Facile and Efficient Synthesis of *ido*-Heptulosan via a Strategy Derived from Mo(VI)-Catalysed Reactions

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Abstract: A simple and high-yielding method for the preparation of 2,7-anhydro-β-D-*ido*-heptulopyranose (IDO) is described. It utilises the ability of molybdate ions to create the conditions for the skeletal rearrangement in the molecule of 2-*C*-branched aldose. This evidence is used in the synthesis of IDO from 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-gulofuranose in one step. The title compound is obtained in 95% yield.

Key words: *ido*-heptulosan, 2,7-anhydro-β-D-*ido*-heptulopyranose, 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-α-D-gulofuranose, 2-*C*-(hydroxymethyl)-D-gulose, Mo(VI) catalysis

Higher saccharides, occurring in small quantities in plants, are known to activate various biochemical processes.[1,2] They are often obtained from natural sources by isolation. However, substantial efforts have also been made to prepare this type of compounds by synthetic methods exclusively. The attention was focussed mainly on those carbohydrates that are useful for pharmaceutical purposes or biochemical studies.[3]

The application of catalysed reactions is one of the most promising techniques in organic synthesis. Recently, it was shown that a convenient synthetic method exists which can be used as an alternative way to obtain some rare carbohydrates.[4–6] This approach is based on molybdic-acid-catalysed reactions[7] that can significantly simplify synthetic procedures. The convenient one-pot methodology, developed for epimerisation of aldoses catalysed by molybdate ions, was shown to be applicable also for the mutual isomerisation of 2-*C*-(hydroxymethyl) aldoses and 2-ketoses. It was confirmed that equilibrium mixtures during these transformations favoured 2-ketoses. Thus, 2-*C*-(hydroxymethyl) aldoses become ideal precursors for the synthesis of 2-ketoses.This method was utilised for the synthesis of D-hamamelose,[4] sedoheptulose,[5] and D-*glycero*-D-*ido*-octulose.[6] On the basis of previous observations on general stereospecificity trends, shown by aldose/*epi*-aldose[8,9] and 2-*C*-(hydroxymethyl) aldose/2-ketose[4,10] mutual isomerisation promoted by Mo(VI), as well as the knowledge of structure of the Mo(VI) carbohydrate complexes,[11–15] we describe herein an efficient and direct route to 2,7-anhydro-β-D-*ido*-heptulopyranose (IDO).

