CHEMISTRY LETTERS, pp. 1131-1132, 1980.

SYNTHESIS OF METHYL β-D-VIRENOSIDE

Juji YOSHIMURA, Namgi HONG, and Ken-ichi SATO
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227

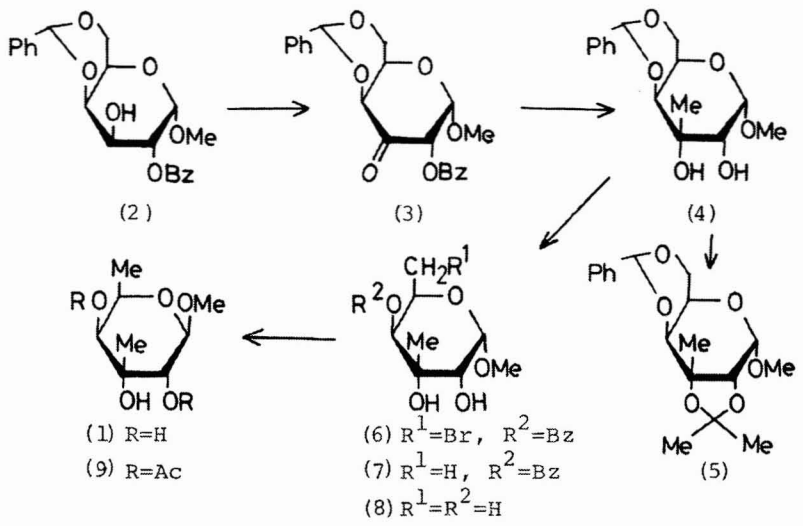
Methyl 6-deoxy-3-C-methyl-β-D-gulopyranoside (1: methyl β-D-virenoside) has been synthesized from galactose. The introduction of methyl branching at C-3 position was achieved by the Grignard reaction.

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] Kulyaeba[2] 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 $\Delta[M]^{cupra\ A,B}$ 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-evermicose[3] 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)] predominantly[6] 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



(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, $CHCl_3$)].

References

1) M. G. Brazhnikova, M. K. Kudinova, V. V. Kulyaeva, N. P. Potapova, and V. I. Ponomalenko, Antibiotiki, 11, 967 (1977).
2) V. V. Kulyaeva, M. K. Kudinova, N. P. Potapova, L. M. Rubasheva, N. G. Brazhnikova, B. V. Rosynoi and A. R. Bekker, Bioorg. Khim., 4, 1087 (1978).
3) M. Funabashi, N. Hong, H. Kodama, and J. Yoshimura, Carbohydr. Res., 67, 139(1978).
4) J. Yoshimura, N. Hong, and K. Sato, Chem. Lett., 1979, 1263.
5) W. Szeja, Synthesis, 1979, 821.
6) G. B. Howarth, W. A. Szarek, and J. K. N. Jones, Carbohydr. Res., 7, 284 (1968).

(Received July 1, 1980)