

Revised Structures of Epohelmins A and B Isolated as Lanosterol Synthase Inhibitors from a Fungal Strain FKI-0929

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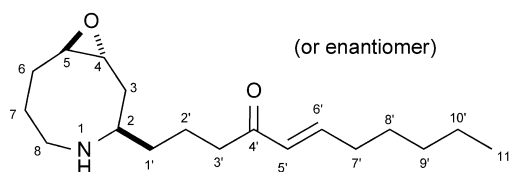
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Abstract The structures of epohelmins A and B isolated as lanosterol synthase inhibitors from a fungal strain FKI-0929 were revised to be 1α -hydroxy- 3α -(4'-oxoundec-(5'*E*)-enyl)-pyrrolizidine and 1β -hydroxy- 3α -(4'-oxoundec-(5'*E*)-enyl)-pyrrolizidine, respectively, by comparison with spectral data of synthetic compounds.

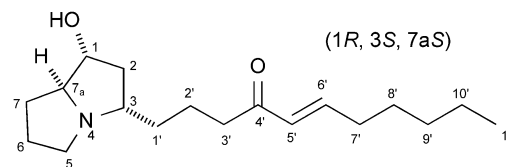
Keywords epohelmin A, epohelmin B, 1-hydroxy- 3α -(4'-oxoundec-(5'*E*)-enyl)-pyrrolizidine, cholesterol biosynthesis, lanosterol synthase

In screening for recombinant human lanosterol synthase inhibitors from microbes, lanopylins [1] and epohelmins [2] were isolated from an actinomycete strain, *Streptomyces* sp. K99-5041, and a fungal strain FKI-0929, respectively.

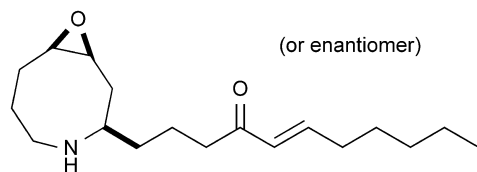
The structures of lanopylins A₁ and B₁ were assigned as (3*E*)-isohexadecylmethylidene-2-methyl-1-pyrroline and (3*E*)-hexadecylmethylidene-2-methyl-1-pyrroline, respectively, by spectroscopic analyses [1]. In a recent



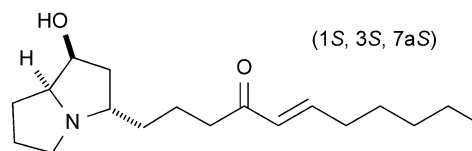
Proposed structure of epohelmin A



Revised structure of epohelmin A



Proposed structure of epohelmin B



Revised structure of epohelmin B

Fig. 1 Structures of epohelmins A and B.

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Table 1 NMR assignment for the acetate salts of epohelmins A and B

Epohelmin A			Epohelmin B		
Position	¹³ C δ ppm	¹ H δ ppm (<i>J</i> in Hz)	Position	¹³ C δ ppm	¹ H δ ppm (<i>J</i> in Hz)
1	74.3	4.17 (1H, td, 6.3, 3.0)	1	70.2	4.38 (1H, br s)
2	40.9	2.06 (1H, m) 2.60 (1H, m)	2	42.3	2.22 (1H, m) 2.10 (1H, m)
3	67.3	2.99 (1H, m)	3	66.7	3.30 (1H, m)
4			4		
5	51.9	3.43 (1H, dt, 12.0, 7.8) 2.96 (1H, dt, 12.0, 6.0)	5	52.9	3.50 (1H, m) 2.88 (1H, dt, 11.0, 6.0)
6	24.2	2.04 (2H, m)	6	26.8	2.04 (2H, m)
7	28.4	2.26 (1H, m) 1.72(1H, m)	7	24.1	2.21 (1H, m) 1.88 (1H, m)
7a	73.9	4.11 (1H, td, 8.3, 3.3)	7a	70.8	4.47 (1H, br dt, 8.5, 4.3)
1'	31.2	1.92 (1H, m) 1.82 (1H, m)	1'	30.4	1.96 (1H, m) 1.81 (1H, m)
2'	21.1	1.64 (2H, ddt, 7.7, 7.7, 7.7)	2'	21.3	1.65 (2H, ddt, 7.5, 7.5, 7.5)
3'	39.1	2.60 (2H, t, 7.0)	3'	39.3	2.61 (2H, td, 7.1, 2.1)
4'	199.6		4'	199.8	
5'	130.1	6.07 (1H, dt, 16.0, 1.5)	5'	130.2	6.07 (1H, dt, 15.5, 1.5)
6'	148.2	6.83 (1H, dt, 15.7, 6.9)	6'	148.1	6.84 (1H, dt, 16.0, 7.0)
7'	32.5	2.21 (2H, tdd, 7.0, 7.0, 1.5)	7'	32.5	2.21 (2H, tdd, 7.0, 7.0, 1.5)
8'	27.7	1.47 (2H, tt, 7.4, 7.4)	8'	27.7	1.46 (2H, tt, 7.4, 7.4)
9'	31.3	1.31 (2H, m)	9'	31.3	1.30 (2H, m)
10'	22.4	1.29 (2H, m)	10'	22.4	1.32 (2H, m)
11'	13.9	0.90 (3H, t, 7.0)	11'	13.9	0.89 (3H, t, 7.0)

¹H (500.00 MHz) and ¹³C (125.65 MHz) NMR spectra were obtained in chloroform-*d*. Epohelmin A contains 0.85~0.90 equiv of HOAc, while epohelmin B contains 1 equiv of HOAc. The acetate absorbs at δ 2.00~2.01 in the ¹H NMR spectra and δ 176.5~177 and δ 22.5~23 in the ¹³C NMR spectra.

report, the structure of lanopylin B₁ was confirmed by synthesis [3].

Epohelmins A and B were proposed to be two of the diastereomers of 4,5-epoxy-2-(4'-oxoundec-(5'*E*)-enyl)-heptamethylenamine, and their relative stereochemical configurations to be (2*R*, 4*R*, 5*R*) or (2*S*, 4*S*, 5*S*) for epohelmin A, and (2*R*, 4*S*, 5*R*) or (2*S*, 4*R*, 5*S*) for epohelmin B, respectively, by spectroscopic analyses [2]. However, in the process of structural determination, we did not place much importance on the evidence that 4,5-epoxy-heptamethylenamines readily cyclize to 1-hydroxypyrrolizidines [4,5], and that the methine hydrogens and carbons of *trans* and *cis*-epoxycyclooctanes absorb at δ 2.8~2.9 and δ 59.6~55.6, respectively [6]. Recently, 1α- and 1β-hydroxy-3α-(4'-oxoundec-(5'*E*)-enyl)-pyrrolizidines were synthesized by Snider and Gao [7], and all of the spectral data were identical to those of epohelmins A and B. Revised NMR assignments for epohelmins, which were isolated as the acetate salts, are

shown in Table 1. We thus here report the revised structures of epohelmins A and B, 1α-hydroxy-3α-(4'-oxoundec-(5'*E*)-enyl)-pyrrolizidine and 1β-hydroxy-3α-(4'-oxoundec-(5'*E*)-enyl)-pyrrolizidine, respectively, and their absolute configurations as (1*R*, 3*S*, 7*aS*) and (1*S*, 3*S*, 7*aS*), respectively.

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