Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1567–1571

TETRAHEDRON: *ASYMMETRY*

Highly stereospecific Mo(VI)-mediated synthesis of D-*glycero*-L-*galacto*-octulose

Zuzana Hricovíniová

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

Received 4 July 2002; accepted 9 July 2002

Abstract—A convenient, practical synthesis of D-*glycero*-L-*galacto*-octulose from a 2-*C*-(hydroxymethyl) branched-chain aldose, utilising the catalytic effect of molybdate ions is presented. 2-*C*-(Hydroxymethyl)-D-*glycero*-L-*talo*-heptose (obtained by elaboration of the appropriately protected aldose) gives access to an eight-carbon sugar in a single step through stereospecific isomerisation. The structure of the final product was determined by NMR spectroscopic analysis and theoretical calculations.

1. Introduction

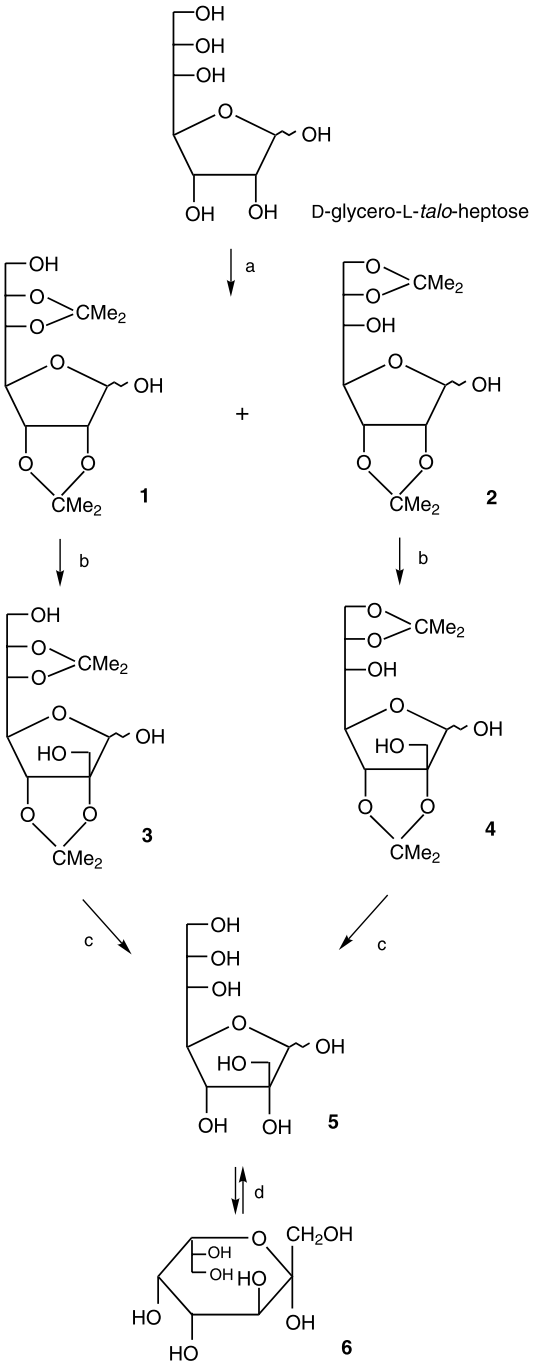
Recent studies on the bioactivities of carbohydrates have led to great interest in their chemistry. A number of saccharides are components of biologically active compounds and play important roles in life processes. Higher saccharides, such as octuloses, occur in plants and are involved in various functions, particularly those related to intracellular communication.[1–3] The demand in various fields for simple and effective synthetic procedures for the preparation of these rare saccharides has thus increased greatly. Transition metal-catalysed reactions appear to be efficient methods as they proceed under mild conditions. One such approach is based on the Mo(VI)-catalysed epimerisation of aldoses.[4] Recent studies on the effect of Mo(VI) ions on the mutual interconversion of saccharides revealed that 2-*C*-(hydroxymethyl)aldoses can be transformed to 2-ketoses and vice versa.[5,6] The equilibrium mixture of 2-*C*-branched aldose/2-ketose is reached in aqueous solutions although the thermodynamic equilibrium of this transformation is shifted in favour of the 2-ketose. Thus, 2-*C*-(hydroxymethyl)-branched chain aldoses are ideal starting compounds for the synthesis of 2-ketoses through molybdic acid-catalysed isomerisation. The utility of this procedure was proved in the successful syntheses of various biologically active monosaccharides.[7–9] The work presented herein is an extension of previous studies on syntheses of relevant higher-carbon sugars and describes the synthesis of D-*glycero*-L-*galacto*-octulose by Mo(VI)-catalysed isomerisation.

