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Pursuing sesterterpene lactams in Australian Irciniidae sponges

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ABSTRACT

Chemical investigation of two Irciniidae sponges collected by hand (SCUBA) from Australian near shore waters, afforded six new examples of a rare class of sesterterpene lactam; ircinialactams B (**1**), G (**2**), H (**5**), and I (**6**), and 8-hydroxyircinialactams C (**3**) and G (**4**); together with the new biosynthetically related lactone, ircinialactone A (**7**). Also isolated were seven biosynthetically related known Irciniidae metabolites; ircinialactams A (**8**) and C (**9**), (7*E*,12*E*,20*Z*,18*S*)-variabilin (**10**), (7*Z*,12*Z*,20*Z*,18*S*)-variabilin (**11**), (7*E*,12*Z*,20*Z*,18*S*)-variabilin (**12**), (7*Z*,12*E*,20*Z*,18*S*)-variabilin (**13**) and irciniafuran A (**14**). The structure elucidation of **1**–**14** was achieved by detailed spectroscopic analysis, and consideration of a plausible biosynthetic relationship linking Irciniidae sesterterpene β-furans, lactams and lactones.

1. Introduction

Sesterterpenes incorporating tetronic acid and β-furanyl termini are characteristic of the secondary metabolites isolated from marine sponges of the family Irciniidae. Indeed, our studies into Australian sponges have resulted in the discovery of many new members of this structure class [1–8], including rare glycinyl-lactams, the ircinialactams [7] and ircinianin lactams [8]. The glycinyl-lactams are particularly interesting as they are unique to Irciniidae sponges, and selected examples exhibited promising modulatory activity against glycine gated chloride channel receptors (GlyR), a novel target for chronic inflammatory pain [7–8]. In an effort to build knowledge of Irciniidae sesterterpene lactams we set out to explore the chemistry of other specimens within our collection. As a result of HPLC-ESIMS profiling, our attention was drawn to two specimens, *Sarcotragus* sp. (CMB-01012) and *Psammocinia* sp. (CMB-01018), each collected by hand (SCUBA) over 30 years ago, at a depth of ~15 m from near shore waters off Durras, on the mid-south coast of New South Wales, Australia. Collectively, a chemical analysis of these specimens yielded an array of new (**1**–**7**) and known (**8**–**14**) sesterterpenes, inclusive of lactams (**1**–**6**, **8**–**9**), β-furans (**10**–**14**), and lactones (**7**) (Fig. 1). This report describes the isolation and structure elucidation of **1**–**14**, and provides commentary on a plausible biosynthesis.

2. Materials and methods

2.1. General

Optical rotation ($[\alpha]_D$) measurements were acquired on a JASCO P-1010 polarimeter. NMR experiments were performed on Bruker Avance NMR spectrometer at 600 MHz for ^{1}H and 150 MHz for ^{13}C NMR. Chemical shifts (ppm) were referenced internally against residual solvent signals (methanol-d_4: δ_H 3.31 ppm, δ_C 49.1 ppm). High-resolution electrospray ionization mass spectra (HRESIMS) were obtained on a Bruker micrOTOF mass spectrometer by direct infusion in MeCN and using sodium formate clusters as an internal calibrant. HRMS data was also acquired using SCIEX × 500 QTOF mass spectrometer with Exion LC integrated system. Liquid chromatography-diode array detector-mass spectrometry (LC-DAD-MS) data were acquired using an Agilent 1100 series separation module equipped with diode array multiple wavelength detector coupled to an Agilent 1100 series LC/MSD mass detector in positive and negative modes using electrospray ionization mode (ESI). Ultra high-performance liquid chromatography (UHPLC) was performed on an Agilent 1290 infinity UHPLC system composed of 1290 infinity binary pump, thermostat, autosampler and photo diode array detector. Analytical, semi-preparative and preparative HPLC were performed on Agilent 1100 series LC module with corresponding detectors and fraction collectors. Agilent Zorbax columns (Aqua, C_8 and C_{18}) were utilized in HPLC and UHPLC.

