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SYNTHESES RELATED TO THE OCTODIOSE IN APRAMYCIN

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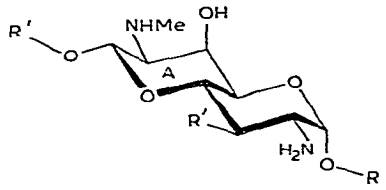
ABSTRACT

A synthesis of 3-*O*-benzyl-6-deoxy-1,2:7,8-di-*O*-isopropylidene-L-*glycero*-D-*glycero*-L-*altro*-octodifuranose (**20**) has been achieved starting with 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-D-arabinofuranose (**6**). Reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-*arabino*-pentodialdo-1,4-furanose (**9**) with allylmagnesium bromide afforded the epimeric 3-*O*-benzyl-6,7,8-trideoxy-1,2-*O*-isopropylidene-α-D-*galacto*- (**11**) and β-L-*altro*-oct-7-enose (**12**), the stereochemistry at C-5 of the compounds was established by the degradation of **12** to the known 2-deoxy-D-*ribo*-hexitol (**24**). Olefin **12** gave 8-azido-3-*O*-benzyl-6,8-dideoxy-1,2-*O*-isopropylidene-L-*glycero*-D-*glycero*-β-L-*altro*-octofuranose (**15**), which were photolyzed to the dialdose derivatives **16** and **19**, respectively. Compound **16** was converted into 3-*O*-benzyl-6-deoxy-1,2:7,8-di-*O*-isopropylidene-L-*glycero*-D-*glycero*-L-*altro*-octodifuranose (**17**) and subsequently into a mixture of methyl glycosides. Similarly, **19** was converted into the D-*glycero* analog (**20**) of **17**. The stereochemistry at C-7 in derivatives **17** and **20** has been tentatively assigned by use of n.m.r. spectroscopy.

INTRODUCTION

Nebramycin[1], produced by *Streptomyces tenebrarius*, is an aminocyclitol antibiotic complex containing, among other factors, apramycin[2] (factor 2) (**1**) and oxyapramycin[3] (factor 7) (**2**). Apramycin is of interest, not only because it has been found to be an extremely potent antibiotic relative to neamine[4] and is not inactivated by any of the known aminoglycoside-inactivating enzymes[4,5], but also because of the unique structure. It is also interesting to note that replacement of the terminal 4-amino-4-deoxy-D-glucose residue with a methyl group yields a compound, namely **3**, having a similar antimicrobial spectrum[4]. In view of the latter result, pseudodisaccharides containing the unique aminooctodialdoses **4** and **5** or their analogs may prove to be of value. Part of the initial work done in this laboratory has been to investigate the synthesis of octodialdoses that are related to **4** and **5** and that might be of use in their synthesis. The present article describes the results of a synthesis of two octodialdoses and an attempt to convert one of them into a *trans*-decalin ring system of the type found in **4**.



1 R = 4-*O*-(2-deoxystreptamine) R' = H R'' = 4-amino-4-deoxy-α-D-glucopyranosyl

2 R = 4-*O*-(2-deoxystreptamine) R' = OH R'' = 4-amino-4-deoxy-α-D-glucopyranosyl

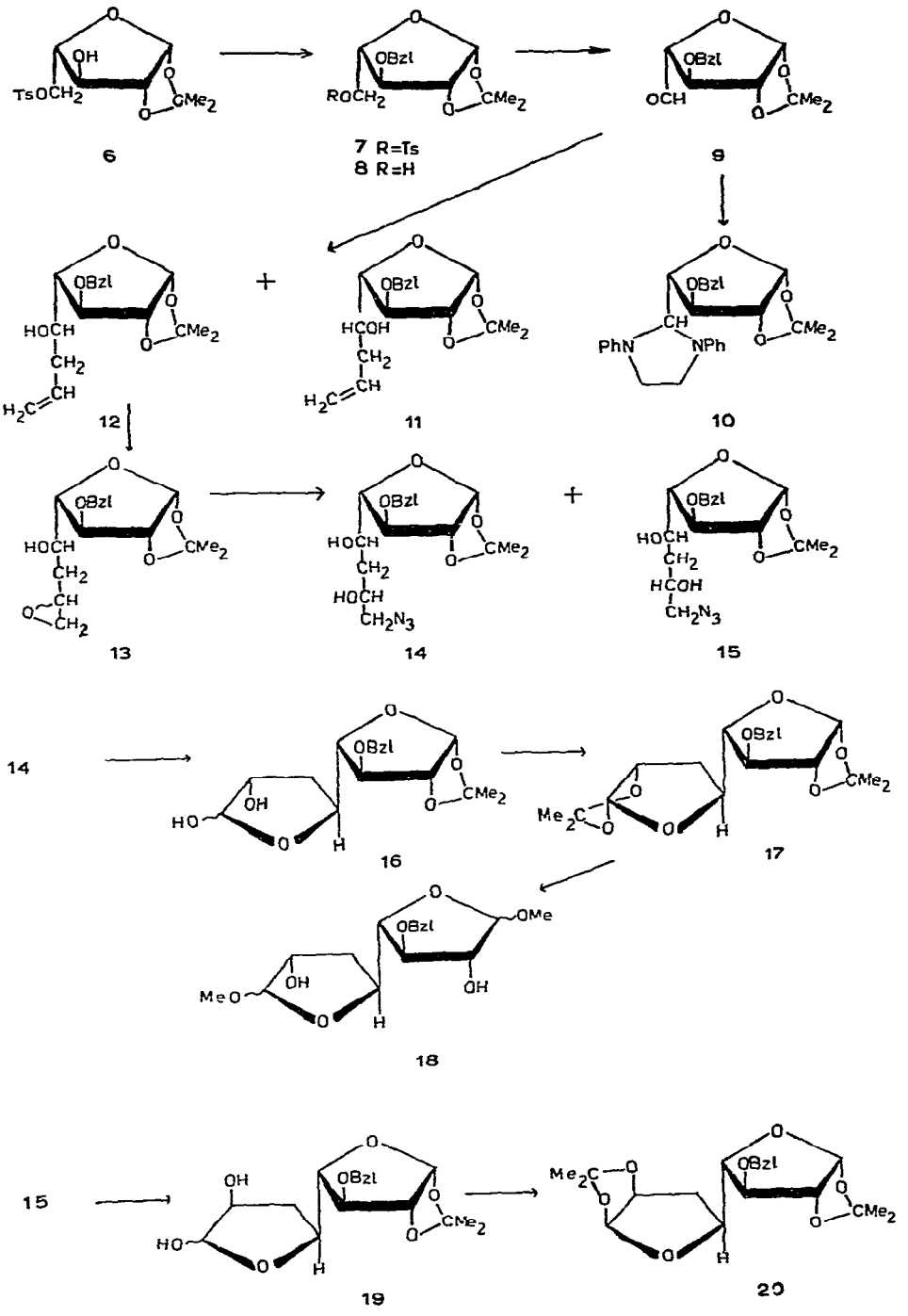
3 R = 4-*O*-(2-deoxystreptamine) R = H R'' = Me

