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# GUILLONEIN, AN EPOXYGUAIANOLIDE FROM *GUILLONEA SCABRA*, X-RAY STRUCTURE DETERMINATION

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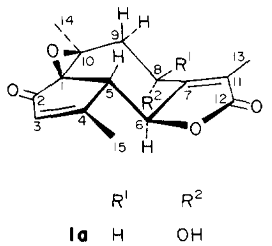
**Key Word Index**—*Guillonea scabra*; Umbelliferae; new guaianolide; absolute configuration; conformational analysis.

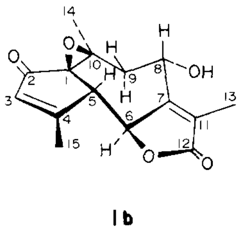
**Abstract**—From the roots of *Guillonea scabra* a new epoxyguaianolide, guillonein, has been isolated and its structure established by X-ray diffraction analysis. A $^1$H NMR spectroscopic study of this new sesquiterpene reveals a conformational difference in its seven-membered ring between the crystal and $CDCl_3$ solution states. The implications of this conformational change with respect to the C-8 configurations previously assigned to shairidin and desangeloylshairidin are briefly discussed.

## INTRODUCTION

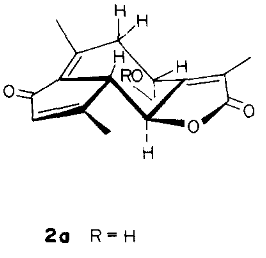
In previous communications [1, 2] we reported several guaianes as the sesquiterpene constituents of the roots of *Guillonea scabra* Cav. Cosson (= *Laserpitium scabrum* Cav.), an umbelliferous plant endemic in the Iberian Peninsula. Careful crystallizations of the chromatographic fractions containing predominantly desangeloylshairidin [2], has now allowed the isolation of a new sesquiterpene, guillonein (**1**), whose structure, absolute configuration and seven-membered ring conformational mobility have been rigorously established by X-ray analysis and by $^1$H NMR spectroscopy.



| | R¹ | R² |
|---|---|---|
| **1a** | H | OH |
| **4** | OH | H |

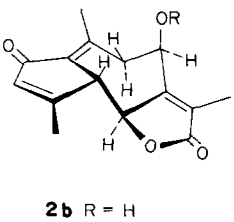


**1b**



**2a** R = H

**3a** R = Ang



**2b** R = H

**3b** R = Ang

## RESULTS AND DISCUSSION

With reference to the desangeloyl derivative of shairidin (**2**) previously described [2], the $^1$H NMR spectrum of guillonein (**1**, Table 1) showed some differences: the resonance of the C-14 methyl group is shifted $\Delta\delta$ 0.66 to a higher field, and the resonances of one of the C-9, and the C-5 and C-6 protons are shifted $\Delta\delta$ $-0.36$, $-0.30$ and 0.31, respectively, whereas the remaining resonances are almost identical in both compounds. As the difference in the molecular formula of guillonein (**1**, $C_{15}H_{16}O_5$) and desangeloylshairidin (**2**, $C_{15}H_{16}O_4$*) is an additional oxygen atom, it is evident that guillonein possesses an ether linkage, which must be an oxirane ring in the C-1–C-10 position in agreement with the above $^1$H NMR data (Table 1) and with its UV spectrum ($\lambda_{\max}^{\mathrm{EtOH}}$ 224 nm, log $\varepsilon$ = 4.065), which lacks the absorption at *ca* 257 nm typical for the $\alpha$, $\beta$-unsaturated cyclopentenone chromophore of desangeloylshairidin (**2**) [2].

