

Studies on the chemical reactivity of *cis*-1(10)-*trans*-4-germacradienolides (Melampolides). Additional derivatives of schkuhriolide.¹

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DELGADO, G.; S. GUZMÁN and R. A. TOSCANO, 1994. Studies on the chemical reactivity of *cis*-1(10)-*trans*-4-germacradienolides (Melampolides). Additional derivatives of schkuhriolide. *An. Esc. nac. Cienc. biol., Méx.* **39**: 109-118.

SUMMARY: As a contribution in the knowledge of the reactivity of 1(10)-*cis*-4-*trans*-germacradienolide, some derivatives of schkuhriolide (**1a**), natural melampolide isolated from *Schkuhria schkuhrioides*, were prepared. When the aldehyde in C-14 or the hydroxy group in C-6 of **1a** were modified, the [3,3] sigmatropic rearrangement was inhibited, since some obtained derivatives remained unchanged, under the same conditions to those **1a** is converted to elemansschkuhriolide (**4**). These suggests that some conformational and/or configurational intermediates are involved in this process. A relactonization of **1a** toward C-6 was also observed. Both, the preferential epoxidation with CrO₃ of the C(4)-C(5) double bond of **1a**, with respect to the alcohol in C-6, and the hydrogenolysis of the isobutyric ester on C-14 of acetyl schkuhriolide (**1b**), may be rationalized considering a relative steric hindrance at C-6.

INTRODUCTION

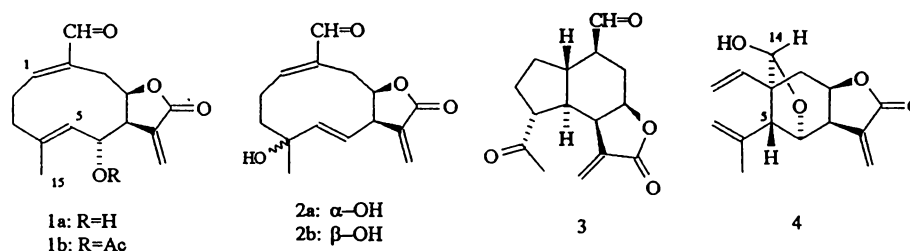
Schkuhriolide (**1a**) is a *cis*-1(10)-*trans*-4-germacradienolide (melampolide) found as the major constituent of *Schkuhria schkuhrioides* (*Asteraceae*, *Heliantheae*)¹ whose structure has been confirmed by crystallographic analysis.² Further chemical studies on the chemical constituents of this plant have established the presence of additional sesquiterpenes closely related to **1a**.^{3,4,5}

Accumulated results from the studies on the chemistry of melampolides indicate that these compounds possess particular reactivity.⁶ Recently it has been described the acid

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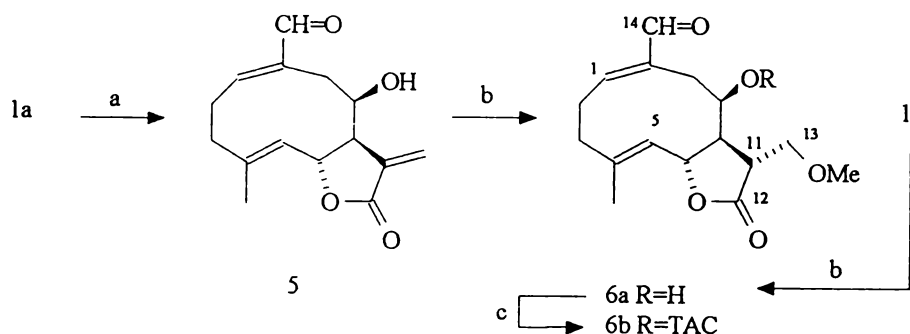
catalyzed transformation of schkuhriolide (**1a**) and its derivative **1b**, which affords the epimers **2a**, **2b** and the oplopanolide **3**, via sequential rearrangements.⁷ On the other hand, the chemical correlation of schkuhriolide (**1a**) to elemanschkuhriolide (**4**), also present in *S. schkuhrioides*, has been reported.⁴ It was considered that the transformation **1a** to **4** proceeds via direct [3,3] sigmatropic reaction, followed by intramolecular hemiacetalization to give the elemanolide **4**, which has a stereochemistry enantiomeric ($C_{14\alpha}$, $H_{5\beta}$) to the stereochemistry of those obtained by the rearrangement of *trans*-1(10)-*trans*-4-germacradienolides (germacrolides).^{8,9,10}



Here are described some modifications of schkuhriolide **1a** obtained to analyse the presumed direct Cope rearrangement of melampolides (**1a** to **4**). This resulted in some unusual transformations which are also reported.

