

THE STRUCTURE AND STEREOCHEMISTRY OF ARTEMIN*

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Key Word Index—*Artemisia maritima*; Compositae; sesquiterpene lactone; artemin.

Abstract—Artemin was isolated from the aerial part of *Artemisia maritima*. Its structure and stereochemistry were determined on the basis of chemical transformations and spectral evidence

INTRODUCTION

As part of our researches into sesquiterpene lactones from the Compositae, especially from the genus *Artemisia*, we have begun a study of *Artemisia maritima* L ssp *Gallica* Willd.

RESULTS AND DISCUSSION

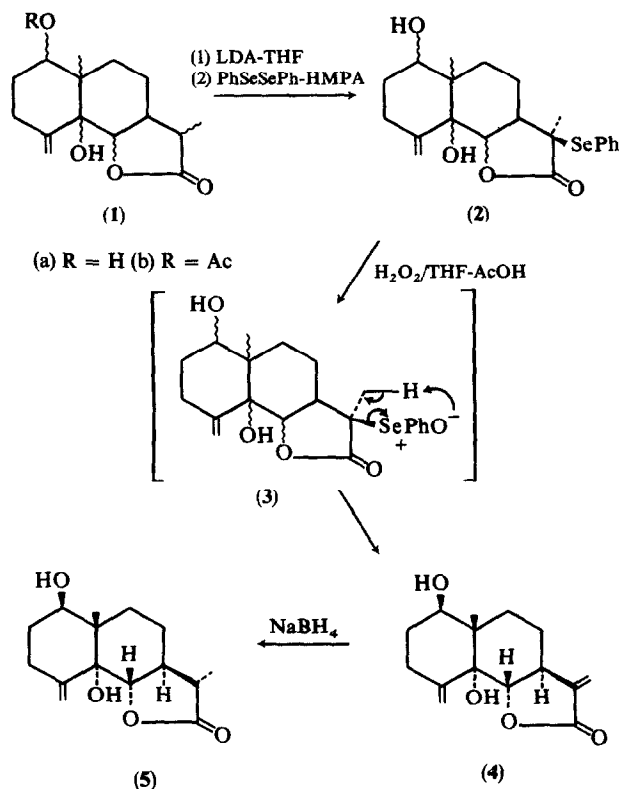
Following the method described in the Experimental we obtained a crystalline product with an intensely bitter taste, mp 238–240°, $C_{15}H_{22}O_4$, $[\alpha]_D^{167}$ (1a). The spectral data indicated a sesquiterpene lactone; thus the IR spectrum showed absorption bands at 3570 (hydroxyl), 1770 (γ -lactone), 1650 and 920 cm^{-1} (methylene double bond). The NMR spectrum showed a broad singlet at δ 5.00 (2 protons, corresponding to a methylene double bond), a group of signals centred at δ 4.20 representative of a lactonic proton at C-6 and a proton geminal to a hydroxyl group; a singlet at δ 0.86 corresponding to an angular methyl and a doublet at δ 1.20 ($J = 6$ Hz) attributable to a secondary methyl. We propose the relative α -configuration for this methyl on the basis of the coupling constant [1, 2]. On treatment of this product with acetic anhydride, a mono-acetate was formed, mp 227–229°, $C_{17}H_{24}O_5$, $[\alpha]_D^{146}$ (1b). Its IR spectrum showed that this substance had the same absorptions as the original alcohol, plus the signal at 1720 cm^{-1} characteristic of an acetate group. The signals typical of secondary and tertiary methyls, as well as those of lactonic proton (doublet at δ 4.28, $J = 11$ Hz) and of the acetyl group (a singlet at δ 2.05), could be observed in the NMR spectrum. The signal of the proton geminal to the secondary hydroxyl showed a paramagnetic shift (under acetylation) of 1.22 ppm, appearing as a doublet of doublets at δ 5.42. At low field, a doublet was seen at δ 5.05, attributable to an isolated methylene. The presence of hydroxyl group absorptions in the IR spectrum of the monoacetate (1b) suggested the presence of a tertiary hydroxyl group.

The constants of artemin, isolated by Rybalko *et al.* [3] from *Artemisia taurica*, are identical to those of our product. The Russian authors give a probable gross structure for artemin (1a) without definitely establishing the position of the secondary hydroxyl group, nor the stereochemistry of the asymmetric centres.

With the idea of determining these points, we carried out a more intensive study of the structure and stereochemistry of artemin. Using Grieco's procedure [4], enolization and subsequent phenylselenylation of the lactone, we obtained the phenylselenide (2). The oxidation of this compound (2) with 30% H_2O_2 in THF/acetic acid gave rise to a selenoxide (3), as intermediate product which suffered a *syn*-elimination to form product 4 which was identified as tanacetin [5] by comparing its IR and NMR spectra with those of an authentic sample. This allowed us to determine the position and stereochemistry of the secondary and tertiary hydroxyls (1β -equatorial, 5α -axial, respectively) as well as the disposition of the C-6 and C-7 hydrogen atoms (6β and 7α axial). $NaBH_4$ reduction of 4 led to product 5, the R_f values of which on TLC with various eluents were identical to those displayed by artemin. This confirmed the α -orientation of the C-11 methyl group since this type of reduction is highly stereospecific and always yields the α -epimer [6]. From the foregoing data, we deduced that the artemin isolated in this laboratory from *Artemisia maritima* is $1\beta,5\alpha$ -dihydroxy- $6\beta,7\alpha$,H-selin-4(15)-en-11 α -methyl-6,12-olide (5).

