Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective de novo synthesis of (5*R*)-3,4:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose

Estefanía Dibello [a], Leopoldo Suescun [b], Gustavo A. Seoane [a,*], Daniela Gamenara [a,*]

[a] *Organic Chemistry Department, Facultad de Química. Universidad de la República (UdelaR), Av. Gral. Flores 2124, 11800 Montevideo, Uruguay*
[b] *Cryssmat-Lab/Cátedra de Física/DETEMA, Facultad de Química. Universidad de la República (UdelaR), Av. Gral. Flores 2124, 11800 Montevideo, Uruguay*

ARTICLE INFO

Article history:
Received 19 November 2016
Revised 9 December 2016
Accepted 16 December 2016
Available online xxxx

ABSTRACT

A concise and stereoselective de novo synthesis of the protected oxidized sugar (5*R*)-3,4:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose is described. The synthetic sequence involves a stereoselective proline-catalyzed aldol reaction of an orthogonally protected L-glyceraldehyde derivative and 2,2-dimethyl-1,3-dioxan-5-one, to obtain 5-*O*-acetyl-6-*O*-benzyl-1,3-isopropylidene-L-psicose as a key intermediate, and the final product in 5 steps and 38% yield.

1. Introduction

Monosaccharides are widespread in Nature and a large variety of them, mainly hexoses and pentoses, has been isolated from natural sources and identified.[1,2] However, only a few of them (D-glucose, D-galactose, D-mannose, D-fructose, D-xylose, D-ribose and L-arabinose) have a significant presence in living organisms, whereas all others are defined as 'rare sugars' by the International Society of Rare Sugars (ISRS).[3] Among the rare sugars, 5-ketoaldoses (hexos-5-uloses) constitute a class of dicarbonyl hexoses, which are poorly studied despite their interesting potential for practical applications.[4] These oxidized sugars are of interest since they have been used as synthetic intermediates for the preparation of 1,5-iminocyclitols (aza sugars),[5–7] alkyl derivatives,[8–12] inositols,[13,14] polyhydroxycyclopentanes,[15] and are also intermediates for more complex molecules with cytostatic[16] or antibiotic activities,[17] as well as being substrates for biochemical studies.[18]

The few reported synthetic approaches to hexos-5-uloses involve their preparation strictly from other hexoses, mainly D-glucose, D-mannose or D-galactose.[6,19–36]

Considering this background, we herein report a simple and stereospecific de novo synthesis of a (5*R*)-D-*ribo*-hexos-5-ulose derivative, namely (5*R*)-3,4:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose, which, to the best of our knowledge, is the first de novo synthesis of 5-ketoaldoses reported to date. Our synthetic strategy involves an organocatalyzed aldol reaction of 2-*O*-acetyl-3-*O*-benzyl-L-glyceraldehyde **1** and 2,2-dimethyl-1,3-dioxan-5-one **2**, to give 5-*O*-acetyl-6-*O*-benzyl-1,3-isopropylidene-L-psicose **3** as a key intermediate.[37]

The use of organocatalyzed aldol reactions for the synthesis of hexoses has been widely described,[38,39] and it is based on the seminal work of MacMillan and Northrup et al. for the preparation of L-hexoses.[40,41] This protocol was improved to involve complete proline control,[42] by the substitution of the second step which is a Mukaiyama aldol reaction, with another (*R*)- or (*S*)-proline-catalyzed reaction. Immediately, Enders and Grondal reported the first diastereo- and enantioselective organocatalytic aldol reaction using a dihydroxyacetone phosphate (C_3 building block)-mimetic, which is used by Nature in the biosynthesis of carbohydrates.[43,44]

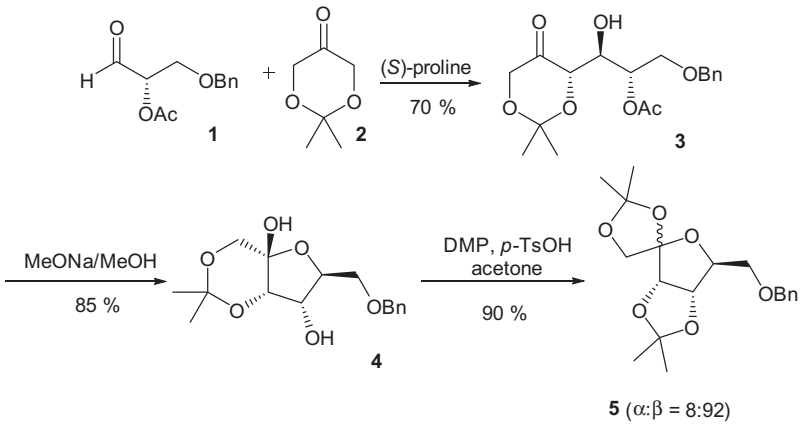
Considering that Enders used protected (*R*)-glyceraldehyde and (*S*)-proline to obtain D-ketoses,[43] we decided to use (*S*)-glyceraldehyde in order to access to the L-series. Taking into consideration several possibilities regarding the use of protecting groups for glyceraldehyde derivatives,[45] we decided to use a selectively diprotected glyceraldehyde derivative, thus providing synthetic versatility to the early steps of the proposed sequence. The preparation of the suitable C_3 building block 2-*O*-acetyl-3-*O*-benzyl-L-glyceraldehyde has been previously described, by using a concise synthetic strategy from commercially available L-gulono-γ-lactone.[46]