DISCUSSION

Alkaline treatment (NaOH, H₂O, HMPA) of schkuhriolide (**1a**) gave alloschkuhriolide (**5**), obtained previously.¹ Relactonization to C-6 also occurred when **1a** was treated with aqueous methanolic K₂CO₃, yielding the adduct **6a**. This compound was also obtained from **5** (Scheme I). **6a** exhibited a methoxy peak ($\delta_H 3.35; \delta_C 59.2$) tables I and II and the AB part of an ABX system was observed in the ¹H NMR for the H-13 hydrogens, which is better resolved in the trichloroacetyl carbamate **6b** ($\delta_H 3.75$, dd, $J=11, 4$ Hz, H-13a; 3.52 , dd, $J=11, 3.5$ Hz, H-13b, Table I). The orientation of H-11 was established as β , due to the equilibration at C-11, according to previous reports.¹¹ These results suggest a preferential C-6 relactonization of melampolides containing C₆ α - and C₈ β -lactonizable oxygen groups. **5** remained unchanged upon thermal treatment at 200°.



SCHEME I. (a): NaOH, HMPA; (b): K₂CO₃, MeOH; (c): TAI, CDCl₃.

Jones oxidation at 0°C of **5** yielded dehydro-alloschkuhriolide **7**. The same reaction performed at room temperature afforded isodehydroalloschkuhriolide **8**, which was also obtained when **7** was treated with Si-gel in CHCl₃ (Scheme II). ¹H NMR of **8** showed signals for two vinylic methyl groups (δ 1.96 and 1.89) and also exhibited the expected paramagnetic shift of H-6 (δ 5.54, table I). ¹³C NMR data of **7**, **8** and **9** (table II) were in agreement with the proposed structures.

TABLE I. ¹H NMR Data of Some Melampolides (80MHz, CDCl₃).

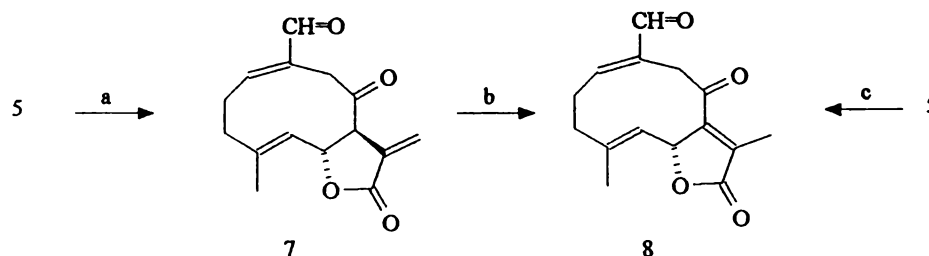
H	1a	1a ^{&}	6a	6b	7	8	14a	14b	15
1	6.64 m	6.47 m	6.54 m	6.60 m	6.78 m	6.15 m	5.64 m	5.80 m	5.22 m
5	4.86 <i>dq</i> 10.1,1.5	5.04 <i>dd</i> 10.5, 1.5	4.90 <i>dq</i> 10.5,1	4.94 <i>dq</i> 10.5,1	5.23 <i>dq</i> 10.5,1	4.65 <i>dq</i> 10.1	2.62 <i>d</i> 10	2.96 <i>d</i> 9	4.72 <i>dq</i> 11,1.5
6	4.07 <i>dd</i> 10,10	4.28 <i>dd</i> 10.5, 10.5	5.06 <i>dd</i> 10.5, 10.5	5.15 <i>dd</i> 10.5, 10.5	4.65 <i>dd</i> 10.5, 10.5	5.54 <i>dq</i> 10,2	3.20 <i>dd</i> 10,10	4.83 <i>dd</i> 10,9	5.31 <i>dd</i> 11,11
7	2.61 <i>m</i>				3.43 <i>ddd</i> 10, 3.5,3			3.27 <i>dd</i> 10.5	
8	5.52 <i>td</i> 12.5,5.5	5.78 <i>td</i> 12.5,5	4.95 <i>m</i>	6.12 <i>ddd</i> 9.2,7			5.00 <i>td</i> 12.5,5	4.76 <i>m</i>	4.70 <i>td</i> 12,6,6
13a	6.29 <i>dd</i> 1,1	6.38 <i>dd</i> 1,1	3.60 <i>d</i> 3.5	3.75 <i>dd</i> 11,4	6.42 <i>d</i> 3.5	1.96 <i>d</i> 2.0	6.26 <i>s</i> <i>W</i> _{1/2} =3	6.25 <i>s</i> <i>W</i> _{1/2} =3	
13b	5.77 <i>dd</i> 1,1	5.92 <i>dd</i> 1,1	3.60 <i>d</i> 3.5	3.52 <i>dd</i> 11,3,5	5.83 <i>d</i> 3		5.84 <i>s</i> <i>W</i> _{1/2} =3	5.68 <i>s</i> <i>W</i> _{1/2} =3	1.23 <i>d</i>
14	9.47 <i>d</i> 1.7	9.45 <i>d</i> 1.5	9.38 <i>d</i> 1.5	9.40 <i>d</i> 1	9.50 <i>s</i> <i>W</i> _{1/2} =2	9.37 <i>s</i>	4.04 <i>s</i> <i>W</i> _{1/2} =5	4.61 <i>d</i> 12	1.77 <i>s</i> <i>W</i> _{1/2} =4
14'								4.13 <i>d</i> 12	
15	1.82 <i>d</i> 1.5	1.59 <i>d</i> 1.5	1.90 <i>d</i> 1	1.93 <i>d</i> 1	1.86 <i>d</i> 1.5	1.89 <i>d</i> 1	1.74 <i>s</i>	1.59 <i>s</i>	1.85 <i>d</i> 1.5

