The Stereochemistry and Solid State Conformation of the Eudesmanolides Torrentin and 11-epi-Torrentin

J. Alberto Marco, Juan F. Sanz, Miguel Carda, and Johann Lex

More About This Article

The permalink http://dx.doi.org/10.1021/np50082a012 provides access to:

- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

THE STEREOCHEMISTRY AND SOLID STATE CONFORMATION OF THE EUDESMANOLIDES TORRENTIN AND 11-*epi*-TORRENTIN

J. Alberto Marco,* Juan F. Sanz,*

Departamento de Química Orgánica, Facultad de Química, E-46100 Burjassot, Valencia, Spain

Miguel Carda,

*Departamento de Química Orgánica, Colegio Universitario de Castellón, E-12080 Castellón, Spain*

and Johann Lex

Institut für Organische Chemie der Universität Köln, Greinstrasse 4, D-5000 Köln 41, FGR

ABSTRACT.—The stereochemistry and solid state conformation of the eudesmanolides torrentin [1] and 11-*epi*-torrentin [2], isolated from *Artemisia herba-alba* subsp. *valentina*, have been definitively established with the aid of X-ray analysis. In both compounds the cyclohexene ring displays a twisted chair conformation, while the lactone ring adopts an envelope conformation with a pseudo symmetry plane through C-7. This solid state geometry is very close to that predicted by the MacroModel program for conformational analysis.

We have previously isolated the eudesmanolides torrentin [1] and 11-*epi*-torrentin [2], along with many other sesquiterpene lactones, from aerial parts of *Artemisia herba-alba* Asso subsp. *valentina* Lam. (Asteraceae) (1–4). The structure initially assigned to torrentin was later shown to be erroneous following high-field nmr studies and chemical correlations (1). As a result of these studies, structure 1 was suggested for the compound. The structure of lactone 2, isolated later from the same species, was assigned on the basis of the close similarity of its nmr spectra with those of 1 (4). We have now carried out X-ray crystallographic analyses (Table 1) of both eudesmanolides in order to establish definitively their stereostructures.

The molecular structures of lactones 1 and 2, Figures 1 and 2, respectively, confirm the stereochemical conclusions drawn previously from spectral and chemical correlation data (1,4). Tables 2 and 3 contain the atomic coordinates of both compounds, and Table 4 displays the values of the dihedral angles for several atomic arrangements. The cyclohexene ring has a twisted chair conformation in both molecules, as deduced from the small value of the dihedral angle C-3–C-4–C-5–C-10, with C-1 below and C-2 above the mean plane defined by the first four atoms. The other six-membered ring displays the usual chair form, and most endocyclic torsion angles do not differ much from 60°. The five-membered lactone ring almost shows an evelope conformation: C-11, C-12, the lactone ether oxygen O-4, and C-6 are nearly planar, and C-7 lies below the plane. Similar geometries of the lactone ring have been observed in other sesquiterpene lactones (5,6). By comparing the data for 1 and 2, it was concluded that inversion of the configuration at C-11 does not produce any essential change in conformation of the
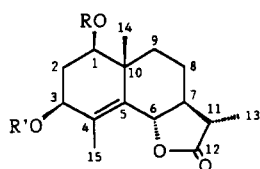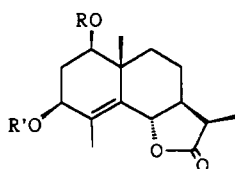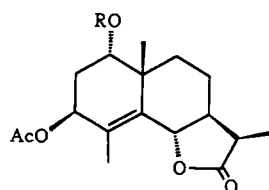
1	R=H, R'=Ac	2	R=H, R'=Ac	5	R=H
3	R=R'=H	4	R=R'=H	6	R=Ac
7	R=Ms, R'=Ac	8	R=Ms, R'=Ac		

TABLE 1.   Crystal Data of Lactones **1** and **2**.

