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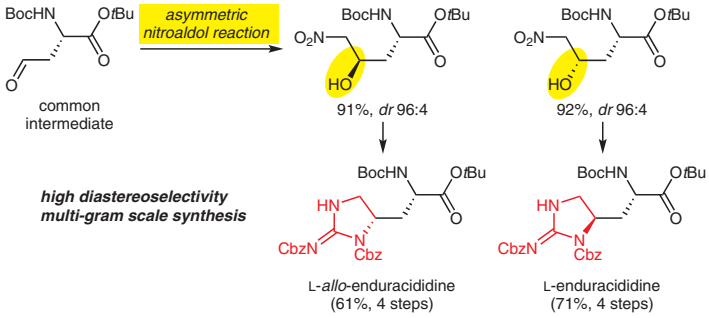
Stereoselective Synthesis of Protected L-*allo*-Enduracididine and L-Enduracididine via Asymmetric Nitroaldol Reaction

Kosuke Ohsawa[a]
Hongbin Zhao[a]
Takuya Tokunaga[a]
Carys Thomas[b]
A. Ganesan[b]
Yuichi Masuda[a,c]
Takayuki Doi*[a]

[a] Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aza-aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan
doi_taka@mail.pharm.tohoku.ac.jp
[b] School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, UK
[c] Graduate School of Bioresources, Mie university, 1577 Kurimamachiya-cho, Tsu 514-8507, Japan



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Abstract The diastereoselecetive and scalable synthesis of cyclic guanidine-containing nonproteinoginic amino acids, enduracididines, has been achieved. Both diastereomers, L-*allo*-enduracididine and L-enduracididine, were prepared via catalyst-controlled asymmetric nitroaldol reaction with the aldehyde precursor derived from L-aspartic acid. The cyclic guanidine of di-Cbz-protected L-*allo*-enduracididine was fully protected with an allyl group to suppress nucleophilic side reactions. Introduced allyl group was efficiently removed via π-allylpalladium chemistry without attaching the Cbz group on the cyclic guanidine moiety.

Key words enduracididines, nonproteinogenic amino acids, cyclic guanidines, asymmetric nitroaldol reactions, guanidine functionalization

Enduracididines,[1] which are one of the unique nonproteinogenic amino acids that contain a five-membered cyclic guanidine moiety, are a component of cyclic peptide and depsipeptide natural products: enduracidins,[2] mannopeptimycins,[3] and teixobactin[4] (Figure 1). These enduracididine-containing macrocycles exhibit potent antibacterial activity against a wide-range of Gram-positive bacteria including multi-drug resistant strains. Among them, teixobactin, isolated from the uncultivable beta-proteobacterium *Eleftheria terrae* by using a new iChip technology, inhibits cell wall biosynthesis by binding to a highly conserved pyrophosphate and the first sugar moieties of both Lipid II (precursor of peptidoglycan) and Lipid III (precursor of wall teichoic acid).[4,5] This dual targeting of cell-wall precursors makes it difficult to develop drug-resistance and therefore, teixobactin is expected to herald a new class of antibiotics. Along with the total synthesis of teixobactin,[6] structure-activity relationship (SAR) studies using various teixobactin analogues have been reported.[6e,7] In many cases, the synthetically challenging L-*allo*-enduracididine residue at the 10 position is replaced by commercially available cationic amino acids such as Arg, Orn, and Lys, reducing antibacterial activity. Several analogues bearing a hydrophobic side chain instead of the cyclic guanidine moiety suggested cationic amino acids at the 10 position are not essential for Lipid II binding and antibacterial activity,[8] though it is unclear whether these hydrophobic analogues show the same dual targeting mechanism as positively charged teixobactin by binding to both Lipid II and Lipid III. Thus, development of an efficient synthetic route to both L-*allo*-enduracididine and L-enduracididine is essential for obtaining sufficient quantities toward a library synthesis of enduracididine-containing teixobactin analogues. Starting with the first diastereoselective synthesis by Shiba et al,[9a] several stereoselective and scalable synthesis of L-*allo*-enduracididine have been accomplished as a building block for teixobactin to date. However, these target-oriented approaches are not accessible for the preparation of its γ-epimer, L-enduracididine, because the chiral center at the γ position was installed by the S_N2 reaction of the hydroxy group in commercially available 4-*trans*-hydroxyproline derivatives,[6d,9b] substrate-controlled reduction of a nitroketone,[6a,9c] or intramolecular double guanidinylation of a terminal olefin in an allylglycine derivative.[6e] Liu et al. has recently reported the synthesis of both L-*allo*-enduracididine and L-enduracididine via the nonselective reduction of the nitroketone followed by chromatographic separation of the resulting two diastereomers in low yields.[6c] Therefore, it is valuable to establish a highly stereocontrolled approach from a common synthetic intermediate to enduracididine and its diastereo-

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mer. Herein, we report the stereoselective synthesis of suitably protected L-*allo*-enduracididine **1a** and its epimer, L-enduracididine **1b**, via asymmetric nitroaldol reaction.

