Tetrahedron Vol. 47, No. 16/17, pp. 2821-2834, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

HIGHLY STEREOSELECTIVE REFORMATSKY REACTIONS OF 3-(2-BROMOPROPIONYL)-2-OXAZOLIDONE DERIVATIVES WITH VARIOUS ALDEHYDES[1)]

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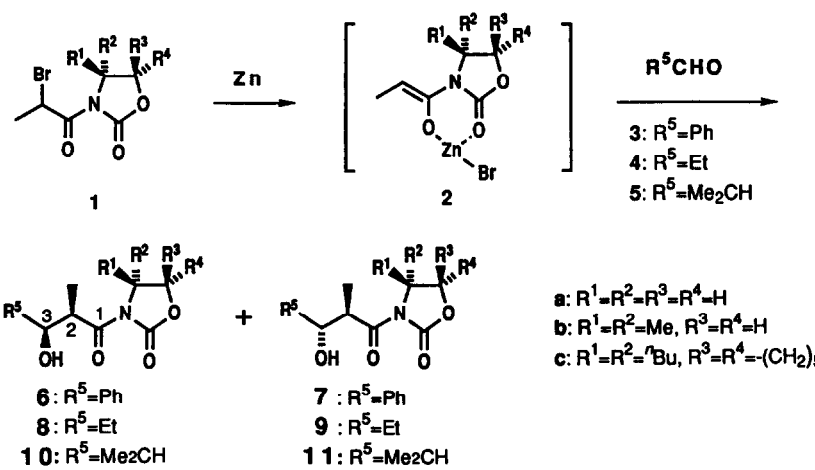
(*Received in Japan* 16 *November* 1990)

Abstract: *The Reformatsky reactions of 3-(2-bromopropionyl)-2-oxazolidone derivatives with various aldehydes were investigated to elucidate the effects of substituents in the 2-oxazolidone moieties on their diastereoselectivities. The highest 2,3-syn-diastereoselectivity (2,3-syn:2,3-anti=98:2) could be realized at -78℃ by employing sterically crowded 3-(2-bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone. While high 2,3-syn-3,4-syn-selectivity (2,3-syn-3,4-syn:2,3-syn-3,4-anti=94:6) was also accomplished by the reaction with dl-2-phenylpropanal, application of this reaction to enantioselective synthesis of 2,3-syn-aldols was found to be unrewarding. The observed diastereoselectivities could be accounted for by the chelating transition state models.*

The Reformatsky reaction has been recognized as one of the most conventional methods for preparing aldols since carbon-carbon single bond can be readily created by mixing α-halocarboxylic acid derivative, aldehyde, and zinc dust in an appropriate solvent.[3)] Unfortunately, however, it has been difficult to control relative stereochemistry with respect to newly created chiral centers. To overcome this problem, a number of researches have been devoted mainly to kinetically controlled aldol reactions employing the metal enolates produced by deprotonation of carboxylic acid derivatives with strong bases such as lithium diisopropylamide.[4)] Although high 2,3-*syn*-diastereoselectivities have been realized by the uses of enolates of



special metals such as boron,[5] tin,[6] or zirconium[7] enolate, the aldol reactions with zinc enolates readily obtainable from 2-bromopropionic acid derivatives and zinc dust, have been remained unsettled.[3,4,8]

Recently, we explored a highly stereoselective synthesis of the 1β-methylcarbapenem key intermediate by the Reformatsky reaction of 3-(2-bromopropionyl)-2-oxazolidone derivatives (**1**) with a 4-acetoxy-2-azetidinone in the presence of zinc dust.[9] The diastereoselectivity was found to highly depend upon bulkiness of the substituents at the C4-positions of oxazolidone moieties and reaction temperatures. Thus, the desired β-methyl diastereoselectivity could be best achieved by employing sterically crowded 2-oxazolidone derivatives such as 3-(2-bromopropionyl)-4,4-dimethyl- and 3-(2-bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone (**1b,c**) in refluxing tetrahydrofuran (THF). These novel findings prompted us to apply this reaction to stereoselective aldol synthesis. We have now found that the Reformatsky reaction of sterically crowded **1** with achiral and chiral aldehydes can similarly take place in a highly stereoselective manner, giving 2,3-*syn*- and 2,3-*syn*-3,4-*syn*-aldols as major products, respectively.[1]

This report concerns with full details of exploration of this highly diastereoselective Reformatsky reaction of sterically crowded **1** with various aldehydes.

The Reformatsky reaction of 3-(2-bromopropionyl)-2-oxazolidone derivatives (1) with achiral aldehydes (3~5).

Aiming to elucidate the 2,3-diastereoselectivity of aldol formation, the Reformatsky reactions of benzaldehyde (**3**) with various zinc enolates (**2**) prepared from **1**[10] and zinc dust were first studied.

As shown in **Table 1**, the 2,3-diastereoselectivities of the aldols (**6** and **7**) were found to highly depend upon steric bulkiness at the C4-positions of 2-oxazolidone moieties in a similar manner to that previously reported for the reactions with a 4-acetoxy-2-azetidinone.[9] Thus, the reaction of **3** with **2c** produced from the most sterically crowded **1c** exclusively gave the 2,3-*syn*-aldol (**6c**) [2,3-syn (**6c**):2,3-anti (**7c**)=98:2] in 98% yield at -78°C in THF (run 5). On the other hand, the 2,3-*syn*-diastereoselectivity slightly decreased when **2b** was employed (run 3) and the opposite 2,3-*anti*-diastereoselectivity was observed for **2a** derived from sterically less crowded **1a** (run 1).[11] High 2,3-*syn*-diastereoselectivity was also realized by the reaction of **2c** with other achiral aldehydes (**4** and **5**) (runs 6~8). Interestingly, the decrease of 2,3-*syn*-diastereoselectivity occurred at higher reaction temperatures contrary to the previous results (runs 2, 3 and 4, 5). Stereochemistries of the Reformatsky products (**6~11**) were assigned by the coupling constants between C2-H and C3-H of carboxyl groups observed in their ^{1}H-NMR spectra.[11] It is well known that the coupling constant between C2-H and C3-H of 2,3-*syn*-diastereomer is smaller than that of 2,3-*anti*-diastereomer due to the intramolecular hydrogen bonding which constructs a rigid six-membered ring.[12] Conversions of some 2,3-*syn*-aldols obtained as the major products (**6b,c**, **8c**, and **10c**) to the corresponding known carboxylic acids (for **6b** and **10c**)[13] or its methyl esters (for **6c** and **8c**)[14,15] further supported the assigned stereochemistries (see the experimental part).

