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Elephantopus-type sesquiterpene lactones from a *Vernonanthura* species, *Vernonanthura nebularum*

G.C. Pollora [a], A. Bardón [a], C.A.N. Catálan [a], T.E. Gedris [b], W. Herz [b,*]

[a] *Instituto de Química Orgánica, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, Ayacucho 491, 4000 S. M. de Tucumán, Argentina*
[b] *Department of Chemistry and Biochemistry, The Florida State University, 32306-4390 Tallahassee, FL, USA*

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Abstract

Aerial parts of *Vernonanthura nebularum*, an Argentine endemic whose occurrence is limited to a small area in northwestern Argentina, afforded seven new sesquiterpene lactones of a type characteristic of some Elephantopodiinae rather than *Vernonanthura* of Vernoniinae. Structures were elucidated by high field ^{1}H-NMR spectrometry.

In revising the generic and subtribal classification of neotropical Vernoniae H. Robinson (Robinson, 1994, 1999) established the new genus *Vernonanthura* as a segregate from *Vernonia* sensu stricto (Robinson, 1992) and subsequently included within it (Robinson, 1995) *Vernonia nebularum* Cabrera as *Vernonanthura nebularum* (Cabr.) H. Robinson (Cabrera, 1978). Earlier chemical studies of *Vernonanthura* species, frequently under the old *Vernonia* binomials (Robinson, 1999), had resulted in the isolation of a variety of flavonoids and sesquiterpene lactones similar to or identical with such compounds found in other Vernonieae (Wagner et al., 1972; Mabry et al., 1975; Bohlmann and Zdero, 1977, 1988; Maldonado et al., 1980; Bohlmann et al., 1981a,b, 1983; Jakupovic et al., 1986, 1987a,b; Catalán et al., 1986, 1988; Stutts, 1988; Bardón et al., 1988, 1992; Budesinsky et al., 1994; Borkosky et al., 1997; Bazon et al., 1997; Kotowicz et al., 1998), while in one instance the occurrence of pimarane and kaurane derivatives was reported (Borkosky et al., 1995). We now describe our

* Corresponding author. Tel.: +1-850-644-2774; fax: +1-850-644-8281.
E-mail address: jdulin@chem.fsu.edu (W. Herz).

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chemical study of *Vernonanthura nebularum*, an Argentine endemic whose occurrence is limited to the Sierra de Calilegua within Jujuy province, Argentina.

Keywords: Vernonanthura nebularum; Vernoniinae; Sesquiterpene lactones

1. Material and methods

1.1. Plant material

Aerial parts of *Vernonanthura nebularum* (Spreng.) H. Robinson were collected at the flowering stage on September 15, 1999, between Abra Cañas and San Francisco, 5 km from the entrance to Calilegua National Park, Jujuy province, Argentina. A voucher specimen (LIL 605007) is on deposit in the herbarium of the Fundación Miguel Lillo, Tucumán.

1.2. General procedures

For HPLC the column used was a Beckman ultrasphere C18(10×250mm). Retention times (R_t) were measured from the solvent peak. ^{1}H-NMR spectra were run on a Varian Inova 500 MHz NMR spectrometer. Mass spectra were run on a Finnigan MAT 90 or a JEOL MS Route 600 H instrument.

