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CALLITRIN, CALLITRISIN, DIHYDROCALLITRISIN, COLUMELLARIN AND DIHYDROCOLUMELLARIN, NEW SESQUITERPENE LACTONES FROM THE HEARTWOOD OF *CALLITRIS COLUMELLARIS*.

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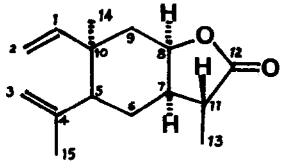
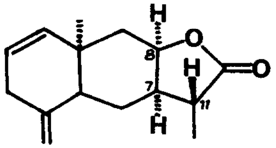
Five new sesquiterpene lactones (1,2,4,5 and 6) have been isolated from the hexane extract of the heartwood of *Callitris columellaris*, F. Muell. (syn. *C. glauca*). In addition, a sixth lactone (3), previously reported[1] as a synthetic compound, has been established as a natural product from the same source. Callitrin (1), callitrisin (2) and the germacranolide (3) were extracted into aqueous silver nitrate solution[2] from the neutral hexane fraction. Treatment of the silver nitrate solution with excess ammonia liberated an oil from which the crystalline lactones (1), (2) and (3) were isolated by chromatography over alumina containing *ca* 10% silver nitrate. Dihydrocallitrisin (4) and the guaianolides dihydrocolumellarin (5) and columellarin (6) were isolated by chromatography of the silver nitrate insoluble portion of the extract using "Merck" prepacked silica gel columns.



(1)



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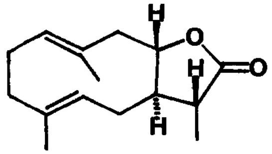

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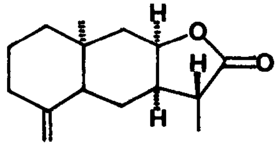

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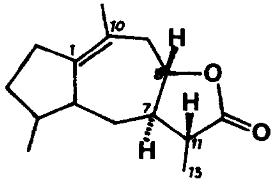
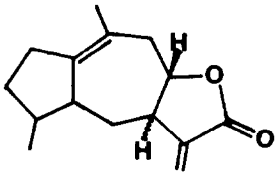


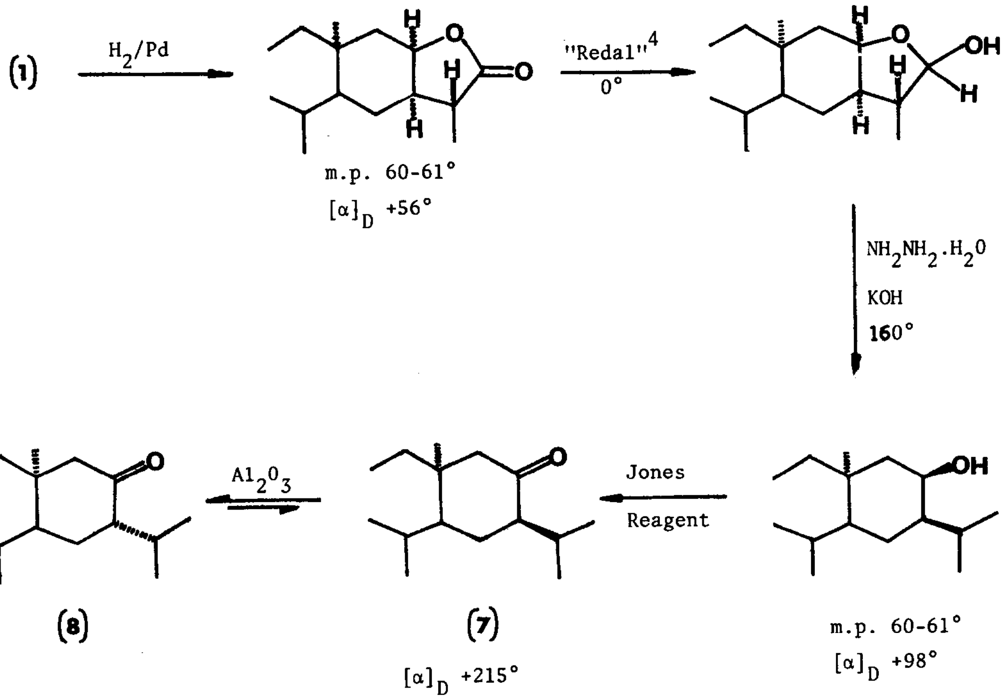
(5)



(6)

Callitrin (1), $C_{15}H_{22}O_2$, m.p. 82-83°, $[\alpha]_D$ +225°, showed a γ-lactone group (1780 cm^{-1}) and two double bonds (1645, 1618, 1005, 907, 890 cm^{-1}, five vinylic n.m.r. protons), a quaternary methyl group (δ 1.02), a methyl on a double bond (δ 1.69) and a doublet methyl (δ 1.15). An elemene-type skeleton was indicated, and a six-line one-proton system at δ 4.47 (*J* 6.5, 6.5 and

11 Hz) due to the proton geminal to the lactone ether oxygen showed that the lactone ring was *cis*-fused at C7/C8, with the indicated stereochemistry. The orientation of the C11 methyl group followed from the $J_{7,11}$ value of 13 Hz, determined by decoupling experiments on Eu(fod)$_3$-doped spectra. A negative C.D. maximum at 215 nm (Δε -1.72) indicated[3] the absolute configuration. The carbon skeleton with absolute configuration was confirmed by the transformations shown in Fig. 1.



m.p. 60-61°
$[\alpha]_D$ +56°

m.p. 60-61°
$[\alpha]_D$ +98°

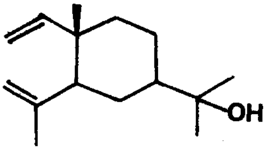
$[\alpha]_D$ +215°

Fig. 1.