[&] Taken in Py-d₅. Coupling constants (in italics) in Hz.

TABLE II. ^{13}C NMR Data of Some Melampolides (20 MHz, CDCl_3).

Carbon	1a	1b	5	6a	8	9
1	155.2d	155.0d	153.8d	153.4d	154.4d	153.1d
2	26.1t	26.4t	26.3t	26.3t	27.5t	24.5t
3	37.1t	37.3t	37.2t	37.3t	37.0t	35.9t
4	138.4s	138.2s	138.0s	136.5s	137.1s	62.6s
5	126.9d	123.2d	126.9d	127.2d	123.0d	64.0d
6	65.5d	68.8d	75.1d	63.8d	77.4d	65.0d
7	49.8d	47.0d	50.9d	49.0d	131.1s	48.8d
8	77.3d	76.4d	63.5d	74.8d	197.8s	75.7d
9	27.5t	27.6t	32.2t	32.6t	41.5t	27.8t
10	141.0s	140.9s	144.0s	144.0s	140.0s	140.0s
11	134.7s	137.9s	137.9s	43.4d	137.1s	137.3s
12	169.8s	169.3s	170.2s	176.5s	156.6s	169.4s
13	124.7t	124.2t	119.9s	68.7d	9.4c	125.8t
14	195.7d	195.5d	195.9d	195.7d	194.0d	195.0d
15	16.8q	17.0q	17.2q	17.1q	17.2q	17.5q
1'		168.8s		59.2q		
2'		20.7q				

