Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3041–3062

TETRAHEDRON

Synthetic studies of carzinophilin. Part 2: Synthesis of 3,4-dibenzyloxy-2-methylidene-1-azabicyclo[3.1.0]hexane systems corresponding to the C1–C17 fragment of carzinophilin☆

Masaru Hashimoto,*,† Miyoko Matsumoto and Shiro Terashima*

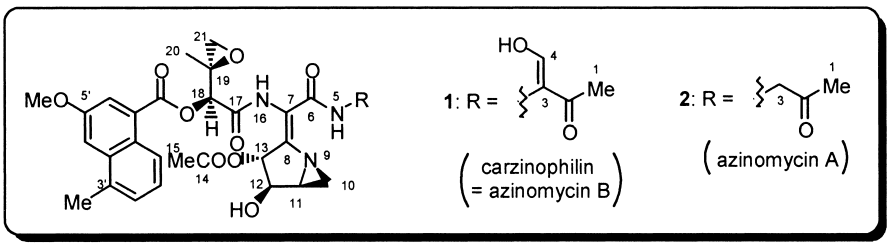
Sagami Chemical Research Center, 2743-1, Hayakawa, Ayase, Kanagawa 252-1193, Japan

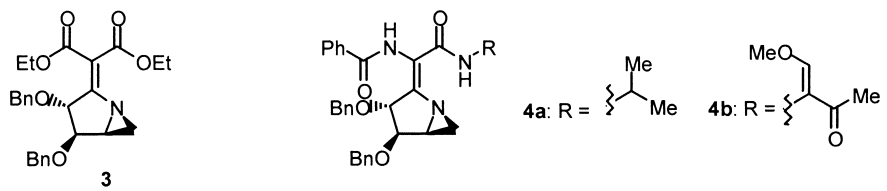
Received 30 January 2003; accepted 6 March 2003

Abstract—A model compound bearing the C1–C17 fragment of carzinophilin was synthesized. The synthesis involved coupling reaction of a cyclic thioimidate with the 4*H*-oxazol-5-one derivative, ring-opening of the 4*H*-oxazol-5-one to furnish a dehydropeptide system, elaboration of the C1–C6 enolamide, and construction of the aziridine ring as key steps. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Carzinophilin (**1**) is an antitumor antibiotic isolated from *Streptomyces sahachiroi* by Hata et al. in 1954.[3] After the structure elucidation and revisions were repeated several times, **1** was proved to have the same structure as azinomycin B,[4] which was isolated by Yokoi et al. in 1986 and disclosed to bear a characteristic (1-azabicyclo[3.1.0]-hex-2-ylidene)glycine system.[5] The unique structure as well as potent bioactivity of **1** attracted chemists to study its total synthesis.[6,7] Recently, Coleman et al. reported successful total synthesis of **2**.[8] However, synthesis of **1** carrying another unique 1-acetyl-2-hydroxyenamide system (the C1–C6 unit), has not been accomplished yet. In the course of our synthetic studies on **1**, we have developed a synthetic method providing a (1-azabicyclo[3.1.0]hex-2-ylidene)glycine system.[1a,b] We have also reported an efficient and stereoselective synthetic route to the C6–C13 pyrrolidine framework[1c] as well as a synthetic scheme giving the unique C1–C6 enamide system.[1c,d] Applying the knowledge accumulated in these studies, syntheses of the C1–C17 fragment of carzinophilin (**3**,**4**) have been achieved and disclosed in communication forms.[1c,d] In the second part of this series of papers, we would like to report full details of these studies.





☆ See refs 1 and 2.

Keywords: carzinophilin; azinomycin; pyrrolidin; (1-azabicyclo[3.1.0.]hex-2-ylidene) glycine; azalactone.

* Corresponding authors. Tel./fax: +81-172-35-0869; e-mail: hmasaru@cc.hirosaki-u.ac.jp; terashima@sagami.or.jp

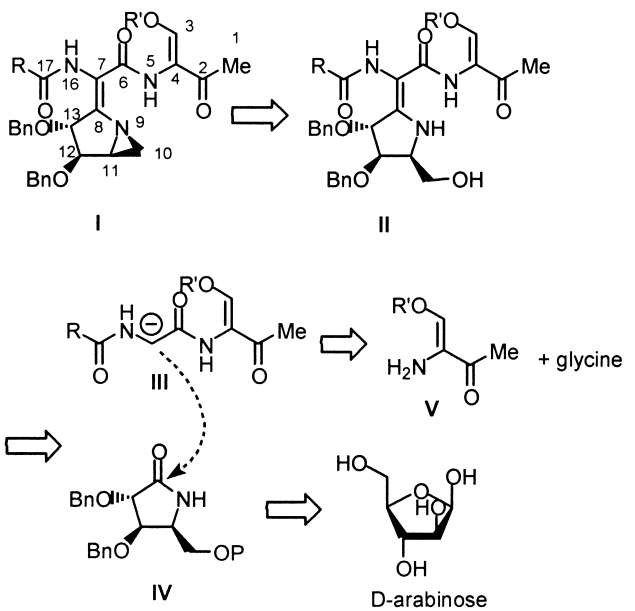
† Present address: Department of Agriculture and Life Science, Hirosaki University, 3 Bunkyo-Cho, Hirosaki, 036-8561, Japan.

doi:10.1016/S0040-4020(03)00378-8

2. Results and discussion

2.1. Synthetic strategy

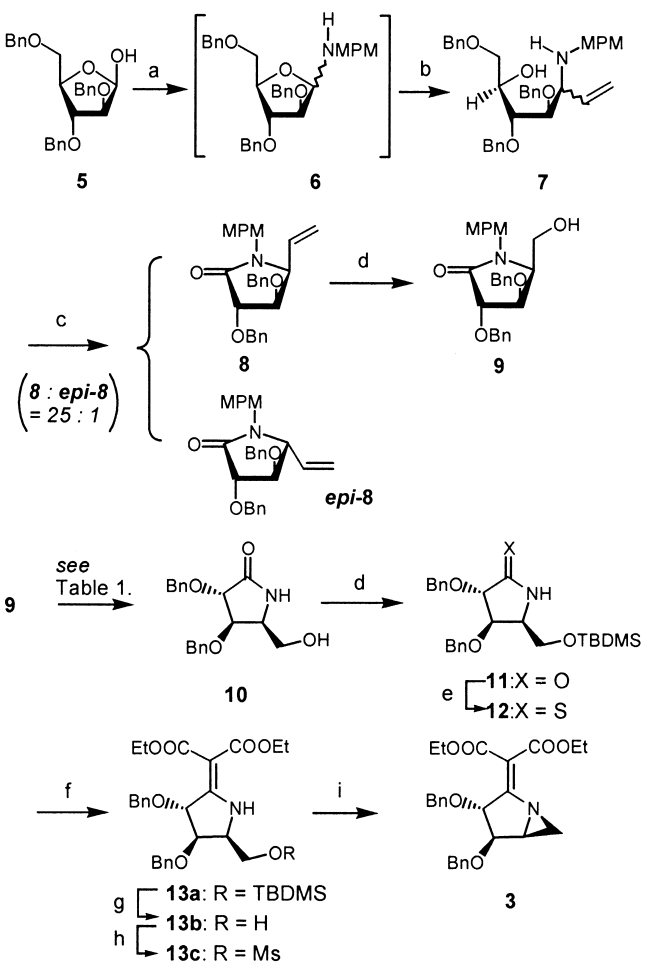
As described in the preceding paper, we have succeeded in preparing the *N*-acyl-(1-azabicyclo[3.1.0]hexan-2-ylidene)-glycine ester system. So, a model compound involving the C1–C16 fragment **I** was set as our next synthetic target. Our basic synthetic strategy is outlined in Scheme 1. Since the 1-azabicyclo[3.1.0]hexane system has been revealed to be labile, the aziridine ring should be constructed at the final stage of the synthesis.[1a,b] Accordingly, (5-hydroxymethyl)-pyrrolidin-2-ylidene derivative **II** was anticipated to be a precursor to the target molecule **I**. The pyrrolidin-2-ylidene amino acid moiety was planned to be furnished by coupling reaction of an anionic species of glycine derivative **III** with pyrrolidin-2-one **IV**. Although we have already accomplished the preparation of (pyrrolinylidene)malonate esters and *N*-acyl-(pyrrolidin-2-ylidene)glycine esters in our previous studies,[1a,b] development of synthetic methodology for the *N*-acyl-(pyrrolidin-2-ylidene)glycine amide system was required in this study. There were no reports about the procedures for this framework except for studies aiming at the synthesis of azinomycins (=carzinophilin) carried out by Coleman et al. and Armstrong et al.[6] The peptide unit **III** might be prepared by a coupling of the glycine unit with 1-acetyl-2-hydroxyethenyl amine **V** or its synthetic equivalent. It was also necessary to establish a route to **V** bearing a structure unprecedented in natural products. The core pyrrolidine part **IV** was planned to be synthesized stereoselectively from D-arabinose applying the protocol developed by Nicotra et al.[9,10]



Scheme 1. Synthetic strategy of the C1–C17 fragment of carzinophilin (**1**).

2.2. Synthesis of the 3,4-dihydroxypyrrolidin-2-one corresponding to the C8–C13 unit[1c]

First, synthesis of the 3,4-dihydroxypyrrolidin-2-one corresponding to the C8–C13 unit was investigated. We applied the protocol disclosed by Nicotra et al. providing (3*S*,4*R*,5*S*)-1-benzyl-3,4-dibenzyloxy-5-vinylpyrrolidin-2-one in a stereoselective manner.[9] Considering a selective deprotection at the later synthetic stages, the (4-methoxyphenyl)methyl (MPM) group was selected for protecting the nitrogen moiety instead of the benzyl group employed by them. Refluxing commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**5**) with $MPMNH_2$ in toluene under azeotropic conditions produced the unstable adduct. Characteristic signals at 4.77 (minor) and 4.85 (major) ppm in the ^1H NMR spectrum of the crude product indicated that the crude material consists of a mixture of isomeric *N*-glycosides **6** but not of the corresponding imines. According to Nicotra's procedure,[9] crude **6** was directly reacted with vinylmagnesium bromide to afford an inseparable diastereomeric mixture of the adduct **7** in 71% yield in two steps. The addition of a vinyl group proceeded stereoselectively (ca. 25:1), but the stereochemistry of the major product was not assigned at this stage. The diastereomeric mixture **7** was subjected to PCC oxidation in the presence of powdered molecular sieves 4A,[9] giving lactam **8** in 71% yield and *epi*-**8** (3%). These isomers were separated by silica gel column chromatography. The vinyl group of the major product **8** was transformed into a



Scheme 2. Synthesis of C8–C13 unit **13**. *Reagents and conditions*: (a) $MPMNH_2$, toluene. reflux, 12 h. (b) CH_2=CHMgBr, THF, 0°C→rt, 12 h, 71% 2 steps. (c) PCC, MS4A, CH_2Cl_2, rt, 4 h, 71%. (d) O_3, EtOH, −25°C, 20 min, then $NaBH_4$, 0°C 20 min, 98%. (d) TBDMSCl, imidazile, DMF, rt, 12 h 89%. (e) Lawesson reagent, toluene, 60°C, 20 min, 83%. (f) $(EtO_2C)CHBr$, CH_2Cl_2, rt, 5 h then DBU, PPh_3, 4 h 82%. (g) TBAF, THF, rt, 1.5 h, 88%. (h) MsCl, Et_3N, CH_2Cl_2, −78°C, 2 h, 88%. (i) KHMDS THF 60°C, 40 min, 63%.

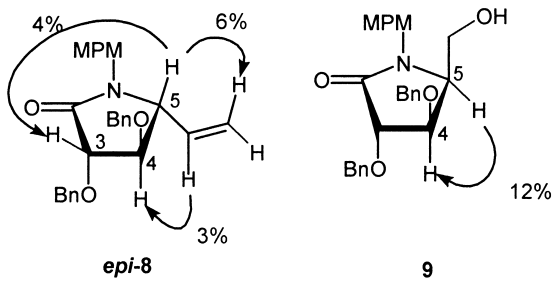
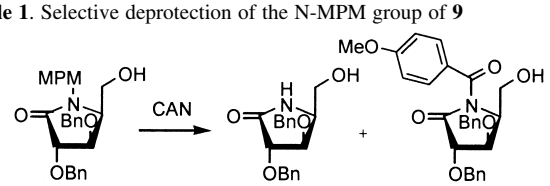


Figure 1. Observed NOEs in *epi*-**8** and **9**.

hydroxymethyl group by O_3 oxidation and following reduction of the ozonide with $NaBH_4$ affording alcohol **9** in 98% overall yield without isomerization (Scheme 2). The stereochemistries of these products were established by ^1H NMR experiments employing NOE technique. Irradiation of the signal due to the C5 proton (3.53 ppm) of *epi*-**8** induced NOEs at the signals of C3H (3.81 ppm) and one of the *exo*-methylene protons (4.92 ppm) as shown in Figure 1. Signal intensity of C4H (3.50 ppm) in *epi*-**8** was increased by another irradiation of C5CH signal (6.05 ppm). On the other hand, an NOE was observed between C4H (4.22 ppm) and C5H (3.53 ppm) in the case of **9**. These observations revealed the stereochemistry of the newly introduced C5 positions of *epi*-**8** and **9** to be *R*- and *S*-configuration, respectively. The X-ray crystallographic analysis of **9** supported these assignments (data not shown).

Next, the MPM group of **9** attached to the nitrogen was selectively removed. The results are summarized in Table 1. When **9** was treated with 10 equiv. of ammonium cerium (IV) nitrate (CAN) in a 1:1 mixture of CH_3CN and H_2O,[11] over-oxidation occurred to afford a considerable amount of imide **14** (35% yield) along with the desired compound **10** (51% yield) (run 1). The selectivity could not be improved by reducing the amount of CAN employed (run 2). The reaction in dry CH_3CN was very slow (run 3) suggesting that this oxidation requires H_2O. Addition of a small amount of H_2O was found to accelerate the oxidation (run 4). Selective removal of the MPM group was finally achieved efficiently by treating **9** with five equivalents of CAN in 19:1 mixture of CH_3CN and H_2O at 0°C, giving **10** in 99% yield (run 5). The reaction completed within 30 min. The

Table 1. Selective deprotection of the N-MPM group of **9**



Run	Amount of CAN (mol equiv.)	Ratio of CH_3CN/H_2O	Time (hr)	Yield (%)		
				9	**10**	**14**
1	10	1:1	2	0	51	35
2	2	1:1	0.7	15	45	15
3	3	1:0	12	36	53	0
4	2	9:1	12	28	66	0.6
5	5	19:1	0.5	0	99	0

alcoholic function was protected in the form of a TBDMS group to afford silyl ether **11** in 96% yield.

With the C8–C13 central domain of **1** in hand, synthesis of the model compound **3** was examined according to our reported methodology.[1a] These studies were carried out with the aim to demonstrate the utility of **11** for the synthesis of the C1–C17 fragment of **1** as well as **1** itself. The amide moiety of **11** was converted into thiolactam by heating with the Lawesson reagent,[12] giving **12** in 83% yield. On successive treatment of **12** with diethyl bromomalonate and DBU, the Eschenmoser coupling, took place yielding pyrrolidin-2-ylidenemalonate **13a**. The reaction employing $KHCO_3$ in place of DBU could not complete the reaction and gave only *S*-malonyl thioimidate **15**. This result is in contrast to our precedent synthesis of the model compound **16** lacking two alkoxy functions at the C12 and C13 positions (*carzinophilin numbering*). The adduct **13a** was converted into mesylate **13c** by the usual methods through alcohol **13b** in good overall yield. Heating **13c** with KHMDS was found to effect the aziridine ring closure to give the desired **3** in 63% yield after silica gel column chromatography. Interestingly, the dibenzyloxy compound **3** seemed to be more stable than **16** by considering the reaction conditions and isolation yield. This was useful information for our further studies (Fig. 2).

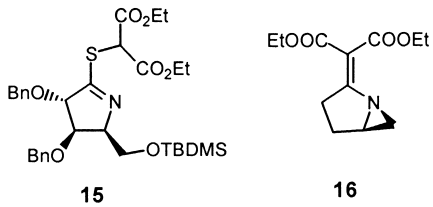


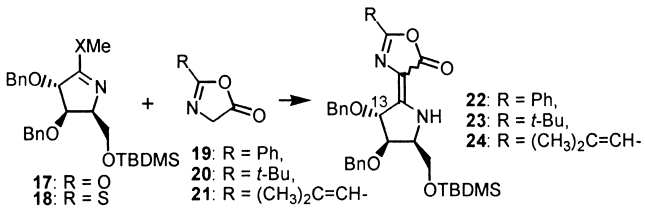
Figure 2. Structures of thioimidate **15** and the previous model compound **16**.

2.3. Development of a synthetic route to *N*-acyl-(pyrrolidin-2-ylidene)glycine amide systems[1d]

Our next focus was the construction of a *N*-acyl-(pyrrolidin-2-ylidene)glycine amide systems. Although it was disclosed that the Herdeis protocol was applicable to *N*-acyl-(pyrrolidin-2-ylidene)glycine esters,[1b] we could not apply this methodology to preparation of *N*-acyl-(pyrrolidin-2-ylidene)glycine amide systems in spite of intensive experimentation. Conversion of the (pyrrolidin-2-ylidene)-malonate **13** into the *N*-acyl-(pyrrolidin-2-ylidene)glycine amide system was also unsuccessful. After much effort, the 4*H*-oxazol-5-one (azlactone) method finally provided us fruitful results as described below.

It was found that *O*-methyl imidate **17** and *S*-methyl thioimidate **18** readily couple with azlactones **19**–**21**. Prior to the coupling reaction, **17** was prepared from **11** in 95% yield by treating with Me_3OBF_4[13] and **18** was produced in 96% yield by treating **12** with methyl iodide in CH_2Cl_2. Azlactone **19**–**21** were prepared from the corresponding *N*-acyl glycines in almost quantitative yields by 1-cyclohexyl-3-(2-morphorinoethyl)carbodiimide metho-*p*-toluenesulfonate in THF.[14] As shown in Table 2, heating **17** with three equivalents of **19**[14] at 80°C in toluene afforded the adduct **22** in 33% yield (run 1). Using pyridine as a

Table 2. Coupling reaction of imidates **17** and **18** with azlactones **19**–**21**



Run	Imidate	Azlactone	Conditions	Product	Yield (%)
1	**17**	**19** (**3** equiv.)	Toluene, 80°C	**22**	33
2	**17**	**19** (**3** equiv.)	Pyridine, 50°C	**22**	0
3	**18**	**19** (**4** equiv.)	Toluene, 80°C	**22**	82
4	**18**	**19** (**3** equiv.)	Toluene, rt	**22**	0
5	**17**	**20** (**3** equiv.)	Toluene, 80°C	**23**	0
6	**18**	**20** (**4** equiv.)	Toluene, 80°C	**23**	1.7
7	**17**	**21** (**1** equiv.)	$CHCl_3$, 40°C	**24**	2.7
8	**18**	**21** (**1** equiv.)	Benzene, 50°C	**24**	7.2

solvent, the reaction did not occur at all (run 2). When four equivalents of **18** was employed instead of **17**, the reaction proceeded more efficiently to give **22** in 82% yield (run 3). The reaction required heating around 80°C (run 4), but higher temperature only accelerated decomposition of both substrates. From the viewpoint of application to the total synthesis of **1**, the scope and limitation of this coupling reaction were also examined employing azlactones bearing different substituents. It was found that 2-*t*-butyl-4*H*-oxazol-5-one (**20**) gave no adduct **23** when **17** was employed. However, **20** afforded a trace amount of the adduct **23** (1.7%) by treating with **18** (run 6). Azlactone **21** substituted with a 2-methylpropenyl group gave the adduct **24** in 2.7 and 7.2% yield by treatment with **17** or **18**, respectively (run 7, 8). Since those conditions were accompanied with decomposition of the azlactones **19**–**21**, excess amounts of **19**,**20** were used for the reaction. However, we could employ only one equivalent of **21** because of supply difficulty. Taking into account the later elaboration steps for left hand moiety as disclosed in the preceding paper, the coupling with azlactones bearing similar substituents to **21** was anticipated to be promising for the total synthesis. An aryl or a vinyl group is expected to stabilize an anionic species of 4*H*-oxazol-5-one (azlactone) by mesomeric effect as shown in Figure 3. In fact, the coupling reaction with azlactones **19**,**21** carrying anion-stabilizing substituents, gave better results than that with **20**, an azlactone without an anion-stabilizing group. Accordingly, a substituent that stabilizes the anion should be incorporated into the azlactone which will be employed in the total synthesis.

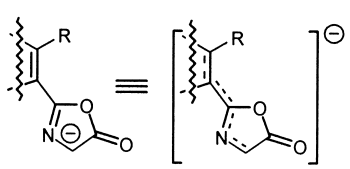


Figure 3. The anion of azlactone stabilized by the substituent.

