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Article

Maigheotides A–C, Peptides from the Deep-Sea Black Coral *Phanopathes* sp.

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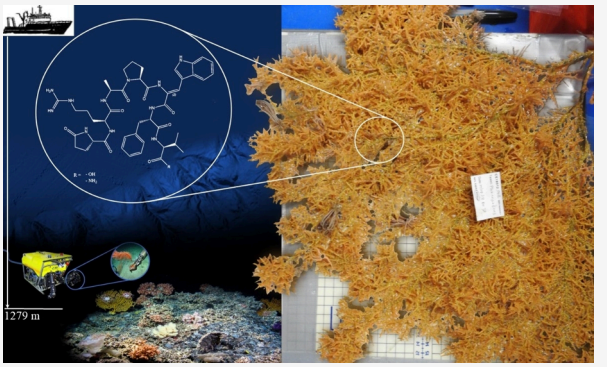
ABSTRACT: Black corals have been poorly studied with respect to their secondary metabolite chemistry. With the aim of discovering new bioactive metabolites, we collected deep-sea black corals from the Irish continental margin. Our analysis of the black coral *Phanopathes* sp. yielded three new peptides (maigheotides A-C). Through a combination of 2D NMR, mass spectrometry, and Marfey's analysis, the absolute configuration of all three structures was elucidated. The maigheotides are characterized by a noncanonical amino acid Δ^{Z}-Trp, the cyclized N-terminal Glu (pyroGlu), and C-terminal amide (maigheotide B). Similar characteristics are critical features found in neuropeptides. Screening in a number of assays has identified only weak activity, although the breadth of assays screened was limited by the small mass of peptides obtained.



Black corals, or antipatharians (Cnidaria: Anthozoa: Hexacorallia: Antipatharia), are best known for their use in jewelry where they have been used since the ancient Greeks wore them as charms; the systematic name is derived from the Greek "anti" and "pathos", reflecting their intended use to avert pain or disease.[1,2] Their pharmaceutical potential has been little explored, possibly due to their listing in Annex II of the CITES Convention, which places restriction on export.[3,4]

Like many marine invertebrates that lack specialized physical defenses, such as soft-bodied sponges, soft corals, and zoanthids, black corals may harbor secondary metabolites as a defense against predation.[5] Shallow-water corals can harbor symbiotic photosynthetic organisms, zooxanthellae, that contribute to their chemical defenses.[6,7] However, many black corals are found below 200 m, the limit of light penetration, and thus are largely azooxanthellate and must depend on their own biosynthetic capabilities to produce chemical defenses.[8]

Previous chemical analysis of black corals resulted in the isolation of steroids, fatty acids, and alkaloids.[9−13] However, antipatharians, like other Cnidaria, have genes for small, neurologically active peptides,[14] few of which have been isolated and chemically characterized. Herein we present the first peptides (Figure 1), the maigheotides (phonetically "mayotides"; Maigh Eo is the Irish name for County Mayo, nearby to the collection site of the corals) isolated from a black coral, *Phanopathes* sp. (Figure 2), that are reminiscent of Cnidarian neurotoxins, bearing nonproteinogenic amino acids that may contribute to peptide stability and bioactivity.

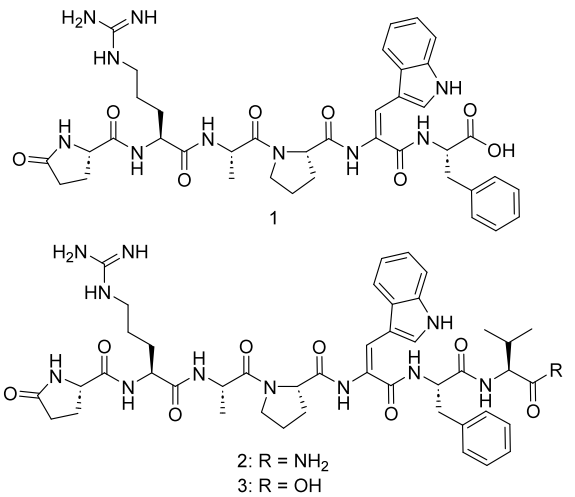


Figure 1. Maigheotides A-C (**1**−**3**, respectively) share two post-translation modifications, pyroGlu and Δ^{Z}-Trp.

