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SYNTHESIS OF ACETYLENIC SUGARS AND URONIC ACIDS *via* TWO-CARBON CHAIN EXTENSION OF D-RIBOSE*

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ABSTRACT

Treatment of methyl β-D-ribofuranoside with acetone gave methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**1**, 90%), whereas methyl α-D-ribofuranoside gave a mixture (30%) of **1** and methyl 2,3-*O*-isopropylidene-α-D-ribofuranoside (**1a**). On oxidation, **1** gave methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**2**), whereas no similar product was obtained on oxidation of **1a**. Ethynylmagnesium bromide reacted with **2** in dry tetrahydrofuran to give a 1:1 mixture (95%) of methyl 6,7-dideoxy-2,3-*O*-isopropylidene-β-D-*allo*- (**3**) and -α-L-*talo*-hept-6-ynofuranoside (**4**). Ozonolysis of **3** and **4** in dichloromethane gave the corresponding D-*allo*- and L-*talo*-uronic acids, characterized as their methyl esters (**5** and **6**) and 5-*O*-formyl methyl esters (**5a** and **6a**). Ozonolysis in methanol gave a mixture of the free uronic acid and the methyl ester, and only a small proportion of the 5-*O*-formyl methyl ester. Malonic acid reacted with **2** to give methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo-trans*-hept-5-enofuranosiduronic acid (**7**).

INTRODUCTION

Various methods have been described[1–5] for the oxidation of the primary alcohol group in carbohydrates to give dialdoses. The synthesis of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**2**) has been described[3,6], but the α anomer **2a** has not been reported. The α anomer is of interest for studies of comparative reactivity. Dialdoses with one aldehyde group are useful for the synthesis of uronic acids[6–9], and we now describe the conversion of **2** into hexuronic and hepturonic acids.

DISCUSSION

Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**1**) has been reported as the only product obtained by treatment of D-ribose with 2,2-dimethoxypropane in dry

*Dedicated to the memory of Sir Edmund Hirst, C.B.E., F.R.S.
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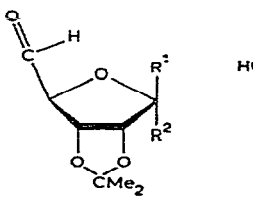
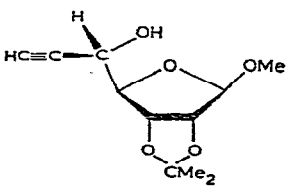
methanol using hydrogen chloride as a catalyst[11]. Whereas treatment of methyl *β*-D-*ribofuranoside with acetone–zinc chloride–phosphoric acid gave 80% of* **1**, *the α anomer gave only a 30% yield of a mixture of glycosides that was fractionated by g.l.c., giving the α and β anomers in the ratio 4:1.* The much poorer reactivity of the α-furanoside towards acetone may explain why the direct method[11] gives only **1**.

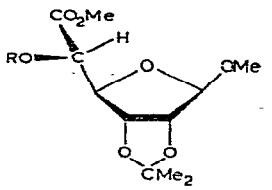
Of the different methods for oxidizing **1**, *that involving the chromium trioxide–pyridine complex*[2] *was the most satisfactory, giving 75% of crystalline* **2** *provided that the reaction was carried out on a small scale (<2.5 g).* On a 5-g scale, the yield was ~40%. The pyridinium chlorochromate method[12] also gave a good yield of **2** and may have an advantage in not being so sensitive towards moisture. Attempted oxidation of **1a** failed; no product corresponding to **2a** could be detected by g.l.c. or other methods. On oxidation of mixtures containing various amounts of **1** and **1a**, only **2** was formed, in a yield corresponding to the amount of **1** present. A similar effect has been observed in a pyranose system[13]. The difference in reactivity of the α- and β-glycosides is attributable to an effect of the methoxyl group. As observed[14] for 2,3-*O*-isopropylidene-D-glyceraldehyde, **2** had to be extracted from the reaction mixture and stored at low temperature. At room temperature, **2** appeared to dimerize or polymerize, as the p.m.r. signal at δ 9.7 and the i.r. carbonyl band at 1730 cm^{-1} slowly disappeared.



