Preparation of Some 2,3-Dideoxylactones by an Unusual Catalytic Hydrogenolysis

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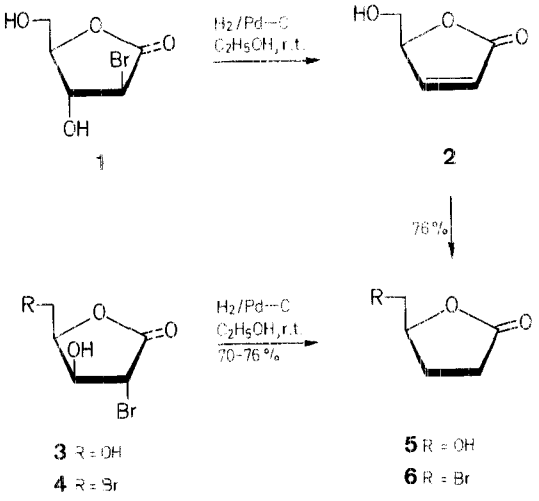
Hydrogenolysis of 2-bromo-2-deoxyaldono-1,4-lactones in ethanol solution with palladium as catalyst gives good yields of the corresponding 2,3-dideoxylactones with removal of not only the bromine atom but also the C-3 hydroxy group.

Bromdeoxyaldono-1,4-lactones are readily obtained by treatment of aldonolactones with hydrogen bromide in acetic acid[1-4]. The bromine of 2-bromo-2-deoxyaldonolactones, such as **1**, **3**, and **4**, can be replaced by hydrogen through catalytic hydrogenolysis[2,3], by treatment by hydrazine[4], or with iodide[1]. When catalytic hydrogenolysis is carried out in the presence of an acid acceptor (triethylamine) a bromine atom at C-2 is rapidly and selectively replaced by hydrogen. On more prolonged treatment with hydrogen, bromine at a primary carbon atom, as in **4**, **8**, or **9**, is also removed giving dideoxyaldonolactones[2,3].

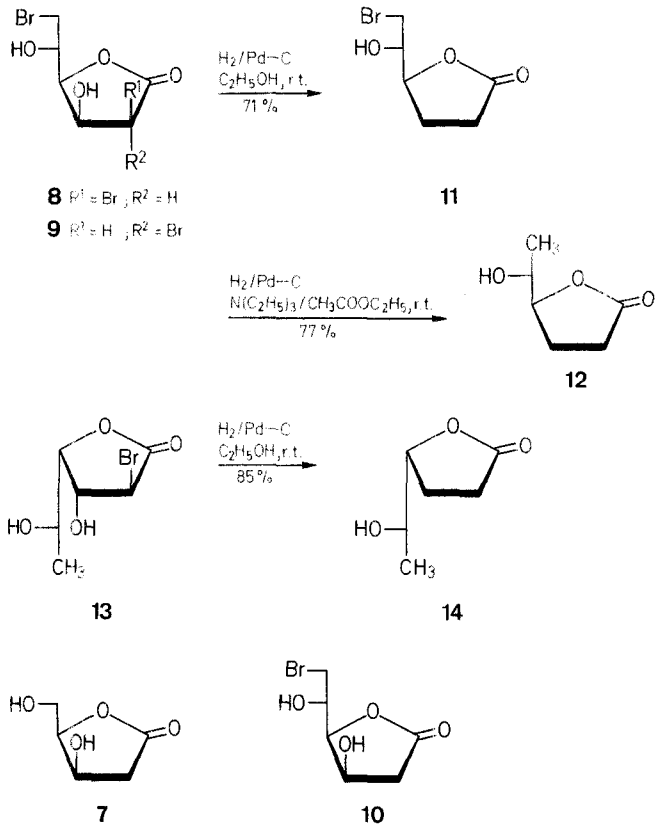
It has now been found that when no acid acceptor is present catalytic hydrogenolysis of 2-brom-2-deoxyaldono-1,4-lactones, having a hydroxy-group at C-3, leads to the formation of 2,3-dideoxyaldono-1,4-lactones. Thus hydrogenolysis of 2-bromo-2-deoxy-D-arabinono-1,4-lactone (**1**) in ethanol solution in the presence of 5% palladium on carbon gave a 76% yield of the optically pure 2,3-dideoxyaldonolactone **5**. The latter was also obtained from the isomeric bromoaldonolactone **3**. Since the 2-bromoaldonolactones, **1** and **3**, are readily available from D-ribono- and D-lyxono-lactone, respectively[3], this method represents a useful alternative to the synthesis of **5** from (*S*)-glutamic acid[5].



