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TRANSANNULAR CYCLIZATION OF HELIANGOLIDES

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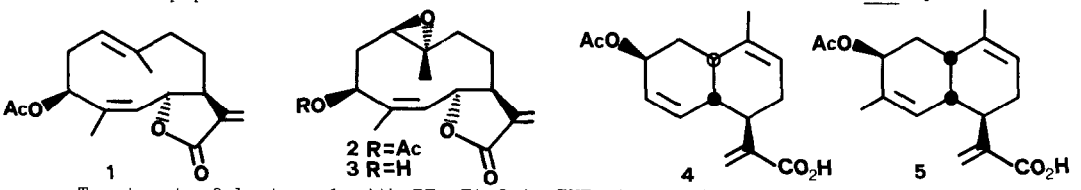
Abstract: 4,5-cis-3β-Acetoxygermacranolide by treatment with $BF_3.Et_2O$, gave a mixture of 2-acetoxycadin-3,8,11(13)-trien-12-oic and 2-acetoxymuurol-3,8,11(13)-trien-12-oic acids, while 4,5-cis-1,10-epoxy-3β-hydroxygermacranolide gave the eudesmanolide tuberiferin.

1(10),4-Germacranolides are generally considered as the biogenetic precursors of eudesmanolides, elemanoides, guaianolides and cadinanolides[1]. The most widely studied transannular cyclization reactions of germacranolides by acids, are those of (E,E)-1(10),4-germacranolides and their epoxy derivatives. The first ones and 1,10-epoxygermacranolides give allways eudesmanolides[2-10], while 1,4-epoxygermacranolides give cis-guaianolides[11-13]. For trans-guaianolides, the melampolides (Z,Z)-1(10),4-germacranolides or their 1,10-epoxy derivatives were proposed as the biogenetic precursors[14,15] and Kazunori et al.[16], have recently communicated the transannular cyclization of heliangolides (4,5-cis-germacranolides) to cadinanolides.

As in Leucanthemopsis pulverulenta (Lag.) Heywood, several heliangolides (hispanolide and related compounds)[17,18], coexist with several cadinane and muurolane type sesquiterpene acids[19], we thought that heliangolides could be the biogenetic precursors of the sesquiterpene acids.

In this paper we communicate the results of treatment of lactones 1-3 by acids:



1 4 5

Treatment of lactone 1 with $BF_3.Et_2O$ in THF at room temperature, for one h., gave a mixture of acids 4 and 5 (25% and 18% respectively).

The methyl esters of 4 and 5 were isolated by CC as oils of $[\alpha]_D$=-11.7º and $[\alpha]_D$= -70.5º respectively, and their properties were identical in all respects with those comunicated for methyl 2-acetylledesmate (methyl 2-acetoxycadin-3,8,11)-trien-12-oate) and methyl 2-acetyl-10-epiledesmate (methyl 2-acetoxymuurol-3,8,11(13)-trien-12-oate) isolated from Leucanthemopsis pulverulenta[19].

Cyclization of lactone 1 to both 4 and 5, can be explained by a concerted process with the $\Delta^{1(10)}$ double bond assistance, to give the carbocations a and b as precursors of the final cyclization products.

The cis and trans-junction for the A/B rings, can be explained through the two stable conformations that can be adopted by heliangolides as 1[16].

The ^{13}C NMR spectra of the methyl esters of 4 and 5 (Table 1) agreed with the

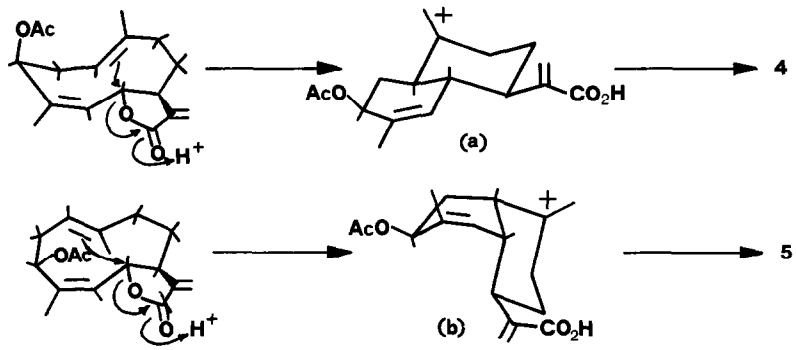


Table 1. ^{13}C NMR Data for Sesquiterpene Acids 4 and 5

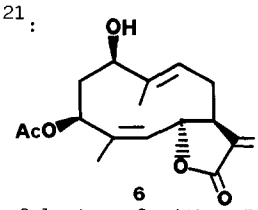
4				5			
Nº C	δ	Nº C	δ	Nº C	δ	Nº C	δ
C-1	35.80*	C-10	46.22	C-1	39.16*	C-10	50.42
C-2	73.54	C-11	142.26	C-2	82.19	C-11	140.63
C-3	133.70	C-12	167.78	C-3	138.67	C-12	168.42
C-4	128.66	C-13	125.92	C-4	127.01	C-13	128.16
C-5	44.40**	C-14	21.24	C-5	43.33	C-14	21.48
C-6	43.32**	C-15	18.96	C-6	38.70	C-15	19.52
C-7	36.02*	OMe	51.96	C-7	37.48*	OMe	52.56
C-8	125.25	MeCO	21.14	C-8	124.75	MeCO	21.14
C-9	149.95	MeCO	170.65	C-9	152.07	MeCO	172.87

The signals were assigned by selective decoupling techniques (DEPT) proposed structures.

