Sesquiterpenoids from *Hedyosmum orientale*

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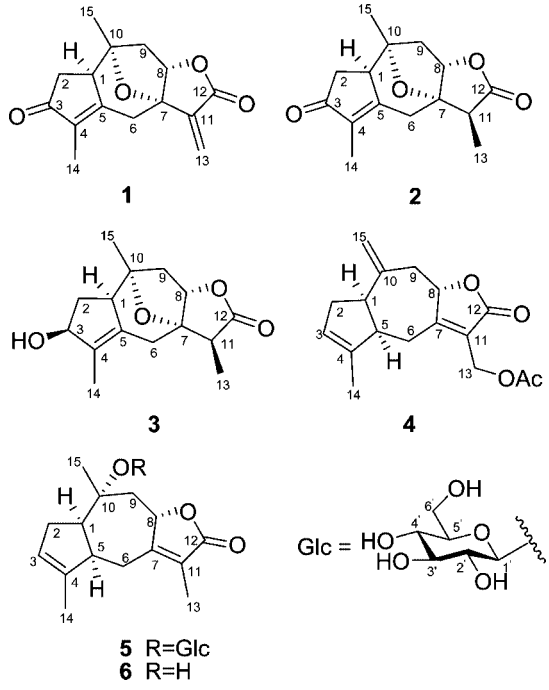
Five new guaiane-type sesquiterpenoids, hedyosumins A−E (**1**−**5**), together with five known ones (**6**−**10**), were isolated from the aerial parts of *Hedyosmum orientale*. Two known sesquiterpenoids, 10α-hydroxy-1,5α*H*-guaia-3,7(11)-dien-8α,12-olide and 9α-hydroxyasterolide, were obtained as natural products for the first time. Their structures were elucidated on the basis of spectroscopic methods. 9α-Hydroxyasterolide (**7**) showed moderate activities against A-549 and HL-60 tumor cell lines with the IC_{50} values of 3.1 and 8.8 μM, respectively.

Plants of the *Hedyosmum* genus (Chloranthaceae) are mainly distributed in the tropical area of America, and only one species, *H. orientale* Merr. et Chun, grows in China.[1]Previous chemical investigations on this genus have led to the isolation of sesquiterpenoids,[2,3] sesterterpenes,[4] and flavonoid glycosides.[5] In this study, five new guaiane-type sesquiterpenoids, hedyosumins A−E, as well as five known ones, 10α-hydroxy-1,5αH-guaia-3,7(11)-dien-8α,12-olide,[6] 9α-hydroxyasterolide,[7] spathulenol,[8] 13-hydroxy-8,9-dehydroshizukanolide,[3] and aromadendrane-4β,10β-diol,[9] were isolated from the ethanolic extract of the aerial parts of *H. orientale*. Sesquiterpenoids 10α-hydroxy-1α,5αH-guaia-3,7(11)-dien-8α,12-olide and 9α-hydroxyasterolide were obtained as natural products for the first time. Isolates **1**−**10** were evaluated for cytotoxic activities against A-549 (human lung adenocarcinoma) and HL-60 (human leukemia) tumor cell lines, and only 9α-hydroxyasterolide (**7**) showed moderate activities against A-549 and HL-60 with IC_{50} values of 3.1 and 8.8 μM, respectively. Herein, details of the isolation and structural elucidation of compounds **1**−**5** are presented.



