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Synthetic studies of carzinophilin. Part 1: Synthesis of 2-methylidene-1-azabicyclo[3.1.0]hexane systems related to carzinophilin☆

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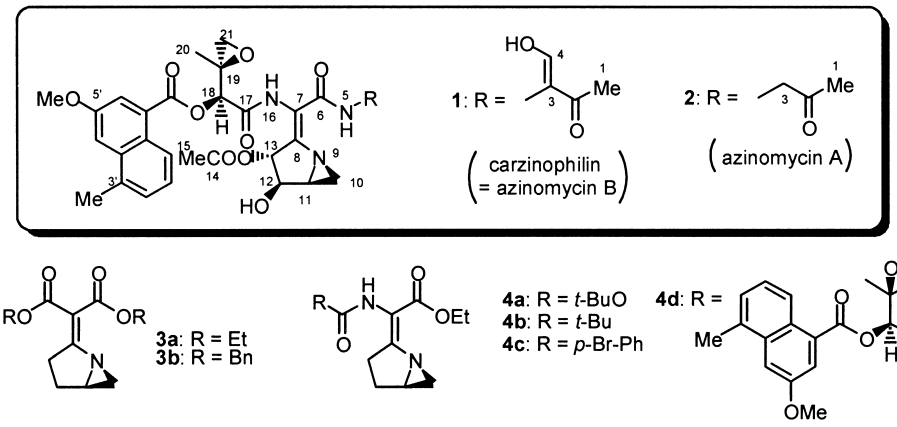
Abstract—Synthesis of the model compounds of carzinophilin carrying 2-methylidene-1-aza-bicyclo[3.1.0]hexane systems was achieved. Formation of malonylidenes or *N*-acyl-glycinylidenepyrrolidines was carried out by utilizing Eschenmoser's sulfide contraction or Herdeis's condensation between the 2-methylthio-Δ^1-pyrrolone derivatives and ethyl nitroacetate, respectively. The 1-azabicyclo-[3.1.0]hexane systems were constructed by base-promoted aziridine formation.

1. Introduction

Carzinophilin (**1**), isolated from *Streptomyces sahachiroi* by Hata et al. in 1954, exhibits potent antitumor activity[3] and is well known as a bisalkylating agent for DNA.[4–6] The structure of **1** was revised several times over more than 30 years.[7,8] In 1991, Armstrong et al. revealed that the ^{1}H- and ^{13}C NMR spectra of **1** were superimposable on those of azinomycin B (AZB),[9] which was isolated in 1986 by Yokoi et al. from *Streptomyces griseofuscus* S4227 along with azinomycin A (AZA) as novel antitumor antibiotics.[10] Yokoi et al. also disclosed their structures which bear a unique 2-methylidene-1-azabicyclo[3.1.0]hexane substructure based on their ^{1}H- and ^{13}C NMR studies.[11] The unique history, intriguing structures, and prominent antitumor activity of **1** and **2** make these compounds attractive targets for total synthesis, and a number of synthetic studies toward AZs have been reported.[9,12–39] While Coleman et al. recently succeeded in the total synthesis of **2**,[19] the synthesis of **1** has not been accomplished yet. In the course of our synthetic studies of **1** with an aim to confirm the structure of **1** by total synthesis as well as to develop potent anticancer agents among the compounds related to **1**, we also achieved and reported the syntheses of model compounds possessing a bicyclic (pyrrolidin-2-ylidene)malonic acid ester **3a,b** and an *N*-acyl-*E*-(pyrrolidin-2-ylidene)glycine



☆ See refs 1 and 2.

Keywords: carzinophilin; malonylidenes; bisalkylating agent.

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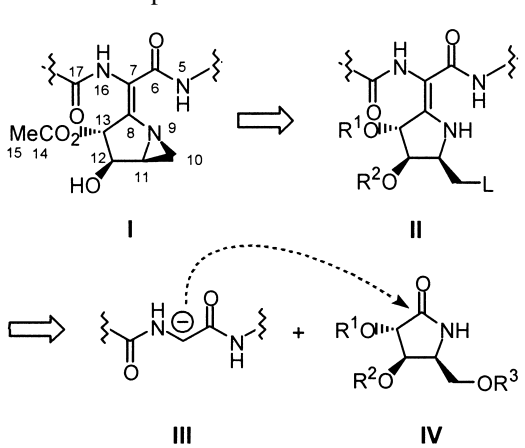
ester **4a**–**d** in communication forms.[2] The most functionalized **4d** involves the C6–C21 framework of **1**. Now, we would like to describe the full details of the preparation of **3** and **4**.[2]

2. Results and discussion

2.1. Basic methodology

The 3-acetoxy-4-hydroxy-2-methylidene-1-azabicyclo-[3.1.0]hexane substructure is the most characteristic framework in carzinophilin (**1**). We first investigated the development of an efficient synthetic method for constructing this central bicyclic dehydropeptide system **I**. Our synthetic strategy for **I** is outlined in Scheme 1. The aziridine ring of **I** should be constructed at the final stage of the synthesis because the aziridine ring carrying an electron withdrawing vinylogous acyl group on the nitrogen seemed to be labile under acidic, basic, and/or reductive conditions. The bicyclic system **I** might be derived from the precursor **II** by 1,3-elimination reaction. The 2-methylidenepyrrolidine system of **II** was planned to be introduced by a coupling reaction of an anionic species of glycine equivalent **III** with the pyrrolidin-2-one **IV** followed by dehydration. As a model component for **IV**, we chose readily available 5-(*tert*-butyldiphenylsiloxymethyl)pyrrolidin-2-one (**5**).[40,41] Shipman et al. also prepared AZ analogues employing similar methodology.[38] Coleman et al. and Armstrong et al. independently reported alternative synthetic routes which furnish the bicyclic system by sequential intramolecular 1,4-addition and 1,2-elimination reaction of δ-aziridin-2-yl-β-bromo-α,β-unsaturated carbonyl systems.[19,22] There was no employable synthetic method providing an *E*-(pyrrolidin-2-ylidene)glycine system when we started this series of synthetic studies. Accordingly, we intended to establish a synthetic route to build a 1-azabicyclo[3.1.0]hexane ring system. First, we attempted to develop an efficient synthetic method for this unique core-frame through syntheses of various model compounds.

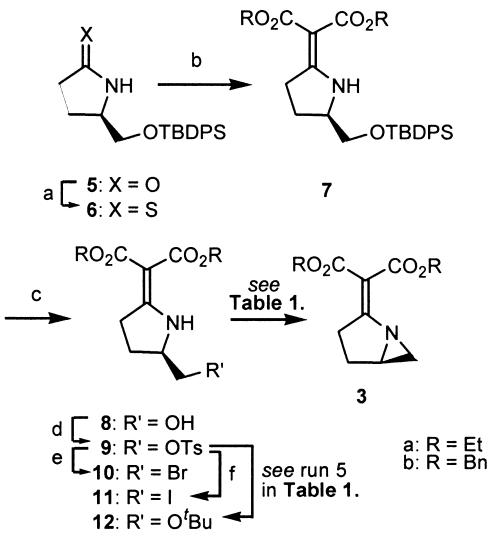


Scheme 1. Synthetic strategy of the 3-acetoxy-4-hydroxy-2-methylidene-1-azabicyclo[3.1.0]hexane system involved in carzinophilin (**1**).

2.2. Synthesis of the bicyclic 2-malonylidene systems[1a]

We first investigated a method to introduce a 2-malonylidene-1-azabicylo[3.1.0]hexane system by utilizing a condensation reaction of a pyrrolidin-2-thione with an α-halomalonic acid ester called the Eschenmoser sulfide contraction.[42]

After pyrrolidin-2-one **5** readily prepared from D-pyroglutamic acid by the reported procedure,[40,41] was converted into pyrrolidin-2-thione **6** by heating with Lawesson's reagent[43] in toluene, **6** was subjected to Eschenmoser sulfide contraction.[42] As expected, on treatment of **6** with diethyl or dibenzyl bromomalonate in CH_2Cl_2 at room temperature followed by the addition of aqueous potassium hydrogen carbonate, the contraction reaction took place giving pyrrolidin-2-ylidene malonates **7a**,**b** in 97 and 99% yields, respectively. The silyl protective groups in **7a**,**b** were removed in good yields by means of tetrabutylammonium fluoride (TBAF) to afford alcohols **8a**,**b** (Scheme 2).



Scheme 2. Synthesis of bicyclic malonylidene derivative **3**. *Reagent and conditions*: (a) Lawesson's reagent, toluene, reflux, 20 min, 96%. (b) $(EtO_2C)_2CHBr$ or $(BnO_2C)_2CHBr$, CH_2Cl_2, rt, 12 h, then aq. $KHCO_3$, 3–4 h, 97% (for **7a**), 99% (for **7b**) (c) TBAF, THF, rt, 1–2 h, 96% (for **8a**), 93% (for **8b**). (d) TsCl, Py., CH_2Cl_2, rt, 1–2 days, 100% (for **9a**), 98% (for **9b**). (e) Bu_4NBr, CH_3CN, reflux, 3–4 h, 93% (for **10a**), 92% (for **10b**). (f) NaI, acetone, reflux, 15–18 h, 92% (for both **11a** and **11b**).

The intermolecular aziridine formation producing bicyclic compounds **3a**,**b** was next examined. In our preliminary experiments, **8a**,**b** as well as some related substrates were subjected to Mitsunobu's conditions[44] with the expectation of inducing 1,3-dehydration, however, the desired bicyclic compounds could not be obtained. Thus, the intramolecular basic substitution between the metal amide and a leaving group was next studied. For this purpose, the hydroxy groups of **8a**,**b** were converted into *p*-toluenesulfonates **9a**,**b** under the usual conditions. They were further elaborated to bromides **10a**,**b** or iodides **11a**,**b** by heating with tetrabutylammonium bromide in CH_3CN or sodium iodide in acetone, respectively.

The results for synthesizing **3a**,**b** are summarized in Table 1. An experiment in which **9a** was treated with potassium carbonate, KHMDS, potassium *tert*-butoxide, or *n*-butyl lithium did not produce the desired **3a** at all (entries 1–4). When the reaction was performed with a potassium carbonate in *tert*-butanol, substitution of the tosylate with *tert*-butoxide occurred to give *tert*-butyl ether **12** (entry 5, the structure in Scheme 1 data not shown). Further

Table 1. Formation of the bicyclic 2-malonylidene derivatives **3a**,**b**

Entry	Substrate	Base	Conditions	Results
1	**9a**[a]	K_2CO_3	THF, rt, 12 h	No reaction
2	**9a**[a]	KHMDS	THF, rt, 12 h	No reaction
3	**9a**[a]	KO*t*-Bu	THF, rt, 12 h	No reaction
4	**9b**[a]	BuLi	THF, rt, 1 h	Complex mixture
5	**9a**[a]	K_2CO_3	*t*-BuOH, rt, 3 days	**12** (trace)
6	**9a**[a]	NaH (oil dispersion)	THF, rt, 40 min	**3a** (9% isolated yield)
7	**9a**[a]	NaH (oil free)	THF, rt, 1 h	No reaction[b]
8	**9a**[a]	KH (oil free)	THF, rt 15 min	**3a** (80% crude yield, 34% isolated yield)
9	**9a**[a]	KH (oil free)	Et_2O, rt, 1 h	No reaction[c]
10	**9b**[a]	KH (oil free)	THF, rt, 40 min	**3b** (4% isolated yield)
11	**9b**[a]	NaH (oil dispersion)	THF, rt, 1 h	**13b** (58%)
12	**10b**	KH (oil free)	THF, rt 15 min	**3b** (27% isolated yield)
13	**11a**[a]	NaH	THF, rt, 1 h	**13a** (58%)
14	**11b**[a]	NaH (oil dispersion)	THF, rt, 3 h	**3b** (detected by only TLC), **13b** (70%)

[a] The corresponding enantiomers were employed as the substrates.
[b] Evolution of H_2 was observed.
[c] Evolution of H_2 was not observed, but it was observed upon addition of dry THF after stirring for 1 h.

investigations revealed that on treatment of **9a** with commercial sodium hydride (ca. 60% dispersion in mineral oil) in THF at room temperature for 40 min, the aziridine formation took place to afford **3a** (entry 6). Interestingly, the reaction did not proceed under similar conditions and **9a** was recovered, when oil-free sodium hydride (prepared by washing with hexane) was employed in place of commercial oil dispersion (entry 7). Under those conditions, evolution of hydrogen gas was observed implying the sodium amide was generated. However, the amide species was not reactive enough for the aziridine formation. These results suggested that mineral oil plays an important role for the reaction, but its function remains unclear. It was found that potassium hydride without mineral oil was also applicable to the reaction, giving **3a** in ca. 80% yield based on the ^{1}H NMR analysis of the crude product, when the reaction was carried out in THF solution (entry 8). Tetrahydrofuran was essential as the reaction solvent. The same reaction in Et_2O did not take place (entry 9). Hydrogen gas generation was observed upon the addition of dry THF into the reaction mixture after stirring several hours in ether. This suggests that potassium hydride cannot pull out the proton from **9a** in Et_2O solution. It was found that **3a** was so unstable under acidic conditions that purification by silica gel column chromatography decomposed a large amount of the product giving pure **3a** in a low yield. Its purification was achieved only by quick Florisil® column chromatography, affording a pure sample of **3a** in 15–34% isolated yield.

Fortunately, a pure sample of **3a** was stable enough in $CDCl_3$ for measuring its ^{1}H NMR spectrum. Figure 1 shows some chemical shifts and characteristic NOEs observed for the ^{1}H NMR spectrum of **3a**. Signals observed at 1.61, 2.40, and 2.88 ppm indicated the existence of an aziridine ring. They were assigned as H_a, H_b, and H_c, respectively, as shown in Figure 1. The signals corresponding to H_a and H_d appeared at higher fields than H_b and H_e, due to shielding by the pyrrolidine and the aziridine ring, respectively. Detection of NOE between H_a and H_d also supported the aziridine ring as shown (Fig. 1).

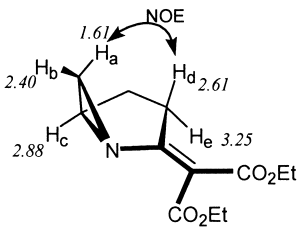
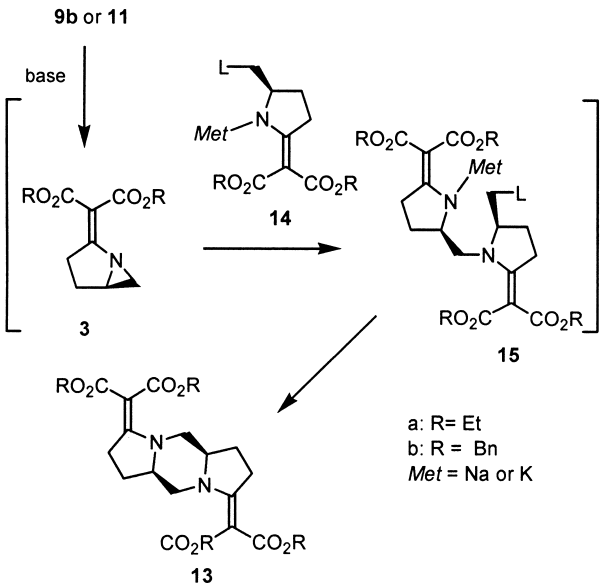


Figure 1. Characteristic chemical shifts (italic, ppm) and observed NOEs in the ^{1}H NMR spectrum of **3a** ($CDCl_3$).

As shown in Table 1, tosylate **9b**, the dibenzyl ester analogue of **9a**, provided **3b** in a lower yield when treated with potassium hydride (oil-free form) in THF solution. This condition had given the best results in the case of **3a** (entry 10). When **9b** was reacted with sodium hydride (dispersed in mineral oil), the dimeric product **13b** was produced along with a trace amount of **3b** (entry 11). The existence of **3b** was detected only by silica gel TLC of the reaction mixture, but it could not be isolated probably due to decomposition during chromatographic separation. Although the TLC spot corresponding to **3b** was detectable just after starting the reaction, neither accumulation nor decay of the spot was observed in the reaction. However, the



Scheme 3. Reaction mechanism for **13**.

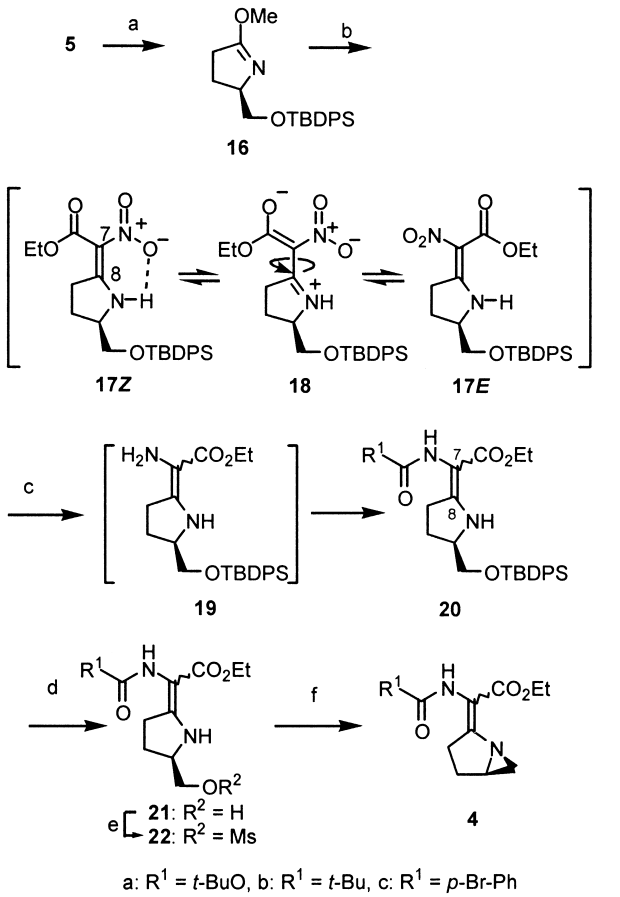
amount of **13b** increased by the time course. These observations suggested that aziridine **3b** was consumed by the nucleophilic attack of metal amide **14b** to the aziridine moiety of **3b** producing the dimeric metal amide **15b** as shown in Scheme 3. Subsequent intramolecular piperazine ring formation resulted in the formation of **13b**. The bromide **10b**, and iodides**11a**,**b** also afforded dimeric products **13a**,**b** (entries 13, 14). These products are considered to be formed by way of a similar mechanism to that described above. As for their cyclization to **3b**, bromide **10b** gave the best results providing **3b** in 27% yield after Florisil® column chromatography (entry 12).

In the same way, a series of enantiomers were also prepared starting with *ent*-**5** obtainable from L-pyroglutamic acid for studies on the structure–cytotoxicity relationships. (Data shown only in Section 3.)

2.3. Synthesis of bicyclic (pyrrolidin-2-ylidene) glycine esters 4[1b]

Preparation of the bicyclic compounds carrying a pyrrolidin-2-ylideneglycine moiety was the next target of our efforts. In the preliminary experiments, we failed in almost all of the Wittig type olefinations of pyrrolidin-2-ones directly giving a (pyrrolidin-2-ylidene)glycine moiety in spite of many trials. Thus, we applied a stepwise protocol established by Herdeis et al.[45] which includes condensation reaction of a 2-methoxy-1-pyrroline with nitroacetate ester to provide 2-nitro-(pyrrolidin-2-ylidene)acetate and subsequent palladium-mediated reduction of the nitro function. The pyrrolidin-2-one **5** was first converted into the 2-methoxy-1-pyrroline **16** by treating with excess dimethyl sulfate in benzene at 60°C.[46] The reagent, dimethyl sulfate, should be removed completely before the next step, because the existence of dimethyl sulfate was found to reduce the yield of the desired adduct **17** considerably and to afford an undesired *N*-methylpyrrolidin-2-one derivative by migration of the *O*-methyl group to the nitrogen atom. Distillative removal of dimethylsulfate under reduced pressure also induced the migration. Chromatographic purification accompanied decomposition of **16**. It was finally found that **16** can be isolated in the form of a methyl hydrogen sulfate salt from the reaction mixture and the salt is insoluble in non-polar solvents. Thus, purification of labile **16** was achieved by the following operations, (i) removal of benzene in vacuo at low temperature, (ii) washing the crude methyl hydrogen sulfate salt of **16** with diethyl ether several times to remove remained dimethyl sulfate, and (iii) extraction with ethyl acetate from basic aqueous solution (Scheme 4).

Heating **16** in ethyl nitroacetate at 60°C underwent β-nitroenamine formation affording the adduct **17** in a moderate yield. After separation by silica gel column chromatography, the adduct **17** (needles, 82.0–83.5°C from MeOH–H_2O) was found to be a mixture of isomers about the C7–C8 double bond (*carzinophilin numbering*) by its ^1H NMR spectrum, and the ratio of the isomers varied with the solvents employed [50:50 (benzene), 60:40 ($CDCl_3$), and 100:0 (CD_3OD), their stereochemistry could not be assigned]. These observations suggested tautomerism between **17***E* and **17***Z* by way of the intramolecular iminium



Scheme 4. Synthesis of the 2-(*N*-acylglycinylidene)-1-azabicyclo-[3.1.0]hexane derivatives **4a**,**b**. *Reagents and conditions*: (a) $(MeO)_2SO_2$, benzene, 60°C, 18 h, 87%. (b) $O_2NCH_2CO_2Et$, 60°C, 8 h, 42%. (c) HCO_2H, Et_3N, 10% Pd/C, MeOH, 3 days, then Boc_2O, 78% (for **20a**), H_2 (5 atm), 10% Pd/C, toluene, rt, 10–12 h, then PivCl, or 4-Br-BzCl, $NaHCO_3$, AcOEt–toluene, 1 h, 84% (for **20b**), 84% (for **20c**). (d) TBAF, THF, rt, 30 min, 1 h, 66% (for **21a**), 74% (for **21b**), 69% (for **21c**). (e) MsCl, Et_3N, CH_2Cl_2, −78°C, 30 min, 86% (for **21a**), 86% (for **22b**), 65% (for **22c**). (f) KH, THF, rt, 15 min, 41% (isolated yield, for **4a**), 56% (isolated yield, for **4b**), 40% (isolated yield for *ent*-**4c**).

salt **18**. This tautomerism was confirmed by detecting the spots corresponding to both **17***E* and **17***Z* not only on the diagonal line but also out of that in its 2D-TLC chromatogram (SiO_2, CH_2Cl_2–benzene). Interestingly, X-ray diffraction analysis revealed that **17** exists as a *Z*-isomer in a crystalline form. The *Z*-isomer **17***Z* might be more stable than **17***E* due to the hydrogen bonding between one of the oxygens in the nitro group and the proton presented on the nitrogen of the pyrrolidine ring.

