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A new and efficient entry to D-*xylo*-hexos-4-ulose and some derivatives thereof through epoxidation of the 3,4-hexeno derivative of diacetone-D-glucose

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Dedicated to the memory of Professor Ivano Morelli

Abstract—A new preparation of D-*xylo*-hexos-4-ulose (**1**) and of its 3-*m*-chlorobenzoate (**2**) has been devised using the epoxidation of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-*erythro*-hex-3-enofuranose (**6**) as the key step. The epoxidation of **6** in CH_2Cl_2 furnished with high yield 1,2:5,6-di-*O*-isopropylidene-3-*O*-*m*-chlorobenzoyl-4-*C*-hydroxy-D-*xylo*-hexos-4-ulo-1,4-furanose as a mixture of C-4 hemiacetal anomers (**7a**,**b**), which, on acid hydrolysis, gave a tautomeric mixture of 3-*O*-*m*-chlorobenzoyl-D-*xylo*-hexos-4-ulose (**2**) with an overall 60% yield from **6**. The formation of 4-*C*-methoxy-diacetone-D-glucose derivatives (**11a**,**b**) through epoxidation–methanolysis of **6**, took place with reduced yield because of the competition between *m*-chlorobenzoic acid (MCBA) and methanol to the opening by attack at C-4 of the intermediate epoxide and the formation of acyclic products arising from the alternative nucleophilic attack at C-1. Acid hydrolysis of derivatives **11** gave D-*xylo*-hexos-4-ulose (**1**) with a 35% overall yield from **6**. NMR analysis showed that **2** is composed, in CD_3CN, mainly by a 7:3 mixture of 4-keto-α- and β-pyranose forms, while **1**, in D_2O, is present as a more complex mixture constituted mainly by 4-keto-α- and β-pyranoses and their respective hydrates in a 17:15:34:34 ratio.

Keywords: D-*xylo*-Hexos-4-ulose; 3-Deoxy-hex-3-enofuranoses; Epoxidation; Tautomeric equilibrium

1. Introduction

Nonacidic products of the oxidation of aldoses having the anomeric centre protected in the furanose or pyranose form, are currently used as important synthetic intermediates for the stereoselective conversion of common monosaccharides into rare sugars or into amino derivatives having applications for other synthetic purposes.[1] Furthermore, some representatives of this class of compounds have been identified as constituents of few naturally occurring compounds.[2] Less investigated are monosaccharides possessing two unprotected dicarbonyl functions (dialdoses, diuloses and aldosuloses), although some of these compounds have long been synthesised or known as intermediates in several degradation reactions.[1] Between the four possible D-glucose derived uloses, the more largely studied is certainly the 2-keto derivative (D-*arabino*-hexos-2-ulose, D-glucosone), known from late 1888.[3] The 3-keto derivative (D-*ribo*-hexos-3-ulose, 3-keto-D-glucose) and the 5-keto isomer (D-*xylo*-hexos-5-ulose, 5-keto-D-glucose) have also been the object of some interest[4] owing to the application of the former for the synthesis of some polyhydroxy substituted heteroaromatic compounds,[4b] and the latter for the biomimetic synthesis of 1-deoxy-D-nojirymicin[4d] and *myo*-inositol.[4e] Furthermore, the structure of the more abundant cyclic forms present in the complex isomeric equilibrium involving two dicarbonyl groups, has been elucidated for 2-keto-,[5a] 3-keto-[5b] and 5-keto-D-glucose.[5c] Surprisingly, very little research has been devoted to the 4-keto derivative

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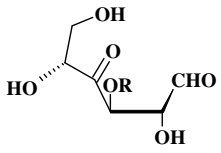
(D-*xylo*-hexos-4-ulose, 4-keto-D-glucose, **1**), the sole synthesis of which was reported, without any structure elucidation, 30 years ago by Williams and co-workers using a six steps sequence with an overall 6.4% yield starting from D-glucose.[6]



1: R = H
2: R = MCB

MCB =*m*-ClC$_6$H$_4$CO

Owing to the potential interest of aldohexos-4-uloses (**5b**) as intermediates for the synthesis of polyhydroxycarbacycles[7] and/or 1,4-iminoalditols,[8] we envisaged a new synthetic plan to this class of dicarbonyl monosaccharides by an extension of the approach (Chart 1) we previously proposed for the isomeric aldohexos-5-uloses (**5a**),[9] based on the epoxidation–methanolysis of a cyclic enol ether of type **3**, to give bis-glycosides **4**, which, after a final deprotection step, are converted into the target aldosuloses **5**.

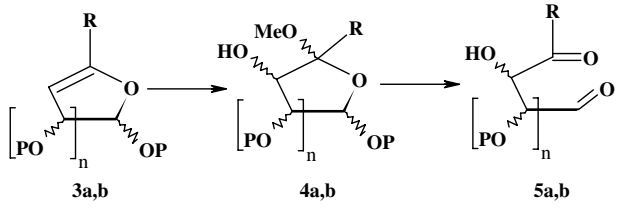
The present paper reports the results of an initial study on the epoxidation of the known 3-deoxy-hex-3-enofuranose **6**[10] in dichloromethane, followed by those on a variant of this epoxidation using methanol as a solvent, leading to D-*xylo*-hexos-4-ulose (**1**) and its 3-*m*-chlorobenzoate **2**.

