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Acetophenone Derivatives from *Acronychia pedunculata*

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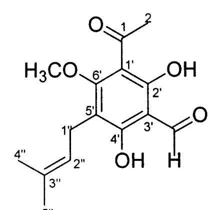
Chemical investigation on the stem and root bark of *Acronychia pedunculata* has resulted in the isolation of five new acetophenones, namely, acronyculatins A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**). The structures of these metabolites were established on the basis of their 1D and 2D NMR spectroscopic and mass spectrometric data and by CD spectroscopy. The antioxidant and antityrosinase activities of these five metabolites and acrovestone (**6**) were evaluated. Among these compounds, **6** showed marginal antioxidant and antityrosinase activities.

Acronychia pedunculata (L.) Miq. (Rutaceae) is a small evergreen tree widely distributed in woodlands of Indonesia, Malaysia, Sri Lanka, and southern mainland China. This is also the only species of *Acronychia* native to Taiwan.[1] The roots, stems, leaves, and fruits have been used extensively in folk medicine for the treatment of diarrhea, cough, asthma, sores, ulcers, itchy skin, scales, pain, and rheumatism and also have antipyretic, antihemorrhagic, and reputed aphrodisiac activities.[2] Previous phytochemical studies on this plant revealed furoquinoline alkaloids, terpenoids, and isoprenylated acetophenones as its chemical constituents.[3−9] A cytotoxic principle, acrovestone (**6**), has been reported from the stem and root bark of *A. pedunculata*.[10] In an antioxidant screening procedure, the crude MeOH extract and the $CHCl_3$ solubles of *A. pedunculata* showed activity that prompted the reinvestigation of this plant for its antioxidant and antityrosinase principles. We report herein the isolation, structural elucidation, and biological activity of five new acetophenone derivatives (**1**−**5**) and a known compound, acrovestone (**6**), from *A. pedunculata*.

Acronyculatin A (**1**), obtained as a colorless syrup, was assigned the molecular formula $C_{15}H_{18}O_5$ by HREIMS. The UV spectrum of **1** exhibited absorption maxima at 344, 275, and 261 nm, similar to those of reported for 2′,4′,6′-trioxygenated acetophenones.[11] This initial structural assignment was supported by the presence of three downfield-shifted quaternary carbon signals at δ 168.5, 168.8, and 168.9 in the ^{13}C NMR spectrum, which is due to an inductive effect of the acetyl group on the *ortho*- and *para*-positions. The IR absorption bands of **1** at 2924 and 1629 cm^{-1} indicated it to be an aromatic compound with chelated hydroxyl and carbonyl groups, and it was further supported by the two D_2O-exchangeable singlets at δ 14.63 (OH-2′) and 13.13 (OH-4′) in the ^{1}H NMR spectrum. A methyl singlet at δ 2.68 combined with carbons at δ 31.0 and 213.1, along with the absence of any aromatic proton signals, suggested a fully substituted 2′-hydroxyacetophenone unit as the basic skeleton for **1**.[12] The proton signals at δ 10.30 (1H, s) and 3.86 (3H, s) showed the presence of a formyl and a methoxyl substituent, respectively. A typical set of signals at δ 5.17 (1H, t, J = 6.6 Hz, H-2″), 3.27 (2H, d, J = 6.6 Hz, H-1″), 1.77 (3H, s, CH_3-4″), and 1.70 (3H, s, CH_3-5″) revealed the presence of an isoprenyl unit in the molecule. The NOE correlations of the methoxyl signal at δ 3.86 with the acetyl methyl and H-1″ in the NOESY spectrum suggested that methoxyl and isoprenyl groups should be at C-6′ and C-5′, respectively. The ^2J,^3J-HMBC connectivities of the methoxyl with the carbon signal at δ 168.5, and H-1″ with carbon signals at δ 168.9, 168.5, and 114.9, permitted the assignment of quaternary carbons at C-4′ (δ 168.9), C-5′ (δ 114.9), and C-6′ (δ 168.5). The remaining quaternary carbons at δ 168.8 and 107.1 were assigned to C-2′ and C-3′, respectively, since compound **1** is a 2′,4′,6′-trioxygenated acetophenone derivative. In addition, ^2J,^3J-correlations between the formyl and carbons at δ 107.1 (C-3′) and 168.9 (C-4′) in the HMBC spectrum inferred that the formyl group could be placed at C-3′. Thus, compound **1** was characterized as 1-[3′-formyl-2′,4′-dihydroxy-6′-methoxy-5′-(3″-methylbut-2″-enyl)]acetophenone, for which the trivial name acronyculatin A was given.