The ^{1}H NMR spectra of the adducts **22**–**24** showed that they exist as mixtures of isomers about the C7–C8 double bonds (*carzinophilin numbering*). It was found that the isomeric ratio of **22** changed by the solvents employed [80:20 (in C_6D_6), 70:30 (in $CDCl_3$), 50:50 (in CD_3OD)]. This implies that tautomerism occurs between these isomers by way of the imine–enamine isomerization. The stereochemistry of these tautomers was determined using **22** based on its ^{1}H NMR spectra to reveal that the major and minor isomer have *E*- and *Z*-configuration, respectively, as described below (Fig. 4). Comparing the chemical shifts of C13H signals (*carzinophilin numbering*) disclosed that the signals of the minor *Z*-isomer appeared at 5.35 ppm in $CDCl_3$ which is 0.23 ppm lower field than that of the major *E*-isomer due to magnetic deshielding by the carbonyl group on the azlactone ring. A signal corresponding to the N9H (*carzinophilin numbering*) of the *E*-isomer (7.82 ppm) was observed at 1.04 ppm lower field than that of the minor *Z*-isomer (6.78 ppm). This observation suggested existence of strong hydrogen bonding between the N9H and the carbonyl group of the azlactone moiety in the case of the major isomer. Hydrogen bonding is also possible in the case of the *Z*-isomer between N9H and the nitrogen atom of the azlactone ring. However, molecular modeling of those compounds showed that the hydrogen bonding of the *Z*-isomer (ca. 2.6 Å length) might be geometrically less favorable than that of the major *E*-isomer (ca. 2.3 Å length).[15]

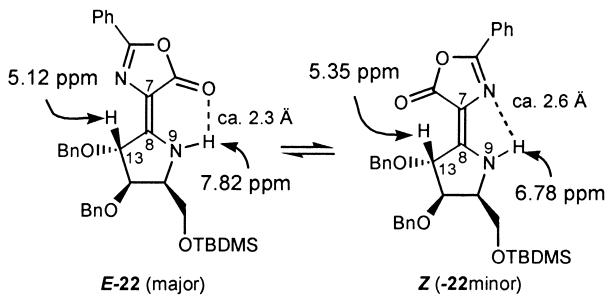
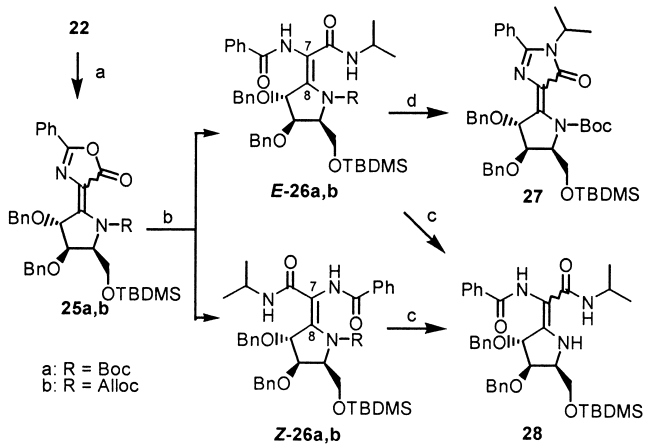


Figure 4. Chemical shifts (N9H and C13H) of the major tautomer *E*-**22** and the minor tautomer *Z*-**22** (minor) in $CDCl_3$.

Transformation of the azlactone ring into the dehydropeptide system was next examined. Contrary to our assumption, the azlactone ring of **22** was found to be quite stable. For example, no reaction occurred by heating **22** with isopropylamine in a sealed tube at 100°C. Simple desilylation was only observed by heating with a highly reactive isopropylchloroalminum amide, the Weinreb amide,[15] in benzene. However, it was found that the azlactone ring can be activated by acylation of the amino group of the pyrrolidine ring in **22**. Thus, reaction of **22** with Boc_2O or $Alloc_2O$ in the presence of DMAP[16] cleanly yielded unstable carbamates **25a** or **25b** and the following additions of isopropylamine into the reaction mixtures effected the aziridine ring-openings, affording a diastereomeric mixture of dehydropeptides **26a**,**b**, respectively (*E*-**26a**: 5.5%, *Z*-**26a**: 55%, *E*-**26b**: 45%, *Z*-**26b**: 20% yields each in 2 steps) (Scheme 3). These isomers were easily separated by column chromatography. It was also found that these isomers undergo no isomerization under the usual conditions. It is worth noting that neither benzoyl chloride nor TrocCl reacts with **22** under similar conditions to those described above.

The stereochemistries of *E*- and *Z*-**26** were determined based on their ^{1}H NMR spectra. The C13H signals of *E*-**25a**,**b** shifted higher field than those of *Z*-**26**. Probably, the C13H of the *E*-isomer is magnetically shielded by the



Scheme 3. Opening of the azlactone rings to provide dehydropeptide systems. *Reagents and conditions*: (a) (for **25a**): Boc_2O, cat. DMAP, THF, rt, 30 min (for **25b**): $Alloc_2O$, cat. DMAP, THF, rt, 30 min then, (b) isopropylamine, rt 30 min, 5.5% (*E*-**26a**), 65% (*Z*-**26a**), 45% (*E*-**26b**), 20% (*Z*-**26b**). (c) $Pd(PPh_3)_4$, dimedone, THF, rt, 10–30 min, 87% (from *E*-**26b**), 92% (from *Z*-**26b**). (d) TMSOTf, 2,6-Lu, CH_2Cl_2, rt 30 min, 68%.

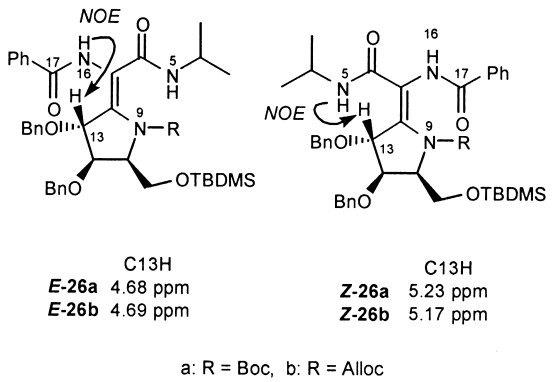


Figure 5. Observed NOEs in each isomer **26** and their chemical shifts of the C13H signal in $CDCl_3$.

C17 carbonyl group. In the cases of *E*-**26a**,**b** characteristic NOEs were observed at the C13H [*carzinophilin numbering*, 4.68 ppm (*E*-**26a**) and 4.69 ppm (*E*-**26b**)] by irradiation of the N16H signal [7.86 ppm (*E*-**26a**) and 7.96 ppm (*E*-**26b**)]. On the other hand, NOEs were detected between C13H (5.23 ppm) and N5 proton signals (9.97 ppm) in the ^1H NMR spectra of *Z*-**26a**. NOE experiments were not performed for *Z*-**26b** because of signal overlapping. The signals of N5H and N16H could be readily distinguished by their signal patterns (N5H=doublet, N16H=singlet).

Conformations of *E*-**26** were further examined by computer-assisted molecular modeling studies.[17] Dehydropeptides *E*-**26** involve complicated conjugation of π-electrons in the molecules. Thus, it was necessary to employ molecular orbital calculations to obtain reliable conformations. We chose a model compound **VI** in Figure 6 in order to save the time required for computations. Conformation search by an ab initio method for **VI** was not still practical due to abundant numbers of atoms existing in the molecule. Thus, stable conformations of **VI** were obtained by the following protocol. First, a conformational search in the PC Spartan Pro[17] was performed for **VI** employing semiempirical AM1 method to give 100 stable conformers. Twenty-six conformers were found within 3.0 kcal/mol from the minimum energy. These geometries were then re-optimized based on 6-31G* base set.[18] Figure 6 shows the conformer with minimum steric energy found by those calculations. This suggests that the pyrrolidine ring is twisted due to repulsion between the C6 side chain and the carbamate group attached to N9. The distance between C13H and the amide proton at N16 was estimated to be 2.54 Å. Accordingly, the NOEs between them can be expected in the cases of *E*-**26a**,**b**.

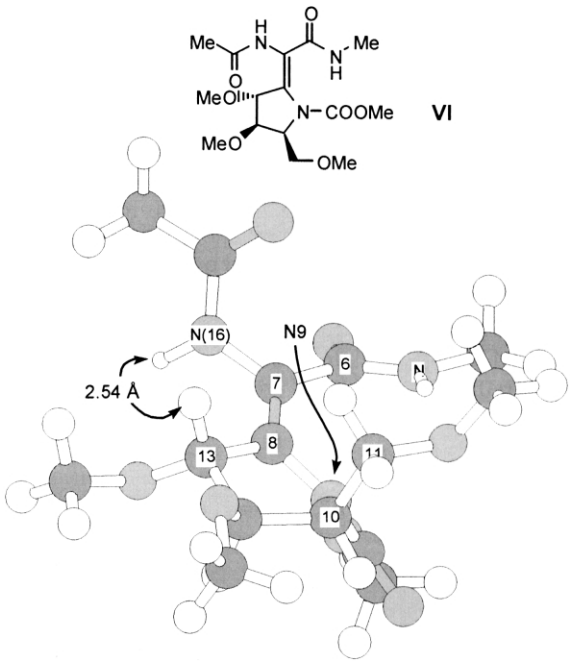
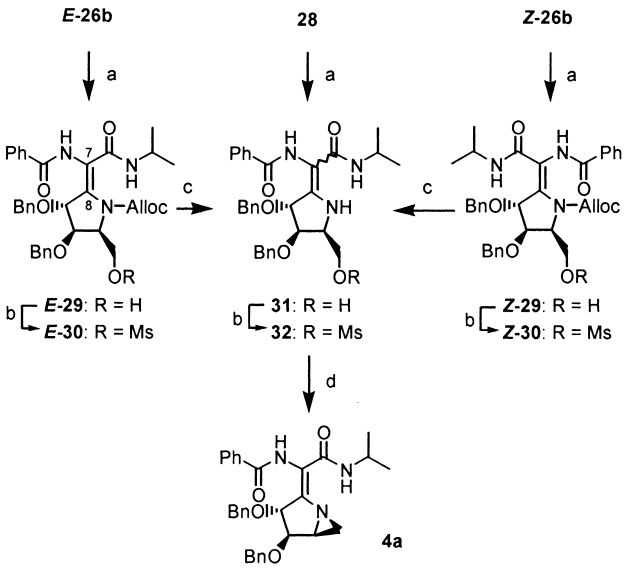


Figure 6. Conformation of **VI** with lowest steric energy obtained by the calculations.

Interestingly, the locked C7–C8 double bond was unlocked again by deprotection of the carbamoyl group. For example, treatment of *E*-**26b** with dimedone and a catalytic amount of $Pd(PPh_3)_4$[19] in THF effected smooth cleavage of the Alloc group providing **28** in 92% yield as an inseparable mixture consisted of three isomers. Deprotection of the Alloc group of *Z*-**26b** was also achieved in 87% yield under the same conditions giving the deprotected pyrrolidine, which was identical with **28** prepared from *E*-**26b**. The isomers in **28** might include not only tautomers about the C7–C8 double bond but also rotamers about the amide bonds. As described, removal of the Alloc group of *E* and *Z*-**26b** resumes these tautomerism. No informative NOEs were obtained for the C7–C8 double bond in the major isomer of **28**, however, the stereochemistry for that olefin moiety in **28** was assigned to be *E*-configuration by observing a signal of the C13H (*carzinophilin numbering*) in the major isomer of **28** at 4.71 ppm which corresponds well to those of *E*-**26a**,**b** and not to those of *Z*-**26a**,**b**. Deprotection of the Boc group of *E*-**26a** with TMSOTf in the presence of 2,6-lutidine brought about dehydration to give imidazolinone **27**.

2.4. Conversion into the analogue 4a, the C6–C13 fragment[1d]

Dehydropeptides *E*-**26b**, *Z*-**26b**, and **28** were successfully converted into **4a** as shown in Scheme 4 by applying the procedures we had developed. The TBDMS group in *E*-**26b**

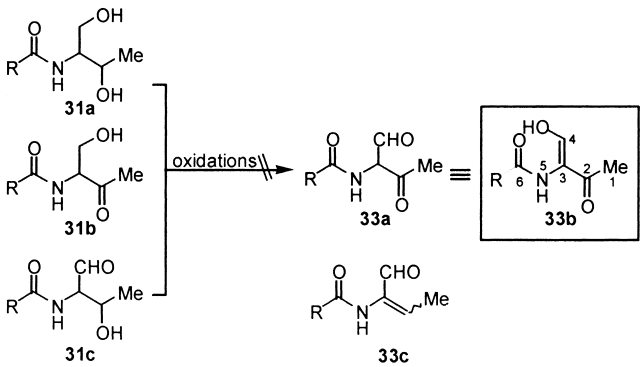


Scheme 4. Transformation of *E*-**26b**, *Z*-**26b**, and **28** into **4b**. *Reagents and conditions*: (a) HCl, MeOH rt, 20 min–1 h, 98% (*E*-**29**), 93% (*Z*-**29**), 77% (**31**). (b) MsCl, Et_3N, CH_2Cl_2, −78°C 30 min–2 h, 88% (*E*-**30**), 96% (*E*-**30**), 68% (**32**). (c) $Pd(PPh_3)_4$, dimedone, rt, THF, 10 min–30 min, 97% (from *E*-**30**), 82% (from *Z*-**30**). (d) KHMDS, THF rt, 5 min, 64%.

was cleaved with HCl in MeOH to give alcohol *E*-**29** in 98% yield. This was further converted into mesylate *E*-**30** by the usual conditions. In these two steps, we observed no isomerization about the C7–C8 double bond. Deprotection of the Alloc group with $Pd(PPh_3)_4$ in the presence of dimedone accompanied isomerization giving rise to N-unprotected mesylate **32** in 97% yield which consists of more than three isomers according to its ^1H NMR spectra. The other isomer *Z*-**26b** was also subjected to the series of three reactions to afford **32** which was identical to the sample prepared from *E*-**26b** in all respects. Thus, the Alloc group was found to lock the configuration of the C7–C8 double bond. The mesylate **32** was also synthesized from **28** by desilylation and subsequent mesylation. As expected, the aziridine ring closure was found to be achieved by treating **32** with KHMDS in THF for 5 min to afford **4a** in 64% as a single isomer. The stereochemistry of **4a** will be discussed later in this report.

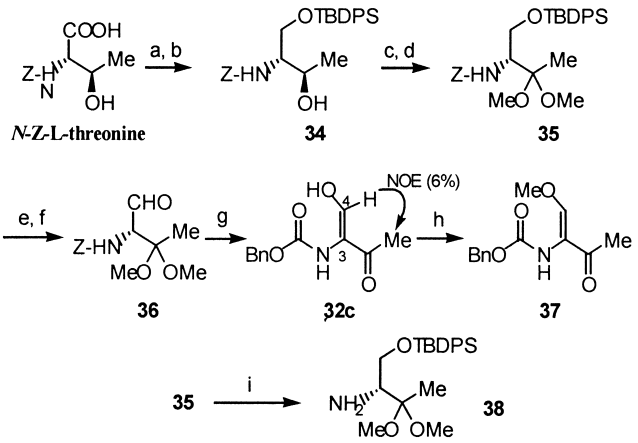
2.5. Development of the synthetic scheme for β-hydroxy-enamide system corresponding to the C1–C6 unit[1d]

Next, we examined a synthetic method for the β-hydroxy enamide system **33b** corresponding to the C1–N6 unit of **1**. Since this system **33b** is synthetically equivalent to the ketoaldehyde **33a**, it was expected that it can be furnished by oxidation of the corresponding 1,3-diol **31a**, 3-hydroxy-ketone **31b**, or 3-hydroxyaldehyde **31c**. However, we could not obtain **33b** (=**33a**) by oxidation of **31a–c**. Most cases of the oxidation of **31a–c** we examined, such as TPAP-NMO,[20] TEMPO,[21] PCC,[22] PDC,[23] SO_3·Py-DMSO,[24] Dess–Martin,[25] and Swern oxidations[26] resulted in complex mixtures of products. Oxidation of **31a** with SO_3·Py-DMSO gave only a certain product but it was α,β-unsaturated aldehyde **33c**. These results suggested that the desired β-hydroxy enamide system **33b** is unstable under oxidative conditions (Scheme 5).



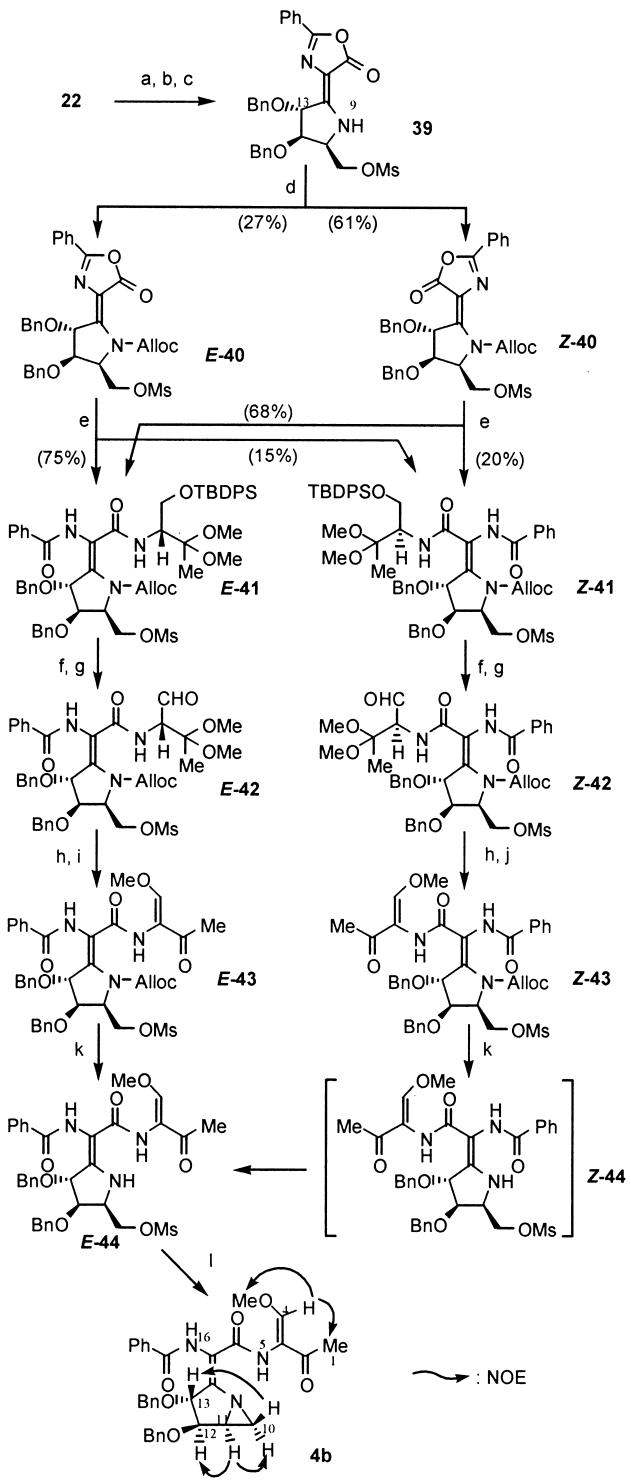
Scheme 5. Preliminary trials for preparing the C1–C6 fragment.

We were able to achieve a preparation of this enamide system by a novel synthetic scheme employing non-oxidative conditions in the key step. Thus, *N*-benzyl-oxycarbonyl-L-threonine was reduced with a borane dimethylsulfide complex in THF. Selective protection of the primary alcohol with TBDPSCl–Et_3N–CH_2Cl_2 gave alcohol **34**. After oxidation of **34** using SO_3·Py-DMSO, the ketone moiety was protected in the form of dimethyl acetal by the usual method to afford acetal **35**. After removal of the TBDPS group, the alcoholic function of **35** was oxidized with PDC in the presence of molecular sieves 4A to give unstable aldehyde **36** in a moderate yield (Scheme 6).



Scheme 6. Preparation of the C1–C6 fragment. *Reagents and conditions*: (a) BH_3·SMe_2, THF, 0°C→rt, 16 h, 75%. (b) TBDPSCl, Et_3N, CH_2Cl_2, 0°C→rt, 16 h, 56%. (c) SO_3·Py, DMSO, Et_3N, rt, 2.5 h, 92%. (d) $(CH_3O)_3CH$, *p*-TsOH, MeOH, rt, 2.5 h, 97%. (e) TBAF, THF, 0°C, 1.5 h, 94%. (f) PDC, MS4A, CH_2Cl_2, rt, 1.5 h, 65%. (g) *p*-TsOH, THF, H_2O, rt, 71%. (h) CH_2N_2, Et_2O, rt, 10 h, 33%. (i) H_2, 10% Pd/C, MeOH, rt, 14 h, 93%.

On deprotection of the dimethyl acetal in **36** the construction of a β-hydroxy enamide system took place to produce **32c**, which was obtained in an almost pure form in 75% yield after aqueous work up. The ^1H NMR spectrum of **32c** showed a signal at 11.65 ppm (doublet, J=11.0 Hz) as an exchangeable proton with D_2O, disclosing that **32c** takes an enol form. The *E*-configuration of the C3–C4 double bond (*carzinophilin numbering*) was ascertained by observing a strong NOE at the C1H_3 (2.28 ppm) on irradiating the olefinic C4H (7.23 ppm). Notably, **32c** appeared as a broad spot on its silica gel TLC and was extracted with AcOEt only under acidic conditions like a carboxylic acid. Thus, **32c** was treated with CH_2N_2 to give methyl enol ether **37**



Scheme 7. Synthesis of the C1–C17 fragment **4b** of carzinophilin. *Reagents and conditions*: (a) TBAF, THF, rt, 2.5 h, 90%. (b) MsCl, Et_3N, CH_2Cl_2, −78°C, 1 h, 90%. (c) recrystallization, >90% recovery. (d) $Alloc_2O$, DMAP, THF, rt, 10 min. (e) **38**, DMAP, 50°C, 1 h, yields are shown in the Scheme. (f) HF·Py, pyridine, 0°C→rt, 93% (from *E*-**41**), 79% (from *Z*-**41**). (g) PDC, MS4A, CH_2Cl_2, rt, 68% (for *E*-**42**), 83% (for *Z*-**42**). (h) *p*-TsOH, aq. THF, rt. (i) CH_2N_2, THF–Et_2O rt, 12 h, 67% in 2 steps (*E*-**43**). (j) CH_2N_2 AcOEt–Et_2O, rt, 12 h, 78% 2 steps (*Z*-**43**). (k) cat. $Pd(PPh_3)_4$, PPh_3, AcOH, THF, rt, 57% (from *E*-**43**), 88% (from *Z*-**43**). (l) TBAF, MS4A, THF, rt, 10 min, 73%.

which could be purified by preparative TLC. It was anticipated that the C1–C6 β-hydroxy enamide system can not survive under the conditions required for the total synthesis. Accordingly, we decided to introduce the C1–N5 unit into the trunk framework in a protected form and to trim functions in the later synthetic stages. Thus, amine **38** derived from **35** by catalytic hydrogenolysis, was employed as the C1–N5 unit.

