Structural Elucidation and Chemistry of a Novel Family of Bioactive Sesquiterpenes: Heliannuols†,[1]

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From the moderately polar active fractions of leaf aqueous extract of *Helianthus annuus* L. var. SH-222 and VYP, we have isolated three new sesquiterpenes which contain a previously unknown skeleton, heliannuols B-D (**2**–**4**). The structural elucidation of heliannuols was based on extensive spectral studies, including $^1H-^1H$ COSY, $^1H-^{13}C$ HETCOR, and NOE difference experiments, X-ray diffraction analysis of **4**, and chemical correlation between **1**, **2**, and **4**. A biosynthetic pathway that involves an oxirane ring opening is proposed for heliannuols A (**1**) and D (**4**), while a phenonium ion intermediate is proposed for heliannuol C (**3**). The oxirane ring opening and the formation of this intermediate have been evaluated using the semiempirical method PM3. Allelopathic activity bioassays of compound **1**–**4** suggest that those members of a new class of bioactive sesquiterpenes may be involved in the cultivar sunflower defense against dicotyledon species.

Introduction

Weed problems constitute an important part of agriculture research. As a consequence of this research, many chemicals have been developed since the 1950's, and their utilization is widely extended. In spite of modern control methods, even in developed countries that rely heavily on chemical herbicides for control, losses due to weeds, including efforts to control them plus losses in yield and quality, are relatively high.

Herbicides will continue to be a key component in most integrated weed management systems in the foreseeable future. Nevertheless, the increase in chemical control has become an overwhelming economical burden, and more important, it could pose a serious threat to the public health and the environment.[2]

Because of these problems and other potential ones, increased attention is being focused on alternative ways for weed control. Allelopathy, which concerns biochemical plant–plant interactions including positive and negative effects,[3] has been proposed as a possible alternative weed management strategy.[4]

Allelopathy can offer an excellent opportunity to help in the search of new natural herbicide models. Learning from nature how a specific plant can biochemically interact with another, we can focus our bioactive natural products isolation based on the appropiate bioassay to find new structural types of herbicides more specific and less harmful than those actually in use in agriculture.[5]

One of the different strategies that can be formulated, based on the origin of the allelopathic compound, is the search of natural herbicide models from a particular ecosystem (natural or agroecosystem) with application on the same ecosystem.

With these concepts in mind, and with the notion that allelopathic compounds have a wide diversity of skeleton type, we have initiated a research project: "Allelopathic Studies on Cultivar Species" where we have initiated systematic allelopathic activity studies on agroecosystems as well as with synthetic bioactive natural product models in order to evaluate their potentiality as allelopathic agents and consequently as natural herbicide models.

Cultivation of sunflowers is predominantly performed to produce oil and plays an important role in southern parts of Europe. Biochemical investigations on sunflowers reveal that this species (*Helianthus annuus*) is a rich source of sesquiterpenoids[6] and other plant metabolites with a wide spectrum in biological activities;[7] nevertheless little is known about the function of its compounds. Recent investigations have shown that sunflowers can actively influence the growth of surrounding plants,[8] but the mechanism of these allelopathic effects is unknown.

In the Andalusia region of Spain 26 different varieties of sunflowers for crop production are used. Following the proposed strategy, we perform a preliminary bioassay with those varieties during four different plant development stages in order to establish which species show

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† This paper is affectionately dedicated to Professor Nikolaus H. Fischer on his 25th anniversary at Louisiana State University.

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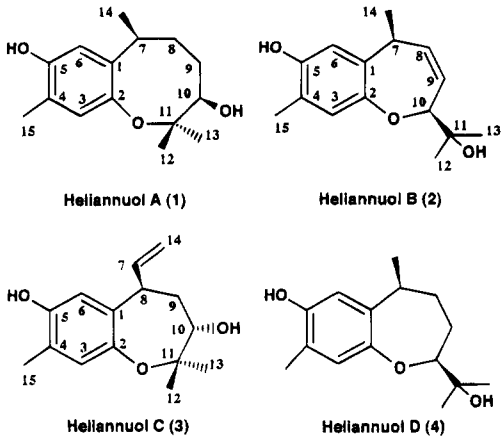

Figure 1.

better significative profile of activity and when is the best stage to use the plant material (fresh leaves) without injuring the plant for the main crop production. As result of this bioassay *H. annuus* var. SH-222 and VYP and the third plant development stage (plants 1.2 m tall with flowers, 1 month before harvest) were selected.

