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Synthetic studies of carzinophilin. Part 3: Synthetic approach toward carzinophilin and successful synthesis of 13-*O*-desacetyl-12,13-di-*O*-benzyl-4-*O*-methylcarzinophilin☆

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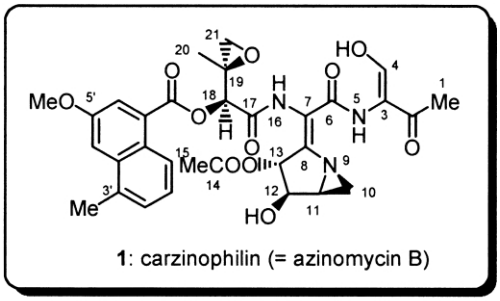
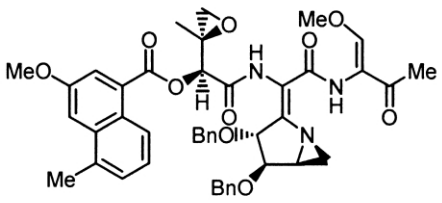
Abstract—The synthetic procedures of the title compound (**2**), a protected form of carzinophilin (**1**), were developed. While efforts toward the total synthesis of **1** failed, comparison of the ^{1}H NMR spectra of **2** and some other related compounds with that of **1** provided definite support for the absolute stereochemistry of **1** which has a complicated history regarding its structure.

1. Introduction

Carzinophilin (**1**) is an antitumor antibiotic isolated from *Streptomyces sahachiroi* by Hata et al. in 1954.[3] It was proved that **1** has 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 attracted chemists to study total synthesis of this compounds.[4,6,7] Recently, Coleman et al. reported their successful total synthesis of azinomycin A lacking the C4-hydroxymethylene group of **1**.[8] However, synthesis of **1**, more functionalized on the right-hand C1–C6 unit, has not been accomplished yet. In the course of our synthetic studies on **1**, we have developed a series of synthetic methods for (i) an aziridine formation reaction giving 1-azabicyclo[3.1.0]-hexan-2-ylidene system,[1a] (ii) a protocol which provides the C8–C13 pyrrolidine ring stereoselectively,[1c] (iii) an efficient method giving the pyrrolidin-2-ylidene system by a coupling reaction between a 4*H*-oxazol-5-one (azlactone) and a methyl thioimidate followed by azlactone ring-opening,[1d] and (iv) a protocol preparing the C1–C6 β-hydroxy enamide system constituting another structural characteristic of **1**.[1d] We have succeeded in the synthesis of various analogues of **1** by employing these methodologies.[1a–d] Although our further efforts have not culminated in a complete total synthesis of **1**, we succeeded in achieving the preparation of 13-*O*-desacetyl-12,13-di-*O*-benzyl-4-*O*-methylcarzinophilin (**2**), the protected form of **1**. Spectral comparisons of natural product **1** with synthetic **2** as well as some related analogues definitely established the structure of carzinophilin, which had been revised several times, as shown.[1e] Now we would like to disclose full details of these studies.



1: carzinophilin (= azinomycin B)



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2. Results and discussion

2.1. Synthetic plan

We have reported that *N*-benzoyl protected dehydropeptide **I** can be readily prepared by employing a phenylazlactone

☆ See refs 1 and 2.

Keywords: azlactone; pyrrolidine unit; dehydropeptide; 13-*O*-desacetyl-12,13-di-*O*-benzyl-4-*O*-methylcarzinophilin.

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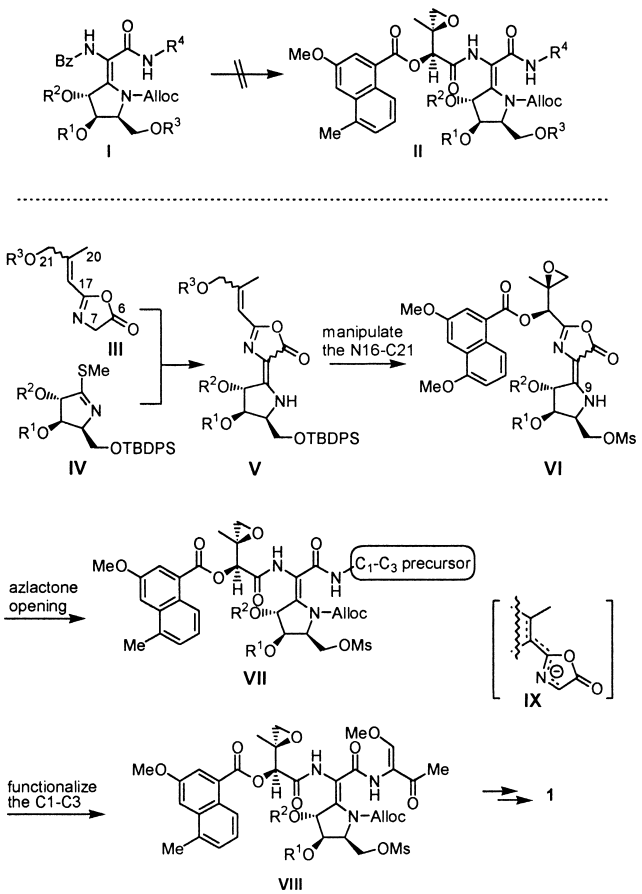
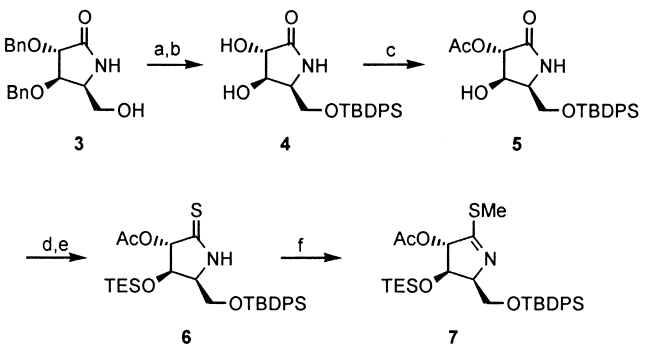
(2-phenyl-4*H*-oxazol-5-one) prepared from hippuric acid. However, it was found the *N*-benzoyl group cannot be replaced with a C17–C21 unit in spite of many efforts. Accordingly, we decided to introduce the C17–C21 framework into the azlactone ring prior to the coupling with methylthioimidate **IV**. We have also disclosed that the azlactone ring is required to carry a substituent, which stabilizes the anionic species **IX** for the coupling reaction with pyrrolidine moiety **IV**. Therefore, an azlactone **III** carrying the 2-alkoxymethylpropen-1-yl group was anticipated to be promising as the coupling unit. The C18–C21 moiety was expected to be functionalized stereoselectively after the coupling reaction with **IV**. Taking our previous studies into account, Alloc protection of the N9 position of the (pyrrolidin-2-ylidene)azlactone **VI** might activate the azlactone ring to receive the amine of the C1–N5 equivalent, the right segment of **1**, and the β-hydroxy enamide system could be constructed by the procedure recently developed.[1d] It was expected that a basic treatment might effect the aziridine ring closure to provide azinomycin **1** after deprotection (Scheme 1).



Scheme 1. Synthetic plan based on the preceding studies.

2.2. Preparation of the C8–C13 pyrrolidine unit

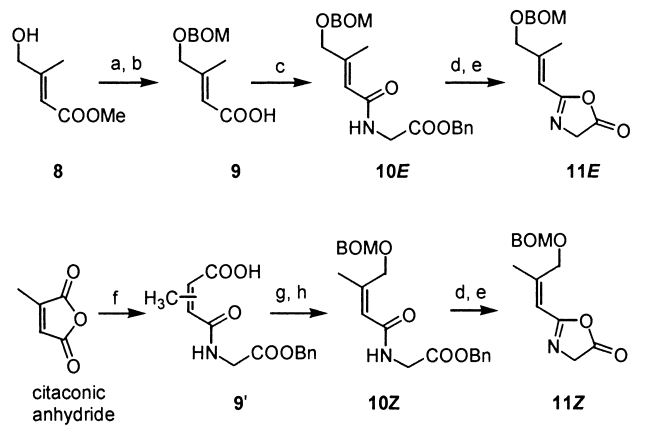
Preparation of the C8–C13 pyrrolidine commenced with 3,4-dibenzyloxy-5-hydroxymethylpyrrolidin-2-one (**3**).[1c] After the benzyl groups of **3** were removed by catalytic reduction, the primary alcohol was protected as a TBDPS ether to give **4** in 85% yield for two steps. Selective acetylation of the C3-hydroxyl group (the C13 position of carzinophilin **1**) was achieved by treating with AcCl (1.1 equiv.) and pyridine (0.82 equiv.) in the presence of DMAP (0.15 equiv.), affording acetate **5** in 89% yield. After protection of the remaining alcohol as a TES ether, the lactam moiety was converted into thiolactam by treating with Lawesson's reagent[9] (→**6**). Methyl thioimidate **7** was obtained in a good yield by treating **6** with excess methyl iodide in CH_2Cl_2. The crude **7** was subjected to the next coupling reaction without purification (Scheme 2).



Scheme 2. Synthesis of the C7–C13 unit. *Reagents and conditions*: (a) H_2, 20% $Pd(OH)_2$/C, MeOH, rt, 12 h. (b) TBDPSCl, ImH, DMF, rt, 85% 2 steps. (c) AcCl, cat. DMAP, pyridine, CH_2Cl_2, −20°C→rt, 12 h, 89%. (d) TESCl, ImH, DMF, 0°c→rt, 90%. (e) Lawesson reagent, toluene, 60°C, 30 min 99%. (f) MeI, CH_2Cl_2, rt, in the dark, 3 h, 99%.

2.3. Preparation of the azlactone bearing C6–C7–N16–C21 unit

As described, our preliminary experiments revealed that (*E*)-4-(2-alkoxymethylpropenyl)azlactones (**11***E*) or its *Z*-isomer **11***Z* might be promising for the C6–C7–N16–C21 unit. As shown in Scheme 3, the alcoholic function of ethyl (*E*)-3-hydroxymethyl-2-butenoate (**8**), prepared according to the procedure reported by Garner et al.,[10] was protected with a BOM group, and subsequent saponification provided carboxylic acid **9**. Condensation of **9** with glycine benzyl ester using 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (WSCI·HCl),

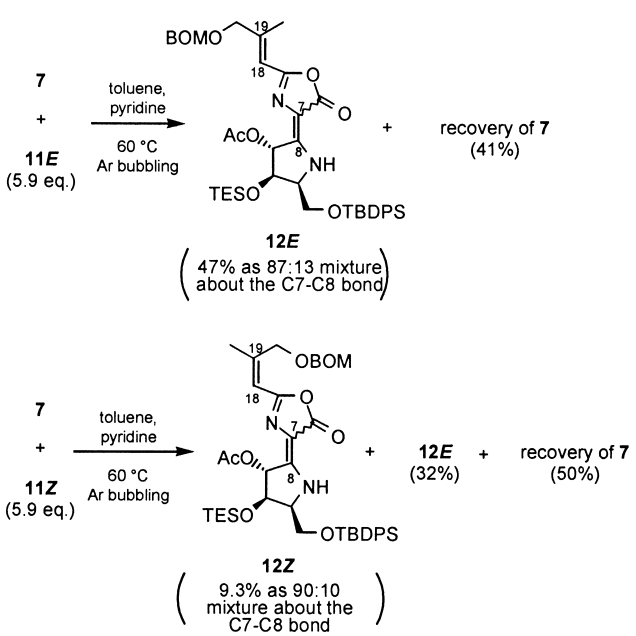


Scheme 3. Synthesis of the C6–C7–N16–C21 azlactones **11***E* and **11***Z*. *Reagents and conditions*: (a) BOMCl, *i*-PrNEt$_2$, CH_2Cl_2, rt, 12 h. (b) NaOH, H_2O, THF, 60°C, 12 h. (c) Gly-OBn·*p*-TsOH WSCI·HCl, Et_3N, CH_2Cl_2, rt. 12 h, 85% 3 steps. (d) NaOH, H_2O, THF, rt, 99% (for both **11***E* and **11***Z*). (e) CMCD (see text), THF, rt, 99%, (for both **11***E* and **11***Z*). (f) Gly-OBn·*p*-TsOH, Et_3N, −10°C, 40 min, 97%. (g) *i*-PrO$_2$CCl, Et_3N, THF, 0°C, 10 min then $NaBH_4$ 10 min, 63%. (h) BOMCl, *i*-PrNEt$_2$, CH_2Cl_2, rt, 12 h, 57%.

gave benzyl *N*-acylglycinate **10***E* in 85% for three steps. After saponification, dehydration employing 1-cyclohexyl-3-(2-morphorinoethyl)carbodiimide metho-*p*-toluenesulfonate (CMCD)[11] in THF at room temperature effected the azlactone ring formation producing **11***E* in a quantitative yield. Another *Z*-isomer **11***Z* was also prepared in a stereoselective manner as follows. On treatment of commercial citraconic anhydride with glycine benzyl ester *p*-toluene sulfonate in the presence of Et_3N, the addition reaction at the C4-position proceeded regioselectively (selectivity=87:13), affording a mixture of carboxylic acids **9′**. The carboxylic acid moiety of **9′** was reduced selectively by way of a mixed anhydride, and the newly produced hydroxyl group was protected as a BOM ether. Following saponification of the ester moiety gave the corresponding glycine derivative in a pure form after recrystallization. Similar dehydration with CMCD to that described above gave **11***Z* also in quantitative yield without isomerization of the *Z*-geometry about the olefin moiety.

2.4. Coupling the azlactones 11*E* and 11*Z* with the C8–C13 pyrrolidine unit 7

With **11***E* and **11***Z* in hand, the coupling reaction with *S*-methyl thioimidate **7**, the C8–C13 pyrrolidine unit was examined (Scheme 4). It was found that coupling product **12***E* was obtained in 47% yield based on the amount of **7** employed, by heating with 5.9 equiv. of **11***E* in a mixture of toluene and pyridine with bubbling of argon gas during the reaction. The starting **7** (41%) was recovered under these conditions. The adduct **12***E* was found to be an 87:13 tautomeric mixture about the C7–C8 double bond (*carzinophilin numbering*) based on its ^1H NMR spectrum. On the other hand, the same treatments employing **11***Z* brought about isomerization of the C18–C19 double bond to produce **12***Z* in 9.3% yield as a tautomeric mixture about the C7–C8 double bond (*E*/*Z*=90:10) along with **12***E* (32%) and recovered **7** (50%). Two-dimensional silica gel TLC analysis of the mixture of **12***E* and **12***Z* revealed that the



Scheme 4. Coupling of methylthioimidate **7** with azlactones **11***E* and **11***Z*.

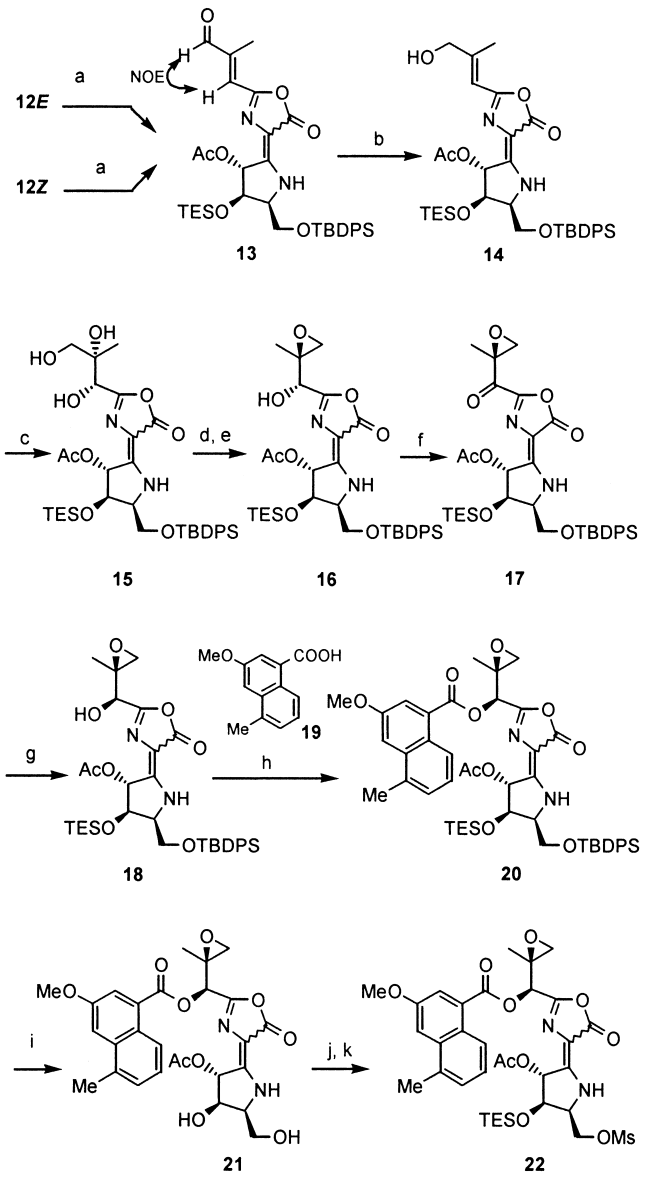
C18–C19 double bond did not isomerize under standard TLC conditions, although tautomerism about the C7–C8 double bond was observed (**12***E*: R_F=0.50 and 0.58, **12***Z*: R_F=0.54 and 0.62; developed with hexane–AcOEt=70:30). Interestingly, these isomers could be separated by careful silica gel column chromatography.

2.5. Elaboration of the C17–C21 functionalities

Contrary to our expectation, hydrogenolysis of the BOM ether in **12***E* employing Pd/C–H_2 failed, and those conditions selectively reduced the C7–C8 double bound. The BOM group of **12***E* was found to be removed smoothly by DDQ oxidation[12] giving aldehyde **13** in 72% yield as an 87:13 mixture of tautomers concerning to the C7–C8 double bond (*carzinophilin numbering*). Interestingly, the same reaction with **12***Z* effected complete isomerization of the C18–C19 double bond, providing **13** in 85% yield. This sample was identical to that prepared from **12***E* in all respects. The stereochemistry of the C18–C19 double bond was determined by observing cross-peaks between the protons for aldehyde and the C18H of both tautomers in their phase-sensitive NOESY spectra. In a preparative scale, crude **13** was directly reduced with $NaBH_4$ without purification to provide alcohol **14** as a mixture of the two tautomers concerning to the C7–C8 double bonds in 82% yield for two steps. As described, we could obtain only *E*-isomer **14**.

According to the *E*-stereochemistry of the C18–C19 double bond, two oxygens should be introduced in an *anti*-relationship. Specifically, the Sharpless asymmetric epoxidation[13] is plausible for this purpose. However, the epoxide obtained by the epoxidation of **14** suffered epoxide ring opening under the standard Sharpless's conditions (TBHP, $Ti(O^iPr)_4$, DIPT) giving the tartarate and isopropanol adducts probably due to the electron-donating azlactone ring.[14] Next, Sharpless asymmetric dihydroxylation[15] of **14** was investigated as an alternative route. It was found that oxidation of **14** with a stoichiometric amount of $(DHQ)_2$-PHAL (1.3 equiv.) and OsO_4 (1.1 equiv.) in CH_2Cl_2 and subsequent degradation of the osmate ester with H_2S gas gave β-triol **15** in 69% yield with nice stereoselectivity (α/β=90:10). Catalytic conditions (AD-mixα, $CH_3SO_2NH_2$) for **14** provided only a trace amount of the product. The reaction using (DHQ)CLB in place of $(DHQ)_2$PHAL reduced the desired α-selectivity. When dihydroxylation of **14** was performed with a stoichiometric amount of $(DHQD)_2$PHAL, the corresponding diastereomer was obtained with complete stereoselectivity. These results suggested that α-selective dihydroxylation of **14** is a so-called 'miss-match' reaction from the viewpoint of double asymmetric induction. The stereochemistry of this dihydroxylation reaction was assigned based on the Sharpless rule (Scheme 5).[15]

The primary hydroxyl group of **15** was mesylated selectively with MsCl in the presence of γ-collidine, and subsequent treatment with DBU took place formation of an *exo*-epoxide to give **16** in 75% yield for two steps. Since the stereochemistry of a hydroxyl group at the C18 in **16** was different from that of **1**, the C18 hydroxyl group was inverted. Mitsunobu inversion[16] for **16** employing the



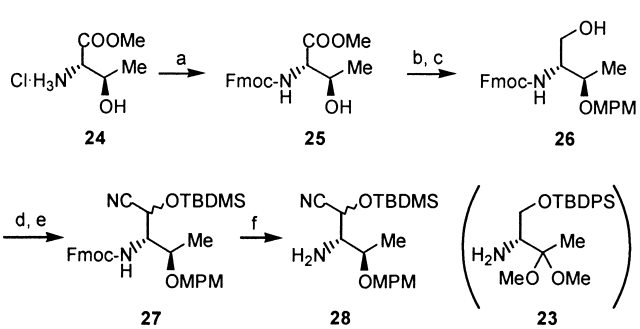
Scheme 5. Elaboration of the C17–C21 functionalities. *Reagents and conditions*: (a) DDQ, CH_2Cl_2, H_2O, 30 min, 85% (from **12***E*), 85% (from **12***Z*). (b) $NaBH_4$, MeOH, 30 min, 82% 2 steps. (c) $(DHQ)_2PHAL$ (1.4 equiv.), OsO_4 (1.1 equiv.), CH_2Cl_2, 0°C, 15 min, 69% (80% de). (d) MsCl, γ-collidine, CH_2Cl_2, 0°C, 2 h. (e) DBU, THF, rt, 1 h, 75% 2 steps. (f) Dess–Martin reagent, CH_2Cl_2, rt, 2 h, 84%. (g) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, −15°C, 10 min, 95%, 80% de. (h) **19**, WSCI·HCl, DMAP, CH_2Cl_2, rt, 97%. (i) TBAF, AcOH, THF, rt, 3 h, 98%. (j) MsCl, γ-collidine, CH_2Cl_2, 0°C, 2 h, 67% (14% recovery of **21**). (k) TESCl, ImH, DMF, rt, 10 min, 97%.

naphthoic acid **19** was found to be fruitless, then sequential oxidation–reduction protocol was examined next. Oxidation of **15** with Dess–Martin reagent[17] gave ketone **17** in 84% yield. Fortunately, **17** was obtained as needles so that recrystallization of **17** removed the minor diastereomer derived in the dihydroxylation step. β-Stereoselective reduction of **17** was achieved by the combined use of $CeCl_3{\cdot}7H_2O$ and $NaBH_4$ in MeOH[18] at 15°C providing **18** in 95% yield with 80% de. When the reduction was performed with $Zn(BH_4)_2$ in Et_2O,[19] the diastereoselectivity was 60% de. The stereochemistry of **18** was determined by comparing its ^1H NMR spectra with that of α-alcohol **16**.

Esterification of **18** with the naphthoic acid **19**[20] was performed employing WSCI·HCl and DMAP in CH_2Cl_2, to afford epoxy ester **20** in 96% yield. Both the TBDPS and TES groups of **20** were removed with TBAF in the presence of AcOH, giving diol **21** in 98% yield. The reaction without using AcOH gave rise to sequential elimination of the naphthoate moiety by 1,6-elimination (between the N9H and the C18OCOAr) and hydration to produce a mixture of **16** and **18** along with their desilylated compounds. Selective mesylation of the primary hydroxy group in **21** using MsCl and γ-collidine and subsequent protection of the C12OH with a TES group furnished the C6–C22 unit **22**. Similarly to **12***E* and **12***Z*, all the (pyrrolidin-2-ylidene)azlactones **13**–**16**, **18**, and **20**–**22** except for **17** were found to be obtained as mixtures of the two tautomers arising from their C7–C8 double bonds. The ratio of these tautomers changed from 50:50 to 80:20 in favor of the *E*-isomers.

2.6. Preparation of the novel C1–N5 unit

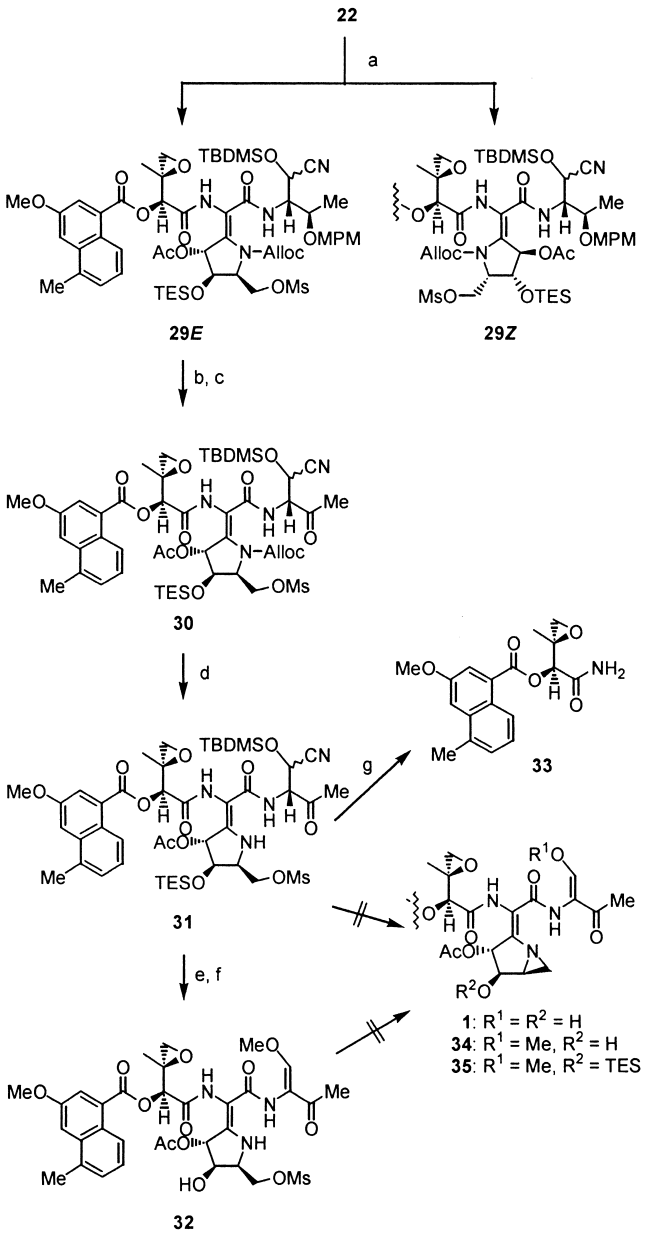
Although we had developed amine **23** as the C1–N5 unit which brought us successful preparation of the C1–C17 model compounds,[1c] our preliminary experiments revealed that the acetal moiety of **23** was not stable enough to be utilized for preparing carzinophilin (**1**). Thus, we designed the alternative C1–N5 unit **28**, which was expected to be more stable under acidic conditions. Commercial L-threonine methyl ester hydrochloride (**24**) was first converted into the 9-fluorenylmethoxycarbonyl (Fmoc) derivative **25** in a quantitative yield by using FmocCl[21] and $NaHCO_3$ under aqueous conditions. After the hydroxyl group in **25** was converted into a MPM ether employing Yonemitsu's imidate,[22] the ester moiety was reduced with $Zn(BH_4)_2$ in Et_2O to provide alcohol **26** in 58% yield for two steps. Oxidation of **26** with Dess–Martin reagent and subsequent treatment with TBDMSCN in CH_3CN at 80°C resulted in the formation of *O*-silyl cyanohydrin, **27** in 92% yield for two steps as a mixture of the diastereomers about the cyanohydrin moiety. Removal of the Fmoc groups of **27** was achieved by treating with piperidine to afford **28** as a diastereomeric mixture in 90% yield. While these diastereomers were separated by silica gel column chromatography, only the major polar isomer was used for the next step in consideration of operational simplicity (Scheme 6).



