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Structure of Elemanschkuhriolide. Melampolides as Possible Biogenetic Precursors of $C_{14}\alpha,H_5\beta$ Elemanolides

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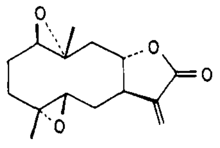
The structure and stereochemistry of the new $C_{14}\alpha,H_5\beta$ elemanolide, elemanschkuhriolide (8) from *Schkuhria schkuhrioides* is reported. Schkuhriolide (2), isolated from the same plant source, was transformed into 8 via a Cope rearrangement and this is the first [3,3] sigmatropic reaction of a melampolide with a lactone ring closed at C(8) and cis annelated. The biogenesis of $C_{14}\alpha,H_5\beta$ elemanolides from melampolides is discussed.

During the course of our systematic investigation of the mexican Compositae, we recently described the germacrolide 11,13-dehydroeriolin (1) and the melampolides schkuhriolide (2) and schkuhrioidin (3) from *Schkuhria schkuhrioides*.[1] We now report structure and stereochemistry of the sesquiterpene lactones in a Valley of Mexico collection of this species and discuss their biogenetic relationships.

Frutescin (4), previously isolated from *Iva frutescens*,[2] and recently reformulated,[3] was found to be a minor constituent of this population of *S. schkuhrioides*.[4]



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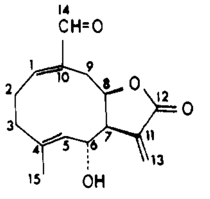

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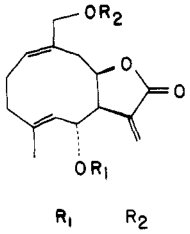
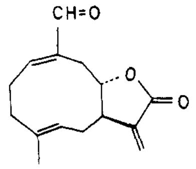


	R1	R2	
3	H	i-BuCO	
5	Ac	i-BuCO	
6	Ac	H	
7	Ac	H	11,13-dihydro



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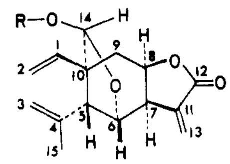
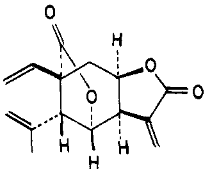
Schkuhriolide (2) was also found and characterized by its physical constants and direct comparison.[1,5] Recently, an X-ray analysis of this substance confirmed its structure.[6] The acetate of schkuhriolide was transformed to acetylschkuhrioidin (5) in a straightforward manner via reduction of the aldehyde at C-10 with $NaBH_4/CeCl_3$ complex[7] without protection of the exocyclic methylene group to give 6, followed by acylation. (See Experimental Section.)



8 R = H

9 R = Ac



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A third lactonic constituent from this population of *S. schkuhrioides* not hitherto reported has been called elemanschkuhriolide (8). This substance, $C_{15}H_{18}O_4$, $[\alpha]^{25}_D$ +123.1° (*c* 0.116, MeOH), contains an α,β-unsaturated γ-lactone as shown by its IR ($\nu_{max}^{CHCl_3}$ 1770, 1665) and UV spectra (λ_{max}^{MeOH} 218 nm, ϵ 8130). The ^{13}C NMR spectra (see Experimental Section for the assignments) show resonances for a carbonyl, three double bonds (one monosubstituted and two disubstituted), three secondary carbons bearing oxygen, one methyl group, one methylene, two methines, and a fully substituted carbon. This pattern clearly indicates the 1,2-divinylcyclohexane skeleton of an elemanolide. Beginning with H-7, all of the cyclohexane ring protons in the sequence C-5 through C-9 were interrelated through spin-decoupling. The presence of the γ-lactol was confirmed by acetylation to give 9 and oxidation to the dilactone 10. The cis fusion of the lactone ring of elemenschkuhriolide (8) is in agreement with the observed coupling constants between H-7 and H-8 (J = 9.0 Hz) and the allylic coupling between H-7 and H-13, H-13′ (3.5, 3.1 Hz) shows that this lactone belongs to the *S* type ($^4J_{7,13} > 3$ Hz).[8] The coupling constant between H-6 and H-7 (3.8 Hz) indicates that H-6 is β (assuming that H-7 is α, as in most of the sesquiterpene lactones formed in higher plants) and therefore that the ethereal oxygen of the lactol is α oriented. Hence C-14 (which supports the OH) is also α oriented; moreover the dihedral angle of ca. 85° between H-6 and H-5 ($^3J \simeq 0$ Hz) is only concordant with β disposition of H-5 (Dreiding models). Therefore, this molecule belongs to the uncommon series of $C_{14}\alpha,H_5\beta$ elemanolides. The constancy of the chemical shift of H-8 (δ 5.22) in 8 and 9 (δ 5.20) suggest that the OH group is exo to the [3.2.1]bicycle, as depicted in 8.

