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Total synthesis and stereochemical reassignment of maedamide

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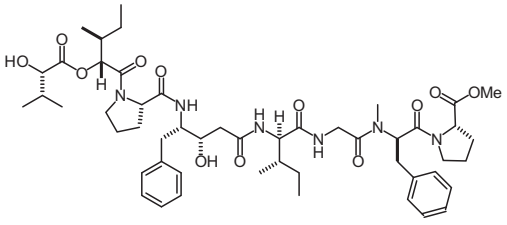
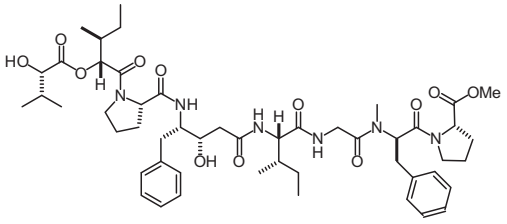
ABSTRACT

The first total synthesis of maedamide, an acyclic peptide isolated from a marine cyanobacterial assemblage of *Lyngbya* sp., was achieved. This synthesis led to reassignment of the *allo*-D-Ile of maedamide to be L-Ile, which was supported by ^{1}H and ^{13}C NMR data.

In 2014, we isolated maedamide, an acyclic depsipeptide, from a marine cyanobacterial assemblage of *Lyngbya* sp.[1] Structurally, maedamide possesses some unusual amino acid residues, such as 4-amino-3-hydroxy-5-phenylpentanoic acid. Maedamide (**2**) inhibited the growth of HeLa and HL60 cells, with IC_{50} values of 4.2 and 2.2 μM, respectively. In addition, maedamide showed inhibitory activity against chymotrypsin, with an IC_{50} value of 45 μM. In this Letter, we describe the first total synthesis and structural reassignment of maedamide.



Originally Proposed Maedamide
(**1**, *allo*-D-Ile)



Maedamide
(**2**, L-Ile)

Our retrosynthetic analysis of maedamide is shown in Scheme 1. Maedamide is formed by carboxylic acid **3** and hexapeptide **4**. Carboxylic acid **3** could be prepared by the condensation of L-valic acid and *allo*-D-isoleucic acid. Meanwhile, hexapeptide **4** could be synthesized by stepwise condensation of the corresponding amino acid moieties, starting with the *C*-terminal residue, *O*-Me-L-Pro.

First, we synthesized carboxylic acid **3** as shown in Scheme 2. Protection of a hydroxyl group of L-valic acid followed by condensation with *O*-Me-*allo*-D-isoleucic acid afforded ester **5**. Demethylation of methyl ester **5** using LiI gave **6**, and removal of the TBS group under acidic conditions provided carboxylic acid **3**.

The synthesis of hexapeptide **4a** commenced with the condensation of the known dipeptide **7**[2] with *N*-Boc-glycine using standard procedures. The obtained tripeptide **8** was further condensed with *N*-Boc-*allo*-D-isoleucine to give tetrapeptide **9a**. Removal of the Boc group of **9a** with TFA and incorporation with known γ-amino acid **11**[3] afforded pentapeptide **10a**. Compound

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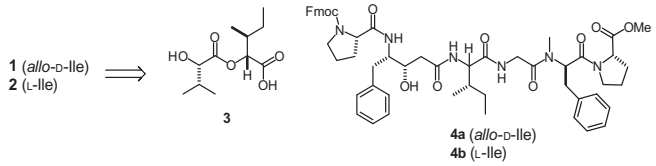
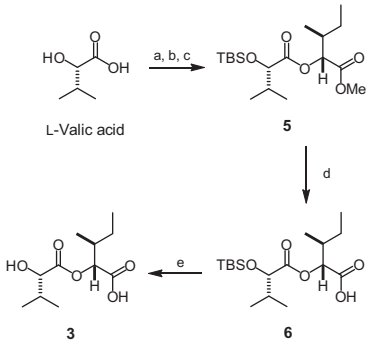
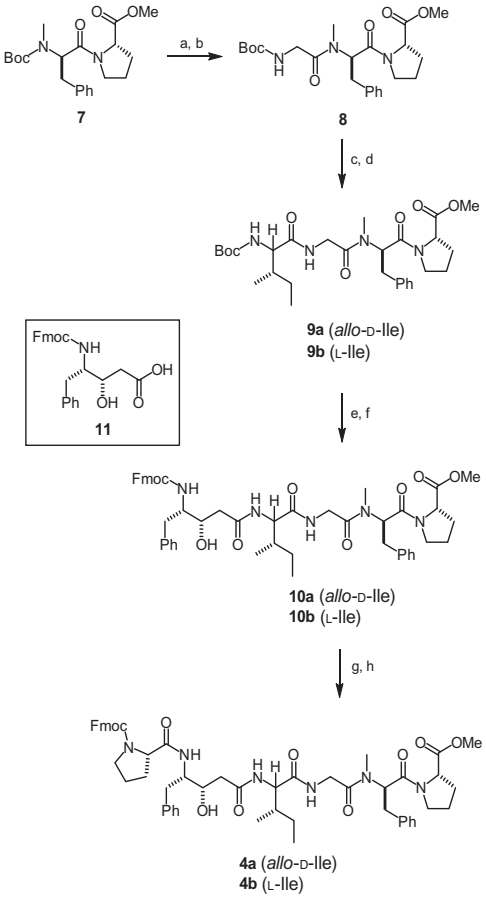
0040-4039/



