Tetrahedron Vol. 47, No. 16/17, pp. 2801-2820, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

HIGHLY STEREOCONTROLLED SYNTHESIS OF THE 1β-METHYLCARBAPENEM KEY INTERMEDIATE BY THE REFORMATSKY REACTION OF 3-(2-BROMOPROPIONYL)-2-OXAZOLIDONE DERIVATIVES WITH A 4-ACETOXY-2-AZETIDINONE[1)]

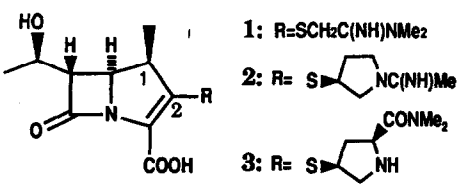
Yoshio Ito,[a)2)] Akira Sasaki,[b)] Kastumi Tamoto,[b)] Makoto Sunagawa,[b)] and Shiro Terashima[a)*]

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan[a)]
Research Laboratories, Research and Development Division, Sumitomo Pharmaceuticals Co. Ltd., Kasugade, Naka, Konohana-ku, Osaka 554, Japan[b)]

(*Received in Japan* 16 *November* 1990)

Abstract: *The key synthetic intermediate (4) of 1β-methylcarbapenems (1~3) was efficiently synthesized by employing highly stereocontrolled Reformatsky reaction (C4-alkylation) of 3-(2-bromopropionyl)-2-oxazolidone derivatives (6) with (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone (5) in the presence of zinc dust followed by removal of 2-oxazolidone moieties. The best diastereoselectivity (β:α=95:5) could be realized by uses of sterically crowded achiral 2-oxazolidone derivatives such as 4,4-dimethyl-, 4,4,5,5-tetramethyl, and 4,4-dibutyl-5,5-pentamethylene-2-oxazolidone and higher reaction temperatures (refluxing tetrahydrofran). The remarkable diastereoselectivities observed for the Reformatsky reactions could be explained by means of the weakly chelating transition state models.*

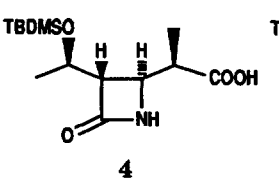
The 1β-methylcarbapenems represented by L-646591 (**1**),[3)] 1β-methyl-RS-533 (**2**),[4)] and SM-7338 (**3**)[5)] were found as synthetic carbapenem antibiotics showing enhanced chemical and metabolic stabilities in addition to excellent antibacterial activity and broad spectra.[3~5)] Since these novel antibiotics which have intriguing structures involving four contiguous asymmetric centers are obtainable only by chemical synthesis, numerous synthetic endeavors have so far been devoted to them.[6)]



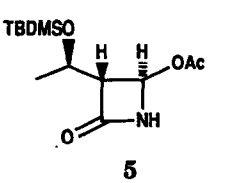
1: R=SCH2C(NH)NMe2

2: R=

3: R=



4



5

In the original synthesis of **1** reported by a research group at Merck,[3)] (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (**4**) was employed as a key synthetic intermediate. After that, synthetic studies have been focused exclusively on **4** since it has been disclosed that **4** can be also converted effectively to other 1β-methylcarbapenems

such as **2** and **3** which have the same frameworks as **1** and different C2-side chains. Introduction of the C2-side chain can be easily achieved after construction of the bicyclic carbapenem framework is completed.[6]

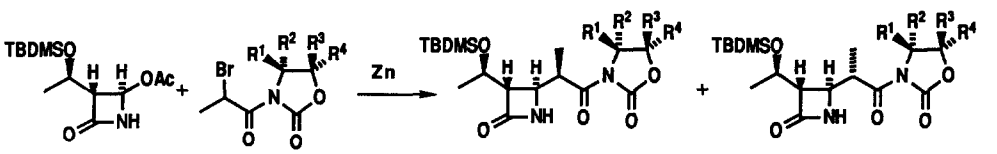
Among a number of the synthetic methods of **4** so far reported,[6] stereoselective substitution at the C4-position of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**5**) with various types of enolates obtainable from propionic acid derivatives is currently recognized as one of the most promising synthetic methods[6] since several highly efficient synthetic routes to **5** or its equivalents have been recently explored.[7,8]

Stereoselective introduction of the 1β-methyl substituent into **5** has hitherto been accomplished using tin enolate of 3-propionyl-2-thiazolidinethione,[9] or 3-propionyl-2-oxazolidinethione derivative,[9b] boron enolate of 3-propionyl-2-oxazolidone[10] or 3-propionyl-2-benzoxazolidone derivative,[4b] zirconium enolate of the thiol ester of propionic acid,[11] and so on.[6] However, these methods seem to accompany much difficulties in a large-scale preparation of **4** because precious chiral sources and/or expensive or toxic reagents such as tin trifluoromethanesulfonate, diethylboron trifluoromethanesulfonate, and bis(cyclopentadienyl)zirconium dichloride are required. With an aim to overcome these problems, we paid attention to the Reformatsky reaction of achiral 2-bromopropionic acid derivatives with **5** in the presence of cheap and less toxic zinc dust.[1]

This report details the highly stereocontrolled synthesis of **4** accomplished by the Reformatsky reation of 3-(2-bromopropionyl)-2-oxazolidone derivatives (**6**) with **5**.

The Reformatsky reaction of various 3-(2-bromopropionyl)-2-oxazolidone derivatives (6) with (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (5).

After accumulating numerous unsuccessful results on the reactions of various 2-bromopropionic acid esters with **5** in the presence of zinc dust,[12] we envisioned that stereochemical outcome of the C4-alkylation may depend largely upon the geometry of the zinc enolate produced from 2-bromopropionic acid derivatives and zinc dust. It was also expected that the enolate geometry can be effectively controlled as (*Z*)-configuration by changing ester group to imide group as reported for deprotonation of a 3-propionyl-2-oxazolidone derivative with lithium diisopropylamide.[13] Based on these considerations, the Reformatsky reactions of several kinds of 3-(2-bromopropionyl)-2-oxazolidone derivatives (**6a~g**) with **5** were attempted.



5 **6** **7β** **7α**

Table 1. Reformatsky reaction of various 3-(2-bromopropionyl)-2-oxazolidones (**6**) with (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**5**).

Run	6	R^1	R^2	R^3	R^4	Solvent	Temp (°C)	Time (min)	Product (7)[a] Yield[b] (%)	Product (7)[a] Ratio[c] 7β:7α
1	**a**	H	H	H	H	THF	0	60	75	45:55
2	**a**	H	H	H	H	THF	25	10	97	45:55
3	**a**	H	H	H	H	THF	67[d]	1	82	48:52
4	**b**	Me	Me	H	H	THF	0	30	90	63:37
5	**b**	Me	Me	H	H	THF	0~67[e]	30 (3)[e]	97	64:36
6	**b**	Me	Me	H	H	THF	25	5	95	73:27
7	**b**	Me	Me	H	H	THF	67[d]	1	94	79:21
8	**b**	Me	Me	H	H	DMF	25	10	81	69:31
9	**b**	Me	Me	H	H	DME	25	10	88	62:38
10	**b**	Me	Me	H	H	DME	70	1	96	81:19
11	**b**	Me	Me	H	H	Dioxane	25	10	99	62:38
12	**b**	Me	Me	H	H	Dioxane	70	1	99	78:22
13	**c** (LM)[f]	Me_2CH	H	H	H	THF	0	30	99	91: 9
14	**c** (M)[f]	Me_2CH	H	H	H	THF	25	10	99	87:13
15	**c** (L)[f]	Me_2CH	H	H	H	THF	25	10	100	88:12
16	**c** (LM)[f]	Me_2CH	H	H	H	THF	67[d]	1	99	81:19
17	**d** (LM)[f]	$PhCH_2$	H	H	H	THF	0	30	91	90:10
18	**e** (LM)[f]	H	Ph	H	H	THF	0	30	99	35:65
19	**e** (LM)[f]	H	Ph	H	H	THF	67[d]	1	90	56:44
20	**f**	Me	Me	Me	Me	THF	67[d]	5	92	87:13
21	**g**	^{n}Bu	^{n}Bu	-$(CH_2)_5$-		THF	25	10	99	90:10
22	**g**	^{n}Bu	^{n}Bu	-$(CH_2)_5$-		THF	67[d]	2	99	95: 5

a) The two diastereomers (7β and 7α) were separated by column chromatography (see the experimental part).

b) Combined yields of 7β and 7α.

c) Determined by measuring the ^{1}H-NMR spectrum of the mixture of 7β and 7α or by the weights of 7β and 7α separated by column chromatography (see the experimental part).

d) The reaction was performed in refluxing THF.

e) The mixture obtained by the reaction performed at 0°C for 30 min was heated at reflux for 3 min before work-up.

f) L, M, and LM mean a less polar isomer, a more polar isomer, and a mixture of less and more polar isomers of **6c~e**, respectively. See the text and experimental part.

Preparations of **6a~g** were achieved by treating 2-bromopropionyl bromide with the 2-oxazolidone derivatives in the presence of bases such as sodium hydride and butyllithium. Among the 2-oxazolidone derivatives, 4,4-dimethyl-, (*R*)-4-phenyl-, 4,4,5,5-tetramethyl-, and 4,4-dibutyl-5,5-pentamethylene-2-oxazolidone, all of which were commercially not available, were prepared from the corresponding amino alcohols (see the experimental part). Synthesis of 2-amino-1,2,2-trimethylpropanol and 2-amino-2-butyl-1,1-pentamethylene-1-hexanol which afford 4,4,5,5-tetramethyl- and 4,4-dibutyl-5,5-pentamethylene-2-oxazolidone, respectively, could be achieved starting from acetone and cyclohexanone according to the reported procedure (see the experimental part).[14]

As shown in **Table 1**, run 1, the zinc enolate produced *in situ* from 3-(2-bromopropionyl)-2-oxazolidone (**6a**) and zinc dust could effectively react with **5** at 25°C in tetrahydrofuran (THF) to give the alkylation product (**7a**) in 97% yield. However, **7a** was found to be a mixture of two diastereomers (**7a**β and **7a**α) in a ratio of 45:55. This disappointingly low diastereoselectivity could not be improved by changing reaction conditions such as solvents and temperatures (runs 1~3) and by employing various Lewis acids.[15] With an aim to further improve the desired β-methyl diastereoselectivity (β-diastereoselectivity), the effect of substituents involved in the 2-oxazolidone moiety on the diastereoselectivity was next studied.

