Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

BRANCHED-CHAIN SUGARS

PART XII*. BRANCHED-CHAIN SUGARS DERIVED FROM METHYL 2,3-*O*-ISOPROPYLIDENE-β-L-*erythro*-PENTOPYRANOSID-4-ULOSE, AND A SYNTHESIS OF L-APIOSE

W. G. OVEREND, A. C. WHITE, AND N. R. WILLIAMS

Chemistry Department, Birkbeck College (University of London), Malet Street, London, W. C. 1. (Great Britain)

(Received February 9th, 1970; in revised form, March 30th, 1970)

ABSTRACT

The preparation of methyl 2,3-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-4-ulose and the conversion of this compound into branched-chain sugar derivatives are described. Reactions at the carbonyl group in the pentopyranosid-4-ulose have been found to give, preferentially, products having the L-*ribo* configuration. A route to L-apiose is outlined.

INTRODUCTION

In continuation of our studies of the synthesis of branched-chain sugars from glycosiduloses, we report now the preparation of methyl 2,3-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-4-ulose (**1**) and an investigation of its reactions with Grignard reagents and with diazomethane. The products obtained can be used as intermediates in the preparation of the L-isomer of apiose. Although alternative procedures starting from (+)-tartaric acid[1], D-glucose[2], or D-arabinose[3] would seem to be more convenient for the synthesis of L-apiose, our results illustrate features of stereochemical interest which are reported in this paper.

DISCUSSION

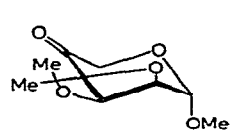
Oxidation of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside with chromic oxide in pyridine yielded methyl 2,3-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-4-ulose (**1**) as a syrup in up to 50% yield, but the material was always contaminated with starting material, even after fractional distillation. Subsequently, ruthenium tetraoxide was used as oxidant to give pure **1** in consistent yields of 70–80%. The ketone was characterised as its crystalline 2,4-dinitrophenylhydrazone.

When a sample of **1** was reduced catalytically, it afforded a methyl 2,3-*O*-isopropylidene-β-L-pentopyranoside shown to have the *ribo* configuration, since it could be de-isopropylidenated to give known methyl β-L-ribopyranoside. Reduction

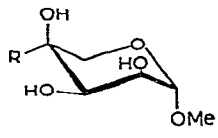
*Part XI: B. M. GOUGH, S. W. GUNNER, W. G. OVEREND, AND N. R. WILLIAMS, *Carbohyd. Res.*, 14 (1970) 173.

could also be effected with lithium aluminium hydride to give a product containing two components, the major one having the same characteristics as that obtained in the catalytic reduction.

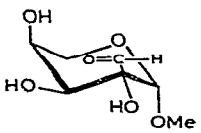
Treatment of compound **1** with phenylethynylmagnesium bromide in ether yielded a syrupy product which was deacetonated to give methyl 4-*C*-phenylethynyl-β-L-ribopyranoside (**2**) as a crystalline solid. Partial hydrogenation of the alkyne group over Lindlar's catalyst afforded methyl 4-*C*-*cis*-styryl-β-L-ribopyranoside (**3**). The *cis* configuration anticipated for this styryl derivative was confirmed by its n.m.r. spectrum (*J* for alkenyl protons = 13 Hz). Further hydrogenation over 10% palladium-on-charcoal gave methyl 4-*C*-phenethyl-β-L-ribopyranoside (**4**). Ozonolysis of compound **3** yielded methyl 4-*C*-formyl-β-L-ribopyranoside (**5**) as a gum that reduced



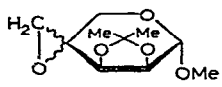
1



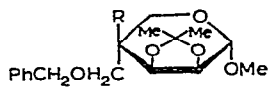
2, R = C≡C—Ph
3, R = CH=CH—Ph (*cis*)
4, R = CH_2CH_2Ph
5, R = CHO
7, R = CH_2OH
10, R = CH_2OCH_2Ph
12, R = Me