In the molecule of guillonein (**1**) H-5 and H-6 are *trans* diaxially oriented ($J_{5,6}$ = 11.2 Hz), as in the case of badkysin [3], shairidin (**3**) [2, 4] and desangeloylshairidin (**2**) [2]. On the other hand, analysis of the C-9 methylene proton resonances as the AB part of an ABX system yielded for $J_{8,9}$ and $J_{8,9'}$ the values of 9.5 and 2.3 Hz, respectively. When an unsaturation between C-7 and C-11 exists and, consequently, H-7 is absent, no information about the conformation of the fragment C-6–C-7–C-8 can be obtained from coupling values. An examination of Dreiding molecular models shows that the seven-membered ring can adopt two main conformations: (a) that depicted on the left hand of the scheme, **1a**, analogous to that observed in badkysin [3]; and (b) the one on the right hand, **1b**, which differs from the latter mainly in the sign of

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* The formulae depicted for **2** and **3** do not necessarily express their absolute configurations.

Table 1. $^1$H NMR chemical shifts ($\delta$, ppm from TMS) and coupling constants ($J$, Hz) of compounds **1**–**3***

| | **1** | **2** | **3** | $\delta$(**3**) − $\delta$(**2**) |
|---|---|---|---|---|
| H-3 | 6.279 *t* | 6.137 | 6.246 | 0.109 |
| H-5 | 2.706 *m* | 3.003 | 3.146 | 0.143 |
| H-6 | 4.986 *m* | 4.674 | 4.567 | −0.107 |
| H-8 | 5.013 *m* | 5.039 | 6.077 | 1.038 |
| H-9α | 2.659 *dd* | 2.689† | 2.828† | 0.139 |
| H-9β | 2.142 *dd* | 2.506† | 2.671† | 0.165 |
| Me-13 | 1.982 *dd* | 1.850 | 2.051 | 0.201 |
| Me-14 | 1.752 *s* | 2.412 | 2.451 | 0.039 |
| Me-15 | 2.428 *t* | 2.254 | 2.345 | 0.091 |
| Coupling constants | | | | |
| \|3, 5\| | 1.2 | 1.1 | 1.0 | — |
| \|3, 15\| | 1.2 | 1.1 | 1.0 | — |
| 5, 6 | 11.2 | 10.5 | 10.5 | — |
| \|5, 15\| | 1.2 | 0.7 | 0.7 | — |
| \|6, 8\| | 1.2 | — | — | — |
| \|6, 13\| | 1.0 | 1.6 | 1.7 | — |
| 8, 9α | 9.5 | 6.3† | 6.4† | — |
| 8, 9β | 2.3 | 1.0† | 0.7† | — |
| \|8, 13\| | 0.8 | — | — | — |
| 9α, 9β | −15.1 | −14.3 | −14.6 | — |

*At 360 MHz, CDCl$_3$ solution, TMS as int. standard, probe temp. 27°.

†Assignment corresponding to a C(7) conformation together with the C-8 hydroxyl (**2a**) or ester group (**3a**) in the α-configuration.

the three torsion angles in the fragment C-7–C-8–C-9–C-10. In Fig. 1, the two conformations are characterized according to their seven torsion angles, as evaluated from the molecular models, and they are designated as C(7) and the TH′(7) (see legend of Fig. 1). The values observed for the vicinal couplings $J_{8,9}$ and $J_{8,9'}$ (see above), are compatible according with the Karplus relation with two structures epimeric at C-8: a TH′(7) conformation with a C-8α hydroxyl group (**1b**), or a C(7) conformation with a β-configuration for the C-8 alcohol function (**4**), because in both cases an axial–axial relationship between H-8 and one of the C-9 methylene protons is obtained.

