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SUGAR ENOLONES, VIII[1].
A FACILE PREPARATION OF DEOXYHEXOSIDULOSES AND DEOXYHEXOSIDES

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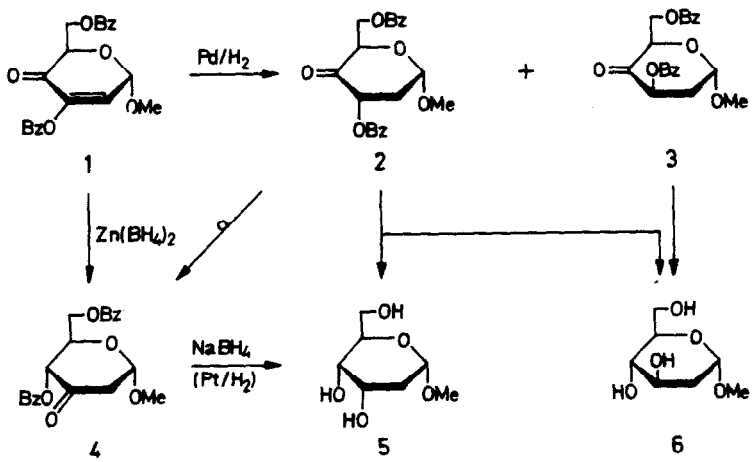
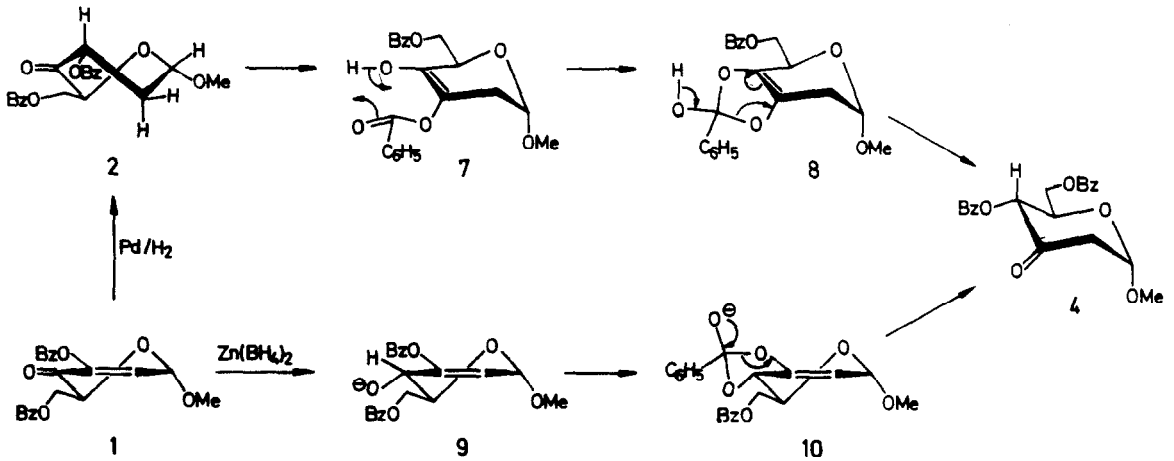
The structural features inherent in pyranoid enolones of type 1 and 11 promise high synthetic potential for the preparation of 4-deoxy- and 2-deoxy-sugars functionalized *via* the carbonyl group at C-2 and C-4, respectively, hence providing access to a variety of deoxy-, amino- and branched-chain sugars. A series of these sugar enolones now being readily accessible[1-4], we have exploited their synthetic utility along this vein and here, firstly, describe a facile preparation of deoxy-hexosiduloses and deoxyhexosides *via* hydrogen and/or hydride addition.

In the 3,4-enolone 1[1] the enolic double bond can readily be saturated without affecting the carbonyl group, e.g. by hydrogenation over Pd/C in methanol/ethyl acetate. The resulting 3:1 mixture (NMR) of *erythro*-2-deoxyhexosid-4-ulose 2 [syrup, $[\alpha]_D$ +230°; 2,4-DNP: m.p. 192 - 194°, $[\alpha]_D$ +815° (c 0.5)][5] and the *threo*-4-uloside 3 [m.p. 88 - 89°, $[\alpha]_D$ +127°; 2,4-DNP: m.p. 157 - 159°, $[\alpha]_D$ -372° (c 0.3)[6]] were separated on silica gel. The yield on 2, however, did not exceed 33 % due to its tendency to rearrange on longer standing or during chromatography to the isomeric *erythro*-3-uloside 4 [m.p. 174 - 176°, $[\alpha]_D$ +195°; 2,4-DNP: m.p. 186°, $[\alpha]_D$ +243°], isolable in yields of up to 10 % on separation of 2 and 3 on silica gel columns. In contrast, the *threo* epimer 3 is entirely unaffected by silica gel.



