Chemical Constituents of the Bark of *Machilus wangchiana* and Their Biological Activities

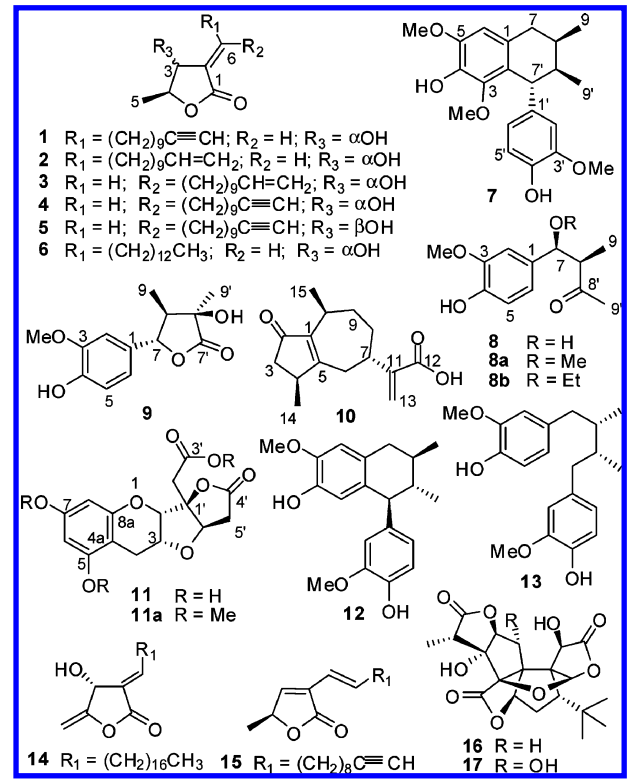
Wei Cheng, Chenggen Zhu, Wendong Xu, Xiaona Fan, Yongchun Yang, Yan Li, Xiaoguang Chen, Wenjie Wang, and Jiangong Shi*

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College (Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education), Beijing 100050, People's Republic of China

Received August 16, 2009

Eleven new metabolites, butanolides **1**−**6**, lignan derivatives **7**−**9**, sesquiterpene **10**, and 3′,4′-seco-flavane derivative **11**, have been isolated from an ethanol extract of *Machilus wangchiana*. Twenty known compounds, including ginkgolides A and B (**16** and **17**), were also isolated. Their structures and absolute configurations were determined by spectroscopic and chemical methods. Compounds **7**, **8a**, **8b**, **9**, **11**, (+)-guaiacin (**12**), *meso*-dihydroguaiaretic acid (**13**), and hamabiwalactone A (**15**) showed potent in vitro activities against the release of β-glucuronidase in rat polymorphonuclear leukocytes (PMNs) induced by platelet-activating factor (PAF), with 42.5−75.6% inhibition at 10^{-5} M. Compounds **8**, **8a**, **8b**, **9**, and **11** reduced DL-galactosamine (GalN)-induced hepatocyte (WB-F344 cells) damage with 39.4 ± 6.3% to 53.6 ± 3.5% inhibition at 10^{-4} M. Isomahubannolide-23 (**14**) was cytotoxic against human stomach cancer (BGC-823) and ovarian cancer (A2780) cell lines, with IC_{50} values of 0.13 and 2.66 μM, respectively.

Species of the genus *Machilus* are widely distributed in southeastern Asia, especially in southern China.[1] Lignans,[2] butanolides,[3] sesquiterpenes,[3] alkaloids,[4] and flavonoids[5] have been reported from several plants of this genus. As part of a program to study traditional Chinese medicines,[6] an ethanolic extract of the bark of *Machilus wangchiana* Chun. (Lauraceae) was investigated. In this paper, we describe the isolation, structural elucidation, and some in vitro bioassays of 11 new compounds, butanolides (**1**−**6**), lignan derivatives (**7**−**9**), a sesquiterpene (**10**), and a 3′,4′-seco-flavan derivative (**11**), and 20 known compounds from this material. It is of interest to note that *Ginkgo biloba* (maidenhair) metabolites, ginkgolides A (**16**) and B (**17**),[7] were present in this material.



Results and Discussion

Compound **1**, a colorless oil, $[\alpha]^{20}_D$ +26 (*c* 0.11, $CHCl_3$), showed the presence of hydroxy (3341 cm^{-1}), alkyne (2117 cm^{-1}), and lactone (1738 and 1678 cm^{-1}) functional groups in its IR spectrum. The molecular formula ($C_{17}H_{26}O_3$) was determined by HRESIMS. The ^{1}H NMR spectrum showed signals similar to those of litsenolide B_2[8] and lincomolide B[9] at δ 6.98 (t, J = 7.5 Hz, H-6), 4.53 (1H, brs, H-3), 4.50 (1H, q, J = 6.5 Hz, H-4), 2.18 (dt, J = 2.0, 7.0 Hz, H-15), 1.94 (d, J = 2.0 Hz, H-17), and 1.34 (d, J = 6.5 Hz, H-5) (Table 1). The chemical shifts and coupling patterns of H-3 and H-4 suggested that the relative configuration of **1** was identical to that of litsenolide B_2. This conclusion was supported by comparison of the ^{13}C NMR data of **1** (Table 2) with those of reported compounds having a *trans*-relationship between H-3 and H-4.[8] The chemical shift for C-5 of **1** (δ 19.7) and C-5 of the *cis*-form occurs near δ 14.0.[8b,9,10] The positive $[\alpha]^{20}_D$ of **1** suggested that its absolute configuration was opposite that of litsenolide B_2.[8a,11] This was verified by chemical transformation[12] and by the modified Mosher method[13] (Supporting Information, Scheme S1). Hydrogenation of **1** (Pd/C) yielded **1a**. Acetylation of **1a** followed by elimination of the acetoxy group yielded **1c** {$[\alpha]^{20}_D$ +27 (*c* 0.12, $CHCl_3$)}, having spectroscopic data consistent with those of (+)-(5*S*)-3-dodecyl-5-methylfuran-2(5*H*)-one {$[\alpha]^{25}_D$ +24.0 (*c* 0.2, dioxane)}.[14] Esterification of **1** with *R*-(−)- and *S*-(+)-α-methoxy-α-(trifuromethyl)phenylacetyl chloride (MTPACl) under normal conditions[15] failed to give the MTPA esters of **1**, but instead gave the decarboxylation product **1d**, (*E*)-hexadeca-3-ene-15-ynyl-2,5-dione, which was identified incorrectly as 2-hydroxy-5-methyl-3-[1-tridecanol]-furan in the literature.[10c] However, the hydrogenated product (**1a**) was esterified successively by *R*-(−)- and *S*-(+)-MTPACl to give the corresponding *S*-MTPA and *R*-MTPA derivatives. The ^{1}H NMR data of the diastereomers (Experimental Section) were assigned on the basis of their ^{1}H−^{1}H COSY experiments. From the MTPA determination rule,[13,16] it was determined that **1a** has a 3*R* configuration. Thus, **1** was determined to be (+)-(2*E*,3*R*,4*S*)-2-(dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide.

Compound **2** had the molecular formula $C_{17}H_{28}O_3$, two hydrogen atoms more than that of **1** (HRESIMS). The IR spectrum of **2** resembled that of **1**; however, the absence of the alkyne absorption suggested that **2** was a 16,17-dihydrogenated analogue of **1**. This was supported by a replacement of the NMR resonances for the ethynyl unit of **1** by those for a terminal vinyl group of **2** [δ_H 5.80 (ddt, J = 17.0, 10.0, and 7.0 Hz, H-16), 4.98 (d, J = 17.0 Hz,

* To whom correspondence should be addressed. Tel: 86-10-83154789. Fax: 86-10-63017757. E-mail: shijg@imm.ac.cn.

10.1021/np900504a
Published on Web 11/16/2009

Table 1. ^{1}H NMR Spectroscopic Data (δ) of Compounds **1**−**6** ($CDCl_3$, 500 MHz)[a]

no.	1	2	3	4	5	6
3	4.53 brs	4.52 brs	4.35 brs	4.33 brs	4.65 d (4.5)	4.56 d (1.5)
4	4.50 q (6.5)	4.50 q (6.5)	4.38 q (6.0)	4.32 q (6.0)	4.55 dq (4.5, 6.5)	4.50 dq (1.5, 6.5)
5	1.34 d (6.5)	1.33 d (6.5)	1.38 d (6.0)	1.38 d (6.0)	1.40 d (6.5)	1.35 d (6.0)
6	6.98 t (7.5)	6.95 t (8.0)	6.53 t (7.5)	6.53 t (7.5)	6.56 t (7.5)	7.01 t (7.5)
7	2.40 m	2.39 m	2.75 m	2.74 m	2.75 m	2.40 m
15	2.18 dt (2.0, 7.0)	2.02 q (7.0)	2.02 q (7.0)	2.17 dt (2.5, 7.0)	2.18 dt (2.0, 7.0)	
16		5.80 ddt (17.0, 10.0, 7.0)	5.81 ddt (17.5, 10.0, 7.0)			
17	1.94 t (2.0)	4.98 d (17.0); 4.92 d (10.0)	4.99 d (17.5); 4.92, d (10.0)	1.93 t (2.5)	1.94 t (2.0)	
19						0.88 t (7.0)

[a] Proton coupling constants (J) in Hz are given in parentheses. The methylene proton resonances at positions 8−14 were overlapped between δ 1.25 and 1.55 for **1**, **2**, and **4**, between δ 1.25 and 1.50 for **3**, and between δ 1.25 and 1.65 for **5**, while the methylene protons at positions 8−18 of **6** were overlapped between δ 1.25 and 1.60.

Table 2. ^{13}C NMR Spectroscopic Data (δ) of Compounds **1**−**6** ($CDCl_3$, 125 MHz)[a]

no.	1	2	3	4	5	6
1	169.4	169.7	168.0	168.1	168.5	169.8
2	129.3	129.3	128.8	128.8	129.3	129.3
3	82.5	82.6	81.2	81.3	77.7	82.4
4	72.2	72.2	75.6	75.6	71.4	72.2
5	19.7	19.7	19.1	19.1	14.1	19.7
6	148.6	147.7	149.3	149.2	149.6	148.7
7	29.7	29.7	27.8	27.7	27.9	31.9
15	18.4	33.8	33.8	18.4	18.4	
16	84.7	139.2	139.2	84.8	84.8	
17	68.1	114.1	114.1	68.1	68.0	
18						22.7
19						14.1

[a] The methylene carbon resonances at positions 8−14 were overlapped between δ 18.4 and 29.3 for **1**, **4**, and **5**, between δ 28.4 and 29.4 for **3**, and between δ 28.8 and 29.4 for **5**. The methylene carbon resonances at positions 8−17 of **6** were overlapped between δ 28.4 and 29.7.

