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Structure and Biogenesis of Roussoellatide, a Dichlorinated Polyketide from the Marine-Derived Fungus *Roussoella* sp. DLM33

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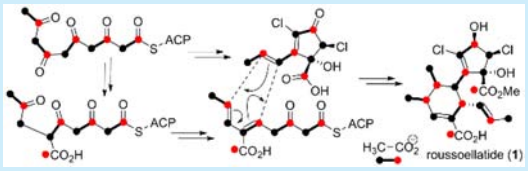
Supporting Information

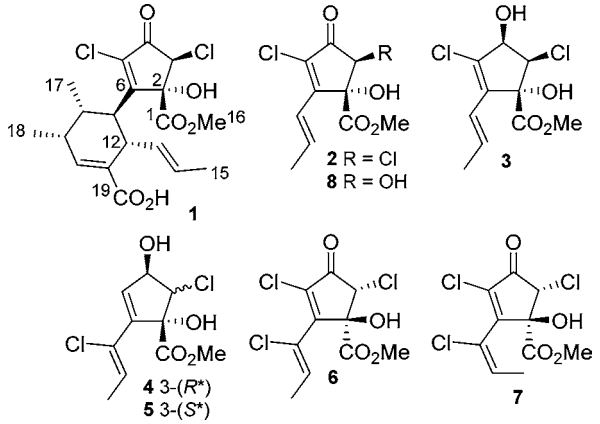
ABSTRACT: The structure of the fungal metabolite roussoellatide (**1**) has been established by spectroscopic and X-ray diffraction analyses. Results from feeding experiments with [1-^{13}C]acetate, [2-^{13}C]acetate, and [1,2-^{13}C]acetate were consistent with a biosynthetic pathway to the unprecedented skeleton of **1** involving Favorskii rearrangements in separate pentaketides, subsequently joined via an intermolecular Diels–Alder reaction.



Chlorination is a common feature found in fungal secondary metabolites with a variety of carbon skeletons and potent biological activities.[1] An example is the small family of metabolites containing the unusual 3,5-dichlorocyclopent-2-ene-1-carboxylic acid moiety embedded in the novel carbon skeleton of the herein reported roussoellatide (**1**). This group of chlorinated polyketides was first exemplified by cryptosporiopsin (**2**).[2−6] Additional members include cryptosporiopsinol (**3**),[7,8] the diastereomers VM 4798-1a (**4**) and VM 4798-1b (**5**),[9] palmaenones A (**6**) and B (**7**),[10] and the monochlorinated analogue **8**.[11] These compounds have shown broad and potent antibacterial, antifungal, and cytotoxic activities.[9,10] Isolation of **1** resulted from our efforts to find structurally unique bioactive fungal metabolites.[12−14]

Compound **1** is the major metabolite produced in culture by a marine-derived strain of the fungus *Roussoella* sp. DLM33. Fractionation of the EtOAc extract of the growth medium of *Roussoella* sp. DLM33 led to the isolation of **1**, which is structurally related to **2**−**8**, but with a further elaborated and unprecedented carbon skeleton.

Roussoellatide **1** was obtained as optically active brown plate crystals that gave an $[M - H]^-$ ion cluster in the HRESIMS at *m*/*z* 415.0719/417.0704/419.0695 with relative intensities of 8.1:5.1:1.0, appropriate for a molecular formula of $C_{19}H_{22}Cl_2O_6$ requiring eight sites of unsaturation. Analysis of the ^{1}H, ^{13}C, gCOSY60, gHSQC, and gHMBC NMR spectra



(Table S1) obtained for **1** enabled us to identify two carboxyl carbonyls [δ_C168.6 (C-1); 167.9 (C-19)], an α,β-unsaturated ketone carbonyl [δ_C 188.0 (C-4)], one disubstituted olefin [δ_H 5.30 (dq, 15.3, 6.4 Hz)/δ_C 126.3 (CH-14); δ_H 5.10 (ddq, 15.3, 8.8, 1.4 Hz)/δ_C 132.2 (CH-13)], a trisubstituted olefin [δ_H 6.84 (bd, J = 6.6 Hz)/δ_C 142.3 (CH-10); δ_C 132.2 (C-11)], and a conjugated tetrasubstituted olefin [δ_C 168.8 (C-6); 131.6 (C-5)].

