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Original article

새로운 베스타틴 유사체의 입체선택적 합성

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Stereoselective Synthesis of Novel Bestatin Analogs

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초 록

두 종류의 새로운 베스타틴(bestatin) 유사체를 D-leucine과 D-valine으로부터 효율적이면서 입체선택적으로 합성하였다. 아미노펩티데이즈 억제제인 베스타틴은 면역조절 효과를 보이며 급성백혈병 치료제로 상품화되어 있다. 주요 중간체인 *trans*-옥사졸리딘 메틸에스터 **2a**와 **2b**는 페닐설포닐나이트로메테인($PhSO_2CH_2NO_2$)과 *N*—하이드록시 메틸기가 보호기로 도입된 α-아미노 알데하이드(**4a**와 **4b**) 간의 일련의 세 단계 연속반응과 연이은 가오존분해 반응으로부터 20 : 1 이상의 입체선택성으로 합성되었다. **2a**와 **2b**의 가수분해 반응 후에 L-Leu-OMe와의 펩타이드 결합을 통하여 베스타틴의 새로운 유사체인 **3a**와 **3b**를 보호기가 도입된 형태로 얻었다. 이소부틸기와 이소프로필기를 갖는 두 종류의 새로운 베스타틴 유사체(**1a**와 **1b**)는 해당 α-아미노알데하이드 **4**로부터 높은 입체선택성으로 6단계에 걸쳐 각각 51%와 38%의 수율로 합성되었다.

Abstract

Two new analogs of bestatin were prepared from D-leucine and D-valine in a stereoselective and efficient way. An aminopeptidase inhibitor bestatin shows significant biological effects on immunomodulation and is marketed for the treatment of acute myelocytic leukemia. The key intermediates, *trans*-oxazolidine methyl esters **2a** and **2b**, were obtained with more than 20 to 1 stereoselectivity in a one-pot procedure by the three cascade reactions between *N*-hydroxymethyl protected α-amino aldehydes (**4a** and **4b**) and phenylsulfonylnitromethane ($PhSO_2CH_2NO_2$) and the following in-situ ozonolysis. Basic hydrolysis of **2a** and **2b**, and then the peptide coupling with L-Leu-OMe produced the protected derivatives of two new bestatin analogs, **3a** and **3b**, respectively. The new isobutyl and isopropyl analogs of bestatin (**1a** and **1b**) were produced in overall 51% and 38% yields, respectively, with high stereoselectivity from the corresponding protected α-amino aldehydes **4** in a six-step process.

Keywords: *bestatin analogs, aminopeptidase inhibitor, β-amino-α-hydroxy acid, intramolecular conjugate addition.*

1. Introduction

Aminopeptidase N (APN), a metal-dependent membrane-bound protease, has been studied as a useful clinical marker because its overexpression affects the protein activation, degradation, and regulation that are closely related to the inflammatory diseases and cancers[1-4]. In order to control the overexpression of APN, several naturally occurring aminopeptidase inhibitors have been developed from microbial culture filtrates. Bestatin, first isolated from a culture filtrate of *Streptomyces olivoreticuli* (MD976-C7)[5], has been extensively studied due to its multiple effects on the immune system, and it has been used to treat acute myelocytic leukemia under a trade name of Ubenimex[6]. For the structure-activity relationship, its analogs have been synthesized (Figure 1(a))[7-10], which has revealed that the *threo*-β-amino-α-hydroxy acid moiety in bestatin interacts with the active site of aminopeptidase N[11].

The bioactive vicinal amino hydroxy acid unit is also widely found in other naturally occurring aminopeptidase inhibitors. For example, amastatin isolated also from the culture filtrate of *Stereptomyces* sp.[12] contains (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (AHMHA) at the N-terminus (Figure 1(b)), and 3-amino-2-hydroxy-4-methylpentanoic acid (AHMPA) is embedded in lapstatin although its stereochemistry has not been established yet (Figure 1 (c))[13].

