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Stereoselective Synthesis of 1-Aminocyclopropanecarboxylic Acid Carnosadines via Inter-intramolecular Double Alkylation with Optically Active 2-Methylaziridine Derivatives

Kosuke Ohsawa, Junya Kubota, Shota Ochiai, and Takayuki Doi*

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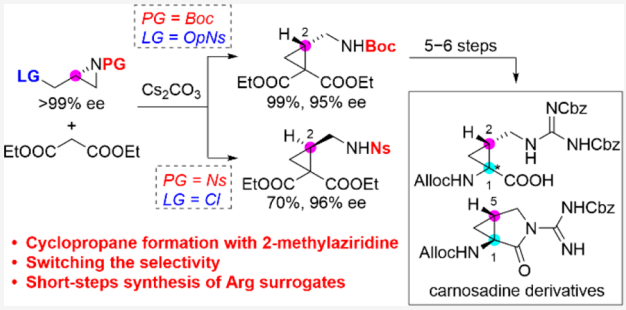
ABSTRACT: The stereoselective and short-step synthesis of *N*-protected *allo*-carnosadine, *ent*-carnosadine, and carnosadine lactam was accomplished from a common cyclopropane intermediate. The inter-intramolecular double alkylation of diethyl malonate with an optically active 2-methylaziridine derivative gave the key cyclopropane in excellent yield and optical purity. The following monohydrolysis of the diester moiety using different reaction conditions provided both diastereomers of monoacids, which were converted to three carnosadine derivatives in 5−6 steps from the common diester.



1-Amino-1-cyclopropanecarboxylic acids (ACCs) are one of the nonproteinogenic amino acids.[1] In particular, 2-substituted ACCs are attractive as conformationally constrained analogues of the corresponding proteinogenic amino acids, and the substitution of one proteinogenic amino acid in biologically active peptides to ACCs contributes to improving the pharmacokinetics: enzymatic stability,[2] selective affinity for target proteins,[3] and stabilization of secondary structures of peptides.[4] Carnosadine, from a red marine alga *Grateloupia carnosa* by Shiba,[5] is one of the guanidino-containing ACCs bridged between the Cα and Cγ positions of Arg (Figure 1).

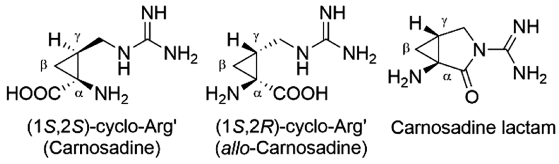


Figure 1. Chemical structures of cyclopropyl-containing Arg surrogates.

The Shiba group determined that the absolute configuration of the natural product is (1*S*,2*S*) based on the chemical synthesis.[6] Recently, the bicyclic form of *allo*-carnosadine, named carnosadine lactam, was found to be a component of antibacterial branched-peptide stalobacin I.[7] Although the biological activity of carnosadine itself has not been examined, carnosadine and its derivatives are attractive building blocks as side-chain-constrained Arg surrogates in peptidomimetics based on naturally occurring polycationic peptides.

Starting with the first synthesis by Shiba et al.,[6] several stereoselective syntheses of carnosadines have been accomplished to date. One of the efficient approaches for the multi-substituted cyclopropane formation is inter/intramolecular double alkylation of enolates with alkylating agents that bear two reactive sites. Husson et al. achieved the first asymmetric synthesis of carnosadine.[8] The key reaction was conducted using the enolate of chiral auxiliary-bearing α-aminonitrile and racemic epibromohydrin, leading to the cyclopropane product with poor diastereoselectivity (Scheme 1a). Burgess et al. developed stereoselective access via double alkylation of malonic diesters with optically active cyclic sulfate (Scheme 1b).[9] Both *N*-protected carnosadine and its α-epimer were provided from a common trisubstituted cyclopropane intermediate, though the total number of steps for the synthesis is long (17−21 steps) due to multistep conversions for installing the amino and guanidinyl groups. Herein, we report the step-economical and stereoselective synthesis of suitably protected *allo*-carnosadine, *ent*-carnosadine, and carnosadine lactam. We envisioned that inter-intramolecular double alkylation using optically active 2-methylaziridine derivatives can produce a multi-substituted cyclopropane bearing an aminomethyl group in one step (Scheme 1c). The product obtained can be quickly converted to carnosadine derivatives.

Our retrosynthetic analysis of suitably protected carnosadines is illustrated in Scheme 2a. The *N*-protected *allo*-

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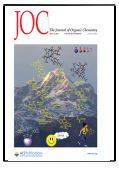
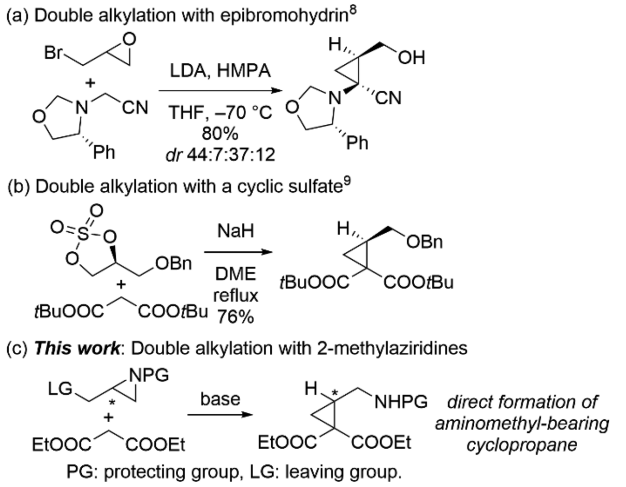
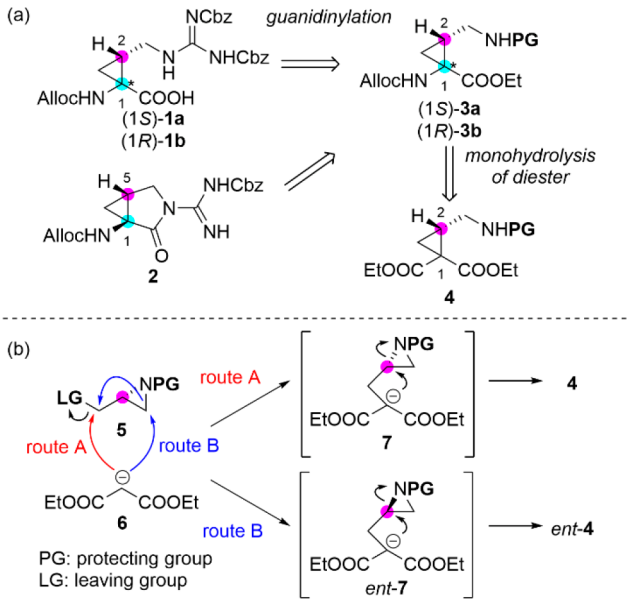


Scheme 1. Synthetic Strategy for Multi-substituted Cyclopropanes in Carnosadines via Inter-Intramolecular Double Alkylation



Scheme 2. (a) Retrosynthetic Analysis of Carnosadines; (b) Two Plausible Pathways for the Asymmetric Synthesis of Cyclopropanes



carnosadine (**1a**) and *ent*-carnosadine (**1b**) can be obtained from **3a** and **3b** by guanidinylation, respectively. The *N*-protected carnosadine lactam (**2**) can also be synthesized from **3b** by guanidinylation and lactamization. Installation of the amino group at the C1 position will be furnished by the monohydrolysis of diester **4**, followed by Curtius rearrangement of the resulting carboxylic acid. We assumed that the different environments surrounding each carbonyl group allow the selective hydrolysis of diesters in **4**, resulting in the formation of both C1 stereoisomers **3a** and **3b**. The 1,1,2-trisubstituted cyclopropane moiety of **4** can be constructed by the inter-intramolecular double alkylation of diethyl malonate (**6**) with enantio-enriched 2-methylaziridine derivatives **5**. The key point for the stereo-controlled synthesis of cyclopropane **4** is the regioselectivity in the initial intermolecular alkylation step. Aziridine intermediates **7** can be formed by two plausible routes: (i) direct displacement of a leaving group in **5** (Scheme 2b, route A), and (ii) opening and regeneration of an aziridine ring (Scheme 2b, route B). Stereoselective formation of cyclopropane with malonate anion and optically active 2-substituted "epoxide" derivatives has been accomplished by both routes.[10] However, there are no reports demonstrating the double alkylation using 2-substituted "aziridine" derivatives in one step.[11] Thus, tuning a protecting group on the aziridine nitrogen and a leaving group in **5** would be necessary to control the alkylation mode, providing **4** without losing the optical purity because routes A and B would give enantiomers.