While the use of 3-(2-bromopropionyl)-2-benzoxazolidone gave no improvement with regard to yield and diastereoselectivity,[16] it was finally found that the reaction performed with 3-(2-bromopropionyl)-4,4-dimethyl-2-oxazolidone (**6b**) at 0°C could produce the desired 1β-methyl β-lactam (**7b**β) as a major product (run 4). Interestingly, the diastereoselectivity was found to highly depend upon the reaction temperature. Thus, contrary to our expectation, the increased β-diastereoselectivity was obtained at higher reaction temperatures (runs 4~7) and the formation ratio of **7b**β to **7b**α reached to 79:21 in refluxing THF (run 7). Although the reaction of **6b** with **5** was further examined in various solvents, no further improvement of the β-diastereoselectivity could be realized (runs 8~12).

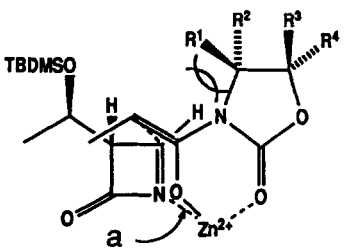
Since it had been uncovered that tin enolate of chiral 3-propionyl-2-thiazolidinethione derivative[9a] and boron enolate of chiral 3-(propionyl)-2-oxazolidone derivative[10] could effect highly stereoselective construction of the 1β-methyl substituent, the Reformatsky reaction of chiral 3-(2-bromopropionyl)-2-oxazolidone derivatives (**6c~e**) with **5** was similarly examined (runs 13~19). Since 2-bromopropionic acid moiety was used as a racemic form, **6c~e** were obtained as mixtures of two diastereomers due to the asymmetric carbons involved in the 2-bromopropionic acid and 2-oxazolidone moieties. These diastereomers could be readily separated by column chromatography to give a more polar isomer (M) and a less polar isomer (L). Although the relative configurations of these diastereomers could not be assigned, the reactivity, chemical yield, and diastereoselectivity of the next Reformatsky reaction were not affected substantially by the configurational difference (runs 14 and 15). The reaction of **6c,d** having (*S*)-4-isopropyl or (*S*)-4-benzyl group with **5** improved the diastereomeric ratios up to *ca.* 9:1 at 0°C and 25°C (runs 13~15 and 17), but almost the same diastereomeric ratio as observed for **6b** was obtained for **6c** in refluxing THF (run 16). Being different from **6c,d**, **6e** carrying (*R*)-4-phenyl group gave low α-diastereoselectivity in the

reaction at 0°C. Similarly, to the results obtained for **6b**, the proportion of **7e**β increased up to 56% in refluxing THF (runs 18 and 19).

The results accumulated using **6a~e** obviously suggest that increase of the steric bulkiness at the C_4-position of **6** may improve the β-diastereoselectivity of the Reformatsky reaction in refluxing THF. Based on this assumption, the sterically more crowded 2-oxazolidone derivatives (**6f,g**) were designed to enhance the β-diastereoselectivity. As expected, the Reformatsky reaction of 3-(2-bromopropionyl)-4,4,5,5-tetramethyloxazolidone (**6f**) with **5** gave higher β-diastereoselectivity in refluxing THF (**7f**β:**7f**α=87:13) (run 20). Ultimately, the highest β-diastereoselectivity (**7g**β:**7g**α=95:5) could be realized by the reaction of the most sterically crowded 3-(2-bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone (**6g**) with **5** in refluxing THF (run 22). Similarly to the cases for **6b**, the β-diastereoselectivity with **6g** lowered at 25°C (run 21). A single recrystallization of the mixture of **7g**β and **7g**α (95:5) from methanol afforded an 85% yield of pure **7g**β.

Mechanistic consideration of the Reformatsky reaction.

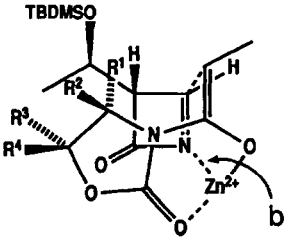
Firstly, the zinc enolate was assumed to have (*Z*)-configuration based on the results previously reported[13] and detailed in the accompanying paper.[17] That the Reformatsky reaction is kinetically controlled was also ascertained by the fact that the β-diastereoselectivity observed for the reaction at 0°C did not change after heating the reaction mixture at 67°C (**Table 1**, run 5). Taking into account these features, the six-membered chelating transition states (**A** and **B**) which correspond to a chair and a boat form, respectively, may be proposed to explain the unique diastereoselectivity of the Reformatsky reaction. In **A** and **B**, the (*Z*)-zinc enolate approaches the CN-double bond of the 1,4-dehydro-2-azetidinone derivative from the direction opposite to the bulky (*R*)-1-(*t*-butyldimethylsilyloxy)ethyl group, giving rise to 7β and 7α, respectively. The 1,4-dehydro-2-azetidinone derivative might be produced by removal of an acetic acid from **5** with the (*Z*)-zinc enolate and/or zinc bromide present in the reaction medium. Steric interaction between the R^2 group and the C_4-H of 1,4-dehydro-2-azetidinone and that between the R^1 group and the C_3-H of 1,4-dehydro-2-azetidinone should play key roles in determining the thermodynamic stability of **A** and **B**, respectively. Similar



A

↓

7β



B

↓

7α

transition states have been proposed for the reactions with tin enolate of 3-propionyl-2-thiazolidinethione[9a] and boron enolate of 3-propionyl-2-oxazolidone[10] with **5**.

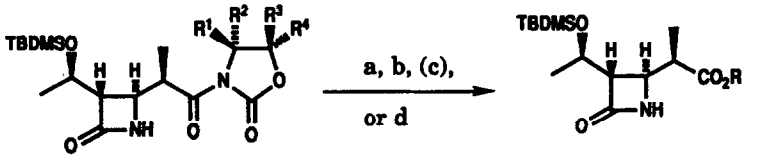
At lower reaction temperatures such as 0°C, the Reformatsky reactions with **6c,d** having (*S*)-configurations (R^1=^{i}Pr or ^{n}Bu, R^2=H) proceeded more preferentially through **A**, producing **7c,dβ** as the major products (**Table 1**, runs 13 and 17). Selective formation of **7eα** from the reaction with **6e** bearing (*R*)-configuration (R^1=H, R^2=Ph) can be similarly explained by **B** (**Table 1**, run 18). Low β-diastereosesectivities observed for the reaction with **6a,b** (R^1=R^2=H or Me) may reflect small thermodynamic differences between **A** and **B** (**Table 1**, runs 1 and 4).

On the other hand, the higher reaction temperatures such as 67°C may result in loosening of the intermolecular chelation between the zinc (II) cation and the nitrogen atom of CN double bond in **A** and **B** (arrow a and b). Steric interaction should be released more effectively in **A** than in **B** by the weakening of intermolecular chelation. Thus, the increases of β-diastereoselectivities observed for the reactions with sterically crowded 2-oxazolidone derivatives (**6b,f,g**) (R^1=R^2=Me or ^{n}Bu) by raising the reaction temperature (**Table 1**, runs 7, 20, and 25) may be explained by **A** in which the intermolecular chelation is weakened. Results obtained with **6e** having (*R*)-configuration (R^1=H, R^2=Ph) by changing the reaction temperature (**Table 1**, runs 18 and 19) strongly suggest that pronounced release of the steric interaction occurs in **A** at higher reaction temperatures. The diastereoselectivities in the reactions with **6a,c** (R^1=^{i}Pr or H, R^2=H) at higher temperatures (**Table 1**, runs 3 and 16) disclose that the release of steric interaction in **A** by loosing the intermolecular chelation is not so much for the 2-oxazolidone derivative in which the R^2 group is hydrogen.

Results obtained at ambient temperatures such as 25°C (**Table 1**, runs 2, 6, 8, 9, 11, 14, 15, 21) may reflect the delicate balances between the chelating transition states (**A** and **B**) and those in which the intermolecular chelations (arrows a and b) become very weak.

Convertion of the Reformatsky products to the 1β-methylcarbapenem key intermediate (4) and determination of their stereochemistries.

