Russujaponols A−F, Illudoid Sesquiterpenes from the Fruiting Body of *Russula japonica*

Kazuko Yoshikawa,* Azusa Kaneko, Yuki Matsumoto, Hiroshi Hama, and Shigenobu Arihara

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-Cho, Tokushima 770-8514, Japan

Received March 6, 2006

Six new illudoid sesquiterpenes, russujaponols A−F (**1**−**6**), were isolated from the fruiting bodies of *Russula japonica* Hongo. Their structures were established primarily by 2D NMR experiments, and the structure of the main compound, russujaponol A (**1**), was confirmed by X-ray crystallographic analysis of its benzoate (**1a**). Russujaponol A (**1**) suppressed invasion of human fibrosarcoma (HT1080) cells into Matrigel in a concentration-dependent manner and caused 63% inhibition at 3.73 μM.

In the course of our program aimed at the discovery of biologically active compounds from fungi,[1,2] we have initiated an investigation of *Russula japonica* Hongo (Russulaceae),[3] which grows in colonies in broad-leaved forests throughout Japan. In this study, six new illudoid sesquiterpenes, russujaponols A−F (**1**−**6**), together with the known compound **4b**[4] and deliquinone,[5] were isolated from the fruiting bodies of *R. japonica*. We describe here the isolation and structure elucidation of **1**−**6**, primarily by extensive NMR and X-ray crystallographic analysis of the benzoate of **1** (**1a**). Their cytotoxic activities against a disease-oriented panel of 39 human cancer cell lines were investigated.

Results and Discussion

Russujaponol A (**1**) gave an $[M + Na]^+$ peak at *m*/*z* 291.1562 (HRFABMS), which corresponds to the molecular formula $C_{15}H_{24}O_4$, requiring four unsaturation equivalents. The IR spectrum of **1** showed absorptions at 3370 (OH) and 1710 (C=O) cm^{-1}. The ^1H NMR spectrum of **1** exhibited two methyl singlets at δ 1.80 and 1.54, one methyl doublet at δ 1.42 (d, J = 6.3 Hz), and one oxygenated methylene group at δ 3.62 and 3.59 (each d, J = 10.2 Hz). The 15 carbon signals in the ^{13}C NMR spectrum were sorted by DEPT experiment into three methyls, five methylenes, one of which is oxygen bearing (δ 70.1); two methines, four sp^3 quaternary carbons, two of which have oxygen substituents (δ 87.5 and 78.3); and one carbonyl carbon (δ 214.3) (Table 1). Combined analysis of COSY, HMQC, and HMBC spectra, together with the chemical shifts and coupling constants, enabled the assignment of all the functional groups on the protoilludane skeleton. As shown in Figure 2, the COSY spectrum revealed the connectivity of H_2-4/H_2-5, H-7/H_3-13, and H-9/H_2-10. Moreover, HMBC correlations from H_3-12 (δ 1.80) to C-2 (δ 87.5), C-3 (δ 52.3), C-4 (δ 24.4), and C-6 (δ 78.3), from H_3-13 (δ 1.42) to C-6 (δ 78.3), C-7 (δ 48.1), and C-8 (δ 214.3), from H_3-15 (δ 1.54) to C-1 (δ 47.3), C-10 (δ 40.5), C-11 (δ 46.6), and C-14 (δ 70.1), and from H-9 [δ 3.53 (dd, J = 10.9, 6.0)] to C-2 and C-8 revealed three methyl groups at C-3, C-7, and C-11, one primary hydroxy group at C-14, two tertiary hydroxy groups at C-2 and C-6, one carbonyl group at C-8, and an ethylene bridge at C-3 and C-6. Thus, the planar structure of **1** was determined as 2a,7a-dihydroxy-6-(hydroxymethyl)-3,6,7b-trimethyloctahydro-1*H*-cyclobuta [*e*]inden-4(2*H*)-one. The relative configuration of the six successive chiral centers at C-2, C-3, C-6, C-7, C-9, and C-11 in **1** was defined by the following NOE analysis. The NOEs between H-9/H-4a (δ 1.60), H_3-15, H_3-12/H_2-1 (δ 2.81, 2.01), H-1α (δ 2.81)/H-7 (δ 3.75), H_2-14 (δ 3.59, 3.62), and H_3-13/H_2-5 (δ 2.19) established the 2*R**, 3*S**, 6*R**, 7*R**, 9*R**, and 11*S** configurations. The X-ray crystallographic analysis[6,7] of the benzoate (**1a**) of **1** confirmed the proposed structure and established the absolute configuration at the six stereocenters (Figure 3).

