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First stereoselective synthesis of an optically pure β-substituted histidine: (2*S*,3*S*)-β-methylhistidine

Sihe Wang, Xuejun Tang and Victor J. Hruby *

Department of Chemistry, University of Arizona, Tucson, AZ 85721, USA

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Abstract

We report the first example of the asymmetric synthesis of the β-substituted histidine, (2*S*,3*S*)-β-methylhistidine. A key in the synthesis is the use of the protecting group, 2-mesitylenesulfonyl (Mts-), for the imidazole ring to minimize epimerization during synthesis.

Keywords: asymmetric synthesis; chiral auxiliary; β-substituted histidine; amino acids; mesitylenesulfonyl.

The binding affinity of bioactive peptides to their receptors and subsequent biological transduction depend not only on the backbone conformation of the peptides, but also on the side-chain orientation of key pharmacophore groups.[1] Topographical considerations are an important approach for exploring the stereochemical requirements for receptor recognition and for signal transduction.[1,2] In this approach, designed side chain constrained novel amino acids are incorporated into peptide templates. The use of pure chiral β-substituted amino acids into bioactive peptide ligands at key pharmacophore residues has proven to be a powerful tool for understanding ligand–receptor binding interactions and in peptidomimetic design.[3] One of our major efforts has been the design and synthesis of novel amino acids with conformationally constrained side chains for the purpose of obtaining highly selective and potent peptide hormone and neurotransmitter analogues. Incorporating several β-substituted novel amino acids (Fig. 1), e.g., β-methylphenylalanine (I), β-methyltyrosine (II), β-methyl-2′,6′-dimethyltyrosine (III), and β-methyltryptophan (IV), has provided new insights into the stereochemical requirements in peptide–receptor interactions.[4] Histidine (V in Fig. 1) is an important amino acid involved in receptor recognition and biological activity for many peptides and proteins. Histidine has been suggested to play a key role in the interaction of glucagon with its receptor and in signal transduction to express its biological activities.[5] It has been our long-term goal to synthesize β-substituted asymmetric histidine derivatives, but we have had difficulties obtaining useful preparative quantities. The difficulty arises from the imidazole ring, which is a general base and a nucleophile. The imidazole group causes epimerization and may participate in other reactions during the synthesis of asymmetric amino acid derivatives. Therefore,

* Corresponding author. Tel: 520 621 6332; fax: 520 621 8407; e-mail: hruby@mail.arizona.edu (V. J. Hruby)

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the protection of the imidazole group is critical to success. In this communication, we report the first successful asymmetric synthesis of (2*S*,3*S*)-β-methylhistidine using 2-mesitylenesulfonyl (Mts-) as a protecting group at τ-N in the imidazole ring. We made this isomer our initial target since the His in glucagon is L-histidine (*S*-histidine).

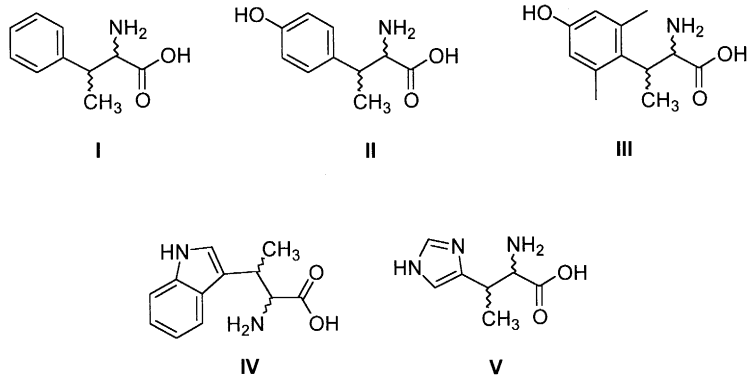
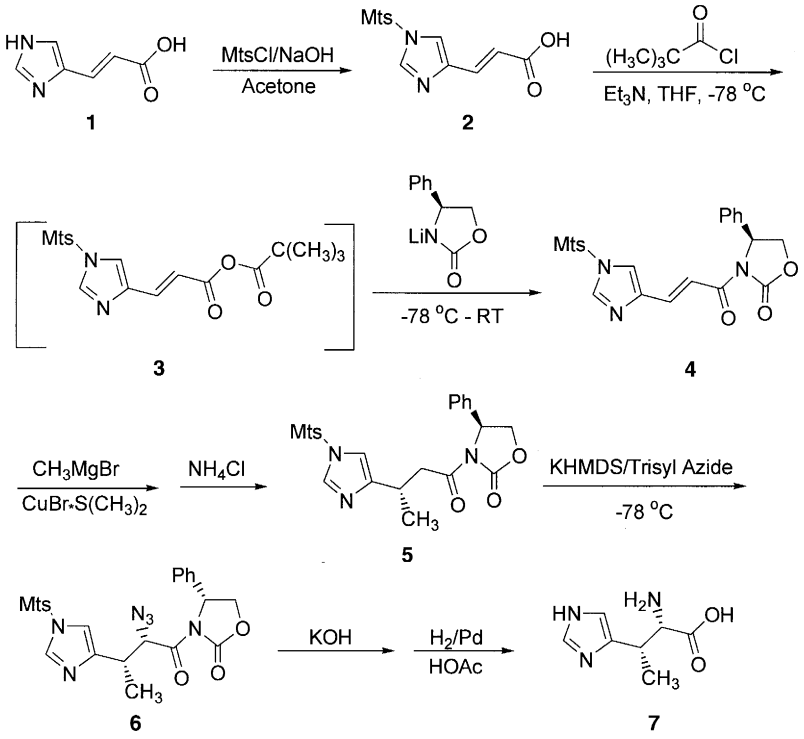


