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VERSATILE SYNTHETIC ROUTES TO *THREO*-β-AMINO HYDROXY CARBOXYLIC ACIDS, STATINE AND ITS ANALOGUES

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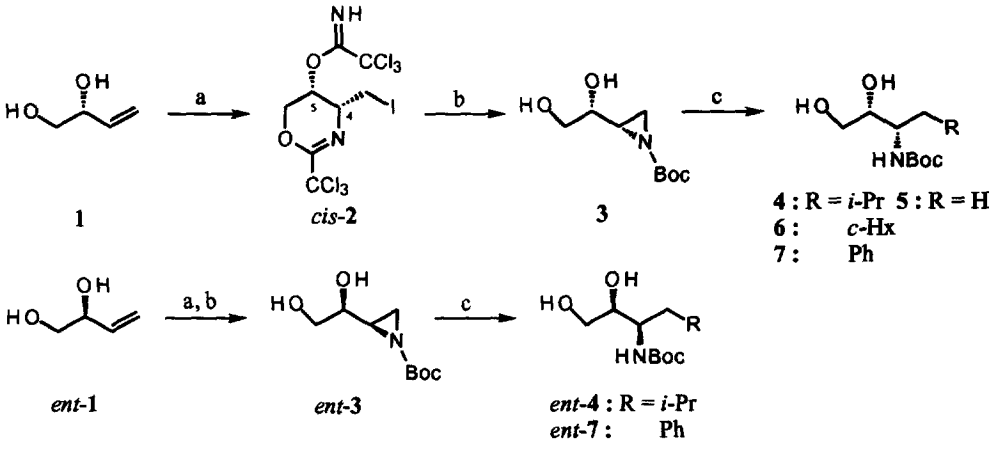
Abstract : Efficient syntheses of statine and its analogues have been attained from aziridine diols **3** and *ent*-**3**, which were prepared *via* iodocyclization of trichloroacetimidates of chiral 3-buten-1,2-diols **1** and *ent*-**1**.

Optically active vicinal *threo*-amino hydroxy carboxylic acids are considered as physiologically valuable compounds.[1] The representative examples are statine and its analogues. Statine[2] is the key constituent amino acid of the naturally occurring pentapeptide pepstatin, which is a strong inhibitor of aspartic proteases such as renin, pepsin and cathepsin D. Since angiotensinogen is converted into angiotensin I by renin, its inhibitors are expected to serve as potential therapeutic agents of hypertension and congestive heart failure. Based on the transition state model of the interaction between renin and angiotensinogen, norstatine[3] and cyclohexylnorstatine[4] were also successfully incorporated into substrate analogues in the development of renin inhibitors. Their observed biological activities are certainly attributed to the inertness to proteolytic cleavage as dipeptide isosteres.[5] Other *threo*-β-amino hydroxy acids are found in amastatin and bestatin, which inhibit aminopeptidase A or B and leucine aminopeptidase. Amastatin has (2*S*, 3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (AHMHA)[6] and bestatin contains (2*S*, 3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA).[7] Herein we describe stereocontrolled and versatile syntheses of the described *threo*-β-amino hydroxy carboxylic acids.

To secure the required *threo*-β-amino alcohols, iodocyclization of olefinic trichloroacetimidate[8] was attempted. (*R*)-Butenediol **1**[9] was treated with trichloroacetonitrile and DBU in acetonitrile at -20 °C, and the resulting imidate was cyclized *in situ* by adding iodine and sodium bicarbonate at 0 °C to give a 28:1 mixture of dihydro-1,3-oxazines *cis*-**2** and *trans*-**2** in 91% yield along with less than 5% of the corresponding oxazolidines. Alternatively, formation of the imidate in propionitrile followed by its *in situ* cyclization using iodine monobromide at -90 °C provided only **2** in 98% yield with the similar level of stereoinduction (Scheme 1). The 6-membered ring structure and the stereochemistry of *cis*-**2** was unambiguously deduced by C=N stretching band[10] at 1673cm^{-1} and the coupling constant J_{H_4, H_5} of 3.0Hz. After chromatographic removal of *trans*-isomer, *cis*-**2**, $[\alpha]_D^{18}$+80.8 ($CHCl_3$, c 0.79) was deprotected completely under acidic conditions and then cyclized into aziridine with sodium bicarbonate in methanol. Although *in situ* treatment of the generated aziridine with di-*t*-butyl dicarbonate afforded the desired *N*-*t*-Boc-aziridine **3**, the aziridine ring was opened by iodide anion to some extent during work-up. This difficulty was overcome by doing the protection reaction in THF to produce **3**, $[\alpha]_D^{17}$ -44.7 ($CHCl_3$, c 0.79) in 89% overall yield.

