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The first total synthesis of emericellamide A

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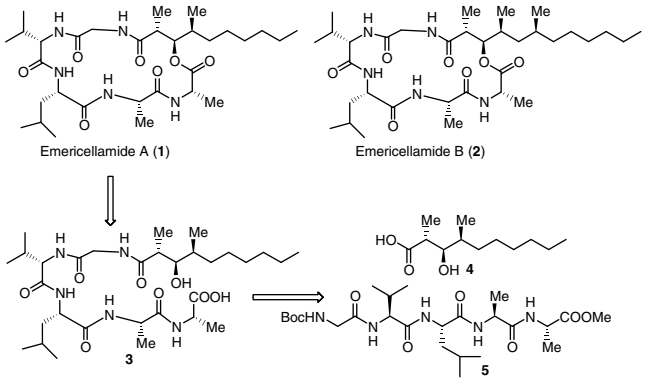
Abstract

A highly convergent asymmetric total synthesis of emericellamide A, a 19-membered antibacterial depsipeptide isolated from the co-culture of an *Emericella* sp. (strain CNL-878) and a *Salinispora arenicola* (strain CNH-665) is described.

Keywords: Emericellamide A; Antibacterial; Macrolactamization

Emericellamides A (**1**) and B (**2**) (Scheme 1) are two novel cyclic depsipeptides that were isolated by Fenical et al. from *Emericella* sp., during co-culture with the marine actinomycete *Salinispora arenicola*.[1] With the help of chemical and spectral methods, the planar structures of these compounds were established and the absolute stereochemistries of **1** and **2** were established with the help of Marfey's method,[2] and the modified Mosher method.[3]

Emericellamide A (**1**) showed antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MIC: 3.8 μM). It also displayed cytotoxicity against HCT-116 human colon carcinoma cell line (IC_{50}: 23 μM). Due to these interesting biological activities, we decided to develop a protocol, which would allow us to synthesize not only the natural product, but also its analogues, so that the structure–activity relationship could be established. Here, we report the first asymmetric total synthesis of emericellamide A.



Scheme 1. Retrosynthetic analysis of **1**.

Retrosynthetically, emericellamide A (**1**) (Scheme 1) can be obtained by the macrolactonization of the acyclic hydroxy acid **3** which, in turn, could be prepared by the amide coupling of the two key intermediates, the long chain fatty acid moiety **4** and pentapeptide component **5**.

For the synthesis of top half acid fragment **4**, we started from the known compound **6**, which was converted to compound **7** according to the reported procedure.[4] The reductive removal of the chiral auxiliary[5] afforded a primary alcohol, which on oxidation followed by Wittig reaction with $Ph_3P{=}CHCOOEt$ in toluene at 90 °C using a catalytic amount of benzoic acid afforded olefinic compound **8** ($E{:}Z = 95{:}5$) in 70% yield.[6] The reduction of the ester functionality with DIBAL-H afforded allylic alcohol **9**, which on epoxidation under Sharpless conditions[7] gave epoxide **10**[14a] with de ⩾ 95% (72% yield over two steps). The regioselective opening of the epoxy alcohol **10** using lithium dimethylcuprate (Me_2CuLi)[8] in ether at −20 °C afforded the required 1,3-diol **11**[14b] as the major product along with a 1,2-diol as a minor product. To remove the minor