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Resonances assigned to two aliphatic methyls [δ_H 0.79 (d, 6.9 Hz)/δ_C 16.5 (Me-17); δ_H 0.93 (d, 7.1 Hz)/δ_C 13.0 (Me-18)], an olefinic methyl [δ_H 1.51 (dd, 6.4, 1.4 Hz)/δ_C 17.9 (Me-15)], a heterosubstituted methyl [δ_H 3.63 (s)/δ_C 53.2 (Me-16)], four aliphatic methines [δ_H 2.76 (dd, 12.1, 8.8 Hz)/δ_C 40.6 (CH-7); δ_H 2.25 (m)/δ_C 32.1 (CH-8); δ_H 2.34 (m)/δ_C 34.1 (CH-9); δ_H 3.50 (t, 8.8 Hz)/δ_C 40.2 (CH-12)], a heteroatom-substituted methine [δ_H 5.20 (s)/δ_C 67.1 (CH-3)], and quaternary carbinol [δ_C 84.8 (C-2)] were present in the ^{1}H and ^{13}C NMR spectra. The three alkenes and three carbonyl functionalities accounted for six of the eight sites of unsaturation required by the molecular formula, requiring that **1** contained two additional rings. One of the six oxygen atoms in the molecular formula was assigned to the α,β-unsaturated ketone [δ_C 188.0 (C-4)], and a second oxygen was assigned to a tertiary alcohol (C-2) based on the observation that a ^{1}H resonance at δ_H 7.36, which failed to correlate to a carbon resonance in the gHSQC experiment, correlated in the gHMBC to the carbinol resonance at δ_C 84.8. The HSQC and MS data together indicated that there was one unobserved exchangeable proton, and because there was no evidence for the presence of a lactone, the four remaining oxygen atoms were assigned to ester and carboxylic acid functionalities.

Analysis of the 2D NMR data (Figure 1) established the constitution of roussoellatide **1**. gCOSY and gHSQC correlations readily identified the dimethyl octene fragment (Figure 1, in bold). gHMBC correlations between H-10 (δ_H 6.84) and C-11 (δ_C 132.2), C-12 (δ_C 40.2), and C-19 (δ_C 167.9), as well as between H-12 (δ_H 3.50) and C-10 (δ_C 142.3), C-11 (δ_C 132.2), and C-19 (δ_C 167.9), established the C-10/C-11 and C-11/C-12 connections and identified the dimethyl pentasubstituted cylcohexene ring of **1** having a carboxylic acid (C-19: δ_C 167.9) at C-11, a 1-propene fragment at C-12, and an alkene at C-7. The remaining carboxyl carbon was assigned to a methyl ester on the basis of the gHMBC correlation observed between the methyl singlet resonating at δ_H 3.63 (Me-16) and the carbonyl at δ_C 168.6 (C-1). H-7, H-8, and H-12 all correlated to the resonance at δ_C 168.8, assigned to the β carbon of the α,β-unsaturated ketone, establishing the C-6/C-7 connection. The tertiary alcohol proton resonating at δ_H 7.36 (2-OH) correlated to the C-6 resonance (δ_C 168.8), to the quaternary carbinol at δ_C 84.8 (C-2), to the isolated methine at δ_C 67.1 (C-3), and to the carbonyl of the methyl ester at δ_C 168.6 (C-1), supporting the C-2/C-6 bond. A cyclopentenone moiety attached to the cyclohexene fragment through the C-6/C-7 bond, with chlorine substituents at C-3 and C-5 and an alcohol and a methyl ester at C-2, satisfied the valences and chemical shifts of all the remaining carbons and accounted for the remaining atoms and the requirement for one additional ring in **1**. gHMBC correlations between H-7 (δ_H 2.76) and the C-2 carbinol (δ_C 84.8) and the second olefinic carbon of the α,β-unsaturated ketone at δ_C 131.6 (C-5), as well as between the H-3 methine (δ_H 5.20) and the unsaturated ketone at 188.0 (C-4), provided further support for the constitution of **1**. The presence of the cyclopentenone moiety was confirmed by comparison of the NMR data for **1** with the literature data for **6** and **7**.[10] A *J* coupling of 15.3 Hz between H-13 (δ_H 5.10) and H-14 (δ_H 5.30), along with the observation of a tROESY correlation between the methyl at δ_H 1.51 (Me-15) and the olefinic methine at δ_H 5.10 (H-13), demonstrated that the C-13/C-14 double bond had the *E* configuration (Figure 2).

