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Application of desymmetrization protocol for the formal total synthesis of emericellamide B

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ABSTRACT

A highly convergent formal total synthesis of emericellamide B, a 19-membered antibacterial depsipeptide is described. The key feature of the strategy is the generation of four stereogenic centers from a bicyclic precursor via desymmetrization technique and utilization for emericellamide B and related natural product synthesis.

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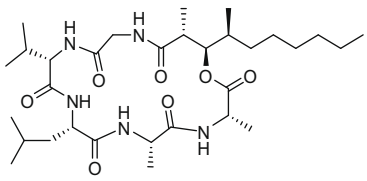
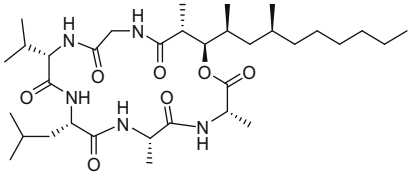
Cyclic peptides and depsipeptides are a rich source of biologically active compounds produced in nature by plants, bacteria, fungi, and lower sea animals.[1,2] In comparison with linear peptides, cyclic peptides are more stable against proteolytic degradation due to their lack of free N- or C-terminus and reduced conformational freedom. The entropic advantages associated with the increased rigidity also makes cyclic peptides tighter binding and potentially more specific ligands of macromolecular receptors. We have been interested in marine cyclopeptides and cyclodepsipeptides from vantage of structure confirmation, modification, and biological activity verification.[3] Emericellamides A (**1**) and B (**2**), two novel cyclic depsipeptides, were isolated from marine-derived fungus *Emericella* sp. with the proposed structures as shown in Figure 1.[4] The planar structures of these two new cyclic depsipeptides contain two main features: a pentapeptide and 3-hydroxy-2,4-dimethyldecanoic acid or 3-hydroxy-2,4,6-trimethyldodecanoic acid. The absolute configurations of the stereogenic centers on the polyketide side chain were established by application of the Marfey's method[5] combined with modified Mosher's method.[6] Emericellamide A (**1**) displayed antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MIC: 3.8 μM). It also showed cytotoxicity against HCT-116 human colon carcinoma cell line (IC_{50} 23 μM). The biological activities of emericellamide B (**2**) were slightly weaker than those of **1**, showing an MIC value of 6.0 μM against methicillin-resistant *S. aureus* and IC_{50} against HCT-116 of 40 μM. Encouraged by the interesting structural feature combined with prominent biological activities and to demonstrate the application of our developed desymmetrization protocol,[7] we embarked on a formal total synthesis of emericellamide B (**2**).

The retrosynthetic analysis (Scheme 1) has shown the desired cyclization at the lactone junction. As it is already reported in the literature about the failure of the lactonization step in the case of



Emericellamide A (**1**)



Emericellamide B (**2**)

Figure 1. Structures of emericellamides A (**1**) and B (**2**).

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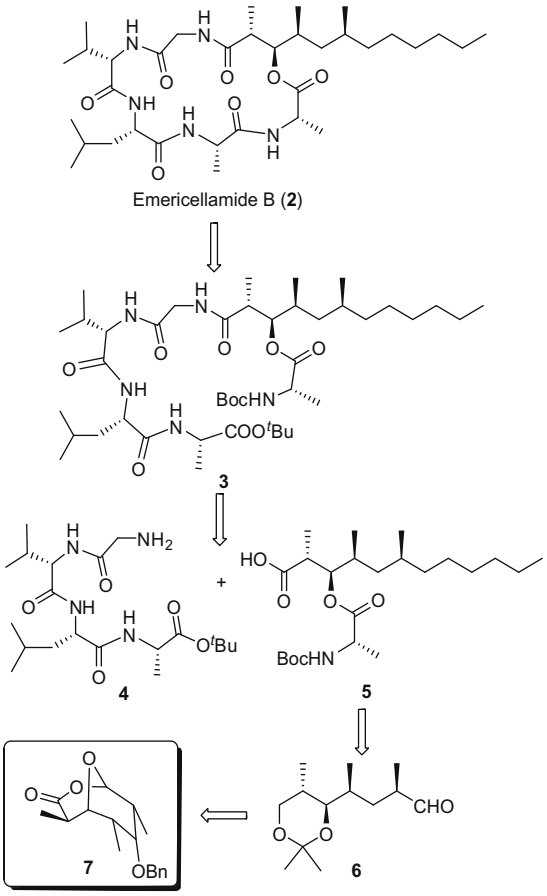
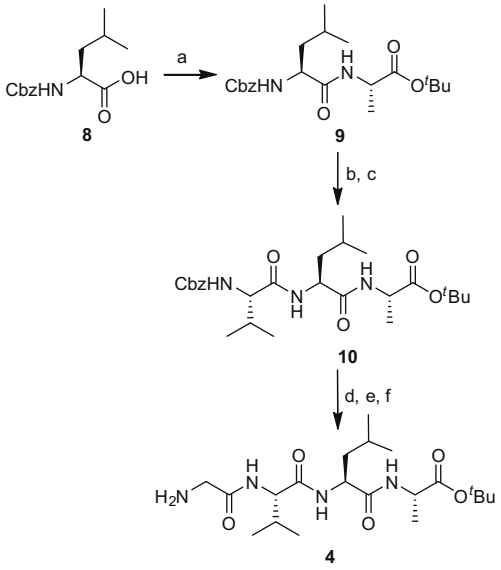


