MOLECULAR STRUCTURE AND ABSOLUTE CONFIGURATION OF TITHONIN, A HELIANGOLIDE FROM *TITHONIA ROTUNDIFOLIA*

J.G. RODRIGUEZ,* A. PERALES,[1] J.C. RODRIGUEZ-UBIS, P. VAZQUEZ, and J. BORGES

*Departamento de Quimica, C1, Facultad de Ciencias, Universidad Autonoma de Madrid,
Canto Blanco, 28049-Madrid, Spain*

ABSTRACT.—The molecular structure and absolute configuration of tithonin [1], a heliangolide isolated from *Tithonia rotundifolia*, have been determined by X-ray diffraction analysis. Correlations between the position and stereochemistry of the γ-lactone ring fusion to the ten-membered ring and the sign of the Cotton effect of the n-π* transition of the C=C-C=O chromophore of 1 have been analyzed.

Tithonin [1], a secondary metabolite isolated from *Tithonia rotundifolia* Blake (Asteraceae) (1) has a molecular formula of $C_{20}H_{28}O_7$ and mp of 134–135°, and the $[\alpha]^{20}D$ −121.3° (MeOH) (2).

An X-ray analysis of the title compound has been undertaken to confirm its molecular structure, because the absolute

TABLE 1. Positional Parameters ($\times 10^4$) and Equivalent Isotropic Temperature Factors (Å^2) for Tithonin [1] ($C_{20}H_{28}O_7$) (e.s.d's. in parentheses.)[a]

Atom	x/a	y/b	z/c	Ueq
O-1	5165 (3)	802 (2)	2997 (3)	50 (1)
O-2	4842 (3)	148 (2)	6303 (4)	57 (1)
O-3	6792 (3)	773 (1)	4670 (3)	38 (1)
O-4	10609 (3)	1645 (2)	3617 (3)	49 (1)
O-5	12647 (3)	1288 (2)	3880 (4)	83 (1)
O-6	10009 (3)	1440 (2)	7061 (3)	44 (1)
O-7	9838 (3)	941 (2)	9128 (3)	68 (1)
C-1	5457 (5)	1626 (2)	5659 (5)	45 (1)
C-2	5853 (5)	1846 (2)	4199 (5)	44 (1)
C-3	6247 (4)	1161 (2)	3546 (5)	43 (1)
C-4	7296 (4)	1203 (2)	2403 (4)	40 (1)
C-5	8559 (4)	1309 (2)	2645 (4)	38 (1)
C-6	9265 (4)	1439 (2)	3981 (4)	38 (1)
C-7	9424 (4)	827 (2)	5017 (4)	38 (1)
C-8	8987 (4)	988 (2)	6485 (4)	39 (1)
C-9	7692 (4)	1383 (3)	6661 (5)	42 (1)
C-10	6458 (4)	1068 (2)	5999 (4)	38 (1)
C-11	10855 (4)	652 (2)	4911 (5)	43 (1)
C-12	11497 (4)	1197 (3)	4103 (5)	51 (1)
C-13	11496 (5)	140 (3)	5477 (7)	67 (2)
C-14	5924 (5)	488 (3)	6912 (5)	47 (1)
C-15	6821 (5)	1111 (4)	939 (5)	53 (1)
C-16	10392 (4)	1330 (2)	8369 (4)	42 (1)
C-17	11579 (4)	1762 (3)	8738 (4)	48 (1)
C-18	11824 (5)	1769 (3)	10279 (5)	60 (1)
C-19	13064 (7)	2148 (4)	10707 (7)	73 (2)
C-20	12728 (7)	1519 (6)	7910 (8)	109 (4)

[a]Ueq = $1/3\Sigma$Uij.ai*.aj*.ai.aj.cos(ai,aj)$\times 10^3$.

[1]Departamento de Rayos-X, Instituto Rocasolano, C.S.I.C., Serrano 119, 28006-Madrid, Spain.

TABLE 2.   Bond distances (Å) for Tithonin [1]. (Standard deviations are in parentheses).

