# Diterpenoids from the Twigs and Leaves of Fokienia hodginsii 

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S Supporting Information


#### Abstract

Five new isopimarane diterpenoids, fokihodgins A-E (1-5), four new labdane diterpenoids, fokihodgins $\mathrm{F}-\mathrm{I}$ (6-9), and one new icetexane diterpenoid, fokihodgin $\mathrm{J}(10)$, as well as 18 known diterpenoids were isolated from Fokienia hodginsii. The structures of the new compounds were determined on the basis of their spectroscopic analysis, and the absolute configurations of 1 and 6 were established by X-  ray crystallographic analysis. Compound 9 showed moderate cytotoxicity against HL-60 and SMMC-7721 cell lines, with $\mathrm{IC}_{50}$ values of 9.10 and $7.50 \mu \mathrm{M}$, respectively.


The family Cupressaceae contains about 22 genera and 150 species, of which eight genera and 29 species are distributed in China. ${ }^{1}$ Many species of this family are economically and medicinally valuable and are used to treat a variety of ailments in traditional Chinese medicine. ${ }^{2}$ Phytochemically, plants of the family Cupressaceae are rich sources of structurally diverse diterpenoids, many of which have been reported to possess cytotoxic and antimicrobial activities. ${ }^{3-7}$

Fokienia hodginsii, belonging to the monotypic genus Fokienia of the Cupressaceae family, is mainly distributed in southwestern China and northern Vietnam. ${ }^{8}$ The heartwood of $F$. hodginsii has been used in Chinese folk medicine for the treatmeat of stomach pain, nausea, and vomiting. ${ }^{9}$ Previous chemical investigations of this plant have been mainly focused on the composition of the essential oil and lipids. ${ }^{10-13}$ As part of our research on bioactive compounds from monotypic genus species, ${ }^{14-17}$ phytochemical investigation of the twigs and leaves of $F$. hodginsii led to the isolation of five new isopimarane diterpenoids, fokihodgins $A-E \quad(1-5)$, four new labdane diterpenoids, fokihodgins $\mathrm{F}-\mathrm{I}(6-9)$, and one new icetexane diterpenoid, fokihodgin $\mathrm{J}(\mathbf{1 0})$, as well as 18 known diterpenoids. Herein, we describe the isolation, structural elucidation, and cytotoxicity evaluation of these compounds.

## RESULTS AND DISCUSSION

The $95 \%$ EtOH extract of the twigs and leaves of F. hodginsii was partitioned between $\mathrm{H}_{2} \mathrm{O}$ and EtOAc. The EtOAc fraction was subjected repeatedly to column chromatography over silica gel, MCI gel, RP-C ${ }_{18}$ gel, Sephadex LH-20, and semipreparative HPLC to afford 10 new ( $\mathbf{1 - 1 0 )}$ and 18 known (11-28) diterpenoids. The known compounds (Supporting Information, Figure S1) were identified as sandaracopimaric acid (11), ${ }^{18}$ isopimara-8(14), 15-dien-11 $\alpha$-ol (12), ${ }^{19}$ isopimara-8(14),15-

diene-3 $\beta$,18-diol (13), ${ }^{20}$ 12S-hydroxylabda-8(17),13(16),14-trien-19-oic acid (14), ${ }^{21}$ trans-communic acid (15), ${ }^{22}$ transcommunal (16), ${ }^{23}$ isocupressic acid (17), ${ }^{24}$ acetylisocupressic acid (18), ${ }^{25}$ 13-epi-cupressic acid (19), ${ }^{24}$ 15-nor-labda-8(17), 12E-diene-14-carboxaldehyde-19-oic acid (20), ${ }^{26}$ pinulisolidic acid (21), ${ }^{22} 8 \alpha$-hydroxylabda-13(16),14-dien-19-yl (E)coumarate (22), ${ }^{27} 8 \alpha$-hydroxylabda-13(16),14-dien-19-yl (E)ferulate (23), ${ }^{28} 8 \alpha$-hydroxylabda-13(16),14-dien-19-yl (Z)-

[^0]Table 1. ${ }^{1} \mathrm{H}$ NMR Data of Compounds $1-5\left(\delta_{\mathrm{H}}, J\right.$ in Hz$)$

| no. | $1^{a}$ | $2^{a}$ | $3^{a}$ | $4^{\text {b }}$ | $5^{b}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $1 \alpha$ | 1.35, m | 1.54, overlap | 1.50, m | 1.44, m | 1.25, m |
| $1 \beta$ | 1.86, m | 1.86, m | 1.89, m | 1.51, m | 1.76, overlap |
| $2 \alpha$ | 1.58, m | 1.55, overlap | 1.69, m | 1.60, m | 1.59, overlap |
| $2 \beta$ | 1.58, m | 1.55, overlap | 1.58, m | 1.60, m | 1.59, overlap |
| $3 \alpha$ | 1.30, overlap | 1.39, overlap | 3.29, dd (11.3, 4.2) | 3.20, dd (11.3, 4.4) | 1.58, overlap |
| $3 \beta$ | 1.46, overlap | 1.39, overlap |  |  | 1.29, m |
| $5 \alpha$ | 1.47, overlap | 1.39, overlap | 1.10, dd (12.5, 2.5) | 1.14, dd (12.5, 2.3) | 1.96, dd (13.2, 2.7) |
| $6 \alpha$ | 1.53, m | 1.51, m | 1.66, m | 1.69, m | 1.74, overlap |
| $6 \beta$ | 1.31, overlap | 1.32, m | 1.36, ddd (17.3, 12.5, 4.4) | 1.40, ddd (17.3, 12.5, 4.5) | 1.59, overlap |
| $7 \alpha$ | 2.08, dt (13.2, 5.4) | 2.02, m | 2.04, dt (13.4, 5.3) | 2.07, m | 4.19, t (2.7) |
| $7 \beta$ | 2.30, m | 2.30, m | 2.34, m | 2.37, m |  |
| $9 \alpha$ | 1.81, d, (4.7) | 1.79, d, (4.5) | 1.71, d, (4.7) | 1.96, d, 6.4 | 2.75, br s |
| 11 | 4.03, dt (6.7, 4.7) | 4.03 , dt (6.5, 4.5) | 4.01, dt (6.7, 4.7) | 5.21, m | 5.69, dd (10.2, 3.4) |
| $12 \alpha$ | 1.64, d (6.7) | 1.64, d (6.5) | 1.64, d (6.7) | 1.47, m | 5.57, m |
| $12 \beta$ | 1.64, d (6.7) | 1.64, d (6.5) | 1.64, d (6.7) | 1.71, m |  |
| 14 | 5.30, br s | 5.31, br s | 5.30, br s | 5.34, br s | 5.46, br s |
| 15 | 5.87, dd (17.5, 10.5) | 5.86, dd (17.5, 10.5) | 5.87, dd (17.5, 10.5) | 5.80 , dd (17.5, 10.6) | 5.79, dd (17.5, 10.5) |
| 16a | 4.99, dd (17.5, 1.2) | 4.99, dd (17.5, 1.1) | 5.01, dd (17.5, 1.2) | 5.01, dd (17.5, 1.2) | 4.95, dd (17.5, 1.2) |
| 16 b | 4.91, dd (10.5, 1.2) | 4.91, dd (10.5, 1.1) | 4.91, dd (10.5, 1.2) | 4.91, dd (10.6, 1.2) | 4.92, dd (10.5, 1.2) |
| 17 | 1.05, s | 1.04, s | 1.05, s | 1.10, s | 1.11, s |
| 18a | 3.40, d (10.9) | 3.87, d (10.9) | 1.01, s | 1.00, s | 3.38, d (11.4) |
| 18b | 3.10, d (10.9) | 3.62, d (10.9) |  |  | 2.99, d (11.4) |
| 19 | 0.79, s | 0.85, s | 0.82, s | 0.81, s | 0.76, s |
| 20 | 0.86, s | 0.85, s | 0.82, s | 0.88, s | 0.79, s |
| OAc |  | 2.06, s |  | 1.99, s |  |
| ${ }^{\text {a }}$ Recorded in $\mathrm{CDCl}_{3}$ at $400 \mathrm{MHz} .{ }^{\text {b }}$ Recorded in methanol $-d_{4}$ at 400 MHz . |  |  |  |  |  |

coumarate (24), ${ }^{28}$ ferruginol (25), ${ }^{29}$ pisiferol (26), ${ }^{30}$ pisiferal (27), ${ }^{30}$ and 5-epi-pisiferol (28), ${ }^{7}$ respectively, by comparison of observed and reported spectroscopic data.