We initially surveyed stereo-controlled cyclopropane formation using optically active aziridines **5**, and the details are summarized in Table 1. Our attempts began with 2-nitrobenzenesuflonyl (Ns)-protected aziridines, which have been used for various nucleophilic substitutions.[12] We envisioned that a good leaving triflate group would be prone to direct substitution of the nucleophile and that a poor leaving chloride atom should assist the prior aziridine-migration pathway. After optimization of the reaction conditions (bases, solvents, and temperature) with the triflate **5a**, double alkylation readily proceeded at 0 °C using the enolate of diethyl malonate generated with a NaH/catalytic amount of 15-crown-5, leading to the desired cyclopropane **4a** in 94% yield (entry 1). Moderate enantiomeric excess (56% ee) was observed by chiral high-performance liquid chromatography (HPLC) analysis of lactam **8**, and the stereochemistry at the C2 position of **4a** was determined to be *S* by comparing the sign of the specific rotation after conversion of **8** to the known compound **9** (Scheme 3).[13]

The loss of the optical purity in the cyclopropane product means that a competitive aziridine migration would occur owing to the strongly electron-withdrawing effect of the Ns group. When the reaction was performed using chloride **5b**,[12a] the desired *ent*-**4a** was obtained in only a 14% yield, accompanied by the di-alkylated product (entry 2). After investigation of the bases, using Cs_2CO_3 instead of NaH slightly improved the yield of *ent*-**4a** up to 25% (entry 3). Monitoring the reaction by TLC comparing with the isolated authentic samples (data not shown) indicated that a second intermolecular alkylation of the mono-alkylated product with **5b** would partially occur prior to the reformation of aziridine owing to the poor leaving ability of the chloride atom. Thus, the yield of *ent*-**4a** increased up to 70% using an excess amount of diethyl malonate (2.7 equiv) and Cs_2CO_3 (12 equiv) with the aziridine **5b** (entry 4). The reproducibility was improved by a slow addition of **5b** to a solution of diethyl malonate and heat-dried Cs_2CO_3. The absolute configuration of the obtained **4a** was determined to be *R* after conversion to lactam *ent*-**8**. Additionally, the high enantiomeric excess of the obtained *ent*-**4a** (96% ee) indicated the expected switching of the regioselectivity in the intermolecular alkylation step (entry 4 vs entry 1). On the basis of these results described in entries 1−4, we assumed that the aziridine-opening can be suppressed by less electron-withdrawing protecting groups on the nitrogen atom of the aziridine.[14] Thus, the cyclopropane formation with *N*-Boc aziridines was then surveyed to optimize the intermolecular alkylation mode. The double alkylation with the triflate **5c** did not, however, proceed using NaH and Cs_2CO_3 as a base at 0 °C, and raising the reaction temperature resulted in the decomposition of the aziridine substrate (entries 5 and 6). After screening the leaving groups in the *N*-Boc aziridines, the 4-nitrobenzenesulfonate **5d**[15] promoted the direct substitution pathway, giving **4b** in 99% yield with

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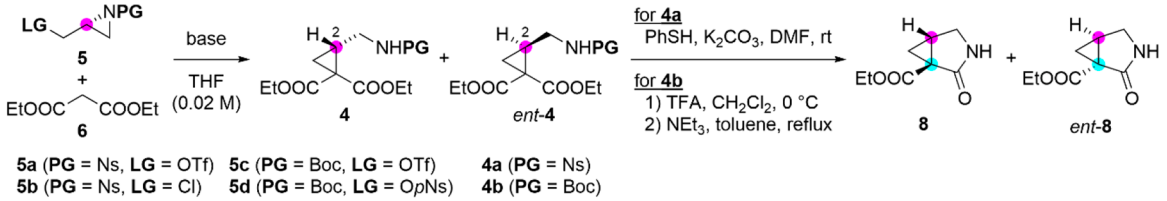
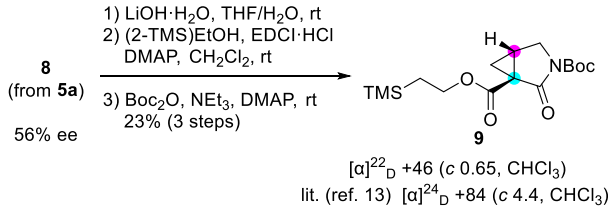
Table 1. Optimization of Conditions for Stereoselective Synthesis of Cyclopropanes via Inter-intramolecular Double Alkylation[a]



entry	aziridines	reagents (equiv)	temp (°C)	time (h)	product	yield (ee)[b,c]
1	**5a**	NaH (3.0), 15-crown-5 (0.3)	0	4	**4a**	94% (56% ee)
2	**5b**[d]	NaH (3.0), 15-crown-5 (0.3)	0	24	*ent*-**4a**	14%[e]
3	**5b**[d]	Cs_2CO_3 (5.0)	rt	6	*ent*-**4a**	25%[e]
4[f,g]	**5b**[d]	Cs_2CO_3 (12)[h]	rt	3	*ent*-**4a**	70% (96% ee)
5	**5c**	NaH (3.0), 15-crown-5 (0.3)	0 to rt	19		
6	**5c**	Cs_2CO_3 (5.0)	30	7		
7	**5d**	Cs_2CO_3 (5.0)	35	24	**4b**	99% (95% ee)

[a]Reaction conditions: **6** (1.0 equiv), aziridine **5** (1.2 equiv), THF (0.02 M). [b]Isolated yield. [c]Enantiomeric excess of **4** was determined by chiral HPLC analysis after conversion to the lactam **8**. [d]0.78 M in benzene solution. [e]The enantiomeric excess of the product was not determined. [f]Reaction conditions: **6** (2.7 equiv), aziridine **5** (1.0 equiv), THF (0.02 M). [g]A solution of **5b** was slowly added (1 mL/h) to a solution of **6** and Cs_2CO_3. [h]Heat dried. Ns = *o*-nitrobenzenesulfonyl, *p*Ns = *p*-nitrobenzenesulfonyl.

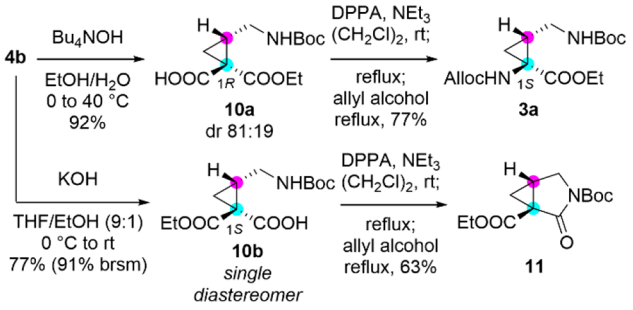
Scheme 3. Synthesis of the Known Compound 9 from 8



95% ee (entry 7). These results suggest that an appropriate combination of a protecting group on the nitrogen atom and the leaving group in the aziridine **5** enabled the stereocontrolled synthesis of both enantiomers of aminomethylcyclopropanes **4**.

