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Total synthesis of emericellamides A and B

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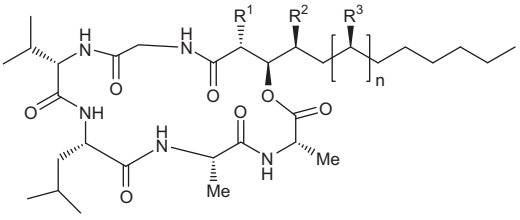
ABSTRACT

A concise total synthesis of emericellamides A and B, two cyclic depsipeptides exhibiting antibacterial and cytotoxic activities, is reported. A Paterson *anti*-aldol reaction and a hydroxy directed 1,3-*anti* reduction were applied for construction of the polypropionate unit with the required stereochemistry in emericellamides A and B. An FDPP mediated macrolactamization was used to construct the macrocycle of emericellamides A and B.

1. Introduction

Although the marine environment is a rich source of secondary metabolites with interesting structures and functions, natural product chemists continue to develop new techniques to harvest novel molecules. The co-culture technique (culturing two different microbial strains in the same culture vessel) is one such method by which one can produce new natural products or increase the production of known natural products through induction.[1] In 2007 Fenical et al. isolated two new depsipeptides, emericellamides A and B, by using this co-culture technique.[2a] Subsequently they have also isolated four new cyclic depsipeptides, named emericellamide C–F[2b] (Fig. 1). Initial biological studies revealed that emericellamides A and B have antibacterial activity against methicillin-resistant *Staphylococcus aureus* with MIC values of 3.8 and 6 μM, respectively. They are also cytotoxic against the HCT-116 human colon carcinoma cell line with IC_{50} values of 23 and 100 μM, respectively. With the help of detailed NMR studies, the structures of emericellamides A and B were established. Marfey's method,[3] *J*-based configurational analysis, and a modified Mosher method[4] were used to establish the absolute stereochemistry of **1** and **2**.



emericellamide A **1**: n=0, $R^1 = R^2 = R^3$ = Me
emericellamide B **2**: n=1, $R^1 = R^2 = R^3$ = Me
emericellamide C **3**: n=0, R^1 = Me, $R^2 = R^3$ = H
emericellamide D **4**: n=0, $R^1 = R^3$ = H, R^2 = Me
emericellamide E **5**: n=1, R^1 = Me, $R^2 = R^3$ = H
emericellamide F **6**: n=1, $R^1 = R^3$ = H, R^2 = Me

Figure 1. Structures of emericellamide A–F.

Due to their interesting structure and biological activities, they have attracted the attention of synthetic organic chemists, for their total synthesis. As a result three total syntheses of emericellamide A and two total syntheses of emericellamide B have appeared in the literature.[5] The first total synthesis of emericellamide A was reported by us,[5a] which involved Evans alkylation, Sharpless asymmetric epoxidation, and Me_2CuLi mediated epoxide opening reactions to construct the polypropionate unit with the requisite stereochemistry and FDPP mediated macrolactamization between Gly and Val for construction of the macrocycle. Li et al. reported the total synthesis of emericellamides A and B via macrolactamization between the two alanine residues.[5b] The decanoic acid moieties of emericellamides A and B with the requisite stereotetrad were synthesized through Evans alkylation and crotylboration reactions. Ma et al. achieved the total synthesis of emericellamide A by applying Evans alkylation, Evans asymmetric aldol, and FDPP meditated macrolactamization reactions.[5c] Yadav et al. reported on the total synthesis of emericellamide B, where a desymmetrization methodology was applied for the synthesis of the decanoic acid.[5d] Herein we report the total synthesis of emericellamides A and B by using a Paterson *anti*-aldol reaction followed by a hydroxy directed stereoselective ketone reduction and FDPP mediated (Scheme 1) macrolactamization as the key steps.

In our previous synthesis of emericellamide A,[5a] the macrolactonization was unsuccessful and the synthesis was accomplished through macrolactamization at the Gly-Val site. With this earlier

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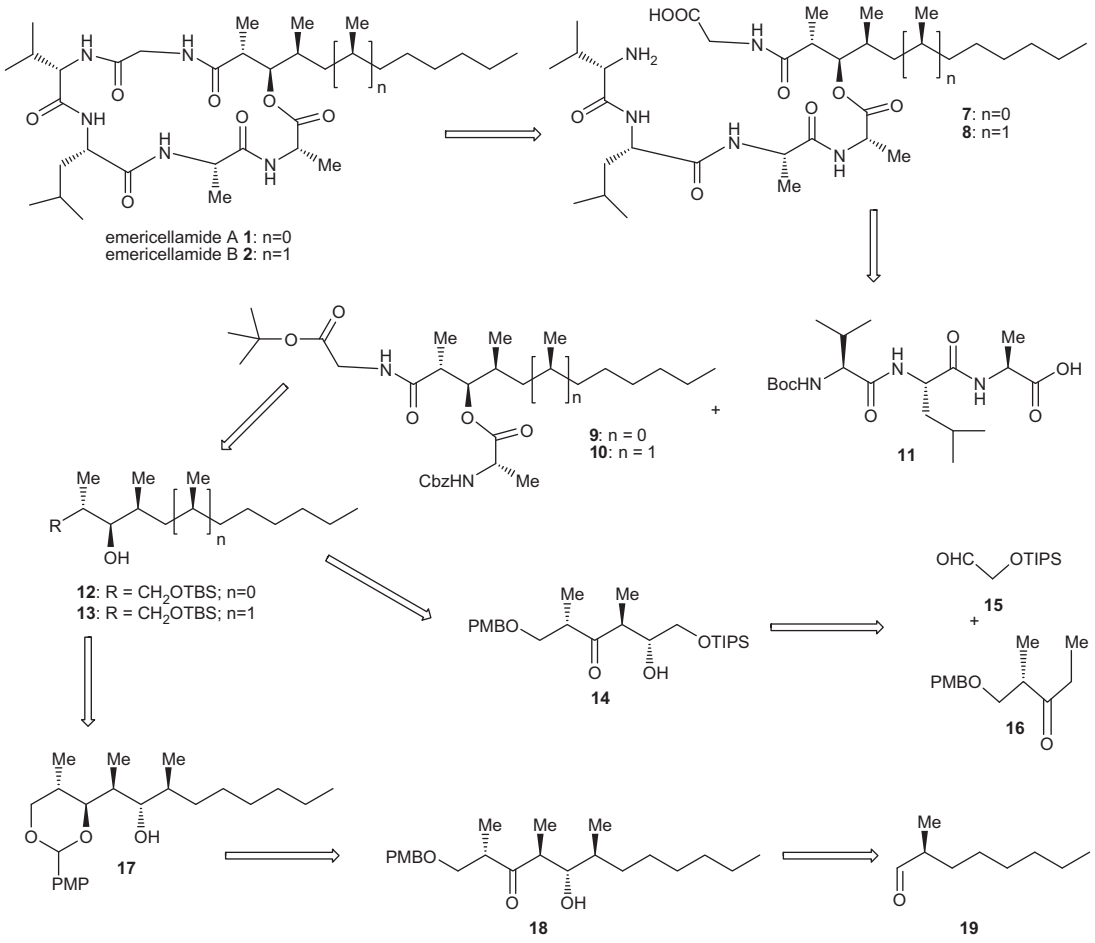


Scheme 1. Retrosynthetic analysis.

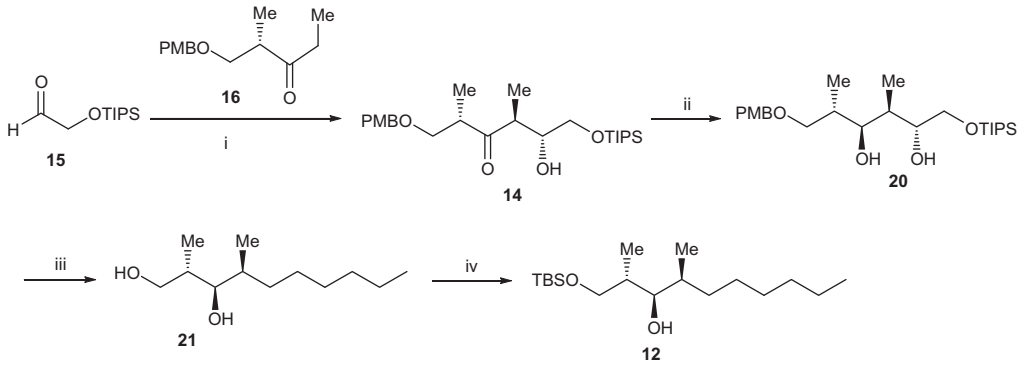
observation in mind, we decided to adopt a similar macrolactamization strategy for the synthesis of the target molecules. However, we planned to synthesize the polypropionate unit via a Paterson *anti* aldol reaction and hydroxy directed 1,3-*anti*-reduction as the key steps. Thus retrosynthetically emericellamides A and B could be obtained via macrolactamization of compounds **7** and **8**, respectively. Compounds **7** and **8** could be obtained from compounds **9** and **10** through peptide chain elongation with **11**. Compounds **9** and **10** could be obtained from the secondary alcohol **12** and **13** via acylation with CbzAlaOH followed by TBS deprotection, oxidation, and amide bond formation with ^{t}BuOGlyNH$_2$. The secondary alcohol **12** could be obtained from the β-hydroxy ketone **14**, via hydroxyl directed 1,3-*anti* reduction followed by functional group manipulation. The β-hydroxy ketone **14** could be obtained by means of a Paterson aldol reaction between aldehyde **15** and ketone **16**. The secondary alcohol **13** required for the synthesis of emericellamide B could be obtained via deoxygenation of the free hydroxyl group of **17**, which might be obtained via hydroxy directed reduction of ketone **18**, which in turn could be obtained via a Paterson aldol reaction between **19** and **16**.

