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A HIGHLY STEREOSELECTIVE SYNTHESIS OF THE 1β-METHYLCARBAPENEM KEY INTERMEDIATE FROM (*R*)-3-HYDROXYBUTYRIC ACID[1)]

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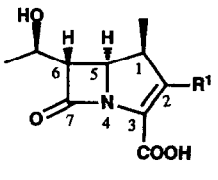
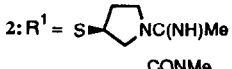
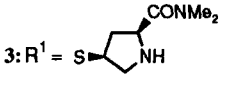
Abstract: *(3R,4R)-4-Acetoxy-3-[(R)-1-(formyloxy)ethyl]-2-azetidinone (6) could be prepared highly stereoselectively from (R)-3-hydroxybutyric acid by employing the [2+2]-cycloaddition reaction of chlorosulfonyl isocyanate with the 2H,4H-1,3-dioxin derivative and the Baeyer-Villiger reaction accompanying novel cleavage of the acetal moiety. The Reformatsky reaction of 6 with sterically crowded 3-(2-bromopropionyl)-2-oxazolidone derivatives readily afforded the title key intermediate after sequential chemical manipulations.*

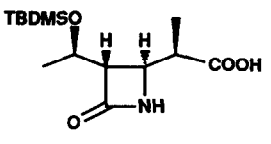
Since the 1β-methylcarbapenem (**1**) was found by a research group at Merck as a synthetic carbapenem antibiotic exhibiting increased chemical and metabolic stability in addition to excellent antibacterial activity and broad spectrum,[3)] a number of synthetic efforts have been devoted to (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (**4**) employed as a key synthetic intermediate of **1**. Following to **1**, the 1β-methylcarbapenems (**2** and **3**) bearing substituted pyrrolidine rings in their C_2-side chains were subsequently reported as carbapenems which show excellent characteristics similar to those of **1**.[4,5)] In the syntheses of **2** and **3**, **4** appeared similarly usable as a key synthetic intermediate.



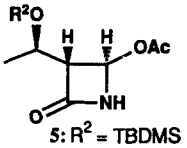
1: R^1 = $SCH_2C(NH)NMe_2$







4



5: R^2 = TBDMS
6: R^2 = HCO
7: R^2 = H

Recently, we succeeded in developing a highly stereoselective synthetic route to **4** by employing the Reformatsky reaction of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**5**) with sterically crowded achiral 3-(2-bromopropionyl)-2-oxazolidone derivatives.[6)] Due to its high β-selectivity, high overall yield, mild reaction conditions, and uses of inexpensive reagents such as zinc dust, the explored synthetic route is anticipated to be one of the most practical methods for preparing **4**. Aiming to further improve efficacy of the Reformatsky route to **4**, another synthetic scheme was sought which would produce **5** or its equivalents more effectively than those reported.[7-9)] We have now found that (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(formyloxy)ethyl]-2-azetidinone (**6**) can be effectively prepared by the [2+2]-cycloaddition reaction of

chlorosulfonyl isocyanate (CSI)[10] with the 2,4-*cis*-disubstituted 2*H*,4*H*-1,3-dioxin derivative (**10**)[11] produced from readily available (*R*)-3-hydroxybutyric acid (**8**).[12,13] The Reformatsky reaction of **6** is found to proceed highly stereoselectively in completely the same manner as reported for **5**, yielding **4** after exchange of protective group followed by usual chemical manipulations.

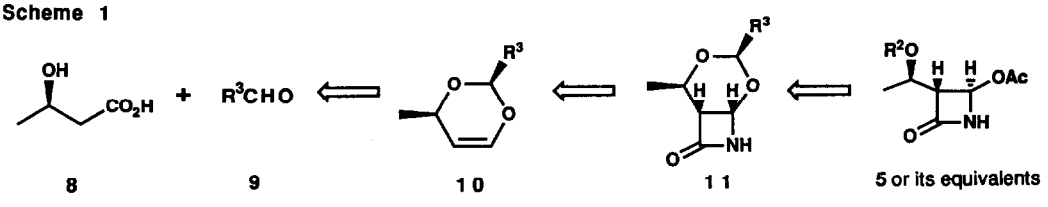
This report details the novel synthesis of **4** from **8** accomplished by the combined use of the [2+2]-cycloaddition reaction of CSI and the Reformatsky reaction of **6**.[1]

1. Synthetic Design

As a novel strategy to produce **5** or its equivalents, we designed the synthetic scheme shown in **Scheme 1**.

Thus, it was envisioned that the bicyclic β-lactam (**11**) could readily afford **5** or its equivalents by opening the 1,3-dioxane moiety followed by addition of an acetate anion to the produced 1,4-dehydro-2-azetidinone and introduction of an appropriate protective group into the (*R*)-1-hydroxyethyl group at the C_3-position. We expected that the [2+2]-cycloaddition reaction of CSI with **10** should proceed in a highly stereoselective manner under an influence of two substituents in the 2*H*,4*H*-1,3-dioxin ring, giving rise to **11** as an almost single diastereomer after cleavage of the initially formed sulfonamide group. It has been well known that CSI reacts with a carbon-carbon double bond to readily afford a β-lactam.[10] Moreover, the synthesis of **5** has been achieved by a Kanegafuchi group by employing the [2+2]-cycloaddition reaction of CSI with an open-chain silyl enol ether.[9e] Condensation of **8** with an appropriate aldehyde (**9**) according to the Seebach's protocol[11] followed by reduction and dehydration would produce **10**.

Scheme 1



8 **9** **10** **11** **5 or its equivalents**

After surveying various structural types of **9**,[13] we found that the use of (*S*)-2-benzyloxypropanal[9f,14] or 2-benzyloxyacetaldehyde[15] could realize the designed synthetic scheme. Among these two sorts of **9**, the former aldehyde was disclosed to be more promising than the latter, yielding **6** effectively. While **6** could be derived to **5** by way of **7**, it was found to undergo the highly stereoselective Reformatsky reaction similar to **5**, producing **4** after sequential chemical manipulations (*vide infra*).

2. Synthesis of (3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-(formyloxy)ethyl]-2-azetidinone (6) from (*R*)-3-Hydroxybutyric acid (8)

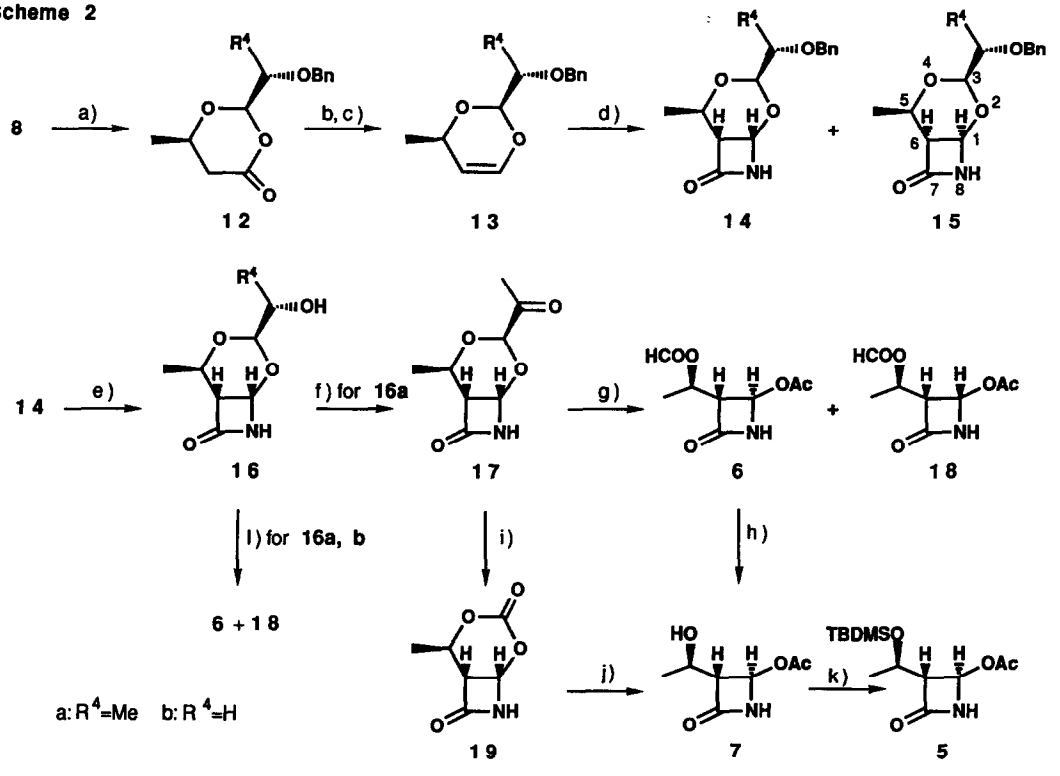
As shown in **Scheme 2**, the explored synthetic route to **6** commences with condensation of **8**[11,12] with (*S*)-2-benzyloxypropanal[9f,14] or 2-benzyloxyacetaldehyde.[15] The condensation reaction proceeded highly stereoselectively in a similar manner to that reported by Seebach,[11] giving rise to the *cis*-1,3-dioxan-4-one derivatives (**12a,b**) in 69% and 89% yields, respectively. The ^{1}H-NMR spectra of **12a,b** obviously disclosed that, while **12b** was contaminated with a minute amount of the undesired *trans*-1,3-dioxan-4-one derivative (*cis*:*trans*=18:1), **12a** solely consisted of the desired *cis*-isomer. Reduction of **12a** with diisobutylaluminium hydride (DIBAL) followed by dehydration by means of thionyl chloride and triethylamine smoothly produced the

2*H*,4*H*-1,3-dioxin derivative (**13a**) in 79% combined yield. While **12b** could be reduced in a similar high yield to that for **12a**, the next dehydration step afforded an only 42% of **13b**.

