Supporting Information

Total Synthesis of (−)-Kaitocephalin

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General Information. NMR spectra were obtained on Bruker DPX400 spectrometer (400 MHz for 1H NMR, 100 MHz for 13C NMR) and measured in CDCl3 if not specified differently. Chemical shifts were recorded in ppm relative to internal standard CDCl3 and coupling constants were reported in Hz. The high resolution mass spectra were recorded on Bruker microTOF-Q II spectrometers. The enantioselectivities were determined by HPLC. HPLC measurements were done on a DIONEX model equipped with P580G pump, UV 525 detector (Thermo Science, Waltham, MA) measured at 254 nm, and chiral column DAICEL AD-H. Eluting solvent was a mixture of 2-propanol and hexane. Reverse phase HPLC was performed on a Shimadzu LC installed with 6AD pump, SPD-M20A UV detector measured at 300 nm and COSMOSIL 5C18-PAQ packed column (20 x 250 mm). All reactions were carried out in oven-dried glassware under a N2 atmosphere. All solvents were distilled from the indicated drying reagents right before use: Et2O and THF (Na, benzophenone), CH2Cl2 (P2O5), and MeCN, 1,4-dioxane and DMF (CaH2). The normal work-up included extraction, drying over Na2SO4 and evaporation of volatile materials in vacuo. Purification by column chromatography was performed using Merck (Darmstadt, Germany) silica gel 60 (230~400 mesh).
Synthesis of the cis-alkene 8

To phosphonium salt 6 (16.42 g, 25.67 mmol) in HMPA (15 mL) and THF (60 mL) was injected nBuLi (2.5 M in hexane, 9.98 mL, 24.96 mmol) dropwise at −78°C, and the mixture was stirred at that temperature for 5 minutes. After changing the dry ice/acetone bath to an ice/water bath, the solution was stirred for 40 minutes, and subsequently the reaction vessel was cooled down to −40°C. Garner’s aldehyde 7 (3.27 g, 14.26 mmol) was added to the generated ylid through a cannula slowly over 8 hours using a 4:1 mixture of THF and HMPA (25 mL). The reaction temperature was raised from −40°C to 0°C, and then the reaction mixture was stirred in an ice/water bath for an additional 2 hours. After the reaction was quenched with water (80 mL) in the ice/water bath, the normal work-up with Et₂O (40 mL x 3) and the following chromatographic purification using 5 wt% K₂CO₃ in silica gel (EtOAc/hexane/Et₃N = 2/60/0.3) afforded the cis-alkene 8 (5.13 g, 73%) and the trans-alkene 26 (658 mg, 9%). For 8: ¹H NMR (400 MHz, CDCl₃, 55°C) δ 7.68-7.65 (m, 4H), 7.40-7.36 (m, 6H), 5.49 (dd, J = 10.7, 6.7 Hz, 1H), 5.47-5.43 (m, 1H), 4.50 (brs, 1H), 3.93 (dd, J = 8.6, 6.3 Hz, 1H), 3.74-3.71 (m, 1H), 3.68-3.61 (m, 1H), 3.55 (dd, J = 8.6, 3.4 Hz, 1H), 2.46-2.37 (m, 2H) 1.63 (s, 3H), 1.51 (s, 3H), 1.43 (s, 9H), 1.07 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, 55°C) δ 151.97, 135.61, 134.10, 131.91, 129.58, 127.62, 127.06, 93.84, 79.68, 68.93, 63.74, 54.65, 31.11, 28.40, 26.84, 24.65, 19.24. HRMS (ESI) m/z calcd for C₃₀H₄₃NNaO₄Si [M+Na]+, 532.2853; found, 532.2853.
Synthesis of the iodide 9

To 8 (2.79 g, 5.47 mmol) in THF (25 mL) was added tetra-n-butylammonium fluoride (1 M in THF, 16.4 mL, 16.4 mmol) in an ice/water bath, and then the mixture was stirred at that temperature for 3 hours. After quenching the reaction by adding water (20 mL) and saturated aqueous NH₄Cl (10 mL), the normal work-up with EtOAc (20 mL x 3) and the subsequent separation (EtOAc/hexane = 1/1) furnished the alcohol 27 (1.44 g, 97%). Imidazole (438 mg, 6.37 mmol) and Ph₃P (1.69 g, 6.37 mmol) were added to CH₂Cl₂ in an ice/water bath, and the mixture was stirred at that temperature for 30 minutes. After adding I₂ (1.62 g, 6.37 mmol) to the solution, the mixture was stirred in the ice/water bath for 30 minutes. 27 (1.44 g, 5.31 mmol) was injected to the resulting solution using CH₂Cl₂ (15 mL), and subsequently stirred at that temperature for 2 hours. The reaction was quenched with 10 wt% aqueous Na₂S₂O₃ (50 mL), and the following normal work-up with EtOAc (20 mL x 3) and chromatographic purification (EtOAc/hexane =1/20) delivered the iodide 9 (1.98 g, 98%). For 9: ¹H NMR (400 MHz, CDCl₃, 55°C) δ 5.54 (ddt, J = 10.8, 9.3, 1.5 Hz, 1H), 5.46-5.35 (m, 1H), 4.57 (s, 1H), 4.05 (dd, J = 8.7, 6.2 Hz, 1H), 3.67 (dd, J = 8.8, 3.1 Hz, 1H), 3.22 (dt, J = 9.6, 6.7 Hz, 1H), 3.07 (dt, J = 9.5, 7.6 Hz, 1H), 2.72 (q, J = 7.5 Hz, 2H), 1.56 (s, 3H), 1.49 (s, 3H), 1.43 (s, 9H), ¹³C NMR (100 MHz, CDCl₃, 55°C) δ 151.97, 132.30, 129.13, 93.99, 79.96, 68.80, 54.59, 31.58, 28.57, 27.01, 24.67, 4.63. HRMS (ESI) m/z calcd for C₁₄H₂₄INaO₃ [M+Na]⁺, 404.0693; found, 404.0697.
Synthesis of the diol 4