2. Results and discussion

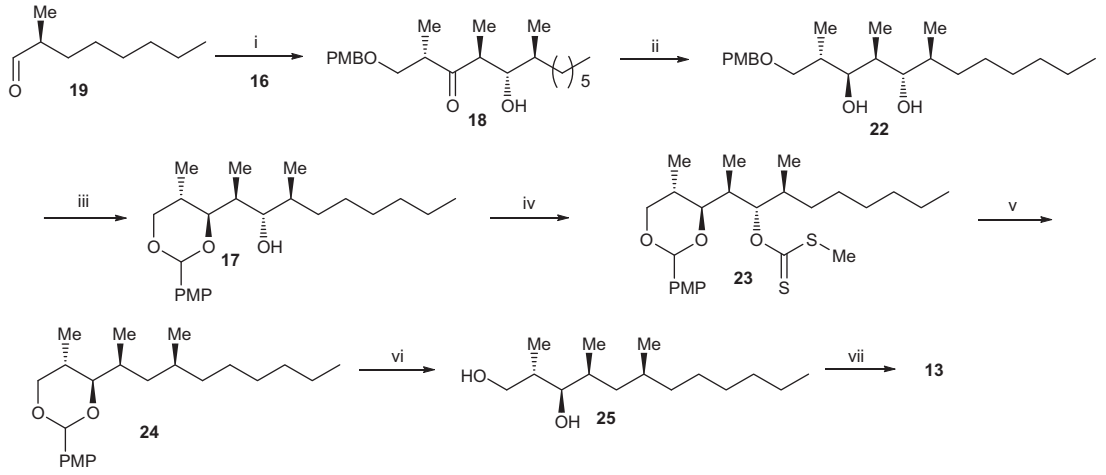
Our synthesis started with the addition of the enolate generated from the known ketone **16**[6] to the known aldehyde **15**[7] under Paterson conditions [8] to provide β-hydroxy ketone **14** in 94% (de >95%). The β-hydroxy ketone **14** was subjected to a hydroxy directed 1,3-*anti* reduction with $Me_4NHB(OAc)_3$[9] to give diastereomerically pure 1,3-*anti* diol compound **20** in 90% yield. The acid catalyzed deprotection of TIPS provided a triol compound, which upon oxidative cleavage followed by Wittig reaction with the ylide $Ph_3P{=}CH{-}(CH_2)_3CH_3$ and reduction of the resulting alkene, furnished the PMB deprotected 1,3-diol compound **21** in 65% yield over four steps. Selective protection of the primary hydroxyl group as a TBS ether afforded (Scheme 2) secondary alcohol **12** in 95% yield.

For the synthesis of the polypropionate unit **13** of emericellamide B, we started from the known aldehyde **19**,[10] which upon reaction with the *E*-enolate generated from ketone **16** provided aldol product **18** in 90% yield as shown in Scheme 3. The hydroxy directed 1,3-*anti* reduction of the keto group of aldol product **18** under Evans conditions furnished the 1,3-*anti* diol compound **22** in 90% yield (de >95%). Oxidative rearrangement of the PMB group was performed with DDQ[11] to give the *p*-methoxybenzylidene protected compound **17** in 80% yield. Compound **24** was synthesized from **23** via a two step Barton–McCombie deoxygenation reaction.[12] Alcohol **17** was converted into xanthate **23**, which upon treatment with Bu_3SnH and AIBN provided the deoxygenated compound **24** in 63% over two steps. Deprotection of the *p*-methoxybenzylidene group under hydrogenation conditions provided diol **25**, whose selective protection of the primary hydroxyl group with TBSCl and imidazole in THF provided fragment **13** in 81% over two steps.

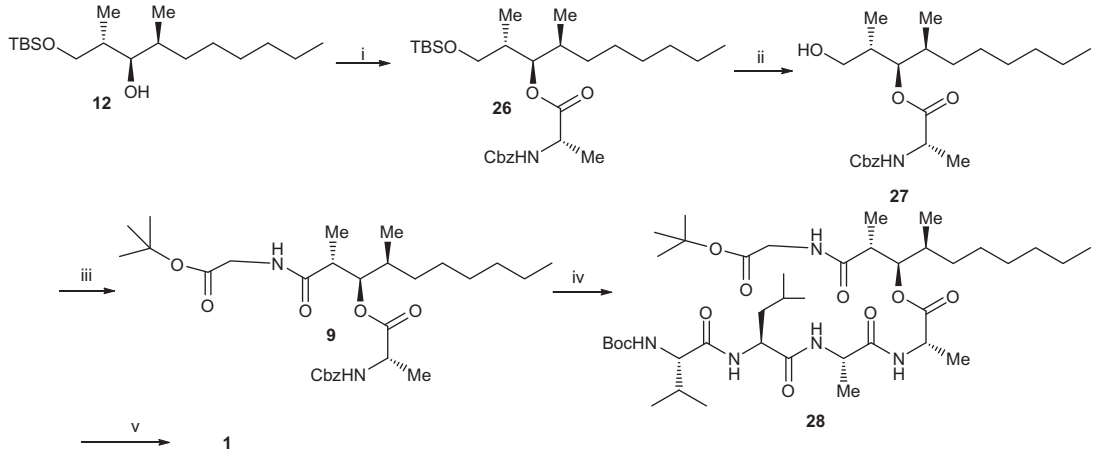
The completion of the synthesis of emericellamide A is depicted in Scheme 4. Acylation of the secondary alcohol **12** with CbzAlaOH under DCC and DMAP conditions afforded the acylated compound



Scheme 2. Synthesis of fragment **12**. Reagents and conditions: (i) *c*-hex$_2$BCl, Et$_3$N, Et$_2$O, −78 to 0 °C, overnight, 94%; (ii) Me$_4$NHB(OAc)$_3$, acetone:AcOH (1:1), −20 °C, 4 h, 90%; (iii) (a) CSA, MeOH:CH$_2$Cl$_2$(1:1), rt, 1 h; (b) NaIO$_4$, THF:H$_2$O (2:1), 0 °C, 30 min; (c) Ph$_3$P=CH–(CH$_2$)$_3$–CH$_3$, NaHMDS, THF, −78 °C, 30 min; (d) H$_2$/Pd–C, MeOH, 2 h, 65% over four steps; (iv) TBSCl, imidazole, THF, 0 °C, 95%.



Scheme 3. Synthesis of fragment **13**. Reagents and conditions: (i) **16**, *c*-hex$_2$BCl, Et$_3$N, Et$_2$O, −78 to 0 °C, overnight, 90%; (ii) Me$_4$NHB(OAc)$_3$, acetone:AcOH (1:1), −20 °C, 30 h, 90%; (iii) DDQ, 4 Å, MS, CH$_2$Cl$_2$, 0 °C, 30 min, 80%; (iv) NaHMDS, CS$_2$, MeI, THF, −78 °C, 85%; (v) Bu$_3$SnH, AIBN, 120 °C, 30 min, 75%; (vi) H$_2$/Pd–C, MeOH, 2 h, 90%; (vii) TBSCl, imidazole, THF, 8 h, 96%.

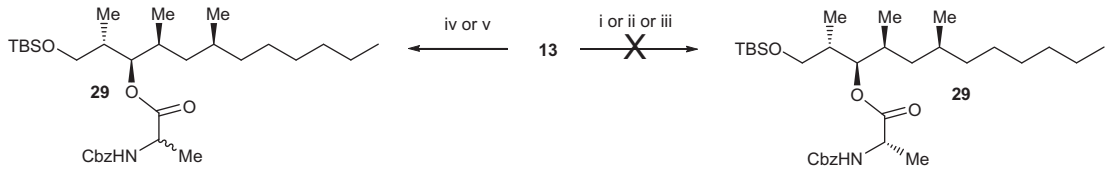


Scheme 4. Synthesis of emericellamide A. Reagents and conditions: (i) Cbz-Ala-OH, DCC, DMAP (cat), 0 °C to rt, 5 h, 75%; (ii) CSA (cat), MeOH:CH$_2$Cl$_2$, (1:1), 0 °C, 0.5 h, 85%; (iii) (a) SO$_3$:Py, DMSO:CH$_2$Cl$_2$ (2:1.8), 0 °C, 1 h (b) NaH$_2$PO$_4$·2H$_2$O, NaClO$_2$, 2-methyl-2-butene, ^{t}BuOH, 0 °C to rt, 1 h; (c) EDCI, HOBt, NH$_2$Gly-O^{t}Bu, 0 °C to rt, 1 h, 81% over two steps; (iv) (a) H$_2$, Pd/C, EtOAc, 1 N, HCl, 10 min; (b) Boc-Val-Leu-Ala-OH, EDCI, HOBt, CH$_2$Cl$_2$, DIPEA, 0 °C, 1 h, 75%; (v) (a) TFA:CH$_2$Cl$_2$ (1:1), 0 °C, 1 h; (b) FDPP, DIPEA, CH$_3$CN, 10^{-3} M, 0 °C to rt, 72 h, 75% over two steps.

