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Azorellane diterpenes from *Azorella cryptantha*

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Abstract

Azorella cryptantha yielded the diterpenes, azorellolide and the dihydroderivative, dihydroazorellolide, together with the known yaretol and 1α,10β,4β,5α-diepoxy-7α-germacran-6β-ol. Both possess a carbon skeleton type that may originate from rearrangement of the mulinane skeleton.

Keywords: *Azorella cryptantha*; Apiaceae; Mulinane diterpenes; Azorellolide; Dihydroazorellolide; X-ray analysis

1. Introduction

Azorella Lam. is a South American genus of the Apiaceae (Umbellifereae) represented by 26 species growing in the Andean Mountains and Patagonia, Argentina, respectively. About 15 species grow in Argentina. While their fruits do not possess wings, *Azorella* is closely related to *Mulinum* Pers. a genus which has winged fruits. Most of the *Azorella* species are commonly known as "yareta".

So far only three *Azorella* species have been investigated chemically. Polyacetylenic compounds have been reported from *Azorella trifurcata* (Bohlmann et al., 1971), while *Azorella compacta* yielded mulinane-type diterpenes (Loyola et al., 1997a,b, 1998a,b, 2001a; Wachter et al., 1999). *Azorella madreporica* yielded one mulinane diterpenoid with antitubercular activity (Wachter et al., 1998) and the norditerpenoid yaretol (Loyola et al., 2002). From *Azorella yareta*, diterpenoids with trichonomicidal activity were reported (Loyola et al., 2001b). The *Mulinum* genus has also been subjected to limited phytochemical studies. The most extensively studied is *Mulinum crassifolium*, from which the mulinane skeleton was first reported (Loyola et al., 1990a). Further investigations on this species led to the isolation of a series of mulinane-type diterpenes (Loyola et al., 1990b, 1991, 1996, 1997c). *Mulinum spinosum* also yielded mulinane-type diterpenes (Nicoletti et al., 1996).

Azorella cryptantha (Clos) Reiche, ex *Mulinum cryptamthum*, commonly known as "soldiers herb", grows in the Andes Mountains of Argentina and Chile. This species was first described as *Mulinum* but was later changed to *Azorella* based on the fact that the fruit lacks wings. Infusion of aerial parts of *A. cryptantha* is used in folk medicine as a blood depurative and as a digestive. As part of a program aimed at the chemical study of *Apiaceae* species, we report the isolation and structure elucidation of two new diterpenes azorellolide (**1**) and dihydroazorellolide (**2**) from the aerial parts of *A. cryptantha*. In addition, we isolated the known terpe-

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noids yaretol (Loyola et al., 2002) and 1α,10β,4β,5α-diepoxy-7α-germacran-6β-ol (Sanz and Marco, 1991) from this species. The known terpenoids were identified by comparison of their spectroscopic data (NMR, MS) with literature values.

2. Results and discussion

Azorellolide (**1**) was isolated as colorless needles. The EIMS molecular ion at *m/z* 302, the base peak at *m/z* 43 and, among others, a fragment corresponding to the $[M-43]^+$ ion, suggested the presence of either an acetyl, or an isopropyl group. The absence of a singlet at ca. δ 2 in the ^{1}H NMR spectrum and the presence of two methyl doublets at δ 0.92 and δ 0.82 confirmed the isopropyl group. The IR spectrum indicated a carbonyl group (1730 cm^{-1}), confirmed by the carbon NMR signal at δ 177.0.

The ^{1}H and ^{13}C NMR spectra of **1** (Table 1) displayed signals corresponding to two tertiary methyl groups and two methylene protons of a cyclopropane ring.

The ^{13}C NMR and DEPT experiments indicated the presence of four primary, seven secondary, four tertiary and five quaternary carbons and suggested that **1** was a tetracyclic diterpene with an extra lactone ring.

The correlations observed in the HMBC (Table 1) between H-15 and C-7, C-8, C-9, C-13, C-14, C-17; H-7 and C-6, C-8, C-15, C-17; H-16 and C-12, C-13, C-14; and H-15 and C-7, C-8, C-9, C-14, C-17 permitted assignment of the lactone group in the A ring.

The full proton and carbon NMR spectral assignments were performed using a combination of COSY, NOESY, HMBC and HMQC 2D experiments. The 3D structure of **1** was finally and unambiguously determined by single crystal X-ray analysis, vide infra.

