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THE STEREOCHEMISTRY OF MATRICIN AND 4-EPIMATRICIN, PROAZULENE SESQUITERPENE LACTONES FROM *ARTEMISIA ARBORESCENS*

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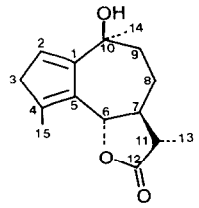
Key Word Index—*Artemisia arborescens*; Compositae; proazulenes; sesquiterpene lactones; 4-epimatricin; matricin; artabsin; artemetin; chemotaxonomy.

Abstract—An investigation of *Artemisia arborescens* afforded, in addition to the known compounds matricin, artabsin and artemetin, the new guaianolide 4-epimatricin. The stereostructures of 4-epimatricin and matricin were assigned on the basis of spectroscopic evidence.

INTRODUCTION

The dark-blue essential oil of *Artemisia arborescens*, containing up to 50% of chamazulene[1], has been the subject of several studies[1–7]. However, nothing was known about the compounds responsible for the formation of this blue hydrocarbon during steam distillation of the plant. Arborescin, a sesquiterpene lactone previously isolated from this plant and claimed to be a proazulene[8], actually fails to produce chamazulene under the mild conditions of steam distillation[9].



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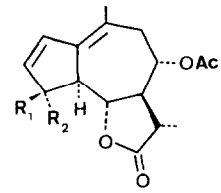
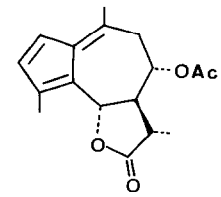
Chemical investigation of the plant revealed the known proazulenes artabsin (**1**)[10] and matricin[11], and yielded a new sesquiterpene lactone, which was the C-4 epimer of matricin, and was therefore called 4-epimatricin. Evidence leading to stereostructures **2** for 4-epimatricin and **3** for matricin is now presented.

RESULTS AND DISCUSSION

Matricin (**3**) and 4-epimatricin (**2**) showed almost superimposable IR, UV and mass spectra, while their ^{1}H NMR spectra differed significantly only for the position of the signals corresponding to the C-2, C-3, C-5, C-6 and C-15 protons (Table 1). As the multiplicity and coupling constants for all the signals were practically the same in both compounds, it was concluded that **2** and **3** differed only in the stereochemistry at the quaternary carbon C-4.



	R_1	R_2
2	OH	Me
3	Me	OH



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Assuming the usual α-orientation for H-7[12], the stereochemistry at C-5, C-6 and C-8 followed by inspection of the coupling constants of the corresponding protons ($J_{5,6} = 10.8$ Hz; $J_{6,7} = 10.8$ Hz; $J_{7,8} = 10.4$ Hz), the α-configuration of the methyl group at C-11 was deduced from the observed upfield shift of the H-13 doublet when changing from deuterochloroform to deuterobenzene as solvent ($\Delta\delta_{CDCl_3/C_6D_6} = -0.18$ for **2** and -0.20 for **3**)[13].

The lower position of the H-5 signal in **3** (δ 2.82 in **3** and 2.22 in **2**) suggested a *cis* relationship and therefore the same α-orientation for this proton and the C-4 hydroxyl group in this epimer. This was confirmed by lanthanide-induced shifts (LISs) upon addition of Eu(fod)$_3$. The shifts for the C-5 hydrogen in **3** were almost double the ones observed under the same conditions for this proton in **2**. In accordance with the β-orientation of the C-4 hydroxyl group in **2**, the shifts for the C-6 proton were higher in **2** than in **3**.

The signals of H-2 and H-3 formed an asymmetric AB system ($J_{2,3} = 5.4$ Hz), the downfield doublet of which (H-2) was sharp, while the upfield one (H-3) was broader. The latter was shown by double-resonance experiments to couple not only with the C-10 methyl, but also with H-5 ($J_{3,5} = 0.8$ Hz). Although similar homoallylic couplings have been

Table 1. ^{1}H NMR spectral data for compounds **2–4** (200 MHz, C_6D_6 except **4** in $CDCl_3$, TMS as internal standard)

Protons	2	Δδ*	3	Δδ*	4
H-2	6.12 *d*	+0.32	6.01 *d*	+0.42	6.16 *d*
H-3	5.78 *br d*	+0.74	5.90 *br d*	+1.12	6.42 *d*
H-5	2.22 *br dq*	+0.78	2.82 *br dq*	+1.46	—
H-6	3.90 *t*	+1.20	3.58 *dd*	+1.14	5.08 *br d*
H-7	1.80 *m*	†	1.80 *m*	†	†
H-8	4.58 *td*	+1.10	4.66 *td*	+1.04	5.24 *td*
H-9_a	2.16 *dd*	†	2.18 *dd*	†	†
H-9_b	†	†	†	†	†
H-11	1.95 *m*	†	1.95 *m*	†	†
H-13	1.14 *d*	+0.60	1.16 *d*	+0.58	1.22 *d*
H-14	1.52 *br s*	+0.28	1.50 *br s*	+0.31	2.16 *s*‡
H-15	1.40 *s*	+0.82	1.30 *s*	+1.28	2.18 *s*‡
OH	2.34 *s*	—	2.34 *s*	—	—
OAc	1.58 *s*	+0.18	1.58 *s*	+0.18	2.06 *s*

Most coupling constants were virtually identical for **2** and **3**; those for **2** are given as representative; values for those that changed significantly in **3** are also given: $J_{2,3} = 5.4$ Hz; $J_{5,6} = 10.8$ Hz; $J_{6,7} = 10.8$ Hz; $J_{7,8} = 10.4$ Hz; $J_{8,9a} = 10.4$ Hz; $J_{8,9b} = 3.2$ Hz; $J_{9a,9b} = 12$ Hz; $J_{11,13} = 6.5$ Hz; $J_{3,5} = 0.8$ Hz; for **3**: $J_{6,7} = 10.0$ Hz. For **4**: $J_{2,3} = 5.0$ Hz; $J_{6,7} = 10.0$ Hz; $J_{11,13} = 6.5$ Hz.

