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Reinvestigation on total synthesis of kaitocephalin and its isomers

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ABSTRACT

Aldol reaction of 2,5-disubstituted pyrrolidine **3b** with (*R*)-Garner aldehyde followed by Sharpless asymmetric dihydroxylation and other four reactions afforded mesylate **8a**, which was introduced by an amide group via three ordinary transformations to provide amide **9a**. Careful deprotection with $AlCl_3$/Me_2S and subsequent HPLC purification furnished kaitocephalin.

1. Introduction

In 1997, Shin-ya and co-workers isolated a novel pyrrolidine-based amino acid, kaitocephalin, from the filamentous fungus *Eupenicillium shearii*.[1a] Biological evaluation of this compound indicated that it has strong antagonistic ability toward AMPA and KA receptors, two subtypes of glutamate receptors that play a role of utmost importance in many physiological processes, such as neural plasticity, memory, and learning.[1a] Through intensive studies using chemical transformation and NMR technology its stereochemistry was initially assigned as 2*S*,3*S*,4*R*,7*R*,9*S* (as indicated in structure **2**, Fig. 1).[1b] About 1 year later the configuration of this natural product was revised as 2*R*,3*S*,4*R*,7*R*,9*S* on the basis of synthetic studies.[2a] The interesting biological activity of this amino acid, together with its unique structural feature, had immediately attracted synthetic studies, even before its structure was not fully established. To date three groups have achieved its total synthesis.[2–4]

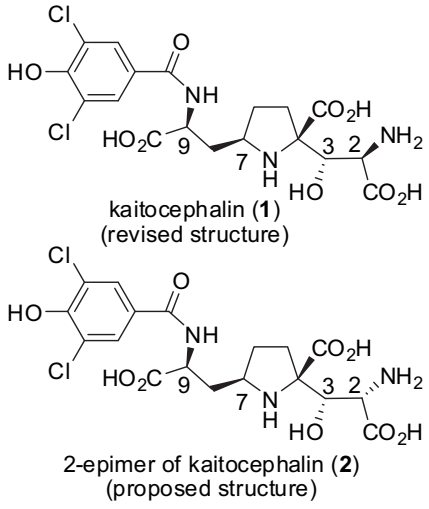

Fig. 1. Structures of kaitocephalin and its 2-epimer.

Based on the initially proposed structure of kaitocephalin, we started our synthetic investigations. As outlined in Scheme 1, we planned to elaborate its right part via an aldol reaction of 2,5-disubstituted pyrrolidine **3** with (*R*)-Garner aldehyde, and introduce the left amino acid moiety through Sharpless asymmetric dihydroxylation and subsequent azidation (Scheme 1). It is noteworthy that in our previous synthesis the final step gave a mixture of two isomers (see studies described later), which was mistakenly assigned as the natural kaitocephalin.[5]

After the correct stereochemistry of kaitocephalin was established,[2a] we found that our designed synthetic protocol for its isomer **2**, indeed, was more suitable for assembling kaitocephalin itself. During the synthetic studies toward **2**, we found that the aldol reaction of **3a** with (*R*)-Garner aldehyde provided oxazolidine **4** exclusively,[5a] in which the stereochemistry at C-3 was opposite to

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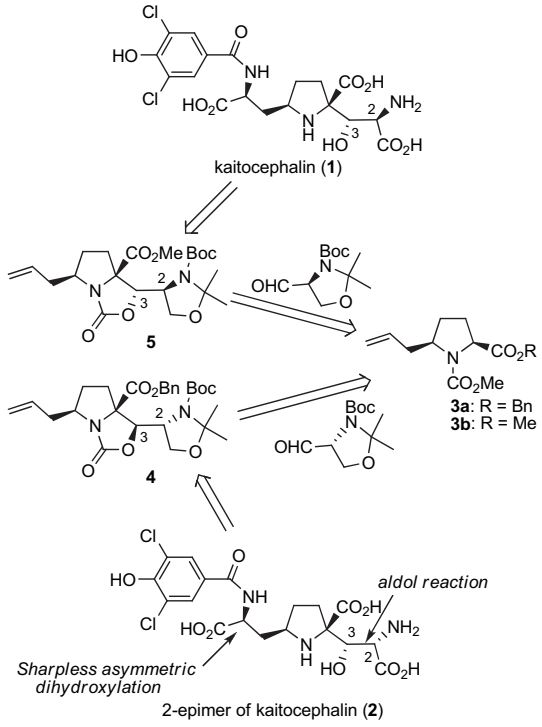
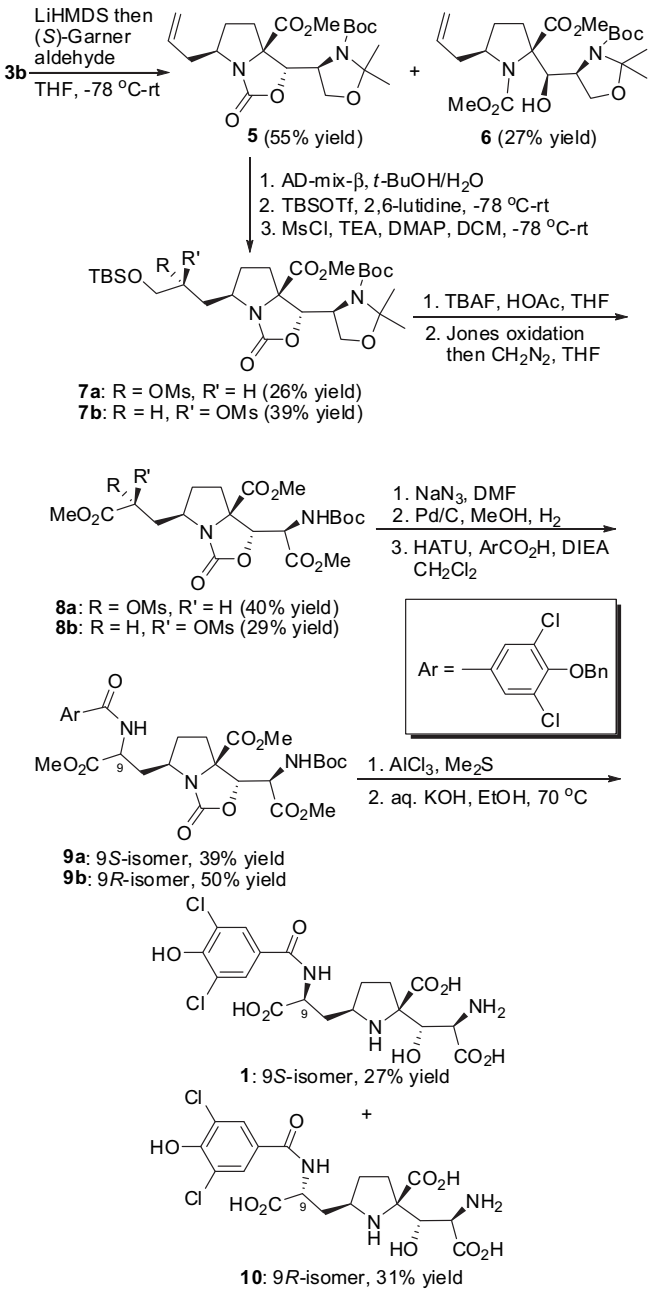


Scheme 1.



