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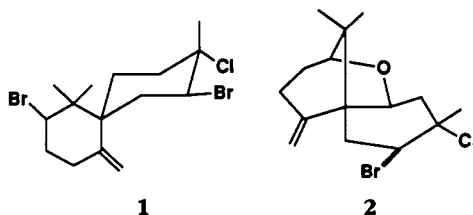
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KAHUKUENES, NEW DITERPENOIDS FROM THE
MARINE ALGA *LAURENCIA MAJUSCULA*MARY ROGER BRENNAN, IN KYU KIM,¹ and KAREN L. ERICKSON*

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ABSTRACT.—Kahukuenes A [4] and B [5], new diterpenoids possessing an unprecedented prenylated chamigrene structure as part of a decalin ring, were isolated from the Hawaiian marine alga *Laurencia majuscula*. Spectroscopic methods, including extensive 1D and 2D nmr studies, were used to establish the structure and relative stereochemistry of these two secondary metabolites.

The *Laurencia* genus of Rhodophyta elaborates an astonishing variety of secondary metabolites (1–3). Most commonly found are sesquiterpenes, especially of the chamigrane class, such as nidificene [1] (4) and nidifocene [2] (5). In contrast, diterpenes are relatively rare in the Rhodophyta. Apart from *Sphaerococcus coronopifolius*, which is a rich source (2,6), the only other Rhodophyta reported to produce diterpenes are *Chondria tenuissima* (7) and several species of *Laurencia* (1–3, 8, 9). Marine molluscs of the genus *Aplysia* occasionally harbor diterpenoids derived from their *Laurencia* algal diet (1–3, 10, 11).



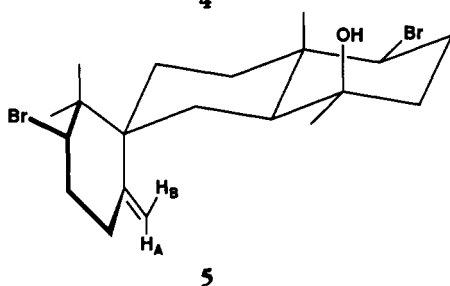
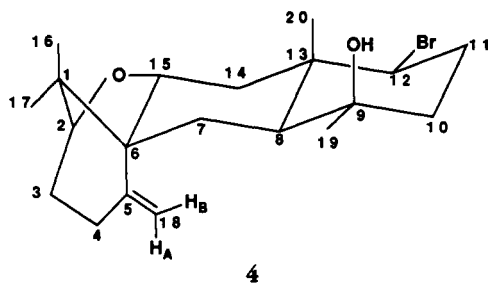
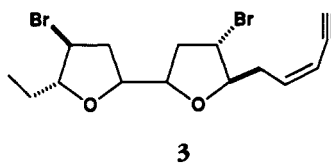
We have now found that a Hawaiian variety of *Laurencia majuscula* (Harvey) Lucas elaborates, in addition to the bistetrahydrofuran lauroxane **3** (12), diterpenes of a new type, kahukuenes A [4] and B [5]. These compounds are unique in that they incorporate an isoprene extension of the basic chamigrane sesquiterpene skeleton.

The alga was collected off the north shore of Oahu, Hawaii, near Kahuku. Short cc (13, 14) and preparative tlc of the CH₂Cl₂ and EtOAc extracts afforded compounds **3** (12), **4**, and **5** in 0.05%, 0.08%, and 0.01% yields, respectively (dry wt).

Kahukuene A [4] has a molecular formula of C₂₀H₃₁O₂Br as determined by hrms. The ir spectrum displayed OH (3600, 3435 cm⁻¹) and terminal vinyl (3083, 1630, 900 cm⁻¹) groups. Broad singlets in the ¹H nmr at δ 4.54 and 4.97 and ¹³C-nmr absorptions at δ 148.8 (s) and 111.7 (t) confirmed the presence of the latter group. Four methyl singlets (δ 1.01, 0.77, 0.88, and 1.35), together with the terminal vinyl group and C₂₀ composition, suggested a diterpenoid structure.

