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Shan Su^a; Wen-Shuang Sun^a; Bin Wang^a; Wei Cheng^a; Hong Liang^a; Yu-Ying Zhao^a; Qing-Ying Zhang^a; Jun Wu^b

^a State Key Laboratory of Natural and Biomimetic Drugs and Department of Natural Medicines, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing, China ^b Key Laboratory of Marine Bio-resources Sustainable Utilization, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou, China

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NOTE

A novel brominated cuparene-derived sesquiterpene ether from the red alga *Laurencia* sp.

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^aState Key Laboratory of Natural and Biomimetic Drugs and Department of Natural Medicines, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing 100191, China;

^bKey Laboratory of Marine Bio-resources Sustainable Utilization, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou 510301, China

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A novel brominated cuparene-derived sesquiterpene ether, 8,10-dibromo-3,7-epoxy-laur-13-ol (**1**), was isolated from *Laurencia* sp. collected in South China Sea. Besides this, two known sesquiterpenes, (9 β)-aristol-1(10)-en-9-ol (**2**) and aristolone (**3**), were also yielded, and aristolone (**3**) was obtained from *Laurencia* for the first time. Their structures were elucidated by spectroscopic methods.

Keywords: *Laurencia*; sesquiterpene; cuparene-derived sesquiterpene ether; 8,10-dibromo-3,7-epoxy-laur-13-ol

1. Introduction

The red algae belonging to the genus *Laurencia* (Ceramiales, Rhodomelaceae), which are distributed in the warm sea waters of intertidal rock, have been proven to be rich sources of structurally unique secondary metabolites. The majority of these metabolites are characterized by their relatively high degree of halogenation, and the core structures of these metabolites mainly consist of terpenes, including sesquiterpenes, diterpenes and triterpenes, and C₁₅ acetogenins [1]. The ecological roles of these metabolites have not been clearly elucidated, but it is suggested that some metabolites have been reported to possess a variety of biological activities such as antifeedant [2], anthelmintic [3,4], antifouling [5],

antimicrobial [5], and cytotoxic [6,7] properties. Despite the fact that *Laurencia* has been studied extensively with respect to secondary metabolite chemistry, new studies on members of this genus frequently lead to the isolation of novel intriguing structures. In the course of our studies on biologically active compounds from natural resources, one *Laurencia* sp. collected in the South China Sea has been investigated and some novel structures have been yielded. In this study, we describe the isolation and structural elucidation of a novel brominated cuparene-derived sesquiterpene ether, 8,10-dibromo-3,7-epoxy-laur-13-ol (**1**), along with two known sesquiterpenes, (9 β)-aristol-1(10)-en-9-ol (**2**) and aristolone (**3**). Aristolone (**3**) was reported to be isolated from *Laurencia* for the first time.

*Corresponding authors. Email: qyzhang@hsc.pku.edu.cn; wwujun2003@yahoo.com

2. Results and discussion

Compound **1** was obtained as a white powder with $[\alpha]_D^{20}$: -12.0 ($c = 1.0$, CHCl_3). Its EI-MS showed ion peaks at m/z 388.1, 390.1, 392.1 with relative intensities 1/2/1 revealing the presence of two bromine atoms in the molecule, and the molecular formula of $\text{C}_{15}\text{H}_{18}\text{O}_2\text{Br}_2$ was deduced from the molecular ion peaks at m/z 387.9638, 389.9661, 391.9643 with relative intensities 1/2/1 in the HR-EI-MS. The ^{13}C NMR spectrum of **1** showed signals for 15 carbons with the multiplicities of the carbon signals determined from the DEPT spectrum, assigned as seven quaternary, two methine, three methylene, and three methyl carbon atoms. Among the 15 carbon signals, six were aryl carbons and nine were aliphatic carbons in which two were oxygenated aliphatic carbons resonating at δ_{C} 88.8 and 66.4. The ^1H NMR spectrum of **1** showed the signals of one aromatic proton singlet at δ_{H} 7.26 (1H, s), one methyl doublet at δ_{H} 0.82 (3H, d, $J = 8.5$ Hz), two methyl singlets at δ_{H} 1.38 (3H, s) and 2.55 (3H, s), three methylenes at δ_{H} 2.04 (2H, m), 1.92, 1.74 (each 1H, m), 3.97, 3.76 (each 1H, d, $J = 11.5$ Hz) among which the signals at δ_{H} 3.97, 3.76 were due to the hydroxy methylene considering the EI-MS fragment peaks at m/z 370.1, 372.1, 374.1 $[\text{M} - \text{H}_2\text{O}]^+$ and two methines at δ_{H} 1.72 (1H, q, $J = 8.5$ Hz), 7.26 (1H, s). Based on the above evidences, compound **1** was deduced to be a sesquiterpenoid with a five-substituted benzene ring. Since **1** has six degrees of unsaturation and does not possess any other double bonds, it must contain two other rings, one of which is the ether-containing ring and the other is a five-membered carbocyclic ring. The ^1H - ^1H COSY correlations of H-12 at δ_{H} 0.82 with H-2 at δ_{H} 1.72 and H-5 at δ_{H} 1.92, 1.74 with H-4 at δ_{H} 2.04 and the HMBC correlations of H-12 at δ_{H} 0.82 with C-1 at δ_{C} 45.6 and C-3 at δ_{C} 88.8, H-14 at δ_{H} 1.38 with C-5 at δ_{C} 41.6 and C-6 at δ_{C} 130.9, H-13 at δ_{H} 3.97, 3.76 with C-2 at δ_{C} 43.3 and C-4 at δ_{C}