As expected, treatments of **13a,b** with CSI followed by reductive removals of the *N*-chlorosulfonyl groups produced the bicyclic β-lactams (**14a,b**) as almost sole products both in 59% yields. While a small amount of the undesired bicyclic β-lactam (**15a**) was isolated along with **14a**, the formation of **15b** could not be detected for the reaction with **13b**. The stereochemistries of **14a** and **15a** could be rigorously determined by observing 4.8% of nuclear Overhauser effect (NOE) between the C_5-H and C_6-H in the ^{1}H-NMR spectrum of **15a**.

With **14a,b** in hand, it was first envisioned that **14a,b** can be directly derived to **7** by successive cleavage of the acetal moieties and addition of an acetate anion to the formed C=N bonds when treated with acetic acid in the presence of an acid catalyst. Additionaly, **14a,b** were also expected to be utilized as substrates for the

Scheme 2



a) MeCH(OBn)CHO-PPTS in CH_2Cl_2, 69% for **12a**; BnOCH$_2$CHO-PPTS in CH_2Cl_2, 89% for **12b** (cis:trans=18:1) b) DIBAL in Et_2O, -78 °C, 96% for the a series; 94% for the b series c) $SOCl_2$-Et_3N in CH_2Cl_2, 82% for **13a**; 42% for **13b** d) $ClSO_2NCO$ in PhMe, -55 °C, then, $NaAlH_2(OCH_2CH_2OMe)_2$ in PhMe, -50 °C, 59% for **14a** (**14a**:**15a**>49:1); 59% for **14b** e) H_2-Pd(OH)$_2$ in EtOH, 100% for **16a**; 96% for **16b** f) $RuCl_3$-$NaIO_4$ in CCl_4-MeCN-H_2O, 94% g) MCPBA in AcOH, 86% (**6**:**18**=10:1) or AcOOH-AcONa in AcOH, 83% (**6**:**18**=11:1) h) 30% H_2O_2 (cat.) in AcOH-H_2O, 25% i) MCPBA in AcOEt, 31% j) AcONa in AcOH, 96% k) TBDMSCl-ImH in DMF, 89% l) Pb(OAc)$_4$-$CaCO_3$ in PhH, 47% from **16a** (**6**:**18**=3.5:1); 19% from **16b** (**6**:**18**=3.0:1).

Reformatsky reaction similarly to **5**. However, all attempts to realize these synthetic steps turned out to be fruitless.

After experimentation, it was finally found that **14a,b** could be converted to **6** by the following sequential reactions. Thus, **14a,b** were subjected to hydrogenolysis, affording excellent yields of the alcohols (**16a, b**). Oxidation of **16a** with a combination of ruthenium(III) chloride and hydroperiodic acid readily produced the methyl ketone (**17**) in 94% yield. On the other hand, treatment of **16b** under the same conditions as for **16a** gave the product anticipated to be a carboxylic acid derivative. However, further derivation of this product turned out to be fruitless due to its low solubility.[16] Attempted oxidations of **16b** under the conditions of Swern oxidation[17] and oxidation with pyridinium chlorochromate(PCC)[18] or sulfer trioxide pyridine complex-triethylamine-dimethyl sulfoxide[19] were also found to be unrewarding.

With **17** in hand, elaboration of **17** to **5** or its equivalents by selective opening of the acetal moiety was next studied. After experimentation, it was found that when **17** was treated under the condition of the Baeyer-Villiger reaction using *m*-chloroperbenzoic acid (MCPBA) in acetic acid, a mixture of **6** and its C_4-epimer (**18**) could be directly produced in a ratio of 10:1 and in 86% yield. The ratio of **6** to **18** could be estimated by the ^{1}H-NMR spectrum. Single recrystallization of the mixture from isopropyl ether yielded a pure sample of **6**. In place of MCPBA, a combination of peracetic acid (AcOOH) and sodium acetate also effected the rearrangement, giving a mixture of **6** and **18** in a ratio of 11:1 and in 83% yield. On the other hand, when ethyl acetate was used as a solvent for the reaction with MCPBA in place of acetic acid, the cyclic carbonate (**19**) was found to be produced in 31% yield. Additionally, a mixture of **6** and **18** could be produced by treating **16a,b** with lead tetraacetate and calcium carbonate in a ratio of 3.5:1 or 3.0:1 and in 47% or 19% yield, respectively. Mechanisms of these oxidation reactions will be discussed in the next section (*vide infra*).

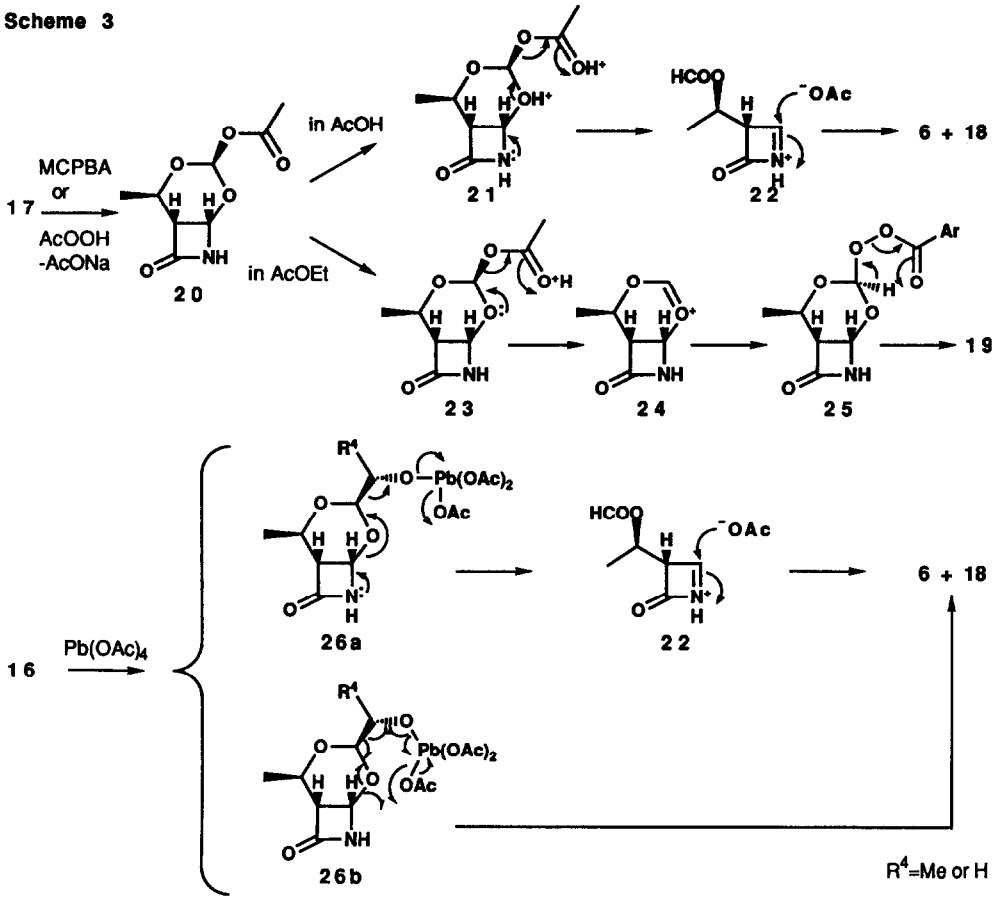
Although **6** was found to be usable for the Reformatsky reaction similarly to **5** (*vide infra*), prepartion of **5** from **6** was next examined by way of **7**. Hydrolysis of **6** under basic conditions resulted in complete decomposition of the β-lactam ring. However, **7** was found to be produced from **6** in 25% yield on treatment with aqueous acetic acid containing a small amount of hydrogen peroxide.[20] The same compound (**7**) could be also prepared from **19** in 96% yield by treating with sodium acetate in acetic acid. Silylation of **7** under the usual conditions furnished **5** in 89% yield. The 4-acetoxy-β-lactam (**5**) was identified with an authentic sample [9f] by spectral comparisions.

