Supporting information

Total Synthesis of (-)-Kaitocephalin

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General Methods

All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Merck & Co., Inc., Nacalai Tesque Company, Ltd., Peptide Institute, Tokyo Kasei Kogyo Co., Ltd., or Wako Pure Chemical Industries, Ltd., and used without further purification unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from phosphoric pentaoxide (P_2O_5). Methanol (MeOH) was distilled from magnesium turning and iodine. Ethanol (EtOH) was distilled from calcium hydride (CaH_2).

Melting points were determined with a Yanaco MP-21 melting point apparatus and were uncorrected. Optical rotations were taken on JASCO P-1030 polarimeter with a sodium lamp (D line). FTIR spectra was measured on a JASCO FT/IR-420 infraed spectrophotometer. ^1H NMR spectra were recorded on an either JEOL JNM-LA 300 (300 MHz), JEOL JNM-LA 400 (400 MHz), or Bruker AVANCE 600 (600 MHz) spectrometer. Chemical shifts of ^1H NMR were reported in parts per million (ppm, δ) relative to CHCl_3 ($\delta = 7.26$) in CDCl_3 or HDO ($\delta = 4.80$) in D_2O , or $\text{C}_6\text{D}_5\text{H}$ ($\delta = 7.15$) in C_6D_6 . ^{13}C NMR spectra were recorded on an either JEOL JNM-LA 300 (75 MHz) or JEOL JNM-LA 400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to CHCl_3 ($\delta = 77.0$) in CDCl_3 , CH_3OH ($\delta = 49.0$) in D_2O , or $\text{C}_6\text{D}_5\text{H}$ ($\delta = 128.0$) in C_6D_6 . Low resolution mass spectra (LRMS) and High resolution mass spectra (HRMS) were obtained on an JEOL JMS-AX500 for fast atom bombardment ionization (FAB), chemical ionization (CI), or electron ionization (EI). Elemental analysis were recorded on a Perkin-Elmer 240C. All reactions were monitored by thin layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm thickness, manufactured by Merck). TLC visualization was accompanied using UV lamp (245 nm) or a charring solution (ethanoic *p*-anisaldehyde, ethanoic phosphomolybdic acid, aqueous potassium permanganate and butanoic ninhydrin). Daisogel IR-60 1002W (40/63 mm) was used for flash column chromatography on silica gel. Reversed phase chromatography was performed on Cosmosil[®] 140C₁₈-PREP.

(2R)-1-*tert*-Butyl 2-(*tert*-butyldimethylsilyloxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate methyl ester (6)

To a solution of **4** (10.0 g, 56.6 mmol) in MeOH (566 mL) was added Dowex[®] 50W x4 (124 g) at room temperature. The reaction mixture was heated to reflux for 12 days, filtered, eluted with MeOH/NEt₃ (9:1), and concentrated under reduced pressure to give δ-lactone intermediate. To a solution of the δ-lactone in MeOH (566 mL) was added NaCN (555 mg, 11.3 mmol) at room temperature. The reaction mixture was heated to reflux for 18 h, filtered through a thin silica gel pad, and concentrated under reduced pressure to give **5**. To a solution of **5** in CH₂Cl₂ (283 mL) was added TBSCl (10.2 g, 67.9 mmol), NEt₃ (11.9 mL, 84.9 mmol) and DMAP (691 mg, 5.66 mmol) at 0 °C. The reaction mixture was stirred at room temperature under argon for 20 h, quenched with sat. NaHCO₃, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in THF (283 mL) was added Boc₂O (14.0 mL, 61.2 mmol), NEt₃ (9.00 mL, 64.0 mmol) and DMAP (781 mg, 6.40 mmol) at 0 °C. The reaction mixture was stirred at room temperature under argon for 15 h, quenched with sat. NH₄Cl, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 15:1 then 8:1) to give **6** (12.3 g, 56%, 4 steps) as colorless oil: [α]²⁵_D

+44.6 (*c* 1.10, CHCl₃); FTIR (neat) 2955, 2932, 2889, 2857, 1794, 1747, 1725, 1472, 1369, 1312, 1257 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.24 (d, *J* = 10.4 Hz, 1H), 3.96 (d, *J* = 10.4 Hz, 1H), 3.71 (s, 3H), 2.67 (ddd, *J* = 17.6, 10.2, 8.8 Hz, 1H), 2.47 (ddd, *J* = 17.6, 10.8, 3.9 Hz, 1H), 2.24 (ddd, *J* = 12.9, 10.2, 3.9 Hz, 1H), 2.10-2.01 (m, 1H), 1.46 (s, 9H), 0.84 (s, 9H), 0.03 (s, 3H), 0.008 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 171.8, 149.2, 83.5, 68.9, 64.9, 52.3, 31.5, 27.9, 26.9, 25.7, 18.0, -5.67; HRMS (FAB) *m/z* (M+H)⁺ calcd for [C₁₈H₃₃NO₆Si+H]⁺ 388.2155, found 388.2153.

(2*R*)-1-*tert*-Butyl 2-(hydroxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate methyl ester (6A)

To a solution of **6** (925 mg, 2.39 mmol) in THF (12 mL) was added AcOH (1.03 mL, 17.9 mmol) and TBAF (1M solution in THF, 5.98 mL, 5.98 mmol) at 0 °C. The reaction mixture was stirred at room temperature under argon for 22 h, quenched with sat. NaHCO₃, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 4:1 then 1:1) to give **6A** (607 mg, 93%) as white solids: mp. 116-117 °C (dec); [α]_D²⁵ +26.2 (*c* 0.65, CHCl₃); FTIR (neat) 3424, 2981, 2946, 1787, 1735, 1308, 1270 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.19 (dd, *J* = 11.5, 4.88 Hz, 1H), 3.82 (dd, *J* = 11.5, 8.8 Hz, 1H), 3.78 (s, 3H), 2.75-2.80 (br m, 1H), 2.50-2.70 (m, 2H), 2.41 (ddd, *J* = 13.2, 9.76, 5.84 Hz, 1H), 2.13 (ddd, *J* = 13.2, 10.0, 8.04 Hz, 1H), 1.50 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 172.7, 149.6, 84.2, 68.6, 64.5, 52.6, 30.7, 27.9, 25.3; HRMS (FAB) *m/z* (M+H)⁺ calcd for [C₁₂H₁₉NO₆+H]⁺ 274.1290, found 274.1287; Anal. Calcd for C₁₂H₁₉NO₆: C, 52.74; H,

7.01; N, 5.13. Found: C, 52.83; H, 7.04; N, 5.05.

(2*R*)-1-*tert*-Butyl 2-formyl-5-oxopyrrolidine-1,2-dicarboxylate methyl ester (3**)**

To a solution of **6A** (6.4 g, 23.4 mmol) in CH_2Cl_2 (60 ml) was added TEMPO (365 mg, 2.34 mmol) and $\text{PhI}(\text{OAc})_2$ (8.30 g, 25.8 mmol) at room temperature. The reaction mixture was stirred at room temperature under argon for 26 h, filtered through thin silica gel pad, eluted with ethyl acetate, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 8:1 then 2:1) to give **3** (6.2 g, 98%) as colorless oil: $[\alpha]^{29}_{\text{D}} +27.5$ (c 0.95, CHCl_3); FTIR (neat) 3541, 1798, 1763, 1740, 1717, 1458, 1437, 1371, 1321, 1293, 1257, 1154 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.98 (s, 1H), 3.86 (s, 3H), 2.53-2.61 (m, 2H), 2.20-2.24 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 193.6, 172.0, 169.7, 148.7, 84.8, 72.1, 53.2, 30.3, 27.7, 24.9; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{12}\text{H}_{17}\text{NO}_6+\text{H}]^+$ 272.1134, found 272.1142.

(2R)-1-tert-Butyl 2-((E)-2-(methoxycarbonyl)vinyl)-5-oxopyrrolidine-1,2-dicarboxylate methyl ester (7)

To a solution of **3** (588 mg, 2.17 mmol) in toluene (7 mL) was added $\text{Ph}_3\text{PCHCO}_2\text{Me}$ (1.09 g, 3.25 mmol) at room temperature. The reaction mixture was stirred at 80 °C under argon for 1.5 h and concentrated under reduce pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 8:1 then 3:1) to give **7** (695 mg, 98%, 2:1 mixture of rotamers) as colorless oil: $[\alpha]^{25}_{\text{D}} +66.9$ (c 1.15, CHCl_3); FTIR (neat) 2981, 2956, 1794, 1749, 1723, 1662, 1437, 1371, 1304, 1258, 1155 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, J = 15.9 Hz, 1/3H), 7.42 (d, J = 15.9 Hz, 2/3H), 5.85 (d, J = 15.9 Hz, 1/3H), 5.84 (d, J = 15.9 Hz, 2/3H), 3.77 (s, 1H), 3.76 (s, 2H), 3.73 (s, 1H), 3.72 (s, 2H), 2.42-2.60 (m, 2H), 2.20-2.34 (m, 1H), 2.00-2.12 (m, 1H), 1.39 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.7, 170.6, 165.9, 148.4, 144.9, 119.9, 84.2, 68.4, 53.0, 51.8, 30.0, 29.9, 27.6; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{15}\text{H}_{21}\text{NO}_7+\text{H}]^+$ 328.1396, found 328.1398.

