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THE BIOMIMETIC CYCLIZATION OF MELAMPOMAGNOLIDE B

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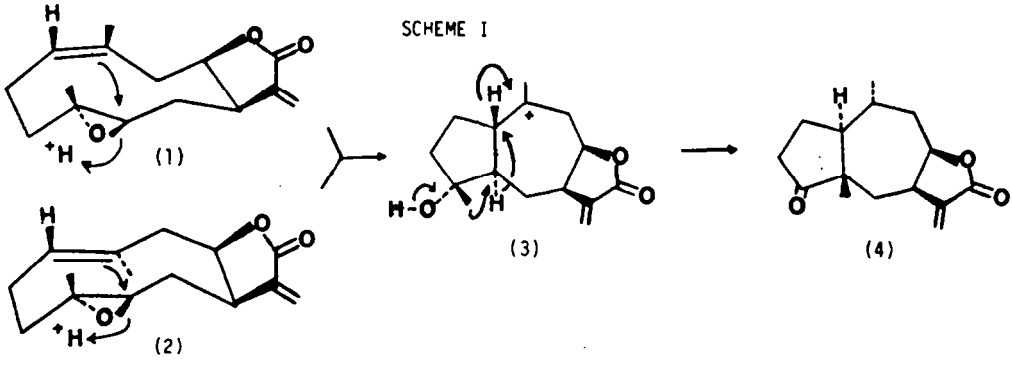
ABSTRACT: Melampomagnolide B (9) was prepared and converted to the epimeric trans-(1αH,5βOH)-guaianolides (19) and 1,5-epoxygermacranolide (15).The 11,13-dihydroderivative (10) afforded (20) and (16).The biogenetic implications of this process are discussed.

The germacranolide epoxyderivatives are reckoned to be biogenetic precursors of other types of sesquiterpene lactone skeletons[1,2] with the acid cyclization of 1β,10α- and 4α,5β-epoxyderivatives giving trans-eudesmanolides[3] and cis-guaianolides[4],respectively.

The 4α,5β-epoxymelampolides (1) have been proposed as the precursors of helenanolides[5] (4) and,according to this theory,the acid cyclization of (1) would give cation (3) which has the stereochemical disposition typical of natural helenanolides[1] and from which (4) could be obtained via the shifts shown in Scheme I.

SCHEME I



The epoxymelampolide must have the TC conformation,as (1) does,since only so can it generate the trans-guaiane cation (3).Fischer[6] has suggested an epoxygermacranolide (2) in a TT conformation as precursor,in view of the fact that the distance between the double bonds of the original 1,5-diene system is greater in a CC melampolide than in a TT germacranolide.

In order to evaluate the possible role played by the epoxymelampolides in the biogenesis of the helenanolides,the cyclizations of the melampomagnolide B (9) and its 11,13-dihydroderivative (10) were studied.

