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ETHYNYLATION OF 1,2-*O*-ISOPROPYLIDENE-α-D-*xylo*-PENTODIALDOSE DERIVATIVES A SYNTHETIC ROUTE TO URONIC ACIDS*†

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ABSTRACT

Ethynylation of periodate-oxidized 1,2-*O*-isopropylidene-α-D-glucofuranose gave 6,7-dideoxy-1,2-*O*-isopropylidene-β-D-*ido*-hept-6-ynofuranose (**2**) together with a proportion of the α-D-*gluco* analog **6**, ozonolysis of **2** and **6** gave 1,2-*O*-isopropylidene-β-L-idofuranurono-6,3-lactone (**8**) and 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**), respectively The heptyne **2** gave a crystalline 3,5-dibenzoate **3**, which on ozonolysis gave 3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranuronic acid (**4**), saponification of **4** with methanolic sodium methoxide led to epimerization at C-5 Ethynylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*aldehydo*-D-*xylo*-pentodialdo-1,4-furanose (**9**) (characterized as its *p*-nitrophenylhydrazone, **13**) gave a separable, 3 4 mixture of 3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hept-6-ynofuranose (**14**) and the β-L-*ido* epimer (**10**), ozonolysis of **14** and **10** followed by hydrogenolysis gave the lactones **8** and **7**, respectively Crystalline 5-benzoates **11** and **15** were obtained from **10** and **14**, respectively Ozonolysis of **11** gave 5-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranuronic acid (**12**), similar treatment of **15** gave the α-D-*gluco* analog (**16**) of **15** Hydrogenolytic cleavage of the benzyl groups, and catalytic de-esterification, of **12** and **16** led to mixtures of the lactones 7 and **8** through epimerization at C-5

INTRODUCTION

The addition of unsaturated Grignard reagents to *aldehydo* sugar derivatives was reported in 1965 by this laboratory[1,2] The reaction is useful in synthetic sugar chemistry because the resultant acetylenic and vinylic derivatives are capable of undergoing a wide range of useful transformations, leading to higher aldoses[1,2,4,5], aldonic acids[1,2,4,5] unsaturated aldehydes[1,2], alditols[2,5,6], 1,2-dideoxyalditols[1,2,4,5], 1-deoxyketoses[2,6], 1,2-anhydroalditols[2], allenes[6], and various other products[7]

*Part VIII in the series "Extension of Sugar Chains Through Acetylenic Intermediates" For preliminary reports of part of this work see references 1 and 2 For part VII of this series see reference 3

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The present paper describes ethynylation of *ω-aldehydo* sugar derivatives and the conversion of the resultant sugar derivatives having the ethynyl group as the non-reducing terminus into uronic acids The fact that the secondary alcohol group adjacent to the ethynyl group is not epimerized by acid or base under the normal conditions of glycoside hydrolysis or saponification of acyl groups[7] makes the ethynylated derivatives attractive as intermediates for synthesis of uronic acids and their derivatives The great facility with which uronic acids and their derivatives are epimerized, in the presence of base, at the position α to the carboxylate group, can be troublesome in synthetic sequences. With the use of the ethynyl group as a "latent" carboxylic acid group it should be possible to retain configurational integrity even under basic conditions, and the carboxylic acid group can be generated by ozonolysis of the acetylene under neutral conditions as a late step in the synthetic sequence

The examples presented describe ethynylation of the products of periodate oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose and its 3-benzyl ether, separation of the 5-epimeric, 7-carbon acetylenic sugars produced, and conversion of the products into derivatives of D-glucuronic and L-iduronic acids

DISCUSSION

In an earlier report[1] it was shown that ethynylmagnesium bromide reacts to give a propargylic alcohol with the product formed[8] by oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose with lead tetraacetate, even though the oxidation product is not a free aldehyde but is a mixture of a dimer[9,10] (**1**) and an adduct[9] with formaldehyde for which the structure **5** has been proposed[11]. In the present work the oxidation was performed with aqueous sodium metaperiodate in the presence of a large excess of formaldehyde As judged by t l c the product was approximately a 9 1 mixture of the dimer **1** and the formaldehyde adduct **5** This mixture was treated with