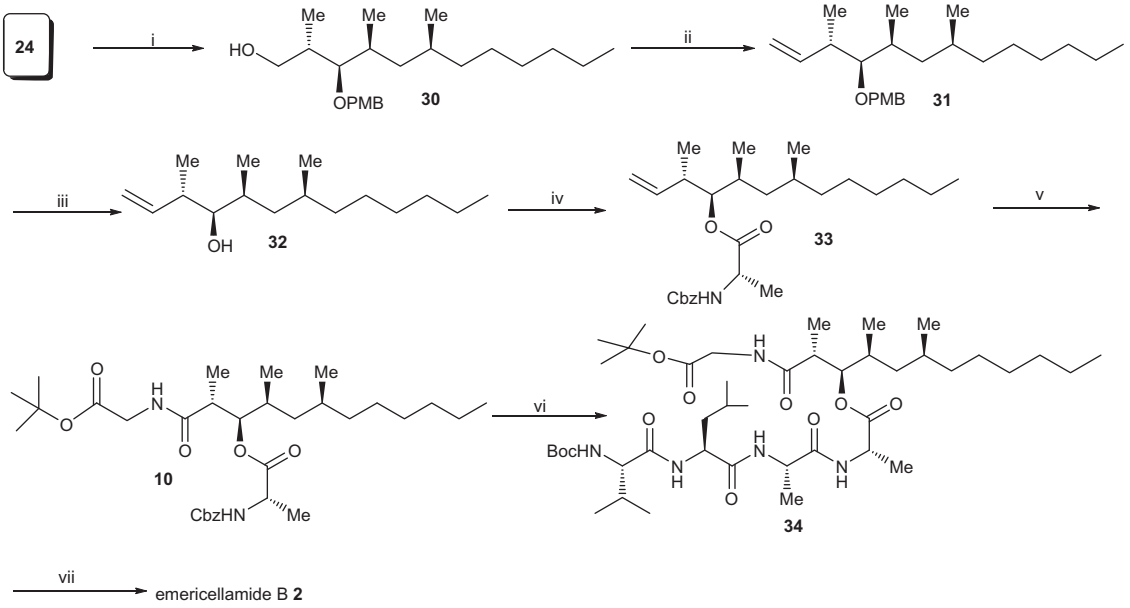
26, which upon TBS deprotection provided primary alcohol **27** in 63% over two steps. Parikh–Doering oxidation[13] of the primary alcohol **27** followed by further oxidation of the aldehyde under Pinnick conditions[14] provided an acid, which upon coupling with the H_2NGlyO^tBu under EDCI conditions furnished compound **9** in 81% over two steps. The Cbz-deprotection of compound **9** provided an amine, which upon coupling with the BocVal-Leu-Ala-OH furnished cyclization precursor **28** in 75% over two steps. Deprotection of Boc and tertiarybutyl groups was achieved with TFA to give a *seco*-amino acid, which upon macrolactamization with penta fluorophenyl diphenylphosphinate[15] (FDPP) at high dilution in CH_3CN afforded emericellamide A **1**, whose analytical data were in good agreement with the literature.[2a]

After completion of the synthesis of emericellamide A, we turned our attention toward the synthesis of emericellamide B by following a similar synthetic strategy. Accordingly, secondary alcohol **13** was subjected to acylation with the CbzAlaOH under DCC/DMAP (cat) conditions. However, we found that the acylation reaction was unsuccessful under DCC/DMAP (cat) conditions. Heating the reaction mixture further or increasing the amount of DMAP (stoichiometric) led to the formation of a product with extensive racemization at Ala center. By using other reagents and conditions, the acylation was unsuccessful (Scheme 5).

This unsuccessful acylation may be explained by the steric crowding around the secondary hydroxyl group. Thus, we felt that by keeping the sterically less hindered group at the C1 position, it might allow the acylation of the hydroxyl group. Accordingly we decided to keep $-CH{=}CH_2$ in place of $-CH_2-$OTBS, so that steric crowding would be much less and the $-C{=}CH_2$ unit could be converted into the acid at the required stage. Thus the *p*-methoxybenzylidene acetal of **24** was opened with DIBAL-H to give the primary alcohol **30**, which was subjected to Ley oxidation[16] followed by Wittig reaction of the resulting aldehyde with the ylide $Ph_3P{=}CH_2$ in ether gave olefinic compound **31** which upon treatment with DDQ furnished secondary alcohol **32** in 70% over four steps (Scheme 6). Acylation of the secondary alcohol proceeded smoothly with good yield and diastereomeric excess (80%, de >95%). Dihydroxylation of the olefinic moiety provided the 1,2-diol compound, which upon oxidative cleavage with $NaIO_4$ followed by Pinnick oxidation of the resulting aldehyde furnished an acid, which upon coupling with $H_2NGlyOtBu$ provided compound **10**. Deprotection of Cbz from compound **10**, followed by peptide chain elongation furnished cyclization precursor **34**, which on treatment with TFA followed by macrolactamization of the resulting *seco*-amino acid provided emericellamide B **2** in 80% over two steps.



Scheme 5. Acylation of **13** with CbzAlaOH. Reagents and conditions: (i) CbzAlaOH, DCC, DMAP (cat), CH_2Cl_2, 0 °C to rt; (ii) EDCI, HOBt, CH_2Cl_2, 0 °C to rt; (iii) EDCI, DMAP (cat), CH_2Cl_2, 0 °C to rt; (iv) CbzAlaOH, DCC, DMAP (1 equiv), CH_2Cl_2, 0 °C to rt; (v) CbzAlaOH, DCC, DMAP (cat), CH_2Cl_2, reflux.



Scheme 6. Synthesis of emericellamide B: (i) DIBAL-H, CH_2Cl_2, −78 to 0 °C, 30 min, 97%; (ii) TPAP, NMO, CH_2Cl_2, 4 Å MS, rt, 10 min; (b) $Ph_3P{=}CH_2$, ^tBuOK, Et_2O, 0 °C, 80%; (iii) DDQ, $CHCl_3$:H_2O (20:1), 0 °C, 30 min, 92%; (iv) Cbz-Ala-OH, DCC, DMAP (cat), CH_2Cl_2, 0 °C to rt, 1 h, 80%; (v) (a) OsO_4, NMO, methane sulfonamide, 0 °C to rt, 4 h, (b) $NaIO_4$, THF:H_2O (1:1), 0 °C to rt, 30 min (c) $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 1 h, H_2O, 2-methyl-2-butene, ^tBuOH; (d) EDCI, HOBt, NH_2Gly-OtBu; 0 °C to rt, 1 h, 70%; (vi) (a) H_2, Pd/C, EtOAc, 1 M HCl, 10 min; (b) BocVal-Leu-Ala-OH, EDCI, HOBt, CH_2Cl_2, DIPEA,1 h, 75%; (vii) (a) TFA:CH_2Cl_2 (1:1), 0 °C, 1 h; (b) FDPP, DIPEA, CH_3CN, 10^{-3} M, 0 °C to rt, 72 h, 80% over two steps.

3. Conclusion

In conclusion we have reported on the total synthesis of emericellamides A and B from compounds **15** (15 steps, 15% overall yield) and **19** (18 steps 9.9% overall yield) respectively. The key features of the synthetic sequence include a diastereoselective Paterson *anti*-aldol reaction, hydroxy directed stereoselective reductions of a β-hydroxyl ketone and FDPP mediated macrolactamization. The total synthesis of other members of the emericellamide and analogues of emericellamide A–F is currently in progress, and will be reported in due course.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz (Avance) and Varian Unity 500 MHz (Innova) spectrometers at ambient temperature in $CDCl_3$ solvent by using TMS as an internal standard. Chemical shifts are reported in ppm with respect to TMS. FTIR spectra were recorded on Alpha (Bruker) infrared spectrophotometer. A Horiba Sepa 300 polarimeter was used to record the optical rotations. All the reactions were carried out under inert atmosphere in flame dried glass apparatus. Freshly distilled anhydrous solvents were used to carry out the reactions. All chemicals from Aldrich were used as such. Column chromatography was carried out on silica gel (60–120 mesh) packed in glass columns.

4.1.1. (2*S*,4*S*,5*R*)-5-Hydroxy-1-(4-methoxybenzyloxy)-2,4-dimethyl-6 (triisopropylsilyloxy)hexan-3-one 14

To a cooled solution of chlorodicyclohexylborane (5.91 mL, 5.91 mmol) in dry ether (12 mL) at −78 °C were added dropwise triethylamine (1 mL, 7.09 mmol) followed by ketone **16** (930 mg, 3.94 mmol) in ether (5 mL). The milky mixture was stirred at 0 °C for 2.5 h. The solution was again cooled to −78 °C before the slow addition of aldehyde **15** (1.27 g, 5.91 mmol) and the resulting solution was stirred for 2 h at the same temperature. The mixture was kept at −25 °C overnight and then stirred at 0 °C for 30 min. The reaction mixture was quenched successively with MeOH (11 mL), pH 7 buffer (11 mL), H_2O_2 (50%) (11 mL), and stirred for 30 min at room temperature. The organic layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed sequentially with water (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. The organic solution was concentrated in vacuo and chromatographed on silica gel (60–120 mesh, 5% EtOAc/hexane) to afford **14** (1.67 g, 94%) as a colorless oil. R_f = 0.4 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{25} = +19.75$ (*c* 2.05 $CHCl_3$). IR (Neat): ν_{max} = 3497, 2936, 2864, 1709, 1613, 1512, 1460, 1370, 1297, 1245, 1173, 1096, 1036, 1003, 919, 880, 808 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.40 (dd, *J* = 15.9, 11.5 Hz, 2H), 3.79 (s, 3H), 3.78–3.55 (m, 4H), 3.42 (m, 1H), 3.10–2.89 (m, 2H), 1.12–0.94 (m, 27H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 141.6, 130.1, 129.1, 113.7, 74.1, 72.9, 71.9, 65.2, 55.2, 47.4, 46.8, 17.9, 13.1, 12.9, 11.9 ppm. MS (ESI): *m*/*z* = 475 [M+Na]$^+$. HRMS (ESI): calcd for $C_{25}H_{44}O_5NaSi$ [M+Na]$^+$ 475.2855, found 475.2858.

4.1.2. (2*R*,3*R*,4*S*,5*S*)-6-(4-Methoxybenzyloxy)-3,5-dimethyl-1-(triisopropylsilyloxy) hexane-2,4-diol 20

Compound **14** (697 mg, 1.54 mmol) was taken in a (1:1) mixture of AcOH and acetone (3 mL each) and cooled to −20 °C. Next, $Me_4NHB(OAc)_3$ (1.21 g, 4.62 mmol) was added very quickly to the reaction mixture and it was stirred at the same temperature for 5 h. After completion of the reaction, it was quenched with a saturated solution of sodium potassium tartrate (5 mL) and stirred at room temperature for 3 h. The organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed sequentially with water (2 × 5 mL), brine (2 × 5 mL) and dried over anhydrous Na_2SO_4. The organic solution was concentrated in vacuo and chromatographed on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford **20** (630 mg, 90%) as a colorless oil. R_f = 0.1 (SiO_2, 15% EtOAc/hexane); $[\alpha]_D^{25} = +15.6$ (*c* 1.08, $CHCl_3$); IR (Neat): ν_{max} = 3442, 2936, 2924, 2864, 1613, 1513, 1461, 1363, 1300, 1247, 1173, 1093, 1040, 996, 921, 882, 813 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.47 (ABq, *J* = 11.5 Hz, 2H), 3.94 (dd, *J* = 9.4, 2.0 Hz, 1H), 3.87–3.77 (m, 4H), 3.76–3.68 (m, 2H), 3.59 (dd, *J* = 9.0, 4.4 Hz, 1H), 3.51 (t, *J* = 9.0 Hz, 1H), 1.99 (m, 1H), 1.83 (m, 1H), 1.73–1.47 (m, 2H), 1.18–1.02 (m, 21H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.5, 129.9, 129.5, 114.0, 76.6, 75.9, 75.1, 73.3, 65.7, 55.4, 35.9, 35.6, 18.1, 13.2, 12.1, 9.4 ppm. MS (ESI): *m*/*z* = 477 [M+Na]$^+$. HRMS (ESI): calcd for $C_{25}H_{46}O_5NaSi$ [M+Na]$^+$ 477.3012, found 477.3007.

