Novel Synthesis of Three Types of C-Terminal Components of Renin Inhibitors from Unnatural (2*S*,3*S*)-Tartaric Acid[1)]

Yuko KOBAYASHI,[a] Teruyo MATSUMOTO,[a] Yoshiji TAKEMOTO,[a] Kazuhiko NAKATANI,[a] Yoshio ITO,[a] Tetsuhide KAMIJO,[b] Hiromu HARADA[b] and Shiro TERASHIMA*,[a]

Sagami Chemical Research Center,[a] 4–4–1, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan and Central Research Laboratories, Kissei Pharmaceutical Co., Ltd.,[b] 19–48, Yoshino, Matsumoto, Nagano 399, Japan. *Received May 8, 1991*

The addition reaction of cyclohexylmethylmagnesium bromide with the imine prepared from unnatural (2*S*,3*S*)-tartaric acid was found to proceed in a highly stereoselective manner in the presence of cerium(III) chloride. A chelation-controlled mechanism could explain the stereochemical outcome of the addition reaction. The addition product could be elaborated into three types of C-terminal components of renin inhibitors by employing oxidative cleavage of the 1,2-diol moiety, epoxide formation with inversion of configuration, and epoxide opening with a nucleophile.

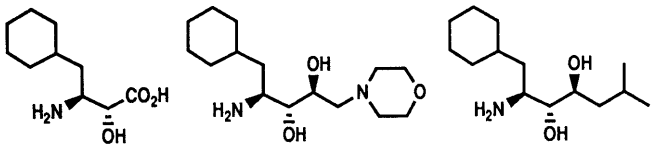
Keywords renin inhibitor; C-terminal component; 1,2-amino alcohol; 1,2,3-amino diol; Grignard reagent; cerium(III) chloride; chelation control; oxidative cleavege; epoxide formation; epoxide opening

Renin is a highly specific aspartic acid protease which cleaves a decapeptide fragment from angiotensinogen to generate angiotensin I.[2)] While no biological activity is observed for angiotensin I, the octapeptide angiotensin II produced from angiotensin I by angiotensin-converting enzyme shows a potent vasoconstricting activity and stimulates the release of aldosterone. Thus, renin inhibitors are currently the object of intensive research aimed at development of novel antihypertensive drugs.[2)]

Some of the renin inhibitors recently developed as promising antihypertensive agents with oral efficacy involve either (2*R*,3*S*)-3-amino-2-hydroxy-4-cyclohexylbutyric acid [(2*R*,3*S*)-cyclohexylnorstatine] (**1**),[3)] (2*S*,3*R*,4*S*)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (**2**),[4)] or (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-6-methyl-3,4-heptanediol (**3**)[5)] as their C-terminal component. These unusual amino alcohols (**1**, **2**, and **3**) were originally synthesized from (*S*)-phenylalanine[3,5)] or D-glucose,[4)] and ingeniously incorporated into renin inhibitors as isosteres of the Leu–Val scissile site in angiotensinogen. Recently, several novel synthetic routes to **1** from (*S*)-phenylalanine[6)] or (*R*)-mandelic acid[7)] and to **2** and **3** from optically active epoxy alcohols[8,9)] have also been reported.

With the aim of preparing **1**, **2**, and **3** from readily available unnatural (2*S*,3*S*)-tartaric acid (**4**), the novel synthetic route depicted in Chart 1 was designed. Thus, the amino alcohols (**1**, **2**, and **3**) could be derived from the amine (**6**) by manipulating its terminal protected diol moiety. Addition of cyclohexylmethylmagnesium bromide with the imine (**5**) would afford **6** if the addition reaction proceeds with the desired high stereoselectivity. Preparation of **5** might be readily achieved from **4** according to the reported procedures.[7,10,11)] After many unsuccessful attempts,[12)] we found that the addition reaction of cyclohexylmethylmagnesium bromide with **5** took place in a highly stereoselective manner in the presence of cerium(III) chloride, yielding **6** as a sole product. The addition product (**6**) could be elaborated to **1**, **2**, and **3** by sequential chemical manipulations.

This report details highly stereoselective syntheses of **1**, **2**, and **3** from **4** accomplished by featuring the novel addition reaction of a Grignard reagent with an imine in the presence of cerium(III) chloride.[13)]

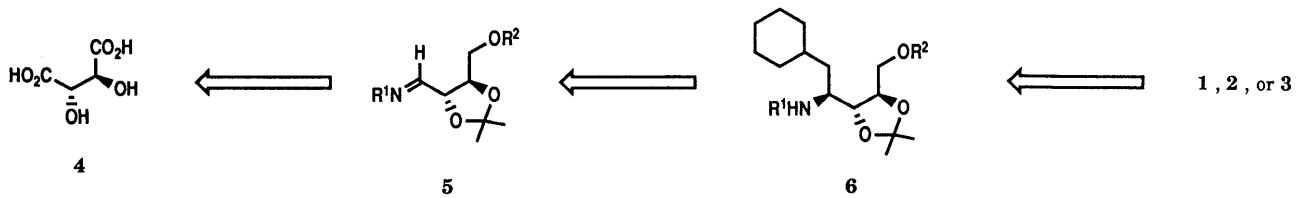


1 **2** **3**

Fig. 1

Results and Discussion

Synthesis of (2*R*,3*S*)-Cyclohexylnorstatine (1) 4-*O*-Benzyl-2,3-isopropylidene-D-threose (**7**) was prepared from **4** according to the reported procedure.[10)] Condensation of **7** with benzylamine ($BnNH_2$) in the presence of anhydrous magnesium sulfate readily afforded the imine (**8**) in a quantitative yield.[7,11)] Initially, the imine (**8**) was allowed to react with cyclohexylmethylmagnesium bromide in various solvents. However, contrary to our expectation, no addition product could be produced and complete recovery of **8** was always observed. After these unsuccessful experiments, it was found, as shown in Chart 2, that when cyclohexylmagnesium bromide was first treated with cerium(III) chloride in a mixture of ether and tetrahydrofuran and the resulting cerium(III) complex was reacted with **8**, the addition reaction could proceed smoothly in a highly stereoselective manner, giving rise to the amine



4 **5** **6** **1**, **2**, or **3**

Chart 1

(**9**), $[\alpha]_D^{20}$ +12.3° (chloroform), as a sole product in 75% yield (*vide infra*).[13]

Since stereoselective addition reaction of an organocopper(I) reagent with an imine had been reported,[15] the reaction of **8** with cyclohexylmethylcopper(I) was next examined. Interestingly, treatment of **8** with cyclohexylmethylcopper(I) in the presence of boron trifluoride-etherate in a mixture of ether and tetrahydrofuran according to the reported procedure[15] was found to give the undesired diastereomer (**13**), $[\alpha]_D^{20}$ +26.7° (chloroform), as a sole product in 52% yield (*vide infra*). The organocopper(I) reagent could be produced *in situ* from cyclohexylmethylmagnesium bromide and copper(I) iodide at −78 °C prior to the addition reaction.

