Tetrahedron Letters No. 25, pp 2155 - 2158, 1977. Pergamon Press. Printed in Great Britain.

SULFERALIN, A NOVEL SULFONYL PSEUDOGUAIANOLIDE SESQUITERPENE LACTONE FROM SENDAI *HELENIUM AUTUMNALE* L.

Yoshikazu Kondo*, Fumihiko Yoshizaki, Fumio Hamada, Jiro Imai, and Genjiro Kusano

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

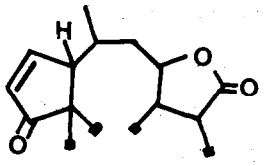
(Received in Japan 28 March 1977; received in UK for publication 16 May 1977)

Several sesquiterpene lactones have recently gained attention as potential experimental tumor inhibitors[1]. Our earlier reports[2,3] described the isolation and structural elucidation of 2-methoxydihydrohelenalin and of picrohelenin, a cytotoxic and intensely bitter pseudoguaianolide from Sendai *Helenium autumnale* L. (Compositae). In the course of the continuing studies on the constituents of Sendai *H. autumnale*, three new sesquiterpene lactones were isolated. One of these lactones was, to our knowledge, the first recognized naturally-occuring sulfonyl pseudoguaianolide. In this communication, we wish to describe the structural elucidation of the sulfur-containing pseudoguaianolide and two closely related guaianolides, which we named sulferalin 1, halshalin 2, and akihalin 3.

Sulferalin 1, mp 255-256°, $[\alpha]_D$-167° (c=0.47, pyridine), was isolated from the roots as colorless needles. The molecular formula $C_{16}H_{22}O_6S$ was assigned on the basis of the elemental analysis and high resolution mass spectrometry [Anal. Calcd. for $C_{16}H_{22}O_6S$: C, 56.16; H, 6.62; S, 9.36; M^+, 342.1137. Found: C, 56.12; H, 6.47; S, 9.04, M^+, 342.1118]. An absorption maximum at 226 nm (ε 6690) in the ultraviolet absorption (UV) spectrum and strong bands at 1765 and 1690 cm^{-1} in the infrared absorption (IR) spectrum revealed the presense of a γ-lactone group and an α,β-unsaturated cyclopentenone group. Additionally, the IR (3300 cm^{-1}) and mass (Calcd. for M^+-18, 324.1031. Found, 324.1022) spectra indicated the presence of a hydroxyl group.

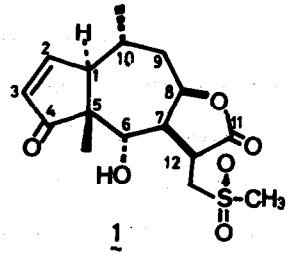
The nuclear magnetic resonance (NMR) spectrum was remarkably instructive. A sharp singlet at 3.16 ppm was characteristic of the methyl sulfonyl group[4] and another singlet (3H) at 1.34 ppm was attributed to the tertiary methyl group. A doublet (3H) at 1.16 ppm (J=7 Hz) was assigned to the secondary methyl group. A pair of two lowfield double doublets at 7.54 (1H, J_1=6 Hz, J_2=2 Hz) and 6.10 ppm (1H, J_1=6 Hz, J_3=3 Hz) which are the AM portions of an AMX system, were assigned to the β-and α-protons in an α,β-unsaturated cyclopentenone system[5] bearing a hydrogen at the γ-position.

A singlet (1H) at 4.72 ppm was assigned to a carbinyl proton and a multiplet (1H) centered at 5.2 ppm was assigned to a lactonic proton. Irradiation of the multiplet centered at 1.7 ppm resulted in the collapse of the doublet methyl signal at 1.16 ppm to a singlet, the methine multiplet around 3.1 ppm to a broad singlet and the methylene multiplet around 2.2 ppm to a deformed multiplet. These observations provide a partial structure A, in addition of which a tertiary methyl group, a methyl sulfonyl group, and a secondary alcohol have been substantiated. The singlet attributed to a carbinyl proton was observed similarly in the NMR spectrum of helenalin 5. Since the α-methylene group attached to γ-lactone is known to be susceptible to the attack of the nucleophiles, such as alkoxyl, sulfhydryl[6,7], and amino groups[7,8], and the partial structure A and the other functional groups are common with those of 5, the addition of methanethiol on the α-methylene group in 5 followed by oxidation could explain the formation of sulferalin 1. Under such a working hypothesis, we demonstrated the synthesis of 1 from 5.

