

ASTERISCUNOLIDE A: HUMULANOLIDE FROM ASTERISCUS AQUATICUS

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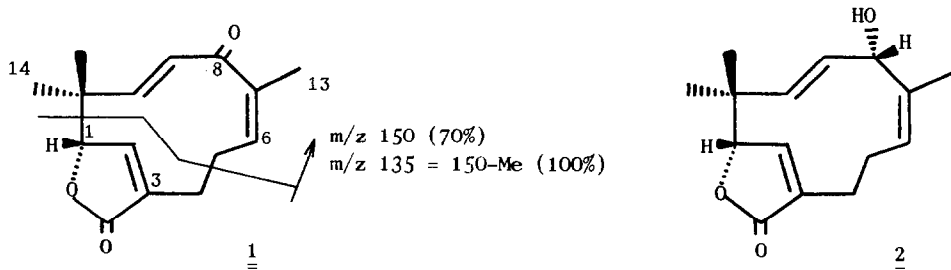
Abstract.- A number of humulanolides and other sesquiterpene lactones have been isolated from Asteriscus aquaticus (L). The structure, absolute stereochemistry and conformation of the major component, asteriscunolide A, have been determined.

Asteriscus aquaticus L. Less (1) (Family Compositae, Tribe Inuleae) is an odoriferous plant distributed through the Mediterranean Region. During the study of the composition of its hexane extract six new sesquiterpene lactones have been isolated (DCC, PLC and crystallization).

Asteriscunolide A, the major component, shows m.p. = 158°C (ether), $[\alpha]_D = -358^\circ$ (c, 1% CHCl₃) and MS with M⁺ at m/z = 246 (C₁₅H₁₈O₃). In the IR spectrum absorptions of an α,β -unsaturated γ -lactone (1755, 1100, 1040 and 1015 cm⁻¹), of a cross-conjugated ketone (3030, 1680 and 1640 cm⁻¹) and of gem-dimethyl (1370 and 1360 cm⁻¹) groups are observed. Its UV spectrum (EtOH) shows maxima at 223 ($\epsilon = 9480$) and 243 nm (sh, $\epsilon = 7040$).

The interpretation of the ¹H-NMR spectrum (Table I) and the comparison with the spectral properties of zerumbone oxide (2), tagitinins (3) and other related compounds (4,5), permitted us to propose the structure of 8-oxo-humula-2,6,9-trien-12,1-olide 1 and the fragmentation pattern in the MS, showing the two major peaks at m/z = 150 (70%) and 135 (100%) originated through cleavage of the doubly allylic bonds C₁-C₁₁ and C₄-C₅, agrees with it.

The Z configuration of the Δ^2 double bond is obviously deduced from the presence of the



γ -lactone ring. The value of the coupling constant $J_{9,10} = 14$ Hz, permits us to assign the E configuration for the Δ^9 double bond and finally, as a 14% NOE $H_6\{H_{13}\}$ has been observed, the Z configuration of the Δ^6 double bond was established. These results agree with the chemical shift of 21.3 ppm for the C_{13} methyl group resonance in the ^{13}C -NMR spectrum (Table II).

Table I.- ^1H -NMR data for 1 and 2 (60 MHz, δ , ppm)

H	<u>1</u>	$\Delta_{\text{C}_6\text{D}_6}^{\text{CDCl}_3}$	$\Delta_{\text{Eu}(\text{fod})_3}^{\times}$	<u>2</u>	$\Delta_{\text{C}_6\text{D}_6}^{\text{CDCl}_3}$	$\Delta_{\text{Eu}(\text{fod})_3}^{\times}$
1	4.68 s	0.65	1.00	4.74 s	0.50	1.00
2	7.00 s	0.75	1.02	6.88 s	0.48	1.13
4,5	2-2.8 m	----	----	1.7-2.8 m	----	----
6	6.00 bt	0.67	0.70	5.40 m	0.43	0.85
8	----	----	----	4.97 dd	0.20	2.69
9	5.29 d	0.35	1.15	5.86 dd	0.15	1.60
10	6.16 d	0.49	1.17	5.47 d	0.45	0.62
13	1.94 bs	0.27	0.78	1.84 bs	0.14	0.95
14	1.20 s	0.28	0.75	1.04 s	0.12	0.55
15	1.41 s	0.34	0.44	1.39 s	0.31	0.39

