Branched-chain Sugars. Part III.[1] Synthesis of D-Nogalose (6-Deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-mannopyranose)

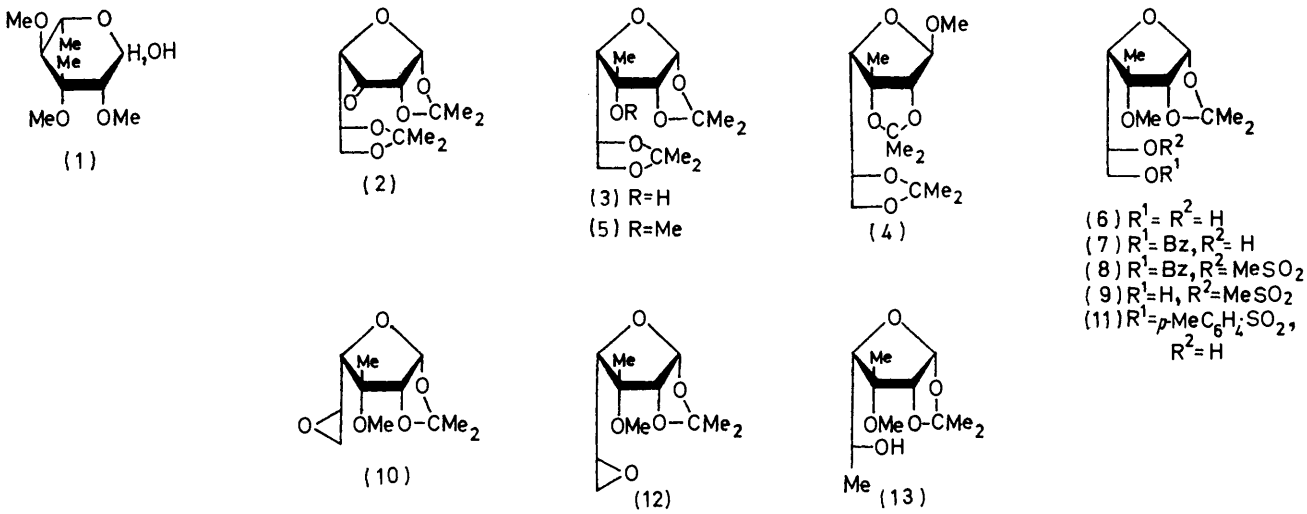
By **John S. Brimacombe** * and **Anthony J. Rollins**, Chemistry Department, The University, Dundee DD1 4HN

D-Nogalose [D-(1)], the enantiomer of a sugar component of the antibiotic nogalamycin, has been synthesized in seventeen steps from methyl α-D-glucopyranoside. The *C*-methyl substituent was introduced by addition of methylmagnesium iodide to 1,2:5,6-di-*O*-isopropylidene-β-D-*arabino*-hexofuranos-3-ulose (15). A related attempt to prepare L-nogalose (1) from 1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranos-3-ulose (2) was unsuccessful, since configurational inversion at C-5 could not be achieved at a later stage of the synthesis.

L-NOGALOSE [2] (1) is a neutral sugar obtained, *inter alia*, on mild acidic hydrolysis of nogalamycin,[3] an antibiotic highly active against gram-positive bacteria and KB cells *in vivo*. The gross structural features of nogalose were revealed by chemical and spectroscopic evidence,[2] but it remained for *X*-ray analysis of *N*-(*p*-bromobenzyl)nogalonamide to establish [4] the absolute configuration and structure.

The synthesis of nogalose requires stereospecific 3-*C*-methylation of a sugar to give a product with the L-*manno*-configuration. The advantages that accrue from approaching the synthesis of such branched-chain sugars by addition of Grignard reagents to 1,2:5,6-di-*O*-isopropylidenehexofuranos-3-uloses have already been noted by us, and have been demonstrated by a stereospecific synthesis of 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-allopyranose from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose.[5] We therefore attempted to synthesize L-nogalose (1) from 1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranos-3-ulose (2), but in the knowledge that the configuration at C-5 must be inverted at some stage in the synthesis.

Oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose [6] with a catalytic quantity of ruthenium tetraoxide in carbon tetrachloride gave the hexulose [7] (2), which furnished 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-gulofuranose (3) on treatment with methylmagnesium iodide in ether. The stereochemistry of the crystalline Grignard product is that expected [5] to result from the reagent's approach from the sterically favoured *exo*-direction with respect to the trioxabicyclo[3.3.0]-octane ring system, and was confirmed by treating compound (3) with acidified methanol–acetone for several days at room temperature; the major product isolated was methyl 2,3:5,6-di-*O*-isopropylidene-3-*C*-



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[5] J. S. Brimacombe, A. J. Rollins, and S. W. Thompson, *Carbohydrate Res.*, 1973, **31**, 108, and references cited therein.

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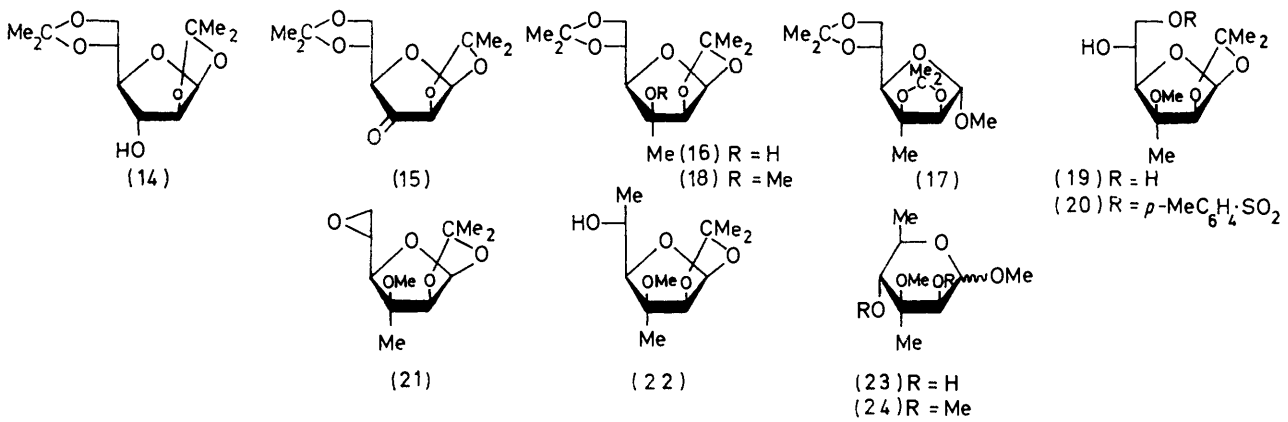
[7] K. N. Slessor and A. S. Tracey, *Canad. J. Chem.*, 1969, **47**, 3989.

methyl-β-D-gulofuranoside (4). The gross structural features of the glycoside (4) were clearly indicated by n.m.r. spectroscopy (see Experimental section), and the presence of a furanoid ring was revealed by a significant peak at *m/e* 101 ($C_5H_9O_2$) in the mass spectrum. This peak is characteristic [8] of 2,3:5,6- and 1,2:5,6-di-*O*-isopropylidenehexofuranoses and results from rupture of the C(4)–C(5) bond. The combined mass and n.m.r. spectral data point unequivocally to structure (4), which logically contains *cis*-disposed hydroxy-groups at C-2 and C-3.

