Tetrahedron Vol. 44, No. 14, pp. 4575 to 4584, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
© 1988 Pergamon Press plc

THE BIOMIMETIC SYNTHESIS OF TRANS-(1β-H,5α-H)-GUAIANOLIDES

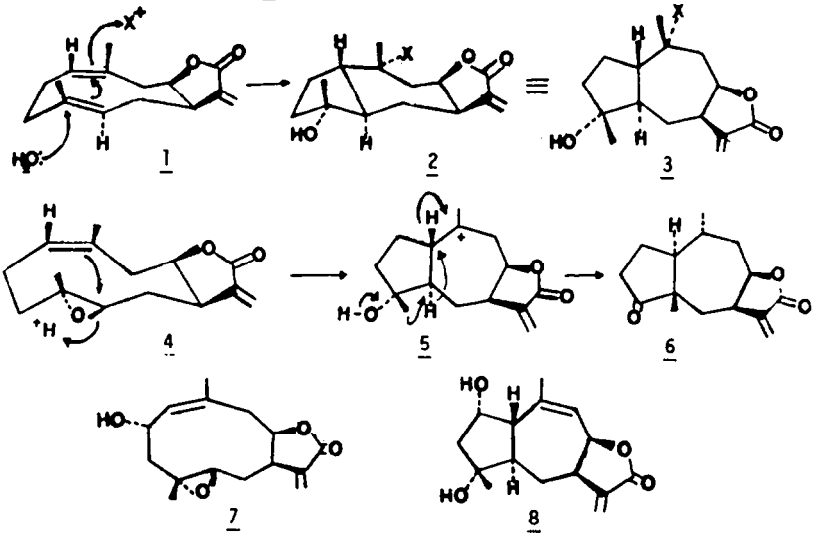
Antonio G. González*,Antonio Galindo,M. Mar Afonso,Horacio Mansilla and J.A. Palenzuela
Centro de Productos Naturales Orgánicos "Antonio González"
La Laguna,Tenerife,Spain
M.A. Gómez Rodriguez and M. Martinez-Ripoll
UEI de Cristalografía,Instituto Rocasolano,CSIC,Serrano 119
Madrid,Spain

(*Received in UK* 29 *April* 1988)

ABSTRACT: 1-epigallicin 11 underwent biomimetic cyclization to trans-(1β-H,5α-H)-guaianolide 22,the stereoespecificity of this cyclization being credited to the fact that it took place via the reacting TC conformation 27.The epimeric nor-guaianolides 15 and 17 were prepared and their rearrangements studied.The biogenetic implications of these processes are discussed.

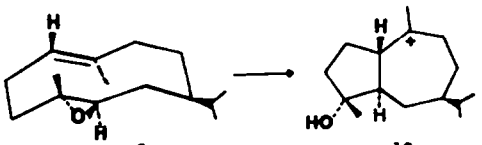
The trans-(1β-H,5α-H)-guaianolides 3 are a fairly rare group of sesquiterpene lactones[1],

SCHEME I



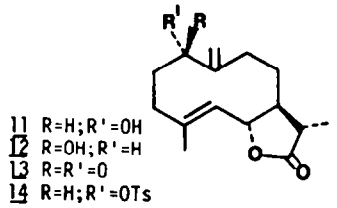
the biogenesis of which has been attributed to an anti-Markownikoff type[2] trans-antiparallel cyclization via the melampolides 1.Herz[3] suggested another possible biogenesis for the trans-guaianolides:4α,5β-epoxide 4 acid-induced cyclization could give rise to the cation 5, with typical trans-guaianolide stereochemistry and this cation could lead to the helenanolides 6 via the chemical shifts shown in Scheme I.This pathway has recently been favoured since the structural reclassification of baileyin 7 as a melampolide skeleton rather than a germacrolide[4] together with an X-ray study demonstrating pleniradin 8 to be a trans-guaianolide[5] strongly suggest that these two lactones isolated from Baileya pleniradiata are biogenetically related[5].Sharma et al[6] were able to convert a guaianolide into a pseudoguaianolide by imitating part of the proposed biogenetic pathway.

In a review of the melampolides,Fischer et al[7] suggested that the distance from centre to centre between the double bonds of 1 is considerably greater than in the four possible conformations of the trans,trans-germacradienes and proposed that the trans-guaiane cation 10 must be formed via a 4α,5β-epoxy-trans-germacrene 9 through a quasi-parallel conformation.

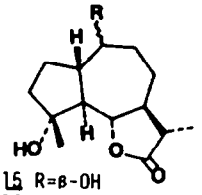


9 10

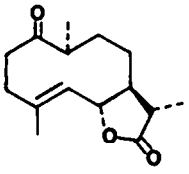
To evaluate the role played by the cis,trans-germacradienes[1] in the biogenesis of trans-guaianolides and the possible implication of 1 in the biogenesis of the helenanolides, we carried out the cyclization of 1-epigallicin 11[8] as well as the study of the rearrangements of the nor-trans-guaianolides 15 and 17.



11 R=H;R'=OH
12 R=OH;R'=H
13 R=R'=O
14 R=H;R'=OTs



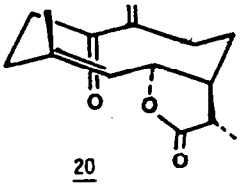
15 R=β-OH
16 R=β-OTs
17 R=α-OH
18 R=α-OTs



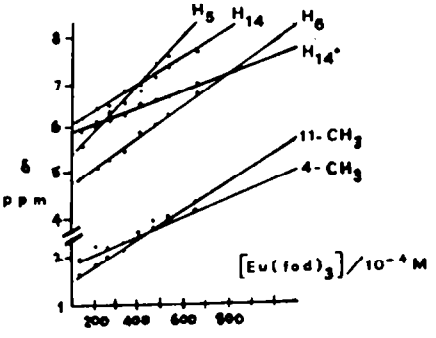
19

RESULTS AND DISCUSSION

The oxidation of gallicin 12 with activated MnO_2 yielded ketone 13 (77%) which,when reduced with $NaBH_4$,gave 1-epigallicin 11[9] (57%),the dihydroketone 19 (21%) and gallicin 12 (4%).The stereoselectivity of the reaction could be due to the fact that the reduction took place via the preferred reacting conformation 20.^{1}H-NMR at various temperatures and LIS studies provided the conformational analysis of 13 in solution.The ^{1}H-NMR spectrum was taken at a standard temperature (35°C) and none of the more important signalds changed significantly between -60°C and +60°C.The addition of $Eu(fod)_3$ caused the chemical shifts shown in Fig. 1.The slight chemical shifts of H-14 in 13 are not compatible with a syn-relationship between the ketone group and the double bond 10(14),which suggests an s-trans disposition for the α,β-unsaturated ketone.Furthermore,the chemical shift of H-5 suggests a syn-axial disposition for H-5 and the ketone group.



