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NEW SESQUITERPENES AND C_{15} ACETOGENINS FROM THE MARINE RED ALGA *LAURENCIA IMPLICATA*

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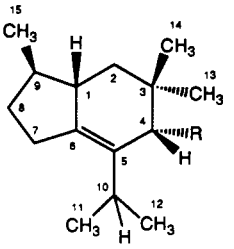
ABSTRACT.—From a single collection of the red alga *Laurencia implicata* fourteen secondary metabolites, including nine sesquiterpenes (**1**, **3**, **5–11**), one diterpene (**12**), and four C_{15}-acetogenins (**13–15**, **17**) have been isolated and characterized. Two of the sesquiterpenes, (1*R**,4*R**,5*Z*,9*S**)-5-isopropyl-3,3,9-trimethylbicyclo[4.3.0]nona-5-en-4-ol [**1**] and (1*R**,4*E*,6*S**,9*R**)-5-(1′-methylethan-1′-ol)-3,3,9-trimethylbicyclo[4.3.0]nona-4-ene [**3**], and the C_{15}-acetogenins (1*R**,4*R**,6*S**,7*S**,9*R**,10*R**,12*S**,13*R**)-4:7,6:12-bisepoxy-9-chloro-1,10,13-tribromopentadeca-1,2-diene [**13**] and (1*R**,4*R**,6*S**,7*S**,9*R**,10*R**,12*R**,13*R**)-1,10-dibromo-4:7,6:13,9:12-trisepoxypentadeca-1,2-diene [**14**], are new natural products. For compounds **5–9** and **11** unambiguous ^{1}H- and ^{13}C-nmr assignments were made.

Algae of the genus *Laurencia* are very diverse with respect to their chemical constituents. Secondary metabolites from plants of this genus are known to include sesquiterpenes, diterpenes, triterpenes, and C_{15}-acetogenins of many different structural types (1). In the course of our continuing studies of the secondary metabolite content of marine algae and their relationship to site and time of collection of the algae, we investigated a sample of *Laurencia implicata* J. Agardh (Rhodomelaceae), collected once again from Britomart Reef (2) (central region of The Great Barrier Reef), Queensland, Australia.

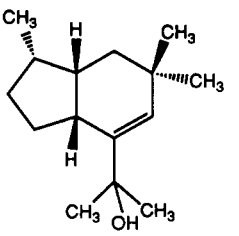
RESULTS AND DISCUSSION

The CH_2Cl_2 solubles from the freeze-dried algal tissue were chromatographed over Si gel (3). Selected fractions were then further purified by hplc according to Table 1 to afford fourteen pure compounds **1**, **3**, **5–15**, and **17**.

Compound **1** had a molecular formula of $C_{15}H_{26}O$. The occurrence of only two resonances in the ^{13}C-nmr spectrum for sp^2 hybridized carbons [133.6 (s), 140.7 (s) ppm] dictated **1** to be a bicyclic molecule. Further, from the ^{13}C-nmr and ir spectroscopic data [72.9 (d) ppm, 3470 cm^{-1}] it was apparent that the oxygen within **1** was present in the form of a secondary hydroxyl function, which underwent smooth acetylation to give **2**. The ^{1}H-nmr data (C_6D_6) for **1** clearly showed the presence of two tertiary methyls [δ 0.74 (s), 1.04 (s)] and three secondary methyl functions, two being part of an isopropyl moiety [δ 0.97 (d, J = 6.2 Hz), 1.02 (d, J = 7.0 Hz), 1.14 (d, J = 7.0 Hz), 2.57 (qq, J = 7.0, 7.0 Hz)]. These data together with the information gained from the ^{1}H-^{1}H COSY spectrum of **1** and the results of one-bond (J = 136 Hz) and long-range (J = 10 Hz) ^{13}C-^{1}H correlation experiments allowed the structure of **1** to be deduced as that of a brasilenol [**4**] derivative (4). The proposed structure of **1** contained three chiral centers, the stereochemistries of which were deduced mainly from the results of 2D NOESY measurements made with **1** and **2**. Thus, in **1** the presence of an nOe between the proton at C-1 and the protons of the C-14 methyl group, which further showed nOe to H-4, clearly position these groups on the same side of the molecule. Additionally, in the acetate **2** of **1**, the observed nOe between the H-1 and the protons of the C-15 methyl group position these two groups on the same side of the molecule. The proposed stereochemistry at C-4 is further supported by the 1.1 Hz W coupling between the H-4 and one of the protons at C-2. For such a coupling to be observed between these two protons, the C-4 proton must be "in plane" with one of the protons at C-2 and thus have the stereochemistry as shown in **1**. Compound **1** is (1*R**,4*R**,5*Z*,9*S**)-5-isopropyl-3,3,9-trimethylbicyclo[4.3.0]nona-5-en-4-ol.