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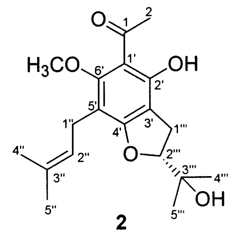

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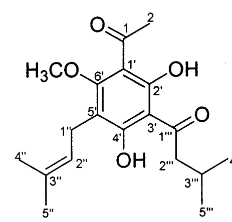

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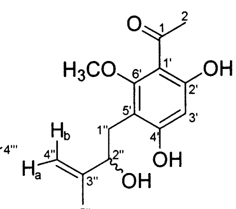

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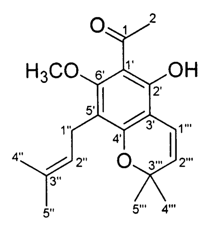

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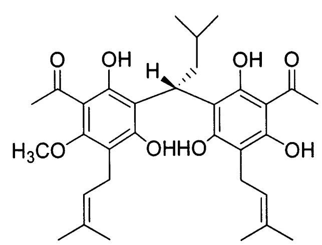

6

Acronyculatin B (**2**) was obtained as colorless powder with optical activity ([α]$^{25}_{D}$ −58.0°). The molecular formula $C_{19}H_{26}O_5$ was determined for **2**, on the basis of the molecular ion peak at *m/z* 334.1780 in its HREIMS. The UV spectrum of **2**, which displayed absorption maxima at

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295 and 224 nm, was also similar to those reported for 2′,4′,6′-trioxygenated acetophenones[11] and was further supported by the oxygenated quaternary carbon signals at δ 156.7, 164.4, and 164.8 in the ^{13}C NMR spectrum. The IR absorption bands at 2965 and 1616 cm^{-1} indicated the presence of chelated hydroxyl and carbonyl groups. In the ^{1}H and ^{13}C NMR spectra, a methyl singlet at δ 2.61 (s) and a chelated hydroxyl group at δ 14.52 (s), and carbons at δ 32.1 and 203.0, respectively, strongly supported a 2′-hydroxyacetophenone skeleton for **2**. The methoxyl group at δ 3.90 (s) must be placed on C-6′ since it correlated with the acetyl methyl (δ 2.61) in the NOESY spectrum. A carbon signal at δ 156.7 was assigned to C-6′ due to the cross-peak between this carbon and OCH$_3$-6′ in the HMBC spectrum. The ^{1}H NMR resonances at δ 5.24 (1H, t, J = 6.6 Hz, H-2″), 3.22 (2H, d, J = 6.6 Hz, H-1″), 1.76 (3H, s, CH$_3$-4″), and 1.67 (3H, s, CH$_3$-5″) were typical of an isoprenyl group, and its position at C-5′ was inferred by the NOE between H-1″ and OCH$_3$-6. The HMBC cross-peaks of H-1″ with carbons at δ 107.1 and 164.8 led us to assign these carbon signals for C-5′ and C-4′, respectively, and also confirmed the placement of the isoprenyl group at C-5′. The other two carbon signals at δ 164.4 and 108.2 were attributed to C-2′ and C-3′, respectively, since **2** is also a 2′,4′,6′-trioxygenated acetophenone derivative. Additionally, proton signals at δ 4.64 (1H, t, J = 8.0 Hz, H-2‴), 3.26 (2H, d, J = 8.0 Hz, H-1‴), 1.36 (3H, s, CH$_3$-5‴), and 1.24 (3H, s, CH$_3$-4‴), associated with a 1-hydroxy-1-methylethyldihydrofuran group, were also observed. HMBC correlations of H-1‴ with C-2′ (δ 164.4), C-3′ (δ 108.2), and C-4′ (δ 164.8) indicated that the dihydrofuran ring is fused at the C-3′ and C-4′ positions. The absence of any aromatic proton signals in its ^{1}H NMR spectrum was in keeping with **2** having a structure containing acetyl, hydroxyl, isoprenyl, methoxyl, and 1-hydroxy-1-methylethyldihydrofuran substituents attached to a benzene ring. The CD spectrum of **2** showed a negative maximum at 485 nm and established the side chain stereochemistry at C-2‴ as R, as in the model compound (2′R)-rotenone.[13] Therefore, the structure of **2** (acronyculatin B) was assigned as 1-[2′-hydroxy-3′,4′-(2‴-isopropanoyldihydrofuran)-6′-methoxy-5′-(3″-methylbut-2″-enyl)]acetophenone.

