Lanuginolide and Dihydroparthenolide, Two New Sesquiterpenoid Lactones from *Michelia lanuginosa*. The Structure, Absolute Configuration, and a Novel Rearrangement of Lanuginolide†

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Summary Chemical and spectral evidence for the 8α-acetoxy-dihydroparthenolide structure of a new sesquiterpene lactone, lanuginolide, isolated from the trunk bark of *Michelia lanuginosa* Wall along with dihydroparthenolide (first natural occurrence) are reported.

WE report the isolation and structure elucidation of two new germacranolides from the trunk bark of *Michelia lanuginosa* Wall.

The minor constituent,‡ $C_{15}H_{22}O_3$ (M^+ 250), m.p. 138°, $[\alpha]_D - 68{\cdot}5°$, was identical (t.l.c., i.r., and ^1H n.m.r., mixed m.p.) with dihydroparthenolide (Ia).[1] This is the first time that dihydroparthenolide has been shown to occur naturally.

The major sesquiterpene lactone, designated lanuginolide (Ib), $C_{17}H_{24}O_5$ (M^+ 308, 3%), m.p. 185°, $[\alpha]_D - 57°$, had no selective absorption above 210 nm; ν_{max} 1770, 1175 (γ-lactone), 1732, 1242 (acetate), 890, 800 (epoxy-ring), 865, and 825 cm^{-1} (·CH:C<); ^1H n.m.r. (δ) 1·28 (3H, s, epoxy CH_3), 1·41 (3H, d, *J* 6 Hz, sec. CH_3), 1·80 (3H, s, vinyl CH_3), 2·09 (3H, s, $OCOCH_3$), 2·63 (1H, d, *J* 9 Hz, epoxy-proton), 3·94 (1H, t, *J* 9 Hz, lactonic methine proton at C-6), 4·85 (1H, dd, *J* 5·5 and 11 Hz, *C*H–OAc), and 5·25 p.p.m. (1H, m, vinyl *H* at C-1).

Perbenzoic acid[2] oxidation of (Ib) gave the corresponding epoxide (55%), $C_{17}H_{24}O_6$ (M^+ 324), m.p. 214°, $[\alpha]_D - 78°$. On treatment with BF_3 or dry HCl gas in dry ether, (Ib) underwent transannular cyclisation to yield a tertiary alcohol (II) (40%) $C_{17}H_{24}O_5$ (M^+ 308), m.p. 165°, $[\alpha]_D - 18°$.

Mild alkaline hydrolysis of (Ib) followed by acetylation of

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† Major part of the work was presented at the Convention of Chemists, I.I.T., Kharagpur, West Bengal, India, December 27—31, 1969, *Abstracts*, paper No. 69-0-30, p. 73.

‡ Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds; i.r. spectra were recorded in KBr; ^1H n.m.r. spectra were taken in Varian A-60D in $CDCl_3$ with internal $SiMe_4$ as standard; optical rotations were measured in $CHCl_3$ at 25°; mass spectra were determined with an AEI MS-9 spectrometer using a direct insertion probe and operating at 70 ev.

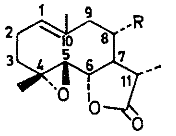
the resulting colourless thick oil and chromatography gave mainly (III) (30%), $C_{17}H_{24}O_5$ (M^+ 308), m.p. 154°, $[\alpha]_D$ +38°.

Lanuginolide (Ib) is quite resistant to hydrogenation. No hydrogen was taken up even after stirring the ethanolic solution for 4 h in the presence of PtO_2. Prolonged (12 h) exposure of (Ib) in ethanol to hydrogen in the presence of an equal amount of PtO_2 brought about an unusual deacetylation to yield [along with a small amount of (Ib) (5%)] the rearranged dihydro-lactone (IVa) (60%), $C_{15}H_{24}O_4$ (M^+ 268), m.p. 114°, $[\alpha]_D$ +17°. Hydrogenation of (III) in presence of PtO_2 afforded (IVb), thus confirming the structure and stereochemistry of (IVa) and (IVb). Thus, lanuginolide is (Ib) and the oxygen functions at C-6 and C-8 are *cis*.

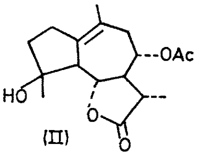
The formation of the more stable lactone involving C-8-OH (less rigid and less strained since the saturated C-6 separates two strained rings, *viz*., the epoxy and the lactone) seems to be the driving force for the novel rearrangement of (Ib) to (IVa).

The 4-CH_3, 5-H, 6-H, and 8-H protons in (Ib) are significantly shielded (by 0·12—0·18 p.p.m.) relative to those of its epoxide, indicating that these protons lie into the shielding cone associated with the π electrons of the double bond (*i.e.* above its plane) in the preferred conformation of the 10-membered ring. This is in agreement with the recently reported conformation of the medium ring of dihydrotamaulipin-A-acetate (V) determined with the aid of nuclear Overhauser effects.[3] Compound (III) shows shielding of the 4-CH_3, 5-H, and 8-H protons (by 0·21, 0·24, and 0·10 p.p.m., respectively) relative to (IVb), suggesting that in the rearranged lactone these protons and not 6-H lie over the plane of the double bond.

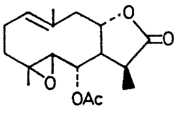
The absence of the more stable lactone (III) in this plant suggests that oxygenation at C-8 must have followed the lactonisation step in the plant cells. Costunolide[4] and parthenolide[1] may thus be regarded as the most probable biogenetic precursors of lanuginolide. The co-occurrence of dihydroparthenolide and lanuginolide also provides circumstantial evidence for this postulate. Furthermore, the close similarity of the ^1H n.m.r. signals of lanuginolide and dihydroparthenolide indicates that they have the same relative stereochemistry; by analogy with dihydroparthenolide (Ia),[5] the absolute configuration of the former at C-6 (and hence at C-8), C-7, and C-11 may be represented as shown (Ib). Lanuginolide should have the preferred conformation (VI), which is consistent with n.m.r. results and with the conformation in (V).[3] We suggest that the epoxide ring of unknown stereochemistry in parthenolide systems is 4α,5β-oriented as shown (I).



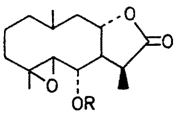
(I) a; R=H
b; R=OAc



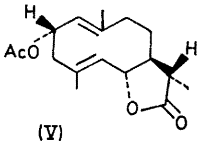
(II)



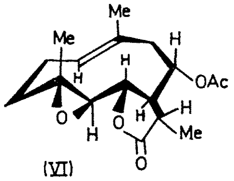
(III)



(IV) a; R=H
b; R=Ac



(V)



(VI)

The mass spectral fragmentation patterns of lanuginolide and all its derivatives are in accord with their assigned structures.

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