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STRUCTURE AND STEREOCHEMISTRY OF 4-DEACETOXY-10-EPI-OLGUINE, A NEW δ-LACTONE FROM HYPTIS OBLONGIFOLIA BENTHAM (LABIATAE)[1]

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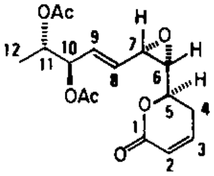
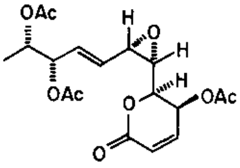
Abstract - A minor secondary metabolite, 4-deacetoxy-10-epi-olguine, has been isolated from the aerial parts of Hyptis oblongifolia (Labiatae). Its structure has been elucidated as that represented by formula 1, based on spectral and crystallographic evidence.

Hyptis is a large genus of approximately 400 species of the Labiatae which is located on the american continent.[2,3] Several species of this genus have been found to possess significant biological activities,[4,5] such as antifertility,[6,7] teratogenic,[8] mycotoxinic and phytotoxinic.[9] As part of our continuing phytochemical study of the Mexican plants, we have investigated the chemistry of Hyptis oblongifolia Bentham, a species widespread throughout Mexico.[10]
Aerial parts (1.7 kg) of this species were extracted with acetone at room temperature. The gum (26.3 g) was chromatographed on silica gel (1 kg, deactivated with 10% water), eluting with increasing concentrations of ethyl acetate in hexane. From the less polar fractions, ursolic and oleanolic acids (3.6 and 4.5 g, respectively) were characterized and identified by direct comparison with authentic samples. 4-Deacetoxy-10-epi-olguine (1), mp 75-76°C (from methanol), $[\alpha]_D^{20}$ +55.2° (c 0.38; MeOH), was isolated (0.025% of dry weight) from the more polar fractions. Combustion analysis and mass spectrometry[11] indicated the molecular composition $C_{16}H_{20}O_7$. The uv spectrum showed absorption at λ_{max}^{MeOH} 203 nm, ε_{max}=14266 and the ir ($CHCl_3$) displayed absorptions at 3028, 1736 (broad), 1594, 1420, 814, 696 cm^{-1}. These data suggest the presence of carbonyl groups and double bonds. In agreement with these assignments, the ^{13}C NMR ($CDCl_3$, 20 MHz) spectrum showed resonances of three carbonyls [two acetates: δ 169.89 s, 169.62 s, and a carbonyl of an α,β-unsaturated δ-lactone: 162.30, C-1 (numbering as in 1)], two disubstituted double bonds (δ 121.48, d, C-2; 144.53, d, C-3; 127.60, d, C-8; 130.50, d, C-9), three secondary carbons bearing oxygen

(δ 73.84, *d*, C-5; 74.27, *d*, C-10; 70.25, *d*, C-11), a disubstituted epoxide ring (δ 57.94, *d*, C-6; 55.86, *d*, C-7), one methylene (δ 27.22, *t*, C-4) and finally, three methyl groups (two from acetates: 20.93, *q*; 20.84, *q*, and one additional, 15.17, *q*, C-12). The location of these structural fragments was established by ^1H NMR, since all the protons in the sequence H-2 through H-12 were interrelated through extensive spin decoupling experiments,[12] and allowed to propose structure **1** for the new compound, in agreement with the molecular formula. The H(5)-H(6), H(6)-H(7), H(7)-H(8) and H(8)-H(9) coupling constants observed in the ^1H NMR spectrum as well as the ^{13}C NMR data for **1** closely corresponded to those of olguine **2**, isolated from a South-American *Hyptis* species,[13] when allowance was made for the lack of a 4-acetoxy group in **1**. This correspondence was taken as evidence that the stereochemistry of **1** was the same as that of **2** at C-5, C-6, C-7, C-8 and C-9. However, due to free rotation around the C(10)-C(11) single bond, spectroscopic arguments are not reliable guides for the stereochemistry of these chiral centers. In addition, different vicinal configuration has been observed in similar natural products, since olguine (**2**) possesses a C(10)-C(11) *parf* configuration and the C(10)-C(11) *pref*[14] stereochemistry was found in anamarine (**3**), a related δ-lactone isolated from the same South-American species.[15] Therefore, an X-ray analysis of **1** was undertaken[16] to confirm the proposed structure and to establish the configuration of the C-10 and C-11 chiral centers.



