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A NOVEL AND EFFICIENT SYNTHESIS OF THE KEY INTERMEDIATE OF 1β-METHYLCARBAPENEM ANTIBIOTICS EMPLOYING [2+2]-CYCLOADDITION REACTION OF DIKETENE WITH A CHIRAL IMINE[1)]

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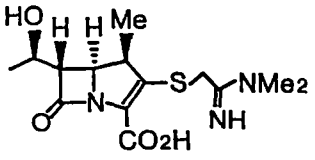
Abstract : The key intermediate (**2**) of 1β-methylcarbapenems was efficiently synthesized from (S)-methyl 3-hydroxy-2-methylpropionate ((S)-**5**) in ten steps and 30 % overall yield. Thus, (S)-3-benzyloxy-2-methylpropanal readily obtainable from (S)-**5**, was condensed with di-p-anisylmethylamine to afford the chiral imine. The [2+2]-cycloaddition reaction of diketene with the imine was found to proceed in a highly diastereoselective manner, giving the desired 3,4-trans-3-acetyl-β-lactam (max. diastereoselectivity 11-15:1). This was readily elaborated to **2** by five sequential operations.



1

The 1β-methylcarbapenems have been the focus of current attention in the field of antibacterial β-lactam agents[2)] since the pioneering work performed by a research group at Merck uncovered that one congener of the 1β-methylcarbapenems such as **1** exhibits pronounced antibacterial activity, broad spectrum, chemical stability, and high resistance to renal dipeptidase-I.[3)] As the 1β-methylcarbapenems are obtainable only by chemical synthesis,[2)] recent synthetic endeavor has been devoted to (3S,4S)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (**2**)[4a,5)] which was efficiently utilized in the original synthesis of **1**.[3)] It is also expected that **2** is usable as a versatile key intermediate in the syntheses of broad structural types of the 1β-methylcarbapenems.[4)] In the syntheses of **2** so far reported,[4a,5)] the β-methyl group of the $C_{1'}$-position of **2** has been constructed by using the chirality involved in β-lactam moiety,[4a,5a,b,f-k)] and/or external chiral auxiliary.[5c,d)] In particular, knowledge of enolate chemistry accumulated for the last decade is ingeniously employed for controlling stereoselective formation of the $C_{1'}$-methyl group.[5c,d,f-i,k)] However, no preparation methods of **2** have yet been explored in which the methyl-bearing chiral center of the precursor induces chirality involved in the β-lactam ring.

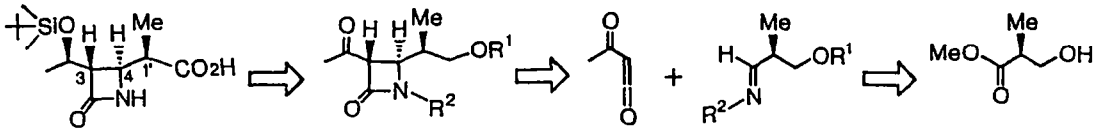
Recently, we have reported that **2** could be prepared from readily available (S)-methyl 3-hydroxy-2-methylpropionate((S)-**5**).[1)] In our synthesis, the methyl group at the chiral center of (S)-**5** was directly transformed into the 1β-methyl group of **2**. The chirality present in the β-lactam ring of **2** was found to be effectively controlled by the [2+2]-cycloaddition reaction of diketene with the

chiral imine (**4**) obtainable from (S)-**5**.

This report concerns with a full detail of the exploration of this novel synthesis of **2**.[1)]

Design of the Novel Synthetic Route to the 1β-Methylcarbapenem Key Intermediate (2)

As the synthetic strategy to produce **2** from (S)-**5**, we envisioned to employ a stereoselective [2+2]-cycloaddition reaction of diketene with **4** as a key step. The designed synthetic route is shown in **Scheme I**. Thus, the optically active 3,4-trans-3-acetyl-β-lactam (**3**) is anticipated to be a reasonable precursor of **2** since the C_3- and C_4- substituents readily occupy trans-configuration due to the presence of 3-acetyl group[6)] and the acetyl group at the C_3-position can be readily transformed into 3-[(R)-1-hydroxyethyl] group in a highly stereoselective manner.[7)] It is expected that **3** can be directly constructed from the chiral imine **4**, if the [2+2]-cycloaddition reaction of acetylketene with **4** proceeds with a desired diastereoselectivity under the influence of the adjacent chiral center and the two protective groups (R^1 and R^2). Preparation of **4** can be readily achieved from (S)-**5** by sequential protection of the hydroxy group, reduction of the ester group to an aldehyde, and condensation of the aldehyde with a primary amine.



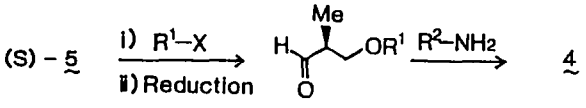
2 **3** **4** (S) - **5**

[Scheme I]

Recent studies on β-lactam synthesis have demonstrated[8,9)] that diketene can be used as an acetylketene equivalent in the reactions with imines derived from aromatic aldehydes[8)] and alkyl glyoxylates,[9)] resulting in the stereoselective production of 3,4-trans-3-acetyl-β-lactams. In the latter case,[9)] it was also reported that the absolute stereochemistry of C_3- and C_4-positions could be effectively controlled to give (3S, 4S)-2-azetidinone derivatives by using chiral imines derived from optically active alkyl glyoxylates. However, at the outset of this work, there have been no reports as to the β-lactam formation from an optically active aliphatic imine carrying a chiral center at the α-position.[10,11)]

The [2+2]-Cycloaddition Reaction of Diketene with the Chiral Imine (4)

According to the synthetic strategy delineated above, our attention was first focused on the [2+2]-cycloaddition reactions of diketene with **4**. Searching for proper protective groups(R^1 and R^2) which can produce **3** bearing the desired stereochemistry, various chiral imines (**4**) were prepared from commercially available (S)-**5**.



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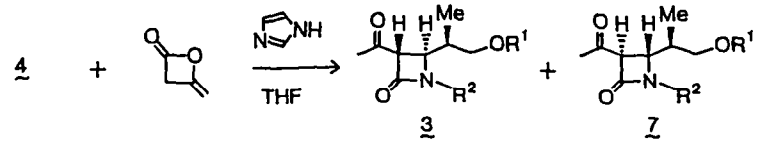
Protection of the hydroxy group of (S)-5 according to the literature procedure[12] followed by reduction of the ester group with lithium aluminum hydride and Swern oxidation[13] of the resulting alcohol afforded the aldehyde **6**. Direct reduction of the protected ester with diisobutylaluminum hydride could also yield **6**. Preparations of **4** were simply achieved in quantitative yields by allowing to react **6** with an appropriate primary amine in the presense of magnesium sulfate in toluene. Taking into account the reported results,[9] p-anisidine (PMP-NH_2) and di-p-anisylmethylamine (DAM-NH_2) were utilized as primary amines.

With various structural types of **4** in hand, the [2+2]-cycloaddition reactions of diketene with **4** were examined in tetrahydrofuran in the presense of imidazole.[9] The results are shown in **Table I.**

As expected, the nature of protective groups of imino and hydroxy groups was found to highly affect the chemical yield and stereoselectivity of addition reaction. Generally, the imines (**4**) derived from DAM-NH_2 gave better results than those derived from PMP-NH_2 in terms of stereoselectivity. The favorable results could be realized for **4n-4p(Table I**, Runs 14-16).

With an aim to obtain the more improved results, the [2+2]-cycloaddition reactions of **4o** were further examined by employing various solvents(**Table II**). As shown in **Table II**, it became evident that the stereoselectivity of reaction depends

Table I [2+2]-Cycloaddition Reactions of Diketene with Chiral Imines (**4**)[a]



Run	Imine	R^1	R^2 [b]	Time(h)	Yield(%)[c]	Ratio of 3 to 7[d]
1	**4a**	Si*t*-BuMe_2	PMP	64	33	0.25 : 1
2	**4b**	Si*t*-BuPh_2	PMP	15	10	0 : 1
3	**4c**	CPh_3	PMP	40	25	0.75 : 1
4	**4d**	CH_2OCH_2Ph	PMP	15	18	1 : 1
5	**4e**	$CH_2O(CH_2)_2OMe$	PMP	60	41	1.5 : 1
6	**4f**	CH_2SMe	PMP	24	38	1.5 : 1
7	**4g**	CH_2SPh	PMP	15	21	1.2 : 1
8	**4h**	CH_2Ph	PMP	60	58	1.6 : 1
9	**4i**	Si*t*-BuMe_2	DAM	36	12	1.5 : 1
10	**4j**	Si*t*-BuPh_2	DAM	60	5	0 : 1
11	**4k**	CPh_3	DAM	34	12	0.25 : 1
12	**4l**	$CH_2O(CH_2)_2OMe$	DAM	43	31	1.3 : 1
13	**4m**	CH_2OMe	DAM	77	44	1.7 : 1
14	**4n**	CH_2SMe	DAM	69	27	2.0 : 1
15	**4o**	CH_2Ph	DAM	60	47	2.5 : 1
16	**4p**	*t*-Bu	DAM	60	26	3.3 : 1

a) All reactions were performed at -30 °C in THF using diketene (5.0-8.0 mol eq.) and imidazole (1.1 mol eq.). For the representative procedure, see the experimental part. b) PMP=p-methoxyphenyl (p-anisyl) ; DAM=di-p-anisylmethyl.
c) Combined yield of **3** and **7**. d) Determined by ^{1}H-NMR spectrum of the mixture of **3** and **7**.

highly upon the polarity of solvent and the use of toluene affords the best selectivity(**Table II**, Run 1). When **4p** in place of **4o** was allowed to react with diketene in toluene, the formation ratio and chemical yield of **3p** and **7p** were found to be 7.7 : 1 and 18 %, respectively. In order to further improve the stereoselectivity and chemical yield of the cycloaddition reaction, the reactions of diketene with **4o** were examined in the presence of various basic catalysts. The results are summarized in **Table III**. Of the catalysts so far examined, 4-methylimidazole gave the best results. This is because 4-methylimidazole has basicity comparable to that of imidazole and is obviously more soluble to toluene than imidazole(**Table III**, Runs 2,3).

