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Note

Efficient syntheses of 1-bromodeoxy-, 1-azidodeoxy- and 1-aminodeoxypentitols from unprotected D-pentono-1,4-lactones

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Abstract

The reduction of unprotected 5-bromo-5-deoxy-D-ribono, D-arabinono and D-xylono-1,4-lactones was achieved with $NaBH_4$ in water–EtOH. The corresponding 1-bromo-1-deoxypentitols were isolated after acetylation in good overall yields (60–90%). 1-Azido-1-deoxypentitols were obtained quantitatively either by nucleophilic substitution by azide ion and deacetylation of the corresponding monobromopentitols or by reduction of the corresponding 5-azido-5-deoxy-D-pentono-1,4-lactones. The reduction of the monoazidopentitols by catalytic hydrogen transfer gave the monoaminopentitol analogues in quantitative yield.

Keywords: Unprotected D-pentono-1,4-lactones; Reduction; Monobromoalditols; Monoazidoalditols; Monoaminoalditols

1. Introduction

Monoaminodeoxyalditols are used as intermediates for the synthesis of their anhydrides [1], which are useful synthons for the synthesis of nucleoside analogues [2,3], and as potential enzyme inhibitors [4–6]. Reductive amination of aldoses with benzylamine–sodium borohydride and subsequent catalytic hydrogenation gave the corresponding 1-amino-1-deoxyalditol hydrochlorides in 39–68% overall yield [1]. To our knowledge, most previously reported 1-amino-1-deoxyalditols belong to the D-series, with 1-amino-1-deoxy-L-rhamnitol [1] being the only example from the L-series.

2. Results and discussion

In the present work, we report two routes for the synthesis of novel 1-amino-1-deoxy-D- and L-pentitols, using 5-bromo-5-deoxy-D-pentono-1,4-lactones as starting material: either via 1-bromo-1-deoxy-D- and L-pentitols (Pathway A, Scheme 1), which are intermediates leading to potential glycosidase inhibitors and anti-HIV iminocyclitols [7–9], or via 5-azido-5-deoxy-D-pentono-1,4-lactones (Pathway B, Scheme 1).

We have previously described the preparation of 5-bromo-5-deoxy-D-pentono-1,4-lactones from unprotected D-pentono-1,4-lactones in good yields (75–95%) [10,11] by means of thionyl bromide in *N*,*N*-dimethylformamide.

Reduction of 5-bromo-5-deoxy-D-ribono-1,4-lactone (**1**) with sodium borohydride gave

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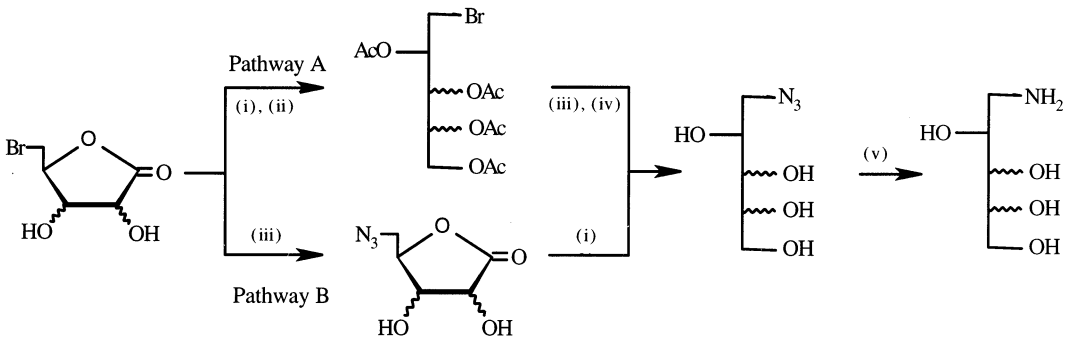
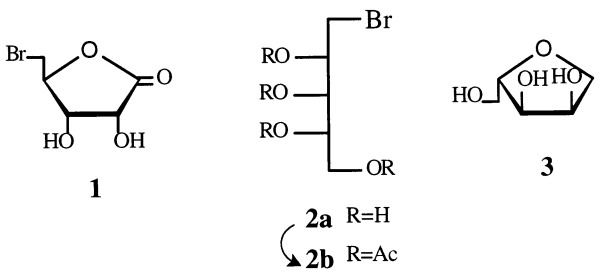