Crystal parameters	Compound	
	1	**2**
Chemical formula	$C_{17}H_{24}O_5 \cdot H_2O$	$C_{17}H_{24}O_5$
Mol wt	326.37	308.36
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Crystal size (mm)	$0.25 \times 0.25 \times 0.2$	$0.1 \times 0.08 \times 0.07$
Cell constants		
a (Å)	5.813(1)	9.501(2)
b (Å)	8.374(2)	12.817(3)
c (Å)	35.584(7)	13.410(3)
Cell volume, Å^3	1732.12	1632.90
ρ_{calc} (g/cm^3)	1.252	1.254
Z	4	4
F(000) (e$^-$)	704	664
Data collection parameters		
μ (cm^{-1})	0.879	0.854
2θ limits	$1°-27°$	$1°-25°$
Reflections collected	2925	1659
Structure refinement		
Reflections for final refinement	1680	918
Parameters refined	312	296
R	0.048	0.043
R$_w$	0.058	0.041

molecule, at least regarding the cyclohexane and lactone rings. Some differences are seen in dihedral angles of the cyclohexene ring, especially in those involving hydrogen atoms H-1 to H-3. These differences, however, could also be attributed to the presence of H_2O molecules in the crystal network of **1** which bind the hydroxy groups of pairs of torrentin molecules by means of a hydrogen bond (Figure 3). Higher rigidity of the
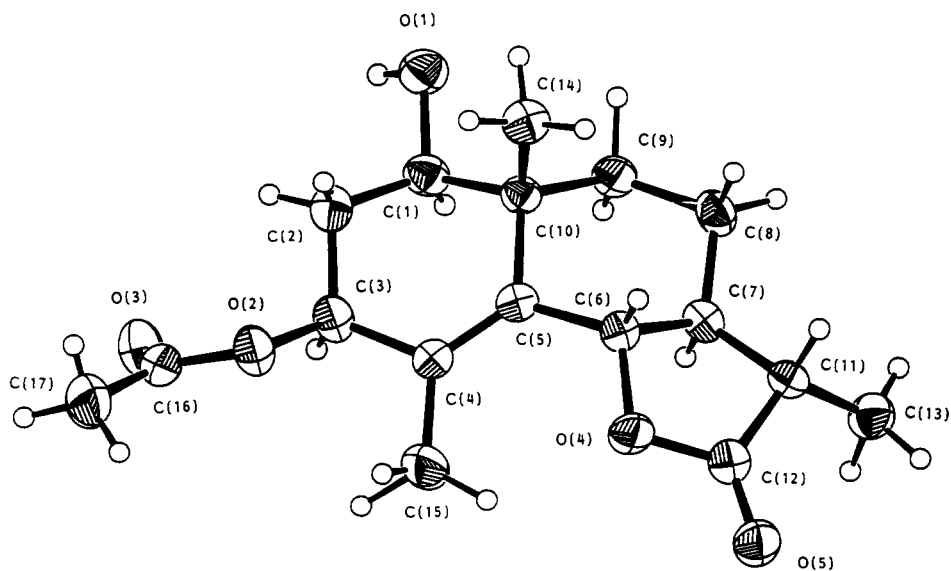
FIGURE 1.   Molecular structure of torrentin [**1**].
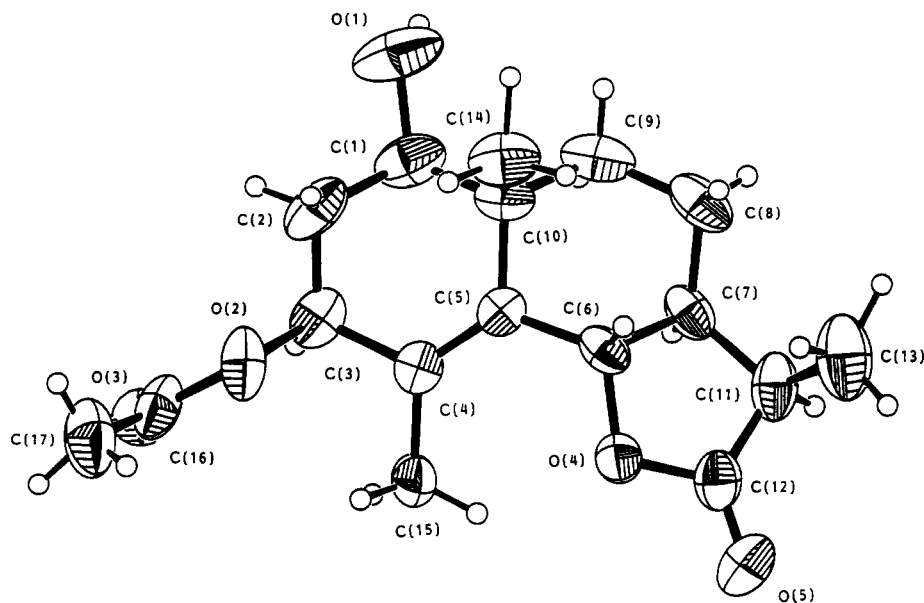
FIGURE 2.   Molecular structure of 11-*epi*-torrentin {2}.

