Synthesis of (2*S*, 3*R*, 4*R*)-3,4-Dihydroxyproline from 2,5-Dibromo-2,5-dideoxy-D-xylono- or -lyxono-1,4-lactone

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(2*S*, 3*R*, 4*R*)-3,4-dihydroxyproline (**8**) has been prepared in three steps from 2,5-dibromo-2,5-dideoxy-D-xylono-1,4-lactone (**1**). Azidolysis of **1** gave the 2-azido-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2**), which by hydrogenolysis and hydrolysis gave **8**. Azidolysis of 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**9**) and 2,3-anhydro-5-bromo-5-deoxy-D-lyxono-1,4-lactone (**10**) also gave **2**. Azidolysis of **10** in the absence of a proton donor led to degradation with evolution of nitrogen.

Dihydroxyprolines and other hydroxypyrrolidine derivatives have recently attracted much interest, because many of these compounds inhibit glycosidases.[1] They have been isolated from both plant and animal sources,[2,3] and it is believed that they act in plants as defence agents against predators and parasites.[4] Synthetic routes to these compounds have been published,[2,5–7] but frequently require multistep procedures, owing to tedious protection/deprotection steps. Dibromodideoxyaldonolactones, prepared from aldonolactones in one step, are ideal synthons for pyrrolidine derivatives especially since the secondary bromide can be selectively substituted in the presence of the primary bromide.[8] As five different 2,6-dibromohexonolactones[9,10] and three 2,5-dibromopentonolactones[11,12] are known, a wide range of stereoisomers is available. In this paper we describe the synthesis of optically pure (2*S*, 3*R*, 4*R*)-3,4-dihydroxyproline (**8**) starting from either 2,5-dibromo-2,5-dideoxy-D-xylono- (**1**) or -D-lyxono-1,4-lactone (**9**).

Results and discussion

2,5-Dibromo-2,5-dideoxy-D-xylono-1,4-lactone[11] (**1**) reacted more slowly with NaN_3 than 2,6-dibromo-2,6-dideoxyhexonolactones[8] and 2-bromo-2-deoxypentonolactones.[13] In boiling MeCN, 15 % of unchanged starting material was present after 6 h, but when the reaction was performed in DMF at 75 °C, no **1** remained after 45 min and a mixture of the monoazides **2** and **3**, and the diazides **4** and **5** in the ratio 10:2:3:1 was isolated in 68 % yield (Fig. 1). From the mixture **2** and **4** could be isolated in a pure state. The lack of stereospecificity in the azide displacement agrees with previous observations.[8,13] The configuration of **2** was confirmed by its conversion into **8** as described below; the stereochemistry of **4** was confirmed by hydrogenolysis to 2,5-diamino-2,5-dideoxy-D-lyxono-1,5-lactam.[14] When **1** was reacted with NaN_3 in DMF at 25 °C for 24 h disubstitution was avoided and a 5:1 mixture of **2** and **3** was

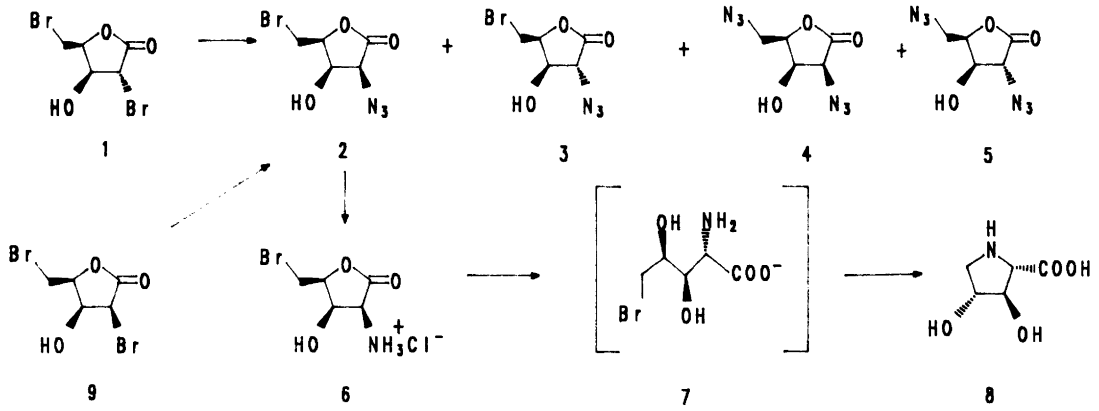

Fig. 1.

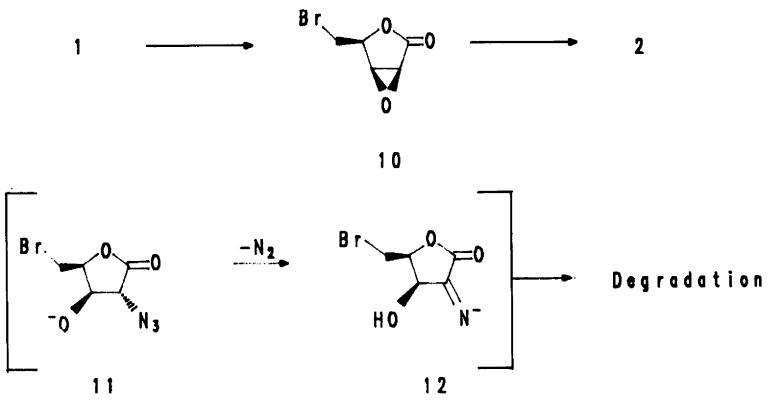

Fig. 2.

isolated in 95 % yield. After flash-chromatography, crystalline **2** could be isolated in 53 % yield.