Russujaponol B (**2**) showed an $[M + Na]^+$ peak at *m*/*z* 317.1732 in its HRFABMS, indicative of the molecular formula $C_{17}H_{26}O_4$, requiring five unsaturation equivalents. The IR spectrum of **2** indicated the hydroxy (3370 cm^{-1}) and acetoxy (1730 and 1245 cm^{-1}) functionalities. The HMQC spectrum of **2** showed the presences of two hydroxy groups [δ_C 71.3 (t), 87.7 (s)], one secondary acetoxy group [δ_H 2.03 (3H, s), δ_C 20.7, 171.2, δ_H 5.54 (1H, br s), δ_C 78.8 (d)], one tetrasubstituted double bond [δ_C 140.3 (s) and 122.8 (s)], and one vinylic methyl group [δ_H 1.70 (br s), δ_C 13.0 (s)]. Combined analysis of COSY, HMQC, and HMBC spectra enabled the assignment of all the functional groups as in **1** (Figure 2). The COSY correlations showed the connectivity due to two vicinal couplings, H_2-1/H-2 and H_2-4/H_2-5, an allylic coupling, H-8/H_3-13, and a homoallylic coupling, H_2-5/H_3-13. HMBC long-range correlations from H_3-12 (δ 1.14) to C-2 (δ 57.0), C-3 (δ 45.1), C-4 (δ 37.3), and C-6 (δ 140.3), from H_3-13 (δ 1.70) to C-6, C-7 (δ 122.8), and C-8 (δ 78.8), from H_3-15 (δ 1.54) to C-1 (δ 37.5), C-10 (δ 48.4), C-11 (δ 44.8), and C-14 (δ 71.3), from H-2 [δ 2.76 (dd, J = 12.6, 7.7)] to C-8 and C-9 (δ 87.7), and from H-8 (δ 5.54) to the carbonyl (δ 171.2) of the acetoxy group revealed three methyl groups at C-3, C-7, and C-11, one primary hydroxy group at C-14, one hydroxy group at C-9, one acetoxy group at C-8, an ethylene bridge at C-3 and C-6, and the C-6−C-7 double bond. Thus, the planar structure of **2** was determined to be 4a-hydroxy-6-(hydroxymethyl)-3,6,7b-trimethyl-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-4-yl acetate. The relative configuration of the chiral centers in **2** was established by a ROESY experiment. Significant NOE correlations between H-2/H-1β (δ 1.63), H_3-15 and between H_3-12/H_2-1, H-8 indicated the β-cis A/B junction, the α-orientations of H_3-12 and the C-14 hydroxymethyl, and the β-orientation of the acetoxy moiety at C-8. On the basis of the above findings and the fact that **2** was isolated in conjunction with **1**, the structure of **2** was established as shown in Figure 1.

Russujaponol C (**3**) has the molecular formula $C_{15}H_{24}O_2$, requiring four unsaturation equivalents, by the ^{13}C NMR data and HREIMS. The IR spectrum of **3** also showed absorptions due to hydroxy functions. The NMR data of **3** showed a close relationship to that of **2**, except for the absence of the acetyl signal at δ 2.03 and of the tertiary hydroxy resonance at δ 87.7 in **2**. The ^1H and ^{13}C NMR spectra of **3** indicated the characteristic signals due to two hydroxy groups [δ_C 73.4 (d), δ_H 4.39 (br d, J = 8.0), and δ_C 71.4 (t), δ_H 3.75 (2H, s)] and to the double bond [δ_C 140.4 (s), 129.0 (s)]. The COSY data revealed the connectivity of H_2-1/H-2, H-9, H-8, H_2-4/H_2-5, and H-9/H_2-10. HMBC correlations of H_3-12 (δ 1.13)/C-2, C-3, C-4, C-6, H_3-13 (δ 1.98)/C-6, C-7, C-8 (δ 73.4), and H_3-15 (δ 1.20)/C-1, C-10, C-11, C-14 (δ 71.4) revealed two hydroxy groups at C-8 and C-14 and one double bond at C-6. Thus, the planar structure of **3** was determined to be 6-(hydroxymethyl)-3,6,7b-trimethyl-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta [*e*]inden-4-ol. The relative configuration at the stereocenters in

* Corresponding author. Tel: +81-88-622-9611. Fax: +81-88-655-3051. E-mail: yosikawa@ph.bunri-u.ac.jp.

