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Facile Total Syntheses of Two Novel 4-Alkenyloxy-2,6-dihydroxyacetophenones† Chusheng Huang,^{a,b} Zhe Zhang,^a Shuhua Li^a and Yulin Li^{*a}

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Two novel acetophenones, 4-(1'-geranyloxy)-2,6-dihydroxyacetophenone 1 and 4-(1'-farnesyloxy)-2,6-dihydroxyacetophenone 2 isolated from the fruit of *Evodia merrillii* and from the aerial parts of *Borronia ramosa* respectively, have been synthesized starting from 2,4,6-trihydroxyacetophenone 3; the key step in their total synthesis is the regioselective alkenylation onto the intermediate 6 with alkenyl bromide.

Phenols containing alkenyl units are potentially valuable intermediates in the synthesis of chromenes, chromans, flavonoids and other complex natural products.¹ Many of these compounds and modifications of these structures observed in nature possess a wide range of physiological actions such as antiflammatory, antibacterial and antioxidative activities.² Two novel acetophenones were recently isolated from the fruits of Evodia merrilli, a small folk medicine tree widely distributed in Taiwan,³ and the aerial pars of Borronia romosa in Australian genus Boronia respectively.⁴ Their structures were elucidated as 4-(1'-geranyloxy)-4,6-dihydroxyacetophenone (1) and 4-(1'farnesyloxy)-2,6-dihydroxyacetophenone (2) by means of spectral analysis. So far as we know, the synthesis of these two compounds has not been reported yet. Herein, we wish to report the first total syntheses of 1 and 2 starting from 2,4,6-trihydroxyacetophenone and alkenyl bromide by five steps. Synthetic routes are outlined in Scheme 1.



Compound **3** was treated with benzyl chloride and K_2CO_3 in dry DMF at 80 °C for 1 h to give **4** in 85% yield. Treatment of **4**, K_2CO_3 and *p*-toluensulfonyl chloride in acetone under reflux generated **5** in 85% yield. Compound **6** was obtained in 94% yield by selective hydrogenolysis of **5** using Pd/C as catalyst. Regioselective geranyl annexation onto **6** with geranyl bromide afforded compound **7a** in 80% yield, similarly by farnesyl annexation onto **6** with farnesyl bromide, **7b** was obtained in 60% yield. Detoluensulfonylation of **7a** in 30% KOH ethanol solution gave the desired natural product 1^3 in 75% yield, similarly hydrolysis of **7b**, 2^4 was obtained in 89% yield. The overall yields of **1** and **2** were 41 and 36% respectively.



Scheme 1 Reagents and conditions: i, BnCl, DMF, K₂CO₃, 80 °C, 1 h; ii, TsCl, K₂CO₃, acetone, reflux, 6 h; iii, H₂–10% Pd/C, MeOH, room temp., 20 h; iv, geranyl bromide (or farnesyl bromide), K₂CO₃, acetone, reflux, 2 h; v, 30% aq. KOH–EtOH (1:1), reflux, 1.5 h

Experimental

Melting points were measured on a Kofler hot stage and uncorrected. IR spectra were obtained on a FT-170-SX spectrometer. ¹H NMR spectra were recorded on a Varian FT-80 A instrument in CDCl₃ solution, and chemical shifts were recorded in ppm units using SiMe₄ as internal standard. MS were measured on a ZAB-HS and MAT-44 S (EI, 70 eV).

4,6-Dibenzyloxy-2-hydroxyacetophenone (4).—A mixture of 3 (1.68 g, 10 mmol), benzyl chloride (2.66 g, 21 mmol) and anhydrous K_2CO_3 (2.76 g, 20 mmol) in dry DMF (30 mL) was heated at 80 °C for 1 h under vigorous stirring. After the solid was filtered off, the filtrate was poured into 20 mL water, and extracted with Et_2O . The extract was washed with water, brine, and dried over anhydrous MgSO₄, and evaporated under reduced pressure to give a solid residue that was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 10:1) to afford 4 (2.96 g, 85%) as colorless needles, mp 94–96 °C (lit.⁵ mp 96–98 °C).