6



8



9 R = OH
11 R = OCH_2Ph
16 R = OTs
17 R = H

Fehling's solution, and was characterised as the 2,4-dinitrophenylhydrazone. The failure of compound **5** to form an intramolecular hemi-acetal, evidenced by the persistent carbonyl absorption at 1720 cm^{-1} in its i.r. spectrum, and the failure to form a methyl glycoside with methanolic hydrogen chloride, contrasted with the behaviour of methyl 2-*C*-formyl-β-L-arabinopyranoside[4] (**6**), and was taken as evidence for the *ribo* configuration of compounds **2**–**5**. Catalytic hydrogenation of compound **5** over Adams' catalyst gave methyl 4-*C*-hydroxymethyl-β-L-ribopyranoside (**7**). A more-direct route to this compound was provided by the reaction of the ketone **1** with ethereal diazomethane to give a syrupy mixture of two spiro-epoxides (**8**) in 3:1 ratio, which, on alkaline hydrolysis followed by mild, acid hydrolysis, afforded a mixture of methyl 4-*C*-hydroxymethylpentosides. This mixture was separated by cellulose-column chromatography to give compound **7** in 59% yield. Alternatively, the spiro-epoxide mixture (**8**) could be treated with sodium benzyloxide to give crystalline methyl 4-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-β-L-ribopyranoside (**9**) which could be deacetonated to afford methyl 4-*C*-benzyloxymethyl-β-L-ribopyranoside (**10**). Catalytic hydrogenation of **10** over palladium-on-charcoal gave compound **7**. Compound **9** was also isolated in poor yield by treating the mixture obtained by alkaline hydrolysis of the spiro-epoxides with benzyl bromide and silver oxide in *N*,*N*-dimethylformamide, a procedure which also gave crystalline

methyl 4-*O*-benzyl-4-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-β-L-ribopyranoside (**11**) in 19% yield.

Further evidence about the configuration of these compounds was obtained by reduction of the spiro-epoxide mixture (**8**) with lithium aluminium hydride, which yielded a syrupy mixture of methyl 2,3-*O*-isopropylidene-4-*C*-methyl-pentopyranosides in 8:1 ratio. After treatment with mild acid to remove the isopropylidene residue, crystalline methyl 4-*C*-methyl-β-L-ribopyranoside (**12**) was obtained in 39% yield. The same glycoside was obtained by treatment of the pyranosidulose **1** with ethereal methylmagnesium iodide, which afforded a mixture (ratio 26:1) in which the *ribo* isomer was preponderant.

Besides the evidence indicating a *ribo* configuration for compound **5**, the same configuration for compound **3**, **10**, and **12** was supported by the evidence summarised in Table I. The infrared band near 3520 cm^{-1} indicates a *cis-cis*-triol structure which allows a strong, intramolecular hydrogen-bond between the *syn*-axial C-2 and C-4 hydroxyl groups[5]. The n.m.r. spectral results suggest that the *C1* (L) chair conformation is preferred, assuming that a chair conformation is adopted in accordance with other simple pyranosides, which would only be expected if, in this conformation, the alkyl group at C-4 is equatorial*.

TABLE I

SPECTRAL CHARACTERISTICS

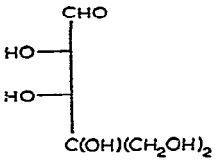
Compound no.	$\nu_{max}^{CCl_4}$	τ (*H-1*)	$J_{1,2}$
3	3520	5.26[a]	1.0
10	3522	5.32[a]	0
12	3517	4.58[b]	0

[a]In $CDCl_3$. [b]In D_2O.

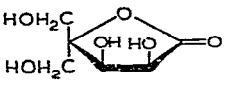
Acid-catalysed hydrolysis of the glycoside **7** gave 4-*C*-hydroxymethyl-L-*erythro*-pentose (**13**) as a syrup, characterised as the phenylosazone which is identical with the compound obtained by Schaffer[2] from 4-*C*-hydroxymethyl-L-*threo*-pentose. Oxidation of compound **13** with bromine and barium benzoate[6] yielded a γ-lactone **14**, characterised as the phenylhydrazide. The Ruff degradation of this lactone, by analogy with the process described for the L-*threo* isomer[1,2], furnished L-apiose (**15**) in low yield, characterised by chromatography with authentic D-apiose.

An attempt was made to convert compound **9** into the 4-deoxypentose analogue,

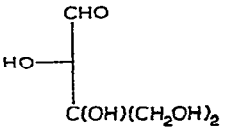
*On the basis of conformational free-energy differences in simple cyclohexanes, methyl and benzyloxymethyl groups would be expected to be sterically more-demanding than hydroxyl groups [see E. L. ELIEL, D. G. NEILSON, AND E. C. GILBERT, *Chem. Commun.*, (1968) 360; E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL, AND G. A. MORRISON, *Conformational Analysis*, Interscience, New York, 1965, p. 433]. Recently, ANGYAL [*Aus. J. Chem.*, 21 (1968) 2737; *Angew. Chem., Intern. Ed. Engl.*, 8, (1969) 157] has suggested that the energy of interaction between an axial methyl group and an axial oxygen atom (2.5 kcal.$mole^{-1}$) is greater than that between two axial oxygen atoms (1.5 kcal.$mole^{-1}$).