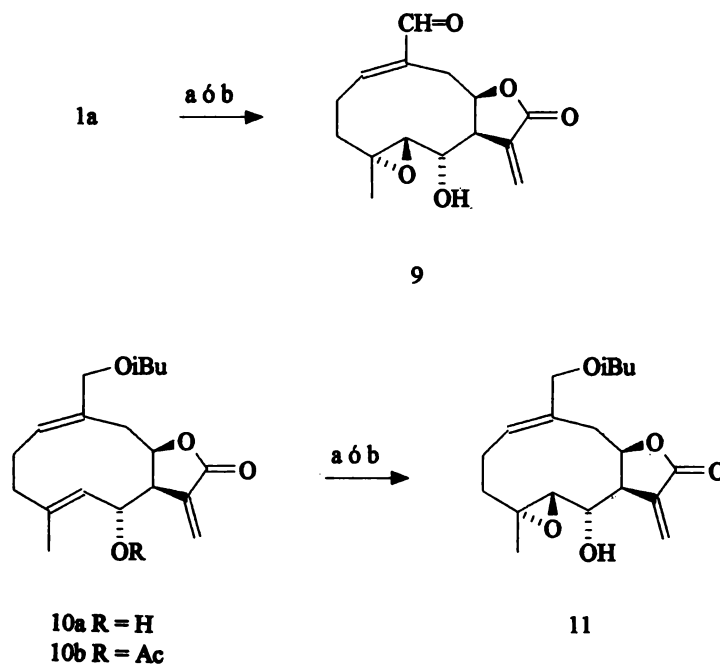
Carbon	11	12	14a	14b	15
1	132.8d	128.3d	127.9d	133.6d	125.5d
2	23.3t	24.4t	22.7t	23.2t	24.4t
3	36.8t	38.4t	37.2t	36.6t	38.6t
4	63.3s	138.4s	61.8s	62.5s	136.0s
5	63.9d	122.3d	63.6d	61.2d	123.0d
6	65.3d	69.4d	64.8d	66.9d	69.1d
7	49.5d	47.2d	49.6d	48.0d	45.8d
8	77.1d	79.0d	77.8d	77.1d	80.1d
9	30.4t	30.1t	30.0t	30.2t	33.0t
10	131.1s	138.4s	138.1s	130.3s	132.6s
11	137.0s	136.7s	135.9s	137.3s	42.0d
12	169.1s	169.3s	169.5s	169.2s	169.4s
13	126.2t	124.4t	124.7t	125.0t	11.4q
14	67.6t	67.5t	65.7t	67.7t	22.6q
15	17.7q	17.1q	17.5q	17.3q	17.0q
1'	176.5s	169.6s		170.2s	177.6s
2'	34.2d	20.8q		20.5q	21.2q
3'	19.0q			168.2s	
4'	17.7q			20.9q	



SCHEME II. (a): $\text{CrO}_3, \text{AcOH}, 0^\circ\text{C}$; (b): Silica gel, CHCl_3 ; (c): $\text{CrO}_3, \text{AcOH}, 25^\circ\text{C}$.

The natural product **1a** did not react with MnO_2 , however, it reacted with Jones reagent at room temperature affording the epoxide **9** as the only product. This compound was identical to that obtained by treatment of **1a** with mcpba.³ The *4R,5R* configurations of **9** were established according to the peripheric approach of the oxidative reagent to the *re, re* face of the C(4)-C(5) double bond of **1a**.

Analogous results were obtained with natural melampolide schkuhrioidine **10a**, which afforded the epoxyderivative **11** (Scheme III). Similar oxidations of allylic alcohols with chromium trioxide have been reported in the literature.^{12,13} In this case, the preferential epoxidation of the C(4)-C(5) double bond with CrO_3 was rationalized by the fact that H-6 in **1a** and **10a** possesses a *syn pseudo axial* orientation with respect to the methyl group at C-4, and therefore, it is not accesible to be abstracted from the intermediate chromic ester in the rate determining step of the oxidation process at C-6. See figure 1 (R: $\text{CH}=\text{O}$ or CH_2OiBu).



SCHEME III. (a): Jones, 0°C ; (b): mcpba, CH_2Cl_2

EXPERIMENTAL SECTION

GENERAL

Melting points were measured in a Fischer-Johns apparatus and are uncorrected. A Varian FT-80 NMR spectrometer operating at 80 MHz for ^1H and 20 MHz for ^{13}C was used for determining the spectra with TMS as the internal standard. Mass spectra were recorded on a Hewlett-Packard 5985-B spectrometer at 70 eV. Compounds **1a** and **10a** were obtained from the natural source as described previously.⁵ The preparation of **1b**,³ **5**,¹ **12**⁴ and **13**⁴ have been previously reported.

(11R)-11,13-Dihydro-13-methoxy-alloschkuhriolide (6a). To a solution of **1a** (123 mg) in MeOH (10 ml) was added K_2CO_3 (90 mg) in H_2O (6 ml) under an atmosphere of dry nitrogen. The reaction was kept for 1 h. Usual procedure and chromatography on silica gel gave 89 mg of **6a**. Mp 177-179°C (from $\text{Me}_2\text{CO}-i\text{Pr}_2\text{O}$). The same product (**6a**) in similar yield was obtained using **5** as starting material. IR (CHCl_3): 3622, 2934, 2898, 2833, 2728, 1769, 1681, 1625, 1456, 1310, 1164, 1099 cm^{-1} ; ^1H and ^{13}C NMR: see Tables I and II; EIMS m/e (rel. int.): 294 (M^+ ,3), 276(5), 262(2), 244(5), 231(5), 191(28), 148(12), 133(12), 123(11), 122(12), 121(13), 107(26), 91(32), 84(40), 69(43), 55(62), 43(100), 41(43).