4.1.3. (2*S*,3*R*,4*S*)-2,4-Dimethyldecane-1,3-diol 21

A solution of compound **20** (600 mg, 1.32 mmol) in CH_2Cl_2/MeOH (1:1, 5 mL) was treated with CSA (camphor sulfonic acid) (613 mg, 2.64 mmol) at 0 °C. After being stirred for 30 min at the same temperature, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (60 mL) and extracted with EtOAc (2 × 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo.

The crude product was then dissolved in THF:H_2O (1:1, 10 mL) and cooled to 0 °C, after which $NaIO_4$ (700 mg, 3.3 mmol) was added and stirred at room temperature for 2 h. The reaction was diluted with water and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude aldehyde was used for the next step.

At first, NaHMDS (7.9 mL, 7.92 mmol) was added to a suspension of $[Ph_3P–CH_2–(CH_2)_3–CH_3]^+Br^-$ (5 g, 13.2 mmol) in dry THF (20 mL) at −78 °C. The mixture was then stirred at the same temperature for 30 min. The resulting ylide was added to a solution of aldehyde in THF (10 mL) at 0 °C. After 0.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated, washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo.

The crude product was dissolved in MeOH (10 mL), after which Pd/C (10%) (300 mg) was added and subjected to hydrogenation under atmospheric pressure using H_2-filled balloon. After 2 h, the reaction mixture was filtered through a short pad of Celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated in vacuo and subjected to column chromatography on silica gel (60–120 mesh, 15% EtOAc/hexane) to afford **21** (200 mg, 70%) as a colorless liquid; R_f = 0.5 (SiO_2, 30% EtOAc/hexane). $[\alpha]_D^{30} = +14.6$ (*c* 4.91, $CHCl_3$). IR (Neat): ν_{max} = 3355, 2959, 2925, 2855, 1460 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.59 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.44 (dd, *J* = 9.1, 3.0 Hz, 1H), 2.99–2.52 (br s, 2H), 1.82 (m, 1H), 1.59 (m, 1H), 1.40–1.21 (m, 10H), 0.93–0.84 (m, 6H), 0.80 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.6, 68.2, 37.1, 34.9, 33.9, 31.8, 29.4, 27.3, 22.5, 13.9, 13.4, 12.1 ppm. MS (ESI): *m*/*z* = 226 [M+Na]$^+$. HRMS (ESI): calcd for $C_{12}H_{26}O_2$ [M+Na]$^+$ 226.1964; found 226.1960.

4.1.4. (2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyldecan-3-ol 12

To a stirred solution of **21** (190 mg, 0.94 mmol) in dry THF (5 mL) was added imidazole (200 mg, 2.82 mmol) at 0 °C. After 10 min TBSCl (213 mg, 1.42 mmol) was added to it. After stirring

for 8 h the reaction was quenched with saturated NH_4Cl at 0 °C. The reaction mixture was extracted with EtOAc (60 mL) and the combined organic extracts were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. It was then subjected to column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to yield pure compound **12** (285 mg, 96%) as a colorless oil; R_f = 0.3 (SiO_2, 15% EtOAc/hexane). $[\alpha]_D^{30} = +22.4$ (*c* 2.75, $CHCl_3$). IR (Neat): ν_{max} = 2957, 2927, 2856, 1743, 1464, 1385, 1254, 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.75 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.58 (dd, *J* = 9.8, 8.3 Hz, 1H), 3.38 (dd, *J* = 8.3, 3.0 Hz, 1H), 1.77 (m, 1H), 1.49 (m, 1H), 1.38–1.19 (m, 10H), 0.93–0.89 (m, 12H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 7.5 Hz, 3H), 0.10–0.06 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.4, 69.3, 37.3, 35.3, 34.1, 31.8, 29.5, 27.4, 25.8, 22.6, 18.1, 14.0, 13.3, 12.4, −5.7 ppm. MS (ESI): *m*/*z* = 317 $[M+H]^+$. HRMS (ESI): calcd for $C_{18}H_{41}O_2Si$ $[M+H]^+$ 317.2875, found 317.2878.

4.1.5. (2*S*,4*S*,5*S*,6*S*)-5-Hydroxy-1-(4-methoxybenzyloxy)-2,4,6-trimethyl dodecan-3-one 18

To a cooled solution of chlorodicyclohexylborane (19.06 mL, 19.0 mmol) in dry ether (50 mL) at −78 °C were added dropwise triethylamine (3.17 mL, 22.8 mmol) followed by ketone **16** (3 g, 12.7 mmol) in ether (10 mL). The milky mixture was stirred at 0 °C for 2.5 h. The solution was again cooled to −78 °C before the slow addition of aldehyde **19** (2.7 g, 19.0 mmol) and the resulting solution was stirred for 2 h at the same temperature. The mixture was then kept at −25 °C overnight after which it was stirred at 0 °C for 30 min. The reaction mixture was quenched successively with MeOH (38 mL), pH 7 buffer (38 mL), H_2O_2 (50%) (38 mL) and then stirred for 30 min at room temperature. The organic layer was extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed sequentially with water (2 × 15 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The organic solution was concentrated in vacuo and chromatographed (SiO_2 10% EtOAc/hexane) to afford **18** (4.7 g, 98%) as a colorless oil; R_f = 0.2 (SiO_2, 15% EtOAc/hexane) = −0.7 (*c* 2.9, $CHCl_3$). IR (Neat): ν_{max} = 2923, 2854, 1708, 1612, 1513, 1459, 1371, 1246, 1174, 1093, 1036, 958 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.34 (dd, *J* = 16.6, 11.6 Hz, 2H), 3.74 (s, 3H), 3.56 (t, *J* = 8.7 Hz, 1H), 3.39 (dd, *J* = 6.9, 4.8 Hz, 1H), 3.31 (dd, *J* = 8.7, 4.8 Hz, 1H), 2.99 (ddq, *J* = 8.7, 4.8, 7.0 Hz, 1H), 2.82 (p, *J* = 7.0 Hz, 1H), 1.44 (m, 1H), 1.32–1.16 (m, 10H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 218, 159.1, 130.6, 129.7, 129.2, 113.7, 78.2, 72.9, 71.9, 55.2, 48.6, 45.5, 35.4, 31.8, 30.0, 29.6, 27.1, 22.6, 16.9, 14.0, 13.7 ppm. MS (ESI): *m*/*z* = 401 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{38}O_4Na$ $[M+Na]^+$ 401.2667, found 401.267.

4.1.6. (2*S*,3*S*,4*S*,5*S*,6*S*)-1-(4-Methoxybenzyloxy)-2,4,6-trimethyldodecane-3,5-diol 22

Compound **18** (3 g, 7.94 m mol) was reduced with $Me_4NHB(OAc)_3$ under the same conditions as used earlier to give compound **22** (2.7 g, 90%). R_f = 0.2 (SiO_2, 20% EtOAc/hexane). $[\alpha]_D^{25} = -9.1$ (*c* 2.5, $CHCl_3$). IR (Neat): ν_{max} = 3442, 2957, 2924, 2855, 1513, 1460, 1247, 1078, 1038, 972, 820 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.41 (dd, *J* = 16.6, 11.4 Hz, 2H), 3.79 (dd, *J* = 9.3, 2.0 Hz, 1H), 3.77 (s, 3H), 3.52 (dd, *J* = 9.3, 4.0 Hz, 1H), 3.41 (t, *J* = 9.0 Hz, 1H), 3.11 (dd, *J* = 8.4, 4.3 Hz, 1H), 1.95 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.34–1.21 (m, 8H), 1.11–1.02 (m, 2H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 129.6, 129.3, 113.8, 80.6, 76.3, 76.2, 73.1, 55.1, 36.5, 35.8, 34.5, 32.3, 31.9, 29.7, 27.0, 22.7, 16.2, 14.1, 13.0, 10.7 ppm. MS (ESI): *m*/*z* = 403 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{40}O_4Na$ $[M+Na]^+$ 403.2824, found 403.2821.

4.1.7. (2*S*,3*S*,4*S*)-2-((4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyldecan-3-ol 17

The 1,3-*anti*-diol compound **22** (1.7 g, 4.47 mmol) was taken in dry CH_2Cl_2 (15 mL) and 4 Å MS (2.2 g, 1.3 equiv with respect to weight) were added. The mixture was stirred for 1 h at room temperature. Next, DDQ (1.52 g, 6.71 mmol) was added to the reaction mixture at 0 °C and kept at the same temperature for 30 min. After complete consumption of the starting material, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (100 mL). The organic extracts were washed with water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), and filtered. After evaporation of the solvents under vacuum the crude mass was subjected to chromatographic purification silica gel (60–120 mesh 5–6% EtOAc/hexane) to afford pure compound **17** (1.35 g, 80%) as a colorless liquid; R_f = 0.40 (SiO_2, 20% EtOAc/hexane). $[\alpha]_D^{24} = +28.4$ (*c* 2.28, $CHCl_3$). IR (Neat): ν_{max} = 3532, 2958, 2926, 2854, 1516, 1461, 1388, 1250, 1169, 1112, 1077, 1032 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.42 (s, 1H), 4.08 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.82 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.78 (s, 3H), 3.48 (t, *J* = 11.0 Hz, 1H), 3.24 (dd, *J* = 6.7, 5.5 Hz, 1H), 2.30 (m, 1H), 2.09 (m, 1H), 1.97 (m, 1H), 1.71–1.51 (m, 2H), 1.40–1.20 (m, 8H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.7, 130.6, 127.1, 113.4, 100.8, 82.9, 79.1, 73.0, 55.1, 36.3, 34.1, 31.8, 31.2, 30.1, 29.5, 26.9, 22.5, 16.2, 14.0, 11.7, 11.2 ppm. MS (ESI): *m*/*z* = 401 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{38}O_4Na$ $[M+Na]^+$ 401.2667, found 401.2671.