Here we report the isolation and structural elucidation of three new members with the novel sesquiterpene heliannuol skeleton. The subsequent bioassays with fractions obtained from the first chromatographic separation led to the isolation of the active principles. From moderately polar fractions, in addition to guaianolides, annuolides A-E,[9] and heliannuol A (**1**),[6b] three new heliannuols, heliannuols B-D (**2**–**4**) were isolated. Their structural elucidation was based on spectroscopic studies (one- and two-dimensional experiments), X-ray diffraction analysis of **4**, and chemical correlation between **1**, **2**, and **4**.

Results and Discussion

Recently, we reported the first member of a new class of bioactive sesquiterpenes, heliannuol A (**1**)[6b] (Figure 1), isolated as the major component from the moderately polar bioactive fractions of the fresh leaf aqueous extract of cultivar *Helianthus annuus* L. var. SH-222. This compound contains an eight-membered ring condensed with a benzene derivative and exists at room temperature as mixture of conformers, as revealed by room temperature ^{1}H NMR spectrum studies. The relative stereochemistry was established by single-crystal X-ray diffraction analysis.

Further studies of these fractions afforded three new related compounds, heliannuols B (**2**), C (**3**), and D (**4**) (Figure 1).

Heliannuol D (**4**) was isolated as colorless crystals, mp 59–61 °C ($CHCl_3$). HRMS shows a *m/z* = 250.1575 in accord with a molecular formula of $C_{15}H_{22}O_3$. The IR, ^{1}H NMR (Table 1), and ^{13}C NMR (Table 2) data are very similar to those previously reported for **1**. However ^{1}H NMR and ^{13}C NMR spectra show well-resolved signals and some differences in the chemical shifts. No conformational equilibrium is observed at room temperature. The main differences are observed in the signals belonging to H-7 and H-10 that appear at δ 3.28 (dd; $J_{9\alpha,10}$ = 1.5 Hz, $J_{9\beta,10}$ = 11 Hz; H-10) and 2.88 (ddq; $J_{7,8\alpha}$ = 3 Hz, $J_{7,8\beta}$ = 5 Hz, $J_{7,14}$ = 7 Hz; H-7) instead of δ 3.56 and 3.25, respectively, in heliannuol A(**1**), as well as those corresponding to the methyls H-12 and H-13 (δ 1.27, s, 6H). A nice correlation between protons 7–10 was established based on the ^{1}H-COSY experiment. The unambiguous assignment of the ^{13}C NMR was established based on APT experiments and following the corresponding correlation on the ^{1}H–^{13}C HETCOR and long range correlation experiments. The different oxygen functions attached at C-10 and C-11 could be clearly established following the corresponding chemical shift observed in the ^{13}C NMR spectrum which is deshielded for C-10 (90.40 ppm, ether function) and shielded for C-11 (72.81 ppm, hydroxyl group) in comparison with those of **1**. These differences could be explained if this compound contains a smaller ring, likely a seven-membered ring with an ether moiety at C-10. Assuming a relative stereochemistry at C-7 and C-10 (7*S*,10*S*) similar to **1**, we calculate the most stable conformer for **4** using semiempirical PM3 calculations.[10] This provided the conformer shown in Figure 2, which is in agreement with the observed NOEs. This was further substantiated by single-crystal X-ray diffraction analysis.[11]

The biogenesis of these two compounds may proceed through a bisabolene-type precursor. This is supported by the recent isolation of three bisabolene-type sesquiterpenes from noncapitate glandular trichomes of *Helianthus annuus*,[12] which present a similar oxidation pattern in the aromatic ring of the heliannuols with a quinone structure type A and a double bond between C-10 and C-11. This double bond may be oxidized to an epoxide moiety (Scheme 1). Then, an acid catalysis must provide heliannuol A. Protonation of the ether should generate a reactive intermediate oxonium ion that located more positive charge on the tertiary than on the secondary carbon. This oxonium ion was evaluated using PM3 semiempirical calculations and it evolved "spontaneously" to the tertiary carbocation that might form an eight-membered ring.