10.1021/np068006a CCC: $33.50
Published on Web 09/02/2006

Table 1. NMR Data for Russujaponols A−F (**1**−**6**) [600 MHz (^{1}H) and 150 MHz (^{13}C) in pyridine-d_5]

	1		**2**		**3**	
position	δ_C	δ_H (mult, *J* in Hz)	δ_C	δ_H (mult, *J* in Hz)	δ_C	δ_H (mult, *J* in Hz)
1	47.3	2.81 (d, *J* =13.7)	37.5	1.88 (dd, 12.6, 12.6)	36.6	1.79 (m)
		2.01 (d, *J* =13.7)		1.63 (dd, 12.6, 7.7, 2.2)		1.48 (ddd, 12.6, 8.1, 1.9)
2	87.5		57.0	2.76 (dd, *J* =12.6, 7.7)	46.4	2.49 (dt, 11.5, 8.1)
3	52.3		45.1		45.9	
4	24.4	1.60 (m), 1.79 (m)	37.3	1.82 (m), 1.93 (m)	36.5	1.80 (2H, m)
5	27.7	2.19 (2H, m)	25.6	2.53 (m), 2.71 (m)	25.2	2.58 (m), 2.74 (m)
6	78.3		140.3		140.4	
7	48.1	3.75 (q, *J* =6.3)	122.8		129.0	
8	214.3		78.8	5.54 (br s)	73.4	4.39 (br d, *J* =8.0)
9	62.2	3.53 (dd, *J* =10.9, 6.0)	87.7		50.5	2.71 (m)
10	40.5	2.41 (dd, *J* =13.7, 6.0)	48.4	2.15 (d, *J* =13.5)	42.5	2.13 (ddd, 12.4, 7.7, 1.9)
		2.33 (dd, *J* =13.7, 10.9)		2.00 (dd, *J* =13.5, 2.2)		1.82 (m)
11	46.6		44.8		45.7	
12	18.0	1.80 (s)	20.2	1.14 (s)	20.6	1.13 (s)
13	8.1	1.42 (d, *J* =6.3)	13.0	1.70 (s)	12.2	1.98 (s)
14	70.1	3.62 (d, *J* =10.2)	71.3	3.70 (2H, s)	71.4	3.75 (2H, s)
		3.59 (d, *J* =10.2)				
15	26.8	1.54 (s)	24.0	1.54 (s)	23.3	1.20 (s)
Ac			20.7, 171.2	2.03 (s)		

	4		**5**		**6**	
position	δ_C	δ_H (mult, *J* in Hz)	δ_C	δ_H (mult, *J* in Hz)	δ_C	δ_H (mult, *J* in Hz)
1	38.0	1.84 (dd, *J* =12.4, 12.4)	42.7	3.19 (d, *J* =15.8)	42.7	3.08 (d, *J* =15.9)
		1.48 (dd, *J* =12.4, 6.9)		2.72 (d, *J* =15.8)		2.58 (d, *J* =15.9)
2	44.8	2.09 (m)	142.0		140.3	
3	45.2		133.2		132.9	
4	25.4	1.34 (m), 1.57 (m)	61.8	4.10 (2H, t, *J* =7.0)	61.6	3.98 (2H, t, *J* =7.6)
5	34.0	2.10 (m), 2.38 (m)	33.1	3.30 (2H, t, *J* =7.0)	34.1	3.15 (2H, t, *J* =7.6)
6	72.0		134.0		133.7	
7	136.2		140.0		134.1	
8	128.4	5.30 (br s)	123.3	7.37 (s)	124.6	6.89 (s)
9	39.1	2.72 (m)	140.6		140.5	
10	43.4	1.88 (dd, *J* =13.3, 1.8)	43.5	3.09 (d, *J* =15.8)	43.4	3.17 (d, *J* =15.7)
		1.72 (dd, *J* =13.3, 8.5)		2.60 (d, *J* =15.8)		2.70 (d, *J* =15.7)
11	44.3		45.0		45.0	
12	22.2	1.45 (s)	15.9	2.20 (s)	16.1	2.23 (s)
13	18.1	1.94 (s)	63.8	5.07 (2H, s)	20.5	2.36 (s)
14	72.2	3.53 (d, *J* =10.2)	69.9	3.75 (2H, s)	69.9	3.75 (2H, s)
		3.59 (d, *J* =10.2)				
15	27.3	1.24 (s)	25.1	1.33 (s)	25.2	1.34 (s)

