Caryophyllene sesquiterpenes from a *Chaetomium globosum* endophyte of the Canadian Medicinal plant *Empetrum nigrum*

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Abstract

Punctaporonins T (**1**) and U (**2**), new caryophyllene sesquiterpenes, were isolated with three known punctaporonins, A (**3**), B (**4**), and C (**5**), from the endophytic fungus *Chaetomium globosum* (TC2-041). The structures and relative configurations of punctaporonins T and U were elucidated based on a combination of HRESIMS, 1D/2D NMR spectroscopic analysis, and X-ray diffraction analysis whilst their absolute configuration is presumed to be consistent with the co-isolated **3**–**5** on biogenetic arguments. Compound **1** showed weak inhibitory activity against both *Mycobacterium tuberculosis* and *Staphylococcus aureus*.

Endophytic fungi, particularly those isolated from medicinal plants continue to be a promising source of natural products.[1–7] Fungi of the genus *Chaetomium* are most commonly isolated from plants[4–11] but have also been isolated from soil,[12] terrestrial invertebrates,[13,14] and the marine environment,[15–19] and represent a source of diverse, new, and bioactive natural products.[4,6,9,17,20–25] *Chaetomium globosum,* in particular, displays a high capacity to produce alkaloids such as the chaetoglobosins and a variety of polyketides, many of which display antibacterial,[20,21,26] antifungal,[20,21,27] antiviral,[28] immunosuppressive,[29] and cytotoxic activities.[22–25,30] During our investigation of endophytic fungi from North American medicinal plants,[31] the ethyl acetate extract of a *Chaetomium globosum* isolate (TC2-041) was found to possess an unique metabolic profile among our extract library.[32] Fractionation of the ethyl acetate extract of a two-week bench-scale fermentation of TC2-041 by liquid-liquid partition, reversed-phase flash chromatography, and HPLC led to the isolation of two new natural products, punctaporonin T (**1**) and punctaporonin U (**2**), along with the known punctaporonins A–C (**3–5**).[33] The punctaporonins[33–40] are caryophyllene sesquiterpenes similar in structure to the pestalotiopsins,[41–47] and the pestaloporinates.[48] Herein, we describe the isolation, structure elucidation, and the antimicrobial activities of these compounds.

The molecular formula of **1** was determined to be $C_{19}H_{26}O_6$ from HRESIMS data. ^{1}H and ^{13}C NMR data indicated three carbonyl groups [δ_C 195.5 (C-14), 173.4 (C-4′), and 171.5 (C-1′)] and two double bonds [δ_C 156.5 (C-7), 141.6 (C-8), 139.8 (C-4), and 124.5 (C-5)]. The molecular formula indicated seven degrees of unsaturation, implying that the structure also contained two rings. The 1D NMR, in conjugation with HSQC data, revealed additional resonances that were assigned to three methyl groups [δ_C 25.8 (C-12), 23.8 (C-13), and 16.9 (C-15)], five methylenes [δ_C 28.9 (C-3′), 28.7 (C-2′), 34.9 (C-2), 34.3 (C-3), and 30.1 (C-10)], one methine [δ_C 41.3 (C-9)],

one oxymethine [δ_C 71.6 (C-6)], one quaternary carbon [δ_C 42.1 (C-11)], and one oxygenated non-protonated carbon [δ_C 78.8 (C-1)].

