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NOVEL SYNTHESES OF THE CARBAPENEM KEY INTERMEDIATES, (3*R*,4*R*)-4-ACETOXY-3-[(*R*)-1-(*t*-BUTYLDIMETHYLSILYLOXY)ETHYL]-2-AZETIDINONE AND (3*S*,4*R*)-3-[(*R*)-1-(*t*-BUTYLDIMETHYLSILYLOXY)ETHYL]-4-CARBOXYMETHYL-2-AZETIDINONE, FROM (*S*)-ETHYL LACTATE[1)]

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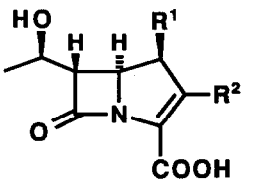
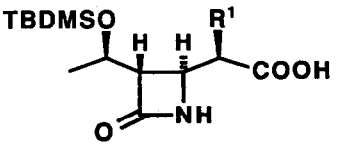
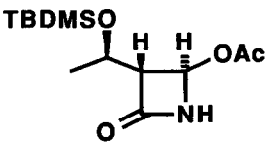
Abstract: *Two types of the carbapenem key intermediates (**4** and **6**) have been efficiently synthesized from inexpensive (S)-ethyl lactate (**7**). Thus, (S)-2-benzyloxypropanal readily obtainable from **7** was condensed with di-p-anisylmethylamine to give the chiral imine. The [2+2]-cycloaddition reaction of diketene with the imine underwent in a highly stereoselective manner, yielding the desired 3,4-trans-3-acetyl-β-lactam (**13a**) as a major product (diastereoselectivity 7~10:1). This was elaborated to **4** and **6** in 9 and 6 steps, respectively.*

The carbapenem antibiotics represented by thienamycin (**1**), have been the focus of recent synthetic attention because these novel compounds exhibit prominent antibacterial activities, broad spectra, and high resistance to bacterial β-lactamases together with unique framework, specifically the 1-carbapen-2-em nucleus, and 6-(1-hydroxyethyl) substituent in place of the traditional amide functionality.[2)] In several syntheses of these novel antibiotics so far reported,[3)] the latter title compound, (3*S*,4*R*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-carboxymethyl-2-azetidinone (**4**), or its equivalents have ingeniously been employed as key synthetic intermediates[4)] in the synthesis of **1** and various novel synthetic routes to these important compounds have hitherto been explored.[5)] The former title compound, (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**6**),[6)] holds more pivotal position than **4** as one of the most versatile carbapenem key intermediates since various types of carbon chains required to construct the five-membered ring fused with β-lactam, can be readily introduced into **6** by substituting its acetoxy group with nucleophiles.[5b,c,7)] The same synthetic strategy has recently



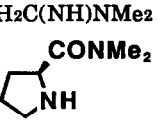




1: R^1=H, R^2=$SCH_2CH_2NH_2$

2: R^1=Me, R^2=$SCH_2C(NH)NMe_2$

3: R^1=Me, R^2=



4: R^1=H

5: R^1=Me

6

been applied for producing the key intermediate (**5**)[8] of 1β-methylcarbapenem such as **2**[9] and **3**,[10] chemically and metabolically more stable carbapenems exhibiting excellent antibacterial activities. It has also been uncovered that various penem compounds can be elaborated from **6** by substituting its acetoxy group with thiol derivatives.[11] As the usefulness of **6** as a raw material in industries as well as in laboratories turns out to be apparent, a number of synthetic methods of **6** have hitherto been explored by employing various chiral compounds as starting materials.[5f,12]

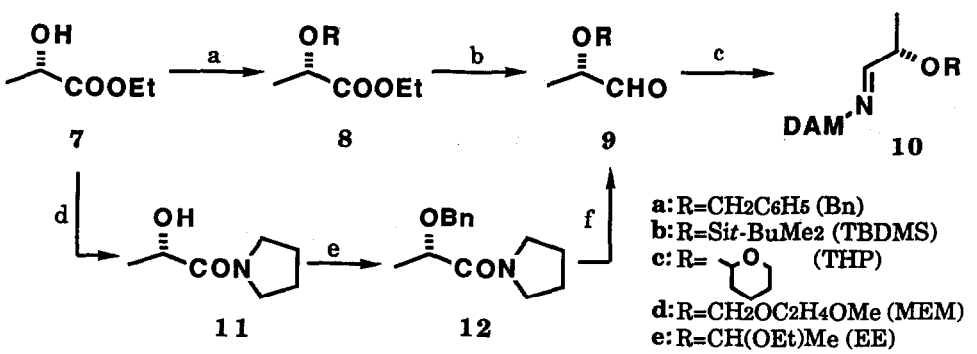
Recently, we have also succeeded in exploring novel synthetic routes to **4** and **6** in which the stereoselective addition of diketene to the optically active imine (**10**) readily obtainable from commercially available inexpensive (*S*)-ethyl lactate (**7**), plays a key role to construct the chiral 3,4-*trans*-3-acetyl-β-lactam (**13**) bearing the desired absolute stereochemistry.[1]

It was recently disclosed that the addition reactions of diketene with imines derived from aromatic aldehydes[13] or alkyl glyoxylates,[14] can proceed in a stereoselective manner to afford 3,4-*trans*-3-acetyl-β-lactams. However, this novel β-lactam formation being formally a [2+2]-cycloaddition reaction of acetylketene presumably produced from diketene, has never been examined with the imine prepared from an optically active aliphatic aldehyde carrying a chiral center at the α-position.[15] We have now found that the absolute stereochemistry of 3,4-*trans*-3-acetyl-β-lactam can be effectively controlled by the adjacent chiral center, and that the highly optically active 3,4-*trans*-3-acetyl-β-lactam (**13a**) can be readily elaborated to **4** and **6**. This report concerns with full details of the novel syntheses of **4** and **6**.

The [2+2]-Cycloaddition Reaction of Diketene with the Chiral Imine (10) Prepared from (*S*)-Ethyl Lactate

As shown in **Scheme 1**, the explored synthetic scheme commences with protection of the hydroxy group of **7**. Thus, after conversion of **7** into the corresponding benzyl ether (**8a**) by treating with *O*-benzyl trichloroacetimidate in the presence of a catalytic amount of trifluoromethanesulfonic acid,[16,17] the ester group of **8a** was effectively reduced with diisobutylaluminium hydride to afford (*S*)-2-benzyloxypropanal (**9a**). Since studies on the [2+2]-cyclo-

Scheme 1

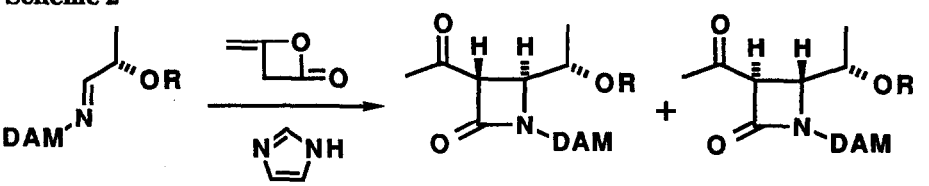


a) $CCl_3C(NH)OBn$-TfOH, 69%; TBDMSCl-imidazole, 96%; DHP-PPTS, 72%; MEMCl-$(Me_2CH)_2NEt$, 59%; $EtOCHCH_2$-TsOH, 91% b) DIBAL in ether, -78 °C, 82% (**9a**); 76% (**9b**); 81% (**9c**); 78% (**9d**); 82% (**9e**) c) DAM-NH_2-$MgSO_4$ in toluene, see text for the yield d) pyrrolidine, 95% e) BnCl-NaH, 87% or BnCl-NaOH-$(C_8H_{17})_3MeNCl$, 92% f) $NaAl(OCH_2CH_2OMe)_2H_2$ in toluene, 88%

addition reaction disclosed that the benzyl group is most favorable with respect to stereoselectivity of the addition reaction (*vide infra*), more economical synthetic method was sought which could afford **9a** without use of expensive *O*-benzyl trichloroacetimidate. After numerous experimentations, it was finally found that (*S*)-*N,N*-tetramethylenelactamide (**11**) readily obtainable by heating **7** with pyrrolidine, could be derived to the corresponding benzyl ether (**12**) by treating with benzyl chloride and sodium hydride or with benzyl chloride and sodium hydroxide under usual phase transfer conditions. These methods of benzylation are clearly more inexpensive than the previous reaction. Reduction of the amide group of **12** was achieved with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®),[18] giving rise to **9a**.

Treatment of **9a** with di-*p*-anisylmethylamine (DAM-NH_2)[19] in the presence of magnesium sulfate as a dehydrating agent produced the chiral imine (**10a**), which was immediately sub-

Scheme 2



10 **13** **14**

Table 1. The [2+2]-cycloaddition reaction of the chiral imine (10) with diketene[a]

Run	Imine	R	Solvent	Yield (%)[b]	Ratio of **13** to **14**[c]
1	**10a**	Bn	THF	78	8.0:1
2			CH_2Cl_2	91	7.3:1
3[d]			CH_2Cl_2	79	5.3:1
4			CH_2Cl_2-*t*BuOH[e]	79	4.9:1
5			DMF	28[f]	1.3:1
6			MeCN	67[f]	10.0:1
7			Et_2O	24[f]	3.5:1
8			MeC_6H_5	21[f]	7.0:1
9	**10b**	TBDMS	THF	58	2.1:1
10			CH_2Cl_2	68	5.4:1
11	**10c**	THP	THF	82	2.4:1[g]
12			CH_2Cl_2	71	6.0:1[g]
13	**10d**	MEM	CH_2Cl_2	87	6.0:1
14	**10e**	EE	THF	76	3.0:1[g]

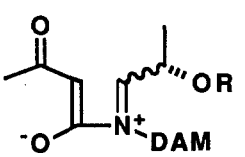
a) The reaction was performed at -35 °C for 3 days with 4~5 equivalents of diketene and 1 equivalent of imidazole when otherwise not mentioned. b) Combined yield of **13** and **14** calculated based on **9**. c) Determined by the ^{1}H-NMR spectrum of the mixture of **13** and **14** when otherwise not mentioned. d) 4-Methylimidazole was used instead of imidazole. e) Ratio of CH_2Cl_2 to *t*-BuOH was 10:1. f) The reaction was quenched after 1 day. g) The ratio was determined by the ^{1}H-NMR spectrum after the mixture of **13** and **14** was derived to that of **16f** and **17f**. See text.

jected to the next [2+2]-cycloaddition reaction (**Scheme 2**). Taking into account the previous results,[14,20] DAM-NH_2 was selected as an amine counterpart for the imine formation. Addition of diketene to **10a** which constitutes the key stereoselective reaction of our synthetic route to **4** and **6** was first examined in tetrahydrofuran (THF) in the presence of 1 equivalent of imidazole. As shown in **Table 1** (run 1), a mixture of the 3,4-*trans*-3-acetyl-β-lactams (**13a** and **14a**) could be produced in 78% yield.[21] The stereoselectivity of the [2+2]-cycloaddition reaction was determined as 8.0:1 by integrating the acetyl protons which appeared as two singlets in the ^{1}H-NMR spectrum of the mixture of **13a** and **14a**. The major isomer (**13a**) isolated as an oil by separating the mixture of **13a** and **14a** with column chromatography, showed $[\alpha]_D^{20}$ -7.3° ($CHCl_3$). The enantiomeric excess of **13a** was estimated to be 96%ee by the ^{1}H-NMR spectrum measured in the presence of the chiral shift reagent, [Eu(hfc)$_3$].[22] Successful preparations of **4** and **6** (*vide infra*) obviously established the absolute stereochemistry of **13a**. By repeating the same [2+2]-cycloaddition reactions in various solvents (runs 2,4~8), it appeared evident that dichloromethane (CH_2Cl_2) is the solvent of choice with respect to the chemical yield and stereoselectivity (run 2). The use of 4-methylimidazole in place of imidazole was ineffective for improving the stereoselectivity and chemical yield of the [2+2]-cycloaddition reaction (run 3). This result distinctly differs from that previously observed for the synthesis of **5** by the [2+2]-cycloaddition of ketene with a chiral imine.[20]

In order to evaluate the effect of protective group on the stereoselectivity and chemical yield, the [2+2]-cycloaddition reactions were further examined employing various types of the imines (**10b~e**) which carry different protective groups. The requisite aldehydes (**9b~e**) could be prepared by way of **8b~e** by sequential protection and reduction. The [2+2]-cycloaddition reactions were attempted in THF or CH_2Cl_2 with **10b~e** similarly produced from **9b~e** and DAM-NH_2. As summarized in **Table 1**, it appeared obvious that exchanges of the protective groups from benzyl to other groups resulted in the decrease of stereoselectivity in the reactions in THF (runs 9,11 and 14) while the high stereoselectivity similar to that observed for **10a** could be recorded in the reactions in CH_2Cl_2 (runs 10, 12 and 13).

Based on the extensive studies described above, we have succeeded in firmly establishing the structure of imine and the reaction conditions which can afford the best result of the [2+2]-cycloaddition reaction. Thus, the reaction performed with diketene (5 equivalents) and **10a** in CH_2Cl_2 at -35°C for 3 days successfully produced a mixture of **13a** and **14a** in a ratio of 7.3:1 and in 91% combined yield (run 2). While **13a** and **14a** were separable by column chromatography, the diastereomers formed at this stage could be nicely separated by recrystallization after the stereoselective reduction of the 3-acetyl group to the 3-[(*R*)-1-hydroxyethyl] group (*vide infra*).

It is quite ambiguous whether the true reactant of the [2+2]-cycloaddition reaction is diketene, acetylketene, or 1-(acetoacetyl)-imidazole. However, since stereoselectivity and chemical yield of the reaction highly depend upon polarity of solvent, it may be reasonable to expect that the [2+2]-cycloaddition reaction proceeds through the zwitter-ionic intermediate such as **15** as previously claimed.[15b,23] While the reaction mechanism is still unclear, it is of interest that the methyl and alkoxy groups of **15** can effectively control stereoselectivity of the reaction even though difference of their steric bulkiness is not large enough.