2. Results and discussion

The acetalation of sugars with 2,2-dimethoxypropane in 1,2-dimethoxyethane in the presence of 4-toluenesulphonic acid provides *cis*-diol protection (including the C2–OH group) and leads to a suitably rigid structure for addition of the C-2 nucleophile to formaldehyde. Thus, acetalation of D-*glycero*-L-*talo*-heptose at room temperature afforded 2,3:5,6-di-*O*-isopropylidene-D-*glycero*-β-L-*talo*-heptopyranose **1** and 2,3:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*talo*-heptofuranose **2** (Scheme 1) as the major products (37 and 25%). The base-catalysed nucleophilic addition of **1** to formaldehyde proceeded smoothly and 2,3:5,6-di-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-*glycero*-β-L-*talo*-heptofuranose **3** was obtained in a good yield (63%). The same procedure was applied to yield 2,3:6,7-di-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-*glycero*-β-D-*gulo*-heptofuranose **4** from **2**. This condensation can be effected without difficulty to yield 2-*C*-branched aldoses. The presence of the hydroxymethyl group at C-2 in **3** and **4** was confirmed by a characteristic ^{13}C resonance at 62.70 and 62.18 ppm, respectively. The structure of both compounds has been confirmed by 2D HSQC and HMBC NMR methods. After release of the isopropylidene groups in **3** and **4** by acid hydrolysis, the identical product, 2-*C*-(hydroxymethyl)-D-*glycero*-L-*talo*-heptose **5**, was isolated as a syrup in a good yield (96, 88%, respectively). Four resonances were observed in the anomeric region of the ^1H NMR spectrum of **5** originating from the four cyclic forms present in aqueous solution. The integral intensities indicate that both furanose forms are prevailing, the α-anomer being more abundant (~35%). The populations of the α- and β-

E-mail: hricovini@savba.sk

0957-4166/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0957-4166(02)00374-9



Scheme 1. *Reagents and conditions*: (a) *p*-Ts-OH, DMP/DME, 25°C, 24 h; (b) CH_2O/CH_3OH, K_2CO_3, 85°C, 46 h; (c) Dowex 50W (H^+), 70°C, 5 h; (d) H_2MoO_4/H_2O, 80°C, 6 h.

