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Note

Synthesis of L-nogalose

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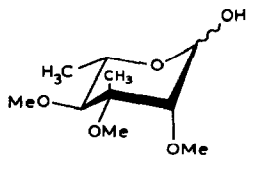
L-Nogalose[1] **1** is the carbohydrate component of nogalamycin[2], an anthracycline antibiotic that is active against Gram-positive bacteria and KB cells *in vivo*. In the two reported syntheses of **1**, the branching methyl group was introduced by: (*1*) the addition[3] of methylmagnesium iodide to hexos-3-ulose **2**, and (*2*) reductive ring-opening of *spiro*-epoxide **3**, which was obtained from the corresponding aldos-3-ulose by a Wittig reaction and oxidation of the resulting alkene[4].



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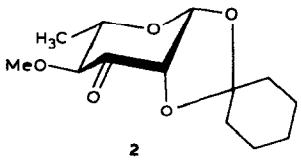

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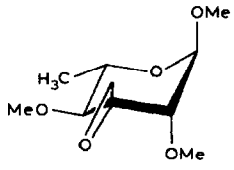

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These approaches gave the desired compound; however, the high degree of stereoselectivity that is often observed in nucleophilic additions to six-membered ketoses was not realized and, in both cases, intermediates epimeric at C-3 were produced as well. We considered that introduction of the methyl branch in **1** with high stereoselectivity could be achieved *via* addition of a Grignard reagent to a suitable ketose in its furanose form. In our studies of synthesis of branched-chain sugars, we have observed that **5**, a new ketose that we have synthesized from L-rhamnose, undergoes exclusive addition of methylmagnesium iodide from the less-hindered, β-face, giving the branched furanoside **6**. Compound **6** is a suitable precursor to nogalose, vinelose[5], sibirosamine[6], and kansosamine[7], all naturally occurring L sugars in which the configurations at C-2 and C-3 match those of **6**. The preparation of **6**, and its conversion into L-nogalose, are described herein.

Methyl 2,5-di-*O*-benzyl-6-deoxy-α-L-mannofuranoside (**4**) was prepared by the method of Kochetkov *et al.*[8], with modification. Oxidation of **4** proved troublesome, and was best conducted with Me_2SO–TFAA (Swern conditions), giving hexosid-3-ulose **5** in 95% crude yield. The 200-MHz, ^{1}H-n.m.r. spectrum of **5** indicated that a single isomer was present; however, when **5** was subjected to

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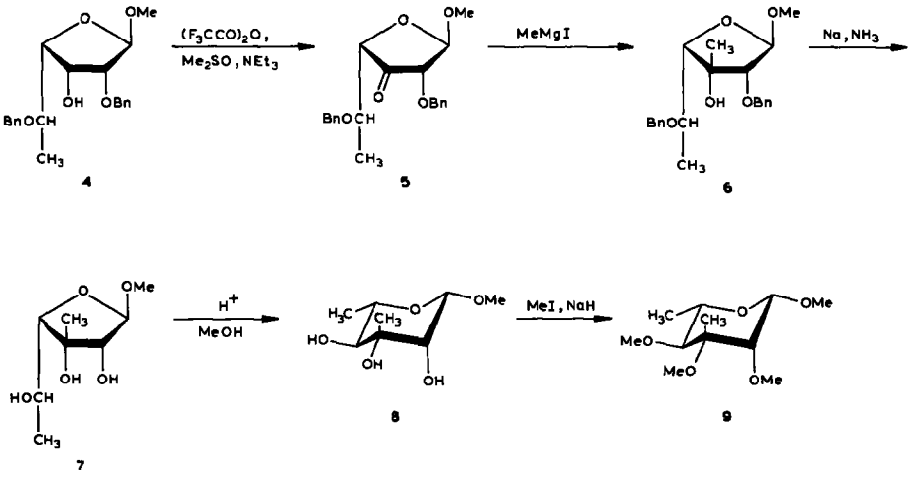
chromatography on a column of silica gel, a mixture of products in which **5** was the major component was isolated. It seems likely that the *syn*-1,3-nonbonded interaction between substituents at C-2 and C-4 renders **5** highly sensitive toward epimerization; thus, it was necessary to use in the subsequent step material isolated from the oxidation without further purification. The reaction of **5** with methylmagnesium iodide in ether gave a single alcohol whose stereochemistry at C-3 was assumed to be that depicted in **6**, which would result from attack of the nucleophile from the less-hindered face. The stereochemical outcome of the Grignard reaction was ultimately confirmed by the transformation of **6** into L-nogalose.