On the other hand, a base-catalyzed opening of the epoxide intermediate may lead to heliannuol D (**4**) as the major product. The attack of the phenolate ion at C-10 and C-11 was studied employing PM3 calculations. The reaction profile for the base-catalyzed process was explored starting from the previously determined geometry of the precursor. The distances between C-11 and C-10 to the oxygen were employed as the reaction coordinates and modified from those previously determinated for the precursor to 1.45 Å. The most stable conformer obtained in each step was studied (Figure 3). The energy profile of these two transformations shows a higher activation energy (214 kJ mol^{-1}) for the eight-membered ring than that observed in the formation of the corresponding ion of **4** (179 kJ mol^{-1}). Additionally smaller energy of the anion of **4** (−547.5 kJ mol^{-1}) is observed in comparison with that of the anion of **1** (−529.3 kJ mol^{-1}).

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Table 1. ^{1}H NMR Data (400 MHz, *J* Values in Hz) for Heliannuols B-D (2–4) ($CDCl_3$)

H	2	3	4
3	6.81 s	6.70 s	6.73 brs
6	6.51 s	6.50 brd ($J_{6,8}$ = 1)	6.53 s
7	3.15 dq ($J_{7,14}$ = $J_{7,8}$ = 7.5)	6.07 ddd ($J_{7,8}$ = 7.5; $J_{7,14}$ = 10.5; $J_{7,14'}$ = 17)	2.88 ddq ($J_{7,8\alpha}$ = 3; $J_{7,8\beta}$ = 5; $J_{7,14}$ = 7)
8α	5.97 brdd ($J_{7,8}$ = 7.5; $J_{8,9}$ = 12)	3.57 dddd ($J_{6,8}$ = 1; $J_{7,8}$ = 7.5; $J_{8,9\alpha}$ = 3.5; $J_{8,9\beta}$ = 8)	1.71 dddd ($J_{7,8\alpha}$ = 3; $J_{8\alpha,8\beta}$ = 13.5; $J_{8\alpha,9\alpha}$ = 3.5; $J_{8\alpha,9\beta}$ = 11)
8β			1.88 dddd ($J_{7,8\beta}$ = 5; $J_{8\alpha,8\beta}$ = 13.5; $J_{8\beta,9\alpha}$ = 3.5; $J_{8\beta,9\beta}$ = 4)
9α	5.48 dd ($J_{8,9}$ = 12; $J_{9,10}$ = 1.5)	1.96 ddd ($J_{8,9\alpha}$ = 3.5; $J_{9\alpha,9\beta}$ = 12; $J_{9\alpha,10}$ = 11)	1.76 dddd ($J_{8\alpha,9\alpha}$ = $J_{8\beta,9\alpha}$ = 3.5; $J_{9\alpha,9\beta}$ = 13; $J_{9\alpha,10}$ = 1.5)
9β		1.91 ddd ($J_{8,9\beta}$ = 8; $J_{9\alpha,9\beta}$ = 12; $J_{9\beta,10}$ = 3.5)	2.03 dddd ($J_{8\alpha,9\beta}$ = $J_{9\beta,10}$ = 11; $J_{8\beta,9\beta}$ = 4; $J_{9\alpha,9\beta}$ = 13)
10	4.11 brs	3.78 dd ($J_{9\alpha,10}$ = 11; $J_{9\beta,10}$ = 3.5)	3.28 dd ($J_{9\alpha,10}$ = 1.5; $J_{9\beta,10}$ = 11)
12	1.32* s	1.25* s	1.27 s
13	1.30* s	1.19* s	1.27 s
14	1.43 d ($J_{7,14}$ = 7.5)	5.10 d ($J_{7,14}$ = 10.5)	1.27 d ($J_{7,14}$ = 7)
14′		5.02 d ($J_{7,14'}$ = 17)	
15	2.19 s	2.16 s	2.15 s

*These values may be interchanged.

