Cytotoxic Constituents of the Fruits of *Cananga odorata*

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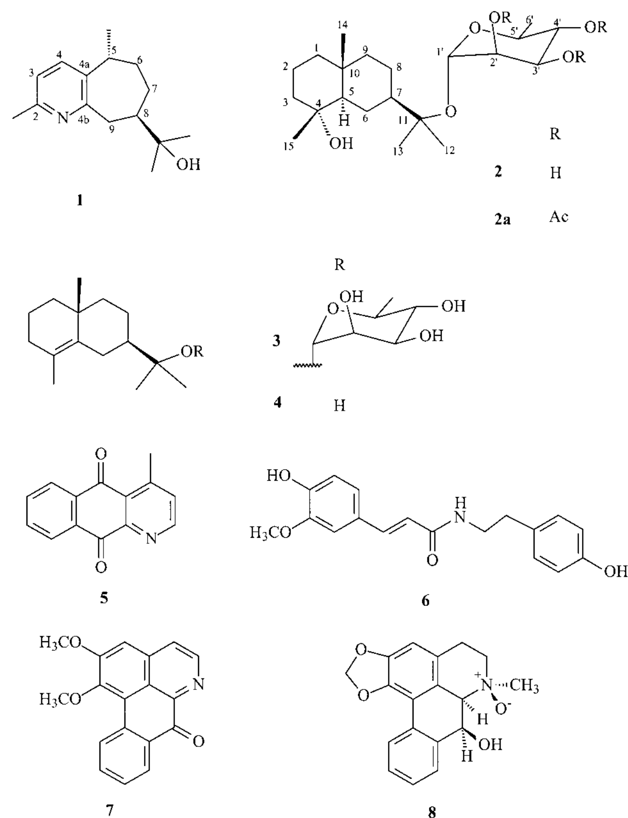
A new guaipyridine sesquiterpene alkaloid, cananodine (**1**), and two new eudesmane sesquiterpenes, cryptomeridiol 11-α-L-rhamnoside (**2**) and γ-eudesmol 11-α-L-rhamnoside (**3**), along with γ-eudesmol (**4**), were isolated from the fruits of *Cananga odorata.* The structures of compounds **1**−**3** were established on the basis of NMR and MS methods. In addition, compounds **1**−**4** and four previously reported alkaloids, cleistopholine (**5**), *N-trans*-feruloyltyramine (**6**), (+)-ushinsunine-β-*N*-oxide (**7**), and lyscamine (**8**), were evaluated for cytotoxicity against two human hepatocarcinoma cell lines.

Cananga odorata Hook. f. & Thomson (Annonaceae) is an evergreen tree distributed in both tropical and subtropical regions. Its trivial name is "Ylang-Ylang", and this species has been used in Taiwanese folk medicine for the treatment of malaria, tinea infections, and fever.[1] Plants of the genus *Cananga* are rich in alkaloids[2−6] and terpenoids.[7,8] Moreover, a series of studies on the microbial transformation of the antifungal alkaloid, sampangine, isolated from *C. odorata*, was reported by Orabi et al.[9−11]

To further understand the chemotaxonomy of the genus *Cananga* and to continue searching for novel bioactive agents from Annonaceous plants,[6] *C. odorata* was chosen for the present phytochemical investigation. In this paper, we report the isolation and characterization of four compounds, including one new guaipyridine sesquiterpene alkaloid, cananodine (**1**), two new eudesmane sesquiterpenes, cryptomeridiol 11-α-L-rhamnoside (**2**) and γ-eudesmol 11-α-L-rhamnoside (**3**), along with one known[12] eudesmane sesquiterpene, γ-eudesmol (**4**), which was isolated for the first time from this plant. The structures of the new compounds **1**−**3** were established on the basis of NMR and MS data interpretation. Furthermore, compounds **1**−**4** and four previously reported alkaloids[6] from this plant, cleistopholine (**5**), *N-trans*-feruloyltyramine (**6**), (+)-ushinsunine-β-*N*-oxide (**7**), and lyscamine (**8**), were evaluated for their cytotoxicity against two human hepatocarcinoma cell lines.