One-proton signals at δ 4.32 (dd), 3.80 (d), and 3.56 (dd) in the ¹H-nmr spectrum coupled with ¹³C-nmr doublets at δ 85.3, 78.7, and 67.4 indicated two methine carbons bearing oxygen and one methine bearing bromine. A singlet at δ 71.2 indicated a quaternary carbon bearing an oxygen. Three additional quaternary carbons, one addi-

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tional methine, and six methylene carbons were further identified by ^1H -nmr and the APT (attached proton) ^{13}C -nmr spectra, completing the C_{20} count.

The HETCOR (one bond ^1H - ^{13}C heteronuclear correlation) spectrum correlated each carbon with its associated protons; expansions provided the correlations of the four protons associated with the overlapping carbons, C-4 and C-11 at δ 30.56 (Table 1). Homonuclear phase sensitive COSY (TPPI) (15) nmr experiments provided the correlation of protons within four isolated groups **I**–**IV**.

Examination of the small long range H-H couplings on the expanded COSY contour maps and simulations (Bruker Panic Software) led to correlations between the isolated groups **I**–**IV** as well as attachment of a *gem*-dimethyl group (C-16 and C-17) through a quaternary carbon (C-1) to an oxymethine carbon, C-2. One of these methyl groups (C-16) is further coupled to H-15, and H-15 is coupled to H_A -18, linking **I** and **IV** through the oxygen and a quaternary C-6. Similarly, long range coupling between H_B -18 and H-7eq links **I** and **II**, giving partial structure **A** for kahukuene A [4].

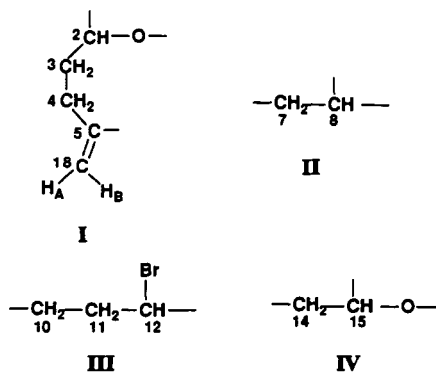


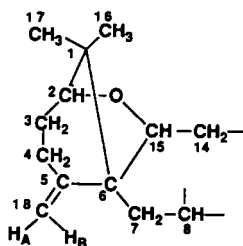
TABLE 1. ^1H - and ^{13}C -nmr Data for Kahukuene A [4].

Position	C (m)	H (m)	J (Hz) ^a	J (Hz) ^b	COLOC ^c	^1H - ^1H OC ^d
1	44.76 (s)	—	—	—	H-3eq, 16, 17	—
2	85.28 (d)	3.80 eq (d)	4.4 (3eq)	1.0 (3ax), 0.6 (4ax), 0.5 (4eq), 0.6 (15), 0.5 (17)	H-16	3eq (m), 3ax (m), 15 (m), 16 (w), 17 (vw)
3	28.84 (t)	1.69 eq	4.4 (2), 13.5 (3ax), 7.9 (4ax)	0.8 (4eq), 0.7 (18B)	—	2, 3ax
4	30.56 (t)	1.47 ax	13.5 (3eq), 11.5 (4ax), 6.2 (4eq)	1.0 (2), 0.5 (18B)	—	3eq, 17
5	148.77 (s)	—	—	—	H-2, 16, 18A, 18B	4eq
6	54.33 (s)	—	—	0.6 (2), 2.2 (18A), 2.3 (18B)	—	4ax, 18A
7	21.77 (t)	1.80 eq	12.6 (7ax)	0.7 (18A)	H-2 ^c , 4eq, 15	—
8	47.82 (d)	1.43 ax	12.6 (7eq), 12.8 (8)	—	H-4eq, 14eq, 16, 17, 18A, 18B	—
9	71.21 (s)	1.50 ax	12.8 (7ax)	0.8 (8), 0.4 (18B)	H-8	7ax, 17, 18B, 19
10	42.35	—	—	0.8 (7eq)	H-10eq, 11eq, 14eq, 19, 20	7eq, 15, 16
11	30.56 (t)	1.21 eq	14.0 (10eq), 4.7 (11eq), 13.5 (11ax)	—	H-10eq, 7eq and/or 11eq, 11ax and/or 14eq, 19	—
12	67.38 (d)	3.56 ax (dd)	14.0 (10ax), 2.7 (11eq), 4.6 (11ax)	—	H-19	8, 10eq, 12
			4.7 (10ax), 2.7 (10eq), 13.4 (11ax), 4.0 (12)	—	H-10ax, H-10eq	10ax, 19
			13.5 (10ax), 4.6 (10eq), 13.4 (11eq), 12.5 (12)	—	—	11ax, 12
			4.0 (11eq), 12.5 (11ax)	0.5 (20)	—	11eq, 20
			—	—	H-8	8 (w), 10ax (w), 11eq (vw), 14ax (m), 3-spin: 10eq (vw)