1



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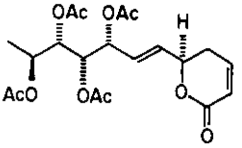

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Crystals of 4-deacetoxy-10-epi-olguine **1** were obtained by slow crystallization from methanol. The crystal was orthorhombic and crystallized in space group $P2_12_12_1$, with a = 7.3663(1)Å, b = 14.7419 (4)Å, c = 15.7355(5)Å, and d_{calc} = 1.259 gcm^{-3} for Z = 4 ($C_{16}H_{20}O_7$). The intensity data were measured on a Nicolet R3m diffractometer (monochromated CuK$_\alpha$ radiation), ω-scans, pulse height discrimination). The size of the crystal used for data collection was approximately 0.23 x 0.22 x

0.26 mm, $\mu = 0.93\ \mathrm{cm}^{-1}$. A total of 1309 accesible reflections were measured for $2\theta<45°$ of which 902 were considered to be observed $[I>2\sigma(I)]$. The structure was solved by direct methods[17] and was refined by blocked cascade matrix least square methods. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and fixed isotropic temperature *factor $U=0.043\ \text{Å}^2$ for the hydrogen atoms. The hydrogen atoms were included in the structure factor* calculations. The final discrepancy indices are $R = 0.0623$ and $R_w = 0.0576$ for the 902 observed reflections. Figure 1 is a computer-generated drawing of the final X-ray model of one possible enantiomer of **1**. As can be seen from the drawing, H-5 is α and axial, the C(6)-C(7) epoxide is cis, the C(8)-C(9) double bond is trans, and the adjacent chiral carbon atoms C(10)-C(11) possess pref relationship. Therefore, this new natural product should be represented as 4-deacetoxy-10-epi-olguine (**1**).

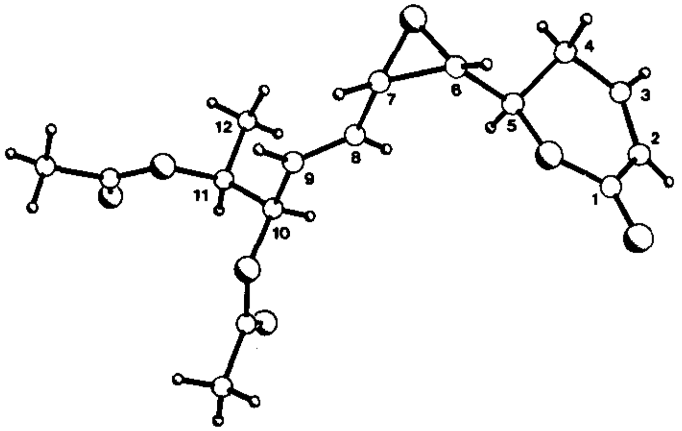

Figure 1.
Computer-generated
perspective drawing of **1**.

The α,β-unsaturated γ-lactone ring takes a pseudo-chair conformation, with C-5 being at the flap, quite similar to that of **2** and **3**.[13,15] The side chain is pseudo-equatorial, H(5)-H(6), H(7)-H(8), as well as H(9)-H(10) are in quasi-anti-periplanar relationship and H(10)-H(11) are in synclinal conformation in the solid state.

An extremely interesting feature of the δ-lactones **1**, **2** and **3**, isolated from Hyptis species is the same general structure but different stereochemistry at various chiral centers. The investigation of other species of Mexican Hyptis is currently underway.

ACKNOWLEDGEMENTS

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10. Our own material came from the Sierra Madre del Sur, State of Guerrero, México. A specimen is deposited at the National Herbarium, Instituto de Biología de la Universidad Nacional Autónoma de México, voucher MEXU-10104-M.
11. EIMS, 70 eV of **1**, m/z (rel. intensity): 324 (M^+, <1), 227 (93), 125 (100), 97 (75), 96 (65), 95 (60), 81 (99), 79 (10), 70 (10), 69 (15), 68 (71), 66 (22), 55 (5). Found: C, 59.33; H, 6.19; O, 34.41 %. $C_{16}H_{20}O_7$ requires: C, 59.25; H, 6.22; O, 34.53 %.
12. ^{1}H NMR (80 MHz, $CDCl_3$) of 1: δ 6.03 (1H, *ddd*, $J_{2-3} = 10$ Hz, $J_{2-4\alpha} \cong J_{2-4\beta} = 1.8$ Hz, H-2), 6.90 (1H, *ddd*, $J_{2-3} = 10$ Hz, $J_{3-4\alpha} \cong J_{3-4\beta} = 4$ Hz, H-3), 2.57 (2H, complex signal, H-4α and H-4β), 4.15 (1H, *ddd*, $J_{4\alpha-5} \cong J_{4\beta-5} = J_{5-6} = 8$ Hz, H-5), 3.28 (1H, *dd*, $J_{5-6} = 8$ Hz, $J_{6-7} = 4$ Hz, H-6), 3.60 (1H, *dd*, $J_{6-7} = J_{7-8} = 4$ Hz, H-7), 5.80 (2H, complex signal, H-8 and H-9), 5.34 (1H, *dd*, $J_{9-10} = J_{10-11} = 4$ Hz, H-10), 5.07 (1H, *dq*, $J_{10-11} = 4$ Hz, $J_{11-12} = 7$ Hz, H-11), 1.18 (3H, *d*, J = 7 Hz, 12 CH_3).
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