The conversion 2 → 4 is not without analogy[7,8] and may be rationalized on the basis of an acid-catalyzed 3,4-enolization followed by an $O^3 \rightarrow O^4$-benzoyl migration *via* an enediol-orthoacid intermediate (7 → 8) and subsequent re-ketonization, as illustrated. Thereby, the skew

conformation adopted by 2 on the basis of NMR-data ($J_{1,2}$ = 5.5 and 7.0, $J_{2,3}$ = 7.5 and 14 Hz), utilization of the quasi-axial proton (H-3) for the initial enolization and the preferential axial attachment of a proton at C-4 in the final step, reasonably account for the remarkable stereoselectivity of the reaction as well as for the higher propensity of *erythro*-4-uloside 2 to undergo this rearrangement. Apparently, in the *threo* isomer 3, which exists in an only slightly distorted $^4C_1$-conformation ($J_{1,2}$ = 2.0 and 4.0, $J_{2,3}$ = 7.0 and 12.4 Hz), the axially disposed proton at C-3 is less amenable to enolization than the quasi-axial H-3 in 2.

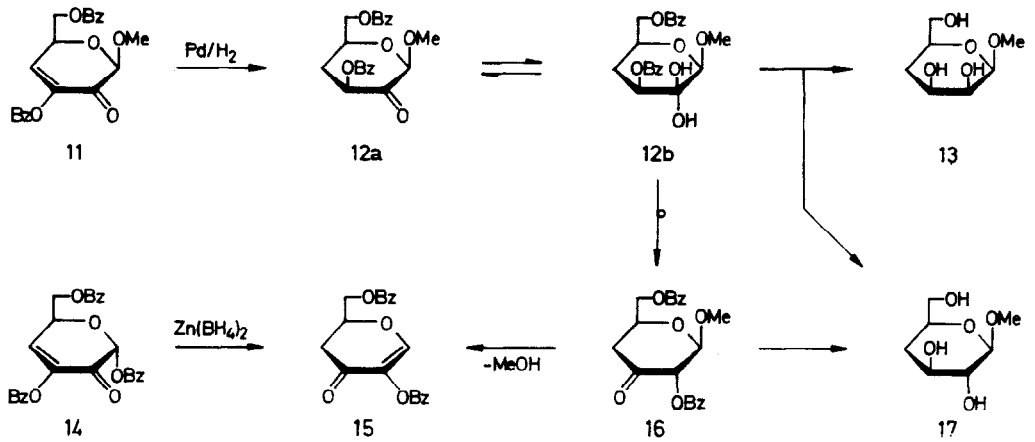


Saturation of the carbonyl group in hexulosides 2 - 4 by Pt/H_2 and subsequent debenzoylation yields 2-deoxyhexosides in distinctly varying degrees of stereoselectivity. Hydrogenation of *threo*-4-uloside 3 proceeded essentially stereospecific to the 2-deoxyarabinoside 6 [m.p. 89 - 91°, $[\alpha]_D^{25}$ +134° (water)[9], isol. yield: 69 %], only a trace of the *lyxo* epimer being detectable[10]. The *erythro*-3-uloside 4 afforded a 3:2 mixture[10] of the 2-deoxyriboside 5 [syrup, $[\alpha]_D^{25}$ +179° (c 0.5, MeOH)[9], 40 % upon separation on silica gel] and 6. In contrast, the hydrogenation of *erythro*-4-uloside 2 proved to be rather complex yielding a mixture of all four 2-deoxyhexosides in the ratio[10] of 20 (*ribo*) : 3 (*arabino*) : 2 (*lyxo*) : 1 (*xylo*). Since the *arabino*-portion cannot originate from direct saturation of the C-4 carbonyl group in 2, but, obviously, from the *erythro*-3-ulose 4, which itself gives a 3:2 mixture of 5 and 6, the relative proportions of isomers obtained allow an assessment of the mechanisms underlying their formation: 60 % of 2 adds hydrogen to the C-4 carbonyl group directly or to the C=C double bond of enediol intermediates 7 or 8 (*cis*-addition) from the sterically less hindered β-side 30 % of 2 is rearranged to the *erythro*-3-ulose 4 which is subsequently hydrogenated with a 3:2 preference for H-addition from above, 7 % of 2 undergoes *cis*-addition of hydrogen to an enediol intermediate from below (→ *lyxo*-portion), whilst only 3 % of 2 saturates the C-4 carbonyl group from the sterically less favored α-side (→ *xylo* isomer). In accord with these rationalizations perhydrogenation of enolone 1 using Pd/C for C=C and Pt for C=O saturation afforded after debenzoylation a 20 (*ribo*) : 12 (*arabino*) : 2 (*lyxo*) : 1 (*xylo*) mixture[10] of 2-deoxyhexosides, from which the major products could readily be obtained in yields of 40 (5) and 23 % (6) by silica gel chromatography.

