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Regioselective halogenation of pentono-1,4-lactones. Efficient synthesis of 5-chloro- and 5-bromo-5-deoxy derivatives

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Abstract

Treatment of unprotected D-ribono, D-arabinono and D-xylono-1,4-lactones with either thionyl chloride or thionyl bromide in dimethylformamide led to 5-chloro- or 5-bromo-5-deoxy derivatives in 70%–95% yields. Under the same conditions, D-lyxono-1,4-lactone resulted in the 2-halogeno compounds. © 1997 Elsevier Science Ltd.

Keywords: Pentono-1,4-lactones; Thionyl chloride; Thionyl bromide; Dimethylformamide; Regioselective halogenation; 5-chloro-5-deoxy-pentono-1,4-lactone; 5-bromo-5-deoxy-pentono-1,4-lactone

1. Introduction

Deoxyhalogenolactones are useful intermediates in organic synthesis. For example, bromo derivatives are convenient precursors in the preparation of deoxy sugars [1,2], aminodeoxy sugars, [3,4] and iminocyclitols [5,6].

The reaction of hexonolactones with hydrogen bromide has been reported by Pedersen and coworkers [7]. Treatment of D-galactono-1,4-lactone with hydrogen bromide in acetic acid followed by acetylation gave the acetylated 6-bromo-6-deoxy derivative in 63% yield. On the other hand, reaction of D-mannono-1,4-lactone and D-glucono-1,4 or 1,5-lactones led to 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone in 72% yield and to 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone in 44% yield respectively [7,8].

The reaction of pentono-1,4-lactones with hydrogen bromide in acetic acid led to a mixture of 2-bromo-2-deoxy-pentono-1,4-lactones and 2,5-dibromo derivatives [8–10]. From D-ribono and D-lyxono-1,4-lactones, 2-bromo-2-deoxy-D-arabinono- and 2-bromo-2-deoxy-D-xylono-1,4-lactones were obtained in 64% and 78% yields respectively and the 2,5-dibromo-2,5-dideoxy derivatives in 5% yield.

To our knowledge, the triphenylphosphine–carbon tetrabromide reagent was the only one which yielded the 5-bromo-5-deoxy derivatives although in low yield. D-Lyxono- and D-ribono-1,4-lactones reacted with this reagent to give 5-bromo-5-deoxy-D-lyxono-1,4-lactone and 5-bromo-5-deoxy-D-ribono-1,4-lactone in 24% and 55% yields respectively [11].

There are only few reports describing the chlorination of aldonolactones. Reaction of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone with *p*-nitrobenzenesulfonyl chloride, mesyl chloride in pyridine or triphenylphosphine-carbon tetrachloride gave 5-chloro-5-

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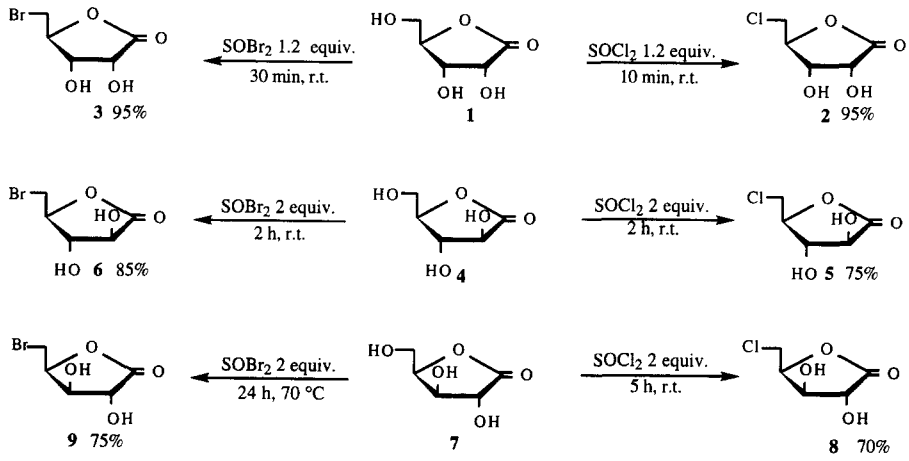


Scheme 1. Regioselective chlorination and bromination of pentono-1,4-lactones in DMF.

deoxy-D-ribono-1,4-lactone in 47% yield [12].