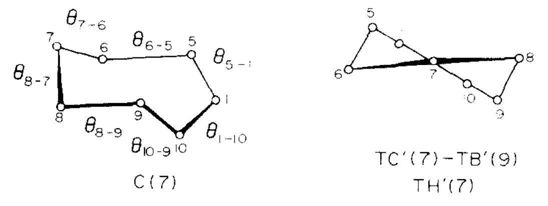

Fig. 1. The two conformations found for the seven-membered ring of guillonein, from the examination of the Dreiding molecular model, are shown. The evaluated torsion angles for the one on the left hand side are: $\theta_{7-6} = -60°$, $\theta_{6-5} = 60°$, $\theta_{5-1} = -65°$, $\theta_{1-10} = -5°$, $\theta_{10-9} = 65°$, $\theta_{9-8} = -80°$ and $\theta_{8-7} = 65°$. The four parameters given by Esteban *et al.* [15] to characterize asymmetrical seven-membered rings (two amplitudes, $\theta_2$ and $\theta_3$, and two phase angles, $\Phi_2$ and $\Phi_3$) are, respectively, 25.4°, 84.5°, 312.5° and 285.1°. This conformation belongs to the C–TC (chair–twist chair) family and can be designated as C(7). Torsion angles for the conformation on the right hand side are: $\theta_{7-6} = -60°$, $\theta_{6-5} = 60°$, $\theta_{5-1} = -20°$, $\theta_{1-10} = -5°$; $\theta_{10-9} = -60°$, $\theta_{9-8} = 80°$ and $\theta_{8-7} = -25°$. The corresponding amplitudes and phase angles are: $\theta_2 = 52.1°$, $\theta_3 = 49.6°$, $\Phi_2 = 62.9°$ and $\Phi_3 = 193.3°$. This conformation is a mixture of those designated ([15] and refs. therein) as TC′(7) and TB′(9) belonging, respectively, to the C–TC and the B–TB (boat–twist boat) families. By assuming that $\theta_{7-6} \cong \theta_{8-7}$, $\theta_{6-5} \cong \theta_{9-8}$ and $\theta_{5-1} \cong \theta_{10-9}$, this conformation approximates to the TH (twist hinge) [15] family and, thus, its designation can be simplified as TH′(7).

This ambiguity, together with the one relative to the configuration of the epoxide ring, prompted us to obtain the X-ray diffraction crystalline molecular structure of guillonein. Figure 2 shows the X-ray molecular model with the found absolute configuration of this new epoxyguaianolide (for details, see Experimental). Accordingly, with the X-ray analysis, guillonein possesses a *trans* relationship between the C-1–C-10 oxirane ring and the C-8 hydroxyl group, and its seven-membered ring conformation in the crystal is C(7) (**1a**). However, torsion angle values for H-8–C-8–C-9–H-9α and H-8–C-8–C-9–H-9β (36° and 70°) in this conformation are not compatible with the actual H-8–H-9 and H-8–H′-9 coupling values in CDCl$_3$ solution (see above), so that we must admit as a plausible hypothesis that on going from the crystal to CDCl$_3$ solution a conformational change of the seven-membered ring takes place and the molecule in solution adopts a TH′(7) conformation (**1b**), in which torsion angle values for H-8β–C-8–C-9–H-9β (*ca* 80°) and H-8β–C-8–C-9–H-9α (*ca* −160°) are now compatible with the observed coupling values of 2.3 and 9.5 Hz, respectively. In this respect, it is noteworthy that in the crystal state, molecules of guillonein can form hydrogen bonds between O-8-H . . . . O-1 of 2.865 Å, which could provide an additional driving force for stabilizing the chair conformation.

The crystalline structure of guillonein (**1a** and Fig. 1) reveals two interesting facts: (a) the seven-membered ring is a slightly-twisted chair with C-7 0.60 Å up and C-1–C-10 1.06 Å down the plane C-5–C-6–C-8–C-9, where the greater out of plane deviation is 0.01 Å; and (b) the epoxide bridge between C-1 and C-10 seems to bend the C-1–C-10 bond. There are two facts supporting this

