$ICH_2C(O)O$-*p*-$C_6H_4NO_2$, 31252-85-4; $BrCH_2C(O)O$-*p*-$C_6H_4NO_2$, 19199-82-7; $ClCH_2C(O)O$-*p*-$C_6H_4NO_2$, 777-84-4; *p*-nitrophenyl cyanoacetate, 80256-92-4; *p*-nitrophenyl methoxyacetate, 31252-86-5; glycine, 56-40-6; glycine methyl ester, 616-34-2; *N*-methylimidazole, 616-47-7; imidazole, 288-32-4; cyanoacetic acid, 372-09-8; methoxyacetyl chloride, 38870-89-2.

Highly Stereocontrolled Synthesis of the Four Individual Stereoisomers of Statine

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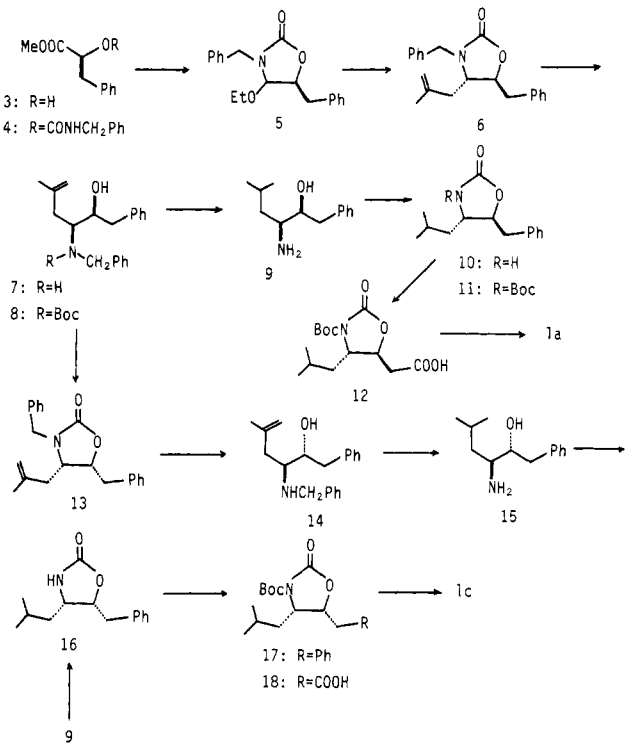
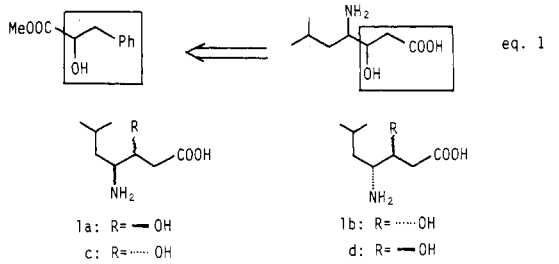
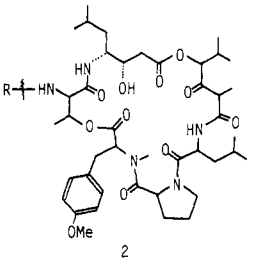
Pepstatin[1] is a natural peptide having the structure Iva-Val-Val-Sta-Ala-Sta, wherein statine is (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (**1a**). Incorporation of statine into appropriate peptide sequences has led to the discovery of potent human renin inhibitors.[2] Several methods for synthesis of statine have been reported.[3-5] The most practical methods among them appear to be those based on the aldol condensation of a N-protected form of (*S*)-leucinal (as the source of C_3 and C_4) with an acetic acid derivative (e.g., metalated, as the source of C_1 and C_2).[3] In the reported examples based on this approach, however, the 3*R*,4*S* isomer **1c** must be separated from (3*S*,4*S*)-statine (**1a**) by somewhat laborious column chromatography. Methods[4] for an asymmetric synthesis of (3*S*,4*S*)-statine of high enantiomeric purity starting from L-leucine have also been reported. Recently, the 3*S*,4*R* isomer **1d** of statine,[6] the isomer derived from D-leucine, has received considerable attention as a key component of the didemnins (**2**),[7,8] compounds with significant antitumor and antiviral activity. We have now developed a new method for synthesis of all four stereoisomers of statine with high enantiomeric purity. The 3*R*,4*S* and 3*S*,4*R* isomers were prepared by diastereoconversion of the 3*S*,4*S* and 3*R*,4*R* isomers, respectively, through an improved method involving cyclocarbamation.[9] Our synthetic strategy utilizes an α-hydroxyphenylpropionic acid ester, both enantiomers of which are readily available, as the synthon for the β-hydroxy carboxylic acid moiety (eq 1), and a highly diastereoselective isobutenylation[10] as the source of the 4-isobutyl group in the final products **1**. The results of these studies are described in this paper.

