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A short enantioselective synthesis of (−)-bestatin via L-proline-catalyzed α-amination of an aldehyde

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ABSTRACT

A short and high yielding enantioselective synthesis of (−)-bestatin, a naturally occurring aminopeptidase inhibitor, is described via L-proline-catalyzed asymmetric α-amination of 3-phenylpropionaldehyde as the key reaction. The methodology also involves a Pd-catalyzed intramolecular cyclization of an allylic acetate giving a *trans*-oxazoline in a highly diastereoselective manner (dr > 14:1).

The aminopeptidases are a group of exopeptidases that specifically cleave polypeptide chains at the amino terminus. (−)-Bestatin (**1**), a naturally occurring small peptide containing a non-proteinogenic α-hydroxy-β-amino acid at the N-terminus of the peptide chain, is an aminopeptidase inhibitor[1] that exhibits immunostimulatory activity as well as cytotoxic activity. It is used clinically as an oral medication for the treatment of cancer,[2] and shows potential as an anti-inflammatory agent and for the treatment of HIV.[3] The stereochemistry of the hydroxyl as well as the amino groups in (−)-bestatin (**1**) plays a vital role in the biological activity of the molecule. Thus, controlling the stereochemistry at the C-2 and C-3 stereogenic centers for the introduction of the desired (2*S*,3*R*) configuration of the N-terminal component becomes important. A variety of stereoselective methods for the formation of β-amino-α-hydroxy acids have been reported, including aminohydroxylation,[4] reduction of α-keto acid derivatives,[5] nucleophilic addition to chiral aminoaldehydes,[6] olefins,[7] imines,[8] ring opening procedures on chiral epoxides,[9] halocyclocarbamation of allylamines,[10] and transformation of chiral sugars[11] and β-amino acids.[12] Due to its promising biological activity and intriguing structure, more than 25 syntheses of bestatin (**1**) have been reported,[6a,13] many of which utilized unnatural D-phenylalanine as a chiral starting material.[5,6b–e,10,13c,14] As part of our program[15] directed toward expanding the synthetic utility of L-proline-catalyzed asymmetric α-amination, we report a short, efficient method for the enantioselective synthesis of (−)-bestatin (**1**) starting from 3-phenylpropionaldehyde (Scheme 1).

Proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as a practical and versatile organocatalyst.[16] Asymmetric α-amination of aldehydes using proline as the catalyst represents[17] a burgeoning field of synthetic efforts toward synthesizing chiral building blocks, such as α-amino acids and alcohols. Also, the Pd-catalyzed intramolecular cyclization of benzamides via a π-allyl palladium complex is an elegant method for the synthesis of highly functionalized compounds, particularly when chirality transfer is involved.[18] We envisaged that *trans*-oxazoline **8**, obtainable via Pd-catalyzed cyclization of allylic acetate **7**, would be a suitable chiral building block for the synthesis of (−)-bestatin (**1**).

Our synthesis of (−)-bestatin (**1**) started with the α-amination of 3-phenyl-propionaldehyde using List's protocol.[17a] Accordingly, 3-phenylpropionaldehyde **2** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of L-proline (10 mol %) to produce an aminoaldehyde, which upon in situ reduction with $NaBH_4$ afforded the protected aminoalcohol **3**[19] in 92% yield and 95% ee.[20] Aminoalcohol **3** was then subjected to hydrogenolysis [over Raney nickel,[21] H_2 (60 psi), 25 °C] to give the free amine, which was protected (BzCl, Et_3N, THF, 25 °C) as its benzamide **4** in 70% yield over two steps. Oxidation of alcohol **4** with Dess–Martin periodinane gave the corresponding aldehyde **5**, which on reaction with vinylmagnesium bromide in THF at 0 °C afforded allylic alcohol **6** as a 1.1:1 mixture of *syn*/*anti* isomers (determined by ^1H NMR analysis) in 85% yield. Acetylation of **6** (Ac_2O, Py, DMAP, CH_2Cl_2, 25 °C) gave the secondary allylic acetate **7** in 98% yield. The Pd-catalyzed intramolecular cyclization[22] of allylic acetate **7** using $Pd(PPh_3)_4$ and K_2CO_3 in CH_3CN proceeded readily to give the desired *trans*-oxazoline **8**[23] as an inseparable mixture of diastereomers (dr > 14:1, as determined by ^1H and ^{13}C NMR spectral analysis) in 79% yield. Oxidative degradation of the vinylic group in **8** was carried out as indicated in the following sequence of reactions: (i) the olefin function in **8** was initially dihydroxylated (OsO_4, NMO); (ii) the diol so formed was subsequently cleaved on treatment with $NaIO_4$,[24] which gave the corresponding aldehyde; (iii) the crude aldehyde, being labile, was immediately oxidized ($NaClO_2$, NaH_2PO_4),[25] without purification, to the corresponding carboxylic acid **9**. Acid **9** was readily condensed with the benzyl ester of L-leucine (DCC, HOBT in THF)[26] to provide the amide **10** in 70% yield over the four steps. Finally, catalytic hydrogenolysis [20% $Pd(OH)_2/C$, H_2 (75 psi), MeOH/AcOH (9:1),