Fig. 1. Some β-substituted amino acid analogues

We chose to use 2-mesitylenesulfonyl as the protecting group at τ-N in imidazole ring because the sulfonamide bond has been reported to be stable in basic solutions and in weak acidic solutions.[6] In addition, the 2-mesitylenesulfonyl group is an electron-withdrawing group, which reduces the nucleophilic ability as well as the basicity of the imidazole ring. Therefore we expected epimerization caused by the imidazole ring would be minimized during the synthesis of the amino acid derivatives and in the synthesis of peptides. It was also expected that the protecting group could be hydrolyzed using trifluoromethanesulfonic acid (TFMSA), similar to the situation for 2-mesitylenesulfonyl protected arginine.[7]

The synthesis (Scheme 1) started from the commercially available urocanic acid **1**. Urocanic acid was reacted with 2-mesitylenesulfonylchloride in sodium hydroxide solution to furnish the derivative protected at the τ-N in imidazole group of **2**. The protected urocanic acid was coupled to an optically pure chiral auxiliary according to a reported procedure[8] to give **4**. The subsequent Michael addition reaction and azide formation were highly enantioselective reactions (>99%) as determined by ^{1}H NMR. Hydrolysis of the chiral auxiliary in compound **6** led to the removal of the Mts-protecting group from the imidazole ring. The final unprotected β-methylhistidine, **7**, was isolated, purified by ion-exchange column (Dowex 50X2-100), and recrystallized from water/ethanol.[9] In the last two steps, some epimerization was observed according to the ^{1}H NMR spectra; thus the Mts- or another protecting group should be reintroduced for use in peptide chemistry. Apparently the free imidazole group can catalyze the epimerization process. Nevertheless, the Mts protection led to the first successful example of asymmetric synthesis of the β-substituted histidine derivative (2*S*,3*S*)-β-methylhistidine.

Procedure for the hydrolysis and hydrogenolysis of azide **6**: Azide **6** (1.30 g, 2.49 mmol) was dissolved in methanol (30 mL) and the solution was cooled to 0°C. Potassium hydroxide solution (2N, 9.96 mL, 19.92 mmol) was added dropwise into the reaction solution, and the resulting reaction mixture was stirred at 0°C for 1 h.[10] The reaction mixture was then neutralized to pH 7 using potassium hydrogensulfate solution (2N). Volatiles were evaporated off under reduced pressure and the aqueous layer was extracted with methylene chloride (20 mL×3). The aqueous solution was then evaporated under reduced pressure and the residue was dissolved in glacial acetic acid (35 mL) and water (15 mL). The resulting solution was bubbled with argon for 45 min, then palladium on carbon (10%, 0.069 g, 0.065 mmol) was added and the reaction mixture was bubbled with argon for an additional 20 min. The reaction mixture was



Scheme 1. Synthesis of (2*S*,3*S*)-β-methylhistidine

washed with hydrogen three times, and then charged with hydrogen (15 psi). After shaking for 24 h, the catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in water and purified using an ion-exchange column (Dowex 50X2-100), eluted with 10% ammonium hydroxide aqueous solution. The elute was evaporated at less than 50°C under reduced pressure, and the residue was dissolved in water and lyophilized. The residue was then dissolved in water (3 mL), and ethanol with hydrogen chloride was added to adjust to pH 4. The solution was then filtered through activated carbon, and evaporated under reduced pressure. The solid was dissolved in a minimum amount of hot water, and solid was obtained by addition of ethanol. 0.124 g (29.5%); m.p. 284–286°C (decomposed); ^{1}H NMR ($CDCl_3$, Varian 200 MHz) δ 8.53 (s, 1 H), 7.26 (s, 1 H), 3.86 (d, J=4.81 Hz, 1H), 3.56 (m, 1H), 1.28 (d, J=7.28 Hz, 3H); C^{13} NMR ($CDCl_3$, Varian 200 MHz) δ 14.00, 32.36, 59.10, 117.89, 113.93, 135.20, 172.53; FAB-MS MH^+ calculated 170.0930, observed 170.0927. Anal. ($C_7H_{12}N_3O_2Cl\cdot 1.2H_2O$) calculated: C 36.96%, H 6.38%, N 18.47% Cl 15.59%; found: C 37.33%, H 6.08%, N 18.12%, Cl 15.52%; $[\alpha]_D^{25}$=+15.52 (c 1.05, 6N HCl aqueous solution).

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