The nitro group in **17** was reduced with Pd/C in methanol using triethylammonium formate.[45] Since the produced enamine **19** was found to be unstable under oxygen, it was immediately acylated in situ with Boc_2O to give the ethyl *N*-*tert*-butylcarbonyl-(pyrrolidin-2-ylidene)glycinate **20a**. For amide **20b**, the reduction was carried out using the H_2 (5 atm)–Pd/C–toluene system, and subsequent amide formation with pivaloyl chloride required the addition of $NaHCO_3$ for completion of the reactions. An amount of 10% Pd–C being the equivalent weight of **17** was required for this palladium-mediated reduction. The TBDMS groups in **20a**–**b** were removed by means of TBAF to give **21a**–**b**,

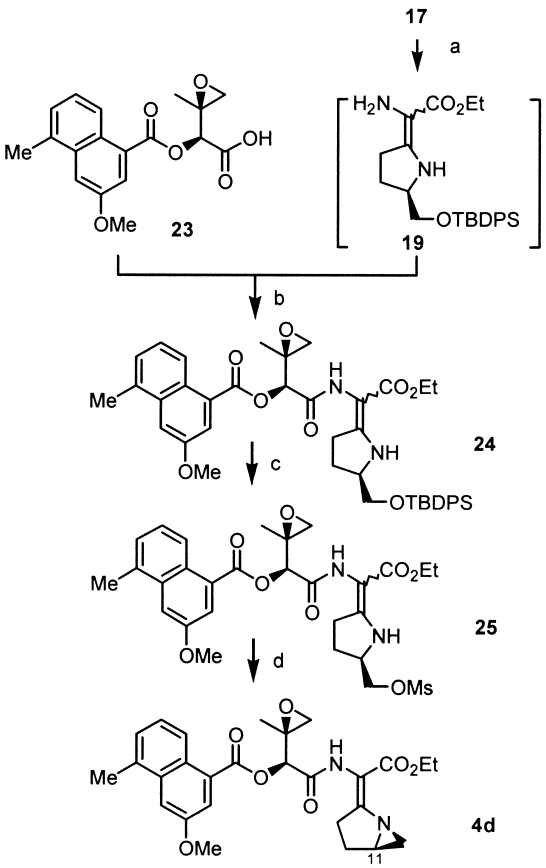
which were converted into mesylates **22a–b** under the usual conditions.

As expected, on treating **22a–c** with potassium hydride in THF, the aziridine formation took place producing the 2-(*N*-acyl-glycinylidene)-1-azabicyclo[3.1.0]hexane **4a–c** in moderate yields after quick purification with Florisil® or silica gel (Merck Art 7754) column chromatography. The stereochemistry of the C7–C8 double bonds (*carzinophilin numbering*) of **4a–c** was tentatively assigned as *E*-configuration (vide infra). Since **4a–c** were unstable under acidic conditions, a considerable amount of the products decomposed during the purification process. For example, the ^{1}H NMR spectrum of the crude reaction product right after aqueous workup suggested the formation of **4b** in more than 80% yield, however, the isolation yield was 56%.

By the same manners, a series of enantiomers *ent*-**4a–c** were also prepared starting with *ent*-**5** obtainable from L-pyroglutamic acid for studies on the structure–cytotoxicity relationships. (Data shown only in Section 3.)

2.4. Synthesis of the carzinophilin analogue 4d with C6–C21 framework[2b]

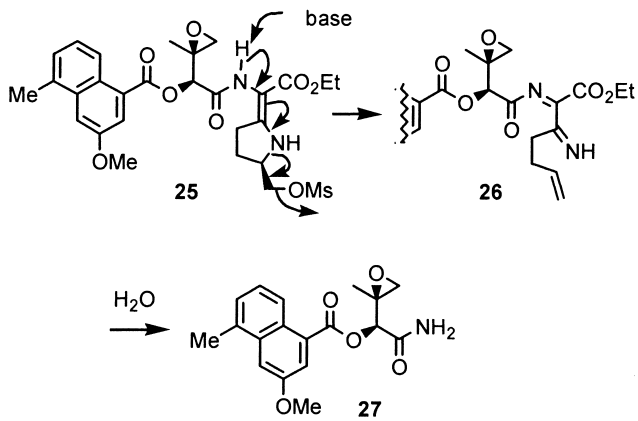
Applying the knowledge accumulated in model studies, synthesis of a carzinophilin analogue **4d** carrying the C6–C21 framework was performed as shown in Scheme 5.



Scheme 5. Synthesis of the carzinophilin analogue **4d**, with C6-C21 framework. *Reagent and conditions*: (a) H_2 (5 atm), 10% Pd–C, toluene, rt, 12 h. (b) **25**, HOBt, DCC, THF, 0°C, 51% in two steps. (c) (i) TBAF, THF, rt, 30 min, 76%. (ii) MsCl, Et_3N, CH_2Cl_2, −78°C, 1 h, 89%. (d) KHMDS, THF, rt, 10 min, 40% (isolated yield).

Carboxylic acid **23** corresponding to the C17–C21 carrying a chromophore moiety was prepared according to the reported methods[33,47] with slight modifications. Then, coupling reaction of the enamine **19** with **23** was performed. After palladium-mediated catalytic reduction of **17**, the reaction mixture was added through a pad of mixture of Celite®–$MgSO_4$ into the HOBt ester of **23** in situ prepared using DCC–HOBt.[48] giving the adduct **24** in 51% yield. Water generated by the nitro group reduction was removed with $MgSO_4$ in order to avoid undesired hydrolysis of the HOBT ester. A mixed anhydride method employing chloroisopropyl formate gave **24** in a lower yield (38%). After the TBDPS ether in **24** was cleaved with TBAF in THF, the obtained alcohol was transformed into mesylate **25** in 68% in two steps.

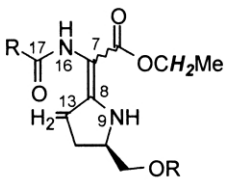
With **25** in hand, aziridine formation was next examined. In the case of more functionalized **25**, potassium hydride gave many products, providing the aziridine derivative **4d** in a trace amount after short silica gel preparative TLC within 10 min. When lithium bis(trimethylsilyl)amide (LHMDS) was employed as the base, the reaction gave a complex mixture. The aziridine ring was found to be constructed more cleanly by potassium bis(trimethylsilyl)amide (KHMDS) to afford **4d** as a single stereoisomer (vide infra). The yield was estimated as ca. 80% based on the ^{1}H NMR spectrum of the crude material. The product **4d** was also unstable under acidic conditions, but quick silica gel column chromatography afforded **4d** in an almost pure form in 34% yield. Florisil® was found to be less effective in this case. In this reaction, a small amount of the amide derivative **27** was obtained which was identical with a synthetic authentic sample kindly provided by Professor M. Shibuya.[32] Production of **27** can be explained by the two-step reaction as shown in Scheme 6: (i) attack of the base to the amide proton attached at N16 and not at the pyrrolidine N9–H (*carzinophilin numbering*) in **25**, which induces elimination of the mesylate to produce diimine **26** and (ii) hydrolysis of the imine moieties during aqueous workup. The amide **27** is known to be isolated along with AZs.[11] Our results might suggest that **2** might be derived in vivo by the biosynthetic pathway similar to that observed for **25**.



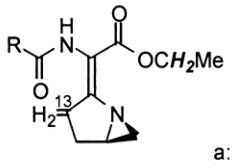
Scheme 6. Proposed mechanism for generation of amide **27**.

In a similar manner, a series of diastereomers about the C11 position (*carzinophilin numbering*) *iso*-**4d**, *iso*-**24**, and *iso*-**25** were also synthesized from *ent*-**5** obtainable from

Table 2. Properties of **4a–d**, **20–22**, **24**, and **25**



20-22, **24**, and **25**



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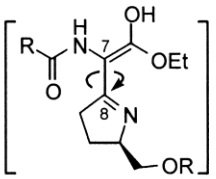
a: R = *t*-BuO
b: R = *t*-Bu
c: R = *p*-Br-Ph



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Compound	Number of isomers (based on ^{1}H NMR in $CDCl_3$)	Isomeric ratio	State	Mp	Chemical shifts (ppm)			
					C13H_2		CH_2 of the ethyl ester	
					Major isomer	Minor isomer	Major isomer	Minor isomer
7a	Single isomer	–	Oil	–	1.77, 2.08	–	4.11 (2H) 4.22 4.31	–
20a[a]	4 isomers	14:2:1:1	Oil	–	2.72 (2H)	NA[a]	4.13 (2H)	4.13 (2H)
20b	2 isomers	87:13	Oil	–	2.63 (2H)	3.03, 3.04	4.13 (2H)	4.14 (2H)
20c	2 isomers	90:10	Oil	–	2.74 (2H)	3.16 (2H)	4.17 (2H)	4.17 (2H)
21a	2 isomers	90:10	Oil	–	2.71, 2.79	3.08 (2H)	4.12 (2H)	4.12 (2H)
21b	2 isomers	80:20	Oil	–	2.62, 2.68	3.09, 3.12	4.10 (2H)	4.13 (2H)
21c[a]	2 isomers	80:20	Oil	–	2.70, 2.79	3.19, 3.49	4.13 (2H)	4.16 (2H)
22a	Single isomer	–	Fine needle	122–123°C	2.79 (2H)	–	4.14 (2H)	–
22b	2 isomers	90:10	Fine needle	93–95°C	2.67, 2.73	3.14 (2H)	4.12 (2H)	4.16 (2H)
22c[a]	2 isomers	80:20	Fine needle	172–173°C	2.77, 2.83	3.21 (2H)	4.16 (2H)	4.18 (2H)
24	2 isomers	90:10	Oil	–	2.65 (2H)	NA[b]	4.13 (2H)	NA[b]
25	2 isomers	85:15	Oil	–	.2.75 (2H)	3.14 (2H)	4.11 (2H)	4.11 (2H)
4a	Single isomer	–	Oil	–	2.60, 3.13	–	4.21 (2H)	–
4b	Single isomer	–	Oil	–	2.64, 3.08	–	4.18, 4.20	–
4c[a]	Single isomer	–	Oil	–	2.70, 3.17	–	4.23 (2H)	–
4d	Single isomer	–	Oil	–	2.73, 3.09	–	4.20 (2H)	–

[a] For **4c**, **20c**, and **22c**, the data obtained for the cooresponding enantiomers were tablated.
[b] Signals for minor isomers could not be assigned due to signal overlapping.

L-pyroglutamic acid for studies on the structure–cytotoxicity relationships. (Data shown only in Section 3.)

2.5. Stereochemistry of the (pyrrolidin-2-ylidene)glycine moieties

With completion of the chemical synthesis of 2-methylidene-1-azabicyclo[3.1.0]hexane systems, the stereochemistries about the C7–C8 double bond (*carzinophilin numbering*) of **4a–d**, **20–22**, **24**, and **25**, are discussed. As summarized in **Table 2**, compounds **20–22** were obtained as mixtures of isomers based on their ^{1}H NMR spectra although they afforded single spots in their TLC analysis. The ratios of isomers varied according to the synthetic stages. Interestingly, **22b** was obtained as crystals (needles, mp: 93–95°C); however, a $CDCl_3$ solution of these crystals contained a 90:10 mixture of the isomers based on its ^{1}H NMR spectra. There might be two possible reasons for this phenomenon. One is the isomerization about the C7–C8 double bond (*carzinophilin numbering*) through rotation of the C7–C8 single bond of imine **28**. And the other is the presence of rotamers caused by rotation about the N16–C17 amide (or carbamoyl) group. Taking into account the fact that bicyclic compounds **4a–c** existed as single isomers, the hydrogen atom attached at N9 (*carzinophilin numbering*) seems to be necessary for isomerization. This suggests the imine–enamine equilibrium may trigger off the isomerization. First, we examined whether those isomers were separable or inseparable tautomers. In the mesylation step giving crystalline **22b**, a small amount **21b** was recovered from the reaction mixture. The isomeric ratio of both the substrate and recovered **21b** was estimated as 80:20 based on the peak intensities of their ^{1}H NMR spectra. The isomeric ratios of the crystalline **22b** and the residue from mother liquid of **22b** were also compared by the ^{1}H NMR spectra showing no difference in the isomeric ratios (90:10) between them. If these exist as separable isomers, the isomeric ratios of substrate **21b** and recovered **21b** should not be identical. In the case where both isomers involved in **21b** are transformed to the corresponding mesylates in the same rate, the isomeric ratio of **22b** must be 90:10. Therefore, it might be suggested that the isomers about **21b** and **22b** resulted from tautomerism not from kinetic resolution by the reactions. As described above, nitro enamine **17** existed as a mixture of tautomeric isomers in spite of no amide groups in the molecule. Accordingly, tautomerism of **20–22**, **24**, and **25** may come from similar isomerization of the C7–C8 enamine moiety to that of **17** via rotation of imine **28**. Only **20a** could include further rotamers arising from its carbamate group.

Unfortunately, NOE experiments provided no clue to the stereochemistry of the tautomers. However, the major isomers of **20–22**, **24**, and **25** were assigned as an *E*-configuration from the following reasons as well as taking into account Lhommet's report.[49,50] As shown in Table 2, the signals corresponding to the C13H_2 (*carzinophilin numbering*) of the major *E*-isomer appear at higher field than those of the minor *Z*-isomer in their ^{1}H NMR spectra in $CDCl_3$ probably due to the shielding effect by the C17 carbonyl group. The *E*-isomer may be stabilized with the hydrogen bonding between the N9–H (*carzinophilin numbering*) and the C6 carbonyl oxygen, which constitutes a favorable six-membered ring. The hydrogen bonding

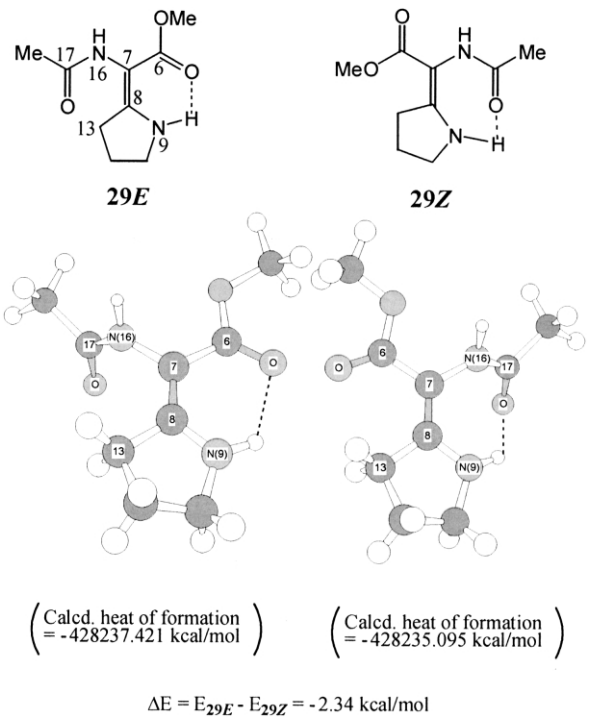

Figure 2. Structures of *E*-**29** and *Z*-**29** and their conformations with minimum steric energy calculated by 6-31G* base set.

between the N9–H (*carzinophilin numbering*) and the C6 amide oxygen in *Z*-isomer makes a less stable seven-membered ring (Fig. 2).

These considerations were further examined by molecular modeling calculations for the model compounds **29***E* and **29***Z*.[51] Taking accuracy into account, we employed ab initio molecular orbital calculations employing 6-31G* basis set.[52] Methodologies based on empirical parameters, molecular mechanics such as MM+[53] or semi-empirical molecular orbital methods such as AM1,[54] might not provide reliable conformations due to the unique enamide system of **29**. After both **29***E* and **29***Z* were subjected to a conformational search program employing semi-empirical AM1, all the conformations found were re-optimized based on 6-31G* to reveal global minimum conformations. These calculations suggested that the conformation of **29***E* with the lowest steric energy is 2.34 kcal/mol more stable than that of **29***Z*. By considering the fact that these isomers were in an equilibrium, the major isomer might have more stable *E*-configuration. Interestingly, the dihedral angle of the enamide moiety (∠C8–C7–N16–C17) for the main conformer of **29***E* was −83°. This means that the lone pair electron on the N16 does not contribute to the conjugation with the C7–C8 double bond.

Bicyclic compounds **44a–d** were obtained as single isomers. Stereochemistries of the C7–C8 double bonds in **4a–d** were tentatively assigned as *E*-configuration. There is no remarkable difference in the methylene signals of the ethyl ester moieties between the major *E*- and minor *Z*-tautomers of monocyclic intermediate **20–22**, **24**, and **25**. On the other hand, the methylene signals of the ethyl ester moieties of bicyclic **4a**,**b** appeared at lower field than those of both *E*- and *Z*-tautomers of **20–22**, **24**, and **25**. This might be construed to mean that the ethyl group of the bicyclic **4** located not only in *syn* geometry but also in co-planer to the aziridine ring. Although Armstrong et al. and Coleman et al. determined the stereochemistries of their model compounds by using NOE technique, NOE between the C13–H and the N16–H (*carzinophilin numbering*) was not observed in the case of our bicyclic compounds.[12,15,21] Incidentally, NOEs between the amide proton and the protons on the pyrrolidine ring were not described by Yokoi et al. in their report concerning the structure determination of AZs, although the stereochemistry about the C1–N5 enamide and C8–C13 pyrrolidine ring moieties was determined mainly based on NOEs.[11] Further, molecular modeling calculations in a similar manner to that described for **29** (a conformation search based on AM1 and following re-optimizations employing 6-31G*) provided a stable conformation of model molecule **30**, which indicates that the distance between C13–H and N16–H is not close enough for the NOE observation. Also, comparison of the conformations of **29** and **30** may indicate that functional transformations on the pyrrolidine ring moiety influence the conformations of the dihydropeptide side chain (Fig. 3).

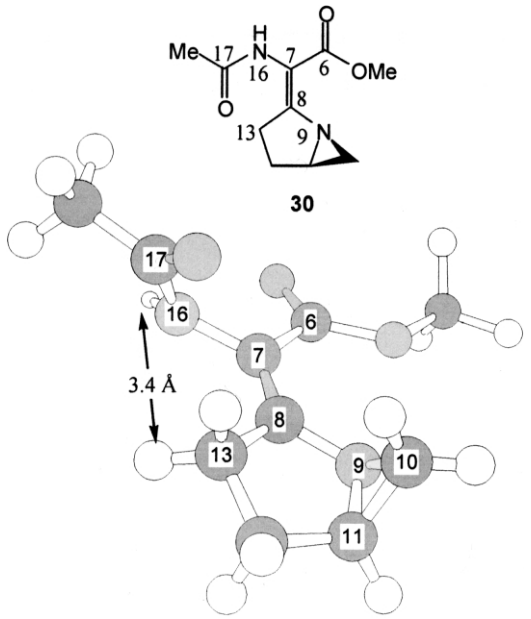

Figure 3. A conformer of Model compound **30** with the lowest steric energy suggested by 6-31G*.

2.6. Conclusion

As described above, we succeeded in developing a basic method for bicyclic (pyrrolidin-2-ylidene)malonic esters **3a**,**b** and *N*-acyl *E*-(pyrrolidin-2-ylidene) glycine esters **4a–c**, as well as in preparing a C6–C21 model compound of carzinophilin **4d**. These studies provided ample of basic knowledges for the synthesis of the C1–C17 analogue of carzinophilin which is the subject of the following report.[55]

3. Experimental

3.1. General

All melting points were determined with a Yamato MP-1

micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker AC200 (200 MHz) and a Bruker AM400 (400 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from the signal of trimethylsilane used as an internal standard. ^{13}C NMR spectra were recorded with a Bruker AM400 (100 MHz) spectrometer using $^{13}CDCl_3$ as an internal standard (77.0 ppm). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), and br (broad). Assignments of the signals are described according to the numbering of IUPAC nomenclature or that of carzinophilin originally reported by Yokoi et al.[11] When the latter numbering is used, '*carzinophilin numbering*' is mentioned. IR spectra were obtained with a JASCO FT/IR-5300 spectrometer. Measurements of electron and chemical ionization-low resolution mass spectra (EI-MS and CI-MS) and high-resolution mass spectra (EI-HIMS) were performed with a Hitachi RMU-6MG and a Hitachi M80A spectrometer, respectively. Optical rotations were measured with a Horiba SEPA-200 photometer. For the compounds consisting of a mixture of tautomers, the optical rotations were not measured. Elemental analyses were performed with a Perkin–Elmer 240 or a Perkin–Elmer 2400CHN elemental analyzers. Analytical and preparative thin-layer chromatographies were carried out using pre-coated silica gel plates, Merck pre-coated silica gel plates Art 5715 and Art 5744, respectively. Silica gel generally used for column chromatography was Merck silica gel 60 Art 7734. Merck silica gel Art 7754, was employed for separation of an unstable compound. Florisil® column chromatography was performed with Florisil® 100–200 mesh Floridin Co. All reactions are carried out under Ar atmosphere using dried solvents excepted for aqueous conditions, reduction with H_2, or oxidation with ozone.