Scheme 1. (i) $NaBH_4$, H_2O, EtOH; (ii) Ac_2O, pyr; (iii) LiN_3, DMF; (iv) MeONa, MeOH; (v) $HCOONH_4$, Pd–C, EtOH.

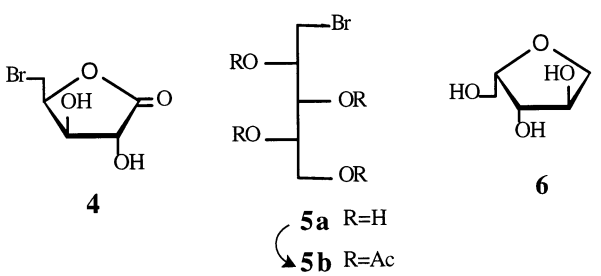
1-bromo-1-deoxy-L-ribitol (**2a**) (62%), with the anhydride **3** (38%) as by-product (Table 1). However, as compound **2a** is rapidly and quantitatively converted into anhydride **3**, we did not succeed in isolating it from the mixture of **2a** and **3**. To avoid any further intramolecular heterocyclisation, we treated the freshly prepared crude material with acetic anhydride in pyridine at room temperature and obtained, after purification, 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-deoxy-L-ribitol (**2b**) in 60% yield.



1 **3**

2a R=H
2b R=Ac

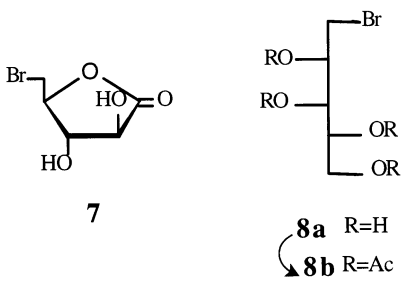
5-Bromo-5-deoxy-D-xylono-1,4-lactone (**4**) was treated under the same reduction conditions to afford 1-bromo-1-deoxy-L-xylitol (**5a**) (75%) and the anhydride **6** (25%). After acetylation of the crude material, **5b** was isolated in 70% yield.



4 **6**

5a R=H
5b R=Ac

Reduction of 5-bromo-5-deoxy-D-arabinono-1,4-lactone (**7**) gave 1-bromo-1-deoxy-D-lyxitol (**8a**) in quantitative yield. After acetylation, **8b** was isolated in 90% yield. In fact, it is well-known that halogenated D-arabinitol, in comparison with others halogenated pentitols, is less prone to cyclise to anhydro derivatives [12].



7

8a R=H
8b R=Ac

1-Azido-1-deoxypentitols were obtained by treatment of 1-bromo-1-deoxypentitols with lithium azide in *N*,*N*-dimethylformamide.

Thus, treatment of **2b** with lithium azide in *N*,*N*-dimethylformamide gave tetra-*O*-acetyl-1-azido-1-deoxy-L-ribitol (**9**) in quantitative

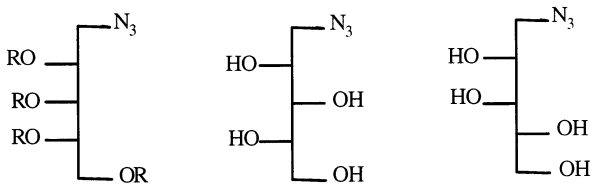
Table 1
Reduction of 5-bromo-5-deoxy-D-pentono-1,4-lactone