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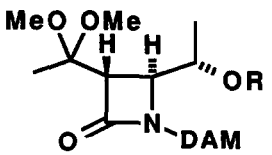
Determination of the Stereochemistry of the [2+2]-Cycloaddition Products

In the explored [2+2]-cycloaddition reaction, the two diastereomeric 3,4-*trans*-3-acetyl-β-lactams (**13** and **14**) were regularly produced. While the absolute stereochemistries of **13a** and **14a** could be firmly established by the successful transformations of **13a** into **4** and **6** (*vide infra*), the absolute stereochemistries of other cycloaddition products (**13b~e** and **14b~e**) were determined by chemical correlations.

Thus, the diastereomeric 3,4-*trans*-3-acetyl-β-lactams (**13a** and **14a**) were first subjected to acetalization with trimethyl orthoformate in the presence of a catalytic amount of camphorsufonic acid, producing the dimethyl acetals (**16a** and **17a**), respectively. Under the same conditions as applied to **13a** and **14a**, **13b** and **14b** were directly transformed to the dimethyl acetals (**16f** and **17f**), respectively, with concomitant cleavage of the *t*-butyldimethylsilyloxy group. The diastereomeric mixture of **13c** and **14c** and that of **13e** and **14e** were similarly derived to the diastereomeric mixture of **16f** and **17f** without change of the diastereomeric ratios. On the other hand, benzylation of **16f** and **17f** under the phase transfer conditions similar to those applied for preparing **12** from **7**, gave **16a** and **17a**, respectively. These products were identified with authentic **16a** and **17a** prepared from **13a** and **14a**, respectively. Since the 2-methoxyethoxymethyl groups present in **13d** and **14d** could not be removed under weakly acidic conditions, acetalization of the mixture of **13d** and **14d** gave rise to a mixture of the dimethyl acetals (**16d** and **17d**). These products were identified with authentic **16d** and **17d**, respectively, which were produced from **16f** and **17f** by treating with 2-methoxyethoxymethyl chloride and base.

Based on these chemical correlations, the absolute stereochemistries of **13a~e** and **14a~e** could be rigorously established as shown in **Table 1** and **Scheme 2**.



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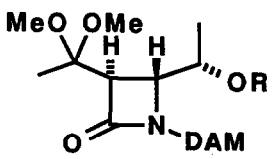


17

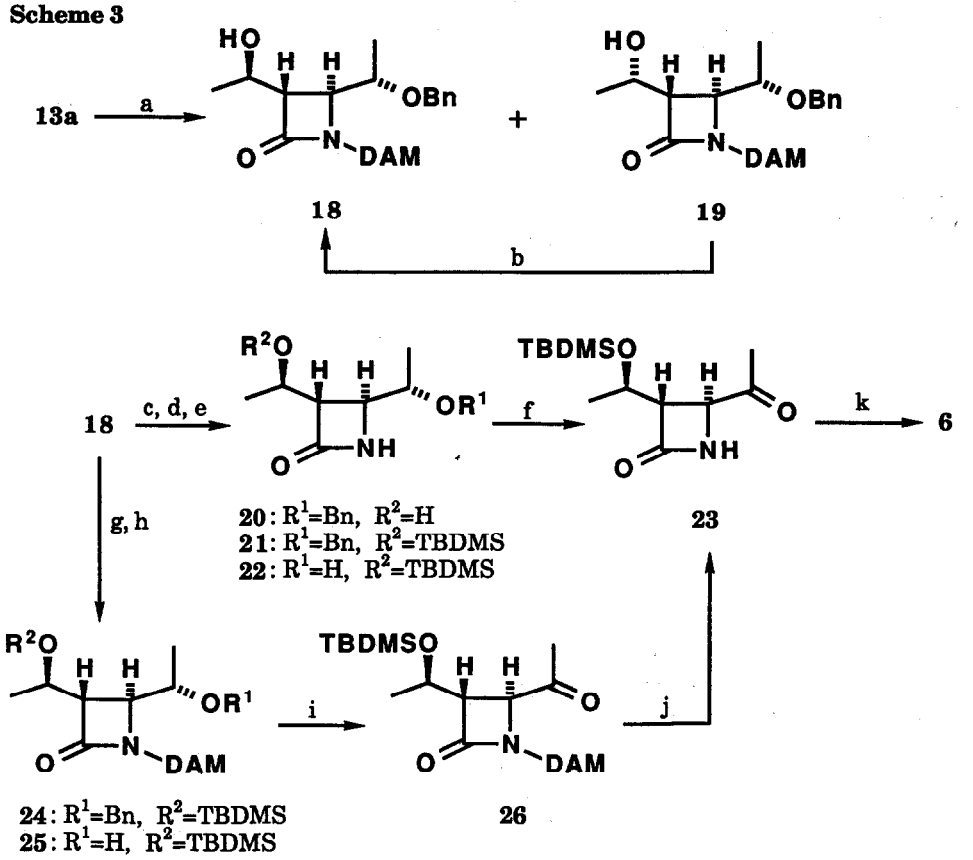
a;R=Bn
d;R=MEM
f; R=H

Preparation of the Carbapenem Key Intermediate (6)

With a large quantity of **13a** in hand, preparation of **6** was next examined as shown in **Scheme 3**. Reduction of the acetyl group of **13a** with potassium tri-*sec*-butylborohydride in the presence of potassium iodide[24] underwent highly stereoselectively to give a mixture of the two epimeric alcohols (**18** and **19**, **18**:**19**=12:1) with 4% recovery of **13a**. On the other hand, complete reduction of **13a** was effected with potassium triethylborohydride,[25] yielding a mixture of **18** and **19** in the same stereoselectivity. The two epimeric alcohols (**18** and **19**) separated showed $[\alpha]_D^{25}$ -5.5° ($CHCl_3$) and $[\alpha]_D^{25}$ +13.8° ($CHCl_3$), respectively. The major alcohol (**18**) could be readily isolated in a pure state in 76% yield by a single recrystallization of the reduction products from isopropanol. It was also found that when a crude diastereomeric mixture of **13a** and **14a** produced under the best conditions of the [2+2]-cycloaddition reaction was reduced with potassium triethylborohydride without separation and the crude mixture of reduction products was immediately recrystallized from isopropanol, an almost pure sample of **18** could be obtained in 58% yield based on **9a** (*vide supra*). This result may be quite useful for a large scale preparation of **6**. The undesired epimer (**19**) could be converted to **18** by the Mitsunobu reaction in an excellent combined yield.[26]

Oxidative removal of the di-*p*-anisylmethyl (DAM) group was first attempted at the stage of **18**. It was effected by employing cerium(IV) ammonium nitrate (CAN)[27] to afford the *N*-unprotected β-lactam (**20**), $[\alpha]_D^{25}$ +61.5° ($CHCl_3$). After protection of the hydroxy group of **20** in a form of *t*-butyldimethylsilyl ether, the produced benzyl ether (**21**), $[\alpha]_D^{25}$ +32.5° ($CHCl_3$), was subjected to hydrogenolysis, giving the alcohol (**22**), $[\alpha]_D^{25}$ -11.5° ($CHCl_3$). Since direct transformation of **22** to **6** by oxidative cleavage of the 1,2-amido alcohol with sodium periodate in the presence of sodium acetate turned out to be fruitless,[28] the following two step procedure was examined. Thus, oxidation of **22** with chromium trioxide gave the ketone (**23**), $[\alpha]_D^{25}$ -14.3° ($CHCl_3$). The same ketone (**23**) could be also obtained by oxidation of **22** with a combination of *N*-chlorosuccinimide, dimethylsulfide, and triethylamine.[29] The latter oxidation method is

Scheme 3



a) KB*sec*-Bu$_3$H-KI in THF, 0 °C, 92% (**18**:**19**=12:1) or KBEt$_3$H in THF, -78 °C, 98% (**18**:**19**=12:1) b) i) EtO_2CNNCO_2Et-PPh_3-HCOOH, ii) K_2CO_3 in MeOH, 90% (2 steps) c) CAN in aq. MeCN, -10 °C, 93% d) TBDMSCl-imidazole in DMF, 97% e) H_2-Pd/C in AcOEt, 100% f) CrO_3 in pyridine, 93% or NCS-Me_2S-Et_3N in toluene, 95% g) TBDMSCl-DMAP in DMF, 95% h) H_2-Pd/C in AcOEt, 98% i) NCS-Me_2S-Et_3N in toluene, 98% j) $Na_2S_2O_8$-Na_2HPO_4 in aq acetone, 89% k) MCPBA in AcOEt, 93% or perphthalic acid in AcOEt, 81%

anticipated to be more promising in a large scale preparation since poisonous chromium trioxide is not utilized.[30]

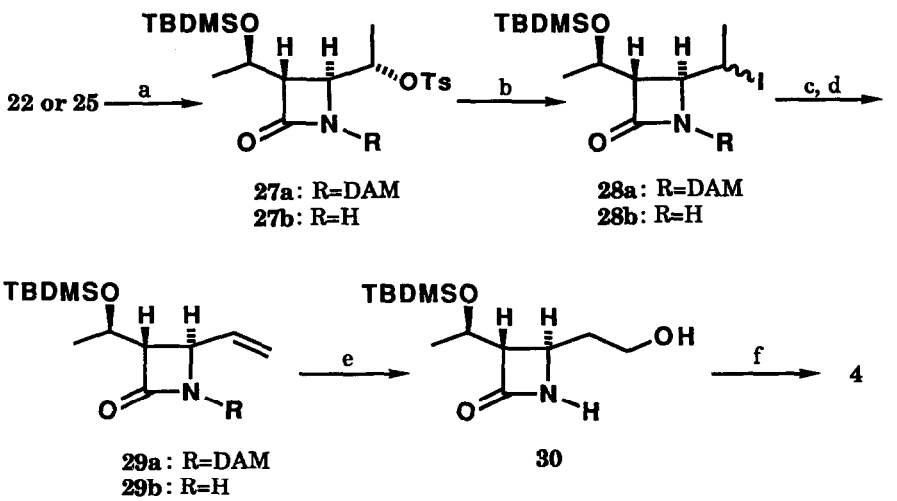
Since CAN is fairly expensive and the oxidation with it sometimes makes trouble during work-up in a large scale reaction due to fine precipitates of the resulting cerium(III) compounds, oxidation with sodium peroxodisulfate was next examined as an alternative deprotection method of DAM group. Accordingly, the alcohol (**18**) was converted to the ketone (**26**), $[\alpha]_D^{20}$ +27.4° ($CHCl_3$), by way of the silyl ether (**24**), $[\alpha]_D^{25}$ +19.8° ($CHCl_3$), and the alcohol (**25**), $[\alpha]_D^{25}$ -29.1° ($CHCl_3$), following the synthetic scheme similar to that employed for the preparation of **23** from **20**. Oxidations of **18**, **24**, and **25** with sodium peroxydisulfate did not give the corresponding deprotected products in high yields due to partial decomposition of the starting materials and/or the deprotected products. However, it was finally found that treatment of **26** with sodium peroxydisulfate in the presence of disodium hydrogenphosphate as buffer cleanly effected removal of the DAM group, giving rise to **23**. Taking into account the operational simplicity, the latter synthetic route to **23** is anticipated to be more practical than the former in which the DAM group has been removed at the stage of **18**.

Oxidation of **23** with *m*-chloroperbenzoic acid,[31] cleanly produced **6**, mp 108~109 °C and $[\alpha]_D^{25}$ +47.8° ($CHCl_3$). Monoperphthalic acid obtainable from phthalic anhydride and hydrogen peroxide was also usable for this Baeyer-Villiger oxidation. The carbapenem key intermediate (**6**) was identified by comparing its physical and spectral data with those reported.[12b,f,g]

Preparation of Thienamycin Intermediate (4)

With completion of the efficient synthesis of **6** from **7** by way of the [2+2]-cycloadduct (**13a**), we next examined elaboration of **13a** to the advanced carbapenem key intermediate (**4**). Although **6** has been recognized as a useful precursor to produce **4** by nucleophilic substitution at the C_4-position,[6] the direct preparation of **4** from **13a** seems to be advantageous since **13a** has

Scheme 4



a) TsCl in pyridine, 0 °C, 82% (**27a**), 85% (**27b**) b) NaI in acetone, reflux, 90% (**28a**), 91% (**28b**) c) DBU in toluene, 100 °C, 91% (**29a**), 24% (**29b**) (see text) d) CAN in aq MeCN, -10 °C, 74% e) BH_3 in THF, rt, 1h, then, H_2O_2-aq NaOH, 22% (see text); 9-BBN in THF-Et_2O, rt, 3 h, then, H_2O_2-aq NaOH, 0 °C, 77% f) $RuCl_3$ (2 mol%)-$NaIO_4$ in CCl_4-MeCN-H_2O, rt, 69%

the same carbon framework as that involved in **4**.

As shown in **Scheme 4**, the alcohol (**25**) prepared from **13a** in 3 steps was readily transformed to the corresponding *p*-toluenesulfonate (**27a**), $[\alpha]_D^{20}$ -22.2° ($CHCl_3$). However, it turned out to be fruitless to directly eliminate the tosyloxy group to produce the olefin (**29a**) by treating **27a** with bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium *t*-butoxide, pyridine, etc. Accordingly, preparation of **29a** was examined by way of the iodide (**28a**). Thus, treatment of **27a** with sodium iodide gave rise to **28a** as a mixture of the two diastereomers. Ratio of the two diastereomers could be roughly estimated as 5:2 by the ^{1}H-NMR spectrum of the mixture. This can be explained by epimerization of the initially formed iodide during the substitution reaction. Without separation of the diastereomers, treatment of **28a** with DBU cleanly produced **29a**, $[\alpha]_D^{20}$ +52.5° ($CHCl_3$). Oxidative removal of the DAM group was effected with CAN without a cleavage of the silyl ether, yielding **29b**, $[\alpha]_D^{20}$ -24.5° ($CHCl_3$). On the other hand, the DAM group was removed at the stage of **18** and the deprotected β-lactam (**20**) was converted to the iodide **28b** by way of **22** by the same synthetic steps as employed for preparing **28a** from **25**. While **28b** was subjected to the elimination reaction in a similar manner to that for **28a**, a 24% of **29b** was only obtained due to partial decomposition of **28b** and/or **29b**.

