The Review of the Synthesis of Bestatin, an Effective Inhibitor of Aminopeptidase N

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Abstract: Bestatin, (2S,3R)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine, is an effective inhibitor of the aminopeptidase N and other leucine and arginine aminopeptidases , having the selectivity toward the Aminopeptidase N (APN) and the Aminopeptidase B (APB) which are all metalloproteases belonging to the M1 aminopeptidase family. In spite of the poor selectivity and toxicity, so far, Bestatin is still the only marketed inhibitor of APN for cancer treatment. Considering that the inhibitor of APN is a promising agent to control and treat cancer, many efforts have been made to curtail the whole synthesis of the Bestatin and this mini-review will introduce the whole synthesis of Bestatin.

Key Words: Aminopeptidase N, inhibitors, bestatin, asymmetric synthesis, stereoselectivity, hydroxyamide, oxidizer, reducer.

INTRODUCTION

Aminopeptidase N (APN/CD13) is a type II metalloprotease that belongs to the M1 family of the MA clan [1], which contents a single zinc ion in its structure. APN, a multifunctional ezyme, common and ubiquitous in many kinds of organs, tissues and cells, can remove the amino acid from the unsubstituted N-terminal of various biologically active peptides such as enkephalins, angiotensins, neurokinins, and cytokines [2]. APN plays an important role in the tumorigenesis, was related with the angiogenesis of tumor [3] and the metastasis of the tumor cells, so inhibiting the activity of APN may be a promising way to control and treat cancer.

Bestatin, (2S,3R)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine, was isolated from Streptomycesolivoreticuli in 1976 by Umezawa *et al.* on the basis of its ability to inhibit aminopeptidase B. Presently, Bestatin is used as oral administration for treatment of cancer such as myelogenous leukemia, lung cancer, gastric cancer, esophageal carcinoma, etc, and bacterial infection in Japan. This drug is often used in conjunction with other antibiotics and anti-cancer agents because of its ability to elicit T cell proliferation, thereby enhancing the immune response. The pharmacokinetics and biotransformation of Bestatin have been examined in detail. In spite of its poor selectivity and toxicity, hitherto, Bestatin is still the only marketed inhibitor of aminopeptidase N to therapy leukaemia.

Beside with treating cancer, Bestatin can also suppress the infection induced by the coronaviruses such as SARS [4]. And based on the studies in recent years, the inhibitor of the APN is also found to have the ability of analgesia by hydrolyzing enkephalin in the central nerve system [5]. So Bestatin is a multifunctional and promising drug in treating various kinds of diseases.

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Nakamura *et al.* used X-ray crystallography to confirm the absolute configuration of Bestatin and Suda *et al.* published the first total synthesis starting from D-phenylalanine. So far, more and more synthesis means have been discovered with more convenience and higher yield which would be introduced one by one below concretely.

THE SYNTHESIS OF THE BESTATIN

The structure of the Bestatin is shown below.

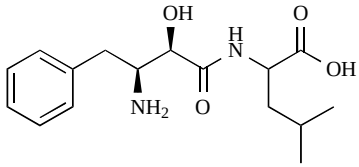

Fig. (1). The structure of the Bestatin (2S, 3R)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine; Molecular Weight 308.38.

Bestatin, as a peptidomimetic, is a natural compound extracted from the dictyo-streptomycete, As the inhibitor of the Aminopeptidase N, Bestatin had been found to have antitumor and anti-virus activity, so more and more attentions and interests have been paid for the complete synthesis of the Bestatin. The key intermedium during synthesis is the 3(S)-amino-2(R)-hydroxy-4-phenylbutyric acid (AHPA) which is present in many medicinally important molecules. And the synthesis of the AHPA has attracted many attentions due to its importance.

Several stereoselective synthetic methods for formation of AHPA were recently presented, including aminohydroxylation [6] reduction of α-ketoacid derivatives, [7] nucleophilic addition to chiral aldehydes [8] amides [9] or imines [10] cycloaddition reactions [11] chiral epoxides [12] and β-lactam ring-opening procedures, [13] halocyclocarbamation of allylamines [14] and chiral α-amino or α-amino acid [15] transformations.