Scheme 2.

the target molecule **2**. An oxidation/reduction operation was then selected to invert the configuration of this position. If the stereochemistry of C-3 in **4** could be introduced by (*R*)-Garner aldehyde part during the aldol reaction, we would be able to obtain oxazolidine **5**, in which the stereochemistry at the 2 and 3 positions are identical with kaitocephalin **1**, by reacting the 2,5-disubstituted pyrrolidine **3b** with less expensive (*S*)-Garner aldehyde.

2. Results and discussion

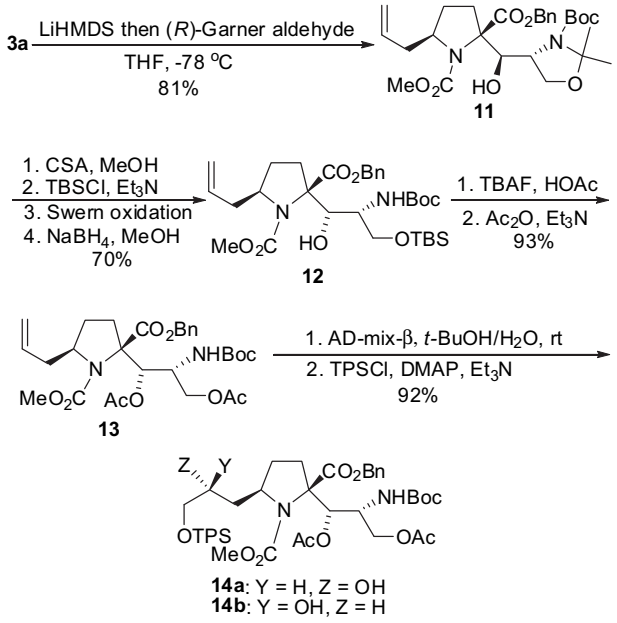
With the idea in mind, we conducted the condensation of a lithium salt of **3b** with (*S*)-Garner aldehyde at −78 °C (Scheme 2). After the reaction mixture was warmed to room temperature, the desired oxazolidine **5** was isolated in 55% yield, together with alcohol **6** in 27% yield. The formation of **6** indicated that the diastereoselectivity in this case was not as good as the aldol reaction of **3** with (*R*)-Garner aldehyde,[5a] indicating that the stereochemistry of the 2,5-disubstituted pyrrolidine also played a role in the asymmetric induction.

Sharpless asymmetric dihydroxylation[6] of **5** was carried out with AD-mix-β in *tert*-butanol and water. The resultant inseparable diastereomer mixture was treated with TBSOTf to selectively protect the primary alcohol, followed by exposure onto MsCl and triethylamine, to afford separable mesylates **7a** and **7b**. The stereochemistry of newly created stereogenic centers in **7a** and **7b** was established by converting them to known kaitocephalin and its 9-epimer **10** as described later. To our surprise, after these transformations the desired isomer **7a** was isolated as a minor component. Since asymmetric dihydroxylation of the terminal olefins with AD-mix-β often provides the diol with *R*-configuration as the major isomer,[6] we assumed that the present stereochemistry outcome was mainly controlled by substrate but not the ligand.

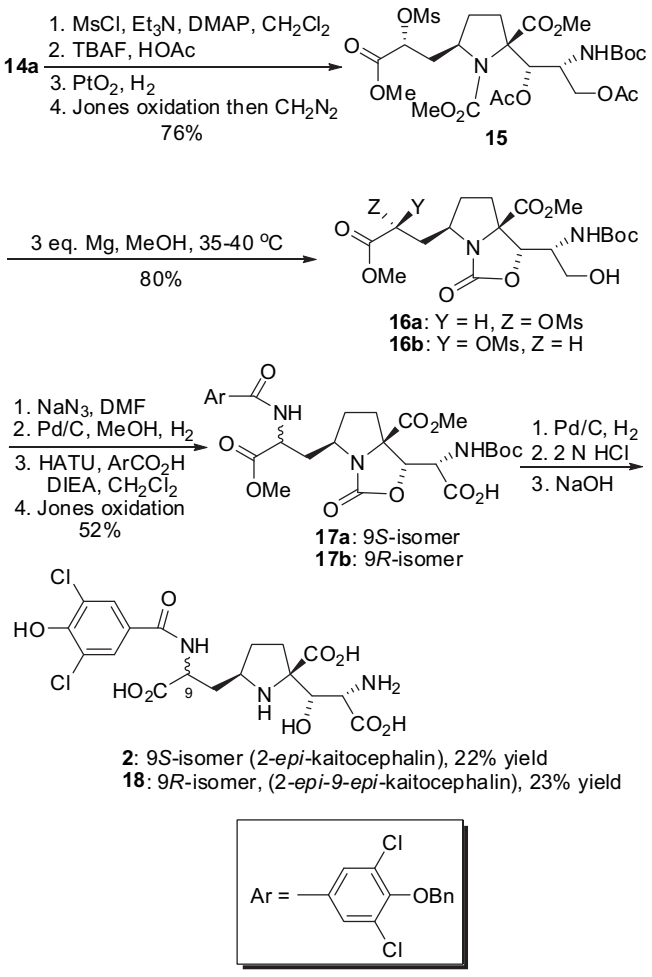
After the silyl protecting group in esters **7** was removed with TBAF, the resultant alcohols were converted into the corresponding acids via Jones oxidation. In this case the acetonide moiety was cleaved and the liberated primary alcohols were further oxidized and therefore diacids were obtained, which were treated with diazomethane to furnish triesters **8**. Transformation of **8** into the corresponding azides via a S_N2 reaction with sodium azide followed by hydrogenation produced amines, which were condensed with 3,5-dichloro-4-benzoxybenzoic acid mediated by HATU to produce amides **9**. Treatment of **9** with $AlCl_3/Me_2S$[3a,7] to remove the benzyl ether, methyl ester, and Boc-protecting groups, and subsequent hydrolysis with KOH to open the oxazolidinone ring, gave rise to kaitocephalin **1** and its 9-epimer **10**, after HPLC purification. It is notable that deprotection of **9** by sequential base- and acid-catalyzed hydrolysis provided a complex mixture.

After obtaining natural kaitocephalin via a new protocol, we decided to reinvestigate our previous synthesis, and hoped to use the newly established HPLC isolation method to purify the mixture obtained in our previous study.[5a] As outlined in Scheme 3,

condensation of **3a** with (*R*)-Garner aldehyde produced alcohol **11**. Treatment of **11** with TsOH in methanol followed by selective protection of the liberated primary hydroxyl group with TBSCl afforded an alcohol, which was subjected to stereochemistry inversion via the oxidation/reduction strategy to deliver alcohol **12** with 70% overall yield. Cleavage of the silyl ether in **12** and subsequent protection with acetic anhydride produced triester **13**, which was treated with AD-mix-β and then protected with TPSCl to provide a separable mixture of **14a** and **14b**.



Scheme 3.