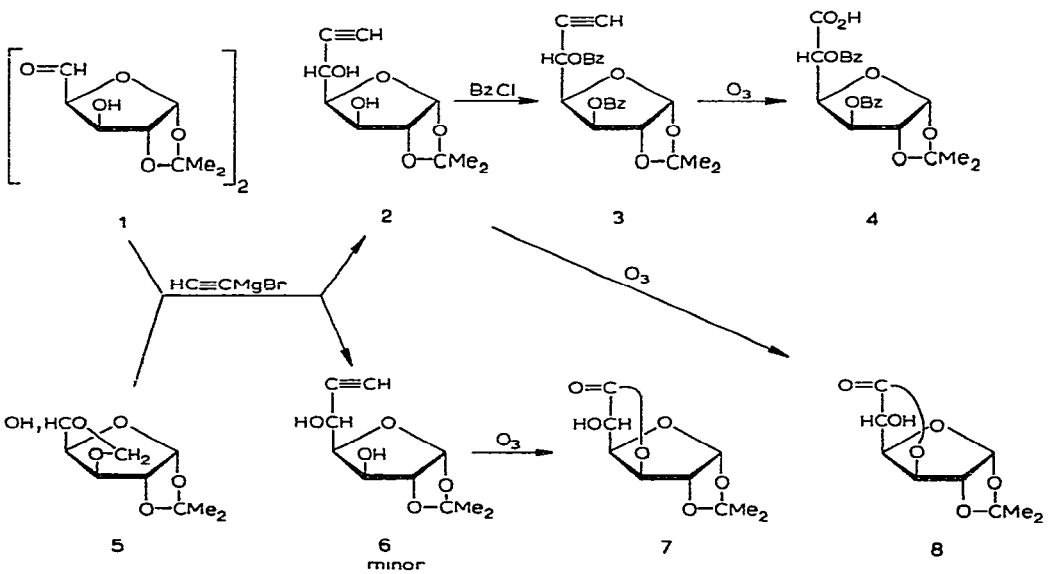


TABLE I

CHEMICAL SHIFTS MEASURED AT 100 MHz IN CHLOROFORM-*d*

Compound	*Solvent*	*Chemical shifts* (τ) *from* 100-MHz *spectra*[a]									
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-7*	*Aryl*	*Benzylic*	CMe_2 (*s*)	*Other*
3	C_6D_6	4 22d	5 66d	4 00d	4 91q	3 45q	8 16d	1 8, 2 8		8 55, 8 92	
4	$CDCl_3$	3 92d	5 32d	4 35d	5 08q	4 24d		2 05, 2 64		8 45, 8 69	0 40[b]
9	$CDCl_3$	3 94d	5 39d	5 72d	5 48q	0 37d		2 76	5 42, 5 61[c]	8 58, 8 72	
10	C_6D_6	4 17d	5 67d	5 98d	5 53q	5 15q[d]	7 88d	2 82	5 70s	8 66, 8 90	7 18[b]
11	C_6D_6	4 18d	5 65d	5 83d	5 12q	3 58q	8 00d	1 9, 2 9, 2 83	5 69s	8 58, 8 90	
12	$CDCl_3$	3 98d	5 37d	4 39d	5 11q	4 28d		2 09, 2 7	6 33s	8 49, 8 71	1 75[b]
13	$(CD_3)_2CO$	4 03d	5 18d	5 90d	5 22q	2 60d		1 88, 2 68, 2 88	5 25, 5 45[c]	8 52, 8 68	−0 25[e]
14	C_6D_6	4 16d	5 72d	5 88d	5 62q	5 21q[d]	7 95d	2 85	5 73s	8 68, 8 93	6 93[b]
15	C_6D_6	4 13d	5 62d	5 99d	5 19q	3 70q	7 87d	2 05, 2 90	5 75, 5 94[c]	8 56, 8 83	
16	$CDCl_3$	3 97d	5 34d	4 33d	5 22q	4 54d		2 1, 2 65	6 60s	8 45, 8 70	2 31[b]

[a]First-order values are given Peak multiplicities d, doublet, q, quartet, s, singlet [b]One proton, OH, disappears on deuteration [c]2-Proton AB system, J_{AB} 11 Hz [d]After deuteration [e]NH proton

ethynylmagnesium bromide in tetrahydrofuran to give a syrupy mixture of 5-epimeric, acetylenic sugar derivatives (**2** and **6**). Ozonolysis of this mixture gave one product having the same characteristics by t l c as 1,2-*O*-isopropylidene-β-L-idofuranurono-6,3-lactone (**8**), together with a second product having t l.c characteristics of 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) Fractional distillation of the mixed acetylenic derivatives (**2** and **6**) gave one epimer essentially pure, as a liquid in 34% yield The latter was identified as the β-L-*ido* derivative **2** by the fact that upon ozonolysis in carbon tetrachloride it gave the β-L-*ido* lactone (**8**), identical by mixed m p , X-ray powder diffraction pattern, and t l c with an authentic sample, the absence of the α-D-*gluco* lactone (**7**) was clearly established by t l c

The β-L-*ido* acetylenic derivative (**2**) gave a crystalline 3,5-dibenzoate (**3**) that melted sharply at 195–196° and gave a satisfactory elemental analysis It showed i r spectral absorptions at 3 06 and 4 71 μm, typical of ≡C–H and C≡C stretching frequencies The n m r spectrum of **3** showed a 1-proton doublet at τ 8 16 for the acetylenic proton (H-7) showing a coupling of 2 Hz with H-5 (full details of 100 MHz n m r data are given in Tables I and II) The signal for H-5 is observed at low field (τ 3 45) because of the deshielding effect of the 5-benzoyloxy group, the signal is a sharp quartet showing the $J_{5,7}$ spacing and also a spacing of 9 0 Hz corresponding to $J_{4,5}$ and indicating that H-4 and H-5 are antiparallel in the favored conformation of **3** The evidence clearly establishes that the product is the single 5-epimer **3** Compound **3** was identical by X-ray powder diffraction pattern with a product previously prepared by J B Hughes[1], and the tentative configurational assignment[1] at C-5 on the latter product, made from chromatographic data, must be reversed on the basis of present evidence