crystal network of **1**, as compared with that of **2**, which manifests in the smaller radius of the probability spheres for the former compound (40% in both cases, see Figures 1 and 2), may be due to the presence of these hydrogen bonds.

TABLE 2.   Final Atomic Coordinates of Torrentin {1}.[a]

Atom	x	y	z
C-1	0.3420 (6)	0.6416 (4)	0.5805 (1)
C-2	0.1441 (8)	0.5476 (4)	0.5649 (1)
C-3	0.0811 (7)	0.4178 (4)	0.59217 (9)
C-4	0.0592 (7)	0.4747 (4)	0.63265 (9)
C-5	0.1460 (6)	0.6151 (4)	0.64338 (9)
C-6	0.1354 (6)	0.6870 (4)	0.68210 (9)
C-7	0.3719 (6)	0.7292 (4)	0.69793 (9)
C-8	0.4789 (6)	0.8593 (4)	0.6743 (1)
C-9	0.4981 (6)	0.7962 (4)	0.6340 (1)
C-10	0.2710 (6)	0.7318 (4)	0.61639 (9)
C-11	0.3166 (6)	0.7542 (3)	0.73908 (9)
C-12	0.1308 (6)	0.6307 (4)	0.74526 (9)
C-13	0.5153 (7)	0.7418 (4)	0.7665 (1)
C-14	0.1144 (7)	0.8732 (4)	0.6070 (1)
C-15	−0.055 (1)	0.3532 (5)	0.6578 (1)
C-16	−0.1427 (7)	0.2328 (4)	0.55626 (9)
C-17	−0.3762 (9)	0.1672 (5)	0.5497 (1)
O-1	0.4317 (5)	0.7518 (3)	0.55375 (7)
O-2	−0.1435 (4)	0.3494 (3)	0.58202 (7)
O-3	0.0301 (5)	0.1895 (3)	0.54055 (7)
O-4	0.0297 (4)	0.5909 (3)	0.71180 (6)
O-5	0.0726 (5)	0.5654 (3)	0.77383 (6)
O-6[b]	0.6628 (6)	0.5832 (3)	0.50039 (7)

[a]Estimated standard deviations in the least significant digit are shown in parentheses. Only the non-hydrogen atoms are included. For atom numbering, see Figure 1.
[b]Hydrogen-bonded H_2O molecule.

TABLE 3.   Final Atomic Coordinates of 11-*epi*-Torrentin [2] [a]

