

CONFORMATION AND ABSOLUTE CONFIGURATION OF NATURALLY OCCURRING LONGIPINENE DERIVATIVES

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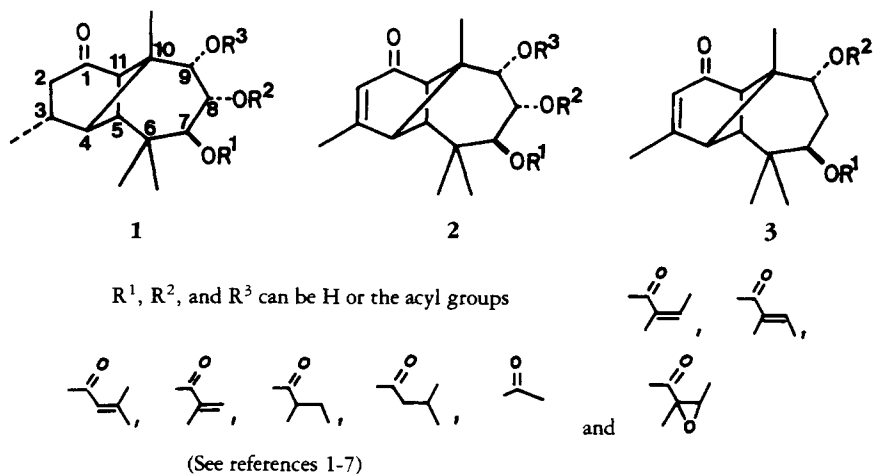
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ABSTRACT.—The conformation of longipinene derivatives of types **1**, **2**, and **3** is established from their proton coupling constants. The seven-membered ring bearing three oxygens exists in a twist-chair conformation where O-7 and O-8 are *pseudo*-equatorial and O-9 is *pseudo*-axial. The seven-membered ring bearing two oxygens shows a similar conformation. The six-membered ring in compounds of type **1** has a conformation midway between Y-shaped and bridged chair, where the methyl groups at C-3 becomes *pseudo*-equatorial, while in 3-*epi*-longipinanes like **6** this ring is almost Y-shaped but slightly displaced to bridged boat. The absolute configuration of these natural products isolated from *Stevia*, *Polypteris*, *Critonia*, and *Artemisia* species is the same as (+)-longipinene as shown by comparison of the cd curves of **3a** and **3c** with that of vulgarone B (**8**).

Several longipinene derivatives of types **1**, **2**, and **3** have been found as constituents of *Stevia* (1-4), *Critonia* (2), *Polypteris* (5), and *Artemisia* (6) species. The relative stereochemistry of these natural products has been established (4) via a single crystal X-ray diffraction study of rastevione acetate (**1a**, Scheme 2) followed by correlation by chemical transformations of rastevione (**1b**) with compounds of types **2** and **3** (7).

Following our investigations concerning these longipinenes, we describe herein a conformational study based on the vicinal proton couplings found in the ¹H-nmr spectra of some of these natural compounds and several synthetic derivatives. We also establish the absolute configuration of these molecules from the cd curves of compounds **3a** and **3c**, which were compared with that of vulgarone B (**8**) (8).

CONFORMATION.—Observation of Dreiding models of these skeletons shows that there are basically three conformational facts to be defined: The shape of the seven-membered ring bearing three oxygens (**1a-1d**, **2a**, and **2b**), of the seven-membered



SCHEME 1. Longipinene derivatives of types **1**, **2**, and **3**.

ring bearing two oxygens (**3a-3c**), and of the six-membered ring in saturated compounds (**1a, 1b, 1d, 1e**, and **6**).

In the seven-membered ring bearing three oxygens, the vicinal proton couplings found in the C₇-C₈-C₉ fragment of compounds of types **1** and **2** gave the conformational information. The assignments of the signals were made from the spectrum of rastevione (**1b**) obtained at 90 MHz in C₆D₆ solutions, which showed at δ 5.83 ppm a doublet ($J=11.0$ Hz) and at δ 5.58 ppm a double doublet ($J=11.0$ and 3.0 Hz). It is clear from the observed multiplicities that the first signal corresponds to H-7 and the second to H-8. The signal for the proton geminal to the hydroxyl group was observed as a doublet at δ 3.60 ppm ($J=3.0$ Hz) upon addition of D₂O.