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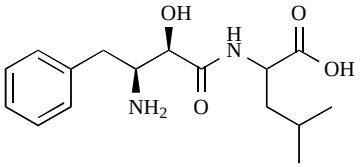
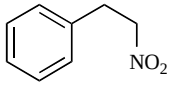
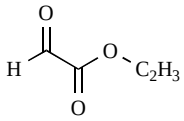
In scheme **1**, the structure of the Bestatin was separated into three synthons as the figure shown below.



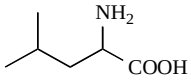
The first synthon is β- nitro-phenylethane.



The second one is ethanal acid ethyl ester.



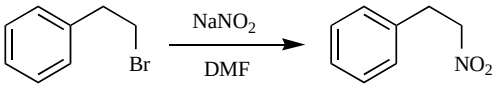
The last one is the L-leucine.



Scheme 1.

I. Synthesis of the β-nitro-phenylethane

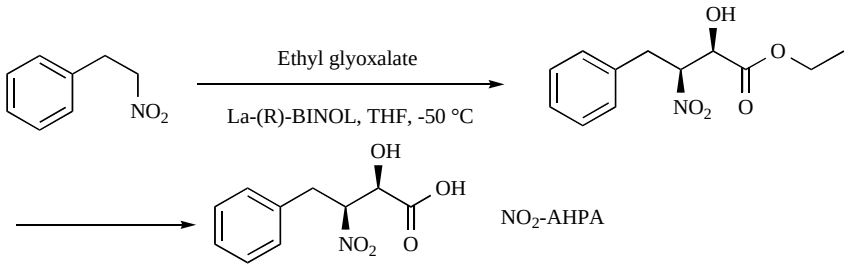
The initial material were β- brom-phenylethane, DMF, sodium nitrite and carbamide.



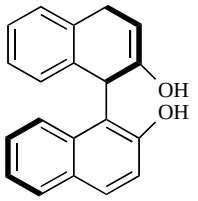
The β- brom-phenylethane was solved in DMF q.s. The solution was mechanically stirred at -5°C. Sodium nitrite and carbamide were added into the solution, and the color of solution would change to yellow. Keep stirring the solution at -5°C for 10 hours to get the β- nitro-phenylethane.

II. Synthesis of 3(R)-nitro-2(S)-hydroxy-4-phenyl-butanoic acid (NO_2-AHPA)

The materials of this step were β- nitro-phenylethane, ethanal acid, solution of sodium hydroxide.



Treatment of ethyl glyoxalate with 2-phenyl-1-nitro-ethane as per the procedure described by Shibasaki [16] *et al.* at -50°C in the presence of the La-(R)-BINOL catalyst (10 mol %) in THF provided (2S,3R) NO_2-AHPA ethyl ester in 81% yield and 93% ee as the sole product. Then hydrating the alcohol engendered the NO_2-AHPA [17].



(R)-BINOL

The catalyst of BINOL has been extensively used in the asymmetric synthesis and the biological recognition. The lanthanum salt of the BINOL has long been used in the catalytic asymmetric nitroaldol reaction. The mechanism of the reaction is shown in Fig. (**2**) [18].

III. The Synthesis of Bestatin

This step utilized the active ester reaction to generate the targeted compound.

The NO_2-AHPA, N-Hydroxybenzotrizole (HOBt) and dicyclohexylcarbodiimide (DCC) were solved in anhydrous THF. Stirring the mixture, the water generated in the reaction was eliminated by the DCC to generate the active ester, and then L-leucine benzyl ester was dropped into the mixture, the L-Leucine substituted the HOBt to form the 3 (R)-nitro -2 (S)-hydroxy-4-phenylbutanoyl-L-leucine benzyl ester. The nitro group and the benzyl ester can be reduced by the 10% Pd/C in hydrogen simultaneously.

The figure of this reaction procedure is shown in Fig. (**3**).

Enzyme catalysis reaction which has high selectivity also plays an important role in the asymmetric synthesis. Scheme **2** utilized the prochiral ketones as the material and carbonyl reductases from bakers yeast as the catalyzer. The enzyme had high stereoselectivity [19].

