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EFFICIENT SYNTHESES OF NATURALLY OCCURRING 3,4-DIHYDROXYPROLINES: ELECTROPHILE-MEDIATED LACTONIZATION OF 2-AMINO-3-HYDROXY-4-PENTENOIC ACID DERIVATIVES

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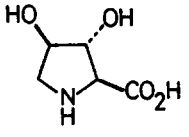
SUMMARY: Stereospecific conversion of β-hydroxyallylglycine derivatives into (2S, 3R,4R) 1 and (2S,3S,4S) 2 via halo- or mercuri-lactonization has been described.

Highly functionalized proline analogues which exhibit an important role in biological systems have been isolated.[1] The increasing interest in these systems has required an efficient synthetic method. Previous reports regarding the synthesis of 3,4-dihydroxyproline analogues 1-3 indicated that there was difficulty during the stereoselective introduction of the C-3 and C-4 hydroxyl moieties.[2,3] We considered the use of halolactonization of 2-amino-3-hydroxy-4-pentenoic acid (β-hydroxyallylglycine) systems (4 and 5), in which the C-3 polar substituent might effect the configuration of the newly forming C-4 chiral center.[4] We wish to describe here the synthesis of 1 and 2 from the acyclic precursors (2S,3R) 4 and (2S,3S) 5.[5]

(1) Synthesis of (2S,3R,4R)-3,4-dihydroxyproline (1), a constituent amino acid of virotoxin.[2] Halolactonization of the erythro isomer 4 with N-bromosuccinimide yielded the (2S,3R,4R)-bromolactone 6 in 70% yield as the sole product; mp 147 °C (decomp); $[\alpha]_D^{23}$ +20.7° (c 1.6, AcOEt); MS 310, 312 (M^+). The configuration of 6 was explained by its NOE experiment as shown in the figure, and ascertained by synthetic conversion of 6 into 1. Thus, the bromolactone 6 was treated with trifluoroacetic acid to remove the N-protecting group and the following hydrolysis with 0.5N NaOH provided (2S,3R,4R) 1 (60% from 6), which was in accord with natural 1 in all respects;[2a] $[\alpha]_D^{19}$ -12.6° (c 0.53, H_2O).



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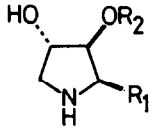

2 $R_1 = CO_2H$, $R_2 = H$

3 $R_1 = CH_2$-(p-OMe-phenyl), $R_2 = Ac$

(2) Synthesis of (2S,3S,4S)-3,4-dihydroxyproline (2), isolated from diatom cell walls. Treatment of the threo isomer 5 with N-bromosuccinimide provided the (2S,3S,4S)-bromolactone 7 in poor yield (10%). Therefore, we employed mercurilactonization, which after bromination produced 7 in 56% yield, exclusively; mp 163-164 °C; $[\alpha]_D^{21}$ -89.5° (c 1.0, acetone); MS 310, 312 (M^+). This was transformed in the same manner as above to (2S,3S,4S)2 (75% from 7), in which spectroscopic data as well as physical constants were identical with those of reported 2;[6] $[\alpha]_D^{22}$ -63.0° (c 0.8, H_2O).

It is noted that the complete stereocontrol of the present study has emerged from the consideration of the transition state 8 and 9, respectively, in which bromonium cation has been stabilized by the C-3 hydroxyl group.[5] The present study provides an efficient method toward the synthesis of other proline analogues such as the antibiotic anisomycin (3) which is currently being investigated.

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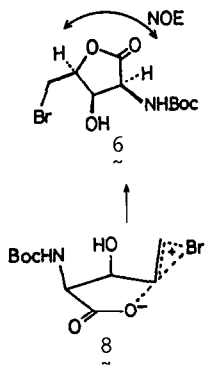
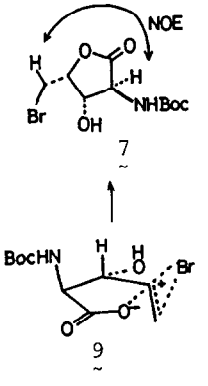
4 R_1 = OH, R_2 = H
5 R_1 = H, R_2 = OH





REACTION CONDITIONS: (4→6): N-bromosuccinimide/THF, 0 °C, 20 min. (5→7): (i) $Hg(OAc)_2$/THF, 0 °C 20 h; (ii) aq NaCl; (iii) Br_2/LiBr/Py saturated with O_2, room temperature, 20 min. (6→1) and (7→2): (i) CF_3COOH; (ii) 0.5N KOH/THF, room temperature, 3h; (iii) Dowex 50w x 4/ 1N NH_3.

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