Fokihodgin A (1) was obtained as colorless crystals. Its molecular formula was established as $\mathrm{C}_{20} \mathrm{H}_{32} \mathrm{O}_{2}$ by HREIMS at $\mathrm{m} / \mathrm{z} 304.2397[\mathrm{M}]^{+}$(calcd 304.2402), requiring five indices of hydrogen deficiency. The IR absorption bands of 1 revealed the presence of hydroxy ( $3419 \mathrm{~cm}^{-1}$ ) and olefinic ( $1635 \mathrm{~cm}^{-1}$ ) functionalities. The ${ }^{1} \mathrm{H}$ NMR spectrum of 1 (Table 1) showed the presence of three tertiary methyls at $\delta_{\mathrm{H}} 1.05\left(\mathrm{~s}, \mathrm{H}_{3}-17\right)$, $0.79\left(\mathrm{~s}, \mathrm{H}_{3}-19\right)$, and $0.86\left(\mathrm{~s}, \mathrm{H}_{3}-20\right)$, a characteristic isolated AB methylene group at $\delta_{\mathrm{H}} 3.10$ and 3.40 (both d, both $J=10.9$ $\mathrm{Hz})$, an oxygenated methine at $\delta_{\mathrm{H}} 4.03(\mathrm{dt}, J=6.7,4.7 \mathrm{~Hz})$, an olefinic methine at $\delta_{\mathrm{H}} 5.30(\mathrm{br} \mathrm{s})$, and a monosubstituted olefinic moiety at $\delta_{\mathrm{H}} 5.87(\mathrm{dd}, J=17.5,10.5 \mathrm{~Hz}), 4.99(\mathrm{dd}, J=$ $17.5,1.2 \mathrm{~Hz}$ ), and $4.91(\mathrm{~d}, ~ J=10.5,1.2 \mathrm{~Hz})$. The ${ }^{13} \mathrm{C}$ NMR and DEPT spectra of 1 (Table 3) displayed 20 carbon signals, consisting of three methyl, eight methylene (one oxygenated and one $\mathrm{sp}^{2}$ ), five methine (one oxygenated and two $\mathrm{sp}^{2}$ ), and four quaternary (one $\mathrm{sp}^{2}$ ) carbons. The aforementioned spectroscopic analysis suggested 1 was an isopimarane diterpenoid with one secondary hydroxy and one hydroxymethyl group. Detailed analysis of the NMR spectroscopic data of 1 with those of isopimara-8(14),15-dien-11 $\alpha$-ol (12) indicated their structural similarity, except for the hydroxymethyl group ( $\delta_{\mathrm{C}} 72.0, \mathrm{C}-18$ ) in 1 instead of a C-18 methyl group in 12. This deduction was supported by HMBC correlations (Figure 1) from H-18a ( $\delta_{\mathrm{H}} 3.40, \mathrm{~d}, J=10.9 \mathrm{~Hz}$ ) and H-18b ( $\delta_{\mathrm{H}} 3.10, \mathrm{~d}, J=10.9 \mathrm{~Hz}$ ) to C-4 ( $\delta_{\mathrm{C}} 37.8$ ), C-5 $\left(\delta_{\mathrm{C}}\right.$ $47.8)$, and C-19 ( $\delta_{\mathrm{C}} 17.9$ ).

The relative configuration of $\mathbf{1}$ was established by a ROESY experiment (Figure 1). The ROESY correlations of $\mathrm{H}-5 / \mathrm{H}-9$ and $\mathrm{H}-5 / \mathrm{H}_{2}-18$ indicated the $\alpha$-orientation of $\mathrm{H}-5, \mathrm{H}-9$, and
the hydroxymethyl group, while the correlations of $\mathrm{H}-11 / \mathrm{H}_{3}$ 17, $\mathrm{H}-11 / \mathrm{H}_{3}-20$, and $\mathrm{H}_{3}-19 / \mathrm{H}_{3}-20$ suggested the $\beta$-orientation of $\mathrm{H}-11, \mathrm{H}_{3}-17, \mathrm{H}_{3}-19$, and $\mathrm{H}_{3}$-20. Finally, the absolute configuration of 1 was determined by X-ray crystallography based on an anomalous dispersion of $\mathrm{Cu} \mathrm{K} \alpha$ radiation (Figure 2). The C-4, C-5, C-9, C-10, C-11, and C-13 absolute configurations were thus assigned as $R, R, S, S, R$, and $R$, respectively. Therefore, the structure of $\mathbf{1}$ was assigned as $11 R$ -isopimara-8(14),15-diene-11,18-diol.

The molecular formula of fokihodgin B (2) was assigned as $\mathrm{C}_{22} \mathrm{H}_{34} \mathrm{O}_{3}$, according to its HREIMS ( $[\mathrm{M}]^{+} \mathrm{m} / z$ 346.2513, calcd 346.2508). The ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data of 2 (Tables 1 and 3 ) were similar to those of 1 . The only difference was the hydroxy group at C -18 in $\mathbf{1}$ was replaced by an acetoxy group in 2, as deduced from the correlations of $\mathrm{H}-18 \mathrm{a}\left(\delta_{\mathrm{H}} 3.87, J=10.9\right.$ Hz ) and $\mathrm{H}-18 \mathrm{~b}\left(\delta_{\mathrm{H}} 3.62, J=10.9 \mathrm{~Hz}\right)$ with an ester carbonyl carbon ( $\delta_{\mathrm{C}}$ 171.3) in the HMBC experiment. The relative configurations of both 2 and $\mathbf{1}$ were identical according to the observed ROESY correlations. Consequently, 2 was determined as 18 -O-acetylisopimara-8(14),15-dien-11 $\alpha$-ol.

Fokihodgin C (3) exhibited the molecular formula $\mathrm{C}_{20} \mathrm{H}_{32} \mathrm{O}_{2}$, as determined on the basis of its HREIMS ( $[\mathrm{M}]^{+} \mathrm{m} / \mathrm{z}$ 304.2397, calcd 304.2402). The ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data of 3 (Tables 1 and 3 ) were similar to those of $\mathbf{1 2}$, suggesting that they were structural analogues. The main difference was the presence of an additional hydroxy group in 3 as compared with 12. The HMBC correlations from $\mathrm{H}-3$ ( $\delta_{\mathrm{H}} 3.29$, dd, $J=11.3$, 4.2 Hz ) to C-1 ( $\delta_{\mathrm{C}} 37.9$ ), C-2 ( $\delta_{\mathrm{C}} 27.6$ ), C-4 ( $\delta_{\mathrm{C}} 39.0$ ), C-5 ( $\delta_{\mathrm{C}}$ $54.2)$, and $\mathrm{C}-19\left(\delta_{\mathrm{C}} 15.8\right)$ indicated the location of the hydroxy group at C-3. The ROESY correlations of $\mathrm{H}-3 / \mathrm{H}-5$ and $\mathrm{H}-3 /$ $\mathrm{H}_{3}-18$ indicated the $\alpha$-orientation of $\mathrm{H}-3$. In addition, $\mathrm{H}-11$ was determined as $\beta$-oriented in view of the ROESY correlations of

