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A Stereoselective Synthesis of the (2*R*,3*S*)- and (2*S*,3*R*)-3-Amino-2-hydroxybutyric Acid Derivatives, the Key Components of a Renin Inhibitor and Bestatin.[1)]

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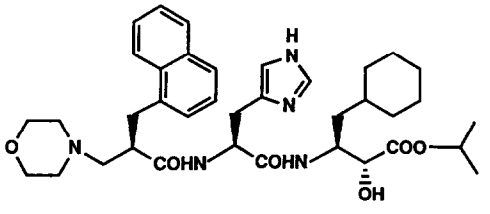
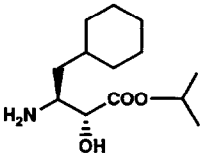
Abstract: *The title synthesis was achieved by featuring the [2+2]-cycloaddition reaction of benzyloxyketene with a chiral imine derived from methyl (R)- or (S)-mandelate, alcoholysis of the formed 3,4-cis disubstituted β-lactam under acidic conditions, and reductive removal of the mandelate-derived benzylic oxygen by way of a 2-oxazolidone derivative. Some preliminary results obtained by the [2+2]-cycloaddition reaction employing achiral and chiral imines derived from benzylamine, p-anisidine, di-p-anisylmethylamine, and (S)-1-phenylethylamine were also reported. Stereoselectivity of the [2+2]-cycloaddition reaction could be explained by the initial formation of a zwitter-ionic intermediate and its subsequent conrotatory ring closure.*

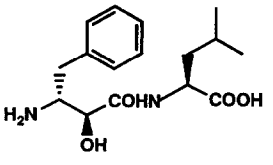
Some medicinally important compounds recently attracting much synthetic attention involve optically active 3-amino-2-hydroxybutyric acids as their key components. Thus, one of the renin inhibitors (**1**) exhibiting promosing antihypertensive activity bears isopropyl (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyrate [(2*R*,3*S*)-**2**] as its C-terminal moiety,[4,5)] and bestatin (**3**) being well known as the immunological response modifier[6)] consists of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid [(2*S*,3*R*)-**4**][5b,c,7)] and (*S*)-leucine.



1



(2*R*,3*S*)-**2**



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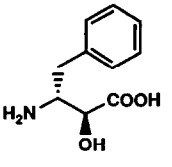
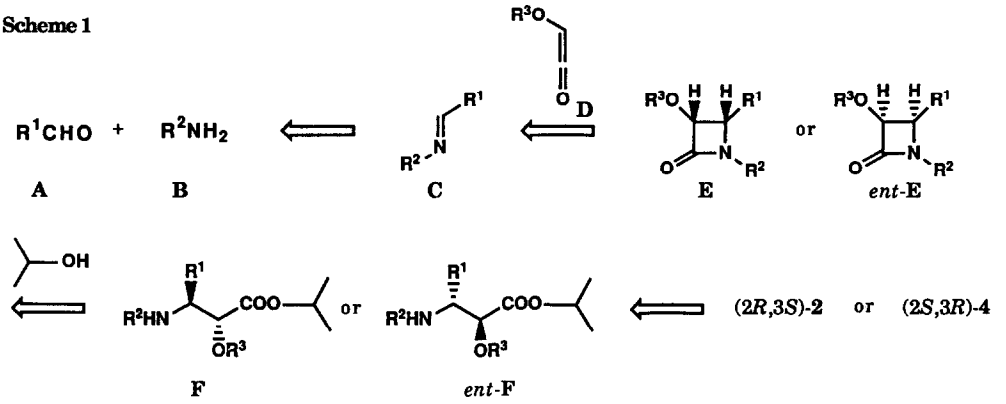


(2*S*,3*R*)-**4**

While various synthetic routes to (2*R*,3*S*)-**2** and (2*S*,3*R*)-**4** have so far been reported,[5,7] a novel preparation method was sought which could produce these key synthetic intermediates more stereoselectively than previously reported.[4,5,7]

It is well recognized that the [2+2]-cycloaddition of an imine with a ketene can produce a 3,4-*cis*-disubstituted β-lactam in a highly stereoselective manner[8,9] and a β-lactam ring is readily susceptible to nucleophilic ring opening due to its enhanced chemical reactivity.[9,10] Based on these facts, the novel method for preparing (2*R*,3*S*)-**2** and (2*S*,3*R*)-**4** was designed as depicted in **Scheme 1**. Thus, sequential functional group manipulations and deprotection or *vice versa* of an optically active 3-amino-2-hydroxybutyric acid derivative (**F** or *ent*-**F**) will readily give rise to (2*R*,3*S*)-**2** or (2*S*,3*R*)-**4**. The butyric acid derivatives (**F** and *ent*-**F**) can be effectively furnished by alcoholysis of 3,4-*cis*-3-alkoxy-4-substituted-β-lactams (**E** and *ent*-**E**, respectively). The [2+2]-cycloaddition reaction of an optically active imine (**C**) with an achiral alkoxy ketene (**D**) may proceed in a highly stereoselective manner under an influence of the asymmetric centers involved in **C**. The optically active imine (**C**) can be prepared by condensing an aldehyde (**A**) and an amine (**B**) when either **A** or **B** is optically active.

Scheme 1



After experimentation, this synthetic scheme turned out to be the case. Although **C** bearing an asymmetric center in the R^2 group gave low diastereoselectivity in the [2+2]-cycloaddition reaction, we have now found that **C** in which an asymmetric center is involved in the R^1 group, can react with **D** in a highly stereoselective manner and that **E** or *ent*-**E** produced as a major addition product depending upon the absolute stereochemistry of the R^1 group, can be ingeniously elaborated to (2*R*,3*S*)-**2** or (2*S*,3*R*)-**4**.

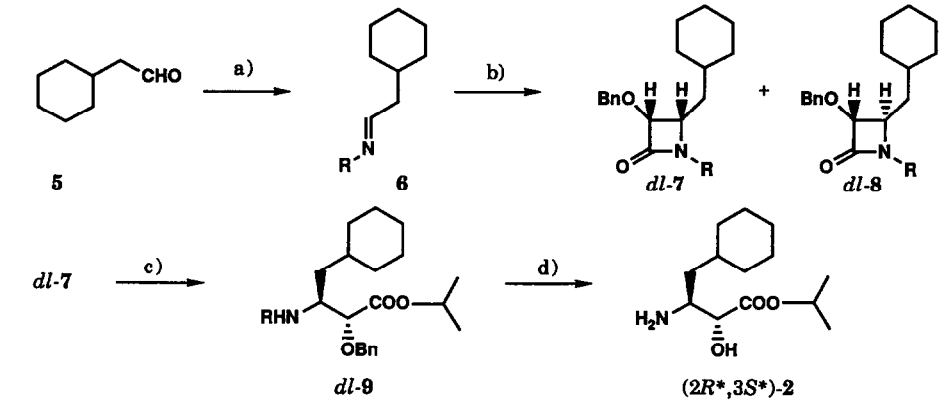
This report details the novel synthesis of (2*R*,3*S*)-**2** and (2*S*,3*R*)-**4** accomplished by employing the highly stereoselective [2+2]-cycloaddition reaction followed by alcoholysis of the formed 3,4-*cis*-disubstituted β-lactam derivatives.[1]

Results and Discussion

1. Synthesis of Isopropyl (2*R**,3*S**)-3-Amino-4-cyclohexyl-3-hydroxybutyrate [(2*R**,3*S**)-2]

In order to explore the feasibility of the designed synthetic scheme, the preparation of (2*R**,3*S**)-**2** was first examined as shown in **Scheme 2**. Thus, cyclohexylacetaldehyde (**5**)[12] was condensed with achiral primary amines such as benzylamine, *p*-anisidine, and di-*p*-anisylmethylamine in the presence of anhydrous magnesium

Scheme 2



a: R= Bn ($PhCH_2$-) **b**: R= *p*-$MeOC_6H_4$- **c**: R= DAM [(*p*-$MeOC_6H_4)_2CH$-]

a) RNH_2-$MgSO_4$ in PhH, 0 °C, 1 h b) $BnOCH_2COCl$-Et_3N in CH_2Cl_2, rt, overnight, 41% (2 steps) (*dl*-**7a**), 30% (2 steps) (*dl*-**7b**), and 94% (2 steps) (*dl*-**7c** and *dl*-**8c**, 11:1) c) HCl in Me_2CHOH, 0 °C→rt, overnight, 94% (*dl*-**9a**) and 96% (*dl*-**9c**) d) H_2-10% Pd/C in Me_2CHOH, rt, 1 d, 95% (from *dl*-**9a**) and 67% (from *dl*-**9c**)

sulfate to afford the crude imines (**6a-c**). The [2+2]-cycloaddition reactions of crude **6a-c** with benzyloxyketene *in situ* produced from benzyloxyacetyl chloride and triethylamine took place smoothly, yielding the *dl*-3,4-*cis*-disubstituted β-lactams (*dl*-**7a-c**) as major products. Interestingly, the yields and diastereoselectivities of the [2+2]-cycloaddition reaction were found to highly depend upon the R groups of **6a-c**. Thus, *dl*-**7a,b** were obtained as sole products in rather low yields [41 and 30% yields (2 steps), respectively], and the formation of the undesired 3,4-*trans*-disubstituted β-lactams (*dl*-**8a,b**) could not be detected. On the other hand, the [2+2]-cycloaddition reaction of **6c** gave an excellent yield of the β-lactam mixture [94% yield (2 steps)] in which desired *dl*-**7c** was highly predominant (*dl*-**7c**:*dl*-**8c**=11:1). The ratio of *dl*-**7c** to *dl*-**8c** was estimated by the ^{1}H-NMR spectrum of the mixture. Structures of *dl*-**7a-c** and *dl*-**8c** were determined by their ^{1}H-NMR spectra (see the experimental part) as well as successful synthesis of (2*R**,3*S**)-**2** from *dl*-**7a,c** .

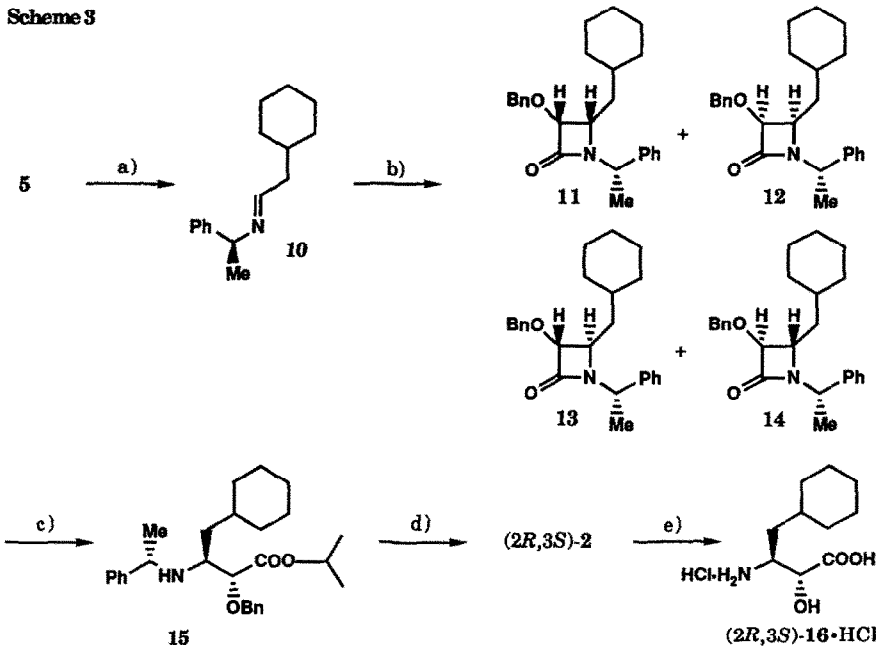
As expected, conversion of *dl*-**7a,c** into (2*R**,3*S**)-**2** was readily accomplished in 2 steps. Thus, the reactions of *dl*-**7a,c** with 2-propanol containing hydrogen chloride at room temperature underwent alcoholysis of the β-lactam moieties, giving rise to the isopropyl esters (*dl* -**9a,c**) in 94% and 96% yields, respectively. It was later found that alcoholysis at higher temperature can effect cleavage of the di-*p*-anisylmethyl group in addition to that of the β-lactam ring (*vide infra*). Subsequent hydrogenolysis of *dl*-**9a,c** furnished (2*R**,3*S**)-**2**, mp 73-75 °C, in 95% and 67% yields, respectively. Comparison of the ^{1}H-NMR and mass spectra of this sample with those of (2*R*,3*S*)-**2** (*vide infra*) unambiguously established its structure.