O-1–C-3	1.409(5)	C-1–C-2. . . .	1.526(7)	C-8–C-9	1.537(6)
O-2–C-14	1.414(5)	C-1–C-10. . .	1.523(6)	C-9–C-10 . . .	1.539(6)
O-3–C-3	1.432(5)	C-2–C-3. . . .	1.523(6)	C-10–C-14 . .	1.528(7)
O-3–C-10	1.444(5)	C-3–C-4. . . .	1.539(6)	· C-11–C-12 . .	1.467(7)
O-4–C-6	1.472(5)	C-4–C-5. . . .	1.327(6)	C-11–C-13 . .	1.307(7)
O-4–C-12	1.339(5)	C-4–C-15. . .	1.504(6)	C-16–C-17 . .	1.515(6)
O-5–C-12	1.207(5)	C-5–C-6. . . .	1.498(6)	C-17–C-18 . .	1.507(6)
O-6–C-8	1.471(5)	C-6–C-7. . . .	1.559(5)	C-17–C-20 . .	1.495(9)
O-6–C-16	1.338(5)	C-7–C-8. . . .	1.517(5)	C-18–C-20 . .	1.521(9)
O-7–C-16	1.193(5)	C-7–C-11. . .	1.504(6)		

TABLE 3.   Hemiacetalic Ring Torsion Angles
(°) for Tithonin [1]. (Standard
deviations are in parentheses).

C-2–C-1–C-10–O-3.	−29.1(4)
C-3–O-3–C-10–C-1.	8.8(4)
C-10–O-3–C-3–C-4.	138.8(3)
C-3–O-3–C-10–C-9.	−109.9(4)
C-10–O-3–C-3–C-2.	15.4(4)
C-10–C-1–C-2–C-3.	38.0(5)

TABLE 4.   γ-Lactone Ring Torsion
Angles (°) for Tithonin [1].
(Standard deviations are in parentheses).

C-6–O-4–C-12–C-11.	−2.8(5)
C-13–C-11–C-12–O-5.	−4.9(9)
C-6–O-4–C-12–O-5	179.4(4)
C-12–O-4–C-6–C-7.	8.9(5)
C-11–C-7–C-6–O-4.	−10.5(4)
C-5–C-6–C-7–C-8	−129.4(4)

configurations of compounds related in structure to tithonin [1] are not well established (2).

Fractional atomic co-ordinates of the carbon and oxygen atom and equivalent temperature factors for **1** are provided in Table 1, and bond lengths are given in Table 2, while Tables 3 and 4 show the torsion angles in the hemiacetal and γ-lactone rings of **1**, respectively. Figure 1 shows a perspective view of the molecule of **1** and the numbering of the atoms.

The X-ray crystallographic analysis confirmed that tithonin [**1**] is constituted by a γ-lactone, a hemiacetal cyclopentane ring, a ten-membered ring, and an ester side-chain. The conformation of the hemiacetal ring, which is bridged by O-3 between C-3–C-10, is an envelope, with the flap at C-2; both torsion angles around O-3 are small (Table 3). The conformation of the γ-lactone ring is closer to an envelope than a half-chair. The asymmetric parameters show the dominant symmetry D_s through C-7 (0.02 Å) and a rotational symmetry D_2 through C-12 (0.02 Å). The difference is very small and the conformation may be described in terms of the puckering am-

plitude (Q), and the phase angle (Φ). These values are in agreement with Duax's parameters (3). Torsion angles of this γ-lactone ring are shown in Table 4.

The ten-membered ring of the heliangolide **1** has been considered in terms of its conformational analysis. Such a ring system is quite common in this kind of sesquiterpenoid, and it can be defined by Hendrickson's symbols (4) as a twist-boat-chair-chair (TBCC) ring; this conformation has been taken with the torsional angles starting at C-9 in a clockwise sense (Table 3 and Figure 2). The dominant symmetry is rotational D_2 through C-9–C-10, with the α,β-methylene-γ-lactone ring trans-fused to the ten-membered ring.

