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NOVEL ACETOPHENONES FROM FRUITS OF *EVODIA MERRILLII*

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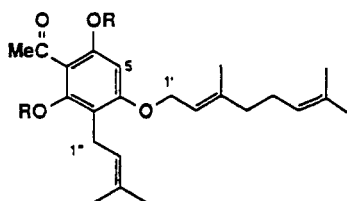
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ABSTRACT.—Four acetophenones, 4-(1'-geranyloxy)-2,6-dihydroxy-3-isopentenylacetophenone [**1**], 2-(1'-geranyloxy)-4,6-dihydroxyacetophenone [**2**], 4-(1'-geranyloxy)-2,6-dihydroxyacetophenone [**3**], and 4-(1'-geranyloxy)- β ,2,6-trihydroxyacetophenone [**4**], were isolated along with pachypodol, kumatakenin, retusin, miquelianin, and adenosine from the fruit of *Evodia merrillii*.

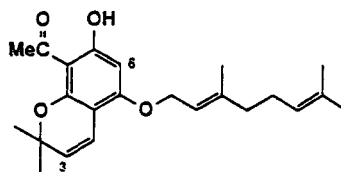
Evodia merrillii Kanehira & Sasaki ex Kanehira (Rutaceae) is a small tree widely distributed in Taiwan and the Lanyu Islet. The fruit of *E. merrillii* was extracted with EtOH and partitioned successively with Et₂O, *n*-BuOH, and H₂O. Chromatography of the Et₂O layer gave three flavonols: pachypodol, kumatakenin, and retusin. All three have also been found from the flowers of this plant (1). Adenosine and miquelianin were identified from the *n*-BuOH fraction; these compounds were not previously found from this plant. We now report the isolation of four new acetophenones **1–4** from the Et₂O fraction after Si gel cc.

The ir spectra of acetophenones **1–4** showed characteristic absorptions of an aromatic ring and H-bonded OH groups, in keeping with the proposed structures.

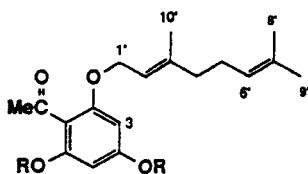
The ¹H-nmr spectrum of **1** revealed an H-bonded OH (δ 11.64), a free OH group (δ 8.41), an unsubstituted aromatic proton (δ 5.98), and an acetyl group (δ 2.64). A set of signals of two Me groups (δ 1.73, 1.80), a vinyl proton triplet (δ 5.17, $J = 7.2$ Hz),



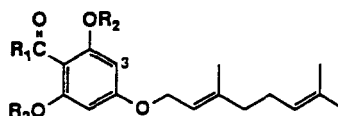
1 R=H
1-diacetate R=Ac
5 R=Me



6



2 R=H
2-diacetate R=Ac



3 R₁=Me, R₂=H
3-diacetate R₁=Me, R₂=Ac
4 R₁=-CH₂OH, R₂=H
4-triacetate R₁=-CH₂OAc, R₂=Ac

and two methylene protons doublets (δ 3.31, $J = 7.2$ Hz) in the spectrum suggested that an isopentenyl group was present. Other Me groups (δ 1.58, 1.66, 1.69), vinyl protons (δ 5.07, 5.42), methylene protons (δ 2.09), and oxygenated methylene protons (δ 4.54) were assigned to the *O*-geranyl group. ^1H - ^1H COSY studies clearly established the relationship of the isopentenyl and *O*-geranyl group. Both ^1H - and ^{13}C -nmr assignments are depicted in Table 1.

The mass spectrum of **1** showed an intense peak at m/z 236 (53.5%), corresponding to the loss of a $\text{C}_{10}\text{H}_{16}$ unit from the molecular ion, and a base peak at m/z 181, corresponding to a further loss of a C_4H_7 unit. The loss of a $\text{C}_{10}\text{H}_{16}$ rather than a C_9H_{14} fragment indicated that an *O*-geranyl group was present (2). Further studies of the ^1H - ^1H homonuclear and ^1H - ^{13}C heteronuclear 2D correlation spectra have supported the proposed structure of **1**. Acetylation of **1** with Ac_2O /pyridine gave the **1**-diacetate, providing further evidence that **1** had two OH groups.