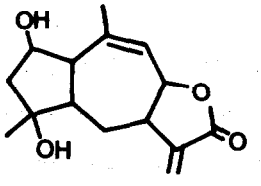


A

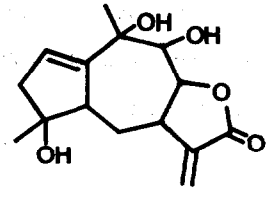
Since direct reaction of helenalin 5 with methanethiol provided a di-S-methyl derivative, 2-methoxydihydrohelenalin[2] 6, which was readily available from helenalin 5, was allowed to react with methanethiol for 3 hr in tetrahydrofuran containing borate buffer (pH 9.2) to afford the addition compound 7, $C_{17}H_{26}O_5S$, mp 165-167°. When the product 7 was maintained in borate buffer (pH 9.2) for 3 hr, the desired methylthioether 8, $C_{16}H_{22}O_4S$, mp 163-165°, was obtained in 36% yield. The spectral data of 7 and 8 were shown as follwws; 7: IR (CS_2) cm^{-1}: 3440 (OH), 1740 (cyclopentanone), 1775 (γ-lactone). NMR ($CDCl_3$) ppm: 4.70 (1H, m, C^8-H), 4.32 (1H, br.s, C^6-H),



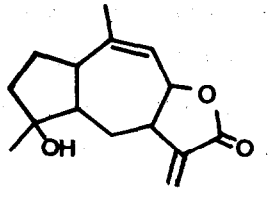
1



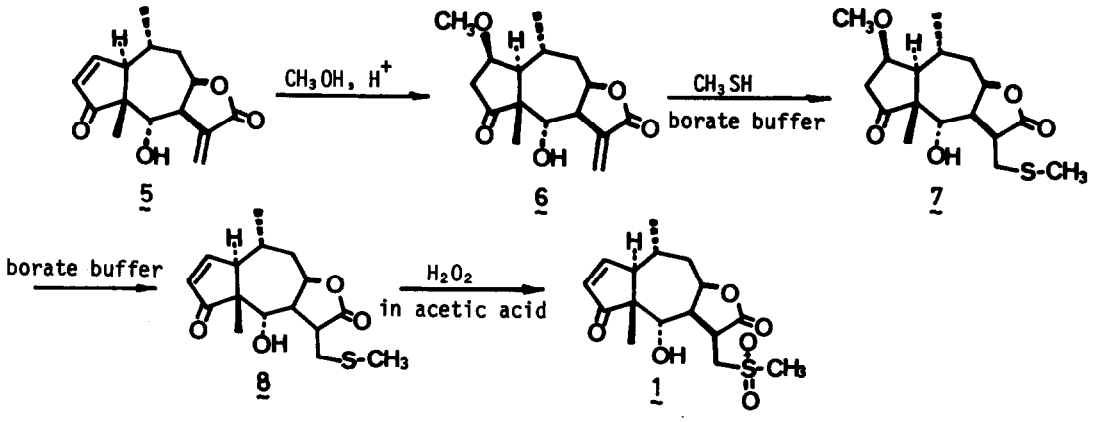
2



3



4



5 6 7 8 1

Scheme 1

3.25 (3H, s, -OC$\underline{H}_3$), 2.21 (3H, s, -SC$\underline{H}_3$), 1.12 (3H, d, J=7 Hz, C^{10}-C$\underline{H}_3$), 1.00 (3H, s, C^5-C$\underline{H}_3$). 8: IR (KBr) cm^{-1}: 3400 (OH), 1760 (γ-lactone), 1693 (cyclopentenone). NMR ($CDCl_3$) ppm: 7.72 (1H, dd, J_1=6 Hz, J_2=2 Hz, C^2-$\underline{H}$), 6.16 (1H, dd, J_1=6 Hz, J_3=3 Hz, C^3-$\underline{H}$), 5.12 (1H, m, C^8-$\underline{H}$), 4.44 (1H, d, J=6 Hz, C^6-$\underline{H}$), 2.20 (3H, s, -SC$\underline{H}_3$), 1.28 (3H, d, J=7 Hz, C^{10}-C$\underline{H}_3$), 1.37 (3H, s, C^5-C$\underline{H}_3$). Treatment of 8 with hydrogen peroxide in acetic acid provided the methyl sulfonyl compound in 65% yield, which was identical with natural sulferalin 1.

