

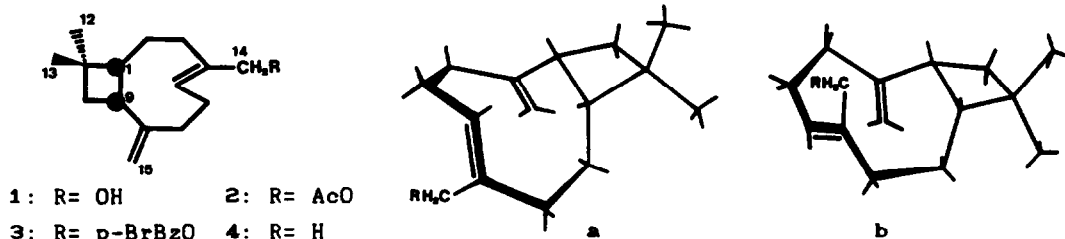
## EVIDENCES ABOUT THE STEREOCHEMISTRY OF 14-HYDROXY-9-EPI- $\beta$ -CARYOPHYLLENE.

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**Abstract:** From natural 14-hydroxy-9-epi- $\beta$ -caryophyllene (1), the acyl derivatives 2 and 3 were prepared. These compounds appeared as a mixture of two conformational isomers (7/3). When 1 was oxidized with MCPBA, epoxides 7 and 9 were obtained. The rigid conformation of 7 and 9 allowed us to establish their skeleton and *cis* interannular junction. Thus, the proposed structure for 1 was confirmed.

In our laboratory, a new natural sesquiterpene alcohol, 14-hydroxy-9-epi- $\beta$ -caryophyllene (1), which was a mixture of two conformational isomers (1a, 1b) at room temperature, has been recently isolated [1]. Treatment of 1 with Ac<sub>2</sub>O and Py yielded the acyl derivative 2 [2] (table 1), while reaction between 1 and N-p-bromobenzoylimidazole [3] generated the compound 3 [4] (table 1). Both 2 and 3 were an oily mixture of the two



conformers 2a and 2b, 3a and 3b in relative proportions 7:3. On the other hand, we have tried to reduce 1, in order to correlate it with the hydrocarbon 4 described by Bohlmann [5]. However the attempts to reduce the allylic alcohol, by means of tosylation followed by treatment with LiAlH<sub>4</sub> [6] were unsuccessful. The tosyl derivative could not be obtained, because the alcohol group is sterically hindered. When 1 was selectively epoxidized with MCPBA, the epoxides 7 and 9 (7/3) were obtained. These compounds also were prepared by spontaneous oxidation of 1, stored at -20°C under air. The CIMS of 7 [7] showed a peak [MH]<sup>+</sup> at m/z = 237, indicating a molecular weight 16 units higher than 1. This fact, together with the <sup>1</sup>H NMR [7] and <sup>13</sup>C NMR (table 1) spectral data, may be explained by a C<sub>15</sub>H<sub>24</sub>O<sub>2</sub> molecular formula. In the <sup>1</sup>H NMR spectrum of 7 [7], the typical signals of a trisubstituted double bond have been replaced by a double doublet at  $\delta$  = 3.04 ppm (J = 4.1 Hz, J = 11.0 Hz), corresponding to an oxiranic proton. In its <sup>13</sup>C NMR spectrum (table 1) two signals appeared at

