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Stereoselective synthesis of (2S, 3R)-N-Boc-3hydroxyglutamic acid

G. Veeresa and Apurba Datta*

Organic III, Indian Institute of Chemical Technology, Hyderabad - 500 007, India.

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Abstract

An efficient method has been developed for the stereoselective synthesis of the title compound, a non-proteinogenic amino acid of structural and biological importance. © 1998 Elsevier Science Ltd. All rights reserved.

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(2S, 3R)-3-Hydroxyglutamic acid (1), component amino acid of the antibiotic peptide S-520 was isolated from a streptomyces strain *Streptomyces diastaticus* [1]. It has also been used as synthetic precursors of biologically important L-tricholomic acid [2] and 3fluoroglutamic acid [3]. The interesting biological activity of 1 and its usefulness as a chiral synthon have made it an attractive target for synthesis [4-8]. As part of a programme directed towards asymmetric synthesis of hydroxy amino acids of biological importance [9-10] we undertook a synthesis of the title amino acid in enantiopure form and report herein the details of the study. It has been shown that chelation controlled addition of Grignard reagents to chiral α -amino aldehydes results in the corresponding *syn* amino alcohols with good to high diastereoselection [9-13]. Following the above protocol, we contemplated an initial synthesis of the key *syn* amino alcohol intermediate 2 (Scheme 1), starting from D-phenylglycine (3). Subsequent oxidation of the phenyl groups to carboxylic acid is then expected to complete the proposed synthesis.



Accordingly, in a one-pot sequence, reduction of D-phenylglycine with lithium aluminium hydride followed by protection of the amino group afforded the N-Boc alcohol 4 (Scheme 2). Swern oxidation of 4 to the corresponding aldehyde and its *in-situ* reaction with benzylmagnesium chloride, following an established procedure [11], yielded the key

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amino alcohol 2 with good diastereoselection (9:1, separated by column chromatography) in favour of the *syn* isomer ¹, which is in agreement with the reported observations [9-13]. Acetonide protection of 2 provided the oxazolidine derivative 5 in good yield. Oxidative



degradation of the phenyl groups yielded the hydroxyglutamic acid derivative 6, which was then converted to its dimethyl ester 7 under standard conditions. From ¹H NMR studies, the observed coupling constant ($J_{4,5} = 7.4$ Hz) between the two protons in the oxazolidine ring indicated a *trans*-relationship, further confirming the assigned stereochemistry. Deprotection of the acetonide linkage yielded the known dimethyl 3-hydroxyglutamic acid derivative 8 whose ¹H NMR and optical rotation {[α]_D = 29.5 (c = 0.65, CHCl₃) : lit. {[α]_D = 28.9 (CHCl₃) [7]} were in good agreement with the reported values, which also conclusively proved the stereochemical assignment. Finally, hydrolysis of the ester groups culminated in an efficient synthesis of the title amino acid 9².

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¹ Assignment of *syn* stereochemistry to the isomer 2, initially based on analogy [Ref.9-13 above], was further proved by NMR studies of subsequent compound 7 and by matching the optical rotation of compound 8 with a reported compound (*vide infra*). ² All the compounds synthesized were fully characterized by their IR, NMR and Mass spectral data.