1 R=OH
2 R=OAc



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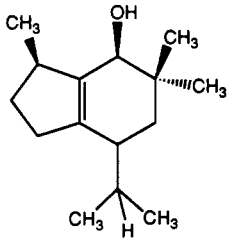

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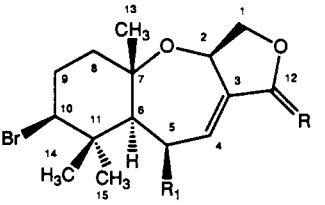
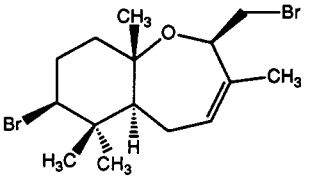


5 R=O, R_1=H
6 R=O, R_1=OH
7 R=H_2, R_1=H



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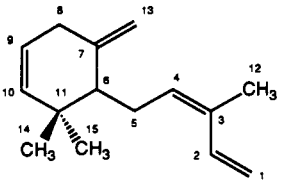

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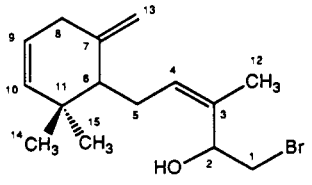

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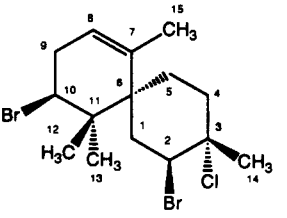

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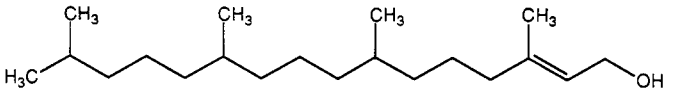
Compound **3**, an oil with molecular formula $C_{15}H_{26}O$, contained a single carbon-carbon double bond [130.9 (d), 143.7 (s) ppm] and a tertiary alcohol [73.3 (s) ppm, 3450 cm^{-1}] function; it was thus bicyclic. From its ^{1}H-nmr spectral data (C_6D_6) four signals for tertiary methyl groups could be discerned [δ 1.33 (s), 1.31 (s), 1.09 (s), 1.07 (s)] as well as a doublet resonance for a secondary methyl funtion [δ 1.05 (d, J = 6.5 Hz)]. Of the four methyl groups, two were part of a *gem*-dimethyl grouping, with the others forming a -C(Me)$_2$OH moiety. As all of these methyl groups showed nOe interactions with the olefinic proton [δ 5.89 (br s)] it was concluded that the associated groupings must be on either side of it. Further from the ^{1}H-^{1}H COSY spectrum of **3** the following coupling patterns could be discerned. The olefinic proton at C-4 showed long-range coupling to one of the protons at C-2 [δ 1.05 (m)] and the proton at C-6 [δ 1.93 (m)]. The proton at C-6 showed couplings to the proton at C-1 [δ 1.19 (m)] and to both of the protons at C-7 [δ 1.42 (m), 1.96 (m)]; these C-7 protons intercoupled, and both had couplings to the protons of the C-8 methylene group. The latter two protons

TABLE 1. Isolation Scheme for Isolates **1**, **3**, **5–15**, and **17** from the CH_2Cl_2 Solubles of *Laurencia implicata*.

Fraction number	3	6	9	10	11	12	14	15	16
Separation method[a]	A	B	C	C	D	E	F	F	F
Isolates and their amounts (mg)	**11** (3) **9** (10)	**11** (5)	**1** (32) **8** (48) **17** (5)	**3** (5) **7** (9) **10** (17) **13** (73) **14** (26)	**7** (46) **10** (31)	**7** (75) **12** (8) **15** (8)	**5** (150)	**6** (57)	**6** (43)

[a]A = Hplc employing normal phase silica and hexane as eluent; B = hplc employing normal phase silica and hexane-EtOAc (99:1) as eluent; C = hplc employing normal phase silica and hexane-CH_2Cl_2-Et_2O (80:18:2) as eluent; D = hplc employing normal phase silica and hexane-EtOAc (93:7) as eluent; E = hplc employing normal phase silica and hexane-EtOAc (90:10) as eluent. F = No hplc was required as **5** and **6** eluted as pure compounds from the initial chromatography.



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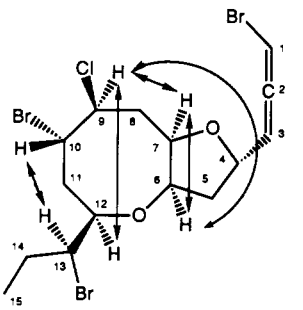

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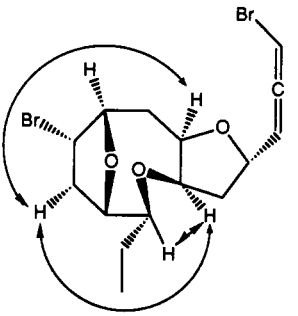
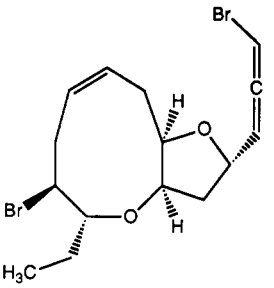


14*

*Arrows indicate nOe's.



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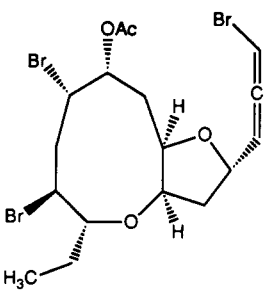

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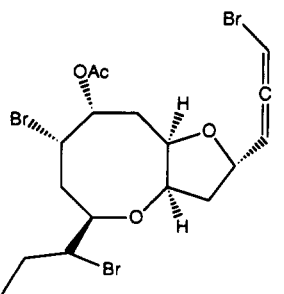

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TABLE 2. ^{1}H-nmr (300 MHz, $CDCl_3$) Data for **5**, **6**, **7**, **9**, and **11**.

