Reaction of Aldonic Acids with Hydrogen Bromide. VII.* Preparation of Some 2,6-Dideoxyhexoses

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Reaction of D-allono, D-gulono-, and D-talono-1,4-lactone with hydrogen bromide in acetic acid led to formation of 2,6-dibromo-2,6-dideoxy-hexono-1,4 lactones, assumed to have the D-*altro* (*2*), D-*ido* (*8*), and D-*galacto* (*11*) configurations, respectively. Catalytic hydrogenolysis of the three dibromolactones gave the corresponding three 2,6-dideoxy-hexono-1,4-lactones with the D-*ribo* (*4*), D-*xylo* (*9*), and D-*lyxo* (*13*) configurations, respectively. The latter three lactones were reduced with diisoamylborane to the corresponding 2,6-dideoxy-D hexoses.

The reaction of a number of aldonolactones, or salts of aldonic acids, with hydrogen bromide in acetic acid has been described.[1-5] Both D-gluco- and D-mannonolactone gave 2,6-dibromo-2,6-dideoxy-D-hexono-1,4-lactones with inversion of stereochemistry at C-2.[1,2] On the other hand, D-galactonolactone yielded 6-bromo-6-deoxy-D-galactono-1,4-lactone and bromine was introduced only to a small extent at C-2.[1] Similar results were found when pentonolactones were treated with HBr/AcOH,[3,4] and the mechanism of the reaction has been discussed briefly.[4] These studies have now been extended to other aldonolactones, all having HO-2 and HO-3 *cis* oriented.

Results and discussion

Treatment of D-gulono-1,4-lactone (*1*) with HBr/AcOH for 2 h at room temperature, followed by deacetylation with methanol, gave a high yield of a syrupy product assumed to be 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (*2a*). The corresponding diacetate (*2b*) was obtained in crystalline form. Analogously, D-allonolactone (*7*) yielded 2,6-dibromo-2,6-dideoxy-D-altrono-1,4-lactone (*8a*) by reaction with HBr/AcOH. Neither *8a* nor its acetate (*8b*) could be induced to crystallize and they were characterized only through their NMR spectra. Finally, crude D-talonolactone (*10*), by the same treatment, gave syrupy 2,6-dibromo-2,6-dideoxy-D-galactono-1,4-lactone (*11a*), characterized through its crystalline acetate (*11b*). Hence, all three lactones (*1*, *7* and *10*) which have HO−2 and HO−3 *cis* oriented gave 2,6-dibromo-2,6-dideoxylactones on treatment with HBr/AcOH. It was assumed that bromine entered at C−2 with inversion of the configuration in analogy with previous results.[1-4] Attempts to prove this by reduction of the 2,6-dibromolactones to the corresponding 2,6-dibromo-2,6-dideoxyhexoses with sodium borohydride, as previously reported,[2] led to complex mistures of products, from which, no pure compounds could be obtained.

The bromine atom at C−2 in dibromolactones can be removed selectively by controlled catalytic hydrogenolysis[1,2] or by treatment with aqueous hydrazine.[5] In agreement therewith, the two dibromolactones (*2a*) and (*8a*) could be converted into the 6-bromo-2,6-dideoxylactones (*3*) and (*6*), respectively. Exhaustive catalytic hydrogenolysis of the dibromolactones (*2a*), (*8a*) and (*11a*) gave the corresponding three 2,6-dideoxylactones (*4a*), (*9a*) and (*13a*) which were characterized by their crystalline acetates. The dideoxylac-

