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AN ENANTIOSPECIFIC AND VERSATILE SYNTHESIS OF STATINE

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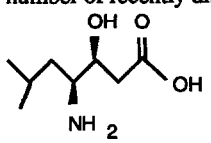
Abstract : A short, enantiospecific synthesis of statine is described, starting from a readily available aldehyde The control of chirality was effected by using the Sharpless asymmetric epoxidation procedure

Statine, (3S, 4S)-4-amino-3-hydroxy-6-methyl-heptanoic acid (**1**), is an unusual amino acid, the key constituent of a number of recently discovered bioactive peptides[1]

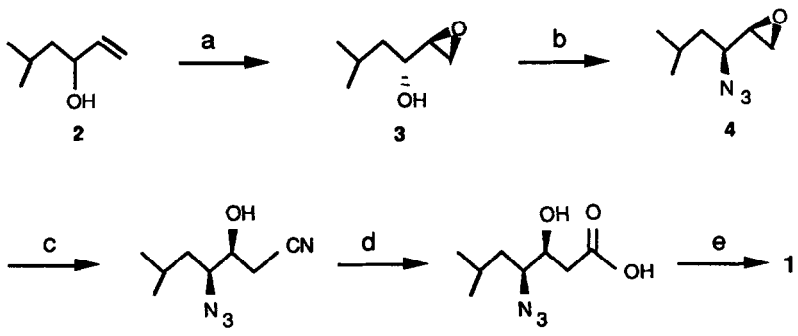


1

Among them pepstatin, an inhibitor of proteolytic enzymes such as pepsin and cathepsin and the blood pressure regulating enzyme renin[1c], has aroused considerable attention for the practical synthesis of this particular amino acid[2]

Most of the published syntheses are based on a nucleophilic addition to an N-protected chiral amino aldehyde Although these routes give a straightforward access to statine, they suffer from two limitations the chiral uncertainty which is associated with the chiral unstability of the starting aldehyde and the low structural versatility of the products, limited to the available amino acids.

To obviate these difficulties we describe here an enantiospecific and versatile route to statine



2 **3** **4** **5** **6**

a- Diisopropyl-D-tartrate, Ti(IV) isopropoxide, tBHP, CH_2Cl_2, -10°, b- diethyl azodicarboxylate, Ph_3P, N_3H,CH_2Cl_2, c- KCN, MeOH, d- NaOH, H_2O_2, e- H_2, Pd/C, MeOH

The racemic allylic alcohol **2** was obtained via a Grignard reaction of isovaleraldehyde with vinyl magnesium bromide Enantiospecific Sharpless epoxidation of this alcohol in the presence of diisopropyl-D-tartrate constituted the key step for the introduction of chirality[3] The resulting optically pure epoxide **3** was transformed into the corresponding inverted azide **4** by the Mitsunobu reagents[4] The chiral purities of **3** and **4** were demonstrated by n m r spectroscopy in the presence of a chiral shift reagent[5][^{1}H NMR, 300 MHz, chiral Eu(hfc)$_3$] Nucleophilic opening of the epoxide with cyanide ion occurred readily and regiospecifically to give the nitrile **5** Subsequent hydrolysis of **5** afforded the acid **6** which was subsequently catalytically reduced to statine **1**[6]

Since the variety of starting aldehyde is quite unlimited and the stereochemistry is reagent controlled, we believe that this route could provide a great number of statine analogs on a large scale

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6- The physical constants of all the compounds described are in agreement with the assigned structures The $[\alpha]^{20}_D$ values and n m r data for typical compounds are as follows **3** $[\alpha]^{20}_D$ = + 8 7 (c 0 1, methanol), ^{13}C NMR ($CDCl_3$) δ(22 01, 23 54, 24 43, 42 51, 43.55, 55 07, 66 87) **4** $[\alpha]^{20}_D$ = - 8 (c 0 1, methanol), ^{13}C NMR ($CDCl_3$) δ(21 86, 23 04, 24 76, 39 99, 44 85, 54 71, 61 89) **5** $[\alpha]^{20}_D$ = - 16 (c 0 12, methanol), ^{13}C NMR ($CDCl_3$) δ(21 67, 22 99, 23 45, 24 96, 39 13, 62 74, 69 87, 117 34) **6** $[\alpha]^{20}_D$ = - 21 (c 0 14, methanol), ^{13}C NMR ($CDCl_3$) δ(21 66, 23 10, 24 99, 38 52, 39 11, 63 40, 70 33, 177 41) **1** $[\alpha]^{20}_D$ = - 21 (c 0 17, H_2O), [lit[7] $[\alpha]^{20}_D$ = - 20 (c 0 64, H_2O)], ^{13}C NMR (D_2O) δ(23 47, 24 68, 26 47, 40 80, 41 39, 56 31, 69 94, 177 73)

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