Results and Discussion

Compound **1** was obtained as a yellow oil, positive to Dragendorff's reagent. The HREIMS gave the $[M]^+$ ion at *m*/*z* 233.1775, corresponding to the molecular formula $C_{15}H_{23}NO$. Peaks at *m*/*z* 233 $[M]^+$, 218 $[M - CH_3]^+$, and 200 $[M - CH_3 - H_2O]^+$ in the EIMS suggested the presence of hydroxyl and methyl groups. The UV absorption maxima at 205, 222 (sh), and 270 nm were characteristic of a typical guaipyridine alkaloid.[13] The IR absorptions at 3360, 2950, 1600, and 1470 cm^{-1} also supported the existence of hydroxyl, methylene, and pyridine units, respectively.[14]

The ^1H NMR spectrum of **1** revealed a typical AB pattern for the protons at δ 6.97 and 7.39 (H-3 and H-4), and the methyl group attached to the pyridine nucleus resonated at δ 2.51.[13] In the aliphatic region, **1** also exhibited eight nonequivalent proton signals at δ 1.40−3.32, one methyl at δ 1.32, and two geminal methyls at δ 1.24 (Table 1). Guaipyridine sesquiterpene alkaloids exist as stereoisomeric mixtures with respect to the chiral center C-5, which has been demonstrated clearly in previous studies.[13−15] Because of its negative optical rotation, the stereochemistry of this methyl group was considered to be α, since the isopropyl groups in naturally occurring guaipyridine sesquiterpene alkaloids have had a β-orientation.[13] Unambiguous complete assignments for the ^1H and ^{13}C NMR signals were made by combination of DEPT, $^1H-^1H$ COSY, HETCOR, and NOESY spectra. Furthermore, in the NOESY spectrum (Figure 1) correlations were observed between H-5/H-9β, H-9β/C-8-C(CH_3)$_2$O, C-8-C(CH_3)$_2$O/H-7β, and H-7β/H-5. Therefore, the methyl group at C-5 was confirmed as α, and the isopropyl group at C-8 was determined as being β-oriented. In the ^{13}C NMR spectrum, five signals

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Table 1. ^{1}H NMR (400 MHz, J in Hz) and ^{13}C NMR (100 MHz) Spectral Data of **1** in $CDCl_3$

position	δ_H, mult. (J in Hz)	δ_C, mult.
2		153.8, s
3	6.97, d (8.0)	121.0, d
4	7.39, d (8.0)	133.0, d
5	3.00, m	35.2, d
6α	1.35, m	36.0, t
6β	1.90, m	
7β	1.61, m	32.7, t
7α	2.07, m	
8	1.42, m	47.9, d
9β	2.88, dd (13.2, 6.4)	38.9, t
9α	3.32, d (13.2)	
4a		138.3, s
4b		160.6, s
8-*C*(CH$_3$)$_2$OH		73.2, s
8-C(*CH$_3$*)$_2$OH	1.24, s	27.8, q
	1.24, s	25.7, q
Me-2	2.51, s	23.3, q
Me-5	1.32, d (6.8)	20.6, q

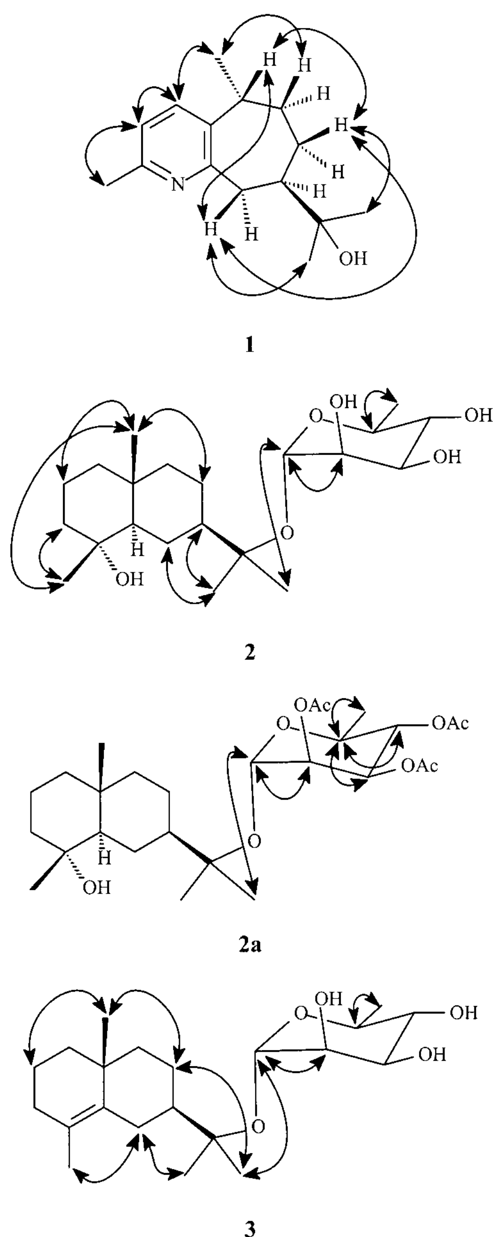

Figure 1. NOESY correlations of **1**, **2**, **2a**, and **3**.

at δ 160.6, 153.8, 138.3, 133.0, and 121.0 and a signal for a methyl group at δ 25.7 revealed the presence of a 2,3-substituted-6-methylpyridine ring (Table 1). The DEPT spectrum also showed four methyls, three methylenes, four methines, and four quaternary carbons, which were consistent with the structure proposed for **1**. From a consideration of all of the above, the structure of **1** was elucidated as 2-(2,5α-dimethyl-6,7,8,9-tetrahydro-5-cyclohepta[*b*]pyridin-8-yl)-β-propan-2-ol, to which the trivial name canano-dine has been assigned.