In previous papers, we already reported the synthesis of α,β-dichloropolyols by regioselective chlorination of polyols with commercial Vilsmeier and Haack's salt [13]. We now report a new and very efficient route to 5-chloro-5-deoxy- or 5-bromo-5-deoxy-pentono-1,4-lactones using thionyl chloride or thionyl bromide in dimethylformamide.

2. Results and discussion

When D-ribono-1,4-lactone (**1**) was treated with 1.2 equiv of thionyl chloride in dimethylformamide, for 10 min at room temperature, 5-chloro-5-deoxy-D-ribono-1,4-lactone (**2**) [12] was obtained regioselectively in 95% yield. Using an excess of thionyl chloride (2 equiv), the chlorination was almost instantaneous and remained regioselective.

When this reaction was applied to D-arabinono-1,4-lactone (**4**) and to D-xylono-1,4-lactone (**7**), only the 5-chloro-5-deoxy-derivatives were obtained (Scheme 1).

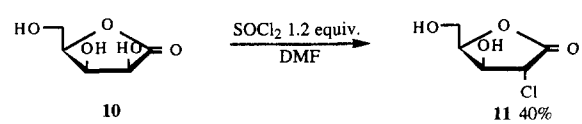
To investigate the solvent effect, chlorination of D-ribono-1,4-lactone (**1**) has been carried out in acetonitrile with thionyl chloride and sulfuric acid. The 5-chloro-5-deoxy derivative was not detected and only 2-chloro-2-deoxy-D-arabinono-1,4-lactone (**12**), resulting from a chlorination with inversion of configuration at C-2, was isolated in 20% yield.

The regioselective chlorination at the primary hydroxyl group in dimethylformamide was ascribed to the bulky structure of the iminium salt formed *in situ* between thionyl chloride and the solvent. Moreover, the arrangement of hydroxyl groups at C-2 and C-3 influenced the substitution step at the primary hydroxyl carbon atom.

The reaction of D-arabinono-1,4-lactone (**4**) with 2 equiv of thionyl chloride afforded the chlorinated derivative **5** in 75% yield. The lower yield as compared to **1** as starting material (20%) could be explained by the stereoelectronic repulsion between the C-2 hydroxyl group and the attacking nucleophile at C-5. D-Xylono-1,4-lactone (**7**) reacted in the same way to yield 70% of **8**. In this case, an interaction by the C-3 hydroxyl group presumably occurred.

A greater repulsion was expected in the case of D-lyxono-1,4-lactone (**10**). In fact, this lactone reacted with 1.2 equiv of thionyl chloride in dimethylformamide to afford only 2-chloro-2-deoxy-D-xylono-1,4-lactone (**11**) in 40% yield (Scheme 2). In this case, the nucleophilic substitution at C-2 was not prevented by stereoelectronic repulsion. When the amount of chlorination reagent (2 equiv), was increased, a syrup was obtained which, analysed by ^{13}C NMR spectroscopy, showed the presence of a mixture of C-2 and C-5 monochlorinated lactones, the latter being detected only in trace quantities.

Similarly, the synthesis of 5-bromo-5-deoxy-pentono-1,4-lactones has been attempted (Scheme 1). The same behaviour, as with thionyl chloride in dimethylformamide, was observed with thionyl bromide in dimethylformamide. Thionyl bromide (1.2 equiv) in dimethylformamide, reacted with the lactone **1** to afford the 5-bromo-5-deoxy-D-ribono-1,4-lactone (**3**) [11] in 95% yield. D-Arabinono-1,4-lac-



Scheme 2.

tone (**4**) or D-xylono-1,4-lactone (**7**) led to 5-bromo-5-deoxy-D-arabinono-1,4-lactone (**6**) in 85% yield or to 5-bromo-5-deoxy-D-xylono-1,4-lactone (**9**) in 75% yield. The reaction of D-lyxono-1,4-lactone (**10**) with thionyl bromide (1.2 equiv) at 50 °C gave only the 2-bromo-2-deoxy-D-xylono-1,4-lactone [10] in 30% yield.

