Laurendecumallenes A–B and Laurendecumenynes A–B, Halogenated Nonterpenoid C_{15}-Acetogenins from the Marine Red Alga *Laurencia decumbens*

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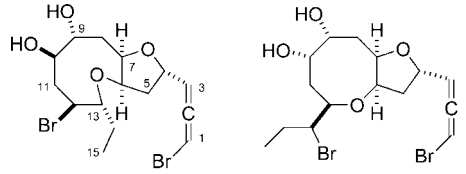
Four new halogenated nonterpenoid C_{15}-acetogenins, 4:7,6:13-bisepoxy-9,10-diol-1,12-dibromopentadeca-1,2-diene (**1**, laurendecumallene A), 4:7,6:12-bisepoxy-9,10-diol-1,13-dibromopentadeca-1,2-diene (**2**, laurendecumallene B), (3*Z*)-6:10,7:13-bisepoxy-12-bromo-9-hydroperoxylpentadeca-3-en-1-yne (**3**, laurendecumenyne A), and (3*Z*)-6:10,9:13-bisepoxy-12-bromo-7-chloropentadeca-3-en-1-yne (**4**, laurendecumenyne B), together with one known halogenated C_{15}-acetogenin elatenyne (**5**) were isolated and identified from the organic extract of the marine red alga *Laurencia decumbens*. Their structures and relative stereochemistry were established by means of spectroscopic analysis including UV, IR, high-resolution electrospray ionization mass spectrometry (HRESIMS), and 1D and 2D NMR techniques. All these metabolites were submitted for the cytotoxic assay against tumor cell line A549 (human lung adenocarcinoma), but all of them were found inactive ($IC_{50} > 10$ μg/mL).

Halogenated nonterpenoid C_{15}-acetogenins are widely distributed among the marine red algae of the genus *Laurencia* (order Ceramiales, family Rhodomelaceae), such as *L. nipponica*, *L. obtusa*, and *L. okamurai*. Structurally, these metabolites can be classified into enyne and bromoallene groups and often contain cyclic ether moieties with different ring sizes.[1] C_{15}-acetogenins have been reported to possess some biological activities.[2,3] In the course of our ongoing investigations toward the discovery of biologically active and structurally new metabolites from Chinese sea waters, we collected the marine red alga *Laurencia decumbens* Kützing from Weizhou island of Guangxi province, P.R. China. The chemical investigation of this alga resulted in the isolation and characterization of four new (**1**–**4**) and one known (elatenyne, **5**)[4] halogenated C-$_{15}$ acetogenins. The structures of the new compounds were identified as 4:7,6:13-bisepoxy-9,10-diol-1,12-dibromopentadeca-1,2-diene (**1**, laurendecumallene A), 4:7,6:12-bisepoxy-9,10-diol-1,13-dibromopentadeca-1,2-diene (**2**, laurendecumallene B), (3*E*)-6:10,7:13-bisepoxy-12-bromo-9-hydroperoxylpentadeca-3-en-1-yne (**3**, laurendecumenyne A), and (3*E*)-6:10,9:13-bisepoxy-12-bromo-7-chloropentadeca-3-en-1-yne (**4**, laurendecumenyne B). This paper reports the isolation, structural determination, and cytotoxic assay of these metabolites.



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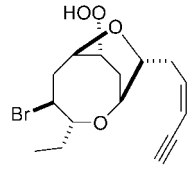

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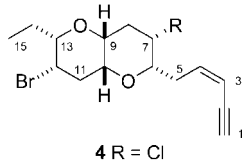

4 R = Cl
5 R = Br

The dried and powdered *L. decumbens* was extracted with the mixture of $CHCl_3$ and MeOH (1:1, v/v), and the residue was further extracted with 95% EtOH. The concentrated extracts were combined and partitioned between H_2O and EtOAc to afford the EtOAc-soluble fraction, which was further purified by a combination of silica gel and Sephadex LH-20 column chromatography, as well as by preparative TLC procedures, to yield the five halogenated C_{15}-acetogenins **1**–**5**.