Table 1. The Reformatsky reaction of 3-(2-bromopropionyl)-2-oxazolidone derivatives (1) with achiral aldehydes (3~5).

Run	1	Aldehyde	Conditions Temp (°C)	Time (h)	Products Yield[b] (%)	Ratio syn:anti	$J_{2,3}$[a] syn (Hz)	anti (Hz)
1	a	3	-78	20	81 (6a+7a)	38:62	3.8	8.3
2	b	3	0	1	96 (6b+7b)	90:10	4.4	6.1
3	b	3	-78	1	99 (6b+7b)	96: 4		
4	c	3	67[c]	3	76 (6c+7c)	80:20	4.9	6.5
5	c	3	-78	1	98 (6c+7c)	98: 2		
6	c	4	-78	0.5	75 (8c+9c)	89:11	2.9	6.8
7	c	5	25	0.17	96 (10c+11c)	85:15	3.1	7.0
8	c	5	-78	1	95 (10c+11c)	95: 5		

a) Coupling constant between C2-H and C3-H of carboxyl group in the ^{1}H-NMR spectrum of product.

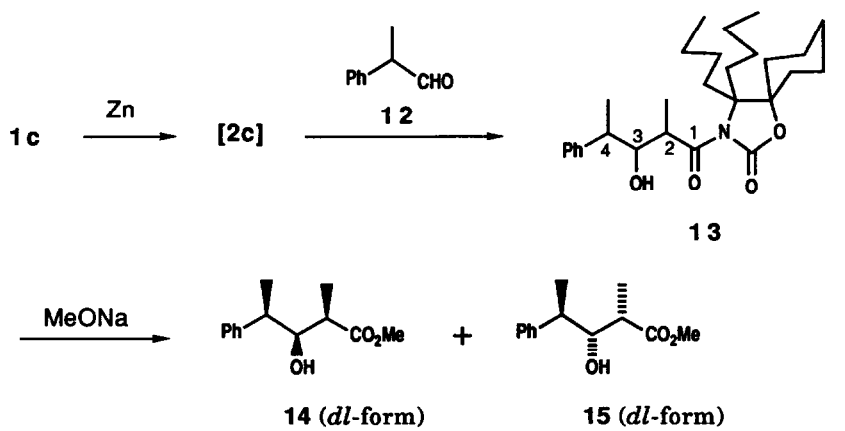
b) Number in parentheses corresponds to the compound number of product.

c) The reaction was performed in refluxing THF.

The Reformatsky reaction of 3-(2-bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone (1c) with *dl*-2-phenylpropanal (12).

Since it was established that **3~5** can produce the 2,3-*syn*-aldols (**6**, **8**, and **10**) exclusively when being allowed to react with sterically crowded **2b,c** at -78°C, the Reformatsky reaction with the aldehyde having an asymmetric center at the α-position was next attempted.

The reaction of **2c** with *dl*-2-phenylpropanal (**12**) took place smoothly at -78°C in THF,

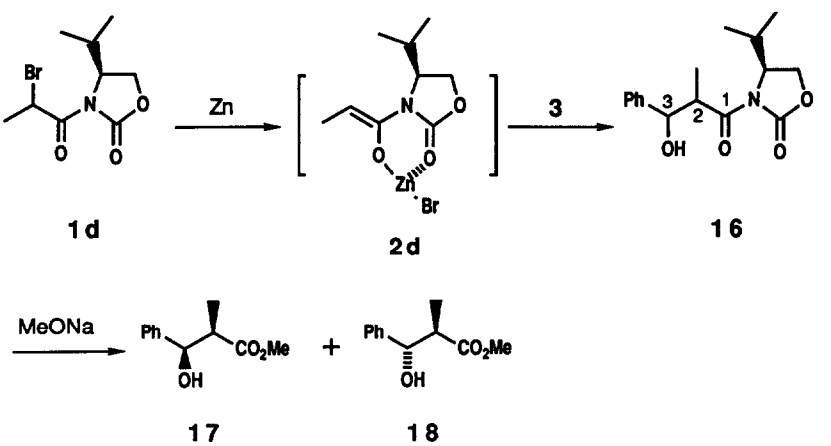


giving a mixture of the aldols (**13**) in 81% yield. Aiming to determine the structures and formation ratio of the diastereomers involved in **13**, the mixture was subjected to methanolysis using sodium methoxide in methanol, affording a mixture of the corresponding methyl esters in 87% yield. The ^{1}H-NMR spectrum (400 MHz) of this sample clearly revealed that the methanolysis product only consisted of two sorts of the methyl esters in a ratio of 94:6. By comparing the ^{1}H-NMR spectrum with those reported,[16] the structures of these two methyl esters were rigorously established as **14** and **15** both of which had 2,3-*syn*-stereochemistries.

The Reformatsky reaction of optically active (4*S*)-3-(2-bromopropionyl)-4-isopropyl-2-oxazolidone (1d) with benzaldehyde (3).

Finally, the reaction of **3** with the chiral zinc enolate (**2d**) produced from **1d** was examined to elucidate applicability of the developed reaction to enantioselective synthesis of chiral aldols.

When **3** was treated with **2d** at -78°C for 20 h in THF, a mixture of the diastereomeric aldols (**16**) was obtained in 93% yield. Since the stereochemistries and ratio of the four possible diastereomers could not be determined at this stage, **16** was subjected to methanolysis conditions, giving the optically active 2,3-*syn*- and 2,3-*anti*-methyl esters (**17** and **18**) in 42% and 39% yields, respectively. Optical yields of **17** and **18** could be calculated as 42% and 100%, respectively, by comparing their optical rotations with those reported.[17,18] Based on these results, the formation ratio of the mixture of **17** and its (2*S*,3*S*)-isomer to that of **18** and its (2*S*,3*R*)-isomer were readily determined as 52:48. The ratios of **17** to its (2*S*,3*S*)-isomer and **18** to its (2*S*,3*R*)-isomer could be also estimated as 71:29 and 100:0, respectively. Although the 2,3-*anti*-aldol (**18**) can be obtained with a high optical purity, the enantioselective synthesis of optically active aldols employing the Reformatsky reaction seems to lack practicality because almost the same amounts of the 2,3-*syn*- and 2,3-*anti*-aldol are produced.