*Plus 0.15 eq $Eu(fod)_3$.

†Could not be assigned because of overlapping signals.

‡Assignments are interchangeable.

reported to occur between the olefinic protons and a β-anti hydrogen in compounds having a strained cyclopentene moiety[14, 15], it is noteworthy that in **2** and **3** the proton at the ring junction (H-5) affected only one of the two β-olefinic hydrogens. The ^{13}C NMR spectral data for **2** and **3** are reported in Table 2. Assignments are based upon chemical shift considerations, evaluation of the residual coupling constants in the single frequency off resonance decoupled spectra and by selective proton decouplings. The most remarkable difference between the two spectra is the chemical shift of C-15 (δ 29.48 in **2**, 25.07 in **3**). The difference in the C-15 resonance between **2**, in which this carbon and C-6 are *trans*, and **3**, where a *cis* relationship between these two carbons exist, is in keeping with the differences observed for the methyl groups in epimeric 1,2-dimethylcyclopentanes [16]. The higher chemical shift of C-5 in **3** is also easily explained by taking into account the larger β-effect attributable to the hydroxyl group with regard to a methyl group[17], and it is in agreement with data reported for epimeric 2-methylcyclopentanoles[16] and 8-hydroxylated iridoids[17]. Inspection of the literature data[18] suggests that these arguments can also explain the chemical shift differences at C-4 and C-5 in other C-4 epimeric guaianolides. The chemical shift of C-13 is in agreement with the *S*-configuration (α-methyl) for the C-11 asymmetric centre in both epimers[19].

Addition of trichloroacetyl isocyanate to the sample in the NMR sample tube has been reported to give the fulvene **4** from **3**[20]. This unexpected instantaneous elimination instead of acylation of the C-4 hydroxyl group was also observed for compound **2** under these conditions.

Different chemotypes of *A. arborescens* seem to exist. Arborescin was not found in the samples investigated and ^{1}H NMR analysis of crude chloroform extracts revealed that some samples contained only 4-epimatricin, whereas mixtures of both epimers were present in others, the method of extraction being the same. Artabsin and the flavonoid artemetin[21] were found in all the samples analysed.

Table 2. ^{13}C NMR spectral data for compounds **2** and **3** (50.3 MHz, $CDCl_3$, TMS as internal standard)

Carbon no.	2	3
C-1	138.91 *s*	136.67 *s*
C-2	132.07 *d*	129.71 *d*
C-3	138.91 *d*	140.54 *d*
C-4	83.30 *s*	84.04 *s*
C-5	57.60 *d*	58.68 *d*
C-6	79.12 *d*	79.18 *d*
C-7	54.81 *d*	56.54 *d*
C-8	71.53 *d*	71.73 *d*
C-9	42.41 *t*	42.37 *t*
C-10	124.69 *s*	123.61 *s*
C-11	40.27 *d*	40.31 *d*
C-12	177.40 *s*	177.47 *s*
C-13	15.15 *q*	15.34 *q*
C-14	23.32 *q*	23.43 *q*
C-15	29.48 *q*	25.07 *q*
OAc	169.67 *s*	169.78 *s*
	21.08 *q*	21.10 *q*

EXPERIMENTAL

Mps are uncorr. ^1H and ^{13}C NMR spectra were run at 200 and 50.3 MHz respectively; NMR solns for shift reagent expts were prepared by the 'incremental dilution technique'[22]. Typical values of $\Delta\delta$ are given in Table 1; trichloroacetyl isocyanate was added to $CDCl_3$ solns of **2** and **3** as described in ref. [20].

Plant material. A. arborescens L. was collected near Sassari (Sardegna, Italy) in May 1981, and was identified by Professor Tommaso Sacco (Università di Torino). A voucher specimen is kept at the Herbarium of the Istituto di Botanica Speciale Veterinaria, Università di Torino.

Isolation of proazulenes. Dried aerial parts (leaves and flowers, 3 kg) were extracted with $CHCl_3$ at room temp. (1×12 l.; 3×10 l.). The tarry residue remaining after removal of the solvent at red. pres. was purified according to standard procedures[23] to afford an unstable thick syrup (110 g) which turned blue upon standing on Si gel. Due to this instability, prep. HPLC proved to be the best technique to obtain the proazulenes without causing extensive decomposition of these compounds[24].

4-Epimatricin. Unstable colorless needles from EtOAc (yield 0.08% on dried plant material); mp: 147°; $[\alpha]_D^{25}$ −80° ($CHCl_3$; *c* 0.52); IR: the most remarkable difference between the IR spectra of **2** and **3** was the position of a medium intensity band in the $\nu_{(C-O)}$ region, found at 1120 cm^{-1} (KBr disc) in **2** and 1070 cm^{-1} (KBr disc) in **3**; UV λ_{max}^{EtOH} nm (log ϵ): 244 (4.28); EIMS: 70 eV, *m/z* (rel. int.): 306 $[M]^+$ (0.3), 291 $[M-15]^+$ (5), 288 $[M-18]^+$ (5), 246 $[M-60]^+$ (65), 231 $[M-60-15]^+$ (100).

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