Acronyculatin C (**3**) was isolated as a colorless syrup. The molecular ion peak at m/z 334.1780 in its HREIMS enabled the molecular formula to be deduced as $C_{19}H_{26}O_5$. The UV spectral behavior of **3** was similar to that of **1** and suggested that **3** is also a 2′,4′,6′-trioxygenated acetophenone derivative,[11] which was further evidenced by one acetyl methyl singlet at δ 2.69 and the resonances at δ 31.0, 203.8, 168.6, 171.0, and 174.1 in the ^{13}C NMR spectrum. The quaternary carbon signals at δ 107.3, 174.1, 107.4, 171.0, 115.3, and 168.6 were assigned to C-1′, 2′, 3′, 4′, 5′, and 6′, respectively, by comparison with those of **1**. The IR spectrum showed chelated hydroxyl (2932 cm^{-1}), carbonyl (1616 cm^{-1}), and aromatic ring (1589 cm^{-1}) functionalities. Two chelated hydroxyls were evident from the ^{1}H NMR spectrum of **3**, as two downfield D$_2$O-exchangeable singlets at δ 15.56 (OH-2′) and 15.12 (OH-4′). A methoxyl group at δ 3.78 (s, OCH$_3$-6′) was placed at C-6′, since it correlated with the carbon at δ 168.6 in the HMBC spectrum. A typical set of signals at δ 5.18 (1H, t, J = 6.3 Hz, H-2″), 3.28 (2H, d, J = 6.3 Hz, H-1″), 1.77 (3H, s, CH$_3$-4″), and 1.69 (3H, s, CH$_3$-5″) was representative of an isoprene unit, whose placement was confirmed at C-5′ on the basis of the ^{2}J and ^{3}J HMBC correlations of H-1″ with C-4′, C-5′, and C-6′, and NOESY cross-peaks from CH$_3$-2 to OCH$_3$-6′ and from OCH$_3$-6′ to H-1″. Finally, a set of proton signals consisting of a doublet at δ 3.03 (2H, J = 6.7 Hz, H-2‴), a multiplet at δ 2.27 (1H, H-3‴), and two singlets at δ 0.98 (3H, CH$_3$-4‴) and 0.97 (3H, CH$_3$-5‴), combined with five carbon signals at δ 22.8, 22.8, 24.9, 53.3, and 207.0, were accounted for by the presence of a 3-methylbutanoyl moiety. The location of this group at C-3′ was deduced from the ^{3}J correlation between H-2‴ and C-3′ in the HMBC spectrum. Consequently, the structure of **3** (acronyculatin C) was defined as 1-[2′,4′-dihydroxy-6′-methoxy-3′-(3‴-methylbutanoyl)-5′-(3″-methylbut-2″-enyl)]acetophenone.