Scheme 1. Retrosynthetic analysis of **2**.



Scheme 2. Reagents and conditions: (a) H-Ala-O^{t}Bu, EDCI, HOBt, CH_2Cl_2, 12 h, 80%; (b) Pd/C (10%), H_2, EtOAc, 2 h; (c) Cbz-Val-OH, EDCI, HOBT, CH_2Cl_2, 14 h, 76%; (d) Pd/C (10%), H_2, EtOAc, 2 h; (e) Cbz-Gly-OH, EDCI, HOBT, CH_2Cl_2, 18 h; (f) Pd/C (10%), H_2, MeOH, 3 h, 64% over three steps.

emericellamide A[8] (**1**), we decided to carry out macrolactamization as the final step of the synthesis. Disconnection of the emericellamide B (**2**) at the two alanine residues would give an advanced intermediate **3** which on further fragmentations would provide tetrapeptide **4** and a polyketide **5**. The tetrapeptide **4** could be obtained following a standard peptide-coupling protocol starting from commercially available protected amino acids. The polyketide fragment **5** could be envisaged following desymmetrization protocol to afford four chiral centers starting from a known bicyclic lactone **7**.[7,9]

Tetrapeptide **4** was synthesized from the commercially available protected amino acids. The coupling of Cbz-leu-OH (**8**) with H-ala-O*t*Bu ester using EDCI (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride and HOBt afforded the dipeptide **9** in 80% yield. Deprotection of the Cbz-group with Pd–C (10%) in ethyl acetate under hydrogen atmosphere followed by coupling with Cbz-val-OH furnished the tripeptide **10** in 76% yield over two steps. Following the same sequence of reactions, **4** was obtained in 64% yield over three steps (Scheme 2).

The synthesis of **5** was initiated (Scheme 3) from a bicyclic intermediate **7**, which was prepared from **12** following desymmetrization with chiral (+)-Ipc$_2$BH, PCC mediated oxidation, Bayer–Villiger oxidation, and diastereoselective alkylation of the lactone **14**. Reduction of the bicyclic lactone **7** with LAH in THF furnished mono-protected tetrol **15** in 89% yield. The 1,3-diol moiety was converted to the acetonide followed by protection of the primary hydroxyl group as its TBS-ether using TBDMSCl and imidazole in CH_2Cl_2 to afford **17**[10] in 94% yield. Deprotection of the benzyl-ether with Pd/C (10%) under hydrogen atmosphere gave **18** in 92% yield. The secondary hydroxyl group was converted to its xanthate derivative **19** and subsequent treatment with Bu_3SnH in the presence of catalytic amount of AIBN under Barton-McCombie[11] conditions to afford **20**[12] (78% yield over two steps). The desilylation of **20** with TBAF in THF provided alcohol **21** in 94% yield. The primary hydroxyl group was oxidized with IBX[13] in DMSO and THF to furnish aldehyde, which on Wittig homologation yielded olefin **22** (74% yield over two steps). Treatment of **22** with catalytic amount of Pd–C (10%) and 6 N HCl in ethyl acetate provided diol **23** (81% yield over two steps). The primary hydroxyl was silylated with TBDMSCl and imidazole to obtain the TBS-ether, esterification of the secondary hydroxyl group with Boc-ala-OH using EDCI and DMAP followed by desilylation with CSA afforded **24**[14] in 56% yield over three steps. The primary hydroxyl group was converted to acid following TEMPO[15]-mediated oxidation to furnish **5** in 78% yield. The acid **5** was activated with EDCI in the presence of HOBt and the amine **4** was coupled to provide our desired final product **3**[16] in 76% yield. The spectral and analytical data of **3** were in good agreement with the previously reported data by Ye et al.[17]