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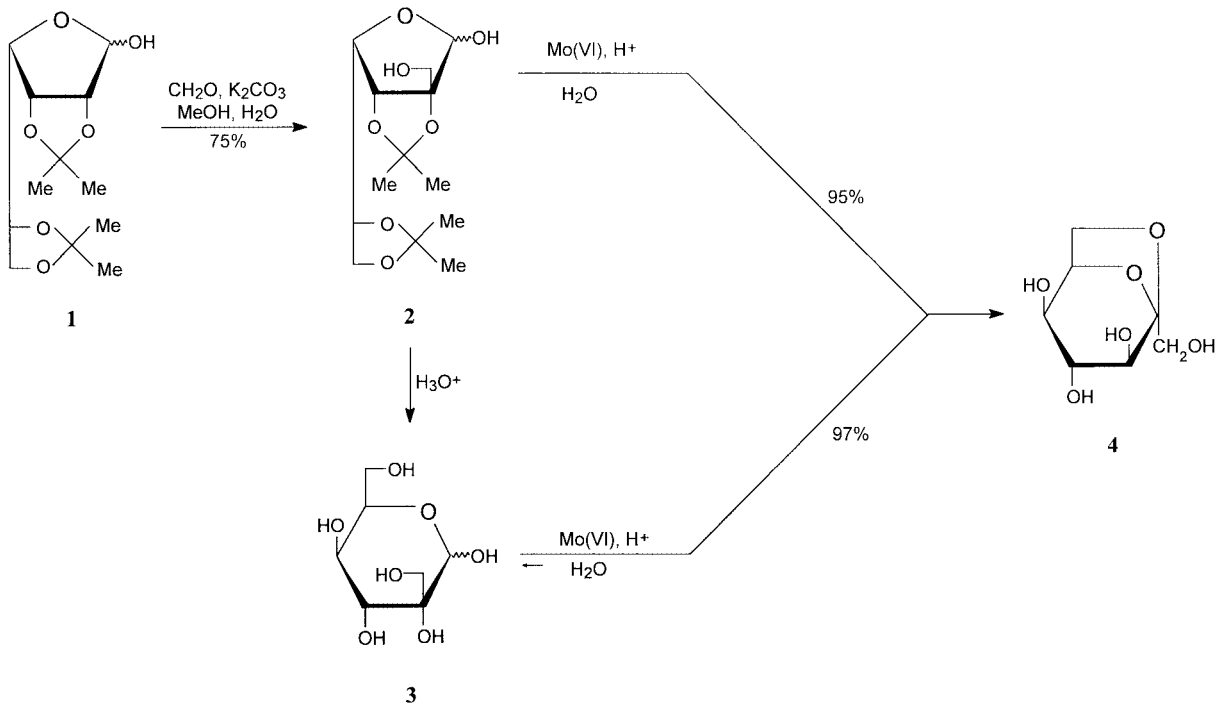
Interconversion of 2-*C*-(hydroxymethyl) aldoses and 2-ketoses with mutually inverted positions of hydroxyl groups at C-2 and C-3 is a consequence of the highly stereospecific carbon skeleton rearrangement that is taking place during the chelation of these sugars in tetradentate dimolybdate complexes. In the present case, the 2,3:5,6-di-*O*-protected derivative of D-gulose was used as the starting compound for the planned synthesis. D-Gulose was acetonated with 2,2-dimethoxypropane and toluene-4-sulfonic acid to give 2,3:5,6-di-*O*-isopropylidene-β-D-gulofuranose (**1**) (Scheme 1) as a colourless crystalline solid (65% yield). The structural assignments were based on ^{1}H and ^{13}C NMR spectra. Introduction of a hydroxymethyl group at C-2 was provided by alkali-based addition of **1** to formaldehyde, yielding the fully characterised 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**2**) in 75% yield. The transformations of the protected sugars were conveniently followed by TLC, since the substrates and products have distinctive R_f values on normal-phase silica plates. A part of product **2** was treated with an ion-exchange resin (H^+ form in H_2O) to give 2-*C*-(hydroxymethyl)-D-gulose (**3**) in 89% yield. The structure of compound **3** was confirmed by NMR spectroscopy. Inspection of both, 1D and 2D NMR spectra revealed that four isomers (α, β, pyranose, and furanose) are present in aqueous solution at 40 °C. As the anomeric signals of both α-forms overlap, the population of the individual isomers was estimated from ^{13}C NMR spectra. The signal intensities indicate that the furanose forms are more abundant (about 60%) and that α- and β-anomers are almost equally populated in both forms. Thus, the abundance of the individual isomers is approximately as follows: 30% α*f*, 30% β*f*, 20% α*p*, and 20% β*p*.

In order to assess the viability of the aforementioned concept, we first explored the isomerisation reaction catalysed by molybdate ions during the conversion of 2-*C*-(hydroxymethyl)-D-gulose (**3**) to D-*ido*-heptulose, and then compared it with the conversion of 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**2**) under the same reaction conditions. The branched-chain aldose **3** was subjected to treatment with a catalytic amount of molybdic acid in acidic aqueous solution at enhanced temperature. The progress of the reaction was monitored by NMR spectroscopy. A smooth isomerisation reaction took place to give the desired product in excellent yield under the previously optimised conditions. The transformation lead relatively fast to an equilibrium mixture of D-*ido*-heptulose and the remaining starting