Table 2. ^{13}C NMR Data (100 MHz) for Heliannuols B-D (2–4) ($CDCl_3$)[a]

C	2	3	4
1	138.3 s	134.9	138.0
2	150.0 s	151.0	151.5
3	114.8 d	126.2	123.5
4	122.6 s	122.2	122.2
5	125.6 s	131.1	149.7
6	124.0 d	114.7	115.7
7	39.6 d	139.7	38.4
8	133.8 d	41.7	31.7 t
9	125.6 d	36.0 t	26.0
10	87.3 d	74.7	90.4
11	72.4 s	79.7	72.8
12	25.2* q	26.7*	25.5*
13	24.6* q	22.0*	24.3*
14	23.2 q	115.3 t	18.6 q
15	29.7 q	15.3	15.3

[a]Degree of protonation and assignments were obtained by ^{1}H–^{13}C NMR correlations; multiplicities are not repeated if identical with those in the preceding column. *These values may be interchanged.

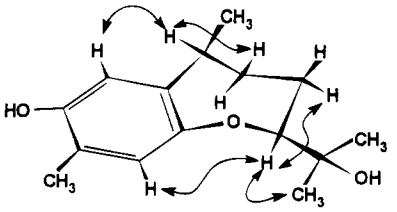


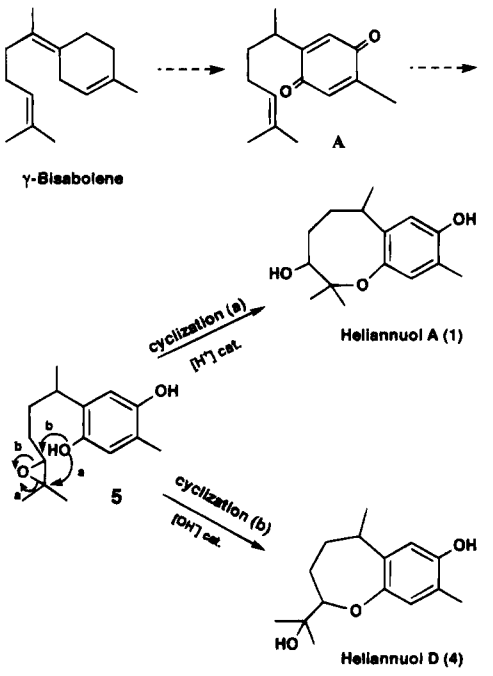
Figure 2. Observed NOEs for the most stable conformer of heliannuol D (**4**) using PM3 calculations.

These results are in agreement with the fact that heliannuol D (**4**) can be obtained by dilute basic treatment of heliannuol A (**1**). Treatment of **1** with aqueous 5% NaOH which was kept for 24 h at room temperature gave heliannuol D(**4**), presumably via the epoxide **5** (Scheme 2).

The third compound, heliannuol B (**2**), was obtained as a colorless oil. Its HRMS spectrum, with a molecular ion at 248.1412, suggests a sesquiterpene with six degrees of unsaturation, according with the molecular formula $C_{15}H_{20}O_3$.

These data and those obtained from the ^{1}H and ^{13}C

Scheme 1. Proposed Biogenesis of Heliannuols A and D



NMR spectra (Tables 1 and 2) suggest an heliannuol skeleton for this compound, with an additional double bond. The presence of two new signals due to vinylic protons in the ^{1}H NMR spectrum at δ 5.97 (dd, $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 12 Hz; H-8) and δ 5.48 (dd, $J_{8,9}$ = 12 Hz, $J_{9,10}$ = 1.5 Hz; H-9) and two olefinic signals belonging to C-8 (δ 133.8, d) and C-9 (δ 125.6, d) in the ^{13}C NMR spectrum confirmed this fact. The position of this double bond is inferred from the signal multiplicities and the following series of coupling protons in the ^{1}H NMR 2D COSY spectrum: H-10 (δ 4.11; brs) with H-9 (δ 5.48; dd; $J_{8,9}$ = 12 Hz, $J_{9,10}$ = 1.5 Hz); H-9 with H-8 (δ 5.95; ddd; $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 12 Hz); H-8 with H-7 (δ 3.15; dq; $J_{7,14}$ = $J_{7,8}$ = 7.5 Hz); as well as H-7 with H-14 (δ 1.43; d; $J_{7,14}$ = 7.5 Hz).