The Grignard product (3) was next converted into the 3-*O*-methyl derivative (5), since it was found that methylation of the tertiary hydroxy-group facilitated acid-catalysed hydrolysis of the 5,6-*O*-isopropylidene group to give the diol (6); partial hydrolysis of compound (3) under similar conditions was complex and significant proportions of the free sugar appeared to be formed. The next stage in the synthesis was designed to effect the required inversion of configuration at C-5. Selective benzoylation of the primary hydroxy-group of the diol (6) afforded the 6-benzoate (7), which was sulphonylated to give 6-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-3-*O*-methyl-5-*O*-methylsulphonyl-α-D-gulofuranose (8). Unfortunately, all attempts to convert compound (8) into the L-*manno*-epoxide (10) by treatment with base met with failure, although the intermediate alcohol (9), resulting from debenzoylation, could be detected by t.l.c. early on in the reaction. However, the solution slowly turned a rich red colour and t.l.c. failed to reveal a product of mobility corresponding to that expected for the epoxide (10). We have previously encountered [9] a similar problem in attempting a related intramolecular displacement on the unbranched analogue series (see ref. 10, for example). By contrast, no difficulty was experienced in converting the primary sulphonate (11), prepared by selective tosylation of the diol (6), into the isomeric D-*gulo*-epoxide (12) with methanolic sodium methoxide. Regiospecific opening of the epoxide (12) with lithium aluminium hydride gave 6-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-3-*O*-methyl-α-D-gulofuranose (13).

We next sought to synthesize D-nogalose [D-(1)], bearing in mind the difficulties encountered in the attempted synthesis of the natural L-sugar. This synthesis has acquired an added significance with the recent discovery of the de-*O*-methylated analogue, D-evalose (6-deoxy-3-*C*-methyl-D-mannose), as a sugar component of the antibiotic everninomicin B.[11] In view of the configurational identity of these sugars, it might be possible to adapt the synthetic route to D-nogalose to yield D-evalose. The logical progenitor for a synthesis of D-nogalose is 1,2:5,6-di-*O*-isopropylidene-β-D-*arabino*-hexofuranos-3-ulose (15), which already possesses the required configuration at C-5. The hexulose (15) can be prepared [12] by oxidation of 1,2:5,6-di-*O*-isopropylidene-β-D-altrofuranose [13] (14) with acetic anhydride–dimethyl sulphoxide. Although the preparation [13,14] of the diacetal (14) from methyl α-D-glucopyranoside is lengthy (seven steps), this disadvantage is offset by the high stereoselectivity obtained in the Grignard reaction on the hexulose (15). Addition of methylmagnesium iodide to (15) gave 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-β-D-mannofuranose (16), whose structure was confirmed by its conversion into methyl 2,3:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-mannofuranoside (17) with acidified methanol–acetone; the structure assigned to compound (17) was based (as before) on n.m.r. and



of (8), although, in this case, *ca.* 20% of the epoxide was obtained. Thus, it seems desirable in future to avoid the epoxide route for effecting configurational inversions at C-5 if viable alternatives are available, although the difficulties encountered may be peculiar to the *gulo*-mass spectral data (see Experimental section). The sequence (16) ⟶ (18) ⟶ (19) ⟶ (20) was accomplished next, by methylation of the tertiary hydroxy-group, partial hydrolysis with aqueous acetic acid, and

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[14] N. K. Richtmyer, *Methods Carbohydrate Chem.*, 1962, **1**, 107.

selective sulphonylation of the primary hydroxy-group of the resulting diol. The primary sulphonate (20) was smoothly converted into the D-*manno*-epoxide (21) on brief treatment with methanolic sodium methoxide at *ca.* −25 °C. Reductive opening of the epoxide (21) with lithium aluminium hydride then furnished 6-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-3-*O*-methyl-β-D-mannofuranose (22), which on sequential acid-catalysed methanolysis and methylation yielded a mixture of products presumed to contain mainly methyl 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-αβ-D-mannopyranoside (24). Finally, acidic hydrolysis of the αβ-glycoside mixture (24) gave, after chromatography, crystalline 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-mannopyranose (D-nogalose) [D-(1)], identified by comparison (t.l.c., i.r. spectroscopy, and *X*-ray powder photograph) with authentic samples of D-[11] and L-nogalose.[2]

The foregoing route to D-nogalose should be capable of adaptation to yield D-evalose[11] (*i.e.* de-*O*-methylated D-nogalose) either by demethylation of the αβ-glycoside mixture (23) or, preferably, by protection of the tertiary hydroxy-group of the branched-chain derivative (16) with a group (*e.g.* benzyloxy) that can be easily removed at a later stage of the synthesis.