TABLE 1. (Continued)

Position	C (m)	H (m)	J (Hz) ^a	J (Hz) ^b	COLOC ^c	¹ H- ¹ H nOe ^d
13	41.81 (s)	—	—	—	H-7eq and/or 11eq, 11ax and/or 14eq, 14ax and/or 20	—
14	42.54 (t)	1.34 a	11.5 (14eq), 13.0 (15)	—	H-20	4ax (m), 8 (m), 12 (m), 14eq (s)
15	78.68 (d)	2.42 e 4.32 a (dd)	11.5 (14ax), 3.2 (15) 13.0 (14ax), 3.2 (14eq)	0.6 (2), 0.5 (16), 0.5 (18A)	H-2, 14ax, 14eq	14ax, 15 2 (m), 7ax (m), 14eq (s), 16 (m), 20. 3 spin: 14ax (m)
16	22.70 (q)	1.01 (s)	—	0.5 (15), 0.6 (17)	H-2, 3eq, 17, 18A	2 (s), 7ax (m), 15 (s), 17 (m), 20 (w)
17	21.09 (q)	0.77 (s)	—	0.5 (2), 0.6 (16)	H-16	2 (m), 3ax (m), 7eq (m), 16 (m), 18A (m), 18B (m). 3-spin: 19 (w)
18A	111.67 (t)	4.97 (br s)	—	2.2 (4ax), 0.7 (4eq), 0.5 (15), 1.6 (18B)	H-4ax	4eq (m), 17 (vw), 18B (s). 3-spin: 4ax (w), 7eq (w), 19 (vw)
18B	—	4.54 (br s)	—	0.7 (3eq), 0.5 (3ax), 2.3 (4ax), 0.4 (7eq), 1.6 (18A)	—	7eq (m), 8 (m), 17 (w), 18A (s), 19 (w)
19	29.78 (q)	0.88 (s)	—	—	H-8, 11eq ^f , 14eq ^f	7eq (s), 8 (m), 10ax (m), 10eq (m), 18B (s). 3-spin: 17 (w)
20	17.80 (q)	1.35 (s) 1.85 ^g	—	0.5 (12)	H-12	11ax (m), 15 (s), OH (w)

^aValues from TPPI-COSY and PANIC simulation.^bValues by PANIC simulation.^cOptimized for J = 9 Hz and J = 4.5 Hz.^dCompilation of NOESY and NOE DIFF data; denotes relative intensities in each individual nOe DIFF spectrum.^eFound on J = 4.5 Hz COLOC only.^fOH, identified in the nOe DIFF spectrum of H-20.