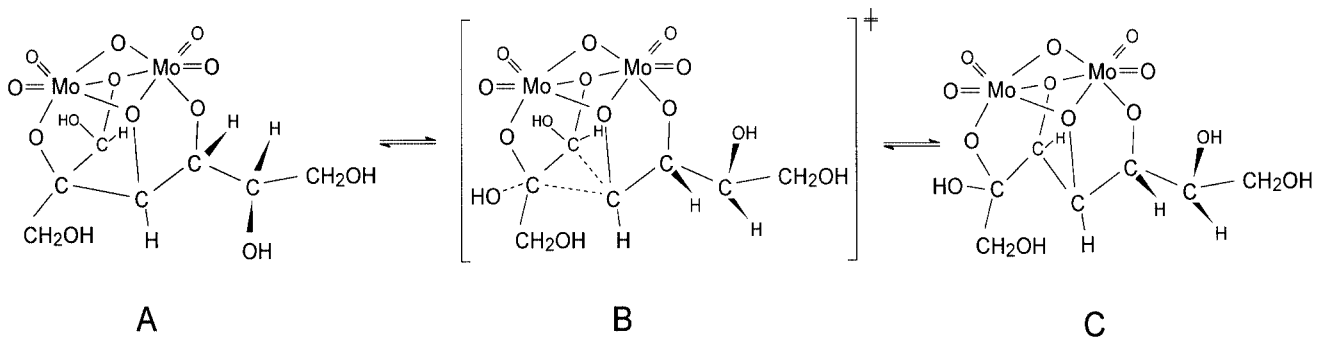


Scheme 1

sugar. The created D-*ido*-heptulose was converted immediately to 2,7-anhydro-β-D-*ido*-heptulopyranose (IDO) (**4**), directly in the reaction mixture. The starting compound was converted to *ido*-heptulosan in almost quantitative yield (97%) after 3 h. Thus, under these conditions a very high yield of IDO (anhydrisation proceeds with marked stereoselectivity) was obtained. The formation of IDO is strongly favoured, because all isomers of D-*ido*-heptulose are rather unstable due to substantial destabilising interactions.[16,17] Apparently, it is readily dehydrated even under mild acidic conditions. So, at 20 °C IDO would furnish more than 91% anhydride.[1]

The formation of the 2-ketose D-*ido*-heptulose is in accordance with the mechanism of isomerisation reactions studied recently.[4,10] In the present case, 2-*C*-(hydroxymethyl)-D-gulose in its acyclic form is bound in a catalytically active dimolybdate complex. This dimolybdate complex involves four O-C bonds to the carbons C-1, C-2, C-3, and C-4 in its hydrated form (**A**). In the transition state of the reaction a bond formation between C-1 and C-3 occurs with simultaneous cleavage of the C-2-C-3 bond (**B**). The dimolybdate complex **C** of the acyclic D-*ido*-heptulose is the product of this transformation (Scheme 2). This transformation involves an isomerisation of the carbon skeleton, and a prolongation of the main chain of the sugar is observed. Thus, a higher sugar (heptulose) is obtained from the lower branched-chain hexose by a stereospecific bond rearrangement, in which the former branch CH_2OH becomes the C-1 carbon of the resulting 2-ketose.

Alternatively, a molybdic acid-catalysed isomerisation of 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**2**) under similar reaction conditions reached the thermodynamic equilibrium mixture of the



Scheme 2

two isomeric saccharides after 6 h. In this case, the kinetics of the conversion of **2** is different. A longer reaction time is required owing to several subsequent reaction steps which take place in a single array: hydrolysis of isopropylidene groups, skeletal rearrangement of 2-*C*-(hydroxymethyl)-D-gulose (**3**) to D-*ido*-heptulose and its subsequent anhydrisation leading to *ido*-heptulosan. The branched-chain aldose **2** was stereospecifically converted to *ido*-heptulosan, as determined from its 1D and 2D NMR spectra. This modification, involving concomitant hydrolysis of the protective groups and simultaneous isomerisation, makes this method more useful from a preparative point of view. Investigations of the scope of the reaction showed that both, 2-*C*-branched aldoses **2** and **3** react readily to give the same anhydro sugar in comparable excellent yield (95–97%) (Scheme 1). The analysis of the components, obtained by separation of the reaction mixture, showed a very small amount (about 2%) of α- and β-D-*threo*-furanose in addition to the product. The formation of D-*threo*-furanose can be explained by a dealdolisation reaction. The acyclic form of D-*ido*-heptulose, created during the release from the dimolybdate complex, undergoes dealdolisation revealing D-threose and 1,3-dihydroxyacetone. Since the acyclic form rearranges immediately to the more stable cyclic form, and further to the anhydro form, the amount of product of the dealdolisation process (D-threose) is nearly negligible.