3. Mechanisms of the Various Oxidation Reactions

As mentioned above, the unprecedented reaction courses were observed for the oxidations of **16** and **17**. These results might be rationalized by the reaction mechanisms shown in **Scheme 3**.

Thus, treatment of **17** with MCPBA or AcOOH will afford the acetate (**20**) as a usual product of the Baeyer-Villiger reaction. In acetic acid, **20** will be immediately protonated to form the diprotonated species (**21**), which subsequently cleaves the acetal moiety with concomitant loss of an acetic acid as shown by the arrows to produce the immonium ion (**22**). Addition of an acetate anion to **22** from the more favorable direction opposite to bulky (*R*)-1-(formyloxy)ethyl group, gives rise to a mixture of **6** and **18** in a ratio of 10~11:1. On the other hand, the monoprotonated species (**23**) will be gradually produced from **20** in ethyl acetate in which the concentration of proton source is obviously lower than in acetic acid. Removal of an acetic acid from **23** yields the oxonium ion (**24**), to which MCPBA being more nucleophilic than acetic acid adds to

Scheme 3



give the *m*-chloroperbenzoate (**25**). Fragmentation of **25** as shown by the arrows with the loss of *m*-chlorobenzoic acid leads to **19**. The reaction course similar to that from **24** to **19** has been reported for the efficient conversion of a cyclic acetal into a lactone.[21]

The reaction with lead tetraacetate will produce the lead compound (**26**), whose fragmentation as indicated by the arrows (**26a**) yields **22**. Trapping of **22** with an acetate anion being present inside or outside the solvent cage will give a mixture of **6** and **18**. Fragmentation of **26** may also occur by the radical mechanism as shown in **26b**,[22] directly producing a mixture of **6** and **18**. The ratios of **6** to **18** being rather lower than those observed for the reaction with peracid, might be explained by trapping of **22** with the acetate anion derived from **26** in the solvent cage, participation of the radical fragmentation process[22] or both.

4. Synthesis of (3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (4) from (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(formyloxy)ethyl]-2-azetidinone (6)

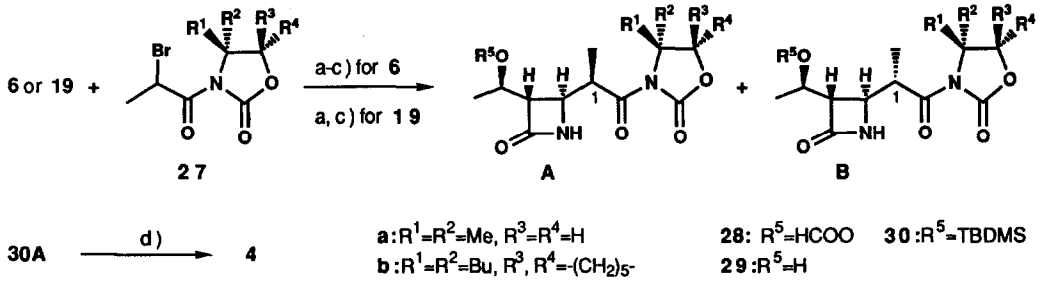
With completion of the synthesis of **6** from **8**, application of the reported Reformatsky reaction[6] was next examined by expecting that **6** can be utilized as a substrate in completely the same manner as that for **5**.

As shown in **Scheme 4**, treatment of **6** with sterically crowded 3-(2-bromopropionyl)-2-oxazolidone derivative (**27a**)[6] in the presence of zinc dust in refluxing tetrahydrofuran afforded the C_4-alkylated products as a mixture of the two diastereomers (**28Aa** and **28Ba**) in 94% yield. The ratio of the desired 1β to the undesired 1α-isomer (**28Aa**:**28Ba**) could be estimated as 5.6:1 by the ^{1}H-NMR spectrum. Similarly, the reaction of **6** with **27b**[6] produced a mixture of **28Ab** and **28Bb** in a ratio of 20:1 and in 97% yield. The ratios of **28Aa,b** to **28Ba,b** were found to be little better than those previously observed for the reactions of **5** with **27a,b** (**30Aa**:**30Ba**=3.8:1 and **30Ab**:**30Bb**=19:1)(*vide infra*).[6]

Without separation, sequential hydrolyses of the mixtures of **28Aa,b** and **28Ba,b** under acidic or basic conditions depending upon the structures of 2-oxazolidone moieties and protections of the formed alcohols (**29Aa,b** and **29Ba,b**) with a *t*-butyldimethylsilyl group gave rise to mixtures of the silyl ethers (**30Aa,b** and **30Ba,b**) in 82% and 90% yields, respectively. The ^{1}H-NMR spectra obviously established that the ratios of **30Aa, b** to **30Ba,b** as 5.6:1 and 23:1, respectively. These compounds (**30Aa,b** and **30Ba,b**) were definitely identified with authentic samples[6] by comparing their ^{1}H-NMR spectra. The major silyl ethers (**30Aa,b**) could be derived to **4** according to the established conditions.[6]

The cyclic carbonate (**19**) was envisioned to be usable for the Reformatsky reactions with **27a,b** similarly to **6** and **7**. However, the reactions of **19** with **27a,b** were found to produce mixtures of **29Aa,b** and **29Ba,b** in the ratios of 2.0:1 and 3.1:1 and in 64% and 70% yields, respectively. Silylations of the mixtures of **29Aa,b** and **29Ba,b** similarly yielded the mixtiures of **30Aa,b** and **30Ba,b** in 72% and 99% yield, respectively, which were identified by comparing their ^{1}H-NMR spectra with those of authentic samples.[6] Accordingly, it appeared evident that **6** is more promising than **19** as a substrate for the Reformatsky reaction. The reason why lower stereoselectivities were observed for the reactions with **19** is quite ambiguous. However, the presence of zinc hemicarbonate group in the C3-substituent of the intermediary 1,4-dehydro-2-azetidinone derivative produced from **19**, might make the transition state leading to **29Aa,b** unstable due to possible dipole-dipole interaction.

Scheme 4



a) Zn in THF, 67 °C, 94% (**28a** from **6**, **28Aa**:**28Ba**=5.6:1), 64% (**29a** from **19**, **29Aa**:**29Ba**=2.0:1), 97% (**28b** from **6**, **28Ab**:**28Bb**=20:1), 70% (**29b** from **19**, **29Ab**:**29Bb**=3.3:1) b) AG50WX2 (acidic form), 89% (**29a** from **28a**, **29Aa**:**29Ba**=5~6:1) or $NaHCO_3$ in H_2O, 95% (**29b** from **28b**, **29Ab**:**29Bb**=19:1) c) TBDMSCl-ImH in DMF, 92% (**30a** from **29a** prepared from **6**, **30Aa**:**30Ba**=5.6:1), 72% (**30a** from **29a** prepared from **19**, **30Aa**:**30Ba**=2:1), 95% (**30b** from **29b** prepared from **6**, **30Ab**:**30Bb**=23:1), 99% (**30b** from **29b** prepared from **19**, **30Ab**:**30Bb**=3.5:1) d) see ref 6.

Conclusions

As mentioned above, we have succeeded in developing a novel synthetic route to **4** from **8** by way of **6** by employing the [2+2]-cycloaddition reaction of CSI, the Baeyer-Villiger reaction accompanying spontaneous cleavage of the acetal moiety, and the Reformatsky reaction. The explored scheme may involve the following merits: 1) use of the readily available starting material (**8**), 2) introduction of a fairly expensive *t*-butyldimethylsilyl group at the later synthetic stage, 3) high stereoselectivities in the formation of the 1,3-dioxan-4-one derivative (**8**→**12**), the β-lactam formation (**13**→**14**), the Baeyer-Villiger reaction (**17**→**6**), and the Reformatsky reaction (**6**→**28**). Taking into account these novel aspects, the overall process may have potential as one of the practical synthetic methods of **4**.

Experimental

General. All melting points were determined with 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) or a Bruker AM spectrometer (400 MHz). All signals were expressed in ppm using tetramethylsilane as an internal standard (δ-value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and broad (br). Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Wakogel C-200 and C-300 were used as an adsorvent for column chromatography. Kieselgel 60F_{254} (Merck) was used for preparative TLC. Unless otherwise noted, all reactions were performed using anhydrous solvents. Tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl were mainly used. The following abbreviations are used for solvents and reagents: acetic acid (AcOH), acetone (Me_2CO), acetonitrile (MeCN), benzene (PhH), carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), chlorosulfonyl isocyanate (CSI), cyclohexane (C_6H_{12}), 1,2-dichloroethane ($ClCH_2CH_2Cl$), dichloromethane (CH_2Cl_2), di-isobutylaluminium hydride (DIBAL), ethanol (EtOH), ether (Et_2O), ethyl acetate (EtOAc), hexane (Hex), isopropyl ether (iPr_2O), *N*,*N*-dimethylformamide (DMF), *m*-chloroperbenzoic acid (MCPBA), methanol (MeOH), peracetic acid (AcOOH), pyridine (Py), pyridium p-toluenesulfonate (PPTS), sodium acetate (AcONa), tetrahydrofuran (THF), thionyl chloride ($SOCl_2$), toluene (PhMe), triethylamine (Et_3N).