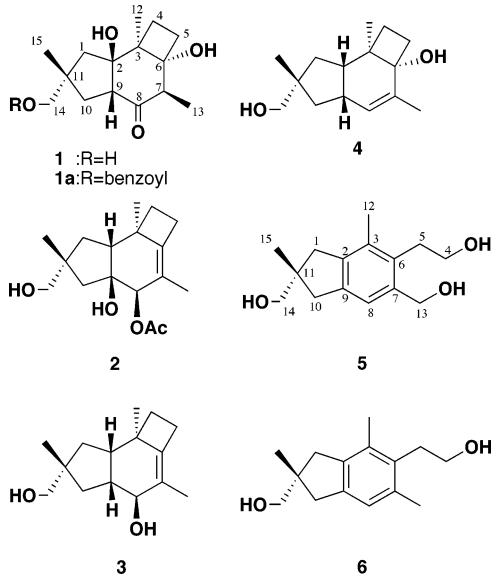

Figure 1. Structures of russujaponols A−F (**1**−**6**).

3 was established by a ROESY experiment, which showed NOE correlations between H-2 (δ 2.49)/H-9 (δ 2.71), H_3-15 and between H-9/H-10β (δ 2.13), H_3-15, and further H_3-12/H-8 (δ 4.39) and H-8/H-10α (δ 1.82) indicated a β-cis A/B ring junction and α-orientations of H-8, H_3-12, and CH_2OH at C-14.

Russujaponol D (**4**) has the same molecular formula, $C_{15}H_{24}O_2$, and molecular ion at *m*/*z* 236.1780 $[M]^+$ in the HREIMS as **3**, requiring four unsaturation equivalents. Indeed, the NMR spectra of **4** were generally similar to those of **3**. The COSY spectrum indicated the connectivity of H_2-1/H-2, H-9, H-8, H_3-13, H_2-4/H_2-5, and H-9/H_2-10. HMBC correlations showed H_3-12/C-2, C-3, C-4, C-6 (δ 72.0), H_3-13/C-6, C-7 (δ 136.2), C-8 (δ 128.4), and H_3-15/C-1, C-10, C-11, C-14 (δ 72.2). These observations confirmed that compound **4** possesses the same skeleton as **1**−**3**. Thus, the planar structure of **4** was determined as 6-(hydroxymethyl)-3,6,-7b-trimethyl-2,2a,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-2a-ol. The relative configuration of **4** was deduced from a NOESY experiment, which indicated the α-orientation of H_3-12, 6-OH, and 14-CH_2OH and the β-orientation of H-2, H-9, and H_3-15. The structure of **4** is thus assigned as shown in Figure 1.

Russujaponol E (**5**) has the molecular formula $C_{15}H_{22}O_3$ on the basis of the ^{13}C NMR data and HREIMS, thus requiring five unsaturation equivalents. The HMQC data of **5** showed a penta-substituted aromatic ring [δ 142.0 (s), 140.6 (s), 140.0 (s), 134.0 (s), 133.2 (s), and δ_C 123.3 (d), δ_H 7.37 (s)], two methyls [δ 1.33 (s), 2.20 (s)], and three primary hydroxy groups [δ 61.8 (t), 63.8 (t), 69.9 (t)]. A comparison of the ^{1}H and ^{13}C NMR data of **5** and those of compound **4b**[4] suggested that compound **5** has the same illudalane skeleton as compound **4b**. The olefinic proton at δ 7.37 showed HMBC correlations to C-2 (δ 142.0), C-6 (δ134.0), C-10