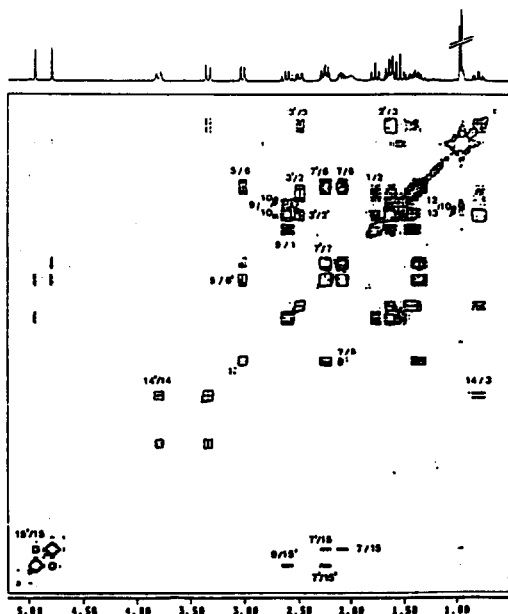
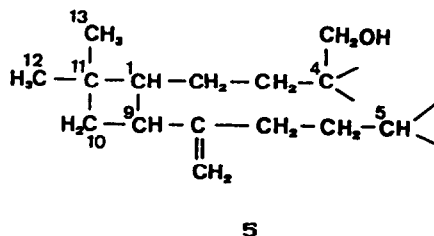


Fig. 1. H/H homonuclear correlation spectrum of 7:

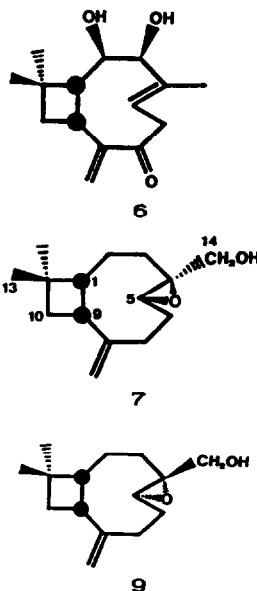
- Upper-left: COSY
- Bottom-right: long-range COSY



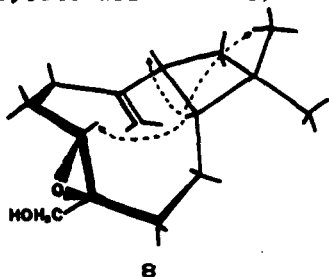
62.9 (C) and 65.1 (CH) ppm, corresponding to the two carbons of an oxirane. Furthermore showed two signals of olefinic carbons. In order to confirm the caryophyllane skeleton of 7, we carried out some 2D NMR experiments [8]: direct heteronuclear correlation H-C, homonuclear correlation H/H (fig.1) and long range heteronuclear correlation H/C [7]. From these spectra, we could deduce some connections that led us to the identification of the carbon skeleton 5.

Table 1.  $^{13}\text{C}$  NMR data ( $\delta$  ppm) for compounds 2, 3, 7 and 9.

C n°	2a	2b	3a	3b	7	9
1	51.2	55.8	51.2	56.0	49.3	54.9
2	28.8	29.6	28.9	29.8	26.5	27.5
3	34.9	31.3	35.0	31.2	33.5	31.3
4	133.3	133.3	133.2	133.2	62.9	63.1
5	131.2	131.1	131.6	131.6	65.1	61.9
6	34.0	30.3	34.0	30.3	30.2	29.1
7	29.3	39.9	29.5	40.0	28.7	36.8
8	152.9	154.7	152.9	154.8	151.5	155.1
9	49.3	49.1	49.4	49.2	49.1	47.3
10	40.3	42.6	40.3	42.6	39.9	42.4
11	33.8	32.8	33.9	32.8	34.5	33.2
12	22.3	21.9	22.3	21.9	21.5	21.7
13	30.0	29.9	30.1	29.9	30.0	29.8
14	61.4	65.4	62.2	65.8	62.1	65.2
15	113.5	111.5	113.7	111.6	113.4	111.9
CH <sub>3</sub> CO <sub>2</sub>	21.1	21.1				
CO <sub>2</sub>	171.2	171.2	166.0	166.0		
1			128.0	128.0		
2			131.2	131.2		
3			131.7	131.7		
4			129.4	129.4		