2. Synthesis of Isopropyl (2*R*,3*S*)-3-Amino-4-cyclohexyl-2-hydroxybutyrate [(2*R*,3*S*)-2] by the Use of (*S*)-1-Phenylethylamine as a Chiral Amine

Since the feasibility of the designed synthetic scheme was definitely established by the successful synthesis of (2*R**,3*S**)-**2**, its application to the preparation of (2*R*,3*S*)-**2** was next studied by employing **C** which bears an asymmetric center in the R^2 group.

As shown in **Scheme 3**, the chiral imine (**10**) prepared from **5** and (*S*)-1-phenylethylamine was subjected to the same [2+2]-cycloaddition reaction with benzyloxyketene as for **6a-c**. (*S*)-1-Phenylethylamine was selected as an optically active amine to produce (2*R*,3*S*)-**2**, based on the results of some preliminary experiments performed by using the both enantiomers.[13] The [2+2]-cycloaddition reaction of **10** proceeded smoothly in a similar manner to that described above, giving rise to a mixture of the β-lactams in 84% yield (2 steps). The ^{1}H-NMR spectrum of this sample clearly disclosed that it consists of four possible diastereomers [**11**, **12**, **13** (or **14**), and **14** (or **13**)] in a ratio of 52:32:10:6 (see the experimental part). Since separation of these four diastereomers by column chromatography was found to be unsuccessful, the mixture was directly subjected to the next alcoholysis. Separation of the reaction products by column chromatography gave the isopropyl ester (**15**) as a major product in 49% yield based on the mixture of **11**, **12**, **13**, and **14** (94% yield based on **11**). Subsequent hydrogenolysis of **15** gave (2*R*,3*S*)-**2**, mp 86-87 °C and $[\alpha]_D^{20}$ -22.0° ($CHCl_3$), in 99% yield. (2*R*,3*S*)-3-Amino-4-cyclohexyl-2-hydroxybutyric acid hydrochloride [(2*R*,3*S*)-**16**·HCl], mp 188-190 °C (decomp.) and $[\alpha]_D^{20}$ -14.2° (1M HCl) [*lit.*,[5b,c] mp 190 °C (decomp.) and $[\alpha]_D^{20}$ -12.4° (1M HCl); *lit.*,[5d,e] mp 191-192 °C (decomp.) and $[\alpha]_D^{20}$ -13.6° (1M HCl)], prepared by treating with 6 M hydrochloric acid was further identified with authentic (2*R*,3*S*)-**16**·HCl[5b-e] by comparing their ^{1}H-NMR spectra and measuring the mixed melting point.

Scheme 3



a) (*S*)-$PhCHMeNH_2$-$MgSO_4$ in PhH, 0 °C→rt b) $BnOCH_2COCl$-Et_3N in CH_2Cl_2, 0 °C→rt, overnight, 84% (2 steps) [**11**,**12**,**13**, and **14** , **11**:**12**:**13** (**14**):**14** (**13**)=52:32:10:6] c) HCl in Me_2CHOH, 0 °C→rt, 6 h, 49% [94% (from **11**)] d) H_2-10% Pd/C in Me_2CHOH, rt, 1 d, 99% e) 6 M HCl, reflux, 4.5 h, 97%

3. Synthesis of Isopropyl (2*R*,3*S*)-3-Amino-4-cyclohexyl-2-hydroxybutyrate [(2*R*,3*S*)-2] by the Use of (*R*)-2-Alkoxy-2-phenylacetaldehydes (20 and 21) as Chiral Aldehydes

It appeared evident that the [2+2]-cycloaddition reaction employing **C** such as **10** which has an asymmetric center in the R^2 group was unrewarding for the preparation of (2*R*,3*S*)-**2** because of its low diastereoselectivity. The asymmetric center in the R^2 group which is fairly far from the reaction site to form the β-lactam ring might explain the observed results. Accordingly, we next examined the [2+2]-cycloaddition reaction of **C** bearing an asymmetric center in the R^1 group. As expected, the optically active imines (**22a-d**) derived from (*R*)-*t*-butyldimethylsilyloxy- or (*R*)-*t*-butoxy-2-phenylacetaldehyde (**20** or **21**), were found to react with benzyloxyketene in a highly stereoselective manner to afford the 3,4-*cis*-disubstituted β-lactams (**23a-d**) as major addition products. The latter compounds (**23a-d**) can be ingeniously elaborated to (2*R*,3*S*)-**2** by sequential alcoholysis, functional group manipulation and deprotection.

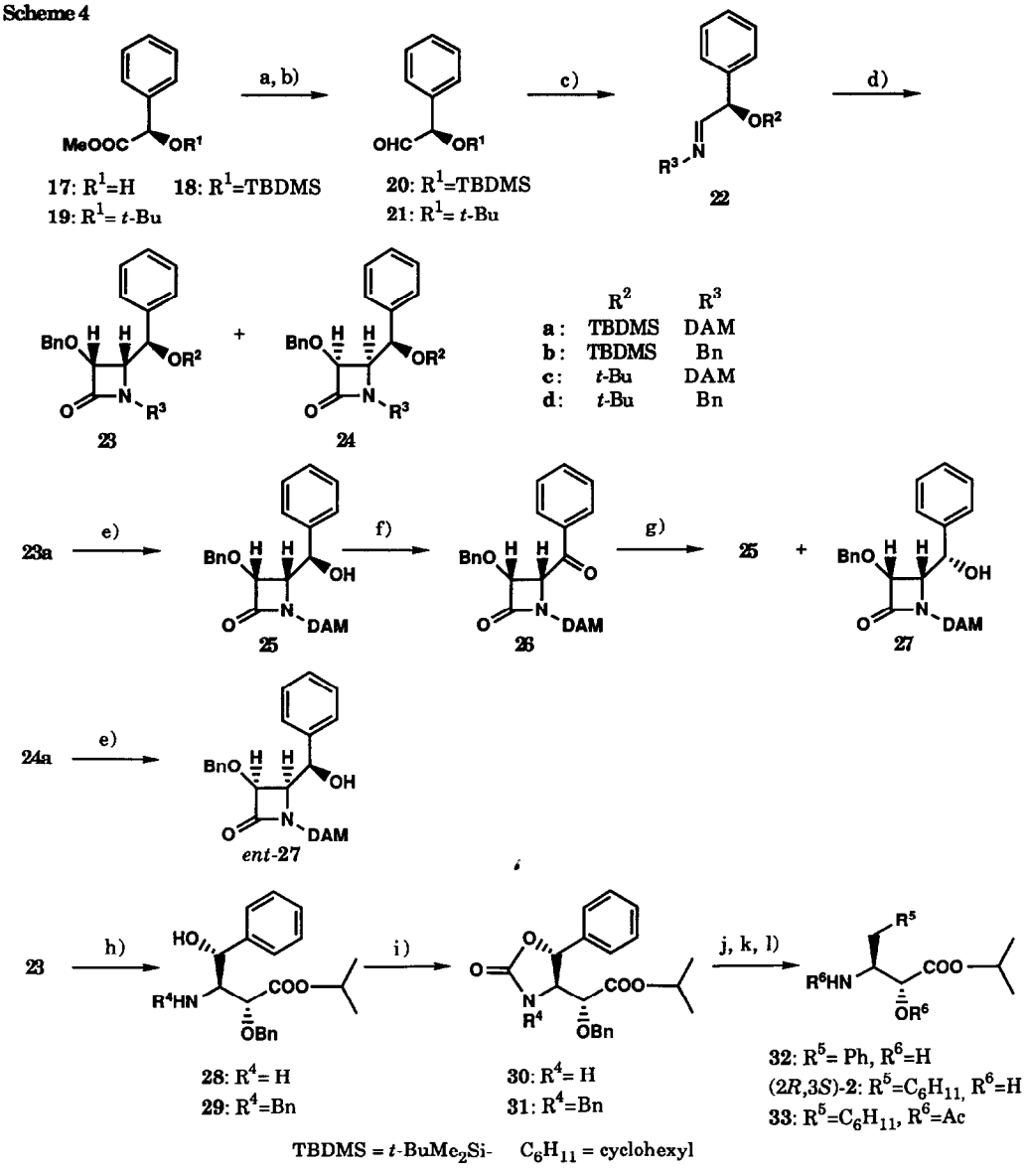
As shown in **Scheme 4**, the aldehydes (**20** and **21**) were prepared from commercially available methyl (*R*)-mandelate (**17**) by way of its *O*-protected derivatives (**18** and **19**) by sequential protection of the hydroxy group of **17** and reduction with diisobutylaluminium hydride. These protective groups were employed since they were expected to be readily removed under the conditions for acidic alcoholysis of β-lactam ring (*vide infra*). Based on our experiences in the synthesis of carbapenem key intermediates,[9b] **20** and **21** derived from **17** were envisioned to afford **23a-d** as major products in the [2+2]-cycloaddition reaction.

Two sorts of the optically active aldehydes (**20** and **21**) were condensed with di-*p*-anisylmethylamine or benzylamine in the presence of anhydrous magnesium sulfate, yielding four types of the optically active imines (**22a-d**). The [2+2]-cycloaddition reactions of **22a-d** took place in a highly stereoselective manner, giving rise to mixtures of the 3,4-*cis*-disubstituted-β-lactams (**23a-d** and **24a-d**) in which the desired diastereomers (**23a-d**) were highly predominant. As shown in the footnotes of **Scheme 4**, the best chemical yield (88%) and diastereoselectivity (15:1) were obtained by the reactions employing **22a** and **22d** as chiral imines, respectively. The ratios of **23a-d** to **24a-d** were calculated by the weights of the separated samples (for **a**, **b**) or by the ^{1}H-NMR spectra of the mixtures (for **c**, **d**) (see the experimental part). Taking into account the chemical yields of the later synthetic stages as well as the chemical yield and diastereoselectivity of the [2+2]-cycloaddition reaction, the reaction with **22a** seems to be most practical.

Stereochemistry of **23a-d** and **24a-d** was assigned by their ^{1}H-NMR spectra (see the experimental part) in addition to successful convergent synthesis of (2*R*,3*S*)-**2** from **23a-d**. Additionally, that both **23a** and **24a** have the $C_{3,4}$-*cis*-stereochemistry was ascertained by the chemical correlation. Thus, desilylation of **23a** followed by oxidation and reduction gave a mixture of the diastereomeric alcohols (**25** and **27**) in a ratio of 1:10 by way of the secondary alcohol (**25**) and the ketone (**26**). The predominantly produced alcohol (**27**) was found to be enantiomeric to the alcohol (*ent*-**27**) independently prepared by desilylation of **24a**. The optical purity of **23a** was calculated to be >95% ee by comparing the ^{1}H-NMR spectrum of the optically active diacetate [(2*R*,3*S*)-**33**] measured in the presence of tris[3-(heptafluoropropylhydroxymethylene)camphorato]europium(III) [Eu(hfc)$_3$] with that of (2*R**,3*S**)-**33** (*vide infra*).