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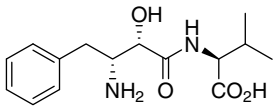
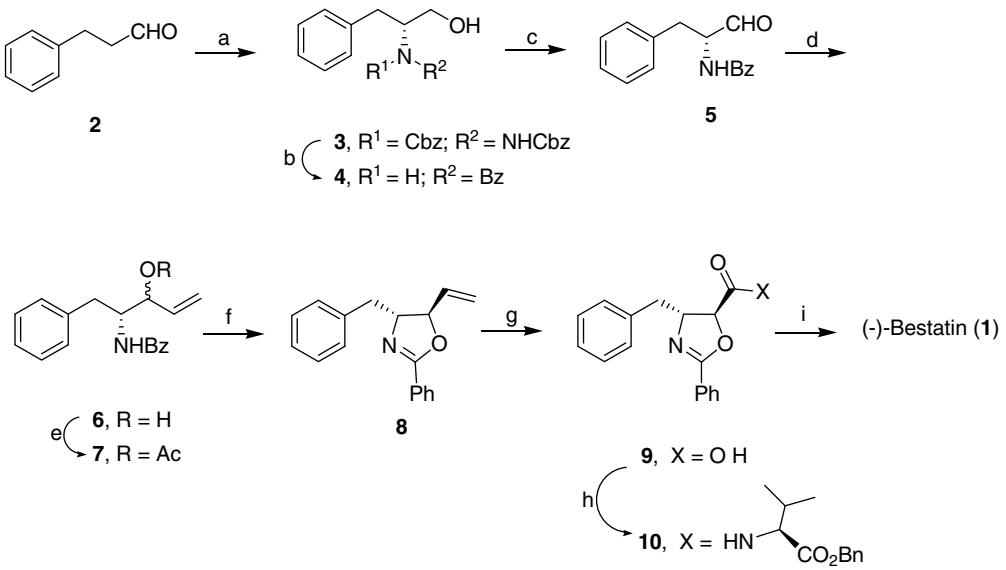


(-)-Bestatin (**1**)



Scheme 1. Reagents and conditions: (a) dibenzyl azodicarboxylate, L-proline (10 mol %), CH_3CN, 0–25 °C, 3 h then $NaBH_4$, EtOH, 0 °C, 30 min, 92%, 95% ee; (b) (i) H_2 (60 psi), Raney nickel, MeOH, AcOH, 25 °C, 20 h; (ii) benzoyl chloride, Et_3N, THF, 0–25 °C, 30 min, 70% (over two steps); (c) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 2 h; (d) CH_2=CHMgBr, THF, 0–25 °C, 1 h, 85% (over two steps); (e) Ac_2O, Py, DMAP, CH_2Cl_2, 25 °C, 12 h, 98%; (f) $Pd(PPh_3)_4$ (5 mol %), K_2CO_3, CH_3CN, reflux, 24 h, 79%, dr > 14:1; (g) (i) OsO_4, 50% aq NMO, acetone/H_2O (9:1), 25 °C, 12 h; (ii) $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (iii) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 25 °C, 2 h; (h) L-leucine benzyl ester·TsOH, DCC, HOBT, THF, 0–25 °C, 16 h, 70% (over 4 steps); (i) 20% $Pd(OH)_2$/C, H_2 (75 psi), MeOH/AcOH (9:1), 25 °C, 36 h, 72%.

25 °C, 36 h][22b] of **10** furnished (-)-bestatin (**1**) in 72% yield {$[\alpha]_D^{25}$ −13.5 (*c* 0.5, 1 N HCl); lit.[26] $[\alpha]_D^{25}$ −14.3 (*c* 0.5, 1 N HCl)}. The spectroscopic data of **1** were in full agreement with those reported in the literature.[26]

In conclusion, we have described a short synthetic route to (−)-bestatin **1** with an overall yield of 22%, which includes a successful application of L-proline-catalyzed asymmetric α-amination of an aldehyde to give the corresponding aminoalcohol in 95% ee. The protocol also demonstrates the synthetic utility of the Pd-catalyzed intramolecular cyclization of benzamide **7** to give *trans*-oxazoline **8** in a highly diastereoselective fashion.

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20. The enantiomeric purity of **3** was determined as 95% by chiral HPLC analysis of the corresponding oxazolidinone obtained from the protected aminoalcohol **3** by following the literature procedure.[17a] HPLC conditions: Kromasil 5-AmyCoat column (250 × 4.6 mm), petroleum ether: *i*-PrOH (90:10), 0.5 mL/min, 254 nm.
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23. Spectral data for **8**: $[\alpha]_D^{25}$ −35.5 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3353, 2945, 2831, 2596, 2044, 1701, 1650, 1450, 1417, 1114, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.85 (dd, *J* = 8.6, 13.7 Hz, 1H), 3.31 (dd, *J* = 5.3, 13.8 Hz, 1H), 4.26–4.36 (m, 1H), 4.81 (t, *J* = 6.6 Hz, 1H), 5.08–5.16 (m, 2H), 5.75 (ddd, *J* = 6.6, 10.2, 17.0 Hz, 1H), 7.27–7.35 (m, 5H), 7.41–7.54 (m, 3H), 8.01–8.05 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.46, 73.75, 84.54, 116.39, 126.51, 128.25, 128.29, 128.43, 129.44, 131.29, 136.21, 137.38, 162.92; Elemental Anal.: $C_{18}H_{17}NO$ (263.33) requires C, 82.10; H, 6.51; N, 5.32. Found: C, 82.43; H, 6.32; N, 5.11.
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