# A Highly Stereoselective Synthesis of (3*S*,4*S*)-Statine and (3*S*,4*S*)-Cyclohexylstatine[1)]

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**The title compounds, which are synthetic intermediates of renin inhibitors, could be prepared from (*S*)-leucine and (*S*)-phenylalanine, respectively, by employing highly stereoselective aldol reactions of *O*-methyl-*O*-trimethylsilyl ketene acetal with an (*S*)-α-amino aldehyde in the presence of titanium(IV) chloride as a key step. Maximum diastereoselectivity of the aldol reaction was found to be more than 95:5.**

**Keywords** renin inhibitor; (3*S*,4*S*)-statine; (3*S*,4*S*)-cyclohexylstatine; aldol reaction; ketene acetal; (*S*)-α-amide aldehyde; Lewis acid; titanium(IV) chloride; chelation-control

Renin is a highly specific enzyme operating in the cascade leading to the release of the hypertensive substance, angiotensin II, and plays a key role in the regulation of blood pressure, as does the angiotensin-converting enzyme (ACE).[2)] Thus, renin cleaves the Leu–Val peptide bond in angiotensinogen, producing a decapeptide, angiotensinogen I, which can be converted to angiotensin II by ACE. With the aim of developing a novel class of antihypertensive agents, intensive studies are currently being conducted on renin inhibitors having lower molecular weights.[2d,3)]

Since the natural peptide, pepstatin, was found to contain (3*S*,4*S*)-statine (**1a**) as the key component related to its inhibitory activity against renin,[4)] numerous synthetic peptide mimics bearing **1a** have been explored as potential renin inhibitors.[5)] Recently, some peptide-like compounds which contain (3*S*,4*S*)-cyclohexylstatine (**1b**) in place of **1a** were also found to exhibit promising profiles as candidate antihypertensive agents.[6)]

Numerous synthetic routes to **1** have been reported.[7,8)] While the aldol reaction of an enolate of an acetic acid derivative with an (*S*)-α-amido aldehyde such as **2**, accessible from (*S*)-leucine (**3a**) or (*S*)-phenylalanine (**3b**), is anticipated to be one of the simplest synthetic routes to **1**, it is well recognized that the addition reaction employing an achiral enolate results in no significant stereoselection[7a,9)] and the desired stereoselectivity can be realized only by using a less readily accessible chiral enolate.[7a,10)]

We have now found that the aldol reaction of *O*-methyl-*O*-trimethylsilyl ketene acetal (**4**)[11)] with **2** proceeds in a highly stereoselective manner in the presence of titanium(IV) chloride ($TiCl_4$), affording a mixture of the addition products (**5** and **6**) in which the desired adduct (**5**) is predominant (**5**:**6**≥95:5). Removal of the protective groups involved in **5** under acidic conditions readily produced **1**. This report details an efficient synthesis of **1** explored by employing the highly stereoselective aldol reaction of **4** with **2**.[12)]

Thus, as shown in Chart 1, (*S*)-**2a** could be readily prepared from (*S*)-**3a** in 4 steps according to the procedure reported for the synthesis of (*S*)-**2b** from (*S*)-**3b**.[13)] Inexpensive isopropoxycarbonyl group was used as a convenient protective group for the amino function.[13)] After some preliminary experiments, it was found that the reaction of (*S*)-**2a** with **4** could proceed highly stereoselectively in the presence of $TiCl_4$ at −78 °C in dichloromethane, giving a mixture of **5a** and **6a** in 89% combined yield (Table I, run 1). The formation ratio of **5a** to **6a** was estimated as 95:5 by analyzing the mixture of **5a** and **6a** by gas liquid

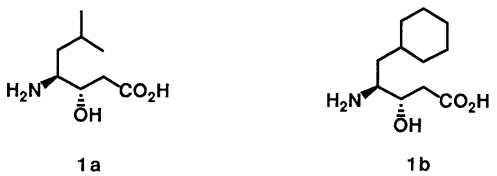
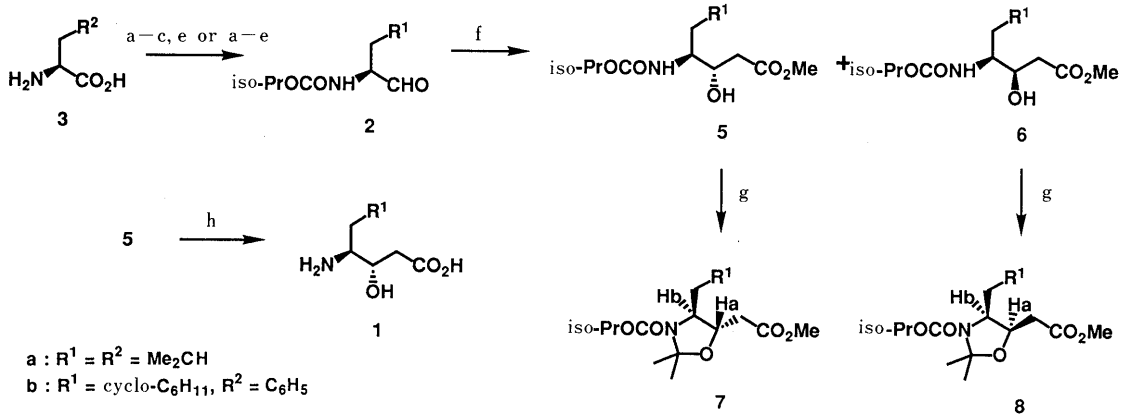