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Figure 2. *Phanopathes* sp., source colony of the material was collected from the Irish continental margin 200 km west of County Mayo, Ireland.

RESULTS AND DISCUSSION

Samples from three colonies of *Phanopathes* sp. were collected from the Irish deep-sea in August, 2018. Freeze-dried corals were extracted with hot dichloromethane using a Soxhlet apparatus and then 3X with MeOH at room temperature. The MeOH extract was fractionated with reverse phase MPLC, and then followed by HPLC separation on a C18 semipreparative column, resulting in three new peptides, maigheotides A-C (**1**–**3**) (Figure 1). Screening of mass spectrometric and NMR data found no matches in Scifinder[15] or Marinlit[16] databases. Maigheotide A (**1**) was assigned the chemical formula $C_{39}H_{48}N_{10}O_8$ with 21 degrees of unsaturation based on HRESIMS+ (m/z 785.3712 $[M + H]^+$, calcd. for $C_{39}H_{49}N_{10}O_8$, 785.3729) and ^{13}C NMR analysis. gHSQC analysis revealed five methine, eight aromatic, one olefinic, nine methylene, and one methyl signals. The observation of five α-methine protons (δ_H 4.08–4.51) was suggestive of a minimum of five amino acids in a peptide sequence. With the addition of ^{13}C NMR data, seven amide/acid-type carbonyls and six aromatic/olefinic quaternary carbons were observed, which were compatible with a hexapeptide structure.

Further analysis of 2D NMR spectra for maigheotide A (Figure 3) established the peptide's N-terminal amine, cyclized as pyroglutamate (pyroGlu) with N–H (δ_H 7.87), a methine (δ_H 4.08, δ_C 55.4 C-α), two methylene groups (δ_H 2.23 H-β_a and 1.89 H-β_b, δ_C 25.2 C-β; δ_H 2.12 H-γ_a and 2.05 H-γ_b, δ_C 29.2 C-γ), lactam carbonyl (δ_C 177.5 C-δ), and peptide carbonyl (δ_C 172.2 C=O). This assignment is based on HMBC correlations between lactam NH (δ_H 7.87), α-methine (δ_H 4.08), and two methylene protons (δ_H 2.12 and 2.05) to the lactam carbonyl. The arginine (Arg) framework was derived from gCOSY and zTOCSY correlations from a N–H at δ_H 7.97 to an α-methine (δ_H 4.45) and three methylene groups (β: δ_H1.86 H-β_a, 1.48 H-β_b; C-γ: δ_H 1.51, and δ: δ_H 3.14 H-δ_a and 2.97 H-δ_b). Overlapping methine signals at δ_H 4.45 were distinguished based on HMBC correlations from NH (δ_H 7.97) to an α-methine carbon at δ_C 51.1. NOE between δ_H 4.08 (α-pyroGlu) and δ_H 4.45 (α-Arg), as well as these protons' HMBC correlations to an amide carbonyl (δ_C 172.2, pyroGlu C=O) confirmed the Arg α-amine formed a peptide bond with the pyroGlu carboxylic acid carbon and, supported by fragmentation in the mass spectrum (Figure S12), established the N-terminus of the peptide as pER.

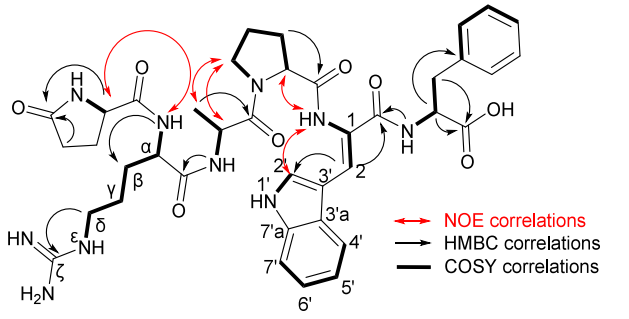

Figure 3. Key NMR correlations used to elucidate the maigheotide A (**1**) structure.