In conclusion, this communication describes a facile synthesis of D-*ido*-heptulosan by a simple, efficient method and complements the series of syntheses of rare saccharides prepared via this approach.[4–6] The method encompasses all the advantages of traditional catalysis-high stereoselectivity and ease of workup procedure. In this regard, the molybdic-acid-catalysed isomerisation proved to be a particularly valuable approach for the preparation of such compounds and can be successfully extended to the preparation of other biologically interesting carbohydrates.

NMR spectra were recorded on a Bruker DPX 300 spectrometer equipped with a 5 mm inverse broadband probe with a shielded *z*-gradient. The experiments were carried out at 40 °C (D_2O) or 25 °C (acetone), respectively. The ^1H and ^{13}C chemical shifts were referenced to internal TSP (D_2O) and TMS (acetone). 5 mm QNP probe was used for measurements of the 1D ^{13}C NMR spectra. Two-dimensional techniques, COSY, HMBC, and HSQC were used to determine the ^1H and ^{13}C chemical shifts. Melting points were measured with a Kofler hotstage and are uncorrected. The optical rotations were measured on a Perkin-Elmer polarimeter (Model 141), at 20 °C. Thin-layer chromatography (TLC) was performed on precoated silica gel GF_{254} glass plates (Merck), exposed to H_2SO_4 spray followed by charring. Chromatography columns of silica gel were prepared with silica gel 60 (40−60 μm, Merck), using the flash technique. Column chromatography was performed on Dowex 50W X8 (200−400 mesh) ion-exchange resin (Fluka) in Ba^{2+} cycle, using H_2O as eluent. Paper chromatography (PC) was performed applying the descending method on Whatman No. 1 paper and using EtOAc-pyridine-H_2O (8:2:1) as mobile phase. An alkaline silver nitrate was used to locate the spots on the chromatograms. All evaporations were carried out under reduced pressure at a bath temperature not exceeding 45 °C.

2,3:5,6-Di-*O*-isopropylidene-β-D-gulofuranose (1)

The reaction mixture of D-gulose (1 g, 5.55 mmol) in 1,2-dimethoxyethane (75 mL), toluene-4-sulphonic acid monohydrate (0.1 g), and 2,2-dimethoxypropane (5 mL, 40.7 mmol) was stirred for 6 h, followed by addition of Drierite (1 g). Then the reaction mixture was allowed to stand at r.t. overnight. After completion of the reaction as revealed by TLC (EtOAc-light petroleum, 3:1) the reaction mixture was neutralised ($NaHCO_3$), the neutral mixture was filtered with suction and washed with MeOH (2 × 20 mL). The filtrate was concentrated to give a colourless syrupy residue which was purified by flash-chromatography on silica gel (EtOAc-light petroleum, 3:1). The main fraction after chromatographic separation, as indicated by TLC, was the major product **1**, isolated as a white, crystalline solid.

Yield 0.94 g (65%); mp 111–113 °C; R_f 0.71 (EtOAc-light petroleum, 3:1); $[\alpha]_D^{20}$–1.54° (c = 1, acetone).

^1H NMR (300.13 MHz, acetone-d_6): δ = 5.30 (H-1), 4.82 (H-3), 4.57 (H-2), 4.27 (H-5), 4.13 (H-6), 4.08 (H-4), 3.77 (H-6').