In the spectra of compounds **1c** and **2b**, we recognized a similar system of signals for the protons of the C₇-C₈-C₉ fragment whose assignments readily followed by analogy with those of rastevione (**1b**). However, for compounds **1a, 1d**, and **2a** these signals gave rise to complex systems. The 200 MHz ¹H-nmr spectrum of **1d** obtained in CDCl₃ solution plus D₂O showed these protons as a strongly coupled system with broadened signals due to long-range coupling to H-5 (Figure 1). We obtained the spectral parameters of the three protons by means of an iterative spin-spin simulation procedure. The experimental and calculated spectra are shown in Figure 1, while the pertinent parameters are described in the experimental part. For the remaining two compounds the coupling constants were obtained from the experimental spectra after addition of Eu(fod)₃.

In all the studied compounds, we found $J_{7,8}$ around 11 Hz and $J_{8,9}$ to be about 3 Hz (Table 1). These values show, as is seen in a set of cyclohexanols and cycloheptanols of known conformation where $J_{trans} = 11$ Hz and J_{gauche} between 2 and 4 Hz (9-11), that the dihedral angles in longipinene derivatives are close to 180° for H₇-C₇-C₈-H₈ and close to 60° for H₈-C₈-C₉-H₉.

The 90 MHz ¹H-nmr spectra of compounds with a seven-membered ring bearing two oxygens (**3a** to **3c**) show for H-7 a double doublet ($J_{7,8\beta}$ around 11 Hz and $J_{7,8\alpha}$ between 2.3 and 4.0 Hz) and for H-9 a triplet ($J_{7,8\alpha} = J_{7,8\beta}$ between 3.5 and 4.0 Hz) (7), the accurate values of each compound being in Table 1. These coupling constant values show that the conformation in this ring is very similar to that found in the three oxygen bearing molecules (**1a-1e, 2a**, and **2b**) (see Table 1 and Scheme 2), where the oxygen attached to C-7 remains *pseudo*-equatorial and that at C-9 remains *pseudo*-axial.

In previous work (7), we described some reactions on the hydroxyl groups of these molecules, such as tosylation of **1d, 2c**, and **3c** and formation of the 7β,8α-acetonide of **1d**. Tosylation of **1d** and **2c** under the reaction conditions described for the preparation of **2b** (7) yields a mixture of 7- and 8-monotosylates which in both cases has essentially the same 1:3 ratio, as judged by 300 MHz ¹H-nmr analysis. On the other hand,

TABLE 1. ¹H-¹H Coupling Constants of the C₇-C₈-C₉ Fragment of Compounds of Types **1, 2**, and **3**

Compound	Coupling constants (Hz)		Compound	Coupling constants (Hz)		
1a	$J_{7,8}$ 11.0 ^a	$J_{8,9}$ 2.5 ^b	2b	$J_{7,8}$ 11.0 ^c	$J_{8,9}$ 3.0 ^c	
1b	11.0 ^b	3.0 ^b	3a	$J_{7,8\beta}$ 11.3 ^b	$J_{7,8\alpha}$ 2.3 ^b	$J_{8\alpha,9} \approx J_{8\beta,9}$ 3.5 ^b
1c	11.0 ^c	2.5 ^c	3b	11.0 ^c	4.0 ^c	3.0 ^c
1d	10.0 ^d	3.3 ^d	3a	11.0 ^c	2.5 ^c	4.0 ^c
2a	11.0 ^a	3.0 ^a				

^aMeasured in C₆D₆ solution + Eu(fod)₃.

^bMeasured in C₆D₆ solution.

^cMeasured in CDCl₃ solution.

^dObtained from data of simulated spectra (Figure 1).

