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Practical Preparation of α-Hydroxy-β-Amino Ester Units; Stereoselective Synthesis of Taxol Side Chain and Norstatine

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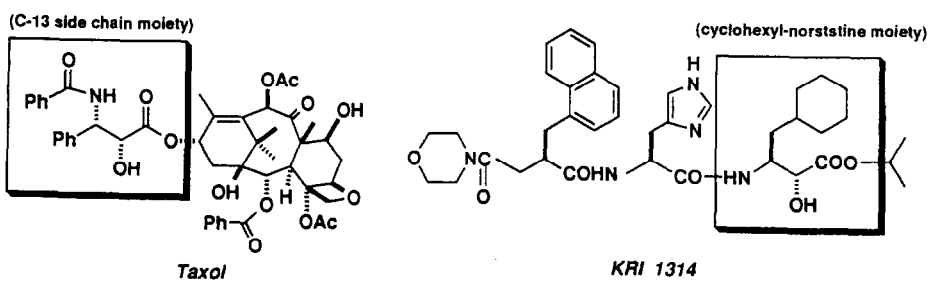
Abstract: An asymmetric reaction of chiral imines with α-silyloxy ketene acetals mediated by chiral boron reagents is described. The key to its success is the use of the chiral boron complex prepared *in situ* from (*R*)- or (*S*)-binaphthol and B(OPh)3. Both diastereomers of α-hydroxy-β-amino ester units are successfully prepared with high selectivities by the chiral boron reagents depending on the geometry of the silyl ketene acetals. The optically pure anti α-hydroxy-β-amino ester is obtained from (*E*)-silyl ketene acetal, while the corresponding syn α-hydroxy-β-amino ester is obtained from (*Z*)-silyl ketene acetal. The method can be efficiently applied to the stereoselective synthesis of taxol C-13 side chain and the norstatine family.

Some medicinally important compounds involve optically active α-hydroxy-β-amino ester units as their key components: taxol, for example, a complex diterpene, is currently considered the most exciting substance in cancer chemotherapy.[1] Taxol possesses high cytotoxicity and strong antitumor activity against cancers which have not responded well to treatment by existing antitumor drugs. It should be noted that the C-13 side chain, N-benzoyl-(2*R*,3*S*)-3-phenylisoserine moiety, is essential for the potent antitumor activity.[2] Accordingly, investigation of the structure-activity relationship for the taxol side chain analogs with some modification appears quite promising to find more effective pharmacological properties. Another example, renin, an asparatic protease, generates angiotensin I from angiotensinogen, and a large number of inhibitory peptides of

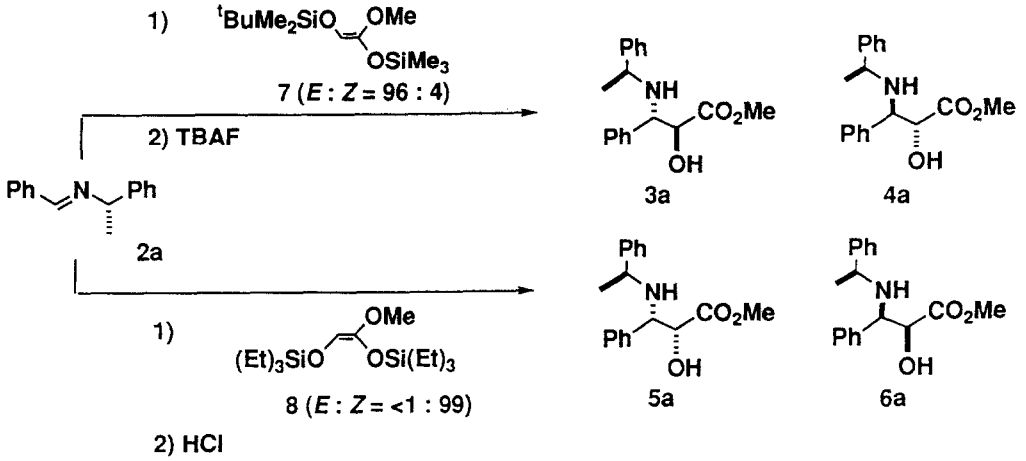
Fig I



human renin have been studied for their potential as agents of antihypertensive therapy.[3] KRI-1314, which is one of the renin inhibitors developed for its promise of antihypertensive activity with oral efficacy, bears isopropyl (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyrate, cyclohexylnorststine, at its active site.[4]