TABLE II

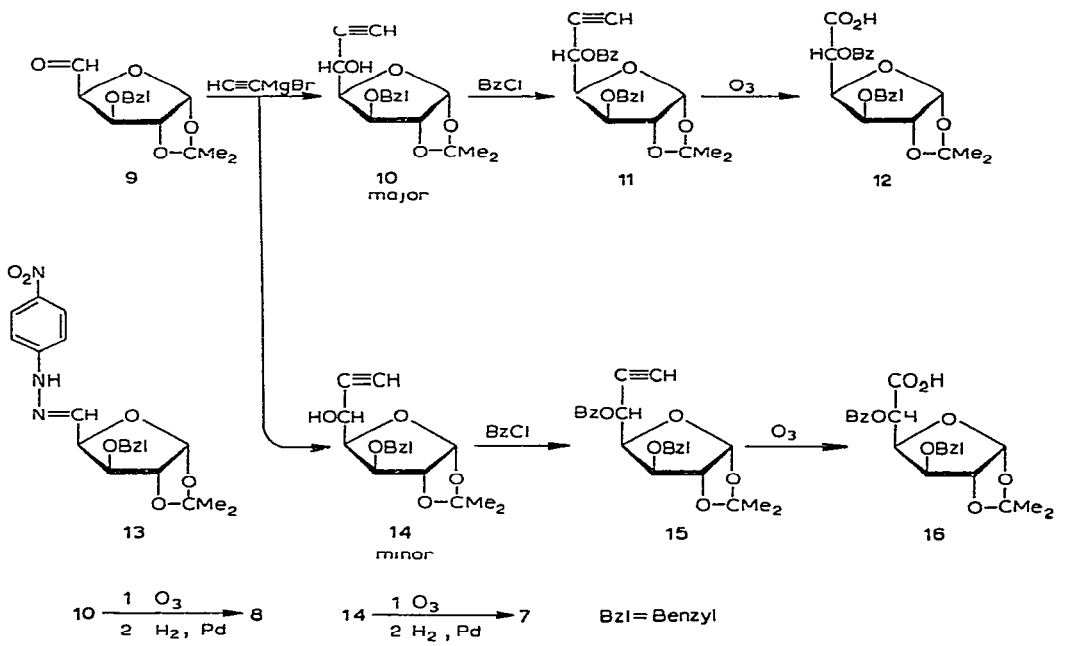
FIRST-ORDER COUPLING CONSTANTS (Hz) FROM 100-MHz SPECTRA

Compound	*Solvent*	*Coupling constants (Hz) from 100-MHz spectra*				
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,7}$
3	C_6D_6	4 0	0	3 0	9 0	2 0
4	$CDCl_3$	4 0	0	3 5	6 0	
9	$CDCl_3$	4 0	0	3 8	2 0	
10	C_6D_6	4 0	0	3 0	8 0	2 0
11	C_6D_6	4 0	0	3 0	9 0	2 0
12	$CDCl_3$	4 0	0	3 5	7 0	
13	$(CD_3)_2CO$	4 0	0	3 5	7 0	
14	C_6D_6	4 0	0	3 0	7 0	2 0
15	C_6D_6	4 0	0	3 0	9 0	2 0
16	$CDCl_3$	3 5	0	3 0	9 0	

Ozonolysis of the acetylenic dibenzoate **3** gave crystalline 3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranuronic acid (**4**) The n m r spectrum of **4** showed an exchangeable proton resonating at τ 0 40, characteristic of carboxylic acids The

remainder of the spectrum could be analyzed on a first-order basis Attempts to debenzoylate **3** with methanolic sodium methoxide, and convert the product into the *β*-L-*ido* lactone **8**, gave instead a mixture that appeared to contain also the α-D-*gluco* lactone (**7**), the base used for saponification is evidently strong enough to cause epimerization at C-5

The reaction sequence performed on the periodate-oxidation product from 1,2-*O*-isopropylidene-α-D-glucofuranose was also evaluated with the aldehyde (**9**) obtained from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose by cleavage of the 5,6-glycol group The C-3 protecting group in **9** prevents cyclization reactions leading to products such as **5**, and the 3-substituent can be removed by hydrogenolysis without recourse to basic conditions The aldehyde **9** was first prepared[12] with the use of lead tetraacetate as the oxidant In our hands, sodium periodate in aqueous methanol proved to be more convenient and **9** was obtained as a syrup in 92% yield The product was a true aldehyde, as evidenced by the carbonyl band at 5 75 μm in the i r spectrum and the low-field (τ 0 37) narrow doublet ($J_{4,5}$ 2 0 Hz) for the aldehyde proton (H-5) in the n m r spectrum The syrupy aldehyde **9** was further characterized as its crystalline *p*-nitrophenylhydrazone (**13**), the n m r spectrum of the latter (see Tables I and II) was fully consistent with the structure assigned