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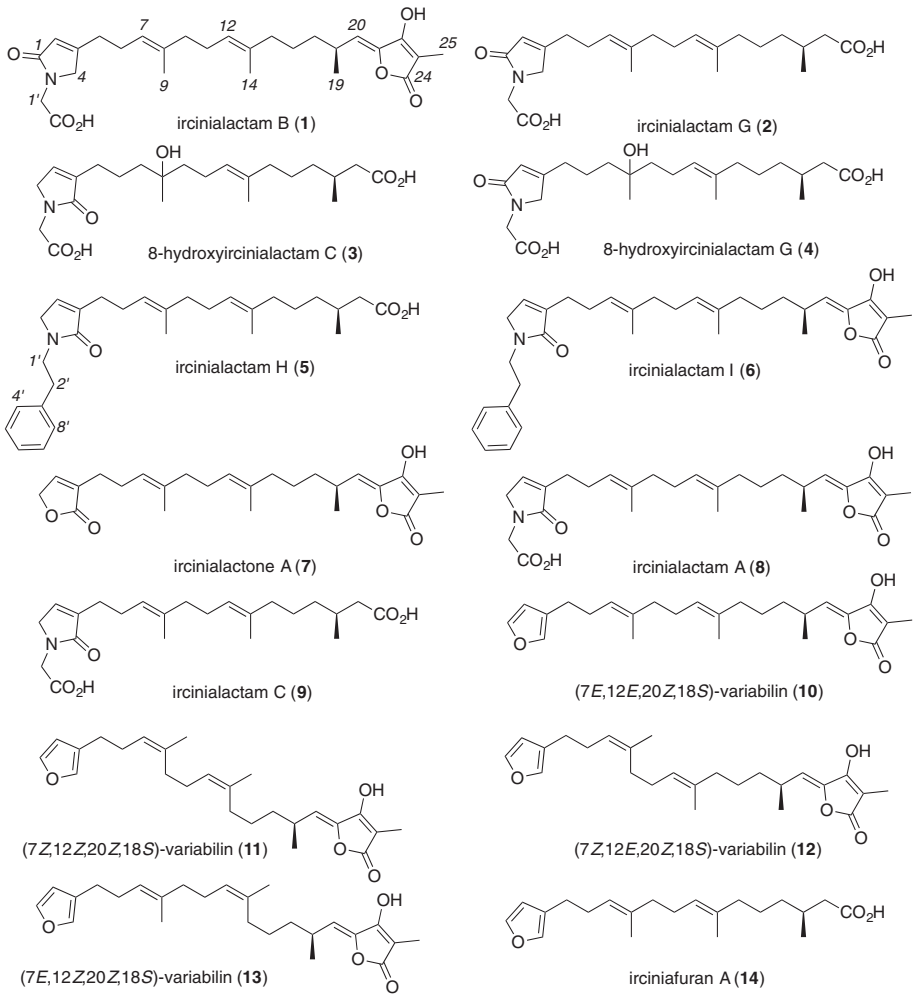

Fig. 1. *Sarcotragus* sp. (CMB-01012) metabolites **2–4**, **9** and *Psammocinia* sp. (CMB-01018) metabolites **1–2**, **5–14**.

2.2. Animal material

Specimens of *Sarcotragus* sp. (CMB-01012) and *Psammocinia* sp. (CMB-01018) were collected by hand (SCUBA) at a depth of ~15 m in near shore waters off Durras, on the mid-south coast of New South Wales, Australia, in 1986 and 1988 respectively. Following collection, samples were transported on ice to the laboratory, where they were documented, diced and stored in EtOH at − 30 °C prior to chemical investigation.

2.2.1. Specimen CMB-01018

Specimen CMB-01018 was identified as a *Psammocinia* sp. (Class: Demospongiae; Order: Dictyoceratida; Family: Irciniidae) with the taxonomic description as follows: texture compressible, arenaceous, very tough to cut; oscules large 5 mm in diameter, raised on mounds; surface opaque, wrinkled; spicules none; ectosome distinct armoured layer of sand and foreign spicule fragments 500–1000 μm thick; choanosome a reticulation of fibres fasciculate and heavily cored by sand and detritus obscuring reticulation, primary fibres indistinct from secondary fibres less heavily cored, collagen fibrils with terminal ampule evident throughout matrix; colour in life grey cortex, beige interior; grey in EtOH. A voucher specimen was deposited with the Museum Victoria (Registry no.: NMVF222665).

2.2.2. Specimen CMB-01012

Specimen CMB-01012 was identified as a *Sarcotragus* sp. (Class: Demospongiae; Order: Dictyoceratida; Family: Irciniidae), with the taxonomic description as follows: Growth form massive to wedge-shaped; texture compressible but tough to cut; oscules not seen; surface conulose; spicules none; colour in EtOH brown surface and beige internally; ectosome dark in colour, unarmoured; choanosome light in colour, primary fibres fasciculate and lightly cored with uniform, spicular debris especially near the surface where they protrude as conules, very little detritus either coring or scattered deeper in the choanosome, collagen fibrils with ampules visible. A voucher specimen was deposited with the Museum Victoria (Registry no.: NMVF233668).

2.3. Extraction and isolation

A portion of the EtOH extract of *Psammocinia* sp. (CMB-01018) was decanted, concentrated *in vacuo* and the residue (1750 mg) partitioned between *n*-BuOH and H_2O. The *n*-BuOH soluble material was concentrated *in vacuo,* and further partitioned and concentrated *in vacuo* to yield *n*-hexane (520 mg) and MeOH (1220 mg) solubles. A portion of the MeOH solubles (870 mg) was subjected to gradient elution from 80% H_2O/MeOH to MeOH through a C_8 solid phase cartridge. Material eluting at 20% H_2O/MeOH was subjected to HPLC fractionation (Zorbax SB-C_{18} 21.5 × 150 mm, 5 μm column, 20.0 mL/min isocratic elution with 40% H_2O/CH_3CN and a 0.01% TFA modifier, over 60 min) to yield **5** (2.4 mg, 0.19%), **6** (2.6 mg, 0.21%), **7** (2.6 mg, 0.21%), **10** (16.1 mg, 1.29%), **11** (2.6 mg, 0.21%), **12/13** (4.8 mg, 0.38%) and **14** (2.0 mg, 0.16%). Material eluting at 40–50% H_2O/MeOH was subjected to C_8 flash chromatography with a 30 min gradient elution from 80% H_2O/MeCN to MeCN with an isocratic 0.05% TFA modifier. Individual fractions were analysed by UHPLC-DAD (Zorbax SB-C_8 2.1 × 50 mm, 1.8 μm column, 0.417 mL/min gradient elution from 90% H_2O/MeCN