The crystal and molecular structure of azorellolide (**1**) was determined by single crystal X-ray diffraction, as shown in Fig. 1, with individual displacement ellipsoids drawn at 30%; Table 2 gives the final atomic parameters for non-hydrogen atoms.

Both enantiomeric models were refined, leading to Flack's parameters of 0.0 (1.7) for the presently reported model and 1.7 (1.8) for the inverted one. (Expected values: 0 for the right handness and 1 for the inverted one, within 3σ). In spite of the rather large esd's obtained, these values strongly suggest that the present model correspond to the correct absolute configuration of the compound. This fact is reinforced by the simi-

Table 1
^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data and HMBC correlations of azorelloide (**1**)[a]

Atom number	**1**		HMBC
	δ^1H (mult., *J*, Hz)	δ^{13}C	H
1	0.96 (*dddd*, 12.7, 12.0, 10.6, 7.5)	21.8 *t*	2-H2, 10-H
	1.15 *m*		
2	1.28 *m*	28.5 *t*	1-H2, 3-H, 4-H
	1.83 *m*		
3	1.08 *m*	58.8 *d*	2-H2, 4-H, 10-H, 18-H3, 19-H3, 20-H3
4	1.51 *m*	31.6 *d*	2-H2, 3-H, 18-H3, 19-H3
5		44.0 *s*	2-H2, 3-H, 6-H2, 10-H, 20-H3
6	1.32 *m*	36.2 *t*	3-H, 7-H2, 10-H, 20-H3
	1.99 (*ddd*, 13.3, 5.0, 3.0)		
7	1.41 *m*	26.3 *t*	6-H2, 15-H2
	2.27 (*td*, 14.5, 5.0)		
8		43.4 *s*	7-H2, 11-H2, 14-H-2, 15-H2
9		19.3 *s*	10-H, 11-H2, 15-H2, 12-H, 1-H2
10	1.93 (*dd*, 12.7, 7.5)	46.2 *d*	1-H2, 2-H2, 6-H2, 11-H2, 12-H, 20-H3
11	0.39 (*ddd*, 7.0, 3.5, 1.0)	5.8 *t*	12-H, 10-H
	0.62 (*dd*, 8.0, 7.0)		
12	0.69 (*dd*, 8.0, 3.5)	20.7 *d*	14-H2, 16-H3, 11-H2
13		78.5 *s*	12-H, 11-H2, 14-H2, 15-H2, 16-H3
14	1.85 (*ddd*, 13.4, 10.8, 4.0)	33.4 *t*	12-H, 15-H2, 16-H3
	1.72 (*ddd*, 13.4, 11.3, 5.0)		
15	1.26 (*ddd*, 13.6, 10.8, 5.0)	25.9 *t*	7-H2, 14-H2
	2.42 (*ddd*, 13.6, 11.3, 4.0)		
16	1.43 (*s*)	25.3 *q*	12-H, 14-H2
17		177.0 *s*	7-H2, 15-H2
18	0.92 (*d*, 6.5)	23.8 *q*[a]	3H, 4-H, 19-H3
19	0.82 (*d*, 6.5)	23.3 *q*[a]	3-H, 4-H, 18-H3
20	0.71 (*s*)	11.9 *q*	3-H, 6H2, 10-H

[a] In $ClCD_3$, TMS as internal standard.

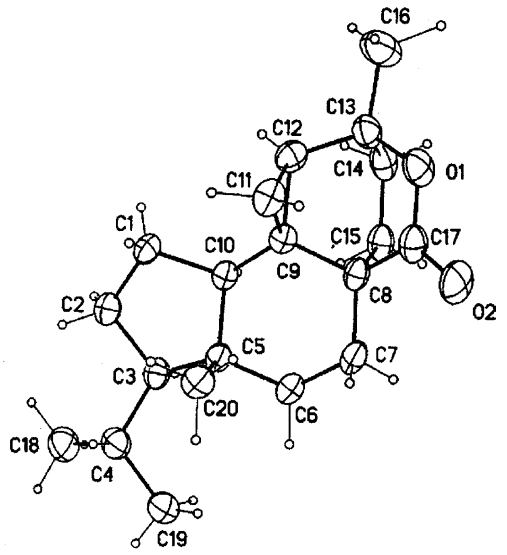


Fig. 1. Molecular drawing of (**1**) showing the numbering scheme used. Displacement ellipsoids drawn at 30% level.