Results and Discussion

Hedyosumin A (**1**), colorless needles (in methanol), possessed a molecular formula of $C_{15}H_{16}O_4$ as determined by HREIMS at *m*/*z* 260.1043 $[M]^+$ (calcd 260.1049), which was compatible with the NMR data (Tables 1 and 2). The IR spectrum of **1** indicated the presence of an α,β-unsaturated ketone (1703 cm^{-1}) group and a γ-lactone (1770 cm^{-1}) moiety.[10] The ^{13}C NMR spectrum with DEPT experiments displayed 15 carbon resonances comprising two methyls, four methylenes (one sp^2), two methines (one oxygenated), five quaternary carbons (two oxygenated and one sp^2 carbon), one ketone carbonyl, and one ester carbonyl. These functionalities accounted for four out of the eight degrees of unsaturation, and the remaining four degrees of unsaturation required compound **1** to be tetracyclic. The aforementioned spectroscopic features implied that compound **1** is a guaiane-type sesquiterpenoid with an oxygen bridge between C-7 at δ_C 84.2 and C-10 at δ_C 87.8 to meet the tetracyclic nature.[2,10] The NMR data of **1** showed similarity to those of the known analogue 10-epoxyhedyosminolide.[2] The only differences were the two methines at C-3 (δ_C 125.3) and C-5 (δ_C 43.3) of 10-epoxyhedyosminolide being replaced by a ketone group (δ_C 206.5) and an olefinic quaternary carbon (δ_C 165.6) in compound **1**. This assignment was finalized by an HMBC experiment (Figure 1A), in which both H_2-2 and Me-14 showed mutual correlations to C-3, C-4, and C-5.

The relative configuration of **1** was deduced from the ROESY spectrum (Figure 1B). The ROESY correlations of H-1/H-2α and H-6α indicated that H-1, H-2α, and H-6α were cofacial and were randomly assigned as α-oriented. The correlations of H-8/H-6β and H-9β suggested that H-8, H-6β, and H-9β were β-oriented. Furthermore, Me-15 was assigned to be α-oriented on the basis of ROESY correlations of H_3-15/H-1 and H-9α. Hence, compound **1** was assigned as 7α,10α-epoxy-3-oxo-1α*H*-guaia-4(5),11(13)-dien-8α,12-olide, namely, hedyosumin A.

Hedyosumin B (**2**) was isolated as colorless needles. The HREIMS showed a molecular ion peak at *m*/*z* 262.1211 $[M]^+$ (calcd 262.1205) corresponding to the molecular formula $C_{15}H_{18}O_4$, which requires seven degrees of unsatutation. The ^1H and ^{13}C NMR spectra of **2** were similar to those of **1**, except for the absence of the $\Delta^{11(13)}$ exocyclic double bond and the presence of a methyl group at C-11, as determined by the resonance at δ_H 1.34 (Me-13, 3H, d, $J = 7.0$ Hz), indicating that **2** was the 11,13-dihydrogenated analogue of **1**. This was supported by the downfield shifted C-12 carbon resonance (ca. $\Delta\delta$ 8.4) of **2** as compared with that of **1** (Table 2). The HMBC correlations from H-13 to C-7, C-11, and C-12 further confirmed this conclusion. The relative configuration of **2** was established by comparing its NMR data with those of **1** and finally confirmed by a ROESY experiment (see Supporting Information). Particularly, the β-orientation of Me-13 was deduced from the ROESY correlation between Me-13 and H-6β and by comparing the NMR data of **2** with those of 4α-hydroxy-7α,10α-epoxy-

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Table 1. ^{1}H NMR (400 MHz) Data of **1**−**6**