(*R*)-3-Hydroxybutyric acid (8) This was prepared from commercially available methyl (*R*)-3-hydroxybutyrate in 87% yield according to the reported procedure.[11,12] bp 130 °C (1 mmHg) and $[\alpha]_D^{20}$ -24.1° (c 4.66, H_2O) [lit.,[11,12a] $[\alpha]_D$-25.2° (c 5, H_2O)]. IR (neat): 3400–2800, 1710, 1400, 1060, 942, 845 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.91 (3H, d, J=6.2 Hz, CH_3), 2.26 (2H, d, J=6.4 Hz, CH_2), 3.2~3.5 (2H, br, OH+COOH), 3.97 (1H, dq, J=6.2 and 6.4 Hz, CH). MS m/z: 105 $(M+1)^+$, 89 $(M-CH_3)^+$, 71, 60.

(2*R*,6*R*)-2-[1-(*S*)-Benzyloxyethyl]-6-methyl-1,3-dioxan-4-one (12a) PPTS (0.829 g, 3.3 mmol) was added to a mixture of **8** (3.52 g, 34 mmol) and (*S*)-2-benzyloxypropanal [9f,14] (3.61 g, 22 mmol) in CH_2Cl_2 (80 ml). The mixture was heated at reflux using a Dean-Stark apparatus to remove the water produced. After being cooled to room temperature, the mixture was diluted with water. The organic layer was separated, washed successively with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chloromatography (Hex-EtOAc 15:1→2:1) to give **12a** as colorless crystals (3.75g, 69%). The ^{1}H-NMR spectrum obviously disclosed that this sample was not contaminated with its undesired (2*S*, 6*R*)-isomer. An analytical sample of **12a** was prepared by recrystallization from iPr_2O, mp 74.5-76 °C and $[\alpha]_D^{20}$ -51.4° (c 1.21, $CHCl_3$). IR (KBr): 3000, 2880, 1750, 1730, 1340, 1258, 1100, 980, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.24 (3H, d, J=6.5 Hz, $\underline{CH_3}$CHOBn), 1.35 (3H, d, J=6.2 Hz, C_6-CH_3), 2.41 (1H, dd, J=10.7 and 17.8 Hz, one of C_5-H), 2.69 (1H, dd, J=4.3 and 17.8 Hz, one of C_5-H), 3.68 (1H, dq, J=3.8 and 6.5 Hz, CHOBn), 4.04 (1H, ddq, J=4.3, 6.2, and 10.7 Hz, C_6-H), 4.67 (2H, s, CH_2Ph), 5.29 (1H, d, J=3.8 Hz, C_2-H), 7.28~7.38 (5H, m, C_6H_5). MS m/z: 251 $(M+1)^+$, 163, 144. Found: C, 67.15; H, 7.17%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

(2*R*,6*R*)-2-(Benzyloxymethyl)-6-methyl-1,3-dioxan-4-one (12b). PPTS (0.250 g, 0.99 mmol) was added to a mixture of **8** (1.11 g, 11 mmol) and benzyloxyacetaldehyde[15] (1.04 g, 6.9 mmol) in CH_2Cl_2 (60 ml). After being heated at reflux for 66 h using a Dean-Stark apparatus to remove the water produced, the mixture was worked up in the same manner as described for the preparation of **12a**, giving **12b** as colorless crystals (1.44 g, 89%) after purification by column chloromatography (Hex-EtOAc 5:1→1:1). The ^{1}H-NMR spectrum obviously showed that this sample was contaminated with a small amount of its (2*S*, 6*R*)-isomer. A representative signal assignable to the (2*S*,6*R*)-isomer is as follows. ^{1}H-NMR ($CDCl_3$): 5.58 (1H, t, J=4.3 Hz, C_2-H). Based on this ^{1}H-NMR spectrum, the ratio of **12b** to its (2*S*, 6*R*)-isomer could be caluculated as 18:1. An analytical sample of **12b** was prepared by recrystallization from iPr_2O, mp 53 °C and $[\alpha]_D^{20}$ -25.2° (c 1.07, $CHCl_3$). IR (KBr): 2980, 2940, 1738,

1320, 1255, 1220, 1102, 760, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.37 (3H, d, J=6.2 Hz, CH_3), 2.44 (1H, dd, J=10.7 and 17.8 Hz, one of C_5-H), 2.69 (1H, dd, J=4.3 and 17.8 Hz, one of C_5-H), 3.65 (1H, dd, J=4.9 and 11.0 Hz, one of CH_2OBn), 3.72 (1H, dd, J=3.8 and 11.0 Hz, one of CH_2OBn), 4.06 (1H, ddq, J=4.3, 6.2, and 10.7 Hz, C_6-H), 4.60 (1H, d, J=12.1 Hz, one of CH_2Ph), 4.65 (1H, d, J=12.1 Hz, one of CH_2Ph), 5.45 (1H, dd, J=3.8 and 4.9 Hz, C_2-H), 7.28~7.38 (5H, m, C_6H_5). MS m/z: 236 $(M)^+$, 130, 115, 107, 91. Found: C, 66.00; H, 6.87%. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%.

(2*R*,4*R*)-2-[1-(*S*)-Benzyloxyethyl]-4-methyl-2*H*,4*H*-1,3-dioxin (13a). a) Prepartion of (2*R*,6*R*)-2-[1-(*S*)-benzyloxyethyl]-6-methyl-1,3-dioxan-4-ol. A solution of DIBAL in Hex (1 M solution, 10.5 ml, 11 mmol) was added to a solution of **12a** (2.21 g, 8.8 mmol) in Et_2O (50 ml) at -60 °C. After stirring for 0.5 h at the same temperature, the mixture was warmed to 0 °C and diluted with aqueous solution of potassium sodium tartarate (0.9 M solution, 40 ml) and Et_2O (40 ml). Stirring was continued until a clear solution was produced (2~4h). The organic layer was washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-Et_2O 4:1→3:1) to give a diastereomeric mixture of (2*R*,6*R*)-2-[1-(*S*)-benzyloxyethyl]-6-methyl-1,3-dioxan-4-ol as a colorless oil (2.14 g, 96%). The ratio of two diastereomers could be calculated as 1:1.1 by the ^{1}H-NMR spectrum described below. IR (KBr): 3500~3000, 2980, 2950, 2890, 1445, 1370, 1100, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (The signals obviously showing the presence of two diastereomers are described) : 1.20, 1.21, 1.22, 1.26 (6H, four d, J=each 6.4, 6.3, 6.5, and 6.2 Hz, $\underline{CH_3}CHOBn$ and C_6-CH_3), 2.89 (0.53H, dd, J=2.0 and 2.3 Hz, OH), 3.24 (0.47H, d, J= 6.7 Hz, OH), 3.73 (0.47H, m, C_6-H), 4.22 (0.53H, m, C_6-H), 4.57 (0.47H, d, J=4.6 Hz, C_2-H), 4.66 (1.06H, s, CH_2Ph), 4.67 (0.94H, s, CH_2Ph), 4.91 (0.47H, ddd, J=2.4, 6.7, and 9.6 Hz, C_4-H), 5.14 (0.53H, d, J=4.6 Hz, C_2-H), 5.42 (0.53H, m, C_4-H), 4.67 (2H, two s, CH_2Ph), 7.3~7.4 (5H, m, C_6H_5). MS m/z: 195, 146, 135, 107, 91.
b) Preparation of **13a**. Et_3N (0.70 ml, 5.0 mmol) and $SOCl_2$ (0.37 ml, 5.1 mmol) were added successively to a solution of (2*R*,6*R*)-2-[1-(*S*)-benzyloxyethyl]-6-methyl-1,3-dioxan-4-ol (1.15 g, 4.6 mmol) in CH_2Cl_2 (16 ml) at 0 °C. After stirring for 1h at room temperature, the mixture was heated at 40 °C, and further amount of Et_3N (0.70 ml, 5.0 mmol) was added. After stirring for 1.5 h at 40 °C, further amount of Et_3N (0.70 ml, 5.0 mmol: total 2.1 ml, 15 mmol) was added to the reaction mixture. After stirring was continued for another 1.5 h, the mixture was cooled to room temperature and diluted with Et_2O and H_2O. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-Et_2O 300:1→50:1) to give **13a** as a yellow oil (871 mg, 82%), $[\alpha]_D^{20}$ -51.9° (c 1.22, $CHCl_3$). IR (film): 2990, 2870, 1640, 1450, 1312, 1220, 730, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.23 (3H, d, J=6.4 Hz, $\underline{CH_3}CHOBn$ or C_4-CH_3), 1.26 (3H, d, J=6.4 Hz, C_4-CH_3, $\underline{CH_3}CHOBn$), 3.62 (1H, dq, J=4.5 and 6.4 Hz, $CH_3\underline{CH}OBn$), 4.52 (1H, m, C_4-H), 4.67 (2H, s, CH_2Ph), 4.78 (1H, dd, J=1.3 and 6.4 Hz, C_5-H), 4.93 (1H, d, J=4.5 Hz, C_2-H), 6.50 (1H, dd, J=1.5 and 6.4 Hz, C_6-H), 7.32 (5H, s, C_6H_5). MS m/z: 234 $(M)^+$, 143 $(M\text{-}Bn)^+$, 135, 91.

