CHEMISTRY LETTERS, pp. 65-68, 1983.

ISOLATION AND STRUCTURES OF HELIOSCOPINOLIDES, NEW DITERPENES FROM EUPHORBIA HELIOSCOPIA L.

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Three new diterpenes, helioscopinolides A, B and C, have been isolated from the plant *Euphorbia helioscopia* L., and their stereostructures also been elucidated on the basis of their spectral and chemical data coupled with an X-ray crystallographic analysis of helioscopinolide A.

In the course of our searching for physiologically active substances of the toxic plant *Euphorbia helioscopia* L. including euphoscopins A and B,[1] we could isolate three new diterpenes (helioscopinolides A, B and C) from the same plant . In the present paper, we wish to describe the stereostructures of these diterpenes.

Fresh leaves and roots of the plant *Euphorbia helioscopia* L. (*ca.* 50 Kg) collected in Kanagawa early in May were immersed in MeOH at room temperature, and then the MeOH extract was concentrated under reduced pressure to leave a greenish brown oil, which was further washed with isooctane and then partitioned between water and ether. The ethereal extract was roughly separated by column chromatography on silica gel (Mallinckrodt, 100 mesh) using a gradient solution of hexane and AcOEt. The fraction eluted with hexane - AcOEt (1 : 1) was further separated by preparative TLC [Kieselgel PF_{254}; hexane - AcOEt (1 : 1)] to afford helioscopinolide A (*ca.* 60 mg) and helioscopinolide B (*ca.* 10 mg). Furthermore, the fraction eluted with AcOEt was also separated by preparative TLC (Kieselgel PF_{254}) using $CHCl_3$ to give helioscopinolide C (*ca.* 50 mg). The physical data of these diterpenes are shown below.

Helioscopinolide A (1): mp 208 - 209 °C (from EtOH); $[\alpha]_D^{22}$ +180° (c 1.1 in $CHCl_3$); $C_{20}H_{28}O_3$ [m/e 316.2041(M^+)]; IR (Nujol) 3500, 1730, 1660 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.83(3H, s), 0.93(3H, s), 1.04(3H, s), 1.84(3H, d, J= 1.5Hz), 2.56(1H, dd, J= 6, 13.5Hz), 3.28(1H, dd, J= 6, 10Hz), 4.87(1H, br.dd, J= 6, 13Hz) and 6.30(1H, br.s).

Helioscopinolide B (2) as a colorless oil: $[\alpha]_D^{22}$ +154° (c 0.74 in $CHCl_3$); $C_{20}H_{28}O_3$ [m/e 316.2041 (M^+)]; IR (film) 3500, 1740br., 1665 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.89(3H, s), 0.96(3H, s), 1.01(3H, s), 1.84(3H, d, J= 1.5Hz), 2.59(1H, dd, J= 6, 13Hz), 3.48(1H, dd, J= 2, 3Hz), 4.89(1H, br.dd, J= 6, 13Hz) and 6.27(1H, br.s).

Helioscopinolide C (3): mp 236 - 237 °C (from MeOH); $[\alpha]_D^{22}$ +140° (c 0.55 in $CHCl_3$); $C_{20}H_{26}O_4$ [m/e 330.1816(M^+)]; IR (Nujol) 3530, 1740, 1715, 1665 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.71(3H, s), 0.92(3H, s), 1.23(3H, s), 1.84(3H, d, J= 1.5Hz), 2.36(1H, br.d, J= 12Hz), 2.73(1H, d, J= 12Hz), 2.2 - 2.8(4H, complex), 3.40(1H, d, J= 5.5Hz, <u>OH</u>), 3.96(1H, d, J= 5.5Hz),[2] 4.85 (1H, br.dd, J= 6, 13Hz) and 6.35(1H, br.s).

As seen in the ^1H NMR spectrum, helioscopinolide A (1) has three tertiary Me groups and one Me group attached to a double bond. In addition, there are one olefinic proton, a secondary OH group and a $\text{-CH}_2\text{-}\underset{|}{\text{C}}\text{H-OCO-}$ (or $\text{-}\underset{|}{\text{C}}\text{H-CH(}\overset{|}{\underset{|}{\text{C}}}\text{H)-OCO-}$) grouping. From these spectral data, presumably, this compound has the structure similar to that of jolkinolide E,[3] in which the stereochemistry at C_9- and C_{12}-positions remains unsettled. Thus, helioscopinolide A was subjected to an X-ray crystallographic analysis, as follows.

CRYSTAL DATA: $C_{20}H_{28}O_3$, MW 316.4, monoclinic, $P2_1$, a = 8.222(1), b = 15.645(3), c = 7.385(1) Å, β = 115.84(1)°, V = 855.0(2) Å^3, Z = 2, D_X = 1.23 g·cm^{-1}, μ(Mo Kα) = 0.75 cm^{-1}.