An alanine (Ala) substructure could be constructed based on gCOSY correlations from an NH proton at δ_H 8.42, to an α-methine at δ_H 4.45 and a methyl group at δ_H 1.20, confirmed with HMBC correlation between the N–H and methine carbon (δ_C 47.2). Further analysis of the HMBC spectrum shows the NH of Ala and the β-methylene protons of Arg (δ_H 1.86 H-β_a and 1.48 H-β_b) correlating to the Arg carbonyl at δ_C 171.0, establishing a peptide bond between Arg and Ala. A carbonyl at δ_C 170.7 had HMBC correlations with the α-methine (δ_H 4.45) and methyl (δ_H 1.20) protons of Ala.

Proline (Pro) was established as the next amino acid in the peptide. Starting from gCOSY and zTOCSY correlations of an α-methine (δ_H 4.51) and three methylene groups (β: δ_H 2.24 H-β_a and 1.88 H-β_b; γ: δ_H 2.08 H-γ_a and 1.89 H-γ_b; δ: δ_H 3.81 H-δ_a and 3.51 H-δ_b), and lack of N–H signal, a carbonyl (δ_C 171.6) could be concatenated based on HMBC correlations from both δ_H 4.51 and δ_H 2.24/1.88. NOE correlations shared between the Ala-methyl (δ_H 1.20) and nitrogen bearing methylene (δ_H 3.81 H-δ_a and 3.51 H-δ_b) connect Pro and Ala with a peptide bond. MS/MS fragmentations observed at m/z 339.1771 (pERA) and 436.2308 (pERAP) supported the Pro-Ala sequence.

An indole moiety was found through gCOSY correlations, linking H-4' through H-7' (δ_H 7.65, 7.11, 7.16, 7.43 respectively), as well as NH-1' (δ_H 11.59) and H-2' (δ_H 7.69). HMBC correlations revealed shared quaternary carbons (δ_C 109.3, 127.1, and 135.4) between H-2' (δ_H 7.69), –4' (δ_H 7.65), and –7' (δ_H 7.43), completing an indole ring. However, the substructure lacked HMBC correlations to an α-methine and β-methylene of tryptophan, instead displaying a proton at δ_H 7.64 (δ_C 123.2) and HMBC-correlated quaternary carbon (δ_C 124.2), suggesting an α,β-unsaturated tryptophan (Δ-Trp). gCOSY correlation placed the NH (δ_H 9.69) allylic to H-2 (δ_H 7.64) and HMBC correlations shared with NH-Δ-Trp (δ_H 9.69) and the Pro α-methine (δ_H 4.51) to a carbonyl (δ_C 171.6) link Pro to Δ-Trp. MS/MS fragmentations observed at m/z 436.2308 (pERAP) and 620.2928 (pERAPΔW) supported the Δ-Trp-Pro sequence.

Finally, a phenylalanine (Phe) subunit was established from gCOSY between aromatic signals δ_H 7.25 (δ), δ_H 7.17 (ε) and δ_H 7.09 (ζ) as well as the NH (δ_H 8.00), α-methine (δ_H 4.36) and β-methylene (δ_H 3.07 H-β_a and 2.76 H-β_b). HMBC from H-2-Δ-Trp (δ_H 7.64) and the Phe α-methine with a peptide carbonyl at δ_C 163.0 complete peptide linkage between Δ-Trp and Phe. A terminal carboxylic acid carbonyl shared HMBC correlations with the Phe α-methine (δ_H 4.36) and Phe β-methylene (δ_H 3.07 H-β_a and 2.76 H-β_b).

Maigheotides B (**2**) and C (**3**) both share the maigheotide A peptide sequence (pERAPΔWF) with an additional valine

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Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data of Maigheotides A (1), B (2), and C (3) in DMSO-d_6