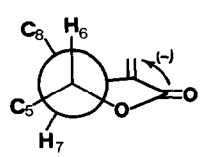
Treatment of lactone 2 with $BF_3.Et_2O$, did not give any cyclization product, but the degradation of the epoxide ring to the hoped allylic alcohol 6, of $[\alpha]_D$=-4.6º, whose spectral data agreed with those reported for 1β-hydroxy-3β-acetoxy-9(10)-en-4,5-cis-germacranolide[18].

The stereochemistry for the double bond at C-9 was assigned as (E), by the ^{13}C NMR signal due to the methyl group at C-10 (16.72 ppm)[20] (Table 2).

The CD curve of 6 recorder in MeOH ahowed dichroic absorptions at 219 nm ($\Delta\varepsilon$=-3.93) and 263 nm ($\Delta\varepsilon$=-0.3). The first CE was just signed as in heliangolides, but the CE at 263 nm, asignable to the lactone ring chirality, was of different sign from that in heliangolides, suggesting a change in the lactone ring conformation, with dihedral angles C-5 - C-8 <120º and H-6 - H-7 >120º[21]:



6



Treatment of lactone 3 with p-TsOH in benzene and N_2 atmosphere, gave 7 as the main reaction product. Compound 7 was a solid of mp 174-75º and $[\alpha]_D$=+2.3º. Its IR spectrum showed the presence of an α-methylene-γ-lactone ring (1770, 1640, 900 cm^{-1}) and a conjugated C=O group (1670, 1600, 810 cm^{-1}). The ^1H NMR spectrum showed signals due to two methyl groups at 1.18(3H,s) and 1.41(3H,d,J=6.8 Hz), four olefinic protons at 6.13 and 5.45 (AB system,J=3.1 Hz,

CH_2=COO) and 6.72 and 5.91 (AB system, J=9.9 Hz, CH=CH-CO); at 3.99 showed a double doublet (J=10.66 and 10.50 Hz) characteristic of the H-6 of an eudesmanolide.

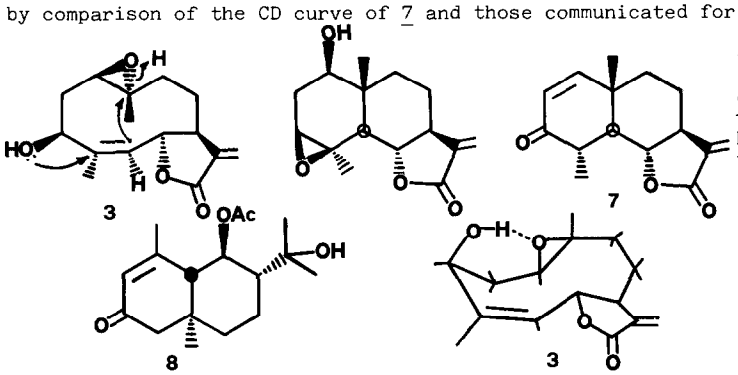
The ^{13}C NMR spectrum of 7 (Table 2), confirmed these functionalities, so as the presence of six methyne carbon atoms. All these data agreed with the proposed structure for tuberiferin[22].

The stereochemistry at C-4 was assigned as (S) by the coupling constant H-4 - H-5 (J=10.66 Hz), showing the equatorial disposition of the methyl group at C-4.

Table 2. ^{13}C NMR Data for Lactones 6 and 7

6				7			
Nº C		Nº C		Nº C		Nº C	
C-1	68.66	C-10	141.31	C-1	150.37	C-10	51.88
C-2	34.27	C-11	138.53	C-2	121.74	C-11	143.58
C-3	78.15	C-12	169.24	C-3	204.05	C-12	170.96
C-4	140.74	C-13	119.35	C-4	34.37	C-13	125.10
C-5	124.51	C-14	23.57	C-5	37.82	C-14	20.85
C-6	74.46	C-15	17.39	C-6	70.46	C-15	21.47
C-7	47.59	MeCO	170.21	C-7	38.18	-	-
C-8	23.12	MeCO	21.05	C-8	30.74	-	-
C-9	122.16	-	-	C-9	32.62	-	-

The trans-junction for the A/B rings, was deduced from the CD curve with dichroic absorptions at 340 nm ($\Delta\varepsilon$=-1.72), 239 nm ($\Delta\varepsilon$=+3.43) and 208 nm ($\Delta\varepsilon$=+6.23). The application of Snatzke and helicity rules [23,24] to the observed signs for the CE, allowed us to assign the 5(S) and 10(S) configurations. These assignements were in quite agreement with those deduced by comparison of the CD curve of 7 and those communicated for ketone 8 and related compounds[25]:



The interpretation of all these data were reinforced by the conformational analysis of lactone 3 which showed that 3, existed only as a unique $_1D^{14}$ $_{15}D_5$ rotational conformer, as was deduced from the study of the ^1H NMR spectrum, the H-H correlation using the H-COSY-4 program and the partial (C-1,4) simulated spectrum of a molecule with the same spatial disposition than 3, using the PANIC program.

^1H NMR coupling constants and dihedral angles for lactone 3

Nº H	J(Hz)	Dihedral angle
1,2	4.40	45º
1,2	10.25	165º
3,2	6.40	66º
3,2	2.44	54º
5,6	10.74	176º
6,7	2.44	105º
7,8	2.44	80º
7,8	10.99	170º
8,9	3.42	54º
8,9	5.37	66º
8.9	12.85	160º
8,9	2.44	45º

The H-H correlations, the coupling constants and the application of the Karplus rule[26,27], allowed us to assign the ^1H NMR signals to each proton in the melecule and to

predict all the dihedral angles for the unique posible rotational conformer of 3^{28}.

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