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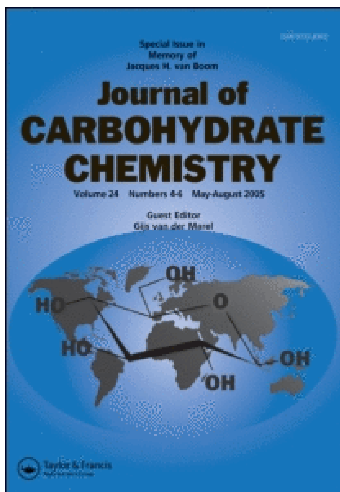

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# MOLYBDIC ACID-CATALYSED ISOMERIZATION OF D-RIBULOSE AND D-XYLULOSE TO THE CORRESPONDING 2-*C*-(HYDROXYMETHYL)-D-TETROSES

Zuzana Hricovíniová, Miloš Hricovíni, and Ladislav Petruš*

Institute of Chemistry, Slovak Academy of Sciences, SK-842 38 Bratislava, Slovakia

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## ABSTRACT

2-*C*-(Hydroxymethyl)-D-erythrose (**2**) and 2-*C*-(hydroxymethyl)-D-threose (**4**) have been stereospecifically synthesized in one-step by a molybdic acid-catalysed isomerization reaction from respective D-xylulose (**1**) and D-ribulose (**3**). In the case of interconversion of **1** to **2**, the content of the 2-*C*-branched chain tetrose in the equilibrium mixture can be doubled if boric acid is present in the reaction mixture in addition to the catalyst.

## INTRODUCTION

Numerous branched chain sugars found as the glycosyl components of antibiotics and other pharmaceutical preparations have stimulated an extensive research on their chemistry and biochemistry. They are of current interest in carbohydrate chemistry since many of them show remarkable biological activity applicable mainly in pharmaceutical chemistry.[1-5]



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2-*C*-(Hydroxymethyl)aldoses with a 2,3-*erythro* configuration are the most easily available branched chain sugars. A simple, general method for their preparation is based on the base-catalysed aldolization of their 2,3-*O*-alkylidene derivatives with formaldehyde. In addition to the corresponding 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene derivatives of D-mannose,[6] D-ribose[7] and D-allose,[8] 2,3-*O*-ethylidene-2-*C*-(hydroxymethyl)-D-erythrofuranose[7] has also been prepared by this approach.

Recently we have shown that 2-*C*-branched chain aldoses can be even more easily prepared in one step by the molybdic acid-catalysed isomerization of 2-ketoses.[9,10] In spite of the equilibria of the interconversions being strongly shifted to the side of 2-ketoses, the method is of a preparative significance because of its extreme simplicity and availability of efficient separation procedures. A shift of the original, thermodynamic equilibria to the side of 2-*C*-(hydroxymethyl)aldoses with the 2,3-*erythro* configuration resulted in improvement of their yields when boric acid was added to the reaction mixtures.[10] Mechanistic studies with isotopically substituted monosaccharides[9,10] have shown that the interconversion of 2-ketoses and 2-*C*-(hydroxymethyl)aldoses with mutually inverted positions of hydroxyl groups at their respective carbon atoms C-3 and C-2, is a consequence of a highly stereospecific carbon skeleton rearrangement of the sugars chelated in the tetradentate dimolybdate complexes. In this respect the molybdic acid-catalyzed interconversion 2-ketose ⇔ 2-*C*-(hydroxymethyl)aldose is similar to the mutual interconversion of isotopically uniform epimeric aldoses, known as the Bílik reaction,[11,12] and can be considered as an extension of this approach. The present contribution broadens further the application of the paradigm to D-pent-2-uloses and describes a simple preparation of 2-*C*-(hydroxymethyl)-D-tetroses.