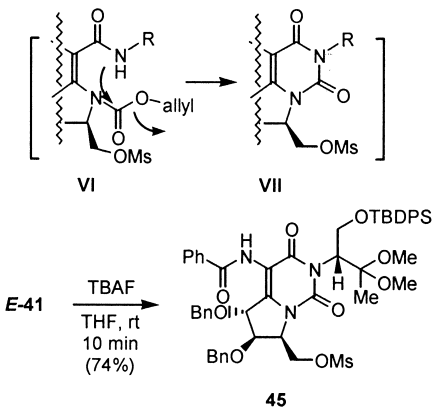
2.6. Synthesis of the C1–C17 fragment 4b

Based on the information accumulated in the studies mentioned above, the C1–C17 fragment **4b** was attempted in order to verify our strategy (Scheme 7). Taking into account the later synthetic stages, the TBDMS group of **22** was replaced with a mesyl group in a good overall yield by sequential deprotection and mesylation prior to introduction of the C1–C5 fragment. Right after purification by column chromatography, the mesylate **39** was obtained as a mixture of *E*- and *Z*-isomers about the C7–C8 double bond (60:40 isomeric ratio based on the ^1H NMR spectrum). Interestingly, recrystallization of **39** from AcOEt–hexane underwent the isomerization, giving the pure *E*-isomer with >90% recovery.[27] The *E*-configuration of **39** was assigned by comparing the chemical shifts for the N9H and C13H of **39** (7.78 and 5.10 ppm, respectively) with those of the isomers *E*-**22** and *Z*-**22** shown in Figure 4. Incorporation of the amine **38** into **39** was attempted after activation of the azlactone ring by N9-acylation. Thus, treatment of **39** with $Alloc_2O$ in the presence of DMAP took place *N*-carbamoylation which was accompanied by isomerization of the C7–C8 double bond giving a mixture of *E*- and *Z*-*N*-Alloc derivatives *E*-**40** and *Z*-**40** in 27 and 61% yield, respectively. These isomers could be separated by silica gel preparative TLC. It was found that heating pure *E*-**40** with **38** at 50°C in high concentration resulted in the azlactone ring-opening as well as isomerization of the double bond to afford a mixture of dehydropeptides *E*-**41** and *Z*-**41** in 75 and 15% yield, respectively. The same treatment of *Z*-**40** also provided a mixture *E*-**41** and *Z*-**41** in 68% and 20% yield, respectively. The stereochemistries of *E*- and *Z*-**41** were established by comparison of their ^1H NMR spectra with those of isomeric pairs of **26b**, which were assigned by NOE experiments as shown in Figure 5.

Next, elaboration of the C1–N6 moiety was studied. The TBDPS group of *E*-**41** was removed selectively in 93% yield by using HF·Py in pyridine and subsequent oxidation of the obtained alcohol with PDC in the presence of molecular sieves 4A in CH_2Cl_2 provided alcohol *E*-**42** in 66% yield. As expected, treatment of *E*-**42** with *p*-TsOH in aqueous THF at room temperature smoothly took place formation of the β-hydroxy enamide system. Since the silica gel TLC of the product gave a broad spot as mentioned, purification was performed after conversion into methyl ether *E*-**43** by methylation of the enol moiety with CH_2N_2. Similar chemical shifts for the C4H and the N5H to those of model compound **37** suggested the *E*-configuration of the newly furnished C3–C4 double bond. The Alloc group of *E*-**43** could be removed by $Pd(PPh_3)_4$-catalyzed reaction employing AcOH as a nucleophile,[28] giving *E*-**44** in 57% yield. Isomerization of the C7–C8 double bonds was not observed in the series of these transformations. The

Z-isomer *Z*-**41** was also subjected to a series of these transformations. Desilylation of *Z*-**41** proceeded in 79% yield and subsequent oxidation provided *Z*-**42** in 78% yield. Construction of the β-hydroxy enamide system in a similar manner to that described above gave *Z*-**43** in 78% yield in two steps. Interestingly, removal of the Alloc group of *Z*-**43** by the same treatment as above resulted in the isomerization of the C7C8 double bond giving *E*-**44** as a single isomer. The ^{1}H NMR spectrum of this sample was identical to that of *E*-**44** prepared from *E*-**43**. The intermediate *Z*-**44** could be obtained by quick purification. Isomerization of *Z*-**44** into *E*-**44** was found to be completed within 6 hours by standing in $CDCl_3$ at room temperature.

In those transformations, the chemical yields of the *Z*-isomers were always slightly better than those for the *E*-isomers. This would be explained by the fact that those reactions with the *E*-isomers accompany formation of uracil derivative **VII** by an attack of the N5 atom to the carbamoyl group as shown in Scheme 8. Actually, the reaction of *E*-**41** with TBAF gave pyrimidin-2,4-dione derivative **45** in good yield.

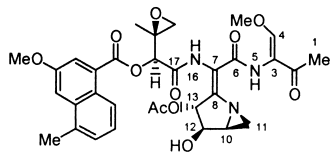


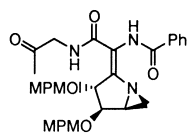
Scheme 8. Undesired formation of uracil ring from *E*-dehydropeptides.

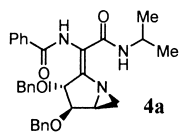
Synthesis of the C1–C17 model compound **4b** was accomplished by the aziridine ring formation. Treatments of *E*-**44** with KH or KHMDS in THF, which provided preferable results in the previous model studies, resulted in decomposition of the starting material. After further experimentation, it was found that a combined use of TBAF and finely powdered molecular sieves 4A in THF achieved the aziridine ring closure, providing **4b** as a single isomer in 73% yield. The product **4b** was readily purified by silica gel column chromatography.

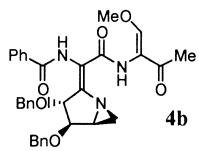
Finally, assignment of the stereochemistry of **4b** was attempted. Stereochemistry of the C3–C4 double bond (*carzinophilin numbering*) and the pyrrolidine moiety could be established rigorously by observing NOEs for C1–H↔C4–H, C4–H↔C4–OCH_3, C10α–H↔C11–H, C10β–H↔C13–H, and C11–H↔C12–H by differential NOE experiments in $CDCl_3$. However, no useful information was obtained by the NOE technique concerning the C7–C8 double bond. Similar experiments employing **4a** also did not give an NOE between N16–H and C13–H. Incidentally, the NOE between the signals of N16–H and C13–H was not described by Yokoi et al. in their report on the structure determination of azinomycins.[5] However, comparison of the ^{1}H NMR spectral data of azinomycin B 4-*O*-methyl ether (AZB-4-*O*-Me═carzinophilin-4-*O*-Me),[5] **4a**,**b**, and Armstrong's *Z*-isomer analogue[29] gave us considerable information. As shown in Table 3, the coupling constants between C12–H and C13–H in **4a**,**b** were observed both as 4.1 Hz, which resembles that of AZB-4-OMe (3.9 Hz). On the contrary, that observed in Armstrong's *Z*-isomer is clearly different (1.0 Hz). Taking these considerations into account, the stereochemistries at the C7–C8 double bond of **4a**,**b** were assigned to have the same *E*-configuration as that of **1**.

Table 3. Chemical shifts (ppm), signal patterns (parenthesized), and coupling constants (italic, Hz) in the AZB-4-*O*Me, **4a**,**b**, and the Armstrong's *Z*-isomer









Proton	AZB-4-*O*Me	**4a**	**4b**	Armstrong's *Z*-isomer
1	2.24 (s)	–	2.23 (s)	
4	7.19 (s)	–	7.16 (s)	
4-O-Me	3.90 (s)	–	3.89 (s)	
5	10.89 (s)	9.47 (br d)	11.03 (s)	6.95 (dd)
		7.5		*4.8*, *4.8*
10a	2.25 (d)	2.23 (d)	2.30 (d)	2.18 (d)
	3.9	*4.1*	*4.1*	*3.6*
10b	2.51 (d)	2.35 (d)	2.44 (d)	2.40 (dd)
	5.4	*5.4*	*4.8*	*1*, *5.3*
11	3.22 (ddd)	3.06 (ddd)	3.10 (ddd)	3.03 (ddd)
	3.9, *5.4*, *5.8*	*4.1*, *5.4*, *5.4*	*4.1*, *4.7*, *4.8*	*3.6*, *4.9*, *5.3*
12	4.63 (dd)	4.55 (dd)	4.59 (dd)	4.42 (dd)
	3.9, *5.8*	*4.1*, *5.4*	*4.1*, *4.7*	*1.0*, *4.9*
13	5.55 (d)	5.01 (dd)	5.01 (dd)	5.012 (dd)
	3.9	*0.9*, *4.1*	*1.0*, *4.1*	*1*, *1*
16	8.50 (s)	8.43 (s)	8.28 (s)	7.89 (s)

Molecular modeling was also studied by the method similar to that as described for the conformation analysis of model compound **VI**. A model compound **VII** was chosen for these calculations. Since the bulky C13 *O*-benzyloxy group and C18 carbons of **4a**,**b** was replaced to methyl groups in model **VII**, the amide bonds N5–C6 and N16–C17 were fixed on *Z*-geometry in the conformation search. Conformer A in Figure 7 is the most stable conformation found by those calculations. The distance between C13H and the amide proton attached to N16 of this conformer is 4.29 Å. The most stable conformer in which the distance C13H↔N16H is within 3.0 Å found by those calculations has 6.9 kcal/mol higher steric energy. Accordingly, it might be reasonable about the absence of NOE between C13H and N16H in the cases of **4a**,**b**. Our calculations for model compounds **VI** and **VII** suggested that stable conformations of the C1–C6 and N16–C18 side chains depend on functions attached to their N9 positions.

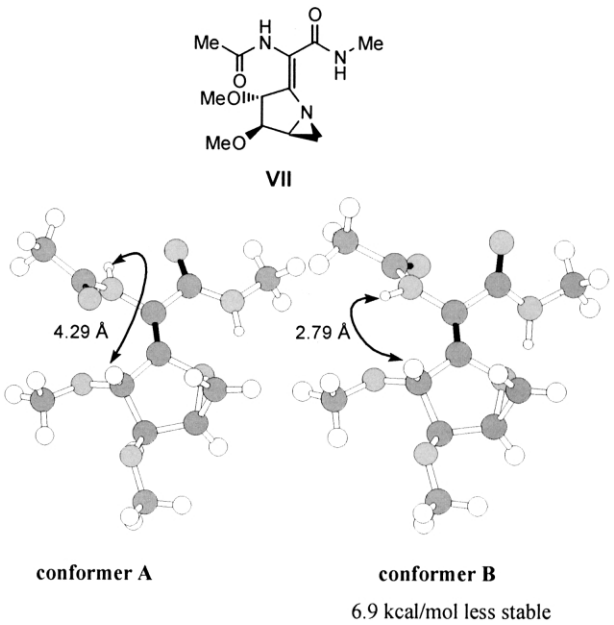


Figure 7. Two conformers of model compound **VII**.

3. Conclusion

As described above, we have succeeded in developing a novel synthetic methodology for **1**. Applying the knowledge accumulated in these studies, we attempted the total synthesis of **1** which will be the subject of the following paper.[30]

4. Experimental

4.1. General

See General in the experimental part for Part 1 of this series of papers. Compounds with large molecular weight (M_W>750) could not be subjected to high-resolution mass spectroscopy.

4.2. (2*R*,3*S*,4*R*,5*S*)-1,3,4-Tribenzyloxy-5-(4-methoxyphenyl)methylamino-6-hepten-2-ol (7)

A solution of 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**5**) (25.0 g, 59.5 mmol) and 4-methoxybenzylamine (8.90 g, 64.9 mmol) in toluene (200 mL) was stirred under reflux using a Dean–Stark condenser to remove the H_2O produced. After stirring for 12 h, the solvent was removed in vacuo to give crude **6** as a viscous oil. After **6** was dissolved in THF (200 mL), vinylmagnesium bromide (0.87 M in THF, 180 mL, 156 mmol) was added at 0°C over 30 min. After the cooling bath was removed, the mixture was stirred at room temperature for 12 h. The mixture was cooled to −78°C, then the reaction was quenched by adding saturated aqueous NH_4Cl solution and the THF was removed in vacuo. The mixture was poured into water, and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=90:10) gave **7** in almost pure form (23.7 g, 71%) as a syrup. $[\alpha]_D^{20}=-4.49°$ (c 1.16, $CHCl_3$). IR (film): 3300, 2900, 2850, 1605, 1505, 1450, 1240, 990, 730, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.45 (1H, dd, *J*=2.2, 8.7 Hz, C5H), 3.53 (1H, d, *J*=12.4 Hz, ArC*H*HN), 3.65 (3H, m, C1H_2, C4H), 3.72 (1H, d, *J*=12.4 Hz, ArC*H*HN), 3.78 (3H, s, CH_3O), 3.84 (1H, dd, *J*=4.3, 6.4 Hz, C3*H*), 3.95 (1H, dd, *J*=4.6, 6.4 Hz, C2*H*), 4.41 (1H, d, *J*=11.5 Hz, PhC*H*HO), 4.50 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.51 (1H, d, *J*=12.1 Hz, PhC*H*HO), 4.54 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.55 (1H, d, *J*=12.1 Hz, PhC*H*HO), 4.66 (1H, d, *J*=11.5 Hz, PhC*H*HO), 5.16 (1H, dd, *J*=1.5, 17.2 Hz, C7*H*H), 5.23 (1H, dd, *J*=1.5, 10.2 Hz, C7*H*H), 5.77 (1H, ddd, *J*=8.7, 10.2, 17.2 Hz, C6*H*), 6.83 (2H, dt, *J*=8.7, 2.0 Hz, aromatic protons for MPM), 7.20–7.34 (17H, m, aromatic protons), EI-MS (rel. int.%): *m*/*z*=568 (0.05, MH^+), 476 (1.7, $[M-Bn]^+$), 460 (0.35, $[M-BnO]^+$), 446 (1.1, $[M-MPM]^+$), 121 (100, $MeOPhCH_2^+$), 91 (53, Bn^+). CI-MS (isobutene): *m*/*z* 568 (MH^+). EI-HIMS: calcd for $C_{36}H_{42}NO_5$ (M^+): *m*/*z*=568.3064. Found *m*/*z*=568.3046.

4.3. (3*S*,4*R*,5*S*)-3,4-Disbenzyloxy-1-(4-methoxyphenylmethyl)-5-vinylpyrrolidin-2-one (8) and its (3*S*,4*R*,5*R*)-diastereomer (*epi*-8)

4.3.1. Reaction procedure. A mixture of **7** (7.30 g, 12.9 mmol), PCC (11.0 g, 51.2 mmol), and powdered molecular sieves 4A (10 g) in CH_2Cl_2 (100 mL) was stirred for 4 h. To the solution, Et_2O (300 mL) and Celite® (10 g) were added successively and the mixture was further stirred for 1 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (Et_2O/hexane=50:50) gave **8** (4.05 g, 71%) and *epi*-**8** (170 mg, 3.0%), and recovered **7** (391 mg, 5.3%).

4.3.2. Data of 8. $[\alpha]_D^{20}=-138°$ (c 2.35, $CHCl_3$). IR (film): 3010, 2900, 1710, 1610, 1510, 1240, 1100, 1030, 730, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (1H, d, *J*=14.5 Hz, ArC*H*HN), 3.81 (3H, s, OCH_3), 3.96 (1H, dd, *J*=8.7, 7.5 Hz, C5*H*), 4.11 (1H, t, *J*=7.5 Hz, C4*H*), 4.34 (1H, ddd, *J*=0.7, 7.5 Hz, C3*H*), 4.46, 4.54 (each 1H, d, *J*=11.6 Hz, PhCH_2O), 4.84 (1H, d, *J*=11.7 Hz, PhC*H*HO), 5.07 (1H, d, *J*=14.5 Hz, ArC*H*HN), 5.13 (1H, d, *J*=11.7 Hz, PhC*H*HO), 5.24 (1H, d, *J*=17.0 Hz, C5CH=C*H*H), 5.39 (1H, d, *J*=10.1 Hz, 5CH=C*H*H), 5.75 (1H, ddd, *J*=8.7, 10.1, 17.0 Hz, C5C*H*=CH_2), 6.88, 7.16 (each 2H, dt, *J*=8.7, 2.9 Hz, aromatic protons for MPM), 7.24–7.36 (8H, m, aromatic protons), 7.43 (2H, m, aromatic protons). EI-MS (rel. int.%): *m*/*z*=444 (0.50, MH^+), 337 (9.7, $[M-BnO]^+$), 121 (63, $MeOPhCH_2^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{28}H_{30}NO_4$ (MH^+): *m*/*z*=444.2176. Found: *m*/*z*=444.2161.

4.3.3. Data of *epi*-8. IR (nujor) 2920, 1680, 1510, 1460, 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.27 (3H, s, CH_3O), 3.50 (1H, dd, *J*=5.3, 5.9 Hz, C4*H*), 3.53 (1H, dd, *J*=5.9, 9.1 Hz, C5H), 3.69 (1H, d, *J*=14.6 Hz, ArC*H*HN), 3.81 (1H, d, *J*=5.3 Hz, C3*H*), 4.23, 4.42 (each 1H, d, *J*=11.7 Hz, PhCH_2O), 4.91 (1H, d, *J*=12.2 Hz, PhC*H*HO), 4.92 (1H, dd, *J*=1.7, 19.1 Hz, C5CH=C*H*H), 5.01 (1H, dd, *J*=1.7, 9.9 Hz, C5CH=C*H*H), 5.03 (1H, d, *J*=14.6 Hz, ArC*H*HN), 5.13 (1H, d, *J*=12.2 Hz, PhC*H*HO), 6.05 (1H, ddd, *J*=9.1, 9.9, 19.1 Hz, C5C*H*=CH_2), 6.72 (2H, br d,

J=8.7 Hz, aromatic protons for MPM), 7.02–7.16 (8H, m, aromatic protons), 7.25 (2H, br d, J=7.2 Hz, aromatic protons), 7.43 (2H, br t, J=7.1 Hz, aromatic protons). EI-MS (rel. int.%): m/z=444 (0.50, MH^+), 337 (6.2, $[M-BnO]^+$), 121 (65, $MeOPhCH_2^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{28}H_{30}NO_4$ (MH^+): m/z=444.2176. Found: m/z=444.2183. Anal. calcd for $C_{28}H_{29}NO_4$: C, 75.82%; H, 6.59%; N, 3.16%. Found C, 75.76%; H, 6.59%; N, 3.11%.

4.4. (3*S*,4*R*,5*S*)-3,4-Dibenzyloxy-5-hydroxymethyl-1-(4-methoxyphenyl)methyl-pyrrolidin-2-one (9)

Ozone gas (O_3/O_2) generated by an ozonizer was bubbled through a solution of **8** (1.07 g, 2.41 mmol) in EtOH (20 mL) at −25°C for 20 min. After TLC showed consumption of the starting material, O_2 gas was further bubbled for 10 min to remove the excess ozone. $NaBH_4$ (300 mg, 7.9 mmol) was added to the ethanolic solution, and the cooling bath was removed. The mixture was stirred at room temperature for 20 min, and neutralized by adding concentrated hydrochloric acid until litmus paper indicated slightly acidic. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography ($CHCl_3$/acetone=90:10) gave **9** (1.06 g, 98%) as a white solid. Analytical sample was prepared by recrystallization from hexane-EtOAc to give colorless needles. Mp: 94.5–96.0°C. $[\alpha]_D^{20}=-142°$ (c 0.940, $CHCl_3$). IR (nujor) 3450, 2920, 1690, 1510, 1450, 1350, 1240, 1120, 1090, 1040, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.04 (1H, dd, J=6.4, 7.3 Hz, alcoholic proton), 3.53 (1H, ddd, J=2.0, 4.0, 7.9 Hz, C5*H*), 3.67 (1H, ddd, J=4.0, 7.3, 12.4 Hz, C5C*H*HO), 3.74 (1H, ddd, J=2.0, 6.4, 12.4 Hz, C5C*H*HO), 4.04 (1H, d, J=14.8 Hz, ArC*H*HN), 4.22 (1H, dd, J=6.9, 7.9 Hz, C4*H*), 4.42 (1H, dd, J=0.7, 6.9 Hz, C3*H*), 4.55, 4.65 (each 1H, d, J=11.7 Hz, PhCH_2O), 4.86 (1H, d, J=11.5 Hz, PhC*H*HO), 4.90 (1H, d, J=14.8 Hz, ArC*H*HN), 5.22 (1H, d, J=11.5 Hz, PhC*H*HO), 6.85, 6.78 (each 2H, dt, J=8.7, 2.9 Hz, aromatic protons for MPM), 7.21–7.45 (10H, m, aromatic protons). EI-MS (rel. int.%) m/z=429 (0.40, $[M-H_2O]^+$), 341 (4.3, $[M-BnO]^+$), 121 (100, $MeOPHCH_2^+$), 91 (68, $PhCH_2^+$). CI-MS (isobutene): m/z=448 (MH^+). Anal. calcd for $C_{27}H_{29}NO_5$: C, 72.46%; H, 6.53%; N, 3.13%. Found: C, 72.36%; H, 6.39%; N, 3.18%.

4.5. (3*S*,4*R*,5*S*)-3,4-Dibenzyloxy-5-hydroxymethyl-pyrrolidin-2-one (10)

4.5.1. Preparation of 10 (Table 1, run 5). A solution of **9** (3.00 g, 6.70 mmol) and ammonium cerium (IV) nitrate (CAN, 18.3 g, 33 mmol) in a mixture of CH_3CN (15 mL) and H_2O (750 μL) was stirred at room temperature for 1 h. The mixture was neutralized by addition of saturated $NaHCO_3$ solution. The resulting suspension was filtered through a pad of Celite® and the filtrate was concentrated in vacuo. The resulting aqueous suspension was extracted with AcOEt and the combined ethyl acetate extracts were washed with brine, dried over $MgSO_4$ then concentrated in vacuo. Purification of the residue by silica gel column chromatography (AcOEt/MeOH=97:3) gave **10** (2.18 g, 6.67 mmol, 99%) as a white solid. Analytical sample was prepared by recrystallization from hexane/EtOAc to give colorless needles. Mp: 109.5–111.0°C. $[\alpha]_D^{20}=-93.7°$ (c 1.11, $CHCl_3$). IR (nujor): 3500, 3280, 1720, 1460, 1380, 1270, 1120, 1100, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.51 (1H, br t, J=6.1 Hz, alcoholic proton), 3.63–3.79 (3H, m, C5*H*, C5CH_2O), 4.33 (1H, t, J=6.9 Hz, C4*H*), 4.37 (1H, d, J=6.9 Hz, C3*H*), 4.58, 4.64 (each 1H, d, J=11.7 Hz, PhCH_2O), 4.79, 5.10 (each 1H, d, J=11.8 Hz, PhCH_2O), 6.49 (1H, br, amide proton), 7.25–7.43 (10H, m, aromatic protons), EI-MS (rel. int.%): m/z=328 (0.2, MH^+), 221 (1.2, $[MH-BnO]^+$), 91 (100, $PhCH_2^+$), EI-HIMS: calcd for $C_{19}H_{22}NO_4$ (MH^+): m/z=328.1550. Found: m/z=328.1555. Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.71%; H, 6.47%; N, 4.28%. Found: C, 69.31%; H, 6.41%; N, 4.20%.