Optically active α-hydroxy-β-amino ester, therefore, is essential to promote the activity, making development of a general method for this unit extremely important to further research in the therapeutic area. Unfortunately, however, though a number of methods have been developed, only a few have proven useful.[5,6] Herein we would like to describe a novel technique which is flexible and practical, both for the preparation of diastereomers of the optically active α-hydroxy-β-amino esters and for application in the stereoselective synthesis of the optically pure taxol side chain and the norstatine family.

Table I. Aldol Reaction Mediated by Lewis Acids[a]

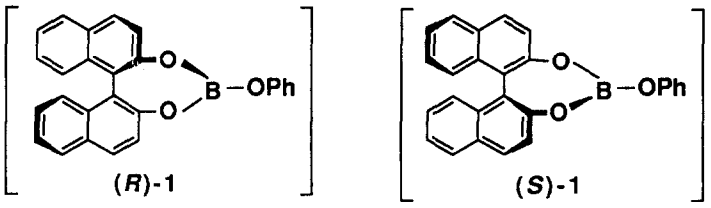


Entry	Lewis acid	Silyl ketene acetal	Yield (%)[b]	Anti (**3a** : **4a**) / Syn (**5a** : **6a**)[c]
1	$TiCl_4$	7	79	56 (89 : 11) / 44 (89 : 11)
2		8	88	21 (84 : 16) / 79 (91 : 9)
3	BF_3OEt_2	7	80	69 (94 : 6) / 31 (89 : 11)
4		8	91	11 / 89 (92 : 8)
5	$ZnCl_2$	7	58	67 (92 : 8) / 33 (80 : 20)
6		8	40	15 / 85 (95 : 5)
7	TMSiOTf	7	52	55 (94 : 6) / 45 (90 : 10)
8		8	47	3 / 97 (95 : 5)
9	$B(OPh)_3$	7	75	80 (93 : 7) / 20
10		8	89	13 / 87 (93 : 7)

[a] Aldol reactions were carried out in dichloromethane using 1 equiv of Lewis acid and 1.2 equiv of silyl ketene acetal at -78°C for 8 h. [b] Isolated yield. [c] Ratio was determined by HPLC.

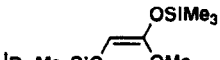
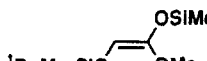
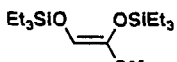
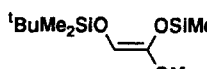
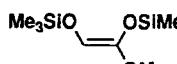
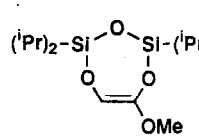
We set about constructing the α-hydroxy-β-amino ester units by aldol reaction of chiral imines with (*E*)- and (*Z*)-silyl ketene acetals derived from α-silyloxy esters with high syn/anti selectivity and diastereofacial selectivity of the products. First, several Lewis acid mediators were utilized in the aldol reaction of the chiral imine **2a** with (*E*)-2-*tert*-butyldimethylsilyloxy-1-methoxy-1-trimethylsilyloxy-ethylene **7** and (*Z*)-1-methoxy-1,2-di(triethylsilyloxy) ethylene **8**.[7] After screening several Lewis acids, it was found that the anti aldol adduct was obtained in the case of $B(OPh)_3$ mediated reaction with *E*-ketene acetal **7** in moderate selectivity, while the syn aldol adduct was preferentially produced in the reaction with Z-ketene acetal **8** by employing every Lewis acid shown in Table I. However, using these typical Lewis acids poses problems in selectivity or reactivity for the preparation of α-hydroxy-β-amino esters.