Scheme I







2

Condensation of benzyl isocyanate with methyl (*S*)-α-hydroxy-β-phenylpropionate (**3**), obtained by esterification of (*S*)-α-hydroxy-β-phenylpropionic acid,[11,12] yielded the carbamate **4** (Scheme I). Reduction of **4** with diisobutylaluminum hydride followed by treatment with ethanol (pH 1–2, 4 h) yielded the 4-ethoxy derivative **5** as a 1:1 mixture of 4,5-cis and -trans isomers in 95% yield from **4**. Isobutenylation at the 4-position was achieved by treatment of **5** with β-methallyltriphenylstannane ($TiCl_4$, CH_2Cl_2, 0 °C → room temperature, 10 h) to give **6** in 84%

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yield, a single product.[10] Ring cleavage of **6** (10% EtOH–NaOH, reflux, 14 h) gave the corresponding *threo*-(4*S*,5*S*)-4-(benzylamino)-5-hydroxy-2-methyl-6-phenylhex-1-ene (**7**) in 88% yield. The optical purity of **7** was determined as >98% ee by analysis of the Mosher esters[13] prepared by esterification of the carbamate **8** with both (+)- and (−)-α-(trifluoromethyl)-α-methoxy-phenylacetic acids. Catalytic hydrogenation of **7** on 10% Pd–C in EtOH under 1 atm of hydrogen afforded an 83% yield of the amino alcohol **9**. Carbonylation of **9** ($ClCOOCH_2Ph$, Et_3N, CH_2Cl_2, room temperature, 24 h) afforded the corresponding (4*S*,5*S*)-oxazolidin-2-one **10**. N-*tert*-Butoxycarbonylation of **10** (NaH, THF, Boc_2O, room temperature) yielded **11**. Conversion of the phenyl group in **11** to carboxyl was accomplished smoothly by oxidation with $RuCl_3$–$NaIO_4$ under Sharpless conditions,[14] providing **12** in 85% yield. Conversion of **12** to (3*S*,4*S*)-statine (**1a**) by hydrolysis of **12** and successive deprotection has been reported[9] previously. These results establish a new method for a stereoselective synthesis of (3*S*,4*S*)-statine or (beginning with (*R*)-**3**) of its 3*R*,4*R* enantiomer.

Several stereochemically controlled syntheses of 2-amino alcohols have been reported.[15,16] as well as a few examples of the conversion of one isomer to the other.[9,17,18] Thus our recent studies[9] have provided a practical method for diastereoconversion of the threo 2-amino alcohols **7** and **9** to the corresponding configurationally inverted oxazolidinones **13** and **16**, 5-epimers of **6** and **10**, respectively, which lead to (3*R*,4*S*)-statine (**1c**). Treatment of **8** with thionyl chloride at room temperature resulted in configurational inversion at the carbinol carbon[9,18] to give (4*S*,5*R*)-3,5-dibenzyl-4-isobutenyloxazolidin-2-one (**13**) in 88% yield. Ring cleavage of **13** as in **6** gave the amino alcohol **14**, which was converted to the corresponding (4*S*,5*R*)-*N*-Boc-5-benzyl-4-isobutyloxazolidin-2-one (**17**) through **15** and **16** according to the same conditions as for **7** through **8**, **9**, and **10**. Compounds **16** was also obtained by N-*tert*-butoxycarbonylation of **9**, followed by treatment with thionyl chloride, but in lower (23%) yield. Oxidation of **17** with $RuCl_3$–$NaIO_4$, as for **11** to **12**, afforded **18**. This step completes the formal synthesis of the 3*R*,4*S* isomer of statine, since transformation of **18** to *N*-Boc-(3*R*,4*S*)-statine has been reported previously.[19]

These stereoselective syntheses of statine (**1a**) and its 3*R*,4*S* diastereomer **1c** are readily adaptable for preparation of the corresponding 3*R*,4*R* (**1b**) and 3*S*,4*R* (**1d**) isomers. Thus, repetition of the synthetic steps described above and outlined in Scheme I using (*R*)-α-hydroxy-β-phenylpropionate, obtained by esterification of (*R*)-α-hydroxy-β-phenylpropionic acid,[11,12,20] in place of the *S* isomer **3** provided the enantiomer of all of the compounds shown in Scheme I, including the 3*R*,4*R* (**1b**) and 3*S*,4*R* (**1d**) isomers of statine. The latter compound, **1d**, is of considerable potential utility for synthesis of the didemnins (**2**).