Ethynylation of the aldehyde **9** gave a 5-epimeric mixture of acetylenic derivatives that could be separated by chromatography on a column of silica gel. The faster-moving component, identified by subsequent conversions as the α-D-*gluco* derivative (**14**), was obtained as a syrup in a 26 5% yield. The slower-moving, major

component was obtained as a syrup in a 33% yield and subsequent conversions showed that it was the β-L-*ido* acetylenic derivative (**10**) Both products showed narrow doublets for H-7 in their n m r spectra, at τ 7 95 for **14** and τ 7 88 for **10**, and a mixture of the epimers showed two distinct doublets for the acetylenic protons

Ozonolysis of the minor, faster-migrating acetylenic derivative, followed by hydrogenolysis of the benzyl group gave 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**), identical with an authentic sample by mixed m p and X-ray powder diffraction pattern, and none of the β-L-*ido* lactone (**8**) could be detected chromatographically This conversion establishes the structure of the acetylenic precursor as 3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hept-6-ynofuranose (**14**) Similarly, ozonolysis of the major, slower-migrating acetylenic product, followed by hydrogenolysis, gave 1,2-*O*-isopropylidene-β-L-idofuranurono-6,3-lactone (**8**), identical with an authentic sample by mixed m p and X-ray powder diffraction pattern, and none of the α-D-*gluco* lactone (**7**) could be detected chromatographically The precursor therefore has the structure 3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-hept-6-ynofuranose (**10**)

Benzoylation of the α-D-*gluco* derivative (**14**) gave the crystalline 5-benzoate (**15**), melting sharply at 139–140°, and the β-L-*ido* derivative (**10**) also gave a crystalline 5-benzoate (**11**), which melted sharply at 124 5–125°, a mixture of **15** and **11** showed a large melting-point depression The 5-benzoates **15** and **11** were prepared most conveniently by benzoylation of the original mixture of acetylenes (**14** and **10**) and separating the products by fractional crystallization As with the precursors, the acetylenic benzoates **15** and **11** showed H-7 resonances as narrow doublets at different field positions (τ 7 87 and 8 00, respectively), and they could readily be detected in admixture by this means The H-5 signal, the lowest-field signal of all protons on the sugar chain because of the deshielding by the benzoyloxy group, was observed as a quartet through spin-coupling with H-7 ($J_{5,7}$ = 2 Hz in each case) and H-4 Although the H-5 signals for **15** and **11** were observed at different field positions (τ 3 70 and 3 58, respectively) the $J_{4,5}$ couplings were identical (9 0 Hz), indicating that the favored conformation in both compounds is that having H-4 and H-5 antiparallel It is not possible, therefore, to use spin-coupling data for assigning configurations to these epimeric acetylenic derivatives, such assignments are possible when the starting aldehyde is attached to a dioxolane ring or when the acetylenic derivative is acyclic[2,4,5]

Ozonolysis of 5-*O*-benzoyl-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-hept-6-ynofuranose (**11**) gave crystalline 5-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranuronic acid (**12**), and similar ozonolysis of the D-*gluco* acetylenic derivative (**15**) gave 5-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranuronic acid (**16**) as a syrup The two acids **12** and **16** were characterized by n m r spectroscopy and **12** by elemental analysis Debenzylation of **12** and **16** could be effected readily by hydrogenolysis over palladium black However, removal of the benzoyl group by saponification with methanolic sodium methoxide led to epimerization at C-5 in each case, mixtures of 1,2-*O*-isopropylidene-α-D-glucofuranurono- and -β-L-idofuranurono-6,3-lactones (**7** and **8**) were obtained from each reaction

The ozonization reactions described in this paper were performed on a small scale, mainly for the purpose of stereochemical characterization, and yields of uronic acids or their lactones were not optimized for preparative purposes However, the ozonolytic cleavage of α-hydroxyacetylenes to α-hydroxyacids can be effected on a larger scale in near-quantitative yields[4,13,14], and the procedure thus offers a useful general route for preparation of uronic acids The established route to uronic acids, by way of a cyanohydrin reaction with an *ω-aldehydo* sugar derivative[9,15,16], requires alkaline conditions and gives an epimeric mixture of products, whereas the present route gives intermediates that are not prone to epimerization, and generation of the carboxylic acid can be effected without epimerization at the adjacent carbon atom.