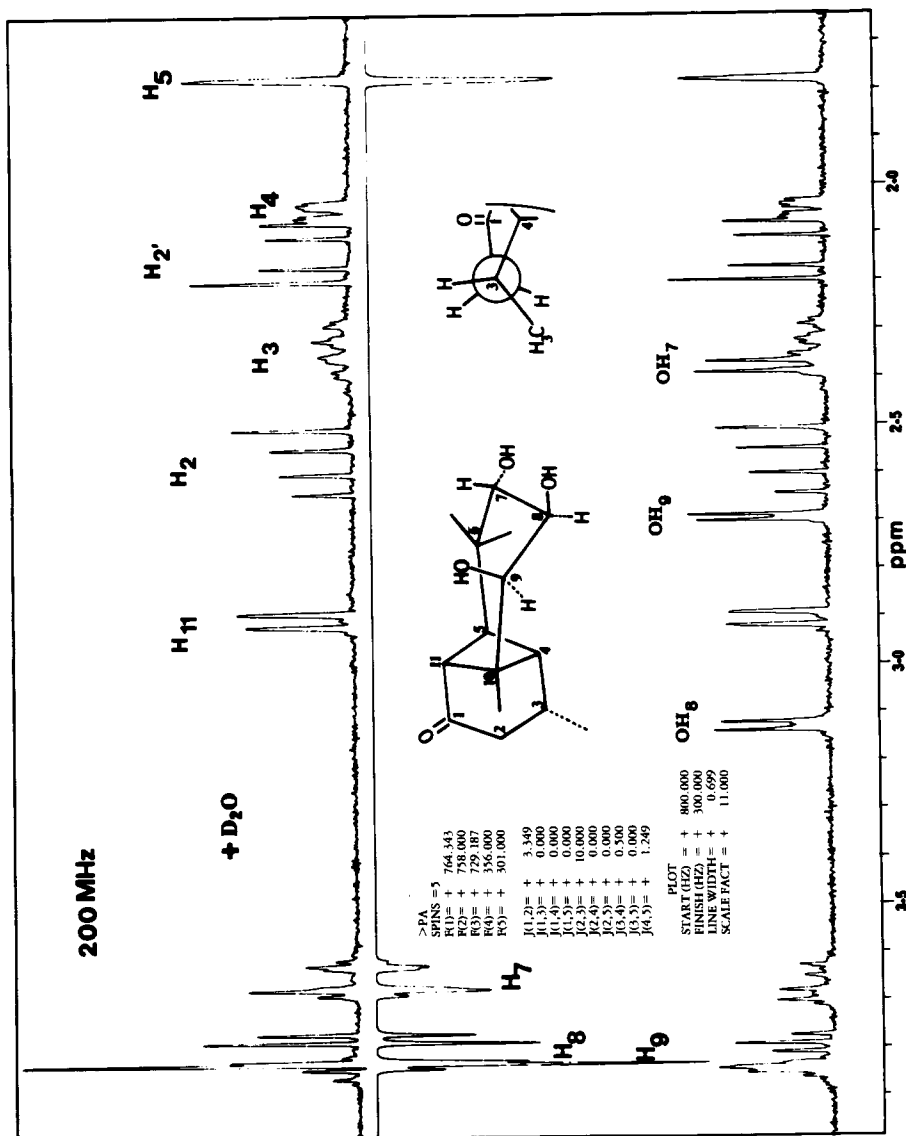
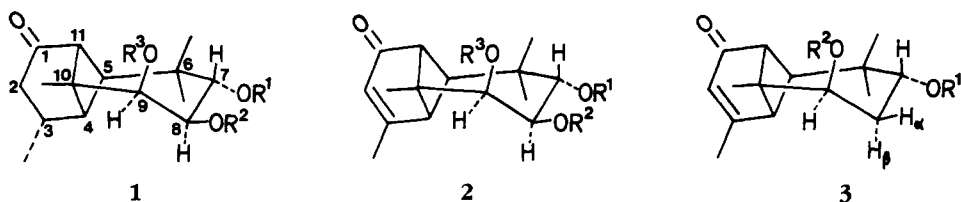


FIGURE 1. Experimental (top) and simulated (inverted) partial ¹H-nmr spectra of **1d**. Upper spectrum obtained in CDCl₃/D₂O, lower spectrum in CDCl₃ alone.