A

This partial structure was verified by COLOC (for long-range ^1H - ^{13}C correlations) spectra optimized for couplings of 9 and 4.5 Hz. Quaternary C-1 was coupled to H-16, H-17, and H-3eq. The quaternary olefinic carbon, C-5, exhibited $^3J_{\text{anti}}$ coupling to H-15, a 2J coupling to H-4eq, and a 4J -coupling to H-2. The quaternary C-6 showed $^3J_{\text{cisoid}}$ coupling to H_B-18 and $^3J_{\text{transoid}}$ couplings to H_A-18, the two bridge methyls (H-16 and H-17), and the equatorial protons, H-4eq and H-14eq. C-15 was coupled across the ether bond to H-2 as well as to the hydrogens on C-14. Additional C-H couplings involving C-2, C-4, and C-16 (Table 1) are in agreement with the proposed linkage of **I**, **II**, and **IV**.

Extension of partial structure **A** and its connection to **III** was made possible through the COLOC spectrum (Table 1). C-8 (partial structure **A**) and C-10 (group **III**) both displayed a 3J coupling to the methyl protons of C-19, while C-9, the OH-bearing carbon, displayed a 2J coupling to H-19 and to H-10eq. Hence, the C-19 methyl is attached to the quaternary OH-bearing C-9, which, in turn, serves as a connecting atom between C-8 of partial structure **A** and C-10 of **III**. Both C-8 and C-14 were coupled to the methyl protons of C-20, which must be attached to the remaining quaternary carbon, C-13. This quaternary carbon, then, serves as a connector between C-8 and C-14. Finally, C-13, as the last remaining carbon, must connect to C-12, the bromine-bearing carbon of **III**. This is supported by the coupling of C-12 to H-8 and of C-20 to H-12. The connectivity of kahukuene **A** can now be written as shown in structure **4**.

NOe experiments (Table 1) were employed to assign stereochemistry and confirm gross structure. H-15 exhibited an nOe with H-2, H-7ax, H-16, and H-20, while irradiation of H-20 enhanced H-15, H-11ax, and the OH thus establishing the relative dispositions of the decalin bridgehead methyl (C-20) and the tertiary OH group. Irradiation of H-14ax produced enhancement of H-8, H-4ax, and H-12, while irradiation of the latter enhanced H-8, H-10ax, and H-14ax. This establishes the axial nature of H-8 and the bromomethine, H-12; confirmation is provided by their J values (12.8 Hz for H-8 and 4.0 and 12.5 Hz for H-12). The olefinic proton assignments were further confirmed by the observation of a measurable nOe effect between H_B-18 and H-7eq, H-8, and H-19, while irradiation of H_A-18 produced a sizeable nOe enhancement of H-4eq. Additional nOe and ^1H - ^1H coupling data corroborating the stereochemistry of kahukuene **A** [4] are found in Table 1.

Kahukuene **B** was isolated from less polar fractions of the crude extract. Its molecular formula was established as $\text{C}_{20}\text{H}_{32}\text{OBr}_2$ by fdms. Sequential losses of H_2O and methyl groups were evident in the spectrum as well as bromine and HBr expulsion. Like kahukuene **A**, the ir spectrum of kahukuene **B** showed OH (3608 cm^{-1}) and terminal vinyl ($3089, 1635, 906\text{ cm}^{-1}$) groups. The latter was verified by proton signals at δ 4.59 and 4.89 and carbon absorptions at δ 147.1 (s) and 114.1 (t). Four methyl signals were also easily identifiable (Table 2).

Kahukuene **B** possesses one less oxygen and one more bromine than kahukuene **A**.

TABLE 2. ^1H - and ^{13}C -nmr Data for Kahukuene B [5].