Acronyculatin D (**4**), obtained as an optically active colorless syrup, was assigned the molecular formula $C_{14}H_{18}O_4$ from its HREIMS. The UV spectrum of **4** showed absorptions at 285 and 219 nm. The IR absorption bands at 3186, 2941, and 1621 cm^{-1} were accounted for by a nonchelated hydroxyl, a chelated hydroxyl, and a carbonyl group, respectively. The observation of a chelated hydroxyl signal at δ 13.03 and a methyl at δ 2.69 (s) in the ^{1}H NMR spectrum, combined with the carbon signals at δ 30.7 and 203.2, were indicative of the 2′-hydroxyacetophenone basic skeleton. The ^{1}H NMR spectrum also revealed an aromatic proton at δ 6.31 (s) and a methoxyl at δ 3.70 (s). A NOESY correlation of the acetyl methyl with a signal at δ 3.70 suggested that the methoxyl group is located at C-6′, and a ^{3}J HMBC cross-peak between this methoxyl and a carbon signal at δ 161.6 permitted its assignment at C-6′. Additional resonances at δ 1.86 (3H, s, CH$_3$-5″), 2.72 (1H, dd, J = 15.2, 9.0 Hz, H-1″), 3.03 (1H, dd, J = 15.2, 1.8 Hz, H-1″), 4.36 (1H, dd, J = 9.0, 1.8 Hz, H-2″), 4.96 (1H, d, J = 0.8 Hz, H-4″a), and 5.03 (1H, d, J = 0.8 Hz, H-4″b) gave evidence for a 2-hydroxy-3-methyl-3-butenyl side chain in the molecule of **4**. The HMBC correlations of H-4″b/C-2″, CH$_3$-5″; H-4″a/C-2″; H-2″/C-4″; H-1″/C-2″; and CH$_3$-5″/C-2″, C-3″, C-4″ also supported the occurrence of the partial structure CH$_2$CHOHC(CH$_3$)=CH$_2$; however, the stereochemistry of the chiral center was not determined. A NOE between H-1″ and OCH$_3$-6′ confirmed the placement of this side chain on C-5′. The quaternary carbon signals at δ 111.9, 161.6, and 163.9 were attributed to C-5′, C-6′, and C-4′ on the basis of HMBC cross-peaks from H-1″ to these carbon signals. An aromatic proton was fixed at C-3′, since it showed a HMQC connectivity with a carbon signal at δ 101.9 and HMBC correlations with C-5′, C-2′, and C-4′. From the foregoing spectral analysis, compound **4** (acronyculatin D) was assigned as 1-[2′,4′-dihydroxy-5′-(2″-hydroxy-3″-methyl-3″-butenyl)-6′-methoxy]acetophenone.

Acronyculatin E (**5**), isolated as a colorless syrup, exhibited a molecular ion peak at m/z 316.1675 in the HREIMS, consistent with the molecular formula $C_{19}H_{24}O_4$. The UV absorption maxima at 313, 264, and 206 nm and IR absorption bands at 2972 and 1646 cm^{-1} suggested a 2′-hydroxyacetophenone basic structure for **5**. The ^{1}H NMR spectrum of **5** showed signals corresponding to methyl, methoxyl, chelated hydroxyl, and isoprenyl groups [δ 2.67 (3H, s, CH$_3$-2); δ 3.72 (3H, s, OCH$_3$-6′); δ 13.52 (1H, s, OH-2′); δ 5.15 (1H, t, J = 6.6 Hz, H-2″), 3.23 (2H, d, J = 6.6 Hz, H-1″), 1.77 (3H, s, CH$_3$-4″), and 1.68 (3H, s, CH$_3$-5″)], respectively. In addition, two olefinic resonances of a *cis*-double bond at δ 6.67 (1H, d, J = 10.0 Hz, H-1‴) and 5.50 (1H, d, J = 10.0 Hz, H-2‴) and signals for a *gem*-dimethyl group at δ 1.43 (6H, s, CH$_3$-4‴, 5‴) were indicative of the presence of a 2,2-dimethylchromene ring, which might result from the cyclization of isoprenyl and hydroxyl groups. The positions of the methoxyl and isoprenyl groups were confirmed unambiguously through the NOESY cross-peaks of OCH$_3$-6′ with CH$_3$-2 and H-1″. In the HMBC experiment, the correlations from OCH$_3$-6′ to the carbon signal at δ 160.9 and from H-1′′ to carbons at δ 158.5, 114.9, and 160.9 enabled the assignments of quaternary carbons at C-4′, C-5′, and C-6′. Finally, the H-1′′′ resonance of the 2,2-dimethylchromene ring showed HMBC correlations with C-2′, C-3′ (δ 105.9), and C-4′, revealing C-3′ and C-4′ as its fused junction. Thus, **5** (acronyculatin E) was assigned as 1-[2′-hydroxy-6′-methoxy-5′-(2′′-hydroxy-3′′-methyl-3′′-butenyl)-3′,4′-(3′′′,3′′′-dimethyl-1′′′-pyrenyl)]acetophenone.