2. Results and discussion

The enol ether **6**, easily obtained as reported,[10] was first subjected to an epoxidation reaction with MCPBA in CH_2Cl_2, leading, after usual work-up and chromatographic purification, to a 7:3 mixture (81% isolated yield) of the two C-4 anomeric 3-*m*-chlorobenzoates **7a**,**b** (Scheme 1). This result is rather unexpected if one takes into account the usual complete regioselective nucleophilic attack in position α to the oxygen atom during the opening of epoxy ethers, such as glycal epoxides[11] or hex-4-[9] and hex-5-pyranosides.[12] The location in position 3 of the acyl group was, however, firmly ascertained by comparison of their ^{1}H NMR data in Me_2SO with those of the 4-*C*-methoxy derivatives **11a** and **11b** and of their 3-acetates **12a** and **12b** (Table 1), allowing also for the assignment of C-4 configurations, as discussed below. Furthermore, the presence of a hemiketal function on the two derivatives **7** was confirmed by their fast equilibration in Me_2SO, revealed through a classical mutarotation measurement {from $[\alpha]_D$ (initial) −4.8 to $[\alpha]_D$ (infinity) +23.5} and through NMR analysis, showing an inversion on the **7a**/**7b** composition from an initial 7:3 to a final 3:7 ratio. It should be noted that, in this case, the scission of the hemiketal derivatives **7** into the ketoaldehyde and acetone, is not spontaneous, as expected. A similar behaviour has been, however, reported for some specific 5-hemiketal of pyranosides,[12] as an apparent consequence of the influence of the protective groups pattern. A possible silica gel promoted acyl shift from the OH-4 to the OH-3 function during the chromatographic process, as observed in the epoxidation of a hex-5-enopyranoside,[12] was excluded through NMR analysis of the crude reaction product, showing the exclusive presence of **7a**,**b**. An identical result was obtained even when the reaction was quenched with a neutral aqueous $Na_2S_2O_3$ solution, instead of an alkaline Na_2CO_3 one, and when the epoxidation reaction of **6** was performed with MCPBA–KF complex in CH_2Cl_2, a reagent operating in neutral conditions, which allows isolation of highly reactive epoxides,[13] such as those derived from glycals.[14]

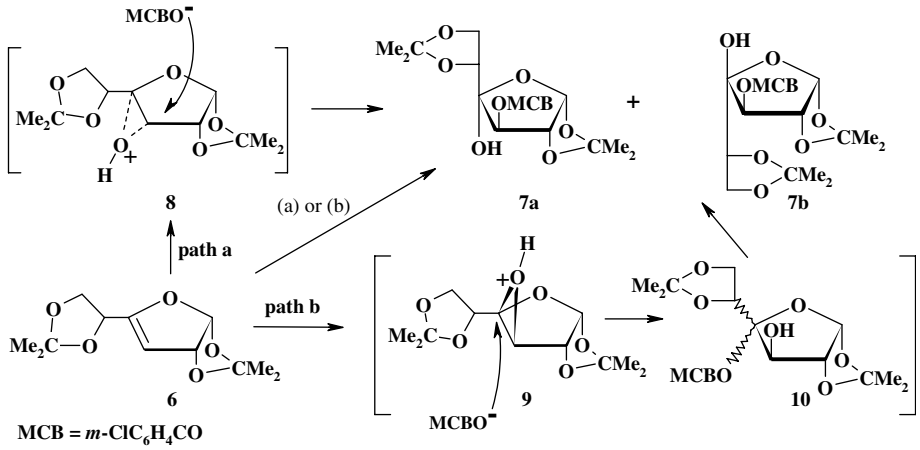
Although the above results could arise, at least in principle, by the attack of the nucleophile (MCBO) at C-3 on the transient protonated epoxide **8** (Scheme 1, path a), the alternative route (Scheme 1, path b) involving an attack at C-4 on the epoxide **9** followed by an acyl migration from the tertiary O-4 to the secondary O-3, appears as the most likely on the basis either of the expected preference of peroxyacid attack on the β-face of **6**, due to the steric effect of the 1,2-*O*-isopropylidene bridge, and of a probable regioselective opening of the intermediate epoxide through an attack at C-4 by the nucleophile. This type of spontaneous acyl migration, which was not previously observed during our studies on the epoxidation of hex-4- and hex-5-enopyranosides,[12] could be ascribed to an easier formation of orthoester intermediates on a furanose ring than on a pyranose one, since greater ring distortion is required in the latter case.

The epoxidation of **6** with MCPBA in MeOH turned out to be much more complex than expected. The crude product, obtained when the reaction was quenched by addition of an aqueous solution of $Na_2S_2O_3$, revealed in TLC analysis (1:1 hexane–EtOAc) the presence of two major components (R_f 0.55 and 0.36) and two minor ones with R_f 0.50 and 0.40. Flash chromatography of



a: n = 2, R = CH_2OP
b: n = 1, R = $CH(OP)CH_2OP$
P = generic protecting group

Chart 1.



Scheme 1. Reagents and conditions: (a) MCPBA, CH_2Cl_2, 2.5 h, 0 °C; (b) MCPBA–KF, CH_2Cl_2, 3.5 h, rt.

Table 1. ^{1}H NMR data (δ, ppm; J, Hz) for compounds **7**, **11** and **12**

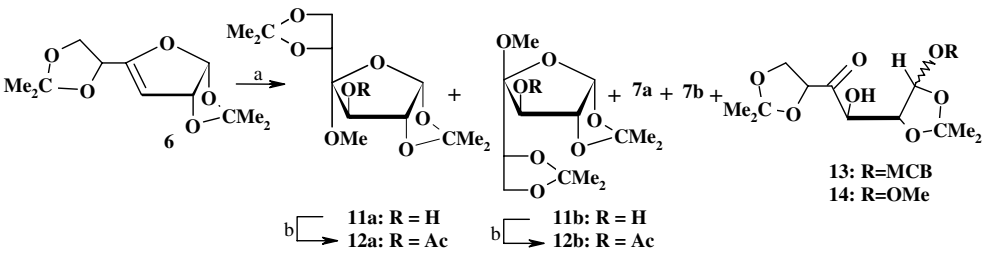
Compound	Solvent	H-1	H-2	H-3	H-5	H-6b	H-6a	OH-3	OH-4	$J_{1,2}$	$J_{2,3}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{3,OH}$
12a	$CDCl_3$	5.97	4.53	5.42	4.27	4.01	3.99	—	—	4.5	1.0	5.6	6.5	8.6	—
11a[a]	$CDCl_3$	6.08	4.57	4.37	4.64	4.13	4.08	3.41	—	4.4	0	7.0	7.8	12.1	6.6
11a[a]	Me_2SO-d_6	5.93	4.41	4.02	4.30	3.85	3.85	5.62	—	4.4	0	6.9	6.9	—	5.4
7a[a]	Me_2SO-d_6	5.99	4.71	5.30	4.28	4.05	4.05	—	6.28	4.3	0	6.9	6.9	—	—
12b	$CDCl_3$	5.90	4.69	5.38	4.33	4.03	3.98	—	—	4.1	2.7	6.8	6.8	8.6	—
11b[a]	$CDCl_3$	5.78	4.54	4.31	4.43	4.10	3.99	3.03	—	3.6	1.6	5.8	7.0	8.9	7.1
11b[a]	Me_2SO-d_6	5.87	4.58	4.19	4.12	3.97	3.85	5.31	—	4.7	3.9	n.d.	7.0	8.5	6.4
7b[a]	Me_2SO-d_6	5.93	4.88	5.36	4.11	4.05	4.05	—	6.68	4.4	2.8	6.9	6.9	—	—