2. Results and discussion

The first step in the designed synthetic route, was the aldol reaction between L-glyceraldehyde derivative **1** and dioxanone **2**, to obtain the orthogonally protected L-psicose **3** (5-*O*-acetyl-6-*O*-benzyl-1,3-isopropylidene-L-psicose) in 70% and with complete stereoselectivity (Scheme 1).[47]

* Corresponding authors. Tel.: +598 2 924 7881; fax: +598 2 924 1906.
E-mail addresses: edibello@fq.edu.uy (E. Dibello), lsuescun@fq.edu.uy (L. Suescun), dgamenar@fq.edu.uy (G.A. Seoane), gseoane@fq.edu.uy (D. Gamenara).

http://dx.doi.org/10.1016/j.tetasy.2016.12.011
0957-4166/



Scheme 1. Preparation of **5** using an organocatalyzed aldol addition as the key step.

With the L-psicose derivative **3** in hand, we proceeded to remove the acetyl group in C5, according to Zemplen conditions using a 25% wt. sodium methoxyde solution in methanol,[48,49] leading to the hemiketal 6-*O*-benzyl-1,3-isopropylidene-β-L-psicofuranose **4** in 85% yield. The cyclization took place in a completely stereoselective fashion, giving **4** as a sole anomer (β), which was determined by nOe experiments.[50]

The synthetic strategy toward the final product required the oxidation of the primary alcohol (now benzylated) to the corresponding aldehyde. Thus, the following step would be the deprotection of this hydroxyl group under hydrogenation conditions. Unfortunately, upon hydrogenation of **4** the product did not maintain its furanose ring, and instead formed a 6-membered-hemiketal. Thus, we decided to protect the anomeric hydroxyl group in **4** before conducting the hydrogenation. Our strategy was to obtain a diacetonide derivative, which could be formed after opening the 1,3-dioxane acetonide in **4**.[51] Using a dimethoxypropane solution in acetone and *p*-toluensulfonic acid as the catalyst, diacetonide **5** was obtained in 90% yield, as a mixture of anomers, α:β = 8:92 (Scheme 1). The anomeric mixture was easily separable by column chromatography and each isomer was characterized and its stereochemistry was confirmed by X-ray diffraction experiments (Fig. 1).[50]

The stable furanose form that the di-*O*-isopropylidene protection gives to **5**, allowed deprotection of the primary hydroxyl group without any undesired cyclization. The debenzylation was carried out by bubbling hydrogen gas through a solution of a mixture of anomers of **5** in ethyl acetate using 10% Pd(C) as catalyst (Scheme 2), and gave a mixture of anomers of **6**, which could be easily separated. Although **6α** was obtained as a colorless oil, it could not be crystallized; the major **β** anomer was a crystalline solid with a melting point in the range of 52–53 °C, which was in reasonable agreement with reported data,[52] and whose structure was confirmed by X-ray diffraction (Fig. 2).[50] Control experiments performed on each individual anomer showed that the debenzylation took place with the same yield for each compound. Crystallographic and spectroscopic data of **6β** compared well with those reported for its enantiomer.[50,53,54]

Finally, the oxidation of the primary alcohol in **6** was not a straightforward task. When using the SO_3·Py (sulfur trioxide-pyridine) complex in DMSO and triethylamine, a low yield of aldehyde was obtained, and the recovered starting material showed an increased ratio of the β-anomer, suggesting a differential reactivity of both isomers to the oxidation conditions. Thus, the oxidation was studied on each isomer separately. After some experimentation, the best conditions for the oxidation of the major isomer were obtained using Swern's protocol,[55] which gave the protected 5-ketoaldose (*R*)-**7** [(5*R*)-3,4:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose] in 80% yield (Scheme 2). The minor α-anomer of **6** instead, could not be oxidized under the oxidation protocols assayed (SO_3·Py complex; PCC, PDC), with complete decomposition occurring in all cases.

Thus, through a short and efficient synthetic scheme, the D-*ribo*-hexos-5-ulose derivative (5*R*)-3,4:5,6-di-*O*-isopropylidene–D-*ribo*-hexos-5-ulo-5,2-furanose (*R*)-**7** was prepared in a completely stereoselective manner from an organocatalyzed aldol reaction as the key step, in 41% overall yield.

