A convenient synthesis of hexulosonic acids by IBX mediated oxidation of D-glucono-1,5-lactone derivatives

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Dedicated to Professors Rita Hoyos de Rossi, Julio C. Podestá, Manuel González Sierra and Oscar S. Giordano

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Abstract

The oxidation of the free hydroxyl group of methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate **2** or its 2,3:5,6-di-*O*-isopropylidene analogue **3**, the products of acetonation of D-glucono-1,5-lactone **1**, has been attempted by alternative procedures. The oxidation of OH-2 in **2**, or OH-4 in **3**, with *o*-iodoxybenzoic acid (IBX) took place to afford the respective 2-keto **4** and 4-keto **7** derivatives in almost quantitative yields. In contrast, the oxidations with pyridinium dichromate were unsuccessful, and those using dimethylsulfoxide–acetic anhydride afforded low yields of **4** or **7**. Selective removal of the isopropylidene groups in **4** or **7** with 88% aqueous acetic acid afforded, respectively, the methyl esters **5** or **8**; whereas treatment with aqueous trifluoroacetic acid led to the free hexulosonic acids **6** or **9**. The tautomeric preferences for the oxidation products **4** and **7**, and their derivatives, have been established by ^{13}C NMR spectroscopy.

Keywords: Gluconolactone, acetonation, carbohydrate oxidation, hexulosonic acid, *o*-iodoxybenzoic acid (IBX)

Introduction

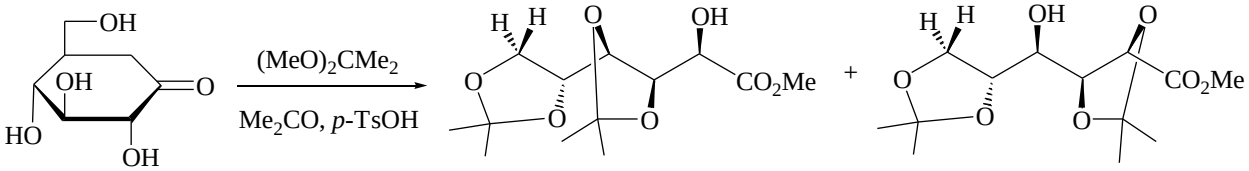
The oxidation of carbohydrates is an important tool for the preparation of compounds that display interesting chemical and biochemical properties. The oxidation products are usually employed as useful intermediates for the synthesis of more complex molecules.[1,2] An important metabolite derived from D-glucose is the D-*arabino*-hex-2-ulosonic acid **6** (sometimes referred to as 2-keto-D-gluconic acid). This acid is a component of polysaccharides obtained from a *Cyttaria*

species of fungus,[3,4] and it has been prepared by catalytic[5] (lead modified Pt/C) or electrochemical oxidation[6] of glucose or gluconic acid. This conversion can also be effected by a number of bacteria species, particularly by the genus *Pseudomonas*.[7-10] Similarly, the enzymatic oxidation of D-glucosone to D-*arabino*-hex-2-ulosonic acid has also been reported.[11] The acid is an important intermediate in the synthesis of D-*erythro*-hex-2-enono-1,4-lactone (D-erythorbic acid)[12] and isoascorbic acid.[13] Moreover, ester derivatives (D-*arabino*-hex-2-ulopyranosonates) have been used as building blocks for the preparation of spiroheterocyclic carbohydrates.[14]

In contrast to D-*arabino*-hex-2-ulosonic acid, which has been found in nature and synthesized by rather numerous chemical or biochemical procedures, as far as we know, its 4-keto analogue (D-*xylo*-hex-4-ulosonic acid) has not yet been isolated or synthesized. We report here our studies on chemical oxidation of selectively protected methyl esters of D-gluconic acid having a free hydroxyl group at C-2 or C-4. The corresponding unprotected 2-keto or 4-keto aldonic acids and their methyl ester derivatives have been obtained.

Results and Discussion

Acetonation of D-glucono-1,5-lactone with 2,2-dimethoxypropane-acetone in the presence of *p*-toluenesulfonic acid afforded the di-*O*-isopropylidene derivatives **2** and **3** (Scheme 1), with a hydroxyl group free at C-2 (major product) and C-4, respectively.[15,16] Compounds **2** and **3** were readily isolated by column chromatography, and were subjected to oxidation with several reagents (Schemes 2 and 3).



