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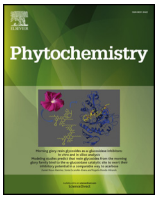

Studies on the sesquiterpene lactones from *Laurus novocanariensis* lead to the clarification of the structures of 1-*epi*-tatridin B and its epimer tatridin B

Braulio M. Fraga[a,*], David Terrero[a,1], Inmaculada Cabrera[b], Matías Reina[a]

[a] *Instituto de Productos Naturales y Agrobiología, CSIC, La Laguna, 38206, Tenerife, Canary Islands, Spain*
[b] *Instituto de Química Bioorgánica "Antonio González", Universidad de La Laguna, Tenerife, Spain*

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ABSTRACT

The germacranolide 1-*epi*-tatridin B has been isolated from the aerial parts of L*aurus novocanariensis*. We have observed that the identification of this lactone and its epimer tetradin B in the scientific literature is confusing and contradictory. We have therefore studied this issue clarifying errors and contributing to the structural elucidation of other related products. Moreover, we have isolated from this plant a lactone with an 1,5-ether bridge, previously obtained from *Australabium candidum*. We have now named it austroliolide, reassigned its ^{13}C NMR spectrum and compared its structure with that of badgerin. In addition, we have also isolated from L. *novocanariensis* the known germacranolides artemorin, costunolide, tatridin A, tulirinol and verlotorin, the eudesmanolides β-cyclopyrethrosin, 1β-hydroxy-arbusculin A, magnoliaolide and reynosin, and the guaianolide dehydrocostus lactone.

1. Introduction

The small genus *Laurus* (Lauraceae) was formed by two species, *L. nobilis* L. and *L. azorica* (Seub) J. Franco, which grow in the Mediterranean and Macaronesian regions, respectively. Recently, the *L. azorica* species from Madeira and the Canary Islands have been reconsidered as a separate taxon, *L. novocanariensis* Rivas Mart., Lousa, Fern. Prieto, E. Díaz, J.C. Costa & C. Aguiar, while the Azores species retains the name *L. azorica* (Rivas-Martínez et al., 2002). These last two Macaronesian species contain mono- and sesqui-terpenes in their essential oils (Hokwerda et al., 1982; Pedro et al., 2001; Pino et al., 2004; Ferrari et al., 2005; Macchioni et al., 2006; Rodilla et al., 2008; Tinoco et al., 2009). We had obtained from the aerial parts of *L. novocanariensis* the sesquiterpenes lauradiol, azoridione, caryophyllenol II and (+)-clovanediol (Fraga et al., 2001). In this work, continuing with its phytochemical study, we have clarified the confusing and contradictory scientific literature on the C-1 configuration of the germacranolides 1-*epi*-tatridin B (**1**) and tatridin B (**2**). Moreover, we have isolated from this plant a lactone with a 1,5-ether bridge, now named austroliolide (**7**), reassigned its ^{13}C NMR spectrum and compared its structure with that of badgerin (**11**). In addition to 1-*epi*-tatridin B (**1**) and austroliolide (**7**), we have also obtained the sesquiterpene lactones artemorin, costunolide, β-cyclopyrethrosin, dehydrocostus lactone, magnolialide, reynosin, tatridin A (**12**), tulirinol (**13**), verlotorin and β-hydroxy-arbusculin A (**14**).

2. Results and discussion

We have assigned structure **1** to a sesquiterpene lactone, obtained from *L. novocanariensis*, considering its MS, ^{1}H and ^{13}C NMR spectra, and those of its diacetate **1a**, also including double resonance experiments and 2D NMR techniques (COSY, NOESY, HMQC and HMBC). The α-stereochemistry of the alcohol at C-1 was assigned considering the NOESY experiment where a connectivity of H-1 with H-8 was observed.

Consulting the chemical literature we found that the ^{1}H NMR spectrum of our product was identical with that of a compound, which had been isolated from *Tanacetum polycephalum* and named 1α-hydroxy-1-desoxotamirin (= tanachin, deacetyldihydrochrysanolide, 1-*epi*-tatridin B) (**1**) (Rustaiyan et al., 1990), and also identical with the spectrum described for its 1β-epimer, tatridin B (**2**), obtained from *T. vulgare* (Sanz and Marco, 1991). Moreover, Rustaiyan et al. (1990) also described 1β-hydroxy-1-desoxotamirin (**2**), whose ^{1}H NMR spectrum was identical with that of the 1α-epimer (**1**), described by Sanz and Marco (1991). These facts indicated that in one of these studies the two epimeric structures were erroneously assigned.

The history of the isolation and structural determination of these germacranolides **1** and **2** has been very confusing for the last forty years. Tatridin B (**2**) was isolated from *Artemisia tridentata* and assigned

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[*] Corresponding author.
E-mail address: bmfraga@telefonica.net (B.M. Fraga).
[1] Current address: Universidad Autónoma de Santo Domingo and Universidad Nacional Evangélica, Dominican Republic.