When the 5:1 mixture of **2** and **3** was hydrogenolyzed in aqueous HCl in the presence of 5 % palladium on carbon, a mixture of the corresponding 2-amino-2-deoxylactones was obtained (96 %), from which the pure hydrochloride of 2-amino-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone (**6**) crystallised in 34 % yield.

Hydrolysis of the lactone **6** in aqueous $Ba(OH)_2$ at pH 9 resulted in spontaneous cyclisation of the intermediate amino acid **7** to give crystalline (2*S*, 3*R*, 4*R*)-3,4-dihydroxyproline (**8**) in 60 % yield. It was necessary to control the pH during the reaction to avoid formation of a 4,5-epoxide in intermediate **7**, which would prevent ring-closure to the pyrrolidine ring according to Baldwin's rules.[15] The configuration of **8** was determined by comparison with data for the known stereoisomers of 3,4-dihydroxyprolines.[2,3,6] The optical rotation and ^1H NMR spectrum of **8** were in accordance with the 2*S*, 3*R*, 4*R* isomer, whereas the 2*S*, 3*S*, 4*S* isomer, the enantiomer of the other possible product, had differing data. Thus the configurations of intermediates **2** and **6** were also confirmed.

Reaction of 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone[12] (**9**) with NaN_3 in DMF at 25 °C gave the same 5:1 mixture of the 2-azidolactones **2** and **3** as was obtained from **1**. Since **1** and **9** gave the same product, it was confirmed that the azide displacement was non-stereospecific.

To study whether the stereochemistry of the 2-azidolactones can be controlled in order to give the D-*xylo*-azidolactone **3**, **1** was converted into the epoxylactone **10**.[16] When NaN_3 was added to a solution of **10** in DMF, vigorous evolution of gas immediately commenced, and the solution became dark. After the gas evolution had terminated a low yield of **2** was isolated as the only product. Though this reaction, to our knowledge, is unknown, 2-azidolactones are known to react with base to give 2-iminolactones and nitrogen.[17] The reaction is most likely initiated by ring opening of **10** by azide to give the azido alkoxide **11** (Fig. 2). Spontaneous loss of nitrogen from **11** gives an unstable imine **12**, which rearranges to many polar products. In contrast, the reaction of **10** with NaN_3 in the presence of triethylammonium chloride was much slower, and no nitrogen evolution was observed. After 18 h a 37 % yield of **2** was obtained. The D-xylo-azide **3** was probably an intermediate, but may readily epimerise to **2** under the basic reaction conditions.

The present synthesis of dihydroxyproline **8** is shorter than previous syntheses,[2,6] efficient, and avoids chromatography. It demonstrates the high value of dibromodideoxyaldonolactones as synthons for this type of compound.

Experimental

Melting points are uncorrected. Optical rotations were measured with a Perkin Elmer 241 polarimeter. NMR spectra were recorded on Bruker WH-90, AC-250 and AM-500 NMR instruments. Dioxane (δ 67.40) was used as an internal reference for ^{13}C NMR spectra, and acetone (δ 2.22) for ^1H NMR spectra in D_2O. Tetramethylsilane was used as the reference for spectra in $CDCl_3$. Column chromatography was performed on silica gel 60 (40–63 μm, Merck 9385) using the flash technique. Spots were visualised on TLC by charring with H_2SO_4. Evaporations were carried out *in vacuo* at 50 °C, unless otherwise indicated. Microanalyses were performed by NOVO Microanalytical Laboratory, Bagsværd, Denmark.

2-Azido-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2**). 2,5-Dibromo-2,5-dideoxy-D-xylono-1,4-lactone (**1**, 5.0 g) was dissolved in DMF (20 ml) and sodium azide (25.0 g) was added. The mixture was stirred at room temperature for 24 h. Ethyl acetate (30 ml) was then added and the solution was filtered. The filtrate was evaporated and redissolved in dichloromethane (50 ml). Filtration through silica gel and concentration left a residue (3.62 g, 84 %) of 2-azido-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2**) containing 10–15 % 2-azido-5-bromo-2,5-dideoxy-D-xylono-1,4-lactone (**3**). This product was pure enough for further reactions, but could be purified by flash-chromatography (EtOAc–pentane 1:2) to give crystalline **2** (2.28 g, 53 %), m.p. 61–66 °C. Recrystallisation from CH_2Cl_2–pentane furnished a product with m.p. 72–74 °C, $[\alpha]_D^{20}$ – 34.8° (*c* 1.2,

EtOAc). ^{13}C NMR ($CDCl_3$): δ 171.1 (C-1), 79.8 (C-4), 69.3 (C-3), 61.7 (C-2) and 25.5 (C-5). Anal: Calc. for $C_5H_6N_3BrO_3$: C 25.44; N 17.80; Br 33.85. Found: C 25.89; H 2.61; N 17.83; Br, 34.21; ^{13}C NMR of **3** ($CDCl_3$): δ 79.4 (C-4), 71.3 (C-3), 62.9 (C-2) and 27.7 (C-5); the C-1 absorbtion was too weak to be measured.

