Syntheses of L-Vallarose (6-Deoxy-3-*O*-methyl-L-altrose) and D-Digitalose (6-Deoxy-3-*O*-methyl-D-galactose)

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The first synthesis of L-vallarose (6-deoxy-3-*O*-methyl-L-altrose) (8), a sugar found in certain cardiac glycosides, has been achieved by a route involving partial hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (2) with acid to give the corresponding 1,2-acetal (3). The latter was converted into 6-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-methylsulphonyl-α-D-galactofuranose(5) and, thence, on solvolysis with methanolic sodium methoxide, into 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-altrofuranose (6). Ring-opening of this anhydro-sugar with lithium aluminium hydride and hydrolysis with acid liberated L-vallarose.

A new, convenient synthesis of D-digitalose (6-deoxy-3-*O*-methyl-D-galactose) (13) was accomplished from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (3) by ring opening of the derived epoxide (11) with lithium aluminium hydride in ether followed by hydrolysis with acid of the 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (12) so formed.

CERTAIN 6-deoxy-3-*O*-methylaldohexoses are found as components of the cardiac glycosides.[1,2] Representatives of all eight pairs of isomers are known [1-5] although some of the procedures used to prepare them are of limited preparative significance. With the recently reported [5] synthesis of L-acofriose (6-deoxy-3-*O*-methyl-L-mannose), the only naturally occurring 6-deoxy-3-*O*-methylhexose to have resisted synthesis is L-vallarose (6-deoxy-3-*O*-methyl L-altrose), although the D-enantiomer was synthesised [6] some time ago. The natural sugar is a component of the cardenolides vallaroside and vallarosolanoside which occur in the seeds of *Vallaris solanacea* (Roth) O.K.[7]

The obvious difficulty presented by a synthesis of L-vallarose is to achieve a means of entry into the L-altrose series. We have recently noted [5] that most of the 1,2:5,6-di-*O*-isopropylidene-D(L)-hexofuranoses have become available [8] and that they are valuable precursors for syntheses of 6-deoxy-3-*O*-methylhexoses. A successful synthesis of L-vallarose (8) has now been achieved from 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-galactofuranose (2), which is available [9] by an eight-stage synthesis from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1). The route used is described in brief only, since the reactions used were straightforward and well characterised products were obtained at each stage.

Partial hydrolysis of the diacetal (2) [9b] in dilute acetic acid at room temperature afforded mainly 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (3), although further hydrolysis to the free sugar was also observed under the conditions used. Unimolar benzoylation of the diol (3) at 0° gave, after chromatography, a syrupy monobenzoate which was confidently identified as 6-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (4) on the expectation that the primary hydroxy-group would be preferentially esterified. Methylsulphonylation then afforded 6-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-methylsulphonyl-α-D-galactofuranose (5), which was briefly treated with methanolic sodium methoxide at *ca.* −25° to give a high

