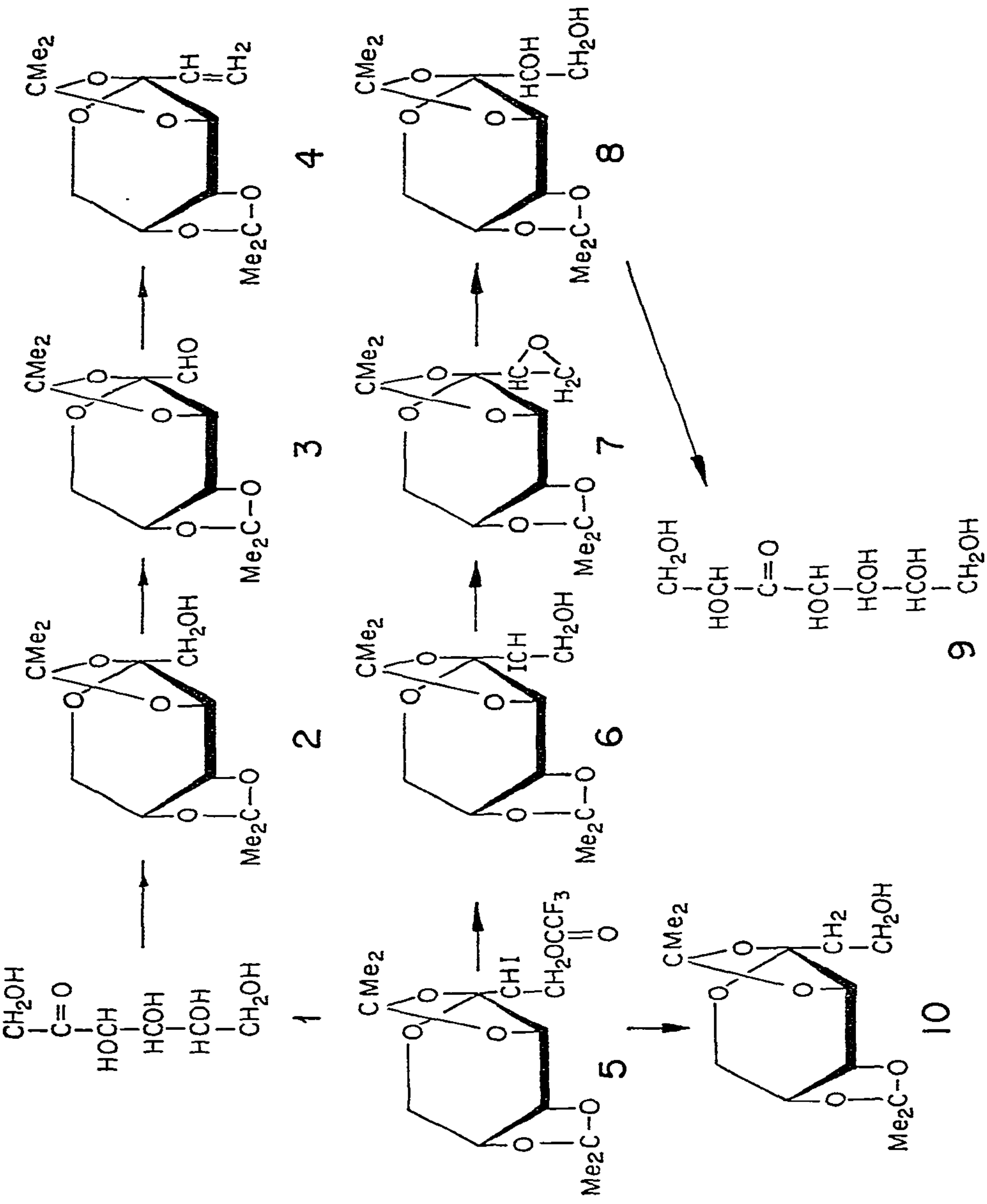
*Since the submission of the present article for publication, a further synthesis of the aldehyde **3** was reported [R. E. Arrick, D. C. Baker, and D. Horton, *Carbohyd. Res.*, 26 (1973) 441], namely, by oxidation of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2**) with chromium trioxide–dipyridine complex. In that work, the product aldehyde was obtained as a syrup in 53% yield; the physical constants of a distilled sample were in agreement with those obtained for **3** in the present work. Horton and coworkers observed also that the aldehyde exists to the extent of ~90% as the aldehydrol in a 3:7 mixture of deuterium oxide and tetrahydrofuran. In both the present work and that of Horton and coworkers, the same value was obtained for the specific rotation of the aldehyde **3**, namely, $[\alpha]_D$ −72° (chloroform); presumably, the first reported[14] value (−41.2°) for this physical constant is incorrect. In another recent study [K. James and S. J. Angyal, *Aust. J. Chem.*, 25 (1972) 1967], oxidation of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2**) was attempted with methyl sulfoxide–acetic anhydride, methyl sulfoxide and sulfur trioxide–pyridine complex, and methyl sulfoxide–phosphorus pentaoxide; the first method was reported to produce mainly the 1-(methylthio)methyl ether of **2**, whereas the other two methods afforded oils, which were claimed to be the aldehyde **3**, but which were, however, uncharacterized except for the report of an n.m.r. signal at τ 0.46 for a distilled sample of the oil obtained from the procedure employing sulfur trioxide–pyridine complex.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Reaction of methylenetriphenylphosphorane with the aldehyde **3** afforded the unsaturated sugar, 1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-β-D-*arabino*-hept-1-en-3-ulo-3,7-pyranose (**4**). The Wittig reaction was performed in ether, and involved preparing the ylid in liquid ammonia with sodium amide as the base, and then replacing the ammonia by ether[15].