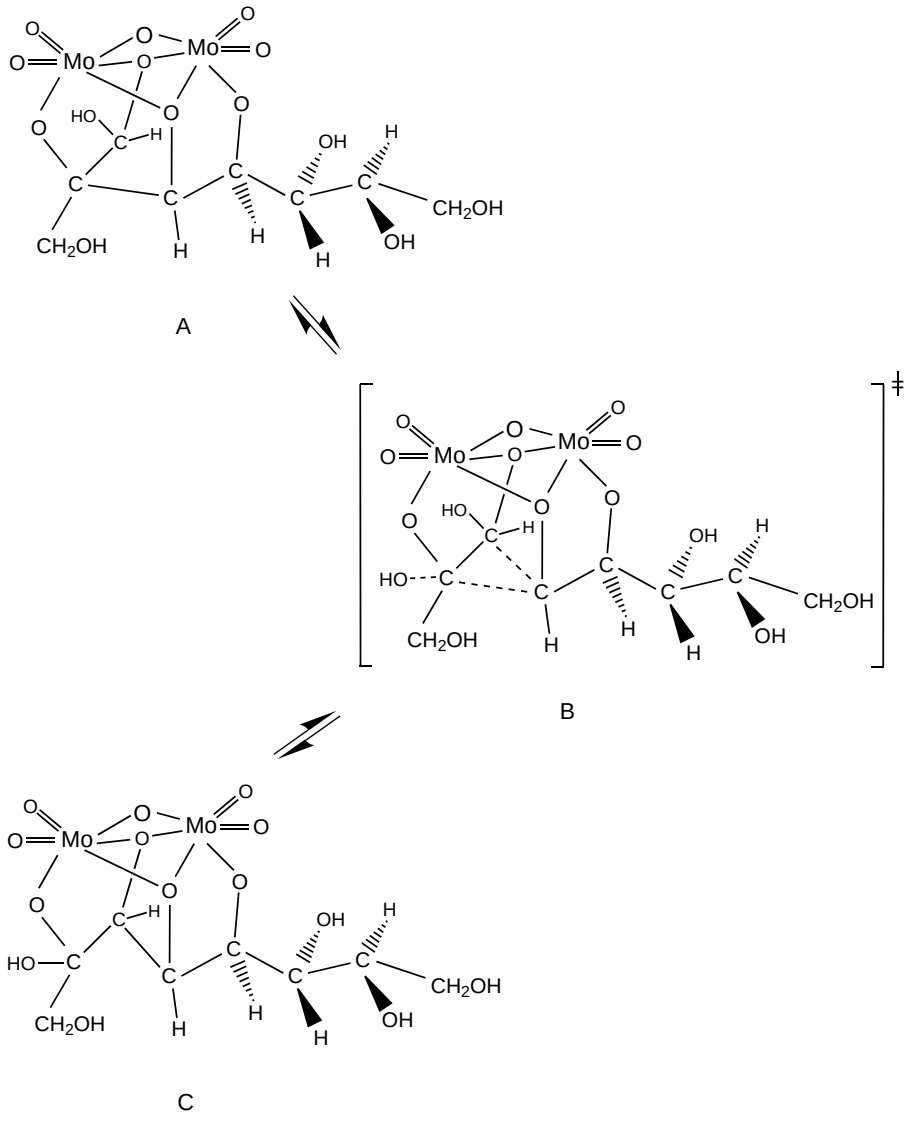
pyranose forms were found to be approximately equal (~20%).

Skeletal rearrangement in the molecule of the 2-*C*-(hydroxymethyl) branched-chain aldose **5** to the desired 2-ketose, D-*glycero*-L-*galacto*-oct-2-ulose **6** is catalysed by molybdate ions. The isomerisation took place in mild aqueous acid solution in the presence of a catalytic amount of molybdic acid. The progress of the reaction was monitored by NMR spectroscopy. An equilibrium mixture of the starting branched chain aldose **5** and the 2-ketose product **6** (Scheme 1) is formed in the ratio of 3:1 as determined by integration of the corresponding signals in the ^1H NMR spectrum of the reaction mixture.

The formation of the 2-ketose is in accord with the mechanism of the isomerisation reaction presented recently.[5,6] Thermodynamic equilibria of these interconversions are strongly shifted to the side of 2-ketoses. It was confirmed that this isomerisation proceeds as an intramolecular process with the C-1–C-2–C-3 rearrangement of carbon skeleton of the starting 2-*C*-branched-aldose. The pertinent carbon atoms become the respective C-3, C-2, and C-4 centres in the skeleton of the 2-ketose, while the CH_2OH branch becomes the C-1 carbon. Moreover, a simultaneous change of configuration at secondary α-carbon atoms occurs. In the present case, the branched-chain aldose **5** in its acyclic form is apparently bound in a catalytically active dimolybdate complex (Scheme 2A) through the four hydroxyl groups (on C-1, C-2, C-3 and C-4) of its hydrated form. The rearrangement occurs through a transition state (Scheme 2B) with the formation of the corresponding dimolybdate complex of acyclic D-*glycero*-L-*galacto*-oct-2-ulose **6** (Scheme 2C). During this transformation, the bond formation between C-1 and C-3 occurring with simultaneous cleavage of the C-2–C-3 bond. Octulose **6** is present in aqueous solution after its release from the dimolybdate complex.