[a] Spectra taken on anomeric mixtures.

the reaction mixture allowed separation of the four components, the most mobile of which (R_f 0.55) corresponded (NMR data) to the previously described mixture of 3-*m*-chlorobenzoates **7a**,**b** (14% yield), while the less mobile of the major components (R_f 0.36) was identified as an about 3:2 mixture of the expected 4-*C*-methoxy furanose derivatives **11a**,**b** (35% yield).

NMR analysis of the two minor reaction products suggested in both cases an acyclic di-acetonated hexose structure. The presence of signals attributed to a *m*-chlorobenzoate or to a methoxy group allowed the structural assignment, respectively, of a 3:2 mixture of the C-1 *m*-chlorobenzoate epimers **13** (4% yield) and of a single 1-methoxy acetal **14** (7% yield) (Scheme 2). The complex reaction mixture was simplified if the quenching of the reaction was performed with a saturated aqueous $NaHCO_3$ solution; in the homogeneous hydro-alcoholic solution a fast disappearance of the 3-*m*-chlorobenzoates **7a**+**7b** took place leading to a consequently easier purification of the remaining reaction products.

Although derivatives **11a** and **11b** could not be separated on silica gel, the assignment of their structure was firmly established on the basis of NMR analysis of the corresponding 3-acetates **12a** and **12b**, easily separated by flash chromatography. High field spectra of **12a** and **12b** allowed a complete assignment of proton



Scheme 2. Reagents and conditions: (a) MCPBA, MeOH, 2.5 h, rt; (b) Ac_2O, Py.

Table 2. ^{13}C NMR data (δ, ppm) for compounds **7**, **11** and **12**

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6
12a	$CDCl_3$	105.6	84.5	78.3	109.5	76.9	65.2
11a[a]	$CDCl_3$	106.3	86.0	79.9	108.3	75.2	65.6
11a[a]	Me_2SO-d_6	106.1	85.9	78.2	107.9	76.3	65.1
7a[a]	Me_2SO-d_6	105.9	83.8	80.6	106.6	75.8	63.6
12b	$CDCl_3$	104.0	85.4	77.9	106.7	75.0	65.0
11b[a]	$CDCl_3$	104.0	87.4	76.3	105.3	73.6	64.9
11b[a]	Me_2SO-d_6	103.2	87.1	77.2	106.9	75.0	64.4
7b[a]	Me_2SO-d_6	103.0	84.6	78.2	103.0	75.8	64.2

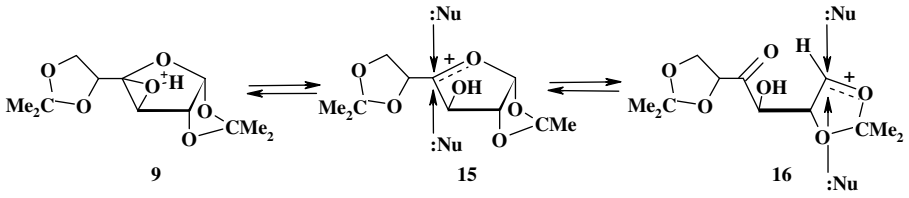
[a] Spectra taken on anomeric mixtures.

and carbon signals (Tables 1 and 2), confirming, in particular, the configuration at C-3 on the basis of the small value of vicinal H-2 and H-3 coupling constants (**12a**: $J_{2,3}$ 1.0 Hz; **12b**: $J_{2,3}$ 2.7 Hz) pointing to a trans disposition between the protons, while an higher value ($J_{2,3}$ 5–6 Hz) should be expected in the case of a cis arrangement.[15] The configuration at C-4, (*R*) for **12a** and (*S*) for **12b**, was established using NOE experiments. The anomer **12b** showed a NOE enhancement between H-1 and OMe, but not between H-3 and OMe, whereas **12a** showed enhancement between H-3, OMe and methyl groups of 1,2-*O*-isopropylidene residue. As anticipated above, the structure of the *m*-chlorobenzoates **7a**,**b** was clearly inferred by comparison of their spectral data with those of **11a**,**b** and **12a**,**b** (Tables 1 and 2), on the basis of the chemical shift values of H-3 signals and of the multiplicity of the exchangeable OH signals in Me_2SO, that are singlets for compounds **7a** and **7b**, in which the hydroxyl group is located in position 4, and doublets for derivatives **11a** and **11b**, having the OH free group in position 3.

In order to explain the product distribution of the epoxidation–methanolysis of **6**, one can observe that the *xylo* configuration of the furanose derivatives **11a** and **11b** confirms the expectation that the peroxyacid attack on the double bond occurs with very high, if not complete, stereoselectivity on the β face, leading to the intermediate protonated epoxide **9**, probably owing to the steric effect of the 1,2-*O*-isopropylidene acetal group, as previously reported for other electrophilic addition to **6**.[16,‡] On the basis of the formation of C-4 anomeric mixtures of methoxy furanose derivatives **11** and of C-1 epimeric mixtures of acyclic derivatives **13**, it could be supposed there is an involvement of the two cyclic oxocarbonium ion intermediates **15** and **16** (Scheme 3), the formation of which is probably favoured by the planarity of the five-membered rings and by the solvent polarity stabilisation. The presence of acyclic intermediates such as **16** was also suggested by Khripach and Galitskii[17] in order to explain the formation of acyclic C-1-methoxy-3-bromo-4-keto-pentoses during the bromination in methanol of 3-deoxy-pent-3-enofuranoses.