Based on these studies, it was finally established that a mixture of **3o** and **7o** (11-15 :1) could be obtained in 49-52 % yield when **4o** was treated with diketene (2.0-5.0 equiv.) in toluene at -30 °C in the presence of 4-methylimidazole (1.1 equiv.) (**Table III**, Runs 2, 3). The desired major isomer **3o**, mp 90-91 °C and $[\alpha]_D^{20}$ -58.1° (c 0.53, $CHCl_3$), was isolated in a pure state by column chromatography followed by separation with preparative thin layer chromatography(TLC). The optical purity of **3o** was determined as 95% ee based on the ^{1}H-NMR spectrum measured in the presence of chiral shift reagent, Eu(hfc)$_3$. On the other hand, direct recrystallization of the mixture of **3o** and **7o** from isopropyl ether gave optically pure **3o**, mp 92-93 °C and $[\alpha]_D^{20}$ -59.0° (c 0.62, $CHCl_3$).

Table II Solvent Effects on the [2+2]-Cycloaddition Reaction of Diketene with the Chiral Imine (**4o**)[a]

Run	Solvent	Dielectric Const.(ε)[b]	Time(h)	Yield(%)[c]	Ratio of **3o** to **7o**[d]
1	Toluene	2.6	39	33	6.7 : 1
2	Et_2O	4.3	39	38	4.7 : 1
3	$CHCl_3$	4.8	39	25	3.0 : 1
4	Hexane-THF(5:1)		60	36	3.0 : 1
5	THF	7.6	60	47	2.5 : 1
6	DMF	36.7	39	12	1.1 : 1

a) All reactions were performed at -30 °C using diketene (5.0 mol eq.) and imidazole (1.1 mol eq.). b) Values quoted from reference 14. c) Combined yield of **3o** and **7o**. d) Determined by ^{1}H-NMR spectrum of the mixture of **3o** and **7o**.

Table III Effects of the Catalysts on the [2+2]-Cycloaddition Reaction of Diketene with the Chiral Imine (**4o**)[a]

Run	Catalyst[b]	Time(h)	Yield(%)[c]	Ratio of **3o** and **7o**[d]
1	Imidazole	39	33	6.7 : 1
2	4-Methylimidazole	60	52	11 : 1
3	4-Methylimidazole[e]	90	49	15 : 1
4	4-Methylimidazole[f]	26	16	9.0 : 1
5	Benzimidazole	96	<10[g]	_[h]
6	Pyridine	80	<10[g]	_[h]

a) All reactions were performed at -30 °C in toluene using diketene (5.0 mol eq.) and catalyst (1.1 mol eq.). b) In addition to the tabulated amines, triethylamine, 4-phenylimidazole, 1,2,4-triazole, 4-dimethylaminopyridine, 4-aminopyridine, and 2-phenylaminopyridine were also employed as catalysts. However, these compounds were found to give no or trace amount of the β-lactams. c) Combined yield of **3o** and **7o**. d) Determined by ^{1}H-NMR spectrum of the mixture of **3o** and **7o**.
e) 2.0 mol eq. of diketene was used. f) 0.5 mol eq. of catalyst was used.
g) Roughly estimated by TLC. h) Not determined.

Since it is presently ambiguous whether true reactant of the cycloaddition reaction is diketene, acetylketene, or 1-(acetoacetyl)imidazole derivative, and the β-lactam formation is concerted, stepwise, or the mixture of both processes, full rationalization of the obtained results seems to be quite difficult. However, since stereoselectivity of the reaction is strongly affected by the polarity of solvents, it may be reasonable to expect that the [2+2]-cycloaddition reaction of diketene with **4** proceeds through a zwitter-ionic intermediate as previously claimed,[15] and that the conformation of the zwitter-ionic intermediate gives an important effect on the stereochemical outcome of the reaction. Although the reaction mechanism is still unclear, it is worth noting that the methyl and benzyloxymethyl groups of **4o** can effectively control stereoselectivity of the cycloaddition reaction even though the difference of their steric bulkiness is very small.

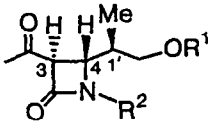
Determination of the Stereochemistry of the [2+2]-Cycloaddition Products (3 and 7)

In the explored [2+2]-cycloaddition reaction, two diastereomeric 3,4-trans-3-acetyl-β-lactams(**3** and **7**) are regularly obtained except for the cases in which the imines(**4b, j**) bearing t-butyldiphenylsilyloxy group were employed. The absolute stereochemistry of **3o** and **7o** could be firmly established by the successful transformation of **3o** into **2**(*vide infra*). As for other cycloaddition products(**3a, c-i, k-n, p** and **7a-n, p**), determination of their absolute stereochemistry was carried out by comparing their ^{1}H-NMR spectra with those of **3o** and **7o**.

In the ^{1}H-NMR spectrum of **3o**, the signal of the methyl group at the $C_{1'}$-position appeared in a lower field than that of **7o** and the difference of chemical shifts of the protons at the C_4- and C_3-positions($\delta\Delta$) is smaller than that observed for **7o**. Accordingly, two diastereomeric products showing the same spectral characteristics as those of **3o** and **7o** could be assigned to have the structrures corresponding to **3** and **7**, respectively. The cycloaddition products obtained from **4b,j** were tentatively assigned as **7b** and **7j** based on the spectral comparisons with other β-lactams(**3** and **7**). These results are summerized in **Table IV**.

In order to further prove the assigned structures, some representative cycloaddition products(**3e, h, m**, and **p**) were correlated with **3o**. Thus, the benzyl groups of **3o** and **7o** were removed by catalytic hydrogenation to give the corresponding 4-[1-(hydroxymethyl)ethyl]-β-lactams(**8** and **9**) in 91% and 86% yields, respectively. A 1.7:1 mixture of **3m** and **7m** was treated under the reported conditions,[16] readily affording **8** and **9** in 47% and 31% yields. Removal of the t-butyl group of **3p** was achieved with trifluoroacetic acid[17] to produce **8** as a sole product. On the other hand, when **3o** and **7o** were oxidized with cerium(IV) ammonium nitrate(CAN),[18] the 3,4-trans-3-acetyl-β-lactams(**10** and **11**) lacking a di-p-anisylmethyl group could be obtained in 55% and 53% yields, respectively. Treatment of a 1.6:1 mixture of **3h** and **7h** with CAN gave rise to **10** and **11** in 51% and 32% yields. Sequential removal of the (methoxyethoxy)methyl group of **3e**,[16] benzylation of the resulting primary alcohol,[19] and oxidative removal of the p-methoxyphenyl gruop[18] also yielded **10** in 44% overall yield. Results of these chemical correlations could afford definite proof for the stereochemistry of **3** and **7** deduced from their ^{1}H-NMR spectra. Notable spectral charasteristics summarized in **Table IV** may also provide a useful tool for assigning the stereochemistry of these types of β-lactam derivatives.

Table IV ^{1}H-NMR Chemical Shifts[a] of Various 3,4-trans-3-Acetyl-β-Lactams (3a-p, and 7a-p) in $CDCl_3$ Solution



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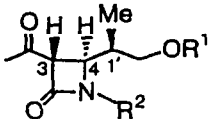

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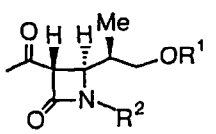
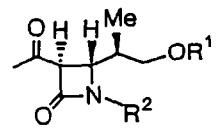
Run	Compound	C_4-H	C_3-H	$\Delta\delta$[b]	$C_{1'}$-Me
1	**3a**	c)	c)	<0.2	1.01
	7a	4.65	4.16	0.49	0.87
2	**7b**	4.78	4.21	0.57	0.85
3	**3c**	4.60	4.37	0.23	1.03
	7c	4.72	4.16	0.56	0.86
4	**3d**	d)	4.36		1.02
	7d	d)	4.13		0.88
5	**3e**	4.56	4.34	0.22	1.05
	7e	4.7[e]	4.11	ca.0.6	0.91
6	**3f**	d)	4.36		1.04
	7f	d)	4.13		0.91
7	**3g**	4.54	4.26	0.28	1.02
	7g	4.63	4.08	0.55	0.90
8	**3h**	4.55	4.4[e]	ca.0.15	1.04
	7h	4.69	4.13	0.56	0.93
9	**3i**	4.14	4.38	-0.24	0.86
	7i	4.33	4.05	0.28	0.84
10	**7j**	4.41	4.02	0.39	0.77
11	**3k**	4.16	4.30	-0.14	0.93
	7k	4.32	4.03	0.29	0.82
12	**3l**	d)	d)		0.87
	7l	d)	d)		0.79
13	**3m**	d)	d)		0.90
	7m	d)	d)		0.82
14	**3n**	c)	c)	<0.1	0.88
	7n	4.30	4.01	0.29	0.80
15	**3o**	4.21	4.12	0.09	0.87
	7o	4.30	4.00	0.30	0.82
16	**3p**	4.08	4.30	-0.22	0.86
	7p	4.26	4.06	0.20	0.79

a) Expressed by ppm downfield from tetramethylsilane used as an internal standard (δ-value). b) $\delta(C_4\text{-H}) - \delta(C_3\text{-H})$ ppm. c) Signal of C_3-H overlaps with that of C_4-H. d) Signals of C_3-H and C_4-H could not be assigned. e) Chemical shift was roughly estimated.



