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Synthesis of heliannane skeletons. Facile preparation of (±)-heliannuol D☆

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Abstract—Heliannuol D is a natural product with a 7,10-heliannane skeleton, isolated from *Helianthus annuus*. It has been synthesized in eight steps, in good yield, using a new biomimetic method. Key steps were a Fries rearrangement, a Grignard reaction and, finally, a base catalyzed cyclization.

1. Introduction

Allelochemicals are an important potential source for new herbicides and agrochemicals, since they offer new modes of action, more specific interaction with weed and less environmental damage.[2]

Between the many organisms from which allelopathic agents have been isolated (mainly plants and micro-organisms), *Helianthus annuus* L. (sunflower), is one of the most interesting ones, because of its high production of secondary metabolites, especially terpenes and phenolic compounds, including sesquiterpene lactones, heliespirones, annuionones, helibisabonols, and heliannuols.[3]

Heliannanes constitute a novel heterocyclic sesquiterpene structural type isolated from *H. annuus*[4a] and from the Indo-pacific sponge *Haliclona fascigera*.[5] Their skeleton has a benzenoid moiety fused to a six, seven, or eight-membered heterocyclic ring (Fig. 1).[6]

Heliannuols, new compounds isolated from *H. annuus*, with the heliannane skeleton, constitute an interesting family of new compounds belonging to the four structural types mentioned above. Heliannuols A, D and E[7] (Fig. 2), have special relevance, due to the high phytotoxic activity shown by them.[4b]

The fact that these allelochemicals can take part in new strategies for weed control, makes very interesting their large scale synthesis, in order to test them in suitable bioassays, evaluate their modes of action and propose them as new herbicide models. The synthetic analogs obtained in their synthesis research are also interesting, since their bioactivity results can offer hints about the structural requirements for bioactivity.

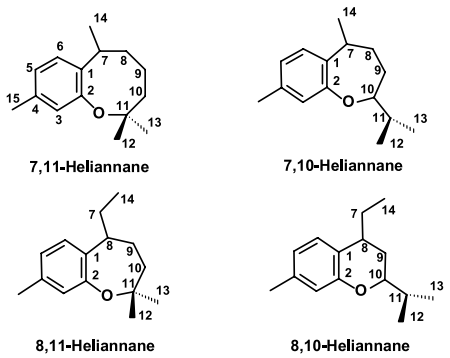

Figure 1. Heliannane skeleton types.

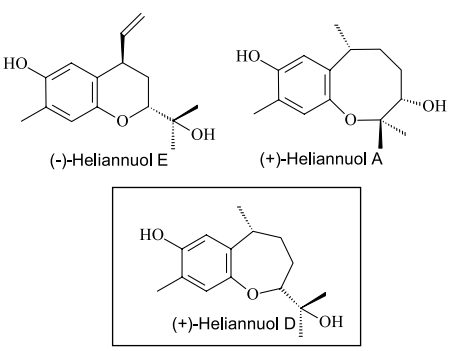

Figure 2. Heliannuols E, A and D.

☆ See Ref. 1.

Keywords: heliannane skeleton; *Helianthus annuus*; heliannuol; allelochemicals; synthesis of sesquiterpenes.

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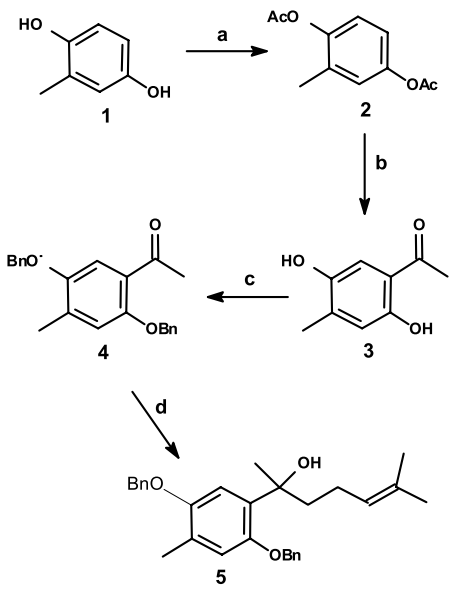


Scheme 1. *Reagents and conditions*: (a) $(CH_3CO)_2O$, Py (quantitative, 24 h, room temperature); (b) $BF_3{\cdot}Et_2O$, (quantitative, 3 h, 120°C); (c) benzyl bromide, K_2CO_3, dimethoxyethane (quantitative, 12 h, 80°C); (d) 5-Br-2-methyl-2-pentene, Mg, I_2, THF_{dry} (81%, 1 h, 65°C).