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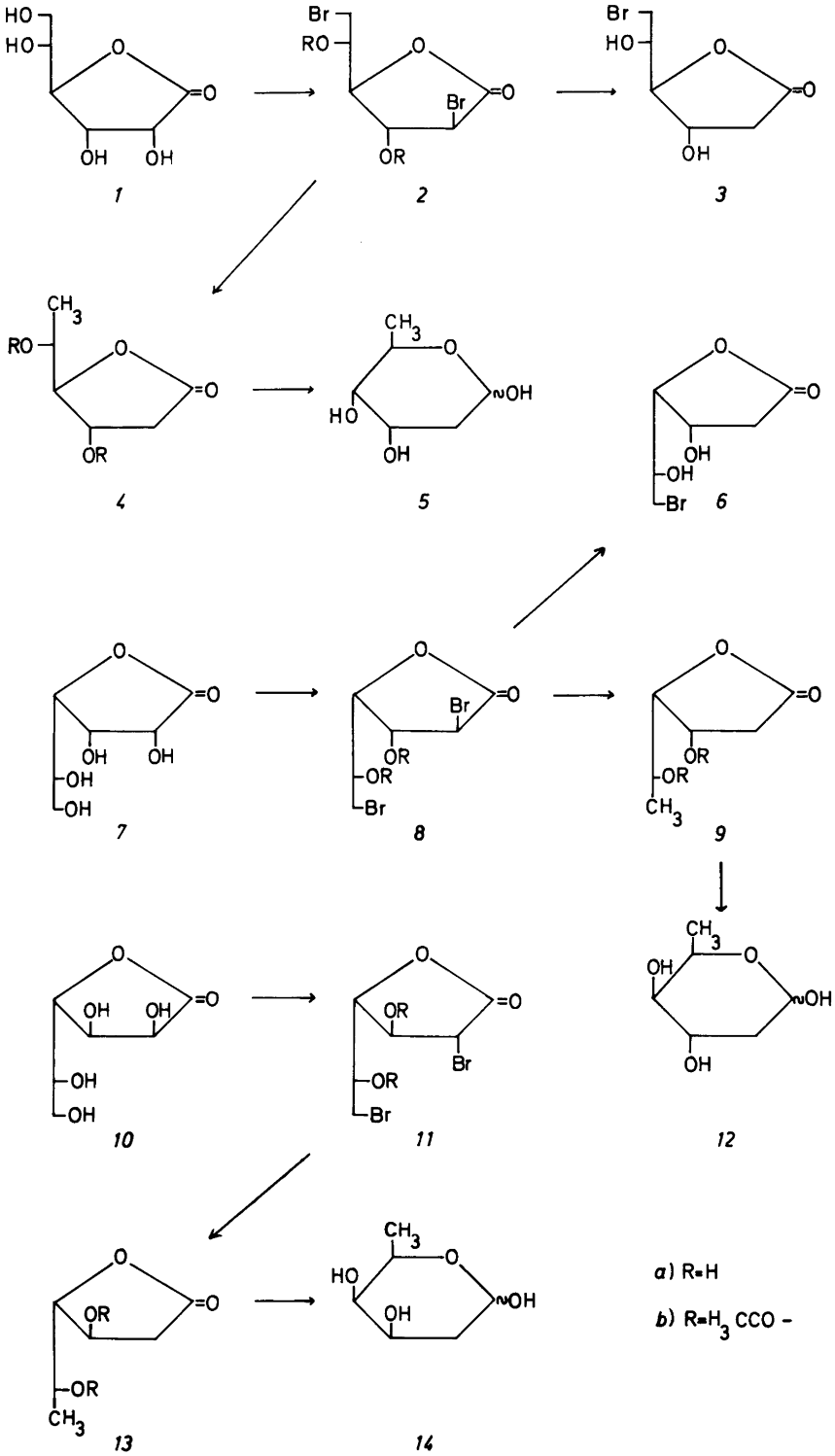
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a) R=H
b) R=H3 CCO -
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tones were subsequently reduced by diisoamylborane to the corresponding 2,6-dideoxyhexose (*5*), (*12*) and (*14*), respectively. These last-named reactions proved the structure of the dibromolactones (*2a*), (*8a*) and (*11a*), except for their configuration at C–2.

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 142 polarimeter. NMR spectra were obtained on Bruker WH–90, HX–270 and AM–500 NMR instruments. Dioxane (67.40 ppm) was used as internal reference for ^{13}C NMR spectra measured in D_2O solution. Column chromatography was done on silica gel 60 (40–63 μm, Merck 9385). The solution of hydrogen bromide in acetic acid (HBr/HOAc) contained 30–32 % by weight of HBr.

