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Microwave assisted stereospecific synthesis of D-*erythro*-L-*gluco*-nonulose

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Abstract—A convenient, highly efficient synthesis of D-*erythro*-L-*gluco*-nonulose from a new 2-*C*-(hydroxymethyl) branched-chain aldose is presented. The nucleophilic addition of the appropriately protected aldose to formaldehyde afforded 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose. The branched sugar bearing a CH_2OH group at C-2 provides access to a nine-carbon sugar in a single step through a stereospecific isomerization. The isomerization exploited the catalytic effect of molybdate ions and microwave irradiation. The structure of the product was analyzed by NMR spectra and quantum-chemical DFT calculations. DFT-computed proton–proton coupling constants were found to be comparable with the experimentally obtained coupling constants and agreed with the pyranose form of this branched-chain aldose.

1. Introduction

Higher sugars are of considerable interest for their participation in biochemical processes, and especially for their role in intracellular communication.[1] They have been identified as subunits in a number of natural products of biological significance. In addition to widely distributed members of this class, such as sialic acids, there are many others which are constituents of natural products possessing interesting biological properties.[2] These carbohydrates have been obtained mainly by their isolation from plants. For example, D-*erythro*-L-*gluco*-nonulose, together with other higher saccharides (heptoses, heptuloses, octuloses), was isolated from a *Sedum* species, from the roots of *Primula officinalis*[3]as well as from avocado (*Persea gratissima*).[4] Synthesis of such compounds is fairly complex despite the relatively simple structure of higher sugars. Most of the synthetic studies were aimed at octuloses[5,6] until now whereas nonuloses have been synthesized only very rarely. The first synthetic D-*erythro*-L-*gluco*-nonulose was prepared from D-*erythro*-L-*gluco*-octonic acid.[7] As there are a limited number of synthetic studies on nonuloses, little is known about their structural properties, especially in relation with the biological activities.

Within the program of the synthesis of biologically important higher-carbon sugars, we have examined the Mo(VI)-catalyzed isomerizations[8–12] of various 2-*C*-branched carbohydrate derivatives to 2-ketoses.[13,14] The ability of molybdate ions to create conditions for the skeletal rearrangements in carbohydrate molecules enabled the preparation of various biologically active saccharides.[14,15] Furthermore, microwave irradiation as a non-conventional energy source has been employed in the acceleration of various organic reactions with the advantages of the optimal use of material and energy and short reaction time, resulting in high stereoselectivity and an increase in the yields of the products compared to conventional methods.[16] As a result, the application of both approaches, catalytic properties of molybdate ions and microwave irradiation, opens up the possibility of optimizing chemical reactions and also equilibria are reached in a very short time. The benefits associated with the effect of microwave irradiation on this type of stereospecific rearrangement are discussed. A comparison is made with results obtained from the classical method.

2. Results and discussion

The condensation of D-*erythro*-L-*manno*-octose[17] and 2,2-dimethoxypropane in the presence of toluene-4-sulfonic acid in 1,2-dimethoxyethane at room temperature afforded 2,3:5,6:7,8-protected D-*erythro*-α-L-*manno*-octofuranose as the major product of the reaction. The substitution anchored the configuration of the sugar at the C-2 carbon

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and left the anomeric centre free for aldolization. The base-catalyzed addition of 2,3:5,6:7,8-tri-*O*-isopropylidene-D-*erythro*-α-L-*manno*-octofuranse **1** to formaldehyde resulted in the formation of 2-*C*-branched octose, namely 2,3:5,6:7,8-tri-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-*erythro*-α-L-*manno*-octofuranose **2** in a 70% yield, similar to the syntheses of the branched sugars D-apiose[18] and D-hamamelose.[19] The presence of the hydroxymethyl group at C-2 was confirmed by a characteristic ^{13}C resonance at 62.63 (CH_2 (C-2)) ppm. The structure of **2** was confirmed by 2D HSQC and HMBC NMR methods. The subsequent removal of the isopropylidene groups by acid hydrolysis afforded a new branched-chain sugar, 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose **3**, in 95% yield. Two characteristic singlet resonances in the anomeric region (5.25 and 5.03 ppm) in the ^1H NMR spectrum of 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose originated from anomeric protons of two pyranose forms in aqueous solution at 40 °C. The ratio of these forms was determined from the ^1H resonance intensities and indicated that the α-pyranose form is more stable than the β-form in aqueous solution (62% α-pyranose, 38% β-pyranose).

