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ROUTES TO HIGHER-CARBON SUGAR DERIVATIVES HAVING *keto*-ACETYLENIC AND -ALKENIC, AND α,β-UNSATURATED ALDEHYDE FUNCTIONALITY*

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ABSTRACT

Oxidative dimerization of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-ynopyranoside (**1**) gave a high yield of the diyne **2**, readily reduced by lithium aluminum hydride to the *trans,trans*-diene (**4**). The structures of **2** and **4** were established spectroscopically and by degradation of **4** to D-*glycero*-D-*galacto*-heptitol (perseitol). A mixture of the alkyne **1** and its 7-epimer **10** was readily oxidized by dimethyl sulfoxide–acetic anhydride to the 6-ketone **11**, and the 8-alkene analog was similarly prepared from the alkenes derived from **1** and **10**. Likewise, oxidation of 6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*(and β-L-*ido*)-hept-6-enopyranose gave the corresponding 5-ketone. The acetylenic ketone **11** gave a crystalline oxime and (2,4-dinitrophenyl)hydrazone, the latter being accompanied by the product of attack of the reagent at the acetylene terminus (C-8). Previous work had shown that formylmethylenetriphenylphosphorane did not convert 1,2:3,4-di-*O*-isopropylidene-6-*aldehydo*-α-D-*galacto*-hexodialdo-1,5-pyranose into the corresponding C_8 unsaturated aldehyde, although the latter was obtainable *via* **1** and **10** by an ethynylation–hydroboration sequence. The Wittig route with formylmethylenetriphenylphosphorane is shown to be satisfactory for obtaining C_7 unsaturated aldehydes from 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodialdo-1,4-furanose (**22**) and the 3-epimer of **22**, respectively. These reactions provide convenient access to higher-carbon sugars and chiral dienes for synthesis of optically pure products of cycloaddition reactions.

INTRODUCTION

Previous work on this project[1–4] has demonstrated wide synthetic potential for acetylenic derivatives as obtained by ethynylation of protected aldehydo sugars;

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hydroboration of these propargyl alcohols affords[5] *trans*-α,β-unsaturated aldehydes under conditions where a direct Wittig approach on the aldehydes fails. This paper documents the synthesis of C_{16} carbon-chain sugars *via* oxidative dimerization of C_8 acetylenic precursors, and the convenient preparation of carbonyl derivatives[1,6,7] from propargylic or vinylic sugar alcohol precursors, together with some reactions of the products; the work also shows the feasibility of the Wittig route for obtaining *trans*-5,6-unsaturated 7-aldehydo derivatives from certain 5-*aldehydo*-pentodialdose derivatives. The products are of interest as dienes for Diels–Alder cycloaddition reactions leading to chiral, polysubstituted carbocycles and heterocycles of potential biological significance.

RESULTS AND DISCUSSION

Oxidative coupling of acetylenic sugars. — Terminal acetylenes may be coupled under very mild conditions to form conjugated polyacetylenes. Naturally occurring polyacetylenes are of considerable interest, particularly the polyhydroxylated polyacetylenes from micro-organisms[8]. The possibility thus exists for extending the synthetic potential of acetylenic sugars through such coupling, as a route to unusual, long-chain sugars.

Oxidative coupling has been demonstrated in one report on alkynyl glycosides[9]. This type of oxidative coupling-reaction with acetylenic sugars has now been applied for coupling the backbone chain of a sugar. By means of a modified Glaser procedure[10], an epimerically pure acetylenic sugar, 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-ynopyranose[6] (**1**), readily obtainable by ethynylation of 1,2:3,4-di-*O*-isopropylidene-6-*aldehydo*-α-D-*galacto*-hexodialdo-1,5-pyranose[11], was dimerized by air oxidation at ~25° in the presence of a catalytic amount of cuprous chloride in 15:1 methanol–pyridine. The conjugated diyne **2** was obtained crystalline in 88% yield, and was further characterized as the crystalline diacetate **3**.

The i.r. spectrum of **2** showed no C≡C-H absorption at 3.05 μm, but very weak absorption at 4.62 μm, characteristic of C≡C stretching, was observed.

The 100-MHz, ^{1}H-n.m.r. spectrum of the diyne **2** did not show the acetylenic-proton signal displayed by its precursor **1**. The anomeric proton showed a doublet, but H-2, -3, -4, and -6 gave unresolved multiplets. In contrast, the acetylated product **3** gave a first-order 100-MHz, ^{1}H-n.m.r. spectrum. The spectrum closely resembles the pattern[6] of the 6-acetate of the acetylenic sugar **1**, but slight differences in chemical shifts were noted. The observation of a doublet for H-6,6′ confirmed the absence of the acetylenic proton. Only one set of signals was observed; this result indicates the equivalence of the environments of the two moieties of the diyne **3**.

The coupling reaction was also attempted with the 6-acetate[6] of the acetylenic sugar **1**, but the procedure caused partial deacetylation, as indicated by ^{1}H-n.m.r. spectrometry.

For reduction of propargylic alcohols in sugar systems to the corresponding allylic alcohols, lithium aluminum hydride has been found[6] to be more effective than

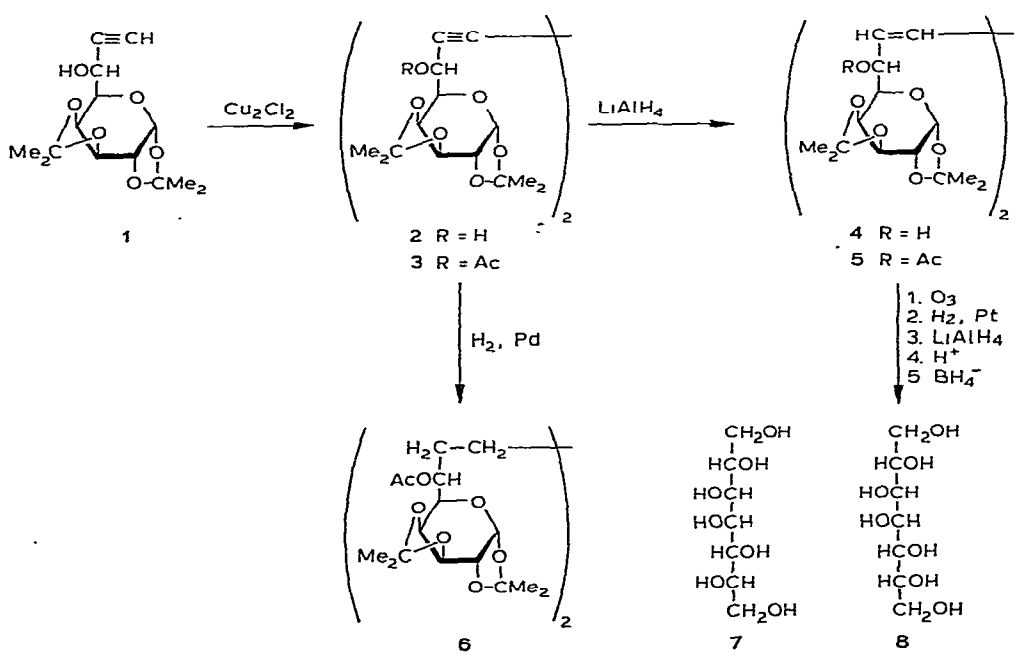
partial hydrogenation over Lindlar catalyst[12]. The mechanism of hydride attack in the reduction of propargylic alcohols to the corresponding allylic alcohols appears to involve intramolecular *trans*-addition of the hydride reagent[13]. This process contrasts with catalytic hydrogenation, which proceeds by *cis*-addition of the hydrogen atoms. Following the conventional procedure[6], reduction of the diyne **2** with lithium aluminum hydride gave the crystalline 1,4-disubstituted *trans,trans*-1,3-butadiene **4** in 80% yield. This compound was also characterized as the corresponding, crystalline, acetylated derivative **5**.

The 100-MHz, ^{1}H-n.m.r. spectrum of the acetate **5** showed patterns for the ring protons similar to those of diyne **3**. The vinyl resonances appeared as two resolved doublets of doublets at δ 5.70 and 5.67 for H-7,7′ and H-8,8′, respectively, and the magnitude of $J_{7,8}$ was 13.0 Hz. As this value is consistent with *trans*-coupling of vinyl protons, the *trans,trans*-1,3-butadiene structure was assigned.

In contrast, in attempts to obtain the *cis,cis*-1,3-butadiene derivative, the diyne **2** was subjected to hemihydrogenation in the presence of Lindlar catalyst. The ^{1}H-n.m.r. spectrum of the product indicated, however, the presence of a mixture of *cis*- and *trans*-1,3-diene isomers, together with the saturated product. Similar results have been observed in other instances[14]; in general, catalytic, partial hydrogenation of 1,3-diyne systems causes isomerization and gives *cis,trans* mixtures.

By using 5% palladium-on-charcoal, the diyne **3** was fully hydrogenated to the saturated derivative **6**, obtained as an amorphous material.

