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An Efficient Synthesis of 5-Hydroxy-4-oxo-L-norvaline from L-Aspartic Acid[1]

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Key words: antibiotics, L-aspartic acid, 5-hydroxy-4-oxo-L-norvaline, multifunctional amino acids, hexafluoroacetone.

Abstract: A synthesis of the antibiotic (-)-HON (5-hydroxy-4-oxo-L-norvaline, RI-331) from L-aspartic acid using hexafluoroacetone as protecting reagent is described.

In 1957 F. Weygand et al.[2] described a synthesis of the fully protected 5-hydroxy-4-oxo-L-norvaline [(-)-HON], before its antibiotic properties were recognized. In 1961 (-)-HON **5** was isolated from *Streptomyces* H-8998[3,4] and later from *Streptomyces akiyoshiensis* novo sp.[5-7].

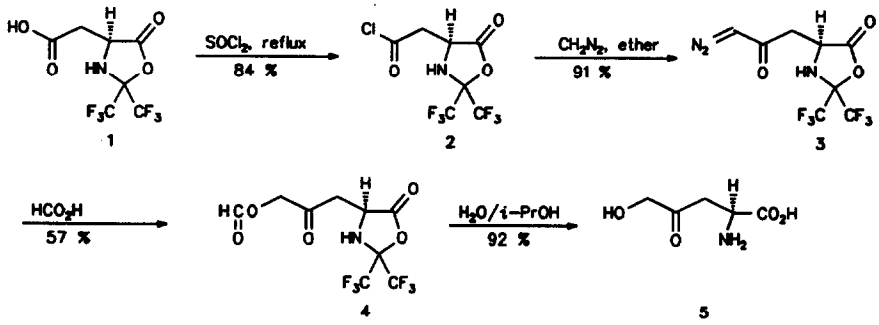
5 exhibits antibiotic activity towards human and bovine types of tuberculum[3,4] and antifungal activity by inhibition of protein synthesis resulting from depletion of several amino acids like isoleucine, methionine, serine and threonine in the cellular pool[5-7].

A synthesis of racemic HON **5** is known since 1960[8]. Stereoselective syntheses of (-)-HON starting from (R)-2,3-O-isopropylideneglyceraldehyde[9] or L-aspartic acid[10] were accomplished recently. These findings prompt us to report on our approach to (-)-HON.

The efficiency of our route is based on a new protective group strategy. Hexafluoroacetone and L-aspartic acid react to give compound **1**. A selective protection of the α-amino and the α-carboxylic group is achieved in only one step. The ω-carboxylic group remains unaffected and can be derivatized regioselectively[11].

On reaction with thionyl chloride the acid chloride **2** is formed (84%[12]), which on treatment with diazomethane is transformed into the diazoketone **3** (91%[13]). Decomposition of **3** with various carboxylic acids provides access to fully protected (-)-HON **4**. The formyl group is superior to other O-protective groups introduced *via* this route. All three protected functional groups in compound **4** can be deprotected simultaneously on treatment with water/isopropanol at room temperature[14]. The total yield of pure (-)-HON[15] *via* this route is 35% referring to L-aspartic acid.

The possibility to transform 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones into the corresponding α-amino acids on treatment with water/isopropanol at room temperature renders hexafluoroacetone an interesting protective group for functional group transformations in certain multifunctional amino acids. Protection and deprotection is achieved without racemization in high yields.



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15. The physical and spectral data of **5** are identical to those quoted for the natural antibiotic[9,10].

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