Supporting Information

Enantioselective Syntheses of Aeruginosin 298-A and its Analogs Using Catalytic Asymmetric Phase-Transfer Reaction and Epoxidation

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General: All reactions were carried out under an argon atmosphere with dry solvents, unless otherwise stated. Reagents were purified by the usual methods. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merk silica gel plates (60F-254). Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^1H NMR and 125.65 MHz for ^{13}C NMR and calibrated using residual undeuterated solvent as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on a Waters micromass ZQ with Waters 2695 Separation Module (for LC-MS). HR-MS spectra were measured on a JEOL JMS-MS700V in positive ion mode.

1. Catalytic Asymmetric Phase-Transfer Alkylation

1.1. Preparation of the Phase-Transfer Catalyst 2

For details, see Experimental Section.

1.2. Substrate Generality

For the reaction procedure, see Experimental Section.

2. Recovery and Reuse of the Phase-Transfer Catalyst

After the reaction completed, the reaction was quenched by the addition of water and diluted with diethyl ether. The phase-transfer catalyst was deposited as a white solid between organic layer and aqueous layer. After stirring vigorously, the white solid was stuck inside the glass wall. Organic layer, which contained the product, and aqueous layer were transferred into separation funnel by simple decantation. The residual solid was dissolved with 30% MeOH in CH_2Cl_2 and filtered through paper filter to remove inorganic salts. The catalyst was obtained as a white powder after evaporation of the solvent (ca.90% yield for **2a** (X=I) and ca. 80% yield for **2c** (X= BF_4)), which was used for the next phase-transfer alkylation without further purification.

Table.

Entry	Catalyst	Electrophile	Counter anion of recovered catalyst	Observed ESI(+)-MS
1	2a (X=I)	ArCH ₂ I	2 I ⁻	989, 839, 591
2	2a (X=I)	ArCH ₂ Br	2 I ⁻	989, 839, 591
3	2c (X=BF ₄)	ArCH ₂ I	2 I ⁻	989, 839, 591
4	2c (X=BF ₄)	ArCH ₂ Br	BF ₄ ⁻ and (BF ₄ ⁻ or Br ⁻)	799, 591

Observed ESI(+)-Mass of **2a** (X=I): 989, 839, 591

Observed ESI(+)-Mass of **2c** (X=BF₄): 909, 799, 591

Catalytic Asymmetric Phase-Transfer Alkylation Using Recovered Catalyst

3. Counter Anion Effects in Catalytic Asymmetric Michael Reaction

Counter anion effects in Catalytic asymmetric Michael reaction was investigated using screening conditions shown below.

Table. Counter Anion Effects

Entry	Counter Anion: X ⁻	Time (h)	Yield (%)	Ee (%)
1	I ⁻ (2b)	10	84	57
2	BF ₄ ⁻ (2d)	0.5	85	69
3	ClO ₄ ⁻	1	89	68
4	TfO ⁻	1	87	54
5	PF ₆ ⁻	1	85	52
6	SbF ₆ ⁻	3.5	43	43

4. Synthesis of the D-Leu Portion

5. Synthesis of the L-Argol Portion

5.1. Synthesis of **10** using Catalytic Asymmetric Michael Reaction

5.2. Synthesis of the Quaternary α-Amino Ester **11b**

6. Synthesis of the Left Dipeptide (Hpla-Leu Portion)

7. Synthesis of the Right Dipeptide (Choi-Arg Portion)

8. Synthesis of the Tetrapeptide (Aeruginosin 298-A and its Analogs)

9. Experimental Section

All ^1H and ^{13}C NMR data for the new compounds were assigned by DEPT, COSY and HMQC experiments. ^1H and ^{13}C and NMR spectra were attached to this Supporting Information.

9.1. Synthesis of Phase-Transfer Catalyst 2 (General Procedure)

Synthesis of (4*S*,5*S*)-2-*tert*-butyl-2-methyl-1,3-dioxolane-4,5-dicarboxamide (24a). A mixture of 3,3-dimethyl-2-butanone (12.5 mL, 0.10 mol), methyl orthoformate (16.4 mL, 0.15 mol), *p*-toluenesulfonic acid monohydrate (95 mg, 5 mmol), and methanol (50 mL) was gently heated while methylformate formed in the reaction was distilled off through a short Vigreux column. To the cooled reaction mixture, diethyl L-tartrate (13.7 mL, 0.08 mol) and toluene (30 mL) was added and brought to reflux for 24 h. The cooled reaction mixture was basified by the addition of potassium carbonate (5 g) and stirred at room temperature for 1 h. After evaporation of reaction mixture, the residue was purified by flush column chromatography (silica gel, 20% EtOAc in hexane) to afford a mixture of methyl and ethyl ester, which was used for the next reaction without further purification.

A solution of the esters (17.5 g) in methanol (100 mL) was cooled to 4 °C and then NH_3 gas was introduced by bubbling. Bubbling was continued for 2 h and then solvent was evaporated to give crude **24a**, which was further purified by recrystallization from methanol (11.2 g, 0.049 mol, 61% from diethyl L-tartrate) as a white crystal. mp 235-238 °C; $[\alpha]_{\text{D}}^{23} +2.7$ (*c* 1.02, CH_3OH); FT-IR (KBr) ν_{max} 3460, 3295, 2979, 1665, 1087 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.52 (br-s, 2 H; CONH_2), 7.43 (br-s 2 H; CONH_2), 4.46 (d, $J = 8.0$ Hz, 1 H; OCH), 4.18 (d, $J = 8.0$ Hz, 1H; OCH), 1.28 (s, 3 H; Me), 0.96 (s, 9 H; *t*-Bu); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 171.4 (CONH_2), 169.9 (CONH_2), 116.5 (*t*-BuCMe), 78.2 (OCH), 77.1 (OCH), 38.4 ($\text{C}(\text{CH}_3)_3$), 25.0 ($\text{C}(\text{CH}_3)_3$), 19.5 (Me); MS [ESI(+)] m/z 253 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_4$: C 52.16, H 7.88, N 12.17; Found C 52.12, H 7.78, N 12.14.

Synthesis of (4*S*,5*S*)-2-*tert*-butyl-2-methyl-1,3-dioxolane-4,5-dimethanamine.^{SI-1} Diamide **24a** (3.45 g, 15 mmol) was placed in a Soxhlet thimble and extracted into a refluxing suspension of lithium aluminium hydride (2.0 g, 52.5 mmol) in anhydrous THF (200 mL). Refluxing was continued for 20 h and the suspension was cooled to rt. Water (2.0 mL) was added dropwise to the mixture, followed by 4 N aqueous NaOH (2.0 mL) and water (6.2 mL). The mixture was filtered, the resulting solid was washed with THF, and the combined filtrates were concentrated to afford the crude diamine (2.99 g, ca. 99%) as a pale brown oil.

Synthesis of (4*S*,5*S*)-2-*tert*-butyl-*N,N,N',N'*-tetrakis[(4-methoxyphenyl)methyl]-2-methyl-1,3-dioxolane-4,5-dimethanamine (25a). A solution of the diamine (2.62 g, 13 mmol), *i*-Pr₂NEt (13.6 mL, 78 mmol) in CH_3CN (30 mL) was treated with 4-methoxybenzyl chloride (8.8 mL, 65 mmol) at 0 °C. After the starting material was consumed completely, the reaction was quenched by the addition of Et₃N (10 mL). After additional stirring for 1 h, water was added and the mixture was extracted with ether (10 mL $\times$ 3), washed with brine (10 mL $\times$ 3), and dried over Na_2SO_4 . After evaporation, the crude mixture was purified by flush column chromatography (silica gel, 10 to 30% EtOAc in hexane) to give **25a** (7.27 g, 82%) as a colorless oil. $R_f = 0.41$ (silica gel, EtOAc-hexane 1:3); $[\alpha]_{\text{D}}^{23} -5.8$ (*c* 0.97, CHCl_3); FT-IR (neat) ν_{max} 2955, 2061, 1883, 1610, 1248, 1087, 821 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25 (d, $J = 9.0$ Hz, 4 H; Ar-H), 7.20 (d, $J = 9.0$ Hz, 4 H; Ar-H), 6.82 (d, $J = 9.0$ Hz, 8 H; Ar-H), δ 3.76 (s, 12 H; OCH_3), 3.43 (dd, $J = 9.0$ Hz, 4 H), δ 2.56 (d, $J = 4.5$ Hz, 2 H; CHCH_2N), 2.54 (dd, $J = 13.5, 3.5$ Hz, 1H; CHCH_2N), 2.48 (dd, $J = 13.5, 7.0$ Hz, 1 H; CHCH_2N), 1.20 (s, 3 H; Me), 0.92 (s, 9 H; *t*-Bu); ^{13}C NMR (125 MHz, CDCl_3) δ 158.9 (Ar-O), 131.9 (Ar), 130.4 (Ar), 114.5 (*t*-BuCMe), 113.9 (Ar), 80.0 (OCH), 78.6 (OCH), 56.2 (OCH_3), 58.1 (Bn), 55.6 (Bn), 54.7 (OCH_3), 39.2 ($\text{C}(\text{CH}_3)_3$), 25.6 ($\text{C}(\text{CH}_3)_3$), 21.2 (Me); MS [ESI(+)] m/z 683 ($\text{M}+\text{H}^+$); HR-MS [FAB(+)] Calcd for $\text{C}_{42}\text{H}_{55}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}^+$):

Synthesis of (4*S*,5*S*)-2-*tert*-Butyl-*N,N,N',N'*-tetrakis[(4-methoxyphenyl)methyl]-*N,N'*-2-trimethyl-1,3-dioxolane-4,5-dimethan ammonium diiodide ((*S,S*)-2a**).** Methyl iodide (11.2 mL, 180 mmol) was added to **25a** (5.92 g, 9.0 mmol) at rt. After stirring for 18 h, the mixture was evaporated and purified by flush column chromatography (silica gel, EtOAc to 20% MeOH in EtOAc) to give (*S,S*)-**2a** (7.74 g, 8.0 mmol, 89%) as a yellow solid. mp 132-135 °C; R_f = 0.35 (silica gel, 10% MeOH in EtOAc); $[\alpha]_D^{23}$ -63 (*c* 1.05, CDCl₃); FT-IR (KBr) $\nu_{\max}$ 3448, 2961, 1611, 1464, 1182, 1027, 841 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, J = 8.5 Hz, 2 H; Ar-H), 7.60 (d, J = 8.5 Hz, 2 H; Ar-H), 7.54 (d, J = 8.5 Hz, 2 H; Ar-H), 7.47 (d, J = 8.5 Hz, 2 H; Ar-H), 6.93 (d, J = 8.5 Hz, 6 H; Ar-H), 6.89 (d, J = 8.5 Hz, 2 H; Ar-H), 5.94 (m, 1 H; OCH), 5.49 (d, J = 13.0 Hz, 1 H; N⁺CH_aH_bAr), 5.40 (d, J = 12.5 Hz, 1 H; N⁺CH_cH_dAr), 5.18 (d, J = 14.5 Hz, 1 H; CHCH_aH_bN⁺), 5.06 (d, J = 12.5 Hz, 1 H; N⁺CH_eH_fAr), 4.78 (d, J = 12.5 Hz, 1 H; N⁺CH_gH_hAr), δ 4.76 (d, J = 12.5, 1 H; OCHCH_cH_dN⁺), 4.71 (d, J = 13.0 Hz, 1 H; N⁺CH_aH_bAr), 4.67 (d, J = 13.0 Hz, 1 H; N⁺CH_eH_fAr), 4.64 (d, J = 12.5 Hz, 1 H; N⁺CH_gH_hAr), 4.56 (m, 1 H; OCH), 4.31 (d, J = 12.5 Hz, 1 H; N⁺CH_cH_dAr), 4.10 (dd, J = 12.5, 10.0 Hz, 1 H; OCHCH_cH_dN⁺), 3.80 (s, 6 H; OCH₃), 3.78 (s, 3 H; OCH₃), 3.73 (s, 3 H; OCH₃), 3.49 (dd, J = 14.5, 6.0 Hz, 1 H; OCHCH_aH_bN⁺), 2.94 (s, 3 H; N⁺CH₃), 2.91 (s, 3 H; N⁺CH₃), 1.83 (s, 3 H; Me), 0.96 (s, 9 H; *t*-Bu); ¹³C NMR (125 MHz, CDCl₃) δ 161.7, 161.6, 135.5, 135.4, 135.2, 135.1, 119.3 (*t*-BuCMe), 118.7, 118.6, 118.4, 118.0, 115.6, 115.0, and 114.9 (Ar), 74.6 (OCH), 73.2 (OCH), 66.2, 65.8, 65.2, and 65.0 (4 C; Bn), 62.1 (OCHCH₂N⁺), 60.6 (OCHCH₂N⁺), 55.8 (OCH₃), 47.6 (N⁺CH₃), 46.1 (N⁺CH₃), 39.2 (C(CH₃)₃), 25.7 (C(CH₃)₃), 22.7 (Me); MS [ESI(+)] m/z 839 [M⁺], 591, 471; Anal. Calcd for C₄₄H₆₂I₂N₂O₇ (M+H₂O): C 53.66, H 6.35, N 2.84; Found C 53.66, H 6.40, N 3.04.

Synthesis of (4*S*,5*S*)-2-*tert*-butyl-*N,N,N',N'*-tetrakis[(4-methoxyphenyl)methyl]-*N,N'*-2-trimethyl-1,3-dioxolane-4,5-dimethanaminium ditetrafluoroborate ((*S,S*)-2c**).** AgBF₄ (428 mg, 2.2 mmol) was added to the solution of **2a** (913 mg, 1 mmol) in CH₂Cl₂ (5 mL). The mixture was stirred at rt for 2 h, and then filtrated to remove AgI. The solvent was evaporated and the residue was purified by flush column chromatography (silica gel, 50 to 100% EtOAc in hexane) to give **2c** (846 mg, 0.95 mmol, 95% yield) as a white solid. mp 171-173.5 °C; R_f = 0.72 (silica gel, EtOAc); $[\alpha]_D^{23}$ -33.2 (*c* 1.11, CHCl₃); FT-IR (KBr) $\nu_{\max}$ 2972, 2841, 1613, 1518, 1468, 1029, 843, 762 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.47-7.37 (m, 8 H; Ar-H), 6.96 (d, J = 9.0 Hz, 2 H; Ar), 6.95 (d, J = 9.0 Hz, 2 H; Ar), 6.90 (d, J = 8.5 Hz, 4 H; Ar), 4.88 (m, 1 H; OCH), 4.76 (d, J = 14.0 Hz, 1 H; N⁺CH_aH_bAr), 4.73 (d, J = 14.0 Hz, 1 H; N⁺CH_cH_dAr), δ 4.58 (d, J = 13.0 Hz, 2 H; N⁺CH_eH_fAr, N⁺CH_gH_hAr), δ 4.41-4.32 (m, 4 H; N⁺CH_aH_bAr, N⁺CH_cH_dAr, N⁺CH_eH_fAr, N⁺CH_gH_hAr), 4.30 (m, 1 H; OCH), 3.82 (s, 6 H; OMe), 3.80 (s, 3 H; OMe), 3.78 (s, 3 H; OMe), 3.76 (m, 2 H; OCHCH₂N⁺), 3.63 (m, 2 H; OCHCH₂N⁺), 2.81 (s, 6 H; N⁺Me), δ 1.49 (s, 3 H; Me), δ 0.90 (s, 9 H; *t*-Bu); ¹³C NMR (126 MHz, CDCl₃) δ 161.7, 161.6, 135.0, 134.9, 134.8, 134.7, 119.0 (*t*-BuCMe), 118.4, 118.3, 118.2, 118.0, 115.1, 115.0, 114.94, and 114.91 (16 C; Ar), 74.0 (OCH), 72.6 (OCH), 67.6, 67.2, 66.6, and 66.2 (4 C; Bn), 62.3(CHCH₂N⁺), 61.6 (CHCH₂N⁺), 55.5 (OCH₃), 46.5 (N⁺CH₃), 45.6 (N⁺CH₃), 38.8 (C(CH₃)₃), 25.3 (C(CH₃)₃), 20.6 (Me); MS [ESI(+)] m/z 799 [M⁺]; HR-MS [FAB (+)] Calcd for C₄₄H₆₀F₄N₂O₆B⁺ (M-BF₄⁻): 799.4475; Found 799.4469.

