JOURNAL OF combinatorial CHEMISTRY

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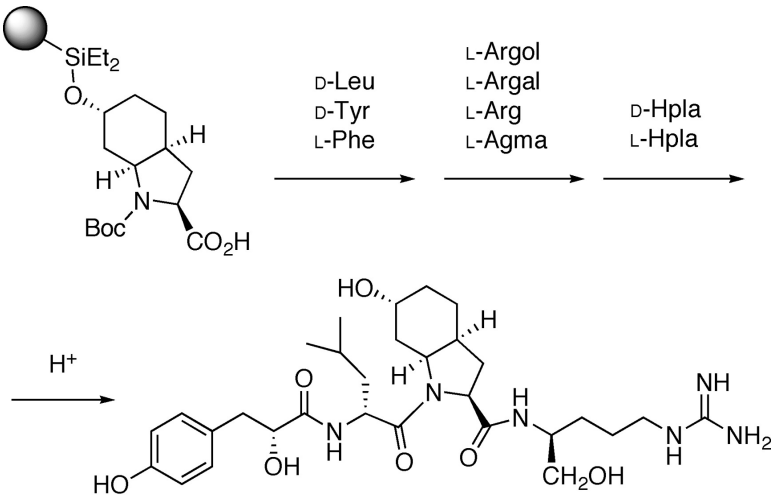
J. Comb. Chem., **2006**, 8 (4), 571-582• DOI: 10.1021/cc0600270 • Publication Date (Web): 19 May 2006



aeruginosin 298-A (**1a**)

+ 23 derivatives

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Solid-Phase Combinatorial Synthesis of Aeruginosin Derivatives and Their Biological Evaluation

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Received March 19, 2006

A 24-member combinatorial library based on the structure of aeruginosin 298-A (**1a**) was synthesized utilizing solid-phase, and their inhibitory activity against trypsin was evaluated. Among the library, we found that D-Hpla-D-Leu-L-Choi-Agma (**1h**) is 300 times more potent than the parent natural product **1a**.

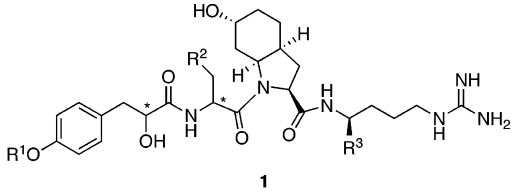
Introduction

A combinatorial synthesis based on natural products is a powerful tool to cover a chemical space for drug candidates.[1] We have studied solid-phase combinatorial syntheses for a variety of naturally occurring skeletons, such as steroids,[2] trisaccharides,[3] peptides,[4−6] macrolides,[7] alkaloids,[8] and prostanoids.[9] We report herein a combinatorial synthesis of aeruginosins and their analogues utilizing a silyl linker on a polymer support and the evaluation of their biological activity.

Aeruginosin 298-A (**1a**), isolated from *Microcystis aeruginosa* (NIES-298), exhibited inhibitory activity for serine proteases (Figure 1).[10,11] Aeruginosin 298-A consists of a *p*-hydroxyphenyllactic acid (D-Hpla) **A1**, a D-leucine (D-Leu) **B1**, an unusual 2-carboxy-6-hydroxyoctahydroindole (L-Choi) (**2a**), and an L-argininol (Argol) **C1** (Figure 2). Other aeruginosins[12−16] and related compounds, microcin (**1b**)[17,18] and oscillarin (**1y**)[19] have also been studied. The more potent aeruginosins (98-A,B, 102-A, 89A, and 205-A,B) possess argininal (Argal) **C2** or agmatine (Agma) **C4** instead of Argol **C1** and a sulfate ester in Hpla or Choi, that is aeruginosin 102-A (**1z**). Although the total syntheses of aeruginosin 298-A have been accomplished by three groups,[20−22] we became interested in the library synthesis of aeruginosin analogues **1a**−**1x** to elucidate structure−activity relationships and to discover more potent compounds.

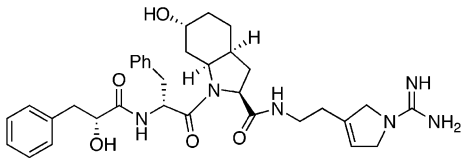
Results and Discussion

Since the Choi **2a** is the core structure in aeruginosins, the 6-hydroxy group in **2a** was chosen for attachment to a polymer support via a silyl linker (Figure 2). We chose the diversity units **A** (D-Hpla and L-Hpla) and **B** (D-Leu, D-Tyr, and L-Phe) at the N-terminus and **C** (L-Argol, L-Argal, L-Arg, and Agma) at the C-terminus in **2b**. These components are



1

aeruginosin 298-A (**1a**) (R^1 = H (D-Hpla), R^2 = *i*-Pr (D-Leu), R^3 = CH_2OH (L-Argol))
microcin SF608 (**1b**) (R^1 = H (L-Hpla), R^2 = Ph (L-Phe), R^3 = H (Agma))
aeruginosin 102-A (**1z**) (R^1 = SO_3H (D-Hpla), R^2 = 4-HO-C_6H_4 (D-Tyr), R^3 = CHO (L-Argal))



oscillarin (**1y**)

Figure 1. Aeruginosin 298-A and related compounds.

mostly contained in aeruginosin 298-A, 102-A, and microcin SF608 (**1b**). The protecting groups in the components used in this combinatorial synthesis are acid-cleavable, such as TBS ethers in Hpla **A1** and **A2**; a *t*-Bu ether in Tyr **B2**; a diethylalkylsilyl linker in Choi **2b**; Boc groups in the unit **C**; and a TBS ether, a diethylacetal, and a MOM ester in Argol **C1**, Argal **C2**, and Arg **C3**, respectively. Therefore, the solid-phase combinatorial synthesis from **2b** with the units **A1**−**A2**, **B1**−**B3**, and **C1**−**C4**, followed by acid cleavage from the polymer support and removal of all the protecting groups could rapidly provide 24 member aeruginosin derivatives **1**.

Synthesis of the units **A1**, **C1**, and **C2** is summarized in Schemes 1−3. Optically pure (+)-**3** was prepared by asymmetric reduction of 4-hydroxyphenylpyruvic acid with (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP−Cl] (Scheme 1).[20b,23] Benzylation of the carboxylic acid in **3**, TBS protection of the phenol and hydroxy groups, and removal of the benzyl ester by hydrogenolysis provided unit **A1**. The unit **A2** was also prepared in the same method using (+)-DIP−Cl in the first step. Esterificaction of Fmoc-arginine-(ω,ω'-di-Boc) (**4**) and $LiBH_4$ reduction afforded argininol **5**

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10.1021/cc0600270 CCC: $33.50
Published on Web 05/19/2006

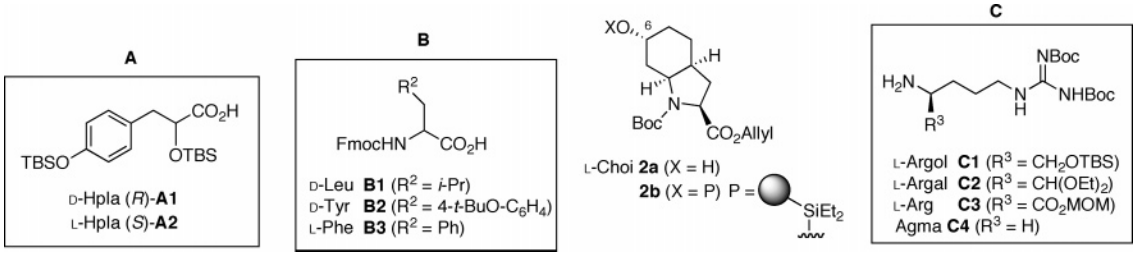
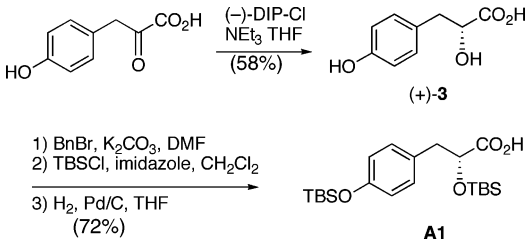
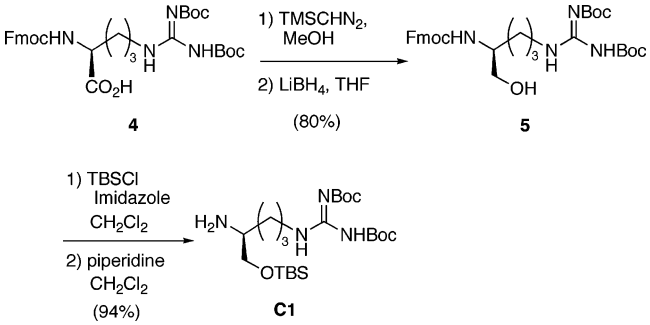


Figure 2. The components of a combinatorial synthesis of aeruginosin derivatives **1**.

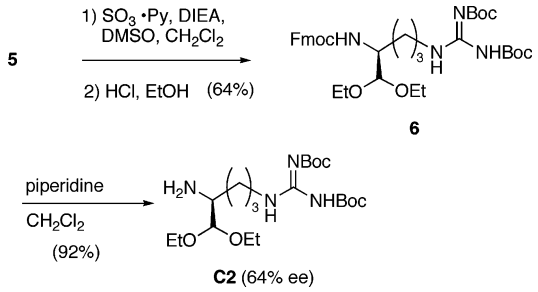
Scheme 1. Preparation of Unit **A1**



Scheme 2. Preparation of Unit **C1**



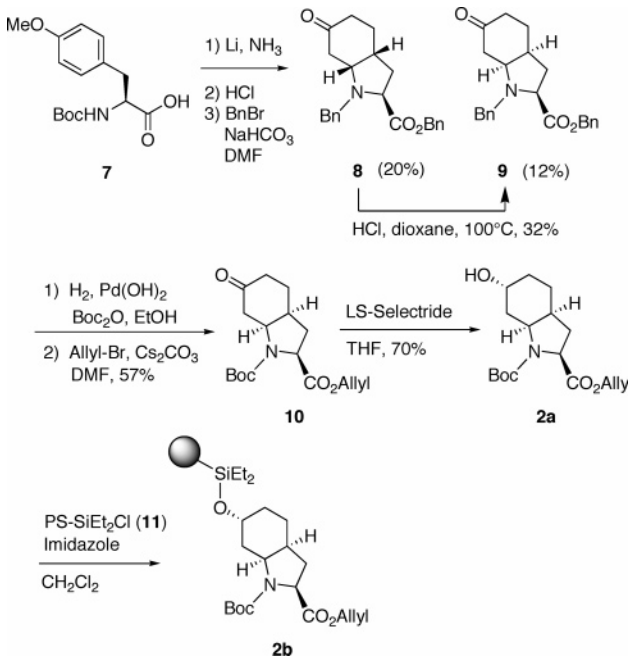
Scheme 3. Preparation of Unit **C2**



(Scheme 2). TBS protection of the hydroxy group in **5**, followed by removal of the Fmoc group, provided unit **C1**. The unit **C2** was prepared from **5** by oxidation of the primary alcohol, followed by diethyl acetal formation and removal of the Fmoc group. Partial racemization observed during the acetal formation in **6** decreased the optical yield of **C2** in 64% ee (Scheme 3).