13



14



15

since similar degradation of this compound would lead finally to the L-isomer of 3-deoxy-3-*C*-hydroxymethyl-*glycero*-tetrose. At one time, the D-isomer was considered to be the naturally occurring sugar cordycepose, but subsequently the correct structure for this sugar was shown to be 3-deoxy-D-*erythro*-pentose. Treatment of the *sodio derivative of compound* **9** *with toluene-p-sulphonyl chloride in N,N-dimethylformamide* yielded methyl 4-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-4-*O*-toluene-*p*-sulphonyl-*β*-L-ribopyranoside (**16**) as an unstable oil. Reduction of this material with lithium aluminium hydride in ether did not furnish compound **17**, as anticipated by analogy with the behaviour of methyl 3,4-*O*-isopropylidene-2-*C*-methyl-2-*O*-toluene-*p*-sulphonyl-*β*-L-arabinopyranoside[4], but, instead, gave compound **9** in high yield, demonstrating that this sulphonic ester of a tertiary alcohol is attacked preferentially by lithium aluminium hydride at sulphur rather than carbon.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Model 521 or 137 spectrophotometer, either as smears or as Nujol mulls on sodium chloride plates. For high-resolution measurements near 3500 cm^{-1}, a Unicam SP 700 recording spectrophotometer was used: compounds were examined as 5mM solutions in carbon tetrachloride, using 1-cm silica cells. Nuclear magnetic resonance (n.m.r.) spectra were measured with a Varian A-60 spectrometer, with deuteriochloroform as solvent and tetramethylsilane as internal reference, except when stated otherwise. For paper chromatography, Whatman No 1 paper was employed with the following solvent systems (ratios are *v/v*): (*A*) butyl alcohol–ethanol–water (4:1:5, organic phase); (*B*) ethyl acetate–pyridine–water (2:1:2); (*C*) acetone–butyl alcohol–water (5:4:1). For visualizing spots, either (*i*) alkaline silver nitrate[7] or (*ii*) aniline hydrogen phthalate[8] was used. Unless stated otherwise, solvent (*A*) with reagent (*i*) is to be assumed. For thin-layer chromatography (t.l.c), precoated plates (Merck A.G.) of silica gel G, H_{254} (fluorescent agent) were employed with either (*a*) chloroform–ethanol (3:1, *v/v*), (*b*) chloroform–light petroleum (b.p. 40–60°) (3:1), or (*c*) butyl alcohol–ethanol–water (4:1:5, organic phase) as solvent system. Spots were visualized with *p*-anisaldehyde[9]. For gas–liquid chromatography (g.l.c.), a Perkin–Elmer Fractometer, model 451, was used with a flame-ionisation detector. Either (*a*) Apiezon L or (*b*) polypropylene glycol was employed as stationary phase. Quantitative estimation of compounds was made by triangulation of peaks. Unless stated otherwise, solvents were removed under diminished pressure at 40–45°.

D-Lyxose was prepared[10] from calcium D-galactonate pentahydrate (305 g)

in 35% yield, and this was converted[11] into methyl α-D-lyxopyranoside in 84% yield. Methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside[11] was prepared from this glycoside in 85% yield by treating it with phosphoric oxide in acetone[12].

Methyl 2,3-O-isopropylidene-β-L-erythro-pentopyranosid-4-ulose (**1**). — (*a*) Chromium trioxide–pyridine complex[13] was prepared from chromium trioxide (40 g) in dry, redistilled pyridine (400 ml). A solution of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside (20 g) in pyridine (200 ml) was added dropwise to a rapidly stirred solution of the yellow complex at room temperature, and the mixture was stirred at room temperature for 18 h. The solvent was removed, and the residue was extracted with ether. The filtered extract was concentrated, and the residue was re-oxidised by repeating the procedure. Fractional distillation of the product afforded compound **1** as a colourless oil (8.9 g, 49%), b.p. 64–66°/0.2 mmHg, $[\alpha]_D^{23}$ +61° (*c* 1, ethanol), ν_{max} 1730 cm^{-1} (C=O). A small peak at 1790 cm^{-1}, attributed to a carbonyl impurity, was also present. G.l.c. ["Golay Q" column, phase (*a*), column temperature 165°] showed peaks having retention times 9.2, 11.2, and 12.4 min, in the ratio 1:37:5.5; the latter two were pentopyranosidulose **1** and starting material, respectively.

(*b*) A solution of ruthenium tetraoxide in carbon tetrachloride[14] (900 ml, 70mM) was added dropwise at 10° to a stirred solution of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside (11.8 g) in carbon tetrachloride (150 ml). After stirring for 4 h at room temperature, a trace of starting material remained (t.l.c.), and so a further portion of ruthenium tetraoxide solution (100 ml) was added. After a further 16 h at 0°, reaction was complete. Propan-2-ol (10 ml) was added, the ruthenium dioxide was filtered off, and the solvent was removed to yield an oil, b.p. 76–78°/0.7 mmHg, $[\alpha]_D^{24}$ +71° (*c* 1.3, ethanol), ν_{max} 1732 (C=O), 1780(sh) cm^{-1}. Compound **1** so obtained (9.38 g, 88%) was a colourless, mobile syrup.