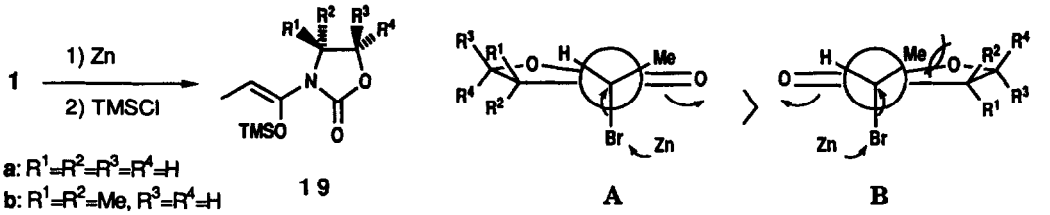
1d **2d** **16**

17 **18**

Mechanistic consideration of the Reformatsky reaction.

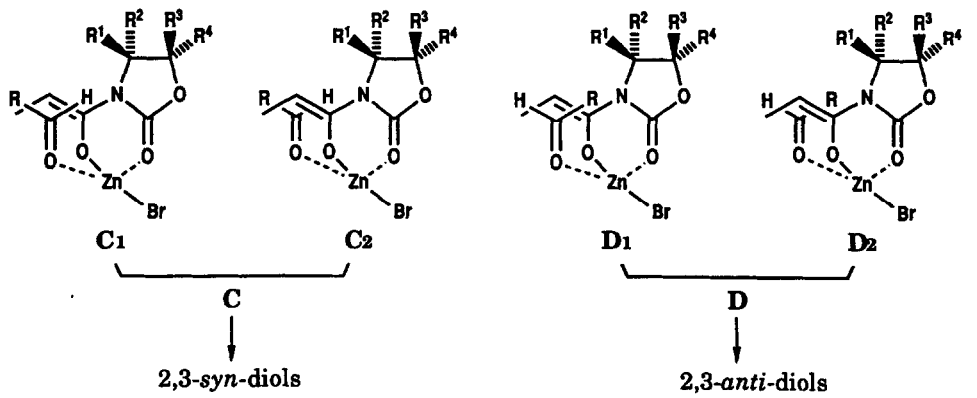
In order to elucidate the mechanism of the Reformatsky reaction, the stereochemistry of the zinc enolate was first studied by means of the 400 MHz ^{1}H-NMR spectra of **2a,b** prepared

from **1a,b** and zinc dust in d8-THF. While the ^{1}H-NMR spectra of **2a,b** showed broad signals probably due to aggregation, the signals corresponding to the silyl enol ethers (**19a,b**) appeared on addition of trimethylsilyl chloride to the mixtures in d8-THF. The stereochemistries of **19a,b** were assumed to be (*Z*)-forms since the conformation **A** leading to **19a,b** is obviously more favored than the conformation **B** producing the (*E*)-isomers of **19a,b** when the 1,3-allylic strain is taken into consideration. The same explanation has already been proposed by Evans for preferential formation of (*Z*)-enolate by deprotonation of a 3-propionyl-2-oxazolidone derivative with lithium diisopropylamide.[19] Taking into account the sensitivity of 400 MHz ^{1}H-NMR spectrum, the ratios of **19a,b** to their (*E*)-isomers were assumed to be more than 97:3. Based on these results, it was also anticipated that the other zinc enolates (**2c,d**) have the same (*Z*)-configurations.



The diastereoselectivities of the Reformatsky reactions may be explained by the chelating transition state models (**C** and **D**) which afford 2,3-*syn*- and 2,3-*anti*-diols, respectively. In **C** and **D**, aldehyde derivatives having two lone pairs available for chelation at the oxygen atom can interact with the (*Z*)-zinc enolates (**2**) only in chair forms. On the other hand, two types of chelating transition state models corresponding to a chair and a boat form, respectively, have been proposed for the Reformatsky reaction with a 4-acetoxy-2-azetizinone since a 1,4-dehydro-2-azetidinone *in situ* produced from a 4-acetoxy-2-azetidinone carrys single lone pair which can participate in chelation.[9]

Thus, the low 2,3-*anti*-diastereoselectivity observed for the reaction of **2a** with **3** at -78°C



(**Table 1**, run 1) is rationalized by assuming that the transition state **D** is slightly more favored than **C** since the phenyl group of **3** may interact with the methyl group of enolate portion more severely than with the C_4-hydrogens of 2-oxazolidone moiety. On the other hand, considering the steric interaction between the substituent of aldehyde and the C_4-alkyl groups (R^1 and R^2) of 2-oxazolidone moiety, the transition state **C** readily accounts for the high 2,3-*syn*-diastereoselectivity observed for the reactions of sterically crowded **2b,c** with achiral and chiral aldehydes (**3~5** and **12**) at -78°C (For **3~5**, **Table 1**, runs 3, 5, 6, and 8). The high 3,4-*syn*-diastereoselectivity observed in the reaction of **2c** with **12** is explained presumably by the Felkin-Anh model.[20]

Increases of the reaction temperatures obviously decrease the 2,3-*syn*-diastereoselectivities (**Table 1**, runs 2, 3; 4, 5; and 7, 8). Similarly to the Reformatsky reaction with a 4-acetoxy-2-azetidinone,[9] these results may be explained by loosening of the intermolecular chelation between the zinc (II) cation and the oxygen atom of aldehyde group. Since the substituent of aldehyde is present in the proximity of the C_4-alkyl groups (R^1 and R^2) of the 2-oxazolidone moiety in **D**, steric interaction should be released more effectively in **D** than in **C** by the weakening of intermolecular chelation. Accordingly, the proportions of the 2,3-anti diols (**7**, **9**, and **11**) may be enhanced by the increased participation of **D** at higher reaction temperatures (runs 2, 4, and 7).

The following explanation may be further proposed to interpret the results of enantioselective synthesis with **2d** examined at -78°C. The 2,3-*anti*-aldol solely consisting of (2*R*, 3*S*)-**16** is produced only through the transition state $\mathbf{D_2}$ where the phenyl group of **3** interacts with the C_4-hydrogen. On the other hand, formation of the 2,3-*syn*-aldol occurs not only through the transition state $\mathbf{C_2}$ but also $\mathbf{C_1}$ since the steric interaction between hydrogen and isopropyl group may not be so severe. That the ratio of (2*R*,3*R*)-**16** to its (2*S*,3*S*)-isomer is 71:29 clearly shows that $\mathbf{C_2}$ is more favored than $\mathbf{C_1}$.

As described above, it appeared evident that the Reformatsky reactions of sterically crowded **1b,c** with achiral and chiral aldehydes in the presence of zinc dust can produce 2,3-*syn*- and 2,3-*syn*-3,4-*syn*-aldols as major products, respectively. It is worth noting that, being different from the previous results obtained using a 4-acetoxy-2-azetidinone,[9] the diastereoselectivities observed in the aldol formations can be reasonably rationalized by the chelating transition state models consisting of chair forms.

