AN EASY ROUTE TO A CHIRAL DIOL IN THE FURAN SERIES FROM 2-DEOXY-ALDOHEXOSES

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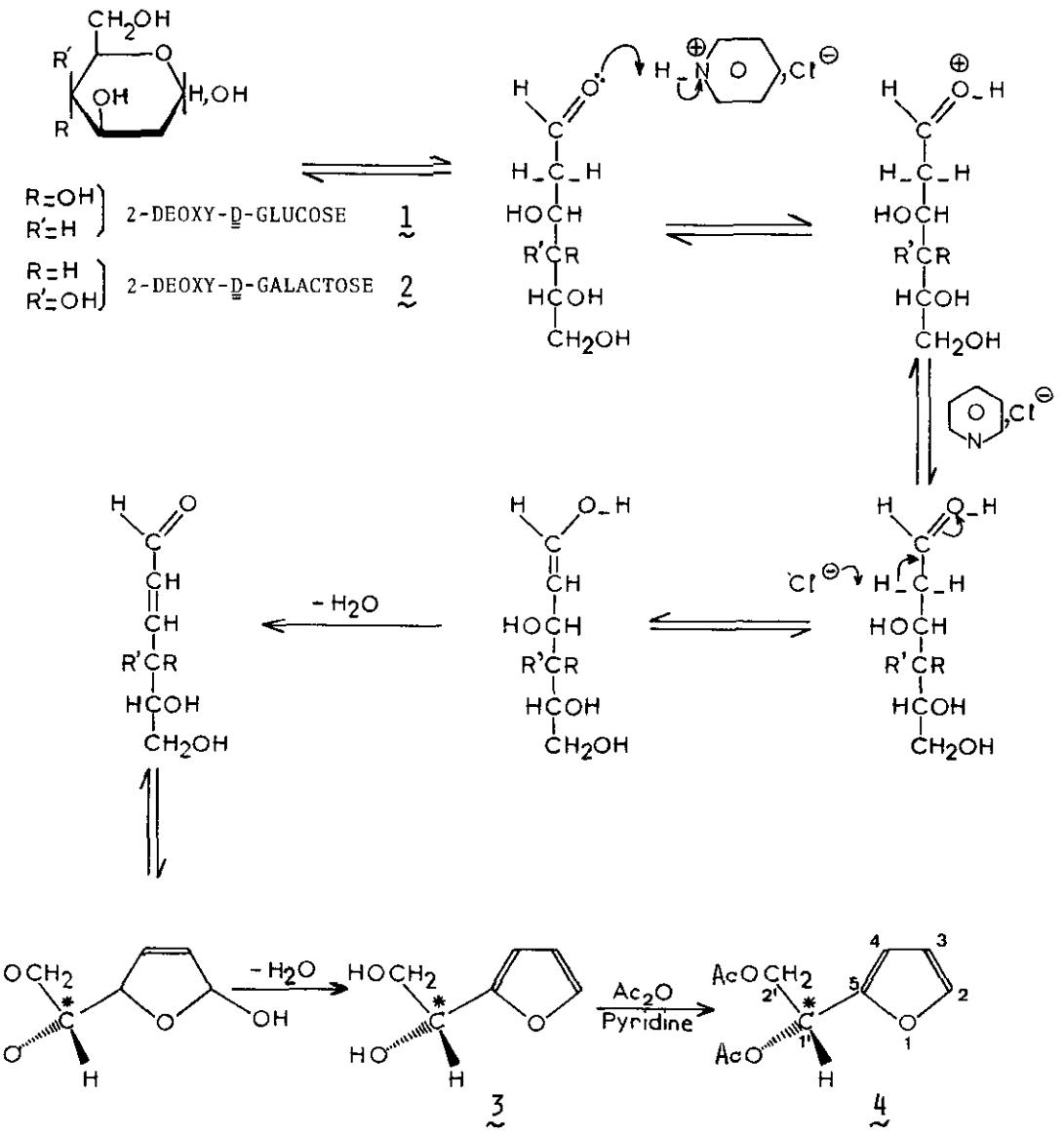
Abstract - A preparative access to a furan substituted by a chiral 1,2-dihydroxyethyl group at position 2 is described. The very simple procedure uses the dehydration of 2-deoxyaldohexoses by heating the sugar with anhydrous pyridinium chloride. This reaction allows comments about general mechanism of dehydration of sugars to furan.

We previously described that direct heating of sugars with anhydrous pyridinium chloride without any solvent can be considered as a very simple one-step procedure for their conversion to furans. Thus 5-hydroxymethyl-2-furaldehyde[1] and a chirally substituted furan (namely 5-(D-glycero-1,2-dihydroxymethyl-2-furaldehyde)[2] are easily available following this method. Due to the now well-established importance of conversion of sugars to non-carbohydrate chiral synthons[3] (or chirons[3c]), and the paucity of access to chirally substituted furans, we tested our procedure with 2-deoxyaldohexoses.

In 1971 it was shown that analytical acid treatment of 2-deoxy-D-glucose gave a compound supposed to be a furan, the chromophoric property of which was proposed as a possible characterization of the sugar[4]. This assumption was more recently supported by the transformation of 2-deoxy-D-glucose with acetic acid at 100°C into a mixture of compounds from which 2-(D-glycero-1,2-dihydroxyethyl)furan was identified[5]. The formation of this compound had been also described in some other reactions[6,7], and especially by Horton, Albano and Tsuchija[7] for the acid hydrolysis of a glycal, namely 4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside.

