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Heliannuol E. A Novel Bioactive Sesquiterpene of the Heliannane Family[†,1]

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Abstract: From the medium polar active fractions of leaf aqueous extracts of *Helianthus annuus* L. cv. SH-222, we have isolated heliannuol E (1) which contains a previously unknown six-membered ring containing bicyclic skeleton. The structural elucidation is based on extensive spectral studies, including ^{1}H-^{1}H COSY, ^{1}H-^{13}C HETCOR, and NOE difference experiments.

The discovery of new allelochemicals from plants or microbes has attracted much attention in the last 20 years. Allelochemicals have been implicated as biocommunicators,[2] and are potential sources of new structural types of herbicides with new modes of action which may be less harmful than those presently used in agriculture.[3] It is becoming increasingly important to develop premixes of herbicides employing different modes of action, so as to get both short-term efficacy and long-term control of a given weed spectrum. Allelopathy,[4] an emerging branch of applied sciences which studies biochemical plant-plant and plant-microorganism interactions, may help in providing new approaches to integral weed control management by providing, for instance, crop varieties having greater ability to smother weeds, generations of natural phytotoxins as herbicides and of synthetic derivatives of natural products as herbicides.

Sunflowers are well-known for producing a variety of secondary metabolites, most commonly terpenoids[5] and phenolics[6] possessing a wide variety of biological properties[7] including allelopathic activity.[8] In our screening of crude extracts for phytotoxic allelopathic activity[9] that can be used as natural herbicide templates,[10] the medium polar active fractions of leaf aqueous extract of two varieties of cultivar sunflowers (*Helianthus annuus* L.) cvs. SH-222® and VYP® displayed a potent profile of activity particularly against dicotyledons. Bioassay-guided

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fractionation of this extract afforded, together with the known heliannuols **A-D**[11] the novel heliannuol **E** (**1**) which contain a previously unknown six-membered ring containing bicyclic skeleton.

The extraction of the fresh leaf aqueous extract of *H. annuus* L. cv. SH-222® with dichloromethane gave material which was fractionated by chromatography on silica gel using hexane-ethyl acetate mixtures of increasing polarity. Plant material was collected during the third plant development stage[9] (plant 1.2 m tall with flowers, 1 month before harvest). Bioassay-guided fractionation of this extract afforded heliannuol **E** (**1**).

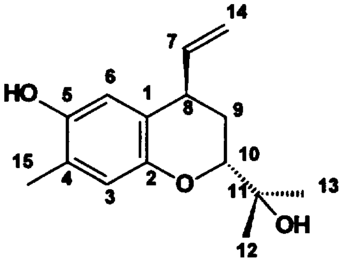


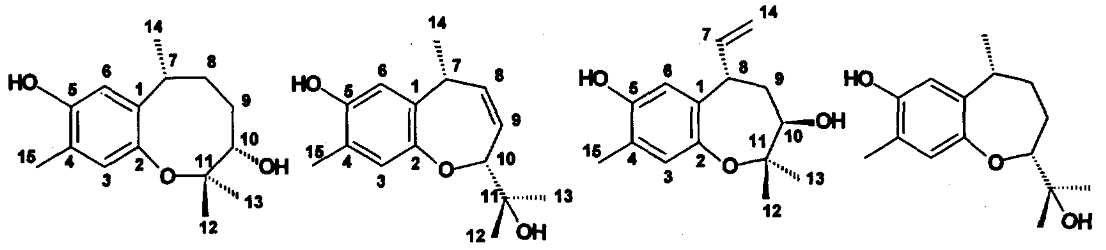
Figure 1. Heliannuol E (1)

Table 1. ^{1}H NMR data (400 MHz, *J* values in Hz) for **1** (CDCl$_3$)

H	6
3	6.65 s
6	6.47 s
7	5.95 ddd ($J_{7,14}$=10.1; $J_{7,8\alpha}$=6.2; $J_{7,14'}$=17.0)
8α	3.46 ddddd ($J_{7,8\alpha}$=6.2; $J_{8\alpha,9\alpha}$=5.5; $J_{8\alpha,9\beta}$=2.2; $J_{8\alpha,14}$=$J_{8\alpha,14'}$= 1.5)
9α	1.89 ddd ($J_{8\alpha,9\alpha}$=5.5; $J_{9\alpha,9\beta}$=13; $J_{9\alpha,10}$=10.1)
9β	1.85 ddd ($J_{8\alpha,9\beta}$=2.2; $J_{9\alpha,9\beta}$=13; $J_{9\beta,10}$=3)
10	3.72 dd ($J_{9\alpha,10}$=10.1; $J_{9\beta,10}$=3)
12	1.28* s
13	1.23* s
14	5.01 ddd ($J_{7,14}$=10.1; $J_{14,14'}$=$J_{8\alpha,14}$=1.5)
14′	4.89 ddd ($J_{7,14'}$=17.0; $J_{14,14'}$=$J_{8\alpha,14}$=1.5)
15	2.18 s

* These values may be interchanged.