EXPERIMENTAL

General methods — Solutions were concentrated under diminished pressure on a rotary evaporator at 30° Specific rotations were measured in a 2-dm tube. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus I r. spectra were measured with a Perkin–Elmer Model 137 "Infracord" i r spectrophotometer. N m r spectra were measured with a Varian HA-100 spectrometer operating at about 28°. Chemical shifts are given on the τ-scale with tetramethylsilane (τ = 10 00) as the internal standard Microanalyses were made by W. N. Rond. X-ray powder diffraction data give interplanar spacings, Å, for CuK_α radiation The relative intensities were estimated visually m, moderate, s, strong, v, very; w, weak The strongest lines are numbered (1, strongest), double numbers indicate approximately equal intensities T l c was performed with Silica Gel G (E Merck, Darmstadt, Germany) as the stationary phase Detection was effected by spraying with sulfuric acid unless specified otherwise Petroleum ether used in recrystallization was a fraction having the boiling range 30–60°. Ozone was generated by using a Welsbach ozonator, model T-408 (The Welsbach Company, Philadelphia, Pennsylvania, U S A)

Preparation of 1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose dimer (**1**) *and 1,2-O-isopropylidene-3,5-O-methylene-α-D-xylo-pentodialdo-1,4-furanose aldehydrol* (**5**) — To a stirred solution of 1,2-*O*-isopropylidene-α-D-glucofuranose (6 g, 27 3 mmoles) in 100 ml of 37% aqueous formaldehyde at 0° was added sodium metaperiodate (6 g, 28.0 mmoles) in water (80 ml) over a period of 30 min The solution was stirred for 1 h at room temperature Ethylene glycol (0 3 ml) was then added to decompose any excess periodate. The solution was concentrated under diminished pressure to one half the original volume and the sodium iodate that separated was filtered off. The solution was extracted five times with 50-ml portions of chloroform. The chloroform extracts were dried (magnesium sulfate) and then concentrated to a syrup, yield 3 2 g (59%) of a mixture of **5** and **1**, R_f (ether) 0 70 and 0 37, respectively[11] in approximately 9.1 proportion

6,7-Dideoxy-1,2-O-isopropylidene-β-L-ido-hept-6-ynofuranose (**2**) *and its α-D-gluco epimer* (**6**) — Ethylmagnesium bromide was prepared from magnesium (2 5 g,

102 mmoles) and ethyl bromide (12 g) in dry tetrahydrofuran (150 ml) Acetylene was passed slowly through dry tetrahydrofuran (250 ml) at room temperature by means of a gas-dispersion tube, and the liquid was stirred magnetically. After 1 h the solution of ethylmagnesium bromide was added dropwise The resulting solution gradually turned bright red and then a dark reddish-brown. The resultant solution of ethynylmagnesium bromide was stirred for 1 h with acetylene still passing through the solution. A solution of the periodate-oxidized product (**5**+**1**, 5 g, 25 3 mmoles) in dry tetrahydrofuran was then added dropwise. After the addition had been completed, the stream of acetylene was maintained for an additional 3 h The tetrahydrofuran was then evaporated off, ethyl ether (250 ml) was added to the residue, and the mixture was shaken with cold, aqueous, saturated ammonium chloride After separation of the layers, the aqueous phase was extracted with ether The combined ether extracts were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated The resultant syrupy mixture contained compound **2** (R_F 0 41, ether) and compound **6** was also present Fractional vacuum distillation gave **2**, yield 1.85 g (8 6 mmoles, 34%), b p 125–135° (0 075 torr, bath temp 175–185°), λ_{max}^{film} 3 08, 4 70 (C≡C–H), 7 23 μm (doublet, CMe_2)

*1,2-O-Isopropylidene-β-*L*-idofuranurono-6,3-lactone* (**8**) — Ozone was passed for 45 min through a solution at 0° of 6,7-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-hept-6-ynofuranose (**2**, 500 mg, 2 34 mmoles) in carbon tetrachloride The solution was evaporated and several small portions of toluene were added to the residual syrup and evaporated Crystallization of the syrup from acetone–ether gave the lactone **8**; yield 80 mg (15%), m p 135–136° (lit [16] m p. 137–138°), R_F 0 25 (9 1 benzene–methanol), X-ray powder diffraction data 6 47 s (2), 5 57 w, 4 97 s (1), 4 45 m, 4 21 m (3), 4 02 w, 3 90 w, 3 63 w, 3 41 m, 3 23 w, 3.12 vw, 3 02 vw, 2 81 w, 2 68 m, 2 52 vw, 2.47 m

The product was identical with an authentic sample of **8** by mixed m p and comparative X-ray powder diffraction pattern No 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) could be detected either in the crystalline product or in the mother liquors, although by t l c compound **7** (R_F 0 40 in 9 1 benzene–methanol) can be clearly differentiated from **8**.