The treatment of 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose with a catalytic amount of molybdic acid at 85 °C for 5 h afforded an equilibrium mixture of tautomeric cyclic forms of D-*erythro*-L-*gluco*-nonulose and the remaining starting sugar. This is in accordance with the mechanism of the isomerization of D-(2-^{13}C)-fructose[13] according to which the branched-chain aldose **3** in its dimolybdate tetradentate complex rearranges to the straight-chain D-*erythro*-L-*gluco*-nonulose **4**. The essential step of the interconversion is the formation of a catalytically efficient complex[14,15] of the 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose via its four hydroxyl oxygen atoms at C-1, C-2, C-3 and C-4 of its hydrated form. In the transition state, a new bond formation between C-1 and C-3 occurs with a simultaneous cleavage of the C-2–C-3 bond. Consequently, the dimolybdate complex of D-*erythro*-L-*gluco*-nonulose is formed. The interconversion is reversible and its thermodynamic equilibrium is strongly shifted to the side of the 2-ketose as a consequence of the different steric demands of both sugars. Separation of the reaction mixture on a column of cation-exchange resin in the Ba^{2+} form afforded two chromatographically pure fractions. The first contained pure title compound, D-*erythro*-L-*gluco*-nonulose. The second fraction contained chromatographically pure starting compound, 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose.

The last step of this synthesis, that is, the interconversion of 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose to nonulose, was also carried out using the effect of microwave irradiation. The microwave-assisted isomerization reached thermodynamic equilibrium after 3–4 min. This result suggests that the ability of molybdate ions to form complexes with reducing saccharides and promote the isomerization processes during microwave irradiation is improved. Fast complex formation, subsequent intramolecular rearrangement and release of the product 2-ketose from the complex resulted in good yields. Both the methods afforded high yields (60% and 80%, respectively) of the product. However, the conversion was better (80%) when using microwave irradiation and, in addition, the reaction time was markedly shortened from 5 h (conventional heating) to 4 min. Microwave heating is energy efficient, thus the heating is fast, and the proper temperatures are reached in a short time. This compares favourably with the standard heating. Similar results were observed in the case of an aldose/epialdose mutual interconversion studied recently.[20]

The structure of **4** in aqueous solution was analyzed by 1D and 2D NMR spectroscopy and by theoretical calculations. Conventional 1D ^1H and ^{13}C spectra, as well as 2D COSY, HSQC and HMBC, enabled assignment of proton and carbon resonances of compound **4**. In addition, three-bond proton–proton coupling constants ($^3J_{H-H}$) have been determined from ^1H 600 MHz spectra and are listed in Table 1. The magnitudes of experimental coupling constants (~10 Hz) between the ring protons, $^3J_{H3-H4}$, $^3J_{H4-H5}$ and $^3J_{H5-H6}$, indicated that these protons are in antiperiplanar positions. Such an arrangement is in agreement with the $^1C_4$ pyranose form of **4**. Further analysis of the D-*erythro*-L-*gluco*-nonulose stereochemistry was carried out using a theoretical analysis. The structure corresponding to the energy minimum, obtained by geometry minimization using the DFT B3LYP method with 6-31+G* basis set and taking into account the solvent effect, is shown in Figure 1. The lowest energy was obtained for the $^1C_4$ pyranose form. In this ring form the side chain (C-7–C-9) is at the equatorial position at C-6, whereas the hydroxymethyl group at C-1, as well as all ring protons, is axially oriented. As already mentioned, such an arrangement is in agreement with the observed experimental $^3J_{H-H}$ values and was confirmed by DFT-computed coupling constants (Table 1). Theoretical and experimental $^3J_{H3-H4}$, $^3J_{H4-H5}$ and $^3J_{H5-H6}$ values were found in good agreement (within about 1 Hz) and confirmed that H-3, H-4, H-5 and H-6 are in *anti*-positions to each other in the pyranose ring (computed torsion angles for these protons were −174° for H-3 and H-4, −175° for H-4 and H-5 and 167° for H-5 and H-6). A smaller agreement between the DFT-computed (5.6 Hz) and the experimental (2.6 Hz) coupling constants was observed for $^3J_{H8-H9a}$. The torsion angle between H-8 and H-9a (−52°) is in agreement with a moderate value of the coupling constant. A smaller experimental $^3J_{H-H}$ value than the theoretical one could be partially due to the mentioned tight coupling between H-7 and H-8.

Table 1. Experimental and computed three-bond proton–proton coupling constants (values in Hz) in D-*erythro*-L-*gluco*-nonulose in aqueous solution at 40 °C

$^3J_{H-C-C-H}$	Experimental	Calculated
H3–H4	9.7	10.8
H4–H5	9.8	9.1
H5–H6	10.0	8.8
H6–H7	[a]	6.3
H7–H8	[a]	6.5
H8–H9a	2.6	5.6
H8–H9b	6.5	7.7
H9a–H9b	−11.8	−10.6

[a] Not determined.