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structure **2**, on the basis of the ^{1}H NMR spectra of its *bis*-trimethylsilyl and dibenzoate derivative, leaving the stereochemistry of the 1α-hydroxy group undetermined (Shafizadeh and Bhadane, 1973). This lactone **2** was subsequently obtained from *Chrisanthemum cinerariaefolium* (Sashida et al., 1983) and from *T. vulgare*, its structure being resolved by X-ray analysis of its dibenzoate (Appendino et al., 1986). These last authors also consider that structure **2** of tatridin B represents its absolute configuration. On the other hand, that of tatridin A (**12**), the $\Delta^{9(10)}$-isomer of 1-*epi*-tatridin B(**1**) had also been determined (Doskotch et al., 1980).

Tanachin (= 1-*epi*-tatridin B) (**1**) was isolated from *T. pseudoachillea* (Yunosov et al., 1976) and its relative stereochemistry was determined years later by X-ray analysis (Makhmudov et al., 1989). However, a comparison with samples or spectra of this compound was never pointed out by other authors.

The Berlin school of Bohlmann et al. obtained the epimer pairs **1** and **2** from *Schistostesphium crataegifolium* (Bohlmann et al., 1983), *Austroliabum candidum* (Jakupovic et al., 1986), *Cassinia subtropica* (Jakupovic et al., 1988) and *Ursinia abrotanifolia* (Jakupovic et al., 1992), but their NMR spectra were never published.

Rustaiyan et al. (1990) reported the isolation, and the ^{1}H NMR spectra, of the germacranolides **1** and **2** from *T. polycephalum*, naming them 1α-hydroxy-1-desoxotamirin (= 1-*epi*-tatridin B) and 1β-hydroxy-1-desoxotamirin (= tatridin B), respectively. These authors do not provide any argument to assign the epimeric structures, citing only an unpublished work of the Bohlmann group. Fortunately, the same structure **1**, which possesses a 1α-hydroxy group, was later assigned to a lactone obtained from *Crysanthemum coronarium* (Lee et al., 2002). These authors also described the isolation of dihydrochrysanolide **1b** (Doskotch et al., 1983) and the novel lactone **2b** from this plant, the structure of **1b** being determined by X-ray analysis, which had also been resolved previously with this technique (El-Feraly et al., 1983). Although **1** and **1b** were not chemically related, both lactones possess a 1α-alcohol because considering their ^{13}C NMR spectra C-1 resonates at δ_C 71.2 and 70.2 in **1** and **1b**, respectively, in comparison with the same carbon in **2b** at δ_C 76.3. Thus, structures **1** and **2** assigned by Rustaiyan et al. (1990) to 1-*epi*-tatridin B and tatridin B, respectively, are correct. Later 1-*epi*-tatridin B (**1**) was identified as a component of *Anthemis altissima* on the basis of its NMR data (Konstantinopoulou et al., 2003).

On the other hand, Sanz and Marco (1991), in a NMR study of sesquiterpene lactones isolated from *T. vulgare*, reported the resonances of **1** and **2** interchanged with respect to those described by Rustaiyan et al. (1990). In other words, as we have indicated above, the spectra of 1-*epi*-tatridin B were assigned to tatridin B and *vice versa*. Consequently, as the structure of tatridin B (**2**) had been resolved by X-ray analysis of its benzoate (Appendino et al., 1986) (see above) and then supplied to Prof. Marco, we think that an interchange of samples occurred accidentally. In support of our assertion, we observed that Sanz and Marco indicate in their article that an unexpected nOe effect was observed between the signal of H-1 and H-8 in its erroneously assigned 1β-hydroxy-derivative (it is truly a 1α-OH) but not in its also wrongly allocated 1α-hydroxy-derivative (it is a 1β-OH). These facts agree with our results reported above, where a crosspeak of H-1 with H-8 was observed in the NOESY spectrum of our 1α-hydroxy-derivative 1-*epi*-tatridin B (**1**).

We believe that these facts probably led other authors to make mistakes in the identification of **1** and **2** in some plants. Thus, Susurluk et al. (2007) describe the isolation of tanachin (= 1-*epi*-tatridin B) (**1**) from *T. cadmium* on the basis of its included ^{1}H NMR spectrum, which according to our work truly corresponds to that of tatridin B (**2**). Moreover, other authors (Gören et al., 1994a; Gören and Tahtasakal, 1994b, 1997; Triana et al., 2001; Çelik et al., 2005) that cite the Sanz and Marco (1991) article could have made the same mistakes in the identification of these lactones as components of several Compositae species.

Table 1
^{13}C NMR data of the sesquiterpene lactones **1**, **1a**, **2**, **2a**, **7**, **12** and **13**.