Atom	x	y	z
C-1	0.4096(5)	0.4535(4)	0.3559(4)
C-2	0.3365(6)	0.4089(4)	0.2680(4)
C-3	0.3553(5)	0.2921(4)	0.2637(3)
C-4	0.3410(4)	0.2378(3)	0.3629(3)
C-5	0.3349(4)	0.2920(3)	0.4476(3)
C-6	0.3129(5)	0.2493(3)	0.5502(3)
C-7	0.4250(5)	0.2796(4)	0.6250(3)
C-8	0.4189(5)	0.3956(4)	0.6411(4)
C-9	0.4432(6)	0.4473(4)	0.5383(5)
C-10	0.3453(5)	0.4127(3)	0.4542(4)
C-11	0.3999(5)	0.2007(4)	0.7091(3)
C-12	0.3483(5)	0.1074(4)	0.6546(3)
C-13	0.2939(7)	0.2323(5)	0.7898(4)
C-14	0.1971(5)	0.4598(4)	0.4699(4)
C-15	0.3414(6)	0.1204(4)	0.3543(3)
C-16	0.2671(5)	0.2115(4)	0.1113(3)
C-17	0.1343(6)	0.1878(5)	0.0554(4)
O-1	0.4003(4)	0.5640(3)	0.3488(3)
O-2	0.2388(3)	0.2538(3)	0.2000(2)
O-3	0.3849(4)	0.1967(3)	0.0818(3)
O-4	0.3019(3)	0.1365(2)	0.5614(2)
O-5	0.3388(4)	0.0189(3)	0.6799(2)

[a]Estimated standard deviations in the least significant digit are shown in parentheses. Only the non-hydrogen atoms are included. For atom numbering, see Figure 2.

Table 4 further shows the dihedral angles calculated for both molecules from computer-generated, energy-optimized geometries (see Experimental). Satisfactory agreement between the calculated and observed values was obtained (hydrogen-bonded H_2O molecules were not considered in the calculations). Furthermore, the [1]H-nmr coupling constants calculated by the program (not given in the table) (7) are in concurrence with those measured in the spectra (1,4). This indicates that there are no important differences between the solid state and solution conformations.

Deacetylation of torrentin and its 11-epimer yielded, respectively, compounds **3** and **4**, small amounts of which had been previously isolated as oils from the plant (4). We have now been able to crystallize these compounds and determine their melting points (see Experimental). We were, however, unsuccessful in our attempts to invert the configuration of C-1 in either **1** or **2**. In the case of the latter compound, this inversion would have served to obtain compound **5**, 1,11-di-*epi*-torrentin, another eudesmanolide isolated (in the form of the acetate **6**) from the same species (4). The Mitsunobu method failed completely with **2** in all attempted reaction conditions (8,9), and only unchanged starting product was recovered. We were able to transform **1** and **2** into the corresponding mesylates, **7** and **8**, but these derivatives did not undergo the desired nucleophilic substitution with any of the oxygen nucleophiles we tried. In all probability, the neopentyl-like secondary hydroxy group in **1** and **2** is too hindered for an S_N2 process to occur at a reasonable rate.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—[1]H-nmr spectra were measured at 200 MHz. Cc was made on Si gel Merck (40–63 μ). For optimization of molecular geometries, the MacroModel program, version 3.0 (Prof. W.C. Still, Columbia University) was utilized. Energy minimizations were performed with the BatchMin program, version 3.1c, using the Monte Carlo multiconformer search (MCMM). Cal-

TABLE 4.   Comparison of Some Selected Torsion Angles (°) in Torrentin [1] and 11-*epi*-Torrentin [2]
with Calculated Values.