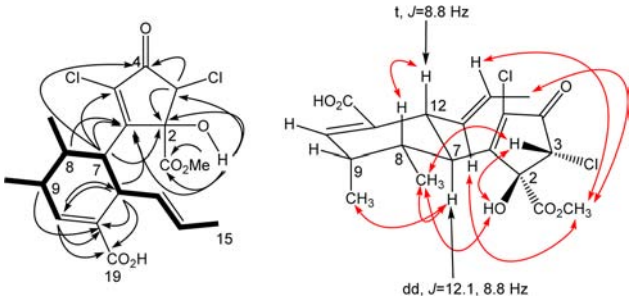

Figure 1. gCOSY (bold bonds), gHMBC (single arrows), and tROESY (red double arrows) correlations observed for roussoellatide **1**.

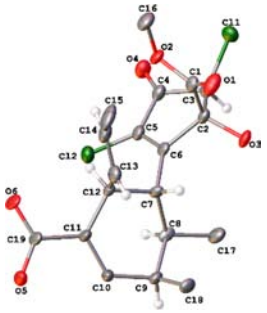

Figure 2. ORTEP diagram generated from the X-ray diffraction analysis of roussoellatide **1**.

Analysis of the tROESY spectrum of **1** established that the six-membered ring was in a pseudo-chair conformation with C-6, Me-17, and C-13 in pseudo-equatorial orientations, while Me-18 was pseudo-axial (Figure 2). The vicinal scalar coupling between H-7 and H-8 (12.1 Hz) and between H-7 and H-12 (8.8 Hz) confirmed that H-7 has a *trans*-pseudo-axial relationship with both H-8 and H-12. tROESY correlations observed between Me-17 (δ_H 0.79) and both OH-2 (δ_H 7.36) and H-3 (δ_H 5.20) and between the methyl singlet of the C-1 ester (δ_H 3.63) and all of the H-13 (δ_H 5.10), H-14 (δ_H 5.30), and Me-15 (δ_H 1.51) resonances established that the ester group and chlorine substituent at C-3 were *cis* relative to each other on the cyclopentene ring and that the relative configuration between the two cyclic fragments was as shown in Figure 1. Additional NOEs observed between H-7 and both Me-17 and Me-18, as well as between H-8 and H-12, provided further support for the relative configuration of **1**.

Recrystallization of **1** from 4:1 EtOAc/MeOH gave crystals suitable for single-crystal X-ray diffraction analysis. The ORTEP diagram (Figure 2) confirmed the proposed constitution and relative configuration of **1**. Assignment of absolute configuration of **1** as 2*S*, 3*S*, 7*R*, 8*S*, 9*R*, 12*S* was made on the basis of the refined Flack *x*-parameter [x = 0.00(2)].[15]

Roussoellatide **1** has the dichlorocyclopentenone moiety of **2** embedded in its structure. Previous biosynthetic investigations showed that the cyclopentenone ring of **2** arises from contraction of a polyketide-derived substituted benzoic acid precursor via a Favorskii-like reaction.[16−18] The additional fragment of **1** was also presumed to have a polyketide origin. However, the exact origin of the cyclohexene ring in **1**, including the vicinal Me-17 and Me-18 substituents and the branching C-19 carboxylic acid, was not obvious. Two possible biogenetic pathways to the skeleton of **1** are shown in Scheme S1. The first one (**A**) involves a linear octaketide precursor and proceeds via a benzoic acid intermediate that would suffer "ring contraction" after oxidative cleavage.[16−18] Methyl alkylation at a carbonyl position of a