(4*S*,5*S*)-*N,N'*-Diethyl-*N,N,N',N'*-tetrakis[(4-methylphenyl)methyl]-2,2-dipropyl-1,3-dioxolane-4,5-dimethanaminium diiodide ((*S,S*)-2b**).** A yellow pale solid; mp 112-115 °C; R_f = 0.41 (silica gel, EtOAc); $[\alpha]_D^{22}$ -56.3 (*c* 1.02, CHCl₃); FT-IR (KBr) $\nu_{\max}$ 2958, 1614, 1464, 1105, 805 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, J = 7.5 Hz, 4 H; Ar-H), 7.49 (d, J = 7.5 Hz, 4 H; Ar-H), 7.24-7.28 (m, 8 H), 5.29 (m, 2 H; OCH), 5.23 (d, J = 12.5 Hz, 2 H; Bn), 5.18 (d, J = 12.5 Hz, 2 H; Bn), 5.09 (d, J = 14.0 Hz, 2 H; OCHCH₂N⁺), 4.73 (d, J = 12.5 Hz, 2 H; Bn), 4.40 (d, J = 12.5 Hz, 2 H; Bn), 3.85 (m, 2

H; OCHCH₂N⁺), 2.97 (s, 6 H; N⁺CH₃), 2.39 (s, 6 H; Ar-CH₃), 2.35 (s, 6 H; Ar-CH₃), 1.89 (m, 2 H), 1.81 (m, 2 H; Pr), 1.33 (m, 4 H; Pr), 0.95 (t, *J* = 7.0 Hz, 6 H; Pr); ¹³C NMR (125 MHz, CDCl₃) δ 141.2 and 141.1 (Ar), 133.4 and 133.2 (Ar), 130.1 and 130.0 (Ar), 123.3 and 123.1 (Ar), 116.7 (PrCPr), 73.0 (2 C; OCH), 66.0 (2 C; Bn), 65.1 (2 C; Bn), 61.4 (2 C; CHCH₂N⁺), 46.4 (N⁺CH₃), 39.7 (Pr), 21.2 (Ar-CH₃), 17.5 (Pr), 14.0 (Pr); MS [ESI(+)] *m/z* 557 (M-2I⁻-CH₂C₆H₄CH₃), 789 [M-I⁻], Anal. Calcd for C₄₅H₆₄N₂O₃ (M+H₂O): C 57.82, H 6.90, N 3.00; Found C 57.77, H 6.86, N 3.04.

(4*S*,5*S*)-*N,N'*-Dimethyl-*N,N,N',N'*-tetrakis[(4-methylphenyl)methyl]-2,2-dipropyl-1,3-dioxolane-4,5-dimethan-aminium ditetrafluoroborate ((*S,S*)-2d**).** A white solid; mp 201-204 °C; *R_f* = 0.68 (silica gel, EtOAc); [α]_D²² -32.4 (*c* 0.98, CHCl₃); FT-IR (KBr) ν_{max} 2963, 1617, 1475, 1074, 790 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, *J* = 8.0 Hz, 4 H; Ar-H), 7.36 (d, *J* = 8.0 Hz, 4 H; Ar-H), 7.28-7.23 (m, 8 H; Ar-H), 4.80 (d, *J* = 13.0 Hz, 2 H; Bn), 4.77 (d, *J* = 12.0 Hz, 2 H; Bn), 4.70 (d, *J* = 7.0 Hz, 2 H; OCH), 4.40 (d, *J* = 12.0 Hz, 2 H; Bn), 4.30 (d, *J* = 13.0 Hz, 2 H; Bn), 3.96 (d, *J* = 13.5 Hz, 2H; OCHCH₂N⁺), 3.78 (dd, *J* = 13.5 Hz, 8.0 Hz, 2 H; OCHCH₂N⁺), 2.40 (s, 6 H; Ar-CH₃), 2.83 (s, 6 H; N⁺CH₃), 2.37 (s, 6 H; Ar-CH₃), δ 1.70 (m, 4 H; Pr), 1.27 (m, 4 H; Pr), 0.91 (t, *J* = 7.5 Hz, 6 H; Pr); ¹³C NMR (125 MHz, CDCl₃) δ 141.5 (Ar), 130.3 (Ar), 123.5 (Ar), 123.3 (Ar), 117.0 (PrCPr), 73.0 (OCH), 67.5 (2 C; Bn), 66.6 (2 C; Bn), 62.5 (OCHCH₂N⁺), 46.1 (N⁺CH₃), 14.2 (Pr), 39.5 (Pr), 21.4 (Ar-CH₃), 17.6 (Pr); MS [ESI(+)] *m/z* 557 (M-2BF₄⁻-CH₂C₆H₄CH₃), 749 [M-BF₄]; Anal. Calcd for C₄₅H₆₂B₂F₈N₂O₂: C 64.60, H 7.47, N 3.35; Found C 64.49, H 7.37, N 3.31.

9.2. Catalytic Asymmetric Phase-Transfer Alkylation

General Procedure for the Catalytic Asymmetric Phase-Transfer Alkylation. A solution of 4-(triisopropylsilanyloxy)benzyl bromide (about 0.2 M in toluene, 7.0 mL, 3.5 mmol, 5.0 equiv) was added to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**3**) (207 mg, 0.70 mmol) and phase-transfer catalyst (*S,S*)-**2a** (67 mg, 0.070 mmol, 10 mol %) in CH₂Cl₂ (3.0 mL, total 0.07 M) at -70 °C. Finally, CsOH•H₂O (1.18 g, 7.0 mmol, 10 equiv) was added directly to the reaction mixture at the same temperature. After stirring for 72 h at the same temperature, the reaction was quenched by the addition of water followed by diethyl ether. After vigorous stirring at rt, both organic and aqueous layers were transferred into separation funnel by simple decantation. The organic layer was separated and washed with brine. The combined aqueous layers were re-extracted with diethyl ether and the combined organic layers were dried over Na₂SO₄. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel deactivated with Et₃N, hexane only to 5% EtOAc in hexane) to give **4b** (343.2 mg, 88%) and excess of the electrophile was recovered (820 mg, 85%). The catalyst was also recovered (60 mg, 90%) using the procedure written in Section 2.

The ketoimine **4b** was treated with 0.5 N aqueous citric acid solution (1.5 mL) in THF (6.2 mL) for 90 min at rt. The mixture was quenched with water and aqueous phase was basified with solid NaHCO₃, extracted with CH₂Cl₂ (three times), and dried over Na₂SO₄. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, 40 to 60% EtOAc in hexane) to give **24b** (198 mg, 82%). Alternatively, transformation of **4b** to **24b** was promoted by 5 mol % of Pd-C in MeOH under hydrogen atmosphere (1 atm) (91% yield).

9.3. Synthesis of D-Leu Portion

***tert*-Butyl (*R*)-2-amino-4-methyl-4-pentenoate (**26a**).**

See ref. SI-2.

Synthesis of 4-(triisopropylsilanyloxy)benzyl bromide. PBr₃ (0.16 mL, 1.68 mmol, 0.56 mol equiv)

was added to a solution of 4-(triisopropylsilanyloxy)benzyl alcohol^{SI-3} (841 mg, 3.0 mmol) in CH₂Cl₂ (24 mL, 0.125 M) at 4 °C. After stirring for 1 h at the same temperature and 3 h at room temperature, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate and extracted with CH₂Cl₂ (twice). The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated *in vacuo* to afford crude 4-(triisopropylsilanyloxy)benzyl bromide (>90% pure based on ¹H NMR analysis), which was used for the next reaction as a 0.2 M toluene solution without further purification.

H₂N-D-Tyr(TIPS)-O-*t*-Bu (26b). A colorless yellow oil; *R_f* = 0.29 (silica gel, EtOAc); [α]_D²⁵ -4.5 (*c* 2.0, CHCl₃, 92% ee); FT-IR (neat) ν_{max} 2945, 2871, 1731, 1509, 1263, 1154, 915 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.04 (d, *J* = 8.5 Hz, 2 H; H-5, H-9), 6.97 (d, *J* = 8.5 Hz, 2 H; H-6, H-8), 3.55 (dd, *J* = 7.0, 5.5 Hz, 1 H; H-2), 2.94 (dd, *J* = 14.0, 5.5 Hz, 1 H; H-3), 2.78 (dd, *J* = 14.0, 7.0 Hz, 1 H; H-3), 1.41 (s, 11 H; NH₂, *t*-Bu) 1.28-1.20 (m, 3 H; TIPS), 1.10-1.06 (m, 18 H; TIPS); ¹³C NMR (125 MHz, CDCl₃) δ 174.4 (C-1), 154.8 (C-7), 130.3 (2 C; C-5, C-9), 129.7 (C-4), 119.7 (2 C; C-6, C-8), 81.0 (*t*-Bu), 56.4 (C-2), 40.5 (C-3), 28.0 (3 C; *t*-Bu), 17.9 (6 C; TIPS), 12.6 (3 C; TIPS); MS [ESI (+)] *m/z* 394 (M+H⁺); Anal. Calcd for C₂₂H₃₉NO₃Si: N 3.56, C 67.13, H 9.99; Found N 3.51, C 66.90, H 10.06; The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/50, flow rate 0.5 mL/min, *t_R* 11.7 min (*R*)-isomer and 12.8 (*S*)-isomer, detected at 254 nm].

H₂N-D-Phe(4-F)-O-*t*-Bu (26c). A colorless oil; *R_f* = 0.50 (silica gel, EtOAc); [α]_D²⁵ -13.0 (*c* 1.1, CHCl₃, >99% ee); FT-IR (neat) ν_{max} 2979, 2933, 1730, 1510, 1363, 1223, 1154 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.17 (dd, *J* = 8.0, 5.5 Hz, 2 H; H-5, H-9), 6.97 (dd, *J* = 8.0, 8.0 Hz, 2 H; H-6, H-8), 3.56 (dd, *J* = 7.5, 6.0 Hz, 1 H; H-2), 2.98 (dd, *J* = 14.0, 6.0 Hz, 1 H; H-3), 2.82 (dd, *J* = 14.0, 7.5 Hz, 1 H; H-3), 1.53 (br-s, 2 H; NH₂), 1.41 (s, 9 H; *t*-Bu); ¹³C NMR (125 MHz, CDCl₃) δ 174.2 (C-1), 161.8 (d, *J* = 244 Hz; C-7), 133.2 (C-4), 130.8 (d, *J* = 8.3 Hz, 2 C; C-5, C-9), 115.2 (d, *J* = 21.6 Hz, 2 C; C-6, C-8), 81.2 (*t*-Bu), 56.3 (C-2), 40.3 (C-3), 28.0 (3 C; *t*-Bu); The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/100, flow rate 1.0 mL/min, *t_R* 24.5 min (*S*)-isomer and 26.1 min (*R*)-isomer, detected at 254 nm].

9.4. Synthesis of L-Choi Portion

Synthesis of (3,3-dimethyl-1,5-dioxaspiro[5,5]undec-8-en-9-yl)methanol: To a solution of 2,4-dihydroanisylalcohol^{SI-4} (4.5 g, 32 mmol), neopentyl glycol (6.66 g, 64 mmol) in THF (20mL) was added BF₃-Et₂O (0.7 mL) with cooling in ice bath. After stirring for 20 min at the same temperature, the mixture was poured into cold saturated NaHCO₃ (15 mL) and extracted with CH₂Cl₂ (six times). The combined extracts were washed with water, dried over Na₂SO₄ and then evaporated to give colorless oil, which by silica gel chromatography afforded the title compound (5.68 g, 84%). *R_f* = 0.45 (silica gel, EtOAc-hexane, 1:1); FT-IR (neat) ν_{max} 3417, 2952, 2867, 1472, 1395, 1362, 1247 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.48 (s, 1 H; H-8), 3.95 (s, 2 H; CH₂OH), 3.53 (d, *J* = 11.2 Hz, 2H; H-2), 3.41 (d, *J* = 11.6 Hz, 2 H; H-4), 2.32 (br-s, 2 H; H-7), 2.07 (br-s, 2 H; H-10), 1.93 (t, *J* = 6.4 Hz, 2 H; H-11), 0.97 (s, 3 H; H-3"), 0.84 (s, 3 H; H-3'); ¹³C NMR (125 MHz, CDCl₃) δ 137.1 (C-9), 119.1 (C-8), 97.2 (C-6), 70.3 (2 C; C-2, C-4), 66.7 (-CH₂OH), 34.7 (C-7), 30.2 (C-10), 27.0 (C-11), 23.8 (C-3), 22.7 (C-3"), 22.4 (C-3'); MS [ESI (+)] *m/z* 235 (M+Na⁺); HR-MS [FAB(+)] Calcd for C₁₂H₂₁O₃⁺ (M+H⁺): 213.1485; Found 213.1495.

Synthesis of 9-bromomethyl-3,3-dimethyl-1,5-dioxaspiro[5.5]undec-8-ene (5): To a solution of (3,3-dimethyl-1,5-dioxaspiro[5,5]undec-8-en-9-yl)methanol (2.75g, 13 mmol), triethylamine (3.61 mL,

26 mmol) in CH₂Cl₂ (70 mL) was added MsCl (1.51 mL, 19.5 mmol) dropwise at –78 °C. The reaction mixture was allowed to stir at the same temperature for 30 min, quenched with water at the same temperature and then allowed to come to room temperature. The organic phase was separated, the aqueous phase was extracted with CH₂Cl₂ (twice), and the combined organic layer was washed with brine, dried over Na₂SO₄, concentrated to afford crude mesylate. The crude mesylate was directly dissolved in acetone (120 mL), added NaBr (13.4 g, 130 mmol) and stirred for overnight at room temperature. Saturated NH₄Cl was added, and the reaction mixture was extracted with Et₂O (six times), the combined organic layer was washed with brine, dried over Na₂SO₄, evaporated at lower temperature. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to afford **5** (2.39 g, 80%), which was stored at low temperature as toluene stock solution (about 1 M).

Synthesis of (S)-2-(benzhydrylidene-amino)-3-(3,3-dimethyl-1,5-dioxaspiro[5.5]undec-8-en-9-yl)-propionic acid *tert*-butyl ester (6**):** A solution of **5** (about 1 M in toluene, 0.7 mL, 0.70 mmol, 5 equiv) was added to the mixture of **3** (41 mg, 0.14 mmol) and phase transfer catalyst (*R,R*)-**2a** (13.5 mg, 0.014 mmol, 10 mol %) in CH₂Cl₂ (0.3 mL) at –70 °C. Finally, CsOH•H₂O (235 mg, 1.4 mmol, 10 equiv) was added directly to the reaction mixture at the same temperature. After stirring for 72 h at –70 °C, the reaction was quenched with the addition of water followed by ether. The aqueous phase was extracted with ether (three times), combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (silica gel, 5% EtOAc in hexane) to give compound **6** (49 mg, 80%) as a colorless oil. *R*_f = 0.30 (silica gel, EtOAc-Hexane, 1:9); [α]_D²² –108.5 (*c* 0.98, CHCl₃, 88% ee); FT-IR (neat) ν_{max} 2953, 1732, 1623, 1445, 1366, 1150, 1112 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 3.0 Hz, 1 H; Ph), 7.90 (d, *J* = 2 Hz, 1 H; Ph), 7.26 (d, *J* = 8.5 Hz, 2 H; Ph), 7.15–7.17 (m, 2 H; Ph), 7.07–7.10 (m, 4 H; Ph), 5.34 (br-s, 1 H; H-8'), 4.35 (dd, *J* = 8.2, 5.2 Hz, 1 H; H-2), 3.26 (d, *J* = 11.5 Hz, 1 H; H-4'), 3.25 (d, *J* = 11.5 Hz, 1 H; H-4'), 3.22 (d, *J* = 11.5 Hz, 1 H; H-2'), 3.20 (d, *J* = 11.5 Hz, 1 H; H-2'), 2.79–2.90 (m, 2 H; H-3), 2.32 (bs, 2 H; H-7'), 1.78–1.97 (m, 4 H; H-10', H-11'), 1.35 (s, 9 H; *t*-Bu), 0.73 (s, 3 H; C-3''), 0.72 (s, 3 H; C-3'); ¹³C NMR (125 MHz, CDCl₃) δ 171.1 (C=N), 169.7 (C-1), 139.7 (C-9'), 136.5, 133.5, 129.9, 128.7, 128.4, 128.1, 127.9, and 127.8 (12 C; Ph), 120.6 (C-8'), 96.9 (C-6'), 80.8 (C(CH₃)₃), 70.0 (2 C; C-2', C-4'), 65.1 (C-2), 41.0 (C-3), 34.1 (C-7'), 30.1 (C-10'), 27.9 (3 C; C(CH₃)₃), 26.5 (C-11'), 22.6 (C-3''), 22.5 (C-3''); MS [ESI (+)] *m/z* 512 (M+Na⁺); HR-MS [FAB(+)] Calcd for C₃₁H₄₀NO₄⁺ (M+H⁺): 490.2952; Found 490.2957; The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OD-H, *i*-PrOH/hexane 1/100, flow rate 0.5 ml/min, *t*_R 13.2 min (*R*-isomer) and *t*_R 18.6 min (*S*-isomer), detected at 254 nm].