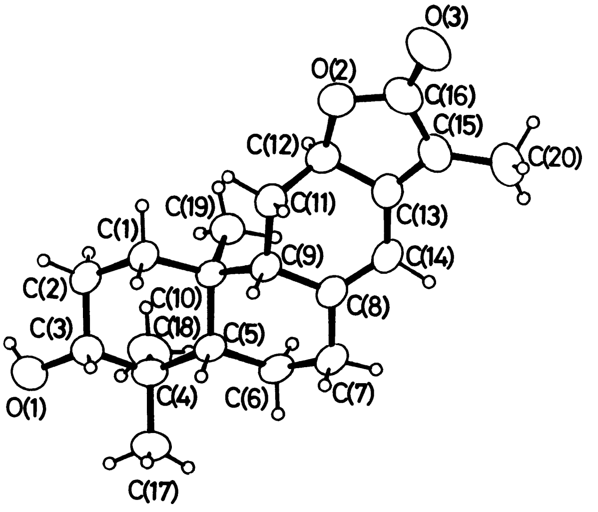
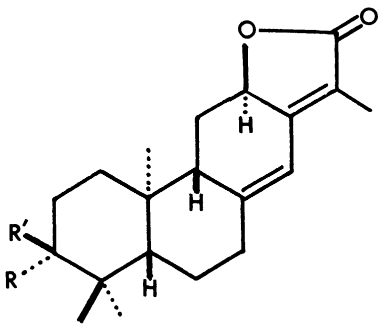


Fig. 1 A computer generated ORTEP drawing of the molecule 1



1 R = OH, R' = H

2 R = H, R' = OH

4 $\overset{R}{\underset{R'}{}}\!\!>$ = O

The intensity measurements were carried out for $2\theta \leqq 55°$ on a RIGAKU AFC-5 diffractometer with graphite-monochromated Mo Kα radiation, a θ- 2θ scan technique, and a crystal of dimensions 0.2 x 0.2 x 0.35 mm. Of the 2210 reflection data measured, 1490 had $|Fo| > 3\sigma(|Fo|)$. The structure was solved by routine application of direct methods by program MULTAN 78;[4] all other computations were carried out using the Universal Crystallographic Computation Program System, UNICS III.[5] Refinement was accomplished by block-diagonal least squares based on F with weights $w^{-1} = \sigma^2(|Fo|) + (0.015|Fo|)^2$. H atoms were located by difference Fourier methods. Non-H atoms were treated anisotropically, and H atoms were refined isotropically. Convergence was achieved with R = 0.049 and Rw = 0.046 for 1490 observed reflections. An ORTEP drawing is shown in Fig. 1, indicating that the stereostructure of helioscopinolide A must be represented by 1.

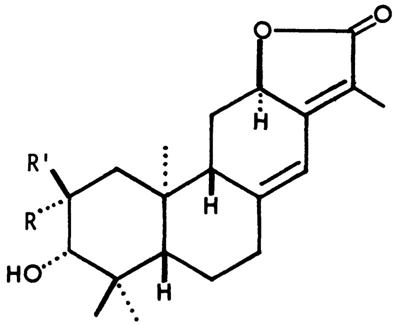
The spectral properties of helioscopinolide B (2) are quite similar to those of helioscopinolide A (1), and the former is regarded as an epimer of 1 at C_3-position: on oxidation with PCC in CH_2Cl_2 (room temp., 12 h), 2 was readily converted into the corresponding ketone (4)[6] in high yield, which was also obtained from 1 under the similar condition. Furthermore, this OH group in 2 is in an axial configuration, as judged from its ^{1}H NMR signal due to an equatorial C_3-H [δ3.48(1H, dd, J= 2, 3Hz)], while 1 has an axial C_3-H [δ3.28(1H, dd, J= 6, 10Hz)].

On the basis of the IR and ^{1}H NMR spectra, the stereostructure of helioscopinolide C (3) seems to be similar to that of helioscopinolide A (1) except for the following point. As shown in Fig. 1, the latter has a $\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-CH(OH)-CH}_2\text{-}$ grouping, while 3 has a $\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-CH(OH)-CO-CH}_2\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-}$ grouping (δ2.36, 2.73, 3.40 and 3.96; ν_{max} 3530 and 1715 cm^{-1}). Accordingly, two possible structures (3 and 5) are given to helioscopinolide C, in which the secondary OH group is equatorial on the basis of the following chemical evidence: on $NaBH_4$ reduction in DMF (room temp., 20 min), helioscopinolide C was readily converted into a glycol (6)[7] [δ3.23(1H, d, J= 4Hz) and 4,21(1H, dt, J= 4, 3Hz)] in quantitative yield, in which the newly formed OH group is in an axial configuration, because the hydrogen atom at C_2-position is equatorial, as judged from its NMR signal at δ4.21. Furthermore, this diol was treated with acetone containing p-TsOH (room temp., 16 h) to give the corresponding acetal (7)[8] in high yield, indicating that the original OH group must be equatorial. Finally, the stereostructure of helioscopinolide C was unambiguously determined to be 3, as follows.

