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Total synthesis of emericellamides A and B

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ABSTRACT

The total synthesis of emericellamides A and B is reported. A convergent, flexible strategy employing peptide chemistry, asymmetric alkylations, and culminating in macrolactamization is described. The previously reported structure of both compounds is confirmed.

1. Introduction

Marine organisms have provided chemists with a wealth of structurally diverse compounds over recent years, and many of these compounds have shown considerable biological activities.[1] To date, antimicrobial, antiviral, antitumor, and anti-inflammatory action has been identified amongst this range of secondary metabolites. Some of these compounds are in advanced clinical trials, and others have proven useful in studies directed toward the elucidation of biochemical pathways.[1,2] The structures vary from cyclopeptides to cyclodepsipeptides that embody both polypeptide and polyketide domains displaying conformational flexibility.[3] This combination of unusual structures and promising biological activity makes these compounds an attractive target for synthetic and medicinal chemists alike. We have been interested for some time in marine cyclopeptides and cyclodepsipeptides,[4] and view their syntheses as a key route to structural modification and subsequent activity control. Here we report on our efforts in the total synthesis of emericellamides A and B.[5]

2. Results and discussion

Emericellamides A and B were isolated from marine-derived fungus *Emericella* sp. with the proposed stereochemistry as shown in Scheme 1 (**1**, **2**).[6] Structurally, the emericellamides (Scheme 1, **1**, **2**) contain two main portions: a pentapeptide and an adjoining di- or trimethyl hydroxy acid. The absolute configurations of the amino acids, and those of the stereogenic centers on the side chain, were established by application of the Marfey's method, by *J*-based configuration analysis, and by application of the modified Mosher method. There was also considerable reliance on NOE data for the configurations on the side chain. Emericellamides A and B showed antibacterial activities against methicillin-resistant *Staphylococcus aureus* with MIC values of 3.8 and 6.0 μM, respectively.

It can be seen from the retrosynthetic analysis that there are a number of possible positions to close the macrocyclic portion of the molecule (Scheme 1). We chose to close the cyclodepsipeptide via macrolactamization between the two alanine residues because it allowed versatility in the construction of the cyclization precursor (**3**, **4a**), in terms of the β-hydroxy acid portion of the molecule. Disconnection at this point gives a polyketide fragment (**6**, **7a**), which can be prepared from the substituted alcohol (**10a**, **11a**). It was envisaged that the peptide couplings would be carried out under standard conditions, which left the disconnection of the acid. There are two target emericellamides and so a versatile approach to each, allowing modification of the acid chain, was sought (**10a**, **11a**). The desired stereochemistry was to be obtained using a combination of alkylations following Evans' protocol[7] and asymmetric crotylations[8] carried out with enantiopure diisopinocampheylborane derived reagents.

Given the small sample available to Fenical and the difficulty in unequivocally interpreting NOE data for side-chains due to possible modes of folding, we took the view that the correct structure for **2** could possibly have been the C-25 epimer, instead of that published. With this in mind, it was decided to make both enantiomers of key alcohols **10a**, **10b** to ensure that both C-25 epimers could be made, as well as the reported structure of emericellamide A.

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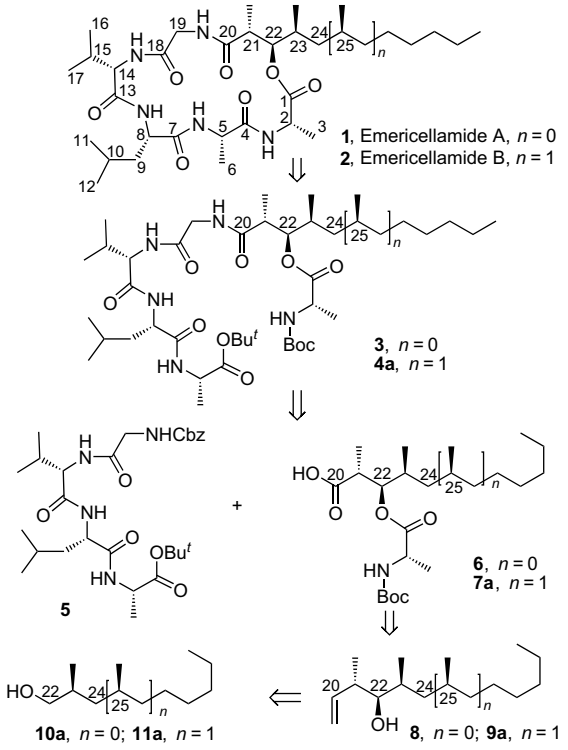
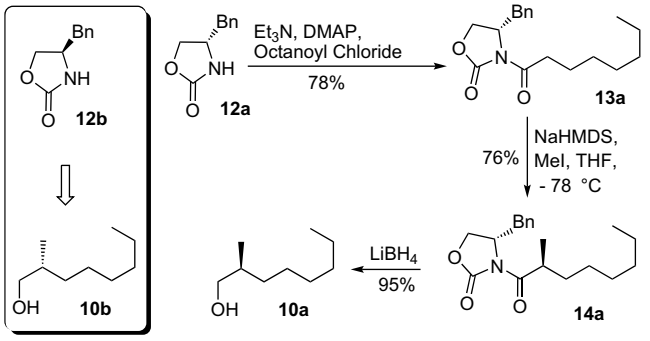


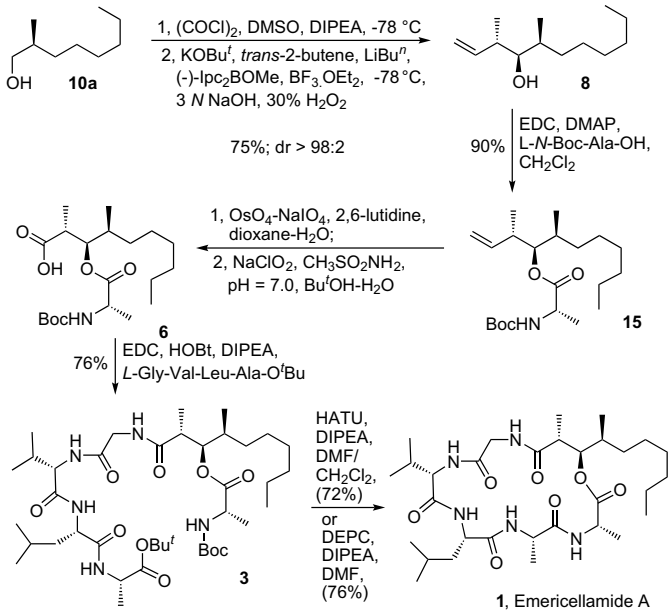
Scheme 1. Retrosynthetic analysis of emericellamides.

The synthesis commenced with formation of both enantiomers of *N*-octanoyl-4-benzyloxazolidinone using standard procedures. Starting from (*S*)-4-benzyloxazolidinone (**12a**), this afforded **13a** in 78%, which was then treated with NaHMDS and methyl iodide in THF at −78 °C to give the alkylated product **14a**[9] in 76% yield as a single diastereoisomer. Reductive cleavage of the chiral auxiliary using $LiBH_4$ gave an almost quantitative yield of substituted alcohol **10a**,[10] which was a precursor to the substituted acid portion of both emericellamide A and B. Alcohol **10b** was prepared from (*R*)-4-benzyloxazolidinone (**12b**) in a similar reaction sequence for the preparation of the C-25 epimer of emericellamide B (Scheme 2).

