Communications to the editor

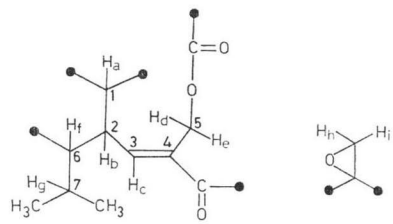
STRUCTURE OF HEPTELIDIC ACID, A NEW SESQUITERPENE ANTIBIOTIC FROM FUNGI

Sir:

As reported in the previous paper,[1] heptelidic acid was isolated from the culture broths of three different strains of fungi identified as *Gliocladium virens*, *Chaetomium globosum* and *Trichoderma viride*. It was characterized as a new skeletal sesquiterpenoid antibiotic with activity against anaerobic bacteria, especially against *Bacteroides fragilis*.

In the present communication structural elucidation of heptelidic acid (**1**) is presented. Treatment of **1** with diazomethane furnished a methyl ester (**2**). The molecular formula, $C_{16}H_{22}O_5$, of **2** was established from the mass and cmr spectral data. The ir spectrum of **2** indicated a lactone at 1750, ester carbonyl at 1720, double bond at 1640 and isopropyl at 1380 and 1370 cm^{-1} in each characteristic region, but indicated none of hydroxy group. The pmr and cmr spectra (Table 1) of **2** displayed the partial structure

Fig. 1.



(a) (b)

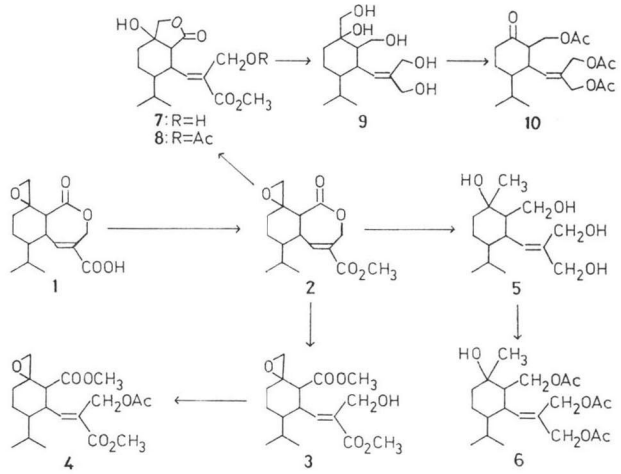
shown in Fig. 1 (a) and (b).

The structure of heptelidic acid was confirmed by following chemical evidences (Fig. 2). Hydrolysis of **2** with alkali followed by treatment with diazomethane afforded diester (**3**) (M^+: 326). The presence of a hydroxy group at 3500 and ester group at 1720 cm^{-1} in the ir spectrum of **3** indicated opening of a lactone ring. In the pmr spectrum of **3**, AB quartet at 5.05 and 5.08 ppm (Hd, He) of **2** shifted upfield to 4.36 (s) ppm. This signal was replaced downfield to 4.84 (s) ppm in its acetate **4** (M^+: 368). The change in chemical shifts of Hd and He between **2** and **3** suggests

Table 1. The PMR and CMR spectral data of **2**.

Protons			Carbons		
δ (ppm)	J (Hz)	Assignment	δ (ppm)	Coupling with proton	Assignment
7.24	4.5, 2.0, 1.5	Hc	170.3	s	>C=O
5.08	14.5, 2.0	He	165.7	s	>C=O
5.05	14.5, 1.5	Hd	145.1	d	–CH=
3.81	5.0	Hh	129.1	s	–C=
3.78	s	$-OCH_3$	61.6	t	$-CH_2-O$
3.55	12.0	Ha	58.1	s	>C<O>
2.60	12.0, 10.0, 4.5	Hb			
2.59	5.0	Hi	52.1	t	>O>CH_2
2.15	m	Hg	52.1	q	$-OCH_3$
1.55	m	Hf	47.0	d	>CH–
1.5~2.5	m	$-CH_2\times2$	45.0	d	>CH–
0.99	7.0	$-CH_3$	42.2	d	>CH–
0.90	7.0	$-CH_3$	33.4	t	$-CH_2-$
			27.4	d	>CH–
			22.4	t	$-CH_2-$
			21.2	q	$-CH_3$
			15.1	q	$-CH_3$

Fig. 2.



the presence of oxygen at C_5 which is bonded to lactone carbonyl.

Reduction of **2** with $LiAlH_4$ in THF gave tetraol **5** (m.p. 158~160°C, $C_{15}H_{28}O_4$). In the pmr spectrum of **5**, a newly appeared singlet of methyl signal was detected at 1.31 ppm and a doublet at 7.24 ppm of olefinic proton of **2** shifted to 5.23 ppm (J=10 Hz) corresponding to a non-conjugated olefinic proton. A complicated multiplet (6H) at 3.6~4.4 ppm of tetraol **5** was clearly assigned to hydroxymethyl signals assembled with one ABX type methylene (4.21, 3.90 ppm, J_1= 11.5, J_2=5.0 and J_3=3.5 Hz) and two allylic methylene in the triacetate (**6**), which was obtained by acetylation of **5** in the conventional procedure. Treatment of **2** with periodic acid or perchloric acid in THF - H_2O gave lactone-alcohol **7** (M^+: 312) with ir bands at 3350 (hydroxy), 1780 (γ-lactone), 1720 (ester) and 1650 cm^{-1} (double bond). Acetate **8** (m.p. 108~110°C, $C_{18}H_{26}O_7$) was obtained by acetylation of **7**, but the presence of unacetylated hydroxy was still observed at 3350 cm^{-1} in its ir spectrum. In the pmr spectrum of **8**, AB quartet (J=10.0 Hz) at 4.2 ppm was assigned to the methylene bearing oxygen of γ-lactone, and another AB system (J=12.0 Hz) at 4.73 ppm was also assigned to the allylic acetoxymethyl group. The above-mentioned results indicated that lactonization took place at α-epoxide to form a γ-lactone during periodate oxidation of **2**. Therefore, an α-epoxide was confirmed to be located at the β position from the lactone carbonyl. Reduction of **7** with $LiAlH_4$ in THF and oxidation of the resulting pentaol **9** (m.p. 142°C, $C_{15}H_{28}O_5$) with periodic acid, followed by acetylation, afforded the keto-triacetate **10** (M^+: 382). The absorption at 1710 cm^{-1} in the ir spectrum of **10** strongly supported the presence of a six-membered ketone.

Finally, the stereochemistry of the ring junction and isopropyl group, except the α-epoxide ring, of **2** was assigned to trans and equatorial substitution from large coupling constant values ($J_{a,b}$=12.0 and $J_{b,f}$=10.0 Hz). Determination of the absolute configuration of heptelidic acid, including that of α-epoxide ring by X-ray analysis will be discussed in a separate report. Heptelidic acid was thus elucidated to have a new skeletal sesquiterpene lactone and it is assumed that this antibiotic is biogenetically derived from γ-cadinene by oxidation.

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Reference

1) ITOH, Y.; K. KODAMA, K. FURUYA, S. TAKAHASHI, T. HANEISHI, Y. TAKIGUCHI & M. ARAI: A new sesquiterpene antibiotic, heptelidic acid. Producing organisms, fermentation, isolation and characterization. J. Antibiotics 33: 468~473, 1980