Experimental

General. All melting points were measured by a Yamato MP-21 melting point apparatus and were uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-90H (90 MHz) and 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-[(2R,3R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-2-oxazolidone* (**6a**) *and its (2R*,3S*)-isomer* (**7a**) (**Table 1**, run 1). Zinc dust (18.3 mg, 0.28 mmol) was added to a solution of **1a**[10] (52.2 mg, 0.24 mmol) in THF (0.94 ml). The mixture was vigorously stirred at rt for 2h, giving a grayish suspension of the corresponding zinc enolate. After cooling to -78°C, **3** (29.8 mg, 0.28 mmol) was added to the mixture and the stirring was continued for 20h at the same temperature. Aqueous phosphate buffer (pH 7, 1.0 ml) was added to quench the reaction. The mixture was allowed to warm up to rt and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The concentration residue was purified by column chromatography (SiO_2, hexane-CH_2Cl_2-AcOEt 7:1:2~7:0:3), affording **6a** as colorless crystals (18.1 mg, 31%) from the less polar fraction and **7a** as colorless crystals (29.1 mg, 50%) from the more polar fraction. The combined yield of **6a** and **7a** was 81%. The ratio of **6a** to **7a** could be calculated as 38:62 by the weights of the separated samples. The minor product (**6a**) recrystallized from hexane-AcOEt showed mp 105~106°C. IR (KBr): 3530, 3000, 1765, 1693, 1480, 1450, 1392, 1368, 1250, 1230, 1210, 1130, 1090, 1039, 983, 944, 862, 774, 757, 723, 708, 660, 553, 510 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.14 (3H, d, J=6.8 Hz, Me), 3.04 (1H, d, J=2.5 Hz, OH), 4.07 (1H, dq, J=3.8, 6.8 Hz, CHCON), 3.8~4.5 (4H, m, CH_2x2), 5.11 (1H, dd, J=2.5, 3.8 Hz, CHOH), 7.2~7.4 (5H, m, Ph). MS m/z: 249 $(M)^+$, 162, 161, 143. Found: C, 62.36; H, 6.22; N, 5.52%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%. The major product (**7a**) recrystallized from hexane-AcOEt showed mp 107~107.5°C. IR (KBr): 3580, 3000, 1763, 1681, 1481, 1450, 1390, 1365, 1250, 1230, 1210, 1185, 1168, 1125, 1090, 1034, 1002, 988, 940, 860, 773, 756, 723, 705, 697, 660, 508 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.04 (3H, d, J=6.8 Hz, Me), 2.91 (1H, d, J=5.9 Hz, OH), 3.9~4.5 (5H, m, CHCON, CH_2x2), 4.78 (1H, dd, J=5.9, 8.3 Hz, CHOH), 7.2~7.4 (5H, m, Ph). MS m/z: 249 $(M)^+$, 143. Found: C, 62.54; H, 6.17; N, 5.53%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%. The structures of **6a** and **7a** were assigned based on the coupling constants between C2-H and C3-H of carboxylic acid moieties observed in their ^{1}H-NMR spectra [$J_{2,3}$=3.8 Hz (**6a**) and 8.3 Hz (**7a**)] (see also ref. 11).

4,4-Dimethyl-3-[(2R,3R*)-3-hydroxy-2-methyl-3-phenylpropionyl]-2-oxazolidone* (**6b**) *and its (2R*,3S*)-isomer* (**7b**). a) The Reformatsky reaction of **1b** with **3** at 0°C (**Table 1**, run 2): Zinc dust (0.146 g, 2.2 mmol) was added to a solution of **1b**[10] (0.430 g, 1.7 mmol). The mixture was vigorously stirred at rt for 0.5 h, then cooled to 0°C. Benzaldehyde (**3**) (0.196 ml, 1.9 mmol) was added to the mixture and the stirring was continued for 1 h at the same temperature. Aqueous phosphate buffer (pH 7, 3.0 ml) was added to quench the reaction. The mixture was allowed to warm up to rt 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, hexane-AcOEt 4:1), affording **6b** as a colorless oil (0.414 g, 86%) from the less polar fraction and **7b** as colorless crystals (50.1 mg, 10%) from the more polar fraction. The combined yield of **6b** and **7b** was 96%. The ratio of **6b** to **7b** could be calculated as 90:10 by the ^{1}H-NMR spectrum of the mixture. The C3-methine protons of carboxylic

moieties of **6b** and **7b** appeared as two doublets at 5.04 and 4.76 ppm with an integration ratio of 90:10. The major product (**6b**) obtained as a colorless oil showed the following spectral data. IR (neat): 3520, 3000, 1779, 1705, 1452, 1380, 1309, 1222, 1180, 1098, 1033, 942, 770, 703, 542 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.14 (3H, d, J=6.7 Hz, MeCH), 1.39, 1.53 (6H, each s, Me_2C), 3.11 (1H, br, OH), 3.86, 3.97 (2H, each d, J=each 8.6 Hz, CH_2), 4.09 (1H, dq, J=4.4, 7.0 Hz, CHCON), 5.04 (1H, d, J=4.4 Hz, CHOH), 7.1~7.6 (5H, m, Ph). MS m/z: 277 $(M)^+$, 260 $(M-OH)^+$, 171. The minor product (**7b**) recrystallized from hexane-AcOEt showed mp 109~110°C. IR (KBr): 3490, 3000, 1790, 1704, 1693, 1455, 1380, 1310, 1248, 1220, 1180, 1103, 1057, 1035, 1020, 940, 768, 710, 610, 580, 540, 512 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.06 (3H, d, J=6.8 Hz, MeCH), 1.46, 1.55 (6H, each s, Me_2C), 3.26 (1H, br, OH), 3.95 (2H, s, CH_2), 4.16 (1H, dq, J=6.1, 6.8 Hz, CHCON), 4.76 (1H, d, J=6.1 Hz, CHOH), 7.2~7.4 (5H, m, Ph). MS m/z: 277 $(M)^+$, 171. Found: C, 64.91; H, 6.97; N, 5.03%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.97; N, 5.03%. The structures of **6b** and **7b** were assigned based on the coupling constants between C2-H and C3-H of carboxylic acid moieties observed in their ^1H NMR spectra [$J_{2,3}$=4.4 Hz (**6b**) and 6.1 Hz (**7b**)]. The major isomer (**6b**) was saponified under the same conditions as described for **10c** (*vide infra*), affording (2*R**,3*R**)-3-hydroxy-2-methyl-3-phenylpropionic acid in 43% yield. ^1H-NMR ($CDCl_3$): 1.14 (3H, d, J=7.3 Hz, MeCH), 2.84 (1H, dq, J=4.2, 7.3 Hz, MeCH), 5.17 (1H, d, J=4.2 Hz, CHOH), 6.55 (2H, br, OH and COOH), 7.33 (5H, m, Ph). This ^1H-NMR spectrum was identical with those reported.[13]