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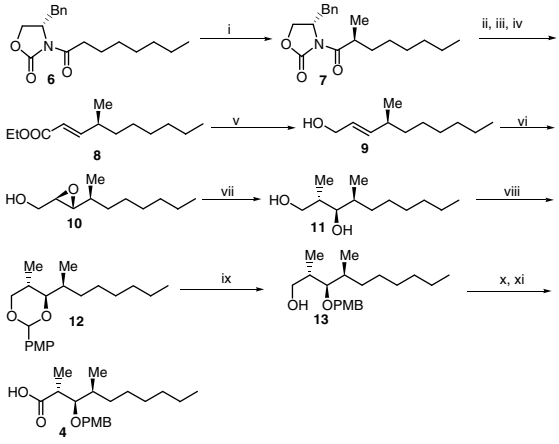
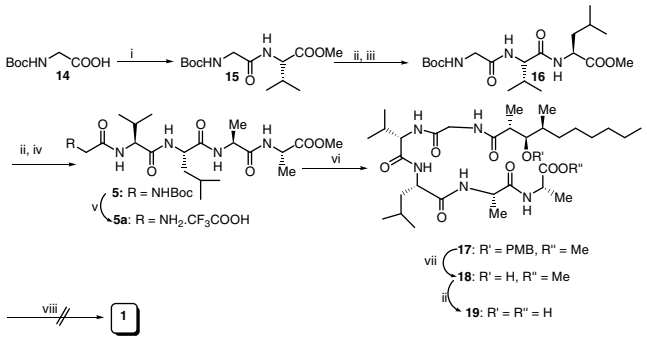
1,2-diol, the crude reaction mixture was subjected to $NaIO_4$ cleavage to convert the 1,2-diol to an aldehyde, which was then easily removed from the 1,3-diol by a standard silica gel chromatography to give pure compound **11** (70% over two steps). The protection of the 1,3-diol compound **11** as *p*-methoxy-benzylidene acetal **12** in 97% yield using the dimethyl acetal of *p*-methoxybenzaldehyde and a catalytic amount of CSA in CH_2Cl_2[9] was followed by the reductive opening of the PMP acetal with DIBAL-H[10] in CH_2Cl_2 to afford the primary alcohol **13**, which was converted to acid **4** using a two-step oxidation protocol (Scheme 2).

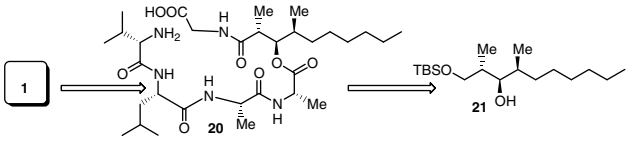
The pentapeptide segment **5** was synthesized from the commercially available protected (L)-amino acids (Scheme 3). The condensation of Boc-Gly-OH and valine methyl ester using EDCI and HOBt as coupling reagents gave dipeptide **15**. The saponification of the ester functionality with LiOH gave the free acid, which was coupled with leucine methyl ester under similar conditions as above to give tripeptide **16** with de $\geqslant$ 98%. The hydrolysis of the ester functionality of **16** followed by coupling with H-Ala-Ala-OMe afforded pentapeptide **5** with de $\geqslant$ 97% (85% over two steps). Boc-deprotection of **5** with TFA in CH_2Cl_2 followed by coupling with **4** under standard peptide coupling conditions as mentioned above gave compound **17**. PMB deprotection using DDQ[11] under biphasic conditions gave secondary alcohol **18**, which on saponification with LiOH in THF–MeOH–H_2O (3:1:1) at 0 °C afforded hydroxy acid **19**. The stage was now set to carry out the crucial macrolactonization reaction. Unfortunately, using the Yamaguchi protocol[12] and varying different conditions we failed to prepare the desired cyclized product. The failure of this macrolactonization forced us to devise



Scheme 2. Reagents and conditions: (i) Ref. 4 (ii) $LiBH_4$, Et_2O–H_2O (50:1), 0 °C, 10 min, 92%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (iv) $Ph_3P{=}CHCOOEt$, benzoic acid (cat), toluene, 90 °C, 0.5 h, 70% over two steps; (v) DIBAL-H, −78 °C, CH_2Cl_2, 0.5 h, 80%; (vi) $Ti(^iOPr)_4$, D(−)DIPT, TBHP, CH_2Cl_2, 4 Å MS, −20 °C, 3 h, 91%; (vii) (a) Me_2CuLi, Et_2O, −20 °C to 0 °C, 3 h; (b) $NaIO_4$, THF–H_2O (2:1), 0 °C, 1 h, 70% over two steps; (viii) PMP-acetal, CSA (cat), CH_2Cl_2, 0 °C to rt, 0.5 h, 97%; (ix) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 80%; (x) DMP, CH_2Cl_2, 0 °C, 1 h; (xi) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, ^{t}BuOH, rt, 70% over two steps.



