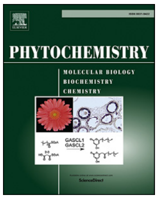
Phytochemistry 143 (2017) 180–185

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem



Bio-active maneonenes and isomaneonene from the red alga *Laurencia obtusa*

Nahed O. Bawakid [a], Walied M. Alarif [b,*], Ali I. Ismail [c], Mohamed E. El-Hefnawy [c,d], Khalid O. Al-Footy [a], Sultan S. Al-Lihaibi [b]

[a] *Department of Chemistry, Faculty of Science, King Abdulaziz University, PO. Box 80203, Jeddah 21589, Saudi Arabia*
[b] *Department of Marine Chemistry, Faculty of Marine Sciences, King Abdulaziz University, PO. Box 80207, Jeddah 21589, Saudi Arabia*
[c] *Department of Chemistry, Rabigh College of Science and Arts, King Abdulaziz University, P.O. Box 344, Rabigh 21911, Saudi Arabia*
[d] *Department of Chemistry, Faculty of Science, Tanta University, Tanta 31527, Egypt*

ARTICLE INFO

Article history:
Received 21 March 2017
Received in revised form
17 May 2017
Accepted 1 August 2017

Keywords:
Laurencia obtusa
Rhodomelaceae
Red algae
Structure elucidation
Cyclic enynes
Haloethers
Anti-inflammatory
Spectroscopy
X-ray

ABSTRACT

Three previously undescribed compounds, maneonenes and isomaneonene derivatives; in addition to five known compounds, two cuparene, one chamigrene, and two *cis*-maneonenes were isolated from the Red Sea red alga *Laurencia obtusa*. The chemical structures of all unknown metabolites were characterized employing spectroscopic methods and then were further confirmed by single crystal X-ray analysis. Jeddahenyne A has C-5-C-12 etheric linkage and C-13-C-14 carbon-carbon double bond; Jeddahenyne B has in addition to the aforementioned etheric linkage a C-13 carbonyl function and absence of halogenation, unusual features for the maneonenes while 12-debromo-12-methoxy isomaneonene A shows unrecorded methoxylation at C-12. The apoptosis-inducing or inhibiting effect of both compounds on apoptosis of peripheral blood neutrophils was studied.

1. Introduction

Red algae belonging to genus *Laurencia* (Rhodomelaceae) are projected to be the most significantly studied genus from the marine environment (Suzuki et al., 2009). It is considered as fruitful producer of halogen-containing compounds such as sesquiterpenes, diterpenes, and C_{15}-acetogenins. Many of these halogenated secondary metabolites have represented a diversity of biological activity, including antifouling, antifeedant, antimicrobial, and cytotoxic activities (Davyt et al., 2001; Ji et al., 2007; Wanke et al., 2015).

Maneonenes are C_{15} nonterpenoid haloethers with one carbocyclic ring originating from polyketide pathway, formed by cyclization of the carbon chain on itself, and are exclusively isolated from members of the most famous red algae genus *Laurencia* (Wanke et al., 2015; Waraszkiewicz et al., 1978). The presence of a terminal conjugated enyne function flanked by a halogen-bearing carbon is the main maneonene characteristic feature, along with a three carbon atoms forming part of the etheric butenyl unit in the other terminus. Maneonenes have the same gross structure; however, they differ in stereochemistry including the geometry around C-3-C-4, C-12-C-13, and the conformation of C-5, C-6, and C-11. Although the roles of these compounds in the living organism are not well defined yet, their importance as chemical defense substances toward marine herbivores had been reported. The apoptosis effect against neurophils blood cells (Ayyad et al., 2011) and antibacterial activities of maneonenes against terrestrial and marine bacteria from algal habitat had also been reported (Vairappan et al., 2001a,b).