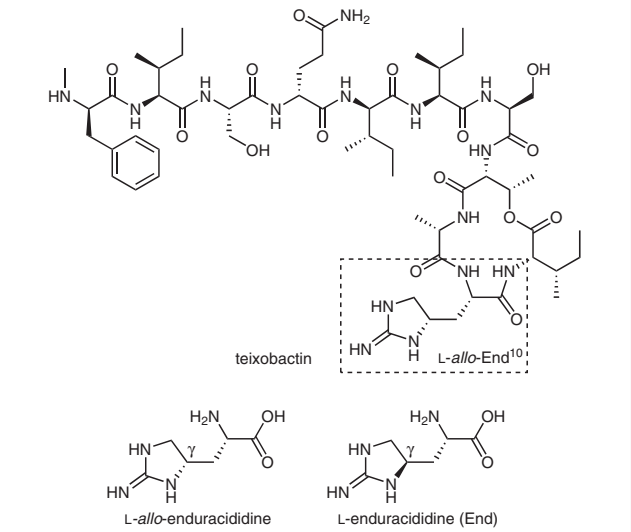
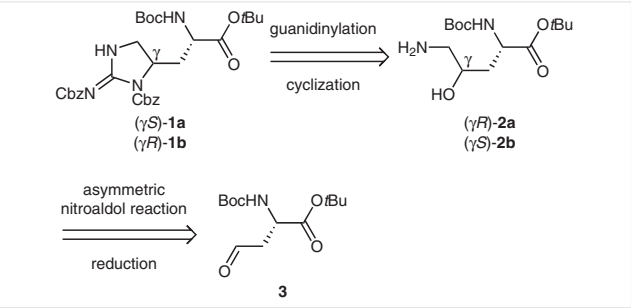


Figure 1 Chemical structures of teixobactin, L-*allo*-enduracididine, and L-enduracididine

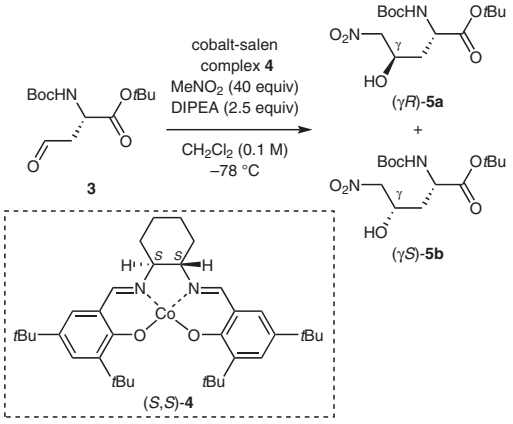
Our retrosynthetic analysis for **1** is illustrated in Scheme 1. The desired cyclic guanidines **1** can be obtained by guanidinylation followed by intramolecular *N*-alkylation of γ-hydroxyornithine **2**, which would be prepared by asymmetric nitroaldol reaction of **3**,[10] followed by reduction of the nitro group. The catalyst-controlled asymmetric nitroaldol reaction could provide both diastereomers corresponding to L-*allo*-enduracididine and L-enduracididine.



Scheme 1 Retrosynthetic analysis of protected enduracididines **1**

Our study began with the asymmetric nitroaldol reaction of the aldehyde **3** readily prepared from L-aspartic acid.[10] Yamada's conditions[11] using commercially available cobalt-salen complex **4**, which has been adopted for the synthesis of (+)-K01-0509 B and its epimer,[12] were surveyed as depicted in Table 1. We initially performed the reactions in the presence of 5 mol% of the catalyst (*S*,*S*)-**4** under various reaction temperatures, which was found to be critical for the yield and stereoselectivity. At –78 °C, the reaction did not complete in 72 hours, providing the desired product (γ*R*)-**5a** in 53% yield and in high diastereoselectivity (dr 95:5, Table 1, entry 1). At –40 °C, the yield of **5a** increased up to 88%, whereas the selectivity decreased (dr 82:18, entry 2). Thus, we utilized 10 mol% catalyst to complete the reaction at –78 °C in 48 hours, leading to **5a** in a high yield and good selectivity (91%, dr 96:4, entry 3). These reaction conditions were applied to the synthesis of (γ*S*)-**5b** using the catalyst (*R*,*R*)-**4** instead of (*S*,*S*)-**4**. The substrate was consumed within 24 hours, and the corresponding **5b** was obtained in high yield and high selectivity (92%, dr 96:4, entry 4). The results suggest that the catalyst-controlled asymmetric nitroaldol reaction was achieved using the cobalt-salen catalyst **4**.