At the last stage of our synthetic studies, the preparation of **4** from 7β was attempted. While treatment of **7bβ** with sodium hydroxide in aqueous methanol accompanied hydrolysis of the 2-oxazolidone moiety to yield an amide derivative in addition to **4**,[18] **7bβ** could be readily converted to the benzyl ester (8β) in 98% yield by treating with lithium benzylate. As shown in **Scheme 1**, 8β was similarly prepared in excellent yields from **7b,f,gβ**. However, fairly low yields were only obtained for **7a,c,d,eβ**. In the latter cases, the nucleophilic openings of 2-oxazolidone moieties with lithium benzylate were always observed as side reactions.[18] These results obviously suggest that the C2-carbonyl groups of sterically crowded **7b,f,gβ** were protected from the nucleophilic attack by lithium benzylate more effectively than those of **7a,c,d,eβ**. Hydrogenolysis of 8β on palladium catalyst produced **4** in 98% yield. From the most sterically crowded **7gβ**, it was also possible to obtain **4** directly in 91% yield by treating



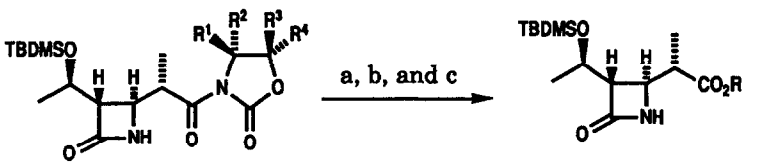
7β 8β: R=Bn, 4: R=H, 9β: R=Me

a) BnOLi in THF, 54% (from **7a**β), 98% (from **7b**β), 67% (from **7c**β), 38% (from **7d**β), 27% (from **7e**β), 90% (from **7f**β), 97% (from **7g**β) b) H_2-Pd/C in AcOEt, 98% c) CH_2N_2, 97% d) NaOH in THF-^{t}BuOH, 91% (from **7g**β)

Scheme 1

7gβ with sodium hydroxide in aqueous *t*-butanol. Esterification of **4** with diazomethane produced the methyl ester (**9**β) in 97% yield. Physical and/or spectral data of **4** and **9**β were identical with those reported.[3,19,20]

Although the convergent syntheses of **4** and **9**β from **7a~g**β obviously established the stereochemistries of **7**α and **7**β, convertions of **7**α to the methyl ester (**9**α) were also attempted by way of the benzyl ester (**8**α) and the carboxylic acid (**10**).[21] Similarly to the previous results, the yields of the benzyl ester formation from **7a~e**α were found to highly depend upon the structures of 2-oxazolidone moieties. Thus, as shown in **Scheme 2**, while **8**α could be produced from **7b,e**α in 95% and 51% yields, respectively, the benzyl ester formation did not take place for **7a**α or gave very low yields of **8**α from **7c,d**α. For **7a,c,d,e**α, the ring openings of 2-oxazolidone moieties seemed to occur along with or in place of the desired alcoholyses.[18] Hydrogenolysis of **8**α over palladium catalyst afforded **10** in 98% yield. The methyl ester (**9**α) could be produced from **10** by treating with diazomethane. Comparisons of the physical and/or spectral data of **10** and **9**α with those reported,[3,22] definitely established their structures.



7α 8α: R=Bn, **10**: R=H, 9α: R=Me

a) BnOLi in THF, 0% (from **7a**α), 95% (from **7b**α), 13% (from **7c**α), 8% (from **7d**α), 51% (from **7e**α). b) H_2-Pd/C in AcOEt, 98% c) CH_2N_2, 98%

Scheme 2

Conclusion

As mentioned above, we have succeeded in exploring a highly stereoselective synthetic route to **4** by featuring the Reformatsky reaction with sterically crowded achiral **6b,f,g** with **5** in the presence of zinc dust. Remarkable increases of the β-diastereoselectivities at higher reaction temperatures could be explained by chelating transition state models. High β-diastereoselectivity of the key step, high overall yield, mild reaction conditions, and uses of inexpensive and less toxic reagents makes this process highly promising as one of the most practical synthetic methods of **4**.

Experimental

General. All melting points were measured by a Yamato MP-21 melting point apparatus or a Thomas Hoover capillary melting point apparatus and were uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter or a JASCO DIP-370 digital polarimeter. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer, a JASCO A-102 IR spectrometer or a Hitachi 260-10 IR spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-90H (90 MHz), a JEOL JNM-GX270 FT-NMR spectrometer (270 MHz), or a Bruker AM-400 spectrometer (400 MHz). All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value). Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Wakogel C-200 and C-300 were used as an adsorbent for column chromatography. Kieselgel 60F254 (Merck) was used for preparative TLC.

3-(2-Bromopropionyl)-2-oxazolidone (**6a**) A solution of *n*-butyllithium in hexane (1.60M solution, 30.0 ml, 48 mmol) and 2-bromopropionyl bromide (5.83 ml, 46 mmol) were added successively to a solution of commercially available 2-oxazolidone (4.00 g, 46 mmol) in THF (70 ml) at 0°C. After stirring for 1 h, the mixture was diluted with saturated aqueous potassium dihydrogen phosphate solution and extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane-CH_2Cl_2 1:1~0:1) to give **6a** as colorless crystals (8.68 g, 84%). An analytical sample obtained by recrystallization from ether showed mp 41°C. IR (KBr): 1779, 1707, 1400, 1372, 1269, 1240, 1230, 1070, 758 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.83 (3H, d, J=6.8 Hz, Me), 4.08 (2H, m, CH_2O), 4.48 (2H, m, CH_2N), 5.69 (1H, q, J=6.8 Hz, CH). MS m/z: 223, 221 $(M)^+$, 142 $(M-80)^+$. Found: C, 32.50; H, 3.59; N, 6.29%. Calcd for $C_6H_8NO_3Br$: C, 32.46; H, 3.63; N, 6.31%.

3-(2-Bromopropionyl)-4,4-dimethyl-2-oxazolidone (**6b**). a) Preparation of 4,4-dimethyl-2-oxazolidone. A mixture of commercially available 2-amino-2-methyl-1-propanol (4.00 g, 45 mmol), diethyl carbonate (10.9 ml, 90 mmol), and anhydrous potassium carbonate (0.100 g, 0.72 mmol) was heated at 120°C for 2h with stirring. After removal of resulting ethanol and excess of diethyl carbonate *in vacuo*, the residue was diluted with 1M HCl (8.0 ml) and ex-

tracted with AcOEt. The combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave 4,4-dimethyl-2-oxazolidone as colorless crystals (5.07 g, 98%). An analytical sample obtained by recrystallization from AcOEt showed mp 56~58°C (*lit.*,[23] 56.5~58°C). IR (KBr): 3250, 1760, 1414, 1220, 1040, 941, 777, 560 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.36 (6H, s, Mex2), 4.08 (2H, s, CH_2), 5.91 (1H, bs, NH). MS m/z: 115 $(M)^+$, 100 $(M-Me)^+$. Found: C, 52.38; H, 7.85; N,12.13%. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17%.

b) Preparation of **6b** by using sodium hydride. 4,4-Dimethyl-2-oxazolidone (1.15 g, 10 mmol) was added to a suspension of sodium hydride (0.24 g, 10 mmol) in THF (100 ml) and the mixture was stirred at rt for 5h. After cooling to 0°C, 2-bromopropionyl bromide (1.05 ml, 10 mmol) was added to the mixture and the stirring was continued for 1h at the same temperature. The mixture was worked-up in the same manner as described in c), affording **6b** as colorless crystals (2.35 g, 90%) after purification by column chromatography. The spectral data [IR (KBr), ^{1}H-NMR ($CDCl_3$), and MS] of this sample were identical with those described in c).

c) Preparation of **6b** by using *n*-butyllithium. Treatments of 4,4-dimethyl-2-oxazolidone (0.384 g, 3.3 mmol) in a similar manner to that described for the preparation of **6a** gave **6b** as colorless crystals (0.701g, 84%) after purification by column chromatography (SiO_2, hexane-CH_2Cl_2 1:1~0:1). An analytical sample obtained by recrystallization from hexane showed mp 73~74°C. IR (KBr): 3030, 1775, 1709, 1370, 1310, 1183, 1105, 1069, 760, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.58, 1.60 (6H, two s, Me_2C), 1.81 (3H, d, J=6.8 Hz, MeCH), 4.06 (2H, s, CH_2), 5.74 (1H, q, J=6.8 Hz, CH). MS m/z: 251, 249 $(M)^+$, 170 $(M-80)^+$. Found: C, 38.39; H, 4.72; N,5.53%. Calcd for $C_8H_{12}NO_3Br$: C, 38.42; H, 4.84; N, 5.60%.

(4S)-3-(2-Bromopropionyl)-4-isopropyl-2-oxazolidone (**6c**). Treatments of commercially available (*S*)-4-isopropyl-2-oxazolidone (0.156 g, 1.2 mmol) in a similar manner to that described for the preparation of **6a** gave **6c** as a mixture of two diastereomers after concentration of the AcOEt extracts *in vacuo*. The mixture (**6c**) could be separated into a less polar fraction (L) and a more polar faction (M) by column chromatography (SiO_2, hexane-CH_2Cl_2 2:3~0:1). The less polar isomer [**6c**(L)] was obtained as colorless crystals (0.177 g, 55%). Recrystallization from hexane-ether gave an analytical sample of **6c**(L), mp 41~43°C and $[\alpha]_D^{26}$ +68.8° (c 1.48, AcOEt). IR (KBr): 2980, 1781, 1709, 1390, 1373, 1300, 1252, 1200, 1060, 775, 757, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.89, 0.94 (6H, each d, J=7.0 Hz, Me_2CH), 1.85 (3H, d, J=6.8 Hz, MeCHBr), 2.38 (1H, m, Me_2CH), 4.33 (3H, m, CH_2, CHN), 5.75 (1H, q, J=6.8 Hz, CHBr). MS m/z: 263, 265 $(M)^+$. Found: C, 40.80; H, 5.34; N, 5.22%. Calcd for $C_9H_{14}NO_3Br$: C, 40.93; H, 5.34; N, 5.30%. The more polar isomer [**6c**(M)] was obtained as colorless crystals (0.134 g, 42%). An analytical sample of **6c**(M) obtained by recrystallization from hexane-AcOEt showed mp 56°C and $[\alpha]_D^{26}$ +92.0° (c 1.04, AcOEt). IR (KBr): 2970, 1784, 1768, 1710, 1400, 1370, 1250, 1210, 1120, 1062 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.94 (6H, d, J=6.8 Hz, Me_2CH), 1.82 (3H, MeCHBr), 2.40 (1H, m, Me_2CH), 4.2~4.7 (3H, m, CH_2, CHN), 5.76 (1H, q, J=6.8 Hz, CHBr).