Recently, iodine trifluoroacetate (produced *in situ* by the reaction of silver trifluoroacetate and iodine) has been shown[16] to add to unsaturated sugars to produce β-iodo trifluoroacetates. In the present work, reaction of compound **4** with iodine trifluoroacetate in dichloromethane gave adduct(s) **5** as a syrup. The assignment of iodine to C-2 was established by the conversion of **5** into 2-deoxy-3,4:5,6-di-*O*-isopropylidene-β-D-*arabino*-3-heptulos-3,7-pyranose (**10**) by hydrogenation over a Raney nickel catalyst in the presence of triethylamine. Deacylation of **5** was achieved at room temperature with triethylamine in methanol to afford crystalline 2-deoxy-2-iodo-3,4:5,6-di-*O*-isopropylidene-β-D-*gluco*-3-heptulos-3,7-pyranose (**6**); the configuration of **6** was established by its eventual conversion into D-*manno*-3-heptulose (**9**) by the sequence of reactions described as follows.

Treatment of the iodohydrin **6** with sodium hydroxide in aqueous 1,4-dioxane for 3 h at reflux temperature gave syrupy 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-β-D-*manno*-3-heptulos-3,7-pyranose (**7**). The epoxide **7** was converted into 3,4:5,6-di-*O*-isopropylidene-β-D-*manno*-3-heptulos-3,7-pyranose (**8**) by a further treatment with sodium hydroxide in aqueous 1,4-dioxane for 48 h at reflux temperature; compound **8** readily yielded a diacetate. Acid-catalyzed hydrolysis [Rexyn-101 (H^+) ion-exchange resin] of the diol **8** afforded D-*manno*-3-heptulose (**9**) as a syrup that crystallized on seeding with an authentic sample of β-D-*manno*-3-heptulose hydrate[10] kindly provided by Dr. Robert Schaffer; the physical constants of the two samples were in agreement. The assignment of the D-*manno* configuration to the sugar synthesized in the present work was confirmed by g.l.c. analysis of the products obtained by reduction of the sugar with sodium borohydride, followed by acetylation with acetic anhydride–pyridine. The presence of D-*glycero*-D-*manno*-heptitol and D-*glycero*-D-*ido*-heptitol heptaacetates was revealed (approximately 1:1), but not of D-*glycero*-D-*galacto*-heptitol or D-*glycero*-D-*gulo*-heptitol heptaacetates; the latter two would be the products if the sugar had had the D-*gluco* configuration. The formation of D-*manno*-3-heptulose (**9**) in the present synthesis permits the assignment, of the D-*manno* configuration to the diol **8** and the epoxide **7**, and, of the D-*gluco* configuration to the iodohydrin **6**; opening of the epoxide ring would be expected to occur by nucleophilic attack at C-1, with retention of configuration at C-2, whereas, formation of the epoxide ring from the iodohydrin would be expected to occur with inversion of configuration at C-2.

It has been reported[10] that treatment of D-*manno*-3-heptulose (**9**) in aqueous methanol with phenylhydrazine–acetic acid gave a crystalline phenylhydrazone of **9**. In our hands, a crystalline product was obtained in low yield, having physical constants different from those reported for the phenylhydrazone, and, whose elemental analysis agreed with that calculated for a dianhydro derivative of the phenylhydrazone of **9**.

The same derivative was isolated in 18% yield on treatment of **9** in aqueous methanol with phenylhydrazine hydrochloride, in the presence of sodium acetate. The structure of the new compound has not been elucidated.

In the present study, an attempt was made to displace an iodo group by trifluoroacetate in adduct(s) **5**; however, no change in the starting material was observed after treatment with silver trifluoroacetate in *m*-xylene for 1 h at reflux temperature. The direct conversion of the unsaturated sugar **4** into the epoxide **7** was also investigated. Thus, compound **4** was treated with *m*-chloroperoxybenzoic acid in dichloromethane at room temperature; however, even after 3 weeks, only, approximately 60% of the starting material had been consumed. Moreover, it was difficult to separate, by column chromatography on silica gel, the remaining starting material from the product, which appeared to be, by n.m.r. spectroscopy, an approximately 1:1 mixture of diastereomeric epoxides. The dihydroxylation of the unsaturated sugar **4** by aqueous potassium permanganate was also studied; a mixture of two *vic*-diols was obtained, which was not resolved. G.l.c. analysis of the products obtained from the mixture by successive acid-catalyzed hydrolysis, reduction with sodium borohydride, and acetylation with acetic anhydride–pyridine indicated that the mixture consisted of 3,4:5,6-di-*O*-isopropylidene-β-D-*manno*-3-heptulos-3,7-pyranose (**8**) and its D-*gluco* isomer in a ratio of approximately 7:3, respectively. It is noteworthy that the D-*manno* diol (**8**) was the preponderant isomer produced by the reaction of **4** with permanganate, whereas the addition of iodine trifluoroacetate to **4**, which, presumably, occurs by way of a cyclic iodonium ion intermediate[16], gave preponderantly, if not exclusively, the D-*gluco* adduct. The resolution of the mixture of the D-*manno* diol (**8**) and its D-*gluco* isomer would make possible a synthesis of D-*gluco*-3-heptulose. Presumably, syntheses of L-*gulo*- and L-*ido*-3-heptuloses from 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose[17] should also be possible by application of the appropriate reactions outlined in the present report.