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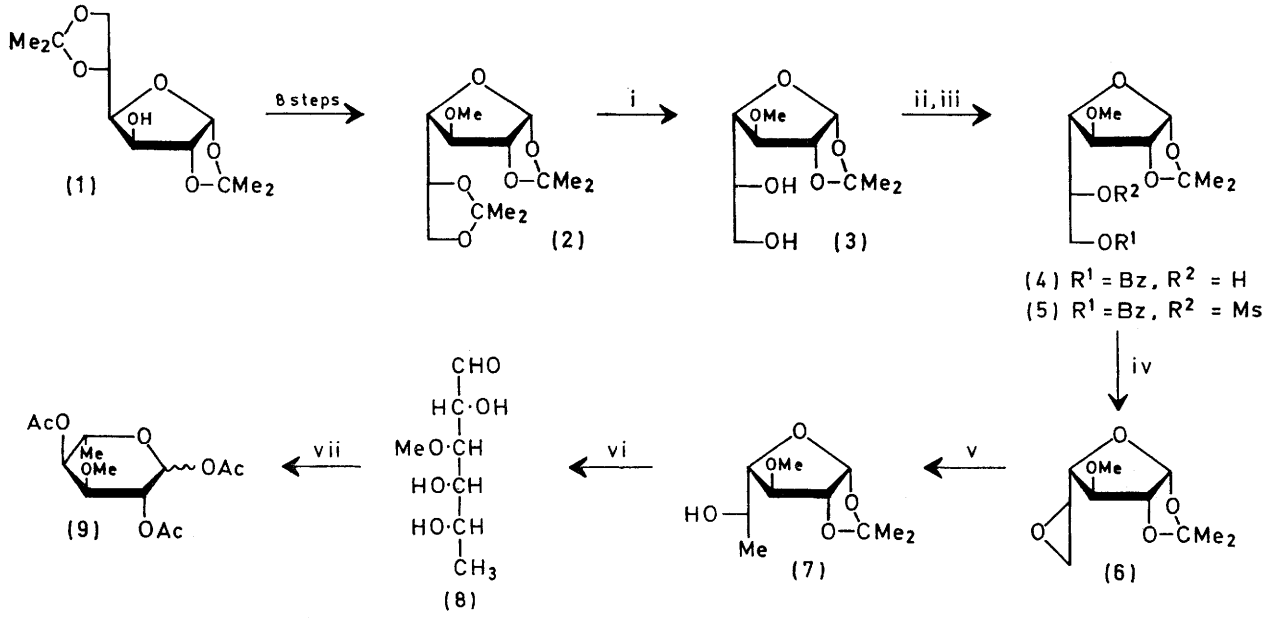
[9] (*a*) J. S. Brimacombe, P. A. Gent, and M. Stacey, *J. Chem. Soc.* (*C*), 1968, 567; (*b*) J. S. Brimacombe, A. M. Mofti, and A. K. Al-Radhi, *ibid.*, 1971, 1363.

yield of 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-altrofuranose (6), presumably by way of the debenzoylated product formed initially. It was necessary to monitor this reaction closely by t.l.c. since slow opening of the epoxide ring by methoxide ion occurred. Reductive opening of the epoxide (6) with lithium aluminium hydride in ether gave 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-altrofuranose (7), which was hydrolysed with an acid resin to liberate 6-deoxy-3-*O*-methyl-L-altrose (L-vallarose) (8). The synthetic sugar crystallised after distillation and had physical constants in close agreement with those reported [2,7] for the natural sugar; it was also indistinguishable from D-vallarose [6] on t.l.c. The identity of synthetic L-vallarose was further established by the preparation of a crystalline triacetate (9).

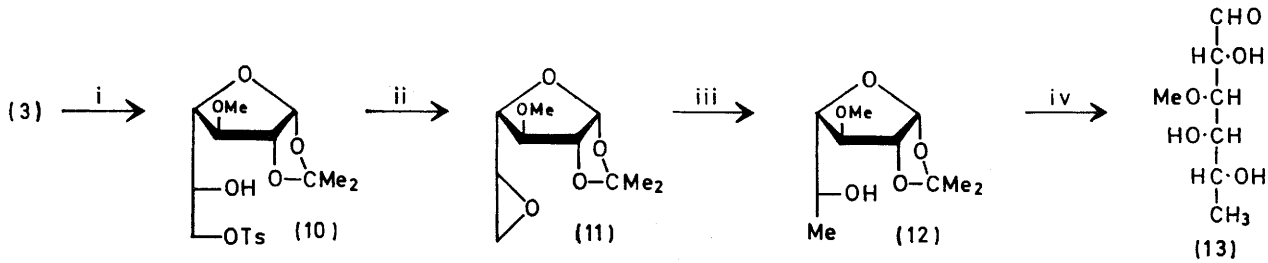
The acetal (3) is also a convenient starting point for a synthesis of D-digitalose (6-deoxy-3-*O*-methyl-D-galactose) (13), a sugar first isolated by Kiliani [10] in 1892 following acidic hydrolysis of the cardiac glycosides extracted from *Digitalinum verum*. D-Digitalose was subsequently obtained [11] in crystalline form after hydrolysis of a cardiac glycoside isolated from the seeds of *Strophanthus emini*, and the sugar is widely distributed among the plant glycosides.[1,2]

D-Digitalose was first prepared by Reber and Reichstein [12] using a multi-stage synthesis from methyl β-D-galactopyranoside, and it was also obtained [13] by an analogous sequence of reactions on the corresponding α-anomer. An alternative and convenient synthesis of D-digitalose is now described.