Comparison of the 400 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **9** with that of **13** established that each addition product (**9** or **13**) was not contaminated with the other diastereomer (**13** or **9**). Taking into account of the accuracy of 400 MHz ^{1}H-NMR spectra, the stereoselectivities for the two sorts of addition reactions could be calculated as more than 98%. The stereochemistries of diastereometric **9** and **13** could be firmly established at the stages of the oxazolidin-2-one derivatives (**10** and **14**) (*vide infra*). As shown in Fig. 2, highly stereoselective formation of **9** may be explained by a chelation-controlled mechanism (A) in which M represents magnesium(II), cerium(III) or a complex of both cations. On the other hand, the dipolar model (B) or the Felkin–Anh model (C) may account for the highly stereoselective addition of cyclohexylmethylcopper(I) with **8**, as claimed for a similar addition reaction.[15]

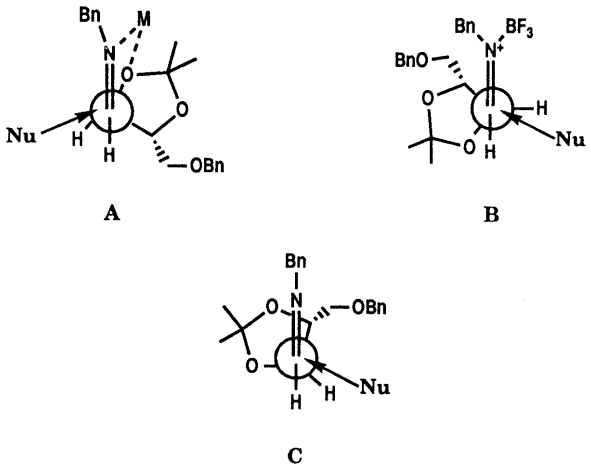
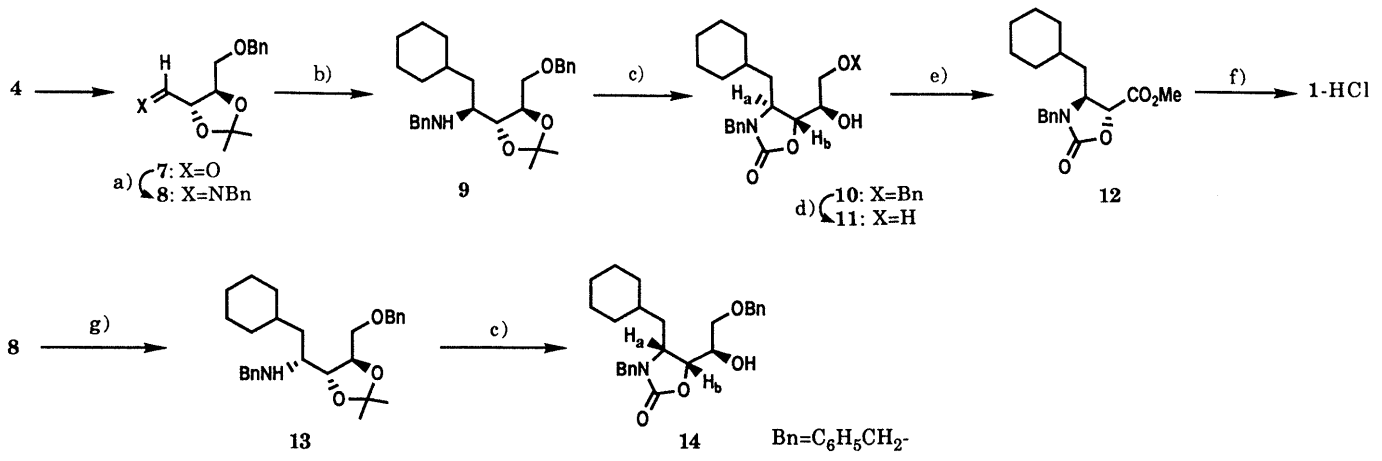


Fig. 2

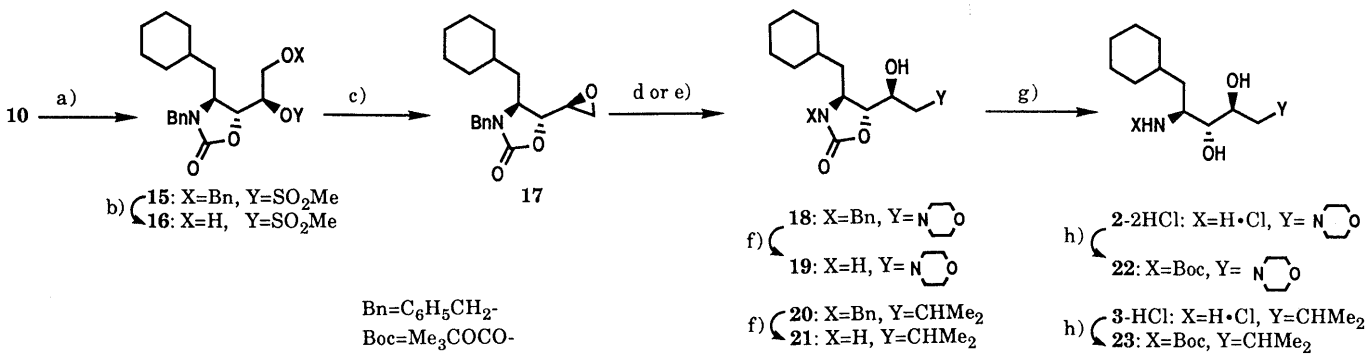
With **9** in hand, elaboration **9** to **1** was next attempted. Thus, methoxycarbonylation of **9** followed by deacetalization and oxazolidin-2-one formation produced **10**, $[\alpha]_D^{20}$ −29.7° (chloroform), in 90% overall yield. The same sequential treatment of **13** gave **14**, $[\alpha]_D^{20}$ −31.6° (chloroform), in 94% overall yield. The coupling constants between H_a and H_b protons in **10** and **14** were found to be 5.1 and 8.5 Hz, respectively. Based on these spectral features as well as successful synthesis of **1** from **10**, the absolute stereochemistries of **10** and **14**, namely those of **9** and **13**, could be rigorously assigned as depicted. Hydrogenation of **10** quantitatively gave the diol (**11**), which, on oxidative cleavage and subsequent esterification, produced the methyl ester (**12**) in 73% combined yield. This was readily derived to the hydrochloride of **1** (**1**·HCl) in 76% overall yield by sequential alkaline hydrolysis of the oxazolidin-2-one moiety, salt formation, hydrogenolysis of the N-benzyl group, removal of inorganic salt with an ion exchange resin, and salt formation. The hydrochloride of **1** (**1**·HCl) thus produced exhibited mp 191—192 °C (dec.) and $[\alpha]_D^{20}$ −13.6° (1 M HCl) [lit.,[6] mp 190 °C (dec.) and $[\alpha]_D^{20}$ −12.4° (1 M HCl)][16] and the same ^{1}H-NMR spectrum as that of an authentic sample.[3c,6]

Synthesis of (2*S*,3*R*,4*S*)-4-Amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (2) and (2*S*,3*R*,4*S*)-2-Amino-1-cyclohexyl-6-methyl-3,4-heptanediol (3) With completion of the synthesis of **1**·HCl from **9**, highly stereo- and regioselective elaboration of **9** to **2** and **3** was next attempted by employing epoxide formation with inversion of configuration followed



a) $BnNH_2$ (1.0 eq)–anhyd. $MgSO_4$ in PhMe, 0 °C, 1.5 h, 100% b) i) $C_6H_{11}CH_2MgBr$ (5.0 eq)–$CeCl_3$ (5.0 eq) in Et_2O–THF, −30 °C, 5 h ii) **8** in Et_2O–THF, −30 °C, 2 h, then, r.t., 12 h, 75% from **8** c) i) $ClCO_2Me$–anhyd. K_2CO_3 in THF, 0 °C, 7 h ii) 80% aq AcOH, 80 °C, 5 h iii) 10% KOH in MeOH, r.t., 3.5 h, 90% (**9**) from **10** or 94% (**14**) from **13** d) H_2 (1 atm)–20% $Pd(OH)_2$/C in MeOH, r.t., overnight, 100% e) i) $RuCl_3 \cdot 3H_2O$–$NaIO_4$ in CCl_4–MeCN–H_2O, r.t., 2 h ii) $TMSCHN_2$ in PhH–MeOH, r.t., 1 h, 73% from **11** f) i) NaOH in MeOH–H_2O, 90 °C, overnight ii) aq HCl iii) H_2 (1 atm)–20% $Pd(OH)_2$/C in MeOH, r.t., overnight iv) Dowex AG 50W-X2, H^+-form v) aq HCl, 76% from **12** g) i) $C_6H_{11}CH_2MgBr$ (2.7 eq)–CuI (2.7 eq) in Et_2O–THF, −78 °C, 10 min ii) **8** in Et_2O–THF, −78 °C, 1 h, then, r.t., 15 h, 52% from **8**

Chart 2



a) $MeSO_2Cl$ (1.3 eq) in Py, 0 °C, 3 h, 96% b) H_2 (1 atm)–20% $Pd(OH)_2/C$ in MeOH, r.t., 2 d, 98% c) NaOMe (8.3 eq) in THF, 0 °C, 0.5 h, 94% d) morpholine (2.1 eq) in MeOH, r.t., 1 d, 94% e) $Me_2CHMgCl$ (3.0 eq)–CuI (0.16 eq) in Et_2O, 1.5 h, 62% f) Na in liq. NH_3, −78 °C, 2 h, 78% (**19**) from **18** or 51% (**21**) from **20** g) 37% HCl, reflux, 3 d, 100% (**2**·2HCl or **3**·HCl) from **19** or **21** h) *tert*-Boc_2O (2.0 eq)–Et_3N (3.0 eq) in $CHCl_3$, r.t., 1 or 2 h, 75% (**22**) from **19** or 84% (**23**) from **21**

Chart 3

by epoxide opening with a nucleophile.

