

β -Triketones from Myrtaceae: Isoleptospermone from *Leptospermum scoparium* and Papuanone from *Corymbia dallachiana*

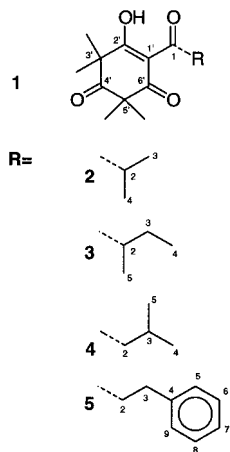
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Naturally occurring β -triketones, isoleptospermone [**3**, 5-hydroxy-4-(2-methyl-1-oxopentyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione] from *Leptospermum scoparium*] and papuanone [**6**, 5-hydroxy-4-(1-oxohexyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione] from *Corymbia dallachiana*], have been synthesized. Full spectral data are reported for the first time. The ¹³C NMR spectra of **3**, **6**, and the other triketones flavesone (**2**), leptospermone (**4**), and grandiflorone (**5**) found in Myrtaceae plants are fully assigned.

β -Triketones (**1**), possessing four methyl substituents on a six-membered ring and an acyl side-chain, are rare natural product structures. These are found mainly in trees and shrubs of the Myrtaceae, particularly the genera *Eucalyptus* and *Leptospermum*.^{1,2} We are interested in these compounds because flavesone (**2**), isoleptospermone (**3**), and leptospermone (**4**) are the main antimicrobial components in the essential oil of one chemotype of manuka, *L. scoparium* J. R. et G. Forst., growing in the East Cape region of New Zealand.³ Grandiflorone (**5**) has also been reported in trace amounts in the essential oil of manuka.⁴ Compounds **2**, **4**, and **5** have been fully characterized, and ¹H NMR, UV, and IR spectra show that enolic tautomers predominate.^{5,6}



Compound **3**, originally named adleptospermone, was first reported as a synthetic reaction product (without spectroscopic data) and was proposed to occur with flavesone and leptospermone, by analogy with humulone and related compounds from hops.⁷ However, some confusion remains over the name adleptospermone, as *Chemical Abstracts* gives compound **7** with a *tert*-butyl side chain this name. Compound **3**, subsequently named isoleptospermone, has since been reported in the essential oil of *E. grandis*,⁸ a species that also contains structurally related plant

growth regulators. We tentatively identified **3** in the essential oil of *L. scoparium*, from GC–MS data,³ but were unable to fully characterize it due to difficulty in separating it from its co-occurring isomer leptospermone (**4**). We now report the synthesis and full characterization of **3**, and confirm its co-occurrence with flavesone (**2**) and leptospermone (**4**) in *L. scoparium* essential oil. Furthermore, the ¹³C NMR spectra of β -triketones **2**, **4**, and **5** are fully assigned for the first time.

We also report the isolation, characterization, and synthesis of a new β -triketone, papuanone (**6**), from *Corymbia dallachiana* (Benth.) K. D. Hill and L. A. S. Johnson. Papuanone (**6**) was originally noted as a constituent of the essential oil of *Eucalyptus papuana* F. Muell.,⁹ with a subsequent paper reporting its mass spectrum.¹⁰ However, taxonomic appraisal of the plant specimen has led to a reclassification and the new name of *Corymbia dallachiana*.¹¹

β -Triketones of this structural type can be synthesized by C-methylation of an acyl-phloroglucinol.⁵ Phloroglucinol will undergo a Friedel–Crafts acylation with a carboxylic acid in the presence of aluminum chloride and phosphorus oxychloride, forming an acid chloride in situ.¹² We found, however, that the reported reaction conditions (either at room temperature or 100 °C) gave predominantly tri- and di-acyl phloroglucinols, with little or no mono-acyl phloroglucinol. Undertaking the reaction at lower temperatures (<6 °C) favored the formation of the mono-acyl product.