Synthesis of methyl (2*S*,3*aS*,7*aS*)-1-benzyl-6-oxo-octahydroindole-2-carboxylate (7a**):** To a solution of **6** (900 mg, 2.1 mmol) in methanol (2 mL) was added 2 mL of MeOH/HCl (4.6 M), the reaction mixture was warmed up to 40 °C and kept at the same temperature for 7 h. The mixture was concentrated to dryness and the residue was dissolved in EtOH (4 mL), NaHCO₃ (2.0 g) and benzyl bromide (0.65 mL, 5.4 mmol) were added, and the mixture was stirred at 70 °C until disappearance of the starting material observed by TLC (9 h). The reaction mixture was filtered, the solvent removed, and the residue taken up with CH₂Cl₂ (10 mL) and washed with 2 N HCl (4 x 5 mL). The aqueous extracts were basified with Na₂CO₃ to pH 10–11 and extracted with CH₂Cl₂ (6 x 5 mL), dried over Na₂SO₄ and concentrated, careful purification of the residue by flash column chromatography (silica gel, hexane/CH₂Cl₂/EtOAc 1:1:0.2) gives *Endo* isomer **7a** (154 mg, 25.5%) and *Exo* isomer **7b** (306 mg, 50 %). The undesired *Exo* isomer was easily transferred to *Endo* isomer by heating at 65 °C with 9 N HCl in MeOH (28 mL per mmol) for 8 h. The crude NMR showed 1:8 mixture of *Exo/Endo*, which was further purified by flash column chromatography under standard conditions mentioned above.

Endo isomer: *R*_f = 0.54 (hexane/CH₂Cl₂/EtOAc 6:9:2); [α]_D²³ –32.7 (*c* 0.5, CHCl₃, 88% ee). Other

spectroscopic data's were matching with the reported one.³

Methyl (2*S*,3*aS*,7*aS*)-1-*tert*-butoxycarbonyl-6-oxo-octahydroindole-2-carboxylate: Prepared by following the literature procedure.³ $[\alpha]_D^{21} +26.8$ (*c* 0.96, CHCl₃, 88% ee).

Methyl (2*S*,3*aS*,6*R*,7*aS*)-1-*tert*-butoxycarbonyl-6-hydroxy-octahydroindole-2-carboxylate (8): Prepared by following the literature procedure.³ $[\alpha]_D^{24} -26.8$ (*c* 1.6, CHCl₃). The product (128 mg, 88% ee, $[\alpha]_D^{24} -29.1$ (*c* 1.6, CH₃OH)) was recrystallized with diisopropyl ether/hexane to give optically pure **8** (98 mg, 77%). $[\alpha]_D^{23} -35.3$ (*c* 1.6, CH₃OH, >99% ee); lit. $[\alpha]_D^{20} -31.1$ (*c* 2.4, CH₃OH).³

9.5. Synthesis of L-Arg Portion

Synthesis of *tert*-butyl (*S*)-2-[(diphenylmethylene)amino]-4-pentenoate (9). CsOH·H₂O (8.40 g, 50 mmol, 10 equiv) was added to the solution of **3** (1.48 g, 5 mmol), and catalyst (*R,R*)-**2c** (443 mg, 0.5 mmol) in solvent (toluene/CH₂Cl₂=7/3, 33.3 mL). The reaction mixture was stirred at -70 °C for 20 min, and then allyl bromide (3.02 g, 25 mmol) was added. The mixture was stirred vigorously for 48 h, and then water was added and the extraction was performed with Et₂O (20 mL×3). The organic phase was washed with brine (50mL) and dried over Na₂SO₄. After concentration, the residue was purified by flush column chromatography (silica gel deactivated with Et₃N, 5% Et₂O in hexane) to give **9** (1.42 g, 4.25 mmol, 85% yield) as a colorless oil. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OD-H, *i*-PrOH/hexane 1/200, flow rate 0.5 mL/min, *t*_R 10.3 min (*S*-isomer) and 11.7 min (*R*-isomer), detected at 254 nm].

Synthesis of methyl (*S*)-2-*tert*-butoxycarbonylamino-4-pentenoate. Compound **9** (1.01 g, 3.0 mmol) was dissolved in HCl-MeOH (4 N, 10 mL) and refluxed for 2 h. The mixture was cooled to rt, and then water was added. The aqueous phase was separated, washed with Et₂O (5 mL), and basified by the addition of saturated aqueous NaHCO₃. Then Boc₂O (982 mg, 4.5 mmol) was added and stirred at rt for 2 h. The mixture was extracted with EtOAc (10 mL×3), washed with brine (20 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flush column chromatography (silica gel, 10 to 20% EtOAc in hexane) to give methyl ester (584 mg, 2.55 mmol, 85%) as a colorless oil. *R*_f = 0.30 (silica gel, EtOAc-hexane 1:5); $[\alpha]_D^{24} +17.4$ (*c* 1.0, CHCl₃, 93% ee); ¹H NMR (500 MHz, CDCl₃) δ 5.72-5.65 (m, 1 H; H-4), 5.15 (bs, 1 H, H-5), 5.12 (br-s, 1 H; H-5), 5.02 (br-s, 1 H; CONH), 4.38 (dd, *J* = 12.5, 5.0 Hz, 1 H; H-2), 3.74 (s, 3 H; CO₂Me), 2.56-2.46 (m, 2 H; H-3), 1.44 (s, 9 H; *t*-Bu); ¹³C NMR (125 MHz, CDCl₃) δ 172.7 (C-1), 155.3 (Boc), 132.4 (C-4), 119.3 (C-5), 80.1 (C(CH₃)₃), 53.0 (C-2), 52.4 (CO₂CH₃), 36.9 (C-3), 28.4 (3 C; C(CH₃)₃).

Synthesis of methyl (*S*)-2-*tert*-Butoxycarbonylamino-5-hydroxy-norvalinate (10). 9-BBN (0.5 M in THF, 14 mL) was added to a solution of methyl (*S*)-2-*tert*-butoxycarbonylamino-4-pentenoate (648 mg, 2.8 mmol) in anhydrous THF (5.0 mL) at 0 °C. The mixture was warmed to rt, stirred for 3 h, and then quenched with H₂O (3 mL). THF (5 mL) was added and the reaction was oxidized with H₂O₂ (30%, 15 mL)/NaOAc (20%, 20 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (10 mL×3). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. After evaporation, the crude mixture was purified by flush column chromatography (silica gel, 10 to 40% EtOAc in hexane) to give **10** (500 mg, 2.0 mmol, 73% yield) as a colorless oil. *R*_f = 0.31 (silica gel, EtOAc-hexane 1:1); $[\alpha]_D^{24} +6.8$ (*c* 0.98, CHCl₃, 93% ee); FT-IR (neat) $\nu_{\max}$ 3370, 2977, 1695, 1520, 1163, 1049 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.21 (br-s, 1 H; Boc), 4.30 (br-s, 1 H; H-2), 3.71 (s, 3 H; CO₂Me), 3.64 (t, *J* = 6.5 Hz, 2 H; H-5), 1.93-1.89 (m, 1H; H-3), 1.57-1.77 (m, 3

H; H-3, H-4), 1.44 (s, 9 H; *t*-Bu); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2 (C-1), 155.4 (Boc), 79.8 ($\text{C}(\text{CH}_3)_3$), 61.8 (C-5), 53.0 (C-2), 52.1 (CO_2CH_3), 30.7 (C-3), 29.3 (C-4), 28.1 ($\text{C}(\text{CH}_3)_3$); MS [ESI(+)] m/z 270 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{11}\text{H}_{21}\text{NO}_5$: C 53.43, H 8.56, N 5.66; Found C 52.89, H 8.39, N 5.52.

Synthesis of L-Arg(δ,ω' -di-Cbz)-OMe (11a). *N,N'*-bis(benzyloxycarbonyl)guanidine^{SI-5} (416 mg, 1.27 mmol) was added to a solution of **x** (261 mg, 1.06 mmol) and PPh_3 (361 mg, 1.38 mmol) in anhydrous THF (5 mL). The mixture was cooled to 0 °C, and diethyl azodicarboxylate (40% in toluene, 0.60 mL, 1.38 mmol) was added dropwise over 10 min. The reaction was stirred at rt for 0.5 h. The solvent was evaporated and chromatographed (silica gel, 10 to 20% EtOAc in hexane). The obtained compound was then treated with $\text{TsOH}\cdot\text{H}_2\text{O}$ (182 mg, 1.06 mmol) in CH_2Cl_2 (5 mL) for 2 h. The saturated aqueous NaHCO_3 was added to the solution and extracted with EtOAc (5 mL $\times$ 3), washed with brine (5 mL), and dried over Na_2SO_4 . After evaporation, the crude mixture was purified by flush column chromatography (silica gel, 30 to 70% EtOAc in hexane) to give **11a** (426 mg, 0.93 mmol, 88% yield) as a colorless oil. R_f = 0.33 (silica gel, EtOAc); $[\alpha]_D^{22}$ +3.8 (*c* 0.8, CHCl_3 , 93% ee); FT-IR (neat) ν_{max} 3390, 2952, 1958, 1714, 807, 743 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.40-7.22 (m, 10 H; Cbz), 5.24 (s, 2 H; Cbz), 5.14 (s, 2 H; Cbz), 4.00 (m, 2 H; H-5), 3.64 (s, 3 H; CO_2CH_3), 3.44 (dd, J = 8.0, 4.5 Hz, 1H; H-2), 1.71-1.66 (m, 2 H; H-3), 1.51-1.48 (m, 2 H; H-4); ^{13}C NMR (125 MHz, CDCl_3) δ 176.5 (C-1), 164.2 (Cbz), 160.9 (Cbz), 156.2 (C=N), 137.3 (Ar), 135.0 (Ar), 129.2 (Ar), 129.1 (Ar), 128.9 (Ar), 128.8 (Ar), 128.7 (Ar), 128.3 (Ar), 128.2 (Ar), 69.3 (Cbz), 67.3 (Cbz), 54.2 (C-2), 52.3 (CO_2CH_3), 44.6 (C-5), 31.9 (C-3), 25.2 (C-4); MS [ESI(+)] m/z 457 ($\text{M}+\text{H}^+$); HR-MS [FAB(+)] Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_6^+$ ($\text{M}+\text{H}^+$): 457.2087; Found 457.2118.

Synthesis of Methyl (S)-2-tert-butoxycarbonylamino-2-methyl-4-pentenoate (28).^{SI-6} $\text{CsOH}\cdot\text{H}_2\text{O}$ (3.36 g, 20 mmol) was added to the solution of *N*-[(4-chlorophenyl)methylene]-alanine *tert*-butyl ester (**13**) (536 mg, 2.0 mmol), and chiral catalyst (*R,R*)-**2c** (177 mg, 0.2 mmol) in solvent (toluene/ CH_2Cl_2 (7/3), 13.0 mL). The reaction mixture was stirred at -70 °C for 20 min, and then allyl bromide (0.86 mL, 10 mmol) was added. The mixture was stirred vigorously for 120 h. The reaction was quenched by the addition of water and extraction was performed with EtOAc (10 mL $\times$ 3). Solvents were evaporated and the residue was dissolved in 0.5 M citric acid (10 mL) and THF (10 mL). The mixture was stirred at rt for 2 h, then diluted with water. The mixture was extracted with Et_2O (10 mL) to remove alkylating reagent and 4-chlorobenzaldehyde, and then the aqueous phase was basified by saturated aqueous NaHCO_3 . Extraction was performed with EtOAc (10 mL $\times$ 3) and the extract was dried over Na_2SO_4 . After concentration, the chemical yield of *tert*-butyl ester was determined by NMR (325 mg, containing 282 mg of **14** (1.5 mmol, 76 % yield), 36 mg of EtOAc (0.47 mmol), and 7 mg of 4-chlorobenzaldehyde), because of the high volatility of **14**. $\text{HCl}\cdot\text{MeOH}$ (4 N, 20 mL) was added to the mixture and refluxed for 2 h. The mixture was cooled to rt and basified by the addition of saturated aqueous NaHCO_3 . Then Boc_2O (0.65 g, 3.0 mmol) was added and stirred at rt for 2 h. The mixture was extracted with EtOAc (10 mL $\times$ 3), washed with brine (20 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by flush column chromatography (silica gel, 5% to 20% EtOAc in hexane) to give **28** (329 mg, 1.36 mmol, 68% yield) as a colorless oil. R_f = 0.37 (silica gel, EtOAc-hexane 1:5); $[\alpha]_D^{22}$ -10.2 (*c* 0.92, CHCl_3 , 88% ee); ^1H NMR (500 MHz CDCl_3) δ 1.42 (s, 9 H; *t*-Bu), 1.50 (s, 3 H; H-6), 2.55 (dd, J = 14.0, 7.5 Hz, 1 H; H-3), 2.69 (m, 1 H; H-3), 3.71 (s, 3 H; CO_2CH_3), 5.08 (dd, J = 12.0, 1.0 Hz, 1 H; H-5), 5.10 (br-s, 1 H; H-5), 5.15 (br-s, 1 H; Boc), 5.63 (m, 1 H; H-4), ^{13}C NMR (125 MHz, CDCl_3) δ 174.6 (C-1), 154.5 (NCO), 32.4 (C-4), 119.5 (C-5), 59.2 (C-2), 52.5 (CO_2CH_3), 41.5 (C-3), 28.4 ($\text{C}(\text{CH}_3)_3$), 23.3 (C-6); The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OD-H, *i*-PrOH/hexane 1/100, flow rate 1.0 mL/min, t_R 8.5 min (*R*-isomer) and 12.4 min (*S*-isomer), detected at 254 nm] after conversion to corresponding *N*-

benzoylamide of **14**.

Methyl (S)-2-tert-Butoxycarbonylamino-5-hydroxy- α -methyl-norvalinate (29). A colorless oil; R_f = 0.42 (silica gel, EtOAc-hexane 1:1); $[\alpha]_D^{22}$ +10.4 (c 0.96, CHCl_3 , 88% ee); FT-IR (neat) ν_{max} 3372, 2937, 1695, 1167, 1059 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.40 (br-s, 1 H; NHCO), 3.74 (s, 3 H; CO_2CH_3), 3.62 (t, J = 6.5 Hz, 2 H; H-5), 1.88 (m, 2 H; H-3), 1.54 (m, 2 H; H-4), 1.52 (s, 3 H; H-6), 1.42 (s, 9 H; t -Bu); ^{13}C NMR (125 MHz, CDCl_3) δ 175.2 (C-1), 154.8 (Boc), 62.6 ($\text{C}(\text{CH}_3)_3$), 59.4 (C-2), 52.7 (CO_2Me), 36.2 (C-3), 28.5 ($\text{C}(\text{CH}_3)_3$), 27.2 (C-6), 23.6 (C-4); MS [ESI(+)] m/z 284 [$\text{M}+\text{Na}^+$]; HR-MS [FAB(+)] Calcd for $\text{C}_{12}\text{H}_{24}\text{NO}_5^+$ ($\text{M}+\text{H}^+$): 262.1649; Found 262.1657.