Hydroboration of **29b** with borane followed by the usual oxidative workup gave a mixture of the desired primary alcohol (**30**) and its regioisomer [a mixture of **22** and its 4-[(*R*)-1-hydroxyethyl]-isomer] in a ratio of 11:9 in 40 % combined yield. However, the use of 9-borabicyclo[3.3.1]nonane in place of borane readily produced **30** as a single product, $[\alpha]_D^{20}$ -22.3° ($CHCl_3$). Oxidation of **30** was achieved smoothly by the procedure reported by Sharpless, *et al.*,[32] to furnish **4**, mp 150~154 °C (decomp.) and $[\alpha]_D^{20}$ +16.1° ($CHCl_3$). This was identified with the authentic sample[4f] by comparisons of their physical and spectral data.

As mentioned above, we have succeeded in exploring novel synthetic routes to two types of the carbapenem key intermediates (**4** and **6**) by featuring the [2+2]-cycloaddition reaction of diketene with a chiral imine as a key stereoselective reaction. The synthetic scheme explored may be characterized by various notable aspects including high stereoselectivity in the β-lactam formation, use of commercially available inexpensive **7** as a starting material, high chemical yields of the overall processes, and ingenious utilization of all the carbon framework of the [2+2]-cycloaddition product for preparing **4**.

Acknowledgement

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Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. Measurements of optical rotation 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 spectrometer (400 MHz). All signals were expressed as ppm downfield 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 60F_{254} (Merck) was used for preparative TLC.

(*S*)-Ethyl 2-Benzyloxypropionate (8a). Trifluoromethanesulfonic acid (0.100 ml, 1.13 mmol) was added to a solution of **7** (3.50 g, 29.6 mmol) and *O*-benzyl trichloroacetimidate[16] (11.0 ml, 59.2 mmol) in cyclohexane-CH_2Cl_2 (7:1) (80 ml) at rt. After stirring for 20h, the mixture was diluted with H_2O (20 ml) and hexane (80 ml), then stirred for additional 3h. The white precipitates resulted was removed by filtration. The aqueous layer of the filtrate was separated and the organic layer was washed with satd aq $NaHCO_3$ and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified by column chromatography (SiO_2, hexane-AcOEt 1:0~30:1), giving **8a** as a colorless oil (4.27 g, 69%), $[\alpha]_D^{20}$ -74.5° (c 2.94, $CHCl_3$). IR (neat): 3000, 1750, 1455, 1271, 1200, 1142, 1067, 1027, 740, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.29 (3H, t, J=7.1 Hz, MeCH_2), 1.43 (3H, d, J=6.8Hz, MeCH), 4.05 (1H, q, J=6.8 Hz, MeCH), 4.22 (2H, q, J=7.1Hz, MeCH_2), 4.43, 4.70 (2H, two d, J=each 11.7 Hz, PhCH_2), 7.33 (5H, s, C_6H_5). MS m/e: 179 $(M\text{-}Et)^+$, 102.

(*S*)-Ethyl 2-(*t*-Butyldimethylsilyloxy)propionate (8b). Imidazole (2.66 g, 39.1 mmol) and *t*-butyldimethylchlorosilane (4.85 g, 32.2 mmol) were added to a solution of **7** (3.12g, 26.4 mmol) in DMF (26 ml). After stirring at rt for 1h, the mixture was diluted with hexane (150 ml) and H_2O (20 ml). The organic layer was separated, washed with H_2O, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified by distillation (bp 88 °C, 20 mmHg), giving **8c** as a colorless oil (5.90g, 96%), $[\alpha]_D^{20}$ -28.7° (c 2.36, $CHCl_3$). IR (neat): 2950, 2870, 1755, 1462, 1255, 1142, 977, 835, 780, 660 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08, 0.10 (6H, two s, Me_2Si), 0.91 (9H, s, Me_3C), 1.35 (3H, t, J=7.0 Hz, MeCH_2), 1.35 (3H, d, J=6.7 Hz, MeCH), 4.18 (2H, q, J=7.0 Hz, CH_2Me), 4.31 (1H, q, J=6.7 Hz, CHMe). MS m/e: 217$(M\text{-}Me)^+$, 175 $(M\text{-}Bu)^+$, 159, 147.

(*S*)-Ethyl 2-Tetrahydropyranyloxypropionate (8c). Dihydropyran (6.00 ml, 65.8 mmol) and pyridinium *p*-toluenesulfonate (1.16 g, 4.62 mmol) were added to a solution of **7** (5.18 g, 43.9 mmol) in CH_2Cl_2 (100 ml). After stirring at rt for 1.5 h, the mixture was diluted with ether (200 ml). The ethereal solution was washed with aq NaCl and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified with distillation (bp 76~78 °C, 1 mmHg), giving **8c** as a colorless oil (6.41 g, 72%). This sample (**8c**) consisted of an almost equal amount of the two diastereomers due to its tetrahydropyranyl group. IR (neat): 2950, 2880, 1750, 1445, 1200, 980, 870, 718 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.27 (3H, t, J=7.1 Hz, MeCH_2), 1.39, 1.44 (3H, two d, J=6.9 Hz, MeCH), 1.5~1.8 (6H, m, $(CH_2)_3$), 3.4~4.0 (2H, m, OCH_2CH_2), 4.19 (2H, q, J=7.1 Hz, MeCH_2), 4.40 (1H, q, J=6.9 Hz, MeCH), 4.71 (1H, m, OCHO). MS m/e: 144 $(M\text{-}(CH_2)_3O)^+$, 129 $(M\text{-}COOEt)^+$, 101, 85.

(*S*)-Ethyl 2-(2-Methoxyethoxymethoxy)propionate (8d). *N,N*-Diisopropylethylamine (9.4 ml, 54 mmol) and 2-methoxyethoxymethyl chloride (6.20 ml, 54.3 mmol) were added to a solution of **7** (4.25 g, 35.9 mmol) in CH_2Cl_2 (35 ml) at 0 °C. After stirring at rt for 12h, the mixture was diluted with H_2O and CH_2Cl_2, and the aqueous phase was separated. The organic phase was washed successively with satd aq $NaHCO_3$, 1M HCl and sat aq NaCl, then dried over anhyd $MgSO_4$. Filtration and evaporation *in vacuo* gave an oily residue which was purified with distillation (bp 84 °C, 1 mmHg), giving **8d** (4.37 g, 59 %), $[\alpha]_D^{20}$ -66.7° (c 1.17, $CHCl_3$). IR (neat): 3000, 2950, 2900, 1742, 1442, 1268, 1100, 1020, 845 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.28 (3H, t, J=7.0 Hz, MeCH_2), 1.43 (3H,d, J=6.8 Hz, MeCH), 3.39 (3H, s, MeO), 3.47~3.59, 3.70~3.81 (4H, two m, OC_2H_4O), 4.19 (2H, q, J=7.0 Hz, CH_2Me), 4.27 (1H, q, J=6.8 Hz, CHMe), 4.79 (2H, s, OCH_2O).

(*S*)-Ethyl 2-(1-Ethoxyethoxy)propionate (8e). Ethyl vinyl ether (18.4 ml, 192 mmol) and *p*-toluenesulfonic acid (ca 1 mg) were added to a solution of **7** (2.50 g, 21.2 mmol) in ether (18 ml) at 0 °C. After stirring at rt for 1h, the mixture was diluted with satd aq $NaHCO_3$ (18 ml) and the aqueous phase was separated. The organic phase was washed with satd aq NaCl, then dried

over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified with column chromatography, affording **8e** as a colorless oil (3.66 g, 91%). IR (neat): 3000, 2950, 1753, 1446, 1375, 1275, 1177, 1148, 1083, 1057, 1027, 967, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.1~1.5 (12H, m, Mex4), 3.4~3.9 (2H, m, $MeCH_2OCH$), 4.20 (2H, t, J=7.2 Hz, CH_2OCO), 4.18, 4.33 (1H, two q, J=each 5.9 Hz, OCHC), 4.78 (1H, q, J=5.5 Hz, OCHO).

(*S*)-2-Benzyloxypropanal (9a). a) Preparation from **8a.** A 1.0 M solution of diisobutylaluminium hydride in hexane (2.70 ml, 2.70 mmol) was added slowly to a solution of **8a** (0.373g, 1.79 mmol) in ether at -78 °C. After stirring at the same temperature for 10 min, the mixture was diluted successively with MeOH (0.1 ml) and H_2O (0.27 ml), then warmed up to rt. After stirring for additional 1h, the resulting suspension was filtered through a pad of celite and the collected materials were washed with ether. The combined filtrates were dried over anhyd $MgSO_4$ and concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, hexane-AcOEt 16:1~9:1) to give **9a** as a colorless oil (0.241 g, 82%). $[\alpha]_D^{25}$ -66.8° (*l*=1, neat) (*lit.*,[31] $[\alpha]_D^{20}$ -65.85° (*l*=1, neat)). IR (neat): 3470, 3058, 3000, 2950, 1740, 1500, 1456, 1380, 1210, 1100, 741, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.32 (3H, d, J=6.8 Hz, Me), 3.88 (1H, dq, J=1.8, 6.8 Hz, $MeCH$), 4.62 (2H, s, $PhCH_2$), 7.35 (5H, s, C_6H_5), 9.66 (1H, d, J=1.8 Hz, CHO). MS m/e: 181 $(M+OH)^+$, 135 $(M-CHO)^+$.

b) Preparation from **12.** A 2.0 M solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene (1.60 ml, 3.20 mmol) was added slowly to a solution of **12** (1.24 g, 5.32 mmol) in toluene at -10 °C. After stirring at the same temperature for 2 h, acetone (0.195 ml) was added and the mixture was stirred for additional 15 min. The reaction mixture was poured into 1M HCl (12.7 ml) cooled in ice bath and extracted with AcOEt. The combined extracts were washed successively with 0.1 M HCl, satd aq NaCl, satd aq $NaHCO_3$, and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave a residue which was purified with column chromatography (SiO_2, hexane-AcOEt 19:1) to give **9a** as a colorless oil (0.76 g, 88%). The IR and ^{1}H-NMR spectra of this sample were superimposable on those of **9a** obtained in a).

(*S*)-2-(*t*-Butyldimethylsilyloxy)propanal (9b). Treatments of **8b** in the same manner as described for the preparation of **9a** from **8a**, gave **9b** as a colorless oil (0.707g, 76%) after purification with bulb-to-bulb distillation (bp 90 °C, 20 mmHg). IR (neat): 2952, 2948, 2852, 1740, 1255, 1135, 838, 778 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.10 (6H, s, Me_2Si), 0.92 (9H, s, Me_3C), 1.28 (3H, d, J=6.8 Hz, $MeCH$), 4.09 (1H, dq, J=1.3, 6.8 Hz, $MeCH$), 9.61 (1H, d, J=1.3 Hz, CHO). MS m/e: 159 $(M-CHO)^+$, 131 $(M-Bu)^+$, 103, 73.

(*S*)-2-Tetrahydropyranyloxypropanal (9c). Treatments of **8c** (0.445 g, 2.20 mmol) in the same manner as described for the preparation of **9a** from **8a**, afforded **9c** as a colorless oil (0.283g, 81%) after sequential purification with column chromatography (SiO_2, hexane-AcOEt 19:1~8:1) and bulb-to-bulb distillation (110 °C/20 mmHg). IR (neat): 2950, 2870, 1738, 1378, 1125, 1080, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.32 (3H, d, J=7.1 Hz, Me), 1.5~1.9 (6H, m, $(CH_2)_3$), 3.4~4.0 (2H, m, OCH_2), 4.27 (1H, dq, J=1.2, 7.1 Hz, $MeCH$), 4.6~4.8 (1H, m, OCHO), 9.65, 9.66 (1H, two d, J=1.2 Hz, CHO). MS m/e: 84 $(THP)^+$, 55, 43.

(*S*)-2-(2-Methoxyethoxymethoxy)propanal (9d). Treatments of **8d** (1.04g, 5.05 mmol) in a similar manner to that described for the preparation of **9a** from **8a**, afforded **9d** as a colorless oil (0.643 g, 78%) after sequential purification with column chromatography (SiO_2, hexane-AcOEt 7:3~3:4) and distillation (bp 100 °C, 1 mmHg). IR (neat): 2950, 2900, 2830, 1738, 1450, 1110, 1038, 847 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.32 (3H, d, J=7.0 Hz, $MeCH$), 3.38 (3H, s, MeO), 3.48~3.59, 3.71~3.78 (4H, two m, OC_2H_4O), 4.08 (1H, dq, J=1.5, 7.0 Hz, $CHMe$), 4.83 (2H, s, OCH_2O), 9.65 (1H, d, J=1.5 Hz, CHO). MS m/e: 133 $(M-CHO)^+$, 119, 89.

(*S*)-2-(1-Ethoxyethoxy)propanal (9e). Reduction of **8e** was performed by the same procedure as described for the preparation of **9a** from **8a**, affording **9e** (R=EE) as a colorless oil (27.6g, 82 %) after distillation (bp 103 °C, 20 mmHg). ^{1}H-NMR ($CDCl_3$): 1.1~1.5 (9H, m, Mex3), 3.4~4.4 (3H, m, other protons), 4.7~5.0 (1H, m, OCHO), 9.61 (1H, t, J=2.4 Hz, CHO).

(*S*)-*N,N*-Tetramethylenelactamide (11). Pyrrolidine (7.80 ml, 93.4 mmol) was added to **7** (10.2 g, 86.0 mmol) at 0°C and stirred at rt for 3 days. After removal of excess pyrrolidine and resulting ethanol *in vacuo*, the oily residue was purified with distillation (108 °C, 1 mmHg) to give **11** (11.8g, 95%) as a colorless oil. $[\alpha]_D^{20}$ -49.2° (c 4.78, $CHCl_3$). IR (neat): 3450, 3000, 2900, 1637, 1440, 1387, 1345, 1133, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.33 (3H, d, J=6.6 Hz, Me), 1.49 (4H, m, $NCH_2\underline{CH_2}x2$), 3.45 (4H, m, NCH_2x2), 3.73 (1H, d, J=7.3 Hz, OH), 4.29 (1H, dq, J=6.6, 7.3 Hz, CHCO). MS m/e: 143 $(M)^+$, 128 $(M\text{-}Me)^+$, 98 $(M\text{-}MeCHOH)^+$. Found: C, 57.00; H, 9.22; N, 9.53%. Calcd for $C_7H_{13}NO_2$: C, 56.93; H, 9.21; N, 9.49%.