Focusing on emericellamide A, a Swern oxidation of alcohol **10a**, using Hunig's base to minimize the chance of racemization, gave the corresponding aldehyde in excellent yield. This was then reacted with (−)-*B*-*E*-crotyl diisopinocampheylborane to give the desired homoallylic alcohol **8** in a good yield and with 98:2 diastereomeric ratio. The alcohol **8** was coupled with L-*N*-Boc-Ala-OH in the presence of EDC and DMAP in DCM to give the ester **15**



Scheme 2. Synthesis of intermediates **10a** and **10b**.



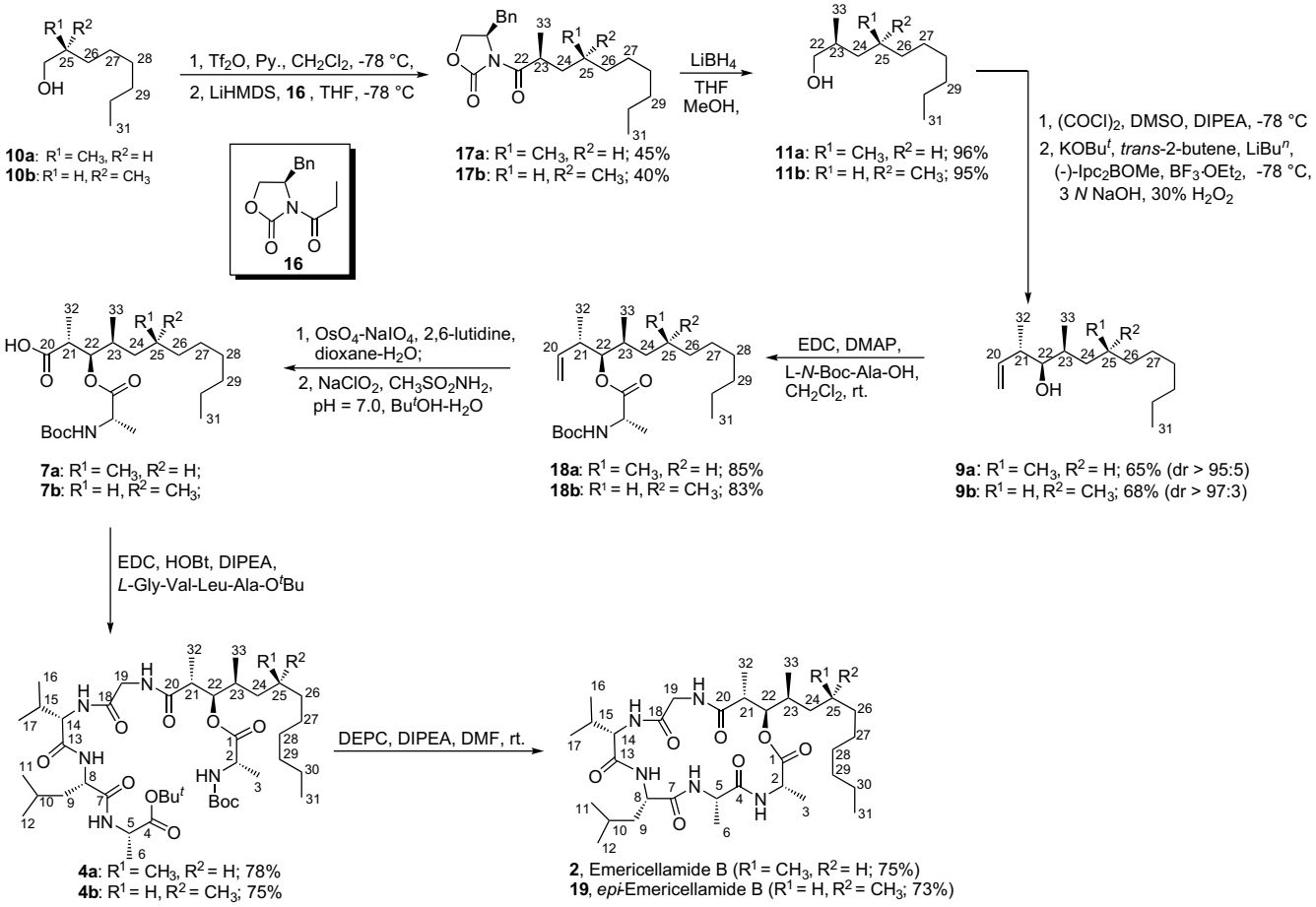
Scheme 3. Synthesis of emericellamide A.

in 76% yield. Oxidative cleavage of the olefin of **15** using OsO_4–$NaIO_4$ in the presence of 2,6-lutidine,[11] followed by Pinnick oxidation[12] afforded the carboxylic acid **6**, which was then activated and coupled with L-Gly-L-Val-L-Leu-L-Ala-O^{t}Bu, to give **3** in 76% yield over the three steps. Simultaneous removal of both Boc and *tert*-butyl protecting groups using TFA in dichloromethane, followed by macrolactamization promoted with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl-uronium hexafluorophosphate (HATU)[13] or diethyl cyanophosphonate (DEPC),[14] gave emericellamide A (**1**) in 72% and 76% yield, respectively (Scheme 3).

The characterization data obtained for compound **1** agreed satisfactorily with that of the natural product, thus confirming its structure. In terms of specific optical rotation, we obtained a value of −39 (*c* 0.28, MeOH) compared to a literature value of −43 (*c* 0.23, MeOH).[6] This result confirmed the stereochemistry of the 3-hydroxy-2,4-dimethyldecanoic acid (HDMD) portion within emericellamide A. The HDMD fragment is known to appear in another natural product, LL-15G256γ, but has been reported with the opposite absolute configuration.[15] Given the common source of each of our target molecules, it was strongly believed that the stereochemistry of the side chain of emericellamide B (**2**) would be analogous to that of **1**. The only stereogenic center to confirm was that at C-25.

For emericellamide B, alcohols **10a** and **10b** were treated with triflic anhydride and the product used to alkylate with (*R*)-(−)-4-benzyl-3-propionyl-2-oxazolidinone (**16**), again following Evans' methodology, thus incorporating the extra methyl substituent on the side chain. Reductive cleavage, Swern oxidation, and asymmetric crotylation as previously employed, secured alcohols **9a** and **9b** in comparable yield as single diastereomers, ready for inclusion into the rest of the synthesis (Scheme 4).

Thus, alcohol **9a** was coupled with L-*N*-Boc-Ala-OH in the same way as **8** and this gave the ester **18a** in 85% yield. Further elaboration of **18a** as was performed on **15** provided the cyclization precursor **4a** (78%, three steps), which was closed to give **2** and this proceeded in 75% yield. However, the data obtained for **2** was not wholly consistent with that published. The synthetic material gave specific optical rotation value of −31 (*c* 0.066, MeOH), it disagreed with the literature value of −34 (*c* 0.076, MeOH).[6] There were also



Scheme 4. Synthesis of emericellamide B and *epi*-emericellamide B.