Substrate	Product (% yield)
1	i) → **2a** R=H (62) + **3** (38); **2b** R=Ac (60)*
4	i) → **5a** R=H (75) + **6** (25); **5b** R=Ac (70)*
7	i) → **8a** R=H (95); **8b** R=Ac (90)*

i) $NaBH_4$, H_2O-EtOH, 0 °C. * Isolated yield

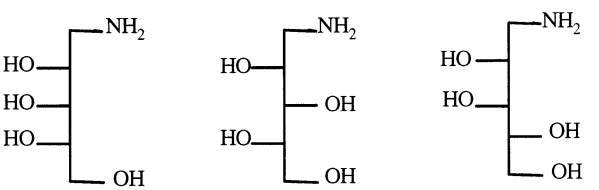
yield. When reduction of **9** was performed, by catalytic hydrogen transfer (CHT) with ammonium formate as hydrogen donor and Pd–C as catalyst in ethanol, acetyl group migration occurred to give tri-*O*-acetyl-1-acetamido-1-deoxy-L-ribitol in 95% yield.

Deacetylation of **9** with sodium methoxide in methanol led to pure 1-azido-1-deoxy-L-ribitol (**10**), without further purification. In the same way, compounds **5b** and **8b** led quantitatively to 1-azido-1-deoxy-L-xylitol (**11**) and D-lyxitol (**12**), respectively.



9 R=Ac
10 R=H
11
12

Reduction of 1-azido-1-deoxy-L-ribitol was performed by CHT and afforded 1-amino-1-deoxy-L-ribitol (**13**) in quantitative yield. 1-Amino-1-deoxy-L-xylitol (**14**) and D-lyxitol (**15**) were also obtained quantitatively from the corresponding 1-azido-1-deoxypentitols.



13 **14** **15**

To prevent anhydride formation, protection–deprotection steps and acetyl group migration, we have investigated a second route to aminopentitols via 5-azido-5-deoxy-D-pentono-1,4-lactones (Pathway B, Scheme 1).

5-Azido-5-deoxy-D-pentono-1,4-lactones were previously prepared in good yields by treatment of the corresponding 5-bromo-5-deoxy derivatives, with lithium azide in *N*,*N*-dimethylformamide [11].

5-Azido-5-deoxy-D-pentono-1,4-lactones were treated with sodium borohydride to give the corresponding 1-azido-1-deoxy-L or D-pentitols. When applied to 5-azido-5-deoxy-D-ribono, D-xylono, and D-arabinono-1,4-lactones this method yielded quantitatively 1-azido-1-deoxy-L-ribitol (**10**), L-xylitol (**11**) and D-lyxitol (**12**) respectively.

Table 2

Product	**13** (%)	**14** (%)	**15** (%)
Pathway A	60	70	90
Pathway B	92	80	84

As previously reported, 1-amino-1-deoxy-L or D-pentitols **13**, **14** and **15** were obtained by CHT from the 1-azido-1-deoxy-L or D-pentitols **10**, **11** and **12** in quantitative yield.

The overall yields of both routes are reported in Table 2. Whilst Pathways A and B are both suitable for the synthesis of **14** and **15**, **13** is better prepared via Pathway B.

In summary, we have described two reliable routes for the synthesis of 1-amino-1-deoxy-L-ribitol (**13**), 1-amino-1-deoxy-L-xylitol (**14**) and 1-amino-1-deoxy-D-lyxitol (**15**). The major advantage of Pathway A is that it allows access to 1-bromo-1-deoxy-D- or L-pentitols, which are interesting intermediates.

3. Experimental

General methods.—^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, D_2O or C_5D_5N 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). Analytical TLC was performed on E. Merck glass-backed Silica Gel sheets (Silica Gel F_{254}).

