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STRUCTURE AND ABSOLUTE CONFIGURATION OF THE 11-NORIRIDOID "CHAPINGOLIDE"

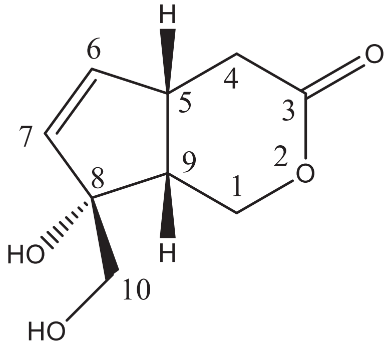
Matilde Villa-García,[a] María Amparo Borja-De-La-Rosa,[b] Holber Zuleta-Prada,[a] Rubén A. Toscano,[c] and Benito Reyes-Trejo[a]*

[a]Laboratorio de Productos Naturales, Área de Química, Departamento de Preparatoria Agrícola, Universidad Autónoma Chapingo, Apartado 74, Oficina de Correos Chapingo, Km 38.5 Carretera México-Texcoco, Chapingo, México 56230, México, [b]Departamento de Productos Forestales. División de Ciencias Forestales, Universidad Autónoma Chapingo, Km 38.5 Carretera México-Texcoco, Chapingo, México 56230, México, and [c]Instituto de Química, Universidad Nacional Autónoma de México, Circuito, Exterior, Ciudad Universitaria, Coyoacán 04510 México, D.F, México. Correspondence email: benijovi@yahoo.com.mx, Tel.: +55-513-31108 (ext. 5760)

Abstract – The natural product chapingolide {systematic name: (4a*S*, 7*R*, 7a*R*)-7-hydroxy-7-(hydroxymethyl)-4,4a,7,7a-tetrahydrocyclopenta[*c*]pyran-3(1*H*)-one}, $C_9H_{12}O_4$, (**1**), is a new 11-*nor*-iridoid isolated from *Calatola mollis* Standl. The colourless compound has a bicyclic structure with an *endo* double bond in the five-membered ring. The absolute configuration was established by mean of the anomalous dispersion of the oxygen scatters present in the structure.

Calatola is a genus of trees in family Icacinaceae. To date, about seven *Calatola* species are recorded in America, and most of them are found in rain forest regions.[1] Approximately, four species of *Calatola* plants were recorded in Mexico[1] of which, *Calatola mollis* Standl is a tree up to 20 m tall. The seeds exhibited potently vomitive-purgative activity.[2] At present *Calatola mollis* species had been poorly investigated with only botanical descriptions reported to date.[1] Even thought, specimens of this species have been misidentified as *Calatola costaricensis*,[1,3] and hence a phytochemical study of plants of *Calatola* genus will be useful to establish differences in secondary metabolites composition as a valuable systematic character. The chapingolide (**1**), a *nor*-iridoid, was obtained from the methanolic extract of the leaves of *Calatola mollis* Standl, as a crystalline colourless compound. Its bicyclic structure is closely related to the structures discussed in Valladares and Rios,[4] and Franzyk and Stermitz.[5] The main differences reside in the oxidation level in the *nor*-iridoid skeleton compared with the previous structures, as well as an *endo* double bond in **1**.[6,7] In order to ascertain unambiguously the relative position of the hydroxyl groups and the double bond in the structure, as well as to establish the absolute configurations of the asymmetric centres, we analyze herein the thus far unreported crystal structure of chapingolide, isolated from *Calatola mollis* Standl. Icacinaceae leaves.