(2R)-1-tert-Butyl 2-((1R,2S)-2-(methoxycarbonyl)-1,2-dihydroxyethyl)-5-oxopyrrolidine-1,2-dicarboxylate methyl ester (8)

To a solution of **7** (1.6 g, 4.89 mmol) in THF (49 mL) was added DMAP (1.43 g, 11.7

mmol) and OsO₄ (1.5 g, 5.91 mmol) at -78 °C. The reaction mixture was stirred at -78 °C under argon for 19 h, quenched with NaHSO₃ (5.1 g, 49.0 mmol) in water (50 mL), stirred at room temperature for 1 h, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 5:1 then 1:1) to give **8** (1.73 g, 98%) as white solids: mp. 148-149 °C (dec); [α]²²_D +31.9 (*c* 1.15, CHCl₃); FTIR (neat) 3470, 1786, 1742, 1304, 1284, 1257, 1155 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.70 (d, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 8.0 Hz, 1H), 4.10 (br d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.30, (br d, *J* = 5.9 Hz, 1H), 2.45-2.60 (m, 3H), 2.10-2.20 (m, 1H), 1.52 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 173.4, 171.6, 151.4, 84.6, 72.2, 71.1, 70.2, 53.2, 52.8, 30.7, 27.9, 25.0; HRMS (FAB) *m/z* (M+H)⁺ calcd for [C₁₅H₂₃NO₉+H]⁺ 362.1451, found 362.1451; Anal. Calcd for C₁₅H₂₃NO₉: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.89; H, 6.42; N, 3.81.

(2R)-1-tert-Butyl 2-((4R,5S)-5-(methoxycarbonyl)-2-thioxo-1,3-dioxolan-4-yl)-5-oxopyrrolidine-1,2-dicarboxylate methyl ester (9**)**

To a solution of **8** (1.2 g, 3.32 mmol) in CH₂Cl₂ (11 mL) was added TCDI (888 mg, 4.98 mmol) at room temperature. The reaction mixture was heated to reflux under argon for 2 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 8:1 then 3:1) to give **9** (1.3 g, 99%) as colorless oil: [α]²⁵_D +78.7 (*c* 0.84, CHCl₃); FTIR (neat) 1797, 1757, 1715, 1311, 1281, 1151 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.88 (d, *J* = 6.1 Hz, 1H),

5.29 (d, $J = 6.1$ Hz, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 2.70-2.82 (m, 1H), 2.63 (ddd, $J = 17.8, 10.2, 5.1$ Hz, 1H), 2.13-2.29 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.3, 171.5, 170.2, 165.8, 149.4, 85.4, 83.2, 80.1, 68.4, 53.8, 53.4, 30.1, 27.8, 22.9; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{16}\text{H}_{21}\text{NO}_9\text{S}+\text{H}]^+$ 404.1015, found 404.1012.

(2R)-Methyl 2-((1S,2R)-2-(methoxycarbonyl)-2-azido-1-hydroxyethyl)-5-oxopyrrolidine-2-carboxylate (11)

To a solution of TFA (16 mL) in CH_2Cl_2 (16 mL) was added a solution of **9** (1.32 g, 3.29 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The reaction mixture was stirred at 0 °C under argon for 1.5 h and concentrated under reduced pressure to give **10**. To a solution of **10** in DMF (17 mL) was added NaN_3 (647 mg, 9.96 mmol) and PPTS (1.67 g, 6.64 mmol) at 0 °C. The reaction mixture was stirred at room temperature under argon for 16 h, quenched with sat. NaHCO_3 , and extracted with ethyl acetate (x4). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 3:1, 1:1 then 1:9) to give **11** (846 mg, 89%) as colorless oil: $[\alpha]^{25}_{\text{D}} +56.3$ (c 0.48, CHCl_3); FTIR (neat) 3333, 2114, 1742, 1692, 1260 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.08 (br s, 1H), 4.21 (d, $J = 7.9$ Hz, 1H), 3.93 (d, $J = 7.9$ Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.26-2.45 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.3, 172.5, 169.2, 73.9, 68.2, 62.4, 53.1, 53.0, 29.4, 25.8; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_6+\text{H}]^+$ 287.0991, found 287.0976.

(2*R*)-Methyl 2-((1*S*,2*R*)-2-(methoxycarbonyl)-2-azido-1-(*tert*-butyldimethylsilyloxy)ethyl)-5-oxopyrrolidine-2-carboxylate (11A**)**

To a solution of **11** (8.8 mg, 31 μmol) in CH_2Cl_2 (0.3 mL) was added TBSOTf (11 μL , 46 μmol) and 2,6-lutidine (9 μL , 77 μmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at room temperature under argon for 4 h, quenched with sat. NaHCO_3 , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 4:1 then 3:2) to give **11A** (11 mg, 89%) as colorless oil: $[\alpha]_D^{26} +35.9$ (c 1.00, CHCl_3); FTIR (neat) 2955, 2929, 2857, 2115, 1745, 1705, 1269, 1217 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.04 (br d, $J = 11.2$ Hz, 1H), 4.41 (d, $J = 5.1$ Hz, 1H), 4.05 (d, $J = 5.1$ Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.27-2.50 (m, 4H), 0.85 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.7, 171.8, 167.8, 74.7, 68.7, 64.5, 53.0, 52.8, 29.4, 25.6, 24.9, 18.0, -4.53, -4.56; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{16}\text{H}_{28}\text{N}_4\text{O}_6\text{Si}+\text{H}]^+$ 401.1856, found 401.1851.

Spirolactam (12)

To a solution of **11A** (14 mg, 35 μmol) in THF-H₂O (3:1) (0.4 mL) was added PPh₃ (18 mg, 70 μmol) at room temperature. The reaction mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 3:1, 1:1 then 1:5) to give **12** (8.6 mg, 72%) as colorless oil: $[\alpha]^{20}_{\text{D}} -2.6$ (c 1.01, CHCl₃); FTIR (neat) 3245, 2956, 2929, 2858, 1728, 1691, 1462, 1437, 1363, 1254, 1223, 1156 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.19 (br s, 1H), 6.51 (br s, 1H), 4.41 (d, J = 7.1 Hz, 1H), 3.93 (d, J = 7.1 Hz, 1H), 3.80 (s, 3H), 2.58-2.66 (m, 1H), 2.30-2.51 (m, 2H), 1.88-2.05 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.1, 175.0, 171.5, 77.3, 67.3, 59.1, 52.8, 29.3, 25.5, 22.7, 17.8, -4.44, -5.46; HRMS (FAB) m/z (M+H)⁺ calcd for [C₁₅H₂₆N₂O₅Si+H]⁺ 343.1739, found 343.1688.

(1*S*,7*aR*)-Methyl 1-((*R*)-(methoxycarbonyl)azidomethyl)-hexahydro-3,3-dimethyl-5-oxopyrrolo[1,2-*c*]oxazole-7*a*-carboxylate (**11B**)

To a solution of **11** (496 mg, 1.73 mmol) in toluene (8.6 mL) was added 2, 2-dimethoxypropane (541 μL , 5.19 mmol) and CSA (40 mg, 0.173 mmol) at room

temperature. The reaction mixture was heated to reflux under argon for 18 h, quenched with sat. NaHCO₃, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 8:1, 5:1, 3:1, 1:1 then 1:10) to give **11B** (169 mg, 30%) as colorless oil and recovery of **11** (248 mg, 50%): $[\alpha]^{25}_{\text{D}} -49.4$ (c 0.79, CHCl₃); FTIR (neat) 2111, 1744, 1710, 1373, 1252, 1171 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.86 (d, J = 9.15 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (d, J = 9.15 Hz, 1H), 2.85 (ddd, J = 16.7, 11.5, 8.4 Hz, 1H), 2.53 (ddd, J = 16.5, 9.0, 0.9 Hz, 1H), 2.34 (ddd, J = 13.2, 11.5, 8.9 Hz, 1H), 2.11 (ddd, J = 13.3, 8.4, 0.9 Hz, 1H), 1.71 (s, 3H), 1.36 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 171.2, 168.2, 93.3, 76.7, 75.0, 61.3, 53.4, 52.9, 35.1, 26.9, 26.6, 26.1; HRMS (FAB) m/z (M+H)⁺ calcd for [C₁₃H₁₈N₄O₆+H]⁺ 327.1304, found 327.1304.

Cbz-amine (**13**)

To a solution of **11B** (48 mg, 0.147 mmol) in ethyl acetate (0.7 mL) was added Pd-C (5 mg, 10 wt%) at room temperature. The reaction mixture was stirred at room temperature under hydrogen for 2.5 h, filtered, and concentrated under reduced pressure. To a solution of the residue in CH₂Cl₂ (0.7 mL) was added CbzOSu (48 mg, 0.191 mmol) and DMAP (23 mg, 0.191 mmol) at 0 °C. The reaction mixture was stirred at room temperature under argon for 21 h, quenched with sat. NH₄Cl, and extracted with ethyl acetate (x3). The combined organic layers were washed with

brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 4:1 then 1:1) to give **13** (57 mg, 89%) as colorless oil: $[\alpha]^{26}_{\text{D}} -33.1$ (c 0.83, CHCl_3); FTIR (neat) 3297, 2996, 2954, 1744, 1709, 1534, 1373, 1266, 1227, 1170 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.26-7.34 (m, 5H), 5.45 (br d, $J = 8.3$ Hz, 1H), 5.11 (s, 2H), 4.56 (d, $J = 10.1$ Hz, 1H), 4.40-4.47 (br m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.78 (ddd, $J = 16.5, 11.7, 8.0$ Hz, 1H), 2.46-2.60 (br m, 1H), 2.15-2.30 (br m, 1H), 1.95 (dd, $J = 13.2, 8.0$ Hz, 1H), 1.72 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.6, 171.5, 170.7, 155.3, 135.7, 128.5, 128.4, 128.2, 93.4, 77.9, 75.2, 67.6, 54.7, 53.4, 52.6, 35.1, 27.1, 26.2, 25.9; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_8+\text{H}]^+$ 435.1767, found 435.1769.