The known compound, acrovestone (**6**), was identified by comparison of its spectral data with those of an authentic sample.[10] The isolated compounds **1**−**6** were examined for their antioxidant properties using the α,α-diphenyl-β-picrylhydrazyl free radical (DPPH) assay. Compounds **1**−**5** were found to be inactive at 500 μM with inhibition percentages 3.1%, 5.3%, 8.3%, 10.3%, and 2.9%, respectively. Compound **6** exhibited weak scavenging activity with an IC_{50} value of 493 μM, compared to the reference compound, vitamin E (IC_{50}, 8.3 μM). In addition, the antityrosinase activities of **1**−**6** were also evaluated. Among these compounds, **1**−**5** were inactive as tyrosinase inhibitors at 500 μM, with 11.8%, 6.5%, 16.8%, 8.1% and 2.5% inhibition, respectively, and **6** exhibited weak inhibitory activity with an IC_{50} value of 333 μM, compared to the reference compound, kojic acid (IC_{50} value 125 μM).

Experimental Section

General Experimental Procedures. Melting points were recorded on a Yanaco MP-S3 micro-melting point apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-370 polarimeter. UV spectra were measured on a Hitachi UV-3210 spectrophotometer. CD spectra were recorded with a JASCO J-720 spectropolarimeter. IR spectra were obtained on a Shimadzu FT-IR 8501 spectrophotometer as KBr disks. ^{1}H, ^{13}C, HMQC, HMBC, and NOESY NMR spectra were measured on Bruker Avance-300, AMX-400, and Varian Unity Plus 400 spectrometers, using tetramethylsilane (TMS) as internal standard; all chemical shifts are reported in ppm (δ). EIMS and HREIMS were determined on a VG 70-250S spectrometer.

Plant Material. *Acronychia pedunculata* (L.) Miq. was collected in April 1985, from Taipei Hsien, Taiwan, and authenticated by Prof. C. S. Kuoh. A voucher specimen (NCKU Wu 1985000008) has been deposited at the herbarium of National Cheng Kung University, Tainan, Taiwan.

Extraction and Isolation. The combined stems and root bark of *A. pedunculata* (4.59 kg) were extracted with hot MeOH (10 L × 4) and concentrated to give a dark brown syrup (534 g), which was partitioned between H_2O and $CHCl_3$. The crude methanolic extract exhibited 37.9% inhibition in the DPPH assay at 500 mg/mL. The chloroform solubles showed DPPH radical-scavenging activity with an IC_{50} value of 295 mg/mL. The condensed chloroform extract (225 g) was dissolved in 5% hydrochloric acid solution and filtered. The residue (120 g) was chromatographed over silica gel using a step gradient of C_6H_6 and Me_2CO (9:1; 5:1; 3:1; 1:1) to afford five fractions. Fraction 1 was rechromatographed over silica gel using mixtures of *n*-hexane and EtOAc (7:1) as eluents and purified by preparative TLC with eluents of *n*-hexane and Me_2CO (9:1) to yield **1** (3.4 mg, 0.0028%), **2** (11.2 mg, 0.0093%), **3** (1.0 mg, 0.00083%), **4** (2.0 mg, 0.0017%), **5** (6.8 mg, 0.0057%), and **6** (6.3 g, 5.25%), successively.