Oxidative cyclization of **1** with DDQ gave **6**. An H-bonded OH singlet, two doublets at δ 5.38 and 6.56 ($J = 10.1$ Hz), respectively, instead of the benzylic methylene protons, were obtained from its ^1H -nmr spectrum. Therefore, structure **6** was confirmed.

Methylation of **1** with $\text{Me}_2\text{SO}_4/\text{K}_2\text{CO}_3$ in Me_2CO gave the dimethyl ether **5**. Its ^1H -nmr spectrum revealed two MeO groups, at δ 3.68 and 3.77. Aromatic proton H-5 was shifted downfield to δ 6.24. From an nOe experiment, the MeO (δ 3.77) and H-1' (δ 4.54) signals were enhanced when irradiated at δ 6.24. This phenomenon indicated

TABLE 1. 2D nmr HETCOR Correlations of Compounds 1-4 (1J).

Carbon	Compound							
	1		2		3		4	
	C to H		C to H		C to H		C to H	
C- α	203.51		203.50		204.07		200.74	
C- β	32.81	2.64	32.99	2.60	32.43	2.68	68.02	4.81
C-1	105.29		106.35		105.20		102.50	
C-2	159.67		162.73		163.77		163.71	
C-3	106.52		91.60	5.90	94.66	5.95	94.76	5.95
C-4	163.01		163.11		165.54		166.50	
C-5	92.77	5.98	96.29	5.96	94.66	5.95	94.76	5.95
C-6	162.52		167.17		163.77		163.71	
Geranyl								
C-1'	65.41	4.51	65.74	4.54	65.11	4.47	65.33	4.51
C-2'	118.90	5.42	118.41	5.48	118.28	5.39	118.26	5.40
C-3'	141.51		142.22		142.16		142.39	
C-4'	39.45	2.09	39.41	2.09	39.39	2.06	39.27	2.07
C-5'	26.28	2.09	26.21	2.09	26.16	2.06	26.24	2.07
C-6'	123.68	5.07	123.56	5.06	123.58	5.04	123.62	5.06
C-7'	131.85		131.97		131.80		131.94	
C-8'	17.66	1.58	17.68	1.59	17.56	1.56	17.66	1.58
C-9'	25.59	1.66	25.62	1.66	25.52	1.64	25.60	1.65
C-10'	16.65	1.69	16.59	1.72	16.54	1.67	16.67	1.70
Isopentenyl								
C-1''	21.59	3.31						
C-2''	121.90		5.17					
C-3''	134.94							
C-4''	17.81	1.79						
C-5''	25.80		1.73					

that the 6-OH group and the 4-*O*-geranyl group were on each side of the aromatic proton (H-5). Further confirmation of the quaternary carbons was obtained by the COLOC spectrum (Figure 1). From the above-mentioned evidence, the structure of **1** as 4-(1'-geranyloxy)-2,6-dihydroxy-3-isopentenylacetophenone was concluded.

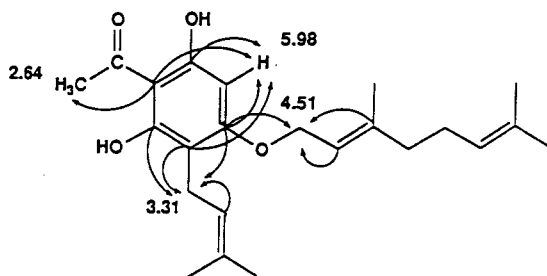


FIGURE 1. COLOC result of acetophenone **1** in CDCl_3 ($J_{\text{CH}} = 8 \text{ Hz}$).

The ^1H -nmr spectrum of **2** indicated the presence of an H-bonded and a free OH group, an acetyl group, an *O*-geranyl group, and two unsubstituted aromatic protons which were at meta positions ($J = 2.2 \text{ Hz}$) to each other. 2-Diacetate showed significant downfield shifts (0.58, 0.62 ppm), suggesting that the aromatic protons at H-3, H-5 were the relationship between oxygenated groups. This suggested placing the *O*-geranyl group at the 2 position of the aromatic ring. The COLOC spectrum confirmed the above assignments; thus, the structure of **2** was established as 2-(1'-geranyloxy)-4,6-dihydroxyacetophenone.