To the malonate 5 (1.93 g, 6.23 mmol) in DMF (12 mL) was added Cs$_2$CO$_3$ (2.03 g, 6.23 mmol) in an ice/water bath and the mixture was stirred at that temperature for 30 minutes. After removal of the ice/water bath, 9 (1.98 g, 5.19 mmol) was injected to the prepared mixture through a cannula using DMF (40 mL) slowly over 5 hours at room temperature, and then the resulting solution was stirred at room temperature for 3 hours. The reaction was quenched with saturated aqueous NH$_4$Cl (60 mL) in an ice/water bath, and the subsequent normal work-up with Et$_2$O (30 mL x 3) and chromatographic purification (EtOAc/hexane = 1/8) gave the alkylated product 28 contaminated by the excessively used malonate 5. To the roughly separated 28 in EtOH (18 mL) was added NaBH$_4$ (1.21 g, 31.38 mmol) in four portions over 20 minutes at room temperature. After stirring the mixture at room temperature for 3 hours, the reaction vessel was placed in an ice/water bath, and then the reaction was quenched by saturated aqueous NH$_4$Cl (25 mL) and water (25 mL). The normal work-up with EtOAc (20 mL x 3) and the following separation (EtOAc/hexane = 1/2, then 2/1) imparted the diol 4 (1.69 g, 68% from 9). For 4: $^1$H NMR (400 MHz, CDCl$_3$, 55°C) δ 7.32-7.28 (m, 5H), 5.86 (brs, 1H), 5.46 (td, $J$ = 10.3, 4.5 Hz, 1H), 5.40-5.31 (m, 1H), 5.06 (d, $J$ = 1.8 Hz, 2H), 4.67 (s, 1H), 3.99 (dd, $J$ = 8.8, 5.9 Hz, 1H), 3.85 (d, $J$ = 11.7 Hz, 1H), 3.72 (d, $J$ = 11.7 Hz, 1H), 3.65-3.56 (m, 2H), 3.51 (d, $J$ = 11.8 Hz, 1H), 2.49 (s, 1H), 1.93 (s, 2H), 1.53 (s, 3H).
1.47 (s, 3H), 1.41 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$, 55°C) $\delta$ 156.55, 151.76, 136.44, 131.51, 128.19, 127.74, 127.69, 93.25, 80.05, 68.25, 66.36, 65.21, 64.79, 59.76, 53.95, 32.03, 28.22, 27.10, 24.55, 21.34. HRMS (ESI) $m/z$ calcd for C$_{25}$H$_{38}$N$_2$NaO$_7$ [M+Na]$^+$, 501.2571; found, 501.2596.

※ Synthesis of the monobenzoate 12

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\begin{align*}
\text{4} & \quad \text{NBOc} \\
\text{CbzNH} & \quad \text{OH} \\
\text{OH} & \quad \text{11} \\
\rightarrow & \quad \text{12} \\
\text{CuCl} & \quad \text{iPr} \\
\text{iPr} & \quad \text{OBz}
\end{align*}
\]