EXPERIMENTAL

General. — Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 26 ±3°. I.r. spectra were recorded with a Unicam SP 1000 spectrophotometer. N.m.r. spectra were recorded at 60 MHz in chloroform-*d* with tetramethylsilane as the internal standard, unless otherwise stated; theoretical spectra were calculated with an IBM 360 computer, equipped with a CALCOMP plotter, by use of a modification of the Laocoon II program of Castellano and Bothner-By[18]. T.l.c. was performed with Silica Gel G as the adsorbent; the developed plates were air-dried, and compounds were located by heating the plates at about 150° after they had been sprayed with either 5% ethanolic sulfuric acid or a 10% aqueous sulfuric acid solution containing 1% cerium sulfate and 1.5% molybdic acid. Column chromatography was performed on Merck silica gel (70–230 mesh). The solvent employed for t.l.c. or column chromatography was 2:3 (*v*/*v*) ethyl acetate–

petroleum ether, unless otherwise stated. The term "petroleum ether" refers to the fraction of b.p. 60–80°. Paper chromatography was carried out by the descending method on Whatman No. 1 filter paper. G.l.c. (F and M Model 402 gas chromatograph) was performed, with helium as the carrier-gas, on columns (115 × 0.4 cm) of (*i*) 10% (w/w) LAC-4R-886 polyester wax on acid-washed, HMDS treated Chromosorb W (100–120 mesh), and (*ii*) 3% (w/w) ECNSS-M on Gas-Chrom Q (100–120 mesh). Retention times (T) are given relative to that of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2**), unless otherwise stated.

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose (**2**). — Compound **2** was prepared from D-fructose (**1**) by the procedure described by Pacsu *et al.*[11b]. Recrystallized from cyclohexane, it had m.p. 94–97°, and n.m.r. spectrum identical with that published by Maeda *et al.*[11d].

*2,3:4,5-Di-O-isopropylidene-β-D-*arabino*-hexosulo-2,6-pyranose* (**3**). — 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (**2**, 25 g) was added to dry (molecular sieves, Type 3A) methyl sulfoxide (450 ml) containing *N,N'*-dicyclohexylcarbodiimide (60 g) and pyridine hydrochloride [prepared by saturation of a solution of pyridine (5 ml) in ether (100 ml) with dry hydrogen chloride and concentration to dryness]. The mixture was stirred for 24 h at room temperature, and the excess of *N,N'*-dicyclohexylcarbodiimide was decomposed by the dropwise addition of oxalic acid (25 g) in methanol (50 ml). The mixture was poured into an aqueous saturated sodium chloride solution (1 l.); *N,N'*-dicyclohexylurea was removed by filtration, and the filtrate was extracted with chloroform (6 × 250 ml). The extracts were washed with aqueous sodium hydrogen carbonate (2 × 250 ml) and then with water (4 × 250 ml). The aqueous washings were extracted with chloroform, and the organic phases were combined, dried (sodium sulfate), and concentrated to dryness. The syrupy residue was dissolved in acetone (50 ml), and a small amount of *N,N'*-dicyclohexylurea was removed by filtration. The filtrate was concentrated to give a yellow syrup. This syrup was distilled twice, with use of a Büchi heating block, to give the aldehyde **3** as a pure, colorless syrup, yield 20.9 g (84%), b.p. 95–96°/0.15 torr, $[\alpha]_D$ −72° (c 4.4, chloroform); $\nu_{\max}^{\text{film}}$ 1745 (C=O), 1380 and 1370 cm^{-1} (CMe$_2$); n.m.r. data: τ 0.52 (1-proton singlet, H-1), 5.38 (doublet of doublets, $J_{3,4}$ 2.5, $J_{4,5}$ 7.8 Hz, H-4), 5.51 (1-proton doublet, H-3), 5.74 (1-proton multiplet, H-5), 6.04, 6.15 (AB of ABX system, $J_{5,6}$ 1.6, $J_{5,6'}$ 1.0, $J_{6,6'}$ 13.4 Hz, H-6,6'), 8.45, 8.60, 8.67 (3-, 6-, and 3-proton singlets, CMe$_2$). The n.m.r. parameters for the ring protons were ascertained by comparing the experimental and computer-simulated spectra. G.l.c. analysis (at 160° with a 60 ml/min flow rate of the carrier-gas) of the product showed only one peak [(*i*) T 0.29].

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.0. Found: C, 55.6; H, 7.1.

