The Absolute Configuration of Isoprelaurefucin[1)]

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Synopsis. (3*Z*)-Isoprelaurefucin has been isolated as a major metabolite from the red alga *Laurencia nipponica* Yamada, and its structure was confirmed by chemical correlation with isoprelaurefucin. Furthermore, the absolute configuration of isoprelaurefucin was established on the basis of chemical evidence.

During our continuing studies on the constituents of the red marine alga *Laurencia nipponica* Yamada, one of the Japanese species of the genus *Laurencia* (Rhodomelaceae; Rhodophyta), we have newly collected at Asari and Hariusu, near Otaru, Hokkaido, and isolated (3*Z*)-isoprelaurefucin (**1**) in 20 and 23% yields of the extracts, respectively. (3*Z*)-Isoprelaurefucin has previously been obtained as the minor metabolite from *L. subopposita*[2)] and *L. nipponica*.[3)] In this note we describe the structural confirmation of (3*Z*)-isoprelaurefucin (**1**) and the absolute configuration of isoprelaurefucin (**2**).[4)]

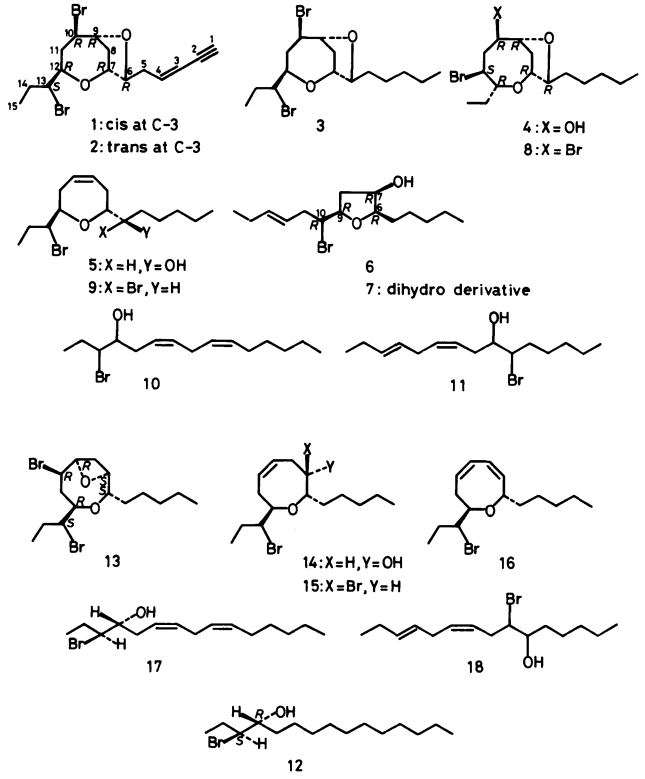
(3*Z*)-Isoprelaurefucin (**1**), $C_{15}H_{20}O_2Br_2$ (*m/z* 394, 392, and 390; M^+), colorless oil, $[\alpha]_D^{21}$ −75.5° (*c* 1.41; $CHCl_3$), indicated in its IR, UV, ^1H NMR, and MS spectra the presence of a *cis*-2-penten-4-ynyl grouping [ν_{max} 3300, 2120, and 760 cm^{-1}; λ_{max} 222 nm (ε 14600); δ=3.11 (1H, d, *J*=2 Hz), 5.59 (1H, br d, *J*=11 Hz), and 6.08 (1H, ddd, *J*=11, 7, 7 Hz); *m/z* 329, 327, and 325; $M^+-C_5H_5$]. The spectral data of **1** were very similar to those of isoprelaurefucin (**2**),[4)] which has previously been isolated as a minor component from *L. nipponica* collected at Moheji, near Hakodate, Hokkaido, suggesting that **1** is the geometric isomer of the double bond at C-3 of **2**. Hydrogenation of **1** over PtO_2 in ethanol gave the hexahydro derivative, $C_{15}H_{26}O_2Br_2$, which was identical with the hydrogenated product **3**[4)] of isoprelaurefucin (**2**) in all respects.

