# Total Synthesis of Emericellamide A: A Secondary Metabolite of Marine Cyclic Depsipeptide with Antimicrobial Properties

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**Abstract:** Emericellamide A is a secondary metabolite of marine cyclic depsipeptide from the co-culture of the marine-derived fungus *Emericella* sp. and actinomycete *Salinispora arenicola*. A general method for the total synthesis of emericellamide A is depicted in this report.

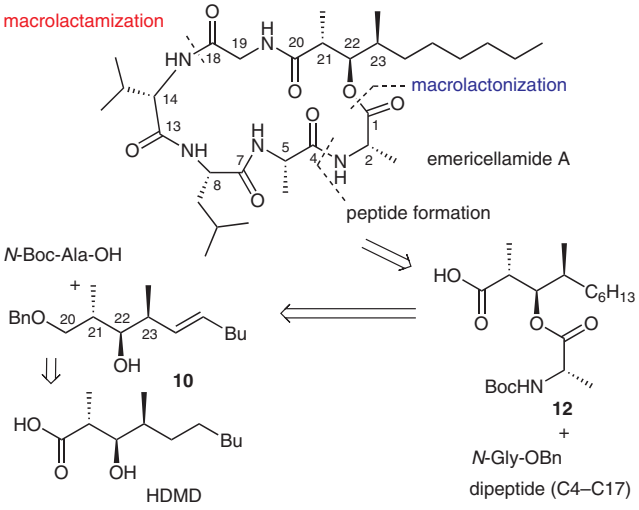
**Key words:** cyclic depsipeptide, macrolactamization, antifungal agents, emericellamide, total synthesis

Emericellamides A and B are secondary metabolites of marine cyclic depsipeptide with interesting bioactivity. They were isolated by Fenical and co-workers[1] from the co-culture of the marine-derived fungus *Emericella* sp. and actinomycete *Salinispora arenicola.* Emericellamide A display an antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MIC 3.8 μM), as well as cytotoxicity against the HCT-116 human colon carcinoma cell line ($IC_{50}$ 23 μM). With the help of chemical and spectroscopic methods, the planar structures of these compounds were established, and the absolute configurations of emericellamides A and B were determined afterwards based on Marfey's method[2] and the modified Mosher method.[3] The first total synthesis of emericellamide A was published by Ghosh and co-workers this year.[4] We report herein the total synthesis of emericellamide A using a novel method.

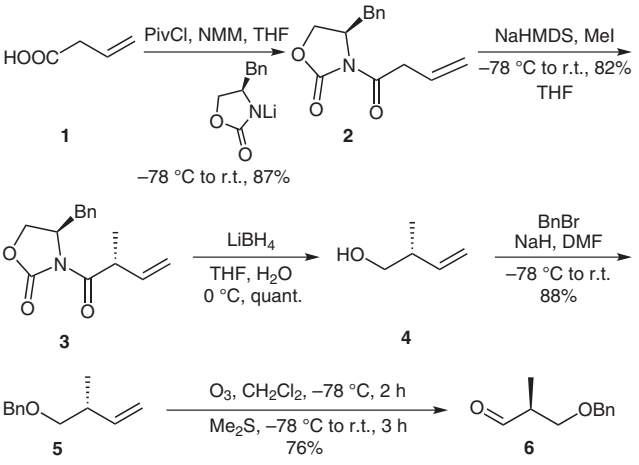
Retrosynthetically, the strategic bond disconnections of the emericellamides are outlined in Scheme 1. For emericellamide A, which contains a highly methylated (2*R*,3*R*,4*S*)-3-hydroxy-2,4-dimethylheptanoic acid (HDMD) unit, the most critical steps in its assembly is the connection of the sterically hindered unit (HDMD) with the other peptide or amino acid moiety. The Yamaguchi protocol was found to be an inefficient for such connection.[4] For this reason, direct esterification with small Ala-OH was our first choice. On the other hand, achieving a general method for preparation of HDMD and convenient removal of the protecting groups for all these units are required.

