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An Enantiodivergent Synthesis of *threo* β-Amino Alcohols: Preparation of Key Intermediates for Bestatin and the Related Peptides

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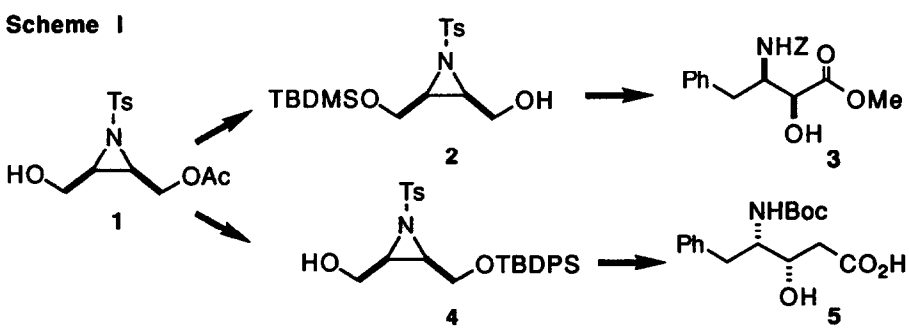
Abstract: An enantiodivergent method for preparation of *threo* β-amino alcohols and *threo* 1,2-diamines has been developed starting with a chiral aziridine **1**. Unusual amino acid derivatives **3** and **5**, which are key synthetic intermediates for bestatin and the related peptides, have been prepared.

Unusual amino acids containing a *threo* β-hydroxyamino group have been found in many biologically active peptides such as bestatin[1], pepstatin[2], and cyclosporine.[3] These amino acids appear to be critically involved in the biological activity. Due to the pharmacological importance of these peptides as well as potential utility of β-amino alcohols as hydroxyethylene dipeptide isosteres,[4] considerable efforts have gone into stereocontrolled synthesis of β-amino alcohols.[5] We report here an enantiodivergent synthesis of *threo* β-amino alcohols starting with a chiral aziridine **1**. To demonstrate our strategy, we have chosen two biologically important *threo* β-amino alcohols as target molecules (Scheme I). One is methyl (2*S*, 3*R*)-3-{*N*-(benzyloxycarbonyl)-amino}-2-hydroxy-4-phenylbutanoate (**3**), a key synthetic intermediate for bestatin.[1b,d] Bestatin is a specific inhibitor of aminopeptidase B and is known to show antitumor activity through activation of immune system.[1c] The other one is (3*S*, 4*S*)-*N*-(*tert*-butoxycarbonyl)-4-amino-3-hydroxy-5-phenylpentanoic acid [(3*S*, 4*S*)-Boc-AHPPA] (**5**), a key synthetic intermediate for a potent pepsin-inhibitory peptide.[6a] AHPPA is also a constituent of a potent renin-inhibitor, ahpatinin G.[6b,7]

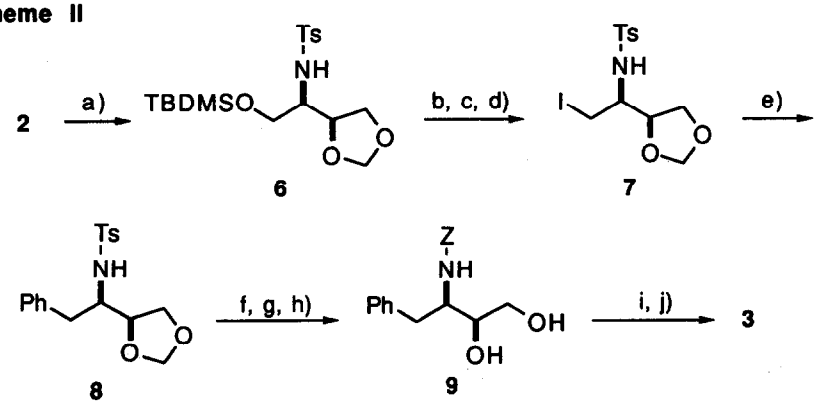
Scheme I



The optically active (≥95% ee) aziridine **1** was obtained by enzymatic transesterification of the corresponding *meso-diacetate*.[8] Silylation of **1** with TBDMS chloride followed by removal of acetyl group (K_2CO_3 in methanol) afforded **2** in 96% yield. On the other hand, **4** was prepared in 89% overall yield through the following sequence: i) ethoxyethylation of the hydroxy group of **1** (ethyl vinyl ether, *p*-TsOH), ii) hydrolysis of the acetate (K_2CO_3, MeOH), iii) silylation of the resulting alcohol (TBDPS chloride, NEt_3, DMAP), iv) removal of the ethoxyethyl group (0.5 M HCl, THF). Thus, a pair of *pseudo-enantiomers*, **2** and **4**, were obtained from **1**. Transformation of **2** into **3** is shown in Scheme II. Regioselective aziridine-ring opening of **2** by S_N2 attack of the hydroxide anion of the hemiacetal formed *in situ*[9] afforded **6** in 88% yield. Removal of the silyl protecting group, tosylation, followed by substitution with iodide ion gave an iodide **7** in 80% yield. Phenyl group was introduced in high yield by treatment of **7** with diphenyl cupper lithium. Conversion of **8** to **9** was accomplished through a sequence of removal of the tosyl group under Birch conditions, removal of the methylene acetal by acidic alcoholysis, and benzyloxycarbonylation of the resulting dihydroxy amine. Selective oxidation of the primary alcohol of **9** in the presence of the secondary one was performed by means of molecular oxygen oxidation catalyzed by platinum oxide.[10] Methylation of the resulting a-hydroxy acid afforded **3** in 75% yield, mp 99-100 °C and $[\alpha]_{577}$ +83° (*c* 0.74, MeOH) {*lit.*[1d] mp 94-95 °C and $[\alpha]_{578}$ +82° (*c* 0.81, MeOH)}. The spectral data were identical with those reported.[1d]