Anal. Calc. for $C_9H_{14}O_5$: C, 53.5; H, 6.9. Found: C, 53.4; H, 7.2.

Treatment of **1** (100 mg) with 2,4-dinitrophenylhydrazine (100 mg) in absolute ethanol (4 ml) containing a trace of dry hydrogen chloride, warming to dissolve solid material, and storage overnight at room temperature, yielded crystals which were recrystallised from absolute ethanol to give methyl 2,3-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-4-ulose 2,4-dinitrophenylhydrazone (59 mg) as yellow needles, m.p. 129–131°, $[\alpha]_D^{25}$ −297° (*c* 0.3, pyridine).

Anal. Calc. for $C_{15}H_{18}N_4O_8$: C, 47.1; H, 4.75; N, 14.7. Found: C, 47.2; H, 4.75; N, 14.7.

When a sample of **1** (1.17 g) in ethanol (30 ml) was shaken in hydrogen at ambient temperature and pressure in the presence of platinum oxide (0.1 g), rapid absorption of hydrogen occurred, and, after 5 min, the reaction was stopped and the catalyst filtered off. Removal of solvent yielded a colourless oil (1.12 g, 95%), b.p. 95–96°/1 mmHg, which solidified to a low-melting solid. The methyl 2,3-*O*-isopropylidene-β-L-ribopyranoside had $[\alpha]_D^{24}$ +68° (*c* 0.9, ethanol), ν_{max} 3500 cm^{-1} (OH), but no absorption in the C=O region.

Anal. Calc. for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 52.5; H, 8.0.

Reduction (83% yield) could also be achieved by treating ketone **1** (1.27 g) in

ether (10 ml) with lithium aluminium hydride (0.7 g) in dry ether (25 ml). In this case, the product comprised two components (g.l.c., Golay R phase, 155°) of relative intensities 27:1.

When methyl 2,3-*O*-isopropylidene-β-L-ribopyranoside (1.1 g) in 50% aqueous ethanol (10 ml) was shaken with resin (Amberlite IR-120, H^+, 2 g) for 18 h at room temperature, it afforded methyl β-L-ribopyranoside (0.52 g, 60%), m.p. 79–80°, $[\alpha]_D^{25}$ +142° (*c* 0.5, chloroform), R_F 0.61. Pedersen and Fletcher[15] gave m.p. 80–81° and $[\alpha]_D^{20}$ +142° for this compound.

Methyl 4-C-phenylethynyl-β-L-ribopyranoside (**2**). — Phenylacetylene (14.7 g) in dry ether (50 ml) was added to a stirred solution of ethylmagnesium bromide [prepared from magnesium (3.5 g) and ethyl bromide (16.5 g) in dry ether (50 ml)]. The mixture was stirred for 1 h at room temperature, and then the pyranosidulose **1** (12.3 g, prepared by method *a*) in dry ether (50 ml) was added dropwise at 0°. The mixture was warmed to ambient temperature, and then heated under reflux for 1 h. Work-up in the usual way gave a product which, on distillation, afforded methyl 2,3-*O*-isopropylidene-4-*C*-phenylethynyl-β-L-ribopyranoside as an impure syrup (13.5 g, 84%), b.p. 154–158°/0.6 mmHg, $[\alpha]_D^{24}$ +10° (*c* 1.8, ethanol). A solution of this material in ethanol (20 ml)–water (5 ml) was shaken for 18 h at room temperature with Amberlite (IR-120, H^+) resin (5 g). The resin was filtered off and washed with ethanol and water. The washings were added to the filtrate, and the whole was concentrated to a yellow oil which was dried by repeatedly distilling ethanol over it. It crystallised from ethyl acetate–light petroleum (b.p. 40–60°) to give compound **2** as colourless needles (7.13 g), m.p. 128–130° (raised to 131–132° on recrystallisation), $[\alpha]_D^{24}$ +36.5° (*c* 1.0, ethanol), ν_{max} 3500–3300 (OH), 2200 (C≡C), 1600 (Ph) cm^{-1}, R_F 0.89.

Anal. Calc. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.3; H, 6.0.

