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An Efficient Synthesis of erythro-β-Hydroxy-L-histidine, the Pivotal Amino Acid of Bleomycin-Fe(II)-O_2 Complex[1)]

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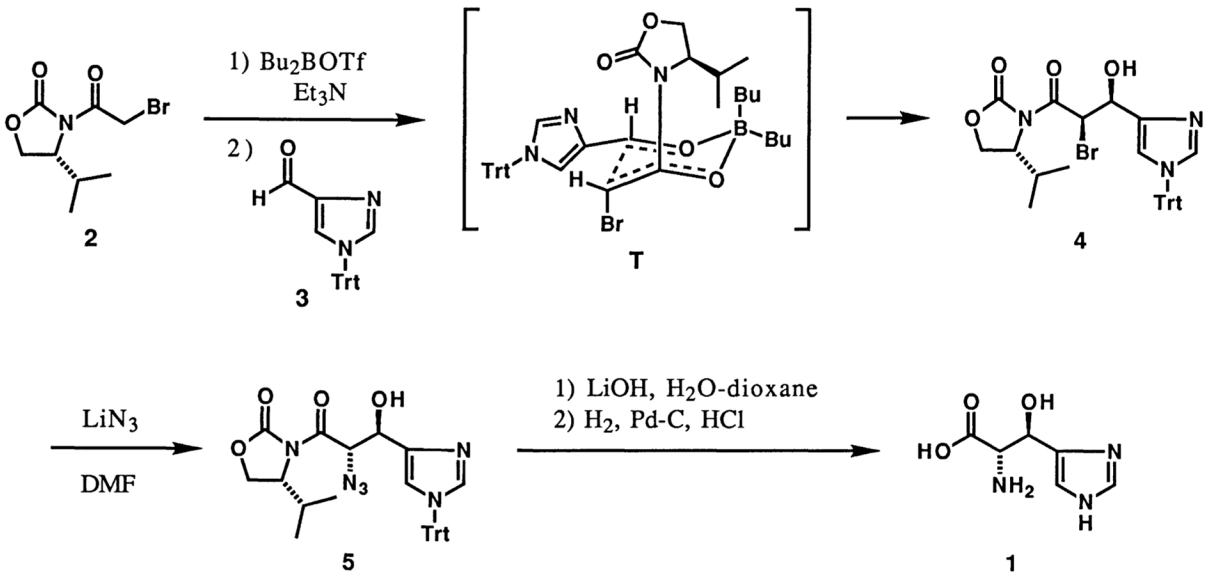
erythro-β-Hydroxy-L-histidine is efficiently synthesized in organic solvents from the aldol reaction of (R)-3-bromoacetyl-4-isopropyl-1,3-oxazolidin-2-one and 1-triphenylmethylimidazole-4-carbaldehyde followed by S_N2 reaction with LiN_3 and hydrogenation.

erythro-β-Hydroxy-L-histidine (**1**) is an amino acid constituent of bleomycins (BLMs), a family of antitumor antibiotics, and the pivotal amino acid to define the gross spatial-structure of BLM-Fe(II)-O_2 complex.[2)] Our continuing effort to develop man-made BLMs required to supply the key amino acid more efficiently. However, the enantioselectivity of our recent attempt[3)] was rather poor and the all procedures developed so far were carried out in aqueous solution and required tedious operations such as work-up with H_2S and optical resolution with D-tartaric acid. We now describe here the most convenient methodology for **1** carried out conveniently in organic solvents and in a large scale.

Thus, we focused our effort on the enantio- and diastereoselective aldol strategy in dry organic solvents. It was found that formylimidazole insoluble in non-aqueous media became soluble in organic solvents by protecting with various groups and that the Evans' reagent **2**[4)] was best. A remarkable stereoselectivity and chemical reactivity were accomplished only with triphenylmethyl (Trt) derivative **3**. Other protective groups such as t-butoxycarbonyl, tosyl, and 2,4-dinitrophenyl were found equally effective in the stereoselectivity but far less effective in the stability or reactivity.

Boron enolate of (R)-3-bromoacetyl-4-isopropyl-1,3-oxazolidin-2-one (**2**)[4)] was reacted with aldehyde **3**[5)] (Et_2O - CH_2Cl_2, -78 °C for 30 min, then 0 °C for 1.5 h) to afford the desired syn-bromohydrin **4** as white crystals in 72% yield; mp 116.5 - 118.5 °C (dec.).[6,7)] This material was shown to be virtually optically pure by the 400 MHz ^1H NMR spectrum. The stereoselection could be explained by the formation of the six-membered ring transition state **T** from the predominant (Z)-enolate. The bulkiness of the triphenylmethyl group appeared to prohibit the other stereoisomeric transition states for this process. Treatment of the bromohydrin **4** with LiN_3 (DMF, 45 °C for 45 min under argon) afforded azide **5** in 85% yield.[7)] 400 MHz ^1H NMR demonstrated the stereochemical integrity of the product and the clean inversion of the configuration at C2. The chiral auxiliary in **5** was removed by treatment with LiOH in aqueous dioxane at 0 °C. After disappearance of **5** on tlc, the reaction mixture was acidified to pH 1 with 2 M



HCl and hydrogenated over 10% Pd-C. After removal of the catalyst and the solvent, the residue was treated with formic acid to remove completely the triphenylmethyl group. The residue was purified according to the previously reported procedure[3] to give crude β-hydroxy-L-histidine which was shown to be a 30 : 1 mixture of L-erythro and other stereoisomer(s) by HPLC analysis. One recrystallization from 50% aqueous EtOH gave erythro-β-hydroxy-L-histidine **1** as white needles in 84% yield from 5; mp 203 - 205 °C, $[\alpha]_D^{25}$ +39.2° (c 1.0, water) (lit. mp 205 °C, $[\alpha]_D^{25}$ +40.0° (c 1.0, water))[3] HPLC analysis indicated the optical purity of this material to be 98.5 %ee. In conclusion, erythro-β-hydroxy-L-histidine **1** is now efficiently available in any desired scale.

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6) About 20% of the starting material **3** was recovered.
7) This material gave satisfactory results for elemental analysis, ^1H NMR (400 MHz), IR, and mass spectra.

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