Scheme 3. Reagents and conditions: (i) EDCI, HOBt, CH_2Cl_2, then HCl·NH_2Val-OMe, DIPEA, 0 °C, 6 h, 90%; (ii) LiOH, THF–MeOH–H_2O (3:1:1), 0 °C, 1 h; (iii) EDCI, HOBt, CH_2Cl_2, then HCl·NH_2Leu-OMe, DIPEA, 0 °C, 6 h, 80%; (iv) EDCI, HOBt, CH_2Cl_2, then H-Ala-Ala-OMe, DIPEA, 0 °C, 0.5 h, 85% over two steps; (v) CF_3COOH, CH_2Cl_2, 0 °C, 0.5 h; (vi) **4**, EDCI, HOBt, DIPEA, CH_2Cl_2, 0 °C, 0.5 h, 80% with respect to **4**; (vii) DDQ, $CHCl_3$–H_2O (18:1), 0 °C, 3 h, 90%; (viii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h, the mixed anhydride was then added to DMAP solution in toluene, 10^{-3} M, 80 °C, 5 h.

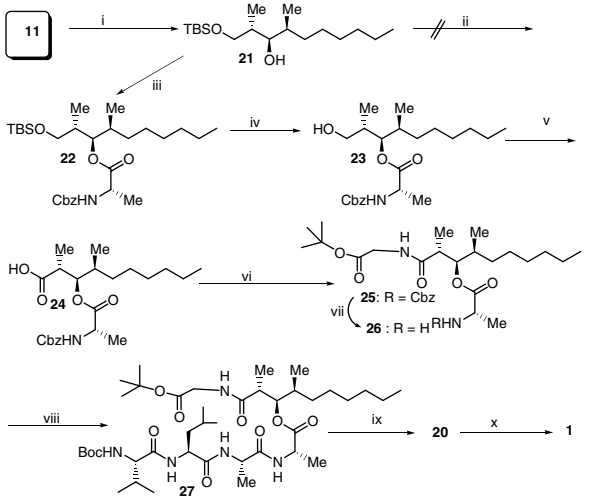


Scheme 4. Revised retrosynthetic analysis.

an alternative strategy by forming the ester bond first and then carrying out a macrolactamization reaction (Scheme 4). To avoid steric hindrance and to minimize racemization, we decided to perform the macrolactamization via the formation of a Gly-Val amide bond.

For this revised strategy, we started from compound **11**. The chemoselective protection of the primary hydroxy group as a TBS ether with TBSCl and imidazole in THF gave **21**. However, the acylation of the secondary alcohol with the acid (Boc-Val-Leu-Ala-Ala-OH) was not successful.

Thus, we thought of first acylating alcohol **21** with Cbz-Ala-OH, which could be followed by the extension of the peptide chain. Thus the acylation of alcohol **21** with Cbz-Ala-OH in the presence of DCC and a catalytic amount of DMAP in CH_2Cl_2 at 0 °C gave compound **22** in 75% yield with de $\geqslant$ 90% (Scheme 5). Acid catalyzed TBS deprotection, followed by a two-step oxidation of the corresponding primary alcohol (**23**) [14c] afforded acid **24** in 90% yield over three steps. Coupling of acid **24** with H-Gly-O^{t}Bu, using EDCI and HOBt as coupling agents gave compound **25**[14d] in 90% yield. Cbz-deprotection of **25** under catalytic hydrogenolysis conditions gave primary amine **26**, which was coupled with Boc-Val-Leu-Ala-OH under the same coupling condition as above to give compound **27**[15] in 75% yield. The deprotection of the Boc group and the hydrolysis of the tertiary butyl ester using TFA in CH_2Cl_2 afforded amino acid **20**, which was sub-