20



In the 2D-NOE study of 13,positive correlations between H-6/H-15 and H-14/H-15 were observed and clearly indicate the syn-disposition of these protons.Furthermore the Cotton effect curve of 13 has a value of $\Delta\varepsilon_{max}$=+9.82 at 240 nm (Band K),which points to a transoid arrangement for the chromophore[10]

These data agree with the crown conformation 20 in which the "si" face of the ketone group is highly hindered and the hydride ion attack takes place on the "re" face,generating 11.

Molecular Mechanics calculations made with the program MMPI[11] on the CC,CT,TT and TC conformations of 13 give the values 30.17;31.63;33.96 and 34.12 kcal/mol clearly showing a conformational preference for the CC conformer (91.93% population).

An X-ray diffraction study of 13 showed this compound to present two crystallographically

independent molecules,identically configured and almost identically conformed if the slight differences in the torsional angles around C(x8)-C(x9) and C(x9)-C(x10) are discounted.A half -normal probability plot[12] calculated from a comparison of all intramolecular distances <4.0 A (between non-H atoms and excluding the distances involved in the above-mentioned torsional angles)gives a linear array with a correlation coefficient of 0.99 and zero intercept at -0.06(3).The ten-membered ring has CCC conformation[13],although slightly distorted owing to the influence of the substituents (Fig. 4).A list of bond lengths,bond angles and torsional angles for compound 13 are given in Table 2.The lactone ring attached to C(x6) and C(x7) shows an envelope conformation,with C(x7) at the flap and 0.562(8) A (x=1) and 0.444(7) A (x=2) out of the plane defined by the other four atoms.

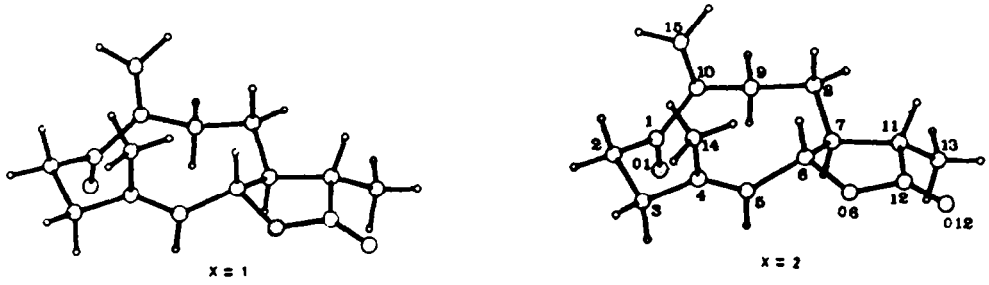


Figure 2. A view of the two crystallographically independent molecules of compound 13.The atomic numbering is arrived at by placing the indicated value of x at the beginning of the numerals shown in the figure.

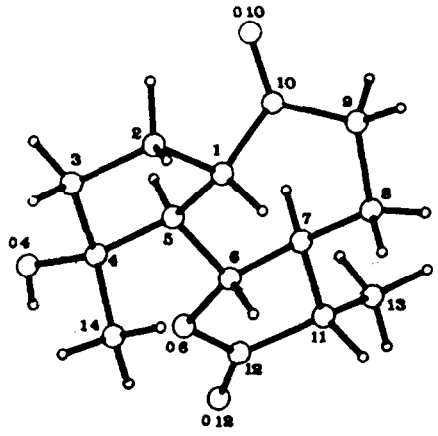


Figure 3. A view of compound 25 showing the atomic numbering.

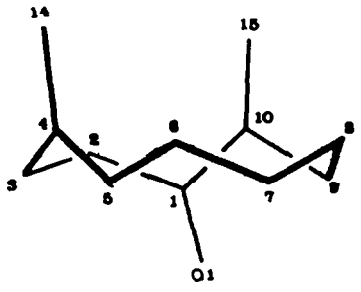
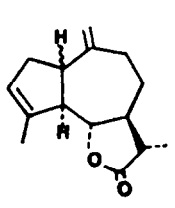


Figure 4. A projection of the ten-membered ring of compound 13 onto the plane normal to the best ring plane.

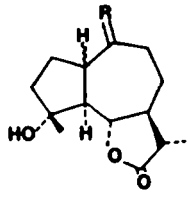
Table 1.Crystal Analysis Parameters at Room temperature

	Compound 13			Compound 25		
Formula	C15H2003			C14H2004		
Symmetry	Monoclinic, P21			Orthorhombic, P212121		
Unit Cell Determination by l.s. Fit to:	45 reflexions (θ<45°)			38 reflexions (θ<40°)		
Unit Cell Dimensions	11.639(1)	12.274(1)	10.593(1)	22.52(1)	10.386(2)	5.689
	90.0	113.040(4)	90.0	90.0	90.0	90.0
Packing: V(A3), Z	1392.6(1)	4		1330.6(7)	4	
Dc(g.cm-3), M, F(000)	1.184	248.32	536	1.260	252.31	544
Technique	Four-circle diffractometer, PW1100, bisecting geometry, CuKα, graphite oriented monochromator, /2θ scans, scan width 1.5°, detector apertures 1° x 1°, up θmax. 60°, 1 min./reflex.					
Number of Reflexions (Friedel pairs)						
Independent	2162			1129		
Observed	1462 [2σ(I) criterion]			1001 [2σ(I) criterion]		
Standard Reflexions	2 reflexions every 90 minutes, no variation					
Solution and Refinement	MULTAN 80 [21], X RAY-76 [22], l.s. on F's					
H Atoms	Difference synthesis					
w-Scheme	Empirical, giving no trends in <w ΔF> vs. <Fo> and <sin θ/λ>					
Final R and Rw	0.073	0.098		0.066	0.075	
Scattering Factors	Int. Tables for X-Ray Crystallography [23]					
Anomalous Dispersion	Int. Tables for X-Ray Crystallography [23]					