Several synthesis procedures for members of the heliannuols have been reported.[7] Herein we present an easy and efficient route to obtain (±)-Heliannuol D. This synthesis procedure is based on a proposed biosynthetic hypothesis.[6]

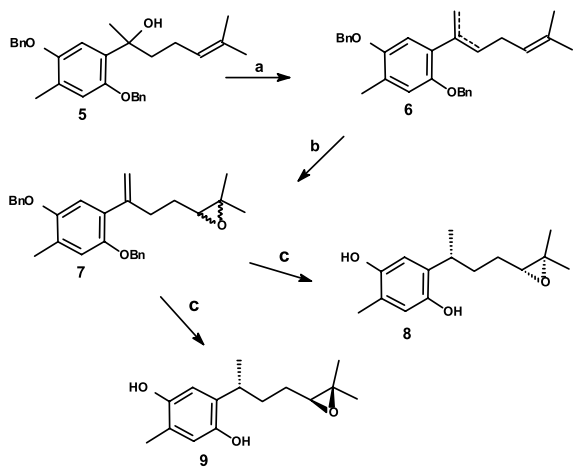
2. Results and discussion

The synthesis procedure described here has two main stages: obtention of the appropriate aromatic bisabolene skeleton from a benzenoid compound with the desired substitution pattern, and cyclization to obtain the benzoxepane moiety.

The synthesis starts (Scheme 1) with the preparation of the appropriate aromatic bisabolene skeleton **5**, as a first key step, using 2-methylhydroquinone (**1**). The desired substitution pattern in the aromatic ring (**3**) was obtained in quantitative yield by an *ortho*-Fries rearrangement[8a] of the diacetyl derivative of 2-methyl-hydroquinone (**2**), carried out at high temperature (120°C) in order to force an intramolecular reaction mechanism to give the *ortho* regioisomer.

This reaction have been used in other aromatic 1,4-diesters with similar results,[8b,c] involving the cleavage of the non-rearranged ester to yield 2,5-dihydroxyphenyl-alkyl ketones.

The hydroxyl groups of **3** were protected to produce the corresponding benzyl derivative (**4**) that was linked to the side-chain by a Grignard reaction that leads to condensation product **5** in an 81% yield after 1 h. This good yield was not observed at reaction temperatures below +65°C, probably due to the high steric hindrance provided by benzyl moiety in position C-2. A similar procedure for side-chain linkage has been used in curcuphenol synthesis procedure reported

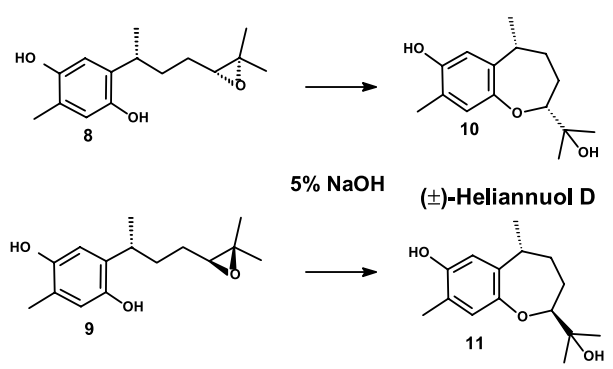


Scheme 2. *Reagents and conditions*: (a) $KHSO_4$, *N*,*N*-dimethylformamide (quantitative, 2 h, 90°C); (b) *m*-CPBA, $KHCO_3$ aq (75%, 2 h, room temperature); (c) H_2/Pd/C, *N*,*N*-dimethylformamide (quantitative, 2 h, room temperature).

by McEnroe and Fenical,[9] and for the obtention of fungal sesquiterpene sydonic acid.[10] Recently, this synthetic pathway has been adapted for the obtention of (±)-helibisabonol A,[3c] a new bisabolenic sesquiterpene from *H. annuus* isolated in our laboratory.[11]