To the catalyst 11 (141 mg, 0.35 mmol) in THF (7 mL) were added a mixture of the diol 4 (841 mg, 1.76 mmol) and benzoyl chloride (412 μL, 3.52 mmol) in THF (9 mL), and Et$_3$N (368 μL, 2.64 mmol) in THF (9 mL) through two separate cannulas, respectively, at the same time over 3 hours at room temperature. After stirring the mixture at room temperature for an additional one hour, the reaction was quenched with saturated aqueous NH$_4$Cl (40 mL). The normal work-up with EtOAc (20 mL x 3) and the subsequent chromatographic separation (EtOAc/hexane = 1/3, then 1/2) gave rise to the monobenzoate 12 (922 mg, 90%, 90% de) and the starting 4 (19 mg, 4%). For 12: $^1$H NMR (400 MHz, CDCl$_3$, 55°C) $\delta$ 8.07-7.97 (m, 2H), 7.53 (m, 1H), 7.48-7.34 (m, 2H), 7.34-7.23 (m, 5H), 5.65 (brs, 1H), 5.42 (dq, $J$ = 14.1, 4.1, 3.5 Hz, 1H), 5.35 (t, $J$ = 10.1 Hz, 1H), 5.12-5.01 (m, 2H), 4.64 (d, $J$ = 11.5 Hz, 2H), 4.48 (d, $J$ = 11.2 Hz, 1H), 3.99 (dd, $J$ = 8.8, 6.1 Hz, 1H), 3.87-3.73 (m, 2H), 3.61 (dd, $J$ = 8.8, 2.6 Hz, 1H), 2.52 (brs, 1H), 1.98 (m, 2H), 1.81 (m, 1H), 1.53 (s, 3H), 1.47 (s, 3H), 1.39 (s, 9H). $^{13}$C NMR (100
MHz, CDCl₃, 55°C) δ 166.40, 156.08, 152.11, 136.69, 133.26, 133.05, 130.12, 129.73, 128.46, 128.42, 128.38, 128.04, 93.53, 80.50, 68.49, 66.65, 65.25, 65.10, 59.27, 59.15, 54.31, 31.68, 28.47, 27.38, 24.84, 21.49. HRMS (ESI) m/z calcd for C₃₂H₄₂N₂NaO₈ [M+Na]⁺, 605.2833; found, 605.2867. [α]D²² –21.6 (c 1.23, CHCl₃).

Synthesis of the conjugated ester 3

The Dess-Martin periodinane (15 wt% in CH₂Cl₂, 6.6 mL, 3.2 mmol) was added to 12 (922 mg, 1.58 mmol, 90% de) in CH₂Cl₂ in an ice/water bath, and the mixture was stirred at that temperature for 5 hours. After quenching the reaction with saturated aqueous NH₄Cl (10 mL) and 10 wt% aqueous Na₂S₂O₃ (10 mL), the normal work-up with EtOAc (15 mL x 3) followed by the chromatographic separation (EtOAc/hexane = 1/3) produced the aldehyde 29 (831 mg, 90%) and the starting alcohol 12 (46 mg, 5%). To 29 (831 mg, 1.43 mmol) in CH₂Cl₂ (12 mL) was added (carbethoxymethylene)-triphenylphosphorane (997 mg, 2.86 mmol) at room temperature, and then the reaction mixture was heated at 50°C for 15 hours. After cooling down the solution to room
temperature, all the volatile materials were evaporated in vacuo, and the residue was separated chromatographically (EtOAc/hexane = 1/6) to supply the conjugated ester 3 (820 mg, 88%), its diastereomer 30 (43 mg, 4.6%) and the cis-isomers 31 (40 mg, 4.3%). For 3: 1H NMR (400 MHz, CDCl₃, 55°C) δ 7.98 (dd, J = 8.4, 1.4 Hz, 2H), 7.57-7.49 (m, 1H), 7.44-7.35 (m, 2H), 7.33-7.25 (m, 5H), 7.06 (d, J = 16.1 Hz, 1H), 5.98 (d, J = 16.0 Hz, 1H), 5.44-5.28 (m, 2H), 5.06 (q, J = 12.3 Hz, 2H), 4.76 (s, 1H), 4.63 (s, 1H), 4.55 (d, J = 8.8, 2.6 Hz, 1H), 2.54 (brs, J = 6.6 Hz, 1H), 2.12-1.97 (m, 2H), 1.88 (m, 1H), 1.52 (s, 3H), 1.46 (s, 3H), 1.37 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl₃, 55°C) δ 165.91, 155.13, 151.98, 148.90, 136.71, 133.07, 130.02, 129.68, 128.43, 128.15, 127.99, 121.12, 93.50, 80.27, 68.45, 66.59, 66.15, 60.41, 58.64, 54.21, 35.31, 28.42, 27.33, 24.81, 21.75, 14.17. HRMS (ESI) m/z calcd for C₃₆H₄₆N₂NaO₉ [M+Na]+, 673.3095; found, 673.3125. [α]D₂₂ +9.72 (c 1.30, CHCl₃).