Purification of the reaction mixture into its components was achieved by chromatography on a cation-exchange resin column in the Ba^{2+} form. D-*glycero*-L-*galacto*-Oct-2-ulose was the main component, isolated in 59% yield. The starting 2-*C*-(hydroxymethyl)-D-*glycero*-L-*talo*-heptose was recovered in 31% yield. Besides the expected compounds a small amount (3%) of another component was isolated from the reaction mixture. This compound was found to be D-xylopyranose as determined by NMR spectral analysis. It is assumed that the partial dealdolisation reaction is a consequence of a relatively high abundance of the acyclic form of octulose in solution, so that 2-ketose is susceptible to dealdolisation, which yields D-xylose and dihydroxyacetone. A similar process occurs during the isomerisation of 2-*C*-(hydroxymethyl)-D-*gulo*-heptose to D-*glycero*-D-*ido*-oct-2-ulose.[9]

The structure of the product **6** in aqueous solution was analysed by 2D NMR spectroscopy and by theoretical calculations. Both ab initio and Monte Carlo conformational search data clearly favoured the $^1C_4$ pyranose form; the optimised energy obtained by both methods was found to be much lower for the pyranose than for the furanose form (the difference was more than 20 kJ/mol in both cases). Furthermore, the β-pyranose form was found to be more stable than the α-pyranose one by 16.7 kJ/mol. This evidence is, however, not surprising as both large groups (hydroxymethyl and the dihydroxyethyl) adopt an equatorial position in the β-anomer. These data were in full agreement with the



Scheme 2.

NMR spectral analysis. The value of the three-bond proton–proton coupling constants between H-3 and H-4 ($^3J_{H3-H4}$) was 10.0 Hz. The large $^3J_{H3-H4}$ value indicates that hydrogens H-3 and H-4 are oriented in an approximately antiperiplanar disposition. The computed dihedral angle between hydrogens H-3 and H-4 for the $^1C_4$ pyranose form was 179.6° (ab initio; 168.6° obtained by Monte Carlo). Unlike the pyranose form, the corresponding dihedral angle in the furanose form was 147.5° as computed by the ab initio method. Even larger differences between these two forms were obtained for the arrangement of hydrogens H-4 and H-5. The value of the experimental $^3J_{H4-H5}$ was 3.3 Hz, which is in agreement with a *syn*-arrangement between H-4 and H-5. The computed dihedral angle between H-4 and H-5 in the pyranose form was −52.0° (ab initio; −56.3° obtained by Monte Carlo calculations). On the other hand, the corresponding dihedral angle in the furanose form was −164.4 or −173.5° (ab initio and Monte Carlo methods, respectively) and is incompatible with the relatively small $^3J_{H4-H5}$ value observed in the NMR spectrum. The small value of the three-bond proton–carbon coupling constant H-3–C-1 ($^3J_{H3-C1}$), inferred from the 2D HMBC spectrum, is in agreement with the $^1C_4$ β-pyranose form. The dihedral angle between H-3 and C-1 is ∼−50° in this stereochemical arrangement. In contrast, the dihedral angle between H-3 and C-1 is ∼−170° in the α-pyranose form as obtained by calculations. Such an arrangement would result in a relatively large value for $^3J_{H3-C1}$ and is thus incompatible with the α-anomeric form. As a result, both theoretical and experimental data show that the $^1C_4$ β-pyranose form of D-*glycero*-L-*galacto*-oct-2-ulose is the prevalent one in aqueous solution at room temperature.

3. Conclusion

In conclusion, a versatile route to D-*glycero*-L-*galacto*-oct-2-ulose has been developed. The key step of this transformation–isomerisation catalysed by Mo(VI) can

be performed conveniently, thus giving synthetic importance to this type of rearrangement. Further experiments will be necessary to establish the full preparative potential of this approach in the synthesis of other bioactive saccharides.