4 R = R = R'' = H

5 R = R'' = H, R' = OH

RESULTS AND DISCUSSION

The synthesis utilizing a chain extension of the L-arabinose derivative **6** corresponds, in effect to extending the skeleton of the ring A of such systems as **4** and **5** Treatment of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-L-arabinofuranose (**6**) (prepared from L-arabinose in four steps[6]) with sodium hydride and benzyl chloride afforded 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-L-arabinofuranose (**7**) in high yield Removal of the *p*-tolylsulfonyl group was accomplished by two methods Rapid detosylation in good yield has been shown with the radical anion sodium naphthalene[7] When **7** was treated with the radical anion, 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-arabinofuranose (**8**) was isolated in only modest yields It is interesting to note that the benzyl ether function appears to be compatible with the particular reaction conditions, since the reaction has been reported[8] to debenzylate nucleosides at position 3 Detosylation of **7** with sodium amalgam by a method similar to that described by Levene and Compton[6] afforded **8** in high yield and, therefore, was the preferred method Oxidation of **8** with the chromium trioxide–dipyridine complex[9] gave aldehyde **9** rapidly and in high yield Aldehyde **9** was readily characterized as its *p*-nitrophenylhydrazone and, on treatment with the Wanzlick reagent[10] (*N,N'*-diphenyl-1,2-diaminoethane), afforded crystalline 2-(3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-*arabino*-tetrofuranos-4-yl)-1,3-diphenylimidazolidine (**10**) Reaction of **9** with allylmagnesium bromide produced the epimeric, trideoxy derivatives **11** and **12** in an ~1 7 ratio, respectively In the p m r spectrum of **9**, H-5 appears as a singlet (τ 0 23), indicating that the vicinal coupling ($J_{4,5}$) is approximately zero Horton *et al* [11] have observed similar results with several dialdose derivatives and have suggested that there are two preferred rotamers in which the carbonyl group eclipses a carbon or an oxygen atom Also, Wolfrom and Hanessian[12] have suggested that the reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose with methylmagnesium bromide involves the chelation of O-5 and O-4 with the Grignard reagent Therefore, a possible explanation for the observed ratio of **11** to **12** may be that the reaction in the case of **9** involves the preferential chelation of the


6
7 R=Ts
8 R=H
9
10
11
12
13
14
15
16
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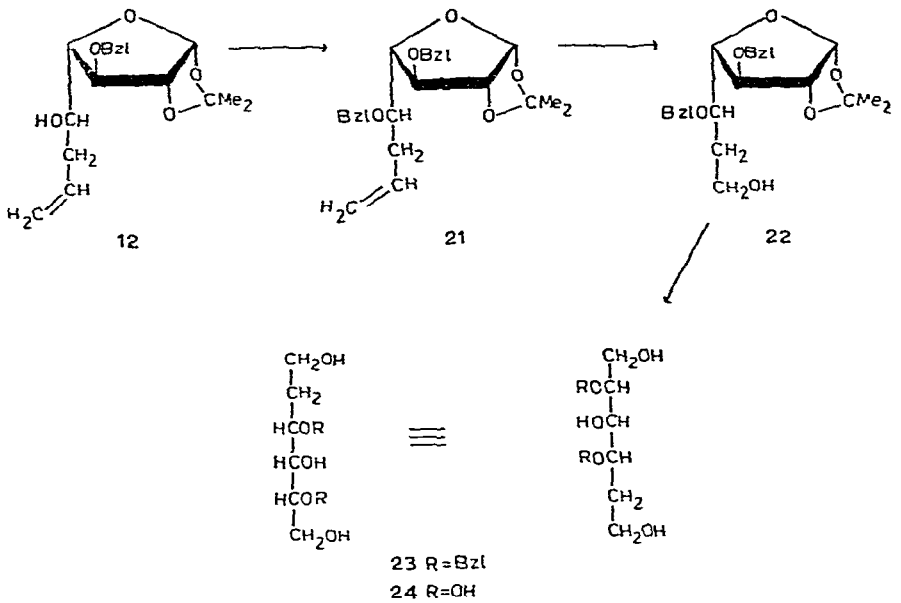
Grignard reagent with O-5 and O-3 in the rotamer in which O-5 eclipses C-3, a feature which would be expected to yield a product having the L-configuration at C-5

