THE X-RAY CRYSTAL STRUCTURE OF PENTALENOLACTONE F METHYL ESTER (*EPI*-PENTALENOLACTONE F)

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(Received for publication July 24, 1987)

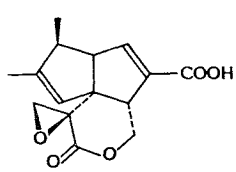
In 1983, we reported the isolation from *Streptomyces* UC5319 of pentalenolactone F,[1] a co-metabolite of the sesquiterpene antibiotic pentalenolactone (**1**). The structure of pentalenolactone F was assigned as **2** primarily on the basis of ^{1}H and ^{13}C NMR spectroscopic evidence. Originally, we assigned the epoxide stereochemistry of **2** by analogy to the known configuration of pentalenolactone itself[2] as well as that of two co-metabolites isolated by SETO *et al.*, pentalenolactone H (**3**)[3] and pentalenolactone G (**4**),[4] which bear hydroxyl or ketone functions, respectively, at C-1. We subsequently demonstrated that both pentalenolactone and pentalenolactone F are derived biosynthetically from pentalenene (**5**), the parent hydrocarbon of this family of sesquiterpene metabolites,[5] thereby establishing that all three metabolites have the same absolute configuration at the respective C-4, C-5 and C-8 centers.

Total syntheses of pentalenolactone F have been carried out by MATSUMOTO *et al.*[6] and in our own laboratories.[7] In the course of each synthesis, both groups independently observed that treatment of the corresponding 9,10-deoxy precursor **6-Me** (pentalenolactone E methyl ester)[8] with basic hydrogen peroxide gave a roughly equal mixture of pentalenolactone F methyl ester and its epoxide epimer. By contrast, we found that the naturally occurring epimer was the major product when **6-Me** was first reduced with diisobutylaluminum hydride (DIBAL), followed by epoxidation with *tert*-BuOOH/VO(acac)$_2$ and Jones oxidation. The latter strategy had originally been developed by DANISHEFSKY in his synthesis of pentalenolactone itself,[9,10] since direct oxidation with basic hydrogen peroxide had generated exclusively the unnatural epoxide epimer. These synthetic results appeared to be consistent with our original assignment of the epoxide stereochemistry.

In 1984, the Hokkaido group noted an unexpected dichotomy in the ^{1}H NMR spectra of pentalenolactones F and H and their corresponding epoxide epimers.[11] These investigators pointed out that, based on the chemical shifts for 12-H_a and 12-H_b as well as the observed $J_{5-H,12-H}$ coupling constants, the methyl esters of pentalenolactone F and *epi*-pentalenolactone H appeared to exist in one lactone conformation, whereas the methyl esters of pentalenolactones G and H as well as the epoxide epimer of pentalenolactone F existed in a second conformation. The latter observations raised the possibility that the epoxide configurations of either pentalenolactone F or pentalenolactones G and H had been misassigned. When SETO subsequently reconfirmed the correctness of the epoxide stereochemical assignment for pentalenolactone G methyl ester by X-ray crystallographic analysis,[12] we decided to carry out a complementary study on pentalenolactone F.

Pentalenolactone F methyl ester was recrystallized by the vapor diffusion method[13] from pentane - THF to give crystals, mp 115.7~

Fig. 1. Structures of pentalenolactone (**1**) and related metabolites.



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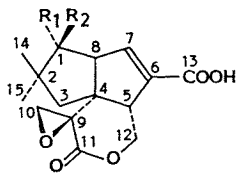

2 $R_1 = R_2 = H$
3 $R_1 = OH$ $R_2 = H$
4 $R_1, R_2 = =O$

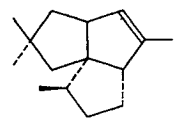

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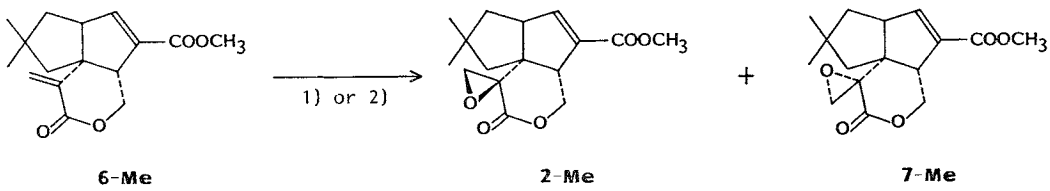
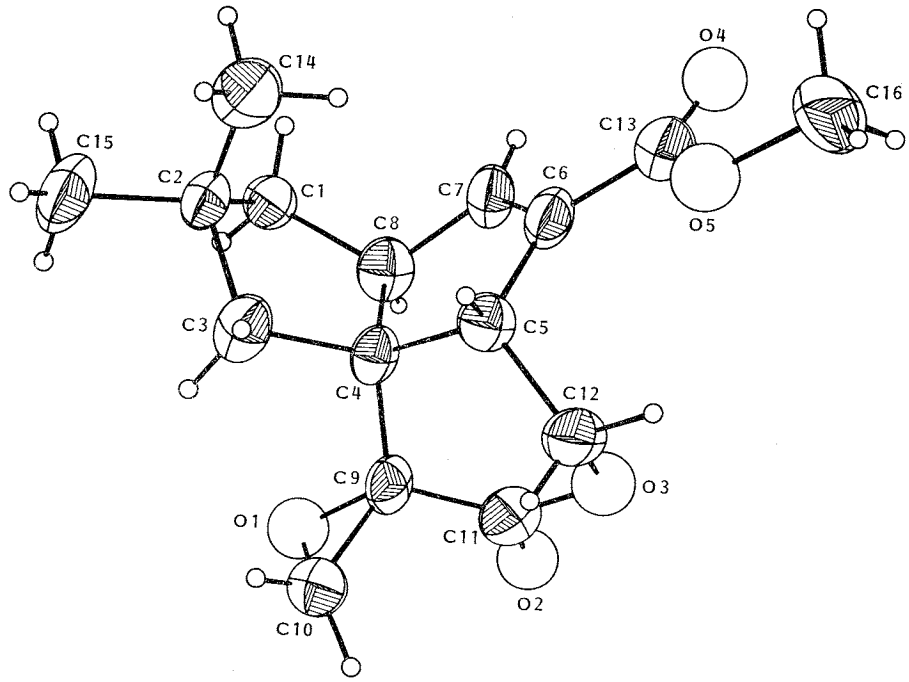
Fig. 2. Chemical conversion of pentalenolactone E methyl ester (**6-Me**) to pentalenolactone F methyl ester epoxide epimers, **2-Me** and **7-Me**.