The structure and stereochemistry of elemanschkuhriolide (8) was confirmed by an X-ray diffraction analysis

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[2] Herz, W.; Bhat, S. V.; Sudarsanam, V. *Phytochemistry* **1972**, *11*, 1829.

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[4] We thank Dr. W. Herz (Florida State University) for spectral data of frutescin.

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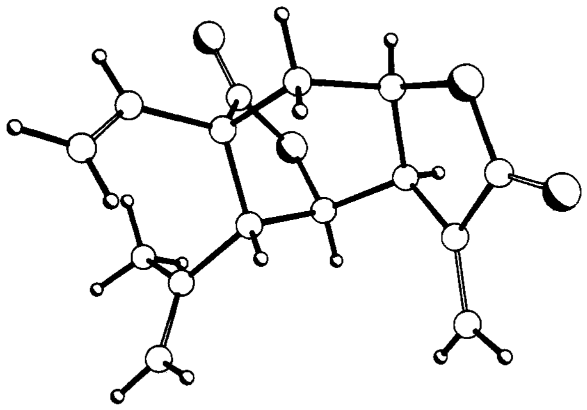

Figure 1. Stereoprojection of dehydroelemanschkuhriolide (10).

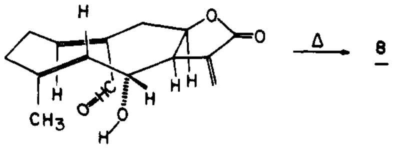

Figure 2.

of the dehydro derivative 10. Figure 1 is a perspective drawing of the final structure. The cyclohexane ring of 10 is a distorted chair with C-14 and O-6 axially oriented and α to the plane of the ring, whereas the vinyl groups are equatorial. The α-methylene γ-lactone is somewhat puckered and H-7 is pseudoequatorial and α. Pertinent data from the crystallographic analysis are available as supplemental material.

Elemanschkuhriolide (8) is the first elemanolide isolated from *Schkuhria* species, since previous work on this genus afforded only heliangolides and melampolides.[9]

The cooccurrence of the aldehydic melampolide 2 and elemanschkuhriolide (8) in the same plant is indicative of their biogenetic relationship. Schkuhriolide (2) could be converted into 8 via a Cope rearrangement followed by hemiacetal formation.[10] The possibility of a Cope rearrangement during the isolation procedure seems to be unlikely since schkuhriolide (2), when heated at 200 °C for 10 min, yielded only a small amount of elemanschkuhriolide (8). Nevertheless, this is the first in vitro Cope rearrangement of a cis-1(10),*trans*-4(5)-germacradien-8-(12)-olide, to give an elemadienolide which has a stereochemistry enantiomeric ($C_{14}\alpha,H_5\beta$) to the stereochemistry of those obtained by the Cope rearrangement of *trans*-1(10),*trans*-4(5)-germacradienolides.[11,12]

This transformation is explained if schkuhriolide (2) adopts a [${}_1D_{14,15}D^5$] conformation[15] (C-14 and H-5 in anti relationship) in the transition state which permits the Cope rearrangement and hemiacetal formation. Figure 2.[16]

The above observations strongly suggest that melampolides (in addition to germacrolides)[17] may be biogenetic precursors of $C_{14}\alpha,H_5\beta$ elemanolides.