Position	C (m)	H (m)	J (Hz) ^a	$J < 1$ Hz ^b	^1H - ^1H nOe ^c
1	44.18 (s)	—	—	—	—
2	65.41 (d)	4.45 ax	14.7 (3ax), 2.7 (3eq)	16eq, 17ax	3eq, 4ax, 7eq and/or 7ax, 16
3	36.48 (t)	2.00 ax 2.04 eq	14.7 (2), 13.5 (4ax), 11.5 (3eq), 6.0 (4eq) 11.5 (3ax), 6.8 (4ax), 4.7 (4eq), 2.7 (2)	—	17 2, 4eq, 7eq
4	33.96 (t)	1.73 eq 1.98 ax	12.8 (4ax), 6.0 (3ax), 4.7 (3eq) 13.5 (3ax), 12.8 (4eq), 6.8 (3eq)	18A, 18B 18A, 18B	3eq, 4ax, 18A. 3-spin: 2, 18B 2, 7eq, 8. 3-spin: 16
5	147.10 (s)	—	—	—	—
6	49.24 (s)	—	—	—	—
7	24.03 (t)	1.59 eq 1.56 ax	10.2 (7ax), 1.1 (8ax) 13.3 (8ax), 10.2 (7eq)	15eq, 18A 18A	2, 4ax, 8. 3-spin: 4eq 16, 20. 3-spin: 15eq
8	47.45 (d)	0.68	13.3 (7ax), 1.1 (7eq)	OH	7ax and/or 7eq, 10ax, 12, 14ax, 18A, 18B
9	70.77 (s)	—	—	—	—
10	42.30 (t)	0.91 ax 1.14 eq	14.2 (10eq), 13.4 (11ax), 4.5 (11eq) 14.2 (10ax), 4.3 (11ax), 2.8 (11eq)	—	8, 10eq, 11eq, 12. 3-spin: 11ax 10ax, 11eq, 11ax
11	30.53 (t)	1.80 eq 2.39 ax (qd)	13.3 (11ax), 4.5 (10ax), 3.8 (12), 2.8 (10eq) 13.4 (10ax), 13.3 (11eq), 12.7 (12), 4.3 (10eq)	—	10ax, 11ax, 12 11eq, 20. 3-spin: 12, 16
12	68.77 (d)	3.63 (dd)	12.7 (11ax), 3.8 (11eq)	20	8, 10ax, 14ax
13	40.30 (s)	—	—	—	—
14	38.65 (t)	1.23 ax 1.70 eq	14.6 (15ax), 13.1 (14eq), 3.5 (15eq) 13.1 (14ax), 4.2 (15ax), 3.1 (15eq)	20 20	8, 12, 14eq, 18B. 3-spin: 15eq, 18A 12, 14ax, 15eq, 20
15	24.36 (t)	1.42 eq 1.46 ax	12.5 (15ax), 3.5 (14ax), 3.1 (14eq) 14.6 (14ax), 12.5 (15eq), 4.2 (14eq)	7eq, 18B 18A	14eq, 16, 17, 18B. 3-spin: 7ax, 18A 14eq, 16, 17, 20
16	23.72 (q)	1.09 (s)	—	2, 17	2, 7eq and/or 7ax, 15eq, 15ax, 17, 20
17	17.72 (q)	0.96 (s)	—	2, 16	15eq, 15ax, 16, 18A, 18B
18A	114.12 (t)	4.89 (br s)	—	4eq, 4ax, 7eq, 7ax, 15ax	4eq, 8, 18B. 3-spin: 4ax
18B		4.59 (br s)	—	4eq, 4ax, 15eq	8, 14ax, 15eq, 18A. 3-spin: 4eq, 4ax, 14eq
19	29.71 (q)	0.64 (s)	—	OH	7eq, 7ax, OH, 10ax, 10eq
20	14.53 (q)	1.29 (s) 1.65 ^{b,d}	—	12, 14eq, 14ax, 8, 19	7ax, OH, 11ax, 14eq, 15ax, 16. 3-spin: 15eq

^aValues from TPPI-COSY and PANIC simulation.^bFrom TPPI-COSY.^cNOE DIFF data. 3-Spin = -nOe.^dC-9 OH.