4. Experimental

4.1. General methods

^{1}H and ^{13}C 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 in aqueous solution at 313 K and in acetone at 298 K, respectively. The chemical shifts were referenced to internal TSP (D_2O) and TMS (acetone). The 5 mm QNP probe was used for the measurements of the 1D ^{13}C NMR spectra. Two-dimensional (2D) techniques, COSY, HMBC and HSQC were used to determine the ^{1}H and ^{13}C chemical shifts; 2D HSQC experiment was performed in phase-sensitive pure-absorption mode.[10] The energy minimisations of both furanose and pyranose forms have been performed by Monte Carlo conformational search within MacroModel V 7.0 program[11] and by ab initio using the 3-21 G basis set. AMBER force field and continuum model for solvent effect evaluation in Monte Carlo search were used to optimise the geometry.

Optical rotations were determined at 20°C with an automatic polarimeter Perkin–Elmer Model 141 using a 10 cm, 1 mL cell. MALDI analyses were carried out on a Bruker Biflex III spectrometer. Reactions were followed by thin-layer chromatography (TLC) on glass plates precoated with silica gel GF_{254} (Merck), detection with 10% sulphuric acid in ethanol and subsequent heating. Silica gel 60 (40–100 μm, Merck) was used for flash column chromatography. Separations of the free sugars were accomplished by column chromatography on a Dowex 50W X8 resin (Fluka) in the Ba^{2+} form (200–400 mesh), using water as the eluant. Paper chromatography (PC) was performed applying the descending method on Whatman No. 1 paper using ethyl acetate–pyridine–water (v/v/v 8:2:1) as mobile phase. The chromatograms were detected with alkaline silver nitrate developer. The evaporation of solvents were conducted under reduced pressure below 45°C.

4.2. 2,3:5,6-Di-*O*-isopropylidene-D-*glycero*-β-L-*talo*-heptofuranose, 1 and 2,3:6,7-di-*O*-isopropylidene-D-*glycero*-β-L-*talo*-heptofuranose, 2

The reaction mixture of D-*glycero*-L-*talo*-heptose (0.45 g; 2.14 mmol), 1,2-dimethoxyethane (45 mL), toluene-4-sulphonic acid monohydrate (0.05 g) and 2,2-dimethoxypropane (3 mL, 24.5 mmol) was stirred vigorously for 8 h. Then, Drierite (1 g) was added and stirring continued at room temperature overnight, until the disappearance of starting material on TLC solvent A (5% MeOH in 6:1 ethyl acetate:hexane). The reaction mixture was neutralised by addition of $NaHCO_3$ (pH 7). The neutral mixture was filtered with suction and washed with methanol (2×20 mL). Concentration of filtrates afforded a syrupy residue that was purified by flash-chromatography on silica gel (solvent A). TLC indicated two products **1**, **2** isolated as a syrups: **1**: yield 0.23 g (40%); R_f 0.78 (solvent A); $[\alpha]_D$ +3→+6.0 (*c* 1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 300.13 MHz): δ 4.78 (H-1), 4.38 (H-3), 4.04 (H-2), 3.83 (H-4), 3.68 (H-5), 3.57 (H-6), 3.30 (H-7, H-7′). ^{13}C NMR (acetone-d_6, 75.45 MHz): δ 112.79 (2,3 CMe_2), 109.86 (5,6 CMe_2), 104.29 (C-1), 87.57 (C-2), 85.93 (C-4), 82.83 (C-3), 79.41 (C-5), 78.68 (C-6), 62.55 (C-7). MS: *m*/*z* 312.66 $[M+Na]^+$; (calcd for $C_{13}H_{22}O_7$ 290.31).