EXPERIMENTAL

T.l.c. was performed on Kieselgel G; spots were located with vanillin–sulphuric acid.[15] I.r. spectra were recorded for Nujol mulls on a Perkin-Elmer Infracord spectrophotometer, and n.m.r. spectra were measured with a Perkin-Elmer R-10 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal reference. Optical rotations were measured at ambient temperature with a Perkin-Elmer 141 automatic polarimeter. Light petroleum refers to the fraction having b.p. 40—60°.

Attempted Synthesis of L-*Nogalose*

1,2:5,6-*Di*-O-*isopropylidene*-α-D-xylo-*hexofuranos*-3-*ulose* (2).—The following procedure was the most effective for relatively large-scale oxidations. To a vigorously stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose[6] (24 g) in methylene chloride (110 ml) were added water (100 ml), sodium periodate (17 g), potassium carbonate (1·8 g), and ruthenium dioxide (0·2 g). The mixture was stirred vigorously for 12 h; t.l.c. (light petroleum–ethyl acetate, 4 : 1) then revealed that some starting material still remained. More sodium periodate (17 g) and potassium carbonate (1·8 g) were added, and stirring was continued until t.l.c. showed that the oxidation was complete. Propan-2-ol (20 ml) was then added and the solution was stirred for 30 min and filtered through Celite. The separated aqueous layer was extracted with methylene chloride (3 × 50 ml) and the organic extracts were combined, dried, and concentrated to give the ketone (2) (16·3 g), m.p. 74·5—76° (from ether–light petroleum), $[\alpha]_D$ −57 ± 1° (*c* 1 in H_2O), $\nu_{max.}$ 1730 cm^{-1} (C=O) {lit.,[7] m.p. 76—77°, $[\alpha]_D$ −58·5° (*c* 0·4 in H_2O)}.

1,2:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-α-D-*gulofuranose* (3).—To a stirred solution of methylmagnesium iodide [from magnesium (3 g) and methyl iodide (16 ml)] in ether (75 ml) was gradually added a solution of the ketone (2) (12·7 g) in ether (125 ml). The solution was heated under reflux for 3 h, after which the excess of Grignard reagent was destroyed by gradual addition of water. The separated ether layer was dried ($MgSO_4$) and concentrated to give the *branched-chain sugar* (3) (8·3 g), m.p. 160—161·5° (from ether–light petroleum), $[\alpha]_D$ −27·5° (*c* 0·8 in $CHCl_3$), $\nu_{max.}$ 3500 cm^{-1} (OH) (Found: C, 56·65; H, 8·05. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·0%); τ 4·12 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·75 (1H, d, $J_{2,1}$ 4 Hz, H-2), and 8·36, 8·55, and 8·62 [15H, each s, intensity ratio 1 : 1 : 3, C(3)Me and 2 × CMe_2].

Methyl 2,3:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-β-D-*gulofuranoside* (4).—To a solution of the diacetal (3) (0·2 g) in dry acetone (4 ml) was added a solution of acetyl chloride (0·3 ml) in methyl acetate (5 ml) and methanol (5 ml). The solution was set aside for several days at room temperature until t.l.c. (ether) showed that all the starting material had reacted. Chromatography on silica gel (elution with ether) gave the *methyl gulofuranoside* (4) (86 mg), b.p. 75—80° (bath) at 0·1 mmHg, $[\alpha]_D$ −53° (*c* 1·2 in $CHCl_3$); τ 5·05 (1H, s, H-1 of β-anomer), 5·80 (1H, s, H-2), 6·60 (3H, s, OMe), and 8·50, 8·55, and 8·65 [15H, each s, intensity ratio 1 : 3 : 1, C(3)Me and 2 × CMe_2], *m/e* 273 (M^+ − 15; highest mass peak) and 101 [$C_5H_9O_2$; C(4)–C(5) cleavage[8]] (Found: *m/e*, 273·1335. $C_{13}H_{21}O_6$ requires 273·1338).

