Halogenated and Non-halogenated Aromatic Sesquiterpenes from the Red Algae *Laurencia okamurai* Yamada[1)]

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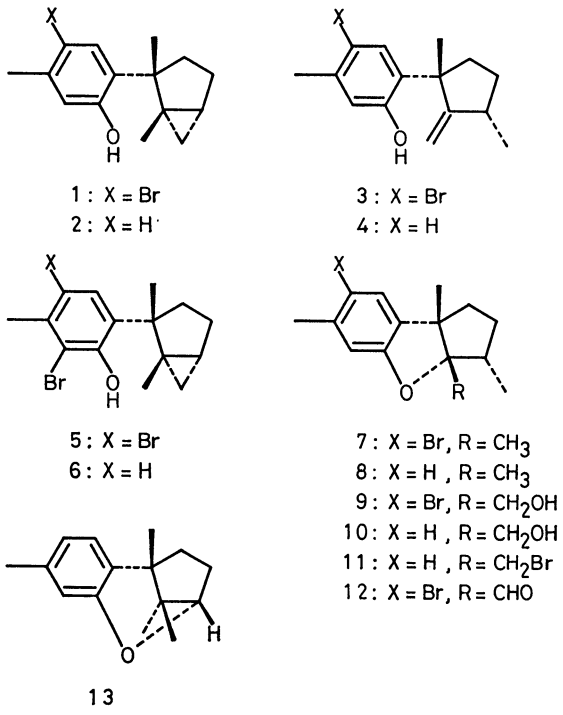
The taxonomic reexamination of the red alga '*L. intermedia* Yamada,' previously collected at Oshoro Bay, Hokkaido, showed that this alga consistd of a mixture of *L. intermedia* Yamada, *L. capituliformis* Yamada, and *L. okamurai* Yamada. Within the Japanese species of genus *Laurencia*, laurinterol and debromolaurinterol were found to be characteristic metabolites of *L. okamurai*, not of *L. intermedia*. In the course of this examination, dibromophenol and debromoaplysinol were newly isolated.

Red algae of the genus *Laurencia* (Rhodomelaceae) are a rich source of halogenated sesquiterpenes, diterpenes, and non-terpenoid C_{15} acetylenic ethers,[2-5)] and various species of *Laurencia* contain unique halogenated metabolites with some overlap ("species-specific"). Since species separation in the genus *Laurencia* is complicated by the high degree of morphological variation within the species, halogenated secondary metabolites might be useful for taxonomic purposes at the species level.[6)]

Previously we reported that laurinterol (**1**) and debromolaurinterol (**2**) were the major components of *L. okamurai* Yamada, specimens of which were collected in two different locations, Hakata-shima, the Inland Sea of Japan[7)] and Okino-shima, Kochi Prefecture,[8)] and also of '*L. intermedia* Yamada,' collected at Oshoro Bay, Hokkaido.[9)] Recently we collected *L. intermedia* Yamada at Inomisaki, Tosa Bay, and examined its neutral oil. There was no halogenated compound in this alga. The above-mentioned results conflicted with the concept of "species-specificity." Therefore, we carried out a taxonomical reexamination of the alga '*L. intermedia*,' previously collected at Oshoro Bay, to reveal that this material consisted of a mixture of *L. intermedia* Yamada, *L. capituliformis* Yamada, and *L. okamurai* Yamada. An examination of fresh algae *L. intermedia* and *L. capituliformis*, collected at Oshoro Bay, showed that these species did not contain any halogenated compound. On the other hand, the freshly collected alga *L. okamurai* was extracted with methanol, and the methanol extracts were subjected to separation by a combination of column and thin-layer chromatography to give laurinterol (**1**), debromolaurinterol (**2**), isolaurinterol (**3**), debromoisolaurinterol (**4**), aplysinol (**9**), isoaplysin (**11**), cuparene-type ether (**13**), bromocuparene (**23**), isobromocuparene (**24**), and isolaurene (**25**). Furthermore, dibromophenol (**5**) and debromoaplysinol (**10**) were newly isolated.