In order to find a general method to prepare HDMD moiety, we selected vinylacetic acid **1** as a starting material. Thus, vinylacetic acid **1** was activated with pivaloyl chloride and added to the lithium salt of oxazolidinone to give amide **2** (yield 87%), which was methylated with MeI at –78 °C to afford product **3** with high diastereoselectivity (96:4) in 82% yield. Removal of the auxiliary[5] ($LiBH_4$, $H_2O$) and protection (NaH, BnBr) of primary alcohol **4** gave benzyl ether **5** in 88% overall yield. Oxidation[6] of the double bond ($O_3$, –78 °C) afforded aldehyde **6** in 76% yield (Scheme 2).

The aldehyde **6** prepared above, was converted to aldehyde **7** according to a known procedure[7] using the well-




**Scheme 1** Strategic bond disconnections of emericellamide A




**Scheme 2**

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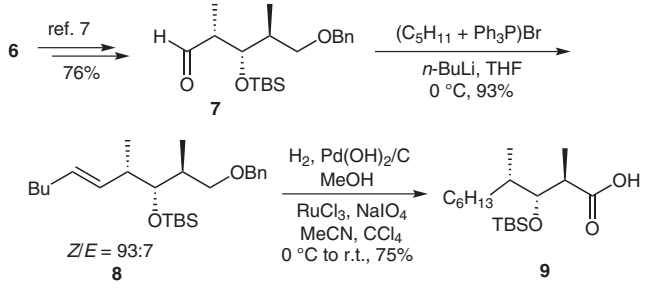
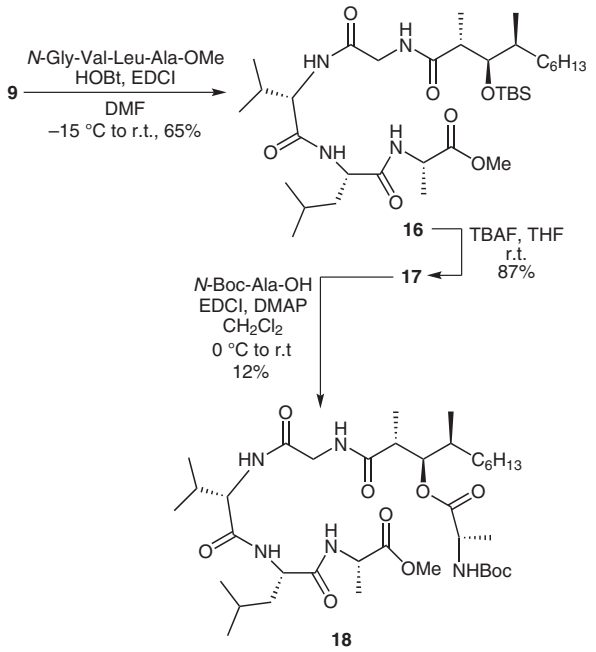
established Evans' asymmetric aldol methodology[8] to built the three contiguous stereogenic centers. The aldehyde **7** was directly subjected to Wittig reaction with pentyltriphenylphosphonium bromide to generate the mixture of olefin **8** (ratio of *Z*/*E* = 93:7), which was easily separated by chromatography on silica gel.[9] Hydrogenation [$Pd(OH)_2$/C, MeOH] and oxidation with $RuCl_3$–$NaIO_4$[10] gave protected acid **9** in 75% overall yield (Scheme 3).