^{13}C NMR (75.45 MHz, acetone-d_6): δ = 114.57 (2,3-*C*Me_2), 111.41 (5,6-*C*Me_2), 103.61 (C-1), 88.46 (C-2), 84.43 (C-4), 82.75 (C-3), 78.54 (C-5), 68.28 (C-6).

2-*C*-(hydroxymethyl)-2,3:5,6-Di-*O*-isopropylidene-α-D-gulofuranose (2)

To the solution of **1** (0.5 g, 1.7 mmol) in MeOH (6.5 mL), K_2CO_3 (0.36 g) and an aq solution of formaldehyde (37%, 4.3 mL, 42 mmol) was added. The mixture was refluxed under Ar atmosphere at 85 °C for 48 h. The conversion was checked with TLC (EtOAc-light petroleum, 3:1) until the disappearance of **1**. After cooling the reaction mixture to 25 °C, it was neutralised with aq H_2SO_4 (10%) and evaporated. The residue was extracted with $CHCl_3$ (3 × 35 mL) and the combined layers were dried ($MgSO_4$) overnight and concentrated. The crude product was purified by flash-chromatography on a column of silica gel (EtOAc-light petroleum, 6:1). TLC indicated one major syrupy product, which solidified on trituration with solvent. Crystallisation from acetone gave **2** as a colourless solid.

Yield 0.42 g (75%); mp 95–96 °C; R_f 0.69 (EtOAc-light petroleum, 3:1); $[\alpha]_D^{20}$–5.57° (c = 1, acetone).

^{13}C NMR (75.45 MHz, acetone-d_6): δ = 114.21 (2,3-*C*Me_2), 109.82 (5,6-*C*Me_2), 104.27 (C-1), 95.77 (C-2), 84.04 (C-3), 83.18 (C-4), 76.69 (C-5), 66.53 (C-6), 62.61 [CH_2(C-2)].

2-*C*-(Hydroxymethyl)-D-gulose (3)

A mixture of **2** (45 mg), H_2O (2 mL), and Dowex 50 W X4 resin in the H^+ form (1 mL) was stirred at 75 °C for 5 h. The resin was removed by filtration, washed with H_2O (3 × 3 mL), and the combined filtrate was purified with charcoal followed by evaporation to dryness giving syrupy **3**.

Yield 29 mg (89%); $[\alpha]_D^{20}$–9.8 to –9.5° (c = 1, H_2O) (24 h).

^{13}C NMR (75.45 MHz, D_2O): δ = 103.73 (C-1 β*f*), 99.43 (C-1 α*f*), 98.79 (C-1 β*p*), 94.43 (C-1 α*p*), 83.35 (C-2 β*f*), 82.34 (C-2 α*f*), 82.21 (C-4 α*f*), 81.08 (C-4 β*f*), 77.73 (C-5 β*p*), 75.73 (C-2 β*p*), 75.45 (C-2 α*p*), 74.46 (C-3 β*f*), 73.77 (C-3 α*f*, C-5 α*f*), 73.65 (C-3 β*p*), 73.23 (C-4 α*p*), 72.77 (C-5 α*p*), 72.28 (C-3 α*p*, C-4 β*p*, C-5 β*f*), 65.80 [*C*H_2(C-2) α*f*], 65.60 (C-6 α*f*), 65.48 [*C*H_2(C-2) α*p*], 65.34 (C-6 β*f*), 65.20 [CH_2(C-2) β*f*], 64.41 [*C*H_2(C-2) β*p*], 63.90 (C-6 β*p*), 62.36 (C-6 α*p*).

