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THE ISOLATION AND STRUCTURAL ELUCIDATION OF PENTALENOLACTONE E.

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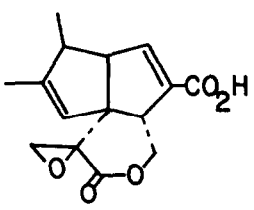
ABSTRACT: Pentalenolactone E, isolated as the methyl ester from cultures of Streptomyces UC5319, has been shown to have structure 5.

Over the last three years, investigations of the culture broth of strains of Streptomyces which produce the acidic lipophilic antibiotic pentalenolactone(1)[2] have led to the isolation and identification of a series of structurally novel sesquiterpenes, pentalenolactones G(2)[3] and H(3)[4] and the tricyclic pentalenic acid (4).[4] Each of these latter substances is a potential intermediate or shunt metabolite in the biosynthesis of pentalenolactone itself. We have recently reported biosynthetic experiments, based on the use of D-[UL-$^{13}C_6$]-glucose as an in vivo precursor of [1,2-$^{13}C_2$]-acetyl CoA, which establish the mevalonoid origin of pentalenolactone, and support a biosynthetic pathway conceivably involving 3 and 4 as intermediates.[5] During the course of these biosynthetic experiments we have isolated the methyl ester of a new metabolite, pentalenolactone E, to which we assign the structure 5, based on the spectroscopic data reported below.



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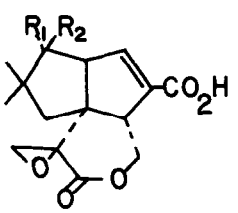
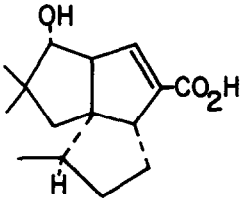


2 R_1,R_2=O

3 R_1=OH, R_2=H



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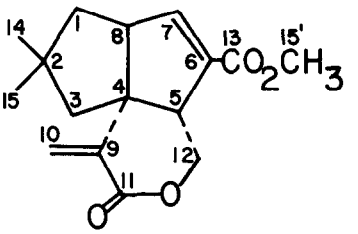

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Ether extraction of the culture filtrate of a 60 hr growth of Streptomyces UC5319,[6] followed by precipitation with benzylamine and treatment of the regenerated acids with diazomethane gave a mixture of methyl esters which was subjected to initial purification by preparative layer chromatography (silica gel, 2:1 benzene/ethyl acetate, Rf 0.55) followed by a second plc (19:1 benzene/ethyl acetate, 5

developments, Rf 0.55) to yield the methyl ester of pentalenolactone E (ca. 3 mg/L. culture), 5, $C_{16}H_{20}O_4$, (m/e, M^+ calcd 276.1362, found 276.1366), oil, $\nu_{max}^{CHCl_3}$ 2860-3050 cm^{-1}, 1710-1730 (lactone, ester), 1635 (double bond).

The ^{13}C nmr spectrum of 5, recorded at both 15.08 and 67.9 MHz,[7] supported the presence of a trisubstituted double bond, C-6(s, 131.0 ppm), and C-7(d, 146.5 ppm) as well as a terminal methylene function, C-9(s, 144.5 ppm) and C-10(t, 119.9 ppm). In further support of these structural features was the presence in the 60 MHz ^1H nmr spectrum of a broad triplet at δ6.85 (H-7), 1H) and a characteristic pair of sharp one proton singlets at 5.91 and 5.57 (H-10), indicating conjugation to a carbonyl function. Indeed the ^{13}C nmr spectrum displayed signals corresponding to ester (C-13, 164.3, s) and lactone carbonyls (C-11, 170.1, s). Additional easily identified features were a hydroxymethyl (C-12, 67.3, t; H-12, 4.31, d, J = 4 Hz, 2H), a methoxyl (C-15', 51.6, q; H-15', 3.76, s, 3H), and geminal methyls (C-14,15, 29.4, q and 29.6, q; C-2, 40.7, s; H-14,15, 1.06, s, 6H). Two C-H groups (C-5 and C-8, 55.1, d and 58.0, d[8]; H-5 and 8, 3.29, m, 2H) were apparent as were two methylenes (C-1 and C-3, 53.4, t and 46.2 t; H-1,3, 1.25-2.3, m, 4H) and a quaternary carbon (C-4, 56.8, s). Comparison with published spectra of pentalenolactones G and H,[3,4] led to assignment of structure 5 for pentalenolactone E methyl ester.

Preliminary experiments indicate that 5 is excreted into the medium during the early stages of growth (between 40 and 60 h) and before full production of pentalenolactone has been established. Labeling experiments to test the precursor role of pentalenolactones E and H are in progress.[9]

References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1978-1980; National Institutes of Health Research Career Development Award, 1978-1983.

2. D. G. Martin, G. Slomp, S. Mizsak, D. J. Duchamp, C. G. Chidester, Tetrahedron Lett., 4901 (1970); D. J. Duchamp and C. G. Chidester, Acta Cryst., B28, 173 (1972); S. Takeuchi, Y. Ogawa, and H. Yonehara, Tetrahedron Lett., 2737 (1969); B. K. Koe, B. A. Sobin, and W. D. Celmer, Antibiot. Ann., 1956-1957, 672.

3. H. Seto, T. Sasaki, J. Uzawa, S. Takeuchi, and H. Yonehara, Tetrahedron Lett., 4411 (1978).

4. H. Seto, T. Sasaki, H. Yonehara, and J. Uzawa, Tetrahedron Lett., 923 (1978).

5. D. E. Cane, T. Rossi, and J. P. Pachlatko, submitted for publication.

6. Strains of Streptomyces UC5319 were provided by Dr. L. J. Hanka of the Upjohn Co.

7. High field (67.9 MHz) ^{13}C nmr spectra were obtained on a Bruker HX-270 at the Southern New England High Field NMR Facility at Yale University, supported by NIH Grant No. 1-P07-PR00798 from the Division of Research Resources.

8. These assignments may be reversed.

9. This work was supported by the National Institutes of Health, GM22172.

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