Compound **1** was obtained as colorless crystals. The broad IR absorption at υ_{max} 3386 cm^{-1} indicated the presence of hydroxyl groups in the molecule. The positive electrospray ionization mass spectrometry (ESIMS) exhibited a characteristic quasimolecular ion peak cluster at *m/z* 451/449/447 (1:2:1) $[M + Na]^+$, suggesting the presence of two bromine atoms in **1**. The molecular formula was determined as $C_{15}H_{22}Br_2O_4$ on the basis of high-resolution ESIMS (*m/z* 448.9746 $[M + Na]^+$, calcd for $C_{15}H_{22}{}^{79}Br^{81}BrO_4Na^+$, 448.9762), suggesting four degrees of unsaturation. The ^{13}C NMR along with the DEPT and HSQC experiments also revealed the presence of 15 carbon atoms including one methyl, four methylene, and nine methine carbon atoms and one quaternary carbon atom. The presence of a bromoallene moiety was indicated by the characteristic carbon signals observed at δ_C 74.3 (CH, C-1), 201.3 (C, C-2), and 102.0 (CH, C-3) in the ^{13}C NMR spectrum.[5] Since no other unsaturated functionalities were indicated by the NMR spectra, **1** was deduced to be bicyclic. The ^1H–^1H COSY correlations indicated the presence of a large spin system and enabled the identification of a continuous chain of connected spins from H-3 to H-15. The two cyclic ether linkages between C-4 and C-7 and between C-6 and C-13 were established by the HMBC correlations from H-4 to C-7 and from H-13 to C-6, respectively. A detailed comparison of the NMR data with those reported for the neo-laurallene revealed that **1** possessed a C_{15}-acetogenin skeleton with terminal bromoallene functionality. However, no signals for the C-9 double bond in neo-laurallene occurred in the NMR spectra at **1**. Instead, two oxygenated methine signals of δ_C 72.4, δ_H 3.43 (CH, C-9) and δ_C 74.1, δ_H 3.95 (CH, C-10) were observed.[5] The above spectral evidence led to the establishment of the planar structure for **1**.

The relative configuration of **1** was determined by the analysis of the NOESY experiment and coupling constants and by comparison with those of literature reports. The large coupling constant ($J = 9.3$ Hz) indicated that H-9 and H-10 are trans. The observed NOESY correlations between H-9 and H-4 and between H-10 and

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H-12 indicated the cis orientation for H-9 and H-4 and for H-10 and H-12. The relative configurations at C-4, C-6, C-7, and C-13 were assigned to be the same as for neo-laurallene upon detailed comparison with NMR data.[5] The lack of NOESY correlations between H-4 and H-6 and between H-4 and H-7 supported this assignment. The above spectral evidence established the structure of **1** to be 4:7,6:13-bisepoxy-9,10-diol-1,12-dibromopentadeca-1,2-diene, which was named as laurendecumallene A.

Compound **2** was obtained as a colorless oil. The broad IR absorption at υ_{max} 3420 cm^{-1} indicated the presence of hydroxyl groups in the molecule. The positive ESIMS exhibited a characteristic quasimolecular ion peak cluster at *m/z* 451/449/447 (1:2:1) $[M + Na]^+$, suggesting the presence of two bromine atoms in **2**. The molecular formula was determined as $C_{15}H_{22}Br_2O_4$ on the basis of high-resolution ESIMS (*m/z* 448.9735 $[M + Na]^+$, calcd for $C_{15}H_{22}{}^{79}Br^{81}BrO_4Na^+$, 448.9762), suggesting four degrees of unsaturation. The ^{13}C NMR along with the DEPT and HSQC experiments revealed the presence of 15 carbon atoms including one methyl, four methylene, and nine methine carbon atoms and one quaternary carbon atom. A comparison of the NMR data revealed that **2** also possessed a C_{15}-acetogenin skeleton with terminal bromoallene unit. The ^1H–^1H COSY correlations indicated the presence of a straight chain-type connection from H-3 to H-15 in **2**. The two cyclic ether linkages between C-4 and C-7 and between C-6 and C-12 were established by the observed HMBC correlations from H-4 to C-7 and from H-12 to C-6, respectively. The above spectral evidences led to the establishment of the planar structure for **2**.