In order to assess the relative frequency of *nor*-iridoids, a search of the Cambridge Structural Database (CSD, Version 5.34)[8] was undertaken. Surprisingly few relevant structures were found. There were only eleven structures with a similar 11-noriridoid system (*cis*-2-oxabicyclo[4.3.0]nonane) and, similarly, only three structures with *cis*-2-oxabicyclo[4.3.0]nonan-3-one system and fused five membered rings with substitution equivalent to **1**.[4,5,9] The bond lengths and angles found for **1** (Table 1) closely match the comparable parameters in these literature structures. In order to complete the full characterization of chapingolide and to elucidate its absolute configuration, its crystal structure has been determined.



chapingolide (**1**)

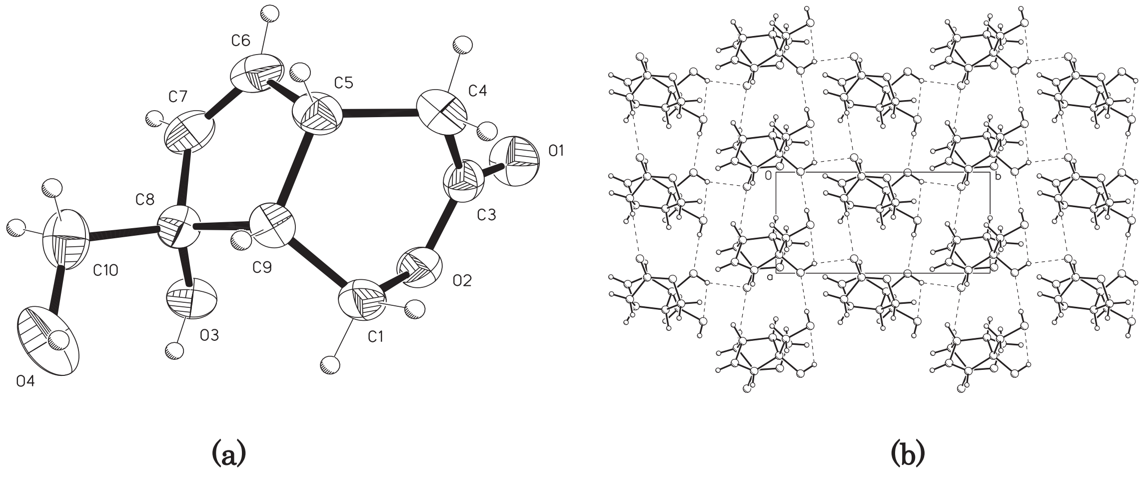
Figure 1a shows an ellipsoid plot of chapingolide. The molecule is made up of a cyclopentene ring fused to a six-membered lactone ring fused showing, a *cis* A/B ring junction, C6=C7 double bond and a *syn* orientation among H-5, H-9 and CH_2-10. In accordance with the biosynthetic origin of the iridoids[10] the *cis* A/B ring junction is α, and **1** corresponds to 8*R*,10-dihydroxy-*cis*-2-oxabicyclo[4.3.0]nonan- 6-en-3-one.

The Cremer & Pople parameters[11] for each ring are as follows: For pyran ring, Q = 0.672(2) Å, θ = 90.53(17) °, and φ = 234.26(18) °, and for cyclopentene ring, Q = 0.090(2) Å, φ = 133.4(15) °, indicating “intermediate conformations”.

In order to assess in a more quantitative way the real significance of the verbal description for “intermediate conformations”, a quantitative conformational analysis was performed by using the program RICON[12] showing that the pyran ring displays an “intermediate conformation” between boat (80%) and twist (19%) conformation, while the cyclopentene ring poses an “intermediate conformation” between twist (61%) and envelope (39%) conformations. The dihedral angle between cyclopentene and pyran rings is 81.99(12)°.