MS m/z: 263, 265 $(M)^+$. Found: C, 40.75; H, 5.48; N, 5.26%. Calcd for $C_9H_{14}NO_3Br$: C, 40.93; H, 5.34; N, 5.30%. The combined yield of **6c**(L) and **6c**(M) could be calculated as 97%.

(4S)-3-(2-Bromopropionyl)-4-benzyl-2-oxazolidone (**6d**). Treatments of commercially available (*S*)-4-benzyl-2-oxazolidone (0.164 g, 0.93 mmol) in a similar manner to that described for the preparation of **6a** gave **6d** as a mixture of two diastereomers after concentration of the AcOEt extracts *in vacuo*. The mixture (**6d**) could be separated into a less polar fraction (L) and a more polar fraction (M) by column chromatography (SiO_2, hexane-CH_2Cl_2 2:3~0:1). The less polar isomer [**6d**(L)] was obtained as colorless crystals (0.137 g, 47%). Recrystallization from hexane-ether gave an analytical sample of **6d**(L), mp 26~28°C and $[\alpha]_D^{22}$ +68.4° (c 1.33, AcOEt). IR (KBr): 1786, 1709, 1394, 1373, 1251, 1200, 740, 700 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.88 (3H, d, J=6.6 Hz, Me), 2.79 (1H, dd, J=9.7, 13.4 Hz, one of $\underline{CH_2}$Ph), 3.32 (1H, dd, J=3.3, 13.4 Hz, one of $\underline{CH_2}$Ph), 4.25 (2H, m, CH_2O), 4.66 (1H, m, CHN), 5.72 (1H, q, J=6.6 Hz, CHBr), 7.29 (5H, m, Ph). MS m/z: 311, 313 $(M)^+$. Found: C, 49.97; H, 4.67; N, 4.47%. Calcd for $C_{13}H_{14}NO_3Br$: C, 50.02; H, 4.52; N, 4.49%. The more polar isomer [**6d**(M)] was obtained as colorless crystals (0.145 g, 50%). An analytical sample of **6d**(M) obtained by recrystallization from hexane-AcOEt showed mp 142~144°C and $[\alpha]_D^{22}$ +92.5° (c 1.25, AcOEt). IR (KBr): 1781, 1706, 1380, 1300, 1248, 1210, 1201, 1180, 1120, 1101, 1016, 991, 952, 760, 740, 701 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.87 (3H, d, J=6.8 Hz, Me), 2.79 (1H, dd, J=9.4, 13.4 Hz, one of $\underline{CH_2}$Ph), 3.33 (1H, dd, J=3.3, 13.4 Hz, one of $\underline{CH_2}$Ph), 4.22 (2H, d, J=5.3 Hz, CH_2O), 4.70 (1H, m, CHN), 5.73 (1H, q, J=6.8 Hz, $\underline{CH}$Me), 7.30 (5H, m, Ph). MS m/z: 311, 313 $(M)^+$. Found: C, 50.03; H, 4.49; N, 4.41%. Calcd for $C_{13}H_{14}NO_3Br$: C, 50.02; H, 4.52; N, 4.49%. The combined yield of **6d**(L) and **6d**(M) could be calculated as 97%.

(4R)-3-(2-Bromopropionyl)-4-phenyl-2-oxazolidone (**6e**). a) Preparation of (*R*)-4-phenyl-2-oxazolidone. The same treatments of commercially available (*R*)-2-amino-2-phenylethanol (0.56 g, 4.1 mmol) as described for the preparation of 4,4-dimethyl-2-oxazolidone gave (*R*)-4-phenyl-2-oxazolidone (0.604 g, 91%) after concentration of the AcOEt extracts *in vacuo*. Recrystallization from toluene gave an analytical sample of (*R*)-4-phenyl-2-oxazolidone, mp 131~132°C (*lit.*,[24a] 135~136°C) and $[\alpha]_D^{23}$ -54.9° (c 1.40, $CHCl_3$) [*lit.*,[24a] $[\alpha]_D^{24}$ -69.7° (c 0.86, AcOEt)]. IR (KBr): 1740,1710,1490, 1402, 1236, 1099, 1037, 1024, 970, 921 cm^{-1}. ^1H-NMR ($CDCl_3$): 4.19 (1H, dd, J=6.4, 7.9 Hz, CHN), 4.73 (1H, m, one of $\underline{CH_2}O$), 4.99 (1H, m, one of $\underline{CH_2}O$), 5.40 (1H, bs, NH), 7.37 (5H, s, Ph). MS m/z: 163 $(M)^+$. Found: C, 66.25; H, 5.56; N, 8.58%. Calcd for $C_9H_9NO_2$: C, 66.08; H, 5.57; N, 8.52%.

b) Preparation of **6e**. Treatments of (*R*)-4-phenyl-2-oxazolidone (0.277 g, 1.7 mmol) in a similar manner to that described for the preparation of **6a** gave **6e** as a mixture of two diastereomers after concentration of the AcOEt extracts *in vacuo*. The mixture (**6e**) could be separated into a less polar fraction (L) and a more polar faction (M) by column chromatography (SiO_2, hexane-CH_2Cl_2 2:3~0:1). The less polar isomer [**6e**(L)] was obtained as colorless crystals (0.295 g, 59%). Recrystallization from hexane-AcOEt gave an analytical sample of **6e**(L), mp 136~137°C and $[\alpha]_D^{23}$ -123° (c 1.31, AcOEt). IR (KBr): 1782, 1700, 1380, 1302, 1198, 1180,

1121, 1039, 701 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.76 (3H, d, J=6.8 Hz, Me), 4.33 (1H, dd, J=3.1, 8.8 Hz, one of CH_2), 4.75 (1H, dd, J=8.4, 8.8 Hz, one of CH_2), 5.42 (1H, dd, J=3.1, 8.4 Hz, CHPh), 5.72 (1H, q, J=6.8 Hz, CHBr), 7.35 (5H, m, Ph). MS m/z: 297, 299 $(M)^+$. Found: C, 48.31; H, 3.96; N, 4.61%. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34; H, 4.06; N, 4.70%. The more polar isomer [**6e**(M)] was obtained as colorless crystals (0.196 g, 39%). An analytical sample of **6e**(M) obtained by recrystallization from hexane-AcOEt showed mp 151~154°C and $[\alpha]_D^{22}$ –81.4° (c 1.06, AcOEt). IR (KBr): 1784, 1709, 1364, 1330, 1256, 1203, 1060, 757, 696 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.77 (3H, d, J=6.8 Hz, Me), 4.27 (1H, dd, J=5.1, 8.8 Hz, one of CH_2), 4.72 (1H, t, J=8.8 Hz, one of CH_2), 5.46 (1H, dd, J=5.1, 8.8, CHN), 5.75 (1H, q, J=6.8 Hz, CHBr), 7.37 (5H, s, Ph). MS m/z: 297, 299 $(M)^+$. Found: C, 48.27; H, 3.97; N, 4.61%. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34; H, 4.06; N, 4.70%. The combined yield of **6e**(L) and **6e**(M) could be calculated as 98%.

3-(2-Bromopropionyl)-4,4,5,5-tetramethyl-2-oxazolidone (**6f**). a) Preparation of 4,4,5,5-tetramethyl-2-oxazolidone.[14] Acetone (1.82 g, 31 mmol) was added to a mixture of trimethylsilyl cyanide (3.05 g, 31 mmol) and a catalytic amount of zinc iodide (*ca.* 1 mg) at 0°C. After stirring at rt for 1h, the mixture was diluted with ether (10 ml). An ethereal solution of methyllithium (1.07 M solution, 64.0 ml, 68 mmol) was added at 0°C and the mixture was stirred overnight at rt. The mixture was cooled to 0°C and diluted with 10M NaOH (50 ml). The aqueous layer was separated and extracted with ether. The ethereal extracts were combined, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. A part of the concentration residue (20%) containing 2-amino-1,2,2-trimethyl-1-propanol was diluted with THF (10 ml) without purification. *N,N'*-Carbonyldiimidazole (3.24 g, 20 mmol) was added to the THF solution and the stirring was continued at 65°C for 4h. After cooling to rt, the mixture was diluted with 1M NaOH (10 ml) and methanol (7.5 ml). After stirring for 4h at the same temperature, the mixture was acidified with concentrated HCl (5 ml) and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, $CHCl_3$-AcOEt 1:0-9:1) to give 4,4,5,5-tetramethyl-2-oxazolidone as colorless crystals (0.360 g, 41% from acetone after corrected for the amount of 2-amino-1,2,2-trimethyl-1-propanol used), mp 109-110°C. IR (Nujol): 3370, 3250, 1755, 1720, 1178, 1022 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.25 (6H, s, Me_2CO), 1.37 (6H, s, Me_2CN), 5.77 (1H, bs, NH). Found: C, 58.89; H, 8.96; N, 9.81%. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78%.

b) Preparation of **6f**. Treatments of 4,4,5,5-tetramethyl-2-oxazolidone (0.600 g, 4.2 mmol) in a similar manner to that described for the preparation of **6a** gave **6f** as colorless crystals (1.05 g, 90%), mp 59.0~60.5°C, after purification by column chromatography (SiO_2, PhMe-AcOEt 1:0~19:1). IR (nujol): 1760, 1693, 1300, 1275, 1142, 1083, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.38, 1.41, 1.44, 1.45 (12H, each s, Me_2Cx2), 1.81 (3H, d, J=6.6 Hz, MeCH), 5.81 (1H, q, J=6.6 Hz, CH). Found: C, 42.96; H, 5.66; N, 4.95%. Calcd for $C_{10}H_{16}NO_3Br$: C, 43.18; H, 5.80; N, 5.04%.