Spectral data of the synthetic β -triketones **2**, **4**, and **5** matched those of the natural products (see Experimental Section). The signals for isoleptospermone (**3**), along with those for flavesone (**2**) and leptospermone (**4**), were clearly visible in both the ¹H and ¹³C NMR spectra of a triketone-rich fraction, from an *L. scoparium* essential oil.³ It should be noted that the synthetic sample of isoleptospermone was a racemate, as the 2-methyl butanoic acid used in the synthesis was racemic. Attempts are underway to resolve the enantiomers, using chiral GC, to determine the absolute stereochemistry of the natural product as it exists in the plant; however, it may prove difficult to isolate isoleptospermone in an enantio-pure form, as extraction conditions may cause racemization.

Papuanone (**6**) was found at high levels (26–38%) in steam-distilled oils (obtained in 0.3–0.7% yield based on dry leaves) from *C. dallachiana* foliage. The assigned structure was confirmed by the identical spectra of the

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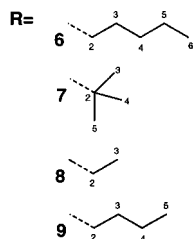
Table 1. Triketone ^{13}C NMR Data in CDCl_3

position	flavesone (2)	isoleptospermone (3)	leptospermone (4)	grandiflorone (5) ^a	papuanone (6)
1'	108.2	109.0	109.5	109.3	109.1
2'	199.3	199.6	199.5	198.7	199.1
3'	52.3	52.6	52.4	52.0	52.1
3'-CH ₃ (× 2)	24.3	24.6 and 24.2	24.3	24.5	24.4
4'	209.9	209.9	210.0	209.9	210.1
5'	57.0	57.0	56.9	56.9	56.9
5'-CH ₃ (× 2)	23.9	23.8 and 23.6	23.9	23.9	23.9
6'	196.8	197.1	196.9	196.7	196.8
1	208.6	207.8	203.6	203.6	204.8
2	35.2	41.5	47.2	41.0	39.2
3	19.1	26.9	26.1	31.0	24.8
4	19.1	11.9	22.7	140.6	31.5
5, (9)		16.9	22.7	128.5	22.5
6, (8)				128.5	14.0
7				126.3	

^a Assigned by HMQC/HMBC.

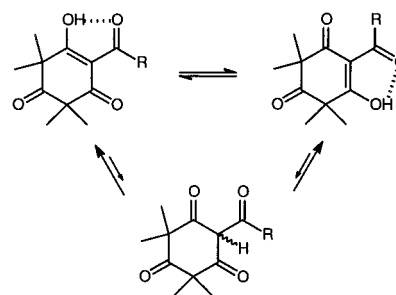
synthetic material. There appear to be chemotypes within *C. dallachiana*. So far papuanone (**6**) has been found only in *C. dallachiana* from the site at Mareeba (see Experimental Section). Collections from other regions in Northern Queensland gave either triketone-free oils in low yield or no oil at all.

The ^1H NMR spectra (CDCl_3) of the β -triketones **3** and **6** showed that enol tautomers predominated (Figure 1), inasmuch as an OH signal was present at a chemical shift of around δ 18.3, indicative of a very strong intramolecular hydrogen bond.¹³ Exchange between the enol tautomers (Figure 1) was slow in CDCl_3 , because distinct ^{13}C NMR signals were seen for the pairs of atoms: C-2' and C-6' and C-3' and C-5' (Table 1). Full assignments of the β -triketone NMR spectra were based on single-bond ^1H - ^{13}C correlation (HMQC) and multiple bond ^1H - ^{13}C correlation (HMBC) NMR spectra run on a sample of grandiflorone (**5**). Key correlations were from the OH proton to carbons C-1', C-2', and C-3' and a four-bond coupling to C-1.¹⁴ Our results are in agreement with those of Ayras et al.¹³ on the ^{13}C NMR spectra of dimethyl filicinic acid derivatives **8** and **9**, with the signal at lowest field being that due to the C-4' carbon. HMBC correlations further allowed us to assign the ring methyl signals. One signal was seen for the two methyl signals at C-3' and one signal for the two methyl signals at C-5' in all the triketones except for **3**, in which a chiral center at C-2 led to magnetic nonequivalence of the geminal methyls (Table 1).