Elaboration of the major products (**23a-d**) to (2*R*,3*S*)-**2** was achieved in 4 steps. Thus, treatments of **23a** and the mixture of **23c** and **24c** (9:1) with acidic 2-propanol at higher temperature than that described in **Section 1** were found to cleanly effect simultaneous alcoholysis of the β-lactam ring and removal of the *O*-

Scheme 4



a) TBDMSCl-ImH in DMF, rt, overnight, 98% (**18**) or $Me_2C{=}CH_2$-conc. H_2SO_4 in CH_2Cl_2, rt, 2 d, 83% (**19**) b) DIBAL in Et_2O-hexane, -78 °C, 20 min, 82% (**20**) or 30 min, 73% (**21**) c) $DAMNH_2$ or $BnNH_2$-anhyd. $MgSO_4$ in PhMe, 0 °C, 1 h, 100% (**22a-c**) or 98% (**22d**) d) $BnOCH_2COCl$-Et_3N in CH_2Cl_2, rt, overnight, 88% (**23a** and **24a**, **23a**:**24a**=10:1), 59% (**23b** and **24b**, **23b**:**24b**=12:1), 77% (**23c** and **24c**, **23c**:**24c**=9:1), or 62% (**23d** and **24d**, **23d**:**24d**=15:1) e) Bu_4NF in THF, rt, 2 h, 99% (for **25**) or 2.5 h, 71% (for *ent*-**27**) f) $(COCl)_2$-DMSO-Et_3N in CH_2Cl_2, ~100% g) $NaBH_4$ in CH_2Cl_2-MeOH, 0 °C, 15 min, 7.7% (for **25**) and 79% (for **27**) h) HCl-Me_2CHOH, rt, overnight, then 60 °C, 3 h, 84% (**28** from **23a**), 50 °C, 3h, (**29** from **23b**), 40 °C, 7 h, 59% (**28** from **23c**), or 40 °C, 5 h, 69% (**29** from **23d**) i) $Cl_3COCOCl$-Py in CH_2Cl_2, 0 °C, 10 min, 90% (**30** from **28**) or 40 °C, 4.5 h, 64% (**31** from **29**) j) H_2-10% Pd/C in EtOAc, rt, overnight, 94% (from **30**) or 81% (from **31**) k) H_2 (5 atm)-5% Rh/Al_2O_3 in AcOH, 97% l) Ac_2O-Py, rt, overnight, 100%

protective groups and the di-*p*-anisylmethyl group, affording the same isopropyl ester (**28**) in 84% and 59% yields, respectively. It is noteworthy that di-*p*-anisylmethyl group was readily cleft under such simple acidic condition. When **23b** and the mixture of **23d** and **24d** (15:1) were subjected to the same conditions as employed above, the isopropyl ester (**29**) was produced in 86% and 69% yields, respectively, without cleavage of the *N*-benzyl groups. In order to remove the benzylic hydroxy groups derived from **17**, two sorts of the isopropyl esters (**28** and **29**) were converted to the 2-oxazolidone derivatives (**30** and **31**) in 90% and 64% yields by treating with trichloromethyl chloroformate and pyridine. Hydrogenolysis of **30** and **31** afforded the same isopropyl (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyrate (**32**) in 94% and 81% yields, respectively. The convergent syntheses of **32** nicely correlated the stereochemistry of **23a-d**. Further catalytic reduction of **32** furnished (2*R*,3*S*)-**2**, mp 86-86.5 °C and $[\alpha]_D^{20}$ -22.0° ($CHCl_3$), in 97% yield. This was definitely identified with (2*R*,3*S*)-**2** prepared in **Section 2**. Acetylation of (2*R*,3*S*)-**2** gave a quantitative yield of (2*R*,3*S*)-**33**. A sample of (2*R*,3*S*)-**33** directly derived from **23a** only by employing purification by column chromatography was used for determining the optical purity of **23a** by the ^{1}H-NMR spectrum (*vide supra*).

4. Mechanistic Consideration of the [2+2]-Cycloaddition Reaction

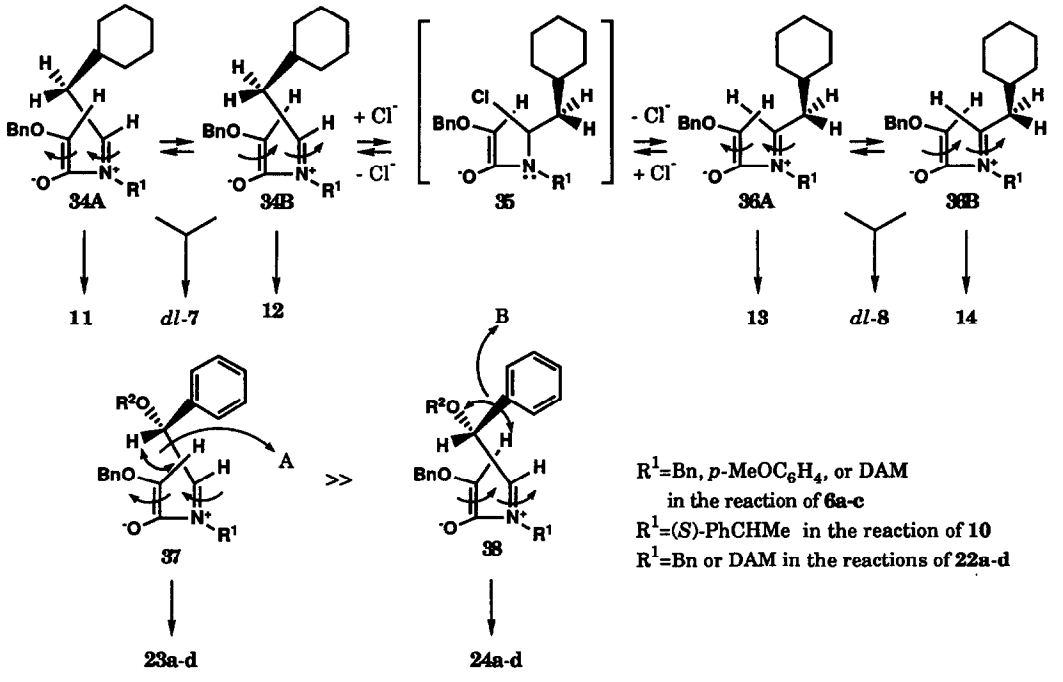
The precise reaction mechanisms which may rationalize the results of various [2+2]-cycloaddition reactions are presently ambiguous. However, as previously suggested for the similar [2+2]-cycloaddition reaction,[14] the observed results may be accounted for by initial formation of a zwitter-ionic intermediate and subsequent conrotatory ring closure.

Thus, as shown in **Scheme 5**, the selective formation of *dl*-**7a-c** in the reaction of **6a-c** with benzyloxyketene can be explained by conrotatory ring closure of the zwitter-ionic intermediates (**34A** and **34B**) to the indicated directions so as to save steric interactions. When **6c** bearing a large di-*p*-anisylmethyl group as the R-group was employed for the reaction, a small amount of the 3,4-*trans*-disubstituted β-lactam (*dl*-**8c**) was produced as a side product. This may be rationalized by the partial isomerization of **34A** and **34B** to **36A** and **36B** by way of the equilibrated intermediate (**35**) followed by conrotatory ring closure. Steric bulkiness and/or electronic effect of the di-*p*-anisylmethyl group which may make **35** more stable can account for this isomerization.

The reaction of **10** with benzyloxyketene can be explained similarly to that of **6a-c**. Thus, formation of the zwitter-ionic intermediates (**34A** and **34B**) followed by their conrotarory ring closures to the indicated directions will produce **11** and **12**, respectively. The formation ratio of **11** to **12** being 52:32 may obviously reflect small thermodynamic difference between **34A** and **34B** due to the long distance between the chiral center and the reaction site. Formation of **13** and **14** may be explained by possible isomerization to the zwitter-ionic intermediates (**36A** and **36B**) followed by conrotatory ring closure in the same manner as described for **34A** and **34B**. The formation ratio of **13** to **14** being 10 (6): 6 (10) can be also rationalized similarly to the case for **11** and **12**.

The zwitter-ionic intermediates (**37** and **38**) may be produced in the reactions of **22a-d** with benzyloxyketene. Since the steric interaction between the olefinic hydrogen and the chiral hydrogen (A) is obviously smaller than that between the olefinic hydrogen and the alkoxy group (B), **37** is envisioned to be thermodynamically more stable than **38**. Accordingly, the mixtures of **23a-d** and **24a-d** were

Scheme 5



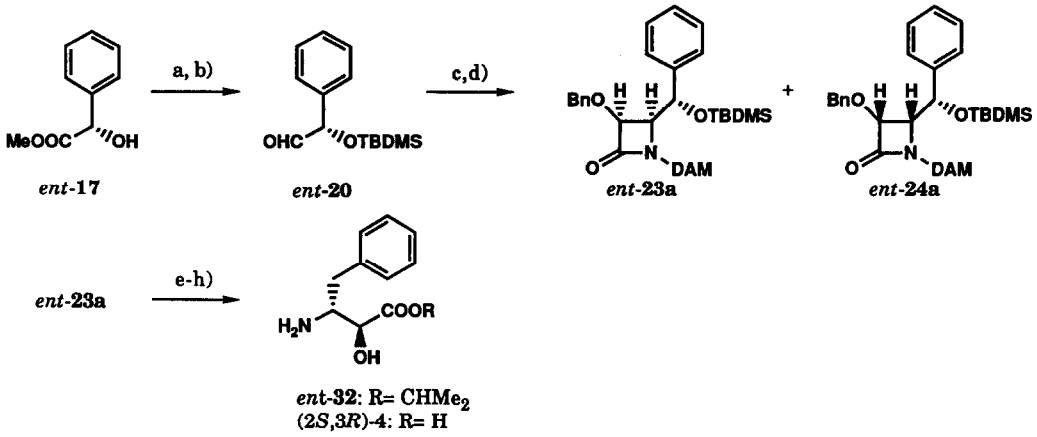
prepared in the ratios of 9~15:1. Presence of the alkoxy groups may prevent the addition of a chloride anion to the C=N bond by steric interaction, resulting in no formations of the *trans*-3,4-disubstituted β-lactams.

5. Synthesis of (2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutyric Acid [(2*S*,3*R*)-4] by the Use of (*S*)-*t*-Butyldimethylsilyloxy-2-phenylacetaldehyde (*ent*-20) as a Chiral Aldehyde.

With completion of the synthesis of (2*R*,3*S*)-2 from **20** and **21**, the explored synthetic routes was next applied to *ent*-**20** to prepare (2*S*,3*R*)-**4**. Thus, as shown in **Scheme 6**, a mixture of *ent*-**23a** and *ent*-**24a** (8:1) was prepared similarly from *ent*-**20** in 2 steps. Preparation of *ent*-**20** from *ent*-**17** was carried out in a similar manner to that described in **Section 3**. A combination of *t*-butyldimethylsilyl and di-*p*-anisylmethyl groups was employed to obtain a higher yield in the [2+2]-cycloaddition reaction (*vide supra*). Elaboration of *ent*-**23a** according to the same procedure as described in **Section 3** gave *ent*-**32**. Acidic hydrolysis of *ent*-**32** furnished the hydrochloride of (2*S*,3*R*)-**4** [(2*S*,3*R*)-**4**·HCl], mp 190-192 °C (decomp.) [*lit.*,[5b,c] mp 190 °C (decomp.)]. This was further treated with an ion exchange resin to give (2*S*,3*R*)-**4**, mp 235-237 °C (decomp.) and $[\alpha]_D^{20}$ +29.9° (1M HCl) [*lit.*,[6] mp 219-221 °C and $[\alpha]_D^{22}$ +27.9° (1M HCl)]. The ^{1}H-NMR spectrum of (2*S*,3*R*)-**4** was identical with those reported.[6]

As mentioned above, we have succeeded in exploring a novel synthetic route to (2*R*,3*S*)-**2** and (2*S*,3*R*)-**4**. Taking into account high stereoselectivity observed for the [2+2]-cycloaddition reactions, expedious elaborations of **23a-d** or *ent*-**23a** to (2*R*,3*S*)-**2** or (2*S*,3*R*)-**4**, and use of commercially available **17** or *ent* -**17** as a starting

Scheme 6



*For reaction conditions for steps a-d), see the footnotes in **Scheme 4**
a) 93%, b) 80%, c) 100%, d) 90% (*ent*-**23a**:*ent*-**24a**=8:1) e) HCl-Me_2CHOH, rt, overnight, then 60°C, 3 h, 70% f) $Cl_3COCOCl$-Py in CH_2Cl_2, 0 °C, 10 min, 93% g) H_2-10% Pd/C in EtOAc, rt, overnight, 92% h) 6 M HCl, 100 °C, 4 h, then ion-exchange resin (AG50XW2, H^+-form), 85%

material, the overall process may have potential as one of the most reliable methods for preparing (2*R*,3*S*)-**2** and (2*S*,3*R*)-**4**.