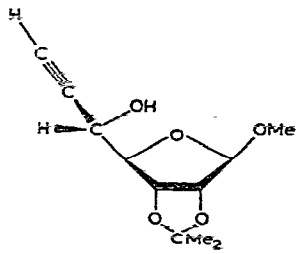
2 R^1 = OMe, R^2 = H
2a R^1 = H, R^2 = OMe



3



5 R = H
5a R = CHO



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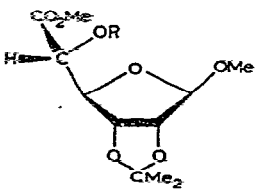
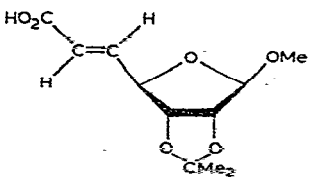


6 R = H
6a R = CHO



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The ethynylation[15,16] *of* **2** gave, in high yield, a mixture of the epimeric acetylenic alcohols **3** and **4** which was not amenable to fractional crystallization, but

fractionation by g.l.c. gave the pure components. The order of elution was **4** {m.p. 63–64°, $[\alpha]_D$ −13° (chloroform)} and then **3** {m.p. 63–64°, $[\alpha]_D$ −96° (chloroform)}. The structure of **3** was determined by X-ray crystallography[17]. The structures of **3** and **4** were also determined by degradation, confirming the D-*allo* and L-*talo* configurations, respectively. A 0.2M solution of **4** in carbon tetrachloride had an i.r. absorption band at 3400 cm^{-1} which was not affected on dilution to 0.006M and is therefore indicative of an intramolecular hydrogen bond involving HO-5 and MeO-1. P.m.r. spectroscopy showed that the hydrogen bond was strong, as no deuterium exchange occurred on boiling a solution of **4** in deuteriomethanol overnight. After 3 days, some exchange had taken place.

The crystal structure of **3** showed an intermolecular hydrogen bond which, according to i.r. spectroscopy, became at least partly intramolecular in solution. Deuterium exchange was much faster for **3** than for **4**.

TABLE I

^{1}H-N.M.R. SPECTRAL DATA[a]

Compound:	**2**[b]	**3**	**4**[c]	**5**	**6**	**7**
Chemical shifts (p.p.m.)						
H-1	5.15 (s)	4.87 (s)	4.90 (s)	4.89 (s)	4.85 (s)	4.88 (s)
H-2	4.58 (d)	4.49 (d)	4.48 (d)	4.50 (d)	4.51 (d)	4.40–4.60 (d)
H-3	5.07 (d)	4.91 (d)	4.71 (d)	4.80 (dd)	4.81 (d)	
H-4	4.50 (s)	4.30–4.39[d]	4.35 (dd)	4.46 (d)	4.69 (s)	4.72 (dd)
H-5	9.70 (s)		4.28 (m)	4.23 (dd)	4.16 (s)	6.95 (dd)
HO-5		3.75	3.81	3.74	4.16	
CMe_2	1.32, 1.47	1.32, 1.47	1.31, 1.47	1.29, 1.45	1.30, 1.46	1.30, 1.41
OMe	3.45	3.38	3.43	3.36	3.36	3.30
Others		2.48 (d) H-7	2.46 (d) H-7	3.74 ester Me	3.72 ester Me	6.06 (d) H-6
Coupling constants (Hz)						
$J_{1,2}$	0	0	0	0	0	
$J_{2,3}$	5.5	5.5	6.0	5.5	—	
$J_{3,4}$	0	0	0	0	—	
$J_{4,5}$	—	4.0	4.0	0	5.0	
$J_{3,5}$	—	—	1.5	0	—	
$J_{5,7}$	2.0	2.0	—		—	
Others		$J_{4,OH}$ 0.5 $J_{5,OH}$ 10.3			$J_{4,6}$ 1.0 $J_{5,6}$ 15.0	

[a]In chloroform-*d* at 98 MHz. [b]At 60 MHz. [c]Analysis confirmed by spectral simulation using the SNFA 01 program on Jeol FX 60. [d]Unresolved. Multiplicity indicated by the usual abbreviations.

