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BRANCHED-CHAIN SUGARS. I. REACTION BETWEEN FURANOSES AND FORMALDEHYDE: A SYNTHESIS OF D-HAMAMELOSE(1).

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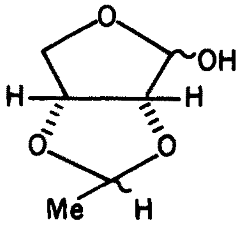
In connection with our synthetic programs, a large amount of the branched-chain 2-C-hydroxymethyl sugar derivative was required. Although many new methods for the preparation of branched carbohydrates have been developed in the past few years (2), it seemed that none of the available methods gave a direct and stereospecific synthesis of the functionalized branched-chain sugar which we desired. It was felt that exploration of an efficient and simple approach was necessary. The present communication reports a one-step and completely stereospecific method for the synthesis of branched carbohydrate derivatives, which appears to be general and very useful.

Reaction of 2,3-O-ethylidene-D-erythrofuranose **1** (3) with excess 37% aqueous solution of formaldehyde and potassium carbonate (at pH 10) in methanol at 80°C for 2 days, after work-up and chromatography on silica gel, afforded the hydroxymethyl derivative **2** (4) as a homogeneous syrup in an isolated yield of 88%, $[\alpha]_D$ -40.5° (C 6.0, $CHCl_3$). It gave ^1H nmr signals at δ 5.46 (S, 1H, C-1 proton), 5.21 (q, 1H, dioxolane proton), 4.60 (d, 1H, C-3 proton), 4.10 (d, 2H, C-4 protons) and 3.92 ppm (broad s, 2H, C-2' protons), and gave ^{13}C nmr signals at δ 103.14 (dioxolane carbon), 102.37 (C-1), 93.17 (C-2), 83.62 (C-3), 71.59 (C-4), 61.32 (C-2'), and 19.27 ppm (CH_3). Clearly, the cyclic acetal still exists in the compound **2**, the stereochemistry of which at C-2 can be assigned as indicated in the formula **2**, since the alternative configuration would require a *trans*-fusion of the furanose and dioxolane ring. Further chemical transformations also agree with the assigned structure 2. Oxidation of 2 with bromine in the presence of barium carbonate in water gave the lactone 3 in good yield. $[\alpha]_D$ -108° (C 4.5, benzene); ν_{max} 3500 (OH), 1780 cm^{-1} (lactone); ^1H nmr δ 5.33 (q, 1H, dioxolane proton), 4.90 (t, 1H, C-3 proton), 4.48 (d, 2H, C-4 protons), 4.00 (s, 2H, C-2' protons), and 1.43 ppm (d, 3H, methyl). The corresponding acetate 4 was prepared under standard conditions in almost quantitative yield, $[\alpha]_D$ -70° (C 1.0, $CHCl_3$); ν_{max} 1780, 1750 cm^{-1}; ^1H nmr δ 2.13 ppm (s, 3H, acetate).

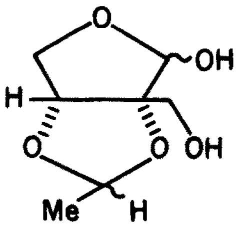
It has been shown that a mixed aldol reaction between aldehyde of a sugar and formaldehyde yielded a condensation product in which the aldehyde had been reduced to alcohol in a crossed-Cannizzaro sequence (5). With compound 1, used in the present study, the hydroxyls are well protected by formation of a rigid dioxolane ring and a small population of the open-chain aldehyde and enol form will be present under the reaction conditions. Hence, on treatment with base, the compound will undergo a simple condensation reaction. The complete stereospecificity could be rationalized by the fact that the relatively bulkier C-3 substituent will prevent the approach of formaldehyde to the enolate ion from the same side as portrayed in Eq. 1.

Compound 2 was converted into its methyl glycoside 5 by reaction with methanol containing acetaldehyde catalyzed by hydrogen chloride in 62% yield, $[\alpha]_D$ -21.3° (C 2.2, $CHCl_3$); ^1H nmr δ 5.21 (q, 1H, dioxolane proton), 4.99 (s, 1H, C-1 proton), 4.64 (d, 1H, C-3 proton), 4.00-3.98 (m, 4H, C-4 and C-2' protons), 3.41 (s, 3H, methoxyl), and 1.40 ppm (d, 3H, methyl). Reaction of 5 with tosyl chloride in pyridine gave quantitatively the tosylate 6, which on treatment with sodium cyanide in dry DMSO at 70°C yielded the nitrile 7 in about 60% yield, $[\alpha]_D$ -128° (C 1.0, $CHCl_3$); ν_{max} 2230 cm^{-1}; ^1H nmr δ 5.39 (q, 1H, dioxolane proton), 4.90 (s, 1H, C-1 proton), 3.01 (s, 3H, methoxyl), 2.98 ppm (s, 2H, $-CH_2CN$). The preparation of the 2-C-cyanomethyl sugar, a possible intermediate for preparation of a branched-chain amino sugar, is of interest, since many amino sugars have been found in antibiotics (6).