Thus, as shown in Chart 3, mesylation of **10** followed by hydrogenolysis of the mesylate (**15**) produced the alcohol (**16**) in 94% combined yield. Treatment of **16** with sodium methoxide afforded the epoxide (**17**), $[\alpha]_D^{20}$ −7.6° (chloroform), as a sole product. That the epoxide formation took place in a highly stereoselective manner with inversion of configuration could be definitely established by the successful synthesis of **2** and **3** from **17**. Reaction of **17** with morpholine effected highly regioselective epoxide opening, giving rise to the alcohol (**18**), $[\alpha]_D^{20}$ −55.2° (chloroform), in 94% yield. Similar highly regioselective epoxide opening could also be achieved by the reaction of **17** with isopropylmagnesium chloride in the presence of copper(I) iodide, affording the alcohol (**20**), $[\alpha]_D^{20}$ −35.0° (chloroform), in 62% yield. Reductive removal of the N-benzyl groups involved in **18** and **20** produced the unprotected oxazolizin-2-one derivatives (**19** and **21**), **19**: mp 173—174 °C, $[\alpha]_D^{20}$ −79.8° (chloroform) and **20**: mp 162—162.5 °C, $[\alpha]_D^{20}$ −81.2° (chloroform), in 78% and 51% yields, respectively. Subsequent acidic hydrolysis of **19** and **21** afforded quantitative yields of **2** and **3** as their hydrochlorides (**2**·2HCl and **3**·HCl). The hydrochlorides of the 1,2,3-amino diols (**2**·2HCl and **3**·HCl) were characterized as their N-*tert*-butoxycarbonyl derivatives (**22** and **23**) prepared by treatment with di-*tert*-butyl dicarbonate and triethylamine. The carbamates (**22** and **23**) showed mp 143.5—144.5 °C, $[\alpha]_D^{20}$ −15.7° (chloroform) [lit.,[8] mp 143—145 °C, $[\alpha]_D^{20}$ −15.8° (chloroform)] and mp 134—135 °C, $[\alpha]_D^{20}$ −67.4° (chloroform) [lit.,[5c] mp 130—131 °C, $[\alpha]_D^{20}$ −64.91° (chloroform)], respectively. Spectral data of **22** and **23** were found to be identical with those reported.[5e,8] Successful syntheses of **2**·2HCl and **3**·HCl from **17** definitely established the steric course of epoxide formation and the regiochemistry of epoxide opening.

As mentioned above, we have succeeded in developing a highly stereoselective addition reaction of cyclohexylmethylmagnesium bromide with **8** in the presence of cerium(III) chloride. The addition product (**9**) could be elaborated to three types of C-terminal components of renin inhibitors (**1**, **2**, and **3**). The novel addition reaction developed here may further find a wide application in the syntheses of various optically active amines.

Experimental

All melting points were determined with a Yamato MP-21 melting point apparatus and a Yamato micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. ^{1}H- and ^{13}C-NMR spectra were measured with Hitachi R-90H (90 MHz) and Brucker AM-400 (400 MHz) spectrometers. All signals were expressed in ppm using tetramethylsilane (0.00 ppm) (in $CDCl_3$) or HDO (4.70 ppm) (in D_2O) as an internal standard (δ-value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q) and broad (br). Infrared (IR) spectra measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. Mass spectra (MS) were taken with Hitachi RMU-6MG (regular mass spectra) and Hitachi M-80A [high resolution and secondary ionization mass spectra (HRMS and SIMS)] mass spectrometers. Unless otherwise noted, all reactions were performed using anhydrous solvents. Tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl were mainly used. Wako Gel C-200 and C-300 were used as adsorbents for column chromatography. The following abbreviations are used for solvents and reagents: acetic acid (AcOH), acetonitrile (CH_3CN), benzene (PhH), carbon tetrachloride (CCl_4), cerium(III) chloride ($CeCl_3$), chloroform ($CHCl_3$), copper(I) iodide (CuI), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), methanol (MeOH), palladium(II) hydroxide ($Pd(OH)_2$), pyridine (Py), ruthenium(III) chloride ($RuCl_3$), tetrahydrofuran (THF), toluene (PhMe), triethylamine (Et_3N).

4-*O*-Benzyl-2,3-*O*-isopropylidine-L-threose (7) According to the reported procedure,[10] this compound could be prepared from **4** in 5 steps. The aldehyde (**7**) obtained as a slightly yellow oil showed bp. 180 °C (1 mmHg) (bath temp.) [(lit.,[10] bp 140—150 °C (0.6 mmHg) (bath temp.)]. ^{1}H-NMR ($CDCl_3$) δ: 1.40, 1.47 (6H, two s, $CH_3 \times 2$), 3.50—3.77 (2H, m, CH_2O), 4.07—4.39 (2H, m, CHCH), 4.59 (2H, s, CH_2Ph), 7.31 (5H, s, C_6H_5), 9.72 (1H, br s, CHO). This ^{1}H-NMR spectrum was identical with that reported.[6]

(4*R*,5*R*)-4-Benzyliminomethyl-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (8) Benzylamine (0.225 ml, 2.06 mmol) and anhydrous $MgSO_4$ (602 mg, 5.00 mmol) were added to a solution of **7** (505 mg, 2.02 mmol) in PhMe (10 ml) cooled in an ice bath, and the mixture was stirred at the same temperature for 1.5 h.[7,11] After being warmed to room temperature, the mixture was filtered. The filtrate was concentrated *in vacuo* to give crude **8** as a pale yellow oil (701 mg, quantitative yield). ^{1}H-NMR δ: 1.44 (6H, two s, $CH_3 \times 2$), 3.49—3.73 (2H, m, CH_2O), 4.12—4.45 (2H, m, CHCH), 4.45—4.81 (4H, m, $CH_2Ph \times 2$), 7.10—7.37 (10H, m, $C_6H_5 \times 2$), 7.79 (1H, br d, J = 5 Hz, CH=N). Since **8** was found to be fairly unstable, it was directly subjected to the next addition reaction.

(4*R*,5*R*)-4-[(*S*)-(1-*N*-Benzylamino-2-cyclohexyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (9) Anhydrous $CeCl_3$ prepared by heating $CeCl_3 \cdot 7H_2O$ (4.00 g, 10.7 mmol) at 130—140 °C for 5 h *in vacuo*, was suspended in THF (20 ml) at room temperature. The suspension was sonicated for 1 h, then stirred for 2 h at room temperature. A solution of cyclohexylmethylmagnesium bromide in Et_2O (1.0 M solution, 10.1 ml, 10.1 mmol) was added to the suspension of anhydrous $CeCl_3$ in THF prepared above with stirring at −30 °C, and stirring was continued at the same temperature for 0.5 h. A solution of crude **8** (701 mg, 2.02 mmol) in THF (10 ml) was added to the reaction mixture with stirring at −30 °C.