As a point of our research to isolate and investigate the bioactive metabolites from the *Laurencia alga* in the Saudi Red Sea, three previously undescribed compounds, two maneonenes were named Jeddahenyne A and B (**1**–**2**) and one isomaneonene was named 12-debromo-12-methoxy isomaneonene A (**3**), in addition to five

---

* Corresponding author.
E-mail addresses: walied1737@yahoo.com, welaref@kau.edu.sa (W.M. Alarif).

http://dx.doi.org/10.1016/j.phytochem.2017.08.001
0031-9422/

known compounds that were gained from the dichloromethane extract of *L. obtusa* (Fig. 1). Comparison of the spectroscopic data of all known isolated compound with those reported in literature, they were recognized as cuparene-3-ol (**4**) (Howard and Fenical, 1975), α-isobromocuparene (**5**) (Suzuki et al., 1975), nidificene (**6**) (Suzuki et al., 1983; Waraszkiewicz and Erickson, 1974), *cis*-maneonene-A (**7**) (Waraszkiewicz et al., 1978), and *cis*-maneonene-E (**8**) (Ayyad et al., 2011).

2. Results and discussion

The dichloromethane extract of the air-dried red algal material was fractionated on aluminum oxide column. The *n*-hexane-ether fractions afforded the maneonene derivatives **1** (0.0019% yield), and **2** (0.0012% yield), together with the isomaneonene derivative **3** (0.0017% yield).

Structural elucidation of compound **1**, isolated as needle crystals, commenced when the HRMS established the molecular formula $C_{15}H_{15}BrO_3$, requires eight degrees of unsaturation. EIMS supports the presence of single bromine atom from the characteristic molecular -ion cluster at *m*/*z* in 1:1 ratio. The UV (223 nm), IR (3274, 2325 cm^{-1}) and ^{1}H and ^{13}C NMR spectra (Table 1, C-1-C-4) established the *cis*-enyne function. Moreover, no absorption due to hydroxyl function, carbonyl or vinyl ether was recorded in the IR spectrum. Intense absorption bands were observed at 1171, 1147, 1112 and 1094 analyzed for ether functions. The presence of vinyl methyl protons signal resonating at δ_H 1.77 ppm ($J = 6.8$ Hz) and a quartet signal at 6.52 ($J = 6.8$ Hz) assigned to an olefinic methine proton (δ_C 126.6 ppm), indicates a1-methyl,2,2-trisubstituted carbon-carbon double bond. DEPT and HSQC NMR experiments allowed the association of all protons and carbons, with no remaining hydrogens, could be assigned to hydroxyl function. DEPT NMR spectrum determined the presence of 1CH_3, 1 CH_2, 10CH, and 3 quaternary carbons. Interpretation of the ^{1}H–^{1}H correlation spectroscopy spectrum showed the presence of one large proton sequence (C-3 to C-11), in addition to the aforementioned methyl ethylidine sequence. The downfield proton signal resonating at δ_H5.15 is correlated with the vinylic proton resonating at δ_H 6.20 and with a proton signal resonating at δ_H 2.82 ppm. The later proton being a part of the cyclohexane system because of a chain of correlations started from it and passed through five proton signals (δ_H 4.66, C-7; 1.93, C-8; 5.12, C-9; 4.62, C-10 and 3.33, C-11) and then closed with it. The molecular formula displays three oxygen atoms that should be part of etheric linkages, supported by IR absorption at 1171, 1147, 1112 and 1094 cm^{-1}. The downfield carbon signals at δ_C 79.0, 85.7, and 79.5 correspond to C-7, C-9 and C-10, respectively, are part of etheric linkages. The correlation from H-11 δ_H (3.33) to C-5 (δ_C 78.3) and C-12 (δ_C 115.8) in the HMBC spectrum and comparing with other maneonene frequently reported from the genus *Laurencia* (Waraszkiewicz et al., 1978), confirming the presence of two vicinal carbon residues of the cyclohexane ring (at C-6 and C-11), along with two etheric linkages (C-7-C-10; C-9-C-12). The HMBC correlation from the vinylic proton H-14 resonating at 6.52 to C-13 (δ_C 125.6) and C-12 (δ_C 115.8) places the methyl ethylidine function attached to C-12. Moreover, the δ_C value corresponds to the quaternary carbon C-13 which indicates its attachment to a bromine atom. The previous discussion illustrates a tricyclic molecule, one of which is carbocyclic; two carbon-carbon double bonds and one acetylenic function. The molecular formula showed one more oxygen atom and one more unsaturation, these imply an ether linkage between C-5 and C-12. The relative stereochemistry was determined by an extensive study of the coupling constant values (*J*) as well as from enhancements observed in the NOESY spectrum. $J_{5exo,6exo} = 0$ Hz indicating a 90° dihedral angle between H-5 and H-6. $J_{6exo,11exo} = 7.7$ Hz, reflecting a ca. 0° dihedral angle between H-6 and H-11. The coupling constant of 5.1 Hz between H-6 and H-7 and between H-7 and H$_{exo}$-8 (Table 1 δ_H 1.93 ppm) displays a ca. 30° dihedral angle between H-6/H-7/H$_{exo}$-8, similarly, the 30° angle between H$_{exo}$-8 and H-9 and H9-10 and H-10 and H-11 fits for the 6 Hz coupling constant (Bovey, 1969; Gagnaire and Payo-Subize, 1963). No correlation was observed between H-11 and the H$_3$-15 in the NOESY spectrum together with the H$_3$-15 being unaffected by the electronic influence of the oxygen atoms, those are away from methyl function, adopting Z-configuration of the ethyledine group.