3-(2-Bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone (**6g**). a) Preparation of 4,4-dibutyl-5,5-pentamethylene-2-oxazolidone.[14] Trimethylsilyl cyanide (9.11 ml, 68 mmol)

was added to a mixture of cyclohexanone (6.10 g, 62 mmol) and a catalytic amount of zinc iodide (*ca.* 1 mg) at 0°C. After stirring at rt for 1 h, an excess amount of trimethylsilyl cyanide was removed *in vacuo* and the residue was dissolved in ether (60 ml). A solution of *n*-butyllithium in hexane (1.71 M solution, 82.0 ml, 0.14 mol) was added to the ethereal solution at 0°C. After stirring overnight at rt, the mixture was diluted with 4M HCl (100 ml). After being stirred for 1h, the mixture was further diluted with 8M NaOH (100 ml) and extracted with ether. The combined extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by distillation (113~125°C, 1 mmHg), giving 2-amino-2-butyl-1,1-pentamethylene-1-hexanol as a colorless oil (13.2 g, 82%). Further purification by column chromatography (Al_2O_3, hexane-ether 9:1) gave an analytical sample of 2-amino-2-butyl-1,1-pentamethylene-1-hexanol. IR (neat): 3420, 2950, 2880, 1588, 1470, 1460, 1447, 1400, 1380, 1261, 1140, 1042, 970, 850 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.92 (6H, m, Mex2), 1.0~2.0 (25H, m, other protons). MS m/z: 241 $(M)^+$, 224 $(M\text{-}Me)^+$. Found: C, 74.78; H, 12.68; N,5.67%. Calcd for $C_{15}H_{31}NO$: C, 74.63; H, 12.94; N, 5.80%. *N,N'*-Carbonyldiimidazole (13.5 g, 83 mmol) was added to a solution of 2-amino-2-butyl-1,1-pentamethylene-1-hexanol (10.0 g, 42 mmol) in THF (40 ml) at rt. After stirring at 65°C for 4 h, the mixture was cooled to rt, then diluted successively with 1M NaOH (40 ml) and methanol (30 ml). The mixture was stirred at rt for 4 h, acidified with concentrated HCl, then extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave 4,4-dibutyl-5,5-pentamethylene-2-oxazolidone as colorless crystals (11.0 g, 99%). An analytical sample was obtained as colorless crystals by recrystallization from MeOH-H_2O, mp 96~97°C. IR (KBr): 3240, 3150, 2950, 2880, 1750, 1473, 1378, 1360, 1322, 1280, 987, 950, 880, 735 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.91 (6H, t, J=6.3 Hz, Mex2), 1.0~2.3 (23H, m, other protons), 5.89 (1H, bs, NH). MS m/z: 268 $(M+1)^+$, 210 $(M\text{-}Bu)^+$. Found: C, 71.95; H, 10.95; N, 5.20%. Calcd for $C_{16}H_{29}NO_2$: C, 71.87; H, 10.93; N, 5.24%.

b) Preparation of **6g**. A solution of *n*-butyllithium in hexane (1.65 M solution, 6.59 ml, 11 mmol) was added to a solution of 4,4-dibutyl-5,5-pentamethylene-2-oxazolidone (2.64 g, 9.9 mmol) in ether (12 ml) at 0°C. After stirring for 5 min, 2-bromopropionyl bromide (1.24 ml, 12 mmol) was added to the mixture. The stirring was continued for additional 10 min, then the mixture was diluted with aqueous phosphate buffer (pH 7, 5.0 ml). The organic layer was separated, washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was dissolved in ethanol (4.5 ml) by heating. On cooling, the ethanolic solution precipitated pure **6g** as colorless crystals (2.49 g, 63%), mp 113~114°C. IR (KBr): 2960, 2880, 1761, 1710, 1450, 1375, 1360, 1290, 1275, 1255, 1240, 1180, 1113, 1060, 990, 960, 881, 770, 720, 643, 540 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.75~1.10 (6H, m, $\underline{Me}CH_2x2$), 1.1~2.5 (22H, m, other protons), 1.81 (3H, d, J=6.8 Hz, $\underline{Me}CH$), 5.87 (1H, q, J=6.8 Hz, CHBr). MS m/z: 346, 344 $(M\text{-}Bu)^+$, 210. Found: C, 56.66; H, 8.09; N, 3.43; Br, 19.57%. Calcd for $C_6H_8NO_3Br$: C, 56.72; H, 8.02; N, 3.48; Br, 19.86%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (**7aβ**) and *its 4-[(S)-1-(2-oxazolidone-3-carbonyl)ethyl]-isomer* (**7aα**) (**Table 1**, run 2). Zinc dust (0.140 g, 2.1 mmol) was added to a solution of **6a** (0.318 g, 1.4 mmol) and **5** (0.205 g, 0.71 mmol) in THF (7 ml) at 25°C. After stirring for 10 min at the same temperature, the mixture was diluted with aqueous phosphate buffer (pH 7, 4.0 ml) and CH_2Cl_2. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, hexane-CH_2Cl_2 1:1, then CH_2Cl_2-acetone 9:1), affording **7aβ** as colorless crystals (0.116 g, 44%) from the less polar fraction and **7aα** as colorless crystals (0.142 g, 53%) from the more polar fraction. The combined yield of **7aβ** and **7aα** was 97%. The ratio of **7aβ** to **7aα** estimated by the weights of the separated samples was 45:55. The minor product (**7aβ**) recrystallized from hexane-AcOEt showed mp 66~67°C and $[\alpha]_D^{27}$ -6.7° (c 0.63, $CHCl_3$). IR (KBr): 2950, 1760, 1700, 1390, 1250, 1100, 833, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 1.21 1.23 (6H, each d, J=each 6.4 Hz, MeCHOSi, MeCHOCN), 3.02 (1H, m, C_3-H), 3.8~4.6 (7H, m, other protons), 5.95 (1H, bs, NH). MS m/z: 355 $(M\text{-}Me)^+$, 327, 313. Found: C, 55.06; H, 8.25; N, 7.20%. Calcd for $C_{17}H_{30}N_2O_5Si$: C, 55.11; H, 8.16; N, 7.56%. The major product (**7aα**) recrystallized from cyclohexane-AcOEt showed mp 177~180°C and $[\alpha]_D^{28}$ +31.4° (c 0.94, $CHCl_3$). IR (KBr): 2950, 1780, 1762, 1694, 1390, 1107, 1047, 830 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.89 (9H, s, Me_3C), 1.25, 1.28 (6H, each d, J=6.2 and 6.6 Hz, MeCHOSi, MeCHOCN), 2.83 (1H, m, C_3-H), 3.5~4.6 (7H, m, other protons), 5.98 (1H, bs, NH). MS m/z: 355 $(M\text{-}Me)^+$, 327, 313. Found: C, 54.84; H, 8.24; N, 7.40%. Calcd for $C_{17}H_{30}N_2O_5Si$: C, 55.11; H, 8.16; N, 7.56%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (**7bβ**) and *its 4-[(S)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl)ethyl]-isomer* (**7bα**) (**Table 1**, run 7). Zinc dust (10.0 mg, 0.15 mmol) was added at once to a refluxing solution of **6b** (24.4 mg, 0.098 mmol) and **5** (14.0 mg, 0.049 mmol) in THF (0.5 ml). After stirring for 1 min, the mixture was cooled to rt and diluted with aqueous phosphate buffer (pH 7, 0.3 ml) and CH_2Cl_2. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, CH_2Cl_2-AcOEt 4:1), affording a mixture of **7bβ** and **7bα** as a colorless solid (18.4 mg, 94%). The ratio of **7bβ** to **7bα** could be calculated as 79:21 by the ^{1}H-NMR spectrum. Thus, the protons at the C_3 positions appeared as two multiplets at 2.81 and 3.01 ppm with an integration ratio of 21:79. The pure samples of **7bβ** and **7bα** were obtained by separation of the mixture with medium pressure column chromatography (MPLC) (SiO_2, lobar column, Merck art. 10401, hexane-CH_2Cl_2-Et_2O 10:3:7~1:1:1). Recrystallization of less polar **7bβ** from hexane-AcOEt gave an analytical sample as colorless crystals, mp 189~190°C and $[\alpha]_D^{20}$ -19.2° (c 2.02, $CHCl_3$). IR (KBr): 2950, 1760, 1717, 1460, 1400, 1386, 1342, 1312, 1312, 1228, 1186, 1087, 1054, 960, 840, 781, 770 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 1.19, 1.21 (6H, each d, J=6.8 and 6.2 Hz, MeCHOSi, MeCHCON), 1.54 (6H, s, Me_2C), 3.01 (1H, m, C_3-H), 3.90 (1H, m, C_4-H), 4.01 (2H, s, CH_2O),