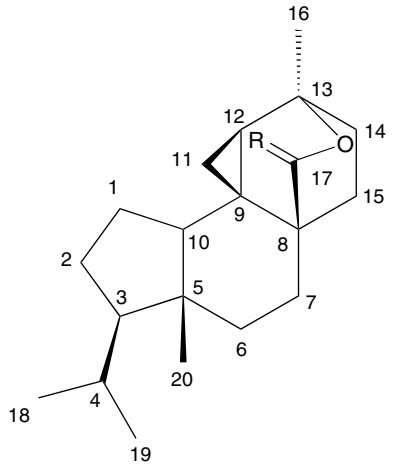
Table 2
Atomic coordinates and equivalent isotropic displacement parameters for **1**[a]

	x	*y*	*z*	U_{eq}
O1	0.0453(3)	0.9482(2)	0.4945(1)	0.065(1)
O2	−0.2204(3)	0.9551(3)	0.5820(2)	0.080(1)
C1	0.4885(5)	0.7486(4)	0.7944(2)	0.055(1)
C2	0.5243(5)	0.7596(4)	0.9076(2)	0.060(1)
C3	0.3602(4)	0.8486(3)	0.9526(2)	0.049(1)
C4	0.3087(6)	0.7962(3)	1.0572(2)	0.062(1)
C5	0.2085(4)	0.8535(3)	0.8676(2)	0.045(1)
C6	0.0790(5)	0.9844(3)	0.8654(2)	0.054(1)
C7	−0.0374(4)	0.9951(4)	0.7675(2)	0.058(1)
C8	0.0798(3)	0.9853(2)	0.6727(2)	0.047(1)
C9	0.2281(4)	0.8638(3)	0.6773(2)	0.043(1)
C10	0.3354(3)	0.8623(3)	0.7748(2)	0.041(1)
C11	0.1948(5)	0.7318(3)	0.6145(2)	0.058(1)
C12	0.3204(5)	0.8469(4)	0.5776(2)	0.056(1)
C13	0.2545(4)	0.9581(4)	0.5035(2)	0.062(1)
C14	0.3000(5)	1.1027(4)	0.5475(3)	0.069(1)
C15	0.1904(5)	1.1234(3)	0.6463(3)	0.059(1)
C16	0.3272(7)	0.9354(7)	0.3979(3)	0.095(1)
C17	−0.0473(4)	0.9617(3)	0.5819(2)	0.059(1)
C18	0.4801(7)	0.8023(5)	1.1279(3)	0.081(1)
C19	0.1419(6)	0.8791(4)	1.1031(3)	0.081(1)
C20	0.0872(5)	0.7166(3)	0.8681(3)	0.056(1)

[a] $U_{eq} = (1/3)\sum_{ij} U_{ij} a_i^* a_j^* a_i a_j$.

larity that the structure bears towards the closely related mulinic acid (Loyola et al., 1990a).

Comparison of both structures showed that they share many common features, the major structural difference being the new C-9, C-12 carbon–carbon bond in azorellolide (**1**), thus splitting the large seven membered ring of mulinic acid into a cyclopropane and a cyclohexane ring in azorellolide (**1**). A drastic change in the bridge across C-11 and C-14 takes place through the oxidation of the methyl group at C-17 and its lactonization towards the OH group at C-13.



1 R = O
2 R = OH

The EIMS spectrum of **2** showed the molecular ion at *m/z* 304, two daltons more than compound **1**. The IR spectrum did not display the carbonyl signal observed in **1**, instead it showed an OH absorption at 3400 cm^{-1}. The ^1H NMR profile of compound **2** (see Section 3) was almost identical to that of compound **1**, except for a broad singlet at δ_H 4.68, assigned to an hemiacetalic proton (H-17), thus indicating that **2** is a dihydroderivative of **1**. The ^{13}C NMR spectrum of **2** lacked a carbonyl carbon signal as observed for **1**, having instead a resonance at δ 105.7 (C-17), indicating reduction of the lactone function in **1** to give a lactol in **2**. Dihydroazorellolide (**2**) was assigned the same absolute stereochemistry as azorellolide (**1**).