Fig. 1



a : $R^1 = R^2 = Me_2CH$
b : $R^1$ = cyclo-$C_6H_{11}$, $R^2 = C_6H_5$

(a) MeOH, $SOCl_2$ (a 100%, b 96%); (b) iso-PrOCOCl, $K_2CO_3$, $CH_2Cl_2$ (a 87%) or iso-PrOCOCl, $Et_3N$, THF (b 91%); (c) $NaBH_4$, LiCl, THF-EtOH (a 100%, b 98%) (d) $H_2$ (4 atm), Rh-$Al_2O_3$, AcOH-MeOH (100%); (e) $SO_3$-Py, DMSO, $Et_3N$, toluene (a 79%, b 78%); (f) $CH_2$=C(OMe)OTMS (**4**); see, the text and Table I; (g) 2,2-dimethoxypropane, *p*-TsOH, $CH_2Cl_2$ (**7a** 86%, **7b** 88%, **8a** 85%, **8b** 91%); (h) 6 M HCl, AcOEt, 100°C; Dowex AG 50W ($H^+$ form) (**1a** 88%, **1b** 93%)

Chart 1

TABLE I. The Aldol Reaction of (*S*)-α-Amido Aldehyde (**2**) with *O*-Methyl-*O*-trimethylsilyl Ketene Acetal (**4**) under Various Conditions

| Run | Compound | $R^1$ | Reaction conditions | | | Yield of **5** and **6** (%) | Ratio of **5** to **6**[b] |
|---|---|---|---|---|---|---|---|
| | | | Lewis acid (eq) | Solv.[a] | Temp. (°C) | | |
| 1 | **2a** | $Me_2CH$ | $TiCl_4$ (1.5) | $CH_2Cl_2$ | −78 | 89 | 95: 5 |
| 2 | **2a** | $Me_2CH$ | $TiCl_4$ (1.5) | $CH_2Cl_2$ | −25 | 82 | 82:18 |
| 3 | **2a** | $Me_2CH$ | $TiCl_4$ (1.5) | PhMe | −78 | 80 | 80:20 |
| 4 | **2a** | $Me_2CH$ | $BF_3 \cdot Et_2O$ (1.2) | $CH_2Cl_2$ | −78 | 72 | 80:20 |
| 5 | **2a** | $Me_2CH$ | $ZnI_2$ (1.2) | THF | −40→0[c] | 45 (61)[d] | 90:10 |
| 6 | **2a** | $Me_2CH$ | $Eu(fod)_3$ (0.05) | $CH_2Cl_2$ | 0→r.t.[e] | 48 (29)[d] | 93: 7 |
| 7 | **2b** | cyclo-$C_6H_{11}$ | $TiCl_4$ (1.5) | $CH_2Cl_2$ | −78 | 95 | 96: 4 |

*a*) Dichloromethane ($CH_2Cl_2$), tetrahydrofuran (THF), or toluene (PhMe). *b*) Determined by GLC analysis (5% Silar 10C, 190 °C) of a mixture of **5** and **6**. *c*) The reaction temperature was gradually raised from −40 °C to 0 °C over 1.0 h. *d*) Recovery of the starting material (**2a**). *e*) The reaction mixture was stirred at 0 °C for 4 h, then at room temperature for 12 h. r.t. = room temperature.

chromatography (GLC).