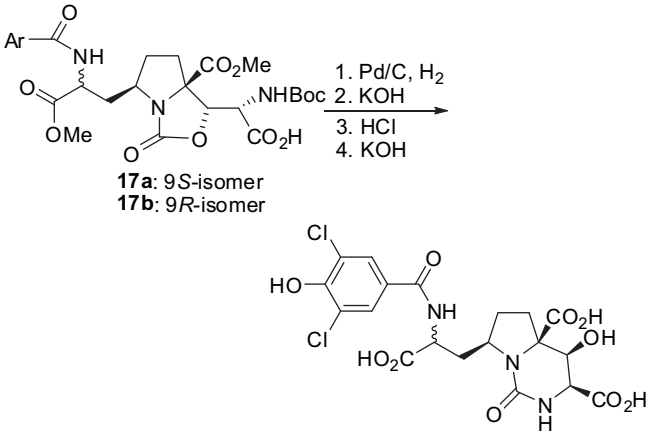


Scheme 4.

Mesylation of **14a** followed by desilylation gave rise to a primary alcohol, which was hydrogenated, oxidized with Jones reagent, and then exposed to diazomethane, providing mesylate **15** in 76% overall yield (Scheme 4). Treatment of **15** with magnesium powder in methanol gave a mixture of **16a** and **16b**, indicating that during the oxazolidinone ring formation partial racemization at the 9-position occurred. This phenomenon has unfortunately not been noticed in our previous study,[5a] mainly because this mixture is inseparable via column chromatography and two sets of proton NMR signals were misunderstood as the signals displayed by two rotamers. In the present case we were able to obtain the single isomer via HPLC purification and found that there is only one set of proton NMR signals for each isomer. Starting from isomer **14b**, we could obtain the 9-epimer of **15**, which reacted with magnesium powder in methanol to provide **16a** and **16b** in about 1/1 ratio. This result gave additional evidence for the undesired partial racemization in oxazolidinone ring formation step.

The mixture of **16a** and **16b** was reacted with sodium azide, followed by Pd/C catalyzed hydrogenation to provide a primary amine. Condensation of this amine with 3,5-dichloro-4-benzoxybenzoic acid under the action of HATU produced an amide, which was subjected to Jones oxidation to give acids **17** as a mixture of 9*S*- and 9*R*-isomers. After hydrogenolysis of **17** to remove the benzyl protecting group, HCl treatment and subsequent NaOH mediated hydrolysis delivered a diastereomeric mixture. This mixture was separated with HPLC to afford **2** (22% yield) and **18** (23% yield). ^{1}H NMR data of these two products were in agreement with those reported for 2-*epi*- and 2-*epi*-9-*epi*-kaitocephalin.[2a] Thus, we concluded that our previous mixture[5] might mainly contain 2-*epi*- and 2-*epi*-9-*epi*-kaitocephalin.

Interestingly, two cyclization products **19a** and **19b**, were isolated in good combined yield when hydrolysis of two ester groups in **17** was carried out before cleavage of the Boc-protecting group with HCl and subsequent KOH-catalyzed hydrolysis (Scheme 5). These results indicated that the reaction sequence for deprotection steps was essential for complete deprotection.



Scheme 5.

3. Conclusions

In conclusion, we have demonstrated that synthesis of kaitocephalin and its stereoisomers could be achieved starting from a 2,5-disubstituted pyrrolidine and the Garner aldehydes. The key steps include the aldol reaction of these two partners and Sharpless asymmetric dihydroxylation. Due to poor diastereoselectivity in these two steps, overall yield was only 0.32% (for 15 steps from L-pyroglutamic acid). Further investigations to solve this problem are required to make this route more useful.

4. Experimental

4.1. Aldol reaction of 3a with (*S*)-Garner aldehyde

To a solution of **3a** (2.29 g, 10.1 mmol) in 10 mL THF was added a solution of LiHMDS (1.0 M in THF, 12.0 mL) at −78 °C. The resultant solution was stirred for 1 h at the same temperature and then warmed to −30 °C during 1 h. The solution was cooled to −78 °C again before a solution of (*S*)-Garner aldehyde (2.99 g, 13.0 mmol) in 50 mL THF was added dropwise. The reaction mixture was stirred for 2 h at −78 °C and then warmed to room temperature during 2 h. The reaction was quenched by adding 50 mL 1 M HCl and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and column flash chromatography (eluting with 1/30 to 1/10 EtOAc/hexanes) gave **5** (2.36 g, 55%) and **6** (1.24 g, 27%) as colorless oils. Compound **5**: $[\alpha]_D^{26}$ −21.7 (*c* 0.95, $CHCl_3$); IR (film) 3078, 2980, 1770, 1702, 1643, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84–5.71 (m, 1H), 5.14–5.05 (m, 2H), 4.87 and 4.69 (due to rotamers, both d, *J*=7.5 and 3.9 Hz, 1H), 4.30–3.83 (m, 4H), 3.97 and 3.79 (due to rotamers, both s, 3H), 2.65–2.57 (m, 1H), 2.55–2.30 (m, 1H), 2.27–2.13 (m, 2H), 1.72–1.55 (m, 2H), 1.52–1.50 (m, 15H); MS (ESI) *m*/*z* 425.2 $(M+H)^+$, 447.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{21}H_{35}N_2O_7$ $(M+H)^+$ 425.2282, found 425.2281. Compound **6**: $[\alpha]_D^{24}$ −5.4 (*c* 1.1, $CHCl_3$); IR (film) 3413, 2981, 2957, 1753, 1716, 1693, 1642, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77–5.67 (m, 1H), 5.10–5.04 (m, 2H), 4.63 (d, *J*=9.3 Hz, 1H), 4.11–4.05 (m, 1H), 3.99 (dd, *J*=4.5, 11.7 Hz, 1H), 3.72 (s, 6H), 3.72–3.63 (m, 2H), 2.45–2.40 (m, 1H), 2.39–2.32 (m, 1H), 2.30–2.24 (m, 1H), 2.15–1.98 (m, 2H), 1.76–1.70 (m, 1H), 1.47 (s, 3H), 1.39 (s, 9H), 1.32 (s, 3H); MS (ESI) *m*/*z* 479.2 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{22}H_{36}N_2O_8Na$ $(M+Na)^+$ 479.2364, found 479.2366.

4.2. Synthesis of mesylates 7

To a solution of **5** (2.11 g, 4.97 mmol) in 25 mL *t*-BuOH, and 25 mL water was added AD-mix-β (7.21 g) at 0 °C. The resultant solution was stirred for 1 h at the same temperature and then overnight at room temperature. After the solution was cooled to 0 °C, 50 mL half-saturated Na_2SO_3 solution was added and the solution was stirred for 1 h at room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL×5). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and column flash chromatography (eluting with EtOAc/hexanes) give a diol (1.66 g, 73%) as white foam.

To the solution of the above diol in 30 mL CH_2Cl_2 were successively added 2,6-lutidine (0.58 mL, 5.0 mmol) and TBSOTf (0.91 mL, 4.0 mL) at −78 °C. The reaction mixture was warmed to room temperature overnight. Concentration and column flash chromatography (eluting with 1/4 to 1/2 EtOAc/hexanes) give the silyl ether (1.87 g, 90%) as white foam.