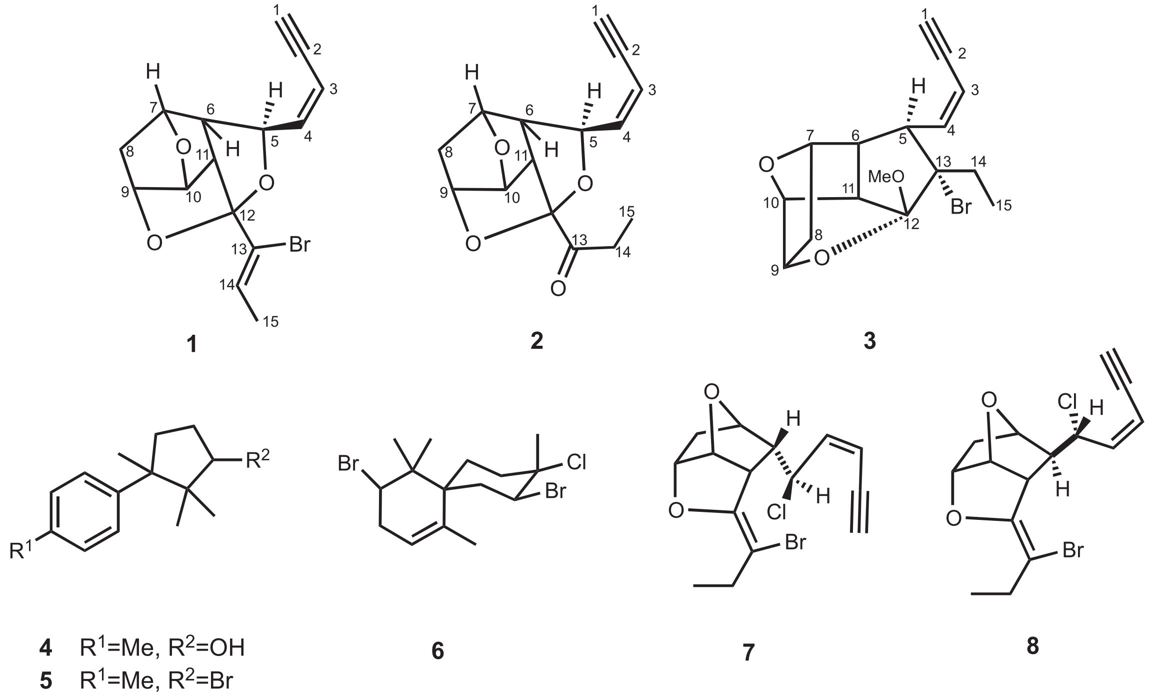


Fig. 1. Chemical structures of the isolated compounds.