The relative configuration of **2** was determined by the comparison with literature data and the analysis of the NOESY and gradient Overhauser enhancement spectroscopy (GOESY) experiments. The relative configurations at C-4, C-6, C-7, and C-12 were assigned upon detailed comparison with literature data,[5] which were further confirmed by the obvious correlations between Hb-14 and Hb-5, Ha-8 and the absent correlations between H-4 and H-6, H-7 in the NOESY experiment. Since the chemical shifts and coupling patterns of protons H-9 and H-10 are quite different from those of **1**, compound **2** was further submitted for 1D GOESY NMR experiments (see the Supporting Information). A selective excitation at δ_H 4.31 (br d, H-9) gave a 1D spectrum with proton signal having a clearly positive NOE effect at δ_H 4.10 (m, H-10), while irradiation at H-10 demonstrated a NOE enhancement for H-9. Therefore, H-9 and H-10 were deduced to be cis. The above spectral evidence allowed the structure of **2** to be identified as 4:7,6:12-bisepoxy-9,10-diol-1,13-dibromopentadeca-1,2-diene, which was named as laurendecumallene B.

Compound **3** was also obtained as a colorless oil. The IR absorption at υ_{max} 3423, 3290, 2093, 3021, 1616, and 751 cm^{-1} indicated the presence of hydroxyl (or hydroperoxyl), terminal acetylene, and disubsituted (*Z*)-alkene groups in the molecule.[4] The positive ESIMS spectrum exhibited a characteristic quasimolecular ion peak cluster at *m/z* 369/367 (1:1) $[M + Na]^+$, suggesting the presence of one bromine atom in **3**. The molecular formula was determined as $C_{15}H_{21}BrO_4$ on the basis of high-resolution ESIMS (*m/z* 367.0520 $[M + Na]^+$, calcd for $C_{15}H_{21}{}^{79}BrO_4Na^+$, 367.0521), suggesting five degrees of unsaturation. The ^{13}C NMR along with the DEPT and HSQC experiments also revealed the presence of 15 carbon atoms including one methyl, four methylene, nine methine, and one quaternary carbon atom. A comparison with the known compound **5** revealed that **3** possessed a C_{15}-acetogenin skeleton with conjugated terminal enyne functionality. The ^1H–^1H COSY correlations indicated the continuous chain-type connections from H-3 to H-15. The two ether linkages between C-6 and C-10 and between C-7 and C-13 were established by the observed HMBC correlations from H-6 to C-10 and from H-13 to C-7, respectively. The chemical shift of δ_C 51.9 ppm for C-12 indicates that the bromine atom is attached there. Two of the four oxygen atoms in the molecular formula of $C_{15}H_{21}BrO_4$ were accounted for by the cyclic ethers, and two oxygens remained to be accounted for. However, only one oxygenated carbon (C-9) remained, which implied that **3** possessed a hydroperoxide. The downfield chemical shift for C-9 at δ_C 78.7 further confirmed its connection with a hydroperoxyl group. The above spectral evidence led to the establishment of the planar structure for **3**.

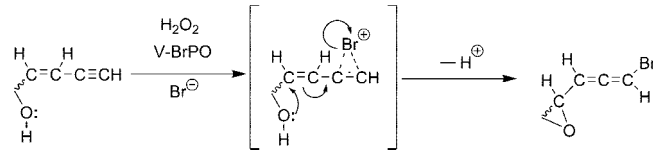

Figure 1. Possible biogenesis of a terminal bromoallene.

The relative configuration of **3** was determined upon the analysis of the NOESY experiment and coupling constants. The observed NOESY correlations between H-5 and H-7 and between H-7 and H-14 indicated the cis orientation for H-5, H-7, and H-14. In addition, the observed correlations between H-10 and H-12 revealed the cis configuration for the substitution at C-10 and C-12. Finally, the NOESY correlations between H-9 and H-6 and between H-9 and H-13 also indicated the cis orientation for H-9, H-6, and H-13. The coupling constant ($J = 10.7$ Hz) indicated the *Z*-configuration for the double bond at C-3. The above spectral evidence established the relative configuration for **3**. On the basis of the above deduction, the chemical structure of **3** was determined to be (3*Z*)-6:10,7:13-bisepoxy-12-bromo-9-hydroperoxylpentadeca-3-en-1-yne, which was named as laurendecumenyne A.