The structure of debromoisolaurinterol (**4**), $C_{15}H_{20}O$, $[\alpha]_D^{23}$ −104°, which has not been obtained in the pure state,[9)] was confirmed by the chemical correlation with aplysin (**7**). Treatment of **4** with bromine in acetic acid afforded a bromo compound, which was found to be identical with aplysin (**7**) by a comparison of the spectral data. The structure of debromoaplysinol (**10**), $C_{15}H_{20}O_2$, $[\alpha]_D^{21}$ −32°, was deduced by a comparison of the spectral data with those of aplysinol (**9**).[7)]

Dibromophenol (**5**), $C_{15}H_{18}OBr_2$ (*m/e* 376, 374, 372; M$^+$), mp 50—52 °C, $[\alpha]_D^{23}$ +8°, exhibited the same intense sharp hydroxyl absorption in the IR spectrum at ν_{max} 3570 cm^{-1} as that of neolaurinterol (**6**), isolated from *L. okamurai* in Okino-shima.[8)] The NMR spectrum exhibited the signals due to a cyclopropane ring at δ 0.2—1.1 (3H, m), two tertiary methyl groups at 1.30 and 1.38 (each 3H, s), an aromatic methyl group at 2.51 (3H, s), and one aromatic proton at 7.59 (1H, s). The signal of the aromatic methyl group was shifted to a lower magnetic field region than those due to the methyl groups of **1** (δ 2.22), **6** (δ 2.33), and other bromophenols. The IR and NMR spectra suggest that dibromophenol should be represented by formula **5**. The structure of **5** was confirmed by the chemical correlation with laurinterol (**1**). Treatment of **1** with *N*-bromosuccinimide in CCl_4[8)] gave a dibromo compound, which was found to be identical with natural **5** in all respects.

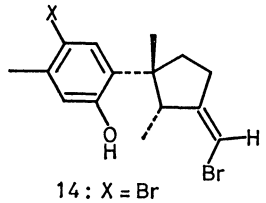


The similarities of the components (Table 1) between the algae *L. okamurai* in Okino-shima[8)] and in Oshoro Bay led to a reexamination of the previous extracts of *L. okamurai* in Hakata-shima[7)] and '*L. intermedia*' in Oshoro Bay.[9)] The results of the reexamination will be described in the experimental section and

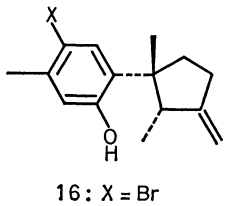
Table 1. Aromatic sesquiterpenes from *Laurencia* species

Species	Location	Compounds
L. okamurai	Oshoro Bay (Japan)	**1, 2, 3, 4, 5, 9, 10, 11, 13, 23, 24, 25**
L. okamurai	Okino-shima (Japan)	**1, 2, 3, 4, 6, 11, 13, 23, 24, 25**
L. okamurai	Hakata-shima (Japan)	**1, 2, 5, 7, 8, 9, 10, 11, 13, 23, 24, 25**
L. pacifica	La Jolla, Calif. (USA)	**1**
L. pacifica	Ensenada (Mexico)	**3**
L. nidifica	Kahala Reef, Hawaii (USA)	**1, 7**
L. desidua	Alpha Helix Baja (Mexico)	**1, 3, 7, 9**
L. nipponica	Moheji, Hokkaido (Japan)	**15, 24, 25, 26**
L. glandulifera	Oshoro Bay (Japan)	**14, 15, 16, 18, 19, 20, 23, 24, 25, 26**
L. filiformis	Port MacDonnell (Australia)	**16, 21, 22, 26**
L. subopposita	La Jolla, Calif. (USA)	**16, 17, 26**
L. species (?)	Cape Omaezaki (Japan)	**1, 3, 7, 9, 12**

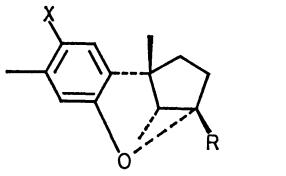
summarized in Table 1. As shown in Table 1, laurinterol (**1**) and debromolaurinterol (**2**) are characteristic major metabolites of Japanese species *L. okamurai*, and several aromatic compounds are common metabolites with only slight differences. Only Hakata-shima's species contained a chamigrene-type sesquiterpene, johnstonol.[10]



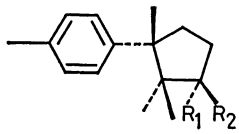
14: X = Br
15: X = H



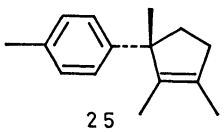
16: X = Br
17: X = H



18: X = Br, R = CH_2Br
19: X = H, R = CH_2Br
20: X = H, R = $CHBr_2$
21: X = Br, R = CH_3
22: X = Br, R = CH_2OH



23: R_1 = H, R_2 = Br
24: R_1 = Br, R_2 = H



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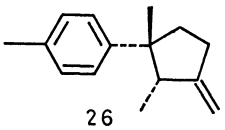