With the optically active multi-substituted cyclopropanes **4** in hand, installing an amino group at the C1 position in **4b** was surveyed (Scheme 4). Selective monohydrolysis of the diester

Scheme 4. Selective Monohydrolysis of the Diester 4b



4b is the next task to provide both C1-diastereomers of carnosadines. We speculated that a sterically less-hindered ethoxycarbonyl group that is *trans* to the aminomethyl group would react with priority,[16] and we employed 10% aqueous Bu_4NOH in EtOH solution to afford the monoacid **10a** in 92% yield as an inseparable mixture of diastereomers at an 81:19 ratio. Intriguingly, the sterically hindered ethoxycarbonyl group in **4b** was selectively hydrolyzed using a stoichiometric amount of KOH in a mixed solvent of THF/EtOH (9:1), providing monoacid **10b** in 77% yield as a single diastereomer. The structures of **10a** and **10b** were determined after conversion by the Curtius rearrangement using diphenylphosphoryl azide (DPPA).[17] When the diastereomeric mixture of **10a** was treated with DPPA, the acyl azide derived from the major (1*R*)-diastereomer was thermally converted to the corresponding isocyanate, which was trapped by an allyl alcohol to give the allyl carbamate **3a**. On the other hand, the acyl azide derived from the minor (1*S*)-diastereomer readily reacted with the proximal *N*-Boc amino group to form a five-membered lactam **11**. These products were separated by silica gel column chromatography, and the desired **3a** was isolated in 77% yield. Treatment of **10b** with the above Curtius rearrangement conditions gave the lactam **11** in 63% yield, not the allyl carbamate **3b**. Although it is unclear why the unexpected monohydrolysis of the sterically hindered ethoxycarbonyl group in **4b** occurred under the typical hydrolysis conditions (KOH in THF/EtOH), the intramolecular hydrogen bond with the proximal amine proton may activate the *cis*-oriented carbonyl group to allow priority attack of the hydroxide anion in a THF-enriched solution.[18]

The synthesis of *N*-protected *allo*-carnosadine (**1a**) and carnosadine lactam (**2**) from the key intermediate **3a** is outlined in Scheme 5a. The basic hydrolysis of the remaining ester in **3a** using KOH, removal of the Boc group under acidic conditions, followed by the guanidinylation with *N*,*N*′-bis(benzyloxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**12**) afforded the *N*-protected **1a** in 49% overall yield.[19] In addition, by employing the guanidinylation procedure for **3a** using Goodman's reagent[20] **13**, the *N*,*N*′-di-Boc guanidine **14** was provided in 82% yield in two steps. After removal of the Boc groups in **14**, the guanidine-bearing lactam formation was successfully performed in the presence of KO*t*Bu and one-pot protection of the guanidine nitrogens with Cbz groups was attempted. However, the *N*,*N*′-di-Cbz protected product was found to be unstable owing to the poor electron density of the guanidinyl group by three electron-deficient carbonyl groups.[21] Thus, a small excess amount of Cbz-OSu was added to the

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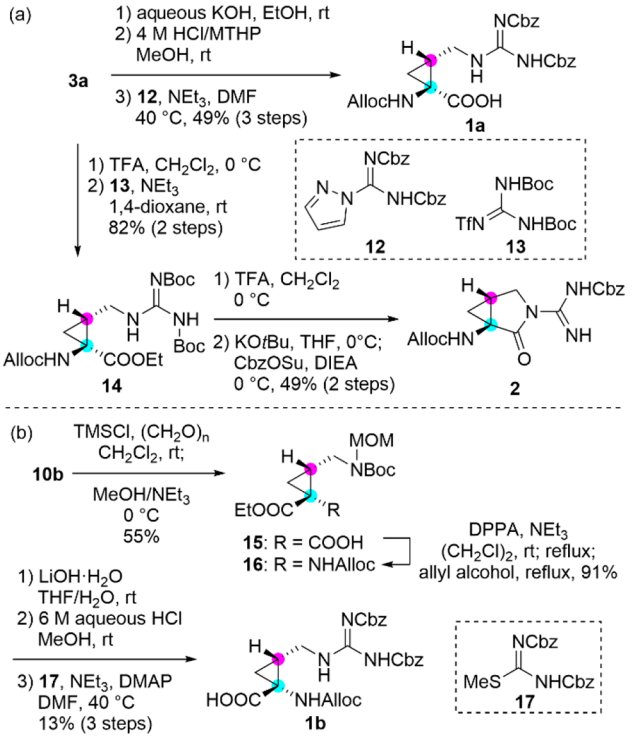
Scheme 5. Synthesis of *N*-Protected (a) *allo*-Carnosadine, Carnosadine Lactam, and (b) *ent*-Carnosadine



reaction mixture to furnish the mono-Cbz-protected **2** in 49% yield in two steps.

With the established synthetic route of **1a**, *N*-protected *ent*-carnosadine (**1b**) was synthesized as depicted in Scheme 5b. Full protection of the amino group in **10b** was essential to suppress the lactam formation during treatment with DPPA. Given the concomitant removal with a Boc group, an acid-labile methoxymethyl (MOM) group was selected as a protecting group. Chemoselective protection of the carbamate in the presence of a carboxyl group was conducted using the one-pot procedure reported by Barnes.[22] The *N*-chloromethyl adduct of **10b**, generated from TMSCl and paraformaldehyde, readily reacted with an excess amount of MeOH/NEt_3 (9:1), providing the *N*-MOM-protected **15** in 55% yield. As expected, the Curtius rearrangement of **15** using DPPA smoothly produced the corresponding isocyanate, and the one-pot addition of allyl alcohol gave the allyl carbamate **16** in 91% yield. Finally, the hydrolysis of the remaining ester in **16**, concomitant removal of the Boc and MOM groups under acidic conditions, and the successive guanidinylation with *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea (**17**) afforded the *N*-protected **1b** in 13% overall yield.[23]

In summary, we have demonstrated the short-step synthesis of *allo*-carnosadine, *ent*-carnosadine, and carnosadine lactam as suitably *N*-protected forms. The multi-substituted cyclopropane in the carnosadine was constructed in one step by the inter-intramolecular double alkylation of diethyl malonate with optically active aziridine derivatives **5**, providing the aminomethyl-bearing **4** in good yield. The reaction mechanism of the intermolecular alkylation step was successfully controlled by tuning a protecting group on a nitrogen atom and a leaving group in **5**, and both enantiomers of **4** were obtained from (*R*)-**5** with excellent optical purity. Monohydrolysis of diester **4b** using different reaction conditions provided both diastereomers **3a** and **3b** with good selectivities. After installing α-amino and δ-guanidinyl groups, we achieved the stereoselective synthesis of carnosadines **1a**, **1b**, and **2** in 5−6 steps from a key synthetic intermediate **4b** and 12−13 steps from commercially available D-Ser. The late-stage guanidinylation strategy is valuable for preparing various guanidine-modified derivatives for peptide synthesis, and the synthesis of stalobacin I and its analogues using **2** is underway.

EXPERIMENTAL SECTION

General Techniques. All commercially available reagents were purchased from commercial suppliers and used as received. Dry THF and CH_2Cl_2 (Kanto Chemical Co.) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina column. All reactions in the solution phase were monitored by TLC carried out on Merck silica gel plates (0.2 mm, 60F-254) with UV light, and visualized by *p*-anisaldehyde/H_2SO_4/EtOH solution, phosphomolybdic acid−EtOH solution, or ninhydrin/AcOH/BuOH solution. Column chromatography was carried out with silica gel 60 N (Kanto Chemical Co. 100−210 μm). Preparative TLC was performed on 0.75 mm Wakogel B-5F PLC plates. ^{1}H NMR spectra (400 and 600 MHz) and ^{13}C NMR spectra (100 and 150 MHz) were recorded on JEOL JNM-AL400 and JEOL JNM-ECA600 spectrometers in the indicated solvent. Chemical shifts (δ) are reported in units parts per million (ppm) relative to the signal for internal TMS (0.00 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77.0 ppm for ^{13}C) and DMSO (2.50 ppm for ^{1}H) or DMSO-d_6 (39.5 ppm for ^{13}C), when an internal standard is not indicated. Multiplicities are reported by using standard abbreviations, and coupling constants are given in hertz. High-resolution mass spectra were recorded on a Thermo Scientific Exactive Plus Orbitrap Mass Spectrometer (for ESI). IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer. Only the strongest and/or structurally important absorptions are reported as the IR data afforded in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points were measured with a Round Science Inc. RFS-10 and are not corrected. SHIMAZU LC-10AT and Shodex RI-101 were used for normal-phase chiral HPLC analysis.

