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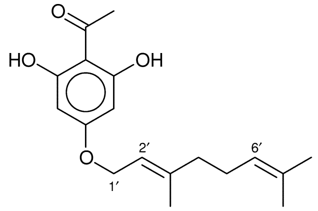
Facile Total Syntheses of Two Novel 4-Alkenyloxy-2,6-dihydroxyacetophenones†

Chusheng Huang,[a,b] Zhe Zhang,[a] Shuhua Li[a] and Yulin Li*[a]

[a]*National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China*
[b]*Institute of Applied Chemistry, Guangxi Teaching College, Nanning 530001, P.R. China*

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.



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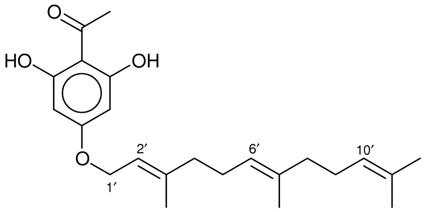

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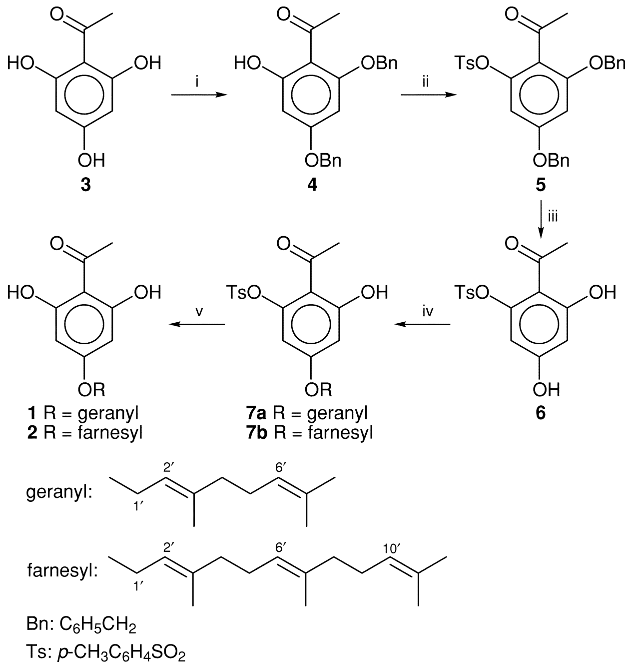
Compound **3** was treated with benzyl chloride and K_2CO_3 in dry DMF at 80 °C for 1 h to give **4** in 85% yield. Treatment of **4**, K_2CO_3 and *p*-toluensulfonyl chloride in acetone under reflux generated **5** in 85% yield. Compound **6** was obtained in 94% yield by selective hydrogenolysis of **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, K_2CO_3, 80 °C, 1 h; ii, TsCl, K_2CO_3, acetone, reflux, 6 h; iii, H_2–10% Pd/C, MeOH, room temp., 20 h; iv, geranyl bromide (or farnesyl bromide), K_2CO_3, 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 $CDCl_3$ solution, and chemical shifts were recorded in ppm units using $SiMe_4$ 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 $MgSO_4$, 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 ν/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, CO*Me*), 4.99 (2 H, s, ArCH_2O), 5.04 (2 H, s, ArCH_2O), 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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*To receive any correspondence (*e-mail:* liyl@lzu.edu.cn).

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J = 8.1 Hz); EIMS *m*/*z* (M^+) 502 (5), 487 (12), 397 (11), 348 (2), 347 (8), 181 (12), 91 (100); HREIMS *m*/*z* (M^+) 504.1410 ($C_{29}H_{26}O_6S$ requires 502.1450).

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 H_2 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 ν/max (KBr) 3407, 3259, 1631, 1595, 1447, 1372, 1265, 1179, 1036 cm^{-1}; δ_H 2.39 (3 H, s, C_6H_4*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*-Me$C_6H_4SO_2$), 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 ($C_{15}H_{14}O_6S$ 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 K_2CO_3 (276 mg, 2 mmol) in acetone (20 mL) was well stirred at room temperature for 2 h. After work-up, **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, C_6H_4*Me*), 2.60 (3 H, s, CO*Me*), 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, C_6H_4 H-5), 7.35, 7.81 (2 H each, d, *J* = 8.1 Hz, *p*-Me$C_6H_4SO_2$), 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 ($C_{25}H_{30}O_6S$ 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 ν/max (KBr) 1627, 1575, 1480, 1380, 1204, 1184, 1157, 1089 cm^{-1}. δ_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, C_6H_4*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*-Me$C_6H_4SO_2$, 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 $C_{30}H_{38}O_6S$: 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 $MgSO_4$, 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 ν/max (KBr) 3134, 1655, 1626, 1560, 1287, 1165 cm^{-1}; δ_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-(1′-*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}; δ_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^+] 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 $C_{23}H_{32}O_4$: 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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