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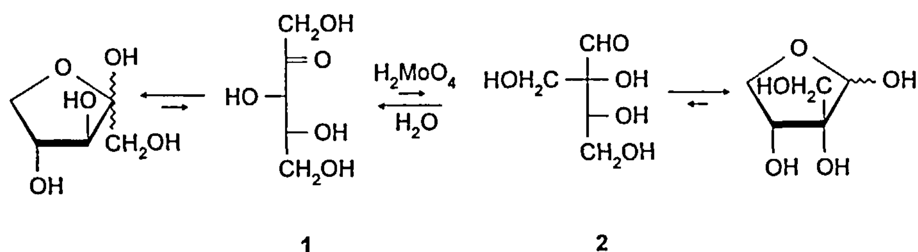
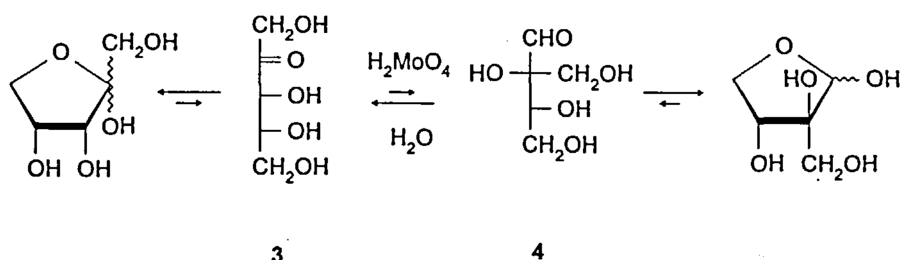
## RESULTS AND DISCUSSION

Preliminary $^1$H NMR screening of both reaction mixtures obtained on treatment of D-xylulose (**1**, Scheme 1) or D-ribulose (**3**, Scheme 2) with a catalytic amount of molybdic acid (*ca* 1 mol %) at 80 °C revealed the presence of a pair of singlets in the anomeric region of the spectrum. Having supposed that the singlets belonged to the respective 2-*C*-(hydroxymethyl)-D-erythrose (**2**) or 2-*C*-(hydroxymethyl)-D-threose (**4**) the expected




Scheme 1




Scheme 2

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branched chain aldoses were isolated by preparative chromatography on a strongly acidic cation-exchange resin in the $Ba^{2+}$ form.

The signal intensities in the $^1H$ and $^{13}C$ NMR spectra of 2-*C*-(hydroxymethyl)-D-threose indicate that both α and β anomers are equally populated in aqueous solution at 40 °C. Two singlet resonances corresponding to α (5.14 ppm) and β (5.21 ppm) anomers, typical for C-2 branched chain sugars, were seen in the $^1H$ NMR spectrum (Fig. 1).

$^3J_{H\text{-}H}$ couplings could be determined in the α anomer; their magnitudes (1.4 Hz for $J_{H3\text{-}H4a}$ and 5.0 Hz for $J_{H3\text{-}H4b}$, respectively) are compatible with a $^2E$ conformation where C-2 is displaced from the plane of the furanose ring, probably as a consequence of an unfavourable *cis* interaction between the hydroxymethyl group at C-2 and the anomeric hydroxyl. The assignments of the $^{13}C$ resonances were based on 1D $^1H$-decoupled $^{13}C$ spectra 2D HSQC spectra that provided additional proof of the structure of branched chain sugar 4. Signals at 104.4 and 100.9 ppm correspond to α and β anomeric carbons, the resonances with lower intensities correspond to quarternary C-2 (85.9 α-anomer, 83.6