Preparation of the Triflate 5a. *(R)-(1-(2-Nitrophenylsulfonyl)-aziridin-2-yl)methanol.* To a solution of (*R*)-(1-tritylaziridin-2-yl)methanol[24] (1.80 g, 5.77 mmol) in dry CH_2Cl_2 (3.0 mL) and dry MeOH (1.0 mL) was added TFA (4.4 mL, 57.7 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped with toluene/MeOH (1:1) to remove excess TFA and diluted with EtOAc. The organic layer was extracted twice with water (9.0 mL). The combined aqueous layers were basified with solid $NaHCO_3$ until pH 8, and EtOAc was added (9.0 mL). To the above mixture was added a solution of NsCl (1.21 g, 5.48 mmol) in EtOAc (9.0 mL) at 0 °C under an argon atmosphere. After being stirred at room temperature for 1.5 h, the organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:2) to afford the *N*-Ns aziridine (1.23 g, 4.76 mmol, 82%) as a colorless oil. $[\alpha]_D^{24}$ +12 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.23 (m, 1H), 7.74−7.80 (m, 3H), 3.99−4.02 (m, 1H), 3.65−3.71 (m, 1H), 3.26−3.30 (m, 1H), 2.93 (dd, 1H, *J* = 7.0, 0.6 Hz), 2.59 (d, 1H, *J* = 5.2 Hz). 1.71 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.5, 134.6, 132.3, 131.7, 131.1, 124.4, 60.3, 42.4, 32.7; IR (neat) 3544, 3097, 2914, 1543, 1369, 1333, 1166, 852 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_9H_{10}N_2O_5SNa$ [M + Na]$^+$ 281.0203, found 281.0202.

*(R)-(1-(2-Nitrophenylsulfonyl)aziridin-2-yl)methyl Trifluoromethanesulfonate (**5a**).* To a solution of the alcohol (520 mg, 2.00 mmol) in dry CH_2Cl_2 (6.0 mL) were added 2,6-lutidine (278 μL, 2.40

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mmol) and Tf_2O (361 μL, 2.20 mmol) at −40 °C under an argon atmosphere. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with 1 M aqueous HCl and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to afford the triflate **5a** (763 mg, 1.96 mmol, 98% crude yield) as a colorless oil. Because decomposition was observed during purification process, the resulting crude triflate **5a** was used for the next reaction without further purification.

Preparation of the Chloride 5b. *(S)-1-Chloro-3-(2-nitrophenylsulfonamido)propan-2-yl Methanesulfonate.* The mesylate was prepared using the reported procedure with partial modification.[12a] To a solution of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (79.9 mg, 132 μmol) in dry CH_2Cl_2 (4.0 mL) was added AcOH (189 μL, 3.31 mmol) at room temperature. After being stirred at the same temperature for 30 min, the reaction mixture was concentrated in vacuo and dried under vacuum. The resulting crude catalyst was dissolved in dry THF (4.0 mL), and (*S*)-epichlorohydrin (612 μL, 7.94 mmol, 1.2 equiv) and *tert*-butyl (2-nitrophenylsulfonyl)-carbamate[25] (2.00 g, 6.62 mmol) were added to the mixture at room temperature under an argon atmosphere. After being stirred at the same temperature for 2.5 h, the reaction mixture was quenched with a solution of PPTS (120 mg) in dry CH_2Cl_2 (4.0 mL) and filtered through a pad of silica gel (80 g, eluted with hexane/EtOAc = 1:1). The filtrate was concentrated in vacuo, and the resulting crude amino alcohol was used for the next reaction without further purification.

To a solution of the crude *N*-Boc amine in dry CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at 0 °C under an argon atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was diluted with EtOAc (150 mL) and basified with saturated aqueous $NaHCO_3$ (120 mL) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting crude amine was used for the next reaction without further purification.

To a solution of the crude alcohol in dry CH_2Cl_2 (36 mL) were added pyridine (1.1 mL, 13.2 mmol, 2.0 equiv), DMAP (80.9 mg, 662 μmol, 0.10 equiv), and Ms_2O (1.73 g, 9.93 mmol, 1.5 equiv) at 0 °C under an argon atmosphere. After being stirred at room temperature for 2 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with 10% aqueous $CuSO_4$ twice and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was recrystallized from EtOAc/hexane to afford the mesylate (1.92 g, 5.16 mmol, 78% in 3 steps) as a white solid. mp 121−122 °C; $[\alpha]_D^{25}$ −16 (*c* 0.50, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.14−8.17 (m, 1H), 7.90−7.93 (m, 1H), 7.78−7.81 (m, 2H), 5.82 (t, 1H, *J* = 6.3 Hz), 4.92 (quin, 1H, *J* = 5.4 Hz), 3.82 (dd, 1H, *J* = 12.0, 5.4 Hz), 3.80 (dd, 1H, *J* = 12.0, 5.4 Hz), 3.54−3.58 (m, 1H), 3.47−3.51 (m, 1H), 3.14 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 148.0, 134.1, 133.14, 133.10, 131.0, 125.7, 78.2, 44.8, 42.8, 38.6; IR (neat) 3333, 2945, 1541, 1346, 1166 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{10}H_{13}N_2O_7S_2ClNa$ $[M + Na]^+$ 394.9745, found 394.9738.

*(R)-2-Chloromethyl-1-(2-nitrophenylsulfonyl)aziridine (**5b**).* To a solution of the *N*-Ns amine (1.00 g, 2.68 mmol) in dry CH_2Cl_2 (268 mL) was added Cs_2CO_3 (961 mg, 2.95 mmol, 1.1 equiv) at 0 °C under an argon atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 2:1) to afford the *N*-Ns aziridine **5b** (737 mg, 2.66 mmol, 99%, >99% ee) as a pale yellow oil. The spectral data of synthetic **5b** were in good agreement with those reported.[12a] The obtained **5b** was stored as a frozen 0.78 M solution in benzene at −25 °C. $[\alpha]_D^{19}$ +17 (*c* 1.0, $CHCl_3$) [lit. (enantiomer) $[\alpha]_D^{25}$ −19.7 (*c* 1.19, $CHCl_3$)].

Preparation of the Triflate 5c and the Nosylate 5d. *1-tert-Butyl 2-Methyl (R)-Aziridine-1,2-dicarboxylate.* To a solution of methyl (*R*)-1-tritylaziridine-2-carboxylate[26] (3.00 g, 8.74 mmol) in dry CH_2Cl_2 (24 mL) were added Et_3SiH (3.2 mL, 20.1 mmol) and TFA (6.7 mL, 201 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 30 min, the reaction mixture was basified with DIEA (22.8 mL, 131 mmol) until pH 8. Boc_2O (1.91 g, 8.74 mmol) was then added to the above mixture at 0 °C, and the mixture was stirred at the same temperature for 1 h. After being stirred at room temperature for 5 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 6:1) to afford the *N*-Boc amine (1.70 g, 8.47 mmol, 97%) as a pale yellow oil. The spectral data of the synthetic compound were in good agreement with those reported.[27] $[\alpha]_D^{20}$ +75 (*c* 1.62, $CHCl_3$) [lit. (enantiomer) $[\alpha]_D^{28}$ −65.6 (*c* 4.3, $CHCl_3$)].

tert-Butyl (R)-2-(Hydroxymethyl)aziridine-1-carboxylate. To a solution of the methyl ester (2.34 g, 11.6 mmol) in dry EtOH (23 mL) and dry THF (12 mL) was added a solution of $LiBH_4$ (2.0 M in THF, 11.6 mL, 23.3 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 13 h, the reaction mixture was diluted with EtOAc and quenched with 10% aqueous citric acid. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1) to afford the *N*-Boc amine (1.30 g, 7.53 mmol, 65%) as a colorless oil. The spectral data of the synthetic compound were in good agreement with those reported.[27] $[\alpha]_D^{20}$ +30 (*c* 0.87, $CHCl_3$) [lit. (enantiomer) $[\alpha]_D^{28}$ −20 (*c* 3.5, $CHCl_3$)].