Trichloroacetylcarbamate of 6a (6b). To a solution of **6a** (7 mg in 0.3 ml CDCl_3) in a NMR tube, was added 3 drops of trichloroacetyl isocyanate (TAI, aldrich) and allowed to stand for 10 min. This compound was characterized by its ^1H NMR spectrum (see Table I).

Dehydroalloschkuhriolide (7). To a solution of **5** (90 mg) in Me_2CO (25 ml) at 0° was added Jones reagent (ca. 0.6 ml). The resultant mixture was stirred for 15 min at 0°, and then MeOH (2 ml) was added. The slurry was poured into saturated NaHCO_3 , and extracted with CHCl_3 . Usual procedure provided 75 mg of **7**. Mp 104-105°C (from $\text{Me}_2\text{CO}-i\text{Pr}_2\text{O}$); IR (CHCl_3): 2994, 1770, 1716, 1682, 1634, 1455, 1402, 1367, 1337, 1250, 1118, 1023, 993 cm^{-1} ; ^1H NMR: see table I; EIMS m/e (rel. int.): 260 (M^+ ,3), 242(5), 163(12), 149(18), 145(19), 124(41), 91(40), 77(34), 67(98), 53(52), 41(42), 39(100).

Isodehydroalloschkuhriolide (8). The same procedure described for the preparation of **7** was performed at room temperature to give **8** in 85% yield. **8** was also obtained when a solution of **7** (25 mg) in CHCl_3 (2 ml) was stirred with silica gel (ca. 100 mg) at room temperature for 3 h. After filtration and concentration at reduced pressure, 22 mg of **8** were obtained as a colorless oil. IR (CHCl_3): 3018, 2925, 2860, 1755, 1680, 1630, 1449, 1388, 1322, 1297, 1260, 1250, 1212, 1190, 1164, 1130, 985 cm^{-1} ; ^1H and ^{13}C NMR: see tables I and II; EIMS m/e (rel. int.): 260 (M^+ ,7), 242(6), 163(13), 149(16), 135(20), 124(43), 122(15), 119(14), 107(16), 105(15), 93(26), 91(38), 77(35), 67(97), 53(52), 41(42), 39(100).

(4R,5R)-4,5-Epoxy-schkuhriolide (9). To a solution of **1a** (130 mg) in Me_2CO (30 ml) at 0°C was added Jones reagent, until the red colour remained. The mixture was stirred for 10 min at 0°C and then MeOH was added. The slurry was poured into saturated NaHCO_3 , and extracted with CHCl_3 . Usual procedure allowed to obtain 76 mg of **9** as

a colorless oil. Physical and spectral data have been reported previously.³ ¹³C NMR data (not previously reported): see Table II.

(4*R*,5*R*)-4,5-Epoxyshkhuroidine (**11**). **11** was obtained from **10a** by the same procedure described above for the preparation of **9** in 82% yield, and characterized by direct comparison.³ ¹³C NMR data (not previously reported): see table II.

(4*R*,5*R*,11*R*)-4,5-Epoxy-11,13-dihydroshkhurolide (**14a**). (4*R*,5*R*)-4,5-epoxyshkhurolide **11** (65 mg) was dissolved in a solution of CeCl₃·7H₂O (Aldrich, 100 mg) and NaBH₄ (15 mg) in MeOH (5 ml) at room temperature. After 10 min, the mixture was diluted with water, neutralized with CH₃COOH and extracted with CHCl₃. Concentration at reduced pressure and chromatography on silica gel gave 45 mg of **14a**. Mp. 118-119°C (from Me₂CO-*i*Pr₂O). IR (CHCl₃): 3632, 3569, 1758, 1655, 1638, 1272, 1166, 1048, 1026, 1001, 825 cm⁻¹; ¹H and ¹³C NMR: see tables I and II; EIMS *m/e* (rel. int.): 264 (M⁺, <1), 246(5), 234(6), 228(8), 212(10), 168(15), 142(32), 43(100), 41(12).

Diacetyl-(4*R*,5*R*,11*R*)-4,5-Epoxy-11,13-dihydroshkhurolide (**14b**). Acetylation of **14a** (41 mg) as usual provided **14b** (38 mg). Mp 140-141°C (from Me₂CO-*i*Pr₂O); IR(CHCl₃): 3037, 2972, 2946, 1774, 1735, 1463, 1372, 1271, 1239, 1161, 1115, 1020, 953 cm⁻¹; ¹H and ¹³C NMR: see tables I and II; EIMS *m/e* (rel. int.): 364, (M⁺, <1), 304(1), 244(5), 251(2), 203(16), 202(4), 201(7), 187(8), 186(5), 157(7), 84(16), 43(100), 41(12).