Table 1 Asymmetric Nitroaldol Reaction of Aldehyde **3** Catalyzed by Cobalt-Salen Complexes (*S*,*S*)-**4** and (*R*,*R*)-**4**

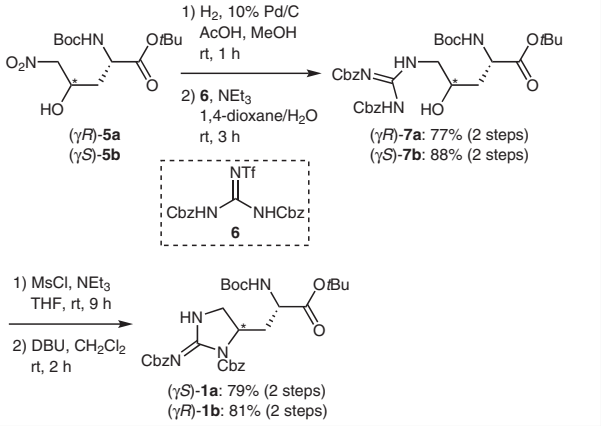


Entry	Cat. (mol%)	Time (h)	Product yield (%)[a]	Ratio of **5a**:**5b**[b]
1	(*S*,*S*)-**4** (5)	72	**5a** (53)[c]	95:5
2[d]	(*S*,*S*)-**4** (5)	18	**5a** (88)	82:18
3	(*S*,*S*)-**4** (10)	48	**5a** (91)	96:4
4	(*R*,*R*)-**4** (5)	24	**5b** (92)	4:96

[a] Isolated yield of a mixture of **5a** and **5b**.
[b] The ratio was determined by chiral HPLC analysis.
[c] Compound **3** was recovered in 13% yield.
[d] The reaction was performed at –40 °C.

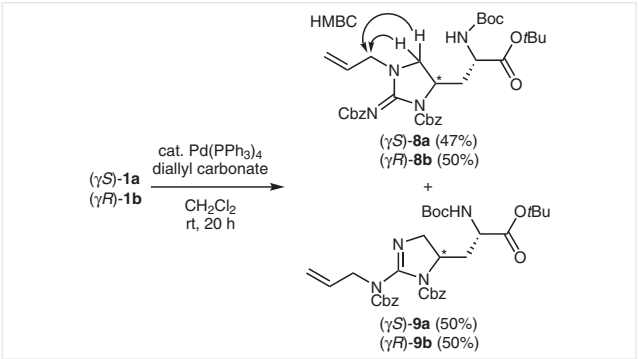
With both **5a** and **5b** in hand, cyclic guanidine formation was performed as shown in Scheme 2. The hydrogenation of the nitro group in **5** followed by the guanidinylation of the resulting amine using Cbz-protected Goodman's reagent **6**[13] afforded acyclic guanidines **7**. After short-column chromatography, trace amount of minor diastereomer was removed by recrystallization to isolate **7** in 77–88% yield over two steps. Although formation of the cyclic guanidine **1** from **7** was precedented (70–79% yield for **1a**[6a,c,9c] and 31% yield for **1b**[6c]), we investigated various reaction conditions for improvement of the total yield. After several attempts, a reported[12] two-step procedure via mesylates was found to

be optimal. Mesylation of **7** with MsCl/NEt_3 followed by the intramolecular S_N2 reaction using DBU provided desired **1** in 79–81% over two steps. Notably, the yield for **1b** dramatically improved and we have established the multi-gram scale synthesis of protected L-*allo*-enduracididine **1a** and L-enduracididine **1b**.



Scheme 2 Synthesis of protected L-*allo*-enduracididine **1a** and L-enduracididine **1b**

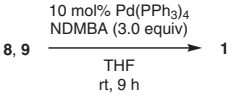
Next, suitable protection of the nucleophilic nitrogen atoms on the cyclic guanidine moiety in **1a** was investigated because fully *N*-protected cyclic guanidine will be valuable to avoid undesired reaction with electrophiles.[14] Dhara et al. have reported partial removal of the Cbz groups in tri-Cbz-protected cyclic guanidine substrate during basic hydrolysis and unsuccessful removal of the remaining Cbz and COOH groups under hydrogenolysis conditions.[9c] It is conceivable that this unexpected instability is due to poor electron density of the guanidinyl group by protection with three electron-deficient alkoxycarbonyl groups. Given selective removal in the presence of Cbz groups, we chose an electron-donating allyl group to protect free nitrogen on cyclic guanidine moiety in **1a**. *N*-Allylation of **1a** was performed at 50 °C using allyl iodide under basic conditions (NaH, K_2CO_3, and Cs_2CO_3). The substrate was consumed, however, partial removal of the Cbz group in allylated products was observed. After several attempts, we found π-allylpalladium chemistry enabled the allylation of **1a** without removal of the Cbz group.[15] Treatment of **1a** with diallyl carbonate in the presence of a catalytic amount of $Pd(PPh_3)_4$ provided unexpectedly two regioisomers **8a** and **9a**, which were separated by column chromatography in 47% and 50% yield, respectively (Scheme 3). The structure of **8a** was determined by observation of the correlation between the allylic carbon and two protons on the cyclic guanidine moiety in the heteronuclear multiple bond correlation (HMBC) spectrum as illustrated in Scheme 3. Allylation of **1b** was also successful, providing **8b** and **9b** in 50% yield, respectively. No migration of the allyl group on the cyclic guanidine moiety in both **8** and **9** was observed in the presence of Pd catalyst.