b) The Reformatsky reaction of **1b** with **3** at -78°C (**Table 1**, runs 3). The zinc enolate produced from **1b** (73.9 mg, 0.30 mmol) under the same conditions as described in a) was allowed to react with **3** (35.9 μg, 0.35 mmol) at -78°C for 1h. Treatments of the reaction mixture in a similar manner to that described in a) afforded a mixture of **6b** and **7b** (80.7 mg, 99%). The ratio of **6b** to **7b** could be similarly calculated as 96:4 by the ^1H-NMR spectrum of the mixture measured in $CDCl_3$. The C3-methine proton of carboxylic acid moieties appeared as two doublets at 5.04 and 4.76 ppm with an integration ratio of 96:4. The spectral data of **6b** and **7b** separated by column chromatography were identical with those described in a).

4,4-Dibutyl-3-[(2R,3R*)-3-hydroxy-2-methyl-3-phenylpropionyl]-5,5-pentamethylene-2-oxazolidone* (**6c**) *and its (2R*,3S*)-isomer* (**7c**). a) The Reformatsky reaction of **1c** with **3** at 67°C (**Table 1**, run 4). Zinc dust (14.5 mg, 0.23 mmol) and **3** (20.6 μl, 0.20 mmol) were added to a solution of **1c**[10] (74.5 mg, 0.19 mmol) in THF (0.74 ml). The mixture was vigorously stirred under reflux for 3 h and the stirring was continued overnight at rt. The usual work-up followed by purification with column chromatography (SiO_2, Hex-AcOEt 9:1) gave **6c** as colorless crystals (48.8 mg, 61%) from the less polar fraction and **7c** as a colorless oil (12.1 mg, 15%) from the more polar fraction. The combined yield of **6c** and **7c** was 76%. The ratio of **6c** to **7c** could be calculated as 80:20 by the weights of the separated samples. The major product (**6c**) recrystallized from hexane showed mp 113~114°C. IR (KBr): 3500, 2950, 2890, 1742, 1703, 1450, 1380, 1360, 1300, 1280, 1260, 1242, 1203, 1180, 1118, 1046, 958, 912, 778, 734, 542 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.21 (3H, d, J=6.8 Hz, MeCH), 0.7~2.2 (28H, m, other protons), 2.88 (1H, d, J=3.0 Hz, OH), 4.11 (1H, dq, J=4.9, 6.8 Hz, CHCON), 4.97 (1H, dd, J=3.0, 4.9 Hz, CHOH), 7.2~7.5 (5H, m, Ph). MS m/z: 429 $(M)^+$, 323, 294. Found: C, 72.80; H, 9.26; N, 3.19%. Calcd for

$C_{26}H_{39}NO_4$: C, 72.69; H, 9.26; N, 3.19%. The minor product (**7c**) showed the following spectrum data. ^{1}H-NMR ($CDCl_3$): 1.19 (3H, d, J=6.6 Hz, MeCH), 0.8~2.2 (28H, m, other protons), 3.49 (1H, d, J=8.0 Hz, OH), 4.14 (1H, dq, J=6.5, 6.6 Hz, CHCON), 4.75 (1H, dd, J=6.5, 8.0 Hz, CHOH), 7.2~7.4 (5H, m, Ph). The structures of **6c** and **7c** were assigned based on the coupling constants between C2-H and C3-H of carboxylic acid moieties observed in their ^{1}H-NMR spectra [$J_{2,3}$=4.9 Hz (**6c**) and 6.5 Hz (**7c**)]. The major isomer (**6c**) was converted to methyl (2*R**,3*R**)-3-hydroxy-2-methyl-3-phenylpropionate in 70% yield according to a similar procedure to that described for methanolysis of **16** (*vide infra*). ^{1}H-NMR ($CDCl_3$): 1.13 (3H, d, J=7.3 Hz, MeCH), 2.79 (1H, dq, J=4.2, 7.3 Hz, MeCH), 2.92 (1H, d, J=3.5 Hz, OH), 3.66 (3H, s, MeO), 5.09 (1H, dd, J=3.5, 4.2 Hz, CHOH), 7.32 (5H, m, Ph). This ^{1}H-NMR spectrum was identical with that reported for methyl (2*R**,3*R**)-3-hydroxy-2-methyl-3-phenylpropionate (**17**).[14]

b) The Reformatsky reaction of **1c** with **3** at -78°C (**Table 1**, run 5). The zinc enolate produced from **1c** (84.9 mg, 0.21 mmol) under the same conditions as described in a) was allowed to react with **3** (25.6 μg, 0.25 mmol) at -78°C for 1h. Treatments of the reaction mixture in a similar manner to that described in a) afforded a mixture of **6c** and **7c** (88.7 mg, 98%) after purification by column chromatography. The ratio of **6c** to **7c** could be calculated as 98:2 by the ^{1}H-NMR spectrum of the mixture measured in $CDCl_3$. The C3-methine protons of carboxylic acid moieties of **6c** and **7c** appeared as two doublets at 4.97 and 4.75 ppm with an integration ratio of 98:2. The spectral data of **6c** and **7c** separated by column chromatography were identical with those described in a).