β-Keto ester prepared from Meldrum`s acid by an acylation/decarboxylation strategy [20, 21] was chlorinated with sulfuryl chloride to afford the initial material. Three kinds of the yeast reductases in the collection: short-chain dehydrogenases YGL039w and YGL157w can catalyze the substrate, namely the initial material to produce the (2S,3S)-chlorohydrin in 41% and >98% ee, respectively. The reduction was carried put in a 1L fermenter and a glucose solution was added along with the compound **1**. In order to prevent the toxicity toward the *E. coli* cells, the compound **1** must be added porionwise.

The ring closure reaction of the compound **2** proceeded smoothly in the presence of excess K_2CO_3 to afford cis-

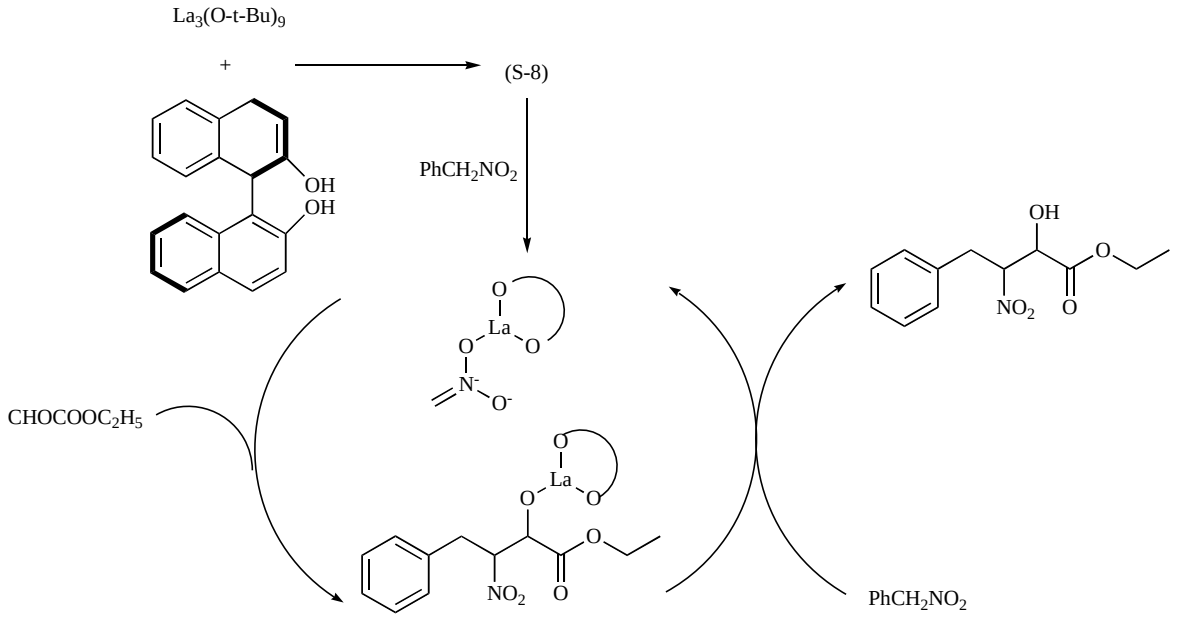


Fig. (2). The mechanism of the reaction.