Scheme 3 Synthesis of *N*-allyl-protected L-*allo*-enduracididines **8** and **9**

The allyl group in **8** and **9** introduced on the cyclic guanidine moiety was simply removed in the presence of a palladium catalyst by treatment with *N*,*N*-dimethylbarbituric acid (NDMBA), which is a superior scavenger of a π-allylpalladium complex, preventing the resulting free guanidine from retrapping the π-allylpalladium complex.[16] As summarized in Table 2, deprotected **1** was obtained by optimal conditions in 68–88% yields (Table 2, entries 1–4).

Table 2 Removal of the Allyl Group in **8** and **9**



Entry	Substrate	Product yield (%)[a]
1	(γ*S*)-**8a**	(γ*S*)-**1a** (70)
2	(γ*S*)-**9a**	(γ*S*)-**1a** (75)
3	(γ*R*)-**8b**	(γ*R*)-**1b** (68)
4	(γ*R*)-**9b**	(γ*R*)-**1b** (88)

[a] Isolated yield.

In summary, we have demonstrated the diastereoselective and scalable synthesis of suitably protected L-enduracididine and L-*allo*-enduracididine derivatives. Stereochemistry at the γ position of ornithine was constructed by catalyst-controlled asymmetric nitroaldol reaction with aldehyde **3**, providing both diastereomers **5a** and **5b** in good yields and high selectivities. During the investigation of cyclic guanidine formation for **7a** and **7b**, a two-step procedure, *O*-mesylation followed by the intramolecular S_N2 reaction using DBU, provided both **1a** and **1b**. Further *N*-protection of the cyclic guanidines of **1** with an allyl group was accomplished via π-allylpalladium chemistry, and deprotection was efficiently carried out without attaching the

Cbz group on the cyclic guanidine moiety. This allyl protection–deprotection strategy should be valuable not only to suppress nucleophilic side reactions but also for late-stage functionalization of the cyclic guanidine moiety toward a SAR study. Synthesis of teixobactin and enduracididine-containing analogues is underway.

All commercially available reagents were purchased from commercial suppliers and used as received. Anhyd 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). ^{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), when 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 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 absorption 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 Round Science Inc. RFS-10, and are not corrected. SHIMAZU LC-10AT and Shodex RI-101 were used for normal-phase chiral HPLC analysis.

Asymmetric Nitroaldol Reaction of the Aldehyde 3; General Procedure A (GP-A)

To a solution of the aldehyde **3**[10] (1.0 equiv) in anhyd CH_2Cl_2 (2.5 mL/mmol) were added $MeNO_2$ (40 equiv) and cobalt-salen complex **4** (0.10 equiv) at rt under an argon atmosphere. The mixture was cooled to –78 °C, and *N*,*N*-diisopropylethylamine (DIPEA) (2.5 equiv) was added to the mixture dropwise. After stirring at the same temperature, the reaction mixture was quenched with sat. aq NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc 3:1) to afford nitro alcohols **5**. The diastereomeric ratio of **5** was determined by chiral HPLC analysis [column: AD-H; elution rate: hexane/*i*PrOH = 9:1 (isocratic); flow rate: 1.0 mL/min; retention time: 13.5 min for **5a**, 20.3 min for **5b**].

tert-Butyl (2*S*,4*R*)-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-5-nitropentanoate (5a) (Table 1, entry 3)

By following GP-A, the nitroaldol reaction of the aldehyde **3** (5.00 g, 18.3 mmol) was performed using (*S*,*S*)-cobalt-salen complex **4** (1.10 g, 1.83 mmol) for 48 h. The nitroalcohol **5a** was obtained in 91% yield (6.11 g, 18.2 mmol, dr 96:4) as a white solid; mp 129–130 °C; $[\alpha]_D^{25}$ –26 (*c* 1.0, $CHCl_3$); R_f = 0.18 (toluene/THF/EtOAc 18:1:1).

IR (neat): 3423, 2979, 2934, 1689, 1556, 1507, 1368, 1253, 1156 cm^{-1}.