4.0~4.4 (2H, m, MeCHOSi, MeCHCON), 5.87 (1H, bs, NH). MS m/z: 341 $(M-Bu)^+$, 327, 313. Found: C, 57.31; H, 8.50; N, 6.99%. Calcd for $C_{19}H_{34}N_2O_5Si$: C, 57.26; H, 8.60; N, 7.03%. Recrystallization of more polar **7bα** from hexane-AcOEt gave an analytical sample as colorless crystals, mp 176~177°C and $[\alpha]_D^{20}$ +31.4° (c 1.09, $CHCl_3$). IR (KBr): 2980, 1780, 1767, 1702, 1380, 1305, 1223, 1178, 1100, 1045, 962, 839, 778 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.89 (9H, s, Me_3C), 1.25 (6H, d, J=6.3 Hz, MeCHx2), 1.56 (6H, s, Me_2C), 2.81 (1H, m, C3-H), 3.72 (1H, m, C4-H), 4.03 (2H, s, CH_2O), 4.1~4.4 (2H, m, MeCHOSi, MeCHCON), 5.81 (1H, bs, NH). MS m/z: 341 $(M-Bu)^+$, 327, 313. Found: C, 57.29; H, 8.51; N, 6.96%. Calcd for $C_{19}H_{34}N_2O_5Si$: C, 57.26; H, 8.60; N, 7.03%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-[(S)-4-isopropyl-2-oxazolidone-3-carbonyl]ethyl]-2-azetidinone (**7cβ**) and *its 4-[(S)-1-[(S)-4-isopropyl-2-oxazolidone-3-carbonyl]ethyl]-isomer* (**7cα**) (**Table 1**, run 15). Zinc dust (13.0 mg, 0.20 mmol) was added to a solution of **6c**(L) (26.2 mg, 0.099 mmol) and **5** (14.0 mg, 0.049 mmol) in THF (0.5 ml) at rt. After stirring for 10 min at the same temperature, the mixture was diluted with aqueous phosphate buffer (pH 7, 0.3 ml) and CH_2Cl_2. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, CH_2Cl_2, then CH_2Cl_2-AcOEt 4:1), affording **7cβ** as colorless crystals (17.4 mg, 88%) from the less polar fraction and **7cα** as colorless crystals (2.4 mg, 12%) from the more polar fraction. The combined yield of **7cβ** and **7cα** was 100%. The ratio of **7cβ** to **7cα** estimated by the weights of the separated samples was 88:12. The major product (**7cβ**) recrystallized from hexane-AcOEt showed mp 123~124°C and $[\alpha]_D^{23}$+27.1° (c 1.15, $CHCl_3$). IR (KBr): 1780, 1699, 1390, 1206, 834, 777 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 0.88, 0.93 (6H, each d, J=6.8 and 6.0 Hz, Me_2CH), 1.19, 1.23 (6H, each d, J=6.8 and 6.2 Hz, MeCHOSi, MeCHCON), 2.34 (1H, m, Me_2CH), 3.03 (1H, dd, J=2.2, 2.9 Hz, C3-H), 3.93 (1H, m, C4-H), 4.1~4.6 (5H, m, other protons), 5.99 (1H, bs, NH). MS m/z: 355 $(M-Bu)^+$. Found: C, 58.07; H, 9.07; N, 7.68%. Calcd for $C_{20}H_{36}N_2O_5Si$: C, 58.22; H, 8.79; N, 6.79%. The minor product (**7cα**) recrystallized from cyclohexane-AcOEt showed mp 176~177°C and $[\alpha]_D^{22}$ +80.8° (c 0.30, $CHCl_3$). IR (KBr): 1781, 1765, 1700, 1390, 1261, 1103, 803 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 0.88, 0.92 (6H, each d, J=each 6.6 Hz, Me_2CH), 1.25, 1.32 (6H, each d, J=6.2 and 5.9 Hz, MeCHOSi, MeCHON), 2.32 (1H, m, Me_2CH), 2.80 (1H, dd, J=1.3, 5.3 Hz, C3-H), 3.8~4.6 (5H, m, other protons), 5.80 (1H, br s, NH). MS m/z: 355 $(M-Bu)^+$. Found: C, 58.17; H, 8.97; N, 6.64%. Calcd for $C_{20}H_{36}N_2O_5Si$: C, 58.22; H, 8.79; N, 6.79%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-[(S)-4-benzyl-2-oxazolidone-3-carbonyl]ethyl]-2-azetidinone (**7dβ**) and *its 4-[(S)-1-[(S)-4-benzyl-2-oxazolidone-3-carbonyl]ethyl]-isomer* (**7dα**). (**Table 1**, run 17): Zinc dust (25 mg, 0.38 mmol) was added to a solution of **6d** (LM) (68.3 mg, 0.22 mmol) and **5** (31.4 mg, 0.11 mmol) in THF (1.1 ml) at 0°C. After stirring for 0.5 h at the same temperature, the mixture was diluted with aqueous phosphate buffer (pH 7, 2.4 ml) and AcOEt. The organic layer was separated, washed with saturated aqueous

NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2), affording **7dβ** as colorless crystals (41.3 mg, 82%) from the less polar fraction and **7dα** as colorless crystals (4.6 mg, 9%) from the more polar fraction. The combined yield of **7dβ** and **7dα** was 91%. The ratio of **7dβ** to **7dα** estimated by the weights of the separated samples was 90:10. The major product (**7dβ**) recrystallized from hexane-AcOEt showed mp 115~116°C and $[\alpha]_D^{20}$ +24.6° (c 0.74, $CHCl_3$). IR (KBr): 2949, 1781, 1700, 1390, 1253, 1215, 1105, 837, 780, 703 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.09 (6H, s, Me_2Si), 0.90 (9H, s, Me_3C), 1.23, 1.25 (6H, each d, J=6.8 and 6.2 Hz, MeCHOSi, MeCHCON), 2.69 (1H, dd, J=10.1, 13.4 Hz, one of CH_2Ph), 3.08 (1H, m, C3-H), 3.33 (1H, dd, J=3.4, 13.4 Hz, one of CH_2Ph), 3.96 (1H, m, C4-H), 4.1~4.8 (5H, m, other protons), 5.94 (1H, bs, NH), 7.29 (5H, m, Ph). MS m/z: 403 $(M\text{-}Bu)^+$. Found: C, 62.53; H, 8.05; N, 6.01%. Calcd for $C_{24}H_{36}N_2O_5Si$: C, 62.58; H, 7.88; N, 6.08%. The minor product (**7dα**) recrystallized from hexane-AcOEt showed mp 143~144°C and $[\alpha]_D^{20}$ +78.5° (c 0.18, $CHCl_3$). IR (KBr): 2950, 1780, 1763, 1700, 1390, 1254, 1236, 1190, 1106, 838, 778 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.10 (6H, s, Me_2Si), 0.90 (9H, s, Me_3C), 1.27, 1.32 (6H, each d, J=6.3 and 6.6 Hz, MeCHOSi, MeCHCON), 2.79 (1H, dd, J=9.4, 13.4 Hz, one of CH_2Ph), 2.81 (1H, m, C3-H), 3.25 (1H, dd, J=3.5, 13.4 Hz, one of CH_2Ph), 3.6~4.8 (6H, m, other protons), 5.84 (1H, bs, NH), 7.28 (5H, m, Ph). MS m/z: 403 $(M\text{-}Bu)^+$. Found: C, 62.60; H, 7.78; N, 6.03%. Calcd for $C_{24}H_{36}N_2O_5Si$: C, 62.58; H, 7.88; N, 6.08%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-[(R)-4-phenyl-2-oxazolidone-3-carbonyl]ethyl]-2-azetidinone (**7eβ**) and *its 4-[(S)-1-[(R)-4-phenyl-2-oxazolidone-3-carbonyl]ethyl]-isomer* (**7eα**) (**Table 1**, run 18). Zinc dust (77 mg, 1.2 mmol) was added to a solution of **6e**(LM) (0.236 g, 0.79 mmol) and **5** (0.114 g, 0.40 mmol) in THF at 0°C. After stirring for 0.5 h at the same temperature, the mixture was diluted with aqueous phosphate buffer (pH 7, 2.4 ml) and AcOEt. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography, affording a mixture of **7eβ** and **7eα** as a caramel (0.176 g, 99%). The ratio of **7eβ** to **7eα** could be calculated as 35:65 by the ^{1}H-NMR spectrum in a similar manner to that described for the mixture of **7bβ** and **7bα**. The mixture was separated by MPLC (SiO_2, CH_2Cl_2-acetone 97:3). The major product (**7eα**) obtained as a colorless caramel from the less polar fraction showed $[\alpha]_D^{20}$ -5.3° (c 1.37, $CHCl_3$). IR (KBr): 2950, 1781, 1703, 1460, 1388, 1255, 1235, 1200, 1108, 1045, 990, 839, 780, 707 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.11 (6H, s, Me_2Si), 0.93 (9H, s, Me_3C), 1.23, 1.35 (6H, each d, J=6.4 and 6.5 Hz, MeCHOSi, MeCHCON), 2.87 (1H, m, C3-H), 3.8~4.4 (4H, m, other protons), 4.78 (1H, t, J=8.8 Hz, one of CH_2), 5.48 (1H, dd, J=3.8, 8.8 Hz, CHPh), 5.50 (1H, bs, NH), 7.42 (5H, m, Ph). MS m/z: 389 $(M\text{-}Bu)^+$. Found: C, 61.64; H, 7.95; N, 6.30%. Calcd for $C_{23}H_{34}N_2O_5Si$: C, 61.85; H, 7.67; N, 6.27%. The minor product (**7eβ**) obtained as a colorless caramel from the more polar fraction showed $[\alpha]_D^{20}$ –70.4° (c 0.66, $CHCl_3$). IR (KBr): 2950, 1783, 1709, 1460, 1388, 1330, 1255, 1201, 1110, 1047, 962, 840, 781, 703 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.11 (6H, s, Me_2Si), 0.91 (9H, s, Me_3C), 1.20, 1.24 (6H, two d, J=7.0 and 6.2 Hz, MeCHOSi and MeCHCON), 3.04 (1H, m, C3-H), 3.98 (1H, m, C4-H), 3.8~4.4 (3H, m, other protons), 4.76 (1H, t, J=8.8 Hz, one of CH_2), 5.49 (1H, dd, J=4.2 and