\times relative to H_1 (deshielded 1.42 and 1.69 ppm for 1 and 2 respectively)

Table II.- ^{13}C -NMR data for 1 (50 MHz, ppm) (\times)

C	δ	C	δ	C	δ
1	88.1	6	138.3	11	42.5
2	147.9	7	133.7	12	173.5
3	138.8	8	198.5	13	21.3
4	29.9	9	136.5	14	24.7
5	23.0	10	133.0	15	30.0

(\times) Assignments of carbons 1, 2, 9, 10, 13, 14 and 15 were confirmed by heteronuclear selective decoupling

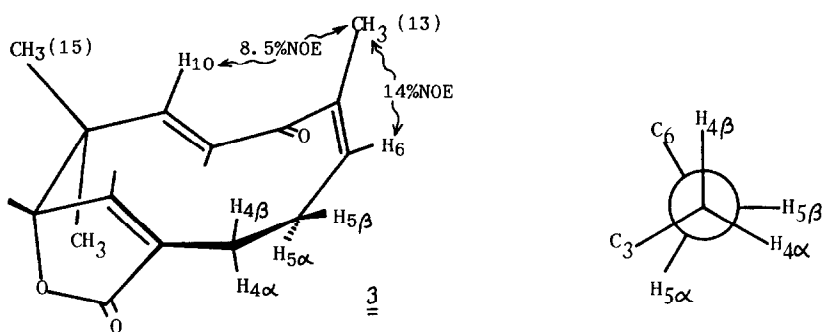
The 200 MHz ^1H -NMR spectrum of 1 showed partially resolved absorptions in the 2-3 ppm region, corresponding to the C_4 and C_5 methylene protons, which were analyzed by double irradiation experiments in which H_6 , H_{13} and the low field portion of this 2-3 ppm region were successively decoupled. The chemical shifts and coupling constants were thus determined, indicating the approximate dihedral angles shown in Table III.

Table III.- $^1\text{H-NMR}$ data for methylene protons at C_4 and C_5 of 1

H	δ ppm	J(Hz)	θ /degrees
4α	2.67	$4\alpha, 4\beta = -10$	--
		$4\alpha, 5\beta = 5$	-30
		$4\alpha, 5\alpha = 0$	90
4β	2.18	$4\beta, 5\alpha = 10$	-150
		$4\beta, 5\beta = 0$	90
5α	2.31	$5\alpha, 5\beta = -10$	--
		$5\alpha, 6 = 10$	150
5β	2.66	$5\beta, 6 = 7$	30

The complete spin system was too big (8 spins: $\text{H}_{4\alpha}$, $\text{H}_{4\beta}$, $\text{H}_{5\alpha}$, $\text{H}_{5\beta}$, H_6 and 3H_{13}) for simulation in the spectrometer minicomputer. However, some degree of success could be achieved when simulating the H_{13} -decoupled spectrum, particularly the H_6 region. Nevertheless, the intensities of the signals could not be exactly reproduced, probably due to the perturbation introduced by spin decoupling.

These data, as well as solvent shifts, lanthanide induced shifts and other NMR data for 1 and its borohydride reduction product 2 (Tables I and II), mostly agree with picture 3 for the conformation of asteriscunolide A, which is also supported by the 8.5% NOE found in $\text{H}_{10}\{\text{H}_{13}\}$ experiments.



The CD curve of asteriscunolide A shows Cotton effects $\Delta\epsilon_{340} = +1.5$, $\Delta\epsilon_{268}(\text{sh}) = -5.0$ and $\Delta\epsilon_{228} = -28.5$. On application of the empirical rules for α, β -unsaturated enones (5) and α, β -unsaturated γ -lactones (6) we were able to conclude that the absolute configuration at C_1 is S, as depicted in 1, 2 and 3. Subsequently, the S configuration at C_8 in 2 was deduced from the most preferred stereochemical course of the carbonyl group reduction.

Most of known sesquiterpene lactones are formed from the germacrene intermediate. Asteriscunolide A is the first example of a natural humulane lactone.

The determination of structures, stereochemistries and conformations of its isomers asteriscunolides B, C and D, will be shortly published.

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