To a solution of the above silyl ether (783 mg, 1.37 mmol), triethylamine (1.2 mL, 8.4 mmol), DMAP (30 mg, 0.25 mmol) in 10 mL CH_2Cl_2 was added MsCl (0.42 mL, 5.4 mmol) at −78 °C. The reaction mixture was warmed to −10 °C during 2.5 h and then quenched by adding brine. The solution was partitioned between EtOAc and water. The organic layer was washed with brine and dried over Na_2SO_4. After the solution was concentrated, the residue was chromatographed (eluting with 1/6 to 1/2 EtOAc/hexanes) to afford **7b** (556 mg, 60%) and **7a** (357 mg, 40%) as white foams. Compound **7a**: $[\alpha]_D^{24}$ −38.3 (*c* 0.99, $CHCl_3$); IR (film) 2956, 2860, 1767, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 and 4.91 (due to rotamers, both d, *J*=9.3 and 7.5 Hz, 1H), 4.87–474 (m, 1H), 4.26–4.18 (m, 1H), 4.13–3.78 (m, 5H) 3.80 (s, 3H), 3.17–3.04 (m, 3H), 2.63–2.57 (m, 1H), 2.45–2.38 (m, 1H), 2.06–1.86 (m, 3H), 1.61–1.50 (m, 15H), 0.89 (s, 9H), 0.09 (s, 6H); MS (ESI) *m*/*z* 673.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{28}H_{50}N_2O_{11}SSiNa$ $(M+Na)^+$ 673.2797, found 673.2798. Compound **7b**: $[\alpha]_D^{24}$ −26.7 (*c* 0.9, $CHCl_3$); IR (film) 2938, 2860, 1766, 1702, 1391 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 and 4.37 (due to rotamers, both d, *J*=9.3 and 10.8 Hz, 1H), 4.86–4.75 (m, 1H), 4.30–4.23 (m, 1H), 4.12–3.93 (m, 3H), 3.91–3.68 (m, 2H), 3.81 and 3.79 (due to rotamers, both s, 3H), 3.18–3.13 (m, 3H), 2.65–2.57 (m, 1H), 2.56–2.39 (m, 1H), 1.94–1.82 (m, 2H), 1.80–1.71 (m, 2H), 1.57–1.48 (m, 15H), 0.95 (s, 9H), 0.06 (m, 6H); MS (ESI) *m*/*z* 673.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{28}H_{50}N_2O_{11}SSiNa$ $(M+Na)^+$ 673.2797, found 673.2806.

4.3. Synthesis of triesters 8

To a solution of **7a** (1.05 g, 1.61 mol) in 25 mL THF were added TBAF (1.0 M in THF, 3.2 mL) and CH_3CO_2H (179 mg, 2.93 mmol) at room temperature. The resultant solution was stirred for 5 h at room temperature and then concentrated. Flash chromatography of the residue eluting with 1/1 to 2/1 EtOAc/hexanes afforded the corresponding alcohol (745 mg, 86%) as white foam.

To the solution of the above alcohol (524 mg, 0.98 mmol) in 30 mL acetone was added 3.6 mL freshly prepared Jones reagent (about 2.7 M) at 0 °C. After the reaction mixture was stirred for 1 h at 0 °C, and 0.5 h at room temperature, the reaction was quenched by adding 3.6 mL *i*-PrOH at 0 °C. The stirring was continued for 1 h before the mixture was filtered. The filtration cake was dissolved in brine and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in 20 mL THF and treated with a solution of CH_2N_2 in ether until the reaction mixture turned yellow. The stirring was continued until the color disappeared. Concentration and flash chromatography (eluting with 1/4 to 1/1 EtOAc/hexanes) gave **8a** (248 mg, 46%) as white foam. $[\alpha]_D^{25}$ −12.3 (*c* 0.93, $CHCl_3$); IR (film) 3365, 2986, 1762, 1717, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (d, *J*=6.6 Hz, 1H), 5.15 (dd, *J*=6.0, 6.6 Hz, 1H), 4.84 (dd, *J*=6.9, 16.8 Hz, 1H), 4.58–4.43 (m, 1H), 4.10–3.97 (m, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.17 (s, 3H), 2.52–2.37 (m, 2H), 2.30–2.16 (m, 2H), 2.09–2.01 (m, 1H), 1.90–1.78 (m, 1H), 1.44 (s, 9H); MS (ESI) *m*/*z* 570.4 $(M+NH_4)^+$, 575.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{21}H_{32}N_2O_{13}SNa$ $(M+Na)^+$ 575.1517, found 575.1506.

Following the same procedure from **7a** to **8a**, **8b** was obtained from **7b** in 29% yield. $[\alpha]_D^{26}$ −41.7 (*c* 1.2, $CHCl_3$); IR (film) 3367, 2938, 1807, 1718, 1522 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (d, *J*=8.1 Hz, 1H), 5.16 (d, *J*=10.5 Hz, 1H), 4.86 (d, *J*=9.0 Hz, 1H), 4.56–4.51 (m, 1H), 4.11–4.06 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H) 3.79 (s, 3H), 3.16 (s, 3H), 2.50–2.40 (m, 1H), 2.30–2.22 (m, 2H), 2.16–1.99 (m, 2H), 1.84–1.73 (m, 1H), 1.43 (s, 9H); MS (ESI) *m*/*z* 575.1 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{21}H_{32}N_2O_{13}SNa$ $(M+Na)^+$ 575.1517, found 575.1529.

4.4. Preparation of amides 9

To a solution of **8a** (70 mg, 0.13 mmol) in 3 mL DMF was added NaN_3 (25 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 36 h. The mixture was partitioned between brine and EtOAc, and aqueous phase was extracted with EtOAc. The

combined organic phase was washed with brine and dried over Na_2SO_4. Concentration and flash chromatography (eluting with 1/6 to 1/2 EtOAc/hexanes) gave the corresponding azide (37 mg, 65%) as white foam.

To a solution of the above azide (32 mg, 0.071 mmol) in 1.5 mL MeOH was added 4 mg of 10% Pd/C. The resultant mixture was stirred under hydrogen at ordinary pressure for 0.5 h. After the catalyst was filtered off, the filtrate was concentrated and the residue was dissolved in 1.5 mL CH_2Cl_2. To this solution were added HATU (41 mg, 0.11 mmol), 4-(benzyloxy)-3,5-dichlorobenzoic acid (32 mg, 0.11 mmol), and DIEA (0.025 mL, 0.14 mmol) at 0 °C. The mixture was stirred at room temperature overnight. After the solution was concentrated, flash chromatography of the residue (eluting with 1/6 to 1/2 EtOAc/hexanes) afforded **9a** (32 mg, 60% yield) as white foam. $[\alpha]_D^{25}$ −52.8 (*c* 0.65, $CHCl_3$); IR (film) 3348, 2956, 1747, 1592, 1537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J*=7.5 Hz, 1H), 7.84 (s, 2H), 7.57–7.54 (m, 2H), 7.44–7.34 (m, 3H), 5.27 (d, *J*=8.7 Hz, 1H), 5.08 (s, 2H), 4.85 (d, *J*=9.3 Hz, 1H), 3.97–3.92 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.49–2.34 (m, 2H), 2.30–2.25 (m, 2H), 2.08–1.91 (m, 1H), 1.91–1.78 (m, 1H), 1.44 (s, 9H); MS (ESI) *m*/*z* 752.4 $(M+H)^+$, 774.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{34}H_{40}N_3O_{12}Cl_2$ $(M+H)^+$ 752.1984, found 752.1974.