The stereochemistry at C-5 in **11** and **12** was established by treating the major product from the Grignard reaction, namely **12**, with sodium hydride and benzyl chloride to give the dibenzyl derivative **21** in high yield Oxidation of **21** with osmium tetroxide in the presence of sodium metaperiodate, followed by reduction of the resulting aldehyde with sodium borohydride, afforded 3,5-di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-*β*-L-*altro*-heptofuranose (**22**) as the sole product Compound **22** was



hydrolyzed with 90% trifluoroacetic acid, and the crude, reducing heptose derivative was oxidized with sodium metaperiodate, the product hexose, without isolation, was reduced to give 3,5-di-*O*-benzyl-2-deoxy-D-*ribo*-hexitol (**23**) Removal of the benzyl groups by hydrogenolysis over palladium-on-charcoal afforded 2-deoxy-D-*ribo*-hexitol (**24**) which had m p , optical rotation, and migration on paper electrophoresis agreeing with those described in the literature[13,14] Thus, the major product of the Grignard reaction, namely **12**, has the L configuration, and **11**, the minor product, has the D configuration

It was felt that the aldehyde function could most readily be introduced by the photolysis of an azide derivative[15], which was only partially protected in this way the necessity of selectively protecting hydroxyl groups might be avoided Epoxidation of **12** with *m*-chloroperbenzoic acid readily afforded the diastereomeric, 7,8-anhydro derivatives **13**, which migrated together as a single spot in t l c Treatment of the anhydro derivatives with sodium azide in the presence of ammonium chloride[16] gave the epimeric 8-azidooctose derivatives **14** and **15**, which were separable by column

chromatography on silica gel The configurations at C-7 in the azides were deduced from the products that resulted from the subsequent transformations of **14** and **15** (see below)

Irradiation with u v light of azide **14** in benzene afforded, after column chromatography on silica gel, crude dialdose **16** Presumably, the intermediate imine[15] was hydrolyzed on exposure to silica gel (see also Ref 17) P m r spectroscopy suggests that the product exists primarily as a difuranoid structure, as evidenced by the lack of an aldehydic-proton signal and by the presence of a second, anomeric-proton resonance (τ 4 65–4 93) in the spectrum of **16** Molecular models reveal that intramolecular interactions are diminished when the second furan ring is formed, a feature which may account for the absence of any significant concentration of the acyclic form of **16** Treatment of **16** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid gave a single product, namely **17** Similarly, azide **15** afforded dialdose **19** which also had a p m r spectrum consistent with a difuranoid structure Isopropylidenation of **19** with 2,2-dimethoxypropane afforded **20** A comparison of the p m r spectra at 100 MHz of **17** and **20** with those of 3-deoxy-1,2 5,6-di-*O*-isopropylidene-D-*ribo*-, -D-*xylo*-, and -D-*arabino*-hexoses[18] revealed that the splitting pattern for H-6,H-6′ of **17** was very similar to that observed for H-3,H-3′ of the *ribo* derivative The pattern for H-6,H-6′ of **20** was similar to that observed for H-3,H-3′ of both of the *xylo*- and *arabino*-hexose derivatives

^{13}C-N m r spectroscopy provided further stereochemical information In the spectrum of 3-deoxy-1,2 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose[20], C-1 resonates at δ 105 0 and C-3 at δ 34 7, while the signals for the corresponding carbon atoms in 3-deoxy-1,2 5,6-di-*O*-isopropylidene-α-D-*xylo*-hexose appear at δ 106 5 and 33 7, respectively The signals for C-1 and C-8, and C-6, in the spectrum of **17** (related to 3-deoxy-1 2 5,6-di-*O*-isopropylidene-D-*ribo*-hexose) occur at δ 105 9 and 36 7, respectively, while those for the corresponding carbon atoms in **20** (related to 3-deoxy-1,2 5,6-di-*O*-isopropylidene-D-*xylo*-hexose) occur at δ 107 0 and 106 2 (interchangeable), and 33 7 The shielding of C-1 in the *ribo*-hexose derivative relative to C-1 in the *xylo*-hexose derivative may be related to the shielding of C-8 in **17** relative to C-8 in **20** The deshielding of C-3 in the *ribo*-hexose derivative with respect to C-3 in the *xylo*-hexose derivative may be related to the deshielding of C-6 in **17** with respect to C-6 in **20** These qualitative arguments may be used to support the conclusions based on the p m r data On the basis of the preceding observations derivatives **17** and **20** are tentatively assigned the L-*glycero*-L-*altro* and D-*glycero*-L-*altro* configuration, respectively