3.2. (*R*)-5-(*tert*-Butyldiphenylsiloxy)methylpyrrolidin-2-one (5) and its enantiomer (*ent*-5)[41]

3.2.1. Preparation of *ent*-5. (*S*)-5-Hydroxymethylpyrrolidin-5-one [mp 86–87°C, $[\alpha]_D^{20}$=+28.9° (*c* 1.71, EtOH)] was prepared following Saijo's procedure from (*S*)-pyroglutamic acid. ^{1}H NMR and IR spectra of the prepared sample were identical to those in the literature.[40] A solution of (*S*)-5-hydroxymethylpyrrolidin-5-one (6.10 g, 53.0 mmol), TBDPSCl (22.2 g, 81.0 mmol), and imidazole (12.0 g, 173 mmol) in DMF (30 mL) was stirred at room temperature for 12 h. The mixture was poured into water and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography ($CHCl_3$/acetone=95:5) gave *ent*-**5** (19.0 g, 100%) as a colorless solid. Analytical sample was prepared by recrystallization from hexane to give needles. Mp: 81–83°C. $[\alpha]_D^{20}$=+15.3° (*c* 1.66, $CHCl_3$). IR (nujor): 3200, 3100, 3060, 1690, 1460, 1105, 700, 505 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (9H, s, C(C*H*$_3$)$_3$), 1.72 (1H, m, C4H*H*), 2.18 (1H, m, C4H*H*), 2.32 (2H, m, C3*H*$_2$), 3.51 (1H, dd, *J*=7.6, 10.2 Hz, C5CH*H*O), 3.62 (1H, dd, *J*=4.0,10.2 Hz, C5CH*H*O), 3.79 (1H, m, C5*H*), 5.84 (1H, br s, N*H*), 7.45 (6H, m, aromatic protons), 7.69 (4H, m, aromatic protons). EI-MS (rel. int. %): *m*/*z*=354 (0.35, $[MH]^+$), 296 (100, $[M-t\text{-Bu}]^+$). Anal. calcd for $C_{21}H_{27}NO_2Si$: C, 71.35%; H, 7.70%; N,3.96%. Found: C,71.21%; H, 7.71%; N, 3.92%.

3.2.2. Preparation of 5. The same treatments of (*R*)-5-hydroxymethylpyrrolidin-2-one (**5**) (4.00 g, 34.8 mmol)[mp 86–88°C, $[\alpha]_D^{20}$=−31.8° (*c* 1.71, EtOH)][40] as described in Section 3.2.1. gave **6** (12.2 g, 99%) as a colorless solid after silica gel chromatography. Analytical sample was prepared by recrystallization from hexane to give needles. Mp: 81–83°C. $[\alpha]_D^{20}$=−15.7° (*c* 1.71, $CHCl_3$). Anal. calcd for $C_{21}H_{27}NO_2Si$: C, 71.35%; H, 7.70%; N,3.96%. Found: C,71.21%; H, 7.84%; N, 4.03%. This sample showed the ^{1}H NMR spectrum identical to that of *ent*-**5**.

3.3. (*R*)-5-(*tert*-Butyldiphenylsiloxy)methylpyrrolidin-2-thione (6) and its enantiomer (*ent*-6)

3.3.1. Preparation of *ent*-6. A solution of *ent*-**5** (5.00 g, 14.2 mmol) and Lawesson's reagent[43] (3.10 g, 7.67 mmol) in toluene (40 mL) was heated at reflux for 20 min. The mixture was cooled to room temperature and filtered through a pad of Celite®. After concentration of the filtrate in vacuo, the residue was purified by silica gel column chromatography (benzene/AcOEt=96:4) to give *ent*-**6** (5.03 g, 97%). Analytical sample was prepared by recrystallization from hexane to give prisms. Mp: 117–118°C. $[\alpha]_D^{20}$=+16.9° (*c* 1.06, $CHCl_3$). IR (nujor): 3200, 2870, 2830, 1535, 1455, 1370, 1300, 1100, 1015, 695, 610, 500 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (9H, s, C(C*H*$_3$)$_3$), 1.82 (1H, dddd, *J*=6.1, 7.9, 9.1, 12.8 Hz, C4H*H*), 2.22 (1H, ddt, *J*=6.4, 12.8, 8.3 Hz, C4H*H*), 2.94 (2H, m, C3*H*$_2$), 3.58 (1H, dd, *J*=7.7, 10.6 Hz, C5CH*H*O), 3.68 (1H, dd, *J*=3.9, 10.6 Hz, C5CH*H*O), 4.05 (1H, m, C5*H*), 7.40–7.70 (10*H*, m, aromatic protons), 7.75 (1H, br s, N*H*). EI-MS (rel. int. %) *m*/*z*=369 (7.0, M^+), 312 (100, $[M-t\text{-Bu}]^+$), 234 (99, $[M-t\text{Bu}-\text{PhH}]^+$). Anal. calcd for $C_{21}H_{27}NOSSi$: C, 68.24%; H, 7.36%; N, 3.79%; S, 8.67%. Found: C, 68.08%; H, 7.41%; N, 3.75%; S, 8.60%.

3.3.2. Preparation of 6. Treatments of **5** (10.2 g, 28.9 mmol) in the same manner as described in Section 3.3.1. gave **6** (10.2 g, 96%) after silica gel column chromatography. Analytical sample was prepared by recrystallization from hexane to give prisms. Mp: 116–117°C. $[\alpha]_D^{20}$=−17.4° (*c* 1.12, $CHCl_3$). Anal. calcd for $C_{21}H_{27}NOSSi$: C, 68.24%; H, 7.36%; N, 3.79%; S, 8.67%. Found: C, 68.28%; H, 7.37%; N, 3.91%; S, 8.68%. This sample showed the ^{1}H NMR spectrum identical to that of *ent*-**6**.

3.4. (*R*)-2-[5-(*tert*-Butyldiphenylsiloxymethyl)-pyrrolidin-2-ylidene]malonic acid diethyl ester (7a), its dibenzyl ester (7b), and their enantiomers (*ent*-7a and *ent*-7b)

3.4.1. Preparation of *ent*-7a. A solution of *ent*-**6** (3.00 g, 8.13 mmol) and diethyl bromomalonate (2.0 mL, 12 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 12 h. A solution of $KHCO_3$ (4.00 g, 40.0 mmol) in H_2O (7.0 mL) was added, and the whole mixture was further stirred at room temperature for 4 h. Upon addition of the solution of $KHCO_3$, gas evolution was observed. The reaction mixture was poured into water, and extracted with Et_2O. The combined extracts were washed with brine, dried over

$MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=96:4) gave **7a** (3.89 g, 97%) as a colorless oil. $[\alpha]_D^{20}=-29.4°$ (*c* 1.76, $CHCl_3$). IR (film): 3300, 2930, 1685, 1645, 1565, 1243, 1105, 1085, 795, 700, 500 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (9H, s, $C(CH_3)_3$), 1.29, 1.31 (each 3H, t, *J*=7.3 Hz, CH_3×2), 1.77 (1H, m, C4H*H*), 2.08 (1H, m, C4H*H*), 3.36 (2H, m, C3H_2), 3.58 (2H, m, C5CH_2O), 3.97 (1H, m, C5*H*), 4.20, 4.21 (each 2H, q, *J*=7.3 Hz, MeCH_2O×2), 7.30–7.70 (10H, m, aromatic protons), 9.60 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$, *C*DCl_3=77.0 ppm): δ 14.40, 14.45, 19.09, 23.81, 26.70, 33.77, 59.40, 59.53, 61.23, 66.55, 87.34, 127.70, 129.73, 132.87, 135.54, 167.62, 169.56, 172.62 ppm. EI-MS (rel. int. %): *m*/*z*=495 (0.80, M^+), 450 (5.4, $[M-EtO]^+$), 438 (6.1, $[M-t\text{-}Bu]^+$), 392 (100, $[M-t\text{Bu}-PhH]^+$), EI-HIMS calcd for $C_{28}H_{37}NO_5Si$ (M^+): *m*/*z*=495.2442. Found *m*/*z*=495.2422.

3.4.2. Preparation of 7a. Treatments of **6** (3.00 g, 8.13 mmol) in a similar manner to that described in Section 3.4.1 gave **7a** (3.90 g, 97%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=+27.9°$ (*c* 1.12, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**7b**.

3.4.3. Preparation of *ent*-7b. Treatments of *ent*-**6** (1.02 g, 2.75 mmol) and dibenzyl bromomalonate (1.00 mL, 2.75 mmol) similarly to those described in Section 3.4.1. gave *ent*-**7b** (1.50 g, 88%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=-19.4°$ (*c* 1.89, $CHCl_3$). IR (film): 3300, 2980, 2950, 2930, 2860, 1685, 1645, 1570, 1285, 1245, 1110, 1085, 700, 500 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 1.75 (1H, ddt, *J*=9.3, 13.0, 6.0 Hz, C4H*H*), 2.05 (1H, dddd, *J*=7.0, 8.4, 9.5, 13.0 Hz, C4H*H*), 3.12 (1H, ddd, *J*=6.0, 9.5, 18.6 Hz, C3H*H*), 3.17 (1H, ddd, *J*=7.0, 9.3, 18.6 Hz, C3H*H*), 3.52 (1H, dd, *J*=6.4, 10.3 Hz, C5CH*H*O), 3.62 (1H, dd, *J*=4.3, 10.3 Hz, C5CH*H*O), 4.01 (1H, m, C5*H*), 5.18 (2H, s, PhCH_2O), 5.23, 5.26 (each 1H, d, *J*=12.8 Hz, PhCH_2O), 7.23–7.43 (20H, m, aromatic protons), 9.83 (1H, br s, N*H*). EI-MS (rel. int. %): *m*/*z*=619 (0.65, M^+), 562 (4.6, $[M-t\text{-}Bu]^+$), 454 (6.3, $[M-hCH_2OH-t\text{-}Bu]^+$), 91 (100, $PhCH_2^+$). EI-HIMS: calcd for $C_{38}H_{41}NO_5Si$ (M^+): *m*/*z*=619.2755, Found: *m*/*z*=619.2736.

3.4.4. Preparation of 7b. Similar treatments of **6** (2.94 g, 7.96 mmol) and dibenzyl bromomalonate (2.90 mL, 7.99 mmol) to those described in Section 3.4.1. gave **7b** (4.87 g, 99%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=+19.2°$ (*c* 2.01, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**7b**.

3.5. (*R*)-2-(5-Hydroxymethylpyrrolidin-2-ylidene)-malonic acid diethyl ester (8a), its dibenzyl ester (8b), and their enantiomers (*ent*-8a and *ent*-8b)

3.5.1. Preparation of *ent*-8a. A solution of *ent*-**7a** (3.80 g, 7.67 mmol) and TBAF (1.0 M in THF, 9.0 mL) in THF (20 mL) was stirred at room temperature for 2 h. After concentration in vacuo, the residue was purified by silica gel column chromatography ($CHCl_3$/acetone=80:20) to give *ent*-**8a** (1.80 g, 91%) as a colorless oil. $[\alpha]_D^{20}=+22.4°$ (*c* 1.06, $CHCl_3$). IR (film): 3430, 3320, 2980, 1685, 1650, 1575, 1440, 1250, 1080, 800 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29, 1.30 (each 3H, t, *J*=7.1 Hz, CH_3×2), 1.78 (1H, dddd, *J*=6.0, 6.7, 9.6, 13.0 Hz, C4H*H*), 2.13 (1H, dddd, *J*=6.0, 8.2, 9.6, 13.0 Hz, C4H*H*), 3.08 (1H, ddd, *J*=6.7, 9.6, 18.3 Hz, C3H*H*), 3.18 (1H, ddd, *J*=6.0, 9.6, 18.3 Hz, C3H*H*), 3.55 (1H, br dd, *J*=6.8, 11.0 Hz, C5CH_2O), 3.78 (1H, br dd, *J*=4.0, 11.0 Hz, C5CH_2O), 4.01 (1H, m, C5*H*), 4.18 (4H, m, MeCH_2O–×2), 9.59 (1H, br s, NH). EI-MS (rel. int. %): *m*/*z*=257 (20, M^+), 226 (36, $[M-CH_2OH]^+$), 212 (36, $[M-EtO]^+$), 180 ($M-[CH_2OH-EtO]^+$). EI-HIMS. calcd for $C_{12}H_{19}NO_5$ (M^+): *m*/*z*=257.1263, Found *m*/*z*=257.1282.

3.5.2. Preparation of 8a. The same treatments of **7a** (3.90 g, 7.88 mmol) as described in Section 3.5.1 gave **8a** (1.94 g, 96%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=-22.4°$ (*c* 1.21, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**8a**.

3.5.3. Preparation of *ent*-8b. Treatments of *ent*-**7b** (1.50 g, 2.42 mmol) in a similar manner to those described in Section 3.5.1 gave *ent*-**8b** (890 mg, 97%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=+17.5°$ (*c* 1.71, $CHCl_3$). IR (film): 3450, 3300, 2940, 1680, 1640, 1560, 1435, 1245, 1070, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.75 (1H, dddd, *J*=6.1, 6.9, 9.3, 13.0 Hz, C4H*H*), 2.10 (1H, dddd, *J*=6.4, 8.4, 9.1, 13.0 Hz, C4H*H*), 3.08 (1H, ddd, *J*=6.1, 9.1, 18.7 Hz, C3H*H*), 3.22 (1H, ddd, *J*=6.4, 9.3, 18.7 Hz, C3H*H*), 3.51 (1H, dd, *J*=6.6, 11.1 Hz, C5CH_2O), 3.72 (1H, dd, *J*=3.7, 11.1 Hz, C5CH_2O), 4.00 (1H, m, C5*H*), 5.18, 5.20 (each 2H, s, PhCH_2O–×2), 7.20–7.40 (10H, m, aromatic protons), 9.70 (1H, br s, N*H*). EI-MS (rel. int. %): *m*/*z*=381 (1.7, M^+), 350 (0.89, $[M-CH_2OH]^+$), 274 (1.9, $[M-PhCH_2O]^+$), 247 (2.4, $MH-[PhCH_2O_2C]^+$), 242 (2.2, $[M-CH_2OH-PhCH_2O]^+$), 216 (4.0, $[M-CH_2OH-PhCH_2O_2C]^+$), 91 (100. $[PhCH_2]^+$). EI-HIMS. calcd for $C_{22}H_{23}NO_5$ (M^+): *m*/*z*=381.1577, Found: *m*/*z*=381.1603.

3.5.4. Preparation of 8b. Treatments of **7b** (4.88 g, 7.86 mmol) in the same manner as described in Section 3.5.1 gave **8b** (2.80 g, 93%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=-17.3°$ (*c* 1.83, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**8b**.

3.6. (*R*)-2-(5-*p*-Toluenesulfoxymethylpyrrolidin-2-ylidene)malonic acid diethyl ester (9a), its dibenzyl ester (9b), and their enantiomers (*ent*-9a and *ent*-9b)

3.6.1. Preparation of *ent*-9a. A solution of *ent*-**8a** (1.80 g, 7.00 mmol), *p*-TsCl (2.00 g, 10.5 mmol), and pyridine (1.96 g, 24.7 mol) was stirred in CH_2Cl_2 (20 mL) at room temperature for 12 h. The mixture was poured into H_2O and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography (benzene/AcOEt=80:20) to give *ent*-**9a** (2.66 g, 92%) as a white solid. Analytical sample was prepared by recrystallization from Et_2O–hexane to give

needles. Mp: 61–63°C. $[\alpha]_D^{20}=-21.4°$ (*c* 1.18, $CHCl_3$). IR (nujor): 3300, 1680, 1630, 1650, 1460 1360, 1270, 1245, 1170, 1080, 940, 870, 665, 550 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26, 1.29 (each 3H, t, *J*=7.1 Hz, $CH_3CH_2O\times2$), 1.72 (1H, m, C4H*H*), 2.13 (1H, m, C4H*H*), 2.41 (3H, m, CH_3Ar), 3.19 (2H, br t, *J*=8.2 Hz, C3H_2), 3.80–4.20 (3H, m, C5*H*, C5CH_2O), 5.16, 5.21 (each 2H, s, PhCH_2O×2), 7.20–7.40 (12H, m, aromatic protons), 7.76 (2H, dt, *J*=8.0, 1.0 Hz, aromatic protons of Ts group), 9.48 (1H, br s, N*H*). ^1H-Anal. calcd for $C_{19}H_{25}NO_7S$: C, 55.46%; H, 6.12%; N, 3.40%; S, 7.79%. Found: C, 55.17%; H, 5.96%; N, 3.35%; S, 7.96%.

3.6.2. Preparation of 9a. The same treatments of **8a** (1.00 g, 3.89 mmol) as described in Section 3.6.1 gave **9a** (1.60 g, 100%) as a white solid after silica gel column chromatography. Analytical sample was prepared by recrystallization from Et_2O–hexane to give needles. Mp: 62–64°C. $[\alpha]_D^{20}=+21.3°$ (*c* 1.83, $CHCl_3$). Anal. calcd for $C_{19}H_{25}NO_7S$: C, 55.46%; H, 6.12%; N, 3.40%; S, 7.79%. Found C, 55.31%; H, 6.02%; N, 3.41%; S=7.94%. This sample showed the ^1H NMR spectrum identical to that of *ent*-**9a**.

3.6.3. Preparation of *ent*-9b. Similar treatments of *ent*-**8b** (600 mg, 1.57 mmol) to those described in Section 3.6.1 gave ant-*ent*-**9b** (786 mg, 94%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=-18.5°$ (*c* 1.08, $CHCl_3$). IR (film): 3300, 2950, 1685, 1640, 1560, 1360, 1270, 1245, 1190, 1170, 1070, 960, 810, 790, 695, 660, 550 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 0.85 (1H, m, C4H*H*), 1.09 (1H, m, C4H*H*), 1.39 (6H, t, *J*=7.1 Hz, CH_3×2), 1.84 (3H, s, CH_3Ar), 2.71 (1H, ddd, *J*=6.2, 9.6, 18.5 Hz, C3H*H*), 2.81 (1H, ddd, *J*=6.5, 9.4, 18.5 Hz, C3H*H*), 3.13 (1H, m, C5*H*), 3.30 (1H, dd, *J*=6.7, 10.2 Hz, C5CH*H*O–), 3.47 (1H, dd, *J*=4.5, 10.2 Hz, C5CH*H*O–), 4.15–4.26 (4H, m, PhCH_2O×2), 6.75, 7.71 (each 2H, br d, *J*=7.7 Hz, aromatic protons of Ts group), 9.47 (1H, br s, N*H*). EI-MS (rel. int. %): *m*/*z*=535 (1.6, M^+), 488 (0.89, $[M-PhCH_2O]^+$), 401 (2.1, $[MH-PhCH_2O_2C]^+$), 91 (100. $PhCH_2)^+$). EI-HIMS. calcd for $C_{29}H_{29}NO_7S$: *m*/*z*= 535.1666, Found: *m*/*z*=535.1677.

3.6.4. Preparation of 9b. Treatments of **8b** (1.00 g, 2.63 mmol) in the same manner as described in Section 3.6.1 gave **9b** (1.37 g, 98%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=+17.6°$ (*c* 1.08, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**9b**.

3.7. (*R*)-2-(5-Bromomethylpyrrolidin-2-ylidene)malonic acid diethyl ester (10a), its dibenzyl ester (11b), and their enantiomers (*ent*-10a and *ent*-10b)

3.7.1. Preparation of *ent*-10a. A solution of *ent*-**9a** (200 mg, 487 μmol) and Bu_4NBr (300 mg, 930 μmol) in CH_3CN (1.5 mL) was heated at reflux for 3 h. The mixture was poured into H_2O and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=90:10) gave *ent*-**10a** (150 mg, 96%) as a solid. Analytical sample was prepared by recrystallization from hexane to give needles. Mp: 85–86°C. $[\alpha]_D^{20}=17.4°$ (*c* 1.06, $CHCl_3$). IR (nujor): 3240, 1665, 1560, 1435, 1360, 1315, 1280, 1240, 800 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29, 1.30 (each 3H, t, *J*=7.1 Hz, CH_3×2), 1.83 (1H, dddd, *J*=5.5, 6.7, 9.3, 12.2 Hz, C4H*H*), 2.24 (1H, dddd, *J*=6.5, 8.0, 9.2, 12.2 Hz, C4H*H*), 3.10 (1H, ddd, *J*=6.6, 9.1, 18.5 Hz, C3H*H*), 3.18 (1H, ddd, *J*=6.5, 9.3, 18.5 Hz, C3H*H*), 3.37 (1H, dd, *J*=6.8, 10.3 Hz, C5CH*H*Br), 3.42 (1H, dd, *J*=5.4, 10.3 Hz, C5CH*H*Br), 4.17 (1H, m, C5*H*), 4.18, 4.12 (each 2H, q, *J*=7.1 Hz, MeCH_2O×2), 9.70 (1H, br s, N*H*). *Anal.* calcd for $C_{12}H_{18}NO_4Br$: C, 45.02%; H, 5.67%; N, 4.37%; Br, 24.96%. Found: C, 44.95%; H, 5.43%; N, 4.29%; Br, 24.80%.