Following the same procedure from **8a** to **9a**, **9b** was obtained from **8b** in 50% yield. Compound **9b**: $[\alpha]_D^{26}$ −45.8 (*c* 1.3, $CHCl_3$); IR (film) 3346, 2959, 1750, 1666, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J*=8.4 Hz, 1H), 7.94 (s, 2H), 7.55 (dd, *J*=1.8, 7.8 Hz, 2H), 7.43–7.36 (m, 3H), 5.21 (d, *J*=8.7 Hz, 1H), 5.08 (s, 2H), 5.07–5.01 (m, 1H), 4.95 (d, *J*=9.9 Hz, 1H), 4.49 (t, *J*=8.7 Hz, 1H), 4.13–4.03 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 2.46–2.40 (m, 1H), 2.34–2.19 (m, 3H), 1.98–1.81 (m, 2H), 1.42 (s, 9H); MS (ESI) *m*/*z* 774.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{34}H_{39}N_3O_{12}Cl_2Na$ $(M+Na)^+$ 774.1803, found 774.1817.

4.5. Kaitocephalin and its 9-epimer

To a solution of **9a** (17 mg, 22.6 μmol) in Me_2S (0.5 mL) was added $AlCl_3$ (85 mg, 0.65 mmol) at room temperature. The reaction mixture was stirred at room temperature for 36 h, quenched with H_2O, and concentrated under reduced pressure. The residue was purified by Dowex 50 W×2 (elution with 1 N NH_4OH) to give the crude product. To a solution of this crude product in 0.5 mL EtOH was added 0.5 mL 1 M KOH. The resultant mixture was stirred at 70 °C for 9 h. The solution was cooled to room temperature and then 0.5 mL 1 M HCl was added to quench the reaction. After the mixture was concentrated, the residue was purified by Dowex 50 W×2 (elution with 1 N NH_4OH), and then HPLC (Sensyu Pak, PEGASIL-ODS φ 4.6×250 mm, elution with 4% MeOH/20 mM diethylamine/CO_2 buffer pH 7, 1 mL/min) to give kaitocephalin **1** (2.95 mg, 27% for two steps) as white foam. $[\alpha]_D^{25}$ −31.4 (*c* 0.11, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.80 (s, 2H), 4.58 (s, 1H), 4.51 (dd, *J*=6.4, 5.9 Hz, 1H), 4.33 (s, 1H), 3.89–3.85 (m, 1H), 2.62–2.57 (m, 1H), 2.48–2.44 (m, 1H), 2.30–2.25 (m, 1H), 2.23–2.16 (m, 2H), 1.82–1.76 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 177.6, 174.3, 170.8, 168.5, 162.1, 127.6, 124.1, 117.7, 76.3, 70.7, 59.2, 55.6, 53.5, 35.2, 32.1, 29.7; MS (ESI) *m*/*z* 494.1 $(M+H)^+$, 492.1 $(M-H)^-$.

Following the same procedure from **9a** to kaitocephalin, 9-epimer of kaitocephalin **10** was obtained from **9b** in 31% yield. Compound **10**: $[\alpha]_D^{23}$ −11.6 (*c* 0.09, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.81 (s, 2H), 4.58 (s, 1H), 4.50 (dd, *J*=3.7, 9.6 Hz, 1H), 4.33 (s, 1H), 3.82–3.77 (m, 1H), 2.50–2.44 (m, 2H), 2.40–2.32 (m, 2H), 2.20–2.16 (m, 1H), 1.81–1.75 (m, 1H); MS (ESI) *m*/*z* 494.1 $(M+H)^+$.

4.6. Aldol reaction of 3b with (*R*)-Garner aldehyde

To a solution of **3b** (2.16 g, 7.11 mmol) in 18 mL THF was added a solution of LiHMDS (1 M in THF, 8.5 mL, 1.2 equiv) at −78 °C. The resultant solution was stirred for 1 h at the same temperature and then warmed to −30 °C slowly. The solution was cooled to −78 °C again before a solution of (*S*)-Garner aldehyde (1.96 g, 8.55 mmol, 1.2 equiv) in 80 mL THF was added in a dropwise manner. After the addition the reaction mixture was stirred for 1 h at the same temperature. To this solution was added 7 mL saturated NH_4Cl at −78 °C to quench the reaction. The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration and flash chromatography (eluting with 1/11 to 1/9 EtOAc/hexanes) gave **11** (3.07 g, 81%) as colorless oil. $[\alpha]_D^{25}$ +23.6 (*c* 0.62, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 5.80–5.54 (m, 1H), 5.30–5.26 (m, 0.5H), 5.17 (s, 1H), 5.06–4.98 (m, 2H), 4.94–4.88 (m, 1H), 4.65–4.61 (m, 0.5H), 4.43–4.38 (m, 0.5H), 4.31–4.27 (m, 1H), 4.19–4.15 (m, 1H), 4.09–4.07 (m, 0.5H), 4.04–3.92 (m, 0.5H), 3.89–3.84 (m, 1H), 3.79–3.69 (m, 2H), 3.41 (s, 1.5H), 2.80–2.76 (m, 0.5H), 2.57–2.53 (m, 1H), 2.50–2.40 (m, 0.5H), 2.18–2.11 (m, 2H), 2.01–1.94 (m, 1H), 1.83–1.76 (m, 1H), 1.60 (s, 3H), 1.49 and 1.43 (due to rotamers, both s, 3H), 1.47 and 1.44 (due to rotamers, both s, 9H); MS (ESI) *m*/*z* 555.2 $(M+Na)^+$.

4.7. Synthesis of alcohol 12

To a solution of **11** (2.53 g, 4.75 mmol) in 50 mL methanol was added CSA (1.16 g, 5 mmol) at 0 °C. After stirring at 0 °C for 7 h, 8 mL saturated $NaHCO_3$ was added to quench the reaction. The solution was concentrated and the residue was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration followed by flash chromatography (eluting with 2/1 EtOAc/hexanes) gave a diol (1.94 g, 83%) as white foam.

To a solution of the above diol (1.44 g, 2.92 mmol) in 14 mL methylene chloride were added triethylamine (1.42 mL, 10.23 mmol) and DMAP (72 mg, 0.58 mmol). The resultant solution was cooled to −20 °C before a solution of TBSCl (529 g, 3.51 mmol) in 5 mL methylene chloride was added. The reaction mixture was warmed to 0 °C and then stirred for 5 h at this temperature. After the solution was washed with 1 N $KHSO_4$, saturated $NaHCO_3$ and brine, it was dried over Na_2SO_4. Concentration followed by flash chromatography (eluting with 1/2 to 1/1 EtOAc/hexanes) gave the corresponding alcohol (1.67 g, 94%) as white foam.