(*S*)-*N,N*-Tetramethlene-2-benzyloxypropionamide (12). a) Preparation of **12** with benzyl chloride and sodium hydride. A solution of **11** (9.98 g, 67.7 mmol) in THF (15 ml) was added slowly to a suspension of sodium hydride (2.00 g, 83.3 mmol) in THF (50 ml) and DMF (25 ml) at 0 °C with vigorous stirring. After stirring for 4.5h at the same temperature, benzyl chloride (8.80 ml, 76.5 mmol) was added to the reaction mixture. Stirring was further continued overnight at 0 °C. The resulting mixture was diluted with H_2O (50 ml) and extracted with AcOEt. The combined extracts were washed with satd aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified with crystallization from hexane-Et_2O to give **12** as colorless crystals (14.1 g, 87%). Recrystallization from dibutyl ether gave an analytical sample of **12** as colorless crystals, mp 42~42.5 °C and $[\alpha]_D^{20}$ -66.9° (c 1.72, $CHCl_3$). IR (KBr): 3050, 3000, 2890, 1430, 1350, 1120, 730 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.42 (3H, d, J=6.8 Hz, Me), 1.85 (4H, m, $NCH_2\underline{CH_2}x2$), 3.50 (4H, m, NCH_2x2), 4.20 (1H, q, J=6.8 Hz, CHCO), 4.11, 4.62 (2H, two d, J=each 11.7 Hz, $Ph\underline{CH_2}$), 7.32 (5H, s, C_6H_5). MS m/e: 234$(M+1)^+$, 127, 98. Found: C, 72.06; H, 8.32; N, 5.90 %. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00 %.
b) Preparation of **12** under phase transfer conditions. Finely powdered sodium hydroxide (0.737 g, 17.5 mmol) and **11** (0.716 g, 5.01 mmol) were added to a solution of benzyl chloride (0.760 g, 6.00 mmol) and tricaprylmethylammonium chloride (0.101 g, 0.250 mmol) in toluene (5 ml) at 0°C and the mixture was stirred vigorously at rt for 6h. The mixture was diluted with toluene and filtered. The filtrate was washed successively with 1M HCl (5 ml) and satd aq $NaHCO_3$, then dried over anhyd $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified with column chromatography (SiO_2, hexane-AcOEt 2:3) to give **12** as colorless crystals (1.07 g, 92%). This sample showed the same ^{1}H-NMR spectrum and optical rotation as that of **12** obtained in a).

Di-*p*-anisylmethylamine (DAM-NH_2).[19] A mixture of 4,4'-dimethoxybenzophenone (9.29g, 37.0 mmol) and ammonium formate (14.1g, 220 mmol) was stirred at 180~190 °C for 4h. Formamide (5.00g, 111mmol) and anhyd $MgCl_2$ (0.247 g, 2.59 mmol) were added to the mixture. After stirring at 180~190 °C for 2h, the mixture was cooled and dissolved in CH_2Cl_2. The dichloromethane solution was washed with H_2O and concentrated *in vacuo* to give crude *N*-formyl-di-*p*-anisylmethylamine (10.3 g) as a solid. A 1 M solution of HCl in MeOH (55ml) was added to the solid and the mixture was heated at reflux for 2h, then concentrated *in vacuo*. The residue was dissolved in H_2O (50 ml) and the aqueous solution was washed with toluene. The aqueous layer was made alkaline with 50% aq NaOH and extracted with toluene. The organic extracts were combined and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave DAM-NH_2 as slightly yellow crystals (8.48 g, 94%). An analytical sample was obtained by recrystallization from ether, mp 59.5~60 °C. IR (KBr): 3010, 2960, 2850, 1605, 1508, 1242, 1173, 1025, 560 cm^{-1}. ^{1}H-NMR($CDCl_3$): 1.70 (2H, s, NH_2), 3.77 (6H, s, MeOx2), 5.12 (1H, s,

CHAr2), 6.78~7.31 (8H, m, aromatics). MS m/e: 244 $(M+1)^+$, 243 (M^+), 227 $(M-NH_2)^+$, 212 $(M-MeO)^+$, 135. Found: C, 73.99; H, 7.14; N, 5.65 %. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%.

(3*S*,4*S*)-3-Acetyl-4-[(*S*)-1-benzyloxyethyl]-1-(di-*p*-anisylmethyl)-2-azetidinone (13a) and Its (3*R*,4*R*)-Isomer (14a) (Table 1, run 2). General procedure of the [2+2]-cycloaddition reaction of diketene with **10**. Anhyd $MgSO_4$ (5.00 g, 41.5 mmol) and DAM-NH_2 (8.08 g, 33.2 mmol) were added to a solution of **9a** (5.45 g, 33.2 mmol) in toluene (15 ml) at 0 °C. After stirring at the same temperature for 1h, the mixture was filtered and the collected materials were washed with toluene. The combined filtrates were concentrated *in vacuo* to give almost pure **10a**. ^{1}H-NMR ($CDCl_3$): 1.36 (3H, d, J=6.4 Hz, MeCH), 3.78, 3.79 (6H, two s, MeOx2), 4.17 (1H, m, MeCH), 4.51 (2H, s, $PhCH_2$), 5.34 (1H, s, Ar_2CH), 6.7~6.9, 7.1~7.3 (8H, two m, C_6H_4x2), 7.28 (5H, s, C_6H_5), 7.70 (1H, d, J=5.5 Hz, N=CH). This was immediately used for the next step without further purification. Imidazole (2.26 g, 33.2 mmol) was added to a solution of **10a** in CH_2Cl_2 (33 ml). The mixture was cooled to -35 °C and diketene (7.80 ml, 99.6 mmol) was added. After stirring at the same temperature for 21h, an additional amount of diketene (5.20 ml, 66.4 mmol) was added to the reaction mixture. Stirring was further continued at the same temperature for 2d. The mixture was diluted with ether and H_2O. After stirring at rt, the aqueous layer was separated. The organic layer was washed successively with H_2O, 1M HCl, satd aq NaCl, 2M NaOH (to remove dehydroacetic acid)[21] and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave a crude mixture of **13a** and **14a** as a slightly yellow oil. The ratio of **13a** to **14a** could be calculated as 7.3:1 based on the ^{1}H-NMR spectrum of the mixture. The methyl groups of acetyl moieties of **13a** and **14a** appear as two singlets at 2.27 and 2.33 ppm with an integration ratio of 7.3:1 (*vide infra*). The concentrated residue was purified with column chromatography (SiO_2, hexane-ether-CH_2Cl_2 5:4:1~4:5:0), affording pure **13a** as a colorless oil (4.87 g, 31%, 2 steps) from the more polar fraction, a mixture of **13a** and **14a** (7.95 g, 51%, 2 steps, **13a**:**14a**=16:1), and pure **14a** as colorless crystals (1.50 g, 9.1%, 2 steps) from the less polar fraction. The combined yield of **13a** and **14a** based on **9a** was 91%. The desired product (**13a**) showed the following physical and spectral data. $[\alpha]_D^{20}$ -7.3° (c 1.48, $CHCl_3$). IR (neat): 2950, 1760, 1720, 1614, 1589, 1514, 1460, 1306, 1250, 1190, 1099, 1036, 828, 740, 702, 598 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.10 (3H, d, J=6.3 Hz, MeCH), 2.27 (3H, s, MeCO), 3.47 (1H, dq, J=6.3, 7.0 Hz, MeCH), 3.77, 3.79 (6H, two s, MeOx2), 3.87 (1H, d, J=2.5 Hz, C_3-H), 4.15 (1H, dd, J=2.5, 7.0 Hz, C_4-H), 4.14, 4.45 (2H, two d, J=each 11.2 Hz, $PhCH_2$), 5.76 (1H, s, Ar_2CH), 6.78~6.85, 7.07~7.33 (13H, m, aromatic protons). MS m/e: 473 (M^+), 382 $(M-Bn)^+$. The ^{1}H-NMR spectrum of this sample measured in the presence of the chiral shift reagent [Eu(hfc)$_3$], clearly showed the methyl group of acetyl moiety as two singlets at 2.57 and 2.75 ppm in an intensity ratio of 98:2 . Since *dl*-**13a**[22] exhibited two singlets of equal intensity at 2.57 and 2.75 ppm, the optical purity of **13a** was estimated as 96 %ee. Accordingly, it appeared evident that each synthetic steps to the stage of **13a** could proceed without substantial racemization. The undesired product (**14a**) recrystallized from EtOH show the following physical and spectral data. Mp 84~85 °C and $[\alpha]_D^{20}$+30.0° (c 1.21, $CHCl_3$). IR (KBr): 2960, 2890, 2850, 1735, 1702, 1605, 1582, 1508, 1460, 1408, 1345, 1282, 1240, 1205, 1180, 1158, 1105, 1020, 818, 736, 690, 568, 532, 508 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.02 (3H, d, J=6.3 Hz, MeCH), 2.33 (3H, s, MeCO), 3.34 (1H, dq, J=1.9, 6.3 Hz, MeCH), 3.75, 3.78 (6H, two s, MeOx2), 4.01 (1H, dd, J=1.9, 2.4 Hz, C_4-H), 4.07, 4.48 (2H, two d, J=each 11.5 Hz, $PhCH_2$), 4.36 (1H, d, J=2.4 Hz, C_3-H), 5.72 (1H, s, $CHAr_2$), 6.72~6.85, 7.10~7.40 (13H, two m, aromatic protons). MS m/e: 473 (M^+), 430 $(M-MeCO)^+$, 382 $(M-Bn)^+$. Found: C, 73.54; H, 6.64; N, 3.17 %. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96 %.

(3*S*,4*S*)-3-Acetyl-4-[(*S*)-1-(*t*-butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-2-azetidinone (13b) and Its (3*R*,4*R*)-Isomer (14b) (Table 1, run 10). Treatments of **9b** (0.594 g, 3.15 mmol) in a similar manner to that described for the preparation of **10a** from **9a** gave **10b** (1.31 g) after

concentration of the toluene solution. ^{1}H-NMR ($CDCl_3$): 0.03, 0.07 (6H, two s, Me_2Si), 0.89 (9H, s, Me_3C), 1.33 (3H, d, J=6.4 Hz, MeCH), 3.80 (6H, s, MeOx2), 4.46 (1H, dq, J=4.8, 6.4 Hz, OCH), 5.32 (1H, s, CHAr2)), 6.86, 7.21 (8H, two d, J=each 8.5 Hz, aromatic protons), 7.68 (1H, d, J=4.8 Hz, N=CH). A part of the imine (**10b**) (0.412 g, 0.997mmol) was subjected to the [2+2]-cycloaddition reaction in CH_2Cl_2 according to the general procedure, giving a mixture of **13b** and **14b** as a colorless oil (0.339 g, 68%, 2 steps) after purification with column chromatography (SiO_2, hexane-AcOEt-CH_2Cl_2 8:1:1~7:1:0). The ratio of **13b** to **14b** could be calculated as 5.4:1 by measuring the ^{1}H-NMR spectrum of the mixture (*vide infra*). These diastereomers (**13b** and **14b**) could be separated with preparative TLC (SiO_2; CH_2Cl_2-AcOEt 97:3, two developments). The desired product (**13b**) obtained as a colorless oil showed the following physical and spectral data. $[\alpha]_D^{20}$ -19.1° (c, 0.51, $CHCl_3$). IR (neat): 2940, 2910, 2850, 1748, 1703, 1602, 1500, 1240, 1165, 1020, 820, 765 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.04, -0.08 (6H, two s, Me_2Si), 0.82 (9H, s, Me_3C), 0.99 (3H, d, J=6.2 Hz, MeCH), 2.27 (3H, s, MeCO), 3.79 (6H, s, MeOx2), 3.39~3.58 (1H, m, C3-H), 4.04~4.16 (2H, m, other protons), 5.75 (1H, s, CHAr2), 6.80~6.90, 7.13~7.26 (8H, two m, aromatic protons). MS m/e: 469 $(M\text{-}CO)^+$, 310, 227. The undesired product (**14b**) obtained as a colorless oil showed the following physical and spectral data. $[\alpha]_D^{20}$ +10.8° (c 0.91, $CHCl_3$). IR (neat): 2950, 2850, 1748, 1710, 1610, 1510, 1242, 1168, 1030, 830, 775 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.01, 0.02 (6H, two s, Me_2Si), 0.90 (9H, s, Me_3C), 0.98 (3H, d, J=6.2 Hz, MeCH), 2.31 (3H, s, MeCO), 3.77, 3.79 (6H, two s, MeOx2), 3.95~4.16 (3H, m, other protons), 5.59 (1H, s, CHAr2), 6.77~6.90, 7.14~7.26 (8H, two m, aromatic protons). MS m/e: 497 (M^+), 469 $(M\text{-}CO)^+$, 310, 227. The stereochemistries of the reaction products were determined by converting the separated samples of **13b** and **14b** to **16f** and **17f**, respectively (*vide infra*).