2-Tolunesulfonyloxy-4,6-dibenzyloxyacetophenone (5).—A mixture of 4 (1.15 g, 3.3 mmol), TsCl (0.940 g, 5.0 mmol) and anhydrous K_2CO_3 (4.45 g, 32 mmol) in dry acetone (100 mL) was refluxed under stirring for 6 h. After work-up, the residue was recrystallized from EtOAc-petroleum ether to give a colorless powder 5 (1.41 g, 85%), mp 122–123 °C; IR v/max (KBr) 1696, 1616, 1575, 1497, 1432, 1374, 1159, 1055 cm⁻¹; δ_H 2.36 (3 H, s, C_6H_4Me), 2.47 (3 H, s, COMe), 4.99 (2 H, s, ArCH₂O), 5.04 (2 H, s, ArCH₂O), 6.53 (2 H, s, H-3 and H-5), 7.27–7.43 (12 H, m, ArH), 7.78 (2 H, d,

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2-Toluenesulfonyloxy-4,6-dihydroxyacetophenone (6).—A well stirred mixture of 5 (1.00 g, 2.0 mmol) and 10% Pd/C (100 mg) in MeOH (20 mL) was passed through H₂ at room temperature for 20 h. The residual black solid and evaporated solution was purified by silica gel column chromatography eluting with petroleum ether–EtOAc (10:1 to 4:1) to give 6 as colorless needles (565 mg, 94%), mp 150–152 °C; IR v/max (KBr) 3407, 3259, 1631, 1595, 1447, 1372, 1265, 1179, 1036 cm⁻¹; $\delta_{\rm H}$ 2.39 (3 H, s, C₆H₄*Me*), 2.51 (3 H, s, COMe), 6.10, 6.25 (1 H each, d, J = 2 Hz, H-3, H-5), 7.35, 7.70 (2 H each, d, J = 8 Hz, *p*-MeC₆H₄SO₂), 13.80 (1 H, s, OH); EIMS *m*/*z* [M⁺] 322 (16), 280 (10), 258 (27), 155 (76), 91 (100); HREIMS *m*/*z* [M⁺] 322.0483 (C₁₅H₁₄O₆S requires 322.0511).

2-Toluensulfonyloxy-6-hydroxy-4-(1'-geranyloxy)acetophenone (7a). —A mixture of **6** (322 mg, 1 mmol), geranyl bromide (217 mg, 1 mmol) and anhydrous K₂CO₃ (276 mg, 2 mmol) in acetone (20 mL) was well stirred at room temperature for 2 h. After workup, 7a (385 mg, 84%) was obtained by silica gel column chromatography, eluting with petroleum ether–EtOAc (10:1 to 4:1), as a colorless gum. IR ν/max (KBr) 1694, 1573, 1429, 1379, 1180, 1154, 1079. δ_H 1.62, 1.70, 1.72 (3 H each, s, Me-8', Me-9', Me-10'), 1.95–2.15 (4 H, m, 2 H-4', 2 H-5'), 2.45 (3 H, s, C₆H₄Me), 2.60 (3 H, s, COMe), 4.48 (2 H, d, J = 6.5 Hz, 2 H-1'), 5.10 (1 H, app. t, H-6'), 5.42 (1 H, app. f, H-2'), 6.40 (2 H, s, H-3, C₆H₄ H-5), 7.35, 7.81 (2 H each, d, J = 8.1 Hz, p-MeC₆H₄SO₂), 13.27 (1 H, OH); EIMS m/z (M⁺) 458 (3), 323 (33), 303 (5), 281 (23), 258 (47), 181(3), 155 (99), 91(100), 69 (71). HREIMS m/z [M⁺] 458.1745 (C₂₅H₃₀O₆S) requires 458.1763).

2-*Toluensulfonyloxy*-6-*hydroxy*-4-(1'-*farnesyloxy)acetophenone* (**7b**). —Similar to the reaction of **6** and geranly bromide, treatment of **6** (1 mmol) with farnesyl bromide (1 mmol) gave a colorless gum **7b** (316 mg, 60%). IR *v*/max (KBr) 1627, 1575, 1480, 1380, 1204, 1184, 1157, 1089 cm⁻¹. $\delta_{\rm H}$ 1.61, 1.0 (12 H, s, 4 Me), 1.95–2.15 (8 H, m, 2 H-4', 2 H-5', 2 H-8', 2 H-9'), 2.47 (3 H, s, C₆H₄*Me*), 2.60 (3 H, s, CO*Me*), 4.47 (2 H, d, *J* = 6.5 Hz, 2 H-1'), 5.12 (2 H, m, H-6', H-10'), 5.41 (1 H, d, *J* = 6.5 Hz, H-2'), 6.17, 6.32 (1 H each, br s, $w_{1/2}$ =2 Hz, H-3, H-5), 7.36, 7.78 (2 H each, d, *J* = 7.9 Hz, *p*-MeC₆H₄SO₂, 13.26 (1 H, s, OH). EIMS *m*/*z* [M⁺] 526 (4), 483 (1), 419 (1), 371 (5), 323 (33), 281 (30), 258 (28), 204 (20), 155 (63), 91 (64), 69 (100). Calc. for C₃₀H₃₈O₆S: C, 68.41; S, 6.09; H, 7.27. Found: C, 68.48; S, 6.10; H, 7.25%.