(4*R*,5*S*)-3-Benzyl 5-((*R*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-oxopyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester (15**)**

To a solution of **13** (18 mg, 0.042 mmol) in CH_2Cl_2 (0.2 mL) was added TFA (0.2 mL) at 0 °C. The reaction mixture was stirred at room temperature under argon for 3 h and concentrated under reduced pressure to give **14**. To a solution of **14** in THF (0.2 mL) was added Boc_2O (14 μL , 62 μmol) and DMAP (7.6 mg, 62 μmol) at room temperature. The reaction mixture was stirred at room temperature under argon for 15 h, quenched with sat. NH_4Cl , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by

flash column chromatography (elution with hexane/EtOAc = 10:1 then 3:1) to give **15** (21 mg, 92%, 2:1 mixture of rotamers) as colorless oil: $[\alpha]^{27}_{\text{D}} +46.6$ (c 0.53, CHCl_3); FTIR (neat) 2981, 2946, 1795, 1752, 1717, 1408, 1352, 1308, 1298, 1258, 1159 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.23-7.35 (m, 5H), 5.15-5.22 (m, 1H), 5.04-5.11 (m, 1H), 4.80-4.98 (m, 2H), 3.80 (s, 1H), 3.78 (s, 2H), 3.70 (s, 1H), 3.53 (s, 2H), 2.42-2.62 (m, 2H), 2.10-2.25 (m, 1H), 1.81-1.96 (m, 1H), 1.73 (s, 2H), 1.67 (s, 1H), 1.51 (s, 2H), 1.49 (s, 6H), 1.48 (s, 3H), 1.45 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 173.2, 170.6, 170.5, 170.47, 170.4, 152.5, 151.3, 149.6, 149.4, 136.1, 135.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 94.4, 93.8, 84.3, 84.2, 75.3, 74.9, 68.4, 68.3, 67.6, 66.8, 61.3, 60.6, 52.7, 52.5, 52.4, 30.9, 30.8, 27.8, 26.1, 25.1, 24.9, 24.0, 21.7, 21.4; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_{10}+\text{H}-\text{Boc}]^+$ 435.1767, found 435.1775.

(4*R*,5*S*)-3-Benzyl 4-methyl 5-((2*R*,5*R*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-allylpyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate (20**)**

To a solution of **15** (159 mg, 0.298 mmol) in THF (3 mL) was added LiBEt_3H (1 M solution in THF, 446 μL , 0.446 mmol) at $-78\text{ } ^\circ\text{C}$. The reaction mixture was stirred at $-78\text{ } ^\circ\text{C}$ under argon for 1 h, quenched with sat. NaHCO_3 / 30% H_2O_2 (1:1, 17 mL), stirred at room temperature for 2 h, and extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (3 mL) was added Ac_2O (42 μL , 0.447 mmol) and DMAP (55 mg, 0.447 mmol)

at room temperature. The reaction mixture was stirred at room temperature under argon for 1.5 h, quenched with sat. NH_4Cl , and extracted with diethyl ether (x3). The combined organic layers were washed with sat. NaHCO_3 , dried over anhydrous MgSO_4 , filtered through thin silica gel pad, and concentrated under reduced pressure to give **18**. To a solution of CuBr dimethylsulfide complex (245 mg, 1.19 mmol) in THF (1.5 mL) was added allylmagnesium bromide (1M solution in Et_2O , 1.2 mL, 1.20 mmol) at $-40\text{ }^\circ\text{C}$ under argon, stirred at $-40\text{ }^\circ\text{C}$ for 1 h, cooled to $-78\text{ }^\circ\text{C}$, added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (321 μL , 1.20 mmol), and stirred at $-78\text{ }^\circ\text{C}$ for 0.5 h. To a mixture was added a solution of **18** in THF (0.5 mL x3) at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h, warmed to $0\text{ }^\circ\text{C}$ for 2 h, quenched with a mixture of sat. NaHCO_3 and 1N NH_4OH , and extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/ EtOAc = 10:1 then 6:1) to give **20** (100 mg, 60%, an inseparable mixture of diastereomers (ca.2:1) and a mixture of rotamers) as colorless oil and recovery of **18** (13.5 mg, 8%).

20: FTIR (neat) 2978, 2952, 1746, 1717, 1699, 1405, 1390, 1365, 1352, 1211 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of diastereomers and rotamers. See appendix.; ^{13}C NMR (75 MHz, CDCl_3) δ 172.4, 172.2, 171.0, 152.6, 151.6, 151.5, 136.4, 136.0, 135.5, 128.5, 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 116.9, 116.4, 93.7, 93.6, 93.2, 93.0, 80.6, 80.3, 80.27, 75.2, 74.5, 69.4, 69.1, 67.5, 67.4, 66.7, 66.6, 61.8, 61.1, 61.9, 58.9, 58.7, 52.3, 52.2, 52.1, 38.7, 38.4, 38.1, 37.1, 29.1, 28.6, 28.3, 27.6, 27.3, 26.9, 26.2, 25.1, 24.9, 24.0, 23.8; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_9+\text{H}]^+$ 561.2812, found 561.2811.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*R*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-(2-(*tert*-butyldimethylsilyloxymethyl)-2-hydroxyethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester (22ab)

To a solution of **20** (100 mg, 0.179 mmol) in *t*-BuOH- H_2O (1.8 mL, 1:1) was added OsO_4 (114 μL , 1g/25 mL in *t*-BuOH) and NMO (26 mg, 0.215 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, quenched with KHSO_3 aq, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (1.8 mL) was added TBSCl (32 mg, 0.215 mmol), triethylamine (37 μL , 0.267 mmol), and DMAP (2 mg, 17.9 μmol) at room temperature under argon for 14 h, quenched with sat. NH_4Cl , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 10:1 then 6:1) to give **22ab** (78 mg, 62%, an inseparable mixture of 4 diastereomers and a mixture of rotamers) as colorless oil: FTIR (neat) 3476, 2953, 2930, 2857, 1748, 1715, 1697, 1457, 1436, 1404, 1353, 1253, 1213 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of diastereomers and rotamers. See appendix.; ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 172.3, 172.0, 171.5, 170.9, 170.8, 170.6, 154.0, 153.7, 153.0, 152.5, 151.5, 151.4, 136.4, 136.2, 136.1, 135.9, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 93.8, 93.6, 93.5, 93.1, 93.0, 81.6, 81.1, 80.8, 80.4, 80.3, 76.5, 75.5, 75.1, 75.0, 74.6, 70.6, 70.0, 69.8, 69.6, 69.5, 69.1, 68.9, 67.8, 67.5, 67.4, 67.2, 66.7, 66.5, 66.4, 62.0, 61.8, 61.7, 61.3, 61.1, 61.0, 60.9, 57.7, 57.1, 56.9, 56.6, 56.5, 56.3, 55.9, 52.3, 52.1, 38.4, 38.0, 37.6, 37.1, 37.0, 31.1, 30.7,

30.2, 29.8, 29.6, 29.4, 29.2, 29.1, 28.7, 28.2, 28.1, 27.4, 26.2, 25.9, 25.8, 25.1, 25.0, 24.99, 24.8, 24.0, 23.9, 23.85, 23.83, 23.81, 23.7, 23.69, 23.65, 18.4, 18.19, 18.17, -5.24, -5.34, -5.44, -5.48; HRMS (FAB) m/z (M+H)⁺ calcd for [C₃₅H₅₆N₂O₁₁Si+H]⁺ 709.3731, found 709.3717.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*R*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-(2-(*tert*-butyldimethylsilyloxymethyl)-2-azidoethyl)pyrrolidin-2-yl)-2,2-dimethyl oxazolidine-3,4-dicarboxylate methyl ester (23ab)

To a solution of **22ab** (78 mg, 0.11 mmol) in THF (0.6 mL) was added DPPA (47 μ L, 0.22 mmol), PPh₃ (58 mg, 0.22 mmol), and DEAD (35 μ L, 0.22 mmol) at room temperature. The reaction mixture was stirred at room temperature under argon for 1 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 10:1 then 7:1) to give **23ab** (80 mg, 99%, an inseparable mixture of 4 diastereomers and a mixture of rotamers) as colorless oil: FTIR (neat) 2953, 2857, 2108, 1746, 1716, 1698, 1457, 1404, 1390, 1352, 1254, 1212, 1161 cm⁻¹; Complex ¹H NMR spectra was observed, because of a mixture of diastereomers and rotamers. See appendix.; ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 172.2, 171.9, 171.7, 170.9, 154.0, 153.5, 153.0, 152.5, 151.5, 151.4, 136.3, 136.0, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 93.7, 93.6, 93.5, 93.3, 93.1, 93.0, 80.83, 80.78, 75.7, 75.5, 75.1, 74.9, 74.5, 69.2, 69.0, 68.6, 67.4, 67.0, 66.96, 66.7, 66.6, 66.3, 65.9, 62.6, 62.4, 61.9, 61.7, 61.5, 61.4, 61.1, 60.9, 58.4, 57.7, 57.0, 56.7, 56.6, 56.5, 56.0, 52.4, 52.3, 52.2, 52.13, 52.11, 52.09, 35.6, 35.4, 35.1, 34.4,

34.3, 34.2, 33.0, 30.6, 30.3, 30.2, 29.9, 29.6, 29.3, 29.28, 29.25, 29.0, 28.9, 28.7, 28.2, 28.17, 27.34, 27.26, 26.2, 25.71, 25.7, 25.2, 25.0, 24.8, 24.2, 24.0, 23.7, 18.14, 18.11, 18.09, -5.59, -5.61, -5.64; HRMS (FAB) m/z ($M+H$)⁺ calcd for $[C_{35}H_{55}N_5O_{10}Si+H]^+$ 734.3796, found 734.3804.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*R*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-(2-(*tert*-butyldimethylsilyloxymethyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester (24ab)

To a solution of **23ab** (80 mg, 0.11 mmol) in THF-H₂O (0.5 mL, 3:1) was added PMe₃ (1M solution in THF, 545 μ L, 0.545 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. To a solution of the residue in CH₂Cl₂ (0.5 mL) was added 4-benzyloxy-3,5-dichlorobenzoic acid (39 mg, 0.13 mmol), BOP reagent (58 mg, 0.13 mmol) and DIPEA (28 μ L, 0.16 mmol) at 0 °C. The reaction mixture was stirred at room temperature under argon for 14 h, quenched with sat. NH₄Cl, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (developed with hexane/EtOAc = 3:1) to give **24ab** (51 mg, 48%, an inseparable mixture of diastereomers and a mixture of rotamers) as colorless oil and (**7*S*, 9*S*)-24a** (29 mg, 27%) as colorless oil.