Synthesis of L-Arg(α -metyl- δ,ω' -di-Cbz)-OMe (11b). A colorless oil; R_f = 0.35 (silica gel, EtOAc); $[\alpha]_D^{24}$ +8.1 (c 1.02, CHCl_3 , 88% ee); FT-IR (neat) ν_{max} 3389, 2951, 1723, 1239, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.43 (br-s, 1 H; NH), 9.24 (br-s, 1 H; NH), 7.69-7.28 (m, 10 H; Cbz), 3.96 (t, J = 7.0 Hz, 2 H; H-5), 5.14 (s, 2 H; Cbz), 5.23 (s, 2 H; Cbz), 3.58 (s, 3 H; CO_2CH_3), 1.69-1.51 (m, 4 H; H-3, H-4), 1.25 (s, 3 H; H-6); ^{13}C NMR (125 MHz, CDCl_3) δ 177.9 (C-1), 164.0 (Cbz), 160.6 (Cbz), 155.9 (C=N), 137.1, 134.8, 128.5, 128.4, 128.1, 128.0, and 127.8 (10 C; Cbz), 68.9 (Cbz), 67.0 (Cbz), 57.7 (C-2), 52.2 (CO_2CH_3), 44.8 (C-5), 37.5 (C-3), 26.5 (C-4), 23.8 (C-6); MS [ESI(+)] m/z 471 [$\text{M}+\text{H}^+$]; HR-MS [FAB(+)] Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_4\text{O}_6^+$ ($\text{M}+\text{H}^+$): 471.2244; Found 471.2237.

Synthesis of N-(Diphenylmethylene)-L-glutamic acid 1-(1,1-dimethylethyl) 5-benzyl ester (12). Benzyl acrylate (487 mg, 3.0 mmol) was added to the solution of **3** (590 mg, 2 mmol), and chiral catalyst (*S,S*)-**2d** (167 mg, 0.2 mmol) in chlorobenzene (13.0 mL). The reaction mixture was stirred at -30°C (or -60°C) for 20 min, and then Cs_2CO_3 (326 mg, 1.0 mmol) was added. The mixture was stirred vigorously at -30°C (or -60°C) for 10 h (168 h, at -60°C). The reaction was quenched by the addition of water and extraction was performed with Et_2O (10 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give **12** (798 mg, 1.74 mmol, 87% yield) as a white solid. It was recrystallized from methanol to give optically pure **12** (393 mg, 0.86 mmol, 43% yield) as a colorless crystal. R_f = 0.40 (silica gel, EtOAc-hexane 1:5); $[\alpha]_D^{23}$ -4.1 (c 1.10, CHCl_3 , >99% ee); FT-IR (KBr) ν_{max} 2978, 1737, 1267, 1147, 953, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (m, 2 H; Ar-H), 7.42-7.28 (m, 11 H; Ar-H), 7.15-7.14 (m, 2 H; Ar-H), 5.03 (s, 2 H; Bn), 3.97 (dd, J = 7.5 Hz, 5.0 Hz, 1 H; H-2), 2.42 (m, 2 H; H-4), 2.24 (m, 2 H; H-3), 1.43 (s, 9 H; t -Bu); ^{13}C NMR (CDCl_3 , 125 MHz) δ 173.3 (2 C; C-1, C-5), 171.1 (C=N), 139.8, 136.8, 136.3, 130.7, 129.2, 128.9, 128.8, 128.5, and 128.3 (15C; Ar), 81.5 ($\text{C}(\text{CH}_3)_3$), 66.5 (Cbz), 65.2 (Cbz), 31.1 (C-4), 29.0 (C-3), 28.4 (3 C, $\text{C}(\text{CH}_3)_3$); MS [ESI (+)] m/z 458 ($\text{M}+\text{H}^+$); Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{NO}_4$: C 76.12, H 6.83, N 3.06; Found C 75.86, H 6.82, N 3.02; The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OD-H, *i*-PrOH/hexane 1/100, flow rate 1.0 mL/min, t_R 10.5 min (*R*-isomer) and 12.1 min (*S*-isomer), detected at 254 nm].

In the case of -60°C , the 1:1 mixture of chlorobenzene and toluene was used as a solvent (13 mL).

Synthesis of methyl (S)-2-tert-butoxycarbonylamino-5-hydroxy-norvalinate (10) from 12. Pd/C (25 mg, 0.025 mmol) was added to a solution of **12** (229 mg, 0.50 mmol) in THF (3 mL), and the mixture was stirred under hydrogen at atmospheric pressure for 20 h. The catalyst was removed by filtration through Celite and washed with MeOH. Evaporation of the solvent and purification by flash column chromatography (silica gel, 30 to 50% EtOAc in hexane) gave **27** (140 mg, 0.46 mmol, 93% yield) as a colorless oil.

Ethyl chloroformate (30.6 μL , 0.32 mmol) was added to the cooled (-10°C) solution of **27** (96 mg,

0.32 mmol) and *N*-methyilmorpholine (35.2 μ L, 0.32 mmol) in THF. After stirring for 30 min, NaBH₄ (36.3 mg, 0.96 mmol) was added in one portion. Then, methanol (5.0 mL) was added dropwise to the mixture over a period of 10 min at 0 °C. The mixture was stirred for 30 min, and then neutralized with 1 N HCl (4 mL). The mixture was extracted with EtOAc (5 mL $\times$ 3), washed with brine (10 mL), and dried over Na₂SO₄. The solvent was evaporated and the residue was treated with HCl-MeOH (4 N, 10 mL) at 80 °C for 2 h. Basification by aqueous NaHCO₃, protection with Boc₂O, and purification by flash column chromatography (silica gel, 10 to 40% EtOAc in hexane) gave **10** (65.4 mg, 0.26 mmol, 82% yield) as a colorless oil. $[\alpha]_D^{22} +7.1$ (*c* 1.0, CHCl₃, >99% ee).

9.6. Synthesis of D-Hpla Portion

Synthesis of 1-(4-phenylimidazol-1-yl)-3-[4-(triisopropylsilanyloxy)phenyl]propenone (15). 1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (3.29 g, 17.2 mmol, 1.1 equiv) was added to a stirred solution of 4-hydroxycinnamic acid (2.19 g, 15.6 mmol) and 4-phenylimidazole (2.25 g, 15.6 mmol, 1.0 equiv) in DMF (62 mL, 0.25 M) at room temperature. After stirring for 12 h at the same temperature, triethylamine (3.3 mL, 23.4 mmol, 1.5 equiv) and triisopropylsilyl chloride (4.6 mL, 17.2 mmol, 1.1 equiv) were added to the reaction mixture at 4 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride. The resulting mixture was extracted with diethyl ether (twice). The combined organic layers were washed with saturated aqueous ammonium chloride followed by brine and dried over Na₂SO₄. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane). The resulting yellow solid was washed with diisopropyl ether to afford imidazolide **15** (5.70 g, 82%, 2 steps) as a yellow solid. $R_f = 0.34$ (silica gel, EtOAc–hexane, 1:3); mp 127.5–128 °C; FT-IR (KBr) $\nu_{\max}$ 2866, 1698, 1624, 1597, 1509, 1394, 1265, 1193, 832 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.39 (s, 1 H; H-2'), 8.05 (d, *J* = 15.5 Hz, 1 H; H-3), 7.91 (s, 1 H; H-5'), 7.86 (d, *J* = 7.0 Hz, 2 H; H-2'', H-5''), 7.58 (d, *J* = 8.5 Hz, 2 H; H-5, H-9), 7.43 (t, *J* = 7.0 Hz, 2 H; H-3'', H-5''), 7.32 (t, *J* = 7.0 Hz, 1 H; H-4''), 6.95 (d, *J* = 15.5 Hz, 1 H; H-2), 6.95 (d, *J* = 8.5 Hz, 2 H; H-6, H-8), 1.33–1.25 (m, 3 H; TIPS), 1.15–1.08 (m, 18 H; TIPS); ¹³C NMR (125 MHz, CDCl₃) δ 161.9 (C-1), 159.7 (C-7), 149.7 (C-3), 143.6 (C-4'), 136.3 (C-2''), 132.7 (C-4), 130.7 (2 C; C-5, C-9), 128.7 (2 C; C-3'', C-5''), 127.9 (C-4''), 126.7 (C-1''), 125.4 (2 C; C-2'', C-6''), 120.6 (2 C; C-6, C-8), 111.8 (C-2), 111.2 (C-5'), 17.9 (6 C; TIPS), 12.7 (3 C; TIPS); MS [ESI (+)] *m/z* 447 (M+H⁺); Anal. Calcd for C₂₇H₃₄N₂O₂Si: N 6.27, C 72.60, H 7.67; Found N 6.23, C 72.61, H 7.85.

Synthesis of (2*R*,3*S*)-3-[4-(Triisopropylsilanyloxy)phenyl]oxirane-2-carboperoxoic acid *tert*-butyl ester (16). A solution of La(O-*i*-Pr)₃ (0.2 M in THF, 5.0 mL, 1.0 mmol, 10 mol %) was added to a mixture of (*S*)-BINOL (286 mg, 1.0 mmol, 10 mol %), triphenylphosphine oxide (835 mg, 3.0 mmol, 30 mol %) and MS 4A (10 g) in dry THF (100 mL, 0.1 M) at room temperature. After stirring for 45 min at the same temperature, a solution of TBHP (5.0 M in decane, 4.8 mL, 24 mmol, 2.4 mol equiv) was added at 4 °C. After stirring for 10 min at the same temperature, imidazolide **15** (4.47 g, 10 mmol, 1.0 equiv) was added directly and the mixture was stirred at room temperature for 90 min. The reaction was quenched by the addition of 1% aqueous citric acid solution at 4 °C. The mixture was extracted with ethyl acetate (twice) and the combined organic layers were washed with 2% aqueous sodium thiosulfate followed by brine, and dried over Na₂SO₄. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) to give epoxy peroxyester **16** (3.88 g, 95%) as a pale yellow oil. $R_f = 0.57$ (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{25} -108$ (*c* 1.8, CHCl₃, 94% ee); FT-IR (neat) $\nu_{\max}$ 2945, 2868, 1788, 1610, 1515, 1270, 1128, 1107, 911 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (d, *J* = 8.5 Hz, 2 H; H-5, H-9), 6.87 (d, *J* = 8.5 Hz, 2 H; H-6, H-8), 4.09 (d, *J* = 1.5 Hz, 1 H; H-3), 3.53 (d, *J* = 1.5 Hz, 1 H; H-2), 1.36 (s, 9 H; *t*-Bu), 1.30–1.22 (m, 3 H; TIPS), 1.12–

–1.05 (m, 18 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 166.0 (C-1), 157.1 (C-7), 127.1 (2 C; C-5, C-9), 126.5 (C-4), 120.2 (2 C; C-6, C-8), 84.5 (*t*-Bu), 58.2 (C-2), 54.9 (C-3), 26.1 (3 C; *t*-Bu), 17.9 (6 C; TIPS), 12.6 (3 C; TIPS); MS [ESI (+)] m/z 431 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_5\text{Si}$: C 64.67, H 8.88; Found C 64.40, H 8.66. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/hexane 1/9, flow rate 0.5 mL/min, t_R 22.5 min (2*S*,3*R*)-isomer and 36.7 min (2*R*,3*S*)-isomer, detected at 254 nm] after conversion to the corresponding methyl amide.

9.7. Synthesis of the Left Dipeptide (Hpla-Leu Portion)

Synthesis of HO-D-Hpla(TIPS)-D-Leu-O-*t*-Bu (17). A solution of **26a** (255 equiv, 1.38 mmol, 2 equiv) in THF (1.0 M, 1.4 mL) was added to **16** at rt. After stirring for 24 h, 10% Pd-C (37 mg, 0.034 mmol, 5 mol %) was added to the reaction directly and argon was replaced with hydrogen (1 atm). After stirring for 24 h, the mixture was filtered thorough Cerite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20 to 40% EtOAc in hexane) to give **17** (308 g, 88%) as a white solid with recovery of excess amine **26d** (82%). mp 108–110 °C; R_f = 0.14 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{24}$ +43.6 (*c* 2.1, CHCl_3); FT-IR (KBr) ν_{max} 3269, 2946, 2868, 1729, 1649, 1508, 1265, 1151, 918 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.08 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 6.84 (s, 1 H; NH (Leu)), 6.81 (d, J = 8.5 Hz, 2 H; H-6, H-8 (Hpla)), 4.47 (dd, J = 14.0, 9.0 Hz, 1 H; H-2 (Leu)), 4.30–4.28 (m, 1 H; H-2 (Hpla)), 3.12 (dd, J = 14.0, 3.5 Hz, 1 H; H-3 (Hpla)), 2.87 (dd, J = 14.0, 7.0 Hz, 1 H; H-3 (Hpla)), 2.57 (br-s, 1 H; OH (Hpla)), 1.60–1.50 (m, 2 H; H-3 (Leu)), 1.50–1.40 (m, 1 H; H-4 (Leu)), 1.45 (s, 9 H; *t*-Bu), 1.28–1.20 (m, 3 H; TIPS), 1.10–1.03 (m, 18 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 172.4 (C-1 (Leu)), 172.0 (C-1 (Hpla)), 155.1 (C-7 (Hpla)), 130.5 (2C; C-5, C-9 (Hpla)), 128.7 (C-4 (Hpla)), 120.0 (2 C; C-6, C-8 (Hpla)), 81.9 (*t*-Bu), 72.8 (C-2 (Hpla)), 50.9 (C-2 (Leu)), 41.7 (C-3 (Leu)), 39.7 (C-3 (Hpla)), 28.0 (3 C; *t*-Bu), 24.8 (C-4 (Leu)), 22.8 (C-5 (Leu)), 22.0 (C-5' (Leu)), 17.9 (6 C; TIPS), 12.6 (3 C; TIPS); MS [ESI (+)] m/z 530 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{28}\text{H}_{49}\text{NO}_5\text{Si}$: N 2.76, C 66.23, H 9.73; Found N 2.75 C 65.99, H 9.69.

HO-D-Hpla(TIPS)-D-Tyr(TIPS)-O-*t*-Bu (17b). A white solid; mp 93–93.5 °C; R_f = 0.17 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{23}$ +1.0 (*c* 1.1, CHCl_3); FT-IR (KBr) ν_{max} 3397, 2944, 2867, 1734, 1663, 1509, 1267, 917 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.08 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 6.97 (m, 1 H; NH (Tyr)), 6.91 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Tyr)), 6.82 (d, J = 8.5 Hz, 2 H; H-6, H-8 (Hpla)), 6.76 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Tyr)), 4.68 (dd, J = 14.5, 6.5 Hz, 1 H; H-2 (Tyr)), 4.22 (dd, J = 8.0, 3.5 Hz, 1 H; H-2 (Hpla)), 3.08 (dd, J = 14.0, 3.5 Hz, 1 H; H-3 (Hpla)), 2.98–2.90 (m, 2 H; H-3 (Tyr)), 2.73 (dd, J = 14.0, 8.0 Hz, 1 H; H-3 (Hpla)), 2.79–2.59 (br-s, 1 H; OH (Hpla)), 1.38 (s, 9 H; *t*-Bu), 1.27–1.19 (m, 6 H; TIPS), 1.14–1.05 (m, 36 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1 (C-1 (Tyr)), 170.5 (C-1 (Hpla)), 155.1 (C-7 (Hpla or Tyr)), 155.0 (C-7 (Hpla or Tyr)), 130.5 (2 C; C-5, C-9 (Hpla)), 130.4 (2 C; C-5, C-9 (Tyr)), 128.9 (C-4 (Hpla or Tyr)), 128.3 (C-4 (Hpla or Tyr)), 120.0 (2 C; C-6, C-8 (Hpla)), 119.7 (2 C; C-6, C-8 (Tyr)), 82.2 (*t*-Bu), 72.8 (C-2 (Hpla)), 53.1 (C-2 (Tyr)), 39.9 (C-3 (Hpla)), 37.5 (C-3 (Tyr)), 27.9 (3 C; *t*-Bu), 17.9 (12 C; TIPS), 12.6 (6 C; TIPS); MS [ESI (+)] m/z 736 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{40}\text{H}_{67}\text{NO}_6\text{Si}_2$: N 1.96, C 67.27, H 9.46; Found N 2.22, C 67.50, H 9.50.