		1		2		3	
Amino Acid	Pos.	δ_C, mult.	δ_H, mult. (J in Hz)	δ_C, mult.	δ_H, mult. (J in Hz)	δ_C, mult.	δ_H, mult. (J in Hz)
pGlu	N−H		7.87, s		7.88, s		8.29, s
	CO	172.2, C		173.0, C		172.7, C	
	α	55.4, CH	4.08, dd (8.5, 4.2)	55.9, CH	4.10, d (6.6)	55.8, CH	4.32, d (7.9)
	β_a	25.2, CH_2	2.23, m	25.6, CH_2	2.25, m	24.6, CH_2	2.15, m
	β_b		1.89, m		1.90, m		
	γ_a	29.2, CH_2	2.12, m	29.7, CH_2	2.14, m	29.8, CH_2	2.14, m
	γ_b		2.05, m		2.09, m		2.06, m
	δ	177.5, C		177.9, C		177.6, C	
Arg	N−H		7.97, d (8.3)		8.26, br		8.60, d (5.6)
	CO	171.0, C		171.4, C		171.6, C	
	α	51.1, CH	4.45, m	52.3, CH	4.30, m	54.7, CH	4.1, m
	β_a	29.8, CH_2	1.86, m	29.5, CH_2	1.72, m	29.7, CH_2	1.77, m
	β_b		1.48, m		1.5, m		1.71, m
	γ_a	24.8, CH_2	1.51, m	25.3, CH_2	1.5, m	25.4, CH_2	1.70, m
	γ_b						1.6, m
	δ_a	39.7, CH_2	3.14, m	40.4, CH_2	3.08, m	40.9, CH_2	3.15, m
	δ_b		2.97, m				3.04, m
	N−H, ε		10.25, br		8.86, br		9.67, br
	ζ	157.3, C		157.7, C		158.1, C	
Ala	N−H		8.42, d (5.9)		8.36, d (6.9)		8.43, d (5.9)
	CO	170.7, C		171.6, C		170.9, C	
	α	47.2, CH	4.45, m	46.8, CH	4.57, m	47.3, CH	4.62, m
	β	16.1, CH_3	1.2, d (7.4)	17.2, CH_3	1.18, d (6.9)	17.4, CH_3	1.25, d (7.0)
Pro	CO	171.6, C		172.5, C		172.1, C	
	α	60.4, CH	4.51, t (7.6)	60.8, CH	4.43, dd (7.7, 4.9)	60.9, CH	4.49, m
	β_a	28.5, CH_2	2.24, m	29.4, CH_2	2.15, m	28.8, CH_2	2.26, m
	β_b		1.88, m		1.91, m		1.90, m
	γ_a	25.4, CH_2	2.08, m	25.2, CH_2	2.00, m	25.9, CH_2	2.09, m
	γ_b		1.89, m		1.89, m		1.91, m
	δ_a	46.8, CH_2	3.81, m	47.4, CH_2	3.63, m	47.4, CH_2	3.8, m
	δ_b		3.53, m				3.53, m
Δ-Trp	N−H		9.69, br		9.59, br		9.81, br
	CO	163.0, C		165.4, C		164.2, C	
	1	124.2, C		123.8, C		124.0, C	
	2	123.2, CH	7.64, s	123.0, CH	7.48, s	124.0, CH	7.66, m
	N−H, 1'		11.59, d (2.0)		11.89, br		11.63, br
	2'	126.6, CH	7.69, d (2.4)	128.1, CH	7.85, s	127.4, CH	7.7, d (2.0)
	3′	109.3, C		109.2, C		109.6, C	
	4'	118.0, CH	7.65, d (7.7)	118.4, CH	7.69, d (7.8)	118.5, CH	7.67, m
	5′	120.0, CH	7.11, m	120.6, CH	7.14, t (7.2)	120.6, CH	7.13, m
	6'	122.0, CH	7.16, m	122.5, CH	7.18, m	122.6, CH	7.18, m
	7'	111.9, CH	7.43, d (8.3)	112.4, CH	7.45, d (7.9)	112.4, CH	7.45, d (7.9)
	7'a	135.4, C		136.0, C		136.0, C	
	3′a	127.1, C		127.6, C		127.5, C	
Phe	N−H		8.00, d (9.3)		7.76, d (7.8)		7.95, m
	CO	176.0, C		171.3, C		170.7, C	
	α	56.7, CH	4.36, td (8.8, 5.9)	55.2, CH	4.60, m	55.1, CH	4.8, q (4.8)
	β_a	39.5, CH_2	3.07, dd (13.6, 5.3)	37.1, CH_2	3.2, dd (14.1, 4.4)	39.6, CH_2	3.01, m
	β_b		2.76, dd (13.0, 8.0)		3.05, m		2.65, m
	γ	140.4, C		138.7, C		138.4, C	
	δ	129.6, CH	7.25, d (7.3)	129.7, CH	7.27, m	129.7, CH	7.20, m
	ε	127.7, CH	7.17, m	128.5, CH	7.25, m	128.4, CH	7.17, m
	ζ	125.3, CH	7.09, m	126.7, CH	7.19, m	126.4, CH	7.12, m
Val	N−H				7.72, d (9.1)		8.22, br
	CO			173.3, C		177.0, C	
	α			58.6, CH	4.09, d (6.7)	63.5, CH	3.63, t (7.7)
	β			30.6, CH	2.03, m	29.7, CH	1.9, m
	γ			19.8, CH_3	0.88, d (3.7)	20.2, CH_3	0.87, d (2.2)
	γ'			18.5, CH_3	0.87, d (3.7)	20.1, CH_3	0.86, d (2.2)