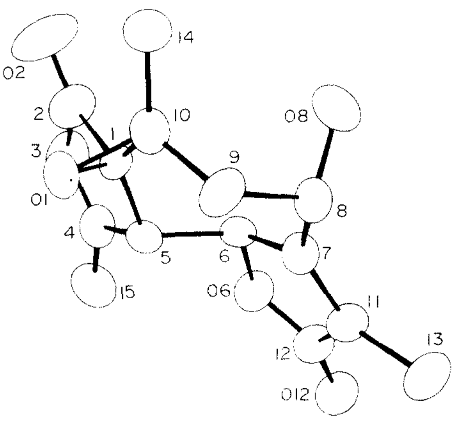

Fig. 2. Absolute X-ray molecular model of guillonein (**1a**). The internal torsional angles in the seven-membered ring are: $\theta_{7-6} = -65°$, $\theta_{6-5} = 74°$, $\theta_{5-1} = -59°$, $\theta_{1-10} = -4°$, $\theta_{10-9} = 67°$, $\theta_{9-8} = -76°$ and $\theta_{8-7} = 62°$. They do not differ much from those evaluated from the Dreiding model.

idea: the short distance of 1.48 Å between these atoms and the planarity observed perpendicular to the epoxide. The sum of the angles around C-1 (2–1–5, 5–1–10, 10–1–2) and around C-10 (1–10–9, 9–10–14, 14–10–1) is very large, 357.8°(α) and 356.4°(β), respectively. This is the usual geometrical deformation found around the epoxide bridge [5], where the values for α or β are between 351° and 359° and the averaged C-1–C-10 distance is 1.46 Å.

Regarding the well established absolute configuration of guillonein (**1**) (see Experimental), it is worth noting that all guaianolides found in the literature, whose absolute configuration has been determined by X-ray diffraction [6, 7], have the antipodal configuration. Moreover, the absolute configuration of guillonein (**1**, Fig. 1) seems to be very rare among the sesquiterpenoids found in higher plants [8].

After having found experimental evidence that the seven-membered ring can adopt, in this series of compounds, two different conformations, a reconsideration of the structures of shairidin (**3**) [2, 4] and its desangeloyl derivative (**2**) [2] is required. As described in ref. [2], no proton–proton diaxial arrangement exists in the C-8–C-9 structural moiety, since no vicinal coupling larger than 6.4 Hz is observed (Table 1). Thus, the –OR substituent at C-8 must be in an axial (or pseudo-axial) configuration. Two alternatives exist for the structures of these compounds: (a) a C(7) conformation for the seven-membered ring with an α-configuration for the C-8 substituent (**2a**, **3a**); or (b) a TH′(7) conformation with a β-configuration for the –OR grouping (**2b**, **3b**). No definite answer about this alternative can be obtained from the $^1$H NMR couplings (see Table 1). A comparison of the $^1$H NMR chemical shifts of compounds **2** and **3** shows that when the hydroxyl group is esterified, the C-8 proton shifts downfield by $\Delta\delta$ 1.038 and all the other signals undergo downfield shifts, in the range $\Delta\delta$ 0.039–0.201, with the exception of the signal corresponding to the C-6 proton, which shifts upfield by $\Delta\delta$ $-0.107$. A search for the differential shielding of an axial proton due to a 1, 3-diaxial hydroxyl group with respect to an acetoxy group in the same orientation confirmed that, whereas both substituents cause downfield shifts, the one from the former is always larger than the one from the latter. For that particular situation, esterification causes an upfield differential shift. In the steroid field [9], average 1, 3-diaxial shifts for hydroxyl and acetoxy are, respectively, $\Delta\delta$ 0.44 and 0.02. In the carbohydrate field, a comparison of chemical shifts of α- and β-glucose and α- and β-mannose with those of their acetylated derivatives [10, 11] yields for this effect average values of $\Delta\delta$ 0.30 (hydroxyl) and 0.13 (acetoxy). These arguments favour structures **3a** and **2a** for shairidin [2, 4] and its desangeloyl derivative [2], respectively. However, a definite decision about the structures and absolute configurations of these compounds must await further study.