(2*R*,4*R*)-2-(Benzyloxymethyl)-4-methyl-2*H*,4*H*-1,3-dioxin (13b). a) Preparation of (2*R*, 6*R*)-2-(benzyloxymethyl)-6-methyl-1,3-dioxan-4-ol. Reduction of **12b** (2.16 g, 9.1 mmol) with DIBAL under the same conditions as described for the preparation of **13a** from **12a** produced a diastereomeric mixture of (2*R*,6*R*)-2-(benzyloxymethyl)-6-methyl-1,3-dioxan-4-ol as a colorless oil (2.04 g, 94 %) after purification by column chromatography (Hex-Et_2O 3:1→1:1). The ratio of two diastereomers could be calculated as 1:1.2 by the ^{1}H-NMR spectrum described below. IR (film): 3600~3300, 2920, 2860, 1445, 1380, 1140, 1100, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$)(The signals obviously showing the persence of two diastereomers are described): 1.22 (1.65H, d, J=6.2 Hz, C_6-CH_3), 1.27 (1.35H, d, J=6.2 Hz, C_6-CH_3), 2.67 (0.55H, dd, J=each 2.5 Hz, OH), 3.02 (0.45H, d, J=6.6 Hz, OH), 3.48 (0.55H, dd, J=5.0 and 10.3 Hz, one of CH_2OBn), 3.53 (0.55H, dd, J=4.2 and 10.3 Hz, one of CH_2OBn), 3.58 (0.90H, d, J=4.5 Hz, one of CH_2OBn). MS m/z: 195 $(M\text{-}57)^+$, 107, 91.
b) Preparation of **13b**. Treatments of (2*R*, 6*R*)-2-(benzyloxymethyl)-6-methyl-1,3-dioxan-4-ol (733 mg, 3.1 mmol) in a similar manner to that described for the preparation of **13a** from **12a** gave **13b** as a colorless oil (287 mg, 42%) after purification by column chromatography (Hex→Hex-Et_2O 80:1), $[\alpha]_D^{20}$ -13.7° (c 1.57, $CHCl_3$). IR (neat): 3090, 3050, 3000, 2880, 1645, 1452, 1220, 1138, 735, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.27 (3H, d, J=6.4 Hz, C_4-CH_3), 3.41 (2H, d, J=4.6 Hz, CH_2OBn), 4.45 ~4.70 (1H, m, C_4-H), 4.62 (2H, s, CH_2Ph), 4.79 (1H, dd, J=1.3 and 6.4 Hz, C_5-H), 5.14 (1H, t, J=4.6 Hz, C_2-H), 6.48 (1H, dd, J=1.5 and 6.4 Hz, C_6-H), 7.31~7.36 (5H, s, C_6H_5). MS m/z: 220 $(M)^+$, 129 $(M\text{-}Bn)^+$, 91.

(1*S*,3*R*,5*R*,6*R*)-8-Aza-3-[1-(*S*)-benzyloxyethyl]-5-methyl-2,4-dioxa-bicylo[4.2.0]octan-7-one (14a) and Its (1*R*,3*R*,5*R*,6*S*)-Isomer (15a). CSI (48 µl, 0.55 mmol) was added to a solution of **13a** (99.4 mg, 0.42 mmol) in PhMe (1.0 ml) at -55° C. After stirring at the same temperature for 3.0 h, the mixture was cooled to -70 °C. A toluene solution of sodium bis(methoxyethoxy)aluminium hydride (2.0 M solution , 0.42 ml, 0.84 mmol) was added to the cooled mixture. The mixture was slowly warmed to -50° C, stirred at the same temperature for 1h, and poured into a mixture of aqueous solution of potassium sodium tartarate (1.1 M solution, 6 ml) and PhMe (3 ml) cooled in an ice bath. After stirring for 0.5 h, the mixture was filtered. The organic layer of the filtrate was washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. Purification of the residue by column chromatography (Hex-Et_2O 4:1→1:1) gave **14a** as colorless crystals (69.7 mg, 59%). Purification by column chromatography also gave **15a** as a colorless caramel (1.4 mg, 1%) from the more polar fraction. An analytical sample of **14a** was prepared by recrystallyzation from Hex-EtOAc, mp 103-103.5 °C and $[\alpha]_D^{20}$ -30.9° (c 1.15, $CHCl_3$). **14a**: IR (KBr): 3200, 1760, 1715, 1380, 1158, 980, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.21 (3H, d, J=6.5 Hz, $\underline{CH_3}CHOBn$), 1.43 (3H, d, J=6.3 Hz,

C_5-CH_3), 2.92 (1H, ddd, J=4.2, 4.6, and 6.3 Hz, C_6-H), 3.56 (1H, dq, J=4.2 and 6.4 Hz, CHOBn), 4.22 (1H, dq, J=each 6.3 Hz, C_5-H), 4.65 (2H, s, CH_2Ph), 4.86 (1H, d, J=4.2 Hz, C_3-H), 5.43 (1H, d, J=4.6 Hz, C_1-H), 6.15 (1H, br, NH), 7.26~7.36 (5H, m, C_6H_5). MS m/z: 278 $(M+1)^+$, 232, 204, 171, 135, 91. Found: C, 64.95; H, 6.99; N, 4.99%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05%. **15a**: IR ($CHCl_3$): 3440, 3000, 2890, 1775, 1140, 1102 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.20 (3H, d, J=6.4 Hz, $\underline{CH_3}$CHOBn), 1.50 (3H, d, J=6.5 Hz, C_5-CH_3), 3.26 (1H, ddd, J=1.7, 4.3, and 4.5 Hz, C_6-H), 3.56 (1H, dq, J=4.2 and 6.4 Hz, CHOBn), 4.06 (1H, dq, J=4.3 and 6.5 Hz, C_5-H), 4.64 (1H, d, J=12.4 Hz, one of CH_2Ph), 4.67 (1H, d, J=12.4Hz, one of CH_2Ph), 4.84 (1H, d, J=4.2 Hz, C_3-H), 5.41 (1H, d, J=4.5 Hz, C_1-H), 6.32 (1H, brs, NH), 7.26~7.38 (5H, m, C_6H_5). In the ^{1}H-NMR spectrum of **15a**, 4.8% NOE was observed between the signals at 3.26 and 4.06 ppm.

(1*S*,3*R*,5*R*,6*R*)-8-Aza-3-(benzyloxymethyl)-5-methyl-2,4-dioxa-bicyclo[4.2.0]octan-7-one (14b). The same treatments of **13b** (280 mg, 1.3 mmol) as described for the preparation of **14a** from **13a** gave **14b** as a colorless oil (196 mg, 59%) after purification by column chromatography (Hex-EtOAc 4:1→2:1), $[\alpha]_D^{20}$ +9.8° (c 1.02, $CHCl_3$). While purification by column chromatography was attempted carefully, formation of the (1*R*,3*R*,5*R*,6*S*)-isomer could not be detected. IR (KBr): 3300, 2990, 2890, 1770, 1380, 1140, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.43 (3H, d, J=6.3 Hz, C_5-CH_3), 2.92 (1H, ddd, J=4.1, 4.6, and 6.3 Hz, C_6-H), 3.53 (1H, dd, J=4.6 and 10.4 Hz, one of CH_2OBn), 3.56 (1H, dd, J=4.6 and 10.4 Hz, one of CH_2OBn), 4.23 (1H, dq, J=each 6.3 Hz, C_5-H), 4.60 (2H, s, CH_2Ph), 5.09 (1H, dd, J=each 4.6 Hz, C_3-H), 5.40 (1H, d, J=4.6 Hz, C_1-H), 6.27 (1H, br, NH), 7.28~7.38 (5H, m, C_6H_5). MS m/z: 264 $(M+1)^+$. 190. 176, 91.