Scheme 6. Preparation of the improved C1–N5 unit. *Reagents and conditions*: (a) FmocCl, $NaHCO_3$, dioxane, H_2O, rt, 1 h, 99%. (b) $MPMC(=NH)CCl_3$, cat. TfOH, Et_2O, rt, 3 h. (c) $Zn(BH_4)_2$, Et_2O, rt, 12 h, 58% 2 steps. (d) Dess–Martin reagent, CH_2Cl_2, rt, 30 min. (e) TBDMSCN, CH_3CN, 80°C, 3 h, 92% 2 steps. (f) Piperidine, DMF, rt, 1 h (90%), then separation of the major polar isomer.

2.7. Opening the azlactone ring to furnish the dihydropeptide system and attempts toward completing the total synthesis of carzinophilin[1]

According to the information accumulated, the azlactone rings of **22** (a 73:27 mixture of the two tautomers) was activated by carbamoylation of the N9 position (*carzinophilin numbering*) with an Alloc group by treating with $Alloc_2O$ in the presence of a catalytic amount of DMAP (5 mol%). Successively, amine **28** was added to the reaction mixture without work-up, and the whole mixture was heated at 40°C in high concentration. These operations effected the opening of the azlactone ring providing *E*-dehydropeptide

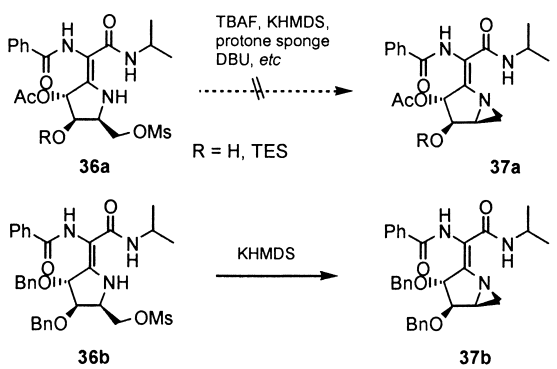


Scheme 7. Construction of the right hand moiety and attempts for completion of the total synthesis. *Reagents and conditions*: (a) cat. DMAP, Alloc2O, THF, rt, 10 min, then **28**, concentration on rotary evaporator at 40°C for 15 min, 69% (**29***E*), 3.3% (**29***Z*). (b) DDQ, CH_2Cl_2, H_2O, 1 h, 97%. (c) Dess–Martin reagent, CH_2Cl_2, rt, 40 min, 97%. (d) $Pd(PPh_3)_4$, PPh_3, AcOH, THF, rt, 10 min, 100%. (e) TBAF, AcOH, THF, 3 h, then aq. $NaHCO_3$, 10 min. (f) CH_2N_2, Et_2O, 1 h, 82% 2 steps. (g) DBU, CH_2Cl_2, rt, 4 h, low yield.

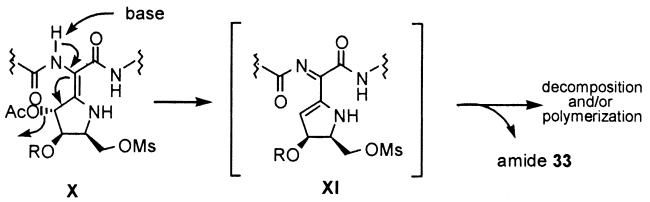
29*E* in 69% yield along with its *Z*-isomer **29***Z* as a minor product (3.3% yield). These isomers were readily separated by silica gel column chromatography. When a larger amount of DMAP was employed for the reaction, yields of products decreased considerably due to production of polar materials. Comparison of the ^1H NMR spectra of **29***E* and **29***Z* with those of the model compounds previously synthesized made it possible to assign their stereochemistries at the C7–C8 double bond. Specifically, the signal for C13H of **29***E* was observed at 5.12 ppm, while that of **29***Z* was at 6.41 ppm in their ^1H NMR spectra. We have already established that signals for the C13H of the *E*-isomers appear around 1 ppm higher field than those of the *Z*-isomers and this phenomena was confirmed by NOE experiments using some model compounds. Accordingly, the stereochemistry of the C7-C8 moiety of **29***E* and **29***Z* was established to be *E*- and *Z*-configuration, respectively (Scheme 7).

Elaboration of the C1–N5 moiety was next studied. After removing the MPM group of **29***E* by DDQ oxidation, the reproduced alcoholic moiety was further oxidized with Dess–Martin reagent to give β-keto cyanohydrin **30** in 94% yield for two steps. The *N*-Alloc group of **30** was cleaved by employing $Pd(PPh_3)_4$-catalyzed reaction in the presence of AcOH,[23] giving the pyrrolidine **31** in a quantitative yield. Contrary to the precedent model compounds, removal of the Alloc group did not give rise to the tautomerism of the C7–C8 double bond, so that **31** was obtained as a single *E*-isomer. The protected cyanhydrin moiety of **31** was deassembled by cleaving the TBDMS ether and subsequent basic treatment. These operations also cleave the TES group. The product was isolated after converting it into the corresponding methyl enol ether with CH_2N_2 affording **32** in 82% yield for two steps.

With the dehydropeptide systems **31** and **32** in hand, construction of the aziridine ring was next attempted. All the conditions so far examined (DBU, KHMDS, TBAF, and phosphazene base P_4–*t*Bu etc.) gave fruitless results, and complex mixtures were obtained, in spite of the fact that some of those conditions brought us successful aziridine formation in the previous model synthesis. This aziridine ring formation was further investigated by employing model **36a** (Scheme 8). However, all the attempts also did not achieve the aziridine formation giving **37a**. In contrast, we have already proved that the model compound **36b**, bearing two benzyloxy groups at the C12 and C13 positions, is



Scheme 8. Aziridine ring formation using the model compounds.



Scheme 9. Proposed pathway for decomposition of **31**, **32a,b**, and **36a**.

cleanly cyclized to give **37b** by employing KHMDS as the base.

Taking these results into account, **31**, **32** and **36a** might be explained by the base-induced 1,4-elimination of the C13-acetate, producing imine **XI**, which decomposes or polymerizes under the reaction conditions as shown in Scheme 9. Notably, treatment of **31** with DBU in CH_2Cl_2 gave amide **33** in a low yield. Amide **33** might be derived from **XI**, and is known to be isolated from the culture broth along with AZs.[5] Since the leaving ability of an acetate function in **36a** is obviously higher than that of the benzyloxy group in **36b**, we expected that the aziridine constructing reaction employing the mesylate **38**, which bears the same two benzyl groups as **36b**, can proceed to furnish the whole carbon framework of carzinophilin (**1**) albeit in a protected form (Fig. 1).

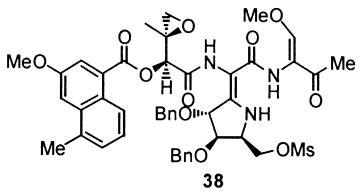


Figure 1. Structure of **38**.

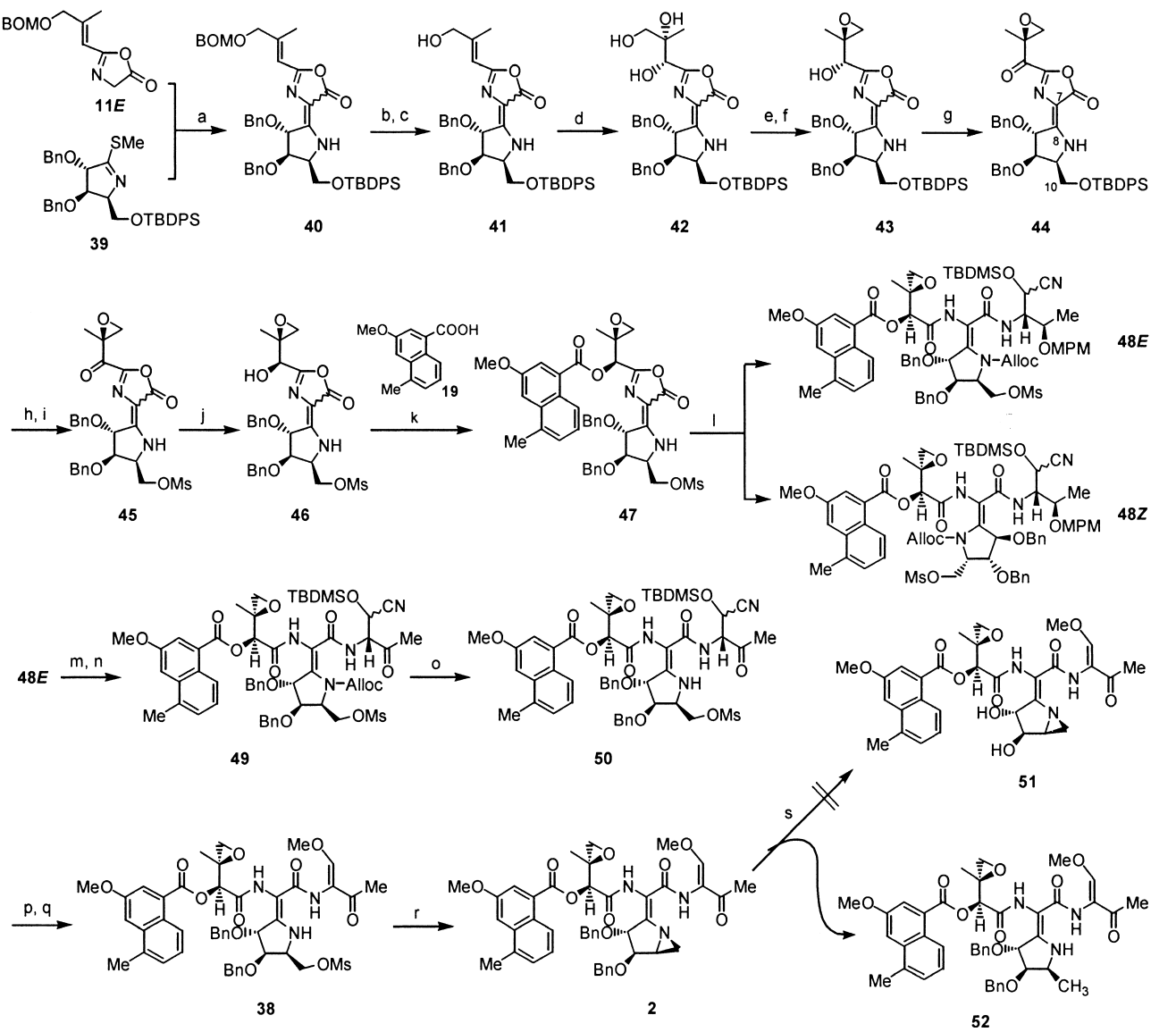
2.8. Successful preparation of 4-*O*-methyl-13-desacetyl-12,13-di-*O*-benzylcarzinophilin 2

As shown in Scheme 10, mesylate **38** was synthesized by a synthetic route similar to that employed for the preparation of **32** with small modifications. Coupling reaction of azlactone **11***E* with methyl thioimidate **39** proceeded in the absence of pyridine, affording the adduct **40** in 58% yield with 17% recovery of **39**. Sequential oxidative cleavage of the BOM ether by DDQ and reduction of the produced aldehyde gave the alcohol **41** in slightly better yield than that of **14** from **12***E*. Being different from the case of **14**, the dihydroxylation of **41** with a stoichiometric amount of OsO_4–$(DHQ)_2PHAL$ was found to proceed in a highly diastereoselective manner, giving triol **42** in 65% yield. The minor diastereomer was not observed in its 400 MHz ^1H NMR spectrum. Thus, the enantiomeric purity of this sample was estimated to be >96% de. After mesylation of the primary alcohol in **42**, the C19–C21 epoxide was introduced by treating with DBU, to provide epoxy alcohol **43**. Then, **43** was converted into epoxy ketone **44** by Dess–Martin oxidation. The ketone **44** was obtained as prisms after recrystallization (mp 145–147°C). The ^1H NMR spectrum measured right after dissolving crystalline **44** with $CDCl_3$ indicated the sole existence of the *E*-isomer about the C7–C8 double bonds (*carzinophilin numbering*), however, signals of corresponding *Z*-isomer gradually appeared after standing the solution at room temperature for 3 h (*E*/*Z*=93:7) and this isomerization attained an equilibrium after 18 h (*E*/*Z*=88:12). Other compounds **40**–**43**,**45**–**47** carrying the azlactone rings were observed as mixtures of the two tautomers (*E*/*Z*=56:44–80:20). Epoxy ketone **44** was insoluble in MeOH which was a preferable solvent for $NaBH_4$–$CeCl_3$ reduction of **17**. Ethanol dissolved **44** well, but the reduction in EtOH gave a complex mixture. Thus, the C10 function of **44** was converted into mesylate **45** prior to the reduction. It was found that mesylate **45** was soluble in MeOH and cerium (III) assisted $NaBH_4$ reduction of **45** in MeOH proceeded stereoselectively (80% de) to provide **46** in 90% yield. The minor α-isomer was removed at the stage of **48**. After the naphthoic acid **19**[20] was attached, the dehydropeptide chain was furnished by sequential N9-carbamoylation and azlactone opening with amine **28**, giving rise to **48***E* and **48***Z*. Similar operations to those described for the preparation of **32** from **29***E* elaborated the C1–C4 functionalities giving **38**. As expected, treatment of **38** with TBAF in the presence of powdered molecular sieves 4A in THF took place the aziridine ring formation furnishing 4-*O*-methyl-13-desacetyl-12,13-di-*O*-benzylcarzinophilin (**2**) in 47% yield. The product was found to be stable enough to be isolated in a pure state by preparative silica gel TLC. The ^1H NMR spectral data of **2** closely resembled that reported for AZB-4-*O*-Me (**54**) by Yokoi et al.[5] except for the chemical shift of C13–H where an acetoxy group is replaced with a benzyloxy group as shown in Table 1. Needless to say, the ^1H NMR spectrum of **2** was also closely coincident with that of our model compounds **53** about the C1–N16 proton signals and not with that of Armstrong's *Z*-isomer **55**. This spectral feature is anticipated to definitely support Yokoi's structure of **1**.

Expecting to further advance the synthetic scheme to **1**, we next examined removal of the two benzyl groups, which protect the two hydroxy groups at the C12 and C13 positions. However, all the attempts met with failure. For example, the hydrogenolytic condition using Pd/C in AcOEt resulted in selective aziridine ring-opening to give 2-methylpyrrolidine **52** in 47% yield with recovery of **2** (24%). Formation of diol **51** was not observed at all. These results led us to conclude that it is impossible to obtain **1** from **2**.

2.9. Relationship of the stereochemistry between the C18 and those of the pyrrolidine moiety

The relative stereochemistry about the C11, C12, and C13 positions of azinomycin B (=carzinophilin **1**) has been established as 11*S**,12*R**, and 13*R** by detailed NOE experiments in the Yokoi's report.[5] On the other hand, the absolute stereochemistry of C18 has been proposed as *S* configuration based on amide **33** isolated from the same culture broth as that producing **1** (Fig. 2). However, the stereochemical relationship between C18 and the pyrrolidine moiety has not been discussed well. Although Coleman et al. reported the total synthesis of azinomycin A, the natural analogue of **1** lacking C4 enol system, they did not mention the stereochemical relationships between them. Accordingly, four diastereomers of the model compounds **57***SE*, **57***SZ*, **57***RE*, and **57***RZ* were synthesized as shown in

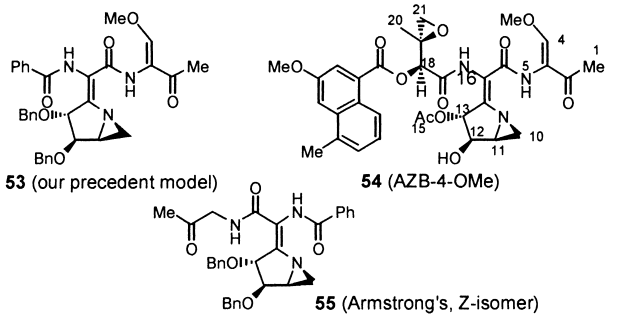


Scheme 10. Successful preparation of 4-*O*-methyl-13-desacetyl-12,13-di-*O*-benzylcarzinophilin. *Reagents and conditions*: (a) toluene, 60°C, Ar gas bubbling, 12 h, 58% (17% recovery of **39**). (b), DDQ, CH_2Cl_2, H_2O, rt, 30 min. (c) $NaBH_4$, MeOH, 0°C, 30 min, 97% 2 steps. (d) $(DHQ)_2PHAL$ (1.2 equiv.), OsO_4 (0.99 equiv.), CH_2Cl_2, −10°C, 15 min, then H_2S, 65% (96% de). (e) MsCl, γ-collidine, CH_2Cl_2, 0°C, 4 h, 81%. (f) DBU, THF, 0°C, 30 min, 84%. (g) Dess–Martin reagent, CH_2Cl_2, 40 min, 92%. (h) TBAF, THF, rt, 12 h. (i) MsCl, γ-collidine CH_2Cl_2, rt, 1 h, 83% 2 steps. (j) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 94% (80% de). (k) WSCI·HCl, DMAP, CH_2Cl_2, rt, 12 h, 91%. (l) $Alloc_2O$, DMAP (0.11 equiv.), 15 min, then **28**, concentration on rotary evaporator at 50°C, 40 min. 78% (**48***E*), 2% (**48***Z*). (m) DDQ, CH_2Cl_2, H_2O, rt, 1 h, 94%. (n) Dess–Martin reagent CH_2Cl_2, rt, 1 h, 98%. (o) $Pd(PPh_3)_4$, PPh_3, AcOH, THF, 89%. (p) TBAF, THF, 2 h, then aq. $NaHCO_3$, 20 min. (q) CH_2N_2, Et_2O, rt, 12 h, 54% 2 steps. (r) TBAF, MS4A, THF, rt, 15 min, 47%. (s) H_2, 10% Pd/C, AcOEt, 3 h, 47%, (24% recovery of **2**).

Scheme 11. Ester **56**, the diastereomer of **20** at C18 position was prepared by acylation of the intermediate **16** with naphthoic acid **19** under the usual conditions. Both **20** and **56** were subjected to the azlactone ring opening reaction with isopropylamine to give stereoisomeric pairs of dehydropeptides **57***SE* and **57***SZ*, and **57***RE* and **57***RZ*, respectively.

With those dehydropeptides in hand, we next studied the ^1H NMR spectral relationship between C18 and the pyrrolidine ring moiety employing four isomers of **57**, carzinophilin (**1**), our synthetic intermediate **32**, and methyl pyrrolidine derivative **58** (Fig. 3). Methylpyrrolidine **58** was derived from **1** by Yokoi et al. in their structure determining studies.[5] First, comparing the chemical shift for C13H between C12-*O*-TES ether **29** and C12 alcohols **32** and **58** suggested that introduction of a TES group at C12 alcohol shifts the C13H signal around 0.2 ppm lower field, however, that small shifting might be disregarded in the discussions. Although isomerization about the C7–C8 double bond of **58** might be possible based on our results obtained in this series of studies, the C7–C8 stereochemistry could be assigned as *E*-geometry, because there is only a small difference of C13H chemical shift between that of **1** and **58**, and we had already disclosed that the C7–C8 stereochemistry affects the chemical shift of C13H. Stereochemistries of the C7–C8 double bonds in four diastereomers of **57** were established by comparing their ^1H NMR spectra with those of our precedent model compounds, the stereochemistries of which had been confirmed based on NOE experiments.

Table 1. Chemical shifts (ppm), signal patterns (parenthesized), and coupling constants (italic, Hz) of **2**, our precedent model compound **53**, AZB-4-OMe **54** (derived from **1**), and Armstrong's *Z*-isomer **55**



Proton	2	53	54	55
1	2.22 (s)	2.23 (s)	2.24 (s)	–
4	7.14 (s)	7.16 (s)	7.19 (s)	–
4-OMe	3.89 (s)	3.89 (s)	3.90 (s)	–
5	10.58 (s)	11.03 (s)	10.89 (s)	6.95 (dd) *4.8, 4.8*
10	2.27 (d) *4.1*	2.30 (d) *4.1*	2.25 (d) *3.9*	2.18 (d) *3.6*
	2.48 (d) *5.1*	2.44 (d) *4.8*	2.51 (d) *5.4*	2.40 (dd) *1, 5.3*
11	3.12 (ddd) *4.1, 4.8, 5.1*	3.10 (ddd) *4.1, 4.7, 4.8*	3.22 (ddd) *3.9, 5.4, 5.8*	3.03 (ddd) *3.6, 4.9, 5.3*
12	4.49 (dd) *3.6, 4.8*	4.59 (dd) *4.1, 4.7*	4.63 (dd) *3.9, 5.8*	4.42 (dd) *1.0, 4.9*
13	4.94 (dd) *1.0, 3.6*	5.01 (dd) *1.0, 4.1*	5.55 (d) *3.9*	5.012 (dd) *1, 1*
16	8.50 (s)	8.28 (s)	8.50 (s)	7.89 (s)
18	5.15 (s)	–	5.08 (s)	–
20	1.53 (s)	–	1.51 (s)	–
21	2.60 (d) *4.6*	–	2.80 (d) *4.3*	–
	2.90 (d)	–	2.99 (s)	–
	4.6	–	*4.3*	–

Similarly to the discussion described in **2.7**, the ^{1}H NMR signals of C13Hs in **29***Z*, **57***SZ*, and **57***RZ* (6.41, 6.41, 6.27 ppm. respectively) appeared around 1.3 ppm lower field than those of the corresponding *E*-isomers **29***E*, **57***SE*, and **57***RE* (5.12, 5.17, 4.84 ppm) due to deshielding by the carbonyl group at C17. Accordingly, comparison of the C13H signals obviously suggested *E*-configurations about the C7–C8 enamine moiety of **1**, methylpyrrolidine derivatives **58**, and **32** (Table 2).

There is a significant difference in the C18H signal between **1** and **58**. However, the stereochemistry of the C18 in **58** must be identical with that of **1**, since **58** was derived from **1**. Thus, it is presumed that the aziridine ring of **1** affects the C18H chemical shift for some reasons. The C18H signals of

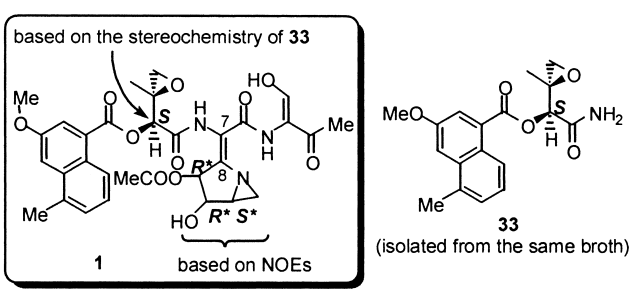
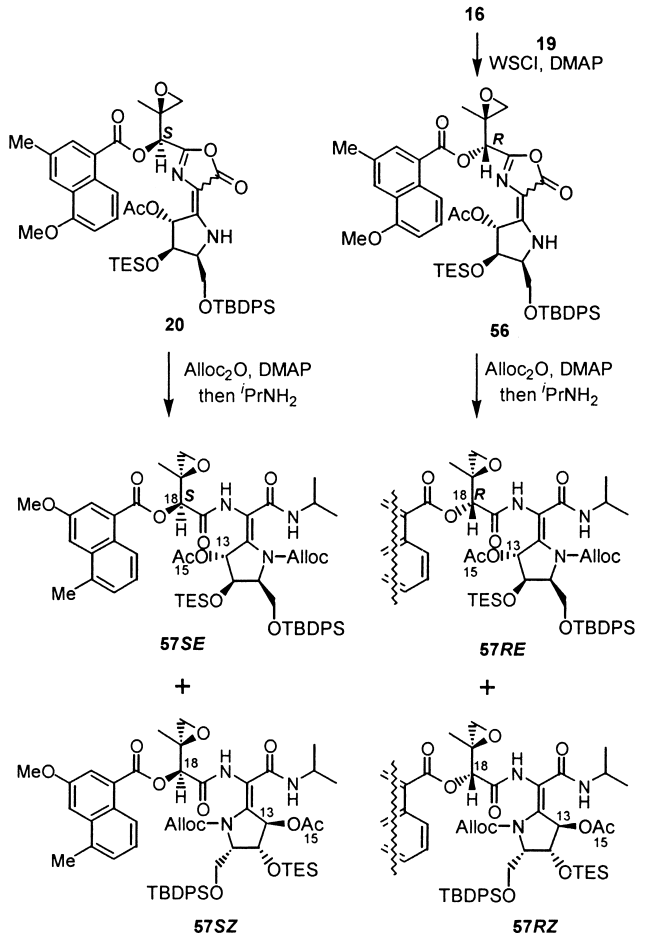


Figure 2. Structure of **33** and planaer structure of **1**.