Table 2. ${ }^{1} \mathrm{H}$ NMR Data of Compounds 6-8 and $10\left(\delta_{H}, J\right.$ in Hz )

| no. | $6^{a}$ | $7^{\text {b }}$ | $8^{\text {b }}$ | $10^{c}$ |
| :---: | :---: | :---: | :---: | :---: |
| $1 \alpha$ | $\begin{aligned} & \text { 1.16, dt (12.0, } \\ & 3.2) \end{aligned}$ | 1.08, overlap | 1.16, m | $\begin{aligned} & 1.43, \mathrm{dt}(13.0, \\ & 3.7) \end{aligned}$ |
| $1 \beta$ | 1.80, m | 1.70, m | 1.81, overlap | $\underset{(12.7)}{1.57, \mathrm{br} \mathrm{~d}}$ |
| $2 \alpha$ | 1.51, m | 1.49, m | 1.49, m | 1.32, m |
| $2 \beta$ | 1.84, m | 1.89, overlap | 1.89, overlap | 1.77, m |
| $3 \alpha$ | $\begin{aligned} & \text { 1.06, dt (13.3, } \\ & 3.6) \end{aligned}$ | 1.07, overlap | 1.07, m | 1.02, m |
| $3 \beta$ | $\underset{(13.3)}{2.14, \mathrm{br} \mathrm{~d}}$ | 2.14, m | 2.14, m | 1.27, m |
| $5 \alpha$ | $\underset{(11.2)}{1.41, \mathrm{br} \mathrm{~d}}$ | 1.41, m | 1.36, m | 0.60, d (7.0) |
| $6 \alpha$ | 2.01, m | 2.01, m | 1.89, overlap | 1.81, m |
| $6 \beta$ | 1.89, m | 1.89, overlap | 2.01, m | 1.28, m |
| $7 \alpha$ | 2.42, m | 2.43, m | 2.43, m | 0.95, m |
| $7 \beta$ | 1.99, m | 1.98, m | 1.98, m | 2.07, m |
| $9 \alpha$ | 2.09, m | 1.74, m | 1.81, overlap |  |
| 11a | 1.67, m | 1.72, m | 1.76, m | 5.84, br s |
| 11 b | 1.67, m | 1.65, m | 1.76, m |  |
| 12 | 4.41, m | $\begin{aligned} & 2.95, \mathrm{dd},(7.2 \text {, } \\ & 3.1) \end{aligned}$ | 2.80, t like |  |
| 14 | $\begin{aligned} & \text { 6.33, dd (17.8, } \\ & \text { 11.1) } \end{aligned}$ | $\begin{aligned} & 5.86 \text {, dd }(17.2, \\ & 11.3) \end{aligned}$ | $\begin{aligned} & 5.63, \mathrm{dd} \\ & (17.4,10.8) \end{aligned}$ | 6.61, br s |
| 15a | 5.41, d (17.8) | $\begin{aligned} & 5.35, \operatorname{dd}(17.2, \\ & 1.4) \end{aligned}$ | $\begin{aligned} & 5.30 \text {, dd }(10.8, \\ & 1.1) \end{aligned}$ | $\begin{aligned} & \text { 2.78, hep } \\ & (7.0) \end{aligned}$ |
| 15b | 5.12, d (11.1) | $\begin{aligned} & 5.30 \text {, dd (11.3, } \\ & 1.4) \end{aligned}$ | $\begin{aligned} & 5.28 \text {, dd (17.4, } \\ & 1.1) \end{aligned}$ |  |
| 16a | 5.21, br s | 1.35, s | 1.39, s | 0.98, d (6.8) |
| 16b | 5.14, br s |  |  |  |
| 17a | 4.52 , br s | 4.92, br s | 4.92, br s | 1.01, d (6.8) |
| 17b | 4.88 , br s | 4.74, br s | 4.74, br s |  |
| 18 | 1.24 s | 1.20 s | 1.21, s | 0.74, s |
| 19 |  |  |  | 0.90, s |
| $20 \alpha$ | 0.57, s | 0.62, s | 0.65, s | 3.11, d (12.7) |
| $20 \beta$ |  |  |  | 2.14, d (12.7) |
| $8-\mathrm{OH}$ |  |  |  | 5.53 , br s |
| $10-\mathrm{OH}$ |  |  |  | 4.33, br s |

${ }^{a}$ Recorded in $\mathrm{CDCl}_{3}$ at 400 MHz . ${ }^{b}$ Recorded in methanol- $d_{4}$ at 400

$\mathrm{H}-11 / \mathrm{H}_{3}-17$ and $\mathrm{H}-11 / \mathrm{H}_{3}-20$. Thus, compound 3 was elucidated as isopimara-8(14),15-diene-3 $\beta, 11 \alpha$-diol.

Fokihodgin D (4) had the molecular formula $\mathrm{C}_{22} \mathrm{H}_{34} \mathrm{O}_{3}$, based on the HRESIMS ( $[\mathrm{M}+\mathrm{Na}]^{+} m / z 369.2395$, calcd 369.2405), which was 42 mass units greater than 3 . Comparing the NMR data of 4 (Tables 1 and 3 ) with those of 3 indicated that the two compounds were related, except for the existence of an acetoxy group in 4 . The acetoxy group was located at C11 based on the HMBC correlations from $\mathrm{H}-11\left(\delta_{\mathrm{H}} 5.21, \mathrm{~m}\right)$ to C-9 ( $\delta_{\mathrm{C}} 56.6$ ), C-12 ( $\delta_{\mathrm{C}} 43.4$ ), and an acetoxy carbonyl carbon ( $\delta_{\mathrm{C}}$ 172.4), which was further confirmed by the downfield shift of $\mathrm{C}-11$ from $\delta_{\mathrm{C}} 66.2$ in 3 to $\delta_{\mathrm{C}} 70.4$ in 4 . The relative configuration of 4 was determined to be the same as 3 based on the detailed analysis of the ROESY spectrum. Accordingly, the structure of compound 4 was elucidated as $11 \alpha-O$-acetylisopi-mara-8(14), 15 -dien-3 $\beta$-ol.

Fokihodgin E (5) gave a molecular formula of $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{2}$ by HREIMS ( $[\mathrm{M}]^{+} m / z$ 302.2249, calcd 302.2246). The ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data of 5 (Tables 1 and 3 ) were similar to those of $\mathbf{1}$, with the main differences being that an oxygenated methine at $\mathrm{C}-11$ and a methylene at C -12 in $\mathbf{1}$ were changed into a double
bond in $\mathbf{5}$, as inferred from the HMBC correlations from $\mathrm{H}-11$ ( $\delta_{\mathrm{H}} 5.69, \mathrm{dd}, J=10.2,3.4 \mathrm{~Hz}$ ) to C-9 ( $\delta_{\mathrm{C}} 48.3$ ), C-10 ( $\delta_{\mathrm{C}} 40.6$ ), and C-12 $\left(\delta_{\mathrm{C}} 134.8\right)$ and from H-12 $\left(\delta_{\mathrm{H}} 5.57, \mathrm{~m}\right)$ to C-11 $\left(\delta_{\mathrm{C}}\right.$ 124.1), C-13 ( $\delta_{\mathrm{C}} 40.5$ ), and C-14 ( $\delta_{\mathrm{C}} 130.5$ ). The other difference between these two compounds was that an oxymethine at $\mathrm{C}-7\left(\delta_{\mathrm{C}} 73.9\right)$ in 5 replaced a methylene in $\mathbf{1}$, as deduced from the HMBC correlations of H-7 ( $\delta_{\mathrm{H}} 4.19, \mathrm{t}, J=$ 2.7 Hz ) with C-5 ( $\delta_{\mathrm{C}} 41.5$ ), C-6 ( $\delta_{\mathrm{C}} 30.9$ ), C-8 ( $\delta_{\mathrm{C}} 136.8$ ), and $\mathrm{C}-14$. The ROESY correlations of $\mathrm{H}-5 / \mathrm{H}_{2}-18$ and $\mathrm{H}-5 / \mathrm{H}-9$ indicated the $\alpha$-orientation of $\mathrm{H}_{2}-18$. Additionally, the hydroxy group at C-7 was $\alpha$-oriented because of the small coupling constant ( $2.7 \mathrm{~Hz} \mathrm{)} \mathrm{between} \mathrm{H-7} \mathrm{and} \mathrm{H}_{2}-6$, which was further confirmed by the cross-peak of $\mathrm{H}-7$ with $\mathrm{H}-14$ in the ROESY spectrum. Hence, the structure of 5 was assigned as isopimara-8(14),11,15-triene-7 $\alpha, 18$-diol.