This structure includes all the molecular formula atoms, except one oxygen. Obviously, C-4 and C-5 are contained in an oxirane ring. The multiplicity and J values of the hydrogens 1, 9, 10 $\alpha$  and 10 $\beta$  of 7 [7], indicated a *cis* interannular junction between the cyclobutane and cyclononane rings of the caryophyllane skeleton. These values agreed with the data reported by Doi et al. [9] about nematoline (6). Furthermore, irradiation on the H-1 proton, caused NOE enhancements in the H-5, H-9 and H-13 signals. Whereas, irradiation on H-5 generated NOE enhancement in the H-1 signal, but not in the H-14 signal. On the other hand, the experiments with Eu(dpm)<sub>3</sub> [7] were in agreement with the *cis* junction too. Consequently, we assigned for 7 the structure of (1R,4S,5R,9R)-4,5-epoxy-14-hydroxycaryophyll-8(15)-ene (or its enantiomer), 8 being the most probable conformation. Compound 7 resulted from oxidation of the endocyclic double bond, at the  $\beta$ -side of 1.



Arrows indicate NOEs observed.

Compound 9 [10] (table 1), isomer of 7, showed in its <sup>1</sup>H NMR spectrum a double doublet ( $\delta$  = 3.13 ppm; J = 2.4 Hz, J = 11.6 Hz) corresponding to a hydrogen of epoxide. Its spectroscopic properties [10], direct heteronuclear correlation H/C and homonuclear correlation H/H, permitted us to establish the (1R,4R,5S,9R)-4,5-epoxy-14-hydroxycaryophyll-8(15)-ene structure (9) for it. Compound 9 resulted from the epoxidation of 1, at the  $\alpha$ -side of the endocyclic double bond.

The structures and stereochemistries of the compounds 7 and 9, confirmed that previously proposed for the natural alcohol 1 [1]. Additionally, the spectroscopic correlations of 7 and 9 with 1-3, allowed us to identify what are the predominant conformers: 1a-3a.

#### References and notes.

- 1.- Barrero, A.F., Sánchez, J.F., Ferrol, N. and San Feliciano, A., *Tetrahedron Lett.* 30, 247 (1989).
- 2.- Compound 2:  $[\alpha]_D^{25} = +14.02^\circ$  (c 1.02, CHCl<sub>3</sub>). EIMS (probe), 70 eV, m/z (%): 206 (1) [M-Me<sub>2</sub>C=CH<sub>2</sub>]<sup>+</sup>, 202 (5) [M-AcOH]<sup>+</sup>, 146 (13) [M-AcOH-Me<sub>2</sub>C=CH<sub>2</sub>]<sup>+</sup>, 91 (45), 78 (79), 63 (100). IR (film)  $\nu_{\max}$ : 1741 (s) (C=O), 1630 (w) (C=C), 1235 (s) (C-O), 890 (w) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.93 (3H, s, H-13 2b), 0.95 (6H, s, H-13 2a, H-12 2b), 0.97 (3H, s, H-12 2a), 2.01 (3H, s, CH<sub>3</sub>CO<sub>2</sub> 2b), 2.03 (3H, s, CH<sub>3</sub>CO<sub>2</sub> 2a), 4.29 (1H, d, J=12Hz, H-14 2b), 4.41 (1H, d, J=12Hz, H-14 2a), 4.65 (2H, d, J=12Hz, H-14' 2a, H-14' 2b), 4.80 (1H, s, H-15 2a),