24ab: FTIR (neat) 3323, 2952, 2929, 2857, 1746, 1717, 1700, 1668, 1541, 1470, 1457, 1405, 1351, 1259, 1212 cm⁻¹; Complex ¹H NMR spectra was observed, because of a

mixture of diastereomers and rotamers. See appendix.; ^{13}C NMR (100 MHz, CDCl_3) δ 171.7, 171.6, 171.5, 170.8, 170.7, 170.5, 170.4, 164.4, 164.2, 153.4, 153.2, 153.1, 152.9, 152.73, 152.71, 152.66, 152.63, 152.55, 151.51, 151.47, 151.4, 136.2, 136.1, 135.94, 135.91, 132.0, 131.99, 131.7, 131.65, 131.61, 130.2, 129.9, 129.7, 128.49, 128.47, 128.43, 128.38, 128.32, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 93.84, 93.80, 93.7, 93.35, 93.33, 93.2, 81.83, 81.81, 81.76, 81.68, 80.6, 76.0, 75.3, 74.9, 69.4, 68.8, 68.73, 68.70, 68.5, 67.5, 67.4, 67.35, 66.7, 66.5, 64.5, 64.1, 62.24, 62.22, 62.0, 61.9, 61.3, 61.2, 61.0, 60.9, 57.04, 57.0, 56.9, 55.63, 55.59, 55.3, 52.4, 52.3, 52.26, 52.2, 52.16, 52.12, 51.0, 50.9, 50.8, 50.7, 50.6, 37.1, 36.7, 36.5, 36.4, 36.1, 31.34, 31.30, 31.2, 30.9, 30.8, 30.6, 29.6, 29.4, 29.0, 28.96, 28.8, 28.32, 28.26, 26.2, 26.1, 25.8, 25.73, 25.70, 25.6, 25.3, 25.22, 25.20, 25.0, 24.99, 24.96, 24.89, 24.2, 23.8, 18.14, 18.07, -5.37, -5.40, -5.49, -5.51; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{49}\text{H}_{65}\text{N}_3\text{O}_{12}\text{Cl}_2\text{Si}+\text{H}]^+$ 986.3793, found 986.3799.

Desilylation of **24ab**

To a solution of **24ab** (51 mg, 51.8 μmol) in THF (0.3 mL) was added AcOH (3 μL , 51.8 μmol) and TBAF (1M solution in THF, 207 μL , 207 μmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at room temperature under argon for 0.5 h, quenched with sat. NaHCO_3 , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (developed with hexane/EtOAc = 1:1) to give **(7R, 9S)-25a** (25 mg, 55%, an inseparable mixture of

diastereomers and a mixture of rotamers) as colorless oil and (**7R, 9R**)-**25b** (17 mg, 38%, a mixture of rotamers) as colorless oil.

(4R,5S)-3-Benzyl 5-((2R,5R)-1-(tert-butoxycarbonyl)-2-(methoxycarbonyl)-5-((S)-2-(hydroxylmethyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7R, 9S)-25a): FTIR (neat) 3322, 2976, 2951, 1746, 1717, 1699, 1669, 1550, 1456, 1406, 1352, 1268, 1214 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of diastereomers and rotamers. See appendix.; ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 171.6, 171.3, 171.2, 170.7, 170.6, 170.5, 170.4, 165.3, 165.1, 154.24, 154.21, 153.50, 153.49, 153.1, 153.0, 152.7, 152.5, 151.5, 151.4, 136.2, 136.1, 135.9, 135.8, 131.5, 131.3, 129.87, 129.85, 128.6, 128.54, 128.49, 128.44, 128.39, 128.37, 128.20, 128.18, 128.03, 128.0, 127.8, 127.79, 93.9, 93.7, 93.5, 93.2, 82.3, 82.28, 82.26, 82.22, 82.19, 76.5, 75.8, 75.1, 75.0, 68.94, 68.90, 68.86, 68.81, 67.7, 67.6, 66.83, 66.80, 64.4, 64.3, 64.2, 62.0, 61.9, 61.3, 61.2, 56.13, 56.10, 55.85, 55.77, 53.6, 36.9, 35.7, 35.6, 31.4, 31.0, 30.9, 29.9, 29.8, 28.9, 28.7, 28.33, 28.26, 26.3, 26.2, 25.4, 25.2, 25.0, 24.97, 24.4, 23.9; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{43}\text{H}_{51}\text{N}_3\text{O}_{12}\text{Cl}_2+\text{H}]^+$ 872.2928, found 872.2924.

(4R,5S)-3-Benzyl 5-((2R,5R)-1-(tert-butoxycarbonyl)-2-(methoxycarbonyl)-5-((R)-2-(hydroxylmethyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7R, 9R)-25b): $[\alpha]^{22}_{\text{D}} +7.5$ (c 0.83, CHCl_3); FTIR (neat) 3339, 2976, 2951, 1746, 1717, 1703, 1669, 1548, 1456, 1405, 1352, 1270, 1213 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of rotamers. See appendix.; ^{13}C NMR (100 MHz, CDCl_3) δ 172.0, 171.8, 170.7, 170.4, 165.9, 165.7, 153.6, 153.5, 153.0, 152.95, 152.7, 151.5, 136.2, 136.0, 135.9, 130.84, 130.83, 129.8, 129.7, 128.6, 128.5, 128.47, 128.4, 128.37, 128.2, 128.0, 127.8, 127.5, 94.1, 93.6, 82.2, 82.16, 76.5, 75.9, 75.1, 69.1, 69.0, 67.7, 67.0, 66.9, 66.8, 61.9, 61.2, 57.4, 57.3, 52.5, 52.48, 52.38, 52.29, 52.25, 52.1, 36.1, 35.8, 31.4, 31.0, 30.2, 29.9, 29.7, 28.5, 28.4, 28.34, 28.30, 26.2, 25.04, 25.0, 23.9; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{43}\text{H}_{51}\text{N}_3\text{O}_{12}\text{Cl}_2+\text{H}]^+$ 872.2928, found 872.2915.

Protected kaitocephalin ((7*R*, 9*S*)-26)

To a solution of **(7*R*, 9*S*)-25a** (25 mg, 28.7 μ mol) in acetone-5% NaHCO₃ aq (0.3 mL, 2:1) was added TEMPO (ca.1 mg), KBr (ca.1 mg), and NaOCl solution (70 μ L) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, acidified with sat. KHSO₄ to pH3, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in ethyl acetate was added a solution of (trimethylsilyl)diazomethane (2.0 M in Et₂O) and concentrated under reduced pressure. The residue was purified by preparative TLC (developed with hexane/EtOAc = 2:1) to give **(7*R*, 9*S*)-26** (18 mg, 72%, an inseparable mixture of diastereomers at C7 position) as colorless oil: FTIR (neat) 3314, 2983, 2951, 1748, 1716, 1700, 1668, 1551, 1456, 1407, 1352, 1269, 1211 cm⁻¹; Complex ¹H NMR spectra was observed, because of a mixture of diastereomers and rotamers. See appendix.; ¹³C NMR (100 MHz, CDCl₃) δ 171.8, 171.5, 171.47, 171.45, 171.2, 171.15, 170.8, 170.6, 170.4, 164.23, 164.17, 153.5, 153.0, 152.96, 152.7, 151.5, 151.4, 136.2, 136.2, 136.0, 135.9, 130.9, 130.8, 129.8, 128.6, 128.5, 128.48, 128.42, 128.40, 128.3, 128.2, 128.1, 128.0, 127.9, 94.0, 93.9, 93.5, 93.3, 82.6, 82.5, 82.4, 82.37, 76.4, 75.8, 75.3, 75.1, 74.7, 68.9, 68.8, 68.5, 67.7, 66.9, 66.8, 62.0, 61.9, 61.3, 61.2, 55.25, 55.20, 52.6, 52.5, 52.48, 52.46, 52.38, 52.33, 52.3, 52.2, 51.9, 51.8, 37.9, 36.7, 31.8, 31.3, 31.0, 30.5, 29.7, 29.0, 28.8, 28.4, 28.3, 26.2, 26.1, 25.4, 25.04, 25.0, 24.96, 24.3, 23.9; HRMS (FAB) *m/z* (M+H)⁺ calcd for [C₄₄H₅₁N₃O₁₃Cl₂+H]⁺ 900.2877, found 900.2900.