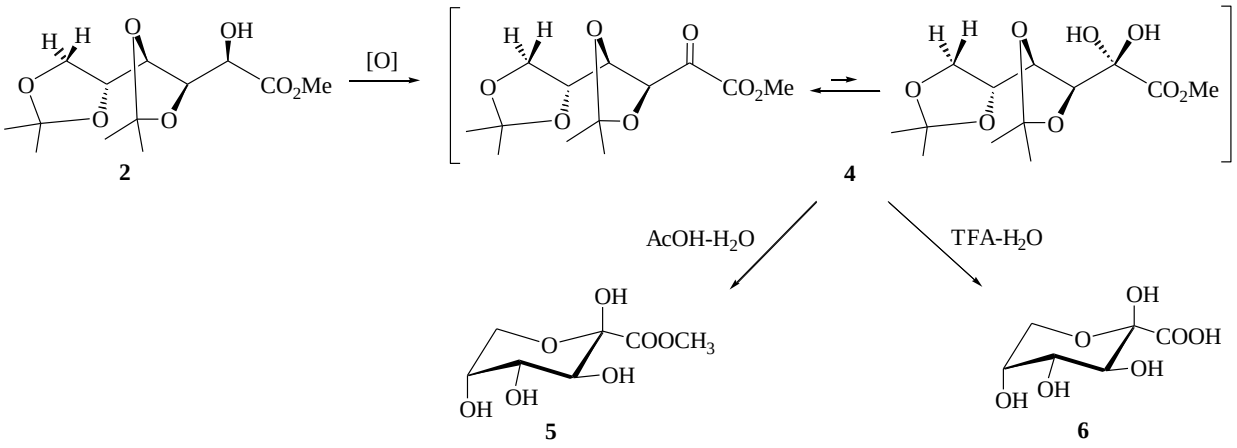
1 **2** **3**

Scheme 1. Acetonation of D-glucono-1,5-lactone.

Attempted oxidations of **2** or **3** with pyridinium dichromate were unsuccessful under varied conditions. Probably the presence of one or two dioxolane rings in **2** or **3**, respectively, hindered the vicinal hydroxyl group to be oxidized. The sterical hindrance could prevent the formation of the chromic ester proposed as an intermediate in the oxidation reaction.[1] Steric effects are known to play an important role in Cr(VI)-promoted oxidations.[1]

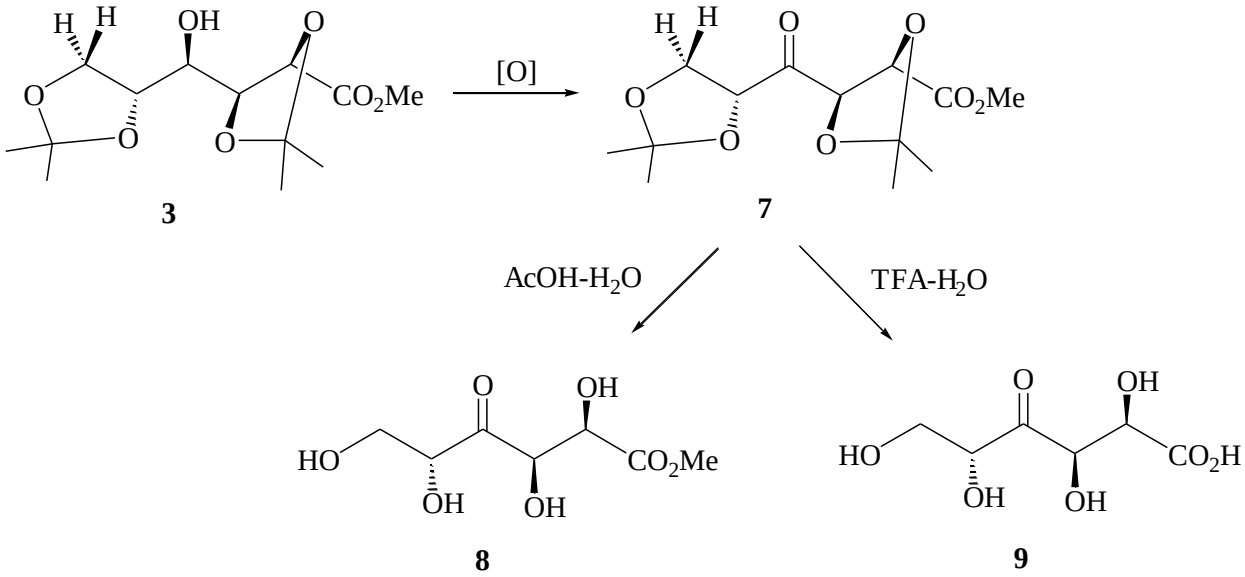
The Pfitzner-Moffatt oxidation of **2** and **3**, using dimethylsulfoxide (DMSO)-acetic anhydride (Ac_2O) was also attempted. The oxidation of **3** took place to afford **7** in a rather low yield (40%); whereas compound **2** could not be fully oxidized even after long reaction time. As