The stereochemistry of the new chiral center (C-17) was determined by both NOESY experiment and molecular modelling. In the NOESY experiment, the proton (H-17) only shows a cross-correlation with H-11. A 3D structure of **2** was generated by AM1 calculation using MOPAC in order to analyse the expected NOE correlation. In this way, it was determined that H-17 shows cross-correlation peak with H-11β (2.95 Å). Based on this experimental evidence the relative stereochemistry for C-17 was assigned as 17S*. The correlation observed in the HMBC between H-7 and C-6, C-8, C-17; H-15 and C-7, C-8, C-9, C-17 and H-16 and C-12, C-13, C-14 permitted establishment of the position of the hemiacetal group in the A ring. The proton and carbon NMR spectroscopic assignments are given in Section 3.

3. Experimental

3.1. General

The 1D and 2D NMR spectroscopic experiments were recorded on a Bruker AC-200 and a Bruker

AMX-500 spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are given in δ downfield from TMS and coupling constants are measured in Hz. COSY, DEPT, HETCOR, HMBC, HMQC and NOESY experiments were obtained using standard Bruker software. IR spectra were recorded on a Nicolet 5-SXC-FTIR spectrophotometer, optical rotations were determined on a Jasco P-1010 polarimeter. EIMS were collected on a Finnigan 3300 F-100 at 70 eV by direct inlet, whereas HREIMS were recorded on a Finnigan MAT spectrometer. CC was performed on silica gel 60 (70–230 mesh ASTM) (Merck) and silica gel 60 H (Merck). TLC was performed on silica gel 60 GF_{254} (Merck).

3.2. Plant material

Azorella cryptantha (Clos) Reiche was collected near Bauchazeta, Departamento de Iglesia, San Juan Province, Argentina, during April 1996 and it was identified by Dr. Luis Ariza Espinar. A voucher specimen is deposited in the Museo Botánico Córdoba (CORD 506), Argentina.

3.3. Extraction and isolation

Leaves and stems (3250 g) of *A. cryptantha* were air-dried and exhaustively extracted with MeOH. The residue obtained after evaporation of the solvent (658 g) was suspended in $MeOH/H_2O$ and extracted sequentially with hexane, CCl_4 and $CHCl_3$. Organic extract was evaporated under reduced pressure, yielding 100, 197and 155 g of gummy residues, respectively.

The $CHCl_3$ extract was purified by CC eluting with benzene, Benzene–EtOAc, EtOAc and combined according to their TLC profiles. Recrystallization of fractions 1–5 yielded azorellolide (**1**) (10 g). Fractions 95–103 were further purified by repeated CC to give dihydroazorellolide (**2**) (25 mg) and 1α,10β,4β, 5α-diepoxy-7α-germacran-6β-ol (181 mg) (Sanz and Marco, 1991). Fractions 130–159 were further purified by repetitive CC to give 9,11-dihydro-8,13-epoxy norazorellolide (87 mg) (Loyola et al., 2002).

3.3.1. Azorellolide (*1*)

Colourless needles (ethyl ether); m.p. 146–147 °C; $[\alpha]_D^{19.8} - 64.94$ (*c* 0.56, $CHCl_3$); IR ν_{max} (AgCl) cm^{-1}: 2960, 1730. HREIMS *m/z* 302.4586 (calcd for $C_{20}H_{30}O_2$, 302.4609). EIMS *m/z* (relative intensity) 302 M^+, (5), 259 (9), 91 (36), 55 (48), 43 (100). For ^1H, ^{13}C NMR spectral data and HMBC correlations, see Table 1.

3.3.2. Single crystal X-ray analysis of azorellolide (*1*)

X-ray diffraction: colourless single crystals of compound **1** were obtained by slow evaporation of ethyl acetate solution.

A specimen measuring $0.35 \times 0.25 \times 0.22$ mm suitable for X-ray diffraction was chosen for data collection on a Siemens R3 diffractometer. Cell dimensions were obtained from the accurate centering of 25 reflections in the range $15° \leqslant 2\theta \leqslant 25°$, at room temperature, using Mo Kα radiation.