- 4.85 (1H, s, H-15 2b), 4.94 (1H, s, H-15' 2a), 4.97 (1H, s, H-15' 2b), 5.52 (1H, bd, J=12Hz, H-5 2b), 5.57 (1H, dd, J=5.5Hz, J=12.5Hz, H-5 2a).
- 3.- Staab, H.A. and Mannschreck, A., *Chem. Ber.*, 1264 (1962).
- 4.- Compound 3:  $[\alpha]_D^{20} = -3.98^\circ$  (c 0.98,  $\text{CHCl}_3$ ). CIMS (probe)  $\text{CH}_4$ , m/z (%): 405 (3), 403 (6)  $[\text{MH}]^+$ ; 203 (100)  $[\text{MH}-\text{BrBzOH}]^+$ . IR (film)  $\nu_{\text{max}}$ : 1841 (s) (C=O), 1225 (s) (C-O), 1071 (s) (O-C), 996 (m), 831 (w), 743 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.96 (3H, s, H-13 3b), 0.97 (6H, s, H-13 3a, H-12 3b), 0.99 (3H, s, H-12 3a), 4.59 (1H, d, J=12Hz, H-14 3b), 4.68 (1H, d, J=12.2Hz, H-14 3a), 4.83 (1H, s, H-15 3a), 4.86 (1H, s, H-15 3b), 4.92 (2H, d, J=12.4Hz, H-14' 3a, H-14' 3b), 4.96 (2H, s, H-15' 3a, H-15' 3b), 5.56 (1H, bd, J=10.5Hz, H-5 3b), 5.63 (1H, dd, J=5.6Hz, J=10.9Hz, H-5 3a), 7.55 (4H, d, J=8.5Hz, 2H meta 3a; 2H meta 3b), 7.89 (4H, d, J=8.5Hz, 2H orto 3a; 2H orto 3b).
- 5.- Bohlmann, F. and Zdero, C., *Phytochemistry* 17, 1135 (1978).
- 6.- Avcibasi, H., Anil, H. and Toprak, M., *Phytochemistry* 26, 2852 (1987).
- 7.- Compound 7:  $[\alpha]_D^{20} = -14.55^\circ$  (c 1.01  $\text{CHCl}_3$ ). CIMS (probe)  $\text{CH}_4$ , m/z (%): 237 (17)  $[\text{MH}]^+$ , 219 (81)  $[\text{MH}-\text{H}_2\text{O}]^+$ , 201 (100)  $[\text{MH}-2\text{H}_2\text{O}]^+$ , 145 (19)  $[\text{MH}-2\text{H}_2\text{O}-\text{Me}_2\text{C}=\text{CH}_2]^+$ , 79 (82)  $[\text{C}_6\text{H}_7]^+$ . IR (film)  $\nu_{\text{max}}$ : 3329 (s) (O-H)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.80 (1H, ddt,  $J_{\text{B},14}=1.1\text{Hz}$ ,  $J_{\text{A},2}=5.5\text{Hz}$ ,  $J_{\text{B},9}=13.0\text{Hz}$ ,  $\Delta\delta=0.25$ , H-3), 0.96 (3H, s, H-13), 0.98 (3H, s, H-12), 1.42 (2H, m, H-2, H-6), 1.55 (1H, t,  $J_{10\beta,10\alpha}=J_{10\beta,9}=10.6\text{Hz}$ ,  $\Delta\delta=0.07$ , H-10 $\beta$ ), 1.64 (1H, m, H-2'), 1.65 (1H, dd,  $J_{10\alpha,9}=8.3\text{Hz}$ ,  $J_{10\alpha,10\beta}=10.6\text{Hz}$ ,  $\Delta\delta=0.07$ , H-10 $\alpha$ ), 1.80 (1H, t, J=10Hz,  $\Delta\delta=0.12$ , H-1), 2.10 (1H, m,  $\Delta\delta=0.10$ , H-7), 2.26 (2H, m, H-6', H-7'), 2.50 (1H, ddd, J=3.0Hz, J=4.3Hz,  $J_{\text{B},9}=13.0\text{Hz}$ ,  $\Delta\delta=0.23$ , H-3'), 2.63 (1H, ddd,  $J_{\text{P},10\alpha}=8.3\text{Hz}$ ,  $J_{\text{P},1}=10\text{Hz}$ ,  $J_{\text{P},10\beta}=10.6\text{Hz}$ ,  $\Delta\delta=0.09$ , H-9), 3.04 (1H, dd,  $J=4.1\text{Hz}$ , J=11.0Hz,  $\Delta\delta=0.28$ , H-5), 3.35 (1H, dd,  $J_{14,9}=1.1\text{Hz}$ ,  $J_{14,14'}=12.3\text{Hz}$ ,  $\Delta\delta=0.46$ , H-14), 3.80 (1H, bd,  $J_{14',14}=12.3\text{Hz}$ ,  $\Delta\delta=0.38$ , H-14'), 4.79 (1H, d,  $J_{15,15'}=1.5\text{Hz}$ ,  $\Delta\delta=0.07$ , H-15), 4.94 (1H, d,  $J_{15,15'}=1.5\text{Hz}$ , H-15').  $\Delta\delta$  were measured with Eu(dpm)<sub>3</sub> (12 mg), 7 (30 mg) and  $\text{CDCl}_3$  (0.8 ml). Long range heteronuclear correlation data: C-1 (H-12, H-13); C-4 (H-4); C-7 (H-15'); C-9 (H-15); C-10 (H-12, H-13); C-11 (H-12, H-13); C-12 (H-13); C-13 (H-12).
- 8.- 2D NMR experiments ( $^1\text{H}$  300 MHz;  $^{13}\text{C}$  75.47 MHz) were made according to the Bruker library programs (1985). Direct heteronuclear correlation, XHCORRD.AUR program, polarization transference optimized for  $^1J_{\text{C,H}}=125\text{ Hz}$ . Homonuclear correlation, COSY.AUR program. Long range heteronuclear correlation, COLOC.AUR program, polarization transference optimized for  $^nJ_{\text{C,H}}=10\text{ Hz}$ .
- 9.- Doi, K., Shibata, T., Nara, M., Tsuboyama, S., Sakurai, T. and Tsuboyama, K., *Chem. Lett.*, 653 (1986).
- 10.- Compound 9:  $[\alpha]_D^{20} = +26.51^\circ$  (c 0.63,  $\text{CHCl}_3$ ). CIMS (probe)  $\text{CH}_4$ , m/z (%): 237 (15)  $[\text{MH}]^+$ , 219 (75)  $[\text{MH}-\text{H}_2\text{O}]^+$ , 145 (10)  $[\text{MH}-2\text{H}_2\text{O}-\text{Me}_2\text{C}=\text{CH}_2]^+$ . IR (film)  $\nu_{\text{max}}$ : 3330 (s) (O-H)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.96 (3H, s, H-12), 1.00 (3H, s, H-13), 1.42 (1H, dd, J=5.2Hz, J=12.5Hz, H-2), 1.49 (1H, m, H-6), 1.60 (1H, m, H-2'), 1.61 (1H, t, J=10.7Hz, H-10 $\beta$ ), 1.66 (1H, ddd, J=2.6Hz, J=5.5Hz, J=15.1Hz, H-7), 1.75 (1H, t, J=9.6Hz, H-1), 1.85 (1H, dd, J=8.2Hz, J=10.7Hz, H-10 $\alpha$ ), 2.04 (1H, ddd, J=1.1Hz, J=8.0Hz, J=12.5Hz, H-7'), 2.12 (1H, m, H-3), 2.14 (1H, m, H-6'), 2.34 (1H, dt,  $J_{\text{P},10\alpha}=9.1\text{Hz}$ ,  $J_{\text{P},10\beta}=J_{\text{P},1}=9.6\text{Hz}$ , H-9), 2.54 (1H, ddd, J=2.1Hz, J=6.3Hz, J=12.8Hz, H-3), 3.13 (1H, dd, J=2.4Hz, J=11.6Hz, H-5), 3.51 (1H, bd,  $J_{14,14'}=11.3\text{Hz}$ , H-14), 3.60 (1H, bd,  $J_{14',14}=11.6\text{Hz}$ , H-14'), 5.02 (1H, s, H-15), 5.13 (1H, s, H-15').