compounds **2** and **4** have a very similar R_f in a variety of solvents employed for tlc, the degree of conversion was estimated by NMR.



Scheme 2. Oxidation of **2** and deprotection of the oxidation product.

Furthermore, in the DMSO-Ac_2O oxidation of **2** or **3** the isolation of the respective products **4** or **7** was rather complicated, as the lyophilization required to remove the large excess of reagents decreases the recovery of material, affording low yields. Therefore, the reaction conditions for this procedure were not optimized.



Scheme 3. Oxidation of **3** and deprotection of the oxidation product.

As alcohols are reported to be readily oxidized with *o*-iodoxybenzoic acid (IBX) in common solvents, at high temperature,[16,17] we applied this protocol for the oxidation of **2** or **3**. In both cases, the reaction was successfully accomplished affording **4** or **7**. The yield of crude **4** or **7**,

obtained by simple filtration and concentration, was almost quantitative and more than 95% pure according to NMR.

The ^{13}C NMR spectrum of **4** showed main signals, that corresponded to the carbonyl compound (C-2 resonance at 192.0 ppm, C-1 at 162.0 ppm), accompanied by satellite signals for C-1 (171.2 ppm) and C-3–C-5. The absence of the carbonyl resonance in the minor component and the new signal at 91.8 ppm indicated the presence of the hydrate form of the carbonyl.

Similar chemical shifts have been reported for 2-keto esters and their 2,2-dihydroxy derivatives.[18] The integral of the signals from the NMR spectra indicated a content of about 20% of the hydrate form.

Furthermore, the ^{1}H NMR spectrum of **4** exhibited a large value for the coupling constant between H-3 and H-4 ($J_{3,4}$ = 7.8 Hz), suggesting a preference for the planar zigzag conformation for **4**, with the isopropylidene groups (C-3–C-4)-*S*-*trans* disposed. This conformational preference can be justified taking into account that the oxidation of HO-2 in **2** removes the 1,3-parallel interaction between HO-2 and HO-4, observed for open-chain derivatives of glucose. Such an interaction induces a shift of the conformational equilibrium to sickle forms.[19]

The NMR spectra of methyl 2,3:5,6-di-*O*-isopropylidene-D-*xylo*-hex-4-ulosonate **7** showed that this compound maintains almost exclusively the carbonyl form ($\delta_{C\text{-}4}$ = 203.8 ppm), since the presence of the hydrate form was not detected.

The electron-ionization mass spectra of the protected keto esters **4** and **7** showed characteristic patterns of fragmentation according to the location of the carbonyl group. The α-cleavage to the ketone function followed by loss of carbon monoxide gave the fragment ions depicted in Figure 1. Subsequent eliminations of acetone or carbon monoxide justify the main peaks observed in the spectra, that showed the acetyl cation (*m/z* = 43) as the base peak.