Protected (9*R*)-isomer of kaitocephalin ((7*R*, 9*R*)-26)

To a solution of **(7*R*, 9*R*)-25b** (17 mg, 19.5 μmol) in acetone-5% NaHCO_3 aq (0.2 mL, 2:1) was added TEMPO (ca.1 mg), KBr (ca.1 mg), and NaOCl solution (48 μL) at 0 $^\circ\text{C}$. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 1 h, acidified with sat. KHSO_4 to pH3, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. To a solution of the residue in ethyl acetate was added a solution of (trimethylsilyl)diazomethane (2.0 M in Et_2O) and concentrated under reduced pressure. The residue was purified by preparative TLC (developed with hexane/ EtOAc = 2:1) to give **(7*R*, 9*R*)-26** (14 mg, 82%, a mixture of rotamers) as colorless oil: $[\alpha]^{22}_{\text{D}} +10.1$ (c 1.04, CHCl_3); FTIR (neat) 3322, 2983, 2952, 1746, 1717, 1700, 1669, 1541, 1457, 1405, 1352, 1270, 1214 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of rotamers. See appendix.; ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 172.1, 172.0, 171.9, 171.7, 170.7, 170.4, 165.0, 164.9, 164.59, 164.56, 153.64, 153.61, 153.1, 152.9, 152.87, 152.7, 151.5, 136.5, 136.2, 135.95, 135.90, 135.8, 130.63, 130.59, 130.0, 129.9, 129.8, 128.6, 128.5, 128.48, 128.4, 128.3, 128.1, 128.0, 127.93, 127.85, 127.5, 94.1, 93.9, 93.6, 82.4, 82.37, 81.4, 76.5, 75.9, 75.1, 74.8, 69.86, 69.83, 69.0, 68.9, 67.9, 67.7, 67.53, 67.51, 66.8, 66.6, 61.9, 61.2, 61.1, 57.3, 57.26, 57.0, 53.0, 52.6, 52.5, 52.45, 52.42, 52.3, 52.1, 37.8, 37.0, 31.4, 31.0, 30.8, 30.75, 30.0, 29.7, 28.4, 28.2, 26.2, 25.1, 25.0, 23.9, 23.8; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{44}\text{H}_{51}\text{N}_3\text{O}_{13}\text{Cl}_2+\text{H}]^+$ 900.2877, found 900.2883.

Kaitocephalin (1)

To a solution of **(7R, 9S)-26** (10 mg, 11.1 μmol) in dimethylsulfide (0.1 mL) was added AlCl_3 (41 mg, 0.311 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h, quenched with H_2O , and concentrated under reduced pressure. The residue was purified by HPLC (Sensyu Pak, PEGASIL-ODS ϕ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine- CO_2 buffer pH7, 1 mL/min.) to give crude kaitocephalin. The crude kaitocephalin was purified by Dowex[®] 50W x4 (elution with 1N NH_4OH) and HPLC (Sensyu Pak, PEGASIL-ODS ϕ 4.6 x 250 mm, elution with 2% MeOH-20mM diethylamine- CO_2 buffer pH7, 1 mL/min.) to give kaitocephalin (**1**) (1.8 mg, 29%) as a white powder along with a trace amount of (7*S*, 9*R*)-isomer of **1**.

Kaitocephalin: $[\alpha]^{24}_{\text{D}} -29.0$ (c 0.30, H_2O), lit. $[\alpha]^{24}_{\text{D}} -30.9$ (c 0.7, H_2O); FTIR (neat) 3379, 3247, 1635, 1589, 1473, 1389, 1354, 1315 cm^{-1} ; ^1H NMR (600 MHz, D_2O) δ 7.67 (s, 2H), 4.44 (s, 1H), 4.37 (dd, $J = 8.2, 5.5$ Hz, 1H), 4.19 (s, 1H), 3.69-3.75 (m, 1H), 2.45 (dt, $J = 14.4, 5.9$ Hz, 1H), 2.31 (ddd, $J = 13.5, 6.5, 2.4$ Hz, 1H), 2.12-2.15 (m, 1H), 2.01-2.10 (m, 2H), 1.60-1.67 (m, 1H); HRMS (FAB) m/z (M-H)⁻ calcd for $[\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_9\text{Cl}_2\text{-H}]^-$ 492.0577, found 492.0581.

(9*R*)-isomer of kaitocephalin (Deprotection of (7*R*, 9*R*)-26)

To a solution of **(7*R*, 9*R*)-26** (12 mg, 13.3 μmol) in dimethylsulfide (0.2 mL) was added AlCl_3 (50 mg, 0.372 mmol) at room temperature. The reaction mixture was stirred at room temperature for 21 h, quenched with H_2O , and concentrated under reduced pressure. The residue was purified by HPLC (Sensyu Pak, PEGASIL-ODS ϕ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine- CO_2 buffer pH7, 1 mL/min.) to give crude **(9*R*)-kaitocephalin**. The crude **(9*R*)-kaitocephalin** was purified by Dowex[®] 50W x4 (elution with 1*N* NH_4OH) and HPLC (Sensyu Pak, PEGASIL-ODS ϕ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine- CO_2 buffer pH7, 1 mL/min.) to give **(9*R*)-isomer of 1** (2.0 mg, 27%) as a white powder.

(9*R*)-isomer of 1: $[\alpha]^{24}_{\text{D}} -27.8$ (c 0.85, H_2O); FTIR (neat) 3388, 3063, 2989, 2729, 2510, 1635, 1590, 1473, 1397, 1348 cm^{-1} ; ^1H NMR (600 MHz, D_2O) δ 7.68 (s, 2H), 4.44 (s, 1H), 4.35 (dd, $J = 9.9, 4.1$ Hz, 1H), 4.19 (s, 1H), 3.66 (tt, $J = 10.3, 5.6$ Hz, 1H), 2.30-2.35 (m, 2H), 2.17-2.26 (m, 2H), 2.00-2.06 (m, 1H), 1.61-1.69 (m, 1H); HRMS (FAB) m/z (M-H)⁻ calcd for $[\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_9\text{Cl}_2\text{-H}]^-$ 492.0577, found 492.0570.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-allylpyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester (19)

To a solution of **15** (212 mg, 0.397 mmol) in THF (2 mL) was added LiBEt₃H (1 M solution in THF, 596 μ L, 0.596 mmol) at -78 °C. The reaction mixture was stirred at -78 °C under argon for 1 h, quenched with sat. NaHCO₃ / 30% H₂O₂ (1:1, 19 mL), stirred at room temperature for 2 h, and extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in CH₂Cl₂ (2 mL) was added Ac₂O (56 μ L, 0.596 mmol) and DMAP (73 mg, 0.596 mmol) at room temperature. The reaction mixture was stirred at room temperature under argon for 1.5 h, quenched with sat. NH₄Cl, and extracted with diethyl ether (x3). The combined organic layers were washed with sat. NaHCO₃, dried over anhydrous MgSO₄, filtered through thin silica gel pad, and concentrated under reduced pressure to give **18**. To a solution of **18** in CH₂Cl₂ (2 mL) was added allyltrimethylsilane (315 μ L, 1.99 mmol) and BF₃·Et₂O (129 μ L, 0.475 mmol) at -78 °C. The reaction mixture was stirred at -78 °C under argon for 1 h, quenched with sat. NaHCO₃, and extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 10:1 then 6:1) to give **19** (189 mg, 85%, 3 steps, a mixture of rotamers) as colorless oil: [α]_D²⁵ +28.3 (*c* 0.86, CHCl₃); FTIR (neat) 2977, 2949, 1746, 1713, 1698, 1390, 1351, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.26-7.35 (m, 5H), 5.60-5.80 (br m, 1H), 5.11-5.28 (m, 2H), 4.80-5.05 (m, 4H), 4.05-4.20 (m, 1/3H), 3.90-4.05 (m, 2/3H), 3.75 (br s, 1H), 3.73 (s, 2H), 3.69 (s, 1H),

3.53 (s, 2H), 2.25-2.50 (m, 2H), 2.05-2.20 (m, 2H), 1.78 (s, 2H), 1.60-1.75 (m, 3H), 1.41 (br s, 9H), 1.45-1.57 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.1, 171.2, 153.6, 152.6, 151.5, 136.4, 136.0, 128.5, 128.4, 128.1, 127.9, 127.6, 116.4, 93.6, 93.1, 80.6, 80.3, 75.6, 74.5, 74.0, 69.1, 68.7, 67.4, 66.6, 62.0, 61.4, 61.1, 58.7, 52.3, 52.2, 52.1, 38.7, 38.1, 28.6, 28.2, 27.6, 27.3, 26.9, 26.2, 25.1, 24.0; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_9+\text{H}]^+$ 561.2734, found 561.2806.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-(2-(*tert*-butyldimethylsilyloxymethyl)-2-hydroxyethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7*S*)-22ab)

To a solution of **19** (260 mg, 0.464 mmol) in *t*-BuOH- H_2O (2.5 mL, 1:1) was added OsO_4 (296 μL , 1g/25 mL in *t*-BuOH) and NMO (67 mg, 0.557 mmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at room temperature for 2 h, quenched with KHSO_3 aq, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (2.5 mL) was added TBSOTf (116 μL , 0.422 mmol) and 2,6-lutidine (70 μL , 0.603 mmol) at -78 $^\circ\text{C}$ under argon for 15 min., quenched with EtOH and sat. NH_4Cl , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 10:1, 8:1 then 1:1) to give **(7*S*)-22ab** (214 mg, 65%, 2:1 inseparable mixture of diastereomers and a

mixture of rotamers) as colorless oil and recovery of diol (63 mg, 23%, 2:1 inseparable mixture of diastereomers and a mixture of rotamers).

(7S)-22ab: FTIR (neat) 3460, 2953, 2857, 1747, 1717, 1683, 1403, 1353, 1253, 1212 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.25-7.35 (m, 5H), 5.10-5.30 (m, 5/3H), 4.85-5.05 (m, 7/3H), 4.10-4.41 (m, 1H), 3.50-3.76 (m, 9H), 2.10-2.50 (m, 2H), 1.39-1.76 (m, 19H), 0.89 (s, 6H), 0.87 (s, 3H), 0.06 (s, 4H), 0.04 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.6, 170.9, 154.0, 152.6, 151.4, 136.3, 136.1, 136.0, 128.6, 128.4, 128.1, 127.9, 127.8, 127.6, 93.7, 93.6, 93.2, 93.0, 81.2, 80.9, 80.6, 75.6, 75.0, 74.7, 70.1, 69.9, 69.0, 67.9, 67.6, 67.4, 66.8, 66.6, 62.0, 61.4, 61.1, 56.7, 56.5, 56.0, 52.4, 52.22, 52.20, 52.17, 52.16, 52.12, 38.5, 29.5, 28.9, 28.8, 28.2, 27.4, 26.2, 26.0, 25.8, 25.2, 25.1, 25.0, 24.1, 24.0, 18.5, 18.2, -5.17, -5.27, -5.36, -5.42; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{35}\text{H}_{56}\text{N}_2\text{O}_{11}\text{Si}+\text{H}]^+$ 709.3653, found 709.3702.