Table 1. Geometric parameters (Å, º) for chapingolide

O(1)-C(3)	1.207(3)	C(1)-O(2)	1.459(3)	C(1)-C(9)	1.505(3)
O(2)-C(3)	1.338(3)	C(3)-C(4)	1.496(3)	C(4)-C(5)	1.542(3)
C(5)-C(6)	1.497(3)	C(5)-C(9)	1.556(3)	C(6)-C(7)	1.312(4)
C(7)-C(8)	1.503(3)	C(8)-O(3)	1.433(3)	C(8)-C(10)	1.525(3)
C(8)-C(9)	1.569(2)	C(10)-O(4)	1.412(4)		
O(2)-C(1)-C(9)	112.47(16)	C(3)-O(2)-C(1)	116.51(16)	O(1)-C(3)-O(2)	118.9(2)
O(1)-C(3)-C(4)	124.9(2)	O(2)-C(3)-C(4)	116.22(19)	C(3)-C(4)-C(5)	111.31(17)
C(6)-C(5)-C(4)	112.18(19)	C(6)-C(5)-C(9)	103.86(17)	C(4)-C(5)-C(9)	111.74(17)
C(7)-C(6)-C(5)	113.4(2)	C(6)-C(7)-C(8)	112.82(19)	O(3)-C(8)-C(7)	109.05(16)
O(3)-C(8)-C(10)	108.11(18)	C(7)-C(8)-C(10)	111.39(19)	O(3)-C(8)-C(9)	113.54(16)
C(7)-C(8)-C(9)	103.45(17)	C(10)-C(8)-C(9)	111.28(16)	C(1)-C(9)-C(5)	110.52(17)
C(1)-C(9)-C(8)	114.86(17)	C(5)-C(9)-C(8)	105.65(16)	O(4)-C(10)-C(8)	111.6(2)
C(9)-C(1)-O(2)-C(3)	56.6(2)	C(1)-O(2)-C(3)-C(4)	-8.0(2)	O(2)-C(3)-C(4)-C(5)	-44.4(2)
C(3)-C(4)-C(5)-C(9)	48.6(2)	C(9)-C(5)-C(6)-C(7)	3.8(2)	C(5)-C(6)-C(7)-C(8)	2.1(3)
C(6)-C(7)-C(8)-C(9)	-7.0(2)	O(2)-C(1)-C(9)-C(5)	-46.8(2)	C(4)-C(5)-C(9)-C(1)	-4.0(2)
C(7)-C(8)-C(9)-C(5)	8.8(2)				



(a) (b)

Figure 1. (a) The molecular structure of (**1**), ellipsoids drawn at the 50% probability level. **(b)** Helical chain in the crystal structure of (**1**), viewed along [001].

As the compound consists only of C, H and O atoms, to establish the absolute configuration of **1** we subject the crystals to a crystallographic analysis by the anomalous X-ray scattering from the oxygen atoms[13] using Cu *K*α radiation and by carefully measuring a large number of Bijvoet differences (812 Friedel pairs, 99%). This yielded a refined Flack x parameter[14] and standard uncertainty (s.u.) of 0.18 (25) for the “hole-in-one” fit. We note that the obtained s.u. value is above the suggested upper confidence limit of 0.10 for the determination of the absolute structure of an enantiopure compound.[13] However, additional confirmation was obtained from the examination of Bayesian statistics on 812 Bijvoet pairs[15] carried out using the program PLATON[16] and suggested that the chapingolide structure is enantiopure: the probability P2 (true) = P3 (true) = 1.000 with P3(racemate-twin) = 0.9×10^{-12}, P3 (false) = 0.2×10^{-59}, G = 0.80(10), and the Hooft parameter y = 0.10 (5) for the C8 *R* enantiomer (5*S*, 9*R*). The SHELXL program[17] was used to refine the structure and it reported a Flack parameter of 0.176(252), a G parameter of 1.03(12) and a Hooft parameter of 0.090(49) (Parsons’ method).[18]

Regarding the supra-molecular structure of (**1**), there is one significant intermolecular interaction, involving the hydroxyl O3—H3 group as donor and carbonylic atom O1 as acceptor (**Table 2**); connecting neighbouring molecules into a C(8) chain structure[19] running along **b** and built up around the twofold screw axis. These [010] chains are connecting by weak O3—H3…O1 and C4—H4C…O1 interactions. This is observable in Figure 1b and quantitatively assessed by the rather low packing index of 72.7.[20] In addition, hydroxyl O3—H3 displays an intramolecular hydrogen bond with the hydroxyl oxygen atom O4, making a 3-center (bifurcate) hydrogen bond (sum of 3 angles about H3 = 359(4) °).