proton	**1**[a] (mult., *J* Hz)	**2**[a] (mult., *J* Hz)	**3**[a] (mult., *J* Hz)	**4**[a] (mult., *J* Hz)	**5**[b] (mult., *J* Hz)	**6**[a] (mult., *J* Hz)
1	2.87 m	2.81 m	2.51 m	3.09 m	2.68 m	2.62 m
2α	2.48 dd (18.8, 6.8)	2.48 dd (18.8, 7.0)	2.42 m	2.43 br d (8.4)	2.25 br d (8.0)	2.50 m
2*β*	1.85 dd (18.8, 2.7)	1.82 dd (18.8, 2.8)	1.02 m	2.43 br d (8.4)	2.25 br d (8.0)	2.28 m
3			4.71 br t	5.42 s	5.35 s	5.36 s
5				2.51 m	3.04 m	2.33 m
6α	2.95 d (14.0)	2.80 d (14.4)	2.42 d (13.6)	1.95 d (13.2)	2.95 dd (13.5, 7.5)	2.91 dd (13.8, 4.1)
6*β*	2.75 d (14.0)	2.68 d (14.4)	2.28 d (13.6)	2.79 d (13.2)	2.12 m	2.18 m
8	4.38 dd (7.2, 2.4)	4.38 dd (7.0, 1.8)	4.45 br d (7.1)	4.71 dd (10.5, 5.5)	5.04 m	4.92 m
9α	1.80 dd (13.7, 2.4)	1.74 dd (14.5, 1.8)	1.63 br d (14.2)	2.05 dd (12.0, 10.5)	2.11 m	1.96 dd (15.2, 5.6)
9*β*	2.12 dd (13.7, 7.2)	1.98 dd (14.5, 7.0)	2.34 dd (14.2, 7.1)	3.05 dd (12.0, 5.5)	2.49 dd (15.6, 6.4)	2.47 dd (15.2, 6.5)
11		2.62 q (7.0)	2.53 q (7.2)			
13	a 5.99 s b 6.46 s	1.34 d (7.0)	1.33 d (7.2)	4.79 d (2.5)	1.79 s	1.79 s
14	1.71 s	1.72 s	1.69 s	1.75 s	1.73 s	1.71 s
15	1.42 s	1.42 s	1.31 s	a 5.06 s b 5.15 s	1.29 s	1.23 s
13-OAc				2.06 s		
Glc-1′					4.37 d (8.0)	
Glc-2′					2.96 m	
Glc-3′					3.18 m	
Glc-4′					3.17 m	
Glc-5′					3.29 m	
Glc-6′					a 3.56 dd (12.0, 6.0) b 3.81 dd (12.0, 6.0)	

[a] Data measured in $CDCl_3$. [b] Data measured in CD_3OD.

Table 2. ^{13}C NMR (100 MHz) Data of **1**−**6**

carbon	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**5**[b]	**6**[a]
1	48.7	48.7	52.6	48.9	53.2	53.3
2	36.1	36.1	34.7	34.5	35.0	33.3
3	206.5	206.8	79.2	124.9	124.9	124.1
4	138.2	137.7	136.2	141.2	145.3	142.5
5	165.6	166.6	133.0	50.7	49.7	48.2
6	32.9	33.9	31.7	25.8	27.9	26.4
7	84.2	86.5	87.3	170.5	164.8	161.9
8	85.2	85.0	86.0	83.6	82.9	80.2
9	39.1	38.8	38.9	39.9	38.6	39.6
10	87.8	87.6	86.6	142.9	82.0	73.0
11	136.5	43.4	43.7	120.6	123.2	121.7
12	168.4	176.8	177.8	170.2	178.7	175.1
13	125.5	8.2	8.2	54.7	8.7	8.1
14	8.0	8.0	10.6	14.9	15.6	14.9
15	24.5	24.6	24.2	116.4	27.9	26.4
AcO				172.4		
				20.8		
Glc-1′					98.3	
Glc-2′					75.6	
Glc-3′					78.0	
Glc-4′					72.8	
Glc-5′					78.5	
Glc-6′					63.9	

[a] Data measured in $CDCl_3$. [b] Data measured in CD_3OD.

1,5,11α*H*,8*βH*-guaian-8,12-olide.[6] The structure of **2** was thus determined as 7α,10α-epoxy-3-oxo-1,11α*H*-guaia-4(5)-en-8α,12-olide.