In conclusion, we have achieved the formal total synthesis of emericellamide B from a bicyclic precursor in 15 longest linear steps with 10% overall yield in a convergent fashion which reconfirmed the absolute stereochemistry of emericellamide B.

Acknowledgments

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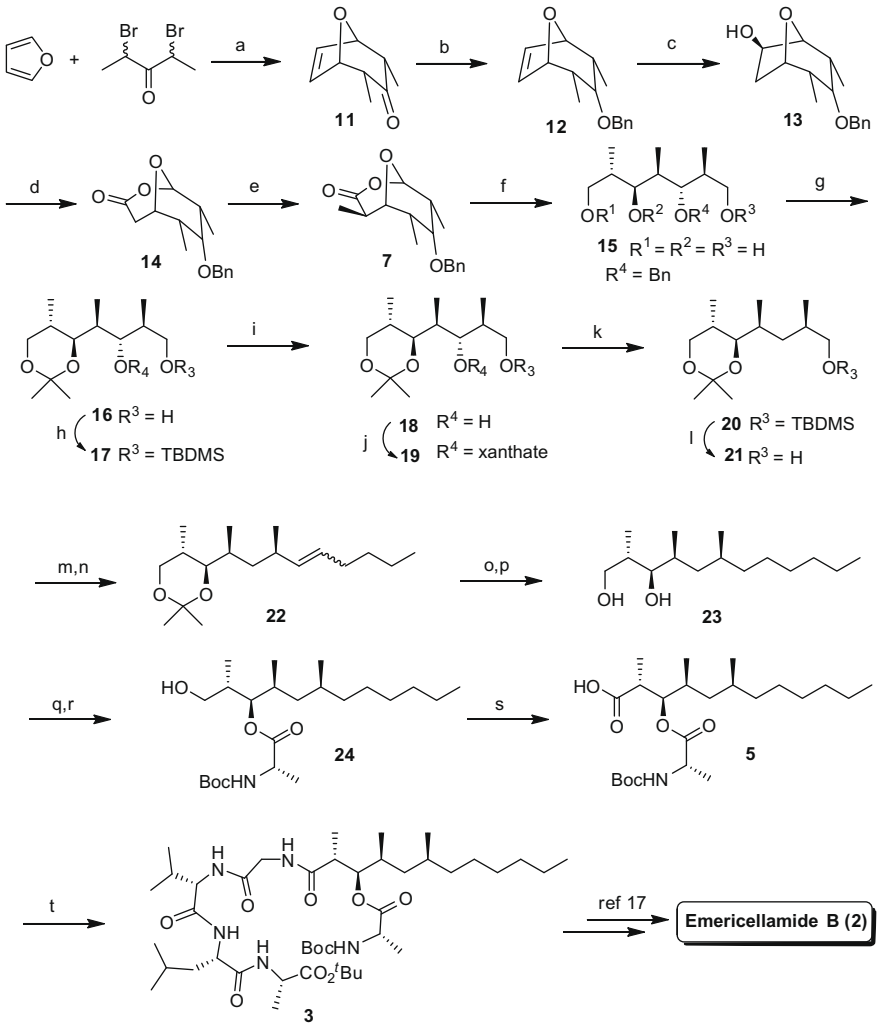
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.015.