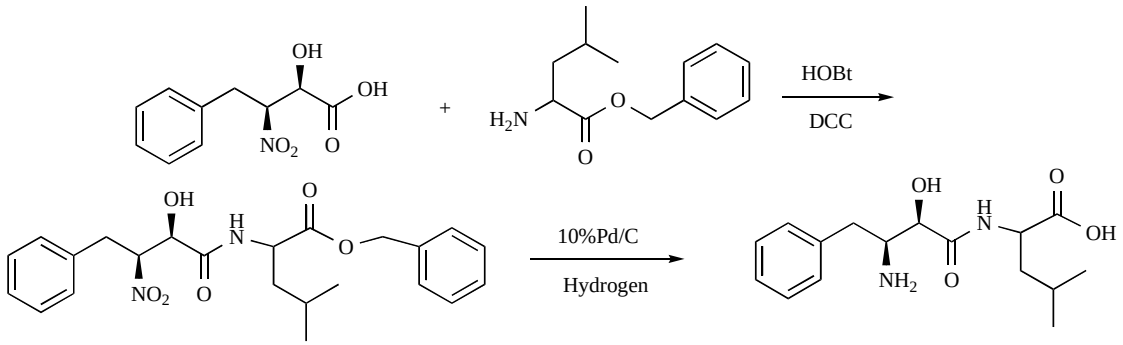
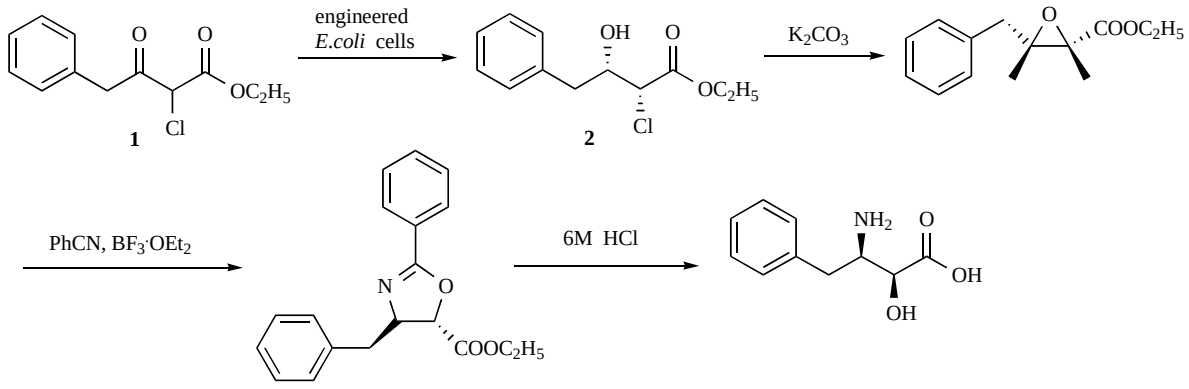


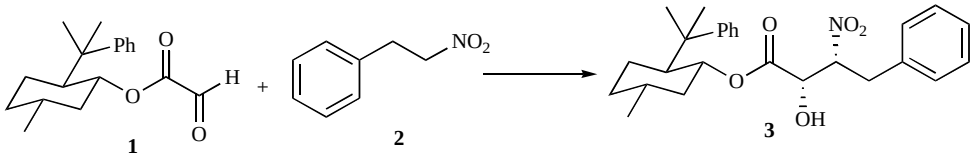
Fig. (3). The generation of Bestatin in Scheme **1**.



Scheme 2.

glycidate 6 [22] whose relative stereochemistry was testified by the J 2, 3 value of NMR. The epoxide was opened by benzonitrile in the presence of a stoichiometric quantity of $BF_3.OEt_2$ to yield a single product. The trans-stereochemistry of 7 was assigned on the basis of its J 2, 3 value of NMR. This Ritter reaction proceeded with no C3 epimerization. The acidic hydrolysis of 7 proceeded uneventfully to afford 2, which was isolated as its hydrochloride salt. The spectral data and specific rotation of the AHPA were identical to those of an authentic sample of the natural product. The transformation of AHPA to the Bestatin had been illustrated in former scheme, so we can get the target compound, Bestatin.

Scheme **3:** This scheme, also a high stereoselective reaction, has certain similarity with the scheme one which is