(3*S*,4*S*)-3-Acetyl-1-di-*p*-anisylmethyl-4-[(*S*)-1-tetrahydropyranyloxyethyl]-2-azetidinone (13c) and Its (3*R*,4*R*)-Isomer (14c) (Table 1, run 12). Treatment of **9c** (0.408 g, 2.58 mmol) in a similar manner to that described for the preparation of **10a** from **9a** gave **10c** (1.02 g) after concentration of the toluene solution. ^{1}H-NMR ($CDCl_3$): 1.33, 1.36 (3H, two d, J=6.6Hz, Me), 1.2~1.9 (6H, m, $(CH_2)_3$), 3.3~4.8 (4H, m, other protons), 3.77 (6H, s, MeOx2), 5.32 (1H, s, CHAr2), 6.83, 7.19 (8H, two d, J=each 8.8 Hz, aromatic protons), 7.66, 7.78 (1H, two d, J=5.5, 4.8 Hz, N=CH). A part of the imine (**10c**) (0.278 g, 0.726 mmol) was subjected to the [2+2]-cycloaddition reaction in CH_2Cl_2 according to the general procedure, giving a mixture of **13c** and **14c** as a colorless oil (0.241 g, 71%, 2 steps) after column chromatography (SiO_2, hexane-AcOEt-CH_2Cl_2 7:2:1~5:2:0). IR (neat): 3510, 2950, 2850, 1750, 1710, 1610, 1582, 1515, 1285, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.97, 1.02, 1.10, 1.15 (3H, four d, J=6.4 Hz, Me), 1.4~1.8 (6H, m, $(CH_2)_3$), 2.27, 2.28, 2.31, 2.34 (3H, four s, MeCO), 3.3~3.7 (2H, m, OCH_2), 3.79 (6H, s, MeOx2), 3.8~4.6 (10H, m, other protons), 5.65, 5.66, 5.73, 5.84 (1H, s, CHAr2), 6.8~6.9, 7.1~7.3 (8H, two m, aromatics). MS m/e: 476 (M^+), 424, 382, 227. The stereochemistries of the reaction products were determined by converting the mixture of **13c** and **14c** to that of **16f** and **17f** (*vide infra*). The ratio of **13c** to **14c** could be calculated as 6.0:1 by the ^{1}H-NMR spectrum of the mixture of **16f** and **17f**.

(3*S*,4*S*)-3-Acetyl-1-di-*p*-anisylmethyl-4-[(*S*)-1-(2-methoxyethoxymethoxy)ethyl]-2-azetidinone (13d) and Its (3*R*,4*R*)-Isomer (14d) (Table 1, run 13). The same treatments of **9d** (0.594 g, 3.15 mmol) as described for the preparation of **10a** from **9a** gave **10d** (1.21g) after concentration of the toluene solution. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, d, J=6.6 Hz, MeCH), 3.34 (3H, s, $MeOCH_2$), 3.38~3.73 (4H, m, OC_2H_5O), 3.77 (6H, s, MeOArx2), 4.42 (1H, m, CHMe), 4.76 ((1H, s, CHAr2), 6.83, 7.18 (8H, two d, J=each 8.8 Hz, aromatic protons), 7.70 (1H, d, J=4.8 Hz, N=CH). A part of the imine (**10d**) (0.489 g, 1.26mol) was subjected to the [2+2]-cycloaddition reaction in CH_2Cl_2 according to the general procedure, giving a mixture of **13d** and **14d** as a colorless oil (0.519 g, 87%, 2 steps) after purification with column chromatography (SiO_2, hexane-AcOEt-CH_2Cl_2 6:4:1~1:1:0). The ratio of **13d** to **14d** could be calculated as 6.0:1 by the ^{1}H-NMR spectrum of the mixture (*vide infra*). IR (neat): 2950, 2850, 1758, 1718, 1610, 1510, 1245, 1180, 1038 cm^{-1}. ^{1}H-

NMR (CDCl3): 1.04, 1.08 (3H, two d, J=6.3, 6.4 Hz, MeCH, intensity ratio; 1:6.0), 2.28, 2.32 (3H, two s, MeCO, intensity ratio; 6.0:1), 3.36, 3.37 (3H, two s, MeO, intensity ratio; 6.0:1), 3.4~4.8 (9H, m, other protons), 3.78, 3.80 (6H, two s, MeOArx2), 5.70 (1H, s, CHAr2), 6.8~7.0, 7.1~7.4 (8H, two m, aromatic protons). MS m/e: 471 (M^+), 443 $(M\text{-}CO)^+$, 428, 227. The stereochemistries of the reaction products were determined by converting the mixture of **13d** and **14d** to that of **16d** and **17d** (*vide infra*).

(3*S*,4*S*)-3-Acetyl-1-di-*p*-anisylmethyl-4-[(*S*)-1-(1-ethoxyethoxy)ethyl]-2-azetidinone (13e) and Its (3*R*,4*R*)-Isomer (14e) (Table 1, run 14). The same treatments of **9e** (1.10g, 7.53 mmol) as described for the preparation of **10a** from **9a** gave **10e** after concentration of the toluene solution. ^{1}H-NMR (CDCl3): 0.96~1.41 (9H, m, Mex3), 3.2~4.5 (3H, m, other protons), 3.77 (6H, s, MeOx2), 4.70 (1H, q, J=5.3 Hz, OCHO), 5.31 (1H, s, CHAr2), 6.7~7.0, 7.1~7.3 (8H, m, aromatic protons), 7.64, 7.72 (1H, two d, J=5.4 Hz, N=CH). The imine (**10e**) was directly subjected to the [2+2]-cycloaddition reaction in CH_2Cl_2 following the general procedure, giving a mixture of **13e** and **14e** as a colorless oil (2.34 g, 76%, 2 steps) after purification with column chromatography (SiO_2; CH_2Cl_2-acetone 98:2). ^{1}H-NMR (CDCl3): 0.9~1.3 (9H, m, Mex3), 2.27, 2.30, 2.32 (3H, three s, MeCO, intensity ratio; 7.4:1.0:1.5), 3.2~4.8 (6H, m, other protons), 3.78 (6H, s, MeOx2), 5.65, 5.73, 5.79 (1H, three s, intensity ratio; 1.0:2.0:1.5), 6.8~7.0, 7.1~7.3 (8H, two m, aromatic protons). The stereochemistries of the reaction products were determined by converting the mixture of **13e** and **14e** to that of **16f** and **17f** (*vide infra*). The ratio of **13e** to **14e** could be calculated as 3.0:1 by the ^{1}H-NMR spectrum of the mixture of **16f** and **17f**.

(3*S*,4*S*)-4-[(*S*)-1-Benzyloxyethyl]-1-di-*p*-anisylmethyl-3-(1,1-dimethoxyethyl)-2-azetidinone (16a) and Its (3*R*,4*R*)-Isomer (17a). a) Preparation from **13a** and **14a**. Camphorsulfonic acid (6.0 mg, 0.026 mmol) and trimethyl orthoformate (0.50 ml, 4.6 mmol) were added to a solution of **13a** (43.9 mg, 0.093 mmol) in MeOH (1.0 ml) at rt. After stirring at rt for 1.5h, the mixture was diluted with H_2O and satd aq $NaHCO_3$, and extracted with ether. The combined ethereal extracts were washed with satd aq NaCl and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was separated with column chromatography (SiO_2, hexane-AcOEt-CH_2Cl_2 8:2:1) to give **16a** as a colorless oil (42.8 mg, 89%), $[\alpha]_D^{20}$ +4.2° (c 2.14, $CHCl_3$). IR (neat): 2950, 2850, 1755, 1618, 1517, 1245, 1038, 738, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.16 (3H, d, J=5.9 Hz, MeCH), 1.27 (3H, s, $MeC(OMe)_2$), 3.17 (1H, m, C3-H), 3.22 (6H, s, $(MeO)_2C$), 3.5~3.7 (2H, m, C4-H and CHOBn), 3.77, 3.78 (6H, two s, MeOArx2), 4.13, 4.48 (2H, two d, J=each 11.4 Hz, CH_2Ph), 5.77 (1H, s, $CHAr_2$), 6.74~6.87, 7.16~7.24 (13H, two m, aromatic protons). MS m/e: 460 $(M\text{-}MeO\text{-}CO)^+$, 444. Treatments of **14a** (56.9 mg, 0.120 mmol) in the same manner as described for the preparation of **16a** from **13a** gave **17a** as a colorless oil (50.0 mg, 80%), $[\alpha]_D^{20}$ +2.2° (c 1.16, $CHCl_3$). IR (neat): 2950, 2850, 1748, 1618, 1517, 1242, 735, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.11 (3H, d, J=6.5 Hz, MeCH), 1.13 (3H, s, $MeC(OMe)_2$), 3.24, 3.26 (6H, two s, $(MeO)_2C$), 3.5~3.7 (3H, m, C3-H, C4-H, and CHOBn), 3.75, 3.77 (6H, s, MeOArx2), 4.17, 4.55 (2H, two d, J=each 11.7 Hz, CH_2Ph), 5.70 (1H, s, $CHAr_2$), 6.69~6.85, 7.15~7.34 (13H, two m, aromatic protons). MS m/e: 460 $(M\text{-}MeO\text{-}CO)^+$, 444, 268, 227.

b) Preparation from **16f** and **17f**. Tricaprylmethylammonium chloride (2.4 mg, 0.006 mmol), powdered NaOH (18 mg, 0.43 mmol), and benzyl chloride (16 µl, 0.14 mmol) were added to a solution of **16f** (50.5 mg, 0.12 mmol) in toluene (0.3 ml) at 0 °C and the mixture was vigorously stirred at rt for 12h. Additional amounts of powdered NaOH (20mg, 0.48 mmol) and benzyl chloride (16 µl, 0.14 mmol) were added to the reaction mixture and stirring was continued for 2.5 h. The mixture was diluted with H_2O and ether. The ethereal layer was washed successively with 0.2 M HCl, satd aq $NaHCO_3$, and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified with column chromatography (SiO_2, hexane-AcOEt-CH_2Cl_2 8:2:1) to give **16a** as an oil (41.3 mg, 68%). The IR and ^{1}H-NMR spectra of this sample were superimposable on those of **16a** obtained in a). The

same treatments of **17f** (17.3 mg, 0.040 mmol) as described above, gave **17a** as a colorless oil (9.1 mg, 44 %) after purification with column chromatography. The ^{1}H-NMR spectrum of this sample were identical with those of **17a** obtained in a).

(3*S*,4*S*)-1-Di-*p*-anisylmethyl-3-(1,1-dimethoxyethyl)-4-[(*S*)-1-(2-methoxyethoxymethoxy)ethyl]-2-azetidinone (16d) and Its (3*R*,4*R*)-Isomer (17d). a) Preparation from **13d** and **14d.** The same treatments of the mixture of **13d** and **14d** (65.7 mg, 0.139 mmol) as described for the preparation of **16a** from **13a** afforded a mixture of **16d** and **17d** as an oil (62.3 mg, 86%) after purification with column chromatography. By comparing the ^{1}H-NMR spectrum of this mixture with those of the pure samples of **16d** and **17d** prepared in b), it appeared evident that the major component involved in the mixture was **16d.**

b) Preparation from **16f** and **17f.** *N*,*N*-Diisopropylethylamine (22 μl, 0.13 mmol) and 2-methoxyethoxymethyl chloride (14.2 μl, 0.124 mmol) were added to a solution of **16f** (36.1 mg, 0.084 mmol) in CH_2Cl_2 (0.2 ml) at 0 °C. After stirring at rt for 12h, additional amounts of *N*,*N*-diisopropylethylamine (22μl, 0.126 mmol) and 2-methoxyethoxymethyl chloride (14.2 μl, 0.124 mmol) were added to the mixture. After stirring was further continued for 12h, the reaction mixture was diluted with H_2O and ether. The ethereal solution was washed successively with satd aq $NaHCO_3$, 0.2M HCl, and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave a residue which was purified with column chromatography (SiO_2, hexane-ether 1:6), giving **16d** as a colorless oil (35.0 mg, 80%). IR ($CHCl_3$): 2950, 2850, 1740, 1610, 1510, 1242, 1030, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.15 (3H, d, J=5.9 Hz, MeCH), 1.26 (3H, s, MeC(OMe)$_2$), 3.18 (1H, m, C$_3$-H), 3.22 (6H, s, (MeO)$_2$C), 3.35 (3H, s, MeOCH$_2$), 3.45~3.70 (6H, m, other protons), 3.78 (6H, s, MeOArx2), 4.44, 4.58 (2H, two d, J=each 7.0 Hz, OCH$_2$O), 5.73 (1H, s, CHAr$_2$), 6.77~6.89, 7.19~7.33 (8H, two m, aromatic protons). MS m/e: 489 (M-CO)$^+$, 442, 428. Sodium hydride (1 mg, 0.04 mmol) and methoxyethoxymethyl chloride (1 ml, 0.009 mmol) were added to a solution of **17f** (1.3 mg, 0.030 mmol) in THF (0.2 ml) at 0 °C. After stirring at the same temperature for 3 h and at rt overnight, the mixture was diluted with H_2O and extracted with ether. The ethereal layer was separated and treated in the same manner as described above, gave **17d** as a colorless oil (1.5 mg, 94%) after purification with column chromatography (SiO_2, hexane-ether 1:6~1:7). IR ($CHCl_3$): 2950, 2850, 1740, 1608, 1508, 1200, 1032, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.13 (3H, d, J=6.2 Hz, MeCH), 1.25 (3H, s, MeC(OMe)$_2$), 3.25, 3.27 (6H, two s, (MeO)$_2$C), 3.33 (1H, m, C$_3$-H), 3.36 (3H, s, MeOCH$_2$), 3.45~3.65 (6H, m, other protons), 3.78 (6H, s, MeOArx2), 4.47, 4.67 (2H, two d, J=each 7.2 Hz, OCH$_2$O), 5.62 (1H, s, CHAr$_2$), 6.78~6.88, 7.18~7.31 (8H, two m, aromatic protons). MS m/e: 489 (M-CO)$^+$, 442, 428, 227.