Fokihodgin F (6) was obtained as colorless crystals and had a molecular formula of $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{3}$ as deduced from the HREIMS at $m / z 318.2200[\mathrm{M}]^{+}$(calcd 318.2195), indicating six indices of hydrogen deficiency. The IR spectrum showed the presence of a hydroxy ( $3440 \mathrm{~cm}^{-1}$ ) and double-bond (1641 and 1650 $\mathrm{cm}^{-1}$ ) groups. Analysis of the ${ }^{1} \mathrm{H}$ NMR, ${ }^{13} \mathrm{C}$ NMR, and DEPT data (Tables 2 and 3) revealed the existence of two tertiary methyl groups, six methylene carbons, two methine carbons, two $\mathrm{sp}^{3}$ quaternary carbons, one oxymethine carbon $\left[\delta_{\mathrm{C}} 69.9\right.$ (d, C-12)], three terminal double bonds $\left[\delta_{\mathrm{C}} 148.9\right.$ ( $\mathrm{s}, \mathrm{C}-8$ ), 150.4 ( $\mathrm{s}, \mathrm{C}-13$ ), 136.0 ( $\mathrm{d}, \mathrm{C}-14$ ), 114.7 ( $\mathrm{t}, \mathrm{C}-15$ ), 113.3 ( $\mathrm{t}, \mathrm{C}-$ 16), 106.5 ( $\mathrm{t}, \mathrm{C}-17$ )], and one carboxy group [ $\delta_{\mathrm{C}} 183.9$ ( $\mathrm{s}, \mathrm{C}$ 18)] in 6. The above spectroscopic data showed that 6 had a structure similar to $12 S$-hydroxylabda-8(17),13(16),14-trien-19-oic acid (13). Their 1D NMR data showed many similarities except for obvious differences of the chemical shifts of the protons and carbons around $\mathrm{C}-12$ in the side chain, suggesting that 6 was likely the stereoisomer of $\mathbf{1 3}$ at $\mathrm{C}-12$. The proposed structure was rigorously determined by a single-crystal X-ray diffraction experiment using $\mathrm{Cu} \mathrm{K} \alpha$ radiation (Figure 3), and its absolute configuration was established as $4 S, 5 R, 9 S, 10 R$, and $12 R$. Accordingly, compound 6 was elucidated as $12 R$ -hydroxylabda-8(17),13(16),14-trien-19-oic acid.

Fokihodgin $\mathrm{G}(7)$ and fokihodgin $\mathrm{H}(8)$ were isolated as a pair of epimers both having the molecular formula $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{3}$ from their HREIMS $\left([\mathrm{M}]^{+} \mathrm{m} / \mathrm{z} 318.2177\right.$, calcd 318.2195), corresponding to six indices of hydrogen deficiency. Their NMR data (Tables 2 and 3) were similar to those of transcommunic acid (14), except that a double bond in 14 was replaced by a trisubstituted epoxide moiety in $7\left[\delta_{\mathrm{C}} 65.4\right.$ (d, C12), 60.6 ( $\mathrm{s}, \mathrm{C}-13$ )] and 8 [ $\delta_{\mathrm{C}} 64.8$ (d, C-12), 59.5 ( $\left.\left.\mathrm{s}, \mathrm{C}-13\right)\right]$. The HMBC correlations from $\mathrm{H}-14$ and $\mathrm{H}_{3}-16$ to $\mathrm{C}-12$ and C 13 and from $\mathrm{H}-12$ to $\mathrm{C}-9, \mathrm{C}-11$, and $\mathrm{C}-13$ confirmed the location of the epoxide group between $\mathrm{C}-12$ and $\mathrm{C}-13$. The absolute configuration of 7 and 8 at C-12 could be elucidated from the chemical shifts of the vinyl protons at C-17. Owing to the deshielding effects of the epoxide group at $\mathrm{C}-12$ and $\mathrm{C}-13$, $\mathrm{H}_{2}-17$ in a $12 S$-isomer appeared at lower field (near $\delta_{\mathrm{H}} 4.75$ and 4.90) than those (near $\delta_{\mathrm{H}} 4.48$ and 4.86 ) in a $12 R$-isomer. ${ }^{31}$ Therefore, the $\mathrm{H}_{2}-17$ signals at $\delta_{\mathrm{H}} 4.74$ and 4.92 of 7 and 8 indicated that both compounds had a $12 S$ configuration. In the ROESY spectra of 7 and $8, \mathrm{H}-12$ correlated to $\mathrm{H}-14$ and $\mathrm{H}_{3}-16$, respectively, suggesting the respective $13 R$ and $13 S$ configuration in 7 and 8 . Accordingly, the structure of compound 7 was elucidated as (12S,13R)-12,13-epoxylabda-8(17),14-dien19 -oic acid, and that of compound 8 as ( $12 S, 13 S$ )-12,13-epoxylabda-8(17),14-dien-19-oic acid.

Table 3. ${ }^{13} \mathrm{C}$ NMR Data of Compounds $1-8$ and $10\left(\delta_{\mathrm{C}}\right)$