1.3. Extraction and isolation of constituents

Flowers and leaves (500 g) were extracted with $CHCl_3$ (3×2.5l) at R_t for several days to give 19.99 g (4%) of crude extract which was suspended in EtOH (143 ml) at 60°C, diluted with H_2O (107 ml) and extracted successively with hexane (3×70ml) and benzene (3×70ml). Evaporation of the hexane extract at reduced pressure furnished 16.68 g (3.34%) of residue which was subjected to CC over Si gel (Merck 230–400 mesh) using $CHCl_3$ containing increasing amounts of EtOAc (5–85%) to give 80 fractions. Frs. 9–14 (2.05 g), which showed significant lactone carbonyl absorption at 1775 cm^{-1} were combined and freed of chlorophyll by CC over florisil using hexane–Et_2O 7:3 to yield two frs. A and B. Fr. A (260 mg) was processed by HPLC (MeOH–H_2O 8:2, 2 ml min^{-1}) using a Beckman ultrasphere column C-18 (10×250mm), retention times being measured from the solvent peak, to give 4.7 mg of **2a** (R_t 4 min), 4.1 mg of **2b** (R_t 6.5 min), 12.2 mg of **3a** slightly contaminated by **2a** (R_t 8 min), 17.3 mg of a mixture of **3a** and **3d** contaminated by **2a** and **2b** (R_t 11 min), 17.3 mg of a 3:1 mixture of **3e** contaminated by **2b** (R_t 15 min) and 1.7 mg of a complex mixture of lactones. A portion (200 mg) of fr. B (1.25 g) on HPLC gave 37 mg of **3b** contaminated by **3d** (R_t 10.5 min) and 6.0 mg

of **3d** (R_t 14 min). Frs. 15 and 16 (209 mg) from the mother column showing lactone absorption at 1770 cm^{-1} were reunited and freed of chlorophyll as before. A portion (60 mg) on HPLC gave 1.9 mg of a mixture of **2a** (minor) and **3a** (major), (R_t 7:5 min), 8.4 mg of **3b** contaminated by **2a** (R_t 10 min) and 1.6 mg of **3e** contaminated by **2b** (R_t 14.5 min). Frs. 17–68, which did not exhibit lactone absorption were not investigated further. Frs. 69–75 from the mother column (913 mg) which exhibited lactone absorption were reunited. A portion (200 mg) on HPLC gave 1.6 mg of a 1:1 mixture of **2a** and **3a** (R_t 3 min), 6.4 mg of a 1:1 mixture of **2b** and **3d** (R_t 4 min), 8.3 mg of **3a** contaminated by **2a** (R_t 5.5 min), 58.7 mg of **3d** slightly contaminated by **2b** (R_t 8 min), 58.7 mg of a complex mixture of methacrylates (R_t 11 min), 1.7 mg of **3c** (R_t 24.5 min), 38.4 mg of **3f** (R_t 35 min) and 35.5 mg of a mixture of lactones.

The benzene extract on evaporation at reduced pressure furnished 2.39 g of residue. CC over Si gel (230–400 mesh) using hexane–EtOAc–MeOH mixtures (17.3:0, 4:1:0, 7:3:0, 6:4:0, 60:32:2 and 12:7:1) gave 15 fractions. Frs. 2 and 3 were combined; flash chromatography over Si gel, ($CHCl_3$–EtOAc 19:1) gave fr. A (254 mg), B (103 mg) and C (80 mg) which were subjected separately to HPLC (MeOH–H_2O 7:3, 2 ml min^{-1}) to give from fr. A **3d** (40 mg, R_t 12.5 min) which was partially transformed to **2b** on keeping, **3a** (52 mg, R_t 17 min) partially changed to **2a** on keeping, **3d** plus a little **3a** (20 mg, R_t 27 min) and 9.4 mg of angelates **3d**, **3e** and some methacrylates (R_t 39.5 min). Fr. C furnished a mixture of methacrylates **2a** and **3a** (16.8 mg, R_t 7.5 min), a mixture of angelates **2b** and **3e** (13.8 mg, R_t 12 min), mainly **3a** (11.6 mg, R_t 17.5 min), and **3e** contaminated by **2b** (11 mg, R_t 26.5 min).

HPLC of a 70 mg portion of fr. 4 (153 mg) from the mother column afforded only complex lactone mixtures. HPLC of a 103 mg portion of fr. 5 (647 mg) gave **1a** (2.5 mg, R_t 4.5 min), **2a** (5 mg, R_t 6 min), a 1:1 mixture of **2b** and **3d** (4 mg, R_t 8.5 min), a 3:1 mixture of **2a** and **3a** (18 mg, R_t 11.5 min) and a 1:2 mixture of **2b** and **3d** (16 mg, R_t 17 min).