The stereochemistry at each carbon atom in **17** is identical to that found in **4**, except at C-2 in the former (which corresponds to C-7 in structure **4**) accordingly, an attempt was made to convert **17** into a *trans*-decalin structure Methanolysis of **17** in the presence of an acidic, ion-exchange resin afforded material that migrated as a single component in t l c , but which was revealed by p m r and ^{13}C-n m r spectroscopy to be a mixture of glycosides as shown by the presence of at least three methyl signals In the ^{13}C-n m r spectrum of the product, signals at δ 110 0 and 109 6 were

assigned to anomeric carbon atoms in furanoid rings in which the substituents at C-1 and C-2 are *trans* oriented Resonances at δ 102 9 and 102 6 were assigned to anomeric carbon atoms of furanosides in which the substituents at C-1 and C-2 are *cis* oriented The chemical shifts and their assignments are in agreement with the observations reported by Ritchie *et al* [19] for methyl aldofuranosides In addition, two signals attributable to C-6 were observed at δ 35 5 and 34 4 Szarek *et al* [20] have reported that ring-methylene carbon atoms in some deoxyaldopyranosides resonate at δ 36 5–39 8, whereas those in several 3-deoxyfuranose derivatives resonate at δ 33 3–34 7 These results suggest that the product is an anomeric mixture of furanosides having structure **18** It would appear then that the formation of a *trans*-decalin structure in this case is not favored Possibly, the requirement that the hydroxyl group at C-2 and the benzyloxy group at C-3 assume axial positions in such a system formed from **17** is sufficient to favor the formation of the difuranoid structure Since the stereochemistry of the octodialdose derivative **18** differs from that of **4** only at one center, presumably, inversion of the configuration of C-2 in the former would permit the formation of the desired *trans*-decalin structure

EXPERIMENTAL

General — Melting points were determined on a Fisher–Johns apparatus and are uncorrected Optical rotations were measured with a Perkin–Elmer model 141 automatic polarimeter at $26\pm3°$ I r spectra were recorded with a Unicam SP 1000 or a Perkin–Elmer 180 spectrophotometer P m r spectra were recorded at 60 MHz or with a Varian HA-100 spectrometer at 100 MHz in chloroform-*d* with tetramethylsilane as the internal standard ^{13}C-N m r (c m r) spectra were determined at 15 09 MHz on a Bunker HX-60 spectrometer equipped with a FT60M Fourier transform accessory, with tetramethylsilane as the internal standard T l c was performed with Silica gel G containing 1–3% of Lumilux Green ZS (Brinkmann) in the following solvent systems (v/v) (*A*) 4 1 benzene–ethyl acetate, (*B*) 8 1 benzene–ethyl acetate, (*C*) 5 2 petroleum ether–ethyl acetate, (*D*) 1 1 benzene–ethyl acetate, and (*E*) ethyl acetate The term "petroleum ether" refers to the fraction of b p 60–80° The developed plates were air dried, and compounds located by heating the plates at ~150° after they had been sprayed with 10% aqueous sulfuric acid containing 1% cerium sulfate and 1 5% molybdic acid, benzyl ethers were detected by irradiation of the developed plates with short-wavelength u v light from a 2537 Å Mineralight Column chromatography was performed on silica gel (70–230 mesh) Paper electrophoresis was performed on Whatman 3MM paper by the enclosed-strip technique with a molybdate buffer[14] Components were detected by spraying the paper with saturated, aqueous potassium periodate, then with ammonical silver nitrate[21], followed by heating at 110° for 5–10 min Mobilities are expressed relative to D-glucitol ($M_{glucitol}$ 1) Ultraviolet irradiations were performed with a 450-W, Hanovia, medium-pressure, mercury-arc lamp (Cat No 679A-36) contained in a water-cooled, quartz immersion-well The whole assembly was mounted in a borosilicate glass reaction-vessel

3-O-Benzyl-1,2-O-isopropylidene-5-O-p-tolylsulfonyl-β-L-arabinofuranose (**7**) — 1,2-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-β-L-arabinofuranose[6] (**6**, 5 1 g) in dry dimethyl sulfoxide (20 ml) was stirred overnight with benzyl chloride (3 ml) and sodium hydride (360 mg) The reaction mixture was poured into ice–water, the resulting mixture was stirred for 1 h, and then extracted with chloroform The dried ($MgSO_4$) chloroform extract was concentrated to a syrup, which was fractionated on a column of silica gel (Solvent *A*) to give **7** as a homogeneous syrup (6 2 g, 93%), $[\alpha]_D^{26}$ −22 5±0 9° (*c* 1 2 chloroform), R_F 0 70, p m r τ 2 20, 2 33, and 2 60–2 87 (9 H, aromatic), 4 19 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5 33–5 60 (3 H, H-2, benzyl-CH_2), 5 67–6 13 (4 H H-3–H-5's), 7 58 (s. 3 H, tolyl-CH_3), 8 63 and 8 75 (6 H, CMe_2)