Hedyosumin C (**3**) was obtained as a white, amorphous powder. A molecular formula of $C_{15}H_{20}O_4$ was assigned from the HREIMS ion at *m*/*z* 264.1372 $[M]^+$ (calcd 264.1362) requiring six degrees of unsatutation. The IR spectrum showed absorptions typical for hydroxy (3427 cm^{-1}) and γ-lactone (1774 cm^{-1}) groups. A fragment at *m*/*z* 246 $[M - H_2O]^+$ observed in the EIMS was compatible with the presence of a hydroxy group as implied by the IR spectrum. The ^{1}H and ^{13}C NMR spectral data of **3** showed similarity to those of **2**, with the only difference being the presence of a hydroxy group at C-3 (δ_H 4.71, br t; δ_C 79.2) of **3** instead of the C-3 keto group of **2**. In the HMBC spectrum, the mutual correlations from both H-1 and H-14 to C-3, C-4, and C-5 further confirmed this deduction. The relative configuration of **3** was established by analysis of NMR data and a ROESY spectrum (Supporting Information). In particular, the 3-OH group was assigned a *β*-orientation from the cross-peaks from H-3 to H-1 and H-2α in the ROESY spectrum. The structure of hedyosumin C (**3**) was therefore assigned as 3*β*-hydroxy-7α,10α-epoxy-1,11α*H*-guaia-4(5)-en-8α,12-olide.

Hedyosumin D (**4**), isolated as a white, amorphous powder, showed a molecular formula of $C_{17}H_{20}O_4$ as determined by HREIMS at *m*/*z* 288.1355 $[M]^+$ (calcd 288.1362). The IR absorptions implied the presence of α,*β*-unsaturated γ-lactone (1761 cm^{-1}) and ester (1747 cm^{-1}) functionalities. The ^{13}C NMR spectrum in conjunction with DEPT experiments displayed 17 carbon resonances comprising two methyls, five methylenes (one oxygenated and one olefinic), four methines (one oxygenated and one olefinic), and six quaternary carbons (two esters and four olefinic ones). The aforementioned data showed similarity to those of 10α-hydroxy-1,5α*H*-guaia-3,7(11)-dien-8α,12-olide (**6**), a semisynthetic compound from santonin.[6] However, the NMR spectra of **4** indicated that the proton and carbon resonances of the oxygenated quaternary C-10, Me-13, and Me-15 of **6** were replaced by an oxygenated methylene (δ_H 4.79; δ_C 54.7) and a $\Delta^{10(15)}$ exocyclic double bond (δ_H 5.06, 5.15; δ_C 142.9, 116.4) in **4**, respectively. In the HMBC spectrum, the strong correlations from two protons of the exocyclic double bond (at δ_H 5.06 and 5.15) to C-1, C-9, and C-10 incorporated the $\Delta^{10(15)}$ double bond between C-1 and C-9; the mutual correlations from H_2-13 to C-7, C-11, C-12, and *C*OCH_3 attached the only O-acetyl group at C-13 (Figure 2A).

In the ROESY spectrum of **4**, the correlations of H-1/H-5 and H-6α indicated that they were cofacial and were randomly assigned as α-oriented, while the correlations of H-8/H-6*β* and H-9*β* indicated a *β*-orientation for H-8 (Figure 2B). Hedyosumin D (**4**) was thus assigned as 13-acetoxy-1α,5α*H*-guaia-3,7(11),10(15)-trien-8α,12-olide.

Hedyosumin E (**5**) was obtained as a white, amorphous powder. The HRESIMS displayed a pseudo molecular ion peak at *m*/*z* 433.1831 $[M + Na]^+$ consistent with the molecular formula $C_{21}H_{30}O_8$ (calcd for $C_{21}H_{30}O_8Na$ 433.1838). The ^{13}C NMR spectrum showed 21 carbon resonances, of which five resonated in the region δ_C 63.9−78.5, and one resonated at δ_C 98.3 assignable to an anomeric carbon, suggesting the presence of a hexose residue. Apart from the sugar moiety, the ^{1}H and ^{13}C NMR data of the aglycone of **5** were similar to those of **6**,[7] indicating that compound **5** was