Treatments of separated **5a** and **6a** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid produced the 2,2-dimethyl-1,3-oxazoline derivatives (**7a** and **8a**) in 86% and 85% yields, respectively. The relative stereochemistries of **5a** and **6a** could be rigorously determined by measuring the proton nuclear magnetic resonance ($^1$H-NMR) spectra of **7a** and **8a**. Since the vicinal protons (Ha and Hb) involved in the 1,3-oxazolidine moieties of **7a** and **8a**, were found to exhibit the coupling constants of 0.0 and 5.0 Hz, repectively, the *trans* and *cis* stereochemistries could be assigned to **7a** and **8a**. Thus, **5a** and **6a** have the desired (3*S*,4*S*)- and the undesired (3*R*,4*S*)-configurations, respectively.[14]

The aldol reaction of **2a** with **4** was further examined under various reaction conditions. Some representative results are shown in Table I. Thus, when the reaction was carried out at higher temperature, such as −25 °C, or in toluene, the mixture of **5a** and **6a** was produced in lower yields and stereoselectivities (runs 2 and 3). The use of boron trifluoride–etherate ($BF_3 \cdot Et_2O$) in place of $TiCl_4$ also decreased the yield and stereoselectivity (run 4). Similarly to the aldol reaction using $TiCl_4$, the reactions employing zinc(II) iodide ($ZnI_2$) or tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) [$Eu(fod)_3$] as a Lewis acid were found to take place in a highly stereoselective manner even at higher reaction temperature (runs 5 and 6). In these cases, however, the recovery of the starting material (**2a**) was always observed, probably due to the lower reaction rate.

When **2b** prepared from (*S*)-**3b**[13] was treated with **4** under the best reaction conditions established with **2a**, a mixture of **5b** and **6b** could be obtained in 95% combined yield (Table I, run 7). The ratio of **5b** to **6b** was similarly determined as 96:4 by GLC analysis. The relative stereochemistries of **5b** and **6b** were assigned as (3*S*,4*S*)- and (3*R*,3*S*)-configurations, respectively, by measuring the $^1$H-NMR spectra of **7b** and **8b** derived from **5b** and **6b** in the same manner as described for **5a** and **6a**.

The preferential formation of **5** may be rationalized in terms of the chelation-controlled mechanism depicted in Fig. 2. This is interesting in view of the reported result that an α-alkoxy aldehyde is not suceptible to similar chelation-controlled diastereofacial selection.[15]

The major aldol product (**5a**) isolated by column chromatography was subjected to acidic hydrolysis, giving **1a**,

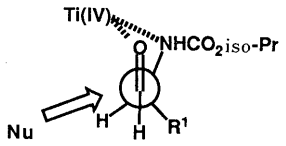



Fig. 2

mp 202—205 °C (dec.) and $[\alpha]_D^{20}$ −20.4° (water), in 88% yield.[7f,16] Treatment of the other major product (**5b**) under the same conditions as for **5a** gave **1b**, mp 213—216 °C (dec.) and $[\alpha]_D^{20}$ −25.3° (1 M hydrochloric acid), in 93% yield.[7c,h]

Thus, we have succeeded in developing an efficient synthetic route to **1a** and **1b** by employing the aldol reaction of (*S*)-**2** with **4** in the presence of $TiCl_4$. Taking into account its directness and operational simplicity, the overall process seems to be one of the most practical synthetic methods available for **1a, b**.

**Experimental**

All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Measuremens of optical rotations were carried out using a Horiba SEPA-200 automatic digital polarimeter. Infrared (IR) spectra measurements were performed with a JASCO A-200 IR spectrometer. $^1$H-NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz), a Bruker AM 400 spectrometer (400 MHz), and a JEOL JNM-GX 500 spectrometer (500 MHz). All signals are expressed as ppm downfield from tetramethylsilane, used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). Mass spectra (MS) were taken with a Hitachi RMU-6MG mass spectrometer and a JEOL JMS-D 300 mass spectrometer. Unless otherwise noted, all reactions were performed in anhydrous solvents. Wako gel C-200 was used as an adsorbent for column chromatography.

**(*S*)-*N*-(Isopropoxycarbonyl)leucinol** According to the reported procedure,[17] methyl (*S*)-leucinate could be prepared in 100% yield by treating **3a** with thionyl chloride in MeOH. Potassium carbonate (228 mg, 1.65 mmol) and isopropyl chloroformate (0.23 ml, 1.98 mmol) were added to a solution of methyl (*S*)-leucinate (239 mg, 1.65 mmol) in $CH_2Cl_2$ (5 ml) at 0 °C and the mixture was stirred for 1 h at the same temperature. After quenching of the reaction with saturated $NaHCO_3$ solution, the resulting mixture was extracted with ether. The ethereal extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (hexane: AcOEt = 4:1) to give methyl (*S*)-*N*-(isopropoxycarbonyl)leucinate (333 mg, 87%). $[\alpha]_D^{20}$ −4.9° (*c* = 1.53, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 0.95 (6H, m), 1.23 (6H, two d, *J* = each 6.1 Hz), 1.3—1.8 (3H, m), 3.73 (3H, s), 4.40 (1H, m), 4.90 (2H, m and doubled q, *J* = each 6.2 Hz). IR ($CHCl_3$): 3460, 2970, 1730, 1710, 1510, 1110 cm$^{-1}$. MS *m/z*: 231 ($M^+$), 172, 86, 43.