4.1.8. *O*-(2*R*,3*S*,4*S*)-2-((4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyldecan-3-yl (*S*)-methyl carbonodithioate 23

Compound **17** (770 mg, 2.03 mmol) was taken in dry THF (10 mL) and then cooled to −78 °C. Next, 1 M NaHMDS (20.3 mL, 20.3 mmol) was added dropwise to it and the reaction mixture was kept at the same temperature for 30 min. Next, CS_2 (2.4 mL, 40.6 mmol) was added to that solution and stirred for 30 min at −78 °C after which MeI (3.7 mL, 60.9 mmol) was added to that reaction mixture and after stirring for 5 min at the same temperature, quenched by saturated aqueous H_2O (5 mL), extracted with EtOAc (2 × 30 mL). The extracts were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (60–120 mesh 5% EtOAc/hexane) furnished **23** (810 mg, 85%) as a colorless liquid; R_f = 0.50 (SiO_2, 10% EtOAc/hexane). $[\alpha]_D^{25} = +62.85$ (*c* 2.97, $CHCl_3$). IR (Neat): ν_{max} = 2926, 2854, 2362, 1516, 1461, 1391, 1224, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.99 (dd, *J* = 9.6, 2.5 Hz, 1H), 5.27 (s, 1H), 4.06 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.76 (s, 3H), 3.42 (t, *J* = 11.2 Hz, 1H), 3.28 (dd, *J* = 10.0, 1.3 Hz, 1H), 2.50 (s, 3H), 2.16 (m, 1H), 2.01 (m, 1H), 1.84 (m, 1H), 1.35–1.11 (m, 10H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.4, 159.7, 131.5, 127.5, 113.3, 100.8, 88.4, 81.4, 73.0, 55.2, 35.7, 35.0, 31.9, 30.1, 29.5, 27.3, 22.6, 18.9, 16.8, 14.1, 12.1, 9.6 ppm. MS (ESI): *m*/*z* = 491$[M+Na]^+$; HRMS (ESI): calcd for $C_{25}H_{40}O_4NaS_2$ $[M+Na]^+$ 491.2265, found 491.2256.

4.1.9. (4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-4-((2*S*,4*S*)-4-methyl decan-2-yl)-1,3-dioxane 24

The methyl xanthate derivative **23** (504 mg, 1.07 mmol) was taken in neat Bu_3SnH (3 mL, used as a reagent as well as solvent) and a catalytic amount of AIBN (17.5 mg, 0.10 mmol) was added. The

mixture was heated at 120 °C for 30 min and after completion of the reaction it was quenched with H_2O (5 mL). The reaction mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (60–120 mesh 2% EtOAc/hexane) afforded **24** (292 mg, 75%) as a colorless liquid; R_f = 0.60 (SiO_2, 10% EtOAc/hexane). $[\alpha]_D^{25} = +15.6$ (*c* 0.4 $CHCl_3$). IR (Neat): ν_{max} = 2945, 2927, 2850, 1457, 1068, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.37 (s, 1H), 4.07 (dd, *J* = 11.1, 4.7 Hz, 1H), 3.79 (s, 3H), 3.44 (t, *J* = 11.1 Hz, 1H), 3.33 (dd, *J* = 9.9, 2.1 Hz, 1H), 2.03 (m, 1H), 1.87 (m, 1H), 1.61–1.42 (m, 2H), 1.38–1.16 (m, 10H), 1.07 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 131.7, 127.2, 113.4, 100.9, 84.5, 73.3, 55.3, 40.8, 37.2, 31.9, 30.6, 30.5, 29.6, 29.6, 26.9, 22.6, 20.0, 14.1, 13.9, 12.0 ppm. MS (ESI): *m*/*z* = 385 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{38}O_3Na$ $[M+Na]^+$ 385.2265, found 385.2258.

4.1.10. (2*S*,3*R*,4*S*,6*S*)-2,4,6-Trimethyldodecane-1,3-diol 25

Compound **24** (270 mg, 0.745 mmol) was dissolved in MeOH (5 mL), after which Pd/C (10% 170 mg) was added and subjected to hydrogenation under atmospheric pressure using an H_2-filled balloon. After 2 h, the reaction mixture was filtered through a short pad of celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated in vacuo and subjected to column chromatography on silica gel (60–120 mesh 20% EtOAc/hexane) to yield pure compound **25** (163 mg, 90%) as a colorless oil.R_f = 0.60 (SiO_2, 45% EtOAc/hexane). $[\alpha]_D^{25} = +4.0$ (*c* 0.7, $CHCl_3$). IR (Neat): ν_{max} = 3350, 2950, 2925, 2855, 1457 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.72 (dd, *J* = 10.7, 3.8 Hz, 1H), 3.64 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.45 (dd, *J* = 9.1, 2.4 Hz, 1H), 3.09–2.48 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H), 1.48 (m, 1H), 1.32–1.14 (m, 11H), 1.05 (m, 1H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 79.7, 68.9, 41.4, 37.4, 37.0, 32.0, 31.9, 29.8, 29.6, 26.9, 22.6, 20.0, 14.0, 13.5, 12.7 ppm. MS (ESI): *m*/*z* = 267 $[M+Na]^+$; HRMS (ESI): calcd for $C_{15}H_{32}O_3Na$ $[M+Na]^+$ 267.4672, found 267.469.

4.1.11. (2*S*,3*R*,4*S*,6*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyldodecan-3-ol 13

The TBS protection of compound **25** (150 mg, 0.614 mmol) was performed to obtain compound **13** (209 mg, 0.58 mmol) by following the same conditions as used above for the synthesis of **12**. $[\alpha]_D^{24} = +14.6$ (*c* 0.9, $CHCl_3$). IR (Neat): ν_{max} = 2957, 2927, 2850, 1742, 1466, 1390, 1254, 1071 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.74 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.59 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.4 (dd, *J* = 8.6, 2.7 Hz, 1H), 1.8 (m, 1H), 1.71–1.46 (m, 3H), 1.44–1.20 (m, 9H), 1.13–1.0 (m, 2H), 1.03 (m, 1H), 0.91–0.85 (m, 15H), 0.84 (d, *J* = 2 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.08 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.9, 69.5, 41.6, 37.4, 36.8, 32.3, 31.9, 29.8, 29.7, 26.9, 25.8, 22.7, 20.1, 18.1, 14.1, 13.3, 12.9, -5.58, -5.6 ppm. MS (ESI): *m*/*z* = 381 $[M+Na]^+$; HRMS (ESI): calcd for $C_{21}H_{46}O_2NaSi$ $[M+Na]^+$ 381.3089, found 381.3085.

4.1.12. (*S*)-((2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyldecan-3-yl)2-(benzyloxycarbonylamino)propanoate 26

To a solution of compound **12** (118 mg, 0.37 mmol) and Cbz-Ala-OH (125 mg, 0.56 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C, DCC (231 mg, 1.12 mmol) followed by DMAP (7 mg, 0.05 mmol) were added. After stirring for 5 h at room temperature, the reaction mixture was filtered through Celite. It was then concentrated in vacuo, diluted with EtOAc (40 mL), washed with saturated aqueous ammonium chloride solution (4 mL), brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. It was then subjected to column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to yield pure compound **26** (146 mg, 75%) as a colorless oil; R_f = 0.3 (SiO_2, 15% EtOAc/hexane). $[\alpha]_D^{30} = -15.1$ (*c* 2.55, $CHCl_3$). IR (Neat): ν_{max} = 3384, 2956, 2928, 2856, 1727, 1506, 1458, 1383, 1337, 1252, 1208, 1093, 1067 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5H), 5.30 (d, *J* = 7.5 Hz, 1H), 5.07 (Abq, *J* = 12.3 Hz, 2H), 4.88 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.32 (p, *J* = 7.1 Hz, 1H), 3.52 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.33 (dd, *J* = 9.8, 6.5 Hz, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.43 (d, *J* = 7.5 Hz, 3H), 1.35–1.21 (m, 9H), 1.08 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90–0.85 (m, 15H), 0.05 (s, 3H), 0.01 (s, 3H) ppm.^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 155.4, 136.3, 128.4, 127.9, 78.7, 66.6, 64.4, 49.7, 37.3, 33.9, 33.8, 31.7, 29.3, 26.9, 25.8, 22.5, 18.9, 18.2, 13.9, 13.9, 13.3, −5.6 ppm. MS (ESI): *m*/*z* = 544 $[M+Na]^+$; HRMS (ESI): calcd for $C_{29}H_{51}NO_5NaSi$ $[M+Na]^+$ 544.3434; found 544.3440.

4.1.13. (*S*)-((2*S*,3*R*,4*S*)-1-Hydroxy-2,4-dimethyldecan-3-yl)2-(benzyloxycarbonylamino)propanoate 27

A solution of compound **26** (135 mg, 0.25 mmol) in CH_2Cl_2/MeOH (1:1, 3 mL) was treated with CSA (60 mg, 0.25 mmol) at 0 °C. After being stirred for 30 min at the same temperature, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL), extracted with EtOAc (2 × 10 mL), washed with water (2 mL), brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography using silica gel (60–120 mesh 25–30% EtOAc/hexane) to give pure compound **27** (89 mg, 85%) as a colorless oil; R_f = 0.3 (SiO_2, 40% EtOAc/hexane). $[\alpha]_D^{30} = -17.9$ (*c* 0.39, $CHCl_3$). IR (KBr): ν_{max} = 3512, 2957, 2928, 2857, 1465, 1386, 1254, 1077, 837, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5H), 5.25 (d, *J* = 6.8 Hz, 1H), 5.08 (s, 2H), 4.88 (dd, *J* = 10.5, 2.2 Hz, 1H), 4.33 (d, *J* = 7.0 Hz, 1H), 3.51 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.41 (dd, *J* = 11.8, 3.0 Hz, 1H), 1.88–1.67 (m, 2H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.35–1.81 (m, 10H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93–0.85 (m, 6H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 155.7, 136.1, 128.5, 128.1, 128.0, 78.6, 66.9, 64.1, 49.9, 36.8, 34.1, 33.6, 31.7, 29.3, 27.0, 22.5, 18.4, 14.0, 13.9, 12.9 ppm. MS (ESI): *m*/*z* = 430 $[M+Na]^+$. HRMS (ESI): calcd for $C_{23}H_{37}NO_5Na$ $[M+Na]^+$ 430.2569, found 430.2574.