Proton	Compound				
	5	**6**	**7**	**9**	**11**
H-1	4.49 (dd, J = 8.7, 9.0 Hz), 3.86 (dd, J = 6.6, 9.0 Hz)	4.56 (dd, J = 8.9, 9.2 Hz), 3.98 (dd, J = 7.0, 9.2 Hz)	3.44 (dd, J = 8.3, 8.4 Hz), 4.07 (dd, J = 8.0, 8.3 Hz)	5.07 (ddd, J = 1.6, 1.7, 10.8 Hz), 5.18 (ddd, J = 0.7, 1.6, 17.3 Hz)	2.24 (m), 2.35 (m)
H-2	5.16 (m)	5.10 (ddd, J = 2.5, 7.0, 8.9 Hz)	4.83 (br s)	6.78 (ddd, J = 0.8, 10.8, 17.3 Hz)	4.92 (dd, J = 8.0, 10.4 Hz)
H-4	6.94 (ddd, J = 2.7, 5.4, 5.8 Hz)	6.92 (dd, J = 2.5, 5.9 Hz)	5.55 (m)	5.37 (dddd, J = 0.8, 2.2, 2.2, 9.8 Hz)	2.24 (m), 2.31 (m)
H-5	2.55 (m)	5.00 (dd, J = 2.5, 5.9 Hz)	2.36 (m)	2.20 (m), 2.40 (m)	1.63 (dddd, J = 1.2, 3.8, 3.8, 14.2 Hz), 2.02 (ddd, J = 6.2, 12.7, 14.2 Hz)
H-6	2.06 (ddd, J = 3.0, 3.8, 12.5 Hz)	1.73 (s)	2.08 (br d, J = 10.0 Hz)	2.04 (dd, J = 4.0, 11.2 Hz)	
H-8	1.81 (ddd, J = 4.2, 13.2, 13.2 Hz), 1.60 (ddd, J = 3.5, 4.0, 13.2 Hz)	1.44 (ddd, J = 3.5, 3.6, 12.8 Hz), 1.86 (ddd, J = 4.8, 12.6, 12.8 Hz)	1.55 (ddd, J = 3.5, 3.6, 13.0 Hz), 1.80 (ddd, J = 4.2, 13.0, 13.2 Hz)	2.65 (m)	5.24 (m)
H-9	2.27 (dddd, J = 3.5, 4.2, 4.5, 13.6 Hz), 2.15 (ddd, J = 0.7, 4.0, 13.6 Hz)	2.23 (m)	2.11 (m), 2.27 (m)	5.50 (dddd, J = 0.6, 3.4, 3.4, 9.8 Hz)	2.53 (m), 2.68 (m)
H-10	3.95 (dd, J = 4.5, 12.6 Hz)	3.93 (dd, J = 5.2, 12.1 Hz)	3.96 (dd, J = 4.5, 12.5 Hz)	5.32 (br d, J = 9.8 Hz)	4.53 (dd, J = 7.0, 10.6 Hz)
H-12			4.37 (m)	1.79 (br s)	1.22 (s)
H-13	1.29 (s)	1.63 (s)	1.27 (s)	4.68 (m), 4.86 (m)	1.99 (br s)
H-14	0.96 (s)	1.28 (s)	0.93 (s)	0.95 (s)	0.95 (s)
H-15	1.18 (s)	1.23 (s)	1.17 (s)	1.03 (s)	1.71 (s)

also intercoupled and showed further coupling to the proton at C-9 [δ 1.44 (m)], which in turn coupled to the protons of the C-15 methyl group and the proton at C-1, which coupled to one of the protons at C-2 [δ 1.05 (m)]. These observations and the implied structural features together with ^{1}H- and ^{13}C-nmr data comparisons between **1** and **3** indicated the latter to be a structural isomer of **1**. The nature of the positional isomerism was deduced from evaluation of inter-proton coupling patterns and additions of lanthanide shift reagent [Eu(fod)$_3$] to the nmr sample of **3**. As a result of Eu(fod)$_3$ additions the resonances for two methyl groups [δ 1.31 (s) , 1.33 (s)], the single olefinic proton [δ 5.49 (dd, J = 1.3, 2.4 Hz)], a methine proton [δ 1.93 (m)], and the protons from the C-7 methylene group [δ 1.42 (m), 1.96 (m)] all moved between 5.7 and 11.1 ppm to higher frequencies; i.e., they became more deshielded. From inter-proton coupling patterns it was also evident that one of the protons at C-2 must have a dihedral angle of approximately 90° with the proton at C-1. The inter-proton coupling pattern observed for the C-1 proton, in the ^{1}H-nmr shifted spectrum of **3**, revealed that this proton had large couplings (ca. 10 Hz) to the protons at C-6 and C-9 as well as a large coupling (12.9 Hz) and a small coupling (2.5 Hz) to the protons at C-2. These observations and the results of the shift reagent study (see Experimental) indicate the C-15 methyl group to be α and the proton at C-6 to be β. Compound **3** is (1*R**, 4*E*,6*S**,9*R**)-5-(1′-methylethan-1′-ol)-3,3,9-trimethylbicyclo[4.3.0]nona-4-ene.