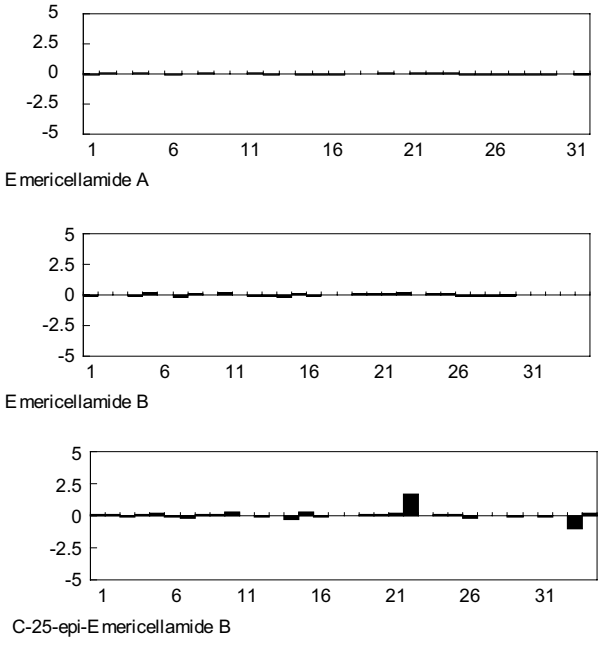


Figure 1. Differences in ^{13}C NMR shifts of natural products between synthetic samples of emericellamides A, B, and C25-*epi*-B. X-axis for carbon number and Y-axis for $\Delta\delta$ (ppm).

slight differences in both the ^{1}H and ^{13}C NMR spectra, with certain signals marginally out of place. Synthesis of the C-25 epimer in exactly the same way starting with **10b**, and relying on the reagent-control of the stereochemistry during the crotylation reaction, provided compound **19**, which had a specific optical rotation value of −33 (*c* 0.1, MeOH), close to the natural material. However, the differences in the NMR spectra provided sufficient evidence that the epimer at C-25 (**19**) was not the correct structure of the natural product. The analysis data for **19** were even more inconsistent with the natural material than for **2**. A comparison of the $\Delta\delta$ values for the C-13 spectra (Fig. 1) shows that there are more differences between **19** and the natural product than those for compound **2**. Consequently, **2** was thus assumed to have the correct stereochemistry for emericellamide B. Although there are some discrepancies between the data for our synthetic sample of emericellamide B (**2**) and the natural material, we feel that this is most likely to have arisen out of either a concentration or pH effect during the recording of the spectra.

3. Conclusions

In summary, the total synthesis of emericellamide A (**1**) was accomplished in an overall yield of 22% in eight reaction vessels. From the same intermediate **10a** employed for the preparation of **1**, the synthesis of emericellamide B (**2**) was completed in 14% overall yield. Through the stereochemically controlled synthesis, we can unambiguously confirm that the originally proposed structures for emericellamides A and B are correct.

4. Experimental

4.1. General methods

All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction vessels were oven-dried. Solvents were distilled prior to use: THF from Na/benzophenone, dichloromethane, DMF, triethylamine and diisopropylethylamine from CaH_2. NMR spectra were recorded on Bruker Avance DPX 300 MHz, AV 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to either a tetramethylsilane internal standard or the signals due to the solvent. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad), coupling constants, and integration. Low- and high-resolution EI and ESI mass spectra were obtained using a Finnigan MAT 95 mass spectrometer. Specific optical rotations were recorded on a Perkin–Elmer 343 polarimeter. TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F_{250}, 0.2 mm) and compounds were visualized at 254 nm, and/or staining in *p*-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with R_f=1.5–3.0 for the desired component) on Qingdao silica gel 60 (230–400 mesh ASTM).

4.2. (*S*)-*N*-Octanoyl-4-benzyl-2-oxazolidinone (13a)

To a solution of *n*-octanoic acid (4.32 g, 30 mmol) in dichloromethane (200 mL) at 0 °C was added oxalyl chloride (13.1 mL, 150 mmol), followed by DMF (0.24 mL, 3 mmol). The reaction was monitored with TLC. After the starting material had been consumed (5 h), the mixture was concentrated in vacuo to provide the corresponding acylchloride, which was used in next step without purification. The chiral auxiliary (**12a**) (3.54 g, 20 mmol) and DMAP (183 mg, 1.5 mmol) were dissolved in dichloromethane (120 mL) at 0 °C, to this solution was added triethylamine (8.3 mL, 60 mmol), followed by the above acylchloride in dichloromethane (50 mL). The reaction was allowed to warm to room temperature and stirred 16 h before being concentrated in vacuo. The residue was then dissolved in ethyl acetate (300 mL) and successively washed with saturated NH_4Cl solution (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). This solution was dried over anhydrous Na_2SO_4 and concentrated to leave a brown oil. The oil was purified by silica gel chromatography using 5%–10% ethyl acetate–hexane as eluent to produce the desired compound (**13a**) (4.7 g, 78%) as a clear oil. $[\alpha]_D^{25}$ +65 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.28–7.25 (2H, m), 7.22–7.19 (1H, m), 7.15–7.13 (2H, m), 4.62–4.59 (1H, m), 4.15–4.08 (2H, m), 3.23 (1H, dd, *J* 13.4, 3.2), 2.94–2.80 (2H, m), 2.70 (1H, dd, *J* 13.4, 10.6), 1.66–1.57 (2H, m), 1.30–1.22 (8H, m), 0.82 (3H, t, *J* 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 173.5, 153.4, 135.4, 129.4, 128.9, 127.3, 66.2, 55.2, 38.0, 35.5, 31.7, 29.1, 29.0, 24.3, 22.6, 14.0; *m*/*z* (EI) 304.1910 ($C_{18}H_{26}NO_3$ $[M+H]^+$ requires 304.1913).

4.3. (*S*)-*N*-[(*S*)-(2-Methyl)octanoyl]-4-benzyl-2-oxazolidinone (14a)

To a solution of NaHMDS (12 mL, 24 mmol, 2.0 M solution in THF) in THF (100 mL) at −78 °C was added dropwise a solution of **13a** (6.06 g, 20 mmol) in THF (100 mL). After 1 h, iodomethane (6.24 mL, 100 mmol) was added slowly via a syringe. The reaction mixture was stirred at −78 °C for 10 h and was quenched by adding saturated aqueous NH_4Cl (150 mL). Volatiles were removed under reduced pressure and the aqueous layer was extracted with dichloromethane (3×100 mL). The combined organic layers were successively washed with 5% $KHSO_4$ (100 mL), aqueous saturated $Na_2S_2O_3$ (100 mL), and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (5%) as eluent, providing the desired compound (4.82 g, 76%) as clear oil. $[\alpha]_D^{25}$ +82 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.35–7.32 (2H, m), 7.29–7.28 (1H, m), 7.23–7.21 (2H, m), 4.71–4.66 (1H, m), 4.22–4.16 (2H, m), 3.75–3.68 (1H, m), 3.28 (1H, dd, *J* 13.3, 3.1), 2.78 (1H, dd, *J* 13.3, 9.6), 1.75–1.71 (1H, m), 1.43–1.39 (1H, m), 1.26 (8H, br s), 1.23 (3H, d, *J* 6.8), 0.88 (3H, t, *J* 6.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 177.4, 153.1, 135.4, 129.5, 129.0, 127.4, 65.9, 55.3, 37.8, 37.8, 33.4, 31.6, 29.2, 27.1, 22.5, 17.3, 14.0; *m*/*z* (EI) 318.2055 ($C_{19}H_{28}NO_3$ $[M+H]^+$ requires 318.2069).