In order to demonstrate the effects of the side chain at the *threo*-vicinal amino hydroxy acid unit on the bioactivity, we planned to substitute the benzyl group at the N-terminus of bestatin with an isobutyl

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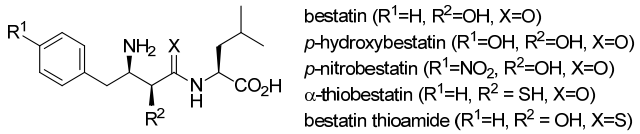
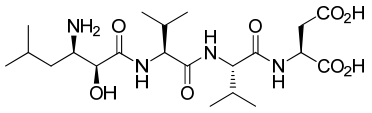
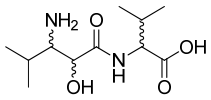


(a) bestatin and its analogs



(b) amastatin



(c) lapstatin

Figure 1. The structure of natural or unnatural aminopeptidase inhibitors.

or isopropyl group, which are present in amastatin or lapstatin, respectively (Figure 1). To the best of our knowledge, this is the first synthetic report for isobutyl or isopropyl substituted bestatin analogs (Figure 2).

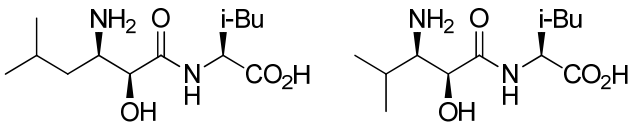
2. Experimental

2.1. General

Materials were obtained from commercial suppliers and were used without further purification. Methylene chloride was distilled from calcium hydride immediately prior to use. Air or moisture sensitive reactions were conducted under nitrogen atmosphere using oven-dried glassware and standard syringe/septa techniques. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) and by visualization with a ninhydrin staining solution. Column chromatography was performed on silica gel 60 (70-230 mesh). Melting point was measured on a Meltemp apparatus in open capillary tubes. Optical rotations were determined at ambient temperature with a digital polarimeter and are the average of ten measurements. ^{1}H and ^{13}C NMR spectra were measured at 400 MHz and 100 MHz, respectively in $CDCl_3$ or MeOH-d_4. The ^{1}H NMR spectral data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz). The ^{13}C NMR spectra were referenced with the 77.16 resonance of $CDCl_3$, 49.00 resonance of MeOH-d_4. Low and high resolution mass spectra were measured by the CI or FAB ionization method and analyzed by magnetic sector mass analyzer.

2.2. General procedure for *trans*-oxazolidine methyl esters 2

To α-amino aldehyde **4a** (R^1 = i-Bu, 646 mg, 2.63 mmol) in THF (2 mL) was added phenylsulfonylnitromethane (636 mg, 3.16 mmol) and DMAP (482 mg, 3.95 mmol). The reaction mixture was stirred at room temperature for 2 days with vigorous stirring until the starting material **4a** disappeared. The mixture was diluted with THF (5 mL) and methanol (5 mL), to which was added DBU (1.19 mL, 7.90 mmol) at room temperature. Then, the reaction mixture was cooled to -78 ℃, and ozone was bubbled through over 30 min. After quenching the reaction with acetic acid (1 mL), the resulting mixture was warmed up to room temperature. After removing the solvent under reduced pressure, the residue was partitioned between EtOAc (20 mL) and an aqueous saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The organic residue was purified by silica gel chromatography (hexane : EtOAc = 8 : 1) to afford the desired ester **2a** (546 mg, 1.90 mmol, 72%) as a colorless oil.



1a **1b**

Figure 2. New bestatin analogs.

2a : 3-*tert*-Butyl 5-methyl (4*R*,5*S*)-4-isobutyloxazolidine-3,5-dicarboxylate : Yield 72% (546 mg); colorless oil; $[\alpha]_D^{16}$ = +5.8 (*c* = 2.8, $CHCl_3$); ^{1}H NMR δ 0.99 (d, 3H, *J* = 6.4), 1.01 (d, 3H, *J* = 6.4), 1.44-1.50 (m, 1H), 1.48 (s, 9H), 1.60 (m, 1H), 1.69 (m, 1H), 3.79 (s, 3H), 4.24 (br s, 1H), 4.37 (d, 1H, *J* = 1.6), 4.85 (d, 1H, *J* = 3.6), 5.28 (s, 1H); ^{13}C NMR δ 22.1, 22.8, 25.2, 28.3, 42.2, 52.3, 57.8, 79.0, 79.0, 80.6, 152.8, 171.4.