Similarly, hydrogenolysis of the 2,5-dibromoaldonolactone **4**, in the absence of an acid acceptor, yielded the 2,3-dideoxy-5-bromoaldonolactone **6** in 70% yield. The bromine at C-5 was not affected, even on prolonged treatment with hydrogen. The two isomeric 2,6-dibromolactones **8** and **9** both yielded 6-bromo-2,3,6-trideoxy-D-*erythro*-hexono-1,4-lactone (**11**) in 71 and 70% yield, respectively, by this procedure. When **11** was subjected to hydrogenolysis in the presence of triethylamine it was smoothly converted into the trideoxy-lactone **12**. Finally, the enantiomer **14** of **12** was obtained by hydrogenolysis of 2-bromo-2,6-dideoxy-L-glucono-1,4-lactone (**13**) without using an acid acceptor.

The hydrogenolysis without an acid acceptor gave in all cases, in addition to the 2,3-dideoxyaldonolactones, small amounts (5–10%) of the corresponding 2-deoxyaldonolactones such as **7** and **10**. Since the latter were the only products obtained in the presence of triethylamine, it was thought that they might be formed in the first stage of the reaction when only small amounts of hydrogen bromide were present.

However, when hydrogen bromide was added to the reaction mixture prior to the treatment with hydrogen, the rate of hydrogenolysis became slower, but the amount of 2-



deoxyaldonolactones formed was unchanged. The use of palladium on barium sulfate as catalyst did not change the course of the reaction. With platinum oxide the rate of hydrogenolysis of **8** was decreased, but the 2,3-dideoxyaldonolactone **11** was still the main product together with ca. 15% of **10**.

When the reactions described above were interrupted after half the amount of hydrogen was consumed, 2,3-unsaturated lactones, such as **2**, were present, providing evidence that these are intermediates in the formation of the 2,3-dideoxylactones. The conversion of bromohydrins to alkenes by treatment with zinc and acetic acid is well known[6]. However, treatment of the 2-bromolactone **3** with this reagent gave only the 2-deoxy-lactone **7**; no unsaturated product was observed.

The direct conversion of a bromohydrin to the corresponding dideoxy-compound has only been described in few cases. Thus it was reported that an α-bromo-β-hydroxyketone, derived from a steroid, gave a dideoxyketone on hydrogenolysis with palladium on calcium carbonate[7].

Melting points are uncorrected. NMR spectra were measured on a Bruker WH-90 instrument. Microanalyses were performed at the NOVO Microanalytical Laboratory.

(*S*)-(+)-4-Hydroxymethyl-γ-butyrolactone (5):
A solution of the 2-bromoaldonolactone **3**[3] (10 g, 0.047 mol) in ethanol (100 ml) containing 5% palladium on carbon („Fluka") (500 mg) is stirred with hydrogen at 20°C and 1 atm. pressure until the hydrogen consumption ceased (~4 h) (the hydrogen uptake is 1.5 l, ~95%). The mixture is then filtered and concentrated; chloroform is added twice and evaporated. The residue is dissolved in chloroform and stirred with solid sodium hydrogencarbonate for ca. 2 min, filtered through carbon and concentrated, leaving 5 g of crude product, which contains **5** and ca. 5% of the 2-deoxylactone **7**[3]. Destillation at 0.5 torr gives pure **5**; yield: 4.2 g (76%); b.p. 125°C; $[\alpha]_D^{20}$ + 53.8° (*c* 5, $CHCl_3$), (reported[8] + 53.5°).

^{13}C-NMR ($CDCl_3$): δ = 178.0 (C-1); 80.9 (C-4); 63.8 (C-5); 28.5; 22.9 ppm (C-2, C-3).

Hydrogenolysis of the isomeric 2-bromoaldonolactone **1**[3] in the same manner gives after distillation 76% of **5**; $[\alpha]_D^{20}$ + 53.2° (*c* 5, $CHCl_3$).