^{1}H NMR (400 Hz, $CDCl_3$): δ = 5.42 (br s, 1 H), 4.50–4.58 (m, 1 H), 4.45 (d, *J* = 5.9 Hz, 2 H), 4.25–4.29 (m, 1 H), 3.38 (br s, 1 H), 2.06–2.10 (m, 1 H), 1.86–1.93 (m, 1 H), 1.48 (s, 9 H), 1.45 (s, 9 H).

^{13}C{^{1}H} NMR (100 Hz, $CDCl_3$): δ = 170.9, 155.7, 82.9, 80.5, 80.2, 66.0, 51.3, 36.8, 28.3, 27.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}N_2O_7Na$: 357.1632; found: 357.1628.

tert-Butyl (2*S*,4*S*)-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-5-nitropentanoate (5b) (Table 1, entry 4)

By following GP-A, the nitroaldol reaction of the aldehyde **3** (1.81 g, 6.63 mmol) was performed using (*R*,*R*)-cobalt-salen complex **4** (400 mg, 0.663 mmol) for 24 h. The nitroalcohol **5b** was obtained in 92% yield (2.03 g, 6.08 mmol, dr 96:4) as a white solid; mp 102–103 °C; $[\alpha]_D^{25}$ +2.9 (*c* 1.0, $CHCl_3$); R_f = 0.24 (toluene/THF/EtOAc 18:1:1).

IR (neat): 3397, 2980, 1691, 1558, 1509, 1368, 1252, 1155 cm^{-1}.

^{1}H NMR (400 Hz, $CDCl_3$): δ = 5.45 (br d, *J* = 6.8 Hz, 1 H), 4.72 (brs, 1 H), 4.32–4.53 (m, 4 H), 1.92–1.99 (m, 1 H), 1.49–1.56 (m, 1 H), 1.48 (s, 9 H), 1.46 (s, 9H).

^{13}C{^{1}H} NMR (100 Hz, $CDCl_3$): δ = 170.9, 157.1, 83.0, 81.1, 79.8, 65.0, 50.5, 38.4, 28.2, 27.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}N_2O_7Na$: 357.1632; found: 357.1628.

Introduction of the Guanidinyl Group in the Nitroalcohols 5; General Procedure B (GP-B)

To a solution of nitroalcohol **5** (1.0 equiv) in anhyd MeOH (10 mL/mmol) were added AcOH (1.0 equiv) and 10% Pd/C (30 wt%) at rt under an argon atmosphere, and the flask was purged three times with H_2. After stirring at rt for 1 h, the reaction mixture was filtered through a pad of Celite. 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 above crude amine in 1,4-dioxane (10 mL/mmol) and H_2O (2 mL/mmol) were added NEt_3 (2.1 equiv) and Goodman's reagent **6** (1.5 equiv) at rt under an argon atmosphere. After stirring at the same temperature for 3 h, the reaction mixture was diluted with EtOAc, and quenched with 10% aq citric acid. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were washed with sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the resulting residue was passed through a short pad of silica gel (eluent: hexane/EtOAc 2:1). The resulting product was recrystallized from CH_2Cl_2/hexane to remove small amount of minor diastereomer to afford guanidines **7** as a white solid.

tert-Butyl (2*S*,4*R*)-5-{(*E*)-2,3-Bis[(benzyloxy)carbonyl]guanidino}-2-[(*tert*-butoxycarbonyl)amino]-4-hydroxypentanoate (7a)

By following GP-B, the introduction of the guanidinyl group in the nitroalcohol **5a** (4.62 g, 13.8 mmol) was performed. The guanidine **7a** was obtained in 77% yield over 2 steps (6.50 g, 10.6 mmol) as a white solid; mp 125–126 °C; $[\alpha]_D^{25}$ +11 (*c* 1.0, $CHCl_3$); R_f = 0.56 (toluene/EtOAc 3:1).

IR (neat): 3338, 2977, 1732, 1643, 1570, 1455, 1367, 1215, 1152 cm^{-1}.

^{1}H NMR (600 Hz, $CDCl_3$): δ = 11.7 (s, 1 H), 8.69 (t, *J* = 5.2 Hz, 1 H), 7.26–7.39 (m, 10 H), 5.40 (br d, *J* = 5.8 Hz, 1 H), 5.19 (s, 2 H), 5.10 (s, 2 H), 4.54 (br s, 1 H), 4.21–4.22 (m, 1 H), 3.95 (br s, 1 H), 3.62–3.65 (m, 1 H), 3.38–3.43 (m, 1 H), 1.95–1.98 (m, 1 H), 1.79–1.84 (m, 1 H), 1.43 (s, 18 H).