Methyl 4-C-cis-styryl-β-L-ribopyranoside (**3**). — Compound **2** (5 g) in ethanol (100 ml) containing synthetic quinoline (0.4 ml) was shaken with hydrogen in the presence of palladium-on-barium sulphate at room temperature and atmospheric pressure. When 1 mole equivalent of hydrogen had been consumed, the rate of reaction decreased, and the mixture was worked up in the usual way. The product was recrystallised from benzene–light petroleum (b.p. 60–80°) to give the title compound (4.61 g, 91%) as colourless needles, m.p. 90–91°, $[\alpha]_D^{24}$ +117° (*c* 1.5, ethanol), R_F 0.89. N.m.r. data: two doublets at τ 3.24 and 4.42, *J* 13 Hz, indicating *cis*-alkenyl protons.

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.2; H, 6.8. Found: C, 63.5; H, 7.0.

Methyl 4-C-2'-phenethyl-β-L-ribopyranoside (**4**). — Compound **2** (275 mg) in ethanol (25 ml) was shaken with hydrogen over palladium-on-charcoal (10%, 50 mg) at room temperature and pressure until hydrogen uptake ceased. The filtered solution was diluted with water and shaken with Amberlite (IR-120, H^+) resin (1 g) for 16 h. After filtration, the solution was concentrated to a colourless syrup which crystallised on trituration with ethyl acetate–light petroleum (b.p. 60–80°) to give compound **4** (86 mg, 31%), m.p. 136–137°, $[\alpha]_D^{24}$ +86° (*c* 0.8, ethanol).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5. Found: C, 62.8; H, 7.35.

Methyl 4-C-formyl-β-L-ribopyranoside (**5**). — The 4-*C*-styryl-glycoside **3** (3 g)

in dry, redistilled ethyl acetate (200 ml) was treated with ozonised oxygen at 10° in normal fashion, and when ozone uptake ceased the solution was hydrogenated over palladium-on-charcoal (10%, 0.5 g) until the cessation of rapid absorption of hydrogen. Filtration and concentration of the filtrate yielded a gum (3.2 g) which was dissolved in water (20 ml) and extracted with light petroleum (b.p. 60–80°) (5 × 10 ml) to remove benzaldehyde. On heating to dryness, the aqueous layer yielded compound **5** as a gum (2.02 g, 93%) which was reducing to Fehling's solution. It showed ν_{max} (chloroform) 3450 (O-H), 1720 (>C=O), and a small peak at 1600 cm^{-1} (aromatic impurity); R_F 0.41 with a trace of material having R_F 0.90.

Treatment of this compound (100 mg) with 2,4-dinitrophenylhydrazine, as described for compound **1**, yielded methyl 4-*C*-formyl-β-L-ribopyranoside 2,4-dinitrophenylhydrazone (30 mg), m.p. 165–167° (from ethanol), $[\alpha]_D^{22}$ +320° (*c* 0.2, pyridine).

Anal. Calc. for $C_{13}H_{16}N_4O_9$: C, 42.0; H, 4.3; N, 15.1. Found: C, 42.0; H, 3.5; N, 15.0.

Methyl 4-C-hydroxymethyl-β-L-ribopyranoside (**7**). — *Method A.* Compound **5** (1.75 g) in ethanol (50 ml) was shaken with hydrogen at room temperature and 46 lb/sq.in. in the presence of Adams' catalyst (0.4 g). When hydrogen uptake ceased, the reaction mixture was no longer reducing to Felhing's solution. Removal of catalyst and solvent afforded the 4-*C*-hydroxymethyl derivative **7** as a colourless syrup (1.4 g, 80%), $[\alpha]_D^{24}$ +98° (*c* 0.9, ethanol), R_F 0.51 with a trace of material having R_F 0.92.

Method B. The pyranosidulose **1** (9.13 g) in methanol (150 ml) at 10° was treated with a solution of diazomethane in ether (150 ml, 0.42M), and the mixture was stored for 18 h at 0°. The solution was filtered, and solvent was removed from the filtrate to leave a mixture of methyl 4,1′-anhydro-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-α-D-(and-β-L-)lyxo-(and ribo-)pyranoside (**8**) as a syrup (8.9 g, 90%), b.p. 85–87°/0.5 mmHg, $[\alpha]_D^{23}$ +53° (*c* 1.0, ethanol).

Anal. Calc. for $C_{10}H_{16}O_5$: C, 55.5; H, 7.4. Found: C, 55.3, H, 7.6.