○ Synthesis of the pyrrolidine 13

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\begin{align*}
\text{To } & 3 \ (220 \text{ mg, } 0.34 \text{ mmol}) \text{ in } \text{CH}_2\text{Cl}_2 \ (7 \text{ mL}) \text{ were added } \text{NaHCO}_3 \ (57 \text{ mg, } 0.68 \text{ mmol}) \\
\text{and } Hg(\text{CF}_3\text{CO}_2)_2 \ (221 \text{ mg, } 0.51 \text{ mmol, in three portions}) \text{ at } -20°C \text{ in sequence, and the mixture was stirred at that temperature for 30 minutes. After the reaction vessel was placed in an ice/water bath, the reaction mixture was stirred for 10 hours. The resulting solution was cooled down to } -78°C, \text{ and then THF } (7 \text{ mL}), \text{Et}_3\text{B} \ (1 \text{ M in THF, } 0.34 \text{ mL,}}
\end{align*}
\]
0.34 mmol) and LiBH$_4$ (2 M in THF, 0.2 mL, 0.4 mmol) were added to the solution sequentially. The reaction mixture was stirred at −78°C for 30 minutes and subsequently quenched with saturated aqueous NaHCO$_3$ (20 mL). The normal work-up with CH$_2$Cl$_2$ (15 mL x 3) and the chromatographic purification (EtOAc/hexane = 1/3) provided the desired pyrrolidine 13 (180 mg, 82%), its diastereomer 32 (9 mg, 4%) and the starting alkene 3 (9 mg, 4%). For 13: $^1$H NMR (400 MHz, CDCl$_3$, 55°C) δ 7.98-7.88 (m, 2H), 7.52-7.44 (m, 1H), 7.34 (t, $J$ = 7.7 Hz, 3H), 7.23 (brm, 4H), 6.94 (d, $J$ = 11.7 Hz, 1H), 5.77 (brs, 1H), 5.19 (d, $J$ = 10.9 Hz, 1H), 5.01 (d, $J$ = 12.1 Hz, 1H), 4.65 (brm, 2H), 4.15 (q, $J$ = 7.0 Hz, 2H), 3.81 (brm, 4H), 2.38 (s, 1H), 1.96-1.57 (m, 5H), 1.44 (s, 3H), 1.41 (s, 3H), 1.35 (s, 9H), 1.24 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 55°C) δ 165.84, 165.75, 153.15, 151.38, 146.03, 136.26, 132.95, 129.84, 129.49, 128.38, 128.33, 127.97, 120.82, 93.47, 79.63, 67.13, 66.64, 60.39, 58.67, 57.49, 55.55, 38.55, 34.34, 32.68, 28.35, 26.94, 25.19, 24.35, 23.29, 14.07. HRMS (ESI) $m/z$ calcd for C$_{36}$H$_{46}$N$_2$NaO$_9$ [M+Na]$^+$, 673.3095; found, 673.3119. [$\alpha$]$_{D}^{22}$ +76.5 (c 0.85, CHCl$_3$).

Synthesis of the epoxy alcohol 16

To 13 (180 mg, 0.28 mmol) in THF (7 mL) was injected DIBAL-H (1.5 M in PhMe, 0.55 mL, 0.83 mmol) dropwise at −78°C, and then the mixture was stirred at that temperature for an hour. EtOAc (5 mL) was added to the reaction mixture at −78°C, and
stirred for 10 minutes to quench the reaction. After removal of the dry ice/acetone bath, the resulting solution was diluted with EtOAc (15 mL), saturated aqueous Rochell salt (25 mL) was added, and the mixture was stirred until it became clear. The normal work-up with EtOAc (15 mL x 3) and the column chromatography (EtOAc/hexane = 2/1) rendered the allylic alcohol 33 (147 mg, 87%). To 33 (147 mg, 0.24 mmol) in CH₂Cl₂ (3 mL) were added NaHCO₃ (41 mg, 0.48 mmol) and mCPBA (83 mg, 0.48 mmol) at −40°C sequentially. The reaction temperature was raised to −20°C over 20 minutes, and the mixture was stirred at that temperature for 10 hours. After quenching the reaction with saturated aqueous NaHCO₃ (10 mL), the normal work-up with EtOAc (10 mL x 3) and the chromatographic separation (EtOAc/hexane = 2/1) procured the epoxy alcohol 16 (148 mg, 98%). For 16: ¹H NMR (400 MHz, CDCl₃) δ 8.03-7.79 (m, 2H), 7.53-7.41 (m, 1H), 7.41-7.23 (m, 7H), 5.24-4.92 (m, 2H), 4.92-4.48 (m, 1H), 4.40-3.93 (m, 1H), 3.88-3.44 (m, 6H), 3.25-3.10 (s, 1H), 2.88 (bs, 1H), 2.33-1.62 (m, 6H), 1.46-1.20 (m, 15H). ¹³C NMR (100 MHz, CDCl₃) δ 165.96, 153.61, 153.40, 151.60, 150.98, 135.95, 133.05, 132.74, 129.38, 129.27, 128.33, 128.29, 127.96, 93.33, 92.84, 79.85, 79.47, 67.40, 66.94, 66.63, 66.07, 65.31, 64.13, 63.78, 62.75, 62.52, 61.69, 61.57, 61.41, 60.52, 58.08, 57.09, 56.92, 56.74, 56.43, 55.58, 55.45, 55.03, 38.23, 37.97, 30.30, 29.99, 28.21, 27.66, 27.55, 26.72, 26.21, 25.63, 24.22, 23.03, 13.89. HRMS (ESI) m/z calcd for C₃₄H₄₄N₂NaO₉ [M+Na]⁺, 647.2939; found, 647.2947. [α]D²⁵ +39.7 (c 1.00, CHCl₃).
Synthesis of the azido diol 17