Compounds **5–11** were all sesquiterpenes that had been previously reported from *Laurencia* species. For compounds **8** (palisadin B) and **10** (palisol) all our spectroscopic data compared well with those reported (5). For compounds **5** (aplysistatin) (6), **6** (5β-hydroxyaplysistatin) (7), **7** (palisadin A) (5), **9** (8), and **11** (9), the assignments of the ^{1}H- and ^{13}C-nmr resonances were either ambiguous, incomplete, or in some cases incorrect, while for **9** and **11** no ^{13}C-nmr data were available. Detailed nmr studies of compounds **5**, **6**, **7**, **9**, and **11** now allow us to provide these data in an unambiguous and complete form (Tables 2 and 3). For each of the compounds **5**, **6**, **7**, **9**, and **11** the assignments were based on 2D ^{13}C-^{1}H one-bond (J = 136 Hz) and long-range (J = 10 Hz) (**5** only) as well as ^{1}H-^{1}H correlation experiments (see Experimental).

Compound **12** was identified as one of the diastereomers of *trans*-phytol (10). We report here (see Experimental) complete ^{1}H- and ^{13}C-nmr data for this compound.

TABLE 3. ^{13}C-nmr (75.5 MHZ, $CDCl_3$) Data for **5**, **6**, **7**, **9**, and **11**.

Carbon	Compound				
	5	**6**	**7**	**9**	**11**
C-1	69.7 (t)	69.8 (t)	71.9 (t)	113.2 (t)	39.5 (t)
C-2	66.6 (d)	66.2 (d)	70.0 (d)	133.9 (d)	63.1 (d)
C-3	131.8 (s)	133.6 (s)	141.8 (s)	132.1 (s)	71.1 (s)
C-4	142.9 (d)	141.9 (d)	121.0 (d)	137.0 (d)	40.4 (t)
C-5	27.1 (t)	67.8 (d)	26.2 (t)	24.9 (t)	31.6 (t)
C-6	50.9 (d)	54.7 (d)	51.7 (d)	52.7 (d)	47.8 (s)
C-7	78.9 (s)	79.2 (s)	77.9 (s)	145.6 (s)	139.7 (s)
C-8	37.5 (t)	39.1 (t)	37.5 (t)	32.6 (t)	123.0 (d)
C-9	32.3 (t)	32.3 (t)	32.6 (t)	123.2 (d)	36.3 (t)
C-10	65.2 (d)	65.7 (d)	66.2 (d)	130.6 (d)	60.9 (d)
C-11	40.8 (s)	41.6 (s)	40.9 (s)	37.2 (s)	42.8 (s)
C-12	169.0 (s)	169.5 (s)	71.0 (t)	19.8 (q)	24.7 (q)
C-13	21.5 (q)	25.2 (q)	21.9 (q)	109.8 (t)	26.0 (q)
C-14	17.8 (q)	19.1 (q)	17.9 (q)	25.1 (q)	17.2 (q)
C-15	30.6 (q)	30.7 (q)	30.8 (q)	30.2 (q)	24.2 (q)

The final group of metabolites **13–17** to be discussed here are all C_{15} acetogenins. Compound **13** had the molecular formula $C_{15}H_{20}Br_3ClO_2$ by ms. From its ^{13}C-nmr data (Table 4) the presence of a bromoallene moiety was suggested [201.6 (s), 101.8 (d), 74.1 (d) ppm] as were seven other carbons bearing electron withdrawing substituents; **13** was thus bicyclic. The oxygen functionalities within **13** were present as ethers since neither the ^{13}C-nmr or ir spectroscopic data evidenced carbonyl or hydroxyl functionality. On the basis of the results from one-bond ^{13}C-^{1}H and ^{1}H-^{1}H correlation experiments a continuous chain of carbons from C-1 to C-15 could be discerned: CHBr=C=CHCH(O)-CH_2-CH(O)-CH(O)-CH_2-CHCl-CHBr-CH_2-CH(O)-CHBr-CH_2-CH_3. The points of closure for the two ethers, between C-4 and C-7 and between C-6 and C-12, were made on the basis of ^{1}H- and ^{13}C-nmr data comparisons between **13**, **15**, and **17** (Table 4). From these comparisons it was also clear that the Cl function must reside at C-9. Stereochemically **13** and **17** [structure established by X-ray (13)] were obviously very similar on the basis of their corresponding ^{1}H- and ^{13}C-nmr data for most centers. The stereochemistry at C-9 was deduced from the results of a 2D NOESY measurement made with **13**. Compound **13** is thus (1*R**,4*R**,6*S**,7*S**,9*R**,10*R**,12*S**,13*R**)-4:7,6:12-bisepoxy-9-chloro-1,10,13-tribromopentadeca-1,2-diene.

TABLE 4. ^{13}C-nmr (75.5 MHZ, $CDCl_3$) Data for **13**, **14**, **15**, and **17**.

