Three cadinane derivatives from the marine brown alga *Dictyopteris divaricata*

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Introduction

As the products of mevalonate pathways, terpenes mainly composed of monoterpenes, sesquiterpenes, diterpenes, and triterpenes are the most prolific secondary metabolites of marine algae. They exhibit the high structural diversity, which arises from the presence of various isomers to a great extent. Among them, the stereo isomers often result in much difficulty for isolation and identification because of their similar physicochemical properties and spectroscopic characteristics, especially for the epimers. In our continuing investigation towards the structurally diverse and biologically active metabolites from the marine algae and their associated fungi, the marine brown alga *Dictyopteris divaricata* collected off the coast of Yantai, China, was chemically examined. As a result, a known cadinane sesquiterpene, cadinan-4(15)-ene-1β,5β-diol (1), and its new epimer, cadinan-4(15)-ene-1β,5α-diol (2), as well as a new naturally occurring norcadinane sesquiterpene, trans-3-norisocalamenen-4-ol (3), were isolated and identified (Fig. 1). The isolation and structure elucidation of these compounds are main subjects of this paper.

Results and discussion

Compound 1 was obtained as a colorless oil. The 1H NMR spectrum displayed three methyl doublets at δH 0.74 (d, J = 6.9 Hz, H-13), 0.86 (d, J = 6.7 Hz, H-11), and 0.96 (d, J = 6.9 Hz, H-14), one doublet at δH 4.31 (d, J = 2.5 Hz, H-5) ascribable to an oxygenated methine, and a pair of broad singlets at δH 4.78 (brs, H-15a) and 4.84 (brs, H-15b) characteristic of an exocyclic methylene. The 13C NMR and DEPT spectra (Table 1) showed fifteen resonances, corresponding to three methyls, five methylenes, five methines, and two quaternary carbon atoms. The aforementioned NMR data with those reported for cadinan-4(15)-ene-1β,5β-diol (1) might be an isomer of 1. The 1H-1H COSY correlations (Fig. 2) clearly indicated the existence of three spin systems, CH3–CH–CH2–CH2–CH––CH–(CH3)2–CH–CH– (C-11 to C-5, C-13, and C-14), –CH2–CH2– (C-2 to C-3), and =CH2 (C-11). The HMBC correlations (Fig. 2) from H-2 to C-1 and C-4, from H-5 to C-4, C-6, C-7, and C-15, from H-11 to C-1, C-9 and C-10, from H-13 to C-7, C-12, and C-14, from H-14 to C-7, C-12, and C-13, and from H-15 to C-3 and C-5 established the connectivity of the aforementioned structural units and then construct the gross structure of 1, which is the same as that of 1. However, the large coupling constants of H-5, H-6, and H-7 indicated them to be axial, and H-5 and H-7 were oriented on the same face by their NOE correlations (Fig. 3). Additionally, the relative configurations at C-1 and C-10 of 2 were the same as those of 1 based on their identical 13C NMR data at C-1 and C-10. The aforementioned evidence established the structure and relative configuration of 2 to be cadinan-4(15)-ene-1β,5α-diol (1).

Compound 3 was isolated as a colorless oil and degraded after several days. The 1H NMR spectrum (Table 1) displayed three methyl doublets, two doublets, and one double doublet ascribable to three aromatic protons, and one broad singlet assignable to an exchangeable proton. The 13C NMR spectrum (Table 1) exhibited 14 resonances, which were classified into three methyl, two methylenes, five methines, and three quaternary carbon atoms. The aforementioned NMR data closely resembled those reported for cadinan-4(15)-ene-1β,5β-diol from the same brown alga collected on the coast of Qingdao, which revealed that the NMR data of compound 2 might be an isomer of 1. The 1H-1H COSY correlations (Fig. 2) clearly indicated the existence of three spin systems, CH3–CH–CH2–CH2–CH––CH–(CH3)2–CH–CH– (C-11 to C-5, C-13, and C-14), –CH2–CH2– (C-2 to C-3), and =CH2 (C-11). The HMBC correlations (Fig. 2) from H-2 to C-1 and C-4, from H-5 to C-4, C-6, C-7, and C-15, from H-11 to C-1, C-9 and C-10, from H-13 to C-7, C-12, and C-14, from H-14 to C-7, C-12, and C-13, and from H-15 to C-3 and C-5 established the connectivity of the aforementioned structural units and then construct the gross structure of 2, which is the same as that of 1. However, the large coupling constants of H-5, H-6, and H-7 indicated them to be axial, and H-5 and H-7 were oriented on the same face by their NOE correlations (Fig. 3). Additionally, the relative configurations at C-1 and C-10 of 2 were the same as those of 1 based on their identical 13C NMR data at C-1 and C-10. The aforementioned evidence established the structure and relative configuration of 2 to be cadinan-4(15)-ene-1β,5α-diol (1).