1-epigallicin 11 suffered a biomimetic-type cyclization to the trans-guaianolide 22 (18%) when treated with TsCl in pyridine.The structure and stereochemistry of 22 were established by comparison with 21;the most important differences between the ^{1}H-NMR spectra of 21 and 22 are those of the H-14 signals (two broad singlets in 22;one broad singlet in 21).The structure of 22 was definitively established by comparison with an authentic sample prepared from 23[14].



21 1α-H
22 1β-H



23 R=CH_2;1α-H
24 R=O ;1α-H
25 R=O ;1β-H
26 R=CH_2;1β-H

The ozonolysis of 23 gave ketone 24 (41%) which was converted into its epimer 25 by treatment with a 0.1 N solution of sodium hydroxide in methanol giving a 7:3 mixture of the ketones 25:24 which could be separated by fractionated crystallization.An X-ray diffraction study of 25 (Figure 3) showed the trans union of rings A and B.A list of bond lengths,bond angles and torsional angles for compound 25 is given in Table 3.The seven-membered ring presents a somewhat distorted twisted-chair conformation of the type TC_1[15] and can be described as having a pseudo-twofold axis passing through C(9) and the midpoint of the

Table 2. Selected bond lengths (Å), bond angles (°) and torsion angles (°) for compound 13

	x=1	x=2		x=1	x=2
C(x1)-C(x2)	1.52(1)	1.54(1)	C(x7)- C(x8)	1.53(1)	1.50(1)
C(x1)-C(x10)	1.49(1)	1.51(1)	C(x7)- C(x11)	1.52(1)	1.57(1)
C(x1)-O(x1)	1.20(1)	1.23(1)	C(x8)- C(x9)	1.55(1)	1.58(1)
C(x2)-C(x3)	1.56(1)	1.56(1)	C(x9)- C(x10)	1.51(1)	1.47(1)
C(x3)-C(x4)	1.50(1)	1.52(1)	C(x10)-C(x15)	1.32(1)	1.36(1)
C(x4)-C(x5)	1.34(1)	1.29(1)	C(x11)-C(x12)	1.51(1)	1.46(1)
C(x4)-C(x14)	1.49(1)	1.50(1)	C(x11)-C(x13)	1.52(1)	1.48(1)
C(x5)-C(x6)	1.49(1)	1.52(1)	C(x12)-O(x6)	1.37(1)	1.37(1)
C(x6)-C(x7)	1.53(1)	1.52(1)	C(x12)-O(x12)	1.20(1)	1.20(1)
C(x6)-O(x6)	1.47(1)	1.46(1)			

	x=1	x=2		x=1	x=2
C(x10)-C(x1)-O(x1)	119.7(7)	118.2(8)	C(x8) -C(x7) -C(x11)	112.9(5)	112.1(6)
C(x2) -C(x1)-O(x1)	119.4(7)	121.1(9)	C(x7) -C(x8) -C(x9)	114.2(6)	114.0(6)
C(x2) -C(x1)-C(x10)	120.9(6)	120.6(8)	C(x8) -C(x9) -C(x10)	116.3(6)	117.4(7)
C(x1) -C(x2)-C(x3)	108.7(6)	107.4(7)	C(x1) -C(x10)-C(x9)	116.5(6)	117.7(7)
C(x2) -C(x3)-C(x4)	109.7(6)	110.1(8)	C(x9) -C(x10)-C(x15)	121.3(7)	123.6(8)
C(x3) -C(x4)-C(x14)	116.2(6)	116.0(7)	C(x1) -C(x10)-C(x15)	121.9(7)	118.3(7)
C(x3) -C(x4)-C(x5)	119.3(6)	118.9(9)	C(x7) -C(x11)-C(x13)	117.3(6)	116.0(6)
C(x5) -C(x4)-C(x14)	124.2(6)	124.7(8)	C(x7) -C(x11)-C(x12)	103.1(5)	104.6(6)
C(x4) -C(x5)-C(x6)	125.3(6)	125.6(8)	C(x12)-C(x11)-C(x13)	113.4(6)	113.3(6)
C(x5) -C(x6)-O(x6)	110.8(5)	109.9(5)	C(x11)-C(x12)-O(x12)	130.4(7)	129.7(8)
C(x5) -C(x6)-C(x7)	114.8(6)	112.6(6)	C(x11)-C(x12)-O(x6)	109.8(6)	110.7(7)
C(x7) -C(x6)-O(x6)	103.5(5)	106.1(5)	O(x6) -C(x12)-O(x12)	119.8(7)	119.6(8)
C(x6) -C(x7)-C(x11)	101.2(5)	101.0(5)	C(x6) -O(x6) -C(x12)	108.8(5)	109.5(6)
C(x6) -C(x7)-C(x8)	116.5(6)	118.3(6)			