The efficiency and simplicity of the condensation reaction described above is probably best illustrated by using the one-step synthesis of D-hamamelose as example. Reaction of 2,3-O-isopropylidene-D-ribose 8 (7) with formaldehyde under similar conditions gave 2,3-O-isopropylidene-D-hamamelose 9 in 84% yield, $[\alpha]_D$ +9.3° (C 3.0, H_2O). Oxidation of 9 with bromine containing barium carbonate in water gave a solid material which crystallized from ether-hexane to yield the lactone 10, m.p. 83°C; $[\alpha]_D$ -17.1° (C 1.4, $CHCl_3$); 86% yield. Its ^1H nmr gave desired signals at δ 4.85 (s, 1H, C-3 proton), 4.70 (t, 1H, C-4 proton), 4.00-3.96 (broad s, 4H, C-5 and C-2' protons),



1



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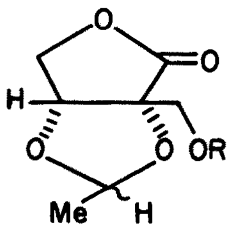
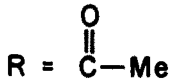
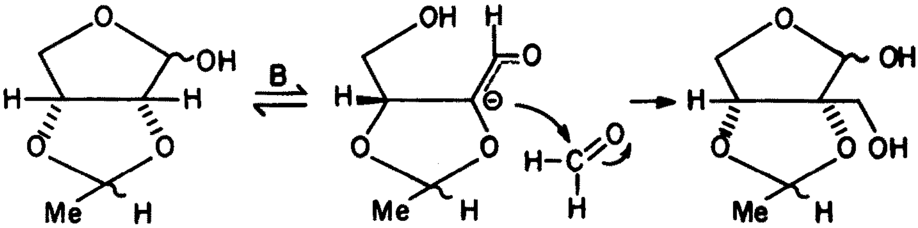


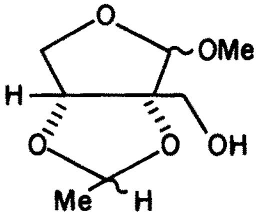
3 R = H



4 $R = \overset{O}{\overset{\|}{C}}-Me$



Eq. I



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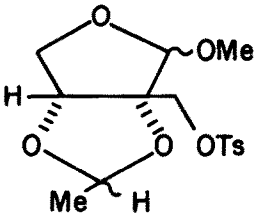

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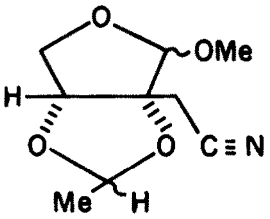

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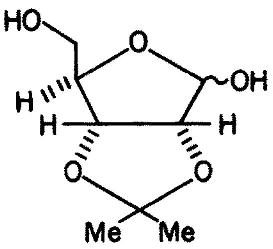

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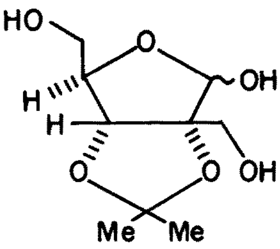

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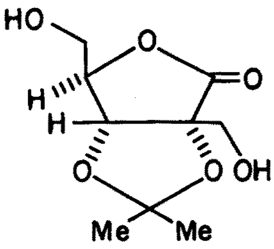

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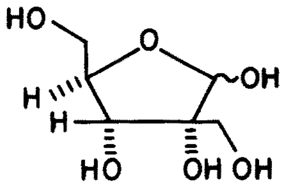

11

and 1.49 ppm (s, 6H, two methyls). The isopropylidene group of 9 was removed in water with Dowex 50 W (H^+) resin at 70°C giving D-hamamelose 11 in excellent yield, $[\alpha]_D$ -6.6° (C 1.5, H_2O); m.p. 110°C. It was identical with synthetic and natural samples in all respects (8,9), and the sugar was further characterized by formation of the crystalline p-nitrophenylhydrazone, m.p. 163°; $[\alpha]_D$ +138° (C 1.6, pyridine) (8).

Acknowledgment

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References and Notes

(1) Issued as NRCC No. 16516.

(2) For recent examples see Carbohydrate Chemistry (Chem. Soc. Specialist Periodical Reports), Vol. 1-9 (1967-1976).

(3) J.N. Van Cleve and C.E. Rist, *Carbohyd. Res., 4* 82 (1967). The yield under our conditions (with addition of acetaldehyde to the reaction mixture) was improved to about 65% after crystallization.

(4) Satisfactory elemental analyses and spectral data were obtained for all compounds described.

(5) (a) R. Schaffer, *J. Amer. Chem. Soc., 81* 5452 (1959).
(b) D.T. Williams and J.K.N. Jones, *Can. J. Chem., 42* 69 (1964).

(6) J.S. Brimacombe, *Angew. Chem. Intern. Ed. Engl., 8* 401 (1969).

(7) P.A. Levene and E.T. Stiller, *J. Biol. Chem., 102* 187 (1933). The yield could be improved to 80%, if the reaction mixture was worked up when completed.

(8) W.G. Overend and N.R. Williams, *J. Chem. Soc.,* 3466 (1965).

(9) H. Gilek, A. Thanbichler, J. Sellmair, and E. Beck, *Carbohyd. Res., 39* 160 (1975).