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A FACILE SYNTHESIS OF METHYL 4,6-DIDEOXY-3-*C*-METHYL-4-METHYLAMINO-α-L-MANNOPYRANOSIDE (SIBIROSAMINIDE)

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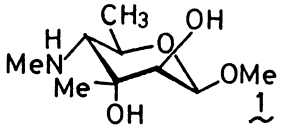
The title branched-chain sugar obtained by methanolysis of sibiromycin was easily synthesized from L-rhamnose through eight-step conversions.

The structure of natural sibirosaminide, obtained by methanolysis of sibiromycin from a culture of *Streptosporangium sibiricum*,[1] was first assigned[2] to be methyl 4,6-dideoxy-3-*C*-methyl-4-methylamino-β-D-altropyranoside (1) from spectroscopic data, the rotational value of periodate oxidation product, and the change of molecular rotation upon complexing in tetraaminecopper(II) sulfate solution, and a few synthetic works on 1 have been reported.[3] However, Parker and Babine revised[4] the configuration at C-3 of 1 by comparison of synthesized N-tosyl derivative (2) and its 3-epimer with that derived from the glycoside which was obtained by methanolysis of sibiromycin, and they further revised 2 to the corresponding L-sugar (3) from their rotational values.[5] This report communicates a facile synthesis of the sibirosaminide 4 having finally revised α-L-configuration.

As the starting material, methyl 6-deoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-L-*lyxo*-hexopyranosid-4-ulose (5) was used, which was obtained by direct 3-*C*-methylation to a carbanion of parent hexopyranosid-4-ulose with methyl iodide.[6] Reaction of 5 with hydroxylamine hydrochloride in pyridine and ethanol gave quantitatively a mixture of *syn* and *anti* forms of the corresponding oxime (6). Catalytic hydrogenation of 6 in acetic acid with palladium-carbon or platinum oxide gave exclusively the corresponding amine (7) having undesired L-*talo* configuration, whereas reduction with lithium aluminium hydride yielded a 1:1 mixture of L-*talo* and L-*manno* derivatives in 94% yield, which was separated after conversion into the corresponding *N*-methoxycarbonyl derivatives {8: sirup; $[\alpha]_D$ -39.8° (*c* 1.5, $CHCl_3$); NMR ($CDCl_3$): δ 5.13 (bd, 1 H, $J_{NH,4}$=10.0 Hz, NH), 4.87 (s, 1 H, H-1), 4.00



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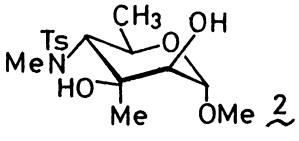

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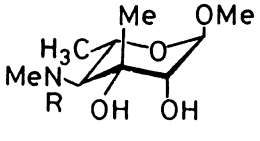
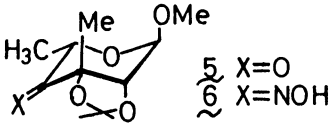
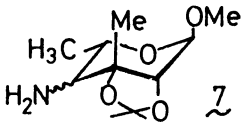


3 R=Ts
4 R=H



5 X=O
6 X=NOH



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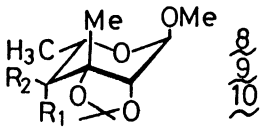

