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SYNTHESIS OF METHYL β-D-VIRENOSIDE

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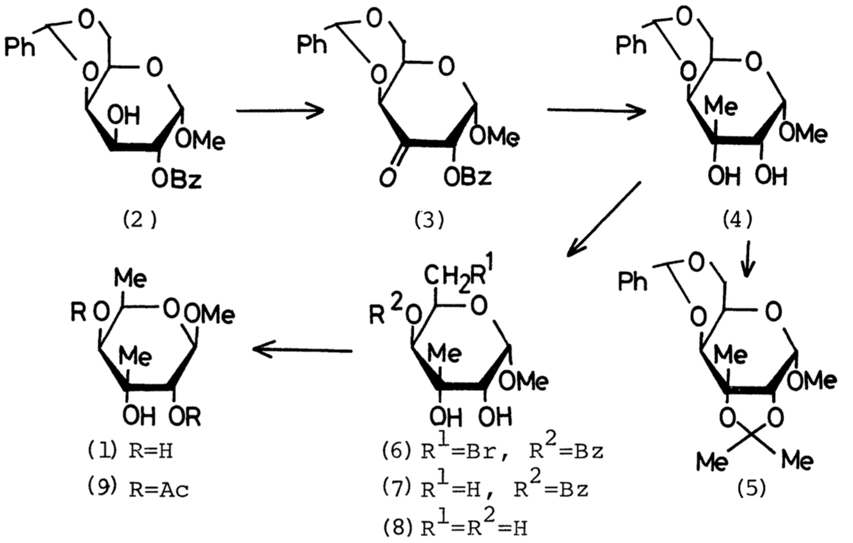
Methyl 6-deoxy-3-C-methyl-β-D-gulopyranoside (1: methyl β-D-virenoside) has been synthesized from galactose. The introduction of methyl branching at C-3 position was achieved by the Grignard reaction.

Virenosa is a new naturally occuring branched-chain sugar found as a component of the antitumor antibiotic virenomycin produced by *Actinomyces virens* sp. nov.1) Kulyaeba2) and her co-werkers have reported the isolation of virenosa as a methyl glycoside and established its structure as methyl 6-deoxy-3-C-methyl-β-D-gulopyranoside from NMR, MS, and IR spectral data, and $\Delta[M]^{\mathrm{cupra\ A,B}}$ rotational values.

In this communication we would like to describe the first synthesis of methyl β-D-virenoside through the stereoselective introduction of C-methyl group by the Grignard reaction of methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-*xylo*-hexopyranosid-3-ulose (3) followed by the same 6-deoxygenation used for the preparation of D-evermicose3) and D-everlose.4)

According to the method of Szeja, the starting material methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-galactopyranoside (2) was obtained in good yield.5) Oxidation of (2) with dimethyl sulfoxide-trifluoroacetic anhydride in methylene dichloride gave the corresponding 3-ulose [3: syrup, $[\alpha]_D^{27}$ +142° (c 1.8, $CHCl_3$), NMR ($CDCl_3$): δ 6.1 (d, $J_{1,2}$=3.8 Hz, H-1), 5.36(d, H-2), 4.54(d, $J_{4,5}$=1.5 Hz, H-4), 3.97(m, H-5), 4.42 (dd, $J_{6,6'}$=13, $J_{5,6}$=1.5 Hz, H-6), 4.15(dd, $J_{5,6'}$=2.0 Hz, H-6'), 3.48(s, OMe), 7.8-8.2 and 7.2-7.6(m, Ph and PhCO), 5.59(PhCH); IR: ν 1730 cm^{-1} (C=O)] in 80% yield. Treatment of (3) with methylmagnesium iodide in ether gave one isomer, methyl 4,6-O-benzylidene-3-C-methyl-α-D-gulopyranosid [4: syrup, $[\alpha]_D^{28}$ +102° [c 1.9, $CHCl_3$), NMR ($CDCl_3$): δ 4.86(d, $J_{1,2}$=3.8Hz, H-1), 3.78(dd, $J_{2,OH}$=12.0, H-2), 3.77(s, H-4), 3.90(broad s, H-5), 4.30(dd, $J_{6,6'}$=13, $J_{5,6}$=2.0 Hz, H-6), 4.04(dd, $J_{5,6'}$=2.0 Hz, H-6'), 2.64(d, OH-2), ca. 3.8(OH-3), 3.46(s, OMe), 1.35(s, CMe), 7.2-7.52(m, Ph), 5.50 (s, PhCH)] predominantly6) in 85% yield. The configuration of (4) was confirmed by the conversion into the corresponding 2,3-O-isopropylidene derivative [5: syrup, $[\alpha]_D^{26}$ +8.6° (c 0.6, $CHCl_3$), NMR ($CDCl_3$): δ 5.18(d, $J_{1,2}$=1.2 Hz, H-1), 3.71(d, H-2), 4.18(s, H-4), 4.0(m, H-5), 4.34(dd, $J_{6,6'}$=12.2, $J_{5,6}$=2.0 Hz, H-6), 3.92(dd, $J_{5,6'}$= 2.0 Hz, H-6'), 3.62(s, OMe), 1.46, 1.50 and 1.52 each (s, 3 x CMe), 7.5-7.2(m, Ph)] with the usual method.