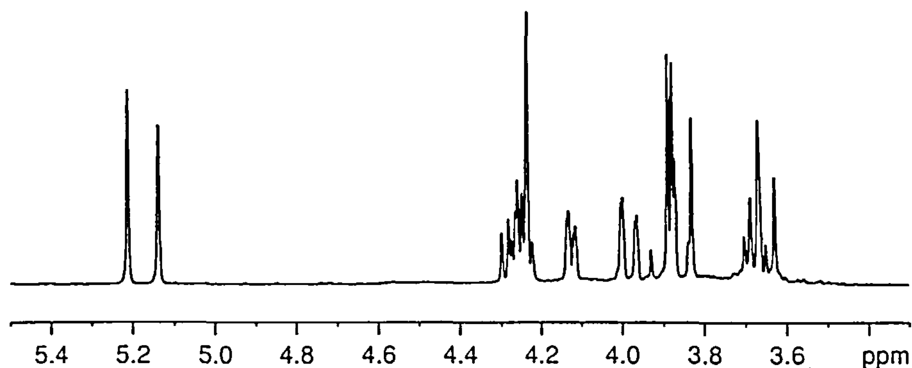


**Figure 1.** The 300 MHz $^{1}$H NMR spectrum of 2-*C*-(hydroxymethyl)-D-threose in aqueous solution at 40 °C. Two singlet resonances at 5.21 and 5.14 ppm originate from β and α anomeric protons, respectively.

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β-anomer). The resonances in the highest field (64.4 and 63.3 ppm) originated from hydroxymethyl groups linked to C-2.

Similar structural evidence based on the analysis of the $^{1}$H and $^{13}$C NMR spectra was obtained also for 2-*C*-(hydroxymethyl)-D-erytrose. The integral intensities of the anomeric $^{1}$H singlet signals were in ratio of 6:4 in favour of α anomer. Since the remaining $^{1}$H resonances were not resolved enough due to the signals overlap and the presence of higher order spin systems in most cases, no conclusions on conformation of the furanose ring could be drawn. The 2D HSQC spectrum in combination with 2D COSY and 1D $^{13}$C spectra, allowed the assignment of the carbon resonances. Anomeric carbons were found at 104.5 ppm (β-anomer) and at 100.0 ppm (α-anomer), quarternary carbons were found at 83.2 ppm (C-2β) and 81.4 (C-2α).

The tautomeric equilibria of both branched chain aldoses **2** and **4** are also striking when compared with those of unbranched aldotetroses. While both D-erythrose and D-threose in aqueous solution contain about 10% of acyclic species,[13,14] the corresponding content of the acyclic species for both their 2-*C*-(hydroxymethyl) derivatives is less than 1%. This is along with an earlier observation[15] that the substitution of the furanose ring enhances the proportions of cyclic forms in solution.

The reaction equilibria were calculated from integral intensities of selected, well-resolved signals in the $^{1}$H NMR spectra of the reaction mixtures. However, it was

necessary to determine also the proportions of the anomero-tautomeric forms of the starting compounds in aqueous solution at 40 °C. This temperature was chosen in order to avoid interference of the anomeric signals of the product aldoses with that of the residual HOD. The integration of the $^1$H signals of three different forms present in solution of D-ribulose gave the following content: 26% of the keto form, 54% of α-furanose and 20% of the β-furanose form. Similar procedure gave the composition of D-xylulose in water solution: 27% of the keto form, 19% of α-furanose and 54% of the β-furanose form.

The integration of both singlet signals at 5.19 ppm and 5.11 ppm of the reaction product (2-*C*-(hydroxymethyl)-D-erythrose) as well as the H-3 proton signal of the keto form of D-xylulose gave their interconversion equilibrium as 1:10. This corresponds well with the value determined by weighing the isolated product (8% of recovery).

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The equilibrium of the mutual interconversion of 2-*C*-(hydroxymethyl)-D-threose and D-ribulose (1:11) was determined from the $^1$H intensities of anomeric protons (at 5.21 ppm and 5.14 ppm) in the $^1$H NMR spectrum of the branched chain aldose **4** and a multiplet originating from the H-3 proton of the keto form and H-4α proton of the furanose form of D-ribulose. The portion of **4** thus found is similar to that obtained in a preparative experiment (7% of recovery). The comparison of the yields of both reactions indicate that the conversions of D-ribulose and D-xylulose to corresponding 2-*C*-(hydroxymethyl)aldoses are similar.

