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Absolute Structures of Monoterpenoids with a δ-Lactone-Containing Skeleton from *Ligularia hodgsonii*

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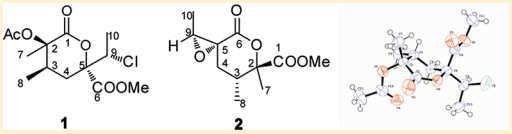
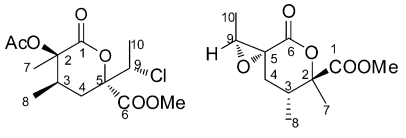
Supporting Information

ABSTRACT: Bioactivity-directed fractionation of a methanol extract of *Ligularia hodgsonii* afforded two new monoterpenoids, liguhodgcins A (**1**) and B (**2**), with an unusual δ-lactone-containing skeleton. Moreover, liguhodgcin A (**1**) contained a chlorine atom. The structures and absolute configurations of the two compounds were elucidated using NMR spectroscopy, X-ray crystallography, ECD data, and computational approaches. A probable biosynthesis pathway to **1** and **2** was also proposed and discussed. The cytotoxicity of compounds **1** and **2** was evaluated against the human leukemia (HL-60), human hepatoma (SMMC-7721), and human cervical carcinoma (HeLa) cell lines.



Selected species of *Ligularia* (Compositae) have been studied by us for their effects on the treatment of influenza, coughs, ulcers, and tuberculosis.[1] This is part of an ongoing program to identify new anticancer and antimicrobial drugs or leads from traditional Chinese herbal medicines. Several types of bioactive sesquiterpenoids and triterpenoids have been found in such studies.[2−6] In our continuing research into this genus, an MeOH extract obtained from *Ligularia hodgsonii* exhibited a positive response to human leukemia (HL-60), human hepatoma (SMMC-7721), and human cervical carcinoma (HeLa) cell lines. Bioactivity-guided fractionation of the MeOH extract afforded two new monoterpenoids: liguhodgcins A (**1**) and B (**2**). The two compounds possess a δ-lactone-containing monoterpenoid framework, an unusual structural feature in natural products. This report deals with the isolation, structure elucidation, absolute configuration, cytotoxicity, and plausible biogenesis of these two new products.



Liguhodgcin A (**1**) was obtained as colorless needles, showing a yellow spot on TLC ($CHCl_3$−EtOAc, 8:1) when sprayed with H_2SO_4−EtOH (5%) followed by heating on a hot plate. The EIMS gave a series of characteristic isotopic fragment peaks with the ratio of 3:1 at *m/z* 247/249, 177/179, and 159/161, suggesting the presence of a chlorine atom.[7] Its molecular formula was determined to be $C_{13}H_{19}O_6Cl$ (four degrees of unsaturation) by positive HRESIMS (*m/z* 324.1213 $[M + NH_4]^+$, calcd for $C_{13}H_{23}O_6NCl$ $[M + NH_4]^+$ 324.1208) associated with NMR data (Table 1). Its IR spectrum displayed a broad absorption band for saturated ester functional groups (1753 cm^{-1}). The presence of an acetoxy and a carboxylic

Table 1. NMR Spectral Data of Compounds 1 and 2 in $CDCl_3$[a]

	1		2	
no.	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1		169.3 C		172.5 C
2		76.8 C		85.1 C
3	1.92 m	35.9 CH	2.57 m	33.5 CH
4α	1.91 dd (14.7, 4.2)	33.5 CH_2	2.11 dd (14.7, 6.6)	34.4 CH_2
4β	2.47 dd (14.7, 14.1)		1.87 dd (14.7, 3.9)	
5		88.1 C		55.6 C
6		170.6 C		167.5 C
7	1.58 s	26.5 CH_3	1.59 s	21.8 CH_3
8	0.97 d (6.6)	14.5 CH_3	1.16 d (7.2)	15.0 CH_3
9	4.37 q (6.9)	59.1 CH	3.03 q (5.4)	63.8 CH
10	1.67 d (6.9)	18.4 CH_3	1.44 d (5.4)	12.8 CH_3
OAc	2.08 s	20.3 CH_3		
		170.8 C		
OMe	3.84 s	53.2 CH_3	3.81 s	53.0 CH_3