*2,3:4,5-Di-O-isopropylidene-β-D-*arabino*-hexosulo-2,6-pyranose 1-aldehydrol.* — A suspension (~25%) of the aldehyde **3** in deuterium oxide was prepared. N.m.r. data (internal standard, sodium 4,4-dimethyl-4-silapentane-1-sulfonate, $\tau = 10.00$): τ 5.07 (1-proton singlet, H-1), 5.2–5.4 (HOD, H-4), 5.54 (1-proton doublet; $J_{3,4}$ 2.4 Hz, H-3), 5.5–5.9 (1-proton multiplet, H-5), 6.15 (2-protonm ultiplet, H-6,6'), 8.45, 8.54, 8.57, 8.63 (four 3-proton singlets, CMe_2); no signal attributable to an aldehyde proton was observed.

The aldehyde **3** was not observed, by n.m.r. spectroscopy, to be hydrated in moist chloroform. A solution (25%) of the aldehyde in chloroform-*d* (0.5 ml), when mixed with 3 drops of deuterium oxide, did not give a signal in its n.m.r. spectrum for an aldehydrol proton; the aldehyde **3** was the only detectable species.

*2,3:4,5-Di-O-isopropylidene-β-*D-arabino-*hexosulo-2,6-pyranose 1-oxime.* — A solution of the aldehyde **3** (1.02 g) in methanol (7 ml), containing hydroxylamine hydrochloride (0.352 g), water (1 ml), and pyridine (1 ml), was heated for 6 h at reflux temperature. The methanol was evaporated under reduced pressure, and the residual solution (~2 ml) was diluted with chloroform (20 ml). The solution was washed successively with M sulfuric acid (2 × 10 ml), aqueous saturated sodium hydrogen carbonate solution (2 × 10 ml), and water (2 × 10 ml). The chloroform solution was dried (sodium sulfate) and evaporated to a crystalline residue. Recrystallization from chloroform–petroleum ether gave the oxime as white needles, which were dried overnight at 65°/0.2 torr, yield 0.628 g (58%), m.p. 137–138°, $[\alpha]_D$ $-38°$ (*c* 1.0, chloroform); $\nu_{max}^{CHCl_3}$ 3600 and 3500–3200 (both OH), 1390 and 1380 cm^{-1} (CMe_2), no absorption attributable to C=O; n.m.r. data: τ 1.06 (1-proton singlet, H-1), 5.36 (doublet of doublets, $J_{3,4}$ 2.5, $J_{4,5}$ 8.8 Hz, H-4), 5.38 (1-proton doublet, H-3), 5.79 (1-proton multiplet, H-5), 6.10, 6.24 (AB of ABX system, $J_{5,6}$ 1.8, $J_{5,6'}$ 0.8, $J_{6,6'}$ 13.6 Hz, H-6,6'), 8.47, 8.57, 8.66 (3-proton singlet, 3-proton singlet, and 6-proton broadened singlet, CMe_2).

Anal. Calc. for $C_{12}H_{19}NO_6$: C, 52.7; H, 7.0; N, 5.1. Found: C, 52.9; H, 7.0; N, 5.3.

*2,3:4,5-Di-O-isopropylidene-β-*D-arabino-*hexosulo-2,6-pyranose 1-(2,4-dinitrophenyl)hydrazone.* — A solution of the aldehyde **3** (1.01 g) in ethanol (60 ml), containing (2,4-dinitrophenyl)hydrazine (1.01 g) and concentrated hydrochloric and (0.1 ml), was heated for 10 min at reflux temperature, and then kept for 1 h at room temperature. Concentration of the solution under reduced pressure to a volume of ~25 ml caused the separation of a precipitate. The product was collected and recrystallized twice from ethanol to give the (2,4-dinitrophenyl)hydrazone as yellow needles, yield 1.11 g (65%), m.p. 180–181°, $[\alpha]_D$ $-100°$ (*c* 1.1, chloroform); $\nu_{max}^{CHCl_3}$ 3320 (NH), 1390 and 1380 (CMe_2), 1345 and 1330 cm^{-1} (NO_2), no absorption attributable to C=O; n.m.r. data: τ 0.64 (1-proton singlet, NH), 0.98–2.20 (3 protons, aromatic H), 2.43 (1-proton singlet, H-1), 5.20–6.35 (5 protons, H-3, H-4, H-5, and H-6,6'), 8.42, 8.52, 8.58, 8.64 (four 3-proton singlets, CMe_2).

Anal. Calc. for $C_{18}H_{22}N_4O_9$: C, 49.3; H, 5.1; N, 12.8. Found: C, 49.5; H, 5.2; N, 12.7.

*1,2-Dideoxy-3,4:5,6-di-O-isopropylidene-β-*D-arabino-*hept-1-en-3-ulo-3,7-pyranose* (**4**). — Methyltriphenylphosphonium bromide (27.6 g) was added to a solution of sodium amide (6.04 g) in liquid ammonia (200 ml) under nitrogen; the mixture was kept for 2 h in a Dry Ice–acetone bath. Anhydrous ether (100 ml) was added, and the solution was heated for 5 h at reflux temperature to remove the ammonia.