Stirring was continued for 2 h at the same temperature, then the reaction mixture was gradually warmed to room temperature, stirred for an additional 12 h, then poured into saturated $NaHCO_3$. The mixture was extracted with EtOAc. The ethyl acetate extracts were combined, washed successively with water and saturated NaCl, dried over anhydrous $MgSO_4$, then filtered. Concentration of the filtrate *in vacuo* gave an oily residue, which was purified by column chromatography (PhMe : EtOAc = 100 : 1 → 50 : 1) to give pure **9** as a colorless oil (660 mg, 75% from **8**), $[\alpha]_D^{20}$ +12.3° (c = 1.22, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.77—1.73 (13H, m, $C_6H_{11}CH_2$), 1.40, 1.42 (6H, two s, $CH_3 \times 2$), 2.66—2.74 (1H, m, $PhCH_2NHCH$), 3.56 (1H, dd, J = 10.3, 5.5 Hz, one of CH_2O), 3.57 (1H, dd, J = 10.3, 5.5 Hz, one of CH_2O), 3.75 (1H, d, J = 13.1 Hz, one of $PhCH_2N$), 3.85 (1H, d, J = 13.1 Hz, one of $PhCH_2N$), 3.88 (1H, dd, J = 7.9, 4.0 Hz, $CHCHCH_2O$), 4.24 (1H, ddd, J = 7.9, 5.5, 4.4 Hz, $CHCHCH_2O$), 4.56 (2H, s, OCH_2Ph), 7.19—7.35 (10H, m, $C_6H_5 \times 2$). IR (neat): 2930, 2870 cm^{-1}. MS m/z: 438 ($[M+1]^+$), 422, 340, 216. HRMS: Calcd for $C_{28}H_{40}NO_3$ ($[M+1]^+$): 438.3005. Found: 438.2987.

(4*R*,5*R*)-4-[(*R*)-(1-*N*-Benzylamino-2-cyclohexyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (13) A solution of cyclohexylmethylmagnesium bromide in Et_2O (1.0 M solution, 1.25 ml, 1.25 mmol) was added to a suspension of CuI (248 mg, 1.30 mmol) in THF (2 ml) with stirring at −78 °C. Stirring was continued at the same temperature for 10 min, then boron trifluoride-etherate (0.155 ml, 1.26 mmol) was added and the reaction mixture was further stirred for 5 min. A solution of crude **8** (82 mg, 0.233 mmol) in THF (1 ml) was added to the reaction mixture at −78 °C. The mixture was stirred at the same temperature for 1 h, gradually warmed up to room temperature, and further stirred for 15 min. After being poured into saturated $NaHCO_3$, the mixture was extracted with EtOAc. The organic extracts were combined, washed successively with H_2O and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration followed by concentration *in vacuo* gave an oily residue, which was purified by column chromatography (PhMe : EtOAc = 100 : 1) to give pure **13** as a pale yellow oil (52% from **8**), $[\alpha]_D^{20}$ +26.7° (c = 1.05, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.72 (13H, m, $C_6H_{11}CH_2$), 1.40, 1.41 (6H, two s, $CH_3 \times 2$), 2.81 (1H, dt, J = 7.4, 4.6 Hz, $PhCH_2NHCH$), 3.57 (1H, dd, J = 10.3, 5.8 Hz, one of CH_2O), 3.67 (1H, dd, J = 10.3, 3.6 Hz, one of CH_2O), 3.77 (1H, d, J = 13.1 Hz, one of $PhCH_2N$), 3.83 (1H, d, J = 13.1 Hz, one of $PhCH_2N$), 3.90 (1H, dd, J = 7.8, 4.6 Hz, $CHCHCH_2O$), 4.15 (1H, ddd, J = 7.9, 5.8, 3.6 Hz, $CHCHCH_2O$), 4.58 (1H, d, J = 12.2 Hz, one of OCH_2Ph), 7.18—7.40 (10H, m, $C_6H_5 \times 2$). IR (neat): 2940, 2850 cm^{-1}. MS m/z: 437 (M^+), 422, 340, 216.

(4*S*,5*R*)-3-Benzyl-5-[(*R*)-(2-benzyloxy-1-hydroxy)ethyl]-4-cyclohexylmethyloxazolidin-2-one (10) a) (4*R*,5*R*)-4-[(*S*)-(1-(*N*-Benzyl-*N*-methoxycarbonyl)amino-2-cyclohexyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan: Anhydrous K_2CO_3 (435 mg, 3.15 mmol) and methyl chloroformate (0.24 ml, 3.11 mmol) was added to a solution of **9** (262 mg, 0.598 mmol) in THF (6.5 ml) with stirring in an ice bath, and the mixture was stirred at the same temperature for 7 h. After being diluted with EtOAc, the ethyl acetate solution was washed successively with dilute HCl, H_2O, and saturated NaCl, dried over anhydrous $MgSO_4$, then filtered. Concentration of the filtrate *in vacuo* gave an oily residue, which was purified by column chromatography (PhMe : EtOAc = 100 : 1) to give the carbamate as a colorless oil (288 mg, 97%), $[\alpha]_D^{20}$ −24.9° (c = 1.05, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.40—2.10 (13H, m, $C_6H_{11}CH_2$), 1.38 (6H, s, $CH_3 \times 2$), 3.69 (3H, s, CO_2CH_3), 4.61 (4H, s, $PhCH_2 \times 2$), 3.46—4.50 (5H, m, $NCHCHCHCH_2O$), 7.27 (5H, s, one of C_6H_5), 7.33 (5H, s, one of C_6H_5). IR (neat): 2950, 2875, 1690 cm^{-1}. MS m/z: 495 (M^+), 480, 437, 274.

b) (2*R*,3*R*,4*S*)-4-(*N*-Benzyl-*N*-methoxycarbonyl)amino-1-benzyloxy-5-cyclohexylpentane-2,3-diol: The carbamate (242 mg, 0.487 mmol) obtained in a) was dissolved in 80% AcOH (12 ml) and the acidic solution was stirred at 80 °C for 5 h. Concentration *in vacuo* gave the crude diol, which was immediately subjected to the next step. ^{1}H-NMR ($CDCl_3$) δ: 0.45—1.90 (13H, m, $C_6H_{11}CH_2$), 3.73 (3H, s, CO_2CH_3), 7.27 (5H, s, one of C_6H_5), 7.32 (5H, s, one of C_6H_5), Other signals could not be assigned.

c) **10**: The crude diol obtained in b) was dissolved in a 10% solution of KOH in MeOH (3 ml), and the solution was stirred at room temperature for 3.5 h. The reaction mixture was neutralized with 1 M HCl and extracted with EtOAc. The ethyl acetate extracts were combined, washed successively with H_2O and saturated NaCl, dried over anhydrous $MgSO_4$, then filtered. Concentration of the filtrate *in vacuo* gave a residue, which was purified by column chromatography (PhMe : EtOAc = 10 : 1) to give **10** as a colorless oil [189 mg, 92% (2 steps)], $[\alpha]_D^{20}$ −29.7° (c = 1.25, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.67—1.70 (13H, m, $C_6H_{11}CH_2$), 2.33 (1H, br s, OH), 3.53 (1H, dd, J = 9.6, 7.3 Hz, one of CH_2O), 3.58 (1H, dd, J = 9.6, 5.1 Hz, one of CH_2O), 3.64—3.75 (2H, m, $NCHCHCHCH_2O$), 4.09 (1H, d, J = 15.3 Hz, one of $PhCH_2N$), 4.20 (1H, dd, J = 5.0, 2.8 Hz, $NCHCHCH_2O$), 4.52 (2H, s, OCH_2Ph), 4.79 (1H, d, J = 15.3 Hz, one of $PhCH_2N$), 7.24—7.38 (10H, m, $C_6H_5 \times 2$). IR (neat): 3300, 2940, 2875, 1735 cm^{-1}. MS m/z: 423 (M^+), 332, 302, 284. HRMS: Calcd for $C_{26}H_{33}NO_4$ (M^+): 423.2407. Found: 423.2431.