Once the bisabolene skeleton obtained, we introduced an epoxide moiety between positions C-10 and C-11, being necessary to eliminate the tertiary hydroxyl group on **5** first (Scheme 2). The dehydration was carried out with $KHSO_4$ in *N*,*N*-dimethylformamide. This elimination procedure has not been widely used, although $KHSO_4$ has been described as a useful reagent for dehydration in the synthesis of some germacrane derivatives.[12] This treatment yielded the mixture of olefins **6** quantitatively. Further treatment of this mixture with MCPBA in a biphasic system CH_2Cl_2/$KHCO_3$ (aq), allowed us obtain compound **7** in 75% yield. This epoxidation method was chosen to avoid possible rearrangements in species sensitive to acid.[13]

Hydrogenation of **7**, catalyzed by Pd/C, provides cleavage of the benzylic ethers and reduction of the conjugated double bond. This reduction yielded the pair of diastereoisomers **8** and **9** in quantitative yield. Finally, cyclization of epoxides **8** and **9** using NaOH 5% (24 h) led us to obtain the



Scheme 3. Base-catalyzed cyclization to obtain both epimers of (±)-heliannuol D.

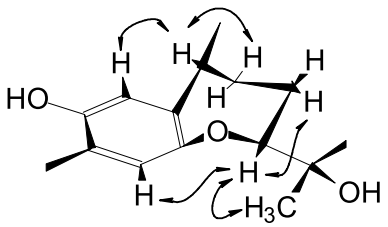


Figure 3. NOEs observed for the most stable conformer of heliannuol D, using PM3 calculations.

corresponding heliannanes **10** and **11**, respectively, in quantitative yield (Scheme 3).

NOEs observed for **10** are in good agreement with the most stable conformer found for heliannuol D by PM3 calculations (Fig. 3), assuming a (7*S*,10*S*) relative configuration (the same as the natural product). Moreover, the exact match of chemical shifts and coupling constants for all proton/carbon resonances between **10** and heliannuol D isolated from *H. annuus* allowed us to identify this synthetic product as the natural epimer.[4]

We want to note that due to a typographic mistake, the mp first reported for natural heliannuol D[4a] was wrong, as indicated by Vyvyan and Looper.[7c] We would like to confirm that the real mp value for the natural product is 159–161°C.

3. Conclusion

In conclusion, we have developed an efficient route (60.7% of overall yield) for the synthesis of (±)-heliannuol D. Further modifications of this procedure would lead us to 7,10-heliannane and several members of this family, and to prepare new synthetic analogs of their hypothetical biogenetic origin.[4] Current efforts in our laboratory are directed toward the development of the asymmetric synthesis of this family of bioactive compounds.

4. Experimental

4.1. General

Commercially available chemicals were used as received. Dry THF was obtained by distillation from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a Varian Unity 400 NMR Spectrometer with a sample temperature of 25°C using $CDCl_3$ as solvent and TMS as internal reference. Mass spectroscopy was carried out using a GC-MS VG1250 apparatus (ion trap detector) in EI mode. FTIR spectra were recorded on a Mattson 5020 spectrometer and UV–VIS spectra were obtained with a Phillips PU 8710 spectrometer. Elemental analysis was carried out in a LECO CHNS apparatus. Mps of both epimers of (±)-heliannuol D were determined on a Büchi Melting Point B-545 apparatus. Purities of synthesized compounds were determined by NMR and HPLC methods, and corroborated by HRMS and elemental analysis when appropriate.

