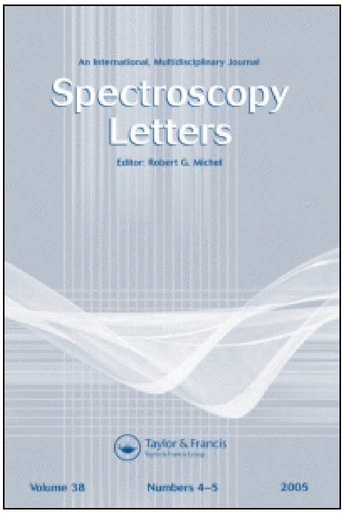

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MOLECULAR STRUCTURE OF THE EUDESMANOLIDE SEPTULINOLIDE

Key Words: *Calea septuplinerva*; eudesmanolide; septuplinolide; X-ray diffraction; COSY; NOESY; HETCOR.

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Abstract: The molecular structure of septuplinolide from *Calea septuplinerva* was determined by single crystal X-ray diffraction analysis. This requires revision of stereochemistry at C4 from 4β-OH to 4α-OH in the septuplinolide molecule. Also, high-field ^1H and ^{13}C NMR spectral assignments of the lactone are given.

INTRODUCTION

We recently reported the structure of septuplinolide, a new eudesmanolide-type sesquiterpene lactone from the Venezuelan Compositae species *Calea septulinervia* [1]. Our structure determination was mainly based on 1-D ^1H and ^{13}C NMR data and spectral correlations with related eudesmanolides. The

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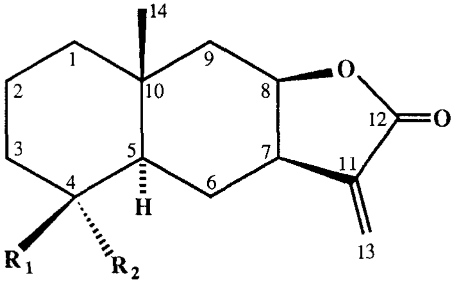
stereochemistry at the chiral center C4 was based on *in situ* acylation of the hydroxyl group with trichloroacetylisocyanate [2]. The absence of a significant shift of the H-5α signal in septuplinolide suggested a β- orientation of the C-4 hydroxyl group. Therefore, stereostructure 2 was suggested for septuplinolide.

In a recent attempt to selectively synthesize septuplinolide, Tada and Kanamori [3] obtained a eudesmanolide, the spectral data of which were not identical with those of the target compound. Since we were able to recrystallize the compound still available from our previous studies [1], its molecular structure was determined by single X-ray diffraction analysis. Our results are described below.



	R_1	R_2
1	CH_3	OH
2	OH	CH_3

RESULTS AND DISCUSSION

NMR data.- High-field ^1H-^1H 2D-COSY [5] and ^{13}C NMR spectra of septuplinolide allowed for the unambiguous assignment of the ^{13}C NMR signals. The ^{13}C-^1H correlation (HETCOR) [6] in Figure 3 confirmed the multiplicities of the carbons as previously reported [1]. H-5 and H-7 are now clearly assigned to the ^{13}C signals at 51.2 and 41.1 ppm respectively. The ambiguities between C-6 (24.6 ppm) and C-9 (44.9 ppm) are now clarified in the cross-peaks of the contour plot.

The remaining three CH_2 signals, C-1, C-2 and C-3, could be assigned in combination with the 2D-NOESY (Figure 2) [7]. First, the