8 : R^1=H, R^2=DAM

10 : R^1=CH_2Ph, R^2=H

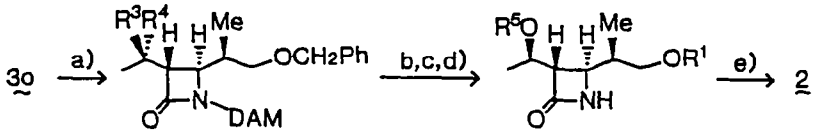


9 : R^1=H, R^2=DAM

11 : R^1=CH_2Ph, R^2=H

Preparation of the 1β-Methylcarbapenem Key Intermediate (2) from the [2+2]-Cycloaddtion Product (3o)

With a fairly large amount of 3o in hand, preparation of 2 was finally examined. This could be readily achieved in 5 steps. Thus, reduction of the acetyl group of 3o was effected in a highly stereoselective manner according to the reported method,[7] giving a mixture of the two epimeric alcohols (12 and 13, 12:13=16:1)in 99 % yield. These epimeric alcohols could be separated by preparative TLC to yield 12 in a pure state, $[\alpha]_D^{20}$ -55.1° (c 0.85, $CHCl_3$). The di-p-anisylmethyl group of 12 was oxidatively removed with CAN to give the N-unprotected β-lactam 14, $[\alpha]_D^{20}$ -5.0° (c 0.44, $CHCl_3$) in 91 % yield. Selective protection of the alcoholic function of 14 with t-butyldimethylsilyl group[6b] followed by reductive removal of the benzyl group, produced the primary alcohol 15, mp 90-91° C and $[\alpha]_D^{20}$ -21.7° (c 0.46, $CHCl_3$). The yields of these two steps were 91 % and 100 %, respectively. Oxidation of 15 with pyridinium dichromate (PDC)[20] furnished 2, mp 146-147 °C and $[\alpha]_D^{20}$ -34.6° (c 0.26, MeOH). The spectral data of 2 were identical with those reported.[3] The overall yield of 2 from 3o was 76 %.



12 : R^3=OH, R^4=H
13 : R^3=H, R^4=OH

14 : R^1=CH_2Ph, R^5=H
15 : R^1=H, R^5=Si-t-$BuMe_2$

a) KBH(s-Bu)$_3$, KI, THF, 0 °C b) CAN, aq.CH_3CN, 0 °C c) t-$BuMe_2SiCl$, Imidazole, DMF, rt d) H_2, Pd-C, AcOEt, rt e) PDC, DMF, rt

Conclusion

A novel and efficient synthesis of 2 was accomplished employing the [2+2]-cycloaddition reaction of diketene with a chiral imine as a key step. Among various synthetic routes to 2 so far explored,[3,4a,5] the present process is anticipated to be one of the most practical methods because of short synthetic steps (overall 10 steps from (S)-5), high overall yield (30 % overall yield from (S)-5), high selectivity in the key diastereoselective reaction (11-15:1), and use of the readily available starting material ((S)-5).

EXPERIMENTAL

General. All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. NMR spectra were measured with a Hitachi R-90H (90 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 (regular mass spectra) and a Hitachi M-80A mass spectrameter (exact mass spectra). Measurements of optical rotation were performed on a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 and Kieselgel 60 were used as an adsorbent for column chromatography. Kieselgel $60F_{254}$(Merck) was used for preparative TLC.

(S)-(+)-3-Benzyloxy-2-methylpropanal (6 ; R^1=CH_2Ph). Prepared according to the Kishi's procedure[21] with slight modifications. Trifluoromethanesulfonic acid (0.17 ml, 1.9 mmol) was added to a solution of commercially avairable (S)-5 (1.14 g, 9.7 mmol) and O-benzyl trichloroacetimidate[19] (3.59 ml, 19.3 mmol) in a mixture of cyclohexane and CH_2Cl_2 (2:1) (20 ml) cooled at 0°C. After stirring at the same temperature for 5 h, the mixture was diluted with ether and washed succesively with H_2O, 0.1M-HCl, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$), filterd, and concentrated in vacuo. The residue was diluted with hexane. The white precipitate formed was removed by filtration and washed with hexane. The combined filtrates were concentrated in vacuo. The residue was purified with column chromatography (SiO_2, etherhexane=7:93) to afford (S)-methyl 3-benzyloxy-2-methylpropionate as a colorless oil (1.75 g, 87 %). ^{1}H-NMR ($CDCl_3$) : 1.18 (3H, d, J=7.1 Hz), 2.6-3.0 (1H, m), 3.4-3.8 (2H, m), 3.69 (3H,s), 4.52 (2H, s), 7.31 (5H,s). A solution of (S)-methyl 3-benzyloxy-2-methylpropionate (1.37 g, 6.7 mmol) in ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (0.22 g, 5.5 mmol) in ether (20 ml) under ice-cooling. After 1 h, H_2O (0.23 ml), 15 % NaOH solution (0.23 ml), and H_2O (0.67 ml) were successively added and the mixture was stirred for 10 min. The resulting suspension was filtered through a pad of celite and the collected materials were washed with EtOAc. The combined filtrates were dried ($MgSO_4$) and concentrated in vacuo. The concentrated residue was purified with column chromatography (SiO_2, ether-hexane=3:2) to afford (S)-3-benzyloxy-2-methylpropanol as a colorless oil (1.18 g, 100 %), $[\alpha]_D^{25}$ +13.0° (c 12.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) : 0.87 (3H, d, J=7.0 Hz), 1.9-2.3 (1H, m), 2.43 (1H, t, J=6.0 Hz, OH), 3.3-3.7 (m, 4H), 4.50 (2H, s), 7.33 (5H, s). Dimethyl sulfoxide (0.67 ml, 9.5 mmol) was added dropwise to a solution of oxalyl chloride (0.41 ml, 4.7 mmol) in CH_2Cl_2 (12 ml) cooled at -60 °C, and the mixture was stirred for 5 min. A solution of (S)-3-benzyloxy-2-methylpropanol (0.57 g, 3.2 mmol) in CH_2Cl_2 (8 ml) was added to the reaction mixture with stirring. After stirring was continued at the same temperature for 15 min, triethylamine (2.64 ml, 19.0 mmol) and CH_2Cl_2 (30 ml) were succesively added to the reaction mixture. The resulting mixture was gradually warmed up to -40 °C over 1 h, stirred for 15min, then diluted with hexane. The hexane solution was washed succesively with 1M-HCl, H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$) and concentrated in vacuo, affording pure **6** as a colorless oil (0.57 g,100 %), $[\alpha]_D^{25}$ +30.6° (c 1.32, $CHCl_3$) [lit.[22] $[\alpha]_D^{25}$ +27.6° (c 4.9, $CHCl_3$) : lit.[23] $[\alpha]_D^{25}$ +30° (c 1.29, $CHCl_3$)]. IR (neat) : 2870, 1730, 1455, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.14 (3H, d, J=7.3 Hz), 2.5-2.8 (1H, m), 3.66 (2H, d, J=5.8 Hz), 4.53 (2H, s), 7.32 (5H, s), 9.73 (1H, d, J=1.5 Hz). Mass m/e : 179 $(M+H)^+$. Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92 %. Found: C, 73.98; H, 7.96 %.

Due to the hidden symmetric nature of methyl 3-hydroxy-2-methylpropionate, the preparation of **6** (R^1=CH_2Ph) could be also achieved staring from (R)-5 according to the reported method[24] (76 % overall yield from (R)-5).

(S)-(+)-2-Methyl-3-methylthiomethoxypropanal(6 ; R^1=CH_2SMe). (S)-Methyl 2-methyl-3-methylthiomethoxypropionate was prepared from (S)-5 in a quantitative yield according to the reported procedure.[25] ^{1}H-NMR ($CDCl_3$) : 1.19 (3H, d, J=7.3 Hz), 2.12 (3H, s), 2.6-2.9 (1H, m), 3.5-3.8 (2H, m), 3.70 (3H, s), 4.63 (2H,s). A 1.0 M solution of diisobutylaluminum hydride in hexane (7.30 ml, 7.30 mmol) was added over 10 min to a solution of (S)-methyl 2-methyl-3-methylthiomethoxypropionate (1.19 g, 6.7 mmol) in ether (35 ml) cooled at -78°C. After stirring at -78 °C for 2 h, MeOH (2.0 ml) was added. The mixture was warmed up to room temperature, diluted with H_2O (2.0ml), and stirred for 5 min. After adding anhydrous $MgSO_4$ (6.0 g) and celite (6.0 g), the resulting suspension was filtered and the collected materials were washed with ether. The combined filtrates were concentrated in vacuo. The residue was purified with column chromatography (SiO_2, ether-hexane=1:4), affording **6** (R^1=CH_2SMe) as a colorless oil (0.59 g, 60 % from (S)-5), $[\alpha]_D^{20}$ +15.8° (c 1.01, $CHCl_3$). IR (neat) : 2930, 1730, 1430, 1075 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.15 (3H, d, J=7.3 Hz), 2.13 (3H, s), 2.5-2.8 (1H, m), 3.75 (2H, d, J=5.9 Hz), 4.63 (3H, s), 9.72 (1H, d, J=1.5 Hz). Mass m/e : 148 $(M)^+$, 101 $(M-SMe)^+$. Anal. Calcd. for $C_6H_{12}O_2S$: C, 48.61; H, 8.16; S, 21.63 %. Fuond: C, 48.42; H, 8.07; S, 21.36 %.