Conversion of **3** into carbamates **4** and **6** was performed through a three-step sequence in one-pot. After protection of **3** as trimethylsilyl (TMS) ether, it was subjected to isopropyl- and cyclohexylmagnesium chloride in THF in the presence of dilithium tetrachlorocuprate followed by acidic work-up to furnish **4**,

Scheme 1

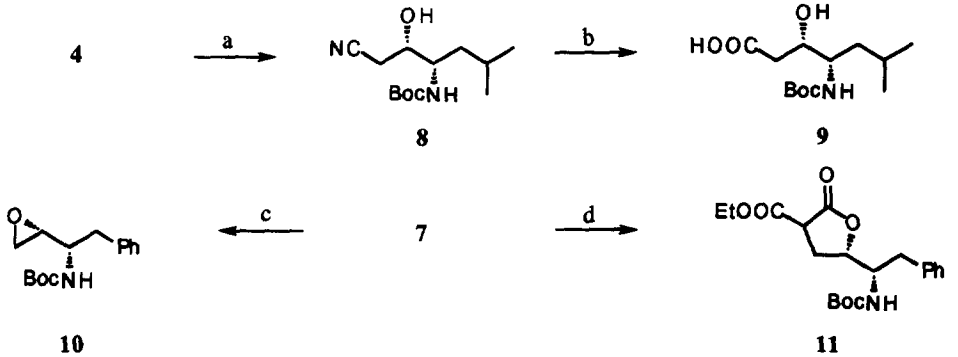


Reagents : a. Cl_3CCN/DBU/EtCN/-20 °C ; IBr/K_2CO_3/-90~-78 °C. b. 6N HCl/MeOH/rt ; $NaHCO_3$/MeOH /rt ; Boc_2O/THF/-30 °C. c. TMSCl/Et_3N/THF/rt ; For **4** or **6** : *i*-PrMgBr or *c*-HxMgCl/Li_2CuCl_4/-30~0 °C ; For **7** : PhMgBr/CuBr·SMe_2/$PhCH_3$; acidic (pH ≈ 3) work-up.

$[\alpha]_D^{17}$-45.5 ($CHCl_3$, c 0.83) and **6**, $[\alpha]_D^{16}$-35.0 ($CHCl_3$, c 0.80) in 77% and 87% overall yield, respectively. It was observed that the isopropyl Grignard reagent yielded about 10% of carbamate **5** derived from hydride transfer.[11] Phenyl derivative **7**, $[\alpha]_D^{17}$-36.5 ($CHCl_3$, c 1.35) was generated in 88% overall yield by performing the cuprate reaction with phenylmagnesium bromide in toluene in the presence of cuprous bromide-dimethyl sulfide complex. On the other hand, the enantiomers of **4** and **7** *i.e.* *ent*-**4**, $[\alpha]_D^{15}$+45.3 ($CHCl_3$, c 0.53) and *ent*-**7**, $[\alpha]_D^{15}$+36.9 ($CHCl_3$, c 0.45) were obtained from (*S*)-butenediol *ent*-**1**[9] by the same sequence as described.