Of the six chiral centers at C-6, C-7, C-9, C-10, C-12, and C-13 in isoprelaurefucin (**2**), the absolute configurations at C-6, C-7, and C-9 were unambiguously established as 6*R*, 7*R*, and 9*R*, respectively,[4)] on the basis of the chemical correlation with the known compound, hexahydrolaurefucin (**4**).[5)] The remaining configurations at C-10, C-12, and C-13, however, were inferred from the biogenetical viewpoint and the chemical observation that the elimination reaction of the hexahydro derivative (**3**) with zinc and acetic acid generated 9-*cis*-12-*trans*-pentadeca-9,12-diene-6,7-diol.[4)] Therefore, in order to confirm the absolute stereochemistries at C-10, C-12, and C-13, we carried out the following chemical correlation with the known compounds.

Treatment of hexahydroisoprelaurefucin (**3**) with zinc and acetic acid in methanol yielded two unsaturated alcohols, **5** and **6**, which have the same molecular formula $C_{15}H_{27}O_2Br$. One of the unsaturated alcohols, compound **6** was hydrogenated in ethanol over PtO_2 to give a saturated compound which was identical with compound **7**,[6)] which has been derived from compound **8**,[6,7)] kumausallene,[6)] and kumausynes.[8)] Hence the absolute configuration at C-10 in **1** was established as *R*.

Another unsaturated alcohol, compound **5** showed in its mass spectrum the relatively intense fragments at *m/z* 219 and 217 ($M^+-C_6H_{13}O$) and 197 ($M^+-C_3H_6Br$), thus indicating that compound **5** was generated from **3** by the oxolane ring cleavage to contain an oxepane ring with 1-bromopropyl and 1-hydroxyhexyl side chains. Furthermore, compound **5** was brominated with carbon tetrabromide and triphenylphosphine[9)] in benzene to give a dibromo ether **9**, $C_{15}H_{26}OBr_2$, whose IR spectrum indicated no hydroxyl absorption. Compound **9**, on treatment with zinc and acetic acid in methanol, afforded two unsaturated bromohydrins **10** and **11**, $C_{15}H_{27}OBr$. Hydrogenation of **10** over PtO_2 in ethyl acetate yielded the saturated bromohydrin **12**, $C_{15}H_{31}OBr$, $[\alpha]_D^{18}$ −3.14°. The fragment ions at *m/z* 185 ($M^+-C_3H_6Br$) and 153 and 151 ($M^+-C_{11}H_{23}$) in the mass spectrum of **12** showed that the bromohydrin **12** is 3-bromo-4-pentadecanol.

On the other hand, treatment of hexahydrolaureatin (**13**)[10)] with zinc and acetic acid in methanol resulted in the cleavage of oxetane ring in **13** to give an unsaturated alcohol **14**, $C_{15}H_{27}O_2Br$, which was further brominated with carbon tetrabromide and triphenylphosphine to yield a dibromo ether **15**, $C_{15}H_{26}OBr_2$, with the concomitant formation of a dehydrobromination product **16**, $C_{15}H_{25}OBr$. Moreover, treatment of **15** with zinc and acetic acid in methanol yielded two unsaturated bromohydrins **17** and **18**, $C_{15}H_{27}OBr$. One of the bromohydrins, compound **17** showed almost identical spectral data with those of **10** derived from isoprelaurefucin. In the ^1H NMR spectra of **10** and **17**, the shape of the signals of the C_8–H_2, flanked by two double bonds, at δ 2.7—2.9 and the olefinic protons at δ 5.1—5.8 is slightly different, indicating that the double bond at C-6 in **10** and **17** cosisted of a mixture of *cis* and *trans* double bonds whose ratio were different. Hydrogenation of **17** over PtO_2 in ethyl acetate gave the saturated bromohydrin, (3*S*,4*R*)-3-bromo-4-pentadecanol (**12**), $[\alpha]_D^{17}$ −2.88°, which was completely identical with the bromohydrin **12** derived from isoprelaurefucin. Thus, the absolute configurations of the remaining chiral centers at C-12 and C-13 were established as *R* and *S*, respectively. Consequently, the structures, including the absolute configuration, of (3*Z*)-isoprelaurefucin and isoprelaurefucin are represented by formulae **1** and **2**, respectively.



