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SYNTHESIS OF METHYL 2,3-DI-*o*-METHYL-α-D-SIBIROSAMINIDE

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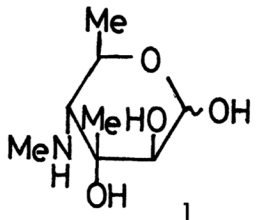
Methyl 2,3-di-*o*-methyl-α-D-sibirosaminide (12; methyl 4,6-dideoxy-3-*c*-methyl-2,3-di-*o*-methyl-4-methylamino-α-D-altropyranoside) has been synthesized from methyl 4,6-*o*-benzylidene-3-*c*-methyl-2-*o*-methyl-α-D-altropyranoside (2). The introduction of methylamino group at *c*-4 position was achieved by hydrogenation of methyl 6-deoxy-3-*c*-methyl-2,3-di-*o*-methyl-α-D-*arabino*-hexopyranosid-4-ulose oxime (8) in the ratio of 2.6:1 (altro:ido) followed by *N*-formylation and reduction.

Sibrosamine, a component sugar of sibiromycin, an antitumor antibiotic produced by *streptosporangium sibiricum*[1] was characterized as 4,6-dideoxy-3-*c*-methyl-4-methylamino-D-altropyranose (1).[2] Recently, Dyong[3] and his co-workers have reported the synthesis of methyl 2-*o*-acetyl-4,6-dideoxy-3-*c*-methyl-4-tosylamino-α-D-altropyranoside, as a key intermediate for the synthesis of sibirosamine, through [2,3]-sigmatropic rearrangement of the corresponding 3-*c*-methyl-hex-2-enopyranoside followed by vicinal *cis*-oxyamination of the C=C bond.[4]

In this communication, the synthesis of methyl 4,6-dideoxy-3-*c*-methyl-2,3-di-*o*-methyl-4-methylamino-α-D-altropyranoside (12) from methyl 4,6-*o*-benzylidene-3-*c*-methyl-2-*o*-methyl-α-D-altropyranoside (2),[5] through successive deoxygenation of *c*-6 and methylamination of *c*-4 positions, is described.



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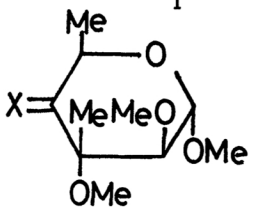
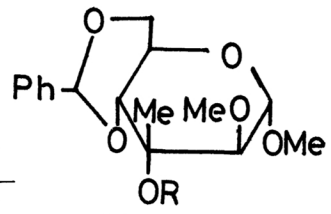
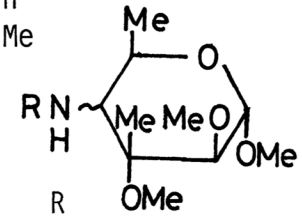