In the ^{13}C -nmr spectrum two of the oxygen-bearing carbons of kahukuene A (δ 85.3 and 78.7) have been replaced by carbons at δ 65.4 (d) and 24.4 (t) in kahukuene B. In the ^1H -nmr spectrum, kahukuene B shows only two deshielded methines (δ 4.45 and 3.63), while kahukuene A displayed three. The simplest explanation for these differences is that kahukuene B lacks the cyclic ether of kahukuene A and a bromine has replaced the ring oxygen at either C-2 or C-15. Both molecules retain the bromomethine at C-12 and the quaternary oxygen-bearing carbon at δ 71, which carries the OH group (Tables 1 and 2).

In the ^1H nmr of kahukuene A, H-11ax (quartet of doublets) and H-14eq (doublet of doublets) appeared as an overlapping pattern at δ 2.42. In the ^1H -nmr spectrum of kahukuene B, H-14eq had shifted upfield. This suggested that the electronegative substituent at the adjacent atom, C-15, had been removed. Moreover, the new bromomethine at δ 4.45 displayed no cross peaks with the C-14 protons in the COSY spectrum but did exhibit a cross peak with protons at δ 2. The latter were correlated to another proton (δ 1.73) which, in turn, showed long-range coupling to the olefinic protons. Placing the second bromine at C-2 adequately accommodates these data. Further COSY and HETCOR correlations (Table 2) fully support structure **5** for kahukuene B.

Lacking the cyclic ether of kahukuene A, kahukuene B is free to adopt a different conformation for the methylenecyclohexyl ring. NOe enhancements between H-7eq and H-2 and H-4ax are observed in kahukuene B, replacing those of H-7eq with H-17 and H_B-18 in kahukuene A. In addition, kahukuene A shows an nOe between H-14ax and H-4ax while kahukuene B instead shows an interaction between H-14ax and H_B-18. If the methylenecyclohexane ring has inverted in kahukuene B so as to place the exocyclic vinyl group to the rear of the molecule, the observed nOe effects are expected. In this conformation the bromine at C-2 assumes an equatorial position and avoids a 1,3-diaxial interaction with C-15.

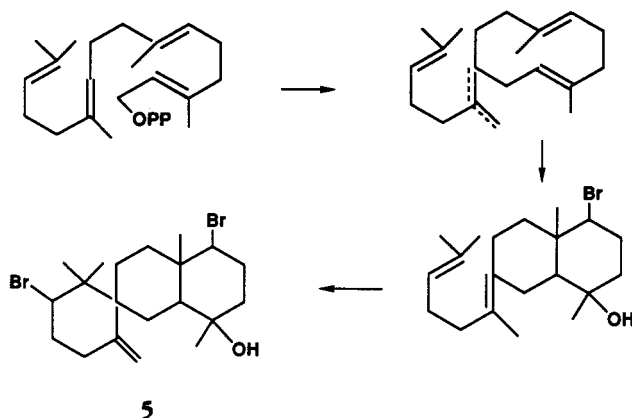
In kahukuene B the axial bridgehead proton of the decalin system, H-8, exhibits a weak nOe with both olefinic protons, H_A-18 and H_B-18, whereas H-8 in kahukuene A gave an nOe only with H_B-18. Moreover a marked upfield shift of H-8 is observed in kahukuene B relative to kahukuene A (δ 0.68 vs. 1.50). Models show this proton to be in the face of the double bond in kahukuene B.

H-20 exhibits a sizeable nOe with H-7ax, H-11ax, and H-15ax and weaker interactions with H-16 and the OH at C-9, suggesting axial stereochemistry for both C-20 and the OH group. Supporting evidence is given by nOe's between the C-9 equatorial methyl (H-19) and H-7eq, H-10ax, and H-10eq.