Crystal data: $C_{20}H_{30}O_2$, FW = 302.44, monoclinic, $P2_1$, $a = 6.973(3)$, $b = 9.423(7)$, $c = 13.329(6)$ Å; $\beta = 90.63(4)°$, $V = 875.7(8)$ Å^3, $Z = 2$. $D_x = 1.147$ g cm^{-3}, μ(Mo Kα) = 0.072 mm^{-1}, $\lambda = 0.71069$ Å. A total of 5640 reflections were collected in the angular range $3.06° \leqslant 2\theta \leqslant 50.10°$, within index ranges $-8 \leqslant h \leqslant 8$, $-11 \leqslant k \leqslant 11$, $-15 \leqslant \lambda \leqslant 15$ using the $\vartheta/2\theta$ scan technique; 3097 of them resulted unique and 2042, with $F_o \geqslant 4\sigma(F_o)$, were observed. The stability of the data collection was monitored by the measurement of two standards out of each 98 measured reflections. The variations found were smaller than 2%. No corrections were applied to account for the (negligible) absorption effects. The structure was solved by direct methods using SHELXS-97 (Sheldrick, 1990) and refined by full matrix least squares on F^2 with the whole data set using SHELXL-97 (Sheldrick, 1997), where the quantity minimized was $\sum \omega(F_o^2 - F_c^2)^2$, $\omega = 1/[\backslash\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = (F_o^2 + 2F_c^2)/3$. All the hydrogen atoms were found from difference Fourier maps, and refined isotropically, while non-H atoms were assigned anisotropic displacement factors. Final refinement on 320 parameters converged to discrepancy indices $R_1 = \sum \| F_o| - |F_c\| / \sum |F_o| = 0.0402$ for the 2042 observed reflections and $\omega R_2 = [\sum[\omega(F_o^2 - F_c^2)^2] / \sum[\omega(F_o^2)^2]]^{1/2} = 0.0915$ for the 3097 unique. The final difference Fourier map was strikingly featureless, displaying a very low ripple (+0.09/−0.11 e Å^{-3}).

3.3.3. Dihydroazorellolide (*2*)

Colourless needles; m.p. 121–122 °C; $[\alpha]_D^{19.8} + 27.84$ (*c* 0.58, $CHCl_3$); IR ν_{max} (AgCl) cm^{-1} 3400, 2972, 2944. HREIMS *m/z* 304.4746 (calcd for $C_{20}H_{32}O_2$, 304.4768). ^1H NMR ($CDCl_3$, 200.3 MHz) 4.14 (1H, *d*, $J = 1.1$ Hz, H-17), 1.96 (1H, *m*, H-6′), 1.93 (1H, *m*, H-10), 1.88 (1H, *m*, H-7′), 1.82 (1H, *m*, H-2′), 1.76 (1H, *m*, H-14′), 1.50 (1H, *m*, H-4), 1.48 (1H, *m*, H-7), 1.48 (1H, *m*, H-14), 1.43 (2H, *m*, H-15), 1.29 (1H, *m*, H-6), 1.26 (1H, *m*, H-2), 1.22 (3H, *s*, H-16), 1.12 (1H, *m*, H-1′), 1.08 (1H, *m*, H-3), 0.94 (1H, *m*, H-1), 0.93 (3H, *d*, $J = 6.5$ Hz, H-18 or H-19), 0.84 (3H, *d*, $J = 6.5$ Hz, H-18 or H-19), 0.74 (1H, *m*, H-11′), 0.74 (3H, *s*, H-20), 0.47 (1H, *m*, H-12), 0.44 (1H, *m*, H-11). ^{13}C NMR ($CDCl_3$, 50.13 MHz) 105.7 (*d*, C-17), 71.1 (*s*, C-13), 58.2 (*d*, C-3), 47.1 (*d*, C-10), 43.4 (*s*, C-5), 36.2 (*t*, C-6), 34.9 (*s*, C-8), 31.1 (*d*, C-4), 32.7 (*t*, C-14), 28.7 (*t*, C-15), 27.8 (*t*, C-2), 25.7 (*t*, C-7), 25.7 (*q*, C-16), 23.1, 22.6 (2 *q*, C-18, 19), 21.0 (*d*, C-12), 21.0 *t*, C-1), 20.1 (*s*, C-9), 11.9 (*q*, C-20), 3.8 (*t*, C-11).

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