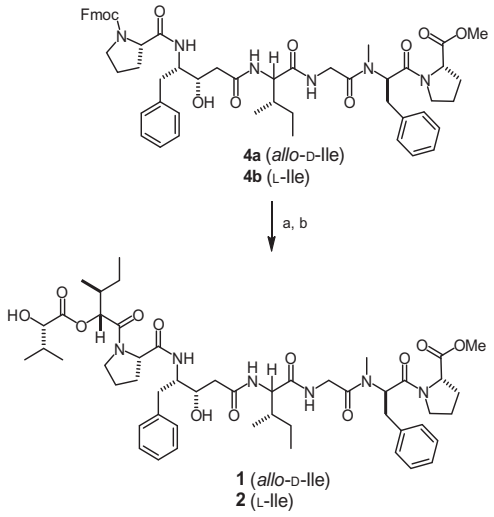
Scheme 1. Retrosynthetic analysis of maedamide.



Scheme 2. Synthesis of carboxylic acid **3**. Reagents and conditions: (a) TBSCl, imidazole, DMF, 40 °C, 22 h, quant; (b) oxalyl chloride, DMF, CH_2Cl_2, 0 °C to rt, 2.5 h; (c) *O*-Me-*allo*-D-isoleucic acid, pyridine, CH_2Cl_2, rt, 4 days, 40% in two steps; (d) LiI, pyridine, reflux, 6 h, quant.; (e) 4 M HCl, 1,4-dioxane, rt, 4 days, quant.



Scheme 3. Synthesis of hexapeptide **4**. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C, 2.5 h; (b) *N*-Boc-glycine, HATU, $^{i}Pr_2NEt$, DMF, 0 °C to rt, 14 h, 80% in two steps; (c) TFA, CH_2Cl_2, 0 °C; (d) *N*-Boc-*allo*-D-isoleucine (**9a**), *N*-Boc-L-isoleucine (**9b**), HATU, $^{i}Pr_2NEt$, DMF, 0 °C to rt, (**9a**) 76% in two steps, (**9b**) 63% in two steps; (e) TFA, CH_2Cl_2, 0 °C, 2 h; (f) **11**, HATU, $^{i}Pr_2NEt$, DMF, 0 °C to rt, 2 h, (**10a**) 54% in two steps, (**10b**) 73% in two steps; (g) Et_2NH, CH_3CN, rt, 3 h; (h) *N*-Fmoc-L-proline, HATU, $^{i}Pr_2NEt$, DMF, 0 °C to rt, 3 h, (**4a**) 48% in two steps, (**4b**) 45% in two steps.



Scheme 4. Synthesis of maedamide **1** and **2**. Reagents and conditions: (a) Et_2NH, CH_3CN, rt, 1 h; (b) **3**, HATU, HOAt, $^{i}Pr_2NEt$, DMF, 0 °C to rt, 1 h, (**1**) 34% in two steps, (**2**) 40% in two steps.

10a was converted to **4a** by condensation with *N*-Fmoc-L-Pro (Scheme 3).

Finally, the condensation of carboxylic acid **3** and hexapeptide **4a** was carried out (Scheme 4). Removal of an Fmoc group of **4a** with DEA in MeCN followed by coupling with carboxylic acid **3** gave the target compound **1**[4] as a colorless oil (10 steps, 5.4% yield from **7**).

However, the NMR data of **1** were inconsistent with those reported for the natural product. A detailed comparison of the NMR data clarified that the ^{1}H NMR and ^{13}C NMR signals assigned to *allo*-D-isoleucine of **1** were most different from the data reported for the natural product. In addition, the structurally related cyanobacterial peptide tasiamide[5] possessed L-isoleucine at the corresponding position. Based on these data, we inferred that maedamide consisted of L-isoleucine rather than *allo*-D-isoleucine. To verify this hypothesis, we synthesized the epimer of **1** possessing L-isoleucine instead of *allo*-D-isoleucine (**2**).

N-Boc-L-isoleucine was condensed with tripeptide **8**, a common intermediate, to give tetrapeptide **9b**. Compound **9b** was converted to **4b** in a similar manner as for **1**. The condensation of **4b** with carboxylic acid **3** afforded the epimer **2**[6] (10 steps, 6.6% yield from **7**). In a comparison of the spectroscopic data of **2** with those of the natural product, **2** corresponded to the natural product.