To assess the chiral stability at the propargylic position during the oxidative coupling-reaction, the *trans,trans*-1,3-butadiene **4** was ozonized, and this step was followed by reductive product-isolation, hydrolysis, and further reduction with

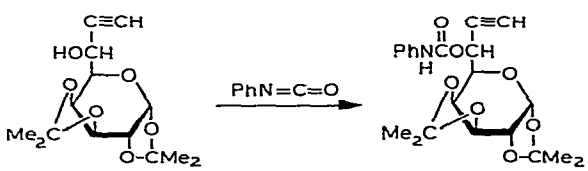


sodium borohydride, whereupon crystalline D-*glycero*-D-*galacto*-heptitol (perseitol, **8**) was obtained pure after one recrystallization from methanol–ether; it was identical with an authentic sample of perseitol kindly furnished by Dr. N. K. Richtmyer. The g.l.c. retention-time[6] of the per-*O*-trimethylsilyl derivative of **8** was identical to that of an authentic sample, whereas the per(trimethylsilyl) ether of the C-6 epimeric heptitol, L-*glycero*-D-*galacto*-heptitol (**7**), had a g.l.c. retention-time[6] different from that of the product from the degraded diyne, thus indicating that the configuration at the propargylic carbon atom is unaffected by the conditions of the oxidative coupling-reaction.

Reactions at the propargylic hydroxyl group. — Ethynylation of a protected aldehydo sugar leads to a pair of diastereoisomers; these are, formally, 1-substituted propargylic alcohols. In addition to the acetylenic group, which provides a potential precursor for varied transformations, the propargylic hydroxyl group may also be employed for synthetic purposes, as in replacement of the hydroxyl group, or an ester thereof, by an external nucleophile for stereochemical interconversion, or introduction of a nitrogen, sulfur, or other atom at the position adjacent to the ethynyl group. Furthermore, oxidation of the hydroxyl group gives ethynyl ketones, which may themselves be of synthetic value.

Several acetylenic compounds have been found useful as drugs[15,16]. Certain acetylenic carbamates display oncolytic activity[15]. The hypnotic activity of various propargyl alcohol derivatives correlates with their partition coefficient between lipids and water[16]. Acetylenic carbamates of decreased lipophilicity have been prepared[17] by treating acetylenic alcohols with a carbohydrate containing a primary isocyanate group.

Carbamate (carbanilate) derivatives of carbohydrates have been used in this laboratory because of the ease of their formation and their ready recrystallization[18]. The present work was limited to the establishment of appropriate synthetic conditions for acetylenic sugar carbanilates. In ether solution, treatment of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-ynopyranose[6] (**1**, the preponderant epimer), with phenyl isocyanate afforded the carbamate **9**, obtained crystalline in 71% yield.



1 **9**

The i.r. spectrum of **9** showed the expected absorptions at 3.05 and 4.66 μm for the terminal, acetylenic, functional group, together with a strong absorption at 5.80 μm, with a weak shoulder at 5.71 μm, which was assigned to the carbonyl group.

The 100-MHz, ^{1}H-n.m.r. spectrum was first-order, and exhibited patterns similar to those of the acetylated derivative of the alkyne **1**.

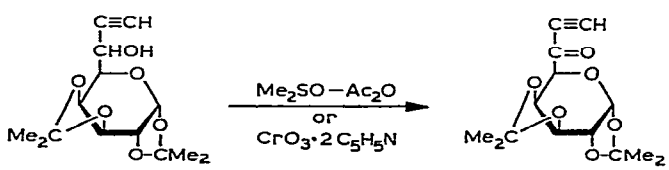
An attempt was made to obtain a water-soluble carbamate by removal of the isopropylidene protecting-groups from the sugar by hydrolysis, either with resin (Amberlite IR-120) or acid (1% hydrogen chloride in methanol). However, the carbamate functional group was itself too readily hydrolyzed under these conditions.

Replacement reactions of simple propargylic alcohol derivatives, suitably substituted to give the oxygen atom good leaving-group character, have already been studied[19]. The major course of the reaction involves direct replacement at the propargylic position by the external nucleophile. Extension of this reaction to the introduction of a nitrogen atom at the propargylic position in 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-ynopyranose (**10**) would give a useful synthetic entry to the lincomycin antibiotics. However, attempts to replace the propargylic hydroxyl group by such a route followed a different pattern[20]. The nucleophilic replacement-reaction is evidently subject to severe interference by the axial substituent at C-4.

An alternative route was envisaged for introducing a nitrogen atom at the propargylic position, namely, by oxidation of a protected propargylic alcohol to an ethynylcarbonyl derivative, followed by oximation and reduction. This sequential conversion of the hydroxyl group into an amino group has been used previously in our laboratory to prepare amino sugars related to antibiotic substances[21]. The present work is devoted principally to the oxidation step.

Oxidants that have been utilized for conversion of secondary alcohol groups into ketones in protected derivatives of sugars include oxygen–platinum oxide[22], chromium trioxide in pyridine[23,24], a chromium trioxide–pyridine complex[25], ruthenium tetraoxide[21,23,26–30], the Pfitzner–Moffatt reagent[31] and related dimethyl sulfoxide-based reagents[26,32,33], manganese dioxide[34,35], and silver carbonate on Celite[36,37]. For oxidation of acetylenic sugar derivatives, the oxidant must attack the secondary hydroxyl group, but not affect the alkynyl group.

Chromium trioxide–pyridine complex has been used to oxidize ethynyl carbinols[38]. The 6-epimeric mixture of acetylenic sugars, 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-(and L-*glycero*)-α-D-*galacto*-oct-7-ynopyranose[6] (**1** and **10**), was oxidized with a 12-molar excess of the chromium(VI) oxide–dipyridine complex, prepared *in situ* in dichloromethane by the modified procedure of Arrick *et al.*[25]. The resultant syrup contained no starting alkyne, but showed only a fast-moving, u.v.-absorbing spot. The product **11** was isolated in 25% yield after column chromatography.



1 and 10 11

Dimethyl sulfoxide–acetic anhydride, employed under the conditions described by Horton and Jewell[32], was found more effective for this oxidation. A solution of the

epimeric propargyl alcohols **1** and **10** in dry dimethyl sulfoxide and acetic anhydride reacted completely during 24 h at room temperature, and the ethynylcarbonyl derivative **11** was isolated analytically pure in 65% yield. No (methylthio)methyl ether, a possible competing side-product[33,39], was encountered.

The ynone showed i.r. carbonyl absorption at 5.86 μm with a weak shoulder at 5.95 μm, together with absorptions at 3.08 and 4.75 μm characteristic of the terminal acetylenic group. The C≡C stretching absorption at 4.75 μm was considerably stronger than in the spectrum of the propargyl alcohol precursor; this increase may be ascribed to the conjugative, polarizing effect of the carbonyl group on the acetylenic C≡C bond.

The 100-MHz, ^{1}H-n.m.r. spectrum (chloroform-*d*) of **11** showed the H-1 signal as a one-proton doublet having $J_{1,2}$ 5.0 Hz. Two two-proton multiplets were assigned to H-3,5 (δ 4.66–4.70) and H-2,4 (δ 4.33–4.39). Diamagnetic deshielding of H-5 by the carboxyl group caused its signal to be shifted to lower field. The acetylenic proton gave a one-proton singlet at δ 3.36; its low-field location is explicable because of conjugation of the ethynyl group with the carbonyl group. When the spectrum was recorded in benzene-d_6, the signals for each proton were shifted upfield, although the H-1 signal still appeared as a characteristic, low-field doublet, and the H-2 resonance appeared as an unperturbed doublet of doublets. The H-3, -4, and -5 patterns overlapped as a multiplet that was, nevertheless, amenable to analysis.

For comparison with these oxidations employing dimethyl sulfoxide–acetic anhydride and the chromium trioxide–pyridine complex, milder oxidizing agents were also examined. Such agents as manganese dioxide, and silver carbonate on Celite, have been used for selective oxidation of allylic alcohols, and manganese dioxide has also been used for oxidation of certain acetylenic alcohols[39]. The present study evaluated both of these oxidants with propargyl alcohols having a protected sugar moiety. Two systems were examined: 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*(and L-*glycero*)-α-D-*galacto*-oct-7-ynopyranose[6] (**1** and **10**), which is a fully protected propargyl alcohol, and 6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*(and β-L-*ido*)-hept-6-ynofuranose[3], which is a partially protected propargyl alcohol. Each was stirred with a suspension of commercial, "activated" manganese dioxide (Ventron, Alfa Inorganics, P. O. Box 159, Beverly, Mass.) in pentane for 12 h. T.l.c. indicated that starting material remained, but no oxidation product was detected. Even under more-vigorous conditions (3 h at 100°), the starting materials were recovered unchanged.

Each of the epimeric mixtures was treated with silver carbonate on Celite, as prepared by Fétizon's procedure[40]. A solution of the propargyl alcohols in dry benzene was mixed with an excess of oxidant (15 equiv.) and boiled for 6 h under reflux. The starting material was consumed (t.l.c.), but the ketone was not detected, and the syrupy product did not migrate in the t.l.c. system, indicating that the desired product was not formed.

Since this work was completed[2,7], independent investigators[35] have described the use of a specially activated form of manganese dioxide which slowly converted

1 + **10** into **11**, but they were unsuccessful in achieving oxidation of **1** to **11** by use of dimethyl sulfoxide–acetic anhydride, chromium trioxide–pyridine, or Fétizon's reagent.