*2,6-Dibromo-2,6-dideoxy-*D*-altrono-1,4-lactone* (2a). A mixture of D-allono-1,4-lactone[6] (2.5 g) and HBr/AcOH (15 ml) was stirred at ~20 °C for 2 h. Methanol (50 ml) was added and the solution kept overnight. It was then evaporated and methanol twice added and evaporated. The residue in water (20 ml) was extracted with Et_2O (6 × 20 ml) the extract dried ($MgSO_4$) and evaporated leaving 4.1 g (96 %) of syrupy, almost pure *2a*, $[\alpha]_D^{20}$ +13.8° (*c* 2.1, $CHCl_3$). ^1H NMR (270 MHz, D_2O): δ 6.31 (H–2); 6.17 (H–3); 6.01 (H–4); 5.71 (H–5); 5.13 (H–6); 4.99 (H–6′). J_{23} 7.4 Hz; J_{34} 6.6; J_{45} 5.2; J_{56} 4.1; $J_{56'}$ 7.0; $J_{66'}$ 11.1. ^{13}C NMR (D_2O): 173.8 ppm (C–1); 46.1 (C–2); 75.8 (C–3); 84.9 (C–4); 70.5 (C–5); 34.2 (C–6).

*3,5-Di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-*D*-altrono-1,4-lactone* (2b). D-Allono-1,4-lactone (1.0 g) was stirred for 2 h with HBr/AcOH (10 ml) and acetic anhydride (4 ml) added. After 1 h, ice was added, the mixture stirred for 30 min, diluted with water and extracted with CH_2Cl_2 (2 × 25 ml). The extract was washed 5 times with water, dried and evaporated leaving 1.95 g (89 %) of surypy *2b*. ^1H NMR (500 MHz, $CDCl_3$): δ 4.42 (H–2); 5.57 (H–3); 4.76 (H–4); 5.35 (H–5); 3.69 (H–6); 3.63 (H–6′); 2.19 (OAc). J_{23} 2.8 Hz; J_{34} 2.5; J_{45} 7.0; J_{56} 5.2; $J_{56'}$ 4.5; $J_{66'}$ 11.5. ^{13}C NMR ($CDCl_3$): 169.3 ppm (C–1); 38.2 (C–2); 75.4 (C–3); 81.6 (C–4); 69.9 (C–5); 29.4 (C–6).

*2,6-Dibromo-2,6-dideoxy-*D*-idono-1,4-lactone* (8a). D-Gulono-1,4-lactone[7] (*7*) (5 g) was treated with HBr/AcOH followed by methanol and worked up as described above to give 8.5 g (99 %) of *8a* as a syrup. ^1H NMR (270 MHz, D_2O): δ 4.61 (H–2); 4.67 (H–3); 4.81 (H–4); 4.28 (H–5); 3.52 (H–6); 3.45 (H–6′). J_{23} 5.0 Hz; J_{34} 6.0; J_{45} 5.0; J_{56} 4.6; $J_{56'}$ 6.8; $J_{66'}$ 10.8. ^{13}C NMR (D_2O): 175.0 ppm (C–1); 43.9 (C–2); 75.1 (C–3); 84.1 (C–4); 68.9 (C–5); 34.3 (C–6).

*Di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-*D*-idono-1,4-lactone* (8b). Reaction of *7* (2 g) with HBr/AcOH and subsequent treatment with Ac_2O as described above gave a product which crystallized from ether/hexane to give 3.0 g (69 %) of *8b* with m.p. 115–116 °C. Recrystallization from the same solvent gave a product with m.p. 118–119 °C, $[\alpha]_D^{18}$ −38.8° (*c* 2.1, $CHCl_3$). Anal. $C_{10}H_{12}Br_2O_6$: C, H, Br. ^1H NMR (90 MHz, $CDCl_3$): δ 5.56 (H–3); 5.2–5.3 (H–4, H–5); 4.45 (H–2); 3.54 (H–6); 3.40 (H–6′). J_{23} 5.8 Hz; J_{34} 6.0; J_{56} 6.2; $J_{56'}$ 5.0; $J_{66'}$ 11.0. ^{13}C NMR: 169.5 ppm (C–1); 38.9 (C–2); 75.7 (C–3); 77.8 (C–4); 68.9 (C–5); 27.9 (C–6).