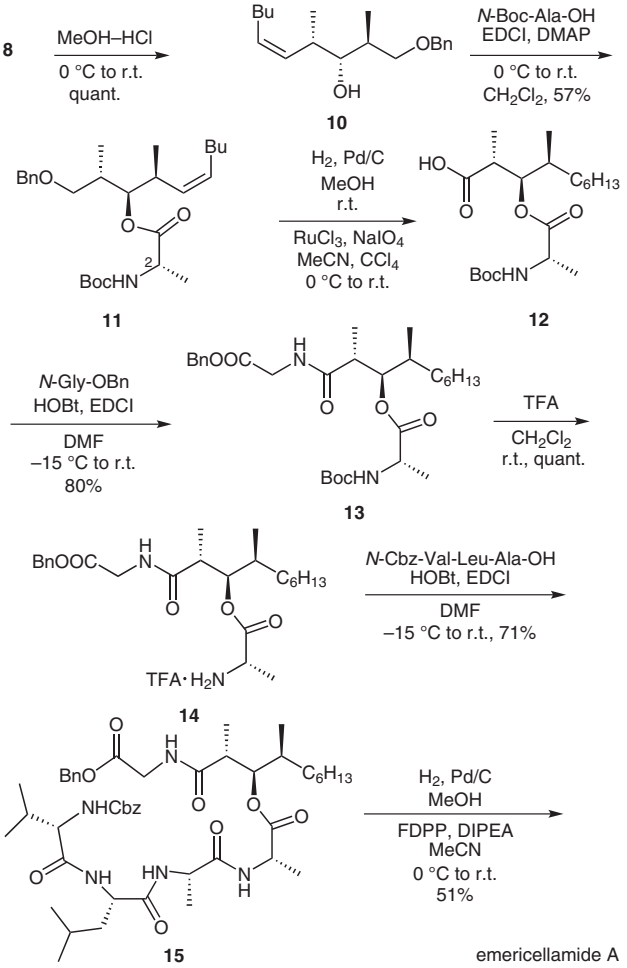



**Scheme 3**

The next step was the macrocyclization reaction. Due to the steric hindrance in emericellamide A, several methods such as the Yamaguchi protocol[11] did not work efficiently for this macrocylization.[4,11] Therefore, we turned to inner condensation reaction between Gly-Val-Leu-Ala-OH and *N*-Ala (Scheme 4). Condensation of acid **9** with *N*-Gly-Val-Leu-Ala-OMe gave tripeptide **16** (EDC, HOBt) in 65% yield. Removal of silyl protecting group with TBAF produced secondary alcohol **17**, which was esterified with *N*-Boc-Ala-OH. Unfortunately, the yield of esterification (DCC or EDC) was very low (12%) and product **18** was epimerized in a 1:1 ratio at C-2, possibly because of the steric hindrance of the secondary alcohol caused by the presence of vicinal methyl groups.[12]




**Scheme 4**




**Scheme 5**

Facing the fact that the esterification of deprotected **17** with Boc-Ala-OH did not work well, we use less hindrance secondary alcohol in **10** instead to complete the crucial esterification step (Scheme 5). Gratefully, connection of **10** with *N*-Boc-Ala-OH in the presence of EDC and DMAP in $CH_2Cl_2$ at 0 °C gave ester **11** in 57% yield and product **11** was epimerized in 12:1 ratio at C-2,[12] while the starting material could be recovered. The minor epimer of **11** was easily separated by chromatography on silica gel.[13] Hydrogenation (Pd/C, quant.) of the ester **11** was followed by oxidation ($RuCl_3$–$NaIO_4$)[10] to afford the crude acid **12**. Without further purification, acid **12** was condensated with *N*-Gly-OBn in the presence of EDC/HOBt to produce **13** in 80% yield (three steps).[14] Deprotection of the Boc group (TFA, $CH_2Cl_2$) of **13** gave salt **14**, which was coupled with Cbz-Val-Leu-Ala-OH under the same conditions as mentioned above to give peptide **15** in 71% yield (two steps).[15] Removal of the Bn and Cbz protecting group (Pd/C, MeOH) gave free acid and amine in one pot, which was subjected to macrolactamization by treatment with pentafluorophenyl diphenylphosphinate (FDPP)[16] and DIPEA under highly diluted solution ($10^{-3}$M) of the substrate in MeCN at room temperature to give emericellamide A in 51% yield (two steps);[4,17] $[\alpha]_D^{25}$ –42.89 (*c* 0.26, MeOH) {lit.[1] $[\alpha]_D^{25}$ –43 (*c* 0.23, MeOH);

lit.[4] $[\alpha]_D^{25}$ –42.99 (*c* 0.2, MeOH)}. The spectroscopic and physical data of the synthetic emericellamide A were identical with those described in the literature.[1,4]