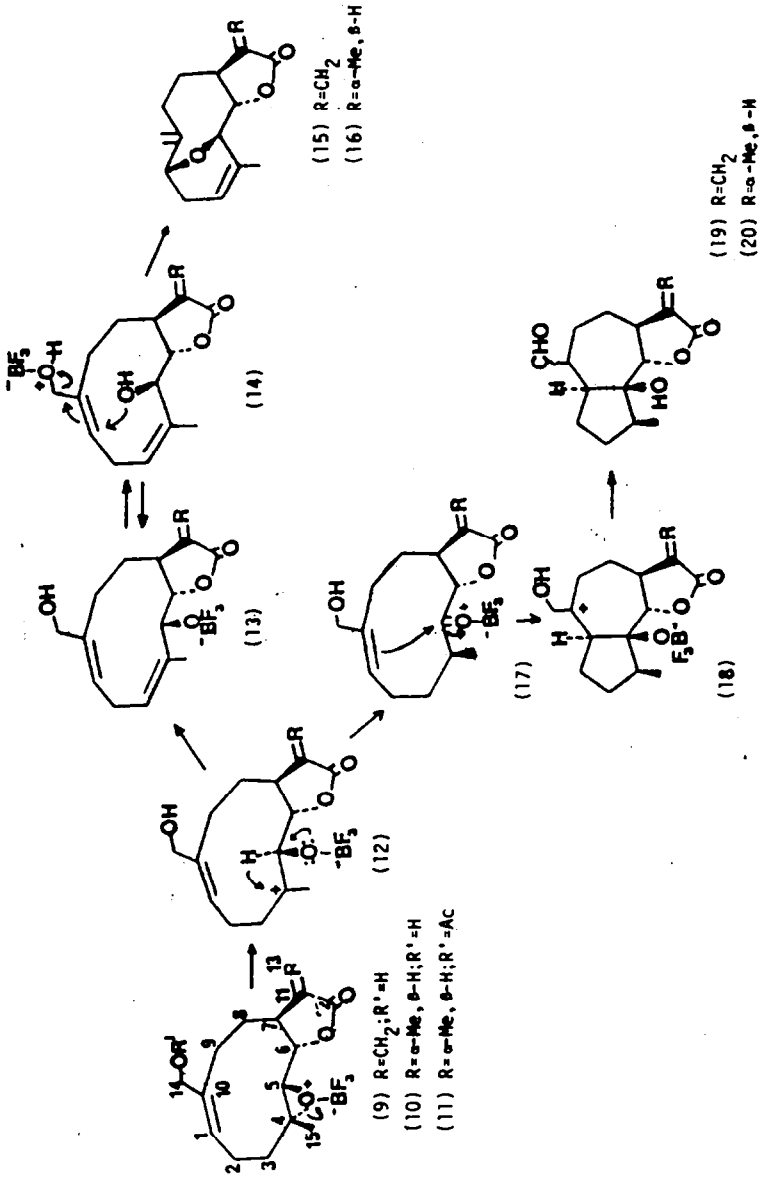
RESULTS AND DISCUSSION

Melampomagnolide B (9) and its 11,13-dihydroderivative (10) were prepared from parthenolide (5)[7] by allylic oxidation with SeO_2-HO^{t}Bu followed by $NaBH_4$ reduction,as described by El Feraly[8].

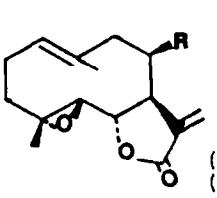
Acid treatment of (9) with BF_3-Et_2O (benzene,r.t.) afforded two epimeric guaianolides (19) (α+β-CHO) and traces of the epoxygermacranolide (15),the structures of which were established from the spectral data.The skeleton of (15) is similar to that of badgerin,a germacranolide isolated by Shafizadeh and Bhadane[9] from Artemisia arbuscula ssp arbuscula.

The low solubility in benzene induced us to use CH_2Cl_2 as solvent and in these conditions (10) led to (16) while (11) gave (8).

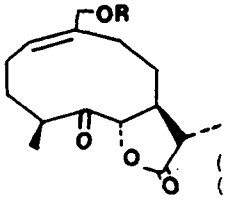
SCHEME II


(9) R=CH2;R'=H
(10) R=α-Me, β-H;R'=H
(11) R=α-Me, β-H;R'=Ac
(12)
(13)
(14)
(15) R=CH2
(16) R=α-Me, β-H
(17)
(18)
(19) R=CH2
(20) R=α-Me, β-H

The transformation of (11) to (8) suggests that the process may take place as shown in Scheme II.The Markownikoff opening of the oxirane ring followed by β-elimination would give (14) which could lead to (15) by a S_N2' process.Alternatively,a hydride shift followed by an intramolecular cyclization would afford the guaiane derivatives[10].