(S)-(+)-3-(2-Methoxyethoxymethoxy)-2-methylpropanal (6 ; R^1=$CH_2OCH_2CH_2OMe$). Preparation of (S)-(+)-methyl 3-(2-methoxyethoxymethoxy)-2-methylpropionate was carried out according to the reported procedure[26] starting from (S)-5 (89 % yield), $[\alpha]_D^{20}$ +12.1° (c 1.34, $CHCl_3$). IR (neat) : 2880, 1740, 1460, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.20 (3H, d, J=7.5 Hz), 2.6-2.9 (1H, m), 3.40 (3H, s), 3.4-3.8 (6H, m), 3.71 (3H, s), 4.72 (3H, s). (S)-(+)-Methyl 3-(2-methoxyethoxymethoxy)-2-methylpropionate (2.06 g, 10.0 mmol) was reduced with diisobutylaluminum hydride as described for the preparation of **6** (R^1=CH_2SMe), affording **6** (R^1=$CH_2OCH_2CH_2OMe$) as a colorless oil (0.90g, 51%), $[\alpha]_D^{20}$ +23.8° (c 1.25, $CHCl_3$). IR (neat) : 2880, 1725, 1450, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.10 (3H, d, J=7.4 Hz), 2.4-2.8 (1H, m), 3.38 (3H, s), 3.4-3.8 (6H, m), 4.70 (2H, s), 9.71 (1H, d, J=2.0 Hz). Mass m/e : 175 $(M-H)^+$, 147 $(M-CHO)^+$, 145 $(M-OMe)^+$. Exact Mass : Calcd. for $C_8H_{15}O_4$ $[(M-H)^+]$: 175.0968. Found: 175.0952.

(S)-2-Methyl-3-phenylthiomethoxypropanal (6 : R^1=CH_2SPh). (S)-Methyl 3-phenylthiomethoxy-2-methylpropionate was prepared from (S)-5 in 23 % yield according to the reported procedure,[27] using chloromethyl phenyl sulfide instead of chloromethyl methyl sulfide. ^{1}H-NMR ($CDCl_3$) : 1.18 (3H, d, J=7.0 Hz), 2.8-3.0 (1H, m), 3.64 (3H, s), 3.72 (1H, d, J=6.2 Hz), 3.77 (1H, d, J=7.0 Hz), 4.99 (2H, s), 7.2-7.6 (5H, m). Reduction of (S)-methyl 3-phenylthiomethoxy-2-methylpropionate (62mg, 0.26mmol) was performed by the same procedure as that described for the preparation of **6** (R^1=CH_2SMe), giving **6** (R^1=CH_2SPh) as a colorless oil(36 mg, 65 %). IR (neat) : 2880, 1730, 1590, 1490, 1075 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.13 (3H, d, J=7.0 Hz), 2.5-2.9 (1H, m), 3.82 (2H, d, J=5.9 Hz), 5.00 (2H, s), 7.2-7.6 (5H, m), 9.68 (1H, d, J=1.5 Hz). Mass m/e : 210 $(M)^+$, 101 $(M-SPh)^+$. Exact Mass : Calcd. for $C_{11}H_{14}O_2S$: 210.0714; Found: 210.0714.

(S)-2-Methyl-3-triphenylmethoxypropanal (6 ; R^1=CPh_3). (S)-Methyl 3-triphenylmethoxy-2-methylpropionate was prepared from (S)-5 in 23 % yield according to the reported procedure.[28] ^{1}H-NMR ($CDCl_3$) : 1.10 (3H, d, J=7.0 Hz), 2.6-2.9 (1H, m), 3.0-3.4 (2H, m), 3.70 (3H, s), 7.1-7.6 (15H, m). (S)-Methyl 3-triphenylmethoxy-2-methylpropionate (744 mg, 2.0 mmol) was reduced with diisobutylaluminum hydride as described for the preparation of **6** (R^1=CH_2SMe), affording **6** (R^1=CPh_3) as a white powder (460 mg, 70 %). IR (KBr) : 3075, 2950, 1725, 1600, 1495, 1450, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.10 (3H, d, J=7.0 Hz), 2.4-2.8 (1H, m), 3.35 (2H, d, J=5.7 Hz), 7.2-7.5 (15H, m), 9.72 (1H, d, J=2.0 Hz). Mass m/e : 330 $(M)^+$, 243 $(CPh_3)^+$. Exact Mass : Calcd. for $C_{23}H_{22}O_2$: 330.1618. Found: 330.1623.

(S)-3-(t-Butyldimethylsilyloxy)-2-methylpropanal (6 ; R^1=$Sit\text{-}BuMe_2$), (S)-3-(t-Butyldiphenylsilyloxy)-2-methylpropanal (6 ; R^1=$Sit\text{-}BuPh_2$), (S)-3-Benzyloxymethoxy-2-methylpropanal (6 ; R^1=CH_2OCH_2Ph), (S)-3-Methoxymethoxy-2-methylpropanal (6 ; R^1=CH_2OMe), and **(S)-3-t-Butoxy-2-methylpropanal (6 ; R^1=t-Bu).** All these aldehydes were prepared according to the reported method,[22,29-33] and characterized by their IR, ^{1}H-NMR, and Mass spectra.

(3S,4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(benzyloxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3o and 7o). General Procedure of the [2+2]-Cycloaddition Reaction of Diketene with a Chiral Imine (4). A solution of di-p-anisylmethylamine (1.30 g, 5.4 mmol) in toluene (15 ml) was added to a suspension of **6** (R^1=CH_2Ph) (0.99 g, 5.6 mmol) and anhydrous $MgSO_4$ (0.81 g, 6.7 mmol) in toluene (15 ml) cooled at 0°C. After stirring at 0 °C for 1.5 h, the mixture was filtered and the collected materials were washed with benzene. The combined filtrates were concentrated in vacuo under 35°C to give almost pure **4o** in a quantitative yield. This was immediately used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) : 1.14 (3H, d, J=6.8 Hz), 2.7-3.0 (1H, m), 3.6-3.8 (2H, m), 3.77 (6H, s), 4.49 (2H, s), 5.28 (1H, s), 6.79 (2H, d, J=8.8 Hz), 6.81 (2H, d, J= 8.8Hz), 7.23 (4H, d, J=8.8 Hz), 7.27 (5H, s), 7.74 (1H, d, J=4.8 Hz). A solution of diketene (1.41 g, 16.8 mmol) in toluene (5 ml) and a solution of 4-methylimidazole (0.50 g, 6.1 mmol) in toluene (5 ml) were simultaneously added over 2 h to a solution of **4o** (5.4 mmol) in toluene (50 ml) cooled at -30 °C. After stirring at -30 °C for 48 h, an additional amount of the solution of diketene (0.93 g, 11.1 mmol) in toluene (5 ml) was added to the reaction mixture over 2 h. Stirring was further continued at the same temperature for 12 h. The reaction mixture was

diluted with EtOAc and washed succesively with 0.1M-HCl, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified with column chromatography (SiO_2, acetone-CH_2Cl_2=1.5:98.5), affording a mixture of **3o** and **7o** as a colorless solid [1.40 g, 52 % from **6** (R^1=CH_2Ph)]. The ratio of **3o** to **7o** was estimated as 11:1 based on the ^{1}H-NMR spectrum of the mixture [**3o** and **7o** exhibited the N-C<u>H</u>(C_6H_4-<u>p</u>-OMe)$_2$ signals at 5.56 and 5.61 ppm, respectively] (vide infra). Further separation of the mixture of **3o** and **7o** (80 mg) with preparative TLC (ether-hexane=2:1, two developments) afforded pure **3o** as a colorless solid (70 mg), mp 90-91°C and $[\alpha]_D^{20}$ -58.1° (c 0.53, $CHCl_3$), and **7o** as a colrless oil (6 mg), $[\alpha]_D^{20}$ +26.3° (c 0.67, $CHCl_3$). Recrystallization of **3o** from isopropyl ether gave pure **3o** as colorless crystals, mp 92-93 °C and $[\alpha]_D^{20}$ -59.0° (c 0.62, $CHCl_3$). IR (KBr) : 2870, 1745, 1715, 1610, 1510, 1255, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.87 (3H, d, J=7.0 Hz), 1.7-2.1 (1H, m), 2.19 (3H, s), 3.1-3.5 (2H, m), 3.77 (3H, s), 3.78 (3H, s), 4.12 (1H, dd, J=5.0 and 2.8 Hz), 4.21 (1H, d, J=2.8 Hz), 4.37 (2H, s), 5.56 (1H, s), 6.80 (2H, d, J=8.8 Hz), 6.83 (2H, d, J=8.8 Hz), 7.09 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.8 Hz), 7.30 (5H, s). Mass m/e : 487 $(M)^+$, 444 $(M-COCH_3)^+$, 396 $(M-CH_2Ph)^+$. Anal. Calcd. for $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87 %. Found: C, 73.73; H, 6.63; N, 2.84 %. In order to estimate an extent of racemization to the stage of **3o**, the ^{1}H-NMR spectrum of **3o** directly obtained by the preparative TLC (vide supra), was measured in the presence of a chiral shift reagent Eu(hfc)$_3$. The methyl group of acetyl moiety was found to appear as two singlets at 2.36 and 2.48 ppm with an intensity ratio of 97.5 : 2.5. Since racemic **3o**[34] exhibited the corresponding methyl group as two singlets of equal intensity at 2.36 and 2.48 ppm, the optical purity of **3o** produced by the [2+2]-cycloaddition reaction was determined as 95 %ee. The undesired product (**7o**) obtained as a colorless oil showed the following spectral data. IR ($CHCl_3$) : 2940, 1745, 1710, 1610, 1510, 1245, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.82 (3H, d, J=6.8 Hz), 1.6-1.9 (1H, m), 2.12 (3H, s), 3.26 (2H, d, J=4.8 Hz), 3.78 (6H, s), 4.00 (1H, d, J=2.4 Hz), 4.30 (1H, dd, J=5.0 and 2.4 Hz), 4.34 (2H, s), 5.61 (1H, s), 6.81 (2H, d, J=8.8 Hz), 6.83 (2H, d, J=8.8 Hz), 7.10 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.8 Hz), 7.30 (5H, s). Mass m/e : 487 $(M)^+$, 444 $(M-CH_3CO)^+$, 396 $(M-CH_2Ph)^+$. Exact Mass : Calcd. for $C_{30}H_{33}NO_5$: 487.2357, Found: 487.2379.