4.4. (*S*)-2-Methyl-1-octanol (10a)

To a cold (0 °C) solution of imide **14a** (3.17 g, 10 mmol) in THF (200 mL) was added 0.5 ml of methanol followed by a solution of $LiBH_4$ (10 mL, 20 mmol, 2.0 M in THF). The reaction was stirred at 0 °C for 2 h and then allowed to warm to room temperature. After 4 h, a solution of 2 M NaOH (20 mL) was added. The resulted solution was stirred until both phases were clear. The organic layer was separated and the aqueous phase was then extracted with Et_2O (3×100 mL). The combined extracts was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, using 10% ethyl acetate–hexane as eluent, to produce the desired product (1.37 g, 95%) as a clear colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.51 (1H, dd, *J* 10.5, 5.8), 3.42 (1H, dd, *J* 10.5, 6.6), 1.63–1.59 (1H, m), 1.43 (1H, s), 1.41–1.37 (1H, m), 1.26 (8H, br s), 1.13–1.09 (1H, m), 0.91 (3H, d, *J* 6.7), 0.88 (3H, t, *J* 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 68.4, 35.8, 33.2, 31.8, 29.6, 26.9, 22.6, 16.6, 14.0; *m*/*z* (EI) 145.1590 ($C_9H_{21}O$ $[M+H]^+$ requires 145.1592).

4.5. (3*S*,4*R*,5*S*)-3,5-Dimethyl-undec-1-en-4-ol (8)

To a solution of oxalyl chloride (1.05 mL, 12 mmol) in dry CH_2Cl_2 (60 mL) at −78 °C was slowly added a solution of DMSO (1.52 mL, 16 mmol) in dry CH_2Cl_2 (60 mL). After stirring for 1 h at −78 °C, alcohol (**10a**) (0.58 g, 4 mmol) in dry CH_2Cl_2 (40 mL) was slowly added to the above solution. 30 min later, diisopropylethylamine (10.4 mL, 60 mmol) was introduced via a syringe. The reaction was then stirred at −78 °C for 30 min and further at −50 °C for 20 min, prior to the addition of aqueous saturated NH_4Cl solution (100 mL). The organic phase was separated and then washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the desired (*S*)-2-methyloctanal (0.56 g, quantitative yield) as a clear oil, which was used in the next step without further purification. Potassium *tert*-butoxide (1.16 g, 10.4 mmol, prior dried at 0.5 mm/80 °C/8 h) in THF (8 mL) was cooled at −78 °C, *trans*-2-butene (1.16 mL, 20.8 mmol) was introduced to the reaction vessel, followed by the addition of *n*-BuLi (2.2 M, 4.73 mL, 10.4 mmol). The resulting orange solution was stirred at −45 °C for 10 min and re-cooled to −78 °C before (−)-methoxydiisopinocampheylborane [1.0 M in THF, 11.2 mL, 11.2 mmol, derived from (+)-α-pinene] was dropwise added. 30 min later at −78 °C, boron trifluoride etherate (1.52 mL, 12 mmol) was added, followed by the above crude (*S*)-2-methyloctanal (0.56 g, 8 mmol) in THF (10 mL). This mixture was stirred at −78 °C for 6 h and then treated with NaOH (3 M, 4.2 mL, 12.6 mmol) and H_2O_2 (30% solution, 1.8 mL) under refluxing temperature for 3 h. Volatiles were removed in vacuo and the aqueous residue was extracted with Et_2O (3×50 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a residue. This was purified by silica gel chromatography, using ethyl 2%–5% ethyl acetate–hexane as eluent, to provide the desired homoallylic

alcohol (**8**) (1.04 g, 75%, dr >98:2 as measured by ^{1}H NMR spectrum) as clear oil. $[\alpha]_D^{25}$ +1.1 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.79–5.71 (1H, m), 5.14–5.11 (2H, m), 3.20 (1H, dd, *J* 8.8, 3.7), 2.29 (1H, dd, *J* 14.0, 7.6), 1.63–1.60 (1H, m), 1.51 (1H, s), 1.47–1.41 (1H, m), 1.28 (9H, s), 0.98 (3H, d, *J* 6.8), 0.88 (3H, t, *J* 7.2), 0.87 (3H, d, *J* 6.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 141.5, 116.1, 77.2, 42.0, 34.7, 34.3, 31.9, 29.6, 27.2, 22.6, 16.7, 14.0, 12.8; *m*/*z* 221.1881 (EI) ($C_{13}H_{26}ONa$ $[M+Na]^+$ requires 221.1881).

4.6. *N*-*tert*-Butyloxycarbonyl-L-alanine-(1*R*,2*S*)-2-methyl-1-[(1*S*)-1-methyl-2-propen-1-yl]-octyl ester (15)

Alcohol **8** (0.2 g, 1 mmol) and *N*-Boc-Alanine (0.85 g, 5 mmol) were dissolved in dichloromethane (30 mL) at 0 °C, after EDC (0.99 g, 5 mmol) and DMAP (1.22 g, 10 mmol) were added, the reaction was stirred at room temperature for 16 h before it was concentrated in vacuo to give a viscous oil, which was dissolved in Et_2O (100 mL) and successively washed with saturated NH_4Cl solution (40 mL), saturated $NaHCO_3$ solution (40 mL), and brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography, using 5% ethyl acetate–hexane as eluent, to afford the desired ester (**15**) (0.33 g, 90%) as clear oil. $[\alpha]_D^{25}$ +3.2 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.70–5.62 (1H, m), 5.05–4.96 (3H, m), 4.77 (1H, dd, *J* 7.0, 4.8), 4.28 (1H, br s), 2.50–2.43 (1H, m), 1.74 (1H, br s), 1.65 (1H, br s), 1.44 (9H, br s), 1.38 (3H, d, *J* 7.1), 1.25 (8H, br s), 1.12–1.05 (1H, m), 0.98 (3H, d, *J* 6.9), 0.87 (3H, t, *J* 6.5), 0.87 (3H, d, *J* 6.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 172.9, 155.0, 140.1, 115.3, 80.4, 78.5, 40.3, 34.1, 33.6, 31.7, 29.4, 28.3, 26.8, 22.6, 17.2, 14.0, 13.8; *m*/*z* (EI) 392.2780 ($C_{21}H_{39}NO_4Na$ $[M+Na]^+$ requires 392.2777).