The n.m.r. data for **3** and **4** are recorded in Table I. All the proton signals for **4** could be identified by spin-decoupling experiments, but those for H-4,5 in **3** could not be resolved. Horton and co-workers[14,16] have used $J_{4,5}$ values to correlate the structure of some epimeric acetylenes; this type of correlation was not valid for **3** and

4. The mass spectra of 3 and 4 contained no appreciable peak for the molecular ion. The first substantial peak was *m/e* 213 (M−15) which is typical of isopropylidene derivatives.

Ozonization of 3 and 4 in dichloromethane or methanol, followed by fractionation of the products and esterification with diazomethane, gave 5 {m.p. 59–60°, $[\alpha]_D$ −57° (chloroform)} and 6 {m.p. 49–50°, $[\alpha]_D$ −55° (chloroform)} which were obtained crystalline after purification by g.l.c. The yields were, however, low. The p.m.r. data for the esters are recorded in Table I. From the dichloromethane reaction, a syrupy product was also isolated; the i.r. and mass spectra indicated this to be a mixture of the formic esters of 5 and 6. With methanol as solvent, some of the methyl esters were formed directly, together with the free acids. The free acids could not be detected by g.l.c., but there was an approximate doubling of the amount of methyl ester after treatment with diazomethane, indicating that the free acid and the methyl ester had been formed in approximately equal amounts. Small proportions of the formic esters were also formed. The formation of formic esters during ozonolysis of propargyl alcohols has been described[18]. The mechanism of this reaction is under further investigation.

Hydrolysis of 5 and 6 gave methyl D-alluronate and L-taluronate, respectively. Oxidation with bromine gave a mixture of the monomethyl ester of the aldaric acid and the corresponding lactone which could be separated by p.c. after methylation of the free acid with diazomethane. Of the two compounds formed from 5, one was optically inactive, indicating the *allo*-configuration; both the compounds obtained from 6 were optically active, in agreement with the *talo*-configuration.

When 2 was treated[19] with malonic acid, the unsaturated uronic acid 7 was isolated crystalline {~50%, m.p. 101–102° (dec.), $[\alpha]_D$ −5° (chloroform)}. The *trans*-configuration of 7 was indicated by the high coupling constant (see Table I), and by the i.r. band at 980 cm^{-1} and the absence of bands in the region 730–675 cm^{-1}.

EXPERIMENTAL

General methods. — Solutions were concentrated below 40° under diminished pressure. Melting points were determined with a Reichert apparatus and are uncorrected. Specific rotations were determined with a Perkin–Elmer 141 polarimeter in 1-dm tubes. I.r. spectra were measured with a Perkin–Elmer IR 457 spectrophotometer, and n.m.r. spectra were measured at 60 or 98 MHz with Varian A60 or HA-100 instruments for solutions in $CDCl_3$ (internal Me_4Si). Mass spectra were recorded with an AEI MS-902 or a Micro Mass 12S g.l.c.–m.s. instrument. Analytical and preparative g.l.c. were performed on Varian Aerograph 1200, 90P, or 200 gas chromatographs with columns [2 mm × 1.8 m (glass) or 10 mm × 2.5 m (steel)] of *A*, 20% of SE 30; *B*, 10% of PEG-4000, and *C*, 15% of QF1 (all on Chromosorb WAW). Ozone was generated using a Welsbach T 2315 generator regulated to give 0.6 mmol/min. Ozonisation was carried out in dichloromethane at −80° or in methanol at 0°.