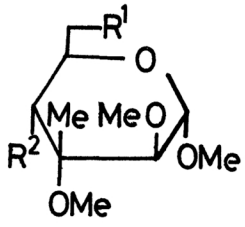
X
7 O
8 NOH



R
2 H
3 Me



R
9 H
10 Ac
11 CHO



R^1	R^2
4 Br	OBz
5 H	OBz
6 H	OH
12 H	NHMe

Compound (2) was 3-*O*-methylated by the usual procedure, and the product (3) was treated with *N*-bromosuccinimide in carbon tetrachloride to give methyl 4-*O*-benzoyl-6-bromo-6-deoxy-3-*C*-methyl-2-*O*-methyl-α-D-altropyranoside (4), mp 136-138°C: $[\alpha]_D^{18}$ +56° (*c* 1.0, MeOH); NMR: δ4.79(d, $J_{1,2}$=2 Hz, H-1), 3.52(d, H-2), 5.24(d, $J_{4,5}$=9.5 Hz, H-4), 4.50(oct, $J_{5,6}$=$J_{5,6'}$=6 Hz, H-5), 3.4-3.6(m, H-6 and H-6'), 8.19-8.0 and 7.7-7.3(m, Ph), 3.32, 3.47(3×OMe), 1.26(s, CMe), in 75% yield. Reduction of (4) in benzene with tributylstannane in the presence of α,α'-azo-bis-isobutyronitrile gave the corresponding 6-deoxy derivative (5), mp 103-104°C; $[\alpha]_D^{18}$ +58° (*c* 1.0, MeOH); NMR: δ4.72(s, H-1), 3.36(s, H-2), 5.17(d, $J_{4,5}$=9.5 Hz, H-4), 4.30(oct, H-5), 1.21 (d, $J_{5,6}$=7 Hz, H-6), 8.20-8.05 and 7.7-7.38(m, Ph), 3.37, 3.45 and 3.49(3×OMe), 1.28(s, CMe), in 70% yield. Treatment of (5) with sodium methoxide gave the required de-*O*-benzoylated product (6) as a syrup, $[\alpha]_D^{18}$ +38° (*c* 1.0, MeOH); NMR: δ4.60(s, H-1), 3.48(s, H-2), 3.16(d, $J_{4,5}$=10 Hz, H-4), 3.82(oct, H-5), 1.30(d, $J_{5,6}$ =6 Hz, H-6), 2.16(d, J=12 Hz, OH), 3.25, 3.37 and 3.41(3×OMe), 1.32(s, CMe), in 90% yield. The oxidation of (6) with dimethyl sulfoxide-trifluoroacetic anhydride in methylene dichloride gave the corresponding 4-ulose (7) as a syrup, $[\alpha]_D^{18}$ +190° (*c* 1.7, MeOH); IR: $\nu_{C=O}$ 1740 cm^{-1}; NMR: δ4.68(d, $J_{1,2}$=4 Hz, H-1), 3.61(d, H-2), 4.18 (q, $J_{5,6}$=7.5 Hz, H-5), 1.34(d, H-6), 3.33, 3.43 and 3.52(3×OMe), 1.44(s, CMe), in 80% yield.

The oximation of (7) with hydroxylamine hydrochloride and sodium acetate in aq. methanol gave methyl 6-deoxy-3-*C*-methyl-2,3-di-*O*-methyl-α-D-*arabino*-hexopyranosid-4-ulose oxime (8), mp 65-67°C; $[\alpha]_D^{14}$ +124° (*c* 1.5, MeOH); NMR: δ4.57(d, $J_{1,2}$=2 Hz, H-1), 3.35(d, H-2), 4.87(q, $J_{5,6}$=7.5 Hz, H-5), 1.49(d, H-6), 3.38, 3.38 and 3.46 (3×OMe), 8.7(s, NOH), 1.51(s, CMe), in 91% yield. Hydrogenation of (8) in glacial acetic acid in the presence of platinum oxide gave a mixture of *altro* and *ido* derivatives (9), IR: ν_{NH_2} 3250 and 3450 cm^{-1}, in 60% yield. The ratio of the two isomers was determined from the NMR spectrum of acetylated products (10) to be 2.6:1 [altro (δ3.94, $J_{4,5}$=5.8 Hz, H-5): ido (δ4.38, $J_{4,5}$=2.0 Hz, H-5)]. The *N*-formylation of (9) with p-nitrophenyl formate in tetrahydrofuran gave *N*-formyl derivative (11) in 76% yield, which was reduced with lithium aluminium hydride in benzene-ether to give a mixture of *N*-methyl derivatives in 85% yield. Separation of the mixture on a silica gel column using chloroform as eluent gave pure (12) of D-altro configuration as a syrup, $[\alpha]_D^{15}$ +67° (*c* 0.9, MeOH), NMR: δ4.59(s, H-1), 3.35(s, H-2), 2.35(d, $J_{4,5}$=10 Hz, H-4), 3.80(oct, $J_{4,5}$=10, $J_{5,6}$=6 Hz, H-5), 1.26(d, H-6), 3.42, 3.36 and 3.22(3×OMe), 2.50(s, NMe), 1.30(s, CMe).

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