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Table 1. continued

		1		2		3	
Amino Acid	Pos.	δ_C, mult.	δ_H, mult. (J in Hz)	δ_C, mult.	δ_H, mult. (J in Hz)	δ_C, mult.	δ_H, mult. (J in Hz)
	N−H′				7.19, br; 7.1, br		

group at the C-terminus. In maigheotide B, the valine substructure was established through gCOSY correlations between the α-methine (δ_H 4.09), β-methylene (δ_H 2.03), and the nonequivalent γ,γ' methyl doublets (δ_H 0.86 and 0.87, respectively). In addition to the valine group, maigheotide B contains a terminal amide (two, nonequivalent N−H at δ_H 7.1 and 7.19) with an HMBC correlation to the valine α-methine (δ_C 58.6) and amide carbonyl (δ_C 173.3). Notably, these N−H correlations are absent in maigheotide C, which is 1 amu larger than that in maigheotide B.

Absolute configuration for maigheotides A-C (**1**-**3**) was established using Marfey's analysis and NOE correlations. Based on retention time comparisons of standard L- and D-amino acids to maigheotide A hydrosylate, the absolute configuration was determined to be L-pyroGlu-L-Arg-L-Ala-L-Pro-Δ^Z-Trp-L-Phe. Maigheotides B and C were also found with L-configured amino acids, including the L-configured valine (maigheotide C) and its amide (maigheotide B). The Z-confirmation of Δ^Z-Trp was established by observation of an NOE between H-2′ (δ_H 7.69) and the Δ-Trp NH (δ_H 9.69).

These new black coral peptides contain multiple types of posttranslational modifications. Modifications to the C- and N-termini of peptides can be linked to peptide stability and bioactivity.[17] Maigheotides A-C all exhibit pyroGlu on the N-terminal, a cyclization that can occur spontaneously, catalyzed by phosphate ions, or enzymatically from glutaminyl cyclase (GC); GC-like enzymes have been documented in many vertebrates, bacteria, and invertebrates including Cnidaria.[17,18] Previous examples of pyroGlu motifs have shown protection against general aminopeptidases as well as aggregation.[18,19] Maigheotide B was the only peptide with the C-terminal amide; C-terminal amide modifications may contribute to secondary folding of peptides or increased binding to membranes.[20,21] Terminal amide motifs have multiple posttranslational modification pathways, but the frequent mechanism in cnidarians is linked to peptidyl-glycine monooxygenase converting a glycine residue into a C-terminal amide.[22] N-terminal pyroGlu and C-terminal amide protecting groups are common motifs found in neuropeptides within the class Hexacorallia, but research on neuropeptides in black corals is still understudied.[22]

Maigheotides A-C contain a nonproteinogenic amino acid, Δ-Trp. α,β-Dehydroamino acids are common modifications to neuropeptides used for cell signaling, although the biosynthetic pathway is not well described in marine organisms.[23] α,β-Dehydroamino acids could contribute to increased bioactivity or increased binding to specific receptors from being a Michael-like acceptor.[23,24] Δ^Z-Trp modification has been found in several peptides that show promising anticancer and antimicrobial bioactivity. Examples include cyclic peptide keramamide F, isolated from a sponge, which showed cytotoxicity against human epidermoid carcinoma KB cells (IC_{50} 1.4 μg/mL)[25] and janthinocin C, from a fresh-water bacterium,[26] which showed comparable bioactivity to vancomycin against Gram-positive bacteria.[26] Although Δ^Z-Trp-bearing sclerotide A was isolated from a coral-derived *Aspergillus*[27] this is the first instance of Δ^Z-Trp appearing in a coral peptide.