	x=1	x=2		x=1	x=2
C(x2) -C(x1)-C(x10)-C(x15)	-33(1)	-28(1)	O(x6) -C(x6) -C(x7) -C(x11)	-36(1)	-28(1)
O(x1) -C(x1)-C(x10)-C(x9)	-23(1)	-16(1)	O(x6) -C(x6) -C(x7) -C(x8)	-159(1)	-151(1)
C(x2) -C(x1)-C(x10)-C(x9)	153(1)	159(1)	C(x6) -C(x7) -C(x11)-C(x12)	32(1)	24(1)
C(x10)-C(x1)-C(x2) -C(x3)	-88(1)	-93(1)	C(x6) -C(x7) -C(x11)-C(x13)	158(1)	150(1)
O(x1) -C(x1)-C(x2) -C(x3)	88(1)	82(1)	C(x6) -C(x7) -C(x8) -C(x9)	-77(1)	-81(1)
O(x1) -C(x1)-C(x10)-C(x15)	150(1)	157(1)	C(x8) -C(x7) -C(x11)-C(x12)	158(1)	151(1)
C(x1) -C(x2)-C(x3) -C(x4)	58(1)	58(1)	C(x8) -C(x7) -C(x11)-C(x13)	-77(1)	-83(1)
C(x2) -C(x3)-C(x4) -C(x5)	-96(1)	-94(1)	C(x11)-C(x7) -C(x8) -C(x9)	167(1)	163(1)
C(x2) -C(x3)-C(x4) C(x14)	77(1)	79(1)	C(x7) -C(x8) -C(x9) -C(x10)	84(1)	75(1)
C(x3) -C(x4)-C(x5) -C(x6)	162(1)	159(1)	C(x8) -C(x9) -C(x10)-C(x1)	-133(1)	-123(1)
C(x14)-C(x4)-C(x5) C(x6)	-11(1)	-14(1)	C(x8) -C(x9) -C(x10)-C(x15)	54(1)	64(1)
C(x4) -C(x5)-C(x6) -C(x7)	-131(1)	-131(1)	C(x7) -C(x11)-C(x12)-O(x6)	-18(1)	-12(1)
C(x4) -C(x5)-C(x6) -O(x6)	113(1)	111(1)	C(x7) -C(x11)-C(x12)-O(x12)	160(1)	166(1)
C(x5) -C(x6)-O(x6) -C(x12)	150(1)	144(1)	C(x13)-C(x11)-C(x12)-O(x12)	32(1)	39(1)
C(x5) -C(x6)-C(x7) -C(x8)	80(1)	89(1)	C(x13)-C(x11)-C(x12)-O(x6)	-145(1)	-140(1)
C(x5) -C(x6)-C(x7) -C(x11)	-157(1)	-148(1)	C(x11)-C(x12)-O(x6) -C(x6)	-8(1)	-8(1)
C(x7) -C(x6)-O(x6) -C(x12)	27(1)	22(1)	O(x12)-C(x12)-O(x6) -C(x6)	176(1)	175(1)

Table 3. Selected bond lengths (Å), bond angles (°) and torsion angles (°) for compound 25

C(1)-C(2)	1.552(8)	C(4)-C(5)	1.555(7)	C(6)-O(6)	1.477(6)	C(10)-O(10)	1.202(7)
C(1)-C(5)	1.567(7)	C(4)-C(14)	1.519(8)	C(7)-C(8)	1.540(8)	C(11)-C(12)	1.509(8)
C(1)-C(10)	1.505(8)	C(4)-O(4)	1.437(6)	C(7)-C(11)	1.537(7)	C(11)-C(13)	1.540(8)
C(2)-C(3)	1.538(11)	C(5)-C(6)	1.513(7)	C(8)-C(9)	1.541(8)	C(12)-O(6)	1.374(6)
C(3)-C(4)	1.538(9)	C(6)-C(7)	1.522(7)	C(9)-C(10)	1.525(9)	C(12)-O(12)	1.200(7)

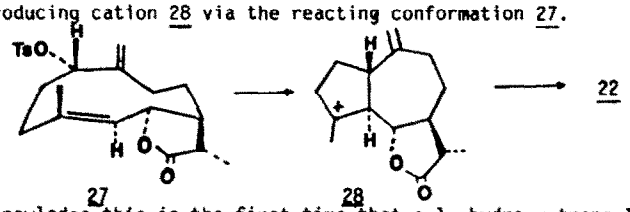
C(5) -C(1)-C(10)	109.9(4)	C(1)-C(5)-C(4)	103.7(4)	C(1) -C(10)-C(9)	119.1(5)		
C(2) -C(1)-C(10)	113.8(5)	C(4)-C(5)-C(6)	116.6(4)	C(9) -C(10)-O(10)	118.9(5)		
C(2) -C(1)-C(5)	104.4(5)	C(1)-C(5)-C(6)	108.8(4)	C(1) -C(10)-O(10)	122.0(6)		
C(1) -C(2)-C(3)	106.8(5)	C(5)-C(6)-O(6)	110.0(4)	C(7) -C(11)-C(13)	116.1(4)		
C(2) -C(3)-C(4)	106.0(5)	C(5)-C(6)-C(7)	116.2(4)	C(7) -C(11)-C(12)	101.2(4)		
C(3) -C(4)-O(4)	107.0(4)	C(7)-C(6)-O(6)	102.8(4)	C(12)-C(11)-C(13)	112.5(5)		
C(3) -C(4)-C(14)	113.4(5)	C(6)-C(7)-C(11)	99.8(4)	C(11)-C(12)-O(12)	129.3(5)		
C(3) -C(4)-C(5)	101.6(4)	C(6)-C(7)-C(8)	112.5(4)	C(11)-C(12)-O(6)	110.0(4)		
C(14)-C(4)-O(4)	110.5(5)	C(8)-C(7)-C(11)	114.0(5)	O(6) -C(12)-O(12)	120.7(5)		
C(5) -C(4)-O(4)	110.8(4)	C(7)-C(8)-C(9)	113.4(5)	C(6) -O(6) -C(12)	107.6(4)		
C(5) -C(4)-C(14)	113.1(4)	C(8)-C(9)-C(10)	118.1(5)				