[a]Recorded at 300 and 75 MHz for ^1H and ^{13}C, respectively.

methyl ester group in **1** was evident from the ^1H NMR signals [δ 2.08 (3H, s), and 3.84 (3H, s)], in combination with the ^{13}C NMR signals (δ 20.3 and 170.8; 53.2 and 170.6),[3,8] which was confirmed by the $C_2H_3O_2$ unit owing to the fragment ion $[M - 59\ (C_2H_3O_2)]^+$ peak at *m/z* 247 in the EIMS. Besides the two carbons of the acetoxy group and the methoxy carbon, the ^{13}C NMR spectrum of **1** also showed 10 carbon resonances due to three methyl, one methylene, two methine (one chlorinated), and four quaternary carbons (two ester carbonyls and two oxygenated). Its ^1H NMR spectrum indicated the presence of

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one tertiary methyl at δ 1.58 (s, H_3-7), two secondary methyl groups at δ 0.97 (d, J = 6.6 Hz, H_3-8) and 1.67 (d, J = 6.9 Hz, H_3-10), one methylene group at δ 1.91 (dd, J = 14.7, 4.2 Hz, H-4α) and 2.47 (dd, J = 14.7, 14.1 Hz, H-4β), one methine proton at δ 1.92 (m, H-3), and one chloromethine proton at δ 4.37 (q, J = 6.9 Hz, H-9). In the ^{1}H−^{1}H COSY spectrum, homonuclear coupling correlations from H_3-8 through H-3 to H_2-4 revealed the presence of the segment CH_3(8)−CH(3)−CH_2(4)−, and the correlation from H_3-10 to H-9 revealed the presence of the segment CH_3(10)−CHCl(9)−. The HMBC experiment showed correlations of H_3-8/C-2, C-3, C-4; H_3-7/C-1, C-2, C-3; H_3-10/C-5, C-9; and H-4β/C-2, C-3, C-5, C-6, C-8, C-9 (Figure 1). These observations suggested that **1** had a highly oxygenated 5-ethyl-2,3-dimethyladipate structure.

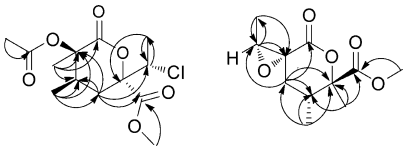

Figure 1. Important HMBC correlations of liguhodgcins A (**1**) and B (**2**) (H→C).

Furthermore, the carboxylic methyl ester group was deduced to be at C-6 due to the cross-peaks of methoxy protons with C-6 in the HMBC spectrum. However, the HMBC spectrum did not provide crucial information as to whether the acetoxy group was located at C-2 or C-5. According to the four degrees of unsaturation of **1**, apart from one acetoxy group and two ester carbonyls, the remaining degree of unsaturation was assumed to be a lactone ring that must be formed between C-1 and C-5. Therefore, the acetoxy group can be located only at C-2, permitting assignment of the molecular structure of **1** as shown.

The structure of **1** was confirmed by single-crystal X-ray diffraction analysis (Figure 2). The presence of a chlorine atom in **1** and the value of the Flack parameter −0.11(3) permitted assignment of the (2*R*, 3*R*, 5*S*, 9*S*) absolute configuration.[9,10]