H-17a), and 4.92 (d, J = 10.0 Hz, H-17b), and δ_C 139.2 (C-16) and 114.1 (C-17)]. In addition, the NMR data for H-3 and H-4 and C-5 of **2** (Tables 1 and 2), together with the positive $[\alpha]^{20}_D$, indicated 3*R*,4*S* configuration for **2**. The configuration was confirmed by chemical transformation from **2** to **1c** using the same procedure as described above. Therefore, **2** was determined to be (+)-(2*E*,3*R*,4*S*)-2-(dodec-11-enylidene)-3-hydroxy-4-methylbutanolide, an enantiomer of litsenolide A_2[8a] or the 3-epimer of lincomolide C.[10d]

Compound **3** displayed spectroscopic data similar to those of **2** (Tables 1 and 2, and Experimental Section). However, H-3, H-4, and H-6 of **3** were shielded by $\Delta\delta_H$ −0.17, −0.12, and −0.42 ppm, respectively, as compared with those of **2**, whereas H-5 and H_2-7 of **3** were deshielded by $\Delta\delta_H$ +0.05 and +0.36 ppm, respectively. In addition, C-1, C-3, and C-7 of **3** were shielded by $\Delta\delta_C$ −1.7, −1.4, and −1.9 ppm, respectively; in turn C-4 and C-6 were deshielded by $\Delta\delta_C$ +3.4 and +1.6 ppm, respectively. These differences indicated that **3** was a 2*Z*-isomer of **2**,[8a,11,17] which was confirmed also by chemical transformation from **3** to **1c**. Accordingly, **3** was determined to be (+)-(2*Z*,3*R*,4*S*)-2-(dodec-11-enylidene)-3-hydroxy-4-methylbutanolide. It is an enantiomer of litsenolide A_1.[8a]

Compound **4** showed IR and ESIMS data (Experimental Section) almost identical to those of **1**. The differences in the NMR data between **4** and **1** (Tables 1 and 2) were similar to those between **3** and **2**. This suggested that **4** was a 2*Z*-isomer of **1**, which was also confirmed by chemical transformation of **4** to **1c**. Therefore, the structure of **4** was assigned as (+)-(2*Z*,3*R*,4*S*)-2-(dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide.

The spectroscopic data of **5** revealed that it was an isomer of **4**. The chemical shifts and coupling patterns for H-3 [δ 4.65 (d, J = 4.5 Hz)] and H-4 [δ 4.55 (dd, J = 4.5, 6.5 Hz)] of **5** and the shift for C-5 (δ 14.1) indicated that H-3 and H-4 are *cis*-oriented in **5**.[8b,9,10c−e] Chemical transformation from **5** to **1c** demonstrated a 4*S* configuration for **5**. The negative specific rotation of **5** {$[\alpha]^{20}_D$ −26 (*c* 0.10, $CHCl_3$)} was consistent with those of (3*S*,4*S*)-2-alkylidene-3-hydroxy-4-methylbutanolides.[9,10d,11,18] Thus, the structure of **5** was assigned as (−)-(2*Z*,3*S*,4*S*)-2-(dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide.

Compound **6**, a colorless oil, displayed IR, MS, and NMR data almost identical to those of the natural product litsenolide C_1[8a] and the synthetic *ent*-litsenolide C_1.[19] However, the specific rotation of **6** {$[\alpha]^{20}_D$ +30} was in good agreement with that of *ent*-litsenolide C_1. Therefore, **6** was identified as *ent*-litsenolide C_1, a new natural product.

The IR spectrum of compound **7** indicated the presence of hydroxy (3366 cm^{-1}) and aromatic ring (1611, 1502, 1460 cm^{-1}) groups. (+)-ESIMS of **7** gave a quasimolecular ion peak at *m*/*z* 397 $[M + K]^+$, and HRESIMS indicated a molecular formula of $C_{21}H_{26}O_5$. The ^{1}H NMR spectrum exhibited signals attributable to a trisubstituted aromatic ring [δ 6.61 (d, J = 1.5 Hz, H-2′), 6.73 (d, J = 8.0 Hz, H-5′), and 6.37 (dd, J = 8.0, 1.5 Hz, H-6′)], a pentasubstituted aromatic ring [δ 6.44 (1H, s, H-6)], and three methoxy groups. In addition, it displayed two methyl doublets [δ 0.88 (d, J = 7.0 Hz, H_3-9) and 0.91 (d, J = 7.5 Hz, H_3-9′)], a methine doublet [δ 4.05 (d, J = 2.0 Hz, H-7′)], and two methine mutiplets [δ 2.02 (H-8) and 1.85 (H-8′)], as well as signals attributable to germinal protons of a methylene attached to a methine [δ 2.70 (dd, J = 16.5, 6.0 Hz, H-7a) and 2.39 (dd, J = 16.5, 11.5 Hz, H-7b)]. These data suggested that **7** was a 2,7′-cyclolignan derivative with three methoxy and two hydroxy groups substituted at the aromatic rings, which was confirmed by the ^{13}C NMR (Experimental Section) and HMBC (Supporting Information, Figure S1) data of **7**. In particular, HMBC correlations from both *Me*O-3 and H-7′ to C-3, from *Me*O-5 to C-5, from H-6 to C-1, C-2, C-4, C-5, and C-7, from both *Me*O-3′ and H-5′ to C-3′, and from H-2′ to C-1′, C-3′, C-4′, and C-6′, together with the chemical shifts of these protons and carbons, indicated that the three methoxy and two hydroxy groups were located at C-3, C-5, and C-3′, and C-4 and C-4′, respectively. In the NOESY spectrum of **7**, cross-peaks between *Me*O-3 and H-7′, between *Me*O-5 and H-6, and between *Me*O-3′ and H-2′ (Supporting Information, Figure S2) confirmed the locations of the three methoxy groups. In addition, NOESY cross-peaks of both H-8 and H-8′ with H-2′ and H-6′ indicated that these protons were oriented on the same side of the tetralin ring, while the *trans*-relationship between H-7′ and H-8′ was supported by the coupling constant $J_{7,8}$ (2.0 Hz).[20] On the basis of the CD exciton chirality rule, in the CD spectrum of **7**, a negative Cotton effect at 274.5 nm ($\Delta\varepsilon$ −1.87) and a positive Cotton effect at 289 nm ($\Delta\varepsilon$ +0.16), opposite those of the co-occurring (+)-guaiacin (**12**)[21] (Supporting Information, Figure S3), indicated that **7** had a 7′*R* configuration. Therefore, **7** was determined to be (−)-(7′*R*,8*R*,8′*R*)-4,4′-dihydroxy-3,3′,5-trimethoxy-2,7′-cyclolignane.[22b]

For compound **8**, $[\alpha]^{20}_D$ +15 (*c* 0.05, $CHCl_3$), IR absorptions for OH (3291 cm^{-1}), carbonyl (1737 cm^{-1}), and aromatic ring

(1462, 1377 cm^{-1}) groups, and (+)-HRESIMS indicated the molecular formula $C_{12}H_{16}O_4$. The ^1H NMR spectrum showed resonances assignable to a 4-hydroxy-3-methoxyphenyl unit at δ 6.88 (d, J = 1.5 Hz, H-2), 6.88 (d, J = 8.0 Hz, H-5), 6.80 (dd, J = 8.0, 1.5 Hz, H-6), and 3.91 (s, *Me*O-3), an O-CH-CH-CH_3 unit at δ 4.68 (d, J = 9.0 Hz, H-7), 2.89 (dq, J = 9.0, 7.5 Hz, H-8), and 0.93 (d, J = 7.5 Hz, H_3-9), and an acetyl unit at δ 2.24 (s, H_3-9′). These data suggested that **8** possessed a planar structure of 4-hydroxy-3-methoxy-1′,2′,3′,4′,5′,6′,7′-heptanorlign-8′-one.[22,23] The ^{13}C NMR data of **8** (Experimental Section) were consistent with the structural assignment. The coupling constant between H-7 and H-8 ($J_{7,8}$ = 9.0 Hz) and the resonances for C-7 (δ 76.5), C-8 (δ 53.9), and C-9 (δ 14.2) indicated a *threo*-relationship between the OH group at C-7 and the acetyl unit at C-8 in **8**.[24] The positive $[\alpha]^{20}_D$ indicated that the absolute configuration of **8** is 7*S*,8*R*.[25] Therefore, the structure of **8** was elucidated as (+)-(7*S*,8*R*)-4-hydroxy-3-methoxy-1′,2′,3′,4′,5′,6′,7′-heptanorlign-8′-one. The methyl and ethyl ethers of **8** (**8a** and **8b**) were also obtained in the isolation procedure; however, they were considered artifacts since storage of **8** in methanol or ethanol at 40 °C for 24 h also yielded **8a** or **8b**.