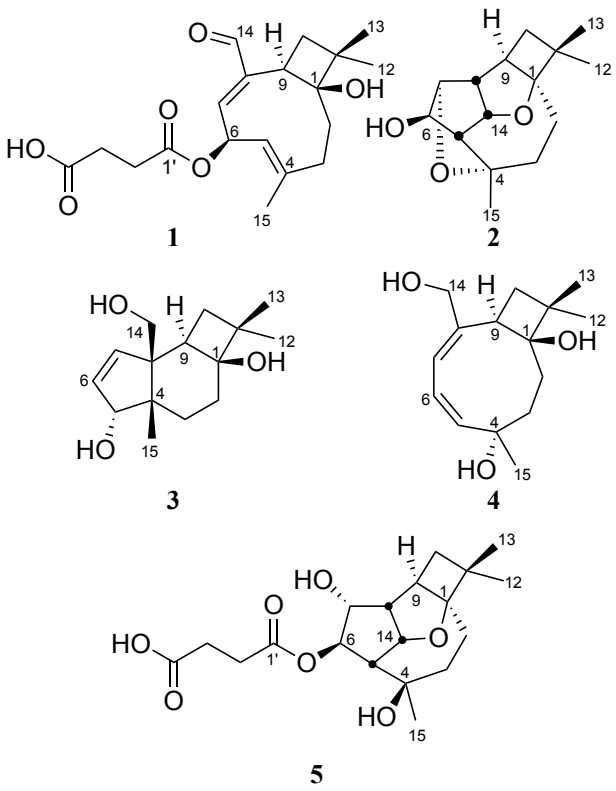

Figure 1. Punctaporonins isolated from *Chaetomium globosum*.

The planar structure of **1** was determined through analysis of COSY and HMBC data (Figure 2). The COSY spectrum indicated the presence of three isolated spin systems [C-2 – C-3, C-7 – C-4 methyl (C-15), and C-9 – C-10], while the HMBC data showed correlations from H_3-13 (δ_H 1.04) and H_3-12 (δ_H 0.98) to C-1, C-10, and C-11, H_3-15 (δ_H 1.91) to C-5, C-4, and C-3, and H-14 (δ_H 9.46) to C-9, C-8, and C-7 that were consistent with the punctaporonin architecture.[33–40] HMBC correlations from H_2-2′ (δ_H 2.56 and 2.50) and H_2-3′ (δ_H 2.56 and 2.50) to C-1′ and C-4′ confirmed the presence of a succinic acid substituent and HMBC correlations from H-6 (δ_H 6.05)

to C-1′ located the succinic acid substituent at C-6. The configuration of the double bonds were both designated an *E* configuration based on NOE correlations between H-14 and H-7 (δ_H 6.69) for C-7 to C-8 and correlations between H_3-15 and H-6 and between H-5 (δ_H 5.41) and H-3a (δ_H 2.47), 1-OH (δ_H 4.20), and H-9 (δ_H 3.15) for C-4 to C-5.

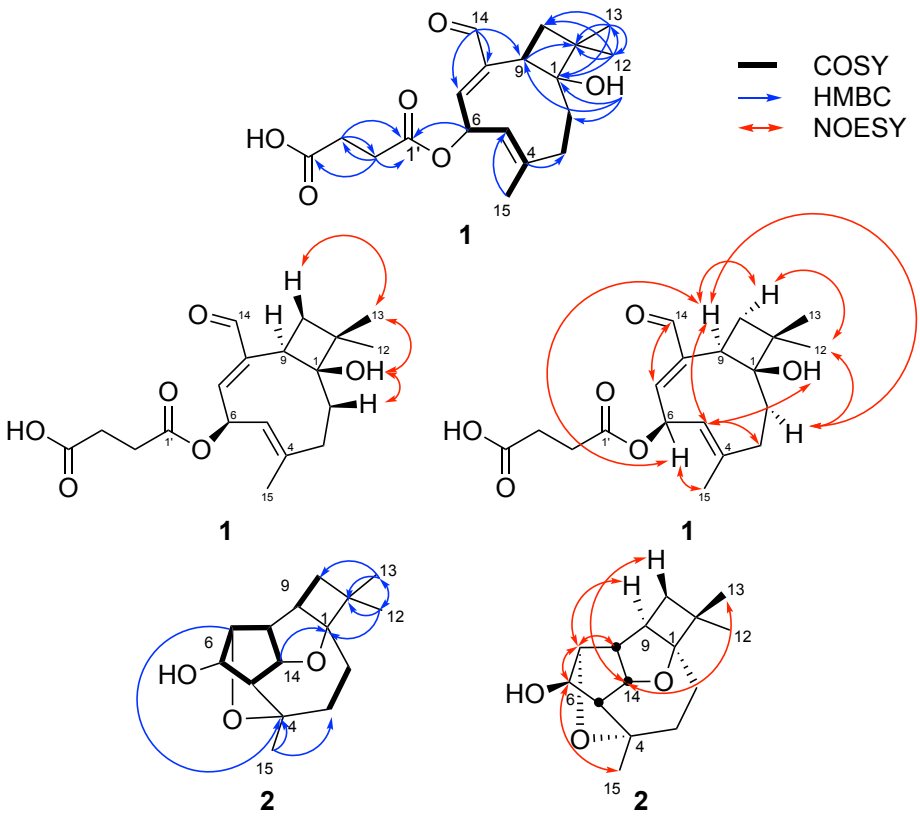

Figure 2. Key 2D NMR data of punctaporonin T (**1**) and U (**2**).