To the solution of methylenetriphenylphosphorane was added dropwise with stirring a solution of the aldehyde **3** (10.02 g) in anhydrous ether (100 ml). The reaction mixture was heated for 2 h at reflux temperature; water (25 ml) was then added dropwise. The ether solution was washed with water (7 × 100 ml), dried (sodium sulfate), and evaporated. The resultant syrup was dissolved in *n*-hexane (100 ml); triphenylphosphine oxide precipitated from the solution and was removed by filtration. The filtrate was concentrated to give a syrup, which was distilled twice to afford the unsaturated sugar **4** as a colorless oil, yield 6.2 g (62%), b.p. 85°/0.12 torr, $[\alpha]_D$ $-25°$ (*c* 1.1, chloroform); ν_{max}^{film} 1410 ($C{=}CH_2$), 1385 and 1375 cm^{-1} (CMe_2), no absorption attributable to an aldehyde group; n.m.r. data: τ 4.03 (1-proton multiplet, $J_{1,2}$ 17.3, $J_{1',2}$ 10.6 Hz, H-2), 4.40 (1-proton multiplet $J_{1,1'}$ 1.9 Hz, H-1), 4.78 (1-proton multiplet, H-1′), 5.40 (doublet of doublets, $J_{4,5}$ 2.6, $J_{5,6}$ 8.4 Hz, H-5), 5.78 (1-proton multiplet, H-6), 5.83 (1-proton doublet, H-4), 6.11, 6.27 (AB of ABX system, $J_{6,7}$ 1.8, $J_{6,7'}$ 1.1, $J_{7,7'}$ 13.5 Hz, H-7,7′), 8.46, 8.54, 8.61, 8.67 (four 3-proton singlets, CMe_2). The n.m.r. parameters for protons, other than those of the isopropylidene groups, were ascertained by comparing the experimental and computer-simulated spectra. The product was revealed in t.l.c. as a single component having R_F 0.71; g.l.c. analysis (at 160° with a 60 ml/min flow rate of the carrier-gas) showed only one peak [(*i*) *T* 0.17].

Anal. Calc. for $C_{13}H_{20}O_5$: C, 60.9; H, 7.9. Found: C, 60.6; H, 7.9.

*Addition of iodine trifluoroacetate to 1,2-dideoxy-3,4:5,6-di-O-isopropylidene-β-*D-arabino*-hept-1-en-3-ulo-3,7-pyranose (4).* — A solution of iodine (11.6 g) in dry dichloromethane (300 ml) was added dropwise with stirring to dichloromethane (150 ml) containing the unsaturated sugar **4** (10.66 g) and silver trifluoroacetate (18.37 g). The mixture was stirred overnight in a flask covered with aluminum foil, and then filtered through Celite. The filtrate was washed with an aqueous saturated sodium thiosulfate solution (3 × 100 ml) and then with water (3 × 100 ml). The dichloromethane solution was dried (sodium sulfate) and concentrated to give adduct(s) **5** as a yellow syrup, yield 20.47 g (99%), $[\alpha]_D$ $-19°$ (*c* 2.8, chloroform); ν_{max}^{film} 1795 (C=O), 1390 and 1380 cm^{-1} (CMe_2); n.m.r. data: τ 5.1–6.4 (8 protons, H-1,1′, H-2, H-4, H-5, H-6, and H-7,7′), 8.48, 8.55, 8.68 (6-, 3-, and 3-proton broadened singlets, CMe_2), no signals in the region (τ 3.7–5.0) attributable to olefinic protons. T.l.c. showed only one spot (R_F 0.79), with tailing.

Anal. Calc. for $C_{15}H_{20}F_3IO_7$: C, 36.3; H, 4.1. Found: C, 36.7; H, 4.1.

*2-Deoxy-3,4:5,6-di-O-isopropylidene-β-*D-arabino*-3-heptulos-3,7-pyranose* (**10**). — A sample of adduct(s) **5** was prepared from the unsaturated sugar **4** (1.67 g) by the procedure described in the preceding experiment. A solution of the product in ethanol (100 ml) containing W-4 Raney nickel catalyst (2 g) and triethylamine (5 ml) was subjected, with shaking, to a hydrogen pressure of 1 atm overnight. The filtered solution was evaporated to give a syrup which was revealed in t.l.c. as two components having R_F values of 0.73 and 0.27; the two components were separated by column chromatography. The n.m.r. spectrum of the faster-moving component suggested that it was a mixture of at least the epoxide **7** and a small amount of the unsaturated sugar **4**. The slower-moving component was the alcohol **10**, yield 1.43 g (80%), $[\alpha]_D$ $-16°$ (*c* 1.2, chloroform); ν_{max}^{film} 3510 (OH), 1390 and 1378 cm^{-1} (CMe_2), no absorption attributable to C=O; n.m.r. data (chloroform-*d* containing 1 drop of deuterium oxide): τ 5.46 (doublet of doublets, $J_{4,5}$ 2.5, $J_{5,6}$ 8.3 Hz, H-5), 5.75 (1-proton doublet, H-4), 5.83 (1-proton multiplet, H-6), 6.17 6.31 (AB of ABX system, $J_{6,7}$ 1.8, $J_{6,7'}$ 0.9, $J_{7,7'}$ 13.4 Hz, H-7,7'), 6.19 (2-proton multiplet, H-1,1'), 7.95 (2-proton multiplet, H-2,2'), 8.50, 8.65 (two 6-proton singlets, CMe_2); in the absence of deuterium oxide, a 1-proton broadened triplet was observed at τ 6.81 (OH).