A suspension of methyl (*S*)-*N*-(isopropoxycarbonyl)leucinate (333 mg, 1.44 mmol), lithium chloride (183 mg, 4.32 mmol), and sodium borohydride (163 mg, 4.32 mmol) in a mixture of tetrahydrofuran (THF) (4 ml) and

EtOH (6 ml) was stirred for 5 h at room temperature. The mixture was concentrated *in vacuo* and the residue was diluted with 1 M HCl under ice cooling. The acidic mixture was extracted with AcOEt. The combined AcOEt extracts were washed with brine, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was chromatographed (hexane : AcOEt = 2 : 1) to give (*S*)-*N*-(isopropoxycarbonyl)leucinol (292 mg, 100%). $[\alpha]_D^{20}$ −30.9° (*c* = 1.05, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.93 (6H, two d, *J* = each 6.4 Hz), 1.23 (6H, two d, *J* = each 6.2 Hz), 1.3—2.0 (3H, m), 2.45 (1H, br s), 3.65 (3H, m), 4.70 (1H, m), 4.90 (1H, doubled q, *J* = each 6.2 Hz). IR ($CHCl_3$): 3460, 2970, 1700, 1510, 1110 cm$^{-1}$. MS *m/z*: 204 ($M^+$ + 1), 172, 130, 86, 43. *Anal.* Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.93; H, 10.40; N, 6.91.

**(*S*)-*N*-(Isopropoxycarbonyl)phenylalaninol** According to the reported procedure,[17] methyl (*S*)-phenylalabinate hydrochloride could be prepared in 96% yield by treating **3b** with thionyl chloride in MeOH. Acylation of methyl (*S*)-phenylalaninate hydrochloride (3.90 g, 13 mmol) with isopropyl chloroformate (2.3 ml, 20 mmol) and triethylamine (5.5 ml, 39 mmol) under the same conditions as reported[13b] gave methyl (*S*)-*N*-(isopropoxycarbonyl)phenylalaninate (4.35 g, 91%) as a colorless solid. $[\alpha]_D^{20}$ +55.4° (*c* = 1.32, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 1.21 (6H, two d, *J* = each 6 Hz), 3.11 (2H, d, *J* = 6 Hz), 3.72 (3H, s), 4.5—5.2 (2H, m), 4.92 (1H, doubled q, *J* = each 6 Hz), 7.04—7.48 (5H, m). IR (KBr): 1740, 1685 cm$^{-1}$. MS *m/z*: 266 ($M^+$ + 1), 206, 162, 131, 120.

Treatment of methyl (*S*)-*N*-(isopropoxycarbonyl)phenylalaninate (2.52 g, 9.5 mmol) with lithium chloride (1.22 g, 29 mmol) and sodium borohydride (1.09 g, 29 mmol) in a mixture of THF (16 ml) and EtOH (25 ml) in a similar manner to that reported[13b] gave (*S*)-*N*-(isopropoxycarbonyl)phenylalaninol (2.21 g, 98%) as a colorless solid after purification by column chromatography (hexane : AcOEt = 5 : 1 → 3 : 1). $[\alpha]_D^{20}$ −25.2° (*c* = 1.03, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 1.21 (6H, two d, *J* = each 6 Hz), 1.96—2.30 (1H, m), 2.88 (2H, d, *J* = 7 Hz), 3.44—4.16 (3H, m), 4.65—5.13 (1H, m), 4.92 (1H, doubled q, *J* = each 6 Hz), 7.05—7.47 (5H, m). IR (KBr): 1690 cm$^{-1}$. MS *m/z*: 237 ($M^+$), 206, 146, 120. *Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.99; H, 8.03; N, 5.81.

**(*S*)-*N*-(Isopropoxycarbonyl)leucinal (2a)** Sulfur trioxide pyridine complex (1.32 g, 8.30 mmol) was added slowly to a stirred solution of (*S*)-*N*-(isopropoxycarbonyl)leucinol (281 mg, 1.38 mmol) and triethylamine (1.16 ml, 8.30 mmol) in a mixture of toluene (1 ml) and dimethylsulfoxide (DMSO) (1.8 ml) under cooling (< 10 °C) and the mixture was stirred for 30 min at room temperature. After quenching of the reaction with ice and water, the mixture was extracted with AcOEt and the combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 8 : 1) to afford **2a** as a colorless oil (219 mg, 79%). $[\alpha]_D^{20}$ +34.4° (*c* = 0.964, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.97 (6H, m), 1.24 (6H, two d, *J* = each 6.2 Hz), 1.3—1.9 (3H, m), 4.25 (1H, m), 4.92 (2H, m and doubled q, *J* = each 6.2 Hz) 9.59 (1H, s). IR ($CHCl_3$): 3460, 2980, 2720, 1720, 1710, 1500, 1380, 1110 cm$^{-1}$. MS *m/z*: 172, 130, 86, 43.