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Laurinterol (**1**) was also isolated from *L. pacifica*,[11] *L. nidifica*,[12] and *L. desidua*.[13] Isolaurinterol (**3**) was also isolated from *L. pacifica*[14] and *L. desidua*.[13] On the other hand, allolaurinterol-type phenols and the related ethers have been obtained from several *L.* species. Allolaurinterol (**16**) and the related ethers, **21** and **22**, were isolated from *L. filiformis*.[15,16] **16** was also isolated from *L. subopposita*[17] along with debromoallolaurinterol (**17**). *L. nipponica*,[18] a Japanese species of *Laurencia*, contained a bromo phenol, laurenisol (**15**), which was also isolated from *L. glandulifera*[20] together with other bromo phenols, **14** and **16**, and the related ethers, **18**, **19**, and **20**. It is interesting to note that these *Laurencia* species contained not only allolaurinterol-type metabolites but also halo-chamigrene derivatives,[19,20] other halo-sesquiterpene derivatives,[16,17] and C_{15} acetylenic ethers.[17,19,20]

Among other Japanese species of the genus *Laurencia*, *L. papillosa* and *L. undulata* did not contain any halogenated compound, and *L. majuscula* contained only halo-chamigrene derivatives.[21,22] Ohta and Takagi have reported the isolation of several aromatic sesquiterpenes, **1**, **3**, **7**, **9**, and **12**, from the red algae *Marginisporum aberrans*, *Amphiroa zonata*, and *Corallina pilulifera* (Corallinaceae), collected at Cape Omaezaki, Shizuoka Prefecture, Japan.[23] As has been described by the authors, these compounds may be derived from *Laurencia* species, for some *Laurencia* species grow in the vicinity of Cape Omaezaki.

Experimental

All the mps were uncorrected. The IR spectra were measured on a Nihon-Bunko IR-S and a A-102 spectrometer. The NMR spectra were recorded on a JEOL JNM-PS-100 spectrophotometer, TMS being used as the internal reference in a CCl_4 soln. The optical rotations were measured in a $CHCl_3$ soln. Alumina (Merck, activity II—III) and silica gel (Mallinckrodt, 100 mesh) were used for the column chromatography. Silica gel (Merck, Kieselgel GF_{254} (Type 60)) was used for the preparative TLC (PLC).

Isolation. *L. okamurai* was collected at Oshoro Bay, Hokkaido, early in August, 1978. The half-dried algae (250 g) were extracted with methanol and then worked up as has previously been described.[9] After the separation of the acidic and basic components, a neutral oil (4 g) was obtained and submitted to column chromatography on neutral alumina.

Hexane Fraction: This fraction consisted of a mixture of hydrocarbons, aromatic ethers, and fatty acid methyl esters. Repeated chromatography on a silica-gel column and a PLC plate yielded isoaplysin (**11**) (0.4% of the neutral oil), cuparene-type ether (**13**) (0.8%), bromocuparene (**23**) (2%), isobromocuparene (**24**) (0.2%), and isolaurene (**25**) (0.6%).

Hexane/Benzene (10 : 1) Fraction: This fraction was rechromatographed on a silica gel column to give dibromophenol (**5**) (0.3%) upon elution with hexane. A benzene eluate gave a mixture of fatty acid methyl esters.

Benzene Fraction: This fraction consisted of laurinterol

(**1**), debromolaurinterol (**2**), isolaurinterol (**3**), and debromoisolaurinterol (**4**). As has previously been described,[9] the isolation and purification of these compounds were carried out *via* their acetates by repeated silica-gel column chromatography and PLC; **1** (40%), **2** (15%), **3** (3.5%), and **4** (2.5%) were thus obtained.

Ether Fraction: This fraction consisted of aplysinol (**9**), debromoaplysinol (**10**), and cholesterol. Repeated chromatography on a PLC plate gave **9** (0.3%) and **10** (0.3%).

Previous Extracts: The neutral oil of '*L. intermedia*,' which was previously collected at Oshoro Bay[9] and stored in an ice box in a N_2 atmosphere, was subjected to separation as described above to give **1** (20%), **2** (10%), **3** (0.6%), **4** (0.3%), **9** (0.1%), **10** (0.2%), **11** (0.1%), **13** (0.7%), **23** (1.1%), **24** (0.3%), and **25** (1.3%). The neutral oil of *L. okamurai*, collected at Hakata-shima,[7] was subjected to separation to give **1** (30%), **2** (13%), **5** (0.1%), **7** (3%), **8** (3%), **9** (0.7%), **10** (0.2%), **11** (0.3%), **13** (0.4%), **23** (0.3%), **24** (0.1%), **25** (1.7%), and johnstonol (0.7%).