Recently, the mechanism of mutual interconversion of 2-ketoses and 2-*C*-(hydroxymethyl)aldoses catalyzed with molybdic acid was studied using $^{13}$C-substituted hex-2-uloses.[9,10] Since pent-2-uloses and hex-2-uloses have comparable arrangement of the C-1—C-5 array of atoms as well as comparable product amounts resulting from their molybdic acid-catalysed isomerizations, one can assume that the mechanisms of these isomerizations are the same.

A possible mechanism of the molybdic acid-catalysed mutual interconversion of pentulose **1** and branched chain aldose **2** is shown in Scheme 3. The pentulose in a zig-zag conformation chelated in its tetradentate dimolybdate complex **5** stereospecifically, rearranges *via* transition state **6** into chelate **7** - a dimolybdate of branched chain aldose **2** present in a sickle conformation. The zig zag and sickle conformations analogous to those proposed here have been found for dimolybdate complexes of acyclic hydrated forms of

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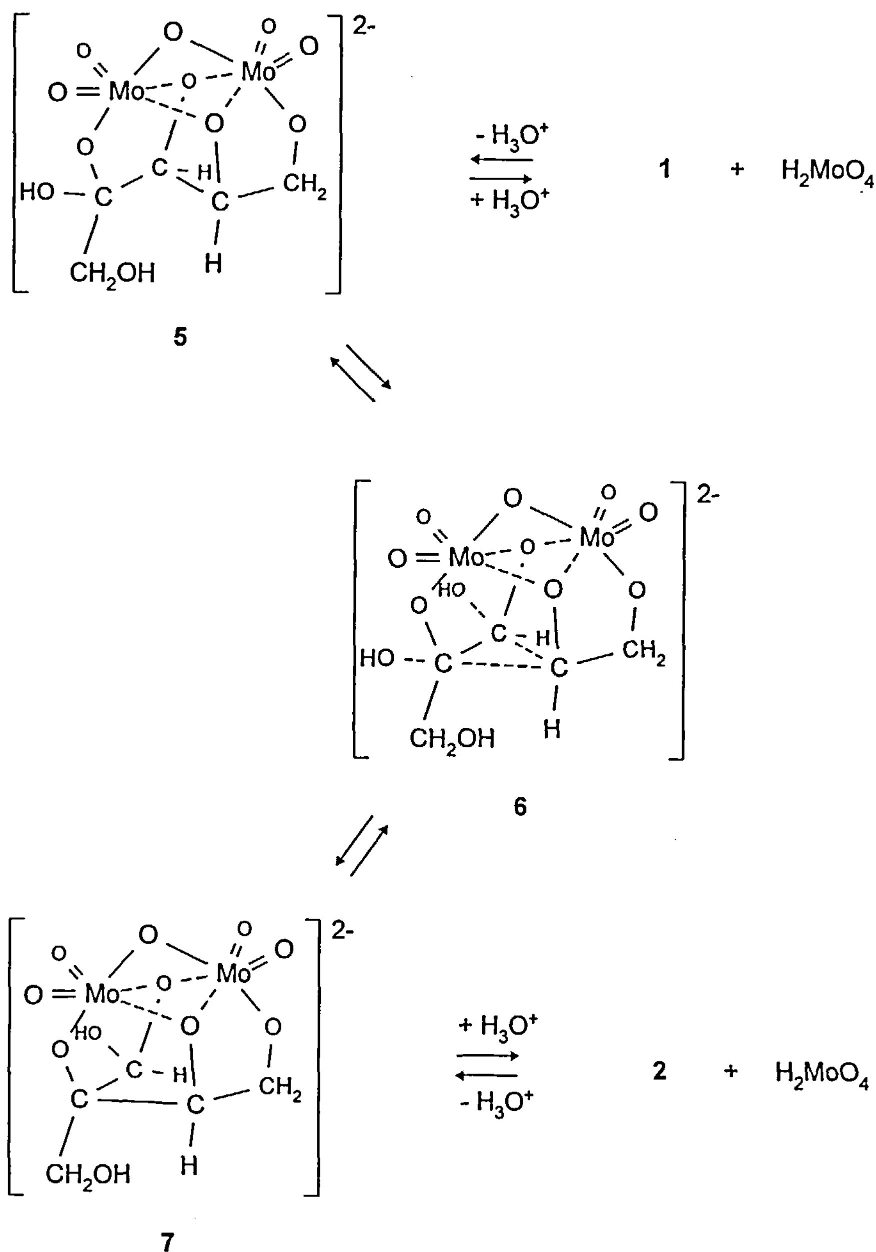


