New Diarylheptanoids from the Stems of *Carpinus cordata*

Ji Sun Lee, Hyoung Ja Kim, Hokoon Park, and Yong Sup Lee*

Division of Life Sciences, Korea Institute of Science & Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea

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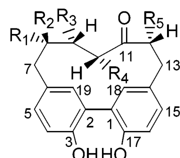
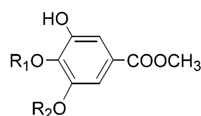
Two new diarylheptanoids, carpinontriols A (**1**) and B (**2**), were isolated from the stems of *Carpinus cordata*, along with the known diarylheptanoid, casuarinondiol (**3**), and five known compounds, (+)-catechin (**4**), methyl gallate (**5**), methyl gallate 3-*O*-*β*-D-glucopyranoside (**6**), methyl gallate 4-*O*-*β*-D-glucopyranoside (**7**), and methyl gallate 3-*O*-*β*-D-(6′-*O*-galloyl)-glucopyranoside (**8**). The structures of **1** and **2** were elucidated by spectral methods. Among the isolated compounds, compounds **4**−**6** and **8** showed radical-scavenging activity in the DPPH assay.

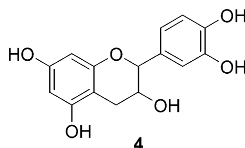
Carpinus cordata Blume (Betulaceae) is a deciduous shrub widely distributed in Korea, Japan, and China. The genus *Carpinus* is known to contain numerous diarylheptanoids as well as tannins.[1,2] During our search for antioxidant compounds from natural products, a crude extract of the stems of *C. cordata* was found to exhibit significant radical-scavenging activity in the 1,1-diphenyl-2-dipicrylhydrazyl (DPPH) test. By means of bioassay-guided chromatographic separation, two new diarylheptanoids, carpinontriol A (**1**) and carpinontriol B (**2**), and the known casuarinondiol (**3**)[3,4] together with five known compounds, (+)-catechin (**4**),[5,6] methyl gallate (**5**),[7] methyl gallate 3-*O*-*β*-D-glucopyranoside (**6**),[8,9] methyl gallate 4-*O*-*β*-D-glucopyranoside (**7**),[8,10] and methyl gallate 3-*O*-*β*-D-(6′-*O*-galloyl)-glucopyranoside (**8**),[11,12] were isolated. Of the isolates, compounds **5**, **6**, and **8**, along with the known antioxidant compound (+)-catechin (**4**) showed significant radical-scavenging effects. We describe herein the isolation of two new diarylheptanoids, the structures of which were determined by analysis of spectral data (^{1}H−^{1}H COSY, DEPT, NOE, HMQC, and HMBC) and the antioxidant evaluation of the isolated compounds.



1 $R_1 = R_3 = R_5 = OH$, $R_2 = R_4 = H$
2 $R_1 = R_3 = R_4 = OH$, $R_2 = R_5 = H$
3 $R_2 = R_5 = OH$, $R_1 = R_3 = R_4 = H$



5 $R_1 = R_2 = H$
6 $R_1 = H$, R_2 = (β)-D-Glc.
7 R_1 = (β)-D-Glc., $R_2 = H$
8 $R_1 = H$, R_2 = 6-galloyl-(β)-D-Glc.



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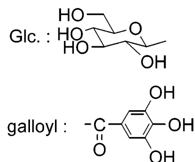

The MeOH extract of the stems of *C. cordata* was suspended in water and then consecutively partitioned with dichloromethane, ethyl acetate, and *n*-butanol. The ethyl acetate extract showed the greatest radical-scavenging activity in the DPPH test; therefore this fraction was purified by column chromatography on Sephadex LH-20, as well as a combination of chromatography over silica gel and RP-18, to afford the new compounds **1** and **2**. The known compounds **3**−**8** were identified by comparison of their spectral data with literature values.