In a previous study, we described that the asymmetric synthesis of chiral imine in the presence of chiral boron complex **1** is an efficient and practical method for the selective construction of enantiomerically pure piperidine alkaloids and β-lactams.[8] This "*double stereodifferentiation technology*" also seems to apply to the novel construction of the optically active α-hydroxy-β-amino ester units.

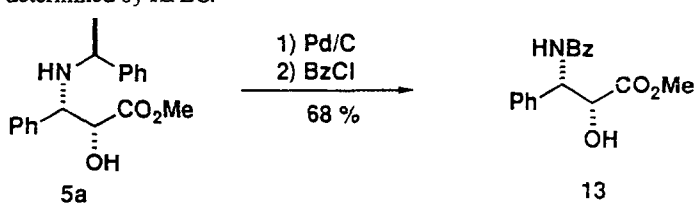


The chiral Lewis acid was prepared from triphenylborate and (*R*)- or (*S*)-binaphthol for 1h at room temperature. In the presence of the equimolar boron reagents the reaction of the chiral imine **2a** with various silyl ketene acetal derivatives proceeded smoothly at -78°C for 8 h to afford the α-hydroxy-β-amino esters, after desilylzation, in good yield. Our results are summarized in Table II. It is noteworthy that the chiral boron reagents produce the almost optically pure α-hydroxy-β-amino esters and that the stereoselectivity of the products completely depends on the geometry of the silyl ketene acetal. The reaction of the (*E*)-ketene acetal **9** mediated (*R*)-**1** produced the anti aldol adduct **3a** with high stereoselectivity (anti/syn = 98/2, diastereofacial ratio = 96/4). In sharp contrast, the reaction of the (*Z*)-ketene acetal **8** mediated (*S*)-**1** produced the enantiomerically pure syn adduct **5a** (syn/anti = 99/1, diastereofacial ratio = 99/1). Generally, using (*R*)-**1** as a Lewis acid was effective to obtain the anti adduct, while using (*S*)-**1** effectively realized the syn adduct. A kind of silyl group acting to protect hydroxy ester influenced the selectivity of the products. The mechanistic reason for this is not clear, however, the distereoselectivity exhibited here is closely related to the assigned geometry of the silyl ketene acetals and the expected structure of the acyclic transition state.[9] Thus, our methodology provides the first practical and efficient route for the selective preparation of both diastereomers of the α-hydroxy-β-amino esters. Furthermore, the syn adduct **5a** was easily transformed into the taxol side chain. **5a** was subjected to hydogenolysis over a palladium catalyst, followed by a Schotten-Baumann reaction to give the desired N-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester **13**, $[\alpha]_D$ -48° (*c* 0.80, methanol) [lit.[10] $[\alpha]_D$ -48° (*c* 1.0, methanol)], in 68 % yield.

Table II. Aldol Reaction Mediated Chiral Boron Reagent[a]

Entry	Boron reagent	Silyl ketene acetal[b]	Yield (%)[c]	Anti(**3a**:**4a**)/Syn(**5a**:**6a**)[d]
1	(*R*)-**1**	 7 (*E*:*Z*=96:4)	95	82 (95 : 5) / 18
2	(*S*)-**1**		81	76 (90 : 10) / 24
3	(*R*)-**1**	 9 (*E*:*Z*=90:10)	91	98 (96 : 4) / 2
4	(*S*)-**1**		96	93 (95 : 5) / 7
5	(*R*)-**1**	 **8** (*E*:*Z*=<1:99)	94	6 / 94 (97 : 3)
6	(*S*)-**1**		91	1 / 99 (99 : 1)
7	(*S*)-**1**	 **10** (*E*:*Z*=<1:99)	81	13 / 87 (95 : 5)
8	(*S*)-**1**	 **11** (*E*:*Z*=<1:99)	91	5 / 95 (94 : 6)
9	(*S*)-**1**	 12	86	9 / 91 (95 : 5)

[a] Aldol reactions were carried out in dichloromethane using 1 equiv of chiral boron reagent and1.2 equiv of silyl ketene acetal at -78°C for 8 h. [b] *E*/*Z* ratio was determined by ^{1}H-NMR. [c] Isolated yield. [d] Ratio was determined by HPLC.