(3*S*,4*S*)-1-Di-*p*-anisylmethyl-3-(1,1-dimethoxyethyl)-4-[(*S*)-1-hydroxyethyl]-2-azetidinone (16f) and Its (3*R*,4*R*)-Isomer (17f). a) Preparation from **13b** and **14b.** Treatments of **13b** (32.1 mg, 0.065 mmol) in the same manner as described in b) afforded **16f** as a colorless oil (17.5 mg, 63%) after purification with column chromatography. The diastereomer (**14b**) (14.0 mg, 0.028 mmol) was similarly treated under acetalization conditions, giving **17f** (1.8 mg, 15%) after purification with column chromatography. ^{1}H-NMR spectra of these compounds were identical with those of **16f** and **17f** obtained in b), respectively.

b) Preparation from **13c** and **14c.** Camphorsulfonic acid (9.4 mg, 0.040 mmol) and trimethyl orthoformate (1.00 ml, 9.14 mmol) were added to a solution of the mixture of **13c** and **14c** (0.101 g, 0.216 mmol) in MeOH (3.0 ml) at rt. After stirring for 1.5 h, the mixture was diluted with H_2O and satd aq $NaHCO_3$, then extracted with ether. The combined ethereal extracts were washed with satd aq NaCl and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave a crude mixture of **16f** and **17f** as an oil. Based on the ^{1}H-NMR spectrum of this sample, the ratio of **16f** and **17f** could be calculated as 6.0:1. The mixture was separated with column chromatography (SiO_2, CH_2Cl_2-AcOEt 4:1), giving the major product (**16f**) as a colorless oil (73.8 mg, 79%) from the less polar fraction, $[\alpha]_D^{20}$ -3.8° (c 1.41, $CHCl_3$). IR ($CHCl_3$): 3000, 2850, 1742,

1618, 1518, 1250, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.13 (3H, d, J=6.2 Hz, MeCHOH), 1.26 (3H, s. MeC(OMe)2), 1.4~1.6 (1H, br, OH), 3.16 (1H, d, J=2.3 Hz, C3-H), 3.21, 3.24 (6H, two s, $(MeO)_2C$), 3.56 (1H, dd, J=2.3, 6.5 Hz, C4-H), 3.78, 3.80 (6H, two s, MeOArx2), 6.8~7.0, 7.2~7.4 (8H, two m, aromatic protons). MS m/e: 429 (M^+), 268, 227. The minor product (**17f**) was also obtained as a colorless oil (10.0 mg, 11%) from the more polar fraction, $[\alpha]_D^{20}$ +8.1° (c 0.76, $CHCl_3$). IR ($CHCl_3$): 3000, 2850, 1742, 1618, 1518, 1250, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 1.07 (3H, d, J=6.4Hz, MeCH), 1.36 (3H, s, MeC), 1.5~1.6 (1H, br, OH), 3.27 (6H, s, C(OMe)2), 3.42 (1H, d, J=2.2 Hz, C3-H), 3.6~3.8 (2H, m, MeCHOH and C4-H), 3.79, 3.80 (6H, two s, MeOArx2), 5.84 (1H, s, CHAr2), 6.8~7.0, 7.2~7.4 (8H, two m, aromatic protons). MS m/e: 429 (M^+), 268, 227.

c) Preparation from **13e** and **14e**. The same treatments of the mixture of **13e** and **14e** (0.100 g, 0.220 mmol) as described in b), gave a mixture of **16f** and **17f** as an oil (88.0 mg, 97%) after purification with column chromatography. The ratio of **16f** to **17f** could be calculated as 3.0:1 by the ^{1}H-NMR spectrum of the mixture.

(3*S*,4*S*)-4-[(*S*)-1-Benzyloxyethyl]-1-di-*p*-anisylmethyl-3-[(*R*)-1-hydroxyethyl]-2-azetidinone and Its 3-[(*S*)-1-Hydroxyethyl]-isomer (18 and 19). a) Preparation of **18** and **19** by the reduction with potassium tri-*sec*-butylborohydride in the presence of potassium iodide.[24] A 1.0 M solution of potassium tri-*sec*-butylborohydride in THF (0.84ml, 0.84 mmol) was added to a suspension of **13a** (0.197g, 0.416 mmol) and potassium iodide (69.0 mg, 0.416 mmol) in THF (4.2 ml) at 0 °C. After stirring at the same temperature for 1h, the reaction mixture was diluted with 1M HCl (0.84 ml) and extracted with AcOEt. The combined extracts were washed with satd aq NaCl, dried over anhyd $MgSO_4$, filtered, then concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, hexane-ether 1:9~0:1) to give a mixture of **18** and **19** as a colorless caramel (0.182 g, 92 %) with recovery of the starting material (**13a**) (7.6 mg, 4%). The ratio of **18** to **19** could be calculated as 12:1 based on the ^{1}H-NMR spectrum of the mixture measured in C_6D_6. The methyl groups of benzyloxyethyl moieties appeared as two doublets at 0.86 and 0.94 ppm with an integration ratio of 12:1. The physical and spectral data of **18** and **19** separated with column chromatography were described in b)

b) Preparation of **18** and **19** by the reduction with potassium triethylborohydride.[25] A 1.0 M solution of potassium triethylborohydride in THF (0.75 ml, 0.75 mmol) was added to a solution of **13a** (0.321g, 0.678 mmol) in THF (6.8 ml) at -78 °C. After stirring at the same temperature for 1h, the reaction mixture was diluted with 1M HCl (0.7 ml), stirred at rt for 1h, and extracted with AcOEt. The combined extracts were washed with satd aq NaCl, dried over anhyd $MgSO_4$, filtered, then concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, CH_2Cl_2-acetone 1:0~9:1) to give a mixture of **18** and **19** as a colorless caramel (0.316 g, 98 %). The ratio of **18** to **19** could be calculated as 12:1 in a similar manner to that described in a). Separation of the mixture of **18** and **19** with medium pressure column chromatography (SiO_2, lobar column, Merck art. 10401, CH_2Cl_2-AcOEt 9:1) afforded pure **18** and **19** both as colorless crystals. Recrystallization of **18** from hexane-AcOEt or isopropanol gave an analytical sample as colorless crystals, mp 102~102.5 °C and $[\alpha]_D^{20}$ -11.5° (c 1.03, $CHCl_3$). IR ($CHCl_3$): 3300~3500 br, 2850~3000 br, 1740, 1618, 1518, 1250, 1038 cm^{-1}, ^{1}H-NMR ($CDCl_3$): 1.13 (3H, d, J=5.9 Hz, MeCHOBn), 1.25 (3H, d, J=6.4 Hz, MeCHOH), 2.0 (1H, br, OH), 2.86 (1H, dd, J=2.2, 5.9 Hz, C3-H), 3.49 (1H, m, CHOBn), 3.70 (1H, m, C4-H), 3.76, 3.78 (6H, two s, MeOx2), 3.9~4.2 (1H, m, CHOH), 4.12, 4.47 (2H, two d, J=11.4 Hz, $PhCH_2$), 5.77 (1H, s, CHAr2), 6.7~7.4 (13H, m, aromatic protons). ^{1}H-NMR (C_6D_6): 0.91 (3H, d, J=6.2 Hz, MeCHOBn), 1.16 (3H, d, J=6.3 Hz, MeCHOH), 1.90 (1H, br, OH), 2.59 (1H, dd, J=2.3, 6.3 Hz, C3-H), 3.26 (1H, m, CHOBn), 3.27, 3.29 (6H, two s, MeOx2), 3.69 (1H, dd, J=2.3, 7.5 Hz, C4-H), 3.90 (1H, m, MeCHOH), 3.91, 4.22 (2H, two d, J=each 11.7 Hz, $PhCH_2$), 5.97 (1H, s, CHAr2), 6.78, 7.36 (8H, two m, C_6H_4x2), 7.16 (5H, s, C_6H_5). MS m/e: 475 (M^+), 447 $(M-CO)^+$, 384 $(M-Bn)^+$, 356. Found: C, 73.05; H, 7.22; N, 3.14 %. Calcd for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95%. The undesired product (**19**) was recrystallized from hexane-AcOEt to give an analytical sample as colorless

crystals, mp 127 °C and $[\alpha]_D^{25}$ +20.0° (c 0.15, $CHCl_3$). IR ($CHCl_3$): 3400~3600 br, 2850~3000 br, 1740, 1610, 1515, 1242, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.14 (3H, d, J=5.9 Hz, MeCHOBn), 1.25 (3H, d, J=6.3 Hz, MeCHOH), 2.35 (1H, br, OH), 2.82 (1H, dd, J=2.0, 6.9 Hz, C3-H), 3.58 (1H, m, CHOBn), 3.64 (1H, dd, J=2.3, 7.0 Hz, C4-H), 3.78, 3.79 (6H, two s, MeOx2), 3.7~4.2 (1H, m, MeCHOH), 4.13, 4.48 (2H, two d, J=11.4 Hz, $PhCH_2$), 5.77 (1H, s, CHAr2), 6.7~7.4 (13H, m, aromatic protons). ^{1}H-NMR(C_6D_6): 0.81 (3H, d, J=6.2 Hz, MeCHOBn), 1.10 (3H, d, J=6.3 Hz, MeCHOH), 1.30 (1H, br, OH), 2.55 (1H, dd, J=2.4, 6.6 Hz, C3-H), 3.22 (1H, m, CHOBn), 3.27, 3.29 (6H, two s, MeOx2), 3.43 (1H, dd, J=2.4, 7.9 Hz, C4-H), 3.83 (1H, m, MeCHOH), 3.90, 4.21 (2H, two d, J=each 11.5 Hz, $PhCH_2$), 5.96 (1H, s, CHAr2), 6.78, 7.36 (8H, m, C_6H_4x2), 7.16 (5H, s, C_6H_5). MS m/e: 475 (M^+), 447 $(M\text{-}CO)^+$, 384 $(M\text{-}Bn)^+$, 340. Found: C, 72.32; H, 7.01; N,3.12 %. Calcd for $C_{29}H_{33}NO_5$ 0.3H_2O: C, 72.42; H, 7.04; N, 2.91 %. The pure sample of **18** could be directly obtained in 76% yield by a single crystallization of the crude reduction product from isopropanol. In another experiment, a crude diastereomeric mixture of **13a** and **14a** (6.90 g) produced under the best conditions of the [2+2]-cycloaddition reaction (**Table 1**, run 2), was reduced with potassium triethylborohydride (19.0 ml, 19.0 mmol) without separation. When the mixture of the crude reduction products (7.00 g) was immediately recrystallized from isopropanol (7.0 ml), an almost pure sample of **18** (3.23 g) could be obtained in 58% overall yield based on **9a** [1.90g, 11.6 mmol (calculated by taking into account the amount of **12** (3.08 g, 13.2 mmol) used for preparation of **9a** and the chemical yield of **9a** from **12**)].

c) Preparation of **18** by the epimerization of **19**.[26] Diethyl azodicarboxylate (6.6 µl, 0.042 mmol) was added to a solution of **19** (5.7 mg, 0.012 mmol), triphenylphosphine (11 mg, 0.042 mmol), and formic acid (1.9 µl, 0.050 mmol) in THF (0.2 ml) at 0 °C. After stirring at rt for 2h, the mixture was diluted with phosphate buffer (pH 5, 0.5 ml) and extracted with AcOEt. The combined extracts were dried over anhyd $MgSO_4$ and concentrated *in vacuo*. The concentration residue was purified with preparative TLC (SiO_2; CH_2Cl_2-AcOEt 9:1) to give (3*S*,4*S*)-4-[(*S*)-1-benzyloxyethyl]-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-formyloxyethyl]-2-azetidinone (5.5 mg, 91%). ^{1}H-NMR ($CDCl_3$): 1.16 (3H, d, J=6.0Hz, MeCHOBn), 1.36 (3H, d, J=6.4 Hz, MeCHOCO), 2.97 (1H, dd, J=1.4, 7.1 Hz, C4-H), 3.59 (2H, m, CHOBn and C4-H), 3.78, 3.79 (6H, two s, MeOx2), 4.10, 4.47 (2H, two d, J=each 11.3 Hz, $PhCH_2$), 5.27 (1H, m, CHOCO), 5.76 (1H, s, CHAr2), 6.72~7.31 (13H, m, aromatic protons), 7.90 (1H, s, HCOO). Anhyd K_2CO_3 (2 mg) was added to a solution of the formate in methanol (2 ml) and the mixture was stirred at rt for 10 min. Filtration and concentration *in vacuo* followed by purification with column chromatography (SiO_2, ether), gave **18** (5.1 mg, 90% from **19**). The ^{1}H-NMR spectrum of this sample were identical with those of **18** obtained in b).

(3*S*,4*S*)-4-[(*S*)-1-Benzyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone (20). A solution of CAN (3.26 g, 5.95 mmol) in H_2O-MeCN (1:9) (19.8 ml) was added to a solution of **18a** (0.943 g, 1.98 mmol) in H_2O-MeCN (1:9) (14.7 ml) at -10 °C. The mixture was stirred vigorously at the same temperature for 3h, then diluted with 2M NaOH (11.8 ml). After stirring at rt for 30 min, the mixture was filtered. The filtrate was neutralized to pH 8 with 1M HCl and extracted with $CHCl_3$. The combined organic extracts were dried over anhyd $MgSO_4$, filtered, and concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, CH_2Cl_2-acetone 4:1~2:1) to give **20** as colorless crystals (0.461 g, 93%). Recrystallization from AcOEt gave an analytical sample of **20** as colorless crystals, mp 129~130 °C and $[\alpha]_D^{25}$ +61.5° (c 1.45, $CHCl_3$). IR (KBr): 3380, 3000, 2900, 1735, 1475, 1452, 1380, 1361, 1335, 1240, 1179, 1136, 1104, 1093, 1069, 1001, 770, 665, 600, 560 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.25 (3H, d, J=5.9 Hz, MeCHOBn), 1.31 (3H, d J=6.4 Hz, MeCHOH), 2.86 (1H, m, C3-H), 3.58 (2H, m, CHOBn and C4-H), 4.16 (1H, m, CHOH), 4.42, 4.70 (2H, two d, J=11.6 Hz, $PhCH_2$), 5.98 (1H, bs, NH), 7.25 (5H, s, C_6H_5). MS m/e: 249 (M^+), 232 $(M\text{-}OH)^+$,204 $(M\text{-}MeCHOH)^+$. Found: C, 67.45; H, 7.82; N, 5.51 %. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62 %.