Polymer-supported Choi **2b** was synthesized as follows (Scheme 4): hydroxyoctahydroindole **2a** was prepared from *N*-Boc-tyrosine-(*O*-methyl) (**7**) by a Bonjoch method.[20] Birch reduction of **7**, followed by treatment with HCl and benzylation, provided a mixture of **8** (20%) and **9** (12%). After separation by silica gel column chromatography, isomerization of **8** to **9** was performed by treatment with HCl in refluxing dioxane in 32% yield with recovery of **8** (43%). Hydrogenolysis of **9** and in situ protection of the resultant amine with Boc_2O, followed by allylation, provided **10**. Stereoselective reduction of the ketone in **10** with LS-

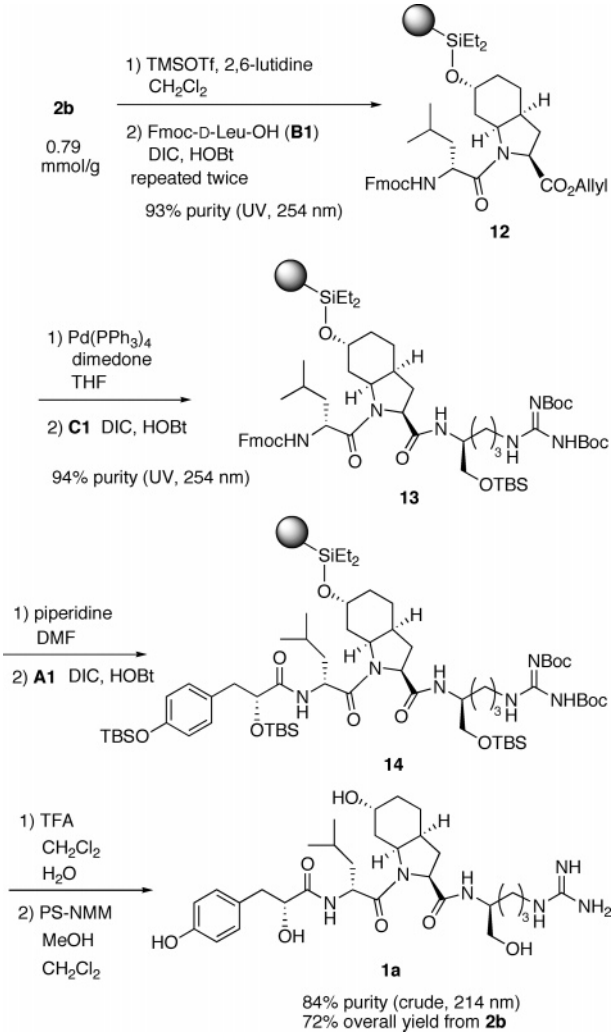
Scheme 4. The Synthesis of Polymer-Supported L-Choi **2b**



Selectride afforded **2a**. Attachment of **2a** (0.2 M, 2 equiv) to PS-DESCl (**11**)[24,25] (imidazole/CH_2Cl_2/rt/14 h) provided polymer-supported **2b**. The loading amount of **2b** was determined to be 0.79 mmol g^{-1} by acid cleavage from the polymer support with TFA/CH_2Cl_2/water (50:45:5).[26]

Removal of the Boc group in **2b** (TMSOTf/2,6-lutidine/CH_2Cl_2),[27] followed by condensation with Fmoc-D-Leu-OH (**B1**) using DIC−HOBt in CH_2Cl_2−DMF (4:1), repeated twice, afforded polymer-supported dipeptide **12** in 93% purity (UV 254 nm) (Scheme 5). To avoid diketopiperazine formation, coupling with Argol **C1** at the *C*-terminus was carried out prior to the removal of the Fmoc group at the N-terminus of **12**. The *O*-allyl ester in **12** was removed with $Pd(PPh_3)_4$/dimedone in THF. Coupling of the free acid with Argol **C1** (DIC−HOBt) afforded **13** in 94% purity (UV 254 nm). After Fmoc deprotection (20% piperidine/DMF) in **13**, D-Hpla **A1** was coupled using DIC−HOBt in CH_2Cl_2−DMF (4:1) in 14 h. Acid cleavage of the polymer-supported **14** and simultaneous removal of the TBS and Boc groups with TFA/CH_2Cl_2/H_2O (50:45:5) provided a mixture of aeruginosin 298-A in 66% purity (UV 214 nm) and its trifluoroacetate derivatives in 25% purity (UV 214 nm). Then the crude mixture was treated with polymer-supported *N*-methylmorphorine (PS−NMM) in MeOH−CH_2Cl_2 to remove the trifluoroacetate providing **1a** in 84% purity (UV 214 nm). After purification by ODS column chromatography, aeruginosin 298-A was isolated in 72% overall yield on the

Scheme 5. Solid-Phase Synthesis of Aeruginosin 298-A



basis of the loading amount of **2b**. The spectral data of **1a** were identical to those reported previously.[10,20−22]

On the basis of the above solid-phase strategy, we constructed a combinatorial library of aeruginosin derivatives **1a**−**1x** using a Quest 210.[28] The polymer-supported Choi **2b** (0.79 mmol g^{-1}) was placed in 24 Teflon tubes, and all reactions were performed in each flask in parallel. The polymer-supported **2b** was treated with **B1**−**B3** (Figure 2), washed, and dried. After deprotection of the allyl ester group, coupling with four amines, **C1**−**C4**, was carried out. After the polymer beads were washed and dried, the Fmoc group was removed, and amidation with **A1** and **A2** was performed. Finally, the polymer beads were treated with acid for cleavage from the polymer support and removal of all protecting groups in separate flasks. Since the products obtained were the mixtures of the desired aeruginosin and their trifluoroacetate derivatives, they were treated with PS−NMM in MeOH−CH_2Cl_2 to remove the trifluoroacetyl groups. As a result, 24 members of aeruginosin derivatives **1a**−**1x** were obtained with high HPLC purity (74−96%) (Table 1).[29]

The results of the in vitro assays of the library compounds **1a**−**1x** against trypsin are summarized in Table 1. Inhibitory activity was measured as IC_{50}. Both D- and L-Hpla (**A1** and **A2**) indicated good activity, except for an L-Phe derivative in the unit **B**. Inhibition activity against trypsin is primarily dependent on the R^3 substituent in the unit **C**. It was reported that Argal-containing aeruginosins 102-A (IC_{50}, 0.2 μg/mL),[13] 89-A (IC_{50}, 0.4 μg/mL)[16] and Agma-containing aeruginosins 205-A,B (IC_{50}, 0.07 μg/mL),[14] 98-A,B (IC_{50}, 0.6 μg/mL),[12] and microcin SF608 B (IC_{50}, 0.5 μg/mL)[17] (entry 24) have stronger trypsin inhibitory activity than Argol-containing aeruginosin 298-A (entry 1), **1j** (entry 9), and Arg-containing analogue **1n** (entry 13).[16] This is in good agreement with our results. However, it is noted that the combination of the units **B** and **C** affected the biological activity; especially, the combination of D-Leu and Agma in **1h** significantly increased the inhibitory activity (IC_{50}, 0.043 μg/mL), about 300 times more potent than aeruginosin 298-A (entry 7 vs entry 1). We purified **1h** by reversed-phase HPLC and investigated its biological activity. The IC_{50} value of purified **1h** was found to be 0.035 μg/mL, that is, in good accordance with the above result. Although there is no sulfate ester in **1h**, **1h** is as potent as Agma-containing sulfated aeruginosins 205-A and B.[30]

Conclusion

We have demonstrated a practical synthetic route for a combinatorial library of aeruginosin derivatives on solid phase. The core Choi **2a** was attached to a polymer support via a silyl linker, and a combinatorial synthesis with the diversity of the units **A**, **B**, and **C** was achieved. We found that D-Hpla-D-Leu-L-Choi-Agma (**1h**) exhibited strong inhibition against trypsin, 300 times more potent than the parent natural products **1a** and **1b** without containing a sulfate ester. Further study for specificity against various serine proteases is underway in our laboratory.

Experimental Section

^{1}H spectra were recorded on JEOL model ECP-400 (400 MHz) or ECA-400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform-*d*, δ 7.26; dimethyl sulfoxide-d_6, δ 2.50). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a JEOL model ECP-400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane, with the solvent resonance as the internal standard (chloroform-*d*, δ 77.0; dimethyl sulfoxide-d_6, δ 39.6). Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Mass spectra were obtained on Applied BioSystems Mariner TK3500 Biospectrometry Workstation (ESI-TOF) mass spectrometers. HRMS (ESI-TOF) were calibrated with angiotensin I (Sigma), bradykinin (Sigma), and neurotensin (Sigma) as an internal standard. Optical rotations were measured with a Yanaco OR-50 polarimeter. Reversed-phase HPLC was performed on a Hewlett-Packard HP-1100 series system with a linear gradient of 10% of B (0−1 min), 10−100% of B (1−10 min), 100% of B (10−12 min) using 0.1% formic acid in water as solvent A, 0.1% formic acid in acetonitrile as solvent B (1.0

Table 1. Purity of the Synthetic Aeruginosin Derivatives **1** and Their Inhibitory Activity against Trypsin

entry	product	components	purity (%)[a]	IC_{50} (μg/mL)
1	D-Hpla-D-Leu-L-Choi-L-Argol (**1a**)[b]	**A1**, **B1**, **2**, **C1**	92	14 (1)[c], (6)[d]
2	L-Hpla-D-Leu-L-Choi-L-Argol (**1c**)	**A2**, **B1**, **2**, **C1**	91	7.9
3	D-Hpla-D-Leu-L-Choi-L-Argal (**1d**)	**A1**, **B1**, **2**, **C2**	92	3.4
4	L-Hpla-D-Leu-L-Choi-L-Argal (**1e**)	**A2**, **B1**, **2**, **C2**	90	3.4
5	D-Hpla-D-Leu-L-Choi-L-Arg-OH (**1f**)	**A1**, **B1**, **2**, **C3**	84	0.48
6	L-Hpla-D-Leu-L-Choi-L-Arg-OH (**1g**)	**A2**, **B1**, **2**, **C3**	81	3.0
7	D-Hpla-D-Leu-L-Choi-Agma (**1h**)	**A1**, **B1**, **2**, **C4**	93	0.043
8	L-Hpla-D-Leu-L-Choi-Agma (**1i**)	**A2**, **B1**, **2**, **C4**	90	0.090
9	D-Hpla-D-Tyr-L-Choi-L-Argol (**1j**)	**A1**, **B2**, **2**, **C1**	89	6.8 (28)[d]
10	L-Hpla-D-Tyr-L-Choi-L-Argol (**1k**)	**A2**, **B2**, **2**, **C1**	89	100
11	D-Hpla-D-Tyr-L-Choi-L-Argal (**1l**)	**A1**, **B2**, **2**, **C2**	89	4.8
12	L-Hpla-D-Tyr-L-Choi-L-Argal (**1m**)	**A2**, **B2**, **2**, **C2**	91	4.6
13	D-Hpla-D-Tyr-L-Choi-L-Arg-OH (**1n**)	**A1**, **B2**, **2**, **C3**	87	0.78 (8.7)[d]
14	L-Hpla-D-Tyr-L-Choi-L-Arg-OH (**1o**)	**A2**, **B2**, **2**, **C3**	87	6.5
15	D-Hpla-D-Tyr-L-Choi-Agma (**1p**)	**A1**, **B2**, **2**, **C4**	88	0.11
16	L-Hpla-D-Tyr-L-Choi-Agma (**1q**)	**A2**, **B2**, **2**, **C4**	90	0.30
17	D-Hpla-L-Phe-L-Choi-L-Argol (**1r**)	**A1**, **B3**, **2**, **C1**	94	>150
18	L-Hpla-L-Phe-L-Choi-L-Argol (**1s**)	**A2**, **B3**, **2**, **C1**	93	1.1
19	D-Hpla-L-Phe-L-Choi-L-Argal (**1t**)	**A1**, **B3**, **2**, **C2**	85	4.0
20	L-Hpla-L-Phe-L-Choi-L-Argal (**1u**)	**A2**, **B3**, **2**, **C2**	95	4.6
21	D-Hpla-L-Phe-L-Choi-L-Arg-OH (**1v**)	**A1**, **B3**, **2**, **C3**	82	>150
22	L-Hpla-L-Phe-L-Choi-L-Arg-OH (**1w**)	**A2**, **B2**, **2**, **C3**	74	>150
23	D-Hpla-L-Phe-L-Choi-Agma (**1x**)	**A1**, **B3**, **2**, **C4**	95	8.7
24	L-Hpla-L-Phe-L-Choi-Agma (**1b**)[e]	**A2**, **B3**, **2**, **C4**	96	11 (0.5)[f]

[a] Purity was determined by HPLC (UV 214 nm). [b] Aeruginosin 298-A. [c] Ref 10. [d] Ref 22b. [e] Microcin SF608. [f] Ref 17.

mL/min). The column was a GL Sciences Inc. Inertsil ODS-3, 3-μm, 4.6 × 75 mm. Peak areas were integrated using 214 or 254 nm. Preparative reversed-phase column chromatography was performed on a Gilson 215 system with a linear gradient of 10% of B (0−2 min), 10−100% of B (2−20 min), 100% of B (20−26 min) using 0.1% formic acid in water as solvent A, 0.1% formic acid in acetonitrile as solvent B (10 mL/min). The column was a GL Sciences Inc. Inertsil ODS-3, 5-μm, 20 × 80 mm. Chiral chromatography was performed on a Waters 2695 system using a Daicel Chiralcel OD-H (4.6 × 250 mm).