1,2:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-α-D-*gulofuranose* (5).—To a cooled (0°) and stirred solution of the branched-chain sugar (3) (4·8 g) in *NN*-dimethylformamide (200 ml) containing sodium hydride (2·4 g) was gradually added methyl iodide (9·5 ml). The mixture was stirred at room temperature for 90 min, then methanol was added to remove the excess of reagents; solvents were removed and the residue was extracted with chloroform (250 ml). The extract was filtered and concentrated to give an almost quantitative yield of the *methyl ether* (5), m.p. 114—114·5° (from ether–light petroleum), $[\alpha]_D$ +5 ± 1° (*c* 1·2 in $CHCl_3$) (Found: C, 58·25; H, 8·3. $C_{14}H_{24}O_6$ requires C, 58·3; H, 8·3%); τ 4·25 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·72 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·67 (3H, s, OMe), and 8·37, 8·57, and 8·65 [15H, each s, intensity ratio 1 : 1 : 3, C(3)Me and 2 × CMe_2].

1,2-O-*Isopropylidene*-3-C-*methyl*-3-O-*methyl*-α-D-*gulofuranose* (6).—A solution of the diacetal (5) (2·2 g) in 70% acetic acid (70 ml) was stored at room temperature for 8 h, during which time complete removal of one isopropylidene group occurred. The solvents were removed and the resulting syrup was chromatographed on silica gel (elution with light petroleum–acetone, 3 : 1) to afford the *diol* (6) (1·3 g), $[\alpha]_D$ +18° (*c* 1·6 in $CHCl_3$), as a syrup; τ 4·12 (1H, d, $J_{1,2}$ 4 Hz, H-1), 5·60 (1H, d, $J_{2,1}$ 4 Hz, H-2), 6·59 (3H, s, OMe), and 8·36, 8·61, and 8·65 [9H, each s, C(3)Me and CMe_2].

6-O-*Benzoyl*-1,2-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-5-O-*methylsulphonyl*-α-D-*gulofuranose* (8).—A cooled (*ca.* 0°) solution of benzoyl chloride (0·4 g) in dry pyridine (5 ml) was added to a cooled and stirred solution of the diol (6) (0·65 g) in dry pyridine (7 ml). The solution was stirred at 0° for 1 h and then at room temperature overnight, and heated at 60—70° for 1 h to ensure complete reaction. The cooled solution was poured onto cracked ice and the products were extracted with chloroform in the usual way. Chromatography on silica gel (elution with light petroleum–acetone, 3 : 1) gave, *inter alia*, the monobenzoate (7) (0·39 g), $\nu_{max.}$ (film) 1730 cm^{-1} (OBz), as a syrup.

The monobenzoate (7) (0·39 g) in dry pyridine (10 ml)

[15] E. Merck A.G., 'Chromatography,' Darmstadt, 2nd edn. p. 30.

was treated with methanesulphonyl chloride (0·35 ml) in dry pyridine (10 ml) in the usual way to give the *diester* (8) (0·35 g), m.p. 116—116·5° (from chloroform–light petroleum), $[\alpha]_D$ −10° (*c* 1 in $CHCl_3$) (Found: C, 52·7; H, 6·1; S, 7·6. $C_{19}H_{26}O_9S$ requires C, 53·0; H, 6·0; S, 7·4%); τ 2·20 (5H, m, aromatic), 4·12 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·56 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·61 (3H, s, OMe), 6·78 (3H, s, OSO_2Me), and 8·27, 8·60, and 8·63 [9H, each s, C(3)Me and CMe_2].