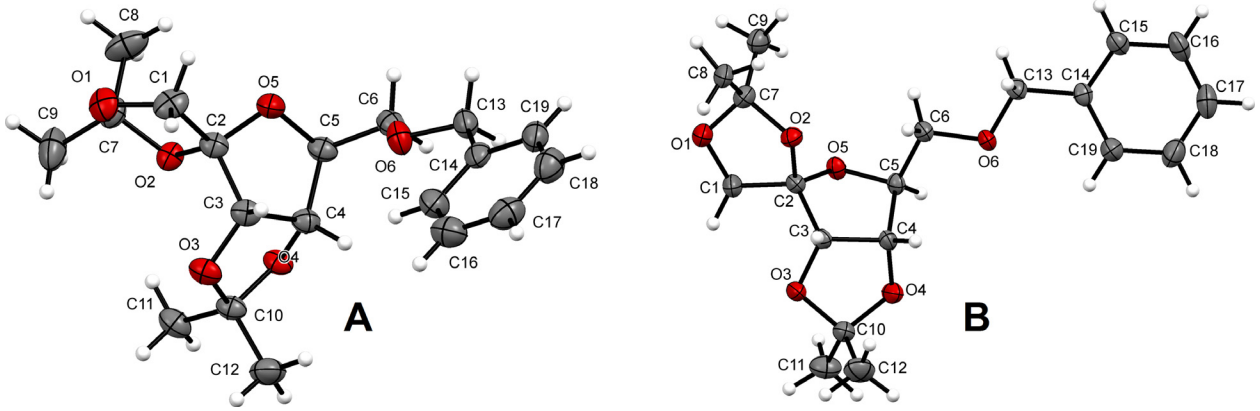
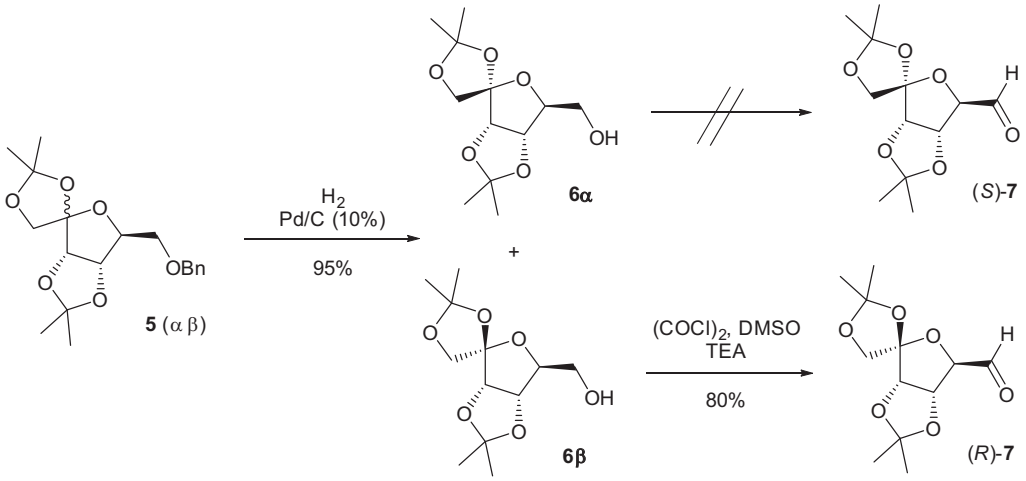


Figure 1. ORTEP plots of **5α** and **5β**. **A**: 6-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-α-L-psicofuranose; **B**: 6-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-β-L-psicofuranose.



Scheme 2. Final steps in the synthetic sequence to 3,4:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose.

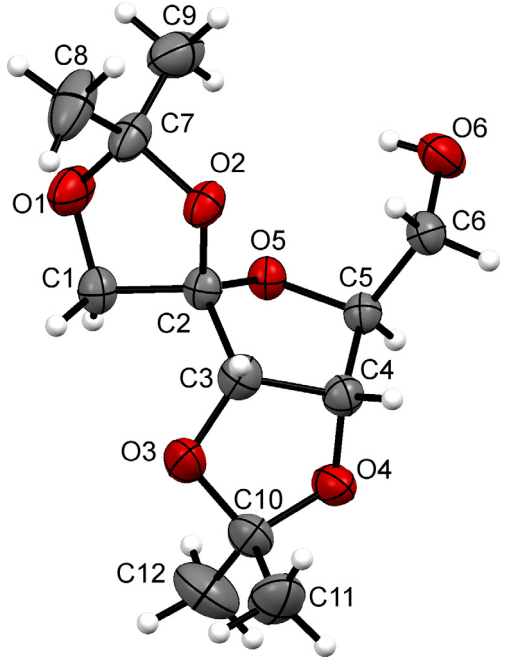


Figure 2. ORTEP plot of 1,2:3,4- di-*O*-isopropylidene-β-L-psicofuranose **6β**.

