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A practical synthesis of trifluorophenyl R-amino acid: The key precursor for the new anti-diabetic drug sitagliptin

Li Li Zeng [a,b], Ying Jie Ding [a,b], Gui Cheng Zhang [a], Hong Rui Song [b], Wen Hui Hu [a,*]

[a] *Laboratory of Anti-diabetic Drug Discovery, Center for Synthetic and Natural Drugs, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510663, China*

[b] *The School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China*

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Abstract

Sitagliptin is the first new anti-diabetic drug in DPP-IV inhibitor class. The general synthesis of sitagliptin is by coupling of the β-amino acid fragment with the heterocycle fragment. Though the specific β-amino acid can be easily made from the corresponding R-amino acid by Arndt-Eistert homologation, the optically pure precursor R-amino acid is difficult to prepare. We herein reported a practical protocol to make the trifluorophenyl substituted R-amino acid **4** in >99.9% ee and 40.3% yield by the enzymatic resolution employing enantioselective hydrolysis and a general separation procedure. This protocol requires only cheap starting materials and friendly reaction condition. The procedure not only allows people to prepare the drug substance, but also provides an alternative method for prepareing the rare α-amino acid and the subsequent β-amino acid.

Keywords: Sitagliptin; β-Amino acid; DPP-IV inhibitor; Practical synthesis

Sitagliptin (compound **1**) is the first dipeptidyl peptidase-4 (DPP-IV) inhibitor in a new class of drugs for the treatment of type 2 diabetes mellitus [1]. It was developed by Merck & Co. Inc. and approved by the US FDA in 2006 [2]. The standard method [3] (Scheme 1) to prepare Sitagliptin is by coupling of fused heterocycle **2** with β-amino acid **3**. Though the intermediate **2** is easy to make, the preparation of optically pure β-amino acid **3** remains a problem. The two methods listed in Scheme 1 represent the most important strategies in making β-amino acid [4] including α-amino acids as chiral pool approach (method 1) and the stereoselective synthesis of β-amino acid from achiral starting material (method 2). Trifluorophenyl β-amino acid **3** was originally synthesized via the Arndt-Eistert homologation of the corresponding R-amino acid **4** (method 1) during the drug discovery stage. But the requirement of chiral auxiliary **5** and extreme reaction condition [5] such as *n*-BuLi and −78 °C made this process not tenable. The so-called medicinal chemistry strategy was then modified into the first generation process [6] (method 2) which was disclosed during the drug development stage. The chiral compound **3** was made through the asymmetric hydrogenation of β-ketoester **6** followed by multi-steps reactions.

Since the synthesis of α-amino acids are well established and so widely used in drug discovery, we decided to develop a new protocol to synthesize the amino acid **4**. In this study, we reported how we made the optically pure

* Corresponding author.
E-mail address: hu_wenhui@gibh.ac.cn (W.H. Hu).

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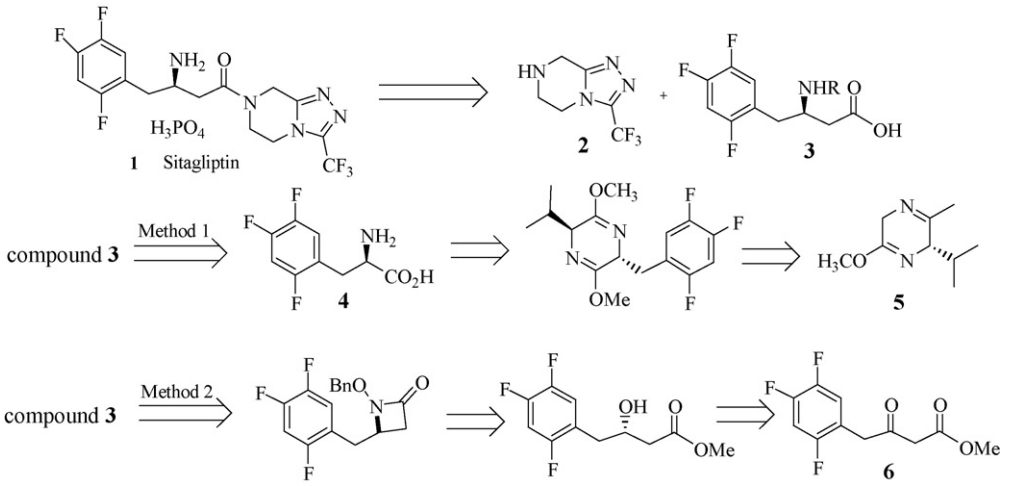
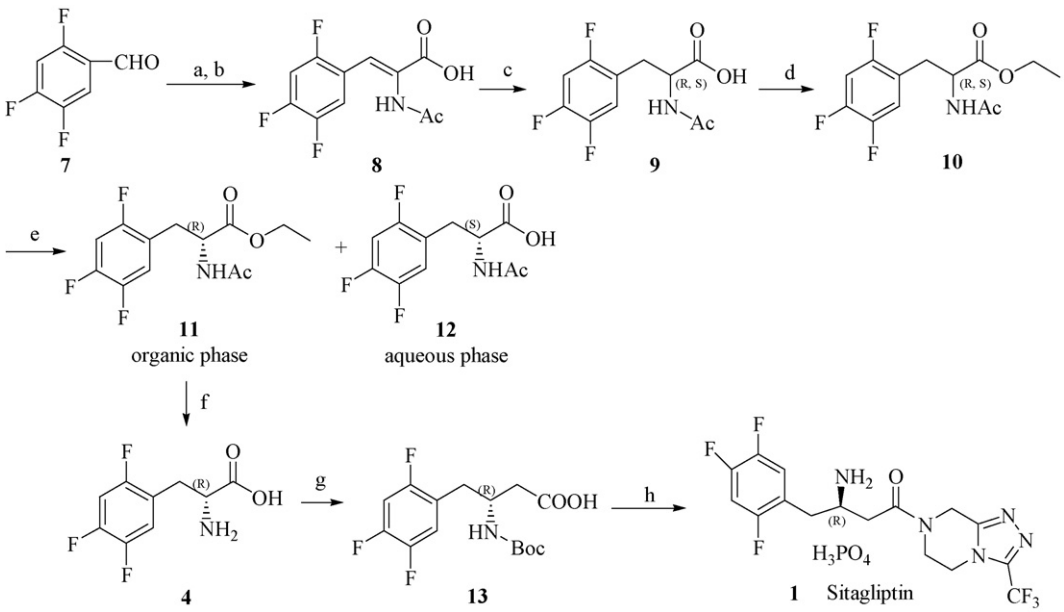