| no. | $1^{a}$ | $2^{a}$ | $3^{a}$ | $4^{\text {b }}$ | $5^{\text {b }}$ | $6^{a}$ | $7{ }^{\text {b }}$ | $8^{\text {b }}$ | $10^{c}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 39.7, $\mathrm{CH}_{2}$ | 39.5, $\mathrm{CH}_{2}$ | 37.9, $\mathrm{CH}_{2}$ | 38.4, $\mathrm{CH}_{2}$ | 39.1, $\mathrm{CH}_{2}$ | 38.7, $\mathrm{CH}_{2}$ | 39.0, $\mathrm{CH}_{2}$ | 39.1, $\mathrm{CH}_{2}$ | 39.2, $\mathrm{CH}_{2}$ |
| 2 | 18.3, $\mathrm{CH}_{2}$ | 18.2, $\mathrm{CH}_{2}$ | 27.6, $\mathrm{CH}_{2}$ | 28.2, $\mathrm{CH}_{2}$ | 19.4, $\mathrm{CH}_{2}$ | 19.8, $\mathrm{CH}_{2}$ | 19.5, $\mathrm{CH}_{2}$ | 19.6, $\mathrm{CH}_{2}$ | 18.6, $\mathrm{CH}_{2}$ |
| 3 | 35.3, $\mathrm{CH}_{2}$ | 35.8, $\mathrm{CH}_{2}$ | 78.8, CH | 79.3, CH | 36.5, CH | $37.8, \mathrm{CH}_{2}$ | 37.7, $\mathrm{CH}_{2}$ | 37.7, $\mathrm{CH}_{2}$ | 40.9, $\mathrm{CH}_{2}$ |
| 4 | 37.8, qC | 37.4, qC | 39.0, qC | 40.0, qC | 38.7, qC | 44.2, qC | 43.6, qC | 43.6, qC | 34.2, qC |
| 5 | 47.8, CH | 48.5, CH | 54.2, CH | 55.2, CH | 41.5, CH | 56.2, CH | 55.6, CH | 55.6, CH | 53.8, CH |
| 6 | 22.8, $\mathrm{CH}_{2}$ | 22.9, $\mathrm{CH}_{2}$ | 22.6, $\mathrm{CH}_{2}$ | 23.7, $\mathrm{CH}_{2}$ | 30.9, $\mathrm{CH}_{2}$ | 26.1, $\mathrm{CH}_{2}$ | 25.8, $\mathrm{CH}_{2}$ | 25.8, $\mathrm{CH}_{2}$ | 17.5, $\mathrm{CH}_{2}$ |
| 7 | 36.0, $\mathrm{CH}_{2}$ | 35.9, $\mathrm{CH}_{2}$ | 36.0, $\mathrm{CH}_{2}$ | 37.0, $\mathrm{CH}_{2}$ | 73.9, CH | 38.9, $\mathrm{CH}_{2}$ | 38.0, $\mathrm{CH}_{2}$ | 38.0, $\mathrm{CH}_{2}$ | $44.6, \mathrm{CH}_{2}$ |
| 8 | 136.1, qC | 135.9, qC | 135.8, qC | 136.6, qC | 136.8, qC | 148.9, qC | 147.9, qC | 148.1, qC | 69.8, qC |
| 9 | 59.8, CH | 59.7, CH | 59.5, CH | 56.6, CH | 48.3, CH | 51.7, CH | 53.6, CH | 53.9, CH | 162.2, qC |
| 10 | 38.9, qC | 38.8, qC | 38.8, qC | 40.2, qC | 40.6, qC | 40.1, qC | 39.0, qC | 39.0, qC | 72.3, qC |
| 11 | 66.1, CH | 66.1, CH | 66.2, CH | 70.4, CH | 124.1, CH | 31.2, $\mathrm{CH}_{2}$ | 22.9, $\mathrm{CH}_{2}$ | 23.3, $\mathrm{CH}_{2}$ | 125.9, CH |
| 12 | 43.4, $\mathrm{CH}_{2}$ | 43.4, $\mathrm{CH}_{2}$ | 43.4, $\mathrm{CH}_{2}$ | 43.4, $\mathrm{CH}_{2}$ | 134.8, CH | 69.9, CH | 65.4, CH | 64.8, CH | 184.9, qC |
| 13 | 37.5, qC | 37.4, qC | 37.5, qC | 38.8, qC | 40.5, qC | 150.4, qC | 60.6, qC | 59.5, qC | 139.6, qC |
| 14 | 127.5, CH | 127.7, CH | 127.7, CH | 129.6, CH | 130.5, CH | 136.0, CH | 136.0, CH | 140.6, CH | 147.6, CH |
| 15 | 149.0, CH | 148.9, CH | 148.9, CH | 149.1, CH | 147.3, CH | 114.7, $\mathrm{CH}_{2}$ | 116.7, $\mathrm{CH}_{2}$ | 114.6, $\mathrm{CH}_{2}$ | 25.2, CH |
| 16 | 110.6, $\mathrm{CH}_{2}$ | 110.7, $\mathrm{CH}_{2}$ | 110.7, $\mathrm{CH}_{2}$ | 110.9, $\mathrm{CH}_{2}$ | 112.1, $\mathrm{CH}_{2}$ | 113.3, $\mathrm{CH}_{2}$ | 20.2, $\mathrm{CH}_{3}$ | 13.8, $\mathrm{CH}_{3}$ | 21.5, $\mathrm{CH}_{3}$ |
| 17 | 26.9, $\mathrm{CH}_{3}$ | 27.0, $\mathrm{CH}_{3}$ | 27.0, $\mathrm{CH}_{3}$ | 26.3, $\mathrm{CH}_{3}$ | 28.1, $\mathrm{CH}_{3}$ | 106.5, $\mathrm{CH}_{2}$ | 106.3, $\mathrm{CH}_{2}$ | 106.5, $\mathrm{CH}_{2}$ | 21.5, $\mathrm{CH}_{3}$ |
| 18 | 72.0, $\mathrm{CH}_{2}$ | 72.7, $\mathrm{CH}_{2}$ | 28.5, $\mathrm{CH}_{2}$ | 29.1, $\mathrm{CH}_{3}$ | 71.7, $\mathrm{CH}_{2}$ | 26.1, $\mathrm{CH}_{3}$ | 27.9, $\mathrm{CH}_{3}$ | 27.9, $\mathrm{CH}_{3}$ | 31.4, $\mathrm{CH}_{3}$ |
| 19 | 17.9, $\mathrm{CH}_{3}$ | 17.8, $\mathrm{CH}_{3}$ | 15.8, $\mathrm{CH}_{3}$ | 16.3, $\mathrm{CH}_{3}$ | 17.8, $\mathrm{CH}_{3}$ | 183.9, qC | 179.6, qC | 179.6, qC | 21.5, $\mathrm{CH}_{3}$ |
| 20 | 16.4, $\mathrm{CH}_{3}$ | 16.4, $\mathrm{CH}_{3}$ | 15.7, $\mathrm{CH}_{3}$ | 16.3, $\mathrm{CH}_{3}$ | 15.5, $\mathrm{CH}_{3}$ | 12.8, $\mathrm{CH}_{3}$ | 11.6, $\mathrm{CH}_{3}$ | 11.6, $\mathrm{CH}_{3}$ | 46.8, $\mathrm{CH}_{2}$ |
| -OAc |  | 21.0, $\mathrm{CH}_{3}$ |  | 21.6, $\mathrm{CH}_{3}$ |  |  |  |  |  |
|  |  | 171.3, qC |  | 172.4, qC |  |  |  |  |  |

${ }^{a}$ Recorded in $\mathrm{CDCl}_{3}$ at 100 MHz . ${ }^{b}$ Recorded in methanol $-d_{4}$ at 100 MHz . ${ }^{c}$ Recorded in DMSO- $d_{6}$ at 150 MHz .


Figure 1. Key 2D NMR correlations of compound 1.


Figure 2. X-ray crystallographic structure of compound 1.
The HREIMS of fokihodgin I (9) exhibited a molecular ion peak at $\mathrm{m} / \mathrm{z} 482.3034[\mathrm{M}]^{+}$(calcd 482.3032), suggesting a molecular formula of $\mathrm{C}_{30} \mathrm{H}_{42} \mathrm{O}_{5}$, with 10 indices of hydrogen deficiency. Detailed comparison of the NMR data of 9 (Table 4) with those of $8 \alpha$-hydroxylabda-13(16),14-dien-19-yl ( $E$ )ferulate (22) indicated that they were structural analogues, and the only difference was the presence of a $(Z)$-feruloyl unit $\left[\delta_{\mathrm{H}}\right.$ $7.73\left(1 \mathrm{H}, \mathrm{d}, J=1.6 \mathrm{~Hz}, \mathrm{H}-2^{\prime}\right), 6.78\left(1 \mathrm{H}, \mathrm{d}, J=8.2 \mathrm{~Hz}, \mathrm{H}-5^{\prime}\right)$,


Figure 3. X-ray crystallographic structure of compound 6.
$7.10\left(1 \mathrm{H}, \mathrm{dd}, J=8.2,1.6 \mathrm{~Hz}, \mathrm{H}-6^{\prime}\right), 6.88(1 \mathrm{H}, \mathrm{d}, J=12.9 \mathrm{~Hz}$, $\left.\mathrm{H}-7^{\prime}\right), 5.80\left(1 \mathrm{H}, \mathrm{d}, J=12.9 \mathrm{~Hz}, \mathrm{H}-8^{\prime}\right)$, and $\left.3.88\left(\mathrm{~s}, \mathrm{OCH}_{3}\right)\right]$ at $\mathrm{C}-19$ in 9 rather than an ( $E$ )-feruloyl moiety in 22. This assignment was inferred from the HMBC correlations of $\mathrm{H}-19 \mathrm{a}$ $\left(\delta_{\mathrm{H}} 4.28, \mathrm{~d}, J=11.1 \mathrm{~Hz}\right)$ and $\mathrm{H}-19 \mathrm{~b}\left(\delta_{\mathrm{H}} 3.95, \mathrm{~d}, J=11.1 \mathrm{~Hz}\right)$ with an ester carbonyl carbon at $\delta_{\mathrm{C}} 168.6$ of the $(Z)$-feruloyl group. Hence, the structure of 9 was assigned as $8 \alpha$ -hydroxylabda-13(16),14-dien-19-yl (Z)-ferulate.

The molecular formula of fokihodgin J (10) was established as $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{3}$ on the basis of its HREIMS at $m / z 318.2198$ [M] ${ }^{+}$ (calcd 318.2195), indicating six indices of hydrogen deficiency. The IR spectrum of 10 showed absorption bands at $3441 \mathrm{~cm}^{-1}$ (hydroxy) and $1666 \mathrm{~cm}^{-1}$ (conjugated carbonyl). The ${ }^{13} \mathrm{C}$ NMR and DEPT spectrum of 10 (Table 3) showed 20 carbons