(3*S*,4*S*)-4-[(*S*)-1-Benzyloxyethyl]-3-[(*R*)-(1-*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (21). A mixture of **20** (0.252g, 0.530 mmol), imidazole (0.252 g, 3.70 mmol), and *t*-butyldimethylchlorosilane (0.16 g, 1.47 mmol) in DMF (2.0 ml) was stirred at rt for 12h. The mixture was diluted with AcOEt and washed with H_2O. The organic phase was separated, dried over anhyd $MgSO_4$, and concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, CH_2Cl_2-acetone 1:0~19:1) to give **21** as a colorless oil (0.302 g, 97%), $[\alpha]_D^{25}$ +32.5° (c 2.37, $CHCl_3$). IR (neat): 3470, 2950, 2880, 1760, 1378, 1259, 1140, 1100, 837, 780, 735, 699 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 1.22 (3H, d, J=6.2 Hz, MeCHOSi), 1.25 (3H, d, J=5.9Hz, MeCHOBn), 2.74 (1H, m, C_3-H), 3.52 (2H, m, CHOBn, C_4-H), 4.17 (1H, m, CHOSi), 4.40, 4.68 (2H, two d, J=each 11.7 Hz, $PhCH_2$), 5.87 (1H, bs, NH), 7.32 (5H, s, C_6H_5). MS m/e: 363 (M^+), 348 $(M-Me)^+$, 306 $(M-Bu)^+$.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*S*)-1-hydroxyethyl]-2-azetidinone (22). A mixture of **21** (45.0 mg, 0.124 mmol) and 10% Pd-C (4 mg) in AcOEt (3.0 ml) was stirred at rt for 1d under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give **22** as a colorless caramel (33.8 mg, quantitative yield), $[\alpha]_D^{25}$ -11.5° (c 1.48, $CHCl_3$). IR (neat): 3300, 2950, 2870, 1742, 1463, 1375, 1255, 1140, 1098, 1054, 960, 834, 810, 777cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.23 (3H, d, J=6.2 Hz, MeCHOH), 1.25 (3H, d, J=6.2Hz, MeCHOSi), 2.85 (1H, m, C_3-H), 3.55 (1H, dd, J=2.2, 6.8 Hz, C_4-H), 3.72 (1H, m, CHOH), 4.20 (1H, quint, J=6.2 Hz, CHOSi), 6.11 (1H, bs, NH). MS m/e: 258 $(M-Me)^+$, 216 $(M-Bu)^+$.

(3*S*,4*S*)-4-Acetyl-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (23). a) Preparation by the oxidation of **22** with chromium(VI) trioxide. Chromium(VI) trioxide (2.08 g, 2.08 mmol) was added slowly to pyridine (21 ml). A solution of **22** (0.570 g, 2.08 mmol) in pyridine (5.0 ml) was added to the pyridine solution containing chromium(VI) trioxide at 0 °C. The mixture was stirred at 30 °C for 1h and at 40 °C for 1.5 h, then diluted with 1M HCl and AcOEt. The organic layer was separated, washed with sat aq NaCl, dried over anhyd $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, hexane-AcOEt 1:1) to give **23** as colorless crystals (0.523 g, 93%). Recrystallization from hexane gave an analytical sample of **23** as colorless crystals, mp 71~74 °C and $[\alpha]_D^{25}$ -14.3° (c 0.57, $CHCl_3$). IR (KBr): 3250, 2980, 2950, 2880, 1754, 1730, 1708, 1364, 1256, 1141, 1073, 1042, 961, 838, 811, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.11 (6H, s, Me_2Si), 0.90 (9H, s, Me_3C), 1.31 (3H, d, J=6.4 Hz, MeCHOSi), 2.25 (3H, s, MeCO), 3.08 (1H, m, C_3-H), 4.28 (2H, m, C_4-H, CHOSi), 6.05 (1H, bs, NH). MS m/e: 256 $(M-Me)^+$, 214 $(M-Bu)^+$. Found: C,57.72; H, 9.46; N, 5.15%. Calcd for $C_{13}H_{25}NO_3Si$, C, 57.53; H, 9.28; N, 5.16%.

b) Preparation by the oxidation of **22** with a combination of *N*-chlorosuccinimide, dimethyl sulfide, and triethylamine. Freshly recrystallized *N*-chlorosuccinimide (0.125 g, 0.936 mmol) was dissolved in toluene (5.0 ml) at 40 °C and the solution was cooled to rt. Dimethyl sulfide (58.1 mg, 0.936 mmol) was added to the toluene solution at rt and the formed suspension was cooled to 0 °C. After stirring at the same temperature for 20 min, the suspension was further cooled to -25 °C. A solution of **22** (64.0 mg, 0.234 mmol) in toluene (0.9 ml) was added to the suspension. After stirring for 2.7h, triethylamine (0.136 ml, 0.976 mmol) was added to the reaction mixture. The mixture was gradually warmed up to rt, stirred for 15 min, then diluted with 1M HCl (1.0 ml). The organic layer was separated, dried over anhyd $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified with column chromatography to give **23** as colorless crystals (60.0 mg, 95%). This sample showed the same ^{1}H-NMR spectrum as that of **23** obtained in a).

c) Preparation by the oxidation of **26** with sodium peroxydisulfate. A solution of sodium peroxydisulfate in H_2O (90%, 0.815 g, 3.08 mmol) and a solution of disodium hydrogenphosphate (0.437 g, 3.08 mmol) in H_2O (7.7 ml) were added slowly to a stirred solution of **26** (0.153 g, 0.308

mmol) in acetone-H_2O (9:1, 16.5 ml) under reflux. The mixture was heated at reflux with stirring for 40 min. After cooling, the mixture was concentrated *in vacuo* to remove acetone and the residual aqueous solution was extracted with AcOEt. The combined extracts were dried over anhyd $MgSO_4$, filtered, then concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, CH_2Cl_2-AcOEt 1:0~9:1) to give **23** as a colorless solid (74.4 mg, 89 %). This sample showed the same ^{1}H-NMR spectrum as that of **23** obtained in a).

(3*S*,4*S*)-4-[(*S*)-1-Benzyloxyethyl]-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-2-azetidinone (24). A mixture of **18** (0.804 g, 1.69 mmol), 4-(dimethylamino)pyridine (0.310 g, 2.54 mmol), and *t*-butyldimethylchlorosilane (0.306g, 2.03 mmol) in CH_2Cl_2 (0.8 ml) was stirred at rt for 1d. The reaction mixture was diluted with CH_2Cl_2 and washed successively with 1M HCl, satd aq $NaHCO_3$, and satd aq NaCl. The organic phase was dried over anhyd $MgSO_4$ and concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2; hexane-AcOEt 4:1) to give **24** as colorless crystals (0.946 g, 95%). An analytical sample of **24** was prepared as colorless crystals by recrystallization from isopropanol. Mp 84~85°C and $[\alpha]_D^{25}$+19.8° (c 1.38, $CHCl_3$). IR (KBr): 3080, 3040, 2980, 2940, 2860, 1742, 1610, 1510, 1390, 1250, 1040, 825 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.05, 0.03 (6H, two s, Me_2Si), 0.82 (9H, s, Me_3C), 1.16 (3H, d, J=5.7 Hz, MeCH), 1.22 (3H, d, J=6.2 Hz, MeCH), 2.75 (1H, dd, J=2, 6.2 Hz, C3-H), 3.4~3.8 (2H, m, CHOBn, C4-H), 3.76, 3.78 (6H, two s, MeOx2), 4.1 (1H, m, CHOSi), 3.99, 4.42 (2H, each d, J=11 Hz, $PhCH_2$), 5.81 (1H, s, $CHAr_2$), 6.7~ 7.0, 7.1~7.3 (13H, two m, aromatic protons). MS m/e: 589 $(M)^+$, 561 $(M\text{-}CO)^+$, 532 $(M\text{-}Bu)^+$. Found: C, 71.40; 8.27; N, 2.33%. Calcd for $C_{35}H_{47}NO_5Si$: C, 71.27; H, 8.03; N, 2.37%.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-4-[(*S*)-1-hydroxyethyl]-2-azetidinone (25). A 5M solution of HCl in MeOH (85 μl) and 5% Pd-C (0.425 g) were successively added to a solution of **24** (2.51 g, 4.25 mmol) in toluene (8.5 ml), and the mixture was stirred at 40 °C for 12h under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, hexane-AcOEt 7:3) to give **25** as a colorless caramel (2.08 g, 98%), $[\alpha]_D^{25}$ -29.1° (c 3.32, $CHCl_3$). IR (KBr): 3400, 2980, 2940, 2870, 1730, 1610, 1510, 1250, 1030, 825 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.06, 0.01 (3H, s, Me_2Si), 0.79 (9H, s, Me_3C), 1.13 (3H, d, J=5.9 Hz, MeCH), 1.23 (3H, d, J=6.2 Hz, MeCH), 2.71 (1H, dd, J=2, 6.5 Hz, C3-H), 3.64 (2H, m, C4-H, CHOH), 3.78, 3.81 (6H, two s, MeOx2), 3.9 (1H, br, OH), 4.03 (1H, m, CHOSi), 5.98 (1H, s, $CHAr_2$), 6.8~7.0, 7.1~7.5 (8H, two m, aromatic protons). MS m/e: 442 $(M\text{-}Bu)^+$. Found: C, 67.24; H, 8.53; N,2.76. Calcd for $C_{28}H_{41}NO_5Si$: C, 67.30; H, 8.27; N, 2.80%.

(3*S*,4*S*)-4-Acetyl-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-2-azetidinone (26). The same treatments of **25** (1.45 g, 2.89 mmol) as described for the prepartion of **23** from **22** to give **26** as colorless crystals (1.41 g, 98%) after purification with column chromatography (SiO_2; CH_2Cl_2-AcOEt 1:0~9:1). An analytical sample of **26** was prepared as colorless crystals by recrystallization from hexane. Mp 85 °C and $[\alpha]_D^{20}$ +27.4° (c 1.32, $CHCl_3$). IR (KBr): 2980, 2940, 2860, 1763, 1730, 1612, 1512, 1248, 1032, 825 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 0.09, 0.10 (6H, two s, Me_2Si), 0.90 (9H, s, Me_3C), 1.23 (3H, d, J=6.2 Hz, MeCH), 1.83 (3H, s, MeCO), 2.93 (1H, m, C3-H), 3.77, 3.78 (6H, s, MeOx2), 4.11 (1H, d, J=2.4 Hz, C4-H), 4.22 (1H, m, CHOSi), 5.81 (1H, s, $CHAr_2$), 6.77~7.31 (8H, m, aromatic protons). MS m/e: 497 (M^+), 440 $(M\text{-}Bu)^+$. Found: C, 67.43; H, 8.01; N, 2.79. Calcd for $C_{28}H_{39}NO_5Si$: C, 67.57; H, 7.90; N, 2.81%.

(3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (6). a) Oxidation with *m*-chloroperbenzoic acid. *m*-Chloroperbenzoic acid (90%, 0.221 g, 1.15 mmol) was added to a solution of **23** (16.3 mg, 0.0602 mmol) in AcOEt (2.0 ml). After stirring at 35 °C for 2h, the mixture was diluted with AcOEt and washed successively with aq $NaHSO_3$, satd aq $NaHCO_3$, and

satd aq NaCl. The organic phase was dried over anhyd $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified with column chromatography (SiO_2, hexane-ether 3:2) to give **6** as colorless crystals (16.1 mg, 93%). Recrystallization from hexane gave an analytical sample of **6** as colorless crystals, mp 108~109 °C and $[\alpha]_D^{25}$ +47.8° (c 0.56, $CHCl_3$) [lit.,[12b] mp 101~103 °C and $[\alpha]_D^{25}$ +47.9° (c 1.00, $CHCl_3$); lit.,[12f] mp 104~106 °C and $[\alpha]_D^{25}$ +48.8° (c 0.41, $CHCl_3$); lit.,[12g] mp 107-108 °C and $[\alpha]_D^{20}$ +50° (c 0.5, $CHCl_3$)]. IR (KBr): 2950, 1787, 1746, 1235, 1164, 1080, 1040, 839, 779 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.87 (9H, s, Me_3C), 1.26 (3H, d, J=6.4 Hz, MeCH), 2.10 (3H, s, MeCO), 3.18 (1H, dd, J=1.3, 3.5 Hz, C3-H), 4.22 (1H, dq, J=3.5, 6.4 Hz, CHOSi), 5.84 (1H,d, J=1.3 Hz, C4-H), 6.51 (1H, bs, NH). MS m/e: 230 $(M\text{-}Bu)^+$. Found: C, 54.45; H, 8.88; N, 4.80%. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H,8.77; N, 4.87%.

b) Oxidation with monoperphthalic acid. Hydrogen peroxide (35%, 2.5 ml, 25 mmol) was added to a solution of Na_2CO_3 (2.29 g, 21.6 mmol) in H_2O (10.8 ml) at 0 °C. Phthalic anhydride (3.20 g, 21.6 mmol) was added to the aqueous solution at -5 °C. After stirring at the same temperature for 1.5 h, the mixture was diluted with a solution of sulfuric acid (2.25 g, 21.6 mmol) in H_2O (4.5 ml) and AcOEt (11 ml). The organic layer was separated, washed with satd aq NH_4OH, and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration gave a solution of monoperphthalic acid in AcOEt. The ketone **23** (0.410 g, 1.51 mmol) was added to the solution of monoperphthalic acid in AcOEt at rt. After stirring at the same temperature for 8h, the mixture was diluted with 20% aq $NaHSO_3$ to precipitate colorless crystals. The crystals were filtered off, and the filtrate was washed with 2M NaOH and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oil which was purified with column chromatography (SiO_2, CH_2Cl_2-AcOEt 1:0~9:1) to give **6** as colorless crystals (0.334 g, 77 %). This sample showed the same ^{1}H-NMR spectrum as that of **6** obtained in a).