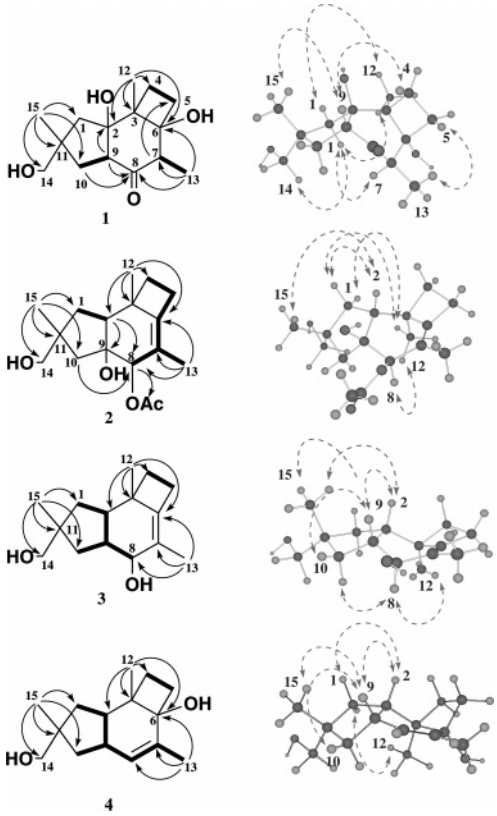

Figure 2. COSY (bold line), selected HMBC (arrow line), and selected ROESY (dashed arrow line) correlations of **1**−**4**.

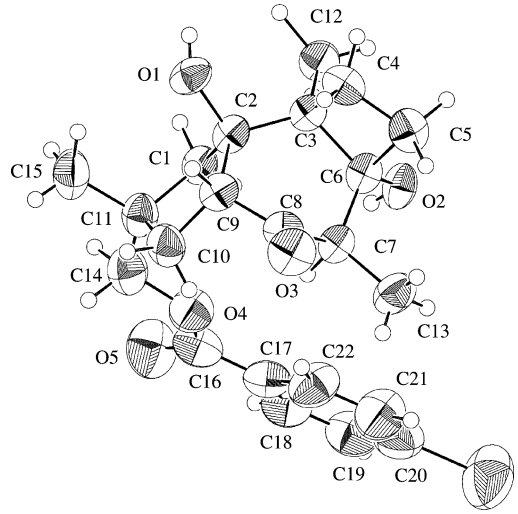

Figure 3. ORTEP drawing for **1a**.

(δ 43.5), and C-13 (δ 63.8). Combined analysis of COSY, HMQC, and HMBC spectra enabled assignment of the hydroxyl groups at C-4, C-13, and C-14. Hence, the structure of **5** was formulated as (6-(2-hydroxyethyl)-2,7-dimethyl-2,3-dihydro-1*H*-indene-2,5-diyl)-dimethanol. On the basis of the above findings and the fact that **5** coexisted with **1**−**4**, the structure of **5** was formulated as shown in Figure 1.

Russujaponol D (**6**) showed the molecular formula $C_{15}H_{22}O_2$, as determined by HREIMS. The ^{1}H NMR data of **6** were compatible with those of **5**, implying that **6** could possess the same skeleton as **5**. The NMR spectra showed one methyl group [δ_H 2.36 (s), δ_C 20.5] instead of the hydroxymethyl group [δ_H 5.07 (2H, s), δ_C 63.8 (t)] in **5**. The HMBC correlations from the methyl signal (δ 2.36)/C-6 [δ 133.7 (s)], C-7 [δ 134.1(s)], and C-8 [δ 124.6 (d)]) confirmed the additional methyl group at C-7. From analysis of all of this data, the structure of **6** was formulated as 2-(2-hydroxymethyl-2,4,6-trimethylindan-5-yl)ethanol. Compound **6** has previously been obtained as the product of Clemmensen reduction of epipterosin L.[8]

Compounds **1**, **2**, and **4** were subjected to a cytotoxic activity assay against cell lines, including 39 human cancer cell lines.[9,10] No activity was observed in the assay. The main compound **1** was investigated for the inhibitory activity on migration of the human HT1080 fibrosarcoma cell line and inhibited invasion of 63% of HT1080 to reconstituted basal membrane, at 3.73 M (positive control, doxorubicin 52% at 0.17 μM).