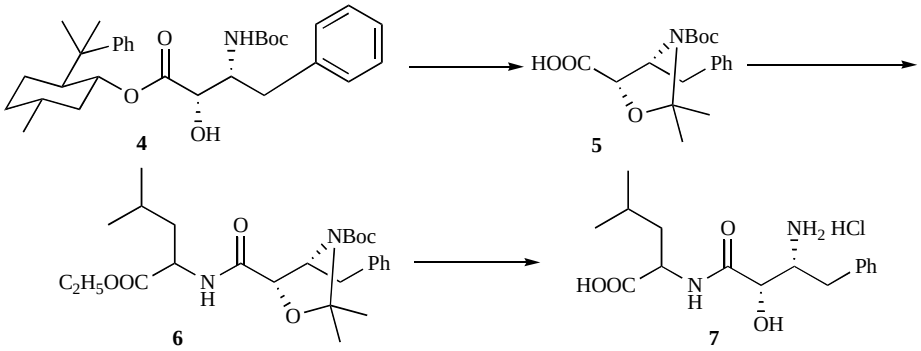
Henry reaction of chiral derivatives of glyoxylic acid bearing various auxiliaries, such as (1*R*)-8-phenylmenthol, (2*R*)-bornane-10,2-sultam, (4*R*) -methyl- (5*S*)- phenyloxazolidinone and 7,7-dimethylnorbornane- (1*S*,2*R*)-oxazolidinone with simple nitroalkanes [23]. And in most cases, this reaction can generate the 3(S)-amino-2(R)-hydroxy-4-phenylbutyric acid, namely the AHPA which is the key intermedium in the Bestatin synthesis.

The initial materials of this reaction was the (1*R*)-8-phenylmenthyl glyoxylate 1 [24] with 1-nitro-2-phenylethane 2, the reaction catalyzed by activated aluminum oxide and carried out at −20°C can afford a mixture (71:19:6:5) of diastereoisomeric nitroalcohols 3 in 89% yield.

The nitro group of compound **3** was reduced through the 10%Pd/C and hydrogen, the amino generated was protected by the Boc group to get the compound **4** which reacted with 2,2-dimethoxypropane (DMP) to give, after hydrolysis of the ester functionality, the acid 5 in 78% yield. Using mixed anhydride method, the compound **6** condensed with the methyl ester of the Leucine, to generate the compound **7** which was finally deprotected in a two-step reaction sequence with 70% overall yield.

Scheme **4**: This is an absolutely different way to synthesize Bestatin, the main material of this scheme is L-phenylalanine, and the synthesis route is shown below.

The first step is synthesis of L-phenylalanine methyl ester. The phenylalanine was added into the excessive methanol under the ice bath. The anhydrous hydrogen chloride was aerated into the solution. The solution would get clarified and then get muddy. The methanol was evaporated to get the phenylalanine methyl ester. The amine in the phenylalanine methyl ester is active which can easily be substituted or oxidized. The phenylalanine methyl ester also can be synthesized by the mixture of the acetyl chloride so before the following reactions, the amine should be protected. We selected the (Boc)2O as the protective group.



Scheme 3.

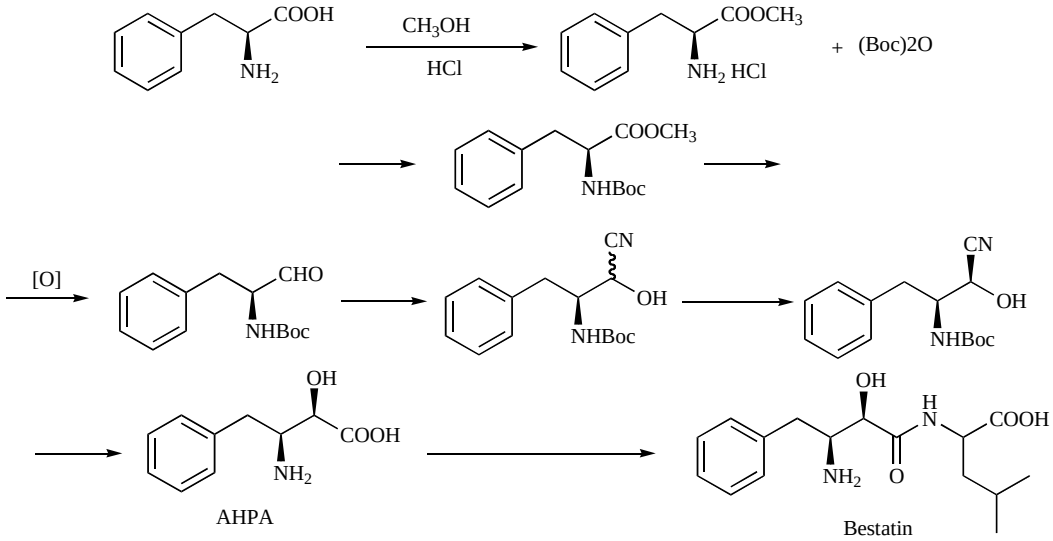
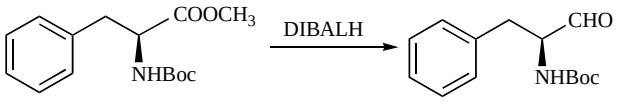


Fig. (4). The synthesis route of Scheme **4**.