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-4-[(*S*)-1-(*p*-toluenesulfonyloxy)ethyl]-2-azetidinone (27a). *p*-Toluenesulfonyl chloride (0.535 g, 2.81 mmol) was added to a solution of **25** (0.933 g, 1.87 mmol) in pyridine (2.0 ml) at 0 °C. After stirring at the same temperature for 12h, the reaction mixture was diluted with AcOEt and H_2O. The organic layer was washed with satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified with column chromatography (SiO_2, hexane-AcOEt 73:27), giving **27a** as a colorless caramel (1.00 g, 82%), $[\alpha]_D^{25}$ -22.2° (c 2.51, $CHCl_3$). IR ($CHCl_3$): 2950, 1750, 1615, 1514, 1368, 1179 cm^{-1}. ^{1}H-NMR $CDCl_3$): -0.04, 0.04 (6H, two s, Me_2Si), 0.83 (9H, s, Me_3C), 1.11 (3H, d, J=6.4 Hz, MeCHOSi), 1.15 (3H, d, J=6.4 Hz, MeCHOTs), 2.43 (3H, s, MePh), 2.85 (1H, dd, J=2, 5 Hz, C3-H), 3.73 (1H, m, C4-H), 3.80 (6H, two s, MeOx2), 4.08 (1H, m, MeCHOSi), 4.46 (1H, m, MeCHOTs), 5.67 (1H, s, $CHAr_2$), 6.83, 7.14 (8H, two m, C_6H_4x2), 7.27, 7.66 (4H, two d, J=each 8.4Hz, $C_6H_4SO_2$). MS m/e: 653 (M^+), 596 $(M\text{-}Bu)^+$.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*S*)-1-(*p*-toluenesulfonyloxy)ethyl]-2-azetidinone (27b). This was prepared from **22** (0.217 g, 0.795 mmol) in a similar manner to that described for the preparation of **27a** from **25**. The *p*-toluenesulfonate (**27b**) obtained as colorless crystals (0.289 g, 85%) after purification with column chromatography, showed mp 125-126 °C (isopropyl ether) and $[\alpha]_D^{20}$ -19.4° (c 1.55, $CHCl_3$). IR (KBr): 3250, 2950, 1754, 1714, 1360, 1258, 1202, 1190, 1175, 1080, 990, 913, 841, 811, 773, 555 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.05, 0.06 (6H, two s, Me_2Si), 0.86 (9H, s, Me_3C), 1.17 (3H, d, J=6.3Hz, MeCHOSi), 1.32 (3H, d, J=6.6 Hz, MeCHOTs), 2.45 (3H, s, MeC_6H_4), 2.73 (1H, m, C3-H), 3.68 (1H, m, C4-H), 4.16 (1H, m, CHOSi), 4.58 (1H, m, $CHOSO_2$), 5.78 (1H, bs, NH), 7.35, 7.79 (4H, two d, J=each 8.4 Hz, C_6H_4). MS m/e: 370 $(M\text{-}Bu)^+$. Found: C, 56.19; H, 7.81; N,3.20; S, 7.60%. Calcd for $C_{20}H_{33}NO_5SSi$; C, 56.17; H, 7.78; N, 3.28; S, 7.50%.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-4-[(*RS*)-1-iodoethyl]-2-azetidinone (28a). Sodium iodide (0.830 g, 5.55 mmol) was added to a solution of **27a** (0.727 g, 1.11

mmol) in acetone (4.5 ml). After heating at reflux for 12h, the reaction mixture was diluted with AcOEt and H_2O. The organic layer was separated, washed with satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified with column chromatography (SiO_2; hexane-AcOEt 4:1), giving **28a** as a colorless oil (0.607 g, 90%). The ^{1}H-NMR spectrum revealed that **28a** consisted of an epimeric mixture with respect to the 1-iodoethyl group in a ratio of 5:2. IR (neat): 2950, 1755, 1610, 1585, 1510, 1460, 1375, 1302, 1250, 1175, 1033, 830, 776 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 0.01, 0.06, 0.07, 0.10 (6H, four s, Me_2Si, intensity ratio 2:5:2:5), 0.87, 0.91 (9H, two s, Me_3C, intensity ratio 2:5), 1.26, 1.31 (3H, two d, J=6.4, 6.2 Hz, MeCHOSi, intensity ratio 5:2), 1.75, 1.77 (3H, two d, J=6.8, 7.0 Hz, MeCHI, intensity ratio 2:5), 2.96 (1H, m, C_3-H), 3.78 (3H, s, MeO), 3.79, 3.80 (3H, two s, MeO, intensity ratio 2:5), 3.8~4.3 (3H, m, C_4-H, CHI, CHOSi), 5.67, 5.83 (1H, two s, $CHAr_2$, intensity ratio 5:2), 6.87, 7.28 (8H, two m, aromatic protons). MS m/e: 552 $(M\text{-}Bu)^+$.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*RS*)-1-iodoethyl]-2-azetidinone (28b). Treatments of **27b** (0.124 g, 0.290 mmol) in the same manner as described for the preparation of **28a** from **27a** gave **28b** as colorless crystals (0.101 g, 91%) after purification with column chromatography, mp 145~146 °C. This sample (**28b**) was found to consist of an epimeric mixture with respect to the 1-iodoethyl group in a ratio of 6:5 by the ^{1}H-NMR spectrum. IR (KBr): 3170, 3100, 2950, 1766, 1722, 1250, 1181, 1138, 1101, 1050, 960, 832, 778 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.25, 1.34 (3H, two d, J=6.2, 6.4 Hz, MeCHOSi), 1.91 (3H, d, J=6.8 Hz, MeCHI), 2.72, 2.89 (1H, two m, C_3-H, intensity ratio 6:5), 3.7~3.9 (1H, m, C_4-H), 4.0~4.3 (2H, m, CHI, CHOSi), 5.91 (1H, bs, NH). MS m/e: 368 $(M\text{-}Me)^+$, 326 $(M\text{-}Bu)^+$. Found: C, 40.72; H, 6.90; N, 3.54%. Calcd for $C_{13}H_{26}IO_2Si$: C, 40.73; H, 6.84; N, 3.65%.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-1-di-*p*-anisylmethyl-4-vinyl-2-azetidinone (29a). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.202 ml, 1.35 mmol) was added to a solution of **28a** (0.411 g, 0.675 mmol) in toluene (2.7 ml). After stirring at 100 °C for 12 h, the mixture was concentrated. The concentration residue was purified with column chromatography (SiO_2, hexane-AcOEt 4:1~7:3) to give **29a** as a colorless oil (0.294 g, 91%), $[\alpha]_D^{25}$+52.5° (c 1.18, $CHCl_3$). IR (neat): 2950, 1755, 1613, 1588, 1513, 1462, 1304, 1250, 1178, 1035, 830, 779 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.02, 0.05 (6H, two s, Me_2Si), 0.83 (9H, s, Me_3C), 1.17 (3H, d, J=6.2Hz, MeCH), 2.88 (1H, dd, J=2, 5 Hz, C_3-H), 3.79, 3.80 (6H, two s, MeOx2), 4.09 (2H, m, C_4-H and CHOSi), 5.03 (1H, bd, J=9.5 Hz, *trans*-CH=CH_2), 5.12 (1H, bd, J=7.5 Hz, *cis*-CH=CH_2), 5.64 (1H, m, CH=CH_2), 5.80 (1H, s, $CHAr_2$), 6.83, 7.17 (8H, two m, aromatic protons). MS m/e: 424$(M\text{-}Bu)^+$.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-vinyl-2-azetidinone (29b). a) Preparation from **29a.** A solution of CAN (0.851 g, 1.55 mmol) in H_2O (5.0 ml) was added to a solution of **29a** (0.249 g, 0.518 mmol) in CH_3CN (5.2 ml) at -10 °C. After vigorous stirring at the same temperature for 1h, the mixture was diluted with 2M NaOH (1.5 ml) and extracted with AcOEt. The organic extracts were conbined, washed with satd aq NaCl, dried over anhyd $MgSO_4$, then concentrated *in vacuo*. The concentration residue was purified with column chromatography (SiO_2, CH_2Cl_2-AcOEt 1:0~9:1) to give **29b** as colorless crystals (98.0 mg, 74%). An analytical sample of **29b** was obtained by recrystallization from pentane, mp 63~64.5 °C and $[\alpha]_D^{25}$ -24.5° (c 1.05, $CHCl_3$). IR (KBr): 2950, 1760, 1720, 1253, 1140, 1104, 1060, 1030, 964, 835, 805, 777 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.21 (3H, d, J=6.4 Hz, MeCH), 2.87 (1H, m, C_3-H), 4.0~4.4 (2H, m, C_4-H, CHOSi), 5.15 (1H, d, J=9.8 Hz, *cis*-CH=CH_2), 5.29 (1H, d, J=15.7 Hz, *trans*-CH=CH_2), 5.96 (1H, ddd, J=6.8, 9.8, 15.7 Hz, CH=CH_2), 5.98 (1H, bs, NH). MS m/e: 178 $(M\text{-}Bu)^+$. Found: C, 60.96; H, 9.78; N, 5.43%. Calcd for $C_{13}H_{25}NO_2Si$: C, 61.13; H, 9.86; N, 5.48%.

b) Preparation from **28b**. Treatments of **28b** (64.0 mg, 0.167 mmol) in the same manner as described for the preparation of **29b** from **29a** gave **29b** as colorless crystals (10.1 mg, 24%) after

purification with column chromatography. This sample showed the ^{1}H-NMR spectrum identical with that of **29b** obtained in a).

(3S,4S)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(2-hydroxyethyl)-2-azetidinone (30). a) Hydroboration with diborane. A 1.0 M solution of borane in THF (0.10 ml, 0.10 mmol) was added to a solution of **29b** (20.1 mg, 0.079 mmol) in THF (0.32 ml) at 0 °C. After stirring at rt for 1h, the mixture was diluted with H_2O (0.1 ml), 2M NaOH (0.1 ml), and 35% H_2O_2 (0.12 ml), and extracted with CH_2Cl_2. The extracts were combined and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was separated with preparative TLC (SiO_2, hexane-AcOEt 1:4) to give a mixture of **22** and its 4-[(*R*)-1-hydroxyethyl]-isomer as an oil from the less polar fraction (3.8 mg, 18%) and **30** as colorless crystals from the more polar fraction (4.7 mg, 22%). The mixture of **22** and its 4-[(*R*)-1-hydroxyethyl]-isomer showed the following ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, Me_2Si), 0.88(9H, s, Me_3C), 1.18~1.28 (6H, m, MeCHOH, MeCHOSi), 2.85, 3.03 (1H, two m, C3-H, integration ratio was 2:3), 3.55, 3.61 (1H, two dd, J=2.2, 6.8 Hz and J=2.1, 4.7 Hz, C4-H), 3.65~4.40 (2H, m, CHOH, CHOSi), 5.93, 6.20 (1H, two bs, NH, integration ratio was 3:2). Based on this ^{1}H-NMR spectrum, the ratio of **22** to its 4-[(*R*)-1-hydroxyethyl]-isomer could be calculated as 2:3. The more polar product (**30**) exhibited the same ^{1}H-NMR spectrum as described in b).
b) Hydroboration with 9-borabicyclo[3.3.1]nonane. A 0.5 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.16 ml, 0.58 mmol) was added to a solution of **29b** (74.5 mg, 0.292 mmol) in ether (0.6 ml) at rt. After stirring at rt for 3h, the mixture was diluted with 2M NaOH (0.3 ml), 35% H_2O_2 (0.25 ml), and EtOH (0.1 ml) at 0 °C. Stirring was continued at 0 °C for 20 min, then at rt for additional 10 min. The mixture was diluted with CH_2Cl_2 and the organic layer was separated, washed with satd aq NaCl, and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified with column chromatography (SiO_2, CH_2Cl_2-MeOH 30:1) to give **30** as colorless crystals (61.5 mg, 77 %). An analytical sample of **30** was obtained by recrystallization from hexane. Mp 85~87 °C and $[\alpha]_D^{25}$ -22.3° (c 1.01, $CHCl_3$). IR (KBr): 2950, 1732, 1258, 1098, 1079, 1065, 1042, 1023, 986, 958, 837, 775 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.10 (6H, s, Me_2Si), 0.89 (9H, s, Me_3C), 1.28 (3H, d, J=6.2 Hz, MeCH), 1.88 (2H, m, CH_2CH_2OH), 2.34 (1H, t, J=5.7 Hz, OH), 2.91 (1H, m, C3-H) 3.73 (3H, m, CH_2OH, C4-H), 4.16 (1H, m, CHOSi), 6.17 (1H, bs, NH). MS m/e: 258 $(M-Me)^+$, 216 $(M-Bu)^+$. Found: C, 57.05; H, 10.12; N, 4.99%. Calcd for $C_{13}H_{27}NO_3Si$: C, 57.10; H, 9.95; N, 5.12%.

(3S,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-carboxymethyl-2-azetidinone (4). Ruthenium trichloride hydrate (1 mg, 0.005 mmol) was added to a two layer solution of **30** (61.5 mg, 0.225 mmol) and sodium metaperiodate (0.145g, 0.676 mmol) in CCl_4 (0.9 ml), MeCN (0.9 ml), and H_2O (1.35 ml). The mixture was stirred vigorously at rt for 1h and diluted with CH_2Cl_2. The organic layer was separated, washed with satd NaCl, and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave a residue which was purified with column chromatography (SiO_2, AcOEt) to give **4** as colorless crystals (44.4 mg, 69%). An analytical sample of **4** was obtained by recrystallization from hexane-AcOEt. Mp 150~154 °C (decomp.) and $[\alpha]_D^{20}$ +16.1° (c 0.69, $CHCl_3$). IR (KBr): 3320, 2950, 1767, 1722, 1255, 1140, 1099, 1062, 1038, 968, 837, 780, 724 cm^{-1}. IR ($CHCl_3$): 3340, 2950, 1740, 1260, 1144 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s, Me_2Si), 0.88 (9H, s, Me_3C), 1.21 (3H, d, J=6.2 Hz, MeCH), 2.65 (2H, m, CH_2COOH), 2.81 (1H, m, C3-H), 3.95 (1H, m, C4-H), 4.18 (1H, quint, J=6 Hz, CHOSi), 6.0~7.4 (1H, br, COOH), 7.11 (1H, bs, NH). This ^{1}H-NMR spectrum was superimposable on that of the authentic sample.[4f] MS m/e: 272 $(M-Me)^+$, 230 $(M-Bu)^+$. Found: C, 54.38; H, 8.69; N, 4.94%. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87%.

References and Notes

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