3. Conclusion

The protected oxidized sugar (5*R*)-3,4:5,6-di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose was prepared, through an organocatalyzed aldol reaction as the key step, in 41% overall yield from starting materials; this is the first de novo synthesis of a 5-ketoaldose reported to date. The ketoaldofuranoside structure of the product induces highly stereoselective organometallic additions,[11] thus increasing the synthetic potential of this dicarbonyl hexose.

4. Experimental

4.1. General

All non-hydrolytic reactions were carried out in a nitrogen atmosphere with standard techniques for the exclusion of air. Solvents were distilled prior to use. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Mass spectra (MS) were recorded on a Shimadzu GC-MS QP 1100 EX instrument using electron impact mode (70 eV). High-Resolution Mass Spectra (HRMS) were performed on a Bruker Daltonics model ToF_{LC} (ESI + mode). Infrared spectra were recorded on NaCl disks, on a Shimadzu DR-8100 FT-IR spectrometer. NMR spectra were acquired in a Bruker Avance DPX 400 and Bruker AVANCE III 500 spectrometer instruments. All experiments were taken at 30 °C, and $CDCl_3$ was used as the solvent. Proton chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS as internal reference, and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm). 1D-NOESY experiments were carried out on a Bruker AVANCE III 500 spectrometer at 25 °C using the DPFGSE-NOE pulse sequence of Stott et al. and a mixing time of 300 ms.[7] Selective excitation of specific protons was achieved with Gaussian shaped pulses. Optical rotations were measured on a Zuzi 412 polarimeter using a 0.5 dm cell. $[\alpha]_D^{21}$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Single-crystal X-ray diffraction data for **5α**, **5β** and **6β** were obtained using a Bruker D8 Venture diffractometer using a PHOTON100 CMOS detector and with INOCOATEC Microfocus CuK_α **5α**,**6β** and SIEMENS Sealed Tube MoK_α **5B** radiation sources. Crystal information, data collection and structure determination results are listed in the Supplementary information. CCDC 1517868 **5α**, 1517866 **5β** and 1517867 **6β** contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

The degree of advance of the reactions and the purity of the reactants were preliminary monitored using analytical TLC on silica gel (Kieselgel HF254 from Macherey–Nagel) and visualized with UV light (254 nm) and/or *p*-anisaldehyde in acidic ethanolic solution. Flash column chromatographies were performed using silica gel (Kieselgel 60, EM reagent, 230–400 mesh) from Macherey–Nagel.

4.2. 6-*O*-Benzyl-1,3-*O*-isopropylidene-β-L-psicofuranose 4

A 25 wt% sodium methoxide solution in methanol was added in one portion to 3 mL of methanolic solution of **3** (54.1 mg, 0.154 mmol). After stirring at room temperature for 1 h, 0.15 g of silica gel were added to the reaction mixture, and the solvent was distilled under reduced pressure. The residue was purified by column chromatography (Hex:EtOAc 6:4) yielding **4** (40.5 mg, 0.131 mmol, 85%) as a colorless oil. $[\alpha]_D^{21}$ = +29.3 (*c* 0.1, MeOH).

IR (NaCl, cm^{-1}): 3400.5, 2939.5, 1375.2, 1201.6, 1082.1, 1055.1, 738.7, 700.2. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.39–7.31 (m, 5H, Ar), 4.68 (ddd, J_1 = 11.4 Hz, J_2 = 6.4 Hz, J_3 = 4.8 Hz,1H, CH), 4.67 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.59 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.15 (dt, J_1 = 6.4 Hz, J_2 = 1.9 Hz, 1H, CH), 4.04 (d, J = 4.8 Hz, 1H, CH), 4.01 (s, 1H, OH), 3.88 (d, J = 12.6 Hz, 1H, CH_2), 3.76 (d, J = 12.7 Hz, 1H, CH_2), 3.73 (dd, J_1 = 3.8 Hz, J_2 = 2.0 Hz, 2H, CH_2), 2.61 (d, J = 11.4 Hz, 1H, OH), 1.51 (s, 3H, CH_3), 1.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) = 136.9, 128.8, 128.4, 128.1, 98.7, 97.3, 84.5, 74.5, 74.0, 71.7, 69.0, 63.7, 28.7, 19.1. MS: m/z (%) = 295 (M^+-CH_3, 1.8%), 203 (M^+-OBn, 0.9%), 107 (OBn, 9.5%), 91 (tropylium, 100.0%). HRMS: calc. for $C_{16}H_{22}O_6 + Na^+$: 333.1309; found: 333.131.

