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LAUREOXOLANE, A NEW BROMO ETHER FROM LAURENCIA NIPPONICA

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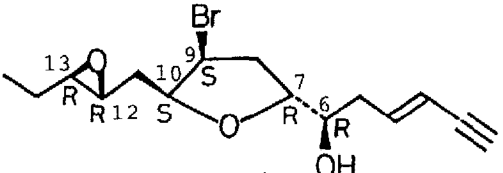
Abstract: The structure of a new bromo ether, isolated from the title alga and designated as laureoxolane, was determined by its physical properties and synthetic correlation.

The title alga is a unique Laurencia species characterized by the fact that even the populations growing in closed distances produce occasionally different second metabolites as a major component.[1)] In our continuing investigation of the L. nipponica collected at Kamoenai, Hokkaido in June, we have now isolated a new bromo ether having both of oxirane and oxolane rings. We wish to report herein the structure and absolute configuration of this compound 1.

Neutral ether-soluble oil (37 g) obtained from methanol extract of the wet alga (12 Kg) was fractionated repeatedly by chromatography over silica gel to give laureepoxide (2)[1)] and laurencin (3).[2)] Crude fraction eluted with hexane and ethyl acetate (9:1) was rechromatographed with HPLC to yield 27 mg of laureoxolane (1) as a colorless unstable oil.



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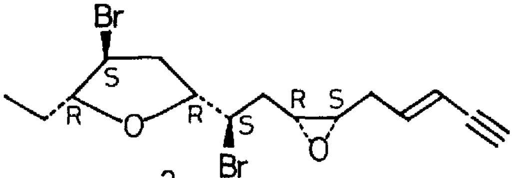

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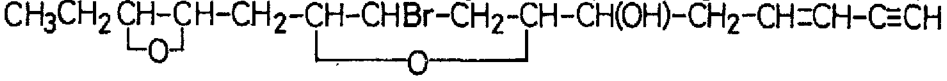
Laureoxolane (1), $C_{15}H_{21}O_3Br$, FI-MS, m/z 328 and 330 (M^+), $[\alpha]_D^{24}$ +21.9° (c 0.32, $CHCl_3$), has IR and UV absorptions due to conjugated (E)-enyne group [IR (neat) 3300, 2100, 1640 and 960 cm^{-1}; UV (EtOH) 224 (ε 8600) and 230 nm (infl. ε 7700)], a hydroxyl and ether groups (IR 3450 and 1100 cm^{-1}).

Measurement of the ^1H NMR (400MHz) combined with spin decoupling led to complete assignment of all protons (Table 1) and elucidation of the planar structure of 1 to be straight-chained skeleton as shown in Fig. 1.



$$CH_3CH_2\overset{13}{C}H\text{-}\overset{12}{C}H\text{-}\overset{11}{C}H_2\text{-}\overset{10}{C}H\text{-}\overset{9}{C}HBr\text{-}\overset{8}{C}H_2\text{-}\overset{7}{C}H\text{-}\overset{6}{C}H(OH)\text{-}\overset{5}{C}H_2\text{-}\overset{4}{C}H{=}\overset{3}{C}H\text{-}\overset{2}{C}{\equiv}\overset{1}{C}H$$

Fig. 1.

Table 1. ^1H NMR data of 1 (400 MHz, $CDCl_3$)

proton assignment	δ /ppm	splitting pattern and J values /Hz	
H_1	2.82	d	2.4
H_3	5.57	ddd	1.5, 2.4, 15.0
H_4	6.29	dt	15.0, 7.5
H_5	2.36	dddd	1.5, 5.8, 7.5, 14.0
$H_{5'}$	2.34	ddd	5.8, 7.5, 14.0
H_6	3.56	qui.	5.8
		(quar. on addition of D_2O)	
O$\underline{H}$ (1H)	2.09	d	5.8(disappeared by D_2O)
H_7	4.25	ddd	4.8, 5.8, 10.0
$H_{8\alpha}$	2.51	ddd	4.8, 10.0, 15.0
$H_{8\beta}$	2.40	ddd	0.93, 4.8, 15.0
H_9	4.62	ddd	0.93, 3.0, 4.8
H_{10}	3.96	dt	3.0, 6.8
H_{11}	2.02	ddd	4.4, 6.8, 14.0
$H_{11'}$	1.97	ddd	5.8, 6.8, 14.0
H_{12}	2.75	ddd	2.4, 4.4, 5.8
H_{13}	2.78	dt	2.4, 5.3
H_{14}	1.59	ddq	5.3, 12.0, 7.5
$H_{14'}$	1.56	ddq	5.3, 12.0, 7.5
H_{15} (3H)	1.00	t	7.5

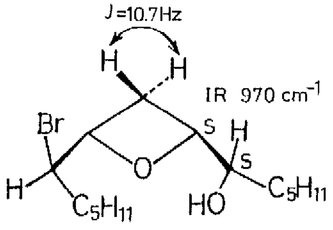


Fig. 2. Geminal coupling constant of the oxetane derived from laureatin.