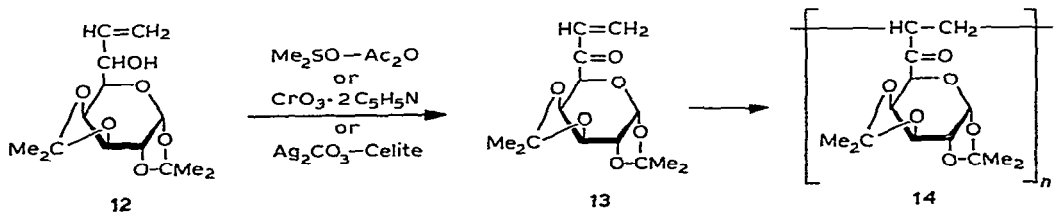
In a further extension, oxidation studies were also conducted with allylic alcohols having sugar components attached.

Treatment of an epimeric mixture of alkenic sugars, 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-(and L-*glycero*)-α-D-*galacto*-oct-7-enopyranose[6] (**12**), with chromium trioxide–pyridine complex or with dimethyl sulfoxide–acetic anhydride gave the corresponding vinylcarbonyl derivative **13**, isolated crystalline in 37 and 54% yields, respectively. Fétizon's reagent was also evaluated; in boiling benzene, t.l.c. after 4 h indicated the presence of both the starting material and a faster-moving compound. A further excess of oxidant was added, and the suspension was boiled for an additional 2 h under reflux. The reaction was still not complete (t.l.c.), but isolation by preparative t.l.c. gave the product **13** in 52% yield. The starting material was recovered unchanged and could be resubjected to oxidation.

The mass spectrum of **13** showed, at highest mass-number, a small peak for the molecule-ion (*m/e* 284). The other fragmentations were readily correlated with the schemes proposed for 1,2:3,4-di-*O*-isopropylidene-α-D-galactose[41]. The i.r. spectrum of **13** showed strong absorptions at 5.88 and 6.18 μm, characteristic of an α,β-unsaturated ketone group.

The 100-MHz, ^{1}H-n.m.r. spectrum of **13** in chloroform-*d* showed the H-1 signal as a doublet ($J_{1,2}$ 5.2 Hz) at low field (δ 5.64 p.p.m.). The H-2,4 and H-3,5 signals appeared as two, unresolved, two-proton multiplets. The anticipated ABX system was observed for the three vinyl protons. The H-7, -8, and -8′ signals appeared as a resolved, four-line pattern at δ 6.87, 6.33, and 5.67. These signals lay 0.8 p.p.m. to lower field than in the spectrum of the corresponding allyl alcohols **12**. The ABX system of the vinyl protons showed a *trans* coupling of 17.5 Hz, a *cis* coupling of 10.5 Hz, and a geminal coupling of 2.1 Hz.

Upon being kept in the n.m.r. tube, the solution of **13** yielded a solid residue whose i.r. spectrum no longer showed absorption at 6.18 μm. The mass spectrum of this product exhibited a peak at an *m/e* value twice that of the original molecule-ion. These results suggest that polymerization of the α,β-unsaturated ketone moiety, presumably to give a product of the type of **14**, must have occurred.



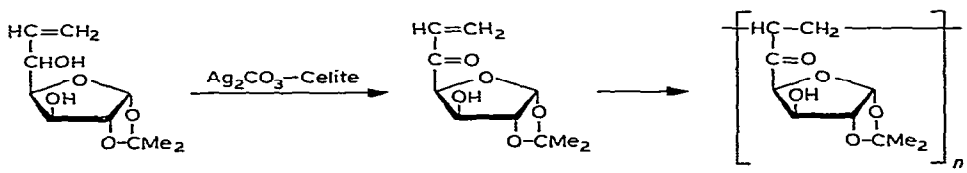
12 **13** **14**

The selectivity of silver carbonate on Celite was examined for oxidation of the partially protected alkenic sugars, 6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*(and

β-L-*ido*)-hept-6-enofuranose[3] (**15** and **16**). The α,β-unsaturated ketone **17** was obtained in 41% yield, and unoxidized starting material was recovered.

The i.r. spectrum of **17** showed absorption at 5.88 and 6.20 μm, characteristic of the α,β-unsaturated ketone group. The 100-MHz, ^{1}H-n.m.r. spectrum in chloroform-*d* showed signals typical of the α,β-unsaturated ketone system, as observed with compound **13**. The H-6 signal resonated at low field as a doublet of doublets showing *trans*-alkenic (17.5 Hz) and *cis*-alkenic coupling (10.0 Hz). The H-7 and -7′ signals were located as two four-line patterns at δ 6.52 and 5.94, respectively, showing a geminal coupling of 2.0 Hz.

Upon being kept in the n.m.r. tube, the solution of **17** yielded a solid residue. Because a 6.20-μm (C=C) band was absent in the i.r. spectrum of this residue, it appeared probable that polymerization (as with compound **13**) to give **18** had taken place.



15 and 16 17 18

For oxidation of acetylenic sugar derivatives at the propargylic position, it is concluded, therefore, that the best route to the α,β-unsaturated ketone involves oxidation with dimethyl sulfoxide and acetic anhydride; the Fétizon reagent was effective only with the alkenic sugar analogs.

The best route to an acetylenic ketone precursor having been established, the introduction of nitrogen at the propargylic position was next evaluated. There are two possible modes of attack by a nitrogen nucleophile on an ethynyl ketone: Michael addition with attack at the terminal carbon atom of the acetylenic moiety; or, alternatively, attack at the carbonyl carbon atom followed by dehydration to give the corresponding oxime, with the subsequent possibility of intramolecular addition of the hydroxyl group to the triple bond, which would lead to an isoxazole derivative.

The ethynyl carbonyl derivative **11** in methanol was treated for 20 min at 100° with hydroxylamine hydrochloride in the presence of potassium hydrogencarbonate, at which point t.l.c. indicated that the starting material had all reacted; two slower-moving spots were observed. The mixture was resolved by column chromatography. The first product eluted, obtained as a solid in 32% yield, was formulated as 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-7-yno-1,5-pyranos-6-ulose 6-oxime (**19**) on the basis of analytical and spectroscopic evidence. Microanalytical data supported the molecular formula assigned. The mass spectrum of the product showed a molecule-ion peak at *m/e* 297, the anticipated $M^+ - \cdot CH_3$ peak, and other fragmentations interpretable in terms of the schemes proposed for 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[4].

The i.r. spectrum showed absorptions at 3.05 and 4.70 μm for the terminal

acetylenic group; an absorption at 2.86 μm was assigned to the hydroxyl group of the oxime. No C=N stretching absorption at 6.10 μm was observed. The absence of such absorption is not unexpected; negligible C=N stretching absorption was noted in the spectra of several carbohydrate oximes in our laboratory, whereas Raman spectra of the compounds showed[42] a strong band near 1650 cm^{-1} (6.06 μm).

The 100-MHz, ^{1}H-n.m.r. spectrum of **19** in chloroform-*d* showed the H-1 doublet in the expected region (δ 5.64), and the H-2 signal, a doublet of doublets, appeared at δ 4.39. The H-3, -4, and -5 signals appeared as an unresolved multiplet. A one-proton singlet at δ 3.05 was assigned to the acetylenic proton. There was no signal at low field in the aromatic region that would have been shown by an isoxazole derivative formed by internal cyclization.

Compound **19** migrated as a single spot in t.l.c., but it did not have a sharp melting point; possibly, it is a mixture of *syn* and *anti* isomers.

Thus, from the i.r.- and ^{1}H-n.m.r.-spectral characterization, the product is the result of 1,2-addition, and it is concluded that no intramolecular addition of a hydroxyl group to the triple bond had taken place.

The other main product, eluted next, was obtained as an uncharacterized syrup.

The low yield of oxime **19** may have been caused by steric interference between O-4 and the carbonyl carbon atom[20]. The sp^3 hybridization at C-6 resulting from nucleophilic attack generates more steric interference than its sp^2-hybridized precursor.

The low yield of the oximation reaction limits its practical application, and alternative intermediates that might be further converted into propargylic amines were considered. Another nitrogen nucleophile, (2,4-dinitrophenyl)hydrazine, was examined.

The ethynylcarbonyl derivative **11** reacted with (2,4-dinitrophenyl)hydrazine in boiling methanol to give a mixture of two major components, having R_F 0.76 and 0.68 (t.l.c. 1:1 ether–petroleum ether), respectively.

These were separated by column chromatography, and the first-eluted product, isolated as an orange solid in 12% yield, was identified as 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-7-yno-1,5-pyranos-6-ulose 6-(2,4-dinitrophenyl)hydrazone (**20**). Microanalytical data supported the molecular formula assigned, and the mass spectrum showed a molecule-ion peak at *m/e* 462. The fragmentation scheme proposed[41] for 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose correlates with the series of peaks at lower *m/e* values.

The characteristic, acetylenic absorptions at 3.05 and 4.74 μm confirmed the retention of a terminal acetylenic group; the absorption at 6.15 μm was assigned to the C=N stretching-mode. No carbonyl absorption was observed.