Fraction 6 (148 mg) on HPLC gave **1a** (5 mg R_t 7.5 min), a mixture of **2a** and **3a** (5 mg, R_t 10.5 min), a 3:1 mixture of **3d** and **2b** (4 mg, R_t 16.5 min) which was completely transformed to **2b** on keeping, a 1:1 mixture of **2a** and **3a** (12 g, R_t 23.5 mg) and a 1:2 mixture of **2b** and **3d** (9 mg, R_t 37 min). Frs. 7–10 (72, 73, 29 and 101 mg) from the mother column yielded nothing of interest. Fr. 11 (151 mg) on HPLC (MeOH–H_2O 7:3, 2 ml min^{-1}) gave a mixture of **2b** and **3d** (2.5 mg, R_t 12.5 min), **3a** (7 mg, R_t 18 min) and **3d** (3.3 mg, R_t 27.5 min^{-1}).

1.4. Identification of new constituents

Lactone **1a** was the previously unknown angelate analog of molephantin (**1b**) and molephantinin (**1c**), two sesquiterpene lactones which have been isolated previously from various collections of *Elephantopus mollis* HBK (Lee et al., 1973, 1975a,b, 1980; McPhail et al., 1974; Banerjee et al., 1986; But et al., 1996b; Fuchiro et al., 2001) as shown by the ^{1}H-NMR data of Table 1, extensive decoupling and the empirical formula. Lactones **2a** and **2b** were 1,10-dihydro hemiacetal derivatives of

Table 1
1^H NMR spectra of compounds 1**a,** 2**a** and 2**b** (500 MHz, $CDCl3_)$

Position	**1a**	**2a**	**2b**
1a	6.19 brs	1.78 td	1.77 m
1b	-	1.72 m	1.72 m
3	6.00 brs	5.66 brs	5.66 quint (1.5)
5	5.43 brs	5.18 dd (2,1.5)	5.18 dd (2, 1.5)
6	4.23 d (3.5)	4.45 dd (7.5, 2)	4.46 dd (7.5,2)
7	3.35 dddd (10.5,3.5,3,2)	3.28 dddd (10.5,7.5,3.5,2.5)	3.25 dddd (10.5,7.5,3.5,2.5)
8	5.25 ddd (10.5,10.5,4)	5.12 ddd (10.5,3.5,2)	5.13 ddd (10.5,3.5,2)
9a	2.78 brdd (12,4)	2.37 brdd (14.5,2)	2.37 brdd (14.5,2)
9b	2.49 dd (12,10.5)	1.67 m	1.71 m
10	-	1.69 m	1.69 m
13a	6.37 d (3)	6.27 d (3.5)	6.27 d (3)
13b	5.80 d (2)	5.74 d (2.5)	5.76 d (3)
14[a]	1.79 brs	0.89 d (6.5)	0.91 d (6.5)
15[a]	2.00 d (1)	1.74 brt (1)	1.73 brt (1)
3′a	6.15 qq (7.5, 1.5)	6.16 brs	6.18 qq (7, 1.5)
3′b	-	5.66 quint (1)	-
4′[a]	1.97 dq (7.5,1.5)	1.99 brs	2.01 dq (7.5, 1.5)
5′[a]	1.90 quint (1.5)		1.93 quint (1.5)

[a] Intensity three protons.

1a and **1b**; chemical shifts and coupling constants listed in Table 1 showed that the stereochemistries at C-6, C-7 and C-8 were identical with those of **1a–c** while the chemical shifts of H-3 and H-5 (as well as those of H-6, H-7 and H-8) corresponded to those of 2-deethoxy-2-hydroxyphantomolin (**4a**) which has been reported recently from a collection of *E. mollis* (But et al., 1996b) (in this article the *Z*-C-1(10) double bond is incorrectly depicted as *E*). The stereochemistry at C-10 could not be established independently due to superposition of the signals of H-1a, b, H-9b and H-10, but is identical with the C-10 configuration of **3a–f** because of the gradual transformation of **3a**,**b**,**d** to **2a,b** (vide infra).