Experimental Section

General Experimental Procedures. All solvents were distilled before use and were removed by rotary evaporation at temperatures up to 45 °C. Davisil, 35–70 μm , 150 Å, was used for Si gel flash chromatography. TLC was carried out using Merck DC-plastikfolien Kieselgel 60 F₂₅₄, first visualized with a UV lamp, and then by dipping in a vanillin solution (1% vanillin, 1% H₂SO₄ in EtOH), and heating. MS, UV, and IR spectra were recorded on Kratos MS-80, Shimadzu UV 240, and Perkin-Elmer 1600 FTIR instruments, respectively. NMR spectra, of CDCl_3 solutions at 25 °C, were recorded at 300 MHz

**Figure 1.** β -Triketone tautomers.

for ^1H and 75 MHz for ^{13}C on a Varian VXR-300 spectrometer. NMR spectra were referenced to TMS at 0.0 ppm, for ^1H experiments; and CDCl_3 at 77.0 ppm for ^{13}C experiments.

Plant Material. Samples of *Corymbia dallachiana* (Benth.) K. D. Hill and L. A. S. Johnson were collected from the property of J. R. Clarkson (Mareeba, Queensland, Australia) in November 1991. A voucher specimen (J. R. Clarkson 9169) was lodged at the Queensland Herbarium (BRI).

Isolation of Papuanone. The leaf essential oil was obtained by steam distillation with cohobation as outlined by Boland et al.⁸ The oil (1.0 g) was dissolved in pentane (20 mL) and extracted with aqueous NaOH (2N, 2 × 20 mL). The aqueous solution was acidified with HCl (2N) and the resultant mixture extracted with Et₂O (3 × 10 mL). The ether solution was dried (Na₂SO₄) and the solvent evaporated to yield the crude papuanone as an oil (0.15 g).

Syntheses of Acyl-phloroglucinols. Dry phloroglucinol (10–12 mM) was added to a stirred solution of phosphorus oxychloride (15 mL) plus anhydrous AlCl₃ (4 g) and stirred under N₂. The carboxylic acid (10 mM, 2-methyl propanoic, 2-methyl butanoic, 3-methyl butanoic, 3-phenyl propanoic, or hexanoic acid) was added and the reaction stirred, under N₂, at 0 °C for 8 h, then in a cold room (ca. 6 °C) for a further 40 h. The reaction mixture was poured onto crushed ice (ca. 100 g) and extracted with Et₂O (2 × 100 mL). The ether extract was washed with saturated NaHCO₃ (500 mL) and then dried over anhydrous MgSO₄. The Et₂O was removed using a rotary evaporator to yield an oily residue. This was applied to a Si gel column (40 g) that had been preequilibrated with cyclohexane–EtOAc (5:1). Fractions containing mostly di- and tri-acyl products eluted first, followed by the desired mono-acylated product in yields between 40 and 54%. The mono-acylated phloroglucinols were all known compounds (registry numbers): pre-**2** [2-methyl-1-(2,4,6-trihydroxyphenyl)-1-propanone, 35458-21-0], pre-**3** [2-methyl-1-(2,4,6-trihydroxyphenyl)-1-butanone, 125074-06-8, 111556-27-5, 98498-56-7 or 39652-80-7], pre-**4** [3-methyl-1-(2,4,6-trihydroxyphenyl)-1-butanone, 26103-97-9], pre-**5** [3-phenyl-1-(2,4,6-trihydroxyphenyl)-1-propanone, 1088-08-0], pre-**6** [1-(2,4,6-trihydroxyphenyl)-1-hexanone, 5665-89-4].