To 16 (148 mg, 0.24 mmol) in DMF (1.6 mL) was added (MeO)$_3$B (53 μL, 0.47 mmol) at room temperature, and the mixture was stirred at that temperature for 20 minutes. Then, NaN$_3$ (31 mg, 0.47 mmol) was added, and the resulting solution was heated at 50°C for 3 hours. After cooling down the solution to room temperature, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ and stirred vigorously for an hour. The normal work-up with Et$_2$O (10 mL x 3) and the subsequent column chromatography (EtOAc/hexane = 2/1) yielded the azido diol 17 (144 mg, 91%). For 17: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.93 (t, $J = 8.5$ Hz, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.44-7.25 (m, 7H), 5.76 (dd, $J = 39.9$, 10.1 Hz, 1H), 5.21 (dd, $J = 12.0$, 6.4 Hz, 1H), 5.08 (dd, $J = 12.0$, 2.7 Hz, 1H), 4.78 (dd, $J = 31.4$, 11.2 Hz, 1H), 4.53 (dd, $J = 42.5$, 11.3 Hz, 1H), 4.00-3.50 (brm, 7H), 3.25 (s, 1H), 2.77 (s, 1H), 2.49-2.27 (m, 1H), 2.27-2.00 (m, 2H), 1.96-1.64 (m, 3H), 1.46-1.35 (m, 9H), 1.33 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.23, 156.19, 155.96, 151.81, 151.07, 135.47, 133.23, 132.96, 129.76, 129.57, 129.48, 128.62, 128.47, 128.36, 93.59, 93.11, 80.13, 79.76, 75.41, 75.06, 69.83, 69.61, 68.20, 66.11, 65.74, 64.64, 63.63, 62.94, 62.84, 59.16, 58.77, 55.51, 55.14, 38.65, 38.50, 32.44, 31.49, 31.34, 28.37, 27.64, 26.98, 26.75, 26.49, 24.29, 23.07, 22.56, 14.04. HRMS (ESI) m/z calcd for C$_{34}$H$_{45}$N$_5$NaO$_9$ [M+Na]$^+$, 690.3109; found,
690.3113. \([\alpha]_D^{25} +4.3\) (c 1.00, CHCl₃).

○ Synthesis of the amide triol 19

3 M HCl (0.5 mL) was added to 17 (94 mg, 0.14 mmol) in MeOH (1.4 mL) at room temperature, and the mixture was heated at 40°C for 10 hours. After cooling down the solution to room temperature, all the volatile materials were evaporated in vacuo. To the residual crude ammonium chloride 34 was added iPr₂NEt (25 μL, 0.14 mmol) at 0°C, and the mixture was stirred at that temperature for 30 minutes. The benzoic acid 18 (42 mg, 0.14 mmol) and BOP (64 mg, 0.14 mmol) were dissolved in CH₂Cl₂ (2.5 mL) at 0°C, iPr₂NEt (30 μL, 0.17 mmol) was added at 0°C, and then the resulting solution was stirred at 0°C for 30 minutes. The prepared benzoic acid solution was injected to the solution of 34 at 0°C, the reaction temperature was raised to room temperature, and subsequently the reaction mixture was stirred at room temperature for 6 hours. After quenching the reaction with saturated aqueous NH₄Cl (8 mL), the normal wok-up with EtOAc (8 mL x 3) followed by the chromatographic separation (EtOAc/hexane = 3/1)
afforded the amide triol 19 (94 mg, 83% from 17). For 19: $^1$H NMR (400 MHz, CD$_3$OD) δ 7.90-7.80 (m, 2H), 7.69 (d, $J = 14.7$ Hz, 2H), 7.44 (m, 2H), 7.40-7.13 (m, 12H), 5.17 (d, $J = 12.0$ Hz, 1H), 5.03 (s, 2H), 4.97 (d, $J = 10.8$ Hz, 1H), 4.88-4.79 (m, 1H), 4.69-4.42 (m, 1H), 4.15-3.88 (m, 4H), 3.77-3.35 (m, 4H), 2.14 (td, $J = 15.2$, 14.4, 8.3 Hz, 3H), 2.01-1.86 (m, 1H), 1.84-1.68 (m, 1H), 1.54 (m, 1H). $^{13}$C NMR (100 MHz, CD$_3$OD) δ 168.03, 166.79, 162.04, 156.38, 154.83, 138.17, 137.87, 137.63, 137.58, 134.78, 134.40, 133.66, 133.34, 131.47, 131.05, 130.97, 130.86, 130.82, 129.98, 129.91, 129.89, 129.82, 129.77, 129.74, 129.67, 129.60, 129.44, 129.39, 76.52, 73.38, 71.82, 68.62, 68.31, 66.72, 66.07, 65.87, 64.87, 64.46, 64.18, 60.46, 60.15, 58.55, 55.25, 52.92, 52.57, 52.30, 38.96, 37.63, 33.94, 30.83, 30.52, 29.38, 29.13. HRMS (ESI) m/z calcd for C$_{40}$H$_{41}$Cl$_2$N$_5$NaO$_9$ [M+Na]$^+$, 828.2173; found, 828.2181. $[\alpha]_D^{25}$ −4.98 (c 1.28, MeOH).

