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# TEURILENE AND THYRSIFERYL 23-ACETATE, *MESO* AND REMARKABLY CYTOTOXIC COMPOUNDS FROM THE MARINE RED ALGA *LAURENCIA OBTUSA* (HUDSON) LAMOUROUX[1)]

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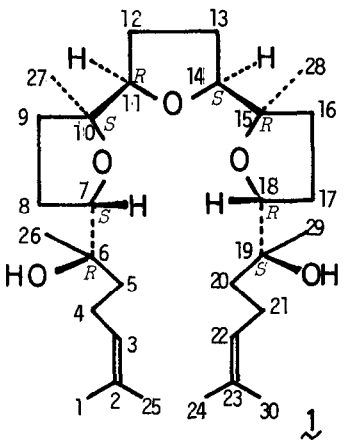
Summary: Two new cyclic ethers consisting of squalene carbon skeleton have been isolated from the red alga *L. obtusa*. The absolute stereostructure of teurilene (1) was elucidated by X-ray crystallographic method, and the structure of thyrsiferyl 23-acetate (2) was established from the spectral and chemical evidence.

In our continuing studies on the marine red algae of the genus *Laurencia*, we newly investigated the constituents of *Laurencia obtusa*[2)] collected from Teuri Island, Hokkaido, Japan. This species is a prolific source of halogenated metabolites and several halogenated sesquiterpenoids, diterpenoids and $C_{15}$ non-terpenoids have been isolated.[3)] A marked variation in the major chemical constituents from this species collected at different locations has been observed. The crude extract of Japanese species exhibited the strong cytotoxic property ($ED_{50}$ of 0.18 μg/ml) against P388[4)] cells and two new squalene derivatives, 1 and 2, have been isolated together with a known com-



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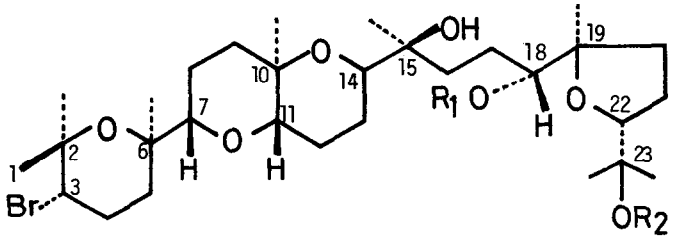

2 $R_1$ = H $R_2$ = Ac  4 $R_1$ = Ac $R_2$ = Ac

3 $R_1$ = H $R_2$ = H  5 $R_1$ = Ac $R_2$ = H

pound, thyrsiferol (3), isolated from *L. thyrsifera*.[5] We are now pleased to report the isolation and structural elucidation of two unique cyclic ethers consisting of squalene carbon skeleton, teurilene (1) for the *meso* compound and thyrsiferyl 23-acetate (2) for the powerful cell growth inhibitor.

The neutral oil from the methanol extract was fractionated on column chromatography over silica gel and the fractions eluted with benzene-ethyl acetate (5:1) were further subjected to HPLC (Finepak-Sil-$C_{18}$, JASCO) with methanol-$H_2O$ (85:15) to give crystals of 1, 2 and 3 in 0.14%, 0.3% and 0.4% yield (neutral oil basis), respectively.

Teurilene (1) [mp 84-85°C (isopropyl ether), $[\alpha]_D^{22}$ 0° (c 0.37, $CHCl_3$)] was analyzed for $C_{30}H_{52}O_5$ [Calcd, C 73.12% and H 10.67%; Found, C 73.17% and H 10.76%: HR-MS Calcd, 492.3814 ($M^+$); Found, 492.3836] and showed 26 protons in $^1H$ NMR ($CDCl_3$, 100 MHz) [δ 1.18 (3H, s), 1.20 (3H, s), 1.61 (3H, br s), 1.69 (3H, br s), 1.4-2.1 (11H, m), 3.8 (2H, m) and 5.11 (1H, br dd, J=7, 7 Hz)] and 15 signals in $^{13}C$ NMR ($CDCl_3$, 25.1 MHz) [δ 17.8 (q), 22.3 (t), 24.3 (q), 24.6 (q), 25.8 (q), 26.0 (t), 27.4 (t), 33.6 (t), 37.5 (t), 72.2 (s), 84.6 (s), 85.4 (d), 86.7 (d), 124.7 (d), and 131.5 (s)]. The IR spectrum of 1 revealed the strong bands (3500, 1100 and 1075 $cm^{-1}$ with no carbonyl absorption) suggesting five oxygens to be hydroxyl and ether groups.