Liguhodgcin B (**2**) was obtained as a colorless oil, showing a red violet spot on TLC ($CHCl_3$−EtOAc, 10:1) when sprayed with 5% H_2SO_4−EtOH (5%) followed by heating on a hot plate. The molecular formula was determined to be $C_{11}H_{16}O_5$ by HRESIMS (229.1072 $[M + H]^+$, calcd for $C_{11}H_{17}O_5$ $[M + H]^+$ 229.1071) and NMR data (Table 1) and indicated four degrees of unsaturation. The IR absorption at 1750 cm^{-1} represented the characteristic band of a δ-lactone moiety. In addition, in its NMR spectra, one carboxylic methyl ester group at δ_H 3.81 (s, OCH_3) and δ_C 53.0 (OCH_3), 172.5 (C-1) was observed. Its ^{1}H NMR spectrum indicated the presence of one tertiary methyl at δ 1.59 (s, H_3-7), two secondary methyls at δ 1.16 (d, J = 7.2 Hz, H_3-8) and 1.44 (d, J = 5.4 Hz, H_3-10), one methylene at δ 2.11 (dd, J = 14.7, 6.6 Hz, H-4α) and 1.87 (dd, J = 14.7, 3.9 Hz, H-4β), and two methines at δ 2.57 (m, H-3) and 3.03 (q, J = 5.4 Hz, H-9). Apart from the methoxy carbons, the ^{13}C NMR spectrum also showed 10 carbon resonances, including three methyl, one methylene, two methine (one oxygenated and one sp^3 hybridized), and four quaternary carbons (two ester carbonyls, two oxygenated). Analyses of the ^{1}H and ^{13}C NMR spectra of **2** showed that their general features resembled those of compound **1** except for the loss of an AcO group and a chlorine atom, indicating that **2** was also a highly oxygenated 5-ethyl-2,3-dimethyladipate derivative.

In the HMBC spectrum of **2** (Figure 1), correlations of OCH_3/C-1 and of H_3-7/C-1, C-2, C-3 indicated that the carboxylic methyl ester group was at C-2. Moreover, the downfield ^{13}C NMR chemical shift for C-2 (δ 85.1) showed that the δ-lactone ring was unambiguously formed between C-6 and C-2. There were no exchangeable protons in **2**; thus the two oxygenated carbons C-5 and C-9 must have been attached to the remaining oxygen atom to form an epoxide moiety. The ^{13}C NMR chemical shifts of C-5 (δ 55.6) and C-9 (δ 63.8) further supported this assignment. On the basis of these data, the molecular structure of **2** was established.

The relative configuration of compound **2** was partially elucidated by the coupling constants and the NOE difference spectra. The doublet of doublets at δ_H 1.87 attributed to H-4β ($J_{4\beta,4\alpha}$ = 14.7 Hz, $J_{4\beta,3}$ = 3.9 Hz) and the one at δ_H 2.11 ascribed to H-4α ($J_{4\alpha,4\beta}$ = 14.7 Hz, $J_{4\alpha,3}$ = 6.6 Hz) showed that H-3 should be β-oriented, and the orientation of Me-8 was α. The strong NOE observed between H_3-8 (δ 1.16) and H_3-7 (δ 1.59) (5%) indicated that Me-7 was in an α-orientation. Although the NOE was observed between H-4β (δ 1.87) and H-9 (δ 3.03) (3%), the relative configuration of the epoxide moiety could still not be determined (Figure 3). Given these conclusions, it was possible to prune a list of possible candidate stereostructures to just those assembled in Figure 4, coded as **i**−**iv**.

The absolute configuration of **2** was established by comparing the observed ECD spectrum with those predicted

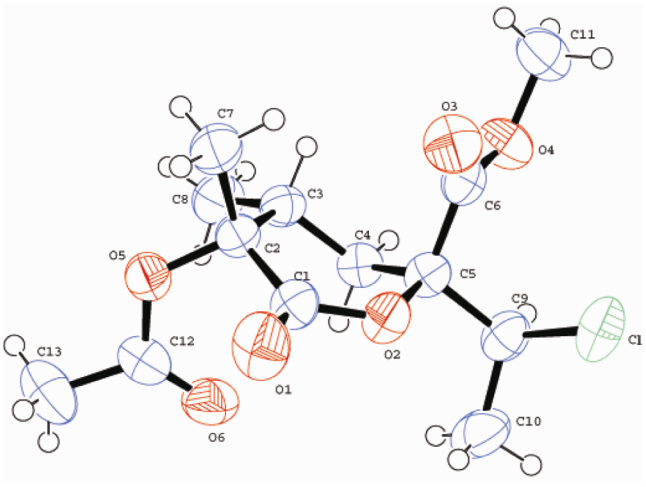

Figure 2. ORTEP drawing of liguhodgcin A (**1**).