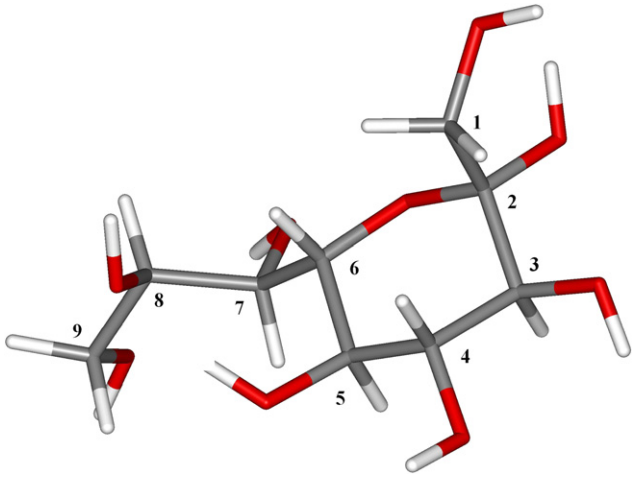

Figure 1. Structure of D-*erythro*-L-*gluco*-nonulose.

In general, most of the computed bond lengths and bond angles are typical for the $^1C_4$ pyranose ring. For example, the distances C-5–O-5 = 1.432 Å, C-2–C-3 = 1.537 Å, C-3–C-4 = 1.519 Å and C-4–C-5 = 1.540 Å agree well with previous findings.[21] On the other hand, the interatomic separation C-2–O-5 = 1.459 Å is slightly longer than expected (compared to the regular pyranose) due to the presence of the hydromethyl group linked to C-2. Similar trends were also seen for other geometrical parameters, bond angles and torsion angles.

The arrangement of the OH-3, OH-4 and OH-5 hydroxyl groups in the pyranose ring is clockwise. The exception is the reversed orientation of OH-2, which is due to the non-bonded interaction OH-2···O-1 (the distance OH-2···O-1 is 1.93 Å). As well as this interaction, two other hydrogen bonds, OH-5···O-8 and OH-7···O-9, were observed. Both the latter interactions stabilize the conformation of the side C-7–C-9 chain. The presented theoretical data are thus in agreement with the observed experimental findings and show that D-*erythro*-L-*gluco*-nonulose is in the $^1C_4$ pyranose form in aqueous solution at room temperature.

3. Conclusion

In conclusion, an efficient synthesis of D-*erythro*-L-*gluco*-nonulose has been developed. The key step, the isomerization of 2-*C*-(hydroxymethyl)-branched-chain aldose to the desired 2-ketose, where molybdate ions function as ligands, proceeds with high stereoselectivity and good yields. Although high yields and high stereoselectivity may equally well result from conventional heating, microwave irradiation offers advantages, such as shorter reaction times and better yields. The structural analysis, based on the experimental NMR data and theoretical DFT calculations, confirmed that this nonulose adopts the $^1C_4$ pyranose form in aqueous solution. Computed geometrical parameters were found to be comparable with previously calculated data. The synthetic route developed here provides an efficient way to prepare higher sugars and can also be applied to the synthesis of other similar compounds. Further experimental details dealing with the methodology for stereocontrolled construction of carbon–carbon bonds are in progress.

4. Experimental

4.1. General methods

The NMR spectra were recorded on a Bruker DPX 300 spectrometer equipped with a 5 mm inverse broadband probe with a shielded *z*-gradient and on a Varian Unity 600. The experiments were carried out in an aqueous solution at 40 °C and in acetone at 25 °C. The chemical shifts were referenced to internal TSP (D_2O) and TMS (acetone). Presaturation of the residual HDO resonance was achieved by low-power irradiation and typically 8–16 scans were collected to achieve a good signal/noise ratio in the one-dimensional spectra. A 5 mm QNP probe was used for the measurements of the 1D ^{13}C NMR spectra. Two-dimensional techniques (2D), COSY, HMBC and HSQC were used to determine the ^1H and ^{13}C chemical shifts; the 2D HSQC experiment was performed in phase-sensitive pure-absorption mode. The geometry of nonulose has been optimized with the JAGUAR program[22] using density functional theory (DFT)[23]with a Lee–Young–Parr (B3LYP)[24] correlation function and the 6-31+G* basis set. Hybrid functionals with the Slater local functional/Becke88 nonlocal gradient correlation[25] and Vosko–Wilk–Nusair local functionals[26] were used. Geometry optimizations were obtained with the gradient optimization routine; the convergence criteria were set to 1×10^{-5}. NMR proton–proton coupling constants were computed with the GAUSSIAN03 program[27] Solvation energies were obtained by self-consistent reaction field method implemented in the JAGUAR program.

