Laurenidificin, a new brominated C\textsubscript{15}-acetogenin from the marine red alga \textit{Laurencia nidifica}

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Abstract

A new brominated C\textsubscript{15}-acetogenin, namely, laurenidificin, was isolated from the marine red alga \textit{Laurencia nidifica}. Its structure was determined on the basis of spectroscopic methods.  
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\textit{Laurencia nidifica} is a marine red alga belonging to the family Rhodomelaceae (order Ceramiales, class Rhodophyceae, and phylum Rhodophycota). It occurs mainly in the South Pacific and Indian Ocean, especially in Hawaii, and there is no record on its occurrence in China previously. Chemical investigation of \textit{L. nidifica} for secondary metabolites started from 1974 [1] and the majority of these metabolites are halogenated sesquiterpenes and C\textsubscript{15}-acetogenins [2,3], many of which possess antimicrobial and antiviral activities [2,4]. In our continuing investigation on halogenated bioactive natural products from \textit{Laurencia} species [5–14], we casually collected the species \textit{L. nidifica} from Sanya coast of Hainan Province. Chemical examination of this species resulted in the isolation and identification of a new brominated C\textsubscript{15}-acetogenin, namely, laurenidificin (1) (Fig. 1). In this paper, the structural elucidation of compound 1 is presented.

Compound 1, colorless oil, \([\alpha] +32.0 (c 0.38, CHCl\textsubscript{3})\) \(\lambda_{\text{max}}(\log c) 238 (3.73)\) nm, was purified from the ethylacetate soluble fraction of the crude extract of \textit{L. nidifica} by repeated column chromatography on silica gel and Sephadex LH-20 as well as by preparative TLC. The IR spectrum exhibited absorption bands at 3444, 3290, 1724, and 759 cm\textsuperscript{-1}, suggesting the presence of hydroxyl group, terminal acetylene, and disubstituted (Z)-alkene groups in the molecule. The molecular formula was determined as C\textsubscript{15}H\textsubscript{21}BrO\textsubscript{3} by positive HR–ESI–MS \((m/z 329.0698, [M + H]\textsuperscript{+}), \text{calcd. for C}_{15}\text{H}_{22}^{79}\text{BrO}_{3}, 329.0747\), indicating five degrees of unsaturation. The \(^{13}\text{C}\) NMR along with DEPT and HSQC experiments (Table 1) exhibited the presence of 15 carbons including one methyl, four methylenes, nine methines, and one quaternary carbon atoms. The \(^{1}\text{H}-^{1}\text{H}\) COSY correlations as shown in Fig. 2 indicated the continuous chain-type connections from H-3 to H-15. The presence of a terminal conjugated enyne group was
suggested by the HMBC correlations from the acetylenic proton at δ_H 3.08 (d, J = 1.8 Hz, H-1) to the olefinic carbon C-3 (δ_C 110.2, CH) and alkyne carbon C-2 (δ_C 80.3, C). Detailed comparison of the 1D NMR data of compound 1 with those of laurenenyne-A [15], a C_15-s-acetogenin isolated from an undescribed Laurencia species, revealed that the structures of these two compounds are very similar, except for two olefinic carbon signals at δ_C 100.0 (C-6, CH) and 156.1 (C-7, C), and one saturated carbon signal at δ_C 45.0 (C-8, CH) in laurenenyne-A were replaced by two oxygenated methines (δ_C 73.3 and 83.8) and one methylene (δ_C 35.3), respectively, in compound 1. This observation implied that the trisubstituted olefin in laurenenyne-A was hydrated, and the Br atom at C-8 was absent in compound 1. This was verified by the observation in 1H NMR spectrum (Table 1). The olefinic proton signal appearing at δ_H 4.94 (dd, J = 7.3, 7.3 Hz) for H-6 and one proton signal at δ_H 4.90 (s) for the brominated carbon (C-8) in laurenenyne-A were absent in the 1H-NMR spectrum of compound 1. Instead, two proton signals at δ_H 3.69 (dt, J = 12.1, 6.2 Hz) and

![Fig. 1. Chemical structure of compound 1.](image1)

![Fig. 2. The 1H-1H COSY (bold lines) and key HMBC (arrows) correlations (A) and values of δ_S-δ_R of the MTPA esters (B) of compound 1.](image2)
δ_H 3.87 (ddd, J = 8.0, 6.3, 6.7 Hz) for H-6 and H-7, respectively, and two proton signals at δ_H 2.25 (m) and 1.95 (ddd, J = 14.0, 6.7, 1.6 Hz) for H_2-8 were observed in compound 1. Furthermore, the structural deduction of compound 1 was also proved by the HMBC correlations from H-6 to C-8 (δ_C 35.3) and C-4 (δ_C 141.4), and from H_2-8 to C-6 (δ_C 73.3) and C-7 (δ_C 83.8) (Fig. 2). Thus, the planar structure for compound 1 was established as shown in Fig. 2.

The relative configuration of compound 1 was determined upon the analysis of coupling constants and the NOESY experiment. The coupling constant between H-3 and H-4 (J = 10.9 Hz) indicated the Z-geometry for the double bond at C-3. The NOE correlations observed from H-9, H-10 to H-12 and H-7 indicated the cis orientation for H-12, H-10, H-9 and H-7, but the relative configuration of C-6 and C-13 were in unknown.

The absolute configuration of the chiral center at C-6 in 1 was determined using the modified Mosher’s method [16,17]. Treatment of 1 with (R)- or (S)-MTPA-Cl gave the (S)- or (R)-MTPA esters, respectively. The 1H NMR signals of the two MTPA esters were clearly assigned on the basis of their 1H–1H COSY spectra, and the Δδ(1S–R) values were then calculated (Fig. 2). The results indicated that the absolute configuration of C-6 was R. However, the absolute configuration of the other asymmetric centers could not be determined because the relative configuration of C-6 was not assigned. Thus, the structure of compound 1 was determined as laurenidificin showed in Fig. 1.

Halogenated C_{15}-acetogenins are widely distributed among the marine red algae of the genus Laurencia. However, literature survey revealed that to date only six C_{15}-acetogenins, with four of them (cis-maneonenes A–C and trans-maneonene B) belonging to the maneonene class [3,18,19] and two of them (isomaneonenes A and B) belonging to the isomaneonene class [3,19], have been identified from the species of L. nidifica. The structures of maneonenes and isomaneonenes differ from those of other C_{15}-acetogenins in that the C_{15} carbon chain has cyclized back on itself to form one and two carbocyclic rings, respectively. Structurally, compound 1, differ from that of maneonene and isomaneonene classes, possessing a rarely reported hexahydrofuro[3,2-b]furan ring system and this is the first isolation of this kind of C_{15}-acetogenin from L. nidifica.

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