$^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ = 171.9, 163.2, 157.0, 155.7, 153.6, 136.5, 134.5, 128.8, 128.7, 128.5, 128.4, 128.0, 127.9, 82.3, 80.0, 68.7, 68.3, 67.1, 52.1, 47.2, 37.8, 28.3, 27.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{43}N_4O_9$: 615.3025; found: 615.3015.

tert-Butyl (2*S*,4*S*)-5-{(*E*)-2,3-Bis[(benzyloxy)carbonyl]guanidino}-2-[(*tert*-butoxycarbonyl)amino]-4-hydroxypentanoate (7b)

By following GP-B, the introduction of the guanidinyl group for the nitroalcohol **5b** (1.56 g, 4.67 mmol) was performed. The guanidine **7b** was obtained in 88% yield over 2 steps (2.52 g, 4.11 mmol) as a white solid; mp 124–125 °C; $[\alpha]_D^{25}$ +10 (*c* 1.0, $CHCl_3$); R_f = 0.58 (toluene/EtOAc 3:1).

IR (neat): 3339, 2977, 1732, 1644, 1570, 1498, 1455, 1276, 1051 cm^{-1}.

^1H NMR (600 Hz, $CDCl_3$): δ = 11.7 (s, 1 H), 8.73 (br s, 1 H), 7.27–7.39 (m, 10 H), 5.42 (br d, *J* = 7.9 Hz, 1 H), 5.19 (s, 2 H), 5.11 (s, 2 H), 4.73 (br d, *J* = 2.8 Hz, 1 H), 4.37 (t, *J* = 8.3 Hz, 1 H), 3.72–3.78 (m, 2 H), 3.25–3.30 (m, 1 H), 1.86–1.90 (m, 1 H), 1.48–1.56 (m, 1 H), 1.45 (s, 9 H), 1.44 (s, 9 H).

$^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ = 171.5, 163.5, 156.9, 156.3, 153.6, 136.7, 134.6, 128.8, 128.7, 128.5, 128.4, 128.1, 127.9, 82.6, 80.6, 68.2, 67.1, 66.2, 50.9, 46.3, 39.2, 28.3, 28.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{43}N_4O_9$: 615.3025; found: 615.3018.

Cyclic Guanidine Formation from 7; General Procedure C (GP-C)

To a solution of alcohol **7** (1.0 equiv) in anhyd THF (12 mL/mmol) were added NEt_3 (2.5 equiv) and MsCl (2.5 equiv) at 0 °C under an argon atmosphere. After stirring at rt for 9 h, the reaction mixture was quenched with 1 M aq HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the resulting crude mesylate was used in the next reaction without further purification.

To a solution of the crude mesylate in anhyd CH_2Cl_2 (12 mL/mmol) was added DBU (2.5 equiv) at 0 °C under an argon atmosphere. After stirring at rt for 2 h, the reaction mixture was quenched with 1 M aq HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc 2:1) to afford the cyclic guanidines **1**.

Boc-*allo*-End(Cbz)$_2$-O*t*Bu (1a)

By following GP-C, the cyclic guanidine formation for the acyclic guanidine **7a** (3.00 g, 4.88 mmol) was performed. The cyclic guanidine **1a** was obtained in 79% yield over 2 steps (2.30 g, 3.85 mmol) as a yellowish oil; $[\alpha]_D^{25}$ +26.7 (*c* 1.0, $CHCl_3$); R_f = 0.46 (hexane/EtOAc 1:1).

IR (neat): 3342, 2977, 1713, 1654, 1616, 1367, 1306, 1256, 1152 cm^{-1}.

^1H NMR (600 Hz, $CDCl_3$): δ = 8.63 (br s, 1 H), 7.29–7.46 (m, 10 H), 5.15–5.28 (m, 5 H), 4.56 (br s, 1 H), 4.10–4.14 (m, 1 H), 3.76 (br s, 1 H), 3.60 (br s, 1 H), 2.27 (br s, 1 H), 1.90 (br s, 1 H), 1.44 (s, 9 H), 1.43 (s, 9 H).

$^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ = 170.5, 164.7, 159.6, 155.1, 150.7, 136.8, 135.2, 128.7, 128.6, 128.3, 128.02, 127.98, 127.93, 127.8, 127.7, 82.9, 80.2, 68.4, 67.3, 53.9, 51.5, 45.2, 37.0, 28.3, 27.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{41}N_4O_8$: 597.2919; found: 597.2912.

Boc-End(Cbz)$_2$-O*t*Bu (1b)

By following GP-C, the cyclic guanidine formation for the acyclic guanidine **7b** (3.39 g, 4.67 mmol) was performed. The cyclic guanidine **1b** was obtained in 81% yield over 2 steps (2.25 g, 3.78 mmol) as a yellowish oil; $[\alpha]_D^{25}$ +7.4 (*c* 1.0, $CHCl_3$); R_f = 0.48 (hexane/EtOAc 1:1).