The sharp signals observed in its ^{1}H NMR spectrum at room temperature suggest that this compound is

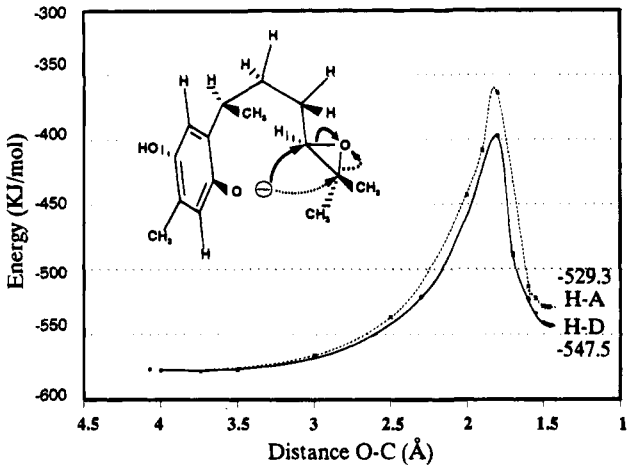
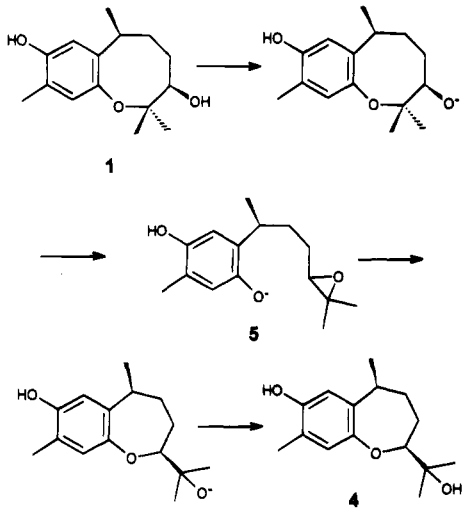


Figure 3. Energy profile on the formation of heliannuols A (**1**) and D (**2**) via base-catalyzed opening of the oxirane **5** using PM3 calculations.

Scheme 2. Proposed Mechanism on the Transformation of Heliannuol A (1) into Heliannuol D (4)



related to **4**, rather than **1**, which has a seven-membered ring in its structure. A similar relative stereochemistry is assigned to **2** based on the NOE difference experiments (Figure 4). The chemical correlation between heliannuol B (**2**) and **4** by the treatment of **2** with H_2 and $Pd/BaSO_4$ as catalyst, which provides **4**, confirms the stereostructure **2** proposed for heliannuol B (Scheme 3).

Heliannuol C (**3**) was isolated as a colorless oil. Its HRMS gave a molecular ion at *m/z* 248.1421, corresponding to $C_{15}H_{22}O_3$. The ^1H and ^{13}C NMR spectra of **3** indicate that it is another member of this sesquiterpene family, with a similar substitution pattern at the aromatic ring: δ 6.70 (s, H-3), 6.50 (s, H-6), 2.15 (s, 3H, H-15) in the ^1H NMR spectrum, and δ 134.9 (s, C-1), δ 151.0 (s, C-2), δ 126.2 (d, C-3), 122.2 (s, C-4), 131.1 (s, C-5), 114.7 (d, C-6) in the ^{13}C NMR spectrum. The ^1H NMR spectrum shows three vinylic protons in an ABC system in accordance with the presence of a vinyl group in the molecule.