Assignments for the 100-MHz, ^{1}H-n.m.r. spectrum of **20** in chloroform-*d* closely followed established patterns for the carbonyl precursor. In addition to the H-1 doublet at δ 5.51 ($J_{1,2}$ 5.0 Hz), the resonances for H-2, -3, and -4 were resolved as doublets of doublets at δ 4.26, 4.55, and 4.34, respectively. A partially overlapped, but discernible, doublet at δ 4.52 was assigned to H-5. The acetylenic proton resonated

TABLE I

CHEMICAL SHIFTS OF PROTONS

Compound	*Solvent*	*Chemical shifts (δ) from 100-MHz spectra*[a]										
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-8*	*Ar*	*CMe_2*	*Other*
2	$CDCl_3$[b]	5.61d	4.30	———	———	3.81dd	4.70m				1.53, 1.38 1.34, 1.30	
3	$CDCl_3$	5.49d	4.30dd	4.59dd	4.20dd	3.96dd	5.46d				1.54, 1.41 1.32, 1.30	2.05s (OAc)
4	$CDCl_3$[b]	5.55d	4.28	———	———	3.69dd	4.68m	6.43dd	5.86m		1.50, 1.46 1.35, 1.28	
5	$CDCl_3$	5.46d	4.28dd	4.58dd	4.24dd	3.82dd	5.37m	5.70dd	5.67m		1.51, 1.42 1.31(2)	2.04s (OAc)
6	$CDCl_3$	5.47d	4.26dd	4.55dd	4.19dd	3.76m	5.00m	1.12	~2.50m		1.51, 1.41 1.30(2)	2.03s (OAc)
9	$CDCl_3$	5.57d	4.34dd	4.62dd	4.30dd	4.05dd	5.48dd		2.54d	7.05–7.45m	1.56, 1.43 1.33, 1.31	
11	$CDCl_3$	5.67d	4.33	———	4.39m				3.36s		1.47, 1.38 1.28(2)	
				4.66	———	4.70m						
	C_6D_6	5.52d	4.12dd	4.39dd	4.33dd	4.32d			2.65s		1.38, 1.22 1.07, 0.98	
13	$CDCl_3$	5.64d	4.29	———	4.34m			6.87dd	6.33dd *trans* 5.67dd *cis*		1.44, 1.35 1.28, 1.24	
				4.58	———	4.60m						
17	$CDCl_3$	6.20d	4.67	———	4.70m	4.92d		6.95dd	6.52dd *trans* 5.94dd *cis*		1.58 1.42	3.57(OH)

19	$CDCl_3$[b]	5.64d	4.39dd	4.65 ———		5.06m			3.05s		1.52, 1.48 1.31(2)	
20	$CDCl_3$[b]	5.51d	4.26dd	4.55dd	4.34dd	4.52d			3.97s	9.15d 8,10dd 7.91d	1.52, 1.42 1.29, 1.26	
21	$CDCl_3$	5.63d	4.37dd	4.66dd	4.55dd	4.29d		3.82– 3.78m	7.64dd	9.06d 8.26dd 7.86d	1.67, 1.64 1.51, 1.48	11.07(NH)
23	$CDCl_3$	6.17d	4.87d	4.22d	5.11dd	6.63dd	6.05dd	9.79d		7.45s	1.49 1.32	4.65d 4.88d (Ar-CH_2-O)
24	$CDCl_3$	5.81d	4.59dd	3.84dd	4.48dd	9.61d				7.32s	1.54 1.32	4.90d 4.62d (Ar-CH_2-O)
25	$CDCl_3$	5.96d	4.86dd	3.93dd	4.82dd	7.51d				9.46d	1.74	11.45(NH) 4.93d 4.66d (Ar-CH_2-O)
26	$CDCl_3$	5.87d	4.66dd	3.56dd	4.75dd	6.82dd	6.43dd	9.68d		7.48s	1.60 1.39	4.90d 4.62d (Ar-CH_2-O)
27	$CDCl_3$	5.89d	4.69dd	3.63dd	4.74dd	6.24dd	6.75dd	7.84d		9.17d 8.41dd 8.02d	1.62 1.38	4.87d 4.64d (Ar-CH_2-O) 11.05(NH)

[a]First-order values are given. Observed multiplicities: d, doublet; dd, doublet of doublets; m, multiplet; s, singlet. [b]Under proton–deuterium exchange, the OH or NH signal disappears.

TABLE II

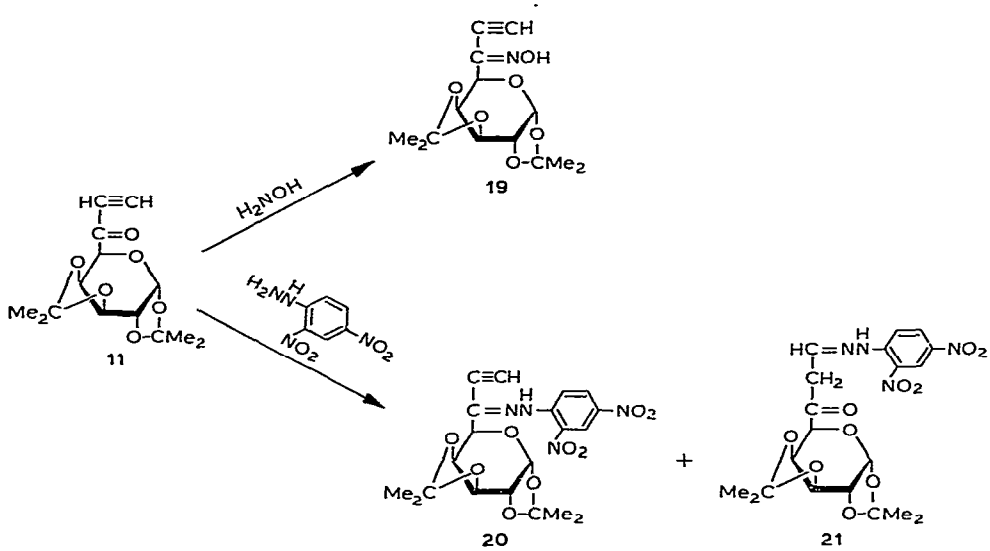
FIRST-ORDER, PROTON–PROTON COUPLING-CONSTANTS

Compound	*Solvent*	*Coupling constants (Hz) from 100-MHz spectra*								
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	*Other*
2	$CDCl_3$[a]	5.0			1.5	6.5					
3	$CDCl_3$	5.0	2.7	8.0	2.0	9.0					
4	$CDCl_3$[a]	5.0			1.5	7.5		4.0	2.0	13.0	
5	$CDCl_3$	4.8	2.5	8.0	2.0	8.2		6.7	2.0	13.0	
6	$CDCl_3$	5.0	2.5	8.0	2.0	8.0					
9	$CDCl_3$	4.0	2.0	5.0	2.0	8.8			2.0		
11	$CDCl_3$	5.0	1.9	2.1	2.1						
	C_6D_6	5.0	2.5	5.0	2.7						
13	$CDCl_3$	5.2	1.8	0	0					17.5 *(trans)* 10.5 *(cis)*	2.1($J_{8,8'}$)
17	$CDCl_3$	3.5	0	3.0				17.5 *(trans)* 10.0 *(cis)*			2.0($J_{7,7'}$)
19	$CDCl_3$[a]	4.8	1.2								
20	$CDCl_3$[a]	5.0	2.5	8.0	2.0						3.0($J_{m,m'}$) 9.5($J_{o,m}$)
21	$CDCl_3$	5.0	2.5	8.0	2.0					3.0 2.5 ($J_{7',8}$)	2.5($J_{m,m}$) 5.0($J_{7,7'}$) 9.5($J_{o,m}$)
22	$CDCl_3$	4.0	0	4.0	6.0	17.0		8.0			13.0(J_{benzyl})
24	$CDCl_3$	3.5	4.2	9.2	1.9						12.5(J_{benzyl})
25	$CDCl_3$	3.5	4.0	9.5	6.0						2.5($J_{m,m'}$) 9.5($J_{o,m}$) 14.0(J_{benzyl})
26	$CDCl_3$	4.0	5.0	10.0	5.0	17.0		8.0			12.0(J_{benzyl})
27	$CDCl_3$	3.6	4.6	9.5	6.0	16.5		9.6			2.4($J_{m,m'}$) 9.6($J_{o,m}$) 13.0(J_{benzyl})

[a]Spectra were simplified by proton-deuterium exchange.

at relatively low field (δ 3.97), because of conjugation of the imino group with the ethynyl group.

The analytical and spectroscopic evidence thus indicates that this product is the result of conventional 1,2-addition, and that no further intramolecular addition to the triple bond had occurred. Although **20** was a solid, it did not show a sharp m.p., nor did it give an X-ray diffractogram for a crystalline compound. It was not determined whether the hydrazone derivative was *syn*, *anti*, or a mixture of both isomers.



The slower-migrating product was a deep-orange solid, obtained pure in 23% yield and formulated from physical data as 7-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-octodialdo-1,5-pyranos-6-ulose 8-(2,4-dinitrophenyl)hydrazone (**21**). Its mass spectrum showed a small peak at highest mass-number for the molecule-ion (*m/e* 480), together with a series of related fragments.

The i.r. spectrum showed carbonyl absorption at 5.78 μm, and an absorption at 6.15 μm was assigned to the C=N stretching-mode by analogy with the i.r. spectrum of the hydrazone **20**.

The 100-MHz, ^{1}H-n.m.r. spectrum in chloroform-*d* was readily analyzed, and the H-1, -2, -3, and -4 signal-patterns closely resembled those of the accompanying hydrazone **20**. The H-5 signal of **21** resonated at δ 4.29, somewhat upfield from the other proton signals. A one-proton doublet of doublets (δ 7.64) and a two-proton multiplet (δ 3.78–3.82) were assigned to H-8 and the methylene protons at C-7; no alkenic proton signals were observed.