Experimental Section

Melting points were determined in a Fisher-Johns apparatus and are uncorrected. Column chromatography was carried out by using Merck silica gel 60 (0.063–0.2 mm). UV and IR spectra were taken on Perkin-Elmer 552 and 283b instruments, respectively. ${}^1H$ and ${}^{13}C$ NMR spectra were obtained on Varian FT-80 spectrometer, in $CDCl_3$ solutions with Me_4Si as internal standard. Mass spectra were recorded on a Hewlett-Packard 5985-B spectrometer at 70 eV.

Isolation of Compounds 2, 4, and 8. Dried and comminuted *S. schkuhrioides* (Link & Otto) Thellung (aerial parts, 8500 g) collected ca. 36 Km north of Mexico City, near Teoloyucan, State of Mexico (voucher deposited in the National Herbarium, Instituto de Biologia de la U.N.A.M.) were extracted as previously described[1] and the chloroform fraction was repeatedly chromatographed over silica gel columns, eluted with $CHCl_3$ and $CHCl_3$–acetone gradient elution system. The fractions eluted with chloroform afforded frutescin (4, 0.021% of dry weight) which was identified by conventional methods.[4] Some fractions eluted with $CHCl_3$–Me_2CO (20:1) which showed a major characteristic blue spot on TLC were combined and the residue was purified over a column eluted with $CHCl_3$ as constant eluent. Some fractions gave an oil which, when purified by preparative TLC using $CHCl_3$–Me_2CO (97:3) as the developing solvent afforded elemanschkuhriolide (8) (0.007% of dry weight), as amorphous solid: mp 127–128 °C (from Me_2CO–*i*-Pr_2O); $[\alpha]^{25}{}_D$ +123.1 (*c* 0.116, MeOH); IR 3420, 3090, 3020, 2930, 2850, 1770, 1665, 1645, 1455, 1420, 1380, 1330, 1285, 1220, 1180, 1120, 1060, 1040, 990, 970, 920, 815 cm^{-1}; UV (MeOH) λ_{max} 218 nm (ϵ 8130); ${}^1H$ NMR δ 6.31 (1 H, d, $J = 3.5$, H-13), 5.78 (1 H, dd, $J = 18, 10$ Hz, H-1), 5.22 (1 H, ddd, $J = 9, 8.4, 7$ Hz, H-8), 5.50 (1 H, d, $J = 3.1$ Hz, H-13′), 5.48 (1 H, s, H-14), 5.30–4.85 (complex, H-2, H-2′, H-3, H-3′), 4.39 (1 H, d, $J = 3.8$ Hz, H-6), 3.61 (1 H, dddd, $J = 3.8, 9, 3.5, 3.1$ Hz, H-7), 2.76 (1 H, dd, $J = 14.9, 8.4$ Hz, H-9), 2.43 (1 H, s, H-5), 1.74 (3 H, dd, $J = 1.4, 0.8$ Hz, 15 CH_3), 1.57 (1 H, dd, $J = 14.9, 7$ Hz, H-9′); ${}^{13}C$ NMR δ 170.16 (s, C-12), 143.47 (s, C-4), 137.44 (d, C-1), 136.61 (s, C-11), 122.47 (t, C-13), 115.96 (t, C-2 or C-3), 113.98 (t, C-2 or C-3), 101.70 (d, C-14), 81.21 (d, C-6), 75.21 (d, C-8), 56.56 (d, C-5), 50.53 (s, C-10), 46.55 (d, C-7), 38.53 (t, C-9), 24.96 (q, C-15); mass spectrum (CI, CH_4), m/z (relative intensity) 263 ($M^+ + 1$, 100), 245 (59), 235 (18), 227 (20), 219 (10), 217 (32), 203 (8), 201 (9), 199 (10), 149 (26). The $CHCl_3$–Me_2CO (4:1) fractions of the initial chromatography which showed the same spot on TLC were combined and rechromatographed.

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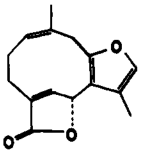
(9) (a) Petei, M. J.; Miura, I.; Kubo, I.; Nakanishi, K. *Heterocycles* **1978**, *11*, 471. (b) Bohlmann, F.; Zdero, C. *Phytochemistry* **1981**, *20*, 2431. (c) Herz, W.; Govindan, S. V. *Ibid.* **1980**, *19*, 1234.