*tert-Butyl (R)-2-((Trifluoromethylsulfonyloxy)methyl)aziridine-1-carboxylate (**5c**).* Compound **5c** was prepared from the alcohol (40.0 mg, 231 μmol) according to the procedure described above for **5a** and was obtained in an 86% crude yield (60.5 mg, 187 μmol) as a colorless oil. Because decomposition was observed during the purification process, the resulting crude triflate was used for the next reaction without further purification.

*tert-Butyl (R)-2-((4-Nitrophenylsulfonyloxy)methyl)aziridine-1-carboxylate (**5d**).* To a solution of the alcohol (680 mg, 3.93 mmol) in dry CH_2Cl_2 (15 mL) were added NEt_3 (708 μL, 5.11 mmol), *p*NsCl (957 mg, 4.32 mmol), and DMAP (48.0 mg, 393 μmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 4.5 h, the reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1) to afford the nosylate **5d** (1.16 g, 3.24 mmol, 82%) as a colorless oil. The enantiomeric excess of **5d** was determined to be >99% by chiral HPLC analysis (column: Chiralpak AD-H; elution rate: hexane/*i*PrOH = 8:1 (isocratic); flow rate: 0.5 mL/min; retention time: 49.2 min for (*R*)-**5d**, 51.2 min for (*S*)-**5d**). The spectral data of synthetic **5d** were in good agreement with those reported.[15] $[\alpha]_D^{24}$ +31 (*c* 1.1, $CHCl_3$).

Synthesis of the Cyclopropane 4a and the Lactam 8 from the Triflate 5a (Table 1, Entry 1). *Diethyl (S)-2-((2-Nitrophenylsulfonamido)methyl)cyclopropane-1,1-dicarboxylate (**4a**).* To a solution of NaH (washed with hexane, 200 mg, 5.01 mmol) in dry THF (10 mL) were added 15-crown-5 (10.0 μL, 50.1 μmol) and diethyl malonate (**6**) (374 μL, 1.67 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 5 min, a solution of the crude triflate **5a** (763 mg, 1.96 mmol) in dry THF (7.0 mL) was added to the mixture dropwise at 0 °C. After being stirred at the same temperature for 4 h, the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The

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combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 9:2) to afford the cyclopropane **4a** (626 mg, 1.57 mmol, 94%, 56% ee determined by the next experiment) as a colorless oil. $[\alpha]_D^{22}$ −3.7 (*c* 1.0, $CHCl_3$).

*Ethyl (1S,5S)-2-Oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**8**).* To a solution of the *N*-Ns amine **4a** (285 mg, 712 μmol) in dry DMF (7.0 mL) were added K_2CO_3 (295 mg, 2.14 mmol) and PhSH (87.2 μL, 854 μmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with EtOAc/MeOH = 40:1) to afford the lactam **8** (71.0 mg, 420 μmol, 59%) as a colorless oil. The enantiomeric excess of **8** was determined to be 56% by chiral HPLC analysis (column: Chiralpak AD; elution rate: hexane/*i*PrOH = 9:1 (isocratic); flow rate: 0.5 mL/min; retention time: 18.4 min for (1*S*,5*S*)-**8**, 21.5 min for (1*R*,5*R*)-**8**). $[\alpha]_D^{19}$ +47 (*c* 0.97, $CHCl_3$).

Determination of the Absolute Configuration of Cyclopropane 4a Obtained from 5a. *3-tert-Butyl 1-(2-(Trimethylsilyl)ethyl)(1S,5S)-2-oxo-3-azabicyclo[3.1.0]hexane-1,3-dicarboxylate (**9**).* To a solution of the ethyl ester **4a** (30.0 mg, 177 μmol) in dry THF (0.7 mL) and water (0.7 mL) was added $LiOH{\cdot}H_2O$ (14.8 mg, 354 μmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 4 h, the reaction mixture was quenched with 10% aqueous citric acid at 0 °C and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting crude carboxylic acid was used for the next reaction without further purification.

To a solution of the crude carboxylic acid in dry CH_2Cl_2 (1.0 mL) were added (2-trimethylsilyl)ethanol (27.8 μL, 195 μmol), DMAP (2.2 mg, 17.7 μmol), and EDCI·HCl (37.4 mg, 195 μmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 7 h, the reaction mixture was quenched with 10% aqueous citric acid. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting crude ester was used for the next reaction without further purification.

To a solution of the crude amide in dry CH_2Cl_2 (0.3 mL) were added Et_3N (74.0 μL, 531 μmol), Boc_2O (57.9 mg, 266 μmol), and DMAP (2.2 mg, 17.7 μmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 8:1) to afford the *N*-Boc amide **9** (23.0 mg, 67.2 μmol, 38% in 3 steps) as a colorless oil. The spectral data and the sign of the specific rotation of synthetic **9** were in good agreement with those reported.[13] $[\alpha]_D^{22}$ +46 (*c* 0.65, $CHCl_3$) [lit. $[\alpha]_D^{24}$ +84 (*c* 4.4, $CHCl_3$)].

Synthesis of the Cyclopropane *ent*-4a and the Lactam *ent*-8 from the Chloride 5b (Table 1, Entry 4). *Diethyl (R)-2-((2-Nitrophenylsulfonamido)methyl)cyclopropane-1,1-dicarboxylate (*ent*-**4a**).* To an oven-dried flask was added Cs_2CO_3 (3.56 g, 10.9 mmol), and the flask was dried using a heat gun under vacuum. Once the flask was cooled, dry THF (60 mL) was added under an argon atmosphere, and the solution was cooled to 0 °C. To the solution was added diethyl malonate (**6**) (381 μL, 2.50 mmol), and the mixture was stirred at room temperature for 5 min. A solution of the chloride **5b** (0.78 M in benzene, 1.2 mL, 936 μL) was then added slowly to the above solution with a syringe pump (1 mL/h, 70 min). After being stirred at the same temperature for an additional 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 2:1) to afford the cyclopropane *ent*-**4a** (261 mg, 651 mmol, 70%, 96% ee determined by the next experiment) as a colorless oil. $[\alpha]_D^{24}$ +13 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.14−8.16 (m, 1H), 7.87−7.89 (m, 1H), 7.72−7.76 (m, 2H), 5.91 (dd, 1H, *J* = 8.5, 4.1 Hz), 4.20−4.27 (m, 2H), 4.11−4.16 (m, 2H), 3.63 (ddd, 1H, *J* = 14.2, 8.5, 5.5 Hz), 2.84 (ddd, 1H, *J* = 14.2, 10.0, 4.1 Hz), 1.92−1.94 (m, 1H), 1.44 (dd, 1H, *J* = 9.3, 5.1 Hz), 1.26−1.31 (m, 4H), 1.24 (t, 3H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.2, 167.8, 147.9, 134.4, 133.6, 132.9, 130.8, 125.4, 62.1, 61.9, 43.8, 33.6, 26.9, 18.8, 13.9; IR (neat) 3318, 2982, 1721, 1542, 1368, 1212, 1169, 731 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{16}H_{20}N_2O_8SNa$ $[M + Na]^+$ 423.0833, found 423.0829.