4.5.2. Treatment of 9 in a 1:1 mixture of CH_3CN-H_2O (Table 1, run 2). A solution of **9** (30.1 mg, 67.0 μmol) and CAN (73.4 g, 135 μmol) in a mixture of CH_3CN (500 μL) and H_2O (500 μL) was stirred at room temperature for 40 min. Similar work up to that described above gave the crude product. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=99:1, 90:10, and AcOEt/MeOH=97:3) gave **14** (4.60 mg, 15%), recovered **9** (4.5 mg, 15%), and **10** (9.8 mg, 45%).

4.5.3. Data of 14. IR (film): 3450, 2920, 1730, 1670, 1600, 1510, 1290, 1250, 1110, 1020, 760, 730, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.23 (1H, dd, J=5.4, 7.6 Hz, alcoholic proton), 3.86 (3H, s, CH_3O), 3.97 (1H, ddd, J=2.9, 7.6, 12.3 Hz, C5C*H*HO), 4.00 (1H, ddd, J=2.7, 5.4, 12.3 Hz, C5C*H*HO), 4.39 (1H, t, J=8.0 Hz, C4*H*), 4.63 (1H, d, J=8.0 Hz, C3*H*), 4.63 (1H, ddd, J=2.7, 2.9, 8.0 Hz, C5*H*), 4.69, 4.73 (each 1H, d, J=11.8 Hz, PhCH_2O), 4.74, 5.11 (each 1H, d, J=11.5 Hz, PhCH_2O), 6.91 (2H, br d, J=8.9 Hz, aromatic protons), 7.27–7.40 (10H, m, aromatic protons), 7.64 (2H, br d, J=8.9 Hz, aromatic protons). EI-MS (rel int.%) m/z=462 (0.5, M^+), 355 (1.0, $[M-BnO+H]^+$), 91 (100, $PhCH_2^+$).

4.6. (3*S*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*t*-butyldimethyl-siloxy)methylpyrrolidin-2-one (11)

A solution of **10** (8.57 g, 26.2 mmol), TBDMSCl (5.25 g, 35.0 mmol) and imidazole (7.13 g, 104 mmol) in DMF (1.0 mL) was stirred at room temperature for 1 h. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=95:5) gave **11** (10.3 g, 89%) as an oil. $[\alpha]_D^{20}=-106°$ (c 1.07, $CHCl_3$). IR (film): 3200, 2950, 2920, 2850, 1710, 1250, 1110, 830, 770, 730, 690 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ −0.01, 0.01 (each 3H, s (CH_3)$_2$Si), 0.92 (9H, s, (CH_3)$_3$CSi), 3.11 (1H, dddd, J=1.5, 3.0, 4.0, 7.5 Hz, C5*H*), 3.33 (1H, dd, J=3.0, 10.5 Hz, C5C*H*HO), 3.57 (1H, dd, J=4.0, 10.5 Hz, C5C*H*HO), 4.12 (1H, t, J=7.5 Hz, C4*H*), 4.36 (1H, d, J=12.0 Hz, PhC*H*HO), 4.45 (1H, d, J=7.5 Hz, C3*H*), 4.48 (1H, d, J=12.0 Hz, PhC*H*HO), 4.96, 5.35 (each 1H, d, J=11.8 Hz, PhCH_2O), 6.88 (1H, br, amide proton), 7.05–7.24 (8H, m, aromatic protons), 7.44 (2H, br d, J=7.0 Hz, aromatic protons). EI-MS (rel. int.%): m/z=442 (0.01, MH^+), 384 (1.0, $[M-tBu]^+$), 91 (100, $PhCH_2^+$). EI-HIMS:

calcd for $C_{25}H_{36}NO_4Si$: (MH^+) m/z=442.2415. Found: m/z= 442.2406.

4.7. (3*S*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*t*-butyldiphenylsiloxy)methylpyrrolidin-2-thione (12)

A mixture of **11** (501 mg, 1.13 mmol) and Lawesson's reagent (460 mg, 1.13 mmol) in toluene (5.0 mL) was heated at 60°C for 40 min. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/Et_2O=70:30) gave **12** (500 mg, 97%) as an oil. $[\alpha]_D^{20}$=−123° (c 2.16, $CHCl_3$). IR (film): 3300, 2800, 1530, 1500, 1380, 1250, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (6H, s, $(CH_3)_2Si$), 0.87 (9H, s, $(CH_3)_3CSi$), 3.73 (1H, dd, J=3.5, 10.6 Hz, C5C*H*HO), 3.76 (1H, dd, J=6.8, 10.6 Hz, C5C*H*HO), 3.89 (1H, ddt, J=1.3, 3.8, 6.8 Hz, C5*H*), 4.23 (1H, dd, J=5.5, 6.8 Hz, C4*H*), 4.42 (1H, d, J=5.5 Hz, C3*H*), 4.47, 4.58 (each 1H, d, J=11.9 Hz, PhCH_2O), 4.89, 5.26 (each 1H, d, J=11.6 Hz, PhCH_2O), 7.20–7.46 (10H, m, aromatic protons), 7.90 (1H, br, amide proton). EI-MS (rel. int.%): m/z=458 (0.10, MH^+), 442 (1.1, $[M-Me]^+$), 400 (3.2, $[M-tBu]^+$), 351 (5.8, $[MH-BnO]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{25}H_{36}NO_3SSi$ (M^+): m/z=458.2187. Found m/z= 458.2714.

4.8. Diethyl (3*R*,4*R*,5*S*)-2-[3,4-dibenzyloxy-5-(*t*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]malonate (13a)

A mixture of **12** (135 mg, 295 μmol) and diethyl bromomalonate (300 mg, 1.26 mmol) was stirred at room temperature for 5 h. 1,8-Diazabicyclo[5.4.0]undec-7-ene (500 μL, 509 mg, 3.3 mmol) was added to the mixture, then the stirring was continued for 3 h. Triphenylphosphine (100 mg, 381 mmol) was added, and the mixture was stirred at room temperature for 5 h. The whole mixture was poured into water and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/Et_2O=65:35) gave **13a** (142 mg, 82%) as an oil. $[\alpha]_D^{20}$=+10.4° (c 0.845, $CHCl_3$). IR (film): 3350, 2920, 1720, 1660, 1590, 1390, 1250, 1100, 1010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.05, 0.06 (each 3H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 1.23, 1.27 (each 3H, t, J=7.1 Hz, OCH_2CH_3×2), 3.75 (1H, dd, J=6.6, 10.4 Hz, C5C*H*HO), 3.77 (1H, dd, J=4.8, 10.4 Hz, C5C*H*HO), 4.04 (1H, br q, J=ca. 6 Hz, C5*H*), 3.90–4.26 (H, C4*H*, OCH_2CH_3×2), 4.47, 4.57 (each 1H, J=10.3 Hz, PhCH_2O), 4.60, 4.65 (each 1H, d, J=11.2 Hz, PhCH_2O), 5.30 (1H, d, J=2.8 Hz, C3*H*), 7.26–7.38 (10H, aromatic protons), 9.03 (1H, br, N*H*). EI-MS (rel. int.%): m/z=584 (0.10, MH^+), 564 (0.4, $[M-Me]^+$), 538 (1.7, $[M-EtO]^+$), 526 (1.4, $[M-tBu]^+$), 480 (2.4, $[M-tBu-EtOH]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{32}H_{46}NO_7Si$ (M^+): m/z=584.3045. Found m/z=584.3021.

4.9. Diethyl (3*R*,4*R*,5*S*)-2-(3,4-dibenzyloxy-5-hydroxymethylpyrrolidin-2-ylidene)malonate (13b)

A mixture of **13a** (120 mg, 205 μmol) and TBAF (1.0 M in THF, 250 μL) in THF (3.0 mL) was stirred at room temperature. After stirring for 1.5 h, the mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=97:3) gave **13b** (85.1 mg, 88%) as an oil. $[\alpha]_D^{20}$=31.8° (c 1.01, $CHCl_3$). IR (film): 3450, 3320, 2950, 2850, 1660, 1590, 1380, 1250, 1090, 1050, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25, 1.28 (each 3H, t, J=7.1 Hz, OCH_2CH_3×2), 2.14 (1H, br t, J=5.5 Hz, alcoholic proto), 3.83 (2H, m, C5C*H*HO), 4.05–4.25 (6H, C4*H*, C5*H*, OCH_2CH_3×2), 4.44, 4.63 (each 1H, J=11.7 Hz, PhCH_2O), 4.62, 4.69 (each 1H, d, J=11.0 Hz, PhCH_2O), 5.37 (1H, d, J=2.8 Hz, C3*H*), 7.25–7.37 (10H, aromatic protons), 9.12 (1H, br, N*H*). EI-MS (rel. int.%): m/z=470 (0.40, MH^+), 424 (2.2, $[M-EtO]^+$), 378 (1.3, $[M-Bn]^+$), 363 (2.4, $[M-BnO]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{26}H_{32}NO_7$ (M^+): m/z=470.2196. Found: m/z=470.2180.

4.10. Diethyl (3*R*,4*R*,5*S*)-2-[3,4-dibenzyloxy-5-(methanesulfoxy)methylpyrrolidin-2-ylidene]malonate (13c)

A mixture of **13b** (84.0 mg, 179 μmol), methanesulfonyl chloride (17.0 mL, 24.7 mg, 215 mmol), and Et_3N (42.0 μL, 30.5 mg, 300 μmol) in CH_2Cl_2 (2.5 mL) was stirred at −78°C. After stirring for 2 h, MeOH (100 μL) was added to the mixture to decompose excess reagent. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=97:3) gave **13c** (86.5 mg, 88%) as an oil. $[\alpha]_D^{20}$=2.83° (c 1.13, $CHCl_3$). IR (film): 3350, 2980, 2920, 1720, 1660, 1590, 1360, 1250, 1180, 1100, 1010, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.28 (3H, t, J=7.1 Hz, OCH_2CH_3), 3.02 (3H, s, CH_3SO_3), 4.09–4.46 (9H, C4*H*, C5*H*, C5C*H*HO, OCH_2CH_3×2, PhCH*H*O), 4.59 (1H, J=11.7 Hz, PhCH*H*O), 4.60, 4.68 (each 1H, d, J=11.1 Hz, PhCH_2O), 5.34 (1H, d, J=2.0 Hz, C3*H*), 7.25–7.37 (10H, aromatic protons), 9.18 (1H, br, N*H*). EI-MS (rel. int.%): m/z=502 (1.2, MH^+), 456 (0.7, $[M-Bn]^+$), 441 (0.6, $[M-BnO]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{27}H_{34}NO_9S$ (M^+): m/z=548.1955. Found: m/z=548.1955.

4.11. Diethyl (3*R*,4*R*,5*S*)-2-[1-aza-3,4-dibenzyloxybicyclo[3.1.0]hex-2-ylidene]malonate (3)

A mixture of **13c** (19.0 mg, 34.0 μmol) and potassium bis(trimethylsilylamide) (0.5 M in toluene, 85 μL) was stirred at 60°C for 40 min. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=90:10) gave **3** (9.6 mg, 63%) as an oil. IR (film): 2970, 2920, 1720, 1650, 1300, 1360, 1340, 1320, 1100, 1080, 750, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26, 1.34 (each 3H, t, J=7.1 Hz, OCH_2CH_3×2), 2.51 (1H, d, J=3.8 Hz, C6H), 2.71 (1H, dd, J=1.7, 5.1 Hz, C6H), 3.14 (1H, ddd, J=3.8, 4.4, 5.1 Hz, C5H), 4.18, 4.22 (each 1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.32 (1H, dd, J=0.6, 4.4 Hz, C4H), 4.29, 4.37 (each 1H, dq, J=10.1, 7.1 Hz, OCH_2CH_3), 4.41, 4.49 (each 1H, d, J=11.7 Hz, PhCH_2O), 4.63, 4.69 (1H, d, J=11.3 Hz, PhCH_2O) 5.24 (1H, d, J=0.6, 1.7 Hz). EI-MS (rel. int.%): m/z=406 (0.1, $[M-EtO]^+$), 360 (0.7, $[M-Bn]^+$), 91 (100,

$PhCH_2^+$). EI-HIMS: calcd for $C_{19}H_{22}NO_6$ ($[M-Bn]^+$): m/z=360.1477 Found: m/z=360.1477.

4.12. (2*S*,3*R*,4*S*)-3,4-Dibenzyloxy-2-(*t*-butyldimethylsiloxy)methyl-5-methoxy-3,4-dihydro-2*H*-pyrrole (17)

A mixture of **11** (116 mg, 259 μmol) and Me_3OBF_4 (70 mg, 473 μmol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 40 min. The mixture was poured into saturated $NaHCO_3$ aqueous solution and extracted with Et_2O. The combined extracts were washed with brine, dried over K_2CO_3, then concentrated in vacuo to give **17** in almost pure form (110 mg, 95%) as an oil. IR (film): 2920, 1640, 1450, 1350, 1250, 1110, 1020, 830, 770, 730, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.01 (6H, s, $(CH_3)_2Si$), 0.86 (9H, s, $(CH_3)_3CSi$), 3.72 (1H, dd, *J*=4.1, 10.5 Hz, C2C*H*HO), 3.86 (3H, s, CH_3O), 3.87 (2H, m, C2*H*, C2C*H*HO), 4.30 (1H, t, *J*=6.5 Hz, C3*H*), 4.59 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.60 (2H, s, $PhCH_2O$), 4.66 (1H, d, *J*=6.5 Hz, C4*H*), 4.80 (1H, d, *J*=11.7 Hz, PhC*H*HO), 7.33 (10H, m, aromatic protons). This sample was immediately subjected to the next step.

4.13. (2*S*,3*R*,4*S*)-3,4-Dibenzyloxy-2-(*t*-butyldimethylsiloxy)methyl-5-methylthio-3,4-dihydro-2*H*-pyrrole (18)

A solution of **12** (500 mg, 1.13 mmol) was stirred in a mixture of methyl iodide (500 μL, 1.14 g, 8.0 mmol) and CH_2Cl_2 (5.0 mL) at room temperature in the dark. After stirring for 12 h, the mixture was poured into a mixture of aqueous saturated $NaHCO_3$ solution (10 mL) and aqueous 10% $Na_2S_2O_3$ solution (10 mL), then extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give an almost pure sample of **18** (500 mg, 1.09 mmol, 97%) as an oil. IR (film) 2920, 1580, 1250, 1110, 1020, 830, 780, 730, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (6H, s, $(CH_3)_2Si$), 0.96 (9H, s, $(CH_3)_3CSi$), 2.30 (3H, s, CH_3S), 3.88 (1H, dd, *J*=3.9, 10.1 Hz, C2C*H*HO), 3.92 (1H, dd, *J*=2.9, 10.1 Hz, C2C*H*HO), 4.15 (1H, dddd, *J*=0.6, 2.9, 3.9, 6.5 Hz, C2H), 4.25 (1H, dd, *J*=5.6, 6.5 Hz, C3*H*), 4.34 (2H, s, $PhCH_2O$), 4.58, 4.70 (each 1H, d, *J*=11.8 Hz, $PhCH_2O$), 4.90 (1H, dd, *J*=0.6, 5.6 Hz, C4*H*), 7.05–7.45 (10H, m, aromatic protons). EI-MS: (rel. int.%) m/z=456 (1.3 $[M-Me]^+$), 414 (56, $[M-tBu]^+$), 91 (100, Bn^+). CI-MS (isobutene): m/z=472 (M^+). This sample was immediately subjected to the next step.

4.14. 2-(1,1-Dimethylethyl)-4*H*-oxazol-5-one (20)

A suspension of *N*-pivaloyl glycine (160 mg, 1.0 mmol) and 1-cyclohexyl-3-(2-morphorinoethyl)carbodiimide metho-*p*-toluenesulfonate[14] (500 mg, 1.18 mmol) in THF (2.0 mL) was stirred at room temperature. After stirring for 3 h, Et_2O was added. The resulting suspension was filtered and the filtrate was concentrated in vacuo to give almost pure **20** (140 mg, quantitative yield) as a colorless oil. IR (film): 1820, 1770, 1190, 1110, 890, 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (9H, s), 4.17 (2H, s). EI-MS (rel int.%) m/z=141 (1.2, M^+), 126 (32, $[M-Me]^+$), 57 (100, tBu^+). This sample gradually colored by being kept at room temperature in high concentration. Thus, it was immediately subjected to the next step.

4.15. 2-(2-Methyl-2-propenyl)-4*H*-oxazol-5-one (21)

Treatments of *N*-3-methylbut-2-enoyl glycine (41.5 mg, 264 mmol) in the same manner as described in Section 4.14 gave crude **21** (36.5 mg, quantitative yield). IR (film): 2930, 1820, 1740, 1120, 910 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.95, 2.14 (each 3H, s), 4.22 (2H, s), 5.76 (1H, s). This sample gradually colored by being kept at room temperature in high concentration. Thus, it was immediately subjected to the next step.

4.16. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*t*-butyldimethylsiloxymethyl)pyrrolidin-2-ylidene]-2-phenyl-4*H*-oxazol-5-one (22)

4.16.1. Preparation from 17 (Table 2, run 1). A mixture of **17** (25.6 mg, 56.3 μmol) and **19**[14] (36.3 mg, 225 μmol) in toluene (100 μL) was stirred at 80°C for 12 h, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=80:20) gave **22** (11.0 mg, 33%) as an oil. IR (film): 3300, 2920, 1720, 1650, 1120, 1100, 840, 700 cm^{-1}. ^1H NMR spectra of this sample showed that it consists of the two tautomers. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.75, *b*=0.25): δ −0.05 [3H×*a*+6×*b*, s, Si(CH_3)(*E*-isomer), Si(CH_3)×2(*Z*-isomer)], −0.01 [3H×*a*, s, Si(CH_3)(*E*-isomer)], 0.89 [9H×*a*, s, $(CH_3)_3$CSi(*E*-isomer)], 0.91 [9H×*b*, s, $(CH_3)_3$-CSi(*Z*-isomer)], 3.51 [1H×*a*, dd, *J*=4.7, 10.2 Hz, C5C*H*H(*E*-isomer)], 3.60 [1H×*b*, dd, *J*=8.0, 10.1 Hz, C5C*H*H(*Z*-isomer)], 3.63 [1H×*a*, dd, *J*=6.8, 10.2 Hz, C5C*H*H(*E*-isomer)], 3.64 [1H×*b*, dd, C5C*H*HO(*Z*-isomer)], 3.81 [1H×*a*, ddd, *J*=4.7, 5.1, 6.8 Hz, C5*H*(*E*-isomer)], 3.89 [1H×*b*, br d, *J*=4.1 Hz, C4*H*(*Z*-isomer)], 3.98 [1H×*a*, dd, *J*=2.4, 5.1 Hz, C4*H*(*E*-isomer)], 3.99 [1H×*b*, C5*H*(*Z*-isomer)], 4.01 [1H×*a*, br d, *J*=12.0 Hz, PhC*H*HO(*Z*-isomer)], 4.09, 4.25 [each 1H×*a*, d, *J*=12.0 Hz, $PhCH_2O$ (*E*-isomer)], 4.27 [1H×*b*, *J*=12.0 Hz, PhC*H*HO(*Z*-isomer)], 4.95 [1H×*a*, d, *J*=11.8 Hz, Ph*H*HO(*E*-isomer)], 4.99, 5.02 [each 1H×*b*, d, *J*=11.3 Hz, $PhCH_2O$(*Z*-isomer)], 5.10 [1H×*a*, d, *J*=11.8 Hz, Ph*H*HO(*E*-isomer)], 5.22 [1H×*a*, d, *J*=2.4 Hz, C3*H*(*E*-isomer)], 5.60 [1H×*b* br s, C3*H*(*Z*-isomer)], 5.98 [1H×*b*, br, amine proton(*Z*-isomer)], 7.00–7.20 (11H, m, aromatic protons), 7.41 [2H×*b*, m, aromatic protons (*Z*-isomer)], 7.50 [2H×*a*, m, aromatic protons(*E*-isomer)], 7.90 [1H×*a*, br, amine proton(*E*-isomer)], 8.00 (2H, m, aromatic protons). EI-MS (rel. int.%): m/z=584 (9.9, M^+), 527 (1.0, $[M-tBu]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{34}H_{40}N_2O_5Si$ (M^+): m/z=584.2708. Found: m/z=584.2688.

4.16.2. Preparation from 18 (Table 2, run 3). Treatments of **18** (15.0 mg, 31.8 μmol) with **19** (20 mg, 124 μmol) in a similar manner to those described in Section 4.16.1 gave **22** (15.3 mg, 82%) after silica gel column chromatography. The ^1H NMR spectrum of this sample was identical to that described in Section 4.16.1.

4.17. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*t*-butyldimethylsiloxymethyl)pyrrolidin-2-ylidene]-2-(1,1-dimethylethyl)-4*H*-oxazol-5-one (23) (Table 2, run 6)

Treatments of **18** (15.0 mg, 31.8 μmol) with **20** (20 mg,

141 μmol) in the same manner as described in Section 4.16.1 gave **23** (300 μg, 0.5 μmol, 1.7%) as an oil, after silica gel column chromatography. The ^{1}H NMR spectrum of this sample showed that it consists of the two tautomers arising from the enamine moiety (*E*/*Z*=77:23). ^{1}H NMR (200 MHz, $CDCl_3$, *a*=0.77, *b*=0.23, some signals of the minor isomer could not be assigned). δ 0.03, 0.58 [each 3H×*a*, s, (CH_3)Si×2(*E*-isomer)], 0.88 [9H×*a*, s, (CH_3)$_3$CSi (*E*-isomer)], 0.90 [9H×*b*, s, (CH_3)$_3$CSi(*Z*-isomer)], 1.29 [9H×*b*, s, (CH_3)$_3$C(*Z*-isomer)], 1.31 [9H×*a*, s, (CH_3)$_3$C(*E*-isomer)], 3.78 (2H, m, C5CH_2O), 4.11 (2H, m, C5*H*, C4*H*), 4.53, 4.48 (each 1H, d, *J*=11.0 Hz, PhCH_2O), 4.83, 4.95 (each 1H, d, *J*=10.6 Hz, PhCH_2O), 4.98 [1H×*a*, s, C3*H*(*E*-isomer)], 5.24 [1H×*b*, s, C3*H*(*E*-isomer)], 6.63 [1H×*b*, br, amine proton(*Z*-isomer)], 7.10–7.45 (10H, m, aromatic protons), 7.60 [1H×*a*, br, amine proton(*E*-isomer)]. EI-MS (rel int.%) *m*/*z*=564 (6.9, M^+), 507 (1.3, [M−*t*Bu]$^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{32}H_{44}N_2O_5Si$ (M^+): *m*/*z*= 564.3021. Found: *m*/*z*=564.3027.