(10) This situation also exists in the isolation of the germacrolide eriofertin and the hemiacetalic elemanolide confertiphyllide from the same plant source. Saitoh, T.; Geissmann, T. A.; Wadell, T. G.; Herz, W.; Bhat, S. V. *Rev. Latinoamer. Quim.* **1971**, *2*, 69.

(11) For a review on this subject, see: Takeda, K. *Tetrahedron* **1974**, *30*, 1525.

(12) Neolinderalactone i underwent a Cope rearrangement to give isolinderalactone ii,[13] but the synthetic melamplolide iii remained unchanged at 175 °C for 2 h and decomposes at higher temperatures.[14]



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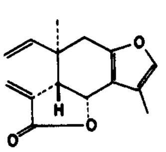

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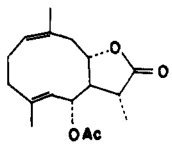

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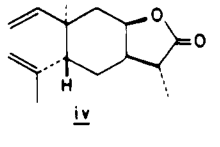
(14) Takeda, K.; Horibe, I. *J. Chem. Soc. Perkin Trans. 1* **1975**, 870.

(15) Samek, Z.; Harmatha, J. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2779.

(16) The conformational change ${}_1D_{14},{}^{15}D_5$ (found in the crystals)[6] to ${}_1D_{14,15}D^5$ (required in the transition state) may well be reached at Cope rearrangement temperatures, and the hemiacetal formation serves to trap the product.

(17) It has been noted[18] that callitrin iv,[19] a $C_{14}\alpha,H_5\beta$ elemanolide could be formed from a germacrolide precursor, which adopts a ${}^1D_{14,15}D^5$ conformation under the conditions of biogenesis. Indeed, when callitrin iv was heated for 2 h at 220 °C, it was transformed to epicallitrin v, through two consecutive Cope rearrangements.[20]



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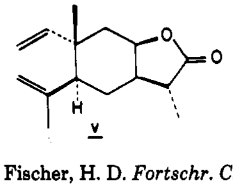

v

(18) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *34*, 218.

(19) Brecknell, D. J.; Carman, R. M. *Tetrahedron Lett.* **1978**, 73.

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Schkuhriolide (**2**, 0.040% of dry weight) was obtained in pure form and identified by direct comparison with an authentic sample using the standard methods.

Reduction of Acetylschkuhriolide with $NaBH_4$–$CeCl_3$ Complex. Acetylschkuhriolide (136 mg), prepared as indicated in ref 1, was dissolved in a solution of $CeCl_3 \cdot 7H_2O$ (Aldrich, 186 mg) in 2 mL of MeOH, and 20 mg of $NaBH_4$ was slowly added with stirring at room temperature, the reaction being monitored by TLC. When the reaction was completed (ca. 8 min), the mixture was treated with water and extracted with $CHCl_3$. Usual workup afforded 114.5 mg of a mixture of two products which was resolved by column chromatography using hexane–ethyl acetate (3:2) as constant eluent. The evaporation of the eluates of the more mobile compound gave 84.2 mg of **6** as a solid: mp 154–156 °C; IR ($CHCl_3$) 3610, 3000, 2940, 2880, 1770, 1735, 1670, 1460, 1435, 1405, 1390, 1370, 1270, 1220, 1185, 1165, 1120, 1060, 1010, 965, 945, 925 cm^{-1}; ^1H NMR δ 6.24 (1 H, t, $J = 0.8$ Hz, H-13), 5.70 (1 H, t, $J = 0.8$ Hz, H-13′), 5.52 (1 H, m, H-1), 5.25 (1 H, t, $J = 11$ Hz, H-6), 4.86 (1 H, m, H-8), 4.81 (1 H, dq, $J = 11, 1.5$ Hz, H-5), 4.08 (2 H, br s, $w_{1/2} = 3$ Hz, 14-CH_2), 3.09 (1 H, br dd, $J = 11, 5$ Hz, H-7), 1.95 (3 H, s, CH_3CO), 1.86 (3 H, d, $J = 1.5$ Hz, 15CH_3); mass spectrum, m/z (relative intensity) 306 (M^+, <1), 228 (10), 215 (18), 171 (12), 169 (14), 157 (12), 143 (18), 131 (20), 117 (19), 105 (28), 91 (57), 79 (28), 77 (27), 67 (27), 43 (100). Evaporation of the eluates of the less mobile compound gave 16.2 mg of **7** as a solid: mp 148–149 °C, IR ($CHCl_3$) 3605, 3005, 2920, 1772, 1732, 1445, 1383, 1372, 1215, 1173, 1150, 1005, 962, 940 cm^{-1}; ^1H NMR δ 5.52 (1 H, m, H-1), 5.32 (1 H, t, $J = 10.5$ Hz, H-6), 4.85 (1 H, m, H-8), 4.76 (1 H, dq, $J = 10.5, 1.5$ Hz), 4.10 (2 H, br s, 14-CH_2), 1.98 (3 H, s, CH_3CO), 1.88 (3 H, d, $J = 1.5$ Hz), 1.22 (3 H, d, $J = 7$ Hz, 13CH_3); mass spectrum, m/z (relative intensity) 308 (M^+, <1), 291 (1), 230 (5), 217 (10), 202 (4), 157 (20), 145 (22), 143 (20), 105 (20), 91 (41), 55 (27), 43 (100), 41 (35).