Debenzylation of **6** was attempted with a variety of catalytic procedures, but the hydrogenolysis desired could not be satisfactorily achieved. Treatment of **6** with sodium in liquid ammonia was successful, and afforded triol **7** in 82% yield. On refluxing in methanol with Dowex-50 ion-exchange resin **7** was converted into methyl β-L-evalopyranoside (**8**). The ^{13}C-n.m.r. spectrum of **8** was identical with that reported[9] by Ollis and co-workers for a methyl D-evalopyranoside (anomeric configuration unspecified) obtained from the antibiotic flambamycin. The physical constants (m.p., optical rotation, and ^{1}H-n.m.r. spectrum) of **8** do not match those reported for methyl α-D-evalopyranoside[10]; therefore, the compound reported by Ollis must be the β-D anomer. The conversion of **7** into **8** did not proceed to completion. It has been suggested that the axial substituent on C-3 in similar branched-chain carbohydrates, such as evermicose, increases the free energy of the pyranose form, and results in a higher equilibrium proportion of the furanose[11]. In the conversion of **7** into **8**, unreacted **7** was separated from **8** by flash chromatography, and recycled. Methylation of **8** with methyl iodide and sodium hydride in Me_2SO gave **9**, which was hydrolyzed to L-nogalose by treatment with M sulfuric acid. The ^{13}C-n.m.r. spectrum of the product revealed a major (α) and a minor (β) anomer, and was identical with that reported[12].

EXPERIMENTAL

General procedures. — Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Flash chromatography was performed on silica gel 60 (230–400 mesh). Infrared spectra were recorded with a Perkin–Elmer 299 infrared spectrometer. ^{1}H-N.m.r. spectra were recorded at 90 MHz with a Perkin–Elmer R-32, and at 200 MHz with a Varian XL-200 spectrometer. ^{13}C-N.m.r. spectra were recorded at 50.3 MHz. Chemical shifts are given relative to tetramethylsilane (δ 0.0).

Methyl 2,5-di-O-benzyl-6-deoxy-α-L-mannofuranoside (**4**). — Sodium hydride (12.7 g of a 50% dispersion in oil, 0.26 mol) was washed with dry hexane under nitrogen in a round-bottomed flask equipped with a magnetic stirrer. The washings were removed by means of a pipet, and tetrahydrofuran (THF; 50 mL) was added, followed by dropwise addition, with stirring, of a solution of 3,4-*O*-isopropylidene-L-rhamnose diethyl dithioacetal (34.4 g, 124 mmol) in THF (150 mL). The mixture was stirred for 40 min after the addition was complete, and tetrabutylammonium iodide (1.0 g) was added, followed by a solution of benzyl bromide (41.4 g, 0.24 mol) in THF (100 mL). The mixture was stirred for 20 h at room temperature, and then partitioned between ether and water. The ether phase was successively washed with aqueous sodium hydroxide solution and water, dried (sodium sulfate), and evaporated, to give 51.7 g of syrupy 2,5-di-*O*-benzyl-3,4-*O*-isopropylidene-L-rhamnose diethyl dithioacetal, which, without purification, was converted into **4** in two steps as follows. Desulfurization was conducted, as described by Kochetkov *et al.*[8], on 7.46 g (16.3 mmol) of the product, and gave 5.78 g (73%) of aldehyde, which was dissolved in 0.3M methanolic HCl and the solution stirred in a stoppered flask for 16 h at room temperature. The acid was neutralized with lead carbonate, the suspension filtered, and the filtrate evaporated, to give 4.76 g (88%) of syrupy **4**. An analytical sample was prepared by flash chromatography with 1:1 ethyl acetate–petroleum ether. Compound **4** had $[\alpha]_D^{20}$ −37.1° (*c* 1, MeOH); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.34 (bs, 10 H, 2 Ph), 4.97 (d, 1 H, H-1, $J_{1,2}$ 5.0 Hz), 4.64 (bs, 4 H, 2 PhCH_2), 4.37 (m, 1 H), 3.92 (m, 3 H), 3.36 (s, 3 H, OCH_3), 2.80 (bs, 1 H), and 1.32 (d, 3 H, H-6, $J_{5,6}$ 6.0 Hz).