In conclusion, we have achieved the first total synthesis of maedamide and revised its structure. The revised structure (**2**) differs from the original (**1**) with respect to the absolute configuration of an Ile residue: the correct stereochemistry of the Ile residue is L rather than *allo*-D.

Acknowledgments

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Japan (24310160) and Keio Gijuku Fukuzawa Memorial Fund for the Advancement of Education and Research.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all compounds. Detailed experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.090.

References and notes

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3. Meloni, M. M.; Taddei, M. *Org. Lett.* **2001**, *3*, 337–340.
4. *Compound* **1**: $[\alpha]_D^{27}$ −4.5 (*c* 4.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.31–7.15 (m, 10H), 5.58 (dd, *J* = 8.2, 8.2, 1H), 5.01 (d, *J* = 6.3, 1H), 4.46 (d, *J* = 5.1, 1H), 4.39–4.34 (m, 2H), 4.24 (m, 1H), 4.18 (d, *J* = 4.4, 1H), 4.16 (d, *J* = 17.4, 1H), 4.13 (m, 1H), 3.90 (d, *J* = 17.4, 1H), 3.86 (m, 1H), 3.71 (s, 3H), 3.58–3.39 (m, 3H), 3.21 (d, *J* = 14.2, 8.2, 1H), 3.03 (s, 3H), 3.00–2.92 (m, 2H), 2.83 (dd, *J* = 14.2, 7.3, 1H), 2.44–2.30 (m, 2H), 2.23–2.11 (m, 2H), 2.06–1.82 (m, 6H), 1.77 (m, 1H), 1.63 (m, 1H), 1.51–1.40 (m, 2H), 1.36–1.22 (m, 3H), 1.07 (d, *J* = 7.0, 3H), 1.05 (d, *J* = 6.7, 3H), 1.01–0.91 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.4, 174.6, 174.3, 174.0, 173.1, 171.4, 170.4, 170.1, 140.0, 138.6, 130.5, 130.4, 129.44, 129.37, 127.6, 127.5, 77.7, 76.3, 71.5, 62.4, 60.6, 58.2, 57.8, 56.3, 52.7, 42.0, 41.5, 37.8, 37.7, 37.2, 35.7, 33.4, 30.6, 30.3, 29.9, 27.3, 26.4, 26.0, 24.7, 19.3, 17.3, 15.0, 14.9, 12.1, 12.0; HR (ESI) *m*/*z* 963.5447, calcd for $C_{51}H_{75}N_6O_{12}$ $[M+H]^+$ 963.5443.
5. Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 1336–1339.
6. *Compound* **2**: $[\alpha]_D^{29}$ +17 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.29–7.16 (m, 10H), 5.55 (dd, *J* = 8.3, 7.8, 1H), 5.01 (d, *J* = 6.2, 1H), 4.36 (m, 1H), 4.35 (m, 1H), 4.28 (d, *J* = 6.5, 1H), 4.20 (m, 1H), 4.17 (d, *J* = 4.4, 1H), 4.13 (m, 1H), 4.09 (d, *J* = 17.5, 1H), 3.94 (d, *J* = 17.5, 1H), 3.86 (m, 1H), 3.71 (s, 3H), 3.53 (m, 1H), 3.38 (m, 1H), 3.37 (m, 1H), 3.20 (dd, *J* = 14.2, 8.3, 1H), 3.03 (s, 3H), 2.98 (m, 1H), 2.92 (m, 1H), 2.82 (dd, *J* = 14.2, 7.8, 1H), 2.38 (m, 1H), 2.37 (m, 1H), 2.18 (m, 1H), 2.16 (m, 1H), 1.97–1.80 (m, 6H), 1.76 (m, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.46 (m, 1H), 1.36–1,31 (m, 2H), 1.21 (m, 1H), 1.07 (d, *J* = 7.0, 3H), 1.05 (d, *J* = 6.7, 3H), 0.97–0.95 (m, 9H), 0.91 (t, *J* = 7.5, 3H);^{13}C NMR (100 MHz, CD_3OD) δ 177.2, 174.1, 174.00, 173.95, 173.3, 171.3, 170.3, 170.2, 140.1, 138.6, 130.5, 130.4, 129.40, 129.36, 127.6, 127.5, 77.6, 76.3, 71.1, 62.4, 60.6, 59.7, 57.8, 56.0, 52.7, 41.9, 41.2, 37.8, 37.9, 37.2, 35.7, 33.2, 30.6, 30.4, 29.9, 26.4, 26.0, 25.7, 24.8, 19.3, 17.1, 16.1, 14.9, 12.0, 11.9; HR (ESI) *m*/*z* 985.5224, calcd for $C_{51}H_{74}N_6O_{12}Na$ $[M+Na]^+$ 985.5262.