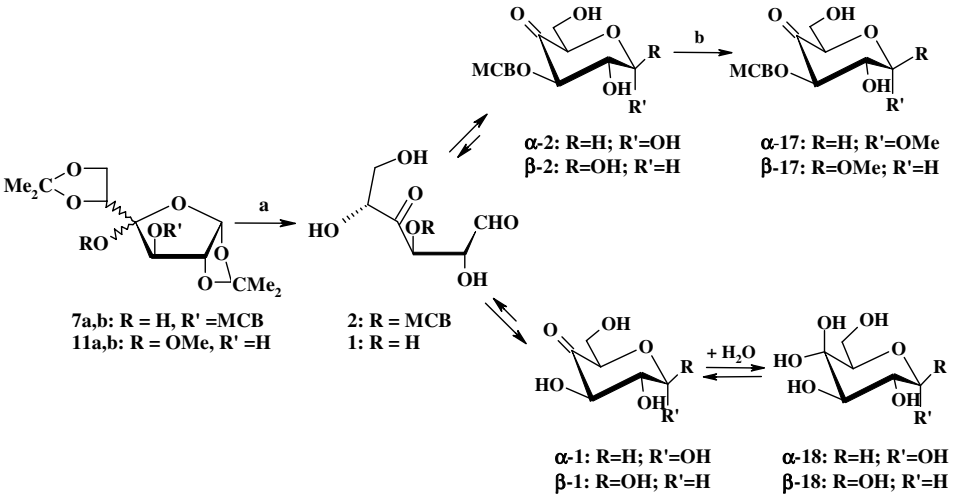
The acid labile protecting groups of **7a**,**b** were removed with CF_3COOH in a 2:1 mixture of MeCN–water (3 h, rt) to give the crude 4-keto-D-glucose derivative **2** (Scheme 4), isolated in good yield (75%) through chromatographic purification. High field NMR analysis (CD_3CN) showed that about 70% of **2** was constituted by two major isomeric forms, identified as the α- and β-4-ketopyranoses (**α**- and **β-2**) in a ratio of about 7:3, estimated on the basis of the relative H-3 signal intensities. The structures of **α**- and **β-2** were firmly established through ^1H NMR analysis on the basis of the vicinal coupling constant of H-1, H-2 and H-3, pointing to an equatorial–axial–axial arrangement ($J_{1,2}$ and $J_{2,3}$, respectively, of 3.5 and 10.4 Hz) for **α-2** and to an axial–axial–axial arrangement ($J_{1,2}$ and $J_{2,3}$, respectively, of 7.3 and 10.0 Hz) for its β anomer. The presence of some minor signals in the less overlapped region of the proton spectrum (δ 4.50–6.00 ppm) indicated that at least four other minor components contributed to the isomeric equilibrium of **2**. Two anomeric doublets [δ 5.23 ($J_{1,2}$ 4.9 Hz), 4.66 ($J_{1,2}$ 7.8 Hz)] could be tentatively attributed to α- and β-anomers of the 4-hydrate-pyranose form, representing about 20% of the tautomeric equilibrium. Two other set of signals, accounting for about 10% of the overall isomeric forms [δ 5.20 ($J_{1,2}$ 4.8 Hz) and 5.96 (d, $J_{2,3}$ 2.4 Hz), and δ 5.15 ($J_{1,2}$ 3.4 Hz and 5.98 (d, $J_{2,3}$ 2.0 Hz)] could be assigned to α- and β-furanosic type structure arising from the closure of the hydrated aldehyde on the C-4 carbonyl group. A more firm structure assignment of these minor tautomeric species, requires further detailed NMR studies, that are, however, out of the scope of the present work. As a further structure confirmation, the tautomeric mixture of **2** was converted into the corresponding methyl glycosides **17** by Fischer's glycosidation with 1% hydrochloric methanol.[18] Chromatographic purification furnished an anomeric mixture (60% yield) of methyl 4-keto-glycopyranosides **17**, in an α:β ratio of about 17:3, estimated on the basis of the integration of the signals for the anomeric protons. As expected, the NMR data

‡ However, obtainment of *xylo*-derivatives **7a**,**b** from the β-epoxide, in what is presumably a borderline-S_N2 attack, can only be rationalised on the assumption that an acyl migration from O-4 to O-3 occurs, as discussed earlier.



Scheme 3.

of **α**- and **β-17** were very close to those of **α**- and **β-2**, with the exception of the signals of the anomeric carbons that were sensibly deshielded ($\Delta\delta$ 7.1 for **α-17** and $\Delta\delta$ 7.7 for **β-17**).



Scheme 4. Reagents: (a) CF_3COOH, 2:1 MeCN–water; (b) MeOH, 1% HCl.

Completely deprotected D-*xylo*-hexos-4-ulose (**1**) was, finally, obtained by hydrolysis of **11a**,**b** with CF_3COOH in 2:1 MeCN–water, giving a crude sample with specific rotation in rough accordance with the value reported by Williams and co-workers[6] for a sample obtained after three final steps without purification. NMR analysis of crude **1** in D_2O evidenced, after equilibration (24 h), the presence of four major constituents, the α- and β-4-keto-pyranose forms (**α-1** and **β-1**) and the corresponding hydrates (**α-18** and **β-18**) in a ratio of about 17:15:34:34, estimated on the basis of the relative H-1 signal intensities at δ 5.31 ($J_{1,2}$ 3.5 Hz), 4.93 ($J_{1,2}$ 7.8 Hz), 5.12 ($J_{1,2}$ 3.7 Hz) and 4.51 ($J_{1,2}$ 7.9 Hz). The presence in the ^{13}C NMR spectrum of two sets of peaks ascribable to carbonyl carbons of **α-1** (δ 205.7) and **β-1** (δ 204.6) and to hydrate carbonyl carbons of **α-18** (δ 94.3) and **β-18** (δ 94.8), confirmed further the proposed composition.