On the basis of only spectral evidence, Tarasov *et al.* [7] gave arsubin the structure that we have established for artemin and they claimed that arsubin and artemin are epimeric at C-11. They determined the C-11 configuration of arsubin by relating it to the downfield shift ($\Delta\delta = +0.12$ ppm) of the C-6 proton in β -santonin as compared with α -santonin [8]. From the downfield shift ($\Delta\delta = +0.23$ ppm) of the C-6 protons in acetylarsubin and acetylartemin, they conclude that the C-11 methyl group in arsubin and β -santonin have the same configuration. However, the formula they assign to arsubin (11 α -methyl) contradicts this theory, while the other configuration (11 β -methyl) would favour their

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argument that arsubin and artemin are probably epimeric at C-11.

EXPERIMENTAL

Mp's are uncorr. Optical activities were measured in CHCl_3 , UV spectra in EtOH and NMR spectra at 90 MHz in CDCl_3 with TMS as internal reference. The standard method referred to below consists of pouring into H_2O , extracting with solvents (CHCl_3 or EtOAc), washing the extract, drying with dry Na_2SO_4 , distilling and crystallizing. The aerial part of the plant (20 kg) was collected at Cabo Corbera (Valencia, Spain) in the months May–July, triturated and exhaustively extracted with hot EtOH. The EtOH extract was concd *in vacuo*, yielding a syrupy liquid with an intensely bitter taste. This was dissolved in 1 l. of hot EtOH with 2 l. of boiling H_2O containing $\text{Pb}(\text{OAc})_4$ (12 g). This was left for 24 hr, then filtered, most of the alcohol being eliminated. The resulting extract was treated in the normal fashion giving an oily liquid (650 g) which was chromatographed on Si gel (6 kg) 0.2–0.5 mm. The column was eluted with C_6H_6 and mixtures of C_6H_6 –EtOAc.

Artemin. The product obtained in 0.4% yield from C_6H_6 –EtOAc elution crystallized in petrol–EtOAc: mp 238–240°; MS m/e : 266 (M^+); $[\alpha]_D^{25}$ 167° (ca 0.5); IR ν_{max} cm^{-1} : 3570, 1770, 1650 and 920; NMR: δ 5.00 (2H, s, C-4=CH₂), 4.20 (2H, C-6 and C-1), 0.86 (3H, s, C-10 Me) and 1.20 (3H, d, J = 6 Hz, C-11 Me). (Found: C, 67.55; H, 8.08. Calc for $\text{C}_{15}\text{H}_{22}\text{O}_4$: C, 67.65; H, 8.33%).

Monoacetylartemin. Ca 55 mg of the alcohol was dissolved in Py and Ac_2O (2 ml) was added. The mixture was left for 12 hr and recovered in the normal way. The monoacetate thus obtained crystallized in EtOAc–petrol: mp 227–229°; MS m/e : 308 (M^+); $[\alpha]_D^{25}$ 146° (ca 0.23); IR ν_{max} cm^{-1} : 3570, 1770, 1720, 1650 and 920; NMR: δ 1.00 (3H, s, C-10 Me), 1.25 (3H, d, J = 7 Hz, C-11 Me), 4.28 (1H, d, J = 11 Hz, C-6), 2.05 (3H, s, OAc), 5.05 (2H, d, J = 4.5 Hz, C-4=CH₂) and 5.42 (1H, dd, C-1). (Found: C, 65.97; H, 7.95. Calc for $\text{C}_{17}\text{H}_{24}\text{O}_5$: C, 66.21; H, 7.84%).

Phenylselenylation of artemin. (*i*-Pr)₂NH (0.09 ml), BuLi (0.4 ml 2 M in hexane) and dry THF (0.4 ml) were placed under dry Ar atmosphere and then cooled to –78°. The lactone (133 mg) was added slowly over 1 hr and then stirred for 20 min at –78°. Once the enolate had formed, diphenyldiselenide (188.5 mg) dissolved in dry THF (0.5 ml) containing HMPA (0.105 mg) was added rapidly in drops. After 40 min at –78°, the temp. was raised to –40° and the mixture stirred for 1.5 hr at that temp. The reaction was halted by the addition of 10% HCl. The resulting phenylselenide was recovered as normal, giving a yellow oil which could not be crystallized. MS m/e : 422 (M^+) ($\text{C}_{15}\text{H}_{21}\text{O}_4\text{PhSe}$); NMR: δ 1.55 (3H, s, C-11 Me), 0.86 (3H, s, C-10 Me), 4.92 (2H, d, J = 12 Hz, C-4=CH₂) and 7.3–7.7 (5H, m, $-\text{C}_6\text{H}_5$).

11-methylenation. Phenylselenide (15 mg) in THF (1 ml) containing HOAc (0.01 ml) was cooled to 0° and 30% H_2O_2 soln (0.04 ml) was added. The mixture was stirred for 30 min at 0°, poured into a cold NaHCO_3 soln, then recovered by the standard process. Crystallization in EtOAc–petrol: mp 206–207°; IR ν_{max} cm^{-1} : 3570, 1770, 1650 and 920; NMR: δ 6.12 and 5.45 (1H each, dd, J = 3.5 Hz, C-11=CH₂), 5.05 (2H, s, C-4=CH₂), 4.30 (1H, d, J = 11 Hz, C-6), 4.15 (1H, m, C-1) and 0.90 (3H, s, C-10 Me).

Reduction with NaBH_4 . About 10 mg of the above product was dissolved in MeOH (8 ml), NaBH_4 (60 mg) added, and the mixture was stirred at 0° for 10 min. The MeOH was then eliminated and the residue acidified with 5% HCl; after the usual work-up, an oily substance was obtained. The R_f of artemin and this compound were identical in C_6H_6 –EtOAc (7:3), EtOAc–petrol (1:1) and Me_2CO –(*i*-Pr)₂O (7:3).

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