4.2. Synthesis of compound 5

4.2.1. 2,5-Diacetoxytoluene (2). To 5 g of 2-methylhydroquinone (**1**) in 25 mL of pyridine, an excess (1:5, 21 mL) of acetic anhydride $(CH_3CO)_2O$ was added. It was further stirred at room temperature during 12 h. After this, 30 mL of AcOEt was added and the mixture was washed with a saturated solution of $CuSO_4$. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to obtain the acetylated derivative **2** in quantitative yield, with no need of chromatographic purification; IR (film, cm^{-1}) ν_{max}: 3066, 1765, 1211; UV (MeOH, nm) λ_{max}: 208.8; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H, Me-7), 2.24* (s, 3H, Me-9′), 2.28* (s, 3H, Me-9), 6.90 (dd, J=8.5, 2.7 Hz, 1H, H-4), 6.97 (d, J=2.7 Hz, 1H, H-6), 6.99 (d, J=8.5 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.12 (C-7), 20.56* (C-9), 20.88* (C-9′), 117.79 (C-1), 119.69 (C-4), 122.52 (C-3), 126.76 (C-6), 131.34 (C-1), 147.92 (C-2), 169.01* (C-8), 169.34* (C-8′); (*values may be interchanged); HRMS calculated for $C_{11}H_{12}O_4$ 208.0735, found 208.0740. Analysis calculated for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.52; H, 5.79.

4.2.2. 2,5-Dihydroxy-4-methylacetophenone (3). 5 g of 2,5-diacetoxytoluene (**2**) were added to a solution of 21 mL (excess 1:5) of boron trifluoride dihydrate ($BF_3{\cdot}2H_2O$) and stirred during 4 h at 130°C. Then, the solution was cooled to 0°C by addition of ice and the mixture extracted with AcOEt (4×30 mL). The organic layers was dried over anhydrous Na_2SO_4, evaporated and filtered over silica gel to obtain **3** in quantitative yield with no need of further purification; IR (film, cm^{-1}) ν_{max}: 3316, 1610, 1200; UV (MeOH, nm) λ_{max}: 232.0; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H, Me-9), 2.48 (s, 3H, Me-8), 6.79 (s, 1H, H-3), 7.03 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.87 (C-9), 26.79 (C-8), 112.92 (C-6), 115.07 (C-3), 117.79 (C-1), 126.09 (C-5), 146.26 (C-4), 156.87 (C-2), 203.68 (C-7); HRMS calculated for $C_9H_{10}O_3$ 166.0629, found 166.0645. Analysis calculated for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.18; H, 6.11.

4.2.3. 2,5-Dibenzyloxy-4-methylacetophenone (4). To a solution of **3** (2.5 g) in dimethoxyethane (30 mL) was added K_2CO_3 (8 g), under nitrogen and the solution was stirred to 80°C in N_2 atmosphere. Then, 2.2 equiv. (3.8 mL) of benzyl bromide and 500 μL of dry *N*,*N*-dimethylformamide were added. The reaction was stirred during 12 h in these conditions and then was quenched with water and extracted 3 times with AcOEt. The organic phases were joined and dried over anhydrous Na_2SO_4 and evaporated the solvent to give crude which was chromatographed (hexane/AcOEt 20%). The desired product 2,5-dibenzyloxy-4-methylacetophenone (**4**) was obtained in 95% of yield. No chromatographic procedures for isolation of the pure product; IR (film, cm^{-1}) ν_{max}: 2911, 1606, 1218; UV (MeOH, nm) λ_{max}=206.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H, Me-9), 2.63 (s, 3H, Me-8), 5.09* (s, 2H, H-7′), 5.13* (s, 2H, H-7′), 6.91 (s, 1H, H-3), 7.40 (m, 10H, protecting group), 7.46 (s, 1H, H-6), (*values may be interchanged); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.83 (C-9), 32.21 (C-8), 112.48 (C-3), 115.97 (C-6), 125.74 (C-1), 152.82 (C-5), 137.10 (C-4), 150.84 (C-2), 203.68 (C-7), Protecting groups: 70.26 (C-7′*), 71.21 (C-7″*), 127.15 (C-2′), 127.15 (C-2″), 127.15 (C-6′), 127.51 (C-6″), 127.69

(C-4′), 127.92 (C-4″), 128.47 (C-3″), 128.47 (C-5″), 128.53 (C-3′), 128.53 (C-5′), 134.08 (C-1′), 137.10 (C-1″), (*values may be interchanged); HRMS calculated for $C_{11}H_{12}O_4$ 346.1569, found 346.1560. Analysis calculated for $C_{11}H_{12}O_4$: C, 79.74; H, 6.40. Found: C, 79.85; H, 6.43.