Scheme 11. Synthesis of four diastereomers **57***SE*, **57***SZ*, **57***RE*, and **57***RZ*.

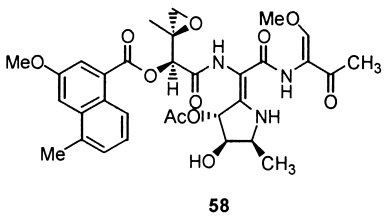


Figure 3. Structure of the methylpyrrolidine derivative **58**.

Table 2. ^{1}H NMR chemical shifts for C13H, C15H, and C18H of **1** and its analogues in $CDCl_3$

	C13H		C15H		C18H	
	C7C8 double bond		C15 position		C18 position	
	E	*Z*	*S*	*R*	*S*	*R*
1	5.53		2.19		5.01	
58	5.36		2.16		5.42	
32	5.37		2.21		5.32	
29*E*	5.12		2.06		5.53	
29*Z*		6.41	2.00		5.43	
57*SE*	5.17		2.04		5.39	
57*SZ*		6.41	2.01		5.45	
57*RE*	4.84			1.59		5.12
57*RZ*		6.27		2.17		5.02

18*S* isomers **32**, **29***E*, **29***Z*, **57***SE*, and **57***SZ* were observed at 5.32–5.53 ppm, while those of 18*R* isomers **57***RE* and **57***RZ* appeared at 5.12 and 5.02 ppm, respectively. These observations disclosed that **1** and **58** carry the same relative stereochemistry about the C13 and the C19 positions as those of **32**, **29***E*, **29***Z*, **57***SE*, and **57***SZ*. The acetyl protons corresponding to C15H$_3$ of them showed normal chemical shifts at 2.0–2.2 ppm. In contrast, that of **57***RE*, carrying another stereochemical relationship between C13 and C18, appeared at 1.59 ppm. This unusual chemical shift might be explained by a shielding effect due to the naphthalene ring in the molecule, although the geometrical relationship between the naphthalene group and C13H is unclear.

On the other hand, the absolute stereochemistries for the C18 and C19 positions of **1** can be identical to those of **33**, being 18*S*, 19*S*, respectively, by taking into account the fact that amide **33** was isolated along with **1** from the same culture broth. Accordingly, stereochemical relationship between C13 and C18 is only required for assigning the absolute stereochemistry for C13 of carzinophilin (**1**). The configuration of C13 of our analogues is incontestably *R* because it comes from the C3 carbon of D-arabinose. By putting these results and considerations together, the stereochemistry of the C13 function of **1** is concluded to be 13*R*, identical to that of **2** which we had synthesized from D-arabinose. Accordingly, these studies might be the first to reveal the absolute stereochemistry of the pyrrolidine ring moiety of **1** as C11*S*, C12*R*, and C13*R*.

3. Conclusion

Although the total synthesis of **1** turned out to be unsuccessful, our synthetic studies culminated in providing 13-*O*-desacetyl-12,13-di-*O*-benzyl-4-*O*-methylcarzinophilin (**2**), the protected form of **1**. Spectral comparisons of **2** with that of **1** confirmed the structure of the natural carzinophilin (**1**) that has had a complicated history regarding its structure. Total synthesis of **1** is still required for final confirmation of its structure, although Coleman has achieved the total synthesis of azinomycin A,[8] the natural analogue of **1** lacking the C4 enol function. Our studies also provided various structural types of azinomycin derivatives. These were subjected to biological assays, which will be the subject of the following report.[24]

4. Experimental

4.1. General

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

4.2. (3*S*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsiloxy)methyl-3,4-dihydroxypyrrolidin-2-one (4)

A suspension of **3** (10.2 g, 31.2 mmol) and 20% Pd(OH)$_2$/C (900 mg) in MeOH (150 mL) was stirred vigorously under H_2 atmosphere at room temperature for 12 h. After the catalyst was removed through a short Celite® column, the eluent was concentrated below 25°C in vacuo. A mixture of the residue, TBDPSCl (11.0 g, 40.1 mmol), and imidazole (6.00 g, 88.1 mmol) in DMF (40 mL) was stirred at room temperature for 12 h. 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_2Cl_2–acetone=50:50) gave **4** (10.2 g, 85% in two steps) as a white powder. Analytical sample was prepared by recrystallization from CH_2Cl_2–hexane to give needles. Mp 142–143°C. $[\alpha]_D^{20}=-72.3°$ (*c* 1.00, $CHCl_3$). IR (nujor): 3300, 3220, 1680, 1120, 710 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04 (9H, s, $(CH_3)_3CSi$), 3.74 (2H, C5C*H*HO, C5*H*), 3.90 (1H, dd, *J*=5.3, 11.7 Hz, C5C*H*HO), 4.45 (2H, m, C3*H*, C4*H*), 6.06 (1H, br, amide proton), 7.40–7.50 (6H, aromatic protons), 7.55–7.65 (4H, aromatic protons). EI-MS (rel int.%): *m*/*z*=386 (trace, MH^+). 328 (6.0, $[M-t\text{Bu}]^+$). 250 (100, $[M-t\text{Bu}-\text{benzene}]^+$). CI-MS (isobutene) *m*/*z*=386 (MH^+). EI-HRMS: Calcd for $C_{21}H_{28}NO_4Si$ (MH^+): *m*/*z*=386.1788. Found: *m*/*z*=386.1786. Anal. calcd for $C_{21}H_{27}NO_4Si$: C, 65.42%; H, 7.06%; N, 3.63%. Found: C, 65.3%; H, 7.13%; N, 3.66%.

4.3. (3*S*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)-methyl-4-hydroxypyrrolidin-2-one (5)

A mixture of **4** (10.1 g, 26.3 mmol), AcCl (2.27 g, 28.9 mmol), DMAP (480 mg, 3.93 mmol), and pyridine (1.87 g, 23.7 mmol) in CH_2Cl_2 (180 mL) was stirred at −23°C The mixture was allowed to warm gradually to room temperature and stirred for 12 h. 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_2Cl_2–acetone=80:20) gave **5** (10.1 g, 89%) as an amorphous solid. $[\alpha]_D^{20}=-31.4°$ (*c* 1.31, $CHCl_3$). IR (film): 3400, 2950, 1720, 1240, 1120, 1090, 740, 710 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (9H, s, $(CH_3)_3CSi$), 2.22 (3H, s, CH_3COO), 3.63 (1H, d, *J*=3.9 Hz, alcoholic proton), 3.75 (2H, C5*H*, C5C*H*HO), 3.96 (1H, dd, *J*=3.7, 10.7 Hz, C5C*H*HO), 4.49 (1H, dt, *J*=3.9, 7.7 Hz, C4*H*), 5.45 (1H, d, *J*=7.7 Hz, C3*H*), 6.10 (1H, br s, amide proton), 7.40–7.50 (6H, aromatic protons), 7.55–7.65 (4H, aromatic protons). EI-MS (rel int.%): *m*/*z*=428 (trace, M^+), 412 (3.6, $[M-Me]^+$), 370 (63, $[M-t\text{-Bu}]^+$), 43 (100, CH_3CO^+). CI-MS (isobutane): *m*/*z*=428 (MH^+). EI-HRMS calcd for $C_{23}H_{30}NO_5Si$ (MH+): *m*/*z*=428.1894. Found: *m*/*z*=428.1872.

4.4. (3*S*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)-methyl-4-(triethylsiloxy)pyrrolidin-2-thione (6)

4.4.1. TES ether formation of 5. A solution of **5** (12.5 g, 29.3 mmol), TESCl (5.70 g, 37.9 mmol), and imidazole (8.00 g, 117 mmol) in DMF (30 mL) was stirred at room temperature for 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 to give (3*S*,4*R*,5*R*)-3-acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(trimethylsiloxy)pyrrolidin-2-one (14.2 g,

90%) as a white solid. Analytical sample was prepared by recrystallization from hexane–AcOEt (75:25) to give needles. Mp 172–174°C. $[\alpha]_D^{20}=-70.9°$ (*c* 1.15, $CHCl_3$). IR (nujor): 3300, 1720, 2700, 1230, 1140, 1110, 1070, 830, 750, 720, 710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.53 (6H, m, $(CH_3CH_2)_3Si$), 0.88 (9H, t, *J*=7.4 Hz, $(CH_3CH_2)_3Si$), 1.06 (9H, s, $(CH_3)_3CSi$), 2.17 (3H, s, CH_3COO), 3.62 (2H, m, C5*H*, C5C*H*HO), 3.87 (1H, dd, *J*=6.07, 11.4 Hz, C5C*H*HO), 4.58 (1H, t, *J*=7.7 Hz, C4*H*), 5.66 (1H, d, *J*=7.7 Hz, C3*H*), 5.87 (1H, br, amide proton), 7.40–7.50 (6H, aromatic protons), 7.55–7.65 (4H, aromatic protons). Anal. calcd for $C_{29}H_{43}NO_5Si_2$: C, 64.28%; H, 7.80%; N, 2.59%. Found: C, 64.30%; H, 7.99%; N, 2.57%.

4.4.2. Treatment with Lawesson reagent to give 6. A mixture of (3*S*,4*R*,5*S*)-3-acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-one (14.2 g, 26.3 mmol) and Lawesson's reagent (10.7 g, 26.4 mmol) in toluene (200 mL) was stirred at 60°C for 40 min. After cooling, the precipitate was removed by filtration and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane–AcOEt=85:15) gave **6** (14.2 g, 97%) as a white solid. Analytical sample was prepared by recrystallization from hexane to give needles. Mp 126–126.5°C. $[\alpha]_D^{20}=+105°$ (*c* 1.10, $CHCl_3$). IR (nujor): 3360, 1740, 1520, 1240, 1120, 740, 710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.55 (6H, m, $(CH_3CH2)3Si$), 0.87 (9H, t, *J*=7.4 Hz, $(CH_3CH_2)_3Si$), 1.06 (9H, s, $(CH_3)_3CSi$), 2.19 (3H, s, CH_3COO), 3.66 (1H, dd, *J*=3.0, 10.4 Hz, C5C*H*HO), 3.73 (1H, m, C5*H*), 3.92 (1H, dd, *J*=5.4, 10.4 Hz, C5C*H*HO), 4.55 (1H, t, *J*=7.4 Hz, C4*H*), 5.66 (1H, d, *J*=7.4 Hz, C3*H*), 7.40–7.50 (6H, aromatic protons), 7.55–7.65 (4H, aromatic protons), 7.79 (1H, br, thioamide proton). Anal. calcd for $C_{29}H_{43}NO_4Si_2S$: C, 62.43%; H, 7.77%; N, 2.51%; S, 5.75%. Found: C, 62.38%; H, 7.86%; N, 2.53%; S, 5.75%.

4.5. (2*S*,3*R*,4*S*)-4-Acetoxy-2-(*tert*-butyldiphenylsiloxy)-methyl-3,4-dihydro-5-methylthio-3-triethylsiloxy-2*H*-pyrrole (7)

A mixture of **6** (2.06 g, 3.69 mmol) and methyl iodide (5.0 mL, excess) in CH_2Cl_2 (5.0 mL) was stirred at room temperature in the dark for 3 h. The mixture was poured into a mixture of aq. $NaHCO_3$ and aq. $Na_2S_2O_3$ solution, then extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give almost pure **7** (2.10 g, 99%) as a solid. Analytical sample was prepared by recrystallization from hexane to give needles. Mp 82–83°C. $[\alpha]_D^{20}=-109°$ (*c* 1.03, $CHCl_3$). IR (nujor): 1750, 1560, 1240, 1220, 1110, 1090, 1090, 1050, 850, 740, 730, 710, 620, 500 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.63 (6H, dq, *J*=1.1, 7.5 Hz, $(CH_3CH_2)_3Si$), 0.97 (9H, t, *J*=7.5 Hz, $(CH_3CH_2)_3Si$), 1.03 (9H, s, $(CH_3)_3CSi$), 2.16 (3H, s, CH_3COO), 2.46 (3H, s, CH_3S), 3.76 (1H, dd, *J*=3.2, 10.8 Hz, C2C*H*HO), 4.00 (2H, m, C2*H*, C2C*H*HO), 4.61 (1H, t, *J*=6.9 Hz, C3*H*), 6.21 (1H, d, *J*=6.9 Hz, C4*H*), 7.40–7.50 (6H, aromatic protons), 7.55–7.65 (4H, aromatic protons), 7.79 (1H, br, thioamide proton). EI-MS (rel int.%) *m*/*z*=542 (2.6, $[M-Et]^+$), 514 (100, $[M-tBu]^+$). Anal. calcd for $C_{30}H_{45}NO_4SSi_2$: C, 63.00%; H, 7.93%; N, 2.45%. Found: C, 62.09%; H, 8.00%; N, 2.44%.

4.6. (*E*)-3-(Benzyloxymethoxy)methyl-2-butenoic acid (9)

A solution of methyl (*E*)-3-hydroxymethyl-2-butenoate (**8**)[10] (2.50 g, 19.2 mmol), *i*-Pr_2NEt (10 mL, 7.42 g, 57.4 mmol), and BOMCl (5.96 g, 47.4 mmol) in CH_2Cl_2 (20 mL) was stirred at 0°C for 12 h. The mixture was poured into dil. HCl solution and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$ then concentrated in vacuo. The residue was diluted with THF (50 mL), and the solution was stirred vigorously with aqueous 1.0 M NaOH solution (70 mL) at 60°C for 12 h. After cooling, THF was removed in vacuo. The residual aqueous solution was washed with Et_2O. The aqueous layer was acidified by the addition of aqueous 2 M HCl solution, then extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give crude **8** (4.5 g). The yield was not calculated because the product was crude material. ^1H NMR (200 MHz, $CDCl_3$) δ 2.12 (3H, d, *J*=1.0 Hz, C4H_3), 4.13 (2H, d, *J*=1.0 Hz, C3CH_2O), 4.64, 4.81 (each 2H, s, OCH_2O, PhCH_2O), 6.03 (1H, hex, *J*=1.0 Hz, C2*H*), 7.35 (5H, m, aromatic protons). This sample was immediately subjected to the next step.

4.7. Benzyl *N*-[(*E*)-3-(benzyloxymethoxy)methyl-2-butenoyl]glycinate (10*E*)

A mixture of crude **8** (4.5 g), benzyl glycinate *p*-toluenesulfonic acid salt (11.0 g, 32.6 mmol), WSCI·HCl (7.60 g, 40.0 mmol), and Et_3N (3.60 g, 35.6 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 12 h. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane–AcOEt=60:40) gave **10***E* (6.29 g, 85% in three steps) as a white solid. Analytical sample was prepared by recrystallization from hexane–AcOEt to give needles. Mp 62–64°C. IR (nujor) 3270, 2920, 2760, 1760, 1670, 1530, 1520, 1460, 1390, 1360, 1190, 1120, 1080, 1060, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.11 (3H, s, C4′H_3), 4.06 (2H, s, C3′CH_2O), 4.12 (2H, d, *J*=5.3 Hz, C2H_2), 4.62, 4.78, 5.20 (each 2H, s, PhCH_2O×2, OCH_2O), 5.92 (1H, br s, C2′*H*), 5.93 (1H, br, amide proton), 7.35 (10H, aromatic protons). EI-MS (rel int.%) *m*/*z*=384 (0.1, M^+), 276 (3.2, $[M-BnO]^+$), 276 (4.3, $[M-BnOH]^+$), 247 (13, $[M-BnOCO]^+$), 91 (100, Bn^+). EI-HRMS calcd for $C_{22}H_{26}NO_5$ (M^+): 384.1812. Found: *m*/*z*=384.1821. Anal. calcd for $C_{22}H_{26}NO_5$: C, 68.91%; H, 6.57%; N, 3.65%. Found: 68.88%; H, 6.58%; N, 3.58%.

4.8. 2-[(*E*)-2-(Benzyloxymethoxy)methyl-1-propenyl]-4*H*-oxazol-5-one (11*E*)

4.8.1. Saponification of 10E. A suspension of **10***E* (250 mg, 653 μmol) in a mixture of THF (3.0 mL) and aqueous 1.0 M NaOH solution (2.0 mL) was stirred vigorously at room temperature for 2 h. After the THF was removed in vacuo, the resulting aqueous solution was washed with Et_2O. The residual aqueous solution was acidified by the addition of aqueous 2.0 M HCl solution, then extracted with AcOEt. The combined extracts were washed with brine, dried over

$MgSO_4$, then concentrated in vacuo to give *N*-[(*E*)-3-(benzyloxymethoxy)methyl-2-butenoyl]glycine (190 mg, 99%) as a white solid. Analytical sample was prepared by recrystallization from hexane–AcOEt to give needles. Mp 90.5–91°C. IR (nujor): 3330, 1750, 1630, 1220, 1040 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.13 (3H, d, J=0.6 Hz, C4′H_3), 4.11 (2H, br s, C3′CH_2O), 4.13 (2H, d, J=5.3 Hz, C2H_2), 4.66, 4.82 (each 2H, s, PhCH_2O, OCH_2O), 5.99 (1H, br s, C2′H), 6.30 (1H, br t, J=5.3 Hz, amide proton), 7.37 (5H, aromatic protons). EI-MS (rel int.%) m/z=172 (4.8, [M−BnOCH_2]+), 91 (100, Bn^+). CI-MS (isobutene) m/z=294 (M^+), 276 ([M−H_2O]$^+$). Anal. calcd for $C_{15}H_{19}NO_5$: C, 61.42%; H, 6.53%; N, 4.78%. Found C, 61.34%; H, 6.51%; N, 4.73%.

4.8.2. Dehydration giving 11E. A mixture of *N*-[(*E*)-3-(benzyloxymethoxy)methyl-2-but-enoyl]glycine (306 mg, 1.04 mmol) and 1-cyclohexyl-3-(2-morphorinoethyl)carbodiimide metho-*p*-toluenesulfonate (CMCD)[11] (650 mg, 1.54 mmol) in THF (5.0 mL) was stirred at room temperature for 4 h. The mixture was filtered, and the filtrate was concentrated in vacuo below 30°C to provide almost pure **11***E* (295 mg, quantitative yield) as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (3H, s, C3′H_3), 4.14, 4.27, 4.63, 4.81 (each 2H, s, C4H_2, C2′CH_2O, PhCH_2O, OCH_2O), 6.14 (1H, br s, C1′H), 7.34 (5H, m, aromatic protons). This sample was immediately used for the next step without further purification.

4.9. Benzyl *N*-[(*Z*)-3-carboxy-2-butenoyl]glycinate (13)

A mixture of citraconic anhydride (**12**) (3.75 g, 33.3 mmol) benzyl glycinate *p*-toluenesulfonic acid salt (12.0 g, 35.6 mmol), and Et_3N (3.67 g, 36.3 mmol) in CH_2Cl_2 (60 mL) was stirred at 0°C for 40 min. The mixture was poured into saturated $NaHCO_3$ and washed with Et_2O. After acidification by the addition of aqueous HCl solution, the aqueous solution was extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated to give **9′** which was contaminated with a small amount of the regioisomer (87:13 ratio, 9.00 g, 97%). ^1H NMR (200 MHz, $CDCl_3$, a=0.87, b=0.13) δ 2.13 (3H×a, d, J=1.3 Hz, C4′H_3 for desired), 2.20 (3H×b, d, J=1.7 Hz, C3′H_3 for undesired), 4.15 (2H, d, J=5.2 Hz, C2H_2), 5.19 (2H×b, s, PhCH_2O for undesired), 5.21 (2H×a, s, PhCH_2O for desired), 6.11 (1H×b, m, C3′H for undesired), 6.41 (1H×a, m, C3′H for desired), 7.39 (6H, aromatic protons, amide proton). This sample was subjected to the next step without further purification.

4.10. Benzyl *N*-[(*Z*)-3-(benzyloxymethoxy)methyl-2-butenoyl]glycinate (10*Z*)

4.10.1. Reduction of the carboxylic acid moiety in 13. A solution of crude **13** (200 mg, 722 μmol), Et_3N (216 mg, 2.13 mmol), and isopropyl chloroformate (164 mg, 1.34 mmol) in THF (5.0 mL) was stirred at 0°C for 10 min. Aqueous $NaBH_4$ solution (100 mg in 1.0 mL, 2.63 μmol) was added to the reaction mixture at 0°C, and the mixture was stirred for additional 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 (CH_2Cl_2–acetone=90:10) gave a mixture of benzyl *N*-[(*Z*)-3-hydroxymethyl-2-butenoylglycinate and its (*E*)-isomer (87:13 ratio, 120 mg, 63%). (200 MHz, $CDCl_3$, a=0.87, b=0.13): δ 1.91 (3H×a, d, J=1.3 Hz, C4′H_3 for desired), 2.04 (3H×b, d, J=1.6 Hz, C3′H_3 for undesired), 4.10 (2H, d, J=5.3 Hz, C2H_2), 4.24 (2H, s, CH_2O), 5.15 (2H×b, s, PhCH_2O for undesired), 5.19 (2H×a, s, PhCH_2O for desired), 5.74 (1H×a, m, C3′H for desired), 5.83 (1H×b, m, C3′H for undesired), 6.42 (1H×a, br, amide proton for desired), 7.39 (6H, m, aromatic protons, amide proton).

4.10.2. BOM ether formation, giving 10Z. A mixture of benzyl *N*-[(*Z*)-3-hydroxymethyl-2-butenoylglycinate containing its (*E*)-isomer (900 mg, 3.42 mmol), BOMCl (2.0 g, 12.8 mmol), and *i*-Pr_2NEt (2.5 g, 19.3 mmol) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 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 (CH_2Cl_2–acetone=96:4) gave **10***Z* (600 mg, 45%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ 1.93 (3H, d, J=1.2 Hz, C4′H_3), 4.00 (2H, d, J=5.4 Hz, C2H_2), 4.61, 4.62, 4.79, 5.16 (each 2H, s, C3′CH_2O, PhCH_2O×2, OCH_2O), 5.77 (1H, br s, C2′H), 6.43 (1H, br, amide proton), 7.35 (10H, m, aromatic protons).

4.11. 2-[(*Z*)-2-(Benzyloxymethoxy)methylpropenyl]-4*H*-oxazol-5-one (11*Z*)

4.11.1. Basic saponification of 10E. The same treatment of **10***Z* (4.90 g, 12.79 mmol) as described in Section 4.8.1 (Saponification of **10***E*) gave *N*-[(*Z*)-3-(benzyloxymethoxy)-methyl-2-butenoyl]glycine (3.70 g, 99%) as an oil. IR (film): 3330, 1740, 1620, 1220, 1110, 1070, 1050, 1030 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.94 (3H, d, J=1.3 Hz, C4′H_3), 3.94 (d, J=5.3 Hz, C2H_2), 4.60, 4.62, 4.79 (each 2H, s, C3CH_2O, PhCH_2O, OCH_2O), 5.77 (1H, br s, C2′H), 6.68 (1H, br t, J=5.3 Hz, amide proton), 7.32 (5H, m, aromatic protons). CI-MS (isobutene): m/z=294 (M^+), 276 ([M−H_2O]$^+$).

4.11.2. Dehydration giving 11Z. Treatments of **10***Z* (52.0 mg, 177 μmol) in the same manner as described in Section 4.8.2 (Dehydration giving **11***E*) gave **11***Z* (48.7 mg, quantitative yield) as an oil. IR (film) 1830, 1650, 1150, 1130 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.06 (3H, s, C3′H_3), 4.22, 4.63, 4.65, 4.81 (each 2H, s, C4H_2, C2′CH_2O, PhCH_2O, OCH_2O), 5.87 (1H, br s, C1′H), 7.34 (5H, m, aromatic protons). CI-MS m/z=276 (MH^+). This sample was immediately used for the next step without further purification.

4.12. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[2-(*E*)-(benzyloxymethoxy)methyl-1-propenyl]-4*H*-oxazol-5-one (12*E*) and its (2*Z*)-isomer (12*Z*)

4.12.1. Reaction with 11E. A mixture of **11***E* (2.90 g, 10.6 mmol) and **7** (1.02 g, 1.79 mmol) in toluene (3.0 mL) and pyridine (3.0 mL) was stirred at 60°C for 12 h with Ar gas bubbling. After concentration in vacuo, the residue was purified by silica gel column chromatography (hexane–AcOEt=90:10→20:80) to give recovered **7** (423 mg, 41%)

as a solid and **12***E* (676 mg, 47%) as an oil. The produced **12***E* was obtained as an 87:13 mixture of tautomers arising from its enamine moiety.

4.12.2. Reaction with 11*Z*. The *Z*-isomer **11***Z* (2.82 g, 10.2 mmol) was treated with **7** (700 mg, 1.23 mmol) in a similar manner to that described previously. Silica gel column chromatography of the residue (AcOEt–hexane=87:13) gave recovered **7** (350 mg, 50%) as an oil, **12***Z* (91.4 mg, 9.3%) as an oil, and **12***E* (312 mg, 32%) as an oil. The ^{1}H NMR spectrum of **12***E* was identical to that of the sample prepared from **11***E*. The product **12***E* was obtained as a 90:10 mixture of tautomers arising from the enamine moiety.