4.1.14. (*S*)-((2*R*,3*R*,4*S*)-1-(2-*tert*-Butoxy-2-oxoethylamino)-2,4-dimethyl-1-oxohexan-3-yl)2-(benzyloxycarbonylamino) propanoate (9)

To a solution of compound **27** (132 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (1.8 mL) was added with stirring, DMSO (2 mL), Et_3N (0.2 mL, 1.62 mmol), and SO_3–Py complex (258 mg, 1.62 mmol) portionwise at 0 °C under a nitrogen atmosphere. It was then allowed to run for 1 h at room temperature, after which the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (5 mL), water (5 mL), brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. The aldehyde thus obtained was purified by column chromatography and used directly for the next reaction.

To a solution of crude aldehyde in ^{t}BuOH/2-methyl-2-butene (2:1, 3 mL) at room temperature, $NaClO_2$ (88 mg, 0.927 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (144 mg, 0.927 mmol), dissolved in the minimum amount of H_2O, were added. After being stirred for 1 h at room temperature it was quenched with 1 M HCl at 0 °C (up to pH 1), the solvent was removed in a rotary evaporator and the residue was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the carboxylic acid as a colorless liquid. The acid thus obtained was used directly for the peptide coupling reaction.

To a solution of crude acid (136 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) at 0 °C, HOBt (65 mg, 0.48 mmol), followed by EDCI (92 mg, 0.48 mmol) were added and stirred for 10 min. Then at the same temperature, compound $NH_2Gly\text{-}O^tBu$ (59 mg, 0.45 mmol) was added followed by DIPEA (0.17 mL, 0.97 mmol). The reaction was monitored via TLC and after completion of the reaction it was quenched with saturated NH_4Cl. Then the crude mixture was extracted with EtOAc (50 mL), washed with 1 M HCl (4 mL), $NaHCO_3$ (4 mL), H_2O (2 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude mass was subjected to column chromatography (SiO_2, 25% EtOAc in petroleum ether eluant) to provide **9** (155 mg, 90%, over three steps) as a colorless oil; R_f = 0.3 (SiO_2, 40% EtOAc/hexane). $[\alpha]_D^{30} = -4.0$ (*c* 2.75 $CHCl_3$). IR (Neat): ν_{max} = 3317, 2925, 2657, 2361, 1726, 1630, 1384, 1217, 1156 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5H), 6.11 (t, *J* = 5.2 Hz, 1H), 5.70 (d, *J* = 7.5 Hz, 1H), 5.15–5.05 (m, 3H), 4.42 (dd, *J* = 15.1, 7.5 Hz, 1H), 3.94 (dd, *J* = 18.1, 5.2 Hz, 1H), 3.78 (dd, *J* = 18.1, 5.2 Hz, 1H), 2.85 (dt, *J* = 15.1, 6.8 Hz, 1H), 1.83–1.61 (m, 3H), 1.52–1.39 (m, 12H), 1.35–1.19 (m, 8H), 1.31 (d, *J* = 7.5 Hz, 3H), 0.91–0.81 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 171.9, 169.3, 155.7, 136.4, 128.3, 127.9, 127.8, 82.1, 78.4, 66.5, 49.7, 43.3, 41.8, 34.1, 33.4, 31.6, 29.2, 27.8, 26.8, 22.5, 18.2, 14.5, 13.9, 13.2 ppm. MS (ESI): *m*/*z* = 557 $[M+Na]^+$. HRMS (ESI): calcd for $C_{29}H_{46}N_2O_7Na$ $[M+Na]^+$ 557.3202, found 557.3197.

4.1.15. (6*S*,9*S*,12*S*,15*S*)-((2*R*,3*R*,4*S*)-1-(2-*tert*-Butoxy-2-oxoethyl amino)-2,4-dimethyl-1-oxohexan-3-yl)-9-isobutyl-6-isopropyl-2,2,12,15-tetramethyl-4,7,10,13-tetraoxo-3-oxa-5,8,11,14-tetra-azahexadecan-16-oate 28

Compound **9** (134 mg, 0.25 mmol) was dissolved in EtOAc (5 mL), after which 1 M HCl (0.5 mL), and Pd/C (10%) (100 mg) were added and subjected to hydrogenation under atmospheric pressure using H_2-filled balloon. After 10 min, the reaction mixture was filtered through a short pad of Celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated in vacuo to give a crude amine salt, which was used in the next step for peptide coupling. To a stirred solution of BocVal-Leu-Ala-OH (301 mg, 0.75 mmol) in dry CH_2Cl_2:DMF (1:1) (5 mL) at 0 °C, HOBt (152 mg, 1.12 mmol), followed by EDCI (214 mg, 1.12 mmol) were added and stirred for 10 min. At the same temperature the amine prepared above was added to the reaction mixture followed by DIPEA (0.4 mL, 2.2 mmol). The reaction was monitored via TLC and after completion of the reaction, it was quenched with saturated NH_4Cl. The crude mixture was then extracted with EtOAc (50 mL), washed with 1 M HCl (4 mL), $NaHCO_3$ (4 mL), H_2O (5 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography (SiO_2, 60% EtOAc /hexane) to yield **28** (147 mg, 75%) as a colorless liquid; R_f = 0.3 (SiO_2, 80% EtOAc/hexane). $[\alpha]_D^{30} = -33.4$ (*c* 3.05, $CHCl_3$). IR (Neat): ν_{max} = 3280, 3079, 2961, 2928, 2857, 1742, 1638, 1544, 1456, 1369, 1216, 1162 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.70 (t, *J* = 5.2 Hz, 1H), 6.42 (d, *J* = 6.9 Hz, 1H), 5.09 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.98 (d, *J* = 5.4 Hz, 1H), 4.60 (m, 1H), 4.46 (m, 1H), 4.35 (m, 1H), 4.01 (dd, *J* = 18.0, 6.9 Hz, 1H), 3.87 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.81 (t, *J* = 5.7 Hz, 1H), 2.73 (m, 1H), 2.16 (m, 1H), 2.02 (m, 1H), 1.77–1.62 (m, 12H), 1.49–1.37 (m, 21H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.01–0.83 (m, 21H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 172.1, 171.1, 171.7, 171.4, 169.4, 156.2, 81.6, 80.1, 78.6, 60.6, 52.0, 48.7, 48.0, 43.1, 41.7, 40.9, 33.9, 33.5, 31.7, 30.6, 29.2, 28.2, 27.9, 27.0, 24.7, 22.9, 22.5, 21.7, 19.1, 18.2, 18.1, 17.8, 14.1, 13.9, 12.9 ppm. MS (ESI): *m*/*z* = 806 $[M+Na]^+$. HRMS (ESI): calcd for $C_{40}H_{73}N_5O_{10}Na$ $[M+Na]^+$ 806.5255, found 806.5250.

4.1.16. Emericellamide A 1

To a stirred solution of **28** (78 mg, 0.099 mmol) in dry CH_2Cl_2 (4 mL) was added TFA (2 mL) at 0 °C and stirred for 1 h. After the reaction mixture was diluted with CH_2Cl_2 and concentrated in vacuo, it was azeotroped 3 times with dry CH_2Cl_2 and this crude mass was subjected to macrolactamization without further characterization.

To a stirred solution of the above crude mass in dry CH_3CN (100 mL, 10^{-3} M) were added FDPP (114 mg, 0.29 mmol) followed by DIPEA (0.03 mL, 0.19 mmol) at 0 °C. Then it was stirred for 72 h at room temperature. The solvent was concentrated in a rotary evaporator to give a crude mass as a white solid. The crude mass was dissolved in a minimum amount of methanol and then poured in large excess dry ether to precipitate out the product. The precipitate was filtered, washed with CH_3CN, dried to give emericellamide A **1** (45.5 mg, 75%) as a white solid. $[\alpha]_D^{30} = -43.0$ (*c* 0.2, MeOH) {literature[2a] $[\alpha]_D^{30} = -43.0$ (*c* 0.23, MeOH)}. IR (Neat): ν_{max} = 3401, 3317, 3067, 2962, 2929, 2858, 1755, 1635, 1549, 1458, 1380, 1326, 1285, 1239, 1169, 1064 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.10 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 3.3 Hz, 1H) 7.98 (d, *J* = 8.2 Hz, 1H), 7.47 (dd, *J* = 5.5, 2.7 Hz, 1H), 7.39 (d, *J* = 6.6 Hz, 1H), 4.92 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.31 (dd, *J* = 17.0, 5.5 Hz, 1H), 4.10–4.01 (m, 3H), 3.98 (dd, *J* = 8.2, 8.2 Hz, 1H), 3.62 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.86 (dq, *J* = 10.0, 7.1 Hz, 1H), 1.89 (m, 1H), 1.67 (m, 1H), 1.60–1.53 (m, 3H), 1.24 (d, *J* = 7.1 Hz, 3H) 1.22 (d, *J* = 7.1 Hz, 3H), 1.28–1.16 (m, 8H), 1.10 (m,1H), 1.02 (m,1H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.0 Hz, 3H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 172.9, 171.4, 171.3, 171.2, 170.8, 168.7, 76.6, 60.1, 51.7, 48.2, 47.3, 42.5, 41.0, 40.8, 33.5, 33.25, 31.2, 30.2, 28.9, 26.6, 24.5, 23.2, 22.1, 20.7, 19.1, 18.8, 18.3, 16.3, 14.3, 14.0, 12.9 ppm. MS (ESI): *m*/*z* = 632 $[M+Na]^+$; HRMS (ESI): calcd for $C_{31}H_{55}N_5O_7Na$ $[M+Na]^+$ 632.3999; found 632.3996.