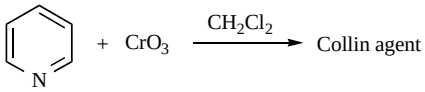
In the synthesis of the aldehyde group, there are two ways can be utilized.

Scheme **1**: This scheme is a one step means using the DIBALH as the reducer to transform the ester to the aldehyde group directly [25-27]. The synthesis route is shown below.



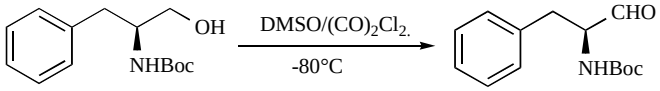
Scheme **2**: This way is transforming the ester to the hydroxyl under the catalyzing of the lithium aluminum hydride ($LiAlH_4$) firstly [28, 29], and then oxidizing the hydroxyl to the aldehyde group. There are three kinds of selective oxidizer supplied in this reaction, Collin agent, DMSO/DCC, and DMSO/$(CO)_2Cl_2$.

The Collin agent is the complex of the chromium trioxide and pyridine [30]. This is a selective oxidizer which can oxidize the primary alcohol to the aldehyde group directly [30, 31].

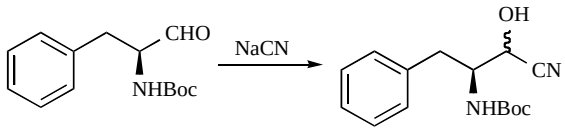


Another selective oxidizer is the system of DMSO and DCC which also can oxidize the primary alcohol to the aldehyde group selectively under the environment of acid [32].

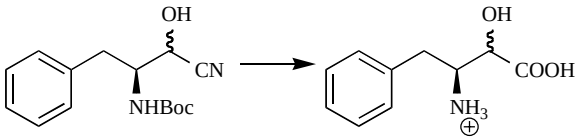
And the last selective oxidizer is the system of DMSO/$(CO)_2Cl_2$ [33,34]. But this reaction must be carried out under a commanding condition such as extremely low temperature.



In order to form the structure of α-hydroxyl- carboxylic acid, the α- hydroxyl- nitrile group must be synthesized firstly [35].



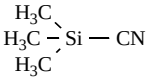
The α- hydroxyl- nitrile group could be transformed to the α- hydroxyl- carboxylic acid group via hydrolysis. During the procedure of the hydrolysis, the concentrated hydrochloric acid is used as the catalyzer. Because of unstability under the environment of the strong acid, the Boc moiety will fall off from the NH_2-, and then the NH_2- will be transformed into the hydrochlorate.



Utilizing the ion exchange column to purify the AHPA salt. Neutralizing the salt to the PH =7-8 can get the AHPA. Separate the AHPA with long silica gel column to get the (2S,3R) AHPA.

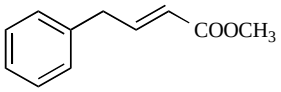
Next step, the AHPA react with the L-Leu to form the Bestatin.

In the preparation of the α- hydroxyl- nitrile group, we can use catalyzer to improve the productivity and the selectivity such as the TMSCN or tributyltin cyanide [36], the structure of the TMSCN is shown below.



The strereoslectivity of the TMSCN can be tested in the present of Lews acid. The nature of the Lews acid is essential for the stereoselectivity, the *syn*-adducts were formed when $MgBr_2$ or $TiCl_4$ were used, whereas the *anti*-addition products were obtained as major diastereoisomers when using $ZnBr_2$, BF_3 or $SnCl_4$ as the Lewis acid. The reaction is undergone at -78°C.

Scheme **5**: In this scheme, the elementary material is an epoxy compound whose structure is shown below.