HRESIMS indicated compound **9** had the molecular formula $C_{13}H_{16}O_5$. The ^1H NMR data of **9** were similar to those of **8**. However, resonances for H-7 and H_3-9 of **9** were deshielded by $\Delta\delta_H$ +0.39 and +0.15, respectively, as compared with those of **8**, whereas those for H-8 and H_3-9′ of **9** were significantly shielded by $\Delta\delta_H$ −0.85 and −0.74, respectively. Comparison of the ^{13}C NMR spectra between **8** and **9** indicated that the ketone carbonyl (δ_C 213.4, C-8′) of **8** was replaced by an ester carbonyl in **9** (δ_C 177.5, C-7′). This was supported by a diagnostic absorption due to a γ-lactone carbonyl (1768 cm^{-1}) in the IR spectrum of **9**. In addition, the ^{13}C NMR spectrum of **9** showed an additional resonance attributable to an oxygen-bearing quaternary carbon (δ_C 74.4, C-8′). These data suggested that **9** was a 4,8′-dihydroxy-3-methxy-1′,2′,3′,4′,5′,6′-hexanorligna-7′,7-lactone,[22,26] which was supported by 2D NMR experiments. In the HMBC spectrum of **9**, long-range correlations (Supporting Information, Figure S1) from H_3-9 to C-7, C-8, and C-8′ and from H_3-9′ to C-7′, C-8, and C-8′, in combination with chemical shifts of these protons and carbons, indicated the presence of the lactone moiety. HMBC correlations from H-7 to C-1, C-2, C-6, C-8, and C-9 confirmed the connection between the phenyl unit and the lactone moiety, while correlations from both H-5 and *Me*O to C-3 proved the methoxy to be on the phenyl moiety. In the NOE difference spectrum of **9**, H_3-9 was enhanced by irradiation of H-7, while H_3-9′ was enhanced by irradiation of H-8. These enhancements indicated a *trans*-orientation of H-8 with H-7 and *H*O-8′ on the lactone moiety of **9**. The absolute configuration of **9** was determined by conversion of **9** to **8**. Reduction of **9** with $LiAlH_4$ followed by oxidation of the product with $NaIO_4$ yielded **8** (Supporting Information, Scheme S2). The spectroscopic data and specific rotation of semisynthetic **8** were identical to those of **8**. Thus, **9** was determined to be (+)-(7*S*,8*R*,8′*R*)-4,8′-dihydroxy-3-methoxy-1′,2′,3′,4′,5′,6′-hexanorligna-7′,7-lactone.[22]

Compound **10** had the molecular formula $C_{15}H_{20}O_3$ (HRESIMS). The ^1H NMR spectrum of **10** showed two broad singlets attributable to an olefinic methylene at δ 6.38 (s, H-13a) and 5.76 (s, H-13b), two methyl doublets at δ 1.11 (d, J = 7.5 Hz, H_3-14) and 1.03 (d, J = 7.0 Hz, H_3-15), and partially overlapped multiplets due to aliphatic methylenes and/or methines between δ 1.50 and 3.10. The ^{13}C NMR spectrum of **10** displayed 15 carbon resonances consisting of two methyls, five methylenes (one sp^2), three methines, and five quaternary carbons (a ketone, a carboxyl, and three olefinic). These data indicated that **10** was a bicyclic sesquiterpene with functional groups of a ketone, a carboxyl, a disubstituted terminal double bond, and a tetrasubstituted double bond. The protonated carbons and their corresponding protons were assigned by the HSQC experiment. $^1H-^1H$ COSY cross-peaks between H-4 and both H_2-3 and H_3-14 and HMBC correlations from H_2-3 to C-1, C-2, C-4, and C-5 and from H_3-14 to C-3, C-4, and C-5, in combination with the coupling patterns and chemical shifts of these protons and carbons, revealed the presence of a 1,5-disubstituted 4-methylcyclopent-5(1)-en-2-one moiety in **10**. A series of $^1H-^1H$ COSY cross-peaks from H_2-6 through H-7 to H_2-8 and then to H_2-9, H-10, and H_3-15, and HMBC correlations from H_2-6 to C-1, C-5, C-7, and C-8 and from H_3-15 to C-1, C-9, and C-10, together with chemical shifts of these protons and carbons, demonstrated the presence of a seven-membered ring in **10**. HMBC correlations from H_2-13 to C-7, C-11, and C-12, along with their shifts and the molecular composition, located an acrylic acid unit at C-7 in **10**. Therefore, **10** was a 2-oxo-guaia-1(5),11(13)-dien-12-oic acid.

The absolute configuration of **10** was determined by analysis of NOE difference combined with the modified Mosher method. Irradiation of H_3-14 gave enhancements of H-3b, H-6b, and H-7, while irradiation of H_3-15 enhanced H-7, H-8a, and H-9a. These data indicated that the methyl groups at C-4 and C-10 were on the same side of the ring system and that the acrylic acid unit at C-7 was on the other side. Methylation of **10** followed by successive hydrogenation (Pd−C/H_2), reduction ($NaBH_4$), and esterification (*R*- or *S*-MTPACl) yielded two pairs of diastereomers, **10b*R*** and **10b*S*** and **10c*R*** and**10c*S*** (Supporting Information, Scheme S3). After a careful assignment of the ^1H NMR data of the two pairs of diastereomers by $^1H-^1H$ COSY and NOE data analysis, chemical shift differences $\Delta\delta_{SR}$ ($\delta_{S\text{-MTPAester}} - \delta_{R\text{-MTPAester}}$) of the two pairs of diastereomers were obtained (Supporting Information, Scheme S3). On the basis of the MTPA determination rule,[13,16] the $\Delta\delta_{SR}$ values indicated a 2*R* configuration for both **10b** and **10c**. In the NOE difference experiments of **10b*R***, irradiation of H-2 enhanced H-1, H-4, and H-3a, indicating that these protons were on the same side of the ring system. This suggested that the absolute configuration at C-4 of **10b**, **10c**, and **10** is *S*. Therefore, **10** was determined to be (−)-(4*S*,7*S*,10*S*)-2-oxo-guaia-1(5),11(13)-dien-12-oic acid.

Compound **11** ($C_{15}H_{14}O_8$) showed IR absorptions for OH (3359 cm^{-1}), carbonyl (1786 and 1728 cm^{-1}), and aromatic ring (1627, 1522, and 1468 cm^{-1}) groups. ^1H NMR resonances at δ 6.05 (d, J = 2.0 Hz, H-6) and 5.91 (d, J = 2.0 Hz, H-8) indicated a tetrasubstituted aromatic ring with two *meta*-coupling protons. An ABX system at δ 4.78 (d, J = 6.8 Hz, H-6′), 3.19 (dd, J = 18.4, 6.8 Hz, H-5′a), and 2.50 (d, J = 18.4 Hz, H-5′b) indicated the presence of an O-$CHCH_2$ unit. In addition to a singlet assignable to an isolated methylene unit at δ 3.20 (s, H_2-2′), resonances due to a vicinal coupling system at δ 4.45 (d, J = 1.6 Hz, H-2), 4.52 (dt, J = 4.8, 1.6 Hz, H-3), 2.91 (dd, J = 18.0, 1.6 Hz, H-4a), and 2.76 (dd, J = 18.0, 4.8 Hz, H-4b) suggested the presence of a $CH(O)CH(O)CH_2$ unit. These units were confirmed by the $^1H-^1H$ COSY data of **11**. The ^{13}C NMR and DEPT spectra of **11** also showed resonances of two carbonyl groups and an oxygen-bearing quaternary carbon. The protonated carbon resonances were assigned from the HMQC experiment. In the HMBC spectrum of **11**, two- and three-bond correlations from both H-6 and H-8 to C-4a and from H_2-4 to C-2, C-3, C-4a, C-5, and C-8a indicated a connection between C-4a and C-4. Correlations from H-2 to C-1′ and C-6′ and from H-2′ to C-2, C-1′, and C-3′ indicated connection of C-1′ to both C-2 and C-2′ and C-2′ to C-3′. Correlations from H_2-5′ to C-1′, C-4′, and C-6′ revealed that C-6′ connected to both C-1′ and C-5′. In addition, a correlation from H-6′ to C-3 and the shifts of H-6′ and C-3 suggested an oxygen-bridged linkage between C-3 and C-6′. Methylation of **11** with CH_3I gave a trimethyl product, **11a**. Comparison of the NMR data between **11a** and **11** (Experimental Section) indicated that H-6 and H-8 and C-4a, C-5, and C-7 of **11a** were deshielded by $\Delta\delta_H$ +0.10 and +0.15 and $\Delta\delta_C$ +6.9, +2.4, and +3.0 ppm, respectively, whereas C-6, C-8, and C-3′ were shielded by $\Delta\delta_C$ −2.3, −3.2, and −1.2 ppm, respectively.

This suggested the presence of free phenolic OH groups at C-5 and C-7 and a free carboxylic OH group at C-3′ in **11**. The HMBC spectrum of **11a** showed correlations from proton resonances of the three methoxy groups to C-5, C-7, and C-3′, respectively. The chemical shifts of C-2, C-8a, C-1′, and C-4′, together with the molecular formula of **11**, indicated that a lactone and an oxygen-bridged linkage were among these carbons. In the IR spectrum of **11**, the characteristic absorption for a γ-lactone ring at 1786 cm^{-1} demonstrated that the lactone must be formed between C-4′ and C-1′ and the oxygen-bridged linkage between C-2 and C-8a in **11**. Thus, **11** was deduced to be an unusual 3′,4′-seco-flavane derivative as shown. The configuration of **11** was proposed from the NMR data and a biogenetic hypothesis. In the ^1H NMR spectra of **11** and **11a**, the respective coupling constants of 1.6 and 2.4 Hz between H-2 and H-3 indicated a *cis*-orientation for the two protons in the two compounds. In the NOE difference experiment of **11a**, irradiation of H-6′ gave an enhancement of H-2′; however, no enhancement of H-2′ and/or H-6′ was observed by irradiation of H-2 or H-3. This suggested that H-2′ and H-6′, opposite H-2 and H-3, were on the same side of the ring. Although three closely related analogues, viniferones A−C, and a plausible biogenesis of viniferone A (C-3 epimer of viniferone B) from (+)-catechin, mediated by catechin quinone and followed by a sequential oxidative cleavage, hydration, and lactonization pathway or by a sequential hydration, oxidative cleavage, and lactonization pathway, were reported,[27] we hypothesize that **11** and viniferones A and C may be biosynthesized from an enzyme-catalyzed oxidative cleavage between C-3′ and C-4′ of the co-occurring (−)-epicatechin followed by a sequential or simultaneous cycloaddition procedure (Supporting Information, Scheme S4). Therefore, the structure of **11** was proposed as (+)-(2*S*,3*R*,1′*S*,6′*R*)-5,7-dihydroxy-3,6′-epoxy-1′,2′3′,4′,5′,6′-hexahydro-3′,4′-secoflava-4′,1′-lactone-3′-oic acid.[28]