^1H NMR data of natural emericellamide A: (500 MHz, DMSO-d_6): δ = 8.08 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 3.5 Hz, 1H) 7.93 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 5.5, 2.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 4.92 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.30 (dd, *J* = 17.5, 5.5 Hz, 1H), 4.01 (m, 1H), 4.07 (m, 1H), 4.05 (m, 1H), 3.97 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.61 (dd, *J* = 17.5, 2.5 Hz, 1H), 2.85 (dq, *J* = 10.0, 7.0 Hz, 1H), 1.88 (m, 1H), 1.66 (m, 1H), 1.55 (m, 3H), 1.24 (d, *J* = 7.5 Hz, 3H) 1.21 (d, *J* = 7.5 Hz, 3H), 1.22–1.10 (m, 10H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR data of natural emericellamide A (125 MHz, DMSO-d_6): δ = 172.6, 171.1, 171.0, 170.9, 170.5, 168.4, 76.3, 59.8, 51.5, 47.9, 47.0, 42.1, 39.1, 40.8, 33.2, 32.9, 30.9, 29.9, 28.6, 26.3, 24.2, 22.9, 21.8, 20.4, 18.7, 18.5, 18.0, 16.0, 14.0, 13.7, 12.7 ppm. MS (ESI): *m*/*z* = 632 $[M+Na]^+$; HRMS (ESI): calcd for $C_{31}H_{55}N_5O_7Na$ $[M+Na]^+$ 632.3999; found 632.3996.

4.1.17. (2*S*,3*R*,4*S*,6*S*)-3-(4-Methoxybenzyloxy)-2,4,6-trimethyl dodecan-1-ol 30

To a solution of **24** (364 mg, 1.0 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C, a solution of DIBAL-H (2.8 mL, 1.4 M in toluene, 4 mmol) was added dropwise and stirred at that temperature for 30 min. The reaction was then quenched by the slow addition of a few drops dry MeOH followed by saturated aqueous potassium–sodium tartrate solution. The reaction mixture was stirred (~2 h) until two clear layers became separated. The aqueous layer was extracted with EtOAc (30 mL) and washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography on silica gel (60–120 mesh 10% EtOAc/hexane) to afford pure compound **30** (355 mg, 97%) as a colorless liquid; R_f = 0.20 (SiO_2, 20% EtOAc/hexane). $[\alpha]_D^{24} = +1.9$ (*c* 0.53, $CHCl_3$). IR

(Neat): ν_{max} = 3459, 2956, 2923, 2855, 1513, 1461, 1248, 1068, 1037 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.58 (d, J = 10.7 Hz, 1H), 4.49 (d, J = 10.7 Hz, 1H), 3.80 (s, 3H), 3.67–3.58 (m, 2H), 3.24 (dd, J = 7.6, 3.2 Hz, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 1.68–1.48 (m, 2H), 1.44 (p, J = 6.7 Hz, 1H), 1.36–1.18 (m, 9H), 1.16–1.01 (m, 2H), 0.94 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.1 Hz, 3H), 0.90–0.85 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 130.6, 129.4, 113.8, 87.8, 74.8, 66.7, 55.2, 42.3, 37.7, 36.6, 33.2, 31.9, 30.1, 29.7, 26.8, 22.7, 20.4, 15.5, 14.8, 14.1 ppm. MS (ESI): m/z = 387 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{40}O_3Na$ $[M+Na]^+$ = 387.2875, found 387.2891.

4.1.18. 1-Methoxy-4-(((3*S*,4*R*,5*S*,7*S*)-3,5,7-Trimethyltridec-1-en-4-yloxy) methyl) benzene 31

Solid TPAP (tetra propyl ammoniumperruthenate) (14 mg, 5 mol %) was added in one portion to alcohol **30** (295 mg, 0.81 mmol), NMO (284 mg, 2.43 mmol), and activated 4 Å MS (100 mg) in CH_2Cl_2 (4 mL) at room temperature under a nitrogen atmosphere. After being stirred for 10 min, the reaction mixture was filtered through a small bed of Celite and the filter cake was washed with EtOAc (20 mL). The combined organic layers were then washed sequentially with water (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude aldehyde without purification and characterization was taken forward for the next reaction.

Potassium *tert*-butoxide (727 mg, 6.48 mmol) was added to a suspension of methyltriphenylphosphonium iodide (3.27 g, 8.1 mmol) in dry ether (20 mL) at 0 °C. The mixture was then stirred at room temperature for 30 min. The resulting methylenetriphenylphosphorane was added to a solution of aldehyde in ether (5 mL) at 0 °C. After 0.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL). The organic layer was separated, washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography on silica gel (60–120 mesh 5% EtOAc/hexane) afforded pure compound **31** (233 mg, 80%) as colorless liquid; R_f = 0.60 (SiO_2, 5% EtOAc/hexane). $[\alpha]_D^{25} = +2.2$ (c 1.58, $CHCl_3$). IR (Neat): ν_{max} = 2956, 2923, 2854, 1513, 1460, 1247, 1070, 1093, 819 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.3 Hz, 1H), 5.76 (ddd, J = 17.6, 10.3, 7.9 Hz, 1H), 5.09–4.93 (m, 2H), 4.53 (d, J = 10.7 Hz, 1H), 4.43 (d, J = 10.7 Hz, 1H), 3.79 (s, 3H), 3.03 (dd, J = 6.3, 4.3 Hz, 1H), 2.48 (q, J = 7.6 Hz, 1H), 1.78 (m, 1H), 1.49 (m, 1H), 1.39 (p, J = 6.8 Hz, 1H), 1.34–1.15 (m, 11H), 1.02 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 142.0, 131.4, 129.1, 114.0, 113.6, 86.4, 74.3, 55.2, 41.9, 41.0, 36.4, 32.9, 31.9, 29.9, 29.7, 26.7, 22.6, 20.3, 17.5, 14.9, 14.1 ppm. MS (ESI): m/z = 383 $[M+Na]^+$; HRMS (ESI): calcd for $C_{24}H_{40}O_2Na$ $[M+Na]^+$ 383.2926, found 383.2935.

4.1.19. (3*S*,4*R*,5*S*,7*S*)-3,5,7-Trimethyltridec-1-en-4-ol 32

To a solution of **31** (100 mg, 0.27 mmol) in $CHCl_3$:H_2O (20:1, 5 mL) was added DDQ (92 mg, 0.401 mmol) at 0 °C. The reaction was continued for 30 min and quenched with saturated $NaHCO_3$ solution (5 mL), after which it was extracted with CH_2Cl_2 (50 mL), washed with brine (2 mL), and dried over anhydrous Na_2SO_4. The organic extract was then concentrated in vacuo and purified by column chromatography on silica gel (100–200 mesh 2% EtOAc/hexane) to give pure compound **32** (61 mg, 92%); R_f = 0.30 (SiO_2, 5% EtOAc /hexane). $[\alpha]_D^{24} = +4.7$ (c 0.83, $CHCl_3$). IR (Neat): ν_{max} = 3453, 2923, 2854, 1729, 1657, 1515, 1281, 1127, 1074 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.73 (m, 1H), 5.18–5.08 (m, 2H), 3.17 (dd, J = 8.1, 2.6 Hz, 1H), 2.28 (m, 1H), 1.74 (m, 1H), 1.48 (br s, 1H), 1.43 (m, 1H), 1.38–1.18 (m, 10H), 1.05 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90–0.84 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.6, 116.3, 76.4, 42.4, 41.8, 36.8, 31.9, 31.4, 29.8, 29.6, 26.8, 22.6, 20.1, 16.6, 14.1, 13.1 ppm. MS (ESI): m/z = 263 $[M+Na]^+$; calcd for $C_{16}H_{32}ONa$ $[M+Na]^+$ 263.2453, found 263.2456.

4.1.20. (*S*)-((3*S*,4*R*,5*S*,7*S*)-3,5,7-Trimethyltridec-1-en-4-yl)2-(benzyloxy carbonylamino)propanoate 33

Acylation of **32** (50 mg, 0.20 m mol) was carried out with CbzAlaOH to give **33** (62 mg, 80%) by using the same procedure as used for the preparation of **26** from **12**. $[\alpha]_D^{30} = +2.8$ (c 1.0, $CHCl_3$). IR (Neat): ν_{max} = 2925, 2855, 1740, 1708, 1695, 1648, 1546, 1531, 1515, 1462, 1395 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5H), 5.62 (m, 1H), 5.31 (d, J = 7.9 Hz, 1H), 5.08 (dd, J = 14.2, 12.4 Hz, 2H), 4.98 (dd, J = 17.1, 1.7 Hz, 1H), 4.95 (dd, J = 10.0, 1.2 Hz, 1H), 4.75 (dd, J = 8.0, 3.9 Hz, 1H), 4.37–4.25 (m, 2H), 2.44 (m, 1H), 1.87 (m, 1H), 1.72–1.46 (m, 3H), 1.42 (d, J = 7.1 Hz, 3H), 1.36–1.14 (m, 10H), 0.99 (d, J = 6.8 Hz, 3H), 0.92–0.81 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 155.4, 140.1, 139.8, 136.3, 128.5, 128.1, 128.0, 115.5, 79.9, 66.7, 49.8, 41.2, 40.4, 36.6, 31.8, 31.0, 29.6, 29.4, 26.7, 22.6, 20.1, 19.1, 17.0, 14.1 ppm. MS (ESI): m/z = 468 $[M+Na]^+$; HRMS (ESI): calcd for $C_{27}H_{43}NO_4Na$ $[M+Na]^+$ 468.3089, found 468.3073.