8.8Hz, CHPh), 5.90 (1H, bs, NH), 7.42 (5H, m, Ph). MS m/z: 389 $(M-Bu)^+$. Found: C, 61.82; H, 7.91; N, 6.24%. Calcd for $C_{23}H_{34}N_2O_5Si$: C, 61.85; H, 7.67; N, 6.27%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(4,4,5,5-tetramethyl-2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (**7fβ**) and *its 4-[(S)-1-(4,4,5,5-tetramethyl-2-oxazolidone-3-carbonyl)ethyl]-isomer* (**7fα**) (**Table 1**, run 20) A solution of **6f** (1.15 g, 4.1 mmol) in THF (6 ml) was added to a refluxing suspension of zinc dust (0.440 g, 6.8 mmol) and **5** (0.540 g, 1.9 mmol) in THF (16 ml) within 15 min. After stirring for 5 min at the same temperature, the mixture was cooled to rt and diluted with aqueous phosphate buffer (pH 6, 11 ml) and AcOEt. The organic layer was separated, washed successively with 1M HCl, water, 5% aqueous $NaHCO_3$, and water, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, $CHCl_3$-AcOEt 1:0~5:1), giving a mixture of **7fβ** and **7fα** as a colorless solid (0.738 g, 92%). The ratio of **7fβ** to **7fα** could be calculated as 87:13 by the ^{1}H-NMR spectrum in a similar manner to that described for the mixture of **7bβ** and **7bα**. The mixture was separated by preparative TLC ($CHCl_3$-AcOEt 5:1, two developments). The major product (**7fβ**) obtained as colorless crystals from the less polar fraction showed mp 148~149°C and $[\alpha]_D^{28}$ -15.4° (c 0.26, $CHCl_3$). IR (KBr): 3150, 1756, 1695, 1378, 1365, 1330, 1298, 1268, 1145, 1128, 1070, 1055, 954, 830, 768 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.06, 0.07 (6H, each s, Me_2Si), 0.87 (9H, s, Me_3C), 1.19, 1.21 (6H, each d, J=6.9 and 6.3 Hz, MeCHOSi, MeCHCON),1.36 (6H, s, Me_2CO), 1.43 (6H, s, Me_2CN), 3.01 (1H, dd, J=2.3, 4.3 Hz, C$_3$-H), 3.91 (1H, dd, J=2.3, 4.0 Hz, C$_4$-H), 4.19 (2H, m, MeCHCOSi, MeCHCON), 5.95 (1H, bs, NH). Found: C, 58.87; H, 9.03; N, 6.46%. Calcd for $C_{21}H_{38}N_2O_5Si$: C, 59.14; H, 8.82; N, 6.53%. The minor product (**7fα**) obtained as colorless crystals from the more polar fraction showed mp 164~165°C and $[\alpha]_D^{28}$ +27.0° (c 0.18, $CHCl_3$). IR (KBr): 3170, 3100, 1782, 1760, 1720, 1694, 1460, 1375, 1302, 1276, 1254, 1222, 1154, 1102, 1084, 1062, 1042, 958, 836, 776, 730 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08, 0.09 (6H, each s, Me_2Si), 0.88 (9H, s, Me_3C), 1.25, 1.25 (6H, each d, J=6.6 and 5.9 Hz, MeCHOSi, MeCHCON),1.36, 1.37 (6H, each s, Me_2CO), 1.43 (6H, s, Me_2CN), 2.81 (1H, dd, J=2.0, 5.3 Hz, C$_3$-H), 3.83 (1H, dd, J=2.0, 9.2 Hz, C$_4$-H), 4.19 (2H, m, MeCHCOSi, MeCHCON), 5.95 (1H, bs, NH). Found: C, 58.87; H, 9.03; N, 6.46%. Calcd for $C_{21}H_{38}N_2O_5Si$: C, 59.12; H, 8.98; N, 6.57%.

(3S,4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (**7gβ**) and *its 4-[(S)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl)ethyl]-isomer* (**7gα**) (**Table 1**, run 22). A solution of **6g** (0.417 g, 1.0 mmol) in THF (1.9 ml) was added at once to a refluxing suspension of **5** (0.135 g, 0.47 mmol) and zinc dust (0.113 g, 1.7 mmol) in THF (1.9 ml) with stirring. After the stirring under reflux was continued for 2 min, the mixture was cooled to rt and diluted with aqueous phosphate buffer (pH 7, 2.0 ml) and AcOEt. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, hexane-CH_2Cl_2 1:1, then hexane-CH_2Cl_2-AcOEt 7:1:3), affording a mixture of **7gβ** and **7gα** as a colorless solid (0.257 g,

99%). The ratio of **7gβ** to **7gα** could be calculated as 95:5 by the ^{1}H-NMR spectrum in a similar manner to that described for the mixture of **7bβ** and **7bα**. Recrystallization from methanol (1.5 ml) gave a pure sample of **7gβ** (0.221 g, 85%) as colorless crystals, mp 158~159°C and $[\alpha]_D^{20}$ -5.0° (c 1.29, $CHCl_3$). IR (KBr): 3450, 2960, 2900, 1780, 1768, 1714, 1380, 1280, 1240, 1108, 1053, 970, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 0.90 (6H, m, MeCH2x2), 1.20, 1.22 (6H, each d, J=6.9 and 6.3 Hz, MeCHOSi, MeCHCO), 1.0~2.2 (22H, m, other protons), 3.05 (1H, m, C3-H), 3.92 (1H, m, C4-H), 4.1~4.3 (2H, m, MeCHOSi, MeCHCON), 5.91 (1H, bs, NH). MS m/z: 493 $(M\text{-}Bu)^+$. Found: C, 65.34; H, 10.06; N, 5.03%. Calcd for $C_{30}H_{54}N_2O_5Si$: C, 65.41; H, 9.88; N, 5.09%. The minor isomer (**7gα**) isolated from the filtrate of recrystallization by preparative TLC (CH_2Cl_2, several developments) showed the following spectral data. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 0.90 (6H, m, MeCH2x2), 1.25 (6H, d, J=6.4 Hz, MeCHOSi, MeCHCON), 1.0~2.3 (22H, m, other protons), 2.84 (1H, m, C3-H), 3.7 (2H, m, MeCHCON, C4-H), 4.19 (1H, m, MeCHOSi), 5.79 (1H, bs, NH). MS m/z: 493 $(M\text{-}Bu)^+$.

(3S,4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(benzyloxycarbonyl)ethyl]-2-azetidinone (**8β**). A solution of lithium benzylate in THF (0.50M solution, 0.77 ml, 0.39 mmol) was added to a solution of **7bβ** (76.6 mg, 0.19 mmol) in THF (0.96 ml) at 0°C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous potassium dihydrogen phosphate (0.8 ml) and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, CH_2Cl_2-AcOEt 1:0~4:1) to give **8β** as colorless crystals (74.1 mg, 98%). Recrystallization from hexane afforded an analytical sample of **8β**, mp 69~70°C and $[\alpha]_D^{20}$ -13.8° (c 0.98, $CHCl_3$). IR (KBr): 2950, 1765, 1738, 1720, 1258, 1175, 1138, 1047, 962, 840, 782, 735, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.11 (6H, s, Me_2Si), 0.91 (9H, s, Me_3C), 1.18, 1.29 (6H, each d, J=6.4 and 7.0 Hz, MeCHOSi, MeCHCO), 2.79 (1H, m, MeCHCO), 3.01 (1H, m, C3-H), 3.96 (1H, m, C4-H), 4.22 (1H, m, MeCHOSi), 5.17 (2H, s, CH_2Ph), 5.91 (1H, bs, NH), 7.39 (5H, s, Ph). MS m/z: 334 $(M\text{-}Bu)^+$. Found: C, 64.42; H, 8.33; N, 3.61%. Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58%. 4,4-Dimethyl-2-oxazolidone (21.7 mg, 98%) was recovered from the more polar fraction by the column chromatography.

Similar treatments of **7a,c~gβ** gave **8β** in the yields shown in **Scheme 1**.

(3S,4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(S)-1-(benzyloxycarbonyl)ethyl]-2-azetidinone (**8α**). The same treatments of **7bα** (23.1 mg, 0.058 mmol) as described for the preparation of **8β** from **7bβ**, gave **8α** as a colorless oil (21.5 mg, 95%), $[\alpha]_D^{25}$ +3.0° (c 1.59, $CHCl_3$). IR (KBr): 2950, 1763, 1739, 1460, 1256, 1183, 1143, 1100, 1043, 960, 833, 778, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.23, 1.25 (6H, each d, J=6.0 and 7.3 Hz, MeCHOSi, MeCHCO), 2.58 (1H, dq, J=7.3, 9.5 Hz, MeCHCO), 2.76 (1H, m, C3-H), 3.71 (1H, dd, J=2.0, 9.5 Hz, C4-H), 4.17 (1H, m, MeCHOSi), 5.15 (2H, s, CH_2Ph), 5.96 (1H, bs, NH), 7.35 (5H, s, Ph). MS m/z: 376 $(M\text{-}Me)^+$, 334 $(M\text{-}Bu)^+$.

Treatments of **7c,d,e**α in a similar manner to that described above gave **8**α in the yields shown in **Scheme 2**.