D-*ido*-Heptulosan (2,7-anhydro-β-D-ido-heptulopyranose) (4)

A mixture of **2** (200 mg, 7 mmol) and a 0.3% (w/w) solution of H_2MoO_4 in 0.3 M HCl (10.5 mL) was stirred at 85 °C for 7 h. The composition of the reaction mixture was examined by paper chromatography (EtOAc-pyridine-H_2O, 8:2:1) until the equilibrium was reached. The mixture was treated batch-wise with an excess of the ion-exchange resin Amberlite IRA-400 in the HCO_3^- form (50 mL)

to remove the catalyst. Then the resin was filtered off and washed with H_2O (3 × 30 mL). The combined filtrates were concentrated under reduced pressure to give a syrup (120 mg). The syrupy residue (120 mg) was fractionated by column chromatography on Dowex 50W X8 (200–400 mesh) in the Ba^{2+} form with H_2O as eluent, at a flow rate of 20 mL/h. Fraction 1 (eluting between 80 and 100 mL) contained 2,7-anhydro-β-D-*ido*-heptulopyranose (114 mg, 95%) (**4**). The syrupy residue (114 mg), obtained after concentration of fraction 1, was triturated with ethanol and kept in a refrigerator for several days to give a crystalline solid. Recrystallisation from ethanol gave colourless needles.

Yield 95 mg (83%); mp 117–118 °C, $[\alpha]_D^{20}$ –41° (c = 1, H_2O) (24 h).

The obtained physical and spectroscopic data are in accordance with the literature.[3]

^{13}C NMR (75.45 MHz, D_2O): δ = 110.47 (C-2), 78.83 (C-6), 77.64 (C-4), 76.75 (C-3), 73.93 (C-5), 68.77 (C-7), 62.68 (C-1).

Fraction 2 (eluting between 100 and 120 mL) showed the presence of α- and β-D-*threo*-furanose (3 mg, 2%) in a mixture with IDO. Fraction 3 (eluting between 140 and 170 mL) contained a small amount of 2-*C*-(hydroxymethyl)-D-gulose (**3**, 1%).

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References

(1) Webber, J. N. *Adv. Carbohydr. Chem.* **1962**, *17*, 43.
(2) Bianchi, G.; Gamba, A.; Murelli, C.; Salamini, F.; Bartels, D. *Plant. J.* **1991**, *1*, 355.
(3) Yokota, A.; Sakane, T.; Imai, K. *J. Ferment. Bioeng.* **1993**, *75*, 417.
(4) Hricovíniová-Bíliková, Z.; Hricovíni, M.; Petruová, M.; Seranni, A. S.; Petru, L. *Carbohydr. Res.* **1999**, *319*, 38.
(5) Hricovíniová-Bíliková, Z.; Petru, L. *Carbohydr. Res.* **1999**, *320*, 31.
(6) Hricovíniová, Z.; Hricovíni, M.; Petru, L.; *Monatsh. Chem.* in press.
(7) (a) Bílik, V. *Chem. Zvesti.* **1972**, *26*, 183. (b) Bílik, V. *Chem. Zvesti.* **1972**, *26*, 187. (c) Bílik, V. *Chem. Zvesti.* **1972**, *26*, 372.
(8) Bílik, V. *Chem. Listy* **1983**, *77*, 496.
(9) Hayes, M. L.; Pennings, N. J.; Serianni, A. S.; Barker, R. *J. Am. Chem. Soc.* **1982**, *104*, 6764.
(10) Hricovíniová, Z.; Hricovíni, M.; Petru, L. *Chem. Papers* **1998**, *52*, 692.
(11) Matulová, M.; Bílik, V. *Chem. Papers* **1990**, *44*, 97.
(12) Matulová, M.; Bílik, V. *Carbohydr. Res.* **1993**, *250*, 203.
(13) Sauvage, J. P.; Chapelle, S.; Verchère, J. F. *Carbohydr. Res.* **1992**, *237*, 23.
(14) Chapelle, S.; Verchère, J. F. *Carbohydr. Res.* **1995**, *277*, 39.
(15) Ramos, M. L.; Caldeira, M. M.; Gil, V. M. S. *Carbohydr. Res.* **2000**, *329*, 387.
(16) Angyal, S. J.; Le Fur, R. *Carbohydr. Res.* **1984**, *126*, 15.
(17) Angyal, S. J.; Tran, T. Q. *Aust. J. Chem.* **1983**, *36*, 937.