Scheme 5. Reagents and conditions: (i) TBSCl, imidazole, THF, 8 h, 96%; (ii) Boc-Val-Leu-Ala-Ala-OH, DCC, DMAP (cat), 0 °C to rt, 5 h, 0%; (iii) Cbz-Ala-OH, DCC, DMAP (cat), 0 °C to rt, 5 h, 75%; (iv) CSA (cat), MeOH–CH_2Cl_2 (1:1), 0 °C, 0.5 h, 85% over two steps; (v) (a) SO_3–Py, DMSO–CH_2Cl_2 (2:1.8), 0 °C, 1 h; (b) $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 2-methyl-2-butene, ^tBuOH, 90% over two steps; (vi) EDCI, HOBt, H-Gly-O^{t}Bu, 0 °C to rt, 1 h, 90%; (vii) H_2, Pd/C, EtOAc, 1 N, HCl, 10 min; (viii) Boc-Val-Leu-Ala-OH, EDCI, HOBt, CH_2Cl_2, then **26**, DIPEA, 0 °C, 1 h, 75% over two steps; (ix) TFA–CH_2Cl_2 (1:1), 0 °C, 1 h; (x) FDPP, DIPEA, CH_3CN, 10^{-3} M, 0 °C to rt, 72 h, 75%.

jected to macrolactamization by the treatment with pentafluorophenyl diphenylphosphinate (FDPP)[13] and DIPEA under high dilution, 10^{-3} M, in CH_3CN at room temperature, to afford emericellamide A in 75% yield. Spectral and analytical data of synthetic emericellamide A were in good agreement with those of the literature data.[1,16]

In conclusion, we have achieved the first total synthesis of emericellamide A in a convergent fashion using FDPP mediated macrolactamization as a key step. The preparation of analogues and their biological study are under progress and will be reported in due course.

