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EVIDENCE FOR THE BIOGENESIS OF *TRANS*-(1β-H;5α-H)-GUAIANOLIDES

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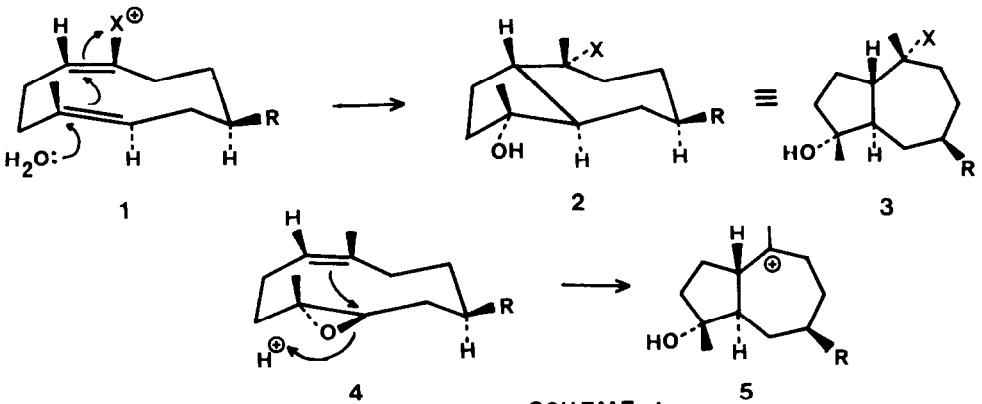
Summary: The biomimetic cyclization of 1-epi-gallicin (8) into the trans-(1β,5α)-guaianolide (15) is carried out. The stereospecificity of the cyclization is explained in terms of a preferred reacting conformation (19). The biogenetic implications of this process are discussed.

It has been postulated that the greater part of the *trans*-guaianes (3) derive from *cis, trans*-germacradiene precursors (1), by the anti-Markovnikoff-type *trans*-antiparallel cyclization[1]. Another plausible suggestion for biogenesis of *trans*-guaianolides was presented by Herz[2]; acid-induced cyclization of the 4α,5β-epoxide (4) would give the cation (5), showing a stereochemical arrangement typical of *trans*-guaianolides (Scheme I).



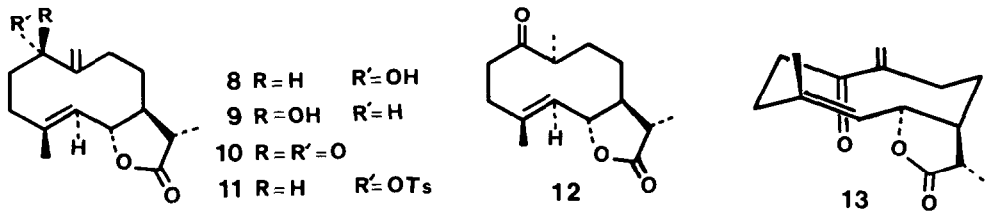
SCHEME I

This last route has recently received strong support, since the structural revision of baileyin from a germacrolide[3a] to a melampolide skeleton, together with the X-ray finding that pleniradin[3b] represents a *trans*-guaianolide, suggest that these two co-occurring lactones (Baileya pleniradiata) are biogenetically related[4].

In a review of melampolides, Fischer and co-workers[5] suggested that the centre-to-centre distance between the two double bonds of (1) is considerably greater than in the four possible conformations of a *trans,trans*-germacradiene. They propose that the *trans*-fused guaiane cation (7) is formed from quasi-parallel conformation, via the 4α,5β-epoxy-*trans*-germacrene (6).

6 7

In order to evaluate the role played by the *cis,trans*-germacradiene derivatives in the biosynthesis of *trans*-guaianolides, the cyclization of 1-epi-gallicin (8) has been studied. Oxidation of gallicin (9)[6] with active MnO_2 yielded the ketone (10) (77%); $NaBH_4$ reduction of (10) afforded 1-epi-gallicin (8)[7] (59%), the dihydroketone (12)[7] (21%) and gallicin (9) (4%).



8 R=H R'=OH
9 R=OH R'=H
10 R=R'=O
11 R=H R'=OTs

12 13

The stereoselectivity of the reaction may be due to the fact that reduction takes place through a preferred reacting conformation (13). The conformational study of (10) in solution was made using variable temperature PMR and LIS. The PMR spectra were taken at ordinary probe temperature (+35°C) as none of the spectral features changed significantly at temperatures from -60° to +60°C. The addition of $Eu(fod)_3$ caused the chemical shifts shown in Figure 1. Slight chemical shifts of H-14 and H*-14 in (10) are not compatible with a *syn* relationship of the carbonyl

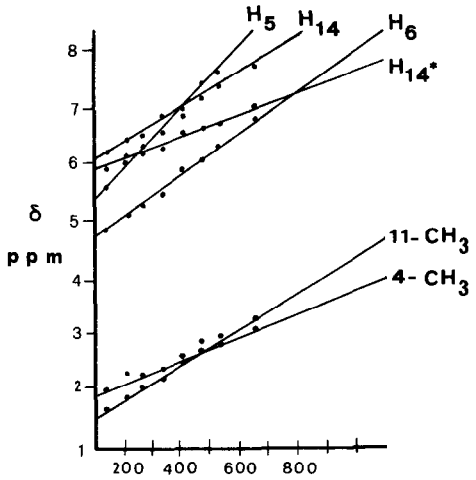
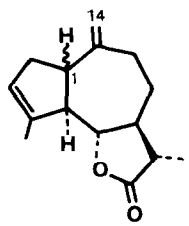


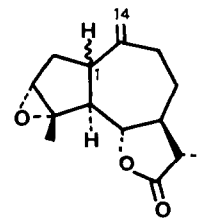
Fig. 1

group and the 10(14) double bond, which suggests the s-*trans* disposition of the α,β-unsaturated ketone. Furthermore, the chemical shift of H-5 suggests the *syn*-axial disposition of H-5 and the carbonyl group at C-1. This data is in agreement with the crown conformation (13); the *si*-face of the carbonyl group at C-1 is highly hindered and the attack by hydride ion takes place on the *re*-face, yielding (8).