Experimental Section

General Methods. ^1H NMR spectra were recorded on either a Varian EM-390 (90 MHz) or Bruker AM-400 (400 MHz) spectrometer. For NMR work, $CDCl_3$ was used as a solvent and tetramethylsilane as an internal standard unless otherwise noted. NMR abbreviations: s, singlet; d, doublet; m, multiplet; br, broad. IR spectra were obtained on a Hitachi 260-30 infrared spectrophotometer. Mass spectra (MS) were taken with a Hitachi RMU-7L instrument. EI MS of **6**, **7**, **9**, **10**, **12**–**17**, and their antipodes did not give M^+ ion peaks, but their $M^+ + 1$ ion peaks were given by their CI MS. Optical rotations were measured on a JASCO DIP-4 instrument.

(*S*)-Methyl 2-Hydroxy-3-phenylpropionate (3). A stirred mixture of (*S*)-2-hydroxy-3-phenylpropionic acid[11] (50 g, 0.3 mol), MeOH (250 mL), toluene (125 mL), and concentrated HCl (1.7 mL) was heated under reflux for 4 h. After the mixture was made neutral with 5% $NaHCO_3$, the solvent was evaporated and extracted. The remaining residue was extracted with benzene. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give 50 g (92% yield) of **3a**: bp 110–115 °C (3 Torr); $[\alpha]_D$ +3.93° (*c* 1.33, methanol); ^1H NMR ($CDCl_3$) δ 2.91 (1 H, dd, *J* = 6, 14 Hz), 3.12 (1 H, *J* = 5, 14 Hz), 3.72 (3 H, s), 4.43 (1 H, dd, *J* = 5, 6 Hz), 7.24 (5 H, br s); MS, *m/z* 180 (M^+); IR ($CHCl_3$) 1740 cm^{-1}.

***R* Isomer of 3.** This compound was obtained from (*R*)-2-hydroxy-3-phenylpropionic acid[11,12,20] (50 g, 0.3 mol) according to the same conditions as above in 90% yield (48.8 g): bp 110–115 °C (3 Torr); $[\alpha]_D$ −3.99° (*c* 1.25, methanol). The spectral data were identical with those of (*S*)-**3**.

***S* Carbamate 4.** A mixture of (*S*)-methyl α-hydroxy-β-phenylpropionate (9 g, 50 mmol), benzyl isocyanate (7.31 g, 55 mmol), and toluene (30 mL) was heated under reflux for 4 h. The solvent was removed, and the residual oil was chromatographed on silica gel (30 g). Elution with hexane–AcOEt (9:1) yielded **4** (15.2 g, 92% yield) as an oil: ^1H NMR δ 2.96 (1 H, dd, *J* = 8, 16 Hz), 3.12 (1 H, dd, *J* = 5, 16 Hz), 3.63 (3 H, s), 4.23 (2 H, d, *J* = 6 Hz), 5.22 (1 H, dd, *J* = 5, 8 Hz), 7.16–7.26 (10 H, m); IR ($CHCl_3$) 1720, 1750 cm^{-1}; MS, *m/z* 331 (M^+).

***R* Isomer of 4.** This compound was prepared from the *R* isomer of **3** (9 g, 50 mmol) and benzyl isocyanate (7.31 g, 55 mmol) according to the same conditions as above in 94% yield (15.6 g) as an oil. The spectral data were identical with those of **4**.

(5*S*)-3,5-Dibenzyl-4-ethoxyoxazolidin-2-one (5). To a stirred solution of **4** (10 g, 33 mmol) in toluene (50 mL) was added a solution of DIBAH (56 mL of a 1 M hexane solution, 56 mmol) at −78 °C. After the stirring had been continued for 40 min, the mixture was decomposed with water. The inorganic precipitate was removed by filtration, and the filtrate was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. To a stirred solution of the residual oil in EtOH (100 mL) was added concentrated HCl (6 mL) at room temperature. After the stirring had been continued for 4 h, the mixture was made basic with saturated $NaHCO_3$. The solvent was evaporated, and the remaining residue was extracted with $CHCl_3$. Removal of the solvent gave **5** (9.75 g, 95% yield) as a 1:1 mixture of 4,5-cis and -trans isomers; this was used for the following reaction without purification.