Two further pairs of constituents consisted of two new 1,10-dihydro analogs **3b** and **3e** of phantomolin (**4c**, $R' =$ MeAcr, $R =$ Et) and the new corresponding methyl ethers **3a** and **3d**. The ^{1}H-NMR spectra of these substances (Table 2) differed significantly from those of **2a** and **2b** only in the chemical shifts of H-3, approximately δ 5.45 vs. δ 5.66, and in small downfield shifts, δ 1.75 vs. δ 1.73 of the signal of the vinyl methyl group (H-15), a difference which can be attributed to the presence of the ether function. On monitoring by ^{1}H-NMR spectrometry the $CDCl_3$ solutions of the various fractions containing **3a**,**b**,**d** and **e**, gradual isomerization appeared to have taken place with the signals of H-3 and H-15 moving to δ 5.66 and δ 1.73. Simultaneously doubling of the other ring signals was observed, the chemical shifts of the new signals being identical with those of **2a** and, respectively, **2b**. We attribute

Table 2
^{1}H-NMR spectra of compounds **3a–f** (500 MHz, $CDCl_3$)

Position	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
1a	1.73 m	1.73	1.76 *dd* (12.5, 4)			1.78 m (12,4.5)
1b	1.73 m	1.73	1.55 *brd* (12)			1.55 brd (12)
3	5.45 quint (1.5)	5.49	5.52 *quint* (1)	5.45 quint (1.5)	5.49	5.52 brs
5	5.14 brdd (2.5,1.5)	5.11	5.15 *brs*	5.13 brdd (2.5, 1.5)	5.11	5.16 brdd
6	4.46 dd (7.5,2.5)	4.45	4.47 *dd* (7.5,2)	4.47 dd (7.5,2)	4.46	4.48 dd (7.5,2)
7	3.29 dddd (11,7.5,3.5,3)	3.29	3.28 *dddd*(11,7.5,3.5,2)	3.26 dddd (11,7.5,3,2.5)	3.26	3.25 (11,7.5,3,2.5)
8	5.10 ddd (11,4,2)	5.11	5.11 *ddd* (11,4,5,2)	5.12 ddd (11,3.5.2)	5.12	5.13 ddd (11,4,2)
9a	2.36 brdd (15,2)	2.35	2.40 *brd* (16)	2.34 brdd (15,2)	2.35	2.40 dd (15.5,2)
9b	1.67 m	1.67	1.66 *dt* (16,4.5)	1.66 m	1.66	1.66 dt (15.5,4)
10	1.69 m	1.69	1.77 *m*	1.70 m	1.75	1.75 m
13a	6.25 d (3.5)	6.25	6.25	6.26 d (3)	6.26	6.26
13b	5.73 d (3)	5.73	5.72	5.74 d (25)	5.74	5.74
14[a]	0.86 d (6)	0.86	0.86	0.88 d (5.5)	0.88 d (6)	0.89 d (5.5)
15[a]	1.77 brs	1.76	1.75	1.77	1.75	1.75
3′a	6.14 brs	6.15	6.15	6.16 qq (7,1.5)	6.16	6.17
3′b	5.65 quint (1)	5.65	5.65			
4′[a]	1.95 brs	1.95	1.96	1.99 dq (7, 1.5)	2.00	2.00
5′[a]				1.91 quint (1.5)	1.92 brs	1.92
OMe[a]	3.11 s			3.11 s		
3′a			4.88 *brs*			4.88 brs
3′b			4.81 *quint* (1)			4.82 brs
4″[a]			1.32 *s*			1.32 s
5″[a]			1.28 *s*			1.29 s
6″[a]			1.75 *brs*			1.75 brs
OEt		3.37 q (7) 3.32 q (7) 1.13 t (7)[a]			3.36 q 3.32 q 1.13 t[a]	

[a] Intensity three protons.

this to gradual conversion of **3a**,**b**,**d** and **e** to **2a**, resp. **2b**, presumably due to traces of acid in $CDCl_3$ solvent, a process which interfered with obtaining satisfactory analytical values for **3a**,**b**,**d** and **e** after recovery from the solutions.