(4*R*,5*R*)-3-Benzyl-5-[(*R*)-(2-benzyloxy-1-hydroxy)ethyl]-4-cyclohexylmethyloxazolidin-2-one (14) a) (4*R*,5*R*)-4-[(*R*)-(1-(*N*-Benzyl-*N*-methoxycarbonyl)amino-2-cyclohexyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane: Anhydrous K_2CO_3 (35.8 mg, 0.259 mmol) and methyl chloroformate (0.02 ml, 0.0514 mmol) were added to a solution of **13** (22.5 mg, 0.259 mmol) in THF (1.1 ml) with stirring in an ice bath, and the mixture was stirred at the same temperature for 9.5 h. Treatments of the reaction mixture in the same manner as described for the preparation of **10** gave the crude carbamate after concentration of the ethyl acetate extracts. This was immediately subjected to the next acidic hydrolysis. ^{1}H-NMR ($CDCl_3$) δ: 0.45—2.00 (13H, m, $C_6H_{11}CH_2$), 1.28, 1.37 (6H, two s, $CH_3 \times 2$), 3.70 (3H, s, CO_2CH_3), 7.26 (5H, s, one of C_6H_5), 7.33 (5H, one of C_6H_5). Other signals could not be assigned.

b) (2*R*,3*R*,4*R*)-4-(*N*-Benzyl-*N*-methoxycarbonyl)amino-1-benzyloxy-5-cyclohexylpentane-2,3-diol: The crude carbamate obtained in a) was treated with 80% AcOH (1 ml) in the same manner as described for the preparation of **10**, giving the crude diol after concentration of the reaction mixture *in vacuo*. This was immediately subjected to the next step. ^{1}H-NMR ($CDCl_3$) δ: 0.60—1.90 (13H, m, $C_6H_{11}CH_2$), 3.80 (3H, s, CO_2CH_3), 7.27 (5H, s, one of C_6H_5), 7.31 (5H, one of C_6H_5). Other signals could not be assigned.

c) **14**: The crude diol obtained in b) was dissolved in a 10% solution of KOH in MeOH (1 ml) and the solution was stirred at room temperature for 3.5 h. Treatments of the reaction mixture in the same manner as described for the preparation of **10** gave pure **14** as a colorless oil [20.4 mg, 94% (3 steps)] after purification by column chromatography (PhMe : EtOAc = 20 : 1 → 10 : 1), $[\alpha]_D^{20}$ −31.6° (c = 0.823, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.84 (13H, m, $C_6H_{11}CH_2$), 2.22 (1H, br d, J = 5.5 Hz, OH), 3.56 (1H, dd, J = 9.2, 5.7 Hz, one of CH_2O), 3.65 (1H, dd, J = 9.2, 7.5 Hz, one of CH_2O), 3.77 (1H, ddd, J = 9.6, 8.5, 4.1 Hz, $PhCH_2NCH$), 3.99 (1H, br q, J = 5.9 Hz, $CHCH_2O$), 4.13 (1H, d, J = 15.5 Hz, one of $PhCH_2N$), 4.43 (1H, dd, J = 8.5, 1.2 Hz, $CHCHCH_2O$), 4.55 (1H, d, J = 11.8 Hz, one of $PhCH_2O$), 4.56 (1H, d, J = 11.8 Hz, one of $PhCH_2O$), 4.78 (1H, d, J = 15.5 Hz, one of $PhCH_2N$), 7.24—7.38 (10H, m, $C_6H_5 \times 2$). IR (neat): 3400, 2920, 2850, 1720 cm^{-1}. MS m/z: 423 (M^+), 332, 326, 314. HRMS: Calcd for $C_{26}H_{33}NO_4$(M^+): 423.2407. Found: 423.2420.

(4*S*,5*R*)-3-Benzyl-4-cyclohexyl-5-[(*R*)-(1,2-dihydroxy)ethyl]oxazolidin-2-one (11) A mixture of **10** (158 mg, 0.372 mmol) and 20% $Pd(OH)_2$ on carbon (catalytic amount) in MeOH (3 ml) was stirred under a hydrogen atmosphere (1 atm) overnight at room temperature. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give **11** as a colorless solid (125 mg, quantitative yield). Recrystallization from EtOAc–C_6H_{14} gave an analytical sample of **11** as colorless crystals, mp 101—102 °C and $[\alpha]_D^{20}$ −43.1° (c = 0.594, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.80 (13H, m, $C_6H_{11}CH_2$), 2.20 (1H, t, J = 5.9 Hz, CHOH), 2.65 (1H, d, J = 6.6 Hz, CHOH), 3.55 (1H, m, CHOH), 3.64 (1H, m, $PhCH_2NCH$), 3.72 (2H, dd, J = 5.8, 5.5 Hz, CH_2OH), 4.10 (1H, d, J = 15.3 Hz, one of $PhCH_2N$), 4.20 (1H, d, J = 5.1, 3.3 Hz, $CHCHCH_2O$), 4.79 (1H, d, J = 15.3 Hz, one of $PhCH_2N$), 7.20—7.40 (5H, m, C_6H_5). IR (KBr): 3440, 3250, 2930, 2885, 1720, 1440, 1042, 702 cm^{-1}. MS m/z: 333 (M^+), 236, 176, 91. *Anal.* Calcd for $C_{19}H_{24}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.22; H, 8.25; N, 4.19.

Methyl (4*S*,5*R*)-3-Benzyl-4-cyclohexylmethyloxazolidin-2-one-5-carboxylate (12) $RuCl_3 \cdot 3H_2O$ (catalytic amount) and $NaIO_4$ (512 mg, 2.40 mmol) was added to a solution of **11** (162 mg, 0.485 mmol) in a mixture of CCl_4, MeCN, and H_2O (2 : 2 : 3) (6.3 ml). After stirring at room temperature for 2 h, the reaction mixture was extracted with $CHCl_3$. The chloroform extracts were combined, dried over anhydrous $MgSO_4$, then filtered. Concentration of the filtrate *in vacuo* gave crude (4*S*,5*R*)-3-benzyl-4-cyclohexylmethyloxazolidin-2-one-5-carboxylic acid, which was dissolved in a mixture of PhH and MeOH (4 : 1) (3 ml). An excess amount of trimethylsilyldiazomethane (10% hexane solution) was added to the solution of the crude carboxylic acid. After stirring at room temperature for 1 h, the mixture was concentrated *in vacuo*. The concentration residue was purified by column chromatography (C_6H_{14} : EtOAc = 9 : 1 → 4 : 1) to give **12** as a colorless oil [117 mg, 73% (2 steps)], $[\alpha]_D^{20}$ −21.5° (c = 1.92, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.70 (13H, m, $C_6H_{11}CH_2$), 3.58 (1H, dt, J = 9.8, 3.8 Hz, $PhCH_2NCH$), 3.78 (3H, s, CO_2CH_3), 4.04 (1H, d, J = 15.3 Hz, one of $PhCH_2N$). 4.55 (1H, d, J = 3.8 Hz, $CHCO_2Me$), 4.83 (1H, d, J = 15.3 Hz, one of $PhCH_2N$), 7.20—7.40 (5H, m, C_6H_5). IR (neat): 2950, 2870, 1775, 1760, 1240, 702 cm^{-1}. MS m/z: 331 (M^+),

234, 205, 91.

(2*R*,3*S*)-3-Amino-4-cyclohexyl-2-hydroxybutyric Acid Hydrochloride [(2*R*,3*S*)-Cyclohexylnorstatine Hydrochloride] (1·HCl) Two molar NaOH solution (4.0 ml) was added to a solution of **12** (127 mg, 0.384 mmol) in MeOH (0.6 ml), and the mixture was stirred overnight at 90 °C. After being acidified (pH = 1) with 1.0 M HCl, the mixture was concentrated *in vacuo*. Addition of MeOH to the residue followed by filtration and concentration *in vacuo* gave crude (2*R*,3*S*)-3-benzylamino-4-cyclohexyl-2-hydroxybutyric acid hydrochloride, which was immediately dissolved in MeOH (6 ml). Twenty percent $Pd(OH)_2$ on carbon (catalytic amount) was added to the methanolic solution prepared above, and the whole mixture was stirred under a hydrogen atmosphere (1 atm) overnight at room temperature. Filtration followed by concentration *in vacuo* gave a residue, to which was added 6.0 M HCl (4 ml). After stirring at 100 °C for 2 h, concentration *in vacuo* gave crude (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid hydrochloride. This was dissolved in a small amount of H_2O, and the aqueous solution was poured onto a column of ion exchange resin (AG50W-X2). After being washed with H_2O, the column was eluted with 25% NH_4OH. The alkaline eluate was concentrated *in vacuo* to give a residue, which was dissolved in 1.0 M HCl. Concentration of the acidic solution to a small volume *in vacuo* gave **1**·HCl as colorless crystals [69.0 mg, 76% (5 steps)]. Recrystallization from H_2O gave an analytical sample of **1**·HCl, mp 191—192 °C (dec.) and $[\alpha]_D^{20}$ −13.6° (*c* = 0.633, 1 M HCl) [lit.,[6] mp 190 °C (dec.) and $[\alpha]_D^{20}$ −12.4° (*c* = 0.482, 1 M HCl)].[12] ^{1}H-NMR (D_2O) δ: 0.8—1.80 (13H, m, $C_6H_{11}CH_2$), 3.67 (1H, dt, *J* = 7.3, 3.5 Hz, CHN), 4.34 (1H, d, *J* = 3.5 Hz, CHO). This ^{1}H-NMR spectrum was identical with that reported.[3c] IR (KBr): 3900—2600, 3350, 2940, 1725, 1485, 1400, 1075 cm^{-1}. MS (SIMS) *m/z*: 202 ([M − Cl])$^+$), 126.