(2*R*)-2-Hydroxy-3-(4-hydroxyphenyl)propionic Acid (D-Hpla) (+)-(3).[20b,23] To a stirring solution of 4-hydroxyphenylpyruvic acid (5.0 g, 28 mmol) in THF (120 mL) was added triethylamine (3.9 mL, 28 mmol) at −20 °C. After stirring for 5 min at this temperature, a solution of (−)-*B*-chlorodiisopinocampheylborane (60% in hexane, 23 mL) was added at −20 °C, and the resulting solution was stirred at room temperature for 6 h. The reaction mixture was quenched with 1 M aqueous NaOH (100 mL). The aqueous layer was washed with Et_2O and acidified with 3 M HCl. The aqueous layer was extracted with EtOAc (200 mL × 4) and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum to afford crude D-Hpla (4.8 g). The crude D-Hpla was recrystallized from water to give pure D-Hpla (+)-(**3**) (2.9 g, 58%) as a white solid. $[\alpha]^{27}_D$ +11 (*c* = 0.52, MeOH) [lit[20b] $[\alpha]^{20}_D$ +10.8 (*c* = 0.52, MeOH)]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.66 (1H, dd, *J* = 8.0, 13.8 Hz; H-3), 2.83 (1H, dd, *J* = 4.6, 8.8 Hz; H-3′), 4.06 (1H, m; H-2), 5.20 (1H, brs; 2-OH), 6.64 (2H, d, *J* = 8.2 Hz; H-6, H-8), 7.01 (2H, d, *J* = 8.2 Hz; H-5, H-9), 9.15 (1H, brs; ArO*H*), 12.40 (1H, brs; CO_2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 39.6 (C-3), 71.7 (C-2), 115.2 (C-6, 8), 128.5 (C-4), 130.7 (C-5, 9), 156.1 (C-7), 175.7 (C-1); IR (KBr) 3197, 1736, 1598, 1509, 1439, 1355, 1234 cm^{-1}.

(2*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-[(4-*tert*-butyldimethylsilyloxy)phenyl]propionic Acid (A1). To a solution of D-Hpla (+)-(**3**) (1.09 g, 5.98 mmol) in DMF (30 mL) was added K_2CO_3 (456 mg, 3.30 mmol) at room temperature. After stirring for 2 h, benzyl bromide (0.785 mL, 6.60 mmol) was added and stirred for 1.5 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to afford benzyl (2*R*)-2-hydroxy-3-(4-hydroxyphenyl)propionate (1.54 g, 95%). $[\alpha]^{24}_D$ +52.9 (*c* = 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.77 (1H, brs; 2-OH), 2.91 (1H, dd, *J* = 6.0, 14.3 Hz; H-3), 3.05 (1H, dd, *J* = 4.8, 14.0 Hz; H-3′), 4.45 (1H, brs; H-2), 5.03 (1H, brs; ArO*H*), 5.16 (1H, d, *J* = 12.1 Hz; OCH_2Ph), 5.20 (1H, d, *J* = 12.1 Hz; OCH_2Ph), 6.67 (2H, d, *J* = 8.2 Hz; H-6, H-8), 6.98 (2H, d, *J* = 8.7 Hz; H-5, H-9), 7.32−7.41 (5H, m; Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 39.4 (C-3), 67.4 (CH_2Ph), 71.4 (C-2), 115.3 (C-6, 8), 127.3 (Ph), 128.5 (C-4, Ph), 130.5 (C-5, 9), 134.8 (Ph), 154.7 (C-7), 174.0 (C-1); IR (KBr) 3392, 2934, 1726, 1611, 1512, 1214, 1067 cm^{-1}; MS (ESI-TOF) *m*/*z* 273 [M + H]$^+$.

To a solution of the benzyl ester (1.12 g, 4.11 mmol) in CH_2Cl_2 (20 mL) was added imidazole (926 mg, 13.6 mmol) at 0 °C. After stirring for 5 min at this temperature, *tert*-butylchlorodimethylsilane (1.85 g, 12.3 mmol) was added, and the resulting solution was stirred at room temperature for 5 h. The reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to afford benzyl (2*R*)-2-(*tert*-butyldimethylsilyloxy)-

3-[(4-*tert*-butyldimethylsilyloxy)phenyl]propionate (1.91 g, 93%, 97% ee). $[\alpha]^{20}_D$ +17.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.24 (3H, s; TBS), −0.17 (3H, s; TBS), 0.16 (6H, s; TBS), 0.76 (9H, s; TBS), 0.97 (9H, s; TBS), 2.81 (1H, dd, J = 9.4, 13.3 Hz; H-3), 3.01 (1H, dd, J = 3.9, 13.5 Hz; H-3′), 4.30 (1H, dd, J = 3.4, 9.2 Hz; H-2), 5.13 (1H, d, J = 12.1 Hz; OCH_2Ph), 5.18 (1H, d, J = 12.1 Hz; OCH_2Ph), 6.73 (2H, d, J = 8.2 Hz; H-6, H-8), 7.05 (2H, d, J = 8.2 Hz; H-5, H-9), 7.32−7.36 (5H, m; Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.6 (TBS), −5.4 (TBS), −4.5 (TBS), 18.2 (TBS), 25.6 (TBS), 25.7 (TBS), 40.8 (C-3), 66.5 (OCH_2Ph), 74.0 (C-2), 119.9 (C-6, C-8), 128.3 (Ph), 128.5 (Ph), 130.2 (C-4), 130.7 (C-5, C-9), 135.6 (Ph), 154.4 (C-7), 173.1 (C-1); IR (neat) 2931, 2859, 1756, 1511, 1256, 837 cm^{-1}; MS (ESI-TOF) m/z 501 $[M + H]^+$. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [Daicel Chiralpak OD-H, 0.2% *i*-PrOH in hexane, flow rate 1.0 mL/min, t_R 22.5 min *S*-isomer and 10.4 min *R*-isomer, detected at 214 nm].

A solution of benzyl (2*R*)-2-(*tert*-butyldimethylsilyloxy)-3-[(4-*tert*-butyldimethylsilyloxy)phenyl]propionate (501 mg, 1.00 mmol) in THF (5 mL) was treated with 5% palladium−carbon (50.0 mg) under hydrogen atmosphere for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1−2/1) to afford **A1** (335 mg, 82%). $[\alpha]^{26}_D$ +13.9 (c = 1.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.17 (3H, s; TBS), −0.07 (3H, s; TBS), 0.17 (6H, s; TBS), 0.85 (9H, s; TBS), 0.98 (9H, s; TBS), 2.86 (1H, dd, J = 8.2, 14.0 Hz; H-3), 3.06 (1H, dd, J = 3.4, 13.5 Hz; H-3′), 4.36 (1H, dd, J = 3.6, 8.0 Hz; H-2), 6.77 (2H, d, J = 8.7 Hz; H-6, H-8), 7.06 (2H, d, J = 8.7 Hz; H-5, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.6 (TBS), −5.5 (TBS), −4.5 (TBS), 18.1 (TBS), 18.2 (TBS), 25.6 (TBS), 25.7 (TBS), 40.5 (C-3), 73.6 (C-2), 120.0 (C-6, C-8), 129.6 (C-4), 130.8 (C-5, C-9), 154.6 (Ph), 177.2 (C-1); IR (KBr) 2933, 2856, 1722, 1510, 1257, 917 cm^{-1}; MS (ESI-TOF) m/z 411 $[M + H]^+$.

(2*S*)-2-Hydroxy-3-(4-hydroxyphenyl)propionic Acid (L-Hpla) (−)-(3). Preparation by above method using (+)-*B*-chlorodiisopinocampheylborane instead. $[\alpha]^{23}_D$ −12 (c = 0.52, MeOH) [lit[18] $[\alpha]_D$ −10 (c = 0.58, MeOH)].

(2*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-[(4-*tert*-butyldimethylsilyloxy)phenyl]propionic Acid (A2). A2 was prepared from (−)-**3** by the same method described above. $[\alpha]^{26}_D$ −13.5 (c = 1.75, $CHCl_3$)

(*S*)-*N*-α-(Fluorenylmethyloxycarbonyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)argininol (5). To a solution of (*S*)-*N*-α-(fluorenylmethyloxycarbonyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)-arginine (**4**) (5.0 g, 8.4 mmol) in MeOH (42 mL) was added trimethylsilyldiazomethane (2.0 M, in hexane, 21 mL, 42 mmol) at 0 °C. After stirring for 15 min at room temperature, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to afford (*S*)-*N*-α-(fluorenylmethyloxycarbonyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)arginine methyl ester (4.7 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (18H, s; Boc), 1.52−1.80 (3H, m; H-3, H-4), 1.87−1.96 (1H, m; H-3′), 3.36−3.52 (2H, m; H-5), 3.76 (3H, s; OCH_3), 4.23 (1H, t, J = 6.8 Hz; Fmoc), 4.41 (2H, d, J = 6.3 Hz; Fmoc), 4.40−4.57 (1H, m; Fmoc), 5.61 (1H, d, J = 8.2 Hz, NH), 7.32 (2H, dt, J = 1.0, 7.5 Hz; Fmoc), 7.40 (2H, t, J = 7.2 Hz; Fmoc), 7.62 (2H, t, J = 7.0 Hz; Fmoc), 7.77 (2H, d, J = 7.7 Hz; Fmoc), 8.35 (1H, brs; NH), 11.50 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3 (C-4), 27.9 (Boc), 28.1 (Boc), 29.3 (C-3), 40.1 (C-5), 47.1 (Fmoc), 52.3 (OCH_3), 53.6 (C-2), 66.8 (Fmoc), 79.2 (Boc), 83.0 (Boc), 119.8 (Fmoc), 125.0 (Fmoc), 126.9 (Fmoc), 127.6 (Fmoc), 141.2 (Fmoc), 143.6 (Fmoc), 143.8 (Fmoc), 153.1 (Boc), 155.8 (Boc), 156.1 (Fmoc), 163.4 (N═C), 172.5 (C-1); IR (KBr) 3331, 2979, 1716, 1611, 1130, 739 cm^{-1}; MS (ESI-TOF) m/z 611 $[M + H]^+$.