**Scheme 3**

aldoses and 2-ketoses.[16,17] In spite of the relatively dramatic structural changes caused by the carbon skeleton rearrangement, the reaction is unambiguously stereospecific due to continuous chelation of the sugar moiety in the complex during the isomerization process. A similar scheme can be drawn for the interconversion of sugar **3** to **4**. However, D-ribulose forms a complex in its sickle conformation, while 2-*C*-(hydroxymethyl)-D-threose forms a complex in a zig-zag conformation.

Considerable differences in the conversion were observed in case of boric acid-assisted molybdic acid catalysed isomerization of the pentuloses. When the reaction was performed in the presence of four equivalents of boric acid (relative to the 2-ketose starting material) the equilibrium of the mutual interconversion of 2-*C*-(hydroxymethyl)-D-erythrose and D-xylulose was shifted more to the side of the product branched-chain aldose and a new equilibrium ratio 1:5 was obtained. The situation was similar to that of co-application of boric acid in the case for preparation of 2-*C*-(hydroxymethyl)-D-ribose (D-hamamelose) from D-fructose, which gave a 20% yield of D-hamamelose by a one-step reaction.[10] The latter methodology is applicable only if C-2 and C-3 adjacent hydroxyls are in the *erythro* configuration in the product 2-*C*-(hydroxymethyl)aldose, which is apparently being removed from the equilibria with boric acid by competetive complex formation. Thus, while the yield of 2-*C*-(hydroxymethyl)-D-erythrose increased two times (from 7% to 14%), the yield of 2-*C*-(hydroxymethyl)-D-threose decreased from 6% to 3%.

The molybdic acid-catalyzed isomerization of pent-2-uloses described herein involves the use of inexpensive starting materials, readily available reagents and represents an efficient and convenient, one-step preparation of rare branched chain saccharides.

## EXPERIMENTAL

**General methods.** D-Ribulose (D-*erythro*-pent-2-ulose) and D-xylulose (D-*threo*-pent-2-ulose) were prepared as described elsewhere.[18] 300.13 MHz $^{1}H$ and 75.45 MHz $^{13}C$ NMR spectra were recorded in aqueous solution at 313 K on a Bruker DPX 300 spectrometer equipped with a 5 mm inverse broadband probe with a shielded *z*-gradient.

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Proton and carbon chemical shifts were expressed relative to external TSP. One-dimensional (1D) $^{1}H$ NMR spectra were recorded with the spectral width of 2400 Hz and 16 transients were accumulated to obtain sufficient signal/noise ratio. Presaturation of the HDO resonance was achieved by low-power irradiation during part of the relaxation delay. A 5 mm QNP probe was used for measurement of 1D $^{13}C$ NMR spectra. About 2000 transients were collected with the relaxation delay of 1.5 s. Two-dimensional (2D) correlated spectroscopy (COSY) and heteronuclear single quantum coherence (HSQC) experiments were performed using *z*-gradients; the latter experiment in phase sensitivity-enhanced pure-absorption mode.[19] 2D heteronuclear multiple bond coherence (HMBC) was recorded with 60 ms delay for evolution of long-range proton-carbon coupling constants. The spectral widths in heteronuclear experiments were 1200 Hz ($^{1}H$) and 5000 Hz ($^{13}C$), the spectra were zero-filled before Fourier transformation giving the digital resolution of 1.2 Hz/pt and 5.9 Hz/pt, respectively.