*Debromoisolaurinterol (**4**)*: Colorless oil; $[\alpha]_D^{23}$ −104° (*c* 1.10); IR (film), ν_{max} 3490, 3070, 1642, 1620, 1575, 1505, 1380, 1291, 1247, 1160, 1138, 950, 901, 889, and 807 cm^{-1}; NMR, δ 1.20 (3H, d, J=7 Hz), 1.43 (3H, s), 2.23 (3H, s), 4.91 (1H, br s), 5.05 (1H, br s), 5.20 (br s: OH), 6.52 (1H, br s), 6.56 (1H, br d, J=8), and 7.08 (1H, d, J=8); MS, *m/e* (rel. intensity) 216 (34, M^+), 201 (100), 173 (15), 160 (20), 159 (60), 115 (3), 91 (45), and 77 (4).

Acetate: Colorless oil; $[\alpha]_D^{23}$ −91° (*c* 1.43); IR (film) ν_{max} 3075, 1773, 1650, 1622, 1577, 1510, 1380, 1200, 1143, 1070, 1020, 955, 900, and 822 cm^{-1}; NMR, δ 1.13 (3H, d, J=7), 1.23 (3H, s), 2.19 (3H, s), 2.30 (3H, s), 4.71 (1H, br s), 4.99 (1H, br s), 6.70 (1H, br s), 6.79 (1H, br d, J=8), and 7.20 (1H, d, J=8); MS, *m/e* 258 (8, M^+), 216 (20), 201 (100), 173 (6), 160 (8), 159 (16), 115 (3), 91 (4), 77 (3), and 43 (10).

*Dibromophenol (**5**)*: Mp 50—52 °C (from MeOH–H_2O); $[\alpha]_D^{23}$ +8° (*c* 1.0); IR ($CHCl_3$), ν_{max} 3570, 1593, 1395, 1380, 1315, 1290, 1187, 1160, 1130, and 890 cm^{-1}; NMR, δ 0.2—1.1 (3H, m), 1.30 (3H, s), 1.38 (3H, s), 2.51 (3H, s), 5.66 (s: OH), and 7.59 (1H, s); MS, *m/e* 376, 374, 372 (45, M^+), 361, 359, 357 (67), 319, 317, 315 (20), 308, 306, 304 (100), 280, 278 (28), 254, 252 (50), 212 (24), 199 (25), 173 (66), 158 (28), 115 (33), 109 (32), 93 (30), 91 (30), and 77 (30).

*Debromoaplysinol (**10**)*: Mp 85—87 °C (from hexane); $[\alpha]_D^{21}$ −32° (*c* 0.44); IR ($CHCl_3$), ν_{max} 3590, 1620, 1595, 1501, 1280, 1267, 1159, 1100, 1081, 1035, 1000, 948, 855, and 805 cm^{-1}; NMR, δ 1.07 (3H, d, J=7), 1.24 (3H, s), 2.26 (3H, s), 3.57, 3.75 (each 1H, br AB-q, J=12), 6.44 (1H, br s), 6.52 (1H, br d, J=8), and 6.78 (1H, d, J=8); MS, *m/e* 232 (86, M^+), 201 (55), 199 (38), 173 (15), 159 (100), 115 (4), 91 (4), and 77 (3).

*Conversion of **4** to Aplysin (**7**)*. One molar equivalent of bromine (9 mg) in acetic acid (2 ml) was added to a soln of **4** (12 mg) in acetic acid (1 ml). The mixture was allowed to stand at room temp for 15 min and then extracted with ether. The ether soln was successively washed with water, 5% aqueous $NaHCO_3$, and saturated brine. After drying over Na_2SO_4, the solvent was removed to yield a colorless oil, which was purified by PLC to give aplysin (**7**) (11 mg); crystals; mp 85 °C (from MeOH). The IR and NMR spectra were superimposable on those of an authentic sample (**7**).

*Conversion of **1** to **5**.* A soln of **1** (30 mg) and *N*-bromosuccinimide (18 mg) in CCl_4 (2.5 ml) was stirred for 1 h at room temp, and then ether was added. The subsequent removal of the solvent, after filtering from an insoluble substance, gave a residual substance, which was chromatographed on a PLC plate to give dibromophenol (**5**) (33 mg); crystals; mp 50 °C (from MeOH–H_2O). The IR and NMR spectra were superimposable on those of natural **5**.

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