In conclusion, we have achieved a general and convenient route for total synthesis of emericellamide A with 5.6% overall yield. Especially, the present method for preparation of aldehyde **7** from vinylacetic acid **1** is rather efficient, this would assist assembling emericellamides A, B, and their analogues in a diversified way that thereby could be beneficial for their structure–activity relationship studies, as well as exploring their possible antimicrobial mechanism.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Preparation of Compound 8**
To a suspension of pentyltriphenylphosphonium bromide (11.2 g, 27.18 mmol) in dry THF (70 mL) was dropped *n*-BuLi (15.9 mL, 1.6 M in hexane, 25.5 mmol) at r.t. under argon atmosphere. After the red mixture was stirred for 30 min, a solution of aldehyde **7** (1.80 g, 5.14 mmol) in dry THF (10 mL) was dropped and stirred for 2 h. The mixture was diluted with EtOAc and washed with sat. aq $NaHCO_3$ and brine. Dried, filtered, and concentrated, the residue was purified by chromatography on $SiO_2$ (EtOAc–PE = 1:150) to give major-**8** (1.79 g, 86.5%) and minor-**8** (135 mg, 6.5%) both as a colorless oil.
**Analytical and Spectral Data of Polypeptide major-8**
$[\alpha]_D^{25}$ +9.5 (*c* 1.2, $CHCl_3$). IR (film): $\nu_{max}$ = 3000, 2928, 2856, 1464, 1406, 1252, 1097 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 5.29–5.17 (m, 2 H), 4.47 (s, 2 H), 3.57 (dd, *J* = 5.09, 9.39 Hz, 1 H), 3.43 (dd, *J* = 3.88, 6.26 Hz, 1 H), 3.27 (dd, *J* = 7.82, 9.40 Hz, 1 H), 2.70–2.59 (m, 1 H), 2.08–1.92 (m, 3 H), 1.35–1.25 (m, 4 H), 0.99 (d, *J* = 7.04 Hz, 3 H), 0.92 (d, *J* = 7.05 Hz, 3 H), 0.90–0.87 (m, 12 H), 0.04 (s, 3 H), 0.03 (s, 3 H) pp.; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 138.8, 133.8, 128.8, 128.2 (2 C), 127.5 (2 C), 127.3, 78.5, 72.9, 72.7, 38.4, 35.3, 31.9, 27.2, 26.2 (3 C), 22.5, 18.4, 17.4, 14.9, 14.0, –3.7, –3.9 ppm. ESI-MS: 427.3 [M + $Na^+$]. HRMS (ESI): *m/z* calcd for [$C_{25}H_{44}O_2Si$ + $Na^+$]: 427.3010; found: 427.3020.
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(13) **Preparation of Ester 11**
To a solution of alcohol **10** (1.50 g, 5.17 mmol), EDCI (4.93 g, 25.83 mmol) in dry $CH_2Cl_2$ (20 mL) was added *N*-Boc-Ala-OH (2.93 g, 15.50 mmol) at 0 °C under argon atmosphere and stirred for 0.5 h, then DMAP (315 mg, 2.58 mmol) was added in one portion. After being stirred for 3 h, the mixture was warmed to r.t. and stirred for 6 h at this temperature. The resulting mixture was diluted with $CH_2Cl_2$ (30 mL), the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic layers were washed with HCl (5%), sat. aq $NaHCO_3$ and brine, then dried and concentrated. The residue was purified by chromatography on $SiO_2$ ($Et_2O$–PE = 1:50 to 1:30) to give ester **11** (1.35 g, yield 57%; 87% based on the recovered starting material) as a light yellow oil.