***5R* Isomer of 5.** This compound was obtained from the *R* isomer of **4** (10 g, 33 mmol) according to the same conditions as above. The spectra were identical with those of **5** in all respects.

(4*S*,5*S*)-4-Isobutenyl-3,5-dibenzyloxazolidin-2-one (6). To a stirred solution of **5** (6.22 g, 20 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (7.3 mL of a 3 M solution in CH_2Cl_2, 22 mmol) with ice cooling. After 3 min, a solution of β-methallyltriphenylstannane (8.91 g, 22 mmol) in CH_2Cl_2 (15 mL) was added at the same temperature. After being stirred for 12 h, the mixture was

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poured onto ice–water, made basic with 28% ammonia, and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on silica gel (30 g). Elution with hexane–AcOEt (10:1) gave the decomposed stannane, which was discarded. Further elution with hexane–AcOEt (3:1) afforded **6** (5.4 g, 84% yield) as an oil: ^1H NMR δ 1.34 (3 H, s), 1.98 (1 H, dd, J = 10, 13.5 Hz), 2.32 (1 H, dd, J = 4, 13.5 Hz), 2.69 (1 H, dd, J = 7, 14 Hz), 2.82 (1 H, dd, J = 7, 14 Hz), 3.18–3.38 (1 H, m), 3.88 (1 H, d, J = 16 Hz), 4.75 (1 H, d, J = 16 Hz), 4.27–4.42 (1 H, m), 4.64–4.85 (2 H, m), 6.91–7.33 (10 H, m); IR ($CHCl_3$) 1750 cm^{-1}; CI MS, m/z 322 (M^+ + 1); $[\alpha]_D$ −22.86° (c 1.25, MeOH).

4*R*,5*R* Isomer of 6. this compound was obtained in 86.3% yield (5.54 g) from the 5*R* isomer of **5** (6.22 g, 20 mmol) according to the same conditions as above. The spectral data were identical with those of **6**: $[\alpha]_D$ +23.40° (c 1.11, MeOH).

(4*S*,5*S*)-4-(Benzylamino)-5-hydroxy-2-methyl-6-phenyl-1-hexene (7). A mixture of **6** (3.21 g, 10 mmol), EtOH (27 mL), and 50% NaOH (6 g) was heated under reflux for 10 h. After the solvent was evaporated, the remaining residue was diluted with water and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (15 g) by using $CHCl_3$ as an eluant. Removal of the solvent gave **7** (2.60 g, 88% yield) as an oil: ^1H NMR δ 1.61 (3 H, s), 2.10–2.33 (2 H, m), 2.58–2.99 (3 H, m), 3.52–3.71 (1 H, m), 3.78 (2 H, s), 4.72–4.84 (2 H, m), 7.21 (5 H, s), 7.27 (5 H, s); CI MS, m/z 296 (M^+ + 1); $[\alpha]_D$ +10.25° (c 2.10, $CHCl_3$).

(4*S*,5*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]-5-hydroxy-2-methyl-6-phenyl-1-hexene (8). To a mixture of **7** (2 g, 6.78 mmol), Et_3N (2.02 g, 20 mmol), and CH_2Cl_2 (5 mL) was added di-*tert*-butyl dicarbonate (1.27 g, 6.80 mmol) with ice cooling. After 4 h, the mixture was decomposed with water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel (15 g). Elution with hexane afforded an uncharacterized product, which was discarded. Successive elution with hexane–AcOEt (7:1) gave **8** (2.57 g, 97% yield): mp 91–93 °C; ^1H NMR δ 1.44 (9 H, s), 1.61 (3 H, s), 2.32–2.82 (3 H, m), 3.66–3.96 (1 H, m), 4.32–4.46 (1 H, m), 4.74 (2 H, br s), 7.18–7.27 (10 H, m); IR ($CHCl_3$) 1750 cm^{-1}; $[\alpha]_D$ −17.20° (c 1.20, $CHCl_3$). The optical purity was determined as >98% ee by analysis of the ^1H NMR spectra (400 MHz) of the Mosher esters obtained from both (+)- and (−)-α-(trifluoromethyl)-α-methoxyphenylacetic acids.

Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.59. Found: C, 75.65; H, 8.33; N, 3.56.

4*R*,5*R* Isomer of 7. This compound was obtained from the 4*R*,5*R* isomer of **6** (3.21 g, 10 mmol) according to the same conditions as above. Its spectral data were identical with those of **7** in all respects: $[\alpha]_D$ −10.03° (c 2.30, $CHCl_3$).

4*R*,5*R* Isomer of 8. This compound was obtained from the 4*R*,5*R* isomer of **7** (2 g, 6.78 mmol) in 95% yield (2.54 g) under the same conditions as above. The spectral data were identical with those of **8**, mp 92–93.5 °C; $[\alpha]_D$ +17.16° (c 2.00, $CHCl_3$).

Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.59. Found: C, 75.75; H, 8.43; N, 3.46.

(2*S*,3*S*)-3-Amino-2-hydroxy-5-methyl-1-phenylhexane (9). A mixture of **7** (2.5 g, 8.47 mmol), EtOH (200 mL), and 10% Pd–C (2 g) was shaken under 1 atm of H_2 at room temperature until uptake had ceased after absorption of the theoretical amount (about 400 mL). The catalyst was removed by filtration, and the filtrate was evaporated. The resulting residue was chromatographed on silica gel (10 g) by using $CHCl_3$ as an eluant. Removal of the solvent gave **9** (1.46 g, 83% yield): mp 71–72.5 °C; ^1H NMR δ 0.87 (3 h, d, J = 6 Hz), 0.90 (3 H, d, J = 6 Hz), 1.18–1.43 (2 H, m), 1.43–2.00 (1 H, m), 2.52–2.96 (3 H, m), 3.40–3.59 (1 H, m), 7.23 (5 H, br s); CI MS, m/z 208 (M^+ + 1); $[\alpha]_D$ −31.40° (c 1.00, $CHCl_3$).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.79. Found: C, 74.99; H, 10.28; N, 6.58.

2*R*,3*R* Isomer of 9. This compound was obtained in 80% yield (1.40 g) from the 4*R*,5*R* isomer of **7** (2.50 g, 8.47 mmol) according to the same conditions used in preparation of **9**, mp 71–72 °C. The spectral data were identical with those of **9**: $[\alpha]_D$ +31.10° (c 1.20, $CHCl_3$).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.79. Found: C, 75.15; H, 10.03; N, 6.57.

(4*S*,5*S*)-5-Benzyl-4-isobutyloxazolidin-2-one (10). To a stirred mixture of **9** (1.3 g, 6.28 mmol), Et_3N (1.9 g, 18.84 mmol), and CH_2Cl_2 (12 mL) was added benzyl chloroformate (4.46 mL of a 30% toluene solution) with ice cooling. After stirring had been continued at room temperature for 18 h, the mixture was diluted with $CHCl_3$ (50 mL) and washed with 5% HCl and H_2O. The solvent was evaporated, and the resulting residue was chromatographed on silica gel (15 g). Elution with hexane–AcOEt (5:1) afforded **10** (1.29 g, 88% yield) as an oil: ^1H NMR δ 0.78 (3 H, d, J = 6.5 Hz), 0.81 (3 H, d, J = 6.5 Hz), 1.13–1.77 (3 H, m), 2.84 (1 H, dd, J = 7, 14 Hz), 3.11 (1 H, ddd, J = 6, 14 Hz), 3.46–3.68 (1 H, m), 4.14–4.37 (1 H, m), 7.29 (5 H, br s); CI MS, m/z 234 (M^+ + 1); IR ($CHCl_3$) 1750 cm^{-1}.

4*R*,5*R* Isomer of 10. This compound was obtained in 86% yield (1.12 g) from the 2*R*,3*R* isomer of **9** (1.30 g, 6.28 mmol) according to the same conditions as above. The spectral data were identical with those of **10**.