Acetophenone **3** is an isomeric compound of acetophenone **2**. The ^1H -nmr spectrum of **3** was similar to that of **2**, except the two aromatic protons were recorded as a singlet at $\delta 5.95$. Acetylation of **3** afforded **3**-diacetate, which exhibited two acetyl groups at $\delta 2.25$ (6H, s) and a significant downfield shift of the aromatic proton signal. This suggested that the acetophenone **3** could have a symmetrical structure. Therefore, the acetophenone **3** was assigned as 4-(1'-geranyloxy)-2,6-dihydroxyacetophenone. The COLOC experiment confirmed the structure.

The ^1H -nmr spectrum of acetophenone **4** showed close resemblance to that of **3** except for the additional presence of a signal at $\delta 4.81$ (2H, s) and the absence of the acetyl group signal at $\delta 2.68$. The ^{13}C -nmr spectrum of **4** (Table 1) also looked like that of **3**, except for the additional oxygenated methylene carbon at $\delta 68.02$ and the absence of an acetyl carbon at $\delta 32.43$. This indicated that the acetyl group was replaced by a hydroxy methyl carbonyl group. In agreement with these observations, the ms revealed a molecular ion at m/z 320. Hence, the structure of 4-(1'-geranyloxy)- β ,2,6-trihydroxyacetophenone [**4**] was proposed. **4**-Triacetate was obtained from acetylation of **4** by Ac_2O and pyridine.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were determined with a Yanagimoto micro mp apparatus. Ir spectra were taken on a Perkin-Elmer 781 ir spectrometer. Eims spectra were recorded on a JEOL JMSD-300, and fabms spectra were recorded on a JEOL JMS-HX 110 spectrometer. Uv spectra were obtained on a Hitachi U-3200 spectrophotometer. ^1H - and ^{13}C -nmr spectra were observed with a Bruker AM-300 spectrometer.

PLANT MATERIAL.—*E. merrillii* fruit was collected at Hsiang Shan, Taipei, Taiwan, in December 1990. A voucher specimen (no. 212807) has been deposited in the herbarium of the Department of Botany of National Taiwan University.

EXTRACTION AND ISOLATION.—The dried fruit (3.8 kg) was extracted with 95% EtOH (7 lit-

ers \times 4). The EtOH extract was concentrated under reduced pressure. H₂O (1 liter) was added into the concentrated EtOH extract, which was then partitioned successively with Et₂O (1 liter \times 3) and *n*-BuOH (1 liter \times 3). The Et₂O layer (500 g) was further subjected successively to chromatography on Si gel (1500 g) with a gradient of *n*-hexane, EtOAc, and MeOH as eluents. In all, eighteen fractions were collected. Fractions 6–11 were a mixture of seven compounds. These fractions were combined and concentrated. After cooling, a precipitate was filtrated. The filtrate (120 g) was rechromatographed on a Si gel (800 g) column and eluted with *n*-hexane–EtOAc (85:15) to give compounds **1** (4.52 g), **2** (2.36 g), **3** (225.1 mg), and **4** (181.3 mg). The precipitate was chromatographed on a Si gel column and eluted with CHCl₃–MeOH (98:2) to give the three known flavonols. The *n*-BuOH layer was subjected repetitively to chromatography on Sephadex LH-20 with a gradient of H₂O/MeOH as eluent, to yield adenosine and miquelianin.