Compound **2** was isolated as colorless needles (EtOAc). The HRFABMS gave a protonated molecular ion at m/z 387.2730 $[M + H]^+$, corresponding to the molecular formula $C_{21}H_{38}O_6$. The EIMS showed fragments at m/z 223 $[M - \text{rhamnosyl}]^+$ and 205 $[M - \text{rhamnosyl} - H_2O]^+$, which were consistent with data expected of an eudesmane-type sesquiterpene with a rhamnosyl sugar unit.[16−23] The IR spectrum revealed absorptions at 3500 cm^{-1} for hydroxyl groups and 2850 cm^{-1} for aliphatic methylenes. The ^{1}H NMR spectrum displayed five methyl groups at δ 1.22, 1.28, 0.85, 1.31, and 1.63 in the aliphatic region, one sugar anomeric proton at δ 5.53, and four sugar methine proton signals at δ 4.53−4.26. In addition, the ^{13}C and DEPT spectra indicated that **2** contained a sesquiterpene skeleton[16,18,20] and a hexose sugar, leading to a total of 21 carbons, consisting of five methyls at δ 18.6, 18.7, 23.1, 23.7, and 23.8 (including C-6′ of the rhamnosyl), six methylenes at δ 20.7, 22.0, 22.5, 41.7, 43.9, and 44.8, seven methines at δ 49.3, 55.1, 69.6, 72.9, 73.7, 74.2, and 95.6 (including one anomeric and four methine carbons of the rhamnosyl unit), and three quaternary carbons at δ 71.0, 78.1, and 34.6. Additionally, evidence for the structural determination of compound **2** was provided by measuring various 2D NMR spectra. Correlations of H-2 to H-1 and H-3 as well as H-6 to H-5 and H-7 were established from the ^{1}H−^{1}H COSY spectrum. The ^{1}H and ^{13}C NMR data of **2** are shown in Table 2. In the HETCOR spectrum, two methyl signals at δ 1.22 and 1.28 correlated to the ^{13}C NMR resonances at δ 23.8 and 23.7, respectively. In the HMBC spectrum, these two methyl signals displayed ^{2}J correlations to the quaternary carbon at δ 78.1 and ^{3}J coupling to the methine carbon at δ 49.3, which suggested that they should be geminal and helped to confirm their placement in a 2-oxygenated isopropyl group. The anomeric proton at δ 5.53 showed a ^{3}J correlation to C-11 at δ 78.1, which confirmed the ether connection between C-11 and a rhamnosyl group. The Me-14 signal revealed a ^{2}J coupling to C-10 and ^{3}J couplings to the C-1, C-5, and C-9 carbons (Figure 2). The remaining methyl signal at δ 1.31 was assigned to Me-15, which exhibited a ^{2}J coupling to an oxygenated quaternary carbon, C-4, at δ 70.0, and ^{3}J interactions with C-5 at δ 55.1 and C-3 at δ 43.9. The relative stereochemistry was established from a NOESY experiment (Figure 1). In this spectrum, H-5 and H-14 did not show any NOE correlation, supporting a *trans* ring A/B junction.[18] Other NOE correlations were observed between H-12, H-13, and H-1′. Accordingly, the rhamnosyl group had to be connected to C-11. Since H-14 showed a NOE correlation with H-15, it was apparent that these two methyls possess a 1,3-diaxial configuration. The typical coupling constant and chemical shift of H-1′ at δ 5.53 (J = 1.6 Hz) and the ^{1}H and ^{13}C NMR signals (Table 2) of the sugar moiety were in accordance with the presence of an α-L-rhamnosyl group.[21−23] The structure of **2** was further supported by acetylation, which gave the triacetate **2a** (Figures 1 and 2 and Table 2). The ^{13}C NMR value at C-4 of **2a** was the same as that of **2**, which suggested the attachment of a tertiary hydroxyl group at this position.

