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NEW ROUTE TO BRANCHED-CHAIN SUGARS BY APPLICATION OF MODIFIED WITTIG REACTION TO KETOSES

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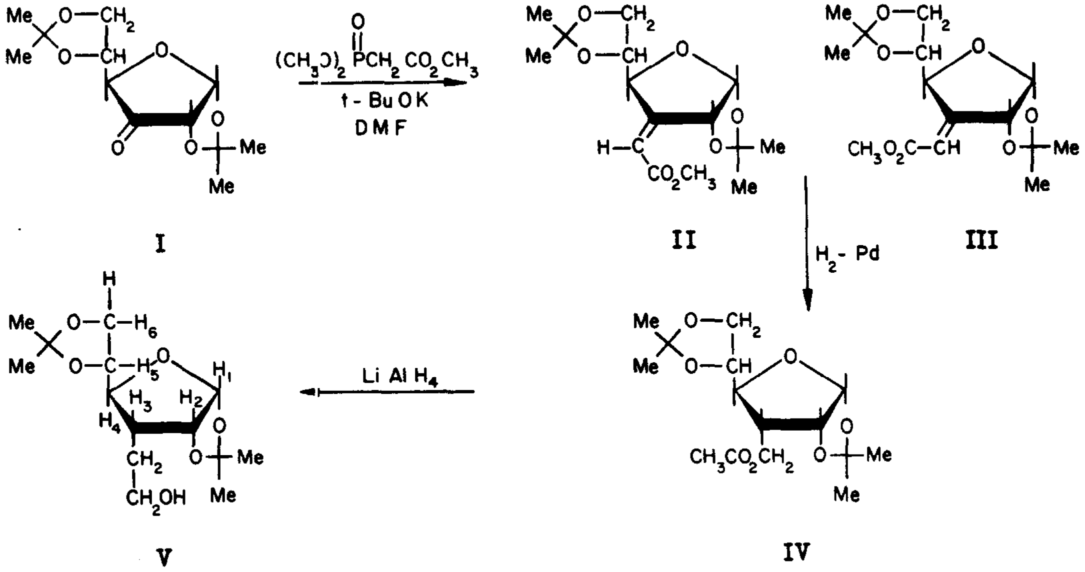
The isolation and chemical study of new antibiotic substances during recent years has resulted in the discovery of several interesting branched-chain sugars (1,2). This discovery, coupled with the fact that several flavone glycosides have been known to contain branched-chain sugars, has given additional impetus to a further study of the general chemistry of the branched-chain sugars. The Birkbeck group of investigators has been at the forefront of much of this work and their research, in addition to that of other investigators, has been reviewed up to 1963 (2). Most synthetic work in this difficult field has involved the condensation of Grignard reagents or diazomethane with ketoses (2,3) or the scission of anhydro sugars with organometallic reagents (4). In addition, the epoxide ring of carbohydrates has been cleaved with diethyl malonate carbanion (5).

We wish now to present a new approach to such synthesis, namely, the application of a modified Wittig reaction (6) to carbohydrate ketoses to afford novel branched-chain unsaturated carbohydrates. The latter compounds are readily converted in excellent yield into saturated branched-chain sugars having a free terminal primary hydroxyl function.

The following is an example of the procedure used at present. An ice-cold solution of phosphonoacetic acid trimethyl ester (2 ml.) and potassium tert-butoxide (0.45 g.) in anhydrous N,N-dimethylformamide (2 ml.) was added to a solution (kept at 0°) of 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (7) (1 g.) in 6 ml. anhydrous N,N-dimethylformamide. The reaction mixture was kept at 0° for 1 h and then at room temperature for 20 h (or until all starting material was consumed as evidenced by monitoring by TLC on silica gel G using benzene: methanol (95:5) as developer) After the solvent was removed under vacuum, water (30 ml.) was added with stirring. The oily product remaining after the water was decanted was dissolved in ether (30 ml.), washed twice with water and then dried over magnesium sulfate. Evaporation of the ether left a partly crystalline product (0.76 g.). Preparative TLC of part of this product (0.35 g.) gave 0.29 g. of two unsaturated branched-chain carbohydrates II and III (in the ratio of 1:3 and each having traces of contamination with the other). The n.m.r. spectrum of each showed the presence of the olefinic protons at 3.7 and 3.8τ, respectively. Infrared spectra confirmed the presence of the olefinic double bond and showed the presence of the carbonyl group. At the present time it is impossible to assign a definitive structure to each particular branched-chain unsaturated carbohydrate.



Hydrogenation of compound II, or III, or of the mixture of these, in ethanol using 10 % palladium on charcoal (1 mole of hydrogen per mole of substrate absorbed) gave compound IV, which was recrystallized from light petroleum ether, m.p. 57-58°; $[\alpha]_D^{22}$ +65 (c 2, ethanol). [Calcd. For $C_{15}H_{24}O_7$: C, 56.95; H, 7.65; mol. wt. 316.35 Found: C, 57.14, H, 7.88; m/e 301 (the base peak in the mass spectrum is at M^+ -15 (loss of CH_3))]. Substance IV was homogeneous (R_f 0.60) by T.L.C. The 100 Mc. n.m.r. of compound IV shows the following proton signals: 4.29 (H 1, doublet, $J_{1,2}$ = 3.7 c.p.s.); 5.25 (one proton triplet, assigned to H-2 and having $J_{2,3}$ = 4.0 c.p.s.); 6.35 (singlet, assigned to methyl ester group); 7.64 (one proton multiplet assigned to H-3).

The configuration of C-3 of compound IV was deduced from the following facts. In the glucofuranose series there is no coupling between H-2 and H-3, thus leading to a doublet for H-2. In the spectrum of compound IV, H-2 signal is a triplet showing that H-2 is also coupled to H-3; therefore, the only possible configuration for C-3 is the allo configuration. This was further proved by spin-spin decoupling experiments. Irradiation of H-2 of IV collapsed H-1 into a singlet and altered H-3. These results are similar to those obtained by irradiating H-2 signal of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose at 5.50 (one proton signal having $J_{2,3}$ = 4 c.p.s.). Therefore, compound IV is undoubtedly 3-deoxy-3-C-(carbomethoxymethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose.

Reduction of compound IV with lithium aluminum hydride in tetrahydrofuran afforded 3-deoxy-3-C-(2'-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (V); $[\alpha]_D^{22}$ +61° (c 2, ethanol); R_f = 0.24; [Calcd. for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39; mol. wt. 288.34. Found: C, 58.20; H, 8.35; m/e = 273 (loss of CH_3).

Sugar V was characterized as its 2'-O-p-toluenesulfonate derivative; m.p. 88-89°; $[\alpha]_D^{22}$ +48° (c 1.3, chloroform).

Studies of the reaction of ketose I with methyl triphenylphosphonium bromide and potassium tert-butoxide according to the procedure of Schlosser and Christman (8), along with an investigation of the application of the modified Wittig reaction to 3,4-O-isopropylidene-2-oxo-β-L-erythro-pentoside (9) and to methyl-α-D-arabino-hexopyranoside-3-ulose (10) will be reported in a future communication.

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