Anal Calc for $C_{22}H_{27}O_7S$ C 60 7, H, 6 2 Found C, 61 0 H, 6 0

3-O-Benzyl-1,2-O-isopropylidene-β-L-arabinofuranose (**8**) — *Method A* A solution of **7** (2 2 g) in dry tetrahydrofuran (25 ml) was added to a tetrahydrofuran solution of sodium naphthalene[7] (10 mmol in 20 ml) which had been cooled (−78°) T l c (solvent *A*) revealed that after 5 min all of **7** had reacted to give one product having R_F 0 14 After water (2 drops) had been added, the reaction mixture was allowed to warm to room temperature and then concentrated to a solid residue that was partitioned between chloroform–water The dried ($MgSO_4$) chloroform extract was concentrated to dryness, and the residue was chromatographed on a column of silica gel benzene eluted naphthalene and side products and then solvent *A* eluted **8** as a yellow oil, which crystallized after some time Recrystallization from hexane gave **8** as white needles (930 mg 66%), m p 74–75°, $[\alpha]_D^{26}$ −22 5±0 5° (*c* 1 2, chloroform), p m r τ 2 67 (5 H aromatic), 4 10 (d 1 H $J_{1,2}$ 4 Hz, H-1) 5 13–5 47 (3 H H-2, benzyl-CH_2) 5 60–6 43 (4 H H-3–H-5's) 7 77 (1 H OH) 8 45 and 8 65 (6 H, CMe_2)

Anal Calc for $C_{15}H_{20}O_5$ C, 64 3 H 7 2 Found C, 64 1 H 7 2

Method B A mixture of **7** (8 76 g) in 80% methanol (380 ml) and 4% sodium amalgam (100 g) was stirred for 18 h at room temperature The reaction mixture was neutralized with Dry Ice and the resulting solution was concentrated to a solid residue, which was extracted with chloroform The dried ($MgSO_4$) extract was concentrated to a syrup which crystallized after some time Recrystallization from hexane afforded **8** as white needles m p 74–75° R_F 0 14 (solvent *A*) p m r spectrum identical with that obtained for the sample that had been prepared by method A

3-O-Benzyl-1 2-O-isopropylidene-β-L-arabino-pentodialdo-1,4-furanose (**9**) — A solution of **8** (556 mg) in dry dichloromethane (5 ml) was added to a vigorously stirred, dichloromethane solution of chromium trioxide–dipyridine complex[9] [prepared from chromium trioxide (2 88 g) and dry pyridine (4 55 g) in dichloromethane (100 ml)] After 25 min the reaction mixture was poured into ice-cold, saturated aqueous sodium hydrogencarbonate and the reaction flask was rinsed with a small amount of diethyl ether the ether solution was added to the separatory funnel and the mixture was shaken at 0° The organic solution was separated, washed twice with water dried ($MgSO_4$), and concentrated to an orange syrup Several additions and evaporations of toluene gave **9** as a homogeneous, orange syrup, ν_{max}^{film} 1750 cm^{-1} (C=O), p m r τ 0 23 (s, 1 H, H-5), 2 65 (5 H, aromatic), 3 92 (d, 1 H, $J_{1,2}$ 3 5 Hz,

H-1), 5 25–5 55 (4 H, H-2, H-4, benzyl-CH_2), 5 68 (s, 1 H, H-3), 3 55 and 8 70 (6 H, CMe_2)

The crude aldehyde was converted, in the usual way, into its *p*-nitrophenylhydrazone, which was crystallized from methanol, m p 159–159 5°, p m r τ 1 72–2 05 (3 H, NH, aromatic), 2 50–2 85 (6 H, H-5, aromatic), 3 03 (2 H, $J_{o\,m}$ 9 Hz, aromatic), 4 02 (d, 1 H, $J_{1\,2}$ 4 Hz, H-1), 5 18 (dd, 1 H, $J_{4\,5}$ 6 Hz, $J_{3\,4} \leq 1$ Hz, H-4), 5 23–5 38 (3 H, H-2, benzyl-CH_2), 5 70 (bs, 1 H, H-3), 8 55 and 8 68 (6 H, CMe_2)

Anal Calc for $C_{21}H_{23}N_3O_6$ C, 61 0 H, 5 6, N, 10 2 Found C, 61 0, H, 5 6, N, 10 2

*2-(3-O-Benzyl-1 2-O-isopropylidene-β-*L-arabino-*tetrofuranos-4-yl)-1,3-diphenylimidazolidine* (**10**) — To a solution of the crude aldehyde **9** (2 mmol) in methanol (10 ml) were added *N,N'*-diphenyl-1,2-diaminoethane (2 2 mmol) and 2 drops of glacial acetic acid and the resulting mixture was refrigerated overnight The crystalline product was collected and recrystallized from methanol to give **10** as white needles (473 mg, 50%), m p 95 5–96 5°, $[\alpha]_D^{26}$ −1 2±0 4° (*c* 2 6, chloroform), $[\alpha]_{365}^{26}$ +51 5±0 4°, p m r τ 2 55–3 50 (15 protons, aromatic), 4 25–4 45 (2 H, H-1, H-2), 5 20–6 55 (9 H, H-4 s H-5's H-2'–H-4', benzyl-CH_2), 8 60 and 8 65 (6 H, CMe_2)

Anal Calc for $C_{29}H_{32}N_2O_4$ C 73 7, H, 6 8 N 5 9 Found C, 73 6 H, 6 8 N, 5 9