C(5) -C(1) -C(10)-O(10)	98.0(7)	C(1) -C(5) -C(6) -O(6)	175.6(4)
C(2) -C(1) -C(10)-O(10)	-18.8(8)	C(5) -C(6) -O(6) -C(12)	154.8(4)
C(5) -C(1) -C(10)-C(9)	-83.3(6)	C(5) -C(6) -C(7) -C(8)	76.7(5)
C(2) -C(1) -C(10)-C(9)	160.0(6)	C(5) -C(6) -C(7) -C(11)	-162.1(4)
C(2) -C(1) -C(5) -C(6)	-155.7(5)	C(7) -C(8) -O(6) -C(12)	30.4(5)
C(10)-C(1) -C(5) -C(4)	-153.4(4)	O(6) -C(6) -C(7) -C(11)	-41.8(4)
C(2) -C(1) -C(5) -C(4)	-31.0(5)	O(6) -C(6) -C(7) -C(8)	-163.1(4)
C(5) -C(1) -C(2) -C(3)	8.2(7)	C(6) -C(7) -C(11)-C(12)	37.7(5)
C(10)-C(1) -C(2) -C(3)	128.0(6)	C(6) -C(7) -C(11)-C(13)	159.8(5)
C(10)-C(1) -C(5) -C(6)	81.9(5)	C(6) -C(7) -C(8) -C(9)	-83.3(6)
C(1) -C(2) -C(3) -C(4)	18.0(7)	C(8) -C(7) -C(11)-C(12)	157.9(4)
C(2) -C(3) -C(4) -C(5)	-36.9(6)	C(8) -C(7) -C(11)-C(13)	-80.0(6)
C(2) -C(3) -C(4) -C(14)	84.8(6)	C(11)-C(7) -C(8) -C(9)	164.0(5)
C(2) -C(3) -C(4) -O(4)	-153.1(5)	C(7) -C(8) -C(9) -C(10)	46.8(7)
C(3) -C(4) -C(5) -C(1)	41.7(5)	C(8) -C(9) -C(10)-C(1)	26.0(8)
C(3) -C(4) -C(5) -C(6)	161.0(5)	C(8) -C(9) -C(10)-O(10)	-155.2(6)
C(14)-C(4) -C(5) -C(1)	-80.2(5)	C(7) -C(11)-C(12)-O(6)	-21.2(5)
O(4) -C(4) -C(5) -C(1)	155.1(4)	C(7) -C(11)-C(12)-O(12)	159.1(6)
C(14)-C(4) -C(5) -C(6)	39.2(6)	C(13)-C(11)-C(12)-O(12)	34.6(8)
O(4) -C(4) -C(5) -C(6)	-65.6(5)	C(13)-C(11)-C(12)-O(6)	-145.8(5)
C(4) -C(5) -C(6) -C(7)	175.3(4)	C(11)-C(12)-O(6) -C(6)	-5.5(5)
C(1) -C(5) -C(6) -C(7)	-68.1(5)	O(12)-C(12)-O(6) -C(6)	174.2(5)
C(4) -C(5) -C(6) -O(6)	59.0(5)		

C(5)-C(6) bond.Both five-membered rings have envelope conformation with C(4) [0.624(5) A out of the plane] and C(7) [0.651(5) A at the flap].

Treatment of 25 with sodium t-amyloxide and triphenylmethylphosphonium bromide in toluene gave an 8:2 mixture of the alkenes 23 and 26,which,dehydrated with SO_2Cl-pyridine,generated the corresponding dienes 21 and 22 which were identified by comparison with authentic samples.

The transformation of 11 to 22 is a 5-endo-tet process and stereospecific[16] which,taken together with the impossibility of isolating the intermediate sulphonic ester 14,strongly suggests that the cyclization takes place via a concerted process with the assistance of the double bond 4(5) producing cation 28 via the reacting conformation 27.



27 28

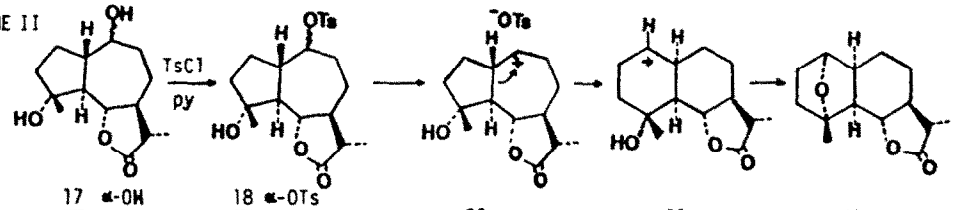
To the best of our knowledge this is the first time that a 1α-hydroxy-trans-10(14)-germacradien-6,12-olide has been cyclized to form a trans-guaianolide,most probably via a reacting conformation similar to that adopted by the melampolides.It is of interest that the stereochemistry of the cyclization product is the same as shown by the few known natural trans-guaianolides,namely pleniradin[17],gaillardin[18],neogaillardin[18],florilenolin and its dihydroderivative[19].

These findings strongly suggest that the biosynthesis of the trans-guaianolides may proceed via the melampolide pathway suggested by Parker et al[2].

In order to study the feasibility of a rearrangement similar to that formulated in Scheme I (6 from 5) we carried out the preparation of 15 and 17 by $NaBH_4$-EtOH reduction of 25,obtaining a 6:4 mixture.When MeOH-H_2O (8:2 v/v) was used as solvent,stereoselectivity was markedly increased and 17 (82%) was obtained with only traces of 15.

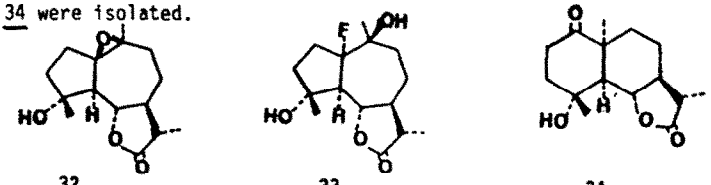
The tosylation of 17 led to epoxy-eudesmanolide 31 (25%) although the intermediate tosylate 18 could not be isolated.Identical results were obtained when the epimer 15 was treated in the same way.These data can be interpreted as shown in Scheme II.

SCHEME II



17 α-OH 18 α-OTs
15 β-OH 16 β-OTs 29 30 31

Our results are completely in agreement with those obtained by Fischer et al[20] when the epoxyderivative 32 was treated with $BF_3.Et_2O$ and the fluoride derivative 33 and the cis-eudesmanolide 34 were isolated.



32 33 34

It would seem that the σ bond (1,10) migrates more easily than H-1,which contradicts the theorized biogenetic hypotheses.