Compounds **4** and **5** were obtained as a colorless oily mixture with a 1:1 ratio. They displayed one spot on TLC analysis, and all attempts to separate them either by CC or by preparative TLC with different solvent systems failed. The chemical structure of **5** was readily identified as elatenyne by detailed analysis of the NMR and MS spectral data and comparison with those in the literature.[4] For compound **4**, the positive ESIMS spectrum exhibited a quasimolecular ion peak cluster at *m/z* 373/371/369 $[M + Na]^+$ with a ratio of ca. 1:4:3, characteristic for the presence of one bromine and one chlorine atom in the molecules. The high-resolution ESIMS (*m/z* 371.0208 $[M + Na]^+$, calcd for $C_{15}H_{20}{}^{81}Br^{35}ClO_2Na^+$, 371.0212) afforded the molecular formula of **4** as $C_{15}H_{20}BrClO_2$, which further supported the presence of a chlorine atom. The difference between **4** and **5** mainly consisted in the chemical shifts of C-7 at δ_C 59.3 for **4** and at δ_C 48.5 for **5**. The other ^{13}C NMR signals of **4** and **5** were almost superposed, except that C-6 and C-8 were shifted to slightly higher field, to δ_C 86.2 and 38.3 ppm, respectively, in **4**. So, instead of a bromine-substitution at C-7 for **5**, a chlorine-substitution presented at C-7 for **4** according to above deduction and literature data.[4,6] On the basis of the above evidence, the chemical structure of **4** was determined to be (3*Z*)-6:10,9:13-bisepoxy-12-bromo-7-chloropentadeca-3-en-1-yne, which was named as laurendecumenyne B. A literature survey revealed that **4** is a stereoisomer of (*Z*)-dactomelyne, which possesses a β-configuration for the bromine substitution at C-12.[7]

The C_{15}-acetogenins are a large group of metabolites that are commonly isolated and reported from the marine red algal genus *Laurencia*. However, the described compounds **1**–**5** in this report are unusual examples with bromoallene and enyne co-occurring. Compounds **1**–**5** might result from a common biogenetic precursor, laurediol, which was suggested as the biosynthetic precursor to a series of halogenated C_{15}-acetogenins in red algae, all substituted by heteroatoms at C-6, C-7, C-9, C-10, C-12, and C-13.[8] The terminal bromoallene moiety in **1** and **2** may be produced biosynthetically by the bromoperoxidase catalyzed reaction of a bromine atom on the terminal enyne, followed by nucleophilic attack of the adjacent C-7 hydroxyl group on the olefinic carbon C-4 (Figure 1).[8,9]

Table 1. ^{1}H NMR Data of Compounds **1–4** (500 MHz, $CDCl_3$, *J* in Hz)