Although the functionality of these peptides remains unknown, their possible biological function might be related to neuropeptides due to their structural similarities. PxFVa-mide neuropeptides have been isolated from multiple species of molluscs and worms.[28] Maigheotides represent the first reported peptide secondary metabolites from black corals and offer the first glimpse into the secondary metabolomics of the genus *Phanopathes*. Bioassay analysis showed that maigheotides exhibited no cytotoxicity in several cell lines and they were inactive against *Candida* spp., ESKAPE and *Mycobacterium bovis* pathogens at concentrations <50 μM. The future potential of these peptides may lie in their similarity to insect neuropeptides, such as pyrokinin, which shares the pyroGlu and C-terminal amide protecting groups,[29] though insufficient supply is available for further screening.

EXPERIMENTAL SECTION

General Experimental Procedures. Solvents were obtained from Fisher Scientific Co. (Hampton, NH, USA) and were HPLC grade (>99% purity) unless otherwise stated. MPLC analysis and fractionation were performed on a Teledyne-Isco CombiFlash system equipped with an evaporative light scattering detector (ELSD). HPLC analysis and fractionation was performed on a Shimadzu LC20-AT system equipped with a Shimadzu ELSD II detector, using semipreparative or preparative C-18 ((250 × 10 mm, 5 μm) or (250 × 21.2 mm, 5 μm)) conditions. High-resolution accurate mass spectrometry-liquid chromatography data were obtained on a Hybrid Quadrupole-Orbitrap Mass Spectrometer (Q Exactive Plus, Thermo) in-line with nanoUHPLC (Ultimate 3000, Thermo). Analysis of MPLC fractions was conducted on an Agilent 6540 LCMS-QTOF coupled with the 1260 Infinity. Marfey's analysis was completed on Sciex TripleTOF 5600+ coupled with a Shimadzu Nexera X2 (LC-30) LC/MS using an Agilent Poroshell HPH-C18 column (3.0 × 100 mm, 2.7 μm). NMR analysis was completed on a 600 MHz 5 mm TXI CryoProbe, Bruker Avance III HD Console, Magnex 14.1 T/54 mm ASC Magnet (Magnet Advanced Magnetic Resonance Imaging and Spectroscopy, McKnight Brain Institute, University of Florida, AMRIS). NMR spectra were acquired in DMSO-d_6 with residual solvent referenced as an internal standard (δ_H = 2.50 ppm; δ_C = 39.5 ppm) for ^{1}H and ^{13}C NMR spectra, respectively. UV absorptions were measured by an Agilent Cary 60 UV−vis spectrophotometer in MeOH, while thin film IR spectra were recorded with an Agilent Cary 630 FTIR. Optical rotations in MeOH were measured using an AutoPol IV polarimeter (Hackettstown, NJ, USA) at 589 nm utilizing a 10 mm path length cell.

Biological Materials. Sampling was conducted along the Celtic continental margin using ROV *Holland* 1 and RV *Celtic Explorer* (Cruise CE18012). Samples from three colonies of *Phanopathes* sp. were collected and exported from Galway University to University South Florida under CITES permit IE-19−000007, at depths between 821 and 1279 m at three locations (SFI-669:54.2600237° N 11.58093894° W, SFI-477:54.06198165° N 12.5492809° W, SFI-466:54.06146186° N 12.54718825° W). Samples were immediately placed in −2 °C seawater, cleaned of epiphytes and freeze-dried until solvent extraction. A small tissue sample of each colony was stored separately in ethanol at −20 °C for subsequent DNA extraction.

Colonies were sequenced across two regions of the mitochondrial genome: (1) igrW (the intergenic region between trnW and ND2), (2) igrN (the intergenic region between ND1 and ND5), and a region

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of the nuclear ribosomal cluster including ITS1 and ITS2. GenBank accession numbers are listed in Table 2.