To a solution of the methyl ester (0.55 g, 0.90 mmol) in THF (5 mL) was added $LiBH_4$ (78 mg, 3.6 mmol) at 0 °C. After stirring for 2.5 h at 0 °C, the reaction mixture was allowed to warm to room temperature and was stirred for 0.5 h. The reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to afford **5** (0.47 g, 90%). $[\alpha]^{25}_D$ +2.83 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40−1.78 (4H, m; H-3, H-4), 1.49 (9H, s; Boc), 1.50 (9H, s; Boc), 2.40 (1H, brs; OH), 3.29−3.77 (5H, m; H-1, H-2, H-5), 4.21 (1H, t, J = 6.8 Hz; Fmoc), 4.43 (2H, d, J = 6.8 Hz; Fmoc), 5.52 (1H, d, J = 8.2 Hz; NH), 7.31(2H, t, J = 7.5 Hz; Fmoc), 7.40 (2H, t, J = 7.2 Hz; Fmoc), 7.61 (2H, t, J = 6.8 Hz; Fmoc), 7.76 (2H, d, J = 7.7 Hz; Fmoc), 8.39 (1H, brs; NH), 11.48 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0 (C-4), 27.9 (C-3, Boc), 28.2 (Boc), 40.4 (C-5), 47.2 (Fmoc), 52.9 (C-2), 64.8 (C-1), 66.4 (Fmoc), 79.3 (Boc), 83.1 (Boc), 119.8 (Fmoc), 124.9 (Fmoc), 126.9 (Fmoc), 127.5 (Fmoc), 141.2 (Fmoc), 143.8 (Fmoc), 153.1 (Boc), 156.2 (Boc), 156.6 (Fmoc), 163.3 (N═C); IR (KBr) 3335, 2978, 1719, 1613, 1132 cm^{-1}; MS (ESI-TOF) m/z 583 $[M + H]^+$.

(*S*)-*N*-ω,ω′-(Di-*tert*-butoxycarbonyl)argininol *tert*-Butyldimethylsilyl Ether (C1). To a solution of **5** (1.63 g, 2.80 mmol) and imidazole (415 mg, 6.10 mmol) in CH_2Cl_2 (28 mL) was added *tert*-butylchlorodimethylsilane (844 mg, 5.60 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1−3/1) to afford (*S*)-*N*-α-(fluorenylmethyloxycarbonyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)argininol *tert*-butyldimethylsilyl ether (1.83 g, 94%). $[\alpha]^{25}_D$ −5.97 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s; TBS), 0.90 (9H, s; TBS), 1.43−1.69 (4H, m; H-3, H-4), 1.49 (9H, s; Boc), 1.50 (9H, s; Boc), 3.25−3.50 (2H, m; H-5), 3.54−3.65 (2H, m; H-1), 3.66−3.76 (1H, m; H-2), 4.23 (1H, t, J = 7.0 Hz; Fmoc), 4.39 (2H, d, J = 6.8 Hz; Fmoc), 5.07 (1H, d, J = 9.2 Hz; NH), 7.31 (2H, t, J = 7.5 Hz; Fmoc), 7.40 (2H, t, J = 7.5 Hz; Fmoc), 7.60 (2H, t, J = 7.2 Hz; Fmoc), 7.76 (2H, d, J = 7.2

Hz; Fmoc), 8.35 (1H, brs; NH), 11.50 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.6 (TBS), −3.7 (TBS), 18.1 (TBS), 25.6 (C-4), 25.8 (TBS), 27.9 (Boc), 28.2 (Boc), 28.7 (C-3), 40.6 (C-5), 47.2 (Fmoc), 52.2 (C-2), 64.7 (C-1), 66.4 (Fmoc), 79.1 (Boc), 82.9 (Boc), 119.1 (Fmoc), 125.0 (Fmoc), 126.9 (Fmoc), 127.5 (Fmoc), 141.2 (Fmoc), 143.8 (Fmoc), 153.2 (Boc), 156.0 (Boc), 156.1 (Fmoc), 163.5 (N═C); IR (KBr) 3334, 2931, 1720, 1638, 1134, 775 cm^{-1}; MS (ESI-TOF) *m*/*z* 697 $[M + H]^+$.

The *tert*-butyldimethylsilyl ether (1.83 g, 2.63 mmol) was dissolved in 10% piperidine in CH_2Cl_2 (10 mL), and the resulting solution was stirred at room temperature for 6 h. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1 − $CHCl_3$/MeOH = 10/1) to afford **C1** (1.25 g, quant.). $[\alpha]^{26}_D$ +5.90 (*c* = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (6H, s; TBS), 0.90 (9H, s; TBS), 1.30−1.51 (2H, m; H-4), 1.50 (18H, s; Boc), 1.57−1.80 (2H, m; H-3), 2.29 (2H, brs; NH), 2.88−2.99 (1H, m; NH_2), 3.32−3.51 (3H, m; H-2, H-5), 3.58 (1H, dd, *J* = 4.1, 9.9 Hz; H-1), 8.42 (1H, brs; NH), 11.47 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4 (TBS), 18.2 (TBS), 25.8 (C-4), 25.9 (TBS), 28.0 (Boc), 28.3 (Boc), 30.5 (C-3), 40.8 (C-5), 52.7 (C-2), 68.0 (C-1), 79.2 (Boc), 83.0 (Boc), 153.2 (Boc), 156.1 (Boc), 163.5 (N═C); IR (neat) 3335, 2931, 1721, 1642, 1134, cm^{-1}; MS (ESI-TOF) *m*/*z* 475 $[M + H]^+$.

***N*-α-(Fluorenylmethyloxycarbonyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)arginal Diethylacetal (6).** To a solution of **5** (248 mg, 0.426 mmol) and diisopropylethylamine (0.366 mL, 2.10 mmol) in DMSO (1.5 mL) was added sulfur trioxide pyridine complex (223 mg, 1.40 mmol) in DMSO (1 mL) at room temperature. After stirring for 20 min, the reaction mixture was quenched with sat. aqueous NH_4Cl with ice cooling bath, and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1−3/2) to afford *N*-α-(fluorenylmethyloxycarbonyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)arginal (210 mg, 85%). $[\alpha]^{26}_D$ +19.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (9H, s; Boc), 1.50 (9H, s; Boc), 1.53−1.76 (4H, m; H-3, H-4), 3.32−3.55 (2H, m; H-5), 4.23 (1H, t, *J* = 6.8 Hz; Fmoc), 4.27−4.40 (1H, m; H-2), 4.45 (2H, d, *J* = 6.8 Hz; Fmoc), 6.00 (1H, d, *J* = 7.2 Hz; NH), 7.32 (2H, t, *J* = 7.5 Hz; Fmoc), 7.40 (2H, t, *J* = 7.5 Hz; Fmoc), 7.61 (2H, t, *J* = 6.8 Hz; Fmoc), 7.77 (2H, d, *J* = 7.7 Hz; Fmoc), 8.40 (1H, brs; NH), 9.61 (1H, s; H-1), 11.48 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4 (C-4), 27.9 (C-3, Boc), 28.1 (Boc), 39.8 (C-5), 47.1 (Fmoc), 59.8 (C-2), 66.7 (Fmoc), 79.2 (Boc), 83.2 (Boc), 119.9 (Fmoc), 125.0 (Fmoc), 127.0 (Fmoc), 127.6 (Fmoc), 141.2 (Fmoc), 143.6 (Fmoc), 143.7 (Fmoc), 153.1 (Boc), 156.2 (Boc, Fmoc), 163.2 (N═C), 199.4 (C-1); IR (KBr) 3328, 2978, 1718, 1639, 1132, 739 cm^{-1}; MS (ESI-TOF) *m*/*z* 581 $[M + H]^+$.

The arginal (471 mg, 0.811 mmol) was dissolved in EtOH (9 mL) containing concentrated HCl (0.150 mL) at room temperature. After stirring for 13 h, the reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1−3/1) to afford **6** (396 mg, 75%). $[\alpha]^{25}_D$ −2.37 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07−1.24 (6H, m; Et), 1.49 (9H, s; Boc), 1.50 (9H, s; Boc), 1.52−1.76 (4H, m; H-3, H-4), 3.34−3.60 (4H, m; Et, H-5), 3.63−3.84 (2H, m, Et), 4.23 (1H, t, *J* = 6.5 Hz; Fmoc), 4.36 (1H, d, *J* = 2.9 Hz; H-2), 4.42 (2H, d, *J* = 6.8 Hz; Fmoc), 5.01 (1H, d, *J* = 9.2 Hz; H-1), 7.31 (2H, t, *J* = 7.0 Hz; Fmoc), 7.40 (2H, t, *J* = 7.5 Hz; Fmoc), 7.61 (2H, t, *J* = 7.2 Hz; Fmoc), 7.76 (2H, d, *J* = 7.7 Hz; Fmoc), 8.33 (1H, brs; NH), 11.50 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.1 (Et), 25.6 (C-4), 26.3 (C-3), 27.9 (Boc), 28.2 (Boc), 40.6 (C-5), 47.2 (Fmoc), 52.9 (C-2), 63.6 (Et), 63.9 (Et), 66.3 (Fmoc), 79.0 (Boc), 82.9 (Boc), 103.2 (C-1), 119.8 (Fmoc), 125.0 (Fmoc), 126.9 (Fmoc), 127.5 (Fmoc), 141.2 (Fmoc), 143.8 (Fmoc), 143.9 (Fmoc), 153.1 (Boc), 156.1 (Boc), 156.3 (Fmoc), 163.5 (N═C); IR (KBr) 3335, 2977, 1719, 1612, 1330, 1130, 740 cm^{-1}; MS (ESI-TOF) *m*/*z* 655 $[M + H]^+$.

***N*-ω,ω′-(Di-*tert*-butoxycarbonyl)arginal Diethylacetal (C2).** Compound **6** (380 mg, 0.580 mmol) was dissolved in 10% piperidine in CH_2Cl_2 (6 mL), and the resulting solution was stirred at room temperature for 3.5 h. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1, $CHCl_3$/EtOH = 10/1) to afford **C2** (246 mg, 98%). $[\alpha]^{18}_D$ +4.62 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (6H, dt, *J* = 2.7, 7.1 Hz; Et), 1.30−1.55 (2H, m; H-4), 1.49 (9H, s; Boc), 1.50 (9H, s; Boc), 1.60−1.85 (2H, m; H-3), 2.90 (1H, t, *J* = 5.6 Hz; H-2), 3.32−3.61 (4H, m; Et, H-5), 3.62−3.80 (2H, m; Et), 4.25 (1H, d, *J* = 5.8 Hz; H-5), 8.43 (1H, brs; NH), 11.46 (1H, brs; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.2 (Et), 25.6 (C-4), 27.9 (Boc), 28.1 (Boc), 29.3 (C-3), 40.7 (C-5), 53.0 (C-2), 63.0 (Et), 63.2 (Et), 79.0 (Boc), 82.8 (Boc), 106.1 (C-1), 153.1 (Boc), 156.0 (Boc), 163.4 (N═C); IR (neat) 3335, 2979, 1723, 1644, 1368, 1134 cm^{-1}; MS (ESI-TOF) *m*/*z* 433 $[M + H]^+$.

Estimation of the Enantiomeric Excess of C2. To a solution of *N*-ω,ω′-(di-*tert*-butoxycarbonyl)arginal diethylacetal (**C2**) (50 mg, 0.11 mmol) in CH_2Cl_2 (1.0 mL) was added pyridine (14 μL, 0.17 mmol) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-(−)-MTPA-Cl), 26 μL, 0.14 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with EtOAc. The combined organic layer was washed with sat. aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1−3/1) to afford *N*-α-(3,3,3-trifluoro-2-methoxy-2-phenylpropionyl)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)arginal diethylacetal (62 mg, 83%). The diastereomeric ratio was determined to be 82:18 by ^{1}H NMR. Those two diastereomers were partially separated by preparative thin-layer chromatography on silica gel (hexane/EtOAc = 2/1). Major product (less polar): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15−1.26 (6H, m; Et), 1.40−1.76 (4H, m; H-3, H-4), 1.50 (9H,

s; Boc), 1.51 (9H, s; Boc), 3.31−3.40 (2H, m; H-5), 3.48−3.60 (2H, m; Et), 3.52 (3H, s; OCH_3), 3.64−3.77 (2H, m; Et), 4.11−4.20 (1H, m; H-2), 4.39 (1H, d, J = 3.4 Hz; H-1), 6.71 (1H, d, J = 9.2 Hz; NH), 7.35−7.46 (3H, m; Ph), 7.57 (2H, d, J = 6.8 Hz; Ph), 8.27 (1H, brs; NH), 11.49 (1H, brs; NH); MS (ESI-TOF) m/z 649 $[M + H]^+$. Minor product (more polar): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (3H, t, J = 7.0 Hz; Et), 1.18 (3H, t, J = 7.0 Hz; Et), 1.45−1.80 (4H, m; H-3, H-4), 1.49 (9H, s; Boc), 1.50 (9H, s; Boc), 3.33−3.57 (4H, m; H-5, Et), 3.39 (3H, s; OCH_3), 3.57−3.74 (2H, m; Et), 4.08−4.18 (1H, m; H-2), 4.35 (1H, d, J = 3.4 Hz; H-1), 6.92 (1H, d, J = 9.2 Hz; NH), 7.36−7.43 (3H, m; Ph), 7.57 (2H, brd, J = 3.9 Hz; Ph), 8.34 (1H, brs; NH), 11.49 (1H, brs; NH); MS (ESI-TOF) m/z 649 $[M + H]^+$.