4,4-Dibutyl-3-[(2R,3S*)-3-hydroxy-2-methylvaleryl]-5,5-pentamethylene-2-oxazolidone* (**8c**) *and its (2R*,3R*)-isomer* (**9c**). The Reformatsky reaction of **1c** with **4** at -78°C (**Table 1**, run 6). The zinc enolate produced from **1c** (43.7 mg, 0.11 mmol) under the same conditions as described for the preparation of a mixture of **6c** and **7c**, was allowed to react **4** (10.4 μg, 0.11 mmol) at -78°C for 0.5 h. The usual work-up afforded a mixture of **8c** and **9c** after concentration of the organic extracts *in vacuo*. Separation of the mixture by preparative TLC (SiO_2, hexane-AcOEt 4:1) gave **8c** as a colorless oil (27.5 mg, 67 %) from the more polar fraction and **9c** as a colorless oil (3.5 mg, 8%) from the less polar fraction. The combined yield of **8c** and **9c** was 75%. The ratio of **8c** to **9c** could be calculated as 89:11 by the weights of the separated samples. The major product (**8c**) showed the following spectral data. IR (neat): 3540, 2950, 2890, 1770, 1702, 1450, 1378, 1359, 1290, 1278, 1239, 1209, 1184, 1116, 962, 932, 772 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.17 (3H, d, J=6.8 Hz, MeCH), 0.8~2.3 (33H, m, other protons), 2.77 (1H, br, OH), 3.86 (1H, dq, J=2.9, 6.8 Hz, CHCON), 3.88 (1H, m, CHOH). MS m/z: 382 $(M+1)^+$, 363 $(M-H_2O)^+$, 352 $(M-Et)^+$, 334, 324. The minor product (**9c**) showed the following spectral data. ^{1}H-NMR ($CDCl_3$): 1.20 (3H, d, J=6.6 Hz, MeCH), 0.7~2.3 (33H, m, other protons), 2.75 (1H, d, J=8.4 Hz, OH), 3.6 (1H, m, CHOH), 3.78 (1H, dq, 6.6, 6.8 Hz, CHCON). MS m/z: 381 $(M)^+$, 366 $(M-Me)^+$, 363 $(M-H_2O)^+$, 352 $(M-Et)^+$, 348. The structures of **8c** and **9c** were assigned based on the coupling constants between C2-H and C3-H of carboxylic acid moieties observed in their ^{1}H-NMR spectra [$J_{2,3}$=2.9 Hz (**8c**) and 6.8 Hz (**9c**)]. The major isomer (**8c**) was converted to methyl (2*R**,3*S**)-3-hydroxy-2-methylvalerate in 49% yield according to a similar procedure to

that described for methanolysis of **16** (*vide infra*). ^{1}H-NMR ($CDCl_3$): 0.97 (3H, t, J=6.6 Hz, MeCH$_2$), 1.18 (3H, d, J=7.3 Hz, MeCH), 1.45 (2H, m, CH$_2$), 2.43 (1H, br, OH), 2.56 (1H, dq, J=3.7, 7.3 Hz, MeCH), 3.70 (3H, s, MeO), 3.78 (1H, m, CHOH). This ^{1}H-NMR spectrum was identical with that reported for methyl (2*R*,3*S*)-3-hydroxy-2-methylvalerate.[15]

4,4-Dibutyl-3-[(2R,3S*)-2,4-dimethyl-3-hydroxyvaleryl]-5,5-pentamethylene-2-oxazolidone* (**10c**) *and its (2R*,3R*)-isomer* (**11c**). a) The Reformatsky reaction of **1c** with **5** at 25°C (**Table 1**, run 7). Zinc dust (34.7 mg, 0.53 mmol) was added to a solution of **1c** (0.142 g, 0.35 mmol) in THF (1.4 ml). After the mixture was vigorously stirred at rt for 1 h, **5** (38.5 μl, 0.42 mmol) was added and the stirring was continued at 25°C for additional 1 h. The usual work-up followed by purification with column chromatography (SiO_2, hexane-AcOEt 97:3) afforded **10c** as a colorless oil (0.114 g, 81%) from the more polar fraction and **11c** as a colorless oil (20.6 mg, 15%) from the less polar fraction. The combined yield of **10c** and **11c** was 96%. The ratio of **10c** to **11c** could be calculated as 85:15 by the weights of the separated samples. The major product (**10c**) showed the following spectral data. IR (neat): 3550, 2980, 2900, 1770, 1701, 1450, 1379, 1360, 1290, 1278, 1238, 1182, 1118, 982, 960, 913, 862, 772, 738, 644 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.90 (6H, m, MeCH$_2$x2), 0.91, 1.02 (6H, each d, J=6.6 and 6.4 Hz, Me$_2$CH), 1.17 (3H, d, J=7.0 Hz, MeCH), 1.0~2.3 (23H, m, other protons), 2.77 (1H, d, J=3.5 Hz, OH), 3.51 (1H, ddd, J=3.1, 3.5, 8.1 Hz, CHOH), 4.02 (1H, dq, J=3.1, 7.0 Hz, CHCON). MS m/z: 396 $(M+1)^+$, 352 $(M-Pr)^+$, 324, 294. The minor product (**11c**) showed the following spectral data. IR (neat): 3530, 2950, 2900, 1770, 1710, 1450, 1380, 1360, 1280, 1240, 1208, 1183, 1116, 1000, 960, 908, 863, 773, 617 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.90 (6H, m, MeCH$_2$x2), 0.94, 0.98 (6H, each d, J=6.6, 6.8 Hz, Me$_2$CH), 1.19 (3H, d, J=6.8 Hz, MeCH), 1.0~2.3 (23H, m, other protons), 2.86 (1H, d, J=9.4 Hz, OH), 3.41 (1H, ddd, J=7.0, 7.3, 9.4 Hz, CHOH), 3.89 (1H, dq, J=6.8, 7.0 Hz, CHCON). MS m/z: 395 $(M)^+$, 378 $(M-OH)^+$, 352 $(M-Pr)^+$, 334. The structures of **10c** and **11c** were determined based on the coupling constants between C2-H and C3-H of carboxylic acid moieties observed in their ^{1}H-NMR spectra [$J_{2,3}$=3.1 Hz (**10c**) and 7.0 Hz (**11c**)]. The major aldol product (**10c**) was converted to (2*R**,3*S**)-3-hydroxy-2,4-dimethylvaleric acid according to the following procedure. A solution of 2M NaOH (0.70 ml, 1.4 mmol) was added to a solution of **10c** (91.9 mg, 0.23 mmol) in *t*-butanol (1.4 ml) at rt. After stirring for 2 days, the mixture was diluted with H_2O (1.0 ml) and hexane. The organic layer was separated and the aqueous layer was acidified with 1M HCl (3.0 ml), saturated with NaCl, then extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, giving (2*R**,3*S**)-2,4-dimethyl-3-hydroxyvaleric acid as a colorless oil (24.5 mg, 72%). IR (neat): 3450, 2970, 1710, 1460, 1385, 1210, 1130, 1105, 1078, 1042, 997, 980, 945 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.89, 1.02 (6H, each d, J=6.6 and 6.4 Hz, Me$_2$CH) 1.21 (3H, d, J=7.0 Hz, MeCH), 1.70 (1H, m, Me$_2$CH), 2.71 (1H, dq, J=3.7, 7.3 Hz, CHCOO), 3.64 (1H, dd, J=3.7, 7.9 Hz, CHOH), 6.47 (2H, br, COOH and OH). MS m/z: 128 $(M-H_2O)^+$, 113, 103, 85. The ^{1}H-NMR spectrum of this sample was identical with those reported.[13]