Anal. Calc. for $C_{13}H_{22}O_6$: C, 56.9; H, 8.1. Found: C, 56.7; H, 8.0.

*2-Deoxy-2-iodo-3,4:5,6-di-*O*-isopropylidene-β-*D-gluco*-3-heptulos-3,7-pyranose* (**6**). — A solution of adduct(s) **5** (18.76 g) in methanol (150 ml) containing triethylamine (2 ml) was kept for 12 h at room temperature. The solution was evaporated to give a crystalline residue, which was washed with 3:2 (*v*/*v*) petroleum ether–ethyl acetate and then recrystallized twice from ethyl acetate–petroleum ether to afford the iodohydrin **6** as white needles, yield 8.56 g (57%), m.p. 115–118° (dec.), $[\alpha]_D$ $-12°$ (*c* 1.0, chloroform); $\nu_{max}^{CHCl_3}$ 3510 (OH), 1390 and 1380 cm^{-1} (CMe_2), no absorption attributable to C=O; n.m.r. data: τ 5.3–6.2 (8 protons, H-1,1', H-2, H-4, H-5, H-6, and H-7,7'), 6.87 (1-proton broad band, disappeared on deuteriation, OH), 8.45, 8.48, 8.51, 8.66 (four 3-proton singlets, CMe_2). The product was revealed in t.l.c. as one component having R_F 0.53.

Anal. Calc. for $C_{13}H_{21}O_6I$: C, 39.0; H, 5.3; I, 31.7. Found: C, 38.6; H, 5.4; I, 31.4.

*1,2-Anhydro-3,4:5,6-di-*O*-isopropylidene-β-*D-manno*-3-heptulos-3,7-pyranose* (**7**). — The iodohydrin **6** (4.00 g) was heated for 3 h at reflux temperature in 1,4-dioxane (100 ml) containing sodium hydroxide (1.5 g) and water (100 ml). Ice (50 g) was added, and the mixture was neutralized, with concentrated hydrochloric acid, and then extracted with chloroform (4 × 50 ml). The extracts were washed successively with M sulfuric acid, aqueous saturated sodium hydrogen carbonate solution, and water. The chloroform solution was dried (sodium sulfate) and concentrated to give the epoxide **7** as a colorless syrup, yield 2.61 g (96%), $[\alpha]_D$ $-8°$ (*c* 1.5, chloroform); ν_{max}^{film} 1390 and 1385 cm^{-1} (CMe_2), no absorption attributable to OH; n.m.r. data: τ 5.41 (doublet of doublets $J_{4,5}$ 2.5, $J_{5,6}$ 8.0 Hz, H-5), 5.65 (1-proton doublet, H-4), 5.81 (1-proton multiplet, H-6), 6.17, 6.31 (AB of ABX system, $J_{6,7}$ 1.7, $J_{6,7'}$ 0.7, $J_{7,7'}$ 13.0 Hz, H-7,7'), 6.91 (1-proton multiplet, $J_{1,2}$ 2.2, $J_{1',2}$ 4.1 Hz, H-2), 7.06 (1-proton multiplet, $J_{1,1'}$ 6.0 Hz, H-1), 7.30 (1-proton multiplet, H-1'), 8.53, 8.66, 8.69 (6-, 3-, and 3-proton singlets, CMe_2). The n.m.r. parameters for protons, other than those of the isopropylidene groups, were ascertained by comparing the experimental and computer-simulated spectra. The product was revealed in t.l.c. as one component having R_F 0.69.

Anal. Calc. for $C_{13}H_{20}O_6$: C, 57.3; H, 7.4. Found: C, 57.3; H, 7.3.

*3,4:5,6-Di-*O*-isopropylidene-β-*D-manno*-3-heptulos-3,7-pyranose* (**8**). — The epoxide **7** (2.43 g) was heated for 48 h at reflux temperature, with stirring, in 1,4-dioxane (100 ml) containing sodium hydroxide (5 g) and water (60 ml). The reaction mixture was processed as described in the preceding experiment to afford a syrupy residue. Purification by column chromatography gave the diol **8** as a colorless gum, yield 1.88 g (72%), $[\alpha]_D$ $-27°$ (*c* 3.3, chloroform); ν_{max}^{film} 3470 (OH), 1390 and 1375 cm^{-1} (CMe_2); n.m.r. data: τ 5.25–5.48 (2-proton multiplet, $J_{4,5}$ 2.5 Hz, H-4, H-5), 5.77 (1-proton multiplet, $J_{5,6}$ 8.0 Hz, H-6), 6.05–6.45 (5 protons, H-1,1', H-2, H-7,7'), 6.5–7.5 (2-proton broad band, disappeared on deuteriation, two OH groups), 8.48, 8.57, 8.67 (3-proton singlet, 6-proton broadened singlet, and 3-proton singlet, CMe_2). The product was revealed in t.l.c. as a single component having R_F 0.11 [2:3 (*v*/*v*) ethyl acetate–petroleum ether] or R_F 0.63 (ethyl acetate); g.l.c. analysis (at 190° with a 90 ml/min flow rate of the carrier-gas) showed only one peak [(*i*) *T* 3.89].

Anal. Calc. for $C_{13}H_{22}O_7$: C, 53.8; H, 7.6. Found: C, 53.5; H, 7.6.