The known compounds were identified by comparison of spectroscopic data with those reported in the literature as (+)-guaiacin (**12**),[21] *meso*-dihydroguaiaretic acid (**13**),[29] isomahubanolide-23 (**14**),[11] hamabiwalactone A (**15**),[10e] ginkgolide A (**16**),[7] ginkgolide B (**17**),[7] 4-(3-methoxy-4-hydroxy)pheny-3-methyl-3-buten-2-one,[30] nectandrin B,[31] machilin-I,[32] kobusin,[33] eudesmin,[33] 2,3-(2*R*,3*R*)-dihydro-2-(4- hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-(*E*)-propenylbenzofuran,[34] (−)-epilitsenolides C_2,[35] lincomolide C,[10d] isolincomolide C,[18a] lincomolide B,[9] 4*R*-2-tetradecylidene-4-methylolbutanolide,[36] (4*S*)-2-(11-dodecenylidene)-4-methylolbutanolide,[36] aromadendrane-4β,10α-diol,[37] and costic acid.[38]

In the in vitro bioassays, at 10^{-5} M, compounds **7**, **8a**, **8b**, **9**, **11**, **12**, **13**, and **15** inhibited the release of β-glucuronidase in rat polymorphonuclear leukocytes (PMNs) induced by platelet-activating factor (PAF) by 47%, 67%, 42%, 76%, 46%, 48%, 54%, and 60%, respectively [the positive control ginkgolide B (BN52021)[39] gave a 76% inhibition]. At 10^{-4} M, compounds **8**, **8a**, **8b**, **9**, and **11** protected hepatocyte (WB-F344 cells) damage induced by DL-galactosamine (GalN) with 43 ± 3%, 47 ± 2%, 54 ± 3%, 39 ± 6%, and 40 ± 8% inhibitions (the positive control bicyclol[40] showed a 41 ± 2% inhibition). Compound **14** was cytotoxic to BGC-823 and A2780 cells with IC_{50} values of 0.13 and 2.66 μM, respectively [positive control camptothecin (CPT), IC_{50} 0.21 and 0.28 μM].

Experimental Section

General Experimental Procedures. Optical rotations were measured on a PE model 343 polarimeter. UV spectra were measured on a Cary 300 spectrometer. CD spectra were recorded on a JASCO-815 CD spectrometer. IR spectra were recorded on a Nicolet 5700 FT-IR microscope instrument. 1D- and 2D-NMR spectra were obtained at 500 or 600 MHz for ^1H and 125 or 150 MHz for ^{13}C, respectively, on INOVA 500 MHz or SYS 600 MHz spectrometers, in $CDCl_3$ or Me_2CO-d_6, with solvent peaks used as references. ESIMS data were measured with a Q-Trap LC/MS/MS (Turbo Ionspray Source) spectrometer. ESIMS and HRESIMS data were measured using an AccuToFCS JMS-T100CS spectrometer. EIMS and HREIMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. Column chromatography (CC) was performed using silica gel (200−300 mesh, Qingdao Marine Chemical Inc. Qingdao, People's Republic of China) and Pharmadex LH-20 (Amersham Biosciences, Inc., Shanghai, People's Republic of China). HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector, using a Prevail (250 × 10 mm i.d.) column packed with C_{18} (5 μm). Preparative TLC separation was performed with high-performance silica gel preparative TLC plates ($HSGF_{254}$, glass precoated, Yantai Jiangyou Silica Gel Development Co., Ltd., Yantai, People's Republic of China). TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV light or by spraying with 7% H_2SO_4 in 95% EtOH followed by heating. Unless otherwise noted, all chemicals were obtained from commercially available sources and were used without further purification.

Plant Material. The bark of *M. wangchiana* was collected at Dayao Moutain, Guangxi Province, China, in August 2006. The plant was identified by Mr. Guang-Ri Long (Guangxi Forest Administration, Guangxi 545005, China). A voucher specimen (no. 06009) was deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica.

Extraction and Isolation. Air-dried bark of *M. wangchiana* (5.3 kg) was powdered and extracted with 95% EtOH (3 × 15 L) at room temperature (3 × 48 h). The extract was evaporated under reduced pressure to yield a dark brown residue (375 g). The residue was suspended in H_2O (1200 mL) and then partitioned with EtOAc (5 × 1200 mL). After removing the solvent, the EtOAc extract (45 g) was subjected to CC over silica gel, eluting with a gradient of increasing MeOH (0−100%) in $CHCl_3$ to afford 10 fractions (A1−A10) on the basis of TLC analysis. Fraction A1 (6.5 g), eluted by $CHCl_3$, was further chromatographed over silica gel, eluting with a gradient of increasing acetone (5−100%) in petroleum ether, to give 15 subfractions (A1-1−A1-15). Fractions A1-2 (135 mg), A1-4 (1.2 g), A1-9 (87 mg), A1-10 (91 mg), A1-11 (1.1 g), and A1-14 (282 mg) were chromatographed separately over Sephadex LH-20 with petroleum ether−$CHCl_3$−MeOH (5:5:1) to afford subfractions A1-2a (21.9 mg), A1-9a (34.8 mg), A1-11a (428.0 mg), and A1-14a (49.2 mg) and pure compounds **12** (522.0 mg) from A1-4 and **15** (11.4 mg) from A1-10. Subfraction A1-2a was separated by RP-HPLC using 70% MeOH in H_2O to yield **14** (6.7 mg). Subfraction A1-9a was separated by RP- HPLC using 80% MeOH in H_2O to yield **3** (9.2 mg). Subfraction A1-11a was separated by RP-HPLC using 50% CH_3CN in H_2O to give **1** (112 mg), **4** (36.1 mg), **5** (48.0 mg), and **7** (37.0 mg). Subfraction A1-14a was separated by RP-HPLC using 55% CH_3CN in H_2O to yield **8** (1.7 mg) and **13** (51.7 mg). Fraction A2 (0.85 g), eluted by 1% MeOH in $CHCl_3$, was chromatographed over silica gel, eluting with a gradient of increasing acetone (5−100%) in petroleum ether, to yield 13 fractions (A2-1−A2-13). Fractions A2-3 (96 mg), A2-6 (224 mg), and A2-7 (152 mg) were chromatographed separately over Sephadex LH-20 with petroleum ether−$CHCl_3$−MeOH (5:5:1) to afford a mixture of A2-3a (41 mg) from A2-3 and pure compounds **2** (39 mg) and **9** (6.1 mg) from A2-7 and **16** (58 mg) and **17** (43 mg) from A2-6. The mixture A2-3a was purified by RP-HPLC with 75% MeOH in H_2O to yield **6** (7.3 mg). Fraction A3 (0.49 g), eluted by 3% MeOH in $CHCl_3$, was chromatographed over silica gel, eluting with a gradient of increasing acetone (7−100%) in petroleum ether, to give nine subfractions (A3-1−A3-9). A3-3 (77 mg) was chromatographed over Sephadex LH-20 with petroleum ether−$CHCl_3$−MeOH (5:5:1) to afford A3-3a (38 mg), which was further purified by RP-HPLC using 65% CH_3CN in H_2O to yield **10** (11.9 mg). Fraction A4 (2.8 g), eluted by 5% MeOH in $CHCl_3$, was chromatographed over silica gel, eluting with a gradient of increasing MeOH (2−20%) in $CHCl_3$, to give 10 subfractions (A4-1−A4-10). A4-10 (43 mg) was chromatographed over Sephadex LH-20 using $CHCl_3$−MeOH (2:1) to afford **11** (8.4 mg).

(+)-(2*E*,3*R*,4*S*)-2-(Dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide (1): colorless oil; $[\alpha]^{20}_D$ +26 (*c* 0.11, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 241 (2.98) nm; IR ν_{max} 3341, 2923, 2117, 1738, 1678, 1459, 1376, 1319, 1109, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; ESIMS *m/z* 279 $[M + H]^+$, 301 $[M + Na]^+$, and 317 $[M + K]^+$; HRESIMS *m/z* 301.1766 $[M + Na]^+$ (calcd for $C_{17}H_{26}O_3Na$, 301.1780).

Chemical Transformation of 1. A solution of **1** (21.0 mg) in EtOH (2.5 mL) was hydrogenated (H_2, 1 atm) over 10% Pd−C (40 mg) at

room temperature for 24 h. The reaction mixture was filtered, and then the solvent was removed under reduced pressure to give **1a** (20.2 mg): amorphous powder; $[\alpha]^{20}_D$ −5 (*c* 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.20 (1H, dq, J = 6.0, 6.6 Hz, H-4), 3.84 (1H, t, J = 6.0 Hz, H-3), 2.55 (1H, dt, J = 6.0, 7.8 Hz, H-2), 1.87 (1H, m, H-6a), 1.61 (1H, m, H-6b), 1.45 (3H, d, J = 6.6 Hz, H_3-5), 1.22−1.56 (m, H_2-7−H_2-16), 0.88 (3H, t, J = 7.2 Hz, H_3-17). A solution of **1a** (4.5 mg) in pyridine (1 mL) and Ac_2O (5 μL) was kept at room temperature for 24 h. After the solvent was removed under reduced pressure, the residue was partitioned between a saturated $CuSO_4$ water solution (10 mL) and EtOAc (10 mL). The EtOAc phase was washed with water and then evaporated under reduced pressure to yield **1b** (4.0 mg): colorless gum; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.92 (1H, t, J = 4.8 Hz, H-3), 4.38 (1H, dq, J = 4.8, 6.6 Hz, H-4), 2.68 (1H, m, H-2), 2.10 (3H, s, OA*c*), 1.46 (3H, d, J = 6.6 Hz, H_3-5), 1.20−1.89 (m, H_2-6−H_2-16), 0.88 (3H, t, J = 6.6 Hz, H_3-17); FABMS *m*/*z* 327 $[M + H]^+$. To a anhydrous THF (1 mL) solution of **1b** (4.0 mg) was added DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 3 μL). The mixture was stirred at room temperature for 1 h and then neutralized with several drops of HOAc and concentrated under reduced pressure to give a residue. The residue was chromatographed over silica gel eluting with $CHCl_3$ to give **1c** [(+)-(5*S*)-3-dodecyl-5-methylfuran-2(5*H*)-one,[14] 2.7 mg]: white powder; $[\alpha]^{20}_D$ +27 (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.98 (1H, brs, H-3), 4.99 (1H, brq, J = 6.6 Hz, H-4), 2.26 (2H, t, J = 7.8 Hz, H_2-6), 1.40 (3H, d, J = 6.6 Hz, H_3-5), 1.20−1.59 (m, H_2-7−H_2-16), 0.88 (3H, t, J = 6.6 Hz, H_3-17); EIMS *m*/*z* 266 $[M]^{+\bullet}$. **1** (5 mg) and 4-dimethylaminopyridine (DMAP, 1.2 mg) were dissolved in anhydrous pyridine (1 mL) at 0 °C, and then the solution was kept at room temperature for 5 h. After removing the solvent under reduced pressure, the residue was partitioned between a saturated $CuSO_4$ water solution (10 mL) and EtOAc (10 mL). The EtOAc phase was evaporated under reduced pressure to give a residue that was separated by preparative TLC using 15% Me_2CO in petroleum ether as developing solvent to yield **1d** [(*E*)-hexadeca-3-ene-15-ynyl-2,5-dione]: colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.83 (2H, s, H-3, H-4), 2.64 (2H, t, J = 7.5 Hz, H_2-6), 2.37 (3H, s, H_3-1), 2.18 (2H, dt, J = 2.5, 7.0 Hz, H_2-14), 1.93 (1H, t, J = 2.5 Hz, H-16), 1.24−1.70 (m, H_2-7-H_2-13); ^{13}C NMR ($CDCl_3$, 125 MHz) 198.5 and 200.6 (C-2, C-5), 136.9 and 137.2 (C-3, C-4), 84.7 (C-15), 68.1 (C-16), 41.4 (C-6), 29.3 (C-1), 23.7−29.1 (C-7−C-13), δ 18.4 (C-14); ESIMS *m*/*z* 249 $[M + H]^+$, 271 $[M + Na]^+$.