Halshalin 2, mp 180-181°, $C_{15}H_{20}O_4$, $[\alpha]_D$ -66.2° (c=0.5, methanol) was obtained from the epigeal parts as colorless needles. The IR spectrum showed bands at 3550, 3350 (OH), 1750 (γ-lactone), and 1665 cm^{-1} (conjugated double bond). The NMR spectrum of 2 was remarkably similar to that of helenium lactone 4 and an additional carbinyl proton signal was observed at 4.56 ppm. (Table I). The location of the hydroxyl group on the C^2 position was established by spin-decoupling experiments in which irradiation of the C^1-methine proton signal at 3.20 ppm collapsed the carbinyl proton signal (C^2-$\underline{H}$) at 4.56 ppm into a doublet (J=7 Hz). These spectral data allowed assignment as the structure 2. Although the structure 2, except the stereochemistry, has been proposed to a desacetylated product of gaillardin[9], which has been isolated from *Gaillardia pulchella*, the physical properties of both halshalin 2 and desacetylgaillardin, mp 149-151°, $[\alpha]_D$ -38° were not identical.

Akihalin 3, mp 209-211°, $C_{15}H_{20}O_5$, $[\alpha]_D$ +75.2° (c=0.4, methanol) was obtained from the epigeal parts as colorless needles. 3 can be regarded as a guaianolide sesquiterpene lactone similar to halshalin 2 by spectral inspection. The IR spectrum of 3 showed hydroxyl bands at 3550, 3400, and 3250 cm^{-1} and the bands at 1760, 1750, and 1655 cm^{-1} attributable to an α-methylene-γ-lactone system. The NMR spectrum of 3, as shown in Table I, allowed to assign the

guaianolide ring system which was confirmed by extensive double resonance experiments. These properties led us to the structure 3 for akihalin. The stereochemistries of 2 and 3 are uncertain at the present time.

Table I. The NMR spectral data of halshalin 2, akihalin 3, and helenium lactone 4 (C_5D_5N).

	C^1-H	C^2-H	C^3-H_a	C^3-H_b	C^5-H	C^6-H	C^7-H	C^8-H	C^9-H	C^{13}-H_a	C^{13}-H_b	C^4-CH_3	C^{10}-CH_3
2	3.20 (dd) J=7 J=12	4.56 (q) J=7					2.96 (m)	5.18	5.23	5.52 (d) J=3	6.26 (d) J=3.5	1.18 (s)	1.92 (s)
3		6.18 (d) J=2	2.44 (dd) J=16 J=1.5	2.82 (d) J=16	3.06 (d) J=12	1.96 (d) J=13	3.40 (m)	4.72 (dd) J=7 J=9	3.98 (d) J=9	5.86 (d) J=3	6.35 (d) J=2.5	1.40 (s)	1.62 (s)
4	3.10 (m)							5.28	5.30 (m)	5.47 (d) J=3	6.28 (d) J=3.8	1.26 (s)	1.62 (d) J<1

References and Notes

1 Reviews: E. Rodriguez, G. H. N. Towers, and J. C. Michell, *Phytochem.*, *15*, *1573 (1976)*; D. Gross, *ibid.*, *14*, *2105 (1975)*.

2 Y. Kondo, F. Hamada, and F. Yoshizaki, *Heterocycles*, *5*, *373 (1976)*.

3 Y. Kondo, T. Tomimori, N. Hiraga, and T. Takemoto, *ibid.*, *6*, *19 (1977)*.

4 G. Van Dyke Tiers, "Characteristic Nuclear Magnetic Resonance Shielding Values for Hydrogen in Organic Structures", 1958.

5 W. Herz, A. R. De Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, *85*, *19 (1963)*.

6 R. W. Doskotch and F. S. El-Feraly, *J. Org. Chem.*, *35*, *1928 (1970)*; S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, *14*, *1147 (1971)*; W. Herz and I. Wahlberg, *J. Org. Chem.*, *38*, *2485 (1973)*; A. Rosowsky, N. Papathanasopoulos, H. Lazarus, G. E. Foley and E. J. Modest, *J. Med. Chem.*, *17*, *672 (1974)*; K. H. Lee, T. kimura, M. Okamoto, and C. M. Cowherd, *Tetrahedron Letters*, *1051 (1976)*.

7 G. Dupuis, J. C. Mitchell, and G. H. N. Towers, *Can. J. Biochem.*, *52*, *575 (1974)*.

8 K. H. Lee, S. H. Kim, H. Furukawa, C. Piantadosi, and E. S. Huang, *J. Med. Chem.*, *18*, *59 (1975)*.

9 T. A. Dullforce, G. A. Sim, and D. N. J. White, *Tetrahedron Letters*, *973 (1969)*.