4.1.21. (*S*)-((2*R*,3*R*,4*S*,6*S*)-1-(2-*tert*-Butoxy-2-oxoethylamino)-2,4,6-trimethyl-1-oxododecan-3-yl)2-(benzyloxycarbonyl amino)propanoate 10

To a stirred solution of the olefinic compound **33** (50 mg, 0.128 mmol) in dioxane:water (1:1, 2 mL), OsO_4 (catalytic), NMO (10.9 mg, 0.09 mmol) and methanesulfonamide (5 mg, 0.07 mmol) were added at 0 °C. The temperature of the reaction mixture was raised to room temperature and stirred for 4 h. After removing the solvent in vacuo, the residue was extracted with EtOAc (10 mL), washed with saturated aqueous Na_2SO_3 (5 mL), water (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–40% EtOAc in hexane eluant) afforded a pure compound as a gummy liquid, which was used directly for the next step without any characterization.

The diol compound was treated with $NaIO_4$ (18 mg, 0.22 mmol) in THF:H_2O (1:1) at 0 °C for 30 min. After completion of the reaction it was quenched with $NaHCO_3$ (5 mL) and extracted with EtOAc (20 mL), washed with saturated aqueous water (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo.

To a solution of the crude aldehyde in ^{t}BuOH/2-methyl-2-butene (2:1, 3 mL) at room temperature, $NaClO_2$ (20 mg, 0.22 mmol) and $NaH_2PO_4.2H_2O$ (34 mg, 0.22 mmol), dissolved in the minimum amount of H_2O, were added. After being stirred for 1 h at room temperature, the reaction mixture was quenched with 1 M HCl at 0 °C (up to pH 1), the solvent was removed on a rotary evaporator, and the residue was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts washed with brine (3 mL), dried (Na_2SO_4), and concentrated in vacuo afforded a crude acid. The acid thus obtained was directly used for the peptide coupling reaction.

To a solution of crude acid (0.07 mmol) in CH_2Cl_2 (5 mL) at 0 °C, HOBt (15 mg, 0.11 mmol), followed by EDCI (21 mg, 0.11 mmol) were added and stirred for 10 min. At the same temperature, compound NH_2Gly-O^{t}Bu (70 mg, 0.53 mmol) was added followed by DIPEA (0.01 mL, 0.22 mmol). The reaction was monitored by TLC and after completion of the reaction, it was quenched with saturated NH_4Cl, and extracted with EtOAc (1 × 50 mL), washed with 1 M HCl (4 mL), $NaHCO_3$ (4 mL), H_2O (2 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography on silica gel (60–120 mesh 25% EtOAc/hexane) to give **10** (46 mg, 70%); R_f = 0.5 (SiO_2, 50% EtOAc /hexane). $[\alpha]_D^{25} = -7.1$ (c 1.2 $CHCl_3$). IR (Neat): ν_{max} = 3330, 2925, 2855, 1728, 1660, 1530, 1457, 1372, 1338, 1219, 1158, 1062 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$):

δ = 7.34–7.31 (m, 5H), 6.04 (t, J = 5.0 Hz, 1H), 5.64 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 5.3 Hz, 1H), 5.04 (dd, J = 8.5, 3.5 Hz, 1H), 4.38 (m, 1H), 3.90 (dd, J = 18.4, 5.2 Hz, 1H), 3.75 (dd, J = 18.4, 4.8 Hz, 1H), 2.55 (m, 1H), 1.87 (m, 1H), 1.76–1.40 (m, 11H), 1.42 (d, J = 7.5 Hz, 3H), 1.34–1.17 (m, 10H), 1.13 (d, J = 7.2 Hz, 3H), 0.93 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 171.9, 169.4, 155.7, 136.4, 128.5, 128.1, 128.0, 82.3, 77.9, 66.6, 49.8, 43.5, 41.9, 41.1, 36.6, 31.9, 31.2, 29.6, 29.4, 27.9, 26.7, 22.6, 20.0, 18.5, 14.5, 14.1, 13.7 ppm. MS (ESI): m/z = 599 $[M+Na]^+$; HRMS (ESI): calcd for $C_{32}H_{52}N_2O_7Na$ $[M+Na]^+$ 599.3672, found 599.3662.

4.1.22. (6*S*,9*S*,12*S*,15*S*)-((2*R*,3*R*,4*S*,6*S*)-1-(2-*tert*-Butoxy-2-oxoe thylamino)-2,4,6-trimethyl-1-oxododecan-3-yl) 9-isobutyl-6-isopropyl-2,2,12,15-tetramethyl-4,7,10,13-tetraoxo-3-oxa-5,8,11,14-tetraazahexadecan-16-oate 34

Compound **10** (35 mg, 0.067 m mol) was coupled with the tripeptide **11** to give **34** (41 mg, 75%) under the same conditions as used for the preparation of compound **28**; $[\alpha]_D^{25} = -26.7$ (c 0.45, $CHCl_3$). IR (Neat): ν_{max} = 3620, 3281, 2925, 2856, 1741, 1635, 1531, 1460, 1367, 1163, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, J = 7.7 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.67 (t, J = 5.4 Hz, 1H), 6.45 (d, J = 6.1 Hz, 1H), 5.06 (dd, J = 9.3, 2.5 Hz, 1H), 5.00 (d, J = 5.8 Hz, 1H), 4.59 (p, J = 7.3 Hz, 1H), 4.46 (p, J = 7.2 Hz, 1H), 4.36 (m, 1H), 4.00 (dd, J = 18.0, 5.2 Hz, 1H), 3.91–3.74 (m, 2H), 2.70 (m, 1H), 2.12 (m, 1H), 1.87 (dq, J = 2.4, 7.1 Hz, 1H), 1.77–1.50 (m, 6H), 1.44 (s, 9H), 1.43 (s, 9H), 1.40 (d, J = 7.3 Hz, 3H), 1.37 (d, 7.2 Hz, 3H), 1.31–1.17 (m, 10H), 1.31 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.4 Hz, 6H), 0.91 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 174.1, 173.3, 171.7, 171.6, 171.0, 169.7, 81.8, 81.0, 78.1, 54.1, 52.7, 49.1, 48.0, 43.2, 41.8, 41.2, 40.5, 36.6, 31.9, 31.0, 29.6, 29.4, 28.2, 28.0, 26.6, 24.9, 24.8, 23.0, 22.8, 22.6, 21.8, 21.6, 20.0, 17.7, 17.4, 14.2, 14.0, 13.4 ppm. MS (ESI): m/z = 848 $[M+Na]^+$; HRMS (ESI): calcd for $C_{43}H_{79}N_5O_{10}Na$ $[M+Na]^+$ 848.3672, found 848.3668.

4.1.23. Emericellamide B 2

Compound **34** (25 mg, 0.03 mmol) was cyclized under similar conditions as used for the cyclization of **28** to give emericellamide B **2** (15 mg, 80%). $[\alpha]_D^{30} = -34.1$ (c 0.12, MeOH), literature[2a] $[\alpha]_D^{30} = -34.0$ (c 0.76, MeOH). IR (Neat): ν_{max} = 3653, 3622, 3388, 3364, 3286, 2922, 2852, 1730, 1650, 1536, 1462, 1375, 1282, 1126, 1076 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.04 (br s, 1H), 7.90 (d, J = 8.9 Hz, 1H), 7.70 (br s, 1H), 7.53 (br s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.31 (dd, J = 17.3, 5.5 Hz, 1H), 4.09–3.96 (m, 4H), 3.62 (dd, J = 17.3, 3.0 Hz, 1H), 2.88 (dq, J = 10.0, 6.8 Hz, 1H), 1.86 (m, 1H), 1.81 (m, 1H), 1.62–1.50 (m, 4H), 1.24 (d, J = 7.5 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.20–1.06 (m, 10H), 1.03 (m, 1H), 0.91–0.89 (m, 6H), 0.88 (d, J = 7.1 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.2 Hz, 3H), 0.82 (d, J = 6.0 Hz, 3H), 0.79 (m, 1H), 0.79 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 172.9, 171.3, 171.2, 171.0, 170.7, 168.7, 75.7, 59.9, 51.6, 48.1, 47.2, 40.9, 40.7, 40.1, 39.6, 36.8, 31.3, 30.1, 30.0, 28.9, 28.6, 26.1, 24.5, 23.2, 22.0, 20.6, 19.4, 18.9, 18.7, 18.3, 16.3, 14.3, 13.9, 13.6 ppm. MS (ESI): m/z = 674 $[M+Na]^+$; HRMS (ESI): calcd for $C_{34}H_{61}N_5O_7Na$ $[M+Na]^+$ 674.4468, found 674.4466. ^{1}H NMR data of natural emericellamide B (500 MHz, DMSO-d_6): δ = 8.53 (d, J = 8.0 Hz, 1H), 8.51 (d, J = 8.5 Hz, 1H) 8.07 (d, J = 3.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.35 (dd, J = 5.5, 2.5 Hz, 1H), 4.92 (dd, J = 10.0, 2.0 Hz, 1H), 4.25 (dd, J = 17.5, 5.5 Hz, 1H), 4.05 (m, 1H), 4.03 (m, 1H),, 3.97 (dd, 8.5, 7.5 Hz, 1H),3.96 (m, 1H),, 3.60 (dd, J = 17.5, 2.5 Hz, 1H), 2.85 (dq, J = 10.0, 7.0 Hz, 1H), 1.92 (m, 1H), 1.81 (m, 1H), 1.53–1.55 (m, 4H), 1.24 (d, J = 7.5 Hz, 3H), 1.20 (d, J = 7.5 Hz, 3H), 1.24–1.01 (m, 11H), 0.90 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H), 0.82 (d, J = 6.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.79 (m, 1H), 0.79 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR data of natural emericellamide B (75 MHz, DMSO-d_6): δ = 172.7, 171.3, 171.3, 171.2, 171.0, 168.6, 75.7, 60.3, 51.7, 48.2, 47.0, 41.1, 40.7, 40.0, 39.6, 36.8, 31.3, 30.1, 30.1, 29.0, 28.7, 26.1, 24.4, 23.2, 22.0, 20.7, 19.4, 19.0, 18.8, 18.4, 16.3, 14.2, 13.9, 13.5 ppm.

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