**Analytical and Spectral Data of Ester 11**
$[\alpha]_D^{25}$ +8.25 (*c* 3.50, $CHCl_3$). IR (film): $\nu_{max}$ = 3373, 2966, 2930, 1716, 1497, 1454, 1366, 1167 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 5.37–5.31 (m, 1 H), 5.14–5.08 (m, 2 H), 4.90–4.84 (m, 1 H), 4.46 (s, 2 H), 4.29 (dd, *J* = 6.74, 7.54 Hz, 1 H), 3.51 (dd, *J* = 4.56, 9.26 Hz, 1 H), 3.24 (dd, *J* = 7.28, 9.26 Hz, 1 H), 2.85–2.81 (m, 1 H), 2.24–2.08 (m, 1 H), 2.04–1.87 (m, 2 H), 1.44 (s, 9 H), 1.39 (d, *J* = 6.90 Hz, 3 H), 1.36–1.25 (m, 4 H), 0.99 (d, *J* = 6.72 Hz, 3 H), 0.91–0.85 (m, 6 H) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 171.6, 155.1, 138.6, 131.0, 130.6, 128.3 (2 C), 127.6 (2 C), 127.5, 80.4, 79.7, 73.1, 71.5, 49.5, 35.5, 35.7, 33.3, 31.7, 28.3 (3 C), 27.3, 22.4, 16.3, 15.0, 14.0 ppm. ESI-MS: 484.3 [M + $Na^+$]. HRMS (MALDI): *m/z* calcd for [$C_{27}H_{43}NO_5$ + $Na^+$]: 484.3039; found: 484.3035.
(14) **Preparation of Peptide 13**
To a suspension of Pd/C (10%, 50 mg) in MeOH (10 mL) was added a solution of **11** (495 mg, 1.074 mmol) in MeOH (2 mL) at r.t. under $H_2$ atmosphere (1.013 bar). After being stirred for 4 h at the same conditions, the catalyst was filtered carefully, and the filtrate was concentrated in vacuo to give the crude alcohol (400 mg, quant.) as a colorless oil.
$[\alpha]_D^{25}$ –27.0 (*c* 1.31, $CHCl_3$). IR (film): $\nu_{max}$ = 3460, 3368, 2965, 2929, 1715, 1518, 1456, 1169 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 6.9 Hz, 1 H), 4.90 (d, *J* = 10.02 Hz, 1 H), 4.32–4.46 (m, 1 H), 3.60–3.56 (m, 1 H), 3.48–3.44 (m, 1 H), 2.47 (br s, 1 H), 1.88–1.83 (m, 1 H), 1.78–1.73 (m, 1 H), 1.45 (s, 9 H), 1.41 (d, *J* = 5.10 Hz, 3 H), 1.32–1.21 (m, 9 H), 1.01 (d, *J* = 6.96 Hz, 3 H), 0.92 (d, *J* = 6.84 Hz, 3 H), 0.88 (t, *J* = 7.00 Hz, 3 H) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 174.8, 155.4, 80.1, 78.4, 64.1, 49.7, 36.9, 34.2, 33.7, 31.8, 29.4, 28.3 (3 C), 27.1, 22.6, 14.0 (2 C), 13.0 (2 C) ppm. ESI-MS: 396.3 [M + $Na^+$]. HRMS (MALDI): *m/z* calcd for [$C_{20}H_{39}NO_5$ + $Na^+$]: 396.2726; found: 396.2730.
To a stirred solution of the above alcohol (400 mg, 1.07 mmol) in $CCl_4$ (5 mL) were added MeCN (5 mL) and $H_2O$ (7.5 mL), then $NaIO_4$ (916 mg, 4.28 mmol) and $RuCl_3$ (10.8 mg, 0.04 mmol) were added sequentially at r.t. After being stirred for 4 h, the reaction was diluted with $Et_2O$ (20 mL) and stirred for 20 min to precipitate black $RuO_2$. Then the mixture was dried and filtered through Celite, the solid residue was washed with $Et_2O$, and the combined organic phases were concentrated in vacuo to give the carboxylic