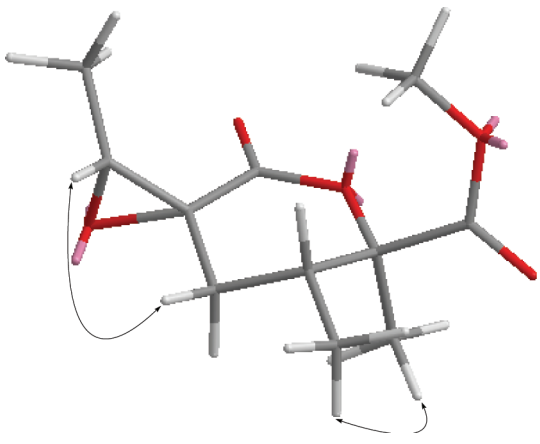

Figure 3. Key NOE correlations of liguhodgcin B (**2**).

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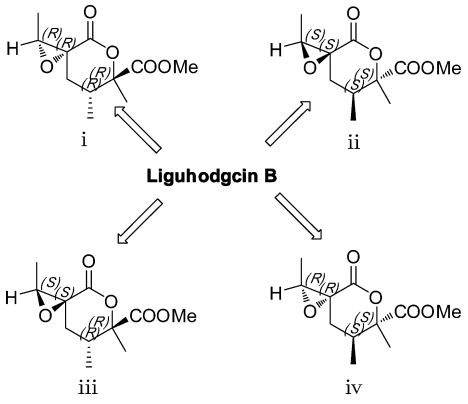

Figure 4. Matrix of possible liguhodgcin B (**2**) configurations.

for candidates **i**–**iv** using the TD-DFT theory method at the B3LYP/6-311++G(d,p) level (Supporting Information).[11] This approach is becoming a powerful tool in the absolute configuration analysis of natural products.[12,13] The results showed that the calculated ECD curve of the (2*R*,3*R*,5*S*, 9*S*)-isomer (**i**) strongly resembled the experimental spectrum (Figure 5). Accordingly, the calculated Cotton effects for the

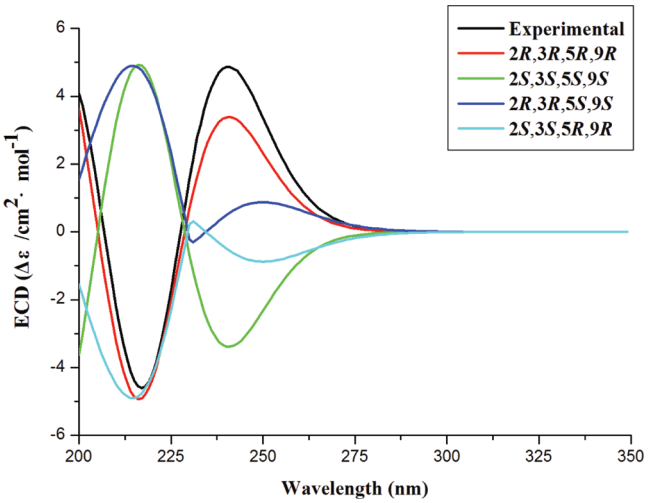

Figure 5. Experimental CD spectrum of liguhodgcin B (**2**) overlaid with calculated spectra for structures shown in Figure 4: (2*R*,3*R*,5*R*, 9*R*)-**i**, (2*S*,3*S*,5*S*,9*S*)-**ii**, (2*R*,3*R*,5*S*,9*S*)-**iii**, (2*S*,3*S*,5*R*,9*R*)-**iv**.

electronic transitions of the n–π* transition of the δ-lactone moiety around 216 (negative) and 242 nm (positive) corresponded to the experimental Cotton effects observed around 217 and 241 nm, respectively. Thus, the absolute configuration of **2** was established as 2*R*, 3*R*, 5*R*, and 9*R*.

