Structures and Stereochemistry of Melicophyllone A and Hypocholesterolemic Melicophyllone B, Novel Sesquiterpene Lactones from *Melicope triphylla*

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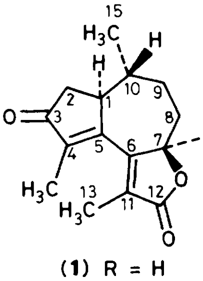
Melicophyllones A and B, two novel skeletal sesquiterpene lactones, have been isolated from *Melicope triphylla* and their structures have been established from spectral data in conjunction with single-crystal *X*-ray analyses; melicophyllone B demonstrated significant hypocholesterolemic activity.

In continuation of our studies on the constituents of Rutaceous plants in Taiwan,[1] we report the isolation and structural characterization of two novel skeletal sesquiterpene lactones,[†] melicophyllones A (**1**) and B (**2**),[‡] from the root bark of Formosan *Melicope triphylla* (Lam.) Merr.

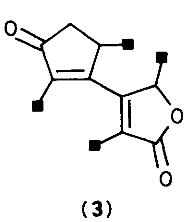
Melicophyllone A (**1**)[§] {colourless plates, $C_{15}H_{18}O_3$, *m/z* 246.1264 (M^+), m.p. 106—107 °C, $[\alpha]_D^{25}$ −371° (*c* 0.064 in $CHCl_3$), $\lambda_{max.}$ (MeOH) (log ε) 212 (1.09) and 288 nm (3.19)} showed i.r. bands at 1770 (α,β-unsaturated γ-lactone) and 1690 cm^{-1} (α,β-unsaturated cyclopentenone). The partial structure (**3**) was suggested by the ^{13}C n.m.r. spectrum [δ 206.4(s), 173.4(s), 159.4(s), 156.0(s), 141.1(s), 81.9(d), 47.9(d), and 41.4(t)]. The ^1H n.m.r. spectrum revealed two pairs of long-range coupled [C(4)–Me/H(1); C(11)–Me/H(7)] signals. From these data, structure (**1**), without stereochemistry, was assigned to melicophyllone A.

Melicophyllone B (**2**)[§] {colourless needles, $C_{15}H_{18}O_4$, *m/z* 262.1203 (M^+), m.p. 171—172 °C, $[\alpha]_D^{25}$ −38° (*c* 0.852 in $CHCl_3$)} has similar u.v. and i.r. spectral data to (**1**). The molecular ion peak difference of 16 a.m.u. between (**1**) and (**2**) pointed to the presence of a hydroxy group in (**2**), a fact which was reinforced by the occurrence of an i.r. band at 3300 cm^{-1}. A sharp singlet for the methyl group at C(11) and the lack of an H(7) resonance in the ^1H n.m.r. spectrum of (**2**), as well as the downfield ^{13}C n.m.r. spectral shifts and multiplicity differences for C(7) [δ 107.5(s) in (**2**) *vs.* 81.9(d) in (**1**)] indicated that the hydroxy group in (**2**) is at C(7). The ^1H and ^{13}C n.m.r. spectra of (**2**) both contain pairs of signals for each resonance, indicating the co-existence of C(7)-hydroxy α- and β-epimers.[¶]

Single-crystal *X*-ray analyses[**] established the complete structures and relative stereochemistry[††] of (**1**) and (**2**). The



(1) R = H
(2) R = OH



(3)

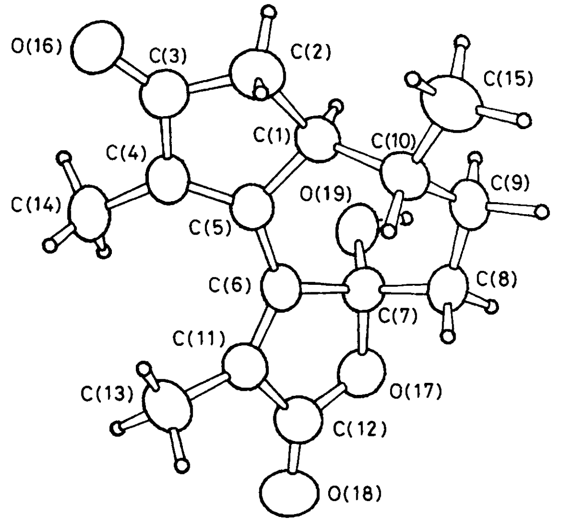


Figure 1. Structure and solid-state conformation of melicophyllone B (**2**); small circles represent hydrogen atoms.