Compound **1** was obtained as white amorphous powder, and its molecular formula was established as $C_{19}H_{20}O_6$ by HREIMS (*m/z* 344.1245 [M]$^+$). The ^{1}H NMR spectrum of **1** displayed signals at δ 6.46 (d, $J = 2.1$ Hz), 6.69 (d, $J = 8.0$ Hz), and 6.90 (dd, $J = 8.1$, 2.3 Hz), and 6.55 (d, $J = 2.3$ Hz), 6.70 (d, $J = 8.0$ Hz), and 6.95 (dd, $J = 8.2$, 2.3 Hz), assignable to six aromatic protons of two ABX systems. The chemical shifts of seven carbons of **1** at δ 39.2 (t), 39.4 (t), 46.6 (t), 69.2 (d), 73.6 (d), 78.0 (d), and 218.5 (s) in the ^{13}C NMR and DEPT spectra implied that this system contained three methylene carbons, three secondary hydroxy groups, and one carbonyl group. In the ^{1}H−^{1}H COSY spectrum of **1**, the signals at δ 3.91−3.96 (m, H-8, H-9) showed correlations with the signals at δ 2.78 of H-7α and 2.86 of H-7β and the signals at δ 2.64 of H-10α and 3.64 of H-10β, respectively. The H-12 methine proton (δ 4.33) appeared as a doublet of doublets ($J = 6.5$, 2.0 Hz) and showed a correlation only with the proton signals (2H, H-13) at δ 2.87 and 3.04. In the HMBC spectrum, the signal at δ 4.33 (H-12) showed a correlation with the carbonyl signal at δ 218.5. Therefore, the positions of these three hydroxy groups were confirmed as C-8, C-9, and C-12, and the carbonyl group was placed at C-11. Also, the signal at δ 6.55 (H-19) of the aromatic ring was correlated with the signal at δ 127.8 (C-1) of another aromatic ring, indicating that the two aromatic rings were connected through a C-1 and C-2 linkage. The aromatic proton signals at δ 6.55 and 6.95 showed a correlation with the signal at δ 39.4 (C-7), and the other aromatic proton signals at δ 6.46 and 6.90 correlated with the signal at δ 39.2 (C-13), indicating the location of these carbons as shown in Figure 1. The relative stereochemistry of H-8 and H-9 was shown to be *syn* by the chemical shifts of two isopropylidene methyl protons (δ_H 1.42 and 1.49) and carbons (δ_C 25.8 and 26.5) of the 8,9-acetonide derivative (**1a**) of **1**, the positions of which were apparent from the downfield shift of C-8 and C-9 as was previously observed in the literature.[13,14] An NOE difference spectrum of **1** allowed the assignment of the relative stereochemistry of hydroxyl groups at C-8, C-9, and C-12. From MM2 calculations and molecular modeling, the most stable conformation of **1** is as proposed in Figure 1. When H-10β was irradiated, the H-19, H-18, H-10α, and H-9 signals showed peak enhancements. On the other hand, when H-10α was irradiated, only the H-12 and H-10β signals showed peak enhancements. The irradiation of the

* To whom correspondence should be addressed. Tel: +82-2-958-5167. Fax: +82-2-958-5189. E-mail: yslee@kist.re.kr.

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Table 1. ^{1}H, ^{13}C NMR Data (δ) and HMBC NMR Correlation of Compounds **1** (CD_3OD) and **2** ($CDCl_3$)[a]

position	1			2		
	^{13}C	^{1}H	HMBC (^{13}C)	^{13}C	^{1}H	HMBC (^{13}C)
1	127.8			126.6		
2	127.1			127.5		
3	152.8			152.8		
4	117.1	6.70 (d, 8.0)	2	117.0	6.76 (d, 8.2)	2, 3, 6
5	130.8	6.95 (dd, 8.2, 2.3)	3, 7, 19	130.8	6.98 (dd, 8.2, 2.2)	3, 7, 19
6	130.4			130.7		
7α	39.4	2.78 (dd, 15.7, 9.3)	8, 9	37.1	2.87 (dd, 15.9, 12.0)	6, 8, 9, 19
7β		2.86 (dd, 16.1, 3.0)	6, 8, 9, 19		3.04 (dd, 15.9, 4.4)	6, 8, 9, 19
8	69.2	3.91−3.96 (m)		68.6	4.71 (dd, 11.8, 4.4)	7
9	73.6	3.91−3.96 (m)		69.8	3.87 (d, 10.1)	10, 11
10α	46.6	2.64 (dd, 18.6, 8.4)	8	78.7	4.21 (d, 10.1)	8, 9, 11
10β		3.64 (dd, 18.4, 1.3)				
11	218.5			215.7		
12α	78.0	4.33 (dd, 6.5, 2.0)	11, 13, 14	37.6	2.91 (ddd, 20.1, 4.9, 2.0)	11, 14
12β					3.48 (ddd, 20.1, 12.6, 2.2)	11, 13
13α	39.2	2.77 (dd, 15.4, 6.5)	11, 12, 14, 15, 18	25.3	3.11 (dd, 16.7, 12.6)	12, 14, 18
13β		3.42 (d, 15.3)	12, 14, 15, 18		2.81 (ddd, 16.7, 4.9, 2.0)	11, 12, 14, 18
14	129.8			131.3		
15	131.4	6.90 (dd, 8.1, 2.3)	13, 17, 18	129.6	7.04 (dd, 8.2, 2.4)	13, 17, 18
16	116.8	6.69 (d, 8.0)	14, 17	117.0	6.79 (d, 8.2)	1, 14, 17
17	153.0			151.9		
18	135.1	6.46 (d, 2.1)	2, 13, 15, 17	135.1	6.32 (d, 1.9)	2, 13, 15, 17
19	135.7	6.55 (d, 2.3)	1, 3, 5, 7	135.0	6.63 (d, 1.9)	1, 3, 5, 7