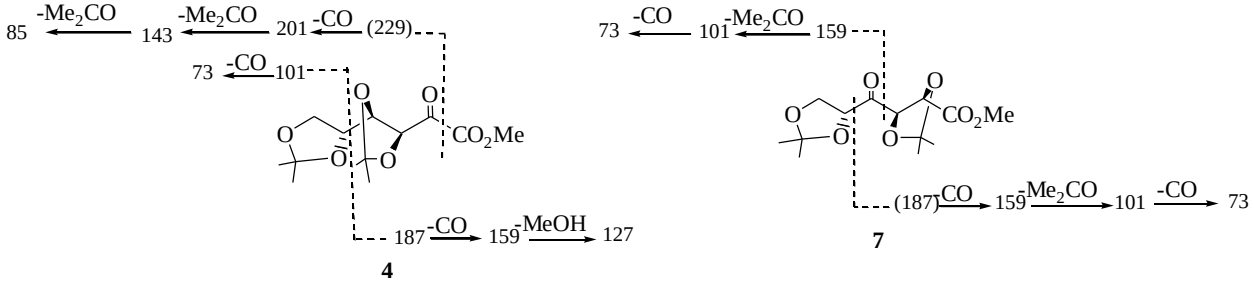


Figure 1. Fragmentation pattern (EI-MS) for compounds **4** and **7.**

Treatment of the 2-keto derivative **4** with 88% aqueous acetic acid promoted the removal of the isopropylidene groups without affecting the ester function. The crystalline methyl ester derivative **5** was dissolved in D_2O and the ^{13}C NMR spectrum, recorded immediately, was coincident with that reported for methyl β-D-*arabino*-hex-2-ulopyranosonate **5**,[20] indicating the presence of this single tautomer. In solution, this material isomerized slowly with contribution of the α and β-hex-2-ulofuranosonates to the equilibrium.[20]

Similar reaction of the 4-keto derivative **7** with 88% aqueous acetic acid afforded the methyl ester **8** as a crystalline product. The ^{13}C NMR spectrum of **8** in D_2O revealed only the presence of the carbonyl compound and its hydrate form (1:1 ratio). This is an expected result as strained three- or four-membered rings (oxirane or oxetane, respectively) are required for the formation of cyclic hemiacetals.

Hydrolysis of the isopropylidene and methyl ester groups of **4** or **7** with a 1:1 mixture of trifluoroacetic acid (TFA)-water gave the corresponding free ulosonic acids **6** or **9**. Similar to the methyl ester derivative **5**, the acid **6** is mainly found as the β-pyranose tautomer. The ^{13}C NMR spectrum of **6** showed no resonance for the C-2 carbonyl but a signal at 97.4 ppm assigned to C-2 of β-D-*arabino*-hex-2-ulopyranosonic acid.[20] On the other hand, the free acid **9** showed exclusively the carboxylic form at C-4 (δ_{C-4} = 210.7 ppm). This compound seems to undergo a slow hydration (if any) of the ketone group in contrast with the methyl ester derivative **8**.

To exclude the possible formation of a 1,5-lactone in **9**, its ^{13}C NMR spectrum was recorded in an alkaline solution of NaOD/D_2O. This spectrum was very similar to that of **9**, indicating that the open chain structure of **9** prevails, and no lactone formation takes place.

Conclusions

The oxidation of the free hydroxyl group at C-2 or C-4 of acetonide derivatives of methyl gluconate was readily accomplished with *o*-iodoxybenzoic acid. The oxidation products have been readily isolated, and in practically quantitative yield, by simple filtration of the reagent and evaporation of the solvent. The selective removal of the isopropylidene protecting groups of the oxidation products with AcOH-H_2O led to the methyl ester of the 2-keto or 4-keto gluconic acids. In contrast, the hydrolysis with TFA-H_2O afforded the respective free hexulosonic acids. The ^{13}C NMR spectra of the D-*arabino*-hex-2-ulosonic acid and its methyl ester confirmed that they prefer the β-hex-2-ulopyranosonic tautomeric form; whereas the D-*xylo*-hex-4-ulosonic acid and its ester are found mainly in the open chain keto form.

Experimental Section

General. D-Glucono-1,5-lactone was purchased from Aldrich Chemical Company, Inc., and used as received. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Analytical thin-layer chromatography (tlc) was performed on silica gel 60 F254 (E. Merck) aluminium-supported plates (layer thickness 0.2 mm). Visualization of the spots was effected by exposure to UV light or by charring with a solution of 5% (v/v) sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was carried out with Silica Gel 60 (230–400 mesh, E. Merck). Optical rotations were measured with a Perkin–Elmer 343 digital polarimeter at 25 ºC. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AMX 500

instrument (^{1}H: 500 MHz; ^{13}C: 125.7 MHz) or a Bruker AC 200 (^{13}C: 50.3 MHz) instruments. The assignments were assisted by 2D COSY, DEPT and HSQC techniques. Electron ionization-mass spectra (EI-MS) were recorded with a Shimadzu QP5050A mass spectrometer, operating at 70 eV. Electrospray ionization-high resolution mass spectra (ESI-HRMS) were recorded with a Bruker micrOTOF-Q II mass spectrometer.

Methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate (2) and methyl 2,3:5,6-di-*O*-isopropylidene-D-gluconate (3) were prepared by acetonation of D-glucono-1,5-lactone (**1**) with 2,2-dimethoxypropane and acetone, as previously described.[15,16]

General procedures for the oxidation of (2) and (3)

The typical procedures for oxidation reactions of **2** and **3** are described below. The reaction conditions employed and the yield of oxidation products (**4** and **7**, respectively) are indicated for each individual preparation.

Oxidation with pyridinium dichromate (PDC). To a solution of **2** or **3** (50 mg; 0.17 mmol) in CH_2Cl_2 (3.8 mL), PDC (88 mg, 0.23 mmol) and 4Å molecular sieves were added. The mixture was stirred at 40 ºC for 24 h and then it was filtered through a short column of silica-gel, using EtOAc. The eluate was concentrated and examined by NMR revealing, in both cases, the unreacted starting material as main component.

Oxidation with Ac_2O-DMSO. To a solution of **3** (0.303 g; 1.04 mmol) in anhydrous DMSO (6 mL) was added Ac_2O (0.55 mL). The solution was stirred under N_2 atmosphere. Then it was freeze-dried and the residue was purified by column chromatography (CH_2Cl_2) to give **7** (0.118 g; 40% yield).

Compound **2** (0.066 g, 0.23 mmol) was oxidized under the same reaction conditions. After the work-up and column chromatography was isolated the oxidation product **4** together with unreacted **2** (0.030 g). The ratio **2**:**4** was 1.7:1, estimated by NMR.

Oxidation with *o*-iodoxybenzoic acid (IBX). To a solution of alcohols **2** or **3** (0.29 g; 1.0 mmol) in dry CH_3CN (6.0 mL) was added IBX (0.608 g; 2.16 mmol). The resulting suspension was stirred at 80 ºC for the time needed to completion of the reaction (7 h for **2** and 3 h for **3**). The mixture was allowed to reach room temperature, diluted with EtOAc and filtered through a Celite bed, which was washed with EtOAc. The combined solutions were concentrated to give crude **4** (0.276 g, 96%) or **7** (0.286, 99%). These products were >95% pure by NMR. Analytical samples were obtained by purification through a silica gel column, which was eluted with CH_2Cl_2-EtOAc 9:1.

Methyl 3,4:5,6-di-*O*-isopropylidene-D-*arabino*-hex-2-ulosonate (4). Syrup; $[\alpha]_D^{20}$ +4 (*c* 2.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$), keto form: δ_H 1.30, 1.34, 1.35, 1.44 (12H, 4 s, $(CH_3)_2C$), 3.88 (3H, s, CH_3O), 3.95 (1H, dd, $^3J_{5,6'}$ = 4.2, $^2J_{6,6'}$ = 8.7 Hz, H-6´), 4.11 (1H, dd, $^3J_{5,6}$ = 6.1, $^2J_{6,6'}$ = 8.7 Hz, H-6), 4.16 (1H, ddd, $^3J_{4,5}$ = 7.8, $^3J_{5,6}$ = 6.1, $^3J_{5,6'}$ = 4.2 Hz, H-5), 4.22 (1H, dd, $^3J_{3,4}$ = 6.0, $^3J_{4,5}$ = 7.8 Hz, H-4), 4.95 (1H, d, $^3J_{3,4}$ = 6.0 Hz, H-3). ^{13}C NMR (125.7 MHz, $CDCl_3$), keto form: δ_C 25.0, 26.0, 26.4, 27.1 (($CH_3)_2C$), 52.8 (CH_3O), 66.8 (C-6), 76.0 (C-5), 78.7 (C-4), 80.1 (C-3), 109.9, 112.2(($CH_3)_2C$), 162.0 (CO_2CH_3), 192.0 (C-2); hydrate form: δ_C 53.5 (CH_3O), 67.9 (C-6), 76.2, 76.4 (C-4, C-5), 82.3

(C-3), 91.8 ($C(OH)_2$), 110.5, 110.6 ($(CH_3)_2C$), 171.2 (CO_2CH_3). EI-MS, *m/z* (%) = 273 (M-Me, 18), 201 (12), 143 (67), 101 (51), 73 (11), 59 (54), 43 (100). ESI-HRMS *m/z* calcd for $C_{14}H_{24}ONaO_8$ [M + MeOH + Na]$^+$: 343.1362, found 343.1363.