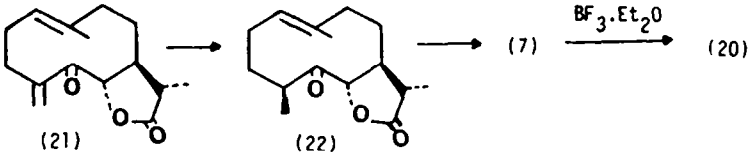
(5) R=H
(6) R=OAc

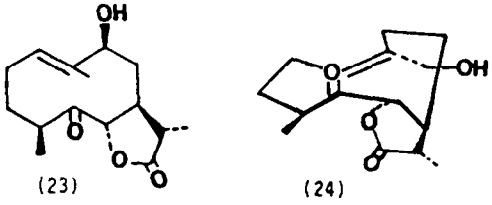


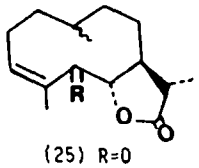
(7) R=H
(8) R=Ac

In order to provide proof for this hypothesis (7) and (8) were synthesized.When (21), prepared by the method of González et al[11] ,was hydrogenated,oxidized as described by Haruna & Ito[12] and then acetylated,it produced (8),identical to the compound obtained from (11). Treatment of the alcohol (7) with $BF_3.Et_2O$ in benzene gave the epimer mixture (20)(Scheme III).

SCHEME III







(25) R=O
(26) R=α-OH,β-H

The trans-(1αH,5βOH) stereochemistry of (20) was stablished by assuming that the cyclization takes place via conformation (24) since Molecular Mechanics calculations[13] show this to be the most stable (18.5 Kcal/mol).The pyridine-induced chemical shift,as compared to the ^{1}H-NMR spectrum in chloroform (Δδ=0.25 ppm) is consonant with the proposed stereochemistry[14].

To conclude,the chemical behaviour of (9) is similar to that described by Doskotch & Wilton for lipipherolide (6)[15] although no trace whatsoever of pseudoguaianolides could be detected.

Our findings do not agree with the biogenetic hypothesis propounded by Herz[5] which may be due to the fact that (9) was not in the required TC conformation.

An X-ray diffraction analysis seems to confirm this idea:Figure 1 is a perspective view of the molecular structure of (9) showing its absolute configuration determined by comparison of the more relevant Bijvoet pairs,and Figure 2 is a stereographic projection of the 10-membered ring of (9).In Figure 2,the (C-15) methyl and the (C-14) hydroxymethyl groups are shown to be "anti" in the context of the median plane of the cyclodecenic ring,with C-14 opposite to H-6.

The data are completely in accordance with those of the X-ray diffraction study of enhydrin bromohydrine carried out by Karth et al[16].

Figure 1

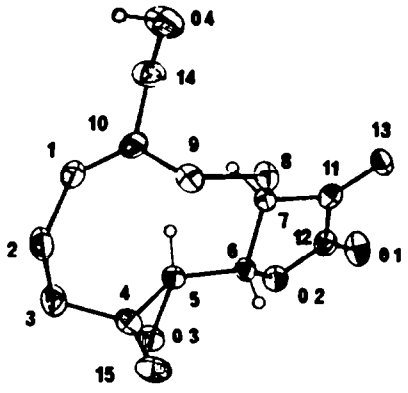
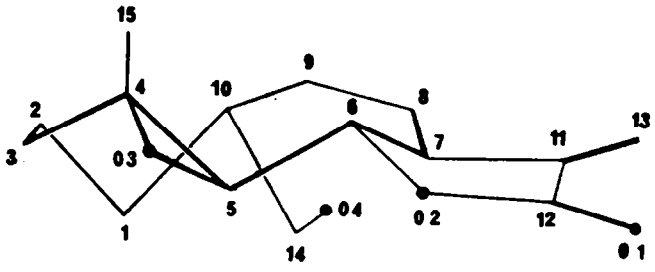


Figure 2



EXPERIMENTAL

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 measured on a VG Micromass ZAB-2F. Unless otherwise stated, column chromatography was carried out using Merck silica gel (0.065-0.2 mm).

Acid treatment of (7), (9), (10) and (11)

a) Freshly-distilled $BF_3.Et_2O$ (0.2 ml) was added to a solution of (9) (100 mg) in dry benzene (5 ml), and the mixture was stirred for 15 minutes, then poured onto water, washed with a saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, concentrated and chromatographed, using 7:3 hexane-EtOAC as eluent. (19) (23 mg),, (15) (traces) and unreacted (9) (58 mg) were obtained. Compound (19), unstable oil: ^{1}H-NMR: δ 9.87, 9.61 (1H, s, H-14); 6.31, 6.26 (1H, d, J=3.5Hz, H-13); 5.60, 5.54 (1H, d, J=3.5Hz, H-13); 4.32, 4.05 (1H, d, J=6.5Hz, H-6); 1.12 (3H, d, J=6.5Hz, H-15); i.r.: ν_{max} ($CHCl_3$) cm^{-1}, 3570 (OH), 1760 (γ-lactone), 1720 (carbonyl).

