The Structure of Isoaplysin, a Brominated Rearranged Cuparane-Type Sesquiterpenoid from the Red Alga *Laurencia okamurai* Yamada[1)]

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Synopsis. The structure of isoaplysin isolated from the red alga *Laurencia okamurai* Yamada has been established by the spectral and chemical methods.

A number of halogenated and nonhalogenated sesquiterpenes with the cuparane or the rearranged cuparane skeleton have been isolated from the red alga *Laurencia* species and also from the sea hare *Aplysia* species.[2)] In the course of our continuing studies on the constituents of the red alga *Laurencia okamurai* Yamada ("Mitsude-sozo"), we have reported, in the preliminary communication,[3)] that the structure of isoaplysin has been shown by formula **1**. However, the possibility of an alternative formula **2** for isoaplysin could not be completely eliminated. In this note, we describe the structural determination of isoaplysin (**1**) in detail.

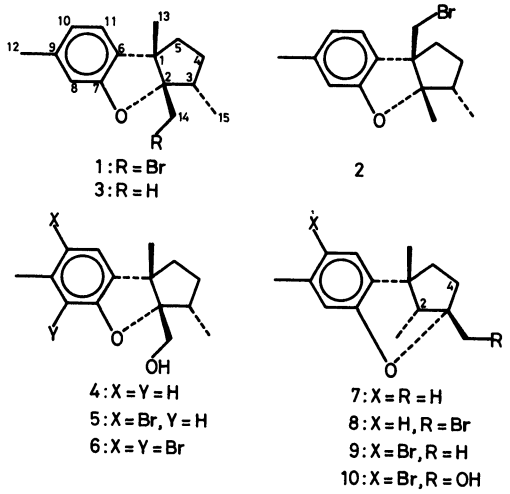
Isoaplysin (**1**) was isolated as a minor metabolite from the methanol extract of *L. okamurai* collected at various locations in Japan by a combination of column and thin-layer chromatography.[3,4)]

Isoaplysin (**1**), colorless oil, $C_{15}H_{19}OBr$ (*m/z* 296 and 294; M^+), $[\alpha]_D^{24}$ −33° ($CHCl_3$), revealed in its ^1H NMR spectrum the presence of a secondary methyl group at δ=1.09 (3H, d, J=6 Hz), a tertiary methyl group at δ=1.50 (3H, s), an aromatic methyl group at δ=2.26 (3H, s), a methylene group with a heteroatom at δ=3.55 (2H, s), and a 1,2,4-trisubstituted phenyl moiety at δ=6.50 (1H, br s), 6.58 (1H, br d, J=8 Hz), and 6.82 (1H, d, J=8 Hz). The IR spectrum of **1** showed no hydroxyl and carbonyl absorptions, indicating that the oxygen atom in **1** was involved in a ether linkage. Since the ^{13}C NMR spectrum of **1** exhibits no signal due to a $-CH_2-O-$ grouping at near 70 ppm, the heteroatom above mentioned, which is adjacent to the methylene group at δ=3.55, must be bromine atom. The ^1H and ^{13}C NMR spectra of **1** were very similar to those of debromoaplysin (**3**), which has been obtained from this species[5)] and also from the sea hare *Aplysia kurodai*.[6)] However, in the ^1H NMR spectra, the distinct difference was observed in the higher magnetic field region as follows. As described above, the ^1H NMR spectrum of **1** indicates the presence of three methyl groups and one bromomethyl group, while the four methyl groups, including one secondary methyl and three tertiary methyls, are present in the spectrum of **3**. This fact suggested that one of the tertiary methyl groups in **3** is replaced by the bromomethyl group. Treatment of **1** with lithium aluminum hydride in tetrahydrofuran gave the debromo ether, $C_{15}H_{20}O$, $[\alpha]_D^{25}$ −53°, which was identical with debromoaplysin (**3**) in all respects. In view of the above-mentioned data, two possible formulae **1** and **2** could be proposed for isoaplysin.

Table 1. Selected ^{13}C NMR Chemical Shifts[a)]

Carbon No	1	3	4	7	8	9[b)]	10[b)]
1	55.5	54.0	55.0	44.6	45.1	44.9	44.9
2	97.1	98.8	99.8	46.6	44.3	46.4	43.1
3	43.7	46.1	43.5	85.0	85.7	85.3	87.4
4	31.5	31.2	31.0	37.3	34.5	37.3	33.0
5	42.6	42.6	43.5	42.1	41.8	42.2	41.8

a) Measured at 25.0 MHz in $CDCl_3$ (TMS=0). b) Quoted from Ref. 9.



In the ^{13}C NMR spectra (Table 1), the signal for C-3 in **1** was shifted upfield by 2.4 ppm compared with that in **3**. The close upfield shift was seen in the spectrum of debromoaplysinol (**4**).[4)] Furthermore, the comparative upfield shifts were also observed for the signals for C-2 and C-4 in the spectra of compounds **7**[7)] and **8**[8)] and also in those of filiformin (**9**)[9)] and filiforminol (**10**).[9)] The upfield shift of the signal for C-3 in isoaplysin is due to the γ-gauche interaction of this carbon with the bromomethyl carbon, whose situation is explicable well only by formula **1**. Confirmation of the structure **1** was obtained by the following chemical correlation.