Methyl 2,3:5,6-di-*O*-isopropylidene-D-*xylo*-hex-4-ulosonate (7). Syrup; $[\alpha]_D^{20}$ -56 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ_H 1.43, 1.45, 1.46, 1.48 (12H, 4 s, $(CH_3)_2C$), 3.82 (3H, s, CH_3O), 4.17 (1H, dd, $^3J_{5,6'}$ = 5.3, $^2J_{6,6'}$ = 8.7 Hz, H-6´), 4.26 (1H, dd, $^3J_{5,6}$ = 7.5, $^2J_{6,6'}$ = 8.7 Hz, H-6), 4.86 (1H, dd, $^3J_{5,6}$ = 7.5, $^3J_{5,6'}$ = 5.3 Hz, H-5), 4.87 (1H, d, $^3J_{2,3}$ = 5.5, H-3), 5.04 (1H, d, $^3J_{2,3}$ = 5.5 Hz, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$), δ_C 25.0, 25.7, 25.8, 26.2 ($(CH_3)_2C$), 52.6 (CH_3O), 65.6 (C-6), 75.1 (C-3), 78.2 (C-5), 80.0 (C-2), 111.0, 113.2($(CH_3)_2C$), 170.4 (CO_2CH_3), 203.8 (C-4). EI-MS, *m/z* (%) = 273 (M - Me, 2), 245 (2), 189 (11), 159 (18), 101 (76), 73 (26), 59 (25), 43 (100). ESI-HRMS *m/z* calcd for $C_{13}H_{20}NaO_7$ [M + Na]$^+$: 311.1101, found 311.1100.

Hydrolysis of 4 or 7 with AcOH-H_2O. Compounds **4** or **7** (50 mg; 0.17 mmol) were dissolved in AcOH (2.80 mL) and H_2O was added (0.04 mL). The mixture was stirred at 45 ºC for 20 h and then it was concentrated to yield quantitatively the methyl esters **5** or **9**, respectively, as crystalline materials.

Methyl β-D-*arabino*-hex-2-ulopyranosonate (**5**). mp = 179 ºC (from MeOH); $[\alpha]_D^{20}$ –66 (*c* 0.6, H_2O). Lit.[21] mp = 184 ºC; ^{13}C NMR (50.3 MHz, D_2O), δ_C 53.9 (CH_3O), 64.8 (C-6), 69.2, 69.4, 69.5 (C-2–C-5), 97.2 (C-2, β-anomer), 170.9 (CO_2CH_3). ESI-HRMS *m/z* calcd for $C_7H_{12}NaO_7$ [M + Na]$^+$: 231.0481, found 231.0475.

Methyl D-*xylo*-hex-4-ulosonate (**9**). mp = 83 ºC; $[\alpha]_D^{20}$ -22 (*c* 0.3, MeOH); ^{13}C NMR (50.3 MHz, D_2O) keto and hydrate forms (1:1 ratio), δ_C 52.9 (CH_3O), 62.4, 62.6 (C-6), 71.2, 71.3, 71.8, 72.1, 75.6, 76.0 (C-2, C-3, C-5), 90.1 (C-4, $C(OH)_2$), 173.2, 174.3 (CO_2CH_3), 210.0 (C-4, CO).

Hydrolysis of 4 or 7 with TFA-H_2O. Compounds **4** or **7** (40 mg; 0.14 mmol) were dissolved in 1:1 TFA-H_2O (0.5 mL) and stirred at 40 ºC for 3 h and then it was concentrated to yield quantitatively the free acids **6** or **10**, respectively.

β-D-*arabino*-hex-2-ulopyranosonic acid (**6**). $[\alpha]_D^{20}$ –84 (*c* 0.8, H_2O). Lit.[11] $[\alpha]_D^{20}$ –86; ^{13}C NMR (50.3 MHz, D_2O), δ_C 65.1 (C-6), 69.7 (C-5), 69.8 (C-3), 70.0 (C-4), 97.4 (C-2), 172.6 (CO_2H).

D-*xylo*-hex-4-ulosonic acid (**10**). $[\alpha]_D^{20}$ –5 (*c* 0.8, MeOH); ^{13}C NMR (50.3 MHz, D_2O), δ_C 63.4 (C-6), 71.8 (C-3), 76.7, 76.8 (C-2, C-5), 175.2 (CO_2H), 210.7 (C-4).

Sodium D-*xylo*-hex-4-ulosonate. ^{13}C NMR (50.3 MHz, D_2O), δ_C 63.4 (C-6), 72.6 (C-3), 76.1, 76.9 (C-2, C-5), 176.3 (CO_2Na), 210.8 (C-4).

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