The carbon-13 n.m.r. spectrum of **21** displayed a low-field signal at δ 205.52 attributed to carbonyl carbon, and a high-field signal at δ 43.55, that appeared as a triplet after off-resonance proton-decoupling, indicative of a secondary carbon atom (CH_2). In the unsaturated–aromatic region of the spectrum (between 145.50 and

116.56 p.p.m.), there appeared seven signals, six of which may be attributed to the benzene ring and one to C-8.

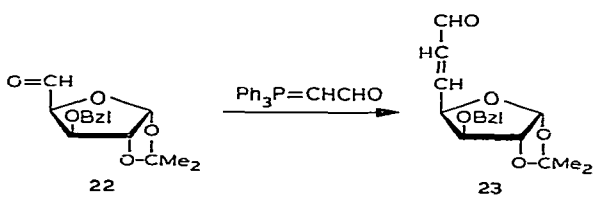
According to these spectral data, this product (**21**) was concluded to have resulted from 1,4-addition followed by proton rearrangement.

Although the first-eluted product (**20**) was the desired intermediate, its low yield, and the tedious separation required, limited its usefulness as a synthetic intermediate.

Synthesis of α,β-unsaturated aldehydo sugar derivatives by the Wittig reaction. — Sugar derivatives containing a terminal, propargylic group have been used in this laboratory to generate α,β-unsaturated, aldehydo sugars by a hydroboration–oxidation sequence[5], and the α,β-unsaturated aldehydo sugars have also been obtained in certain instances by treating an aldehydo sugar derivative with formylmethylenetriphenylphosphorane. This Wittig reaction affords α,β-unsaturated, aldehydo sugars by a two-carbon chain-extension from the same aldehydes employed as precursors for the ethynylation step used to generate the propargyl derivatives[5]. Although the Wittig route is superior in principle, as it gives the unsaturated aldehydo derivatives in high yield in a single step, it has failed in certain instances; specifically, when the precursor has the aldehyde group attached to a pyranoid ring-system.

In the present study, use of the Wittig approach for synthesis of α,β-unsaturated aldehydo sugars from derivatives having the aldehyde group attached to a furanoid ring was examined, and two successful examples are described.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodialdo-1,4-furanose[43,44] (**22**) was prepared as a distilled oil[43], and allowed to react with formylmethylenetriphenylphosphorane[45] in boiling benzene for 1 h. Chromatographic purification gave the crystalline, analytically pure adduct **23** in 79% yield.



22 23

Bzl = $PhCH_2$

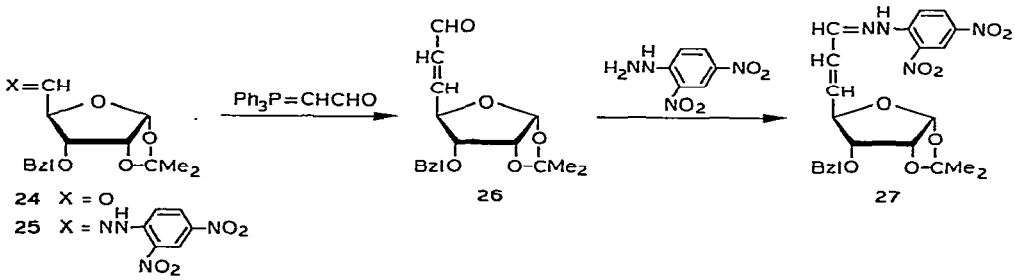
The i.r. spectrum of **23** showed absorptions characteristic of the α,β-unsaturated aldehyde group, and the 100-MHz, ^{1}H-n.m.r. spectrum in chloroform-*d* was readily interpretable, showing a wide doublet ($J_{6,7}$ 8.0 Hz) at δ 9.79 for the aldehydic proton; the H-6 signal (at δ 6.05) was strongly coupled ($J_{5,6}$ 17.0 Hz) to H-5, and displayed a small, long-range coupling ($J_{4,6}$ 1 Hz) with H-4, indicative of the *trans*-alkene structure[12,46]. The H-5 signal resonated at a somewhat lower field (δ 6.63) than H-6, and showed moderate coupling ($J_{4,5}$ 6.0 Hz) to H-4. This overall pattern is typical of similar, *trans*-2,3-unsaturated aldehydes[5]. The signals for the ring protons closely resembled the general pattern previously reported for 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose derivatives[47]. A 1:1 intensity ratio between the H-1 and H-7

signals was observed, indicating that the unsaturated aldehyde had not undergone appreciable hydration. This absence of hydration had also been observed in previous work[5] with *trans*-2,3-unsaturated aldehydo sugars. In contrast, saturated aldehydo sugar derivatives exist extensively in the hydrated aldehyde form when water is present[11,47].

The other aldehydo sugar used in this experiment was 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*ribo*-pentodialdo-1,4-furanose (**24**), obtained by glycol cleavage of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[28] by a procedure similar to that used for preparation[44] of compound **22**. The chromatographically homogeneous oil obtained by vacuum distillation crystallized after refrigeration*. Its i.r. spectrum showed absorptions typical of the aldehyde group, and its 100-MHz, ^{1}H-n.m.r. spectrum exhibited doublets of doublets at δ 4.59, 3.84, and 4.48 for H-2, -3, and -4, respectively. This pattern is consistent with that observed for related derivatives having the 1,2-*O*-isopropylidene-α-D-ribofuranose structure[28]. The benzylic protons resonated as an AB doublet of doublets overlapping with the H-2 signal. Two apparent doublets, at δ 5.80 and 9.61, were assigned to H-1 and the aldehydic proton, respectively; their 1 : 1 intensity ratio confirmed that no hydration of the aldehydo group had occurred.

The aldehydo sugar **24** was further characterized as its crystalline (2,4-dinitrophenyl)hydrazone **25**.

Treatment of this aldehydo sugar **24** with the Wittig reagent by the procedure used for the 3-epimer **22** gave the *trans*-2,3-unsaturated, aldehydo sugar **26** in 73% yield as a syrup. Its i.r. and ^{1}H-n.m.r. spectra showed signals typical of the *trans*-2,3-unsaturated aldehyde system, as observed for the 3-epimer **23**.



The *trans*-2,3-unsaturated aldehyde **26** was also characterized by conversion into its crystalline (2,4-dinitrophenyl)hydrazone **27**.

EXPERIMENTAL

General methods. — These were as given in the accompanying paper[1]. ^{13}C-N.m.r. spectra were recorded at 22.6 MHz with a Bruker HX-90 spectrometer.

*This crystallization was achieved by W. R. Turner of this laboratory.

*1,4-Bis(1,2:3,4-di-*O*-isopropylidene-*D*-glycero-α-*D*-galacto-hexopyranos-6-yl)-1,3-butadiyne* (**2**). — Air was bubbled for 3 h at 30–35° through a mixture of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-oct-7-ynopyranose[6] (**1**; 1.0 g) and cuprous chloride (200 mg) in pyridine (1 mL) and methanol (15 mL). Saturated, aqueous ammonium chloride (10 mL) was then added, and the mixture was extracted with ether. The ether layer was washed with dilute sodium carbonate, dried (magnesium sulfate), and evaporated, and the residue recrystallized from benzene–petroleum ether, to give the diyne **2**; yield 884 mg (88%); m.p. 192–193°, $[\alpha]_D^{25}$ −86° (*c* 1.0, chloroform); R_F 0.13 (*A*), 0.32 (*B*); λ_{max}^{KBr} 2.90 (OH), 4.62 (C≡C), and 7.28 μm (doublet, CMe_2); X-ray powder diffraction data: 9.50 s (2), 8.11 m (3,3,3), 7.40 w, 6.77 w (5,5), 6.21 w (5,5), 5.62 m (3,3,3), 5.09 vs (1), 4.87 vw, 4.62 m, 4.33 w (4,4), 4.07 m (3,3,3), 3.83 w (4,4), and 3.52 w.

Anal. Calc. for $C_{28}H_{38}O_{12}$: C, 59.36; H, 6.71. Found: C, 59.08; H, 6.69.

*1,4-Bis(6-*O*-acetyl-1,2:3,4-di-*O*-isopropylidene-*D*-glycero-α-*D*-galacto-hexopyranos-6-yl)-1,3-butadiyne* (**3**). — A solution of diyne derivative **2** (400 mg) in acetic anhydride (1.3 mL) was heated with anhydrous sodium acetate (120 mg) for 30 min at 90°, and then boiled for 1 min. Conventional processing afforded the diacetate **3**, obtained as prisms after recrystallization from ethanol; yield 402 mg (88%); m.p. 164–165°, $[\alpha]_D^{25}$ −260° (*c* 0.9, chloroform); R_F 0.28 (*A*), 0.61 (*B*); λ_{max}^{KBr} 4.60 (C≡C), 5.70 (C=O), and 7.25 μm (doublet, CMe_2); X-ray powder diffraction data: 11.48 m (3,3,3), 10.52 w, 9.30 m (3,3,3), 7.83 w, 5.98 w, 5.47 vs (1), 5.27 vw, 5.06 w, 4.59 s (2), 4.29 m (3,3,3), 4.04 w, and 3.67 w.

Anal. Calc. for $C_{32}H_{42}O_{14}$: C, 59.07; H, 6.46. Found: C, 58.94; H, 6.30.