Acronyculatin A (1): colorless syrup; UV (MeOH) λ_{max} (log ϵ) 344 (4.35), 275 (4.87), 261 (4.90) nm; IR ν_{max} 2924, 1629, 1436, 1368, 1311 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70 (3H, s, CH_3-5′′), 1.77 (3H, s, CH_3-4′′), 2.68 (3H, s, CH_3-2), 3.27 (2H, d, J = 6.6 Hz, H-1′′), 3.86 (3H, s, OCH_3-6′), 5.17 (1H, t, J = 6.6 Hz, H-2′′), 10.30 (1H, s, CHO-3′), 13.13 (s, OH-4′), 14.63 (s, OH-2′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9 (C-5′′), 21.9 (C-1′′), 25.7 (C-4′′), 31.0 (C-2), 62.7 (OCH_3-6′), 106.9 (C-1′), 107.1 (C-3′), 107.8 (C-4), 114.9 (C-5′), 121.8 (C-2′′), 132.6 (C-3′′), 168.5 (C-6′), 168.8 (C-2′), 168.9 (C-4′), 193.4 (CHO-3′), 213.1 (C-1); EIMS *m/z* 278 [M]$^+$ (71), 263 (100), 245 (17), 235 (32), 223 (37), 193 (19); HREIMS *m/z* 278.1154 [M]$^+$ (calcd for $C_{15}H_{18}O_5$, 278.1154).

Acronyculatin B (2): colorless powder; mp 118−119 °C; $[\alpha]^{25}_D$ −58.0° (*c* 0.013, MeOH); UV (MeOH) λ_{max} (log ϵ) 295 (4.23), 224 (4.24) nm; CD (*c* 0.00007, MeOH) (nm) $[\theta]_{506}$ −40.6, $[\theta]_{494}$ −20.5, $[\theta]_{485}$ −4.4, $[\theta]_{482}$ 0, $[\theta]_{456}$ +17.5; IR ν_{max} 2965, 2925, 2358, 1616, 1430, 1417, 1368, 1312 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (3H, s, CH_3-4′′′), 1.36 (3H, s, CH_3-5′′′), 1.67 (3H, s, CH_3-5′′), 1.76 (3H, s, H-4′′), 2.61 (3H, s, CH_3-2), 3.22 (2H, d, J = 6.6 Hz, H-1′′), 3.26 (2H, d, J = 8.0 Hz, H-1′′′), 3.90 (3H, s, OCH_3-6′), 4.64 (1H, t, J = 8.0 Hz, H-2′′′), 5.24 (1H, t, J = 6.6 Hz, H-2′′), 14.52 (s, OH-2′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8 (C-4′′), 22.1 (C-1′′′), 25.7 (C-4′′′), 25.8 (C-5′′, C-5′′′), 28.9 (C-1′′), 32.1 (C-2), 59.1 (OCH_3-6′), 71.8 (C-3′′′), 90.1 (C-2′′′), 106.5 (C-1′), 107.1 (C-5′), 108.2 (C-3′), 121.9 (C-2′′), 131.7 (C-3′′), 156.7 (C-6′), 164.7 (C-2′), 164.8 (C-4′), 203.0 (C-1); EIMS *m/z* 334 [M]$^+$ (100), 320 (80), 280 (83), 279 (37); HREIMS *m/z* 334.1780 [M]$^+$ (calcd for $C_{19}H_{26}O_5$, 334.1780).

Acronyculatin C (3): colorless syrup; UV (MeOH) λ_{max} (log ϵ) 340 (3.54), 262 (4.14) nm; IR ν_{max} 2932, 2358, 1697, 1616, 1589, 1420, 1369 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, s, CH_3-5′′′), 0.98 (3H, s, CH_3-4′′′), 1.69 (3H, s, CH_3-5′′), 1.77 (3H, s, CH_3-4′′), 2.27 (1H, sept, H-3′′′), 2.69 (3H, s, CH_3-2), 3.03 (2H, d, J = 6.7 Hz, H-2′′′), 3.28 (2H, d, J = 6.3 Hz, H-1′′), 3.77 (3H, s, OCH_3-6′), 5.18 (1H, t, J = 6.3 Hz, H-2′′), 15.12 (1H, s, OH-4′), 15.56 (1H, s, OH-2′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9 (C-5′′), 22.3 (C-1′′), 22.8 (C-4′′′, 5′′′), 24.9 (C-3′′′), 25.7 (C-4′′), 31.0 (C-2), 53.3 (C-2′′′), 62.6 (OCH_3-6′), 107.3 (C-1′), 107.4 (C-3′), 115.3 (C-5′), 122.3 (C-2′′), 132.2 (C-3′′), 168.6 (C-6′), 171.0 (C-4′), 174.1 (C-2′), 203.8 (C-1), 207.0 (C-1′′′); EIMS *m/z* 334 [M]$^+$ (15), 318 (16), 280 (100), 278 (11); HREIMS *m/z* 334.1780 [M]$^+$ (calcd for $C_{19}H_{26}O_5$, 334.1780).