Unimolar *p*-tolylsulphonylation of the acetal (3) gave a syrupy monosulphonate, which was purified by chromatography on silica gel and assumed to be 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-*p*-tolylsulphonyl-α-D-galactofuranose (10). Solvolysis of the latter with methanolic sodium methoxide at *ca.* −25° gave 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (11) in high yield. The 6-deoxy-function was then introduced by opening of the epoxide ring with lithium aluminium hydride, whereafter hydrolysis of the product (12) with



Reagents: i, aq. AcOH; ii, BzCl, pyridine; iii, MsCl, pyridine; iv, NaOMe,MeOH; v, $LiAlH_4$; vi, H_3O^+; vii, Ac_2O, pyridine



Reagents: i, TsCl, pyridine; ii, NaOMe,MeOH; iii, $LiAlH_4$; iv, H_3O^+

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[11] I. D. Lamb and S. Smith, *J. Chem. Soc.*, 1936, 442.
[12] F. Reber and T. Reichstein, *Helv. Chim. Acta*, 1946, **29**, 343.
[13] C. Tamm, *Helv. Chim. Acta*, 1949, **32**, 163.

an acid resin and distillation afforded 6-deoxy-3-*O*-methyl-D-galactose (D-digitalose). The distillate crystallised on seeding and the physical constants of the crystalline material were in good agreement with those reported [11] for natural D-digitalose.

EXPERIMENTAL

T.l.c. was performed on silica gel [Kieselgel H (nach Stahl)]; spots were located with vanillin–sulphuric acid.[14] N.m.r. spectra were determined for *ca.* 10% solutions in the solvent indicated (tetramethylsilane as internal reference) with a Perkin-Elmer R-10 spectrometer. I.r. spectra were recorded either for Nujol mulls or liquid films with a Perkin-Elmer Infracord spectrometer. Optical rotations at the sodium D-line were measured at ambient temperature with a Perkin-Elmer model 141 polarimeter.

Synthesis of L-*Vallarose*

1,2-O-*Isopropylidene*-3-O-*methyl*-α-D-*galactofuranose* (3).—Graded hydrolysis of the diacetal (2) with acid was shown in trial experiments to give the optimum yield of the 1,2-monoacetal (3) under the conditions now detailed.

The diacetal (2) [9b] (1·3 g) in aqueous 70% acetic acid (40 ml) was stirred for 6 h at room temperature, after which time t.l.c. [benzene–methanol (95 : 5)] indicated that most of the starting material had reacted. The hydrolysate was evaporated to dryness and the last traces of acetic acid were removed by repeated evaporation of toluene from the residue. The mixture of products was chromatographed on silica gel [elution with ether–methanol (8 : 2)] to give the *monoacetal* (3) (0·92 g, 83%), b.p. 110—112° (bath) at 0·1—0·2 mmHg, $[\alpha]_D$ −31 ± 1° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ (film) 3380br (OH) and 1380 and 1390 cm^{-1} (isopropylidene) (Found: C, 51·3; H, 7·9. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·75%).

6-O-*Benzoyl*-1,2-O-*isopropylidene*-3-O-*methyl*-α-D-*galactofuranose* (4).—A cold solution of benzoyl chloride (0·6 g) in dry pyridine (10 ml) was added to a stirred and cooled (0°) solution of the monoacetal (3) (1·1 g) in dry pyridine (10 ml), and the mixture was kept for 15 min at room temperature; t.l.c. (ether–n-hexane) then showed that the reaction was essentially complete. The solution was poured into ice–water; the aqueous solution was extracted with chloroform (3 × 100 ml), and the combined extracts were washed with dilute hydrochloric acid, 3% sodium hydrogen carbonate solution, and water. The dried ($MgSO_4$) extracts were concentrated, and the crude material was chromatographed on silica gel (elution with ether) to give the syrupy 6-*benzoate* (4) (0·93 g, 60%), $[\alpha]_D$ −20 ± 1° (*c* 1 in $CHCl_3$), together with some dibenzoate (0·21 g, 20%) and unchanged starting material (0·12 g, 11%). The n.m.r. spectrum ($CDCl_3$) of the monobenzoate confirmed its general structure, and the i.r. spectrum exhibited bands at 3500 (OH) and 1730 cm^{-1} (benzoate).