*1,4-Bis(1,2:3,4-di-*O*-isopropylidene-*D*-glycero-α-*D*-galacto-hexopyranos-6-yl)-*trans,trans*-1,3-butadiene* (**4**). — The diyne **2** (500 mg, 0.88 mmol) in dry ether (10 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (300 mg, 7.9 mmol) in ether (40 mL). The solution was boiled gently for 3 h under reflux, and the excess of hydride was decomposed by the procedure of Steinhart[48]. Water (0.3 mL) was added very slowly, followed by 15% aqueous sodium hydroxide (0.3 mL), and more water (1 mL). The mixture was filtered, and the filtrate evaporated, to give **4** as a solid that was recrystallized from ether–petroleum ether; yield 400 mg (80%); m.p. 105–107°, $[\alpha]_D^{25}$ −88° (*c* 1.0, chloroform); R_F 0.16 (*A*), 0.38 (*B*); λ_{max}^{KBr} 2.85 (OH), 3.35 (C=C-H), 6.12 (C=C), and 7.25 μm (doublet, CMe_2).

Anal. Calc. for $C_{28}H_{42}O_{12}$: C, 58.95; H, 7.37. Found: C, 58.84; H, 7.54.

The product, although solid, did not show a sharp X-ray diffraction pattern, and was thus presumed to be amorphous.

*1,4-Bis(6-*O*-acetyl-1,2:3,4-di-*O*-isopropylidene-*D*-glycero-α-*D*-galacto-hexopyranos-6-yl)-*trans,trans*-1,3-butadiene* (**5**). — The acetylation procedure already described for **3** was applied to 230 mg of diene **4**. The product (**5**) was recrystallized from ethanol as prisms; yield 224 mg (85%); m.p. 152–154°, $[\alpha]_D^{25}$ −117° (*c*, 0.9 chloroform); R_F 0.33 (*A*), 0.55 (*B*); λ_{max}^{KBr} 5.70 (C=O) and 7.25 μm (doublet, CMe_2); X-ray powder diffraction data: 11.55 w, 8.30 s (2,2), 6.12 vw, 5.59 vs (1), 5.38 w, 5.02 w, 4.70 s (2,2), 4.38 m (3,3,3), 4.12 m (3,3,3), and 3.97 m (3,3,3).

Anal. Calc. for $C_{32}H_{46}O_{14}$: C, 58.72; H, 7.03. Found: C, 59.00; H, 7.04.

*1,4-Bis(6-O-acetyl-1,2:3,4-di-O-isopropylidene-*D-glycero-*α*-D-galacto-*hexopyranos-6-yl)butane* (**6**). — Palladium catalyst on powdered charcoal (5%, 80 mg) was added to a solution of the diyne diacetate **3** (264 mg) in ethyl acetate (30 mL). The mixture was shaken under hydrogen at a pressure of 20 lb.in.$^{-2}$ for 90 min at 25°, and filtered, and the filtrate was evaporated to a solid. Trituration with ether–petroleum ether gave **6** as a solid; yield 224 mg (84%); m.p. 71–74°, $[\alpha]_D^{25}$ −78° (*c* 0.7, chloroform); R_F 0.50 (*A*), 0.83 (*B*); λ_{max}^{KBr} 5.70 (C=O) and 7.25 μm (doublet, CMe_2).

Anal. Calc. for $C_{32}H_{50}O_{14}$: C, 58.36; H, 7.59. Found: C, 58.31; H, 7.69.

As with compound **5**, this product failed to give a sharp X-ray diffractogram.

*Conversion of 1,4-bis(1,2:3,4-di-*O*-isopropylidene-*D-glycero-*α*-D-galacto-*hexopyranos-6-yl)*-trans,trans-1,3-butadiene* (**4**) *into* D-glycero-D-galacto-*heptitol* (*perseitol*, **8**). — Ozonized oxygen was passed for 15 min through a solution of **4** (413 mg, 0.72 mmol) in ethyl acetate (30 mL), the temperature being maintained at −70° throughout this stage. Oxygen was then passed through the solution. After 10 min, Adams' catalyst (platinum black, 100 mg) was added, and the solution was shaken under hydrogen at 10 lb.in.$^{-2}$ for 1 h, the catalyst filtered off, and the solvent removed by evaporation. The resultant syrup was dissolved in ether (10 mL), and the solution added to a suspension of lithium aluminum hydride (400 mg) in ether (30 mL). After 1 h, the reaction was quenched by the same procedure as used in the preparation of compound **4**. Filtration of the mixture, and evaporation of the filtrate, gave a syrup that contained (t.l.c.) 1,2:3,4-di-*O*-isopropylidene-D-*glycero*-*α*-D-*galacto*-heptose as the major product.

The syrup was dissolved in 9:1 trifluoroacetic acid–water (10 mL), and the solution was kept for 10 min at 25°. The solvent was then evaporated off, water (30 mL) was added, and the solution was cooled to 0°. Sodium borohydride (200 mg) was added, and the solution was stirred for 2 h at 0°. Amberlite IR-120 (H^+) ion-exchange resin (20 mL) was then added, and filtered off after 10 min. The filtrate was evaporated, and boric acid was removed by addition and evaporation of methanol. A solid was obtained that was recrystallized from aqueous methanol to yield pure perseitol (**8**; 117 mg, 37%), m.p. 185–186° (lit.[9] m.p. 187–188°).

The product was identical with an authentic sample[6] by i.r. spectrum and X-ray powder diffraction pattern.

Per-O-trimethylsilyl derivatives of D-glycero-D-galacto-*heptitol*[6] *and* L-glycero-D-galacto-*heptitol*[6]. — The per-*O*-trimethylsilyl derivatives of heptitols **7** and **8** were prepared by shaking a sample (2 mg) of each with a mixture (0.3 mL) of chlorotrimethylsilane and hexamethyldisilazane in pyridine (Tri-Sil, Pierce Chemical Company, Rockford, Illinois) in a Reacti-Vial (Applied Science Laboratories, Inc.). The prepared samples were kept for 20 min before injection into a g.l.c. column. The per(trimethylsilyl) ether of **7** had retention times of 23.2 min (150°) and 40.7 min (140°) in column *A*, and 30 min (180°) in Column *B*. The per(trimethylsilyl) ether

of the D-*glycero* epimer (**8**) had retention times of 24.8 min (150°) and 43.8 min (140°) in column *A*, and 31.2 min (180°) in column *B*.

The per-*O*-trimethylsilyl derivative of D-*glycero*-D-*galacto*-heptitol (**8**, obtained from oxidative cleavage of the 1,3-butadiene derivative **4**), showed retention times identical to those of the per(trimethylsilyl) ether of an authentic sample[6] of perseitol (**8**).

7,8-Dideoxy-1,2:3,4-di-O-*isopropylidene-6*-O-(*phenylamino*)*carbonyl*-D-glycero-α-D-galacto-*oct-7-ynopyranose* (**9**). — To a solution of the acetylenic alcohol[6] **1** (500 mg, 1.76 mmol) in dry ether (15 mL) were added pyridine (3 mL) and phenyl isocyanate (0.3 mL, 2.74 mmol). The solution was stirred overnight at room temperature, and then ether (30 mL) and water (30 mL) were added, and the mixture was shaken. The organic layer was dried (magnesium sulfate) and evaporated to give a solid. Recrystallization from methanol gave the pure carbanilate **9** as prisms; yield 504 mg (71%); m.p. 177–178°, $[\alpha]_D^{25}$ −75° (*c* 0.9, chloroform); R_F 0.65 (*A*), 0.85 (*B*); λ_{max}^{KBr} 3.04 (C≡C-H), 3.35 (Ar-H), 4.66 (C≡C), 5.70, 5.80 (C=O), 6.20 (Ar), 6.55, 7.60, 8.0 (C-N), and 7.25 μm (doublet, CMe_2); X-ray powder diffraction data: 10.91 s (2), 9.61 m (3,3,3), 8.50 m (3,3,3), 6.86 w (4,4,4), 6.04 w, 5.66 m (3,3,3), 5.17 vs (1), 4.80 m, 4.61 vw, 4.45 w (4,4,4), 4.30 w, 4.10 w, and 3.85 w (4,4,4).

Anal. Calc. for $C_{21}H_{25}NO_7$: C, 62.53; H, 6.20; N, 3.47. Found: C, 62.75; H, 6.08; N, 3.40.

7,8-Dideoxy-1,2:3,4-di-O-*isopropylidene*-α-D-galacto-*oct-7-yno-1,5-pyranos-6-ulose* (**11**). — *A. By oxidation of* **1** *and* **10** *with dimethyl sulfoxide–acetic anhydride.* A 7-epimeric mixture of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*(and L-*glycero*)-α-D-*galacto*-oct-7-ynopyranoses[6] (**1** and **10**; 500 mg, 1.76 mmol) was dissolved in dry dimethyl sulfoxide (5.6 mL). Acetic anhydride (3.7 mL) was added, and the resulting solution was kept for 24 h at ~25°. The pale-yellow solution was extracted with dichloromethane (30 mL), and the extract successively washed with water (2 × 30 mL), saturated aqueous sodium hydrogencarbonate (2 × 20 mL), and water (1 × 20 mL), dried (magnesium sulfate), and evaporated, to afford a yellow syrup.