Relative to the bond lengths and angles, the molecular structure of tithonin [**1**] in the solid state presents some remarkable points. For example, in the trans-fused γ-lactone ring is observed the longest bond distance, C-6–C-7 = 1.563(7) Å, which is also present in the ten-membered ring. Moreover, in the same ring, the lactone group shows some polar character due to the contribution of the following forms:
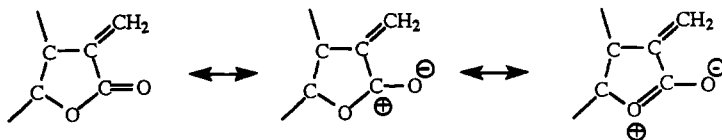
The exocyclic double bond in the γ-lactone ring remains unaffected by the polarization of the carbonyl group, which agrees well with the observed bond lengths and the deviation of the methylene group from the mean plane of the pentagonal ring.

On the other hand, the ester side-chain affixed at C-8 shows a similar polarization effect and thus the O-5 and O-7 atoms exhibit a basic character as evidenced by the contribution to hydrogen bridge interaction. In effect, the mol-ecules in the crystal are stabilized by hydrogen bonds through these O-5 and O-7 atoms and the O-2H and O-1H hydroxyl groups. The geometry of these hydrogen bonds is given below:

	d_1	d_2	d_3 (Å)	α (°)
O-1-H(01)...O-5	0.89(5)	2.04(5)	2.876(5)	155.3(5)
O-2-H(02)...O-7	0.82(4)	2.25(4)	3.004(5)	153.8(4)

Molecular packing of the molecules in the unit cell view down the a axis is shown in Figure 3, with the hydrogen bonds indicated by dashed lines.
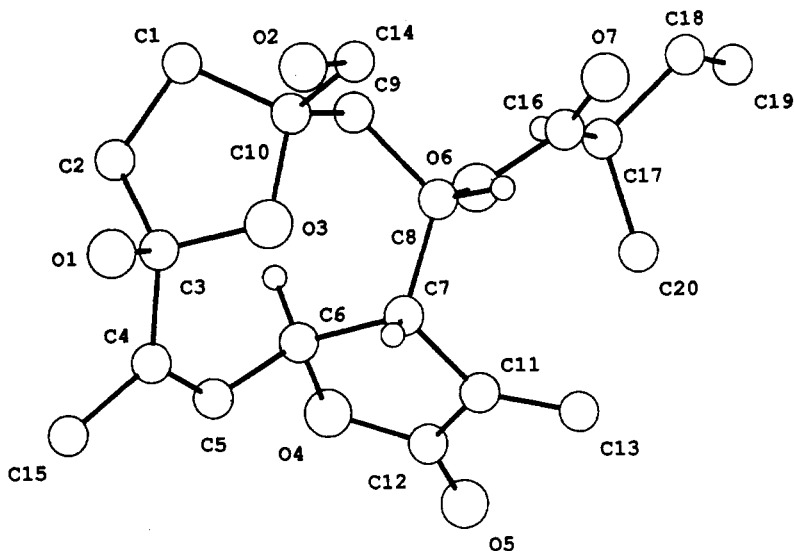

FIGURE 1.   Perspective view of the molecule and numbering of the atoms of tithonin [1].
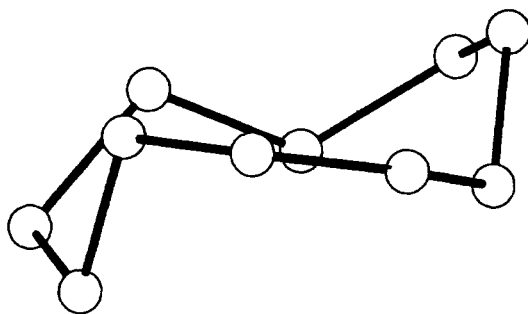

FIGURE 2.   TBCC conformation of the ten-membered ring of tithonin [1].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The mp was determined in a Büchi apparatus and is uncorrected. The optical rotation was measured with a Perkin-Elmer 141 polarimeter, with a 1 dm cell. Elemental analysis was carried out using a Heraeus CHN-O-rapid analyzer.