2b : 3-*tert*-Butyl 5-methyl (4*R*,5*S*)-4-isopropyloxazolidine-3,5-dicarboxylate : 50% (415 mg), colorless oil; $[\alpha]_D^{16}$ = +10.5 (*c* = 0.64, $CHCl_3$); ^{1}H NMR δ 0.94 (d, 3H, *J* = 7.0), 0.96 (d, 3H, *J* = 7.0), 1.44 (s, 9H), 1.48 (m, 1H), 3.46 (s, 3H), 3.74 (br s, 1H), 4.44 (s, 1H), 4.80 (d, 1H, *J* = 3.2), 5.23 (br s, 1H); ^{13}C NMR δ 17.8, 18.9, 28.3, 31.0, 52.4, 64.6, 76.8, 80.0, 80.8, 153.3, 171.9.

2.3. General procedure for dipeptide derivatives 3

To **2a** (R^1 = i-Bu, 753 mg, 2.62 mmol) in THF (6 mL) at 0 ℃ was added 2 N NaOH (6 mL). After the reaction mixture was stirred at room temperature for 1 h, it was acidified with 2 N aq. HCl to pH 1 at 0 ℃. The resulting mixture was then partitioned between EtOAc (20 mL) and brine (5 mL). The aqueous phase was extracted with EtOAc (20 mL × 2), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude **2a**.

To crude **2a** in THF (10 mL) at 0 ℃, HOBt (203 mg, 1.50 mmol) and L-Leu-OMe (250 mg, 1.38 mmol) were added. Then, EDC·HCl (288 mg, 1.50 mmol), and *N*,*N*-diisopropylethylamine (44 μL, 3.13 mmol) were added to the reaction mixture. The mixture was stirred at room temperature overnight. After the removal of the solvent, the residue was partitioned between a saturated aq. solution of NH_4Cl (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL × 2), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The organic residue was purified by silica gel chromatography (hexane : EtOAc = 8 : 1) to afford the dipeptide intermediate **3a** as a colorless oil.

3a : [3-*tert*-Butyl 5-methyl (4*R*,5*S*)-4-isobutyloxazolidine-5-carboxylic acid]-L-leucine methyl ester : Yield 74% (370 mg); $[\alpha]_D^{10}$ = -17.4 (*c* = 0.88, $CHCl_3$); colorless oil; ^{1}H NMR δ 0.94 (dd, 6H, *J* = 2.8, 6.2), 1.00 (t, 6H, *J* = 6.4), 1.47 (s, 9H), 1.54-1.63 (m, 3H), 1.66-1.77

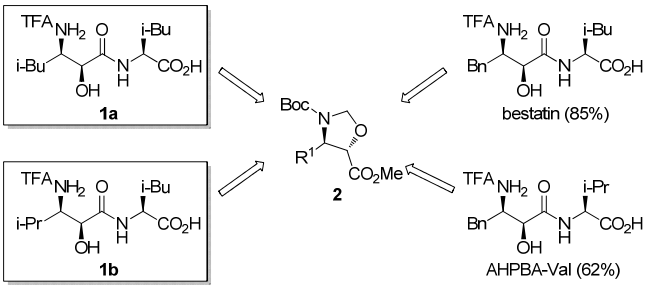


Figure 3. Dipeptide synthesis from *trans*-oxazolidine methyl esters 2.

(m, 2H), 3.76 (s, 3H), 4.22 (d, 1H, J = 2.8), 4.38 (dt, 1H, J = 2.5, 7.3), 4.61-4.65 (m, 1H), 4.77 (d, 1H, J = 4.8), 5.31 (d, 1H, J = 3.2), 6.86 (d, 1H, J = 8.4); ^{13}C NMR δ 21.9, 22.4, 22.8, 24.9, 25.0, 28.3, 41.4, 42.7, 50.3, 52.3, 57.9, 78.2, 80.9, 81.7, 152.9, 170.4, 172.9; HRMS (CI) calcd for $C_{20}H_{37}N_2O_6$ 401.2652 ([M+H]$^+$), found 401.2651.