3.7.2. Preparation of 10a. Treatments of **9a** (1.00 g, 3.89 mmol) in a similar manner to that described in Section 3.7.1 gave **10a** (145 mg, 93%) as a white solid after silica gel column chromatography. Analytical sample was prepared by recrystallization from Et_2O–hexane to give needles. Mp: 85–86°C. $[\alpha]_D^{20}=+17.6°$ (*c* 1.03, $CHCl_3$). Anal. calcd for $C_{12}H_{18}NO_4Br$: C, 45.02%; H, 5.67%; N, 4.37%; Br, 24.96%. Found C, 45.00%; H, 5.56%; N, 4.29%; Br, 24.88%. This sample showed the ^1H NMR spectrum identical to that of *ent*-**10a**.

3.7.3. Preparation of *ent*-10b. Treatments of *ent*-**9b** (149 mg, 279 μmol) similarly to those described in Section 3.7.1 gave *ent*-**10b** (117 mg, 95%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=-12.9°$ (*c* 0.93, $CHCl_3$). IR (film): 3300, 3030, 2950, 1685, 1640, 1575, 1430, 1275, 1240, 1070,1020, 795, 725 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.81 (1H, dddd, *J*=5.6, 6.6, 9.3, 13.2 Hz, C4H*H*), 2.24 (1H, dddd, *J*=6.5, 8.1, 9.2, 13.2 Hz, C4H*H*), 3.14 (1H, ddd, *J*=6.6, 9.2, 18.7 Hz, C3H*H*), 3.26 (1H, ddd, *J*=6.5, 9.4, 18.7 Hz, C3H*H*), 3.33 (1H, dd, *J*=6.7, 10.4 Hz, C5CH*H*Br), 3.44 (1H, dd, *J*=5.4, 10.4 Hz, C5CH*H*Br), 4.19 (1H, br quint, *J*=6.0 Hz, C5*H*), 5.18, 5.23 (each 2H, s, PhCH_2O×2), 7.20–7.40 (10H, m, aromatic protons), 9.75 (1H, br s, N*H*). EI-MS (rel. int. %) *m*/*z*=445, 443 (0.75, 0.60, respectively, M^+), 338, 336 (0.51, 0.53, respectively, $[M-PhCH_2O]^+$), 311, 309 (0.66, 0.68 respectively, $[MH-PhCH_2O_2C]^+$), 248, 246 (0.91, 0.93 respectively, $[M-PhCH_2O-PhCH_2]^+$), 91 (100. $PhCH_2^+$). EI-HIMS. calcd for $C_{22}H_{22}NO_4^{81}Br$ (M^+), $C_{22}H_{22}NO_4^{79}Br$ (M^+): *m*/*z*=445.0713, 443.0732, Found: *m*/*z*=445.0710, 443.0726, respectively.

3.7.4. Preparation of 10b. Similar treatments of **9b** (178 mg, 333 μmol)to those described in Section 3.7.1 gave *ent*-**10b** (137 mg, 92%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=+12.1°$ (*c* 1.08, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**10b**.

3.8. (*R*)-2-(5-Iodomethylpyrrolidin-2-ylidene)malonic acid diethyl ester (11a), its dibenzyl ester (11b), and their enantiomers (*ent*-11a and *ent*-11b)

3.8.1. Preparation of *ent*-11a. A solution of *ent*-**10a** (172 mg, 418 μmol) and NaI (144 mg, 961 μmol) in acetone (3.0 mL) was heated at reflux for 15 h in the dark. After cooling to room temperature, the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ solution and extracted

with Et_2O. The combined ethereal extracts were washed successively with water and brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=90:10) gave *ent*-**11a** (151 mg, 98%) as a solid. Analytical sample was prepared by recrystallization from Et_2O–hexane to give needles. Mp: 119–120°C. $[\alpha]_D^{20}=-58.7°$ (*c* 1.19, $CHCl_3$). IR (nujor): 3240, 1665, 1625, 1560, 1435,1280, 1240, 1090, 800 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (3H, t, *J*=7.1 Hz, C*H*$_3$), 1.30 (3H, t, *J*=7.2 Hz, C*H*$_3$), 1.77 (1H, dddd, *J*=5.6, 6.8, 9.4, 13.2 Hz, C4H*H*), 2.26 (1H, dddd, *J*=6.1, 7.9, 9.3, 13.2 Hz, C4H*H*), 3.00–3.38 (4H, C3*H*$_2$, C5C*H*$_2$I), 4.09 (1H, br quint, *J*=6.0 Hz, C5*H*), 4.17 (2H, q, *J*=7.1 Hz, MeC*H*$_2$O–), 4.20 (2H, q, *J*=7.2 Hz, MeC*H*$_2$O), 9.70 (1H, br s, N*H*). Anal. calcd for $C_{12}H_{18}NO_4I$: C, 39.25%; H, 4.94%; N, 3.81%. Found: C, 39.09%; H, 5.00%; N, 3.74%.

3.8.2. Preparation of 11a. The same treatments of **10a** (162 mg, 394 μmol) as described in Section 3.8.1 gave **11a** (133 mg, 92%) as a white solid after silica gel column chromatography. Analytical sample was prepared by recrystallization from Et_2O–hexane to give needles. Mp: 117–118°C. $[\alpha]_D^{20}=+57.7°$ (*c* 1.11, $CHCl_3$). Anal. calcd for $C_{12}H_{18}NO_4I$: C, 39.25%; H, 4.94%; N, 3.81%. Found: C, 39.30%; H, 4.78%; N, 3.68%. This sample showed the ^1H NMR spectrum identical to that of *ent*-**11a**.

3.8.3. Preparation of *ent*-11b. Treatments of *ent*-**10b** (160 mg, 299 μmol) in the same manner as described in Section 3.8.1 gave *ent*-**11b** (143 mg, 97%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=-43.4°$ (*c* 1.04, $CHCl_3$). IR (film): 3270, 2950, 1685, 1640, 1560, 1270, 1240, 1070, 1010, 795, 730, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.79 (1H, dddd, *J*=5.7, 6.6, 9.5, 12.4 Hz, C4H*H*), 2.26 (1H, dddd, *J*=6.1, 7.9, 9.3, 12.4 Hz, C4H*H*), 3.00–3.40 (4H, C3*H*$_2$, C5C*H*$_2$I), 4.19 (1H, br quint, *J*=6.0 Hz, C5*H*), 5.21, 5.23 (each 2H, s, PhC*H*$_2$O×2), 7.20–7.40 (10H, aromatic protons), 9.73 (1H, br s, N*H*). EI-MS (rel. int. %): *m*/*z*=491 (0.39, M^+), 384 (0.79, $[M-PhCH_2O]^+$), 357 (1.2, $[MH-PhCH_2O_2C]^+$), 294 (1.1, $[MH-PhCH_2O-PhCH_2]^+$), 254 (0.94, $[MH-PhCH_2O-PhCH_2O_2C)^+$), 91 (100, $PhCH_2^+$). EI-HIMS, calcd for $C_{22}H_{22}NO_4I$ (M^+): *m*/*z*=491.0595, Found: *m*/*z*=491.0568.

3.8.4. Preparation of 11b. Treatments of **10b** (158 mg, 295 μmol) in a similar manner to that described in Section 3.8.1 gave **11b** (133 mg, 92%) as a colorless oil after silica gel column chromatography. $[\alpha]_D^{20}=+44.0°$ (*c* 1.13, $CHCl_3$). This sample showed the ^1H NMR spectrum identical to that of *ent*-**11b**.

3.9. (*R*)-2-(1-Azabicyclo[3.1.0]hex-2-ylidene)malonic acid diethyl ester (3a), its dibenzyl ester (3b), and their enantiomers (*ent*-3a and *ent*-3b)

3.9.1. Preparation of *ent*-3a. To a suspension of KH (freshly washed with hexane, 10.0 mg, 250 μmol) in THF (10 mL), a solution of *ent*-**9a** (103 mg, 250 μmol) in THF (1.0 mL) was added at room temperature under Ar atmosphere. After stirring 15 min at the same temperature, the reaction mixture was poured into H_2O and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, then concentrated in vacuo. The ^1H NMR (200 MHz) spectrum of the residue (65 mg) showed that it only consisted of *ent*-**3a** and starting *ent*-**9a**. Accordingly, the chemical yield of this reaction was estimated to be ca. 80%. Purification of the residue by Florisil® column chromatography (benzene/AcOEt=97:3 to 90:10) gave a pure sample of *ent*-**3a** (20.7 mg, 34%) as a pale yellow oil along with recovered *ent*-**9a** (11.3 mg, 18% recovery). *ent*-**3a**: $[\alpha]_D^{20}=+104°$ (*c* 0.750, $CHCl_3$). IR (film): 2980, 1730, 1710, 1640, 1290, 1260, 1230, 1070, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20, 1.28 (each 3H, t, *J*=7.1 Hz, C*H*$_3$×2), 1.61 (1H, d, *J*=5.1 Hz, C6*H*$_\beta$), 2.14 (2H, m, C4*H*$_2$), 2.40 (1H, dd, *J*=1.0, 4.3 Hz, C6*H*$_\alpha$), 2.61 (1H, ddt, *J*=1.0, 17.9, 9.1 Hz, C3*H*$_\beta$), 2.88 (1H, m, C5*H*), 3.25 (1H, ddd, 6.4, 8.7, 17.9 Hz, C3*H*$_\alpha$), 4.11 (2H, q, *J*=7.1 Hz, MeC*H*$_2$O), 4.22, 4.31 (each 1H, dq, *J*=10.8, 7.2 Hz, MeC*H*$_2$O). ^{13}C NMR (100 MHz, CDCl3,*C*DCl_3=77.0 ppm): δ=14.07, 14.09, 24.34, 29.79, 39.76, 44.77, 60.54, 61.16, 115.76, 164.26, 166.29, 174.64 ppm. EI-MS (rel. int. %): *m*/*z*=239 (2.3, M^+), 210 (2.6, $[M-Et]^+$), 194 (4.3, $[M-EtO]^+$), 180 (100, $[M-EtO-CH_2]^+$). EI-HIMS, calcd for $C_{12}H_{17}NO_4$ (M^+): *m*/*z*=239.1158, Found: *m*/*z*=239.1158.

3.9.2. Preparation of 3a. Treatments of **9a** (139 mg, 388 μmol) in a similar manner to that described in Section 3.9.1 gave crude **3a** after concentration of the combined ethereal extracts in vacuo. Similarly to the case of *ent*-**3a**, the chemical yield of **3a** was estimated as ca. 70% based on its ^1H NMR spectrum. Purification of this sample in the same manner as described in Section 3.9.1 gave pure **3a** (15.7 mg, 19%) as a pale yellow oil along with recovered **9a** (28.3 mg, 20% recovery). $[\alpha]_D^{20}=-93.0°$ (*c* 0.800, $CHCl_3$). The ^1H NMR spectrum of this sample was identical to that recorded for *ent*-**3a**.

3.9.3. Preparation of *ent*-3b. Similar treatments of *ent*-**10b** (40.0 mg, 90.1 μmol) to those described in Section 3.9.1 gave crude *ent*-**3b** after concentration of the combined ethereal extracts in vacuo. Purification of the crude sample by Florisil® (benzene/AcOEt=98:2 to 95:5) in a similar manner as described in Section 3.9.1 afforded pure *ent*-**3b** (5.7 mg, 17%) and recovered *ent*-**10b** (16.0 mg, 40% recovery) both as a viscous oil. The $[\alpha]_D^{20}$ value of *ent*-**3b** could not be measured due to its instability. IR (film): 3030, 2950, 1720, 1640, 1560, 1290, 1260, 1220, 1070, 1015, 750, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.67 (1H, d, *J*=4.3 Hz, C6H$_\beta$), 2.19 (2H, m, C4H$_2$), 2.42 (1H, dd, *J*=0.9, 5.0 Hz, C6H$_\alpha$), 2.70 (1H, ddt, *J*=0.9, 20.1, 8.0 Hz, C3H$_\beta$), 2.98 (1H, m, C5H), 3.33 (1H, ddd, *J*=6.9, 7.1, 20.1 Hz, C3H$_\alpha$), 5.15 (2H, s, $PhCH_2O$), 5.21, 5.35 (each 1H, d, *J*=12.3 Hz, PhC*H*$_2$O–), 7.20–7.40 (10H, aromatic protons). EI-MS (rel. int. %): *m*/*z*=363 (0.25, M^+), 350 (0.20, $[M-CH_2-H]^+$), 272 (5.4, $[M-PhCH_2]^+$), 256 (0.48, M−PhCH2O+), 242 (4.6, $[M-PhCH_2O-CH_2-H]^+$), 91 (100, $PhCH_2^+$). EI-HIMS, calcd for $C_{22}H_{21}NO_4$ (M^+): *m*/*z*=363.1471, Found: *m*/*z*=363.1459.

3.9.4. Preparation of *ent*-3b. Treatments of the bromide **10b** (25.0 mg, 87.0 μmol) in the same manner as described in Section 3.9.1 gave crude *ent*-**3b** after concentration of the combined ethereal extracts in vacuo. Purification of this sample in the same manner as described in Section 3.9.1 gave pure **3b** (5.2 mg, 27%) as a pale yellow oil. The $[\alpha]_D^{20}$

value of **3b** was not measured due to instability. The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**3b**.

3.10. (3*R*,9*R*)-1,7-Diaza-6,12-bis[bis(ethoxycarbonyl)-methylidene]tricyclo[7.3.0.0^{3,7}]dodecane (13a) and (3*R*,9*R*)-1,7-diaza-6,12-bis[bis(benzyloxycarbonyl)-methylidene]tricyclo[7.3.0.0^{3,7}]dodecane (13b)

3.10.1. Preparation of *ent*-13a. Sodium hydride (60% dispersion in mineral oil, 4.2 mg) was added to a solution of the iodide *ent*-**11a** (34.0 mg, 92.6 μmol) in THF (2.0 mL) at room temperature under Ar atmosphere. After stirring for 2 h, the mixture was poured into H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by preparative silica gel TLC (benzene/AcOEt=80:20, R_f=0.5) gave *ent*-**13a** (13.0 mg, 58%) as a viscous oil. IR (film): 2970, 1680, 1560, 1365, 1335, 1090 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (12H, br t, *J*=7.1 Hz, C*H*$_3$×4), 1.57 (2H, m, C6H*H*, C12H*H*), 2.15 (2H, m, C6H*H*, C12H*H*), 3.04 (2H, ddd, *J*=6.5, 8.8, 17.7 Hz, C5H*H*, C11H*H*), 3.11 (2H, t, *J*=12.1 Hz, C2H*H*, C8H*H*), 3.28 (2H, ddd, *J*=5.6, 9.3, 17.7 Hz, C5H*H*, C11H*H*), 3.56 (2H, dd, *J*=4.2, 12.1 Hz, C2H*H*, C8H*H*), 4.18 (8H, m, CH_3CH_2O×4). 4.25 (2H, m, C1H, C7H). EI-MS (rel. int. %) *m*/*z*=478 (9.6, M^+), 433 (11, $[M-EtO]^+$), 29 (100, Et^+).

3.10.2. Preparation of *ent*-13b. Treatments of *ent*-**11b** (23.0 mg, 46.8 μmol) in the same manner as described in Section 3.10.1 gave *ent*-**13b** (12.0 mg, 16.5 μmol, 70%) as a colorless oil after preparative TLC. IR (film): 2930, 1680, 1555, 1260, 1230, 1155, 1090, 1070, 740, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (2H, m, C6H*H*, C12H*H*), 1.89 ((2H, m, C6H*H*, C12H*H*), 2.72 (2H, t, *J*=12.4 Hz, C2H*H*, C8H*H*), 2.96 (2H, ddd, *J*=6.8, 9.0, 17.5 Hz, C5H*H*, C11H*H*), 2.97 (2H, ddd, *J*=6.5, 9.1, 17.5 Hz, C5H*H*, C11H*H*), 3.23 (2H, dd, *J*=4.3, 12.4 Hz, C2H*H*, C8H*H*), 4.07 (2H, m, C1H*H*, C7H*H*), 5.12, 5.15 (each 2H, d, *J*=12.6 Hz, PhC*H*$_2$O×2), 7.28 (20H, m, aromatic protons).

3.11. (*R*)-2-(*tert*-Butyldiphenylsiloxymethyl)-5-methoxy-3,4-dihydro-2H-pyrrole (16) and its enantiomer (*ent*-16)

3.11.1. Preparation of *ent*-16. A solution of *ent*-**6** (300 mg, 850 μmol) and Me_2SO_4 (81 μL, 860 mmol) in benzene (1.0 mL) was stirred at 60°C for 18 h. After cooling, hexane (1.0 mL) was added. The mixture was stirred vigorously for 1 min, left standing at room temperature for 10 min, then the upper layer was removed by a pipette. Ether (2.0 mL) was added to the residual lower layer, and vigorous stirring was continued for 1 min. After standing at room temperature, the separated ethereal layer was removed by a pipette. These operations were further repeated twice. The residual oil was diluted with CH_2Cl_2 and washed successively with aqueous 1 M NaOH solution and brine. The dichloromethane layer was dried over K_2CO_3 and concentrated in vacuo to give almost pure *ent*-**16** (275 mg, 88%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (9H, s, $(CH_3)_3CSi$), 2.10 (2H, m, C3*H*$_2$), 2.60 (2H, m, C4*H*$_2$), 3.66 (1H, dd, *J*=5.5, 9.9 Hz, C2CH*H*O), 3.81 (3H, s, C*H*$_3$O), 3.82 (1H, dd, *J*=4.0, 9.9 Hz, C2CH*H*O), 7.45 (6H, m, aromatic protons), 7.67 (4H, m, aromatic protons). This sample was immediately subjected to the next step.

3.11.2. Preparation of 16. Treatments of **6** (5.50 g, 15.6 mmol) in the same manner as described in Section 3.11.1 gave **16** (4.97 g, 87%) as a colorless oil after concentration of the dichloromethane extracts in vacuo. The ^{1}H NMR spectrum of this sample was identical to that of *ent*-**16**. This sample was immediately subjected to the next step.

3.12. Ethyl (*R*)-2-[5-(*tert*-butyldiphenylsiloxymethyl)-pyrrolidin-2-ylidene]-2-nitroacetate (17) and its enantiomer *ent*-17

3.12.1. Preparation of *ent*-17. A mixture of *ent*-**16** (275 mg, 750 μmol) and ethyl nitroacetate (1.0 mL, 9.0 mmol) was stirred at 60°C for 8 h. After cooling, the mixture was directly subjected to silica gel column chromatography (hexane/Et_2O=65:35) to give *ent*-**17** (235 mg, 67%) as a yellow solid. Analytical sample was prepared by recrystallization from MeOH–H_2O to give pale yellow needles. m.p: 82.0–83.5°C. The $[\alpha]_D$ value was not measured for this compound, because it consisted of a mixture of the tautomers whose ratio varied depending on the solvent. IR (nujor): 3300, 1710, 1585, 1465, 1095, 500 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 1.03 (9H, s, $(CH_3)_3CSi$), 1.31 (3H, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 2.05 (1H, ddt, *J*=9.5, 12.9, 4.0 Hz, C4H*H*), 2.23 (1H, dddd, *J*=8.0, 8.8, 9.9, 12.9 Hz, C4H*H*), 3.14 (1H, br ddd, *J*=4.0, 9.9, 17.6 Hz, C3H*H*), 3.27 (1H, br t, *J*=8.8, 17.6 Hz, C3H*H*), 3.70 (1H, dd, *J*=4.3, 10.8 Hz, C5CH*H*O), 3.86 (1H, dd, *J*=3.0, 10.8 Hz, C5CH*H*O), 4.22 (1H, m, C5*H*), 4.27 (2H, q, *J*=7.1 Hz, CH_3CH_2O), 7.45 (6H, m, aromatic protons), 7.64 (4H, m, aromatic protons). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s, $(CH_3)_3CSi$), 1.34 [1H×0.6, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O(major)], 1.35 [1H×0.4, *J*=7.1 Hz, C*H*$_3$CH$_2$O (minor)], 1.85 (1H. m, C4H*H*), 2.16 (1H. m, C4H*H*), 3.11 [1H×0.6, ddd, *J*=6.1, 9.7, 18.5 Hz, C3H*H* (major)], 3.20 [1H×0.6, ddd, *J*=6.6, 9.5, 18.5 Hz, C3H*H* (major)], 3.28 [1H×0.4, ddd, *J*=6.1, 9.4, 19.0 Hz, C3H*H* (minor)], 3.36 [1H×0.4, ddd, *J*=6.6, 9.2, 19.0 Hz, C3H*H* (minor)], 3.57 [1H×0.4, dd, *J*=6.6, 10.6 Hz, C5CH*H* (minor)], 3.59 [1H×0.6, dd. *J*=6.6, 10.5 Hz, C5CH*H* (major)], 3.72 [1H×0.4, dd, *J*=4.0, 10.6 Hz, C5H*H* (minor)], 3.76 [1H ×0.6, dd, *J*=3.8, 10.5 Hz, C5H*H* (major)], 4.15 (1H, m, C5*H*), 4.28 [2H×0.6, q, *J*=7.1 Hz, CH_3CH_2O (major)], 4.33 [2H×0.4, m, CH_3CH_2O (minor)], 7.42 (6H, m, aromatic protons), 7.63 (4H, m, aromatic protons), 9.65 [1H×0.4, br s, N*H* (minor)], 9.93 [1H×0.6, br s, N*H* (major)]. (400 MHz, C_6D_6): δ 0.79, 0.94 (each 1H×0.5, m, C4H*H*), 1.00–1.15 (13H, m, C4H*H*, $(CH_3)_3CSi$, C*H*$_3$CH$_2$O), 2.59 [1H×0.5, ddd, *J*=6.0, 9.9, 18.5 Hz, C3H*H* (one isomer)], 2.66 [1H×0.5, ddd, *J*=6.3, 9.8, 18.7 Hz, C3H*H* (another isomer)], 2.81 (1H, m, C3H*H*), 2.98 (1H, m, C5CH*H*O), 3.12 (1H, m, C5CH*H*O), 3.20 (1H, m, C5*H*), 4.16 [2H×0.5, dq, *J*=0.6, 7.1 Hz, CH_3CH_2O (one isomer)], 4.18 [2H×0.5, q, *J*=7.1 Hz, CH_3CH_2O (another isomer)], 7.24 (6H, m, aromatic protons), 7.64 (4H, m, aromatic protons), 9.39, 9.42 (each 1H×0.5, N*H*). EI-MS (rel. int. %) *m*/*z*=469 (trace, M^+), 453 (0.1, $[MH-O]^+$), 411 (38, $[M-t\text{-}Bu]^+$), 199 (100, $[Ph_2SiOH]^+$). Anal. calcd for $C_{14}H_{14}N_2O_5Si$: C, 64.08%; H, 6.88%; N, 5.98%. Found: C, 63.85%; H, 6.87%; N, 6.00%.