A solution of this syrup in 1:1 ether–petroleum ether (10 mL) was passed through a small column (2 × 40 cm) packed with silica gel, to give, after removal of the solvent, the solid product **11**. The latter was recrystallized from ether–petroleum ether, to give fluffy, fine needles; yield 324 mg (65%); m.p. 128–129°, $[\alpha]_D^{25}$ −117° (*c* 0.8, chloroform); λ_{max}^{MeOH} 212 nm (ε_{mM} 5.94); R_F 0.81 (*A*) and 0.88 (*B*); λ_{max}^{KBr} 3.08 (C≡C-H), 4.75 (C≡C), 5.86, 5.95 (C=O), and 7.24 μm (doublet, CMe_2); X-ray powder diffraction data: 9.50 vw, 7.43 s (2,2), 6.70 m (3,3,3), 6.37 m (3,3,3), 6.15 m (3,3,3), 5.90 w, 5.64 vs (1), 4.90 s, 4.64 m, 4.35 m, 4.13 m, 3.95 w (4,4), 3.80 w (4,4), and 3.59 w.

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.38. Found: C, 59.80; H, 6.54.

B. By oxidation of **1** *and* **10** *with chromium trioxide–dipyridine complex.* The general oxidation procedure of Arrick, Baker, and Horton[25] was employed. A solution containing ~10% of the $CrO_3 \cdot 2\ C_5H_5N$ complex was prepared by addition of

chromium trioxide (2.13 g, 21.3 mmol) to a solution of dry pyridine (3.54 mL, 42.6 mmol) in dichloromethane (35 mL). The mixture was stirred, with exclusion of moisture, for 15–20 min at ~25°, whereupon it became deep red. A solution of the mixed acetylenic derivatives **1** and **10** (500 mg, 1.76 mmol) in dichloromethane was added in one portion to the solution of the oxidant (21.3 mmol); a tarry deposit of chromium reduction-products was formed immediately. After being stirred for an additional 15–20 min at ~25°, the supernatant solution was decanted into a separatory funnel containing an equal volume of ice-cold, saturated, aqueous sodium hydrogencarbonate. The residual tar was extracted with a little ether, and this extract was added to the contents of the separatory funnel, which were thoroughly agitated at 0°. The organic layer was separated, washed with water, dried (magnesium sulfate), and evaporated, to give the crude ketone **11**. Toluene was several times added to and evaporated from the residue, to remove traces of pyridine. The syrupy residue was passed through a column packed with silica gel, with 1 : 1 ether–petroleum ether as the eluant. The product **11** was isolated pure; yield 124 mg (25%), m.p. 128–129°; it was indistinguishable, by ^{1}H-n.m.r. spectrum, i.r. spectrum, and X-ray powder diffraction pattern, from **11** prepared by procedure *A*.

Since this work was first described[1,7], an independent preparation of **11** by oxidation of **1** + **10** with active manganese dioxide has been reported[35]; m.p. 123.5–125°, $[\alpha]_D^{27}$ −97° (chloroform).

*7,8-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galacto-oct-7-eno-1,5-pyranos-6-ulose* (**13**). — *A. By oxidation of the alkenes* (**12**) *with dimethyl sulfoxide–acetic anhydride.* The mixed, epimeric alkenes **12**, obtained[6] by reducing the mixed acetylenic derivatives **1** and **10** (500 mg, 1.74 mmol), were oxidized with a mixture of dimethyl sulfoxide (5.6 mL) and acetic anhydride (3.7 mL) under the conditions (*A*) described in the preceding experiment. Isolation by the same procedure gave a slightly yellow solid which, on recrystallization from ether–petroleum ether, gave the vinyl ketone **13** as fluffy, cotton-like crystals; yield 272 mg (54%); m.p. 81–83°, $[\alpha]_D^{25}$ −104° (*c* 0.6, chloroform); R_F 0.80 (*A*) and 0.91 (*B*); λ_{max}^{KBr} 3.35, 3.40 (C=C-H), 5.88 (C=O), 6.18 (C=C), and 7.25 μm (doublet, CMe_2); X-ray powder diffraction data: 14.14 w, 9.07 vs (1), 8.01 vw, 7.34 vw, 6.77 vw, 5.73 w, 5.23 m, 4.89 s (2), 4.58 vw, 4.08 m (3,3), and 3.76 m (3,3).

Anal. Calc. for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 59.25; H, 7.04.

Upon being kept in an n.m.r. tube for 2 days at 25°, the solution yielded a solid that no longer showed an i.r. band at 6.18 μm (C=C).

B. By oxidation of **12** *with chromium trioxide–dipyridine complex.* The epimeric mixture of alkenes **12** (500 mg) was oxidized with chromium trioxide–dipyridine complex[25] by procedure (*B*) described in the preceding experiment. The yield of compound **13** was 182 mg (37%), and it was identical (mixed m.p., i.r. spectrum, and ^{1}H-n.m.r. spectrum) with that prepared by procedure *A*.

C. By oxidation of the alkenes (**12**) *with silver carbonate–Celite.* The oxidant, silver carbonate on Celite, was prepared by Fétizon's procedure[40]. Celite (15 g) was added to a solution of silver nitrate (17 g) in distilled water (200 mL). The

suspension was stirred for a few sec until it became uniform, and a solution of sodium carbonate decahydrate (15 g) in distilled water (300 mL) was then added slowly with stirring. The precipitate was filtered off, and washed with distilled water until the filtrate became neutral. The yellow precipitate was dried by repeated evaporation of benzene from it.

The mixture of allylic alcohols **12** (400 mg, 1.39 mmol) in benzene (60 mL) was mixed with 9 g of the prepared oxidant, and benzene (20 mL) was evaporated from the mixture to ensure dryness. The suspension was boiled for 4 h under reflux; t.l.c. then indicated that the reaction was incomplete. An additional 5 equiv. (2.8 g) of oxidant was added, and the suspension was boiled under reflux for an additional 2 h. The reaction was still incomplete (t.l.c.), but the product was isolated at this stage. The precipitate was filtered off, and washed with benzene. The benzene solution was then evaporated, and the syrupy product was purified by preparative t.l.c. on silica gel, with 1 : 1 ether–petroleum ether as the eluant, to give crystalline **13**; yield 206 mg (52%), identical with that prepared by procedures *A* and *B*.

*6,7-Dideoxy-1,2-*O*-isopropylidene-α-*D*-xylo-hept-6-eno-1,4-furanos-5-ulose* (**17**). 6,7-Dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*(and β-L-*ido*)-hept-6-enofuranose[3] (**15** and **16**; 400 mg, 1.85 mmol) was oxidized with silver carbonate on Celite in the same way as described in part *C* of the preceding experiment. The product (**17**) was obtained as a syrup; yield 161 mg (41%); $[\alpha]_D^{25}$ −103° (*c* 4.2, chloroform); R_F 0.30 (*A*) and 0.40 (*B*); λ_{max}^{film} 2.90 (OH), 5.85 (C=O), 6.20 (C=C), and 7.30 μm (CMe_2).

Anal. Calc. for $C_{10}H_{14}O_5$: C, 56.01; H, 6.58. Found: C, 56.08; H, 6.74.

Upon being kept in chloroform-*d* in an n.m.r. tube for 1 day, the solution yielded a solid that no longer showed the 6.20-μm (C=C) band in the i.r. spectrum.

*7,8-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galacto-oct-7-yno-1,5-pyranos-6-ulose 6-oxime* (**19**). — Hydroxylamine hydrochloride (600 mg, 8.7 mmol), potassium hydrogencarbonate (700 mg), and water (0.1 mL) were added to a solution of the unsaturated ketone **11** (335 mg, 1.19 mmol) in methanol (20 mL). The mixture was boiled for 20 min under reflux, whereupon t.l.c. indicated complete disappearance of **11**. The mixture was evaporated, and the solid residue extracted with hot dichloromethane (three 30-mL portions). Evaporation of the extracts, and chromatography of the residue on a column of silica gel 7734 with 1 : 1 ether–petroleum ether as the eluant, gave 114 mg (32%) of **19**; m.p. 182–185° (dec.), $[\alpha]_D^{25}$ −129° (*c* 0.65, chloroform); R_F 0.56 (*A*) and 0.64 (*B*); λ_{max}^{KBr} 2.86 (OH), 3.05 (C≡C-H), 4.70 (C≡C), and 7.25 μm (doublet, CMe_2); X-ray powder diffraction data: 12.36 m (3,3,3), 9.45 w, 8.54 s (2,2), 7.22 w, 6.39 vw, 5.77 m (3,3,3), 5.45 m (3,3,3), 5.13 vs (1), 4.28 s (2,2), 3.89 w, 3.52 m, and 3.21 m.

Anal. Calc. for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.76. Found: C, 56.39; H, 6.15; N, 4.81.