(4*S*,5*R*)-3-Benzyl-4-cyclohexylmethyl-5-[(*R*)-(2-benzyloxy-1-methanesulfonyloxy)ethyl]oxazolidin-2-one (15) Methanesulfonyl chloride (70 μl, 0.90 mmol) was added to a solution of **10** (306 mg, 0.723 mmol) in pyridine (2 ml) cooled in an ice bath, and the mixture was stirred in an ice bath for 3 h. After being diluted with EtOAc, the ethyl acetate solution was washed successively with H_2O and saturated NaCl, and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a residue, which was purified by column chromatography (C_6H_{14} : EtOAc = 4 : 1→3 : 2) to give pure **15** as a colorless oil (347 mg, 96%). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.70 (13H, m, $C_6H_{11}CH_2$), 2.87 (3H, s, SO_2CH_3), 3.65 (2H, m, NCH and one of CH_2OBn), 3.70 (1H, dd, *J* = 10.6, 4.9 Hz, one of CH_2OBn), 4.12 (1H, d, *J* = 15.1 Hz, one of $PhCH_2N$), 4.38 (1H, dd, *J* = each 4.0 Hz, $C\underline{H}CH_2O$), 4.47 (1H, d, *J* = 11.7 Hz, one of OCH_2Ph), 4.52 (1H, d, *J* = 11.7 Hz, one of OCH_2Ph), 4.68 (1H, m, $CHOSO_2$), 4.71 (1H, d, *J* = 15.1 Hz, one of $PhCH_2N$), 7.24—7.38 (10H, m, $C_6H_5 \times 2$). IR (neat): 3050, 2950, 2875, 1760, 1180, 922, 702 cm^{-1}. MS *m/z*: 501 (M^+), 410 ([M − $C_6H_5CH_2$]$^+$), 404.

(4*S*,5*R*)-3-Benzyl-4-cyclohexylmethyl-5-[(*R*)-(2-hydroxy-1-methanesulfonyloxy)ethyl]oxazolidin-2-one (16) Twenty percent $Pd(OH)_2$ on carbon (80 mg, catalytic amount) was added to a solution of **15** (645 mg, 1.29 mmol) in MeOH (5 ml), and the mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 2 d. Filtration and concentration *in vacuo* gave crude **16** as a colorless oil (517 mg, 98%). This was immediately subjected to the next reaction. ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.70 (13H, m, $C_6H_{11}CH_2$), 2.34 (1H, t, *J* = 6.0 Hz, OH), 2.87 (3H, s, SO_2CH_3), 3.66 (1H, m, CHN), 3.84 (2H, m, CH_2OH), 4.09 (1H, d, *J* = 14.9 Hz, one of $PhCH_2N$), 4.40 (dd, *J* = 4.5, 3.4 Hz, CHOCO), 4.60 (1H, ddd, *J* = 6.3, 4.7, 3.4 Hz, $CHOSO_2$), 4.75 (1H, d, *J* = 15.0 Hz, one of $PhCH_2N$), 7.30—7.40 (5H, m, C_6H_5). IR (neat): 3700—3200, 2945, 2855, 1740, 1442, 1175, 915, 702 cm^{-1}. MS *m/z*: 411 (M^+), 314 ([M − $C_6H_{11}CH_2$]$^+$), 218, 91.

(4*S*,5*R*)-3-Benzyl-4-cyclohexylmethyl-5-[(*S*)-oxiran-2-yl]oxazolidin-2-one (17) Sodium methoxide (560 mg, 10.4 mmol) was added to a solution of **16** (515 mg, 1.25 mmol) in THF (10 ml) with stirring in an ice bath. Stirring was continued in the ice bath for 30 min, then the reaction mixture was diluted with EtOAc, washed succesively with H_2O and saturated NaCl, and then dried over $MgSO_4$. Filtration and concentration *in vacuo* gave a residue, which was purified by column chromatography (C_6H_{14} : EtOAc = 19 : 1→3 : 1) to give **17** as a colorless oil (370 mg, 94%), $[\alpha]_D^{20}$ −7.6° (*c* = 0.706, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.70 (13H, m, $C_6H_{11}CH_2$), 2.68 (1H, dd, *J* = 4.7, 2.5 Hz, one of CH_2O), 2.84 (1H, dd, *J* = 4.7, 4.0 Hz, one of CH_2O), 2.94 (1H, ddd, *J* = 6.1, 4.0, 2.5 Hz, $C\underline{H}OCH_2$), 3.50 (1H, ddd, *J* = 9.8, 4.2, 3.9 Hz, CHN), 3.84 (1H, dd, *J* = 6.1, 4.2 Hz, CHOCO), 4.05 (1H, d, *J* = 15.2 Hz, one of $PhCH_2N$), 4.83 (1H, d, *J* = 15.2 Hz, one of $PhCH_2N$), 7.25—7.38 (5H, m, C_6H_5). IR (neat): 2950, 2855, 1760, 1422, 1240, 702 cm^{-1}. MS *m/z*: 315 (M^+), 218 ([M − $C_6H_{11}CH_2$]$^+$), 91.

(4*S*,5*R*)-3-Benzyl-4-cyclohexylmethyl-5-[(*S*)-(1-hydroxy-2-morpholin-4-yl)ethyl]oxazolidin-2-one (18) A mixture of **17** (70.5 mg, 0.224 mmol) and morpholine (40 μl, 0.459 mmol) in MeOH (1.5 ml) was stirred at room temperature for 1 d. After being diluted with EtOAc, the ethyl acetate solution was washed successively with H_2O and saturated NaCl, and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a residue, which was purified by column chromatography (C_6H_{14} : EtOAc = 1 : 7) to give **18** as a colorless caramel (84.4 mg, 94%), $[\alpha]_D^{20}$ −55.2° (*c* = 0.782, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.70 (13H, m, $C_6H_{11}CH_2$), 2.34 (1H, dd, *J* = 12.5, 10.0 Hz, one of $C\underline{H}_2NCH_2CH_2O$), 2.39 (2H, m, $NC\underline{H}_2CH_2O$), 2.55 (1H, dd, *J* = 12.5, 3.5 Hz, one of $C\underline{H}_2NCH_2CH_2O$), 2.58 (2H, m, $NC\underline{H}_2CH_2O$), 3.53 (1H, ddd, *J* = 10.0, 7.2, 3.5 Hz, C<u>H</u>OH), 3.59 (1H, m, CHN), 3.68 (4H, m, CH_2OCH_2), 3.96 (1H, dd, *J* = 7.2, 3.6 Hz, CHOCO), 4.05 (1H, d, *J* = 15.1 Hz, one of $PhCH_2N$), 4.81 (1H, d, *J* = 15.1 Hz, one of $PhCH_2N$), 7.26—7.38 (5H, m, C_6H_5). IR (neat): 3700—3200, 2948, 2855, 1755, 1442, 1120, 702 cm^{-1}. MS *m/z*: 401 ([M − 1]$^+$), 340, 258, 100 ([CH_2=N$(CH_2CH_2)_2O$]$^+$).