Attempted Preparation of 5,6-*Anhydro*-1,2-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-β-L-*mannofuranose* (10).—To a cooled (−25°) solution of the 6-*O*-benzoyl-5-*O*-methylsulphonyl derivative (8) (0·26 g) in chloroform (1 ml) was added methanolic M-sodium methoxide (1·4 ml); after 30 min t.l.c. (ethyl acetate–light petroleum, 1 : 2) showed the formation of a single, slower-moving product presumed to be 1,2-*O*-isopropylidene-3-*C*-methyl-3-*O*-methyl-5-*O*-methylsulphonyl-α-D-gulofuranose (9), τ 4·14 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·59 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·60 (3H, s, OMe), 6·81 (3H, s, OSO_2Me), 8·31 [3H, s, C(3)Me], and 8·57 and 8·66 (6H, each s, CMe_2). However, the solution slowly turned a rich red colour, but t.l.c. revealed that no faster-moving component, of mobility corresponding to that expected for the desired epoxide (10) (*cf.* refs. 9 and 10), was formed. Work-up as previously described gave an intractable mixture of products that exhibited little mobility on thin-layer chromatograms.

5,6-*Anhydro*-1,2-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-α-D-*gulofuranose* (12).—A cold solution of toluene-*p*-sulphonyl chloride (0·62 g) in dry pyridine (8 ml) was added to a stirred and cooled (0°) solution of the diol (6) (0·62 g) in dry pyridine (8 ml) and the solution was set aside for 8 h at room temperature; t.l.c. (light petroleum–ethyl acetate, 2 : 1) then showed that most of the starting material had reacted. Work-up in the usual way gave the 6-sulphonate (11) (*ca.* 1 g) as a syrup that was used in the next step without further purification; τ 2·30 (4H, m, aromatic), 4·17 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·68 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·68 (3H, s, OMe), 7·54 (3H, s, ArMe), and 8·43 and 8·67 [9H, each s, intensity ratio 1 : 2, C(3)Me and CMe_2].

To a cooled (−25°) solution of the 6-sulphonate (11) (0·92 g) in dry chloroform (3·2 ml) was added methanolic M-sodium methoxide (3·2 ml), and, after 45 min, solid carbon dioxide was added to neutralize the base and the solvent was removed. The residue was extracted with ether; the extract was filtered and chromatographed on silica gel (elution with light petroleum–ethyl acetate, 2 : 1) to give the *anhydro-sugar* (12) (0·21 g) after sublimation (45° and 0·1 mmHg), m.p. 59—60° (from light petroleum), $[\alpha]_D$ +9° (*c* 0·6 in $CHCl_3$) (Found: C, 57·2; H, 7·9. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·8%); τ 4·15 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·62 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·59 (3H, s, OMe), and 8·34 and 8·62 [9H, each s, intensity ratio 1 : 2, C(3)Me and CMe_2].

6-*Deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-α-D-*gulofuranose* (13).—Lithium aluminium hydride (75 mg) was added in portions to a stirred solution of the anhydro-sugar (12) (0·16 g) in dry ether (3 ml) and, after 30 min, more ether (10 ml) was added, followed by a few drops of water to destroy the excess of hydride. The ethereal layer was dried ($MgSO_4$) and concentrated. Distillation of the oily residue gave the *6-deoxy-sugar* (13) (0·12 g), b.p. 55—60° (bath) at 0·1 mmHg, $[\alpha]_D$ +18° (*c* 1 in $CHCl_3$) (Found: C, 57·1; H, 8·9. $C_{11}H_{20}O_5$ requires C, 56·9; H, 8·6%); τ 4·19 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·65 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·61 (3H, s, OMe), 8·37, 8·63, and 8·66 [9H, each s, C(3)Me and CMe_2], and 8·81 (3H, d, $J_{5.6}$ 6 Hz, HC*Me*).

Synthesis of D-*Nogalose*

1,2:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-β-D-*mannofuranose* (16).—To a stirred solution of methylmagnesium iodide [from magnesium (0·5 g) and methyl iodide (2·2 ml)] in ether (11 ml) was gradually added a solution of the ketone (15) [12] (1·8 g) in ether (20 ml). The mixture was heated under reflux for 3 h, then processed as described for the isomeric compound to give the *C-methyl derivative* (16) (0·95 g), m.p. 82·5—83° (from ether–light petroleum), $[\alpha]_D$ +22° (*c* 0·7 in $CHCl_3$), $\nu_{max.}$ 3400 cm^{-1} (OH) (Found: C, 56·7; H, 8·2%); τ 4·30 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·72 (1H, d, $J_{2.1}$ 4 Hz, H-2), and 8·40 and 8·60 [15H, each s, intensity ratio 1 : 4, C(3)Me and 2 × CMe_2].