Preparation of MTPA Esters of 1a. 1a (6.0 mg) and DMAP (4-dimethylaminopyridine, 1.5 mg) were dissolved in anhydrous pyridine (1.5 mL) at 0 °C, and then (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)-(−)-MTPACl, 10 μL] was added to the solution. After stirring at room temperature for 5 h, the reaction mixture was evaporated under reduced pressure to give a residue, which was partitioned between a saturated $CuSO_4$ water solution (10 mL) and EtOAc (10 mL). The EtOAc extract was evaporated under reduced pressure to give a residue that was purified by preparative TLC using 15% Me_2CO in petroleum ether as developing solvent to give *S*-MTPA-**1a** (5.6 mg). *R*-MTPA-**1a** (4.9 mg) was prepared by using the same procedure with **1a** (5.1 mg) and (*S*)-(+)-MTPACl (10 μL) as starting material and reagent, respectively. *S*-MTPA-**1a**: colorless gum; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.4−7.5 (5H, m, aromatic protons of MTPA moiety), 5.12 (1H, t, J = 6.0 Hz, H-3), 4.32 (1H, dq, J = 6.0, 6.6 Hz, H-4), 3.52 (3H, s, *Me*O of MTPA moiety), 2.75 (1H, dt, J = 6.0, 7.8 Hz, H-2), 1.88 (1H, m, H-6a), 1.66 (1H, m, H-6b), 1.47 (3H, d, J = 6.6 Hz, H_3-5), 1.2−1.6 (m, H_2-7−H_2-16), 0.88 (3H, t, J = 7.2 Hz, H_3-17). *R*-MTPA-**1a**: colorless gum; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.4−7.5 (5H, m, aromatic protons of MTPA moiety), 5.11 (1H, t, J = 6.0 Hz, H-3), 4.43 (1H, dq, J = 6.0, 6.0 Hz, H-4), 3.54 (3H, s, *Me*O of MTPA moiety), 2.67 (1H, dt, J = 6.0, 7.2 Hz, H-2), 1.83 (1H, m, H-6a), 1.61 (1H, m, H-6b), 1.51 (3H, d, J = 6.0 Hz, H_3-5), 1.2−1.6 (m, H_2-7−H_2-16), 0.88 (3H, t, J = 7.2 Hz, H_3-17).

(+)-(2*E*,3*R*,4*S*)-2-(Dodec-11-enylidene)-3-hydroxy-4-methylbutanolide (2): colorless oil; $[\alpha]^{20}_D$ +16 (*c* 0.12, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 242 (2.86) nm; IR ν_{max} 3421, 2919, 1738, 1678, 1461, 1377, 1201, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; ESIMS *m*/*z* 281 $[M + H]^+$, 303 $[M + Na]^+$, 319 $[M + K]^+$; HRESIMS *m*/*z* 303.1950 $[M + Na]^+$ (calcd for $C_{17}H_{28}O_3Na$, 303.1936).

(+)-(2*Z*,3*R*,4*S*)-2-(Dodec-11-enylidene)-3-hydroxy-4-methylbutanolide (3): colorless oil; $[\alpha]^{20}_D$ +2 (*c* 0.09, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 241 (2.91) nm; IR ν_{max} 3402, 2922, 1737, 1678, 1462, 1377, 1196, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; ESIMS *m*/*z* 281 $[M + H]^+$, 303 $[M + Na]^+$; HRESIMS *m*/*z* 303.1937 $[M + Na]^+$ (calcd for $C_{17}H_{28}O_3Na$, 303.1931).

(+)-(2*Z*,3*R*,4*S*)-2-(Dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide (4): colorless oil; $[\alpha]^{20}_D$ +13 (*c* 0.11, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 241 (3.37) nm; IR ν_{max} 3340, 2923, 1736, 1669, 1427, 1372, 1107, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; ESIMS *m*/*z* 279 $[M + H]^+$, 301 $[M + Na]^+$; HRESIMS *m*/*z* 301.1784 $[M + Na]^+$ (calcd for $C_{17}H_{26}O_3Na$, 301.1774).

(−)-(2*Z*,3*S*,4*S*)-2-(Dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide (5): colorless oil; $[\alpha]^{20}_D$ −26 (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 241 (2.8) nm; IR ν_{max} 3310, 2919, 1736, 1674, 1461, 1376, 1182, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; ESIMS *m*/*z* 279 $[M + H]^+$, 301 $[M + Na]^+$; HRESIMS *m*/*z* 301.1787 $[M + Na]^+$ (calcd for $C_{17}H_{26}O_3Na$, 301.1774).

Chemical Transformation of 2−5. A solution of each compound in EtOH (2.0 mL) was hydrogenated (H_2, 1 atm) over 10% Pd−C (40 mg) at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. Pyridine (1.0 mL) and Ac_2O (5 μL) were added to the residue and kept at room temperature overnight. After the solvent was removed under reduced pressure, the residue was partitioned between a saturated $CuSO_4$ water solution (10 mL) and EtOAc (10 mL). Each EtOAc extract was washed by water and evaporated under reduced pressure. After anhydrous THF (1 mL) and DBU (5 μL) were added to the residue, the solution was kept at room temperature for 1 h and then neutralized with several drops of HOAc followed by concentrating under reduced pressure. The residue was separated by TLC with $CHCl_3$ as a developing solvent to yield **1c**. The ^{1}H NMR, EIMS, and specific rotation data of **1c**, obtained from the transformation of **2**−**5**, were identical to those of [(+)-(5*S*)-3-dodecyl-5-methylfuran-2(5*H*)-one[14]].

***ent*-Litsenolide C_1 (6):** colorless oil; $[\alpha]^{20}_D$ +30 (*c* 0.09, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 249 (2.6) nm; IR ν_{max} 3387, 2920, 1730, 1462, 1378, 1216, 1034, 991 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; ESIMS *m*/*z* 311 $[M + H]^+$, 333 $[M + Na]^+$; HRESIMS *m*/*z* 333.2370 $[M + Na]^+$ (calcd for $C_{19}H_{34}O_3Na$, 333.2400).

(−)-(7′*R*,8*R*,8′*R*)-4,4′-Dihydroxy-3,3′,5-trimethoxy-2,7′-cyclolignane (7): amorphous powder; $[\alpha]^{20}_D$ −13 (*c* 0.03, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 203 (4.72), 231 (4.15), 281 (3.71) nm; CD (MeOH) 289 ($\Delta\varepsilon$ +0.16), 274.5 ($\Delta\varepsilon$ −1.87) nm; IR ν_{max} 3366, 2949, 1611, 1502, 1460, 1271, 1225, 1121, 1102, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.73 (1H, d, J = 8.0 Hz, H-5′), 6.61 (1H, d, J = 1.5 Hz, H-2′), 6.44 (1H, s, H-6), 6.37 (1H, dd, J = 8.0, 1.5 Hz, H-6′), 4.05 (1H, d, J = 2.0 Hz, H-7′), 3.89 (3H, s, *Me*O-5), 3.83 (3H, s, *Me*O-3′), 3.36 (3H, s, *Me*O-3), 2.70 (1H, dd, J = 16.5, 6.0 Hz, H-7a), 2.39 (1H, dd, J = 16.5, 11.5 Hz, H-7b), 2.02 (1H, m, H-8), 1.85 (1H, m, H-8′), 0.91 (3H, d, J = 7.5 Hz, H_3-9′), 0.88 (3H, d, J = 7.0 Hz, H_3-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.2 (C-5), 146.1 (C-3′), 145.6 (C-3), 143.4 (C-4′), 140.0 (C-1′), 136.7 (C-4), 128.0 (C-2), 123.5 (C-1), 121.2 (C-6′), 113.4 (C-5′), 111.2 (C-2′), 105.9 (C-6), 59.8 (*Me*O-3), 56.0 (*Me*O-5), 55.9 (*Me*O-3′), 46.9 (C-7′), 40.7 (C-8′), 33.4 (C-7), 25.9 (C-8), 18.8 (C-9), 13.7 (C-9′); ESIMS *m*/*z* 397 $[M + K]^+$; HRESIMS *m*/*z* 397.1436 $[M + K]^+$ (calcd for $C_{21}H_{26}O_5K$, 397.1417).

(+)-(7*S*,8*R*)-4-Hydroxy-3-methoxy-1′,2′,3′,4′,5′,6′,7′-heptanorlign-8′-one (8): white, amorphous powder; $[\alpha]^{20}_D$ +15 (*c* 0.05, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 230 (4.29), 280 (3.92) nm; IR ν_{max} 3291, 2922, 1737, 1462, 1377, 1191, 1085, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (1H, d, J = 1.5 Hz, H-2), 6.88 (1H, d, J = 8.0 Hz, H-5), 6.80 (1H, dd, J = 8.0, 1.5 Hz, H-6), 4.68 (1H, d, J = 9.0 Hz, H-7), 3.91 (3H, s, *Me*O-3), 2.89 (1H, dq, J = 9.0, 7.5 Hz, H-8), 2.24 (3H, s, H_3-9′), 0.93 (3H, d, J = 7.5 Hz, H_3-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.4 (C-8′), 146.3 (C-3), 145.4 (C-4), 134.0 (C-1), 119.9 (C-6), 114.1 (C-5), 108.7 (C-2), 76.5 (C-7), 56.0 (*Me*O-3), 53.9 (C-8), 29.7 (C-9′), 14.2 (C-9); ESIMS *m*/*z* 247 $[M + Na]^+$; HRESIMS *m*/*z* 247.0923 $[M + Na]^+$ (calcd for $C_{12}H_{16}O_4Na$, 247.0941).