A 2D COSY study showed the following series of coupled protons for the largest ring: H-14 (δ 5.10; brd; $J_{7,14}$ = 10.5 Hz) and H-14′ (δ 5.02; brd; $J_{7,14'}$ = 17 Hz) to H-7 (δ 6.06; ddd; $J_{7,8}$ = 7.5 Hz; $J_{7,14}$ = 10.5 Hz; $J_{7,14'}$ = 17 Hz); H-7 with H-8 (δ 3.57; dddd; $J_{6,8}$ = 1 Hz; $J_{7,8}$ = 7.5 Hz; $J_{8,9\alpha}$ = 3.5 Hz; $J_{8,9\beta}$ = 8 Hz); H-8 with H-9α (δ 1.96; ddd; $J_{8,9\alpha}$ = 3.5 Hz; $J_{9\alpha,9\beta}$ = 12 Hz; $J_{9\alpha,10}$ = 11 Hz) and H-9β (δ 1.91; ddd; $J_{8,9\beta}$ = 8 Hz; $J_{9\alpha,9\beta}$ = 12 Hz; $J_{9\beta,10}$ = 3.5 Hz); and finally H-9 and H-9′ with H-10 (δ 3.78; dd; $J_{9\alpha,10}$ = 11 Hz; $J_{9\beta,10}$ = 3.5 Hz). This correlation and the presence of only one proton at the C-8 position implied that the second ring is closed at that position in this compound. This is further substantiated by the well-resolved ^1H NMR spectrum obtained at room temperature. The ^{13}C NMR spectrum of heliannuol C (**3**) was assigned with the aid of heteronuclear multipulse APT experiments, 2D ^1H-COSY, and $^1H-^{13}C$ correlations. The functional oxygen group attached at C-10 was established as an hydroxyl group based on the ^{13}C NMR data. A direct comparison of the chemical shift corresponding to C-10 (δ 74.7) and C-11 (δ 79.7) for **3** and those of **1** [C-10 (δ 74.7, d); C-11 (δ 79.7, s)] and **4** [C-10 (δ 90.4, d); C-11 (δ 72.8, s)] is in good agreement with a seven-membered ring closed at C-11 supporting a hydroxyl group at C-10.

There are two possibilities of stereochemistry for **3** represented as isomers A and B (Figure 5) with the most stable conformations obtained using PM3 calculations. Only isomer A stereostructure can explain the observed NOEs (Figure 5).

The biosynthesis of **3** cannot be easily accommodated by the isoprene rule, but it is reasonable to propose that the seven-membered ring might be derived from an intermediate precursor containing both a double bond at C-8–C-9 and an eight-membered ring (Scheme 4), protonation of which may generate a carbocation at the C-8 position[13] that would transform into the corresponding oxonium ion (**6**) by transannular participation of the ether oxygen. This can be rearranged to the cation (**8**) via a phenonium ion (**7**). Further deprotonation of this carbocation could yield helianuuol C.

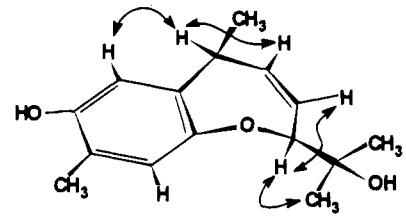
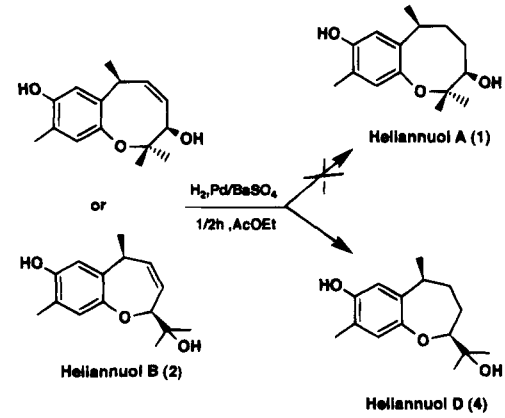


Figure 4. Observed NOEs for the most stable conformer of heliannuol B (**2**) using PM3 calculations.