IR (neat): 3345, 2973, 1712, 1654, 1616, 1368, 1307, 1257, 1153 cm^{-1}.

^1H NMR (600 Hz, $CDCl_3$): δ = 8.65 (br s, 1 H), 7.28–7.45 (m, 10 H), 5.24–5.27 (m, 2 H), 5.07–5.21 (m, 3 H), 4.37 (br s, 1 H), 4.13–4.16 (m, 1 H), 3.80 (br s, 1 H), 3.55 (br s, 1 H), 1.98 (br s, 2 H), 1.44 (s, 9 H), 1.42 (s, 9 H).

$^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ = 170.6, 155.8, 136.7, 135.1, 128.6, 128.3, 128.0, 127.9, 82.9, 80.2, 68.3, 67.4, 53.5, 50.6, 45.0, 36.7, 28.2, 27.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{41}N_4O_8$: 597.2919; found: 597.2910.

N-Allylation of the Cyclic Guanidines 1; General Procedure D (GP-D)

To a solution of guanidine **1** (1.0 equiv) in anhyd CH_2Cl_2 (20 mL/mmol) were added diallyl carbonate (1.2 equiv) and $Pd(PPh_3)_4$ (0.10 equiv) at rt under an argon atmosphere. After stirring at the same temperature for 20 h, the reaction mixture was quenched with sat. aq NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc 3:2 to 1:1) to afford the *N*-allylated guanidines **8** and **9**.

N-Allylated *allo*-Enduracididines 8a and 9a

By following GP-D, the *N*-allylation of the cyclic guanidine **1a** (300 mg, 500 μmol) was performed. The *N*-allylated guanidines **8a** and **9a** were obtained in 47% yield (150 mg, 235 μmol) as a colorless oil and 50% yield (159 mg, 250 μmol) as a colorless oil, respectively.

8a

$[\alpha]_D^{25}$ +4.3 (*c* 1.0, $CHCl_3$); R_f = 0.42 (hexane/EtOAc 1:1).

IR (neat): 3349, 2977, 1716, 1620, 1392, 1366, 1262, 1153, 1024 cm^{-1}.

^1H NMR (600 Hz, $CDCl_3$): δ = 7.28–7.37 (m, 10 H), 5.73–5.78 (m, 1 H), 5.31 (br d, *J* = 7.1 Hz, 1 H), 5.25–5.27 (m, 1 H), 5.23 (br s, 1 H), 5.18 (d, *J* = 12.2 Hz, 1 H), 5.02 (d, *J* = 12.4 Hz, 1 H), 4.99 (d, *J* = 12.2 Hz, 1 H), 4.94 (d, *J* = 12.4 Hz, 1 H), 4.50 (br s, 1 H), 4.06 (q, *J* = 7.1 Hz, 1 H), 4.00 (dd, *J* = 15.2, 6.9 Hz, 1 H), 3.96 (dd, *J* = 15.2, 6.4 Hz, 1 H), 3.59 (dd, *J* = 10.3, 8.2 Hz, 1 H), 3.30 (d, *J* = 10.3 Hz, 1 H), 2.25–2.30 (m, 1 H), 1.96 (dt, *J* = 1.57, 7.1 Hz, 1 H), 1.42 (s, 18 H).

$^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ = 170.5, 160.0, 155.2, 151.5, 137.0, 135.0, 131.3, 128.6, 128.52, 128.47, 128.3, 128.2, 127.7, 119.6, 82.6, 80.0, 68.5, 67.2, 54.1, 51.4, 47.7, 47.6, 37.0, 28.3, 27.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{44}N_4O_8Na$: 659.3051; found: 659.3045.

9a

$[\alpha]_D^{25}$ +37.1 (*c* 1.0, $CHCl_3$); R_f = 0.65 (hexane/EtOAc 1:1).

IR (neat): 3360, 2977, 1731, 1637, 1394, 1354, 1270, 1153, 1021 cm^{-1}.

^{1}H NMR (600 Hz, $CDCl_3$): δ = 7.31–7.37 (m, 8 H), 7.20 (br s, 2 H), 5.83–5.87 (m, 1 H), 5.22 (d, *J* = 16.9 Hz, 1 H), 5.10 (d, *J* = 10.3 Hz, 1 H), 4.96–5.02 (m, 4 H), 4.40 (br s, 1 H), 4.25 (br s, 2 H), 4.03 (br s, 1 H), 3.75 (br s, 1 H), 3.63–3.66 (m, 1 H), 1.58 (br s, 2 H), 1.44 (s, 9 H), 1.43 (s, 9 H).

^{13}C{^{1}H} NMR (150 Hz, $CDCl_3$): δ = 170.9, 155.0, 153.6, 151.1, 150.3, 135.2, 132.9, 128.8, 128.6, 128.5, 128.4, 117.8, 82.3, 79.9, 68.3, 67.8, 56.6, 55.2, 51.5, 51.3, 36.0, 28.3, 27.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{44}N_4O_8Na$: 659.3051; found: 659.3046.