**(*S*)-3-Cyclohexyl-2-(isopropoxycarbonyl)aminopropanal (2b)** According to the reported method,[13] a mixture of (*S*)-*N*-(isopropoxycarbonyl)phenylalaninol (2.05 g, 8.6 mmol), Rh-$Al_2O_3$ (403 mg), and AcOH (0.6 ml) in MeOH (6 ml) was stirred under a hydrogen atmosphere (4 atm) for 5 h at room temperature. The mixture was filtered to remove the catalyst and the combined filtrates were concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 5 : 1) to give (*S*)-3-cyclohexyl-2-(isopropoxycarbonyl)aminopropanol as an oil (2.09 g, 100 %). $[\alpha]_D^{20}$ −26.4° (*c* = 1.78, $CHCl_3$) [lit.,[13b] $[\alpha]_D^{23}$ −27.2° (*c* = 1.06, $CHCl_3$)]. $^1$H-NMR ($CDCl_3$) *δ*: 1.23 (6H, two d, *J* = each 6 Hz), 0.71—2.13 (13H, m), 3.36—4.02 (3H, m), 4.51—5.15 (1H, m), 4.93 (1H, doubled q, *J* = each 6 Hz). IR (neat): 1690 cm$^{-1}$. MS *m/z*: 244 ($M^+$ + 1), 212, 170, 126. *Anal.* Calcd for $C_{13}H_{25}NO_3 \cdot 0.1H_2O$: C, 63.69; H, 10.36; N, 5.71. Found: C, 63.56; H, 10.39; N, 5.75.

Sulfur trioxide pyridine complex (491 mg, 3.1 mmol) were added slowly to a stirred solution of (*S*)-3-cyclohexyl-2-(isopropoxycarbonyl)aminopropanol (138 mg, 0.57 mmol) and triethylamine (0.43 ml, 3.1 mmol) in a mixture of toluene (0.33 ml) and DMSO (0.67 ml) under cooling (< 10 °C) in a similar manner to that reported.[13b] The resulting mixture was stirred for 20 min at room temperature. After quenching of the reaction with ice and water, the mixture was extracted with AcOEt. The combined organic extracts were washed successively with water and brine, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 10 : 1 → 5 : 1) to afford **3b** as a colorless oil (107 mg, 78%). $[\alpha]_D^{20}$ +26.6° (*c* = 0.939, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.60—2.06 (13H, m), 1.23 (6H, two d, *J* = each 7 Hz), 4.03—4.43 (1H, m), 4.93 (1H, doubled q, *J* = each 6.2 Hz), 5.20—5.52 (1H, m), 9.56 (1H, s). IR (neat): 1730, 1690 cm$^{-1}$. MS *m/z*: 242 ($M^+$ + 1), 212, 170, 126.

**Methyl (3*S*,4*S*)-3-Hydroxy-6-methyl-4-(isopropoxycarbonyl)aminoheptanoate (5a) and Its (3*R*,4*S*)-Isomer (6a)** Experimental procedures for Table I, runs 1 and 4, will be described as representative examples.

a) Table I, Run 1: A solution of $TiCl_4$ in $CH_2Cl_2$ (1.0 M solution, 0.065 mmol) was added slowly to a suspension of **2a** (8.7 mg, 0.043 mmol), **4** (19 mg, 0.13 mmol), and molecular sieves 4Å (4 mg) in $CH_2Cl_2$ (0.5 ml) at −78 °C under an argon atmosphere. After being stirred for 1 h at the same temperature, the mixture was quenched with a small amount of saturated $NaHCO_3$ solution and filtered through a pad of Celite. The combined filtrate and washing were concentrated *in vacuo*. The residue obtained as an oil was purified by column chromatography (hexane : AcOEt = 4 : 1), giving a mixture of **5** and **6** (10.6 mg, 89%). The ratio of **5a** to **6a** was determined as 95 : 5 by GLC analysis of the residue (5% Silar 10C, 190 °C). For the physical and spectral data of **5a** and **6a**, see b).