Experimental

General. All melting points were determined with Yamato MP-21 or Yamato micro melting point apparatuses 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 Bruker AM-400 (400 MHz) spectrometers. All signals were expressed in ppm using tetramethylsilane (in $CDCl_3$) as an internal standard (δ-value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and broad (br). Infrared (IR) spectral 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 GC mass spectra (HRMS and GC-MS)] mass spectrometers. Unless otherwise noted, all reactions were performed using anhydrous solvents. Tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl were mainly used. Wakogel C-200 and C-300 were used as an adsorvent for column chromatography. Kieselgel $60F_{254}$ (Merck) was used for preparative TLC. The following abbreviations are used for solvents and reagents: acetic acid (AcOH), acetonitrile (MeCN), benzene (PhH), carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), diisobutylaluminum hydride (DIBAL), N,N-dimethylformamide (DMF), ether (Et_2O), ethyl acetate (EtOAc), hexane (Hex), 2-propanol (Me_2CHOH), methanol (MeOH), palladium(II) hydroxide [$Pd(OH)_2$], pyridine (Py), tetrabutylammonium fluoride (TBAF), tetrahydrofuran (THF), toluene (PhMe), triethylamine (Et_3N).

Cyclohexylacetaldehyde (5) DIBAL in Hex (1M solution, 72.2 ml, 72 mmol) was added to a solution of ethyl cyclohexylacetate (11.2 g, 66 mmol) in Et_2O (131 ml) at -78 °C. After stirring at the same temperature for 1 h, the mixture was poured into a solution of potassium sodium (2*R*,3*R*)-tartrate (40 g) in H_2O (200 ml). After stirring was continued at room temperature for 2 h, the mixture was diluted with Et_2O. The upper organic layer was separated, washed successively with 0.5 M HCl, saturated NaCl, saturated $NaHCO_3$, and sarurated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-Et_2O, 1:0→19:1) to give pure **5** as a colorless oil (7.10 g, 85%), bp 85 °C (13 mmHg). IR (film): 2930, 2860, 1722, 1445 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.7-2.0 (11H, m, C_6H_{11}), 2.28 (2H, m, $C\underline{H}_2CHO$), 9.75 (1H, dt, J=0.7 and 2.3 Hz, CHO). GC-MS m/z: 126 (M^+), 108, 97, 95.

(3*R,4*S**)-1-Benzyl-3-benzyloxy-4-cyclohexylmethyl-2-azetidinone (*dl*-7a)** Benzylamine (0.161 ml, 1.5 mmol) was added to a stirred mixture of **5** (205 mg, 1.6 mmol) and anhydrous $MgSO_4$ (0.4 g) in PhH (3 ml) at 0 °C, and the mixture was stirred at the same temperature for 1 h. After insoluble materials were filtered off, the filtrate was concentrated *in vacuo* to give crude

6a as an oil. This was directly subjected for the next [2+2]-cycloaddition reaction. ^{1}H-NMR ($CDCl_3$): 0.8-1.9 (11H, m, C_6H_{11}), 2.21 (2H, m,$C\underline{H}_2CHN$), 4.56 (2H, s, $PhC\underline{H}_2$), 7.27 (5H, s, Ph), 7.78 (1H, t, J=5.3 Hz, CHN). A solution of benzyloxyacetyl chloride (0.350 ml, 2.3 mmol) in CH_2Cl_2 (0.35 ml) was added to a mixture of crude **6a** and Et_3N (1.03 ml, 7.4 mmol) in CH_2Cl_2 (1.5 ml) over 30 min with stirring at 0 °C. The mixture was warmed to room temperature, stirred overnight at the same temperature, then diluted with 1M HCl (8 ml). The aqueous mixture was extracted with Et_2O. The ethereal extracts were combined, washed successively with saturated NaCl, saturated $NaHCO_3$, and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 20:1→5:1) to give *dl*-**7a** as a colorless oil [218 mg, 41% (2 steps)]. IR (film): 3050, 2930, 2865, 1750, 1499, 1448, 1403, 1345, 1160, 1075, 1023, 736, 699 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.5-1.8 (13H, m, $C_6H_{11}CH_2$), 3.63 (1H, dt, J=5.1 and 6.6 Hz, C_4-H), 4.08 (1H, d, J=15.2 Hz, one of $PhCH_2O$), 4.61 (1H, d, J=5.1 Hz, C_3-H), 4.66 (1H, d, J=15.2 Hz, one of $PhCH_2O$), 4.67 (1H, d, J=11.9 Hz, one of $PhCH_2N$), 4.90 (1H, d, J=11.9 Hz, one of $PhCH_2N$), 7.3 (10H, m, Phx2). MS m/z: 454 [$(M+Bn)^+$], 426 [$(M+Bn-CO)^+$], 364 [$(M+1)^+$]. Formation of the (3*R**,4*R**)-isomer (*dl*-**8a**) could not be detected for this [2+2]-cycloaddition reaction.

(3*R,4*S**)-1-(*p*-Anisyl)-3-benzyloxy-4-cyclohexylmethyl-2-azetidinone (*dl*-7b)** The same treatments of **5** (196 mg, 1.6 mmol) and *p*-anisidine (172 mg, 1.4 mmol) as described for the preparation of *dl*-**7a** gave pure *dl*-**7b** as a colorless oil [175 mg, 30% (2 steps)] by way of **6b** after purification by column chromatography. ^{1}H-NMR ($CDCl_3$): 0.8-2.0 (13H, m, $C_6H_{11}CH_2$), 3.78 (3H, s, CH_3O), 4.21 (1H, m, C_4-H), 4.73 (1H, d, J=5.3 Hz, C_3-H), 4.74 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 4.97 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 6.86 (2H, d, J=9.0 Hz, two of *p*-$MeOC_6H_4$), 7.30 (2H, d, two of *p*-$MeOC_6H_4$), 7.36 (5H, s, Ph). Formation of the (3*R**,4*R**)-isomer (*dl*-**8b**) could not be detected for this [2+2]-cycloaddition reaction.

(3*R,4*S**)-3-Benzyloxy-4-cyclohexylmethyl-1-(di-*p*-anisylmethyl)-2-azetidinone (*dl*-7c) and Its (3*R**,4*R**)-Isomer (*dl*-8c)** A mixture of **5** (740 mg, 5.9 mmol), di-*p*-anisylmethylamine (1.30 g, 5.3 mmol), and anhydrous $MgSO_4$ (1.43 g) in PhH (5 ml) was treated in the same manner as described for the preparation of **6a** gave crude **6c** as an oil after filtration followed by concentrated *in vacuo*. One fifth of crude **6c** was subjected to the [2+2]-cycloaddition reaction in a similar manner to that described for the preparation of *dl*-**7a**, affording a mixture of *dl*-**7c** and *dl*-**8c** as a colorless oil (487 mg, 99%) after purification by column chromatography (Hex-Et_2O-CH_2Cl_2, 79:20:1). The ^{1}H-NMR spectrum of this sample showed two singlets at 5.82 and 5.84 ppm assignable to the (*p*-$MeOC_6H_4)_2C\underline{H}$ of *dl*-**7c** and *dl*-**8c**, respectively. Based on the intensity of these signals, the ratio of **7c** to **8c** could be calculated as 11:1. Further separation of the mixture by column chromatography (Hex-EtOAc, 19:1→9:1→85:15) gave pure samples of *dl*-**7c** (394 mg) and *dl*-**8c** (16.1 mg) and a mixture of *dl*-**7c** and *dl*-**8c** (53.7 mg) (total amount of *dl*-**7c** and *dl*-**8c**: 464 mg, 94%). *dl*-**7c**: IR (film): 2940, 2850, 1744, 1508, 1244, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.7-1.8 (13H, m, $C_6H_{11}CH_2$), 3.64 (1H, m, C_4-H), 3.799 (3H, s, one of CH_3O), 3.802 (3H, s, one of CH_3O), 4.57 (1H, d, J=5.0 Hz, C_3-H), 4.70 (1H, d, J=12.0 Hz, one of $PhCH_2O$), 4.91 (1H, d, J=12.0 Hz, one of $PhCH_2O$), 5.84 [1H, s, (*p*-$MeOC_6H_4)_2C\underline{H}$], 6.82-6.88 (4H, m, aromatic protons), 7.10-7.20 (4H, m, aromatic protons), 7.25-7.40 (5H, m, Ph). MS m/z: 500 [$(M+1)^+$], 269, 227, 91. *dl*-**8c**: IR (film): 2940, 2850, 1746, 1508, 1244, 1026 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-1.8 (13H, m, $C_6H_{11}CH_2$), 3.52 (1H, ddd, J=1.7, 3.5, 10.3 Hz, C_4-H), 3.80 (6H, s, CH_3O), 4.26 (1H, d, J=1.7 Hz, C_3-H), 4.67 (1H, d, J=11.7 Hz, one of $PhCH_2O$), 4.83 (1H, d, J=11.7 Hz, one of $PhCH_2O$), 5.82 [1H, s, (*p*-$MeOC_6H_4)_2C\underline{H}$], 6.82-6.90 (4H, m, aromatic protons), 7.12-7.20 (4H, m, aromatic protons), 7.27-7.38 (5H, m, Ph). MS m/z: 500 [$(M+1)^+$], 269, 227, 91.

Isopropyl (2*R,3*S**)-3-Benzylamino-2-benzyloxy-4-cyclohexylbutyrate (*dl*-9a)** A solution of *dl*-**7a** (118 mg, 0.33 mmol) in Me_2CHOH (5 ml) was saturated with dry HCl gas at 0 °C. The reaction mixture was gradually warmed up to room temperature and stirred overnight at the same temperature. After concentrated *in vacuo*, PhMe was added to the residue and the toluene solution was further concentrated *in vacuo*. The residue was diluted successively with Et_2O and saturated $NaHCO_3$, and the upper ethereal layer was separated. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 1:0→30:1) to give *dl*-**9a** as a colorless oil (129 mg, 94%). IR (film): 2930, 2860, 1739, 1449 1372, 1262, 1196, 1143, 1102, 1026, 732, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-1.8 (14H, m, $C_6H_{11}CH_2$ and NH), 1.23 [3H, d, J=6.2 Hz, one of $(C\underline{H}_3)_2CH$], 1.29 [3H, d, J=6.2 Hz, one of $(C\underline{H}_3)_2CH$], 3.05 (1H, m, C_3-H), 3.72 (2H, s, $PhCH_2N$), 3.90 (1H, d, J=4.0 Hz, C_2-H), 4.37 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 4.81 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 5.12 [1H, dq, J=each 6.2 Hz, $(CH_3)_2C\underline{H}$]. MS m/z: 424 [$(M+1)^+$], 336, 326, 216.

Isopropyl (2*R,3*S**)-2-Benzyloxy-4-cyclohexyl-3-(di-*p*-anisylmethyl)aminobutyrate (*dl*-9c)** Treatments of *dl*-**7c** (266 mg, 0.53 mmol) in the same manner as described for the preparation of *dl*-**9a** gave almost pure *dl*-**9c** as a colorless oil (288 mg, 96%) after purification by column chromatography (Hex-EtOAc, 19:1→9:1). IR (film): 2930, 2860, 1740, 1610, 1509, 1450, 1243, 1195, 1174, 1102, 1032, 820, 740, 698, 558 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-2.0 (13H, m, $C_6H_{11}CH_2$), 1.19 [3H, d, J=6.2 Hz, one of $(C\underline{H}_3)_2CH$], 1.29 [3H, d, J=6.2 Hz, one of $(C\underline{H}_3)_2CH$], 2.95 (1H, m, C_3-H), 3.74 (3H, s, one of CH_3O), 3.76 (3H, s, one of CH_3O), 3.95 (1H, d, J=3.0 Hz, C_2-H), 4.34 (1H, d, J=12.3 Hz, one of $PhCH_2$), 4.78 (1H, d, J=12.3 Hz, one of $PhCH_2$), 4.82 [1H, s, (*p*-$MeOC_6H_4)_2C\underline{H}$], 5.10 [1H, dq, J=each 6.2 Hz, $(CH_3)_2C\underline{H}$], 6.72-7.26 [8H, m, (*p*-$MeOC_6H_4)_2CH$], 7.30 (5H, s, Ph). MS m/z: 558 [$(M-1)^+$], 516.