Ozonolysis of a small amount of the undistilled product of the preceding ethynylation experiment, by the same procedure used for the conversion of **2** into **8**, gave a product that by t l c (9 1 benzene–methanol) showed the β-L-*ido* lactone **8** as a major component (R_F 0 25), and the α-D-*gluco* lactone **7** (R_F 0 40) as a minor component

*3,5-Di-O-benzoyl-6,7-dideoxy-1,2-O-isopropylidene-β-*L*-ido-hept-6-ynofuranose* (**3**) — Benzoyl chloride (3 ml) in dichloromethane (10 ml) was added slowly to a solution at 0° of 6,7-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-hept-6-ynofuranose (**2**, 1.85 g, 8.6 mmoles) in dry pyridine (10 ml), and the solution was stirred overnight. The reaction mixture was poured into ice–water (50 ml) and stirred for 1 h. The product was extracted with dichloromethane, and the extract was washed sequentially with 20 ml of 10% aqueous hydrochloric acid, two 20-ml portions of 10% aqueous

sodium hydrogen carbonate, and water The extract was dried (magnesium sulfate) and evaporated to a syrup that crystallized from absolute methanol to give **3**, yield 1 80 g (49%), m p 195–196°, $[\alpha]_D^{18}$ −16 ±3° (*c* 1, chloroform), R_F 0 90 (3 1 chloroform–ether), 0 48 (5 5 2 benzene–petroleum ether–ether), λ_{max}^{KBr} 3 06, 4 71 (C≡C–H), 5.80 (C=O), 7 40 (doublet, CMe_2), 13 15, 14 15 μm (aryl), X-ray powder diffraction data 12 62 m, 7 03 vw. 6 21 s (1), 5 59 w. 4 97 w, 4 68 m (3), 4 41 m, 4 05 s (2), 3 62 vw. 3 45 vw, 3 18 vw

Anal Calc for $C_{24}H_{22}O_7$ C, 68 25, H, 5 21 Found C, 68 35, H. 5 34 Further recrystallization gave no change in the m p of this product The X-ray powder diffraction pattern was identical with that of a product[1] having m p 191–193° earlier believed to be the D-*gluco* analog

*3,5-Di-O-benzoyl-1,2-O-isopropylidene-β-*L*-idofuranuronic acid* (**4**). — Ozone was passed for 45 min through a solution of **3** (500 mg, 1 2 mmoles) in carbon tetrachloride (100 ml) that was kept at 0° The solution was evaporated water (50 ml) was added to the residue, and the mixture was evaporated again Crystallization of the resultant syrup from ether–petroleum ether gave **4** yield 106 mg (20%), m p 176- 179° (decomp), $[\alpha]_D^{21}$ +1 1 ±1° (*c* 0 9, chloroform), λ_{max}^{KBr} 3 0 (CO_2H), 5 75 (C=O) 7 25 (doublet, CMe_2), 14 1 μm (aryl), X-ray powder diffraction data 10 46 s (1), 8 30 w, 7 02 vw, 6 44 m, 5 94 vw, 5 45 vw, 5 19 s (2), 4 72 s (3), 4 45 w, 4 25 s

Anal Calc for $C_{23}H_{22}O_9$ C, 62 44, H, 5 01 Found 62 36, H, 4 91

A solution of **4** in abs methanol was treated with ~1 1 molar equivalents of sodium methoxide solution After 1 h at 30°, the solution was neutralized with acetic acid. evaporated, and toluene was added twice to the residue and evaporated T l c of the product showed components having R_f 0 40 and 0 25 (9 1 benzene–methanol) corresponding to 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) and the β-L-*ido* analog (**8**)

*Preparation of 3-O-benzyl-1,2-O-isopropylidene-α-*D*-glucofuranose* — To a solution of 5,6-di-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[17] (7 0 g, 17 7 mmoles) in abs methanol (50 ml) was added a catalytic amount of sodium methoxide After 4 h at room temperature, the solution was neutralized with a few drops of acetic acid, and then evaporated The resultant thick syrup was dissolved in warm benzene and the solution was filtered through Celite Evaporation of the solution gave the product as a colorless syrup, yield 5 27 g (96%), R_f 0 17 (3 1 chloroform–ether), λ_{max}^{film} 2 90 (OH), 7 25 (doublet, CMe_2), 13 35, 14 30, 14 70 μm (aryl), carbonyl absorption absent.

*Preparation of 3-O-benzyl-1,2-O-isopropylidene-5-*aldehydo-α-D-xylo-*pertodialdo-1,4-furanose*[12] (**9**) — A solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (5 27 g, 17 mmoles) in abs methanol (50 ml) was stirred at 0°, and sodium metaperiodate (4 g, 18 mmoles) in water (50 ml) was added dropwise After the addition had been completed, the solution was stirred for 1 5 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 3 × 50-ml portions of chloroform, and the dried (magnesium sulfate) extract was evaporated to give **9** as a chromato-

graphically homogeneous syrup, yield 4 33 g (92%). R_F 0.42 (3 1 chloroform–ether) The product was distilled, b.p. 145–155° (0.02 torr, bath 200°), λ_{max}^{film} 5 75 (aldehyde C=O), 7 25 (doublet, CMe_2), 13 50, 14 30 μm (aryl).