3b : [3-*tert*-Butyl 5-methyl (4*R*,5*S*)-4-isopropyloxazolidine-5-carboxylic acid]-L-leucine methyl ester : Yield 76% (264 mg); $[\alpha]_D^{10}$ = -13.7 (c = 0.81, $CHCl_3$); colorless oil; ^{1}H NMR δ 0.92 (dd, 6H, J = 1.6, 6.4), 0.99 (t, 6H, J = 7.0), 1.45 (s, 9H), 1.54-1.61 (m, 2H), 1.63-1.69 (m, 1H), 1.94-1.99 (m, 1H), 3.74 (s, 3H), 4.10 (dd, 1H, J = 2.2, 6.6), 4.34 (d, 1H, J = 2.8), 4.59-4.65 (m, 1H), 4.74 (d, 1H, J = 4.8), 5.31 (br s, 1H), 6.91 (d, 1H, J = 8.4); ^{13}C NMR δ 18.7, 18.9, 21.9, 23.0, 25.0, 28.3, 31.5, 41.5, 50.4, 52.5, 64.9, 79.3, 81.0, 153.4, 171.0, 173.0; HRMS (FAB) calcd for $C_{19}H_{35}N_2O_6$ 387.2495 ([M+H]$^+$), found 387.2496.

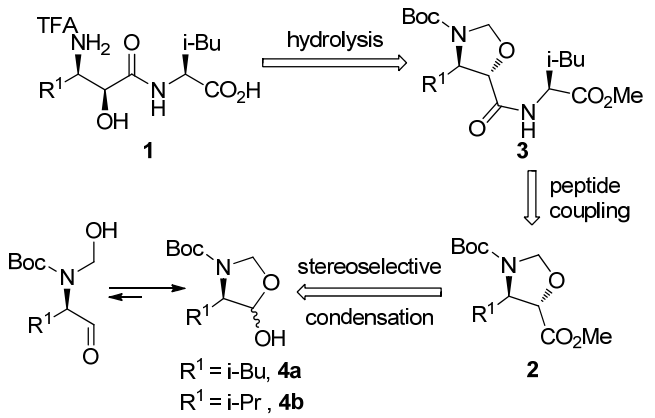
2.4. General procedure for bestatin analogs 1

To **3a** (R^1 = i-Bu, 370 mg, 0.92 mmol) in THF (6 mL) at 0 ℃ was added 2 N NaOH (6 mL). After the reaction mixture was stirred at room temperature for 1 h, it was acidified with 2 N HCl to pH 1 at 0 ℃. The reaction mixture was then partitioned between EtOAc (20 mL) and brine (5 mL). The aqueous phase was extracted with EtOAc (20 mL × 2), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

To the obtained crude in CH_2Cl_2 was added trifluoroacetic acid (39 μL, 5.15 mmol) and the reaction mixture was reacted at room temperature overnight. After the removal of the solvents, the reaction mixture was diluted with water (10 mL). The aqueous layer was washed with EtOAc (10 mL) three times and then the aqueous layer was condensed under reduced pressure to afford bestatin analog **1a** as a white solid in 95% yield.

1a : (2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanamindo-4-methylpentanoic acid : Yield 95% (235 mg); Mp. 131 ℃; $[\alpha]_D^{10}$ = -20.4 (c = 2.1, H_2O); ^{1}H NMR (MeOH-d_6) δ 0.98 (m, 12H), 1.50 (m, 1H), 1.63-1.77 (m, 5H), 3.50 (br s, 1H), 4.22 (br s, 1H), 4.43-4.46 (m, 1H); ^{13}C NMR (MeOH-d_6) δ 22.0, 22.3, 22.9, 23.3, 25.2, 26.1, 39.2, 41.3, 52.2, 53.3, 71.1, 173.6, 175.7; HRMS (FAB) calcd for $C_{13}H_{27}N_2O_4$ 275.1971 ([M+H]$^+$), found 275.1977.

1b : (2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanamindo-4-methylpropanoic acid : colorless film; Yield quant. (223 mg); Mp. 61 ℃; $[\alpha]_D^{10}$ = -28.4 (c = 2.2, H_2O); ^{1}H NMR (MeOH-d_6) δ 0.97 (dd, 6H,



Scheme 1. Retrosynthetic scheme for bestatin analogs.