4.3. 6-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-L-psicofuranose 5

To a stirred solution of **4** (435.9 mg, 1.41 mmol) in acetone (6 mL) at 0 °C, dimethoxypropane (DMP) (3 mL) and catalytic *p*-toluensulfonic acid were added. The reaction was stirred for 1–2 h, until complete consumption of the starting material. A small amount of $NaHCO_3$ was added, and acetone was distilled under reduced pressure. The crude was taken in EtOAc (5 mL) and washed with brine (1 × 3 mL). The aqueous layer was extracted with EtOAc (3 × 3 mL) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was distilled under reduced pressure and the residue was purified by column chromatography (Hex: EtOAc 9:1) yielding **5** (444.7 mg, 1.27 mmol, 90%). Compound **5** was obtained as a mixture of α:β anomers (8:92), which could be separated by column chromatography (Hex:EtOAc 9:1). HRMS: calc. for $C_{19}H_{26}O_6 + Na^+$: 373.1622; found: 373.1621. α-Anomer: MP: 55–57 °C. $[\alpha]_D^{21} = -19.3$ (c 0.5, MeOH). IR (NaCl, cm^{-1}): 2985.8, 2935.7, 2866.2, 1456.3, 1371.4, 1271.1, 1095.6, 1066.6, 738.7, 698.2. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.35–7.29 (m, 5H, Ar), 4.65 (dd, J_1 = 6.5 Hz, J_2 = 2.3 Hz, 1H, CH), 4.57 (d, J = 12.1 Hz, 1H, CH_2Ph), 4.53 (d, J = 12.1 Hz, 1H, CH_2Ph), 4.50 (d, J = 6.5 Hz, 1H, CH), 4.31 (q, J = 3.5 Hz, 1H, CH), 4.09 (d, J = 9.2 Hz, 1H, CH_2), 3.99 (d, J = 9.2 Hz, 1H, CH_2), 3.60 (d, J = 3.5 Hz, 2H, CH_2), 1.60 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 137.9, 128.6, 127.9, 115.1, 111.8, 109.8, 81.6, 81.1, 80.5, 73.8, 72.5, 70.4, 26.9, 26.2, 26.1, 26.0. MS: m/z (%) = 350 (M^+, 0.3%), 335 (M^+-CH_3, 6.7%), 229 (M^+-Bn-CH_3-CH_3, 2.2%), 107 (OBn, 10.2%), 91 (tropylium, 100.0%). β-Anomer:[56] MP: 29–31 °C. $[\alpha]_D^{21} = +52.4$ (c 1.6, MeOH). IR (NaCl, cm^{-1}): 3030.2, 2987.7, 2939.5, 2866.2, 1454.3, 1373.3, 1211.3, 1068.6, 1028.1, 736.8, 698.2. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.35–7.28 (m, 5H, Ar), 4.75 (dd, J_1 = 5.9 Hz, J_2 = 0.9 Hz, 1H, CH), 4.60 (d, J = 5.9 Hz, 1H, CH), 4.58 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.54 (d, J = 11.9 Hz, 1H, CH_2Ph), 4.32–4.28 (m, 1H, CH_2), 4.28 (d, J = 9.7 Hz, 1H, CH_2), 4.05 (d, J = 9.7 Hz, 1H, CH_2), 3.58 (dd, J_1 = 9.7 Hz, J_2 = 6.3 Hz, 1H, CH_2), 3.52 (dd, J_1 = 9.7 Hz, J_2 = 8.3 Hz, 1H, CH_2), 1.45 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.2, 128.5, 127.8, 127.7, 113.7, 112.7, 111.6, 85.3, 84.0, 82.7, 73.5, 71.0, 70.0, 26.6, 26.6, 26.5, 25.3. MS: m/z (%) = 350 (M^+, 0.9%), 335 (M^+-CH_3, 7.2%), 229 (M^+-Bn-CH_3-CH_3, 11.2%), 107 (OBn, 9.6%), 91 (tropylium, 100.0%).

