STUDIES ON THE BIOSYNTHESIS OF PENTALENOLACTONE VI[1]. THE X-RAY CRYSTAL STRUCTURE INVESTIGATION OF PENTALENOLACTONE G AND STRUCTURAL REVISION OF PENTALENOLACTONE F

Sir:

During the course of biosynthetic studies on pentalenolactone[2] (**7**), a sesquiterpene antibiotic produced by a variety of *Streptomyces* species, we isolated pentalenolactone G[3] (**5**) and pentalenolactone H[4] (**6**), pentalenic acid[4] (**4**), a hydrocarbon, pentalenene[5] (**1**) and, very recently, deoxypentalenylglucuron[1] (**2**) from the fermentation broth of *Streptomyces chromofuscus* and *S. griseochromogenes* (Fig. 1). Independently CANE *et al.* obtained pentalenolactone E[6] (**8**) and pentalenolactone F[7] (**9**) from *Streptomyces* UC 5319.

The structures of **5** and **6** were established by ^{1}H and ^{13}C NMR spectral analysis and the latter metabolite was assumed to be a biosynthetic intermediate between the sesquiterpene hydrocarbon **1** and the acid, **7**[4]. **5** was structurally correlated to **6** by $NaBH_4$ reduction[4].

Recently OHTSUKA *et al.*[8] synthesized **6**, **9** and their C-9 epimers by epoxidation of the corresponding monodeoxy derivatives such as **8**. Based on detailed NMR spectral analysis of these compounds, they suggested that the configuration of the epoxide carbon (C-9) of **5** and **6** had to be inverted and that the two compounds would therefore be shunt pathway products in the biosynthesis of **7**.

Since we assigned the stereochemistry of the epoxide carbon of **5** solely based on biosynthetic considerations[3], but without any experimental evidence, we investigated the X-ray crystal structure of the methyl ester of **5**. The result described herein has proved the structures of **5** and **6** proposed by us[3,4] to be correct and the structure of **9** to be revised as shown in Fig. 1.

The crystal of pentalenolactone G methyl ester ($C_{16}H_{18}O_6$)[3] recrystallized from benzene-hexane solution, is orthorhombic, space group $P2_12_12_1$ with four molecules in a cell of dimensions, $a=10.893$ (5), $b=21.868$ (10), $c=6.482$ (3) Å, and $\alpha=\beta=\gamma=90°$, Dx=1.26 g/cm^3, V=1544.06 Å^3.

All the measurements were performed on a Philips PW 1100 diffractometer with graphite monochromated CuK radiation. The cell parameters were determined by a least-squares fit to the setting for 20 reflections. A total of 1743 reflections was recorded as being above the 2 (I) level within the range of $3\sim78$. The structure was solved by the direct method using the MULTAN program and refined by block-diagonal least-squares methods. The R value

Fig. 1. Biosynthetic intermediates and shunt pathway products of pentalenolactone.

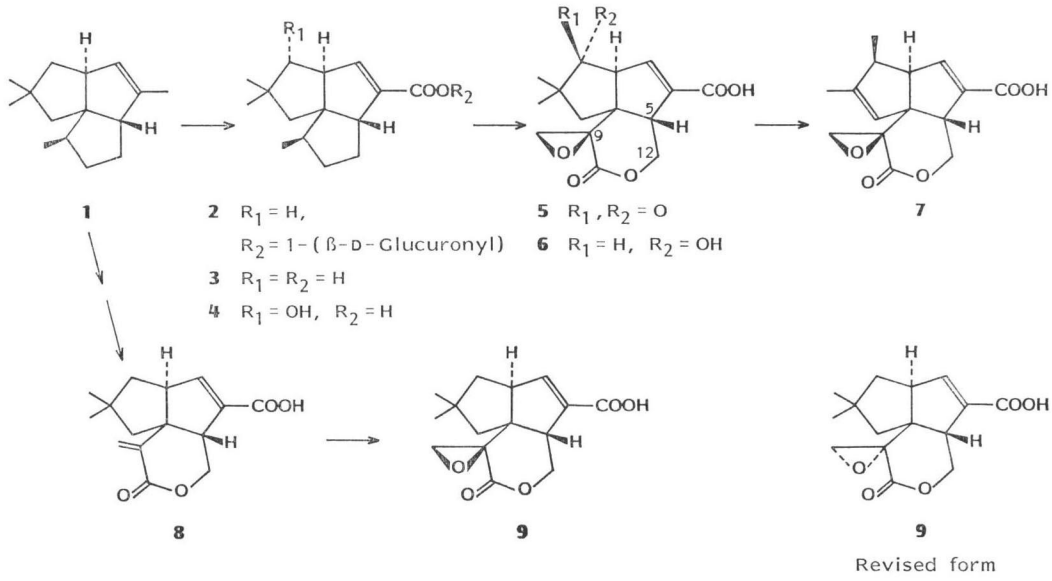

Fig. 2. X-Ray crystallographic structure of pentalenolactone G methyl ester.