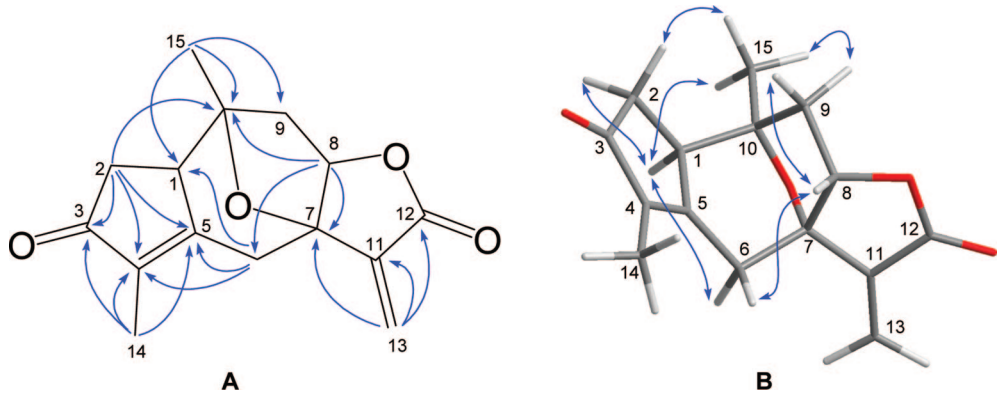

Figure 1. Key HMBC (A: H→C) and ROESY (B: ↔) correlations of **1**.

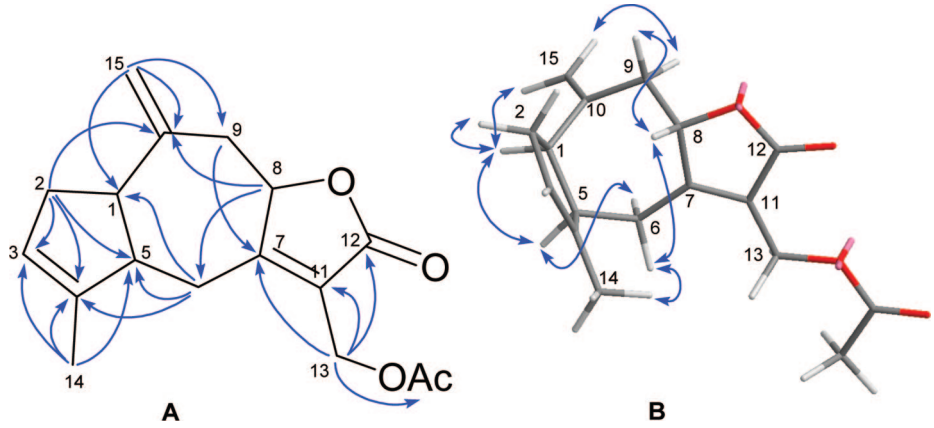

Figure 2. Key HMBC (A: H→C) and ROESY (B: ↔) correlations of **4**.

likely a glycosidic derivative of **6**. The sugar moiety was attached to C-10 by the HMBC correlation between H-1′ (δ_H 4.37) and C-10 (δ_C 82.0). In the ^{1}H NMR spectrum, the coupling constant of the anomeric proton at δ_H 4.37 (H-1′, d, J = 8.0 Hz) indicated that the sugar moiety was a β-glucopyranose, which was further determined to be β-D-glucopyranose as judged from the specific rotation ($[\alpha]^{20}_D$ + 36.0, *c* 1.0, H_2O)[11] obtained on acid hydrolysis of **5**. The relative configuration of the aglycone was established to be the same as **6** by comparing their NMR data and the analysis of the ROESY spectrum of **5** (Supporting Information). Thus, the structure of hedyosumin E (**5**) was assigned as 1α,5α,8β*H*-guaia-3,7(11)-dien-8,12-olide-10-*O*-β-D-glucopyranoside.

Five known sesquiterpenoids were identified as 10α-hydroxy-1,5α*H*-guaia-3,7(11)-dien-8α,12-olide (**6**),[6] 9α-hydroxyasterolide (**7**),[7] spathulenol (**8**),[8] 13-hydroxy-8,9-dehydroshizukanolide (**9**),[3] and aromadendrane-4β,10β-diol (**10**)[9] on the basis of the ^{1}H and ^{13}C NMR and EIMS data. Compounds **6** and **7** have been isolated as natural products for the first time.