X-RAY CRYSTAL STRUCTURE ANALYSIS OF TITHONIN [1].—Crystals of tithonin [1] were isolated from the $CHCl_3$ eluent through a Si gel column and used for diffraction analysis. Crystal data: $C_{20}H_{28}O_7$, mol wt 380.44, transparent colorless needles, orthorhombic, space group $P2_12_12_1$, with $a=10.213(2)$, $b=19.365$ (1), $c=9.644$ (4) Å (from least-squares refinement based on 25 reflections); $V=1907.3$ (9) Å^3, $Z=4$, $\mu=7.87$ cm^{-1}, $Dc=1.323$ gcm^{-3}, $F(000)=816$, Cu-Kα radiation ($\lambda=1.5407$ Å). Crystal dimensions: $0.2\times0.3\times0.3$ mm. Three-dimensional data were collected on a Philips PW1100 diffractometer, employing graphite-oriented monochromated Cu-Kα radiation by the ω-2θ scan technique. The standard reflections, measured every 90 min, showed no crystal decomposition. The intensity for 3253 independent reflections up to $\theta<65°$ were recorded. A total of 2492 reflections was considered as observed with the criterion $I>2\sigma(I)$ and used in subsequent calculations. The data were corrected for Lorentz and polarization factors but no absorption correction was applied. The structure was solved by direct methods, MULTAN (5), and Fourier synthesis. Refinement was done by full-matrix least-squares analysis with anisotropic temperature factors. All H atoms were found in a difference synthesis and included in subsequent refinements as isotropic contribution. A convenient weighting scheme (6) was used to prevent bias on $<w\Delta^2F>$ vs $<Fo>$ and vs $<sin\theta/\lambda>$ for $\pm$hkl reflections (Friedel pairs). Final full matrix anisotropic weighted refinement (isotropic for H atoms) gave the discrepancy index $R=0.066$ and $Rw=0.068$. The absolute configuration was determined with Bijvöet differences in two experiments using the anomalous dispersion of C and O atoms. The averaged Bijvöet difference was 0.988 for the right vs. 1.041 for the wrong enantiomer (7).

Atomic scattering factors and anomalous dispersion factors were taken from "International Tables for X-Ray Crystallography" (8). Most calculations were performed using the X-Ray 76 System (9).^{2}

Circular dichroism of tithonin [1] was carried out in $CHCl_3$ and the Cotton effect showed a negative sign.

LITERATURE CITED

1. P.C. Standley and S. Calderón, "Lista Preliminar de las Plantas de El Salvador." Ediciones Culturales de la Universidad de El Salvador, San Salvador, 1944.
2. M. Alonso-López, J. Borges del Castillo, J.C. Rodríguez-Ubis, and P. Vazquez-Bueno, *J. Chem. Soc., Perkin Trans. I*, 2017 (1986).
3. W.L. Duax, C.M. Weeks, and D.C. Rohner, Eds., "Topics in Stereochemistry," Vol. 9 (1979).
4. J.B. Hendrickson, *J. Am. Chem. Soc.*, **86**, 4854 (1964).
5. P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declerq, and M.M. Woolfson, "MULTAN 80," Universities of York, England, and Louvain, Belgium, 1980.
6. M. Martinez-Ripoll and F.H. Cano. "Pesos Program," Instituto Rocasolano, CSIC, Madrid, Spain, 1975.
7. M. Martinez-Ripoll and J. Fayos, "CONFAB Program," Instituto Rocasolano, CSIC, Madrid, Spain.
8. "International Tables for X-Ray Crystallography," Birmingham, UK, Kinoch Press, 1974, Vol. IV, p. 72.
9. J.M. Stewart, F.A. Kundell, and J.C. Baldwin, "The X-Ray 76 System." Computer Science Center, University of Maryland, 1976.

---

^{2}A list of atomic coordinates and Fo-Fc values for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EZ, UK.