To a solution of oxalic chloride (1.8 mL, 19 mmol) in 25 mL methylene chloride was added dropwise a mixture of DMSO (2.4 mL, 32 mmol) and 3 mL methylene chloride at −78 °C for 15 min. After the resultant solution was stirred for 5 min, a solution of above alcohol (6.06 g, 10 mmol) in 25 mL methylene chloride was added dropwise. After the addition the solution was allowed to warm to −50 to 40 °C, and then the stirring was continued for 1 h. To this solution was added 5 mL triethylamine before it was warmed to 0 °C. After 20 mL saturated $NaHCO_3$ was added, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. Concentration and column flash chromatography (eluting with 1/5 to 1/4 EtOAc/hexanes) gave a ketone (5.75 g, 95%) as white foam.

A mixture of the above ketone (1.43 g, 2.36 mmol) in 50 mL dry ether was cooled to −50 °C before $NaBH_4$ (536 mg, 14.18 mmol) and 6 mL anhydrous methanol was added, respectively. The reaction mixture was allowed to warm to 10 °C and then the stirring was continued for 1 h. To this solution 50 mL saturated NH_4Cl was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. Concentration and column flash chromatography (eluting with 1/15 to 1/10 EtOAc/hexanes) gave **12** (1.22 g, 85%) and its 3*R*-isomer alcohol (143 mg, 10%) as white foam. Compound **12**: $[\alpha]_D^{25}$ −27.1

(*c* 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.31 (m, 5H), 6.55 (d, *J*=9.6 Hz, 1H), 5.65–5.59 (m, 1H), 5.28 (d, *J*=11.4 Hz, 1H), 5.18(d, *J*=12.6 Hz, 1H), 5.01–4.94 (m, 2H), 4.81 (d, *J*=10.5 Hz, 1H), 4.38 (d, *J*=9.9 Hz, 1H), 3.99–3.95 (m, 1H), 3.84–3.81 (m, 1H), 3.78 (s, 3H), 3.46–3.56 (m, 2H), 2.55–2.50 (m, 1H), 2.30–2.24 (m, 2H), 2.04–1.91 (m, 2H), 1.68–1.65 (m, 1H), 1.41 (s, 9H), 0.84 (s, 9H), 0.03 (s, 6H); MS (ESI) *m*/*z* 629.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{31}H_{50}N_2O_8SiNa$ $(M+Na)^+$ 629.3229, found 629.3234.

4.8. Conversion of 12 to triester 13

A solution of **12** (2.83 g, 4.67 mmol) in 10 mL THF was cooled to 0 °C before a solution of TBAF (1 M in THF, 9.3 mL) and acetic acid (504 mg, 8.40 mmol) were added. The reaction solution was stirred at room temperature for 1 h and then concentrated. The residue was allowed to pass a short column of silica gel to afford a diol. This diol was dissolved in 25 mL methylene chloride. To this solution were added triethylamine (4.6 mL, 32.7 mmol), DMAP (240 mg, 2 mmol), and acetic anhydride (2.2 mL, 20 mmol) at 0 °C. The resultant mixture was stirred at room temperature overnight. Concentration and column flash chromatography (eluting with 1/15 to 1/9 EtOAc/hexanes) gave the trimester **13** (2.50 g, 93%). $[\alpha]_D^{26}$ +44.61 (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.34 (m, 5H), 5.82–5.74 (m, 1H), 5.69 (s, 1H), 5.22–5.09 (m, 2H), 5.07–5.01 (m, 2H), 4.86–4.82 (m, 1H), 4.60–4.55 (m, 1H), 4.16–4.00 (m, 2H), 3.97–3.91 and 3.88–3.78 (m, 1H), 3.66 and 3.38 and 3.34 (due to rotamers, both s, 3H), 2.72–2.67 (m, 1H), 2.52–2.46 (m, 1H), 2.24–2.14(m, 2H), 2.11 and 2.08 (due to rotamers, both s, 3H), 2.01 and 1.99 (due to rotamers, both s, 3H), 1.79–1.73 (m, 1H), 1.70–1.58 (m, 1H), 1.45 (s, 9H); MS (ESI) *m*/*z* 599.2 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{29}H_{40}N_2O_{10}Na$ $(M+Na)^+$ 599.2575, found 599.2568.

4.9. Preparation of alcohols 14

A solution of AD-mix-β (2.06 g) in 7.4 mL *t*-BuOH and 7.4 mL water was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and the olefin **13** (850 mg, 1.47 mmol) was added. The mixture was stirred for 16 h at 0 °C, and 16 h at room temperature. After the solution was cooled to 0 °C, 1.91 g of Na_2SO_3 was added and the solution was stirred for 1 h at room temperature to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give the crude diol.

The above diol was dissolved in 15 mL methylene chloride and then triethylamine (1.0 mL, 7.35 mmol) and DMAP (36 mg, 0.29 mmol) were added. To this stirring solution was added dropwise a solution of TBDPSCl (485 mg, 1.76 mmol) in 3 mL methylene chloride at −78 °C. The reaction mixture was warmed to room temperature overnight before it was partitioned between ethyl acetate and saturated NH_4Cl. The organic layer was separated, washed with saturated $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4. Concentration and column flash chromatography (eluting with 1/4 to 1/2 EtOAc/hexanes) gave the silyl ether **14a** (766 mg, 61%) and **14b** (384 mg, 31%) as white foam. Compound **14a**: $[\alpha]_D^{27}$ +36.7 (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J*=6.9 Hz, 4H), 7.46–7.36 (m, 6H), 7.26–7.20 (m, 5H), 5.82 and 5.69 (due to rotamers, both s, 1H), 5.19–5.04 (m, 2H), 4.84 (d, *J*=9.9 Hz, 1H), 4.65–4.54 (m, 1H), 4.18–4.00 (m, 3H), 3.71–3.35 (m, 3H), 3.64 and 3.31 (due to rotamers, both s, 3H), 2.68–2.41 (m, 2H), 2.18–1.94 (m, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.77–1.65 (m, 2H), 1.46 (s, 9H), 1.06 (s, 9H); MS (ESI) *m*/*z* 871.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{45}H_{60}N_2O_{12}SiNa$ $(M+Na)^+$ 871.3808, found 871.3836. Compound **14b**: $[\alpha]_D^{27}$ +24.2 (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ7.65 (d, *J*=4.5 Hz, 4H), 7.46–7.36 (m, 6H), 7.26–7.205 (m, 5H), 5.80 and 5.67 (due to rotamers, both s, 1H), 5.21–5.96 (m, 2H), 4.83 (d, *J*=10.2 Hz, 1H), 4.64–4.54 (m, 1H), 4.16–4.06 (m, 3H), 3.81–3.67 (m, 1H), 3.60–3.42 (m, 3H), 3.29 (s, 3H), 2.64–2.54 (m, 1H), 2.26–2.17 (m, 2H), 2.05–1.98 (m, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.89–1.84 (m, 2H), 1.46 (s, 9H), 1.06 (s, 9H); MS (ESI) *m*/*z* 871.4 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{45}H_{60}N_2O_{12}SiNa$ $(M+Na)^+$ 871.3808, found 871.3826.