The relative configuration of **1** was determined by analysis of NOESY data (Figure 2). NOE correlations between H-10a (δ_H 2.57) and H_3-13, H_3-13 and 1-OH, and 1-OH and H-2b (δ_H 1.63) clearly placed the 1-OH and 13-Me on the same face of the molecule, along with the C-6 ester substituent based on correlations between H-2a (δ_H 2.13) and H-9 and H-9 and H-6. Confirmatory correlations were observed on the opposite face of the molecule between H-2a and H_3-12, and H_3-

12 and H-10b (δ_H 1.58) completing the assignment of the relative configuration of **1**. Given that **1** was co-isolated with **3–5**, which all gave NMR, MS and polarimetric data in agreement with literature data,[33,49] the absolute configuration of **1** is presumed to be 1*S*, 6*R* and 9*R* on biogenetic arguments (see Supporting Information Figure S1).

The molecular formula of **2** was determined to be $C_{15}H_{22}O_3$ from HRESIMS data. Analysis of ^{1}H and ^{13}C NMR data showed structural similarities between **2** and **5**, with the absence of the succinic acid residue at C-6 (δ_C 77.9) and the hydroxy groups at C-4 (δ_C 80.0) and C-7 (δ_C 78.1). The chemical shifts of these three carbon atoms indicated that they were oxygenated, while HMBC correlations between H-7 (δ_H 3.70) and C-4 suggested an ether linkage between C-4 and C-7, and left C-6 as the position of the remaining hydroxy group [6-OH (δ_H 5.10)]. Furthermore, **2** provided crystals that were suitable for X-ray diffraction analysis (Figure 3). Whilst the x-ray structure confirmed the planar structure and the relative configuration of **2**, the absolute configuration could not be confidently assigned given the calculated Flack parameter (0.1(4)). Once again, however, given the co-isolation of **2** and **3–5**, the absolute configuration is presumed to be 1*S*, 4*S*, 5*R*, 6*R*, 7*R*, 8*R*, 9*R* and 14*S* (see Supporting Information Figure S1).

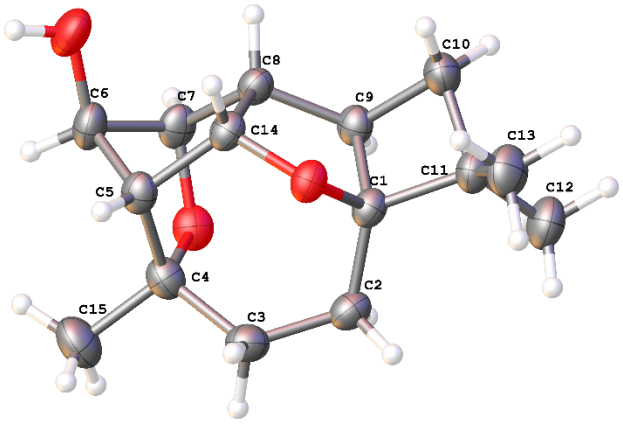

Figure 3. ORTEP drawing of the crystal structure of punctaporonin U (**2**).