Acronyculatin D (4): colorless syrup; $[\alpha]^{25}_D$ −31.0° (*c* 0.029, MeOH); UV (MeOH) λ_{max} (log ϵ) 285 (3.97), 219 (4.05) nm; IR ν_{max} 2941, 1621, 1417, 1366, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86 (3H, s, CH_3-5′′), 2.69 (3H, s, CH_3-2), 2.72 (1H, dd, J = 15.2, 9.0 Hz, H-1′′), 3.03 (1H, dd, J = 15.2, 1.8 Hz, H-1′′), 3.70 (3H, s, OCH_3-6′), 4.36 (1H, dd, J = 9.0, 1.8 Hz, H-2′′), 4.96 (1H, d, J = 0.8 Hz, H-4′′a), 5.03 (1H, d, J = 0.8 Hz, H-4′′b), 6.31 (1H, s, H-3′), 13.03 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0 (C-5′′), 29.6 (C-1′′), 30.7 (C-2), 63.2 (OCH_3-6′), 78.3 (C-2′′), 101.9 (C-3′), 109.3 (C-1′), 111.5 (C-4′′), 111.9 (C-5′), 146.5 (C-3′′), 161.6 (C-6′), 163.9 (C-4′), 164.6 (C-2′), 203.2 (C-1); EIMS *m/z* 266 [M]$^+$ (13), 195 (100), 181 (12); HREIMS *m/z* 266.1153 [M]$^+$ (calcd for $C_{14}H_{18}O_5$, 266.11154).

Acronyculatin E (5): colorless syrup; UV (MeOH) λ_{max} (log ϵ) 313 (3.84), 264 (4.30), 206 (4.06) nm; IR ν_{max} 2972, 2926, 1646, 1610, 1458, 1311 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (6H, s, CH_3-4′′′, 5′′′), 1.68 (3H, s, H-5′′), 1.77 (3H, s, H-4′′), 2.67 (3H, s,CH_3-2), 3.23 (2H, d, J = 6.6 Hz, H-1′′), 3.72 (3H, s, OCH_3-6′), 5.15 (1H, t, J = 6.6 Hz, H-2′′), 5.50 (1H, d, J = 10.0 Hz, H-2′′′), 6.67 (1H, d, J = 10.0 Hz, H-1′′′), 13.52 (s, OH-2′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9 (C-4′′), 22.2 (C-1′′), 25.7 (C-5′′), 28.3 (C-4′′′, 5′′′), 30.9 (C-2), 62.8 (OCH_3-6′), 77.9 (C-3′′′), 105.9 (C-3′), 108.9 (C-1′), 114.9 (C-5′), 116.1 (C-2′′′), 123.1 (C-2′′), 126.7 (C-1′′′), 131.3 (C-3′′), 158.5 (C-4′), 159.0 (C-2′), 160.9 (C-6′), 203.5 (C-1); EIMS *m/z* 316 [M]$^+$ (28), 302 (100); HREIMS *m/z* 316.1675 [M]$^+$ (calcd for $C_{19}H_{24}O_4$, 316.1675).

Antioxidant Assay. The antioxidant assay was based on methods reported by Ko et al.[14] and Mellors and Tappel.[15] The percentage values of inhibition were recorded after incubating for 30 min.

Antityrosinase Assay. The antityrosinase assay was based on the method of Bernard and Berthon.[16]

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