Experimental

The IR spectra were measured on a Hitachi EPI-G2 or a JASCO A-102 spectrophotometers. The UV spectra were obtained on a Shimadzu UV-240 spectrophotomer. The ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-FX 100 or a JEOL JNM-FX 270 spectrometers, using tetramethylsilane as an internal reference in $CDCl_3$. The low and high resolution mass spectra were taken with a JEOL JMS-D300 or a JEOL JMS-DX300 spectrometers. Optical rotations were determined on a JASCO DIP-140 or a Atago Polax polarimeters in $CHCl_3$. Silica gel (Merck, Kieselgel 60, 70—230 mesh) was used for column chromatography. High-performance liquid chromatography was performed on a JASCO TRI ROTAR-III with a Megapak SIL CN column.

Collection. Algae were collected at Asari and Hariusu, near Otaru, Hokkaido, in June 18, 1982.

Isolation of (3*Z*)-Isoprelaurefucin (1). Half-dried alga (60 g), collected at Asari, was extracted with MeOH, and the resulting MeOH extract was treated with 0.5 mol dm^{-3} aqueous KOH in the usual manner to give a neutral oil (0.77 g) which was chromatographed on a silica-gel column. The earlier benzene fraction was further subjected to repeated silica-gel column chromatography to yield pure (3*Z*)-isoprelaurefucin (**1**) (150 mg); oil; $[\alpha]_D^{21}$ −75.5° (*c* 1.41); UV (EtOH), λ_{max} 222 (ε 14600) and λ_{inf} 214 (ε 12800) and 231 (ε 10900) nm; IR (film), ν_{max} 3300, 2120, 1293, 1245, 1200, 1140, 1105, 1088, 1075, 1055, 1020, 975, 863, and 760 cm^{-1}; ^1H NMR and ^{13}C NMR, Table 1; MS (70 eV), *m/z* (rel intensity) 394, 392, 390 (0.3:0.6:0.3; M^+), 329, 327, 325 (5:11:6; $M^+-C_5H_5$), 313, 311 (12:11; M^+−Br), 271, 269 (7:4; $M^+-C_3H_6Br$), 231 (22; M^+−Br−HBr), 137 (24), 123 (26), 121 (54), 119 (21), 109 (45), 107 (27), 95 (59), 93 (66), 91 (23), 81 (43), 79 (38), 71 (35), and 69 (31). Found: *m/z* 311.0648. Calcd for $C_{15}H_{20}O_2$ ^{79}Br: M−Br, 311.0647.

Hydrogenation of (3*Z*)-Isoprelaurefucin (1). (3*Z*)-Isoprelaurefucin (**1**) (296 mg) was hydrogenated in EtOH over PtO_2-catalyst. After removal of the catalyst and the solvent, the residual oil was chromatographed on silica-gel column to yield **3** (287 mg); oil; $[\alpha]_D^{22}$ −48.6° (*c* 1.20); IR (film), ν_{max} 1197, 1180, 1140, 1108, 870, 835, 792, 759, and 691 cm^{-1}; ^1H NMR, δ=0.89 (3H, br t, *J*=6 Hz), 1.06 (3H, dd, *J*=7, 7 Hz), 3.6—3.9 (2H, m), 4.1—4.4 (3H, m), and 4.61 (1H, br d, *J*=7 Hz); MS (75 eV), *m/z* 319, 317 (12:12; M^+−Br), 318, 316 (20:19; M^+−HBr), 277, 275 (2:2; $M^+-C_3H_6Br$), 238 (14; M^+−Br−Br), 237 (74; M^+−Br−HBr), 167 (12), 137 (39), 123 (100), 122 (57), 109 (34), 99 (35), 95 (26), 93 (50), 71 (28), 67 (43), 55 (32), 43 (26), and 41 (34). These spectral data were consistent with those of hexahydroisoprelaurefucin (**3**).[4]

