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57-NORMAJUSCULAMIDE C, A MINOR CYCLIC DEPSIPEPTIDE ISOLATED FROM *LYNGBYA MAJUSCULA*

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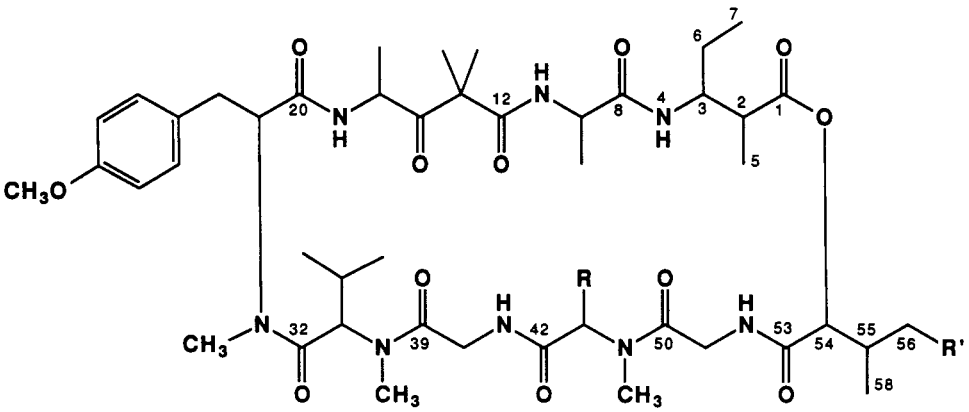
We have previously reported the isolation and structure elucidation of majusculamide C [**1**], a novel cyclic depsipeptide constituent of the deep-water variety of *Lyngbya majuscula* growing in the lagoon of Enewetak Atoll in the Marshall Islands (1). Majusculamide C has been shown to possess significant activity against fungal plant pathogens including *Phytophora infestans* and *Plasmopora viticola*, the causative organisms of tomato late blight and grape downy mildew, respectively (1,2). Recently Kamano *et al.* (3) have reported the structure of dolastatin 11 [**2**], the major antineoplastic constituent of the sea hare *Dolabella auricularia* from the Indian Ocean. Dolastatin 11 was shown to be identical with majusculamide C [**1**] except for substitution of an *N*-methylleucine residue in place of the *N*-methylisoleucine residue found in majusculamide C. This report has prompted us to recount our isolation of a trace majusculamide C homolog, 57-normajusculamide C [**3**], which we encountered in the course of characterizing a partially purified sample of majusculamide C for plant antifungal studies. Like majusculamide C, **3** exhibited antimycotic activity against the indicator organism *Saccharomyces pastorianus*.

The presence of the molecular ion at *m/z* 970 in the field desorption mass spectrum of **3** suggested that **3** was a CH_2 lower homolog of **1**. A comparison of the ^{1}H-nmr spectra of **3** and **1** obtained in $CDCl_3$ revealed significant differences only in the region of Me resonances between ca. 0.86 and ca. 0.96 ppm and the positions of one-proton multiplets between ca. 2.0 and ca. 2.4 ppm. The proton assignments of isoleucic acid, the hydroxy acid residue found in **1**, are shown in Figure 1a. The doublet at 5.19 ppm in **1** is slightly shifted to 5.17 ppm in **3**. The proton at 5.17 is coupled to a methine proton at 2.35 ppm, which in turn is coupled to two methyl doublets at 0.92 ppm. Irradiation of the proton at 2.35 ppm col-



1 R=$CH(CH_3)CH_2CH_3$, R′=Me
2 R=$CH_2CH(CH_3)_2$, R′=Me
3 R=$CH(CH_3)CH_2CH_3$, R′=H

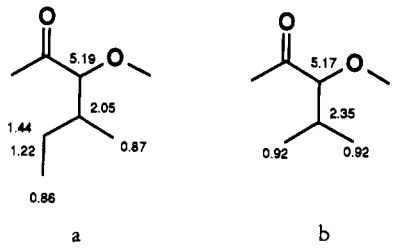


FIGURE 1. ^{1}H-nmr chemical shifts (ppm) for α-hydroxy acid residues of majusculamide C [**1**] (1) (a) and 57-normajusculamide C [**3**] (b).

lapsed the doublet at 5.17 and the doublets at 0.92 ppm; irradiation at 0.92 ppm collapsed the multiplet at 2.35 ppm to a doublet. Thus, **3** contains the α-hydroxyisovaleric acid residue (see Figure 1b) in place of the isoleucic acid residue of **1**.

The amino acid sequence and the substitution of an α-hydroxyisovaleric acid unit for the isoleucic acid residue in **1** were further supported by difference nOe spectroscopy. Essentially the same nOes were observed for **1** and **3** (1). The amino acid sequence was also corroborated by eims. The eims of saponified **3**, for example, showed fragment ions at *m/z* 101, 158, 285, 342, 455, and 646, which were 16 amu lower than the ones seen for **1**. As expected these ions shifted to *m/z* 87, 186, 313, 384, 497, and 688 (Figure 2) upon methylation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr spectra were recorded on a Bruker WH360 spectrometer. Field desorption mass spectra were obtained on a Varian-MAT 731 spectrometer. Electron impact mass spectra were obtained on a Varian-MAT 311 instrument.

ISOLATION OF 57-NORMAJUSCULAMIDE C [**3**].—Nearly pure majusculamide C (23 mg dissolved in 100 μl MeOH), obtained as previously described (1), was subjected to final reversed-phase hplc on a Dupont Zorbax C-8 column (9.4 mm × 25 cm) using a mobile phase of MeCN-H_2O (9:1) at a flow rate of 4.0 ml/min. Uv absorption was monitored at 280 nm, and peaks were manually collected. The minor cyclic depsipeptide factor **3** eluting at 15 min was concentrated to dryness to give a white film (0.65 mg). Majusculamide C [**1**] (9 mg, calculated from peak areas) eluted at 18 min.

DERIVATIVES.—Saponification of **3** and permethylation of the resulting acyclic hydroxy acid were carried out using previously described procedures (1).

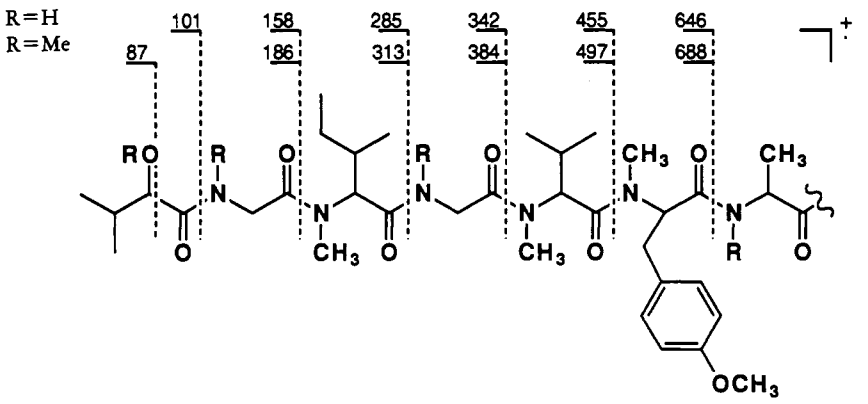


FIGURE 2. Mass spectral fragmentation of 57-normajusculamide C [**3**] and permethylated derivative.

ACKNOWLEDGMENTS

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