(3S,4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (**4**). a) Preparation of **4** by hydrogenolysis of **8**β. Palladium on carbon (10%, 5 mg) was added to a solution of **8**β (53.5 mg, 0.14 mmol) in AcOEt (1 ml) and the mixture was stirred vigorously for 4 hr under a hydrogen atmosphere. Removal of the catalyst by filtration followed by concentration *in vacuo* gave **4** as colorless crystals (40.3 mg, 98%). An analytical sample obtained as colorless crystals by recrystallization from hexane-AcOEt showed mp 148~149°C (decomp.) (*lit.*[3] 140~143°C, *lit.*[4] 138~141°C, *lit.*[19] 143.5~144°C, *lit.*[20] 146~147°C) and $[\alpha]_D^{20}$ –32.4° (c 1.07, MeOH) [*lit.*[19] $[\alpha]_D^{25}$ -36.9° (c 0.469, MeOH), *lit.*[20] $[\alpha]_D^{20}$ -34.6° (c 0.26, MeOH)]. IR (KBr): 3280, 2950, 1720, 1462, 1281, 1259, 1142, 1040, 839, 780 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.20, 1.28 (6H, each d, J=6.1 and 6.6 Hz, MeCHOSi, MeCHCO), 2.82 (1H, m, CHCO), 3.10 (1H, dd, J=2.0, 4.4 Hz, C_3-H), 4.00 (1H, dd, J=2.0, 5.4 Hz, C_4-H), 4.27 (1H, m, CHOSi), 6.01 (1H, bs, NH). MS m/z: 286 $(M-Me)^+$, 244 $(M-Bu)^+$. Found: C, 55.63; H, 9.19; N, 4.49%. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.66; H, 9.03; N, 4.57%.
b) Preparation of **4** by hydrolysis of **7g**β. A mixture of **7g**β (54.3 mg, 0.099 mmol), *t*-butanol (0.37 ml), H_2O (0.10 ml), and 2M NaOH (0.104 ml, 0.21 mmol) was stirred at rt for 3 days, then diluted with H_2O (0.80 ml) and hexane (4.0 ml). The organic layer was separated and the aqueous layer was washed with hexane. The aqueous layer was acidified with 1M HCl and extracted with AcOEt. The AcOEt extracts were combined, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, CH_2Cl_2-AcOEt-AcOH 150:50:1) to give **4** as colorless crystals (27.0 mg, 91%). This sample showed the same physical and spectral data as those described in a).

(3S,4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(S)-1-carboxyethyl]-2-azetidinone (**10**). The same treatments of **8**α (14.7 mg, 0.038 mmol) as described for the preparation of **4** by hydrogenolysis of **8**β, gave **10** as colorless crystals (11.1 mg, 98%). An analytical sample obtained as colorless crystals by recrystallization from hexane-AcOEt showed mp 177~183°C (decomp.) and $[\alpha]_D^{25}$ -5.0° (c 0.44, MeOH). IR (KBr): 2950, 1720, 1463, 1380, 1258, 1103, 1043, 839, 778 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.25, 1.28 (6H, each d, J=6.2 and 7.2 Hz, MeCHOSi, MeCHCON), 2.61 (1H, m, MeCHCO), 2.77 (1H, m, C_3-H), 3.72 (1H, dd, J=1.8, 9.6 Hz, C_4-H), 4.19 (1H, t, J=5.8 Hz, MeCHOSi), 6.10 (1H, bs, NH). The ^1H-NMR spectrum was identical with that reported.[22] MS m/z: 286 $(M-Me)^+$, 244 $(M-Bu)^+$. Found: C, 55.87; H, 9.16; N, 4.56%. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.66; H, 9.03; N, 4.57%.

(3S,4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(methoxycarbonyl)ethyl]-2-azetidinone (**9**β). A solution of diazomethane in ether was added to **4** (15.8 mg, 0.052 mmol) at rt. The resulting slightly yellowish ethereal solution was concentrated *in vacuo*, affording **9**β as colorless crystals (16.0 mg, 97%). An analytical sample obtained by recrystallization from cyclohexane showed mp 121~122°C (*lit.*[3] 120~121°C) and $[\alpha]_D^{20}$ -27.8° (c 0.39, CH_2Cl_2) [*lit.*[3]

$[\alpha]_D^{22}$ -21.0° (c 2.09, CH_2Cl_2)]. IR (KBr): 2950, 1765, 1738, 1720, 1258, 1175, 1138, 1047, 962, 840, 782, 735, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 1.17, 1.23 (6H, each d, J=6.4 and 7.0 Hz, MeCHOSi, MeCHCON), 2.71 (1H, m, CHCO), 2.99 (1H, m, C_3-H), 3.70 (3H, s, MeO), 3.87 (1H, dd, J=2.5, 5.0 Hz, C_4-H), 4.21 (1H, m, CHOSi), 5.82 (1H, bs, NH). MS m/z: 300 $(M-Me)^+$, 258 $(M-Bu)^+$. Found: C, 57.14; H, 9.45; N, 4.35%. Calcd for $C_{15}H_{29}NO_4Si$: C, 57.11; H, 9.26; N, 4.44%.

(3S,4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(S)-1-(methoxycarbonyl)ethyl]-2-azetidinone (9α). The same treatments of **10** (4.0 mg, 0.013 mmol) as described for the preparation of 9β from **4**, gave 9α as colorless crystals (4.1 mg, 98%). An analytical sample obtained by recrystallization from cyclohexane showed mp 132~133°C (*lit.*[3] 133~134°C) and $[\alpha]_D^{25}$ +9.0° (c 0.15, CH_2Cl_2) [*lit.*[3] $[\alpha]_D^{22}$ +6.0° (c 2.0, CH_2Cl_2)]. IR (KBr): 2950, 1762, 1469, 1253, 1198, 1180, 1149, 1042, 964, 830, 778 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.24 (6H, d, J=6.6 Hz, MeCHOSi, MeCHCO), 2.55 (1H, m, CHCO), 2.78 (1H, m, C_3-H), 3.72 (3H, s, MeO), 3.87 (1H, dd, J=2.5, 5.0 Hz, C_4-H), 4.18 (1H, m, CHOSi), 5.98 (1H, bs, NH). MS m/z: 300 $(M-Me)^+$, 258 $(M-Bu)^+$. Found: C, 57.21; H, 9.33; N, 4.36%. Calcd for $C_{15}H_{29}NO_4Si$: C, 57.11; H, 9.26; N, 4.44%.

References and Notes

1. Part of this work has been the subject of a preliminary communication. Ito, Y.; Terashima, S. *Tetrahedron Lett.*, **1987**, *28*, 6625 (1987).
2. Present address: Department of Chemistry, Faculty of Science, Kyushu University, Higashi-ku, Fukuoka, 812, Japan.
3. Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles*, **1984**, *21*, 29.
4. a) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.*, **1985**, *26*, 4739. b) Shibata. T.; Sugimura, Y. *J. Antibiot.*, **1985**, *42*, 374.
5. a) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *Program and Abstracts of the 27th Interscience Conf. on Antimicrob. Agents and Chemother. New York*, **1987**, p. 228, No. 752. b) Idem, *J. Antibiot.*, **1990**, *43*, 519.
6. Ito, Y.; Terashima, S. *Yuki Gosei Kagaku Kyokai Shi*, **1989**, *47*, 606.
7. Nagahara, T.; Kametani, T. *Heterocycles*, **1987**, *25*, 729.
8. a) Hanessian, S.; Bedeschi, A.; Battistini, C.; Monglli, N. *J. Am. Chem. Soc.*, **1985**, *107*, 1438. b) Ohashi, T.; Suga, K.; Sada, I.;Miyama, T.; Watanabe, K. *Japan Kokai Tokkyo Koho* JP 61-18791 (1986). c) Ito, Y.; Kawabata, T.; Terashima, S. *Tetrahedron Lett.*, **1986**, *27*, 5751. Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron*, **1988**, *45*, 5767. d) Ishiguro, M.; Iwata, H.; Nakatsuka, T.; Tanaka, R.; Maeda, Y.; Nishihara, T.; Noguchi, T. *J. Antibiot.*, **1988**, *41*, 1685.
9. a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.*, **1986**, *108*, 4673. b) Déziel, R.; Favreau, D. *Tetrahedron Lett.*, **1986**, *27*, 5687.

10. Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.*, **1986**, *108*, 4675.
11. Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron Lett.*, **1987**, *28*, 507.
12. Almost the same unsuccessful results were reported by Endo. Endo, M. *Can. J. Chem.*, **1987**, *65*, 2140.
13. Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure & Appl. Chem.*, **1981**, *53*, 1109.
14. Amouroux, R.; Axiotis, G. P. *Synthesis*, **1981**, 270.
15. Diethylaluminium chloride, tributylborane, tin(II) chloride, titanium(IV) tetraisopropoxide and so on were employed as an additive. However, these lewis acids seemed to enhance the undesired α-diastereoselectivity. Ito, Y.; Terashima, S. unpublished results.
16. The ratio of the desired 1β–isomer to the undesired 1α-isomer was found to be almost 1:1. Ito, Y.; Terashima, S. unpublished results.
17. Ito, Y.; Terashima, S. *Tetrahedron*, the accompanying paper.
18. Ito, Y.; Terashima, S. unpublished results.
19. Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.*, **1987**, *52*, 2563.
20. Kawabata, T.; Kimura, Y.; Ito, Y.; Tereahima, S.; Sasaki, A.; Sunagawa, M.; *Tetrahedron Lett.*, **1986**, *27*, 6241. *Idem*, *Tetrahedron*, **1988**, *44*, 2149.
21. It has been reported that the carboxylic acid (**10**) can be convert to **4** *via* a partial epimerization of **9**α derived from **4** (ref. 3). However, though such transformation obviously lacks practicality.
22. Fliri, H.; Mak, C.-P. *J. Org. Chem.*, **1985**, *50*, 3438.
23. Close, W. J. *J. Am. Chem. Soc.*, **1951**, *73*, 95.
24. a) Plattner, J. J.; Fung, A. K. L.; Parks, J. A.; Pariza, R. J.; Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Dodge, P. W. *J. Med. Chem.*, **1984**, *27*, 1016. b) (*S*)-4-Phenyl-2-oxazolidone was reported to exhibit mp 132~133°C and $[\alpha]_D^{22}$ +49.5° (c 2.1, $CHCl_3$). Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.*, **1985**, *26*, 3783.