Table 1. ^{1}H and ^{13}C NMR data of Punctaporonin T (**1**) and U (**2**)

	Punctaporonin T (**1**)[a]		Punctaporonin U (**2**)[a]	
Position	δ_C[b], type	δ_H[c] (*J* in Hz)	δ_C[b], type	δ_H[c] (*J* in Hz)
1	78.8, C		92.8, C	
2	34.9, CH_2	2.13, m	28.0, CH_2	1.64, m
		1.63, m		1.59, ddd (13.7, 7.3, 1.6)
3	34.3, CH_2	2.47, m	34.7, CH_2	1.81, ddd (14.2, 11.6, 7.4)
		1.88, m		1.49, m
4	139.8, C		80.0, C	
5	124.5, CH	5.41, d (10.4)	53.2, CH	1.91, dd (4.7, 1.7)
6	71.6, C	6.05, dd (10.6, 2.3)	77.9, CH	4.50, t (2.2)
7	156.5, CH	6.69 (bs)	78.1, CH	3.70, t (2.7)
8	141.6, C		50.0, CH	2.54, dd (8.2, 2.7)
9	41.3, CH	3.15, dd (10.8, 5.7)	41.3, CH	2.44, t (8.5)
10	30.1, CH_2	2.57, m	37.1, CH_2	1.67, dd (10.5, 8.3)
		1.58, t (11.5)		1.50, m
11	42.1, C		37.6, C	
12	25.8, CH_3	0.98, s	24.9, CH_3	1.05, s
13	23.8, CH_3	1.04, s	21.7, CH_3	0.86, s
14	195.5, CH	9.46, s	87.6, CH	5.05, dd (8.2, 4.6)
15	16.9, CH_3	1.91, s	31.4, CH_3	1.09, s
1'	171.5, C			
2'	28.7, CH_2	2.56, m		
		2.50, m		
3'	28.9, CH_2	2.56, m		
		2.50, m		
4'	173.4, C			
1-OH		4.20		
4'-OH		12.25		
6-OH				5.10

[a]In DMSO-d_6. [b]Recorded at 700 MHz. [c]Recorded at 175 MHz.

Caryophyllene sesquiterpenoids are biosynthesized by several fungal species,[33,38,40,42,43,45–47] however this is the first report of their isolation from *Chaetomium globosum*. Other caryophyllene sesquiterpenes have exhibited cytotoxicity against A549, HeLa, and SMMC-7721 cell lines, with pestalotiopsin C showing activity levels (IC_{50} = 28.3 μM) comparable to etoposide (IC_{50}= 23.2 μM) when tested against SMMC-7721.[46,47] The punctaporonins have shown both anti-inflammatory and antibiotic activities, in addition to activity against numerous cancer cell lines.[40,44,46] All of the compounds isolated here were assessed for inhibitory activity against *Staphylococcus aureus* (ATCC 29213), *Pseudomonas aeruginosa* (ATCC 10145), *Mycobacterium tuberculosis* H37Ra (ATCC 25177), and *Candida albicans* (ATCC 14053). Compound **1** was found to have selective but weak activity against *M. tuberculosis* H37Ra and *S. aureus* [IC_{50} values of 105 μM (36.8 μg/mL) and 237 μM (83.0 μg/mL) respectively] whilst **2**–**5** were inactive against all test organisms (screened at 100 μg/mL). Whilst mild *S. aureus* activity has previously been reported for other caryophyllene sesquiterpenes,[37,40] this is the first report of activity against *M. tuberculosis*. Our antimicrobial data also supports the recent observation of Tayone et al.[44] that the aldehyde functionality at C-14 of pestalotiopsin M contributed to its cytotoxicity, as the punctaporonins that lacked this functionality were not active in our assays.

This is the first isolation of **1** and **2**, two new caryophyllene sesquiterpenes that possess uncommon structural motifs compared to similar caryophyllene derivatives. Specifically, **1** possesses a C-14 aldehyde, previously present only in pestalotiopsin M,[44] and a succinic acid residue, previously present only in punctaporonin C.[33,35] Compound **2** possesses an ether linkage between C-4 and C-7 that has previously only been observed in pestalotiopsin H[46] and pestaloporinate D.[44] These investigations enrich the chemical diversity of *Chaetomium globosum*

and may attract the interest of synthetic chemists as has been the case for caryophyllene sesquiterpenes in the past.[49–62]