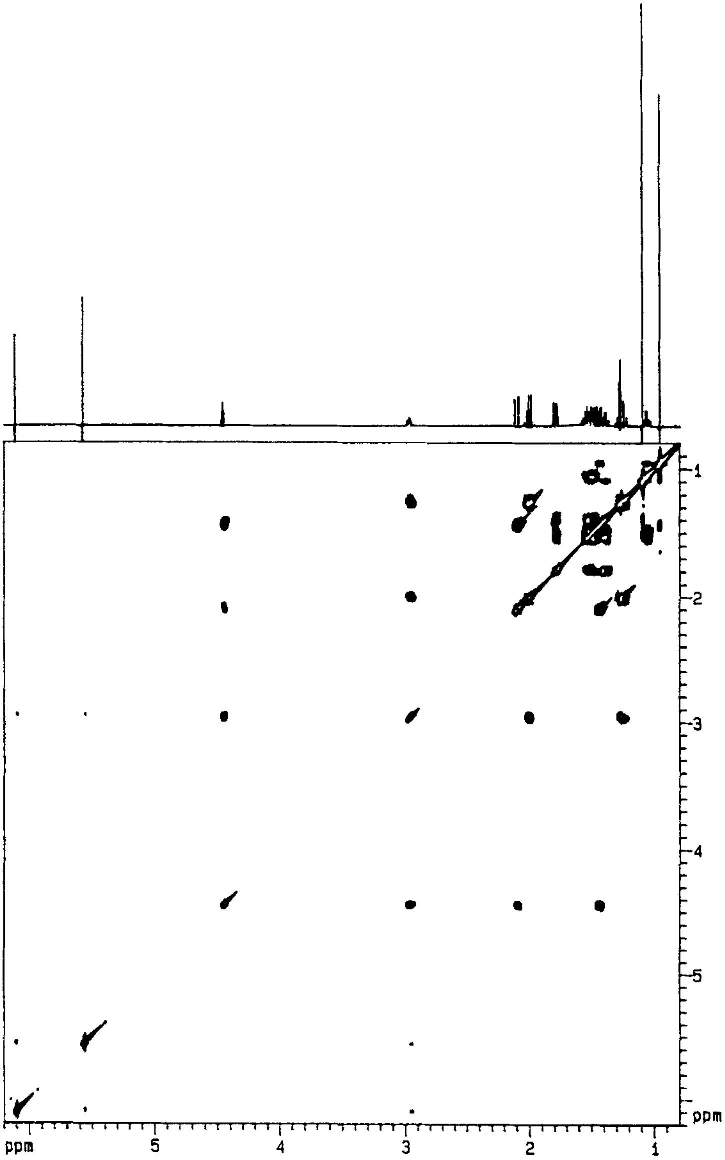


Figure 1.- 2D ^1H-^1H COSY spectrum of septuplinolide (1).

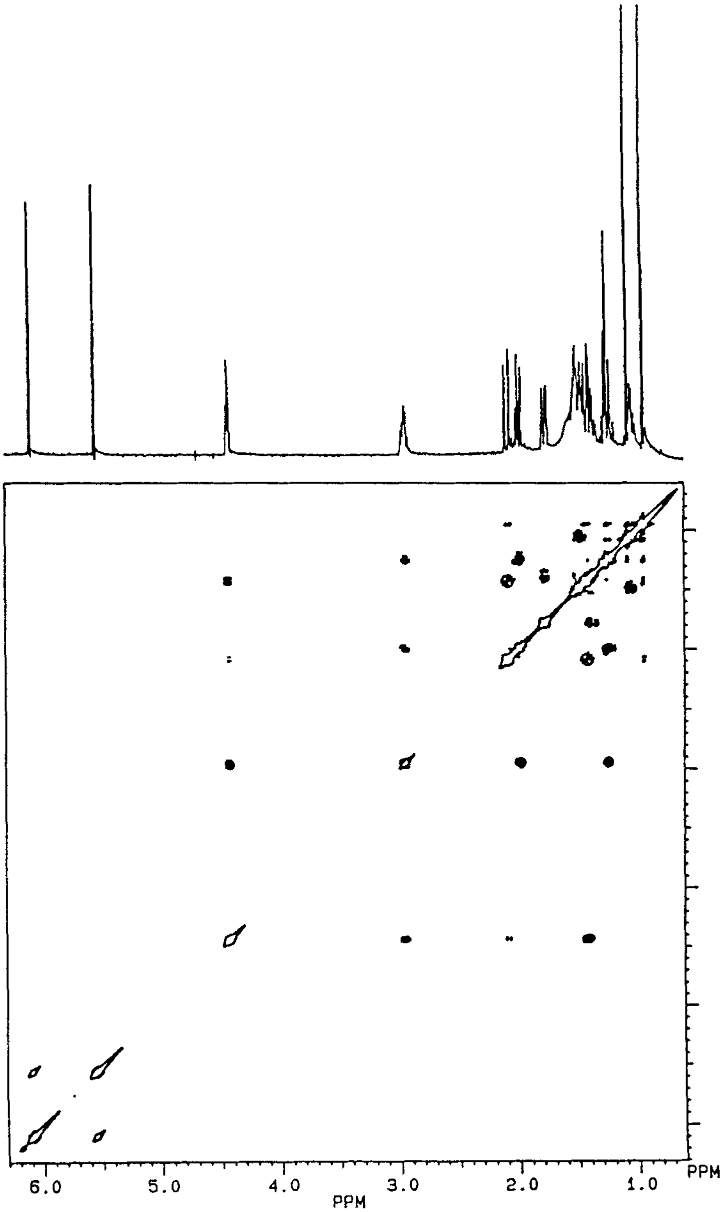


Figure 2- 2D NOESY spectrum of septuplinolide (1).