Scheme 1. The reported synthesis of sitagliptin [13,14].

trifluorophenyl R-amino acid **4** in >99.9% ee and 40.3% overall yield. This protocol is not only applicable to scale up but also be adoptable to the synthesis of important α-amino acids and the corresponding β-amino acids.

Resolution of racemic mixture is a classic method to obtain chiral compound with highly enantiomerical purity, theoretically, in 100% ee. Though the maximum product yield generally cannot exceed 50%, the recent development of dynamic kinetic resolution [7] offers a way to increase the yield to 90%. Thus, it is worthy of further exploration of making α-amino acid from simple achiral starting material with the enzymatic resolution of racemates employing enantioselective hydrolysis of the α-amino acid ethyl ester.

During the protocol development, we found that the N-acetyl-protected α-amino acid **9** (Scheme 2) was well soluble in water, whereas its ethyl ester **10** was not. This observation guide us to separate R and S amino acid by protease catalyzed hydrolysis followed by the general separation. The racemate **10** was treated with α-chymotrypsin



Scheme 2. The proposed synthetic method. (a) $CH_3CONHCH_2COOH$, Ac_2O, AcONa; (b) acetone, water; (c) H_2/10% Pd-C, CH_3OH; (d) $SOCl_2$, EtOH; (e) a-chymotrypsin; (f) 6 mol/L HCl; (g) (1) $(Boc)_2O$, (2) CH_2N_2, (3) CH_3COOAg; (h) (1) 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride, EDCI, HOBt, Et_3N, (2) MeOH/HCl, (3) $NaHCO_3$, (4) H_3PO_4.

[8] under mild condition, consequently, the S-configured ester was quickly turned into S-amino acid (**S-4**) and stayed in aqueous solution. Whereas the R-configured ester (**11**) remained unchanged and was extracted out for further purification. The highly optical pure S-configured amino acid could be easily collected by neutralization.

The synthesis of the key precursor **4** [9] began with commercial supplied 2,4,5-trifluorobenzaldehyde **7** showed in Scheme 2. Condensation of the aldehyde **7** with 2-acetamidoacetic acid gave a cyclized intermediate [10] which was easily hydrolyzed to provide the α, β-unsaturated acid **8**. The hydrogenation [11] of **8** gave rise to the N-protected α-amino acid which was then transferred into ethyl ester **10** to facilitate the later enzymatic hydrolysis. Under mild condition, the R-configured ethyl its ethyl ester **10** remained unchanged and then extracted and purified to provide the intermediate **11**, while the S-configured isomer was hydrolyzed by α-chymotrypsin and became water soluble. The free amino acid **4** was finally obtained in 99.9% ee after the hydrolysis by concentrated HCl. Following the reported procedures of Arndt-Eistert homologation and coupling reaction, both trifluorophenyl β-amino acid **13** and the final drug substance **1** [12] could be easily prepared.

In summary, a practical process to make the biologically important α-amino acid and β-amino acid was presented. This protocol takes advantages of the major difference of physical properties between the N-protected α-amino acid and its ethyl ester. The easy enzymatic hydrolysis followed by a general separation procedure and deprotection gave rise to the highly optically pure R-amino acid in >99.9% ee. This protocol not only provides an alternative method to make the specific amino acid for the important drug substance, but also is adoptable to the synthesis of other rare non-natural α-amino acids and β-amino acids. Though the drawback of this protocol is the low production yield during the resolution of R, S-amino acid, it has a great potential to be improved by either recyclization of S-amino acid or the employment of dynamic kinetic resolution (DKR).

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