(4R,5S)-3-Benzyl 5-((2R,5S)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-(2-(*tert*-butyldimethylsilyloxymethyl)-2-azidoethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7S)-23ab)

To a solution of **(7S)-22ab** (233 mg, 0.329 mmol) in THF (2 mL) was added DPPA (212 μL , 0.987 mmol), PPh_3 (258 mg, 0.987 mmol), and DEAD (156 μL , 0.987 mmol) at room temperature. The reaction mixture was stirred at room temperature under argon for 1 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 10:1 then 8:1) to give **(7S)-23ab** (234 mg, 97%, an inseparable mixture of diastereomers and a mixture of

rotamers) as colorless oil: FTIR (neat) 2953, 2931, 2857, 2106, 1746, 1716, 1701, 1457, 1436, 1404, 1392, 1352, 1253, 1212, 1180 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of diastereomers and rotamers. See appendix.; ^{13}C NMR (75 MHz, CDCl_3) δ 172.0, 171.1, 171.0, 152.6, 151.5, 136.3, 128.5, 128.4, 128.2, 127.9, 127.8, 127.6, 93.7, 93.6, 93.5, 93.0, 81.0, 80.99, 80.97, 80.92, 80.86, 67.5, 66.7, 66.3, 62.0, 61.5, 61.3, 61.1, 56.1, 52.4, 52.2, 52.1, 35.5, 35.2, 34.4, 43.3, 28.4, 28.2, 25.3, 25.1, 25.0, 24.2, 24.0, 18.2, -5.53, -5.59; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{35}\text{H}_{55}\text{N}_5\text{O}_{10}\text{Si}+\text{H}]^+$ 734.3796, found 734.3817.

Reduction of (7S)-23ab followed by acylation of the resulting amines

((7S, 9S)-24a and (7S, 9R)-24b)

To a solution of (7S)-23ab (205 mg, 0.280 mmol) in $\text{THF}-\text{H}_2\text{O}$ (2.8 mL, 3:1) was added PMe_3 (1M solution in THF, 1.40 mL, 1.40 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (2.8 mL) was added 4-benzyloxy-3,5-dichlorobenzoic acid (100 mg, 0.336 mmol), BOP reagent (149 mg, 0.336 mmol) and DIPEA (73 μL , 0.420 mmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at room temperature under argon for 15 h, quenched with sat. NH_4Cl , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with

hexane/EtOAc = 8:1, 6:1 then 5:1) to give less polar isomer **(7*S*, 9*R*)-24b** (75 mg, 27%) as colorless oil and (elution with hexane/EtOAc = 5:1) to give more polar isomer **(7*S*, 9*S*)-24a** (165 mg, 60%) as colorless oil.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-((*S*)-2-(*tert*-butyldimethylsilyloxymethyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7*S*, 9*S*)-24a): $[\alpha]^{20}_{\text{D}} +12.3$ (c 0.53, CHCl_3); FTIR (neat) 3335, 2953, 1748, 1716, 1697, 1670, 1540, 1470, 1457, 1405, 1354, 1257 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of rotamers. See appendix.; ^{13}C NMR (75 MHz, CDCl_3) δ 171.9, 171.5, 171.4, 171.2, 170.9, 170.7, 164.5, 164.1, 153.3, 153.2, 152.8, 152.7, 152.6, 151.5, 151.4, 136.3, 136.26, 136.1, 136.0, 135.95, 135.7, 131.8, 130.1, 129.7, 128.6, 128.5, 128.45, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.63, 127.61, 93.8, 93.6, 93.3, 81.53, 81.50, 80.5, 75.3, 75.1, 75.0, 74.7, 74.6, 69.0, 68.3, 67.6, 66.8, 66.7, 66.6, 65.37, 65.35, 64.3, 62.0, 61.3, 61.1, 56.6, 52.4, 52.3, 52.2, 50.8, 49.1, 37.1, 36.2, 29.6, 29.5, 29.4, 29.1, 29.0, 28.3, 28.2, 27.4, 26.2, 25.8, 25.3, 25.1, 25.0, 24.2, 24.13, 24.12, 18.2, 18.1, -5.34, -5.44; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{49}\text{H}_{65}\text{N}_3\text{O}_{12}\text{Cl}_2\text{Si}+\text{H}]^+$ 986.3793, found 986.3800.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-((*R*)-2-(*tert*-butyldimethylsilyloxymethyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7*S*, 9*R*)-24b): $[\alpha]^{21}_{\text{D}} +42.2$ (c 1.35, CHCl_3); FTIR (neat) 3314, 2952, 2929, 1749, 1716, 1700, 1667, 1541, 1457, 1406, 1351, 1258 cm^{-1} ; Complex ^1H NMR spectra was observed, because of a mixture of rotamers. See appendix.; ^{13}C NMR (75 MHz, CDCl_3) δ 171.6, 170.9, 164.2, 153.2, 152.6, 151.4, 136.2, 136.0, 132.1, 132.0, 129.7, 128.6, 128.51, 128.47, 128.40, 128.2, 128.03, 128.02, 127.8, 75.4, 75.0, 74.8, 68.5, 67.6, 66.8, 62.3, 62.1, 61.4, 55.3, 52.4, 52.3, 52.23, 52.20, 51.0, 36.5, 30.9, 30.8, 30.7, 29.7, 29.1, 29.0, 28.9, 28.3, 26.2, 25.9, 25.3, 25.1, 24.2, 18.2, -5.31, -5.44; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{49}\text{H}_{65}\text{N}_3\text{O}_{12}\text{Cl}_2\text{Si}+\text{H}]^+$ 986.3793, found 986.3776.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-((*S*)-2-(methoxycarbonyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7*S*, 9*S*)-26)

To a solution of **(7*S*, 9*S*)-24a** (165 mg, 0.168 mmol) in THF (0.8 mL) was added AcOH (9.6 μ L, 0.168 mmol) and TBAF (1M solution in THF, 670 μ L, 0.67 mmol) at 0 $^{\circ}$ C. The reaction mixture was stirred at room temperature under argon for 0.5 h, quenched with sat. NaHCO₃, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in acetone-5% NaHCO₃ aq (1.7 mL, 2:1) was added TEMPO (3 mg, 16.8 μ mol), KBr (2 mg, 16.8 μ mol), and NaOCl solution (412 μ L) at 0 $^{\circ}$ C. The reaction mixture was stirred at 0 $^{\circ}$ C for 0.5 h, acidified with sat. KHSO₄ to pH3, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of diazomethane in diethyl ether was added a solution of the residue in ethyl acetate at 0 $^{\circ}$ C, stirred at 0 $^{\circ}$ C for 0.5 h, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 6:1 then 2:1) to give **(7*S*, 9*S*)-26** (118 mg, 78%, a mixture of rotamers) as colorless oil: $[\alpha]^{20}_{\text{D}} +27.9$ (*c* 1.21, CHCl₃); FTIR (neat) 3335, 2983, 2952, 1746, 1716, 1697, 1669, 1548, 1454, 1405, 1352, 1270 cm^{-1} ; Complex ¹H NMR spectra was observed, because of a mixture of rotamers. See appendix.; ¹³C NMR (75 MHz, CDCl₃) δ 172.2, 172.1, 171.3, 171.2, 170.9, 170.7, 165.0, 164.7, 153.7, 153.6, 152.9, 152.89, 152.6, 151.4, 136.1, 135.9, 135.87, 130.9, 130.6, 130.0, 129.8, 128.6, 128.5, 128.47, 128.4, 128.3, 128.1, 127.9, 93.9, 93.4, 82.2, 82.1, 81.2, 75.2, 75.1, 74.6, 69.54, 69.53, 68.3, 67.7, 66.9, 62.0, 61.3,

57.1, 56.7, 52.5, 52.4, 52.39, 52.3, 52.29, 37.7, 29.5, 29.4, 29.1, 28.9, 28.4, 28.2, 27.7, 26.2, 25.7, 25.3, 25.0, 24.7, 24.3; HRMS (FAB) m/z (M+H)⁺ calcd for [C₄₄H₅₁N₃O₁₃Cl₂+H]⁺ 900.2877, found 900.2879.