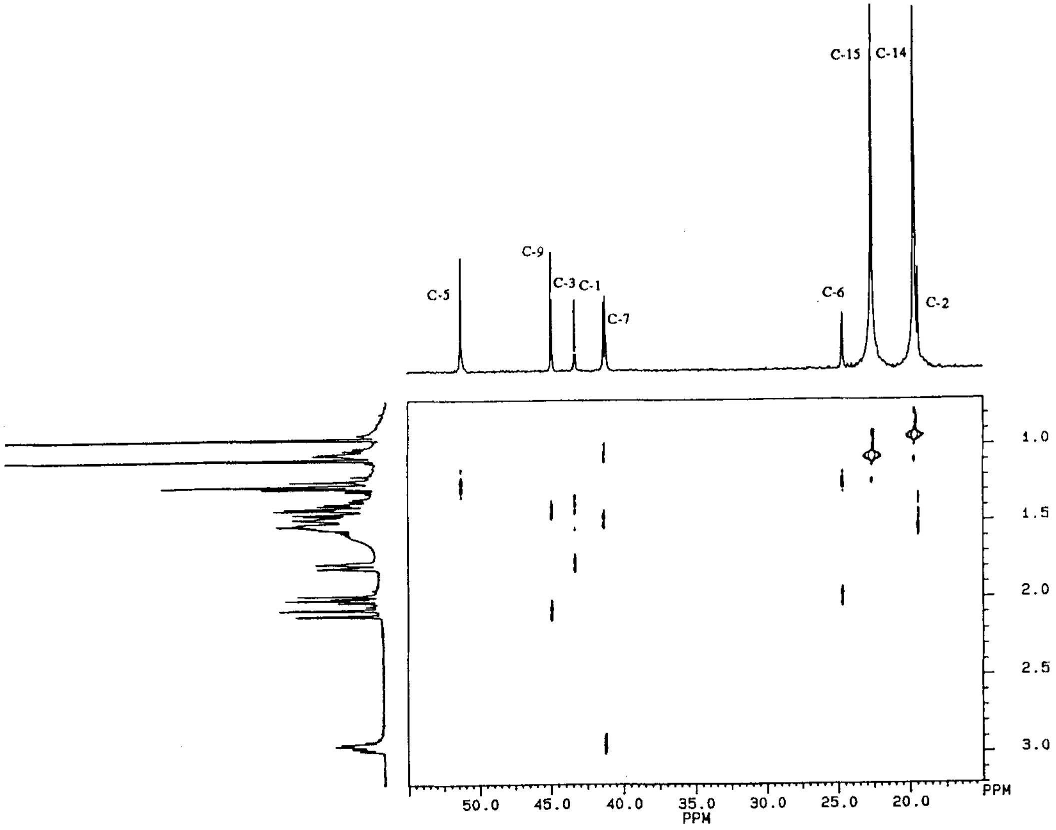


Figure 3- Upfield region of the ^{13}C-^{1}H correlation (HETCOR) of septuplinolide (1).

Table 1 .- ^{13}C and ^{1}H NMR assignments of septuplinolide (1) in $CDCl_3$.[a]

Carbon	$\delta(^{13}C)$ ppm (100.62 MHz)	Proton	$\delta(^{1}H)$ ppm; mult.[b] (J).[c] (500.13 MHz)
C-1	41.2	H-1α	1.07; ddd brd. (13.5, 13.5, 4.2)
		H-1β	1.48; m obs.
C-2	19.3	H-2α	1.54; m obs.
		H-2β	1.49; m obs.
C-3	43.3	H-3α	1.41 dddd (12.3, 12.3, 4.3, 0.8)
		H-3β	1.80 dddd (12.3, 3.1, 3.1, 1.7)
C-4	71.6		
C-5	51.2	H-5	1.28; m (11.4, 2.5)
C-6	24.6	H-6α	2.01; ddd (11.4, 6.7, 2.5)
		H-6β	1.27; m (11.4, 5.6)
C-7	41.1	H-7	2.96; m (11.3, 6.7, 4.8,1.2, 1.0)
C-8	76.8	H-8	4.45; ddd (4.8, 4.8, 1.8)
C-9	44.2	H-9α	1.44; ddd (15.4, 4.8, 0.9)
		H-9β	2.10; dd (15.4, 1.8)
C-10	33.1		
C-11	141.0		
C-12	170.7		
C-13	120.1	H-13a	6.10; d (1.2)
		H-13b	5.56; d (1.1)
C-14	19.6	3H	0.94; dd (0.8, 0.9)
C-15	22.5	3H	1.11; d brd. (0.8)