HO-D-Hpla(TIPS)-D-Phe(4-F)-O-*t*-Bu (17c). A colorless oil; R_f = 0.34 (silica gel, EtOAc–hexane, 1:2); $[\alpha]_D^{23}$ –1.9 (*c* 1.0, CHCl_3); FT-IR (KBr) ν_{max} 3394, 2944, 2868, 1732, 1655, 1509, 1265, 1155 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.08 (d, J = 8.0 Hz, 2 H; H-5, H-9 (Hpla)), 7.04–6.92 (m, 5 H; H-5, H-6, H-8, H-9, NH (Phe)), 6.83 (d, J = 8.0 Hz, 2 H; H-6, H-8 (Hpla)), 4.71 (dd, J = 14.0, 6.0 Hz, 1 H; H-2 (Phe)), 4.28–4.24 (m, 1 H; H-2 (Hpla)), 3.10 (dd, J = 14.0, 3.5 Hz, 1 H; H-3 (Hpla)), 3.05–2.96 (m, 2 H; H-3 (Phe)), 2.78 (dd, J = 14.0, 8.0 Hz, 1 H; H-3 (Hpla)), 2.39 (br-s, 1 H; OH (Hpla)), 1.39 (s, 9 H;

t-Bu), 1.27–1.20 (m, 3 H; TIPS), 1.12–1.05 (m, 18 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1 (C-1 (Hpla or Phe)), 170.2 (C-1 (Hpla or Phe)), 162.0 (d, $J = 241$ Hz; C-7 (Phe)), 155.3 (C-7 (Hpla)), 131.8 (C-4 (Phe)), 130.9 (d, $J = 8.3$ Hz, 2 C; C-5, C-9 (Phe)), 130.5 (2 C; C-5, C-9 (Hpla)), 128.6 (C-4 (Hpla)), 120.1 (2 C; C-6, C-8 (Hpla)), 115.1 (d, $J = 21.6$ Hz, 2 C; C6, C-8 (Phe)), 82.5 (*t*-Bu), 72.8 (C-2 (Hpla)), 53.1 (C-2 (Phe)), 39.9 (C-3 (Hpla)), 37.5 (C-3 (Phe)), 27.9 (3 C; *t*-Bu), 17.9 (6 C; TIPS), 12.6 (3 C; TIPS); HR-MS [FAB (+)] Calcd for $\text{C}_{31}\text{H}_{47}\text{FNO}_5\text{Si}^+$ ($\text{M}+\text{H}^+$): 560.3202; Found 560.3204.

9.8. Synthesis of the Right Dipeptide (Choi-Arg Portion)

Synthesis of Boc-L-Choi(TIPS)-L-Arg(δ,ω' -di-Cbz)-OMe (20). A solution of LiOH (0.1 N in water, 16 mL) was added to a cooled (0 °C) solution of ester **8** (0.175 g, 0.6 mmol) in THF (15 mL), and the mixture was stirring at rt for 20 h. The mixture was extracted with Et_2O , and the aqueous phase was acidified with 5% aqueous NaHSO_4 to pH 4. Extraction of the aqueous layer with CH_2Cl_2 (six times) gave crude carboxylic acid. WSC·HCl (153 mg, 0.80 mmol) was added to a cooled (–20 °C) solution of the crude acid, **11a** (319 mg, 0.70 mmol), and HOBt (108 mg, 0.80 mmol) in anhydrous CH_2Cl_2 (10 mL). After stirring for 90 min at rt, the reaction was quenched by the addition of water. The mixture was extracted with Et_2O (10 mL $\times$ 3) and washed with 0.5 M citric acid (10 mL), saturated aqueous NaHCO_3 (10 mL), and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude **19**. TIPSOTf (0.32 mL, 1.2 mmol) was added to the cooled (0 °C) solution of the crude mixture and 2,6-lutidine (0.24 mL, 2.1 mmol). The mixture was stirred for 3 h at rt, and water was added. The solution was extracted with Et_2O (10 mL $\times$ 3), washed with brine (20 mL), and dried over Na_2SO_4 . After concentration, the residue was purified and the diastereomer was separated by flush column chromatography (silica gel, 10 to 30% EtOAc in hexane) to give **20** (385 mg, 0.44 mmol, 73% yield) as a white solid. mp 45.3–47.0 °C; $R_f = 0.82$ (silica gel, EtOAc-hexane, 1:1); $[\alpha]_D^{23} -22.8$ (c 1.0, CHCl_3), FT-IR (KBr) ν_{max} 3388, 2941, 1692, 1252, 1098, 698 cm^{-1} , ^1H NMR (500 MHz, CDCl_3) δ 9.45 (br-s, 1 H; *NHH*), 9.24 (br-s, 1 H; *NHH*), 7.38–7.25 (m, 10 H; Ar-H), 5.20 (s, 2 H; Cbz), 5.12 (s, 2 H; Cbz), 4.52 (m, 1 H; H-2 (Arg)), 4.17–4.09 (m, 3 H; H-2, H-6, H-7a (Choi)), 4.07–3.96 (m, 2 H; H-5 (Arg)), 3.60 (s, 3 H; CO_2CH_3), 2.20–2.00 (m, 4 H; H-3, H-3a, H-5 (Choi)), 1.92 (br-s, 1 H; H-3 (Choi)), 1.80 (br-s, 1 H; H-3 (Arg)), 1.66 (br-s, 3 H; H-4, H-3 (Arg)), 1.50–1.37 (m, 4 H; H-4, H-7 (Choi)), 1.38 (s, 9 H; *t*-Bu), 1.05 (s, 21 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 172.6 (C-1 (Arg)), 163.9 (Cbz), 160.7 (Cbz), 155.9 (C=N), 155.1 (C-1 (Choi)), 137.0 (Ar), 134.8 (Ar), 128.9 (Ar), 128.8 (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 80.0 ($\text{C}(\text{CH}_3)_3$), 68.9 (Cbz), 67.1 (Cbz), 67.0 (C-6 (Choi)), 60.4 (C-2 (Choi)), 55.1 (C-7a (Choi)), 52.3 (2 C; CO_2CH_3 , C-2 (Arg)), 44.3 (C-5 (Arg)), 36.2 (C-3 (Choi)), 35.1 (2 C; C-3a, C-7 (Choi)), 29.2 (C-3 (Arg)), 28.4 ($\text{C}(\text{CH}_3)_3$), 24.9 (C-4 (Arg)), 19.9 (2 C; C-5, C-4 (Choi)), 18.2 (TIPS), 12.3, (TIPS); MS [ESI(+)] m/z 880 [$\text{M}+\text{H}^+$], Anal. Calcd for $\text{C}_{46}\text{H}_{69}\text{N}_5\text{O}_{10}\text{Si}$: C 62.77, H 7.90, N 7.96; Found C 62.96, H 7.63, N 8.04.

Synthesis of Boc-L-Choi(TIPS)-L-Arg(α -methyl- δ,ω' -di-Cbz)-OMe (20b). A white solid. mp 50.5–53.0 °C; $R_f = 0.52$ (silica gel, EtOAc-hexane 1:2); $[\alpha]_D^{24} -38.1$ (c 0.86, CHCl_3); FT-IR (KBr) ν_{max} 3391, 2941, 1720, 1247, 1107, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.43 (br-s, 1 H; *NHH*), 9.22 (br-s, 1 H; *NHH*), 7.40–7.25 (m, 10 H; Ar-H), 5.22 (d, $J = 12.0$ Hz, 1 H; Cbz), 5.20 (d, $J = 12.0$ Hz, 1 H; Cbz), 5.11 (s, 2 H, Cbz), 4.20–4.09 (m, 3 H; H-2, H-6, H-7a (Choi), H-3 (Arg)), 3.94 (t, $J = 7.5$ Hz, 2 H; H-5 (Arg)), 3.56 (s, 3 H; CO_2CH_3), 2.18–1.76 (m, 7 H; H-3, H-3a, H-5, H-7 (Choi)), 1.54 (m, 1 H; H-7 (Choi)), 1.50–1.31 (m, 5 H; H-4 (Choi), H-4, H-3 (Arg)), 1.45 (s, 3 H; H-6 (Arg)), 1.40 (s, 9 H; *t*-Bu), 1.04 (s, 21 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 174.3 (C-1 (Arg)), 171.6 (C-1 (Choi)), 163.7 (Cbz), 160.3 (Cbz), 155.7 (C=N), 155.1 (Boc), 136.8 (Ar), 134.5 (Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.8 (Ar), 127.7 (Ar), 89.9 ($\text{C}(\text{CH}_3)_3$), 68.7 (Cbz), 66.9 Cbz), 66.7 (C-6 (Arg)), 59.4

(2C; C-2 (Choi), C-2 (Arg)), 55.1 (C-7a (Choi)), 52.3 (CO₂CH₃), 44.4 (C-5 (Arg)), 35.9 (C-3 (Choi)), 35.0 (2 C; C-3a, C-5 (Choi)), 33.1 (C-7 (Choi)), 28.2 (C(CH₃)₃), 27.6 (C-3 (Arg)), 23.4 (C-4 (Arg)), 22.6 (C-6 (Arg)), 20.0 (C-4 (Choi)), 18.0 (TIPS), 12.1 (TIPS); MS [ESI(+)] *m/z* 894 [M+H⁺]; HR-MS [FAB(+)] Calcd for C₄₇H₇₂N₅O₁₀Si⁺ (M+H⁺): 894.5043; Found 894.5051.

9.9. Synthesis of the Tetrapeptide

Synthesis of TIPS-O-D-Hpla(TIPS)-D-Leu-L-Choi(TIPS)-L-Arg(δ,ω' -di-Cbz)-OMe (22). TIPSOTf (15.9 μ L, 62 μ mol, 1.1 equiv) was added to a solution of **17** (27.2 mg, 53.6 μ L), *i*-Pr₂NEt (28.0 μ L, 0.170 mmol, 3 equiv) in dioxane (0.54 mL) at 10 °C. After stirring for 30 min, TMSOTf (20 μ L, 0.102 mmol, 1.9 equiv) was added and the reaction was refluxed for 1 h. After cooling to rt, the mixture was quenched by the addition of water followed by 1 N aqueous HCl. The aqueous layer was extracted with CH₂Cl₂ (three times), and the combined organic layers were dried over Na₂SO₄ and concentrated to give crude carboxylic acid **18**. Zn₂Br (60 mg, 0.268 mmol, 5 equiv) was added to a solution of **20** (47.2 mg, 53.6 μ L) in CH₂Cl₂ (2.7 mL). After stirring for 18 h at rt, the reaction was quenched by the addition of saturated aqueous NaHCO₃, extracted with CH₂Cl₂ (three times), dried over Na₂SO₄, and concentrated to give crude amine **21**. HATU (24 mg, 64.3 μ mol, 1.2 equiv) was added to a solution of the crude **18**, the crude **21**, *i*-Pr₂NEt (11 μ L, 64.3 μ mol, 1.2 equiv) in DMF at -5 °C (ice and NaCl). After stirring for 18 h at rt, the reaction was quenched by the addition of saturated aqueous NH₄Cl, extracted with CH₂Cl₂ (three times), dried over Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (silica gel, 10 to 20% EtOAc in hexane) to give tetrapeptide **22** (39.5 mg, 54%) as a colorless oil. *R_f* = 0.20 (silica gel, EtOAc–hexane, 1:3); [α]_D²⁴ -2.8 (*c* 1.3, CHCl₃); FT-IR (neat) $\nu_{\max}$ 3383, 2943, 2866, 1720, 1645, 1607, 1509, 1256, 1104 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.52 (br-s, 1 H; NHH (Arg)), 9.34 (br-s, 1 H; NHH (Arg)), 7.65 (d, *J* = 7.5 Hz, 1 H; NH (Arg)), 7.40–7.25 (m, 10 H; Cbz), 7.03 (d, *J* = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 6.80 (d, *J* = 8.0 Hz, 1 H; NH (Leu)), 6.71 (d, *J* = 8.5 Hz, 2 H; H-6, H-8 (Hpla)), 5.27 (d, *J* = 11.5 Hz, 1 H; Cbz), 5.24 (d, *J* = 11.5 Hz, 1 H; Cbz), 5.16 (d, *J* = 13.0 Hz, 1 H; Cbz), 5.12 (d, *J* = 13.0 Hz, 1 H; Cbz), 4.49 (dd, *J* = 12.8, 6.0 Hz, 1 H; H-2 (Arg)), 4.45–4.40 (m, 2 H; H-2 (Hpla), H-2 (Leu)), 4.29 (t, *J* = 9.0 Hz, 1 H; H-2 (Choi)), 4.20 (dt, *J* = 14.8, 7.6 Hz, 1 H; H-5 (Arg)), 4.16–4.12 (m, 1 H; H-6 (Choi)), 4.10–4.04 (m, 1 H; H-7a (Choi)), 3.90 (dt, *J* = 14.8, 7.6 Hz, 1 H; H-5 (Arg)), 3.62 (s, 3 H, CO₂CH₃), 2.99 (dd, *J* = 13.5, 4.5 Hz, 1 H; H-3 (Hpla)), 2.93 (dd, *J* = 13.5, 5.6 Hz, 1 H; H-3 (Hpla)), 2.20–2.00 (m, 3 H; H-3, H-3a, H-7 (Choi)), 1.83–1.60 (m, 6 H; H-3, H-7 (Choi), H-3, H-4 (Arg)), 1.55–1.30 (m, 4 H; H-4, H-5 (Choi)), 1.28–1.16 (m, 3 H; H-3, H-4 (Leu)), 1.10–0.99 (m, 63 H; TIPS), 0.84 (d, *J* = 6.0 Hz, 3 H; H-5 (Leu)), 0.78 (d, *J* = 6.0 Hz, 3 H; H-5' (Leu)); ¹³C NMR (125 MHz, CDCl₃) δ 172.33, 172.27, 171.5, and 170.7 (4 C; C-1 (Hpla, Leu, Choi, and Arg)), 163.9 (Cbz), 161.0 (C=N), 156.0 (Cbz), 154.6 (C-7 (Hpla)), 136.9 (Cbz), 134.7 (Cbz), 131.1 (2 C; C-5, C-9 (Hpla)), 129.1 (C-4 (Hpla)), 128.8, 128.4, 128.3, 128.0, 127.9, and 127.8 (10 C; Cbz), 119.2 (2 C; C-6, C-8 (Hpla)), 74.5 (C-2 (Hpla)), 68.9 (Cbz), 67.0 (Cbz), 66.7 (C-6 (Choi)), 59.9 (C-2 (Choi)), 55.0 (C-7a (Choi)), 52.7 (C-2 (Arg)), 52.0 (CO₂CH₃), 48.9 (C-2 (Leu)), 44.4 (C-5 (Arg)), 42.6 (C-3 (Leu)), 40.4 (C-3 (Hpla)), 36.6 (C-3a (Choi)), 34.3 (C-7 (Choi)), 29.5 (C-3 (Choi)), 27.5 (C-3 (Arg)), 26.7 (C-5 (Choi)), 25.1 (C-4 (Arg)), 24.3 (C-4 (Leu)), 23.4 (C-5 (Leu)), 22.0 (C-5' (Leu)), 19.3 (C-4 (Choi)), 18.1 (18 C; TIPS), 12.6 and 12.1 (9 C; TIPS); MS [ESI (+)] *m/z* 1392 (M+Na⁺); HR-MS [FAB (+)] Calcd for C₇₄H₁₂₁N₆O₁₂Si₃⁺ (M+H⁺): 1369.8345; Found 1369.8354.