In conclusion, thionyl bromide and thionyl chloride in dimethylformamide allowed the regioselective bromination and chlorination at the primary carbon of D-ribono-, D-arabinono-, and D-xylono-1,4-lactones in good yields (70%–95%). In dimethylformamide, the formation of an iminium salt was directly responsible for the observed regioselectivity. In contrast, D-lyxono-1,4-lactone (**10**) was brominated or chlorinated at the secondary C-2 carbon atom. When acetonitrile was used instead of dimethylformamide for the chlorination of D-ribono-1,4-lactone, the regioselectivity was different. Further study of the solvent effect on the halogenation of aldonolactones is presently in progress.

3. Experimental

General methods.—^{1}H NMR spectra and ^{13}C NMR spectra were recorded in Me_2SO-d_6 with Me_4Si as internal standard on a Bruker 300 MHz spectrometer. Measurement of $[\alpha]_D$ values was effected with a JASCO DIP-370 digital polarimeter, using a sodium lamp ($\lambda = 589$ nm), at 20 °C. Column chromatography was performed on Silica gel (E. Merck 230–400 mesh) using EtOAc–petroleum ether. Analytical TLC was performed on Merck glass backed silica gel sheets (Silica Gel F_{254}) and EtOAc as eluent.

D-Ribono-1,4-lactone (**1**) and D-xylono-1,4-lactone (**7**) were from commercial source.

D-Arabinono-1,4-lactone (**4**) *and D-lyxono-1,4-lactone* (**10**) [14].—To a soln of barium carbonate (5.96 g, 30 mM) and D-arabinose or D-lyxose (3 g, 20 mM) in distilled water (25 mL) cooled at 0 °C, bromine (3 × 0.38 mL, 22 mM) was added at twenty min intervals. The reaction mixture was stirred at this temperature for 1 h and then for 3 h at room temperature. Sodium thiosulfate was added to destroy the excess of bromine and the solvent was removed to give a white solid which was extracted with boiling acetone (3 × 75 mL). Solvent removal afforded the lactones as a yellow syrup for **4** and a white solid for **10**, respectively.

4: (2.68 g, 90%); $[\alpha]_D$ +69.5° (*c* 0.88, H_2O), lit. +73.7° (H_2O) [15]; ^{1}H NMR (Me_2SO-d_6): δ 4.0 (m, 2 H, H-2–3), 4.22 (m, 1 H, H-4), 3.70 (m, 1 H, H-5), 3.49 (m, 1 H, H-5′); ^{13}C NMR (Me_2SO-d_6): δ 174.6 (C-1), 73.6 (C-2), 72.3 (C-3), 81.1 (C-4), 59.1 (C-5).

10: (2.64 g, 90%); mp 110–112 °C, lit. 110–112 °C [16]; $[\alpha]_D$ +76° (*c* 1.41, MeOH), lit. +82.5° (H_2O) [16]; ^{1}H NMR (Me_2SO-d_6): δ 4.42 (d, 1 H, $J_{2,3}$ 4.7 Hz, H-2), 4.20 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 4.30 (m, 1 H, $J_{4,5}$ 4.8 Hz, H-4), 3.67 (dd, 1 H, $J_{5,5'}$ 12.0 Hz, H-5), 3.59 (dd, 1 H, $J_{4,5'}$ 7.1 Hz, H-5′); ^{13}C NMR (Me_2SO-d_6): δ 176.1 (C-1), 70.3 (C-2), 68.9 (C-3), 80.4 (C-4), 59.3 (C-5).