[a] Values in parentheses are coupling constants (in Hz). Spectra were measured at 125 and 500 MHz.

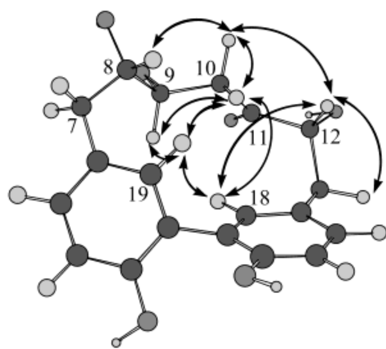

Figure 1. ChemDraw 3D model of carpinontriol A (**1**) showing NOE correlations (↔).

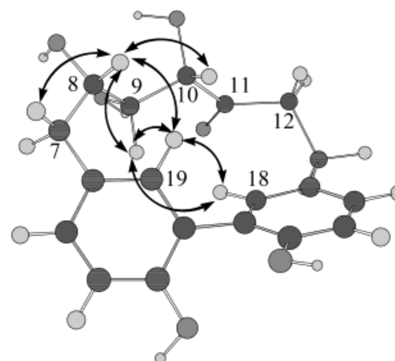

Figure 2. ChemDraw 3D model of carpinontriol B (**2**) showing NOE correlations (↔).

H-12 signal also enhaned the H-13 and H-18 signals. These results enabled the hydroxy groups at C-8, C-9, and C-12 to be assigned in the α-configuration. Accordingly, the structure of **1** was determined as shown in Figure 1, and the compound has been named carpinontriol A.

Compound **2** was obtained as colorless needles, and its molecular formula was established as $C_{19}H_{20}O_6$ by HREIMS (*m/z* 344.1263 [M]$^+$). The structure of **2** was similar to that of **1**, except for the positional difference of the hydroxy group located on the aliphatic ring. The ^{1}H and ^{13}C NMR spectrum of **2** suggested that this compound is also a diarylheptanoid with two aromatic rings as ABX systems, as well as three hydroxy groups on the aliphatic ring. In the ^{1}H−^{1}H COSY spectrum of **2**, the H-8 methine proton at δ 4.71 (dd, J = 11.8, 4.4 Hz) showed a correlation with the proton signals (2H, H-7) at δ 2.87 (dd, J = 15.9, 12.0 Hz) and δ 3.04 (dd, J = 15.9, 4.4 Hz). The signal at δ 3.87 (d, J = 10.1 Hz, H-9) correlated with the signal at δ 4.21 (d, J = 10.1 Hz, H-10). However, the coupling of H-8 and H-9 was not observed, probably due to the gauche dihedral angle. The HMBC spectrum also showed cross-peaks between H-7 and C-8, H-9 and C-10, and H-10 and C-11. The H-8 signal showed a correlation only with the signal of C-7. Therefore, the position of these hydroxy groups was confirmed as C-8, C-9, and C-10, and the position of the carbonyl group was determined as C-11. The relative stereochemistry of H-8, H-9, and H-10 was shown to be *syn* from the chemical shift of isopropylidene methyl groups in the 8,9- and 9,10-acetonide derivatives (**2a-1** and **2a-2**) of **2**.[3,4] From MM2 calculations and molecular modeling, the most stable conformation of **2** is as proposed in Figure 2. In the NOE difference spectrum of **2**, when H-9 was irradiated, the H-19, H-18, and H-8 signals showed peak enhancements. When H-19 was irradiated, the H-18, H-9, and H-8 signals showed peak enhancements. These results indicated that three hydroxy groups at C-8, C-9, and C-10 are located in the same orientation. Thus, the structure of **2** was assigned as shown in Figure 2, and the compound has been named carpinontriol B.