TIPS-O-D-Hpla(TIPS)-D-Tyr(TIPS)-L-Choi(TIPS)-L-Arg(δ,ω' -di-Cbz)-OMe (22b). A colorless oil; *R_f* = 0.34 (silica gel, EtOAc–hexane, 1:3); [α]_D²⁴ +7.5 (*c* 1.1, CHCl₃); FT-IR (neat) $\nu_{\max}$ 3391, 2924, 2867, 1719, 1645, 1604, 1509, 1459, 1260 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.54 (br-s, 1 H; NHH (Arg)), 9.35 (br-s, 1 H; NHH (Arg)), 7.42–7.25 (m, 10 H; Cbz), 7.07 (d, *J* = 8.5 Hz, 2 H; H-5, H-9

(Hpla)), 6.98 (t, $J = 8.5$ Hz, 1 H; NH (Arg)), 6.92 (d, $J = 8.5$ Hz, 2 H; H-5, H-9 (Tyr)), 6.88 (d, $J = 7.5$ Hz, 1 H; NH (Tyr)), 6.74 (d, $J = 8.5$ Hz, 2 H; H-6, H-8 (Hpla)), 6.72 (d, $J = 8.5$ Hz, 2 H; H-6, H-8 (Tyr)), 5.27 (d, $J = 12.5$ Hz, 1 H; Cbz), 5.25 (d, $J = 12.5$ Hz, 1 H; Cbz), 5.19 (d, $J = 13.0$ Hz, 1 H; Cbz), 5.10 (d, $J = 13.0$ Hz, 1 H; Cbz), 4.65-4.59 (m, 1 H; H-2 (Tyr)), 4.49 (dd, $J = 13.0, 6.0$ Hz, 1 H; H-2 (Arg)), 4.44 (t, $J = 4.4$ Hz, 1 H; H-2 (Hpla)), 4.32-4.24 (m, 1 H; H-5 (Arg)), 4.07-3.98 (m, 2 H; H-2, H-6 (Choi)), 3.92-3.84 (m, 1 H; H-5 (Arg)), 3.63 (s, 3 H, CO₂CH₃), 3.52-3.46 (m, 1 H; H-7a (Choi)), 3.02-2.91 (m, 2 H; H-3 (Hpla)), 2.72 (dd, $J = 12.0, 3.5$ Hz, 1 H; H-3 (Tyr)), 2.39 (t, $J = 12.0$ Hz, 1 H; H-3 (Tyr)), 1.92 (br-d, $J = 13.0$ Hz, 1 H; H-7 (Choi)), 1.82-1.65 (m, 5 H; H-3a (Choi), H-3, H-4 (Arg)), 1.54 (t, $J = 13.0$ Hz, 1 H, H-7 (Choi)), 1.40-1.10 (m, 6 H; H-3, H-4, H-5 (Choi)), 1.10–0.90 (m, 84 H; TIPS); ¹³C NMR (125 MHz, CDCl₃) δ 172.4, 171.9, 171.4, and 169.1 (4 C; C-1 (Hpla, Tyr, Choi, and Arg)), 163.9 (Cbz), 161.0 (C=N), 156.0 (Cbz), 154.9 (C-7 (Hpla or Tyr)), 154.7 (C-7 (Hpla or Tyr)), 136.8 (Cbz), 134.7 (Cbz), 131.2 (2 C; C-5, C-9 (Hpla)), 130.5 (2 C; C-5, C-9 (Tyr)), 129.1, 128.6, 128.44, 128.3, 127.89, and 127.86 (10 C; Cbz), 128.7 (C-4 (Hpla or Tyr)), 128.35 (C-4 (Hpla or Tyr)), 119.4 (2 C; C-6, C-8 (Hpla)), 119.1 (2 C; C-6, C-8 (Tyr)), 74.4 (C-2 (Hpla)), 68.9 (Cbz), 67.0 (Cbz), 66.6 (C-6 (Choi)), 59.9 (C-2 (Choi)), 55.0 (C-7a (Choi)), 52.5 (C-2 (Arg)), 52.0 (CO₂CH₃), 51.6 (C-2 (Tyr)), 44.4 (C-5 (Arg)), 40.7 (C-3 (Hpla)), 39.2 (C-3 (Tyr)), 35.8 (C-3a (Choi)), 34.2 (C-7 (Choi)), 29.8 (C-3 (Choi)), 27.4 (C-3 (Arg)), 26.6 (C-5 (Choi)), 25.0 (C-4 (Arg)), 19.0 (C-4 (Choi)), 17.8 (24 C; TIPS), 12.5 and 12.2 (12 C; TIPS); MS [ESI (+)] m/z 1598 (M+Na⁺); HR-MS [FAB (+)] Calcd for C₈₆H₁₃₉N₆O₁₃Si₄⁺ (M+H⁺): 1575.9472; Found 1575.9492.

TIPSO-D-Hpla(TIPS)-D-Phe(4-F)-L-Choi(TIPS)-L-Arg(δ,ω' -di-Cbz)-OMe (22c). A colorless oil; $R_f = 0.48$ (silica gel, EtOAc–hexane, 1:2); $[\alpha]_D^{24} +4.8$ (c 1.0, CHCl₃); FT-IR (neat) $\nu_{\max}$ 3383, 2943, 2866, 1720, 1643, 1608, 1509, 1456, 1258 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.57 (br-s, 1 H; NH (Arg)), 9.39 (br-s, 1 H; NH (Arg)), 7.47 (d, $J = 8.3$ Hz, 1 H; NH (Arg)), 7.42-7.28 (m, 10 H; Cbz), 7.08 (d, $J = 8.5$ Hz, 2 H; H-5, H-9 (Hpla)), 6.98 (dd, $J = 8.6, 6.4$ Hz, 2 H; H-5, H-9 (Phe)), 6.92 (d, $J = 7.4$ Hz, 1 H; NH (Phe)), 6.88 (dd, $J = 8.6, 8.6$ Hz, 2 H; H-6, H-8 (Phe)), 6.74 (d, $J = 8.5$ Hz, 2 H; H-6, H-8 (Hpla)), 5.28 (d, $J = 11.9$ Hz, 1 H; Cbz), 5.24 (d, $J = 11.9$ Hz, 1 H; Cbz), 5.18 (d, $J = 12.5$ Hz, 1 H; Cbz), 5.14 (d, $J = 12.5$ Hz, 1 H; Cbz), 4.64-4.60 (m, 1 H; H-2 (Phe)), 4.53 (dd, $J = 14.1, 6.4$ Hz, 1 H; H-2 (Arg)), 4.44 (dd, $J = 4.6, 4.6$ Hz, 1 H; H-2 (Hpla)), 4.33 (dt, $J = 14.4, 7.2$ Hz, 1 H; H-5 (Arg)), 4.06 (br-s, 1 H; H-6 (Choi)), 3.98 (t, $J = 9.0$ Hz, 1 H; H-2 (Choi)), 3.82 (dt, $J = 14.4, 7.2$ Hz, 1 H; H-5 (Arg)), 3.62 (s, 3 H, CO₂CH₃), 3.42-3.36 (m, 1 H; H-7a (Choi)), 3.00 (dd, $J = 14.0, 4.6$ Hz, 1 H; H-3 (Hpla)), 2.95 (dd, $J = 14.0, 4.0$ Hz, 1 H; H-3 (Hpla)), 2.77 (dd, $J = 12.5, 4.6$ Hz, 1 H; H-3 (Phe)), 2.42 (dd, $J = 12.5, 10.7$ Hz, 1 H; H-3 (Phe)), 1.87 (br-d, $J = 14.0$ Hz, 1 H; H-7 (Choi)), 1.83-1.64 (m, 5 H; H-3a (Choi), H-3, H-4 (Arg)), 1.57 (t, $J = 12.5$ Hz, 1 H, H-7 (Choi)), 1.40-1.10 (m, 6 H; H-3, H-4, H-5 (Choi)), 1.10–0.90 (m, 63 H; TIPS); ¹³C NMR (125 MHz, CDCl₃) δ 172.4, 171.9, 171.1, and 168.5 (4 C; C-1 (Hpla, Phe, Choi, and Arg)), 163.9 (Cbz), 161.8 (d, $J = 244$ Hz; C-7 (Phe)), 161.1 (C=N), 156.0 (Cbz), 154.7 (C-7 (Hpla)), 136.8 (Cbz), 134.7 (Cbz), 131.2 (2 C; C-5, C-9 (Hpla)), 130.0 (d, $J = 8.2$ Hz, 2 C; C-5, C-9 (Phe)), 129.0 (C-4 (Phe)), 128.8, 128.5, 128.4, 128.3, 128.2, and 128.0 (10 C; Cbz), 127.9 (C-4 (Hpla)), 119.1 (2 C; C-6, C-8 (Hpla)), 115.1 (d, $J = 20.6$ Hz, 2 C; C-6, C-8 (Phe)), 74.4 (C-2 (Hpla)), 69.0 (Cbz), 67.1 (Cbz), 66.5 (C-6 (Choi)), 60.1 (C-2 (Choi)), 55.0 (C-7a (Choi)), 52.6 (C-2 (Arg)), 52.1 (CO₂CH₃), 51.4 (C-2 (Phe)), 44.5 (C-5 (Arg)), 40.6 (C-3 (Hpla)), 39.0 (C-3 (Phe)), 36.1 (C-3a (Choi)), 34.3 (C-7 (Choi)), 29.9 (C-3 (Choi)), 27.0 (C-3 (Arg)), 26.6 (C-5 (Choi)), 25.1 (C-4 (Arg)), 19.0 (C-4 (Choi)), 17.8 (18 C; TIPS), 12.6 and 12.1 (9 C; TIPS); HR-MS [FAB (+)] Calcd for C₇₇H₁₁₈FN₆O₁₂Si₃⁺ (M+H⁺): 1421.8094; Found 1421.8112.

TIPSO-D-Hpla(TIPS)-D-Tyr(TIPS)-L-Choi(TIPS)-L-Arg(α -methyl- δ,ω' -di-Cbz)-OMe (22d). A colorless oil; $R_f = 0.57$ (silica gel, EtOAc–hexane, 1:2); $[\alpha]_D^{23} -1.8$ (c 1.4, CHCl₃); FT-IR (neat) $\nu_{\max}$ 3384, 2944, 2867, 1721, 1609, 1510, 1463, 1263, 1106 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.43 (br-s,

1 H; *NHH* (Arg)), 9.24 (br-s, 1 H; *NHH* (Arg)), 7.42-7.25 (m, 10 H; Cbz), 7.06 (d, *J* = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 7.02 (s, 1 H; NH (Arg)), 6.90 (d, *J* = 8.5 Hz, 2 H; H-5, H-9 (Tyr)), 6.79-6.78 (m, 1 H; NH (Tyr)), 6.76 (d, *J* = 8.5 Hz, 2 H; H-6, H-8 (Hpla)), 6.71 (d, *J* = 8.5 Hz, 2 H; H-6, H-8 (Tyr)), 5.24 (s, 2 H; Cbz), 5.13 (s, 1 H; Cbz), 4.64-4.57 (m, 1 H; H-2 (Tyr)), 4.50 (t, *J* = 4.6 Hz, 1 H; H-2 (Hpla)), 4.09 (br-s, 1 H; C-6 (Choi)), 4.06 (t, *J* = 8.9 Hz, 1 H; H-2 (Choi)), 3.94 (t, *J* = 7.3 Hz, 1 H; H-5 (Arg)), 3.67-3.61 (m, 1 H; H-7a (Choi)), 3.58 (s, 3 H, CO₂CH₃), 3.00 (dd, *J* = 14.1, 4.6 Hz, 2 H; H-3 (Hpla)), 2.94 (dd, *J* = 14.1, 4.6 Hz, 2 H; H-3 (Hpla)), 2.59 (dd, *J* = 12.8, 4.9 Hz, 1 H; H-3 (Tyr)), 2.44 (t, *J* = 12.8 Hz, 1 H; H-3 (Tyr)), 2.09-2.03 (m, 1 H; H-7 (Choi)), 2.02-1.93 (m, 1 H; H-3a (Choi)), 1.88-1.77 (m, 2 H; H-3 (Arg)), 1.57-1.34 (m, 7 H; H-3, H-7 (Choi), H-4, H-5 (Arg)), 1.39 (s, 3 H; α-Me (Arg)), 1.18-1.10 (m, 2 H; H-4 (Choi)), 1.10-0.90 (m, 84 H; TIPS); ¹³C NMR (125 MHz, CDCl₃) δ 173.9, 172.0, 170.6, and 169.9 (4 C; C-1 (Hpla, Tyr, Choi, and Arg)), 163.9 (Cbz), 160.5 (C=N), 155.9 (Cbz), 155.1 (C-7 (Hpla or Tyr)), 154.8 (C-7 (Hpla or Tyr)), 137.0 (Cbz), 134.8 (Cbz), 131.1 (2 C; C-5, C-9 (Hpla)), 130.4 (2 C; C-5, C-9 (Tyr)), 128.8 (C-4 (Hpla or Tyr)), 128.7, 128.4, 128.2, 127.9, 127.80, and 127.76 (10 C; Cbz), 127.73 (C-4 (Hpla or Tyr)), 119.5 (2 C; C-6, C-8 (Tyr)), 119.1 (2 C; C-6, C-8 (Hpla)), 74.3 (C-2 (Hpla)), 68.8 (Cbz), 67.0 (Cbz), 66.6 (C-6 (Choi)), 59.8 (C-2 (Choi)), 59.1 (C-2 (Arg)), 55.5 (C-7a (Choi)), 52.2 (CO₂CH₃), 51.7 (C-2 (Tyr)), 44.6 (C-5 (Arg)), 40.6 (C-3 (Hpla)), 38.8 (C-3 (Tyr)), 35.4 (C-3a (Choi)), 34.0 (C-3 (Arg)), 33.9 (C-7 (Choi)), 29.2 (C-3 (Choi)), 26.7 (C-4 (Arg)), 23.2 (C-5 (Choi)), 22.3 (α-Me (Arg)), 19.1 (C-4 (Choi)), 18.0 (24 C; TIPS), 12.7 and 12.2 (12 C; TIPS); HR-MS [FAB (+)] Calcd for C₈₇H₁₄₁N₆O₁₃Si₄⁺ (M+H⁺): 1589.9628; Found 1589.9641.