Position	**1**	**1a**	**2**[a]	**2a**[a]	**7**	**12**	**13**
1	70.3	70.6	76.60	77.83	75.3	66.9	78.4
2	30.7	27.2	36.27[b]	33.42	26.9	27.3	28.3
3	34.3	34.2	36.47[b]	36.69	28.1	35.4	38.1
4	136.4	138.0	138.19[b]	140.63	144.1	143.0	71.2
5	130.8	127.1	127.85	124.72	73.0	126.0	56.5
6	70.6	72.5	71.38	73.05	72.2	73.2	80.9
7	51.6	48.5	58.06	50.37	53.5	49.3	50.4
8	78.7	78.0	83.46	82.26	81.6	74.3	21.8
9	41.7	42.3	41.92	42.72	42.7	126.5	39.0
10	146.6	141.5	152.90	148.50	149.7	138.0	41.9
11	136.5	135.7	137.30[b]	137.16	139.1	137.1	138.1
12	170.0	170.5	170.09	169.96	169.4	169.4	169.6
13	125.7	125.4	124.5	123.42	121.5	123.0	118.1
14	114.7	118.0	113.02	116.14	117.7	16.9	13.6
15	17.4	17.1	17.79	17.62	107.1	15.6	24.3

[a] Values taken from Sanz and Marco (1991) for 1-*epi*-tatridin B and its diacetate, and now assigned to tetradin B (**2**) and its diacetate (**2a**), respectively.
[b] Interchangeable values.

Our study has also allowed us to make several contributions to the structures of other lactones related to 1-*epi*-tatridin B (**1**) and tatridin B (**2**). Barrero et al. (1988) described the isolation of one of the two epimers, **1** or **2**, from *Santolina rosmarinifolia*. Now we have identified it as the lactone **1**, by comparison of the ^{1}H NMR spectrum of its diacetate with that of our diacetyl derivative **1a**.

The best way to determine the stereochemistry of the hydroxyl group at C-1 in derivatives of 1-*epi*-tatridin B (**1**) and tatridin B (**2**) is to consider the resonances of this carbon, which occur at δ_C 70.3 (1α-OH) and 76.6 (1β-OH), respectively (Table 1). Thus, in chiliophyllin, a 1,6-dihydroxy-germacranolide isolated from *T. chiliophyllum* (Gören and Tahtasakal, 1993), a 1β-stereochemistry (**3**) was assigned considering only the coupling of its geminal proton, which is not conclusive because both 1-epimers could have similar coupling constants, as occurs in compounds **1** and **2**. However, we can observe that C-1 and C-6 in **3** resonate at δ_C 70.9 and 73.0, erroneously assigned by the authors as interchanged values at δ_C 73.0 and 70.9 in $CDCl_3$ and correctly at 71.2 and 73.3 in d_6-acetone, respectively. These facts seem to indicate that this lactone possesses a 1α-hydroxy structure (**4**), and not a 1β-hydroxy one. This also was confirmed in the ^{1}H NMR spectrum of **4** where H-1 appears at δ_H 3.95, compared with δ_H 3.84 in **1** (1α-OH) and 4.38 in **2** (1β-OH).

The structures of the lactones **5** and **6**, the corresponding 1-hydroperoxides of **1** and **2**, were first described as components of two *Mikania* species by Bohlmann et al. (1982) indicating that “a clear decision on the stereochemistry at C-1 was difficult”. Now, considering the chemical shifts of H-5 and H-6 at δ_H 5.09 and 4.26 in **5**, compared with those at 5.04 and 4.26 in **1**, respectively, and δ_H 5.28 and 4.44 in **6** compared with 5.25 and 4.41 in **2**, we can say that the structures given for the hydroperoxides **5** and **6** seem to be correct.

We have assigned structure **7** to another sesquiterpene lactone, isolated from *L. novocanariensis*, on the basis of the following considerations: In its MS the higher mass peak was observed at m/z 262. Its ^{1}H NMR spectrum showed the signals of an α-methylene-γ-lactone as a pair of doublets at δ_H 6.07 (J = 3.2 Hz) and 6.23 (J = 3.6 Hz). The protons of two other exocyclic double bonds appeared as a pair of doublets at δ_H 5.12 and 5.37 (J = 2 Hz), those situated at C-14, and also as two doublets δ_H 4.95 (J = 2 Hz) and 4.98 (J = 1.4 Hz), those at C-15. Resonances of four geminal hydrogens to oxygen atoms at δ_H 3.48, 4.06, 4.20 and 4.44 can also be observed in this spectrum. These signals were assigned at H-5, H-8, H-6 and H-1, respectively, by way of double resonance experiments. Moreover, H-6, H-7 and H-8 possess a *trans, trans, trans* stereochemistry considering the coupling observed between them in the ^{1}H NMR spectrum.

In the ^{13}C NMR spectrum signals of methyl groups do not appear, but rather six methylene groups, three of which are of exocyclic double