Epimerisation of ketone (7) over alumina[5] yielded an equilibrium mixture of (7) and (8) in the ratio 1:3, in agreement with equilibrium ratios reported for 2-isopropylcyclohexanones.[6] Ketone (7), with an axial isopropyl group at C7, showed the predicted strong positive Cotton Effect, and the o.r.d. curve of the equilibrium mixture agreed well with that calculated for a 1:3 mixture from the values for (7) and the known enantiomer of (8), which was prepared[7] from (-)elemol (9) for comparison.

Callitrisin (2), $C_{15}H_{20}O_2$, m.p. 163.5-164.5° $[\alpha]_D$ -41°, was also a γ-lactone (1760 cm^{-1}) containing two double bonds (1650, 895, 731, 683 cm^{-1}, four vinylic protons) separated by a single methylene group (broad AB system at δ 2.88, J_{AB} -19 Hz), together with two methyl groups (δ 0.84, singlet, and δ 1.21, doublet). The eudesmane structure (2) was indicated, with the lactone ring arranged as in callitrin (1), since H8 and H11 exhibited the same coupling constants as in (1). N.m.r. assignments were confirmed by decoupling experiments (on Eu(fod)$_3$-doped samples where necessary). The absolute configuration followed from the negative C.D. maximum for the lactone chromophore at 222 nm (Δε -1.27). Catalytic hydrogenation yielded a mixture of two tetrahydro derivatives, with the major isomer assigned structure (10) since the C10 and C4 methyl groups both resonated at lower field[8] than the corresponding groups in the minor isomer, and because hydrogenation should occur more readily at the face of the molecule opposite to the axial C10 methyl group.

The germacranolide (3), $C_{15}H_{22}O_2$, m.p. 132-133° (lit.[1] 132.5-133), $[\alpha]_D$ +139° (lit.[1] +135°), showed a broad n.m.r. spectrum characteristic of this class of compound. It was identified through the two transformation products (11) and (12). Multiplets at *ca* 3.9-4.0 ppm in the n.m.r. spectra of both of the Cope rearrangement product (11) and the acid-cyclisation product (12) exhibited couplings of about 10, 12 and 4 Hz, indicating in each case a *trans*-fused lactone ring involving C8. The identities of (3) and (11) were confirmed by spectral comparison with authentic material.[9]



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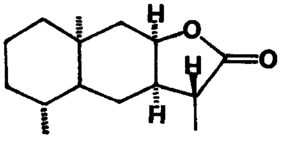
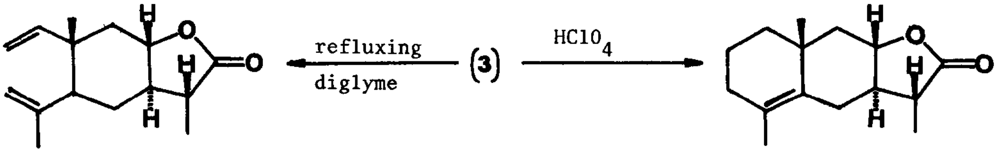


(10)

m.p. 109-110°

$[\alpha]_D$ -33°

Dihydrocallitrisin (4), $C_{15}H_{22}O_2$, m.p. 127-128° $[\alpha]_D$ -39°, showed the familiar H8 coupling pattern of (1) and (2), together with a quaternary methyl group (δ 0.76) and an exocyclic double bond (δ 4.51, 4.78; 896 cm^{-1}). Hydrogenation converted compound (4) into a mixture of two dihydro derivatives giving as the major isomer compound (10) (g.l.c., mixed m.p., i.r., n.m.r. and o.r.d.).



(11)

(12)

m.p. 69-70°

$[\alpha]_D$ +164°

The guaianolide dihydrocollumellarin (5), $C_{15}H_{22}O_2$, m.p. 77-77.5, $[\alpha]_D$ +18.9°, was a γ-lactone (1775 cm^{-1}), showed no quaternary methyl or vinyl protons in the n.m.r. spectrum, but gave two doublet methyls and a methyl on a tetrasubstituted double bond. The proton geminal to the lactone oxygen showed three couplings, confirming ring-closure to C8, as in all compounds in the series. Catalytic dehydrogenation produced guaiazulene (albeit in low yield) to establish the carbon skeleton. The double bond was located in the 1,10 position when ozonolysis yielded a product containing a cyclopentanone unit (1740 cm^{-1}). The $J_{7,8}$ value of 9.5 Hz suggests a *trans* lactone fusion,[10] while a *trans* coplanar relationship of H7 and H11 is indicated by a $J_{7,11}$ value of 13 Hz. The rather small splitting of the C4 methyl (6 Hz) suggests that it is in a pseudo-equatorial position.[11]

Columellarin (6), $C_{15}H_{20}O_2$, m.p. 43-44° $[\alpha]_D$ -44.7°, exhibited a pair of low-field doublets in the n.m.r. (δ 5.42 and 6.11) characteristic of an α-methylene lactone. The spectrum otherwise resembled that of dihydrocolumellarin (5), and hydrogenation of (6) produced (5) as the major product. The coupling constants of the two C13 vinylic protons in (6) (each 3.2 Hz) adds weight to the 7,8-*trans* assignment for both (5) and (6).[10]

Current studies using lanthanide-induced shifts on compounds (5) and (6) are expected to further clarify their stereochemistries.

References and Notes

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