The antioxidant activities of the *C. cordata* isolates were investigated. The activity data of resveratrol and (−)-epigallocatechin gallate (EGCG) were included as standard compounds for comparison due to their well-known antioxidant activities. As shown in Table 2, compounds **1** and **2** showed only weak antioxidant activity with IC_{50} values of >100 and 80.2 μg/mL, respectively. On the other hand, methyl gallate (**5**), methyl gallate 3-*O*-β-D-glucopyranoside (**6**), and methyl gallate 3-*O*-β-D-(6′-*O*-galloyl)glucopyranoside (**8**) showed significant radical-scavenging activity in the DPPH assay (IC_{50} = 4.6−4.9 μg/mL). The activities of these compounds were more potent than resveratrol (IC_{50} = 16.2 μg/mL) and comparable to EGCG (IC_{50} = 2.7 μg/mL). Interestingly, methyl gallate 4-*O*-β-D-glucopyranoside (**7**) exhibited no radical-scavenging activity at a concentra-

Table 2. Antioxidant Activities of Compounds **1**−**8** in the DPPH Assay[a]

compound	IC_{50} (μg/mL)	compound	IC_{50} (μg/mL)
1	>100	**6**	4.6
2	80.2	**7**	>100
3	>100	**8**	4.9
4	2.7	resveratrol	16.2
5	4.9	EGCG[b]	2.7

[a] IC_{50} values with standard deviation are from at least three independent experiments. [b] EGCG = (−)-epigallocatechin gallate.

tion of 100 μg/mL. The potent antioxidant activity of **6** and **8** as compared with that of **7** is likely due to the position of the glucose unit in the methyl gallate molecule. Among the isolates obtained, (+)-catechin (**4**) had the most potent radical-scavenging activity (IC_{50} = 2.7 μg/mL), consistent with previous biological results.[15]

Experimental Section

General Experimental Procedures. Melting points were measured on a Thomas-Hoover capillary melting apparatus and are uncorrected. Optical rotations were determined on an Autopol III automatic polarimeter (Rudolph Research Co., Flanders, NJ). IR spectra were recorded on Perkin-Elmer 16F-PC FT-IR and Midac 101025 instruments using potassium bromide pellets. ^{1}H NMR spectra were recorded on Bruker 300 and 500 (300 and 500 MHz) spectrometers using TMS as internal standard. ^{13}C NMR spectra were recorded on Bruker 300 and 500 (75 and 125 MHz) spectrometers. ^{1}H−^{1}H COSY, HMQC, and HMBC NMR spectra were obtained with the usual pulse sequences, and data processing was performed with the standard Bruker software. HREIMS and HRCIMS were determined on a JEOL JMS-HX 110/100A (Japan) mass spectrometer. Preparative HPLC was performed on a Waters pump (model 510) with a photodiode array detector (Waters model 996) using a ChiraSper (10 mm × 250 mm, Merck) column. TLC and column chromatography were carried out on precoated silica gel F_{254} plates (Merck, art. 5715), RP-18 F_{254S} plates (Merck, art. 15423), silica gel 60 (230−400 mesh, Merck), and Lichroprep RP-18 (Merck, 40−63 μm).

Plant Material. The stems of *Carpinus cordata* were collected at Mt. Odae, Korea, in October 1997 and identified by Dr. J. H. Kwak. Voucher specimens (642-16C) were deposited in our laboratory at the Korea Institute of Science & Technology.