4.7. Cbz-Gly-Val-Leu-Ala-O^{t}Bu (5)

Cbz-Gly-L-Val-OH (942 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) was treated with EDC (1.19 g, 6.0 mmol) and HOBt (810 mg, 6.0 mg) at 0 °C for 10 min, then H-L-Leu-L-Ala-O^{t}Bu (851 mg, 3.3 mmol) in CH_2Cl_2 (20 mL) was added via a cannula followed by DIPEA (1.74 mL, 10 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h. The solution was then diluted to 150 mL with CH_2Cl_2, and successively washed with HCl (0.5 *N*, 25 mL), saturated $NaHCO_3$ solution (25 mL), and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated to give a yellow oil. The oil was purified by silica gel chromatography, eluting with 60% ethyl acetate–hexane, to give the titled tetrapeptide (1.93 g, 82%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.54 (1H, d, *J* 8.7), 7.44 (1H, d, *J* 8.4), 7.32 (5H, br s), 7.14 (1H, d, *J* 8.3), 5.94 (1H, br s), 5.10 (2H, s), 4.65–4.61 (1H, m), 4.49–4.40 (2H, m), 4.02 (2H, br s), 2.06–2.00 (1H, m), 1.66–1.60 (2H, m), 1.54–1.50 (1H, m), 1.51 (9H, br s), 1.29 (3H, d, *J* 6.9), 0.91–0.85 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 171.8, 171.5, 171.1, 169.0, 156.6, 136.3, 128.5, 128.1, 128.0, 81.7, 67.0, 58.3, 51.6, 48.7, 44.4, 41.3, 31.7, 27.9, 24.7, 22.7, 22.2, 19.0, 18.3, 18.0; *m*/*z* (EI) 571.3104 ($C_{28}H_{44}N_4O_7Na$ $[M+Na]^+$ requires 571.3108).

4.8. *N*-*tert*-Butyloxycarbonyl-L-alanine-(1*R*,2*S*)-2-methyl-1-[(1*R*)-1-carboxyethyl]octyl ester (6)

To a solution of ester **15** (127 mg, 0.34 mmol) in dioxane–water (3:1, 5 mL) were added 2,6-lutidine (0.08 mL, 0.68 mmol), OsO_4 (2.5 wt % in 2-methylpropan-2-ol, 0.3 mL, 0.015 mmol), and $NaIO_4$ (335 mg, 1.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C and monitored by TLC. After the starting material is consumed, the reaction was quenched with saturated Na_2SO_3 solution (15 mL) for 30 min before it was concentrated in vacuo and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to produce the crude aldehyde, which was subjected to next reaction immediately. The above crude aldehyde was dissolved in *tert*-butanol–water (5 mL, 1:1) at 0 °C, and treated with a pre-mixed aqueous solution of $NaClO_2$ (80%, 125 mg, 1.36 mmol) and NaH_2PO_4 (pH=7), in the presence of $CH_3SO_2NH_2$ (78 mg, 0.82 mmol) for 2.5 h. The mixture was then poured into ethyl acetate (20 mL) and organic layer was separated. The aqueous layer was further extracted with ethyl acetate (2×20 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the desired acid (**6**, 110 mg, 85%, 2 steps) as a viscous oil, which was used directly in the next step.

4.9. 1-[*N*-[*N*-[*N*-[(2*R*,3*R*,4*S*)-(2,4-Dimethyl)-3-[(2*S*)-2-[[*tert*-butyloxycarbonyl]amino]-1-oxopropoxy]decanoyl]glycyl]-L-valyl]-L-leucyl]-L-alanine-*tert*-butyl ester (3)

Tetrapeptide Cbz-Gly-L-Val-L-Leu-L-Ala-O^{t}Bu (**5**) (1.1 g, 2.0 mmol) in dry methanol (15 mL) was treated with hydrogen in the presence of catalytic amount of Pd/C (10%) at ambient temperature for 2 h. The solution was then filtered through a pad of Celite to remove the catalyst powder, the cake was washed with methanol (15 mL). The combined solution was concentrated in vacuo to afford the crude amine in quantitative yield, which was pure enough for the next reaction. The above crude acid **6** (110 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was treated with EDC (140 mg, 0.71 mmol) and HOBt (96 mg, 0.71 mg) at 0 °C for 10 min, before a solution of above amine (**5**) (177 mg, 0.43 mmol) in CH_2Cl_2 (3 mL) was added via a cannula, followed by DIPEA (0.25 mL, 1.42 mmol). The reaction was then allowed to warm to room temperature and stirred for 24 h. The solution was diluted to 50 mL with CH_2Cl_2, washed successively with HCl (0.5 N, 15 mL), saturated $NaHCO_3$ solution (15 mL), and brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a viscous oil. The residue was purified by silica gel chromatography, using 2%–5% methanol–dichloromethane as eluent, to produce the key precursor (**3**) (200 mg, 92% or 76% total yield from **15**) as light yellow viscous oil. $[\alpha]_D^{25}$ −42.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.62 (1H, d, *J* 7.9), 7.80 (1H, br s), 7.70 (1H, br s), 7.35 (1H, br s), 5.57 (1H, br s), 5.11 (1H, d, *J*=5.6), 4.73–4.68 (1H, m), 4.45–4.41 (1H, m), 4.44–4.40 (1H, m), 4.24–4.14 (2H, m), 3.86 (1H, d, *J* 10.4), 2.79–2.74 (1H, m), 2.02–1.97 (1H, m), 1.70–1.60 (2H, m), 1.50 (1H, br s), 1.42 (9H, s), 1.38 (9H, s), 1.32 (3H, d, *J* 7.0), 1.29 (3H, d, *J* 7.1), 1.27 (3H, d, *J* 7.3), 1.22 (8H, br s), 1.08 (3H, d, *J* 6.8), 0.87–0.81 (15H, m, 5×Me), 0.82 (3H, d, *J* 7.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 174.2, 172.3, 171.7 (2×C), 171.1, 169.2, 155.2, 81.4 (2×C), 78.3, 58.4, 51.5, 48.7, 43.1, 41.4, 34.2, 33.7, 31.8, 31.7, 29.6, 29.3, 28.4, 27.9, 27.8, 27.0, 24.7, 22.7, 22.5, 22.4, 19.1, 18.5, 18.4, 17.9, 14.7, 13.9, 13.3; *m*/*z* (EI) 806.5265 ($C_{40}H_{73}N_5O_{10}Na$ $[M+Na]^+$ requires 806.5255).