Carbon	Compound			
	13	**14**	**15**	**17**
C-1	74.1 (d)	74.1 (d)	73.9 (d)	74.0 (s)
C-2	201.6 (s)	201.3 (s)	201.4 (s)	201.8 (s)
C-3	101.8 (d)	101.2 (d)	102.1 (d)	101.8 (d)
C-4	74.1 (d)	72.5 (d)	74.5 (d)	74.4 (d)
C-5	39.3 (t)	38.3 (t)	39.0 (t)	39.0 (t)
C-6	81.5 (d)	75.2 (d)	72.7 (d)	81.9 (d)
C-7	78.4 (d)	77.1 (d)	79.6 (d)	78.4 (d)
C-8	37.3 (t)	31.0 (t)	26.7 (t)	32.9 (t)
C-9	59.5 (d)	78.7 (d)	127.2 (d)	70.3 (d)
C-10	58.6 (d)	59.7 (d)	129.3 (d)	57.0 (d)
C-11	40.6 (t)	31.3 (t)	34.7 (t)	40.3 (t)
C-12	79.0 (d)	74.8 (d)	52.8 (d)	79.2 (d)
C-13	60.2 (d)	86.8 (d)	84.4 (d)	60.3 (d)
C-14	27.2 (t)	21.7 (t)	23.1 (t)	27.0 (t)
C-15	12.3 (q)	10.4 (q)	11.4 (q)	12.3 (q)
				21.3 (q)
				170.2 (s)

Compound **14**, had the molecular formula $C_{15}H_{20}O_3Br_2$ and was found to be a tricyclic molecule, a trisether. Again, as for compound **13**, it was possible to establish linkages between all fifteen carbons on the basis of 2D ^{1}H-^{1}H and ^{13}C-^{1}H correlation spectra obtained with **14** dissolved in either C_6D_6 or $CDCl_3$: CHBr=C=CH-CH(O)-CH_2-CH(O)-CH(O)-CH_2-CH(O)-CHBr-CH_2-CH(O)-CH(O)-CH_2-CH_3. Once the C_{15} chain for **14** had been pieced together, the points of closure for the three ethers and the position of the bromine remained to be established. From comparisons of ^{13}C-nmr data of **14** and **13**, **15**, **17** (Table 4), it appeared that the ether linkages occur as a result of closures between C-4 and C-7, and C-6 with either C-12 or C-13, and C-9 with either C-12 or C-13, with the bromine residing at C-10. To resolve the last two points of closure for the ethers, a long range ^{13}C-^{1}H correlation experiment ($J = 7$ Hz) was

performed. The results of this experiment revealed a long-range coupling between H-12 and C-9, clearly indicating the final two ether linkages to occur between C-9 and C-12, and between C-6 and C-13. Once the basic framework for **14** was completed, the Dreiding model for **14** was constructed in such a way as to satisfy all of the inter-proton coupling information as well as the results obtained from a 2D NOESY measurement made with **14**. The two most critical pieces of structural information for assigning the relative stereochemistry within **14** were the observations that one of the C-11 protons (δ 2.32 d, $J = 11.5$ Hz) had an almost 0 Hz coupling to both the protons at C-10 and C-12 as well as having an nOe interaction with the protons at C-6 and C-7, clearly defining the stereochemistry for a major part of the molecule. The centers not confirmed stereochemically from these observations (C-4 and C-13) were assigned on the basis of ^{13}C-nmr data comparisons (Table 4) and the results of the aforementioned 2D NOESY measurement. Compound **14** is thus (1*R**,4*R**,6*S**,7*S**,9*R**,10*R**,12*R**,13*R**)-1,10-dibromo-4:7,6:13,9:12-trisepoxypentadeca-1,2-diene.

Compound **15** proved to be the known metabolite neo-laurallene (11).

Compound **17** was also a previously reported acetogenin (12). In the report for **17** (12), ^{13}C- and ^{1}H-nmr resonances were assigned on the basis of literature comparisons that have since proved to be unreliable; therefore a one-bond ^{13}C-^{1}H ($J = 136$ Hz) correlation experiment was performed. As a direct result of this measurement and the resulting assignments, it was clear that the proposed structure **16** should be revised to **17**, which has been recently reported as a semi-synthetic compound (13).

Three previous chemical investigations of *L. implicata* from The Great Barrier Reef region of Australia yielded either a predominance of terpenes or C_{15} acetogenins (2, 12). A prior investigation of *L. implicata* from Britomart Reef (2) afforded only terpenoid metabolites. In the current investigation of *L. implicata*, once again from Britomart Reef, both C_{15} acetogenins and terpenes were clearly shown to co-occur in the same sample; they thus provide a further example of secondary metabolite variation within an algal species.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All one-bond ^{13}C-^{1}H correlation experiments were performed with proton detection (Bruker invbtp) with delays optimized for $J = 136$ Hz. Long-range ^{13}C-^{1}H correlation experiments were performed with carbon detection (Bruker hxco) with delays optimized for either $J = 7$, 10, or 15 Hz. Remaining details are as in König *et al.* (14).

PLANT MATERIAL.—The algal material was obtained in September 1989, from Britomart Reef in the central region of The Great Barrier Reef, Australia. Plants growing at 0–3 m depth were collected, deep frozen, and, on return to the laboratory, freeze-dried. A voucher specimen is deposited at the Department of Chemistry and Biochemistry, James Cook University, Townsville, Australia (voucher number BR891B).

EXTRACTION AND ISOLATION.—The dry algal tissue (370 g) was exhaustively extracted with 2 liters of CH_2Cl_2 and then with an equivalent volume of MeOH to afford 3.7 g (1%) of CH_2Cl_2-soluble material. Vacuum liquid chromatography (vlc) (3) of the crude extract over Si gel using hexane with increasing proportions of EtOAc as eluent afforded 16 fractions each of approximately 90 ml. Tlc and ^{1}H-nmr investigation of these fractions indicated fractions 3, 5, 9–12, and 14–16 to be of further interest. Separation of these fractions according to Table 1 yielded 14 pure compounds.