EXPERIMENTAL

Mp's were determined using a Kofler hot-plate apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 and NMR spectra were taken at 90 MHz on a Perkin-Elmer R-123 and at 200 MHz on a Bruker 200 SY, with $CDCl_3$ as solvent. Mass spectra were taken on a VG-Micromass ZAB-2F. Unless otherwise stated, column chromatography was carried out using Merck silica gel (0.065-0.2 mm).

Cyclization of 1-epigallicin 11

TsCl (250 mg) was added to a solution of 1-epigallicin 11 (314 mg) in minimal dry pyridine. After 24 h at -10°C, it was poured onto ice and water, frozen, washed with aqueous $NaHCO_3$ and NaCl-saturated solutions, extracted with $CHCl_3$, dried, concentrated and chromatographed with hexane-EtOAc 9:1 as eluent, 22 (54 mg, 18.5%) was obtained as an oil: ^{1}H-NMR: δ 5.45(1H, bs, H-3); 5.05, 4.95(1H each, s, H-14), 3.75(1H, dd, J=9 and 10Hz, H-6), 1.81(3H, s, H-15); 1.20(3H, d, J=7Hz, H-13); i.r.: ν_{max}($CHCl_3$)cm^{-1}, 1770(γ-lactone), 1600(double bonds); h.r.m.s., m/z 232.1428($C_{15}H_{20}O_2$).

Ozonolysis of 23

A current of ozone (200 mg/h) was passed through a solution of 23, prepared according to González et al [14], (900 mg) in CH_2Cl_2 for 40 minutes at -78°C. Me_2S (1 ml) was added, the mixture was allowed to reach room temperature (4 h), and ice and a NaCl-saturated solution were added. It was extracted with CH_2Cl_2, dried, concentrated and chromatographed with hexane-EtOAc 9:1 as eluent. 24 (376 mg, 41.5%) was obtained: mp 146-148°C; [α] -27.4° ($CHCl_3$, 0.21); ^{1}H-NMR: δ 3.86 (1H, dd, J=9 and 10Hz, H-6); 1.29(3H, s, H-15); 1.28(3H, d, J=7Hz, H-13); ^{13}C-NMR: 56.38(C-1), 21.10[a](C-2), 40.94(C-3), 80.71(C-4), 51.90[b](C-5), 85.27(C-6), 50.50[b](C-7), 22.34[a](C-8), 42.84(C-9), 209.50(C-10), 39.18(C-11), 177.53(C-12), 12.49(C-13), 23.00(C-15). The signals marked [a] are interchangeable as are [b]. i.r.: ν_{max}($CHCl_3$)cm^{-1}, 3580(OH), 1775(γ-lactone), 1705(carbonyl); m.s., m/z 252; 237; 234.

Epimerization of 24

A methanolic solution (0.1 N) of NaOH (5 ml) was added to a solution of 24 (54 mg) in MeOH (2 ml) and stirred for 30 minutes at 0°C. It was neutralized with an aqueous solution of HCl (5%), extracted with CH_2Cl_2, dried and concentrated, yielding a 7:3 mixture of 25 and 24. Compound 25 was obtained by fractionated crystallization with hexane-EtOAc: mp 203-205°C; $[\alpha]_D$ 44.1° ($CHCl_3$, 0.12); ^{1}H-NMR: δ 4.08(1H, dd, J=9 and 10Hz, H-6); 1.38(3H, s, H-15), 1.27(3H, d, J=7Hz, H-13); ^{13}C-NMR: 53.78(C-1), 28.67(C-2), 40.31(C-3), 79.88(C-4), 50.54[a](C-5), 83.46(C-6), 50.43[a](C-7), 23.00 (C-8), 44.30(C-9), 210.58(C-10), 41.06(C-11), 177.35(C-12), 13.47(C-13). The signals marked [a] are interchangeable. i.r.: ν_{max}($CHCl_3$)cm^{-1}, 3580(γ-lactone), 1705(carbonyl); h.r.m.s., m/z 252.1508 ($C_{14}H_{20}O_4$).

X-ray Measurements

The experimental conditions and details of the X-ray analyses are given in Table 1. The final atomic parameters are given in Tables 4 and 5. In compound 13, both the atomic coordinates and the thermal parameters for the H-atoms were kept fixed during the last stages of refinement but in compound 25, only the thermal parameters. Both hkl and -h-k-l reflexions were used in the refinement. The absolute configuration[24] was confirmed using the 45 more relevant Friedel pairs with Fc>0.08 and Fo>10σ(Fo) for compound 13 and with the 100 more relevant Friedel pairs with Fc>0.06 and Fo>10σ(Fo) for compound 25. The averaged Bijvoet difference for 13 was 1074 for the right enantiomer as against 1226 for the wrong model, the corresponding averaged Bijvoet ratio being 1045 compared with 1063. For compound 25, the averaged Bijvoet difference was 0.446 for the right enantiomer as opposed to 0.521 for the wrong model, the corresponding averaged Bijvoet ratio being 1052 compared with 1069[25].

A view of the molecules with their atomic numbering is given in Figures 2 and 3.

Preparation of 22

A solution of freshly prepared sodium t-amyloxide (0.5 M) in toluene was added to triphenylmethylphosphonium bromide (370 mg) and stirred under inert atmosphere until a yellow precipitate was formed. 25 (210 mg) dissolved in dry toluene (3 ml) was added and refluxed for 36 h then neutralized with aqueous solution of HCl (10%). After extraction with CH_2Cl_2, it was dried, concentrated and chromatographed, using hexane-EtOAc 7:3 as eluent. A mixture of 23 and 26 (8:2) which could not be separated was obtained. This mixture was dissolved in dry pyridine (0.5 ml) and freshly distilled $SOCl_2$ (0.5 ml) was added, stirred for 5 minutes at 0°C, then poured over ice and water. An aqueous $NaHCO_3$-saturated solution was added, the mixture was extracted with CH_2Cl_2, dried, concentrated and chromatographed with hexane-EtOAc 9:1 as eluent. 21 and 22 were obtained in a 8:2 mixture which could not be separated and were identified by comparison with authentic samples using gas chromatography.