All the isolates **1**−**10** were evaluated for their cytotoxic activities against A549 (human lung adenocarcinoma) and HL-60 (human leukemia) tumor cell lines, and only 9α-hydroxyasterolide (**7**) showed moderate activities against A549 and HL-60 with IC_{50} values of 3.1 and 8.8 μM, respectively.

Experimental Section

General Experimental Procedures. Melting points were measured on an SGW X-4 melting point instrument and were uncorrected. IR spectra were recorded on a Perkin-Elmer 577 spectrometer with KBr disks. UV spectra were measured on a Shimadzu UV-2550 UV−visible spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter at room temperature. NMR spectra were measured on a Bruker AM-400 spectrometer with TMS as internal standard. EIMS (70 eV) and ESIMS were carried out on a Finnigan MAT 95 mass spectrometer and an Esquire 3000plus LC-MS instrument, respectively. All solvents used were of analytical grade (Shanghai Chemical Plant, Shanghai, People's Republic of China). Si gel (300−400 mesh), C18 reversed-phase Si gel (150−200 mesh, Merck), MCI gel (CHP20P, 75−150 μM, Mitsubishi Chemical Industries Ltd.), and Sephadex LH-20 gel (Amersham Biosciences) were used for column chromatography, and precoated Si gel GF-254 plates (Qingdao Marine Chemical Plant, Qingdao, People's Republic of China) were used for TLC. Semi-preparative HPLC was performed on a Waters 515 pump equipped with a Waters 2487 detector and a YMC-Pack ODS-A column (250 × 10 mm, S-5 μM, 12 nm).

Plant Material. The aerial parts of *H. orientale* were collected in August of 2005 from Hainan Province of China, and were authenticated by Prof. S. M. Huang, Department of Biology, Hainan University of China. A voucher specimen has been deposited in Shanghai Institute of Materia Medica, Chinese Academy of Sciences, P. R. China (accession no. HO-2005-1Y).

Extraction and Isolation. The air-dried powder of the aerial parts (3.5 kg) of *H. orientale* was extracted with 95% EtOH (3 × 10 L) at room temperature to give a dark green residue (550 g), which was then partitioned between EtOAc and H_2O to give the EtOAc-soluble fraction E (113 g). Fraction E was subjected to a column of MCI gel eluted with MeOH−H_2O (5:5 to 9:1) to obtain five fractions, F1−F5. Fraction F1 (8.2 g) was chromatographed on a Si gel column eluted with $CHCl_3$−MeOH (8:1), and the major component was purified on a column of Sephadex LH-20 eluted with EtOH to yield compound **5** (17 mg). F3 (15 g) was chromatographed on a Si gel column eluted with petroleum ether−Me_2CO (15:1−5:1) to afford five subfractions, F3a−F3e. F3b was then separated on a column of Sephadex LH-20 eluted with EtOH to afford compounds **8** (11 mg), **9** (35 mg), and **10** (21 mg). F3c was subjected to a column of reversed-phase RP-18 eluted with MeOH−H_2O (6:4 to 8:2) to give three major fractions, F3c1−F3c3. F3c2 was separated on a Si gel column eluted with $CHCl_3$−MeOH (100:1) to obtain two major compounds, each of which was then purified on a column of Sephadex LH-20 eluted with EtOH to yield compounds **1** (25 mg) and **2** (12 mg), respectively. F3c3 was chromatographed over a Si gel column eluted with $CHCl_3$−MeOH (100:1) to afford

compounds **3** (10 mg) and **4** (15 mg). F3d was subjected to a column of Si gel eluted with petroleum ether−Me_2CO (10:1−5:1) to give a major fraction containing two compounds, which was then separated by semipreparative HPLC with the mobile phase of 60% MeCN in H_2O to afford compounds **6** (7 mg) and **7** (8 mg).