Table 1. ^{13}C and ^1H NMR Data for (3*Z*)-Isoprelaurefucin (**1**)

Carbon	$^{13}C^{a)}/\delta$	$^1H^{b)}/\delta$	Multiplicity (*J* in Hz)
1	82.3 (d)	3.11	d, *J*=2
2	79.9 (s)		
3	110.5 (d)	5.59	br d, *J*=11
4	140.5 (d)	6.08	ddd, *J*=11, 7, 7
5	33.3 (t)	2.88	br ddd, *J*=14.5, 8, 7
		2.66	br ddd, *J*=14.5, 7, 7
6	81.7 (d)	3.89	ddd, *J*=8, 7, 2
7	76.0 (d)[c)]	4.31	dd, *J*=4, 2
8	40.5 (t)	2.44	br d, *J*=14
		2.19	br ddd, *J*=14, 8.5, 4
9	82.9 (d)	4.63	br d, *J*=8.5
10	50.2 (d)	4.16	br dd, *J*=11, 6
11	29.4 (t)	2.56	br dd, *J*=15, 6
		2.29	ddd, *J*=15, 11, 9
12	75.6 (d)[c)]	4.29	dd, *J*=9, 4
13	62.0 (d)	3.89	ddd, *J*=10, 4, 4
14	27.5 (t)	1.93	ddddd, *J*=14, 7, 7, 7, 4
		1.79	ddddd, *J*=14, 7, 7, 7, 10
15	12.8 (q)	1.07	dd, *J*=7, 7

a) Spectrum was measured at 25.0 MHz in $CDCl_3$ (TMS as int. standard). b) Spectrum was recorded at 270 MHz in $CDCl_3$ (TMS as int. standard). Assignments were made with the aid of 2D-COSY and spin decoupling (in part) experiments. c) Assignments may be reversed.

Treatment of 3 with Zn-AcOH. To a solution of **3** (230 mg) in MeOH (5 ml) was added zinc dust (500 mg) and acetic acid (0.25 ml). The mixture was stirred for 15 h at room temperature and then filtered to remove the zinc dust. The filtrate was extracted with ether. The ethereal solution was successively washed with water, 5% aqueous $NaHCO_3$, and water, dried over Na_2SO_4, and then evaporated to leave a residual oil, which was chromatographed on silica-gel column to give **5** (97 mg) and **6** (15 mg): **5**; oil; $[\alpha]_D^{22}$ −5.23° (*c* 2.86); IR (film), ν_{max} 3440, 3020, 1657, 1218, 1195, 1132, 1100, 1020, 1000, 929, 905, and 795 cm^{-1}; ^1H NMR, δ=0.89 (3H, br t, *J*=6 Hz), 1.08 (3H, dd, *J*=7, 7 Hz), 3.48 (1H, m), 3.9—4.4 (3H, m), and 5.70 (2H, m); MS (75 eV), *m/z* 320, 318 (1:1; M^+), 302, 300 (0.6:0.6; M^+-H_2O), 239 (9; M^+−Br), 238 (15; M^+−HBr), 219, 217 (47:43; $M^+-C_6H_{13}O$), 197 (61; $M^+-C_3H_6Br$), 139 (33), 137 (100), 121 (53), 119 (24), 114 (24), 109 (98), 99 (52), 97 (33), 95 (49), 93 (73), 83 (40), 81 (31), 79 (43), 71 (33), 67 (82), 55 (51), and 41 (44).

Hydrogenation of 6. Compound **6** (12 mg) was hydrogenated in EtOH over PtO_2-catalyst in the usual manner to give **7** (12 mg); oil; $[\alpha]_D^{22}$ +3.46° (*c* 0.867); whose spectral

properties were compatible with those of compound **7**,[6] which was derived from compound 8,[7] kumausallene,[6] and kumausynes.[8]