Alternatively, **1** (3.0 g) was stirred with NaN_3 (13 g) in DMF (12 ml) at 75 °C. After 40 min the reaction was quenched with EtOAc (200 ml). The mixture was filtered and concentrated to a syrupy residue (1.76 g), which contained primarily **2** but also **3** and the diazidolactones **4** and **5**, the ratio being 10:2:3:1. Flash chromatography (EtOAc–pentane 1:2) gave fractions containing **2** and **3** (0.66 g, 26 %), **2** only (0.47 g, 18 %) and **4** only (0.18 g, 8 %). ^{13}C NMR ($CDCl_3$), **4**: δ 79.2 (C-4), 69.6 (C-3), 61.4 (C-2) and 48.9 (C-5); the C-1 absorbtion was to weak to be measured. **5**: δ 78.1 (C-4), 71.3 (C-3), 62.5 (C-2) and 49.2 (C-5); the C-1 absorbtion was to weak to be measured.

2-Amino-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone hydrochloride (**6**). 2-Azido-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2**, 0.41 g containing 15 % **3**) was dissolved in 10 ml of 50 % aqueous dioxane, then hydrochloric acid (0.6 ml, 4 M) and 5 % palladium on carbon (100 mg) were added, and the mixture was hydrogenolyzed at 101 kPa for 3 h. After filtration and evaporation the resulting residue (0.41 g, 96 %) could be crystallised from EtOH to give 2-amino-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone hydrochloride **6** (145 mg, 34 %), m.p. 193–195 °C (decomp.). Recrystallisation from MeOH–EtOH–CH_2Cl_2 gave m.p. 194–196 °C (decomp.), $[\alpha]_D^{20}$ + 22.0° (*c* 2.2, MeOH). ^{13}C NMR (D_2O): δ 172.9 (C-1), 83.2 (C-4), 68.3 (C-3), 54.2 (C-2) and 26.8 (C-5). Anal. $C_5H_9BrClNO_3$: C, H, N, Cl.

(2S,3R,4R)-3,4-Dihydroxyproline (**8**). 2-Amino-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone hydrochloride (**6**, 140 mg) was dissolved in water (10 ml) and a suspension of $Ba(OH)_2$ in H_2O (1 g in 50 ml) was added dropwise until the pH reached 9. The solution was stirred for 3 h, while the pH was maintained at 9 by adding more $Ba(OH)_2$. The solution was applied to a column of cation-exchange resin (Amberlite IR-120, H^+, 10 ml), and the column was eluted with NH_4OH (5 %, 100 ml) using standard column techniques. Evaporation of the resulting effluent yielded crystalline **8** (50 mg, 60 %). M.p. 230 °C (decomp.). $[\alpha]_D^{20}$ −12.3° (*c* 1.1, H_2O). (Lit.[2] m.p. 250 °C (decomp.). $[\alpha]_D^{20}$ −19° (*c* 0.4, H_2O) Lit.[6] $[\alpha]_D^{20}$ −12.6° (*c* 0.53, H_2O). ^{13}C NMR (D_2O): δ 172.6 (C-1), 79.5 (C-3), 75.0 (C-4), 68.4 (C-2) and 51.9 (C-5). ^1H NMR (D_2O): δ 4.6 (br s, 1 H, H-3), 4.4 (q, 1 H, H-4, *J* 1.5 Hz), 4.1 (d, 1 H, H-2, J_{23} 1.0 Hz) and 3.6 (m, 2 H, H-5 and H-5').

Reaction of 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**9**) *with* NaN_3. Treatment of 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**9**, 0.30 g) with sodium azide (1.50 g) in DMF (10 ml) at room temperature for 3 days gave, after addition of EtOAc (50 ml), filtration and evaporation, a syrupy 5:1 mixture of **2** and **3** (0.16 g, 62 %), as seen by ^{13}C NMR spectroscopy.

Azidolysis of 2,3-anhydro-5-bromo-5-deoxy-D-lyxono-1,4-lactone (**10**). 2,3-Anhydro-5-bromo-5-deoxy-D-lyxono-1,4-lactone (**10**, 0.20 g) was stirred with NaN_3 (1.0 g, 15 equiv.) and triethylammonium chloride (0.5 g, 3.5 equiv.) in acetonitrile (2 ml) for 18 h at room temperature. EtOAc (50 ml) was added, and the solution was filtered and washed with HCl (1 M, 10 ml) followed by $NaHCO_3$ solution (saturated, 10 ml). Drying ($MgSO_4$) and concentration left 2-azido-5-bromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2**, 0.09 g, 37 %), seen by ^{13}C NMR spectroscopy.

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