Synthesis of TIPSO-D-Hpla(TIPS)-D-Leu-L-Choi(TIPS)-L-Argol(δ,ω'-di-Cbz) (23). A 0.5 M THF suspension of LiBH₄ (64 μL, 31.8 μmol, 1.0 equiv) was added to a solution of **22** (43.0 mg, 31.8 μmol) in THF (0.64 mL) six times (total 6.0 equiv) every 15 min at 4 °C. After stirring for additional 1 h at the same temperature, the reaction was quenched by the addition of water followed by saturated aqueous NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ (three times), dried over Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (silica gel, 20 to 100% EtOAc in hexane) to give **23** (28.6 mg, 54%, conv. 93%) as a colorless oil with recovery of **22** (18.2 mg, 42%). *R_f* = 0.37 (silica gel, EtOAc–hexane, 1:1); [α]_D²² –3.8 (*c* 1.4, CHCl₃); FT-IR (neat) ν_{max} 3389, 2942, 2862, 1724, 1648, 1612, 1515, 1463, 1258, 1104 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 9.46 (br-s, 1 H; *NHH* (Arg)), 9.25 (br-s, 1 H; *NHH* (Arg)), 7.40-7.25 (m, 10 H; Cbz), 6.97 (d, *J* = 8.3 Hz, 2 H; H-5, H-9 (Hpla)), 6.83 (d, *J* = 8.9 Hz, 1 H; NH (Leu)), 6.73 (d, *J* = 8.3 Hz, 2 H; H-6, H-8 (Hpla)), 6.70 (d, *J* = 3.0 Hz, 1 H; NH (Arg)), 5.26 (d, *J* = 12.2 Hz, 1 H; Cbz), 5.23 (d, *J* = 12.2 Hz, 1 H; Cbz), 5.14 (s, 2 H; Cbz), 4.50 (br-s, 1 H; H-2 (Hpla)), 4.47 (t, *J* = 8.9 Hz, 1 H; H-2 (Choi)), 4.24 (br-s, 1 H; H-6 (Choi)), 4.16-4.10 (m, 1 H; H-7a (Choi)), 4.06-4.01 (m, 3 H; H-2, H-5 (Arg)), 3.88 (br-s, 1 H; H-2 (Leu)), 3.51-3.42 (m, 2 H; H-1 (Arg)), 3.02 (dd, *J* = 14.0, 2.0 Hz, 1 H; H-3 (Hpla)), 2.93 (dd, *J* = 14.0, 4.8 Hz, 1 H; H-3 (Hpla)), 2.44 (br-d, *J* = 14.0 Hz, 1 H; H-7 (Choi)), 2.34-2.24 (m, 2 H; H-3, H-3a (Choi)), 2.17 (br-s, 1 H; OH (Arg)), 1.96-1.89 (m, 1 H; H-3 (Choi)), 1.80-1.45 (m, 8 H; H-3 (Leu), H-5, H-7 (Choi), H-3, H-4 (Arg)), 1.35-1.20 (m, 4 H; H-3, H-4 (Leu), H-4 (Choi)), 1.20–1.00 (m, 63 H; TIPS), 0.79 (d, *J* = 6.1 Hz, 6 H; H-5, H-5' (Leu)); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 171.5, and 170.6 (3 C; C-1 (Hpla, Leu, and Choi)), 164.0 (Cbz), 160.7 (C=N), 156.0 (Cbz), 154.9 (C-7 (Hpla)), 137.1 (Cbz), 134.8 (Cbz), 130.9 (2 C; C-5, C-9 (Hpla)), 128.8, 128.7, 128.4, 128.3, 127.8, and 127.7 (10 C; Cbz), 128.2 (C-4 (Hpla)), 119.2 (2 C; C-6, C-8 (Hpla)), 73.6 (C-2 (Hpla)), 68.8 (Cbz), 67.0 (Cbz), 66.6 (C-6 (Choi)), 63.3 (C-1 (Arg)), 60.7 (C-2 (Choi)), 55.3 (C-7a (Choi)), 51.0 (C-2 (Leu)), 50.7 (C-2 (Arg)), 44.7 (C-5 (Arg)), 40.0 (C-3 (Hpla)), 39.9 (C-3 (Leu)), 36.9 (C-3a (Choi)), 34.3 (C-7 (Choi)), 30.8 (C-3 (Choi)), 27.8 (C-3 (Arg)), 26.9 (C-5 (Choi)), 25.5 (C-4 (Arg)), 24.8 (C-4 (Leu)), 23.2 (C-5 (Leu)), 21.7 (C-5' (Leu)), 19.3 (C-4 (Choi)), 18.1 and 18.0 (18 C; TIPS), 12.7 and 12.2 (9 C; TIPS); MS [ESI (+)] *m/z* 1364 (M+Na⁺); HR-MS [FAB (+)] Calcd for C₇₃H₁₂₁N₆O₁₁Si₃⁺ (M+H⁺): 1341.8396; Found 1341.8401.

TIPSO-D-Hpla(TIPS)-D-Tyr(TIPS)-L-Choi(TIPS)-L-Argol(δ,ω' -di-Cbz) (23b). A colorless oil; R_f = 0.04 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{22}$ +0.7 (c 1.1, CHCl_3); FT-IR (neat) ν_{max} 3385, 2943, 2867, 1719, 1641, 1609, 1509, 1460, 1261 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.45 (br-s, 1 H; NH (Arg)), 9.26 (br-s, 1 H; NH (Arg)), 7.40-7.25 (m, 10 H; Cbz), 7.00 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 6.93 (d, J = 8.0 Hz, 2 H; H-5, H-9 (Tyr)), 6.82 (t, J = 9.0 Hz, 1 H; NH (Arg)), 6.79 (d, J = 8.5 Hz, 2 H; H-6, H-8 (Hpla)), 6.75 (d, J = 7.5 Hz, 1 H; NH (Tyr)), 6.73 (d, J = 8.0 Hz, 2 H; H-6, H-8 (Tyr)), 5.25 (d, J = 12.0 Hz, 1 H; Cbz), 5.21 (d, J = 12.0 Hz, 1 H; Cbz), 5.13 (s, 2 H; Cbz), 4.48 (t, J = 4.5 Hz, 1 H; H-2 (Hpla)), 4.29-4.21 (m, 2 H; H-2 (Tyr), H-2 (Choi)), 4.15-4.10 (m, 1 H; H-6 (Choi)), 4.08-3.96 (m, 2 H; H-5 (Arg)), 3.89-3.81 (m, 1 H; H-2 (Arg)), 3.64-3.57 (m, 1 H; H-7a (Choi)), 3.50-3.46 (m, 2 H; H-1 (Arg)), 2.96 (d, J = 4.5 Hz, 2 H; H-3 (Hpla)), 2.74 (d, J = 11.0 Hz, 1 H; H-3 (Tyr)), 2.65 (dd, J = 11.0, 5.5 Hz, 1 H; H-3 (Tyr)), 2.32-2.25 (m, 1 H; H-7 (Choi)), 2.05-1.98 (m, 1 H; H-3 (Choi)), 1.80-1.60 (m, 3 H; H-3 (Choi), H-4 (Arg)), 1.60-1.49 (m, 2 H, H-3 (Arg)), 1.48-1.18 (m, 6 H; H-3a, H-4, H-5, H-7 (Choi)), 1.10–1.00 (m, 84 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 174.4, 171.7, and 169.7 (3 C; C-1 (Hpla, Tyr, and Choi)), 163.9 (Cbz), 160.7 (C=N), 156.0 (Cbz), 155.4 (C-7 (Hpla or Tyr)), 154.9 (C-7 (Hpla or Tyr)), 137.0 (Cbz), 134.8 (Cbz), 130.9 (2 C; C-5, C-9 (Hpla)), 130.4 (2 C; C-5, C-9 (Tyr)), 128.8, 128.7, 128.4, 128.24, 127.8, and 127.7 (10 C; Cbz), 128.5 (C-4 (Hpla or Tyr)), 128.16 (C-4 (Hpla or Tyr)), 119.7 (2 C; C-6, C-8 (Tyr)), 119.3 (2 C; C-6, C-8 (Hpla)), 74.0 (C-2 (Hpla)), 68.8 (Cbz), 66.9 (Cbz), 66.5 (C-6 (Choi)), 63.5 (C-1 (Arg)), 60.7 (C-2 (Choi)), 55.2 (C-7a (Choi)), 52.9 (C-2 (Arg)), 51.3 (C-2 (Tyr)), 44.6 (C-5 (Arg)), 40.4 (C-3 (Hpla)), 37.2 (C-3 (Tyr)), 36.0 (C-3a (Choi)), 33.9 (C-7 (Choi)), 30.7 (C-3 (Choi)), 27.6 (C-3 (Arg)), 26.8 (C-5 (Choi)), 25.5 (C-4 (Arg)), 19.1 (C-4 (Choi)), 17.9 (24 C; TIPS), 12.7 and 12.1 (12 C; TIPS); MS [ESI (+)] m/z 1570 ($\text{M}+\text{Na}^+$); HR-MS [FAB (+)] Calcd for $\text{C}_{85}\text{H}_{139}\text{N}_6\text{O}_{12}\text{Si}_4^+$ ($\text{M}+\text{H}^+$): 1547.9523; Found 1547.9512.

TIPSO-D-Hpla(TIPS)-D-Phe(4-F)-L-Choi(TIPS)-L-Argol(δ,ω' -di-Cbz) (23c). A colorless oil; R_f = 0.54 (silica gel, EtOAc–hexane, 1:1); FT-IR (neat) ν_{max} 3384, 2943, 2866, 1720, 1644, 1608, 1509, 1455, 1259 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.46 (br-s, 1 H; NH (Arg)), 9.27 (br-s, 1 H; NH (Arg)), 7.39-7.25 (m, 10 H; Cbz), 6.99-6.97 (m, 4 H; H-5, H-9 (Hpla), H-5, H-9 (Phe)), 6.93 (t, J = 8.5 Hz, 2 H; H-6, H-8 (Phe)), 6.85 (d, J = 8.6 Hz, 1 H; NH (Arg)), 6.77 (d, J = 8.6 Hz, 2 H; H-6, H-8 (Hpla)), 6.74 (d, J = 4.0 Hz, 1 H; NH (Phe)), 5.25 (d, J = 12.0 Hz, 1 H; Cbz), 5.22 (d, J = 12.0 Hz, 1 H; Cbz), 5.13 (s, 2 H; Cbz), 4.48 (dd, J = 4.5, 4.0 Hz, 1 H; H-2 (Hpla)), 4.30-4.23 (m, 2 H; H-2 (Phe), H-2 (Choi)), 4.13 (br-s, 1 H; H-6 (Choi)), 4.08-4.02 (m, 1 H; H-5 (Arg)), 4.01-3.95 (m, 1 H; H-5 (Arg)), 3.89-3.80 (m, 1 H; H-2 (Arg)), 3.58-3.54 (m, 1 H; H-7a (Choi)), 3.46 (br-s, 2 H; H-1 (Arg)), 2.98 (dd, J = 14.0, 4.0 Hz, 1 H; H-3 (Hpla)), 2.94 (dd, J = 14.0, 4.5 Hz, 1 H; H-3 (Hpla)), 2.78 (dd, J = 13.1, 9.5 Hz, 1 H; H-3 (Phe)), 2.70 (dd, J = 13.1, 6.4 Hz, 1 H; H-3 (Phe)), 2.28-2.22 (m, 1 H; H-7 (Choi)), 2.07-2.00 (m, 1 H; H-3 (Choi)), 1.85-1.60 (m, 3 H; H-3 (Choi), H-4 (Arg)), 1.60-1.50 (m, 2 H, H-3 (Arg)), 1.45-1.20 (m, 6 H; H-3a, H-4, H-5, H-7 (Choi)), 1.10–1.04 (m, 63 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 174.3, 171.5, and 169.3 (3 C; C-1 (Hpla, Phe, and Choi)), 163.8 (Cbz), 160.6 (C=N), 160.0 (d, J = 244 Hz, C-7 (Phe)), 156.0 (Cbz), 154.8 (C-7 (Hpla)), 137.0 (Cbz), 134.7 (Cbz), 130.9 (2 C; C-5, C-9 (Hpla)), 130.6 (2 C; C-5, C-9 (Phe)), 128.8, 128.7, 128.4, 128.3, 127.8, and 127.7 (12 C; C-4 (Hpla), C-4 (Phe), Cbz), 119.4 (2 C; C-6, C-8 (Hpla)), 115.4 (2 C; C-6, C-8 (Phe)), 73.8 (C-2 (Hpla)), 68.8 (Cbz), 66.9 (Cbz), 66.4 (C-6 (Choi)), 63.5 (C-1 (Arg)), 60.7 (C-2 (Choi)), 55.3 (C-7a (Choi)), 52.6 (C-2 (Phe)), 51.3 (C-2 (Arg)), 44.6 (C-5 (Arg)), 40.2 (C-3 (Hpla)), 36.8 (C-3 (Phe)), 36.3 (C-3a (Choi)), 34.0 (C-7 (Choi)), 30.6 (C-3 (Choi)), 27.4 (C-3 (Arg)), 26.7 (C-5 (Choi)), 25.4 (C-4 (Arg)), 19.1 (C-4 (Choi)), 17.9 (18 C; TIPS), 12.6 and 12.2 (9 C; TIPS); MS [ESI (+)] m/z 1570 ($\text{M}+\text{Na}^+$); HR-MS [FAB (+)] Calcd for $\text{C}_{76}\text{H}_{118}\text{FN}_6\text{O}_{11}\text{Si}_3^+$ ($\text{M}+\text{H}^+$): 1393.8145; Found 1393.8165.

TIPSO-D-Hpla(TIPS)-D-Tyr(TIPS)-L-Choi(TIPS)-L-Argol(α -methyl- δ -Cbz) (23d). The reaction was performed at rt and 5 equiv of LiBH_4 was added in 1 portion because almost no reaction proceeded

using standard conditions. A colorless oil; $R_f = 0.05$ (silica gel, EtOAc–hexane, 1:1); $[\alpha]_D^{22} +2.9$ (c 1.7, CHCl_3); FT-IR (neat) ν_{max} 3416, 2943, 2867, 1641, 1510, 1462, 1266 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.27 (m, 5 H; Cbz), 7.01 (dd, $J = 8.5, 2.1$ Hz, 2 H; H-5, H-9 (Hpla)), 6.92 (dd, $J = 8.5, 2.1$ Hz, 2 H; H-5, H-9 (Tyr)), 6.84 (br-d, $J = 4.5$ Hz, 1 H; NH (Tyr)), 6.78 (dd, $J = 8.5, 2.1$ Hz, 2 H; H-6, H-8 (Hpla)), 6.73 (dd, $J = 8.5, 2.1$ Hz, 2 H; H-6, H-8 (Tyr)), 6.39 (br-s, 1 H; NH (Arg)), 5.18 (s, 2 H; Cbz), 4.48–4.44 (m, 1 H; H-2 (Hpla)), 4.43–4.37 (m, 1 H; H-2 (Tyr)), 4.13 (br-s, 1 H; H-6 (Choi)), 4.07 (t, $J = 8.3$ Hz, 1 H; H-2 (Choi)), 3.68–3.60 (m, 1 H; H-7a (Choi)), 3.52–3.46 (m, 2 H; H-1 (Arg)), 3.18–3.11 (m, 2 H; H-5 (Arg)), 2.97–2.93 (m, 2 H; H-3 (Hpla)), 2.65–2.60 (d, $J = 11.0$ Hz, 1 H; H-3 (Tyr)), 2.30–2.20 (m, 2 H; H-3a, C-7 (Choi)), 2.01 (s, 1 H; α -Me (Arg)), 1.97–1.90 (m, 1 H; H-3 (Choi)), 1.88–1.73 (m, 2 H; H-3 (Choi), H-3 (Arg)), 1.65–1.52 (m, 3 H, H-3, H-4 (Arg)), 1.49–1.18 (m, 5 H; H-4, H-5, H-7 (Choi)), 1.10–1.00 (m, 84 H; TIPS); ^{13}C NMR (125 MHz, CDCl_3) δ 178.1 (Cbz), 173.6, 172.2, and 170.2 (3 C; C-1 (Hpla, Tyr, and Choi)), 155.4 (C-7 (Hpla or Tyr)), 155.0 (C-7 (Hpla or Tyr)), 136.1 (Cbz), 130.9 (2 C; C-5, C-9 (Hpla)), 130.4 (2 C; C-5, C-9 (Tyr)), 128.4, 128.0, and 127.8 (5 C; Cbz), 127.8 (C-4 (Hpla or Tyr)), 126.9 (C-4 (Hpla or Tyr)), 119.7 (2 C; C-6, C-8 (Tyr)), 119.3 (2 C; C-6, C-8 (Hpla)), 74.2 (C-2 (Hpla)), 68.4 (C-1 (Arg)), 67.1 (Cbz), 66.5 (C-6 (Choi)), 61.0 (C-2 (Choi)), 57.8 (C-2 (Arg)), 55.5 (C-7a (Choi)), 52.5 (C-2 (Tyr)), 41.6 (C-5 (Arg)), 40.7 (C-3 (Hpla)), 39.8 (C-3 (Tyr)), 35.8 (C-3a (Choi)), 34.0 (C-7 (Choi)), 32.8 (C-3 (Arg)), 30.3 (C-3 (Choi)), 26.8 (C-5 (Choi)), 23.0 (C-4 (Arg)), 22.7 (α -Me (Arg)), 19.0 (C-4 (Choi)), 17.9 (24 C; TIPS), 12.7 and 12.1 (12 C; TIPS).