*3-O-Benzyl-6,7,8-trideoxy-1,2-O-isopropylidene-α-*D-galacto- (**11**) *and -β-*L-altro-*oct-7-enofuranose* (**12**) — A solution of **9** (prepared from 2 22 g of **8**) in dry diethyl ether (20 ml) was added dropwise to a stirred solution of allylmagnesium bromide [prepared from magnesium (764 mg) and allyl bromide (1 4 ml)] in diethyl ether T l c (solvent *A*) revealed that after 8 h all of **9** had reacted to give two major products having R_F values 0 47 and 0 35 Ice-cold, 10% aqueous ammonium chloride (30 ml) was added dropwise and the resulting mixture was stirred for 30 min The organic phase was decanted, the aqueous phase was extracted with diethyl ether (2 × 25 ml), and the combined, dried ($MgSO_4$) ether solution was concentrated to a syrup Fractionation of the syrup on a column of silica gel (solvent *A*) afforded **12** as a homogeneous, colorless syrup (1 0 g, 39%), $[\alpha]_D^{26}$ −14±0 4° (*c* 1 0, chloroform). R_F 0 47, ν_{max}^{film} 3540 (OH) and 1650 cm^{-1} (C=C) p m r τ 2 67 (5 H, aromatic), 3 70 (2 H, vinyl, H-1), 6 65–5 15 (2 H, vinyl), 5 27–5 55 (3 H, H-2, benzyl-CH_2), 5 70–6 45 (3 H H-3–H-5) 7 27–7 90 (3 H, H-6 s, OH), 8 50 and 8 65 (6 H, CMe_2)

Anal Calc for $C_{18}H_{24}O_5$ C, 67 5 H, 7 6 Found C, 67 5, H, 7 6

Compound **11** was isolated as a homogeneous, colorless syrup (0 14 g, 5 4%), $[\alpha]_D^{26}$ −27±1° (*c* 1 2 chloroform) R_f 0 35, p m r τ 2 72 (5 H, aromatic), 3 89–4 55 (2 H, vinyl, H-1), 4 62–5 25 (2 H, vinyl), 5 31–5 58 (3 H, H-2, benzyl-CH_2), 5 85–6 45 (3 H, H-3–H-5), 7 22–7 41 (1 H, OH), 7 60–7 95 (2 H, H-6's), 8 50 and 8 67 (6 H, CMe_2)

Anal Calc for $C_{18}H_{24}O_5$ C, 67 5 H, 7 6 Found C, 66 8, H, 7 5

*3,5-Di-O-benzyl-6,7,8-trideoxy-1,2-O-isopropylidene-β-*L-altro-*oct-7-enofuranose* (**21**) — Compound **12** (865 mg) in dry dimethyl sulfoxide (5 ml) was treated overnight with sodium hydride (200 mg) and benzyl chloride (0 4 ml) to give a single product

having R_f 0 77 (solvent *A*) The reaction product was isolated in the usual way (see preparation of **7**) and purified by column chromatography on silica gel (solvent *B*) to give **21** as a homogeneous, yellow syrup (1 0 g, 90%), $[\alpha]_D^{26}$ +28 9±0 4° (*c* 2 2, chloroform), no i r absorption attributable to OH, p m r τ 2 75 (10 H, aromatic), 3 70–4 50 (2 H, vinyl, H-1), 4 70–5 23 (2 H, vinyl), 5 35–6 53 (8 H, H-2–H-5, 2 benzyl-CH_2), 7 37–7 70 (2 H, H-6's), 8 55 and 8 70 (6 H, CMe_2)

Anal Calc for $C_{25}H_{30}O_5$ C, 73 1, H, 7 4 Found C, 73 2, H, 7 4

*3,5-Di-O-benzyl-6-deoxy-1,2-O-isopropylidene-β-*L-altro*-heptofuranose* (**22**) — A 1% solution of osmium tetraoxide in *tert*-butanol (3 ml) was added to a stirred solution of **21** (750 mg) in diethyl ether–water [40 ml, 1 1 (v/v)] followed by the addition of sodium metaperiodate (2 3 g) in small portions T l c (solvent *C*) indicated that all of **21** had reacted The organic phase was decanted, and the aqueous phase was extracted with diethyl ether (20 ml) The combined diethyl ether solution was diluted with methanol (20 ml) and sodium borohydride (200 mg) was added After 30 min, the reaction mixture was neutralized with glacial acetic acid (pH 7), filtered, and the filtrate evaporated to a residue which was concentrated several times after addition of methanol to give a black syrup Column chromatography on silica gel (solvent *C*) afforded **22** as a homogeneous syrup (580 mg, 76 3%), $[\alpha]_D^{26}$ +4±0 3° (*c* 1 9, chloroform), $[\alpha]_{365}^{26}$ +14±0 2° p m r τ 2 75 (10 H aromatic), 4 12 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5 30–5 60 (5 H, H-2 2 benzyl-CH_2), 5 72–6 45 (5 H, H-3–H-5, H-7 s), 7 65 (bs, 1 H OH, exchanged), 7 80–8 30 (2 H, H-6's), 8 50 and 8 69 (6 H, CMe_2)