4.12.3. Physical data of 12*E*. IR (film): 3320, 2960, 2930, 1760, 1720, 1640, 1230, 1210, 1140, 1110, 1060, 740, 700 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*=87:13). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (200 MHz, $CDCl_3$, *a*=0.87, *b*=0.13): δ 0.58 (6H, m, $(CH_3CH_2)_3Si$), 0.90 (9H, t, *J*=8.2 Hz, $(CH_3CH_2)_3Si$), 1.03 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.03 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 2.05 (3H, s, C3′*H*$_3$), 2.15 (3H, s, C*H*$_3$COO), 3.65 [1H×*a*, dd, *J*=5.1, 12.8 Hz, C5C*H*HO (*E*-isomer)], 3.88 (2H, m, C5H, C5C*H*HO), 4.13 (2H, br s, C2′C*H*$_2$O), 4.60 [1H×*a*, t, *J*=6.2 Hz, C4*H*], 4.63 (2H, s, OC*H*$_2$O or PhC*H*$_2$O), 4.80 [2H×*a*, s, OC*H*$_2$O (*E*-isomer) or PhC*H*$_2$O (*E*-isomer)], 4.82 [2H×*b*, s, OC*H*$_2$O (*Z*-isomer) or PhC*H*$_2$O (*Z*-isomer)], 6.10 (1H, hext, *J*=1.3 Hz, C1′*H*), 6.15 [2H×*b*, C2′*H* (*Z*-isomer), C3*H* (*Z*-isomer)], 6.43 [1H×*a*, d, *J*=6.2 Hz, C3*H* (*E*-isomer)], 6.62 [1H×*b*, br, amine proton (*Z*-isomer)], 7.40 (11H, m, aromatic protons), 7.67 (4H, aromatic protons), 7.77 [1H, br s, amine proton (*E*-isomer)]. EI-MS (rel int.%) *m*/*z*=798 (99, M$^+$), 769 (6.0, [M−Et]$^+$), 741 (4.1, [M−*t*Bu]$^+$), 199 (100, Ph_2Si^+=O), 91 (68, Bn$^+$). EI-HRMS calcd for $C_{44}H_{58}N_2O_8Si_2$ (M$^+$): *m*/*z*=798.3733. Found: *m*/*z*=798.3740.

4.12.4. Physical data of 12*Z*. IR (film): 3330, 2970, 2940, 1770, 1740, 1650, 1220, 1150, 1110, 1060, 1045, 1030, 740, 710 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*=90:10). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (200 MHz, $CDCl_3$, *a*=0.90, *b*=0.10, *carzinophilin numbering*): δ 0.59 (6H, m, $(CH_3CH_2)_3Si$), 0.89 (9H, t, *J*=8.2 Hz, $(CH_3CH_2)_3Si$), 1.02 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.04 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 2.00 [3H×*a*, s, C20*H*$_3$ (*E*-isomer)], 2.03 [3H×*b*, s, C20*H*$_3$ (*Z*-isomer)], 2.11 [3H×*b*, s, C*H*$_3$COO (*Z*-isomer)], 2.15 [3H×*a*, s, C*H*$_3$COO (*E*-isomer)], 3.64 [1H×*a*, dd, *J*=5.1, 12.8 Hz, C11C*H*HO (*E*-isomer)], 3.88 (2H, m, C5H, C11C*H*HO), 4.57 [1H×*a*, t, *J*=6.2 Hz, C12*H*(*E*-isomer)], 4.63 (2H, s, PhC*H*$_2$O), 4.63–4.84 (4H, m, C21C*H*$_2$O, OC*H*$_2$O), 5.88 [1H×*a*, hext, *J*=1.3 Hz, C18*H* (*E*-isomer)], 5.60 (1H, m, C18*H* (*Z*-isomer)), 6.18 [1H×*b*, d, *J*=3.5 Hz, C13*H* (*Z*-isomer)], 6.41 [1H×*a*, d, *J*=6.2 Hz, C13*H* (*E*-isomer)], 6.77 [1H×*b*, br, amine proton (*Z*-isomer)], 7.25–7.52 (11H, aromatic protons), 7.57–7.70 (4H, aromatic protons), 7.76 [1H×*a*, br s, amine proton(major)]. CI-MS (isobutene) *m*/*z*=798 (99, M$^+$), 769 (6.0, [M−Et]$^+$), 741 (4.1, [M−*t*-Bu]$^+$). EIMS of this sample gave no useful information. Accordingly EI-HRMS was not measured.

4.13. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-(2-formyl-1-propenyl)-4*H*-oxazol-5-one (13)

4.13.1. Preparation from 12*E*. A mixture of **12***E* (14.0 mg, 17.5 μmol) and DDQ (6.0 mg, 264 μmol) in a mixture of CH_2Cl_2 (1.0 mL) and H_2O (100 μL) was stirred at room temperature for 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 preparative TLC (hexane–AcOEt=70:30) gave **13** (R_F=0.55, 8.2 mg, 85%) as a yellow oil. IR (film): 3300, 2960, 2870, 1770, 1720, 1690, 1650, 1620, 1610, 1520, 121, 1170, 1150, 1110, 1020, 830, 730, 700, 500 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*=90:10). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (400 MHz, $CDCl_3$, *a*=0.90, *b*=0.10, *carzinophilin numbering*): δ 0.58 [6H×*a*, m, $(CH_3CH_2)_3Si$ (*Z*-isomer)], 0.62 [6H×*a*, q, *J*=8.0 Hz, $(CH_3CH_2)_3Si$ (*E*-isomer)], 0.86 [9H×*b*, t, *J*=7.2 Hz, $(CH_3CH_2)_3Si$ (*Z*-isomer)], 0.92 [9H×*a*, t, *J*=7.2 Hz, $(CH_3CH_2)_3Si$ (*E*-isomer)], 2.13 [3H×*b*, C*H*$_3$COO (*Z*-isomer)], 2.17 [3H×*a*, s, C*H*$_3$COO (*E*-isomer)], 2.19 [3H×*a*, d, *J*=1.3 Hz, C20*H*$_3$ (*E*-isomer)], 2.22 [3H×*b*, d, *J*=1.3 Hz, C20*H*$_3$ (*Z*-isomer)], 3.67 [1H×*a*, dd, *J*=2.3, 10.1 Hz, C11C*H*HO (*E*-isomer)], 3.79 [1H×*b*, dd, *J*=3.7, 10.9 Hz, C11C*H*HO (*Z*-isomer)], 3.88–4.00 (2H, C11*H*, C5C*H*HO), 4.40 [1H×*b*, dd, *J*=3.1, 5.4 Hz, C12*H* (*Z*-isomer)], 4.63 [1H×*a*, t, *J*=6.4 Hz, C12*H* (*E*-isomer)], 6.18 [1H, d, *J*=3.1 Hz, C13*H* (*Z*-isomer)], 6.51 [1H×*a*, d, *J*=6.4 Hz, C13*H* (*E*-isomer)], 6.69 (1H, hext, *J*=1.3 Hz, C18*H*), 7.00 [1H×*b*, br s, amine proton (*Z*-isomer)], 7.35–7.47 (6H, aromatic protons), 7.58–7.70 (4H, aromatic protons), 8.13 [1H×*a*, br s, amine proton(*E*-isomer)], 9.54 [1H×*a*, s, C21*H* (*E*-isomer)], 9.58 [1H×*b*, s, C21*H* (*Z*-isomer)]. NOE cross peaks were observed between the signals at δ 9.54↔δ 6.51, δ 9.58↔δ 6.51 by phase sensitive NOESY spectrum. EI-MS (rel int.%) *m*/*z*=676 (0.2, M$^+$), 647 (0.1, [M−Et]$^+$), 277 (100, [M−HOC(Me)=CH–AcOH–TBDPSOCH$_3$]$^+$). CI-MS (isobutene): *m*/*z*=677 (MH$^+$). EI-HIMS: calcd for $C_{36}H_{48}N_2O_7Si_2$ (M$^+$): *m*/*z*=676.3001. Found: *m*/*z*=676.2994. In a preparative scale, the crude sample was not purified and directly subjected to the next step.

4.13.2. Preparation from 12*Z*. Treatments of **12***Z* (6.0 mg, 8.9 μmol) similarly to those described previously gave **13** (4.2 mg, 86%) as an oil after preparative TLC. The ^{1}H NMR spectrum of this sample was identical to that of an authentic sample prepared from **12***E*.

4.14. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-(2-hydroxymethyl-1-propenyl)-4*H*-oxazol-5-one (14)

A mixture of **12***E* (2.60 g, 3.25 mmol) and DDQ (890 mg, 3.92 mmol) in a mixture of CH_2Cl_2 (25 mL), and H_2O (250 μL) was stirred at room temperature for 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. A mixture of the residue, and $NaBH_4$ (150 mg, 3.97 mmol) in MeOH (15 mL) was stirred at 0°C for 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 (hexane–AcOEt=60:40) gave **14** (1.81 g, 82% in two steps) as an oil. IR (film): 3400, 2970, 2950, 1740, 1720, 1640, 1460, 1370, 1230, 1120, 1080, 740, 710 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=75:25). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.75, *b*=0.25, *carzinophilin numbering*): δ 0.65 (6H, m, $(CH_3CH_2)_3Si$), 0.85 [9H×*b*, t, *J*=7.8 Hz, $(CH_3CH_2)_3Si$ (*Z*-isomer)], 0.90 [9H×*a*, t, *J*=7.8 Hz, $(CH_3CH_2)_3Si$ (*E*-isomer)], 1.02 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)] 1.07 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.90 [1H×*a*, br t, *J*=6.1 Hz, alcoholic proton (*E*-isomer)], 2.09 [3H×*a*, s, C20H_3 (*E*-isomer)], 2.11 [3H×*b*, s, CH_3COO (*Z*-isomer)], 2.15 [3H×*a*, s, CH_3COO (*E*-isomer)], 2.70 [1H×*b*, br t, *J*=6.1 Hz, alcoholic proton (*Z*-isomer)], 3.65 [1H×*a*, m, C11C*H*HO (*E*-isomer)], 3.78 [1H×*b*, dd, *J*=3.7, 10.8 Hz, C11C*H*HO (*Z*-isomer)], 3.85 [1H×*b*, dd, *J*=7.6, 10.8 Hz, C11C*H*HO (*Z*-isomer)], 3.86–3.93 [2H×*a*, m, C11*H* (*E*-isomer), C11C*H*HO (*E*-isomer)], 3.98 [1H×*b*, m, C11*H* (*Z*-isomer)], 4. 16 (2H, br d, *J*=6.1 Hz, C21*H*), 4.34 [1H×*b*, dd, *J*=3.0, 5.1 Hz, C4*H* (*Z*-isomer)], 4.59 [1H×*a*, t, *J*=6.4 Hz, C12*H* (*E*-isomer)] 6.11 [1H×*a*, hext, *J*=1.4 Hz, C18H (*E*-isomer)], 6.12 [1H×*a*, *J*=3.0 Hz, C13*H* (*Z*-isomer)], 6.16 [1H×*b*, *J*=1.4 Hz, C18*H* (*Z*-isomer)], 7.05 [1H×*b*, br, amine proton (*Z*-isomer)], 7.35–7.46 (6H, aromatic protons), 7.59–7.68 (4H, aromatic protons), 7.77 [1H×*a*, br, amine proton (*E*-isomer)]. EI-MS (rel int.%) *m*/*z*=678 (1.1, M^+), 649 (1.1, $[M-Et]^+$), 87 (100, $[M-AcOH-OH]^+$). EI-HRMS: calcd for $C_{36}H_{50}N_2O_7Si_2$ (M^+): *m*/*z*=678.3158. Found: *m*/*z*=678.3149.

4.15. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(1*R*,2*S*)-1,2,3-trihydroxy-2-methylpropyl]-4*H*-oxazol-5-one (15)

In a hood, a solution of **13** (1.00 g, 1.47 mmol) in CH_2Cl_2 (3.0 mL) was added to a mixture of OsO_4 (374 mg, 1.47 mmol) and $(DHQ)_2PHAL$[15] (1.38 g, 1.77 mmol) in CH_2Cl_2 (20 mL) at 0°C with stirring. After stirring for 15 min, H_2S gas was bubbled through the mixture to give a black suspension. Celite® (3 g) and AcOEt (50 mL) were added to the suspension, and the whole mixture was stirred at room temperature for additional 30 min with H_2S bubbling. After filtration through a pad of Celite®, the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane–AcOEt=60:40→10:90) gave recovered **14** (70 mg, 7%) and **15** (730 mg, 69%) both as oil. The ^1H NMR spectrum of **15** indicated that diastereomeric excess of this sample about the C18 position (*carzinophilin numbering*) was 80% *de* based on the signal intensity for C15H_3 observed at 2.04 (7*Z*,18*S* isomer), 2.11 (7*Z*,18*R* isomer), 2.15 (7*E*18*R* isomer), and 2.16 (7*E*18*S* isomer). IR (film): 3380, 2960, 2950, 2880, 1750, 1650, 1590, 1230, 1140, 1115, 1060, 740, 705 cm^{-1}. The ^1H NMR spectrum of this sample was complicated due to existence of the two tautomers arising from its enamine moiety (*E*/*Z*=75:25) as well as the two diastereomers at the C18 position. Assignments of signals for the main 7*E*18*R*-isomer and some of the second major 7*Z*,18*R*-isomer are described. ^1H NMR (200 MHz, $CDCl_3$, *a*=0.75, *b*=0.25) δ 0.58 (6H, m, $(CH_3CH_2)_3Si$), 0.85, [9H×*b*, $(CH_3CH_2)_3Si$ (7*Z*,18*R*-isomer)], 0.89 [9H×*a*, $(CH_3CH_2)_3Si$ (7*E*,18*R*-isomer)], 1.00 [9H×*a*, $(CH_3)_3CSi$ (7*E*,18*R*-isomer)], 1.05 [9H×*b*, $(CH_3)_3CSi$ (7*Z*,18*R*-isomer)], 2.04 [3H×trace, s, (7*Z*,18*S* isomer)], 2.11 [3H×*a*, s, (7*Z*,18*R* isomer)], 2.15 [3H×*a*, s, (7*E*,18*R* isomer)], and 2.16 [3H×trace, s, (7*E*,18*S* isomer)], 2.95, 3.33 [each 1H×*a*, alcoholic protons (7*E*18*R*-isomer)], 3.47–4.00 (6H m, C11*H*, C11C*H2*O, C21*H2*O, C18*H*), 4.35 [1H×*b*, dd, *J*=3.4, 4.8 Hz, C13*H* (7*Z*,18*R*-isomer)], 4.59 [1H×*a*+1H, C12*H* (7*E*,18*R*-isomer), alcoholic proton], 6.13 [1H×*a*, d, *J*=3.4 Hz, C13*H* (7*Z*,18*R*-isomer)], 6.44 [1H×*a*, d, *J*=6.4 Hz, C13*H* (7*E*,18*R*-isomer)], 6.45 [1H×trace, d, *J*=6.4 Hz, C13*H* (7*E*,18*S*-isomer)], 7.40 (6H, aromatic protons), 7.62 (4H, m, aromatic protons), 7.74 [1H×*a*, amine proton (7*E*,18*R*-isomer)]. CI-MS *m*/*z*=713 (MH^+), 695 ($[M-H_2O]^+$). EI-MS of this sample provided no useful information.

4.16. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(1*R*,2*S*)-2,3-epoxy-1-hydroxy-2-methylpropyl]-4*H*-oxazol-5-one (16)

A mixture of **15** (1.10 g, 1.54 mmol), γ-collidine (431 mg, 3.56 mmol), and MsCl (266 mg, 2.32 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. After MeOH (100 μL) was added in order to decompose excess MsCl, 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 to give the crude mesylate containing γ-collidine. A mixture of the crude mesylate, and DBU (250 mg, 1.67 mmol) in CH_2Cl_2 (10 mL) was stirred with 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 (hexane–AcOEt=65:35) gave **16** (802 mg, 75%) as an oil. Separation of the minor diastereomer was not attempted. IR (film): 330, 2960, 2930, 2870, 1760, 1650, 1590, 1370, 1230, 1220, 1150, 1120, 1060, 1010, 910, 840, 740, 710, 510 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z* =65:35). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.65, *b*=0.35, *carzinophilin numbering*): δ 0.51–0.61 (6H, m, $(CH_3CH_2)_3Si$), 0.85 [9H×*b*, t, *J*=7.8 Hz, $(CH_3CH_2)_3Si$ (*Z*-isomer)], 0.91 [9H×*a*, t, *J*=7.8 Hz, $(CH_3CH_2)_3Si$ (*E*-isomer)], 1.02 (9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)), 1.07 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 1.32 [3H×*a*, s, C20H_3 (*E*-isomer)], 1.37 [3H×*b*, s, C20H_3 (*Z*-isomer)], 2.11 [3H×*b*, s, CH_3COO (*Z*-isomer)], 2.16 [3H×*b*, s, CH_3COO (*E*-isomer)], 2.68 [1H×*a*, d, *J*=4.6 Hz, C21*H* (*E*-isomer)], 2.72 [1H×*b*, d, *J*=4.5 Hz, C21*H* (*Z*-isomer)], 2.93 [1H×*a*, br d, *J*=6.8 Hz, alcoholic

proton (*E*-isomer)], 2.96 [1H×*a*, d, *J*=4.6 Hz, C21*H* (*E*-isomer)], 2.99 [1H×*b*, d, *J*=4.5 Hz, C21*H* (*Z*-isomer)], 3.09 [1H×*b*, br d, *J*=6.4 Hz, alcoholic proton (*Z*-isomer)], 3.62–3.98 (3H, C11*H*, C11CH_2O), 4.29 [1H×*a*, br d, *J*=6.8 Hz, C18*H* (*E*-isomer)], 4.30 [1H×*b*, br d, *J*=6.4 Hz, C18*H* (*Z*-isomer)], 4.37 [1H×*b*, dd, *J*=3.4, 5.2 Hz, C12*H* (*Z*-isomer)], 4.60 [1H×*a*, t, *J*=6.4 Hz, C12*H* (*E*-isomer)], 6.16 [1H×*b*, d, *J*=3.4 Hz, C13*H* (*Z*-isomer)], 6.43 [1H×*a*, d, *J*=6.4 Hz, C13*H* (*E*-isomer)], 6.82 [1H×*b*, br, amine proton (*Z*-isomer)], 7.36–7.47 (6H, m, aromatic protons), 7.56–7.69 (4H, m, aromatic protons), 7.71 [1H×*a*, br, amine proton (*E*-isomer)]. EI-MS (rel. int.%): *m*/*z*=694 (2.4, M^+), 676 (0.8, $[M-H_2O]^+$), 665 (1.0, $[M-Et]^+$), 653 (1.3, $[M-Ac]^+$), 637 (4.0, $[M-t\mathrm{Bu}]^+$ and/or $[M-CH_3COCH_2]^+$), 199 (100, $Ph_2Si^+{=}O$) CI-MS (isobutene): *m*/*z*=695 (MH^+), EI-HRMS calcd for $C_{36}H_{50}N_2O_8Si_2$ (M^+): *m*/*z*=694.3107. Found: *m*/*z*=694.3079.

4.17. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(*S*)-2,3-epoxy-2-methylpropionyl]-4*H*-oxazol-5-one (17)

A mixture of **16** (700 mg, 1.01 mmol) and Dess–Martin reagent (535 mg, 1.30 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. The mixture was poured into a 1:1 mixture of aqueous 10% $Na_2S_2O_3$ solution and aqueous saturated $NaHCO_3$ solution, then 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–AcOEt=70:30) gave **17** (587 mg, 84%) as a yellow solid. Analytical sample was prepared by recrystallization from hexane–Et_2O to give yellow needles. Mp 97–102°C. IR (nujor): 3350, 2970, 2930, 1760, 1720, 1640, 1520, 1210, 1140, 1110, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.62 (6H, q, *J*=7.7 Hz, $(CH_3CH_2)_3Si$), 0.93 (9H, t, *J*=7.7 Hz, $(CH_3CH_2)_3Si$), 1.00 (9H, s, $(CH_3)_3CSi$), 1.65 (3H, s, C20H_3), 2.23 (3H, s, CH_3COO), 2.89 (1H, d, *J*=5.9 Hz, C21*H*H), 3.58 (1H, d, *J*=5.9 Hz, C21*H*H), 3.64 (1H, dd, *J*=2.6, 10.8 Hz, C11C*H*HO), 3.96 (1H, m, C11*H*), 3.98 (1H, dd, *J*=3.8, 10.8 Hz, C11C*H*HO), 4.69 (1H, t, *J*=7.1 Hz, C12*H*), 6.66 (1H, d, *J*=7.1 Hz, C13*H*), 7.35–7.35 (6H, aromatic protons), 7.56 (2H, aromatic protons), 7.68 (2H, m, aromatic protons), 8.34 (1H, br s, amine proton). EI-MS (rel. int.%): *m*/*z*=692 (4.5, M^+), 676 (1.5, $[M-H_2O]^+$), 663 (1.5, $[M-Et]^+$), 635 (36, $[M-t\mathrm{Bu}]^+$), 199 (100, $Ph_2Si^+{=}O$). CI-MS (isobutane): *m*/*z*=693 (MH^+), 677 ($[M-H_2O]^+$). EI-HRMS: calcd for $C_{36}H_{48}N_2O_8Si_2$ (M^+): *m*/*z*=692.2950. Found: *m*/*z*=692.2955. Anal. calcd for $C_{36}H_{50}N_2O_9Si_2$ ($M+H_2O$): C, 60.64%; H, 7.35%; N, 3.93%. Found C, 60.67%; H, 6.99%; N, 3.81%.

4.18. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(1*S*,2*S*)-2,3-epoxy-1-hydroxy-3-methylpropyl]-4*H*-oxazol-5-one (18)

Sodium borohydride (41.0 mg, 1.08 mmol) was added to a mixture of **17** (625 mg, 903 μmol) and $CeCl_3{\cdot}7H_2O$ (165 mg, 430 μmol) in MeOH (50 mL) at −15°C with stirring. After stirring for 10 min, the mixture was poured into aqueous. 5% citric acid solution and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt–hexane=40:60) gave **18** (594 mg, 95%) as an oil. IR (film): 3320, 2960, 2940, 2880, 1760, 1740, 1655, 1590, 1370, 1210, 1215, 1150, 1110, 1070, 1060, 1015, 910, 830, 730, 705, 500 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=80:20). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.80, *b*=0.20, *carzinophilin numbering*): δ 0.60 (6H, m, $(CH_3CH_2)_3Si$), 5 [9H×*b*, t, *J*=7.8 Hz, $(CH_3CH_2)_3Si$ (*Z*-isomer)], 0.91 [9H×*a*, t, *J*=7.8 Hz, $(CH_3CH_2)_3Si$ (*E*-isomer)], 1.01 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.07 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 1.36 [3H×*a*, s, C20H_3 (*E*-isomer)], 1.41 [3H×*b*, s, C20H_3 (*Z*-isomer)], 2.12 [3H×*b*, s, CH_3COO (*Z*-isomer)], 2.14 [3H×*a*, s, CH_3COO (*Z*-isomer)], 2.69 (1H, m, C21*H*H), 2.87 [1H×*a*, br d, *J*=3.3 Hz, alcoholic proton (*E*-isomer)], 2.95 [1H×*b*, br d, *J*=3.3 Hz, alcoholic proton (*Z*-isomer)], 3.06 (1H, m, C21*H*H), 3.63 [1H×*a*, m, C11C*H*HO (*E*-isomer)], 3.76 [1H×*b*, dd, *J*=3.5, 10.9 Hz, C11C*H*HO (*Z*-isomer)], 3.82–4.00 (H, C11*H*, C11C*H*HO), 4.36 [1H×*b*, dd, *J*=3.3, 5.1 Hz, C12*H* (*Z*-isomer)], 4.46 [1H×*a*, br d, *J*=3.3 Hz, C18*H* (*E*-isomer)], 4.54 [1H×*b*, br d, *J*=3.3 Hz, C18*H* (*Z*-isomer)], 4.61 [1H×*a*, t, *J*=6.5 Hz, C12*H* (*E*-isomer)], 6.16 [1H×*b*, d, *J*=3.3 Hz, C13*H*(*Z*-isomer)], 6.45 [1H×*a*, d, *J*=6.5 Hz, C13*H* (*E*-isomer)], 7.41 (6H, m, aromatic protons), 7.58–7.65 (4H, m, aromatic protons), 7.75 [1H×*a*, br, amine proton(*E*-isomer)]. EI-MS (rel. int.): *m*/*z*=694 (7.6, M^+), 676 (1.7, $[M-H_2O]^+$), 637 (14, $[M-t\mathrm{Bu}]^+$), 199 (100, $Ph_2Si^+{=}O$). CI-MS (isobutene): *m*/*z*=695 (MH^+), 637 (14, $[M-t\text{-Bu}]^+$). EI-HRMS: calcd for $C_{36}H_{50}N_2O_8Si_2$ (M^+): *m*/*z*=694.3107. Found: *m*/*z*=694.3093.