8 R_1=NHCO$_2$Me, R_2=H
9 R_1=H, R_2=NHCO$_2$Me
10 R_1=H, R_2=NHMe

(dq, 1 H, $J_{4,5}$=1.4, $J_{5,6}$=6.4 Hz, H-5), 3.74 (s, 1 H, H-2), 3.71 (s, 3 H, CO_2Me), 3.52 (bd, 1 H, H-4), 3.39 (s, 3 H, OMe), 1.47 (s, 6 H, Ip), 1.38 (s, 3 H, CMe), 1.23 (d, 3 H, H-6), 9: mp 184-185 °C; $[\alpha]_D$ -57.8° (*c* 1.0, $CHCl_3$); NMR: δ 4.90 (s, 1 H, H-1), 4.60 (bd, $J_{NH,4}$=10.0 Hz, NH), 3.91 (t, 1 H, $J_{NH,4}=J_{4,5}$=10.0 Hz, H-4), 3.83 (s, 1 H, H-2), 3.72 (s, 3 H, CO_2Me), 3.60 (dq, 1 H, $J_{5,6}$=6.2 Hz, H-5), 3.40 (s, 3 H, OMe), 1.63, 1.37 and 1.32 (each s, 9 H, Ip and CMe), 1.26 (d, 3 H, H-6)}. Reduction of 9 in diethyl ether with lithium aluminium hydride gave methyl 4,6-dideoxy-2,3-*o*-isopropylidene-3-*c*-methyl-4-methylamino-α-L-mannopyranoside [10: syrup, $[\alpha]_D$ -69.5° (*c* 1.7, $CHCl_3$); NMR ($CDCl_3$): δ 4.83 (s, 1 H, H-1), 3.75 (s, 1 H, H-2), 3.50 (dq, 1 H, $J_{4,5}$=10.0, $J_{5,6}$=6.2 Hz, H-5), 3.37 (s, 3 H, OMe), 2.54 (s, 3 H, NMe), 2.48 (d, 1 H, H-4), 1.53, 1.35 and 1.30 (each s, 9 H, Ip and CMe), 1.29 (d, 3 H, H-6)] in 96% yield. Treatment of 10 with 80% acetic acid at 90 °C for 18 h gave quantitatively methyl 4,6-dideoxy-3-*c*-methyl-4-methylamino-α-L-mannopyranoside HOAc salt [free 4: syrup; NMR ($CDCl_3$): δ 4.71 (d, 1 H, $J_{1,2}$=1.4 Hz, H-1), 3.64 (dq, 1 H, $J_{4,5}$=10.0, $J_{5,6}$=6.2 Hz, H-5), 3.57 (d, 1 H, H-2), 3.37 (s, 3 H, OMe), 2.63 (s, 3 H, NMe), 2.47 (d, 1 H, H-4), 1.29 (s, 6 H, Ip), 1.37 (d, 3 H, H-6)], which was first assigned as 1. The identity of 4 with sibirosaminide was confirmed by derivation into the corresponding 2,*N*-diacetate [mp 67-69 °C (monohydrate); $[\alpha]_D$ -65° (*c* 0.5, MeOH), mp 132-133 °C (anhydrous), NMR ($CDCl_3$): δ 4.75 (bs, 1 H, H-1), 4.69 (d, 1 H, $J_{4,5}$=10.0 Hz, H-4), 4.64 (bs, 1 H, H-2), 3.99 (dq, 1 H, $J_{5,6}$= 6.2 Hz, H-5), 3.40 (s, 3 H, OMe), 2.97 (s, 3 H, NMe), 2.16 (s, 6 H, OAc and NAc), 1.37 (s, 3 H, CMe), 1.23 (d, 3 H, H-6); lit.[2] mp 135-136°C, $[\alpha]_D$ -70° (0.4% MeOH)] and 2,3,*N*-tri-acetate [mp 130-131°C, $[\alpha]_D$ -23° (*c* 0.7, MeOH), NMR ($CDCl_3$): δ 5.59 (d, $J_{1,2}$=1.5, H-2), 4.69 (d, 1 H, H-1), 4.16 (dq, $J_{4,5}$=10.0, $J_{5,6}$=5.4 Hz, H-5), 3.97 (d, 1 H, H-4), 3.42 (s, 3 H, OMe), 2.86 (s, 3 H, NMe), 2.28, 2.07 and 1.97 (each s, 9 H, 2 x OAc and NAc), 1.24 (d, 3 H, H-6), lit.[2] mp 127-128 °C, $[\alpha]_D$ -25° (0.3% MeOH)].

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