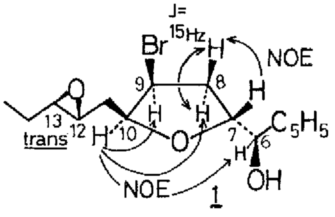
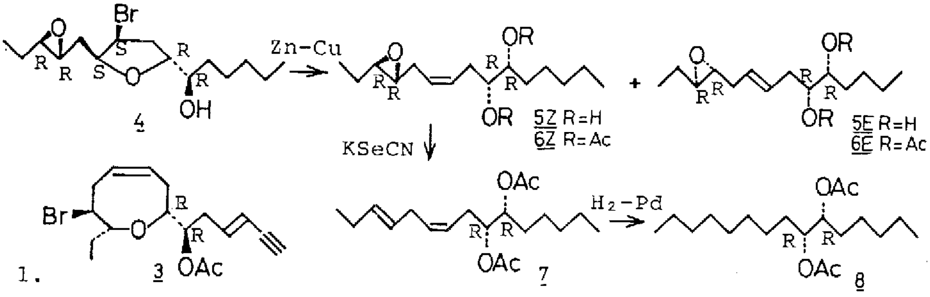


Fig. 3. NOE experiment of laureoxolane.

The chemical shift of each of proton signal at δ 4.62 (H_9) and 3.96 (H_{10}) suggested that these protons should be assigned to a bromo methine and a methine bearing ether oxygen, respectively. The presence of the oxolane ring was supported by geminal coupling constant (J=15 Hz) of the methylene group at C_8 (Fig. 2, 3), by the occurrence of IR absorption at 1100 cm^{-1} (ν C-O-C) and by the absence of that around 970 cm^{-1} due to oxetane.[3)]

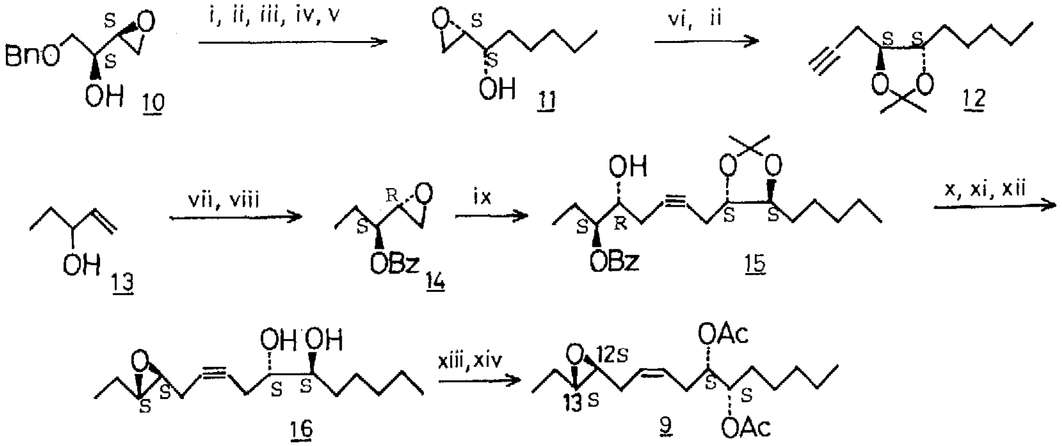
The compound 1 consumed 3 moles of hydrogen over Pd-C in ethanol, giving hexahydrolaureoxolane (4), $C_{15}H_{27}O_3Br$, $[\alpha]_D^{24}$ +37.5° (c 0.17, $CHCl_3$), [FI-MS, m/z 334 and 336 (M^+); IR 3500, 1100 and 1070 cm^{-1}; ^{13}C NMR δ 80.5 (d), 78.9 (d), 73.4 (d), 59.7 (d), 55.4 (d), 54.9 (d), 39.2 (t), 35.7 (t), 33.4 (t), 31.7 (t), 25.3 (t), 24.9 (t), 22.5 (t), 13.9 (q) and 9.7 (q)]. Treatment of 4 with Zn-Cu couple[4)] in acetic acid afforded two products, which were separated over silver nitrate-impregnated silica gel to give isomeric unsaturated glycols 5Z, (^1H NMR δ 5.59 and 5.54, each 1H, dt, J=10.9, 6.8 Hz) and



Scheme 1.

