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BIOMIMETIC SYNTHESIS OF 5α-HYDROXY-GUAIANOLIDES

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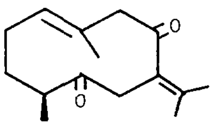
ABSTRACT: A 5α-hydroxy-guaianolide was synthesized biomimetically from a 5-oxo-E-1(10)-germacrenolide, the stereoselectivity of the cyclization being attributed to preferred conformation.

Is has been hypothesized that 1,5-germacradienes are biogenetic precursors of guaianic sesquiterpenes[1], although the cyclization of a trans-trans-germacradiene to form a guaiane would require an anti-Markownikoff attack on the double bond system, which is possible only with some 1,5-cyclodecadiene derivatives[2]. The 5-oxo-E-1(10)-germacrene derivatives may be considered as the biogenetic precursors of 5-hydroxy-guaianes and, thus, dehydrocurdione (1) has been biomimetically transformed[3] to curcumenol (2) and isocurcumenol (3) when treated with K_2CO_3 in MeOH or alumina in benzene and (4) treated with refluxing benzene or silica gel has quantitatively yielded[4] the guaianolide (5).



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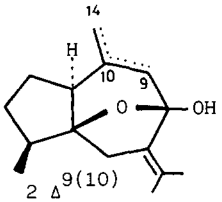
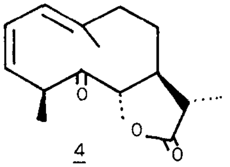


2 $\Delta^{9(10)}$
3 $\Delta^{10(14)}$



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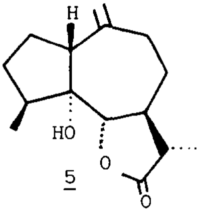

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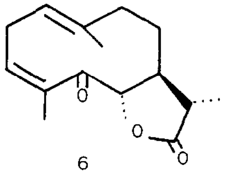
Our aim was to prepare ketone (6) using vulgarin (7)[5] as starting material and then carry out a biomimetic cyclization, forming the cis-(1α-H,5α-OH)-guaianolide (12). (7) was therefore treated with zinc (HOAc, reflux), reduced and tosylated, yielding (10) which, after allylic oxidation[6], gave the hydroxy-tosylate (11) [57% yield of (7)]. When (11) was treated with $KOBu^t$-$HOBu^t$, the guaianic derivative (12) was produced stereoselectively (79%). NMR revealed the presence of ketone (6)[7], highly unstable and decomposing to guaiane (12)[8] in chloroform solution or by the action of silica gel.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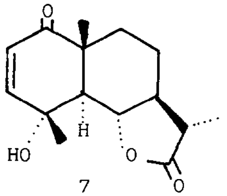
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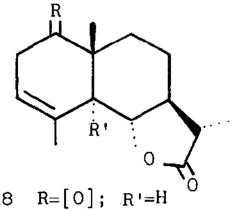
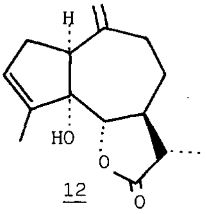

8 R=[O]; R'=H
9 R=[β-OH;α-H]; R'=H
10 R=[β-OTs;α-H]; R'=H
11 R=[β-OTs;α-H];R'=OH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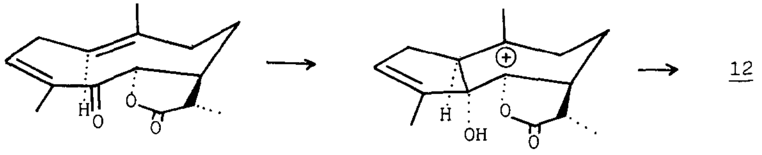
The configuration S was assigned to C-5 on the basis of the pyridine-induced chemical shifts[9]. The slight shift at H-6 ($\Delta\delta$=0.09 ppm) clearly shows that the 5-OH of (12) should be α-disposed since the H-6 is β-axial. The stereoselectivity of the cyclization and the S configuration (α-H) assigned to C-1 may be accounted for by the process occurring via preferred reacting conformation (13).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The conformational analysis of (6) in solution (using LIS studies)[10] provides experimental evidence favouring this hypothesis. When Eu(fod)$_3$ was added, the chemical shifts shown in Figure 1 occurred. The slight chemical shifts at 10-Me and the greater one at H-1 (Table 1) suggest a syn axial disposition for H-1 and the C-5 carbonyl. Again, a syn coplanar disposition for C-5 carbonyl and 4-Me is not compatible with the variation observed for this last one. These results strongly suggest that (13) would be the preferred conformation for (6) in solution.

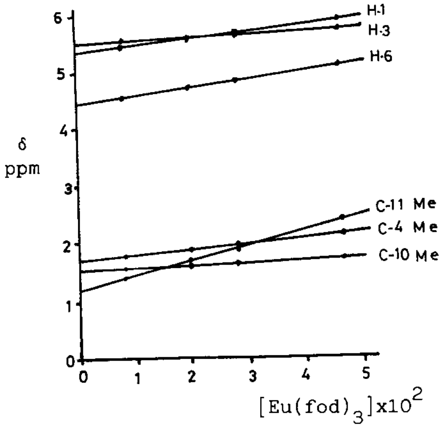

TABLE I

signal	slope
11-Me	0.26
H-6	0.19
H-1	0.08
4-Me	0.07
10-Me	0.04
H-3	0.04

It is notable that this is the first time that a 5-oxo-E-1(10)-Z-3-germacradien-6,12-olide has been cyclized to give a cis-(1α-H,5α-OH)-guaianolide[11] and that the stereochemistry in this case is identical to the vast majority of natural 5-hydroxy-guaianolides [A/B cis; 1α-H, 5α-OH][12], which differs from those previously reported for products (2) and (3) [A/B trans; 1α-H, 5β-OH][3] and (5) [A/B trans; 1β-H, 5α-OH][4].

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8.- Spectral properties of (6): IR, ν 1770, 1690 cm^{-1}; NMR, δ 1.33 (3H, d, J=6; 11-Me), 1.60 (3H, bs; 10-Me), 1.88 (3H, bs; 4-Me), 4.50 (1H, d, J=8; H-6), 5.32 (1H, bs; H-1), 5.45 (1H, bs; H-3). Spectral properties of (12): IR ν 3590, 1770 cm^{-1}; MS, m/z 248.1417 ($C_{15}H_{22}O_2$); NMR, δ 1.21 (3H, d, J=6; 11-Me), 1.88 (3H, d, J=2; 4-Me), 3.87 (1H, d, J=10; H-6), 5.10 (1H, s; H-14), 5.23 (1H, s; H*-14), 5.65 (1H, bs; H-3).

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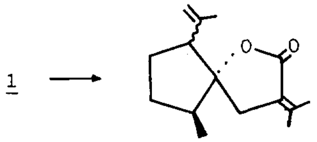
11.- Acid treatment of (1) yielded[3] two epimeric spirolactones.



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