Anal Calc for $C_{24}H_{30}O_6$ C, 69 5 H, 7 3 Found C, 69 5, H, 7 1

3,5-Di-O-benzyl-2-deoxy-D-ribo-*hexitol* (**23**) — The heptose derivative **22** (800 mg) was treated with 90% trifluoroacetic acid (10 ml) for 20 min at room temperature, and the solution was then concentrated to dryness The residue was dissolved in methanol–water [30 ml, 1 1 (v/v)], and the resulting solution was neutralized (pH 7) with sodium hydrogencarbonate T l c (solvent *D*) revealed the presence of two components having R_F values of 0 73 and 0 36, respectively, compound **22** had the same value as the former The neutralized mixture was treated with sodium metaperiodate (600 mg) for 2 h, and then 1,2-ethanediol (3 drops) was added Sodium borohydride (200 mg) was added to the filtered, reaction mixture, after 30 min the product was isolated in the usual way to give a syrup, which was shown by t l c (solvent *D*) to contain two components, one of which had the same mobility as **22** The syrup, which did not reduce Fehling s solution, was fractionated on a column of silica gel (solvent *E*) to give **23** as a homogeneous, yellow syrup (320 mg, 50%), $[\alpha]_D^{26}$ −20 2±0 9° (*c* 1 1, chloroform), R_F 0 40 (solvent *E*), p m r τ 2 68 (10 H, aromatic), 5 27–5 70 (4 H, 2 benzyl-CH_2), 5 80–6 75 (10 H, H-1 s–H-4, H-6's 3 OH 3 exchanged), and 8 00–8 50 (2 H, H-5's)

Anal Calc for $C_{20}H_{26}O_5$ C, 69 3, H, 7 6 Found C, 69 3, H, 8 1

2-Deoxy-D-ribo-*hexitol* (**24**) — 2,5-Di-*O*-benzyl-2-deoxy-D-*ribo*-hexitol (**23**) (100 mg) in ethanol was hydrogenated [4 2 kg/cm^2] over 10% palladium-on-charcoal for 24 h The reaction mixture was filtered and the filtrate concentrated to a white solid Recrystallization from methanol–diethyl ether afforded **24** (51 mg),

m p 84–85°, $[\alpha]_D^{26}$ −20 4±0 6° (*c* 1 6, methanol), $M_{D\text{-}glucitol}$ (Mo) 0 10–0 44, lit [13] m p 90–91°, $[\alpha]_D$ −19 0±2° (*c* 2 26, methanol), lit [14] $M_{D\text{-}glucitol}$ (Mo) 0 13–0 57

*7 8-Anhydro-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-*D*- and* L*-glycero-β-*L*-altro-octofuranose* (**13**) — Compound **12** (3 1 g) in dry dichloromethane (50 ml) was treated with *m*-chloroperbenzoic acid (1 72 g) for 48 h at room temperature The reaction mixture was diluted with chloroform (50 ml), and the resulting mixture was washed with aqueous sodium hydrogencarbonate, the organic phase was dried ($MgSO_4$) and concentrated to a syrup Fractionation of the syrup on a column of silica gel (solvent *A*) afforded **13** as a homogeneous, colorless syrup (2 78 g, 89 9%), $[\alpha]_D^{26}$ −14 4±0 7° (*c* 1 4, chloroform) R_F 0 19, p m r τ 2 70 (5 H, aromatic), 4 19 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5 30–5 55 (3 H, H-2, benzyl-CH_2), 5 70–6 27 (3 H, H-3–H-5), 6 75–7 75 (4 H, OH, H-7–H-8's, one exchanged), and 8 00–8 85 (8 H, H-6's, CMe_2)

Anal Calc for $C_{18}H_{25}O_6$ C, 64 3, H 7 2 Found C, 63 8, H, 6 9

*8-Azido-3-*O*-benzyl-6 8-dideoxy-1,2-*O*-isopropylidene-*L*-glycero-* (**14**) *and* D*-glycero-β-*L*-altro-octofuranose* (**15**) — The anhydro derivatives **13** (795 mg) in 2-methoxyethanol (10 ml)–water (1 ml) was boiled under reflux in the presence of sodium azide (450 mg) and ammonium chloride (150 mg) After 1 h the reaction mixture was concentrated to dryness and the residue extracted with chloroform, the chloroform extract was washed with water, dried ($MgSO_4$) and concentrated to a syrup The crude products were separated by column chromatography on silica gel (solvent *C*) to give **14** as a colorless, homogeneous syrup (200 mg, 22%), which crystallized after some time Recrystallization from benzene–petroleum ether gave **14** as white needles, m p 58 5–59° $[\alpha]_D^{26}$ −23±1° (*c* 1 0, chloroform) R_F 0 62 (solvent *D*), ν_{max}^{KBr} 3480 (OH) and 2105 cm^{-1} (N_3), p m r τ 8 60 (5 H, aromatic) 4 10 (d 1 H $J_{1,2}$ 4 Hz H-1) 5 23–5 43 (3 H, H-2, benzyl-CH_2), 5 66–6 83 (8 H, H-3–H-5 H-7 H-8's 2 OH 2 exchanged), and 8 15–8 77 (8 H, H-6's, CMe_2)

Anal Calc for $C_{18}H_{25}N_3O_6$ C, 57 0 H, 6 6, N, 11 1 Found C 56 7 H, 7 1 N 11 0

Compound **15** was obtained as a homogeneous colorless syrup (270 mg 30%), $[\alpha]_D^{26}$ −19 2±0 6° (*c* 1 7 chloroform), R_F 0 58 (solvent *D*) ν_{max}^{film} 3480 (OH) and 2100 cm^{-1} (N_3), p m r τ 2 65 (5 H, aromatic), 4 18 (d, 1 H, $J_{1,2}$ 4 Hz, H-1) 5 23–5 50 (3 H H-2, benzyl-CH_2), 5 70–6 25 (4 H, H-3, H-4 H-7, OH, 1 exchanged), 6 60–6 85 (3 H, H-8's, OH 1 exchanged), and 8 17–8 80 (8 H, H-6's, CMe_2)