## EXPERIMENTAL

For general details see refs. [1, 2].

*Isolation of guillonein* (**1**). The residue obtained from the mother liquors after crystallization of desangeloylshairidin (**2**) [2] was carefully and repeatedly crystallized from EtOAc and MeOH yielding pure guillonein (15 mg), mp 225–230°; $[\alpha]^{20}_{D}$ $+7°$ ($CHCl_3$; *c* 0.12); IR $\nu^{KBr}_{max}$ cm$^{-1}$: 3470 (OH), 1755 (α, β-unsatd γ-lactone), 1712, 1620 (cyclopentenone), 2950, 2935, 1440, 1380, 1323, 1208, 1095, 1083, 1055, 1020, 900, 855, 752, 690; UV $\lambda^{EtOH}_{max}$ nm (log ε): 224 (4.065). $^1$H NMR (360 MHz, $CDCl_3$): see Table 1. EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 276 $[M]^+$ (14), 258 (3), 216 (5), 215 (5), 201 (3), 151 (100), 126 (31), 111 (26), 109 (16), 98 (14), 91 (15), 77 (16), 69 (84), 53 (53), 43 (67), 41 (93). (Found: C, 65.02; H, 6.03. $C_{15}H_{16}O_5$ requires: C, 65.21; H, 5.84%.)

*X-ray structure determination of guillonein* (**1**). Guillonein, $C_{15}H_{16}O_5$ crystallizes in the space group $P2_12_12_1$, $Z = 4$ with $a = 15.4858(3)$, $b = 12.5769(3)$ and $c = 6.8154(1)$ Å, $D_c = 1.383$ g/cm$^3$. A crystal of 0.13 × 0.20 × 0.23 mm was used to measure the intensities of the 1384 independent Friedel pairs up to $\theta = 67°$. The data were collected on a computer-controlled four-circle diffractometer, using graphite-monochromated CuKα radiation ($\lambda = 1.5418$ Å) and $\omega/2\theta$ scan technique at 0.028°/sec. No crystal decomposition was observed during the expt. No absorption correction ($\mu = 8.25$ cm$^{-1}$) was done. The structure was solved by MULTAN [12] and refined using the 1310 observed reflexions with $I > 2\sigma(I)$. The H atoms were located on a difference map. Then, a weighting scheme was selected to prevent bias in $\langle w\Delta^2F\rangle$ vs $\langle F_0\rangle$ and vs $\langle \sin\theta/\lambda\rangle$. Several cycles of weighted anisotropic refinement (fixed isotropic contributions for H atoms), using both *hkl* and $\overline{hkl}$ reflexions converged to $R = 0.046$ and $R_w = 0.060$ [13].

The absolute configuration of guillonein (see Fig. 2) was determined using the more relevant Bijvoet pairs with $F_0 > 10\sigma(F_0)$. There are 31 pairs with $\Delta F_c > 0.10$, the averaged Bijvoet difference for these is 0.28 for the correct enantiomer vs 0.35 for the wrong one. Considering the 93 pairs with $\Delta F_c > 0.07$, the averaged Bijvoet differences are 0.29 vs 0.36 [14]. In order to confirm this result, the intensities of the 16 Bijvoet pairs with $\Delta F_c > 0.11$ and $F_0 > 10\sigma(F_0)$ were carefully remeasured in all equivalent reflexions and using two different crystals. The total averaged Bijvoet difference which resulted was 0.056 vs 0.251, confirming clearly the previous result and, thus, establishing the absolute configuration of guillonein as **1**. Molecules of guillonein chain through hydrogen bonds O-8-H.... O-1 of 2.865 Å.[*]

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[*] A list of atomic parameters, bond distances and angles, torsion angles, a table with the 16 relevant remeasured Bijvoet pairs and $F_0 - F_c$ tables are deposited at the Cambridge Crystallographic Data Centre.

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