Table 4. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz ) and ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) Data of Compound 9 in Methanol- $d_{4}, \delta$ in ppm, $J$ in Hz

| no. | $\delta_{\mathrm{H}}$ | $\delta_{\text {C }}$ | no. | $\delta_{\mathrm{H}}$ | $\delta_{\text {C }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $1 \alpha$ | 1.08, m | 41.0, $\mathrm{CH}_{2}$ | 14 | $\begin{aligned} & \text { 6.38, dd } \\ & (17.6, \\ & 10.7) \end{aligned}$ | 140.2, CH |
| $1 \beta$ | 1.74, m |  | 15 a | $\begin{gathered} 5.34, \mathrm{~d} \\ (17.6) \end{gathered}$ | 115.9, $\mathrm{CH}_{2}$ |
| $2 \alpha$ | 1.45, overlap | 19.1, $\mathrm{CH}_{2}$ | 15b | $\begin{aligned} & 5.05, \mathrm{~d} \\ & (10.7) \end{aligned}$ |  |
| $2 \beta$ | 1.64, m |  | 16a | 5.03, br s | 113.8, $\mathrm{CH}_{2}$ |
| $3 \alpha$ | 1.03, m | 17.5, $\mathrm{CH}_{2}$ | 16b | 4.99, br s |  |
| $3 \beta$ | 1.66, m |  | 17 | 1.12, s | 23.7, $\mathrm{CH}_{3}$ |
| 4 |  | 38.2, qC | 18 | 0.96, s | 28.0, $\mathrm{CH}_{3}$ |
| $5 \alpha$ | 1.14, m | 58.0, CH | 19a | $\begin{aligned} & \text { 4.28, d } \\ & (11.1) \end{aligned}$ | 67.9, $\mathrm{CH}_{2}$ |
| $6 \alpha$ | 1.76, m | 21.8, $\mathrm{CH}_{2}$ | 19b | $\begin{aligned} & 3.95, \mathrm{~d} \\ & (11.1) \end{aligned}$ |  |
| $6 \beta$ | 1.40, m |  | 20 | 0.85, s | 16.6, $\mathrm{CH}_{3}$ |
| $7 \alpha$ | 1.84, m | 45.5, $\mathrm{CH}_{2}$ | $1^{\prime}$ |  | 128.3, qC |
| $7 \beta$ | 1.44, overlap |  | $2^{\prime}$ | 7.73, d (1.6) | 114.8, CH |
| 8 |  | 74.8, qC | $3^{\prime}$ |  | 149.2, qC |
| $9 \alpha$ | 1.18, t (3.5) | 62.9, CH | $4^{\prime}$ |  | 148.4, qC |
| 10 |  | 40.1, qC | $5^{\prime}$ | 6.78, d (8.2) | 115.7, CH |
| 11a | 1.38, m | 26.3, $\mathrm{CH}_{2}$ | $6^{\prime}$ | $\begin{aligned} & 7.10, \mathrm{dd}, \\ & (8.2,1.6) \end{aligned}$ | 126.4, CH |
| 11 b | 1.68, m |  | $7^{\prime}$ | $\begin{aligned} & 6.88, \mathrm{~d} \\ & (12.9) \end{aligned}$ | 145.1, CH |
| 12a | $\begin{aligned} & 2.45, \mathrm{dt} \\ & (13.4, \\ & 4.8) \end{aligned}$ | 46.2, $\mathrm{CH}_{2}$ | $8^{\prime}$ | $\begin{gathered} 5.80, \mathrm{~d} \\ (12.9) \end{gathered}$ | 116.9, CH |
| 12b | $\begin{aligned} & 2.22, \mathrm{dt} \\ & (13.4, \\ & 4.9) \end{aligned}$ |  | $9^{\prime}$ |  | 168.6, qC |
| 13 |  | 149.4, qC | $\mathrm{OCH}_{3}$ | 3.88, s | 56.3, $\mathrm{CH}_{3}$ |

attributed to four methyl, six methylene, four methine (two $\mathrm{sp}^{2}$ ), and six quaternary (one conjugated carbonyl, two oxygenated, and two $\mathrm{sp}^{2}$ ) carbons. In the ${ }^{1} \mathrm{H}$ NMR spectrum (Table 1), two methyl signals at $\delta_{\mathrm{H}} 0.98$ and 1.01 (each $3 \mathrm{H}, \mathrm{d}, J$ $=6.8 \mathrm{~Hz}, \mathrm{Me}-16$ and $\mathrm{Me}-17$ ) and a methine signal at $\delta_{\mathrm{H}} 2.78$ $(1 \mathrm{H}$, hep, $J=7.0 \mathrm{~Hz}, \mathrm{H}-11)$ suggested the presence of an isopropyl group. The above NMR data resembled those of sawaradienone, with the only difference being the presence of a methylene at $\delta_{\mathrm{C}} 46.8$ (C-20) in 10 instead of an oxymethine in sawaradienone, ${ }^{32}$ which was confirmed by the HMBC correlations (Figure 4) from $\mathrm{H}_{2}-20\left(\delta_{\mathrm{H}} 2.14, \mathrm{~d}, J=12.7 \mathrm{~Hz}\right.$; $3.11, \mathrm{~d}, J=12.7 \mathrm{~Hz}$ ) to C-5 ( $\delta_{\mathrm{C}} 53.8$ ), C-9 ( $\delta_{\mathrm{C}} 162.2$ ), and C10 ( $\delta_{\mathrm{C}} 72.3$ ). The ROESY correlations (Figure 4) between H-5 and $\mathrm{H}_{3}-18$ suggested the $\alpha$-orientation of $\mathrm{H}_{3}-18$ and $\mathrm{H}-5$. In addition, the $8-\mathrm{OH}$ and $10-\mathrm{OH}$ were assigned as $\beta$-oriented based on the cross-peaks of $\mathrm{H}-6 \beta / 8-\mathrm{OH}, \mathrm{H}-6 \beta / 10-\mathrm{OH}, 8-\mathrm{OH} /$ $\mathrm{H}-20 \beta, \mathrm{H}-20 \beta / 10-\mathrm{OH}$, and $\mathrm{OH}-10 / \mathrm{H}_{3}-19$ in the ROESY


Figure 4. Key 2D NMR correlations of compound 10.
experiment. Thus, the structure of 10 was assigned as $8 \beta, 10 \beta$ -dihydroxyicetexa-9(11),13-dien-12-one.

All compounds were tested for their cytotoxicity against human myeloid leukemia (HL-60), hepatocellular carcinoma (SMMC-7721), lung cancer (A-549), breast cancer (MCF-7), and colon cancer (SW-480) cell lines using the MTT method as previously reported. ${ }^{33}$ Cisplatin (Sigma, USA) was used as the positive control. The results showed that compounds 2224, 27, and 28 exhibited weak cytotoxicity against the above cancer cell lines. Compound 9 also showed weak cytotoxicity against A-549, MCF-7, and SW-480 cell lines; however, it exhibited moderate cytotoxicity against HL-60 and SMMC7721 cell lines, with $\mathrm{IC}_{50}$ values of 9.10 and $7.50 \mu \mathrm{M}$, respectively (Table 5). The other compounds were inactive ( $\mathrm{IC}_{50}>40 \mu \mathrm{M}$ ).

Table 5. Cytotoxicity of Compounds 9, 22-24, 27, and 28 against Five Tumor Cell Lines ( $\mathrm{IC}_{50} \boldsymbol{\mu} \mathbf{M}$ )

| compound | HL-60 | SMMC-7721 | A-549 | MCF-7 | SW-480 |
| :--- | ---: | :---: | :---: | :---: | :---: |
| $\mathbf{9}$ | 9.10 | 7.50 | 17.32 | 15.37 | 17.61 |
| $\mathbf{2 2}$ | 11.77 | 15.48 | 20.35 | 16.58 | 19.30 |
| $\mathbf{2 3}$ | 14.28 | 14.05 | 16.77 | 13.45 | 16.94 |
| $\mathbf{2 4}$ | 14.05 | 16.24 | 17.05 | 15.05 | 13.64 |
| $\mathbf{2 7}$ | 14.28 | 19.70 | 21.01 | 15.62 | 14.36 |
| $\mathbf{2 8}$ | 15.48 | 15.23 | 20.68 | 15.02 | 15.12 |
| cisplatin $^{a}$ | 1.14 | 14.51 | 12.76 | 19.61 | 17.54 |
| ${ }^{\boldsymbol{a}}$ Positive control. |  |  |  |  |  |

## EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were obtained on an X-4 micro melting point apparatus. Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. IR spectra were obtained by a Tensor 27 spectrophotometer with KBr pellets. 1D and 2D spectra were run on a Bruker AM-400 or an Avance III 600 spectrometer with TMS as the internal standard. X-ray data were collected using a Bruker APEX DUO instrument. Chemical shifts ( $\delta$ ) were expressed in ppm with reference to the solvent signals. ESIMS and HRESIMS were performed on an API QSTAR time-of-flight spectrometer. EIMS and HREIMS were recorded on a Waters Autospec Premier P776 spectrometer. Semipreparative HPLC was performed on an Agilent 1200 apparatus equipped with a UV detector and a Zorbax SB-C-18 (Agilent, $9.4 \mathrm{~mm} \times 25 \mathrm{~cm}$ ) column. MPLC was performed on a Lisui EZ Purify III System including pump manager P03, detector modules P02, and fraction collector P01 (Shanghai Lisui Chemical Engineering Co., Ltd., Shanghai, China). Column chromatography (CC) was performed using silica gel (200-300 mesh and H, Qingdao Marine Chemical Co. Ltd., Qingdao, China), RP-C $\mathrm{C}_{18}$ gel ( $40-63 \mu \mathrm{~m}$, Merck, Darmstadt, Germany), MCI gel (75$150 \mu \mathrm{~m}$; Mitsubishi Chemical Corporation, Japan), and Sephadex LH20 (Amersham Pharmacia Biotech, Sweden). Fractions were monitored by TLC (GF254, Qingdao Marine Chemical Co. Ltd., Qingdao, China), and spots were visualized by heating silica gel plates sprayed with $10 \% \mathrm{H}_{2} \mathrm{SO}_{4}$ in EtOH. All solvents were distilled prior to use.