*3-O-Benzyl-1,2-O-isopropylidene-5-*aldehydo-D-xylo-*pentodialdo-1,4-furanose* p-*nitrophenylhydrazone* (**13**) — To a solution of the aldehyde **9** (500 mg, 1 8 mmoles) in methanol (5 ml) was added *p*-nitrophenylhydrazine hydrochloride (500 mg) in a mixture of water (5 ml) and pyridine (1 ml) The mixture was kept for 24 h at room temperature and then concentrated to a thick syrup. The syrup was dissolved in benzene (50 ml) and the solution was extracted with 25-ml portions of water, 5% sodium hydrogen carbonate, 10% sulfuric acid, and water The benzene solution was dried (magnesium sulfate) and evaporated The resultant syrup was crystallized from benzene–ethanol to give **13** as yellow crystals, yield 570 mg (79%), m p. 141–142°, $[\alpha]^{23}$ −143 ±3° (*c* 1 2, chloroform), R_F 0 55 (3 1 chloroform–ether), λ_{max}^{KBr} 3 06 (N–N), 6 24 (C=N), 6 50, 7 55 (NO_2), 7 25 (doublet, CMe_2), 13 28, 14 37 μm (aryl), X-ray powder diffraction data 10 64 vw, 9 57 m (2), 7 98 w, 7 29 vw, 6 84 w, 6 49 w, 6 12 vw, 5 59 m (2), 5 01 s (1), 4 51 m

Anal Calc for $C_{21}H_{23}N_3O_6$ C, 61 01, H, 5 61, N, 10 16 Found C, 60 97, H, 5 82, N, 10 43

*3-O-Benzyl-6,7-dideoxy-1,2-*O-*isopropylidene-α-*D-gluco-*hept-6-ynofuranose* (**14**) *and its β-*L-ido *epimer* (**10**) — Ethynylmagnesium bromide (80 mmoles) was prepared as before from magnesium (2 g) and ethyl bromide (9 g) in tetrahydrofuran (300 ml) A solution of the aldehyde **9** (10 84 g, 39 mmoles) in dry tetrahydrofuran (50 ml) was added with stirring and with passage of a continuous, slow stream of acetylene to the solution of Grignard reagent during 30 min at room temperature After a further 3 h the solution was evaporated, ether (250 ml) was added to the residue, and the resulting solution was shaken with cold, saturated, aqueous ammonium chloride (200 ml) The separated aqueous phase was extracted with ether, and the combined ether extracts were washed with saturated aqueous sodium chloride (75 ml) The dried (magnesium sulfate) ether extract was evaporated to give a mixture of **10** and **14** as a yellow syrup, yield 8 41 g, R_F 0 43 and 0 64 (3 1 chloroform–ether) A suspension of 300 g of silica gel (Silica Gel Davison, Grade 950, 60–120 mesh, a product of the Davison Division of the W R Grace Chemical Co , Baltimore, Md , U. S A.) in 3 1 dichloromethane–ether was poured into a column (2 8 × 43 cm) and allowed to settle The syrupy mixture of **10** and **14**, dissolved in 5 ml of 3 1 dichloromethane–ether, was placed on top of the column Elution with 3 1 dichloromethane–ether gave the two components resolved completely from each other The first product to be eluted, the D-*gluco* epimer (**14**) was obtained as an oil, yield 3 14 g (27%), R_F 0 64 (3 1 chloroform–ether) The second component to be eluted, the L-*ido* epimer (**10**), was also obtained as an oil, yield 3 96 g (33%), R_F 0 43 (3 1 chloroform–ether)

*Conversion of 3-O-benzyl-6,7-dideoxy-1,2-*O-*isopropylidene-α-*D-gluco-*hept-6-ynofuranose* (**14**) *into 1,2-*O-*isopropylidene-α-*D-*glucofuranurono-6,3-lactone* (**7**) — Ozone was passed for 45 min through a solution of **14** (140 mg, 0 47 mmoles) in carbon tetrachloride (100 ml) at 0° The solution was shaken with water (50 ml) and

the mixture concentrated to a syrup The syrup was dissolved in abs ethanol (75 ml) and hydrogenated at atmospheric pressure for 24 h with palladium black (15 mg) as catalyst The mixture was filtered through Celite, the filtrate was evaporated, and small portions of toluene were added to the resultant syrup and evaporated Crystallization from acetone–ether gave the D-*gluco* lactone (**7**), yield 20 mg (20%), m p 118–119° (lit [16] m p 120°), X-ray powder diffraction data 10 84 m (3), 7 03 w, 5 49 s (1), 4 64 m (2), 4 08 w, 3 91 vw, 3 51 w, 3 26 vw, 3 15 vw, 2 97 w

The product was identical with an authentic sample[16] by mixed m p and X-ray powder diffraction pattern None of the 5-epimeric lactone **8** could be detected in the mother liquors by t l c

*Conversion of 3-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-β-*L*-ido-hept-6-ynofuranose* (**10**) *into 1,2-O-isopropylidene-β-*L*-idofuranurono-6,3-lactone* (**8**) — Compound **10** (100 mg, 0 33 mmoles) was subjected to the sequence of reactions of the preceding experiment, and the crystalline *β-*L*-ido* lactone (**8**) was obtained, yield 24 mg (35%), m p 135–136° (lit [16] 137–138°), identical with authentic **8** by mixed m p and X-ray powder diffraction pattern The 5-epimeric lactone (**7**) could not be detected in the mother liquors by t l c