Melting points were measured on a Kofler hotstage microscope. Optical rotations were determined at 20 °C with an automatic polarimeter Perkin–Elmer Model 141 using a 10 cm, 1 mL cell. Experiments were conducted using domestic microwave oven producing continuous irradiation operated at 0–800 W. The progress of the reactions was checked by thin layer chromatography (TLC) on Merck Silica Gel $60F_{254}$ glass plates. Detection was effected by spraying the chromatograms with 10% ethanolic sulfuric acid and heating them to 100 °C. Flash column chromatography was performed with silica gel (40–100 μm, Merck). Separations of the free sugars were accomplished by column chromatography on a Dowex 50W X8 resin in the Ba^{2+} form (200–400 mesh), using water as the eluent. Paper chromatography (PC) was performed by the descending method on the Whatman No. 1 paper using ethyl acetate–pyridine–water (8:2:1) as the mobile phase. The chromatograms were made visible by means of alkaline silver nitrate. All concentrations were carried out under reduced pressure at a bath temperature not exceeding 50 °C.

4.2. 2,3:5,6:7,8-Tri-*O*-isopropylidene-D-*erythro*-α-L-*manno*-octofuranose, 1

The reaction mixture of D-*erythro*-L-*manno*-octose[17] (1 g, 4.2 mmol), 1,2-dimethoxyethane (200 mL), toluene-4-sulfonic acid monohydrate (80 mg) and 2,2-dimethoxypropane

(5 mL, 40.5 mmol) was stirred vigorously for 10 h. Then Drierite (1.5 g) was added and stirring continued at room temperature for 24 h until the disappearance of starting material on TLC solvent A (6% MeOH in 6:1 ethyl acetate–petroleum ether). The reaction mixture was neutralized by the addition of sodium carbonate. The neutral mixture was filtered with suction, washed with methanol and evaporated. A syrupy isopropylidene derivative was purified by flash-chromatography on silica gel (solvent A). TLC indicated major product **1** isolated as a syrup, left at rt for 24 h whereupon **1** crystallized from its solution in acetone. Yield 1.25 g (83.3%); $R_f = 0.85$ (solvent A); $[\alpha]_D^{20} = +13$ (*c* 1, acetone); mp 58–59 °C; δ_H (acetone-d_6, 300.13 MHz): 5.41 (H-1), 4.81 (H-3), 4.57 (H-2), 4.30 (H-7), 4.20 (H-6), 4.16 (H-5), 4.09 (H-4), 3.97 (H-8, H-8′). δ_C (acetone-d_6, 75.45 MHz): 102.30 (C-1), 86.90 (C-2), 81.47 (C-4), 80.95 (C-3, C-6), 76.60 (C-7), 75.61 (C-5), 65.52 (C-8).

4.3. 2,3:5,6:7,8-Tri-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-*erythro*-L-α-*manno*-octofuranose, 2

A reaction mixture of **1** (1 g, 2.5 mmol), potassium carbonate (0.95 g), methanol (20 mL) and 37% aqueous solution of formaldehyde (10 mL, 98 mmol) was refluxed in an argon atmosphere at 85 °C for 55 h until the disappearance of **1** on TLC solvent B (6:1 ethyl acetate–petroleum ether). The reaction mixture was then neutralized with 10% aqueous sulfuric acid and evaporated. Extraction with chloroform (4 × 30 mL) gave a combined fraction that was dried over anhydrous $MgSO_4$ overnight. The organic layer was evaporated to give syrupy **2**, which was purified by column chromatography on silica gel (solvent B). TLC indicated one major product **2** isolated as a syrup. Yield 0.76 g (70.2%); $R_f = 0.78$ (solvent B); $[\alpha]_D^{20} = +5.0$ (*c* 1, acetone); δ_H (acetone-d_6, 300.13 MHz): 5.22 (H-1), 4.59 (H-3), 4.25 (H-7), 4.16 (H-5), 4.14 (H-6), 4.04 (H-4), 3.77 (H-8, H-8′). δ_C (acetone-d_6, 75.45 MHz): 104.43 (C-1), 95.36 (C-2), 83.76 (C-3), 81.90 (C-4), 80.88 (C-6), 76.51 (C-7), 75.46 (C-5), 65.48 (C-8), 62.63 (*C*H_2(C-2)).