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. IR spectra were recorded on a JASCO FT/IR-410, UV spectra were recorded on a Shimadzu UV-1650PC, and NMR spectra were recorded on a Varian UNITY 600 spectrometer in C_5D_5N and $CDCl_3$ using TMS as internal standard. Coupling constants (*J* values) are given in Hz. The MS spectra were measured on a JEOL AX-500 mass spectrometer.

Fungus Material. The fruiting bodies of *R. japonica* were collected at Tokushima, Japan, in autumn 1999. A voucher specimen (TB3066) is deposited in the Herbarium of the Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima, Japan.

Extraction and Isolation. The fresh fruiting bodies (3.8 kg) of *R. japonica* were extracted with 70% EtOH at room temperature for 4 weeks (×2). The EtOH extract was partitioned between EtOAc and H_2O. The EtOAc-soluble portion (36.0 g) was subjected to silica gel column chromatography with diisopropyl ether−MeOH (50:1−25:8) to afford fractions 1−6. Fraction 2 was purified by preparative HPLC (ODS, 36% MeOH) to afford russujaponols D (**4**, 5 mg) and F (**6**, 63 mg). Fraction 3 was passed through silica gel with diisopropyl ether−MeOH (30:1) to afford fractions 3-1 to 3-4. Fractions 3-2 and 3-3 were successively purified by preparative HPLC (ODS, 30−32% MeOH) to afford compound **4b** (45 mg) and deliquinone (20 mg) from fraction 3-2 and russujaponols B (**2**, 5 mg) and C (**3**, 10.2 mg) from fraction 3-3, respectively. Fraction 5 was passed through silica gel with diisopropyl ether−MeOH−H_2O (25:2:0−25:6:0.1) to afford fractions 5-1 to 5-4. Similar purification by silica gel column chromatography and preparative HPLC (ODS, 30−32% MeOH) afforded russujaponol A (**1**, 226.5 mg) from fraction 5-2 and russujaponol E (**5**, 16.5 mg) from fraction 5-3.

Russujaponol A (1): amorphous powder; $[\alpha]^{25}_D$ −110.1 (*c* 1.5, MeOH); FT-IR (film) ν_{max} 3370, 1710, 1080, 1070 cm^{-1}; HRFABMS *m/z* [M + Na]$^+$ 291.1562 (calcd for $C_{15}H_{24}O_4$ + Na, 291.1572).

Russujaponol B (2): amorphous powder; $[\alpha]^{25}_D$ −100.2 (*c* 0.4, MeOH); FT-IR (film) ν_{max} 3370, 1730, 1245, 1085, 1070 cm^{-1}; HRFABMS *m/z* [M + Na]$^+$ 317.1732 (calcd for $C_{17}H_{26}O_4$ + Na, 317.1729).

Russujaponol C (3): amorphous powder; $[\alpha]^{25}_D$ −48.6 (*c* 0.4, MeOH); FT-IR (film) ν_{max} 3370, 1080, 1070 cm^{-1}; HREIMS *m/z* [M]$^+$ 236.1791 (calcd for $C_{15}H_{24}O_2$, 236.1776).

Russujaponol D (4): amorphous powder; $[\alpha]^{25}_D$ −26.2 (*c* 0.5, MeOH); FT-IR (film) ν_{max} 3370, 1080, 1070 cm^{-1}; HREIMS *m/z* [M]$^+$ 236.1780 (calcd for $C_{15}H_{24}O_2$, 236.1776).

Russujaponol E (5): amorphous powder; $[\alpha]^{25}_D$ −18.2 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ϵ) 230 (4.16), 280 (4.13); FT-IR (film) ν_{max} 3370, 1600, 1070 cm^{-1}; HREIMS *m/z* [M]$^+$ 250.1562 (calcd for $C_{15}H_{22}O_3$, 250.1569).

Russujaponol F (6): amorphous powder; $[\alpha]^{25}_D$ +1.3 (*c* 3.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 230 (4.16), 280 (4.13); FT-IR (film) ν_{max} 3370, 1080, 1070 cm^{-1}; HREIMS *m/z* [M]$^+$ 234.1615 (calcd for $C_{15}H_{22}O_2$, 234.1620).