Plant Material. The twigs and leaves of $F$. hodginsii were collected from the Kunming Botany Garden, Yunnan Province, People's Republic of China, in December 2010, and identified by one of the authors (X. Gong). A voucher specimen (KIB20101215f01) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried and powdered twigs and leaves of $F$. hodginsii ( 15 kg ) were extracted three times with $95 \%$
$\mathrm{EtOH}(60 \mathrm{~L} \times 3)$ at room temperature and concentrated in vacuo to yield a residue ( 1.4 kg ), which was partitioned between $\mathrm{H}_{2} \mathrm{O}$ and EtOAc. The EtOAc fraction ( 840 g ) was subjected to silica gel CC with a gradient elution of petroleum ether-acetone (1:0 to $0: 1$ ) to afford six fractions, A-F. Fraction B (180 g) was crystallized from petroleum ether-acetone ( $1: 1$ ) to yield $15(11.5 \mathrm{~g})$. The filtrate was condensed to give a yellow residue, which was chromatographed repeatedly over silica gel eluted with petroleum ether-EtOAc (9.5:0.5 to $7: 3)$ to obtain $12(5.5 \mathrm{mg}), \mathbf{1 6}(7.0 \mathrm{mg}), \mathbf{1 8}(11.4 \mathrm{mg})$, and $25(4.5$ $\mathrm{mg})$. Fraction C $(85 \mathrm{~g})$ was fractionated by MPLC (RP-C $\mathrm{C}_{18}$ ), eluting with $\mathrm{MeOH}-\mathrm{H}_{2} \mathrm{O}$ (60:40 to 100:0), to provide six subfractions, $\mathrm{C} 1-$ C6. Subfraction C 2 was subjected to silica gel CC eluted with petroleum ether-acetone ( $9: 1$ to $6: 3$ ), then recrystallized from MeOH , and compounds $21(22.6 \mathrm{mg})$ and $22(185.3 \mathrm{mg})$ were obtained. The mother liquor was further chromatographed over silica gel repeatedly and then purified by semipreparative HPLC (MeOH$\left.\mathrm{H}_{2} \mathrm{O}, 64: 33\right)$ to afford $\mathbf{6}(13.7 \mathrm{mg})$ and $14(2.5 \mathrm{mg})$. Compounds 1 $(8.2 \mathrm{mg}), 3(27.5 \mathrm{mg}), 5(14.5 \mathrm{mg})$, and $13(18.4 \mathrm{mg})$ were obtained from subfraction C 3 by CC over silica gel using $\mathrm{CHCl}_{3}-\mathrm{Me}_{2} \mathrm{CO}$ (9.5:0.5 to 7:3). Subfraction C4 was further subjected to CC over silica gel eluted with petroleum ether-acetone ( $9: 1$ to $7: 3$ ) and purified on Sephadex LH-20 ( MeOH ) to provide $2(18.4 \mathrm{mg}), 4(24.3 \mathrm{mg}), 17$ ( 154.5 mg ), and $23(8.7 \mathrm{mg})$. Compound $11(5.5 \mathrm{~g})$ was obtained by recrystallization in MeOH from subfraction C 5 directly. Fraction D ( 55 g ) was chromatographed on MPLC (MCI gel) eluting with $\mathrm{MeOH}-\mathrm{H}_{2} \mathrm{O}$ (60:40 to 100:0) to yield five subfractions, D1-D5. Subfraction D2 was separated by silica gel CC $\left(\mathrm{CHCl}_{3}-\mathrm{Me}_{2} \mathrm{CO}, 9: 1\right.$ to $1: 1$ ) and then by Sephadex LH-20 ( MeOH ) to give $26(35.3 \mathrm{mg})$ and $28(12.5 \mathrm{mg})$. Compounds $9(18.2 \mathrm{mg}), 19(22.3 \mathrm{mg})$, and 24 $(15.5 \mathrm{mg})$ and the pair of epimers 7 and $8(2.1 \mathrm{mg})$ were isolated from subfraction D3 by repeated CC over silica gel eluted with petroleum ether-acetone ( $9: 1$ to $1: 1$ ). Fraction $\mathrm{E}(25 \mathrm{~g})$ was subjected to repeated column chromatography and purified by Sephadex LH-20 and semipreparative HPLC to afford $10(22.6 \mathrm{mg}), 20(5.4 \mathrm{mg})$, and 27 ( 11.6 mg ).

Fokihodgin $A(1):$ colorless needles; mp $87-89{ }^{\circ} \mathrm{C}$; $[\alpha]_{\mathrm{D}}^{26}-30.2(c$ $0.3, \mathrm{MeOH})$; UV $(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 209(3.89) \mathrm{nm}$; IR $(\mathrm{KBr}) \nu_{\text {max }}$ 3419, 2932, 2867, 1635, 1458, 1411, 1384, 1134, 1026, 908, 861, 686, $668 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 1 and 3; EIMS m/z 304 $[\mathrm{M}]^{+}(42), 286$ (33), 274 (45), 273 (78), 256 (62), 255 (97), 121 (100), 95 (89); HREIMS [M] ${ }^{+} m / z 304.2397$ (calcd for $\mathrm{C}_{20} \mathrm{H}_{32} \mathrm{O}_{2}$, 304.2402).

Fokihodgin $B$ (2): colorless oil; $[\alpha]_{\mathrm{D}}^{26}-25.6(c 0.3, \mathrm{MeOH})$; UV $(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 208$ (3.95), 244 (3.0) nm; IR (KBr) $\nu_{\max } 3433$, 2928, 2867, 1738, 1634, 1459, 1411, 1380, 1242, 1038, 911, 863, 668 $\mathrm{cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 1 and 3; EIMS $m / z 346[\mathrm{M}]^{+}$ (53), 303 (8), 328 (28), 274 (15), 273 (49), 256 (22), 255 (61), 135 (100), 121 (68); HREIMS [M] ${ }^{+} m / z 346.2513$ (calcd for $\mathrm{C}_{22} \mathrm{H}_{34} \mathrm{O}_{3}$, 346.2508).

Fokihodgin $C$ (3): amorphous powder; $[\alpha]_{\mathrm{D}}^{26}-63.1(c 0.2, \mathrm{MeOH})$; $\mathrm{UV}(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 208(4.12) \mathrm{nm}$; IR $(\mathrm{KBr}) \nu_{\text {max }} 3396,2939$, 2870, 1635, 1451, 1382, 1365, 1181, 1090, 1035, 995, 909, $618 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 1 and 3; EIMS $m / z 304[\mathrm{M}]^{+}(18)$, 286 (25), 268 (15), 153 (20), 152 (56), 135 (100), 105 (37); HREIMS [M] ${ }^{+} m / z 304.2397$ (calcd for $\mathrm{C}_{20} \mathrm{H}_{32} \mathrm{O}_{2}, 304.2402$ ).