b) The Reformatsky reaction of **1c** with **5** at -78°C (**Table 1**, run 8). The zinc enolate produced from **1c** (68.0 mg, 0.17 mmol) under the same conditions as described in a) was allowed to react with **5** (18.4 ml, 0.20 mmol) at -78°C for 1h. Treatments of the reaction mixture in a

similar manner to that described in a) afforded a mixture of **10c** and **11c** (63.2 mg, 95%). The ratio of **10c** to **11c** could be calculated as 95:5 by the ^{1}H-NMR spectrum of the mixture measured in $CDCl_3$. The hydroxy protons of **10c** and **11c** appeared as two doublets at 2.77 and 2.86 ppm with an integration ratio of 95:5. The physical and spectral data of **10c** and **11c** separated by column chromatography were identical with those described in a).

4,4-Dibutyl-3-(3-hydroxy-2-methyl-4-phenylvaleryl)-5,5-pentamethylene-2-oxazolidone (**13**). Zinc dust (29.8 mg, 0.46 mmol) was added to a solution of **1c** (0.122 g, 0.30 mmol) in THF (1.2 ml) and the mixture was vigorously stirred at rt for 1 h. After cooling to -78°C, **12** (44 μl, 0.33 mmol) was added to the cooled mixture and the stirring was continued for 1 h at the same temperature. After the usual work-up, the residue obtained by concentration of the organic extracts *in vacuo* was purified by column chromatography (SiO_2, hexane-AcOEt 19:1) to give **13** as a colorless oil (0.113 g, 81%). This aldol product (**13**) was found to consist of a mixture of two diastereomers by converting it to a mixture of the corresponding methyl esters (**14** and **15**). IR (neat): 3530, 2950, 2870, 1770, 1698, 1497, 1450, 1376, 1358, 1284, 1275, 1235, 1182, 1112, 970, 930, 769, 734, 700, 540 cm^{-1}. The ^{1}H-NMR spectrum of the major aldol could be only assigned as follows. ^{1}H-NMR ($CDCl_3$): 0.91 (6H, m, MeCH2x2), 1.16 (3H, d, J=6.8 Hz, MeCHCON), 1.37 (3H, d, J=7.0 Hz, MeCHPh), 1.0~2.3 (28H, m, other protons), 2.82 (1H, dq, J=6.8, 8.2 Hz, CHPh), 2.86 (1H, d, J=3.3, OH), 3.67 (1H, dq, 3.3, 7.0 Hz, CHCON), 4.02 (1H, dt, J=3.3, 8.2 Hz, CHOH), 7.1~7.5 (5H, m, Ph). MS m/z: 440 $(M-OH)^+$, 439 $(M-H_2O)^+$, 352, 334.

Methyl (2R,3S*,4R*)-3-hydroxy-2-methyl-4-phenylvalerate* (**14**) *and its (2S*,3R*,4R*)-isomer* (**15**). A solution of 2M sodium methoxide in MeOH (0.34 ml, 0.68 mmol) was added to an ice cooled methanolic solution of **13** (0.155 g, 0.34 mmol). After stirring for 1h, an additional amount of the sodium methoxide solution (0.17 ml, 0.34 mmol) was added to the reaction mixture and the stirring was further continued overnight. The resulting mixture was diluted with 1M HCl (1.0 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, hexane-Et_2O 9:1), affording a mixture of **14** and **15** as a colorless oil (65.5 mg, 87%). Comparison of the ^{1}H-NMR spectrum with those reported,[16] obviously revealed that the product consisted of **14** and **15** having (2*R**,3*S**,4*R**)- and (2*S**,3*R**,4*R**)-configurations, respectively. The ratio of **14** to **15** could be calculated as 94:6 by an integration ratio of two sets of signals observed in the ^{1}H-NMR spectrum. IR (neat): 3500, 2970, 1732, 1500, 1454, 1436, 1202, 1078, 1040, 1015, 990, 972, 938, 762, 704, 543 cm^{-1}. ^{1}H-NMR (CCl_4) (400 MHz) (2*R**,3*S**,4*R**)-Isomer (**14**): 1.11 (3H, d, J=7.2 Hz, MeCHCOO), 1.33 (3H, d, J=6.9 Hz, MeCHPh), 2.18 (1H, dq, J=2.9, 7.2 Hz, CHCOO), 2.59 (1H, d, J=3.1 Hz, OH), 2.70 (1H, dq, J=6.8, 9.1 Hz, CHPh), 3.61 (3H, s, MeO), 3.96 (1H, ddd, J=2.9, 3.1, 9.1 Hz, CHOH), 7.09~7.26 (5H, m, Ph). (2*S**,3*R**,4*R**)-isomer (**15**): 1.17 (3H, d, J=7.1 Hz, MeCHCOO), 1.25 (3H, d, J=7.1 Hz, MeCHPh), 1.70 (1H, d, J=4.9 Hz, OH), 2.52 (1H, dq, J=4.6, 7.1 Hz, CHCOO), 3.63 (3H, s, MeO), 3.91 (1H, ddd, J=4.6, 4.9, 7.2 Hz, CHOH), 7.09~7.26 (5H, m, Ph) MS m/z: 223 $(M+1)^+$, 205 $(M-OH)^+$, 204 $(M-H_2O)^+$, 191 $(M-MeO)^+$.

3-(3-Hydroxy-2-methyl-3-phenylpropionyl)-4-(S)-isopropyl-2-oxazolidone (**16**). The zinc enolate produced from **1d**[10] (62.0 mg, 0.24 mmol) in a similar manner to that described for the reaction of **1a** with **3**, was allowed to react with **3** (28.6 μl, 0.28 mmol) at -78°C for 20h. The usual work-up followed by purification with column chromatography afforded **16** as a diastereomeric mixture (63.4 mg, 93%). The ratio and optical purity of two diastereomers were determined by converting to the corresponding optically active methyl ester (**17** and **18**) (see the following experimental). IR ($CHCl_3$): 3550, 2980, 1779, 1695, 1490, 1450, 1382, 1300, 1192, 1140, 1120, 1102, 1082, 1057, 1012, 986, 953, 698 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.6~1.3 (9H, m, Mex3), 2.0~2.5 (1H, m, CHMe2), 3.2 (1H, br, OH), 4.0~4.6 (4H, m, CH_2, CHPh, CHCON), 4.74, 5.05, 5.10 (1H, each d, J=7.9, 5.1, 5.2 Hz, CHOH), 7.2~7.5 (5H, m, Ph). MS m/z: 291 (M^+), 274 $(M-OH)^+$, 239, 185.