○ Synthesis of the silyl ether 20

![Diagram](image)
To 19 (81 mg, 0.10 mmol) in CH₂Cl₂ were added Et₃N (42 μL, 0.30 mmol) and benzoyl chloride (35 μL, 0.30 mmol) at 0°C, and the mixture was stirred at 0°C for an hour. The reaction was quenched with saturated aqueous NH₄Cl (4 mL), worked up with EtOAc (4 mL x 3), and purified by column chromatography (EtOAc/hexane = 1/2) to deliver the tribenzoate 35 (91 mg, 89%). To 35 (91 mg, 0.09 mmol) in CH₂Cl₂ (2 mL) were added 2,6-lutidine (63 μL, 0.54 mmol) and TBSOTf (103 μL, 0.45 mmol) at −78°C. After replacing the dry ice/acetone bath by an ice/water bath, the reaction solution was stirred for 6 hours. The reaction was quenched with saturated aqueous NaHCO₃ (5 mL), worked up with EtOAc (5 mL x 3), and separated chromatographically (EtOAc/hexane = 1/2) to furnish the silyl ether tribenzoate 36 (98 mg, 97%). To 36 (98 mg, 0.09 mmol) in MeOH (2 mL) was added K₂CO₃ (36 mg, 0.26 mmol) at 0°C, and the mixture was stirred at 0°C for 3 hours. The following quench with saturated aqueous NH₄Cl (5 mL), normal work-up with EtOAc (5 mL x 3) and chromatographic purification (EtOAc/hexane = 2/1) gave the silyl ether 20 (67 mg, 95%). For 20: ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 0.5H), 7.63 (s, 1.5H), 7.55-7.49 (m, 2H), 7.43-7.32 (m, 8H), 6.39 (d, J = 8.0 Hz, 1H), 5.30-5.15 (m, 1.2H), 5.07 (d, J = 9.8 Hz, 2H), 5.00 (d, J = 11.6 Hz, 0.8H), 4.93 (d, J = 1.7 Hz, 0.8H), 4.41 (d, J = 2.6 Hz, 0.2H), 4.04 (ddd, J = 7.5, 5.1, 2.1 Hz, 1H), 3.94-3.62 (m, 6H), 3.61-3.37 (m, 2H), 2.38 (dd, J = 13.1, 7.5 Hz, 1H), 2.17 (ddt, J = 16.7, 10.8, 5.1 Hz, 2H), 1.92-1.70 (m, 2H), 1.62-1.44 (m, 2H), 0.89 (s, 6H), 0.86 (s, 3H), 0.16 (s, 2H), −0.03 (s, 2H), −0.05 (s, 1H), −0.13 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 164.24, 156.03, 154.47, 153.69, 135.92, 135.74, 135.42, 135.16, 131.36, 130.13, 129.96, 129.05, 128.95, 128.64, 128.57, 128.53, 128.11, 127.74, 75.37, 75.20, 72.91, 72.13, 71.60, 70.67, 68.30, 68.20, 66.53, 66.36, 62.56, 62.49, 57.62, 49.73, 36.12, 29.77, 28.12, 26.04, 18.14, −4.44, −4.53, −4.84, −4.97. HRMS (ESI) m/z
calcd for C_{39}H_{51}Cl_{2}N_{5}NaO_{8}Si [M+Na]^+, 838.2776; found, 838.2780. [\alpha]_{D}^{21} +11.3 (c 1.10, CHCl_{3}).

Synthesis of kaitocephalin diethylamine salt (1·HNEt_{2}) from the silyl ether 20