(4*S*,5*R*)-3-Benzyl-4-cyclohexylmethyl-5-[(*S*)-(1-hydroxy-3-methyl)butyl]oxazolidin-2-one (20) A solution of isopropylmagnesium chloride in Et_2O (1.0 M solution, 0.70 ml, 0.70 mmol) was added to a suspension of CuI (7 mg, 0.037 mmol) in Et_2O (2 ml) with stirring at 0 °C. Stirring was continued at the same temperature for 10 min, then a solution of **17** (73.4 mg, 0.233 mmol) in Et_2O (1 ml) was added to the reaction mixture at 0 °C. The whole was stirred at the same temperature for 1.5 h, then diluted with EtOAc. The ethyl acetate solution was washed successively with saturated $NaHCO_3$ and saturated NaCl, and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a residue, which was purified by column chromatography (C_6H_{14} : Et_2O = 2 : 1) to give **20** as a colorless caramel (51.8 mg, 62%), $[\alpha]_D^{20}$ −35.0° (*c* = 0.982, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, *J* = 6.6 Hz, CH_3), 0.91 (3H, d, *J* = 6.7 Hz, CH_3), 0.70—1.70 (16H, m, $C_6H_{11}CH_2$ and CH_2CHMe_2), 3.50 (1H, m, CHN), 3.67 (1H, m, C<u>H</u>OH), 4.03 (1H, t, *J* = 4.2 Hz, CHOCO), 4.07 (1H, d, *J* = 15.2 Hz, one of $PhCH_2N$), 4.80 (1H, d, *J* = 15.2 Hz, one of $PhCh_2N$), 7.24—7.38 (5H, m, C_6H_5). IR ($CHCl_3$): 2940, 2850, 1740, 1442, 1092 cm^{-1}. MS *m/z*: 359 (M^+), 262, 176, 91.

(4*S*,5*R*)-4-Cyclohexylmethyl-5-[(*S*)-(1-hydroxy-2-morpholin-4-yl)ethyl]-oxazolidin-2-one (19) A solution of **18** (84.4 mg, 0.210 mmol) in Et_2O (3 ml) was added to liquid ammonia (5 ml) containing sodium metal (*ca.* 50 mg, 2.2 mmol) at −78 °C. Stirring was continued at the same temperature for 2 h, then the reaction was quenched by adding NH_4Cl and liquid ammonia was evaporated off. Water was added to the evaporation residue and the aqueous mixture was extracted with EtOAc. The ethyl acetate extracts were combined, washed with saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a residue, which was purified by column chromatography (C_6H_{14} : EtOAc = 1 : 4→EtOAc) to give **19** as colorless crystals (50.8 mg, 78%). An analytical sample of **19** was prepared by recrystallization from EtOAc, mp 173—174 °C and $[\alpha]_D^{20}$ −79.8° (*c* = 0.694, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.80 (13H, m, $C_6H_{11}CH_2$), 2.39 (1H, dd, *J* = 12.6, 9.9 Hz, one of $C\underline{H}_2NCH_2CH_2O$), 2.46 (1H, m, $NC\underline{H}_2CH_2O$), 2.66 (1H, dd, *J* = 12.6, 3.6 Hz, one of $C\underline{H}_2NCH_2CH_2O$), 2.64 (2H, m, $NC\underline{H}_2CH_2O$), 3.71 (4H, m, CH_2OCH_2), 3.79 (1H, ddd, *J* = 9.9, 7.1, 3.6 Hz, CHO), 3.92 (1H, m, CHN), 3.97 (1H, dd, *J* = 7.1, 4.7 Hz, CHOCO), 5.54 (1H, br s, NH). IR ($CHCl_3$): 2940, 2855, 1740, 1118, 1090 cm^{-1}. MS *m/z*: 313 ([M + 1]$^+$), 130,100. *Anal.* Calcd for $C_{16}H_{28}N_2O_4 \cdot 0.2H_2O$: C, 60.81; H, 9.06; N, 8.87. Found: C, 60.89; H, 9.09; N, 8.72.

(4*S*,5*R*)-4-Cyclohexyl-5-[(*S*)-(1-hydroxy-3-methyl)butyl]oxazolidin-2-one (21) Treatment of **20** (118 mg, 0.328 mmol) in the same manner as described for **18** gave **21** as colorless crystals (44.9 mg, 51%) after purification by column chromatography (C_6H_{14} : EtOAc = 4 : 1→3 : 2). An analytical sample of **21** was obtained by recrystallization from EtOAc, mp 162—162.5 °C and $[\alpha]_D^{20}$ −81.2° (*c* = 0.739, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, *J* = 6.6 Hz, CH_3), 0.97 (3H, d, *J* = 6.7 Hz, CH_3), 0.80—1.90 (16H, m, $C_6H_{11}CH_2$ and CH_2CHMe_2), 2.40 (1H, br s, OH), 3.92 (2H, m, CHN and C<u>H</u>OH), 4.02 (1H, dd, *J* = 5.4, 3.7 Hz, CHOCO), 5.45 (1H, br s, NH). IR ($CHCl_3$): 2940, 2855, 1758, 1092 cm^{-1}. MS *m/z*: 270 ([M + 1]$^+$), 251 ([M − H_2O]$^+$), 212, 122, 86. *Anal.* Calcd for $C_{15}H_{27}NO_3 \cdot 0.1H_2O$: C, 66.44; H, 10.11; N, 5.16. Found: C, 66.51; H, 10.10; N, 5.12.

(2*S*,3*R*,4*S*)-4-Amino-5-cyclohexyl-1-morpholin-4-yl-2,3-pentanediol Dihydrochloride (2·2HCl) A mixture of **19** (37.2 mg, 0.119 mmol) and concentrated HCl (3 ml) was heated at reflux for 3 d. Concentration *in vacuo* gave **2**·2HCl as a colorless caramel (48.4 mg, quantitative yield). ^{1}H-NMR (D_2O) δ: 0.70—1.70 (13H, m, $C_6H_{11}CH_2$), 3.10 (2H, m, $NC\underline{H}_2CH_2O$), 3.18 (1H, dd, *J* = 13.5, 10.5 Hz, one of $C\underline{H}_2NCH_2CH_2O$),

3.22 (1H, dd, J=13.5, 2.8 Hz, one of $CH_2NCH_2CH_2O$), 3.46 (3H, m, $CHNH_3^+$ and NCH_2CH_2O), 3.56 (1H, dd, J=7.0, 2.6 Hz, $CH(OH)CH(OH)CH_2$), 3.75 (2H, m, CH_2OCH_2), 3.98 (2H, m, CH_2OCH_2), 4.06 (1H, ddd, J=10.5, 7.0, 2.8 Hz, $CH(OH)CH_2$). ^{13}C-NMR (D_2O) δ: 28.27, 28.31, 28.65, 35.17, 35.35, 35.63, 39.80, 51.93, 53.80, 56.24, 62.13, 66.28 (C×2), 67.98, 72.99. SIMS m/z: 287 ($[M+1-2HCl]^+$), 200, 100. This compound (**2**·2HCl) was further characterized as **22**.

(2*S*,3*R*,4*S*)-2-Amino-1-cyclohexyl-6-methyl-3,4-heptanediol Hydrochloride (3·HCl) A mixture of **21** (42.8 mg, 0.159 mmol) and concentrated HCl (4 ml) was heated at reflux overnight. Concentration of the mixture *in vacuo* gave **3**·HCl as a colorless caramel (47.7 mg, quantitative yield). ^{1}H-NMR (D_2O) δ: 0.85 (3H, d, J=6.6 Hz, CH_3), 0.89 (3H, d, J=6.7 Hz, CH_3), 0.80—1.80 (16H, m, $C_6H_{11}CH_2$ and CH_2CHMe_2), 3.56 (2H, m, CHO and CHN), 3.82 (1H, m, CHO). SIMS m/z: 244 ($[M+1-HCl]^+$), 126, 55. This compound was further characterized as **23**.