Scheme 3. Chemical Correlation of Heliannuol B (2) and Heliannuol D (4)



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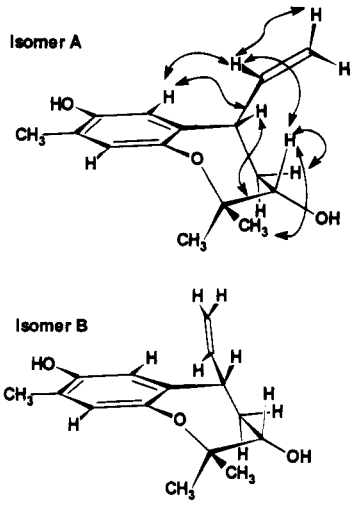
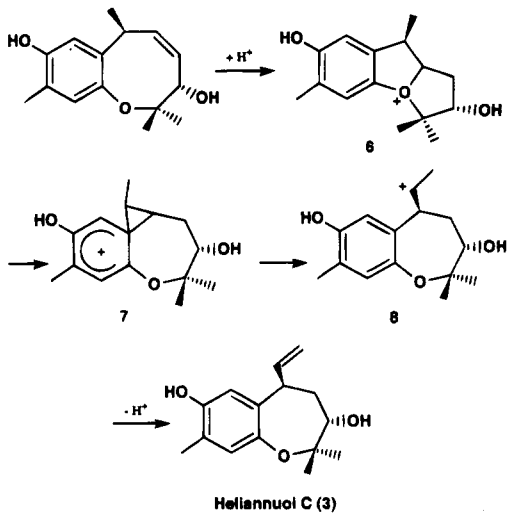


Figure 5. Observed NOEs for the more stable conformations of the two possible isomers of heliannoul C (**3**), using PM3 calculations.

Scheme 4. Biogenetic Hypothesis for Heliannuol C



This proposal was evaluated using PM3 calculations, and the energy profile obtained (Figure 6) shows a very short energetic barrier between the hypothetical phenonium ion and the subsequent cation. Nevertheless, this profile might be substantially different in polar solution, which should promote the aryl participation.[14]

Heliannuols A-D (**1**–**4**) represent relatively unusual structures of particular interest since these are the first members of a new class of bioactive sesquiterpenes. When heliannuols A-D were tested for allelopathic activity against dicotyledon species (*Lactuca sativa* and *Lepidium sativum*) and monocotyledon species (*Hordeum vulgare* and *Triticum aestivum*) in a range of 10^{-4}–10^{-9} M concentration, significant bioactivity was found, particularly for compounds **1** and **4**.[8e] These results suggest that compounds **1**–**4** may be significantly involved in the cultivar sunflower (*Helianthus annuus*) defense against dicotyledon species. Consequently, they are excellent candidates to be used as a natural herbicides models with certain specificity against dicotyledon species.

(14) Schadt, F. L., III; Lancelot, C. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1978**, *100*, 228–246.

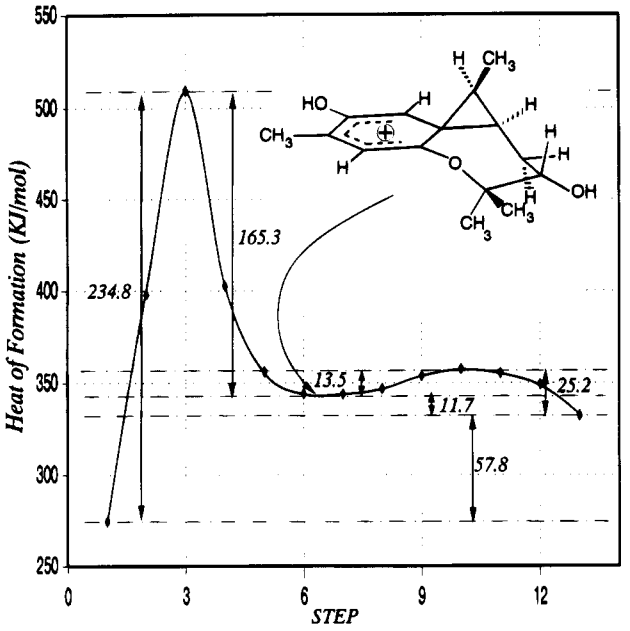


Figure 6. Energy profile of cationic transformation on the formation of heliannuol C (**3**) via phenonium ion using PM3 calculations.

Experimental Section

Plant Material. Leaves of *H. annuus* L. var. SH-222 and VYP commercialized by "Semillas Pacífico" and KOIPE (Spain), respectively, were collected in August 1991 during the third plant development stage (plant 1.2 m tall with flowers, 1 month before harvest) and were provided by Rancho de la Merced, Agricultural Research Station, Junta de Andalucía, Jerez, Spain.