(4*S*,5*R*)-3,5-Dibenzyl-4-isobutenyloxazolidin-2-one (13). To a solution of **8** (1 g, 2.53 mmol) in CH_2Cl_2 (5 ml) was added thionyl chloride (3 g, 25.3 mmol) with ice cooling. After stirring had been continued at room temperature for 10 h, the mixture was poured onto ice–water and made basic with 28% ammonia. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave **13** (714 mg, 88% yield): mp 91–94 °C; ^1H NMR δ 1.66 (3 H, s), 2.10–2.63 (2 H, m), 2.77–3.17 (2 H, m), 3.74–4.00 (1 H, m), 4.14 (1 H, d, J = 16 Hz), 5.36 (1 H, d, J = 16 Hz), 4.53–4.80 (1 H, m), 4.74–4.92 (2 h, m), 7.20–7.30 (10 H, m); CI MS, m/z 322 (M^+ + 1); $[\alpha]_D$ +47.70° (c 0.65, MeOH).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.75; H, 7.46; N, 4.15.

4*R*,5*S* Isomer of 13. This compound was obtained in 88% yield (714 mg) from the 4*R*,5*R* isomer of **8** (1 g, 2.53 mmol) according to the same conditions as above, mp 91–94 °C. The spectral data were identical with those of **13**: $[\alpha]_D$ −47.6° (c 0.30, MeOH).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.54; H, 7.28; N, 4.51.

(4*S*,5*R*)-4-(Benzylamino)-5-hydroxy-2-methyl-6-phenyl-1-hexene (14). A mixture of **13** (1.6 g, 50 mmol), EtOH (15 mL), and 50% NaOH (4 g) was heated under reflux for 10 h and worked up as in **7** to yield **14** (1.33 g, 90% yield) as an oil: ^1H NMR δ 1.53 (3 H, s), 2.14–2.36 (2 H, m), 2.51–2.98 (3 H, m), 3.57 (1 H, d, J = 14 Hz), 3.81 (1 H, d, J = 14 Hz), 3.88–4.11 (1 H, m), 4.71–4.87 (2 H, m), 7.23 (5 H, s), 7.27 (5 H, s); CI MS, m/z 296 (M^+ + 1).

4*R*,5*S* Isomer of 14. This compound was obtained in 88% yield (1.30 g) as an oil from the 4*R*,5*S* isomer of **13** (1.6 g, 50 mmol) according to the same conditions as above. The spectral data were identical with those of **14**.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-methyl-1-phenylhexane (15). A mixture of **14** (1 g, 3.39 mmol), 10% Pd–C (0.8 g), and EtOH (100 mL) was stirred under 1 atm of H_2 and worked up as in **9** to give **15** (575 mg, 82% yield): mp 82–85 °C; ^1H NMR δ 0.89 (3 H, d, J = 6 Hz), 0.98 (3 H, d, J = 6 Hz), 1.11–1.92 (3 H, m), 2.48–3.00 (3 H, m), 3.56–3.79 (1 H, m), 7.30 (5 H, br s); $[\alpha]_D$ +14.0° (c 1.5, $CHCl_3$).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.19; H, 10.28; N, 6.58.

2*S*,3*R* Isomer of 15. This compound was obtained from the 4*R*,5*S* isomer of **14** (1 g, 3.39 mmol) in 80% yield (561 mg): mp 81–83 °C; $[\alpha]_D$ −14.6° (c 1.20, $CHCl_3$). The spectral data were identical with those of **15**.

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.39; H, 10.34; N, 6.65.

(4*S*,5*R*)-5-Benzyl-4-isobutyloxazolidin-2-one (16). Method A. This compound was obtained from **15** (500 mg, 2.42 mmol) in 84% yield (473 mg) according to the same conditions as in **10**: mp 113–115 °C; ^1H NMR δ 0.90 (3 H, d, J = 6.5 Hz), 1.00 (3 H, d, J = 6.5 Hz), 1.20–1.83 (3 H, m), 2.82 (1 H, dd, J = 5, 14 Hz), 3.06 (1 H, dd, J = 9, 14 Hz), 3.78–4.02 (1 H, m), 4.69–4.93 (1 H, m), 7.28 (5 H, s); CI MS, m/z 234 (M^+ + 1); $[\alpha]_D$ +33.31° (c 0.75, MeOH). **Method B.** To a stirred mixture of **9** (500 mg, 2.4 mmol), Et_3N (730 mg, 7.2 mmol), and CH_2Cl_2 (10 ml) was added Boc_2O (500 mg, 2.7 mmol) with ice cooling. After stirring had been continued for 4 h, the mixture was diluted with $CHCl_3$ and washed