Finally we obtained two relatively stable ethers **3c** and **3f** containing a previously undescribed 2,3-dimethyl-3-propen-2-oxy ether unit on C-2. Structure assignments of **3c** and **3f** are based on the mass spectra, the ^{1}H-NMR spectra of **3c** and **3f** (Table 2) and the ^{13}C-NMR spectrum of **3f** (Table 3), the only compound available pure in reasonable quantity after recovery from the $CDCl_3$ solutions. In the case of these two substances the signals of H-1a, H-1b and H-9b were sufficiently distinct from those of H-10 and H-15 to permit identification. Irradiation of the frequencies of H-9a and H-14 identified the usually obscured signal of H-9b as a *dt* at δ 1.66 and that of H-10 as a multiplet at δ 1.77, thus leading to identification of the H-1b multiplet at δ 1.55 and that of H-1a near δ 1.76. In NOE measurements irradiation at the frequency of H-14 resulted solely in enhancement of the H-14 signal thus, indicating that the methyl group on C-10 was α-orientatated, a conclusion which obviously also applied to **3a**,**b**,**d** and **e.** (5*S*∗,6*S*∗,7*R*∗,8*S*∗)-2-Oxo-5-hydroxy-8-angeloxygermacra-1(10)E,3Z,11(13)-trien-6,12-olide(**1a**). Gum; MS (FAB$^+$, Na, NBA) 383 (55, M+Na), 361 (23, M+H), 343 (38, M+H–H_2O), 261 (16, M+H–$C_5H_8O_2$), 243 (25, M+H–$C_5H_8O_2$–H_2O); ^{1}H–NMR spectrum in Table 1.

(2*S*∗,5*S*∗,6*S*∗,7*R*∗,8*S*∗,10*R*∗)-2-Hydroxy-2,5-epoxy-8-methacryloxygermacra-3Z, 11(13)-dien-6,12-olide(**2a**). Gum; MS (FAB$^+$, Na, NBA) 371 (63, M+Na), 349 (47, M+H), 331 (100, M+H–H_2O), 231, (43, M+H–H_2O–$C_4H_6O_2$); ^{1}H-NMR spectrum in Table 1.

(2*S*∗,5*S*∗,6*S*∗,7*R*∗,8*S*∗,10*R*∗)-2-Hydroxy-2,5-epoxy-8-angeloxygermacra-3Z,11 (13)-dien-6,12-olide(**2b**). Gum; MS (FAB, Na, NBA) 385 (85, M+Na), 345 (68, M+H–H_2O), 263 (41, M+H–H_2O), 263, (41, M+H–$C_5H_8O_2$) 245 (79, M+H–H_2O–$C_5H_8O_2$); ^{1}H-NMR spectrum in Table 1.

(2*S*∗,5*S*∗,6*S*∗,7*R*∗,8*S*∗,10*R*∗)-2-Methoxy-2,5-epoxy-8-methacryloxygermacra-

Table 3
^{13}C NMR spectrum of compound **3c** (67.5 MHz, $CDCl_3$)

C		C	
1	40.5 t	14	25.4 q
2	117.9 s	15	13.2 q
3	126.6 d	1′	83.1 s
4	141.9 s	2′	136.6 s
5	86.0 d	3′	126.0 t
6	78.8 d	4′	18.3 q
7	40.2 d	1″	83.1 s
8	76.7 d	2″	148.7 s
9	36.6 t	3″	110.9 t
10	23.6 d	4″	18.8 q
11	136.2 s	5″	24.7 q
12	168.5 s	6″	24.5 q
13	125.0 t		

3Z,11(13)-dien-6,12-olide(**3a**). Gum. The ^{1}H-NMR spectrum of the pure substance as isolated originally is shown in Table 2. By the time the various fractions were recovered from solution the NMR spectra had changed partially, in some instances completely, to the spectrum of **2a**, the mass spectra indicating the presence of a mixture of **2a** and **3a**. The latter (FAB, Na, NBA) was presumably responsible for the presence of peaks at *m/z* 385 (M+Na), and *m/z* 363 (M+H).