Reduction of 25

$NaBH_4$ (5 mg) was added to a solution of 25 (100 mg) in EtOH (5 ml), stirred for 30 minutes at 0°C, poured over ice and water, neutralized with aqueous solution of HCl (10%), concentrated at reduced pressure, extracted with Et_2O, dried, concentrated and chromatographed with hexane-EtOAc 4:6 as eluent. Compounds 17 (26 mg) and 15 (15 mg) were obtained. Compound 17: mp 158-160°C; $[\alpha]_D$ 19.8° ($CHCl_3$, 0.21); ^{1}H-NMR: δ 4.04(1H, t, J=4Hz, H-10); 3.90(1H, dd, J=9.5 and 10Hz, H-6); 1.31(3H, s, H-15); 1.18(3H, d, J=6.5Hz, H-13); i.r.: ν_{max}($CHCl_3$)cm^{-1}, 3565(OH), 1760(γ-lactone); h.r.m.s., m/z 239.1283($C_{13}H_{19}O_4$, M+-CH_3); 236.1414($C_{14}H_{20}O_3$, M+-H_2O). Compound 15, oil: ^{1}H-NMR: δ 4.58(1H, dd, J=9 and 10Hz, H-6); 3.90(1H, d, J=7Hz, H-10); 1.35(3H, s, H-15); 1.19(3H, d, J=7Hz, H-13); i.r.: ν_{max}($CHCl_3$)cm^{-1}, 3580(OH), 1760(γ-lactone); h.r.m.s., m/z 254.1508($C_{14}H_{22}O_4$); 239.2590 ($C_{13}H_{19}O_4$); 236.1408($C_{14}H_{20}O_3$).

If MeOH-H_2O 4:1 was used instead of EtOH, as solvent, only 17 (82%) was obtained.

Table 4. Final atomic parameters for compound 13.

Thermal parameters as:
$Ueq=(1/3).\Sigma[U_{ij}.a_i^*.a_j^*.a_i.a_j.\cos(a_i,a_j)].10^3$

Atom	x/a	y/b	z/c	Ueq
C(11)	0.2359(6)	0.2285(6)	0.4543(7)	65(3)
C(12)	0.2571(6)	0.2438(6)	0.3226(8)	72(3)
C(13)	0.2773(7)	0.3675(7)	0.3045(7)	74(3)
C(14)	0.3862(6)	0.4085(5)	0.4268(6)	52(2)
C(15)	0.3655(6)	0.4575(5)	0.5285(6)	52(3)
C(16)	0.4607(6)	0.4750(5)	0.6697(6)	52(3)
C(17)	0.4200(6)	0.4398(5)	0.7849(6)	58(3)
C(18)	0.4292(6)	0.3180(6)	0.8186(7)	63(3)
C(19)	0.3234(6)	0.2481(6)	0.7139(7)	66(3)
C(110)	0.3428(6)	0.2124(5)	0.5877(8)	64(3)
C(111)	0.5056(6)	0.5089(6)	0.9036(6)	60(3)
C(112)	0.5219(7)	0.6111(7)	0.8337(7)	68(3)
C(113)	0.4641(8)	0.5306(8)	1.0205(7)	83(4)
C(114)	0.5128(6)	0.3802(7)	0.4318(7)	68(3)
C(115)	0.4450(7)	0.1601(6)	0.5969(8)	72(3)
O(11)	0.1315(4)	0.2347(7)	0.4511(6)	105(3)
O(16)	0.4881(4)	0.5919(4)	0.6964(4)	68(2)
O(112)	0.5546(6)	0.7004(5)	0.8789(6)	106(3)
C(21)	0.8756(9)	0.3487(8)	0.8811(8)	91(4)
C(22)	0.9201(8)	0.2522(10)	0.9809(8)	98(4)
C(23)	0.8742(9)	0.1457(9)	0.8952(10)	103(5)
C(24)	0.9243(8)	0.1402(7)	0.7831(8)	77(3)
C(25)	0.8560(7)	0.1763(6)	0.6626(7)	68(3)
C(26)	0.9033(6)	0.2113(6)	0.5539(6)	58(3)
C(27)	0.8524(5)	0.3214(5)	0.4919(6)	54(2)
C(28)	0.9237(7)	0.4215(6)	0.5592(7)	72(3)
C(29)	0.8997(8)	0.4600(7)	0.6895(8)	82(4)
C(210)	0.9591(7)	0.3967(6)	0.8169(7)	68(3)
C(211)	0.8457(6)	0.3066(6)	0.3423(7)	61(3)
C(212)	0.8364(6)	0.1886(8)	0.3196(8)	72(3)
C(213)	0.7461(7)	0.3687(8)	0.2339(7)	85(3)
C(214)	1.0571(10)	0.1039(9)	0.8267(10)	113(5)
C(215)	1.0844(8)	0.3890(9)	0.8864(9)	101(4)
O(21)	0.7689(7)	0.3841(8)	0.8447(7)	129(4)
O(26)	0.8623(4)	0.1340(4)	0.4406(5)	70(2)
O(212)	0.8085(5)	0.1379(6)	0.2144(6)	95(3)

Table 5. Final atomic parameters for compound 25.