Sequential treatment of **4** with tosyl chloride in pyridine and sodium cyanide in DMSO gave nitrile **8**, $[\alpha]_D^{16}$-57.2 ($CHCl_3$, c 0.57) in 77% yield (Scheme 2). Acidic hydrolysis of **8** generated the desired carboxylic

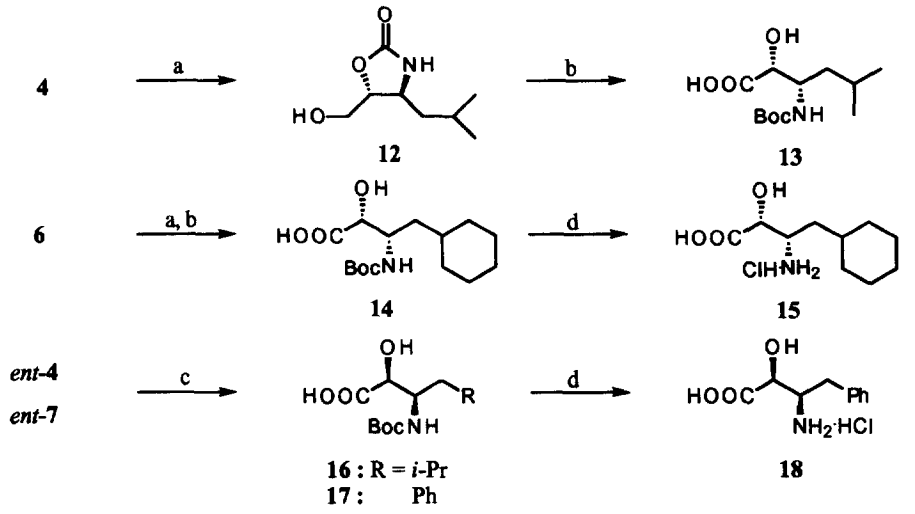
Scheme 2



Reagents : a. TsCl/pyridine/0 °C ; NaCN/DMSO/60 °C. b. 6N HCl/reflux ; Boc_2O/$NaHCO_3$/MeOH/rt. c. TsCl/pyridine/0 °C ; aqueous NaOH/0 °C. d. TsCl/pyridine/0 °C ; $CH_2(COOEt)_2$/EtONa/EtOH/rt.

acid with concomitant deprotection of *t*-Boc group. Subsequently, the resulting amino acid was protected with di-*t*-butyl dicarbonate to provide *N*-*t*-Boc-statine **9**, $[\alpha]_D^{16}$ -38.8 (MeOH, c 0.57) in 93% overall yield.[12] In addition, diol **7** was converted into epoxide **10**, $[\alpha]_D^{18}$+14.4 ($CHCl_3$, c 0.31) and lactone **11** *via* monotosylate in 86% and 60% overall yield, respectively. They were previously employed as precursors of hydroxyethylene dipeptide isosteres for the development of peptidase inhibitors.[12a, 13]

Scheme 3



Reagents : a. KOH/THF/MeOH/H_2O/rt. b. Jones reagent ; 6N HCl/sealed tube/120 °C ; Boc_2O/$NaHCO_3$/ MeOH/rt. c. O_2/PtO_2/dioxane/H_2O/rt. d. 6N HCl/100 °C.

Cyclization of **4** with potassium hydroxide afforded oxazolidinone **12** in 85% yield. It was sequentially oxidized by using Jones reagent, deprotected under acidic conditions and then protected with di-*t*-butyl dicarbonate to produce *N*-*t*-Boc-norstatine **13**, $[\alpha]_D^{16}$-49.5 (MeOH, c 0.28)[14] in 51% overall yield. Oxidation of **6**, *ent*-**4** and *ent*-**7** with oxygen in the presence of platinum oxide[15] furnished *N*-*t*-Boc-cyclohexylnorstatine **14**, $[\alpha]_D^{17}$ -44.0 (MeOH, c 0.18), *N*-*t*-Boc-AHMHA **16**, $[\alpha]_D^{14}$+49.9 (MeOH, c 0.23) and *N*-*t*-Boc-AHPBA **17**, $[\alpha]_D^{15}$+62.9 (MeOH, c 0.25) in 60%, 68% and 69%, respectively. The optical purities of **14** and **17** were confirmed by converting them into cyclohexylnorstatine·HCl **15**, $[\alpha]_D^{18}$-11.3 (H_2O, c 0.29)[16] and AHPBA·HCl **18**, $[\alpha]_D^{12}$ +28.0 (1N HCl, c 0.18).[17] Our synthetic compounds showed satisfactory spectroscopic as well as physical data identical with those reported.

In conclusion, we established a practical synthetic route to *threo*-β-amino alcohols and showed their versatile transformation into statine and its structurally related analogues.

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