(+)-(7*S*,8*R*)-4-Hydroxy-3,7-dimethoxy-1′,2′,3′,4′,5′,6′,7′-heptanorlign-8′-one (8a): colorless gum; $[\alpha]^{20}_D$ +11 (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89 (1H, d, J = 8.5 Hz, H-5), 6.82 (1H, d, J = 1.5 Hz, H-2), 6.78 (1H, dd, J = 8.5, 1.5 Hz, H-6), 4.11 (1H, d, J =

10.0 Hz, H-7), 3.91 (3H, s, *Me*O-3), 3.10 (3H, s, *Me*O-7), 2.84 (1H, dq, J = 10.0, 7.5 Hz, H-8), 2.26 (3H, s, H_3-9′), 0.77 (3H, d, J = 7.5 Hz, H_3-9); ESIMS m/z 261 $[M + Na]^+$; HRESIMS m/z 261.1098 $[M + Na]^+$ (calcd for $C_{13}H_{18}O_4Na$, 261.1097).

(+)-(7*S*,8*R*)-7-Ethoxy-4-hydroxy-3-methoxy-1′,2′,3′,4′,5′,6′,7′-heptanorlign-8′-one (8b): colorless gum; $[\alpha]^{20}_D$ +13 (c 0.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.87 (1H, d, J = 8.0 Hz, H-5), 6.83 (1H, d, J = 1.5 Hz, H-2), 6.77 (1H, dd, J = 8.0, 1.5 Hz, H-6), 4.19 (1H, d, J = 9.5 Hz, H-7), 3.91 (3H, s, *Me*O-3), 3.29 (1H, dq, J = 9.5, 7.0 Hz, H-1″a), 3.20 (1H, dq, J = 9.5, 7.0 Hz, H-1″b), 2.84 (1H, dq, J = 9.5, 7.5 Hz, H-8), 2.27 (3H, s, H_3-9′), 1.07 (3H, t, J = 7.0 Hz, H_3-2″), 0.76 (3H, d, J = 7.5 Hz, H_3-9); ESIMS m/z 275 $[M + Na]^+$; HRESIMS m/z 275.1253 $[M + Na]^+$ (calcd for $C_{14}H_{20}O_4Na$, 275.1254).

(+)-(7*S*,8*R*,8′*R*)-4,8′-Dihydroxy-3-methoxy-1′,2′,3′,4′,5′,6′-hexanorligna-7′,7-lactone (9): amorphous powder; $[\alpha]^{20}_D$ +14 (c 0.05, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 203 (4.20), 231 (2.90), 280 (2.46) nm; CD (MeOH) 235 ($\Delta\varepsilon$ −0.96), 279 ($\Delta\varepsilon$ −0.03) nm; IR ν_{max} 3437, 2921, 1768, 1611, 1515, 1273, 1240, 1030, 951, 937, 847, 821, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.92 (1H, d, J = 8.5 Hz, H-5), 6.82 (1H, d, J = 1.5 Hz, H-2), 6.82 (1H, dd, J = 8.5, 1.5 Hz, H-6), 5.07 (1H, d, J = 9.5 Hz, H-7), 3.91 (3H, s, *Me*O-3) 2.04 (1H, dq, J = 9.5, 6.5 Hz, H-8), 1.50 (3H, s, H_3-9′), 1.08 (3H, d, J = 6.5 Hz, H_3-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5 (C-7′), 146.8 (C-3), 146.2 (C-4), 128.6 (C-1), 119.9 (C-6), 114.3 (C-5), 108.5 (C-2), 85.5 (C-7), 74.7 (C-8′), 56.1 (*Me*O-3), 49.6 (C-8), 22.0 (C-9′), 7.6 (C-9); ESIMS m/z 253 $[M + H]^+$ and 275 $[M + Na]^+$; HRESIMS m/z 253.1071 $[M + H]^+$ (calcd for $C_{13}H_{17}O_5$, 253.1076).

Chemical Transformation of 9. To a solution of **9** (5.0 mg) in dry THF (1.0 mL) was added a suspension of $LiAlH_4$ (2.5 mg) in dry THF (0.5 mL). The reaction mixture was stirred at room temperature for 5 h. After workup, the solution was neutralized with 10% HCl to pH 4 and then partitioned between H_2O (30 mL) and EtOAc (30 mL). The EtOAc phase was evaporated under reduced pressure to give a residue that was separated by preparative TLC using 50% Me_2CO in petroleum ether as developing solvent to yield **9a** (3.0 mg): colorless gum; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.88 (1H, d, J = 7.8 Hz, H-5), 6.86 (1H, d, J = 1.8 Hz, H-2), 6.81 (1H, dd, J = 7.8, 1.8 Hz, H-6), 4.55 (1H, d, J = 10.8 Hz, H-7), 4.02 (1H, d, J = 9.6 Hz, H-7′a), 3.95 (1H, d, J = 9.6 Hz, H-7′b), 3.91 (3H, s, *Me*O-3), 1.79 (1H, dq, J = 10.8, 6.6 Hz, H-8), 1.35 (3H, s, H_3-9′), 0.96 (3H, d, J = 6.6 Hz, H_3-9); ESIMS m/z 255 $[M - H]^-$. To a solution of **9a** (3 mg) in THF (0.7 mL)−H_2O (0.2 mL) was added dropwise a solution of $NaIO_4$ (5 mg) in water (0.1 mL). After stirring at room temperature overnight, the reaction mixture was diluted with H_2O (30 mL) and then partitioned with EtOAc (30 mL). The EtOAc phase was evaporated under reduced pressure to give a residue, which was separated by preparative TLC using 4% MeOH in $CHCl_3$ to yield **8** (2.4 mg): white, amorphous powder; $[\alpha]^{20}_D$ +23 (c 0.09, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) and ESIMS data, identical to those of the natural product.

(−)-(4*S*,7*S*,10*S*)-2-Oxo-guaia-1(5),11(13)-dien-12-oic acid (10): colorless needles; $[\alpha]^{20}_D$ −16 (c 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.99), 240 (4.06) nm; CD (MeOH) 218 ($\Delta\varepsilon$ −2.21), 236 ($\Delta\varepsilon$ +0.63), 244 ($\Delta\varepsilon$ −0.07), 249 ($\Delta\varepsilon$ +0.06), 256 ($\Delta\varepsilon$ −0.33), 268 ($\Delta\varepsilon$ +0.04), 301 ($\Delta\varepsilon$ −0.21) nm; IR ν_{max} 2925, 1695, 1639, 1391, 1274, 1224, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.38 (1H, s, H-13a), 5.76 (1H, s, H-13b), 3.01 (1H, m, H-10), 2.75 (1H, dq, J = 6.5, 7.5 Hz, H-4), 2.61 (1H, dd, J = 18.5, 6.5 Hz, H-3a), 2.61 (1H, m, H-7), 2.60 (1H, m, H-6a), 2.44 (1H, m, H-6b), 1.98 (1H, d, J = 18.5 Hz, H-3b), 1.93 (1H, m, H-8a), 1.85 (1H, m, H-8b), 1.80 (1H, m, H-9a), 1.59 (1H, m, H-9b), 1.11 (3H, d, J = 7.5 Hz, H_3-14), 1.03 (3H, d, J = 7.0 Hz, H_3-15); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.1 (C-2), 175.9 (C-5), 170.6 (C-12), 145.7 (C-1), 145.4 (C-11), 125.5 (C-13), 43.0 (C-3), 39.3 (C-7), 37.8 (C-4), 37.0 (C-6), 32.6 (C-9), 30.9 (C-8), 26.7 (C-10), 19.1 (C-14), 17.5 (C-15); ESIMS m/z 249 $[M + H]^+$, 271 $[M + Na]^+$; HRESIMS m/z 249.1512 $[M + H]^+$ (calcd for $C_{15}H_{21}O_3$, 249.1491).