Syntheses of β -Triketones. Sodium methoxide was prepared by dissolving 0.3 g sodium in 5 mL MeOH. MeI (3 mL) was added to the NaOMe solution followed by the addition of mono-acyl phloroglucinol (1.5–2.5 mM) under N_2 . The reaction mixture was heated under reflux for 3 h. The solvent was evaporated under vacuum and the extract acidified with 1M HCl (50 mL) and extracted with Et_2O (3×50 mL). The ether phase was then extracted with 5% Na_2CO_3 (200 mL). The Na_2CO_3 extract was acidified with concentrated HCl, extracted with Et_2O (2×200 mL) and dried over anhydrous $MgSO_4$ to yield the triketone (yields between 70 and 85%). Final purification was achieved by high-vacuum bulb-to-bulb distillation (1 mmHg, 150 °C). Spectral data for flavesone⁵ [2, 5-hydroxy-4-(2-methyl-1-oxobutyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione, RN 22595-45-5], leptospermone⁵ [4, 5-hydroxy-4-(3-methyl-1-oxobutyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione, RN 567-75-9], and grandiflorone⁶ [5, 5-hydroxy-4-(1-oxo-3-phenylpropyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione, RN 50861-53-5 or 10499-26-0] matched the reported literature values.

Isoleptospermone [3, 5-hydroxy-4-(2-methyl-1-oxobutyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione, RN 7375-66-8] was obtained as a pale yellow oil (yield 70%): found C 67.35% H 8.19%, calcd for $C_{15}H_{22}O_4$, C 67.64% H 8.33%. Si gel TLC R_f 0.56 (9:1 hexane–EtOAc, UV/vis); UV (MeOH) λ_{max} (log ϵ) 279 (4.04), 238 (3.83) nm; IR (CHCl₃, film) ν_{max} 2978, 2931, 2872, 1719, 1672, 1549, 1467, 1425, 1378, 1308, 1232, 1044, 961, 873, 850, 767 cm^{-1} ; EIMS 70 eV 266 [M]⁺ (100), 251 (48), 233 (19), 209 (34), 196 (75), 178 (32), 163 (20), 140 (23), 113 (22), 96 (54), 81 (21), 70 (35), 57 (79), 43 (48); ¹H NMR δ 18.46 (OH, s, 2'-OH), 3.62 (H, sextet, $J = 7$ Hz, H-2), 1.75 (H, m, $W_{1/2} = 2.4$ Hz, $J = 7$ Hz, H-3), 1.43 (H, m (hidden¹⁵), H-3), 1.45 (3H, s, 3'-CH₃), 1.44 (3H, s, 3'-CH₃), 1.37 (3H, s, 5'-CH₃), 1.36 (3H, s, 5'-CH₃), 1.18 (3H, d, $J = 7$ Hz, H-5), 0.92 (3H, t, $J = 7$ Hz, H-4); ¹³C NMR in Table 1.

Papuanone [6, 5-hydroxy-4-(1-oxohexyl)-2,2,6,6-tetramethyl-4-cyclohexene-1,3-dione] was obtained as a pale yellow oil (yield 70%): found C 68.73% H 8.73% calcd for $C_{16}H_{24}O_4$, C 68.55% H 8.63%. Si gel TLC R_f 0.46 (9:1 hexane–EtOAc, UV/vis); UV (MeOH) λ_{max} (log ϵ) 282 (3.99), 238 (3.72) nm; IR (CHCl₃, film) ν_{max} 2942, 2872, 1713, 1666, 1596, 1555, 1472, 1420, 1378, 1308, 1226, 1161, 1049, 961, 861, 767 cm^{-1} ; EIMS

70 eV 280 [M]⁺ (92), 265 (20), 237 (52), 224 (30), 210 (100), 196 (14), 167 (20), 154 (30), 149 (29), 139 (20), 126 (21), 113 (28), 99 (39), 96 (85), 81 (32), 70 (53), 55 (46); ¹H NMR δ 18.37 (OH, s, 2'-OH), 2.98 (t, $J = 7$ Hz, H-2), 1.66 [2H, br m (27 Hz), H-3], 1.45 (6H, s, 3'-CH₃) 1.37 (6H, s, 5'-CH₃), 1.35 [4H, m (hidden¹⁵), H-4 + 5] 0.90 (3H, t, $J = 7$ Hz, H-6); ¹³C NMR in Table 1; GC (DB-1 column) Kovats Retention Index = 1778 was measured as described previously.³

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