General procedure for reduction of 5-bromo- or 5-azido-5-deoxy-D-pentono-1,4-lactones.—To a solution of 5-bromo- or 5-azido-5-deoxy-D-pentono-1,4-lactones (5.8 mM) in 2:1 water–EtOH (21 mL) was added ion-exchange resin (Amberlite IR-120H$^+$, 3 mL). The mixture was cooled at 0 °C and stirred while $NaBH_4$ (1.6 equiv, 350 mg) was added at such a rate that the pH was maintained below 7. Then a further amount of $NaBH_4$ (1.9 equiv, 415 mg) was added to increase the

pH to 9. Stirring was continued at 0 °C for 1 h, before adding more ion-exchange resin (Dowex 50 × 8-100 ion) to decrease the pH to 3. The resin was then removed by filtration. The filtrate was concentrated and co-concentrated with MeOH (3 × 18 mL) to give the crude mixture, which was chromatographed on silica gel (4:1 EtOAc–MeOH). For the 1-bromo-1-deoxy-D- or L-pentitols, the crude material was treated with Ac_2O (10 equiv) in pyridine (10 mL). Silica gel chromatography (9:1 and 7:3 petroleum ether–EtOAc) gave 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-deoxy-D- or L-pentitols.

2,3,4,5-Tetra-O-*acetyl-1-bromo-1-deoxy*-L-*ribitol* (**2b**).—(1.33 g, 60%); $[\alpha]_D$ −3.1° (*c* 1.27, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.02 (m, 1 H, H-1a), 4.22 (m, 1 H, H-1b), 5.11–5.17 (m, 2 H, H-2, H-4), 5.22 (m, 1 H, H-3), 3.33 (m, 1 H, H-5a), 3.52 (m, 1 H, H-5b), 1.93 (s, 3 H, CH_3), 1.98 (s, 6 H, CH_3), 2.01 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 61.6 (C-1), 70.2, 69.4 (C-2; C-4), 70.5 (C-3), 29.8 (C-5), 20.5, 20.6 (CH_3), 169.0, 169.5, 169.6, 170.3 (CO). Anal. Calcd for $C_{13}H_{19}O_8Br$: C, 40.77%; H, 4.96%; Br, 20.86%. Found: C, 40.56; H, 5.01; Br, 20.81.

2,3,4,5-Tetra-O-*acetyl-1-bromo-1-deoxy*-L-*xylitol* (**5b**).—(1.55 g, 70%); $[\alpha]_D$ −8.7° (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.96 (m, 1 H, H-1a), 4.16 (m, 1 H, H-1b), 5.05–5.15 (m, 2 H, H-2, H-4), 5.36 (m, 1 H, H-3); 3.27–3.34 (m, 2 H, H-5a, H-5b), 1.94, 1.95, 1.97, 2.0 (4s, 4 × 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 61.6 (C-1), 69.0, 71.6 (C-2, C-4), 69.7 (C-3), 29.3 (C-5), 20.3, 20.4, 20.5, 20.7 (CH_3), 169.4, 169.6, 169.7, 170.1 (CO).). Anal. Calcd for $C_{13}H_{19}BrO_8$: C, 40.77; H, 4.96; Br, 20.86. Found: C, 40.65; H, 4.90; Br, 20.84.

2,3,4,5-Tetra-O-*acetyl-1-bromo-1-deoxy*-D-*lyxitol* (**8b**).—(2.0 g, 90%); $[\alpha]_D$ +34.1° (*c* 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.89 (dd, 1 H, $J_{1a,2}$ 6.9 Hz, H-1a), 4.21 (dd, 1 H, $J_{1b,2}$ 5.0 Hz, H-1b), 5.28–5.35 (m, 2 H, H-2, H-3), 5.12 (m, 1 H, $J_{4,5a}$ 5.7 Hz, H-4), 3.36 (dd, 1 H, H-5a), 3.50 (dd, 1 H, $J_{4,5b}$ 3.3 Hz, $J_{5a,5b}$ 11.6 Hz, H-5b), 1.98, 2.02, 2.04, 2.09 (4s, 4 × 3 H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$): δ 61.6 (C-1), 68.0; 70.0 (C-2; C-3), 68.6 (C-4), 30.8 (C-5), 20.5 (CH_3), 169.4, 169.6, 169.9, 170.2 (CO). Anal. Calcd for $C_{13}H_{19}BrO_8$: C, 40.77; H, 4.96; Br, 20.86. Found: C, 40.92; H, 4.88; Br, 20.95.