On addition of $Eu(fod)_3$ (0.1 equiv.), the induced shift ratios of the three methyls [δ0.71 (C_4-Me (ax)), 0.92(C_{10}-Me) and 1.23(C_4-Me (eq))] and C_3-H (δ3.96) are shown in Table 1, indicating that the two methyl groups (δ0.71 and 1.23) are spatially located near the OH group at C_3-position. In addition, on irradiation at δ0.92(C_{10}-Me), the broad doublet at δ2.36(C_1-H (ax)) became pretty sharp one. These findings are compatible with the structure (3).

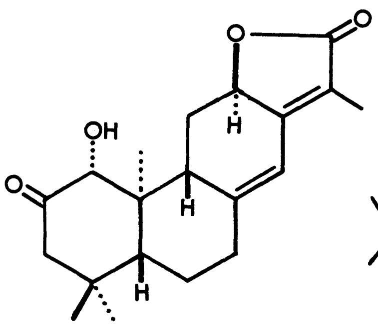
Table 1. The induced shift ratios of the three methyls and C_3-H

Proton	C_4-Me (ax)	C_4-Me (eq)	C_{10}-Me	C_3-H
ΔH (ppm)	1.73	1.46	0.94	3.60



3 $\mathrm{R, R'} >= O$

6 R = OH, R' = H



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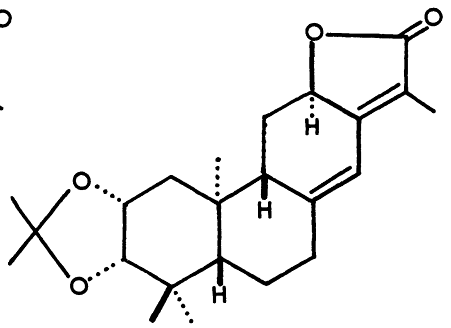

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Both helioscopinolides and jolkinolides[3] constitute a small group of novel diterpenes having an $\alpha\beta,\gamma\delta$-unsaturated 5-membered ring lactone, and have the same stereochemistry,[9] as judged from their spectral data. Particularly, helioscopinolides are oxygenated on the A ring.

The authors wish to thank Messers J. Ohtsuka and K. Suyama for their technical assistance. This research has been supported in part by grants from the Foundation for the Promotion of Research on Medicinal Resources, to which greatful acknowledgment is made.

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6. **4**: mp 232 - 233 °C; $C_{20}H_{26}O_3$ [m/e 314.1866(M^+)]; IR (film) 1740, 1695, 1660 and 1600 cm^{-1}.
7. **6** as an oil: $C_{20}H_{28}O_4$ [m/e 332.1963(M^+)]; IR (film) 3480br., 1735, 1665 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.05(6H, s), 1.18(3H, s), 1.83(3H, d, J= 1.5Hz), 2.40(1H, dd, J= 3, 13.5Hz), 2.57(1H, dd, J= 6, 13Hz), 2.80(2H, br.s, OH), 2.1 - 2.8(3H, complex, overlapped with other signals), 3.23(1H, d, J= 4Hz), 4.21(1H, dt, J= 4, 3Hz), 4.95(1H, br.dd, J= 6, 13Hz) and 6.32(1H, br.s).
8. **7** as an oil: $C_{23}H_{32}O_4$ [m/e 372.2290(M^+)]; IR (film) 1750, 1670 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.97(3H, s), 1.04(3H, s), 1.10(3H, s), 1.35(3H, s), 1.50(3H, s), 1.84(3H, d, J= 1.5Hz), 2.40(1H, dd, J= 2.5, 14Hz), 2.60(1H, dd, J= 6, 13.5Hz), 2.1 - 2.7(3H, complex), 3.83(1H, d, J= 6Hz), 4.42(1H, dt, J= 2.5, 6Hz), 4.91(1H, br.dt, J= 6, 13Hz) and 6.30(1H, br.s).
9. The absolute configuration of helioscopinolides seems to be the same one as that of jolkinolides, because both of them have the same positive and large optical rotation mainly contributed by an $\alpha\beta,\gamma\delta$-unsaturated 5-membered ring lactone

(Received November 4, 1982)