In summary, we have proposed a new straightforward synthetic access to D-*xylo*-hexos-4-ulose (**1**) and to its 3-*m*-chlorobenzoate (**2**), and determined the structure of their major isomeric forms in solution. We have also reported some observations on the course of the epoxidation of the enol ether **6**, suggesting the presence of mechanistically interesting differences between the reaction of hex-4-enofuranose and hex-5-enopyranose enol ethers. Considering, finally, the simplicity of the synthetic procedure and the easy availability of the starting material, this approach appears attractive to further studies on the synthetic applications of γ-ketohexoses. In particular, the syntheses of biologically relevant 1-deoxyazafuranoses by double reductive amination is now under investigation in our laboratory and the results of this study will be reported in a forthcoming paper.

3. Experimental

3.1. General methods

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 ± 2 °C. NMR spectra were recorded with a Bruker AC 200 instrument operating at 200.13 MHz (^1H) and 50.33 (^{13}C) and with a Varian INOVA600 spectrometer operating at 600 and 150 MHz for ^1H and ^{13}C, respectively, using Me_4Si as internal reference. Assignments were made, when possible, with the aid of DEPT, HETCOR, HSQC, NOE experiments, by comparison of values for known compounds and applying the additivity

rules.[19] In the case of mixtures, assignments were made by referring to the differences in the peak intensities. Low resolution mass spectra were recorded on a LCQ Advantage ThermoFinnigan spectrometer equipped with an ion trap analyzer (Thermo Electron Company, San Jose, CA, USA). High resolution mass spectra (electrospray) were performed on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer. All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulfuric acid, and heating. Kieselgel 60 (E. Merck, 70–230 and 230–400 mesh, respectively) was used for column and flash chromatography. Solvents were dried and purified by distillation according to standard procedure,[20] and stored over 4 Å molecular sieves activated for at least 24 h at 200 °C. $MgSO_4$ was used as the drying agent for solutions.

3.2. (4*R*)- and (4*S*)-3-*O*-*m*-Chlorobenzoyl-4-*C*-hydroxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose (7a and 7b)

A soln of **6**[10] (3.00 g, 12.4 mmol) in dry CH_2Cl_2 (105 mL) was treated at 0 °C under argon with a predried ($MgSO_4$) soln of 70% commercial MCPBA (3.66 g, 14.9 mmol) in dry CH_2Cl_2 (30 mL) and stirred at 0 °C until the starting material was completely disappeared (2.5 h, TLC, 1:1 hexane–EtOAc). The reaction mixture was stirred for 30 min with anhyd KF (1.72 g, 29.7 mmol) in order to eliminate the excess of MCPBA and MCBA. After filtration of the insoluble complex, the organic soln was washed with satd aq Na_2CO_3 (2 × 40 mL), dried and concentrated to give a crude product (solid foam, 4.77 g, 93% yield) showing a single spot in TLC analysis (R_f 0.55, 1:1 hexane–EtOAc). ^1H NMR analysis ($CDCl_3$) of the crude product revealed the exclusive presence of a mixture of **7a** and **7b** in a ratio of 7:3, measured on the relative intensities of H-1 signals (Table 1). Chromatographic purification over silica (7:3 hexane–EtOAc) of the crude product gave a 7:3 mixture of **7a** and **7b** as a solid foam (4.15 g, 81% yield); R_f 0.55 (1:1 hexane–EtOAc); $[\alpha]_D$ (initial) −4.8 (*c* 1.0, Me_2SO); $[\alpha]_D$ (infinity) +23.5 (*c* 1.0, Me_2SO). Diagnostic NMR data are collected in Tables 1 and 2; residual signals are as follows. ^1H NMR (200 MHz, Me_2SO-d_6): anomer **7a** δ 1.31, 1.28, 1.25, 1.12 (4s, each 3H, 2 × CMe_2); anomer **7b** δ 1.26, 1.31, 1.33, 1.54 (4s, each 3H, 2 × CMe_2); clusters of signals for both anomers: δ 8.09–7.91 (m, 4H, H-2′, H-6′), 7.78–7.73 (m, 2H, H-4′), 7.62–7.54 (m, 2H, H-5′); ^{13}C NMR (50 MHz, Me_2SO-d_6): anomer **7a** δ 163.2 (C=O), 112.6, 108.6 (2 × CMe_2), 26.8, 26.3, 25.7, 25.1 (2 × CMe_2); anomer **7b** δ 163.6 (C=O), 113.4, 109.1 (2 × CMe_2), 27.5, 27.2, 25.7, 25.0 (2 × CMe_2); clusters of signals for both anomers: δ 133.8–130.6 (4 × aromatic C), 133.3–127.1 (aromatic CH). ESIMS: calcd for $C_{19}H_{23}ClO_8Na$ $[M+Na]^+$ 437.8, found 437.4. Anal. Calcd for $C_{19}H_{23}ClO_8$: C, 55.01; H, 5.59. Found: C, 55.24; H, 5.49.

An identical result was obtained when the reaction (**6**, 500 mg, 2.06 mmol), was diluted with CH_2Cl_2 (20 mL), quenched with 10% aq $Na_2S_2O_3$ (15 mL), extracted with CH_2Cl_2 (2 × 30 mL) and the collected organic phases were dried and concentrated under diminished pressure. In an alternative preparation anhyd KF (480 mg, 8.26 mmol), obtained from commercial KF activated for 2 h at 120 °C and 0.01 mmHg, was added to 34 mL of a soln of 0.12 M of MCPBA[21] in dry CH_2Cl_2. The suspension was stirred at room temperature for 30 min and then a soln of **6** (412 mg, 1.70 mmol) in dry CH_2Cl_2 (5 mL) was added. The mixture was stirred until complete disappearance of the starting material (TLC, 1:1 hexane–EtOAc) and formation of a single spot (R_f 0.55). After 3.5 h, the insoluble complex was filtered off and the solvent removed under reduced pressure to give a crude mixture of 3-*m*-chlorobenzoate **7a** and **7b** (solid foam, 691 mg, 98% yield) having NMR parameters identical to those of the sample prepared above.