6-Me **2-Me** **7-Me**

1) H_2O_2, OH^-; 2) a) DIBAL, b) ^{t}BuOOH/VO(acac)$_2$, c) CrO_3.

Fig. 3. X-Ray crystal structure of pentalenolactone F (*epi*-pentalenolactone F) methyl ester (**7-Me**).



116°C (literature[7] mp (±)-pentalenolactone F methyl ester, 128~130°C), belonging to the non-centrosymmetric, orthorhombic space group $P2_12_12_1$. The unit cell parameters were determined to be a=7.806(6) Å, b=8.666(3) Å, c=22.149(7) Å, and $\alpha=\beta=\gamma=90.00°$ by least squares fitting to the positions of 25 independent reflections in the range $24°\leq 2\theta\leq 34°$. This unit cell contained four asymmetric units of molecular formula $C_{16}H_{20}O_5$ in a volume of 1500.38 (1.33) Å^3, which produced a calculated density of 1.30 g/cm^3. A total of 1382 reflections were recorded in the range $3.5°\leq 2\theta\leq 46°$ with a Nicolet R3m/E crystallographic system using the $\theta:2\theta$ scan routine and graphite monochromated MoKα radiation (λ=0.71069 Å). A total of 1144 unique reflections were observed using the criterion [$F_0\geq 3.0\sigma(F_0)$]. After Lorentz and polarization corrections, the structure was solved by the SHELXTL 5.1 programs. All non-hydrogen atoms were refined anisotropically. The approximate location of all hydrogen atoms was determined by Fourier difference syntheses. In the final stages of refinement the hydrogen atoms were placed in calculated positions and allowed to ride with the atom to which they are attached. The final agreement factors are R= 0.0454 and weighted R=0.0521 for 190 independent parameters where weighted R= $[\Sigma(w*\Delta^2)/\Sigma(w*F_0^2]^{1/2}$; $\Delta=|F_0-F_c|$ and the

weighting scheme is $w=1/[\sigma^2(F_0)+0.0002F_0^2]$. A computer generated plot with atom labels is illustrated in Fig. 3.†

From the crystallographic data, it is evident that the stereochemistry of the naturally occurring metabolite, heretofore called pentalenolactone F, must be revised to reflect the fact that the epoxide configuration is opposite to that previously established for all other co-metabolites, including pentalenolactones G and H as well as pentalenolactone itself. We therefore concur with the suggestion of Professor SETO[12] that the known metabolite henceforth be termed "*epi*-pentalenolactone F," whose methyl ester is represented as **7-Me**. Finally, it will be noted that the solid state conformation demonstrated for **7-Me** is fully consistent with the solution phase conformation previously deduced by the Hokkaido group on the basis of ^{1}H NMR coupling constants.[9,10] In particular, the measured torsion angles, H-C(5) – C(12)-H_a=54.5°, and H-C(5) – C(12)-H_b=−64.9°, and H-C(5) – C(12)-O(3)=174.8° are consistent with the observed 5-H – 12-H coupling constants 3.1 and 2.1 Hz. The fact that the biosynthesis of *epi*-pentalenolactone F, which presumably occurs by epoxidation of the corresponding deoxy metabolite, pentalenolactone E, takes place with the opposite stereochemical course to that observed for the biological formation of pentalenolactone H is in itself noteworthy, and establishes that *epi*-pentalenolactone F can not be a precursor of either pentalenolactone H or pentalenolactone. The factors which influence both the enzymatic and non-enzymatic oxidation of pentalenane metabolites are clearly worthy of further study. In this connection, it will be noted that the conformation of the lactone ring in pentalenolactone E methyl ester appears to resemble that of *epi*-pentalenolactones F, G and H; $J_{5-H,12-H}$=4.0 and 4.7 Hz, indicating approximately equal H-C(5) – C(12)-H_a and H-C(5) – C(12)-H_b torsion angles.

Acknowledgment

This work was supported by NIH Grants GM22172 to DEC and GM35982 to PGW. The Bruker WM 250 used in this work was purchased with funds provided by the NSF and the Montedison Group of Milan, Italy. The Nicolet R3m/E crystallographic system was purchased with funds provided by the NSF.

† Tables of atomic coordinates, bond lengths and angles, and anisotropic thermal parameters have been sent to the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

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