4.19. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(1*S*,2*S*)-2,3-epoxy-1-(3-methoxy-5-methyl-1-naphthoxy)-2-methylpropyl]-4*H*-oxazol-5-one (20)

A mixture of **18** (594 mg, 856 μmol), and the naphthoic acid **19** (370 mg, 1.71 mmol), DMAP (335 mg, 2.74 mmol), and WSCI·HCl (320 mg, 1.66 mmol) in CH_2Cl_2 (10 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 (hexane–AcOEt=80:20) gave **20** (741 mg, 97%) as an oil. IR (film): 3320, 2950, 2930, 1760, 1730, 1650, 1590, 1230, 1210, 1070, 750, 700 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=75:25). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (200 MHz, $CDCl_3$, *a*=0.75, *b*=0.25, *carzinophilin numbering*): δ 0.59 (6H, m, $(CH_3CH_2)_3Si$), 0.84 [9H×*b*, t, *J*= 7.7 Hz, $(CH_3CH_2)_3Si$ (*Z*-isomer)], 0.89 [9H×*a*, t, *J*=7.7 Hz, $(CH_3CH_2)_3Si$ (*E*-isomer)], 1.02 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.04 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 1.51 [3H×*a*, C20H_3 (*E*-isomer)], 1.55 [3H×*b*, C20H_3 (*Z*-isomer)], 1.99 [3H×*a*, s, CH_3COO (*E*-isomer)], 2.04 [3H×*b*, s, CH_3COO (*Z*-isomer)], 2.67 (3H, s, CH_3Ar),

2.70 [1H×*a*, d, *J*=5.0 Hz, C21*H*H (*E*-isomer)], 2.74 [1H×*b*, d, *J*=4.6 Hz, C21*H*H (*Z*-isomer)], 3.05 [1H×*a*, d, *J*=5.0 Hz, C21*H*H (*E*-isomer)], 3.11 [1H×*b*, d, *J*=4.6 Hz, C21*H*H (*Z*-isomer)], 3.58–3.98 (3H, m, C11*H*, C11H_2O), 3.98 (3H, s, CH_3OAr), 4.34 [1H×*b*, dd, *J*=3.1, 4.5 Hz, C12*H* (*Z*-isomer)], 4.59 [1H×*a*, t, *J*=6.4 Hz, C12*H* (*E*-isomer)], 5.82 [1H×*b*, s, C18*H* (*Z*-isomer)], 5.86 [1H×*a*, s, C18*H* (*E*-isomer)], 6.15 [1H×*b*, d, *J*=3.1 Hz, C13*H* (*Z*-isomer)], 6.43 [1H×*a*, d, *J*=6.4 Hz, C13*H* (*E*-isomer)], 6.99 [1H×*b*, br s, amine proton (*Z*-isomer)], 7.33–7.77 (13H, aromatic protons), 7.80 [1H×*a*, br s, amine proton (*E*-isomer)], 7.84 [1H×*a*, d, *J*=2.6 Hz, C2′*H* (*E*-isomer)], 7.89 [1H×*b*, d, *J*=2.6 Hz, C2′*H* (*Z*-isomer)], 8.62 (1H, m, C8′H). SI-MS (3-nitrobenzylalcohol): *m*/*z*=893 (MH^+), 863 ([M−Et]$^+$), 835 ([MH−isobutene]$^+$). Neither EI- nor CI-MS of this sample gave informative peaks. So, EI-HRMS was not measured.

4.20. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-4-hydroxy-5-hydroxymethylpyrrolidin-2-ylidene]-2-[(1*S*,2*S*)-2,3-epoxy-2-methyl-1-(3-methoxy-5-methyl-1-naphthoxy)propyl]-4*H*-oxazol-5-one (21)

A mixture of **20** (24.5 mg, 27.4 μmol), AcOH (50 μL), TBAF (1.0 M in THF, 80 μL) in THF (1.0 mL) was stirred at room temperature for 3 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=60:40) gave **21** (14.5 mg, 98%) as an oil. IR (film): 3370, 2850, 1730, 1650, 1490, 1240, 1070, 1040, 910, 730 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=55:45). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (200 MHz, $CDCl_3$, *a*=0.55, *b*=0.45, *carzinophilin numbering*): δ 1.52 [3H×*a*, s, C20*H3* (*E*-isomer)], 1.59 [3H×*b*, s, C20H_3 (*Z*-isomer)], 1.92[3H×*a*, s, CH_3COO (*E*-isomer)], 2.11 [3H×*b*, s, CH_3COO (*Z*-isomer)], 2.66 (3H, s, CH_3Ar), 2.73 (1H, m, C21*H*H), 3.08 (1H, m, C21*H*), 3.96 [3H×*b*, s, CH_3OAr (*Z*-isomer)], 3.97 [3H×*a*, s, CH_3OAr (*E*-isomer)], 3.65–4.15 (3H, m, C11*H*, C11CH_2O), 4.38 [1H×*b*, dd, *J*=3.5, 6.1 Hz, C12*H* (*Z*-isomer)], 4.53 [1H×*a*, dd, *J*=5.4, 7.3 Hz, C12*H* (*E*-isomer)], 5.77 [1H×*b*, s, C18*H* (*Z*-isomer)], 5.82 [1H×*a*, s, C18*H* (*E*-isomer)], 6.03 [1H×*b*, d, *J*=3.1 Hz, C13*H* (*E*-isomer)], 6.10 [1H×*a*, d, *J*=5.4 Hz, C13*H* (*Z*-isomer)], 7.36 (2H, C6′*H*, C7′*H*), 7.46 [1H×*a*, br s, C4′*H*], 7.87 (1H, m, C2′*H*), 8.61 (1H, m, C8′*H*). SI-MS (3-nitrobenzylalcohol) *m*/*z*=541 (MH^+). Neither EI- nor CI-MS of this sample gave informative signals. So, EI-HRMS was not measured.

4.21. 4-[(3*R*,4*R*,5*S*)-3-Acetoxy-5-metanesulfoxymethyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(1*S*,2*S*)-2,3-epoxy-2-methyl-1-(3-methoxy-5-methyl-1-naphthoxy)-propyl]-4*H*-oxazol-5-one (22)

4.21.1. Selective mesylation of 21. Methanesulfonyl chloride (20.7 mg, 181 μmol) was added to a mixture of **21** (90.0 mg, 167 μmol) and γ-collidine (37.0 mg, 303 mmol) in CH_2Cl_2 (2.0 mL) at 0°C with stirring. The cooling bath was removed after 30 min and the mixture was further stirred for 10 h at room temperature. The mixture was poured into aqueous 5% citric acid 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 (CH_2Cl_2–acetone 70:30→50:50) gave the mesylate (69.0 mg, 67%) and recovered **21** (13.5 mg, 14%), both as an oil.

4.21.2. Physical data of the mesylate. IR (film) 3350, 2940, 1735, 1855, 1600, 1360, 1235, 1220, 1175, 1070, 960, 910, 730, 530 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=50:50). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.54 [3H×0.5, s, C20H_3 (one isomer)], 1.56 [3H×0.5, s, C20H_3 (another isomer)], 1.97 [3H×0.5, s, CH_3COO (one isomer)], 2.13 [3H×0.5, s, CH_3COO (another isomer)], 2.67 (3H, s, CH_3Ar), 2.72 [1H×0.5, d, *J*=4.7 Hz, C21*H*H (one isomer)], 2.76 [1H×0.5, d, *J*=4.9 Hz, C21*H*H (another isomer)], 3.05 [3H×0.5, s, CH_3SO_3 (one isomer)], 3.07 [3H×0.5, s, (another isomer)], 3.57 [1H×0.5, br, alcoholic proton (one isomer)], 3.69 [1H×0.5, br, alcoholic proton (another isomer)], 3.97 (3H, s, CH_3OAr), 4.30–4.45 (2H, C11*H*, C11C*H*HO), 4.46–4.63 (2H, C12*H*, C11C*H*HO), 5.77 [1H×0.5, s, C18*H* (one isomer)], 5.79 [1H×0.5, s, C18*H* (one isomer)], 5.98 (1H, C3*H*) 7.11 [1H×0.5, br, amine proton(*Z*-isomer)], 7.36 (2H, m, C6′*H*, C7′*H*), 7.47 (1H, d, *J*=2.4 Hz, C4′*H*), 7.78 [1H×0.5, br, amine proton (*E*-isomer)], 7.88 (1H, m, C2′*H*), 8.62 (1H, m, C8′*H*). SI-MS (3-nitrobenzylalcohol): *m*/*z*=619 (MH^+). Neither EI- nor CI-MS of this sample gave useful signals. So, EI-HRMS was not measured.

4.21.3. Formation of the TES ether giving 22. A mixture of the mesylate (140 mg, 226 μmol), imidazole (160 mg, 2.35 mmol, 10 equiv.), and TESCl (150 mg, 1.0 mmol, 4.5 equiv.) in DMF (5.0 mL) was stirred 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 silica gel column chromatography (hexane–AcOEt=1:1) gave **22** (160 mg, 97%) as an oil. IR (film): 3350, 2950, 2880, 1740, 1750, 1650, 1600, 1360, 1280, 1220, 1240, 1180, 1080, 735 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=60:40). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (200 MHz, $CDCl_3$, *a*=0.60, *b*=0.40, *carzinophilin numbering*): δ 0.68 (6H, m, $(CH_3CH_2)_3Si$), 0.91 (9H, t, *J*=7.7 Hz, $(CH_3CH_2)_3Si$), 1.52 [3H×*a*, s, C20H_3 (*E*-isomer)], 1.52 [3H×*b*, s, C20H_3 (*Z*-isomer)], 2.00 [3H×*a*, s, CH_3COO (*E*-isomer)], 2.10 [3H×*b*, s, CH_3COO (*Z*-isomer)], 2.67 (3H, s, CH_3Ar), 2.70 [1H×*a*, d, *J*=4.9 Hz, C21*H*H (*E*-isomer)], 2.74 [1H×*b*, d, *J*=4.7 Hz, C21*H*H (*Z*-isomer)], 3.076 [3H×*a*, s, CH_3SO_3 (*E*-isomer)], 3.083 [3H×*b*, s, CH_3SO_3 (*Z*-isomer)]. 3.07 (1H, m, C21*H*H), 3.97 (3H, s, CH_3OAr), 4.25–4.50 (3H+1H×*b*, m, C11*H*, C11CH_2O, C12*H* (*Z*-isomer)), 4.62 [1H×*a*, t, *J*=5.3 Hz, C12*H* (*E*-isomer)], 5.76 [1H×*b*, s, C18*H* (*Z*-isomer)], 5.81 [1H×*a*, s, C18*H* (*E*-isomer)], 6.03 [1H×*b*, d, *J*=1.9 Hz, C13*H* (*Z*-isomer)],

6.13 [1H×*a*, *J*=5.3 Hz, C13*H* (*E*-isomer)], 6.93 [1H×*b*, br, amine proton (*Z*-isomer)], 7.37 (2H, C6′*H*, C7′*H*), 7.48 (1H, br s, C4′*H*), 7.77 [1H×*a*, br, amine proton (*E*-isomer)], 7.85 [1H×*a*, d, *J*=2.6 Hz, C2′*H* (*E*-isomer)], 7.90 [1H×*b*, d, *J*=2.6 Hz, C2′*H* (*Z*-isomer)], 8.63 (1H, m, C8′*H*). CI-MS (isobutane): *m*/*z*=733 (MH^+), 675 ($[M-MeC(O)CH_2]^+)^+$). EI-MS of this sample gave no informative peaks. EI-HRMS was not measured.

4.22. *N*-(9-Fluorenylmethoxycarbonyl)-L-threonine methyl ester (25)

A suspension of L-threonine methyl ester hydrochloride **24** (3.30 mg, 19.3 mmol) and FmocCl (5.00 g, 19.3 mmol) in a mixture of dioxane (10 mL) and aqueous $NaHCO_3$ solution (4.0 g in 20 mL) was stirred vigorously for 1 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 to give a crude solid. Recrystallization from Et_2O gave **25** (6.80 g, 99%) as fine needles. $[\alpha]_D^{20}=-13.6°$ (*c* 1.01, $CHCl_3$). Mp 126–127°C. IR (nujor): 3470, 3300, 2950, 2930, 1720, 1700, 1540, 1450, 1380, 1280, 1255, 1090, 1060, 1020, 1000, 760, 740 cm^{-1}. ^1H NMR (200 MHz $CDCl_3$, amino acid numbering) δ 1.24 (3H, d, *J*=6.2 Hz, C4H_3), 2.05 (1H, d, *J*=4.8 Hz, alcoholic proton), 3.78 (3H, s, CH_3O), 4.20–4.46 (5H, m, C2*H*, C3*H*, two methylenes and a methyne protons for Fmoc), 5.58 (1H, br d, *J*=8.7 Hz, amide proton), 7.35 (4H, m, aromatic protons), 7.61 (2H, br d, *J*=7.1 Hz, aromatic protons), 7.76 (2H, d, *J*=6.9 Hz, aromatic protons). Anal. calcd for $C_{20}H_{21}NO_5$: C, 67.59%; H, 5.96%; N, 3.94%. Found: C, 67.65%; H, 5.98%; N, 3.83%.

4.23. (2*R*,3*R*)- 2-(9-Fluorenylmethoxycarbonylamino)-3-(4-methoxyphenyl)methoxybutanol (26)

Trifluoromethanesulfonic acid (20 μL, 3.38 mg, 20 μmol) was added to a mixture of **25** (3.30 g, 9.24 mmol) and 4-methoxyphenylmethyl trichloroacetoimidate (3.00 g, 10.6 mmol) in a mixture of THF (20 mL) and Et_2O (40 mL) at room temperature with stirring. After 3 h, the mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane–AcOEt=80:20) gave the MPM ether containing trichloroacetoamide. Analytical sample was obtained as an oil by purification with preparative silica gel preparative TLC (hexane–AcOEt=80:20). IR (film) 3440, 3360, 2950, 1750, 1730, 1520, 1250, 1215, 1080, 1030, 760, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.24 (3H, d, *J*=6.3 Hz, C4H_3), 3.81 (3H, s, CH_3O), 4.11 (3H, s, CH_3O), 4.00–4.46 (6H, m, C2*H*, C3*H*, ArC*H*HO, two methylenes and a methyne protons for Fmoc), 4.53 (1H, d, *J*=11.5 Hz, ArC*H*HO), 5.58 (1H, br d, *J*=9.6 Hz, amide proton), 6.89 (2H, br d, *J*=6.8 Hz, aromatic protons), 7.20 (2H, br d, *J*=6.8 Hz, aromatic protons), 7.33 (4H, aromatic protons), 7.63 (2H, dd, *J*=5.2, 8.7 Hz, aromatic protons), 7.76 (2H, d, *J*=6.0 Hz, aromatic protons). CI-MS (isobutene) *m*/*z*=476 (MH^+). The crude MPM ether thus obtained was diluted with Et_2O (10 mL). The solution was mixed with $Zn(BH_4)_2$ (ca. 4 M in Et_2O, 20 mL, 8.0 mmol) and the mixture was stirred at room temperature for 12 h. After methanol was added to the mixture in order to decompose excess reagent, the mixture was poured into aqueous 10% citric acid solution (100 mL), then 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=50:50) gave **26** (2.40 g, 58% in two steps) as an oil. $[\alpha]_D^{20}=-17.5°$ (*c* 1.26, $CHCl_3$). IR (film): 3430, 2980, 2960, 2950, 1710, 1520, 1450, 1250, 1110, 1080, 1040, 830, 760, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, d, *J*=6.3 Hz, C4H_3), 2.45 (1H, br, alcoholic proton), 3.77 (2H, m, C1H_2), 3.81 (3H, s, CH_3O), 3.81 (1H, m, C2*H*), 4.22 (1H, t, *J*=6.9 Hz, methyne proton of Fmoc), 4.28 (1H, d, *J*=11.1 Hz, ArC*H*HO), 4.42 (2H, methylene proton of Fmoc), 4.58 (1H, d, *J*=11.1 Hz, ArC*H*HO), 5.32 (1H, br, amide proton), 6.89 (2H, br d, *J*=8.6 Hz, aromatic protons), 7.20 (2H, br d, *J*=8.6 Hz, aromatic protons), 7.33 (4H, m, aromatic protons), 6.63 (2H, d, *J*=7.2 Hz, aromatic protons), 7.76 (2H, d, *J*=7.0 Hz, aromatic protons). CI-MS (isobutene): *m*/*z*=448 (MH^+), 429 ($M-H_2O^+$). No useful information was obtained by EI-MS. So, EI-HRMS could not be measured.

4.24. (2*RS*,3*S*,4*R*)-2-(*tert*-Butyldiphenylsiloxy-3-(9-fluorenylmethoxycarbonyl)amino-4-(4-methoxyphenyl)-methoxypentanonitrile (27)

A mixture of **26** (86.0 mg, 192 μmol) and Dess–Martin reagent (150 mg, 364 μmol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 30 min. The mixture was poured into 5:2:10 mixture of aqueous 5% $Na_2S_2O_3$ solution, aqueous saturated $NaHCO_3$, and water, then extracted with AcOEt. The combined ethyl acetate extracts were washed with brine, dried with $MgSO_4$, then concentrated in vacuo. After the residue was dissolved in CH_3CN (3.0 mL), TBDMSCN (150 mg, 1.06 mmol) was added to the solution. The mixture was stirred at 80°C for 3 h, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt=80:20) to give **27** (103 mg, 92%) as a 75:25 mixture of the diastereomers. IR (film): 3440, 3350, 2860, 2840, 2250 (weak) 1730, 1615, 1515, 1250, 1110, 1040, 840, 780, 760, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, *a*=0.75, *b*=0.25): δ 0.13 (3H, s, (CH_3)Si), 0.20 [3H×*a*, s, (CH_3)Si (major)], 0.22 [3H×*b*, s, (CH_3)Si (minor)], 0.89 [9H×*a*, s, (CH_3)$_3$CSi (major)], 0.91 [3H×*b*, s, (CH_3)$_3$CSi (minor)], 1.22 [3H×*a*, d, *J*=6.3 Hz, C5H_3 (major)], 1.24 [3H×*a*, d, *J*=7.1 Hz, C5H_3 (minor)], 3.81 (3H×*a*, s), 3.82 [3H×*b*, s, CH_3O (major)], 3.90–4.60 (8H, m), 5.27 [1H×*b*, br d, *J*=8.7 Hz, amide proton (minor)], 5.38 [1H×*a*, br d, *J*=9.1 Hz, amide proton (major)], 6.90 (2H, br d, *J*=8.6 Hz, aromatic protons), 7.20–7.45 (4H, m, aromatic protons) 7.59 (2H, d, *J*=7.3 Hz, aromatic protons), 7.76 (2H, d, *J*=7.3 Hz, aromatic protons). CI-MS *m*/*z*=588 (MH^+), 587 (M^+). EIMS did not provide informative peaks. So, EI-HRMS was not measured.

4.25. (2*R* or 2*S*, 3*S*,4*R*)-2-*tert*-Butyldiphenylsiloxy-3-amino-4-(4-methoxyphenyl)methoxypentanenitrile (28)

4.25.1. Reaction procedure. A solution of **27** (2.60 g, 4.44 mmol) in a mixture of DMF (20 mL) and piperidine (4.0 mL) was stirred at room temperature for 1 h. The mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography

(hexane–AcOEt=90:10) gave **28** (1.04 g, 64%) and its diastereomer (453 mg, 27%).

4.25.2. Physical data of 28. R_F=0.35 (silica gel, hexane–AcOEt=70:30). $[\alpha]_D^{20}=-9.10°$ (*c* 1.23, $CHCl_3$). IR (film): 3400, 2970, 2940, 2870, 1610, 1515, 1465, 1250, 1110, 1070, 1035, 840, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.13, 0.21 (each 3H, s, (CH_3)Si×2), 0.91 (9H, s, (CH_3)$_3$CSi), 1.30 (3H, d, *J*=6.2 Hz, C5H_3), 2.80 (1H, dd, *J*=3.0, 7.1 Hz, C3*H*), 3.80 (3H, s, CH_3O), 3.82 (1H, m, C4*H*), 4.33 (1H, d, *J*=7.2 Hz, C2*H*), 4.35 (1H, d, *J*=11.3 Hz, ArC*H*HO), 4.57 (1H, d, *J*=11.3 Hz, ArC*H*HO), 6.88 (2H, br t, *J*=8.7 Hz, aromatic protons), 7.21 (2H, br d, *J*=8.7 Hz, aromatic protons); CI-MS (isobutene): *m*/*z*=365 (MH^+), 338 ([M−HCN]$^+$). EIMS provided no informative peaks. So, EI-HRMS was not measured.

4.25.3. Physical data of the diastereomer of 28. R_F=0.45 (silica gel, hexane–AcOEt=70:30). $[\alpha]_D^{20}=-51.3°$ (*c* 1.16, $CHCl_3$). IR (film): 3420, 2970, 2940, 2870, 1610, 1515, 1470, 1250, 1100, 1040, 840, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.12, 0.21 (each 3H, s, (CH_3)Si×2), 0.91 (9H, s, (CH_3)$_3$CSi), 1.31 (3H, d, *J*=6.2 Hz, C5H_3), 2.83 (1H, dd, *J*=2.9, 7.7 Hz, C3*H*), 3.76 (1H, m, C4*H*), 3.80 (3H, s, CH_3O), 4.27 (1H, d, *J*=10.9 Hz, ArC*H*HO), 4.40 (1H, d, *J*=7.6 Hz, C2*H*), 4.55 (1H, d, *J*=10.9 Hz, ArC*H*HO), 6.87 (2H, br d, *J*=8.7 Hz, aromatic protons), 7.21 (2H, br d, *J*=8.7 Hz, aromatic protons); CI-MS *m*/*z*=365 (MH^+), 338 ([M−HCN]$^+$). EIMS provided no informative peaks. So, EI-HRMS was not measured.

4.26. (3*R*,4*R*,5*S*)-3-Acetoxy-2-[(*E*)-1-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methylnaphthoxy)-3-methyl-butyryl-amino]-1-[*N*-[(1*R* or 1*S*,3*R*)-[1-*tert*-butyldimethylsiloxy-1-cyano-3-(4-methoxyphenylmethoxy)but-2-yl]-carbamoyl]]methylidene-4-triethylsiloxy-5-(methane-sulfonyl)oxymethyl-1-(2-propenyloxycarbonyl)-pyrrolidine (29*E*) and its *Z*-isomer (29*Z*)

4.26.1. Reaction procedure. A mixture of **22** (130 mg, 177 μmol), DMAP (1.0 mg, 8.2 μmol), and $Alloc_2O$ (49.0 mg, 265 μmol) in THF (5.0 mL) was stirred at room temperature. After 10 min, a solution of **28** (90 mg, 247 μmol) in THF (4.0 mL) was added to the mixture. The whole mixture was concentrated in vacuo at 40°C over 15 min. Purification of the residue by silica gel column chromatography (hexane–AcOEt=80:20→60:40) gave **29***Z* (7.0 mg, 3.3%) and **29***E* (144 mg, 69%) both as an oil.

4.26.2. Physical data of 29*E*. $[\alpha]_D^{20}=+62.0°$ (*c* 1.21, $CHCl_3$). IR (film): 3420, 3320, 2860, 2840, 1730, 1690, 1620, 1510, 1360, 1280, 1240, 1180, 1090, 850, 810, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.14, 0.19 (each 3H, s, (CH_3)$_2$Si), 0.58 (6H, m, (CH_3CH_2)$_3$Si), 0.88 (9H, t, *J*=7.9 Hz, (CH_3CH_2)$_3$Si), 0.89 (9H, s, (CH_3)$_3$CSi), 1.29 (3H, d, *J*=6.4 Hz, C1H_3), 1.57 (3H, s, C20H_3), 2.06 (3H, s, CH_3COO), 2.67 (3H, s, CH_3Ar), 2.70 (1H, d, *J*=4.7 Hz, C21*H*H), 2.95, (3H, s, CH_3SO_3), 3.08 (1H, d, *J*=4.7 Hz, C21*H*H), 3.96 (3H, s, CH_3OAr), 4.05 (2H, m, C3*H*, C11*H*), 4.13 (1H, br q, *J*=6.4 Hz, C2*H*), 4.43 (1H, m, C11C*H*HO), 4.44 (1H, d, *J*=4.1 Hz, C12*H*), 4.47, 4.50 (each 1H, d, *J*=10.5 Hz, $OCH_2CH{=}CH_2$), 4.61 (1H, d, *J*=5.4 Hz, C4*H*), 4.66 (2H, br d *J*=4.5 Hz, $CH_2{=}CHCH_2O$), 4.72 (1H, dd, *J*=3.2, 10.2 Hz, C11C*H*HO), 5.12 (1H, s, C13*H*), 5.25 (1H, br d *J*=10.1 Hz, C*H*H=CHCH$_2$O), 5.34 (1H, br d *J*=16.4 Hz, C*H*H=CHCH$_2$O), 5.53 (1H, s, C18*H*), 5.97 (1H, DDT, *J*=10.1, 16.4, 5.9 Hz, $CH_2{=}CHCH_2O$), 6.33 (1H, br d, *J*=7.9 Hz, N5*H*), 6.83 (2H, br d *J*=8.7 Hz, aromatic protons for MPM), 7.30–7.37 (4H, m, aromatic protons for MPM, C6′*H*, C7′*H*), 7.47 (1H, d, *J*=2.6 Hz, C4′*H*), 8.14 (1H, d, *J*=2.6 Hz, C2′*H*), 8.70 (1H, m, C8′*H*), 9.32 (1H, br s, N16*H*). SI-MS (3-tirobenzylalcohol) *m*/*z*=1181 (MH^+). Neither EI-MS nor CI-MS of this sample gave informative signals. So, EI-HRMS was not measured.