Isopropyl (2*R,3*S**)- or (2*R*,3*S*)-3-Amino-2-hydroxy-4-cyclohexylbutyrate [(2*R**,3*S**)- or (2*R*,3*S*)-Cyclohexylnorstatine Isopropyl Ester [*dl*-or (2*R*,3*S*)-2]** a) Preparation of *dl*-**2** from *dl*-**9a**: A mixture of *dl*-**9a** (57.1 mg, 0.13

mmol) and 10% Pd on carbon (20 mg) in Me_2CHOH (1.5 ml) was stirred at room temperature under a hydrogen atmosphere (1 atm) for 1 day. Filtration followed by concentration *in vacuo* gave *dl*-**2** as colorless crystals (31.2 mg, 95%). An analytical sample of *dl*-**2** was prepared by recrystallization from Hex, mp 73-75 °C. IR (film): 3450, 2930, 2860, 1738, 1596, 1441, 1380, 1222, 1196, 1146, 1110, 985 cm^{-1}. The ^1H-NMR and mass spectra of this sample were identical with those of (2*R*,3*S*)-**2** described in d). Found: C, 63.91; H, 10.21; N, 5.63%. Calcd for $C_{13}H_{25}O_3N$: C, 64.17; H, 10.35; N, 5.76%.

b) Preparation of *dl*-**2** from *dl*-**9c**: A mixture of *dl*-**9c** (258 mg, 0.46 mmol) and 10% Pd on carbon (10 mg) , and conc. HCl (3 drops) in Me_2CHOH (4 ml) was stirred at room temperature under a hydrogen atmosphere (1 atm) for 1 day. Filtration followed by concentration *in vacuo* gave a residue, which was purified by column chromatography (Hex-EtOAc-Et_3N, 20:30:1) to give *dl*-**2** as colorless crystals (75.4 mg, 67%). The ^1H-NMR spectrum of this sample was identical with that described in d).

c) Preparation of (2*R*,3*S*)-**2** from **15**: Treatments of **15** (74.3 mg, 0.17 mmol) in a similar manner to that described in a) gave (2*R*,3*S*)-**2** as a colorless crystals (40.0 mg, 99%) after filtration followed by concentrated *in vacuo*. An analytical sample of (2*R*,3*S*)-**2** was prepared as colorless crystals by recrystallization from Hex, mp 86-87 °C and $[\alpha]_D^{20}$ -22.0° (c 1.08, $CHCl_3$). The IR, ^1H-NMR, and mass spectra of this sample were identical with those of (2*R*,3*S*)-**2** described in d).

d) Preparation of (2*R*,3*S*)-**2** from **32**: A mixture of **32** (43.7 mg, 0.18 mmol) and 5% Rh on Al_2O_3 (22 mg) in AcOH (1 ml) was stirred overnight at room temperature under a hydrogen atmosphere (5 atm). After filtration, the filtrate was concentrated *in vacuo*, and EtOAc and saturated $NaHCO_3$ were added successively to the residue. The upper ethyl acetate layer was separated, washed with saturated NaCl, then dried over anhydrous $MgSO_4$. Concentration *in vacuo* gave (2*R*,3*S*)-**2** as colorless crystals (43.5 mg, 97%). Recrystallization from Hex gave an analytical sample of (2*R*,3*S*)-**2** as colorless crystals, mp 86-86.5 °C and $[\alpha]_D^{20}$ -22.0° (c 1.18, $CHCl_3$), IR (KBr): 2920, 2850, 1735, 1592, 1438, 1192, 1141, 1101, 980 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.8-1.8 (16H, m, $C_6H_{11}CH_2$, NH_2, and OH), 1.29 [3H, d, J=6.3 Hz, one of $(CH_3)_2CH$], 1.30 [3H, d, J=6.3 Hz, one of $(CH_3)_2CH$], 3.15 (1H, m, C_3-H), 3.96 (1H, d, J=2.5 Hz, C_2-H), 5.13 [1H, dq, J=each 6.3 Hz, $(CH_3)_2CH$]. MS m/z: 244 [$(M+1)^+$], 184, 156, 126, 44. Found: C, 64.44; H, 10.61; N, 5.69% Calcd for $C_{13}H_{25}O_3N$: C, 64.17; H, 10.35; N, 5.76%. (2*R*,3*S*)-**2** was further derived to (2*R*,3*S*)-**16**•HCl for its further identification. Thus, (2*R*,3*S*)-**2** (11.6 mg, 0.048 mmol) was added to 6 M HCl (1 ml) and the mixture was heated at reflux for 4.5 h. After cooling, the acidic solution was concentrated *in vacuo* to give (2*R*,3*S*)-**16**•HCl as a colorless solid. This was washed with PhMe to afford pure (2*R*,3*S*)-**16**•HCl as colorless crystals (11.0 mg, 97%), mp 188-190 °C (decomp.) and $[\alpha]_D^{20}$ -14.2° (c 0.563, 1M HCl)[lit.,[5b,c] mp 190 °C (decomp.) and $[\alpha]_D^{20}$ -12.4 (c 0.482, 1M HCl); lit.,[5d,e] mp 191-192 °C (decomp.) and $[\alpha]_D^{20}$ -13.6° (c 0.633, 1M HCl)]. The ^1H-NMR spectrum of this sample was identical with those reported.[5b-e]

(3*R*,4*S*)-3-Benzyloxy-4-cyclohexylmethyl-1-[(*S*)-1-phenylethyl]-2-azetidinone (11) and Its (3*S*,4*R*)-, (3*R*,4*R*)-, and (3*S*,4*S*)- Isomers (12, 13, and 14) (*S*)-1-Phenylethylamine (0.162 ml, 1.3 mmol) was added to a stirred mixture of **5** (159 mg, 1.3 mmol) and anhydrous $MgSO_4$ (0.3 g) in PhH (2 ml) at 0 °C, and the mixture was gradually warmed up to room temperature. Filtration and concentrated *in vacuo* gave crude **10** as an oil. ^1H-NMR ($CDCl_3$): 0.8-2.0 (11H, m, C_6H_{11}), 1.49 (3H, d, J=6.8 Hz, CH_3), 2.17 (2H, m, CH_2CHN), 4.28 (1H, q, J=6.8 Hz, PhCH), 7.30 (5H, s, Ph), 7.74 (1H, t, J=5.5 Hz, CHN). The crude imine (**10**) was dissolved in CH_2Cl_2 (1.5 ml). After Et_3N (876 mg, 6.3 mmol) was added to the solution of **10** in CH_2Cl_2 cooled at 0 °C, a solution of benzyloxyacetyl chloride (0.298 ml, 1.9 mmol) in CH_2Cl_2 (0.3 ml) was added over 30 min with stirring at the same temperature. After the mixture was gradually warmed up to room temperature, the stirring was continued overnight at the same temperature. The mixture was diluted with 1M HCl (8 ml) and Et_2O, and the upper ethereal layer was separated. The organic layer was washed successively with saturated NaCl, saturated $NaHCO_3$, and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 9:1) to give a mixture of **11**, **12**, **13**, and **14** as a colorless oil (40 mg, 84%). IR (film): 3050, 2930, 2865, 1750, 1499, 1448, 1403, 1345, 1160, 1075, 1023, 736, 699 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.6-2.0 (16H, m, $C_6H_{11}CH_2$ and CH_3), 3.42 (0.06H, ddd, J=1.6, 4.2 and 10.4 Hz, C_4-H), 3.47 (0.10H, J=1.6, 4.0 and 10.4 Hz, C_4-H), 3.56 (0.52H, ddd, J=4.6, 9.0, and 9.0 Hz, C_4-H), 3.63 (0.32H, ddd, J=4.8, 8.3, and 8.3 Hz, C_4-H), 4.0-4.9 (4H, $PhCH_2$, MeCH, and C_3-H), 7.2-7.4 (10H, m, aromatic protons). Based on the coupling constants of the C_3- and C_4-positions of β-lactams, $J_{3,4}$-*cis*>$J_{3,4}$-*trans*, the major and the minor two products could be assigned to have the 3,4-*cis* and 3,4-*trans*-configurations (**11**+**12** and **13**+**14**) respectively. Since **15** having (2*R*,3*S*)-configuration could be prepared from the mixture of **11**, **12**, **13**, and **14** in 49% yield, the predominantly produced *cis*-isomer was established to have the (3*R*,4*S*)-configuration (**11**:**12**=52:32). However, the ratio of **13** to **14** could not be determined. Thus, the ratio of **11**, **12**, **13**, to **14** could be estimated as 52:32:10(6):6(10). Since separation of this mixture was found to be very difficult, it was directly subjected to the next alcoholysis.

Isopropyl (2*R*,3*S*)-2-Benzyloxy-4-cyclohexyl-3-[(*S*)-(1-phenylethyl)amino]butyrate (15) A solution of the mixture of **11**,**12**,**13**, and **14** (193 mg, 0.51 mmol) in Me_2CHOH (1 ml) was saturated with dry HCl gas at 0 °C. The mixture was gradually warmed up to room temperature, and stirred at the same temperature for 6 h. After concentration *in vacuo*, the residue was diluted with Et_2O and saturated $NaHCO_3$. The upper ethereal layer was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was separated by column chromatography (Hex-Et_2O, 1:0→20:1→15:1) to give **15** as a colorless oil (110 mg, 49% based on the mixture of **11**, **12**, **13**, and **14** or 94% based on **11**), $[\alpha]_D^{20}$ -1.5° (c 1.18, $CHCl_3$). Based on this result, the major product of the [2+2]-cycloaddition reaction was assigned to have the (3*R*,4*S*)-configuration . IR (film): 2940, 2860, 1740, 1447, 1372, 1268, 1195, 1002, 735, 699 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.4-1.8 (22H, m, $C_6H_{11}CH_2$

and CH_3x2), 2.88 (1H, m, C_3-H), 3.81 (1H, q, J=6.4 Hz, PhCHN), 3.93 (1H, d, J=3.1 Hz, C_2-H), 4.35 (1H, d, J=12.2 Hz, one of $PhCH_2O$), 4.77 (1H, d, J=12.2 Hz, one of $PhCH_2O$), 5.15 [1H, dq, J=each 6.2 Hz, $CH(CH_3)_2$], 7.25 (5H, s, one of Ph), 7.30 (5H, one of Ph). MS m/z: 438 [$(M+1)^+$], 422, 350.

Methyl (*R*)-2-*t*-Butyldimethylsilyloxy-2-phenylacetate and Its Enantiomer (18 and *ent*-18) A mixture of **17** (3.13 g, 19 mmol), *t*-butyldimethylchlorosilane (4.82 g, 32 mmol), and imidazole (2.60 g, 38 mmol) in DMF (20 ml) was stirred overnight at room temperature, then diluted with Hex and H_2O. The upper organic phase was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 1:0→10:1) to give **18** as colorless crystals (5.17 g, 98%). Recrystallization from MeOH afforded an analytical sample of **18** as colorless crystals, mp 40-41 °C and $[\alpha]_D^{20}$ -50.0° (c 1.04, $CHCl_3$). IR (KBr): 2950, 2870, 1735, 1256, 1118, 1004, 841, 780, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.03 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.92 [9H, s, $C(CH_3)_3$], 3.68 (3H, s, OCH_3), 5.23 (1H, s, PhCH), 7.3-7.4 (5H, m, Ph). MS m/z: 265 [$(M-CH_3)^+$], 223, 89. Found: C, 64.08; H, 8.72%. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63%. The same treatments of *ent*-**17** (2.47 g, 15 mmol) as described for **17** gave *ent*-**18** as colorless crystals (3.86 g, 93%). Recrystallization from MeOH gave an analytical sample of *ent*-**18** as colorless crystals, mp 40.5-41.5°C and $[\alpha]_D^{20}$ +51.3° (c 1.03, $CHCl_3$). The IR, ^{1}NMR, and mass spectra of this sample were identical with those recorded for **18**.