Table 2. Hydrogen bond geometry (Å, °) for chapingolide

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H4*B*···O3^{i}	0.97	2.65	3.362(3)	130
C4—H4*C*···O1^{ii}	0.97	2.32	3.221(3)	154
O3—H3···O1^{iii}	0.84(4)	2.29(3)	2.988(2)	141(3)
O3—H3···O4	0.84(4)	2.34(3)	2.789(3)	114(3)
O4—H4···O3^{ii}	0.79(5)	2.15(5)	2.939(3)	175(5)

Symmetry codes: (i) -*x*, *y*-1/2, -*z*+2; (ii) *x*+1, *y*, *z*; (iii) -*x*, *y*+1/2, -*z*+2.

EXPERIMENTAL

Optical Rotation was measured on a Perkin-Elmer 343 polarimeter. IR spectra were determined with an Agilent Cary FTIR-ATR 630 spectrophotometer. The ^{13}C and ^{1}H NMR spectra were recorded on an Agilent 400 MR DD2 spectrometer (SantaClara, CA, USA) operating at 100 MHz for ^{13}C and 400 MHz for ^{1}H. The ^{13}C and ^{1}H chemical shifts were measured in $CDCl_3$ relative to TMS as an internal standard.

HRFAB MS spectrum was measured on a JEOL the MStation JMS-700.

Isolation

Methanol extract (30 g) from the leaves of *C. mollis* (2 kg) was chromatographed over silica gel (200 g) starting with CH_2Cl_2 and increasing the polarity with MeOH. Fractions eluted with CH_2Cl_2/MeOH (95:5) provided 50 mg of a crystalline colourless solid which was submitted to X-ray diffraction study and identified as chapingolide (**1**). For related structures, see: Ban *et al*. (2013); Tada *et al.* (1998).[6,7]

Chapingolide (1): colourless solid; mp 129-131 °C (CH_2Cl_2/MeOH (95:5)); $[\alpha]_D^{20}$ +89.4 (*c* 0.17, MeOH); IR (neat) 3439, 1711, 1014 cm^{-1}; ^1H NMR δ 2.56 (dd, *J* = 14, 4 Hz, 1H), 2.68 (dt, *J* = 9, 4 Hz, 1H), 2.74 (dd, *J* = 14, 7 Hz, 1H), 3.35 (m, 1H), 3.50 (d, *J* = 11 Hz, 1H), 3.61 (d, *J* = 11 Hz, 1H), 4.28 (dd, *J* = 14, 4 Hz, 1H), 4.57 (dd, *J* = 14, 3.5 Hz, 1H), 5.82 (br d, *J* = 6 Hz, 1H), 5.85 (br d, *J* = 6 Hz, 1H); ^{13}C NMR δ 34.35, 40.56, 41.26, 66.87, 69.27, 86.32, 135.51, 136.00, 172.29; HRFAB MS *m/z* 185.08131 $(M+H)^+$ Anal. Calcd for $C_9H_{13}O_4$.

X-RAY STRUCTURE DETERMINATION OF 1

A colorless prism crystal of $C_9H_{12}O_4$ having approximate dimensions of 0.41 × 0.17 × 0.04 mm was mounted on a glass fiber. All measurements were made on a Bruker Venture κ-diffractometer using Cu-Kα radiation monochromated by multilayer mirror. Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions: a = 5.1034(7) Å, b = 10.8665(15) Å, c = 7.6481(10) Å, β = 92.595(6) °, V = 423.7(1) Å^3. The crystal belongs to the space group $P2_1$. Of the 17267 reflections that were collected, 1729 were unique (Rint = 0.030); equivalent reflections were merged. Data were collected and processed using APEX2 (Bruker). The structure was solved by direct methods and expanded using Fourier techniques. Deposition number CCDC-1056178 for compound No. 1. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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