Preparation of 10a and MTPA Esters of 10b and 10c. Compound **10** (3.1 mg), DMAP (4-dimethylaminopyridine, 1.5 mg), and EDCI [1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride, 4.8 mg) were dissolved in anhydrous CH_2Cl_2 (1 mL). After the solution was cooled at 0 °C, anhydrous MeOH (2 μL) was added. The reaction mixture was stirred at room temperature for 1.5 h, and then the solvent was removed. The residue was chromatographed over silica gel (0.5 g) eluting with $CHCl_3$ to yield **10a** (2.3 mg): colorless gum; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.22 (1H, s, H-13a), 5.64 (1H, s, H-13b), 3.78 (3H, s, *Me*O), 3.01 (1H, m, H-10), 2.74 (1H, dq, J = 6.6, 7.2 Hz, H-4), 2.61 (1H, dd, J = 18.6, 6.6 Hz, H-3a), 2.60 (1H, m, H-6a), 2.59 (1H, m, H-7), 2.42 (1H, m, H-6b), 1.98 (1H, d, J = 18.6 Hz, H-3b), 1.92 (1H, m, H-8a), 1.82 (1H, m, H-8b), 1.78 (1H, m, H-9a), 1.58 (1H, m, H-9b), 1.11 (3H, d, J = 7.2 Hz, H_3-14), 1.02 (3H, d, J = 7.2 Hz, H_3-15). **10a** (2.3 mg) was hydrogenated in EtOH (1 mL) over 10% Pd−C (2.5 mg) at room temperature for 24 h. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give a mixture of two isomers. The mixture was further reduced with $NaBH_4$ (0.3 mg) in anhydrous EtOH (1 mL) at room temperature for 3 h. The solvent was removed, and the residue was chromatographed on silica gel eluting with $CHCl_3$ to afford another mixture, of which the ^1H NMR spectrum indicated that it contained **10b** and **10c** (Supporting Infromation), which we were unable to separate. The mixture was dissolved in anhydrous pyridine (1 mL), and the solution was divided into two portions, which were treated with *S*- and *R*-MTPACl at room temperature for 4 h, respectively. After pyridine was evaporated from the reaction solutions, by using a reversed-phase semipreparative HPLC separation with 85% CH_3CN in H_2O as mobile phase, **10b*R*** (0.5 mg) and **10c*R*** (0.5 mg) were obtained from the portion reacted with *S*-MTPACl, while **10b*S*** (0.3 mg) and **10c*S*** (0.3 mg) were isolated from the portion reacted with *R*-MTPACl. **10b*R***: colorless gum; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.3−7.5 (5H, m, aromatic protons of MTPA moiety), 5.36 (1H, m, H-2), 3.64 (3H, s, *Me*O-12), 3.52 (3H, s, *Me*O of MTPA moiety), 2.49 (1H, dt, J = 14.5, 8.0 Hz, H-3a), 2.23 (1H, m, H-11), 2.01 (1H, m, H-1), 1.95 (1H, m, H-4), 1.88 (1H, m, H-10), 1.86 (1H, m, H-7), 1.77 (1H, m, H-5), 1.65 (1H, m, H-9a), 1.40 (1H, m, H-8a), 1.26 (1H, m, H-8b), 1.06 (2H, m, H-3b, H-9b), 1.05 (1H, m, H-6a), 0.99 (1H, dt, J = 11.5, 12.5 Hz, H-6b), 0.94 (3H, d, J = 7.0 Hz, H_3-13), 0.91 (3H, d, J = 7.5 Hz, H_3-15), 0.84 (3H, d, J = 7.0 Hz, H_3-14). **10c*R***: colorless gum; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.3−7.5 (5H, m, aromatic protons of MTPA moiety), 5.33 (1H, m, H-2), 3.64 (3H, s, *Me*O-12), 3.54 (3H, s, *Me*O of MTPA moiety), 2.49 (1H, dt, J = 14.0, 8.0 Hz, H-3a), 2.15 (1H, m, H-11), 2.00 (1H, m, H-1), 1.94 (1H, m, H-4), 1.89 (1H, m, H-10), 1.81 (1H, m, H-7), 1.73 (1H, m, H-5), 1.63 (1H, m, H-9a), 1.47 (1H, m, H-8a), 1.28 (1H, m, H-8b), 1.24 (1H, m, H-6a), 1.08 (1H, m, H-9b), 1.05 (1H, m, H-3b), 0.92 (3H, d, J = 7.0 Hz, H_3-13), 0.92 (3H, d, J = 7.0 Hz, H_3-15), 0.85 (3H, d, J = 7.0 Hz, H_3-14), 0.77 (1H, dt, J = 11.0, 13.0 Hz, H-6b). **10b*S***: colorless gum; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.3−7.5 (5H, m, aromatic protons of MTPA moiety), 5.33 (1H, m, H-2), 3.66 (3H, s, *Me*O-12), 3.63 (3H, s, *Me*O of MTPA moiety), 2.53 (1H, dt, J = 15.0, 8.0 Hz, H-3a), 2.33 (1H, m, H-11), 1.97 (2H, m, H-1, H-4), 1.88 (1H, m, H-7), 1.81 (1H, m, H-5), 1.76 (1H, m, H-10), 1.2−1.5 (6H, m, H-3b, H_2-6, H_2-8, and H-9a), 1.07 (3H, d, J = 7.0 Hz, H_3-13), 0.95 (3H, d, J = 6.5 Hz, H_3-14), 0.78 (1H, m, H-9b), 0.61 (3H, d, J = 7.0 Hz, H_3-15). **10c*S***: colorless gum; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.3−7.5 (5H, m, aromatic protons of MTPA moiety), 5.33 (1H, m, H-2), 3.66 (3H, s, *Me*O-12), 3.62 (3H, s, *Me*O of MTPA moiety), 2.53 (1H, dt, J = 15.0, 8.0 Hz, H-3a), 2.31 (1H, m, H-11), 1.98 (2H, m, H-1, H-4), 1.88 (1H, m, H-7), 1.78 (2H, m, H-5, H-10), 1.2−1.5 (6H, m, H-3b, H_2-6, H_2-8, and H-9a), 1.08 (3H, d, J = 7.0 Hz, H_3-13), 0.96 (3H, d, J = 7.0 Hz, H_3-14), 0.85 (1H, m, H-9b), 0.64 (3H, d, J = 7.5 Hz, H_3-15).

(+)-(2*S*,3*R*,1′*S*,6′*R*)-5,7-Dihydroxy-3,6′-epoxy-1′,2′,3′,4′,5′,6′-tetrahydro-3′,4′-secoflava-4′,1′-lactone-3′-oic acid (11): colorless gum; $[\alpha]^{20}_D$ +39 (c 0.06, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.18), 230 (3.48), 277 (2.92) nm; CD (MeOH) 218 ($\Delta\varepsilon$ +0.70), 227 ($\Delta\varepsilon$ +0.65), 277 ($\Delta\varepsilon$ −0.04) nm; IR ν_{max} 3359, 2922, 1786, 1728, 1627, 1522, 1468, 1398, 1153, 1047 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 6.05 (1H, d, J = 2.0 Hz, H-6), 5.91 (1H, d, J = 2.0 Hz, H-8), 4.78 (1H, d, J = 6.8 Hz, H-6′), 4.52 (1H, dt, J = 4.8, 1.6 Hz, H-3), 4.45 (1H, d, J = 1.6 Hz, H-2), 3.20 (2H, s, H_2-2′), 3.19 (1H, dd, J = 18.4, 6.8 Hz, H-5′a), 2.91 (1H, dd, J = 18.0, 1.6 Hz, H-4a), 2.76 (1H, dd, J = 18.0, 4.8 Hz, H-4b), 2.50 (1H, d, J = 18.4 Hz, H-5′b); ^{13}C NMR (acetone-d_6, 125 MHz) δ 176.0 (C-4′), 172.0 (C-3′), 157.5 (C-7), 157.0 (C-5), 154.6 (C-8a), 98.6 (C-4a), 96.6 (C-6), 95.8 (C-8), 94.3 (C-1′), 80.8 (C-6′), 79.3 (C-2), 72.6 (C-3), 37.5 (C-5′), 36.9 (C-2′), 21.1 (C-4); ESIMS m/z 321 $[M - H]^-$, 345 $[M + Na]^+$; HRESIMS m/z 345.0627 $[M + Na]^+$ (calcd for $C_{15}H_{14}O_8Na$, 345.0586).

Methylation of 11. A solution of **11** (1.5 mg) in dry acetone (1 mL) was treated with K_2CO_3 (1.5 mg) and CH_3I (2 mg) at 40 °C for 8 h. The reaction mixture was then evaporated under reduced pressure

to give a residue. The residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). After removing solvent, the EtOAc extract was purified by RP-HPLC using a mobile phase of CH_3CN-H_2O (67:33) to afford **11a** (0.8 mg): white powder; IR ν_{max} 2965, 2948, 1794, 1742, 1621, 1597, 1502, 1465, 1431, 1371, 1219, 1149, 1058, 838 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) δ 6.15 (1H, d, J = 2.4 Hz, H-6), 6.06 (1H, d, J = 2.4 Hz, H-8), 4.76 (1H, d, J = 6.6 Hz, H-6′), 4.54 (1H, ddd, J = 4.8, 2.4, 1.8 Hz, H-3), 4.50 (1H, d, J = 2.4 Hz, H-2), 3.79 (3H, s, *Me*O-5), 3.73 (3H, s, *Me*O-7), 3.69 (3H, s, *Me*O-3′), 3.27 (1H, d, J = 17.4 Hz, H-2′a), 3.23 (1H, d, J = 17.4 Hz, H-2′b), 3.17 (1H, dd, J = 18.6, 7.2 Hz, H-5′a), 2.89 (1H, dd, J = 18.0, 1.8 Hz, H-4a), 2.75 (1H, dd, J = 18.0, 4.8 Hz, H-4b), 2.53 (1H, d, J = 18.6 Hz, H-5′b); ^{13}C NMR (acetone-d_6, 125 MHz) δ 175.7 (C-4′), 170.8 (C-3′), 160.5 (C-7), 159.4 (C-5), 154.1 (C-8a), 105.5 (C-4a), 94.3 (C-6), 93.9 (C-1′), 92.6 (C-8), 80.6 (C-6′), 79.0 (C-2), 72.4 (C-3), 55.8 (*Me*O-7), 55.5 (*Me*O-5), 52.0 (*Me*O-3′), 37.2 (C-5′), 36.6 (C-2′), 21.0 (C-4); HRESIMS m/z 387.1064 $[M + Na]^+$ (calcd for $C_{18}H_{20}O_8Na$, 387.1050).

Anti-inflammatory Activity Assay. See ref 39.

Cells, Culture Conditions, and Cell Proliferation Assay. See ref 41.

Protective Effect on Cytotoxicity Induced by DL-Galactosamine in WB-F344 Cells. The hepatoprotective effects were determined by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay[42] in WB-F344 cells, with some modification. Each cell suspension of 1×10^4 cells in 200 μL of Dulbecco's modified Eagle's medium (DMEM) containing fetal calf serum (10%), penicillin (100 units/mL), and streptomycin (100 μg/mL) was plated in a 96-well microplate and precultured for 24 h at 37 °C under a 5% CO_2 atmosphere. After fresh medium (200 μL) containing bicyclol (the positive control) or test sample was added, the cells were cultured for 1 h. Then, the cultured cells were exposed to 50 mM DL-galactosamine for 24 h. Cytotoxic effects of test samples were measured simultaneously in the absence of DL-galactosamine. The medium was changed into a fresh one containing 0.5 mg/mL MTT. After 4 h incubation, the medium was removed and 150 μL of DMSO was added to dissolve formazan crystals. The optical density (OD) of the formazan solution was measured on a microplate reader at 490 nm. Inhibition (%) was obtained by the following formula:

$$\text{inhibition (\%)} = [(OD_{(sample)} - OD_{(control)})/(OD_{(normal)} - OD_{(control)})] \times 100$$

All values were expressed as ±SD. The Student's t-test for unpaired observations between normal or control and tested samples was carried out to identify statistical differences; p values less than 0.05 were considered as significantly different.