6-O-*Benzoyl*-1,2-O-*isopropylidene*-3-O-*methyl*-5-O-*methylsulphonyl*-α-D-*galactofuranose* (5).—A cooled (0°) and stirred solution of the monobenzoate (4) (0·4 g) in dry pyridine (10 ml) was treated with a cold solution of methanesulphonyl chloride (0·36 ml, 0·55 g) in dry pyridine (10 ml) for 1 h at 0° and afterwards stored at room temperature for 3 h; t.l.c. [ether–n-hexane (2 : 1)] then indicated that the starting material had reacted completely. Water (2 ml) was added to the solution followed, after 30 min, by a further 10 ml of water. The solution was extracted with chloroform (3 × 100 ml), and the combined extracts were washed with dilute hydrochloric acid, 3% sodium hydrogen carbonate solution, and water. The dried ($MgSO_4$) extracts were evaporated, leaving a solid, which after two recrystallisations from ether–light petroleum (40—60°) gave the *methanesulphonate* (5) (0·45 g, 92%), m.p. 98—98·5°, $[\alpha]_D$ −18° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 1714, 1218, 715 (benzoate), and 1350 and 1168 cm^{-1} (sulphonic ester) (Found: C, 52·1; H, 5·9; S, 7·9. $C_{18}H_{24}O_9S$ requires C, 51·9; H, 5·8; S, 7·7%), τ ($CDCl_3$) *ca.* 2·50 (m, 5 aromatic protons), 4·24 (1H, d, $J_{1,2}$ 4 Hz, H-1), 6·63 (3H, s, OMe), 6·93 (3H, s, OMs), and 8·43 and 8·63 (each 3H, s, CMe_2).

It was found subsequently that purification of the benzoate (4) was unnecessary since methylsulphonylation of the mixture of esters gave the methanesulphonate (5) (*ca.* 56%) in crystalline form.

5,6-*Anhydro*-1,2-O-*isopropylidene*-3-O-*methyl*-β-L-*altrofuranose* (6).—A solution of compound (5) (1·14 g) in dry chloroform (5 ml) was cooled to *ca.* −25° and treated with a solution of sodium methoxide [from sodium (0·35 g)] in methanol (6 ml); after 1 h at room temperature, t.l.c. [ether–light petroleum (b.p. 40—60°) (2 : 1)] demonstrated that all the starting material had been converted into a single product. The mixture was neutralised with carbon dioxide and concentrated to dryness at room temperature. The residue was dissolved in chloroform (50 ml), insoluble material was filtered off, and the solution was dried ($MgSO_4$) and concentrated at room temperature. A solution of the syrupy residue in benzene was chromatographed on silica gel [elution with ether–light petroleum (b.p. 40—60°) (2 : 1)] to give the *epoxide* (6) (0·54 g, 92%), which on distillation had b.p. 100—105° (bath) at *ca.* 15 mmHg (water pump), $[\alpha]_D$ −19 ± 1° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ (film) 3050 (epoxide) and 1375 and 1385 cm^{-1} (isopropylidene) (Found: C, 55·7; H, 7·2. $C_{10}H_{16}O_5$ requires C, 55·55; H, 7·45%), τ (CCl_4) 4·30 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·58 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·68 (3H, s, OMe), and 8·51 and 8·71 (each 3H, s, CMe_2).