Acylation of 6. Treatment of 40.5 mg of **6** with isobutyric anhydride/pyridine gave, after TLC purification using $CHCl_3$–Me_2CO (9:1) as the developing solvent, 34.8 mg of acetylschkuhrioidin (**5**), identical in all respects[1] with an authentic sample.

Acetylelemanschkuhriolide (9). To a solution of 50.3 mg of **8** in 2 mL of dry pyridine was added 2 mL of acetic anhydride. The reaction mixture was kept for 6 h at room temperature. After usual workup, 40.1 mg of **9** was obtained as colorless oil: IR ($CHCl_3$) 2960, 2930, 2860, 1760, 1460, 1380, 1370, 1335, 1285, 1275, 1125, 1030, 1020, 1000, 950, 925, 910 cm^{-1}; ^1H NMR δ 6.35 (1 H, d, $J = 3.5$ Hz, H-13), 6.21 (1 H, s, H-14), 5.77 (1 H, dd, $J = 18, 10$ Hz, H-1), 5.52 (1 H, d, $J = 3.1$ Hz, H-13′), 5.20 (1 H, ddd, $J = 9, 8.4, 7$ Hz, H-8), 5.25–4.90 (complex, H-2, H-2′, H-3, H-3′), 4.49 (1 H, d, $J = 3.8$ Hz, H-6), 3.62 (1 H, dddd, $J = 9, 3.8, 3.5, 3.1$ Hz, H-7), 2.75 (1 H, dd, $J = 14.9, 8.4$ Hz, H-9), 2.46 (1 H, s, H-5), 1.76 (3 H, dd, $J = 1.4, 0.8$ Hz, 15CH_3), 1.58 (1 H, dd, $J = 14.9, 7$ Hz, H-9′); mass spectrum, m/z (relative intensity) 304 (M^+, <1), 219 (15), 225 (19), 171 (18), 133 (30), 129 (20), 119 (35), 105 (63), 91 (44), 79 (30), 77 (31), 57 (18), 55 (27), 43 (100).