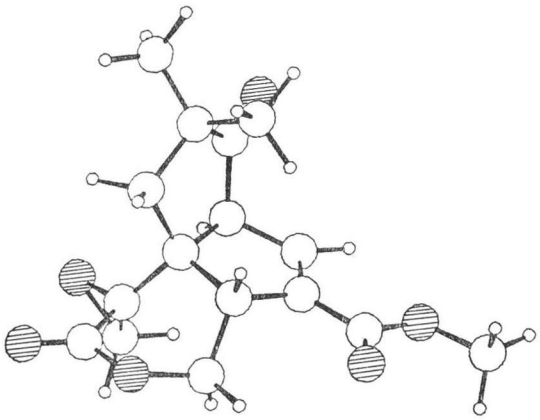

Table 1. ^{1}H NMR chemical shifts and coupling constants of H-12 in pentalenolactone derivatives.[8]

Compound (Methyl ester)	Chemical shift (H-12, in ppm)	Coupling constant ($J_{5,12}$, in Hz)
6	4.18, 4.89	9 and 6
epi-6	4.50, 4.72	3.5 and 3.5
9	4.43, 4.76	2.5 and 2.0
epi-9	4.19, 4.88	9 and 6
5	4.20, 4.98	9.5 and 6

reached 0.066 for the 1743 reflections including anisotropic temperature factors for 16 carbons and 6 oxygen atoms, and isotropic temperature factors for 18 hydrogen atoms. The molecular structure of the methyl ester of **5** drawn by PLUTO* is illustrated in Fig. 2.

This conclusion is completely in agreement with the structures of **5** and **6** previously proposed[3,4]. On the other hand, the ^{1}H NMR spectral data of **9**, in particular the ^{1}H NMR chemical shifts and coupling constants between H-5 and H-12 which almost completely identical with those of the C-9 epimer of **6**[8], are affected by the configuration of the epoxide carbon, are but considerably different from **6** (see Table 1). In addition, the ^{1}H NMR spectrum of the C-9 epimer of **9** is very close to that of **6**. Therefore the configuration of C-9 of **9** should be revised as shown in Fig. 1. As a consequence, biosynthesis of **7** is concluded to proceed from **1** to the final product *via* deoxypentalenic acid (**3**), **4** and **6**; **9** and most probably **8** are therefore believed to be shunt pathway products.

* Cambridge Crystallographic Data Center, Cambridge CB2 IEW, England (1979).

In order to avoid confusion in future, we would like to propose to rename pentalenolactone F as epipentalenolactone F and to reserve the name "pentalenolactone F" for the hypothetical metabolite (to be isolated in future ?) with the same stereochemistry at C-9 as **6**.

HARUO SETO
Institute of Applied Microbiology,
The University of Tokyo,
1-1-1 Yayoi, Bunkyo-ku, Tokyo, 113 Japan
HIROSHI NOGUCHI
USHIO SANKAWA
YOICHI IITAKA
Faculty of Pharmaceutical Science,
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, 113 Japan

(Received January 13, 1984)

References

1) For Part IV, see TAKAHASHI, S.; M. TAKEUCHI, M. ARAI, H. SETO & N. ŌTAKE: Studies on the biosynthesis of pentalenolactone. V. Isolation of deoxypentalenylglucuron. J. Antibiotics 36: 226~228, 1983
2) TAKEUCHI, S.; Y. OGAWA & H. YONEHARA: The structure of pentalenolactone (PA-132). Tetrahedron Lett. 1969: 2737~2740, 1969
3) SETO, H.; T. SASAKI, H. YONEHARA & J. UZAWA: Studies on the biosynthesis of pentalenolactone. I. Application of long range selective proton decoupling (LSPD) and selective ^{13}C-[^{1}H] NOE in the structural elucidation of pentalenolactone G. Tetrahedron Lett. 1978: 923~926, 1978
4) SETO, H.; T. SASAKI, J. UZAWA & H. YONEHARA: Studies on the biosynthesis of pentalenolactone. II. Isolation of pentalenic acid and pentalenolactone H. Tetrahedron Lett. 1978: 4411~4412, 1978
5) SETO, H. & H. YONEHARA: Studies on the biosynthesis of pentalenolactone. III. Isolation of a biosynthetic intermediate hydrocarbon, pentalenene. J. Antibiotics 33: 92~93, 1980
6) CANE, D. E. & T. ROSSI: The isolation and structural elucidation of pentalenolactone E. Tetrahedron Lett. 1979: 2973~2974, 1979
7) TILLMAN, A. M. & D. E. CANE: Pentalenolactone F, a new metabolite isolated from *Streptomyces*. Isolation and structure elucidation. J. Antibiotics 36: 170~172, 1983
8) OHTSUKA, T.; K. HAYASAKA, H. SHIRAHAMA & T. MATSUMOTO: Biomimetic conversion of humulene to cyclohumulanoids. Synthesis of dactylol and pentalenolactone. Abstract of the 26th Symposium on the Chemistry of Natural Products, pp. 315~321, Kyoto, 1983