Acknowledgment. Financial support from the National Natural Sciences Foundation of China (NNSFC; grant no. 30825044), the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT, grant no. IRT0514), and the National "973" Program of China (grant nos. 2004CB13518906 and 2006CB504701) is acknowledged.

Supporting Information Available: Figure S1, main HMBC correlations for compounds **7**, **9**−**11**, and **11a**. Figure S2, main NOESY correlations for compounds **7**, **9**, **10**, **10b*R***, and **11a**. Figure S3, CD spectra of compounds **7** and (+)-guaiacin (**12**). Scheme S1, chemical transformation from **1** to (+)-(5*S*)-3-dodecyl-5-methylfuran-2(5*H*)-one (**1c**) and **1d**, and $\Delta\delta_{SR}$ ($\delta_S - \delta_R$) values obtained from the ^1H NMR spectra of the MTPA esters of **1a**. Scheme S2, chemical transformation from **9** to **8**. Scheme S3, preparation of derivatives of **10** and $\Delta\delta_{SR}$ ($\delta_S - \delta_R$) values obtained from the ^1H NMR spectra of the MTPA esters of **10b** and **10c**. Scheme S4, proposed biogenetic cycloaddition pathway from (−)-*epi*-catechin to **11** and viniperferones B and C. IR, MS, 1D and 2D NMR spectra of **1**, **1a**−**1d**, *S*- and *R*-MTPA-**1a**, **2**−**8**, **8a**, **8b**, **9**, **9a**, **10**, **10a**, **10b*S***, **10b*R***, **10c*S***, **10c*R***, **11**, **11a**, and **12**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Lee, S. K.; Wei, F. N. *Guihaia* **1984**, *4*, 93–106. (b) Zhuang, X. Y. *Guihaia* **1997**, *17*, 291–294. (c) Lin, X. Z. *Sci. Silvae Sin.* **2007**, *43*, 151–156.

(2) Yu, Y. U.; Kang, S. Y.; Park, H. Y.; Sung, S. H.; Lee, E. J.; Kim, S. Y.; Kim, Y. C. *J. Pharm. Pharmacol.* **2000**, *52*, 1163–1169.

(3) Cheng, M. J.; Jayaprakasam, B.; Ishikawa, T.; Seki, H.; Tsai, I. L.; Wang, J. J.; Chen, I. S. *Helv. Chim. Acta* **2002**, *85*, 1909–1914.

(4) (a) Talapatra, B.; Goswami, S.; Ghash, A.; Talapetra, S. K. *J. Indian Chem. Soc.* **1982**, *59*, 1364–1368. (b) Liu, M. T.; Lin, S.; Wang, Y. H.; He, W. Y.; Li, S.; Wang, S. J.; Yang, Y. C.; Shi, J. G. *Org. Lett.* **2007**, *9*, 129–132.

(5) (a) Kim, S. H.; Park, J. C. *Sikmul Hakhoechi* **1993**, *36*, 297–300. (b) Lee, J. S.; Kim, J.; Yu, Y. U.; Kim, Y. C. *Arch. Pharm. Res.* **2004**, *27*, 1043–1047.

(6) Gan, M. L.; Zhang, Y. L.; Lin, S.; Liu, M. T.; Song, W. X.; Zi, J. C.; Yang, Y. C.; Fan, X. N.; Shi, J. G.; Hu, J. F.; Sun, J. D.; Chen, N. H. *J. Nat. Prod.* **2008**, *71*, 647–654, and references therein.

(7) Van Beek, T. A.; Lankhorst, P. P. *Tetrahedron* **1996**, *52*, 4505–4514.

(8) (a) Takeda, K. I.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1972**, *28*, 3757–3766. (b) Chen, I. S.; Lai-Yaun, I. L.; Duh, C. Y.; Tsai, I. L. *Phytochemistry* **1998**, *49*, 745–750.

(9) Tsai, I. L.; Hung, C. H.; Duh, C. Y.; Chen, J. H.; Lin, W. Y.; Chen, I. S. *Planta Med.* **2001**, *67*, 865–866.

(10) (a) Tanaka, H.; Nakamura, T.; Ichino, K.; Ito, K.; Tanaka, T. *Phytochemistry* **1990**, *29*, 857–859. (b) Pupo, M. T.; Vieira, P. C.; Fernandes, J. B.; Da Silva, M. F. D. G. F. *Phytochemistry* **1998**, *48*, 307–310. (c) Claros, B. M.; da Silva, A. J.; Vasconcellos, M. L.; de Brito, A. P.; Leitão, G. G. *Phytochemistry* **2000**, *55*, 859–862. (d) Tsai, I. L.; Hung, C. H.; Duh, C. Y.; Chen, I. S. *Planta Med.* **2002**, *68*, 142–145. (e) Min, B. S.; Lee, S. Y.; Kim, J. H.; Kwon, O. K.; Park, B. Y.; An, R. B.; Lee, J. K.; Moon, H. I.; Kim, T. J.; Kim, Y. H.; Joung, H.; Lee, H. K. *J. Nat. Prod.* **2003**, *66*, 1388–1390.

(11) Juan, C.; Martinez, V.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1981**, *20*, 459–464.

(12) (a) Qian, Y.; Yao, Z. J.; Chen, X. G.; Wu, Y. L. *J. Org. Chem.* **1999**, *64*, 2440–2445. (b) Lee, S. S.; Chang, S. M.; Chen, C. H. *J. Nat. Prod.* **2001**, *64*, 1548–1551.

(13) Omata, K.; Fujiwara, T.; Kabuto, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1655–1662.

(14) Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron* **2000**, *56*, 389–395.

(15) (a) Su, B. N.; Park, E. J.; Mbwambo, Z. H.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, *65*, 1278–1282. (b) Yang, L.; Andersen, R. J. *J. Nat. Prod.* **2002**, *65*, 1924–1926. (c) That, Q. T.; Jossang, J.; Jossang, A.; Kim, P. P.; Jaureguiberry, G. *J. Org. Chem.* **2007**, *72*, 7102–7105.

(16) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

(17) Chen, C. Y.; Chen, C. H.; Wong, C. H.; Liu, Y. W.; Lin, Y. S.; Wang, Y. D.; Hsui, Y. R. *J. Nat. Prod.* **2007**, *70*, 103–106.

(18) (a) Kwon, H. C.; Baek, N. I.; Choi, S. U.; Lee, K. R. *Chem. Pharm. Bull.* **2000**, *48*, 614–616. (b) Garcez, F. R.; Garcez, W. S.; Martins, M.; Matos, M. F. C.; Guterres, Z. R.; Mantovani, M. S.; Misu, C. K.; Nakashita, S. T. *Planta Med.* **2005**, *71*, 923–927.

(19) Chen, M. J.; Lo, C. Y.; Chin, C. C.; Liu, R. S. *J. Org. Chem.* **2000**, *65*, 6362–6367.

(20) (a) Krauss, A. S.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1335–1340. (b) Carroll, A. R.; Krauss, A. S.; Taylor, W. C. *Aust. J. Chem.* **1993**, *46*, 277–292.

(21) Majumder, P. L.; Chatterjee, A.; Sengupta, G. C. *Phytochemistry* **1972**, *11*, 811–814.

(22) (a) The semisystematic nomenclature of **8** and **9** is based on the lignane parent structure. (b) Moss, G. P. *Pure Appl. Chem.* **2000**, *72*, 1493–1523.

(23) Yang, X. F.; Wang, M.; Varma, R. S.; Li, C. J. *Org. Lett.* **2003**, *5*, 657–660.

(24) (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324. (b) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294–4299.

(25) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435–1444.

(26) Kuo, Y. H.; Lin, S. T. *Chem. Pharm. Bull.* **1993**, *41*, 1507–1512.

(27) Fan, P.; Lou, H.; Yu, W.; Ren, D.; Ma, B.; Ji, M. *Tetrahedron Lett.* **2004**, *45*, 3163–3166.

(28) The semisystematic nomenclature of **11** is based on the flavane parent structure.

(29) Hwu, J. R.; Tseng, W. N.; Gnabre, J.; Giza, P.; Huang, R. C. C. *J. Med. Chem.* **1998**, *41*, 2994–3000.

(30) Suri, K. A.; Sood, R. P.; Suri, O. P.; Atal, C. K.; Singh, G. B. *Indian J. Pharm. Sci.* **1981**, *43*, 226–228.

(31) Hattori, M.; Hada, S.; Kawata, Y.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Chem. Pharm. Bull.* **1987**, *35*, 3315–3322.

(32) Shimomura, H.; Sashida, Y.; Oohara, M. *Phytochemistry* **1988**, *27*, 634–636.

(33) Iida, T.; Nakano, M.; Ito, K. *Phytochemistry* **1982**, *21*, 673–675.

(34) Achenbach, H.; Grob, J.; Dominguez, X. A.; Cano, G.; Star, J. V.; Del Carmen Brussolo, L.; Munoz, G.; Salgado, F.; Lopez, L. *Phytochemistry* **1987**, *26*, 1159–1166.
(35) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114–4125.
(36) Fraga, B. M.; Terrero, D. *Phytochemistry* **1996**, *41*, 229–232.
(37) Goldsby, G.; Burke, B. A. *Phytochemistry* **1987**, *26*, 1059–1063.
(38) Oksuz, S.; Topcu, G. *Phytochemistry* **1992**, *31*, 195–197.
(39) Song, W. X.; Li, S.; Wang, S. J.; Wu, Y.; Zi, J. C.; Gan, M. L.; Zhang, Y. L.; Liu, M. T.; Lin, S.; Yang, Y. C.; Shi, J. G. *J. Nat. Prod.* **2008**, *71*, 922–925.
(40) Liu, G. T. *Chin. J. New Drugs* **2001**, *10*, 325–327.
(41) (a) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63. (b) Carmichael, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936–942. (c) Mo, S. Y.; Wang, S. J.; Zhou, G. X.; Yang, Y. C.; Li, Y.; Chen, X. G.; Shi, J. G. *J. Nat. Prod.* **2004**, *67*, 823–828.
(42) (a) Xiong, Q.; Hase, K.; Tezuka, Y.; Tani, T.; Namba, T.; Kadota, S. *Planta Med.* **1998**, *64*, 120–125. (b) Xu, F. M.; Morikawa, T.; Matsuda, H.; Ninomiya, K.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 569–576.

NP900504A