4.26.3. Physical data of 29*Z*. IR (film): 3430, 3350, 2260, 1720, 1620, 1510, 1470, 1360, 1230, 1180, 1115, 1090, 1030, 960, 840, 730 cm^{-1}. ^1H NMR (200 MHz $CDCl_3$, *carzinophilin numbering*): δ 0.19, 0.21 (each 3H, s, (CH_3)$_2$Si), 0.69 (6H, m, (CH_3CH_2)$_3$Si), 0.88 (9H, s, (CH_3)$_3$CSi), 0.95 (9H, t, *J*=7.1 Hz, (CH_3CH_2)$_3$Si), 1.18 (3H, d, *J*=6.2 Hz, C1H_3), 1.43 (3H, s, C20H_3), 2.00 (3H, s, CH_3COO), 2.29 (3H, d, *J*=4.1 Hz, C21*H*H), 2.67 (3H, s, CH_3Ar), 2.95 (3H, s, CH_3SO_3), 2.97 (3H, d, *J*=4.1 Hz, C21*H*H), 3.54 (1H, br dd, *J*=5.5, 12.9 Hz, C11C*H*HO), 3.79 (3H, s, CH_3OAr), 3.98 (3H, s, MeOAr), 4.00–4.57 (9H, m, C2*H*, C3*H*, C11*H*, C12*H*, C11C*H*HO, $CH_2{=}CHCH_2O$, ArCH_2O), 4.73 (1H, d, *J*=7.0 Hz, C11*H*), 4.88 (1H, dq, *J*=17.0, 1.4 Hz, C*H*H=CHCH$_2$O), 4.98 (1H, dq, *J*=10.4, 1.4 Hz, C*H*H=CHCH$_2$O), 5.43 (1H, s, C18*H*), 5.44 (1H, m, $CH_2{=}CHCH_2O$), 6.41 (1H, s, C13*H*), 6.83 (2H. br d *J*=8.7 Hz, aromatic protons for MPM). 6.97 (1H, br d *J*=8.9 Hz, N5H), 7.33 (4H, m, aromatic protons for MPM, C6′*H*, C7′*H*), 7.50 (1H, d, *J*=2.5 Hz, C4′*H*), 8.07 (1H, d, *J*=2.5 Hz, C1′*H*), 8.74 (1H, dd, *J*=3.0, 6.7 Hz, C8′*H*), 8.99 (br s, N16*H*). SI-MS (3-nitrobenzylalcohol): *m*/*z*=1181 (MH^+), 1121 (M−AcO$^+$); SI-MS (3-nitrobenzylalcohol+KCl): *m*/*z*=1219 ([M+K]$^+$). Neither EI- nor CI-MS of this sample gave informative signals. So, EI-HRMS was not measured.

4.27. (3*R*,4*R*,5*S*)-3-Acetoxy-2-[(*E*)-1-[(2*S*,3*S*)-3,4-epoxy-3-methyl-2-(3-methoxy-5-methyl-1-naphthoxy)butyryl-amino]-1-[*N*-[(1*R* or 1*S*,3*R*)-[1-*tert*-butyldimethylsiloxy-1-cyano-3-oxobut-2-yl]carbamoyl]]methylidene-4-tri-ethylsiloxy-5-(methanesulfoxymethyl-1-(2-propenyl-oxycarbonyl)pyrrolidine (30)

4.27.1. Removal of the MPM group in 29*E*. A mixture of the **29***E* (40.0 mg, 33.8 μmol) and DDQ (30.0 mg, 132 μmol) in a mixture of CH_2Cl_2 (2.0 mL) and H_2O (200 μL) was stirred at room temperature for 1 h. The mixture was poured into a 1:1 mixture of aqueous 5% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solutions, then extracted with AcOEt. The organic extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane–AcOEt=50:50) afforded the corresponding alcohol (35 mg, 97%) as a colorless caramel. $[\alpha]_D^{20}=+91.6°$ (*c* 1.11, $CHCl_3$). IR (film): 3430, 1730, 1690, 1510, 1360, 1280, 1235, 1180, 1080, 840, 810, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.16, 0.21 (each 3H, s, (CH_3)$_2$Si), 0.70 (6H, m, (CH_3CH_2)$_3$Si), 0.90 (9H, s, (CH_3)$_3$CSi), 0.94 (9H, t, *J*=8.2 Hz, (CH_3CH_2)$_3$Si), 1.30 (3H, d, *J*=6.4 Hz, C1H_3), 1.58 (3H, s, C20H_3), 2.06

(3H, s, CH_3COO), 2.44 (1H, br, alcoholic proton), 2.67 (3H, s, CH_3Ar), 2.72 (1H, d, J=4.6 Hz, C21HH), 3.00 (3H, s, CH_3SO$_3$), 3.07 (1H, d, J=4.6 Hz, C21HH), 3.96 (3H, s, CH_3OAr), 3.97 (1H, m, C3H), 4.37 (1H, br, C2H), 4.40–4.55 (3H, C11H, C12H, C11CHHO), 4.63 (3H, CH$_2$=CHCH_2O, C11CHHO), 4.80 (1H, d, J=6.6 Hz, C4H), 5.18 (1H, s, C18H), 5.20 (1H, dq, J=10.3, 1.0 Hz, CHH=CHCH$_2$O), 5.32 (1H, dq, J=17.0, 1.0 Hz, CHH=CHCH$_2$O), 5.50 (1H, s, C13H), 5.94 (1H, ddt, J=10.3, 17.0, 5.9 Hz, CH$_2$=CHCH$_2$O), 6.44 (1H, br d J=8.5 Hz, N5H), 7.34 (2H, C6′H, C7′H), 7.48 (1H, d, J=2.5 Hz, C4′H), 8.13 (1H, d, J=2.5 Hz, C2′H), 8.68 (1H, m, C8′H), 9.35 (1H, br s, N16H). SI-MS (3-nitrobenzylalcohol): m/z=1061 (MH$^+$), 1003 ([M−CH$_2$=CHCH$_2$O]$^+$), 817 ([M−CH$_3$CH(OH)CH(CH(CN)(OTBS))NH]$^+$). Neither EI-MS nor CI-MS of this sample gave informative peaks. So, EI-HRMS was not measured.

4.27.2. Oxidation giving 30. A mixture of the alcohol (148 mg, 139 μmol) and Dess–Martin reagent (120 mg, 291 μmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 40 min. The mixture was poured into a 1:1 mixture of aqueous 5% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution, then 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 **30** (144 mg, 98%) as a colorless caramel. $[\alpha]_D^{20}$=+72.9° (*c* 1.13, $CHCl_3$). IR (film): 3440, 3410, 330, 2960, 2260 (weak), 1730, 1690, 1500, 1370, 1280, 1240, 1180, 900, 840, 810, 735 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.21, 0.23 (each 3H, s, (CH_3)$_2$Si), 0.68 (6H, m, (CH$_3$CH_2)$_3$Si), 0.92 (9H, s, (CH_3)$_3$CSi), 0.94 (9H, t, J=8.3, (CH$_3$CH$_2$)$_3$Si), 1.53, 2.06, 2.34, 2.67 (each 3H, s, C20H_3, CH_3COO, C1H_3, CH_3Ar, respectively), 2.71 (1H, d, J=4.7 Hz, C21HH), 3.02 (3H, s, CH_3SO$_3$), 3.07 (1H, d, J=4.7 Hz, C21HH), 3.96 (3H, s, CH_3OAr), 4.40–4.80 (7H, C3H, C11H, C12H, C11CH_2O, CH$_2$=CHCH_2O), 5.03 (1H, d, J=4.0 Hz, C4H), 5.17 (1H, s, C13H), 5.27 (2H, m, CH_2=CHCH$_2$O), 5.44 (1H, s, C18H), 5.92 (1H, ddt, J=10.4, 17.1, 5.8 Hz, CH$_2$=CHCH$_2$O), 6.70 (1H, br d J=6.3 Hz, N5H), 7.34 (2H, m, C6′H, C7′H), 7.47 (1H, d, J=2.5 Hz, C4′H), 8.11 (1H, d, J=2.5 Hz, C2′H), 8.68 (1H, m, C8′H), 9.36 (1H, br s, N16H). SI-MS (3-nitrobenzylalcohol+NaCl): m/z=1081 ([M+Na]$^+$), 1059 (MH$^+$). Neither EI-MS nor CI-MS of this sample gave useful information. So, EI-HRMS was not measured.

4.28. (3*R*,4*R*,5*S*)-3-Acetoxy-2-[(*E*)-1-[(2*S*,3*S*)-3,4-epoxy-3-methyl-2-(3-methoxy-5-methylnaphthoxy)butyryl-amino]-1-[*N*-[1*R* or 1*S*, (3*R*)-[1-*tert*-butyldimethylsiloxy-1-cyano-3-oxobutan-2-yl]carbamoyl]]methylidene-4-triethylsilyloxy-5-(methanesulfoxymethylpyrrolidine (31)

A mixture of **30** (16.3 mg, 15.4 μmol), AcOH (3.0 μL), PPh_3 (800 μg, 3.0 μmol), and Pd(PPh$_3$)$_4$ (1.3 mg, 1.2 μmol) in THF (1.0 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was purified by silica gel column chromatography (AcOEt–hexane=60:40) to give **31** (15.0 mg, 100%) as a colorless caramel. $[\alpha]_D^{20}$=−38.9° (*c* 1.11, $CHCl_3$). IR (film): 3350, 2960, 1750, 1720, 1660, 1629, 1600, 1510, 1500, 1420, 1360, 1280, 1235, 1215, 1180, 1100, 1070, 1050, 1000, 960, 840, 810, 750 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.16, 0.23 (each 3H, s, (CH_3)$_2$Si), 0.45 (6H, m, (CH$_3$CH_2)$_3$Si), 0.70 (9H, t, J=7.2 Hz, (CH$_3$CH_2)$_3$Si), 0.91 (9H, s, (CH_3)$_3$CSi), 1.53, 2.11, 2.22, 2.69 (each 3H, s, C20H_3, CH_3COO, C1H_3, CH_3Ar, respectively), 2.76 (1H, d, J=4.4 Hz, C21HH), 3.03 (3H, s, CH_3SO$_3$), 3.37 (1H, d, J=4.4 Hz, C21HH), 4.00 (3H, s, CH_3OAr), 4.20 (3H, C11H, C12H, C11CHHO), 4.18 (1H, m, C11CHHO), 4.94 (1H, dd, J=3.4, 9.0 Hz, C3H), 5.11 (1H, d, J=3.4 Hz, C4H), 5.39, 5.68 (each 1H, s, C13H, C18H, respectively), 7.13 (1H, br s, N9H), 7.22 (1H, br d J=9.0 Hz N5H). 7.37 (2H, C6′H, C7′H), 7.50, 8.02 (each 1H, d, J=2.5 Hz, C4′H, C2′H, respectively), 8.64 (1H, br s, N16H), 8.73 (1H, m, C8′H). SI-MS (3-nitrobenzylalcohol): m/z=975 (MH$^+$). Neither EI- nor CI-MS of this sample gave useful peaks. So, EI-HRMS was not measured.

4.29. (3*R*,4*R*,5*S*)-3-Acetoxy-2-[(*E*)-1-[(2*S*,3*S*)-3,4-epoxy-3-methyl-2-(3-methoxy-5-methylnaphthoxy)butyryl-amino]-1-[*N*-[(3*R*)-(*Z*)-1-methoxymethylene-2-oxo-propyl1-[1-hydroxy-1-cyano-3-oxobutan-2-yl]-carbamoyl]]methylidene-4-triethylsilyloxy-5-(methane-sulfonyl)oxymethyl-carbonylpyrrolidine (32)

A mixture of **31** (11.0 mg, 11.3 μmol) and TBAF (1.0 M in THF, 34 μL) in a mixture of THF (1.5 mL) and AcOH(25 μL) was stirred at room temperature for 3 h. After saturated aqueous $NaHCO_3$ solution (200 μL) was added to the mixture, the mixture was stirred at room temperature for 10 min. The mixture was poured into aqueous 10% citric acid solution, and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. After the residue was dissolved in CH_2Cl_2 (1.0 mL), an ethereal CH_2N_2 (1.0 mL, excess) was added to the solution. The mixture was kept standing at room temperature for 1 h. After concentration, the residue was purified by silica gel column chromatography (CH_2Cl_2–acetone=50:50) to give **32** (6.8 mg, in 82% two steps) as a colorless caramel. $[\alpha]_D^{20}$=−9.1° (*c* 0.31, $CHCl_3$). IR (film): 3370, 2950, 1740, 1730, 1710, 1690, 1680, 1640, 1620, 1605, 1510, 1500, 1360, 1240, 1220, 1180, 1080, 1050, 970, 735 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*, 2.0 mg/mL; The spectral pattern of this sample changed depending upon the concentration): δ 1.58, 2.207, 2.213, 2.69 (each 3H, s, C20H_3, C1H_3, CH_3COO, CH_3Ar, respectively), 2.81 (1H, d, J=4.3 Hz, C21HH), 3.80 (1H, d, J=3.6 Hz, alcoholic proton), 3.83 (1H, d, J=4.3 Hz, C21HH), 3.83, 4,00 (each 3H, s, CH_3O×2), 4.27–4.34 (3H, m, C11H, C12H, C11CHHO), 4.42 (1H, d, J=3.8, 10.3 Hz, C11CHHO), 5.32 (1H, s, C18H), 5.37 (1H, d, J=3.2 Hz, C13H), 7.21 (1H, s, C4H), 7.22, 7.33 (each 1H, br s, N5H, N9H), 7.33 (2H, m, C6′H, C7′H), 7.54, 8.00 (each 1H, d, J=2.6 Hz, C4′H, C2′H, respectively), 8.57 (1H, s, N16H), 8.63 (1H, m, C8′H). SI-MS (3-nitrobenzylalcohol): m/z=734 (MH$^+$), 634 ([M−(CH$_3$C(O)C(=CHOMe))$^+$], 619 ([M−(CH$_3$-C(O)C(=CHOMe)NH)]$^+$). SI-MS (3-nitrobenzylalcohol+NaCl): m/z=756 ([M+Na]$^+$), 734 (MH$^+$), 634 ([M−(CH$_3$-C(O)C(=CHOMe))$^+$], 619 ([M−(CH$_3$C(O(=CHOMe)-NH))$^+$]. Neither EI- nor CI-MS of this sample gave useful peaks. So, EI-HRMS was not measured.

4.30. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*tert*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]-2-[2-(*E*)-(benzyloxymethoxy)methyl-1-propenyl]-4*H*-oxazol-5-one (40)

4.30.1. Reaction procedure. A mixture of **11***E* (610 mg, 1.02 mmol) and **7** (1.88 g, 6.82 mmol) in toluene (2.0 mL) was stirred at 60°C for 12 h under Ar gas bubbling. After concentration, the residue was purified by silica gel column chromatography (hexane–AcOEt=90:10→30:70) to give recovered **7** (105 mg, 17%) and **40** (489 mg, 58%) both as an oil.

4.30.2. Physical data of 40. IR (film): 3400, 3030, 3010, 2930, 2860, 1720, 1635, 1455, 1110, 1060, 910, 735, 700, 610, 500 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=80:20). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.80, *b*=0.20, *carzinophilin numbering*): δ 1.03 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.07 [9H×*b*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 2.15 [3H×*b*, s, C20H_3 (*Z*-isomer)], 2.16 [3H×*a*, s, C20H_3 (*E*-isomer)], 3.76 [1H×*a*, dd, *J*=4.1, 10.6 Hz, C11C*H*HO (*E*-isomer)], 3.85 [1H×*a*, dd, *J*=6.0, 10.6 Hz, C11C*H*HO (*E*-isomer)], 3.86 [2H×*b*, m, C11CH_2O (*Z*-isomer)], 4.16 (3H, m, C11*H*, C21CH_2O), 4.37 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.49 [1H×*b*, PhC*H*HO (*Z*-isomer)], 4.52 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.64 [2H×*b*, s, PhCH_2O (*Z*-isomer)], 4.65 [1H×*a*, s, PhCH_2O (*E*-isomer)], 4.81 [2H×*b*, s, OCH_2O (*Z*-isomer)], 4.82 [2H×*a*, s, OCH_2O (*E*-isomer)], 4.83 [1H×*a*, d, *J*=11.6 Hz PhC*H*HO (*E*-isomer)], 5.00 [1H×*a*, d, *J*=11.6 Hz PhC*H*HO (*E*-isomer)], 5.10 [1H×*a*, d, *J*=2.3 Hz, C13*H* (*E*-isomer)], 5.26 [1H×*b*, s, C13*H* (*Z*-isomer)], 6.15 [1H×*b*, hext, *J*=1.3 Hz, C18*H* (*Z*-isomer)], 6.18 [1H×*a*, hext, *J*=1.3 Hz, C18*H* (*E*-isomer)], 6.74 [1H×*b*, br s, amine proton (*Z*-isomer)], 7.08 [2H×*b*, m, aromatic protons (*Z*-isomer)], 7.12 [2H×*a*, aromatic protons (*E*-isomer)], 7.22–7.45 (14H, aromatic protons), 7.63 (4H, m, aromatic protons), 7.90 (1H×*a*, br s, amine proton). EI-MS (rel. int.%): *m*/*z*=822 (trace, M^+), 765 (trace, $[M-t\text{Bu}]^+$), 687 (trace, $[M-t\text{Bu}-\text{PhH}]^+$), 91 (100, Bn^+). CI-MS (isobutene): *m*/*z*=823 (MH^+). EI-HRMS calcd for $C_{50}H_{54}N_2O_7Si$ (M^+): *m*/*z*=822.3702. Found: *m*/*z*=822.3706.

4.31. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*tert*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]-2-[2-(*E*)-hydroxymethyl-1-propenyl]-4*H*-oxazol-5-one (41)

A mixture of **40** (1.10 g, 1.33 mmol) and DDQ (400 mg, 1.76 mmol) in a mixture of CH_2Cl_2 (15 mL) and H_2O (1.5 mL) was stirred at room temperature for 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. After the residue was dissolved in MeOH (5.0 mL), $NaBH_4$ (100 mg, 2.63 mmol) was added at 0°C. The mixture was stirred at the same temperature for 30 min, poured into water, then extracted with AcOEt. 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 (hexane–AcOEt=70:30) gave **41** as an oil. IR (film) 3370, 2930, 2860, 1720, 1660, 1635, 1455, 130, 1210, 1110, 1070, 1030, 910, 740, 700, 505 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=70:303). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (200 MHz, $CDCl_3$, *a*=0.70, *b*=0.30, *carzinophilin numbering*) δ 0.96 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.00 [9H×*a*, s, $(CH_3)_3CSi$ (*Z*-isomer)], 1.96 [3H×*b*, s, C3′H_3 (*Z*-isomer)], 2.04 [3H×*a*, s, C20H_3 (*E*-isomer)], 2.38 [1H×*a*, br, alcoholic proton (*E*-isomer)], 3.71 [1H×*a*, dd, *J*=4.3, 10.5 Hz, C11C*H*HO (*E*-isomer)], 3.78 [1H×*b*, dd, *J*=4.9, 10.3 Hz, C11C*H*HO (*Z*-isomer)], 3.80 [1H, dd, *J*=6.2, 10.5 Hz, C11C*H*HO (*E*-isomer)], 3.82 [1H×*b*, dd, *J*=8.2, 10.3 Hz, C11C*H*HO (*Z*-isomer)], 3.99 [2H×*b*, br s, C2′CH_2O (*Z*-isomer)], 4.08–4.20 [2H+1H×*b*, C11*H*, C12*H*, PhC*H*HO (*E*-isomer)], 4.31 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.41 [1H×*b*, d, *J*=12.0 Hz, PhC*H*HO (*E*-isomer)], 4.45 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.70 [1H×*a*, d, *J*=9.6 Hz, PhC*H*HO (*Z*-isomer)], 4.75 [1H×*a*, d, *J*=10.9 Hz PhC*H*HO (*E*-isomer)], 4.79 [1H×*b*, d, *J*=9.6 Hz, PhC*H*HO (*Z*-isomer)], 5.55 [1H×*a*, d, *J*=2.6 Hz, C13*H*(*E*-isomer)], 5.20 [1H×*b*, s, C13*H* (*Z*-isomer)], 6.09 [1H×*b*, m, C18*H* (*Z*-isomer)], 6.13 [1H, hext, *J*=1.3 Hz, C18*H* (*E*-isomer)], 7.01 [2H×*b*, aromatic protons (*Z*-isomer)], 7.15–7.40 [14H, aromatic protons], 7.53–7.62 (4H, aromatic protons), 7.83 [1H×*a*, br s, amine proton(*E*-isomer)]. CI-MS (isobutene) *m*/*z*=703 (MH^+), 687 ($[M-\text{Me}]^+$). EI-MS provided gave only a fragmented signal [*m*/*z*=199, (Ph_2Si^+=O)]. EI-HRMS was not measured.

4.32. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*tert*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]-2-[(1*R*,2*S*)-1,2,3-trihydroxy-2-methylpropyl]-4*H*-oxazol-5-one (42)

In a hood, a solution of **41** (1.75 g, 2.49 mmol) in CH_2Cl_2 (3.0 mL) was added to a mixture of OsO_4 (624 mg, 2.46 mmol) and $(DHQ)_2PHAL$[15] (2.40 g, 3.08 mmol) in CH_2Cl_2 (20 mL) at 0°C with stirring. After stirring for 15 min, H_2S gas was bubbled into the mixture to give a black suspension. Celite® (3 g) and AcOEt (50 mL) were added to the suspension, and the whole mixture was stirred at room temperature for additional 30 min with H_2S bubbling. After filtration through a pad of Celite®, the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (AcOEt–hexane=90:10) gave **42** (1.19 g, 65%) as an oil. The signals due to 18*S* isomer (*carzinophilin numbering*) was not observed by 400 MHz ^1H NMR spectrum of this sample. Thus, the diastereomeric purity was estimated to be >96% de. IR (film) 3360, 2940, 2860, 1720, 1650, 1590, 1455, 1430, 1380, 1110, 1065, 910, 730, 700, 505 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=56:44). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.56, *b*=0.44, *carzinophilin numbering*) δ 1.03 [9H×*a*, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.06 [9H×*b*, $(CH_3)_3CSi$ (*Z*-isomer)], 1.15 [3H×*b*, C20H_3 (*Z*-isomer)], 1.18 [3H×*a*, C20H_3 (*E*-isomer)], 2.70 [1H×*a*, br, alcoholic proton (*E*-isomer)], 3.02 [1H×*b*, br, alcoholic proton (*Z*-isomer)], 3.30 (1H, br, alcoholic proton), 3.57 (2H, m,

C11C*H*HO, alcoholic proton), 3.75 (1H, m, C11C*H*HO), 8.88 [1H+1H×*a*, C11*H*, C12*H* (*E*-isomer)], 3.96 [1H×*b*, d, *J*=4.1 Hz, C12*H* (*Z*-isomer)], 4.18 (2H, br s, C21H_2O), 4.27 [1H×*b*, d, *J*=11.9 Hz, PhC*H*HO (*Z*-isomer)], 4.41 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.49 [1H×*b*, d, *J*=11.9 Hz, PhC*H*HO (*Z*-isomer)], 4.55 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.57 (1H, br, C18*H*), 4.74 [1H×*b*, d, *J*=11.0 Hz, PhC*H*HO (*Z*-isomer)], 4.76 [1H×*a*, d, *J*=11.6 Hz, PhC*H*HO (*E*-isomer)], 4.84 [1H×*b*, d, *J*=11.0 Hz, PhC*H*HO (*Z*-isomer)], 4.89 [1H×*a*, d, *J*=11.6 Hz, PhC*H*HO (*E*-isomer)], 5.09 [1H×*a*, d, *J*=2.3 Hz, C13*H* (*E*-isomer)], 5.23 [1H×*b*, s, C13*H* (*Z*-isomer)], 7.08–7.16 (2H, aromatic protons), 7.23–7.50 (14H, aromatic protons), 7.62 (4H, aromatic protons), 7.87 [1H×*a*, br s, amine proton(*E*-isomer)]. CI-MS (isobutane) *m*/*z*=737 (MH^+), 675 ([M−$HOCH_2CMe$]$^+$). EI-MS of this sample provided no structural information. So, EI-HRMS was not measured.

4.33. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*tert*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]-2-[(1*R*,2*S*)-2,3-epoxy-1-hydroxy-2-methylpropyl]-4*H*-oxazol-5-one (43)

4.33.1. Selective mesylation of 42. A mixture of **42** (624 mg, 774 μmol), MsCl (130 mg, 1.14 mmol), and γ-collidine (187 mg, 1.50 mmol), in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 4 h. After MeOH (100 μL) was added in order to decompose excess MsCl, 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–AcOEt=60:40) gave the mesylate (514 mg, 81%). IR (film): 3350, 2930, 2860, 1760, 1650, 1480, 1360, 1175, 1110, 1070, 1000, 970, 910, 740, 700, 505 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*=56:44). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (400 MHz, $CDCl_3$, *a*=0.56, *b*=0.44, *carzinophilin numbering*) δ 1.02 [9H×*a*, s, (CH_3)$_3$CSi (*E*-isomer)], 1.07 [9H×*b*, s, (CH_3)$_3$CSi (*E*-isomer)], 1.30 [3H×*b*, C20H_3 (*Z*-isomer)], 1.31 [3H×*a*, s, C20H_3 (*E*-isomer)], 3.00 [3H×*b*, s, CH_3SO_3 (*Z*-isomer)], 3.02 [3H×*a*, s, CH_3SO_3 (*Z*-isomer)], 3.17 [1H×*a*, C19O*H* (*E*-isomer)], 3.23 [1H×*a*, br d, *J*=6.5 Hz, C18O*H* (*E*-isomer)], 3.53 [1H×*b*, br, C19O*H* (*Z*-isomer)], 3.75 [1H×*a*, dd, *J*=4.0, 10.9 Hz, C11C*H*HO (*E*-isomer)], 3.87 [2H×*a*, alcoholic proton, C11C*H*HO (*E*-isomer)], 3.97 [1H×*b*, C12*H* (*Z*-isomer)], 4.19 [3H×*a*, C12*H* (*E*-isomer), C18*H* (*E*-isomer), C11*H* (*E*-isomer)], 4.25, 4.29 [each 1H×*a*, d, *J*=10.2 Hz, C21H_2O (*E*-isomer)], 4.41, 4.53 [each 1H×*a*, d, *J*=11.9 Hz, PhCH_2O (*E*-isomer)], 4.74 [1H×*b*, *J*=11.0 Hz, PhC*H*HO (*Z*-isomer)], 4.76 [1H×*a*, *J*=11.5 Hz, PhC*H*HO (*E*-isomer)], 4.85 [1H×*b*, *J*=11.0 Hz, PhC*H*HO (*Z*-isomer)], 4.89 [1H×*a*, *J*=11.5 Hz, PhC*H*HO (*Z*-isomer)], 5.08 [1H×*a*, d, *J*=2.7 Hz, C13*H* (*E*-isomer)], 5.21 [1H×*b*, s, C13*H* (*Z*-isomer)], 6.91 [1H×*a*, br, amine proton (*Z*-isomer)], 7.08 [2H×*b*, aromatic protons (*Z*-isomer)], 7.14 [2H×*a*, aromatic protons (*E*-isomer)], 7.21–7.48 (14H, aromatic protons), 7.62 (4H, aromatic protons), 7.89 [1H×*a*, amine proton (*E*-isomer)]. EI-MS (rel int.%): *m*/*z*=718 (trace, [M−MsOH]$^+$), 661 (trace, [M−MsOCH_2-C(OH)Me]$^+$), 199 (100, Ph_2Si^+=O). EI-HRMS: calcd for $C_{42}H_{46}N_2O_7Si$ ([M−MsOH]$^+$): *m*/*z*=718.3076. Found *m*/*z*=718.3071.