4-(1'-Geranyloxy)-2,6-dihydroxy-3-isopentenylacetophenone [1].—Colorless needle-shaped crystals from *n*-hexane: mp 98–101°; eims *m/z* [M]⁺ 372 (12.0%), 236 (53.5), 193 (29.0), 181 (100.0), 69 (94.5); ir (KBr) 3220, 1635, 1585, 1515 cm⁻¹; uv max (MeOH) 289.0 nm (log ϵ = 4.31); ¹H nmr δ 1.58 (3H, s, Me-8'), 1.66 (3H, s, Me-9'), 1.69 (3H, s, Me-10'), 1.73 (3H, s, Me-5''), 1.79 (3H, s, Me-4''), 2.09 (4H, m, H₂-4', H₂-5'), 2.64 (3H, s, β -Me), 3.31 (2H, d, *J* = 7.2 Hz, H₂-1''), 4.51 (2H, d, *J* = 6.4 Hz, H₂-1'), 5.07 (1H, m, H-6'), 5.17 (1H, t, *J* = 7.2 Hz, H-2''), 5.42 (1H, t, *J* = 6.4 Hz, H-2'), 5.98 (1H, s, H-5), 8.41 (br s, -OH), 11.64 (br s, -OH); ¹³C nmr see Table 1.

Acetylation of 1.—Compound **1** with Ac₂O/pyridine at room temperature for 1 h gave **1**-diacetate [4-(1'-geranyloxy)-2,6-diacetoxy-3-isopentenylacetophenone]: an oil; ir (neat) 1775, 1645, 1610, 1190 cm⁻¹; eims *m/z* 277 (61.5%), 252 (34.5), 235 (100.0), 181 (83.0) (the molecular ion peak did not appear); ¹H nmr δ 2.23, 2.26 (each 3H, s, 2 \times OAc), 6.52 (1H, s, H-5).

Cyclization of 1.—Compound **1** was refluxed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in C₆H₆ for 18 h. The usual workup followed by chromatography (EtOAc/*n*-hexane) gave **6**: an oil; ir (neat) 3450, 1640, 1615, 1585 cm⁻¹; eims *m/z* [M]⁺ 370 (4.6%), 234 (21.11), 219 (100.0), 69 (33.5); ¹H nmr δ 1.24, 1.47, 1.59, 1.66, 1.70 (each 3H, s, 5 \times Me), 2.08 (4H, m, H₂-4', H₂-5'), 2.64 (3H, s, β -Me), 4.54 (2H, d, *J* = 6.3 Hz, H₂-1'), 5.08 (1H, m, H-6'), 5.38 (1H, d, *J* = 10.1 Hz, H-3), 5.43 (1H, t, *J* = 6.3 Hz, H-2'), 5.98 (1H, s, H-6), 6.56 (1H, d, *J* = 10.1 Hz, H-4), 13.77 (br s, -OH).

Methylation of 1.—Compound **1** was refluxed with Me₂SO₄ and K₂CO₃ in Me₂CO for 16 h. The usual workup followed by chromatography (EtOAc/*n*-hexane) gave **5** [4-(1'-geranyloxy)-2,6-dimethoxy-3-isopentenylacetophenone]: an oil; ir (neat) 1700, 1600 cm⁻¹; eims *m/z* [M]⁺ 400 (1.4%), 264 (34.2), 249 (100.0), 209 (35.6), 69 (51.4); ¹H nmr δ 3.68, 3.77 (each 3H, s, 2 \times OMe), 6.24 (1H, s, H-5).

2-(1'-Geranyloxy)-4,6-dihydroxyacetophenone [2].—Colorless needles formed from EtOAc/*n*-hexane: mp 147–150°; eims *m/z* [M]⁺ 304 (1.3%), 219 (1.7), 181 (2.2), 153 (28.0), 81 (34.0), 69 (100.0); ir (KBr) 3120, 1655, 1630, 1545 cm⁻¹; uv max (MeOH) 288.8 nm (log ϵ = 4.28); ¹H nmr δ 1.59 (3H, s, Me-8'), 1.66 (3H, s, Me-9'), 1.72 (3H, s, Me-10'), 2.09 (4H, m, H₂-4', H₂-5'), 2.60 (3H, s, β -Me), 4.54 (2H, d, *J* = 6.6 Hz, H₂-1'), 5.06 (1H, m, H-6'), 5.48 (1H, t, *J* = 6.6 Hz, H-2'), 5.90 (1H, d, *J* = 2.2 Hz, H-3), 5.96 (1H, d, *J* = 2.2 Hz, H-5), 6.17 (br s, -OH), 13.96 (br s, -OH); ¹³C nmr see Table 1.