1a $R^1=R^2=Ang; R^3=Ac$
1b $R^1=R^2=Ang; R^3=H$
1c $R^1=R^2=Ts; R^3=H$
1d $R^1=R^2=R^3=H$
1e $R^1=R^2=R^3=Ac$

2a $R^1=R^2=R^3=Ac$
2b $R^1=R^3=H; R^2=Ts$
2c $R^1=R^2=R^3=H$

3a $R^1=R^2=Ac$
3b $R^1=Ts; R^2=H$
3c $R^1=R^2=H$

SCHEME 2. Conformation of the seven-membered ring of compounds of types **1**, **2**, and **3**. The protons of the methylene group in compounds of type **3** were designated α and β according to the projection of Scheme 1.

tosylation of diol **3c** yields monotosylate **3b**. The difference in reactivity between the hydroxyl group at C-9 and the hydroxyl groups at C-7 and C-8 can now be explained by consideration of the ring conformation, since the group at C-9 is *pseudo-axial* while those of C-7 and C-8 are *pseudo-equatorial*. In addition, a steric interaction of the *gem*-dimethyl group reflected at position 7, might explain the tosylation ratio found in **1d** and **2c**.

From the series of molecules containing the saturated six-membered ring, we studied compounds **1a**, **1b**, **1d**, and **1e**. This series has the methyl group at C-3 *trans* to the angular methyl group at C-10, and we named it the α series. From the β series, which has the opposite chirality at C-3, we studied compound **6**.

The spectra of compounds of both series showed, for the methylene group adjacent to the carbonyl group, two signals as double doublets whose coupling constants gave conformational information (Table 2 and Scheme 3). By using these values in the Williamson and Johnson equation (12), one can correlate coupling constants with dihedral angles.

Since, for the α series, assignment of the individual signals for the methylene group protons was not known, we derived the two possible sets of values for dihedral angles that correspond to two possible conformations. For example, rastevione (**1b**) showed $J_{2,3}=10$ Hz and $J_{2',3}=6$ Hz. These values gave dihedral angles of 0 and 128° for one possibility and of 142 and 30° for a second. That implies for the first case a Y-shaped

TABLE 2. 1H - 1H Coupling Constants of the C₂-C₃ Fragment and the Calculated Dihedral Angles for Compounds of Type **1**

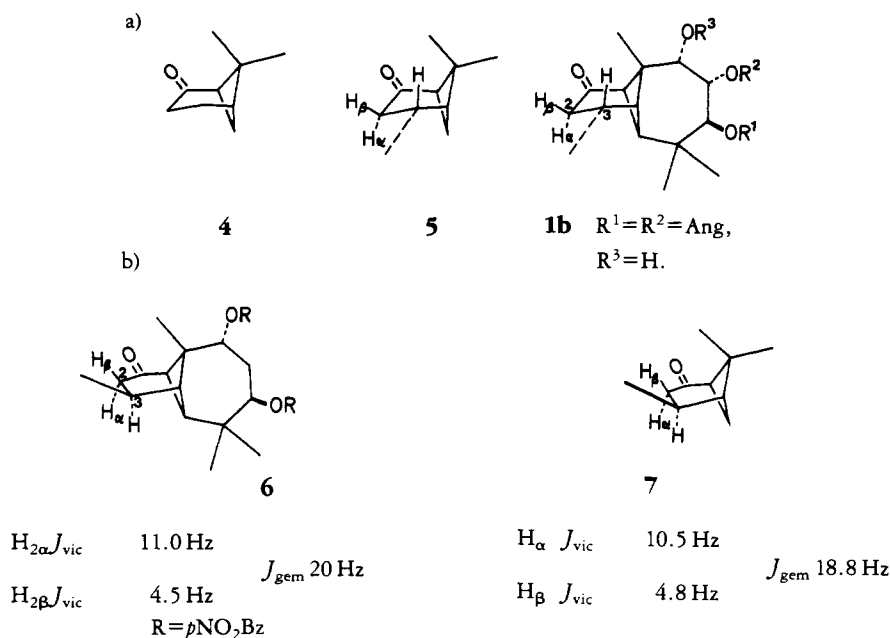
Compound	Coupling constants (Hz)			Calculated dihedral angles (°) ^d	
	Geminal	Vicinal		H _{2α} C ₂ C ₃ H ₃	H _{2β} C ₂ C ₃ H ₃
1a	$J_{2\alpha,2\beta}$ 19.5 ^a	$J_{2\alpha,3}$ 10.0 ^a	$J_{2\beta,3}$ 6.3 ^b	142	37
1b	20.0 ^a	10.0 ^a	6.0 ^b	142	39
1d	18.5 ^c	8.1 ^c	6.2 ^c	135	38
1e	20.0 ^a	10.0 ^a	6.0 ^b	142	39