Methyl (*R*)-2-*t*-Butoxy-2-phenylacetate (19) A mixture of **17** (2.15 g, 13 mmol), isobutene (30 g, 54 mmol), and conc. H_2SO_4 (10 drops) in CH_2Cl_2 (20 ml) was stirred in a sealed tube at room temperature for 2 days. After evaporation of excess isobutene under an atmospheric pressure, the mixture was diluted with CH_2Cl_2 and H_2O. The lower organic layer was separated, washed successively with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 1:0→5:1) to afford **19** as a colorless oil (2.40 g, 83%), $[\alpha]_D^{20}$ -43.0° (c 2.85, $CHCl_3$). IR (film): 3000, 1760, 1738, 1370, 1100, 725, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.25 [9H, s, $C(CH_3)_3$], 3.70 (3H, s, OCH_3). 5.08 (1H, s, PhCH), 7.2-7.4 (5H, m, Ph). MS m/z: 163 [$(M-COOCH_3)^+$], 107, 57.

(*R*)-2-*t*-Butyldimethylsilyloxy-2-phenylpropanal and Its Enantiomer (20 and *ent*-20) A solution of DIBAL in Hex (1M solution, 5.6 ml, 5.6 mmol) was added to a solution of **18** (1.55 g, 5.5 mmol) in Et_2O (5.6 ml) with stirring at -78 °C, and the mixture was stirred at the same temperature for 20 min. The reaction was quenched by the addition of H_2O (0.6 ml), and stirring was continued at room temperature for 1 h. After insoluble materials were removed by filtration through a pad of celite, the filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography (Hex-Et_2O, 1:0→20:1) to afford **20** as a colorless oil (1.14 g, 82%), $[\alpha]_D^{20}$ +3.1° (c 1.22, $CHCl_3$). IR (film): 2945, 2860, 1735, 1255, 1108, 838, 780, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.04 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.95 [9H, s, $C(CH_3)_3$], 5.00 (1H, d, J=2.1 Hz, PhCH), 7.37 (5H, s, Ph), 9.51 (1H, d, J=2.1 Hz, CHO). MS m/z: 235 (M^+), 193, 73. The same treatments of *ent*-**18** (1.44 g, 5.1 mmol) as described for **18** gave *ent*-**20** as a colorless oil (1.02 g, 80%). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **20**.

(*R*)-2-*t*-Butoxy-2-phenylpropanal (21) Treatments of **19** (1.50 g, 6.8 mmol) in a similar manner to that described for the preparation of **20** from **18** gave **21** as a colorless oil (950 mg, 73%) after purification by column chromatography (Hex-Et_2O, 1:0→15:1). IR (film): 2995, 1736, 1365, 1185, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 [9H, s, $C(CH_3)_3$], 4.87 (1H, d, J=2.4 Hz, PhCH), 7.2-7.4 (5H, m, Ph), 9.54 (1H, d, J=2.4 Hz, CHO). MS m/z: 163 [$(M-CHO)^+$], 107, 57. In order to ascertain the optical purity of **21**, it was derived to (*R*)-2-*t*-butoxy-2-phenylethyl (*R*)-α–methoxy-α-(trifluoromethyl)phenylacetate [(*R*)-MTPA-ester] and (*R*)-2-*t*-butoxy-2-phenylethyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate [(*S*)-MTPA-ester] by sequential reduction with $NaBH_4$ in EtOH (86%) and acylation with (*R*)-and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in Py (81% and 76%). Comparision of the ^{1}H-NMR spectra of the (*R*)-and (*S*)-MTPA esters obviously disclosed that the optical purity of **21** was >95% ee.

(3*R*,4*R*)-3-Benzyloxy-4-[(*R*)-1-(*t*-butyldimethylsilyloxy)benzyl]-1-(di-*p*-anisylmethyl)-2-azetidinone, Its (3*S*,4*S*)-isomer (23a and 24a), and Their Enantiomers (*ent*-23a and *ent*-24a) A mixture of **20** (1.48 g, 5.9 mmol), di-*p*-anisylmethylamine (1.46 g, 6.0 mmol), and anhydrous $MgSO_4$ (1.84 g) in PhMe (5 ml) was stirred at 0 °C for 1 h. Filtration followed by concentrated *in vacuo* gave crude **22a** as a pale yellow oil. IR (film): 2950, 2875, 1510, 1245, 836 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.01 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.89 [9H, s, $C(CH_3)_3$], 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.28 (1H, brs, NCH), 5.38 (1H, d, J=5.9 Hz, PhCH), 6.74-7.55 (13H, m, aromatic protons), 7.58 (1H, dd, J=0.9 and 5.9 Hz, PhCHCHN). A part of crude **22a** (741 mg, 15 mmol) was dissolved in CH_2Cl_2 (2.3 ml), to which were added Et_3N (0.32 ml, 2.3 mmol) and benzyloxyacetyl chloride (0.33 ml, 2.1 mmol) at 0 °C. After being stirred at room temperature overnight, the mixture was diluted with Et_2O and H_2O. The upper ethereal layer was separated, washed successively with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-Et_2O, 5:1→4:1) to give more polar **23a** as a colorless caramel (764 mg) and less polar **24a** as a colorless solid (76.0 mg) (the total yield of **23a** and **24a** was 88%, **23a**:**24a**=10:1). **23a**: $[\alpha]_D^{20}$ +32.4° (c 1.11, $CHCl_3$). IR ($CHCl_3$): 2950, 2870, 1742, 1610, 1456, 1244, 1060, 1024, 836 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.41 (3H, s, $SiCH_3$), -0.13 (3H, s, $SiCH_3$), 0.77 [9H,s, $C(CH_3)_3$], 3.80 (6H, two s, OCH_3x2), 3.96 (1H, dd, J=5.3 and 8.4 Hz, C_4-H), 4.22 (1H, d, J=5.3 Hz, C_3-H), 4.31 (1H, d, J=12.2 Hz, one of $PhCH_2$), 4.45 (1H, d, J=12.2 Hz, one of $PhCH_2$), 5.13 (1H, d, J=8.4 Hz, PhCHO), 5.84 (1H, brs, NCH), 6.83-7.34 (18H, m, aromatic

protons). MS m/z: 504, 297, 227, 91. **24a**: mp 96-97 °C (recrystallized from Hex) and $[\alpha]_D^{20}$+ 2.5° (c 1.22, $CHCl_3$). IR (KBr): 3010, 2940, 2855, 1752, 1505, 1244, 1175, 832, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.34 (3H, s, $SiCH_3$), -0.05(3H, s, $SiCH_3$), 0.77 [9H, s, $C(CH_3)_3$], 3.77 (6H, two s, OCH_3x2), 3.81 (1H, brs, NCH), 3.82 (1H, dd, J=5.1 and 8.5 Hz, C_4-H), 4.61 (1H, d, J=5.1 Hz, C_3-H), 4.82 (1H, d, J=11.9 Hz, one of $PhCH_2$), 4.94 (1H, d, J=11.9 Hz, one of $PhCH_2$), 5.00 (1H, d, J=8.5 Hz, PhCHO), 6.7-7.5 (18H, m, aromatic protons). MS m/z: 623 (M^+), 566, 297, 91. Found: C, 73.15; H, 7.31; N, 2.22%. Calcd. for $C_{38}H_{45}O_3NSi$: C, 73.16; H, 7.27; N, 2.25%. Treatments of *ent*-**20** (980 mg, 3.9 mmol) under the same conditions as described for **20** gave a mixture of *ent*-**23a** and *ent*-**24a** as a colorless caramel (2.20 g, 90%) by way of *ent*-**22a** (1.92 g, quantitative yield). The ^{1}H-NMR spectrum of this mixture showed two sets of the doublets at 4.22 and 4.61 ppm assignable to the C_3-H of ent-**23a** and *ent*-**24a**, respectively. Based on the intensity of these signals, the ratio of ent-**23a** to *ent*-**24** could be calculated as 9:1. Further separation of this mixture by column chromatography (Hex-Et_2O, 5:1→3:1) gave pure samples of more polar *ent*-**23a** and less polar *ent*-**24a** both as a colorless caramel. ent-**23a**: $[\alpha]_D^{20}$ -32.1° (c 1.15, $CHCl_3$) and ent-**24a**: $[\alpha]_D^{20}$ -2.3° (c 0.711, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra of ent-**23a** and ent-**24a** were identical with those recorded for **23a** and **24a**, respectively.

(3*R*,4*R*)-1-Benzyl-3-benzyloxy-4-[(*R*)-1-(*t*-butyldimethylsilyloxy)benzyl]2-azetidinone (23b) and Its (3*S*,4*S*)-Isomer (24b) Condensation of **20** (325 mg, 1.3 mmol) and benzylamine (140 µl, 1.3 mmol) under the same conditions as described for the preparation of **22a** gave crude **22b** as a pale yellow oil (450 mg, quantitative yield) after filtration followed by concentration *in vacuo*. ^{1}H-NMR ($CDCl_3$): 0.05 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.92 [9H, s, $C(CH_3)_3$], 4.55 (2H, s, $PhCH_2$), 5.37 (1H, d, J=6.2 Hz, CHO), 7.2-7.7 (11H, m, aromatic protons and PhCHCHN). A part of crude **22b** (283 mg, 0.83 mmol) was subjected to the [2+2]-cycloaddition reaction under the same conditions as described for the preparation of **23a** and **24a**, affording **23b** as a more polar product (221 mg) and **24b** as a less polar product (19.0 mg) (the total yield of **22b** and **23b** was 59%, **23b**:**24b**=12:1) after purification by column chromatography (Hex-EtOAc, 1:0→5:1). IR (film): 3050, 2950, 1755, 1252, 1160, 699 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.23 (3H, s, $SiCH_3$), 0.39 (3H, s, $SiCH_3$), 0.96 [9H, s, $C(CH_3)_3$], 3.81 (1H, dd, J=5.1 and 8.6 Hz, C_4-H), 4.30 (1H, d, J=5.1 Hz, C_3-H), 4.34 (1h, d, J=14.7 Hz, one of $PhCH_2N$), 4.35 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 4.51 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 4.92 (1H, d, J=14.7 Hz, one of $PhCH_2N$), 5.04 (1H, d, J=8.6 Hz, PhCHO), 7.1-7.4 (15H, m, aromatic protons). MS m/z: 488 [$(M+1)^+$], 430, 297, 221, 91. **23b**: IR (film): 3040, 2940, 2850, 1758, 1248, 836, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.36 (3H, s, $SiCH_3$), -0.07 (3H, s, $SiCH_3$), 0.75 [9H, s, $C(CH_3)_3$], 2.48 (1H, d, J=14.9 Hz, one of $PhCH_2N$), 3.68 (1H, dd, J=4.9 and 8.3 Hz, C_4-H), 4.43 (1H, d, J=14.9 Hz, one of $PhCH_2N$), 4.66 (1H, d, J=4.9 Hz, C_3-H), 4.84 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 4.93 (1H, d, J=8.3 Hz, PhCHO), 4.94 (1H, d, J=11.9 Hz, one of $PhCH_2O$), 6.67 (2H, m, aromatic protons), 7.2-7.5 (13H, m, aromatic protons). MS m/z: 430 [$(M-C(CH_3)_3)^+$], 297, 221, 91.

(3*R*,4*R*)-3-Benzyloxy-4-[(*R*)-1-(*t*-butoxy)benzyl]-1-(di-*p*-anisylmethyl)-2-azetidinone (23c) and Its (3*S*,4*S*)-Isomer (24c) Condensation of **21** (909 mg, 4.7 mmol) and di-*p*-anisylmethylamine (1.15 g, 4.7 mmol) under the same conditions as described for the preparation of **22a** gave crude **22c** as a pale yellow oil (2.02 g, quantitative yield) after filtration followed by concentration *in vacuo*. ^{1}H-NMR ($CDCl_3$): 1.21 [9H, s, $C(CH_3)_3$], 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.27 (1H, d, J=5.9 Hz, PhCHO), 5.30 (1H, brs, NCH), 7.64 (1H, d, J=5.9 Hz, PhCHCH). The total amount of crude **22c** was subjected to the [2+2]-cycloaddition reaction under the same conditions as described for the preparation of **23a** and **24a**, affording a mixture of **23c** and **24c** as an amorphous solid (2.07 g, 77%) after purification by column chromatography (Hex-Et_2O 4:1→1:2). The ^{1}H-NMR spectrum of this sample showed two doublets at 4.21 and 4.59 ppm assignable to the C_3-H of **23c** and **24c**, respectively. Based on the intensity of these signals, the ratio of **23c** to **24c** was calculated as 9:1. Spectral data of the major product (**23c**) are as follows. IR (KBr):3040, 2970, 2945, 2850, 1755, 1604, 1508, 1242, 1130, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.92 [9H, s, $C(CH_3)_3$], 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.90 (1H, dd, J=5.3 and 9.2 Hz, C_4-H), 4.21 (1H, d, J=5.3 Hz, C_3-H), 4.33 (1H, d, J=12.2 Hz, one of $PhCH_2$), 4.45 (1H, d, J=12.2 Hz, one of $PhCH_2$), 4.99 (1H, d, J=9.2 Hz, PhCHO), 5.93 (1H, s, NCH), 6.8-7.4 (18H, m, aromatic protons). MS m/z; 566 [$(M+1)^+$], 508, 446, 227, 91.