Anal. Calc. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.21; H, 7.46.

Methyl 2,5-di-O-benzyl-6-deoxy-α-L-mannofuranosid-3-ulose (**5**). — To a solution of dry dimethyl sulfoxide (1.9 mL, 26.8 mmol) in dry dichloromethane (26 mL) in a 3-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel, a low-temperature thermometer, and a Firestone valve was added, dropwise under nitrogen, a solution of trifluoroacetic anhydride (TFAA) (2.82 mL, 20 mmol) in dichloromethane (6.7 mL). The mixture was stirred for 10 min after addition of the TFAA was complete, and then a solution of **4** (4.76 g, 13.3 mmol) in dichloromethane (40 mL) was added dropwise while the temperature was main-

tained below −65°. After stirring for 30 min, triethylamine (5.32 mL, 13.6 mmol) was added carefully (temperature again kept below −65°) and then the mixture was allowed to warm to room temperature, washed with water, dried ($MgSO_4$), and evaporated, to give 4.51 g (95%) of syrupy hexosid-3-ulose **5**, which was used without purification. An analytical sample was prepared by flash chromatography with 1:4 ethyl acetate–petroleum ether. Compound **5** had $[\alpha]_D^{20}$ −134° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1764 cm^{-1} (C=O); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 7.33 (bs, 10 H, 2 Ph), 5.15 (bs, 1 H, H-1), 4.65 (m, 4 H, 2 PhCH_2), 4.22 (d, 1 H, H-4, $J_{4,5}$ 3.6 Hz), 3.90 (m, 1 H, H-5), 3.63 (bs, 1 H, H-2), 3.42 (s, 3 H, OCH_3), and 1.29 (d, 3 H, 3 H-6, $J_{5,6}$ 6.3 Hz).

Anal. Calc. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.97; H, 6.90.

*Methyl 2,5-di-*O*-benzyl-6-deoxy-3-*C*-methyl-α-*L*-mannofuranoside* (**6**). — Methylmagnesium iodide was prepared from magnesium turnings (1.50 g, 62.5 mmol) and methyl iodide (3.94 mL, 63 mmol) in ether (26 mL). A solution of **5** (4.51 g, 12.7 mmol) in ether (26 mL) was added dropwise with stirring, and the mixture was stirred for 40 min at room temperature. Aqueous ammonium chloride solution was added dropwise, the mixture was transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted with ether, and the ether extracts were combined, dried (magnesium sulfate), and evaporated, to give syrupy **6** (4.2 g, 89%). An analytical sample was purified by flash chromatography with 1:4 ethyl acetate–petroleum ether. Compound **6** had $[\alpha]_D^{20}$ −14° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3535 cm^{-1} (OH); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 7.37 (bs, 10 H, 2 Ph), 4.92 (d, 1 H, H-1, $J_{1,2}$ 4.0 Hz), 4.72 (ABq, 2 H, PhCH_2), 4.62 (ABq, 2 H, PhCH_2), 3.98 (m, 1 H, H-5), 3.70 (d, 1 H, H-4, $J_{4,5}$ 8 Hz), 3.63 (d, 1 H, H-2), 3.36 (s, 3 H, OCH_3), 2.68 (bs, 1 H, O*H*), 1.38 (s, 3 H, CH_3-3), and 1.30 (d, 3 H, 3 H-6, $J_{5,6}$ 8 Hz); ^{13}C-n.m.r. (50.3 MHz, $CDCl_3$): δ 128.6, 128.4, 128.2, 128.2, 128.0, 127.9, 127.6, 127.0, 106.6, 89.1, 85.8, 73.8, 73.2, 71.3, 55.2, 24.8, 24.8, and 17.1.

*Anal.*Calc. for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 70.70; H, 7.51.