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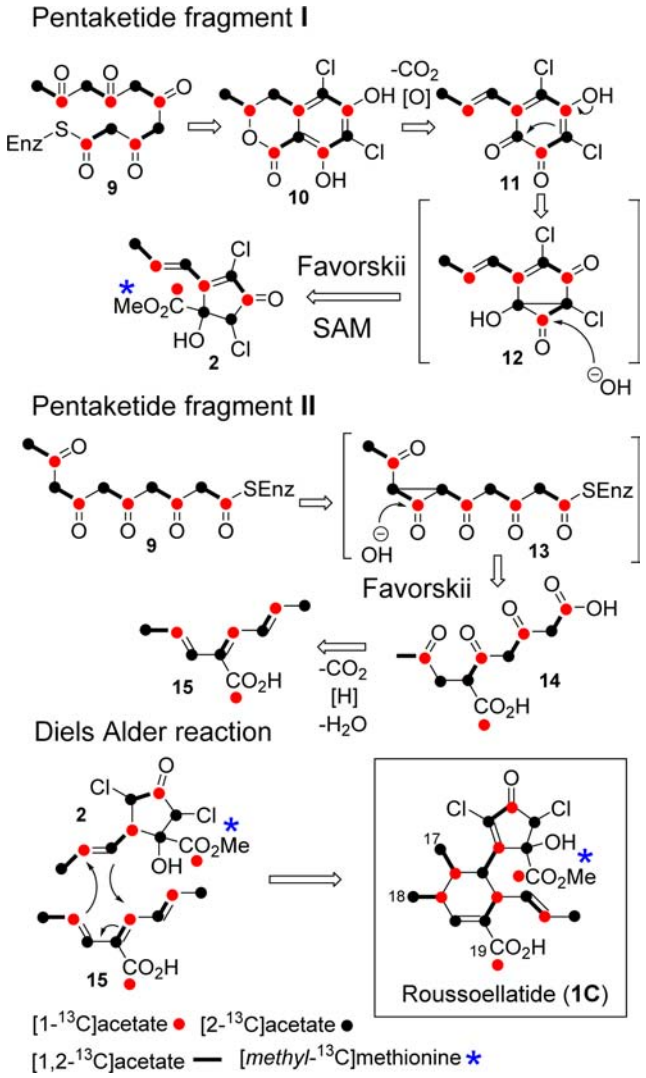
polyketide chain by C-2 of acetate to give Me-17 as proposed in pathway **A** has been observed in bacteria and dinoflagellates, but never in fungi.[19−24] An alternate pathway **B** (Scheme S1) involves an intermolecular Diels−Alder reaction of **2** and a linear tetraketide-derived triene. Pathways **A** and **B** (Scheme S1) differ in the origins of Me-17 (C-2 of a cleaved acetate vs C-2 of an intact acetate) and Me-18 (SAM vs C-1 of acetate).

These alternate biogenetic possibilities led us to investigate the origin of the carbon skeleton of roussoellatide **1** after the optimization of its production (Supporting Information).[12] The complete stable isotope labeling pattern observed for **1** is shown in **1C** in Scheme 1. Incorporation of [1-^{13}C]acetate showed

Scheme 1. Proposed Biogenesis of Roussoelatide (1) Based on Feeding Experiments with [1-^{13}C]- and [1,2-^{13}C]Acetate



enhancements at C-1, C-4, C-6, C-8, C-9, C-12, C-14, and C-19 in the ^{13}C NMR spectrum of **1**, while incorporation of [2-^{13}C]acetate showed enhancements at C-2, C-3, C-5, C-7, C-10, C-11, C-13, C-15, C-17, and C-18 (Table S12). The methyl group of the C-1 ester functionality showed significant incorporation of [methyl-^{13}C]methionine (58.7%). Analysis of the INADEQUATE spectrum of **1** resulting from feeding double-labeled [1,2-^{13}C]acetate showed unequivocal correlations for intact acetate units at C-4/C-5, C-6/C-7, C-8/C-17, C-9/C-18, C-11/C-12, and C-13/C-14. Unexpectedly, the observed labeling pattern found in roussoellatide, shown in **1C** in Scheme 1, did not match either of the proposed routes **A** and **B** in Scheme S1. In particular, as shown in **1C**, Me-18 comes from C-2 of an intact acetate unit, C-19 comes from C-1 of acetate, and C-10 comes from C-2 of a cleaved acetate unit.