(1*R**,4*R**,5*Z*,9*S**)-5-Isopropyl-3,3,9-trimethylbicyclo[4.3.0]nona-5-en-4-ol [**1**] was obtained as an equilibrium mixture of oil and solid at room temperature (32 mg, 0.009%): $[\alpha]^{22}_{D}$ −45.0° ($CHCl_3$, $c = 0.03$); ir ν max (film) 3470, 2900, 1450, 1385, 1010, 985 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 0.66 (br d, $J = 7.5$ Hz, 1H, OH), 0.78 (s, 3H, H-13), 1.01 (d, $J = 7.0$ Hz, 3H, H-11), 1.01 (d, $J = 7.0$ Hz, 3H, H-12), 1.02 (s, 3H, H-14), 1.13 (d, $J = 6.8$ Hz, 3H, H-15), 1.14 (m, 1H, H-2), 1.34 (m, 1H, H-9), 1.36 (m, 1H, H-2), 1.63 (br ddd, $J = 5.6$, 11.2, 11.4 Hz, 1H, H-1), 1.89 (m, 2H, H-8), 2.27 (m, 2H, H-7), 2.63 (qq, $J = 7.0$, 7.0 Hz, 1H, H-10), 3.50 (br d, $J = 7.5$ Hz, H-4); ^{1}H nmr (C_6D_6, 300 MHz) δ 0.74 (s, 3H, H-13), 0.97 (d, $J = 6.2$ Hz, 3H, H-15), 1.02 (d, $J = 7.0$ Hz, 3H, H-11), 1.04 (s, 3H, H-14), 1.10 (m, 1H, H-2), 1.10 (m, 1H, H-8), 1.14 (d, $J = 7.0$ Hz, 3H, H-12), 1.25 (m, 1H, H-

9), 1.30 (ddd, J = 1.1, 5.7, 12.6 Hz, 1H, H-2), 1.54 (ddd, J = 5.7, 11.2, 11.2 Hz, 1H, H-1), 1.79 (m, 1H, H-8), 2.15 (m, 2H, H-7), 2.57 (qq, J = 7.0, 7.0 Hz, 1H, H-10), 3.45 (br d, J = 5.3 Hz, 1H, H-4); ^{13}C nmr ($CDCl_3$, 75.5 MHz) 17.9 (q, C-15), 21.3 (q, C-11), 21.8 (q, C-12), 23.8 (q, C-13), 26.6 (t, C-7), 27.4 (q, C-14), 30.3 (d, C-10), 32.9 (t, C-8), 33.8 (t, C-2), 34.6 (s, C-3), 40.8 (d, C-9), 47.0 (d, C-1), 72.9 (d, C-4), 133.6 (s, C-6), 140.7 (s, C-5) ppm; ^{1}H-^{13}C nmr long range correlations ($CDCl_3$, J = 10 Hz) H-2 (C-1, C-2, C-6), H-4 (C-5, C-6), H-7 (C-5, C-6, C-7), H-11 (C-5, C-10, C-11, C-12), H-12 (C-5, C-10, C-11, C-12), H-13 (C-2, C-3, C-4, C-13, C-14), H-14 (C-2, C-3, C-4, C-13, C-14), H-15 (C-1, C-8, C-9, C-15); eims *m/z* (rel. int.) $[M]^+$ 222 (58), 207 (35), 205 (37), 204 (43), 193 (13), 189 (50), 180 (49), 179 (70), 167 (58), 166 (78), 123 (83), 43 (100); hrms 222.1913 (calcd for $C_{15}H_{26}O$, 222.1985).

ACETYLATION OF COMPOUND **1**.—To a CH_2Cl_2 solution of **1** (9 mg in 2 ml), 500 μl of Ac_2O was added, followed by 2 mg of dimethylaminopyridine. The resultant solution was stirred for 3 h at room temperature. At the end of this period the reaction was quenched with H_2O (5 ml), and the CH_2Cl_2 and H_2O phases separated. The aqueous layer was further extracted with 2 × 5 ml portions of Et_2O. The organic fractions were combined and the solvents removed in vacuo to yield 8.7 mg of material that was purified by hplc [normal phase silica with EtOAc-hexane (1:99) as eluent] to yield 7.3 mg of pure **2**.

Compound **2** was obtained as an oil (7.3 mg): $[\alpha]^{22}D$ −133.5° ($CHCl_3$, c = 0.15); ir ν max (film) 2950, 1735, 1365, 1235, 1015, 955 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H, H-13), 0.88 (s, 3H, H-14), 0.91 (d, J = 6.9 Hz, 3H, H-11), 0.98 (d, J = 6.9 Hz, 3H, H-12), 1.01 (d, J = 7.1 Hz, 3H, H-15), 1.19 (m, 1H, H-2′), 1.21 (m, 1H, H-8′), 1.36 (ddd, J = 1.2, 5.6, 12.4 Hz, 1H, H-2), 1.43 (m, 1H, H-9), 1.65 (ddd, J = 5.7, 11.6, 12.3 Hz, 1H, H-1), 1.91 (m, 1H, H-8), 2.01 (s, 3H, H-17), 2.31 (m, 2H, H-7), 2.57 (qq, 6.9, 6.9 Hz, 1H, H-10), 5.12 (s, 1H, H-4); ^{13}C-nmr ($CDCl_3$, 75.5 MHz) 17.9 (q, C-15), 20.5 (q, C-11), 21.0 (q, C-12), 21.6 (q, C-17), 23.6 (q, C-13), 26.7 (q, C-14), 27.0 (t, C-7), 30.3 (d, C-10), 32.9 (t, C-8), 34.6 (s, C-3), 35.0 (t, C-2), 40.5 (d, C-9), 46.8 (d, C-1), 74.0 (d, C-4), 129.3 (s, C-6), 143.4 (s, C-5), 171.0 (s, C-16) ppm; eims *m/z* (rel. int.) $[M]^+$ 264 (1), 222 (1), 204 (76), 189 (48), 166 (100), 161 (47), 119 (32), 105 (28).