no.	1	2	3	4
1	6.07 (dd, 5.6, 1.9)	6.06 (dd, 5.7, 1.7)	3.10 (d, 2.1)	3.13 (br s)
3	5.45 (dd, 5.6, 5.6)	5.45 (dd, 5.7, 5.7)	5.54 (dd, 10.7, 2.1)	5.60 (br d, 10.9)
4	4.84 (m)	4.77 (m)	6.05 (dt, 10.7, 7.5)	6.05 (dt, 10.9, 7.5)
5a	2.08 (ddd, 13.4, 7.7, 5.3)	2.19 (ddd, 13.2, 6.6, 1.8)	2.83 (m)	2.65 (m)
5b	2.21 (m)	2.07 (m)	2.70 (m)	2.59 (m)
6	4.14 (br s)	4.20 (m)	3.76 (dt, 7.1, 1.8)	4.07 (m)
7	4.12 (m)	4.18 (m)	3.98 (m)	4.07 (m)
8a	2.23 (m)	2.42 (ddd, 15.8, 7.3, 1.6)	2.28 (d, 15.4)	2.32 (m)
8b	1.88 (ddd, 14.8, 3.4, 3.4)	1.97 (m)	2.00 (m)	2.23 (m)
9	3.43 (ddd, 9.3, 3.4, 3.4)	4.31 (br d, 7.3)	4.14 (dd, 9.7, 4.0)	4.15 (m)
10	3.95 (ddd, 9.3, 5.5, 2.5)	4.10 (m)	4.00 (br s)	4.15 (m)
11a	2.74 (ddd, 16.4, 5.8, 2.5)	2.06 (m)	3.05 (ddd, 15.2, 9.6, 1.7)	2.32 (m)
11b	2.47 (ddd, 16.4, 5.5, 3.7)		2.31 (dd, 15.2, 5.2)	
12	4.01 (ddd, 10.5, 5.8, 3.7)	3.82 (m)	4.59 (dd, 9.5, 9.5)	3.97 (m)
13	3.73 (td, 10.5, 10.5, 2.1)	3.87 (m)	3.89 (ddd, 11.3, 9.5, 2.6)	4.00 (m)
14a	2.18 (m)	2.01 (m)	1.95 (m)	1.66 (m)
14b	1.63 (m)	1.77 (m)	1.69 (m)	1.50 (m)
15	1.06 (t, 7.3)	1.06 (t, 7.2)	1.05 (t, 7.4)	0.98 (t, 7.4)

Table 2. ^{13}C NMR Data of Compounds **1–4** (125 MHz, $CDCl_3$)

no.	1	2	3	4
1	74.3 CH	74.0 CH	81.9 CH	82.4 CH
2	201.3 C	201.3 C	80.2 C	80.0 C
3	102.0 CH	102.3 CH	110.2 CH	111.1 CH
4	73.6 CH	73.4 CH	141.5 CH	139.8 CH
5	40.3 CH_2	40.2 CH_2	30.2 CH_2	34.6 CH_2
6	72.4 CH	81.3 CH	83.3 CH	86.2 CH
7	80.6 CH	78.5 CH	70.3 CH	59.3 CH
8	32.7 CH_2	32.5 CH_2	33.1 CH_2	38.3 CH_2
9	72.4 CH	69.1 CH	78.7 CH	79.6 CH
10	74.1 CH	70.7 CH	70.5 CH	79.3 CH
11	41.9 CH_2	35.2 CH_2	38.8 CH_2	39.0 CH_2
12	47.8 CH	78.8 CH	51.9 CH	48.8 CH
13	84.1 CH	60.8 CH	83.3 CH	88.7 CH
14	22.8 CH_2	27.4 CH_2	23.1 CH_2	26.7 CH_2
15	11.6 CH_3	12.1 CH_3	11.8 CH_3	10.0 CH_3

Compounds **1–5** were evaluated for the cytotoxicity against a human lung adenocarcinoma (A549) cell line. However, all of them were found to be inactive (IC_{50} > 10 μg/mL).

Experimental Section

General Experimental Procedures. Melting points (uncorrected) were determined on a SGW X-4 micro melting point apparatus. Optical rotations were measured on an Atago Polax-L polarimeter. UV spectra were determined on a Beckman DU 640 UV–visible spectrophotometer. IR spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer. 1D and 2D NMR spectra were obtained on a Bruker Avance 500 spectrometer at 500 and 125 MHz for ^{1}H and ^{13}C, respectively. Mass spectra were collected using a VG Autospec 3000 mass spectrometer. Column chromatography (CC) was performed on silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Qingdao, China) and Sephadex LH-20 (Sigma). TLC was carried out with precoated silica gel plates (GF-254, Qingdao Haiyang Chemical Co., Qingdao, China).

Plant Material. The marine red alga *Laurencia decumbens* Kützing was collected at Weizhou Island of Guangxi province, P. R. China, in April, 2006, and was identified by Prof. B.-M. Xia at the Institute of Oceanology, Chinese Academy of Sciences (IOCAS). A voucher specimen (HZ0604a) has been deposited at the Key Laboratory of Experimental Marine Biology of IOCAS.