The structure of 1 was established by X-ray crystallographic study including the absolute configuration. The crystal data for 1 were as follows: $C_{30}H_{52}O_5$, triclinic, space group $P\bar{1}$, a=11.938(4), b=12.896(5), c=10.672(4) Å, α=108.31(3), β=91.17(3), γ=103.49(3)°, Z=2, $D_c$=1.084 g $cm^{-3}$, μ(Mo Kα)=0.669 $cm^{-1}$. The intensities of 3946 independent reflections with 2θ < 50° were measured on a Rigaku four-circle diffractometer with graphite-monochromated Mo Kα radiation, using the θ-2θ scanning technique.[6] The structure was solved by the Monte Carlo direct method[7] on the basis of 992 |E| values above 1.30. The 10th random phase set for the 10 strongest reflections led to the correct solution; an E-map based on 980 phases revealed the locations of all the 35 non-hydrogen atoms. The structure obtained was refined by the block-diagonal least-squares method with anisotropic thermal parameters. After 49 hydrogen atoms had been located in a difference Fourier map, several cycles of the least-squares refinement were carried out including the hydrogen atoms; the final R value was 0.092. The molecular skeleton is depicted in Fig. 1.[8]

Thyrsiferyl 23-acetate (2), mp 118-119°C (MeOH-$H_2O$), $[\alpha]_D^{29}$ +1.99° (c 4.4, $CHCl_3$), IR $\nu_{max}$ 3450, 1730, 1270, 1165, 1120, 1105, 1095, 1025, 1010, 980, 955, 940, 920 and 890 $cm^{-1}$, was analyzed for $C_{32}H_{55}O_8Br$ [HR-MS: 630.2887; Calcd for $C_{32}H_{53}O_7{}^{81}Br$, ($M^+$- $H_2O$), 630.2853]. The compound (2) showed the following spectral properties; $^1H$ NMR ($CDCl_3$, 100 MHz) δ 1.09, 1.15, 1.18, 1.19, 1.26, 1.39, 1.44, 1.48, 1.98 (each 3H, s), 2.9-3.1 (2H, m) and 3.3-4.1 (4H, m); $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 20.1 (q), 20.7 (t), 21.2 (t), 21.4 (q), 22.0 (q), 22.2 (q), 22.4 (q), 22.8 (q), 23.0 (t), 23.2 (q), 23.7 (q), 25.4 (t), 26.7 (t), 28.2 (t), 31.0 (q), 32.0 (t), 33.7 (t), 37.0 (t), 38.5 (t), 58.9 (d), 71.9 (s), 73.2 (s), 74.4 (s), 74.9 (s), 76.0 (d), 76.3 (d), 77.5 (d), 82.5 (s),

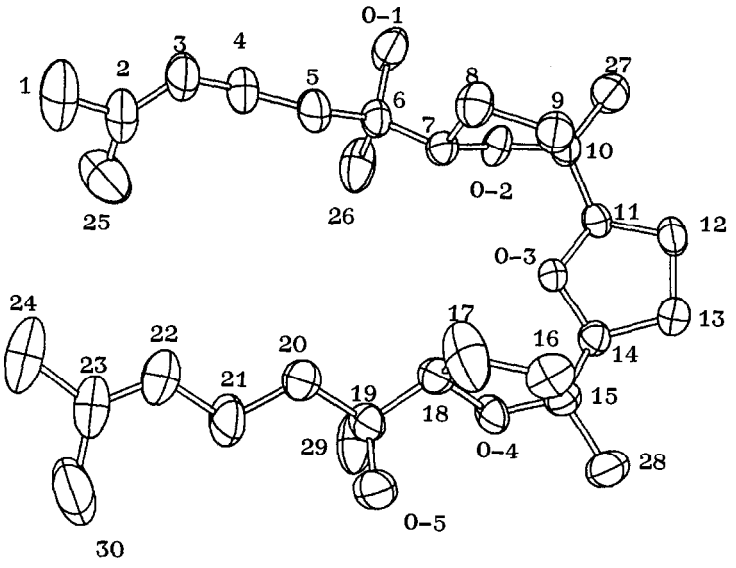


Fig. 1; A perspective drawing of teurilene (1)

85.8 (d), 86.3 (s), 86.5 (d) and 170.3 (s). Treatment of 2 with $K_2CO_3$ in MeOH yielded the corresponding hydrolyzed product, $C_{30}H_{53}O_7Br$, whose IR, and $^1H$ and $^{13}C$ NMR spectra were identical with those of 3. An arrangement of acetoxyl group on C-23 in 2 was established on the bases of the absence of a proton ($-\underline{C}\underline{H}-OCOCH_3$) in $^1H$ NMR of 2 and the fragment (*m/z* 185.1188, Calcd for $C_{10}H_{17}O_3$, 185.1178) in HR-MS of 2. Bromo ether (2) showed a remarkably cytotoxic property ($ED_{50}$ of 0.3 *n*g/ml) against P388 in vitro cell line and the results of cytotoxicity evaluation of the pure compounds, 1, 2 and 3, and their acetyl derivatives,[9] 4 and 5, are given in Table 1. Our purification was monitored with the P388 cytotoxicity method and led to isolation of 2 and 3. Furthermore, the neutral oil from this alga showed the presence of many other remarkably cytotoxic constituents under this purification procedure and their isolation and structural elucidation are now in progress.

Table 1

Cytotoxicity data against P388

| compd | $ED_{50}$(*n*g/ml) |
|---|---|
| 1 | inactive |
| 2 | 0.3 |
| 3 | 10 |
| 4 | 520 |
| 5 | 300 |

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7) A. Furusaki, *Acta Crystallogr.*, Sect. A, 35, 220 (1979).

8) Final crystallographic coordinates and the structure factor table have been deposited in the Cambridge Crystallographic Data Center.

9) Compounds 4 and 5 have been obtained by the treatment of 2 and 3 with acetic anhydride in pyridine, respectively.

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