(1*R**,4*E*,6*S**,9*R**)-5-(1′-Methylethan-1′-ol)-3,3,9-trimethylbicyclo[4.3.0]nona-4-ene [**3**] was isolated as an oil (5.0 mg, 0.0015%): $[\alpha]^{22}D$ −3.0° ($CHCl_3$, c = 0.17); ir ν max (film) 3450, 2920, 1460, 1375 cm^{-1}; ^{1}H nmr (C_6D_6, 300 MHz) δ 1.05 (m, 1H, H-2), 1.05 (d, J = 6.5 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 1.09 (s, 3H, H-13), 1.19 (m, 1H, H-1), 1.31 (s, 3H, H-11), 1.33 (s, 3H, H-12), 1.38 (m, 1H, H-8), 1.42 (m, 1H, H-7), 1.44 (m, 1H, H-9), 1.67 (ddd, J = 1.3, 2.2, 12.2 Hz, 1H, H-2), 1.92 (m, 1H, H-8), 1.93 (m, 1H, H-6), 1.96 (m, 1H, H-7), 5.49 (dd, J = 1.3, 2.4 Hz, 1H, H-4); ^{1}H nmr (C_6D_6, 300 MHz) with Eu(fod)$_3$ added δ 1.99 (d, J = 6.6 Hz, 3H, H-15), 2.43 (ddd, J = 6.1, 10.4, 10.8 Hz, 1H, H-8), 2.46 (s, 3H, H-13), 2.49 (s, 3H, H-14), 3.26 (m, 1H, H-9), 3.33 (m, 1H, H-8), 3.44 (dd, J = 2.5, 12.2 Hz, 1H, H-2), 3.62 (dd, J = 12.2, 12.9 Hz, 1H, H-2), 4.54 (dddd, J = 2.5, 9.8, 10.1, 12.9 Hz, 1H, H-1), 7.13 (m, 1H, H-7), 7.77 (m, 1H, H-6), 7.85 (m, 1H, H-7), 11.15 (br s, 3H, H-12), 12.41 (br s, 3H, H-11), 13.99 (br s, 1H, H-4); ^{1}H nmr (C_6D_6, 300 MHz) Δδ values from Eu(fod)$_3$ shift reagent study H-1 (3.35), H-2 (1.77, 2.27), H-4 (8.50), H-6 (5.84), H-7 (5.71, 5.89), H-8 (0.41, 1.41), H-9 (1.82), H-11 (11.10), H-12 (9.82), H-13 (1.37), H-14 (1.42), H-15 (0.94); ^{13}C nmr ($CDCl_3$, 75.5 MHz) 18.9 (q, C-15), 29.2 (t, C-7), 29.8 (q, C-14), 29.8 (q, C-11), 29.9 (q, C-12), 31.9 (q, C-13), 32.3 (t, C-8), 34.5 (s, C-3), 36.4 (d, C-9), 40.9 (t, C-2), 45.8 (d, C-6), 49.4 (d, C-1), 73.3 (s, C-10), 130.9 (d, C-4), 143.7 (s, C-5) ppm; eims *m/z* (rel. int.) $[M]^+$ 222 (10), 207 (49), 204 (35), 189 (30), 164 (40), 149 (50), 133 (18), 107 (34), 95 (31), 59 (80); hrms 222.1922 (calcd for $C_{15}H_{26}O$, 222.1985).

Compound **12** was isolated as a thick clear oil (8 mg, 0.002%): $[\alpha]^{22}D$ −7.7° ($CHCl_3$, c = 0.16); ir ν max (film) 3400, 2945, 1735, 890 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 0.95 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 1.10–1.62 (m, 19H), 1.53 (br s, 3H), 1.98 (dd, J = 7.4, 7.6 Hz, 2H), 4.03 (d, J = 6.7 Hz, 2H), 5.45 (br dd, J = 6.7, 6.7 Hz, 1H); ^{13}C nmr ($CDCl_3$, 75.5 MHz) 16.1 (q), 19.9 (q), 20.0 (q), 22.8 (q), 22.9 (q), 25.0 (t), 25.2 (t), 25.5 (t), 28.3 (d), 33.1 (d), 33.2 (d), 37.0 (t), 37.7 (t), 37.8 (t), 37.9 (t), 39.7 (t), 40.1 (t), 59.4 (t), 124.8 (d), 138.5 (s) ppm.