4.4. 1,2:3,4-Di-*O*-isopropylidene-L-psicofuranose 6

Hydrogen gas was bubbled through a stirred suspension of **5** (265.0 mg, 0.76 mmol) and Pd(C) 10% (63 mg) in EtOAc (15 mL). The reaction mixture was stirred for 2 h at room temperature, then the catalyst was filtered and the solvent was distilled under reduced pressure. The residue was purified by column chromatography (Hex:EtOAc 8:2) yielding **6** (187.8 mg, 0.72 mmol, 95%) as an anomeric mixture. α-Anomer: Colorless oil. $[\alpha]_D^{21} = -20.0$ (c 0.6, MeOH). IR (NaCl, cm^{-1}): 3508.5, 2987.7, 2937.6, 1383.0, 1217.1, 10099.4, 1058.9. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.69 (dd, J_1 = 6.9 Hz, J_2 = 2.9 Hz, 1H, CH), 4.47 (d, J = 6.9 Hz, 1H, CH), 4.23 (q, J = 3.2 Hz, 1H, CH), 4.09 (d, J = 9.2 Hz, 1H, CH_2), 4.05 (d, J = 9.2 Hz, 1H, CH_2), 3.85 (d, J = 11.5 Hz, 1H, CH_2), 1.76 (s, 1H, OH), 3.72 (d, J = 11.3 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 115.8, 112.2, 109.5, 81.9, 81.3, 80.4, 71.7, 62.9, 27.1, 26.2, 26.1. MS: m/z (%) = 245 (M^+-CH_3, 61.3%), 229 (M^+-CH_2OH, 6.7%), 187 (M^+-$O_2C_3H_6$, 9.2%), 144 (M^+-2 × $(CH_3)_2CO$ 42.0%), 117 (M^+-, 100%), 97 (M^+-CH_2OH-2 × $(CH_3)_2CO$-O 45.3%), 85 (45.2%), 68 (66.7%). HRMS: calc. for $C_{12}H_{20}O_6 + Na^+$: 283.1152; found: 283.1198. β-Anomer: MP: 52–53 °C. $[\alpha]_D^{21} = +52.1$ (c 0.7, MeOH). IR (NaCl, cm^{-1}): 3487.3, 2989.7, 2941.4, 1373.3, 1211.3, 1068.6, 1020.3. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.92 (dd, J_1 = 5.9 Hz, J_2 = 0.9 Hz, 1H, CH), 4.66 (d, J = 5.9 Hz, 1H, CH), 4.34 (d, J = 9.8 Hz, 1H, CH_2), 4.30 (t, J_1 = 2.9 Hz, 1H, CH), 4.07 (d, J = 9.8 Hz, 1H, CH_2), 3.77 (dt, J_1 = 12.6 Hz, J_2 = 2.7 Hz, 1H, CH_2), 3.65 (ddd, J_1 = 12.6 Hz, J_2 = 10.6 Hz, J_3 = 3.6 Hz, 1H, CH_2), 3.19 (dd, J_1 = 10.6 Hz, J_2 = 3.0 Hz, 1H, OH), 1.51 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 113.6, 112.5, 111.9, 87.0, 86.0, 81.8, 70.1, 64.1, 26.7, 26.5, 26.3, 25.0. MS: m/z (%) = 245 (M^+-CH_3, 47.2%), 229 (M^+-CH_2OH, 19.2%), 187 (M^+-$O_2C_3H_6$, 5.8%), 149 (100%), 113 (M^+-CH_2OH-2 × $(CH_3)_2CO$, 81.6%). HRMS: calc. for $C_{12}H_{20}O_6 + Na^+$: 283.1152; found: 283.1152.

4.5. (5*R*)-3,4:5,6-Di-*O*-isopropylidene-D-*ribo*-hexos-5-ulo-5,2-furanose (*R*)-7

Dimethylsulfoxide (0.10 mL, 1.48 mmol) was added to a 2 M solution of oxalyl chloride (0.37 mL, 0.74 mmol) in CH_2Cl_2, in a flame-dried flask equipped with a bubbler, and stirred for 30 min at −78 °C. Compound **6** (39.0 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (0.75 mL) and added via syringe over 5 min. to the stirred solution. After 2 h, Et_3N (0.20 mL, 1.48 mmol) was added to the reaction mixture and stirring was continued until it reached room temperature. The reaction was then diluted with CH_2Cl_2 (5 mL) and the organic layer was washed with water (1 × 5 mL), brine (1 × 5 mL) and dried with anhydrous Na_2SO_4. Solvent was distilled under reduced pressure and the residue purified by column chromatography (Hex:EtOAc 9:1) yielding **7** (30.9 mg, 0.12 mmol, 80%). Colorless oil. $[\alpha]_D^{21} = +15.1$ (c 1.0, MeOH). IR (NaCl, cm^{-1}): 2989.7, 2939.5, 1734.9, 1373.3, 1211.3, 1074.3, 1016.5. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.68 (s, 1H, CHO), 5.12 (d, J = 5.7 Hz, 1H, CH), 4.50 (d, J = 5.8 Hz, 1H, CH), 4.39 (s, 1H, CH), 4.34 (d, J = 10.0 Hz, 1H, CH_2), 4.19 (d, J = 10.0 Hz, 1H, CH_2), 1.53 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.332 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 201.4, 113.9, 113.1, 112.6, 88.6, 84.3, 81.5, 69.3, 26.5, 26.4, 26.4, 25.2. MS: m/z (%) = 243 (M^+-CH_3, 24.9%), 229 (M^+-CHO, 36.9%), 113 (M^+-CHO-2 × $(CH_3)_2CO$, 96.0%), 43 (100%). HRMS: calc. for $C_{12}H_{18}O_6 + Na^+$: 281.0996; found: 281.1022.