Other 2-azetidinone derivatives (**3a, c-i, k-n, p,** and **7a-n, p**) were prepared according to the reaction procedures similar to that described above.

(3<u>S</u>, 4<u>R</u>)-1-(<u>p</u>-Anisyl)-3-acetyl-4-[(<u>R</u>)-1-(<u>t</u>-butyldimethylsilyloxymethyl)ethyl]-2-azetidinone and Its (3<u>R</u>, 4<u>S</u>)-Isomer (3a and 7a). Prepared from **6** (R^1=Si<u>t</u>-$BuMe_2$)[29] and <u>p</u>-anisidine. **3a** : colorless oil. IR (neat) : 2930, 1745, 1715, 1510, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.03 (3H, s), 0.05 (3H, s), 0.90 (9H, s), 1.01 (3H, d, J=7.5 Hz), 2.1-2.3 (1H, m), 2.34 (3H, s), 3.5-3.7 (2H, m), 3.81 (3H, s), 4.5-4.8 (2H, m), 6.88 (2H, d, J=8.8 Hz), 7.33 (2H, d, J=8.8 Hz). **7a** : colorless oil. IR ($CHCl_3$) : 2930, 1745, 1715, 1610, 1505, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.03 (3H, s), 0.05 (3H, s), 0.87 (3H, d, J=6.0 Hz), 0.89 (9H, s), 2.2-2.5 (1H, m), 2.34 (3H, s), 3.5-3.7 (2H, m), 3.77 (3H, s), 4.16 (1H, d, J=2.8 Hz), 4.65 (1H, dd, J=4.5 and 2.8 Hz), 6.86 (2H, d, J= 8.8 Hz), 7.32 (2H, d, J=8.8 Hz).

(3<u>R</u>, 4<u>S</u>)-1-(<u>p</u>-Anisyl)-3-acetyl-4-[(<u>R</u>)-1-(<u>t</u>-butyldiphenylsilyloxymethyl)ethyl]-2-azetidinone(7b). Prepared as a sole product from **6** (R^1=Si<u>t</u>-$BuPh_2$)[23,29b,30] and <u>p</u>-anisidine. Colorless oil. IR (neat) : 2940, 1750, 1715, 1510, 1245, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.85 (3H, d, J=7.5 Hz), 1.05 (9H, s), 2.2-2.5 (1H, m), 2.32 (3H, s), 3.5-3.7 (2H, m), 3.81 (3H, m), 4.21 (1H, d, J=2.5 Hz), 4.78 (1H, dd, J=4.5 and 2.5 Hz), 6.7-7.8 (14H, m). Mass m/e : 515 $(M)^+$, 458 $(M-t\text{-}Bu)^+$. Exact Mass : Calcd. for $C_{31}H_{37}NO_4Si$: 515.2489. Found: 515.2488.

(3<u>S</u>, 4<u>R</u>)-1-(<u>p</u>-Anisyl)-3-acetyl-4-[(<u>R</u>)-1-(triphenylmethoxymethyl)ethyl]-2-azetidinone and Its (3<u>R</u>, 4<u>S</u>)-Isomer (3c and 7c). The 2-azetidinone derivatives (**3c** and **7c**) prepared from **6** (R^1=CPh_3) and <u>p</u>-anisidine, were obtained as a 0.75 : 1 mixture after purification with preparative TLC. Colorless oil. IR (neat) : 2980, 2940, 1750, 1720, 1515, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.86, 1.03 (3H, two d, J=7.0 Hz and 7.5 Hz, intensity ratio=4:3), 2.20, 2.28 (3H, two s, intensity ratio=4:3), 2.1-2.6 (1H, m), 2.9-3.2 (2H, m), 3.79 (3H, s), 4.16, 4.37 (1H, two d, J=2.8 Hz and 2.8Hz,

intensity ratio=4:3), 4.60, 4.72 (1H, two dd, J=5.5, 2.8 Hz and 3.5, 2.8 Hz, intensity ratio=3:4), 6.7-7.6 (19H, m).

(3S, 4R)-1-(p-Anisyl)-3-acetyl-4-[(R)-1-(benzyloxymethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3d and 7d).). The 2-azetidinone derivatives (3d and 7d) prepared from 6 (R^1=CH_2OCH_2Ph)[31] and p-anisidine, were obtained as a 1 : 1 mixture after purification with preparative TLC. Colorless oil. IR (neat) : 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.88, 1.02 (3H, two d, J=6.8 Hz and 6.8 Hz, intensity ratio=1:1), 2.2-2.7 (1H, m), 2.35 (3H, s), 3.4-3.7 (2H, m), 3.78 (3H, s), 4.13, 4.36 (1H, two d, J=2.5 Hz and 2.5 Hz, intensity ratio=1:1), 4.4-4.9 (5H, m), 6.87 (2H, br d, J=8.8 Hz), 7.2-7.5 (7H, m). Mass m/e : 397 $(M)^+$, 276 $(M-CH_2OCH_2Ph)^+$. Exact mass : Calcd. for $C_{23}H_{27}NO_5$: 397.1887. Found: 397.1870.

(3S, 4R)-1-(p-Anisyl)-3-acetyl-4-[(R)-1-(2-methoxyethoxymethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3e and 7e). Prepared from 6 (R^1=$CH_2OCH_2CH_2OMe$) and p-anisidine. 3e : colorless oil, $[\alpha]_D^{20}$ -26.0° (c 1.20, $CHCl_3$). IR (neat) : 2940, 1740, 1710, 1510, 1250, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.05 (3H, d, J=6.8 Hz), 2.3-2.6 (1H, m), 2.35 (3H, s), 3.38 (3H, s), 3.4-3.8 (6H, m), 3.80 (3H, s), 4.34 (1H, d, J=2.4 Hz), 4.56 (1H, dd, J=5.3 and 2.4 Hz), 4.65 (2H, s), 6.85 (2H, d, J=9.0 Hz), 7.29 (2H, d, J=9.0 Hz). Mass m/e : 365 $(M)^+$, 290 $(M-OCH_2CH_2OMe)^+$, 258 (M-p-anisyl)$^+$. Exact Mass : Calcd. for $C_{19}H_{27}NO_6$: 365.1836. Found: 365.1812. 7e : colorless crystal (from isopropyl alcohol), mp 113-114 °C and $[\alpha]_D^{20}$ -2.2° (c 0.78, $CHCl_3$). IR (KBr) : 2940, 1745, 1715, 1515, 1255, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.91 (3H, d, J=7.0 Hz), 2.35 (3H, s), 2.4-2.7 (1m, m), 3.40 (3H, s), 3.4-3.8 (6H, m), 3.80 (3H, s), 4.11 (1H, d, J=2.6 Hz), 4.6-4.8 (1H, m), 4.69 (3H, s), 6.87 (2H, d, J=9.0 Hz), 7.31 (2H, d, J=9.0 Hz). Mass m/e : 365 $(M)^+$, 290 $(M-OCH_2CH_2OMe)$, 258 (M-p-anisyl)$^+$. Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.45; H, 7,45; N, 3.83 %. Found: C,. 62.19; H, 7.57; N, 3.71 %.

(3S, 4R)-1-(p-Anisyl)-3-aetyl-4-[(R)-1-(methylthiomethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3f and 7f). The 2-azetidinone derivatives (3f and 7f) prepared from 6 (R^1=CH_2SMe) and p-anisidine, were obtained as a 1.5 : 1 mixture after purification with preparative TLC. Colorless oil. IR (neat) : 2930, 1750, 1715, 1510, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0,91, 1.04 (3H, two d, J=7.0 Hz and 7.0 Hz, intensity ratio=2:3), 2.12, 2.14 (3H, two s, intensity ratio=3:2), 2.2-2.6 (1H, m), 2.36 (3H, s), 3.4-3.6 (2H, m), 3.79 (3H, s), 4.13, 4.36 (1H, two d, J=1.8 Hz and 2.2 Hz, intensity ratio=2:3), 4.55, 4.59 (2H, two s, intensity ratio= 3:2), 4.6-4.8 (1H, m), 6.87 (2H, d, J=9.0 Hz), 7.30 (2H, d, J=9.0 Hz). Mass m/e : 337 $(M)^+$, 290 $(M-SMe)^+$. Exact mass : Calcd. for $C_{17}H_{23}NO_4S$:337.1346. Found: 337.1334.