^aMeasured from C₆D₆ solution.

^bMeasured from C₆D₆ solution + Eu(fod)₃.

^cMeasured from CDCl₃ solution.

^dEstimated with the relationship $J=J_0\cos^2\Phi$ where $J_0=10$ Hz for $0^\circ < \Phi < 90^\circ$ and $J_0=16$ Hz for $90^\circ < \Phi < 180^\circ$ (12).



SCHEME 3. a) Nopinone (**4**), verbanone (**5**), and rastevione (**1b**). b) Comparison between conformations and coupling constants found in isoverbanone (**7**) with compound **6**.

conformation, that is to say, a conformation in which C-1 to C-4 and C-11 are in the same plane with the hydrogens at C-2 and C-3 and the methyl group at C-3 being eclipsed. For the second possibility, a conformation midway between Y-shaped and bridged chair in which C-2 is bent away from the methyl group at C-10 and the methyl group at C-3 becomes *pseudo*-equatorial is consistent with the data.

It is possible to rule out the Y-shaped conformation, since in a conformational study of nopinone (**4**) (13) it was found that the six-membered ring is buckled in the opposite direction to the dimethyl bridge but much less than in the classical bridged chair conformation. The assumption that a methyl group at C-3 might induce, due to its *pseudo*-equatorial position, greater ring buckling led to the suggestion that in verbanone (**5**) the ring is more buckled than in nopinone (**4**) (13). The above study supports a conformation between Y-shaped and bridged chair because of the structural relationship of **5** with the longipinanes of the α series (see Scheme 3). On the other hand, the large value of the geminal coupling $H_{2\alpha}$ - $H_{2\beta}$ (20 Hz) found in rastevione (**1b**) shows, according to the equation proposed by Gutowsky, Karplus, and Grant (14), that the geminal angle is less than 109° and, therefore, its projection is less than 120° . The difference between the calculated dihedral angles for this compound for the Y-shaped conformation is higher than 120° and for the conformation midway between Y-shaped and bridged chair, less than that. These facts only agree by consideration of the conformation midway between Y-shaped and bridged chair. Establishment of the conformation allows assignment of the signals of the methylene group. The double doublet with vicinal coupling of 10 Hz, which in all compounds is always shifted to lower field, corresponds to H-2 α , and the double doublet with vicinal coupling of 6 Hz corresponds to H-2 β .

As far as the β series is concerned, the coupling constants of the methylene group found in the spectrum of compound **6** are very similar to those found in the spectrum of isoverbanone (**7**) (see Scheme 3). These results allow the assignment of the signals as

TABLE 3. Dihedral Angles from the X-ray Diffraction Study of **1a** (4)

ATOM		Φ
x	y	$H_x-C_x-C_y-H_y$
2 α	3	143°
2 β	3	32°
3	4	78°
4	5	92°
5	11	105°
7	8	192°
8	9	45°

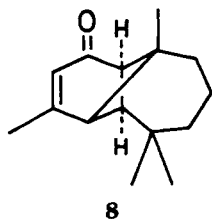
well as of the conformation of the ring as almost Y-shaped, where C-2 is slightly displaced towards the methyl group at C-10 as it is described for isoverbanone (**7**) (13).

The cyclobutane ring presents a fixed geometry and inspection of Dreiding models shows that the dihedral angles $H_4-C_4-C_5-H_5$ and $H_5-C_5-C_{11}-H_{11}$ are both close to 90° , thus providing a nonobservable coupling constant. Furthermore, a long-range coupling between H_4 and H_{11} is in analogy with studies on bridged cyclobutanes (15).