b) When (10) was subjected to identical treatment, (16) and (20) were obtained in the same proportions as (15) and (19) above. Compound (16), oil: ^{1}H-NMR: δ 5.68 (1H, bs, H-3); 5.04, 4.93 (1H, s, H-14); 4.48 (1H, bs, H-5); 4.39, 4.33 (2H, complex, H-1 and H-6); 1.54 (3H, d, J=1.5Hz, H-15); 1.16 (3H, d, J=7Hz, H-13); ^{13}C-NMR: 72.0 (C-1), 34.4 (C-2), 122.2 (C-3), 131.2 (C-4), 73.4 (C-5), 85.0 (C-6), 42.6 [a] (C-7), 25.7 [b] (C-8), 26.7 [b] (C-9), 150.4 (C-10), 42.9 [a] (C-11), 177.9 (C-12), 13.9 (C-13), 14.2 (C-14), 21.2 (C-15). (The signals marked [a] are interchangeable as are [b]); i.r.: ν_{max} ($CHCl_3$) cm^{-1}, 1770 (γ-lactone); h.r.m.s., m/z 248.1404 ($C_{15}H_{20}O_3$). Compound (20), oil: ^{1}H-NMR: δ 9,85, 9.58 (1H, s, H-14); 4.32, 4.05 (1H, d, J=9.4Hz, H-6); 1.23 (3H, d, J=7Hz, H-13); 1.12 (3H, d, J=6Hz, H-15); ^{1}H-NMR (C_5D_5N): 10.12, 9.64 (1H, s, H-14); 4.54, 4.30 (1H, d, J=10Hz, H-6); 1.30 (3H, d, J=6.5Hz, H-13); 1.24 (3H, d, J=7Hz, H-15); i.r. ν_{max} ($CHCl_3$) cm^{-1}, 3575 (OH), 1760 (γ-lactone), 1720 (carbonyl); h.r.m.s., m/z 266.1515 ($C_{15}H_{22}O_4$), 248.1415 ($C_{15}H_{20}O_3$).

When the solvent used was CH_2Cl_2, only (20) and traces of (16) were obtained.

c) (11) was subjected to identical treatment in benzene and (8) (19%) and unreacted starting material were obtained. Compound (8), oil: ^{1}H-NMR: δ 5.56-5.47 (1H, complex, H-1); 4.52, 4.33 (1H, d, J=12Hz, H-14); 4.10 (1H, d, J=10Hz, H-6); 2.92-2.85 (1H, complex, H-4); 2.05 (3H, s, OAc); 1.27 (3H, d, J=6.5Hz, H-13); 1.13 (3H, d, J=7Hz, H-15); i.r.: ν_{max} ($CHCl_3$) cm^{-1}, 1780 (γ-lactone), 1720 (carbonyl); h.r.m.s., m/z 308.1635 ($C_{17}H_{24}O_5$).

d) The same mixture of (20) and (16) as in b) was obtained when the same conditions were applied to (7).

Preparation of (21)

The procedure described by González et al was followed[11].

Hydrogenation of (21)

(21) (50 mg) dissolved in EtOH was hydrogenated at room temperature and atm. pressure on C-Pd (10%) (10 mg), then filterd through celite, concentrated and chromatographed. With an 8:2 hexane-EtOAc eluent, (22) (40%) and (25) (20%) were obtained. Compound (22), oil: ^{1}H-NMR: δ 5.15 (1H, bs, H-1); 4.67 (1H, d, J=7.5Hz, H-6); 1.64 (3H, s, H-14); 1.28 (3H, d, J=7.5Hz, H-13); 1.20 (3H, d, J=7.5Hz, H-15); i.r.: ν_{max} ($CHCl_3$) cm^{-1}, 1770 (γ-lactone), 1710 (carbonyl); h.r.m.s., m/z 250.1584 ($C_{15}H_{22}O_3$). Compound (25), oil: ^{1}H-NMR: δ 5.25-5.17 (1H, complex, H-3); 4.11 (1H, d, J=10Hz, H-6); 1.60 (3H, s, H-15); 1.23 (3H, d, J=6.5Hz, H-13); 1.14 (3H, d, J=7Hz, H-14); i.r. ν_{max} ($CHCl_3$) cm^{-1}, 1780 (γ-lactone), 1710 (carbonyl); m.s., m/z 250 (M+), 232 (M+-H_2O).