4.10. Synthesis of mesylate 15

To a mixture of **14a** (2.22 g, 2.61 mmol), triethylamine (3.3 mL, 23.6 mmol), DMAP (96 mg, 0.8 mmol), and 16 mL anhydrous methylene chloride were added MsCl (0.81 mL, 10.5 mmol) at −78 °C. The reaction mixture was warmed to 0 °C in 1 h. After it was stirred for 1 h at the same temperature, the solution was partitioned between ethyl acetate and water. The organic layer was washed with 1 N $KHSO_4$, saturated $NaHCO_3$, and brine. The solution was dried over anhydrous Na_2SO_4. Concentration and flash chromatography (eluting with 1/3 to 1/2 EtOAc/hexanes) gave the corresponding mesylate (2.40 g, 99% yield) as white foam. After this mesylate was dissolved in 68 mL THF, a solution of TBAF (1 M in THF, 6.8 mL) and acetic acid (315 mg, 5.2 mmol) were added. The resultant solution was stirred for 1 h at room temperature before it was concentrated. Column flash chromatography (eluting with 1/1 EtOAc/hexanes) gave the corresponding alcohol (1.66 g, 92% yield) as white foam.

To a solution of the above alcohol (1.6 g, 2.32 mmol) in 140 mL ethyl acetate, 160 mg PtO_2 was added. The resultant mixture was stirred under hydrogen atmosphere at ordinary pressure until the starting material disappeared monitored by TLC. The mixture was filtered and the filtrate was dissolved in 70 mL acetone. To this solution was added 7.7 mL freshly prepared Jones reagent at 0 °C. After the resultant solution was stirred for 40 min at room temperature, 3 mL *i*-PrOH was added to quench the reaction. After the stirring was continued for 20 min, the mixture was partitioned between brine and chloroform. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in 40 mL THF and treated with a solution of CH_2N_2 in ether until the reaction mixture turned yellow. The stirring was continued until the color disappeared. Concentration and flash chromatography (eluting with 1/2 to 2/3 EtOAc/hexanes) gave diester **15** (1.23 g, 83% yield) as white foam. Compound **15**: $[\alpha]_D^{23}$ +56.6 (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 and 5.71 (due to rotamers, both s, 1H), 5.11 and 5.04 (due to rotamers, both dd, *J*=3.0, 10.2 Hz, 1H), 4.85 and 4.84 (due to rotamers, both d, *J*=10.2 Hz, 1H), 4.57–4.53 (m, 1H), 4.16–4.00 (m, 3H), 3.82 (s, 3H), 3.79 and 3.75 (due to rotamers, both s, 3H), 3.68 and 3.62 (due to rotamers, both s, 3H), 3.21 (s, 3H), 2.63–2.33 (m, 2H), 2.24–2.18 (m, 2H), 2.11–2.02 (m, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.90–1.84 (m, 1H), 1.46 (s, 9H); MS (ESI) *m*/*z* 663.1 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{25}H_{40}N_2O_{15}SNa$ $(M+Na)^+$ 663.2042, found 663.2039.

4.11. Conversion of the mesylate 15 to 16

To a solution of **15** (480 mg, 0.75 mmol) in 15 mL methanol was added Mg (54 mg, 2.25 mmol, 3 equiv). The resultant mixture was heated at 35–40 °C for 2 h and then to it was added 1 N HCl to adjust pH=6–7. The solution was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed eluting with 50/50/1 petroleum ether/ethyl acetate/methanol to afford **16** (314 mg, 80%) as a mixture of 9*R* and 9*S* isomer (about 1/1 ratio). Pure **16b** could be obtained by HPLC purification (Grace Vydac cat: 238DE1022, C18 Monomeric, 120A. elution with $MeCN/H_2O$=30/70, 2 mL/min, 0–5 min **16b**, 5–40 min **16a** and **16b**). Compound **16b**:

$[\alpha]_D^{26}$ −28.4 (*c* 0.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (dd, *J*=1.8, 10.8 Hz, 1H), 4.98 (d, *J*=9.9 Hz, 1H), 4.91 (d, *J*=2.4 Hz, 1H), 4.13–4.07 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.71–3.66 (m, 2H), 3.25 (s, 3H), 2.34–2.20 (m, 4H), 2.03 (ddd, *J*=3.9, 10.8, 14.7 Hz, 1H), 1.77–1.67 (m, 2H), 1.44 (s, 9H); MS (ESI) *m*/*z* 547.2 $(M+Na)^+$. Data for mixture of **16a** and **16b**: $[\alpha]_D^{22}$ −12.5 (*c* 0.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 and 5.16 (both dd, *J*=1.5, 10.5 , 6.0, 7.2 Hz, 1H), 4.97–4.94 (m, 1H), 4.91 and 4.87 (both d, *J*=2.7 , 1.8 Hz, 1H), 4.16–4.02 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.72–3.64 (m, 2H), 3.26 and 3.19 (both s, 3H) 2.43–2.20 (m, 4H), 2.08–1.99 (m, 1H), 1.77–1.67 (m, 2H), 1.44 (s, 9H); MS (ESI) *m*/*z* 547.2 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{20}H_{32}N_2O_{12}SNa$ $(M+Na)^+$ 547.1568, found 547.1572.

4.12. Preparation of the acids 17

A mixture of **16a** and **16b** (157 mg, 0.3 mmol), sodium azide (65 mg, 1.0 mmol), and 4 mL DMF was stirred at room temperature for 7 h. The solvent was removed in vacuo and the residue was chromatographed to give the azides (116 mg, 82%) as white foam.

To a solution of the above azides (116 mg, 0.25 mmol) in 5 mL methanol was added 12 mg of 10% Pd/C. The resultant mixture was stirred under hydrogen atmosphere at ordinary pressure until the starting material disappeared monitored by TLC. After catalyst was filtered off, the filtrate was concentrated and the residue was dissolved in 2.5 mL CH_2Cl_2. To this solution were added HATU (145 mg, 0.38 mmol), 4-(benzyloxy)-3,5-dichlorobenzoic acid (82 mg, 0.28 mmol), and DIEA (0.09 mL, 0.50 mmol) at 0 °C. The mixture was stirred at room temperature overnight before it was concentrated. Flash chromatography of the residue (eluting with 1/6 to 1/2 EtOAc/hexanes) afforded amide (136 mg, 75%) as white foam.

The above amide (136 mg, 0.19 mmol) was dissolved in 2 mL acetone. To this solution was added 0.2 mL freshly prepared Jones reagent at 0 °C. After the resultant solution was stirred for 40 min at room temperature, 0.5 mL *i*-PrOH was added to quench the reaction. After the stirring was continued for 20 min, the mixture was partitioned between brine and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was chromatographed eluting with 50/5/1 ethyl acetate/methanol/HOAc to afford a mixture of acids **17a** and **17b** (115 mg, 85%) as white foam. ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.94 and 7.86 (s, 2H), 7.58–7.48 (m, 2H), 7.42–7.34 (m, 3H), 5.80 (br s, 1H), 5.28 (s, 1H), 5.06 (s, 2H), 4.99–4.86 (m, 1H), 4.46–4.18 (m, 1H), 4.15–3.92 (m, 1H), 3.81 and 3.78 (s, 3H), 3.72 and 3.69 (s, 3H), 2.26–2.05 (m, 5H), 1.81–1.54 (m, 1H), 1.38 (s, 9H); MS (ESI) *m*/*z* 738.2 $(M+H)^+$, 760.1 $(M+Na)^+$.