4.4. 2-*C*-(Hydroxymethyl)-D-*erythro*-L-*manno*-octopyranose, 3

A mixture of **2** (0.5 g, 1.8 mmol), water (15 mL) and Dowex 50 W X4 resin in the H^+ form (10 mL) was stirred at 75 °C for 6 h. The resin was filtered, and the filtrate purified with charcoal and evaporated to afford syrupy **3**. Yield 0.33 g (95.4%); $[\alpha]_D^{20} = -27.0 \rightarrow -25.0$ (*c* 1, H_2O) (24 h); δ_H (D_2O, 300.13 MHz): 5.25 (H-1α), 5.03 (H-1β), 4.15 (H-5α), 4.02 (H-7α), 4.01 (H-8α, β), 3.99 (H-4β), 3.95 (H-4α, H-6β), 3.94 (CH_2(C-2) α), 3.93 (H-7β), 3.92 (H-6α), 3.87 (H-3α, H-8′ α, β), 3.85 (H-3β), 3.80 (CH_2(C-2) β), 3.68 (H-5β). δ_C (D_2O, 75.45 MHz): 97.27 (C-1 α), 97.18 (C-1 β), 78.35 (C-2 α), 78.02 (C-2 β), 76.34 (C-5 β), 75.24 (C-3 β), 74.60 (C-3 α), 73.72 (C-6 α), 73.51 (C-7 β), 72.52 (C-5 α), 71.10 (C-7 α), 70.94 (C-4 β), 69.77 (C-4 α), 69.68 (C-6 β) 66.44 (C-8 β), 66.19 (C-8 α, *C*H_2(C-2) α), 63.30 (*C*H_2(C-2) β).

4.5. D-*erythro*-L-*gluco*-Nonulose, 4

A mixture of **3** (0.15 g) and 0.2% aqueous solution of molybdic acid (10 mL) was heated at 85 °C for 5 h. The composition of the reaction mixture was examined by ^{1}H NMR spectroscopy until the equilibrium mixture was reached. The reaction mixture was stirred with Amberlite IRA-400 in the HCO_3^- form (15 mL). The filtrates were concentrated to a syrup that was fractionated by column chromatography. The syrupy residue (0.135 g) containing a complex equilibrium mixture of D-*erythro*-L-*gluco*-nonulose and remaining 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose was applied on a column (1.5 cm × 95 cm) of Dowex 50W X8 in the Ba^{2+} form and eluted with water at a flow rate of 10 mL/h. Fraction 1 contained chromatographically pure title compound D-*erythro*-L-*gluco*-nonulose. Yield 82 mg (61%); $[\alpha]_D^{20} = -47.5$ (*c* 0.8, H_2O) (24 h), that is in accordance with the literature.[7]

δ_H (D_2O, 600 MHz): 3.930 (H-6), 3.850 (H-9), 3.741 (H-4), 3.685 (H-1), 3.637 (H-9′), 3.546 (H-5), 3.506 (H-3), 3.495 (H-1′). δ_C (D_2O, 75.45 MHz): 98.28 (C-2) 74.81 (C-4), 71.52 (C-8), 71.10 (C-3), 70.92 (C-6), 69.99 (C-5), 69.08 (C-7), 64.63 (C-1), 64.16 (C-9).

Fraction 2 contained D-*erythro*-L-*gluco*-nonulose with admixture of 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose (19 mg, 14%). Fraction 3 contained chromatographically pure starting compound, 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose (24 mg, 18%); $[\alpha]_D^{20} = -27.5$ (*c* 1, H_2O) (24 h).

4.6. Mo(VI) catalyzed isomerization of the 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose to D-*erythro*-L-*gluco*-nonulose under microwave irradiation

A mixture of branched-chain aldose **3** (100 mg, 0.37 mmol) was dissolved in D_2O (5 mL) and molybdic acid (10 mg, 0.006 mmol) was added. The reaction mixture was exposed to microwave irradiation (700 W) for different lengths of time. Samples (0.5 mL) were taken at selected intervals (2, 3, 4, 5 min), treated with Amberlite IRA-400 in the HCO_3^- form (3 mL) to remove the catalyst. The composition of the reaction mixture was determined by ^{1}H NMR spectroscopy. The rest of the reaction mixture was also treated batch-wise with an excess of the ion-exchange resin, filtered off, washed with water and combined filtrates were evaporated. Fractionization of the syrupy residue afforded D-*erythro*-L-*gluco*-nonulose **4** (76 mg, 76%) and 2-*C*-(hydroxymethyl)-D-*erythro*-L-*manno*-octose (12 mg, 12%).

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