acid **12** without further purification. The crude acid **12** (415 mg, 1.07 mmol) and HOBt (159 mg, 1.18 mmol) were added in dry DMF (8 mL) and stirred for 15 min at r.t., then the reaction mixture was cooled to –15 °C, and EDCI (225 mg, 1.18 mmol) was added in one portion. After being stirred for 1.5 h at –15 °C, *N*-Gly-OBn (194 mg, 1.18 mmol) was added and stirred overnight at r.t. The mixture was quenched with $H_2O$ (20 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with $H_2O$, sat. aq $NaHCO_3$ and brine. Dried and concentrated, the residue was purified by chromatography on $SiO_2$ (EtOAc–PE = 1:5) to give **13** (458 mg, 80%) as a colorless oil.

**Analytical and Spectral Data of Peptide 13**

$[\alpha]_D^{25}$ –9.56 (*c* 0.68, $CHCl_3$). IR (film): $\nu_{max}$ = 3323, 2929, 2929, 1744, 1716, 1525, 1456, 1174 $cm^{-1}$. $^1H$ NMR (600 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 5 H), 6.40 (m, 1 H), 5.21 (d, *J* = 12.24 Hz, 1 H), 5.17 (d, *J* = 12.24 Hz, 1 H), 5.09–5.06 (m, 1 H), 4.34–4.27 (m, 1 H), 4.09 (dd, *J* = 2.40, 4.74 Hz, 2 H), 2.71–2.67 (m, 1 H), 1.81–1.77 (m, 1 H), 1.42 (s, 9 H), 1.39 (d, *J* = 7.20 Hz, 3 H), 1.36–1.21 (m, 9 H), 1.16 (d, *J* = 7.08 Hz, 3 H), 1.15–1.10 (m, 1 H), 0.90–0.86 (m, 6 H) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 173.7, 172.7, 170.1, 155.3, 135.2, 128.6 (2 C), 128.5 (2 C), 128.3, 79.8, 78.6, 67.2, 49.4, 43.6, 41.4, 34.3, 33.5, 31.8, 29.4, 28.3 (3 C), 26.8, 22.6, 14.7, 14.1 (2 C), 13.6 (2 C) ppm. ESI-MS: 557.3 [M + $Na^+$]. HRMS (MALDI): *m/z* calcd for [$C_{29}H_{46}N_2O_7$ + $Na^+$]: 557.3203; found: 557.3193.

(15) **Preparation of Peptide 15**

To a solution of **13** (200 mg, 0.374 mmol) in $CH_2Cl_2$ (3 mL) was added TFA (3 mL) and stirred for 2 h at r.t. The solvent was removed in vacuo, and the residue was dissolved in DCE (3 mL) and removed. This process repeated for three times to give crude amide **14**. HOBt (50.5 mg, 0.374 mmol) was added to a solution of *N*-Cbz-Val-Leu-Ala-OH (148 mg, 0.339 mmol) in dry DMF (5 mL) at –15 °C. After 30 min of stirring, EDCI (71.2 mg, 0.374 mmol) was added and stirred at –15 °C for 1.5 h, then NMM (82 μL, 0.745 mmol) and a solution of salt **14** in DMF was added. After being stirred for overnight at r.t., the reaction was quenched with $H_2O$ (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with $H_2O$, sat. aq $NaHCO_3$ and brine. Dried and concentrated, the residue was purified by chromatography on $SiO_2$ (MeOH–$CH_2Cl_2$ = 1:60) to give **15** (225 mg, 71%) as a white solid.

**Analytical and Spectral Data of Polypeptide 15**

$[\alpha]_D^{25}$ –34.2 (*c* 0.32, $CHCl_3$). IR (film): $\nu_{max}$ = 3279, 2959, 2928, 1741, 1699, 1634, 1538, 1210 $cm^{-1}$. $^1H$ NMR (600 MHz, DMSO-$d_6$): δ = 8.24 (m, 1 H), 8.03 (m, 1 H), 7.92–7.87 (m, 2 H), 7.38–7.28 (m, 11 H), 5.11 (d, *J* = 12.72 Hz, 1 H), 5.09 (d, *J* = 12.72 Hz, 1 H), 5.03 (d, *J* = 14.49 Hz, 1 H), 5.01 (d, *J* = 14.49 Hz, 1 H), 4.94 (dd, *J* = 2.28, 9.48 Hz, 1 H), 4.33–4.23 (m, 3 H), 3.89–3.82 (m, 2 H), 3.77 (m, 1 H), 2.66 (ddd, *J* = 6.84, 13.58, 16.60 Hz, 1 H), 1.96–1.91 (m, 1 H), 1.71–1.65 (m, 1 H), 1.62–1.56 (m, 1 H), 1.43–1.38 (m, 2 H), 1.27–1.14 (m, 15 H), 1.04–0.99 (m, 1 H), 0.95 (d, *J* = 6.96 Hz, 3 H), 0.86–0.77 (m, 18 H) ppm. $^{13}C$ NMR (150 MHz, DMSO-$d_6$): δ = 174.0, 172.0, 171.9, 171.6, 171.5, 170.3, 156.6, 137.6, 136.4, 128.9 (2 C), 128.8 (2 C), 128.5 (2 C), 128.4 (2 C), 128.2, 128.1, 79.6, 77.5, 66.3, 65.8, 60.7, 51.2, 48.2, 48.0, 42.1, 41.1, 33.8, 33.6, 31.7, 30.7, 29.3, 27.0, 24.5, 23.5, 22.5, 21.9, 19.7, 18.7, 18.6, 17.8, 14.6, 14.4, 13.6 ppm. ESI-MS: 874.5 [M + $Na^+$]. HRMS (MALDI): *m/z* calcd for [$C_{46}H_{69}N_5O_{10}$ + $Na^+$]: 874.4942; found: 874.4931.