*2,6-Dibromo-2,6-dideoxy-*D*-galactono-1,4-lactone* (11a). A solution of D-talose (9.2 g) in water (60 ml) containing $CaCO_3$ (7 g) was stirred and bromine (0.64 ml) added. After stirring for 24 h, the mixture was filtered and the solution passed through an ion exchange resin [Amberlite IR-120 (H^+)] to remove calcium ion. Evaporation left a brown, semicrystalline residue which was almost pure D-talono-1,4-lactone (*10*) as seen from a ^{13}C NMR spectrum.[8]

Crude D-talonolactone (from 2 g of D-talose) was treated with HBr/AcOH and subsequently with methanol as described above to give 2.42 g (72 %) of crude, syrupy *11a*. ^{13}C NMR (D_2O): 173.4 ppm (C–1); 46.2 (C–2); 76.2 (C–3); 84.9 (C–4); 69.6 (C–5); 33.8 (C–6).

*3,4-Di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-*D*-galactono-1,4-lactone* (11b). The crude lactone (*10*), from 2 g of D-talose, was treated with HBr/AcOH and then acetylated as described above to give 2 g of a product which crystallized from ether/pentane yielding 0.87 g (22 %) of *11b*, m.p. 91–97 °C. Recrystallization gave a product with m.p. 97–98 °C, $[\alpha]_D^{20}$+ 6.5° (*c* 2.0, $CHCl_3$). Anal.

$C_{10}H_{12}Br_2O_6$: C, H, Br. ^1H NMR (500 MHz, $CDCl_3$): δ 4.56 (H−2); 5.32 (H−3); 4.89 (H−4); 5.34 (H−5); 3.56 (H−6); 3.50 (H−6′). J_{23} 4.5 Hz; J_{34} 3.7; J_{45} 2.6; J_{56} 10.3; $J_{56'}$ 8.8. ^{13}C NMR ($CDCl_3$): 169.6 ppm (C−1); 34.4 (C−2); 77.3 (C−3); 81.4 (C−4); 70.8 (C−5); 27.1 (C−6).

6-Bromo-2,6-dideoxy-D-ribo-*hexono-1,4-lactone* (3). A solution of *2a* (2.8 g) in ethyl acetate (50 ml) containing Et_3N (3 ml) and 5 % palladium on carbon (300 mg) was stirred under H_2 for 30 min until 1 molar equiv. of H_2 (230 ml) was consumed. The mixture was filtered and the solution washed with 4M HCl, dried and evaporated leaving 1.8 g (87 %) of crude *3*. A sample was purified by preparative TLC (ethyl acetate/pentane) giving a syrup. ^1H NMR (D_2O): δ 2.96(H−2); 2.49 (H−2′); 4.57 (H−3); 4.45 (H−4); 3.93 (H−5); 3.57 (H−6); 3.46(H−6′). $J_{22'}$ 18.6 Hz; J_{23} 7.2; $J_{2'3}$ 2.7; J_{34} 2.3; $J_{4,5}$ 6.0; J_{56} 3.9; $J_{56'}$ 6.6; $J_{66'}$ 11.1. A ^{13}C NMR spectrum was identical with that of the L enantiomer.[5]

6-Brom-2,6-dideoxy-D-xylo-*hexono-1,4-lactone* (6). To a suspension of *8a* (6.45 g) in water (80 ml) was added 80 % aqueous hydrazine hydrate (3.2 ml, ~3 mol. equiv) Evolution of N_2 ceased after a few min and the solution was then cooled in ice while bromine (~5 ml) was added dropwise until a persistent bromine colour was obtained. The resulting solution was evaporated and water twice added and evaporated. The residue in water (30 ml) was saturated with NaCl and extracted with ethyl acetate (5 × 30 ml). Drying and evaporation gave 4.0 g (80 %) of partly crystalline *6*, which was crystallized from Et_2O to give 3.3 g (70 %) with m.p. ~127 °C. Two recrystallizations from ethyl acetate/pentane gave a product with m.p. 129–130 °C, $[\alpha]_D^{20}$ −32.9° (*c* 2.2, H_2O). Anal. $C_6H_9Br\ O_4$: C, H, Br. ^{13}C NMR (D_2O): 179.9 ppm (C−1); 40.0 (C−2); 69.4, 68.3 (C−3, C−5); 86.9 (C−4); 34.9 (C−6).