3.3. Epoxidation–methanolysis of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-*erythro*-hex-3-enofuranose (6)

A soln of **6** (1.01 g, 4.17 mmol) in MeOH (10 mL) was treated at 0 °C under stirring with a soln of commercial 70% MCPBA (1.18 g, 4.80 mmol) in MeOH (12 mL). The soln was allowed to warm to room temperature and stirred until the TLC analysis (1:1 hexane–EtOAc) showed the complete disappearance of the starting material (2.5 h) and the formation of four components (R_f 0.55, 0.50, 0.40 and 0.36), two of them (R_f 0.55 and 0.50) visible under UV light. After 2 h the mixture was treated with 10% aq $Na_2S_2O_3$ (30 mL) and concentrated under diminished pressure. The crude residue was partitioned between CH_2Cl_2 (30 mL) and water (20 mL), the aq phase extracted with CH_2Cl_2 (4 × 30 mL) and the organic ones were collected, dried and concentrated under diminished pressure. The crude mixture (1.28 g) was subjected to flash chromatography on silica gel eluting with hexane–EtOAc from 4:1 to 7:3 and gave, after a first sample of **7a**+**7b** (242 mg, 14% yield), the following products.

3.3.1. (1*R*)- and (1*S*)-1-*m*-Chlorobenzoyl-1,2:5,6-di-*O*-isopropylidene-D-*xylo*-hexos-4-ulose (13). Syrup (69 mg, 4% yield) in a ratio of about 3:2 measured on the relative intensities of the H-1 signals; selected ^1H NMR (200 MHz, CD_3CN) signals: *major component* δ 7.98 (m, 2H, H-2′, H-6′), 7.65 (m, 1H, H-4′), 7.50 (m, 1H, H-5′), 6.41 (d, 1H, $J_{1,2}$ 2.7 Hz) 1.47, 1.43, 1.41, 1.33 (4s, each 3H, 2 × CMe_2); *minor component* δ 7.98 (m, 2H, H-2′, H-6′), 7.65 (m, 1H, H-4′), 7.50 (m, 1H, H-5′), 6.38 (d, 1H, $J_{1,2}$ 2.4 Hz) 1.44, 1.40, 1.37, 1.34

(4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, CD_3CN): *major component* δ 208.1 (C-4), 165.4 (C=O), 135.1, 132.5 (aromatic C) 114.3 (2 × *C*Me$_2$), 98.9 (C-1), 83.2, 79.2, 74.7 (C-2, C-3, C-5), 66.5 (C-6), 26.7, 26.6, 26.0, 24.8 (2 × C*Me*$_2$); *minor component* δ 208.1 (C-4), 165.4 (C=O), 135.1, 132.5 (aromatic C) 111.5 (2 × *C*Me$_2$), 97.0 (C-1), 83.9, 82.7, 78.8 (C-2, C-3, C-5), 66.7 (C-6). Cluster of signals for both anomers δ 134.4–128.8 (aromatic CH), 27.6–24.8 (C*Me*$_2$). ESIMS: calcd for $C_{19}H_{23}ClO_8Na$ $[M+Na]^+$ 437.8, found 437.1. Anal. Calcd for $C_{19}H_{23}ClO_8$: C, 55.01; H, 5.59. Found: C, 55.28; H, 5.51.

3.3.2. (1*R*)- or (1*S*)-1-Methoxy-1,2:5,6-di-*O*-isopropylidene-D-*xylo*-hexos-4-ulose (14). Syrup (85 mg, 7% yield); R_f 0.40 (1:1 hexane–EtOAc); ^{1}H NMR (200 MHz, CD_3CN): δ 5.06 (d, 1H, $J_{1,2}$ 2.8 Hz, H-1), 4.87 (dd, 1H, $J_{5,6a}$ 5.7 Hz, H-5), 4.54 (dd, 1H, $J_{2,3}$ 2.2 Hz, $J_{3,OH}$ 4.2 Hz, H-3), 4.48 (dd, 1H, H-2), 4.23 (t, 1H, $J_{6a,6b} = J_{5,6b}$ 8.4 Hz, H-6b), 3.97 (dd, 1H, H-6b), 3.37 (s, 3H, O*Me*), 2.65 (br s, 1H, OH-3), 1.44, 1.39, 1.37, 1.33 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, CD_3CN): δ 208.4 (C-4), 112.2, 111.1 (2 × *C*Me$_2$), 105.1 (C-1), 82.8, 79.2, 74.8 (C-2, C-3, C-5), 66.6 (C-6), 55.8 (OMe), 27.1, 27.0, 26.0, 24.8 (2 × C*Me*$_2$). ESIMS: calcd for $C_{13}H_{22}O_7Na$ $[M+Na]^+$ 313.3, found 313.2. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.69; H, 7.70.

3.3.3. (4*R*)- and (4*S*)-1,2:5,6-Di-*O*-isopropylidene-4-*C*-methoxy-α-D-*xylo*-hexofuranose (11a and 11b). As a mixture (424 mg, 35% yield) in a ratio of about 3:2 measured on the relative intensities of the H-1 signals; solid foam; R_f 0.36 (1:1 hexane–EtOAc). *NMR data of the major component* **11a**: ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 3.40 (s, 3H, OCH_3), 1.51, 1.50, 1.38, 1.31 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 112.7, 110.4 (2 × *C*Me$_2$), 50.1 (OCH_3), 26.2, 25.9, 25.8, 24.5 (2 × C*Me*$_2$). *NMR data of the minor component* **11b**: ^{1}H NMR (200 MHz, $CDCl_3$): see Table 1 and δ 3.46 (s, 3H, OCH_3), 1.55, 1.50, 1.48, 1.36 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 114.4, 110.1 (2 × *C*Me$_2$), 49.7 (OCH_3), 27.6, 26.8, 26.1, 24.5 (2 × C*Me*$_2$). ESIMS: calcd for $C_{13}H_{22}O_7Na$ $[M+Na]^+$ 313.3, found 313.3. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.58; H, 7.69.

In another run, after the complete disappearance of the starting material (**6**, 600 mg, 2.48 mmol), the reaction mixture was neutralised by addition of satd aq $NaHCO_3$ (15 mL) and the hydro-alcoholic soln was stirred at room temperature. After 20 min, TCL analysis (1:1 hexane–EtOAc) indicated the complete disappearance of the compounds **7a**,**b** (R_f 0.55). The reaction mixture was concentrated and partitioned between CH_2Cl_2 (20 mL) and H_2O (10 mL), the aq phase extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were collected, dried and concentrated under diminished pressure. Flash chromatography on silica gel (7:3 hexane–EtOAc) of the crude residue (540 mg) led to **13** (41 mg, 4% yield), **14** (50 mg, 7% yield) and a 3:2 mixture of **11a** and **11b** (252 mg 35% yield).