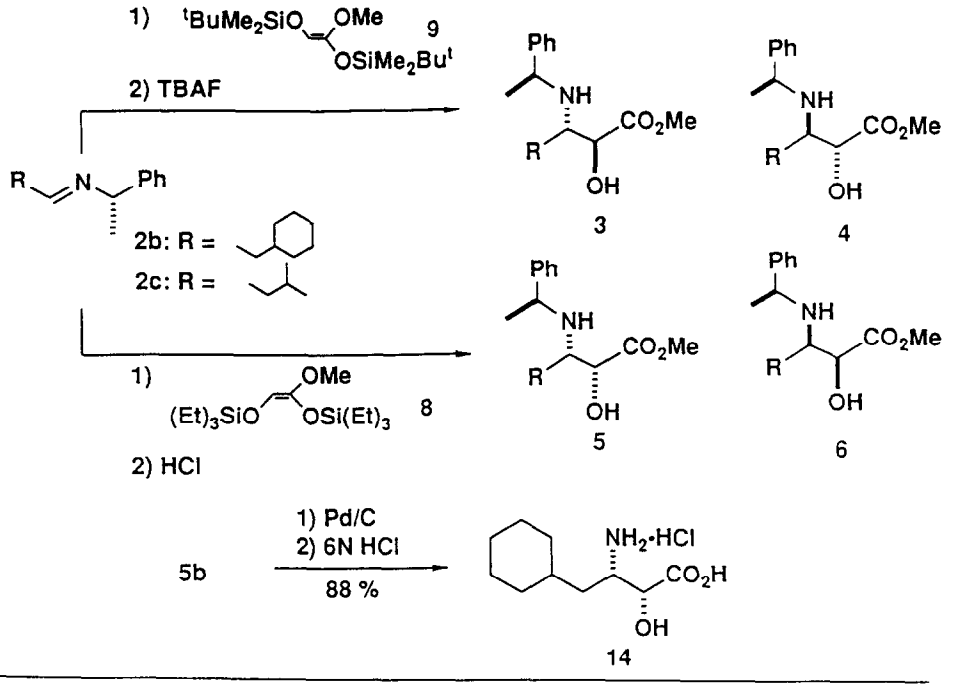


5a **13**

Next, we investigated the reactions of aliphatic imines under the same conditions used for the norstatine family. The imines **2b** and **2c** reacted with *E*-ketene acetal **9** to furnish the corresponding aldol adducts in good yields, however, anti/syn selectivity was low with any of the boron reagents. When **2b** was treated with *Z*-ketene acetal **8** in the presence of (*S*)-**1**, the syn adduct **5b** could be obtained in high yield with almost complete diastereoselectivity (syn/anti = 99/1, diastereofacial ratio = 99/1). Similarly, **2c** smoothly reacted under the same conditions to give the optically pure syn adduct **5c**. The syn adducts **5b** and **5c** were available for cyclohexylnorstatine and norstatine. For example, **5b** was deprotected by the benzyl group by hydrogenolysis over the palladium catalyst, followed by hydrolysis with refluxing 6N HCl to afford **14** as the hydrochloride

salt of cyclohexylnorstatine, $[\alpha]_D$ -14.6° (*c* 0.30, 1N HCl) [lit.[11] $[\alpha]_D$ -13.6° (1N HCl)], in 88% yield. Thus, the desired norstatine family could be easily obtained with high selectivity by our method.