G.l.c. analysis [Golay R column, phase (*b*), 155°] showed two peaks, retention times 20.6 and 23.2 min, with an area ratio of 1:3. This mixture was treated in either of the following two ways: (*1*) A sample (13.5 g) of the mixture [derived from compound **1** prepared by method (*a*) and containing some methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside] was dissolved in M sodium hydroxide (150 ml), and the solution was stored for 18 h at room temperature. After neutralisation with 3M sulphuric acid, the solution was concentrated to dryness, and the residue was extracted with propan-2-ol. The extract was filtered and concentrated to a syrup which was distilled to give impure methyl 4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-α-D-(and β-L-)lyxo-(and ribo-)pyranoside (11.1 g), b.p. 114–118°/0.1 mmHg, $[\alpha]_D^{25}$ +49° (*c* 0.9, ethanol). This material (5.52 g) in water (30 ml) and ethanol (10 ml) was shaken with resin (Amberlite IR-120, H^+, 10 g) for 18 h at room temperature. After filtration and concentration, a glass (4.5 g) was obtained. On paper chromatography, this showed two components with R_F 0.39 (trace) and 0.51. A portion (1.56 g) of this mixture was applied to a column of Whatman cellulose powder No. 1 (240 g) which was developed with

water-saturated butanone. This yielded (*i*) methyl 4-*C*-hydroxymethyl-β-L-ribopyranoside (**7**) (920 mg), $[\alpha]_D^{24}$ +107° (*c* 1.0, ethanol), R_F 0.50 (solvent *A*), 0.72 (solvent *B*). (*Anal.* Calc. for $C_7H_{14}O_6$: C, 43.3; H, 7.3. Found: C, 43.0; H, 7.6). (*ii*) Methyl α-D-lyxopyranoside (163 mg); and (*iii*) possibly methyl 4-*C*-hydroxymethyl-α-D-lyxopyranoside (110 mg), R_F 0.40, which was not investigated further.

(*2*) The spiro-epoxide mixture **8** (8.9 g) was treated with a solution of sodium benzyl oxide [prepared from sodium (2.6 g) in dry benzyl alcohol (80 ml) at 100°]. The mixture was stirred for 18 h at room temperature. Ether (400 ml) was added, and the solution was washed sequentially with water, 2M hydrochloric acid, and saturated, aqueous sodium hydrogen carbonate. Removal of ether and benzyl alcohol at 1 mmHg gave a syrup which was crystallised from light petroleum (b.p. 40–60°). Recrystallisation (twice) from light petroleum (b.p. 60–80°) yielded methyl 4-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-β-L-ribopyranoside (**9**) (7.6 g, 58%) as colourless needles, m.p. 77–78°, $[\alpha]_D^{24}$ +37° (*c* 1.0, chloroform).

Anal. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.5. Found: C, 62.9; H, 7.4.

This material (3.94 g) dissolved in water (50 ml) and ethanol (30 ml) was stirred with resin (Amberlite IR-120, H^+, 8 g) for 16 h at room temperature. Removal of resin and solvent yielded methyl 4-*C*-benzyloxymethyl-β-L-ribopyranoside (**10**) (2.73 g, 76%), m.p. 112–113° after crystallisations from benzene–light petroleum (b.p. 60–80°), $[\alpha]_D^{24}$ +77° (*c* 1.0, ethanol).

Anal. Calc. for $C_{14}H_{20}O_6$: C, 59.1; H, 7.1. Found: C, 59.2; H, 7.2.

A further crop of compound **10** (880 mg) was obtained after similar treatment of the residue (5.4 g) obtained from the mother liquors of the crystallisation of compound **9**. Compound **10** (2.48 g) in ethanol (50 ml) was shaken with hydrogen in the presence of a catalyst of palladium-on-charcoal (10%, 300 mg) at 40° and atmospheric pressure. In 40 min, 1 mole equivalent of hydrogen was absorbed. Removal of catalyst and solvent afforded a quantitative yield of compound **7** as a colourless glass, $[\alpha]_D^{26}$ +104.5° (*c* 1.4, ethanol).

Shaking the crude mixture of methyl 4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-pentopyranosides (1.14 g) in dry *N*,*N*-dimethylformamide (20 ml) with silver oxide (3.25 g) and redistilled benzyl bromide (3 ml) for 16 h at room temperature, followed by filtration and concentration, yielded an oil which was partially soluble in light petroleum (b.p. 60–80°). The soluble fraction (1.54 g), on repeated recrystallisation from 80% aqueous ethanol, afforded methyl 4-*O*-benzyl-4-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-β-L-ribopyranoside (**11**) (0.38 g, 19%), m.p. 80–81°.

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.5; H, 7.3. Found: C, 69.9; H, 7.3.

Concentration of the mother liquors, with crystallisation of the residue from light petroleum (b.p. 60–80°), yielded compound **9** (0.42 g, 27%).

Methyl 4-C-methyl-β-L-ribopyranoside (**12**). — The spiro-epoxide mixture **8** (1.44 g), containing 10–15% of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside, was added in dry ether (10 ml) to a stirred suspension of lithium aluminium hydride (0.5 g) in ether (50 ml). The mixture was heated under reflux for 2 h and then cooled. Water (5 ml) was added cautiously, followed by anhydrous magnesium sulphate.