To 20 (48 mg, 0.06 mmol) in MeCN (0.8 mL) and phosphate buffer (pH 6.8, 0.8 mL) were added PhI(OAc)$_2$ (174 mg, 0.53 mmol) and AZADO (5 mg, 0.03 mmol) at room temperature, and the mixture was stirred at that temperature for 8 hours. The solution was acidified to pH 2 by adding aqueous HCl (6 M, 0.5 mL) at room temperature, and stirred for 3 hours. The reaction mixture was extracted with EtOAc (2 mL x 5), and then the organic layer was washed with brine (1 mL x 3). After evaporation of all the volatile materials in vacuo, the crude tricarboxylic acid 21 was dissolved in a mixture of EtOH (1.5 mL) and CHCl$_3$ (0.15 mL) at room temperature. To the prepared solution was added Pd(OH)$_2$/C (20 wt%, 25 mg), and an atmospheric hydrogen balloon was installed. During the installation, the reaction flask was flushed three times under reduced pressure by a rotary evaporator. After stirring the mixture at room temperature for 2 hours, the solution was filtered through cotton using EtOH (5 mL). All the volatile
materials were removed in vacuo, and then the residue was treated by the same procedure again as described in the aforementioned hydrogenolysis/hydrogenation process. The resulting residue was purified through Dowex® 50WX4 (H⁺ form, 100-200 mesh, 0.6 g, prewashed with water until the eluted water became neutral) using NH₄OH (1 M) to collect the uv-active fraction. The volatile materials of the fraction were evaporated in vacuo, and the residue was separated through COSMOSIL 75C₁₈-OPN (0.6 g) using water to receive the uv-active fraction. Evaporation of the fraction in vacuo produced kaitocephalin ammonium salt. The salt was further purified by a reverse phase HPLC through a column (20 x 250 mm) packed with COSMOSIL 5C₁₈-PAQ using 5% MeOH in 20 mM Et₂NH/CO₂ buffer (pH 7, flow rate = 6 mL/min) to provide kaitocephalin diethylamine salt 1·HNEt₂ (8.6 mg, 26% from 20). 20 mM Et₂NH/CO₂ buffer solution was prepared by bubbling CO₂ into 20 mM aqueous Et₂NH solution until its pH became 7. For 1·HNEt₂: ¹H NMR (400 MHz, D₂O) δ 7.73 (s, 2H), 4.51 (s, 1H), 4.45 (dd, J = 8.3, 5.3 Hz, 1H), 4.28 (s, 1H), 3.84-3.76 (m, 1H), 2.53 (dt, J = 14.3, 6.0 Hz, 1H), 2.41-2.37 (m, 1H), 2.23-2.08 (m, 3H), 1.76-1.66 (m, 1H). ¹³C NMR (100 MHz, D₂O) δ 177.41, 174.14, 170.54, 168.36, 161.82, 127.41, 123.88, 117.61, 76.11, 70.47, 58.93, 55.33, 53.26, 34.90, 31.90, 29.47. HRMS (ESI) m/z calcd for C₁₈H₂₃Cl₂N₃O₉ [M+H]⁺, 494.0728; found, 494.0688. [α]D²² = −29.9 (c 0.34, H₂O).

- Synthesis of the oxazolidinone 23
To NaH (60% dispersion in mineral oil, 14 mg, 0.35 mmol) in THF (1 mL) was added 17 (46 mg, 0.07 mmol) using THF (1 mL) through a cannula in an ice/water bath, and the mixture was stirred at that temperature for an hour. After quenching the reaction with saturated aqueous NH₄Cl (4 mL), the normal work-up with EtOAc (3 mL x 3) and the subsequent column chromatography (EtOAc/hexane = 2/1) offered the oxazolidinone 22 (27 mg, 86%). 3 M HCl (0.2 mL) was added to 22 (27 mg, 0.06 mmol) in MeOH (0.6 mL) at room temperature, and the mixture was heated at 40°C for 10 hours. After cooling down the solution to room temperature, all the volatile materials were evaporated in vacuo. To the residual crude ammonium chloride was added iPr₂NEt (11 μL, 0.06 mmol) at 0°C, and the mixture was stirred at that temperature for 30 minutes. The benzoic acid 18 (18 mg, 0.06 mmol) and BOP (28 mg, 0.06 mmol) were dissolved in CH₂Cl₂ (1 mL) at 0°C, iPr₂NEt (13 μL, 0.07 mmol) was added at 0°C, and then the resulting solution was stirred at 0°C for 30 minutes. The prepared benzoic acid solution was injected to the solution of the crude ammonium chloride at 0°C, the reaction temperature was raised to room temperature, and subsequently the reaction mixture was stirred at room temperature for 6 hours. After quenching the reaction with saturated aqueous NH₄Cl (3 mL), the normal wok-up with EtOAc (3 mL x 3) followed by the chromatographic separation (EtOAc, then 3% MeOH in EtOAc) afforded the amide triol 23 (30 mg, 84% from 17). For 23: ¹H NMR (400 MHz, CD₃OD) δ 7.81 (s,
2H), 7.47-7.43 (m, 2H), 7.34-7.27 (m, 3H), 5.04 (s, 2H), 4.47 (d, J = 10.0 Hz, 1H), 4.09 (dq, J = 10.7, 5.3 Hz, 1H), 4.00-3.87 (m, 2H), 3.74-3.59 (m, 4H), 3.56 (d, J = 12.0 Hz, 1H), 3.42 (d, J = 12.0 Hz, 1H), 2.35 (dt, J = 10.4, 7.9 Hz, 1H), 2.01-1.70 (m, 5H). $^{13}$C NMR (100 MHz, CD$_3$OD) δ 169.44, 167.17, 162.53, 154.77, 137.63, 133.78, 132.51, 131.03, 130.05, 129.92, 129.77, 129.67, 129.65, 76.50, 76.04, 74.63, 65.79, 64.67, 63.95, 63.46, 63.00, 58.40, 52.54, 39.16, 33.75, 29.64, 14.57. HRMS (ESI) m/z calcd for C$_{26}$H$_{29}$Cl$_2$N$_5$NaO$_7$ [M+Na]$^+$, 616.1336; found, 616.1334. [α]$_D^{25}$$^2$ -25.8 (c 1.1, MeOH).