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(17) To a suspension of Pd/C (10%, 15 mg) in MeOH was added a solution of **15** (105 mg, 0.123 mmol) in MeOH (3 mL) at r.t. under $H_2$ atmosphere (1.013 bar). After being stirred for 3 h at the same conditions, the catalyst was filtered carefully, and the filtrate was concentrated in vacuo to give the crude product (73 mg, 95%) without further purification. The crude product was suspended in anhyd MeCN (120 mL, $1.0 \cdot 10^{-3}$ M) and cooled to 0 °C, pentafluorophenyldiphenylphosphinate (FDPP) reagent (90 mg, 0.234 mmol) was added in one portion and stirred for 20 min at the same temperature. Then DIPEA (82 μL, 0.468 mmol) was slowly dropped over a period of 30 min. After beeing stirred for 26 h at r.t., the mixture was concentrated in vacuo. The residue was purified by RP C18 HPLC with 70% aq MeCN (Sepaxtech Amethyst C18 semipreparative column, 10 mm × 150 mm, 2 mL/min, refractive index detection) to give emericellamide A (37 mg, 51%).

**Analytical and Spectral Data of Emericellamide A**

$[\alpha]_D^{25}$ –42.89 (*c* 0.26, MeOH) {lit.[1] $[\alpha]_D^{25}$ –43 (*c* 0.23, MeOH); lit.[4] $[\alpha]_D^{25}$ –42.99 (*c* 0.2, MeOH)}. IR (KBr): $\nu_{max}$ = 3323, 2931, 1755, 1668, 1650, 1538 $cm^{-1}$. $^1H$ NMR (600 MHz, DMSO-$d_6$): δ = 8.07 (d, *J* = 6.24 Hz, 1 H), 8.01 (br s, 1 H), 7.94 (d, *J* = 7.74 Hz, 1 H), 7.51 (br s, 1 H), 7.39 (d, *J* = 6.18 Hz, 1 H), 4.92 (dd, *J* = 2.40, 10.02 Hz, 1 H), 4.31 (dd, *J* = 5.73, 17.52 Hz, 1 H), 4.09–4.00 (m, 3 H), 3.97 (dd, *J* = 8.22, 8.28 Hz, 1 H), 3.61 (dd, *J* = 2.40, 17.52 Hz, 1 H), 2.85 (dq, *J* = 6.96, 9.81 Hz, 1 H), 1.91–1.84 (m, 1 H), 1.69–1.63 (m, 1 H), 1.59–1.52 (m, 2 H), 1.31–1.16 (m, 8 H), 1.23 (d, *J* = 7.38 Hz, 3 H), 1.21 (d, *J* = 6.96 Hz, 3 H), 1.15–1.08 (m, 1 H), 1.05–0.98 (m, 1 H), 0.89 (d, *J* = 6.78 Hz, 3 H), 0.88 (d, *J* = 6.84 Hz, 3 H), 0.87 (d, *J* = 7.08 Hz, 3 H), 0.86 (d, *J* = 7.03 Hz, 3 H), 0.83 (t, *J* = 6.94 Hz, 3 H), 0.82 (d, *J* = 7.08 Hz, 3 H), 0.80 (d, *J* = 6.48 Hz, 3 H) ppm. $^{13}C$ NMR (150 MHz, DMSO-$d_6$): δ = 173.3, 171.9, 171.7, 171.6, 171.3, 169.2, 77.1, 60.5, 52.3, 48.7. 47.8, 42.9, 41.5, 33.9, 33.7, 31.6, 30.6, 29.3, 27.0, 25.0, 23.6, 22.5, 21.2, 19.5, 19.2, 18.7, 16.8, 14.8, 14.4, 13.4 ppm. ESI-MS: 610.4 [M + $H^+$]. HRMS (MALDI): *m/z* calcd for [$C_{31}H_{55}N_5O_7$ + $Na^+$]: 632.3999; found: 632.4004.