*Ethyl (1R,5R)-2-Oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (*ent*-**8**).* Compound *ent*-**8** was prepared from the *N*-Ns amine *ent*-**4a** (26.9 mg, 67.2 μmol) according to the procedure described above for **8** and was obtained in a 64% yield (7.3 mg, 43.0 μmol) as a colorless oil. The enantiomeric excess of *ent*-**8** was determined to be 96% by chiral HPLC analysis as above-mentioned. $[\alpha]_D^{28}$ -1.0×10^2 (*c* 0.14, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (brs, 1H), 4.19−4.30 (m, 2H), 3.56 (dd, 1H, *J* = 10.5, 6.0 Hz), 3.31 (d, 1H, *J* = 10.5 Hz), 2.44−2.47 (m, 1H), 1.96 (dd, 1H, *J* = 8.1, 4.5 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.20 (t, 1H, *J* = 4.5 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 172.8, 168.5, 61.5, 42.1, 30.5, 25.7, 20.6, 14.2; IR (neat) 3271, 2982, 2893, 1719, 1697, 1326, 1271, 1152 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_8H_{11}NO_3Na$ $[M + Na]^+$ 192.0631, found 192.0630.

Synthesis of the Cyclopropane 4b and the Lactam 8 from the Nosylate 5d (Table 1, Entry 7). *Diethyl (S)-2-((tert-Butoxycarbonylamino)methyl)cyclopropane-1,1-dicarboxylate (**4b**).* To a solution of diethyl malonate (**6**) (389 μL, 2.55 mmol) in dry THF (60 mL) were added Cs_2CO_3 (4.15 g, 12.7 mmol) and a solution of the nosylate **5d** (1.10 g, 3.06 mmol) in dry THF (60 mL) at 0 °C under an argon atmosphere. After being stirred at 35 °C for 24 h in an oil bath, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 7:1) to afford the cyclopropane **4b** (793 mg, 2.51 mmol, 99%, 95% ee determined by the next experiment) as a pale yellow oil. $[\alpha]_D^{20}$ −17 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (brs, 1H), 4.15−4.27 (m, 4H), 3.59−3.62 (m, 1H), 2.73−2.80 (m, 1H), 2.02−2.10 (m, 1H), 1.44−1.49 (m, 10H), 1.24−1.37 (m, 7H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 168.0, 155.5, 79.4, 61.7, 61.6, 40.74, 33.7, 28.3, 27.6, 18.8, 13.99, 13.97; IR (neat) 3391, 2977, 1721, 1513, 1368, 1272, 1171, 1030 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{15}H_{25}NO_6Na$ $[M + Na]^+$ 338.1574, found 338.1573.

*Ethyl (1S,5S)-2-Oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**8**).* To a solution of the *N*-Boc amine **4b** (39.9 mg, 126 μmol) in dry CH_2Cl_2 (1.2 mL) was added TFA (193 μL, 2.52 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped with toluene/MeOH (1:1) to remove excess TFA, and the crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry toluene (2.4 mL) was added NEt_3 (87.3 μL, 630 μmol) at 0 °C under an argon atmosphere. After being stirred at reflux for 12 h in an oil bath, the reaction mixture was cooled to room temperature, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and

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filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with EtOAc/MeOH = 40:1) to afford the lactam **8** (15.4 mg, 91.0 μmol, 72% in 2 steps) as a colorless oil. The enantiomeric excess of **8** was determined to be 95% by chiral HPLC as above-mentioned. $[\alpha]_D^{19}$ +1.2 × 10^2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (brs, 1H), 4.17−4.31 (m, 2H), 3.56 (dd, 1H, *J* = 10.4, 5.6 Hz), 3.31 (d, 1H, *J* = 10.4 Hz), 2.43−2.48 (m, 1H), 1.96 (dd, 1H, *J* = 8.2, 4.8 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.20 (t, 1H, *J* = 4.8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8, 168.4, 61.5, 42.1, 30.5, 25.7, 20.6, 14.2; IR (neat) 3282, 2924, 1725, 1692, 1271, 1152 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_8H_{12}NO_3$ $[M + H]^+$ 170.0812, found 170.0810.

Selective Monohydrolysis of the Diester 4b, Followed by Curtius Rearrangement. *(1R,2S)-2-(tert-Butoxycarbonylamino)-methyl-1-(ethoxycarbonyl)cyclopropane-1-carboxylic Acid (**10a**).* To a solution of the diester **4b** (1.39 g, 4.41 mmol, 1.0 equiv) in dry EtOH (44 mL) was added 10% aqueous Bu_4NOH (12 mL, 5.29 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at the same temperature 1 h. After being stirred at 40 °C for 19 h in an oil bath, the reaction mixture was cooled to room temperature, quenched with 10% aqueous citric acid, and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:2) to afford the monocarboxylic acid **10a** (1.17 g, 4.08 mmol, 92%, dr 81:19) as a pale yellow oil.

The spectral data of the synthetic **10a** were obtained after separation of the minor diastereomer. To a solution of the carboxylic acid **10a** (dr 81:19, 1.17 g, 4.08 mmol) in dry EtOAc (42 mL) was added Cy_2NH (811 μL, 4.08 mmol, 1.0 equiv) at 0 °C under an argon atmosphere. After being stirred at room temperature for 3.5 h, the reaction mixture was concentrated in vacuo, and the resulting residue was recrystallized from EtOAc/hexane. The dicyclohexylamine salt of **10a** was suspended in EtOAc, and 10% aqueous citric acid was added to the above mixture at room temperature. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the single diastereomer of the monocarboxylic acid **10a** (684 mg, 2.38 mmol, dr > 95:5) was obtained as a pale yellow oil. $[\alpha]_D^{20}$ −4.3 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (brs, 1H), 4.33 (q, 2H, *J* = 7.2 Hz), 3.52 (dt, 1H, *J* = 10.2, 4.8 Hz), 3.32 (brs, 1H), 2.27 (brs, 1H), 1.98 (dd, 1H, *J* = 9.2, 4.4 Hz), 1.79 (dd, 1H, *J* = 8.4, 4.4 Hz), 1.43 (s, 9H), 1.34 (*t*, 3H, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.0, 171.7, 155.6, 79.6, 62.8, 38.5, 33.5, 31.3, 28.3, 21.8, 13.9; IR (neat) 3369, 2979, 2936, 1715, 1519, 1369, 1252, 1168, 1045 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{13}H_{21}NO_6Na$ $[M + Na]^+$ 310.1261, found 310.1254.

*(1S,2S)-2-(tert-Butoxycarbonylamino)methyl-1-(ethoxycarbonyl)cyclopropane-1-carboxylic Acid (**10b**).* To a solution of the diester **4b** (850 mg, 2.70 mmol) in dry THF (27 mL) was added a solution of KOH (1.0 M in EtOH, 3.0 mL, 2.96 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 1 h. After being stirred at room temperature for 3 h, the reaction mixture was quenched with 1 M aqueous HCl and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1 to 1:2) to afford the monocarboxylic acid **10b** (596 mg, 2.07 mmol, 77%, dr > 95:5) as a pale yellow oil and recovered **4b** (129 mg, 410 μmol, 15%) as a pale yellow oil. $[\alpha]_D^{19}$ −32 (*c* 0.76, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.84 (brs, 1H), 422−4.29 (m, 2H), 3.61−3.63 (m, 1H), 3.31−3.36 (m, 1H), 2.49 (brs, 1H), 1.95−1.97 (m, 1H), 1.86−1.89 (m, 1H,), 1.44 (s, 9H), 1.29 (*t*, 3H, *J* = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.3, 169.0, 156.0, 79.6, 63.1, 38.1, 36.0, 29.8, 28.3, 23.8, 13.8; IR (neat) 3360, 2979, 1716, 1520, 1368, 1283, 1169, 773 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{13}H_{22}NO_6$ $[M + H]^+$ 288.1442, found 288.1434.