with 5% HCl and water. The solvent was evaporated, and the resulting residue was chromatographed on silica gel (10 g). Elution with hexane–AcOEt (7:1) gave *N*-Boc-**9** (645 mg, 88% yield) as an oil: ^{1}H NMR δ 0.98 (3 H, d, J = 6 Hz), 0.91 (3 h, 6 Hz), 1.47 (9 H, s), 1.10–2.07 (3 H, m), 2.69–2.96 (2 H, m), 3.50–3.84 (1 H, m), 4.60–4.87 (1 H, m), 7.27 (5 H, br s); this material was used for the following reaction without further purification. To a stirred solution of this in CH_2Cl_2 (2 mL) was added $SOCl_2$ (2 mL) with ice cooling. After the stirring had been continued at room temperature for 12 h, the mixture was decomposed with water, made basic with 28% ammonia, and extracted with $CHCl_3$. The solvent was evaporated, and the remaining residue was chromatographed on silica gel (10 g). Elution with hexane afforded an uncharacterized product, which was discarded. Successive elution with hexane–AcOEt (5:1) gave **16** (129 mg, 23% yield).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.84; H, 8.19; N, 5.98.

4*R*,5*S* Isomer of 16. Method A. This compound was obtained from the 2*S*,3*R* isomer of **15** (500 mg, 2.42 mmol) in 85% yield (478 mg) according to the same conditions used to prepare **10** from **9**: mp 113–115 °C; $[\alpha]_D$ −33.43° (*c* 0.61, MeOH). The spectral data were identical with those of **16**. **Method B.** A stirred mixture of the 2*R*,3*R* isomer of **9** (500 mg, 2.4 mmol), Et_3N (730 mg, 7.2 mmol), and CH_2Cl_2 (10 mL) was treated with Boc_2O (500 mg, 2.7 mmol) with ice cooling and worked up as in the preparation of **16**. The product was treated with $SOCl_2$ (2 mL) and worked up as above to give the 4*R*,5*S* isomer of **16** (120 mg, 21.4% yield).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.95; H, 8.03; N, 6.08.

General Procedure for 3-*tert*-Butoxycarbonylation of 10, 16, and Their Antipodes. To a stirred suspension of NaH (94 mg of a 60% suspension in oil, used after removal of oil by washing with petroleum ether) in THF (5 mL) was added a solution of **10** (or **16** or their antipodes) (500 mg, 2.15 mmol) in THF (5 mL). To this solution was added Boc_2O (400 mg, 2.15 mmol) with ice cooling. After stirring had been continued for 10 h at room temperature, the mixture was poured into H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated.

(4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-4-isobutyl-5-benzyloxazolidin-2-one (11). This compound was obtained in 86% yield (615 mg) as an oil: ^{1}H NMR δ 0.68 (3 H, d, J = 6 Hz), 0.88 (3 h, d, J = 6 Hz), 1.03–1.63 (3 H, m), 1.50 (9 H, s), 2.83 (1 H, dd, J = 7, 14 Hz), 3.04 (1 H, dd, J = 5.5, 14 Hz), 3.87–4.04 (1 H, m), 4.23–4.40 (1 H, m), 7.27 (5 H, br s); EI and CI MS did not give either M^+ or $M^+ + 1$.

4*R*,5*R* Isomer of 11. This compound was obtained in 88% yield (629 mg) as an oil, the spectral data of which were identical with those of **11**.

(4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-4-isobutyl-5-benzyloxazolidin-2-one (17). This compound was obtained in 85% yield (607 mg): mp 119–121 °C; ^{1}H NMR δ 0.97 (3 H, d, J = 6.5 Hz), 1.01 (3 H, d, J = 6.5 Hz), 1.09–1.69 (3 H, m), 1.53 (9 H, s), 2.86 (1 H, dd, J = 5, 14 Hz), 3.09 (1 H, dd, J = 8, 14 Hz), 4.22–4.43 (1 H, m), 4.62–4.84 (1 H, m), 7.30 (5 H, br s); $[\alpha]_D$ +26.0° (*c* 1.10, MeOH).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.42; H, 8.11; N, 4.01.

4*R*,5*S* Isomer of 17. This compound was obtained in 86% yield (615 mg), mp 120–121 °C. The spectral data were identical with those of **17**: $[\alpha]_D$ −26.7° (*c* 1.05, MeOH).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.40; H, 8.01; N, 4.11.