Methyl 2,3-O-isopropylidene-β-D-ribofuranoside (**1**). — A mixture of methyl β-D-ribofuranoside[19] (2 g), dry acetone (150 ml), anhydrous zinc chloride (2 g), and phosphoric acid (0.5 ml, 85%) was stirred for 6 h, and then neutralized (40% potassium hydroxide), filtered, and concentrated. Water (50 ml) was added to the residue followed by extraction with chloroform (3 × 50 ml). The combined extracts were washed twice with water, dried ($MgSO_4$), and concentrated. Diacetone alcohol was removed *in vacuo* from the residue, leaving chromatographically pure **1** (2.25 g, 90%) as a colourless syrup.

By a similar procedure, chromatographically pure methyl α-D-ribofuranoside gave a 4:1 mixture (30%) of **1a** and **1** which was fractionated by g.l.c. (column *A*, 170°), giving pure **1** and **1a**.

Compound **1** (9.5 g, b.p. 73–75°/0.3 mmHg) was also prepared from D-ribose (10 g), as described by Leonard and Carraway[11].

Methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside (**2**). — Oxidation of **1** (2.5 g) was carried out as described by Horton and co-workers[3], to give chromatographically homogeneous (g.l.c., column *A*, 170°) **2** (1.85 g, 75%), m.p. 60–61° (from hexane), $[\alpha]_D^{20}$ −218° (*c* 0.6, chloroform).

Similar oxidation of **1a**, and of mixtures (4:1, 1:1, and 1:4) of **1** and **1a**, gave no product corresponding to **2a**, whereas **2** was obtained (75% of **1** present in the mixtures).

Methyl 6,7-dideoxy-2,3-O-isopropylidene-β-D-allo- (**3**) *and -α-L-talo-hept-6-yno-furanoside* (**4**). — A solution of ethylmagnesium bromide, prepared from magnesium (0.31 g) and ethyl bromide (1.5 ml) in dry tetrahydrofuran (15 ml), was added dropwise with stirring to a saturated solution of dry acetylene in tetrahydrofuran (15 ml). Dry acetylene was passed through the mixture during the addition and for 60 min thereafter. After cooling to 0°, a solution of **2** (1.3 g) in tetrahydrofuran (10 ml) was added during 30 min. Acetylene was passed through the solution throughout the addition and for a further 3 h. The mixture was then allowed to attain room temperature, stirred thereat overnight, and then concentrated. A solution of the residue in ether (50 ml) was washed (3 × 50 ml) with saturated, aqueous ammonium chloride at 0° and water (50 ml), dried ($MgSO_4$), and concentrated. The resulting crystalline mixture of **3** and **4** (1.4 g) was fractionated by preparative g.l.c. (column *B*, 190°) to give **3** (48%) as white needles, m.p. 93–94°, $[\alpha]_D^{20}$ −96° (*c* 0.5, chloroform), *T* 1.22 (*cf.* 1.00 for **4**); and **4** (52%), m.p. 63–64°, $[\alpha]_D^{20}$ −13° (*c* 0.5, chloroform). The mass spectra of **3** and **4** were similar: *m/e* 213 (8%, M−Me), 173 (75, M−C_3H_3O), 115 (20, M−C_3H_3O−C_3H_6O), 113 (29), 100 (9), 87 (19), 81 (11), 71 (12), 61 (14), 59 (70), 67 (12), and 43 (100). The i.r. spectra of **3** and **4** were almost identical: $\nu_{max}^{CHCl_3}$ 3415 (OH), 3310 (C≡CH), 1380 and 1317 cm^{-1} (isopropylidene).

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found for **3**: C, 57.93; H, 6.94; **4**: C, 58.02; H, 7.02.