*Ethyl (1S,2R)-1-Allyloxycarbonylamino-2-((tert-butoxycarbonylamino)methyl)cyclopropane-1-carboxylate (**3a**).* To a solution of the carboxylic acid **10a** (dr 81:19, 800 mg, 2.79 mmol) in dry $(CH_2Cl)_2$ (25 mL) were added NEt_3 (659 μL, 4.18 mmol) and DPPA (659 μL, 3.06 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at the room temperature for 30 min. After being stirred at reflux for 1.5 h in an oil bath, the reaction mixture was cooled to room temperature, and allyl alcohol (381 μL, 5.57 mmol) was added to the mixture. After being stirred at reflux for 3 h in an oil bath, the reaction mixture was cooled to room temperature, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/acetone = 9:1) to afford the *N*-Alloc amine **3a** (732 mg, 2.14 mmol, 77%) as a colorless oil. $[\alpha]_D^{25}$ +75 (*c* 1.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, rotamer mixture) δ 5.92 (brs, 1H), 5.15−5.44 (m, 3H), 4.60−4.76 (m, 2H), 4.15−4.23 (m, 2H), 3.56−3.59 (m, 1H), 3.23−3.27 (m, 1H), 1.83 (brs, 1H), 1.61 (brs, 1H), 1.38−1.44 (m, 10H), 1.26 (t, 3H, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rotamer mixture) δ 171.1, 156.63, 156.55, 155.8, 132.5, 117.7, 79.1, 66.3, 65.8, 62.0, 61.7, 38.8, 38.7, 37.9, 37.8, 31.0, 28.4, 22.0, 21.9, 14.1; IR (neat) 3344, 2979, 2934, 2148, 1714, 1512, 1322, 1250, 1179 cm^{-1}; IR (neat) 3344, 2979, 2934, 2148, 1714, 1512, 1322, 1250, 1179 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{16}H_{26}N_2O_6Na$ $[M + Na]^+$ 365.1684, found 365.1679.

*Ethyl (1S,5S)-3-tert-Butoxycarbonyl-2-oxo-3-azabicyclo[3.1.0]-hexane-1-carboxylate (**11**).* Compound **11** was prepared from the carboxylic acid **10b** (48.0 mg, 167 μmol) according to the procedure described above for **3a** and was obtained in a 63% yield (28.3 mg, 105 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 6:1). $[\alpha]_D^{18}$ +99 (*c* 0.91, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21−4.29 (m, 2H), 3.82 (dd, 1H, *J* = 11.3, 5.7 Hz), 3.68 (d, 1H, *J* = 11.3 Hz), 2.35−2.38 (m, 1H), 1.99 (dd, 1H, *J* = 7.8 Hz, 5.1 Hz), 1.51 (s, 9H), 1.31 (t, 1H, *J* = 7.1 Hz), 1.26 (t, 1H, *J* = 5.0 Hz); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 167.6, 167.4, 150.3, 83.2, 61.8, 46.0, 32.7, 28.0, 22.1, 20.5, 14.1; IR (neat) 2979, 2925, 1789, 1764, 1716, 1368, 1311, 1157, 972 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{13}H_{19}NO_5Na$ $[M + Na]^+$ 292.1155, found 292.1151.

Synthesis of *N*-Protected *allo*-Carnosadine (1a) and Carnosadine Lactam (2) from 3a. *(1S,2R)-1-Allyloxycarbonylamino-2-(2,3-bis(benzyloxycarbonylguanidino)methyl)cyclopropane-1-carboxylic Acid (**1a**).* To a solution of the ester **3a** (267 mg, 780 μmol) in dry EtOH (2.0 mL) was added 1 M aqueous KOH (1.2 mL, 1.17 mmol) at 0 °C. After being stirred at room temperature for 21 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting crude carboxylic acid was used in the next reaction without further purification.

To a solution of the crude *N*-Boc amine in dry MeOH (2.0 mL) was added 4M HCl/4-methyl-tetrahydropyran (MTHP) (2.0 mL) at 0 °C under an argon atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo, and the crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry DMF (7.0 mL) were added NEt_3 (544 μL, 3.90 mmol) and *N*,*N*′-bis(benzyloxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**12**) (443 mg, 1.17 mmol) at room temperature under an argon atmosphere. After being stirred at 40 °C for 24 h in an oil bath, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4,

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and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with $CHCl_3$/MeOH = 49:1) to give the desired product containing a small amount of impurities. Further purification by column chromatography on silica gel (eluted with EtOAc) afforded the guanidine **1a** (200 mg, 382 μmol, 49% in 3 steps) as a colorless oil. $[\alpha]_D^{25}$ −22 (*c* 1.0, CH_3OH); ^1H NMR (600 MHz, DMSO-d_6, 50 °C) δ 11.6 (brs, 1H), 8.36 (s, 1H), 7.81 (s, 1H), 7.31−7.41 (m, 10H), 5.88 (brs, 1H), 5.06−5.29 (m, 6H), 4.45−4.46 (m, 2H), 3.73 (brs, 1H), 3.45 (brs, 1H), 1.77−1.80 (m, 1H), 1.41 (brs, 1H), 1.21−1.22 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6, 50 °C) δ 172.6, 162.7, 155.8, 154.9, 152.4, 136.7, 134.9, 133.3, 128.32, 128.25, 128.1, 128.0, 127.7, 127.6, 116.7, 67.4, 66.3, 64.1, 37.2, 31.0, 28.1, 21.1; IR (neat) 3323, 2946, 1725, 1620, 1567, 1235, 1202, 1050 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{26}H_{29}N_4O_8$ $[M + H]^+$ 525.1980, found 525.1988.

*Ethyl (1S,2R)-1-Allyloxycarbonylamino-2-(2,3-bis(tert-butoxycarbonylguanidino)methyl)cyclopropane-1-carboxylate (**14**).* To a solution of the *N*-Boc amine **3a** (193 mg, 564 μmol) in dry CH_2Cl_2 (2.8 mL) was added TFA (435 μL, 5.64 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 4 h, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped with toluene/MeOH (1:1) to remove excess TFA, and the crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry 1,4-dioxane (5.6 mL) were added NEt_3 (315 μL, 2.26 mmol) and Goodman's reagent[20] **13** (221 mg, 564 μmol) at room temperature under an argon atmosphere. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with EtOAc and quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 3:1) to afford the guanidine **14** (224 mg, 461 μmol, 82% in 2 steps) as a pale yellow oil. $[\alpha]_D^{24}$ −16 (*c* 0.88, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 11.5 (brs, 1H), 9.05 (brs, 0.7H), 8.70 (brs, 0.3H), 5.83−5.93 (m, 1H), 5.51 (brs, 0.7H), 5.19−5.31 (m, 2.3H), 4.56−4.60 (m, 2H), 4.17−4.22 (m, 2H), 4.06−4.08 (m, 1H), 3.61 (brs, 0.7H), 3.50 (brs, 0.3H), 2.01−2.06 (m, 1H), 1.65 (brs, 1H), 1.51−1.55 (m, 19H), 1.26 (t, 3H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 2:1 rotamer mixture) δ 171.3, 161.4, 156.2, 155.1, 152.5, 132.6, 117.6, 84.4, 82.2, 62.6, 61.9, 40.2, 39.6, 38.0, 29.9, 28.0, 27.9, 22.9, 14.0; IR (neat) 3327, 2981, 1721, 1648, 1620, 1370, 1329, 1186, 1156, 1134 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{22}H_{37}N_4O_8$ $[M + H]^+$ 485.2606, found 485.2596.

*Allyl (1S,5R)-3-N-(Benzyloxycarbonyl)carbamimidoyl-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl Carbamate (**2**).* To a solution of the *N*-Boc guanidine **14** (200 mg, 413 μmol) in dry CH_2Cl_2 (2.0 mL) was added TFA (318 μL, 4.13 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 4 h, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped with toluene/MeOH (1:1) to remove excess TFA, and the crude guanidine was used for the next reaction without further purification.