(3*R*,4*R*)-1-Benzyl-3-benzyloxy-4-[(*R*)-1-(*t*-butoxy)benzyl]-2-azetidinone (23d) and Its (3*S*,4*S*)-Isomer (24d) Condensation of **21** (399 mg, 2.1 mmol) and benzylamine (227 µl, 2.1 mmol) under the same conditions as described for the preparation of **22a** gave crude **22d** as a pale yellow oil (573 mg, 98%) after filtration followed by concentration *in vacuo*. ^{1}H-NMR ($CDCl_3$): 1.25 (9H, s, $C(CH_3)_3$), 4.55 (2H, s, $PhCH_2$), 5.20 (1H, d, J=6.4 Hz, PhCHO), 7.2-7.5 (10H, m, aromatic protons), 7.67 (1H, d, J=6.4 Hz, PhCHCHN). A part of crude **22d** (178 mg, 0.63 mmol) was treated under the conditions for the [2+2]-cycloaddition reaction in a similar manner to that described for the preparation of **23a** and **24a**, affording a mixture of **23d** and **24d** as a colorless caramel (168 mg, 68%) after purification by column chromatography (Hex-EtOAc, 1:0→5:1). The ^{1}H-NMR spectrum of this sample showed two doublets at 4.28 and 4.66 ppm assignable to the C_3-H of **23d** and **24d**, respectively. Based on the intensity of these signals, the ratio of **23d** to **24d** could be determined as 15:1. Spectral data of the major product (**23d**) are as follows. IR (film): 3080, 3050, 3000, 2950, 1760, 1455, 1190, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.12 [9H, s, $C(CH_3)_3$], 3.68 (1H, dd, J=5.1 and 9.3 Hz, C_4-H), 4.28 (1H, d, J=5.1 Hz, C_3-H), 4.39 (1H, d, J=12.0 Hz, one of $PhCH_2$), 4.44 (1H, d, J=14.3 Hz, one of $PhCH_2N$), 4.56 (1H, d, J=12.0 Hz, one of $PhCH_2O$), 4.90 (1H, d, J=14.3Hz, one of $PhCH_2N$), 4.94 (1H, d, J=9.3 Hz, PhCHO), 7.2-7.5 (15H, m, aromatic protons). MS m/z: 430 [$(M+1)^+$], 296, 238, 91.

(3*R*,4*S*)-3-Benzyloxy-1-(di-*p*-anisylmethyl)-4-[(*R*)-1-hydroxybenzyl]-2-azetidinone (25) A solution of TBAF in THF (1M solution, 0.2 ml, 0.20 mmol) was added to a solution of **23** (121 mg, 0.19 mmol) in THF (0.5 ml) with stirring at 0 °C. After 1 h's and 2 h's reactions at room temperature, further amounts of the solution of TBAF in THF (1M solution, each 0.05 ml, total 0.30 ml, 0.30 mmol) were added to the mixture, and stirring was continued for further 30 min. The mixture was diluted with EtOAc and H_2O. The organic phase was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 4:1→2:1) to give **25** as a colorless amorphous solid (97.7 mg, 99%), $[\alpha]_D^{20}$ -16.6° (c 0.785, $CHCl_3$). IR (film): 3600-3200, 2940, 1740, 1504, 1242, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.95-3.05 (1H, brs, OH), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.99 (1H, dd, J=4.2 and 5.1 Hz, C_4-H), 4.59 (1H, d, J=5.1 Hz, C_3-H), 4.59 (1H, d, J=11.8 Hz, one of $PhCH_2$), 4.83 (1H, d, J=11.8 Hz, one of $PhCH_2$), 5.01 (1H, d, J=4.1 Hz, PhC<u>H</u>O), 5.16 (1H, s, NCH), 6.8-7.4 (18H, m, aromatic protons). MS m/z: 509 (M^+), 262, 227, 91.

(3*R*,4*R*)-4-Benzoyl-3-benzyloxy-1-(di-*p*-anisylmethyl)-2-azetidinone (26) DMSO (0.22 ml, 3.1 mmol) was added to a solution of oxalyl chloride (0.25 ml, 2.9 mmol) in CH_2Cl_2 (2.0 ml) with stirring at -78 °C. After stirring at the same temperature for 5 min, a solution of **25** (145 mg, 0.28 mmol) in CH_2Cl_2(2.0 ml) was added, and stirring was continued at the same temperature for 30 min. After addition of Et_3N (0.40 ml, 2.9 mmol) , the mixture was warmed up to -30 °C and further stirred for 20 min, then diluted with EtOAc and H_2O. The upper organic layer was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 5:1→4:1) to give **26** as colorless crystals (144 mg, quantitative yield). Recrystallization from EtOAc-Hex yielded an analytical sample of **26** as colorless crystals, mp 172-173 °C and $[\alpha]_D^{20}$ +42.0° (c 1.01, $CHCl_3$). IR (KBr): 1742, 1684, 1505, 1240, 1172, 1022, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.56 (1H, d, J=12.1 Hz, one of $PhCH_2$), 4.66 (1H, d, J=12.1 Hz, one of $PhCH_2$), 5.00 (2H, two s, C_3-H and C_4-H), 5.82 (1H, brs, NCH), 6.8-7.8 (18H, m, aromatic protons). MS m/z: 508 [(M+1)$^+$], 239, 227, 91. Found: C, 75.65; H, 5.75; N, 2.76%. Calcd for $C_{32}H_{29}O_5N$: C, 75.72; H, 5.76; N, 2.76%.

(3*R*,4*S*)-3-Benzyloxy-1-(di-*p*-anisylmethyl)-4-[(*S*)-1-hydroxybenzyl)-2-azetidinone (27) and Its 4-[(*R*)-1-Hydroxybenzyl]isomer (25) $NaBH_4$ (9.5 mg, 0.25 mmol) was added to a solution of **26** (42.7 mg, 0.084 mmol) in a mixture of CH_2Cl_2 (0.2 ml) and MeOH (1 ml) with stirring at 0 °C. After stirring at the same temperature for 15 min, the mixture was diluted with EtOAc and H_2O. The upper organic phase was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was separated by preparative TLC (Hex-Et_2O, 1:2) to give **27** (33.9 mg, 79%) and **25** (3.3 mg, 7.7%). **27**: $[\alpha]_D^{20}$ +26.1° (c 1.31, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra of this sample was identical with those of *ent*-**27**. The compound (**25**) was identified with an authentic sample prepared from **23a** by comparison of their IR and ^{1}H-NMR spectra.

(3*S*,4*R*)-3-Benzyloxy-1-(di-*p*-anisylmethyl)-4-[(*R*)-1-hydroxybenzyl]-2-azetidinone (*ent*-27) Treatments of **24a** (231 mg, 0.37 mmol) in a similar manner to that described for the preparation of **25** gave *ent*-**27** as an amorphous solid (135 mg, 71%) after purification by column chromatography (Hex-EtOAc, 4:1→2:1), $[\alpha]_D^{20}$ -26.9° (c 1.20, $CHCl_3$). IR (KBr): 3600-3400, 2930, 2850, 1742, 1602, 1502, 1244, 1010, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.54 (1H, d, J=7.6 Hz, OH), 3.79 (3H, s, OCH_3) 3.80 (3H, s, OCH_3), 3.90 (1H, dd, J=5.1 and 5.5 Hz, C_4-H), 4.65 (1H, d, J=11.7 Hz, one of $PhCH_2$), 4.69 (1H, d, J=5.1 Hz, C_3-H), 4.82 (1H, dd, J=5.5 and 7.6 Hz, C<u>H</u>OH), 4.88 (1H, d, J=11.7 Hz, one of $PhCH_2$), 6.8-7.5 (18H, m, aromatic protons). MS m/z: 509 (M^+), 317, 269, 227, 91.

Isopropyl (2*R*,3*S*,4*R*)-3-Amino-2-benzyloxy-4-hydroxybutyrate and Its Enantiomer (28 and *ent*-28) a) Preparations from **23a** and *ent*-**23a**: Dry HCl gas (*ca.* 200 ml) was passed through a solution of **23a** (189 mg, 0.30 mmol) in Me_2CHOH (4 ml) cooled at 0°C, and the mixture was stirred at room temperature overnight, then at 60 °C for 3h. After concentration *in vacuo* , Et_2O and saturated $NaHCO_3$ were successively added to the residue. The upper ethereal layer was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc, 7:3→6:4) to give **28** as a colorless oil (87.4 mg, 84%). IR (film): 3700-3100, 3050, 3000, 1730, 1452, 1208, 1102, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.25 [6H, two d, J=each 6.2 Hz, CH(C<u>H</u>$_3$)$_2$], 3.13 (1H, dd, J=2.8 and 7.3 Hz, C_3-H), 1.8-2.5 (3H, brs, NH_2 and OH), 3.77 (1H, d, J=2.8 Hz, C_4-H), 4.27 (1H, d, J=11.0 Hz, one of $PhCH_2O$), 4.57 (1H, d, J=7.3 Hz, C_2-H), 4.76 (1H, d, J=11.0 Hz, one of $PhCH_2O$), 5.10 [1H, dq, J=each 6.2 Hz, C<u>H</u>(CH$_3$)$_2$], 7.28 (5H, s, aromatic protons), 7.37 (5H, s, aromatic protons). MS m/z: 344 [(M+1)$^+$], 236, 91. The same treatments of *ent*-**23a** (208 mg, 0.33 mmol) as described for **23a** gave *ent*-**28** as colorless crystals (80.2 mg, 70%). Recrystallization from Hex-EtOAc gave an analytical sample of *ent*-**28** as colorless crystals, mp 94.5-95 °C and $[\alpha]_D^{20}$ -61.7° (c 1.09, $CHCl_3$). The ^{1}H-NMR and mass spectra of this sample were identical with those recorded for **28**. Found: C, 69.79; H, 7.39; N, 3.96%. Calcd for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.34; N, 4.08%.
b) Preparation from the mixture of **23c** and **24c**: Dry HCl gas (*ca* 200 ml) was passed through a solution of the mixture of **23c** and **24c** (507 mg, 0.90 mmol) (**23c**:**24c**=9:1) cooled at 0 °C. The mixture was gradually warmed up to 40 °C, stirred at the same temperature for 7 h, then worked up in a similar manner to that described in a) to afford **28** as a colorless oil (182 mg, 59%) after purification by column chromatography (Hex-Et_2O, 1:1→1:3). The ^{1}H-NMR spectrum of this sample was identical with that of **28** described in a). Isolation of the (2*S* ,3*R*, 4*R*)-isomer of **28** which was expected to be produced from **24c** was not attempted.