4.33.2. The epoxide cyclization giving 43. A mixture of the mesylate (990 mg, 1.22 mmol) and DBU (220 mg, 1.44 mmol) in CH_2Cl_2 (10 mL) was stirred at 0°C for 30 min. 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 (hexane–AcOEt=65:35) gave **43** (738 mg, 84%) as an oil. IR (film) 3420, 2940, 2860, 1730, 1650, 1490, 1460, 1430, 1280, 1210, 1110, 1070, 910, 735, 700, 610, 505 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*=68:32). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (200 MHz, $CDCl_3$, *a*=0.68, *b*=0.32, *carzinophilin numbering*) δ 1.04 [9H×*a*, s, (CH_3)$_3$CSi (*E*-isomer)], 1.07 [9H×*b*, s, (CH_3)$_3$CSi (*Z*-isomer)], 1.37 (3H, s, C20H_3), 2.70 [1H×*a*, d, *J*=4.6 Hz, C21*H*H (*E*-isomer)], 2.71 [1H×*b*, d, *J*=4.6 Hz, C21*H*H (*Z*-isomer)], 2.98 (1H, d, *J*=4.6 Hz, C21*H*H), 3.01[1H×*a*, d, *J*=6.7 Hz, alcoholic proton (*E*-isomer)], 3.40 [1H×*b*, d, *J*=6.4 Hz, alcoholic proton (*Z*-isomer)], 3.77 [1H×*a*, dd, *J*=3.7, 10.3 Hz, C11C*H*HO (*E*-isomer)], 3.86 [2H×*b*+1H×*a*, C11C*H*HO (*E*-isomer), C11CH_2O], 3.99 [1H×*b*, d, *J*=4.3 Hz, C12*H* (*Z*-isomer)], 4.19 [2H×*a*, C12*H* (*E*-isomer), C11*H* (*E*-isomer)], 4.27 [1H×*b*, *J*=6.4 Hz, C18*H* (*Z*-isomer)], 4.33 [1H×*a*, d, *J*=6.7 Hz, C18*H* (*E*-isomer)], 4.42, 4.56 [each 1H×*a*, d, *J*=11.8 Hz, PhCH_2O (*E*-isomer)], 4.74 [1H×*b*, *J*=11.1 Hz, PhC*H*HO (*Z*-isomer)], 4.81 [1H×*a*, *J*=11.5 Hz, PhC*H*HO (*E*-isomer)], 4.86 [1H×*b*, *J*=11.1 Hz, PhC*H*HO (*Z*-isomer)], 4.97 [1H×*a*, *J*=11.5 Hz, PhC*H*HO (*E*-isomer)], 5.10 [1H×*a*, d, *J*=2.0 Hz, C13*H* (*E*-isomer)], 5.22 [1H×*a*, s, C13*H* (*Z*-isomer)], 6.94 [1H×*b*, br, amine proton (*Z*-isomer)], 7.12 (2H, aromatic protons), 7.2–7.45 (11H, aromatic protons), 7.63 (4H, aromatic protons), 7.85 [1H×*a*, br s, amine proton (*E*-isomer)]. EI-MS (rel. int.%): *m*/*z*=718 (1.0, M^+), 700 (0.5, [M−H_2O]$^+$), 199 (68, Ph_2Si^+=O), 91 (100, Bn^+). EI-HRMS calcd for $C_{42}H_{46}N_2O_7Si$ (M^+): *m*/*z*=718.3076. Found: *m*/*z*=718.3064.

4.34. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(*tert*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]-2-[(2*S*)-2,3-epoxy-2-methylpropionyl]-4*H*-oxazol-5-one (44)

A mixture of **43** (738 mg, 1.03 mmol) and Dess–Martin reagent (550 mg, 1.33 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 40 min. The mixture was poured into aqueous 10% $Na_2S_2O_3$ 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–AcOEt=65:35) gave **44** (676 mg, 92%) as a yellow solid. Analytical sample was prepared by recrystallization from hexane–Et_2O to give yellow needles. Mp 145–147°C. $[\alpha]_D^{20}$=+10.7° (*c* 1.07, $CHCl_3$). IR (nujor): 3280, 1720, 1690, 1620, 1510, 1320, 1110 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, measured right after dissolved, *carzinophilin numbering*): δ 1.02 (9H, s, (CH_3)$_3$CSi), 1.73 (3H, s,

C20H_3), 2.83, 3.33 (each 1H, d, J=5.6 Hz, C21H_2), 3.72 (1H, dd, J=3.7, 11.0 Hz, C11CHHO), 3.90 (1H, dd, J=5.4, 11.0 Hz, C11CHHO), 4.22 (2H, m, C12H, C11H), 4.37, 4.51 (each 1H, d, J=11.8 Hz, PhCH_2O), 4.85, 5.06 (each 1H, d, J=11.8 Hz, PhCH_2O), 5.14 (1H, d, J=3.1 Hz, C13H), 7.14 (2H, m, aromatic protons), 7.20–7.50 (14H, aromatic protons), 7.60 (4H, aromatic protons), 8.56 (1H, br s, amine proton). ^{1}H NMR (200 MHz, $CDCl_3$, measured kept standing for 10 h after dissolved, a=0.90, b=0.10, assignment of the main isomer and some for the minor isomer are described): δ 1.02 [9H×a, s, (CH_3)$_3$CSi (*E*-isomer)], 1.09 [9H×b, s, (CH_3)$_3$CSi (*Z*-isomer)], 1.72 [3H×b, s, C20H_3 (*Z*-isomer)], 1.73 [3H×a, s, C20H_3 (*E*-isomer)], 2.83 [1H×a, d, J=5.6 Hz, C21HH (*E*-isomer)], 2.91 [1H×b, d, J=5.7 Hz, C21HH (*Z*-isomer)], 3.33 [1H×a, d, J=5.6 Hz, C21HH (*E*-isomer)], 3.40 [1H×b, d, J=5.7 Hz, C21HH (*Z*-isomer)], 3.72 [1H×a, dd, J=3.7, 11.0 Hz, C11CHHO (*E*-isomer)], 3.90 [1H×a, dd, J=5.4, 11.0 Hz, C11CHHO (*E*-isomer)], 4.22 (2H, m, C12H, C11H), 4.37, 4.51 [each 1H×a, d, J=11.8 Hz, PhCH_2O (*E*-isomer)], 4.85, 5.06 [each 1H×a, d, J=11.8 Hz, PhCH_2O (*E*-isomer)], 5.14 [1H×a, d, J=3.1 Hz, C13H (*E*-isomer)], 5.29 [1H×b, s, C13H (*Z*-isomer)], 7.14 (2H, aromatic protons), 7.20–7.50 (14H, aromatic protons), 7.60 (4H, aromatic protons), 8.56 [1H×a, br s, amine proton (*E*-isomer)]. EI-MS (rel. int.%): m/z=716 (1.0, M^+), 659 (3.6, [M−tBu]$^+$), 199 (100. Ph_2Si^+=O), 91 (62, Bn^+). CI-MS (isobutene): m/z=717 (MH^+), 701 ([M−O]$^+$). EI-HIMS calcd for $C_{42}H_{44}N_2O_7Si$ (M^+): m/z=716.2919. Found: m/z=716.2890. Anal. calcd for $C_{42}H_{44}N_2O_7Si$: C, 70.37%; H, 6.19%; N, 3.91%. Found: C, 70.16%; H, 6.23%; N, 3.85%.

4.35. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(methanesulfoxy)methylpyrrolidin-2-ylidene]-2-[(2*S*)-2,3-epoxy-2-methylpropionyl]-4*H*-oxazol-5-one (45)

A mixture of **44** (crystalline, 50.0 mg, 69.8 μmol) and TBAF (1.0 M in THF, 100 μL) in THF (1.5 mL) was stirred at room temperature for 12 h. The mixture was poured into aqueous 1 M H_3PO_4 solution and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. After the residue was dissolved in CH_2Cl_2 (1.5 mL), MsCl (10.5 mg, 129 μmol), and γ-collidine (30 mg, 248 μmol) were added to the solution at room temperature and the mixture was stirred for 10 h. After addition of MeOH (100 μL) in order to decompose excess MsCl, the mixture was poured into aqueous 1 M H_3PO_4 solution and extracted with AcOEt. 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 (CH_2Cl_2–acetone=93:7) gave **45** (32.5 mg, 83% in two steps) as an oil IR (film) 3450, 3300, 1720, 1680, 1630, 1510, 1320, 1100, 1070, 750, 700 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*=77:23). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (200 MHz, $CDCl_3$, a=0.77, b=0.23, *carzinophilin numbering*): δ 1.72 [3H×b, s, C20*H3* (*Z*-isomer)], 1.75 [3H×a, s, C20H_3 (*E*-isomer)], 2.81 [1H×a, d, J=5.7 Hz, C21HH (*E*-isomer)], 2.87 [1H×b, d, J=5.6 Hz, C21HH (*Z*-isomer)], 2.98 [3H×a, s, CH_3SO$_3$ (*E*-isomer)], 3.01 [3H×b, s, CH_3SO$_3$ (*Z*-isomer)], 3.33 [1H×b, d, J=5.6 Hz, C21HH (*Z*-isomer)], 3.37 [1H×a, d, J=5.7 Hz, C21HH (*E*-isomer)], 4.01 [1H×b, d, J=3.5 Hz, C4H (*Z*-isomer)], 4.13–4.50 [5H+1H×a, C11H, C11CH_2O, PhCH_2O, C12H (*E*-isomer)], 4.72 [1H×b, d, J=11.6 Hz, PhCHH (*Z*-isomer)], 4.74 [1H×a, d, J=11.8 Hz, PhCHH (*E*-isomer)], 4.78 [1H×b, d, J=11.6 Hz, PhCHH (*Z*-isomer)], 4.85 [1H×a, d, J=11.8 Hz, PhCHH (*E*-isomer)], 4.96 [1H×a, d, J=1.9 Hz, C13H (*E*-isomer)], 5.26 [1H×b, s, C13H (*Z*-isomer)], 7.25 (2H, m, aromatic protons), 7.44 (8H, m, aromatic protons), 8.55 [1H×a, br s, amine proton (*E*-isomer)]. EI-MS (rel. int.%): m/z=556 (1.0, M^+), 540 (trace, [M−O]$^+$), 91 (100, Bn^+). EI-HIMS calcd for $C_{27}H_{28}N_2O_9S$ (M^+): m/z=556.1516. Found m/z=556.1524.

4.36. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(methanesulfoxy)methylpyrrolidin-2-ylidene]-2-[(1*S*,2*S*)-2,3-epoxy-1-hydroxy-2-methylpropyl]-4*H*-oxazol-5-one (46)

Sodium borohydride (8.0 mg, 212 μmol) was added to a mixture of **45** (130 mg, 188 μmol) and $CeCl_3$·7H_2O (30.0 mg, 80.0 μmol) in MeOH (10 mL) at −15°C with stirring. After stirring for 10 min, the mixture was poured into aqueous. 5% citric acid solution, then extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt=65:35) gave **46** (123 mg, 94%) as an oil. IR (film) 3330, 2930, 1740, 1660, 1490, 1360, 1175, 1070, 960 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*=65:35). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (200 MHz, $CDCl_3$, a=0.65, b=0.35, *carzinophilin numbering*): δ 1.43 [3H×a, C20H_3 (*E*-isomer)], 1.46 [3H×b, C20H_3 (*E*-isomer)], 2.72 (1H, d, J=4.5 Hz, C21HH), 2.90 [1H×a, d, J=3.1 Hz, alcoholic proton (*E*-isomer)], 3.03 [3H×a, s, CH_3SO$_3$ (*E*-isomer)], 3.05 [3H×b, s, CH_3SO$_3$ (*Z*-isomer)], 3.01 [1H×a, d, J=4.5 Hz, C21HH (*E*-isomer)], 3.12 [1H×b, d, J=3.5 Hz, alcoholic proton (*Z*-isomer)], 4.43–4.58 (6H, C12H, C11H, C11CH_2O, PhCH_2O), 4.74 [1H×b, d, J=11.7 Hz, PhCHHO (*Z*-isomer)], 4.75 [1H×a, d, J=11.7 Hz, PhCHHO (*E*-isomer)], 4.86 (1H, d, J=11.7 Hz, PhCHHO), 5.00 [1H×a, d, J=1.6 Hz, C13H (*E*-isomer)], 5.28 [1H×b, s, C13H (*Z*-isomer)], 7.09 [1H×b, br s, amine proton (*Z*-isomer)], 7.20 (2H, aromatic protons), 7.35 (8H, aromatic protons), 7.78 [1H×a, amine proton (*E*-isomer)]. EI-MS (rel. int.%) m/z=558 (1.0, M^+), 91 (100, Bn^+). CI-MS (isobutene) m/z=559 (MH^+), 541 ([M−H_2O]$^+$). EI-HIMS calcd for $C_{27}H_{30}N_2O_9S$ (M^+): m/z=558.1673. Found m/z=558.1675.

4.37. 4-[(3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-5-(methanesulfoxy)methylpyrrolidin-2-ylidene]-2-[(1*S*,2*S*)-2,3-epoxy-1–(3-methoxy-5-methyl-1-naphthoxy)-2-methylpropyl]-4*H*-oxazol-5-one (47)

A mixture of **46** (35.0 mg, 62.7 μmol), and the naphthoic acid **19** (20 mg, 92.6 μmol), DMAP (11 mg, 90 μmol), and WSCI·HCl (17 mg, 89 μmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 12 h. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in

vacuo. Purification of the residue by silica gel column chromatography (hexane–AcOEt=60:40) gave **47** (43.0 mg, 91%) as an oil. IR (film) 3330, 2940, 1730, 1660, 1600, 1360, 1280, 1240, 1210, 1180, 1070 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=58:42). Assignments of signals for the main isomer and some for the minor isomer are described. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.58, *b*=0.42, *carzinophilin numbering*): δ 1.57 [9H×*a*, s, C20*H* (*E*-isomer)], 1.58 [9H×*b*, s, C20*H* (*Z*-isomer)], 2.66 [3H×*a*, s, CH_3Ar (*E*-isomer)], 2.67 [3H×*b*, s, CH_3Ar (*Z*-isomer)], 2.75 [1H×*a*, d, *J*=4.8 Hz, C21*H*H (*E*-isomer)], 2.77 [1H×*b*, d, *J*=4.8 Hz, C21*H*H (*Z*-isomer)], 3.02 [3H×*b*, s, CH_3SO_3 (*Z*-isomer)], 3.03 [3H×*a*, s, CH_3SO_3 (*E*-isomer)], 3.12 [1H×*a*, d, *J*=4.8 Hz, C21*H*H (*E*-isomer)], 3.13 [1H×*b*, d, *J*=4.8 Hz, C21*H*H (*Z*-isomer)], 3.94 [3H×*a*, s, CH_3OAr (*E*-isomer)], 3.98 [3H×*b*, s, CH_3OAr (*Z*-isomer)], 4.07 [1H×*b*, br d, *J*=3.2 Hz, C12*H* (*Z*-isomer)], 4.15 [1H×*b*, br d, *J*=4.8 Hz, C12*H* (*E*-isomer)], 4.26 [1H×*b*, d, *J*=11.7 Hz, PhC*H*HO (*Z*-isomer)], 4.30 [1H×*a*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.30–4.49 (3H, C11*H*, C11CH_2O), 4.52 [1H×*b*, d, *J*=11.8 Hz, PhC*H*HO (*E*-isomer)], 4.54 [1H×*b*, d, *J*=11.7 Hz, PhC*H*HO (*Z*-isomer)], 4.71 [1H×*b*, d, *J*=11.6 Hz, PhC*H*HO (*E*-isomer)], 4.79 [1H×*b*, d, *J*=11.1 Hz, PhC*H*HO (*Z*-isomer)], 4.80 [1H×*b*, d, *J*=11.6 Hz, PhC*H*HO (*E*-isomer)], 4.86 [1H×*b*, d, *J*=11.1 Hz, PhC*H*HO (*Z*-isomer)], 5.03 [1H×*a*, d, *J*=1.2 Hz, C13*H* (*E*-isomer)], 5.28 [1H×*b*, s, C13*H* (*Z*-isomer)], 5.81 [1H×*b*, s, C18*H* (*Z*-isomer)], 5.90 [1H×*a*, s, C18*H* (*E*-isomer)], 7.18 (2H, aromatic protons), 7.26–7.40 (10H, aromatic protons), 7.45 [1H×*a*, br d, *J*=2.5 Hz, C4″*H* (*E*-isomer)], 7.49 [1H×*b*, br d, *J*=2.7 Hz, C4″*H* (*Z*-isomer)], 7.90 [1H×*b*, br d, *J*=2.7 Hz, C2″*H* (*Z*-isomer)], 7.91 [1H×*a*, br d, *J*=2.5 Hz, C2″*H* (*E*-isomer)], 8.65 (1H, m, C8″*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=779 ([M+Na]$^+$), 757 (MH$^+$). Neither EI- nor CI-MS of this sample gave structural information. EI-HRMS was not measured.

4.38. (3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-2-[(*E*)-1-((2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoxy)-3-methylbutyrylamino)-1-[(1*R*, or *S*,3*R*)-(1-*tert*-butyldimethylsiloxy-1-cyano-3-(4-methoxyphenylmethyloxy)but-2-yl)carbamoyl]]methylidene-5-(methanesulfoxy)methyl-1-(2-propenyloxycarbonyl)pyrrolidine (48*E*) and its (*Z*)-isomer (48*Z*)

4.38.1. Reaction procedure. A mixture of **47** (28.0 mg, 37.1 μmol), DMAP (500 μg, 4.1 μmol), and $Alloc_2O$ (10.3 mg, 55.4 μmol) in THF (1.0 mL) was stirred at room temperature for 10 min. A solution of **28** (50 mg, 137 μmol) in THF (4.0 mL) was added into the mixture. The mixture was concentrated in vacuo by a rotary evaporator at 40°C over 15 min. Purification of the residue by silica gel column chromatography (hexane–AcOEt=70:30→60:40) gave **48***Z* (1.0 mg, 2%) and **48***E* (35.0 mg, 78%) as oils.

4.38.2. Physical data of 48*E*. $[\alpha]_D^{20}$=+80.1° (*c* 0.824, $CHCl_3$). IR (film): 3430, 3370, 2960, 2930, 1730, 1715, 1690, 1620, 1600, 1510, 1470, 1360, 1300, 1280, 1250, 1240, 1210, 1175, 1090, 1050, 990, 960, 910, 850, 810, 780, 730, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*). δ 0.15, 0.20 (each 3H, s, (CH_3)$_2$Si), 0.89 (9H, s, (CH_3)$_3$CSi), 1.25 (3H, d, *J*=6.3 Hz, C1H_3), 1.50, 2.66 (each 3H, s, C20H_3, CH_3Ar, respectively), 2.69 (1H, d, *J*=4.5 Hz, C21*H*H), 2.77 (3H, s, CH_3SO_3), 2.98 (1H, d, *J*=4.5 Hz, C21*H*H), 3.73, 3.90 (each 3H, s, CH_3OAr×2), 4.01–4.18 (4H, m, C2*H*, C12*H*, C11CH_2O), 4.41 (1H, d, *J*=10.9 Hz, ArC*H*HO), 4.44–4.61 (8H, m, C3*H*, C4*H*, C11*H*, ArCH_2O×2, ArC*H*HO), 4.63, 4.69 (each 1H, br dd, *J*=5.9, 13.1 Hz, CH_2=CHCH_2O), 4.73 (1H, d, *J*=2.1 Hz, C13*H*), 5.03 (1H, s, C18*H*), 5.22 (1H. br d, *J*=10.6 Hz, C*H*H=CHCH_2O), 5.32 (1H, dq, *J*=17.0, 1.2 Hz, C*H*H=CHCH_2O), 5.94 (1H, ddt, *J*=10.6, 17.0, 5.9 Hz, CH_2=C*H*CH_2O), 6.53 (1H, br d, *J*=8.7 Hz, N5*H*), 6.72, 7.18 (each 2H, br d, *J*=8.6 Hz, aromatic protons for MPM), 7.22–7.36 (12H, m, aromatic protons for Bn, C6′*H*, C7′*H*), 7.44 (1H, dd, *J*=2.6 Hz, C4′*H*), 7.47 (1H, br s, N16*H*), 8.57 (1H, br d, *J*=8.4 Hz, C8′*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=1227 ([M+Na]$^+$), 1204 (MH$^+$). Neither EI-MS nor CI-MS of this sample gave structural information. So, EI-HRMS was not measured.

4.38.3. Physical data of 48*Z*. IR (film) 3420, 3340, 2930, 1710, 1510, 1470, 1380, 1360, 1300, 1280, 1250, 1170, 1070, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, *carzinophilin numbering*) δ 0.17, 0.20 (each 3H, s, (CH_3)$_2$Si), 0.90 (9H, s, (CH_3)$_3$CSi), 1.46 (3H, s, C20H_3), 1.17 (3H, d, *J*=6.3 Hz), 2.36 (1H, d, *J*=4.2 Hz, C21C*H*H), 2.66 (3H, s, CH_3Ar), 2.72 (3H, s, CH_3SO_3), 3.04 (1H, d, *J*=4.2 Hz, C21C*H*H), 3.53 (1H, br dd, *J*=5.2, 10.3 Hz, C11C*H*HO), 3.76 (3H, s, CH_3OAr), 3.98 (3H, s, CH_3OAr), 4.02 (1H, m, CH_2=CHC*H*HO), 4.05 (1H, dd, *J*=0.8, 4.9 Hz, C12*H*), 4.10 (1H, dq, *J*=1.7, 6.3 Hz, C2*H*), 4.19 (1H, m, CH_2=CHC*H*HO), 4.25 (1H, t, *J*=10.3 Hz, C11C*H*HO), 4.36 (1H, d, *J*=11.6 Hz, ArC*H*HO), 4.42 (2H, m, C3*H*, C11*H*), 4.20 (1H, d, *J*=10.9 Hz, ArC*H*HO), 4.44, 4.48 (each 1H, d, *J*=11.4 Hz, ArCH_2O), 4.49 (1H, d, *J*=10.9 Hz, ArC*H*HO), 4.68 (1H, d, *J*=11.6 Hz, ArC*H*HO), 4.76 (1H, d, *J*=7.0 Hz, C4*H*), 4.90 (1H, dq, *J*=17.2, 1.4 Hz, C*H*H=CHCH_2O), 4.97 (1H, dq, *J*=10.4, 1.4 Hz, C*H*H=CHCH_2O), 5.42 (1H, ddd, *J*=5.8, 10.4, 17.2 Hz, CH_2=C*H*CH_2O), 5.43 (1H, s, C1′*H*), 5.30 (1H, br s, C13*H*), 6.81 (2H, br d, *J*=8.7 Hz, aromatic protons for MPM), 7.08 (1H, br d, *J*=9.1 Hz, N5*H*), 7.48–7.42 (14H, m, aromatic protons), 7.51 (1H, d, *J*=2.5 Hz, C4′*H*), 8.07 (1H, d, *J*=2.5 Hz, C2′*H*), 8.74 (1H, br d, *J*=7.9 Hz, C8′*H*), 8.96 (1H, br s, N16*H*).

4.39. (3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-2-[(*E*)-1-((2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoxy)-3-methylbutyrylamino)-1-[*N*-(1*R*, or *S*,3*R*)-(1-*tert*-butyldimethylsiloxy-1-cyano-3-oxobut-2-yl)carbamoyl]]methylidene-5-(methanesulfoxy)methyl-1-(2-propenyloxycarbonyl)-pyrrolidine (49)

4.39.1. Removal of MPM group in 48*E*. A mixture of **48***E* (31.0 mg, 25.7 μmol) and DDQ (11.3 mg, 49.8 μmol) in a mixture of CH_2Cl_2 (2.0 mL) and H_2O (200 μL) was stirred at room temperature for 1 h. The mixture was poured into a 1:1 mixture of aqueous 5% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solutions, then 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=50:50) afforded the corresponding alcohol

(26.2 mg, 94%) as a colorless caramel. $[\alpha]_D^{20}$=+85.3° (1.08, $CHCl_3$). IR (film): 3500, 3400, 2960, 2930, 1730, 1590, 1500, 1495, 1470, 1390, 1360, 1280, 1235, 1210, 1175, 1090, 1050, 990, 960, 850, 810, 780, 750, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.16, 0.20 (each 3H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 1.28 (3H, d, *J*=6.5 Hz, C1*H*$_3$), 1.53 (3H, s, C20*H*$_3$), 2.55 (1H, d, *J*=5.6 Hz, alcoholic proton), 2.66 (3H, s, C*H*$_3$Ar), 2.76, 2.98 (each 1H, d, *J*=4.5 Hz, C21*H*$_2$), 3.92 (3H, s, C*H*$_3SO_3$), 4.01 (1H, ddd, *J*=2.9, 4.8, 8.5 Hz, C11*H*), 4.20 (1H, dd, *J*=3.1, 6.6 Hz, C12*H*), 4.34 (1H, m, C2*H*), 4.47–4.73 (10H, m, C3*H*, C4*H*, C11C*H*$_2$O, CH_2=CHC*H*$_2$O, PhC*H*$_2$O×2), 4.75 (1H, d, *J*=3.1 Hz, C13*H*), 4.95 (1H, s, C18*H*), 5.23 (1H, dq, *J*=10.4, 1.2 Hz, C*H*H=CHCH$_2$O), 5.31 (1H, dq, *J*=17.2, 1.4 Hz, C*H*H=CHCH$_2$O), 5.93 (1H, ddt, *J*=10.4, 17.2, 5.9 Hz, CH_2=C*H*CH$_2$O), 6.70 (1H, br d, *J*=8.8 Hz, N5*H*), 7.24–7.36 (12H, aromatic protons), 7.45 (1H, d, *J*=2.5 Hz, C4′*H*), 7.68 (1H, br s, N16*H*), 7.88 (1H, d, *J*=2.5 Hz, C2′*H*), 8.60 (1H, dd, *J*=1.7, 7.8 Hz, C8′*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=1107 ($[M+Na]^+$), 1084 (MH^+). Neither EI-MS nor CI-MS of this sample gave structural information. So, EI-HRMS was not measured.