(4*R*,5*S*)-3-Benzyl 5-((2*R*,5*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-5-((*R*)-2-(methoxycarbonyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)ethyl)pyrrolidin-2-yl)-2,2-dimethyloxazolidine-3,4-dicarboxylate methyl ester ((7*S*, 9*R*)-26)

To a solution of **(7*S*, 9*R*)-24b** (75 mg, 76 μmol) in THF (0.8 mL) was added AcOH (4.3 μL , 76 μmol) and TBAF (1M solution in THF, 305 μL , 305 μmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at room temperature under argon for 1 h, quenched with sat. NaHCO₃, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in acetone-5% NaHCO₃ aq (0.8 mL, 2:1) was added TEMPO (1.2 mg, 7.6 μmol), KBr (1 mg, 7.6 μmol), and NaOCl solution (187 μL) at 0 $^\circ\text{C}$. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 0.5 h, acidified with sat. KHSO₄ to pH3, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of diazomethane in diethyl ether was added a solution of the residue in ethyl acetate at 0 $^\circ\text{C}$, stirred at 0 $^\circ\text{C}$ for 0.5 h, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 6:1 then 2:1) to give **(7*S*, 9*R*)-26** (45 mg, 66%, 2:1 mixture of rotamers) as colorless oil: $[\alpha]^{21}_{\text{D}} +41.1$ (c

1.22, CHCl₃); FTIR (neat) 3314, 2976, 2952, 1747, 1716, 1667, 1551, 1456, 1407, 1368, 1351, 1267, 1212 cm⁻¹; Complex ¹H NMR spectra was observed, because of a mixture of rotamers. See appendix.; ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 171.2, 170.8, 170.6, 164.2, 153.5, 152.6, 151.4, 136.2, 136.0, 130.9, 130.0, 128.6, 128.5, 128.49, 128.46, 128.43, 128.3, 128.1, 128.07, 127.9, 93.9, 93.3, 82.5, 82.4, 75.3, 75.1, 74.8, 68.5, 67.7, 66.9, 62.0, 61.3, 55.2, 52.5, 52.4, 52.3, 52.27, 52.2, 52.0, 36.7, 30.5, 29.7, 29.0, 28.8, 28.4, 26.1, 25.4, 25.0, 24.3; HRMS (FAB) *m/z* (M+H)⁺ calcd for [C₄₄H₅₁N₃O₁₃Cl₂+H]⁺ 900.2877, found 900.2875.

(7*S*, 9*S*)-isomer of 1 (Deprotection of **(7*S*, 9*S*)-26**)

To a solution of **(7*S*, 9*S*)-26** (2 mg, 2.22 μmol) in dimethylsulfide (0.1 mL) was added AlCl₃ (8.3 mg, 62.3 μmol) at room temperature. The reaction mixture was stirred at room temperature for 17 h, quenched with H₂O, and concentrated under reduced pressure. The residue was purified by HPLC (Sensyu Pak, PEGASIL-ODS φ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine-CO₂ buffer pH7, 1 mL/min.) to give crude **(7*S*, 9*R*)-kaitocephalin**. The crude **(7*S*, 9*R*)-kaitocephalin** was purified by Dowex[®] 50W x4 (elution with 1*N* NH₄OH) and HPLC (Sensyu Pak, PEGASIL-ODS φ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine-CO₂ buffer pH7, 1 mL/min.) to give **(7*S*, 9*S*)-isomer of 1** (0.4 mg, 32%) as a white powder. **(7*S*, 9*S*)-isomer of 1**: [α]_D²¹ -7.6 (*c* 0.83, H₂O); FTIR (neat) 3382, 3251, 3089, 2996, 1637, 1590, 1477, 1379, 1319, 1292 cm⁻¹; ¹H NMR (600 MHz, D₂O) δ 7.69 (s, 2H), 4.47 (s, 1H), 4.34-4.38 (m, 1H), 4.12 (s, 1H), 3.55-3.60 (m, 1H), 2.22-2.31 (m, 2H),

2.12-2.18 (m, 2H), 1.71-1.79 (m, 1H); HRMS (FAB) m/z (M-H)⁻ calcd for [C₁₈H₂₁N₃O₉Cl₂-H]⁻ 492.0577, found 492.0582.

(7*S*, 9*R*)-isomer of 1 (Deprotection of **(7*S*, 9*R*)-26**)

To a solution of **(7*S*, 9*R*)-26** (3.5 mg, 3.89 μ mol) in dimethylsulfide (0.1 mL) was added AlCl₃ (15 mg, 0.109 mmol) at room temperature. The reaction mixture was stirred at room temperature for 19 h, quenched with H₂O, and concentrated under reduced pressure. The residue was purified by HPLC (Sensyu Pak, PEGASIL-ODS ϕ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine-CO₂ buffer pH7, 1 mL/min.) to give crude (7*S*)-kaitocephalin. The crude (7*S*)-kaitocephalin was purified by Dowex[®] 50W x4 (elution with 1*N* NH₄OH) and HPLC (Sensyu Pak, PEGASIL-ODS ϕ 4.6 x 250 mm, elution with 5% MeOH-20mM diethylamine-CO₂ buffer pH7, 1 mL/min.) to give **(7*S*, 9*R*)-isomer of 1** (0.7 mg, 30%) as a white powder. **(7*S*, 9*R*)-isomer of 1**: [α]_D²² -9.1 (*c* 0.90, H₂O); FTIR (neat) 3395, 3063, 2869, 2510, 1635, 1587, 1473, 1388, 1328, 1291 cm⁻¹; ¹H NMR (600 MHz, D₂O) δ 7.67 (s, 2H), 4.47 (s, 1H), 4.40 (dd, *J* = 8.8, 5.5 Hz, 1H), 4.10 (s, 1H), 3.59-3.62 (m, 1H), 2.44 (dt, *J* = 14.3, 5.8 Hz, 1H), 2.07-2.18 (m, 4H), 1.68-1.78 (m, 1H); HRMS (FAB) m/z (M-H)⁻ calcd for [C₁₈H₂₁N₃O₉Cl₂-H]⁻ 492.0577, found 492.0564.

Stereochemical assignment of **8** (ref. 10)

(*R*)-Methyl 2-((1*R*,2*S*)-2-(methoxycarbonyl)-1,2-diacetoxyethyl)-5-thioxopyrrolidine-2-carboxylate (**8A**)

To a solution of **8** (18 mg, 49.9 μ mol) in CH₂Cl₂ (0.3 mL) was added Ac₂O (14 μ L, 0.15 mmol) and DMAP (24 mg, 0.20 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred under argon for 1 h, quenched with sat. NH₄Cl, and extracted with ethyl acetate (x3). The combined organic layers were washed with sat. NaHCO₃, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in CH₂Cl₂ (0.25 mL) was added TFA (0.25 mL) at 0 °C. The reaction mixture was stirred at 0 °C under argon for 1 h and concentrated under reduced pressure. To a solution of the residue in toluene (0.5 mL) was added Lawesson's reagent (11 mg, 27.4 μ mol) at room temperature. The reaction mixture was stirred at 90 °C under argon for 2 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 8:1, then 1:1) to give **8A** (18 mg, quant, 3 steps) as colorless oil: $[\alpha]^{28}_{\text{D}} +49.9$ (*c* 1.20, CHCl₃); FTIR (neat) 3495, 3157, 2957, 1753, 1500, 1436, 1374, 1212, 1169 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (br s, 1H), 5.77 (d, *J* = 2.0 Hz, 1H), 5.30 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 2.84-2.99 (m, 2H), 2.50-2.62 (m, 2H), 2.21 (s, 3H), 2.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.9, 169.8, 169.7, 169.0, 166.8, 74.7, 71.6, 69.3, 53.6, 53.0, 42.0, 28.6, 20.6, 20.2; HRMS (EI) *m/z* (M)⁺ calcd for [C₁₄H₁₉NO₈S]⁺ 361.0831, found 361.0833.

(1*R*,2*S*,7*aR*)-Methyl 1,2-diacetoxy-hexahydro-3-oxo-1*H*-pyrrolizine-7*a*-carboxylate (8B**)**

To a solution of **8A** (18 mg, 49.9 μmol) in EtOH (0.2 mL) was added freshly prepared Raney Ni W-2 (ca.4 mg) at room temperature. The reaction mixture was stirred under hydrogen for 2 h, filtered, and concentrated under reduced pressure. To a solution of the residue in toluene (0.5 mL) was added triethylamine (1 drop) at room temperature. The reaction mixture was heated to reflux, stirred under argon for 36 h, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 6:1 then 1:1) to give **8B** (12.5 mg, 84%) as colorless oil: $[\alpha]^{26}_{\text{D}} -168.7$ (c 0.52, CHCl_3); FTIR (neat) 1750, 1728, 1218 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.91 (d, $J = 8.8$ Hz, 1H), 5.28 (d, $J = 8.8$ Hz, 1H), 3.79 (s, 3H), 3.60-3.70 (m, 1H), 3.09-3.18 (m, 1H), 2.69-2.79 (m, 1H), 2.14 (s, 3H), 2.08-2.13 (m, 1H), 2.06 (s, 3H), 1.81-1.96 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 169.8, 169.5, 166.5, 78.7, 75.6, 72.7, 53.1, 41.9, 34.6, 24.8, 20.7, 20.5; HRMS (CI) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{13}\text{H}_{17}\text{NO}_7+\text{H}]^+$ 300.1083, found 300.1096.

Strong NOEs were observed between C2-H and C3-acetyl, and C3-acetyl and C4-methoxy groups (p.60) which unambiguously assigned **8** to have 2*S*,3*S* configuration.