Acknowledgements

The authors wish to thank Dra. A. Rodríguez and Lic. Victoria Panzl for HRMS ESI TOF-MS analyses (Polo Tecnológico-FQ, Proyecto Enlaces UE-URY-2003-5906) and Dr. G. Moyna (Departamento de Química del Litoral, Paysandú, UdelaR) for performing the NOE Experiments. Support for this work from CSIC-UdelaR (Comisión Sectorial de Investigación Científica): I+D 620, Grupos I+D 981 and Equipamiento 2013, ANII (Agencia Nacional de Investigación e Innovación): FCE-3-2011-6528 and EQC_X_2012_1_07, and PEDECIBA (Programa de Desarrollo de las Ciencias Básicas) is

gratefully acknowledged. E. Dibello thanks ANII and CAP-UdelaR (Comisión Académica de Posgrado) for a PhD scholarship.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.12.011.

References

1. Lederkremer, R. M. d.; Gallo-Rodriguez, C. Naturally Occurring Monosaccharides: Properties and Synthesis In Horton, D., Ed.; Advances in Carbohydrate Chemistry and Biochemistry; Elsevier: San Diego, USA, 2004; Vol. 59, pp 9–67.
2. Witczak, Z. J. Monosaccharides: Occurrence, Significance, and Properties. In *Glycoscience. Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds., 2nd ed.; Springer-Verlag: Heidelberg, 2008; pp 815–840.
3. Granström, T. B.; Takata, G.; Tokuda, M.; Izumori, K. *J. Biosc. Bioeng.* **2004**, *97*, 89–94.
4. Lederkremer, R. M. d.; Marino, C. Acids and Other Products of Oxidation of Sugars In *Advances in Carbohydrate Chemistry and Biochemistry*; Elsevier, 2003; Vol. 58, pp 199–306.
5. Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175–3185.
6. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F. *Tetrahedron* **1997**, *53*, 8665–8674.
7. D'Andrea, F.; Catelani, G.; Mariani, M.; Vecchi, B. *Tetrahedron Lett.* **2001**, *42*, 1139–1142.
8. Biela-Banás, A.; Gallienne, E.; Front, S.; Martin, O. R. *Tetrahedron Lett.* **2014**, *55*, 838–841.
9. Fröhlich, R. F. G.; Furneaux, R. H.; Mahuran, D. J.; Saf, R.; Stütz, A. E.; Tropak, M. B.; Wicki, J.; Withers, S. G.; Wrodnigg, T. M. *Carbohydr. Res.* **2011**, *346*, 1592–1598.
10. Schitter, G.; Steiner, A. J.; Pototschnig, G.; Scheucher, E.; Thonhofer, M.; Tarling, C. A.; Withers, S. G.; Fantur, K.; Paschke, E.; Mahuran, D. J.; Rigat, B. A.; Tropak, M. B.; Illaszewicz, C.; Saf, R.; Stütz, A. E.; Wrodnigg, T. M. *ChemBioChem* **2010**, *11*, 2026–2036.
11. Godin, G.; Compain, P.; Masson, G.; Martin, O. R. *J. Org. Chem.* **2002**, *67*, 6960–6970.
12. Guazelli, L.; Catelani, G.; D'Andrea, F.; Gragnani, T.; Griselli, A. *Eur. J. Org. Chem.* **2014**, *29*, 6527–6537.
13. Pistarà, V.; Barili, P. L.; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *41*, 3253–3256.
14. Catelani, G.; Corsaro, A.; D'Andrea, F.; Mariani, M.; Pistarà, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3313–3315.
15. Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L. *Tetrahedron Lett.* **1998**, *29*, 2021–2024.
16. Rocherolle, V.; Olesker, A.; Lukacs, G. *J. Antibiot.* **1989**, *42*, 1393–1397.
17. Calvo Mateo, A.; Camarasa, M. J.; de las Heras, F. *J. Carbohydr. Chem.* **1984**, *3*, 475–483.
18. Samuelsson, B. *Angew. Chem., Int. Ed.* **1983**, *22*, 805–815.
19. Varela, O. Oxidative Reactions and Degradations of Sugars and Polysaccharides In *Advances in Carbohydrate Chemistry and Biochemistry*; Elsevier, 2003; Vol. 58, pp 307–369.
20. Brimacornbe, J. S. *Angew. Chem., Int. Ed.* **1969**, *8*, 401–468.
21. Kiely, D. E.; Fletcher, H. G. J. *J. Am. Chem. Soc.* **1968**, *90*, 3289–3290.
22. Barili, P. L.; Bergonzi, M. C.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F. *J. Carbohydr. Chem.* **1999**, *18*, 1037–1049.
23. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F.; Goracci, G. *J. Carbohydr. Chem.* **1998**, *17*, 1167–1180.