Fokihodgin $D$ (4): colorless oil; $[\alpha]_{\mathrm{D}}^{26}-65.3(c 0.4, \mathrm{MeOH})$; UV $(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 208(3.91), 263(2.68) \mathrm{nm} ; \mathrm{IR}(\mathrm{KBr}) \nu_{\max } 3385$, 2939, 2872, 1772, 1637, 1459, 1435, 1382, 1239, 1090, 1022, 916, 668 $\mathrm{cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 1 and 3; positive ESIMS $\mathrm{m} / \mathrm{z}$ $369[\mathrm{M}+\mathrm{Na}]^{+}$; positive HRESIMS $[\mathrm{M}+\mathrm{Na}]^{+} m / z 369.2395$ (calcd for $\mathrm{C}_{22} \mathrm{H}_{34} \mathrm{O}_{3} \mathrm{Na}, 369.2405$ ).

Fokihodgin $E$ (5): colorless oil; $[\alpha]_{\mathrm{D}}^{26}-28.1$ (c 0.3, MeOH); UV $(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 207$ (3.69) nm; IR (KBr) $\nu_{\max } 3423,2927,2867$, 1726, 1630, 1452, 1384, 1360, 1287, 1041, 912, 871, $731 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 1 and 3; EIMS $m / z 302[\mathrm{M}]+$ (8), 284 (9), 254 (10), 253 (32), 157 (37), 145 (40), 144 (100), 131 (58); 123 (81); HREIMS [M] ${ }^{+} m / z 302.2249$ (calcd for $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{2}, 302.2246$ ).

Fokihodgin $F$ (6): colorless cubic crystals; mp $81-83{ }^{\circ} \mathrm{C}$; $[\alpha]_{\mathrm{D}}^{26}$ $+62.9(c 0.3, \mathrm{MeOH}) ; \mathrm{UV}(\mathrm{MeOH}) \lambda_{\max }(\log \varepsilon) 208$ (3.92), 222 (3.98) nm; IR (KBr) $\nu_{\max } 3440,2934,2851,1693,1650,1641,1467$,

1447, 1386, 1269, 1174, 1034, 890, $668 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 2 and 3; EIMS $m / z 318[\mathrm{M}]^{+}(22), 300$ (29), 285 (25), 222 (45), 221 (67), 133 (82), 121 (100), 81 (89); HREIMS [M] ${ }^{+} \mathrm{m} / \mathrm{z}$ 318.2200 (calcd for $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{3}, 318.2195$ ).

Fokihodgins $G$ (7) and $H$ (8): colorless oil; $[\alpha]_{\mathrm{D}}^{27}+25.6$ (c 0.3, $\mathrm{MeOH})$; UV $(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 208(3.58) \mathrm{nm}$; IR (KBr) $\nu_{\text {max }}$ 3449, 2934, 2848, 1692, 1642, 1467, 1450, 1385, 1271, 1176, 1128, 890, $668 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 2 and 3; EIMS $\mathrm{m} / \mathrm{z}$ $318[\mathrm{M}]^{+}(7), 303$ (6), 248 (10), 247 (15), 189 (48), 133 (38), 121 (88), 81 (86), 55 (100); HREIMS [M] ${ }^{+} m / z 318.2177$ (calcd for $\left.\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{3}, 318.2195\right)$.

Fokihodgin I (9): colorless oil; $[\alpha]_{\mathrm{D}}^{27}+9.9$ (c 0.3, MeOH); UV $(\mathrm{MeOH}) \lambda_{\max }(\log \varepsilon) 220(4.35), 324(4.14) \mathrm{nm}$; IR (KBr) $\nu_{\max } 3441$, 2930, 2853, 1709, 1631, 1515, 1452, 1388, 1271, 1161, 1124, 1033 $\mathrm{cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Table 4; EIMS $m / z 482[\mathrm{M}]^{+}(5)$, 444 (4), 270 (5), 194 (31), 177 (100), 145 (23), 121 (100), 81 (27), 55 (28); HREIMS $[\mathrm{M}]^{+} m / z 482.3034$ (calcd for $\mathrm{C}_{30} \mathrm{H}_{42} \mathrm{O}_{5}$, 482.3032).

Fokihodgin J (10): colorless oil; $[\alpha]_{\mathrm{D}}^{27}-122.8(c 0.2, \mathrm{MeOH})$; UV $(\mathrm{MeOH}) \lambda_{\text {max }}(\log \varepsilon) 200(3.70), 245(4.05) \mathrm{nm} ; \mathrm{IR}(\mathrm{KBr}) \nu_{\max } 3441$, 2934, 2869, 1666, 1628, 1466, 1387, 1251, 1161, 1110, 1045, 921 $\mathrm{cm}^{-1}$; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data, see Tables 2 and 3; EIMS $m / z 318[\mathrm{M}]^{+}$ (38), 300 (89), 285 (57), 275 (59), 174 (66), 165 (100), 153 (80), 69 (78); HREIMS [M] ${ }^{+} m / z 318.2198$ (calcd for $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}_{3}, 318.2195$ ).

X-ray Crystal Structure Analysis. Colorless crystals of 1 and 6 were obtained from MeOH . The intensity data were collected on a Bruker APEX DUO diffractometer with $\mathrm{Cu} \mathrm{K} \alpha$ radiation. The crystal structures of $\mathbf{1}$ and $\mathbf{6}$ were solved by the direct method (SHLXS-97), expanded using difference Fourier technique, and refined by the program and the full-matrix least-squares calculations. The nonhydrogen atoms were refined anisotropically, and hydrogen atoms were fixed at calculated positions. Crystallographic data for the structures of $\mathbf{1}$ and 6 have been deposited in the Cambridge Crystallographic Data Centre (deposition numbers: CCDC 914619 and 914620). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or desposit@ccdc.cam.ac.uk).

Crystal data of fokihodgin $A$ (1): $\mathrm{C}_{20} \mathrm{H}_{32} \mathrm{O}_{2}, M=304.5$, orthorhombic, space group, $P 2_{1} 2_{1} 2_{1}, a=8.3140(2) \AA, b=$ $10.5467(3) \AA, c=20.9187(6) \AA$; $\alpha=\beta=\gamma=90.00^{\circ}, V=$ 1834.26(9) $\AA^{3}, Z=4, \mu(\mathrm{CuK} \alpha)=0.53 \mathrm{~mm}^{-1}, \rho_{\text {calc }}=1.10 \mathrm{~g} / \mathrm{cm}^{3}$, $F(000)=672,3068$ reflections independent and 3068 reflections observed $\left(w=1 / \sigma|F|^{2}\right)$. The final $R_{1}=0.034, w R_{2}=0.098$, Flack parameter $=0.2(2)$.

Crystal data of fokihodgin $F$ (6): $\mathrm{C}_{20} \mathrm{H}_{32} \mathrm{O}_{2} \cdot \mathrm{H}_{2} \mathrm{O}, M=336.46$, tetragonal, space group, $I_{4}, a=20.0401(8) \AA, b=20.0401(8) \AA, c=$ $9.4689(4) \AA$ A $\alpha=\beta=\gamma=90^{\circ}, V=3802.8(3) \AA^{3}, Z=8, \rho_{\text {calc }}=1.175 \mathrm{~g} /$ $\mathrm{cm}^{3}, \mu(\mathrm{CuK} \alpha)=0.638 \mathrm{~mm}^{-1}, F(000)=1472,3327$ reflections independent and 3197 reflections observed $\left(w=1 / \sigma|F|^{2}\right)$. The final $R_{1}$ $=0.051, w R_{2}=0.135$, Flack parameter $=0.0(3)$.

Cytotoxicity Assay. The cytotoxicity of the compounds against HL-60, SMMC-7721, A-549, MCF-7, and SW-480 cell lines was assessed using the MTT method. Cells were plated in 96 -well plates 12 $h$ before treatment and continuously exposed to different concentrations of compounds. After $48 \mathrm{~h}, 20 \mu \mathrm{~L}$ of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution was added to each well, which were incubated for another 4 h . Then $20 \%$ SDS (100 $\mu \mathrm{L}$ ) were added to each well. After 12 h at room temperature, the OD value of each well was recorded at 595 nm . The $\mathrm{IC}_{50}$ value of each compound was calculated by the Reed and Muench method. ${ }^{34}$

## ASSOCIATED CONTENT

## S Supporting Information

Structures of known compounds, 1D and 2D NMR spectra, and MS spectra of fokihodgins $A-E(\mathbf{1 - 1 0})$. These materials are available free of charge via the Internet at http://pubs.acs. org.

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## Notes

The authors declare no competing financial interest.

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