Heliannuol **E** (**1**) showed a HRMS spectrum with a molecular ion at *m/z* 248.1420, corresponding to the molecular formula $C_{15}H_{20}O_3$. Both ^{1}H NMR (Table 1) and ^{13}C NMR spectra[12] indicated that it had a heliannuol skeleton: δ 6.65, 6.47, 2.18 in the ^{1}H NMR spectrum and δ 124.5, 148.2, 118.5, 120.6, 147.5, 115.8 in the ^{13}C NMR spectrum. ^{1}H NMR spectra indicated the presence of a vinylic moiety, similar to that shown by heliannuol **C** (**4**)[11] [H-14(δ 5.01), H-14'(δ 4.89), H-7(δ 5.95)]. Study of 2D COSY and 2D HETCOR spectra confirmed the same oxygenation pattern as in **4**: H-7 is coupled with H-8 (δ 3.46), H-8 with H-9α (δ 1.89), H-9β (δ1.85) and H-9α, H-9β with H-10 (δ 3.72). Coupling constants suggested a six-membered ring, with H-8α and H-9β at equatorial positions and H-9α and H-10β at axial ones. The chemical shift observed for the signal corresponding to C-11 (δ 71.1) is in good agreement with an ether function at C-10, as in heliannuol **B** (**3**)[11] (C-11, δ 72.4) and **D** (**5**) (C-11, δ 72.8) instead of an ether function attached at C-11 as in heliannuol **A** (**2**) (C-11, δ 79.7) and **C** (**4**)[11] (C-11, δ 79.7). Consequently, the structure was assigned as represented in Figure 1 and constitutes the first isolated heliannuol with a six-membered ring. The stereochemistry was assigned on the basis of a NOE experiment (figure 3),



2 3 4 5

Figure 2. Heliannuols A-D

where effects between H-10 and H-7; H-10 and H-9β; as well as between H-8 and H9α were observed. Both, the stereochemistry and the presence of a six-membered ring are corroborated with the good agreement observed between the angles found for the most stable conformation and the experimental coupling constants (Table 2).

Table 2. Observed coupling constants *vs* *Φ* obtained for the most stable conformer

Protons	Calculated *Φ*	Observed *J* (Hz)
8α-9α	41.5	5.5
8α-9β	75.2	2.2
9α-10β	179.6	10.1
9β-10β	64.9	3.0

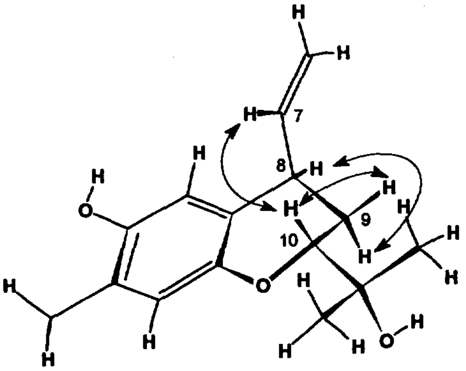


Figure 3. Observed NOEs for the most stable conformer of 1 using PM3 calculations.[13]

This compound is of particular interest since it is the first member of a new heliannuol skeleton with potential allelopathic activity. Based on its bioassay results,[14] it is likely to be significantly involved in the allelopathic action of cultivar sunflowers. Its biogenesis may proceed through a bisabolene-type precursor as proposed for the recently reported heliannuols.[11] As for **4**, its biosynthesis cannot be easily accommodated by the isoprene rule, but may involve a rearrangement via a phenonium ion to afford the six-membered heterocyclic ring.

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REFERENCES AND NOTES

† This paper is affectionately dedicated to Professor Francisco Rodríguez-Luís on the occasion of his 60th birthday, wishing him the best in life and in chemistry.

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12. Yellow oil; $[\alpha]^{D}_{25} = -68.6$ ($CHCl_3$, c=0.1); IR ν_{max} $^{(neat, KBr)}$ cm^{-1}:3423 (hydroxyl group); 1632 (C=C); 1195 (ether); ^{1}H NMR is listed in Table 1; ^{13}C NMR δ: 124.5 (*s*, C-1); 148.2 (*s*, C-2); 118.5 (*d*, C-3); 120.6 (*s*, C-4); 147.5 (*s*, C-5); 115.8 (*d*, C-6); 142.1 (*d*, C-7); 37.9 (*d*, C-8); 27.5 (*t*, C-9); 78.1 (*d*, C-10); 71.1 (*s*, C-11); 25.1 (*q*, C-12); 24.2 (*q*, C-13); 113.1 (*d*, C-14), 15.7 (*q*, C-15).; EIMS, *m/z* (rel. int.): 248 $[M]^+$ (86.5), 230 $[M - H_2O]^+$ (58.5), 23 $[M-CH_3]^+$(9.5), 215 $[M-H_2O-CH_3]^+$ (70), HREIMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1420.
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