2,6-Dideoxy-D-ribo-*hexono-1,4-lactone* (4a). The dibromolactone (*2a*) (2.0 g) in ethyl acetate (25 ml) and Et_3N (3 ml) was stirred overnight under H_2 (101 kPa) in the presence of 5 % palladium on carbon (120 mg). The mixture was filtered and evaporated leaving 945 mg of syrupy *4a* which was characterized only thorugh its ^{13}C NMR spectrum, identical with that of the L enantiomer.[5]

3,5-Di-O-acetyl-2,6-dideoxy-D-ribo-*hexono-1,4-lactone* (4b). Crude *4a* (945 mg) was acetylated in the usual way with Ac_2O and perchloric acid giving 1.23 g (81 %) of *4b*, m.p. 110 °C. Recrystallization from EtOH gave 960 mg (64 %) with m.p. 112–113 °C, $[\alpha]_D^{20}$ −17.4° (*c* 2.0, $CHCl_3$). (Reported for the L enantiomer[5] m.p. 111–112.5 °C $[\alpha]_D^{20}$ +17.1°). Anal. $C_{10}H_{14}O_6$: C, H. The ^1H NMR spectrum was identical with that of the L enantiomer.[5] ^{13}C NMR ($CDCl_3$): 176.6 ppm (C−1); 34.8 (C−2); 69.5, 69.3 (C−3, C−5); 85.5 (C−4); 15.4 (C−6).

3,5-Di-O-acetyl-2,6-dideoxy-D-xylo-*hexono-1,4-lactone* (9b). The crude dibromolactone (*8a*) (1.0 g) was hydrogenated as described above to give crude 2,6-dideoxy-D-*xylo*-hexono-1,4-lactone (*9a*) contaminated with some triethylammonium bromide. ^{13}C NMR (D_2O): 180.3 ppm. (C−1); 40.4 (C−2); 68.6, 66.6 (C−3, C−5); 90.0 (C−4); 18.2 (C−6).

The product was acetylated in the usual way with Ac_2O and perchloric acid yielding 0.48 g (63 %) of *9b*, m.p. 125–130 °C. Recrystallization from ether/pentane gave a product with m.p. 131–131.5 °C, $[\alpha]_D^{20}$ −22.5° (*c* 2.0, $CHCl_3$). Anal.: $C_{10}H_{14}O_6$: C, H. ^1H NMR (270 MHz, $CDCl_3$): δ 2.89 (H−2); 2.63 (H−2′); 5.49 (H−3); 4.57 (H−4); 5.20 (H−5); 1.28 (H−6). J_{23} 7.3 Hz; $J_{2'3}$ 4.5; $J_{22'}$ 18.0; J_{34} 5.6; J_{45} 5,6; J_{56} 6.3. ^{13}C NMR ($CDCl_3$): 172.8 ppm (C−1); 35.4 (C−2); 69.1, 67.6 (C−3, C−5); 82.0(C−4); 16.0 (C−6).

3,5-Di-O-acetyl-2,6-dideoxy-D-lyxo-*hexono-1,4-lactone* (13b). The crude dibromolactone (*11a*) (1.1 g) was hydrogenated as described above to give 2,6-dideoxy-D-*lyxo*-hexono-1,4-lactone (*13a*) mixed with some triethylamine hydrobromide. It was characterized only through its ^{13}C NMR spectrum (D_2O): 180.3 ppm (C−1); 38.4 (C−2); 69.6, 67.8 (C−3, C−5); 92.7 (C−4); 18.9 (C−6).

Acetylation of the crude *13a* gave 650 mg (78 %) of *13b* which was purified by preparative TLC (ethyl acetate/pentane, 1:1) and crystallized from ether/pentane, m.p. 66–67°, $[\alpha]_D^{25}$ +0.8° (*c* 2.1, $CHCl_3$). Anal.: $C_{10}H_{14}O_6$: C, H. ^1H NMR (500 MHz, $CDCl_3$): δ 2.93 (H−2); 2.57 (H−2′); 5.15 (H−3); 4.46 (H−4); 5.16 (H−5); 1.37 (H−6). $J_{22'}$ 18.6 Hz; J_{23} 7.6; $J_{2'3}$ 2.0; J_{34} 1.6; J_{45} 2.8; J_{56} 6.4. ^{13}C NMR ($CDCl_3$): 173.8 ppm (C−1);

34.6 (C−2); 71.2, 69.5 (C−3, C−5); 85,8 (C−4); 15.8 (C−5).