4.39.2. Oxidation giving 49. A mixture of the alcohol (240 mg, 221 μmol) and Dess–Martin reagent (180 mg, 437 μmol) in CH_2Cl_2 (4.0 mL) was stirred at room temperature for 1 h. The mixture was poured into a 50:50 mixture of aqueous 5% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solutions, then 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 **49** (234 mg, 98%) as a colorless caramel. $[\alpha]_D^{20}$=+75° (*c* 0.82, $CHCl_3$). IR (film): 3370, 2860, 2830, 1720, 1690, 1500, 1360, 1280, 1240, 1215, 1180, 1090, 1050, 990, 960, 840, 810, 780, 740, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.19, 0.21 (each 3H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 1.55, 2.37, 2.66 (each 3H, s, C20*H*$_3$, C1*H*$_3$, C*H*$_3$Ar, respectively), 2.76 (1H, d, *J*=4.5 Hz, C21*H*H), 2.98 (3H, s, C*H*$_3SO_3$), 2.98 (1H, d, *J*=4.5 Hz, C21*H*H), 3.93 (3H, s, C*H*$_3$OAr), 4.19 (1H, dd, *J*=3.0, 6.2 Hz, C12*H*), 4.48–4.72 (10H, m, C4*H*, C11*H*, C11C*H*$_2$O, CH_2=CHC*H*$_2$O, PhC*H*$_2$O×2), 4.74 (1H, d, *J*=3.0 Hz, C13*H*) 4.91 (1H, s, C18*H*), 5.00 (1H, d, *J*=3.7 Hz, C3*H*), 5.20 (1H, dq, *J*=10.4, 1.1 Hz, C*H*H=CHCH$_2$O), 5.28 (1H, dq, *J*=17.2, 1.1 Hz, C*H*H=CHCH$_2$O), 5.90 (1H, ddt, *J*=10.4, 17.2, 5.4 Hz, CH_2=C*H*CH$_2$O), 6.99 (1H, br d, *J*=6.7 Hz, N5*H*), 7.22–7.35 (12H, m, aromatic protons), 7.46 (1H, d, *J*=2.5 Hz, C4′*H*), 7.61 (1H, br s, N16*H*), 7.87 (1H, d, *J*=2.5 Hz, C2′*H*), 8.61 (1H, dd, *J*=2.4, 7.5 Hz, C8′*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=1105 ($[M+Na]^+$), 1083 (MH^+). Neither EI-MS nor CI-MS of this sample gave informative peaks. So, EI-HRMS was not measured.

4.40. (3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-2-[(*E*)-1-((2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoxy)-3-methylbutyrylamino)-1-[*N*-(1*R* or *S*,3*R*)-(1-*tert*-butyldimethylsiloxy-1-cyano-3-oxobut-2-yl)carbamoyl]]methylidene-5-(methanesulfoxy)methylpyrrolidine (50)

A mixture of the **49** (22.0 mg, 20.3 μmol), AcOH (3.0 μL), PPh_3 (1.5 mg, 5.7 μmol), $Pd(PPh_3)_4$ (0.3 mg, 0.27 μmol) in THF (2.0 mL) was stirred at room temperature for 10 min. After the mixture was concentrated in vacuo, the residue was purified by silica gel column chromatography (AcOEt–hexane=60:40) to give **50** (18.0 mg, 89%) as a colorless caramel. $[\alpha]_D^{20}$=+22.5° (*c* 1.00, $CHCl_3$). IR (film): 3400, 3360, 2930, 2860, 1720, 1710, 1660, 1620, 1600 1510, 1500, 1420, 1360, 1280, 1260, 1240, 1215, 1175, 1090, 1050, 845 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.20 0.22 (each 3H, s, $(CH_3)_2Si$), 0.92 (9H, s, $(CH_3)_3CSi$), 1.56, 2.30, 2.67 (each 3H, s, C20*H*$_3$, C1*H*$_3$, C*H*$_3$Ar, respectively), 2.87 (1H, d, *J*=4.5 Hz, C21*H*H), 2.99 (3H, s, C*H*$_3SO_3$), 3.02 (1H, d, *J*=4.5 Hz, C21*H*H), 3.97 (3H, s, C*H*$_3$OAr), 4.05 (1H, br d, *J*=2.5 Hz, C12*H*), 4.25 (3H, m, C11C*H*$_2$O, PhC*H*HO), 4.38 (1H, m, C11*H*), 4.44 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.66 (1H, d, *J*=11.3 Hz, PhC*H*HO), 4.73 (1H, d, *J*=1.8 Hz, C13*H*), 4.78 (1H, dd, *J*=4.0, 7.7 Hz, C3*H*), 4.80 (1H, d, *J*=11.3 Hz, PhC*H*HO), 4.86 (1H, s, C18*H*), 5.00 (1H, d, *J*=4.0 Hz, C4*H*) 6.90 (1H, br s, N9*H*), 6.91 (1H, br d, *J*=7.7 Hz, N5*H*), 7.10 (2H, m, aromatic protons), 7.19 (3H, m, aromatic protons), 7.26–7.38 (7H, aromatic protons), 7.49 (1H, d, *J*=2.6 Hz, C4′*H*), 7.95 (1H, d, *J*=2.6 Hz, C2′*H*), 8.46 (1H, br s, N16*H*), 8.69 (1H, br d, 7.8 Hz, C8′*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=1021 ($[M+Na]^+$), 999 (MH^+). Neither EI-MS nor CI-MS of this sample gave informative peaks. So, EI-HRMS was not measured.

4.41. (3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-2-[(*E*)-1-((2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methylnaphthoxy)-3-methylbutyrylamino)-1-(*N*-(*Z*)-1-methoxymethylene-2-oxopropyl)carbamoyl]]methylidene-5-methanesulfoxymethylpyrrolidine (38)

A mixture of **50** (28.0 mg, 28.0 mmol) and TBAF (1.0 M in THF, 50 μL) in a mixture of THF (1.0 mL) and AcOH(30 μL) was stirred at room temperature for 3 h. After saturated aqueous $NaHCO_3$ solution (200 μL) was added to the mixture, the mixture was stirred at room temperature for 10 min, poured into aqueous 10% citric acid solution, then extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. After the residue was dissolved in CH_2Cl_2 (1.0 mL), ethereal CH_2N_2 (1.0 mL, excess) was added to the solution. The mixture was kept standing for 1 h at room temperature. After concentration, the obtained residue was purified by silica gel column chromatography (CH_2Cl_2–acetone=70:30) to give **38** (13.2 mg, 54%) as a colorless caramel. $[\alpha]_D^{20}$=+17° (*c* 0.44, CH_3CN). IR (film): 3370, 2940, 1700, 1665, 1640, 1620, 1600, 1500, 1420, 1355, 1240, 1175, 1090, 1050, 960, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.59, 2.22, 2.68 (each 3H, s, C20*H*$_3$, C1*H*$_3$, C*H*$_3$Ar, respectively), 2.84 (1H, d, *J*=4.4 Hz, C21*H*H), 2.98 (3H, s, C*H*$_3SO_3$), 3.07 (1H, d, *J*=4.4 Hz, C21*H*H), 3.83 3.98 (each 3H, s, C*H*$_3$O×2), 4.45 (1H, dd, *J*=1.9, 4.6 Hz, C12*H*), 4.23 (2H, m, C11*H*, C11C*H*HO), 4.29 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.40 (1H, dd, *J*=2.7, 9.0 Hz, C5C*H*HO), 4.45 (1H, d, *J*=11.7 Hz, PhC*H*HO), 4.63 (1H, d, *J*=11.1 Hz, PhC*H*HO), 4.73 (1H, d, *J*=1.9 Hz, C13*H*), 4.83 (1H, d, *J*=11.1 Hz, PhC*H*HO), 7.01 (1H, br s, N*H*), 7.13 (2H, m, aromatic protons), 7.15 (1H, s, C4*H*), 7.17 (1H, br s, N*H*), 7.18–7.37 (7H, aromatic protons), 7.51 (1H, d, *J*=2.6 Hz, C4′*H*), 7.97 (1H, d, *J*=2.6 Hz, C2′*H*), 8.47 (1H, br s, N16*H*), 8.68 (1H, br d,

8.2 Hz, C8′*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=894 ([M+Na]$^+$), 872 (MH$^+$). Neither EI-MS nor CI-MS of this sample gave informative peaks. So, EI-HRMS was not measured.

4.42. 13-Desacetyl-12,13-di-*O*-benzyloxy-4-*O*-methylcarzinophilin (2)

A mixture of **38** (3.7 mg, 4.9 μmol), powdered molecular sieves 4A (10 mg), and TBAF (1.0 M in THF, 6.0 μL) in THF (1.0 mL) was stirred at room temperature for 15 min. After filtration, the filtrate was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, then concentrated in vacuo. Purification by preparative silica gel TLC (CH_2Cl_2–acetone=70:30) gave **2** (1.8 mg, 47%) as a colorless caramel. $[\alpha]_D^{20}$=+8.5° (*c* 0.082, CH_3CN). IR (film): 3360, 2930, 1705, 1640, 1620, 1600, 1510, 1500, 1280, 1235, 1210, 1190, 1170, 1085, 1045 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*) δ 1.53 (3H, s, C20H_3), 2.22 (3H, s, C1H_3), 2.27 (1H, d, *J*=4.1 Hz, C10*H*), 2.48 (1H, d, *J*=5.1 Hz, C10*H*), 2.60 (1H, d, *J*=4.6 Hz, C21*H*H), 2.66 (3H, s, CH_3Ar), 2.90 (1H, d, *J*=4.6 Hz, C21*H*H), 3.12 (1H, ddd, *J*=4.1, 4.8, 5.1 Hz, C11*H*), 3.89 3.96 (each 3H, s, CH_3O×2), 4.49 (1H, dd, *J*=3.6, 4.8 Hz, C12*H*), 4.53 (2H, br s, PhCH_2O), 4.54, 4.60 (each 1H, d, *J*=11.5 Hz, PhCH_2O), 4.94 (1H, dd, *J*=1.0 3.6 Hz, C13*H*), 5.16 (1H, s, C18*H*), 7.14 (1H, s, C4*H*), 7.20–7.40 (12H, aromatic protons), 7.48 (1H, d, *J*=2.6 Hz, C4′*H*), 7.96 (1H, d, *J*=2.6 Hz, C2′*H*), 8.21 (1H, br s, C16*H*), 8.60 (1H, dd, *J*=2.4, 7.4 Hz, C8′*H*), 10.58 (1H, br s, N5*H*). SI-MS (3-nitrobenzylalcohol+NaCl): *m*/*z*=798 ([M+Na]$^+$), 776 (MH$^+$). Neither EI-MS nor CI-MS of this sample gave informative peaks, so EI-HRMS was not measured.

4.43. (3*R*,4*R*,5*S*)-3,4-Dibenzyloxy-2-[(*E*)-1-((2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoxy)-3-methylbutanoylamino)-1-*N*-((*Z*)-1-methocymethylidene-2-oxypropyl)carbamoyl-5-methypyrrolidine (52)

4.43.1. Reaction procedure. A suspension of **2** (4.2 mg, 5.4 μmol) and 10% Pd/C (1.0 mg) in AcOEt (1.0 mL) was stirred vigorously for 3 h under H_2 atmosphere. After filtration, the mixture was concentrated in vacuo. The residue was purified by preparative silica gel TLC (CH_2Cl_2–acetone 70:30) to give **52** (2.0 mg, 47%) and recovered **2** (1.0 mg, 24%). The ^{1}H NMR spectrum of recovered **2** was identical with that of an authentic sample.

4.43.2. Physical data of 52. (IR (film) 3380, 2930, 1700, 1650, 1640, 1620, 1600, 1490, 1280, 1230, 1180 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.21 (3H, d, *J*=6.6 Hz, C11CH_3), 1.61, 2.23, 2.69 (each 3H, s, C20*H3*, C1H_3, CH_3Ar, respectively), 2.81, 3.10 (each 1H, d, *J*=4.5 Hz, C20H_2), 3.80 (1H, C12*H*), 3.80, 3.98 (each 3H, s, CH_3O×2), 4.08 (1H, dq, *J*=4.9, 6.6 Hz, C11*H*), 4.31, 4.43 (each 1H, d, *J*=12.0 Hz, PhCH_2O), 4.60 (1H, d, *J*=11.1 Hz, PhC*H*HO) 4.65 (1I, d, *J*=1.5 Hz, C13*H*), 4.81 (1H, d, *J*=11.1 Hz, PhC*H*HO), 5.13 (1H, s, C18*H*), 7.03 (1H, br s, N*H*), 7.12–7.40 (13H, N*H*, aromatic protons), 7.51, 7.97 (each 1H, d, *J*=2.5 Hz, C2′*H*, C5′*H*, respectively), 8.26 (1H, br s, N*H*), 8.69 (1H, br d, *J*=10.9 Hz).

4.44. (3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)-methyl-4-(triethylsiloxy)pyrrolidin-2-ylidene]-2-[(1*R*,2*S*)-2,3-epoxy-1-(3-methoxy-5-methyl-1-naphthoxy)-2-methylpropyl]-4*H*-oxazol-5-one (56)

Treatment of **16** (31.0 mg, 43.2 μmol) and **19** (14.0 mg, 64.8 μmol) in the same manner as described in Section 4.19 gave **56** (31.0 mg, 78%) as an oil after silica gel column chromatography. IR (film): 3320, 2940, 1730, 1650, 1590, 1280, 1240, 1210, 1190, 1110, 1080, 910, 740, 700 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*= 80:20). Assignments of signals for the main isomer and some for the minor isomer are described. ^{1}H NMR (200 MHz, $CDCl_3$, *a*=0.80, *b*=0.20, *carzinophilin numbering*) δ 1.00 (9H, s, (CH_3)$_3$CSi), 1.56 [3H×*a*, s, C2CH_3 (*E*-isomer)], 1.57 [1H×*b*, C2CH_3 (*Z*-isomer)], 2.67 (3H, s, CH_3Ar), 2.80, 3.07 (each 1H, d, *J*=4.3 Hz, C12H_2), 3.70 (1H, m, C13*H*), 3.89 (1H, m, C11C*H*HO), 3.91 (3H, s, CH_3OAr), 4.15 (2H, m, C11*H*, C11C*H*HO), 4.31, 4.45 [each 1H×*a*, d, *J*=11.9 Hz, PhCH_2O (*E*-isomer)], 4.70 [1H×*a*, d, *J*=11.4 Hz, PhC*H*HO (*E*-isomer)], 4.75, 4.85 [each 1H×*b*, d, *J*=10.9 Hz, PhC*H2*O (*Z*-isomer)], 4.93 [1H×*a*, d, *J*= 11.4 Hz, PhC*H*HO (*E*-isomer)], 5.00 [1H×*a*, d, *J*=2.7 Hz, C13*H* (*E*-isomer)], 5.20 [1H×*b*, s, C3*H* (*Z*-isomer)], 5.50 (1H, s, C1′*H*), 6.61 [1H×*b*, br s, amine proton (*Z*-isomer)], 7.10 (2H, m, aromatic protons), 7.18–7.48 (17H, aromatic protons), 7.60 (4H, m, aromatic protons), 7.64 [1H×*a*, br s, amine proton (*E*-isomer)], 7.99 (1H, d, *J*=2.6 Hz, C2″*H*), 8.69 (1H, dd, *J*=2.5, 7.3 Hz, C8″*H*). SI-MS (nitrobenzylalcohol+NaCl) *m*/*z*=939 ([M+Na]$^+$), 917 (MH$^+$). Neither EI-MS nor CI-MS of this sample gave useful structural information.

4.45. (3*R*,4*R*,5*S*)-3-Acetoxy-5-(*tert*-butyldiphenylsiloxy)methyl-2-[(*E*)-1-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoxy)-3-methylbutyrylamino]-1-(*N*-isopropylcarbamoyl)]methylidene-4-triethylsiloxy-1-(2-propenyloxylcarbony)pyrrolidine (57*SE*) and its *Z*-isomer (57*SZ*) and those diastereomers (57*RE*) and (57*RZ*)

4.45.1. Reaction procedure for 57*SE* and 57*SZ*. A mixture of **20** (7.3 mg, 8.2 μmol), $Alloc_2O$ (2.0 μL, 12 μmol), and DMAP (1.0 mg, 8.1 μmol) in THF (1.0 mL) was stirred at room temperature for 10 min. Isopropyl amine (100 μL) was added to the mixture and the mixture was stirred for 30 min at room temperature. After concentration in vacuo, purification of the residue by preparative silica gel column TLC (CH_2Cl_2–acetone=90:10) gave **57***SZ* (4.0 mg, 3.0 mmol, 47%) and **57***SE* (3.0 mg, 35%) both as an oil.

4.45.2. NMR data of 57*SE*. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 0.59 (6H, m, (CH_3CH_2)$_3$Si), 0.88 (9H, t, *J*=7.9 Hz, (CH_3CH$_2$)$_3$Si), 1.02 (3H, d, *J*=6.5 Hz, C4CH_3), 1.07 (9H, s, (CH_3)$_3$CSi), 1.08 (3H, d, *J*=6.5 Hz, C4CH_3), 1.59 (3H, s, C20H_3), 2.04 (3H, s, CH_3COO), 2.67 (3H, s, CH_3Ar), 2.73 (1H, d, *J*=5.6 Hz, C21*H*H), 3.09 (1H, d, *J*=5.6 Hz, C21*H*H), 3.97 (3H, s, CH_3OAr), 4.00 (1H, m, C4*H*), 4.19 (3H, m, C11*H*, C11CH_2), 4.49 (1H, dd, *J*=1.5, 4.5 Hz, C12*H*), 4.66 (2H, br d *J*=4.5 Hz, CH_2=CHCH_2O), 5.06 (1H, dd *J*=1.4, 10.5 Hz, C*H*H=CHCH$_2$O), 5.09 (1H, dd *J*=1.5, 15.4 Hz,

C*H*H=CHCH$_2$O), 5.17 (1H, d, *J*= 1.5 Hz, C13*H*), 5.39 (1H, s, C18*H*), 5.59 (1H, bd, *J*=8.6 Hz, N5*H*), 5.68 (1H, ddt, *J*=10.5, 15.4, 5.5 Hz, CH$_2$=C*H*CH$_2$O), 7.30–7.50 (12H, m, aromatic protons C6′*H*, C7′*H*), 7.49 (1H, d, *J*=2.4 Hz, C4′*H*), 8.03 (1H, d, *J*=2.4 Hz, C2′*H*), 8.69 (1H, m, C8′*H*), 9.06 (1H, br s, N16*H*).

4.45.3. NMR data of 57*SZ*. ^{1}H NMR (400 MHz, CDCl$_3$, *carzinophilin numbering*): δ 0.68 (6H, m, (CH$_3$C*H*$_2$)$_3$Si), 0.92 (9H, t, *J*=7.8 Hz, (C*H*$_3$CH$_2$)$_3$Si), 1.13 (3H, d, *J*=6.5 Hz, C4*CH*$_3$), 1.07 (9H, s, (*CH*$_3$)$_3$CSi), 1.16 (3H, d, *J*=6.5 Hz, C4*CH*$_3$), 1.43 (3H, s, C20*H*$_3$), 2.01 (3H, s, C*H*$_3$COO), 2.66 (3H, s, C*H*$_3$Ar), 2.67 (1H, d, *J*=4.7 Hz, C21*H*H), 3.17 (1H, d, *J*=4.7 Hz, C21*H*H), 3.39 (1H, ddt, *J*=5.5, 13.6, 1.3 Hz, OC*H*HCH=CH$_2$), 3.82 (1H, ddt, *J*=5.8, 13.6, 1.3 Hz, OC*H*HCH=CH$_2$), 3.98 (3H, s, C*H*$_3$OAr), 3.8–4.2 (4H, C11H, C11CH2, C4H), 4.40 (1H, dd, *J*=2.5, 5.2 Hz, C12*H*), 6.41 (1H, s, C13H), 4.86 (1H, dq *J*=10.5, 1.4 Hz, C*H*H=CHCH$_2$O), 4.75 (1H, dq *J*=17.2, 1.5 Hz, C*H*H=CHCH$_2$O), 5.45 (1H, s, C18*H*), 6.70 (1H, bd, *J*= 7.9 Hz, N5*H*), 5.25 (1H, ddt, *J*=10.5, 17.2, 5.6 Hz, CH$_2$=C*H*CH$_2$O), 7.30–7.50 (12H, m, aromatic protons C6′*H*, C7′*H*), 7.49 (1H, d, *J*=2.6 Hz, C4′*H*), 8.15 (1H, d, *J*=2.6 Hz, C2′*H*), 8.68 (1H, dd, *J*=8.7 Hz, C8′*H*), 9.17 (1H, br s, N16*H*).

4.45.4. Reaction procedure for 57*SE* and 57*SZ*. Treatment of **56** (3.0 mg, 3.3 μmol) in the same manner as described previously gave **57***RZ* (1.4 m, 42%) and **57***RE* (1.3 mg, 39%) as oils.

4.45.5. NMR data of 57*SE*. ^{1}H NMR (400 MHz, CDCl$_3$, *carzinophilin numbering*): δ 0.62 (6H, m, (CH$_3$C*H*$_2$)$_3$Si), 0.89 (9H, t, *J*=7.7 Hz, (C*H*$_3$CH$_2$)$_3$Si), 0.93 (3H, d, *J*= 6.5 Hz, C4*CH*$_3$), 1.07 (9H, s, (*CH*$_3$)$_3$CSi), 1.56 (3H, d, *J*= 6.5 Hz, C4*CH*$_3$), 1.59 (3H, s, C*H*$_3$COO), 1.66 (3H, s, C20*H*$_3$), 2.69 (3H, s, C*H*$_3$Ar), 2.83 (1H, d, *J*=4.4 Hz, C21*H*H), 3.15 (1H, d, *J*=4.4 Hz, C21*H*H), 3.97 (3H, s, C*H*$_3$OAr), 3.97 (1H, m, C4*H*), 4.19 (3H, m, C11*H*, C11C*H*$_2$), 4.38 (2H, m, OC*H*$_2$CH=CH$_2$), 4.46 (1H, dd, *J*=1.3, 4.3 Hz, C12*H*), 4.84 (1H, s, C13H), 5.06 (1H, dd *J*=1.4, 10.5 Hz, C*H*H=CHCH$_2$O), 5.07 (1H, dd *J*=1.5, 15.4 Hz, C*H*H=CHCH$_2$O), 5.12 (1H, s, C18*H*), 5.50 (1H, bd, *J*=8.0 Hz, N5*H*), 5.65 (1H, ddt, *J*=10.6, 17.0, 5.8 Hz, CH$_2$=C*H*CH$_2$O), 7.30–7.50 (12H, m, aromatic protons C6′*H*, C7′*H*), 7.51 (1H, d, *J*=2.6 Hz, C4′*H*), 8.12 (1H, d, *J*=2.4 Hz, C2′*H*), 8.69 (1H, dd, *J*=2.3, 7.4 Hz, C8′*H*), 9.28 (1H, br s, N16*H*).

4.45.6. NMR data of 57*RZ*. ^{1}H NMR (400 MHz, CDCl$_3$, *carzinophilin numbering*): δ 0.65 (6H, m, (CH$_3$C*H*$_2$)$_3$Si), 0.91 (9H, t, *J*=7.7 Hz, (C*H*$_3$CH$_2$)$_3$Si), 1.11 (3H, d, *J*=6.5 Hz, C4*CH*$_3$), 1.03 (9H, s, (*CH*$_3$)$_3$CSi), 1.17 (3H, d, *J*=6.5 Hz, C4*CH*$_3$), 1.32 (3H, s, C20*H*$_3$), 2.17 (3H, s, C*H*$_3$COO), 2.67 (3H, s, C*H*$_3$Ar), 2.67 (1H, d, *J*=4.4 Hz, C21*H*H), 3.11 (1H, d, *J*=4.4 Hz, C21*H*H), 3.96 (3H, s, C*H*$_3$OAr), 4.40 (2H, m, OC*H*$_2$CH=CH$_2$), 3.95 (2H, m, C11C*H*$_2$O), 4.05 (1H, m, C18H), 4.16 (1H, m, C11*H*), 4.40 (2H, m, C11*H*$_2$), 5.02 (1H, s, C18*H*), 5.08 (1H, dq, *J*=10.3, 1.4 Hz, C*H*H=CHCH$_2$O), 5.10 (1H, dq, *J*=17.2, 1.4 Hz, C*H*H=CHCH$_2$O), 5.60 (1H, ddt, *J*=10.3, 17.2, 5.8 Hz), 6.27 (1H, d, *J*=2.5 Hz, C13*H*), 6.45 (1H, br d, *J*=7.8 Hz, N5*H*), 7.30–7.50 (12H, m, aromatic protons C6′*H*, C7′*H*), 7.48 (1H, d, *J*=2.6 Hz, C4′*H*), 8.11 (1H, d, *J*=2.6 Hz, C2′*H*), 8.65 (1H, dd, *J*=8.2 Hz, C8′*H*), 9.26 (1H, br s, N16*H*).

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