Methyl (2R,3R)-3-hydroxy-2-methyl-3-phenylpropionate (**17**) *and its (2S,3R)-isomer* (**18**). A solution of 2M sodium methoxide in MeOH (0.20 ml, 0.40 mmol) was added to a solution of **16** (59.0 mg, 0.20 mmol) in MeOH (0.8 ml) at -5°C. After stirring for 0.5 h, the mixture was diluted with 1M HCl (0.60 ml), saturated with NaCl, then 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, hexane-AcOEt 9:1), affording **17** as a colorless oil (16.4 mg, 42%) from the less polar fraction and **18** as a colorless oil (15.3 mg, 39%) from the more polar fraction. The combined yield of **17** and **18** was 81%. The ratio of **17** and **18** could be calculated as 52:48 by the weights of the separated samples. The major product (**17**) showed $[\alpha]_D^{20}$ +9.8° (c 0.79, $CHCl_3$). Since an optically pure sample of **17** had been reported to exhibit $[\alpha]_D^{20}$ +23.2° (c 3.2, $CHCl_3$),[17] the optical purity of **17** obtained here could be calculated as 43% ee. IR (neat): 3500, 2950, 1722, 1450, 1430, 1350, 1250, 1198, 1170, 1121, 1060, 1030, 992, 899, 770, 700 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.13 (3H, d, J=7.0 Hz, MeCH), 2.79 (1H, dq, J=4.4, 7.0 Hz, MeCH), 2.92 (1H, d, J=3.3 Hz, OH), 3.66 (3H, s, MeO), 5.09 (1H, dd, J=3.3, 4.4 Hz, CHOH), 7.32 (5H, s, Ph). MS m/z: 194 $(M)^+$, 177 $(M-OH)^+$, 163 $(M-MeO)^+$. The minor product (**18**) showed $[\alpha]_D^{20}$ -57.3° (c 0.99, $CHCl_3$). Since an optically pure sample of **18** had been report to exhibit $[\alpha]_D^{25}$ -57.1° (c 0.123, $CHCl_3$),[18] the methyl ester (**18**) obtained here was found to be optically pure. IR (neat): 3500, 2950, 1730, 1450, 1432, 1378, 1250, 1200, 1168, 1120, 1052, 1020, 907, 765, 700, 608 cm^{-1}. ^1H-NMR ($CDCl_3$): 1.00 (3H, d, J=7.2 Hz, MeCH), 2.82 (1H, dq, J=7.2, 8.6 Hz, MeCH), 2.96 (1H, d, J=4.4 Hz, OH), 3.72 (3H, s, MeO), 4.74 (1H, dd, J=4.4, 8.6 Hz, CHOH), 7.33 (5H, s, Ph). MS m/z: 194 (M^+), 177 $(M-OH)^+$, 163 $(M-MeO)^+$, 121. The ^1H-NMR spectra of **17** and **18** were identical with those reported.[14,18]

3-[(Z)-1-Trimethylsilyloxyprop-1-enyl]-2-oxazolidone (**19a**). Zinc dust was added to a solution of **1a** (25.0 mg, 0.11 mmol) in d_8-THF (0.44 ml) at rt. After stirring for 0.4h at the same temperature, trimethylsilyl chloride (21.5 μl, 0.17 mmol) was added. Insoluble materials were filtered off and the filtrate was subjected to measurement of 400 MHz ^1H-NMR spectrum without further purification. Since the 400MHz ^1H-NMR spectrum showed that the enol silyl ether obviously contains a single isomer, the isomeric purity could be estimated as >97:3. The (*Z*)-configuration was anticipated for **19a** by the mechanistic consideration detailed in the

text. ^{1}H-NMR (400 MHz, d8-THF): 0.22 (9H, s, Me3C), 1.56 (3H, d, J=6.8 Hz, MeCH), 3.68 (2H, m, CH2O), 4.24 (2H, m, CH2N), 4.70 (1H, q, J=6.8 Hz, CH).

4,4-Dimethyl-3-[(Z)-1-trimethylsilyloxyprop-1-enyl]-2-oxazolidone (**19b**). The same treatments of **1b** as described for **1a** gave a solution of **19b** in d8-THF. The isomeric purity and configuration of **19b** could be similarly determined as >97:3 and (*Z*)-form, respectively. ^{1}H-NMR (400MHz, d8-THF): 0.22 (9H, s, Me3C), 1.28 (6H, s, Me2C), 1.60 (3H, d, J=6.8 Hz, MeCH), 3.96 (2H, s, CH2O), 4.68 (1H, q, J=6.8 Hz, CH).

References and Notes

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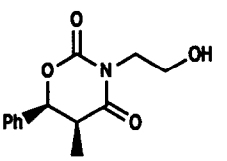
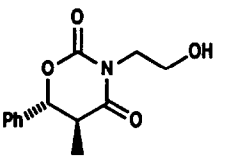
10. For the preparation methods of **1**, see ref. 9.
11. In the Reformatsky reaction of **1a** with **3**, a mixture of the cyclic carbamates (**20** and **21**, **20**:**21**=38:62) was obtained in 83% yield by intramolecular nucleophilic attack of the zinc alkoxide to the carbonyl group of 2-oxazolidone when the reaction temperature was raised to 0°C before work-up.



20



21

The stereochemistries of **20** and **21** could be assigned based on the coupling constants ($J_{5,6}$) observed in the ^{1}H-NMR spectrum of the mixtrure. Thus, 5,6-*trans*-isomer (**21**) showed its benzyl proton at δ 5.16 as a doublet with larger coupling constant ($J_{5,6}$=12.2 Hz), while the *cis*-isomer (**20**) exhibited the corresponding doublet at δ 5.74 with smaller coupling constant (J=4.0 Hz). ^{1}H-NMR (CDCl3): 1.05 (3H, d, J=6.8 Hz, Me), 2.60 (1H, br, OH), 2.8~3.2 (1H, m, MeCH), 3.7~4.3 (4H, m, CH2x2), 5.16 (1Hx0.62, d, J=12.2 Hz, CHPh of **21**), 5.74 (1Hx0.38, d, J=4.0 Hz, CHPh of **20**). This result obviously supported the assigned structures of **6a** and **7a**.

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