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STEREOCHEMISTRY OF THE ESTER SIDE CHAIN OF THE GERMACRANOLIDES OF *VIGUIERA HYPARGYREA*[1]

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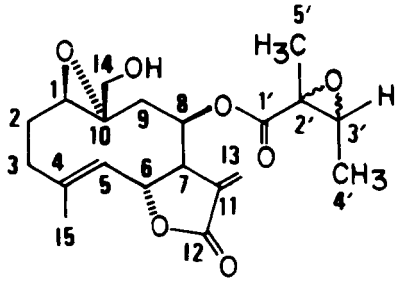
In earlier articles (1-4), the chemical constituents of several *Viguiera* species (Compositae) were reported, and the results obtained indicate that the terpenoids are useful in discerning infrageneric groups and are in agreement with the accepted biogenetic relationships between members of the Helianthineae (*Helianthus, Tithonia, Syncretocarpus,* among others) (5). Furthermore, the presence of sesquiterpene lactones of advanced biogenetic complexity in *Helianthus* and *Tithonia* (but not in *Viguiera*) supports the putative derivatization of these genera from a Viguieroid stock (6).

In accordance with these findings, several novel germacranolides have recently been isolated from *Viguiera hypargyrea* (6). However, the complete stereochemical expression of **1** and **2** were not established, because the configuration of the five carbon ester side chain was not determined.

The two possible diastereoisomers (2′*R*,3′*R* and 2′*S*,3′*S*) of epoxyangeloyloxy sesquiterpene lactones are found in nature (7), but arguments based on spectral data are not reliable guides for discrimination. Therefore, an X-ray structure determination of **1** or **2** (or a derivative) was desirable. The natural products did not give suitable crystals, but acid treatment of **3** [obtained by acetylation of **1** or by epoxidation of **2** (6)] with HCl afforded the crystalline chlorhydrin **4** (see Experimental) which was satisfactory for this study.

Details of this analysis are given in the experimental section and listings of pertinent crystallographic data are available as supplementary material. Atomic coordinates for chlorhydrin **4** are given in Table 1, and Figure 1 is a computer-generated drawing of the enantiomer which, based on the anomalous scattering of the chlorine atom, also represents the absolute configuration.

The 2′*R*,3′*S* configuration of the ester side chain of **4** (Figure 1) indicates a 2′*R*,3′*R* stereochemistry of the



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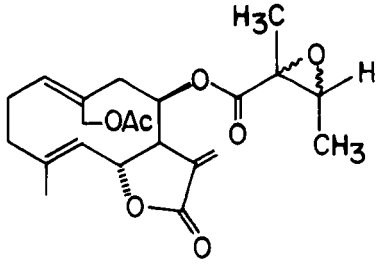

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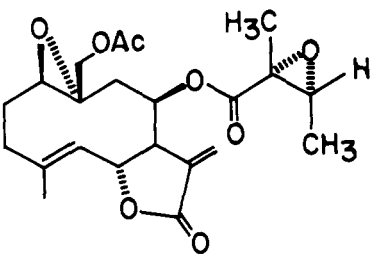

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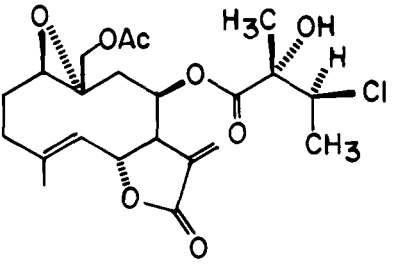

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epoxyangeloyl residue of **3** (and, therefore, of **1** and **2**) due the regio-differentiated S_N2 ring opening of the oxirane with inversion at C-3′.

The $_1D^{14},{}^{15}D_5$ crown conformation of the macrocycle depicted in Figure 1 is not significantly different from those determined by X-ray analysis for other germacranolides with *trans*-lactones closed to C-6 such as hanphyllin (8) and euserotin (9), although the four extreme conformers (due to diastereofacial arrangements of the double bonds of their equivalents) are found in the germacrolide series (10).