Finally, we made a comparison between the conformation in solution with that found in the solid state for rastevione acetate (**1a**). The positional parameters of atoms from an X-ray diffraction study (4) of this compound were loaded into the SHELXTL program to obtain Newman projections (Table 3 and Scheme 4). The dihedral angles found in these projections indicate that the conformation in the solid state is essentially the same as that found in solution.

SCHEME 4. Newman projections for C-2, C-3 and C-8, C-9 from the X-ray diffraction study of **1a** (4).

ABSOLUTE CONFIGURATION.—The chemical correlation mentioned earlier was done by transformation (7) of rastevione (**1b**) into diol **3c**, which is the product of hydrolysis of the natural diesters of type **3**. The ORD curves of **3c** prepared from rastevione (**1b**) and **3c** obtained by hydrolysis of the natural diesters were identical. When the ORD curves of **3c** and its diacetate (**3a**) were compared with that of a closely related molecule, vulgarone B (**8**) (8), we found a good correspondence among them. They showed the following positive maxima: **3a** $[\theta]_{329} + 1800$, **3c** $[\theta]_{336} + 1800$, and **8** $[\theta]_{329} + 906$. Since the absolute configuration of vulgarone B (**8**) is known by correla-



tion with (+)-longipinene, these results show the natural longipinene derivatives to have the absolute configuration shown (**8**).

EXPERIMENTAL

The ^1H -nmr spectra were measured on Varian Associates EM-390, XL-200 and XL-300GS spectrometers from solutions containing TMS as the internal reference. The ^{13}C -nmr measurements were performed from similar solutions on a Varian Associates XL-300GS spectrometer.

The cd and ord curves were obtained on a Jasco J-500 spectropolarimeter and on Perkin-Elmer 141M and 241 polarimeters, respectively.

Spectral simulation was performed in a VDM 620 L-100 computer and the results were plotted on a Varian Associates XL-100A NMR spectrometer.

The Newman projections were obtained using the Data General Nova 4 and Tektronix 4105 computer system linked to a Nicolet R3m single crystal X-ray diffractometer.

RASTEVIONE ACETATE (**1a**) (4).— ^1H nmr (90 MHz, C_6D_6) δ 5.46 (d, 1H, $J_{8,9}=2.5$ Hz, H-9); addition of $\text{Eu}(\text{fod})_3$ (0.019 mM) to a solution containing 0.053 mM of δ **1a** allowed observation of the following signals: 6.28 (d, 1H, $J_{7,8}=11.0$ Hz, H-7), 3.84 (dd, 1H, $J_{2\alpha,2\beta}=19.5$, $J_{2\alpha,3}=10$ Hz, H-2 α), 3.22 ppm (dd, 1H, $J_{2\alpha,2\beta}=19.5$, $J_{2\beta,3}=6.3$ Hz, H-2 β).

RASTEVIONE (**1b**) (4).— ^1H nmr (90 MHz, C_6D_6) δ 5.83 (d, 1H, $J_{7,8}=11.0$ Hz, H-7), 5.58 (dd, 1H, $J_{7,8}=11.0$, $J_{8,9}=3.0$ Hz, H-8) 3.60 (broad singlet which resolves into a doubler upon addition of D_2O , 1H, $J_{8,9}=3.0$ Hz, H-9), 2.24 (dd, 1H, $J_{2\alpha,2\beta}=20$, $J_{2\alpha,3}=10$ Hz, H-2 α); H $_{2\beta}$ was observed at 3.03 ppm as dd, $J_{2\alpha,2\beta}=20$ Hz and $J_{2\beta,3}=6$ Hz upon addition of 0.010 mM of $\text{Eu}(\text{fod})_3$ to a solution containing 0.046 mM of **1b**.

LONGIPINANE-7 β ,8 α ,9 α -TRIOL-1-ONE 7,8-DITOSYLATE (**1c**).— ^1H nmr (90 MHz, CDCl_3) described in Román *et al.* (7).