3.12.2. Preparation of 17. The same treatments of **16** (4.51 g, 12.0 mmol) as described in Section 3.12.1 gave **17** (3.68 g, 65%) as a yellow solid after silica gel column chromatography. Analytical sample was prepared by recrystallization from MeOH–H_2O to give pale yellow needles. Mp: 83–85°C. Anal. calcd for $C_{14}H_{14}N_2O_5Si$: C, 64.08%; H, 6.88%; N, 5.98%. Found: C, 63.89%; H, 6.92%; N, 5.92%. This sample showed the ^{1}H NMR spectrum identical to that of *ent*-**17**.

3.13. Ethyl (*R*)-2-(*tert*-butoxycarbonyl)amino-2-[5-(*tert*-butyldiphenylsiloxymethyl)pyrrolidin-2-ylidene]acetate (20a) and its enantiomer (*ent*-20a)

3.13.1. Preparation of *ent*-20a. A suspension of *ent*-**17** (110 mg, 235 μmol), HCO_2H (100 μL), Et_3N (200 μL), and 10% Pd/C (50 mg) in MeOH (10 mL) was stirred vigorously at room temperature under Ar atmosphere for 3 days. After filtration, Boc_2O (76 mg, 350 μmol) was added immediately to the filtrate. The mixture was further stirred at room temperature for 15 min, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=90:10) gave *ent*-**20a** (92.0 mg, 72%) as a mixture of the two tautomers and their rotamers. IR (film). 3370, 2950, 2930, 2850, 1715, 1670, 1590, 1480, 1365, 1250, 1160, 1110, 700 cm^{-1}. Since the ^{1}H NMR spectrum of this sample was found to be complex due to co-existence of the two tautomers about the C7–C8 double bond as well as the rotamers about the carbamoyl group, complete assignments of all signals could not be achieved. Accordingly, signals of the major isomer (ca. 80%) are described. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*) δ 1.05 (9H, s, (CH_3)$_3$CSi), 1.25 (3H, t, *J*=7.1 Hz, CH_3CH2O), 1.46 (9H, s, (CH_3)$_3$CO), 1.70 (1H, m, C12H*H*), 2.05 (1H, m, C12H*H*), 2.72 (2H, br t, *J*=7.5 Hz, C13H_2), 3.55 (2H, m, C11CH_2O), 3.97 (1H, m, C11*H*), 4.13 (2H, br q, *J*=7.1 Hz, CH_3CH_2O), 5.36 (1H, br s, N*H*), 7.41 (6H, m, aromatic protons), 7.65 (4H, m, aromatic protons), 8.10 (1H, br s, N*H*). EI-MS (rel. int. %): *m*/*z*=538 (6.0, M$^+$), 482 (3.9, [M−isobutene]$^+$), 438 (49, [M−isobutene−CO_2]$^+$), 57 (100, *t*-Bu$^+$).

3.13.2. Preparation of 20a. Similar treatments of **17** (200 mg, 427 μmol) to those described in Section 3.13.1 gave **20a** (179 mg, 78%) as an oil after silica gel column chromatography. The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**3b**.

3.14. Ethyl (*R*)-2-[5-(*tert*-butyldiphenylsiloxymethyl)-pyrrolidin-2-ylidene]-2-(*tert*-butylcarbonylamino)-acetate (20b), its enantiomer (*ent*-20b), and ethyl (*S*)-2-[5-(*tert*-butyldiphenylsiloxymethyl)-pyrrolidin-2-ylidene]-2-(4-bromobenzoylamino)acetate (*ent*-20c)

3.14.1. Preparation of *ent*-20b. A suspension of *ent*-**17** (120 mg, 261 μmol) and 10% Pd/C (120 mg) in toluene (5 mL) was stirred vigorously under H_2 atmosphere (5 atm) at room temperature for 12 h. The reaction mixture was added through a glass filter to a suspension of pivaloyl chloride (100 mg, 793 μmol) and $NaHCO_3$ (100 mg, 1.20 mmol) in AcOEt (10 mL). After stirring at room temperature for additional 1 h, the mixture 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 of the residue by silica gel column chromatography (benzene/AcOEt=80:20) gave *ent*-**20b** (79.2 mg, 58%) as a mixture of the two tautomers (*E*:*Z*=87:13). IR (film): 3300, 2950, 2920, 1670, 1595, 1110, 700, 500 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, a=0.87, b=0.13): δ 1.04 [9H×b, s, (CH_3)$_3$CSi (*Z*-isomer)], 1.06 [9H×a, s, (CH_3)$_3$CSi(*E*-isomer)], 1.24 (3H, t, *J*=7.1 Hz, CH_3CH_2O), 1.25 [9H×a, s, (CH_3)$_3$CSi(*E*-isomer)], 1.27 [9H×b, s, (CH_3)$_3$CSi (*Z*-isomer)], 1.64 (1H, br, C12H*H*), 2.02 [1H×a, m, C12H*H*(*E*-isomer)], 2.10 [1H×b, m, C12H*H*(*Z*-isomer)], 2.63 [2H×a, t, *J*=7.8 Hz, C13H_2(*E*-isomer)], 3.03 [1H×b, ddd, *J*=5.4, 9.4, 18.2 Hz, C13H*H* (*Z*-isomer)], 3.04 [1H×b, ddd, *J*=8.0, 9.7, 18.2 Hz, C13H*H* (*Z*-isomer)], 3.51 [1H×b, dd, *J*=8.0, 10.0 Hz, C11CH*H*O (*Z*-isomer)], 3.56 [1H×a, dd, *J*=7.0, 10.3 Hz, C11CH*H*O (*E*-isomer)], 3.60 [1H×a, dd, *J*=5.2, 10.3 Hz, C11CH*H*O (*E*-isomer)], 3.61 [1H×b, C11CH*H*O (*Z*-isomer)], 3.94 [1H×b, m, C11*H* (*Z*-isomer)], 3.98 [1H×a, br quint, *J*=6.6 Hz, C11*H* (*E*-isomer)], 4.13 [2H×a, br q, *J*=7.1 Hz, CH_3CH_2O (*E*-isomer)], 4.14 [2H×b, q, *J*=7.1 Hz, CH_3CH_2O (*Z*-isomer)], 6.05 [1H×b, br, N*H* (*Z*-isomer)], 6.43 [1H×a, br, N*H* (*E*-isomer)], 7.08 [1H×b, br, N*H* (*Z*-isomer)], 7.40 (6H, m, aromatic protons), 7.64 (4H, m, aromatic protons), 8.09 [1H×a, br, N*H* (*E*-isomer)]. EI-MS (rel. int. %): *m*/*z*=522 (19, M$^+$), 477 (1.0, [M−Et]$^+$), 465 (4.1, [M−*t*-Bu]$^+$), 422 (5.4, [M−*t*BuCONH]$^+$), 419 (4.8, [M−EtOH−*t*-Bu]$^+$), 253 (31, M−TBDPSOCH$_2$)$^+$), 57 (100, *t*-Bu$^+$). EI-HIMS: calcd for C30H42N2O4Si: (M+): *m*/*z*=522.2915; Found: *m*/*z*=522.2928.

3.14.2. Preparation of 20b. The same treatments of **17** (500 mg, 1.07 mmol) as described in Section 3.14.1 gave **20b** (470 mg, 84%) as an oil after silica gel column chromatography. The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**20b**.

3.14.3. Preparation of *ent*-20c. Similar treatments of **17** (135 mg, 288 μmol) to those described in Section 3.14.1 gave **20c** (151 mg, 84%) as an oil after silica gel column chromatography. IR (film) 3350, 2950, 2920, 2850, 1720, 1665, 1590, 1475, 1385, 1240, 1110, 730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, a=0.80, b=0.20): δ 1.01 [9H×b, s, (CH_3)$_3$CSi (*Z*-isomer)], 1.07 [9H×a, s, (CH_3)$_3$CSi (*E*-isomer)], 1.24 [3H×a, t, *J*=7.1 Hz, CH_3CH_2O (*E*-isomer)], 1.27 [3H×b, t, *J*=7.1 Hz, CH_3CH_2-O(*Z*-isomer)], 1.68 (1H, m, C12H*H*), 2.12 [1H×b, m, C12H*H* (*Z*-isomer)], 2.25 [1H×a, dq, *J*=15.4, 7.7 2.02 Hz, C12H*H* (*E*-isomer)], 2.74 [2H×a, t, *J*=7.9 Hz, C13H_2 (*E*-isomer)], 3.16 [2H×b, m, C13H_2 (*Z*-isomer)], 3.55 [1H×b, dd, *J*=7.2, 10.0 Hz, C11CH*H*O (*Z*-isomer)], 3.59 [1H×a, dd, *J*=6.9, 10.3 Hz, C11CH*H*O (*E*-isomer)], 3.64 [1H×a, dd, *J*=4.6, 10.3 Hz, C11CH*H*O (*E*-isomer)], 3.65 [1H×b, m, C11CH*H*O (*Z*-isomer)], 3.98 [1H×b, m, C11*H* (*Z*-isomer)], 4.04 [1H×a, br quint, *J*=7.0 Hz, C11*H* (*E*-isomer)], 4.17 (2H, m, CH_3CH_2O), 6.13 [1H×b, br, N*H* (*Z*-isomer)], 6.92 [1H×a, br, N*H* (*E*-isomer)], 7.40 (10H, m, aromatic protons), 7.65 (1H, m, aromatic proton), 8.26 [1H×a, br, N*H* (*E*-isomer)]. EI-MS (rel. int. %): *m*/*z*=622 (1.3, M$^+$), 620 (1.0, M$^+$), 565 (0.30, [M−*t*-Bu]$^+$), 563 (0.40, [M−*t*-Bu]$^+$), 519 (0.6,

[M−EtOH−*t*-Bu]$^+$), 517 (0.6, [M−EtOH−*t*-Bu]$^+$), 380 (100).

3.15. Ethyl (*R*)-2-(*tert*-butoxycarbonylamino)-2-(5-hydroxymethylpyrrolidin-2-ylidene)acetate (21a), ethyl (*R*)-2-(*tert*-butylcarbonylamino)-2-(5-hydroxymethylpyrrolidin-2-ylidene)acetate (21b), their enantiomers (*ent*-21a and *ent*-21b), and ethyl (*S*)-2-(4-bromobenzoylamino)-2-(5-hydroxymethylpyrrolidin-2-ylidene)acetate (*ent*-21c)

3.15.1. Preparation of *ent*-21a. A solution of *ent*-**20** (243 mg, 452 μmol) and TBAF (1.0 M in THF, 550 μL) in THF (6.0 mL) was stirred at room temperature for 30 min. After the mixture was concentrated in vacuo, purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=80:20) gave *ent*-**21a** (133 mg, 96%) as an amorphous solid. The ^{1}H NMR spectrum of this sample showed that it consists of the two tautomers arising from its enamine moiety (*E*/*Z*=9:1). IR (film) 3360, 2970, 2930, 1720, 1700, 1660, 1590, 1490, 1360, 1250, 1070, 1050 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, a=0.90, b=0.10) δ 0.96 (3H×b, t, *J*=7.4 Hz, C*H*$_3$CH2O[*Z*-isomer]), 1.25 (3H×a, t, *J*=7.1 Hz, C*H*$_3$-CH2O[*E*-isomer]), 1.45 (9H, s, (C*H*$_3$)$_3$CO), 1.79 (1H, m, C12H*H*), 2.08 (1H×a, dddd, *J*=6.5, 7.8, 9.3, 12.9 Hz, C12H*H*[*E*-isomer]), 2.12 (1H×b, m, C12H*H*[*Z*-isomer]), 2.71 (1H×a, ddd, *J*=6.5, 9.7, 17.4 Hz, C13H*H*[*E*-isomer]), 2.79 (1H×a, ddd, *J*=6.0, 9.3, 17.4 Hz, C13H*H*[*E*-isomer]), 3.08 (2H×b, m, C13*H*$_2$[*Z*-isomer]), 3.47 (1H×b, dd, *J*=5.6, 13.6 Hz, C11CH*H*O[*Z*-isomer]), 3.52 (1H×a, dd, *J*=5.8, 11.3 Hz, C11CH*H*O[*E*-isomer]), 3.67 (1H×b, dd, *J*=3.4, 13.6 Hz, C11CH*H*O[*Z*-isomer]), 3.69 (1H×a, dd, *J*=3.8, 11.3 Hz, C11CH*H*O[*E*-isomer]), 3.99 (1H, m, C11*H*), 4.12 (2H, br q, *J*=7.1 Hz $CH_3C\mathit{H}_2O$), 5.15 (1H×b, br, N*H*[*Z*-isomer]), 5.40 (1H×a, br, N*H*[*E*-isomer]), 6.80 (1H×b, br, N*H*[*Z*-isomer]), 8.00 (1H×a, br, N*H*[*E*-isomer]). EI-MS (rel. int. %) *m*/*z*=300 (5.0, M$^+$), 244 (4.3, [M−isobutene]$^+$), 227 (4.6, [M−*t*BuO]$^+$), 213 (3.1, [M−$HOCH_2$]$^+$), 57 (100, *t*-Bu$^+$).

3.15.2. Preparation of 21a. Treatments of **20a** (179 mg, 332 μmol) in the same manner as described in Section 3.15.1 gave **21a** (66.0 mg, 66%) as an oil after silica gel column chromatography. The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**21a**.

3.15.3. Preparation of *ent*-21b. Similar treatments of *ent*-**21b** (460 mg, 151 μmol) to those described in Section 3.15.1 gave *ent*-**22b** (239 mg, 95%) as a mixture of the two tautomers (*E*/*Z*=80:20), after silica gel column chromatography (CH_2Cl_2/acetone=65:35). IR (film): 3300, 2950, 1650, 1590, 1500, 1360, 1290, 1240, 1050 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, a=0.80, b=0.20) δ 0.96 [3H×b, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*Z*-isomer)], 1.23 [3H×a, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.24 (9H×a, s, (C*H*$_3$)$_3$CO[*E*-isomer]), 1.28 [9H×b, s, C(*H*$_3$)$_3$CO (*Z*-isomer)], 1.79 [1H×a, dddd, *J*=6.1, 6.4, 9.4, 12.5 Hz, C12H*H* (*E*-isomer)], 1.85 [1H×b, m, C12H*H* (*Z*-isomer)], 2.04 [1H×a, dddd, *J*=6.6, 8.0, 9.5, 12.5 Hz, C12H*H* (*E*-isomer)], 2.11 [1H×b, m, C12H*H* (*Z*-isomer)], 2.62 [1H×a, ddd, *J*=6.2, 9.4, 17.3 Hz, C13H*H* (*E*-isomer)], 2.68 [1H×a, ddd, *J*=6.6, 9.4, 17.3 Hz, C13H*H* (*E*-isomer)], 3.09 [1H×b, ddd, *J*=5.3, 9.5, 18.2 Hz, C13H*H* (*Z*-isomer)], 3.12 [1H×b, dt, *J*=18.2, 7.7 Hz, C13H*H* (*Z*-isomer)], 3.48 [1H×b, dd, *J*=5.9, 11.6 Hz, C11CH*H*O (*Z*-isomer)], 3.52 [1H×a, dd, *J*=5.8, 11.3 Hz, C11CH*H*O (*E*-isomer)], 3.68 [1H×b, dd, *J*=3.5, 11.6 Hz, C11CH*H*O (*Z*-isomer)], 3.70 [1H×a, dd, *J*=3.7, 11.3 Hz, C11CH*H*O[*E*-isomer]], 3.83 [1H×b, m, C11*H* (*Z*-isomer)], 3.98 [1H×a, m, C11*H* (*E*-isomer)], 4.10 [2H×a, br q, *J*=7.1 Hz $CH_3C\mathit{H}_2O$ (*E*-isomer)], 4.13 [2H×b, br q, *J*=7.1 Hz $CH_3C\mathit{H}_2O$ (*Z*-isomer)], 5.43 [1H×b, br, N*H* (*Z*-isomer)], 6.47 (1H×a, br, N*H* (*E*-isomer)), 7.16 [1H×b, br, N*H* (*Z*-isomer)], 8.05 [1H×a, br, N*H* (*E*-isomer)]. EI-MS (rel. int. %): *m*/*z*=284 (22, M$^+$), 253 (17, [M−$HOCH_2$]$^+$), 227 (13, [M−EtOH−$HOCH_2$]$^+$), 199 (67, M−*t*BuCO)$^+$), 57 (100, *t*-Bu$^+$). EI-HIMS: calcd for $C_{14}H_{24}N_2O_4$ (M$^+$): *m*/*z*=284.1737; Found: *m*/*z*=284.1736.

3.15.4. Preparation of 21b. The same treatments of **20b** (470 mg, 900 μmol) as described in Section 3.15.1 gave **21b** (191 mg, 74%) as an oil after silica gel column chromatography. The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**21b**.

3.15.5. Preparation of *ent*-21c. Similar treatments of *ent*-**20c** (141 mg, 227 μmol) to those described in Section 3.15.1 gave *ent*-**21c** (60.0 mg, 157 μmol) as a mixture of the two tautomers (*E*/*Z*=80:20), after silica gel column chromatography (CH_2Cl_2/acetone=65:35). ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, *a*=0.80, *b*=0.20): δ 0.94 [3H×b, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O(*Z*-isomer)], 1.23 [3H×a, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.81 [1H×a, ddt, *J*=9.3, 12.5, 6.5 Hz, C12H*H* (*E*-isomer)], 1.81 [1H×b, m, C12H*H*(*Z*-isomer)], 2.07 [1H×a, dddd, *J*=6.9, 7.9, 9.3, 12.5 Hz, C12H*H* (*E*-isomer)], 2.15 [1H×b, m, C12H*H*(*Z*-isomer)], 2.70 [1H×a, ddd, *J*=6.5, 9.3, 17.3 Hz, C13H*H* (*E*-isomer)], 2.79 [1H×a, ddd, *J*=6.6, 9.5, 17.3 Hz, C13H*H* (*E*-isomer)], 3.12 [1H×b, ddd, *J*=5.6, 9.7, 18.2 Hz, C13H*H* (*Z*-isomer)], 3.19 [1H×b, ddd, *J*=5.6, 7.8, 18.2 Hz, C13H*H* (*Z*-isomer)], 3.49 [1H×b, dd, *J*=5.9, 11.5 Hz, C11CH*H*O (*Z*-isomer)], 3.53 [1H×a, dd, *J*=6.0, 11.3 Hz, C11CH*H*O (*E*-isomer)], 3.72 [1H×b, dd, *J*=3.7, 11.5 Hz, C11CH*H*O (*Z*-isomer)], 3.73 [1H×a, dd, *J*=3.7, 11.3 Hz, C11CH*H*O (*E*-isomer)], 3.88 [1H×b, m, C11*H* (*Z*-isomer)], 4.02 [1H×a, m, C11*H* (*E*-isomer)], 4.13 [2H×a, br q, *J*=7.1 Hz, $CH_3C\mathit{H}_2O$ (*E*-isomer)], 4.16 [2H×b, q, *J*=7.1 Hz, $CH_3C\mathit{H}_2O$ (*Z*-isomer)], 5.75 [1H×b, br N*H* (*Z*-isomer)], 7.05 [1H×a, br N*H* (*E*-isomer)], 7.58 (2H, m, aromatic protons), 7.68 (2H, m, aromatic protons), 8.19 [1H×a, br N*H* (*E*-isomer)].