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Specific optical rotations were measured with automatic polarimeter Perkin–Elmer, Model 141. The composition of reaction mixtures was examined by paper chromatography on Whatman No. 1 sheets in 5:1:4 (v/v/v/) 1-butanol–ethanol–water ($S_1$) or 8:2:1 (v/v/v) ethyl acetate–pyridine–water ($S_2$) followed by visualisation with alkaline silver nitrate. Column chromatography was performed on column $C_1$ (95×1.6 cm) of Dowex 50W X-8 (37–75 μm) in the $Ba^{2+}$ form using water as the eluant. All evaporations were carried out under reduced pressure at a bath temperature not exceeding 45 °C.

**2-*C*-(Hydroxymethyl)-D-erythrose (2).** A solution of D-xylulose (0.85 g) and 0.2% aqueous molybdic acid (50 mL) was heated at 80 °C for 6 h. The composition of the reaction mixture was tested by PC and $^{1}H$ NMR spectroscopy until equilibrium was reached. The cold mixture was deionized with Amberlite IRA 400 in the $HCO_3^-$ form (100 mL). After 15–20 min the resin was filtered off and washed with water (3×30 mL). The deionized solution was concentrated to a syrup, which was fractionated on column $C_1$ using water as the eluant at the flow-rate 5 mL $h^{-1}$. A considerable amount of starting D-xylulose (0.68 g; 80%) was recovered from fraction *1* (eluted between 100–120 mL). Fraction *2* (collected in the volume 145–175 mL) contained pure 2-*C*-(hydroxymethyl)-D-erythrose (by PC and $^{1}H$ NMR) (55 mg; 7%), $[\alpha]_D$ (*c* 1, water) -3.2° (24 h); $R_{fru}$ 1.9 ($S_1$). $^{1}H$ NMR (300.13 MHz, $D_2O$) δ 5.19 (H-1β, s), 5.11 (H-1α, s), 4.28 (H-4aα, m), 4.21 (H-

4bα, m), 4.05 (H-4aβ, H-4bβ, ABq), 3.78-3.89 (H-2'aβ, H-2'bβ, m), 3.83 (H-3β, m), 3.67 (H-3α, m), 3.54 (H-2'aα, H-2bα, s). $^{13}$CNMR (75.45 MHz, $D_2O$) δ 104.48 (C-1β), 99.98 (C-1α), 83.21 (C-2β), 81.43 (C-2α), 73.69 (C-4α), 73.45 (C-3β), 73.12 (C-4β), 72.77 (C-3α), 66.19 (C-2'α), 65.33 (C-2'β). Fraction *3* (eluted between 180–225 mL) contained D-ribulose with admixture of 2-*C*-(hydroxymethyl)-D-erythrose (20 mg; 2.5%).

**2-*C*-(Hydroxymethyl)-D-threose** (4). D-Ribulose (0.85 g) was treated with molybdic acid and the reaction mixture was further worked up using a similar procedure as for D-xylulose. Chromatography of the sirupy mixture of sugars obtained on $C_1$ at flow-rate 5 mL $h^{-1}$ afforded three fractions. Fraction *1* (eluted between 105–120 mL) contained chromatographically pure title compound 2-*C*-(hydroxymethyl)-D-threose (45 mg, 5.5%), $[\alpha]_D^{20}$ -7.9° (c 1, water) (24 h); $R_{fru}$ 1.9 ($S_1$). $^1$H NMR (300.13 MHz, $D_2O$) δ 5.21 (H-1β, s), 5.14 (H-1α, s), 4.27 (H-4aα, dd, $J_{H3\text{-}H4a}$ 5.0 Hz, $J_{H4a\text{-}H4b}$ 10.1 Hz), 4.25 (H-4aβ, m), 4.24 (H-3β, m), 4.13 (H-3α, dd, $J_{H3\text{-}H4a}$ 5.0 Hz, $J_{H3\text{-}H4b}$ 1.4 Hz), 3.98 (H-4bα, dd, , $J_{H3\text{-}H4b}$ 1.4 Hz, $J_{H4a\text{-}H4b}$ 10.1 Hz), 3.89 (H-2'aα, H-2'bα ABq), 3.85, 3.65 (H-2'aβ, H-2'bβ,d, $J_{H2'a\text{-}H2'b}$ 12.1 Hz), 3.68 (H-4bβ, m). $^{13}$C NMR (75.45 MHz, $D_2O$) δ 104.44 (C-1α), 100.93 (C-1β), 85.92 (C-2α), 83.60 (C-2β), 78.43 (C-3β), 77.57 (C-3α), 77.18 (C-4α), 74.68 (C-4β), 64.48 (C-2'β), 63.32 (C-2'α). Fraction *2* (eluted between 120–135 mL) contained D-xylulose with admixture of 2-*C*-(hydroxymethyl)-D-threose (55 mg; 7%). Fraction *3* (eluted between 280–350 mL) contained recovered D-ribulose (690 mg; 81%).

