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A total synthesis of (−)-bestatin using Shibasaki's asymmetric Henry reaction

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Abstract—A total synthesis of the potent aminopeptidase inhibitor (−)-bestatin has been achieved using Shibasaki's asymmetric Henry reaction catalyzed by an optically active rare earth lanthanum-(*R*)-binaphthol complex in 26% overall yield.

The α-hydroxy β-amino acid (AHBA) moiety is a common structural fragment in numerous natural products.[1] The presence of this moiety and the stereochemistry of the hydroxy as well as the amino group play a vital role in the biological activity of the molecules containing it. Moreover, a number of their amide derivatives, isolated from bacterial cultures display significant activity against aminopeptidases.[2] One such molecule (−)-bestatin **1** (Fig. 1), a dipeptide, was isolated from *Streptomyces olivoreticulithe* by Umezawa et al. in 1976.[3]

This potent aminopeptidase inhibitor also exhibits immunomodulatory activity[4] and is used clinically as an adjuvant in cancer chemotherapy[5] and in hypertension.[6] Structure-modification studies on bestatin and similar molecules like phebestin **2**[7] and probestin **3**[8] indicated that the presence of *syn*-amino alcohol fragments and the 2*S*-configuration of the α-hydroxy group are important factors for tight interaction with the enzyme.[9]

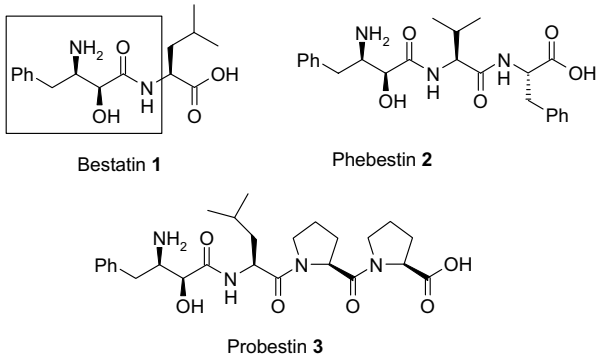

Figure 1.

The biological activity of bestatin has attracted considerable interest in its total synthesis.[10] However, most of the reported syntheses still have difficulties in controlling the stereochemistry at the C-2 and C-3 stereogenic centres for the introduction of the desired (2*S*,3*R*)-configuration of the *N*-terminal component.

In continuation of our interest on the synthesis of pharmacologically important natural products using aliphatic nitro compounds,[11] we report here a potentially significant route to (−)-bestatin that is not only considerably shorter and higher in yield, but also experimentally much simpler involving Shibasaki's asymmetric Henry reaction as the key step.

Treatment of ethyl glyoxalate with 2-phenyl-1-nitroethane as per the procedure described by Shibasaki et al.[12] at −50 °C in the presence of the La-(*R*)-BINOL catalyst[13] (10 mol %) in THF provided (2*S*,3*R*)-**4** in 81% yield and 93% ee[14] as the sole product (Scheme 1). The assigned C-2, C-3 relative stereochemistry rested on the observed coupling constant ($J_{2,3} = 3.6$ Hz). Our attempt to reduce selectively the nitro group in the presence of the ester using $NaBH_4$ (2.5 equiv) and Pd–C in THF[15] was unsuccessful and resulted in reduction of the ester to an alcohol with survival of the nitro group. We then

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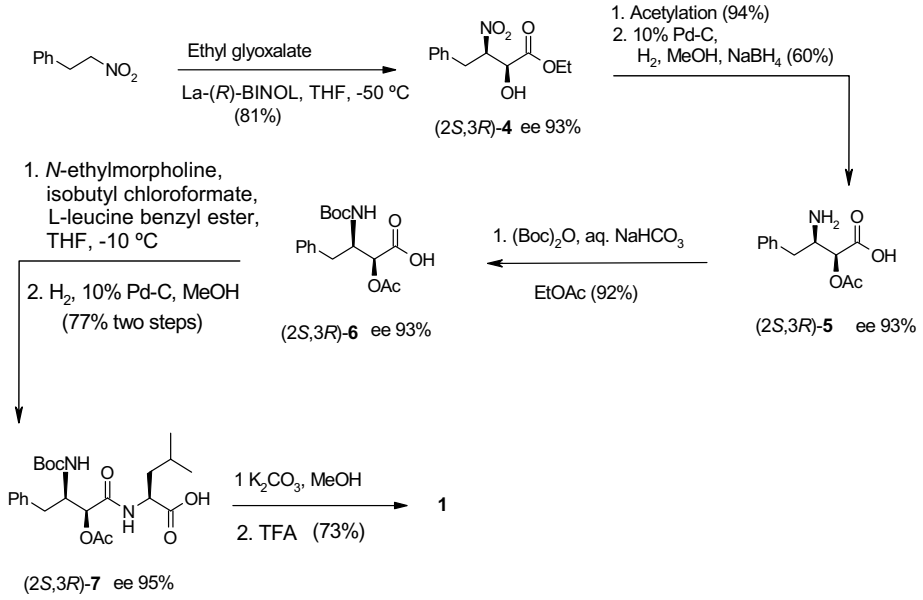

Scheme 1.

tried the reaction with $NaBH_4$ in the presence of $Cu(OAc)_2$,[16] but we observed only decomposition of the starting material. Therefore, the nitroaldol product was acetylated under standard conditions and the resulting nitroacetate hydrogenated with 10% Pd–C at 1 atm H_2 in methanol in the presence of $NaBH_4$ (0.5 equiv) furnished the aminoacetate (2*S*,3*R*)-**5** in 60% yield. Boc-protection of the amino group provided (2*S*,3*R*)-**6** in 92% yield. Coupling of the protected β-amino α-hydroxy acid (2*S*,3*R*)-**6** with the benzyl ester of L-leucine and subsequent hydrogenation delivered (2*S*,3*R*)-**7** in 77% yield over two steps. Finally, deprotection of both the protecting groups in two-steps furnished the target molecule, which had physical and spectral properties identical with those reported in the literature.[3a]

In conclusion, we have demonstrated a short and efficient route to (−)-bestatin, which may also be applicable to several other substituted analogues such as phebestin and probestin, or molecules like statin, norstatin, microgenin, etc.

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