24. Guazzelli, L.; Catelani, G.; D'Andrea, F. *Carbohydr. Res.* **2010**, *345*, 369–376.
25. Enright, P. M.; O'Boyle, K. M.; Murphy, P. V. *Org. Lett.* **2000**, *2*, 3929–3932.
26. Enright, P. M.; Tosin, M.; Nieuwenhuyzen, M.; Cronin, L.; Murphy, P. V. *J. Org. Chem.* **2002**, *67*, 3733–3741.
27. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F. *Tetrahedron Lett.* **1991**, *32*, 959–962.
28. Izumori, K.; Tsusaki, K. Process for producing L-ketohexose. US Patent 5811271, 1998.
29. Kiely, D. E.; Harry O'Kuru, R. E.; Morris, P. E. J.; Morton, D. W.; Riodan, J. M. *J. Carbohydr. Chem.* **1997**, *16*, 1159–1177.
30. Moradei, O.; du Mortier, C.; Fernández Cirelli, A.; Thiem, J. *J. Carbohydr. Chem.* **1995**, *14*, 525–532.
31. Batey, J. F.; Bullock, C.; Hall, J.; Williams, J. M. *Carbohydr. Res.* **1975**, *40*, 275–283.
32. Humphries, H. P.; Theander, O. *Carbohydr. Res.* **1971**, *16*, 317–325.
33. Heusinger, H. *Carbohydr. Res.* **1988**, *181*, 67–75.
34. Blattner, R.; Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1523–1527.
35. Ferrier, R. J.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1528–1534.
36. Takeshita, K.; Shimonishi, T.; Izumori, K. *J. Ferment. Bioeng.* **1996**, *81*, 212–215.
37. Both organocatalyzed and enzyme-mediated aldol reactions have been used to prepare ketoaldoses, mainly through the "inverted" strategy of Whitesides et al., (Borysenko, C. W.; Spaltenstein, A.; Straub, J. A.; Whitesides, G. M. *J. Am. Chem. Soc.* 1989, *111*, 9275-9276; Schmid, W.; Heidlas, J.; Mathias, J. P.; Whitesides, G. *Liebigs Ann. Chem.* 1992, *1*, 95-97) later extended to the organocatalytic domain by Enders (Enders, D.; Narine, A. A. *J. Org. Chem.* 2008, *73*, 7857-7870). However, although the preparation of pentos-4-uloses and 2-deoxy-5-ketoaldohexoses is documented through this approach, hexos-5-uloses have not been reported using aldol reactions.
38. Limbach, M. *Chem. Biodivers.* **2005**, *2*, 825–836.
39. Mlynarski, J.; Gut, B. *Chem. Soc. Rev.* **2012**, *41*, 587–596.
40. Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752–1755.
41. Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152–2154.
42. Córdova, A.; Ibrahem, I.; Casas, J.; Sundén, H.; Engqvist, M.; Reyes, E. *Chem. Eur. J.* **2005**, *11*, 4772–4784.
43. Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212.
44. Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329–337.
45. Dibello, E.; Gamenara, D.; Seoane, G. *Org. Prep. Proc. Int.* **2015**, *47*, 415–442.
46. Dibello, E.; Brovetto, M.; Seoane, G.; Gamenara, D. *Tetrahedron Lett.* **2013**, *54*, 5895–5897.
47. Dibello, E.; Gamenara, D.; Seoane, G. *Synthesis* **2016**. http://dx.doi.org/10.1055/s-0036-1588325. in press.
48. D'Antona, N.; El-Idrisi, M.; Ittobane, N.; Nicolosi, G. *Carbohydr. Res.* **2005**, *340*, 319–323.
49. Wang, Z. *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: Hoboken, NJ, 2010.
50. See supporting information.
51. Previous attempts at protection using a TBS-ketal and an acetate gave the corresponding protected ketal with a lower overall yield of 29%.
52. Steiger, M.; Reichstein, T. *Helv. Chim. Acta* **1935**, *18*, 790–799.
53. Gullapalli, P.; Yoshihara, A.; Morimoto, K.; Rao, D.; Akimitsu, K.; Jenkinson, S. F.; Fleet, G. W. J.; Izumori, K. *Tetrahedron Lett.* **2010**, *51*, 895–898.
54. Watkin, D. J.; Glawar, A. F. G.; Soengas, R.; Izumori, K.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2005**, *61*, o2949–o2951.
55. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1998**, *43*, 2480–2482.
56. Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133–2144.