Stereochemical assignment of (7*S*, 9*S*)-24a and (7*S*, 9*R*)-24b

(4*R*,5*S*)-3-benzyl 4-methyl 5-((2*R*,5*R*,7a*S*)-5-(methoxycarbonyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)-hexahydro-3-oxo-1*H*-pyrrolizin-5-yl)-2,2-dimethyl-oxazolidine-3,4-dicarboxylate ((7*S*, 9*R*)-25bA)

To a solution of (7*S*, 9*R*)-25b (22 mg, 25.6 μmol) derived from less polar isomer (7*S*, 9*R*)-24b in acetone-5% NaHCO₃ aq (0.4 mL, 2:1) was added TEMPO (0.6 mg, 3.8 μmol), KBr (0.4 mg, 3.4 μmol), and NaOCl solution (70 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, acidified with sat. KHSO₄ to pH3, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. To a solution of the residue in CH₂Cl₂ (0.2 mL) was added TFA (0.2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h and concentrated under reduced pressure. To a solution of the residue in THF (0.4 mL) was added DEPBT (10 mg, 33.8 μmol) and NEt₃ (7 μL, 50.7 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h, quenched with sat. NH₄Cl, and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution with hexane/EtOAc = 6:1 then 1:1) to give (7*S*, 9*R*)-25bA (9 mg, 46%, 3 steps, 2:1 mixture of rotamers) as colorless oil: [α]_D²⁵ -17.6 (*c* 0.83, CHCl₃); FTIR (neat) 3315, 2951, 1748, 1713, 1701, 1405, 1353, 1270 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 7.58 (s, 4/3H), 7.56 (s, 2/3H), 7.43 (d, *J* = 7.3 Hz, 2H), 6.99-7.17 (m, 8H), 6.51 (d, *J* = 6.3 Hz, 2/3H), 6.50 (d, *J* = 6.3 Hz, 1/3H), 6.36 (brd, *J* = 5.4 Hz, 2/3H),

6.33 (brd, $J = 5.3$ Hz, 1/3H), 5.21 (d, $J = 12.5$ Hz, 2/3H), 5.09 (d, $J = 12.3$ Hz, 1/3H), 5.05 (d, $J = 6.3$ Hz, 1/3H), 4.99 (d, $J = 12.3$ Hz, 1/3H), 4.87 (d, $J = 12.5$ Hz, 2/3H), 4.85 (d, $J = 6.3$ Hz, 2/3H), 4.82 (s, 2H), 4.56-4.65 (m, 1H), 3.45-3.51 (m 1H), 3.38 (s, 1H), 3.36 (s, 2H), 3.24 (s, 1H), 3.19 (s, 2H), 2.45-2.56 (m, 2H), 2.33 (dd, $J = 12.8, 8.6$ Hz, 1/3H), 2.27 (dd, $J = 12.8, 7.4$ Hz, 2/3H), 1.96 (s, 2H), 1.78 (s, 1H), 1.75 (s, 2H), 1.55 (s, 1H), 1.47-1.54 (m, 1H), 1.29-1.39 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.5, 170.1, 170.0, 169.9, 169.05, 169.0, 164.5, 164.4, 154.1, 154.0, 152.7, 151.7, 137.1, 136.7, 136.6, 128.7, 128.6, 128.57, 128.4, 128.3, 128.2, 128.16, 128.05, 95.4, 94.5, 75.0, 72.8, 72.2, 67.5, 67.1, 67.0, 66.7, 61.4, 60.5, 59.2, 57.03, 57.0, 52.3, 52.25, 51.7, 51.6, 36.6, 36.5, 32.0, 31.9, 31.0, 30.97, 29.9, 26.6, 25.5, 25.4, 24.4; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{38}\text{H}_{39}\text{N}_3\text{O}_{10}\text{Cl}_2+\text{H}]^+$ 768.2090, found 768.2083.

NOE was observed between C7-H and C9-H as depicted in p.61.

(4*R*,5*S*)-3-benzyl 4-methyl 5-((2*S*,5*R*,7*aS*)-5-(methoxycarbonyl)-2-(4-(benzyloxy)-3,5-dichlorobenzamido)-hexahydro-3-oxo-1*H*-pyrrolizin-5-yl)-2,2-dimethyl-oxazolidine-3,4-dicarboxylate ((7*S*, 9*S*)-25aA)

To a solution of **(7*S*, 9*S*)-25a** (10 mg, 11.5 μmol) derived from more polar isomer **(7*S*, 9*S*)-24a** in acetone-5% NaHCO_3 aq (0.2 mL, 2:1) was added TEMPO (0.3 mg, 1.7 μmol), KBr (0.2 mg, 1.7 μmol), and NaOCl solution (28 μL) at 0 $^\circ\text{C}$. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 0.5 h, acidified with sat. KHSO_4 to pH3, and

extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (0.1 mL) was added TFA (0.1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (0.1 mL) was added BOP reagent (5.2 mg, 11.8 μmol) and DIPEA (2.8 μL , 15.8 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, quenched with sat. NH_4Cl , and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (developed with hexane/EtOAc = 1:1) to give **(7*S*, 9*S*)-25aA** (3.8 mg, 43%, 3 steps, 2:1 mixture of rotamers) as colorless oil: $[\alpha]^{25}_{\text{D}} +10.3$ (*c* 1.20, CHCl_3); FTIR (neat) 3303, 2951, 1746, 1714, 1703, 1666, 1550, 1456, 1406, 1352, 1270, 1212 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.72 (s, 2/3H), 7.70 (s, 4/3H), 7.52-7.54 (m, 2H), 7.28-7.41 (m, 7H), 7.25-7.27 (m, 1H), 7.21 (br s, 2/3H), 7.04 (br s, 1/3H), 6.09 (d, J = 6.4 Hz, 1/3H), 6.07 (d, J = 6.4 Hz, 2/3H), 5.21 (d, J = 12.3 Hz, 1/3H), 5.17 (d, J = 12.3 Hz, 1/3H), 5.16 (d, J = 12.4 Hz, 2/3H), 5.08 (s, 2/3H), 5.07 (s, 4/3H), 5.01 (d, J = 12.4 Hz, 2/3H), 4.79 (d, J = 6.4 Hz, 1/3H), 4.73 (d, J = 6.4 Hz, 2/3H), 4.58 (quint, J = 5.2 Hz, 1/3H), 4.52 (quint, J = 6.4 Hz, 2/3H), 4.16-4.30 (m, 1H), 3.88 (s, 3H), 3.67 (s, 1H), 3.57 (s, 2H), 2.48-2.56 (m, 1H), 2.12-2.34 (m, 3H), 2.01-2.05 (m, 1H), 1.75 (s, 2H), 1.68 (s, 1H), 1.57 (s, 2H), 1.50 (s, 1H), 1.46-1.56 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 170.0, 169.9, 169.8, 169.7, 169.6, 164.6, 164.5, 153.8, 152.7, 151.6, 136.3, 136.0, 135.9, 135.8, 130.54, 130.46, 130.0, 129.97, 128.6, 128.57, 128.5, 128.45, 128.2, 128.0, 127.9, 127.8, 94.9, 94.4, 75.2, 71.6, 71.0, 67.7, 67.0, 66.9, 66.8, 61.6, 61.4, 60.7, 60.0, 56.5, 56.2, 53.5, 52.9, 52.4, 32.3, 31.5, 30.5, 29.7, 26.5, 25.5, 25.4, 24.3; HRMS (FAB) m/z ($\text{M}+\text{H}$) $^+$ calcd for $[\text{C}_{38}\text{H}_{39}\text{N}_3\text{O}_{10}\text{Cl}_2+\text{H}]^+$ 768.2090, found 768.2087.

NOE between C7-H and C9-H was not observed in contrast to the case of **(7*S*, 9*R*)-25bA** as depicted in p.62.

Comparison of the NOE data of **(7*S*, 9*S*)-25aA** and **(7*S*, 9*R*)-25bA** clearly indicated that

less polar isomer (***7S*, *9R***)-**25bA** possessed a *cis* relationship between C7-H and C9-H. Thus, the stereochemistries of the less polar isomer and more polar isomer were assigned to be (***7S*, *9R***)-**24b** and (***7S*, *9S***)-**24a**, respectively.

[illegible] $7R:7S = \text{ca. } 2:1$

23ab

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lambda

¹H NMR

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RESOL			
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SPINNING			22.8 C
TEMP

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[illegible]

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Current Data Parameters

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PROCNO 1

acq8

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d1 2.000000 sec
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===== CHANNEL f1 =====

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F1 Acquisition Parameters

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FIDRES 9.30024 Hz
SM 8.011 ppm

F2 Processing parameters

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WDW 512
SSB 2
LB 0.00 Hz
GB 0
PC 18.00

F1 Processing parameters

SI 32768
SF 600.130053 MHz
WDW 512
SSB 2
LB 0.00 Hz
GB 0

2D NMR plot parameters

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F2F1 4729.04 Hz
F2F2 0.111 ppm
F2F3 -78.66 Hz
F2F4 7.840 ppm
F2F5 4729.04 Hz
F2F6 0.111 ppm
F2F7 -78.66 Hz
F2F8 0.00555 ppm/cm
F2F9 240.38411 Hz/cm
F2F10 0.00555 ppm/cm
F2F11 240.38411 Hz/cm

MK2096_NOESY_c6d6_temp25

Synthetic kaitocephalin (1)

5% MeOH-20 mM Phosphate buffer pH 7

Flow: 1 mL/min, Detection: 300 nm

COSMOSIL 5C18-PAQ, 4.6x250mm

Natural + Synthetic 1

5% MeOH-20 mM Phosphate buffer pH 7

Flow: 1 mL/min, Detection: 300 nm

COSMOSIL 5C18-PAQ, 4.6x250mm

(9*R*)-isomer of 1

5% MeOH-20 mM Phosphate buffer pH 7
Flow: 1 mL/min, Detection: 300 nm
COSMOSIL 5C18-PAQ, 4.6x250mm

** 定量計算結果 **			
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2	2	5.571	
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			36518
AREA	316795	3672	
HEIGHT	36068	451	
MK	S	T	
IDNO			
CONC	98.8543	1.1457	
			100

(7*S*, 9*S*)-isomer of 1

5% MeOH-20 mM Phosphate buffer pH 7
Flow: 1 mL/min, Detection: 300 nm
COSMOSIL 5C18-PAQ, 4.6x250mm

** 定量計算結果 **			
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2	2	5.523	
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			29687
AREA	243159	6451	
HEIGHT	28964	723	
MK			
IDNO			
CONC	97.4156	2.5844	
			100

(7*S*, 9*R*)-isomer of 1

5% MeOH-20 mM Phosphate buffer pH 7
Flow: 1 mL/min, Detection: 300 nm
COSMOSIL 5C18-PAQ, 4.6x250mm

** 定量計算結果 **			
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1	1	5.035	
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			10035
AREA	94562	10035	
HEIGHT	10035	10035	
MK			
IDNO			
CONC	100	100	
			100