(3S, 4R)-1-(p-Anisyl)-3-acetyl-4-[(R)-1-(phenylthiomethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3g and 7g). The 2-azetidinone derivatives (3g and 7g) prepared from 6 (R^1=CH_2SPh) and p-anisidine, were obtained as a 1.2 : 1 mixture after purification with preparative TLC. Colorless oil. IR ($CHCl_3$) : 1745, 1715, 1510, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.90, 1.02 (3H, two d, J=7.0 Hz and 6.8 Hz, intensity ratio=5:6), 2.28 (3H, s), 2.3-2.6 (1H, m), 3.4-3.7 (2H, m), 3.78 (3H, s), 4.08, 4,26 (1H, two d, J=2.5 Hz and 2.5 Hz, intensity ratio=5:6), 4.54, 4.63 (1H, two dd, J=5.0, 2.5 Hz and 5.0, 2.5 Hz, intensity ratio=6:5), 4.93, 4.96 (2H, two s, intensity ratio=6:5), 6.84 (2H, d, J= 9.0Hz), 7.2-7.6 (7H, m). Mass m/e : 399 $(M)^+$, 290 $(M-SPh)^+$. Exact Mass : Calcd. for $C_{22}H_{25}NO_4S$: 399.1502. Found: 399.1507.

(3S,4R)-1-(p-Anisyl)-3-acetyl-4-[(R)-1-(benzyloxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3h and 7h). The 2-azetidinone derivatives (3h and 7h) prepared from 6(R^1=CH_2Ph) and p-anisidine, were obtained as a 1.6 : 1 mixture after purification with preparative TLC. Colorless oil. IR (neat) : 2970, 2940, 1750, 1715, 1510, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.93, 1.04 (3H, two d, J=6.8 Hz and 7.0 Hz, intensity ratio=5:8), 2.25, 2.28 (3H, two s, intensity ratio=5:8), 2.3-2.6 (1H, m), 3.3-3.6 (2H, m), 3.78 (3H, s), 4.13 (0.4H, d, J=3.0 Hz), 4.41, 4.43(2H, two s, intensity ratio=8:5), 4.55, 4.69 (1H, two dd, J=5.5, 3.0 Hz and 4.5, 3.0 Hz, intensity ratio=8:5), 6.83 (2H, d, J=9.0 Hz), 7.1-7.5 (7H, m). Mass m/e : 367 $(M)^+$, 276 $(M-CH_2Ph)^+$. Exact Mass : Calcd. for $C_{22}H_{25}NO_4$: 367.1781. Found: 367.1768.

(3S, 4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(t-butyldimethylsilyloxymethyl)-ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3i and 7i). Prepared from **6** (R^1= Si*t*-BuMe)[29] and di-*p*-anisylmethylamine. **3i** : colorless oil. IR ($CHCl_3$) : 2955, 1745, 1710, 1610, 1510, 1460, 1250, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.03 (3H, s), 0.06 (3H, s), 0.86 (3H, d, J=7.5 Hz), 0.88 (9H, s), 1.6-1.9 (1H, m), 2.26 (3H, s), 3.3-3.7 (1H, m), 3.77 (3H, s), 3.79 (3H, s), 4.14 (1H, dd, J=5.2 and 2.5 Hz), 4.38 (1H, d, J=2.5 Hz), 5.63 (1H, s), 6.85 (2H, d, J=9.0 Hz), 6.88 (2H, d, J=9.0 Hz), 7.16 (2H, d, J=9.0 Hz), 7.28(2H, d, J=9.0 Hz). Mass m/e : 511 $(M)^+$, 468 $(M-CH_3CO)$. Exact Mass : Calcd. for $C_{29}H_{41}NO_5Si$: 511.2752. Found: 511.2779. **7i** : colorless oil. IR ($CHCl_3$) : 2955, 1745, 1715, 1610, 1510, 1465, 1250, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.03 (3H, s), 0.04 (3H, s), 0.84 (3H, d, J=7.5 Hz), 0,87 (9H, s), 1.6-1.9 (1H, m), 2.28 (3H, s), 3.3-3.6 (2H, m), 3.82 (6H, s), 4.05 (1H, d, J=2.3 Hz), 4.33 (1H, dd, J=4.2 and 2.3 Hz), 5.67 (1H, s), 6.86 (2H, d, J=8.8 Hz), 6.89 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.8 Hz), 7.21 (2H, d, J=8.8 Hz). Mass m/e : 511 $(M)^+$, 468 $(M-CH_3CO)^+$. Exact Mass : Calcd. for $C_{29}H_{41}NO_5Si$: 511.2752. Found: 511.2774.

(3R, 4S)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(t-butyldiphenylsilyloxymethyl)-ethyl]-2-azetidinone(7j). Prepared as a sole product from **6** (R^1=Si*t*-$BuPh_2$)[22,29b,30] and di-*p*-anisylmethylamine. Colorless oil. IR ($CHCl_3$) : 2950, 1750, 1715, 1610, 1510, 1250, 1180, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.77 (3H, d, J=7.0 Hz), 1.01 (9H, s), 1.5-1.8 (1H, m), 2.23 (3H, s), 3.42(2H, d, J=5.1 Hz), 3.77 (6H, s), 4.02 (1H, d, J=2.3 Hz), 4.41 (1H, dd, J=4.4 and 2.3 Hz), 5.60 (1H, s), 6.82 (4H, d, J=8.0 Hz), 7.12 (2H, d, J=8.0 Hz), 7.14 (2H, d, J=8.0 Hz), 7.3-7.7 (10H, m). Mass m/e : 635 $(M)^+$, 396 $(M-Sit\text{-}BuPh_2)^+$. Exact Mass : Calcd. for $C_{39}H_{45}NO_5Si$: 635.3065. Found: 635.3086.

(3S, 4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(triphenylmethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3k and 7k). Prepared from **6** (R^1=CPh_3) and di-*p*-anisylmethylamine. **3k** : colorless oil. IR ($CHCl_3$) : 2970, 1750, 1715, 1610, 1510, 1250, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.93 (3H, d, J=7.0 Hz), 1.6-1.9 (1H, m), 2.18 (3H, s), 2.95 (2H, d, J=6.0 Hz), 3.75 (3H, s), 3.78 (3H, s), 4.16 (1H, dd, J=5.1 and 2.6 Hz), 4.30 (1H, d, J=2.6 Hz), 5.34 (1H, s), 6.7-7.4 (23H, m). Mass m/e : 396 $(M-CPh_3)^+$. **7k** : colorless oil. IR ($CHCl_3$) : 2920, 1745, 1710, 1610, 1510, 1245, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.82(3H, d, J=6.8 Hz), 1.6-1.9 (1H, m), 2.16 (3H, s), 2.8-3.1 (2H, m), 3.78 (6H, s), 4.03 (1H, d, J=2.4 Hz), 4.32 (1H, dd, J=4.2 and 2.4 Hz), 5.53 (1H, s), 6.82 (4H, d, J=8.8 Hz), 7.13(4H, d, J=8.8 Hz), 7.26 (15H, br s). Mass m/e : 396 $(M-CPh_3)^+$.

(3S, 4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(2-methoxyethoxymethoxymethyl)-ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3l and 7l). The 2-azetidinone derivatives (**3l** and **7l**) prepared from **6** (R^1=$CH_2OCH_2CH_2OMe$) and di-*p*-anisylmethylamine, were obtained as a 1.3 : 1 mixture after purification with preparative TLC. Colorless oil. IR ($CHCl_3$) : 2945, 1750, 1715, 1610, 1510, 1460, 1250, 1175, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.79, 0.87 (3H, two d, J=7.4 Hz and 7.4 Hz, intensity ratio=3:4), 1.7-2.0 (1H, m), 2.27 (3H, s), 3.3-3.7 (6H, m), 3.35, 3.37 (3H, two s, intensity ratio=4:3), 3.78 (6H, s), 3.9-4.3 (2H, m), 4.57, 4.61 (2H, two s, intensity ratio=4:3), 5.59, 5.61 (1H, two s, intensity ratio=4:3), 6.8-7.3 (8H, m). Mass m/e : 485 $(M)^+$, 442 $(M-CH_3CO)^+$, 396 $(M-CH_2OCH_2CH_2OMe)^+$. Exact Mass : Calcd. for $C_{27}H_{35}NO_7$: 485.2411. Found: 485.2383.

(3S, 4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(methoxymethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3m and 7m). The 2-azetidinone derivatives (**3m** and **7m**) prepared from **6** (R^1=CH_2OMe)[32] and di-*p*-anisylmethylamine, were obtained as a 1.7 : 1 mixture after purification with preparative TLC. Colorless oil. IR (neat) : 2940, 1750, 1715, 1610, 1515, 1250, 1180, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.82, 0.90 (3H, two d, J=7.0 Hz and 7.0 Hz, intensity ratio=3:5), 1.7-2.0 (1H, m), 2.23 (3H, s), 3.27, 3.30 (3H, two s, intensity ratio=3:5), 3.2-3.5 (2H, m), 3.79 (6H, s), 4.0-4.4 (2H, m), 4.48, 4.51 (2H, two s, intensity ratio=3:5), 5.62, 5.65 (1H, two s, intensity ratio=5:3), 6.85 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 7.15 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz). Mass m/e : 396 $(M-CH_2OMe)^+$.