This Hawaiian variety of *L. majuscula* is unique in its secondary metabolite composition. While Japanese, Australian, and Mediterranean varieties of this alga elaborate only sesquiterpenoids, the Hawaiian variety produces lauroxolanes (12) and diterpenoids but no sesquiterpenoids. Instead, the chamigrene sesquiterpenoid skeleton, so common throughout the *Laurencia* genus, is captured in diterpenoid form in the kahukuenes. A plausible biogenesis of kahukuene B is illustrated in Scheme 1.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All nmr experiments were performed on a Bruker AC-200 spectrometer. ^1H -nmr spectra were recorded at 200.1 MHz in C_6D_6 with TMS as an internal standard at 0.0 ppm. ^{13}C -nmr spectra were recorded at 50.3 MHz in C_6D_6 and are referenced to solvent at 128.0 ppm. All 1D and 2D pulse sequences were run using standard Bruker software. Carbon multiplicities were determined by a *J*-modulated spin echo sequence. The ^1H - ^{13}C shift correlations were obtained with XHCORRD, COLOC, and DEPT sequences. Also, a COLOC with delays adjusted for 1J (16) was used for kahukuene B to correlate five methylene carbons. ^1H - ^1H correlations were obtained by COSY-TPPI. Homonuclear ^1H nOe's were obtained by nOe DIFF spectra and, for kahukuene A, NOESY (TPPI) (15) with mixing times of 0.8, 1.3, and 2 sec (least informative). Optical rotations were measured in a 3.5



SCHEME 1

mm \times 100 mm cell on a JASCO DIP-360 polarimeter. Mass spectra were determined on Varian MAT 731 and Finnigan MAT 95 spectrometers.

ISOLATION AND PURIFICATION.—The alga was collected in shallow water off the north shore of Oahu, Hawaii near Kahuku in July 1974. It was immediately air-dried at 40° and extracted successively (2–5 days each) with petroleum ether, CH₂Cl₂, and EtOAc. The CH₂Cl₂ extract (325 mg from 58 g of dry alga) was subjected to short cc (13, 14) on Si gel. Fractions eluting with CH₂Cl₂ afforded mixtures of enyne **3** and kahukuene B [**5**], which were resolved by preparative tlc on Si gel, eluting with CH₂Cl₂. EtOAc/CH₂Cl₂ (20%) fractions from the short column afforded kahukuene A, further purified by preparative tlc on Si gel with 5% EtOAc/CH₂Cl₂ (2 \times). Total quantities obtained from the alga were: lauroxane **3** (12), 27 mg (0.05%); kahukuene A [**4**], 47 mg (0.08%); and kahukuene B [**5**], 7 mg (0.01%).

Kabukuene A [**4**].—Colorless oil; [α]_D +25° (1.12 g/100 ml, CHCl₃); ir (CCl₄) 3600, 3435, 3083, 2955, 1630, 1457, 1388, 1370, 1360, 1292, 1191, 1163, 1128, 1114, 1057, 1035, 1010, 910, 900, 710 cm⁻¹; ¹H nmr and ¹³C nmr see Table 1; eims *m/z* (rel. int.) 384 (8), 382 (8), 366 (20), 364 (20), 285 (39), 267 (41), 241 (21), 227 (20), 213 (22), 201 (25), 199 (35), 185 (20), 183 (18), 175 (30), 163 (43), 147 (48), 145 (44), 119 (52), 121 (54), 109 (85), 107 (53), 105 (54), 86 (72), 84 (100), 69 (54), 55 (50), 51 (56); hrms calcd for C₂₀H₃₁O₂Br⁷⁹ [M]⁺ 382.1507, found 382.1515.

Kabukuene B [**5**].—Colorless oil; [α]_D +29° (0.30 g/100 ml, CHCl₃); ir (CCl₄) 3608, 3089, 2980, 2956, 1635, 1455, 1392, 1374, 1361, 1178, 1138, 1126, 906, 890, 865 cm⁻¹; ¹H nmr and ¹³C nmr see Table 2; fdms *m/z* (rel. int.) 450 (50), 448 (100), 446 (50), 430, 415, 400, 390, 369, 368, 367, 366, 365, 362, 279; hrms calcd for C₂₀H₃₂OBr₂⁷⁹ [M]⁺ 446.0811, found 446.0850.

ACKNOWLEDGMENTS

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