$NaBH_4$ reduction of (25) gave (26), identical to the compound reported by Govindachari et al[17].

Allylic oxidation of (22)

A mixture of SeO_2 (7 mg) and HOO^tBu (0.2 ml) in dry CH_2Cl_2 was stirred under inert atmosphere for 30 minutes. A solution of (22) (28 mg) in dry CH_2Cl_2 (2 ml) was added dropwise and the resulting mixture was stirred for 24 hours and then concentrated at reduced pressure and chromatographed with 3:7 hexane-EtOAc as eluent. (7) (7 mg), (23) (6 mg) and unreacted (22) were obtained. Compound (7), oil: ^{1}H-NMR: δ 5.55-5.47 (1H, complex, H-1); 4.11 (1H, d, J=10Hz, H-6); 4.03 (2H, bs, H-14); 1.24 (3H, d, J=1.5Hz, H-15); 1.12 (3H, d, J=7Hz, H-13); i.r. ν_{max} ($CHCl_3$) cm^{-1}, 3600 (OH), 1780 (γ-lactone), 1705 (carbonyl); h.r.m.s., m/z 266.1512 ($C_{15}H_{22}O_4$); 248.1406 ($C_{15}H_{20}O_3$).

Compound (23), oil: ^{1}H-NMR: δ 5.13-5.09 (1H, bs, H-1); 4.54 (1H, d, J=7.5Hz, H-6); 3.95-3.89 (1H, complex, H-2); 1.65 (3H, s, H-14); 1.26 (3H, d, J=7Hz, H-13); 1.18 (3H, d, J=7Hz, H-15); i.r. ν_{max} ($CHCl_3$) cm^{-1}, 3560 (OH), 1760 (γ-lactone), 1680 (carbonyl); h.r.m.s., m/z 266.1508 ($C_{15}H_{22}O_4$); 248.1393 ($C_{15}H_{20}O_3$).

Acetylation of (7)

(7) (17 mg) was acetylated in the usual way and yielded (8) (16 mg).

X-Ray structure determination of (9)

$C_{15}H_{20}O_4$ crystallizes in the orthorhombic space group $P2_12_12_1$ with Z=4,a=8.292(1),b=12.081(3), c=13.990(1) A,V=1401.54 A^3.The molecular weight is 264.32 and the calculated density,1.25g/cm^3. The intensities of 1136 independent reflections up to θ=50° were collected with θ:w scan using a SIEMENS AED 4 diffractometer with graphite monochromated CuKα radiation (λ=1.54178 A); crystal size 0.5x0.3x0.9 mm.Two standard reflections monitored every hour showed no intensity decay.No absorption correction was applied (μ=6.98 cm^{-1}).After Lorentz and polarization corrections,1110 reflections were considered as observed according to the criterion $I>3\sigma(I)$. The scattering factors used[18] and anomalous dispersion corrections for C and O were those for neutral atoms.The structure was solved by MULTAN[19] and refined by full-matrix least-squares.

Several cycles of anisotropic refinement for non-hydrogen atoms (H atoms as fixed isotropic contributors) gave a final discrepancy index of R=0.074.The absolute configuration of (9) was confirmed by comparing the 20 more relevant Bijvoet pairs[20] with $Fo>5\sigma(Fo)$ and $\Delta Fc>0.08$ which are in the ranges $10<Fo<50$ and $.2 \sin\theta/\lambda<.5$,showing an averaged Bijvoet difference of 0.237 for the right enantiomer (vs 0.342 for the wrong one) and an averaged Bijvoet ratio of 1.011 (vs 1.017)[21].

ACKNOWLEDGEMENTS

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