Conversion of 5 into 9. A solution of **5** (54 mg) in dry benzene (3.5 ml) was refluxed with triphenylphosphine (110 mg) and carbon tetrabromide (140 mg) for 1 h in N_2 atmosphere. The subsequent removal of the solvent gave a residual substance, which was purified by silica-gel column chromatography to afford **9** (64 mg); oil; $[\alpha]_D^{22}$ −5.36° (*c* 0.933); IR (film), ν_{max} 3010, 1217, 1168, 1092, 1022, 799, and 670 cm^{-1}; ^1H NMR, δ=0.90 (3H, br t, *J*=6 Hz), 1.07 (3H, dd, *J*=7 Hz), 3.9—4.3 (4H, m), and 5.70 (2H, m); MS (75 eV), *m/z* 384, 382, 380 (0.9:1.7:1.1; M^+), 261, 259 (41:40; $M^+-C_3H_6Br$), 232, 230 (10:10; $M^+-Br-C_5H_{11}$), 219, 217 (60:61; $M^+-C_6H_{12}Br$), 151 (38), 137 (40), 109 (100), 95 (39), 93 (30), 81 (30), 79 (40), 67 (69), 55 (28), and 41 (39).

Treatment of 9 with Zn-AcOH. To a solution of **9** (60 mg) in MeOH (1.2 ml) was added zinc dust (150 mg) and acetic acid (0.06 ml). The mixture was stirred for 22 h at room temperature and then worked up in a manner similar to the case of **3**. The resulting oily substance was subjected to HPLC eluted with hexane-isopropyl alcohol (100:0.25) to yield **10** (13 mg) and **11** (8 mg): **10**; oil; $[\alpha]_D^{17}$ +5.21° (*c* 1.30); IR (film), ν_{max} 3420, 3020, 1285, 1050, 1037, 1027, 970, and 803 cm^{-1}; ^1H NMR, δ=0.88 (3H, br t, *J*=6 Hz), 1.08 (3H, dd, *J*=7, 7 Hz), 2.41 (2H, t, *J*=5.5 Hz), 2.7—2.9 (2H, m), 3.76 (1H, br ddd, *J*=5.5, 5.5, 5.5 Hz), 4.07 (1H, ddd, *J*=8, 5.5, 5 Hz), and 5.1—5.8 (4H, m); MS (70 eV), *m/z* 223 (11; M^+-Br), 205 (20; M^+-Br-H_2O), 95 (44), 93 (30), 81 (58), 79 (53), 71 (100), 69 (58), 67 (81), 55 (66), 43 (92), and 41 (73); **11**; oil; ^1H NMR, δ=0.90 (3H, br t, *J*=6 Hz), 0.97 (3H, dd, *J*=7, 7 Hz), 2.40 (2H, t, *J*=6 Hz), 2.7—2.9 (2H, m), 3.74 (1H, m), 4.19 (1H, m), and 5.1—5.8 (4H, m).

Hydrogenation of 10. Compound **10** (13 mg) was hydrogenated in EtOAc over PtO_2-catalyst in the usual manner to yield **12** (12 mg); oil; $[\alpha]_D^{18}$ −3.14° (*c* 1.21); IR (film), ν_{max} 3400, 1285, 1125, 1075, 1055, 1040, 1020, 920, and 803 cm^{-1}; ^1H NMR, δ=0.88 (3H, br t, *J*=6 Hz), 1.08 (H, dd, *J*=7, 7 Hz), 3.69 (1H, m), and 4.09 (1H, ddd, *J*=7.5, 6, 3.5 Hz); MS (70 eV), *m/z* 291, 289 (0.3:0.3; M^+-H_2O+H), 227 (2; M^+-Br), 185 (85; $M^+-C_3H_6Br$), 153, 151 (4:4; $M^+-C_{11}H_{23}$), 111 (69), 97 (97), 83 (94), 69 (100), 57 (59), 55 (89), 43 (89), and 41 (92).