Angle	Compound			
	1[a]	1[b]	2[a]	2[b]
H-1–C-1–C-2–H-2α	−65.9	−62.4	−63.2	−62.8
H-1–C-1–C-2–H-2β	167.7	179.3	176.4	−179.6
H-2α–C-2–C-3–H-3	53.4	44.3	41.2	44.1
H-2β–C-2–C-3–H-3	169.9	161.6	157.7	161.5
H-6–C-6–C-7–H-7	−176.4	−172.1	−177.2	−171.1
H-7–C-7–C-8–H-8α	−66.0	−62.9	−54.1	−64.1
H-7–C-7–C-8–H-8β	179.4	179.0	−178.9	−177.3
H-7–C-7–C-11–H-11	169.3	167.5	32.0	33.9
H-8α-C-8-C-9–H-9α	60.1	51.5	60.8	51.6
H-8α-C-8-C-9–H-9β	−59.2	−62.5	−61.8	−62.3
H-8β–C-8-C-9–H-9α	175.0	170.1	−177.7	170.1
H-8β–C-8-C-9–H-9β	55.7	56.2	59.7	56.2
C-3–C-4–C-5–C-10	0.9	−3.4	−1.6	−3.3
C-4–C-5–C-10–C-1	−17.1	−16.7	−17.8	−16.5
C-2–C-3–C-4–C-5	−16.2	−9.3	−10.1	−9.4
C-10–C-1–C-2–C-3	−65.6	−62.7	−63.7	−62.3
C-5–C-6–C-7–C-8	64.8	67.3	65.4	66.9
C-6–C-7–C-8–C-9	−59.2	−61.9	−58.9	−61.8
C-7–C-8–C-9–C-10	53.9	52.4	54.5	52.7
C-6–C-5–C-10–C-9	47.4	47.5	46.4	47.6
C-5–C-6–C-7–C-11	−165.4	−166.3	−163.6	−164.3
O-4–C-6–C-7–C-11	−37.2	−37.0	−33.7	−34.9
C-11–C-12–O-4–C-6	−1.6	−0.2	−2.8	−1.2
C-7–C-11–C-12–O-4	−22.0	−23.2	−18.8	−20.9
C-7–C-6–O-4–C-12	24.6	24.0	23.6	23.2

[a]X-ray; this work.
[b]Computed by MacroModel, see text.

culations of the coupling constants were done in the nmr Analysis submode of the program and are based on an extended Karplus equation (7). Identification of plant material and isolation of compounds 1 and 2 were as described previously (1–4).

DEACETYLATION OF 1 AND 2.—Deacetylation was performed by treatment with K_2CO_3 in MeOH (stirring at room temperature for 6 h). Standard workup and cc on Si gel [hexane-EtOAc (1:4)] yielded 3, colorless needles, mp 116–117° (from hexane/Et_2O), and 4, colorless needles, mp 137–138° (from hexane/Et_2O), respectively. For spectroscopic data, see Sanz and Marco (4).
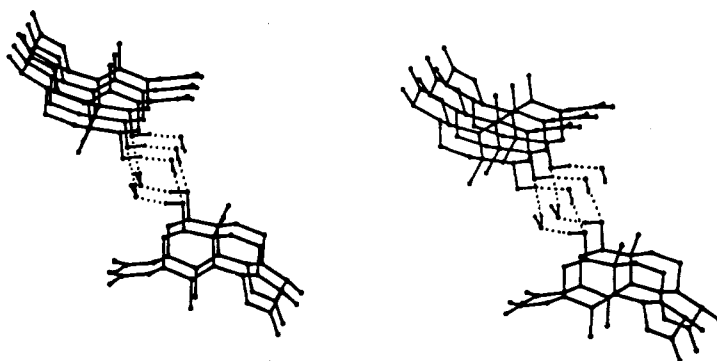

FIGURE 3.   Crystal network of torrentin [1], showing the hydrogen-bonded
water molecules (stereoview).

ATTEMPTS AT MITSUNOBU REACTION WITH **1** AND **2**.—Reactions were attempted using several of the reaction conditions previously described (8). Use of either THF or C_6H_6 as the solvents, at either room temperature or at reflux, with either HCO_2H or 3,5-dinitrobenzoic acid (9) as the added nucleophile led only to recovery of starting product.

TRANSFORMATION OF **1** AND **2** INTO THE MESYLATES **7** AND **8**.—The following conditions were used (10): methansulfonic anhydride (260 mg, 1.5 mmol) was added to a solution of lactone **1** or **2** (308 mg, 1 mmol) and triethylamine (0.35 ml, 2.5 mmol) in CH_2Cl_2 (25 ml). After stirring at room temperature for 18 h, the reaction mixture was subjected to standard aqueous workup, followed by cc on Si gel [hexane-EtOAc (2:3)]. The desired mesylates **7** and **8** were obtained as oils in ca. 80% yield. Compound **7**: ^{1}H nmr 5.38 (br t, J = 8.5 Hz, H-3), 4.60 (dd, J = 12.5, 3.5 Hz, H-1, overlapping the signal of H-6), 3.05 (3H, s, OMs), 2.30 (dq, J = 12, 7 Hz, H-11), 2.09 (3H, s, OAc), 1.80 (3H, br s, H-15), 1.24 (3H, s, H-14), 1.22 (3H, d, J = 7. Hz, H-13). Compound **8**: ^{1}H nmr 5.38 (br t, J = 8.5 Hz, H-3), 4.77 (br dq, J = 11.7, 1 Hz, H-6), 4.60 (dd, J = 12.5, 3.5 Hz, H-1), 3.03 (3H, s, OMs), 2.67 (dq, J = 7, 7 Hz, H-11), 2.07 (3H, s, OAc), 1.78 (3H, br s, H-15), 1.21 (3H, s, H-14), 1.17 (3H, d, J = 7 Hz, H-13).

