Diastereoselective Epoxidation of *cis*-4-Amino Allylic Alcohol with *m*-Chloroperbenzoic acid. An Efficient Synthesis of Statine

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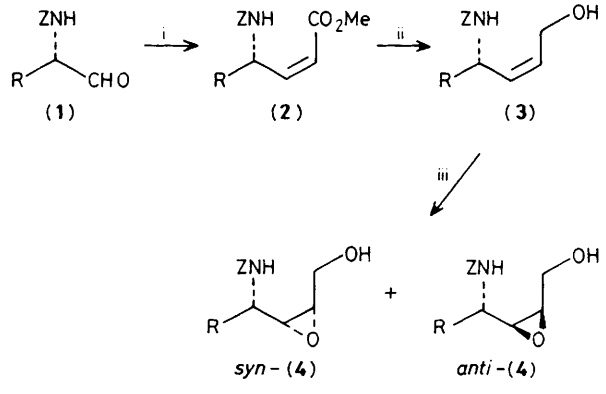
High diastereoselective epoxidation of *cis*-4-amino allylic alcohol (**3**) with *m*-chloroperbenzoic acid is described and the reaction is applied to the stereoselective synthesis of the β-hydroxy-γ-amino acid, statine.

The epoxide functional group is one of the most useful intermediates in organic synthesis.[1] Stereoselective epoxidation of allylic alcohols has been used for the synthesis of macrolides, polyethers, sugars, and other types of natural products.[2] Recently, Kishi reported a method of preparing polyols *via* stereoselective epoxidation of *cis*-allylic alcohol derivatives with peracid based on the co-operative effect concept.[3]

This communication describes a highly diastereoselective synthesis of *syn* amino epoxide, a useful synthetic intermediate for the synthesis of *syn* β-hydroxy-γ-amino acids, a component of biologically important peptides. The basis of the synthesis is the epoxidation of a *cis*-4-amino allylic alcohol, with the amino group protected by a carbonyl group that can form a hydrogen bond with the peracid.

Readily available *N*-benzyloxycarbonyl α-amino aldehyde (**1**) prepared from the α-amino acid without any racemization,[4] was converted into the *cis*-γ-amino-α,β-unsaturated ester (**2**) with the anion derived from $(CF_3CH_2O)_2P(O)CH_2CO_2Me$[5] (1 equiv.) (*cis* isomer >30 : 1) (Scheme 1). The pure *cis*-γ-amino-α,β-unsaturated ester (**2**) was reduced with diisobutylaluminium hydride (DIBAL) (2 equiv.) to *cis*-4-amino allylic alcohol (**3**).† The *m*-chloroperbenzoic acid (MCPBA) (3 equiv.) epoxidation of the *cis*-4-amino allylic alcohol (**3**) yielded almost exclusively the *syn* epoxide (**4**). The results are summarized in Table 1. The highly diastereoselective epoxidation of (**3**) can be explained in terms of the co-operative effect reported by Kishi.[3] Namely, it is postulated that the hydroxy group of the allylic alcohol and the carbonyl oxygen form hydrogen bonds with the peracid in the transition state as shown in Figure 1.

Since this approach proved to be successful, we undertook the stereoselective synthesis of the novel *syn* β-hydroxy-γ-



Z = benzyloxycarbonyl

Scheme 1. *Reagents:* i, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6–MeCN, $(Me_3Si)_2NK$, tetrahydrofuran (THF), −78 °C; ii, DIBAL, CH_2Cl_2, −78 °C; iii, MCPBA, CH_2Cl_2, −10 °C.

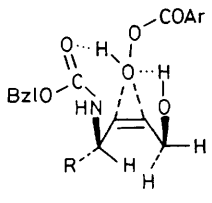


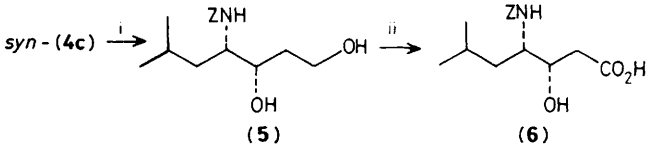
Figure 1

† Recently, it has been reported that reduction of the trans-γ-amino-α,β-unsaturated ester with DIBAL preferentially gave the 1,4-reduction product (ref. 6).

Table 1. Diastereoselective epoxidation of *cis*-4-amino allylic alcohols.

Entry	Aldehyde (**1**)	Yield/%[a] (**2**)	(**3**)	(**4**)	Isomer ratios[b] *syn* : *anti*
1	**a**; R = Me	86	73	98	10 : 1
2	**b**; R = Pr^i	95	76	99	28 : 1
3	**c**; R = Bu^i	86	75	98	21 : 1
4	**d**; R = $PhCH_2$	89	86	98	21 : 1
5	**e**; R = $MeCHCH_2$ (OBu^{t}Me$_2$Si)	85	72	98	20 : 1
6	**f**; ZNC(H)(CHO)$CH_2CH_2CH_2$	79	53	98	16 : 1

[a] Isolated yield. [b] Determined by h.p.l.c. and/or ^{1}H n.m.r. analyses.



Scheme 2. *Reagents:* i, Red-Al, THF, 0 °C; ii, Pt, O_2, $NaHCO_3$, H_2O, room temperature.

amino acid, statine,[7] in the form of its *N*-benzyloxycarbonyl derivative (**6**). The *syn* epoxide (**4c**), {$[\alpha]_D^{25}$ 16.7° (*c* 0.93, MeOH), m.p. 99—100 °C} was treated with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (2 equiv.) to give the *syn* amino diol (**5**) {$[\alpha]_D^{25}$ −35.5° (*c* 0.97, MeOH), m.p. 89—90 °C} with the desired regioselective epoxide opening[8] in 93% yield. Selective oxidation of the primary alcohol with air in the presence of a platinum catalyst[9] resulted in a 95% yield of *N*-benzyloxycarbonyl statine (**6**) {$[\alpha]_D^{25}$ −34.1° (*c* 1.25, MeOH), m.p. 117—118 °C}. Comparison with a sample‡ of (**6**) {$[\alpha]_D^{25}$ −33.9° (*c* 1.32, MeOH), m.p. 117—118 °C} made from natural statine, by ^{1}H n.m.r., optical rotation, and melting point confirmed its absolute configuration as that of statine.[10]

The method provides an efficient synthesis of the *syn*-δ-amino-β,γ-epoxy alcohol (**4**) which is a useful starting material for the formation of various β-hydroxy-γ-amino acids or amino polyols.

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‡ The natural statine used to prepare (**6**) was purchased from Sigma.

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