Benzyl (2*S*,3a*R*,7a*R*)- and (2*S*,3a*S*,7a*S*)-(1-Benzyl-6-oxooctahydroindole-2-carboxylate (8 and 9). These compounds were obtained by following a Bonjoch method.[20] To a solution of Boc-Tyr(Me)−OH (**7**) (10 g, 34 mmol) in a mixture of THF (90 mL) and *t*-BuOH (120 mL) was added ammonia (200 mL) at −78 °C. Then lithium (1.9 g, 270 mmol) was added, and the resulting deep blue solution was stirred for 1.5 h at −78 °C. The reaction mixture was quenched with NH_4Cl at this temperature and then warmed to room temperature. After removing the ammonia and solvent under vacuum, aqueous NaH_2PO_4 was added to the residue to acidify the reaction mixture. The aqueous solution was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum, then 4 M HCl in 1,4-dioxane (200 mL) was added to the residue and stirred for 15 h at room temperature. After removing solvent under vacuum, the residue was dissolved in DMF (200 mL). $NaHCO_3$ (14 g, 170 mmol) and benzyl bromide (9.7 mL, 81 mmol) were added to the solution, and the resulting solution was stirred at 60 °C for 3 h. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1−2/1) to afford **8** (2.4 g, 20%) and **9** (1.5 g, 12%). Exo isomer **8**: $[\alpha]^{19}_D$ −48.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72 (1H, dq, J = 5.2, 13.9 Hz; H-4), 1.85 (1H, dt, J = 8.5, 13.0 Hz; H-3), 1.99−2.08 (2H, m; H-3′, H-4′), 2.22 (1H, ddd, J = 4.8, 5.8, 18.8 Hz; H-5), 2.41 (1H, ddd, J = 4.7, 10.5, 18.5 Hz; H-5′), 2.55 (2H, d, J = 4.8 Hz; H-7), 2.79 (1H, m; H-3a), 3.51 (1H, d, J = 13.5 Hz; NCH_2Ph), 3.57 (1H, d, J = 7.7 Hz; H-2), 3.74 (1H, dt, J = 4.8, 9.2 Hz; H-7a), 3.83 (1H, d, J = 13.0 Hz; NCH_2Ph), 5.06 (1H, d, J = 12.1 Hz; OCH_2Ph), 5.17 (1H, d, J = 12.1 Hz; OCH_2Ph), 7.08−7.40 (10H, m; Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4 (C-4), 33.2 (C-3), 34.2 (C-3a), 35.2 (C-5), 42.0 (C-7), 52.0 (NCH_2Ph), 59.2 (C-7a), 61.8 (C-2), 65.7 (OCH_2Ph), 126.9 (Ph), 128.1 (Ph), 128.2 (Ph), 128.6 (Ph), 135.7 (Ph), 138.5 (Ph), 173.5 (CO_2Bn), 212.1 (C═O); IR (neat) 2294, 1728, 1496, 1455, 1148 cm^{-1}; MS (ESI-TOF) m/z 364 $[M + H]^+$. Endo isomer **9**: $[\alpha]^{21}_D$ −43.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75 (1H, ddd, J = 6.0, 8.6, 12.8 Hz; H-3), 1.83−1.97 (2H, m; H-4), 2.18 (1H, ddd, J = 4.8, 8.2, 17.4 Hz; H-5), 2.34 (1H, ddd, J = 8.3, 8.3, 12.9 Hz; H-3′), 2.40−2.47 (2H, m; H-3a, H-7), 2.49−2.55 (1H, m; H-5), 2.56 (1H, dd, J = 5.3, 15.9 Hz; H-7′), 3.09 (1H, dt, J = 4.8, 8.2 Hz; H-7a), 3.33 (1H, t, J = 8.2 Hz; H-2), 3.63 (1H, d, J = 14.0 Hz; NCH_2Ph), 3.84 (1H, d, J = 14.0 Hz; NCH_2Ph), 4.86 (2H, s; OCH_2Ph), 7.18−7.38 (10H, m; Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5 (C-4), 34.6 (C-3a), 34.7 (C-3), 36.6 (C-5), 42.1 (C-7), 56.1 (NCH_2Ph), 61.6 (C-7a), 65.5 (C-2), 66.1 (OCH_2Ph), 127.1 (Ph), 127.9 (Ph), 128.0 (Ph), 128.4 (Ph), 128.7 (Ph), 129.4 (Ph), 135.6 (Ph), 136.6 (Ph), 173.1 (CO_2Bn), 211.4 (C═O); IR (KBr) 2945, 1712, 1494, 1456, 1193 cm^{-1}; MS (ESI-TOF) m/z 364 $[M + H]^+$.

Isomerization of 8 to 9. Exo isomer **8** (190 mg, 0.52 mmol) was treated with 4 M HCl in dioxane at 65 °C for 23 h. The reaction mixture was cooled to room temperature and poured into water, then the mixture was neutralized with $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1−2/1) to afford **8** (82 mg, 43%) and **9** (60 mg, 32%).

Allyl (2*S*,3a*S*,7a*S*)-1-*tert*-butoxycarbonyl-6-oxooctahydroindole-2-carboxylate (10). A solution of endo isomer (2*S*,3a*S*,7a*S*)-1-benzyl-6-oxooctahydroindole-2-carboxylate (**9**) (469 mg, 1.29 mmol) and Boc_2O (0.758 mL, 3.30 mmol) in EtOH (2.6 mL) was treated with 20% $Pd(OH)_2$−carbon (80.0 mg) under a hydrogen atmosphere (balloon) for 24 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc/HCO_2H = 30/15/1−20/20/1) to afford (2*S*,3a*S*,7a*S*)-1-*tert*-butoxycarbonyl-6-oxo-octahydroindole-2-carboxylic acid (211 mg, 58%). $[\alpha]^{23}_D$ +21 (c = 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (9H, s; Boc), 1.88 (2H, m), 2.14−2.32 (2H, m), 2.37−2.52 (2H, m), 2.52−2.63 (2H, m), 2.79−2.88 (1H, m), 4.12−4.47 (2H, m); IR (KBr) 2974, 1691, 1397, 1162 cm^{-1}; MS (ESI-TOF) m/z 284 $[M + H]^+$.

To a solution of the carboxylic acid (564 mg, 2.00 mmol) in DMF (10 mL) was added Cs_2CO_3 (391 mg, 1.20 mmol) at room temperature. After stirring for 1 h, allyl bromide (0.260 mL, 3.00 mmol) was added, and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1−3/2) to afford **10** (640 mg, 99%). $[\alpha]^{21}_D$ +18.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, cis−trans rotamer mixture) δ: 1.40−1.46 (9H, m; Boc), 1.84−1.97 (1H, m; H-4), 2.00−2.08 (2H, m; H-3, H-4), 2.15−2.22 (1H, m; H-5), 2.35−2.51 (2H, m; H-3, H-5′), 2.53−2.74 (2H, m; H-3a, H-7), 2.85−3.30 (1H, m; H-7′), 4.12−4.30 (1H, m; H-7a), 4.57−4.74 (2H, m; OCH_2CH═CH_2), 5.26 (1H, brs; OCH_2-CH═CH_2), 5.35 (1H, d, J = 17.4 Hz; OCH_2CH═CH_2), 5.87−5.97 (1H, m; OCH_2CH═CH_2). ^{13}C NMR (100 MHz,

$CDCl_3$, cis−trans rotamer mixture) δ: 24.4 (C-4), 24.5 (C-4), 28.2 (Boc), 28.3 (Boc), 33.1 (C-3), 34.2 (C-3), 35.5 (C-3a), 36.5 (C-5), 36.6 (C-5), 43.0 (C-7), 43.9 (C-7), 57.3 (C-7a), 57.4 (C-7a), 59.4 (C-2), 59.8 (C-2), 65.8 (OCH_2-$CH{=}CH_2$), 80.5 ($OCMe_3$), 118.4 ($OCH_2CH{=}CH_2$), 118.9 ($OCH_2CH{=}CH_2$), 131.6 ($OCH_2CH{=}CH_2$), 131.7 ($OCH_2CH{=}CH_2$), 152.9 (OCON), 153.4 (OCON), 172.7 (CO_2Allyl), 209.6 (C=O), 210.1 (C=O); IR (neat) 2977, 1748, 1695, 1394, 1183 cm^{-1}; MS (ESI-TOF) *m*/*z* 324 $[M + H]^+$.

Allyl (2*S*,3a*S*,6*R*,7a*S*)-1-*tert*-butoxycarbonyl-6-hydroxyoctahydroindole-2-carboxylate (Boc-L-Choi-OAllyl) (2a). To a solution of **10** (565 mg, 1.75 mmol) in THF (9 mL) was added LS-Selectride (1.0 M in THF, 2.1 mL, 2.1 mmol) at −78 °C. After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to room temperature, then it was cooled to −78 °C and quenched with AcOH (4.5 mL) at the same temperature. The mixture solution was warmed to room temperature again. EtOAc was added, and the organic layer was washed with 1 M HCl, aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1−1/1) to afford **2a** (396 mg, 70%). $[\alpha]^{24}_D$ −34.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, cis−trans rotamer mixture) δ: 1.35−1.75 (13H, m; Boc, H-4, H-5, H-5′, H-7), 1.88−2.03 (1H, m; H-3), 2.07−2.32 (3H, m; H-3′, H-4′, H-7′), 2.32−2.42 (1H, m; H-3a), 4.14 (1H, brs; H-6), 4.17−4.35 (2H, m; H-7a, H-2), 4.55−4.74 (2H, m; $OCH_2CH{=}CH_2$), 5.20−5.29 (1H, m; $OCH_2CH{=}CH_2$), 5.34 (1H, d, *J* = 16.9 Hz; $OCH_2CH{=}CH_2$), 5.86−5.98 (1H, m; $OCH_2CH{=}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, cis−trans rotamer mixture) δ: 19.5 (C-4), 26.4 (C-5), 26.6 (C-5), 28.3 (Boc), 31.6 (C-3), 32.6 (C-3), 33.7 (C-7), 35.8 (C-3a), 36.4 (C-3a), 53.6 (C-7a), 53.7 (C-7a), 59.0 (C-2), 59.4 (C-2), 65.5 ($OCH_2CH{=}CH_2$), 65.9 (C-6), 66.1 (C-6), 79.7 ($OCMe_3$), 79.9 ($OCMe_3$), 118.0 ($OCH_2CH{=}CH_2$), 118.6 ($OCH_2CH{=}CH_2$), 131.8 ($OCH_2CH{=}CH_2$), 132.0 ($OCH_2CH{=}CH_2$), 153.3 (OCON), 154.0 (OCON), 173.0 (CO_2Allyl), 173.3 (CO_2Allyl); IR (neat) 3446, 2934, 1748, 1694, 1404, 1178, 1014 cm^{-1}; MS (ESI-TOF) *m*/*z* 326 $[M + H]^+$.