We found that heating of 2-deoxy-D-glucose (1) with anhydrous pyridinium chloride in pyridine at reflux, followed by acetylation using direct addition of acetic anhydride at room temperature, afforded a 30% yield of 2-(D-glycero-1,2-diacetoxyethyl) furan (4). This compound was identified by NMR spectroscopy. The ^{1}H-NMR spectrum (see Experimental Section) showed inter alia characteristic signals for furanic



protons H-3, 4 and 5, and A_2X spectrum for H-1' and CH_2-2'. Catalytic deacetylation with methanolic sodium methoxide gave quantitatively the diol 3. We repeated the same sequence starting from 2-deoxy-D-galactose (2) and we obtained the same results and yields. Comparison of these results with those obtained from D-glucose and D-galactose themselves, shows that the dehydration of the 2-deoxy derivatives is much easier (30% yield) than the dehydration of the hexoses (0-5% yield). In our opinion, this observation is in favor of a mechanism of the dehydration of sugars

to furans involving the classic enediol intermediate[8], more than the furanose tautomeric form of the sugar as it is proposed by some authors[9]. If we invoke the intermediacy of the furanose tautomer one cannot explain: (i) the difference of reactivity between D-glucose and its 2-deoxy homologue as the furanoses for both sugar represent less than 1% at equilibrium; (ii) the similarity between reactivities for the two deoxyhexoses (2-deoxy-D-glucose and -D-galactose), for which a significant difference can be expected for the respective proportion of furanose (the equilibria depend mostly from the interaction between the C-3—O-3 and C-4—C-5 bonds). The easier dehydration of the 2-deoxy-D-glucose and -D-galactose compared to that of the corresponding hexoses, should be due to a possible higher rate of the enolisation step of the deoxysugars, as well as an easier β-dehydration when a methylene group is involved instead of a CHOH group.

EXPERIMENTAL

Melting points determined on a Büchi apparatus. Evaporations were performed under a diminished pressure. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in 1-dm tubes. Column chromatography was performed with Kieselgel 60 Merck and t.l.c. with precoated plates (Merck 5724), with detection by charring with sulfuric acid. ^{1}H-NMR spectra were performed on a Varian T 60 spectrometer (s: singlet; d: doublet; t: triplet; m: multiplet; δ are given in ppm and coupling in Hz). ^{13}C-NMR spectra were recorded with a JEOL FX 60 instrument.

Reaction of 2-deoxy-D-glucose or 2-deoxy-D-galactose with pyridinium chloride. Synthesis of 2-(D-glycero-1,2-diacetoxyethyl)furan (4): A suspension of 2-deoxy-D-glucose (1) or 2-deoxy-D-galactose (2) (2.5g, 0.015 mole) and pyridinium chloride (5g) in anhydrous pyridine (20ml) was refluxed for 2 h. After cooling at room temperature, acetic anhydride (12 g) was added. The mixture was stirred for 24 h at 20°C and then poured onto ice and sodium bicarbonate. The product was extracted with dichloromethane, and the extracts were washed with saturated aqueous sodium hydrogencarbonate, dried with sodium sulfate. Evaporation of the solvent gave an oily product which was purified by chromatography on a silica gel column (1:3 ethyl acetate-hexane); 0.9 g of crystallized 4 was obtained: yield 30%; m p 29-30°C; $[\alpha]_D$ + 136.4° (c 0.1, chloroform), lit[6] $[\alpha]_D$ + 115.5° (chloroform). ^{1}H-NMR ($CDCl_3$): 2.10 (6H, m, OAc), 4.45 (m, CH_2-2'), 6.15 (m, H-1'), 6.40 (m, H-3 and H-4), 7.45 (m, H-5). ^{13}C-NMR ($CDCl_3$) 170.4 and 169.8 (CO), 149.4 (C-5), 143.1 (C-2), 110.5 and 109.6

(C-3,C-4), 66.2 and 63.3 (C-1', C-2'), 20.9 and 20.6 (CH_3).
Treatment of 2-deoxy-D-galactose (2) under the same conditions gave a compound identical (mp, NMR) to the furan 5 in a comparable yield.

Preparation of 2-(D-glycero-1,2-diacetoxyethyl)furan (3): A catalytic amount of sodium methoxide in anhydrous methanol was added to a stirred solution of 4 in methanol. T.l.c. (ethyl acetate) indicated that the reaction was complete after one hour. The mixture was then stirred with Amberlite IRA-400 for 2 h. The suspension was filtered and the solvent evaporated. Pure 3 was quantitatively obtained as a yellow syrup. $[\alpha]_D$ + 33° (c 0.1, chloroform), lit[7] $[\alpha]_D$ + 36.7° (chloroform). ^{1}H-NMR ($CDCl_3$): 3.75 (d, CH_2-2'), 4.25 (s, OH), 4.75 (t, H-1'), 6.25 (m, H-3 and H-4), 7.30 (m, H-5) $J_{3,4}$ 6.7.

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