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Doliculols A and B, the Non-halogenated C_{15} Acetogenins with Cyclic Ether from the Sea Hare *Dolabella auricularia*

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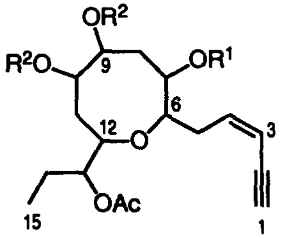
***Abstract*:** Doliculols A (1) and B (2), the first non-halogenated C_{15} acetogenins with cyclic ether, were isolated from the sea hare *Dolabella auricularia*. The gross structures of these compounds were elucidated by using spectroscopic and chemical methods.

There have been isolated a number of C_{15} acetogenins containing cyclic haloether(s) with a terminal enyne or allene moiety from red algae of the genus *Laurencia* as well as the sea hares that feed on them.[1] In the course of our study on novel metabolites of the sea hare *Dolabella auricularia*, we have found new C_{15} acetogenins, doliculols A (1) and B (2), which were the first non-halogenated cyclic ethers of this class.[2] In this communication we describe the isolation and structural elucidation of these compounds.

The sea hare *D. auricularia* was collected on the Pacific coast of Mie Prefecture, Japan. The EtOAc-soluble material from the methanolic extract was partitioned between hexane and 90% MeOH. The 90% MeOH portion was subjected to repeated normal-phase chromatography followed by reversed-phase HPLC to afford doliculol A (**1**, 4.7 x 10^{-5}% wet wt) and doliculol B (**2**, 4.4 x 10^{-5}%)[3] as colorless oils.

Doliculol A (**1**), $[\alpha]^{26}_{D}$ +37° (*c* 0.78, $CHCl_3$), has a molecular formula $C_{17}H_{26}O_6$ [high-resolution EIMS: *m/z* 326.1753 (M^+), Δ +2.4 mmu]. ^1H and ^{13}C NMR signals were assigned as shown in Table 1 by a ^1H-^{13}C COSY experiment. The IR absorption bands at 3570, 3400, 2090, and 1730 cm^{-1} ($CHCl_3$) indicated the presence of hydroxyl, acetylene, and ester functionalities. The presence of a conjugated *cis* enyne unit was proved by the UV absorption band at 223 nm (ε 10,700) (MeOH) and the comparison of the NMR data between **1** and the related enyne compound, laureatin.[4] All the carbon connectivities were determined by a COSY experiment and the characterization of six oxymethines was accomplished by the comparison of ^1H NMR data between **1** and the acetate **3**[5] obtained by acetylation (Ac_2O, pyr) of **1**. Thus, the positions of three hydroxyl groups in **1** were determined by acetylation shifts at H-7 (δ 3.69$\rightarrow$4.79), H-9 (δ 4.31$\rightarrow$5.62), and H-10 (δ 3.62$\rightarrow$5.14) in **3**. Since the relatively low-field chemical shift (δ 4.89) due to H-13 in **1** indicated that the acetoxyl group was located on C-13, the remaining two oxymethine carbons (C-6 and C-12) in **1** were linked through an oxygen atom to form an eight-membered cyclic ether. These findings suggested that the gross structure of doliculol A is shown in the formula **1**.



1, $R^1 = R^2 = H$
2, $R^1 = Ac, R^2 = H$
3, $R^1 = R^2 = Ac$

Doliculol B (**2**),[5] $[\alpha]^{25}_{D}$ + 40° (*c* 0.90, $CHCl_3$), was presumed to be a monoacetate of **1** from the molecular formula $C_{19}H_{28}O_7$ [high-

Table 1. NMR Spectral Data of **1** – **3**.