Preparation of Resin-Bound Boc-L-Choi-OAllyl 2b. The PS-DES resin (690 mg, 1.00 mmol, 1% cross-linked poly(styrene-*co*-divinylbenzene), 1.45 mmol/g) was treated with a solution of 1,3-dichloro-5,5-dimethylhydantoin (788 mg, 4.00 mmol) in CH_2Cl_2 (10 mL) at room temperature and gently agitated for 1 h. After filtration, the resin **11** was washed three times with CH_2Cl_2 (1 min per wash), then the resin was treated with a solution of Boc-L-Choi-OAllyl (**2a**) (650 mg, 2.00 mmol) and imidazole (272 mg, 4.00 mmol) in CH_2Cl_2 (10 mL) at room temperature and gently agitated at the same temperature for 14 h. After filtration, the resin was washed three times with CH_2Cl_2 (1 min per wash), twice with THF−H_2O (3/1), twice with MeOH, twice with DMF, and three times with CH_2Cl_2 and dried under vacuum to afford **2b** (910 mg, 0.79 mmol/g). The loading value was determined by weight of the cleaved compound (H-L-Choi-OAllyl) with a cleavage solution (TFA/H_2O/CH_2Cl_2 = 10:1:9).

General Procedure for Removal of Boc Group of Resin-Bound 3 and Coupling Reactions with Unit B. Resin-Bound Fmoc-D-Leu-L-Choi-OAllyl 12. Resin-bound Boc-L-Choi-OAllyl **2b** (20 mg, 16 μmol) was treated with a Boc deprotection solution (1 M of TMSOTf and 1.5 M of 2,6-lutidine in CH_2Cl_2, 2 mL) at room temperature and gently agitated at the same temperature for 1 h. After filtration, the resin was washed twice with CH_2Cl_2, three times with MeOH, three times with DMF, and three times with CH_2Cl_2 to afford resin-bound H-L-Choi-OAllyl. Resin-bound H-L-Choi-OAllyl was treated with a solution of Fmoc-D-Leu-OH (**B1**) (353 mg, 1.00 mmol), DIC (0.157 mL, 1.00 mmol), and HOBt (135 mg, 1.00 mmol) in DMF−CH_2Cl_2 (2 mL, DMF−CH_2Cl_2 = 1:4) at room temperature and gently agitated at the same temperature for 14 h. After filtration, the resin was washed four times with DMF and four times with CH_2Cl_2, then the resin was reacted under the same coupling conditions as described above. After filtration, the resin was washed four times with DMF and four times with CH_2Cl_2 to afford **12**. DMF/CH_2Cl_2 = 1:1 was used for the coupling reaction of Fmoc-L-Phe-OH (**B3**).

General Procedure for Removal of Allyl Ester and Coupling Reactions with Unit C. Resin-Bound Fmoc-D-Leu-L-Choi-L-Argol(ω,ω′-di-Boc)(*O*-TBS) 13. Resin-bound Fmoc-D-Leu-L-Choi-OAllyl **12** (20 mg, 16 μmol) was treated with an allyl ester deprotection solution (0.01 M of $Pd(PPh_3)_4$ and 0.1 M of dimedone in degassed THF, 2 mL) at room temperature and gently agitated at the same temperature for 14 h. After filtration, the resin was washed four times with THF, four times with DMF, and four times with CH_2Cl_2.

Resin-bound Fmoc-D-Leu-L-Choi-OH (16 μmol) was treated with a solution of (*S*)-*N*-ω,ω′-(di-*tert*-butoxycarbonyl)argininol *tert*-butyldimethylsilyl ether (**C1**) (47 mg, 0.10 mmol), DIC (0.031 mL, 0.20 mmol), and HOBt (27 mg, 0.20 mmol) in DMF−CH_2Cl_2 (2 mL, DMF/CH_2Cl_2 = 1:4) at room temperature and gently agitated at the same temperature for 14 h. After filtration, the resin was washed four times with DMF and four times with CH_2Cl_2 to afford **13**.

General Procedures for Removal of Fmoc Group and Coupling Reactions with Unit A. Resin-Bound D-Hpla-(*O*-di-TBS)-D-Leu-L-Choi-L-Argol(ω,ω′-di-Boc)(*O*-TBS) 14. Resin-bound Fmoc-D-Leu-L-Choi-L-Argol(ω,ω′-di-Boc)(*O*-TBS) **13** was treated with piperidine/DMF (2 mL, piperidine/DMF = 1:4) at room temperature and gently agitated at the same temperature for 1 h. After filtration, the resin was washed four times with DMF and four times with CH_2Cl_2.

Resin-bound D-Leu-L-Choi-L-Argol(ω,ω′-di-Boc)(*O*-TBS) (16 μmol) was treated with a solution of (2*R*)-2-(*tert*-butyldimethylsilyloxy)-3-[(4-*tert*-butyldimethylsilyloxy)phenyl]propionic acid (**A1**) (41 mg, 0.10 mmol), DIC (0.016 mL, 0.10 mmol), and HOBt (14 mg, 0.10 mmol) in DMF−CH_2Cl_2 (2 mL, DMF−CH_2Cl_2 = 1:4) at room temperature and gently agitated at the same temperature for 14 h. After filtration, the resin was washed four times with DMF and four times with CH_2Cl_2 to afford **14**.

General Procedures for Cleavage from Polymer Support and Removal of the Acid-Labile Protecting Groups. Synthesis of Aeruginosin 298-A Hydrochloride. Resin-bound D-Hpla(*O*-di-TBS)-D-Leu-L-Choi-L-Argol(ω,ω′-di-

Boc)(*O*-TBS) (16 μmol) **14** was treated with the cleavage solution (TFA/H_2O/CH_2Cl_2 = 10:1:9, 2 mL) at room temperature and gently agitated at the same temperature for 1 h. After filtration, the solution was concentrated under vacuum. The residue was dissolved in MeOH−CH_2Cl_2 (2 mL, MeOH−CH_2Cl_2 = 1:1). PS−NMM (1.9 mmol/g, 1% cross-linked poly(styrene-*co*-divinylbenzene), 0.10 g, 0.19 mmol) was added to the solution at room temperature and gently agitated at the same temperature for 2 h. After filtration, the solution was concentrated under vacuum to afford crude aeruginosin 298-A TFA salt (14 mg, HPLC purity (214 nm) 92%).

The crude aeruginosin 298-A TFA salt (16 mg) was purified by preparative HPLC as described in general procedure to give aeruginosin 298-A formic acid salt. After addtion of 0.1 M HCl (1 mL), the solution was concentrated under vacuum to afford aeruginosin 298-A hydrochloride (8.3 mg, 72% based on the loading). t_R 3.95 min; $[\alpha]^{28}_D$ +6.6 (c = 0.29, H_2O) [lit[20b] $[\alpha]_D$ −72.7 (c = 0.23, H_2O), lit[21] $[\alpha]_D$ +16 (c = 0.17, H_2O), lit[22a] $[\alpha]^{23}_D$ −34 (c = 0.13, H_2O)]. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (6:1)) δ: 0.82 (3H, d, J = 6.3 Hz; Leu-5), 0.88 (3H, d, J = 5.8 Hz; Leu-5′), 1.17−1.62 (10H, m; Choi-4, Choi-4′, Choi-5, Leu-3, Leu-3′, Leu-4, Arg-3, Arg-3′, Arg-4, Arg-4′), 1.67 (1H, t, J = 12.6 Hz; Choi-7), 1.76−1.86 (1H, m; Choi-3), 1.95−2.11 (3H, m; Choi-3′, Choi-5′, Choi-7′), 2.23−2.34 (1H, m; Choi-3a), 2.65 (1H, dd, J = 7.5, 13.8 Hz; Hpla-3), 2.86 (1H, brd, J = 13.5 Hz; Hpla-3′), 3.02−3.15 (2H, m; Arg-5, Arg-5′), 3.18−3.27 (1H, m; Arg-1), 3.27−3.36 (1H, m; Arg-1′), 3.58−3.68 (1H, m; Arg-2), 3.93 (1H, brs; Choi-6), 4.00−4.11 (2H, m; Choi-7a, Hpla-2), 4.18 (1H, t, J = 8.9 Hz; Choi-2), 4.48−4.58 (2H, m; Leu-2, Choi-6-OH), 4.62−4.71 (1H, brd, J = 4.3 Hz; Arg-1-OH), 5.73 (1H, brs; Hpla-2-OH), 6.64 (2H, d, J = 8.2 Hz; Hpla-6, Hpla-8), 6.99 (2H, d, J = 8.2 Hz; Hpla-5, Hpla-9), 7.47 (1H, d, J = 8.2 Hz; Leu-NH), 7.50−7.53 (1H, m; Arg-5-NH), 7.58−7.71 (2H, m; Arg-2-NH), 9.15 (1H, brs; Hpla-7-OH). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) δ: 19.1 (Choi-4), 21.5 (Leu-5), 23.5 (Leu-5′), 24.0 (Leu-4), 25.1 (Arg-4), 26.1 (Choi-5), 28.0 (Arg-3), 30.6 (Choi-3), 33.5 (Choi-7), 36.1 (Choi-3a), 39.4 (Hpla-3), 40.8 (Arg-5), 42.0 (Leu-3), 48.1 (Leu-2), 50.3 (Arg-2), 54.1 (Choi-7a), 59.9 (Choi-2), 63.3 (Arg-1), 63.9 (Choi-6), 72.2 (Hpla-2), 114.7 (Hpla-6, Hpla-8), 128.2 (Hpla-4), 130.5 (Hpla-5, Hpla-9), 155.8 (Hpla-7), 156.9 (Arg-N=C), 169.8 (Leu-1), 171.3 (Choi-1), 172.8 (Hpla-1); IR (KBr) 3252, 2954, 1613, 1446, 1228 cm^{-1}; HRMS (ESI-TOF) calcd for **1a** $[C_{30}H_{48}N_6O_7 + H]^+$ 605.3663, found m/z 605.3643.

Microcin SF608 (1b)[17,18] Hydrochloride. The crude microcin SF608 was synthesized and purified in the same manner as aeruginosin 298-A. Crude microcin SF608 (24 mg) was purified by reversed-phase column chromatography to afford microcin SF608 hydrochloride (13 mg, 82%). t_R 4.14 min; $[\alpha]^{28}_D$ −23 (c = 0.65, MeOH) [lit[17] $[\alpha]^{25}_D$ −19.1 (c = 1.0, MeOH), lit[18] $[\alpha]_D$ −27.4 (c = 1.25, MeOH)]. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.32−1.54 (7H, m; Choi-4, Choi-4′, Choi-5, Agm-2, Agm-2′, Agm-3, Agm-3′), 1.70 (1H, d, J = 8.7 Hz; Choi-7), 1.78−1.89 (1H, m; Choi-3), 1.91−2.08 (3H, m; Choi-3′, Choi-5′, Choi-7′), 2.15−2.25 (1H, m; Choi-3a), 2.44 (1H, dd, J = 8.5, 13.8 Hz; Hpla-3), 2.67−2.74 (1H, m; Hpla-3′), 2.76−2.85 (1H, m; Phe-3), 2.86−2.93 (1H, m; Phe-3′), 3.04−3.19 (4H, m; Agm-1, Agm-1′, Agm-4, Agm-4′), 3.88 (1H, brs; Choi-6), 3.92 (1H, dd, J = 3.9, 8.2 Hz; Hpla-2), 4.26 (1H, dd, J = 8.2, 9.7 Hz; Choi-2), 4.39−4.47 (1H, m; Choi-7a), 4.66−4.73 (1H, m; Phe-2), 6.64 (2H, d, J = 8.7 Hz; Hpla-6, Hpla-8), 6.92 (2H, d, J = 8.2 Hz; Hpla-5, Hpla-9), 7.16−7.29 (5H, m; Phe-5, Phe-6, Phe-7, Phe-8, Phe-9), 7.64 (1H, d, J = 8.2 Hz; Phe-NH), 7.80 (1H, brt, J = 5.6 Hz; Agm-4-NH), 7.93−7.97 (1H, m; Agm-1-NH). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) δ: 19.1 (Choi-5), 25.9 (Agm-2), 26.2 (Choi-4), 26.3 (Agm-3), 30.5 (Choi-3), 30.9 (Hpla-3), 34.3 (Choi-7), 36.5 (Choi-3a), 38.0 (Agm-1), 38.2 (Phe-3), 40.5 (Agm-4), 50.6 (Phe-2), 54.6 (Choi-7a), 59.9 (Choi-2), 64.1 (Choi-6), 72.3 (Hpla-2), 114.8 (Hpla-6, Hpla-8), 126.5 (Phe-7), 128.2 (Phe-6, Phe-8), 128.4 (Hpla-4), 129.6 (Phe-5, Phe-9), 130.4 (Hpla-5, Hpla-9), 137.1 (Phe-4), 155.8 (Hpla-7), 157.1 (Agm-5), 169.6 (Phe-1), 171.3 (Choi-1), 172.9 (Hpla-1); IR (neat) 3334, 1652, 1237 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{32}H_{45}N_6O_6 + H]^+$ 609.3401, found m/z 609.3397.