3.16. Ethyl (*R*)-2-(*tert*-butoxycarbonylamino)-2-(5-methanesulfoxymethylpyrrolidin-2-ylidene)acetate (22a), ethyl (*R*)-2-(*tert*-butylcarbonylamino)-2-(5-methanesulfoxymethylpyrrolidin-2-ylidene)acetate (22b), their enantiomers (*ent*-22a and *ent*-22b), and ethyl (*S*)-2-(4-bromobenzoylamino)-2-(5-methanesulfoxymethylpyrrolidin-2-ylidene)acetate (*ent*-22c)

3.16.1. Preparation of *ent*-22a. A solution of *ent*-**21a** (37.0 mg, 123 μmol), MsCl, (14.8 mg, 129 μmol), and Et_3N (29.0 mg, 285 μmol) in CH_2Cl_2 (1.0 mL) was stirred at −78°C for 30 min, then MeOH (100 μL) was added to the mixture. The mixture was poured into H_2O 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/AcOEt=90:10) gave *ent*-**22a** (42.6 mg, 92%) as a solid. Analytical sample was prepared by recrystallization from isopropyl ether to give needles. Mp: 122–124°C. $[\alpha]_D^{20}=-29.6°$ (*c* 1.27, $CHCl_3$). IR (nujor): 3350, 1695, 1660, 1580, 1500, 1460, 1370, 1250, 1160, 960, 825 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*) δ 1.26 (3H, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 1.46 (9H, s, (C*H*$_3$)$_3$C), 1.78 (1H, dddd, *J*=6.0, 6.7, 9.0, 13.1 Hz, C12H*H*), 2.17 (1H, dddd, *J*=7.0, 7.4, 9.1, 13.1 Hz, C12H*H*), 2.79 (2H, m, C13*H*$_2$), 3.06 (3H, s, C*H*$_3$SO$_3$), 4.08 (1H, dd, *J*=6.8, 10.0 Hz, C11CH*H*O), 4.14 (2H, br q, *J*=7.1 Hz, CH$_3$C*H*$_2$O), 4.17 (1H, m, C11*H*), 4.27 (1H, dd, *J*=4.0, 10.0 Hz, C11CH*H*O), 5.37 (1H, br, N*H*), 8.05 (1H, br, N*H*). EI-MS (rel. int. %): *m*/*z*=378 (4.1, M^+), 322 (1.9, [M−isobutene]$^+$), 305 (3.8, [M−*t*-BuO]$^+$), 278 (66, [M−MsOH]$^+$), 57 (100, *t*-Bu$^+$). Anal. calcd for $C_{15}H_{26}N_2O_7S$: C, 47.60%; H, 6.92%; N, 7.40%; S, 8.47%. Found C, 47.53%; H, 6.73%; N, 7.25%; S, 8.68%.

3.16.2. Preparation of 22a. Treatments of **21a** (66.0 mg, 220 μmol) similarly to those described in Section 3.16.1 gave **22a** (68.0 mg, 82%) as a white solid after silica gel column chromatography. Analytical sample was prepared by recrystallization from isopropyl ether to give needles. Mp: 121–123°C. $[\alpha]_D^{20}=+29.7°$ (*c* 0.854, $CHCl_3$). The ^1H NMR spectrum of this sample was identical to that recorded for *ent*-**22a**.

3.16.3. Preparation of *ent*-22b. Similar treatments of *ent*-**21b** (38.0 mg, 134 μmol) to those in described in Section 3.16.1 gave *ent*-**22b** (44.1 mg, 91%) as a mixture of the two tautomers (*E*/*Z*=90:10) after silica gel column chromatography. Analytical sample was prepared by recrystallization from hexane–AcOEt to give needles. Mp: 93–95°C. IR (nujor): 3350, 3320, 2920, 1650, 1590, 1500, 1360, 1170. 950, 520 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *a*=0.90, *b*=0.10): δ 1.24 [3H×a, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.25 [9H×a, s, (C*H*$_3$)$_3$C (*E*-isomer)], 1.27 [3H×b, t. *J*=7.1 Hz, C*H*$_3$CH$_2$O (*Z*-isomer)], 1.28 [9H×b, s, (C*H*$_3$)$_3$C (*Z*-isomer)], 1.78 [1H×a, dddd, *J*=5.3, 6.4, 9.1, 13.1 Hz, C12H*H* (*E*-isomer)], 1.80 [1H×b, m, C12H*H* (*Z*-isomer)], 2.17 [1H×a, dddd, *J*=5.3, 6.4, 9.1, 13.1 Hz, C12H*H* (*E*-isomer)], 2.22 [1H×b, m, C12H*H* (*Z*-isomer)], 2.67 [1H×a, ddd, *J*=6.4, 9.2, 17.4 Hz, C13H*H* (*E*-isomer)], 2.73 [1H×a, ddd, *J*=7.1, 9.1, 17.4 Hz, C13H*H* (*E*-isomer)], 3.07 [3H×a, s, C*H*$_3$SO$_3$ (*E*-isomer)], 3.08 [3H×b, s, C*H*$_3$SO$_3$ (*E*-isomer)], 3.14 [2H×b, m, C13*H*$_2$ (*Z*-isomer)], 4.09 (1H, dd, *J*=5.3, 12.0 Hz, C11CH*H*O), 4.12 [2H×a, br q, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 4.16 [2H×b, br q, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*Z*-isomer)], 4.17 (1H, m, C11*H*), 4.23 [1H×b, dd, *J*=3.9, 12.0 Hz, C11H*H*O (*Z*-isomer)], 4.28 [1H×a, dd, *J*=3.9, 12.0 Hz, C11H*H*O [*E*-isomer]], 6.04 [1H×b, br, N*H* (*Z*-isomer)], 6.48 [1H×b, br, N*H* (*E*-isomer)], 7.19 [1H×b, br, N*H* (*Z*-isomer)], 8.08 [1H×b, br, N*H* (*E*-isomer)]. Anal. calcd for C, 49.71%; H, 7.23%; N, 7.73%; S, 8.85%. Found: C, 49.61%; H, 7.00%; N, 7.68%; S, 8.86%.

3.16.4. Preparation of 22b. Treatments of **21b** (191 mg, 672 μmol) similarly to those described in Section 3.16.1 gave **22b** (208 mg, 86%) as a white solid after silica gel column chromatography. Analytical sample was prepared by recrystallization from isopropyl ether to give needles. Mp: 121–123°C. $[\alpha]_D^{20}=+29.7°$ (*c* 0.854, $CHCl_3$). The ^1H NMR spectrum of this sample was identical to that recorded for *ent*-**22a**.

3.16.5. Preparation of *ent*-22c. Similar treatments of *ent*-**21c** (91.0 mg, 237 μmol) to those in described in Section 3.16.1 gave *ent*-**22c** (71.4 mg, 65%) as a mixture of the two tautomers (*E*/*Z*=90:10) and recovered *ent*-**21c** (9.0 mg, 10%) after silica gel column chromatography. Analytical sample was prepared by recrystallization from hexane–AcOEt to give needles. Mp: 172–173°C. $[\alpha]_D^{20}=-12.4°$ (*c* 1.16, $CHCl_3$). IR (nujor): 3350, 3300, 1660, 1640, 1580, 1520, 1460, 1370, 1340 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, *a*=0.80, *b*=0.20): δ 1.24 [3H×a, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.29 [3H×b, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O(*Z*-isomer)], 1.81 [1H×a, dddd, *J*=5.4, 6.6, 9.0, 13.2 Hz, C12H*H* (*E*-isomer)], 1.86 [1H×b, m, C12H*H*(*Z*-isomer)], 2.20 [1H×a, dddd, *J*=6.9, 7.9, 9.0, 13.2 Hz, C12H*H* (*E*-isomer)], 2.26 [1H×b, m, C12H*H*(*Z*-isomer)], 2.77 [1H×a, ddd, *J*=6.5, 9.0, 17.4 Hz, C13H*H* (*E*-isomer)], 2.83 [1H×a, ddd, *J*=6.6, 8.8, 17.4 Hz, C13H*H* (*E*-isomer)],3.08 [3H×b, m, C*H*$_3$SO$_3$(*Z*-isomer)], 3.09 [3H×a, m, C*H*$_3$SO$_3$(*E*-isomer)], 3.21 [2H×b, br t, *J*=7.2 Hz, C13*H*$_2$ (*Z*-isomer)], 4.11 (1H, dd, *J*=6.6, 10.2 Hz, C11CH*H*), 4.16 [2H×a, br q, *J*=7.1 Hz, CH$_3$C*H*$_2$O (*E*-isomer)], 4.18 [2H×b, q, *J*=7.1 Hz, CH$_3$C*H*$_2$O (*Z*-isomer)], 4.22 (1H, m, C11*H*), 4.31 (1H, dd, *J*=3.8, 10.2 Hz, C11CH*H*O), 6.61 [1H×b, br N*H* (*Z*-isomer)], 6.95 [1H×a, br N*H* (*E*-isomer)], 7.59, 7.69 (each 2H, m, aromatic protons), 8.23 [1H×a, br N*H* (*E*-isomer)]. Anal. calcd for $C_{17}H_{21}N_2BrO_6S$: C, 44.26%; H, 4.59%; N, 6.07%; S, 6.95%; Br, 17.32%, Found: C, 44.20%; H, 4.64%; N, 5.95%; S, 6.96%; Br, 17.31%.

3.17. Ethyl 2-[(*R*)-1-azabicyclo[3.1.0]hex-2-ylidene]-2-(*tert*-butoxycarbonylamino)acetate (4a), ethyl 2-[(*R*)-1-azabicyclo[3.1.0]hex-2-ylidene]-2-(*tert*-butoxycarbonyl)-acetate (4b), their enantiomers (*ent*-4a and *ent*-4b), and ethyl 2-[(*R*)-1-azabicyclo[3.1.0]hex-2-ylidene]-2-(4-bromobenzoylamino)acetate

3.17.1. Preparation of *ent*-4a. A solution of *ent*-**22a** (40.0 mg, 105 μmol) in THF (1.0 mL) was added to a suspension of KH (freshly washed with hexane, 4.3 mg, 105 μmol) in THF (3.0 mL) at room temperature. After stirring for 15 min, the mixture was poured into H_2O and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, then concentrated in vacuo to give crude *ent*-**4a** (18 mg). The ^1H NMR spectrum of this sample showed that it is in an almost pure state. Purification of crude *ent*-**4a** by silica gel column chromatography (Merck 7754, Et_2O/AcOEt=95:5) gave pure *ent*-**4a** (8.90 mg, 32%) as a white solid. Analytical sample was prepared by recrystallization from isopropyl ether to give needles. Mp: 134–137°C. $[\alpha]_D^{20}=+48.8°$ (*c* 0.250, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.29 (3H, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 1.47 (9H, s, (C*H*$_3$)$_3$C), 1.68 (1H, d, *J*=4.2 Hz, C10*H*$_\alpha$), 2.18 (2H, m, C12*H*$_2$), 2.37 (1H, d, *J*=5.2 Hz, C10*H*$_\beta$), 2.60 (1H, 1H, dt, *J*=19.2, 9.3 Hz, C13*H*$_\alpha$), 2.83 (1H, m, C11*H*), 3.13 (1H, ddd, *J*=3.5, 9.8, 19.2 Hz, C13*H*$_\beta$), 4.21 (2H, dq, *J*=1.0 and 7.1 Hz, CH$_3$C*H*$_2$O), 6.21 (1H, br, NH). EI-MS (rel. int. %):

m/*z*=282 (1.4, M^+), 226 (i.6, [M−isobutene]$^+$), 209 (2.3, [M−*t*-BuO]$^+$), 57 (100, *t*-Bu$^+$). EI-HIMS: calcd for $C_{14}H_{22}N_2O_4$ (M^+): *m*/*z*=282.1584; Found *m*/*z*=282.1581 Anal. calcd for. $C_{14}H_{22}N_2O_4$: C, 59.57%; H, 7.85%; N, 9.92%. Found: C, 59.48%; H, 8.38%; N, 9.87%.

3.17.2. Preparation of 4a. Treatments of **22a** (28.5 mg, 75.3 μmol) in the same manner as described in Section 3.17.1 gave **4a** (8.9 mg, 41%) as a white solid after silica gel column chromatography (Merck 7754). The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**4a**.

3.17.3. Preparation of *ent*-4b. Similar treatments of *ent*-**22b** (31.0 mg, 85.6 mmol) to those described in Section 3.17.1 gave **4b** (12.3 mg, 54%) as a colorless oil after silica gel column chromatography (Merck 7754). $[\alpha]_D^{20}$=+122° (*c* 1.50, $CHCl_3$). IR (film): 3290, 1710, 1670, 1490, 1385, 1120, 1035 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.27 (3H, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 1.28 (9H, s, (C*H*$_3$)$_3$C), 1.69 (1H, dd, *J*=0.8, 4.4 Hz, C10H$_\alpha$), 2.17 (2H, m, C12*H*$_2$), 2.34 (1H, d, *J*=5.2 Hz, C10*H*$_\beta$), 2.64 (1H, 1H, ddt, *J*=0.8, 19.0, 9.3 Hz, C13*H*$_\alpha$), 2.81 (1H, m, C11*H*), 3.08 (1H, ddd, *J*=3.4, 10.2, 19.0 Hz, C13*H*$_\beta$), 4.18 and 4.20 (each 1H, dq, *J*=10.3, 7.1 Hz, CH$_3$C*H*$_2$O), 7.29 (1H, br, NH). EI-MS (rel. int. %): *m*/*z*=266 (1.7, M^+), 210 (7.6, [M−isobutene]$^+$), 209 (8.6, [M−*t*-Bu]$^+$), 57 (100, *t*-Bu$^+$). EI-HIMS: calcd for $C_{14}H_{22}N_2O_3$ (M^+): *m*/*z*=266.1632; Found: *m*/*z*=266.1615.

3.17.4. Preparation of 4b. Treatments of **22a** (64.0 mg, 176 μmol) in the same manner as described in Section 3.17.1 gave **4a** (26 mg, 56%) after silica gel column chromatography (Merck 7754). $[\alpha]_D^{20}$=−127° (*c* 1.63, $CHCl_3$). The ^{1}H NMR spectrum of this sample was identical to that recorded for *ent*-**4a**.

3.17.5. Preparation of *ent*-4c. Similar treatments of *ent*-**22c** (47 mg, 102 mmol) to those described in Section 3.17.1 gave **4b** (15.0 mg, 40%) as a colorless oil after silica gel column chromatography (Merck 7754). IR (film): 3300, 1710, 1660, 1590, 1510, 1480, 1380, 1315, 1290, 1260, 1190 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.28 (3H, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 1.76 (1H, dd, *J*=0.8, 4.4 Hz, C10*H*$_\alpha$), 2.22 (2H, m, C12*H*$_2$), 2.38 (1H, d, *J*=5.3 Hz, C10*H*$_\beta$), 2.70 (1H, 1H, dt, *J*=19.0, 9.4 Hz, C13*H*$_\alpha$), 2.85 (1H, m, C11*H*), 3.17 (1H, ddd, *J*=2.0, 10.2, 19.0 Hz, C13*H*$_\beta$), 4.23 (2H, q, *J*=7.1 Hz, CH$_3$C*H*$_2$O), 7.60, 7.77 (each 2H, m, aromatic protons). EI-MS (rel. int. %): *m*/*z*=366 (8.0, M^+), 364 (8.3, M^+), 324 (10, [M−ethylene−methylene]$^+$), 322 (11, [M−ethylene−methylene]$^+$), 185 (98, BrArCO$^+$), 183 (100, BrArCO$^+$). EI-HIMS: calcd for $C_{16}H_{17}N_2O_3{}^{79}Br$ (M^+): *m*/*z*=364.0423; Found: *m*/*z*=364.0405.

3.18. (2*S*,3*S*)-3,4-Epoxy-2-(3-methoxy-5-methyl-naphthoyl)butyric acid (23)[33,47]

The butyric acid derivative **23** was synthesized according to the procedure independently reported by Shibuya[33] and Hirama[47] with some modifications.

3.18.1. 3-Methoxy-5-methyl-1-naphthoic acid. 3-Methoxy-5-methyl-1-naphthoic acid was prepared from 2-bromotoluene according to the procedure reported by Shibuya.[33] Analytical sample was prepared by recrystallization from AcOEt. Mp. 186–187°C (lit.[33] 179–180°C), IR (KBr): 2950, 1670, 1610, 1590, 1440, 1410, 1280, 1240, 1210, 1040, 840, 800 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (3H, s, C5C*H*$_3$), 3.99 (3H, s, C3OC*H*$_3$), 7.35–7.42 (2H, m, C6*H*, C7*H*), 7.54 (1H, br d, *J*=2.6 Hz, C4*H*), 8.04 (1H, d, *J*=2.6 Hz, C2*H*), 8.80 (1H, m, C8*H*). Anal. calcd for $C_{13}H_{12}O_3$: C, 72.21%; H, 5.59%, Found: C, 72.02%; H, 5.55%.

3.18.2. Allyl 4-methoxyphenylmethyl ether.[47] Allyl bromide (180 g, 1.5 mmol) was added to a suspension of 4-methylbenzylalcohol (69.8 g, 505 mmol) and powdered NaOH (40.0 g, 2.5 mmol) was added over 30 min with stirring at room temperature. The mixture was heated at 70°C with stirring for further 12 h. After cooling to room temperature, the mixture was diluted with H_2O (1.0 L) and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, then concentrated in vacuo with keeping the bath temperature below 25°C. Distillation of the residue gave allyl 4-methoxyphenyl methyl ether (88.3 g, 98%) as a colorless oil. bp: 85–86°C (3.0 mm Hg). IR (film): 2850, 1610, 1510, 1245, 1080, 1035, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OC*H*$_3$), 4.05 (2H, dt, *J*=5.7, 1.4 Hz, C1*H*$_2$), 4.46 (2H, s, C1′*H*$_2$), 5.25 (1H, dq, *J*=10.4, 1.4 Hz, C3*H*), 5.30 (1H, dq, *J*=17.3, 1.4 Hz, C3*H*), 5.94 (1H, ddt, *J*=10.4, 17.3, 5.7 Hz, C2*H*), 6.90, 7.27 (each 2H, dt, *J*=8.7, 2.8 Hz, aromatic protons). EI-MS (rel. int. %): *m*/*z*=178 (14, M^+) 36 (39, [*p*-MeOPhCHO]$^+$), 121 (100, [*p*-MeOPhCH$_2$]$^+$). EI-HIMS: calcd for $C_{11}H_{14}O_2$ (M^+): *m*/*z*=178.0994; Found: *m*/*z*=178.0963.

3.18.3. Ethyl (*E*)-4-(4-methoxyphenyl)methoxy-2-methylbut-2-enoate.[47] Ozone gas (O_3/O_2) generated by an ozonizer was bubbled through a solution of allyl *p*-methoxyphenylmethyl ether (560 mg, 3.15 mmol) in MeOH (5.0 mL) at −78°C for 30 min. After TLC showed complete consumption of the starting material, O_2 gas was further bubbled for 10 min to remove the excess ozone. Methyl sulfide (587 mg, 9.45 mmol) was added to the mixture and the cooling bath was removed. The mixture was stirred at room temperature for 30 min, and then concentrated in vacuo with keeping the bath temperature below 25°C. The residue was dissolved in CH_2Cl_2 (10 mL), and (1-ethoxycarbonyl)ethylidenetriphenylphosphorane (2.28 g, 6.30 mmol) was added at 0°C. After stirring at room temperature for 10 h, the mixture was diluted with hexane (20 mL). The precipitates were removed by filtration, and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt) gave ethyl (*E*)-4-(4-methoxyphenyl)methoxy-2-methylbut-2-enoate (748 mg, 90%) as a colorless oil. IR (film): 2930, 2850, 1710, 1510, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.81 (3H, q, *J*=1.3 Hz, C2C*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 4.18 (2H, dq, *J*=6.0, 1.3 Hz, C4*H*$_2$), 4.19 (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.47 (2H, s, OC*H*$_2$Ar), 6.88 (1H,tq, *J*=6.0, 1.3 Hz, C3*H*), 6.89, 7.27 (each 2H, dt, *J*=8.7, 2.8 Hz, aromatic protons). EI-MS (rel. int. %): *m*/*z*=264 (0.25, M^+), 235 (0.35, [M−Et]$^+$), 121 (100, *p*-MeOPhCH$_2^+$). EI-HIMS: calcd for $C_{15}H_{20}O_4$ (M^+): *m*/*z*=264.1362; Found: *m*/*z*=264.1349.

3.18.4. (*E*)-4-(4-Methoxyphenyl)methoxy-2-methylbut-2-enol.[47] Diisobutylaluminum hydride (0.93 M in hexane, 87 ml, 80 mmol) was added to a solution of ethyl (*E*)-4-(4-methoxyphenyl)methoxy-2-methylbut-2-enoate (9.47 g, 35.9 mmol) in toluene (50 mL) at −78°C over 10 min. After stirring for 1 h at −60°C, AcOEt (100 mL), MeOH (100 mL), water (2.0 mL), and Celite® (5.0 g) were successively added to the reaction mixture. The resulting suspension was stirred at room temperature for 1 h. After filtration, the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=80:20) gave (*E*)-4-(4-methoxyphenyl)-methoxy-2-methylbut-2-enol (7.54 g, 95%) as a colorless oil. IR (film): 3400, 2850, 1610, 1510, 1250, 1070, 1030, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (3H, s, C2CH_3), 3.80 (3H, s, OCH_3), 4.03 (2H, br s,C1H_2), 4.05 (2H, dd, J=1.0, 6.0 Hz, C4H_2), 4.45 (2H, s, OCH_2Ar), 5.66 (1H, *t*-hex, J=6.6, 1.0 Hz, C3H), 6.89, 7.28 (each 2H, dt, J=8.7, 2.8 Hz, aromatic protons). EI-MS (rel. int. %): m/z=222 (4.2, M^+), 191 (3.4, [M−$HOCH_2$]$^+$), 121 (100, *p*-MeOPhCH_2^+). HI-HIMS: calcd for $C_{13}H_{18}O_3$ (M^+): m/z=222.1256; Found: m/z=222.1243.