Anal Calc for $C_{18}H_{25}N_3O_6$ C, 57 0, H, 6 6, N, 11 1 Found C 56 9 H 6 9 N, 11 1

The stereochemical assignments for **14** and **15** are tentative (see Results and Discussion)

*3-*O*-Benzyl-6-deoxy-1,2 7,8-di-*O*-isopropylidene-*L*-glycero-L-altro-octodifuranose* (**17**) — A solution of **14** (500 mg) in benzene (50 ml) under a nitrogen atmosphere was irradiated with u v light for 4 h at room temperature Concentration of the reaction mixture to dryness and column chromatography of the residue on silica gel (solvent *D*) afforded **16** (160 mg) as an orange syrup, which reduced Fehling's solution, R_F 0 17 p m r τ 2 67 (5 protons, aromatic), 4 17 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4 65–4 93 (1 H,

H-8), 5 20–4 23 (9 H, benzyl-CH_2, H-2–H-5, H-7, 2 OH, 2 exchanged), 7 75–8 10 (2 H, H-6's), 8 47 and 8 67 (6 H, CMe_2)

A mixture of the crude product in 2,2-dimethoxypropane (10 ml) containing *p*-toluenesulfonic acid (~5 mg) was stirred for 1 h at room temperature After neutralization with ion-exchange resin (OH^-), the reaction mixture was filtered, and the filtrate was concentrated to a syrup Column chromatography on silica gel (solvent *C*) afforded **17** as a colorless syrup (83 mg, 16%), $[\alpha]_D^{26}$ −27 8±1 2° (*c* 0 8, chloroform), R_F 0 45 (solvent *C*), p m r τ 2 65 (5 H, aromatic), 4 00–4 27 (2 d, 2 H, $J_{1,2} = J_{7,8}$ 4 Hz, H-1, H-8), 5 15–6 10 (7 H, benzyl-CH_2, H-2–H-5, H-7), 7 47–8 35 (2 H, H-6's), 8 45, 8 47, and 8 65 (12 H, 2 CMe_2)

Anal Calc for $C_{21}H_{28}O_7$ C, 64 3, H, 7 2 Found C, 63 8, H, 7 1

3-O-Benzyl-6-deoxy-1,2 7,8-di-O-isopropylidene-D-glycero-L-altro-*octodifuranose* (**20**) — Compound **15** (970 mg) in dry benzene (50 ml) was irradiated, and the reaction product was isolated by the procedure described for **16** Compound **19** was obtained as a colorless syrup (380 mg), which reduced Fehling's solution, R_F 0 30 (solvent *D*), p m r τ 2 65 (5 H, aromatic), 4 15 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4 60–4 95 (1 H, H-8), 5 20–6 20 (8 H, benzyl-CH_2, H-2–H-5, H-7, OH), 6 35–6 83 (1 H, OH) 7 25–8 15 (2 H, H-6's), 8 45 and 8 69 (6 H, CMe_2)

Crude **19** was treated with 2,2-dimethoxypropane as just described (see preparation of **17**) to give, after column chromatography, **20** as a syrup, which crystallized after some time Recrystallization from petroleum ether gave white needles (250 mg, 25%) m p 95–98°, $[\alpha]_D^{26}$ +55 3±1° (*c* 0 98, chloroform), R_F 0 88 (solvent *A*) p m r τ 2 62 (5 H, aromatic), 4 05 and 4 12 (2 d, 2 H, $J_{1,2} = J_{7,8}$ 4 Hz, H-1 H-8), 5 07–5 47 (4 H, benzyl-CH_2, H-2, H-7), 5 50–5 87 (3 H, H-3–H-5), 7 35–8 05 (2 H, H-6's), 8 45, 8 51, and 8 69 (12 H, 2 CMe_2)

Anal Calc for $C_{21}H_{28}O_7$ C, 64 3, H, 7 2 Found C, 64 1, H, 7 4

Methanolysis of 3-O-benzyl-6-deoxy-1,2 7,8-di-O-isopropylidene-L-glycero-L-altro-*octodifuranose* (**17**) — A solution of **17** (230 mg) in dry methanol (30 ml) was boiled under reflux in a nitrogen atmosphere in the presence of Dowex 50 (H^+) ion-exchange resin After 16 h, t l c (solvent *E*) revealed complete reaction of **17** to give a major product (R_F 0 46) and a trace of a minor product (R_F 0 62) The reaction mixture was filtered and the filtrate was concentrated to a yellow syrup, which was fractionated on a column of silica gel to give the major component **18** as a colorless syrup (140 mg, 67 6%), $[\alpha]_D^{26}$ −75 7±1 4° (*c* 0 69, chloroform) p m r τ 2 65 (5 H, aromatic), 5 08–7 00 (15 H, H-1–H-5, H-7, H-8, benzyl-CH_2, 2 OMe), 7 00–7 73 (2 H, 2 OH, exchanged), and 7 75–8 35 (2 H H-6's), c m r δ 110 0, 109 6, 102 9, and 102 6 (C-1's, C-8's), 55 5, 55 0, and 54 6 (OMe's), and 35 5 and 34 4 (C-6 s)

Anal Calc for $C_{17}H_{24}O_7$ C, 60 0, H, 7 1 Found C, 60 3, H, 7 3

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