Position	1		2		3
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	3.52 d (2.3)	84.1 d	3.56 d (2.3)	84.1 d	3.21 d (1.7)
2	–	81.1 s	–	80.9 s	–
3	5.55 ddd (10.8, 2.3, 1.2)	111.6 d	5.54 ddd (10.9, 2.3, 2.0)	111.9 d	5.57 ddd (11.0, 1.7, 1.3)
4	6.03 ddd (10.8, 7.8, 7.8)	142.2 d	5.91 ddd (10.9, 8.9, 6.4)	140.8 d	5.88 ddd (11.0, 9.0, 7.6)
5	2.67 ddd (14.8, 8.4, 7.8) 2.59 dddd (14.8, 7.8, 6.1, 1.2)	35.4 t	2.68 ddd (14.2, 9.2, 8.9) 2.38 dddd (14.2, 6.4, 5.6, 2.0)	35.5 t	2.75 ddd (13.9, 9.0, 9.0) 2.49 dddd (13.9, 7.6, 5.4, 1.3)
6	3.83 dd (8.4, 6.1)	74.5 d	4.05 dd (9.2, 5.6)	73.2 d	3.92 dd (9.0, 5.4)
7	3.69 dd (2.4, 2.4)	69.9 d	4.81 dd (3.3, 3.0)	73.0 d	4.79 br d (5.3)
8	1.81–1.85 m	41.9 t	1.87–1.92 m	38.4 t	2.15 dd (16.2, 5.3) 1.79 ddd (16.2, 9.2, 2.0)
9	4.31 ddd (8.8, 6.6, 2.7)	70.2 d	4.26 ddd (8.6, 6.6, 2.6)	70.4 d	5.62 dd (9.2, 9.2)
10	3.62 ddd (8.8, 4.2, 2.7)	75.6 d	3.62 ddd (8.6, 4.0, 2.6)	75.3 d	5.14 ddd (9.2, 4.3, 2.3)
11	2.05 ddd (16.1, 9.0, 2.7) 1.72 ddd (16.1, 4.2, 1.8)	30.6 t	2.14 ddd (15.8, 9.3, 2.6) 1.75 ddd (15.8, 4.0, 1.7)	30.4 d	2.04 m 1.95 m
12	4.07 ddd (9.0, 7.4, 1.8)	73.2 d	4.12 ddd (9.3, 6.8, 1.7)	73.4 d	4.04 ddd (11.9, 7.7, 2.3)
13	4.89 ddd (7.4, 7.4, 4.1)	77.5 d	4.91 ddd (7.3, 6.8, 4.6)	77.7 d	4.93 ddd (7.7, 7.7, 4.0)
14	1.88 ddq (14.8, 4.1, 7.4) 1.59 ddq (14.8, 7.4, 7.4)	26.1 t	1.83 ddq (14.6, 4.6, 7.3) 1.60 ddq (14.6, 7.3, 7.3)	26.2 t	1.84 ddq (15.2, 4.0, 7.6) 1.60 ddq (15.2, 7.7, 7.6)
15	0.92 t (7.4)	10.0 q	0.92 t (7.3)	10.0 q	0.90 t (7.6)
Ac	2.07 s –	21.1 q 172.6 s	2.11, 2.08 s	21.1, 21.3 q 172.3, 172.5 s	2.21, 2.07, 2.05, 1.96 s

Spectra were recorded at 270 MHz for ^{1}H and at 67.8 MHz for ^{13}C using CD_3OD (for 1 and 2) and $CDCl_3$ (for 3) as solvents and TMS as internal standard. Chemical shifts are in δ values. Coupling constants in Hz are in parenthesis.

resolution EIMS, *m/z* 368.1810 (M^+), Δ -2.5 mmu] and the fact that acetylation of **2** afforded **3**. The detailed comparison of ^{1}H NMR spectra (Table 1) between **1** and **2** revealed that **2** was 7-*O*-acetyl derivative of **1**.

One of the structural features of various C_{15} acetogenins of marine origin is that they contain halogen(s),[1a,b] and the biosynthetic role played by the halogen for the cyclic ether formation has been disclosed recently.[1c] To our knowledge doliculols A and B are the first non-halogenated C_{15} acetogenins with cyclic ether, and thus their isolation is significant from the biosynthetic viewpoint of these structurally interesting compounds.

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2. Dehydrobromolaurefucin, although this compound does not contain halogens, is regarded as a derivative of the bromine-containing C_{15} enyne laurefucin: Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343.
3. Conditions for chromatographic separation: **1**, 1) silica gel, EtOAc/MeOH, step gradient, 2) silica gel, hexane/acetone, step gradient, 3) silica gel, $CHCl_3$/MeOH, linear gradient, 4) silica gel, hexane/EtOAc/MeOH 46:46:8, 5) silica gel C_6H_6/MeCN 1:1, 6) HPLC, ODS, 45% MeOH; **2**, 1) and 2) same as the conditions 1) and 2) for **1**, 3) alumina, EtOAc/MeOH, step gradient, 4) HPLC, ODS, 55% MeOH.
4. Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron* **1970**, *26*, 851.
5. **2**: UV (MeOH) λmax 223 nm (ε 11800); IR ($CHCl_3$) 3580, 3430, 3300, 2090, 1730, 1240 cm^{-1}. **3**: colorless needles, mp 154–155 °C (hexane-EtOAc); $[\alpha]^{26}_D$ +58° (*c* 0.13, $CHCl_3$); UV (MeOH) λmax 223 nm (ε 9300); IR ($CHCl_3$) 3300, 3050, 1730, 1240 cm^{-1}; HRMS *m/z* 452.2015 (Δ –3.2 mmu).

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