Filtration and removal of the solvent gave a syrup which was distilled to give a mixture of methyl 2,3-*O*-isopropylidene-4-*C*-methylpentopyranosides (1.15 g, 80%), b.p. 90–91°/1mmHg, $[\alpha]_D^{25}$ +56° (*c* 1.0, ethanol).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.0; H, 8.3. Found: C, 55.2; H, 8.5.

G.l.c. analysis (Golay R, phase (*b*), 150°) gave 3 peaks with retention times of 17.5, 20.0, and 29.0 min, in the ratios 10.5:86:3.5. The last peak corresponded to methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside. A similar mixture was obtained by treatment of the pyranosidulose **1** (0.824 g) (prepared by method *a*) in dry ether (10 ml) with an excess of ethereal methylmagnesium iodide (50 ml), the mixture being heated under reflux for 1 h. Work-up in the usual way afforded a similar mixture (0.59 g, 67%), b.p. 91–92°/1.0 mmHg, $[\alpha]_D^{23}$ +61° (*c* 1.0, ethanol), shown by g.l.c. analysis to be in the ratios 3.5:93:3.5.

The product (1.15 g) prepared from **8** was shaken in water (20 ml) with resin (Amberlite IR-120, H^+, 5 g) for 20 h at room temperature. Filtration and removal of solvent afforded a syrup which was crystallised from ethyl acetate–light petroleum (b.p. 40–60°), and twice recrystallised from this solvent to give compound **12** as colourless rhombs (362 mg, 39%), m.p. 91–92°, $[\alpha]_D^{26}$ +115° (*c* 1.0, ethanol), R_F 0.70.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.2; H, 7.9. Found: C, 47.4; H, 8.2.

*4-C-Hydroxymethyl-*L*-erythro-pentose* (**13**). — Compound 7 (1.32 g) in water (20 ml) was heated under reflux with resin (Amberlite IR-120, H^+, 5 g) for 36 h. Filtration and concentration of the filtrate afforded the title compound **13** as a colourless syrup (1 g, 83%), $[\alpha]_D^{26}$ −0.7° (*c* 1.0, water), R_F 0.19 (solvent *A*, reagents *i* and *ii*), 0.52 (solvent *B*, reagent *i*).

Anal. Calc. for $C_6H_{12}O_6$: C, 39.9; H, 6.7. Found: C, 40.0; H, 6.7.

The phenylosazone of 4-*C*-hydroxymethyl-L-*glycero*-pentose (obtained by treatment of compound **13** with phenylhydrazine) was obtained as yellow plates, m.p. 163–165° (from aqueous methanol), $[\alpha]_D^{20}$ −40° (*c* 1.0, acetone). Schaffer[2] reported m.p. 167°, $[\alpha]_D^{19}$ −44°, for this compound.

*4-C-Hydroxymethyl-*L*-erythro-pentonic acid γ-lactone* (**14**). — A mixture of compound **13** (2.54 g), bromine (2.96 g), and barium benzoate (8.03 g) in water (150 ml) was stirred in the dark for 16 h at room temperature[6]. Sulphuric acid (0.5M, 20 ml) was added, and the solution was filtered to remove barium salts. Bromide ions were removed by stirring the solution with silver carbonate and filtering. The filtrate was extracted with chloroform to remove benzoic acid. On evaporation to dryness and repeated evaporation with glacial acetic acid, crystalline material was obtained from which the lactone **14** was isolated as colourless rhombs (1.68 g, 63%), m.p. 136–138° (from glacial acetic acid), $[\alpha]_D^{25}$ +1.4° (*c* 1.0, water), ν_{max} 1785 cm^{-1} (C=O; γ-lactone), R_F 0.34; n.m.r. data (deuterium oxide): τ 5.17 (*d*) and 5.57 (*d*) (H-2 and H-3, $J_{2,3}$ 6 Hz) 6.18(*s*) and 6.21(*s*) (two CH_2, C-4 and C-1′).

Anal. Calc. for $C_6H_{10}O_6$: C, 40.45; H, 5.7. Found: C, 40.75; H, 5.7.

Treatment of the lactone **14** (178 mg) with phenylhydrazine (236 mg) in water (1.5 ml) afforded 4-*C*-hydroxymethyl-L-*erythro*-pentonic acid phenylhydrazide (130

mg) as colourless needles, m.p. 156–157° (decomp.) (from ethanol), $[\alpha]_D^{24}$ −6.5° (*c* 1.0, ethanol).

Anal. Calc. for $C_{12}H_{18}N_2O_6$: C, 50.3; H, 6.3; N, 9.8. Found: C, 50.3; H, 6.0; N, 10.0.

