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Short stereocontrolled synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid

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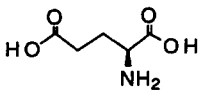
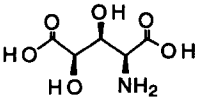
Abstract

The first enantioselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid was efficiently achieved in six steps from (3*R*,4*R*,5*R*)-1-*tert*-butoxycarbonyl-3,4-epoxy-5-(1-ethoxy)ethoxymethyl pyrrolidin-2-one **4** derived from (*S*)-pyroglutaminol.

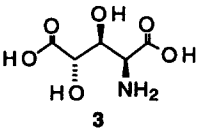
L-Glutamic acid **1** plays a crucial role as excitatory neurotransmitter in the mammalian central nervous system. It is implicated in several neurological disorders and it has, accordingly, generated extensive interest.[1] Many derivatives of this aminodiacid,[1–3] as for instances 4-alkylated analogues,[4] have been synthesized in order to modulate its biological activities, but 4-hydroxylated derivatives have been less studied.[5] Few 3,4-disubstituted derivatives have been described and, while (2*S*)-3,4-dihydroxyglutamic acid has been isolated from *Lepidium sativum* and *Rheum rhaponticum*,[6] the 3*S*,4*R* diastereomer **2** has never been synthesized. A synthesis of the 3*S*,4*S* diastereomer **3** has been reported recently.[7] We describe here the stereocontrolled synthesis of **2**.



1



2



3

A stereoselective route to highly functionalized hydroxy-oxazolidin-2-ones of definite configurations was recently developed in our laboratory through intramolecular ring opening of epoxides with the mediation of neighbouring *tert*-butyl carbamates.[8] These results suggested a straightforward pathway to the (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid **2**, in which an oxazolidinone ring served as β-aminoalcohol protective group (Scheme 1). Thus, the opening of the epoxide **5** (derived, through **4**, from (*S*)-pyroglutaminol) with participation of the vicinal *N*-Boc group occurred cleanly when **5** was adsorbed on silica gel and quantitatively afforded the oxazolidinone **6**.[8] The secondary alcohol of **6** was protected as *tert*-butyldimethylsilylether according to a classical protocol (**7**, 90%) and the primary alcohol function

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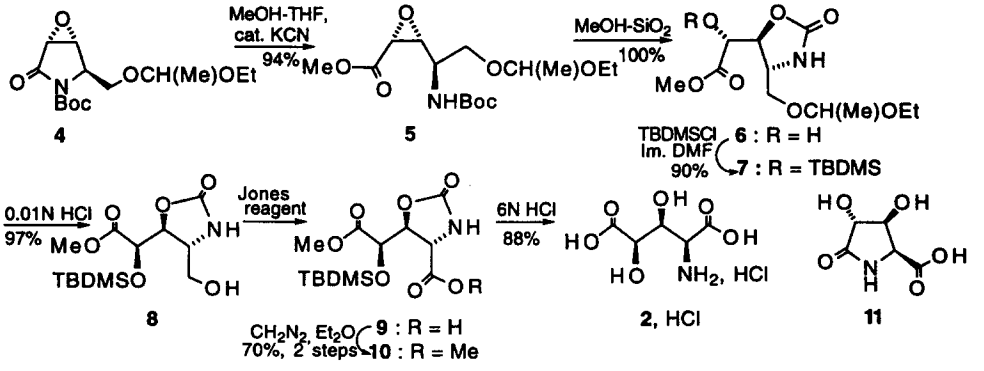
was selectively deprotected smoothly under mild acid conditions to give **8** (97%). Attempts to oxidize **8** into the corresponding carboxylic acid, with sodium periodate in excess and catalytic ruthenium trichloride (CCl_4–CH_3CN–H_2O, rt) did not lead to the expected result, although this oxidizing system has been widely used with polyfunctionalized molecules.[9] The oxidation of **8** with Jones reagent was efficient. It kept the *tert*-butyldimethylsilyloxy group unaltered, giving rise to the carboxylic acid **9** which gave broad signals in ^1H NMR and, for this reason, was fully characterized as its methyl ester **10** (70% for two steps, not optimized).



Scheme 1.

As natural (2*S*)-3,4-dihydroxyglutamic acid is known to be unaffected by strong acidic conditions,[6a] all the protecting groups of the dimethylester **10** were removed in one pot by heating at 80°C in 6N HCl.[10,11] The crude aminodiacid **2** was isolated as its hydrochloride by evaporation at 40°C of the reaction mixture, followed by precipitation of the residue in H_2O–EtOH–Et_2O (88%). Its mass spectrum (FAB) exhibited a peak $(M+H)^+$ at *m/z* 180, and NMR spectra indicated no cyclization to the dihydroxypyroglutamic acid **11**.[12]

Thus, the first enantioselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid was efficiently achieved from the epoxide **4**.

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11. It was thought that these conditions would be suitable because (2*S*,4*R*)-4-hydroxyglutamic acid is not sensitive to lactonization in acidic media, compared with the (2*S*,4*S*)-diastereomer.[5a–d] 3,4-Dihydroxypyroglutamic acid **11**, which could constitute a by-product, would be converted to the aminodicarboxylic acid **2** in 6N HCl.[6a]
12. Data for **2**, HCl: $[\alpha]_D^{28}$=+8.5 (*c* 1.08, 18% HCl). MS (FAB) *m/z*=180 $(M+H)^+$. ^{1}H NMR [300 MHz, D_2O, HOD: δ=4.80 ppm, *J* (hertz)]: 4.36 (d, 1H, *J*=3.6), 4.65 (d, 1H, *J*=1.5), 4.69 (m, 1H); ^{13}C NMR (75.0 MHz, D_2O, dioxane: δ=67.34 ppm): 175.3 (CO), 170.9 (CO), 73.5 (CH), 69.1 (CH), 56.9 (CH).