(2*S*,3*R*,4*S*)-4-*N*-*tert*-Butoxycarbonylamino-5-cyclohexyl-1-morpholin-4-yl-2,3-pentanediol (22) Di-*tert*-butyl dicarbonate (48.0 mg, 0.220 mmol) and Et_3N (30 μl, 0.22 mmol) were added to a solution of **2**·2HCl (15.1 mg, 0.042 mmol) in CH_2Cl_2 (0.3 ml), and the mixture was stirred at room temperature for 1 h. After being diluted with EtOAc and H_2O, the ethyl acetate layer was separated, washed with saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a residue, which was purified by column chromatography (EtOAc) to give **22** as colorless crystals (12.2 mg, 75%). Recrystallization from EtOAc–C_6H_{14} gave an analytical sample of **22**, mp 143.5—144.5 °C and $[\alpha]_D^{20}$ −15.7° (c=0.82, $CHCl_3$) [lit.,[8] mp 143.5—145 °C and $[\alpha]_D^{20}$ −15.8° (c=1.07, $CHCl_3$)]. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.82 (13H, m, $C_6H_{11}CH_2$), 1.46 (9H, s, $C(CH_3)_3$), 2.52 (2H, m, $CH_2N(CH_2CH_2)_2O$), 2.60—2.85 (4H, m, $N(CH_2CH_2)_2O$), 3.43 (2H, m, $CH(OH)CH(OH)$), 3.71 (4H, m, $N(CH_2CH_2)_2O$), 3.97 (1H, ddd, J=14.2, 9.7, 4.7 Hz, $CHNHCO$), 4.66 (2H, two br d, J=each 9.5 Hz, NH and OH). IR (KBr): 3000—3600, 2940, 2860, 1678 cm^{-1}. MS m/z: 387 (M^+), 313, 100. These ^{1}H-NMR and IR spectra of **22** were identical with those reported.[8] HRMS: Calcd for $C_{20}H_{39}N_2O_5$: 387.2859. Found: 387.2867.

(2*S*,3*R*,4*S*)-2-*tert*-Butoxycarbonylamino-1-cyclohexyl-6-methyl-3,4-pentanediol (23) A mixture of **3**·HCl (47.0 mg, 0.159 mmol), di-*tert*-butyl dicarbonate (70.0 mg, 0.321 mmol), and Et_3N (67 μl, 0.48 mmol) in $CHCl_3$ (1 ml) was stirred at room temperature for 2 h. The mixture was worked up in the same manner as described for the preparation of **22** to give **23** as colorless crystals (45.9 mg, 84%) after purification by column chromatography (C_6H_{14} : EtOAc = 3 : 1→1 : 1). Recrystallization from cyclohexane gave an analytical sample of **23**, mp 134—135 °C and $[\alpha]_D^{20}$ −67.4° (c=1.17, $CHCl_3$) [lit.,[5c] mp 130—131 °C and $[\alpha]_D^{20}$ −64.91° (c=2.20, $CHCl_3$)]. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.50 (15H, m, $C_6H_{11}CH_2$ and CH_2CHMe_2), 0.89 (3H, d, J=6.6 Hz, CH_3), 0.95 (3H, d, J=6.7 Hz, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 1.94 (1H, m, $CHMe_2$), 3.20 (1H, m, $CH(OH)CH(OH)CH_2$), 3.33 (1H, m, $CH(OH)CH(OH)CH_2$), 4.04 (1H, m, CHN), 4.16 (1H, d, J=4.3 Hz, OH), 4.54 (1H, d, J=9.0 Hz, NH). IR ($CHCl_3$): 3450, 2940, 1680, 1502, 1160 cm^{-1}. These ^{1}H-NMR and IR spectra of **23** were identical with those reported.[5c] MS m/z: 344 ($[M+1]^+$), 288, 226, 57. *Anal.* Calcd for $C_{19}H_{37}NO_4$: C, 66.44; H, 10.86; N, 4.08. Found: C, 66.32; H, 10.77; N, 3.87.

References and Notes

1) Part of this work has been the subject of two preliminary communications. *a*) T. Matsumoto, Y. Kobayashi, Y. Takemoto, Y. Ito, T. Kamijo. H. Harada, and S. Terashima, *Tetrahedron Lett.*, **31**, 4175 (1990); *b*) Y. Kobayashi, K. Nakatani, Y. Ito, and S. Terashima, *Chemistry Lett.*, **1990**, 1709.

2) *a*) J. Boger, *Ann. Rep. Med. Chem.*, **20**, 257 (1985); *b*) H. Koike, *Gendai Kagaku*, **1989**, 55.

3) *a*) K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama, and Y. Kiso, *J. Chem. Soc., Chem. Commun.*, **1989**, 1678; *b*) K. Iizuka, T. Kamijo, H. Harada, T. Kubota, H. Umeyama, T. Ishida, and Y. Kiso, *J. Med. Chem.*, **33**, 2707 (1990); *c*) H. Harada, A. Iyobe, A. Tsubaki, T. Yamaguchi, K. Hirata, T. Kamijo, K. Iizuka, and Y. Kiso, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2497.

4) *a*) H. Morishima, Y. Koike, M. Nakano, S. Atsuumi, S. Tanaka, H. Funabashi, J. Hashimoto, Y. Sawaki, N. Mino, M. Nakano, K. Matsushima, K. Nakamichi, and M. Yano, *Biochem. Biophys. Res. Commun.*, **159**, 999 (1989); *b*) M. Nakano, S. Atsuumi, Y. Koike, S. Tanaka, H. Funabashi, J. Hashimoto, and H. Morishima, *Tetrahedron Lett.*, **31**, 1569 (1990).

5) *a*) H. D. Kleinert, J. R. Luly, R. A. Marcotte, T. J. Perum, J. J. Plattner, and H. Stein, *FEBS Lett.*, **230**, 38 (1988); *b*) J. R. Luly, N. BaMaung, J. Soderquist, A. K. L. Fung, H. Stein, H. D. Kleinert, P. A. Marcotte, D. A. Egan, B. Bopp, I. Merits, G. Bolis, J. Greer, T. J. Parun, and J. J. Plattner, *J. Med. Chem.*, **31**, 2264 (1988); *c*) J. R. Luly, C.-N. Hsiao, N. BaMaung, and J. J. Plattner, *J. Org. Chem.*, **53**, 6109 (1988).

6) F. Matsuda, T. Matsumoto, M. Ohsaki, Y. Ito, and S. Terashima, *Chemistry Lett.*, **1990**, 723.

7) *a*) Y. Ito, T. Kamijo, H. Harada, and S. Terashima, *Heterocycles*, **30**, 299 (1990); *b*) Y. Kobayashi, Y. Takemoto, Y. Ito, and S. Terashima, *Tetrahedron Lett.*, **31**, 3031 (1990).

8) S. Atsuumi, M. Nakano. Y. Koike, S. Tanaka, H. Funabashi, J. Hashimoto, and H. Morishima, *Chem. Pharm. Bull.*, **38**, 3460 (1990).

9) J. L. Wood, D. R. Jones, R. Hirschmaun, and A. B. Smith, III, *Tetrahedron Lett.*, **31**, 6329 (1990).

10) T. Mukaiyama, K. Suzuki, and T. Yamada, *Chemistry Lett.*, **1982**, 929.

11) Y. Ito, Y. Kobayashi, T. Kawabata, M. Takase, and S. Terashima, *Tetrahedron*, **45**, 5767 (1989).

12) At the outset of this work, the addition reaction of cyclohexylmethylmagnesium bromide with 4-*O*-benzyl-2,3-isopropylidene-D-threose (**7**), the precursor of **5**, was extensively studied in various solvents and in the presence of Lewis acids such as cerium(III) chloride, copper(I) iodide–boron trifluoride and zinc(II) chloride. While mixtures of two diastereomeric alcohols could be obtained in 31—70% yields, their formation ratios were found to be unrewarding (45 : 55—77 : 23). T. Matsumoto, Y. Ito, and S. Terashima, unpublished results.

13) While many successful results have so far been reported for the addition reactions of organocerium(III) reagents with various carbonyl compounds,[14] the addition reaction of organocerium(III) reagent with an imine has never been reported.

14) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989).

15) M. Wada, Abstracts of Papers, The 55th Symposium on Organic Synthesis, Tokyo, June 1989, p. 71.

16) Although the melting point and optical rotation of **1**·HCl had been reported as mp 172—175 °C and $[\alpha]_D^{23}$ −11.2° (c=2.0, H_2O) by Kiso *et al.*,[3c] an authentic sample of **1**·HCl prepared at Sagami was found to show mp 190 °C (dec.), $[\alpha]_D^{20}$ −12.4° (c=0.482, 1 M HCl), and $[\alpha]_D^{20}$ −12.2° (c=2.05, H_2O).[6] Accordingly, the values in parenthesis reported in ref. 6 were used as the melting point and optical rotation of authentic **1**·HCl.