Methyl (methyl 2,3-O-isopropylidene-α-L-talofuranosid)uronate (**6**) *and its 5-formate* (**6a**). — Ozonized oxygen (3 equiv.) was passed through a solution of **4** (200 mg) in dichloromethane (20 ml) at −80°. After evaporation of the solvent, the

ozonide decomposed spontaneously. The residue was treated with diazomethane, giving mainly **6** and **6a** (170 mg) which were separated by g.l.c. (column *C*, 165°) to give **6a**, *T* 1.50 (*cf.* 1.00 for **6**), as a syrup, $\nu_{max}^{CHCl_3}$ 1760, 1740 (diester), 1380 and 1370 cm^{-1} (isopropylidene); and **6**, m.p. 49–50°, $[\alpha]_D^{20}$ −55° (*c* 0.9, chloroform), $\nu_{max}^{CHCl_3}$ 3430 (OH), 1750 (ester), 1380 and 1370 cm^{-1} (isopropylidene).

Mass spectra: **6**, *m/e* 247 (17%, M−Me), 215 (55, M−Me−MeOH), 173 (96, $M-C_3H_5O_3$), 171 (19), 144 (15), 127 (34), 126 (41), 115 (38), 113 (50), 100 (16), 87 (44), 85 (85), 71 (85), 61 (22), 59 (98), 57 (47), and 43 (100); **6a**, *m/e* 275.0765 ($C_{11}H_{15}O_8$, 25%; M−Me), 173 (12, $M-C_4H_5O_4$), 169 (16, $M-C_4H_5O_4-2H_2$), 127 (15), 126 (17), 115 (7), 113 (11), 98 (20), 85 (22), 68 (100), 59 (95), and 43 (99).

Anal. Calc. for **6** $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found: C, 50.55; H, 6.84. Calc. for **6a** $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.43; H, 6.28.

Methyl (methyl 2,3-O-isopropylidene-β-D-allofuranosid)uronate (**5**). — When prepared in the same way as **6**, using methanol (0°) and a 1:1 mixture of **3** and **4** (500 mg), with purification by g.l.c. (column *C*, 170°, *T* 1.25 relative to **6**), **5** had m.p. 59–60°, $[\alpha]_D^{20}$ −57° (*c* 0.8, chloroform), and gave i.r. and mass spectra similar to those of **6**.

Anal. Calc. for $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found: C, 50.60; H, 6.86.

Partial hydrolysis of **5** and **6** (100 mg) was performed with trifluoroacetic acid–water^{20} (10:1; 10 ml), and the products were oxidized with saturated, aqueous bromine (2 ml). Excess of bromine, hydrogen bromide, and water were removed, and the residue was dried *in vacuo* prior to esterification with diazomethane. P.c. (ethyl acetate–acetic acid–water, 9:2:2) then revealed two main products: R_F 0.38 and 0.50 from **5**, and R_F 0.44 and 0.52 from **6**. The component R_F 0.38 (isolated by preparative p.c.) was optically inactive, but the other three components were optically active.

Methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-trans-hept-5-enofuranosid-uronic acid (**7**). — To a solution of **2** (0.85 g) in dry pyridine (2.5 ml), malonic acid (0.49 g) was added, and the mixture was heated to 100°. Piperidine (3 drops) was added, and the solution was stirred at 100° for 1 h and then at room temperature overnight. The solution was concentrated and traces of pyridine were removed by repeated evaporation with light petroleum. Crystallization of the syrupy product from ether–light petroleum (1:4) gave **7** (0.51 g), m.p. 101–102° (dec.), $[\alpha]_D^{20}$ −5°, $[\alpha]_{365}$ +39° (*c* 0.7, chloroform); $\nu_{max}^{CHCl_3}$ 3300–2500 (OH), 1700 (C=O), 1660 (C=C in C=C–C=O), 1380 and 1370 cm^{-1} (isopropylidene). Mass spectrum: *m/e* 229 (28%, M−Me), 173 (3), 169 (8), 126 (31), 115 (6), 113 (12), 108 (22), 85 (100), 59 (98), and 43 (79).

Anal. Calc. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.32; H, 6.53.

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