1-Epi-gallicin (8) undergoes a biomimetic-type cyclization to *trans*-guaianolide (15) (18%) when treated with TsCl in pyridine. The *trans*-stereochemistry of the AB ring junction was established by comparison with (14)[8]. The most important differences between the PMR spectra of (14) and (15) are the signals of H-14 (two broad singlets in (15); one broad singlet in (14)). Compounds (14) and (15) are selectively epoxidated on the 3,4-double bond yielding (16) and (17), respectively. The PMR spectra of these compounds only differ in the signals of H-14 (broad singlet at 4.92 ppm in (17); two broad singlets at 4.90 and 5.00 in (16))[9].

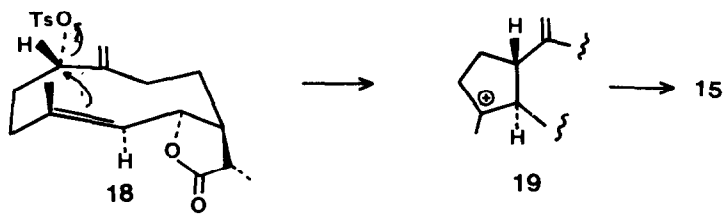


14 1_α-H
15 1_β-H



16 1_α-H
17 1_β-H

The transformation of (8) to *trans*-guaiane (15) is stereospecific[10] and this fact, coupled with the impossibility of isolating the intermediate sulfonic ester (11), strongly suggests that the cyclization is carried out in a concerted process with assistance of the 4(5) double bond producing the cation (19), via the reacting conformation (18)[11].



18 **19** **15**

As far as we know, this is the first time that a 1α-hydroxy-*trans*-4(5)-10(14)-germacradien-6,12-olide has been cyclized to form a *trans*-guaianolide, and it is interesting that the stereochemistry of the cyclization product is the same as is found in the few natural *trans*-fused guaianolides pleniradin[3b], gaillardin[12], neogaillardin[13], florilenalin[14] and its dihydro-derivative[15].

These results strongly suggest that the biosynthesis of the *trans*-guaianolides may proceed via the melampolide route formulated by Parker et al.[1].

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7. Compound (8), m.p. 93-95°C, $C_{15}H_{22}O_3$, M^+ at *m/z* 250'1564 (high resolution); IR ν_{max}^{KBr} 3612, 1770, 1640 cm^{-1}. PMR ($CDCl_3$)δ 1.22 (*d*, *J* = 7Hz, 3H) 1.72 (*d*, *J* = 2Hz, 3H) 3.98 (*c*, 1H) 4.40 (*dd*, *J* = 10 and 9Hz, 1H) 4.85 (*s*, 1H) 5.13 (*s*, 1H) and 5.21 (*d*, *J* = 9Hz, 1H). Compound (12), m.p. 107-109°C, $C_{15}H_{22}O_3$, M^+ at *m/z* 250; IR $\nu_{max}^{CHCl_3}$ 1760, 1705 cm^{-1}; PMR (Cl_4C) 0.97 (*d*, *J* = 7Hz, 3H) 1.16 (*d*, *J* = 7Hz, 3H) 1.92 (*s*, 3H) 4.38 (*dd*, *J* = 10 and 9Hz, 1H) and 5.02 (*d*, *J* = 10Hz, 1H).
8. A.G. González, A. Galindo and H. Mansilla, *Tetrahedron*, 36, 2015 (1980). Compound (15), oil, $C_{15}H_{20}O_2$, M^+ at *m/z* 232'1418 (high resolution); IR $\nu_{max}^{CHCl_3}$ 1760, 1640, 900 cm^{-1}. PMR ($CDCL_3$)δ 1.20 (*d*, *J* = 7Hz, 3H) 1.81 (*bs*, 3H) 3.75 (*dd*, *J* = 9 and 10Hz, 1H) 4.95 (*bs*, 1H) 5.05 (*bs*, 1H) 5.45 (*bs*, 1H).
9. Compound (16) (dihydroestafiatin), oil, $C_{15}H_{20}O_3$, M^+ at *m/z* 242'1396 (high resolution); IR $\nu_{max}^{CHCl_3}$ 1755, 1630 cm^{-1}. PMR ($CDCl_3$)δ 1.22 (*d*, *J* = 6Hz, 3H) 1.60 (*s*, 3H) 4.01 (*dd*, = 9 and 10Hz, 1H) 4.90 (*s*, 1H) 5.03 (*s*, 1H). Compound (17), $C_{15}H_{20}O_3$, M^+ at *m/z* 248'1403 (high resolution); IR $\nu_{max}^{CHCl_3}$ 1760, 1635 cm^{-1}. PMR ($CDCl_3$)δ 1.21 (*d*, *J* = 7Hz, 3H) 1.58 (*s*, 3H) 3.35 (*s*, 1H) 4.01 (*dd*, *J* = 9 and 10Hz, 1H) 4.95 (*s*, 2H).
10. Gallicin (9) suffers identical transformation to *cis*-guaianolides. See reference 8.
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