Table III. Aldol Reaction of Aliphatic Imins 2b and 2c Mediated Boron Reagent[a]



Entry	Imine	Ketene acetal	Boron reagent	Yield (%)[b]	Anti (3 : 4) / Syn (5 : 6)[c]
1	2b	9	$B(OPh)_3$	82	48 (90 : 10) / 52 (90 : 10)
2			(*R*)-1	85	62 (88 : 12) / 38 (86 : 14)
3			(*S*)-1	73	65 (92 : 8) / 35 (91 : 9)
4		8	$B(OPh)_3$	90	4 / 96 (96 : 4)
5			(*R*)-1	95	7 / 93 (91 : 9)
6			(*S*)-1	87	1 / 99 (99 : 1)
7	2c	9	$B(OPh)_3$	85	56 (91 : 9) / 43 (85 : 15)
8			(*R*)-1	81	54 (96 : 4) / 46 (93 : 7)
9			(*S*)-1	90	52 (94 : 6) / 48 (97 : 3)
10		8	$B(OPh)_3$	98	8 / 92 (93 : 7)
11			(*R*)-1	99	4 / 96 (91 : 9)
12			(*S*)-1	98	1 / 99 (99 : 1)

[a] Aldol reactions were carried out in dichloromethane using 1 equiv of boron reagent and 1.2 equiv of silyl ketene acetal at -78°C for 8 h. [b] Isolated yield. [c] Ratio was determined by HPLC.

In conclusion, the present method offers a means for the construction of the optically active α-hydroxy-β-amino ester units. In the course of this study, a unique feature of chiral boron reagent was recognized as a Lewis acid to perform the high stereoselectivity. The flexibility and novel procedure make this a very practical approach for the asymmetric synthesis of the taxol side chain and the norstatine family.

Experimental section

General: Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^{1}H-NMR spectra were measured on a Varian Gemini-200 or a VSR-500S spectrometer. All NMR samples were dissolved in $CDCl_3$. High-performance liquid chromatography (HPLC) analysis was carried out on a Shimadzu LC-6A instrument with a SPD-6A UV detector. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. All experiments were performed under an atmosphere of dry argon unless otherwise specified. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Mass spectra were analyzed at the laboratories of Fujisawa Pharmaceutical Co.. Methylene chloride was stored over 4A MS. (*R*)- and (*S*)-1,1'-Bi-2-naphthol were purchased from Wako Pure Chemical Industries, LTD. Triphenyl borate was purchased from Tokyo Kasei Co., LTD.

Preparation of imines. Imine **2a** was prepared by the previous method.[8] **2b** and **2c** were prepared in the same manner.

N-[(*S*)-Methylbenzyl]cyclohexylacetaldimine (2b): bp 151-153°C/7 mmHg; NMR δ 0.8-1.8(11H, m), 1.49(3H, d, J = 6.8 Hz), 2.18(2H, dd, J = 5.4, 6.8 Hz), 4.28(1H, q, J = 6.8 Hz), 7.2-7.4(5H, m), 7.76(1H, t, J = 5.4 Hz); IR(neat) 1670 cm^{-1}.

N-[(*S*)-methylbenzyl]methylbutanaldimine (2c): bp 88°C/7 mmHg; NMR δ 0.94(3H, d, J = 6.8 Hz), 0.94(3H, d, J = 6.8 Hz), 1.52(3H, d, J = 6.8 Hz), 1.92(1H, m), 2.19(2H, dd, J = 5.4, 7.0 Hz), 4.30(1H, q, J = 6.8 Hz), 7.2-7.4(5H, m), 7.77(1H, t, J = 5.4 Hz); IR(neat) 1670 cm^{-1}.