4.2.4. 2-*O*,5-*O*-Dibenzyl-7-hydroxycurcuhydroquinone (5). 300 mg of magnesium are stirred overnight in N_2 atmosphere with a catalytic amount of I_2 at room temperature. Then, 40 mL of dry THF were added to the mixture at 65°C. 387 μL of 5-bromo-2-methyl-2-pentene were added and then the color of the reaction changes from orange to uncolored. After 30 min, it was added 500 mg of 2,5-dibenzyloxy-4-methylacetophenone (**4**) and the reaction was stirred during 90 min, then it was filtered and 40 mL of water was added. The reaction was extracted with AcOEt (4×). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The mixture was chromatographed (hexane/Ethyl ether 20%). **5** was obtained in 81% yield.; IR (film, cm^{-1}) ν_{max}: 3446, 2960, 2924, 1506, 1198, 1035; UV (MeOH, nm) λ_{max}: 208.8; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50* (s, 3H, Me-12), 1.55 (s, 3H, Me-14), 1.65* (s, 3H, Me-13), 1.85 (m, 1H, H-9a), 1.85 (m, 1H, H-9b), 1.85 (m, 1H, H-8a), 2.02 (m, 1H, H-8b), 2.27 (s, 3H, Me-15), 5.05* (s, 1H, H-7′), 5.07* (s, H, H-7″), 6.82 (s, 1H, H-3), 6.94 (s, 1H, H-6) (*values may be interchanged), 7.40 (m, 10H, protecting group); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.15 (C-12), 17.58 (C-13), 23.29 (C-15), 25.65 (C-9), 27.72 (C-14), 42.07 (C-8), 71.04 (C-7′), 71.07 (C-7″), 75.10 (C-7), 112.08 (C-3), 115.44 (C-6), 124.56 (C-1), 127.28 (C-2′*), 127.28 (C-6′*), 127.52 (C-2″*), 127.52 (C-6″*), 127.71 (C-4′*), 128.09 (C-4″*), 128.43 (C-3′*), 128.43 (C-5′*), 128.68 (C-3″*), 128.68 (C-5″*), 133.11 (C-4), 136.70 (C-1′*), 137.61 (C-1″*), 149.85 (C-5), 150.81 (C-2); HRMS calcd for $C_{29}H_{34}O_3$ 430.2508, found 430.2508. Analysis calculated for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96; Found: C, 80.79; H, 7.92.

4.3. Synthesis of (±)-heliannuol D

4.3.1. $\Delta^{7,14}$-2-*O*,5-*O*-Dibenzyl-curcuhydroquinone (6a) and $\Delta^{7,8}$,2-*O*,5-*O*-dibenzyl-curcuhydroquinone (6b). 500 mg of **5** were dissolved in 10 mL of *N*,*N*-dimethylformamide, 174 mg of $KHSO_4$ were added and the mixture was stirred during 1 h at 80°C. Then, 25 mL of AcOEt were added and washed 6 times with water to eliminate the solvent. After low pressure evaporation, the residue was chromatographed (2% AcOEt/hexane) to obtain the desired products **6** were obtained quantitatively; UV (MeOH, nm) ν_{max}: 212.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66* (s, 3H, Me-12), 1.80* (s, 3H, Me-13), 2.20 (m, 2H, H-8a), 2.40 (s, 6H, Me-14b, Me-15), 2.70 (m, 2H, H-9a), 3.01 (m, 2H, H-9b), 5.08 (s, 2H, H-14a), 5.12 (s, 2H, H-14a′), 5.21* (s, H, H-7″), 5.25 (m, 1H, H-10a), 5.28* (s, 1H, H-7′), 5.36 (m, 1H, H-10b), 5.61 (m, 1H, H-8b), 6.89 (s, 1H, H-3), 6.91 (s, 1H, H-6) (*values may be interchanged), 7.50 (m, 10H, protecting group). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 16.19 (C-15a), 16.25 (C-15b), 17.71 (C-13), 25.62 (C-14b), 26.73 (C-12), 27.46 (C-9b), 36.47 (C-9a), 113.90 (C-14a) 114.40 (C-8b), 122.70 (C-3a), 124.22 (C-3b), 126.62 (C-10b), 128.27 (C-10a), 130.50 (C-8b), 131.13 (C-6a), 131.58 (C-6b), 149.65 (C-5b), 150.03 (C-2b), 150.89 (C-5a), 150.89 (C-2a). HRMS calculated for $C_{29}H_{32}O_2$ 412.2402, found 412.2410. Analysis calculated for $C_{29}H_{32}O_2$: C, 84.43; H, 7.82. Found: C, 84.45; H, 7.89.