*1,2-Di-O-acetyl-3,4:5,6-di-O-isopropylidene-β-*D-manno*-3-heptulos-3,7-pyranose.* — A solution of the diol **8** (1.058 g) in pyridine (20 ml) containing acetic anhydride (4 ml) was kept for 12 h at room temperature. The reaction mixture was processed in the usual manner to give a syrupy residue. Purification by column chromatography gave the diacetate of **8** as a gum, yield 1.05 g (77%), $[\alpha]_D$ $+14°$ (*c* 2.4, chloroform); ν_{max}^{film} 1758 and 1750 (C=O), 1380 cm^{-1} (CMe_2), no absorption attributable to OH; n.m.r. data: τ 4.64 (1-proton multiplet, $J_{1,2}$ 2.2, $J_{1',2}$ 9.6 Hz, H-2), 5.26 (1-proton multiplet $J_{1,1'}$ 12.5 Hz, H-1), 5.43 (doublet of doublets, $J_{4,5}$ 2.5 Hz, H-5), 5.71 (1-proton multiplet, $J_{5,6}$ 7.8 Hz, H-6) 5.78 (1-proton doublet, H-4), 5.89 (1-proton multiplet H-1'), 6.17, 6.22 (AB of ABX system, $J_{6,7}$ ~1, $J_{6,7'}$ ~1, $J_{7,7'}$ 13.2 Hz, H-7,7'), 7.88, 8.02 (two 3-proton singlets, OAc), 8.50, 8.59, 8.67 (6-, 3-, and 3-proton singlets, CMe_2). The n.m.r. parameters for protons, other than those of the acetyl and isopropylidene groups, were ascertained by comparing the experimental and computer-simulated spectra. The product was revealed in t.l.c. as one component having R_F 0.51.

Anal. Calc. for $C_{17}H_{26}O_9$: C, 54.5; H, 7.0. Found: C, 54.9; H, 7.2.

D-manno*-3-Heptulose* (**9**). — A suspension of 3,4:5,6-di-*O*-isopropylidene-β-D-*manno*-3-heptulos-3,7-pyranose (**8**) (0.866 g) in water (50 ml) was stirred for 6 h at 70° in the presence of Rexyn-101 (H^+) ion-exchange resin (6 g). The resin was removed by filtration, and the cloudy filtrate was treated with decolorizing charcoal; the clear solution was evaporated to a syrup (0.582 g). A solution of the syrup in 95% ethanol was concentrated to an oil, which slowly desposited a crystalline product (0.448 g) on seeding with an authentic sample of β-D-*manno*-3-heptulose hydrate[10]. Recrystallization from 95% ethanol gave pure D-*manno*-3-heptulose hydrate, yield 0.354 g (52%), $[\alpha]_D$ $-40°$, final 3 min (*c* 1.0, water); lit.[10] $[\alpha]_D^{27}$ $-70°$, 2.6 min→ $-39°$, final 1 h (*c* 1, water). The melting properties of the authentic sample of β-D-*manno*-heptulose hydrate provided by Dr. Robert Schaffer and the sample prepared in the present work were indistinguishable in that each sample softened at 82° and did not melt completely until 90°, with a major change occuring at 84–85.5°; the same behaviour was observed with a mixed sample. For β-D-*manno*-3-heptulose hydrate, m.p. 84–85.5° has been reported[10]. Paper-chromatographic analysis of the product revealed only one component having $R_{Glucose}$ 0.98 in 4:1:5 (*v*/*v*) butanol–ethanol–

water (component detected by alkaline silver nitrate[19] or *p*-anisidine hydrochloride[20] spray reagents).

Anal. Calc. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.8; H, 7.1. Found: C, 36.9; H, 7.3.

A portion (20 mg) of the product obtained above was dissolved in water (3 ml) containing sodium borohydride (20 mg), and the solution was kept for 12 h at room temperature. Rexyn-101 (H^+) ion-exchange resin was then added to the stirred solution. When gas evolution had ceased, the resin was removed by filtration, and the filtrate was evaporated. Boric acid was removed by repeated distillation with methanol. A solution of the residue in pyridine (1 ml) containing acetic anhydride (1 ml) was heated for 15 min at 100°. The excess of acetic anhydride was decomposed with methanol and the solution was evaporated. G.l.c. analysis (at 200° with a 90 ml/min flow rate of the carrier-gas) of the product revealed two peaks having retention times corresponding to those of D-*glycero*-D-*manno*-heptitol heptaacetate [(*ii*) *T'* 1.91]* and D-*glycero*-D-*ido*-heptitol heptaacetate [(*ii*) *T'* 2.58]; D-*glycero*-D-*galacto*-heptitol and D-*glycero*-D-*gulo*-heptitol heptaacetates were found to have *T'* values of 2.22 and 2.31, respectively, with column *ii*. Samples of the four heptitol heptaacetates were prepared from the appropriate heptoses or heptonolactones by reduction with sodium borohydride, followed by acetylation of the resultant heptitols.