***p*-Bromobenzoylation of 1.** To a solution of **1** (15 mg) in pyridine (2 mL) were added *p*-bromobenzoyl chloride (15 mg) and 4-(dimethylamino)pyridine (2 mg). The reaction mixture was stirred at room temperature for 24 h and then concentrated in vacuo to give a residue, which was purified by HPLC (ODS, 40% MeOH) to afford **1a** (5 mg) as colorless plates from diethyl ether−EtOH, mp 180 °C. X-ray crystallographic analysis confirmed the structure of **1a** (absolute configuration; ORTEP diagram, Figure 2).

Crystal Data for 1a. Data collection: DIP image plate. Cell refinement: Scalepack (HKL). Data reduction: maXus. Program used to solve structure: maXus.[8] Program used to refine structure: SHELXS-97.[9] Refinemen on F^2: full matrix least-squares. Diffractometer: DIP image plate. Colorless crystal of $C_{22}H_{27}BrO_5$ having approximate dimensions 0.5 × 0.2 × 0.05 mm, MW 451.3508, monoclinic, $P2_1$, a = 6.5200(4) Å, b = 12.0380(5) Å, c = 13.6460(11) Å, β = 91.679-(2)°, V = 1070.58(12) Å, Z = 2, Mo Ka radiation, λ = 0.71073 Å, μ = 1.949 mm^{-1}, 3758 reflections, 253 parameters; only coordinates of H atom refined, R = 0.0541, R_w = 0.1442, S = 1.028, Flack parameter = −0.008.

Acknowledgment. We are grateful to Mr. T. Ohashi, fungologist, Tokushima Prefectural Tomioka Nishi High School, for confirming the identification of the fungus and to Ms. Ohashi for gathering the fungus. We are grateful to Dr. S. Takaoka for the X-ray spectral measurement. We would like to thank the Screening Committee of Anticancer Drugs supported by a Grant-in Aid for Scientific Research on Priority Area "Cancer" from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Yoshikawa, K.; Kouso, K.; Takahashi, J.; Matsuda, A.; Okazoe, M.; Umeyama, A.; Arihara, S. *J. Nat. Prod.* **2005**, *68*, 911−914.
(2) Yoshikawa, K.; Inoue, M.; Matsumoto, Y.; Sakakibara, T.; Miyataka, H.; Matsumoto, H.; Arihara, S. *J. Nat. Prod.* **2005**, *68*, 69−73.
(3) Imazeki, R.; Hongo, T. *Colored Illustrations of Mushrooms of Japan*; Hoikusha Press: Osaka, Japan, 1998; Vol II, p 47.
(4) Clericuzio, M.; Fu, J.; Pan, F.; Pang, Z.; Sterner, O. *Tetrahedron* **1997**, *53*, 9725−9740.
(5) Clericuzio, M.; Han, F.; Pan, F.; Pang, Z.; Sterner, O. *Acta. Chem. Scand.* **1998**, *52*, 1333−1337.
(6) Sheldrick, G. M. *SHELXS*-97, Programs for Crystal Structure Solution and the Refinement of Crystal Structures; University of Gottingen: Germany, 1997.
(7) Mackay, S.; Gilmore, C. J.; Edwards, C.; Stewart, N.; Shankland, K. *maXus*, Computer Program for the Solution and Refinement of Crystal Structures; Bruker Nonius: The Netherlands; MacScience: Japan; The University of Glasgow, 1999.
(8) Fukuoka, M.; Kuroyanagi, M.; Yoshihira, K.; Natori, S. *Chem. Pharm. Bull.* **1978**, *26*, 2365−2385.
(9) Yamori, T.; Matsunaga, A.; Sato, S.; Yamazaki, K.; Komi, A.; Ishizu, K.; Mita, I.; Edatsugi, H.; Matsuba, Y.; Takezawa, K.; Nakanishi, O.; Kohno, H.; Nakajima, Y.; Komatsu, H.; Andoh, T.; Tsuruo, T. *Cancer Res.* **1999**, *59*, 4042−4049.
(10) Ogasawara, M.; Matsunaga, T.; Takahashi, S.; Saiki, I.; Suzuki, H. *Biol. Pharm. Bull.* **2002**, *25*, 1491−1493.

NP068006A