4.18. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*t*-butyldimethylsiloxymethyl)pyrrolidin-2-ylidene]-2-(2-methyl-propen-1-yl)-4*H*-oxazol-5-one (24) (Table 2, run 8)

Treatments of **18** (124 mg, 271 μmol) with **21** (36.5 mg, 264 μmol) in the same manner as described for Section 4.16.1 gave **24** (10.8 mg 7.2%) as an oil after silica gel column chromatography. The ^{1}H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=78:22). ^{1}H NMR (400 MHz, $CDCl_3$, *a*=0.78, *b*=0.22, some signals of the minor isomer could not be assigned). δ 0.45 [3H×*a*, s, (CH_3)Si(*E*-isomer)], 0.70 [6H×*b*+3H×*a*, s, (CH_3)Si×2(*Z*-isomer)], (CH_3)Si(*Z*-isomer)], 1.94, 2.17 (each 3H, br s, C=C(CH_3)$_2$), 3.78 [2H×*a*, d, *J*=5.6 Hz, C5CH_2O(major)], 3.97 [2H×*b*, d, *J*=4.2 Hz, C5CH_2O(major)], 4.13 (2H, m, C5*H*, C4i), 4.32 [1H×*b*, d, *J*=12.0 Hz, PhC*H*HO(*Z*-isomer)], 4.40 [1H×*a*, d, *J*=12.0 Hz, PhC*H*HO(*E*-isomer)], 4.44 (1H, d, *J*=12.0 Hz, PhC*H*HO), 4.77 [1H×*b*, d, *J*=11.0 Hz, PhC*H*HO(*Z*-isomer)], 4.78 [1H×*a*, d, *J*= 11.8 Hz, PhC*H*HO(*Z*-isomer)], 4.83 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO(*Z*-isomer)], 4.85 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO(*Z*-isomer)], 5.03 [1H×*a*, d, *J*=1.3 Hz, C3*H*(*E*-isomer)], 5.28 (1H×*a*, s, C3*H*(*E*-isomer)), 5.80 [1H, quint, *J*=1.2 Hz, C*H*=C(CH_3)$_2$(*Z*-isomer)], 5.82 [1H, quint, *J*=1.2 Hz, C*H*=C(CH_3)$_2$(*E*-isomer)], 6.65 [1H×*b*, br, amine proton(*Z*-isomer)], 7.15–7.42 (10H, m, aromatic protons), 7.75 [1H, br s, amine proton(*E*-isomer)]. EI-MS (rel int.%) *m*/*z*=562 (9.4, M^+), 414 (30, [M−Bn−isobutene]$^+$), 91 (100, $PhCH_2^+$).

4.19. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-1-(1,1,-dimethylethoxyl)carbonyl-5-(*t*-butyldimethylsiloxy)-methylpyrrolidine (*E*-26a) and its *Z*-isomer (*Z*-26a)

4.19.1. Reaction procedure. A mixture of **22** (23.0 mg, 39.4 μmol), DMAP (7.20 mg, 59.0 μmol), and Boc_2O (12.7 mg, 58.0 mmol) in THF (1.0 mL) was stirred at room temperature for 30 min. Isopropyl amine (100 μL, excess) was added to the mixture and stirring was continued for additional 30 min. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (Et_2O/hexane=50:50→80:20) gave *Z*-**26a** (19.0 mg, 65%) and *E*-**26a** (1.50 mg, 5.5%) both as an oil.

4.19.2. Data of *E*-26a. IR (film): 3270, 2950, 2920, 1690, 1670, 1510, 1470, 1370, 1370, 1250, 1150, 1110, 1060, 830, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.007, 0.014 (each 3H, s, (CH_3)Si ×2), 0.86 (9H, s, (CH_3)$_3$CSi), 1.16, 1.13 (each 3H, d, *J*=6.5 Hz, (CH_3)$_2$CH−), 3.85 (1H, dd, *J*=8.9, 9.8 Hz, C11C*H*HO), 3.92 (1H, dd, *J*=6.5, 9.8 Hz, C11C*H*HO), 4.11 (1H, dd, *J*=1.3, 5.1 Hz, C12*H*), 4.14 (1H, m, (CH_3)$_2$C*H*−), 4.26 (1H, ddd, *J*=5.0, 6.5, 9.8 Hz, C11*H*), 4.41, 4.55 (each 1H, d, *J*=11.3 Hz, PhCH_2O), 4.65, 4.69 (each 1H, d, *J*=11.7 Hz, PhCH_2O), 5.23 (1H, br s, C13*H*), 6.59 (1H, br d, *J*=8.0 Hz, N5*H*), 7.20–7.35 (10H, aromatic protons), 7.44 (2H, m, aromatic protons), 7.51 (1H, br t, *J*=7.3 Hz, aromatic proton), 7.93 (2H, br d, *J*=7.3 Hz, aromatic protons), 9.97 (1H, br s, N16*H*). EI-MS (rel int.%) *m*/*z*=743 (1.5, M^+), 686 (0.5, [M−*t*Bu]$^+$), 643 (3.2, [M−*t*BuCOO+H]$^+$), 91 (100, $PhCH_2^+$).

4.19.3. Data of *Z*-26a. IR (film) 3420, 3350, 1730, 1650, 1520, 1470, 1380, 1280, 1250, 1100, 840, 780, 750, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.05, 0.08 (each 3H, s, (CH_3)Si×2), 0.88 (9H, s, (CH_3)$_3$CSi), 1.15 (each 3H, d, *J*=6.7 Hz, (CH_3)$_2$CH−), 1.25 (each 3H, d, *J*=6.3 Hz, (CH_3)$_2$CH−), 3.91 (1H, dd, *J*=4.8, 10.3 Hz, C11C*H*HO), 3.93 (1H, dd, *J*=3.4, 10.3 Hz, C11C*H*HO), 4.11 (1H, m, (CH_3)$_2$C*H*−), 4.20 (1H, dd, *J*=4.6, 7.1 Hz, C12*H*), 4.42 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.44 (1H, m, C11*H*), 4.51 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.61, 4.66 (each 1H, d, *J*=11.3 Hz, PhCH_2O), 4.68 (1H, d, *J*=4.8 Hz, C13*H*), 6.03 (1H, br d, *J*=8.1 Hz, N5*H*), 7.16–7.39 (12H, aromatic protons), 7.45 (1H, br t, *J*=7.5 Hz, aromatic proton), 7.58 (2H, br dd, *J*=1.3, 7.5 Hz, aromatic protons), 7.86 (1H, br s, N16*H*). EI-MS (rel int.%) *m*/*z*=743 (1.0, M^+), 686 (1.0, [M−*t*Bu]$^+$), 643 (3.1, [M−*t*BuCOO+H]$^+$), 91 (100, $PhCH_2^+$).

4.20. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-1-(2-propenyloxy)carbonyl-5-(*t*-butyldimethylsiloxy)methylpyrrolidine (*E*-26b) and its *Z*-isomer (*Z*-26b)

4.20.1. Reaction procedure. Treatments of **22** (520 mg, 890 μmol) with DMAP (1.0 g, 8.3 mmol) and $Alloc_2O$ (202 mg, 1.08 mmol) in THF (1.0 mL) and following addition of isopropyl amine (200 μL) in a similar manner to that described in **4.19.1** gave *Z*-**26b** (127 mg, 20%) and *E*-**26b** (296 mg, 45%) both as an oil, after silica gel column chromatography.

4.20.2. Data of *E*-26b. $[\alpha]_D^{20}$=+147° (c 1.06, $CHCl_3$). IR (film): 3400, 3270, 2920, 2850, 1720, 1660, 1470, 1380, 1280, 1250, 1100, 830, 780, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.04, 0.08 (each 3H, s, (CH_3)Si×2), 0.88 (9H, s, (CH_3)$_3$CSi), 1.11 (3H, d, *J*=6.6 Hz, (CH_3)$_2$CH−), 1.22 (3H, d, *J*=6.5 Hz, (CH_3)$_2$CH−), 3.93 (2H, d, *J*=3.5 Hz, C11CH_2O), 4.12 (1H, m, (CH_3)$_2$C*H*−), 4.25 (1H, dd, *J*=5.0, 7.4 Hz, C12*H*),

4.40 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.49 (1H, dt, *J*=3.5, 7.4 Hz, C11*H*), 4.55 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.59 (1H, d, *J*=9.6 Hz, PhC*H*HO), 4.59 (1H, m, CH_2=CHC*H*HO), 4.65 (1H, d, *J*=9.6 Hz, PhC*H*HO), 4.65 (1H, m, CH_2=CHC*H*HO), 4.69 (1H, d, *J*=5.0 Hz, C13*H*), 5.24 (1H, dq, *J*=10.4, 1.2 Hz, C*H*H=CHCH$_2$O), 5.32 (1H, dq, *J*=17.0, 1.2 Hz, C*H*H=CHCH$_2$O), 5.91 (1H, br d, *J*=8.3 Hz, N5*H*), 5.98 (1H, ddt, *J*=10.4, 17.0, 6.1 Hz, CH_2=C*H*CH$_2$O), 7.15–7.37 (12H, aromatic protons), 7.40 (1H, tat, *J*=7.4, 1.2 Hz, aromatic protons), 7.59 (2H, dq, *J*=7.4, 1.2 Hz, aromatic protons), 7.98 (1H, br s, N16*H*). EI-MS (rel. int.%): *m*/*z*=727 (0.7, M^+), 670 (2.1, $[M-t\mathrm{Bu}]^+$), 612 (3.0, $[M-t\mathrm{Bu}-Me_2CHNH]^+$), 105 (69, $PhCH_2O^+$), 91 (100, $PhCH^{2+}$). EI-HIMS: calcd for $C_{41}H_{53}N_3O_7Si$ (M^+): *m*/*z*=727.3654. Found: *m*/*z*= 727.3619.

4.20.3. Data of *Z*-26b. $[\alpha]_D^{20}=-19.1°$ (c 1.76, $CHCl_3$). IR (film): 3400, 3270, 2950, 2920, 2850, 1700, 1670, 1510, 1460, 1380, 1310, 1250, 1110, 1060, 830, 770, 730, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.020, 0.024 (each 3H, s, (C*H*$_3$)Si×2), 0.87 (9H, s, (C*H*$_3$)$_3$CSi), 1.01 (3H, d, *J*=6.6 Hz, (C*H*$_3$)$_2$CH–), 1.13 (3H, d, *J*=6.5 Hz, (C*H*$_3$)$_2$CH–), 3.88 (1H, t, *J*=9.4 Hz, C11C*H*HO), 3.95 (1H, dd, *J*=4.6, 9.4 Hz, C11C*H*HO), 4.12 (1H, dd, *J*=1.3, 4.7 Hz, C12*H*), 4.12 (1H, m, (CH$_3$)$_2$C*H*–), 4.33 (1H, dt, *J*=9.4, 4.7 Hz, C11*H*), 4.42, 4.56 (each 1H, d, *J*=11.8 Hz, PhC*H*HO), 4.66, 4.69 (each 1H, d, *J*=11.8 Hz, PhC*H*HO), 4.71 (2H, dd, *J*=1.1, 5.8 Hz, CH_2=CHC*H*$_2$O), 5.17 (1H, br s, C13*H*), 5.23 (1H, dq, *J*=10.4, 1.1 Hz, C*H*H=CHCH$_2$O), 5.36 (1H, dq, *J*=17.2, 1.1 Hz, C*H*H=CHCH$_2$O), 5.92 (1H, ddt, *J*=10.4, 17.2, 4.7 Hz, CH_2=C*H*CH$_2$O), 5.99 (1H, br d, *J*=7.3 Hz, N5*H*), 7.23–7.36 (10H, aromatic protons), 7.45 (2H, br t, *J*=7.5 Hz, aromatic protons), 7.52 (1H, br t, *J*=7.5 Hz, aromatic protons), 7.91 (2H, br d, *J*=7.5 Hz, aromatic protons), 9.79 (1H, br s, N16*H*). EI-MS (rel. int.%) *m*/*z*=727 (1.0, M^+), 670 (1.7, $[M-t\mathrm{Bu}]^+$), 105 (80, BnO^+), 91 (100, Bn^+). EI-HIMS: calcd for $C_{41}H_{53}N_3O_7Si$ (M^+): *m*/*z*=727.3654. Found *m*/*z*=727.3636.

4.21. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*t*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]-1-(1-methyl)ethyl-2-phenyl-2-imidazol-5-one (27)

A mixture of *E*-**26a** (12.0 mg, 16.1 μmol), 2,6-di-*t*-butyl pyridine (5.0 μL, 4.03 mg, 22.0 μmol), and TMSOTf (4.2 μL, 4.83 mg, 22.0 μmol) in CH_2Cl_2 (1.0 mL) was stirred at 0°C for 30 min. The mixture was poured into water and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=80:20) gave **27** (8.0 mg, 68%) as an oil. IR (film), 2950, 2920, 1710, 1700, 1650, 1380, 1360, 1300, 1280, 1250, 1130, 1090, 835, 775, 690 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.02, 0.04 (each 3H, s, (C*H*$_3$)Si2), 1.43 (3H, d, *J*=6.5 Hz, (C*H*$_3$)$_2$CH–), 1.47 (9H, s, (C*H*$_3$)$_3$C–), 1.52 (3H, d, *J*= 6.5 Hz, (C*H*$_3$)$_2$CH–), 3.96 (1H, t, *J*=10.0 Hz, C11C*H*H), 4.05–4.35 (4H, C11*H*, C12*H*, C11C*H*H, (CH$_3$)$_2$C*H*), 4.51–4.3.78 (4H, PhCH$_2$O×2), 5.59 (1H, s, C13H), 7.28–7.63 (20H, aromatic protons). EI-MS (rel. int.%): *m*/*z*=726 (0.1, MH^+), 626 (1.7, $[M-\mathrm{Boc}]^+$), 91 (100, $PhCH_2^+$).

4.22. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-5-(*t*-butyldimethylsiloxymethyl)pyrrolidine (28)

4.22.1. From *E*-26b. A mixture of *E*-**26b** (15.0 mg, 20.6 μmol), PPh_3 (2.0 mg, 7.6 μmol), and dimedone (4.0 mg, 28.6 μmol) in THF (1.0 mL) was stirred with $Pd(PPh_3)_4$ (1.7 mg, 1.4 μmol) at room temperature for 10 min. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/Et_2O=75:25) gave **28** (11.6 mg, 87%) as an oil. Since the ^{1}H NMR spectrum of this sample was found to be complicated due to the existence of tautomers arising from the C7–C8 double bond as well as the rotamers due to the carbamoyl groups, assignment of all signals could not be performed. Accordingly, signals of the major isomer (ca. 90%) are described. ^{1}H NMR ($CDCl_3$): δ 0.06, 0.07 (each 3H, s, (C*H*$_3$)Si×2), 0.89 (9H, s, (C*H*$_3$)$_3$CSi), 1.11, 1.14 (each 3H, d, *J*=6.5 Hz, (C*H*$_3$)$_2$CH–), 3.67 (1H, dd, *J*=6.4, 10.1 Hz, C11C*H*HO), 3.79 (1H, dd, *J*=4.7, 10.4 Hz, C11C*H*HO), 3.39 (1H, m, C11*H*), 4.07 (1H, m, (CH$_3$)$_2$C*H*–), 4.25 (1 h, d, *J*=11.4 Hz, PhC*H*HO), 4.27 (1H, dd, *J*=4.6, 6.3 Hz, C12*H*), 4.52 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.57 (1H, d, PhC*H*HO), 4.61 (1H, d, PhC*H*HO), 4.71 (1H, d, *J*=4.6 Hz, C13*H*), 5.60 (1H, br d, *J*=7.8 Hz), 7.05 (2H, m, aromatic protons), 7.20–7.52 (10H, aromatic protons), 7.68 (2H, br d, *J*=7.5 Hz, aromatic protons), 8.42 (1H, br s, N16*H*). EI-MS (rel. int.%): *m*/*z*=643 (0.1, M^+), 586 (1.7, $[M-t\mathrm{Bu}]^+$), 481 (9.2, $[M-t\mathrm{Bu}-\mathrm{PhCO}]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{37}H_{49}N_3O_5Si$ (M^+): *m*/*z*=634.3441. Found *m*/*z*= 643.3459.

4.22.2. From *Z*-26b. The same treatments of *Z*-**26b** (210 mg, 28.8 μmol) as described in Section 4.22.1 gave **28** (17.1 mg, 92%) as an oil. ^{1}H NMR spectrum of this sample was identical with that described in Section 4.22.1.

4.23. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-1-(2-propenyloxy)carbonyl-5-hydroxymethylpyrrolidine (*E*-29)

A solution of *E*-**26b** (108 mg, 148 μmol) and conc. HCl (12 M, 20 μL) in MeOH (3.0 mL) was stirred at room temperature for 30 min. The mixture was poured into a mixture of brine and saturated aqueous $NaHCO_3$ solution (1:1) and extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=85:15) gave *E*-**29** (89 mg, 98%) as an oil. $[\alpha]_D^{20}=+126°$ (c 1.30, $CHCl_3$). IR (film): 3500, 3200, 2970, 2920, 1720, 1640, 1480, 1380, 1100, 1020, 730, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.12, 1.14 (each 3H, d, *J*=7.2 Hz, (C*H*$_3$)$_2$CH–), 3.07 (1H, br t, *J*=7.2 Hz, alcoholic proton), 4.06 (3H, C11C*H*$_2$O, (CH$_3$)$_2$C*H*–), 4.42 (1H, m, C11*H*), 4.44 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.55 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.57 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.59 (1H, br dd, *J*=5.8, 12.9 Hz, CH_2=CHC*H*HO), 4.68 (1H, br dd, *J*=5.8, 12.9 Hz, CH_2=CHC*H*HO), 4.83 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.84 (1H, br s, C3*H*), 5.23 (1H, dq, *J*=10.5,

1.3 Hz, CH*H*=CHCH$_2$O), 5.34 (1H, dq, *J*=17.2, 1.3 Hz, CH*H*=CHCH$_2$O), 5.91 (1H, ddt, *J*=10.5, 17.2, 5.8 Hz, CH$_2$=C*H*CH$_2$O), 7.20–7.60 (13H, aromatic protons), 7.72–7.75 (4H, aromatic protons, NH×2), EI-MS (rel. int.%): *m*/*z*=613 (2.0, M$^+$), 528 (5.6, [M−(CH$_3$)$_2$CHNHCO+H]$^+$), 105 (84, PhCH$_2$O$^+$), 91 (100, PhCH^{2+}). EI-HIMS: calcd for $C_{35}H_{39}N_3O_7$ (M$^+$): *m*/*z*=613.2790. Found: *m*/*z*=613.2792.

4.24. (3*R*,4*R*,5*S*)-2-[(*Z*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-1-(2-propenyloxy)carbonyl-5-hydroxymethylpyrrolidine (*Z*-29)

Treatments of *Z*-**26b** (13.0 mg, 17.9 μmol) in the same manner as described in Section 4.23 gave *Z*-**29** (10.2 mg, 93%) as an oil, after silica gel column chromatography. $[\alpha]_D^{20}$=+23.4° (c 1.41, CHCl$_3$). IR (film): 3400, 3300, 2970, 1700, 1670, 1510, 1470, 1390, 1310, 1070, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, *carzinophilin numbering*): δ 1.12, 1.18 (each 3H, d, *J*=6.5 Hz, (C*H*$_3$)$_2$CH−), 2.51 (1H, br, alcoholic proton), 4.16 (1H, m, (CH$_3$)$_2$C*H*−), 4.17 (1H, dd, *J*=1.0, 6.0 Hz, C12*H*), 4.37 (1H, *J*=3.2, 6.0 Hz, C11*H*), 4.48 (1H, d, *J*=11.9 Hz, PhCH*H*O), 4.52, 4.59 (each 1H, d, *J*=11.6 Hz, PhC*H*$_2$O), 4.67 (2H, br d, *J*=5.6 Hz, CH$_2$=CHC*H*$_2$O), 4.82 (1H, d, *J*=11.9 Hz, PhCH*H*O), 5.19 (1H, dq, *J*=10.5, 1.5 Hz, CH*H*=CHCH$_2$O), 5.28 (1H, dq, *J*=17.3, 1.5 Hz, CH*H*=CHCH$_2$O), 5.56 (1H, br s, C3*H*), 5.87 (1H, ddt, *J*=10.5, 17.3, 5.6 Hz, CH$_2$=C*H*CH$_2$O), 6.24 (1H, br d, *J*=8.1 Hz, N5*H*), 7.25–7.40 (10H, aromatic protons), 7.46–7.92 (5H, m, aromatic protons), 9.56 (1H, br, N16*H*). EI-MS (rel. int.%): *m*/*z*=613 (4.3, M$^+$), 570 (0.5, [M−isopropyl]$^+$), 555 (0.8, [M−ally alcohol]$^+$), 528 (0.7, [M−(CH$_3$)$_2$CHNHCO+H]$^+$), 105 (83, PhCH$_2$O$^+$), 91 (100, PhCH^{2+}). EI-HIMS: calcd for $C_{35}H_{39}N_3O_7$ (M$^+$): *m*/*z*=613.2790. Found: *m*/*z*=613.2765.