(1*S*,3*R*,5*R*,6*R*)-8-Aza-3-[1-(*S*)-hydroxyethyl]-5-methyl-2,4-dioxa-bicylo[4.2.0]octane-7-one (16a). Twenty percent $Pd(OH)_2$ on carbon (3 mg) was added to a solution of **14a** (13.4 mg, 0.048 mmol) in EtOH (0.5 ml) and the mixture was stirred vigorously at room temperature for 2 h under a hydrogen atmosphere (1 atm). Removal of the catalyst by filtration followed by concentration *in vacuo* gave **16a** as colorless crystals (9.0 mg, quantitative yield). An analytical sample of **16a** was prepared as colorless crystals by recrystallization from Hex-EtOAc, mp 91.5-92 °C and $[\alpha]_D^{20}$ +17.8° (c 1.08, $CHCl_3$). IR (KBr):3450, 3350, 1758, 1380, 1105, 995, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.22 (3H, d, J=6.6 Hz, $\underline{CH_3}$CHOH), 1.43 (3H, d, J=6.2 Hz, C_5-CH_3), 2.08 (1H, d, J=4.6 Hz, $CH_3CH\underline{OH}$), 2.92 (1H, ddd, J=4.2, 4.6, and 6.2 Hz, C_6-H), 3.7~3.9 (1H, m, $CH_3\underline{CH}OH$), 4.24 (1H, dq, J=each 6.2 Hz, C_5-H), 4.72 (1H, d, J=4.6 Hz, C_3-H), 5.45 (1H, d, J=4.6 Hz, C_1-H), 6.16~6.28 (1H, brs, NH). MS m/z: 188 $(M+1)^+$, 142 $(M-CH_3CHOH)^+$, 126, 98. Found: C, 51.20; H, 7.12; N,7.43%. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48%.

(1*S*,3*R*,5*R*,6*R*)-8-Aza-3-(hydrozymethyl)-5-methyl-2,4-dioxa-bicyclo[4.2.0]octan-7-one (16b). The same treatments of **14b** (400 mg, 1.5 mmol) as described for the preparation of **16a** from **14a** gave **16b** as colorless crystals (0.252 g, 96%) after filtration followed by concentration *in vacuo*. An analytical sample was prepared as colorless crystals by recrystallization from Hex-EtOAc, mp 95.5-96 °C and $[\alpha]_D^{20}$ +35.1° (c 1.36, $CHCl_3$). IR (KBr): 3700~3200, 2995, 2890, 1768, 1740, 1380, 1168, 1148, 1058, 1022, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.45(3H, d, J=6.3 Hz, C_5-CH_3), 1.85 (1H, t, J=6.6 Hz, OH), 2.96 (1H, ddd, J=4.2, 4.6, and 6.3 Hz, C_6-H), 3.64 (1H, ddd, J=4.3, 6.6, and 11.8 Hz, one of $\underline{CH_2}OH$), 3.70 (1H, ddd, J=4.3, 6.6, and 11.8 Hz, one of $\underline{CH_2}OH$), 4.27 (1H, dq, J=each 6.3 Hz, C_5-H), 5.00 (1H, t, J=4.3 Hz, C_3-H), 5.44 (1H, d, J=4.6 Hz, C_1-H), 6.23 (1H, br, NH). MS m/z: 142 $(M-CH_2OH)^+$, 130, 69. Found: C, 48.50; H, 6.48; N, 7.82%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09%.

(1*S*,3*R*,5*R*,6*R*)-8-Aza-3-acetyl-5-methyl-2,4-dioxa-bicylo[4.2.0]octan-7-one.(17). $RuCl_3 \cdot nH_2O$ (10 mg, a catalytic amount) and $HIO_4 \cdot 2H_2O$ (820 mg, 3.6 mmol) were added to a solution of **16a** (428 mg, 2.3 mmol) in a mixture of MeCN (5 ml), CCl_4 (5 ml), and H_2O (7.5 ml) at room temperature. After stirring for 1 h at the same temperature, the mixture was extracted with CH_2Cl_2 and the upper aqueous phase was further extracted with a mixture of $CHCl_3$-MeOH (3:1). The organic extracts were combined, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_2$-Me_2CO 1:0→9:1) to give **17** as colorless crystals (400 mg, 94%). An analytical sample was prepared by recrystallization from Hex-EtOAc, mp 86.5-87 °C and $[\alpha]_D^{20}$ +16.9° (c 1.14, $CHCl_3$). IR (KBr): 3200, 3000, 1750, 1735, 1140, 740, cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.48 (3H, d, J=6.4 Hz, C_5-CH_3), 2.26 (3H, s, CH_3CO), 3.00 (1H, ddd, J=4.2, 4.4, 6.4 Hz, C_6-H), 4.32 (1H, dq, J=each 6.4 Hz, C_5-H), 5.06 (1H, s, C_3-H), 5.48 (1H, d, J=4.4 Hz, C_1-H), 6.3~6.6 (1H, br, NH). MS m/z: 186 $(M+1)^+$, 142 $(M-CH_3CO)^+$, 98, 69. Found: C, 51.65; H, 5.98; N, 7.40%. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56%.

(3*R*,4*R*)-4-Acetoxy-3-[1-(*R*)-formyloxyethyl]-2-azetidinone (6) and Its (3*R*,4*S*)-Isomer (18). a) Preparation from **17** 1) MCPBA (80%, 234 mg, 1.1 mmol) was added to a soution of **17** (172 mg, 0.93 mmol) in AcOH (3.5 ml) at 10 °C. After stirring for 2 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 7:3) to give a diastereomeric mixture of **6** and **18** as a colorless solid (162 mg, 86%). The ^{1}H-NMR spectrum of this sample obviously showed the signals corresponding to **18** in addition to those of **6** described below. The signals assignable to **18** are as follows. ^{1}H-NMR ($CDCl_3$):1.49 (3H, d, J=6.4 Hz, $\underline{CH_3}$CH), 2.09 (3H, s, CH_3CO), 3.59 (1H, ddd, J=2.0, 4.2, and 10.0 Hz, C_3-H), 5.57 (1H, m, $CH_3\underline{CH}$), 5.90 (1H, d, J=4.2 Hz, C_4-H), 8.00 (1H, s, HCOO). Based on this ^{1}H-NMR spectrum, the ratio of **6** to **18**

could be calculated as 10:1. Recrystallization of the mixture of **6** and **18** from iPr_2O gave an analytical sample of **6** as colorless crystals, mp 48-48.5 °C, and $[\alpha]_D^{20}$ +123° (c 1.21, $CHCl_3$). IR (KBr): 3300, 1770, 1750, 1720, 1362, 1225, 1172, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.44 (3H, d, J=6.4 Hz, $\underline{CH_3}CH$), 2.13 (3H, s, CH_3CO), 3.38 (1H, d, J=1.2 and 6.5 Hz, C_3-H), 5.38 (1H, dq, J=6.4 and 6.5 Hz, $CH_3\underline{CH}$), 5.80 (1H, d, J=1.2 Hz, C_4-H), 6.59 (1H, brs, NH), 8.04 (1H, s, HCOO). MS m/z: 183 $(M\text{-}CO)^+$, 158 $(M\text{-}CH_3CO)^+$, 142 $(M\text{-}CH_3COO)^+$. Found: C, 47.70; H, 5.53; N, 6.74%. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.69%.
2) A solution of AcOOH in AcOH (10%, 0.30 ml, 0.44 mmol) was added to a solution of **17**(40.7 mg, 0.22 mmol) and AcONa (79.4 mg, 0.97 mmol) in AcOH (0.3 ml) at room temperature. After stirring for 4 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 4:1→3:2) to give a diastereomeric mixture of **6** and **18** (36.9 mg, 83%). The ratio of **6** to **18** was determined as 11:1 by the ^{1}H-NMR spectrum in a similar manner to that described in 1).
b) Preparation from **16** 1) A mixture of **16a** (30.2 mg, 0.16 mmol), $Pb(OAc)_4$, and $CaCO_3$ (126 mg, 1.3 mmol) in PhH (1 ml) was stirred at 80 °C for 4 h. After being cooled, the reaction mixture was filtered to remove insoluble materials. The filtrate was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (Hex-EtOAc 7:3→6:4) to give a diastereomeric mixture of **6** and **18** as an oil (16.4 mg, 47%). The ratio of **6** to **18** was determined as 3.5:1 by the ^{1}H-NMR spectrum in a similar manner to that described in a).
2) Treatment of **16b** (31.6 mg, 0.18 mmol) in the same manner described above gave a diastereomeric mixture of **6** and **18** as an oil (7.5 mg, 19%) after purification by column chromatography. The ^{1}H-NMR spectrum of this sample diclosed that the ratio of **6** to **18** was 3.0:1.