Compounds 1 and 2 were assayed for antifungal activity against plant pathogens *Colletotrichum lagenarium* and *Fusarium acuminatum*. 

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oxysporum using standard agar diffusion test at 30 μg/disk and brine shrimp lethality against Artemia salina at 100 μg/mL. Unfortunately, they were inactive against these organisms.

**Experimental**

**General experimental procedures**

Mass spectrum was determined on a VG Autospec 3000 mass spectrometer (VG, Manchester, UK). IR spectrum was obtained on a JASCO FT/IR-4100 Fourier Transform InfraRed spectrometer (JASCO, Tokyo, Japan). Optical rotation was measured on a JASCO P-1020 polarimeter (JASCO, Tokyo, Japan). Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Qingdao, China), RP-18 reversed-phase silica gel (YMC, Kyoto, Japan), and Sephadex LH-20 (GE, Uppsala, Sweden). Thin-layer chromatography was carried out with precoated silica gel plates (GF-254, Qingdao Haiyang Chemical Co., Qingdao, China). All solvents were of analytical grade.

**NMR spectra**

The 1D and 2D NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer (Bruker Corp., Billerica, MA, USA) and a Bruker Avance III 500 NMR spectrometer (Bruker Corp., Billerica, MA, USA) in CDCl₃ at 298 K. Chemical shifts (δ) in ppm are referenced to tetramethylsilane at 0.00 ppm for ¹H and ¹³C. Coupling constants (J) are given in Hertz. The pulse conditions were as follows: for ¹H, spectrometer frequency (SF) = 500.1 MHz, spectral width (SWH) = 10330.6 Hz for ¹ and ² and 5000.0 Hz for ³, pulse 90° width (P₁) = 11.4 μs for ¹ and ² and 12.0 μs for ³, Fourier transform size (SI) = 32768, line broadening (LB) = 0.0 Hz for ¹ and ² and 0.3 Hz for ³, and relaxation delay (D₁) = 2.0 s for ¹ and ² and 1.0 s for ³; for ¹³C, SF = 125.8 MHz, SWH = 30030.0 Hz for ¹ and ² and 29761.9 Hz for ³, P₁ = 11.0 μs for ¹ and ² and 9.4 μs for ³, SI = 32768; LB = 2.0 Hz for ¹ and ² and 1.0 Hz for ³, and D₁ = 2.0 s; for NOESY of ², mixing time (D₈) = 0.9 s.

**Plant material**

The brown alga Dictyopteris divaricata was collected off the coast of Yantai (lat. 37°31 15 N, long. 121°26 59 E), China, in July, 2008. It was...
identified by one of the authors (Nai-Yun Ji), and a voucher specimen (MBA0807) has been deposited at the Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences.

**Extraction and isolation**

The dried and powdered brown alga *D. divaricata* (2 kg) was extracted with a mixture of CHCl$_3$ and MeOH (1:1, v/v, 2 L). The concentrated extract was further partitioned between H$_2$O and EtOAc to give the EtOAc-soluble extract (90 g), which was subjected to silica gel CC with a step-gradient petroleum ether (PE)/EtOAc solvent system to afford 10 fractions (Fr.s I–X). Fr. V eluted with PE/EtOAc (10:1) and was further purified by CC on silica gel (PE/EtOAc, 10:1) and preparative thin-layer chromatography (PE/EtOAc 3:1) to afford 1 (3 mg) and 2 (5 mg).

**Bioassay**

Antifungal activity against plant pathogens *Colletotrichum lagenarium* and *Fusarium oxysporum* and brine shrimp lethality against *Artemia salina* were assayed as described previously.\(^{[12]}\)

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**Supporting information**

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