*Methyl 6-deoxy-3-*C*-methyl-α-*L*-mannofuranoside* (**7**). — A 3-necked, round-bottomed flask equipped with a Dry Ice condenser and a nitrogen inlet was charged with freshly cut sodium (0.19 g, 7.8 mmol), and a solution of **6** (0.38 g, 1.0 mmol) in THF (2 mL), at −78°, was added. Ammonia (~6 mL) was added, and the mixture was stirred for 30 min. Ammonium chloride was added, and the mixture was warmed to room temperature, whereupon the ammonia evaporated. The remaining solvent was decanted, and the residue was thoroughly extracted with ethyl acetate. The extracts were combined, and evaporated, to give 160 mg (82%) of syrupy **7**; $[\alpha]_D^{20}$ −98.6° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 4.81 (bs, 1 H, H-1), 4.11 (m, 1 H, H-5), 3.68 (bs, 1 H, H-2), 3.62 (bs, 1 H, H-4), 3.52 (bs, 3 H, 3 O*H*), 3.38 (s, 3 H, OCH_3), 1.47 (s, 3 H, CH_3-3), and 1.38 (d, 3 H, 3 H-6, $J_{5,6}$ 8 Hz).

Anal. Calc. for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 49.78; H, 8.17.

*Methyl 6-deoxy-3-*C*-methyl-β-*L*-mannopyranoside (methyl β-*L*-evalopyranoside)* (**8**). — A mixture of compound **7** (1.0 g, 5.2 mmol), Dowex 50 (H^+) resin (3.0

g), and methanol (50 mL) was boiled and stirred under reflux for 23 h, and filtered, and the filtrate was evaporated to a syrup that contained **7** (R_F 0.3, ethyl acetate) and **8** (R_F 0.24). The mixture was purified by flash chromatography, to give 300 mg (30%) of crystalline **8** and 150 mg of **7**. Compound **8** displayed the following characteristics: m.p. 128–131°, lit.[13] (enantiomer) m.p. 132°, $[\alpha]_D^{20}$ −76.6° (*c* 1, CH_3OH); ^{1}H-n.m.r. (200 MHz, C_5D_5N): δ 5.14 (bs, 1 H, H-1), 4.26–3.96 (m, 3 H, H-2,4,5), 3.38 (s, 3 H, OCH_3), 1.84 (s, 3 H, CH_3-3), and 1.61 (d, 3 H, 3 H-6, $J_{5,6}$ 6.0 Hz). The ^{13}C-n.m.r. spectrum of **8** was identical with that reported[9] for its enantiomer.

*6-Deoxy-3-C-methyl-2,3,4-tri-O-methyl-*L*-mannopyranose (*L*-nogalose)* (**1**). — Sodium hydride (0.83 g of a 50% dispersion in oil, 17.3 mmol) was washed with dry hexane in a round-bottomed flask, and the washings were removed by means of a pipet. A solution of **8** (260 mg, 1.35 mmol) in dry Me_2SO (7.0 mL) was added, and the mixture was stirred for 0.5 h. Methyl iodide (1.3 mL, 20.8 mmol) was added, the mixture was stirred for 22 h at room temperature, and the reaction was quenched with a few drops of methanol. The mixture was partitioned between water and chloroform, and the aqueous phase was separated and extracted with chloroform. The extracts were combined, washed once with water, dried (magnesium sulfate), and evaporated, to give 220 mg (69%) of methyl 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-β-L-mannopyranoside (**9**); $[\alpha]_D^{20}$ −7.89° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 4.67 (d, 1 H, H-1, $J_{1,2}$ 2 Hz), 3.47 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 3.04–2.84 (m, 3 H, H-2,4,5), 1.24 (s, 3 H, CH_3-3), and 1.24 (d, 3 H, 3 H-6, $J_{5,6}$ 6.0 Hz).

A solution of **9** (210 mg, 0.9 mmol) in M sulfuric acid (7.0 mL) was heated for 0.5 h at 95° with stirring. The mixture was cooled, the acid neutralized with lead carbonate, the suspension filtered, and the solid washed with methanol. The filtrate was evaporated, and the residue was azeotroped with absolute ethanol, to give 166 mg (88%) of solid **1**, which was purified by column chromatography with 1:1 ethyl acetate–petroleum ether, and by sublimation; m.p. 113–118° (lit.[1] m.p. 115–121°); $[\alpha]_D^{20}$ −14.4° (*c* 1, methanol) {lit.[1] $[\alpha]_D^{25}$ −10.6° (*c* 1, methanol), $[\alpha]_D^{25}$ +15.5° (*c* 1, H_2O)}.

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