LONGIPINANE-7 β ,8 α ,9 α -TRIOL-1-ONE (**1d**) (4).— ^1H nmr (200 MHz, CDCl_3) described in Román *et al.* (4); H-4 and H-5 are interchanged. Simulated spectrum (Figure 1): spins=5, frequencies=746.32, 758.00, 729.19, 356.00, and 301.00 Hz, coupling constants= $J_{1,2}=3.349$, $J_{1,3}=0$, $J_{1,4}=0$, $J_{1,5}=0$, $J_{2,3}=10.000$, $J_{2,4}=0$, $J_{2,5}=0$, $J_{3,4}=0.5$, $J_{3,5}=0$, $J_{4,5}=1.249$, start 800 Hz, finish 300 Hz, line width 0.699, scale fact 11. These values provide: δ 3.82 (d, 1H, $J_{8,9}=3.3$ Hz, H-9), 3.79 (dd, 1H, $J_{7,8}=10.0$, $J_{8,9}=3.3$ Hz, H-8) and 3.65 ppm (dd, 1H, $J_{7,8}=10.0$, $J_{5,7}=0.5$ Hz, H-7). The parameters for H-5 were only introduced to the calculation to provide an adequate broadening of H-7.

LONGIPINANE-7 β ,8 α ,9 α -TRIOL-1-ONE TRIACETATE (**1e**) (4).— ^1H nmr (90 MHz, C_6D_6) addition of $\text{Eu}(\text{fod})_3$ (0.012 mM) to a solution containing 0.076 mM of **1e** allowed observation of H-2 α at δ 3.09 (dd, 1H, $J_{2\alpha,2\beta}=20$, $J_{2\alpha,3}=10$ Hz) and H-2 β at 2.52 ppm (dd, 1H, $J_{2\alpha,2\beta}=20$, $J_{2\beta,3}=6$ Hz).

LONGIPIN-2-ENE-7 β ,9 β -TRIOL-1-ONE TRIACETATE (**2a**) (7).— ^1H nmr (90 MHz, C_6D_6) addition of $\text{Eu}(\text{fod})_3$ (0.039 mM) to a solution containing 0.076 mM of **2a** allowed observation of the following signals: δ 7.03 (d, 1H, $J_{7,8}=11$ Hz, H-7), 6.81 (d, 1H, $J_{8,9}=3$ Hz, H-9) and 6.63 ppm (dd, 1H, $J_{7,8}=11$, $J_{8,9}=3$ Hz, H-8).

LONGIPIN-2-ENE-7 β ,8 α ,9 α -TRIOL-1-ONE 8-TOSYLATE (**2b**) (7).— ^1H nmr (90 MHz, CDCl_3) described in Román *et al.* (7).

LONGIPIN-2-ENE-7 β ,9 α -DIOL-1-ONE DIACETATE (**3a**) (7).— ^1H nmr (90 MHz, C_6D_6) δ 5.12 (dd, 1H, $J_{7,8\beta}=11$, $J_{7,8\alpha}=2.3$ Hz, H-7), 4.90 ppm (t, 1H, $J_{8\alpha,9}=J_{8\beta,9}=3.5$ Hz, H-9); CD (MeCN) $[\theta]_{378}+150$, $[\theta]_{360}+600$, $[\theta]_{355}+800$, $[\theta]_{342}+1150$, $[\theta]_{336}+1750$, $[\theta]_{329}+1800$, $[\theta]_{320}+1750$, $[\theta]_{318}+1550$, $[\theta]_{304}+900$, $[\theta]_{284}+150$, $[\theta]_{275}-300$, $[\theta]_{250}-4250$, $[\theta]_{225}+8700$, $[\theta]_{221}+13900$, $[\theta]_{205}+22450$.

LONGIPIN-2-ENE-7 β ,9 α -DIOL-1-ONE 7-TOSYLATE (**3b**).— ^1H nmr (90 MHz, CDCl_3) described in Román *et al.* (7).