The compound (4) was treated with N-bromosuccinimide in carbon tetrachloride to give methyl 4-O-benzoyl-6-bromo-6-deoxy-3-C-methyl-α-D-gulopyranoside [6: syrup, $[\alpha]_D^{27}$ +120.7° (c 1.8, $CHCl_3$), NMR ($CDCl_3$): δ 4.92(d, $J_{1,2}$=3.8 Hz, H-1), 3.79(d, H-2), 5.26



(2) (3) (4)

(1) R=H

(9) R=Ac

(6) R^1=Br, R^2=Bz

(7) R^1=H, R^2=Bz

(8) R^1=R^2=H

(5)

(s, H-4), 4.46(dd, $J_{5,6}$=8.0, $J_{5,6'}$=4.0 Hz, H-5), 3.44(dd, $J_{6,6'}$=11.0 Hz, H-6'), 3.26 (dd, H-6), 3.54(s, OMe), 1.26(s, CMe), 7.9-8.1 and 7.3-7.5(m, PhCO)] in 75%, yield. Reduction of (6) in benzene with tributylstannane in the presence of α,α'-azobis-isobutyronitrile gave the corresponding 6-deoxy derivative [7: mp 133-134°C, $[\alpha]_D^{28}$ +142° (c 1.0, $CHCl_3$), NMR ($CDCl_3$): δ 4.87(d, $J_{1,2}$=4.0 Hz, H-1), 3.78(dd, $J_{2,OH}$=12.0 Hz, H-2), 5.12(s, H-4), 4.41(q, $J_{5,6}$=6.0 Hz, H-5), 1.17(d, H-6), 3.52(s, OMe), 3.84 (s, OH-3), 2.40(d, OH-2), 1.25(s, CMe), 8.0-8.16 and 7.30-7.60(m, PhCO)] in 85% yield. Treatment of (7) with sodium methoxide gave the required de-O-benzoylated product [8: $[\alpha]_D^{27}$ +123° (c 0.3, $CHCl_3$)] as a syrup in quantitative yield.

Anomerization of (8) with cationic ion exchange resin IR 120 in methanol by refluxing for 20 hr gave the methyl β-D-virenoside (1) as crystals (n-hexane-chloroform) [yield 80%, mp 134-135°C, $[\alpha]_D^{29}$ -30° (c 0.3, $CHCl_3$), lit.$^{2)}$ mp 131°C, $[\alpha]_D^{20}$ -39° (c 0.35, $CHCl_3$)]. NMR ($CDCl_3$) parameters of (1) [δ 4.41(d, $J_{1,2}$=8.0 Hz, H-1), 3.39 (d, H-2), 3.26(d, $J_{4,5}$=1.2 Hz, H-4), 4.22(q, $J_{5,6}$=6.5 Hz, H-5), 1.28(d, H-6), 1.40 (s, CMe), 3.54(s, OMe)] were in very good agreement with those reported.$^{2)}$ Finally, acetylation of (1) in pyridine with acetic anhydride gave the di-O-acetyl derivative [9: mp 140-141°C, $[\alpha]_D^{28}$ -24° (c 0.3, $CHCl_3$); NMR ($CDCl_3$): δ 4.58(d, $J_{1,2}$=8.0 Hz, H-1), 4.81(d, H-2), 4.80(d, $J_{4,5}$=1.2 Hz, H-4), 4.23(q, $J_{5,6}$=6.5 Hz, H-5), 1.14(d, H-6), 1.12(s, CMe), 2.14(s, 2 × Ac), 3.54(s, OMe)], physical constants of which were also identical with those of reported [lit.$^{2)}$ mp 140°C, $[\alpha]_D^{20}$ -27° (c 0.3, $CHCl_3$)].

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