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A Novel Wittig Reaction of Oxazolidinones : Stereospecific Synthesis of N-BOC-(3*S*,4*S*)-Statine and N-BOC-(3*S*,4*S*)-AHPPA

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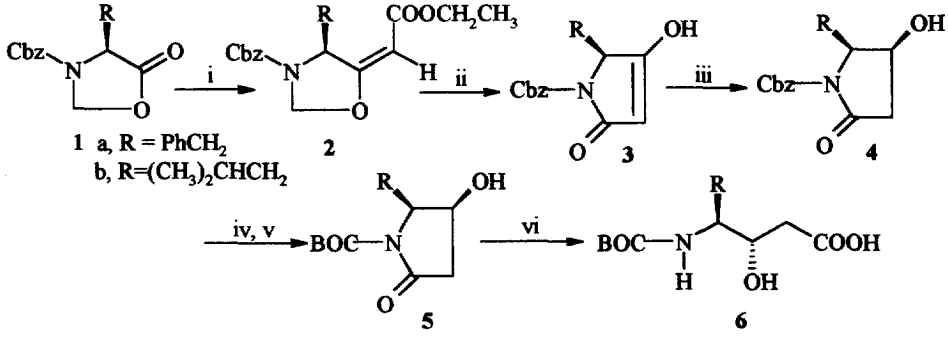
Abstract

Stereospecific synthesis of N-BOC-(3*S*,4*S*)-Statine and N-BOC-(3*S*,4*S*)-AHPPA is achieved *via* a novel Wittig reaction of oxazolidinones in an efficient manner.

Key words : Acylation; Amino acids and derivatives; Wittig reaction; stereospecificity

Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methyl heptanoic acid, is a nonproteinogenic amino acid, a key component of the naturally occuring peptidic aspartate protease inhibitor pepstatin[1]. Due to the potential inhibitory activity of pepstatin towards the aspartate proteases such as pepsin, renin and cathepsin D[2], much effort has been directed toward the enantioselective synthesis of statine and its analogues[3-10], especially (3*S*,4*S*)-4-amino-3-hydroxy-5-phenyl pentanoic acid (AHPPA). In this letter, we report a novel Wittig reaction of oxazolidinones **1** [11] derived from N-Cbz-α-aminoacids and their conversion to N-BOC-(3*S*,4*S*)-statine and N-BOC-(3*S*,4*S*)-AHPPA in a stereospecific manner.



Reagents and conditions: i) $Ph_3P{=}CHCO_2CH_2CH_3$, $PhCH_3$, 3-4 h; ii) 6N HCl, ether,RT,6h; iii) $NaBH_4$, MeOH, O^0C,; iv)10% Pd/C,H_2, MeOH, v)BOC_2O, DMAP, $CHCl_3$, vi)1N NaOH, 1,4-dioxane.

Scheme – 1

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The oxazolidinones **1** were subjected to Wittig reactions with ethoxycarbonylmethylenetriphenylphosphorane to give the corresponding α,β-unsaturated esters **2** in excellent yields (Scheme - 1). A single isomer was obtained in all cases. All the α,β-unsaturated esters **2** obtained were fully characterized by spectroscopic data, important characteristic signals of **2a**, ^{1}H NMR : δ 1.30 (t, 3H, J= 6.4 Hz), 4.20 (q, 2H, J =6.4 Hz), 5.35(s, 1H); IR (KBr) : (cm^{-1})1680, 1650 clearly indicating the ethoxycarbonyl group and olefin functionality.

Syntheses of N-BOC-(3*S*,4*S*)-AHPPA and N-BOC-(3*S*,4*S*)-statine were achieved starting from **2a** and **2b** by the following sequence (scheme-1). Treatment of compounds **2a** and **2b** with 6N HCl in ether at room temperature cleanly afforded the tetramic acids **3a** and **3b** in excellent yields (94% and 91% respectively). Sodium borohydride reduction of **3a** and **3b** resulted in the exclusive formation of **4a** and **4b**. The absolute configuration of newly created stereocentre was found to be *S* in both the cases by converting into known N-BOC-AHPPA (**6a**) and N-BOC-statine (**6b**), and by comparing specific rotation and spectroscopic data with those in the literature. Thus, Pd/C (10%) catalyzed hydrogenolysis of **4a** and **4b**, followed by treatment with BOC_2O gave **5a** and **5b** in good yields (93% and 95% respectively). Treatment of **5a** and **5b** with 1N NaOH in 1,4-dioxane smoothly afforded N-BOC-AHPPA(**6a**) as colorless needles, mp 152^{0}C, $[\alpha]_D^{25}$ -38.2 (c 1, methanol), [lit.[8] mp 151-152^0 C, $[\alpha]_D^{25}$ -37.5 (c 1, methanol)] and N-BOC-statine (**6b**) as colorless needles, mp 120-121^{0}C, $[\alpha]_D^{25}$ -40.2 (c 1, methanol), [lit.[8] mp 118-120^0 C, $[\alpha]_D^{25}$ -38.5 (c 1, methanol)] in good yields (92% and 89% respectively), and are found to be in good agreement with reported data[8], thereby confirming the optical purities and structural assignments.

In summary, a novel Wittig reaction of oxazolidinones, and their conversion to N-BOC-(3*S*, 4*S*)-statine and N-BOC-(3*S*, 4*S*)–AHPPA in a stereospecific and efficient manner is described for the first time. The present methodology is a straightforward and racemization free route to optically active β-hydroxy- γ-amino acids and enables the synthesis of analogous series of compounds. Further work is in progress and will be reported in due course.

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