Following the same procedure, pure **17b** could be obtained from **16b**. Compound **17b**: $[\alpha]_D^{23}$ −35.7 (*c* 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.98 (br s, 1H), 8.21 (br s, 1H), 7.94 (s, 2H), 7.54 (d, *J*=6.6 Hz, 2H), 7.40–7.38 (m, 3H), 5.95 (br s, 1H), 5.24 (s, 1H), 5.06 (s, 2H), 4.98–4.96 (m, 1H), 4.41–4.27 (m, 1H), 4.03 (t, *J*=6.6 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.30–2.17 (m, 5H), 1.83–1.67 (m, 1H), 1.38 (s, 9H); MS (ESI) *m*/*z* 738.2 $(M+H)^+$, 736.3 $(M-H)^-$; HRMS *m*/*z* calcd for $C_{33}H_{37}N_3O_{12}Cl_2Na$ $(M+Na)^+$ 760.1646, found 760.1660.

4.13. 2-*epi*-Aitocephalin 2 and 2-*epi*-9-*epi*-kaitocephalin 18

A mixture of **17a** and **17b** (17 mg, 0.023 mmol), 2 mg of 10% Pd/C, and 1.2 mL anhydrous methanol was stirred under hydrogen atmosphere (1 atm) for 15 min. After Pd/C was filtered off, the filtrate was concentrated. The residue was dissolved in 1.2 mL 2 N HCl. The resultant solution was stirred at room temperature for 3 h and then at 50 °C for 1 h. To the cooled solution were added 1.1 mL MeOH, 1.1 mL THF, and 144 mg NaOH. The resultant mixture was stirred at 50 °C for 18 h. The cooled solution was neutralized to pH=7.0 and then concentrated. The residue was purified by Dowex 50 W×2 (elution with 1 N NH_4OH) and then HPLC (Agilent, ZORBAX SB-C18 φ 9.4×250 mm, elution with 5% MeOH/20 mM diethylamine/CO_2 pH=7 buffer, 2 mL/min) to give **18** (3.2 mg) and **2** (3.1 mg) as white foam. Compound **2**: $[\alpha]_D^{24}$ −23.0 (*c* 0.05, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.62 (s, 2H), 4.36 (dd, *J*=5.0, 8.5 Hz, 1H), 4.30 (d, *J*=2.5 Hz, 1H), 3.79 (d, *J*=2.5 Hz, 1H), 3.61–3.53 (m, 1H), 2.34–2.27 (m, 2H), 2.13–2.08 (m, 2H), 2.05–2.02 (m, 1H), 1.58–1.52 (m, 1H); MS (ESI) *m*/*z* 494.2 $(M+H)^+$, 516.1 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{18}H_{20}Cl_2N_3O_9$ $(M-H)^-$ 492.0582, found 492.0577. Compound **18**: $[\alpha]_D^{24}$ −12.6 (*c* 0.09, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.71 (s, 2H), 4.40 (dd, *J*=5.0, 8.0 Hz, 1H), 4.34 (d, *J*=4.5 Hz, 1H), 3.87 (d, *J*=4.5 Hz, 1H), 3.68–3.60 (m, 1H), 2.40 (dd, *J*=6.5, 12.0 Hz, 1H), 2.30–2.18 (m, 4H), 1.69–1.65 (m, 1H); MS (ESI) *m*/*z* 494.2 $(M+H)^+$, 516.3 $(M+Na)^+$; HRMS *m*/*z* calcd for $C_{18}H_{20}Cl_2N_3O_9$ $(M-H)^-$ 492.0582, found 492.0574 $(M-H)^-$.

4.14. Synthesis of 19

A mixture of **17** (15 mg, 0.02 mmol), 2 mg of 10% Pd/C, and 1.0 mL anhydrous methanol was stirred under hydrogen atmosphere (1 atm) for 15 min. After Pd/C was filtered off, the filtrate was concentrated. The residue was dissolved in 0.64 mL THF and 0.64 mL 1% KOH. The resultant solution was stirred at room temperature for 1.5 h and then concentrated to remove solvents. The residue was dissolved in 2 mL 2 N HCl, and stirred at room temperature for 3 h and then at 50 °C for 1 h. The solution was cooled to room temperature and concentrated to 1 mL. The residue was purified by Dowex 50 W×2 (elution with 1 N NH_4OH) to afford an acid as light yellow foam.

After 0.5 mL 1 N KOH in MeOH solution was added to the above product, the resultant mixture was stirred at 65 °C for 10 h. The cooled solution was neutralized to pH=7.0 and then concentrated. The residue was purified by Dowex 50 W×2 (elution with 1 N NH_4OH) and HPLC (Sensyu Pak, PEGASIL-ODS φ 4.6×250 mm, elution with 2% MeOH/20 mM diethylamine/CO_2 buffer pH 7, 1 mL/min) to give **19a** (7.2 mg, 42% for four steps) and **19b** (7.5 mg, 44% for four steps) as white foam. Compound **19a**: $[\alpha]_D^{29}$ +12.4 (*c* 0.72, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.85 (s, 2H), 4.44 (s, 1H), 4.32 (s, 1H), 4.03 (d, *J*=7.4 Hz, 1H), 4.01 (s, 1H), 2.73 (d, *J*=12.0 Hz, 1H), 2.52–2.50 (m, 1H), 2.26–2.22 (m, 1H), 2.11–2.05 (m, 1H), 1.80 (dd, 1H, *J*=11.7, 20.2 Hz), 1.65–1.55 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 181.2, 180.1, 178.1, 170.2, 161.0, 158.6, 130.3, 125.6, 125.5, 75.2, 73.3, 60.9, 58.3, 57.1, 41.6, 39.1, 31.9; MS (ESI) *m*/*z* 517.8 $(M-H)^-$; HRMS *m*/*z* calcd for $C_{19}H_{18}Cl_2N_3O_{10}$ $(M-H)^-$ 518.0375, found 518.0380. Compound **19b**: $[\alpha]_D^{29}$ +3.67 (*c* 0.52, H_2O); ^1H NMR (500 MHz, D_2O) δ 7.89 (s, 2H), 4.38 (d, *J*=12.2 Hz, 1H), 4.35 (d, *J*=3.3 Hz, 1H), 4.08–4.03 (m, 1H), 3.99 (d, *J*=3.4 Hz, 1H), 2.54 (dd, *J*=6.7, 11.0 Hz, 1H), 2.44 (dt, *J*=5.3, 14.6 Hz, 1H), 2.28–2.22 (m, 1H), 1.80 (dd, *J*=1.5, 20.1 Hz, 1H), 1.62–1.59 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 182.0, 180.2, 177.8, 170.4, 161.1, 158.2, 130.4, 125.6, 125.5, 76.0, 73.1, 60.6, 58.3, 57.4, 40.4, 38.4, 30.7; MS (ESI) *m*/*z* 517.8 $(M-H)^-$; HRMS *m*/*z* calcd for $C_{19}H_{18}Cl_2N_3O_{10}$ $(M-H)^-$ 518.0375, found 518.0381.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.068.

References and notes

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