[†] The location of an isopropylene (or isopropyl) moiety at C(6) rather than at C(7) in naturally occurring sesquiterpenes is rare and has been previously encountered only in zierone.[2] Moreover, structures (**1**) and (**2**) represent the first examples in which the lactonic atom is located at C(7) instead of C(6) or C(8).

[‡] Melicophyllone B demonstrated significant (≥20% at 100 mg per kg) hypocholesterolemic activity (33% at 100 mg per kg) in mice.

[§] I.r. and ^1H and ^{13}C n.m.r. spectral data for (**1**) and (**2**) are consistent with the assigned structures.

[¶] Separation of these two epimers is being attempted.

[**] *Crystal data:* Melicophyllone A (**1**), $C_{15}H_{18}O_3$, M = 246.31, orthorhombic, space group $P2_12_12_1$, a = 7.274(2), b = 28.975(7), c = 6.089(2) Å, U = 1283.3 Å^3, Z = 4, D_c = 1.275 g cm^{-3}, μ(Cu-K_α radiation, λ = 1.5418 Å) = 6.7 cm^{-1}. Melicophyllone B (**2**), $C_{15}H_{18}O_4$, M = 262.31, orthorhombic, space group $P2_12_12_1$, a = 8.026(2), b = 27.657(4), c = 6.093(1) Å, U = 1352.5 Å^3, Z = 4, D = 1.288 g cm^{-3}, μ(Cu-K_α) = 7.2 cm^{-1}. One octant of intensity data from each crystal was recorded with an Enraf-Nonius CAD-4 diffractometer (Cu-K_α radiation, incident-beam graphite monochromator; ω–2θ scans, θ_{max} = 67°). Structure analyses were based on 1206 (**1**) and 1299 (**2**) reflections with $I > 3.0\sigma(I)$ from totals of 1378 and 1435 independent measurements, respectively. Full-matrix least-squares refinement of atomic parameters (anisotropic C, O; isotropic H) converge at R = 0.045 (R_w = 0.063) for (**1**) and R = 0.050 (R_w = 0.061) for (**2**). Atomic co-ordinates, thermal parameters, and bond lengths and angles for (**1**) and (**2**) have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

[††] Attempts to establish the absolute configurations of (**1**) and (**2**) by use of the anomalous scattering of oxygen were not definitive.

crystal structure of (**2**) was solved by direct methods (MULTAN11/82) and that of (**1**) followed from its isomorphous nature. A view of the solid-state conformation of (**2**) is provided in Figure 1. Molecules of (**2**) related by unit translation along *a* in the crystal are associated by an intermolecular O–H · · · O hydrogen bond [O(19) · · · O(16) 2.745(2) Å]. Endocyclic torsion angles in (**1**) are similar to those in (**2**) ($\Delta_{max} = 2.0°$, $\Delta_{mean} = 0.8°$); thus the absence of a corresponding hydrogen bond in crystals of (**1**) has little effect either on the molecular packing arrangement or on the solid-state conformation. In both compounds, the endocyclic torsion angles in the cyclopentenone and cycloheptane rings are related by approximate C_2 symmetry axes passing respectively through C(4) and C(5). The γ-lactone ring in (**1**) has a fairly flat envelope form with C(7) as the out-of-plane atom ($\Delta = 0.140$ Å), whereas in (**2**) small changes in the endocyclic torsion angles about the C(6)–C(11) and C(11)–C(12) bonds result in a conformation which lies closer to a half-chair form with its C_2 axis passing through C(11).

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