Treatment of D-manno-*3-heptulose* (9) *with phenylhydrazine.* — To a solution of the 3-heptulose 9 (275 mg) in water (0.5 ml) and methanol (5 ml) were added phenylhydrazine hydrochloride (201 mg) and sodium acetate (60 mg), and the mixture was kept for 2 h at 70°. The solution was then evaporated, and the residue was extracted with hot ethanol (5 ml). The extract was evaporated to give a crystalline product. Two recrystallizations from ethanol afforded white needles, whose elemental analysis agreed with that calculated for a dianhydro derivative of the phenylhydrazone of 9, yield 56 mg (18%), m.p. 152–153°, $[\alpha]_D$ −49° (*c* 0.6, methanol). Paper-chromatographic analysis of the product revealed only one component having R_{Ribose} 2.28 in 3:1:1 (*v*/*v*) butanol–ethanol–water (component detected by alkaline silver nitrate spray reagent[19]). Schaffer[10] reported m.p. 147–148° (dec.) and $[\alpha]_D^{25}$ +80 ±5° (*c* 0.5, methanol) for D-*manno*-3-heptulose phenylhydrazone. The new compound was also obtained in 6% yield, when a portion (256 mg) of the D-*manno*-3-heptulose prepared in the present work was treated in aqueous methanol with phenylhydrazine–acetic acid (260 mg) as described by Schaffer[10].

Anal. Calc. for $C_{13}H_{16}N_2O_4$: C, 59.1; H, 6.1; N, 10.6. Found: C, 58.8; H, 6.2; N, 10.7.

Treatment of 5 *with silver trifluoroacetate.* — A solution of adduct(s) 5 (~2 g) in *m*-xylene (150 ml) containing silver trifluoroacetate (1.3 g) was heated for 1 h at reflux temperature. The mixture was filtered, and the filtrate was washed with an aqueous saturated sodium thiosulfate solution (3 × 50 ml) and then with water (3 × 60 ml). The dried (sodium sulfate) *m*-xylene solution was evaporated at 40°/0.2 torr to leave a syrupy residue (1.8 g), which migrated in t.l.c. at the same rate as the

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*The retention times designated *T'* are relative to that of D-glucitol hexaacetate.

starting material, and, whose n.m.r. spectrum was indistinguishable from that of the starting material. Treatment of the syrup with methanol containing triethylamine gave a product which migrated in t.l.c. at the same rate as the iodohydrin **6**.

*Treatment of 1,2-dideoxy-3,4:5,6-di-O-isopropylidene-β-*D-arabino*-hept-1-en-3-ulo-3,7-pyranose* (**4**) *with* m-*chloroperoxybenzoic acid.* — A solution of the unsaturated sugar **4** (2.09 g) and 85% *m*-chloroperoxybenzoic acid (1.81 g) in dichloromethane (60 ml) was stirred for 3 weeks at room temperature. G.l.c. analysis (at 180° with a 70 ml/min flow rate of the carrier-gas) indicated that approximately 60% of **4** had been converted into another component having a retention time of 2.40 relative to that of **4**; t.l.c. [1:3 (v/v) ethyl acetate–petroleum ether] revealed the presence of **4** (R_F 0.53) and another component (R_F 0.49). The reaction mixture was filtered, and the filtrate was washed with aqueous saturated sodium hydrogen carbonate solution (3 × 30 ml) and then with water (3 × 30 ml). The dried (sodium sulfate) solution was evaporated to give a syrup which was chromatographed on silica gel, with 1:3 (*v*/*v*) ethyl acetate–petroleum ether as eluant. Three fractions were obtained, namely, the unsaturated sugar **4** (0.125 g), a mixture (1.05 g) of **4** and the new component having R_F 0.49, and the new component (0.400 g). The n.m.r. spectrum of the new component suggested that it was an approximately 1:1 mixture of the epoxide **7** and its C-2 epimer; the elemental analysis of the new component also agreed with that calculated for the epoxides.

Anal. Calc. for $C_{13}H_{20}O_6$: C, 57.3; H, 7.4. Found: C, 57.0; H, 7.3.

*Treatment of 1,2-dideoxy-3,4:5,6-di-O-isopropylidene-β-*D-arabino*-hept-1-en-3-ulo-3,7-pyranose* (**4**) *with potassium permanganate.* — A solution of potassium permanganate (1.31 g) in water (30 ml) was added dropwise with stirring to a mixture, kept at 4°, of ethanol (30 ml) and water (40 ml) containing the unsaturated sugar **4** (2.12 g) and magnesium sulfate (2.5 g); the reaction mixture was stirred for 3 h, and then filtered through Celite. The filtrate was extracted with chloroform (4 × 50 ml); the dried (sodium sulfate) extracts were evaporated to give a yellow syrup. T.l.c. showed the presence of the starting material (R_F 0.71) and a new component (R_F 0.11); the two components were isolated by column chromatography in yields of 0.462 g and 1.45 g, respectively. The n.m.r. spectrum of the new component was similar to that of the diol **8**, except that the signals were broadened. G.l.c. analysis (see experiment for the preparation of D-*manno*-3-heptulose) of the heptitol heptaacetates obtained from the new component by successive acid-catalyzed hydrolysis, reduction with sodium borohydride, and acetylation with acetic anhydride–pyridine indicated that the new component was an approximately 7:3 mixture of 3,4:5,6-di-*O*-isopropylidene-*β*-D-*manno*-3-heptulos-3,7-pyranose (**8**) and its D-*gluco* isomer, respectively.

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