5E, (δ 5.52, 2H, m; IR 970 cm^{-1}). Acetylation of 5Z and 5E yielded the corresponding diacetates 6Z, $[\alpha]_D^{23}$ +16.2° (c 0.16, $CHCl_3$) and 6E, $[\alpha]_D^{23}$ +22.2° (c 0.2, $CHCl_3$), respectively. The former was subjected to deepoxidation with potassium selenocyanate[5] in methanol, followed by acetylation to give diene 7, whose ^1H NMR spectra showed two-proton multiplet at δ 2.72 (2H, m) flanked by two double bonds. Hydrogenation of 7 yielded saturated diacetate 8 $[\alpha]_D^{23}$ +28.2° (c 0.21, $CHCl_3$), which was identical to the authentic sample derived from laurencin (3).[2] This result indicated that the absolute configurations at C_6 and C_7 were R and R. Relative and absolute configurations at C_9 and C_{10} on oxolane moiety were elucidated by NOE experiment (Fig. 3). Irradiation of H_7 at δ 4.25 showed large NOE on $H_{8\beta}$ at δ 2.40. Medium NOE was observed between $H_{10\alpha}$ and $H_{8\alpha}$ as well as H_9. In addition, small NOE was detected between $H_{10\alpha}$ and H_6. These spectral results indicated that orientation of two side chains of the oxolane should be *trans* and therefore, the configurations at C_9 and C_{10} should be S and S.

On the other hand, the relative stereochemistry of the oxirane moiety was assumed to be *trans* according to its coupling constant (J=2.4 Hz)[6] between two methine protons at δ 2.75 and 2.78, and the absolute configurations at C_{12} and C_{13} were determined by synthetic correlation with epoxydiacetate 6Z as shown in Scheme 2.



Scheme 2. Bn=benzyl; Bz=Benzoyl. Reagents: i) BuLi-CuCN, THF, -45°C, 2h (100%): ii) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 5h (79%): iii) Li-NH_3, -78°C, 16h (91%): iv) MsCl, Et_3N, CH_2Cl_2, -78°C→rt, 3h (100%): v) 2M HCl, MeOH; $Ba(OH)_2$, CH_2Cl_2, H_2O, rt, 3h (80%): vi) LiC≡CH·EDA, DMSO, 0°C→rt, 5h (83%): vii) $Ti(O^iPr)_4$-^tBuOOH, diisopropyl L-(+)-tartarate, CH_2Cl_2, -20°C, 4h: viii) BzCl, Et_3N, DMAP, rt (18% from 13): ix) 12, BuLi, $BF_3 \cdot Et_2O$, THF, -78°C, 1h (51%): x) MsCl, Et_3N, C_6H_6, CH_2Cl_2, 0°C→rt, 2d: xi) 1M HCl, MeOH, rt, 2h (70%): xii) 1M KOH, EtOH, rt, 1h (65%): xiii) Ac_2O, Py, DMAP, rt, 7h (100%): xiv) H_2, Pd-$CaSO_4$, quinoline, rt, 9h (70%).

In order to synthesize epoxydiacetate 9, (2R,3R)-L-(+)-tartaric acid was transformed into (2S,3S)-1-benzyloxy-3,4-epoxy-2-butanol (10),$^{7)}$ corresponding to $C_5 \sim C_8$ unit with two asymmetric centers at C_6 and C_7 of laureoxolane (1). Elongation using butyllithium and copper cyanide and then lithium acetylide ethylenediamine complex was performed by known procedures to afford the acetylenic acetonide 12, $C_{13}H_{22}O_2$, $[\alpha]_D^{24}$ -19.8°(c 4.78, $CHCl_3$), via epoxy alcohol 11.$^{8)}$ The $C_{11} \sim C_{15}$ unit was synthesized from 1-penten-3-ol (13). Kinetic Sharpless epoxidation of 13, followed by benzoylation gave (2R,3S)-1,2-epoxy-3-benzoyloxypentane (14), $[\alpha]_D^{24}$ -7.6°(c 0.64, $CHCl_3$). Coupling reaction of 14 and 12 by Yamaguchi method afforded 15,$^{9)}$ $[\alpha]_D^{24}$ +8.5° (c 1.0, $CHCl_3$). Mesylation of 15, followed by treatment with acid and then alkali afforded the epoxydiol 16. Acetylation of 16 and hydrogenation over Lindlar catalyst yielded (6S,7S,12S,13S)-epoxydiacetate (9), $[\alpha]_D^{24}$ -11.2°(c 0.50, $CHCl_3$),$^{10)}$ which was identical with 6Z in all respects except the sign of optical rotation. Consequently, the whole structure of laureoxolane was determined as 1.

Laureoxolane (1) is closely related to laureepoxide (2) which also has oxirane at C_6 and C_7, along with oxolane at C_{10} and C_{13}. The co-occurrence of 1 and 2 in the same specimen suggests that enzymatic bromoether formation reaction in vivo would not be so regioselective and that bromo-cation might initiate the reaction.

References and Notes

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   (b) The coupling constant (J=10.7 Hz) of geminal protons at C_8 of the oxetane (Fig. 2) derived from laureatin gave evidence for the presence of five membered ether in 1.
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10) Treatment of (2S,3R)-1,2-epoxy-3-benzoyloxypentane with the same procedures gave (6S,7S,12R,13R)-epoxydiacetate, $[\alpha]_D^{24}$ -0.8°(c 0.25, $CHCl_3$), which was diastereoisomer of 9.

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