b) Table I, Run 4: A solution of $BF_3 \cdot Et_2O$ in $CH_2Cl_2$ (1.0 M solution, 0.17 mmol) was added slowly to a suspension of **2a** (28.9 mg, 0.144 mmol), **4** (63 mg, 0.43 mmol), and molecular sieves 4Å (5 mg) in $CH_2Cl_2$ (0.5 ml) at −78 °C under an argon atmosphere. After being stirred for 1 h at the same temperature, the mixture was quenched with saturated $NaHCO_3$ solution and extracted with AcOEt. The combined organic extracts were washed with 1 M HCl and brine, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue, obtained as an oil, was purified by column chromatography (hexane : AcOEt = 4 : 1) to yield **5a** (19.4 mg), **6a** (6.5 mg), and a mixture of **5a** and **6a** (2.6 mg) (the totol yield of **5a** and **6a**, 72%). The ratio of **5a** to **6a** was calculated as 80 : 20 by GLC analysis of the residue (5% Silar 10C, 190 °C). **5a**: oil, $[\alpha]_D^{20}$ −43.2° (*c* = 1.07, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.93 (6H, m), 1.23 (6H, two d, *J* = each 6.2 Hz), 1.35 (1H, m), 1.54 (1H, m), 1.66 (1H, m), 2.53 (2H, m), 3.30 (1H, br s), 3.67 (1H, m), 3.72 (3H, s), 4.03 (1H, br s), 4.82 (1H, br d, *J* = 9.7 Hz), 4.98 (1H, doubled q, *J* = each 6.2 Hz). IR ($CHCl_3$): 3470, 2980, 1710, 1505, 1110 cm$^{-1}$. MS *m/z*: 276 ($M^+$ + 1), 216, 172, 130, 86, 43. *Anal.* Calcd for C, 56.70; H, 9.15; N, 5.09. Found: C, 56.50; H, 9.33; N, 5.18. **6a**: mp 63—65 °C (from $Et_2O$–hexane), $[\alpha]_D^{20}$ −29.8° (*c* = 0.650, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.94 (6H, two d, *J* = each 6.5 Hz), 1.23 (6H, two d, *J* = each 6.1 Hz), 1.34 (2H, m), 1.68 (1H, m), 2.50 (2H, m), 3.35 (1H, br s), 3.71 (4H, s and m), 4.02 (1H, br s), 4.62 (1H, br d, *J* = 7.8 Hz), 4.89 (1H, doubled q, *J* = each 6.1 Hz). IR ($CHCl_3$): 3460, 2970, 1710, 1505, 1110 cm$^{-1}$. MS *m/z*: 316 ($M^+$ + 1), 256, 212, 170, 126, 71, 43. *Anal.* Calcd for $C_{13}H_{25}NO_5 \cdot 0.1H_2O$: C, 56.34; H, 9.17; N, 5.05. Found: C, 56.21; H,9.12; N, 4.93.

**Methyl (3*S*,4*S*)-5-Cyclohexyl-3-hydroxy-4-(isopropoxycarbonyl)aminopentanoate (5b) and Its (3*R*,4*S*)-Isomer (6b)** Table I, Run 7: A solution of $TiCl_4$ in $CH_2Cl_2$ (1.0 M solution, 0.15 mmol) was added slowly to a suspension of **2b** (23.7 mg, 0.098 mmol), **4** (43 mg, 0.30 mmol), and molecular sieves 4Å (10 mg) in $CH_2Cl_2$ (1 ml) at −78 °C under an argon atmosphere. The mixture was stirred for 1 h at the same temperature, and, after quenching of the reaction with a small amount of saturated $NaHCO_3$ solution, filtered through a pad of Celite. The combined filtrate and washings were concentrated *in vacuo*. The residue, obtained as an oil, was purified by column chromatography (hexane : AcOEt = 4 : 1), affording **5b** (27.4 mg) and **6b** (2 mg) (the total yield of **5b** and **6b**, 95%). The ratio of **5b** to **6b** was determined as 96 : 4 by GLC analysis of the residue (5% Silar 10C, 190 °C). **5b**: oil, $[\alpha]_D^{20}$ −36.6° (*c* = 1.11, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.8—1.1 (2H, m), 1.1—1.3 (2H, m), 1.23 (6H, two d, *J* = each 6.2 Hz), 1.3—1.6 (2H, m), 1.66 (4H, m), 1.82 (1H, br s), 2.52 (2H, m) 3.24 (1H, br s), 3.69 (1H, m), 3.71 (3H, s), 4.02 (1H, br d, *J* = 6.7 Hz), 4.77 (1H, br d, *J* = 9.8 Hz), 4.88 (1H, doubled q, *J* = each 6.2 Hz). IR ($CHCl_3$): 3470, 2940, 2870, 1710, 1505, 1440, 1110 cm$^{-1}$. MS *m/z*: 316 ($M^+$ + 1), 256, 212, 170, 126, 100, 43. *Anal.* Calcd for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.60; H, 9.18; N, 4.34. **6b**: mp 73—74 °C (from hexane) and $[\alpha]_D^{20}$ −30.8° (*c* = 0.510, $CHCl_3$). $^1$H-NMR ($CDCl_3$) *δ*: 0.7—1.1 (2H, m), 1.23 (6H, two d, *J* = each 6.0 Hz), 1.1—1.5 (5H, m), 1.53—1.76 (4H, m), 1.83 (1H, br d, *J* = 13.0 Hz), 2.48 (2H, m), 3.38 (1H, br s), 3.71 (3H, s), 3.77 (1H, m), 4.02 (1H, m), 4.60 (1H, br d, *J* = 7.7 Hz), 4.89 (1H, doubled q, *J* = each 6.0 Hz). IR ($CHCl_3$): 3690, 3460, 2930, 2860, 1710, 1500, 1430, 1110 cm$^{-1}$. MS *m/z*: 276, 216, 172, 130, 86, 43. *Anal.* Calcd for $C_{16}H_{29}NO_5 \cdot 0.2H_2O$: C, 60.24; H, 9.29; N, 4.39. Found: C, 60.33; H, 9.31; N, 4.25.