Typical procedure for Aldol reaction with boron reagent (*R*)-1: To a suspension of powdered 4A molecular sieves (1.0 g) in CH_2Cl_2 (10 mL) were added (*R*)-binaphthol (100 mg, 0.35 mmol) and $B(OPh)_3$ (101 mg, 0.35 mmol) at room temperature under argon. After being stirred for 1 h, the mixture was cooled to 0°C, and a solution of imine **2a** (73 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was added. After being stirred for 10 min at the same temperature, the mixture was cooled to -78°C, and a solution of ketene acetal **9** (133 mg, 0.42 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After being stirred for 8 h, the solution was washed with water and saturated $NaHCO_3$, and then dried over $MgSO_4$. Following evaporation of solvent, the obtained residue was dissolved in THF (7mL) and treated with tetra-*n*-butylammonium fluoride (1.1 mL of 1M solution in THF) at room temperature for 2h. The reaction mixture was poured into water and extracted with ether (20 mL x 2). The combined organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by eluting with a mixture of hexane/ether to give a mixture of **3a**, **4a**, **5a**, and **6a** (95 mg, 91% yield). Ratio of products was determined by HPLC. When silyl ketene acetals **8** and **11** were used, crude aldol product was treated with 12N HCl (0.5 mL in 7 mL of MeOH) at room temperature for 2 h, followed by standard workup instead of treatment by tetra-*n*-butylammonium fluoride.

Methyl (2*S*,3*S*)-2-hydroxy-3-phenyl-3-[(*S*)-1-methylbenzylamino]propanoate (3a):

NMR($CDCl_3$) δ 1.33(3H, d, *J* = 6.6 Hz), 3.67(3H, s), 3.76(1H, q, *J* = 6.6 Hz), 4.09(1H, d, *J* = 4.0 Hz), 4.58(1H, d, *J* = 4.0 Hz), 7.1-7.4(10H, m); IR(Nujol) 3300, 1730 cm-1; Anal. Calcd for $C_{18}H_{21}N_1O_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.51; H, 7.18; N, 4.62; FABMS, 300(M+1).

(2*R*,3*R*)-isomer (4a): NMR($CDCl_3$) δ (discernible from mixture) 4.39(1H, d, *J* = 4.2 Hz).

Methyl (2*R*,3*S*)-2-hydroxy-3-phenyl-3-[(*S*)-1-methylbenzylamino]propanoate (5a): NMR($CDCl_3$) δ 1.27(3H, d, *J* = 6.4 Hz), 3.65(1H, q, *J* = 6.4 Hz), 3.78(3H, s), 4.15(1H, d, *J* = 3.4 Hz), 4.28(1H, d, *J* = 3.4 Hz), 7.1-7.4(10H, m); IR(Nujol) 3650, 1726 cm-1; Anal. Calcd for $C_{18}H_{21}N_1O_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.12; H, 7.19; N, 4.71; FABMS, 300(M+1).

(2*S*,3*R*)-isomer (6a): NMR($CDCl_3$) δ (discernible from mixture) 4.18(1H, d, *J* = 3.0 Hz).

Methyl (2*S*,3*S*)-2-hydroxy-4-*c*-hexyl-3-[(*S*)-1-methylbenzylamino]butanoate (3b): NMR($CDCl_3$) δ 0.6-1.8(13H, m), 1.36(3H, d, *J* = 6.6 Hz), 2.75(1H, dt, *J* = 10.0, 3.2 Hz), 3.81(3H, s), 3.88(1H, q, *J* = 6.6 Hz), 4.45(1H, d, *J* = 3.2 Hz), 7.2-7.4(5H, m); IR(neat) 3650, 1736 cm-1; Anal. Calcd for $C_{19}H_{29}N_1O_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.24; H, 9.26; N, 4.32; FABMS, 320(M+1).

(2*R*,3*R*)-isomer (4b): NMR($CDCl_3$) δ (discernible from mixture) 4.08(1H, d, *J* = 3.8 Hz).

Methyl (2*R*,3*S*)-2-hydroxy-4-*c*-hexyl-3-[(*S*)-1-methylbenzylamino]butanoate (5b): NMR($CDCl_3$) δ 0.6-1.8(13H, m), 1.28(3H, d, *J* = 6.6 Hz), 2.97(1H, dt, *J* = 6.8, 1.6 Hz), 3.59(1H, q *J* = 6.6 Hz), 3.81(3H, s), 3.97(1H, d, *J* = 1.6 Hz), 7.1-7.4(5H, m); IR(neat) 3500, 1735 cm-1; Anal. Calcd for $C_{19}H_{29}N_1O_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.24; H, 9.26; N, 4.32; FABMS, 320(M+1).