Compound **2**: yield 0.16 g (25%); R_f 0.69 (solvent **A**); $[\alpha]_D$ +5.4→−2.8 (*c* 0.714, $CHCl_3$); ^{1}H NMR (acetone-d_6, 300.13 MHz): δ 4.77 (H-1), 4.38 (H-3), 4.04 (H-2), 3.75 (H-4), 3.71 (H-6), 3.58 (H-7), 3.36 (H-7′), 3.24 (H-5). ^{13}C NMR (acetone-d_6, 75.45 MHz): δ 112.29 (2,3 CMe_2), 109.78 (6,7 CMe_2), 104.47 (C-1), 87.80 (C-2), 87.74 (C-4), 83.64 (C-3), 78.07 (C-6), 73.45 (C-5), 66.37 (C-7). MS: *m*/*z* 312.50 $[M+Na]^+$; (calcd for $C_{13}H_{22}O_7$ 290.31).

4.3. 2,3:5,6-Di-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-*glycero*-β-L-*talo*-heptofuranose, 3 and 2,3:6,7-di-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-*glycero*-β-L-*talo*-heptofuranose, 4

A mixture of **1** (0.2 g, 0.69 mmol), potassium carbonate (0.18 g), methanol (4 mL) and 37% aqueous solution of formaldehyde (2 mL, 19.5 mmol) was heated under reflux under an argon atmosphere at 85°C for 50 h until the disappearance of **1** by TLC (solvent **A**). The reaction mixture was neutralised with 10% aqueous sulphuric acid and evaporated. Extraction with chloroform (4×10 mL) gave a combined fraction that was dried over anhydrous Na_2SO_4 overnight. The organic layer was evaporated to give syrupy **3**, which was purified on a column of silica gel (solvent A). TLC indicated one major product **3** isolated as syrup. Yield 1.4 g (63%); R_f 0.57 (solvent A); $[\alpha]_D$ +2.0→+ 5.0 (*c* 1, $CHCl_3$); ^{13}C NMR (acetone-d_6, 75.45 MHz): δ 114.52 (2,3 CMe_2 α), 109.73 (5,6 CMe_2 α), 100.19 (C-1α), 92.74 (C-2 α), 84.89 (C-3 α), 80.94 (C-4), 80.59 (C-5α), 78.29 (C-6 α), 62.89 (C-7 α), 62.70 (CH_2(C-2) α). MS: *m*/*z* 342.31 $[M+Na]^+$; (calcd for $C_{14}H_{24}O_8$ 320.34).

The same workup of **2** afforded **4**: yield 60%; R_f 0.48 (solvent A); $[\alpha]_D$ +10.0→+12.0 (*c* 1, $CHCl_3$); ^{13}C NMR (acetone-d_6, 75.45 MHz): δ 114.46 (2,3 CMe_2 α), 113.50 (2,3 CMe_2 β), 109.73 (6,7 CMe_2 α), 109.73 (6,7 CMe_2 β), 105.39 (C-1 β), 99.89 (C-1 α), 95.82 (C-2 β), 92.60 (C-2 α), 88.06 (C-4 β), 86.01 (C-3 β), 84.92 (C-3 α), 82.87 (C-4 α), 77.96 (C-6 β), 77.81 (C-6 α), 74.09 (C-5 α), 73.15 (C-5 β), 68.33 (C-7 α), 66.30 (C-7 β), 63.14 (CH_2(C-2) α), 62.18 (CH_2(C-2) β). MS: *m*/*z* 342.33 $[M+Na]^+$; (calcd for $C_{14}H_{24}O_8$ 320.34).