Extraction and Isolation. The dried and powdered alga *L. decumbens* (500 g) was extracted with a mixture of $CHCl_3$ and MeOH (1:1, v/v), and the residue was further extracted with 95% EtOH. The concentrated extracts were combined and partitioned between H_2O and EtOAc. The EtOAc-soluble fraction was chromatographed on Si gel, eluting with a step gradient of increasing EtOAc (0–100%) in petroleum ether (PE) to give six fractions I–VI. Fraction II eluted with PE/EtOAc 30:1 and was further purified by preparative TLC to afford **4** and **5** (25.6 mg). Fraction V eluted with PE/EtOAc 2:1 and was further separated by Si gel ($CHCl_3$/MeOH 1:1) CC, Sephadex LH-20 ($CHCl_3$/MeOH 1:1) CC, and preparative TLC to afford **1** (12.8 mg), **2** (13.0 mg), and **3** (11.0 mg).

Laurendecumallene A (1): colorless crystals; mp 142–144 °C; $[\alpha]_D^{18}$ +40.9 (*c* 0.31, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 233 (4.50) nm; IR ($CHCl_3$) υ_{max} 3386, 3060, 2913, 1960, 1458, 1363, 1109, 1039 cm^{-1}; ^{1}H NMR data ($CDCl_3$) (see Table 1); ^{13}C NMR data ($CDCl_3$) (see Table 2); ESIMS *m/z* 451, 449, 447 $[M + Na]^+$ (1:2:1); HRESIMS *m/z* 448.9746, $[M + Na]^+$ (calcd for $C_{15}H_{22}{}^{79}Br^{81}BrO_4Na^+$, 448.9762).

Laurendecumallene B (2): colorless oil; $[\alpha]_D^{18}$ +60.6 (*c* 0.33, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 233 (4.50) nm; IR ($CHCl_3$) υ_{max} 3420, 3060, 2932, 1960, 1456, 1370, 1108, 1068 cm^{-1}; ^{1}H NMR data ($CDCl_3$) (see Table 1); ^{13}C NMR data ($CDCl_3$) (see Table 2); ESIMS *m/z* 451, 449, 447 $[M + Na]^+$ (1:2:1); HRESIMS *m/z* 448.9735, $[M + Na]^+$ (calcd for $C_{15}H_{22}{}^{79}Br^{81}BrO_4Na^+$, 448.9762).

Laurendecumenyne A (3): colorless oil; $[\alpha]_D^{18}$ +9.6 (*c* 0.33, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 237 (4.27) nm; IR ($CHCl_3$) υ_{max} 3423, 3290, 3021, 2934, 2093, 1616, 1459, 1370, 1148, 1065, 751 cm^{-1}; ^{1}H NMR data ($CDCl_3$) (see Table 1); ^{13}C NMR data ($CDCl_3$) (see Table 2); ESIMS *m/z* 369, 367 $[M + Na]^+$ (1:1); HRESIMS *m/z* 367.0520, $[M + Na]^+$ (calcd for $C_{15}H_{21}{}^{79}BrO_4Na^+$, 367.0521).

Laurendecumenyne B (4): colorless oil; IR ($CHCl_3$) υ_{max} 3293, 2928, 2090, 1623, 1460, 1379, 1068, 750 cm^{-1}; ^{1}H NMR data ($CDCl_3$) (see Table 1); ^{13}C NMR data ($CDCl_3$) (see Table 2); ESIMS *m/z* 373, 371, 369 $[M + Na]^+$ (1:4:3); HRESIMS *m/z* 371.0208 $[M + Na]^+$ (calcd for $C_{15}H_{20}{}^{81}Br^{35}ClO_2Na^+$, 371.0212).

Cytotoxicity Assay. Cytotoxic assay toward the human lung adenocarcinoma (A549) cell line was carried out as previously reported.[10]

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Supporting Information Available: 1D and selected 2D NMR spectra of compounds **1–4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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