General procedure for halogenation.—The lactone (1 g, 6.8 mM) was stirred with anhyd DMF (10 mL) under inert atmosphere. Freshly distilled $SOCl_2$ or $SOBr_2$ was added dropwise at 0 °C. The mixture was stirred at room temperature or at 70 °C, then MeOH was added and the soln was kept for 10 min at room temperature and concd. The crude product was purified by column chromatography using EtOAc–petroleum ether.

5-Chloro-5-deoxy-D-arabinono-1,4-lactone (**5**).—This compound was prepared by the reaction of D-arabinono-1,4-lactone (**4**) with $SOCl_2$ (2 equiv, 0.99 mL, 13.6 mM) at room temperature for 2 h as described in the general procedure. After purification by chromatography (1:1 EtOAc–petroleum ether) the product **5** was isolated as a colourless solid (0.84 g, 75%); mp 108 °C; $[\alpha]_D$ +14.5° (*c* 0.86, AcOEt); ^{1}H NMR (Me_2SO-d_6): δ 4.29 (m, 2 H, $J_{2,3}$ 8.4 Hz, H-2–4), 4.0 (m, 1 H, H-3), 3.81 (dd, 1 H, $J_{4,5}$ 5.3 Hz, $J_{5,5'}$ 12.7 Hz, H-5), 3.96 (dd, 1 H, $J_{4,5'}$ 2.5 Hz, H-5′); ^{13}C NMR (Me_2SO-d_6): δ 175.7 (C-1), 73.4 (C-2), 73.8 (C-3), 78.7 (C-4), 43.5 (C-5). Anal. Calcd for $C_5H_7ClO_4$: C, 36.05%; H, 4.24%; Cl, 21.28%. Found: C, 36.10%; H, 4.32%; Cl, 21.19%.

5-Chloro-5-deoxy-D-xylono-1,4-lactone (**8**).—This compound was prepared by reaction of D-xylono-1,4-lactone (**7**) with $SOCl_2$ (2 equiv, 0.99 mL, 13.6 mM) at room temperature for 5 h as described in the general procedure. After purification by chromatography (1:1 EtOAc–petroleum ether), **8** was obtained as a yellow syrup (0.78 g, 70%); $[\alpha]_D$ +51.2° (*c* 1.05, AcOEt); ^{1}H NMR (Me_2SO-d_6): δ 4.69 (m, 1 H, H-4), 4.22 (m, 2 H, H-2–3), 3.85 (dd, 1 H, $J_{4,5'}$ 7.1 Hz, H-5), 3.91 (dd, 1 H, $J_{4,5}$ 4.2 Hz, $J_{5,5'}$ 11.9 Hz, H-5′); ^{13}C NMR (Me_2SO-d_6): δ 174.5 (C-1), 72.6 (C-2), 72.3 (C-3), 79.5 (C-4), 42.7 (C-5). Anal. Calcd for $C_5H_7ClO_4$: C, 36.05%; H, 4.24%; Cl, 21.28%. Found: C, 36.25%; H, 4.40%; Cl, 21.25%.

2-Chloro-2-deoxy-D-xylono-1,4-lactone (**11**).—Treatment of D-lyxono-1,4-lactone (**10**) with $SOCl_2$ (1.2 equiv, 0.59 mL, 8.16 mM) at 60 °C for 3 h, as described in the general procedure, gave an oil

which was purified by column chromatography (7:3 EtOAc–petroleum ether) to give **11** as a yellow syrup (0.45 g, 40%); $[\alpha]_D$ +49.6° (*c* 0.38, AcOEt); ^{1}H NMR (Me_2SO-d_6): δ 4.64 (d, 1 H, $J_{2,3}$ 6.1Hz, H-2), 4.45 (tr, 1 H, $J_{3,4}$ 6.2 Hz, H-3), 4.56 (m, 1 H, $J_{4,5}$ 3.2 Hz, H-4), 3.66 (dd, 1 H, $J_{4,5'}$ 4.1 Hz, H-5), 3.74 (dd, 1 H, $J_{5,5'}$ 12.4 Hz, H-5'); ^{13}C NMR (Me_2SO-d_6): δ 170.9 (C-1), 56.8 (C-2), 73.9 (C-3), 81.7 (C-4), 58.2 (C-5). Anal. Calcd for $C_5H_7ClO_4$: C, 36.05%; H, 4.24%; Cl, 21.28%. Found: C, 36.12%; H, 4.20%; Cl, 21.32%.