3.18.5. (2*R*,3*R*)-2,3-Epoxy-4-(4-methylphenyl)methoxy-2-methylbutanol.[47] Titanium(VI) isopropoxide (770 mg, 3.29 mmol) was added to a suspension of diisopropyl D-tartarate (770 mg, 3.29 mmol) and finely powdered, activated molecular sieves 4 Å (2.5 g) in CH_2Cl_2 (50 mL) at −10°C and the mixture was stirred for 20 min. *tert*-Butyl hydroperoxide (3.0 M in CH_2Cl_2, 17 mL, 51 mmol) was added to the mixture at the same temperature and the stirring was continued for 20 min. After cooling to −23°C, a solution of (*E*)-4-(4-methoxyphenyl)methoxy-2-methylbut-2-enol (5.30 g, 23.4 mmol) in CH_2Cl_2 (15 mL) was added, and the mixture was further stirred at the same temperature for 2 h. Sodium hydroxide in brine (30% w/v, 7.0 mL) and Celite® (5.0 g) were added successively to the reaction mixture, and the cooling bath was removed. After stirring for 30 min, the mixture was filtered. The filtrate was washed successively with H_2O and brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=80:20) gave (2*R*,3*R*)-2,3-epoxy-4-(4-methylphenyl)methoxy-2-methylbutanol (5.50 g, 97%) as a colorless oil. $[\alpha]_D^{20}$=+10.8° (*c* 1.11, $CHCl_3$). IR (film): 3450, 3050, 1610, 1510, 1245, 1070, 1030, 815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (3H, s, C2′CH_3), 1.73 (1H, dd, J=4.6, 8.7 Hz, OH), 3.31 (1H, dd, J=4.4, 6.2 Hz, C3′H), 3.57 (1H, dd, J=6.2, 11.1 Hz, C3′CHH), 3.58 (1H, dd, J=8.7, 12.4 Hz, C1HH), 3.68 (1H, dd, J=4.6, 12.4 Hz, C1HH), 3.70 (1H, dd, J=4.4, 11.1 Hz, C3′CHH), 3.81 (3H, s, OCH_3), 4.77, 4.58 (each 1H, d, J=11.5 Hz, OCH_2Ar), 6.89, 7.28 (each 2H, dt, J=8.6, 2.0 Hz, aromatic protons). EI-MS (rel. int. %): m/z=238 (1.4, M^+), 121 (100, *p*-MeOPhCH_2^+). EI-HIMS: calcd for $C_{13}H_{18}O_4$ (M^+): m/z=238.1205; Found: m/z=238.1201. The optical purity of this sample was determined as (>95% ee) by measuring the ^1H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA esters.

3.18.6. (2*S*,3*R*)-4-(4-Methoxyphenyl)methoxy-2-methylbutan-1,2,3-triol.[47] A mixture of (2*R*,3*R*)-2,3-epoxy-4-(4-methylphenyl)methoxy-2-methylbutanol. (5.50 g, 23.1 mmol) and $HClO_4$ (700 μL) in a mixture of THF (70 mL) and H_2O (60 mL) was stirred vigorously at room temperature for 12 h. The mixture was neutralized by adding saturated aqueous $NaHCO_3$ solution, and concentrated in vacuo. The residue was diluted with AcOEt. The AcOEt solution was washed with brine, dried over $MgSO_4$, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (acetone/CH_2Cl_2=50:50) gave (2*S*,3*R*)-4-(4-methoxyphenyl)methoxy-2-methylbutan-1,2,3-triol (4.71 g, 79%) as a solid. Since partial racemization might occur in this step according to Hirama's report, recrystallization from AcOEt–hexane was performed to give a sample (4.35 g, 74%) with high optical purity (>96% ee, vide infra) as colorless prisms. Mp: 81.0–82.5°C. $[\alpha]_D^{20}$=+10.5° (*c* 1.07, $CHCl_3$). IR (nujor): 3350, 3050, 2900, 1610, 1510, 1460, 1240, 1100, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, s, C2CH_3), 2.54 (1H, dd, J=5.8, 6.8 Hz, C1OH), 2.79 (1H, d, J=5.4 Hz, C3OH), 3.06 (1H, s, C2OH), 3.44 (1H, dd, J=6.8, 11.4 Hz, C1HH), 3.57 (1H, dd, J=6.3, 9.7 Hz, C4HH), 3.66 (1H, dd, J=5.8, 11.4 Hz, C1HH), 3.67 (1H, dd, J=4.5, 9.7 Hz, C4HH), 3.76 (1H, ddd, J=4.5, 5.4, 6.3 Hz, C3H), 3.81 (3H, s, OCH_3), 4.49, 4.51 (each 1H, d, J=11.8 Hz, OCH_2Ar), 6.89, 7.25 (each 2H, dt, J=8.6, 2.0 Hz, aromatic protons). Anal. calcd for $C_{13}H_{20}O_5$: C, 60.75%; H, 7.84%. Found: C, 60.86%; H, 7.69%.

3.18.7. (2*S*,3*R*)-2,3-Dihydroxy-4-(4-methoxyphenyl)-methoxy-2-methylbutyl *p*-toluenesulfonate.[47] A solution of (2*S*,3*R*)-4-(4-methoxyphenyl)methoxy-2-methylbutan-1,2,3-triol (2.00 g, 7.81 mmol), *p*-TsCl (3.20 g, 17 mmol), and pyridine (2.65 g, 33.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. The mixture was poured into H_2O 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 (2*S*,3*R*)-2,3-dihydroxy-4-(4-methoxyphenyl)methoxy-2-methylbutyl *p*-toluenesulfonate (2.45 g, 77%) as a colorless oil. $[\alpha]_D^{20}$=−1.1° (*c* 1.12, $CHCl_3$). IR (film): 3450, 2920, 1610, 1510, 1360, 1250, 1100, 1080,820, 670, 560 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, C2CH_3), 2.45 (3H, s, ArCH_3), 2.69 (1H, br, OH), 2.97 (1H, br, OH), 3.57 (1H, dd, J=6.1, 9.8 Hz, C4HH), 3.65 (1H, dd, J=3.6, 9.8 Hz, C4H), 3.72 (1H, dd, J=3.6, 6.1 Hz, C3H), 3.81 (3H, s, OCH_3), 3.92, 4.01 (each 1H, d, J=9.9 Hz, C1H_2), 4.44 (2H, s, OCH_2Ar), 6.89, 7.25 (each 2H, dt, J=8.6, 2.0 Hz, aromatic protons of the MPM group), 7.35, 7.89 (each 2H, br d, J=8.5 Hz, aromatic protons of the *p*-Ts group). EI-MS (rel. int. %) m/z=410 (0.55, M^+), 229 (1.98, [M−MPMOCH_2CH (OH)]$^+$), 121 (100, [*p*-MeOPhCH_2]$^+$). EI-HIMS. calcd for $C_{20}H_{26}O_7S$ (M^+): m/z=410.1400; Found m/z=410.1416.

3.18.8. (2*R*,3*S*)-3,4-Epoxy-1-(4-methoxyphenyl)methoxy-3-methyl-2-butanol.[47] A suspension of (2*S*,3*R*)-2,3-dihydroxy-4-(4-methoxyphenyl)methoxy)-2-methylbutyl p-toluenesulfonate (2.44 g, 59.5 mmol) and K_2CO_3 (823 mg. 5.95 mmol) in MeOH (50 mL) was stirred at 0°C 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=55:45) gave (2*R*,3*S*)-3,4-epoxy-1-(4-

methoxyphenyl)methoxy-3-methylbutan-2-ol (1.37 g, 96%) as a colorless oil. The optical purity of this sample was determined as >96% ee by measuring the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA esters (vide supra). $[\alpha]_D^{20}=-2.3°$ (*c* 1.23, $CHCl_3$). IR (film): 3450, 2950, 1610, 1510, 1250, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, s, C2′C*H*$_3$), 2.44 (1H, br d, *J*=1.5 Hz, O*H*), 2.62, 2.89 (each 1H, d, *J*=4.8 Hz, C3′*H*$_2$), 3.52 (1H, dd, *J*=6.5, 10.0 Hz, C2H*H*), 3.62 (1H, dd, *J*=3.5, 10.0 Hz, C2H*H*), 3.75 (1H, br ddd, *J*=1.5, 3.5, 6.5 Hz, C1*H*), 3.81 (3H, s, OC*H*$_3$), 4.49, 4.52 (each 1H, d, *J*=11.6 Hz,OC*H*$_2$Ar), 6.89, 7.25 (each 2H, dt, *J*=8.6, 2.0 Hz, aromatic protons). EI-MS (rel. int. %): *m*/*z*=238 (0.60, M^+), 220 (0.6, $[M-H_2O]^+$), 137 (29, $[p$-MeOPhCH_2O$]^+$), 121 (100, $[p$-MeOPhC$H_2]^+$). EI-HIMS: calcd for $C_{13}H_{18}O_4$ (M^+): *m*/*z*=238.1203; Found: *m*/*z*=238.1199.

3.18.9. (2*R*,3*S*)-3,4-Epoxy-1-(4-methoxyphenyl)methoxy-3-methylbutan-2-yl 3-methoxy-5-methyl-1-naphthoate.[47] A solution of (2*R*,*S*)-3,4-epoxy-1-(4-methoxyphenyl)methoxy-3-methylbutan-2-ol (781 mg, 3.28 mmol), 3-methoxy-5-methylnaphthoic acid (850 mg, 3.93 mmol), 4-(dimethylamino)pyridine (300 mg, 2.46 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.26 g, 6.6 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 4 h. The mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=85:15) gave (2*R*,3*S*)-3,4-epoxy-1-(4-methoxyphenyl)methoxy-3-methylbutan-2-yl 3-methoxy-5-methyl-1-naphthoate (1.30 g, 91%) as a colorless oil. $[\alpha]_D^{20}=-3.1°$ (*c* 1.11, $CHCl_3$). IR (film): 2950, 1720, 1620, 1510, 1240, 805, 750 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (3H, s, C2(C*H*$_3$), 2.65 (1H, d, *J*=4.9 Hz, C3H*H*), 2.68 (3H, s, C5C*H*$_3$), 3.01 (1H, d, *J*=4.9 Hz, C3H*H*), 3.78 (3H, s, OC*H*$_3$ of the MPM group), 3.81 (2H, d, *J*=5.2 Hz, C2′*H*$_2$), 3.96 (3H, s, C3OC*H*$_3$), 4.51, 4.56 (each 1H, d, *J*=11.7 Hz, OC*H*$_2$Ar), 5.23 (1H, t, *J*=5.2 Hz, C1′*H*), 6.84, 7.26 (each 2H, dt, *J*=8.6, 2.0 Hz, aromatic protons *of the MPM group*), 7.33 (2H, m, C6*H*, C7*H*), 7.45 (1H, d, *J*=2.7 Hz, C4*H*), 7.79 (1H, d, *J*=2.7 Hz, C2*H*), 8.60 (1H, m, C8*H*). EI-MS (rel. int. %): *m*/*z*=436 (8.8, M^+), 300 (2.8, $[M-p$-MeOPhCH_2O+H$]^+$), 285 (6.1, $[M-[p$-MeOPhCH_2-OC$H_2]^+$], 237 (4.5, $[M-$ArCO$]^+$), 216 (55, ArCOOH^+), 199 (69, ArCO^+), 121 (100, p-MeOPhCH_2^+). EI-HIMS: calcd for $C_{26}H_{28}O_6$ (M^+): *m*/*z*=436.1886; Found: *m*/*z*=436.1862.

3.18.10. (2*R*,3*S*)-3,4-Epoxy-1-hydroxy-3-methylbutan-2-yl 3-methoxy-5-methyl-1-naphthoate.[47] A mixture of (2*R*,3*S*)-3,4-epoxy-1-(4-methoxyphenyl)methoxy-3-methylbutan-2-yl 3-methoxy-5-methyl-1-naphthoate (312 g, 710 μmol) and 2,3-dichloro-5,6-dichlorobenzoquinone (245 mg, 1.08 mmol) in a mixture of CH_2Cl_2 (5.0 mL) and H_2O (500 μL) was stirred at room temperature for 4 h. The mixture was diluted with AcOEt and washed successively with saturated aqueous $NaHCO_3$ solution and brine. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt=70:30) gave (2*R*,3*S*)-3,4-epoxy-1-hydroxy-3-methylbutan-2-yl 3-methoxy-5-methyl-1-naphthoate (209 mg, 93%) as a colorless oil. $[\alpha]_D^{20}=+3.7°$ (*c* 0.64, $CHCl_3$). IR (film): 3500, 2950, 1720, 1620, 1600, 1415, 1280, 1240, 1080, 1045, 810, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (3H, s, C2″C*H*$_3$), 2.10 (1H, br t, *J*=6.0 Hz, O*H*), 2.68 (3H, s, C5C*H*$_3$), 2.71, 3.02 (each 1H, d, *J*=4.7 Hz, C3″*H*$_2$), 3.98 (3H, s, C3OC*H*$_3$), 4.00 (1H, br dt, *J*=12.2, 6.0 Hz, C2′H*H*), 4.04 (1H, br ddd, *J*=3.8, 6.0, 12.2 Hz, C2′H*H*), 5.11 (1H, dd, *J*=3.8, 6.0 Hz, C1″*H*), 7.37 (2H, m, C6*H*, C7*H*), 7.47 (1H,d, *J*=2.6 Hz, C4*H*), 7.82 (1H, d, *J*=2.6 Hz, C2*H*), 8.60 (1H, m, C8*H*). EI-MS (rel. int. %) *m*/*z*=316 (64, M^+), 285 (1.8, $[M-HOCH_2]^+$), 216 (82, ArCO_2H$^+$), 199 (100, ArCO^+), 121 (100, p-MeOPhCH_2^+). EI-HIMS: calcd for $C_{18}H_{20}O_5$ (M^+): *m*/*z*=316.1311; Found: *m*/*z*=316.1311.

3.18.11. (2*S*,3*S*)-3,4-Epoxy-2-(3-methoxy-5-methylnaphthoyl-3-methylbutyric acid (23).[47] Trifluoroacetic anhydride (490 μL, 2.38 mmol) was added to a solution of DMSO (517 mg, 6.63 mmol) in CH_2Cl_2 (3.0 mL) at −50°C. After stirring for 10 min, (2*R*,3*S*)-3,4-epoxy-1-hydroxy-3-methylbutan-2-yl 3-methoxy-5-methyl-1-naphthoate (350 mg, 1.10 mmol) in CH_2Cl_2 (3.0 mL) was added at the same temperature. After stirring at −50°C for 20 min, Et_3N (390 mg, 386 μmol) was added to the reaction mixture, and stirring was further continued for 30 min. The mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give (2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methylnaphthoyl-3-methylbutanal, which was dissolved in *t*-BuOH (2.5 mL). After adding 2-methyl-2-butene (1.0 mL), a mixture of $NaClO_2$ (198 mg, 2.20 mmol) and $NaHPO_4$ (260 mg, 2.19 mmol) in H_2O (2.0 mL) was added to the *t*-BuOH solution at 15°C. After stirring for 30 min, the mixture was poured into a solution of $Na_2S_2O_3$ (400 mg, 2.53 mmol) and $NaHCO_3$ (168 mg, 2.0 mmol) in H_2O (20 mL). The aqueous mixture was washed with Et_2O, acidified (pH5) by adding a solution of H_3PO_4, then extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give almost pure **23** (330 mg, 91%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (3H, s, C2″C*H*$_3$), 2.68 (3H, s, C5C*H*$_3$), 2.77, 3.05 (each 1H, d, *J*=4.6 Hz, C3″*H*$_2$), 3.98 (3H, s, C3OC*H*$_3$), 5.25 (1H, s, C2′*H*), 7.37 (2H, m, C6*H*, C7*H*), 7.50 (1H, d, *J*=2.6 Hz, C4*H*), 7.93 (1H, d, *J*=2.6 Hz, C2*H*), 8.60 (1H, m, C8*H*). The ^{1}H NMR spectral data of this sample were in good accordance with the reported values.[25,31] This carboxylic acid was directly used for the next reaction without further purification.

3.19. Ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl)-3-methylbutyryl]amino-2-[(*R*)-5-(*tert*-butyldimethylsiloxy)methylpyrrolidin-2-ylidene]acetate (24)

A solution of DCC (195 mg, 947 μmol) and HOBT (162 mg, 1.2 mmol) in THF (5.0 mL) was stirred at 0°C for 15 min. To this solution, a solution of **19** in toluene was added through a pad of a mixture of Celite® and $MgSO_4$ at 0°C. The solution of **19** in toluene was freshly prepared by stirring a mixture of **17** (600 mg, 1.3 mmol) and 10% Pd/C (600 mg) in toluene (3.0 mL) for 12 h under H_2 atmosphere (5 atm) at room temperature. The mixture was stirred for additional 30 min, then filtered through a pad of Celite®.

The filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (benzene/AcOEt=70:30) gave **24** (380 mg, 51%) as an amorphous solid. IR (film): 3350, 2950, 2920, 1720, 1670, 1590, 1250, 1100, 700 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of a mixture of the two tautomers arising from its enamine moiety (*E*/*Z*=90:10). All the signals of the major isomer and some of the minor isomer are assigned. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, *a*=0.90, *b*=0.10): δ 1.02 [9H×a, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.04 [9H×b, s, $(CH_3)_3CSi$ (*Z*-isomer)], 1.16 [3H×b, t, *J*=7.1 Hz, CH_3CH_2O (*Z*-isomer)], 1.22 [3H×a, s, *J*=7.1 Hz, CH_3CH_2O (*E*-isomer)], 1.59 [3H×a, s, C20H_3 (*E*-isomer)], 1.65 [1H×a, m, C12H*H* (*E*-isomer)], 2.02 [1H×a, m, C12H*H* (*E*-isomer)], 2.09 [1H×b, m, C12H*H* (*Z*-isomer)], 2.65 [2H×a, m, C13H_2 (*E*-isomer)], 2.68 (3H, s, C5′CH_3), 2.73 [1H×b, d, *J*=4.6 Hz, C21H*H* (*Z*-isomer)], 2.77 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.07 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.11 [1H×b, d, *J*=4.6 Hz, C21H*H* (*Z*-isomer)], 3.53 [1H×a, dd, *J*=6.8, 10.2 Hz, C11C H*H* (*E*-isomer)], 3.56 [1H×a, dd, *J*=4.9, 10.2 Hz, C11C H*H* (*E*-isomer)], 3.98 (3H, s, C3′OCH_3), 4.11 (1H, m, C11*H*), 4.13 [2H×a, br q, *J*=7.1 Hz, CH_3CH_2O (*E*-isomer)], 5.32 [1H×a, s, C18*H* (*E*-isomer)], 5.42 [1H×b, s, C18*H* (*Z*-isomer)], 6.02 [1H×b, br s, N*H* (*Z*-isomer)], 6.93 [1H×a, br s, N*H* (*E*-isomer)], 7.37 (8H, m, six aromatic protons of the TBDPS group, C6′H, C7′H), 7.490 [1H×a, d, *J*=2.4 Hz, C4′*H* (*E*-isomer)], 7.495 [1H×a, C4′*H* (*Z*-isomer)], 7.62 (4H, m, four aromatic protons of the TBDPS group), 7.930 (1H×a, d, *J*=2.4 Hz, C2′*H*[*E*-isomer]), 7.935 [1H×b, C2′*H* (*Z*-isomer)], 8.19 [1H×a, br, N*H* (*E*-isomer)], 8.66 [1H×a, m, C8*H* (*E*-isomer)]. EI-MS (rel. int. %): *m*/*z*=750 (5.3, M^+), 693 (1.0, $[M-t\text{-Bu}]^+$), 693 (0.8, $[M-t\text{-Bu}-EtOH]^+$), 636 (2.0, $[M-t\text{-Bu}-EtOH]^+$), 534 (17, $[M-ArCO_2H]^+$), 216, (100, $ArCO_2H^+$), 199 (80, $ArCO^+$). EI-HIMS: calcd for $C_{43}H_{50}O_8Si$ (M^+): *m*/*z*=750.3338; Found: *m*/*z*=750.3318.

3.20. Ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl)naphthoyl-3-methylbutyryl]amino-2-[(*S*)-5-(*tert*-butyldimethylsiloxy)methylpyrrilidin-2-ylidene]acetate (*iso*-24)

Treatments of *ent*-**17** (300 mg, 909 μmol) similarly to those described in Section 3.19 gave *iso*-**24** (422 mg, 62%) after silica gel column chromatography. IR (film): 3350, 2950, 2920, 2850, 1720, 1660, 1590, 1290, 1250, 700 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of a mixture of the two tautomers arising from its enamine moiety (*E*/*Z*=90:10). All the signals of the major isomer and some of the minor isomer are assigned. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*. *a*=0.90, *b*=0.10): δ 1.05 [9H×a, s, $(CH_3)_3CSi$ (*E*-isomer)], 1.20 [3H×a, s, *J*=7.0 Hz, CH_3CH_2O (*E*-isomer)], 1.35 [3H×b, t, *J*=7.1 Hz, CH_3CH_2O (*Z*-isomer)], 1.59 [3H×a, s, C20H_3 (*E*-isomer)], 1.65 [1H×a, m, C12H*H* (*E*-isomer)], 2.00 [1H×a, m, C12H*H* (*E*-isomer)], 2.68 [2H×a, m, C12H_2 (*E*-isomer)], 2.68 (3H, s, C5′CH_3), 2.78 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.06 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.09 [1H×b, d, *J*=4.6 Hz, C21H*H* (*Z*-isomer)], 3.55 [1H×a, dd, *J*=6.8, 10.2 Hz, C11CH*H* (*E*-isomer)], 3.60 [1H×a, dd, *J*=4.9, 10.2 Hz, C11CH*H* (*E*-isomer)], 3.98 (3H, s, C3′OCH_3), 4.12 (3H, m, CH_3CH_2O and C11*H*), 5.28 [1H×a, s, C18*H* (*E*-isomer)], 6.00 [1H×b, br s, N*H* (*Z*-isomer)], 6.93 [1H×a, br s, N*H* (*E*-isomer)], 7.38 (8H, m, *six* aromatic protons of the TBDPS group, C6′*H*, C7′*H*), 7.49 [1H×a, d, *J*=2.6 Hz, C4′*H* (*E*-isomer)], 7.62 (4H, m, *four* aromatic protons of the TBDPS group), 7.930 [1H×a, d, *J*=2.6 Hz, C2′*H* (*E*-isomer)], 7.935 [1H×b, C2′*H* (*Z*-isomer)], 8.19 [1H×a, br, N*H* (*E*-isomer)], 8.66 (1H×a, m, C8′*H*). EI-MS (rel. int. %): *m*/*z*=750 (4.9, M^+), 693 (1.0, $[M-t\text{-Bu}]^+$), 693 (1.1, $[M-t\text{-Bu}-EtOH]^+$), 636 (5.9, $[M-t\text{-Bu}-EtOH]^+$), 534 (21, $[M-ArCO_2H]^+$), 216 (100, $ArCO_2H^+$), 199 (75, $ArCO^+$). EI-HIMS: calcd for $C_{43}H_{50}O_8Si$ (M^+): *m*/*z*=750.3338; Found: *m*/*z*=750.3352.