Thermal parameters as:
$Ueq=(1/3).\Sigma[U_{ij}.a_i^*.a_j^*.a_i.a_j.\cos(a_i,a_j)].10^3$

Atom	x/a	y/b	z/c	Ueq
C(1)	0.0819(2)	0.6772(5)	0.4734(10)	43(2)
C(2)	0.0766(4)	0.5400(7)	0.3675(14)	70(3)
C(3)	0.1183(4)	0.5352(7)	0.1540(12)	65(2)
C(4)	0.1616(2)	0.6487(5)	0.1837(9)	42(2)
C(5)	0.1203(2)	0.7534(5)	0.2907(8)	32(1)
C(6)	0.1504(2)	0.8642(5)	0.4158(9)	33(1)
C(7)	0.1100(2)	0.9716(5)	0.5028(9)	37(2)
C(8)	0.0761(3)	0.9344(6)	0.7278(11)	50(2)
C(9)	0.0193(2)	0.8562(6)	0.6796(14)	59(2)
C(10)	0.0232(2)	0.7436(6)	0.5081(11)	52(2)
C(11)	0.1561(2)	1.0790(5)	0.5384(11)	40(2)
C(12)	0.1969(2)	1.0561(5)	0.3320(10)	45(2)
C(13)	0.1318(3)	1.2175(6)	0.5450(16)	60(2)
C(14)	0.2146(3)	0.6172(7)	0.3386(12)	56(2)
O(4)	0.1809(2)	0.6851(4)	-0.0476(6)	49(1)
O(6)	0.1907(1)	0.9320(3)	0.2525(7)	41(1)
O(10)	-0.0210(2)	0.7094(5)	0.4075(10)	91(2)
O(12)	0.2312(2)	1.1287(4)	0.2396(9)	65(2)

Tosylation of 17 and 15

To 17 (117 mg) dissolved in dry pyridine (1 ml) TsCl (105 mg) was added and the mixture kept at room temperature for three days,then poured over ice and water,washed with an $NaHCO_3$-saturated solution,extracted with CH_2Cl_2 ,dried,concentrated and chromatographed with hexane:EtOAc 7:3 as eluent.32 (37 mg) and 18 (17 mg) were obtained.Compound 18 decomposed rapidly.Compound 32:mp 141-142°C,$[\alpha]_D$ 64.1° ($CHCl_3$,0,18),^{1}H-NMR:δ 4.05-3.91 (2H,complex,H-1 and H-6),1.35(3H,s,H-15);1.21(3H,d,J7Hz,H-13),^{1}H-NMR(C_6D_6):δ 3.40-3.25 (1H,complex,H-]);3.20(1H,dd,J=9 and 10Hz,H-6);1.11(3H,s,H-15);0.90(3H,d,J=7Hz,H-13);i.r.: ν_{max}($CHCl_3$)cm^{-1},1765(γ-lactone);h.r.m.s.,m/z 236.1394($C_{14}H_{20}O_3$);221.1216($C_{13}H_{17}O_3$);218.1322 ($C_{13}H_{18}O_2$).

When 15 was tosylated (24 h) product 32 (35%) was also obtained.

ACNOWLEDGEMENTS

This work was subsidized in part by the CAICYT,Spain (Grant No 3190/84).MMA and JAP thank the MEC and CSIC,respectively,for research grants.

We are indebted to Prof. C.Jaime,Universidad Autónoma de Barcelona,Spain,for Molecular Mechanics Calculations.

REFERENCES AND NOTES

1 N.H.Fischer,E.J.Olivier and H.D.Fischer,"Progress in the Chemistry Of Natural Products vol. 38,eds. W.Herz,H.Grisebach and G.W.Kirby,Springer-Verlag,New York,p 146 and 189 (1979).
2 W.Parker,J.S.Roberts and R.Ramage,Quart.Rev.,21,331 (1967).
3 W.Herz,Isr.J.Chem.,16,32 (1977).
4 T.G.Waddell and T.A.Geissman,Phytochemistry,8,2371 (1969).
5 W.Herz,R.Murari and J.F.Blount,J.Org.Chem.,44,1873 (1979).
6 M.J.Bordoloi,R.P.Sharma and J.C.Sarma,Tetrahedron Lett.,27,4633 (1986).
7 N.H.Fischer,Rev.Latinoam.Quím.,9,41 (1978).
8 A.G.González,A.Galindo,H.Mansilla and J.A.Palenzuela,Tetrahedron Lett.,24,969 (1983).
9 A.G.González,A.Galindo,H.Mansilla and A.Gutiérrez,J.C.S. Perkin I,881 (1982).
10 C.Djerassi,R.Records,E.Bunnenberg,K.Mislow and A.Moskowitz,J.Am.Chem.Soc.,84,870 (1962).
11 N.L.Allinger and J.T.Sprague,J.Am.Chem.Soc.,95,3893 (1973).
12 S.C.Abrahams and E.T.Keve,Acta Crystallogr.,A27,157 (1971).
13 J.B.Hendrickson,J.Am.Chem.Soc.,89,7036 (1967).
14 A.G.González,A.Galindo and H.Mansilla,Tetrahedron,36,2015 (1980).
15 F.H.Cano and C.Foces-Foces,J.Mol.Struct. (TEOCHEM),94,209 (1983).
16 Gallicin 12 suffers identical transformation to cis-guaianolides.See ref. 14.If the process takes place via a carbenium ion it would be a 5-endo-trig ring closure which is not favoured,see J.E.Baldwin,J.C.S. Chem.Comm.,734 (1976).
17 T.A.Dullforce,G.A.Sim,D.N.J.White,J.E.Kelsey and S.M.Kupchan,Tetrahedron Lett.,973 (1969).
18 A.T.McPhail and K.D.Onan,J.C.S. Perkin II,492 (1975).
19 M.Kozuka,K.H.Lee,A.T.McPhail and K.D.Onan,Chem.Pharm.Bull.,23,1895 (1975).
20 N.H.Fischer,Y.F.Wu-Shih,G.Chiari,R.F.Fronczek and S.F.Warkins,J.Nat.Pro.,44,104 (1981).
21 P.Main,S.J.Fiske,S.E.Hull,L.Lessinger,G.Germain,J.P.Declerq and M.M.Woolfson,"MULTAN 80 System",University of York,York,England (1980).
22 J.M.Stewart,P.A.Machin,C.W.Dickinson,H.L.Ammon,H.Heck and H.Flack,"The X-Ray System", University of Maryland,USA (1976).
23 "International Tables for X-Ray Crystallography,vol. IV",Kynoch Press,Birmingham,England (1974).
24 M.Martínez-Ripoll and J.Fayos,Z.Kristallogr.,152,189 (1971).
25 Lists of observed and calculated structure factors,final anisotropic parameters for heavy atoms,positional and thermal parameters for H-atoms,are available from the Cambridge Crystallographic Data centre,University Chemical Laboratory,Lensfield Road,Cambridge CB2.