Epoxidating the double bond can get the structure of epoxyethane. Then utilizing the asymmetrical means can get the structure of the hydroxyamides [37].

The synthesis route is shown below.

In spite of suffering from some drawbacks such as regioselectivity, this is still a good means to synthesize the hydroxyamides.

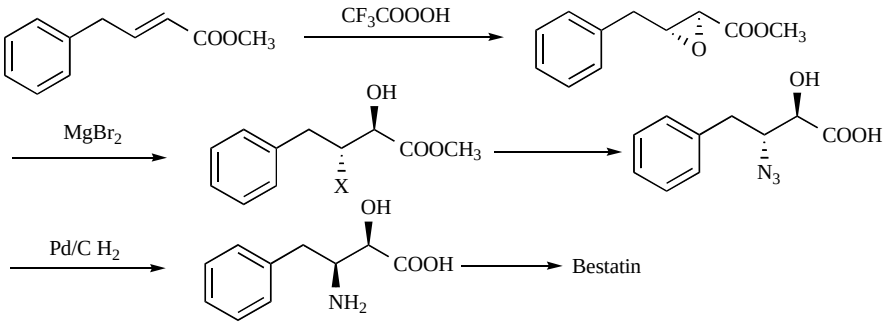


Fig. (5). The synthesis route of the Scheme **5**.

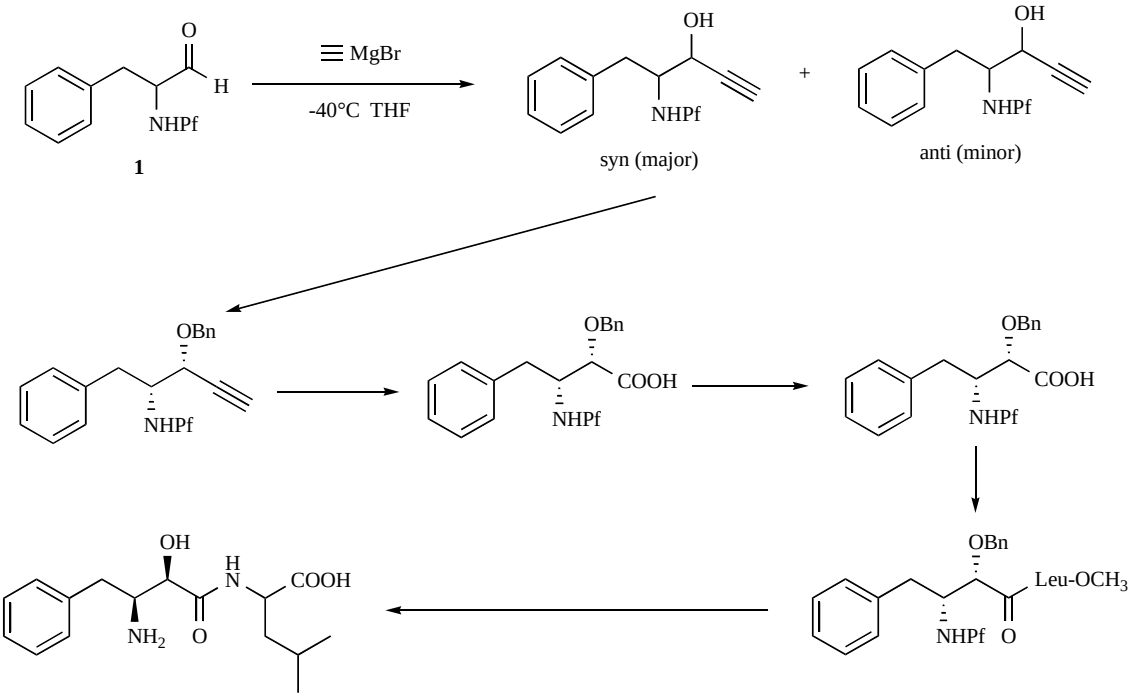


Fig. (6). The synthesis route of Scheme **6**.