6-*Deoxy*-1,2-O-*isopropylidene*-3-O-*methyl*-β-L-*altrofuranose* (7).—A solution of the epoxide (6) (0·56 g) in dry ether (25 ml) was treated with lithium aluminium hydride (0·27 g) for 30 min at room temperature; t.l.c. [benzene–methanol (95 : 5)] then showed that all the starting material had reacted to form a single product. Ethyl acetate and water were added to decompose the excess of hydride, the solution was filtered, and the solids were washed thoroughly with ether. The combined filtrate and washings were dried ($MgSO_4$) and the solvents were removed at room temperature to give the *product* (0·53 g, 95%), b.p. 118—120° (bath) at *ca.* 15 mmHg (water pump), $[\alpha]_D$ −14 ± 2° (*c* 1 in $CHCl_3$), $\nu_{max.}$ (film) 3450 (OH) and 1375 cm^{-1} (isopropylidene) (Found: C, 55·1; H, 8·5. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%), τ (CCl_4) 4·30 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·55 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·64 (3H, s, OMe), 8·50 and 8·73 (each 3H, s, CMe_2), and 8·85 (3H, d, $J_{5,6}$ 6 Hz, HC*Me*).

6-*Deoxy*-3-O-*methyl*-L-*altrose* (L-*Vallarose*) (8).—A solution of the acetal (7) (0·4 g) in water (20 ml) containing sufficient ethanol to effect dissolution was stirred with Amberlite IR-120 (H^+) resin (*ca.* 3 g) for 4 h at room temperature; t.l.c. [benzene–methanol (95 : 5)] then showed that the hydrolysis was complete. The resin was filtered off and washed

[14] 'Chromatography,' E. Merck AG, Darmstadt, 2nd edn., p. 30.

thoroughly with acetone, and the combined filtrate and washings were concentrated. Distillation of the residue gave the free sugar as a thick syrup, b.p. 105—108° (bath) at 10^{-4} mmHg, which slowly crystallised during 6 days. Two recrystallisations from acetone–ether gave L-*vallarose* (0·29 g, 89%), m.p. 113—114°, $[\alpha]_D$ −22° (final *c* 1·1 in H_2O) (Found: C, 46·9; H, 7·7. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9%). Natural L-vallarose has [7] m.p. 106—110°, $[\alpha]_D$ −17·2° (final *c* 0·8 in H_2O), and the D-enantiomer has [6] m.p. 111—113°, $[\alpha]_D$ +22·3° (final *c* 0·6 in H_2O). The chromatographic properties of the latter sugar were indistinguishable from those of the synthetic product.

1,2,4-*Tri*-O-*acetyl*-6-*deoxy*-3-O-*methyl*-α-L-*altropyranose* (1,2,4-*Tri*-O-*acetyl*-α-L-*vallarose*) (9).—A solution of syrupy L-vallarose (0·2 g) in dry pyridine (2 ml) and acetic anhydride (0·5 ml) were set aside at room temperature for 2 h whereupon t.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1)] revealed that the starting material had been converted into a major product and a small proportion of another product. A few drops of water were then added and, after 30 min, the mixture was partitioned between water and chloroform; the organic layer was washed with dilute hydrochloric acid, 3% sodium hydrogen carbonate solution, and water. The dried ($MgSO_4$) extract was concentrated and the residue was chromatographed on silica gel [elution with ether–light petroleum (b.p. 40—60°) (1 : 2)] to give a *triacetate* (9) (0·24 g), which after recrystallisation from ether–light petroleum (b.p. 40—60°) had m.p. 112—113° (sintering) and 122—123° (completely), $[\alpha]_D$ −12 ± 1° (*c* 1 in $CHCl_3$) (Found: C, 51·55; H, 6·5. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·6%). The D-enantiomer has [6] m.p. 112—113° (sintering) and 121—122° (completely), $[\alpha]_D$ +14·8 ± 2° (*c* 1·96 in $CHCl_3$).

