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THE SYNTHESIS OF L-NOGALOSE

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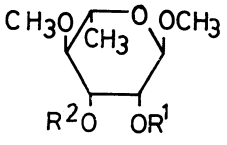
L-Nogalose (1: 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-L-manno-pyranose), the sugar component of antibiotic nogalamycin, has been synthesized from L-rhamnose. The *C*-methyl branching was introduced by successive epoxidation and reduction of methyl 3,6-dideoxy-2,4-di-*O*-methyl-3-*C*-methylene-α-L-*arabino*-hexopyranoside.

L-Nogalose (1) is the component sugar of nogalamycin[1], an antibiotic highly active against gram-positive bacteria and KB cells *in vivo*, and the absolute configuration was established to be 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-L-manno-pyranose by Wiley and co-workers[2]. Brimacombe and Rollins have recently reported the synthesis of D-nogalose through an addition of methylmagnesium iodide to 1,2:5,6-di-*O*-isopropylidene-β-D-*arabino*-hexofuranos-3-ulose, but the synthesis of L-nogalose through the configurational inversion at *C*-5 of 6-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-3-*C*-methyl-5-*O*-methylsulfonyl-α-D-gulofuranose was unsuccessful[3].

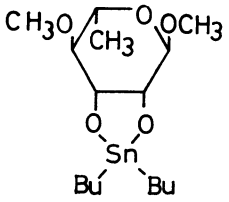
In this communication we would like to describe the first synthesis of L-nogalose through the successive epoxidation and reduction[4] of methyl 3,6-dideoxy-2,4-di-*O*-methyl-3-*C*-methylene-α-L-*arabino*-hexopyranoside.

For a selective protection of an equatorial hydroxyl group, methyl 4-*O*-methyl-α-L-rhamnopyranoside[5] (2) was first of all converted into the corresponding 2,3-*O*-dibutylstanylene derivative[6] (3), which was successively treated with a slightly excess benzyl bromide in *N*,*N*-dimethylformamide at 100°C for 20 min. to give the expected 3-*O*-benzyl derivative [4: $[\alpha]_D^{26}$ -39.7° (*c* 1.0, MeOH)] of 2 as a syrup in 62% yield. Treatment of 4 with methyl iodide and sodium hydride in dimethyl sulfoxide gave the corresponding 2-*O*-methyl derivative [5: syrup $[\alpha]_D^{17}$ -48.6° (*c* 1.0, CCl_4)] quantitatively. The compound 5 in 70% acetic acid was then hydrogenated in the presence of palladium on carbon (10%) to give methyl 2,4-di-*O*-methyl-α-L-rhamnopyranoside [6: syrup, $[\alpha]_D^{17}$ -51.4° (*c* 1.0, CCl_4)].

Oxidation of 6 with ruthenium tetroxide in chloroform gave methyl 6-deoxy-2,4-di-*O*-methyl-α-L-*threo*-hexopyranosid-3-ulose [7: syrup, $[\alpha]_D^{17}$ -167.4° (*c* 1.0, CCl_4), IR; $\nu_{C=O}$ 1745 cm^{-1}]. The compound 7 was converted to the corresponding 3-*C*-methylene derivative [8: syrup, $[\alpha]_D^{26}$ -171° (*c* 1.14, MeOH), NMR; δ 5.12 and 5.31 (Methylene)] in 65% yield by the usual Wittig reaction. The compound 8 was treated with *m*-chloroperbenzoic acid in 1,2-dichloroethane to give two epimeric epoxides [9: syrup, $[\alpha]_D^{27}$ -99.4° (*c* 1.09, MeOH), NMR; δ 2.84 (q, J_{gem} = 5 Hz,



	R^1	R^2
2	H	H
4	H	Bn
5	CH_3	Bn
6	CH_3	H



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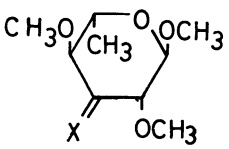
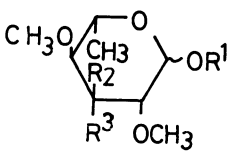
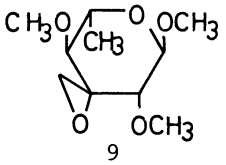


	X
7	O
8	CH_2



	R^1	R^2	R^3
11	α-CH_3	CH_3	OH
12	α-CH_3	OH	CH_3
13	α-CH_3	CH_3	OCH_3
1	H	CH_3	OCH_3



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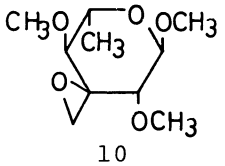

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epoxymethylene) and 10] in 64% yield. The ratio of 9 to 10 was estimated to be 1:1 from the NMR spectrum, and only 9 was isolated in a pure state. Reduction of 9 with lithium aluminium hydride in ether gave methyl 6-deoxy-3-*C*-methyl-2,4-di-*O*-methyl-α-L-mannopyranoside [11: syrup, $[\alpha]_D^{17}$ -62° (*c* 1.0, MeOH), NMR; δ 1.29 (3-CH_3)]. The configuration of 11 was supported by comparison with its 3-epimer [12: $[\alpha]_D^{17}$ -63.6° (*c* 1.0, CCl_4), NMR; δ 1.35 (3-CH_3)] which was obtained by the addition of methylmagnesium iodide[7] to 7.

Treatment of 11 with sodium hydride and methyl iodide in dimethyl sulfoxide gave the corresponding 3-*O*-methyl derivative (13) in 85% yield, which was purified by sublimation at 35°/0.03 Torr to give colorless crystals [Yield 50%, mp 41-43°C, $[\alpha]_D^{16}$ -59.4° (*c* 1.06, MeOH), lit.[2b] mp 41-43°C, $[\alpha]_D^{25}$ -48.4° (*c* 1.0, MeOH)]. NMR parameters of 13 [δ 1.28 (d, $J_{5,6}$=6.3 Hz, CH_3), 1.31 (3-CH_3), 3.07 (d, $J_{4,5}$=9.5 Hz, H_4), 3.28, 3.36, 3.49, and 3.53 (each s, 4×OMe), 3.37 (d, H_2), 3.60 (m, H_5) and 4.72 (d, $J_{1,2}$=2.0 Hz, H_1)] were in very good agreement with those reported[2b].
Finally, acid hydrolysis of 13 with 2N sulfuric acid at 90-95°C for 30 min. gave L-nogalose (1) in 78% yield, which was also sublimed at 60°/0.01 Torr to give crystals [mp 110-115°C, $[\alpha]_D^{17}$ -14 → -8.4° (*c* 1,0, 24 h; MeOH); lit.[2b] mp 115-121°C, $[\alpha]_D^{25}$ -10.6° (*c* 1.0, MeOH), $[\alpha]_D$ -17.1 → -5.1° (24 h; MeOH)[8]]. Thus L-nogalose could be synthesized through the introduction of *C*-methyl branching of desired configuration by successive epoxidation and reduction of the methylene function of 8.

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