2,6-Dideoxy-D-ribo-*hexose* (5). To a solution of diisoamylborane (prepared from the borane-dimethyl sulfide complex (3.3 ml) in THF (8 ml) and 2-methyl-2-butene (7.3 ml)[9] was added a solution of *4a* (964 mg) in THF (6 ml) at 0 °C with Ar protection. The solution was kept overnight. Water (5 ml) was added and the mixture boiled for 1 h then partially concentrated. More water (20 ml) was added and the mixture extracted 3 times with CH_2Cl_2. Evaporation of the aqueous phase left 720 mg of a syrup which contained D-digitoxose (5) as seen from a ^{13}C NMR spectrum. Column chromatography using ethyl acetate/acetone (25:4) as eluant gave 250 mg (26 %) of product, m.p. 95 °C. Recrystallization from ethyl acetate/ether gave a product with m.p. 107 °C, $[\alpha]_D^{20}$ +47.7° (final) (*c* 1.5, H_2O), in agreement with reported values.[10] A ^{13}C NMR spectrum (D_2O) showed a mixture of α- and β-pyranose; the chemical shift values were identical with those of the L enantiomer.[5]

2,6-Dideoxy-L-xylo-*hexose* (12). The crude dideoxylactone (*9a*) (1.96 g) was reduced with diisoamylborane as described above to give 1.45 g (74 %) of syrupy *12* as a mixture of α- and β-pyranoses (α:β ratio 1:4.7) containing ~10 % of other products. ^{13}C NMR (D_2O), α anomer: 93.6 ppm (C−1); 38.5 (C−2); 69.8, 69.2; 66.5 (C−3, C−4, C−5); 17.9 (C−6). β-Anomer: 94.5 (C−1); 36.5(C−2); 72.0, 71.7, 71.2 (C−3, C−4, C−5); 18.4(C−6). $J_{C-1,H-1}$ was 167.8 Hz for the α anomer and 160.6 for the β anomer. Crystallization from acetone/ether gave *12* with m.p. 85–102 °C, $[\alpha]_D^{20}$ −2.3° → +1.2° (*c* 2.0, H_2O); (reported[11] m.p. 100–103°, $[\alpha]_D$ −2° → +4°).

2,6-Dideoxy-D-lyxo-*hexose* (14). A solution of crude *13a* (1.4 g), containing some triethylamine hydrobromide, was reduced with diisoamylborane as described above to give 916 mg (64 %) crude, syrupy *14*. A ^{13}C NMR spectrum was identical with that published[12] for the D,L form and showed that the product was a mixture of pyranose (α:β ratio 1:1.2) and ~10 % furanose form.

Purification by column chromatography using ethyl acetate/acetone (1:1) as eluant gave a crystalline product, m.p. 98–103 °C, $[\alpha]_D^{20}$ +59.8 → 55.5° (reported[11] m.p. 103–106°, $[\alpha]_D$ 90 → 61°). NMR data: ^1H (500 MHz, D_2O): α-pyranose: δ 6.79 (H−1); 5.41 (H−5); 5.36 (H−3); 4.96 (H−4); 3.15 (H−2a); 3.07 (H−2e); 2.51 (H−6α or β); $J_{1,2a}$ 3.6 Hz; $J_{1,2e}$ ~ 0; $J_{2,2}$ 12.8; $J_{2a,3}$ 12.0; $J_{2e,3}$ 5.6; $J_{3,4}$ 3.4; $J_{4,5}$ ~ 0; $J_{5,6}$ 6.8. β-Pyranose: δ 6.09 (H−1); 5.15 (H−3); 4.94 (H−5); 4.87 (H−4); 3.25 (H−2e); 2.88 (H−2a); 2.47 (H−6 α or β); $J_{1,2a}$ 9.6 Hz; $J_{1,2e}$ 2; $J_{2e,3}$ 5.6; $J_{2,2}$ 12.2; $J_{2a,3}$ 12.2; $J_{3,4}$ 3.2; $J_{4,5}$ ~0; $J_{5,6}$ 6.8.

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