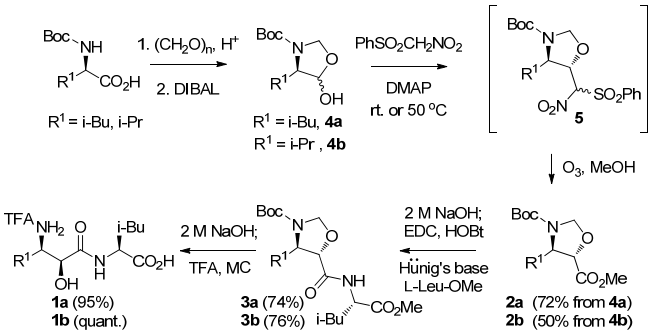
J = 5.6, 9.2), 1.08 (m, 1.08 (m, 6H), 1.73 (m, 3H), 2.10 (qt, 1H, J = 6.7, 13.4), 3.2.3 (br s, 1H), 4.37 (s, 2H), 4.42 (m, 1H); ^{13}C NMR (MeOH-d_6) δ 18.5, 19.5, 22.0, 23.2, 26.1, 29.3, 41.3, 52.5, 60.5, 69.6, 174.1, 175.7; HRMS (CI) calcd for $C_{12}H_{25}N_2O_4$ 261.1814 ([M+H]$^+$), found 261.1819.

3. Results and discussion

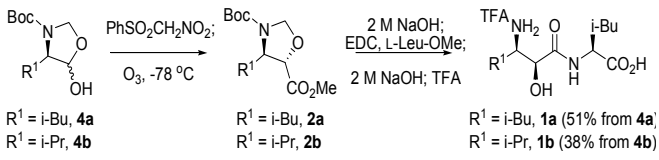
The key strategy for the synthesis of bestatin and its analogs is how to prepare the *threo*-β-amino-α-hydroxy acids moiety[14-17]. Recently, we have reported an efficient and stereoselective method for bestatin and its analog AHPBA-Val from chiral synthons, *trans*-oxazolidine methyl esters **2**, which are properly protected forms of *threo*-β-amino-α-hydroxy acids (Figure 3)[18]. In our previous study, bestatin and AHPBA-Val were synthesized efficiently with more than 20:1 stereoselectivity. Based on the successful synthesis of bestatin and AHPBA-Val, we wished to utilize the chiral key intermediates **2** for the synthesis of the isobutyl or isopropyl substituted bestatin analogs, **1a** and **1b**.

In order to substitute the benzyl group in bestatin with an isobutyl or isopropyl group, we planned to prepare the desired *trans*-oxazolidines **2** from *N*-hydroxymethyl protected α-amino aldehydes **4a** and **4b** via the stereoselective condensation reactions (Scheme 1). The basic hydrolysis of **2** and the following peptide coupling with L-Leu-OMe were expected to afford dipeptide derivatives **3**, which would be readily converted to the desired dipeptides **1** with a global deprotection reaction.

The required starting compounds, two stable α-amino aldehydes **4a** and **4b**, were obtained from Boc-D-Leu-OH and Boc-D-Val-OH, respectively, according to the previously reported procedure [19-20]. In addition to a role of an *N*-hydroxymethyl group as a stabilizer of labile α-amino aldehydes, it was also utilized to produce several *trans*-oxazolidines with a high stereoselectivity by an intramolecular conjugate addition[21-24]. For example, the intramolecular conjugate addition reactions between the *N*-hydroxymethyl group and the α,β-unsaturated ester group resulted in the *trans*-oxazolidine derivatives with more than 10 to 1 stereoselecitvity, which were transformed into several natural



Scheme 2. Synthesis of new bestatin analogs, 1a and 1b.



Scheme 3. Proposed mechanism for *trans*-oxazolidines 5.

or unnatural bioactive γ-amino-β-hydroxy acids, such as (-)-statine[21], 3-aminodeoxystatin[22], *threo*-β-hydroxy-L-glutamic acid[23], and (3*R*,4*S*)-AHPPA derivatives[24].

