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SYNTHESIS OF 2R,3S,4R-DIHYDROXYPROLINE FROM D-RIBONOLACTONE

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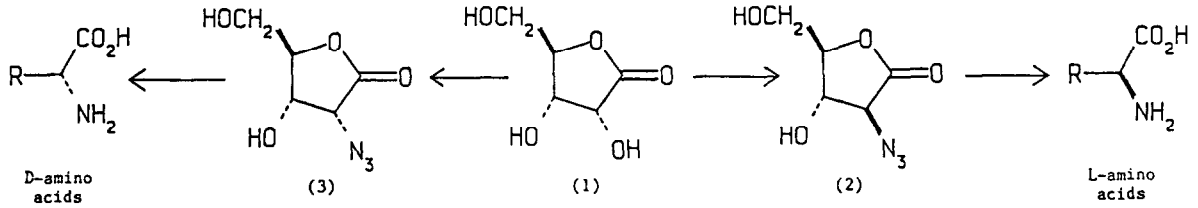
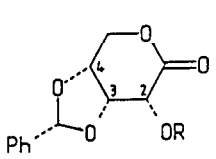
A synthesis of 2R,3S,4R-dihydroxyproline is described in which an azide is introduced into C-2 positon of D-ribonolactone with retention of configuration.

Sugar lactones, in which all the functionality other than the hydroxyl group on the carbon adjacent to the carbonyl group can readily be protected, may be suitable starting materials for the synthesis of polyhydroxylated amino acids. Replacement of C-2 OH group in D-ribonolactone (1) by azide with inversion of

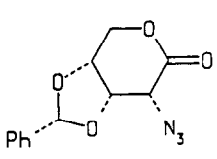


configuration would give an intermediate (2) suitable for elaboration to L-amino acids, whereas introduction of azide with retention (3) should allow the synthesis of D-amino acids. This paper describes the efficient synthesis of 2-azido-2-deoxy-D-ribonolactone (3), in which the configuration at C-2 is unexpectedly retained during the introduction of azide, and the conversion of (3) to the D-amino acid, 2R,3S,4R-dihydroxyproline (8);[1] the enantiospecific synthesis of the two other diastereomers of 3,4-dihydroxyproline from allylglycine has been reported recently.[2]

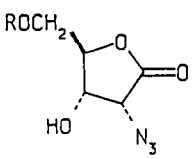
D-Ribonolactone (1) reacts with benzaldehyde in concentrated hydrochloric acid to give Zinner's lactone (4)[3,4], in which only the C-2 OH group remains unprotected, in 89% yield.[5] Reaction of this alcohol (4) with trifluoromethane sulphonic anhydride in pyridine at -10° gave the corresponding triflate[6] (5), m.p. 172-173°, $[\alpha]_D^{20}$ -129° (c, 0.56 in EtOAc) which may be recrystallised from ethanol; subsequent treatment with sodium azide in dimethyl formamide at room temperature formed the azidolactone (6),[7] m.p. 145° (dec.), $[\alpha]_D^{20}$ -245° (c, 0.42 in EtOAc) [64% yield from (4)]. The retention of configuration during the conversion of the alcohol (4) to the azide (6) was not anticipated. Since the coupling constants between the protons attached to C-2 and C-3 in the alcohol (4) [$J_{H2,H3}$ =3.1Hz], the triflate (5) [$J_{H2,H3}$ =3.4Hz] and the azide (6) [$J_{H2,H3}$ =3.3Hz] are very similar, the triflate (5) also probably has the ribo configuration; thus the



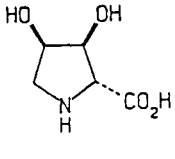
(4) R = H
(5) R = CF_3SO_2



(6)



(3) R = H
(7) R = CH_3SO_2



(8)

displacement of triflate in (5) by azide proceeds efficiently with overall retention of configuration, possibly by equilibration of the product epimeric azides. Hydrolysis of the 1,5-lactone (6) with aqueous trifluoracetic acid at 50° formed the 1,4 -lactone (3)[7], m.p. 84-85° $[\alpha]_D^{20}$ +54.2° (c, 0.28 in EtOAc) in 94% yield. Selective esterification of the primary hydroxyl group in the azidodiol (3) with methane sulphonyl chloride in pyridine at -20° gave the mesylate (7),m.p. 68-69° $[\alpha]_D^{20}$ +37.3° (c, 0.48 in EtOAc) in 71% yield. The chemical shifts of C-3 and C-4 in the 13C NMR spectra of the 1,5-lactones (4), (5) and (6) are all within the range δ 73 to 77, whereas in the 1,4-lactones (1), (3) and (7) C-3 is in the range δ 69.5-72.5 and C-4 in the range δ 84-89. Hydrogenation of (7) in the presence of palladium black in ethyl acetate, followed by treatment of the resulting aminolactone with aqueous sodium hydroxide gave, after purification by ion exchange chromatography, 2R,3S,4R-dihydroxyproline (8),[7,8] which decomposes without melting at 247°, $[\alpha]_D^{20}$ -6.8° (c, 0.43 in water) in 51% yield [20% overall yield from from ribonolactone].

Although the majority of naturally occurring non-protein amino acids have the L-configuration, there are many polyfunctionalised D-amino acids which are natural products;[9] the 1,5-azidolactone (3) and 1,4-azidolactone (6) are readily prepared by the above procedures on a 10 g scale in 57% and 54% yields from ribonolactone, and they may be convenient intermediates for the enantiospecific synthesis of a number of D-amino acids.[10]

References

1. The racemic form of (8) has been previously prepared by osmium tetroxide oxidation of 2,5-dihydropyrrole-1-carboxylic acid, but no NMR data was reported: C.R.Hudson, A.V.Robertson and W.R.J.Simpson, Aust. J. Chem., 1968, 21, 769.
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5. S.Y.Chen and M.M.Jouillie, J. Org. Chem., 1984, 49, 2168.
6. All new compounds in this paper have satisfactory analytical data and spectra consistent with the structures reported.
7. The stereochemistry of the azides (3) and (6), and the D-amino acid (8) was established by X-ray crystallography; details will be reported in a full paper.
8. Data for D-Amino acid (8): FAB MS (M+H)$^+$ m/e 148; 1H NMR (D_2O) δ 3.17 (dd, H5), 3.41 (dd, H5'), 3.85 (d, H2), 4.2 (m,H3,H4). J(2,3) 5.0, J(4,5) 4.2, J(4,5') 4.9, J(5,5')12.4 Hz. 13C NMR (D_2O) δ 48.21(t), 64.13(d), 69.77(d), 73.92(d), 171.9(s).
9. B.Hunt in Non-Protein Amino Acids, Chapter 4 in Chemistry and Biochemistry of Amino Acids, ed. G.C.Barratt, Chapman & Hall, London 1985.
10. An SERC post-graduate award (to PWS) is acknowledged.

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