Liguhodgcins A (**1**) and B (**2**) are rare examples of δ-lactone-containing monoterpenoids. Only three δ-lactone-containing monoterpenoids have been reported: (2α,3β,5α)-2-(acetyloxy)-9-methoxy-5-(methoxycarbonyl)-2,3-dimethylheptano-5-lactone and (2*E*,4*R*,5*S*)-2-ethylidene-5-(methoxycarbonyl)-4-methylhexano-5-lactone isolated from *Ligularia dentate*[14] and bisline lactone, isolated as a metabolite from isoline by rat liver microsomes.[15] A plausible biogenetic pathway for liguhodgcins A (**1**) and B (**2**) is proposed in Scheme 1. According to the pathway of the biogenesis for senecic acid and its derivatives as proposed by Crout et al.,[16] key intermediate **A** is formed through oxidation of senecic acid that was derived from L-threonine and finally changed into liguhodgcins A (**1**) and B (**2**) via pathways a and b, respectively. This process comprised several reactions including chlorination, intramolecular esterification, acetylation, and methyl esterification.

The cytotoxicity of compounds **1** and **2** was evaluated against human leukemia (HL-60), human hepatoma (SMMC-7721), and human cervical carcinoma (HeLa) cell lines using the sulforhodamine B (SRB) method as previously reported.[17] The two compounds exhibited weak activity against the three lines ($IC_{50} \approx 150$ μM/L) (Table 2), and mitomycin was used as positive control with an $IC_{50} \approx 3$ μM/L. Although the two compounds were not the active components, their discovery added to an extremely diverse and complex array of δ-lactone-containing monoterpenoids.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on an X-4 digital display micromelting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. The UV spectrum was measured using a Shimadzu UV-260 spectrophotometer. The ECD spectrum was obtained on a JASCO J-720 spectropolarimeter. NMR spectra were recorded on a Varian Mercury-300BB NMR (300 MHz) spectrometer with TMS as internal standard. EIMS data were obtained on an HP5988AGCMS spectrometer. HRESIMS data were measured on a Bruker Daltonics APEX II 47e spectrometer. The X-ray crystallographic data were collected on a Bruker Smart CCD diffractometer using graphite-monochromated Mo Kα radiation. Silica gel (200–300 mesh) used for CC and silica gel GF_{254} (10–40 μ) used for TLC were supplied by Qingdao Marine Chemical Factory, Qingdao, P. R. China. Spots were detected on TLC under UV light or by heating after spraying with 5% H_2SO_4 in EtOH (v/v).

Plant Material. The aerial parts of *L. hodgsonii* were collected from Enshi city, Hubei Province, People's Republic of China, in August 2005, and authenticated by Prof. Guoliang Zhang from the School of Life Science, Lanzhou University. A specimen (No. 20050812) was deposited at the Natural Product Laboratory of the College of Chemistry and Chemical Engineering, Lanzhou University.

Extraction and Isolation. The air-dried aerial parts of *L. hodgsonii* (1.95 kg) were pulverized and extracted with MeOH (×3, 7 days each) at room temperature. The solvent was evaporated under reduced pressure to obtain an extract (233 g), which was suspended in hot H_2O (60 °C, 0.5 L). This suspension was extracted successively with petroleum ether, $CHCl_3$, and *n*-BuOH. The petroleum ether- and $CHCl_3$-soluble fractions were mixed and concentrated under reduced pressure to afford a residue (61 g), which was subjected to silica gel column chromatography (200–300 mesh, 300 g) with a gradient of petroleum ether–acetone (1:0, 30:1, 10:1, 5:1, 2:1, 1:1, 0:1) as eluent, and five fractions (A, B, C, D, and E) were collected according to TLC analysis.