Extraction and Isolation. Dried stems (4.6 kg) of *C. cordata* were cut into small pieces and percolated three times with MeOH at room temperature to afford 190.6 g of a residue on removal of solvent under reduced pressure. The methanol extract was suspended in water and then partitioned in turn with dichloromethane, ethyl acetate, and *n*-butanol. The ethyl acetate extract was evaporated under reduced pressure to yield 8.83 g of a residue. The residue was separated by column chromatography (50 × 340 mm) on Sephadex LH-20 with MeOH. Fractions were combined based on their TLC pattern to yield six fractions designated as C1−C6. Fraction C3 (2.3 g) was chromatographed over silica gel (100 g) with a CH_2Cl_2−MeOH−H_2O gradient system to give six subfractions (C3A−C3F). Subfraction C3C was further purified by column chromatography over RP-18 using CH_3CN−H_2O (3:7) as eluent to afford 74.4 mg of compound **1**. Subfraction C3D was chromatographed over silica gel with CH_2Cl_2-MeOH (15:1) and finally purified by preparative HPLC (ChiraSpher 250−10, Merck) eluted with *n*-hexane-IPA-MeOH (63:21.1:15.9) to give 36.4 mg of compound **2** and 15.6 mg of compound **3**. Subfraction C3E was further purified by column chromatography over RP-18 using CH_3CN−H_2O (35:65) to give (+)-catechin (**4**) (50.7 mg) as white needles. Fraction C4 (389.9 mg) was subjected to a series of purification steps using Sephadex LH-20, RP-18, and silica gel column chromatography to obtain methyl gallate (**5**) (28.7 mg), methyl gallate 3-*O*-β-D-glucopyranoside (**6**) (10.1 mg), methyl gallate 4-*O*-β-D-glucopyranoside (**7**) (10.2 mg), and methyl gallate 3-*O*-β-D-(6′-*O*-galloyl)-glucopyranoside (**8**) (8.9 mg).

Carpinontriol A (1): amorphous powder; mp 157−159 °C; $[\alpha]^{28}_{D}$ +12.7° (*c* 0.58, MeOH); IR (KBr) ν_{max} 3402, 2927, 1704, 1510 cm^{-1}; ^{1}H, ^{13}C, and HMBC NMR data, see Table 1; HREIMS *m*/*z* 344.1245 [M]$^+$ (calcd for $C_{19}H_{20}O_6$ 344.1260).

Acetonide of 1 (1a). A solution of **1** (9.3 mg) in dry acetone (10 mL) containing one drop of concentrated H_2SO_4 was left to stand at room temperature for 30 min. The solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to give **1a** (8,9-acetonide **1**; 10.1 mg). Compound **1a**: amorphous powder; mp 132−135 °C; $[\alpha]^{28}_{D}$ −64.8° (*c* 0.4, EtOAc); IR (KBr) ν_{max} 3420, 2927, 1708, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42, 1.49 (each 3H, s, isopropylidene-Me_2), 3.02 (1H, dd, *J* = 16.2, 5.0 Hz, H-13), 3.04 (1H, m, H-7), 3.08 (1H, d, *J* = 20.5 Hz, H-10), 3.14 (1H, dd, *J* = 15.1, 3.0 Hz, H-7), 3.67 (1H, d, *J* = 14.6 Hz, H-13), 3.82 (1H, d, *J* = 20.6 Hz, H-10), 4.16 (1H, m, H-8), 4.49 (1H, dd, *J* = 5.1, 2.4 Hz, H-12), 4.90 (1H, t, *J* = 6.2 Hz, H-9), 6.57 (1H, d, *J* = 2.0 Hz, H-19), 6.75 (1H, d, *J* = 2.0 Hz, H-18), 6.83 (1H, d, *J* = 7.8 Hz, H-16), 6.84 (1H, d, *J* = 8.0 Hz, H-4), 7.00 (1H, dd, *J* = 8.2, 2.1 Hz, H-15), 7.04 (1H, dd, *J* = 8.2, 2.1 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.7, 27.3 (isopropylidene-Me_2), 38.2 (C-13), 40.3 (C-7), 47.8 (C-10), 76.2 (C-9), 76.7 (C-12), 81.4 (C-8), 109.0 (isopropylidene quaternary carbon), 116.5 (C-16), 116.7 (C-4), 125.9 (C-1, 2), 127.4 (C-14), 129.1 (C-6), 129.7 (C-5), 129.9 (C-15), 133.3 (C-18, 19), 151.3 (C-3), 151.4 (C-17), 213.5 (C-11); HRCIMS *m*/*z* 385.1651 [M + H]$^+$ (calcd for $C_{22}H_{25}O_6$ 385.1651).