4.25. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-1-(2-propenyloxy)carbonyl-5-methansulfoxymethylpyrrolidine (*E*-30)

A mixture of *E*-**29** (87.0 mg, 142 μmol), Et$_3$N (40 μL, 29 mg, 285 μmol), and MsCl (15 μL, 22.0 mg, 193 μmol) in CH$_2$Cl$_2$ (3.0 mL) was stirred at −78°C for 2 h. After excess reagent was decomposed by MeOH (100 μL), the mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH$_2$Cl$_2$/acetone 85:15) gave *E*-**30** (86.5 mg, 88%) as an oil. $[\alpha]_D^{20}$=+147° (c 1.01, CHCl$_3$). IR (film): 3370, 2970, 2920, 1720, 1655, 1645, 1380, 1280, 1170, 750, 700 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, *carzinophilin numbering*): δ 1.12, 1.14 (each 3H, d, *J*=6.6 Hz, (C*H*$_3$)$_2$CH−), 3.08 (3H, s, CH$_3$SO$_3$−), 4.11 (1H, (CH$_3$)$_2$C*H*−), 4.29 (1H, dd, *J*=4.2, 7.4 Hz, C12H), 4.40–4.71 (9H, C11*H*, C11C*H*$_2$O, PhC*H*$_2$O×2, CH$_2$=CHC*H*$_2$O), 4.73 (1H, d, *J*=1.2 Hz, C13*H*), 5.26 (1H, dq, *J*=10.4, 1.3 Hz, CH*H*=CHCH$_2$O), 5.32 (1H, dq, *J*=17.2, 1.3 Hz, CH*H*=CHCH$_2$O), 5.91 (1H, ddt, *J*=10.4, 17.2, 5.8 Hz, CH$_2$=C*H*CH$_2$O), 6.36 (1H, br d, *J*=8.1 Hz, N5*H*), 7.17 (1H, br d, *J*=7.2 Hz, aromatic protons) 7.24–7.38 (10H, aromatic protons), 7.50 (1H, tt, *J*=1.1 Hz, 7.4 Hz, aromatic protons), 7.61 (2H, br d, *J*=7.4 Hz, aromatic protons), 7.94 (1H, br s, N16*H*). EI-MS (rel. int.%): *m*/*z*=691 (0.05, M$^+$), 105 (75, PhCH$_2$O$^+$), 91 (100, PhCH^{2+}).

4.26. (3*R*,4*R*,5*S*)-2-[(*Z*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-1-(2-propenyloxy)carbonyl-5-methansulfoxymethylpyrrolidine (*Z*-30)

Treatments of *Z*-**29** (103 mg, 168 μmol) in the same manner as described in Section 4.25 gave *Z*-**30** (111 mg, 96%) as an oil, after silica gel column chromatography. $[\alpha]_D^{20}$=−3.54° (c 1.30, CHCl$_3$). IR (film): 3380, 3270, 2970, 2930, 1700, 1670, 1650, 1510, 1460, 1360, 1170, 1060, 980, 960, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, *carzinophilin numbering*): δ 1.09, 1.17 (each 3H, d, *J*=6.6 Hz, (C*H*$_3$)$_2$CH−), 2.79 (3H, s, CH$_3$SO$_3$), 4.36 (1H, t, C11C*H*HO), 4.46 (1H, dd, *J*=1.2, 5.7 Hz, C12*H*), 4.47 (1H, m, (CH$_3$)$_2$C*H*−), 4.50 (3H, C5C*H*HO, PhC*H*HO×2), 4.57 (1H, d, *J*=11.1 Hz, PhC*H*HO), 4.62 (1H, ddd, *J*=4.7, 5.7, 9.1 Hz, C11*H*), 4.71 (2H, br d, *J*=5.7 Hz, CH$_2$=CHC*H*$_2$O), 4.77 (1H, d, *J*=11.5 Hz, PhC*H*HO), 5.24 (1H, dq, *J*=10.5, 1.1 Hz, CH*H*=CHCH$_2$O), 5.33 (1H, dq, *J*=17.3, 1.1 Hz, CH*H*=CHCH$_2$O), 5.51 (1H, br s, C3*H*), 5.91 (1H, ddt, *J*=10.5, 17.3, 5.7 Hz, CH$_2$=C*H*CH$_2$O), 6.13 (1H, br d, *J*=8.1 Hz, N5*H*), 7.17 (2H, br dd, *J*=1.6, 7.3 Hz, aromatic protons), 7.24–7.38 (10H, aromatic protons), 7.46–7.92 (5H, m, aromatic protons), 9.54 (1H, br, N16*H*). CI-MS (isobutane): *m*/*z*=732 ([M+C$_4$H$_7$]$^+$), 692 (MH$^+$), 633 ([MH−isopropylamine]$^+$).

4.27. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-5-hydroxymethylpyrrolidine (31)

Treatments of **28** (14.0 mg, 21.7 μmol) in the same manner as described in Section 4.23 gave **31** (9.0 mg, 77%) as an oil, after silica gel column chromatography. The ^{1}H NMR spectrum of this sample showed that it consists of the four isomers arising from tautomers and rotamers (isomer ratio=5:2:2:1). ^{1}H NMR (400 MHz, some signals of the minor isomer could not be assigned.): d 0.78, 0.80 [each 3H×0.2, d, *J*=6.6 Hz, (C*H*$_3$)$_2$CH−(the second isomer)], 1.11, 1.13 [each 3H×0.5, d, *J*=6.6 Hz, (C*H*$_3$)$_2$CH−(major isomer)], 1.12, 1.14 [each 3H×0.2, d, *J*=6.6 Hz, (C*H*$_3$)$_2$CH−(another second isomer)], 2.72–3.00 (1H, br, O*H*), 3.19 [1H×0.2, dd, *J*=3.9, 10.7 Hz, C5C*H*HO−(the second isomer)], 3.73 [2H×0.5, m, C5C*H*$_2$O(major isomer)], 4.06 (1H, m, (CH$_3$)$_2$C*H*−), 4.25 (1H, m, C5CH*H*O)], 3.38 [1H×0.5, dd, *J*=5.2, 6.7 Hz, C12*H*(major)], 4.55–4.72 (2H, PhCH$_2$O), 4.67 [1H×0.2, d, *J*=11.2 Hz, PhC*H*HO(the second isomer)], 4.77 [[1H×0.2, d, *J*=11.2 Hz, PhC*H*HO (the second isomer)], 4.78 [1H×0.2, d, *J*=11.2 Hz, PhC*H*HO (the second isomer)], 4.82 [1H×0.5, d, *J*=5.2 Hz, C12*H*(major isomer)], 4.95 [1H×0.2, dd, *J*=3.9, 2.7 Hz, C12*H*(the second isomer)], 5.08 [1H×0.2, d, *J*=4.2 Hz, C13*H*(the second isomer)], 5.40 [1H×0.2, br d, *J*=5.5 Hz, N*H*(the second isomer)], 5.53 [1H×0.5, br d, *J*=7.8 Hz, NH (major isomer)], 6.78 [1H×0.2, br d, *J*=7.8 Hz, NH (the second isomer)], 6.98–7.90 (15H, aromatic protons), 8.12, 8.13 [each 1H×0.2, br N*H*(the second isomer)×2], 8.48[1H×0.5, br s, N*H* (major isomer)].

EI-MS (rel int.%) m/z=529 (1.1, M^+), 444 (13, $[M-(CH_3)_2CHCO]^+$), 105 (85, $PhCH_2O^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{31}H_{35}N_3O_5$ (M^+): m/z=529.2563. Found: m/z=529.2579.

4.28. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[*N*-(1-methylethyl)carbamoyl]methylidene]-3,4-dibenzyloxy-5-methansulfoxymethylpyrrolidine (32)

4.28.1. Preparation from *E*-30. A mixture of *E*-**30** (36.0 mg, 52.1 μmol), PPh_3 (4.0 mg, 15.3 μmol), and dimedone (8.0 mg, 57.0 μmol) in THF (1.0 mL) was stirred with $Pd(PPh_3)_4$ (4.0 mg, 3.6 μmol) at room temperature. After stirring for 10 min, the mixture was filtered through a pad of silica gel, and filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=90:10) gave **28** (31.0 mg, 97%) as an oil. Since the ^{1}H NMR spectrum of this sample was found to be complicated due to the existence of more than three isomers, signals of the major isomer are mainly assigned. IR (film): 3370, 3320, 2920, 1720, 1650, 1510, 1350, 1250, 1170, 1120, 1100, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11, 1.12 (each 3H, d, J=6.5 Hz, $(CH_3)_2CH$), 2.91 (3H×0.04, s, CH_3SO_3), 2.98 (3H×0.02, CH_3SO_3), 3.00 (3H×0.04, s, CH_3SO_3), 3.09 (1H×0.9, s, CH_3SO_3), 4.06 (1H, m, $(CH_3)_2CH$), 4.10–4.66 (8H, C11*H*, C11CH_2O, C13*H*, PhCH_2O×2), 4.69 (1H, d, J=4.6 Hz, C13*H*), 5.55 (1H, br d, J=7.7 Hz, N5H), 7.00–7.85 (15H, aromatic protons), 8.60 (1H, br, N16H). EI-MS (rel. int.%): m/z=607 (0.08, M^+), 522 (7.8, $[M-(CH_3)_2CHCO]^+$), 105 (69, $PhCH_2O^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{32}H_{37}N_3O_7S$ (M^+): m/z=607.2358. Found: m/z=607.2352.

4.28.2. Preparation from *Z*-30. Treatments of *Z*-**30** (30.2 mg, 43.6 μmol) in the same manner as described in Section 4.28.1 gave **32** (21.8 mg, 82%) as an oil, after silica gel column chromatography. The ^{1}H NMR spectrum of this sample was almost identical to that of an authentic sample except for small differences in the isomeric ratio.

4.28.3. Preparation from 31. A mixture of **31** (9.0 mg, 16.0 μmol), Et_3N (6.0 μL, 4.3 mg, 42 μmol), and MsCl (1.5 μL, 2.2 mg, 19.3 μmol) in CH_2Cl_2 (1.0 mL) was stirred at −78°C for 1 h. After excess reagent was decomposed by MeOH (100 μL), the mixture was poured into water and extracted with AcOEt. Combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=90:10) gave **32** (6.6 mg, 68%) as an oil. The ^{1}H NMR spectrum of this sample was almost identical to that of an authentic sample except for small differences in the isomeric ratio.

4.29. (3*R*,4*R*,5*S*)-2-[1-Benzoylamino-2-[*N*-(1-methylethyl)carbamoyl]methylene]-3,4-dibenzyloxy-1-azabicyclo[3.1.0]hexane (4a)

A mixture of **32** (14.9 mg, 24.5 μmol) and potassium bis(trimethylsilylamide) (0.5 M in hexane, 50 μL, 25 μmol) in THF (1.5 mL) was stirred at room temperature for 5 min. The mixture was poured into water and extracted with AcOEt. Combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (AcOEt/hexane=50:50) gave **4a** (8.2 mg, 64%) as an oil. $[\alpha]_D^{20}$=51.6° (c 0.760, $CHCl_3$). IR (film): 3280, 1720, 1650, 1640, 1540, 1520, 1480, 1380, 1250, 1100, 1070, 1020, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17, 1.19 (each 3H, d, J=6.5 Hz, $(CH_3)_2CH-$), 2.23 (1H, d, J=4.1 Hz, C10H_β), 2.35 (1H, d, J=5.4 Hz, C10H_α), 3.06 (1H, dt, J=4.1, 5.4 Hz, C11*H*), 4.08 (1H, m, $(CH_3)_2CH-$), 4.31, 4.49 (each 1H, d, J=10.8 Hz, PhCH_2O), 4.55 (1H, dd, J=4.1, 5.4 Hz, C12*H*), 4.64, 4.67 (each 1H, d, J=12.0 Hz, PhCH_2O), 5.01 (1H, dd, J=0.9, 4.1 Hz, C13*H*), 6.99 (2H, br dd, J=1.5, 7.0 Hz, aromatic protons), 7.07 (2H, br dd, J=1.5, 7.0 Hz, aromatic protons), 7.12 (1H, tt, J=1.5, 7.0 Hz, aromatic protons), 7.30–7.42 (7H, aromatic protons), 7.47 (1H, tt, J=1.5, 7.0 Hz, aromatic protons), 7.75 (2H, br dd, J=1.5, 7.0 Hz, aromatic protons), 8.43 (1H, br s, N16*H*), 9.47 (1H, br d, J=7.5 Hz, N5*H*). EI-MS (rel int.%); m/z=511 (2.7, M^+), 420 (13, $[M-Bn]^+$), 105 (97, $PhCH_2O^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{31}H_{33}N_3O_4$ (M^+): m/z=511.2485. Found: m/z=511.2479.

4.30. (2*R*,3*R*)-3-(Benzyloxycarbonyl)amino-4-*t*-butyldiphenylsiloxy-2-butanol (34)

4.30.1. Reduction of *N*-Z-L-threonine. A solution of *N*-benzyloxycarbonyl-L-threonine (10.2 g, 40.3 mmol) and added borane methylsulfide complex (10 M, 15 mL) in THF (80 mL) was stirred at 0°C. The mixture was allowed to warm to room temperature. After stirring for 16 h, the mixture was cooled to 0°C again, and water was added to decompose the excess reagent. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification by silica gel column chromatography (CH_2Cl_2/acetone=60:40) gave (2*R*,3*R*)-2-(benzyloxycarbonyl)amino-1,3-butanediol (7.27 g, 75%) as an oil. The ^{1}H NMR spectral data were identical to those reported in the literature.[31]

4.30.2. Protection with TBDPS group giving 34. A mixture of (2*R*,3*R*)-2-(benzyloxycarbonyl)amino-1,3-butanediol (2.10 g, 8.78 mmol), TBDPSCl (4.50 g, 16.4 mmol), and Et_3N (2.60 g, 25.7 mmol) in CH_2Cl_2 (18 mL) was stirred at 0°C. The mixture was allowed to warm to room temperature. After stirring for 12 h, the mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=85:15) gave **34** (2.35 g, 56%) as a white solid. Analytical sample was prepared by recrystallization from ether–hexane to give needles. Mp: 88–89°C. $[\alpha]_D^{20}$=0.00° (c 1.13, $CHCl_3$). IR (nujor): 3520, 3300, 1680, 1550, 1460, 1270, 1130, 1110, 1070, 700, 500 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (9H, s, $(CH_3)_3CSi$), 1.18 (3H, d, J=6.4 Hz, C1H_3), 2.87 (1H, br, alcoholic proton), 3.58 (1H, br m, C3*H*), 3.83 (2H, br d, J=3.7 Hz, C4H_2O), 4.21 (1H, br q, J=6.4 Hz, C2*H*), 5.10 (2H, s, PhCH_2O), 5.40 (1H, br, amide proton), 7.30 (11H, m, aromatic protons), 7.62 (4H, m, aromatic protons). Anal. calcd for $C_{28}H_{35}NO_4Si$: C, 70.41%; H, 7.39%; N, 2.92%. Found C, 70.21%; H, 7.44%; N, 2.78%.

4.31. (3*R*)-3-(Benzyloxycarbonyl)amino-4-*t*-butyldiphenylsiloxy-2,2-dimethoxybutane (35)

4.31.1. Oxidation of the alcohol in 34. Sulfur trioxide pyridine complex (3.60 g, 22.0 mmol) was added to a mixture of **34** (2.70 g, 5.66 mmol) and Et_3N (4.0 mL, 2.88 g, 28.5 mmol) in DMSO (12.0 mL) at room temperature. After stirring for 2.5 h, the mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=96:4) gave (3*R*)-3-(benzyloxycarbonyl)amino-4-*t*-butyldiphenylsiloxy-2-butanone (2.49 g, 5.24 mmol, 92%) as a white solid. Analytical sample was prepared by recrystallization from ether-hexane to give needles. Mp: 63–64°C. IR (nujor): 3280, 1720, 1700, 1270, 1130, 1110, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (9H, s, $(CH_3)_3CSi$), 2.21 (3H, s, C1H_3), 3.93, 4.11 (each 1H, dd, J=3.3, 10.8 Hz, C4H_2O), 4.48 (1H, dt, J=7.3, 3.3 Hz, C3H), 5.09 (2H, s, PhCH_2O), 5.80 (1H, br d, J=7.3 Hz, amide proton), 7.38 (11H, m, aromatic protons), 7.63 (4H, m, aromatic protons). EI-MS (rel. int.%) m/z=432 (1.0, $[M-MeC{=}O]^+$), 418 (3.2, $[M-tBu]^+$), 91 (100, Bn^+).

4.31.2. Dimethyl acetal formation giving 35. A solution of the (2*R*,3*R*)-3-(benzyloxycarbonyl)amino-4-*t*-butyldiphenylsiloxy-2-butanone (38.0 mg, 80.0 μmol) in a mixture of MeOH (1.0 mL) and trimethyl orthoformate (1.0 mL) was stirred in the presence of *p*-TsOH·H_2O (3.0 mg, 15 μmol) at room temperature. After neutralization with Et_3N, the mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/Et_2O=95:5) gave **35** as an oil. $[\alpha]_D^{20}$=+11.3° (c 1.04, $CHCl_3$). IR (film): 3350, 2950, 2930, 1730, 1510, 1110, 1050, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.03 (9H, s, $(CH_3)_3CSi$), 1.28 (3H, s, C1H_3), 3.15 (3H, s, CH_3O), 3.19 (3H, br s, CH_3O), 3.75 (1H, dd, J=4.8, 10.5 Hz, C4HHO), 3.81 (1H, dd, J=4.0, 10.5 Hz, C4HHO), 4.05 (1H, m, C3H), 4.96 (1H, br d, J=10.5 Hz, amide proton), 5.08, 5.15 (each 1H, d, J=7.42 Hz, PhCH_2O), 7.42 (11H, m, aromatic protons), 7.65 (4H, m, aromatic protons). EI-MS (rel int.%): m/z=490 (0.1, $[M-MeO]^+$), 464 (0.6, $[M-tBu]^+$), 432 (1.0, $[M-MeC(OMe)_2]^+$), 91 (88, Bn^+), 89 (100, $MeC^+(OMe)_2$). EI-HIMS: calcd for $C_{29}H_{36}NO_4Si$ ($[M-MeO]^+$): m/z=490.2415. Found m/z=490.2401.

4.32. (2*R*)-2-(Benzyloxycarbonyl)amino-3,3-dimethoxybutanal (36)

4.32.1. Removal of the TBDPS group in 35. A mixture of **35** (1.40 g, 2.68 mmol) and TBAF (1.0 M in THF, 2.7 mL) in THF (10 mL) was stirred at room temperature for 1.5 h. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=93:7) gave (2*R*)-3-(benzyloxycarbonyl)amino-3,3-dimethoxybutanol (716 mg, 94%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (3H, s, C1H_3), 3.23, 3.26 (each 3H, s, CH_3O×2), 3.75 (2H, br, C4H_2O), 3.89 (1H, dt, J=7.1, 4.8 Hz, C3i), 5.12 (2H, s, PhCH_2O), 5.24 (1H, br d, J=7.1 Hz, amide proton), 7.35 (5H, m, aromatic protons).

4.32.2. Oxidation giving 36. A suspension of (2*R*)-3-(benzyloxycarbonyl)amino-3,3-dimethoxybutanol (97.0 mg, 343 μmol), PDC (645 mg, 1.72 mmol), and powdered molecular sieves 4A (450 mg) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 1.5 h. Celite® (2.0 g) and Et_2O (20 mL) were added to the mixture, and the whole mixture was further stirred at room temperature for 20 min. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=93:7) gave **36** (68.5 mg, 71%). IR (film) 3330, 2940, 1720, 1530, 1240, 1170, 1150 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.23 (3H, s, C1H_3), 3.27 (3H, s, CH_3O), 3.34 (3H, br s, CH_3O), 4.66 (1H, br d, J=8.2 Hz, C2H), 5.12 (2H, s, PhCH_2O), 5.37 (1H, br d, J=8.2 Hz, amide proton), 7.36 (5H, m, aromatic protons), 9.77 (1H, s, C1HO).

4.33. (*Z*)-3-(Benzyloxycarbonyl)amino-4-hydroxybut-3-ene-2-one (32c)

A mixture of **36** (17.0 mg, 64.9 mmol) and *p*-TsOH·H_2O (3.0 mg, 15.7 μmol) in a mixture of THF (700 μL) and H_2O (300 μL) was stirred at room temperature for 2 h. The mixture was poured into sat. $NaHCO_3$ solution, and the aqueous solution was washed with Et_2O. The aqueous solution was acidified with conc. HCl and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give **32c** (11.4 mg, 75%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (3H, s, C1H_3), 5.17 (2H, s, PhCH_2O), 7.22 (1H, dd, J=1.2, 12.2 Hz, C4H), 7.38 (5H, m, aromatic protons), 7.60 (1H, br s, amide proton), 11.55 (1H, d, J=12.2 Hz, OH). EI-MS (rel int.%) m/z=236 (1.6, MH^+), 235 (1.7, M^+), 91 (100, Bn^+).

4.34. (*Z*)-3-(Benzyloxycarbonyl)amino-4-methoxybut-3-ene-2-one (37)

An ethereal solution of CH_2N_2 (excess amount) was added to a solution of **32c** (11.4 mg, 48.5 μmol) in Et_2O (3.0 mL) at room temperature. After stirring for 10 h, the mixture was concentrated in vacuo. Purification of the residue by preparative silica gel TLC (CH_2Cl_2/acetone=90:10) gave **37** (4.0 mg, 33%) as an oil. IR (film): 3300, 1720, 1640, 1500, 1250, 1120, 1050 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.24 (3H, s, C1H_3), 3.93 (3H, s, CH_3O), 5.14 (2H, s, PhCH_2O), 6.03 (1H, br s, NH), 7.14 (1H, s, C4H), 7.35 (5H, m, aromatic protons). EI-MS (rel int.%): m/z=249 (0.5, M^+), 206 (3.4, $[M-MeCO]^+$), 91 (100, Bn^+). Anal. calcd for $C_{13}H_{15}NO_4$: C, 62.64%; H, 6.07%; N, 5.61%. Found: C, 62.41%; H, 6.05%; N, 5.50%.