4.3.2. $\Delta^{7,14}$,2-*O*,5-*O*-Dibenzyl-10,11-epoxycurcuhydroquinone (7). 500 mg of **6** were dissolved in 20 mL of CH_2Cl_2, and then 20 mL of $KHCO_3$ aq. were added close to an excess 1:1.2 of MCPBA. The mixture was stirred during 2 h at room temperature and then washed with NaOH aq. (0.5 M) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, evaporated and chromatographed (hexane/ethyl ether 20%) to obtained **7** in 74% yield. IR (film, cm^{-1}) ν_{max} 2963, 1609, 1250; UV (MeOH, nm) 206.4 λ_{max}: 224.2; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17* (s, 3H, Me-13), 1.24* (s, 3H, Me-12), 1.59 (m, 2H, H-9), 2.34 (s, 3H, Me-15), 2.68 (m, 1H, H-8a), 2.68 (dd, *J*=7.2, 7.2 Hz, 1H, H-10), 5.06 (s, 2H, H-7′), 5.08 (s, 2H, H-7″), 5.08 (d, *J*=1.4 Hz, 1H, H-14a′), 5.15 (d, *J*=1.4 Hz, 1H, H-14a), 6.73 (s, 1H, H-3), 6.80 (s, 1H, H-6), 7.43 (m, 10H, protecting group). (*values may be interchanged); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.31 (C-15), 24.79 (C-13), 24.81 (C-12), 27.62 (C-9), 33.31 (C-8), 58.21 (C-11), 64.01 (C-10), 70.87 (C-7″), 71.49 (C-7′), 114.54 (C-14), 114.61 (C-6), 116.43 (C-3), 138.49 (C-1), 147.63 (C-4), 149.70 (C-5), 151.05 (C-2); HRMS calculated for $C_{29}H_{32}O_3$ 428.2351, found 428.2406. Analysis calculated for $C_{29}H_{32}O_3$: C, 81.27; H, 8.86. Found: C, 80.90; H, 8.82.

4.3.3. 10(*R),11-Epoxycurcuphenol (8) and 10(*S**),11-epoxycurcuphenol (9).** A catalytic amount of Pd/C was added a 200 mg of **7** solved in *N*,*N*′-dimethylformamide (DMF) and them a current of H_2 was bubbled. After 1 h stirring in these conditions, reaction was filtering; 25 mL of AcOEt were added and washed with water (×5) to eliminate DMF. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The mixture was chromatographed (hexane/AcOEt 10%) and then **8** and **9** were obtained in 57 and 43% yield, respectively. 10(*R**)-*Epoxycurcuphenol* (**8**). IR (film, cm^{-1}) ν_{max}: 3394, 2960, 2855, 1704, 1618; UV (MeOH, nm) λ_{max}: 223.9; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (m, 1H, H-9a), 1.21* (s, 3H, Me-12), 1.21 (d, *J*=6.8 Hz, 3H, Me-14), 1.32* (s, 3H, Me-13), 1.69 (m, 1H, H-9b), 1.72 (m, 1H, H-8a), 1.84 (m, 1H, H-8b), 2.27 (s, 3H, Me-15), 2.84 (dd, *J*=9.2, 3.2 Hz, 1H, H-10), 3.17 (ddq, *J*=6.8, 6.8, 4.4 Hz, 1H, H-7), 6.56 (s, 1H, H-3), 6.62 (s, 1H, H-6) (*values may be interchanged); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.01 (C-12), 18.58 (C-15), 20.89 (C-14), 24.75 (C-13), 25.85 (C-9), 31.12 (C-7), 32.98 (C-8), 58.88 (C-11), 66.01 (C-10), 113.54 (C-3), 117.92 (C-6), 121.57 (C-1), 132.02 (C-4), 146.23 (C-5), 148.03 (C-2); HRMS calcd for $C_{15}H_{22}O_3$ 250.1568, found 250.1562; 10(*S**)-*Epoxycurcuphenol* (**9**). IR (film, cm^{-1}) ν_{max}: 3413, 2959, 2853, 1692, 1614; UV (MeOH, nm) λ_{max}: 224.2; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J*=6.9 Hz, 3H, Me-14), 1.20* (s, 3H, Me-12), 1.28* (s, 3H, Me-13), 1.47 (m, 2H, H-9), 1.60 (m, 1H, H-8a), 1.75 (m, 1H, H-8b), 2.13 (s, 3H, Me-15), 2.75 (dd, *J*=6.2, 6.2 Hz, 1H, H-10), 3.05 (ddq, *J*=6.9, 6.9, 6.4 Hz, 1H, H-7), 6.52 (s, 1H, H-3), 6.55 (s, 1H, H-6) (*values may be interchanged); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.34 (C-12), 18.58 (C-15), 20.92 (C-14), 24.78 (C-13), 26.67 (C-9), 31.76 (C-7), 33.59 (C-8), 58.81 (C-11), 64.69 (C-10), 113.48 (C-3), 117.90 (C-6), 121.94 (C-1), 131.31 (C-4), 146.89 (C-5), 148.02 (C-2); HRMS calculated for $C_{15}H_{22}O_3$ 250.1568, found 250.1572.