General Procedure for Oxidation of 11, 17, and Their Antipodes. A mixture of **11** (or **17** or their antipodes) (333 mg, 1 mmol), $RuCl_3 \cdot 3H_2O$ (5.75 mg, 0.022 mmol), $NaIO_4$ (3.2 g, 15 mmol), CH_3CN (2 mL), CCl_4 (2 mL), and H_2O (3 mL) was stirred over 48 h at room temperature. The mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel (10 g). Elution with hexane–AcOEt (1:1) yielded **12** (or **18**).

(4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-5-(carboxymethyl)-4-isobutyloxazolidin-2-one (12). This compound was obtained in 85% yield (256 mg): mp 70–72 °C (lit.,[9] oil); $[\alpha]_D$ +23.4° (*c* 1.04, $CHCl_3$) (lit.[9] $[\alpha]_D$ +23.32° (*c* 0.92, $CHCl_3$)). The spectral data were identical with those of the authentic specimen.[9]

4*R*,5*R* Isomer of 12. This compound was obtained in 82% yield (247 mg): mp 70–72 °C; $[\alpha]_D$ −23.5° (*c* 0.92, $CHCl_3$). The spectral data were identical with those of **12**.

(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-5-(carboxymethyl)-4-isobutyloxazolidin-2-one (18). This compound was obtained in 83% yield (250 mg): mp 67–69 °C (lit.[16] mp 68–70 °C); $[\alpha]_D$ +34.6° (*c* 0.96, MeOH) (lit.[19] $[\alpha]_D$ +34.64° (*c* 0.56, MeOH)). The spectral data were identical with those of the authentic specimen.[19]

4*R*,5*S* Isomer of 18. This compound was obtained in 83% yield (250 mg): mp 66–69 °C; $[\alpha]_D$ −34.0° (*c* 0.67, MeOH). The spectral data were identical with those of **18**.

Synthesis of (3*S*,4*S*)-Dihydro-4-ethyl-3-hydroxy-4-methyl-2(3*H*)-furanone, a Pantolactone Homologue Isolated from *Marshallia tenuifolia*[1]

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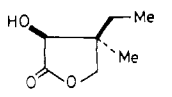
Recently, Herz and Bruno reported the isolation and structural determination of several natural products from the $CHCl_3$ extracts of the above-ground parts of *Marshallia tenuifolia*.[2] These included *p*-hydroxybenzaldehyde, phloroglucinol derivatives, new flavonoids, polyacylated inositols, and optically active γ-lactones. Among these natural products, a hitherto unknown γ-lactone, (3*S*,4*S*)-dihydro-4-ethyl-3-hydroxy-4-methyl-2(3*H*)-furanone (**1**), arouses interest from the biosynthetic point



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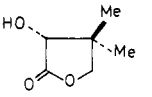

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of view. The absolute configuration of **1** was assigned by comparison of the CD spectrum of **1** with that of (*R*)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone (**2**),[3] a degradation product of pantothenic acid in the liver. The biosynthesis of pantoic acid, (*R*)-2,4-dihydroxy-3,3-dimethylbutanoic acid, from L-valine via α-ketoisovalerate and α-ketopantoate involves an overall inversion at C-2 with the secondary hydroxyl group.

Consequently, if the absolute configuration is correct and if the biosynthesis of **1** follows an analogous course to that of pantoic acid, conversion of L-isoleucine, a likely precursor, into **1** would entail overall retention at C-2 as well as C-3.[2] Therefore, it is important to establish the absolute configuration of **1** for elucidation of the biosynthetic correlation between **1** and **2**. We wish to disclose in this Note the confirmation of the proposed absolute configuration for the pantolactone homologue **1** through its enantiospecific synthesis.

Our synthesis of **1** commenced with the enantiomerically pure highly substituted tetrahydrofuran derivative **3**, which was readily prepared from D-glucose by employing the ortho ester Claisen rearrangement for the introduction of the quaternary carbon.[4] The configuration of the qua-

(1) This work was presented at the 56th National Meeting of the Japan Chemical Society in Tokyo, April 1–4, 1988; Abstract 1IXB30.
(2) Herz, W.; Bruno, M. *Phytochemistry* **1987**, *26*, 1175.
(3) Schippers, P. H.; Dekkers, H. P. J. *Anal. Chem.* **1981**, *53*, 778.

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