Ruff degradation[16] of compound **14** (1.31 g) with Fenton's reagent yielded a product corresponding to D-apiose by t.l.c. (solvent *c*). An attempt was made to purify the product *via* a crystalline di-*O*-isopropylidene derivative by treating[17] it with dry acetone (200 ml) containing conc. sulphuric acid (10 ml) at room temperature. However, only a crude syrup (1.30 g) containing acetone polymers and a component identical with authentic di-*O*-isopropylidene-D-apiose on g.l.c. (polysilicone stationary phase, 130° column temperature) was obtained. The syrup was hydrolysed by heating under reflux with water (10 ml) and Amberlite IR-120 (H^+) resin for 3 h. The cooled solution was extracted with ether and concentrated to a syrup (322 mg), $[\alpha]_D^{22}$ −9.4° (*c* 2.5, ethanol); Weygand and Schmiechen[1] gave $[\alpha]_D$ −8.2°; R_F 0.28 (solvent *A*) and 0.30 (solvent *C*). Authentic apiose showed the same R_F values in these solvents.

Methyl 4-C-benzyloxymethyl-2,3-O-isopropylidene-4-O-toluene-p-sulphonyl-β-L-ribopyranoside (**16**). — Methyl 4-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-β-L-ribopyranoside (1.3 g) in dry *N,N*-dimethylformamide (5 ml) was added dropwise to a stirred suspension of sodium hydride (0.13 g) in the same solvent (10 ml) at 5–10°. Toluene-*p*-sulphonyl chloride (0.95 g) in dry *N,N*-dimethylformamide (10 ml) was added at 10–15°, and the resulting solution was kept for 2 h. Saturated, aqueous sodium hydrogen carbonate (30 ml) was added, and the mixture was extracted with benzene (5 × 10 ml). The extract was washed with water and concentrated to afford compound **16** as a yellow, viscous syrup (1.8 g) which darkened on storage in air; ν_{max} 1360 cm^{-1} ($ROSO_2R$) (absent in the spectrum of compound **9**); the absorption at 3500 cm^{-1} was negligible in comparison with that of the starting material (**9**). Treatment of this syrup with lithium aluminium hydride (2 g) in dry ether (20 ml) at reflux temperature for 8 h, with work-up in the usual way, afforded a product (1.1 g) which, after recrystallisation from light petroleum (b.p. 60–80°), was found to be identical with compound **9** by m.p., mixture m.p., and infrared spectral characteristics.

REFERENCES

1 F. WEYGAND AND R. SCHMIECHEN, *Ber.*, 92 (1959) 535.
2 R. SCHAFFER, *J. Amer. Chem. Soc.*, 81 (1959) 5452.
3 D. T. WILLIAMS AND J. K. N. JONES, *Can. J. Chem.*, 42 (1964) 69.
4 J. S. BURTON, W. G. OVEREND, AND N. R. WILLIAMS, *J. Chem. Soc.*, (1965) 3433.
5 R. J. FERRIER, W. G. OVEREND, G. A. RAFFERTY, H. M. WALL, AND N. R. WILLIAMS, *Proc. Chem. Soc.*, (1963) 133.
6 C. S. HUDSON AND H. S. ISBELL, *J. Amer. Chem. Soc.*, 51 (1929) 2225.
7 W. E. TREVELYAN, D. P. PROCTER, AND J. S. HARRISON, *Nature*, 166 (1950) 444.
8 S. M. PARTRIDGE, *Nature*, 164 (1949) 443.
9 U. KALTENBACH AND E. STAHL, *J. Chromatogr.*, 5 (1961) 351.

10 H. G. FLETCHER, JR., H. W. DIEHL, AND C. S. HUDSON, *J. Amer. Chem. Soc.*, 72 (1950) 4546.
11 P. W. KENT AND P. F. V. WARD, *J. Chem. Soc.*, (1953) 416.
12 J. HONEYMAN, *J. Chem. Soc.*, (1946) 990.
13 G. I. POOS, G. E. ARTH, R. E. BEYLER, AND L. H. SARETT, *J. Amer. Chem. Soc.*, 75 (1953) 422.
14 P. J. BEYNON, P. M. COLLINS, P. T. DOGANGES, AND W. G. OVEREND, *J. Chem. Soc.* (C), (1966) 1131.
15 C. PEDERSEN AND H. G. FLETCHER, JR., *J. Amer. Chem. Soc.*, 82 (1960) 945.
16 R. L. WHISTLER AND J. N. BEMILLER, *Methods Carbohyd. Chem.*, 1 (1962) 79.
17 D. J. BELL, *Methods Carbohyd. Chem.*, 1 (1962) 260.