*5-O-Benzoyl-3-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-β-*L*-ido-hept-6-ynofuranose* (**11**) *and its* α-D-gluco *epimer* (**15**) — To an unseparated mixture of 3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hept-6-ynofuranose (**14**) and the *β-*L*-ido* epimer (**10**) (2 0 g, 6 58 mmoles) in dry pyridine (10 ml) was added benzoyl chloride (2 g) slowly with stirring After 12 h ice and water (50 ml) were added, and the mixture was stirred for 2 h The product was extracted with two 30-ml portions of dichloromethane, and the combined extracts were washed successively with 20 ml of 10% hydrochloric acid, 2 × 20 ml of aqueous sodium hydrogen carbonate, and 2 × 20 ml of water The dried (magnesium sulfate) extract was evaporated, and an ether solution of the product was decolorized with activated charcoal Evaporation of the solvent gave a pale-yellow syrup that crystallized from abs methanol to give a white, crystalline mixture of **11** and **15**, yield 1 39 g (52%), R_F 0 76 (3 1 chloroform–ether)

Fractional recrystallization of the mixture from abs methanol gave the two separate epimers The less-soluble epimer was the *β-*L*-ido* derivative (**11**), which formed rectangular prisms, yield 510 mg (19%), m p 124 5–125°, $[\alpha]_D^{20}$ −32 ±3° (*c* 1, chloroform), R_F 0 38 (5 5 1 petroleum ether–benzene–ether), λ_{max}^{KBr} 3 10, 4 72 (C≡C–H), 5 80 (C=O), 7 22 (doublet, CMe_2), 13 65, 14 05 μm (aryl), X-ray powder diffraction data 12 44 m (3), 9 02 vw, 7 06 vw, 6 15 s (1), 5 61 w, 4 70 m (2), 4 41 w, 4.11 w, 3 85 vw, 3 65 w

Anal Calc for $C_{24}H_{24}O_6$ C, 70 57, H, 5 92 Found C, 70 30, H, 5 93

The more-soluble epimer, the α-D-*gluco* derivative (**15**) was obtained as rectangular prisms, yield 470 mg (18%), m p 139–140°, $[\alpha]_D^{23}$ −79 ±3° (*c* 1 1, chloroform), R_F 0 29 (5 5 1 petroleum ether–benzene–ether); λ_{max}^{KBr} 3.10, 4 72 (C≡C–H), 5 80 (C=O), 7 25 (doublet, CMe_2), 13 45, 14 05 μm (aryl), X-ray powder diffraction data 11 89 m,

8 95 s (2), 7 51 w, 6 56 vs (1), 5 99 s, 5 14 s (3), 4 77 m, 4 25 s, 4 05 s, 3 36 m, 3 20 w, 3 02 w.

Anal Calc for $C_{24}H_{24}O_6$ · C, 70 57, H, 5 92 Found C, 70 50, H, 5 91

A mixture of **11** and **15** melted over the range 115–139° When the separated epimers were benzoylated individually **10** gave **11**, and **14** gave **15**

5-O-Benzoyl-3-O-benzyl-1,2-O-isopropylidene-β-L-idofuranuronic acid (**12**) — Ozone was passed for 30 min through a solution of **11** (100 mg, 0 25 mmoles) in carbon tetrachloride (100 ml) at 0°. The solution was shaken with water (50 ml), and the mixture was evaporated to a syrup that crystallized from ether–petroleum ether to give **12**, yield 51 mg (51%), m p. 157–158°, X-ray powder diffraction data· 10 39 s (1), 8 16 w, 6 42 w, 5 88 vw, 5 17 m (3), 4 75 m (2), 4 38 w, 4 19 w, 3 74 vw, 3 41 vw, 3 22 vw, 3 09 vw

Anal. Calc for $C_{23}H_{24}O_8$ C, 64 47, H, 5 61 Found C, 64 91, H, 5 54

Compound **12** was hydrogenated in ethanol for 24 h in the presence of palladium black. Treatment of the product in abs methanol with sufficient sodium methoxide to split off the benzoyl group, with subsequent neutralization with acetic acid, evaporation of the solution, and evaporation of toluene from the residue, gave a product that, by t l c , contained two components, migrating as 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) and the *β-L-ido* analog (**8**), indicating epimerization at C-5 in the debenzoylation step.

5-O-Benzoyl-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranuronic acid (**16**) — Compound **15** (300 mg, 0 7 mmoles) was ozonized as in the preceding experiment, to give **16** as a syrup, yield 98 mg (33%) When this product was successively debenzylated, saponified, and lactonized by the procedure used with **12**, a mixture of the two lactones **7** and **8** was again obtained, indicating that epimerization at C-5 had occurred during the saponification step

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