Isopropyl (2*R*,3*S*,4*R*)-3-Benzylamino-2-benzyloxy-4-hydroxybutyrate (29) a) Preparation from **23b:** Dry HCl gas (*ca* 200 ml) was passed through a solution of **23b** (112 mg, 0.23 mmol) in Me_2CHOH (4 ml) cooled at 0 °C. The mixture was gradually warmed to 50 °C, stirred at the same temperature for 3 h, then worked up in a similar manner to that described for the preparation of **28**. Purification of the residue obtained by concentration of the ethyl acetate extracts *in vacuo* by column chromatography (Hex-EtOAc, 1:0→9:1) gave **29** as a colorless oil (85.5 mg, 86%), $[\alpha]_D^{20}$ -16.3° (c 1.37, $CHCl_3$). IR (film): 3600-3300, 3048, 2995, 1740, 1452, 1100, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 [6H, two d, J=each 6.4 Hz, $CH(C\underline{H}_3)_2$], 1.3-1.9 (2H, brs, NH and OH), 3.17 (1H, dd, J=2.3 and 7.9 Hz, C_3-H), 3.59 (1H, d, J=12.6 Hz, one of $PhC\underline{H}_2N$), 3.73 (1H, J=2.3 Hz, C_4-H), 3.88 (1H, d, J=12.6 Hz, one of $PhC\underline{H}_2N$), 4.30 (1H, d, J=11.4 Hz, one of $PhC\underline{H}_2O$), 4.45 (1H, d, J=7.9 Hz, C_2-H), 4.81 (1H, d, J=11.4 Hz, one of $PhC\underline{H}_2O$), 5.10 [1H, dq, J=each 6.4 Hz, $C\underline{H}(CH_3)_2$], 7.2-7.4 (15H, m, aromatic protons). MS m/z: 434 [$(M+1)^+$], 326, 282, 91.
b) Perparation from the mixture of **23d** and **24d:** Dry HCl gas (*ca.* 200 ml) was passed through a solution of the mixture of **23d** and **24d** (126 mg, 0.29 mmol) (**23d**:**24d**=15:1) cooled at 0 °C. The mixture was gradually warmed to 40 °C, stirred at the same temperature for 5 h, then worked up in a similar manner to that described for the preparation of **28** to afford **29** as a colorless oil (87.9 mg, 69%) after purification by column chromatography (Hex-EtOAc, 1:0→9:1). The ^{1}H-NMR spectrum of this sample was identical with that described in a). Isolation of the (2*S*,3*R*,4*R*)-isomer of **29** which was expected to be produced from **24d** was not attempted.

(4*R*,5*R*)-5-[(*R*)-(1-Benzyloxy-1-isopropoxycarbonyl)methyl]-4-phenyl-2-oxazolidone and Its Enantiomer (30 and *ent*-30) Py (200 µl, 2.5 mmol) and trichloromethyl chloroformate (72 µl, 0.60 mmol) was successively added to a solution of **28** (207 mg, 0.60 mmol) in CH_2Cl_2 (2 ml) cooled at 0 °C. After stirring at the same temperature for 10 min, the mixture was diluted with H_2O and EtOAc. The upper ethyl acetate layer was separated, washed successively with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo* . The residue was purified by column chromatography (Hex-EtOAc, 4:1→3:1) to afford **30** as a colorless oil (199 mg, 90%), $[\alpha]_D^{20}$ +99.7° (c 1.62, $CHCl_3$). IR (film): 3300, 3000, 1760-1735, 1455, 1100, 1002, 688 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.21 [3H, d, J=6.4 Hz, one of $CH(C\underline{H}_3)_2$], 1.25 [3H, d, J=6.4 Hz, one of $CH(C\underline{H}_3)_2$], 3.96 (2H, two d, J=each 2.0 Hz, C_4-H and CHCOO), 4.52 (1H, d, J=11.4 Hz, one of $PhC\underline{H}_2$), 4.83 (1H, d, J=11.4 Hz, one of $PhC\underline{H}_2$), 5.14 [1H, dq, J=each 6.4 Hz, $C\underline{H}(CH_3)_2$], 5.38 (1H, dd, J=each 2.0 Hz, C_5-H), 5.6-5.7 (1H, brs, NH), 7.2-7.4 (10H, m, aromatic protons). MS m/z: 370 [$(M+1)^+$], 282, 208, 91. The same treatments of *ent*-**28** (287 mg, 0.84 mmol) as described for **28** gave *ent*-**30** as a colorless oil (288 mg, 93%), $[\alpha]_D^{20}$ -104° (c 1.02, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **30**.

(4*R*,5*R*)-1-Benzyl-5-[(*R*)-(1-benzyloxy-1-isopropoxycarbonyl)methyl]-4-phenyl-2-oxazolidone (31) Py (90 µl, 1.1 mmol) was added to a solution of **29** (59.8 mg, 0.14 mmol) in CH_2Cl_2 (1 ml) cooled at 0 °C. The mixture was gradually warmed to 40 °C, and stirred at the same temperature for 4.5 h. Work-up of the reaction mixture in a similar manner to that described for the preparation of **30** gave **31** as colorless crystals (40.3 mg, 64%) after purification by column chromatography. IR (KBr): 1758, 1442, 1420, 1204, 1121, 1099, 725, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.24 [3H, d, J=6.3 Hz, one of $CH(C\underline{H}_3)_2$], 1.27 [3H, d, J=6.3 Hz, one of $CH(C\underline{H}_3)_2$], 3.72 (1H, dd, J=3.8 and 4.7 Hz, C_5-H), 4.08 (1H, d, J=4.7 Hz, CHCOO), 4.10 (1H, d, J=15.3 Hz, one of $PhC\underline{H}_2N$), 4.41 (1H, d, J=11.7 Hz, one of $PhC\underline{H}_2O$), 4.77 (1H, d, J=11.7 Hz, one of $PhC\underline{H}_2O$), 4.93 (1H, d, J=15.3 Hz, one of $PhC\underline{H}_2N$), 5.10 [1H, dq, J=each 6.3 Hz, $C\underline{H}(CH_3)_2$], 5.47 (1H, d, J=3.8 Hz, C_4-H) ,7.0-7.5 (15H, m, aromatic protons). MS m/z: 459 (M^+), 252, 208, 91.

Isopropyl (2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyrate and Its Enantiomer (32 and *ent*-32) a) Preparations from **30** and *ent*-**30:** A mixture of **30** (206 mg, 0.56 mmol) and 10% Pd on carbon in EtOAc (0.3 ml) was stirred overnight at room temperature under an hydrogen atmosphere (1 atm). Filtration and concentration *in vacuo* gave **32** as colorless crystals (124 mg, 94%). Recrystallization from Hex-EtOAc gave an analytical sample of **32** as colorless crystals, mp 112.5-113 °C and $[\alpha]_D^{20}$ -32.7° (c 1.04, $CHCl_3$). IR (KBr): 3700-2400, 3300, 2990, 1728, 1598, 1200, 1102, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.27 [6H, two d, J=6.3 Hz, $CH(C\underline{H}_3)_2$], 1.0-2.2 (3H, brs, NH_2 and OH), 2.72 (1H, dd, J=13.4 and 8.5 Hz, one of C_4-H_2), 2.93 (1H, dd, J=13.4 and 6.4 Hz, one of C_4-H_2), 3.32 (1H, ddd, J=8.5, 6.4, 2.2 Hz, C_3-H), 4.02 (1H, d, J=2.2 Hz, C_2-H), 5.12 [1H, dq, J=each 6.3 Hz, $C\underline{H}(CH_3)_2$], 7.2-7.4 (5H, m, aromatic protons). MS m/z: 238 [$(M+1)^+$], 120, 104, 91. Found: C, 65.86; H, 8.24; N, 5.67%. Calcd for $C_{13}H_{19}O_3N$: C, 65.80; H, 8.07; N, 5.90%. The same treatments of *ent*-**30** (286 mg, 0.78 mmol) as described for **30** gave *ent*-**32** as colorless crystals (170 mg, 92%). An analytical sample of *ent*-**32** was prepared by recrystallization from Hex-EtOAc, mp 114-115 °C and $[\alpha]_D^{20}$ +31.3° (c 0.504, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **32**. Found: C, 65.20; H, 8.04; N, 5.94%. Calcd for $C_{13}H_{19}O_3N$: C, 65.80; H, 18.07; N, 5.90%.
b) Preparation from **31:** Treatments of **31** (37.5 mg, 0.082 mmol) in the same manner as described in a) gave **32** as colorless crystals (15.7 mg, 81%) after filtration followed by concentration *in vacuo* . The physical data of this sample were identical with those described in a).

Isopropyl (2*R*,3*S*)-and (2*R,3*S**)-3-Acetamido-2-acetoxy-4-cyclohexylbutyrate (33 and *dl*-33)** A mixture of (2*R*,3*S*)-**2** (29.5 mg, 0.12 mmol) and Ac_2O (45 µl, 0.48 mmol) in Py (0.3 ml) was stirred overnight at room temperature. Concentration of the mixture *in vacuo* followed by purification by column chromatography (Hex-EtOAc, 7:3→6:4) gave **33** as colorless crystals (39.5 mg, quantitative yield). An analytical sample of **33** was prepared by recrystallization from EtOAc-Hex, mp

78-79 °C and $[\alpha]_D^{20}$ -53.0° (c 0.93, $CHCl_3$). IR (KBr): 3260, 3100, 2945, 1758, 1738, 1645, 1562, 1372, 1225, 1076, 938 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.24 [3H, d, J=6.3 Hz, one of $CH(CH_3)_2$], 1.27 [3H, d, J=6.3 Hz, one of $CH(CH_3)_2$], 0.9-1.9 (13H, m, $C_6H_{11}CH_2$), 1.95 (3H, s, one of CH_3CO), 2.18 (3H, s, one of CH_3CO), 4.66 (1H, m, C_3-H), 4.97 (1H, d, J=2.4 Hz, C_2-H), 5.02 [1H, dq, J=each 6.3 Hz, $CH(CH_3)_2$], 5.52 (1H, d, J=9.7 Hz, NHCO). MS m/z: 328 [$(M+1)^+$], 327 (M^+), 268, 168, 43. Found: C, 62.25; H, 9.00; N, 4.04%. Calcd for $C_{17}H_{29}O_5N$: C, 62.36; H, 8.93; N, 4.28%. The same treatments of (2*R**,3*S**)-**2** as described for (2*R*,3*S*)-**2** followed by purification by column chromatography and recrystallization from EtOAc-Hex gave an analytical sample of (2*R**,3*S**)-**2** as colorless crystals, mp 141-143 °C. The ^{1}H-NMR spectrum of (2*R**,3*S**)-**2** was identical with that of (2*R*,3*S*)-**2** described above. In order to establish the optical purity of **23a** produced from **22a**, **33** was prepared from **23a** by way of **28**, **30**, **32**, and (2*R*,3*S*)-**2** only by employing purification by column chromatography. Comparisons of the ^{1}H-NMR spectrum of this sample measured in the presence of tris [3-(heptafluoropropylhydroxymethylene)-*d*-camphoratoeuropium (III) [Eu(hfc)$_3$] with those of **33** and *dl*-**33** recorded under the same conditions obviously disclosed that the optical purity of **23a** was >95% ee.

(2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutyric acid [(2*S*,3*R*)-4] A solution of *ent*-**32** (39.2 mg, 0.17 mmol) in 6 M HCl (2 ml) was stirred at 100 °C for 4.5 h. Concentration *in vacuo* gave (2*S*,3*R*)-**4**•HCl as colorless crystals, mp 190-192 °C (decomp.) [lit.,[5b,c] mp 191 °C (decomp.)]. ^{1}H-NMR (CD_3OD): 3.06 (2H, d, J=7.5 Hz, $PhCH_2$), 3.81 (1H, dt, J=7.5 and 2.6 Hz, C_3-H), 4.11 (1H, d, J=2.6 Hz, C_2-H), 7.34 (5H, s, aromatic protons). This ^{1}H-NMR spectrum was identical with that reported.[6] (2*S*,3*R*)-**4**•HCl was dissolved in a small volume of H_2O, and the aqueous solution was poured onto a column of ion-exchange resin (AG50X-W2, H^+ form). After the column was thoroughly washed with H_2O, it was eluted with *ca.* 5% NH_4OH. The alkaline eluates were combined and concentrated *in vacuo* to give (2*S*,4*R*)-**4** as colorless crystals (27.4 mg, 85%). An analytical sample of (2*S*,4*R*)-**4** was prepared by recrystallization from H_2O, mp 235-237 °C and $[\alpha]_D^{20}$ +29.9° (c 0.214, 1M HCl) [lit., [6] mp 219-221 °C and $[\alpha]_D^{22}$ +27.9° (c 0.717, 1M HCl); lit.,[7a] $[\alpha]_D^{22}$ +27.7 ° (c 1.0, 1M HCl)]. MS m/z: 196 [$(M+1)^+$], 120, 104.

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