a.- Chemical shifts in δ (ppm) relative to TMS.

b.- multiplicities: m= multiplet, d= doublet, brd= broad, obs= obscured due to signal overlap.

c.-J= coupling constant or line separations in herz

nOe between Me-C-4 and Me-C-10 indicates that the two methyl groups are on the same side of the molecule, as it was confirmed by the X-ray structure. Furthermore, nOe's of the angular methyl group (0.94 ppm) with H-1β (1.48 ppm), H-6β (1.26 ppm) and H-9β (2.01 ppm) provided the basis for the assignment of the chemical shifts and relative stereochemistry of these protons (Table 1). Likewise, the C-4-Me exhibits nOe's with H-6β, H-2β (ca. 1.49 ppm) and H-3β (1.79 ppm). It is noteworthy the small splitting of the two CH_3 groups due to long range coupling (^{4}J), with H-1α and H-9α for the

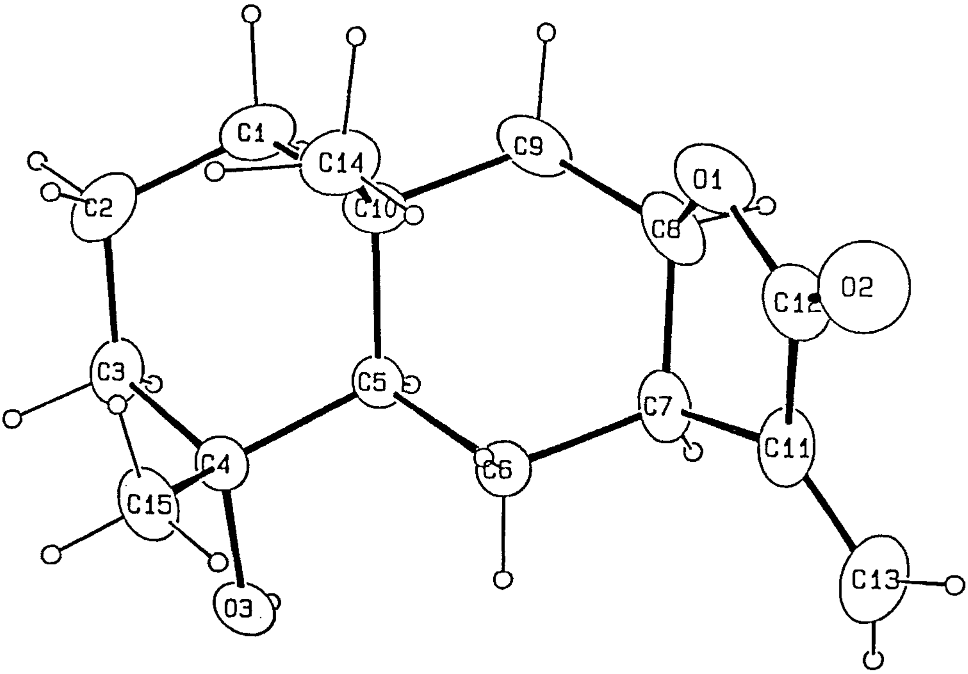


Figure 4.- X-ray molecular structure of septuplinolide (**1**).

C-10-Me and H-3α for the C-4-Me as confirmed by double resonance decoupling experiments.

X-ray data.- Both six-membered rings are in the chair conformation. The one consisting of C1 through C5 and C10 is a much more regular chair, having endocyclic torsions varying in magnitude over the limited range 50.5(2)-57.5(2)°. The *cis*-fusion of the lactone ring causes asymmetry in the cyclohexane ring to which it is fused, the endocyclic torsion angle about C7-C8 being -35.5(2)°, while that about C5-C10 is 62.2(2)°. The lactone ring is in the half-chair conformation with C12 on the twist axis, and the exocyclic C13-C11-C12-O2 torsion angle is -10.9(3)°. The hydroxy group is involved in intermolecular hydrogen bonds as both donor and acceptor, O3···O3' 2.769(2)Å, with angle at H 173(3)°.