N-Allylated Enduracididines 8b and 9b

By following GP-D, the *N*-allylation of the cyclic guanidine **1b** (200 mg, 340 μmol) was performed. The *N*-allylated guanidines **8b** and **9b** were obtained in 50% yield (110 mg, 170 μmol) as a colorless oil and 50% yield (110 mg, 170 μmol) as a colorless oil, respectively.

8b

$[\alpha]_D^{25}$ +5.7 (*c* 1.0, $CHCl_3$); R_f = 0.16 (hexane/EtOAc 3:1).

IR (neat): 2978, 1738, 1718, 1393, 1366, 1253, 1153 cm^{-1}.

^{1}H NMR (600 Hz, $CDCl_3$): δ = 7.24–7.36 (m, 10 H), 5.72–5.77 (m, 1 H), 5.23–5.26 (m, 2 H), 5.15 (d, *J* = 12.0 Hz, 1 H), 5.10 (br d, *J* = 8.4 Hz, 1 H), 5.06–5.10 (m, 2 H), 4.97 (d, *J* = 12.4 Hz, 1 H), 4.35 (t, *J* = 8.6 Hz, 1 H), 4.07–4.12 (m, 2 H), 3.90 (dd, *J* = 15.1, 6.2 Hz, 1 H), 3.63 (dd, *J* = 10.6, 8.6 Hz, 1 H), 3.26 (d, *J* = 10.6 Hz, 1 H), 1.99–2.06 (m, 2 H), 1.45 (s, 9 H), 1.40 (s, 9 H).

^{13}C{^{1}H} NMR (150 Hz, $CDCl_3$): δ = 170.5, 159.9, 155.8, 151.2, 151.1, 137.0, 135.0, 131.3, 128.6, 128.5, 128.24, 128.19, 127.6, 119.4, 82.8, 80.1, 68.4, 67.3, 53.5, 50.7, 47.5, 47.4, 37.3, 28.2, 27.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{45}N_4O_8$: 637.3232; found: 637.3231.

9b

$[\alpha]_D^{25}$ –35 (*c* 1.0, $CHCl_3$); R_f = 0.21 (hexane/EtOAc 3:1).

IR (neat): 2977, 1738, 1717, 1637, 1394, 1155 cm^{-1}.

^{1}H NMR (600 Hz, $CDCl_3$): δ = 7.19–7.38 (m, 10 H), 5.87 (br s, 1 H), 5.24 (d, *J* = 16.1 Hz, 1 H), 5.00–5.12 (m, 6 H), 4.28 (br s, 3 H), 4.07 (br s, 1 H), 3.81 (br s, 1 H), 3.64 (d, *J* = 14.5 Hz, 1 H), 1.76 (br s, 2 H), 1.42 (s, 9 H), 1.41 (s, 9 H).

^{13}C{^{1}H} NMR (150 Hz, $CDCl_3$): δ = 171.1, 155.7, 153.7, 150.1, 135.2, 132.9, 128.7, 128.6, 128.4, 128.1, 117.8, 82.3, 79.9, 68.4, 67.8, 56.2, 55.2, 51.7, 50.6, 36.2, 28.3, 27.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{45}N_4O_8$: 637.3232; found: 637.3228.

Removal of the Allyl group in 8 and 9; General Procedure E (GP-E)

To a solution of *N*-allylguanidine **8** and **9** (1.0 equiv), respectively, in anhyd THF (12 mL/mmol) were added NDMBA (3.0 equiv) and $Pd(PPh_3)_4$ (0.10 equiv) at 0 °C under an argon atmosphere. After stirring at rt for 9 h, the reaction mixture was diluted with EtOAc and quenched with sat. aq $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc 3:1) to afford the guanidines **1** as a yellowish oil.

Boc-*allo*-End(Cbz)$_2$-O*t*Bu (1a)

By following GP-E, the removal of the allyl group in **8a** (50.0 mg, 78.5 μmol) and **9a** (50.0 mg, 78.5 μmol) was performed. The deprotected guanidines **1a** were obtained in 70% yield (33.0 mg, 55.3 μmol, from **8a**) and 75% yield (35.0 mg, 58.7 μmol, from **9a**), respectively.

Boc-End(Cbz)$_2$-O*t*Bu (1b)

By following GP-E, the removal of the allyl group in **8b** (25.0 mg, 39.2 μmol) and **9b** (50.0 mg, 78.5 μmol) was performed. The deprotected guanidines **1b** were obtained in 68% yield (15.5 mg, 26.0 mmol, from **8b**) and 88% yield (41.0 mg, 68.7 μmol, from **9b**), respectively.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691522.

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