(2*S*∗,5*S*∗,6*S*∗,7*R*∗,8*S*∗,10*R*∗)-2-(2,3-Dimethyl-3-propene-2-oxy)-8-methacryloxygermacra-3Z,11(13)-dien-6,12-olide(**3c**). Gum; MS (FAB, Na, NBA) 453 (35, M+Na), 345 (33, M+H–$C_4H_6O_2$), 245 (75, M−$C_4H_6O_2$–$C_6H_{12}O$); ^{1}H-NMR spectrum in Table 2.

(2*S*∗,5*S*∗,6*S*∗,7*R*∗,8*S*∗,10*R*∗)-2-Methoxy-2,5-epoxy-8-angeloxygermacra-3Z,11(13)-dien-6,12-olide(**3d**). Gum. The ^{1}H-NMR spectrum of the pure substance as isolated originally is listed in Table 2. As in the case of **3a** in time the ^{1}H-NMR spectra of the fractions containing **3d** indicated the presence of **2b** as well. In the mass spectrum (FAB, Na, NBA) peaks at *m/z* 399 (M+Na), 377 (M+H) and 277 (M–$C_5H_8O_2$) indicated the presence of **3d** in addition to that of **2b**.

(2*S*∗,5*S*∗,6*S*∗,7*R*∗,8*S*∗,10*R*∗)-2-(2,3-Dimethyl-3-propene-2-oxy)-8-angeloxygermacra-3Z,11(13)-dien-6,12-olide(**3f**). Gum; M (FAB, Na, NBA) 467 (21, M+Na), 445 (6, M+H), 345 (23, M−$C_5H_8O_2$ or $C_6H_{12}O$), 245 (81, M−$C_5H_8O_2$–$C_6H_{12}O$); ^{1}H-NMR spectrum in Table 2; ^{13}C-NMR spectrum in Table 3.

2. Chemotaxonomic significance

In revising the generic and subtribal classification of neotropical Vernoniae H. Robinson (Robinson, 1994, 1999) established the new genus *Vernonanthura* as a segregate from *Vernonia* sensu stricto (Robinson, 1992) and subsequently included within it (Robinson, 1995) *Vernonia nebularum* Cabrera as *Vernonanthura nebularum* (Cabr.) H. Robinson. Sesquiterpene lactones of type **1**–**3**, however, are unprecedented in *Vernonanthura* or in fact within the entire subtribe Vernoniinae to which it belongs (for reviews of the chemistry of Vernonieae through 1993 see Bohlmann and Jakupovic, 1990; Herz, 1994). Analogs **1b** (molephantin), **1c** (molephantinin) and 1,10-dehydro derivatives **4a**–**c** similar to **3a**–**f** have been previously found only in various collections of *E. mollis* HBK (Elephantopodiinae, Vernonieae) (Lee et al., 1973, 1975a,b, 1980; McPhail et al., 1974; Banerjee et al., 1986; But et al., 1996b; Fuchiro et al., 2001) and the unusual ether side chain A has not previously been encountered in any natural product. On the other hand, the chemistry of *E. mollis* seems unique among members of Elephantopodiinae whose other taxa such as *E. carolinianus*, *elatus*, *nudatus*, *scaber* and *tomentosus*, typically elaborate germacradiendiolides such as deoxy- and deoxyiso-elephantopin and their precursors (Bohlmann and Jakupovic, 1990; But et al., 1996a; Hayashi et al., 1999). In this connection the identification of *E. mollis* as the source of such dilactones from a Brazilian collection (,b) seems suspect. On the other hand the reports which describe isolation of lactones typical or identical with lactones characteristic of *Vernonanthura* species from *Pseudoelephatopus spicatus*, the sole representative of the second genus within

Elephantopodiinae (Jakupovic et al., 1986; Ragasa et al., 1993; Ragasa and Rideout, 2001) seem to distinguish this species chemically from the genus *Elephantopus*. The taxonomic implications of these findings, if any, are not clear.

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