(2*S*,3*R*)-isomer (6b): NMR($CDCl_3$) δ (discernible from mixture) 4.00(1H, d, *J* = 1.6 Hz).

Methyl (2*S*,3*S*)-2-hydroxy-5-methyl-3-[(*S*)-1-methylbenzylamino]hexanoate (3c): NMR($CDCl_3$) δ 0.54(3H, d, *J* = 6.6 Hz), 0.68(3H, d, *J* = 6.6 Hz), 1.35(3H, d, *J* = 6.6 Hz), 1.1-1.8(3H, m), 2.65-3.00(1H, m), 3.67(3H, s), 3.88(1H, q, *J* = 6.6 Hz), 4.43(1H, d, *J* = 3.0 Hz), 7.1-7.4(5H, m); IR(neat) 3650, 1730 cm-1; Anal. Calcd for $C_{16}H_{25}N_1O_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.40; H, 9.36; N, 4.62; FABMS, 280(M+1).

(2*R*,3*R*)-isomer (4c): NMR($CDCl_3$) δ (discernible from mixture) 4.06(1H, d, *J* = 2.0 Hz).

Methyl (2*R*,3*S*)-2-hydroxy-5-methyl-3-[(*S*)-1-methylbenzylamino]hexanoate (5c): NMR($CDCl_3$) δ 0.65(3H, d, *J* = 6.6 Hz), 0.78(3H, d, *J* = 6.6 Hz), 1.25(3H, d, *J* = 6.6 Hz), 1.1-1.7(3H, m), 2.91(1H, dt, *J* = 7.0, 1.6, Hz), 3.61(1H, q, *J* = 6.6 Hz), 3.78(3H, s), 3.96(1H, d, *J* = 1.6 Hz), 7.1-7.5(5H, m); IR(neat) 3650, 1730 cm-1; Anal. Calcd for $C_{16}H_{25}N_1O_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.39; H, 9.33; N, 4.57; FABMS, 280(M+1).

(2*S*,3*R*)-isomer (6c): NMR($CDCl_3$) δ (discernible from mixture) 4.01(1H, d, *J* = 2.0 Hz).

Synthesis of C-13 side chain, (2*R*,3*S*)-N-benzoyl-3-phenylisoserine methyl ester (13): To a solution of **5a** (300 mg, 1.0 mmol) in MeOH (30 mL) was added Pd/C (10% weight on carbon, 30 mg) and this was stirred for 30 h under H_2 atmosphere at room temperature. After filtration, solvent was removed *in vacuo*. The residue was dissolved in a mixture of THF (10 mL) and water (10 mL) and to the solution was added dropwise benzoyl chloride (0.17 mL, 1.5 mmol) at 0°C maintaining a pH 9-10 with 1N sodium hydroxide. After the mixture was vigorously stirred for another 30 min, the crude product was extracted with ether (20 mL x 2). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by eluting with a mixture of dichioromethane/ether (9/1) to give **13** (206 mg, 68%). $[\alpha]_D^{24}$ -48° (*c* = 0.8, methanol); Anal. Calcd for $C_{17}H_{17}N_1O_4$: C, 68.22; H, 5.72;

N, 4.68. Found: C, 68.17; H, 5.70; N, 4.66; FABMS, 300(M+1). The spectral data were identical with those described in ref 10.

Synthesis of cyclohexylnorstatine hydrochloride salt (14): After **5b** was hydrogenolyzed over Pd/C in the above manner, the crude product was dissolved in 6N hydrochloric acid (20 mL) and stirred for 4 h under reflux. The solvent was removed *in vacuo* to give the crude solid and this was washed with toluene to afford pure **14** as a colorless solid (150 mg, 88%). $[\alpha]_D^{24}$ -14.6° (*c* = 0.5, 1N HCl); FABMS for $C_{10}H_{19}N_1O_3$, 202(M+1). The spectral data were identical with those described in ref 11.

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