Acknowledgements

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14. (a) *Analytical and spectral data of compound* **10**: $[\alpha]_D^{30}$ +34.90 ($c = 1.86$, $CHCl_3$); IR (neat): ν_{max} 3427, 2926, 2857, 1630 and 1384 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.87 (dd, $J = 12.4$, 2.9 Hz, 1H), 3.58 (dd, $J = 12.4$, 3.6 Hz, 1H), 2.90 (m, 1H), 2.67 (m, 1H), 1.63 (m, 1H), 1.38–1.22 (m, 10H), 1.01 (d, $J = 5.9$ Hz, 3H), and 0.89 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.8, 60.6, 58.5, 35.4, 33.5, 31.7, 29.4, 27.0, 22.5, 17.0 and 13.9; ESIMS: $[M-H_2O+H]^+ = 169$; (b) *Analytical and spectral data of compound* **11**: $[\alpha]_D^{30}$ +14.64 ($c = 4.91$, $CHCl_3$); IR (neat): ν_{max} 3355, 2959, 2925, 2855 and 1460 cm^{-1}; ^1H 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), 2.96–2.52 (br s, 2H), 1.82 (m, 1H), 1.59 (m, 1H), 1.40–1.21 (m, 10H), 0.93–0.84 (m, 6H) and 0.80 (d, $J = 6.8$ Hz, 3H); ^{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 and 12.1; ESIMS: $[M-H_2O+Na]^+$: 207. (c) *Analytical and spectral data of compound* **23**: $[\alpha]_D^{30}$ −17.94 ($c = 0.39$, $CHCl_3$); IR (neat): ν_{max} 3512, 2957, 2928, 2857, 1465, 1386, 1254, 1077, 837 and 776 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 (dq, $J = 6.8$, 7.5 Hz, 1H), 3.51 (dd, $J = 12.0$, 3.0 Hz, 1H), 3.41 (dd, $J = 12.0$, 2.2 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) and 0.93–0.85 (m, 6H): ^{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 and 12.9; HRMS (ESI): calcd for $C_{23}H_{37}NO_5Na$ $[M+Na]^+$: 430.2569, found: 430.2574. (d) *Analytical and spectral data of compound* **25**: $[\alpha]_D^{30}$ −3.99 ($c = 2.75$, $CHCl_3$); IR (neat): ν_{max} 3317, 2925, 2657, 2361, 1726, 1630, 1384, 1217 and 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 (dq, $J = 6.8$, 7.5 Hz, 1H), 3.94 (dd, $J = 18.1$, 5.1 Hz, 1H), 3.78 (dd, $J = 18.1$, 4.5 Hz, 1H), 2.58 (dq, $J = 6.8$, 15.1 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) and 0.91–0.81 (m, 6H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 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 and 13.2; HRMS (ESI): calcd for $C_{29}H_{46}$ N_2O_7Na $[M+Na]^+ =$ 557.3202, found: 557.3197.
15. *Analytical and spectral data of compound* **27**: $[\alpha]_D^{30}$ −33.40 ($c = 3.05$, $CHCl_3$); IR (neat): ν_{max} 3280, 3079, 2961, 2928, 2857, 1742, 1638, 1544, 1456, 1369, 1216 and 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, $J = 8.3$ Hz, 1H), 7.04 (d, $J = 8.3$ Hz, 1H), 6.71 (t, $J = 5.3$ Hz, 1H), 6.44 (d, $J = 6.8$ Hz, 1H), 5.09 (dd, $J = 8.3$, 3.0 Hz, 1H), 4.98 (d, $J = 5.3$ Hz, 1H), 4.60 (dq, $J = 6.8$, 7.5 Hz, 1H), 4.47 (dq, $J = 6.8$, 7.5 Hz, 1H), 4.36 (m, 1H), 4.02 (dd, $J = 17.3$, 6.8 Hz, 1H), 3.87 (dd, $J = 17.3$, 4.5 Hz, 1H), 3.82 (m, 1H), 2.74 (dq, $J = 7.5$, 8.3 Hz, 1H), 2.16 (m, 1H), 1.68 (m, 1H), 1.45 (s, 9H), 1.44 (s, 9H), 1.48–1.37 (m, 6H), 1.33–1.20 (m, 10H), 1.13 (d, $J = 6.8$ Hz, 3H) and 1.05–0.83 (m, 21H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 172.1, 171.7, 171.4, 171.1, 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 and 12.9; HRMS (ESI): calcd for $C_{40}H_{73}N_5O_{10}Na$ $[M+Na]^+ = 806.5255$, found: 806.5242.
16. *Analytical and spectral data of emericellamide A*: $[\alpha]_D^{30}$ −42.99 ($c = 0.2$, MeOH), reported −43 ($c = 0.23$, MeOH); IR (KBr): ν_{max} 3401, 3317, 3067, 2962, 2929, 2858, 1755, 1635, 1549, 1458, 1380, 1326, 1285, 1239, 1169 and 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), 4.32 (dd, $J = 17.0$, 5.5 Hz, 1H), 4.12–4.00 (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), 1.65–1.55 (m, 3H), 1.24 (d, $J = 7.1$ Hz, 3H), 1.23 (d, $J = 7.1$ Hz, 3H), 1.24–1.18 (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) and 0.80 (d, $J = 6.0$ Hz, 3H): ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.9, 171.4, 171.3, 171.2, 170.8, 168.8, 76.6, 60.1, 51.7, 48.2, 47.3, 42.5, 41.0, 40.8, 33.5, 33.2, 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 and 12.9:HRMS (ESI): calcd for $C_{31}H_{55}N_5O_7Na$ $[M+Na]^+ = 632.3999$, found: 632.3986.