**Methyl 1-[(4*S*,5*S*)-4-(2-Methyl)propyl-2,2-dimethyl-3-isopropoxycarbonyl-1,3-oxazolidin-5-yl]acetate (7a)** A mixture of **5a** (16.4 mg, 0.060 mmol),

2,2-dimethoxypropane (12.4 mg, 0.12 mmol), and *p*-toluenesulfonic acid (1.1 mg) in $CH_2Cl_2$ (2 ml) was stirred for 6 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution and the mixture was extracted with ether. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purifed by column chromatography (hexane : AcOEt = 4 : 1), giving **7a** as an oil (16.2 mg, 86%). $[\alpha]_D^{20}$ +6.5° (*c* = 0.430, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.94 (6H, two d, *J* = each 6.3 Hz), 1.26, 1.27 (6H, two d, *J* = each 6.2 Hz), 1.5—1.7 (3H, m), 1.52, 1.61 (each 3H, s), 2.60 (1H, dd, *J* = 6.5, 15.3 Hz), 2.68 (1H, dd, *J* = 7.5, 15.3 Hz), 3.71 (3H, s), 3.62 (1H, m), 4.33 (1H, dd, *J* = 6.5, 7.5 Hz), 4.94 (1H, m). IR ($CHCl_3$): 2970, 1730, 1690, 1400, 1110 1090 $cm^{-1}$. MS *m/z*: 300, 258, 214, 172, 140, 99, 43.

**Methyl [(4*S*,5*R*)-4-(2-Methyl)propyl-2,2-dimethyl-3-isopropoxycarbonyl-1,3-oxazolidin-5-yl]acetate (8a)** This compound was prepared as an oil in 85% yield (13.7 mg) from **6a** (14.1 mg, 0.051 mmol) by the same procedure as described for the preparation of **7a**. $[\alpha]_D^{20}$ −11.7° (*c* = 0.426, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.94 (6H, m), 1.25, 1.26 (6H, two d, *J* = each 6.1 Hz), 1.2—1.6 (3H, m), 1.56 (6H, s), 2.58 (1H, dd, *J* = 6.8, 16.3 Hz), 2.68 (1H, br dd, *J* = 7.3, 16.3 Hz), 3.72 (3H, s), 4.06 (1H, m), 4.44 (1H, ddd, *J* = 5.0, 6.8, 7.3 Hz), 4.95 (1H, m). IR ($CHCl_3$): 2980, 1735, 1685, 1405, 1110, 1095 $cm^{-1}$. MS *m/z*: 300, 258, 214, 172, 43.

**Methyl [(4*S*,5*S*)-4-Cyclohexylmethyl-2,2-dimethyl-3-isopropoxycarbonyl-1,3-oxazolidin-5-yl]acetate (7b)** The same treatments of **5b** (16.8 mg, 0.0533 mmol) as described for the preparation of **7a** gave **7b** as an oil (16.7 mg, 88%) after purification by column chromatography. $[\alpha]_D^{20}$ +3.8° (*c* = 0.630, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.8—1.8 (13H, m), 1.21 (6H, two d, *J* = each 6.3 Hz), 1.46, 1.56 (6H, two s), 2.55 (1H, dd, *J* = 6.5, 14 Hz), 2.63 (1H, dd, *J* = 7.5, 14 Hz), 3.66 (3H, s), 3.78 (1H, m), 4.28 (1H, ddd, *J* = 1.4, 6.5, 7.5 Hz), 4.88 (1H, br s). IR ($CHCl_3$): 3000, 2940, 2860, 1730, 1690, 1405, 1110 $cm^{-1}$. MS *m/z*: 340, 254, 215, 172, 70, 55, 43.