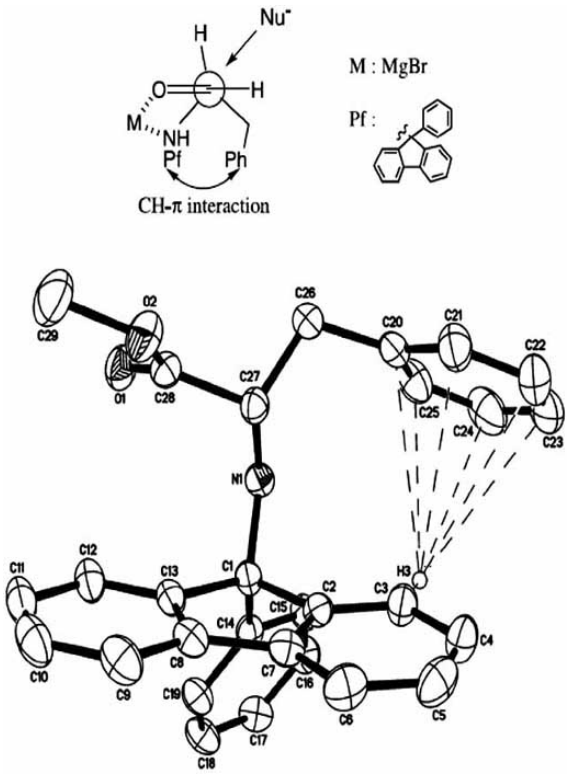


Fig. (7). The mechanism of the CH-π interaction.

Scheme **6**: This is a diastereoselective synthesis of syn-amino-alcohols *via* contributing CH-π interaction. The benzyl group allowed diastereoselectivity with a high degree in nucleophilic addition of α-aminoaldehydes, but produced an *anti*-aminoalcohols with non-chelating control [38]. Thus, aromatic α-amino acids have been modified by a number of methods [39]. In this reaction, 9-phenylfluoren-9-yl (Pf) group acted as the protective group of the amino which can simultaneously supplied a CH-π interaction to generate the syn-aminoalcoholes with high degree [40].

The initial material, compound **1** can be easily prepared from the phenylalanine. And many kinds of the N-protected aromatic α-aminoaldehydes exposed to the same reaction condition can all give syn- products with high stereoselectivity and yields due to the CH-π interaction between the CH in the Ph and the Pf shown below. But if the aromatic α-aminoaldehydes were substituted to the aliphatic α-aminoaldehydes, the stereoselectivity would greatly decrease.

Scheme **7**: This scheme is a one-pot reaction. This is a new and novel method to synthesize R-Hydroxyamides such as the Bestatin [41]. The synthesis route is shown below.

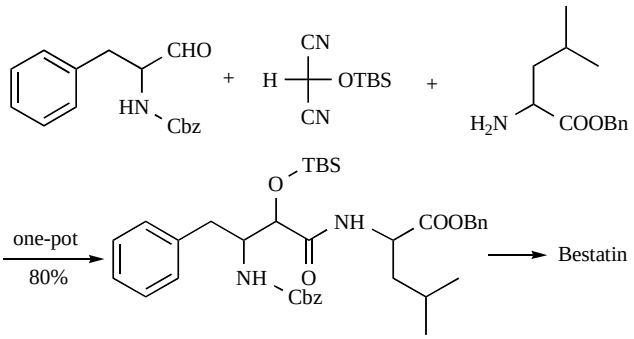


Fig. (8). The synthesis route of Scheme **7**.

CONCLUSION

Aminopeptidase N is a new and promising target in therapy of many kinds of diseases such as cancer, virus infection, acute pain, etc. So the inhibitor of the APN such as

Bestatin can be used in the therapy of the cancers. Because of the zinc dependence, the hydroxyl, amine, and the carbonyl all play important role in the combination with the zinc ion. And the key moiety of 3(S)-amino-2(R)-hydroxy-4-phenylbutyric acid in the structure of Bestatin appears also in many other inhibitors of the aminopetidase N, such as the Prebestin, Probestim and many other kinds of drugs. The total synthesis of the Bestatin attracted many attentions these years due to its values in the inhibition of the APN. And many kinds of concise and easy synthesis means have been discovered, and following the development of the study, more and more better synthesis means will be discovered.

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