Dehydroelemanschkuhriolide (10). Jones reagent was added dropwise to a solution of 150 mg of **8** in 15 mL of Me_2CO at 0 °C, the reaction being monitored by TLC. Usual workup yielded a gummy residue which was purified by column chromatography using $CHCl_3$ as constant eluent; 78 mg of dehydroelemanschkuhriolide (**10**), mp 130–131 °C, was obtained from Me_2CO–i-Pr_2O: IR ($CHCl_3$) 3030, 2980, 2860, 1770, 1665, 1645, 1445, 1420, 1405, 1385, 1360, 1330, 1280, 1190, 1140, 1110, 1050, 1000, 990, 930, 910 cm^{-1}; ^1H NMR δ 6.47 (1 H, d, $J = 3.5$ Hz, H-13), 5.88 (1 H, dd, $J = 18, 10$ Hz, H-1), 5.72 (1 H, d, $J = 3.1$ Hz, H-13′), 5.36 (1 H, d, $J = 18$ Hz, H-2), 5.35 (1 H, d, $J = 10$ Hz, H-2′), 4.95 (1 H, ddd, $J = 9, 8, 7$ Hz, H-8), 5.01–4.82 (complex, H-3, H-3′), 1.98 (1 H, dd, 14.9, 7 Hz, H-9′), 1.67 (3 H, dd, $J = 1.4, 0.8$ Hz, 15CH_3); ^{13}C NMR δ 176.25 (s), 176.25 (s, C-14), 168.41 (s, C-12), 140.99 (s, C-4), 134.12 (s, C-11), 133.09 (d, C-1), 124.09 (t, C-13), 118.44 (t, C-2), 115.73 (t, C-3), 80.94 (d, C-6), 72.86 (d, C-8), 53.31 (d, C-5), 47.64 (d, C-10), 42.66 (d, C-7), 39.78 (t, C-9), 21.27 (q, C-15); mass spectrum, m/z (relative intensity) 260 (M^+, <1), 215 (18), 201 (9), 197 (22), 179 (20), 155 (22), 143 (20), 120 (32), 119 (28), 105 (100), 93 (42), 91 (90), 77 (38), 65 (18), 63 (20), 43 (30).

Thermal Rearrangement of Schkuhriolide (2). A total of 80 mg of **2** in several sealed semicapillary tubes were heated for 10 min at 200 °C. (at lower temperatures the sample remained unchanged). The reaction gave a resinous residue which was separated by column chromatography on silica gel using $CHCl_3$–Me_2CO (20:1) as constant eluent, affording 43.3 mg of starting material **2** and elemanschkuhriolide (4.3 mg of recrystallized product). Both compounds were identified by standard methods and direct comparison with authentic specimens.

Crystallographic Study of Dehydroelemanschkuhriolide (10). Single crystals of **8** were obtained by slow crystallization from ethyl acetate. They were orthorhombic, space group $P2_12_12_1$, with $a = 6.566$ (2) Å, $b = 13.843$ (5) Å, $c = 14.717$ (5) Å, and $d_{calcd} = 1.291$ cm^3 for $Z = 4$ ($C_{15}H_{16}O_4$). The intensity data were measured on a Nicolet R3m diffractometer (monochromated Cu $K\alpha$ radiation, ω scans, pulse hight discrimination). The size of the crystal used for data collection was approximately 0.20 × 0.08 × 0.08 mm, $\mu = 7.31$ cm^{-1}. A total of 826 independent reflections were measured for $2\theta < 100$, of which 606 were considered observed $|F| > 3\sigma|F|$. The structure was solved by direct methods and was refined by blocked cascade matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations. The final discrepancy indices are $R = 0.0632$ and $R_W = 0.0627$ for the 606 observed reflections. The final difference map has no peaks greater than ± 0.272 e $Å^{-3}$.

Acknowledgment. We thank Ms. Sc. F. J. Espinoza (National Herbarium, Instituto de Biología de la U.N.A.M.) for identification of plant material. We acknowledge the assistance of chemists J. Cárdenas and R. A. Toscano (Instituto de Química de la U.N.A.M.). This work was supported in part by the Consejo Nacional de Ciencia y Tecnología, México, Proyecto PCCBBNA-002049.

Registry No. 2, 73675-60-2; 2 (acetate), 90605-40-6; 4, 36790-43-9; 6, 90605-35-9; 7, 90605-36-0; 8, 90605-37-1; 9, 90623-23-7; 10, 90605-38-2; i, 26379-18-0; ii, 90605-39-3; iii, 57589-54-5; iv, 66964-63-4; v, 73335-81-6.

Supplementary Material Available: Tables I–V listing atom coordinates, bond lengths, bond angles, anisotropic temperature factors, and hydrogen coordinates of dehydroelemanschkuhriolide (**10**) (3 pages). Ordering information is given on any current masthead page.