4.35. (3*R*)-3-Amino-4-(*t*-butyldiphenylsilyl)oxy-2-butanone dimethyl acetal (38)

A suspension of **35** (2.61 g, 5.01 mmol) and 10% Pd/C (300 mg) in MeOH (40 mL) was stirred vigorously at room temperature under H_2 atmosphere (1 atm) for 14 h. The catalyst was removed by short Celite® column to give **38** (1.80 g, 93%) as an oil. $[\alpha]_D^{20}$=+13.0° (c 1.16, $CHCl_3$). IR (film): 330, 2930, 1430, 1110, 1060, 1040, 820, 700, 500 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.06 (9H, s, $(CH_3)_3CSi$), 1.19 (3H, s, C1H_3), 3.03, 3.14 (each 3H, s,

CH_3O×2), 3.14 (1H, dd, J=3.4, 7.5 Hz, C3*H*), 3.57 (1H, dd, J=7.5, 9.8 Hz, C4*H*HO), 3.77 (1H, dd, J=3.4, 9.8 Hz, C4*H*HO), 7.37, 7.65 (6H, H, respectively, m, aromatic protons). EI-MS (rel int.%) m/z=355 (1.5, [M−MeOH]$^+$), 330 (1.3, [M−*t*Bu]$^+$), 298 (17, [M−*t*Bu−MeOH], 89 (100, MeC$^+$(OMe)$_2$). EI-HIMS: calcd for $C_{21}H_{30}NO_2Si$ ([M−MeO]$^+$): m/z=356.2047. Found: m/z=356.2036.

4.36. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(methanesulfoxy)methylpyrrolidin-2-ylidene]-2-phenyl-4*H*-oxazol-5-one (39)

4.36.1. Removal of the TBDMS ether in 25b. A mixture of **25b** (170 mg, 291 μmol) and TBAF (1.0 M in THF, 500 μL) in THF (2.0 mL) was stirred at room temperature for 2.5 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=55:45) gave 4-[(3*R*,4*R*,5*S*)-3,4-dibenzyloxy-5-hydroxymethylpyrrolidin-2-ylidene]-2-phenyl-4*H*-oxazol-5-one (123 mg, 90%) as an oil. IR (film): 3300, 2920, 1720, 1640, 1600, 1580, 1320, 1300, 1090, 1070, 890, 740, 690 cm^{-1}. The ^{1}H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=60:40). ^{1}H NMR (400 MHz, $CDCl_3$, a=0.60, b=0.40, some signals of the minor isomer could not be assigned). δ 2.36 [1H×*a*, br dd, J=6.6, 5.2 Hz, alcoholic proton (*Z*-isomer)], 3.83–4.03 [2H+1H×*b*, C5CH_2O, alcoholic proton (*Z*-isomer)], 4.10 [1H×*b*, d, J=4.3 Hz, C4*H*(*Z*-isomer)], 4.20–4.29 [1H+1H×*a*, C5*H*, C4*H*(*E*-isomer)], 4.30 [1H×*b*, d, J=11.9 Hz, PhC*H*HO(*Z*-isomer)], 4.39, 4.59, [each 1H×*a*, d, J=11.8 Hz, PhC*H*HO(*E*-isomer)], 4.60 [1H×*b*, d, J=11.9 Hz, PhC*H*HO(*Z*-isomer)], 4.84, 4.91 [each 1H×*b*, PhC*H*HO], (*Z*-isomer)), 4.92, 5.03 [each 1H×*a*, d, J=11.6 Hz, PhCH_2-O(*E*-isomer)], 5.13 [1H×*a*, d, J=2.2 Hz, C3*H*(*E*-isomer)], 5.37 [1H×*b*, s, C3*H*(*Z*-isomer)], 7.22 (2H, m, aromatic protons), 7.30–7.50 (11H, m, aromatic protons), 7.59 [1H×*b*, br, amine proton (*Z*-isomer)], 7.82 [1H×*a*, br, amine proton(*E*-isomer)], 7.91–8.00 (2H, m, aromatic protons). EI-MS (rel. int.%): m/z=470 (12, M$^+$), 91 (100, Bn$^+$). EI-HIMS: calcd for $C_{28}H_{26}N_2O_5$ (M$^+$): m/z=470.1842. Found: m/z=470.1839.

4.36.2. Mesylation giving 39. A mixture of 4-[(3*R*,4*R*,5*S*)-3,4-dibenzyloxy-5-hydroxy-methylpyrrolidin-2-ylidene]-2-phenyl-4*H*-oxazol-5-one (590 mg, 1.26 mmol), MsCl (281 mg, 2.45 mmol), and Et_3N (377 mg, 3.74 mmol) in CH_2Cl_2 (6.0 mL) was stirred at −78°C for 1 h. After MeOH (300 μL) was added to decompose excess MsCl, the mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=60:40) gave **39** (630 mg, 95%) as an oil. The ^{1}H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=60:40). ^{1}H NMR (400 MHz, $CDCl_3$, a=0.60, b=0.40, some signals assignable are only described.): δ 3.04 [3H×*a*, s, CH_3SO$_3$(*E*-isomer)], 3.07 [3H×*b*, s, CH_3SO$_3$(*Z*-isomer)], 5.10 [1H×*a*, d, J=1.8 Hz, C3*H*(*E*-isomer)], 5.36 [1H×*b*, s, C3*H*(*Z*-isomer)], 7.03 [1H×*b*, br, amine proton(*Z*-isomer)], 7.78 [1H×*a*, br, amine proton(*E*-isomer)].

4.36.3. Recrystallization of 39. A tautomeric mixture (*E*/*Z*=60:40) of **39** (630 mg) was dissolved in a mixture of hexane/AcOEt (ca. 3:1). Standing the solution at room temperature gave *E*-isomer of **39** (570 mg) as needles. Mp: 126–129°C. $[\alpha]_D^{20}$=−74.6° (c 1.08, $CHCl_3$). IR (nujor): 3280, 1720, 1640, 1360, 1360, 1340, 1100, 950, 730, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (3H, s, CH_3SO_3), 4.21 (1H, dd, J=1.8, 4.7 Hz, C4*H*), 4.35 (1H, d, J=11.8 Hz, PhC*H*HO), 4.36 (1H, dd, J=7.6, 10.0 Hz, C5C*H*HO), 4.42–4.52 (2H, C5H, PhC*H*HO), 4.56 (1H, d, J=11.8 Hz, PhC*H*HO), 4.90, 4.96 (each 1H, d, J=11.7 Hz, PhCH_2O), 5.10 (1H, d, J=1.8 Hz, C3*H*), 7.21 (2H, br dd, J=2.0, 7.9 Hz, aromatic protons), 7.32–7.50 (11H, aromatic protons), 7.78 (1H, br, amine proton), 7.99 (2H, m, aromatic protons). Anal. calcd for $C_{29}H_{28}N_2O_7S$: C, 63.49%; H, 5.14%; N, 5.11%; S, 5.84%. Found: C, 63.57%; H, 5.08%; N, 5.07%; S, 5.81%.

4.37. (*E*)-4-[(3*R*,4*R*,5*S*)-1-allyoxycarbonyl-3,4-dibenzyloxy-5-(methanesulfoxy)methylpyrrolidin-2-ylidene]-2-phenyl-4*H*-oxazol-5-one (*E*-40) and its *Z*-isomer (*Z*-40)

4.37.1. The reaction procedure. A mixture of **39** (20.0 mg, 36.5 μmol), DMAP (10 mg, 82.0 μmol), and Alloc$_2$O (13.5 mg, 72.3 μmol) in THF (1.0 mL) was stirred at room temperature for 10 min. The mixture was poured into water, and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by preparative silica gel TLC (benzene/AcOEt=90:10) gave *E*-**40** (R_f=0.77, 6.3 mg, 27%) and *Z*-**39** (R_f=0.73, 14.0 mg, 61%) as oils.

4.37.2. Data of *E*-40. $[\alpha]_D^{20}$=+108° (c 0.461, $CHCl_3$). IR (film): 3420, 1790, 1720, 1570, 1360, 1255, 1170, 1110, 1055, 990, 960, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (3H, s, CH_3SO$_3$), 4.23 (1H, dd, J=1.0, 5.3 Hz, C3*H*), 4.53 (1H, t, J=9.2 Hz, C5C*H*HO), 4.55, 4.62 (each 1H, d, J=11.7 Hz, PhCH_2O), 4.66–4.74 (4H, C5*H*, CH$_2$=CHC*H*HO, PhCH_2O), 4.77 (1H, ddt, J=5.6, 13.0, 1.5 Hz, CH$_2$=CHC*H*HO), 4.85 (1H, dd, J=4.0, 9.3 Hz, C5C*H*HO), 5.08 (1H, br s, C3*H*), 5.25 (1H, dq, J=10.4, 1.5 Hz, CH*H*=CHCH$_2$O), 5.32 (1H, dq, J=17.2, 1.5 Hz, CH*H*=CHCH$_2$O), 5.93 (1H, ddt, J=10.4, 17.2, 5.6 Hz, CH$_2$=C*H*CH$_2$O), 7.23–7.40 (10H, aromatic protons), 7.51 (2H, br t, J=7.7 Hz, aromatic protons), 7.57 (1H, br t, J=7.7 Hz, aromatic proton), 8.05 (2H, br t, J=7.7 Hz, aromatic protons). EI-MS (rel int.%): m/z=632 (trace, M$^+$), 496 (3.8, [M−CH$_2$=CHCH$_2$OMs]$^+$), 105 (66, PhCO$^+$), 91 (100, PhCH$_2^+$). CI-MS (isobutane): m/z=633 (MH$^+$). EI-HIMS: calcd for $C_{33}H_{32}N_2O_9S$ (M$^+$): m/z=632.1828. Found: m/z=632.1831.

4.37.3. Data of *Z*-40. $[\alpha]_D^{20}$=+193° (c 1.39, $CHCl_3$). IR (film): 3400, 1770, 1620, 1570, 1360, 1280, 1170, 990, 960, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (3H, s, CH_3SO$_3$), 4.21 (1H, dd, J=1.0, 4.8 Hz, C3*H*), 4.50–4.65 (5H, PhC*H*HO×3, C5*H*, C5C*H*HO), 4.68 (1H, ddt, J=5.8, 13.0, 1.4 Hz, CH$_2$=CHC*H*HO), 4.72 (1H, d, J=11.4 Hz, PhC*H*HO), 4.78 (1H, ddt, J=5.8, 13.0, 1.4 Hz, CH$_2$=CHC*H*HO), 4.97 (1H, dd, J=3.8, 8.8 Hz, C5C*H*H), 5.20

(1H, dq, J=10.4, 1.4 Hz, C*H*H=CHCH$_2$O), 5.33 (1H, dq, J=17.2, 1.4 Hz, C*H*H=CHCH$_2$O), 5.46 (1H, br s, C3*H*), 5.91 (1H, ddt, J=10.4, 17.2, 5.8 Hz, CH$_2$=C*H*CH$_2$O), 7.25–7.35 (10H, aromatic protons), 7.49 (2H, br t, J=7.5 Hz, aromatic protons), 7.57 (1H, br t, J=7.5 Hz, aromatic proton), 8.05 (2H, br t, J=7.5 Hz, aromatic protons). EI-MS (rel. int.%) m/z=632 (0.05, M^+), 526 (0.70, [M−PH CHO]$^+$), 496 (2.5, [M−CH$_2$=CHCH$_2$OMs]$^+$), 105 (89, PhCO$^+$), 91 (100, PhCH$_2^+$). EI-HIMS: calcd for $C_{33}H_{32}N_2O_9S$ (M^+): m/z=632.1828. Found: m/z= 632.1803.

4.38. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-[1-(*t*-butyldiphenylsiloxy)methyl-2,2-dimethoxypropyl]-carbamoyl]methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine (*E*-41) and its *Z*-isomer (*Z*-41)

4.38.1. Preparation employing *E*-40. A mixture of *E*-**40** (4.30 mg, 6.80 μmol), **38** (4.0 mg, 10.3 μmol), and DMAP (1.0 mg, 8.2 μmol) in toluene (2.0 mL) was concentrated by a rotary evaporator. The mixture was heated at 50°C for 2 h. Purification of the mixture by silica gel column chromatography (benzene/AcOEt=90:10→80:20) gave *Z*-**41** (1.1 mg, 15%) and *E*-**41** (5.2 mg, 75%) both as an oil.

4.38.2. Preparation employing *Z*-40. Treatments of *Z*-**40** (13.5 mg, 21.4 μmol) in the same manner as described in Section 4.38.1 gave *Z*-**41** (4.3 mg, 4.3 μmol, 20%), and *E*-**41** (15.0 mg, 14.7 μmol, 68%) both as oils.

4.38.3. Data of *E*-41. $[\alpha]_D^{20}$=+93.8° (c 1.06, $CHCl_3$). IR (film) 3370, 2920, 1715, 1670, 1500, 1470, 1355, 1270, 1170, 1110, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.90 (9H, s, (C*H*$_3$)$_3$CSi), 1.40 (3H, s, C1*H*$_3$), 3.04 (3H, s, C*H*$_3$SO$_3$), 3.15, 3.21 (each 3H, s, C*H*$_3$O×2), 3.70 (1H, dd, J=5.3, 10.3 Hz, C4*H*HO), 3.86 (1H, dd, J=3.5, 10.3 Hz, C4*H*HO), 4.23 (1H, dd, J=3.6, 6.7 Hz, C12*H*), 4.31 (1H, m, C3*H*), 4.35–4.66 (10H, m, C13*H*, C11*H*, C11C*H*$_2$O, PhC*H*$_2$O×2, CH2=CHC*H*$_2$O), 5.14 (1H, dq, J=10.4, 1.4 Hz, C*H*H=CHCH$_2$O), 5.21 (1H, dq, J=17.2, 1.4 Hz, C*H*H=CHCH$_2$O), 5.81 (1H, ddt, J=10.4, 17.2, 5.7 Hz, CH$_2$=C*H*CH$_2$O), 6.90 (1H, br d, J=8.8 Hz, N5*H*), 7.12 (2H, m, aromatic protons), 7.23–7.40 (11H, m, aromatic protons), 7.49 (1H, br t, J=7.9 Hz, aromatic proton), 7.57 (4H, m, aromatic protons), 7.63 (2H, br dd, J=1.6, 7.9 Hz, aromatic protons), 7.73 (1H, br s, N16*H*). EI-MS (rel int.%) m/z=914 (0.04, [M−PhCO]$^+$), 872 (3.6, [M−*t*Bu−CH$_3$C(OCH$_3$)$_2$−H]$^+$), 851 (1.6, [M−CH$_3$C(OCH$_3$)$_2$−H−PhH]$^+$), 794 (3.7, [872−PhH]$^+$ and/or [851−*t*Bu]$^+$), 105 (84, PhCO$^+$), 91 (100, Bn$^+$). SI-MS (3-nitrobenzylalcohol): m/z=988 ([M−CH$_3$O]$^+$). SI-MS (3-nitrobenzylalcohol+NaCl): m/z=1042 ([M+Na]$^+$).

4.38.4. Data of *Z*-41. $[\alpha]_D^{20}$=+33.88° (c 0.96, $CHCl_3$). IR (film): 3400, 3270, 2950, 2920, 1700, 1670, 1380, 1360, 1300, 1170, 1110, 1060, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.93 (9H, s, (C*H*$_3$)$_3$CSi), 1.37 (3H, s, C1H3), 2.70 (3H, s, C*H*$_3$SO$_3$), 3.15, 3.18 (each 3H, s, CH$_3$O×2), 3.81 (1H, dd, J=4.3, 10.5 Hz, C4*H*HO), 3.89 (1H, dd, J=4.0, 10.5 Hz, C4*H*HO), 4.14 (1H, br d, J=6.3 Hz, C12H), 4.31 (1H, t, J=9.3 Hz, C11C*H*HO), 4.43 (1H, d, J=11.4 Hz, PhC*H*HO), 4.44 (1H, m, C3*H*), 4.47 (1H, dd, J=4.5, 9.3 Hz, C11C*H*HO), 4.57 (2H, s, PhC*H*$_2$O), 4.59 (1H, m, C11*H*), 4.69 (2H, br d, J=5.7 Hz, CH$_2$=CHC*H*$_2$O), 4.82 (1H, d, J=11.4 Hz, PhC*H*HO), 5.21 (1H, dq, J=10.4, 1.4 Hz, C*H*H=CHCH$_2$-O), 5.30 (1H, dq, J=17.2, 1.4 Hz, C*H*H=CHCH$_2$O), 5.71 (1H, br s, C13*H*), 5.88 (1H, ddt, J=10.4, 17.2, 5.7 Hz, CH$_2$=C*H*CH$_2$O), 7.18–7.56 (15H, m, aromatic protons, N5*H*), 7.63 (4H, m, aromatic protons), 7.88 (2H, br d, J=7.2 Hz, aromatic protons), 9.25 (1H, br s, NH). EI-MS (rel. int.%): m/z=872 (1.3, [M−*t*Bu−CH$_3$C(OCH$_3$)$_2$−H]$^+$), 851 (2.5, [M−CH$_3$C(OCH$_3$)$_2$−H−PhH]$^+$), 794 (5.1, [872-PhH]$^+$ and/or [851−*t*Bu]$^+$), 105 (83, PhCO$^+$), 91 (100, PhCH$_2^+$). SI-MS (3-nitrobenzylalcohol): m/z=988 ([M−CH$_3$O]$^+$); SI-MS (3-nitrobenzylalcohol+NaCl): m/z=1042 ([M+Na]$^+$).

4.39. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-(1-formyl-2,2-dimethoxypropyl)carbamoyl]methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine (*E*-42)

4.39.1. Removal of the TBDPS group in *E*-41. A mixture of *E*-**41** (135 mg, 132 μmol) and HF–pyridine complex (Aldrich, 300 μL) in pyridine (3.0 mL) was stirred at 0°C for 30 min. After the mixture was further stirred for 1 h at room temperature, the mixture was poured into sat. $NaHCO_3$ solution and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=60:40) gave (3*R*,4*R*,5*S*)-2-[(*E*)-1-benzoylamino-1-(1-hydroxymethyl-2,2-dimethoxypropyl)-carbamoyl]methyllidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxycarbonyl-5-(methanesulfoxy)-methylpyrrolidine (95.8 mg, 93%) as an oil. $[\alpha]_D^{20}$=+139° (c 0.745, $CHCl_3$). IR (film): 3400, 2930, 1720, 1660, 1510, 1470, 1370, 1280, 1170, 1040, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.26 (3H, s, C1*H*$_3$), 3.09 (3H, s, C*H*$_3$SO$_3$), 3.21, 3.23 (each 3H, s, C*H*$_3$O×2), 3.68–3.83 (3H, m, C4*H*$_2$O, alcoholic proton), 4.09 (1H, m, C3*H*), 4.30 (1H, dd, J=4.3, 7.1 Hz, C12*H*), 4.43 (1H, d, J=11.5 Hz, PhC*H*HO), 4.46 (1H, dd, J=4.0, 10.3 Hz, C11C*H*HO), 4.52 (1H, d, J=4.8, 10.3 Hz, C11C*H*HO), 4.61 (1H, d, J=11.7 Hz, PhC*H*HO), 4.62–4.69 (4H, m, C13H, C11H, CH$_2$=CHC*H*HO, PhC*H*HO), 4.72 (1H, ddt, J=5.8, 13.0, 1.4 Hz, CH$_2$=CHC*H*HO), 5.27 (1H, dq, J=10.4, 1.4 Hz, C*H*H=CHCH$_2$O), 5.34 (1H, dq, J=17.2, 1.4 Hz, C*H*H=CHCH$_2$O), 5.95 (1H, ddt, J=10.4, 17.2, 5.8 Hz, CH$_2$=C*H*CH$_2$O), 6.45 (1H, br d, J=6.7 Hz, N5*H*), 7.17 (2H, m, aromatic protons), 7.26–7.58 (10H, m, aromatic protons), 7.50–7.58 (3H, m, aromatic protons), 7.91 (1H, br, N16*H*). EI-MS (rel. int.%): m/z=673 (0.3, [M−BnOH]$^+$), 105 (75, PhCO$^+$), 91 (100, PhCH$_2^+$). SI-MS (3-nitrobenzylalcohol+KCl): m/z=820 ([M+K]$^+$), 750 ([M−CH$_3$O]$^+$).

4.39.2. Oxidation giving *E*-42. A mixture of (3*R*,4*R*,5*S*)-2-[(*E*)-1-benzoylamino-1-(1-hydroxymethyl-2,2-dimethoxypropyl)carbamoyl]methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine (93.5 mg, 120 μmol), powdered molecular sieves 4A (100 mg), and PDC (220 mg, 568 μmol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 2 h. Celite® (300 mg) and Et_2O (15 mL), were added to the mixture

successively, and the whole mixture was further stirred for 20 min at room temperature. After filtration, the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=60:40) gave *E*-**42** (63.8 mg, 68%). $[\alpha]_D^{20}$=+191° (c 1.07, $CHCl_3$). IR (film): 3400, 2930, 1720, 1650, 1380, 1270, 1170, 1020, 1000, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.34 (3H, s, C1H_3), 3.08 (3H, s, CH_3SO_3), 3.26, 3.36 (each 3H, s, CH_3O×2), 4.30 (1H, dd, *J*=4.0, 7.0 Hz, C12*H*), 4.42 (1H, d, *J*=11.5 Hz, PhC*H*HO), 4.50–4.69 (8H, m, C13H, C11CH_2O, PhC*H*HO×3, CH_2=CH_2O), 4.79 (1H, m, C11*H*), 4.89 (1H, d, *J*=8.1 Hz, C3*H*), 5.24 (1H, dq, *J*=1.4, 10.4 Hz, C*H*H=CH_2O), 5.30 (1H, dq, *J*=1.4, 17.2 Hz, C*H*H=CH_2O), 5.93 (1H, ddt, *J*=10.4, 17.2, 5.9 Hz, OCH2C*H*=CH2), 6.81 (1H, br d, *J*=8.1 Hz, N5*H*), 7.15 (2H, br dd, *J*=1.5, 7.5 Hz, aromatic protons), 7.25–7.38, (10H, m, aromatic protons), 7.50 (1H, tt, *J*=1.2, 8.0 Hz, aromatic proton), 7.56 (2H, bb, *J*=1.2, 8.0 Hz, aromatic protons), 7.81 (1H, br, N16*H*), 9.77 (1H, s, C4*H*O). EI-MS (rel. int.%): *m*/*z*=593 (0.70, [M−BnOH−$CH_3C(CH_3)_2^+$], 105 (82, $PhCO^+$), 91 (100, Bn^+). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=818 ($[M+K]^+$).