3.4. (4*R*)-3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-4-*C*-methoxy-α-D-*xylo*-hexofuranose (12a) and (4*S*)-3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-4-*C*-methoxy-α-D-*xylo*-hexofuranose (12b)

A sample of **11a**,**b** (3:2 mixture, 211 mg, 0.73 mmol) was treated with a 2:1 mixture of pyridine and Ac_2O (3 mL), and stirred at room temperature. After 20 h, the starting material completely disappeared (TLC, 99:1 CH_2Cl_2–MeOH) and the reaction mixture was repeatedly co-evaporated with toluene (4 × 5 mL) under diminished pressure. Flash chromatographic purification over silica (4:1 hexane–EtOAc) of the syrupy residue (247 mg) gave **12a** (128 mg, 53% yield) and **12b** (84 mg, 35% yield). Compound **12a** was a syrup; R_f 0.28 (7:3 hexane–EtOAc); $[\alpha]_D$ −26.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): see Table 1 and δ 3.51 (s, 3H, OCH_3), 2.01 (s, 3H, *Me*CO), 1.56, 1.46, 1.31, 1.30 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 168.9 (Me*CO*), 113.5, 109.7 (2 × *C*Me$_2$), 51.5 (OCH_3), 26.7, 26.3, 25.8, 24.7 (2 × C*Me*$_2$), 20.7 (*Me*CO). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.30; H, 7.31. Compound **12b** was a solid foam; R_f 0.20 (7:3 hexane–EtOAc); mp 53–55 °C; $[\alpha]_D$ +74.2 (*c* 1.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): see Table 1 and δ 3.45 (s, 3H, OCH_3), 2.14 (s, 3H, *Me*CO), 1.60, 1.41, 1.37, 1.34 (4s, each 3H, 2 × C*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): see Table 2 and δ 169.6 (Me*CO*), 114.8, 109.8 (2 × *C*Me$_2$), 50.3 (OCH_3), 27.4, 27.1, 26.0, 24.8 (2 × C*Me*$_2$), 20.7 (*Me*CO). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.35; H, 7.29.

A crude sample of **11a**,**b** obtained as usual by epoxidation–methanolysis of **6** (583 mg, 2.40 mmol) was acetylated with pyridine–Ac_2O as described before and the reaction, after quenching by treatment with satd aq $NaHCO_3$, led to **12a** (syrup, 170 mg, 24% yield) and **12b** (solid foam, 100 mg, 14% yield).

3.5. 3-*O*-*m*-Chlorobenzoyl-D-*xylo*-hexos-4-ulose (2)

A 7:3 anomeric mixture of **7a**,**b** (1.50 g, 3.62 mmol) was dissolved in 2:1 MeCN–water (42 mL), treated with CF_3COOH (5.50 mL, 71.8 mmol) and stirred at room temperature. After 3 h, TLC analysis (EtOAc) showed the complete disappearance of the starting material (R_f 0.70) and the formation of one component (R_f 0.26). The soln was concentrated under diminished pressure and repeatedly co-evaporated with toluene

(4 × 30 mL). The residue partitioned between EtOAc (80 mL) and satd aq NaCl soln (30 mL) and the aq phase extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried and concentrated to give a crude residue (1.23 g) that was directly subjected to a flash chromatographic purification, eluting with EtOAc to give **2** (858 mg, 75% yield) as a solid foam. The ^{1}H NMR spectrum in CD_3CN of **2** showed that about 70% of the product was accounted for by a mixture of α,β-4-keto-pyranoses forms (**α-2** and **β-2**) in a 7:3 ratio estimated on the basis of the relative H-3 signal intensities. Anomeric proton signals for minor components were identified at δ 5.23, 4.66, 5.20, 5.15 and the splitting of signals (4.9, 7.8, 4.8 and 3.4 Hz) suggested the presence of the α- and β-pyranosic hydrate forms (20%) and the α- and β-furanosic type structure (10%), respectively. The structures of furanosic forms were confirmed by resonance of H-3 protons at δ 5.98 (d, $J_{2,3}$ 2.0 Hz) and δ 5.96 (d, $J_{2,3}$ 2.4 Hz). R_f 0.26 (EtOAc); mp 71–75 °C, $[\alpha]_D$ +76.2 (*c* 1.0, MeCN); selected ^{1}H NMR (600 MHz, CD_3CN) signals of major components: **α-2**: δ 5.68 (d, 1H, $J_{2,3}$ 10.4 Hz, H-3), 5.44 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.54 (dd, 1H, $J_{5,6a}$ 4.1 Hz, $J_{5,6b}$ 5.0 Hz, H-5), 4.12 (dd, 1H, H-2), **β-2**: δ 5.57 (d, 1H, $J_{2,3}$ 10.0 Hz, H-3), 5.10 (d, 1H, $J_{1,2}$ 7.3 Hz, H-1), 4.26 (dd, 1H, $J_{5,6a}$ 3.7 Hz, $J_{5,6b}$ 5.7 Hz, H-5), 3.90 (dd, 1H, H-2), clusters of signals for both anomers: δ 8.11–7.87 (m, 4H, H-2′, H-6′), 7.68–7.52 (m, 2H, H-4′), 7.50–7.42 (m, 2H, H-5′), 3.90–3.70 (m, 4H, H-6a, H-6b); ^{13}C NMR (50 MHz, CD_3CN): **α-2**: δ 199.5 (C-4), 165.3 (C═O), 93.2 (C-1), 78.8 (C-3), 73.9 (C-5), 73.1 (C-2), 60.5 (C-6), **β-2**: δ 199.1 (C-4), 166.5 (C═O), 97.1 (C-1), 79.7 (C-3), 76.6 (C-5), 69.8 (C-2), 61.0 (C-6), clusters of signals for both anomers: δ 135.2–132.2 (aromatic C), 134.4–129.0 (aromatic CH). HR-ESIMS: calcd for $C_{13}H_{13}ClNaO_7$ $[M+Na]^+$: 339.0242, found 339.0244.