**Isomerization of pent-2-uloses catalysed with molybdic acid in the presence of boric acid.** A solution of D-xylulose (0.5 g; 3.3 mmol) and boric acid (0.8 g; 12.9 mmol) in 2% aqueous molybdic acid (2.5 mL) was heated at 80 °C for 10 h. The reaction mixture was evaporated to dryness and then again from methanol (4×5 mL) and the mixture was treated with Amberlite IRA-400 in the $HCO_3^-$ form (50 mL). The resin was filtered off and deionized solution was concentrated and fractionated to obtain 2-*C*-(hydroxymethyl)-D-erythrose (68 mg; 14%). Similar procedure performed with D-ribulose instead of D-xylulose yielded 15 mg (3%) of 2-*C*-(hydroxymethyl)-D-threose.

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## REFERENCES


1. F. Shafizadeh, *Adv. Carbohydr. Chem. Biochem.*, **11**, 263 (1956).
2. R. R. Watson and N. S. Orenstein, *Adv. Carbohydr. Chem. Biochem.*, **31**, 135 (1975).
3. H. Masaki, T. Atsumi and H. Sakurai, *J. Dermatol. Sci.*, **10**, 25 (1995).
4. V. V. Kulyayeva, M. K. Kudinova, N. P. Potapova, L. M. Rubasheva, M. G. Brazhnikova, B. V. Rosynov and A. R. Bekker, *Bioorg. Khim.*, **4**, 1087 (1978).
5. R. Toman, L. Škultéty, P. Ftácek and M. Hricovíni, *Carbohydr. Res.*, **306**, 291 (1998).
6. P. T. Ho, *Can. J. Chem.*, **57**, 381 (1979).
7. P. T. Ho, *Tetrahedron Lett.*, 1623 (1978).
8. Z. Hricovíniová and L. Petruš, *Carbohydr. Res.*, **320** (1999) 31-36.
9. Z. Hricovíniová, M. Hricovíni and L. Petruš, *Chem. Papers*, **52**, 692 (1998).
10. Z. Hricovíniová, M. Hricovíni, M. Petrušová, A. S. Serianni and L. Petruš, *Carbohydr. Res.*, **319** (1999) 38-46.
11. V. Bílik, *Chem. Zvesti*, **26**, 183,187,372 (1972).
12. V. Bílik, *Chem. Listy*, **77**, 496 (1983).
13. J. Pierce, A. S. Serianni and R. Barker, *J. Am. Chem. Soc.*, **107**, 2448 (1985).
14. A. S. Serianni, J. Pierce, S.-G. Huang and R. Barker, *J. Am. Chem. Soc.*, **104**, 4037 (1982).
15. J. R. Snyder and A. S. Seranni, *Carbohydr. Res.*, **210**, 21 (1991).
16. M. Matulová and V. Bílik, *Chem. Papers*, **44**, 97 (1990).
17. M. Matulová and V. Bílik, *Chem. Papers*, **46**, 253 (1992).
18. C. Glatthaar and T. Reichstein, *Helv. Chim. Acta*, **18**, 80 (1935).
19. J. Schleucher, M. Satter and C. Griesinger, *Angew. Chem., Int. Ed. Engl.*, **32**, 1489 (1993).


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