EXPERIMENTAL

8β-[Epoxyangeloyloxy]-14-hydroxy-tithifolin

TABLE 1. Positional Parameters ($\times 10^4$) and Equivalent Isotropic Temperature Factors ($Å^2$) for Compound **4**

	x	*y*	*z*	U_{eq}
Cl	3512(2)	7418(2)	6708(2)	70(1)
O(1)	10465(4)	2184(4)	10453(3)	49(1)
O(2)	1833(4)	3608(4)	12816(3)	49(1)
O(3)	5411(4)	4098(3)	8923(3)	36(1)
O(4)	−306(4)	5776(5)	12540(4)	77(2)
O(5)	9051(4)	1375(4)	8249(3)	48(1)
O(6)	5888(4)	4230(4)	5293(3)	57(1)
O(7)	7413(4)	5407(4)	6844(3)	54(1)
O(8)	8222(6)	−1220(5)	8262(4)	89(2)
C(1)	8936(5)	1924(5)	11753(4)	44(2)
C(2)	8759(6)	115(6)	12729(4)	51(2)
C(3)	6878(6)	−78(6)	13889(4)	53(2)
C(4)	5345(6)	478(5)	13216(4)	43(2)
C(5)	4764(5)	2163(5)	13029(4)	38(2)
C(6)	3753(5)	3141(5)	12020(4)	37(2)
C(7)	4597(5)	4918(5)	11160(4)	39(2)
C(8)	6136(5)	4953(5)	9739(4)	37(2)
C(9)	8113(5)	4311(5)	9750(4)	39(2)
C(10)	8586(5)	2411(5)	10360(4)	37(2)
C(11)	2913(6)	6089(5)	11053(4)	46(2)
C(12)	1276(6)	5226(6)	12172(5)	51(2)
C(13)	2789(8)	7606(7)	10180(5)	71(2)
C(14)	8135(6)	1030(5)	9784(4)	41(2)
C(15)	4758(7)	−907(6)	12688(5)	60(2)
C(16)	6074(5)	4570(5)	7499(4)	37(1)
C(17)	4885(5)	3967(5)	6779(4)	40(2)
C(18)	3058(6)	5126(6)	7010(4)	49(2)
C(19)	4449(7)	2050(6)	7369(4)	54(2)
C(20)	1955(7)	4994(8)	6061(6)	72(2)
C(21)	8992(6)	94(5)	7610(4)	43(2)
C(22)	9882(7)	603(6)	6042(4)	59(2)

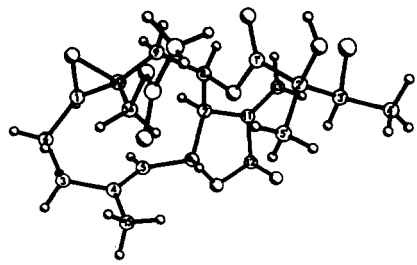

FIGURE 1. Computer perspective drawing of **4**

[**1**] and 8β-[epoxyangeloyl]-14-acetoxyeupatolide [**2**] were the substrates for **3** (via acetylation of **1** or epoxidation of **2**) as described in the previous work (6).

ACID TREATMENT OF **3** TO **4**.—8β-[Epoxyangeloyloxy]-14-acetoxy-tithifolin [**3**] (80 mg) was treated with dry HCl gas in Et_2O (75 ml) at −5° for 2 min. The reaction mixture was diluted with H_2O, washed with saturated aqueous $NaHCO_3$, and the organic phase dried and evaporated. The residue was chromatographed over Si gel column using hexane-EtOAc (3:1) as eluent. The product (43 mg) was crystallized from Me_2CO/iPr_2O to afford crystals of **4**, mp 220-222°; ir ($CHCl_3$) 3560, 1765, 1740, 1735, 1640 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 6.32 (1H, d, *J*=3.5 Hz, H-13), 5.72 (1H, m, H-8), 5.62 (1H, d, *J*=3.5 Hz, H-13′), 5.37 (1H, dq, *J*=10, 1 Hz, H-5), 5.12 (1H, dd, *J*=9, 10 Hz, H-6), 4.16 (1H, d, *J*=9 Hz, H-14a), 4.01 (1H, d, *J*=9 Hz, H-14b), 3.25 (1H, m, H-9a), 2.93 (1H, q, *J*=7 Hz, H-3′), 2.05 (3H, s, CH_3CO), 1.84 (3H, d, *J*=1 Hz, 15CH_3), 1.48 (3H, *J*=7 Hz, 4′CH_3), 1.31 (3H, s, 5′CH_3); ^{13}C nmr (20 MHz, $CDCl_3$) δ 173.32 (s, C-1′), 170.69 (s, CH_3CO), 168.77 (s, C-12), 144.57 (s, C-4), 135.41 (s, C-11), 124.93 (d, C-5), 122.21 (t, C-13), 77.34 (d, C-3′), 73.75 (d, C-6), 69.93 (d, C-2′), 66.88 (d, C-1), 64.85 (t, C-14), 62.69 (d, C-8), 59.85 (s, C-10), 53.21 (d, C-7), 38.23 (t, C-9), 35.80 (t, C-3), 24.53 (q, C-5′), 22.11 (t, C-2), 20.81 (q, CH_3CO), 18.19 (q, C-4′), 17.18 (q, C-15); cims *m/z* (rel. int.) 459 (9) $[M+1]^+$, 457 (29), 439 (15), 417 (34), 415 (92), 381 (10), 379 (32), 305 (33), 263 (42), 246 (18), 245 (75), 227 (100), 107 (5). (Found: C, 58.18%; H, 6.44. $C_{22}H_{29}O_8Cl$ requires: C, 57.90; H, 6.30).