Scheme 1 shows a revised proposal consistent with all of the stable isotope incorporation data. The labeling pattern observed in the linear carbon chain extending from C-1 to C-8 and on to Me-17 is identical to that found previously in experiments designed to explain the origin of **2** and **3** from **10** (Scheme 1, fragment **I**).[16−18] The putative biogenesis of **2** starts with a pentaketide chain **9** and proceeds through coumarin **10** that then undergoes decarboxylation and oxidation to give orthoquinone **11** prior to a Favorskii-like ring contraction to give the cyclopentenone ring found in **2**. Introduction of the chlorine atoms in **10** is presumed to be mediated by either a halogenase or a haloperoxidase.[25]

The Me-18 to C-15 linear chain and the C-19 branching carbon in **1** come from a second pentaketide chain **9** (fragment **II**, Scheme 1). The modification of **9** involves a Favorskii rearrangement via intermediate **13** to give **14**. An analogous Favorskii rearrangement has been observed in the biosynthesis of aspyrone.[26,27] Further modifications of the polyketide chain generates **15**. An intermolecular Diels−Alder reaction between the triene **15** and the alkene **2** completes the assembly of the novel carbon skeleton of **1**. The difference in the ranges of incorporations in carbons arising from [1-^{13}C]acetate in fragment **I** (12.0−19.0%) and fragment **II** (3.3−4.7%) (Table S12) supports the proposal of an intermolecular Diels−Alder reaction joining the two separately preformed pentaketide-derived fragments. Isolation of **10** from cultures of *Roussoella* sp. provided additional support for the biogenetic proposal in Scheme 1.

Two distinct enzymes are likely to be operative in the Favorskii-like rearrangements in the roussoellatide biosynthesis since the rearrangement substrate in the transformation of **11** to **2** must be significantly different than the one in the transformation of **9** to **15**. Additional polyketides whose biosynthesis is mediated by a Favorskii rearrangement include enterocin,[28] dinoflagellate toxins,[22a,b,29] and ambruticin.[30] In the case of enterocin, the Favorskii rearrangement occurs during the polyketide formation.[28c,d] We have assumed the same timing of the rearrangement in the biosynthesis of roussoellatide.

The proposed intermolecular Diels−Alder step joining the two polyketide fragments to create the cyclohexene ring of **1** is of particular interest. While intramolecular Diels−Alder reactions in the biosynthesis of secondary metabolites are well-documented,[31−33] the involvement of intermolecular Diels−Alder reactions in the biosynthesis of natural products is much less common.[34−36] Such reactions are more likely to involve Diels−Alderases since diene−dienophile interactions should be less effective when the substrates are separated, compared with the intramolecular version of such reactions, for which the molecular constraints often facilitate a non-enzymatic spontaneous reactivity.

In conclusion, roussoelatide **1** has an unprecedented polyketide carbon skeleton. Stable isotope feeding experiments have provided evidence for a complex biogenetic origin of **1**, involving two separate but identical pentaketide chains, each undergoing Favorskii-like rearrangements before being joined via an intermolecular Diels−Alder reaction. This unique combination of rare biosynthetic steps has generated unprecedented structural diversity and complexity in this family of natural

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products. Efforts to uncover the genetic and enzymatic details of the roussoelatide biosynthetic pathway are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02060.

Experimental procedures, X-ray diffraction analysis, and NMR data (PDF)

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Author Contributions

#E.L.F.F. and D.E.W. contributed equally.

Notes

The authors declare no competing financial interest.

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