(1*S*,5*R*,6*R*)-8-Aza-5-methyl-2,4-dioxa-bicyclo[4.2.0]octan-3,7-dione (19). MCPBA (80% pure, 151 mg, 0.70 mmol) was added to a solution of **17** (32.4 mg, 0.18 mmol) in AcOEt (0.5 ml) at 0 °C. After stirring for 10 mim at the same temperature, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2-Me_2CO 1:0→9:1) to give **19** as colorless crystals (8.6 mg, 31%). An analytical sample of **19** was prepared by recrystallization from $ClCH_2CH_2Cl$, mp 127-127.5 °C and $[\alpha]_D^{20}$ -140 ° (c 1.02, AcOEt). IR (KBr) : 3270, 3200, 1775, 1740, 1400, 1200, 1080, 1000, 600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.54 (3H, d, J=6.9 Hz, C_5-CH_3), 3.50 (1H,ddd, J=1.7, 2.3, and 4.4 Hz, C_6-H), 4.92 (1H, dq, J=1.7 and 6.9 Hz, C_5-H), 5.80 (1H, d, J=4.4 Hz, C_1-H), 6.7-7.0 (1H, br, NH). MS m/z: 158 $(M+1)^+$, 113 $(M\text{-}CO_2)^+$, 98, 69. Found: C, 45.79; H, 4.36; N, 8.90%. Calcd for $C_6H_7NO_4$: C, 45.87; H, 4.49; N, 8.91%.

(3*R*,4*R*)-4-Acetoxy-3-[1-(*R*)-hydroxyethyl]-2-azetizinone (7). a) Preparation from **6**. A mixture of **6** (12.8 mg, 0.064 mmol), 30% H_2O_2 (1 drop, a catalytic amount), and H_2O (0.1 ml) in AcOH (0.5 ml) was stirred overnight at 60 °C, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 2:3→3:7) to afford **7** as a colorless solid (2.8 mg, 25%). The ^{1}H-NMR spectrum of this sample was identified with that described in b).
b) Preparation from **19**. A mixture of **19** (48.6 mg, 0.31 mmol), AcONa (127 mg, 1.6 mmol) in AcOH (1 ml) was stirred overnight at room temperature, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAct 2:3→3:7) to give **7** as colorless crystals (51.6 mg, 96%), mp 113-114 °C and $[\alpha]_D^{20}$ +78.0° (c 1.07, MeOH). IR (KBr): 3500, 3250, 3000, 1750, 1725, 1241, 991, 699 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, d, J=6.4 Hz, $\underline{CH_3}CH$), 2.10 (1H, d, J=3.5 Hz, OH), 2.12 (3H, s, CH_3CO), 3.22 (1H, dd, J=1.3 and 5.9 Hz, C_3-H), 4.19 (1H, m, $CH_3\underline{CH}$), 5.81 (1H, d, J=1.3 Hz, C_4-H), 6.45 (1H, brs, NH). MS m/z: 174 $(M+1)^+$, 130 $(M\text{-}CH_3CO)^+$, 115, 87. Found: C, 48.42; H, 6.39; N, 8.00%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09%.

(3*R*, 4*R*)-4-Acetoxy-3-[1-(*R*)-(t-butyldimethylsilyloxy)ethyl]-2-azetizinone (5). A mixture of **7** (51.6 mg, 0.30 mmol), *t*-butyldimethylchlorosilane (117 mg, 0.78 mmol), and imidazole (71.0 mg, 1.0 mmol) in DMF (1 ml) was stirred overnight at room temperature. The mixture was diluted with H_2O and extracted with AcOEt. The extracts were combined, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 7:1) to give **5** as colorless crystals (76 mg, 89%), mp 107-107.5 °C [*lit.*,[9f] mp 108-109 °C] and $[\alpha]_D^{20}$ +45.1 ° (c 1.07, $CHCl_3$) [*lit.*, [9f]] $[\alpha]_D^{20}$ +47.8 ° (c 0.56, $CHCl_3$)]. The IR and ^{1}H-NMR spectra of this sample were identical with those reported.[9f]

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (30Aa) and Its 4-[(*S*)-1-(4,4-dimethyl-oxazolidone-3-carbonyl)ethyl]-Isomer (30Ba). a) Preparation from **6**. A solution of 3-(2-bromopropionyl)-4,4-dimethyl-2-oxazolidone [6](238 mg, 0.95 mmol) in THF (1.6 ml) was added to a refluxing suspension of Zn dust (187 mg, 2.9 mmol) and **6** (84.8 mg, 0.42 mmol) in THF (1 ml). After stirring under reflux was continued for 2 min, the reaction mixture was cooled to room temperature and diluted with aqueous phosphonate buffer (pH 7) and EtOAc. The organic layer was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 4:1→1:1) to give (3*S*,4*R*)-3-[(*R*)-1-formyloxyethyl]-4-[(*R*)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (**28Aa**) and its 4-[(*S*)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl) ethyl]-isomer (**28Ba**) as a colorless caramel (124 mg, 94%). IR (film): 3300, 2990, 2945, 1780~1690, 1450, 760, 698 cm^{-1}. Principal signals are shown for the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): 1.20 [3H, d, J=6.9 Hz, $\underline{CH_3}CHCO$ (**28Aa**)], 1.23 [3H, d, J=6.5 Hz, $\underline{CH_3}CHCO$ (**28Ba**)], 1.42 [3H, d, J=6.4 Hz, $\underline{CH_3}CHO$, (**28Aa**)], 1.44 [3H, d, J=6.3 Hz, $\underline{CH_3}CHO$, (**28Ba**)],

1.55 [3H, s, $\underline{CH_3}CCH_3$ (**28Ba**)], 1.56 [3H, s, $\underline{CH_3}CCH_3$ (**28Aa**)], 1.57 [3H, s, $CH_3C\underline{CH_3}$ (**28Aa**)], 1.57 [3H, s, $CH_3C\underline{CH_3}$ (**28Ba**)], 3.05 [1H, dd, J=1.8 and 8.0 Hz, C_3-H (**28Ba**)], 3.22 [1H, dd, J=2.2 and 7.5 Hz, C_3-H (**28Aa**)], 3.76 [1H, m, C_4-H (**28Ba**)],3.81 [1H, dd, J=2.2 and 4.9 Hz, C_4-H (**28Aa**)], 6.01 [1H, brs, NH (**28Ba**)],6.08 [1H, brs, NH (**28Aa**)], 8.03 [1H, s, HCOO (**28Aa**)], 8.04 [1H, s, HCOO (**28Ba**)]. Based on the intensity of signals at 3.05 and 3.22 ppm, the ratio of **28Aa** to **28Ba** could be calculated as 5.7:1. MS m/z: 313 $(M+1)^+$, 239, 223. Without separation, the mixture of **28Aa** and **28Ba** (227 mg, 0.73 mmol) was dissolved in MeOH (1 ml). Ion-exchange rasin (AG50X-W2) (30 mg) was added to the methanolic solution and the mixture was stirred for 4 h at room temperature. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 1:3→1:4) to give (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-[(*R*)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl)ethyl]-2-azetidinone (**29Aa**) and its 4-[(*S*)-1-(4,4-dimethyl-2-oxazolidone-3-carbonyl)ethyl]-isomer (**29Ba**) as a colorless caramel (184 mg, 89%). IR (film): 3600~3200, 1780-1740, 1700, 1380, 1305, 1178, 1095, 1040, 762 cm^{-1}. Principal signals are shown for the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): 1.24 [3H, d, J=6.9 Hz, $\underline{CH_3}CHCO$ (**29Aa**)], 1.26 [3H, d, J=6.7 Hz, $\underline{CH_3}CHCO$ (**29Ba**)], 1.32 [3H, d, J=6.3 Hz, $\underline{CH_3}CHO$ (**29Aa**)], 1.35 [3H, d, J=6.4 Hz, $\underline{CH_3}CHO$ (**29Ba**)], 1.56 [3H, s, CCH_3 (**29Aa**)], 1.56 [3H, s, $\underline{CH_3}CCH_3$ (**29Ba**)], 1.58 [3H, s, $CH_3C\underline{CH_3}$ (**29Aa**)], 1.58 [3H, s, $CH_3C\underline{CH_3}$ (**29Ba**)], 2.32 [1H, d, J=4.5 Hz, OH (**29Ba**)], 2.36 [1H, d, J=3.8 Hz, OH (**29Aa**)], 2.95 [1H, dd, J=1.9 and 6.9 Hz, C_3-H (**29Ba**)], 2.98 [1H, dd, J=2.2 and 6.9 Hz, C_3-H (**29Aa**)], 3.84 [1H, dd, J=1.9 and 4.1 Hz, C_4-H (**29Ba**)], 3.85 [1H, dd, J=2.2 and 6.0 Hz, C_4-H (**29Aa**)], 5.90 [1H, brs, NH (**29Ba**)], 6.02 [1H, brs, NH (**28Aa**)]. Based on the intensity of signals at 2.32 and 2.36 ppm, the ratio of **29Aa** to **29Ba** could be roughly estimated as 5:1~6:1. Without separation, the mixture of **29Aa** and **29Ba** (64.1 mg, 0.23 mmol) was dissolved in DMF (0.2 ml). Imidazole (27.8 mg, 0.41 mmol) and *t*-butyldimethylchlorosilane (49.9 mg, 0.32 mmol) were added to the DMF solution. The mixture was stirred at room temperature and diluted with H_2O and EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 9:1→3:1) to give a mixture of **30Aa** and **30Ba** as colorless crystals (82.9 mg, 92%). Comparision of the ^{1}H-NMR spectrum of this sample with those of authentic samples of **30Aa** and **30Ba** [6] clearly showed that the intensity ratio of signals at 3.01 and 2.81 ppm (C_3-H) was 5.6:1. Accordingly, the ratio of **30Aa** to **30Ba** could be calculated as 5.6:1.