**Methyl [(4*S*,5*R*)-4-Cyclohexylmethyl-2,2-dimethyl-3-isopropoxycarbonyl-1,3-oxazolidin-5-yl]acetate (8b)** Treatments of **6b** (5.3 mg, 0.017 mmol) by the same procedure as described for the preparation of **8a** gave **8b** (5.4 mg, 91%) as an oil after purification by column chromatography. $[\alpha]_D^{20}$ −9.6° (*c* = 0.499, $CHCl_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 0.8—1.9 (13H, m), 1.25, 1.27 (6H, two d, *J* = each 6.2 Hz), 1.55 (6H, s), 2.58 (1H, dd, *J* = 6.8, 16.4 Hz), 2.68 (1H, dd, *J* = 7.5, 16.4 Hz), 3.72 (3H, s), 4.07 (1H, m), 4.44 (1H, ddd, *J* = 4.8, 6.8, 7.5 Hz), 4.92 (1H, m). IR ($CHCl_3$): 3010, 2950, 2880, 1735, 1685, 1410, 1110 $cm^{-1}$. MS *m/z*: 340, 254, 180, 172, 55, 43.

**(3*S*,4*S*)-Statine (1a)** A mixture of **5a** (40.7 mg, 0.15 mmol), 6 M HCl (2 ml), and AcOEt (0.5 ml) was heated at 100 °C for 13 h. After concentration *in vacuo*, the residue was purified by column chromatography using an ion exchange resin [Dowex AG50W-X2, 1 M pyridine–AcOH buffer solution (pH 5)], giving **1a** as colorless crystals (22.9 mg, 88%). A pure sample of **1a** was obtained by recrystallization from water–EtOH, mp 202—205 °C (dec.), $[\alpha]_D^{20}$ −20.4° (*c* = 0.501, $H_2O$) [ref. 7*f* mp 214—215 °C (dec.), $[\alpha]_D^{20}$ −20.8° (*c* = 2.3, $H_2O$); ref. 16 mp 201—203 °C (dec.), $[\alpha]_D$ −20° (*c* = 0.64, $H_2O$)]. $^1$H-NMR ($D_2O$) $\delta$: 0.94 (6H, two d, *J* = each 5.7 Hz), 1.2—1.9 (3H, m), 2.48 (1H, dd, 7.0, 15 Hz), 2.53 (1H, dd, *J* = 5.1, 15 Hz), 3.30 (1H, m), 4.10 (1H, m). IR (KBr): 3440, 3220, 2970, 2890, 1600, 1550, 1510, 1430, 1390, 1170, 720 $cm^{-1}$. MS *m/z*: 176 ($M^+ + 1$), 172, 157, 140, 118, 100, 86, 40.

**(3*S*,4*S*)-Cyclohexylstatine (1b)** A mixture of **5b** (16.0 mg, 0.051 mmol), 6M HCl (2ml), and AcOEt (0.5 ml) was heated at 100 °C for 8 h. The reaction mixture was treated in the same manner as described for the preparation of **1a** to give **1b** (10.2 mg, 93%) as colorless crystals after concentration of the eluate from a column of ion exchange resin. A pure sample of **1b** was precipitated from a solution of **2a** in 1M HCl by neutralizing with 1 M NaOH. mp 213—216 °C (dec.), $[\alpha]_D^{20}$ −25.3° (*c* = 0.435, 1 M HCl). [ref. 7*c* mp 230—231 °C (dec.), $[\alpha]_D^{25}$ −26.2° (*c* = 1.0, 1 M HCl); ref. 7*h* mp 214—216 °C (dec.), $[\alpha]_D^{23}$ −22.49° (*c* = 0.979, 1 M HCl)]. $^1$H-NMR ($D_2O$) $\delta$: 0.8—2.0 (13H, m), 2.55 (2H, m), 3.35 (1H, m), 4.00 (1H, m). IR (KBr): 3430, 3220, 2950, 2880, 1610, 1550, 1510, 1440, 1385, 1335, 1115, 1070, 1035, 980, 885 $cm^{-1}$. MS *m/z*: 216 ($M^+ + 1$), 197, 126, 100, 55.

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