2,3,4,5-Tetra-O-*acetyl-1-azido-1-deoxy*-L-*ribitol* (**9**).—(441.5 mg, 98%); $[\alpha]_D$ −4.6° (*c* 0.88, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 4.24 (dd, 1 H, $J_{1a,2}$ 3.3 Hz, H-1a), 4.05 (dd, 1 H, $J_{1a,1b}$ 12.3 Hz, H-1b), 5.17 (m, 1 H, $J_{1b,2}$ 6.2 Hz, H-2), 5.24 (m, 1 H, $J_{2,3}$ 5.3 Hz, H-3), 5.10 (m, 1 H, $J_{3,4}$ 5.3 Hz, H-4), 3.44 (dd, 1 H, $J_{4,5a}$ 3.6 Hz, H-5a), 3.34 (dd, 1 H, $J_{4,5b}$ 6.8 Hz, $J_{5a,5b}$ 13.4 Hz, H-5b), 1.95 (s, 3 H, CH_3), 2.01 (s, 6 H, CH_3), 2.04 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 61.6 (C-1), 69.4 (C-2), 69.6 (C-3), 70.3 (C-4), 50.1 (C-5), 20.5, 20.7 (CH_3), 169.2, 169.7, 170.4 (CO). Anal. Calcd for $C_{13}H_{19}N_3O_8$: C, 45.25; H, 5.51; N, 12.17. Found: C, 45.10; H, 5.62; N, 12.40.

1-Azido-1-deoxy-L-*ribitol* (**10**).—(1.0 g, 98%); mp 59–61 °C; $[\alpha]_D$ −7.3° (*c* 0.54, MeOH); ^1H NMR (300 MHz, pyr-d_5): δ 4.30–4.44 (m, 3 H, H-1a, H-1b, H-2), 4.49 (m, 1 H, H-3), 4.66 (m, 1 H, H-4), 3.87–3.89 (m, 2 H, H-5a, H-5b). ^{13}C NMR (75 MHz, pyr-d_5): δ 65.1 (C-1), 74.4 (C-2), 75.0 (C-3), 74.0 (C-4), 55.1 (C-5). Anal. Calcd for $C_5H_{11}N_3O_4$: C, 33.92; H, 6.21; N, 23.73. Found: C, 33.86; H, 6.35; N, 23.53.

1-Azido-1-deoxy-L-*xylitol* (**11**).—(985.6 mg, 96%); $[\alpha]_D$ +3.2° (*c* 0.40, MeOH); ^1H NMR (300 MHz, pyr-d_5): δ 3.98–4.03 (m, 3 H, H-1a, H-1b, H-3), 4.16 (m, 1 H, H-2), 4.22 (m, 1 H, $J_{4,5a}$ 4.2 Hz, $J_{4,5b}$ 7.5 Hz, H-4), 3.65 (dd, 1 H, H-5a), 3.56 (dd, 1 H, $J_{5a,5b}$ 12.8 Hz, H-5b). ^{13}C NMR (75 MHz, pyr-d_5): δ 64.7 (C-1), 74.0 (C-2), 73.2 (C-3; C-4), 55.3 (C-5). Anal. Calcd for $C_5H_{11}N_3O_4$: C, 33.92; H, 6.21; N, 23.73. Found: C, 33.77; H, 6.11; N, 23.62.