(3S, 4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(methylthiomethoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3n and 7n). Prepared from **6** (R^1=CH_2SMe) and di-p-anisylmethylamine. **3n** : colorless oil. IR (neat) : 2970, 2930, 1755, 1715, 1610, 1515, 1250, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.88 (3H, d, J=7.0 Hz), 1.7-2.0 (1H, m), 2.09 (3H, s), 2.27 (3H, s), 3.2-3.5 (2H, m), 3.79 (6H, s), 4.1-4.3 (2H, m), 4.52 (2H, s), 5.62 (1H, s), 6.85 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.15 (2H, d, J=9.0 Hz), 7.22 (2H, d, J=9.0 Hz). Mass m/e : 457 $(M)^+$, 396 $(M-CH_2SMe)^+$. Exact Mass : Calcd. for $C_{25}H_{31}NO_5S$: 457.1921. Found: 457.1927. **7n** : colorless oil. IR ($CHCl_3$) : 1750, 1715, 1610, 1510, 1250, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.80 (3H, d, J=7.0 Hz), 1.7-1.9 (1H, m), 2.06 (3H, s), 2.28 (3H, s), 3.30 (2H, d, J=5.0 Hz), 3.79 (6H, s), 4.01 (1H, d, J=2.5 Hz), 4.30 (1H, dd, J=4.5 Hz and 2.5 Hz), 4.49 (2H, s), 5.66 (1H, s), 6.82 (2H, d, J=8.5 Hz), 6.84 (2H, d, J=8.5 Hz), 7.17 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz). Mass m/e : 457 $(M)^+$, 396 $(M-CH_2SMe)^+$. Exact Mass : Calcd. for $C_{25}H_{31}NO_5S$: 457.1921. Found: 457.1891.

(3S, 4R)-2-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(t-butoxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (3p and 7p). Prepared from **6** (R^1=t-Bu)[33] and di-p-anisylmethylamine. **3p** : colorless oil, $[\alpha]_D^{20}$ -45.6° (c 0.51, $CHCl_3$). IR (neat) : 2980, 1755, 1715, 1610, 1515, 1250, 1175, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.86 (3H, d, J=6.8 Hz), 1.11 (9H, s), 1.6-1.9 (1H, m), 2.26 (3H, s), 3.1-3.2 (2H, m), 3.79 (6H, s), 4.08 (1H, dd, J=5.5 Hz and 2,4 Hz), 4.30 (1H, d, J=2.4 Hz), 5.62 (1H, s), 6.83 (2H, d J=8.8 Hz), 6.85 (2H, d, J=8.8 Hz), 7.15 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz). Mass m/e : 453 $(M)^+$, 396 $(M-t\text{-}Bu)^+$. Exact Mass : Calcd. for $C_{27}H_{35}NO_5$: 453.2512. Found: 453.2479. **7p** : colorless oil, $[\alpha]_D^{20}$ +17.9° (c 0.86, $CHCl_3$). IR (neat) : 2975, 1750, 1715, 1610, 1510, 1250, 1175, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.79 (3H, d, J=6.8 Hz), 1.06 (9H, s), 1.6-1.8 (1H, m), 2.25 (3H, s), 3.14 (2H, d, J=5.4 Hz), 3.79 (6H, s), 4.06 (1H, d, J=2.4 Hz), 4.26 (1H, dd, J=4.0 and 2.4 Hz), 5.63 (1H, s), 6.83 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.23 (2H, d, J=8.8 Hz). Mass m/e : 453 $(M)^+$, 396 $(M-t\text{-}Bu)^+$. Exact Mass : Calcd. for $C_{27}H_{35}NO_5$: 453.2512. Found: 453.2485.

(3S, 4R)-1-(Di-p-anisylmethyl)-3-acetyl-4-[(R)-1-(hydroxymethyl)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (8 and 9). a) Preparation of 8 from 3o : A mixture of **3o** (58 mg, 0.12 mmol) and 5 % Pd-C (25 mg) in EtOAc (2 ml) was vigorously stirred under a hydrogen atmosphere at room temperature. After 12 h, additional amount of 5 % Pd-C (25 mg) was added, and stirring was further continued for 20 h. The reaction mixture was filtered through a pad of celite and the collected materials were washed with EtOAc. The combined filtrates were concentrated *in vacuo*. The residue was purified with preparative TLC (EtOAc-hexane=9:1), affording **8** as a colorless oil (43 mg, 91 %), $[\alpha]_D^{20}$ -68.7° (c 0.96, $CHCl_3$). IR ($CHCl_3$) : 3500, 3020, 2970, 1750, 1715, 1615, 1510, 1250, 1175, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.90 (3H, d, J=6.8 Hz), 1.6-2.0 (1H, m), 2.28 (3H, s), 3.49 (2H, dd, J=5.3 and 1.8 Hz), 3.79 (3H, s), 3.80 (3H, s), 4.06 (1H, dd, J=5.7 and 2.9 Hz), 4.17 (1H, d, J=2.9 Hz), 5.64 (1H, s), 6.84 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=8.8 Hz), 7.15 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz). Mass m/e : 397 $(M)^+$, 354($M-CH_3CO)^+$. Exact Mass : Calcd. for $C_{23}H_{27}NO_5$: 397.1888. Found: 397.1913.

b) Preparation of 9 from 7o : Debenzylation of **7o** (5.0 mg, 0.010 mmol) was performed as described for that of **3o**, giving **9** as a colorless oil (3.5 mg, 86 %), $[\alpha]_D^{20}$ +53.6° (c 0.28, $CHCl_3$). IR ($CHCl_3$) : 3500, 3010, 2970, 1750, 1715, 1615, 1510, 1250, 1180, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.78 (3H, d, J=6.8 Hz), 1.5-2.0 (1H, m), 2.33 (3H, s), 3.3-3.6 (2H, m), 3.79 (6H, s), 3.98 (1H, d, J=2.5 Hz), 4.25 (1H, dd, J=4.5 and 2.5 Hz), 5.65 (1H, s), 6.84 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.19 (2H, d, J=8.8 Hz). Mass m/e : 397 $(M)^+$, 354 $(M-CH_3CO)^+$. Exact Mass : Calcd. for $C_{23}H_{27}NO_5$: 397.1888. Found: 397.1912.

c) Preparation of 8 and 9 from the mixture of 3m and 7m : Dimethyl sulfide (0.15 ml, 2.0 mmol) and boron trifluoride etherate (37 µl, 0.30 mmol) was added to a solution of a 1.7 : 1 mixture of **3m** and **7m** (40 mg, 0.090 mmol) in CH_2Cl_2 (0.5 ml) cooled at 0 °C.[16] After stirring at 0 °C for 2 h, the reaction mixture was diluted with EtOAc and succesively washed with H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified with preparative TLC (acetone-CH_2Cl_2=1:9, two developments) to give **8**

(7 mg, 47 %) and **9**(11 mg, 31 %). The spectral data of **8** and **9** were identical with those of the authentic samples obtained in a) and b), respectively.

d) Preparation of 8 from 3p : Treatment of **3p** (6.0 mg, 0.013 mmol) with trifluoroacetic acid according to the reported procedure[17] (0 °C, 3 h) gave **8** (0.7 mg, 13 %). The spectral data of **8** were identical with those of the authentic sample obtained in a).

(3S, 4R)-3-Acetyl-4-[(R)-1-(benzyoxymethyloxy)ethyl]-2-azetidinone and Its (3R, 4S)-Isomer (10 and 11). a) Preparation of 10 from 3o : A fifteen percent aqueous CAN solution (1.4 ml, 0.38 mmol) was added to a solution of **3o** (61 mg, 0.13 mmol) in acetonitrile (1.5 ml) cooled at 0 °C.[18] After stirring at 0 °C for 1 h, the reaction mixture was diluted with EtOAc and washed succesively with H_2O, saturated $NaHCO_3$, saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified with column chromatography (SiO_2, acetone-CH_2Cl_2=5:95) to afford **10** as a colorless oil (18 mg, 55 %), $[\alpha]_D^{20}$ +8.2° (c 0.72, $CHCl_3$). IR (neat) : 3280, 2880, 1765, 1715, 1360, 1175, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.97 (3H, d, J=6.8 Hz), 1.8-2.2 (1H, m), 2.17 (3H, s), 3.39 (1H, dd, J=9.0 and 7.0 Hz), 3.52 (1H, dd, J=9.0 and 4.6 Hz), 3.93 (1H, dd, J=7.5 and 2.4Hz), 4.08 (1H, d, J=2.4 Hz), 4.41 (2H, s), 5.9 (1H, br s, NH), 7.30 (5H, s). Mass m/e : 218 $(M-CH_3CO)^+$, 170 $(M-CH_2Ph)^+$.

b) Preparation of 11 from 7o : The same treatments on **7o** (21 mg, 0.043 mmol) as those described in a) gave **11** as a colorless oil (6.0mg, 53%). IR (neat) : 3300, 2870, 1760, 1715, 1360, 1180, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.87 (3H, d, J=7.0 Hz), 1.8-2.2 (1H, m), 2.30 (3H, s), 3.36 (1H, t, J=8.6 Hz), 3.55 (1H, dd, J=8.6 and 4.8 Hz), 3.7-3.9 (2H, m), 4.46 (2H, s), 6.1 (1H, br s, NH), 7.31 (5H, s). Mass m/e : 261 $(M)^+$, 218 $(M-CH_3CO)^+$, 170 $(M-CH_2Ph)^+$.

c) Preparation of 10 and 11 from a mixture of 3h and 7h : Treatments of a 1.6:1 mixture of **3h** and **7h** (58 mg, 0.16 mmol) in a similar manner to that descrived in a), followed by purification with flash column chromatography (SiO_2, acetone-CH_2Cl_2=6:94), afforded **10** (21 mg, 51 %) and **11**(13 mg, 32 %). The spectral data of **10** and **11** were identical with those of the authentic samples obtained in a) and b), respectively.

d) Preparation of 10 from 3e : Dimethyl sulfide (0.22 ml, 3.0 mmol) and boron trifluoride etherate (37 µl, 0.30 mmol) were added to a solution of **3e** (11 mg, 0.030 mmol) in CH_2Cl_2 (0.5 ml) cooled at 0°C, and the mixture was stirred at the same temperature for 1 h.[16] The reaction mixture was diluted with EtOAc and succesively washed with H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo* to give crude (3S, 4R)-1-(p-anisyl)-3-acetyl-4-[(R)-1-(hydroxymethyl)ethyl]-2-azetidinone. ^{1}H-NMR ($CDCl_3$) : 1.04(3H, d, J=7.0 Hz), 2.1-2.4 (1H, m), 2.36 (3H, s), 3.61 (2H, d, J=4.7 Hz), 3.78 (3H, s), 4.36 (1H, d, J=2.4 Hz), 4.55 (1H, dd, J=5.5 and 2.4 Hz), 6.86 (2H, d, J=9.2 Hz), 7.29 (2H, d, J=9.2 Hz). The crude sample was benzylated according to the reported procedure (0 °C, 3 h).[20] The resulting crude benzyl ether was oxidized with CAN as described in a), affording **10** (3.5 mg, 44 % from **4e**). The spectral data of **10** were identical with those of authentic sample obtained in a).