33.5 confirmed the substituent type of the five-membered carbocyclic ring. The ether bridge was placed on carbons C-3 and C-7 based on the heteronuclear correlation between H-11 (δ_{H} 7.26) and C-7 (δ_{C} 148.6) and the presence of the oxygenated quaternary carbon of C-3 (δ_{C} 88.8) and C-7 (δ_{C} 148.6). The aryl methyl at δ_{H} 2.55 (3H, s, H-15) and the two bromine atoms were determined to be attached at C-9, C-8, and C-10, respectively, according to the HMBC correlations of H-15 (δ_{H} 2.55) with C-9 (δ_{C} 136.2), C-8 (δ_{C} 112.9), and C-10 (δ_{C} 114.9), and H-11 (δ_{H} 7.26) with C-7 (δ_{C} 148.6), C-9 (δ_{C} 136.2), and C-10 (δ_{C} 114.9). Considering the tension of the six-membered ring strain, the relative stereochemistry of the methyl and hydroxy methylene groups at C-1 and C-3 was assigned to be *cis*-form. The relative stereochemistry at C-2 was determined on the basis of the 1D GOESY experiment. In the 1D GOESY spectrum, the strong NOE of H-2 (δ_{H} 1.72) with H-5 (δ_{H} 1.92) and H-4 (δ_{H} 2.04) and the absence of correlations of H-12 (δ_{H} 0.82) with H-5 (δ_{H} 1.92) and H-4 (δ_{H} 2.04) indicated clearly that the methyl group at C-2 was equatorial and thus must be *trans*-form to the methyl at C-1 and the hydroxy methylene at C-3. Thus, the relative stereochemistry at C-1, C-2, and C-3 was determined as shown in Figure 1.

To the best of our knowledge, 46 cuparene-derived sesquiterpenes have been isolated from the genus *Laurencia* up to date. Most of the cuparene-derived sesquiterpenes obtained have no bromine or one bromine atom at either C-10, C-13, or sometimes at C-3. Only five cuparene-derived sesquiterpenes with two bromines have been reported to be yielded from this genus, and the two bromines are linked to either C-10 and C-12 [8], C-10 and C-13 [9–11] or both at C-13 [11]. In addition, cuparene-derived sesquiterpenes bearing an ether bridge are not so popular in the genus *Laurencia*. It is reported that 16 cuparene-derived sesquiterpenes with ether bridge have been isolated from the

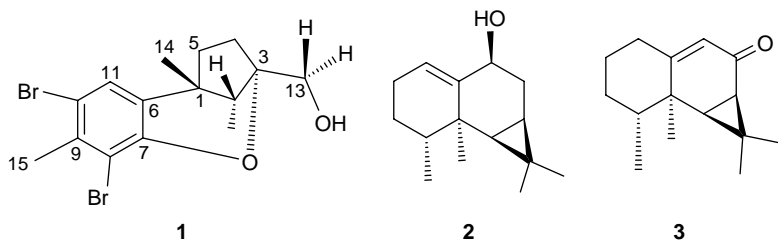


Figure 1. The structures of compounds 1–3.

genus *Laurencia*, and only two compounds contain the ether bridge on carbons C-3 and C-7 [9,12], while the ether bridge of other 14 compounds [8,11,13–17] is on carbons C-2 and C-7. In this paper, a novel cuparene-derived sesquiterpene with two bromines substituted at C-8 and C-10 and an ether bridge on C-3 and C-7 was reported for the first time. Moreover, compound **1** contained a hydroxyl methylene group at C-3 which has never been found in the previously obtained cuparene-derived sesquiterpenes.

Compounds **2** and **3** were identified as (9 β)-aristol-1(10)-en-9-ol [18] and aristolone [19,20], respectively, by comparing their spectral data with those reported in the literatures.