Carpinontriol B (2): colorless needles; mp 232−235 °C; $[\alpha]^{28}_{D}$ +65.9° (*c* 0.735, MeOH); IR (KBr) ν_{max} 3408, 2937, 1720, 1526, 1421 cm^{-1}; ^{1}H, ^{13}C, and HMBC NMR data, see Table 1; HREIMS *m*/*z* 344.1263 [M]$^+$ (calcd for $C_{19}H_{20}O_6$, 344.1260).

Acetonides of 2 (2a-1 and 2a-2). Compound **2** (13.6 mg) was transformed to the 8,9-acetonide of **2** (**2a-1**, 3.3 mg) and the 9,10-acetonide of **2** (**2a-2**, 12.7 mg) by the same method with compound **1**. Compound **2a-1:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49, 1.54 (each 3H, s, isopropylidene-Me_2), 2.85−3.30 (6H, m, H-7, 12, 13), 4.41 (1H, m, H-8), 4.51 (1H, dd, *J* = 7.5, 2.3 Hz, H-10), 4.85 (1H, dd, *J* = 5.9, 2.4 Hz, H-9), 6.43 (1H, d, *J* = 2.1 Hz, H-19), 6.50 (1H, d, *J* = 2.1 Hz, H-18), 6.78 (1H, d, *J* = 8.2 Hz, H-4), 6.85 (1H, d, *J* = 8.1 Hz, H-16), 7.04 (1H, dd, *J* = 8.2, 2.1 Hz, H-5), 7.06 (1H, dd, *J* = 8.0, 2.1 Hz, H-15); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.2, 28.0 (isopropylidene-Me_2), 27.8 (C-13), 36.8 (C-7), 39.4 (C-12), 77.0 (C-8), 77.4 (C-9), 79.1 (C-10), 109.9 (isopropylidene quaternary carbon), 116.6 (C-4), 116.7 (C-16), 124.8 (C-1), 126.4 (C-2), 128.9 (C-6, 15), 130.5 (C-5), 131.5 (C-14), 133.6 (C-19), 133.8 (C-18), 149.8 (C-17), 151.5 (C-3), 210.2 (C-11); HRCIMS *m*/*z* 385.1648 [M + H]$^+$ (calcd for $C_{22}H_{25}O_6$ 385.1651).

Compound 2a-2: amorphous powder; $[\alpha]^{28}_{D}$ +27.0° (*c* 0.64, EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48, 1.50 (each 3H, s, isopropylidene-Me_2), 2.72 (1H, dd, *J* = 16.3, 12.4 Hz, H-7), 2.85−2.92 (2H, m, H-12, 13), 3.20 (1H, m, H-13), 3.25 (1H, dd, *J* = 16.2, 4.2 Hz, H-7), 3.55 (1H, dd, *J* = 20.9, 3.4 Hz, H-12), 4.49−4.55 (3H, m, H-8, 9, 10), 6.37 (1H, br s, H-18), 6.46 (1H, br s, H-19), 6.81 (1H, d, *J* = 8.2 Hz, H-16), 6.84 (1H, d, *J* = 8.2 Hz, H-4), 7.01 (1H, br d, *J* = 8.2 Hz, H-5), 7.07 (1H, dd, *J* = 8.2, 1.9 Hz, H-15); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1 (C-13), 26.8, 27.2 (isopropylidene-Me_2), 35.6 (C-10), 37.1 (C-7), 65.9 (C-8), 76.2 (C-9), 82.7 (C-10), 111.4 (isopropylidene quaternary carbon), 116.5 (C-16), 116.6 (C-4), 125.0 (C-1), 125.7 (C-2), 129.0 (C-15), 129.2 (C-6), 130.0 (C-5), 130.6 (C-14), 133.2 (C-18), 133.3 (C-19), 149.5 (C-17), 151 (C-3), 209.3 (C-11); HRCIMS *m*/*z* 385.1653 [M + H]$^+$ (calcd for $C_{22}H_{25}O_6$ 385.1651).

Evaluation of Antioxidant Activity. The potential antioxidant activity of plant extracts and pure compounds was assessed on the basis of the scavenging activity of the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical. Reaction mixtures containing test samples (dissolved in EtOH) and 100 μM DPPH ethanolic solution in 96-well microtiter plates were incubated at 37 °C for 30 min, and absorbances were measured at 515 nm. Percent inhibition was determined by comparison

with an ethanol-treated control group. IC_{50} values denote the concentration of samples required to scavenge 50% DPPH free radicals.[16]

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