Table 2. GenBank Accession Numbers for Specimens in This Study

Specimen	igrW	igrN	ITS1/ITS2
SFI669	PV952383	PV952380	PV939375
SFI477	PV952384	PV952381	PV939376
SFI466	PV952385	PV952382	PV939377

Extraction and Isolation of Natural Products. Specimens were extracted with dichloromethane by Soxhlet, then steeped in MeOH 3X for 24 h each. The peptides were found in the MeOH extract, which was fractionated initially with reverse phase MPLC with water and MeOH (10 g dry-loaded with 60 g C18 on an 86 g C18 column; 10−100% MeOH gradient over 60 min, 45 mL/min), with 12 fractions collected. LCMS-QTOF analysis revealed MPLC fractions 4−6 (collected at 16.5−22 min, 22−27.5 min, and 27.5−33 min, respectively) contained masses >700 Da that did not match known structures in MarinLit database for Antipatharia. Fractions 4−6 were further purified on reverse phase HPLC with water and ACN on phenyl hexyl semipreparative column (100 μL injections of 50 mg/mL solutions, 10% ACN isocratic for 10 min and 10−60% ACN gradient over 40 min, 5 mL/min). Three pure compounds were collected at 15.8 min (compound 1), 19.5 min (3), and 22.0 min (2). Compounds 1−3 were dried through vacuum and resulted in 6.5 mg, 12.4 mg, and 1.9 mg of material, respectively. ^{1}H and ^{13}C NMR spectra were recorded in 0.2 mL of DMSO-d_6 using a 3 mm tube. ^{1}H and ^{13}C NMR assignments were supported by gCOSY, gHSQC-DEPT, gHMBC, zTOCSY, and NOESY spectra. The absolute configurations were established by Marfey's analysis. Each peptide (0.3 mg) was hydrolyzed at 100 °C with 2 M HCl for 24 h and dried. The dried hydrolysate was mixed with 40 μL of L-FDAA in 1% acetone and 20 μL of 1 M $NaHCO_3$ for 1 h at 40 °C, then neutralized with 20 μL of 1 M HCl, diluted with 400 μL ACN. Amino acid profiles from each peptide were compared by 1 h gradient (10−100% ACN with 0.1% formic acid) on LC/MS to L- and D-amino acid standards to determine absolute configuration.

Maigheotide A (1). Clear oil, $[\alpha]_D^{22}$-72.0 (*c* 0.1, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 327 nm (4.26); IR υ (thin film): 3315, 2950, 2835, 2195, 1620, 1430, 1390, 1085, 1010 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 785.3712 $[M + H]^+$ (calcd. for $C_{39}H_{49}N_{10}O_8$, 785.3729).

Maigheotide B (2). Clear oil, $[\alpha]_D^{22}$-44.7 (*c* 0.1, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 331 nm (3.79); IR υ (thin film): 3290, 3205, 2985, 2885, 1650, 1515, 1445, 1420, 1355, 1310, 1230, 1115, 1075, 990, 710, 675 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 883.4549 $[M + H]^+$ (calcd. for $C_{44}H_{59}N_{12}O_8$, 883.4573).

Maigheotide C (3). Clear oil, $[\alpha]_D^{22}$-43.1 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 335 nm (4.03); IR υ (thin film): 3205, 3090, 3005, 2945, 2170, 1635, 1595, 1550, 1495, 1460, 1445, 1390, 1340, 1235, 1190, 1120, 1090, 1030, 745, 690, 585 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 884.4385 $[M + H]^+$ (calcd. for $C_{44}H_{58}N_{11}O_9$, 884.4419).

■ ASSOCIATED CONTENT

Data Availability Statement

The NMR experimental data of maigheotides A−C (1−3) have been deposited in the Natural Products Magnetic Resonances Database (NP-MRD; www.np-mrd.org) and are available under accession numbers NP0351516 (maigheotide A), NP0351517 (maigheotide B) and NP0351518 (maigheotide C).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.5c01028.

NMR spectra for maigheotides A-C (**1**−**3**), including ^{1}H and ^{13}C 1D spectra as well as COSY, ^{1}H−^{13}C HSQC, HMBC (3, 8, and 13 Hz), ^{1}H−^{15}N HSQC and ROESY 2D spectra is available in the Supporting Information. HRESIMS for **1**−**3** as well as data table and LC/MS traces of Marfey's products (PDF)

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Notes

The authors declare no competing financial interest.

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