4.10. Emericellamide A (1)

Precursor **3** (80 mg, 0.1 mmol) was treated with a solution of dry TFA–CH_2Cl_2 (40% 2.5 mL) at 0 °C for 3 h. The reaction was allowed to warm to room temperature and stirred for a further 4 h. The solvents were evaporated under reduced pressure to give the crude product, which was then dissolved in DMF (100 mL) and treated with DEPC (66 μL, 0.4 mmol) at 25 °C for 30 min, and then DIPEA (0.11 mL, 0.6 mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at this temperature for 48 h and DMF was then removed by distillation under vacuum at the temperature below 50 °C. The resulting crude product was purified by flash column chromatography on silica gel, using 2% MeOH in dichloromethane as eluent to afford the emericellamide A (**1**) (46 mg, 76% over two steps) as a white solid. $[\alpha]_D^{25}$ −39 (*c* 0.28, MeOH); lit. $[\alpha]_D^{25}$ −43 (*c* 0.23, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.00 (1H, br s), 7.98 (1H, br s), 7.86 (1H, d, *J* 8.6 Hz), 7.44 (1H, br s),

7.36 (1H, d, *J* 7.0), 4.91 (1H, d, *J* 9.8), 4.30 (1H, dd, *J* 17.5, 5.5), 4.09–3.96 (4H, m), 3.61 (1H, d, *J* 10.4), 2.87–2.81 (1H, m), 1.90–1.85 (1H, m), 1.68–1.63 (1H, m), 1.60–1.52 (3H, m), 1.31–1.20 (14H, m), 1.14–1.09 (1H, m), 1.04–1.00 (1H, m), 0.99–0.78 (21H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 172.6, 171.2, 171.0, 170.9, 170.5, 168.4, 76.4, 59.7, 51.6, 48.0, 47.0, 42.2, 40.9, 39.2, 33.1, 33.0, 30.8, 29.8, 28.5, 26.2, 24.2, 22.8, 21.7, 20.5, 18.7, 18.4, 17.9, 16.0, 14.0, 13.5, 12.6; *m*/*z* (EI) 632.4008 ($C_{31}H_{55}N_5O_7Na$ [M+Na]$^+$ requires 632.3999).

4.11. (*R*)-*N*-[(2*S*,4*S*)-(2,4-Dimethyl)decanoyl]-4-benzyl-2-oxazoli-dinone (17a)

To a solution of alcohol (**10a**) (1.44 g, 10 mmol) and pyridine (0.98 mL, 12 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added dropwise trifluromethanesulfonic anhydride (Tf_2O) (1.85 mL, 11 mmol). The reaction was stirred at −78 °C for 3 h, quenched with brine (50 mL), and warmed to room temperature. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the corresponding triflate as a colorless oil, which was subjected to next alkylation reaction without further purification. To LiHMDS (16 mL, 16 mmol, 1.0 M in THF) in THF (100 mL) at −78 °C was added dropwise a solution of (*R*)-(−)-4-benzyl-3-propionyl-2-oxazolidinone **16** (4.66 g, 20 mmol) in THF (100 mL). After 1 h, the crude triflate in dry Et_2O (20 mL) was added slowly via a cannula. The reaction mixture was then stirred at −78 °C for 4 h and room temperature for additional 1.5 h, before it was poured into saturated NH_4Cl solution (150 mL). Volatiles were removed in vacuo and the aqueous phase was extracted with dichloromethane (3×100 mL). The combined extracts was successively washed with 5% $KHSO_4$ solution (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated to leave a residue. The residue was purified by silica gel chromatography, using 5% ethyl acetate–hexane as eluent, to afford the desired compound (**17a**) (1.17 g, 45% for two steps) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.34–7.31 (2H, m), 7.28–7.25 (1H, m), 7.22–7.21 (2H, m), 4.71–4.67 (1H, m), 4.20–4.13 (2H, m), 3.98–3.91 (1H, m), 3.30 (1H, dd, *J* 13.3, 3.4), 2.73 (1H, dd, *J* 13.3, 9.7), 1.90–1.86 (1H, m), 1.44 (1H, br s), 1.33 (2H, br s), 1.26 (8H, br s), 1.17 (3H, d, *J* 6.8), 1.16–1.11 (1H, m), 0.92 (3H, d, *J* 6.6), 0.87 (3H, t, *J* 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 177.7, 153.1, 135.4, 129.4, 128.9, 127.3, 65.9, 55.3, 41.4, 38.0, 36.8, 35.2, 31.9, 30.8, 29.6, 26.8, 22.7, 19.9, 18.0, 14.1; *m*/*z* (EI) 382.2341 ($C_{22}H_{33}NO_3Na$ [M+Na]$^+$ requires 382.2358).

4.12. (*R*)-*N*-[(2*S*,4*R*)-(2,4-Dimethyl)decanoyl]-4-benzyl-2-oxazo-lidinone (17b)

This compound was prepared according to the procedure described for the synthesis of **17a**, using **10b** as a starting material. The reaction was carried out at 8 mmol scale and the yield over two steps was 40%. The product is a clear oil. $[\alpha]_D^{25}$ −44.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.35–7.32 (m, 2H), 7.29–7.27 (1H, m), 7.23–7.22 (2H, m), 4.72–4.67 (1H, m), 4.21–4.15 (2H, m), 3.91–3.84 (1H, m), 3.31 (1H, dd, *J* 13.3, 3.2), 2.73 (1H, dd, *J* 13.3, 9.9), 1.64–1.59 (1H, m), 1.52 (1H, br s), 1.44–1.39 (1H, m), 1.30 (9H, br s), 1.18–1.13 (1H, m), 1.16 (3H, d, *J* 6.7), 0.92 (3H, d, *J* 6.5), 0.89 (1H, t, *J* 6.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 177.9, 153.0, 135.4, 129.4, 128.9, 127.3, 66.0, 55.3, 40.9, 38.1, 37.5, 35.4, 31.9, 30.5, 29.6, 26.9, 22.6, 19.2, 16.7, 14.0; *m*/*z* (EI) 382.2349 ($C_{22}H_{33}NO_3Na$ [M+Na]$^+$ requires 382.2358).

4.13. (2*S*,4*S*)-2,4-Dimethyldecanol (11a)

To a cooled (0 °C) solution of imide **17a** (1.44 g, 4 mmol) in THF (50 mL) was added 0.2 mL of methanol followed by a solution of $LiBH_4$ (4 mL, 8 mmol, 2.0 M in THF). The reaction was stirred at 0 °C for 2 h and then allowed to warm to room temperature. After 4 h, a solution of 2 M NaOH (20 mL) was added and stirring was continued until both phases were clear. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic extracts were washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel, using 10% acetate–hexane as eluent, to afford (2*S*,4*S*)-2,4-dimethyldecan-1-ol (**11a**) (0.71 g, 96%) as a clear, colorless oil. $[\alpha]_D^{25}$ −1.9 (*c*, 0.9, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.52 (1H, dd, *J* 10.5, 5.2), 3.38 (1H, dd, *J* 10.5, 6.7), 1.75–1.69 (1H, m), 1.52–1.46 (1H, m), 1.41 (1H, br s), 1.33–1.27 (11H, m), 1.08–1.03 (1H, m), 0.92 (3H, d, *J* 6.7), 0.89 (3H, d, *J* 6.8), 0.88 (3H, t, *J* 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 68.5, 41.2, 36.8, 33.3, 31.9, 30.2, 29.7, 26.9, 22.7, 20.4, 17.3, 14.1; *m*/*z* (EI) 209.1885 ($C_{12}H_{26}ONa$ [M+Na]$^+$ requires 209.1881).

4.14. (2*S*,4*R*)-2,4-Dimethyldecanol (11b)

Alcohol **11b** was prepared according to the procedure described for the synthesis of **11a**, 1.8 g (5 mmol) of **17b** afforded 883 mg (95%) of **11b** as a clear oil. $[\alpha]_D^{25}$ −17.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.48 (1H, dd, *J* 10.3, 5.7), 3.39 (1H, dd, *J* 10.3, 6.7), 1.75–1.67 (1H, m), 1.49 (1H, br s), 1.27 (11H, m), 1.17–1.08 (2H, m), 0.89 (3H, d, *J* 6.6), 0.88 (3H, d, *J* 6.9), 0.84 (3H, t, *J* 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 69.1, 40.7, 38.0, 33.2, 31.9, 29.9, 29.6, 27.0, 22.7, 19.4, 16.3, 14.1; *m*/*z* (EI) 209.1888 ($C_{12}H_{26}ONa$ [M+Na]$^+$ requires 209.1881).