4.40. (3*R*,4*R*,5*S*)-2-[(*Z*)-1-Benzoylamino-1-(1-formyl-2,2-dimethoxypropyl)carbamoyl]methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxycarbonyl-5-(methanesulfoxy)-methylpyrrolidine (*Z*-42)

4.40.1. Removal of TBDPS group in *E*-41. Treatments of *Z*-**41** (25 mg, 24.5 μmol) in the same manner as described in Section 4.39.1 gave (3*R*,4*R*,5*S*)-2-[(*Z*)-1-benzoylamino-1-(1-hydroxymethyl-2,2-dimethoxypropyl)-carbamoyl]-methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine (15.3 mg, 79%) as an oil after silica gel column chromatography. $[\alpha]_D^{20}$=−7.74° (c 1.11, $CHCl_3$). IR (film): 3480, 3250, 2920, 1700, 1660, 1510, 1475, 1390, 1355, 1310, 1170, 1060, 960, 730, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.22 (3H, s, C1H_3), 2.80 (3H, s, CH_3SO_3), 3.12, 3.20 (each 3H, s, CH_3O×2), 3.69 (1H, ddd, *J*=4.6, 5.9, 11.6 Hz, C4*H*HO), 3.91 (1H, ddd, *J*=3.5, 9.2, 11.6 Hz, C4*H*HO), 4.12 (1H, br dd, *J*=4.6, 9.2 Hz, O*H*), 4.18 (1H, dd, *J*=1.2, 5.6 Hz, C12*H*), 4.37 (1H, t, *J*=8.9, Hz, C11C*H*HO), 4.45 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.51–4.64 (4H, C5*H*, C5C*H*HO, PhC*H*HO×2), 4.73 (2H, br d, *J*=5.8 Hz, CH_2=CHCH_2O), 4.83 (1H, d, *J*=11.7 Hz, PhC*H*HO), 5.25 (1H, dq, *J*=10.4, 1.4 Hz, C*H*H=CHCH_2-O), 5.34 (1H, dq, *J*=17.2, 1.4 Hz, C*H*H=CHCH_2O), 5.35 (1H, 1H, br s, C13*H*), 5.92 (1H, ddt, *J*=10.4, 17.2, 5.8 Hz, CH_2=C*H*CH_2O), 6.40 (1H, br d, *J*=8.5 Hz, N5*H*), 7.23–7.29 (10H, aromatic protons), 7.46 (2H, br t, *J*=7.8 Hz, aromatic protons), 7.55 (1H, br t, *J*=7.8 Hz, aromatic protons), 7.91 (1H, br t, *J*=7.8 Hz, aromatic protons). EI-MS (rel. int.%): *m*/*z*=673 (0.2, $[M-BnOH]^+$), 105 (72, $PhCO^+$), 91 (100, $PhCH_2^+$). SI-MS (3-nitrobenzylalcohol): *m*/*z*=750 ($[M-CH_3O]^+$). SIMS (3-nitrobenzylalcohol+NaCl): *m*/*z*=804 ($[M+Na]^+$).

4.40.2. Oxidation giving *Z*-42. Treatments of (3*R*,4*R*,5*S*)-2-[(*Z*)-1-benzoylamino-1-(1-hydroxymethyl-2,2-dimethoxypropyl)carbamoyl]methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine (40.0 mg, 120 μmol) in the same manner as described in Section 4.39.2 gave *Z*-**41** (33.2 mg, 83%) as an oil after silica gel column chromatography. $[\alpha]_D^{20}$=+42.6° (c 1.04, $CHCl_3$) IR (film): 3400, 2920, 2850, 1730, 1710, 1700, 1670, 1650, 1380, 1260, 1170, 1120, 730, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.27 (3H, s, C1H_3), 2.75 (3H, s, CH_3SO_3), 3.19, 3.27 (each 3H, s, CH_3O×2), 4.17 (1H, dd, *J*=1.2, 5.6 Hz, C12*H*), 4.36 (1H, t, *J*=9.0 Hz, C11C*H*HO), 4.45 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.52 (2H, m, C11C*H*HO, PhC*H*HO), 4.60 (1H, d, *J*=11.5 Hz, PhC*H*HO), 4.63 (1H, m, C11*H*), 4.73 (2H, dt, *J*=5.7, 1.2 Hz, CH_2=CHCH_2O), 4.83 (1H, d, *J*=11.4 Hz, PhC*H*HO), 4.83 (1H, d, *J*=6.8 Hz, C3*H*), 5.25 (1H, dq, *J*=10.4, 1.2 Hz, C*H*H=CHCH_2O), 5.34 (1H, dq, *J*=17.2, 1.2 Hz, C*H*H=CHCH_2O), 5.69 (1H, s, C13*H*), 5.92 (1H, ddt, *J*=10.4, 17.2, 5.7 Hz, CH_2=C*H*CH_2O), 6.77 (1H, br d, *J*=6.8 Hz, N5*H*), 7.26–7.38 (10H, m, aromatic protons), 7.46 (2H, br t, *J*=7.3 Hz, aromatic protons), 7.55 (1H, br t, *J*=7.3 Hz, aromatic proton), 7.90 (12H, br d, *J*=7.3 Hz, aromatic protons), 9.61 (1H, br, N16*H*), 9.76 (1H, s, C4*H*O). EI-MS (rel int.%): *m*/*z*=593 (0.20, [M−BnOH−$CH_3C(CH_3)_2^+$], 105 (86, $PhCO^+$), 91 (100, Bn^+). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=802 ($[M+Na]^+$), 741 ($[M-MeO]^+$).

4.41. (3*R*,4*R*,5*S*)-2-[(*E*)-1-benzoylamino-1-((*Z*)-4-methoxybut-3-en-2-on-3-ylcarbamoyl)methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine (*E*-43)

A solution of *E*-**42** (9.30 mg, 11.3 μmol) in a mixture of THF (1.0 mL) and H_2O (0.5 mL) was stirred with *p*-TsOH·H_2O (1.0 mg, 5.3 μmol) at room temperature for 30 min. The mixture was poured into water, extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give a crude (3*R*,4*R*,5*S*)-2-[(*E*)-1-benzoylamino-1-((*Z*)-4-hydroxybut-3-en-2-on-3-ylcarbamoyl)methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)carbonyl-5-(methanesulfoxy)methylpyrrolidine as an oil. IR (film): 3400, 3030, 2930, 1720, 1670, 1630, 1360, 2280, 1170, 960, 730, 700 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ=2.23, 3.11 (each 3H, s, C1H_3, CH_3SO_3, respectively), 4.32 (1H, dd, *J*=4.5, 6.9 Hz, C12H), 4.36 (1H, d, *J*=12.1 Hz, PhC*H*HO), 4.40–4.77 (9H, m, C13*H*, C11H, C11CH_2O, PhC*H*HO×3, CH_2=CHCH_2O), 5.24 (1H, dq, *J*=10.3, 1.2 Hz, C*H*H=CHCH_2O), 5.31 (1H, dd, *J*=17.1, 1.2 Hz, C*H*H=CHCH_2O), 5.88 (1H, ddt, *J*=10.3, 17.1, 6.1 Hz, CH_2=C*H*CH_2O), 7.10–7.18 (2H, m, aromatic protons), 7.26 (1H, s, C4*H*OH), 7.27–7.48 (10H, m, aromatic protons), 7.50–7.55 (3H, m, aromatic protons), 7.89, 8.65 (each 1H, br s, N5*H*, N16*H*), 12.48 (1H, br, C4HO*H*). This sample was dissolved in a mixture of THF (1.0 mL) and Et_2O (2.0 mL). An excess amount of ethereal CH_2N_2 was added, and the mixture was stood at room temperature for 12 h. After concentration in vacuo, purification of the residue by silica gel column chromatography (AcOEt/benzene=70:30) gave *E*-**43** (5.7 mg, 67% for 2 steps) as an oil. $[\alpha]_D^{20}$=+90.0° (c 0.620, $CHCl_3$). IR (film): 3370, 2930, 1720, 1660, 1355, 1280, 1260, 1170, 1100, 960, 730, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 2.28, 3.06, 3.86 (each 3H, s, C1H_3, CH_3SO_3, CH_3O, respectively), 4.29 (1H, dd, *J*=3.7,

7.0 Hz, C12*H*), 4.42 (1H, d, *J*=11.6 Hz, PhC*H*HO), 4.46–4.55 (3H, m, C11CH_2O, PhC*H*HO), 4.61 (2H, m, CH_2=CHCH_2O), 4.65 (2H, br s, PhCH_2O), 4.67 (1H, d, *J*=3.7 Hz, C13*H*), 4.76 (1H, m, C11*H*), 5.21 (1H, dq, *J*=10.4, 1.2 Hz, C*H*H=CHCH_2O), 5.27 (1H, dq, *J*=17.2, 1.2 Hz, C*H*H=CHCH_2O), 5.89 (1H, ddt, *J*=10.4, 17.2, 6.0 Hz, CH_2=C*H*CH_2O), 7.02 (1H, s, C4*H*), 7.14–7.27 (1H, m, aromatic protons), 7.27–7.42 (10H, m, aromatic protons), 7.51 (1H, dt, *J*=7.4, 1.3 Hz, aromatic proton), 7.58 (2H, br dd, *J*=1.3, 7.4 Hz, aromatic protons), 7.62, 7.76 (each 1H, br s, N5H, N16H). EI-MS (rel. int.%): *m*/*z*=689 (0.1, [M−allyl alcohol]$^+$), 651 (0.2, [M−MsOH]$^+$), 105 (82, PhCO$^+$), 91 (100, PhCH_2^+). CI-MS (isobutane): *m*/*z*=748 (M^+).

4.42. (3*R*,4*R*,5*S*)-2-[(*Z*)-1-benzoylamino-1-((*Z*)-4-methoxybut-3-en-2-on-3-ylcarbamoyl)methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxycarbonyl-5-(methanesulfoxy)methylpyrrolidine (*Z*-43)

Similar treatments of *Z*-**42** (33.2 mg, 42.6 μmol) to those described in Section 4.41 gave crude (3*R*,4*R*,5*S*)-2-[(*Z*)-1-benzoylamino-1-((*Z*)-4-hydroxybut-3-en-2-on-3-ylcarbamoyl)methylidene-3,4-dibenzyloxy-1-(prop-2-en-1-yloxy)-carbonyl-5-(methanesulfoxy)methylpyrrolidine. IR (film): 3310, 3020, 2930, 1700, 1670, 1630, 1520, 1510, 1380, 1360, 1300, 1245, 1170, 1065, 960, 730, 700 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 2.27 (3H, s, C1H_3), 2.80 (3H, s, CH_3SO_3), 4.17 (1H, dd, *J*=1.3, 5.7 Hz, C12*H*), 4.36 (1H, dd, *J*=8.5, 9.2 Hz, C11C*H*HO), 4.41–4.58 (4H, m, C11C*H*HO, PhC*H*HO×3), 4.62 (1H, m, C11H), 4.69 (2H, br d, *J*=5.7 Hz, CH_2=CHCH_2O), 4.80 (1H, d, *J*=11.5 Hz, PhC*H*HO), 5.25 (1H, dq, *J*=10.4, 1.2 Hz, C*H*H=CHCH_2O), 5.31 (1H, dq, *J*=17.1, 1.2 Hz, C*H*H=CHCH_2O), 5.57 (1H, d, *J*=1.3 Hz, C13*H*), 5.93 (1H, ddt, *J*=10.4, 17.1, 5.7 Hz, CH_2=C*H*CH_2O), 7.20–7.25 (2H, aromatic protons), 7.26 (1H, s, C4*H*OH), 7.26–7.60 (8H, aromatic protons), 7.43–7.60 (3H, m, aromatic protons), 7.90 (2H, aromatic protons), 8.80, 9.57 (each 1H, br s, N5*H*, N16*H*), 12.37 (1H, br, C4HO*H*). The same treatments as described in Section 4.42 gave *Z*-**43** (24.9 mg, 78% in 2 steps) as an oil after silica gel column chromatography. $[\alpha]_D^{20}$=+5.10° (c 0.980, $CHCl_3$). IR (film): 3270, 2920, 1700, 1670, 1500, 1470, 1380, 1360, 1255, 1170, 1065, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 2.30 (3H, s, C1H_3), 2.78 (3H, s, CH_3SO_3), 3.84 (3H, s, CH_3O), 4.16 (1H, dd, *J*=1.1, 5.6 Hz, C12*H*), 4.36 (1H, t, *J*=9.0 Hz, C11C*H*HO), 4.49 (1H, d, *J*=11.3 Hz, PhC*H*HO), 4.50 (1H, dd, *J*=2.4, 9.0 Hz, C11C*H*HO), 4.51 (1H, d, *J*=11.3 Hz, PhC*H*HO), 4.56 (1H, d, *J*=11.3 Hz, PhC*H*HO), 4.62 (1H, m, C11*H*), 4.71 (2H, br d, *J*=5.7 Hz, CH_2=CHCH_2O), 4.80 (1H, d, *J*=11.3 Hz, PhC*H*HO), 5.23 (1H, dq, *J*=10.4, 1.1 Hz, C*H*H=CHCH_2O), 5.32 (1H, dq, *J*=17.2, 1.1 Hz, C*H*H=CHCH_2O), 5.69 (1H, br s, *J*=C13*H*), 5.91 (1H, ddt, *J*=10.4, 17.2, 5.7 Hz, CH_2=C*H*CH_2O), 7.18 (1H, s, C4*H*), 7.21–7.39 (10H, m, aromatic protons), 7.47 (2H, br t, *J*=7.7 Hz, aromatic protons), 7.55 (1H, br t, *J*=7.7 Hz, aromatic proton), 7.61 (1H, br s, NH), 7.93 (2H, br d, *J*=7.3 Hz, aromatic protons), 9.55 (1H, br s, NH). SI-MS (3-nitrobenzylalcohol+NaCl) *m*/*z*=770 (M+Na). EI-MS spectrum of this sample provided no useful information about its structure.

4.43. (3*R*,4*R*,5*S*)-2-[(*E*)-1-benzoylamino-1-((*Z*)-4-methoxybut-3-en-2-on-3-ylcarbamoyl)methylidene-3,4-dibenzyloxy-5-(methanesulfoxy)methylpyrrolidine (*E*-44)

4.43.1. Preparation from *E*-43. A mixture of *E*-**43** (5.7 mg, 7.63 μmol), Ph_3P (1.0 mg, 3.8 μmol), AcOH (1.0 μL), and $Pd(Ph_3P)_4$ (1.0 mg, 1.0 μmol) in THF (1.0 mL) was stirred at room temperature for 10 min. After benzene (5.0 mL) was added, the mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=70:30) gave *E*-**44** (2.90 mg, 57%) as an oil. $[\alpha]_D^{20}$=+47.2° (c 1.14, $CHCl_3$). IR (film) 3400, 3320, 3030, 3000, 2930, 1650, 1480, 1350, 1250, 1170, 1100, 960, 750, 700, 525 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 2.22 (3H, s, C1H_3), 3.09 (3H, s, CH_3SO_3), 3.87 (3.H, s, CH_3O), 4.17 (1H, m, C11H), 4.20 (1H, m, C11C*H*HO), 4.29 (1H, d, *J*=11.1 Hz, PhC*H*HO), 4.33 (1H, dd, *J*=4.8, 6.8 Hz, C12*H*), 4.39 (1H, m, C11C*H*HO), 4.56, 4.57 (each 1H, d, *J*=11.9 Hz, PhCH_2O), 4.58 (1H, d, *J*=11.1 Hz, PhC*H*HO), 4.74 (1H, d, *J*=4.8 Hz, C13*H*), 7.02 (2H, m, aromatic protons), 7.21–7.39 (10H, aromatic protons), 7.42 (1H, br s, NH), 7.53 (1H, br t, *J*=7.3 Hz, aromatic proton), 7.72 (2H, br d, *J*=7.3 Hz, aromatic protons), 8.59 (1H, br s, NH). EI-MS (rel. int.%) *m*/*z*=631 (0.02, [M−MeOH]$^+$), 105 (79, PhCO$^+$), 91 (100, PhCH_2^+). CI-MS (isobutane): *m*/*z*=664 (MH^+).

4.43.2. Preparation from *Z*-43. The same treatments of *Z*-**43** (24.9 mg, 33.0 μmol) as described in Section 4.43.1 gave *Z*-**44** (19.3 mg, 88%) after silica gel column chromatography. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.21 (3H, s, C1H_3), 2.97 (3H, s, CH_3SO_3), 3.77 (3H, s, CH_3O), 4.20–4.75 (8H, m, C12*H*, C11*H*, C11CH_2O, PhCH_2O×2), 5.31 (1H, s, C13*H*), 6.37 (1H, br s, N*H*), 7.12 (1H, s, CC4*H*OMe), 7.20–7.52 (13H, m, aromatic protons), 7.85 (3H, m, N*H*, aromatic protons), 8.45 (1H, br s, N*H*). The ^{1}H NMR spectrum of this sample changed to one identical to that of *Z*-**44** after standing its $CDCl_3$ solution at room temperature for 12 h.

4.44. (3*R*,4*R*,5*S*)-2-[(*E*)-1-Benzoylamino-1-(4-methoxy-3-buten-2-on-3-ylcarbamoyl)]methylidene-3,4-dibenzyloxy-1-azabicyclo[3.1.0]hexane (4b)

Tetrabutylammonium fluoride (1 M in THF, 10 μL) was added to a suspension of *E*-**44** (5.2 mg, 8.4 μmol) and powdered molecular sieves 4A (10 mg) in THF (1.0 mL). After stirring at room temperature for 10 min, the mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by preparative silica gel TLC (AcOEt) gave **4b** (R_f=0.4, 3.5 mg, 73%) as an oil. $[\alpha]_D^{20}$=+43.5° (c 0.630, $CHCl_3$). IR (film): 3270, 3060, 3030, 2970, 2920, 1650, 1510, 1480, 1250, 1100, 730, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 2.23 (1H, s, C1H_3), 2.30 (1H, d, *J*=4.1 Hz, C10*H*β), 2.44 (1H, d, *J*=4.8 Hz, C10*H*α), 3.10 (1H, ddd, *J*=4.1, 4.1, 4.8 Hz, C11*H*), 3.89 (3H, s, CH_3O), 4.31 (1H, d, *J*=10.7 Hz, PhC*H*HO), 4.52 (1H, d, *J*=10.7 Hz, PhC*H*HO), 4.59 (1H, dd, *J*=4.1, 4.7 Hz, C12H), 4.65, 4.69 (each 1H, d, *J*=1.8 Hz, PhCH_2O), 5.01 (1H, dd, *J*=1.0, 4.1 Hz, C13*H*), 6.97 (2H, br

d, J=7.3 Hz, aromatic protons), 7.07 (2H, tt, J=1.2, 7.3 Hz, aromatic protons), 7.14 (1H, tt, J=1.2, 7.3 Hz, aromatic proton), 7.16 (s, C4*H*OMe), 7.48 (1H, tt, J=1.5, 5.7 Hz, aromatic protons), 7.74 (2H, tt, J=1.5, 5.7 Hz, aromatic proton), 8.28 (1H, br s, N16*H*), 11.03 (1H, br s, N5*H*). EI-MS (rel. int.%): m/z=567 (0.43, M^+), 550 (0.30, $[M-OH]^+$), 536 (0.30, $[M-CH_3O]^+$), 524 (0.40, $[M-CH_3CO]^+$), 476 (1.1, $[M-BnOH]^+$), 105 (84, $PhCO^+$), 91 (100, $PhCH^{2+}$). CI-MS (isobutane): m/z=568 (MH^+), 550 ($[M-OH]^+$), 536 ($[M-CH_3O]^+$).

References

1. Parts of this series of papers have been the subject of five preliminary communications: (a) Hashimoto, M.; Yamada, K.; Terashima, S. *Chem. Lett.* **1992**, 975. (b) Hashimoto, M.; Matsumoto, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1994**, *35*, 2207. (c) Hashimoto, M.; Terashima, S. *Chem. Lett.* **1994**, 1001. (d) Hashimoto, M.; Terashima, S. *Tetrahedron Lett.* **1994**, *35*, 9409. (e) Hashimoto, M.; Terashima, S. *Heterocycles* **1998**, *47*, 59.
2. For preliminary communications, see Ref. 1c,d.
3. Hata, T.; Koga, F.; Sano, Y.; Kanamori, K.; Matsumae, A.; Sunagawa, R.; Hoshi, T.; Shima, T.; Ito, S.; Tomizawa, S. *Antibiot. Ser. A.* **1954**, *7*, 107.
4. Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 3807.
5. Yokoi, K.; Nagaoka, K.; Nakashima, T. *Chem. Pharm. Bull.* **1986**, *34*, 4554.
6. For reviews on the chemical synthesis of carzinophilins A and B, see (a) Coleman, R. S. *Synlett* **1998**, 1031. (b) Hodgkinson, T. J.; Shipman, M. *Tetrahedron* **2001**, *57*, 4467.
7. See references in Part 1 of this series of papers. Hashimoto, M.; Matsumoto, M.; Terashima, S. *Tetrahedron* **2003**, *59*, 3019.
8. Coleman, R. S.; Li, J.; Navarro, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 1736.
9. Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555.
10. Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc, Chem. Commun.* **1989**, 297.
11. Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C.; Bossone, E. *Synthesis* **1985**, 609.
12. Pedersen, B. S.; Lawesson, S.-O. *Tetrahedron* **1979**, *35*, 2433.
13. Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem.* **1968**, *33*, 1679.
14. Hoyng, C. F.; McKenna, M.; Novak, K. *Syn. Commun.* **1980**, *10*, 761.
15. Levin, J. I.; Turos, E.; Weinreb, S. M. *Syn. Commun.* **1982**, *12*, 989.
16. Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.
17. PC Spartan Pro Ver.1.08 (Wavefunction Inc.) was employed for calculations.
18. Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.
19. Kunz, H.; Unverzagt, C. *Angew. Chem. Int. Ed.* **1984**, *23*, 1984.
20. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc, Chem. Commun.* **1987**, 1625.
21. Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462.
22. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.
23. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
24. Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
25. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
26. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
27. In the previous communication. Hashimoto, M.; Matsumoto, M.; Terashima, S. *Tetrahedron* **2003**, *59*, 3019.
28. Hayakawa, Y.; Kato, H.; Uchiyama, H.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400.
29. Armstrong, R. W.; Tellew, J. E.; Moran, E. J. *J. Org. Chem.* **1993**, *58*, 7848.
30. Hashimoto, M.; Sugiura, M.; Terashima, S. *Tetrahedron* **2003**, *59*, 3063.
31. Chang, P. K.; Lachman, L. B.; Handschumacher, R. E. *Int. J. Pept. Prot. Res.* **1979**, *14*, 27.