X-RAY STRUCTURE ANALYSIS.—The chlorhydrin **4** was crystallized by slow evaporation from EtOAc solution. Crystal data: $C_{22}H_{29}O_8Cl$, Mω=456.9, triclinic, space group Pl, a=7.689 (4), b=7.869 (4), c=10.189 (4)Å, α=75.42 (4), β=70.27 (3), γ=82.19 (4)°, V=561 (1)Å^3, D_c=1.35 g cm^{-3}, F(000)=242, T=293 K, Z=1, μ(MoKα)=2.11 cm21. Using a crystal 0.18×0.27×0.32 mm, lattice parameters were obtained from 25 machine-centered reflections with 5.3<2θ<21.4°. Reflections in a hemisphere of reciprocal space were measured with an index range of h 0/7, k±8, 1±10, using ω scanning mode with graphitemonochromatized MoKα radiation on a Nicolet R3m four circle diffractometer, variable scan speed (max 29.3°/min; min 3.91°/min), scan width 1.0 (°ω), two standard reflections (1,1,-1; 0,1,-2) monitored every 50 measurements. The intensities were corrected for Lorentz and polarization effects, but no absorption corrections were applied. Of the 1595 reflections within the 2θ range of 3 - 45° collected, 1457 had values of 3σ(I) their estimated standard deviations, and these were used in the final refinement of structural parameters. The structure was solved by direct methods (11), using 200 phases with |E|>1.2 and 12 reflections in the starting set, and refined by cascade matrix least squares techniques with anisotropic temperature factors for the non hydrogen atoms. The H atoms of the tertiary CH, secondary CH_2, and primary CH_3 groups were assigned coordinates based on the expected bonding geometry. All H atoms coordinates were refined with a fixed anisotropic temperature factor of U=0.06 Å^2. The function minimized was $\Sigma\omega(\Delta F)^2$ with a statistical weight of the form $\omega = \sigma^2(F_o)+0.0005\,(F_o)^2\,^{-1}$, where σ is the standard deviation of the observed amplitudes based on counting statistics. The conventional R factor was 0.035 and ωR=0.040 ($\omega R=|\Sigma\omega(|Fol-|Fcl)^2/\Sigma|Fol^2|^{1/2}$, scattering factors for Cl, O, C, and H atoms were from International Tables for X-ray Crystallography (12), and the isotropic extinction parameter x=0.00173. A final difference Fourier synthesis revealed no peaks higher than those assigned earlier to hydrogen atoms, and the weighting appeared reasonable.

As all correction terms allowing for anomalous scattering were introduced at the beginning of refinements, a significance test (13) was used to discriminate between the two possible enantiomorphs. For comparison with R_g+=.0400, the R− of the other enantiomorph was obtained by a least-squares refinement calculated with inverted coordinates. The residual for this enantiomorph was R_g−=0.0402, R−/R+ Hamilton's R−factor test showed that the second absolute

configuration can be rejected at a confidence level >99.0%.

Although this seemed quite satisfactory, a new Hamilton's R−factor test using data collected with Cu-filtered radiation was performed, confirming the last assignment as a high confidence level (>99.5%), R+=.0957, R−=.1045, R−/R+=1.092.

The final atomic coordinates for the nonhydrogen atoms are listed in Table 1, and pertinent data are available as supplementary material.[4]

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[4]The supplementary material is available on request to the senior author. Atomic coordinates for the structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Rd., Cambridge, CB2 1EW, UK.