Table 2.- Coordinates and Equivalent Isotropic Thermal Parameters for Septuplinolide (1).

Atom	x	y	z	B_{eq}(Å^2)
O1	0.84546(6)	0.33368(5)	0	5.44(3)
O2	0.85276(7)	0.30026(6)	-0.3083(3)	6.63(4)
O3	0.95856(4)	0.62667(4)	0.0373(2)	3.25(2)
C1	0.80995(9)	0.47570(9)	0.3896(3)	4.82(4)
C2	0.80231(7)	0.53463(8)	0.3408(3)	4.72(4)
C3	0.86652(7)	0.59127(6)	0.2635(3)	3.67(3)
C4	0.89270(6)	0.57355(5)	0.0783(2)	2.75(2)
C5	0.89689(5)	0.51082(5)	0.1224(2)	2.62(2)
C6	0.92353(6)	0.48916(6)	-0.0526(2)	3.02(3)
C7	0.94290(6)	0.43822(6)	0.0112(3)	3.80(3)
C8	0.89052(9)	0.38352(7)	0.1433(3)	4.70(4)
C9	0.8536(1)	0.40285(7)	0.2882(3)	4.80(4)
C10	0.83343(7)	0.45172(6)	0.2096(3)	3.49(3)
C11	0.94359(7)	0.39946(7)	-0.1686(3)	4.37(3)
C12	0.87771(8)	0.33930(7)	-0.1747(4)	4.71(4)
C13	0.98888(8)	0.41270(8)	-0.3060(4)	5.59(5)
C14	0.77629(8)	0.41688(8)	0.0590(3)	4.83(4)
C15	0.85445(7)	0.57004(7)	-0.1098(3)	3.83(3)

$$B_{eq} = (8\pi^2/3)\,\Sigma_i\Sigma_j U_{ij}\, a_i^* a_j^* a_i \cdot a_j$$

The single crystal X-ray analysis of septuplinolide established the molecular structure as shown in Fig. 4. This requires revision of the chiral center at C4 of the molecule from stereostructure **2** to **1**.

EXPERIMENTAL

NMR .- ^1H and COSY [5] and NOESY [7] experiments were performed in an AMX-500 Bruker NMR spectrometer at 500.13 MHz using a 2K by 2K data matrix with zero filling on t_1 after acquisition of 400 increments. A sinebell window function was applied in both dimensions prior to fourier transformation in both dimensions The ^{13}C-^1H correlation (HETCOR) [6] was carried out in a Bruker AM-400 spectrometer at a ^{13}C frequency of 100.62 MHz using 4K data points in the t_2 dimension and 256 increments on t_1. A gaussian window function was applied in the t_2 dimension and a sinebell window function was applied to the t_1 dimension. Zero filling to 1K was also applied in the ^1H dimension.

X-ray .- Data were collected on an Enraf-Nonius CAD4 diffractometer equipped with CuKα radiation (λ = 1.54184 Å) and a graphite monochromator, using a colorless crystal of dimensions 0.10 x 0.20 x 0.65 mm. Crystal data are as follows: $C_{15}H_{22}O_3$, FW= 250.3, trigonal space group R3 with hexagonal axes a = 23.453(3), c = 6.6607(7)Å, V = 3172.8(7)Å^3, Z = 9, D_c = 1.179 g·cm^{-3}, μ = 6.1 cm^{-1}, T = 24 °C. A hemisphere of data were collected by ω–2θ scans of rates varying 1.27 - 3.30° min^{-1}, within $2<\theta<75°$. Data reductions included corrections for background, Lorentz-polarization, and absorption by psi scans, with minimum relative transmission coefficient 89.72%. A total of 4358 data were merged to yield 1582 unique data, of which 1505 had $I>3\sigma(I)$ and were used in the refinement.

The structure was solved by direct methods and refined by full-matrix least squares based on F with weights $w = \sigma^{-2}(Fo)$. Nonhydrogen atoms were treated anisotropically, while hydrogen atoms were located from difference maps and refined isotropically. At convergence, R = 0.026 for 251 variables and the maximum residual density was 0.19 eÅ^{-3}. The molecular structrure is illustrated in Fig. 4, and fractional coordinates are tabulated in Table 2.

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