6*a*-Acetoxy-(11*S*)-11,13-dihydro-*cis*-1(10)-*trans*-4-germacadien-*cis*-8,12-olide (**15**). A sample of **10b** (60 mg) dissolved in EtOAc (10 ml) was reduced over 10% Pd-C (6 mg) presaturated with hydrogen at ambient temperature. The residue, after removal of catalyst and solvent, was chromatographed on silica-gel, to give 38 mg of **15** as colorless crystals. Mp 144-145°C (from EtOAc-*i*Pr₂O). IR (CHCl₃): 2860, 1770, 1450, 1380, 1370, 1343, 1280, 1148, 1112, 1002, 957 cm⁻¹, ¹H and ¹³C NMR: see tables I and II; EIMS *m/e* (rel. int.): 292 (M⁺, <1), 233(6), 232(20), 217(8), 187(6), 177(9), 176(32), 171(8), 161(20), 160(20), 159(100), 134(32), 119(34), 93(35), 91(29), 43(73).

Thermal treatment of 5, 12, 13 and 15. 15 mg of each compound in sealed semicapillary tubes were heated for 10 and 30 min at 170, 200 and 230°C (24 experiments). At 170 and 200°C for 10 and 30 min, the samples remained unchanged. At 230°C (for 10 and 30 min) the compounds partially decomposed to an insoluble tar.

X-ray crystallography. A crystal of acetyl-11,13-dihydroshkhurolide was mounted on a R3M Nicolet automated diffractometer. Crystal size: 0.28 × 0.4 × 0.4 mm. Unit cell dimensions *a* = 5.717 (1), *b* = 8.049 (2), *c* = 17.708 (5) Å, β = 94.14 (2)° (monoclinic P₂) were determined by least-squares refinement of the best angular setting for 25 independent reflections in the range 5.56 < 2θ < 15.53° using MoKα radiation (λ = 0.71073 Å). Data (1286 reflections) were collected at room temperature using ω scan mode to a maximum 2θ value of 45°. The intensities of two standard reflections were measured every 50 reflections and as the intensities of these reflections showed less than 3% variation, corrections for decay were deemed unnecessary. Intensities were corrected for Lorentz and polarization effects, but no absorption correction was made. A total of 1040 unique reflections were considered observed (F > 3σ (F)). The structure was solved by direct methods included in SHELXTL package¹⁵ to located all the non-hydrogen atoms having the structure. Refinement of scale factor, positional and anisotropic thermal parameters

for all non-hydrogen atoms was carried out to convergence, minimizing the function $w(F_o - F_c)^2$. All H-atoms were located at idealized geometric positions with constant $U=0.06 \text{ \AA}^2$. The final cycle of refinement led to a final agreement factor $R=0.042$ ($R_w=0.047$) with maximum residual density in the final difference map of $0.17e \text{ \AA}^{-3}$. Atomic scattering factors were taken from Vol. IV of International Tables for X-ray Crystallography.

RESUMEN

Con el objeto de contribuir al conocimiento de la reactividad del 1(10)-*cis*-4-*trans*-germacradienólido se obtuvieron algunos derivados de la melampólida natural eschkuhriólida (**1a**), aislada de *Schkuhria schkuhrioides*. La modificación del aldehído en C-14 o del hidróxilo en C-6 de este compuesto inhibe la reacción sigmatrópica [3,3], ya que algunos derivados obtenidos no se transforman en las condiciones en las que **1a** se convierte a elemanoeschkuhriólida (**4**), por lo que se concluye que esta transformación podría incluir varios intermediarios (conformacionales y/o configuracionales). Se observa también que **1a** tiende a relactonizarse a C-6. Por otro lado, la epoxidación preferencial del doble enlace C(4)-C(5) en competencia con la oxidación del alcohol en C-6 con CrO_3 de la eschkuhriólida (**1a**), así como la hidrogenólisis del éster isobutírico en C-14 de la acetileschkuhrioidina (**1b**), pueden racionalizarse por el congestionamiento estérico relativo en C-6.

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Received in January 1992. Accepted to be issued in July 1993.