Methyl 2,3:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-α-D-*mannofuranoside* (17).—The *C*-methyl compound (16) (0·2 g) in acetone (4 ml) was treated with acetyl chloride (0·3 ml) and methyl acetate (5 ml) in methanol (5 ml) for 4 days at room temperature, during which time t.l.c. (ether) revealed the formation of one main product. The mixture was processed as before and the product was isolated by chromatography on silica gel (elution with ether) and characterized as the *methyl mannofuranoside* (17) (90 mg), b.p. 82—85° (bath) at 0·1 mmHg, $[\alpha]_D$ +115° (*c* 0·6 in $CHCl_3$); τ 5·10 (1H, s, H-1 of α-anomer), 5·72 [1H, s (overlapped by t), H-2], 6·63 (3H, s, OMe), and 8·41 and 8·55 [15H, each s, intensity ratio 1 : 4, C(3)Me and 2 × CMe_2]; *m/e* 273 (M^+ − 15; highest mass peak) and 101 [$C_5H_9O_2$; C(4)–C(5) cleavage [8]] (Found: *m/e* 273·1345. $C_{13}H_{21}O_6$ requires 273·1338).

1,2:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-β-D-*mannofuranose* (18).—Sodium hydride (0·42 g) was gradually added to a cooled (0°) and stirred solution of the branched-chain sugar (16) (0·85 g) in *NN*-dimethylformamide (33 ml); methyl iodide (1·7 ml) was then added in portions. After 1 h, the mixture was processed essentially as described earlier. Distillation gave the *methylated compound* (18) (0·7 g), b.p. 70—75° (bath) at 0·1 mmHg, $[\alpha]_D$ +16° (*c* 1·5 in $CHCl_3$) (Found: C, 58·2; H, 8·5%); τ 4·30 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·69 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·54 (3H, s, OMe), and 8·42, 8·60, and 8·68 [15H, each s, intensity ratio 1 : 3 : 1, C(3)Me and 2 × CMe_2].

1,2-O-*Isopropylidene*-3-C-*methyl*-3-O-*methyl*-6-O-p-*tolylsulphonyl*-β-D-*mannofuranose* (20).—A solution of the methylated diacetal (18) (0·56 g) in 70% acetic acid (18 ml) was set aside overnight at room temperature, then concentrated with occasional additions of toluene. The diol (19) (*ca.* 0·5 g), $\nu_{max.}$ (film) 3400br cm^{-1} (OH), was obtained as a syrup that was used in the next step without further purification; τ 4·21 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·66 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·53 (3H, s, OMe), and 8·40, 8·60, and 8·68 [9H, each s, C(3)Me and CMe_2].

A solution of toluene-*p*-sulphonyl chloride (0·48 g) in pyridine (5 ml) was added to the diol (19) (0·5 g) in pyridine (7 ml) and the reaction was allowed to proceed overnight at room temperature. The syrupy *tosylate* (20) (0·79 g), $[\alpha]_D$ +19° (*c* 0·8 in $CHCl_3$), was isolated in the usual way; τ 2·30 (4H, m, aromatic), 4·26 (1H, d, $J_{1.2}$ 4 Hz, H-1), 6·56 (3H, s, OMe), 7·46 (3H, s, ArMe), and 8·54, 8·66, and 8·73 [9H, each s, C(3)Me and CMe_2].