L-Hpla-D-Leu-L-Choi-L-Argol (1c). t_R 3.77 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (5:1)) δ: 0.86 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 8.5 Hz), 1.22−1.63 (10H, m), 1.67 (1H, d, J = 12.4 Hz), 1.79−1.90 (1H, m), 1.95−2.13 (3H, m), 2.23−2.35 (1H, m), 2.47−2.58 (1H, m), 2.85 (1H, dd, J = 3.7, 14.0 Hz), 3.01−3.16 (2H, m), 3.21−3.40 (2H, m), 3.60−3.73 (1H, m), 3.93 (1H, brs), 4.00−4.11 (2H, m), 4.20 (1H, t, J = 9.0 Hz), 4.45−4.56 (2H, m), 4.66 (1H, t, J = 5.2 Hz), 5.53 (1H, d, J = 6.3 Hz), 6.65 (2H, d, J = 8.2 Hz), 7.00 (2H, d, J = 8.1 Hz), 7.48 (1H, brs), 7.57 (1H, d, J = 8.5 Hz), 7.81 (1H, d, J = 7.8 Hz), 9.13 (1H, s); MS (ESI-TOF) m/z 605 $[M + H]^+$.

D-Hpla-D-Leu-L-Choi-L-Argal (1d). t_R 4.00 (hydrate) and 4.13 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 0.81 (3H, d, J = 6.1 Hz), 0.88 (3H, d, J = 4.5 Hz), 1.13−1.19 (12H, m), 1.93−2.14 (3H, m), 2.18−2.37 (1H, m), 2.60−2.70 (1H, m), 2.79−2.90 (1H, m), 2.98−314 (1H, m), 3.20−3.49 (2H, m), 3.93 (1H, brs), 3.97−4.13 (2H, m), 4.18−4.33 (1H, m), 4.46−4.66 (2H, m), 5.75 (1H, s), 6.62 (2H, d, J = 8.1 Hz), 6.98 (2H, d, J = 8.0 Hz), 7.26−7.60 (2H, m), 9.11 (1H, brs); MS (ESI-TOF) m/z 603 $[M + H]^+$.

L-Hpla-D-Leu-L-Choi-L-Argal (1e). t_R 3.82 (hydrate) and 4.08 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 0.81−0.95 (6H, m), 1.20−1.93 (12H, m), 1.94−2.15 (3H, m), 2.20−2.37 (1H, m), 2.54−2.68 (1H, m), 2.81−2.92 (1H, m), 2.97−315 (1H, m), 3.22−3.52 (2H, m), 3.93 (1H, brs), 3.97−4.14 (2H, m), 4.20−4.35 (1H, m), 4.46−4.67 (2H, m), 5.42−5.53 (1H, s), 6.65 (2H, d, J = 6.8 Hz), 7.00 (2H, d, J = 7.8 Hz), 7.39−7.70 (2H, m), 9.13 (1H, brs); MS (ESI-TOF) m/z 603 $[M + H]^+$.

D-Hpla-D-Leu-L-Choi-L-Arg-OH (1f). t_R 4.15 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (4:1)) δ: 0.82 (3H, d, J = 6.0 Hz), 0.87 (3H, d, J = 5.8 Hz), 1.16−1.70 (11H, m), 1.72−1.91 (1H, m), 1.95−2.12 (3H, m), 2.20−2.35 (1H, m), 2.64 (1H, dd, J = 7.2, 13.7 Hz), 2.76−2.90 (1H, m), 2.98−3.11 (2H, m), 3.75−3.87 (1H, m), 3.91 (1H, brs), 3.97−4.12 (1H, m), 4.12 (1H, t, J = 8.9 Hz), 4.43−

4.58 (1H, m), 4.60−4.73 (1H, m), 6.63 (2H, d, J = 8.2 Hz), 6.99 (2H, d, J = 8.0 Hz), 7.14−7.57 (5H, m), 9.12 (1H, brs); MS (ESI-TOF) m/z 619 $[M + H]^+$.

L-Hpla-D-Leu-L-Choi-L-Arg-OH (1g). t_R 3.99 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (2:1)) δ: 0.85 (3H, d, J = 6.3 Hz), 0.89 (3H, d, J = 6.1 Hz), 1.23−1.72 (11H, m), 1.77−1.89 (1H, m), 1.97−2.10 (3H, m), 2.21−2.34 (1H, m), 2.54−2.64 (1H, m), 2.82−2.90 (1H, m), 2.97−3.12 (2H, m), 3.80−3.95 (1H, m), 3.92 (1H, brs), 3.98−4.16 (1H, m), 4.24 (1H, t, J = 8.8 Hz), 4.42−4.56 (1H, m), 4.60−4.75 (1H, m), 5.80 (1H, brs), 6.64 (2H, d, J = 8.2 Hz), 7.00 (2H, d, J = 8.4 Hz), 7.37 (2H, brs), 7.43−7.57 (2H, m), 7.59−7.67 (1H, m), 9.14 (1H, brs); MS (ESI-TOF) m/z 619 $[M + H]^+$.

D-Hpla-D-Leu-L-Choi-Agma (1h). t_R 4.06 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (3:1)) δ: 0.82 (3H, d, J = 6.4 Hz), 0.88 (3H, d, J = 6.3 Hz), 1.16−1.52 (10H, m), 1.69 (1H, m), 1.80 (1H, m), 1.94−2.11 (3H, m), 2.23−2.34 (1H, m), 2.65 (1H, dd, J = 7.4, 14.0 Hz), 2.78−2.89 (1H, m), 2.95−3.12 (4H, m), 3.93 (1H, brs), 3.99−4.08 (2H, m), 4.13 (1H, t, J = 8.9 Hz), 4.46−4.58 (2H, m), 5.73 (1H, brs), 6.63 (2H, d, J = 8.5 Hz), 6.99 (2H, d, J = 8.5 Hz), 7.35−7.43 (1H, m), 7.47−7.64 (1H, m), 7.83 (1H, t, J = 5.6 Hz), 9.10 (1H, brs); MS (ESI-TOF) m/z 575 $[M + H]^+$.

L-Hpla-D-Leu-L-Choi-Agma (1i). t_R 3.92 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (3:1)) δ: 0.86 (3H, d, J = 6.4 Hz), 0.90 (3H, d, J = 6.4 Hz), 1.18−1.54 (10H, m), 1.68 (1H, m), 1.75−1.88 (1H, m), 1.95−2.14 (3H, m), 2.23−2.34 (1H, m), 2.55−2.64 (1H, m), 2.83−2.90 (1H, m), 3.02−3.13 (4H, m), 3.94 (1H, brs), 4.00−4.10 (2H, m), 4.16 (1H, t, J = 8.9 Hz), 4.45−4.58 (2H, m), 6.65 (2H, d, J = 8.5 Hz), 7.00 (2H, d, J = 8.5 Hz), 7.64−7.82 (2H, m); MS (ESI-TOF) m/z 575 $[M + H]^+$.

D-Hpla-D-Tyr-L-Choi-L-Argol (1j). t_R 1.68 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.12−1.97 (13H, m), 2.53−2.65 (2H, m), 2.70−2.78 (1H, m), 2.84 (1H, dd, J = 3.1, 13.9 Hz), 3.03−3.12 (2H, m), 3.16−3.27 (2H, m), 3.58−3.72 (2H, m), 3.85 (1H, brs), 4.01 (1H, dd, J = 3.4, 8.0 Hz), 4.07 (1H, t, J = 8.8 Hz), 4.47 (1H, brs), 4.62 (1H, t, J = 7.1 Hz), 6.65 (2H, d, J = 8.4 Hz), 6.66 (2H, d, J = 8.5 Hz), 6.87 (2H, d, J = 8.5 Hz), 6.99 (2H, d, J = 8.5 Hz), 7.39−7.71 (2H, m); MS (ESI-TOF) m/z 655 $[M + H]^+$.

L-Hpla-D-Tyr-L-Choi-L-Argol (1k). t_R 1.42 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.12−2.23 (13H, m), 2.43−2.70 (2H, m), 2.72−2.79 (1H, m), 2.83 (1H, dd, J = 3.3, 14.0 Hz), 3.01−3.15 (2H, m), 3.18−3.42 (2H, m), 3.60−3.78 (2H, m), 3.86 (1H, brs), 4.01 (1H, dd, J = 3.4, 9.3 Hz), 4.10 (1H, t, J = 8.8 Hz), 4.47 (1H, brs), 4.60 (1H, t, J = 7.3 Hz), 6.65 (2H, d, J = 8.4 Hz), 6.66 (2H, d, J = 8.2 Hz), 6.95 (2H, d, J = 8.5 Hz), 6.99 (2H, d, J = 8.5 Hz), 7.53 (1H, d, J = 8.6 Hz); MS (ESI-TOF) m/z 655 $[M + H]^+$.

D-Hpla-D-Tyr-L-Choi-L-Argal (1l). t_R 3.70 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.21−2.05 (13H, m), 2.15−2.35 (1H, m), 2.53−2.64 (1H, m), 2.65−2.75 (1H, m), 2.77−2.87 (1H, m), 2.96−3.46 (3H, m), 3.57−3.73 (1H, m), 3.85 (1H, brs), 3.94−4.05 (1H, m), 4.10−4.20 (1H, m), 4.45−4.56 (1H, m), 4.58−4.73 (1H, m), 5.69−5.80 (1H, m), 6.55−6.70 (4H, m), 6.84 (2H, d, J = 8.1 Hz), 6.99 (2H, d, J = 8.2 Hz), 7.30−7.78 (3H, m), 9.10−9.22 (1H, m), 9.26−9.35 (1H, m); MS (ESI-TOF) m/z 653 $[M + H]^+$.

L-Hpla-D-Tyr-L-Choi-L-Argal (1m). t_R 3.70 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.20−2.04 (13H, m), 2.19−2.34 (1H, m), 2.40−2.53 (1H, m), 2.60−2.88 (2H, m), 2.97−3.45 (3H, m), 3.60−3.72 (1H, m), 3.86 (1H, brs), 3.96−4.03 (1H, m), 4.17 (1H, t, J = 8.9 Hz), 4.43−4.53 (1H, m), 4.60−4.72 (1H, m), 6.61−6.68 (2H, m), 6.67 (2H, d, J = 8.4 Hz), 6.94 (2H, d, J = 8.5 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.33−8.08 (3H, m), 9.12 (1H, brs); MS (ESI-TOF) m/z 653 $[M + H]^+$.

D-Hpla-D-Tyr-L-Choi-L-Arg-OH (1n). t_R 3.74 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.20−2.00 (13H, m), 2.31−2.47 (1H, m), 2.56−2.69 (2H, m), 2.79 (1H, dd, J = 2.7, 13.7 Hz), 2.98−3.10 (2H, m), 3.72−3.79 (1H, m), 3.79−3.92 (1H, m), 3.94−4.02 (1H, m), 4.07−4.17 (1H, m), 4.45−4.51 (1H, m), 4.73 (1H, dd, J = 7.7, 15.3 Hz), 6.64 (2H, d, J = 8.2 Hz), 6.65 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.18−7.45 (5H, m), 9.14 (1H, brs), 9.26 (1H, brs); MS (ESI-TOF) m/z 669 $[M + H]^+$.