Sodium borohydride reduction of enolone 1 in methanol gave the same products in a 17 (5) : 10 (6) : 1 (*lyxo*) : 1 (*xylo*) ratio[10] yet *via* an entirely different mechanism: preferential addition of the hydride species to the carbonyl carbon from the less hindered β-side (1 → 9) is followed by an $O^3 \rightarrow O^4$-benzoyl migration through orthoacid intermediate 10 to liberate the

carbonyl group at C-3; the resulting *erythro*-3-uloside 4 subsequently is reduced with a 3:2 preponderance of hydride attack from above to yield 5 and 6. This rationalization is proved by the isolation of 4, in 44 % yield, on reduction of enolone 1 with the less reactive zinc borohydride in dimethoxyethane, by the formation of a specifically C-4 deuterated 4 upon treatment with $Zn(BD_4)_2$ (absence of the 9.5 Hz doublet for H-4 at δ 5.56), and by the 1.6 : 1 preference of 4 for hydride addition from the β-side on reduction with sodium borohydride.

Analogous mechanistic and steric preferences govern the hydrogen and hydride additions to 3,2-enolones, e.g. 11 and 14. In an essentially stereospecific hydrogenation (Pd/C) 11 afforded the 4-deoxy-*threo*-2-uloside as its monohydrate 12b [needles of m.p. 101 - 103°, $[\alpha]_D^{25}$ -35.3° (c 0.5), H-3 at δ 5.22 as dd with $J_{3,4}$ = 6.5 and 11.0 Hz, isolated yield: 43 %], which contained up to 20 % of uloside 12a (H-3 at δ 5.77 with $J_{3,4}$ = 7.0 and 12.5 Hz), its proportion varying with the solvent of recrystallization. The product 12a/12b readily undergoes $O^3 \rightarrow O^2$-benzoyl migration (12 → 16) and subsequent elimination of the anomeric substiuent (16 → 15) on longer standing or in contact with silica gel. Thus, the *erythro*-3-uloside 16 [m.p. 119 - 120°, $[\alpha]_D$ -57.1° (c 0.3), 8.5 Hz-d for H-1 and H-2 at δ 4.82 and 5.85] and dibenzoyl-dihydrokojic acid 15 [m.p. 144 - 145°, $[\alpha]_D$ +124°, H-5 at 4.95 with $J_{4,5}$ = 6.5 and 13 Hz] are obtained in yields of 6 and 11 % yield on purification of 12 on silica gel columns. Nevertheless, enolone 11 can be utilized for an effective preparation of the hitherto inaccessible 4-deoxy-lyxoside 13 [syrup, 1.0 Hz-d for H-1 at δ 4.75 in D_2O; tris-p-nitrobenzoate: m.p. 142°, $[\alpha]_D$ -108°, 69 %], since on perhydrogenation, employing Pd/C for C=C and Pt for C=O saturation, the side reactions of the intermediate ulose 12 are suppressed to give an essentially stereospecific H-addition to the carbonyl group from the α-side, i.e. a 26 : 1 mixture (glc) of 13 and its *xylo* epimer 17.