Synthesis of kaitocephalin diethylamine salt (1·HNE$_2$) from the oxazolidinone 23

To 23 (43 mg, 0.07 mmol) in MeCN (1 mL) and phosphate buffer (pH 6.8, 1 mL) were added PhI(OAc)$_2$ (215 mg, 0.65 mmol) and AZADO (6 mg, 0.04 mmol) at room temperature, and the mixture was stirred at that temperature for 8 hours. The solution was acidified to pH 2 by adding aqueous HCl (1 M, 1 mL) at room temperature, and stirred for 3 hours. The reaction mixture was extracted with EtOAc (3 mL x 5), and then the organic layer was washed with brine (1 mL x 3). After evaporation of all the volatile materials in vacuo, the crude tricarboxylic acid 24 was dissolved in a mixture of EtOH
(2 mL) and CHCl₃ (0.2 mL) at room temperature. To the prepared solution was added Pd(OH)₂/C (20 wt%, 25 mg), and an atmospheric hydrogen balloon was installed. During the installation, the reaction flask was flushed three times under reduced pressure by a rotary evaporator. After stirring the mixture at room temperature for 2 hours, the solution was filtered through cotton using EtOH (6 mL). All the volatile materials were removed in vacuo, and then the residue was treated by the same procedure again as described in the aforementioned hydrogenolysis/hydrogenation process. The resulting residue was purified through Dowex® 50WX4 (H⁺ form, 100–200 mesh, 0.6 g, prewashed with water until the eluted water became neutral) using NH₄OH (1 M) to collect the uv-active fraction. The volatile materials of the fraction were evaporated in vacuo, and the residue was dissolved in a mixture of EtOH (1.2 mL) and 2 M NaOH (1.2 mL). The mixture was heated at 40–42°C for 20 hours. After placing the reaction vessel into an ice/water bath, it was neutralized to pH 7 with 1 M aqueous HCl, and then evaporated in vacuo. The resulting residue was purified through Dowex® 50WX4 (H⁺ form, 100–200 mesh, 1 g, prewashed with water until the eluted water became neutral) by loading it with water, and subsequently eluting it with water to remove salts (NaCl and/or NH₄Cl) and finally with NH₄OH (1 M) to collect the uv-active fraction. The volatile materials of the fraction were evaporated in vacuo, and the residue was separated through COSMOSIL 75C₁₈-OPN (0.6 g) using water to receive the uv-active fraction. Evaporation of the fraction in vacuo produced kaitocephalin ammonium salt. The salt was further purified by a reverse phase HPLC through a column (20 x 250 mm) packed with COSMOSIL 5C₁₈-PAQ using 5% MeOH in 20 mM Et₂NH/CO₂ buffer (pH 7, flow rate = 6 mL/min) to provide kaitocephalin diethylamine salt 1·HNEt₂ (9.3 mg, 22.5% from 23). For 1·HNEt₂: ¹H NMR (400 MHz, D₂O) δ 7.78
(s, 2H), 4.56 (s, 1H), 4.49 (dd, J = 8.3, 5.3 Hz, 1H), 4.32 (s, 1H), 3.88-3.81 (m, 1H), 2.57 (dt, J = 14.1, 6.0 Hz, 1H), 2.46-2.41 (m, 1H), 2.29-2.13 (m, 3H), 1.81-1.73 (m, 1H).

$^{13}$C NMR (100 MHz, D$_2$O) δ 177.35, 174.11, 170.46, 168.26, 160.52, 127.46, 123.64, 118.66, 76.12, 70.44, 58.92, 55.29, 53.27, 34.86, 31.88, 29.46. HRMS (ESI) m/z calcd for C$_{18}$H$_{22}$Cl$_2$N$_3$O$_9$ [M + H]$^+$, 494.0728; found, 494.0715. $[\alpha]_D^{22}$ −29.3 (c 0.31, H$_2$O).
Synthetic kaitocephalin·HNEt\textsubscript{2} from 20

\begin{center}
\includegraphics[width=0.4\textwidth]{synthetic_kaitocephalin_hnet2_20}
\end{center}

Synthetic kaitocephalin·HNEt\textsubscript{2} from 23

\begin{center}
\includegraphics[width=0.4\textwidth]{synthetic_kaitocephalin_hnet2_23}
\end{center}

Mixture of synthetic kaitocephalin·HNEt\textsubscript{2} from 20 and 23

\begin{center}
\includegraphics[width=0.4\textwidth]{mixture_synthetic_kaitocephalin_hnet2}
\end{center}

\textbf{Preparative HPLC conditions}

- **Column**: COSMOSIL 5C\textsubscript{18}-PAQ Packed Column 20 x 250 mm
- **Eluent**: 5\% MeOH / 20 mM Et\textsubscript{2}NH-CO\textsubscript{2} buffer pH 7.0
- **Flow rate**: 6 mL/min
- **Detection**: 300 nm