4.4. 2-*C*-(Hydroxymethyl)-D-*glycero*-L-*talo*-heptose, 5

A mixture of **3** (0.135 g), water (3 mL) and Dowex 50 W X4 resin in the H^+ form (2 mL) was stirred at 75°C for 5 h. The resin was filtered, washed with water (3×5 mL), the combined filtrate was purified with charcoal and evaporated in vacuo to afford syrupy **5**. Yield 0.097 g (96%); $[\alpha]_D$ −3.8 (*c* 1, H_2O); ^{13}C NMR (D_2O, 75.45 MHz): δ 103.84 (C-1 β*f*), 100.44 (C-1 α*f*), 97.76 (C-1 α*p*), 97.41 (C-1 β*p*), 84.72 (C-4 β*f*), 83.56 (C-4α*f*), 80.40 (C-2 α*f*), 80.40 (C-2 β*f*), 78.23 (C-2 β*p*), 77.82 (C-2 α*p*), 77.71 (C-5 β*p*), 75.27 (C-5 α*f*), 74.85 (C-6 β*f*), 74.75 (CH_2(C-2) α*p*), 74.38 (C-3 β*f*), 74.26 (C-6 β*p*), 74.07 (C-4 α*p*), 73.83 (C-5 β*f*), 73.45 (C-3 α*f*), 73.06 (C-3 α*p*), 72.85 (C-6 α*f*), 72.80 (C-6 α*p*), 72.13 (C-4 β*p*), 70.14 (C-3 β*p*), 68.85 (C-5 α*p*), 66.34 (C-7 α*p*), 65.81 (CH_2(C-2) α*f*), 65.41 (CH_2(C-2) β*f*), 65.40 (C-7 β*f*), 65.26 (C-7 α*f*), 64.67 (C-7) β*p*), 62.84 (CH_2(C-2) β*p*). MS: *m*/*z* 262.48 $[M+Na]^+$; (calcd for $C_8H_{16}O_8$ 240.21). The identical compound **5** was obtained by workup of the compound **4**. Yield 88%; $[\alpha]_D$ −3.9 (*c* 1, H_2O).

4.5. D-*glycero*-L-*galacto*-Oct-2-ulose, 6

A mixture of 2-*C*-(hydroxymethyl)-D-*glycero*-D-*talo*-heptose, **5** (150 mg; 0.62 mmol) and molybdic acid (16 mg, 0.1 mmol) in water (7.5 mL) was heated at 80°C for 6 h. The cold reaction mixture was stirred with Amberlite IRA-400 in the HCO_3^- form (20 mL). The resin was filtered off and washed with water. The filtrates were concentrated to a syrup, containing a complex equilibrium mixture of D-*glycero*-L-*galacto*-oct-2-ulose and unreacted **5**. The syrupy residue was fractionated on a column (95 cm×1.6 cm) of Dowex 50W X8 (200–400 mesh) in the Ba^{2+} form eluted with water at a flow rate 10 mL/h. Fraction 1 (eluting between 140 and 150 mL) contained chromatographically pure D-xylose (5 mg, 3%). Fraction 2 (eluting between 160 and 190 mL) contained the mixture of dihydroxyacetone and D-xylose (6 mg, 4%). Fraction 3 (eluting between 310 and 360 mL) contained chromatographically pure title compound D-*glycero*-L-*galacto*-octulose **6** (88 mg, 59%); $[\alpha]_D$ −62.6→−61.7 (*c* 1, H_2O) (24 h), that is in accordance with literature.[12] ^1H NMR (D_2O, 300.13 MHz): δ 4.02 (H-5), 3.97 (H-7), 3.96 (H-6), 3.87 (H-4), 3.77 (H-3, H-8), 3.71 (H-1), 3.67 (H-8′), 3.63 (H-1′).^{13}C NMR (D_2O, 75.45 MHz): δ 100.33 (C-2), 74.18 (C-6), 73.81 (C-7), 73.23 (C-4), 72.50 (C-5), 70.52 (C-3), 66.98 (C-1), 64.72 (C-8). MS: *m*/*z* 262.12 $[M+Na]^+$; (calcd for $C_8H_{16}O_8$ 240.21).

Fraction 4 (eluting between 370 and 380 mL) contained D-*glycero*-L-*galacto*-octulose with a mixture of 2-*C*-(hydroxymethyl)-D *glycero*-L-*talo*-heptose (5 mg, 3%). Fraction 5 (eluting between 390 and 520 mL) contained 2-*C*-(hydroxymethyl)-D *glycero*-L-*talo*-heptose (31 mg, 21%).

Acknowledgements

This research was supported by VEGA grant No. 2/2002/22. The author thanks Dr. E. Urso, (Institute for Chemical and Biochemical Research 'G. Ronzoni', Milan) for recording MALDI spectra.

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