Treatment of Hexahydrolaureatin (13) with Zn-AcOH. To a solution of hexahydrolaureatin (**13**)[10] (500 mg) in MeOH (12.5 ml) was added zinc dust (1.25 g) and acetic acid (0.63 ml). The mixture was stirred for 110 min at room temperature and then worked up in a manner similar to the case of **3**. The resulting oil was chromatographed on silica-gel column to give **14** (183 mg); oil; $[\alpha]_D^{22}$ +93.7° (*c* 1.33); IR (film), ν_{max} 3450, 3010, 1655, 1280, 1195, 1120, 1060, 1045, 797, and 692 cm^{-1}; ^1H NMR, δ=0.89 (3H, br t, *J*=6 Hz), 1.09 (3H, dd, *J*=7, 7 Hz), 3.5—4.1 (4H, m), and 5.6—6.0 (2H, m); MS (70 eV), *m/z* 320, 318 (0.5:0.5; M^+), 239 (5; M^+-Br), 220, 218 (6:6; $M^+-C_5H_{11}-C_2H_5$), 197 (28; $M^+-C_3H_6Br$), 121 (37), 114 (79), 113 (83), 109 (67), 95 (75), 67 (100), 55 (97), 43 (77), and 41 (69).

Bromination of 14. A solution of **14** (150 mg) in dry benzene (6 ml) was refluxed with triphenylphosphine (280 mg) and carbon tetrabromide (350 mg) for 70 min in N_2 atmosphere. After removal of the solvent, the residual oil was chromatographed over silica-gel column to yield **15** (23 mg) and **16** (30 mg): **15**; oil; $[\alpha]_D^{22}$ −34.1° (*c* 1.40); IR (film), ν_{max} 3020, 1660, 1285, 1219, 1198, 1070, 1089, 1071, 1050, and 695 cm^{-1}; ^1H NMR, δ=0.90 (3H, br t, *J*=6 Hz), 1.07 (3H, dd, *J*=7, 7 Hz), 3.8—4.2 (4H, m), and 5.5—5.9 (2H, m); MS (70 eV), *m/z* 384, 382, 380 (0.3:0.6:0.3; M^+), 303, 301 (25:25; M^+-Br), 261, 259 (30:32; $M^+-C_3H_6Br$), 220, 218 (44:45), 203, 201 (99:100; $M^+-C_5H_{11}-C_2H_5$), 192, 190 (45:45), 179 (39), 151 (35), 95 (40), 79 (39), 67 (55), 55 (37), 43 (28), and 41 (35); **16**; oil; $[\alpha]_D^{17}$ +151° (*c* 1.40); UV (EtOH), λ_{max} 225 nm (ε 4930); IR (film), ν_{max} 3010, 1080, 1060, 1020, 805, and 792 cm^{-1}; ^1H NMR, δ=0.88 (3H, br t, *J*=6 Hz), 1.06 (3H, dd, *J*=7, 7 Hz), 3.5—4.3 (3H, m), 5.27 (1H, dd, *J*=10.5, 8 Hz), and 5.2—6.2 (3H, m); MS (75 eV), *m/z* 302, 300 (4:4; M^+), 231, 229 (4:4; $M^+-C_5H_{11}$), 221 (68; M^+-Br), and 79 (100).

Treatment of 15 with Zn-AcOH. To a solution of **15** (23 mg) in MeOH (0.5 ml) was added zinc dust (50 mg) and acetic acid (0.03 ml). The mixture was stirred for 3 h at room temperature and then worked up in a manner similar to the case of **3**. The resulting oil was subjected to HPLC eluted with hexane-isopropyl alcohol (100:0.20) to give **17** (12 mg) and **18** (5 mg): **17**; oil; $[\alpha]_D^{18}$ +6.33° (*c* 1.29); whose spectral data were almost identical with those of **10** derived from isoprelaurefucin; **18**; oil; ^1H NMR, δ=0.90 (3H, br t, *J*=6 Hz), 0.97 (3H, dd, *J*=7, 7 Hz), 2.5—2.9 (4H, m), 4.16 (1H, m), and 5.3—5.7 (4H, m).

Hydrogenation of 17. Compound **17** (12 mg) was hydrogenated in EtOAc over PtO_2-catalyst in the usual manner to give **12** (10 mg); oil; $[\alpha]_D^{17}$ −2.88° (*c* 1.14); whose spectral properties were identical with those of **12** derived from isoprelaurefucin.

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