Acetylation of 2 with Ac₂O/pyridine and usual workup yielded **2**-diacetate [2-(1'-geranyloxy)-4,6-diacetoxyacetophenone]: ir (neat) 3050, 1780, 1695, 1615, 1245, 1200 cm⁻¹; eims *m/z* [M + 1]⁺ 389; ¹H nmr δ 2.10 (3H, s, OAc), 2.17 (3H, s, OAc), 2.44 (3H, s, β -Me), 6.48 (1H, d, *J* = 1.9 Hz, H-3), 6.58 (1H, d, *J* = 1.9 Hz, H-5).

4-(1'-Geranyloxy)-2,6-dihydroxyacetophenone [3].—Waxy substance with eims *m/z* [M]⁺ 304 (0.6%), 168 (26.0), 153 (38.0), 81 (28.5), 69 (100.0); ir (neat) 3300, 1630, 1585 cm⁻¹; uv max (MeOH) 285.6 nm (log ϵ = 4.24); ¹H nmr δ 1.56 (3H, s, Me-8'), 1.64 (3H, s, Me-9'), 1.67 (3H, s, Me-10'), 2.05 (4H, m, H₂-4', H₂-5'), 2.68 (3H, s, β -Me), 4.47 (2H, d, *J* = 6.5 Hz, H₂-1'), 5.04 (1H, m, H-6'), 5.39 (1H, t, *J* = 6.5 Hz, H-2'), 5.95 (2H, s, H-3, H-5); ¹³C nmr see Table 1.

Acetylation of 3 by the usual method and purification by cc yielded **3**-diacetate [4-(1'-geranyloxy)-2,6-diacetoxyacetophenone]: ir (neat) 1775, 1690, 1620, 1185, 1150 cm⁻¹; eims *m/z* [M + 1]⁺ 389 (5.0%), 347 (18.0), 253 (21.5), 211 (45.0), 168 (80.5), 153 (56.5), 81 (37.5), 69 (100.0); ¹H nmr δ 2.25 (6H, s, 2 \times OAc), 2.40 (3H, s, β -Me), 6.55 (2H, s, H-3, H-5).

4-(1'-Geranyloxy)- β ,2,6-trihydroxyacetophenone [4].—Colorless crystals from EtOAc/*n*-hexane; mp 106–108°; eims *m/z* [M]⁺ 320 (0.8%), 185 (11.9), 153 (73.3), 136 (13.5), 69 (100.0); ir (KBr) 3410, 3190, 1645, 1600, 1515 cm⁻¹; uv max (MeOH) 287.4 (log ϵ = 4.26); ¹H nmr δ 1.58 (3H, s, Me-8'), 1.65 (3H, s, Me-9'), 1.70 (3H, s, Me-10'), 2.07 (4H, m, H₂-4', H₂-5'), 4.33 (br s, D₂O-exchangeable, -OH), 4.51 (2H, t, *J* = 6.5 Hz, H₂-1'), 4.81 (2H, s, H₂- β), 5.06 (1H, m, H-6'), 5.40 (1H, t, *J* = 6.5 Hz, H-2'), 5.95 (2H, s, H-3, H-5), 10.45 (br s, D₂O exchangeable, -OH); ¹³C nmr see Table 1.

Acetylation of 4 by the usual method yielded **4**-triacetate [4-(1'-geranyloxy)- β ,2,6-triacetoxyacetophenone]: ir (neat) 1775, 1750, 1620, 1570, 1218, 1180 cm⁻¹; eims 269 (15.6%), 237

(42.8), 195 (41.8), 153 (42.8), 136 (30.0), 81 (40.8), 69 (100.0) (molecular ion peak did not appear); ^1H nmr δ 2.11 (3H, s, OAc), 2.27 (6H, s, $2 \times$ OAc), 4.94 (2H, s, H_2 - β), 6.58 (2H, s, H-3, H-5).

ACKNOWLEDGMENTS

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