*7,8-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galacto-oct-7-yno-1,5-pyranos-6-ulose 6-(2,4-dinitrophenyl)hydrazone* (**20**) *and 7-deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galacto-octodialdo-1,5-pyranos-6-ulose 8-(2,4-dinitrophenyl)hydrazone* (**21**). — A solution of the unsaturated ketone **11** (580 mg, 2.04 mmol) and (2,4-dinitrophenyl)-

hydrazine (420 mg, 2.12 mmol) in methanol (30 mL) was boiled for 10 min under reflux, and then evaporated. The residue was dissolved in benzene, and the solution washed successively with ice-cold, 5% sulfuric acid, aqueous sodium hydrogencarbonate, and water, dried (magnesium sulfate), and evaporated. T.l.c. of the dark-red residue indicated two major products, which were separated by chromatography on a column of silica gel 7734 with 1 : 1 ether–petroleum ether as the eluant. Compound **20** was eluted first, and isolated as a yellow solid. Trituration with ether–petroleum ether gave **20** as an amorphous material; yield 120 mg (12%), m.p. 105–108°, $[\alpha]_D^{25}$ −149° (*c* 0.4, chloroform); λ_{max}^{MeOH} 356 (ε_{mM} 38.2), 254 (16.9), and 206 nm (20.3); R_F 0.76 (*A*) and 0.86 (*B*); λ_{max}^{KBr} 3.05 (C≡C-H), 4.74 (C≡C), 6.15 (C=N), 6.25 (Ar), 6.55, 7.48 (NO_2), 7.22 (CMe_2), and 13.5 μm (aryl).

Anal. Calc. for $C_{20}H_{22}N_4O_9$: C, 51.94; H, 4.76; N, 12.12. Found: C, 52.21; H, 5.02; N, 11.99.

The second product to be eluted, compound **21**, was obtained as a deep-orange solid. Trituration with ether–petroleum ether gave pure **21**, yield 240 mg (24%), m.p. 97–100°, $[\alpha]_D^{25}$ −143° (*c* 0.42, chloroform); λ_{max}^{MeOH} 355 (ε_{mM} 18.0), 252 (11.3), and 222 nm (14.1); R_F 0.68 (*A*) and 0.60 (*B*); λ_{max}^{KBr} 5.78 (C=O), 6.15 (C=N), 6.25 (Ar), 6.48, 7.50 (NO_2), 7.25 (CMe_2), and 13.45 μm (aryl).

Anal. Calc. for $C_{20}H_{24}N_4O_{10}$: C, 50.00; H, 5.00; N, 11.66. Found: C, 50.07; H, 5.26; N, 11.37.

Both compounds were presumed to be amorphous, as neither showed a sharp X-ray diffraction pattern.

trans-*3*-O-*Benzyl*-*5,6*-*dideoxy*-*1,2*-O-*isopropylidene*-*7*-aldehydo-α-D-xylo-*hept*-*5*-*enodialdose* (**23**). — A solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodialdo-1,4-furanose[44] (**22**) (403 mg, 1.45 mmol) and formylmethylenetriphenylphosphorane[45] (440 mg, 1.45 mmol) in benzene (30 mL) was boiled for 1 h under reflux. Evaporation of the benzene, and chromatography of the product on a column of silica gel with 3 : 1 benzene–ether as the eluant, gave **23**, obtained analytically pure after recrystallization from ether–petroleum ether; yield 349 mg (79%); m.p. 94–95°, $[\alpha]_D^{25}$ −42° (*c* 0.5, chloroform); λ_{max}^{MeOH} 222 (ε_{mM} 21.6) and 210 nm (30.4); R_F 0.68 (*A*) and 0.88 (*B*); λ_{max}^{KBr} 3.50 (-CHO), 5.98 (C=C-C=O), 6.20 (Ar), and 7.30 μm (doublet, CMe_2); X-ray powder diffraction data: 12.81 m, 7.83 m, 6.06 s (2,2,2), 5.53 m, 5.03 s (2,2,2), 4.62 s (2,2,2), 4.39 w, 3.91 m, 3.80 vs (1), 3.63 vw, 3.30 w, and 3.14 w.

Anal. Calc. for $C_{17}H_{20}O_5$: C, 67.10; H, 6.58. Found: C, 66.87; H, 6.37.

3-O-*Benzyl*-*1,2*-O-*isopropylidene*-*5*-aldehydo-α-D-ribo-*pentodialdo*-*1,4*-*furanose* (**24**). — A solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[28] (3.7 g, 12.0 mmol) in methanol (50 mL) was stirred at 0°, and sodium metaperiodate (2.82 g, 13.2 mmol) in water (50 mL) was added dropwise. After the addition had been completed, the solution was stirred for 1 h at 0°. Ethylene glycol (0.5 mL) was added to decompose any excess of oxidant, and the methanol was evaporated off. The aqueous solution was extracted with three 50-mL portions of chloroform, and the extract was dried, and evaporated to a syrup. Analytically pure **24** was obtained by

vacuum distillation, with collection of the fraction having b.p. 145–150° (0.04 torr, bath temperature 190°); yield 1.95 g (59%); m.p. 57–58°, $[\alpha]_D^{25}$ +64° (*c* 0.6, chloroform); R_F 0.10 (*A*) and 0.20 (*B*); λ_{max}^{KBr} 3.50 (-CHO), 5.72 (C=O), 6.20 (Ar), and 7.28 μm (doublet, CMe_2); X-ray powder diffraction data: 12.81 m, 7.43 w, 6.65 m, 5.82 s (2,2), 5.18 s (2,2), 4.72 vs (1), 4.46 vw, 4.19 w, 4.05 m (3,3), 3.72 m (3,3), 3.54 w, and 3.40 m.

Anal. Calc. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.47. Found: C, 64.45; H, 6.71.

*3-O-Benzyl-1,2-O-isopropylidene-5-*aldehydo-α-D-ribo-*pentodialdo-1,4-furanose 5-(2,4-dinitrophenyl)hydrazone* (**25**). — To a solution of **24** (380 mg, 1.37 mmol) in methanol (20 mL) was added (2,4-dinitrophenyl)hydrazine (280 mg, 1.42 mmol). The mixture was stirred overnight at ~25° and then evaporated, to give a solid residue that was dissolved in benzene (30 mL). The solution was washed successively with ice-cold 10% sulfuric acid, and 5% aqueous sodium hydrogencarbonate, dried, and evaporated, giving crystals. Recrystallization from benzene–methanol gave **25** as yellow needles; yield 473 mg (76%); m.p. 170–171°, $[\alpha]_D^{25}$ +21° (*c* 0.9, chloroform); λ_{max}^{MeOH} 354 (ε_{mM} 21.5), 252 (11.1), 226 (13.4), and 207 nm (19.3); R_F 0.87 (*A*), 0.90 (*B*); λ_{max}^{KBr} 3.05 (NH), 6.18 (C=N), 6.26 (Ar), 6.62, 7.52 (NO_2), 7.25 (CMe_2), 6.65 (C=N), 13.50, and 14.30 μm (aryl); X-ray powder diffraction data: 11.94 s (2,2), 9.25 vw, 7.16 w, 6.44 m, 5.45 s (2,2), 4.99 s (3,3), 4.68 s (3,3), 4.36 vs (1), 3.89 w, 3.53 m, 3.40 m, and 3.17 m.

Anal. Calc. for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.80; N, 12.22. Found: C, 55.08; H, 5.08; N, 12.28.

trans-*3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-7-*aldehydo-α-D-ribo-*hept-5-enodialdose* (**26**). — A solution of the aldehyde **24** (662 mg, 2.38 mmol) and formylmethylenetriphenylphosphorane[45] (740 mg, 2.44 mmol) in benzene (30 mL) was boiled for 1 h under reflux. The solvent was removed, and the residue purified chromatographically on a 1-mm layer of silica gel with 3:1 benzene–ether as the eluant, to give pure **26** as a syrup; yield 530 mg (73%); $[\alpha]_D^{25}$ +69° (*c* 0.8, chloroform); λ_{max}^{MeOH} 225 (ε_{mM} 16.7) and 205 nm (33.9); R_F 0.62 (*A*) and 0.88 (*B*); λ_{max}^{film} 3.45 (-CHO), 5.90 (C=C-C=O), 6.20 (Ar), and 7.25 μm (doublet, CMe_2).

Anal. Calc. for $C_{17}H_{20}O_5$: C, 67.10; H, 6.58. Found: C, 66.88; H, 6.72.

trans-*3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-*α-D-ribo-*hept-5-enodialdose 7-(2,4-dinitrophenyl)hydrazone* (**27**). — A solution of the unsaturated aldehyde **26** (340 mg, 1.12 mmol) and (2,4-dinitrophenyl)hydrazine (230 mg, 1.16 mmol) in methanol (20 mL) was boiled for 30 min under reflux, and then evaporated. The residue was dissolved in benzene, and the solution was washed successively with ice-cold 10% sulfuric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The deep-red residue was chromatographed on a column of silica gel with 3:1 benzene–ether as the eluant, to give the hydrazone **27** as a solid; yield 195 mg (37%); m.p. 167–168°, $[\alpha]_D^{25}$ −7.8° (*c* 0.4, chloroform); λ_{max}^{MeOH} 372 (ε_{mM} 13.4), 258 (10.4), and 208 nm (11.6); R_F 0.72 (*A*) and 0.60 (*B*); λ_{max}^{KBr} 3.02 (NH), 6.05 (C=C), 6.15 (C=N), 6.22 (Ar), 6.60, 7.50 (NO_2), 7.25 (CMe_2), 13.50, and 14.40 μm (aryl); X-ray powder diffraction data: 11.40 w, 8.88 w, 7.65 vs (1), 6.48 m (3,3,3), 5.38 m

(3,3,3), 5.07 m, 4.72 m, 4.53 m, 4.20 s (2), 4.03 w, 3.90 w, 3.73 vs, and 3.12 m (3,3,3).

Anal. Calc. for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.96; N, 11.57. Found: C, 57.08; H, 4.72; N, 11.36.

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