Hedyosumin A (1): colorless needles (EtOAc); mp 170−172 °C; $[\alpha]^{20}_D$ +70.0 (*c* 0.160, MeOH); UV (MeOH) λ_{max} (log ε) 270 (4.56) nm; IR (KBr) ν_{max} 2928, 1770, 1703, 1655, 1383, 1333, 1126, 1032 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; EIMS *m/z* 260 $[M]^+$ (43), 219 (6), 218 (32), 202 (41), 200 (100), 173 (15), 146 (23), 91 (19); HREIMS *m/z* 260.1043 $[M]^+$ (calcd for $C_{15}H_{16}O_4$, 260.1049).

Hedyosumin B (2): colorless needles (EtOAc); mp 122−124 °C; $[\alpha]^{20}_D$ +183.0 (*c* 0.110, MeOH); UV (MeOH) λ_{max} (log ε) 268 (3.94) nm; IR (KBr) ν_{max} 2983, 1778, 1701, 1657, 1381, 1205, 1059, 1018 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; EIMS *m/z* 262 $[M]^+$ (100), 219 (26), 204 (14), 177 (28), 148 (26), 123 (15), 109 (13), 91 (13), 77 (8); HREIMS *m/z* 262.1211 $[M]^+$ (calcd for $C_{15}H_{18}O_4$, 262.1205).

Hedyosumin C (3): colorless, amorphous powder; $[\alpha]^{20}_D$ +6.0 (*c* 0.080, MeOH); UV (MeOH) λ_{max} (log ε) 269 (3.92) nm; IR (KBr) ν_{max} 3427, 2931, 1774, 1635, 1448, 1379, 1203, 1094, 1016 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; EIMS *m/z* 264 $[M]^+$ (17), 262 (37), 246 (65), 219 (18), 203 (65), 161 (47), 157 (100), 149 (52), 133 (37), 91 (61); HREIMS *m/z* 264.1372 $[M]^+$ (calcd for $C_{15}H_{20}O_4$, 264.1362).

Hedyosumin D (4): colorless, amorphous powder; $[\alpha]^{20}_D$ +26.0 (*c* 0.090, MeOH); UV (MeOH) λ_{max} (log ε) 270 (4.46) nm; IR (KBr) ν_{max} 2928, 2854, 1761, 1747, 1674, 1446, 1369, 1236, 1084, 1020 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; EIMS *m/z* 288 $[M]^+$ (2), 229 (14), 228 (100), 213 (24), 200 (15), 183 (10), 171 (8), 157 (18), 105 (36), 91 (39); HREIMS *m/z* 288.1355 $[M]^+$ (calcd for $C_{15}H_{20}O_4$, 288.1362).

Hedyosumin E (5): colorless, amorphous powder; $[\alpha]^{20}_D$ +19.0 (*c* 0.110, MeOH); UV (MeOH) λ_{max} (log ε) 268 (4.68) nm; IR (KBr) ν_{max} 3440, 2933, 1735, 1682, 1379, 1077, 1039 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 433 $[M + Na]^+$ (100); HRESIMS *m/z* 433.1831 (calcd for $C_{15}H_{20}O_4Na$, 433.1838).

Acidic Hydrolysis of 5. Compound **5** (5 mg) in 5 mL of 2 N HCl was heated at 90 °C on a water bath for 2 h. After workup, the reaction mixture was extracted with $CHCl_3$. The aqueous phase was concentrated under reduced pressure to give a residue, which was purified on a Si gel column eluted with CH_3Cl_3−MeOH−H_2O (7:3:0.5) to afford the sugar (1.5 mg). The sugar was identified as D-glucose by comparison with an authentic sample on TLC and specific rotation ($[\alpha]^{20}_D$ +36.0, *c* 1.0, H_2O).

Cytotoxic Assay. The *in vitro* cytotoxicities against A-549 and HL-60 cell lines were evaluated by using the MTT and SRB methods, respectively, and with pseudolaric acid B (IC_{50} = 0.30 μM against A-549) and etoposide (IC_{50} = 0.20 μM against HL-60) as the positive controls. The tests were performed according to the protocols described in the litrerature.[12]

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Supporting Information Available: IR, MS, and 1D and 2D NMR spectra of **1**−**5** are available free of charge via the Internet at http://pubs.acs.org.

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