2 - Chloro - 2 - deoxy - D - *arabinono - 1, 4 - lactone* (**12**).—Colourless solid; mp 86 °C; $[\alpha]_D$ +69.0° (*c* 0.65, AcOEt); ^{1}H NMR (Me_2SO-d_6): δ 4.86 (d, 1 H, $J_{2,3}$ 8.4 Hz, H-2), 4.24 (tr, 1 H, $J_{3,4}$ 8.4 Hz, H-3), 4.19 (m, 1 H, $J_{4,5}$ 4.0 Hz, $J_{4,5'}$ 2.0 Hz, H-4), 3.74 (dd, 1 H, $J_{5,5'}$ 12.7 Hz, H-5'), 3.55 (dd, 1 H, H-5); ^{13}C NMR (Me_2SO-d_6): δ 169.8 (C-1), 59.2 (C-2), 73.4 (C-3), 83.2 (C-4), 58.5 (C-5). Anal. Calcd for $C_5H_7ClO_4$: C, 36.05%; H, 4.24%; Cl, 21.28%. Found: C, 36.30%; H, 4.15%; Cl, 21.21%.

5 - Bromo - 5 - deoxy - D - *arabinono - 1, 4 - lactone* (**6**).—D-Arabinono-1,4-lactone (**4**) was treated with $SOBr_2$ (2 equiv, 1.05 mL, 13.6 mM) at room temperature for 2 h as described in the general procedure. After separation by chromatography (1:1 EtOAc–petroleum ether) the product **6** was isolated as a white solid (1.21 g, 85%); mp 123 °C; $[\alpha]_D$ +27.9° (*c* 0.96, AcOEt); ^{1}H NMR (Me_2SO-d_6): δ 4.31 (d, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 3.95 (tr, 1 H, $J_{3,4}$ 8.1 Hz, H-3), 4.24 (m, 1 H, $J_{4,5}$ 2.8 Hz, $J_{4,5'}$ 5.8 Hz, H-4), 3.84 (dd, 1 H, $J_{5,5'}$ 11.8 Hz, H-5), 3.67 (dd, 1 H, H-5'); ^{13}C NMR (Me_2SO-d_6): δ 173.7 (C-1), 73.4 (C-2), 75.1 (C-3), 78.4 (C-4), 32.8 (C-5). Anal. Calcd for $C_5H_7BrO_4$: C, 28.46%; H, 3.34%; Br, 37.87%. Found: C, 28.35%; H, 3.33%; Br, 37.80%.

5 - Bromo - 5 - deoxy - D - *xylono - 1, 4 - lactone* (**9**).—D-Xylono-1,4-lactone (**7**) was treated with $SOBr_2$ (2 equiv, 1.05 mL, 13.6 mM) at 70 °C for 24 h as described in general procedure. After purification by chromatography (7:3 EtOAc–petroleum ether), the product was obtained as a yellow syrup (1.07 g, 75%); $[\alpha]_D$ +43.7° (*c* 2.94, AcOEt); ^{1}H NMR (Me_2SO-d_6): δ 4.21 (m, 2 H, H-2–3), 4.74 (m, 1 H, H-4), 3.74 (dd, 1 H, $J_{4,5}$ 4.3 Hz, $J_{5,5'}$ 11.0 Hz, H-5), 3.67 (dd, 1H, $J_{4,5'}$ 8.0 Hz, H-5'); ^{13}C NMR (Me_2SO-d_6): δ 174.6 (C-1), 72.8 (C-2), 72.3 (C-3), 79.7 (C-4), 31.0 (C-5). Anal. Calcd for $C_5H_7BrO_4$: C, 28.46%; H, 3.34%; Br, 37.87%. Found: C, 28.42%; H, 3.36%; Br, 37.75%.

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