Scheme 3. Reagents and conditions: (a) Zn–Cu couple, DME, −10 °C, 6 h, 82%; (b) (1) DIBAL-H, CH_2Cl_2, −10 °C, 1 h, 74% (required product); (2) NaH, BnBr, THF, 50 °C, 94%; (c) (+)-$(Ipc)_2BH$, THF, −20 °C, five days, 92%; (d) (1) PCC, CH_2Cl_2, rt, 3 h, 90%; (2) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 90%; (e) LDA, MeI, THF, −78 °C, 1 h, 94%; (f) LAH, THF, 0 °C to rt, 12 h, 89%; (g) 2,2-DMP, *p*-TSA, CH_2Cl_2, 12 h, 91%; (h) TBDMSCl, imidazole, CH_2Cl_2, 1 h, 94%; (i) Pd/C, H_2, dry hexane, 12 h, rt, 92%; (j) NaHMDS, CS_2, MeI, THF, −78 °C, 1 h; (k) Bu_3SnH, AIBN, PhH, 80 °C, 3 h, 78% over two steps; (l) TBAF, THF, 3.5 h, 94%; (m) IBX, DMSO, THF, 3 h; (n) $Ph_3PC_5H_{11}Br$, NaHMDS, THF, 1 h, 74% over two steps; (o) Pd/C (10%), H_2, EtOAc, 2 h; (p) 6 N HCl, 81% over two steps; (q) TBDMSCl, imidazole, CH_2Cl_2, 1 h, 93%; (r) (i) Boc-Ala-OH, EDCI, DMAP, 0 °C to rt, 12 h, 70%; (ii) CSA, CH_2Cl_2/MeOH (1:1), 0 °C, 1 h, 86%; (s) BAIB, TEMPO, CH_3CN/H_2O (1:1), 78% over two steps; (t) H-Gly-Val-Leu-Ala-O^{t}Bu, EDCI, HOBt, DIPEA, CH_2Cl_2, 12 h, 76%.

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10. *Spectral and analytical data of* ***17***: $[\alpha]_D^{27}$ +27.9 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 2957, 2858, 1462, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.59 (ABq, *J* = 21.1, 12.1 Hz, 2H), 3.84 (dd, *J* = 9.8, 0.75 Hz, 1H), 3.77 (dd, *J* = 9.8, 6.0, 1H), 3.63 (dd, *J* = 11.3, 5.3 Hz, 1H), 3.49–3.39 (m, 2H), 3.37 (dd, *J* = 9.8, 1.5 Hz, 1H), 2.09–1.90 (m, 2H), 1.89–1.76 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.0 Hz, 3H), 0.70 (d, *J* = 6.0 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.44, 128.20, 127.11, 126.85, 97.94, 82.76, 74.61, 73.47, 66.32, 64.16, 38.24, 36.84, 30.30, 29.86, 25.94, 19.48, 15.95, 12.44, 9.91, −5.36; ESIMS: $[M+H]^+$ 451.
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NMR (75 MHz, $CDCl_3$) δ 173.82, 155.14, 74.40, 68.24, 64.03, 49.27, 41.74, 36.92, 36.33, 31.87, 31.24, 29.77, 29.64, 28.25, 26.87, 22.61, 19.99, 18.52, 14.04, 13.84, 12.39; ESIMS: $[M+Na]^+$ 438.

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16. *Spectral and analytical data of* ***3***: $[\alpha]_D^{27}$ −33.1 (*c* 0.4, CH_2Cl_2); mp 117 °C; IR (neat): ν_{max} 3281, 2962, 2928, 1733, 1688, 1635, 1538, 1455, 1369, 1220, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.65 (br s, 1H), 7.16 (br s, 1H), 5.55 (d, *J* = 7.6 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 1H), 4.71–4.57 (m, 1H), 4.50–4.38 (m, 2H), 4.29–4.13 (m, 2H), 3.91 (d, *J* = 14.6 Hz, 1H), 2.79–2.68 (m, 1H), 2.14–1.98 (m, 1H), 1.93–1.82 (m, 1H), 1.74–1.58 (m, 3H), 1.52 (m, 2H), 1.46 (s, 9H), 1.41 (s, 9H), 1.32 (d, *J* = 7.8 Hz, 3H), 1.30 (d, *J* = 7.8 Hz, 3H), 1.24 (br s, 11H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.04–0.97 (m, 1H), 0.95–0.85 (m, 18H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.22, 172.28, 171.67, 170.90, 169.25, 155.31, 81.48, 79.61, 77.67, 60.32, 58.67, 51.39, 49.42, 48.64, 43.10, 41.15, 36.59, 31.85, 31.49, 31.44, 29.58, 29.41, 28.35, 27.89, 26.67, 24.60, 22.80, 22.60, 22.10, 19.98, 19.13, 18.47, 18.09, 17.92, 14.45, 14.04, 13.52; HRMS calcd for $C_{43}H_{79}O_{10}$ $[M+Na]^+$ 848.5724; found 848.5710.
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