Synthesis of HO-D-Hpla-D-Leu-L-Choi-L-Argol: Aeruginosin 298-A (1a). HF•Py (0.1 mL) was added to a solution of **23** (17.0 mg, 12.7 μmol) in THF (0.5 mL) at rt. After stirring for 24 h at the same temperature, the reaction was cooled with ice bath and quenched by the addition of saturated aqueous NaHCO_3 , extracted with CH_2Cl_2 (three times), dried over Na_2SO_4 , and concentrated. The residue was briefly purified by short column chromatography (silica gel, EtOAc to 5% MeOH in EtOAc) to give a mixture of triol-diCbz and triol-Cbz. 10% Pd-C (1.4 mg, 1.3 μmol , 10 mol %) was added to a solution of the mixture in EtOH (0.25 mL) and argon was replaced with hydrogen (1 atm). After stirring for 1 h, the mixture was filtered through Cerite pad and concentrated under reduced pressure. The residue treated with 0.5% TFA in EtOH (0.5 mL) and concentrated again. The TFA salt was purified by R-HPLC (Shiseido CAPCELL PAK C18, 30% MeOH in water, 1 mL/min, t_R 32 min, detected at 280 nm) to give TFA salt of **1** (7.3 g, 80%) as a white solid. $[\alpha]_D^{23} -34$ (c 0.13, H_2O): lit. $[\alpha]_D -72.7$ (c 0.23, H_2O), $[\alpha]_D +16$ (c 0.17, H_2O)⁴; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.11 (s, 1 H; 7-OH (Hpla)), 7.54 (d, $J = 8.6$ Hz, 1 H; 2-NH (Arg)), 7.48–7.44 (m, 2 H; NH (Leu), 5-NH (Arg)), 6.98 (d, $J = 8.5$ Hz, 2 H; H-5, H-9 (Hpla)), 6.62 (d, $J = 8.5$ Hz, 2 H; H-6, H-8 (Hpla)), 5.69 (d, $J = 5.5$ Hz, 1 H; 2-OH (Hpla)), 4.62 (t, $J = 5.5$ Hz, 1 H; OH (Arg)), 4.54–4.48 (m, 2 H; H-2 (Leu), OH (Choi)), 4.16 (t, $J = 9.1$ Hz, 1 H; H-2 (Choi)), 4.06–4.02 (m, 2 H; H-2 (Hpla), H-7a (Choi)), 3.91 (br-s, 1 H; H-6 (Choi)), 3.66–3.61 (m, 1 H; H-2 (Arg)), 3.30 (dd, $J = 10.5, 5.0$ Hz, 1 H; H-1 (Arg)), 3.21 (dd, $J = 10.5, 6.0$ Hz, 1 H; H-1 (Arg)), 3.10–3.04 (m, 2 H; H-5 (Arg)), 2.85 (dd, $J = 14.1, 3.5$ Hz, 1 H; H-3 (Hpla)), 2.63 (dd, $J = 14.1, 7.7$ Hz, 1 H; H-3 (Hpla)), 2.31–2.24 (m, 1 H; H-3a (Choi)), 2.09–1.95 (m, 3 H; H-3, H-4, H-7 (Choi)), 1.80 (td, $J = 12.4, 10.4$ Hz, 1 H; H-3 (Choi)), 1.65 (t, $J = 12.0$ Hz, 1 H; H-7 (Choi)), 1.60–1.18 (m, 10 H; H-3, H-4 (Leu), H-4, H-5 (Choi), H-3, H-4 (Arg)), 0.87 (d, $J = 6.1$ Hz, 3 H; H-5 (Leu)), 0.82 (d, $J = 6.1$ Hz, 3 H; H-5' (Leu)); ^{13}C NMR (125 MHz, CDCl_3) δ 174.8 (C-1 (Hpla)), 171.2 (C-1 (Choi)), 169.7 (C-1 (Leu)), 156.6 (C=N), 155.7 (C-7 (Hpla)), 130.4 (2 C; C-5, C-9 (Hpla)), 128.0 (C-4 (Hpla)), 114.6 (2 C; C-6, C-8 (Hpla)), 72.1 (C-2 (Hpla)), 63.8 (C-6 (Choi)), 63.2 (C-1 (Arg)), 59.8 (C-2 (Choi)), 54.0 (C-7a (Choi)), 50.1 (C-2 (Arg)), 48.1 (C-2 (Leu)), 41.8 (C-3 (Leu)), 40.7 (C-5 (Arg)), 39.0 (C-3 (Hpla)), 35.9 (C-3a (Choi)), 33.4 (C-7 (Choi)), 30.5 (C-3 (Choi)), 27.9 (C-3 (Arg)), 26.5 (C-5 (Choi)), 25.0 (C-4 (Arg)), 23.9 (C-4 (Leu)), 23.3 (C-5 (Leu)), 21.3 (C-5' (Leu)), 18.9 (C-4 (Choi)); MS [ESI (+)] m/z 605 ($\text{M}+\text{H}^+$); HR-MS [FAB (+)] Calcd for $\text{C}_{30}\text{H}_{48}\text{N}_6\text{NaO}_7^+$ ($\text{M}+\text{Na}^+$): 627.3477; Found 627.3491.

HO-D-Hpla-D-Tyr-L-Choi-L-Argol (31b). A white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.32 (br-s, 1 H; 7-OH (Hpla or Tyr)), 8.65 (br-s, 1 H; 7-OH (Hpla or Tyr)), 7.65-7.52 (m, 3 H; NH (Tyr), 2-NH, 5-NH (Arg)), 6.98 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 6.85 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Tyr)), 6.68-6.64 (m, 4 H; H-6, H-8 (Hpla), H-6, H-8 (Tyr)), 5.88 (br-s, 1 H; 2-OH (Hpla)), 4.80-4.73 (m, 1 H, OH (Arg)), 4.64-4.58 (m, 1 H; H-2 (Tyr)), 4.47 (s, 1 H; OH (Choi)), 4.07 (t, J = 8.5 Hz, 1 H; H-2 (Choi)), 4.04-3.99 (m, 1 H; H-2 (Hpla)), 3.84 (br-s, 1 H; H-6 (Choi)), 3.70-3.60 (m, 2 H; H-7a (Choi), H-2 (Arg)), 3.35-3.25 (m, 1 H; H-1 (Arg)), 3.23-3.17 (m, 1 H; H-1 (Arg)), 3.11-3.04 (m, 2 H; H-5 (Arg)), 2.82 (dd, J = 14.0, 2.8 Hz, 1 H; H-3 (Hpla)), 2.75 (dd, J = 13.5, 5.2 Hz, 1 H; H-3 (Tyr)), 2.62-2.55 (m, 2 H; H-3 (Hpla), H-3 (Tyr)), 1.93-1.75 (m, 2 H; H-3, H-7 (Choi)), 1.72-1.55 (m, 2 H; H-3, H-3a (Choi)), 1.55-1.40 (m, 5 H; H-5, H-7 (Choi), H-3, H-4 (Arg)), 1.40-1.23 (m, 4 H; H-4, H-5 (Choi), H-3 (Arg)); ^{13}C NMR (125 MHz, CDCl_3) δ 172.7, 171.2, and 168.7 (3 C; C-1 (Hpla, Tyr, and Choi)), 157.2, 156.2, and 155.7 (3 C; C=N, C-7 (Hpla), C-7 (Tyr)), 130.4 (2 C; C-5, C-9 (Hpla)), 130.2 (2 C; C-5, C-9 (Tyr)), 128.0 (C-4 (Hpla or Tyr)), 126.2 (C-4 (Hpla or Tyr)), 114.9 (2 C; C-6, C-8 (Hpla)), 114.7 (2 C; C-6, C-8 (Tyr)), 72.1 (C-2 (Hpla)), 63.8 (C-6 (Choi)), 63.2 (C-1 (Arg)), 59.7 (C-2 (Choi)), 54.1 (C-7a (Choi)), 51.3 (C-2 (Tyr)), 50.1 (C-2 (Arg)), 40.8 (C-5 (Arg)), 39.2 (C-3 (Hpla)), 38.0 (C-3 (Tyr)), 35.7 (C-3a (Choi)), 33.2 (C-7 (Choi)), 30.3 (C-3 (Choi)), 28.0 (C-3 (Arg)), 25.7 (C-5 (Choi)), 25.0 (C-4 (Arg)), 18.8 (C-4 (Choi)); MS [ESI (+)] m/z 655 ($\text{M}+\text{H}^+$); HR-MS [FAB (+)] Calcd for $\text{C}_{33}\text{H}_{47}\text{N}_6\text{O}_8^+$ ($\text{M}+\text{H}^+$): 655.3450; Found 655.3453.

HO-D-Hpla-D-Phe(4-F)-L-Choi-L-Argol(α -methyl) (31c). A white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.14 (br-s, 1 H; 7-OH (Hpla)), 7.59 (d, J = 7.3 Hz, 1 H; NH (Phe)), 7.55-7.50 (m, 2 H; 5-NH (Arg), 2-NH (Arg)), 7.08 (d, J = 8.5 Hz, 4 H; H-5, H-9 (Hpla), H-5, H-9 (Phe)), 6.98 (d, J = 8.5 Hz, 2 H; H-6, H-8 (Phe)), 6.65 (d, J = 8.5 Hz, 2 H; H-6, H-8 (Hpla)), 5.72 (br-d, J = 4.3 Hz, 1 H; 2-OH (Hpla)), 4.70-4.62 (m, 1 H; H-2 (Phe)), 4.59 (t, J = 5.2 Hz, 1 H; OH (Arg)), 4.50 (br-s, 1 H; OH (Choi)), 4.10 (t, J = 8.4 Hz, 1 H; H-2 (Choi)), 4.05-4.00 (m, 1 H; H-2 (Hpla)), 3.87 (br-s, 1 H; H-6 (Choi)), 3.76-3.70 (m, 1 H; H-7a (Choi)), 3.67-3.60 (m, 1 H; H-2 (Arg)), 3.35-3.25 (m, 1 H; H-1 (Arg)), 3.23-3.17 (m, 1 H; H-1 (Arg)), 3.10-3.02 (m, 2 H; H-5 (Arg)), 2.87-2.78 (m, 2 H; H-3 (Hpla), H-3 (Phe)), 2.75 (dd, J = 13.1, 7.6 Hz, 1 H; H-3 (Phe)), 2.58 (dd, J = 13.1, 7.9 Hz, 1 H; H-3 (Hpla)), 2.00-1.80 (m, 2 H; H-3, H-7 (Hpla)), 1.75-1.68 (m, 2 H; H-3, H-3a (Choi)), 1.62-1.25 (m, 9 H; H-4, H-5, H-7 (Choi), H-3, H-4 (Arg)); ^{13}C NMR (125 MHz, CDCl_3) δ 172.8, 171.1, and 168.3 (3 C; C-1 (Hpla, Phe, and Choi)), 160.2 (C-7 (Phe)), 156.8 (C=N), 155.7 (C-7 (Hpla)), 132.5 (C-4 (Phe)), 131.2 (2 C; C-5, C-9 (Phe)), 130.4 (2 C; C-5, C-9 (Hpla)), 128.2 (C-4 (Hpla)), 114.9 (2 C; C-6, C-8 (Phe)), 114.7 (2 C; C-6, C-8 (Hpla)), 72.1 (C-2 (Hpla)), 63.8 (C-6 (Choi)), 63.2 (C-1 (Arg)), 59.8 (C-2 (Choi)), 54.1 (C-7a (Choi)), 51.0 (C-2 (Tyr)), 50.2 (C-2 (Arg)), 40.4 (C-5 (Arg)), 39.4 (C-3 (Hpla)), 37. (C-3 (Phe)), 35.8 (C-3a (Choi)), 33.1 (C-7 (Choi)), 30.4 (C-3 (Choi)), 28.0 (C-3 (Arg)), 25.8 (C-5 (Choi)), 25.0 (C-4 (Arg)), 18.8 (C-4 (Choi)); MS [ESI (+)] m/z 655 ($\text{M}+\text{H}^+$); HR-MS [FAB (+)] Calcd for $\text{C}_{33}\text{H}_{46}\text{FN}_6\text{O}_7^+$ ($\text{M}+\text{H}^+$): 657.3407; Found 657.3402.

HO-D-Hpla-D-Tyr-L-Choi-L-Argol(α -methyl) (31d). A white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.29 (br-s, 1 H; 7-OH (Hpla or Tyr)), 9.14 (br-s, 1 H; 7-OH (Hpla or Tyr)), 7.69 (br-s, 1 H; 5-NH (Arg)), 7.51 (d, J = 7.6 Hz, 1 H; NH (Tyr)), 7.23 (s, 1 H; 2-NH (Arg)), 6.98 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Hpla)), 6.84 (d, J = 8.5 Hz, 2 H; H-5, H-9 (Tyr)), 6.4 (d, J = 8.5 Hz, 4 H; H-6, H-8 (Hpla), H-6, H-8 (Tyr)), 5.70 (d, J = 5.2 Hz, 1 H; 2-OH (Hpla)), 4.65-4.59 (m, 2 H; H-2 (Tyr), OH (Arg)), 4.47 (br-s, 1 H; OH (Choi)), 4.05 (t, J = 8.5 Hz, 1 H; H-2 (Choi)), 4.04-3.08 (m, 1 H; H-2 (Hpla)), 3.83 (br-s, 1 H; H-6 (Choi)), 3.66-3.61 (m, 1 H; H-7a (Choi)), 3.45-3.30 (m, 2 H; H-1 (Arg)), 3.05-2.98 (m, 2 H; H-5 (Arg)), 2.81 (br-d, J = 13.0 Hz, 1 H; H-3 (Hpla)), 2.70 (dd, J = 13.2, 6.8 Hz, 1 H; H-3 (Tyr)), 2.63-2.54 (m, 2 H; H-3 (Hpla), H-3 (Tyr)), 2.16 (t, J = 7.5 Hz, 2 H; H-3, H-7 (Choi)), 1.90-1.25 (m, 12 H; H-3, H-3a (Choi), H-4, H-5, H-7 (Choi), H-3, H-4 (Arg)), 1.10 (s, 3 H; α -Me (Arg)); ^{13}C NMR (125 MHz,

CDCl₃) δ 172.7, 171.2, and 168.7 (3 C; C-1 (Hpla, Tyr, and Choi)), 156.8 (C=N), 156.2 (C-7 (Hpla or Tyr)), 156.0 (C-7 (Hpla or Tyr)), 130.4 (2 C; C-5, C-9 (Hpla)), 130.2 (2 C; C-5, C-9 (Tyr)), 128.0 (C-4 (Hpla or Tyr)), 126.2 (C-4 (Hpla or Tyr)), 114.9 (2 C; C-6, C-8 (Hpla)), 114.7 (2 C; C-6, C-8 (Tyr)), 72.1 (C-2 (Hpla)), 63.8 (C-6 (Choi)), 63.2 (C-1 (Arg)), 59.7 (C-2 (Choi)), 54.1 (C-7a (Choi)), 51.3 (C-2 (Tyr)), 50.1 (C-2 (Arg)), 40.8 (C-5 (Arg)), 39.2 (C-3 (Hpla)), 38.0 (C-3 (Tyr)), 35.7 (C-3a (Choi)), 33.2 (C-7 (Choi)), 30.3 (C-3 (Choi)), 28.0 (C-3 (Arg)), 25.7 (C-5 (Choi)), 25.0 (C-4 (Arg)), 18.8 (C-4 (Choi)); MS [ESI (+)] m/z 669 (M+H⁺); HR-MS [FAB (+)] Calcd for C₃₄H₄₉N₆O₈⁺ (M+H⁺): 669.3606; Found 669.3612.

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