Analysis calculated for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.76.

4.3.4. 10(S^*)-Heliannuol D (10) and 10(R^*)-heliannuol D (11). Stirring during 24 h at room temperature 200 mg of **8** in 10 mL of NaOH 1 M, permits to obtain after neutralization with HCl 1 M, extraction with AcOEt (×4) and low pressure evaporation, the heliannuol **10**, pure and in quantitative yield. The same procedure for **9** permits to obtain **11** in the same yield. Colorless crystals were obtained in both cases. 10(S^*)-*Heliannuol D* (**10**). IR (film, cm^{-1}) ν_{max}: 3360, 2955, 2930, 1614, 1256; UV (MeOH, nm) λ_{max}: 208.5, 276.7; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, 3H, Me-14), 1.21* (s, 3H, Me-12), 1.21* (s, 3H, Me-13), 1.74 (m, 1H, H-8b), 1.74 (m, 1H, H-9a), 1.82 (m, 1H, H-8a), 1.96 (m, 1H, H-9b), 2.21 (s, 3H, Me-15), 2.91 (ddq, J=9.8, 9.8, 7.2 Hz, 1H, H-7), 3.25 (dd, J=5.3, 3.5 Hz, 1H, H-10), 6.50 (s, 1H, H-3), 6.65 (s, 1H, H-6) (*values may be interchanged); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.31 (C-12), 18.52 (C-15), 24.37 (C-14), 25.41 (C-13), 25.80 (C-9), 31.74 (C-7), 38.45 (C-8), 72.56 (C-11), 90.31 (C-10), 115.47 (C-3), 122.48 (C-6), 123.34 (C-1), 137.76 (C-4), 150.154 (C-5), 151.11 (C-2); HRMS calculated for $C_{15}H_{22}O_3$ 250.1568, found 250.1553. Analysis calculated for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.99; H, 8.95. Mp 161–162°C (these data match exactly with those for natural heliannuol D). 10(R^*)-*Heliannuol D* (**11**). IR (film, cm^{-1}) ν_{max}: 3369, 2964, 2935, 1617, 1228; UV (MeOH, nm) λ_{max}: 208.0, 276.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29* (s, 3H, Me-12), 1.30* (s, 3H, Me-13), 1.34 (d, J=7.2 Hz, 3H, Me-14), 1.30 (m, 1H, H-8b), 1.93 (m, 1H, H-9a), 1.93 (m, 1H, H-8a), 1.93 (m, 1H, H-9b), 2.26 (s, 3H, Me-15), 3.03 (ddq, J=7.2, 7.2, 2.8 Hz, 1H, H-7), 3.30 (dd, J=11.2, 1.3 Hz, 1H, H-10), 6.55 (s, 1H, H-3), 6.61 (s, 1H, H-6) (*values may be interchanged); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.25 (C-12), 18.42 (C-15), 23.97 (C-14), 25.40 (C-13), 25.75 (C-9), 31.33 (C-7), 39.45 (C-8), 72.46 (C-11), 90.12 (C-10), 115.57 (C-3), 122.48 (C-6), 123.24 (C-1), 137.85 (C-4), 150.13 (C-5), 150.56 (C-2); HRMS calculated for $C_{15}H_{22}O_3$ 250.1568, found 250.1551. Analysis calculated for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.92. Mp 158–159°C.