5,6-*Anhydro*-1,2-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-β-D-*mannofuranose* (21).—The sulphonate (20) (0·95 g) in dry chloroform (5 ml) at −25° was treated with cold

methanolic M-sodium methoxide (5 ml) for 15 min; t.l.c. (light petroleum–acetone, 3 : 1) then showed that the reaction was complete. Work-up as previously described gave an oil that was distilled to give the *anhydro-sugar* (21) (0·38 g), b.p. 100—105° (bath) at 4 mmHg, $[\alpha]_D$ +31° (*c* 1 in $CHCl_3$) (Found: C, 57·5; H, 8·0%); τ 4·16 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·60 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·49 (3H, s, OMe), and 8·38, 8·60, and 8·65 [9H, each s, C(3)Me and CMe_2].

6-*Deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-3-O-*methyl*-β-D-*mannofuranose* (22).—To a solution of the anhydro-sugar (21) (0·23 g) in dry ether (10 ml) was added lithium aluminium hydride (0·5 g) and, after 20 min, ether (10 ml) was added followed by wet ethyl acetate to decompose the excess of hydride. Solids were filtered off and the filtrate was dried ($MgSO_4$) and concentrated. Recrystallization of the solid residue from light petroleum gave the 6-*deoxy-compound* (22) (0·16 g), m.p. 76—76·5°, $[\alpha]_D$ −19° (*c* 0·8 in $CHCl_3$) (Found: C, 56·6; H, 8·9%); τ 4·22 (1H, d, $J_{1.2}$ 4 Hz, H-1), 5·69 (1H, d, $J_{2.1}$ 4 Hz, H-2), 6·55 (3H, s, OMe), 8·43, 8·62, and 8·70 [9H, each s, C(3)Me and CMe_2], and 8·83 (3H, d, $J_{5.6}$ 6 Hz, HC*Me*).

Methyl 6-*Deoxy*-3-C-*methyl*-2,3,4-*tri*-O-*methyl*-αβ-D-*manno-pyranoside* (24).—Methanolysis of the acetal (22) (0·17 g) was accomplished in refluxing 2·5% methanolic hydrogen chloride (15 ml) during 15 min. The solution was neutralized ($PbCO_3$) and filtered, and the filtrate was concentrated to furnish a syrupy mixture of glycosides (23) (0·11 g).

Sodium hydride (0·13 g) was added in portions to a cooled (0°) and stirred solution of the glycosides (23) (0·11 g) in *NN*-dimethylformamide (8 ml), whereafter methyl iodide (0·7 ml) was carefully added and the mixture was stored for 1 h at room temperature. Methanol was then added to decompose the excess of reagents and the solution was concentrated. The residue was extracted with chloroform (15 ml) and the extract was filtered, washed with water, and dried ($MgSO_4$). Removal of the solvent left a syrupy αβ-mixture of the methylated glycosides (24) (90 mg). Integration of the n.m.r. spectrum gave the ratio of *O*- to *C*-methyl groups as 2 : 1.

6-*Deoxy*-3-C-*methyl*-2,3,4-*tri*-O-*methyl*-D-*mannopyranose* (D-*Nogalose*) [D-(1)].—The foregoing mixture of glycosides (24) (90 mg) in ethanol (0·6 ml) and M-sulphuric acid (0·18 ml) was heated for 2 h on a boiling water-bath, during which time complete hydrolysis occurred. The hydrolysate was neutralized ($BaCO_3$), and the filtered solution was concentrated to a syrupy residue. Chromatography on silica gel (elution with light petroleum–acetone, 3 : 1), to remove impurities, gave crystalline D-*nogalose* [D-(1)] (20 mg), m.p. 115—120° (from ethyl acetate), $[\alpha]_D$ +16° ⟶ +3° (24 h, equilib., *c* 0·3 in MeOH) (Found: C, 54·5; H, 9·1. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·15%) {lit.,[11] m.p. 115—120°, $[\alpha]_D$ +18·3° ⟶ +6·3° (24 h, MeOH); natural L-enantiomer,[2] m.p. 115—121°, $[\alpha]_D$ −10·6° (MeOH)}. The synthetic material was indistinguishable from authentic D-nogalose (t.l.c. and *X*-ray powder photograph) and from a sample of the natural L-sugar [i.r. spectra (KBr)]. The downward mutarotation implies that the crystalline D-sugar possesses the α-configuration.

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