L-Hpla-D-Tyr-L-Choi-L-Arg-OH (1o). t_R 3.44 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.25−2.16 (13H, m), 2.31−2.43 (1H, m), 2.65−2.78 (2H, m), 2.82 (1H, dd, J = 3.3, 14.1 Hz), 3.06−3.15 (2H, m), 3.64−3.76 (1H, m), 3.85 (1H, brs), 3.95−4.04 (1H, m), 4.10−4.21 (1H, m), 4.41−4.53 (1H, m), 4.67 (1H, dd, J = 7.6, 14.7 Hz), 5.45−5.61 (1H, m), 6.61−6.69 (4H, m), 6.94 (2H, d, J = 8.5 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.53−7.63 (1H, m), 7.69 (1H, d, J = 7.9 Hz), 8.14 (1H, d, J = 7.7 Hz), 9.13 (1H, brs), 9.29 (1H, brs); MS (ESI-TOF) m/z 669 $[M + H]^+$.

D-Hpla-D-Tyr-L-Choi-Agma (1p). t_R 3.71 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.20−1.95 (13H, m), 2.53−2.64 (2H, m), 2.66−2.75 (1H, m), 2.83 (1H, dd, J = 3.1, 13.9 Hz), 2.94−3.14 (4H, m), 3.60−3.71 (1H, m), 3.85 (1H, brs), 3.96−4.08 (2H, m), 4.47 (1H, brs), 4.63 (1H, dd, J = 7.8, 14.1 Hz), 5.72 (1H, brs), 6.64 (2H, d, J = 8.5 Hz), 6.65 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.4 Hz), 6.99 (2H, d, J = 8.4 Hz), 7.48 (1H, d, J = 7.7 Hz), 7.53−7.64 (1H, m), 7.81 (1H, d, J = 5.6 Hz), 9.14 (1H, brs), 9.28 (1H, brs); MS (ESI-TOF) m/z 625 $[M + H]^+$.

L-Hpla-D-Tyr-L-Choi-Agma (1q). t_R 3.50 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.21−2.02 (13H, m), 2.31−2.43 (1H, m), 2.65−2.74 (1H, m), 2.75−2.87 (2H, m), 2.96−3.15 (4H, m), 3.60−3.72 (1H, m), 3.86 (1H, brs), 3.95−4.03 (1H, m), 4.06 (1H, t, J = 8.6 Hz), 4.46 (1H, brs), 4.59 (1H, dd, J = 7.1, 14.3 Hz), 5.52 (1H, brs), 6.65 (2H, d, J = 8.2 Hz), 6.66 (2H, d, J = 8.1 Hz), 6.94 (2H, d, J = 8.4 Hz), 6.99 (2H, d, J = 8.5 Hz), 7.50−7.90 (3H, m), 9.14 (1H, brs), 9.29 (1H, brs); MS (ESI-TOF) m/z 625 $[M + H]^+$.

D-Hpla-L-Phe-L-Choi-L-Argol (1r). t_R 3.85 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (2:1)) δ: 1.28−1.66 (7H, m), 1.68−2.10 (5H, m), 2.17−2.28 (1H, m), 2.42 (1H, dd, J = 8.5, 13.9 Hz), 2.67 (1H, dd, J = 3.5, 13.9 Hz), 2.78−2.84 (1H, m), 2.85−2.93 (1H, m), 3.02−3.15 (2H, m), 3.20−3.45 (2H, m), 3.67−3.79 (1H, m), 3.87−3.97 (1H, m), 3.89 (1H, brs), 4.28 (1H, t, J = 8.9 Hz), 4.36−4.50 (1H, m), 4.57 (1H, brs), 4.66 (1H, dd, J = 8.6, 13.2 Hz), 4.72 (1H, brs), 5.28 (1H, brs), 6.60 (2H, d, J = 8.4 Hz), 6.88 (2H, d, J =

8.5 Hz), 7.12 (1H, d, $J = 6.6$ Hz), 7.16−7.29 (5H, m), 7.93−8.00 (1H, m), 9.08−9.16 (1H, m); MS (ESI-TOF) *m*/*z* 639 $[M + H]^+$.

L-Hpla-L-Phe-L-Choi-L-Argol (1s). t_R 3.98 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (2:1)) δ: 1.27−1.66 (7H, m), 1.68−2.10 (5H, m), 2.16−2.27 (1H, m), 2.42 (1H, dd, $J = 8.5$, 13.8 Hz), 2.64−2.73 (1H, m), 2.74−2.82 (1H, m), 2.83−2.92 (1H, m), 3.04−3.15 (2H, m), 3.22−3.55 (2H, m), 3.66−3.78 (1H, m), 3.85−3.95 (2H, m), 4.27 (1H, t, $J = 8.8$ Hz), 4.38−4.48 (1H, m), 4.71 (1H, dd, $J = 8.2$, 13.2 Hz), 6.62 (2H, d, $J = 8.4$ Hz), 6.91 (2H, d, $J = 8.4$ Hz), 6.95−6.98 (1H, m), 7.15−7.28 (5H, m), 7.46−7.61 (2H, m), 7.65−7.76 (1H, m), 7.93−8.00 (1H, m), 9.14 (1H, brs); MS (ESI-TOF) *m*/*z* 639 $[M + H]^+$.

D-Hpla-L-Phe-L-Choi-L-Argal (1t). t_R 3.83 (hydrate) and 4.12 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.18−2.11 (12H, m), 2.15−2.30 (1H, m), 2.35−2.48 (1H, m), 2.60−2.71 (1H, m), 2.75−2.81 (1H, m), 2.81−2.95 (1H, m), 2.98−3.33 (3H, m), 3.77−4.12 (3H, m), 4.18−4.56 (2H, m), 4.60−4.70 (1H, m), 6.60 (2H, d, $J = 7.2$ Hz), 6.89 (2H, d, $J = 8.2$ Hz), 7.10−7.33 (5H, m), 7.43−7.89 (3H, m), 9.13 (1H, brs); MS (ESI-TOF) *m*/*z* 637 $[M + H]^+$.

L-Hpla-L-Phe-L-Choi-L-Argal (1u). t_R 3.96 (hydrate) and 4.21 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.18−2.13 (12H, m), 2.15−2.30 (1H, m), 2.35−2.53 (1H, m), 2.58−2.75 (1H, m), 2.75−2.96 (2H, m), 2.98−3.31 (3H, m), 3.73−4.16 (3H, m), 4.20−4.53 (2H, m), 4.63−4.77 (1H, m), 6.63 (2H, d, $J = 8.2$ Hz), 6.92 (2H, d, $J = 8.4$ Hz), 6.95−7.08 (1H, m), 7.10−7.32 (5H, m), 7.37−7.80 (3H, m), 9.14 (1H, brs); MS (ESI-TOF) *m*/*z* 637 $[M + H]^+$.

D-Hpla-L-Phe-L-Choi-L-Arg-OH (1v). t_R 4.05 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (3:1)) δ: 1.31−1.73 (7H, m), 1.76−2.10 (5H, m), 2.19−2.30 (1H, m), 2.43 (1H, dd, $J = 8.4$, 13.7 Hz), 2.68 (1H, dd, $J = 3.1$, 14.0 Hz), 2.77−2.84 (1H, m), 2.85−2.93 (1H, m), 3.07−3.17 (2H, m), 3.89 (1H, brs), 3.93 (1H, dd, $J = 3.8$, 8.3 Hz), 4.20−4.30 (1H, m), 4.36 (1H, t, $J = 8.9$ Hz), 4.42−4.50 (1H, m), 4.65 (1H, dd, $J = 8.2$, 12.8 Hz), 5.29 (1H, brs), 6.60 (2H, d, $J = 8.5$ Hz), 6.89 (2H, d, $J = 8.4$ Hz), 7.13−7.30 (6H, m), 7.56−7.63 (1H, m), 7.82 (1H, d, $J = 8.0$ Hz), 8.21 (1H, d, $J = 7.7$ Hz), 9.13 (1H, brs); MS (ESI-TOF) *m*/*z* 653 $[M + H]^+$.

L-Hpla-L-Phe-L-Choi-L-Arg-OH (1w). t_R 4.18 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer) δ: 1.31−1.73 (7H, m), 1.75−2.09 (5H, m), 2.17−2.30 (1H, m), 2.42 (1H, dd, $J = 8.4$, 13.9 Hz), 2.65−2.74 (1H, m), 2.75−2.83 (1H, m), 2.84−2.92 (1H, m), 3.06−3.17 (2H, m), 3.84−3.96 (2H, m), 4.21−4.30 (1H, m), 4.36 (1H, t, $J = 8.9$ Hz), 4.44 (1H, dd, $J = 8.6$, 15.2 Hz), 4.56 (1H, brs), 4.70 (1H, dd, $J = 8.2$, 13.2 Hz), 5.52 (1H, brs), 6.63 (2H, d, $J = 8.5$ Hz), 6.91 (2H, d, $J = 8.5$ Hz), 6.96−7.04 (1H, m), 7.13−7.30 (5H, m), 7.52−7.66 (2H, m), 8.23 (1H, d, $J = 7.9$ Hz), 9.14 (1H, brs); MS (ESI-TOF) *m*/*z* 653 $[M + H]^+$.

D-Hpla-L-Phe-L-Choi-Agma (1x). t_R 4.03 min. ^{1}H NMR (400 MHz, DMSO-d_6, major rotamer (2:1)) δ: 1.27−1.58 (7H, m), 1.61−2.10 (5H, m), 2.17−2.27 (1H, m), 2.42 (1H, dd, $J = 8.6$, 13.9 Hz), 2.67 (1H, dd, $J = 3.5$, 13.9 Hz), 2.80 (1H, dd, $J = 8.8$, 13.9 Hz), 2.88−2.96 (1H, m), 3.05−3.16 (4H, m), 3.89 (1H, brs), 3.94 (1H, dd, $J = 3.6$, 8.3 Hz), 4.24 (1H, t, $J = 8.9$ Hz), 4.36−4.50 (1H, m), 4.65 (1H, dd, $J = 8.3$, 13.3 Hz), 5.28 (1H, brs), 6.60 (2H, d, $J = 8.2$ Hz), 6.89 (2H, d, $J = 8.4$ Hz), 7.13 (1H, d, $J = 6.8$ Hz), 7.17−7.30 (5H, m), 7.58−7.65 (1H, m), 7.79−7.90 (1H, m), 9.13 (1H, brs); MS (ESI-TOF) *m*/*z* 609 $[M + H]^+$.

Protease Inhibitory Assay. Protease inhibitory assay was performed according to a previous report[17] with slight modifications. In brief, trypsin was diluted to 1 mg/mL with 50 mM Tris−HCl (pH 7.8) containing 100 mM NaCl and 1 mM $CaCl_2$. A 5 mM *N*-benzoyl-D,L-arginine-*p*-nitroanilide in the buffer solution was used as substrate solution. Each of the test samples was dissolved in dimethyl sulfoxide and diluted with the same buffer solution that was used for the trypsin and substrate. A 70-μL portion of buffer solution, 10 μL of trypsin solution, and 20 μL of test solution were mixed and preincubated at 37 °C for 5 min, then 100 μL of substrate solution was added, and the mixture was incubated at 37 °C for 30 min. After incubation, the absorbance was measured at 405 nm by spectrophotometer (U-3010, Hitachi, Japan).

Acknowledgment. This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 14103013). We thank Professors Naoki Toyooka and Hideo Nemoto (University of Toyama) for fruitful discussions.

Supporting Information Available. NMR spectra of **1a**−**1x**. This material is available free of charge via Internet at http://pubs.acs.org.

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CC0600270