3. Experimental

3.1 General experimental procedures

UV was measured on a TU-1901 spectrometer. IR spectra were recorded on a Nicolet FT-IR Avatar 360 spectrophotometer (Thermo Nicolet Corporation, Madison, WI, USA). Optical rotations were obtained on an AA-10R automatic process polarimeter (Optical Activity Ltd, Ramsey, England). One- and two-dimensional NMR spectra were recorded on a Bruker DRX AV-500, using TMS as the internal standard. The HR-EI-MS spectra were recorded on an AutoSpec Ultima-TOF mass spectrometer and the EI-MS spectra were recorded on a TRACE EI-MS instrument. HPLC preparation was performed on a Gilson preparative HPLC

system (Villiers Le Bel, France) consisting of two 306 pumps an 811C dynamic mixer, an 806 manometric module connected to a 118 UV-vis detector, and a 506C system interface module using Phenomenex ODS column (5 μ , 22 mm \times 250 mm) (Torrance, CA) with the flow rate of 8 ml/min. HPLC analysis was performed on a JASCO analysis HPLC system (Tokyo, Japan) consisting of two PU-1580 pumps and an AM-1510 multi-wavelength detector using Phenomenex ODS column (5 μ , 4.6 mm \times 250 mm) with the flow rate of 1 ml/min. Column chromatography was carried out on silica gel (200–300 mesh; Qingdao Marine Chemical Industry Factory, Qingdao, China) and Sephadex LH-20 (GE, Atlanta, GA, USA). Reversed-phase column chromatographic separation was carried out using RP C₁₈ silica gel (100–200 mesh; YMC, Kyoto, Japan). TLC was performed on Kieselgel 60 F254 silica gel plates (Merck, Darmstadt, Germany) and RP C₁₈ silica gel plates (Merck).

3.2 Plant material

The *Laurencia* sp. was collected in South China Sea, in October 2006, and identified by Prof. Jun Wu. A voucher specimen (no. 20061001) has been deposited in the Department of Natural Medicines, School of Pharmaceutical Science, Peking University Health Science Center.

3.3 Extraction and isolation

The dried red algae (4.5 kg) were exhaustively extracted 10 times with 95% EtOH

Table 1. NMR spectral data of compound **1** (^1H : 500 MHz; ^{13}C : 125 MHz; in CDCl_3 , δ in ppm, J in Hz).

Position	δ_{C}	δ_{H} (J , Hz)	HMBC	$^1\text{H}-^1\text{H}$ COSY	NOESY
1	45.6				
2	43.3	1.72 (1H, q, 8.5)	C-1, -6, -12	H-12	H-4, -5a, -12, -13a, -13b, -14
3	88.8				
4	33.5	2.04 (2H, m)	C-1, -3, -5	H-5	H-2
5	41.6	1.92 (1H, m, Ha) 1.74 (1H, m, He)	C-1, -2, -3, -4, -6 C-4, -6	H-4	H-2
6	130.9				
7	148.6				
8	112.9				
9	136.2				
10	114.9				
11	127.6	7.26 (1H, s)	C-1, -7, -9, -10		H-14
12	8.0	0.82 (3H, d, 8.5)	C-1, -2, -3	H-2	H-13a, -13b
13	66.4	3.97 (1H, d, 11.5, H-a) 3.76 (1H, d, 11.5, H-b)	C-2, -3, -4 C-2, -4	H-13b H-13a	H-2, -12
14	20.2	1.38 (3H, s)	C-1, -5, -6		H-2, -12
15	23.6	2.55 (3H, s)	C-8, -9, -10		

(15 liters each time) at room temperature. After removal of the solvent, the residue was extracted with MeOH to remove the salt. The MeOH extract was concentrated under vacuum to give a residue (450 g) which was suspended in water (1.2 liters) and then partitioned with petroleum ether (PE) to afford PE extract (100 g). The PE extract was subjected to column chromatography on silica gel (200–300 mesh) eluted with PE–EtOAc (100:0 \rightarrow 9:1 \rightarrow 5:1 \rightarrow 2:1 \rightarrow 0:100) to afford 10 fractions (Fr. 1–10). Fraction 4 (2.3 g) was purified by RP-HPLC eluted with 80% MeOH to afford compounds **2** ($R_t = 90$ min, 20 mg) and **3** ($R_t = 35$ min, 50 mg). Fraction 5 (2.0 g) was purified by RP-HPLC eluted with 80% MeCN to afford compound **1** ($R_t = 60$ min, 12 mg).

3.3.1 8,10-Dibromo-3,7-epoxy-laur-13-ol (**1**)

A white powder, $[\alpha]_{\text{D}}^{20} -12.0$ ($c = 1.0$, CHCl_3). UV (MeOH) λ_{max} nm: 211, 235 (sh), 286 (sh), 295. IR $\nu_{\text{max}}^{\text{KBr}}$: 3534, 3437,

2960, 2926, 2867, 1685, 1607, 1443, 1383, 1238, 1097, 1024, 731 cm^{-1} . ^1H , ^{13}C NMR and 2D NMR spectral data: see Table 1. EI-MS m/z : 388.1, 390.1, 392.1 $[\text{M}]^+$, 370.1, 372.1, 374.1 $[\text{M} - \text{H}_2\text{O}]^+$, 354.9, 357.0, 359.1 $[\text{M} - \text{H}_2\text{O} - \text{CH}_3]^+$. HR-EI-MS m/z : 387.9638, 389.9661, 391.9643 (1/2/1) $[\text{M}]^+$ (calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2\text{Br}_2$, 387.9674, 389.9653, 391.9633).

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