Synthesis of D-*Digitalose*

1,2-O-*Isopropylidene*-3-O-*methyl*-6-O-p-*tolylsulphonyl*-α-D-*galactofuranose* (10).—To a cooled (0°) and stirred solution of the monoacetal (3) (2 g) in dry pyridine (20 ml) was added toluene-*p*-sulphonyl chloride (1·8 g), and the solution was kept for 3 h at room temperature; t.l.c. [benzene–methanol (95 : 5)] then showed that one major product had been formed. Water (2 ml) was added and, after 20 min, the compound was partitioned between chloroform and water. The separated chloroform layer was washed with dilute hydrochloric acid, 3% sodium hydrogen carbonate solution, and water; the dried ($MgSO_4$) extracts were concentrated leaving a syrup. Chromatography on silica gel [elution with ether–light petroleum (b.p. 40—60°) (1 : 1)] gave the *tosylate* (10) (2·9 g, 87%), $[\alpha]_D$ −20 ± 2° (*c* 0·9 in $CHCl_3$), as a syrup which could not be induced to crystallise, τ (CCl_4) *ca.* 2·50 (m, 4 aromatic protons), 4·34 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·56 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·68 (3H, s, OMe), 7·60 (3H, s, ArMe), and 8·55 and 8·72 (each 3H, s, CMe_2).

5,6-*Anhydro*-1,2-O-*isopropylidene*-3-O-*methyl*-α-D-*galactofuranose* (11).—A solution of the sulphonate (10) (0·92 g) in dry chloroform (8 ml) was cooled to *ca.* −25° and treated with a solution of sodium methoxide [from sodium (*ca.* 0·22 g)] in dry methanol (4 ml). The solution was kept at room temperature for 2 h, after which t.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1)] revealed the formation of a single product. The solution was worked up as before and the resulting syrup was chromatographed on silica gel [elution with ether–light petroleum (b.p. 40—60°) (1 : 1)] to give the *epoxide* (11) (0·41 g, 80%), which on distillation had b.p. 118—120° (bath) at *ca.* 15 mmHg (water pump), $[\alpha]_D$ −30 ± 1° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ (film) 3050 (epoxide) and 1375 and 1385 cm^{-1} (isopropylidene) (Found: C, 55·8; H, 7·3. $C_{10}H_{16}O_5$ requires C, 55·55; H, 7·45%), τ (CCl_4) 4·40 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·60 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·68 (3H, s, OMe), and 8·56 and 8·72 (each 3H, s, CMe_2).

6-*Deoxy*-1,2-O-*isopropylidene*-3-O-*methyl*-α-D-*galactofuranose* (12).—A solution of the epoxide (11) (0·39 g) in dry ether (20 ml) was treated with lithium aluminium hydride (0·2 g) for 30 min at room temperature, whereafter t.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1)] indicated that the starting material had been converted into a single product. Ethyl acetate and water were added dropwise to decompose the excess of hydride, the solution was filtered, and solids were washed well with ether. The combined filtrate and washings were dried ($MgSO_4$) and concentrated at room temperature to give the *product* (0·34 g, 86%), b.p. 110—115° (bath) at *ca.* 15 mmHg (water pump), $[\alpha]_D$ −27·5° (*c* 0·8 in $CHCl_3$) (Found: C, 54·7; H, 8·3. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%), τ (CCl_4) 4·30 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·60 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·67 (3H, s, OMe), 8·52 and 8·71 (each 3H, s, CMe_2), and 8·85 (3H, d, $J_{5,6}$ 6 Hz, HC*Me*).

6-*Deoxy*-3-O-*methyl*-D-*galactose* (D-*Digitalose*) (13).—A solution of the acetal (12) (0·32 g) in water (15 ml) containing sufficient ethanol to effect dissolution was treated at room temperature for 2 h with Amberlite IR-120 (H^+) resin (*ca.* 2 g), during which time complete reaction occurred. The resin was filtered off and washed with acetone, and the combined filtrate and washings were concentrated to a thick syrup, which was distilled [b.p. 105—108° (bath) at 10^{-4} mmHg]. The syrup crystallised on seeding and on recrystallisation from ethyl acetate gave D-*digitalose* (0·21 g, 80%), m.p. 104—106·5°, $[\alpha]_D$ +109 ± 2° (final *c* 0·8 in H_2O) (Found: C, 47·0; H, 8·2. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9%). The m.p. of the synthetic sugar was not depressed on admixture with the natural sugar, which also had m.p. 104—106° {lit.,[11] m.p. 106°, $[\alpha]_D$ +106° (final *c* 1·7 in H_2O); lit.,[12] $[\alpha]_D$ +115·4 ± 2° (final *c* 2·75 in H_2O)}. The chromatographic properties of the synthetic sugar were indistinguishable from those of the natural sugar.

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