In a separate experiment the hydrogenolysis of **1** is performed as described above, but interrupted when 1 molar equiv. of hydrogen is consumed. A ^{13}C-NMR spectrum showed that the product thus obtained contains the dideoxyaldonolactone **5**, the unsaturated lactone **2**[9], and **1** in a ratio of 1:2.3:1.2.

^{13}C-NMR of **2** ($CDCl_3$): δ = 173.4 (C-1); 154.0 (C-3); 122.5 (C-2); 84.2 (C-4); 61.9 ppm (C-5).

(*S*)-(+)-5-Bromomethyl-γ-butyrolactone (6):
The 2,5-dibromoaldonolactone **4**[3] (10 g, 0.036 mol) is hydrogenolysed for 20 h and worked up as described above. The crude product (6.4 g) is distilled at 1 torr to give **6**; yield: 4.9 g (71%); b.p. 105–108°. After an additional distillation pure **6** is obtained; yield: 4.2 g (61%); $[\alpha]_D^{20}$ + 3.8° (*c* 7, $CHCl_3$).

$C_5H_7BrO_2$	calc.	C 33.54	H 3.94	Br 44.64
(179.0)	found	33.66	3.98	44.94

^{13}C-NMR ($CDCl_3$): δ = 174.9 (C-1); 77.5 (C-4); 34.2, 27.9, 25.6 ppm (C-2, C-3, C-5).

6-Bromo-2,3,6-trideoxy-D-*erythro*-hexono-1,4-lactone (11):
The dibromoaldonolactone **8**[1,2] (10 g, 0.033 mol) in ethanol (100 ml) containing 5% palladium on carbon (500 mg) is hydrogenolysed until no more hydrogen is consumed (the uptake is 1.5 l, i.e. 95%). Work-up as described above gives 7.0 g of crude product which crystallized from ether to give pure **11**; yield: 4.95 g (71%); m.p. 76–78°C; $[\alpha]_D^{20}$ + 20.3° (*c* 5, $CHCl_3$).

$C_6H_9BrO_3$	calc.	C 34.47	H 4.34	Br 38.23
(209.1)	found	34.61	4.37	37.82

^{13}C-NMR ($CDCl_3$): δ = 177.4 (C-1); 80.1 (C-4); 71.4 (C-5); 34.2 (C-6); 28.0, 22.3 ppm (C-2, C-3).

A ^{1}H-NMR spectrum at 500 MHz further confirms the structure. When the isomeric dibromoaldonolactone **9**[2] is used as the starting material, the same product **11** is obtained in ca. 70% yield.

2,3,6-Trideoxy-L-*erythro*-hexono-1,4-lactone (14):
Hydrogenolysis of the 2-bromo-2,6-dideoxyaldonolactone **13**[2] (10 g, 0.044 mol) for 20 h as described above, followed by distillation gives **14**; yield: 4.9 g (85%); b.p. 106–110°C/0.2 torr; $[\alpha]_D^{20}$ − 8.7° (*c* 4, $CHCl_3$); (reported[10] $[\alpha]_D$ − 9.4° for a product which was 95% pure).

$C_6H_{10}O_3$	calc.	C 55.37	H 7.75	
(130.2)	found	55.20	7.79	

^{13}C-NMR ($CDCl_3$): δ = 178.1 (C-1); 87.3 (C-4); 67.3 (C-5); 28.3, 20.9 (C-2, C-3); 17.7 ppm (C-6).

2,3,6-Trideoxy-D-*erythro*-hexono-1,4-lactone (12):
The 6-bromo-2,3-dideoxyaldonolactone **11** (4.9 g, 0.023 mol) is hydrogenolysed for 20 h in ethyl acetate (50 ml) containing triethylamine (7 ml) and 5% palladium on carbon (500 mg). The mixture is filtered and the filtrate is washed once with 4 molar hydrochloric acid (25 ml). The aqueous phase is extracted twice with ethyl acetate and the combined organic phase dried with magnesium sulfate, filtered and evaporated leaving 2.5 g (83%) of almost pure **12**. Distillation gives pure **12**; yield: 2.3 g (77%); b.p. 110–115°C/0.3 torr; $[\alpha]_D^{20}$ + 9.1° (*c* 4.6, $CHCl_3$).

$C_6H_{10}O_3$	calc.	C 55.37	H 7.75	
(130.2)	found	55.37	7.79	

The ^{13}C-NMR spectrum is identical with that of the L-enantiomer **14**.

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