Experiment Section

General Experimental Procedures. Optical rotations were recorded on an Optical Activity Ltd. AA-10 polarimeter at 589 nm. NMR spectra of **1** and **2** were recorded on a Bruker AVIII 700 instrument equipped with a QNP cryoprobe in DMSO-d_6 and were calibrated to residual protonated solvent resonances (δ_H 2.50 and δ_C 39.52). NMR spectra of **3**, **4**, and **5** were recorded on an Agilent 400-MR DD2 instrument in DMSO-d_6, CD_3OD, or C_5D_5N and were calibrated to residual protonated solvent resonances (δ_H 2.50, 3.31 and 8.74; δ_C 39.52, 49.00, and 123.87, respectively). HRESIMS data were recorded on a Thermo LTQ Exactive instrument with an ESI source. Solvents for extraction and isolation were purchased from Fisher Scientific (Ottawa, ON, Canada) and deuterated solvents for NMR spectroscopy were purchased from Sigma-Aldrich (Oakville, ON, Canada). Flash chromatography was performed using a Biotage Flash+ chromatography system fitted with C_{18} SiliaSep cartridges (40-63 μm, 60 Å, 25 g; SiliCycle, QC, Canada). Semi-preparative reversed-phase HPLC was performed on a Phenomenex Luna C_{18} column (250 × 10 mm, 10 μm, 100 Å) using an Agilent 1100 HPLC system comprising a G1311A quaternary pump and a G1315C diode array detector.

Fungal Material. The fungus TC2-041 was isolated from the leaves of *Empetrum nigrum* (New Brunswick Museum voucher specimen NBM VP-37479) collected from Spruce Lake in Saint John, NB, Canada (N 45° 11.955' W 66° 13.800') in August 2010.[31] Isolate TC2-041 was identified as *Chaetomium globosum* through an examination of spore morphology and colonies grown on cornmeal, Czapek-Dox, malt extract, and potato dextrose agars (Figure S2). The

taxonomic classification was confirmed by comparison of the internal transcribed spacer (ITS) and 5.8S rRNA gene DNA regions with corresponding sequences available in the GenBank database (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA). The genomic DNA of TC2-041 was isolated using a DNEasy® plant mini kit (Qiagen, Toronto, Ontario) as directed by the manufacturer, the ITS gene was amplified by PCR using the ITS 1 and ITS 4 universal fungal primers (Invitrogen, Burlington, Ontario) as previously described,[63] and the amplified ITS DNA was sequenced by Genome-Québec (Montreal, Québec). The TC2-041 DNA sequence was checked for ambiguity before being compared with existing GenBank sequence data using BLAST. The ITS gene sequence of TC2-041 was found to have 100% homology with numerous conspecific *C. globosum* isolates and has been deposited in GenBank (accession number: KC916674).

Fermentation, Extraction, and Purification. TC2-041 was fermented in 1.2% potato dextrose broth at room temperature with ambient light, while shaking (150 rpm) for 2 weeks (10 L; 100 × 100 mL batches in 250 mL Erlenmeyer flasks stoppered with foam baffles). The fungal material was separated from the broth using filtration before the broth was extracted using EtOAc (3 × 3 L). The organic fraction was concentrated *in vacuo* to give a broth EtOAc extract (241 mg). The broth EtOAc extract was dissolved in 9:1 MeOH-H_2O (50 mL) and extracted with hexanes (3 x 20 mL). The aqueous fraction was then diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The CH_2Cl_2 fraction (201 mg) was subjected to reversed-phase HPLC (gradient from 95:5 H_2O-MeCN to 100% MeCN over ten minutes and held at 100% MeCN for five min) to give two fractions. Fraction two (Retention time 10.6 – 11.0 min, 54 mg) was subjected to reversed-phase HPLC (65:35 H_2O-MeCN) to give **1** (22 mg). Fraction one (250 mg) was subjected to C_{18} flash chromatography using a stepwise gradient of 19:1 H_2O-MeCN to 1:1 H_2O-MeCN. The

eluents were combined according to their respective TLC profiles to yield ten fractions. Fraction 6 (55 mg) and 7 (25 mg) were further purified using reversed-phase HPLC. Fraction 6 (80:20 H_2O-MeCN) afforded **3** (2 mg), **4** (4 mg), and **5** (14 mg) and fraction 7 (75:25 H_2O-MeCN) afforded **2** (9 mg).