To a solution of the crude guanidine in dry THF (4.0 mL) was added KO*t*Bu (116 mg, 1.03 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 4 h. DIEA (72.2 μL, 413 μmol) and CbzOSu (103 mg, 413 μmol) were added to the above mixture at 0 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with EtOAc and quenched with water. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:2) to afford the cyclic guanidine **2** (75.0 mg, 201 μmol, 49% in 2 steps) as a yellowish oil. $[\alpha]_D^{18}$ −50 (*c* 0.76, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.06 (brs, 1H), 9.01 (brs, 1H), 7.39−7.40 (m, 2H), 7.33−7.35 (m, 2H), 7.29−7.30 (m, 1H), 5.87−5.92 (m, 1H), 5.63 (brs, 1H), 5.31 (d, 1H, *J* = 17.2 Hz), 5.23 (d, 1H, *J* = 10.3 Hz), 5.15 (d, 1H, *J* = 12.4 Hz), 5.13 (d, 1H, *J* = 12.4 Hz), 4.59 (s, 2H), 4.01−4.03 (m, 1H), 3.94 (d, 1H, *J* = 11.6 Hz), 2.24 (brs, 1H), 1.50−1.64 (m, 1H), 1.10 (t, 1H, *J* = 5.2 Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 175.5, 163.6, 158.7, 156.0, 136.6, 132.4, 128.4, 128.2, 127.9, 118.3, 67.1, 66.3, 46.9, 41.8, 19.6, 19.2; IR (neat) 3386, 3292, 1720, 1609, 1515, 1253, 1168 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{18}H_{21}N_4O_5[M + H]^+$ 373.1506, found 373.1505.

Synthesis of *N*-Protected *ent*-Carnosadine (1b) from 10b. *(1S,2S)-2-((tert-Butoxycarbonyl)(methoxymethyl)amino)methyl-1-ethoxycarbonylcyclopropane-1-carboxylic Acid (**15**).* To a solution of the amine **10b** (595 mg, 2.07 mmol) in dry CH_2Cl_2 (8.0 mL) were added paraformaldehyde (93.3 mg, 3.11 mmol) and TMSCl (789 μL, 6.21 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 4 h. A mixture of dry MeOH/NEt_3 (9:1, 8.0 mL) was then added to the above mixture at 0 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with EtOAc and quenched with 10% aqueous citric acid. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:2) to afford the *N*-MOM amine **15** (380 mg, 1.15 mmol, 55%) as a yellowish oil. $[\alpha]_D^{18}$ −21 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, DMSO-d_6, 50 °C, rotamer mixture) δ 4.65−4.68 (m, 1H), 4.57−4.61 (m, 1H), 4.08−4.15 (m, 2H), 3.40−3.43 (m, 1H), 3.18 (s, 3H), 3.07 (brs, 1H), 2.05 (brs, 1H), 1.39−1.43 (m, 10H), 1.33 (brs, 1H), 1.16−1.21 (m, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6, 50 °C, rotamer mixture) δ 169.2, 168.3, 154.5, 79.5, 78.3, 60.8, 55.2, 54.5, 44.5, 33.1, 27.7, 27.3, 25.3, 19.1, 13.7; IR (neat) 3105, 2979, 2937, 1704, 1418, 1391, 1273, 1155 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{15}H_{25}NO_7Na$ $[M + Na]^+$ 354.1523, found 354.1519.

*Ethyl (1R,2R)-1-(Allyloxycarbonyl)amino-2-(((tert-butoxycarbonyl)(methoxymethyl)-amino)methyl)cyclopropane-1-carboxylate (**16**).* Compound **16** was prepared from the carboxylic acid **15** (104 mg, 314 μmol) according to the procedure described above for **3a** and was obtained in a 91% yield (111 mg, 287 μmol) as a colorless oil after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1). $[\alpha]_D^{25}$ −32 (*c* 0.95, $CHCl_3$); ^1H NMR (600 MHz, DMSO-d_6, 50 °C) δ 7.70 (s, 1H), 5.90 (brs, 1H), 5.30 (d, 1H, *J* = 16.5 Hz), 5.18 (d, 1H, *J* = 10.0 Hz), 4.65−4.67 (m, 2H), 4.49−4.51 (m, 2H), 4.06 (q, 2H, *J* = 6.9 Hz), 3.48 (d, 1H, *J* = 13.8 Hz), 3.18 (s, 3H), 3.05 (dd, 1H, *J* = 13.8, 7.7 Hz), 1.92 (brs, 1H), 1.46 (dd, 1H, *J* = 8.9, 4.8 Hz), 1.43 (s, 9H), 1.15 (t, 3H, *J* = 6.9 Hz), 1.05 (brs, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6, 50 °C) δ 171.8, 156.3, 154.6, 133.3, 166.6, 79.5, 78.5, 64.3, 60.5, 54.5, 44.7, 37.3, 27.7, 25.9, 20.7, 13.8; IR (neat) 3327, 2979, 2936, 1729, 1703, 1368, 1239, 1178, 1155, 1082 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{18}H_{30}N_2O_7Na$ $[M + Na]^+$ 409.1945, found 409.1948.

*(1R,2R)-1-(Allyloxycarbonyl)amino-2-((2,3-bis(benzyloxycarbonyl)guanidino)methyl)cyclopropane-1-carboxylic Acid (**1b**).* To a solution of the ester **16** (105 mg, 272 μmol) in dry THF (1.0 mL) was added a solution of LiOH·H_2O (17.1 mg, 408 μmol) in water (1.0 mL) at 0 °C. After being stirred at room temperature for 7 h, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting crude carboxylic acid was used in the next reaction without further purification.

To a suspension of the crude *N*-Boc amine in MeOH (1.5 mL) was added 6 M aqueous HCl (1.5 mL) at 0 °C under an argon atmosphere. After being stirred at room temperature for 6 h, the reaction mixture was concentrated in vacuo, and the crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry DMF (0.5 mL) were added NEt_3 (190 μL, 1.36 mmol), DMAP (3.3 mg, 27.2 μmol, 0.1 equiv), and a solution of *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea[23]

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(**17**) (133 mg, 408 μmol) in DMF (0.5 mL) at room temperature under an argon atmosphere. After being stirred at 40 °C for 24 h in an oil bath, the reaction mixture was diluted with EtOAc and quenched with 1 M aqueous HCl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC (eluted with $CHCl_3$/MeOH = 49:1) to give the desired product containing a small amount of impurities. Further purification by preparative TLC (eluted with EtOAc) afforded the guanidine **1b** (19.0 mg, 36.2 μmol, 13% in 3 steps) as a colorless oil. $[\alpha]_D^{18}$ −11 (*c* 0.85, CH_3OH); ^1H NMR (600 MHz, DMSO-d_6, 50 °C) δ 12.3 (brs, 1H), 11.5 (s, 1H), 8.58 (s, 1H), 7.87 (s, 1H), 7.31−7.41 (m, 10H), 5.84−5.90 (m, 1H), 5.28 (d, 1H, *J* = 17.5 Hz), 5.22 (s, 2H), 5.14 (d, 1H. *J* = 10.3 Hz), 5.05 (s, 2H), 4.44−4.50 (m, 2H), 3.56−3.59 (m, 1H), 3.22−3.23 (m, 1H), 1.86 (brs, 1H), 1.43−1.46 (m, 1H), 0.92−0.94 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6, 50 °C) δ 173.4, 162.7, 156.4, 154.9, 152.2, 136.7, 135.0, 133.2, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 116.7, 67.4, 66.1, 64.2, 37.3, 31.8, 26.0, 19.4; IR (neat) 2980, 1747, 1727, 1441, 1393, 1370, 1330, 1308, 1235, 1205 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{26}H_{29}N_4O_8$ $[M + H]^+$ 525.1980, found 525.1977.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00680.

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra for all new and known compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Takayuki Doi − *Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan;* orcid.org/0000-0002-8306-6819; Email: doi_taka@mail.pharm.tohoku.ac.jp

Authors

Kosuke Ohsawa − *Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan*

Junya Kubota − *Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan*

Shota Ochiai − *Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00680

Notes

The authors declare no competing financial interest.

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