4.15. (3*S*,4*R*,5*S*,7*S*)-3,5,7-Trimethyl-tridec-1-en-4-ol (9a)

Homoallylic alcohol (**9a**) was prepared according to the procedures described for the synthesis of **8**. The yield for 2.0 mmol scale reaction was 65% yield (as a single diastereoisomer, which was determined by analysis of the ^{1}H NMR of crude product). The product is a clear oil. $[\alpha]_D^{25}$ +2.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.78–5.71 (1H, m), 5.15–5.11 (2H, m), 3.18 (1H, dd, *J* 8.2, 3.4), 2.34–2.25 (1H, m), 1.76–1.71 (1H, m), 1.57 (1H, br s), 1.55–1.51 (1H, m), 1.45–1.40 (1H, m), 1.32–1.27 (10H, m), 1.09–1.02 (1H, m), 0.99 (3H, d, *J* 6.8), 0.90–0.86 (9H, m, Me×3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 141.7, 116.1, 76.5, 42.1, 41.9, 36.9, 31.9, 31.6, 29.9, 29.7, 26.8, 22.6, 20.2, 16.6, 14.0, 13.0; *m*/*z* (EI) 263.2377 ($C_{16}H_{32}ONa$ [M+Na]$^+$ requires 263.2351).

4.16. (3*S*,4*R*,5*S*,7*R*)-3,5,7-Trimethyl-tridec-1-en-4-ol (9b)

Homoallylic alcohol (**9b**) was prepared according to the procedures described for the synthesis of **8**. The yield for 2.0 mmol scale reaction was 68% yield (as a single diastereoisomer, which was determined by analysis of the ^{1}H NMR of crude product). The product is a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.79–5.72 (1H, m), 5.14–5.11 (2H, m), 3.14 (1H, dd, *J* 7.5, 3.9), 2.33–2.28 (1H, m), 1.74–1.69 (1H, m), 1.48 (2H, br s), 1.32–1.26 (10H, br s), 1.18–1.11 (1H, m), 1.02 (3H, d, *J* 6.8), 0.88–0.83 (9H, m, Me×3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 141.3, 116.1, 78.1, 41.9, 41.8, 37.8, 32.0, 31.9, 30.0, 29.6, 26.9, 22.7, 19.4, 16.8, 14.1, 12.7; *m*/*z* (EI) 263.2365 ($C_{16}H_{32}ONa$ [M+Na]$^+$ requires 263.2351).

4.17. *N*-*tert*-Butyloxycarbonyl-L-alanine-(1*R*,2*S*,4*S*)-2,4-dimethyl-1-[(1*S*)-1-methyl-2-propen-1-yl]decanoyl ester (18a)

Ester **18a** was prepared according to the procedure described for the synthesis of **15**, 120 mg (0.5 mmol) of **9a** and 189 mg (1.0 mmol) of *N*-Boc-Ala-OH afforded 175 mg (85%) of **18a** as a clear oil. $[\alpha]_D^{25}$ +1.3 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.68–5.61 (1H, m), 5.06 (1H, br s), 5.01–4.96 (2H, m), 4.75 (1H, dd, *J* 7.3, 4.1), 4.28

(1H, br s), 2.50–2.44 (1H, m), 1.89–1.85 (1H, m), 1.53–1.48 (1H, m), 1.44 (9H, br s), 1.38 (3H, d, *J* 7.0), 1.25 (11H, br s), 1.02–0.98 (1H, m), 0.98 (3H, d, *J* 6.8), 0.96–0.92 (1H, m), 0.93–0.86 (6H, m, 2×Me), 0.84 (3H, d, *J* 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 172.9, 155.0, 140.2, 115.4, 79.9, 79.6, 49.5, 41.4, 40.5, 36.7, 36.5, 31.9, 31.4, 29.7, 29.6, 28.4 (3×C), 26.7, 22.7, 20.2, 17.1, 14.2, 14.1; *m*/*z* (EI) 434.3265 ($C_{24}H_{45}NO_4Na$ $[M+Na]^+$ requires 434.3246).

4.18. *N*-*tert*-Butyloxycarbonyl-L-alanine-(1*R*,2*S*,4*R*)-2,4-dimethyl-1-[(1*S*)-1-methyl-2-propen-1-yl]decanoyl ester (18b)

Ester **18b** was prepared according to the procedure described for the synthesis of **15**, 120 mg (0.5 mmol) of **9b** and 189 mg (1.0 mmol) of *N*-Boc-Ala-OH afforded 175 mg (83%) of **18b** as a clear oil. $[\alpha]_D^{25}$ −2.8 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.70–5.63 (1H, m), 5.07 (1H, br s), 5.02–4.98 (2H, m), 4.73 (1H, dd, *J* 6.9, 5.0), 4.29 (1H, br s), 2.55–2.45 (1H, m), 1.88–1.83 (1H, m), 1.44 (9H, br s), 1.38 (3H, d, *J* 7.2), 1.25 (11H, br s), 1.11–1.04 (2H, m), 0.98 (3H, d, *J* 7.4), 0.88 (3H, d, *J* 6.9), 0.84 (3H, d, *J* 6.7), 0.78 (3H, d, *J* 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 173.0, 155.1, 140.0, 115.4, 81.2, 79.7, 49.6, 41.0, 40.3, 37.9, 31.9, 31.7, 29.8, 29.6, 28.4 (4×C), 26.9, 22.6, 19.3, 17.3, 14.0, 13.6; *m*/*z* (EI) 434.3258 ($C_{24}H_{45}NO_4Na$ $[M+Na]^+$ requires 434.3246).

4.19. 1-[*N*-[*N*-[*N*-[(2*R*,3*R*,4*S*,6*S*)-(2,4,6-Trimethyl)-3-[(2*S*)-2-[[*tert*-butyloxycarbonyl]amino]-1-oxopropoxy]dodecanoyl]-glycyl]-L-valyl]-L-leucyl]-L-alanine-*tert*-butyl ester (4a)