LONGIPIN-2-ENE-7 β ,9 α -DIOL-1-ONE (**3c**) (7).— ^1H nmr (90 MHz, CDCl_3) described in Román *et al.* (7); cd (CH_3CN) $[\theta]_{378}+100$, $[\theta]_{360}+500$, $[\theta]_{355}+800$, $[\theta]_{342}+1550$, $[\theta]_{336}+1800$, $[\theta]_{329}+1750$, $[\theta]_{320}+1650$, $[\theta]_{318}+1550$, $[\theta]_{304}+750$, $[\theta]_{284}0$, $[\theta]_{275}-1100$, $[\theta]_{250}-11900$, $[\theta]_{225}-200$, $[\theta]_{221}0$, $[\theta]_{205}+8250$.

3-EPI-LONGIPINANE-7 β ,9 α -DIOL-1-ONE DI-*p*-INITROBENZOATE (**6**).—A solution of 3-*epi*-longipinane-7 β ,9 α -diol-1-one (7) (80 mg) in pyridine (4 ml) was treated with *p*-nitrobenzoyl chloride (300

mg). The reaction mixture was refluxed for 30 min, poured over ice-water, and extracted with EtOAc. The organic layer was washed with diluted HCl, H₂O, aqueous NaHCO₃, and H₂O, dried over anhydrous Na₂SO₄, filtered, and evaporated under vacuum. The residue was crystallized from MeOH to afford **6** (110 mg, 62%). Recrystallizations from MeOH and from CHCl₃/hexane provided the pure compound as white needles mp 250-252° (uncorrected); ir (Nicolet MX-1-FT) ν max (CHCl₃) 1723 (C=O, ketone and esters), 1609 (C=C, aromatic), 1531 (NO₂), and 1280 cm⁻¹ (C-O); [α]₅₈₉+49°, [α]₅₇₈+51°, [α]₅₄₆+60°, [α]₄₃₆+124° (c 0.1, CHCl₃); uv (Unicam SP-800) λ max (EtOH) 258 nm (log ϵ 4.27); ¹H nmr (90 MHz, C₆D₆) δ 8.08 and 7.75 (2d, 2H, each J =9 Hz, *p*-nitrobenzoate), 7.69 (s, 4H, *p*-nitrobenzoate), 5.41 (dd, 1H, $J_{7,8}$ =10, $J_{7,8}$ =3 Hz, H-7), 5.11 (t, 1H, $J_{8\alpha,9}$ ≈ $J_{8\beta,9}$ ≈3.5 Hz, H-9), 3.37 (d, 1H, $J_{4,11}$ =5.5 Hz, H-11), 2.72 (dd, 1H, $J_{2\alpha,2\beta}$ =20, $J_{2\alpha,3}$ =11 Hz, H-2 α), 1.45 (s, 1H, H-5), 0.93 (s, 6H) and 0.81 (s, 3H) (*gem*-dimethyl and Me at C-3), 0.87 (d, 3H, $J_{3,12}$ =6 Hz, Me at C-3), the remaining 5 protons (H-2 β , H-3, H-4, H-8 α and H-8 β) overlap in 2.4-1.7 ppm region, H-2 β was observed (dd, 1H, $J_{2\alpha,2\beta}$ =20 and $J_{2\beta,3}$ =4.5 Hz) in 2.81 ppm upon addition of Eu(fod)₃ (0.007 mM) to a solution containing 0.027 mM of **6**; ¹³C nmr (75.4 MHz, CDCl₃) δ 210.56 (s, C-1), 164.53 and 163.89 (2s, 2 COO), 150.80 and 150.69 (2s, aromatics *para*), 135.59 and 135.54 (2s, 2 aromatics *ipso*), 130.96 and 130.62 (2d, 4 aromatics *ortho*), 123.72 and 123.57 (2d, 4 aromatics *meta*), 77.35 (d, C-9), 74.75 (d, C-7), 52.99 (2d, C-11 and C-5), 45.48 (d, C-4), 45.12 (s, C-10), 41.60 (t, C-2), 36.69 (s, C-6), 32.86 (d, C-3), 32.51 (t, C-8), 26.67 (q, Me), 22.36 (q, Me), 20.89 (q, Me), 18.68 ppm (q, Me at C-3).

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