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References

1. Part 14 in the series Natural products as Allelochemicals. For part 13 see: Macías, F. A.; Galindo, J. C. G.; Castellano, D.; Velasco, R. F. *J. Agric. Food Chem.* **2000**, *48*, 5288–5296.
2. (a) Vyvyan, J. R. *Tetrahedron* **2002**, *58*, 1631–1646. (b) Duke, S. O. *Rev. Weed Sci.* **1986**, *2*, 15–44. (c) Macías, F. A. In *Allelopathy: Organisms, Processes, and Applications. ACS Symposium Series, 582*; Inderjit, Dakshini, K. M. M., Einhellig, F. A., Eds.; ACS: Washington, DC, 1995; pp 310–329, Chapter 23. (d) Duke, S. O. In *The Science of Allelopathy*; Putnam, A. R., Tang, C. S., Eds.; Wiley: New York, 1986; pp 287–304, Chapter 17. (e) Duke, S. O.; Dayan, F. E.; Hernandez, A. *Proceedings of Weeds. The 1997 Brighton Crop Protection Conference*; Pallett, K. E., Ed.; British Crop Protection Council: Farnham, UK, 1997; Vol. 2, pp 579–586. (f) Rice, E. L. *Biological Control of Weeds and Plant Diseases*; University of Oklahoma Press: Norman, USA, 1995. (g) Waller, G. R.; Yamasaki, K. *Saponins used in Food and Agriculture. Advances in Experimental Medicine and Biology*; Plenum: New York, 1996; Vol. 405.
3. (a) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett.* **1998**, *39*, 427–430. (b) Macías, F. A.; Oliva, R. M.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Phytochemistry* **1999**, *52*, 613–621. (c) Macías, F. A.; Torres, A.; Galindo, J. L. G.; Varela, R. M.; Álvarez, J. A.; Molinillo, J. M. G. *Phytochemistry* **2002**, *61*, 687–692.
4. (a) Macías, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A. *J. Org. Chem.* **1994**, *59*, 8261–8266. (b) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Nat. Prod.* **1999**, *62*, 1636–1639.
5. Harrison, B.; Crews, P. *J. Org. Chem.* **1997**, *62*, 2646–2648.
6. Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Chem. Ecol.* **2000**, *26*, 2173–2186.
7. (a) Grim, E. L.; Levac, S.; Trimble, L. A. *Tetrahedron Lett.* **1994**, *35*, 6847–6850. (b) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808–2809. (c) Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151–1154. (d) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807–1808. (e) Sato, K.; Yoshimura, T.; Shindo, M.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309–314.
8. (a) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 2. pp 745–747. (b) Boyer, J. L.; Krum, J. E.; Myers, M. C.; Fazal, A. N.; Wigal, C. T. *J. Org. Chem.* **2000**, *65*(15), 4712–4714. (c) Rieck, J. A.; Grunwell, J. R. *J. Org. Chem.* **1980**, *45*, 3512–3513.
9. McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661–1664.
10. Hamasaki, T.; Nagayama, K.; Hatsuda, Y. *Agric. Biol. Chem.* **1978**, *42*(1), 37–40.
11. Macías, F. A.; Marín, D.; Chinchilla, D.; Molinillo, J. M. G. *Tetrahedron Lett.* **2002**, *43*, 6417–6420.
12. Mathur, S. B.; Kulkarni, G. H.; Kelkar, G. R.; Bhattacharyya, S. C. *Tetrahedron* **1964**, *12*(20), 2903–2909.
13. Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267–2268.