Extraction and Isolation. Fresh leaves (6.0 kg) were soaked in H_2O (weight plant:vol. solvent 1:3) for 24 h at 25 °C in the dark. The H_2O extracts were extracted (×8) with 0.5 L of CH_2Cl_2 for each 1.0 L of H_2O, and the combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to yield 16.0 g of crude extract termed H_2O–CH_2Cl_2 extract which was separated by column chromatography on silica gel using hexane–EtOAc mixtures of increasing polarity yielding 170 × 50 mL fractions, which were reduced to 17 fractions after comparison by TLC.

Following bioactive evaluation, hexane:EtOAc 9:1 and 8:2 fractions were selected and chromatographed using Merck-Hitachi L-6200A HPLC with a Hibar Si60 (Merck) column, hexane:EtOAc mixtures as eluent, and 4 mL min^{-1} flow rate. Heliannuols B (**2**) (0.1% from SH-222 and 0.3% from VYP) and D (**4**) (0.5% from SH-222 and 0.1% from VYP) were obtained from the first fraction, and heliannuols A (**1**) (1% from SH-222 and 0.5% from VYP) and C (**3**) (0.2% from SH-222 and 0.2% from VYP) from the second one. Yields of pure compounds are referred to the CH_2Cl_2 extract.

Heliannuol B (2): colorless oil, $[\alpha]^{25}_D$ −18° (*c* 0.10, $CHCl_3$); $[\alpha]^{25}_D$ −15° (*c* 0.10, MeOH); IR ν_{max} (neat, KBr) cm^{-1}: 3401 (hydroxyl group), 1638 (aromatic and double bond), 1257 (ether); ^1H and ^{13}C NMR are listed in Tables 1 and 2; EIMS *m/z* (rel intensity) 248 (31), 230 (6), 215 (40), 190 (68), 175 (70), 161 (36); HREIMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1412.

Heliannuol C (3): colorless oil; $[\alpha]^{25}_D$ −38° (*c* 0.10, $CHCl_3$); $[\alpha]^{25}_D$ −51° (*c* 0.10, MeOH); IR ν_{max} (neat, KBr) cm^{-1} 3400 (hydroxyl group), 1628 (aromatic and double bond), 1257 (ether); ^1H and ^{13}C NMR are listed in Tables 1 and 2; EIMS *m/z* (rel intensity) 248 (45), 230 (24), 215 (34), 205 (40),187 (26), 175 (33), 163 (85), 161 (100); HREIMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1421.

Heliannuol D (4): colorless crystals; mp 59–61 °C ($CHCl_3$); $[\alpha]^{25}_D$ +16° (*c* 0.10, $CHCl_3$); $[\alpha]^{25}_D$ +18° (*c* 0.10, MeOH); IR ν_{max} (neat, KBr) cm^{-1} 3387 (hydroxyl group), 1617 (aromatic and

double bond), 1263 (ether); ^1H and ^{13}C NMR are listed in Tables 1 and 2; EIMS *m/z* (relative intensity) 250 (42), 232 (5), 217 (9), 191 (28), 163 (20), 152 (22), 151 (100); HREIMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1575.

Preparation of Heliannuol D (4) from Heliannuol A (1). Heliannuol A (**1**) (4 mg) was dissolved In 5 mL of 5% aqueous NaOH and the mixture stirred at room temperature for 24 h. The mixture was quenched with 1% aqueous HCl to pH 7 and extracted with $CHCl_3$ (×4). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude products showed two major components which after separation using preparative TLC with hexane:EtOAc (8:1) afforded **1** (1 mg) and **4** (3 mg).

Preparation of Heliannuol D (4) from Heliannuol B (2). Heliannuol B (**2**) (2 mg) was dissolved in 3 mL of freshly distilled EtOAc and stirred continuously at room temperature for 30 min under hydrogen atmosphere with a small amount of $Pd/BaSO_4$ (1 mg). After the usual workup, 1 mg of **4** was obtained.

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Supplementary Material Available: Copies of NMR spectra and ORTEP (12 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.