(1*R**,4*R**,6*S**,7*S**,9*R**,10*R**,12*S**,13*R**)-4:7,6:12-Bisepoxy-9-chloro-1,10,13-tribromopentadeca-1,2-diene [**13**] was a clear mobile oil (73 mg, 0.02%): $[\alpha]^{22}D$ +115.9° ($CHCl_3$, c = 0.24); ir ν max (film) 2930, 1435, 1060, 755, 655 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.10 (t, J = 7.2 Hz, 3H, H-15), 1.76 (m, 1H, H-14′), 1.96 (ddq, J = 2.0, 7.2, 7.3 Hz, 1H, H-14), 2.09 (m, 1H, H-5′), 2.25 (ddd, J = 2.1, 6.8, 13.5 Hz, 1H, H-5), 2.49 (m, 2H, H-11), 2.50 (m, 1H, H-8′), 2.80 (ddd, J = 1.5, 7.5, 16.3 Hz, 1H, H-8), 3.80 (m, 1H, H-13), 3.82 (m, 1H, H-12), 4.07 (br d, J = 8.0 Hz, 1H, H-7), 4.19 (m, 1H, H-6), 4.78 (br t, J = 4.8 Hz, 1H, H-10), 4.84 (m, 1H, H-9), 4.85 (m, 1H, H-4), 5.46 (dd, J = 5.7, 5.8 Hz, 1H, H-3), 6.11 (dd, J = 1.7, 5.7 Hz, 1H, H-1); ^{13}C nmr ($CDCl_3$, 75.5 MHz) see Table 4; eims *m/z* (rel. int.) $[M]^+$ 512, 510, 508, 506 (1, 2, 3, 2), 475 (1), 473 (2), 471 (2), 433 (2), 427 (3), 393 (15), 392 (10), 391 (71), 390 (14), 389 (100), 388 (6), 387 (44), 345 (10), 309 (8), 227 (17), 191

(19), 147 (26), 107 (38), 81 (71); hrms 505.8961 (calcd for $C_{15}H_{20}{}^{79}Br_2{}^{81}Br^{35}ClO_2$, 505.8684), hrms 386.9481 (calcd for $C_{12}H_{18}{}^{79}Br_2{}^{35}ClO_2$, 386.9364).

(1*R**,4*R**,6*S**,7*S**,9*R**,10*R**,12*R**,13*R**)-1,10-Dibromo-4:7,6:13,9:12-trisepoxypentadeca-1,2-diene [**14**] was isolated as an oil (26 mg, 0.007%): $[\alpha]^{22}D$ −21.4° ($CHCl_3$, $c = 0.19$); ir ν max (film) 2900, 1190, 1150, 1065, 655 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ 0.96 (dd, $J = 7.5$, 8.4 Hz, 3H, H-15), 1.75 (m, 2H, H-14), 1.82 (br dd, $J = 5.5$, 14.7 Hz, 1H, H-8′), 1.96 (dddd, $J = 1.0$, 3.8, 9.4, 15.5 Hz, 1H, H-11′), 2.06 (ddd, $J = 6.3$, 6.5, 12.7 Hz, 1H, H-5′), 2.22 (ddd, $J = 3.9$, 7.8, 12.7 Hz, 1H, H-5), 2.32 (d, $J = 15.5$ Hz, 1H, H-11), 2.68 (ddd, $J = 1.8$, 10.4, 14.7 Hz, 1H, H-8), 3.72 (ddd, $J = 2.2$, 7.0, 9.1 Hz, 1H, H-13), 4.09 (dd, $J = 2.2$, 3.8 Hz, 1H, H-12), 4.27 (m, 1H, H-6), 4.29 (m, 1H, H-9), 4.30 (m, 1H, H-10), 4.58 (ddd, $J = 1.2$, 6.6, 10.4 Hz, 1H, H-7), 4.65 (m, 1H, H-4), 5.39 (dd, $J = 5.4$, 5.7 Hz, 1H, H-3), 6.11 (dd, $J = 2.0$, 5.7 Hz, 1H, H-1); ^1H nmr (C_6D_6, 300 MHz) δ 0.96 (dd, $J = 7.4$, 7.4 Hz, 3H, H-15), 1.40 (ddd, $J = 3.7$, 9.3, 15.6 Hz, 1H, H-11′), 1.81 (m, 2H, H-14), 1.86 (m, 2H, H-5), 1.95 (m, 1H, H-8′), 2.07 (br d, $J = 15.6$ Hz, 1H, H-11), 2.76 (ddd, $J = 1.8$, 10.4, 14.7 Hz, 1H, H-8), 3.34 (ddd, $J = 2.0$, 7.0, 7.1 Hz, 1H, H-13), 3.57 (m, 1H, H-12), 3.98 (dd, $J = 6.7$, 14.0 Hz, 1H, H-6), 4.18 (m, 1H, H-10), 4.20 (m, 1H, H-9), 4.39 (m, 1H, H-4), 4.67 (ddd, $J = 1.0$, 6.6, 10.3 Hz, 1H, H-7), 5.06 (dd, $J = 5.1$, 5.5 Hz, 1H, H-3), 5.67 (dd, $J = 2.1$, 5.7 Hz, 1H, H-1); ^{13}C nmr see Table 4; eims *m/z* (rel. int.) $[M]^+$ 410, 408, 406 (1, 2, 2), 391 (1), 389 (1), 364 (1), 362 (1), 329 (2), 327 (2), 247 (22), 245 (65), 209 (7), 191 (10), 153 (9), 97 (24), 81 (33), 57 (100); hrms 329.0595 (calcd for $C_{15}H_{20}{}^{81}BrO_3$, 329.0576).

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