(3S, 4R)-1-(Di-p-anisylmethyl)-3-[(R)-1-hydroxyethyl]-4-[(R)-1-(benzyloxymethyl)-ethyl]-2-azetidinone and Its 3-[(S)-1-Hydroxyethyl]-Isomer (12 and 13). A suspension of **3o** (227 mg, 0.47 mmol) and KI (93 mg, 0.56 mmol) in THF (10 ml) was stirred at room temperature for 30 min,[7] then cooled at 0 °C. A 1.0 M solution of K-Selectride(R) in THF (1.12 ml, 1.12 mmol) was added dropwise to the reaction mixture. After stirring at 0 °C for 1 h, the reaction mixture was diluted with EtOAc, and succesively washed with 0.1M-HCl, saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The concentration residue was separated with column chromatography (SiO_2, ether) to give a mixture of **12** and **13** (226 mg, 99 %). The epimeric mixture (125 mg) were further separated with preparative TLC (acetone-CH_2Cl_2=1:9, two developments) to afford pure **12** (115 mg) and **13** (7 mg). The isomeric ratio of **12** to **13** was

determined as 16:1 based on the isolated yields. **12** : colorless oil, $[\alpha]_D^{20}$ -55.1° (c 0.85, $CHCl_3$). IR (neat) : 3460, 2980, 1735, 1610, 1510, 1250, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.94 (3H, d, J=6.8 Hz), 1.24 (3H, d, J=6.4 Hz), 1.8-2.1 (1H, m), 2.20 (1H, br s, OH), 3.00 (1H, dd, J=6.4 and 2.4 Hz), 3.35 (2H, d, J=5.3 Hz), 3.70 (1H, dd, J=5.7 and 2.4 Hz), 3.77 (3H, s), 3.79 (3H, s), 4.0-4.2 (1H, m), 4.42 (2H, s), 5.55 (1H, s), 6.81 (2H, d, J=8.8 Hz), 6.83 (2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.21 (3H, d, J=8.8 Hz), 7.31 (5H, s). Mass m/e : 489 $(M)^+$, 444 $(M-CH_3CHOH)^+$, 398 $(M-CH_2Ph)^+$. Exact Mass : Calcd. for $C_{30}H_{35}NO_5$: 489.2513. Found: 489.2511. **13** : colorless oil, $[\alpha]_D^{20}$ -26.7° (c 0.73, $CHCl_3$). IR (neat) : 3490, 2960, 1740, 1615, 1515, 1250, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.93 (3H, d, J=6.4 Hz), 1.16 (3H, d, J=6.4 Hz), 1.9-2.2 (1H, m), 2.35 (1H, d, J=4.5 Hz, OH), 2.99 (1H, dd, J=7.2 and 2.4 Hz), 3.33 (2H, d, J=5.5 Hz), 3.55 (1H, dd, J=5.1 and 2.4 Hz), 3.78 (6H, s), 3.9-4.1 (1H, m), 4.42 (2H, m), 5.53 (1H, s), 6.82 (4H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.19 (2H, d, J=8.8 Hz), 7.31 (5H, s). Mass m/e : 489 $(M)^+$, 444 $(M-CH_3CHOH)^+$, 398 $(M-CH_2Ph)^+$. Exact Mass : Calcd. for $C_{30}H_{35}NO_5$: 489.2513. Found: 489.2526.

(3S, 4R)-3-[(R)-1-Hydroxyethyl]-4-[(R)-1-(benzyloxymethyl)ethyl]-2-azetidinone (14). A fifteen percent aqueous CAN solution (2.0 ml, 0.55 mmol) was added to a solution of **12** (88 mg, 0.18 mmol) in acetonitrile (2.0 ml) cooled at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. The same workup as described for the preparation of **10** from **3**, followed by purification with column chromatography (SiO_2, acetone-CH_2Cl_2=1:3), afforded **14** as a colorless oil (43 mg, 91 %), $[\alpha]_D^{20}$ -5.0° (c 0.44, $CHCl_3$). IR (neat) : 3600-3200, 2995, 1745, 1450, 1370, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.98 (3H, d, J=6.8 Hz), 1.29 (3H, d, J=6.4 Hz), 1.8-2.1 (1H, m), 2.53 (1H, d, J=4.8 Hz, OH), 2.99 (1H, ddd, J=7.7, 2.2, and 1.0 Hz), 3.3-3.7 (3H, m), 3.9-4.2 (1H, m), 4.49 (2H, s), 5.90 (1H, br s, NH), 7.32 (5H, s). Mass m/e : 264 $(M+H)^+$.

(3S, 4R)-3-[(R)-1-(t-Butyldimetylsilyloxy)ethyl]-4-[(R)-1-(benzyloxymethyl)ethyl]-2-azetidinone(15). A mixture of **14** (33 mg, 0.13 mmol), imidazole (51 mg, 0.75 mmol), t-butyldimethylchlorosilane (95 mg, 0.63 mmol) in DMF (1.0 ml) was stirred at room temperature for 14 h.[6b] The reaction mixture was diluted with EtOAc and washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified with column chromatography (SiO_2 , EtOAc-hexane=1:2), affording **15** as a colorless oil (47 mg, 99 %), $[\alpha]_D^{20}$ -13.1° (c 0.35, $CHCl_3$). IR (neat) : 3260, 2960, 2890, 1755, 1460, 1375, 1260, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.07 (6H, s), 0.88 (9H, s), 1.01 (3H, d, J=6.8 Hz), 1.20 (3H, d, J=6.4 Hz), 1.9-2.2 (1H, m), 2.92 (1H, ddd, J=5.7, 2.2, and 1.0 Hz), 3.41 (2H, d, J=5.3 Hz), 3.68 (1H, dd, J=5.5 and 2.2 Hz), 4.1-4.3 (1H, m), 4.47 (2H, s), 5.80 (1H, br s, NH), 7.31 (5H, s). Mass m/e : 362 $(M-Me)^+$, 320 $(M-t-Bu)^+$.

(3S, 4R)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(hydroxymethyl)ethyl]-2-azetidinone(16). A mixture of **15** (45 mg, 0.12 mmol), 5 % Pd-C (10 mg) in EtOAc (2.0 ml) was stirred under a hydrogen atomosphere at room temperature for 20 h. The mixture was filtered through a pad of celite and the collected materials were washed with EtOAc. The combined filtrates were concentrated in vacuo to give pure **16** as colorless crystals (35 mg, 100 %). An analytical sample was obtained by recrystallization from ether-hexane, mp 90-91 °C and $[\alpha]_D^{20}$ -21.7° (c 0.46, $CHCl_3$). IR (KBr) : 3450, 3190, 3115, 2960, 1755, 1255 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.13 (6H, s), 0.90 (3H, d, J=6.8 Hz), 0.92 (9H, s), 1.35 (3H, d, J=6.2 Hz), 1.8-2.1 (1H, m), 2.95 (1H, dd, J=8.3 and 5.3 Hz, OH), 3.17 (1H, ddd, J=9.0, 2.2, and 1.0 Hz), 3.29 (1H, dd, J=9.0 and 2.2 Hz), 3.4-3.7 (2H, m), 4.13 (1H, dq, J=9.0 and 5.4 Hz), 5.93 (1H, br s, NH). Mass m/e : 272 $(M-Me)^+$, 230 $(M-t-Bu)^+$. Anal. Calcd. for $C_{14}H_{29}NO_3Si$: C, 58.50; H, 10.17; N, 4.87 %. Found: C, 58.38; H, 9.90; N, 4.80 %.

(3S, 4S)-3-[(R)-1-(t-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone(2). A suspension of **16** (22 mg, 0.077 mmol) and pyridinium dichromate[20] (144 mg, 0.38 mmol) in DMF (1.0 ml) was stirred at room temperature for 15 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The concentration residue was purified with column chromatography (SiO_2, CH_2Cl_2-EtOAc-AcOH=60:40:0.5) to afford **2** as colorless crystals (21 mg, 91 %). An analytical sample was obtained by recrys-

tallization from EtOAc-hexane, mp 146-147°C (decomp) (lit.[3] 140-143°C) and $[\alpha]_D^{25}$ -34.6° (c 0.26, MeOH). IR (KBr) : 3280, 2950, 1720, 1460, 1280, 1260, 1140, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.07 (6H, s), 0.88 (9H, s), 1.20 (3H, d, J=6.6 Hz), 1.26 (3H, d, J=6.8 Hz), 2.74 (1H, dq, J=5.4 and 6.8 Hz), 3.03 (1H, dd, J=4.5 and 2.2 Hz), 3.94 (1H, dd, J=5.4 and 2.2 Hz), 4.20 (1H, dq, J=4.5 and 7.7 Hz), 6.05 (1H, br s, NH). Mass m/e : 286 $(M-Me)^+$, 244 $(M-t-Bu)^+$. Anal. Calcd. for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65 %. Found: C, 55.89; H, 8.97; N, 4.60 %.

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