Fraction B (3.1 g) was separated on a silica gel column (200–300 mesh, 50 g) eluting with petroleum ether–EtOAc (50:1, 30:1, 15:1) to give four fractions, FrB.1–FrB.4. FrB.3 (1.5 g) was separated on a silica gel column (200–300 mesh, 30 g) using petroleum ether–CH_3Cl (1:5) to give four crude fractions, FrB.3.1–FrB.3.4. FrB.3.1 (0.5 g) was further separated on a silica gel column (200–300 mesh, 10 g) with petroleum ether–EtOAc (15:1) as eluent to obtain **1** (6 mg). Fraction C (3 g) was separated on a silica gel column (200–300 mesh, 60 g) eluting with petroleum ether–EtOAc (5:1, 2:1) to give five fractions, FrC.1–FrC.5. FrC.4 (1.0 g) was separated on a silica gel column (200–300 mesh, 30 g) using petroleum ether–EtOAc (2:1) to give six fractions, FrC.4.1– FrC.4.6. FrC.4.4 (0.1 g) was further separated on a silica gel column (200–300 mesh, 1 g) with CH_3Cl–EtOAc (30:1) as eluent to obtain **2** (4 mg).

Liguhodgcin A (1): colorless crystals; mp 110–111 °C (CH_3Cl–acetone); $[\alpha]^{20}_D$ +70 (*c* 0.5, $CHCl_3$); UV (CH_3OH) λ_{max} 241, 299, 338 nm; IR (KBr) ν_{max} 2924, 1753, 1675 cm^{-1}; ^1H NMR (300 Hz)

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Scheme 1. Plausible Biosynthesis Pathway of Liguhodgcins A (1) and B (2)

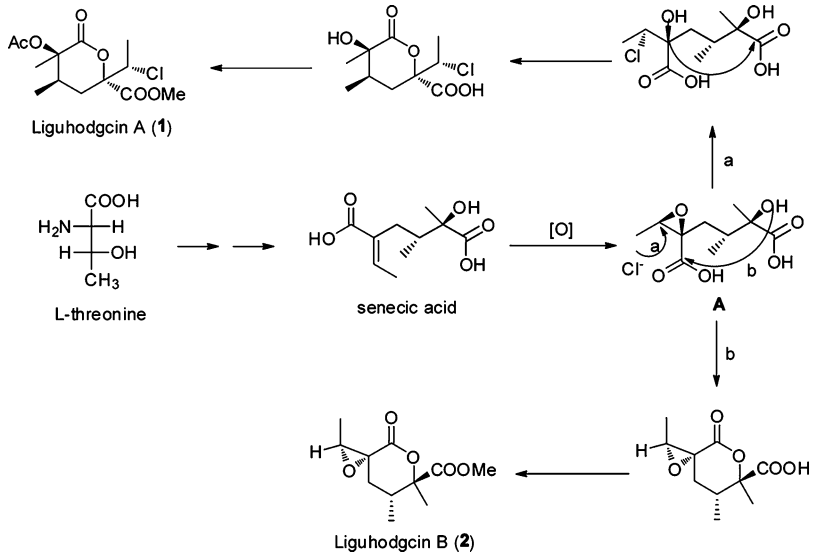

Table 2. IC_{50} Values for Cytotoxicity of Compounds 1 and 2

	IC_{50} (μM/L)		
compound	HL-60 cell	SMMC-7721 cell	HeLa cell
1	140.8 ± 15.9	156.1 ± 17.8	171.3 ± 23.6
2	151.4 ± 23.7	162.2 ± 21.4	168.4 ± 17.9
mitomycin	1.8 ± 0.6	5.6 ± 1.4	3.4 ± 1.7

and ^{13}C NMR (DEPT) (75 Hz) see Table 1; EIMS m/z (rel int) 249 (1), 247 (4), 177 (80), 159 (100), 152 (45); HRESIMS m/z 324.1213 $[M + NH_4]^+$ (324.1208 calcd for $C_{13}H_{23}O_6NCl$).