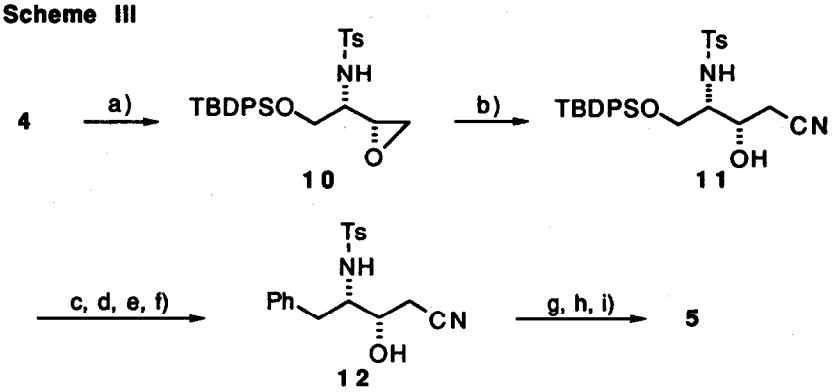
Transformation of **4** into **5** is shown in Scheme III. On base treatment, the aziridine **4** was converted into a epoxide **10** via intramolecular S_N2 replacement by the hydroxide anion. Nucleophilic opening of the epoxide **10** by cyanide ion with the aid of lithium perchlorate[11] proceeded regioselectively to give **11** in 95% yield. Conversion of the TBDPS ether into a phenyl group was performed by the similar four-step sequence employed for the conversion of **6** to **8**, affording **12** in 55% overall yield. Hydrolysis of the cyano group, Birch reduction, followed by *t*-butoxycarbonylation furnished **5**, mp 147-149 °C and $[\alpha]_D$ -39° (*c* 0.38, MeOH) {*lit.*[6a] mp 148-148.5 °C, $[\alpha]_D$ -37° (*c* 1.1, MeOH)}. The spectral data were identical with those reported.[6a]

Scheme II



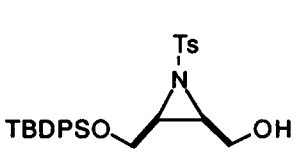
a) $CsCO_3$, HCHO / CH_3CN, 88%, b) Bu_4NF / THF, c) TsCl / Py, d) NaI / acetone, 80% (3 steps), e) Ph_2CuLi / THF, 97%, f) Na / NH_3, g) HBr / MeOH, h) Z-Cl, $NaHCO_3$ / MeOH-H_2O, 71% (3 steps), i) O_2, PtO_2 / H_2O, j) CH_2N_2 / THF, 75% (2 steps)

Scheme III



a) *t*-BuOLi / HMPA-THF, 95%, b) KCN, $LiClO_4$, / CH_3CN, 95%, c) Bu_4NF / THF, d) TsCl / Py, e) NaI / acetone, f) Ph_2CuLi / THF, 55% (4 steps), g) NaOH / H_2O_2 -H_2O, h) Na / NH_3, i) $(Boc)_2O$, NaOH / dioxane-H_2O, 40% (3 steps)

To extend the present enantiodivergent strategy, a pair of enantiomers of a *threo* 1,2-diamine derivative were prepared. Chiral aziridine **13**, an enantiomer of **4**, was prepared in 80% yield by silylation of **1** with TBDPS chloride followed by hydrolysis of the acetate. Aziridino alcohol **13** was first converted to the benzylurethane derivative (BnNCO, *i*Pr2NEt, toluene), which was then treated with potassium *t*-butoxide in THF,[12] yielding a cyclic urethane **14** in 74% yield through regioselective opening of the aziridine ring,[13] $[\alpha]_D$ +48° (*c* 1.7, $CHCl_3$). Similarly, aziridine **4** was converted into **15** in 82% yield, $[\alpha]_D$ -47° (*c* 1.5, $CHCl_3$). The enantiomeric pair of the chiral diamine derivatives **14** and **15**, are expected to be potentially useful chiral ligands in asymmetric synthesis.[14] In conclusion, we have established a method for a preparation of an enantiomeric pair of *threo* β-amino alcohols as well as *threo* 1,2-diamines starting with a chiral aziridine **1**.



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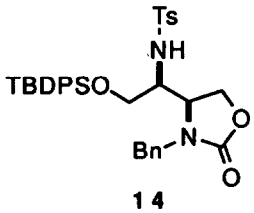

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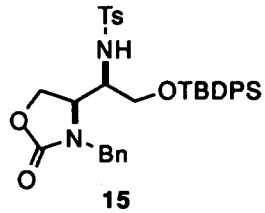

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7. The absolute configuration of AHPPA contained in ahpatinin G has not been referred.[6b] However it is reasonably assumed that it must to be (3*S*, 4*S*) since the configuration is an essential requirement for the biological activity of the related peptides, see reference 6a and also; Rich, D. H. *J. Med. Chem.*, **1985**, *28*, 263.
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13. The presence of a five-membered urethane ring rather than a six-membered one was evident from its IR spectrum [ν_{max} ($CHCl_3$) 1745 cm^{-1}].
14. For examples, see: a) Oishi, T.; Hirama M. *J. Org. Chem.*, **1989**, *54*, 5834. b) Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis*, **1990**, 1023.

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