ATTEMPTED S_N2 INVERSION OF **7** AND **8**.—No reaction was observed when either mesylate **7** or **8** was allowed to react with potassium formate and 18-crown-6 in either THF or toluene at either room temperature or at reflux. When reaction of either mesylate with KO_2 and 18-crown-6 in either DME or DMSO/DME (11) at 0° or room temperature was performed, only extensive decomposition was observed.

X-RAY ANALYSIS[1].—Lactones **1** and **2** crystallized as colorless needles from EtOAc. Crystallographic data were collected with an Enraf-Nonius CAD-4 diffractometer. Measurements were performed at room temperature with graphite-monochromated MoKα radiation, using an ω–2θ scan mode with scan width = 0.70 + 0.35 tan θ and ω scan speed 1.1 degrees per min. After data reduction, reflections with $I > 2\sigma(I)$ were taken as observed (for specific data see Table 1). The structure was solved by direct methods (MULTAN11/82), using the Enraf-Nonius SDP package (12,13); hydrogen atoms were obtained from a difference Fourier map. Full-matrix least-squares refinement with anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for hydrogen atoms led to the R and R_w values indicated in Table 1 [weighting scheme $w^{-1} = \sigma^2(F)$]. Scattering factors are from Cromer and Weber (14).

ACKNOWLEDGMENTS

LITERATURE CITED

1.   J.A. Marco, J.F. Sanz, and M. Carda, *Phytochemistry*, **28**, 2505 (1989).
2.   J.A. Marco, J.F. Sanz, E. Falcó, J. Jakupovic, and J. Lex, *Tetrahedron*, **46**, 7941 (1990).
3.   J.F. Sanz, E. Falcó, and J.A. Marco, *J. Nat. Prod.*, **53**, 940 (1990).
4.   J.F. Sanz and J.A. Marco, *Planta Med.*, **57**, 74 (1991).
5.   M. Martínez-V., A. Muñoz-Zamora, and P. Joseph-Nathan, *J. Nat. Prod.*, **51**, 221 (1988).
6.   J.A. Marco, O. Barberá, J. Lex, P. De Clercq, and A. De Bruyn, *J. Nat. Prod.*, **52**, 547 (1989).
7.   C.A.G. Haasnoot, F.A.A.M. de Leeuw, and C. Altona, *Tetrahedron*, **36**, 2783 (1980).
8.   O. Mitsunobu, *Synthesis*, 1 (1981).
9.   G. Brussani, S.V. Ley, J.L. Wright, and D.J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 303 (1986).
10.   S. Kobayashi, K. Kamiyama, and M. Ohno, *J. Org. Chem.*, **55**, 1169 (1990).
11.   E.J. Corey, K.C. Nicolaou, M. Shibasaki, Y. Machida, and C.S. Shiner, *Tetrahedron Lett.*, 3183 (1975).
12.   P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. De Clercq, and M.M. Woolfson, "MULTAN11/82, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data," University of York, England, 1982.
13.   B.A. Frenz and Associates, Inc., College Station, Texas 77840 and Enraf-Nonius, Delft, Holland, 1983.
14.   D.T. Cromer and J.T. Weber, "International Tables for X-ray Crystallography," The Kynoch Press, Birmingham, England, 1974, Vol. IV, Table 2.2B.

---

[1]Atomic coordinates for these structures 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 1EW, UK.