3.6. Methyl 3-*O*-*m*-chlorobenzoyl-α,β-D-*xylo*-hexopyranosid-4-ulose (α-17 and β-17)

A tautomeric mixture of **2** (235 mg, 0.74 mmol) was treated with 6 mL of 0.2 M methanolic HCl, warmed at reflux and stirred until the TLC analysis (EtOAc) revealed the complete disappearance (7 h) of the starting material (R_f 0.26) and the formation of one major product at R_f 0.51. The soln was allowed to cool to room temperature, neutralised by addition of solid $NaHCO_3$, filtered, concentrated under diminished pressure and the residue partitioned between EtOAc (20 mL) and satd aq $NaHCO_3$ soln (10 mL). The aq phase was extracted with EtOAc (4 × 30 mL), the combined organic extracts were dried and concentrated to give a crude residue (225 mg) that was directly subjected to chromatographic purification (1:9 hexane–EtOAc) to give **17** (149 mg, 60% yield) as a syrup constituted (NMR, CD_3CN) by a mixture α,β-keto-pyranose derivatives (**α-17** and **β-17**) in a ratio of about 85:15 estimated on the basis of the relative H-1 signal intensities; R_f 0.29 (1:9 hexane–EtOAc), $[\alpha]_D$ +133.5 (*c* 1.1, $CHCl_3$). NMR data for the major component **α-17**: ^{1}H NMR (200 MHz, CD_3CN): δ 8.06 (t, 1H, $J_{2',4'} = J_{2',6'}$ 2.0 Hz, H-2′), 7.98 (dt, 1H, $J_{4',5'}$ 7.9 Hz, $J_{4',6'}$ 1.3 Hz, H-4′), 7.65 (ddd, 1H, $J_{5',6'}$ 7.9 Hz, H-6′), 7.50 (t, 1H, H-5′), 5.63 (d, 1H, $J_{2,3}$ 10.4 Hz, H-3), 5.02 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.30 (dd, 1H, $J_{5,6a}$ 4.0 Hz, $J_{5,6b}$ 5.2 Hz, H-5), 4.16 (ddd, 1H, $J_{2,OH}$ 7.4 Hz, H-2), 3.78 (m, 2H, H-6a, H-6b), 3.52 (s, 3H, OMe), 3.38 (d, 1H, OH-2); ^{13}C NMR (50 MHz, CD_3CN): δ 199.1 (C-4), 166.2 (C═O), 135.1, 132.1 (aromatic C), 134.4, 131.4, 130.3, 129.0 (aromatic CH), 100.3 (C-1), 78.9 (C-3), 74.3 (C-5), 72.7 (C-2), 60.3 (C-6), 56.4 (OMe). Selected data for the minor component **β-17**: ^{1}H NMR (200 MHz, CD_3CN): δ 5.58 (d, 1H, $J_{2,3}$ 10.0 Hz, H-3), 4.79 (d, 1H, $J_{1,2}$ 7.3 Hz, H-1), 3.58 (s, 3H, OMe); ^{13}C NMR (50 MHz, CD_3CN): δ 199.1 (C-4), 104.8 (C-1), 79.0 (C-3), 77.5 (C-5), 71.8 (C-2), 60.7 (C-6). ESIMS: calcd for $C_{14}H_{15}ClO_7Na$ $[M+Na]^+$ 353.7, found 353.7. Anal. Calcd for $C_{14}H_{15}ClO_7$: C, 50.84; H, 4.57. Found: C, 50.79; H, 4.54.

3.7. D-*xylo*-Hexos-4-ulose (1)

A 3:2 anomeric mixture of **11a**,**b** (701 mg, 2.41 mmol) was dissolved in 2:1 MeCN–water (27 mL), treated with CF_3COOH (4.0 mL, 52.6 mmol) and stirred at room temperature. After 1 h, the starting material had disappeared (TLC, EtOAc), the soln was concentrated under diminished pressure and repeatedly co-evaporated with toluene (4 × 30 mL). The crude residue was a solid foam (quantitative yield) having R_f 0.40 (7:3 EtOAc–MeOH); $[\alpha]_D$ +45.2 (*c* 1.0, water), lit.[6] $[\alpha]_D$ +38 (water). ^{1}H NMR analysis (600 MHz, D_2O) shows the presence of four major constituents (80%), identified as a mixture of 4-keto-pyranoses **α-1** and **β-1** and the corresponding hydrates **α-18** and **β-18** in a ratio of about 17:15:34:34 estimated on the basis of the relative H-1 signal intensities (see below). The presence of four low resolved minor signals (δ 5.58, 5.27, 5.09 and 4.78) suggests the presence of other, although not assigned, minor isomeric forms in total accounting for about 20%. Selected ^{1}H NMR (600 MHz, D_2O) data of major components: **α-18**: δ 5.12 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 3.49 (dd, 1H, $J_{2,3}$ 9.9 Hz, H-2), **β-18**: δ 4.51 (d, 1H, $J_{1,2}$ 7.9 Hz, H-1), 3.20 (dd, 1H, $J_{2,3}$ 9.6 Hz, H-2), **α-1**: δ 5.31 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), **β-1**: δ 4.93 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); selected ^{13}C NMR data (50 MHz, D_2O): **α-18**: δ 94.3 (C-4), 92.8 (C-1), 71.3 (C-2), **β-18**: δ 97.1 (C-1), 94.8 (C-4), **α-1**: δ 205.7 (C-4), 93.0 (C-1), **β-1**: δ 204.6 (C-4), 97.2 (C-1), 74.1 (C-2), Unassigned signals: δ 77.8, 77.8, 77.7, 76.9, 76.1, 75.1 74.1, 73.4, 73.4, 72.8 (CH pyranosic), 60.2, 60.1, 60.1, 59.9 (C-6). HR-ESIMS: calcd for $C_6H_{10}NaO_6$ $[M+Na]^+$ 201.0370, found 201.0370.

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