Contrast to the previous syntheses of γ-amino-β-hydroxy acids, the phenylsulfonylnitroolefin group was selected as a suitable Michael acceptor for the synthesis of β-amino-α-hydroxy acids because the phenylsulfonylnitromethyl group on **5** (Scheme 2), resulted from the intramolecular conjugate addition of the *N*-hydroxymethyl group to the phenylsulfonylnitroolefin group of **7** (see below, Schemes 3), could be readily converted to the methyl ester group by ozonolysis in a methanolic solution via an oxidative Nef reaction[25].

Thus, the condensation reactions between configurationally stable α-amino aldehydes **4** and phenylsulfonylnitromethane ($PhSO_2CH_2NO_2$) under the weakly basic conditions[26] yielded the diastereomeric mixture of *trans*-oxazolidines **5**, which were oxidized in-situ to give the desired β-amino-α-hydroxy acid derivatives, **2a** and **2b**, with an excellent stereoselectivity[18]. No minor *cis*-stereoisomers of **2a** and **2b** were observed on their ^{1}H NMR spectra. The desired absolute stereochemistry of **2a** and **2b** was derived from the corresponding D-amino acids, whereas the previous synthesis of *threo*-β-amino-α-hydroxy acids from the L-amino acids gave the enantiomers of **2a** and **2b**[18].

Here, the different reactivity between **4a** and **4b** needs to be mentioned. Most of a valinal derivative **4b** remained intact after the reaction with phenylsulfonylnitromethane at room temperature, whereas a leucinal derivative **4a** smoothly reacted to produce the condensation product **5a** under the same reaction conditions, which was converted into the corresponding methyl ester **2a** in a 72% overall yield. The disappointing result with **4b** was solved by simply raising the reaction temperature to 50 ℃, from which the methyl ester **2b** was obtained in a 50% overall yield after the in-situ ozonolysis.

Formation of the condensation products **5** could be explained by the three cascade reactions as shown in Scheme 3[18]. The initial nitro-alcohols **6** resulted from the nitro-aldol reaction between **4** and $PhSO_2CH_2NO_2$ were dehydrated in-situ to result in the phenylsulfonylnitroolefin intermediates **7**, which underwent the intramolecular conjugate addition to yield the cyclized adducts **5**. The excellent stereoselectivity (>20:1) for *trans*-oxazolidines **5** could be rationalized by the favored *H*-eclipsed conformation of **7**[27-28]. The slower reactivity by the isopropyl analog **4b** (R = i-Pr) might be also explained from the proposed mechanism (Scheme 3). The dehydration step of **6b** (R = i-Pr) with the bulky isopropyl group would be slower compared to that of **6a** (R = i-Bu) because the increased allylic strains (both $A^{1,3}$ and $A^{1,2}$ strains) between the R group the substituents ($-NO_2$ or $-SO_2Ph$, and -CH=C) on the double bond.

With *trans*-oxazolidine methyl esters **2a** and **2b** in hand that were properly protected forms of β-amino-α-hydroxy acids, the peptide coupling of **2a** and **2b** with L-Leu-OMe afforded the corresponding dipeptide precursors, **3a** and **3b**, in 74% and 76% yields, respectively, after the basic hydrolysis of methyl esters **2** to the corresponding carboxylic acids (not shown). Finally, the global deprotection under the sequential basic and acidic hydrolysis conditions produced the desired isobutyl or isopropyl substituted bestatin analogs, **1a** and **1b**, in more than 95% yields.

4. Conclusions

We have reported an efficient and stereoselective synthesis of two new alkyl substituted bestatin analogs **1** from the appropriately protected β-amino-α-hydroxy acid derivatives **2**, which were in turn successfully prepared with more than 20:1 stereoselectivity from stable α-amino aldehydes **4** via the stereoselective condensation reactions with phenylsulfonylnitromethane followed by the in-situ ozonolysis. Therefore, the isobutyl and isopropyl analogs of bestatin, **1a** and **1b**, were reported for the first time. The new isobutyl and isopropyl analogs of bestatin, **1a** and **1b**, were produced in overall 51% and 38% yields with high stereoselectivity from the corresponding protected α-amino aldehydes **4** in 6 steps, respectively. Further biological tests of the two bestatin analogs will be performed soon.

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