Punctaporonin T (**1**): $[\alpha]^{22}_D$ −198.8 (*c* 0.14, MeOH); ^1H and ^{13}C NMR data see Table 1 and for NMR spectra see Supporting Information (Figures S3-9); HRESIMS *m/z* 351.1801 $[M+H]^+$ (calcd for $C_{19}H_{27}O_6^+$, 351.1802)

Punctaporonin U (B): colorless needles ($CHCl_3$); $[\alpha]^{22}_D$ +76 (*c* 0.87, MeOH); ^1H and ^{13}C NMR data see Table 1 and for NMR spectra see Supporting Information (Figures S10-16); HRESIMS *m/z* 251.1642 $[M+H]^+$ (calcd for $C_{15}H_{23}O_3^+$, 251.1647)

X-ray Chrstallographic Analysis. Crystals of compound **2** were recrystallized from $CHCl_3$ at 25 °C. A suitable crystal was selected and loaded on a Bruker APEX-II CCD diffractometer. The crystal was kept at 296.15 K during data collection. Using Olex2,[64] the structure was solved with the XT[65] structure solution program using Intrinsic Phasing and refined with the XL[66] refinement package using Least Squares minimization. Crystallographic data for compound **2** has been deposited under CCDC 2078962 at the Cambridge Crystallographic Data center. The data can be obtained free of charge at http://www.ccdc.cam.ac.uk/products/csd/request (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; deposit@ccdc.cam.ac.uk).

Crystal data for compound **1:** $C_{15}H_{22}O_3$ (*M* =250.32 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 8.0529(19) Å, *b* = 9.067(2) Å, *c* = 9.348(2) Å, *β* = 104.959(5)°, *V* = 659.5(3) Å^3, *Z* = 2, *T* = 296.15 K, *μ*(Mo Kα) = 0.086 mm^{-1}, D_{calc} = 1.261 g/cm^3, 11656 reflections

measured ($4.51° \leq 2\Theta \leq 60.824°$), 3954 unique ($R_{int}$ = 0.0208, R_{sigma} = 0.0285) which were used in all calculations. The final R_1 was 0.0384 ($I > 2\sigma(I)$) and wR_2 was 0.0949 (all data) (Figure 3).

Biological Assays. Antimycobacterial assays against *M. tuberculosis* H37Ra (ATCC 25177) and antibacterial and antifungal assays against *S. aureus* (ATCC 29213), *P. aeruginosa* (ATCC 10145), methicillin-resistant *S. aureus* (ATCC 33591), and *C. albicans* (ATCC 14053) were performed as previously described.[67,68]

Associated Content

Data Availability Statement: The NMR data for compounds **1** and **2** have been deposited to the Natural Products Magnetic Resonance Database (NP-MRD; www.np-mrd.org). Accession numbers will be generated when the manuscript is accepted for publication and included when galley proofs are reviewed.

Supporting information: HRESIMS, ^{1}H, ^{13}C and 2D NMR spectra for compounds **1** and **2** (PDF). X-ray crystallographic data for compound **2** (CIF).

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Author Contributions: The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes: The authors declare no competing financial interest.

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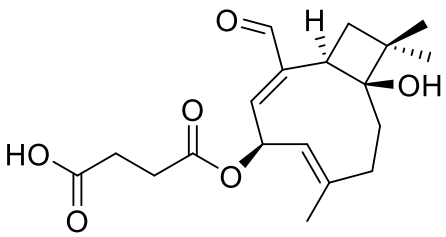

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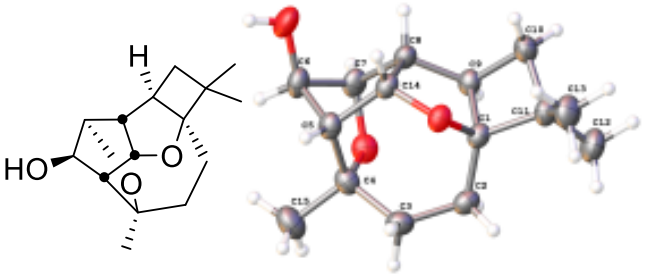

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Morehouse, Nicholas J.; Clark, Trevor N.; Kerr, Russell G.; Johnson, John A.; Gray, Christopher A.

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