b) Preparation from **19** Treatments of **19** (31.0 mg, 0.47 mmol) in a similar manner to that described in a) produced a mixture of **29Aa** and **29Ba** as a colorless caramel (13.9 mg, 64%) after purification by column chromatography. Without determining the ratio of **29Aa** to **29Ba**, the mixture was subjected to silylation under the same conditions as described in a), giving a mixture of **30Aa** and **30Ba** as colorless crystals (14.0 mg, 72%) after purification by column chromatography. The ratio of **30Aa** to **30Ba** was determined as 2.0:1 in a similar manner to that described in a).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl)ethyl]-2-azetizinone (30Ab) and its 4-[(*S*)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl)ethyl]-isomer (30Bb). a) Preparation from **6**. A solution of 3-(2-bromopropionyl)-4,4-dibutyl-5,5-pentamethylene-2-oxazolidone[6] (329 mg, 0.82 mmol) in THF (2.3 ml) was added to a refluxing suspension of Zn dust (185 mg, 2.8 mmol) and **6** (73.5 mg, 0.37 mmol) in THF (1 ml). After stirring was continued under reflux for 2 min, the mixture was cooled to room temperature and diluted with aqueous phosphate buffer (pH 7) and EtOAc. The organic layer was separated, washed with saturated NaCl, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 9:1→2:1) to give (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-[(*R*)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl]ethyl]-2-azetidinone (**28Ab**) and its 4-[(*S*)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl)ethyl]-isomer (**28Bb**) as a colorless caramel (164 mg, 97%). IR (film): 3280, 2945, 2865, 1760, 1720, 1700, 1442, 1378, 768 cm^{-1}. Principal signals are described for the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): 0.91 [6H, two t, J=each 7.0 Hz, $\underline{CH_3}CH_2CH_2CH_2$x2 (**28Ab**)], 1.21 [3H, d, J=6.9 Hz, $\underline{CH_3}CHCO$ (**28Ab**)], 1.42 [3H, d, J=6.3 Hz, $\underline{CH}CHO$ (**28Ab**)], 3.04 [1H, dd, J=2.3 and 7.7 Hz, C_3-H (**28Bb**)], 3.27 [1H, dd, J=2.2 and 7.6 Hz, C_3-H (**28Ab**)], 3.81 [1H, dd, J=2.2 and 5.1 Hz, C_4-H (**28Ab**)], 4.08 [1H, dq, J=5.1 and 6.9 Hz, $CH_3\underline{CH}CO$ (**28Ab**)], 5.36 [1H, dq, J=6.3 and 7.6 Hz, $CH_3\underline{CH}O$ (**28Ab**)], 6.02 [1H, brs, NH (**28Ab**)], 8.02 [1H, s, HCOO (**28Ab**)]. Based on the intensity of signals at 3.04 and 3.27 ppm, the ratio of **28Ab** to **28Bb** could be calculated as 19:1. MS m/z: 465 $(M+1)^+$, 436 $(M-CO)^+$, 418, 376, 210. Without separation, the mixture of **28Ab** and **28Bb** (154 mg, 0.31 mmol) was dissolved in MeOH (2 ml). After addition of saturated $NaHCO_3$ (2 drops), the mixture was stirred at room temperature for 1 h, and extracted with EtOAc. The organic extracts were combined, dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (Hex-EtOAc 7:3→1:1) to give (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-[(*R*)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl)ethyl]-2-azetizinone (**29Ba**) and its 4-[(*S*)-1-(4,4-dibutyl-5,5-pentamethylene-2-oxazolidone-3-carbonyl) ethyl]-isomer (**29Bb**) as a colorless caramel (130 mg, 95%). IR (film): 2960, 2890, 1762, 1700, 1372, 1275, 1238, 1041 cm^{-1}. Principal signals are described for the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): 0.91 [3H, t, J=7.1 Hz, $\underline{CH_3}CH_2CH_2CH_2$ (**29Ab**)], 0.91[3H, t, J=7.1 Hz, $\underline{CH_3}CH_2CH_2CH_2$ (**29Ab**)] 1.26 [3H, d, J=7.0 Hz, $\underline{CH_3}CHCO$ (**29Ab**)], 1.32 [3H, d, J=6.3 Hz, $\underline{CH_3}CHO$ (**29Ab**)], 2.27 [1H, d, J=3.9 Hz, OH (**29Ab**)], 2.94 [1H, dd, J=2.0 and 6.9 Hz, C_3-H (**29Bb**)], 2.99 [1H, dd, J=2.1 and 7.0 Hz, C_3-H (**29Ab**)], 3.83 [1H, dd, J=2.1 and 6.0 Hz, C_4-H (**29Ab**)], 4.04 [1H, dq, J=6.0 and 7.0 Hz, $CH_3\underline{CH}CO$ (**29Ab**)], 4.14 [1H, m, $CH_3\underline{CH}O$ (**29Ab**)], 5.93 [1H, brs, NH (**29Ab**)]. Based on the intensity of signals at 2.94 and 2.99 ppm, the ratio of **29Ab** to **29Bb** could be estimated as 19:1. Without separation, the mixture of **29Ab** and **29Bb** (118 mg, 0.27 mmol) was subjected to silylation similarly to that of **29Aa** and **29Ba** , giving a mixture of **30Ab** and **30Bb** as a colorless caramel (142 mg, 95%) after purification by column chromatography (Hex-EtOAc 7:1). Comparision of the ^{1}H-NMR spectrum of this sample with those of

authentic samples of **30Ab** and **30Bb**,[6] clearly showed that the intensity ratio of signals at 3.04 and 2.81 ppm (C_3-H) was 23:1. Accordingly, the ratio of **30Ab** to **30Bb** could be calculated as 23:1.

b) Preparation from **19**. Treatments of **19** (28.7 mg, 0.44 mmol) in a similar manner to that described in a) afforded a mixture of **29Ab** and **29Bb** as a colorless caramel (21.8 mg, 70%) after purification by column chromatography (Hex-EtOAc 7:3→6:4→1:1). The ratio of **29Ab** to **29Bb** could be determined as 3.3:1 in the same manner as described in a). Without separation, the mixture of **29Ab** and **29Bb** was silylated in a similar manner to that described in a), giving a mixture of **30Ab** and **30Bb** as a colorless caramel (21.3 mg, 99%) after purification by column chromatography (Hex-EtOAc 7:1). The ratio of **30Ab** to **30Bb** was determined as 3.5:1 by the same manner as described in a).

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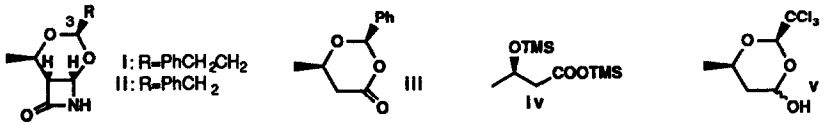
13) In addition to (*S*)-2-benzyloxypropanal and 2-benzyloxyacetaldehyde, the uses of 3-phenylpropanal, 2-phenylacetaldehyde, benzaldehyde, and chloral as an aldehyde derivative were studied. Thus, the bicyclic β-lactams (i and ii) corresponding to **14** could be prepared from 3-phenylpropanal and 2-phenylacetaldehyde, respectively, by employing the same procedures as that described in the text. However, being different from **14**, they could not be elaborated to **5** or its equivalents due to the lack of oxygen atom in the C_3-substituents. Reduction of the 1,3-dioxan-4-one derivative (iii) obtained from the bis-silylated derivative (iv) of **8** and benzaldehyde also turned out to be fruitless. While the 1,3-dioxan-4-ol (v) could be synthesized from **8** and chloral, its dehydrogenation was found to be unsuccessful. Kobayashi, Y.; Ito, Y.; Terashima, S. unpublished results.



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