1-Azido-1-deoxy-D-*lyxitol* (**12**).—(1.02 g, 99%); mp 73–75 °C; $[\alpha]_D$ −10.1° (*c* 0.54, MeOH); ^1H NMR (300 MHz, pyr-d_5): δ 4.29–4.33 (m, 3 H, H-1a, H-1b, H-3), 4.76 (m, 1 H, H-2), 4.62 (m, 1 H, H-4), 3.81 (dd, 1 H, $J_{4,5a}$ 6.8 Hz, H-5a), 3.94 (m, 1 H, $J_{5a,5b}$ 12.4 Hz, H-5b).^{13}C NMR (75 MHz, pyr-d_5): δ 65.2 (C-1), 71.9 (C-2), 73.2 (C-3), 72.3 (C-4), 56.1 (C-5). Anal. Calcd for $C_5H_{11}N_3O_4$: C, 33.92; H, 6.21; N, 23.73. Found: C, 33.91; H, 6.25; N, 23.80.

General procedure for reduction of 1-azido-1-deoxy-D- *or* L-*pentitols by catalytic hydrogen transfer*.—To a solution of 1-azido-1-deoxy-

D- or L-pentitols (200 mg) in EtOH (8 mL) was added, under an argon atmosphere, ammonium formate (5 equiv, 356 mg) and Pd–C (0.33 equiv). The reaction mixture was stirred at 70 °C for 1 h. After removal of the catalyst by filtration and evaporation of the solvent, the monoaminoalditol was obtained as the sole product.

*1-Amino-1-deoxy-*L*-ribitol* (**13**).—(167.2 mg, 98%); $[\alpha]_D$ −47.6° (*c* 0.47, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 3.59–3.65 (m, 2 H, H-1a, H-3), 3.71–3.82 (m, 3 H, $J_{4,5a}$ 8.6 Hz, H-1b, H-2, H-4), 2.77 (dd, 1 H, H-5a), 2.96 (dd, 1 H, $J_{4,5b}$ 3.1 Hz, $J_{5a,5b}$ 13.4 Hz, H-5b). ^{13}C NMR (75 MHz, D_2O): δ 64.8 (C-1), 74.3; 73.4 (C-2; C-4), 75.4 (C-3), 44.2 (C-5). Anal. Calcd for $C_5H_{13}NO_4$: C, 39.76; H, 8.61; N, 9.27. Found: C, 39.70; H, 8.70; N, 9.11.

*1-Amino-1-deoxy-*L*-xylitol* (**14**).—(167.2 mg, 98%); $[\alpha]_D$ −2.8° (*c* 0.35, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 3.61–3.73 (m, 3 H, H-1a, H-1b, H-4), 3.79–3.89 (m, 2 H, H-2, H-3), 2.92–2.98 (m, 2 H, H-5a, H-5b).^{13}C NMR (75 MHz, D_2O): δ 64.7 (C-1), 74.2; 73.1 (C-2; C-3), 74.1 (C-4), 45.0 (C-5). Anal. Calcd for $C_5H_{13}NO_4$: C, 39.76; H, 8.61; N, 9.27. Found: C, 39.53; H, 8.33; N, 9.53.

*1-Amino-1-deoxy-*D*-lyxitol* (**15**).—(168.9 mg, 99%); $[\alpha]_D$ −8.2° (*c* 1.79, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 3.60–3.63 (m, 2 H, H-1a, H-1b), 3.87 (m, 1 H, H-2), 3.50 (q, 1 H, $J_{2,3}$; $J_{3,4}$ 1.8; 8.1 Hz, H-3), 3.80 (m, 1 H, $J_{4,5a}$ 8.8 Hz, H-4), 2.89 (dd, 1 H, H-5a), 3.21 (dd, $J_{4,5b}$ 2.7 Hz, $J_{5a,5b}$ 13.1 Hz, H-5b).^{13}C NMR (75 MHz, D_2O): δ 65.2 (C-1), 72.3 (C-2), 74.2 (C-3), 70.7 (C-4), 44.9 (C-5). Anal. Calcd for $C_5H_{13}NO_4$: C, 39.76; H, 8.61; N, 9.27. Found: C, 39.66; H, 8.17; N, 9.48.

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