3.21. Ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl)-3-methylbutyryl]amino-2-[(*R*)-5-methanesulfoxymethylpyrrolidin-2-ylidene]acetate (25) and its (5*S*)-isomer (*iso*-25)

3.21.1. Cleaving the TBDPS group of 24. A solution of **24** (380 mg, 506 μmol) and TBAF (1.0 M in THF, 550 μL) in THF (5.0 mL) was stirred at room temperature for 30 min. After concentration in vacuo, purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone=70:30) gave ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl)-3-methylbutyryl]amino-2-[(*R*)-5-hydoxymethylpyrrolidin-2-ylidene]acetate (197 mg, 76%) as an amorphous solid. IR (film): 3350, 2870, 1720, 1660, 1590, 1380, 1280, 1230, 1080, 1040 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of a mixture of the two tautomers arising from its enamine moiety (*E*/*Z*=8:2). All the signals of the major isomer and some of the minor isomer are assigned. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, *a*=0.80, *b*=0.20): δ 1.20 [3H×a, s, *J*=7.1 Hz, CH_3CH_2O (*E*-isomer)], 1.23 [3H×b, t, *J*=7.1 Hz, CH_3CH_2O (*Z*-isomer)], 1.58 [3H×a, s, C20H_3 (*E*-isomer)], 1.61 [3H×b, s, C20H_3 (*Z*-isomer)], 1.75 [1H×a, m, C12H*H* (*E*-isomer)], 1.84 [1H×b, m, C12H*H* (*Z*-isomer)], 2.05 [1H×a, dq, *J*=12.9, 8.0 Hz, C12H*H* (*E*-isomer)], 2.13 [1H×b, m, C12H*H* (*Z*-isomer)], 2.69 (3H, s, C5′CH3), 2.70 [2H×a, m, C13H_2 (*E*-isomer)], 2.79 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 2.80 [1H×b, d, *J*=4.8 Hz, C21H*H* (*Z*-isomer)], 3.05 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.12 [1H×b, d, *J*=4.6 Hz, C21H*H* (*Z*-isomer)], 3.12 [2H×b, m, C13H_2 (*Z*-isomer)], 3.51 [1H×a, dd, *J*=6.0, 11.2 Hz, C11CH*H* (*E*-isomer)], 3.68 [1H×a, dd, *J*=3.8, 11.2 Hz, C11CH*H* (*E*-isomer)], 3.69 [1H×b, C11*H* (*Z*-isomer)], 3.99 (3H×a, s, C3′OCH_3 [*E*-isomer]), 4.00 (3H×b, s, C3′OCH_3 (*E*-isomer)), 4.00 [1H×a, m, C11*H* (*E*-isomer)], 4.11 (2H×a, br q, *J*=7.1 Hz, CH_3CH_2O (*E*-isomer)), 4.12 [2H×b, br q, *J*=7.1 Hz, CH_3CH_2O (*Z*-isomer)], 5.29 [1H×a, s, C18*H* (*E*-isomer)], 5.33 [1H×b, s, C18*H* (*Z*-isomer)], 5.65 [1H×b, br s, N*H* (*Z*-isomer)], 6.97 [1H×a, br s, N*H* (*E*-isomer)], 7.37 (2H, m, C6′*H*, C7′*H*), 7.49 [1H×a, d, *J*=2.6 Hz, C4′*H*(*E*-isomer)], 7.51 [1H×b, d, *J*=2.6 Hz, C4′*H* (*Z*-isomer)], 7.93 [1H×b, d, *J*=2.6 Hz, C2′*H* (*E*-isomer)], 7.95 [1H×a, d, *J*=2.6 Hz, C2′*H* (*Z*-isomer)], 8.14 [1H×0.9, br, N*H* (*E*-isomer)], 8.65 (1H×0.9, m, C8′*H*). EI-MS (rel. int. %): *m*/*z*=512 (6.8, M^+), 329 (13, $[M-ArCO_2]^+$), 216 (31, $[ArCO_2H]^+$), 199 (100, $ArCO^+$). EI-HIMS: calcd for $C_{27}H_{32}O_8N_2$ (M^+): *m*/*z*=512.2160; Found: *m*/*z*=512.2150.

3.21.2. Cleaving the TBDPS group of *iso*-25. The same treatments of *iso*-**25** (422 mg, 563 μmol) as described in

Section 3.21.1 gave ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl)-3-methylbutyryl]amino-2-[(*S*)-5-hydroxymethylpyrilidin-2-ylidene]acetate (195 mg, 68%) after silica gel column chromatography. IR (film): 3350, 2920, 1720, 1660, 1610, 1590, 1510, 1410, 1380, 1280, 1230, 1180, 1080, 1040, 700 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of a mixture of the two tautomers arising from its enamine moiety (*E*/*Z*=80:20). All the signals of the major isomer and some of the minor isomer are assigned. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, a=0.80, b=0.20): δ 1.17 [3H×b, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*Z*-isomer)], 1.20 [3H×a, s, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.58 (3H, s, C20*H*$_3$), 1.76 [1H×a, m, C12H*H* (*E*-isomer)], 1.89 [1H×b, m, C12H*H* (*Z*-isomer)], 2.05 [1H×a, dq, *J*=12.9, 8.0 Hz, C12H*H* (*E*-isomer)], 2.15 [1H×b, m, C12H*H* (*Z*-isomer)], 2.69 (3H, s, C5′C*H*$_3$), 2.70 [2H×a, m, C13*H*$_2$ (*E*-isomer)], 2.78 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 2.81 [1H×b, d, *J*=4.6 Hz, C21H*H* (*Z*-isomer)], 3.06 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.13 [2H×b, m, C13*H*$_2$ (*Z*-isomer)], 3.16 [1H×b, d, *J*=4.6 Hz, C21H*H* (*Z*-isomer)], 3.42 [1H×b, br, C11CH*H* (*Z*-isomer)], 3.53 [1H×a, dd, *J*=5.9, 11.3 Hz, C11CH*H* (*E*-isomer)], 3.59 [1H×b, br d, *J*=11 Hz, C11CH*H* (*Z*-isomer)], 3.70 [1H×a, dd, *J*=3.9, 11.2 Hz, C11CH*H* (*E*-isomer)], 3.86 [1H×b, m, C11*H* (*Z*-isomer)], 3.98 [1H×a, m, C11*H* (*E*-isomer)], 3.98 [3H×a, s, C3′OCH$_3$ (*E*-isomer)], 3.99 [3H×b, s, C3′OCH$_3$ (*Z*-isomer)], 4.10 [2H×a br q, *J*=7.1 Hz, CH$_3$C*H*$_2$O (*E*-isomer)], 4.11 [2H×b, br q, *J*=7.1 Hz, CH$_3$C*H*$_2$O (*Z*-isomer)], 5.29 [1H×a, s, C18*H* (*E*-isomer)], 5.32 [1H×b, s, C18*H* (*Z*-isomer)], 5.58 [1H×b, br s, N*H* (*Z*-isomer)], 6.96 [1H×a, br s, N*H* (*E*-isomer)], 7.37 [2H, m, C6′*H*, C7′*H*], 7.42 (1H×b, br, N*H* (*Z*-isomer)), 7.49 [1H×a, d, *J*=2.6 Hz, C4′*H* (*E*-isomer)], 7.51 [1H×b, d, *J*=2.6 Hz, C4′*H*(*Z*-isomer)], 7.93 (1H, d, *J*=2.6 Hz, C2′*H*), 8.13 [1H×a, br, N*H* (*E*-isomer)], 8.65 (1H, m, C8′*H*). EI-MS (rel. int. %) *m*/*z*=512 (11, M^+), 329 (15, [M−ArCO$_2$]$^+$), 216 (52, [ArCO$_2$H]$^+$), 199 (100, ArCO$^+$). EI-HIMS. calcd for $C_{27}H_{32}O_8N_2$ (M^+): *m*/*z*=512.2160; Found: *m*/*z*=512.2173.

3.21.3. Mesylation giving 25. A solution of ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl)-3-methylbutyryl]amino-2-[(*R*)-5-hydroxymethylpyrilidin-2-ylidene]acetate (197 mg, 384 μmol), MsCl (58.0 mg, 507 μmol), and Et_3N (100 mg, 990 μmol) in CH_2Cl_2 (3.0 mL) was stirred at 78°C 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 ($CHCl_3$/acetone=85:15) gave **26** (201 mg, 89%) as an amorphous solid. IR (film): 3350, 2970, 2920, 1720, 1665, 1595, 1505, 1415, 1300, 1240, 1170, 1090, 1040, 950, 730, 520 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of a mixture of the two tautomers arising from its enamine moiety (*E*/*Z*=85:15). All the signals of the major isomer and some of the minor isomer are assigned. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, a=0.85, b=0.15): δ 1.15 [3H×b, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*Z*-isomer)], 1.19 [3H×a, s, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.58 [3H×a, s, C20*H*$_3$ (*E*-isomer)], 1.59 [3H×b, s, C20*H*$_3$ (*Z*-isomer)], 1.76 [1H×a, ddt, *J*=5.1, 1.2, 7.5 Hz, C12H*H* (*E*-isomer)], 2.16 [1H×a, dq, *J*=13.2, 7.5 Hz, C12H*H* (*E*-isomer)], 2.22 [1H×b, m, C12H*H* (*Z*-isomer)], 2.69 (3H, s, C5′C*H*$_3$), 2.75 [2H×a, t, *J*=7.5 Hz, C13*H*$_2$ (*E*-isomer)], 2.80 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 2.81 [1H×b, not assignable, C21H*H* (*Z*-isomer)], 3.04 [3H×a, s, C*H*$_3$SO$_3$ (*E*-isomer)], 3.05 [3H×b, s, C*H*$_3$SO$_3$ (*Z*-isomer)], 3.05 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.14 [2H×b, m, C13*H*$_2$ (*Z*-isomer)], 3.99 [3H×a, s, C3′C*H*$_3$ (*E*-isomer)], 4.00 [3H×b, s, C3′C*H*$_3$ (*Z*-isomer)], 4.05 [1H×a, dd, *J*=6.7, 10.2 Hz, C11CH*H*O (*E*-isomer)], 4.11 (2H br q, *J*=7.1 Hz, CH$_3$C*H*$_2$O), 4.17 (1H, m, C11*H*), 4.26 [1H×a, dd, *J*=3.9, 10.2 Hz, C11CH*H*O (*E*-isomer)], 5.26 [1H×a, s, C18*H* (*E*-isomer)], 5.32 [1H×b, s, C18*H* (*Z*-isomer)], 5.97 [1H×b, br s, N*H* (*Z*-isomer)], 6.97 [1H×a, br s, N*H* (*E*-isomer)], 7.37 [2H, m, C6′*H*, C7′*H*], 7.50 [1H×a, d, *J*=2.6 Hz, C4′*H* (*E*-isomer)], 7.51 [1H×b, d, *J*=2.7 Hz, C4′*H* (*Z*-isomer)], 7.94 [1H×a, d, *J*=2.6 Hz, C2′*H* (*E*-isomer)], 7.96 [1H×b, d, *J*=2.7 Hz, C2′*H* (*Z*-isomer)], 8.15 [1H×0.7, br, N*H* (*E*-isomer)], 8.67 (1H, m, C8′*H*). EI-MS (rel. int. %): *m*/*z*=590 (9.9, M^+), 494 (10, [M−MsOH]$^+$), 216 (100, ArCO$_2$H$^+$), 199 (96, ArCO$^+$). EI-HIMS: calcd for $C_{28}H_{34}O_{10}N_2S$ (M^+): *m*/*z*=590.1935; Found: *m*/*z*=590.1913.

3.21.4. Mesylation giving *ent*-25. Treatments of ethyl 2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl)-3-methylbutyryl]amino-2-[(*S*)-5-hydroxymethylpyrilidin-2-ylidene]acetate (182 mg, 355 μmol) in the same manner as described in Section 3.21.3 gave *iso*-**26** (192 mg, 92%) after silica gel column chromatography. IR (film): 3280, 2880, 1720, 1670, 1600, 1510, 1410, 1350, 1280, 1230, 1170, 1090, 1040, 950 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of a mixture of the two tautomers arising from its enamine moiety (*E*/*Z*=85:15). All the signals of the major isomer and some of the minor isomer are assigned. ^1H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*, *a*=0.85, *b*=0.15): δ 1.15 [3H×b, t, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*Z*-isomer)], 1.19 [3H×a, s, *J*=7.1 Hz, C*H*$_3$CH$_2$O (*E*-isomer)], 1.58 [3H×a, s, C20*H*$_3$ (*E*-isomer)], 1.59 [3H×b, s, C20*H*$_3$ (*Z*-isomer)], 1.76 [1H×a, ddt, *J*=5.1, 1.2, 7.5 Hz, C12H*H* (*E*-isomer)], 2.16 [1H×a, dq, *J*=13.2, 7.5 Hz, C12H*H* (*E*-isomer)], 2.22 [1H×b, m, C12H*H* (*Z*-isomer)], 2.69 (3H, s, C5′C*H*$_3$), 2.75 [2H×a, t, *J*=7.5 Hz, C13*H*$_2$ (*E*-isomer)], 2.80 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 2.81 [1H×b, C21H*H* (*Z*-isomer)], 3.04 (3H×a, s, C*H*$_3$SO$_3$ (*E*-isomer)), 3.05 [3H, b, s, C*H*$_3$SO$_3$ (*Z*-isomer)], 3.05 [1H×a, d, *J*=4.6 Hz, C21H*H* (*E*-isomer)], 3.14 [2H×b, m, C13*H*$_2$ (*Z*-isomer)], 3.99 [3H×a, s, C3′OC*H*$_3$ (*E*-isomer)], 4.00 [3H×b, s, C3′OC*H*$_3$ (*Z*-isomer)], 4.05 [1H×a, dd, *J*=6.7, 10.2 Hz, C11CH*H*O (*E*-isomer)], 4.11 (2H br q, *J*=7.1 Hz, CH$_3$C*H*$_2$O), 4.17 (1H, m, C11*H*), 4.26 [1H×a, dd, *J*=3.9, 10.2 Hz, C11CH*H*O (*E*-isomer)], 5.26 [1H×a, s, C18*H* (*E*-isomer)], 5.32 [1H×b, s, C18*H* (*Z*-isomer)], 5.97 [1H×b, br s, N*H* (*Z*-isomer)], 6.97 [1H×a, br s, N*H* (*E*-isomer)], 7.37 (2H, m, C6′*H*, C7′*H*), 7.50 [1H×a, d, *J*=2.6 Hz, C4′*H* (*E*-isomer)], 7.51 [1H×b, d, *J*=2.7 Hz, C4′*H*(*Z*-isomer)], 7.94 [1H×a, d, *J*=2.6 Hz, C2′*H* (*E*-isomer)], 7.96 [1H×b, d, *J*=2.7 Hz, C2′*H* (*Z*-isomer)], 8.15 [1H×0.7, br, N*H* (*E*-isomer)], 8.67 (1H, m, C8′*H*). EI-MS (rel. int. %): *m*/*z*=590 (1.1, M^+), 494 (1.1, [M−MsOH]$^+$), 216 (52, ArCO$_2$H$^+$), 199 (100, ArCO$^+$). EI-HIMS: calcd for $C_{28}H_{34}O_{10}N_2S$ (M^+): *m*/*z*=590.1935; Found: *m*/*z*=590.1936.

3.22. Ethyl 2-[(*R*)-1-azabicyclo[3.1.0]hex-2-ylidene]-2-[(2*S*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyl-butyryl]aminoacetate (4d) and its (5*S*)-isomer (*iso*-4d)

3.22.1. Preparation of 4d. Potassium trimethylsilylamide (0.5 M in toluene, 60 μL) was added to a solution of **24** (14.0 mg, 29 μmol) in THF (1.0 mL) at room temperature. After stirring for 10 min, the mixture was poured into H_2O and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, then concentrated in vacuo. Purification of the residue by silica gel column chromatography (Merck 107754, CH_2Cl_2/acetone=90:10) gave almost pure **4a** (4.3 mg, 40%, ca. 90% pure by its ^{1}H NMR) along with **27** (0.4 mg, 6%). IR (film): 3350, 2920, 1700, 1620, 1690, 1270, 1230, 1210, 1180, 1080 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*): δ 1.28 (3H, s, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 1.60 (3H, s, C20*H*$_3$), 1.69 (1H, dd, *J*=0.6, 4.3 Hz, C10*H*), 2.19 (2H. m. C12*H*$_2$), 2.37 (1H, br d, *J*=5.0 Hz, C10*H*), 2.68 (3H, s, C5′CH$_3$), 2.76 (1H, d, *J*=4.7 Hz, C21H*H*), 2.70–2.85 (2H, m, C11*H*, C13H*H*), 3.10 (1H, d, *J*=4.7 Hz, C21H*H*), 3.16 (1H, ddd, *J*=3.7, 9.4, 19.4 Hz, C13H*H*), 3.97 (3H, s, C3′OC*H*$_3$), 4.20, 4.27 (each 1H, dq, *J*=7.1, 10.8 Hz, CH$_3$*H*$_2$O), 5.44 (1H, s, C18*H*), 7.37 (2H, m, C6′*H*, C7′*H*), 7.48 (1H, d, *J*=2.6 Hz, C4′*H*), 7.77 (1H, br, N*H*), 7.94 (1H, d, *J*=2.6 Hz, C2′*H*), 8.63 (1H, m, C8′*H*). EI-MS (rel. int. %): *m*/*z*=494 (1.1, M$^+$), 313 (2.7, Me(CH$_2$O)CCH(O$_2$CAr)CO$^+$), 216 (15, ArCO$_2$H$^+$), 209 (19, [M−Me(CH$_2$O)CCH(O$_2$CAr)]$^+$), 199 (100, ArCO$^+$).

3.22.2. Preparation of *iso*-4d. Treatments of *iso*-**26** (19.4 mg, 32.9 μmol) in a similar manner to that described in Section 3.22.1 gave almost pure *iso*-**4d** (4.70 mg, 29%, ca. 90% pure by its ^{1}H NMR) along with **27** (0.3 mg, 3%) after silica gel column chromatography. IR (film): 3350, 2920, 1700, 1620, 1690, 1270, 1230, 1210, 1180, 1080 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *carzinophilin numbering*) δ 1.23 (3H, s, *J*=7.1 Hz, C*H*$_3$CH$_2$O), 1.60 (3H, s, C20*H*$_3$), 1.70 (1H, br d, *J*=3.6 Hz, C10H*H*), 2.19 (2H. m. C12*H*$_2$), 2.37 (1H, br d, *J*=5.1 Hz, C10H*H*), 2.68 (3H, s, C5′C*H*$_3$), 2.73 (1H, m, C13*H*), 2.79 (1H, d, *J*=4.6 Hz, C21H*H*), 2.85 (1H, m, C11*H*), 3.09 (1H, d, *J*=4.6 Hz, C21H*H*), 3.21 (1H, ddd, *J*=4.8, 9.6, 19.4 Hz, C13H*H*), 3.98 (3H, s, C3′OC*H*$_3$), 4.20 (2H, m, CH$_3$C*H*$_2$O), 5.36 (1H, s, C18*H*), 7.37 (2H, m, C6′*H*, C7′*H*), 7.49 (1H, d, *J*=2.6 Hz, C4′*H*), 7.68 (1H, br, N*H*), 7.95 (1H, d, *J*=2.6 Hz, C4′*H*), 8.63 (1H, m, C8′*H*). EI-MS (rel. int. %) *m*/*z*=94 (5.7, M$^+$), 313 (2.2, Me(CH$_2$O)CCH(O$_2$CAr)CO$^+$), 216 (26, ArCO$_2$H$^+$), 209 (8.8, [M−Me(CH$_2$O)CCH(O$_2$CAr)]$^+$), 199 (100, ArCO$^+$).

3.22.3. Physical data of 27. Mp: 152–154°C [from hexane/$CHCl_3$ (83:17)]. (lit.[33] 153–154°C). $[\alpha]_D^{20}$=+42° (c0.400, $CHCl_3$) [lit.[33] +48° (*c* 0.33, $CHCl_3$)]. IR (CH_2Cl_2 solution): 3430, 3350, 2920, 1720, 1695, 1610, 1600, 1275, 1235, 1080, 980 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.56 (3H, s), 2.69 (3H, s), 2.80, 3.03 (each 1H, d, *J*=4.2 Hz), 5.59, 6.16 (each 1H, br), 7.37 (2H, m), 7.50 (1H, br d, *J*=2.5 Hz), 7.92 (1H, d, *J*=2.58.64 Hz (1H, m). EIMS (rel. int., %): 329 (66, M$^+$), 285 (5.1. [M−(CONH$_2$)]$^+$), 216 (27, ArCOOH$^+$), 199 (100, ArCO$^+$) Anal. calcd for C, 65.64%; H, 5.81%; N, 4.25%; Found: C, 65.59%; H, 6.09%; N, 4.34%. The ^{1}NMR spectra of this sample was identical to that kindly provided by Professor Shibuya (Tokushima University).

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