Liguhodgcin B (2): colorless oil; $[\alpha]^{20}_D$ +20 (c 0.3, $CHCl_3$); UV (CH_3OH) λ_{max} 229, 241 nm; IR (KBr) ν_{max} 2928, 1750 cm^{-1}; ^1H NMR (300 Hz) and ^{13}C NMR (DEPT) (75 Hz) see Table 1; EIMS m/z (rel int) 168 (3), 114 (34), 83 (25), 69 (48) 43 (100); HRESIMS m/z 229.1072 $[M + H]^+$ (229.1071 calcd for $C_{11}H_{17}O_5$).

X-ray Crystal Structure Determination of Liguhodgcin A (1). A colorless block crystal of **1** was grown via the slow evaporation of a CH_3Cl–acetone solution at room temperature. A crystal with dimensions 0.32 × 0.30 × 0.26 mm was selected for X-ray analysis (CCDC 840479). Structure analysis was performed using the SHELEXTL-97 program on a PC. Data were collected over a hemisphere of reciprocal space, by a combination of three sets of exposures. At T = 273(2) K the crystals were found to belong to the orthorhombic space group $P2_12_12_1$, with a = 8.807(7) Å, b = 12.790(10) Å, c = 14.382(11) Å, V = 1620(2) Å^3, Z = 4, D_{calc} = 1.258 g/cm^3, λ = 0.71073 Å, μ(MoKα) = 0.255 mm^{-1}, and F(000) = 648. Multiscans as programmed in the Bruker SMART program were used to make data corrections. A total of 8346 reflections, collected in the range 2.13° ≤ θ ≤ 25.49°, yielded 3035 unique reflections. The structure was solved using direct methods and was refined by full-matrix least-squares on F^2 values for 2678 $I > 2\sigma(I)$. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at calculated positions and refined using a riding mode. The absolute configuration was assigned on the basis of the absolute structure parameter, which refined to a value of −0.11(3). The final indices were R = 0.0295, R_w = 0.0809 with goodness-of-fit = 1.031. Scattering factors were taken from *International Tables for X-ray Crystallography*.[18]

Biological Activity. The cytotoxicity of compounds **1** and **2** toward human leukemia (HL-60), human hepatoma (SMMC-7721), and human cervical carcinoma (HeLa) cell lines was determined in 96-well microtiter plates by the SRB method. Briefly, exponentially growing HL-60, SMMC-7721, and HeLa cells were harvested and seeded in 96-well plates with the final volume of 100 μL containing 4 × 10^3 cells per well. After 24 h incubation, cells were treated with various concentrations of **1** and **2** for 48 h. The cultures were fixed at 4 °C for 1 h by addition of ice-cold 50% trichloroacetic acid to give a final concentration of 10%. Fixed cells were rinsed five times with deionized H_2O and stained for 10 min with 0.4% SRB dissolved in 0.1% HOAc. The wells were washed five times with 0.1% HOAc and left to dry overnight. The absorbed SRB was dissolved in 150 μL of unbuffered 1% Tris base [tris(hydroxymethyl)aminomethane] solution in H_2O (pH 10.5). The absorbance of extracted SRB at 515 nm was measured on a microplate reader (Bio-Rad). The experiments were carried out in triplicate. Each run entailed five or six concentrations of the compounds being tested. The percentage survival rates of cells exposed to the compounds were calculated by assuming the survival rate of untreated cells to be 100%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D, 2D NMR and HRESIMS spectra of compounds **1** and **2**; computational details for **2**. This material is 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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