2-(1'-Geranyloxy)-4,6-dihydroxyacetophenone (1).—Compound 7a (229 mg, 0.5 mmol) was hydrolyzed with 30% KOH (2 mL) and EtOH (2 mL) under reflux and stirring for 1.5 h. Dilute HCl was then added to pH 3, and the solution extracted with Et_2O . The extract was washed with water, brine, and dried over anhydrous MgSO₄, then purified by silica gel column chromatography (eluting with petroleum ether–EtOAc 6:1) to afford 1 (114 mg, 75%) as a colorless powder, mp 147–148 °C (lit.³ 147–150 °C). IR v/max (KBr)

3134, 1655, 1626, 1560, 1287, 1165 cm⁻¹; $\delta_{\rm H}$ 1.63, 1.70, 1.75 (3 H each, s, Me-8', Me-9' Me-10'), 2.11 (4 H, m, 2 H-4', 2 H-5'), 2.64 (3 H, s, COMe), 4.57 (2 H, d, J = 6.5 Hz, 2 H-1'), 5.09 (1 H, br s, $w_{1/2} = 7$ Hz, H-6'), 5.44 (1 H, t, J = 6.5 Hz, H-2'), 5.92, 5.99 (1 H each, d, J = 2.4 Hz, H-3, H-5), 13.98 (1 H, s, OH); EIMS m/z [M⁺] 304 (7), 181 (5), 168 (100), 153 (91), 137 (32), 121 (7), 81 (33), 69 (68); HREIMS m/z (M⁺) 304.1695 ($C_{18}H_{24}O_4$ requires 304.1674). The spectral data of 1 are essentially identical with those of natural 1 as reported in ref. 4.

4-(1²-Farnesyloxy)-2,6-dihydroxyacetophenone (**2**).—Likewise treatment of **7b** (90 mg, 0.17 mmol) in KOH–EtOH, gave compound **2** (57 mg, 89%) as a white gum. IR ν /max 3124–2966, 2927, 2845, 1710, 1624, 1550, 1463, 1371, 1287, 1257, 1165, 1072, 947, 820, 800 cm⁻¹; $\delta_{\rm H}$ 1.60 (6 H, s, 2 Me), 1.67, 1.73 (3 H each, s, 2 me), 1.94–2.25 (8 H, m, 2 H-4', 2 H-5', 2 H-8', 2 H-9'), 2.61 (3 H, s, COMe), 4.54 (2 H, d, J = 6.5 Hz, 2 H-1'), 5.09 (2 H, br s, $w_{1/2} = 7.0$ Hz, H-10', H-6'), 5.46 (1 H, t, J = 6.2 Hz, H-2'), 5.92 (2 H, s, H-2, H-5), 13.97 (1 H, s, OH); EIMS m/z [M⁺¹] 372 (5), 357 (1), 303 (8), 235 (8), 204 (7), 168 (22), 153 (30), 137 (12), 123 (7), 121 (12), 119 (8), 93 (15), 81 (51), 69 (100), Calc. for C₂₃H₃₂O₄: C, 74.16; H, 8.66. Found: C, 74.14; H 8.66%. The spectral data of **2** are essentially identical with those of natural as reported in ref. 5.

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References

- G. P. Ellis, Chromenes, Chromanones and Chromones, John Wiley and Sons, New York, 1977; J. B. Harborne, The Flavonoids: Advances in Research since 1980, Chapman and Hall, New York, 1988.
- H. Fukui, H. Egawa, K. Koshimizu and T. Mitsui, *Agric. Biol. Chem.*, 1973, **37**, 417; W. S. Bowers, T. Ohta, J. S. Cleere and P. A. Marseilla, *Science*, 1976, **193**, 542; W. R. Phillips, N. J. Baj, A. A. L. Gunatilaka and D. G. I. Kingston, *J. Nat. Prod.*, 1996, **59**, 495; M. L. Barrett, A. M. Scott and F. J. Evans, *Experientia*, 1986, **42**, 452; R. K. Razdan, W. R. Thompson, H. G. Parks and F. E. Gramchelli, *Tetrahedron Lett.*, 1967, 3405.
- 3 C. J. Chou, I. C. Lin and C. F. Chen, J. Nat. Prod., 1992, 55, 795.
- 4 A. Monira, I. G. Alexander and G. W. Peter, *J. Nat. Prod.*, 1994, **57**, 673.
- 5 M. Tsukayama, K. Fujimoto, T. Horie, M. Masumura and M. Nakayama, *Bull. Chem. Soc. Jpn*, 1985, **58**, 1.