Considerably less stereoselective proved to be the $NaBH_4$-reduction of 11 affording a 3 : 1 : 1 : 1 mixture of four products (glc), from which the major, lyxoside 13, and the highly crystalline *xylo* isomer 17[11] were isolable in yields of 40 and 13 %, respectively. Since on $NaBD_4$-reduction of 11 no deuterium was incorporated into the C-4 position of either 13 or 17 (NMR), the conversion comprises an initial hydride addition to the carbonyl group with a 2 : 1 preference for attack from the α-side — not unexpected from the steric course of hydride reductions of other methyl β-D-glycosid-2-uloses[12]; the respective intermediates then undergo an $O^3 \rightarrow O^2$-benzoyl shift to 16 (minor product) and the C-2-epimeric *threo*-3-uloside (major), of which the C-3 carbonyl functions are again reduced with preference of hydride addition from the less-hindered α-side[13].

As in the 3,4-enolone case (1 → 4), zinc borohydride reduction was less comprehensive, the β-enolone 11 giving a mixture of 16, 15 and two other products (tlc), whilst α-enolone 14 afforded an approximate 1 : 1 mixture (tlc) of an unstable tribenzoyl-4-deoxy-ulose of conceivable α-D-*erythro* configuration and 15, from which the latter is isolable in good yield.

The foregoing results suggest considerable potential of sugar enolones for a specific access not only to various branched chain and deoxy-amino-sugars — Michael and Grignard type additions as well as reduction of ulose-oximes should exhibit the same or at least very similar stereoselectivities — but, given the availability of *erythro*-3-uloside 2 from enolone 1, also to key intermediates for the synthesis of thromboxane B type natural products[14]. These and other aspects of the chemistry of sugar enolones are presently under investigation.

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5. All compounds gave satisfactory elemental analyses and mass spectral data; rotations were determined in chloroform at c=1 and 25°C unless otherwise stated; ^{1}H-NMR spectral data refer to 100 MHz and $CDCl_3$; 2,4-DNP denotes the 2,4-dinitrophenyl-hydrazone of the respective ulose, prepared by the standard procedure.
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8. J. Hersovici, M. Bessodes, and K. Antonakis, *J.Org.Chem.*, 41, 3827 (1976).
9. For unequivocal characterization, 5 and 6 were converted into their highly crystalline tri-O-p-nitrobenzoates, cf. C.C. Bhat, K.V. Bhat, and W.W. Zorbach, *Carbohydr.Res.*, 10, 197 (1969)
10. G.l.c. on metal columns packed with 3 % OV 101 on gaschrom Q with N_2 as carrier at 155°; retention times for per-O-trimethylsilylated samples of authentic material: 7.9 min (2-deoxy-xyloside), 8.8 (5), 9.8 (2-deoxy-lyxoside) and 10.8 (6).
11. Cf. H.W.H. Schmidt and H. Neukom, *Carbohydr.Res.*, 10, 361 (1969).
12. G.J.F. Chittenden, *Carbohydr.Res.*, 15, 101 (1970); Y. Kondo, N. Kashimura, and K. Onodera, *Agric.Biol.Chem.Jap.*, 38, 2553 (1974); M. Miljković, M. Gligorijević, and D. Miljković, *J.Org.Chem.*, 39, 2118 (1974).
13. The predominant formation of 4-deoxy-lyxoside 13 on $NaBH_4$-reduction of 11 is contrasted by the hydride addition to a β-theophyllinyl-enolone which exclusively (isolated yield: 58 %) gave the 4-deoxy-β-*xylo*-nucleoside in an "unusual attack of hydride ion from the most hindered side"[8], i.e. *cis* to the aglycon. In view of the exceedingly bulky heterocycle as anomeric substituent which will preferentially adopt an *anti*-arrangement relative to the pyranoid ring in a sofa conformation, the hydride attack at the C-2 carbonyl group appears, in fact, to be less sterically hindered from the β-side, as seen from molecular models. Thus, the different steric preferences for hydride addition of a β-methoxy-(11) versa a β-theophyllinyl-enolone are readily accounted for.
14. Cf: S. Hanessian and P. Lavallee, *Can.J.Chem.*, 55, 562 (1977).