In the previous paper,[4)] the structure of debromoaplysinol (**4**) was deduced from the spectral properties. Debromoaplysinol (**4**), on treatment with bromine in acetic acid, yielded aplysinol (**5**)[5,6,10)] in poor yield along with dibromo ether (**6**). On the other hand, treatment of **4** with carbon tetrabromide and triphenylphosphine in benzene gave a bromo ether, $C_{15}H_{19}OBr$, $[\alpha]_D^{18}$ −42°, which was identified as isoaplysin (**1**) by comparison of the spectral data. Accord-

ingly, the structure of isoaplysin is represented by formula **1**, including the absolute configuration.

Experimental

The melting points were uncorrected. The IR spectra were recorded on a JASCO A-102 or a JASCO IR-S spectrophotometer. The ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-PS-100 or a JEOL JNM-FX 100 spectrometer, using tetramethylsilane as an internal standard. The low and high resolution mass spectra were taken with a JEOL JMS-D300 spectrometer. Specific rotations were measured on a JASCO DIP-140 or a Hitachi PO-B polarimeter, using $CHCl_3$ as solvent. Silica gel (Merck, Kieselgel 60, 70—230 mesh) was used for column chromatography. Silica gel (Merck, Kieselgel 60 GF_{254}) was used for preparative TLC. High-performance liquid chromatography was performed on a JASCO TRI ROTAR-III with a Finepak SIL-C_{18}column.

Isoaplysin (1): Colorless oil; $[\alpha]_D^{24}$ −33° (*c* 0.69); IR (film), ν_{max} 1620, 1597, 1501, 1275, 1265, 1255, 1135, 1001, 987, 960, 950, 855, and 802 cm^{-1}; ^1H NMR (CCl_4), in the text; ^{13}C NMR (25.0 MHz, $CDCl_3$), δ=158.7 (s; C-7), 138.2 (s; C-9), 132.9 (s; C-6), 122.1 (d; C-11), 121.4 (d; C-10), 109.3 (d; C-8), 97.1 (s; C-2), 55.5 (s; C-1), 43.7 (d; C-3), 42.6 (t; C-5), 34.5 (t; C-14), 31.5 (t; C-4), 22.9 (q; C-13), 21.5 (q; C-12), and 13.8 (q; C-15); MS (70 eV), *m/z* (rel intensity) 296, 294 (47 : 47; M^+) 281, 279 (7 : 7), 239, 237 (7 : 7), 215 (35), 201 (20), 199 (12), 173 (16), 159 (100), 145 (15), 135 (75), 121 (31), 115 (11), 107 (11), and 91 (12). Found: *m/z* 294.0607. Calcd for $C_{15}H_{19}O^{79}Br$: M, 294.0618.

Conversion of Isoaplysin (1) to Debromoaplysin (3). To a solution of **1** (13 mg) in dry tetrahydrofuran (7 ml) was added lithium aluminum hydride (50 mg), and the mixture was refluxed for 5 h, cooled, and mixed with water. After filtration and evaporation of the filtrate, the residue was extracted with ether. The ethereal solution was washed with saturated brine, dried over Na_2SO_4, and evaporated to leave an oily substance which was chromatographed on a silica-gel plate to give **3** (4 mg); oil; $[\alpha]_D^{25}$ −53° (*c* 0.15); The IR, ^1H NMR, and MS spectra were consistent with those of authentic debromoaplysin.

Conversion of Debromoaplysinol (4) to Aplysinol (5). To a solution of **4** (7 mg) in acetic acid (1 ml) was added a small excess of bromine in acetic acid, and the mixture was allowed to stand at room temperature for 30 min and then extracted with ether. The ethereal solution was successively washed with water, 5% aqueous $NaHCO_3$, and saturated brine. After drying over Na_2SO_4, the solvent was evaporated to give an oily residue which was subjected to high-performance liquid chromatography eluted with methanol/water (85 : 15) to afford **5** (2 mg) and **6** (6 mg): **5**: Mp 156—157 °C; $[\alpha]_D^{21}$ −53° (*c* 0.23); The IR and ^1H NMR spectra were identical with those of authentic aplysinol; **6**: Mp 91—93 °C; $[\alpha]_D^{19}$ −34° (*c*0.96); ^1H NMR ($CDCl_3$) δ=1.12 (3H, d, *J*=6 Hz), 1.50 (3H, s), 2.50 (3H, s), 3.86 (2H, m), and 7.14 (1H, s); MS (70 eV), *m/z* 392, 390, 388 (51 : 100 : 52; M^+).

Conversion of Debromoaplysinol (4) to Isoaplysin (1). A solution of **4** (8 mg) in dry benzene (1 ml) was refluxed with triphenylphosphine (35 mg) and carbon tetrabromide (40 mg) for 1 h in N_2 atmosphere. After removal of the solvent, the residual oil was chromatographed on silica-gel column to yield **1** (8 mg); oil; $[\alpha]_D^{18}$ −42° (*c* 0.77); The spectral properties were compatible with those of natural isoaplysin.

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7) Compound **7** was synthesized in high yield from compound **8**[8] by treatment with W-7 Raney nickel in ethanol; **7**: $[\alpha]_D^{17}$ −12° (*c* 1.20; $CHCl_3$); ^1H NMR ($CDCl_3$), δ=0.77 (3H, d, *J*=7 Hz), 1.34 (3H, s), 1.39 (3H, s), 2.25 (3H, s), 6.54 (1H, br s), 6.63 (lH, br d, *J*=8 Hz), and 6.98 (1H, d, *J*=8 Hz); MS (70 eV), *m/z* 216 (44; M^+) and 201 (100; $M^+ - CH_3$).

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