Precursor **4a** was prepared according to the procedure described for the synthesis of **3**, 86 mg (0.2 mmol) of **18a** and 124 mg (0.3 mmol) of tetrapeptide L-Gly-Val-Lue-Ala-O^{t}Bu afforded 135 mg (78%) of **4a** as a viscous clear oil. $[\alpha]_D^{25}$ −32 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.52 (1H, br s), 7.37 (1H, br s), 7.14 (1H, br s), 6.99 (1H, br s), 5.49 (1H, br s), 5.07 (1H, d, *J* 6.4), 4.65–4.60 (1H, m), 4.45–4.38 (2H, m), 4.26 (1H, br s), 4.11 (1H, m), 3.90 (1H, d, *J* 10.5), 2.72–2.67 (1H, m), 2.11–2.07 (1H, m), 1.89–1.85 (1H, m), 1.70–1.62 (1H, m), 1.58–1.50 (3H, m), 1.44 (9H, s), 1.42 (9H, s), 1.35 (3H, d, *J* 7.3), 1.33 (3H, d, *J* 7.2), 1.23 (11H, br s), 1.12 (3H, d, *J* 6.9), 1.02–0.97 (1H, m), 0.92–0.85 (18H, m, 6×Me), 0.82 (3H, d, *J* 7.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 174.3, 171.7 (2×C), 171.5, 171.0, 169.3, 155.5, 81.6 (2×C), 77.9, 60.3, 58.9, 51.6, 48.7, 43.5, 43.4, 41.3, 41.1, 36.7, 31.9, 31.4, 29.6, 29.5, 28.4 (3×C), 28.3, 27.9 (3×C), 26.7, 24.7, 22.8, 22.6 (2×C), 22.1, 20.0, 19.1, 18.1, 18.0, 14.5, 14.0, 13.7; *m*/*z* (EI) 848.5714 ($C_{43}H_{79}N_5O_{10}Na$ $[M+Na]^+$ requires 848.5725).

4.20. 1-[*N*-[*N*-[*N*-[(2*R*,3*R*,4*S*,6*R*)-(2,4,6-Trimethyl)-3-[(2*S*)-2-[[*tert*-butyloxycarbonyl]amino]-1-oxopropoxy]dodecanoyl]-glycyl]-L-valyl]-L-leucyl]-L-alanine-*tert*-butyl ester (4b)

Precursor **4b** was prepared according to the procedure described for the synthesis of **3**, 86 mg (0.2 mmol) of **18b** and 124 mg (0.3 mmol) of tetrapeptide L-Gly-Val-Lue-Ala-O^{t}Bu afforded 135 mg (75%) of **4b** as a viscous clear oil. $[\alpha]_D^{25}$ −33 (*c*, 0.48, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.68 (1H, br s), 7.52 (1H, br s), 7.27 (1H, br s), 7.12 (1H, br s), 5.55 (1H, d, *J* 7.6), 5.05 (1H, dd, *J* 7.5, 3.3), 4.66 (1H, br s), 4.48–4.41 (2H, m), 4.29–4.25 (1H, m), 4.20–4.16 (1H, m), 3.91–3.85 (1H, m), 2.74 (1H, br s), 2.18–2.14 (1H, m), 2.08–2.03 (1H, m), 1.88–1.83 (1H, m), 1.70–1.60 (2H, m), 1.56–1.51 (1H, m), 1.45 (9H, s), 1.41 (9H, s), 1.36 (3H, d, *J* 7.2), 1.32 (3H, d, *J* 7.2), 1.22 (11H, br s), 1.15 (3H, d, *J* 6.7), 1.10–1.04 (1H, m), 0.90–0.84 (18H, m, 6×Me), 0.78 (3H, d, *J* 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 174.2, 172.5, 171.7, 171.6, 171.0, 169.3, 155.4, 81.5, 79.6, 79.2, 58.7, 51.6, 49.6, 48.7, 43.3, 42.2, 41.3, 41.1, 37.8, 31.9, 31.7, 29.8, 29.7, 28.4 (3×C), 28.3, 28.0 (3×C), 26.9, 24.7, 23.5, 22.89, 22.6, 22.2, 19.2, 19.1, 18.2, 18.0, 14.7, 14.0, 13.0; *m*/*z* (EI) 848.5718 ($C_{43}H_{79}N_5O_{10}Na$ $[M+Na]^+$ requires 848.5725).

4.21. Emericellamide B (2)

Emericellamide B (**2**) was prepared according to the procedure described for the synthesis of emericellamide A (**1**). 86 mg (0.1 mmol) of precursor **4a** afforded 49 mg (75%) of **2** as a white solid. $[\alpha]_D^{25}$ −31 (*c* 0.066, MeOH); lit. $[\alpha]_D^{25}$ −34 (*c* 0.076, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.50 (br s, 1H), 8.47 (1H, br s), 8.06 (1H, br s), 7.44 (1H, br s), 7.36 (1H, d, *J* 6.0), 4.91 (1H, d, *J* 9.8), 4.25 (1H, dd, *J* 17.5, 5.5), 4.09–3.96 (4H, m), 3.61 (1H, d, *J* 10.4), 2.87–2.82 (1H, m), 1.90–1.85 (1H, m), 1.84–1.78 (2H, m), 1.60–1.50 (4H, m), 1.31–1.18 (15H, m), 1.14–1.09 (1H, m), 1.04–1.00 (1H, m), 0.99–0.78 (24H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 172.8, 171.2, 171.1, 170.8, 168.6, 75.9, 60.1, 51.8, 48.2, 47.2, 41.2, 40.8, 40.1, 39.6, 36.7, 31.2, 30.2, 30.1, 28.9, 28.8, 26.0, 24.4, 22.0, 20.7, 23.1, 19.4, 19.0, 18.7, 18.4, 16.3, 14.2, 13.9, 13.5; *m*/*z* (EI) 674.4449 ($C_{34}H_{61}N_5O_7Na$ $[M+Na]^+$ requires 674.4469).

4.22. C-25-*epi*-Emericellamide B (19)

C-25-*epi*-Emericellamide B (**19**) was prepared according to the procedure described for the synthesis of emericellamide A (**1**), 83 mg (0.1 mmol) of precursor **4b** afforded 47 mg (73%) of **19** as a straw-yellow viscous oil. $[\alpha]_D^{25}$ −33 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 7.98 (1H, d, *J* 8.6), 8.05 (1H, br s), 7.85 (1H, d, *J* 8.9), 7.43 (1H, br s), 7.34 (1H, d, *J* 7.0), 4.86 (1H, d, *J* 10.0), 4.26 (1H, dd, *J* 17.5, 5.4), 4.10–3.98 (4H, m), 3.62 (1H, dd, *J* 17.5, 2.1), 2.88–2.83 (1H, m), 1.88–1.83 (1H, m), 1.82–1.77 (1H, m), 1.61–1.54 (4H, m), 1.44 (1H, br s), 1.22–1.19 (15H, m), 1.08–1.03 (1H, m), 1.02–0.98 (1H, m), 0.99–0.87 (24H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 172.8, 171.4, 171.2, 170.8, 168.6, 77.4, 60.0, 51.8, 48.3, 47.2, 41.2, 40.8, 40.2, 39.7, 36.6, 31.2, 30.4, 30.1, 29.0, 28.8, 26.1, 24.5, 22.0, 20.7, 23.1, 19.6, 19.0, 18.7, 18.3, 16.2, 14.2, 13.8, 12.5; *m*/*z* (EI) 674.4451 ($C_{34}H_{61}N_5O_7Na$ $[M+Na]^+$ requires 674.4469).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.082.

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5. During the preparation of this manuscript, another synthesis of emericellamide A was reported, using a similar approach, where the polyketide fragment was obtained via epoxide-opening as the key step. However, total synthesis of emericellamide B, which contains an additional stereogenic center at the side chain was not reported. See: Ghosh, S.; Pradhan, T. K. *Tetrahedron Lett.* **2008**, *49*, 3697–3700.
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