Table 2. ^{1}H NMR (400 MHz, *J* in Hz) and ^{13}C NMR (100 MHz) Spectral Data of **2**, **2a**, and **3** in C_5D_5N

	δ_H, mult. (*J* in Hz)			δ_C, mult.		
position	**2**	**2a**	**3**	**2**	**2a**	**3**
1	1.06, m	1.05, m	1.14, 1.49, m	41.7, t	41.5, t	42.3, t
2	1.50, m	1.60, m	1.53, m	20.7, t	22.0, t	19.3, t
3	1.04, m	1.10, m	1.93, 1.85, m	43.9, t	44.0, t	33.2, t
4				71.0, s	71.0, s	124.0, s
5	1.49, m	1.42, m		55.1, d	54.9, d	135.5, s
6	2.41, d (12.8)	2.34, d (12.8)	2.64, 1.57, m	22.0, t	22.0, t	26.4, t
7	1.51, m	1.47, m	1.21, m	49.3, d	48.6, d	49.7, d
8	1.56, m	1.60, m	1.56, m	22.5, t	22.5, t	23.1, t
9	1.45, 1.19, m	1.41, 1.09, m	1.44, 1.26, m	44.8, t	44.8, t	40.3, t
10				34.6, s	34.6, s	34.6, s
11				78.1, s	80.4, s	78.1, s
12	1.22, s	1.19, s	1.14, s	23.8, q	23.9, q	22.2, q
13	1.28, s	1.24, s	1.32, s	23.7, q	23.8, q	23.1, q
14	0.85, s	0.94, s	1.01, s	18.6, q	18.8, q	24.5, q
15	1.31, s	1.30, s	1.59, s	23.1, q	23.0, q	19.2, q
1′	5.53, d (1.6)	5.39, d (1.6)	5.52, d (1.6)	95.6, d	92.1, d	95.4, d
2′	4.51, dd (2.8, 1.6)	5.56, m	4.53, m	72.9, d	71.7, d	72.7, d
3′	4.40, dd (10.4, 2.8)	5.55, m	4.46, m	73.7, d	72.6, d	73.5, d
4′	4.24, t (10.4)	5.80, dd (10.4, 3.2)	4.27, t (10.4)	74.2, d	69.9, d	74.0, d
5′	4.36, dq (10.4, 6.0)	4.33, m	4.36, dq (10.4, 6.0)	69.6, d	66.9, d	69.3, d
6′	1.63, d (6.0)	1.32, d (6.0)	1.62, d (6.0)	18.7, q	17.7, q	18.4, q
CH$_3$CO		2.00, s			20.5, q	
CH$_3$CO		2.03, s			20.5, q	
CH$_3$CO		2.04, s			20.6, q	
CH$_3$*CO*					170.2, s	
CH$_3$*CO*					170.3, s	
CH$_3$*CO*					170.5, s	

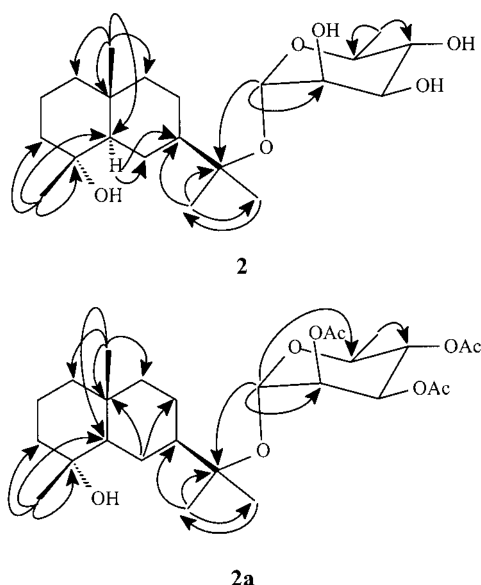

Figure 2. HMBC correlations of **2** and **2a**.

From the analysis of all of these data, the structure of **2** was determined to be cryptomeridiol 11-α-L-rhamnoside.

Compound **3** was isolated as a gum. The HRFABMS gave a protonated molecular ion at *m/z* 391.2518 [M + Na]$^+$, corresponding to the molecular formula $C_{21}H_{36}O_5$. The EIMS showed fragments at *m/z* 205 [M − rhamnosyl]$^+$, consistent with a eudesmane-type sesquiterpene with a single rhamnosyl unit.[20–23] The IR spectrum revealed absorptions at 3401 cm^{-1} for one or more hydroxyl groups. Significant features of the ^{1}H NMR spectrum of **3** included the presence of four singlets together with one doublet (due to the rhamnosyl residue), corresponding to methyl groups in the molecule. The ^{1}H and ^{13}C NMR signals of **3** were similar to those of **2** (Table 2),[12,20] which indicated that **3** is an olefinic derivative of **2** through dehydration. Inspection of the ^{13}C NMR spectrum (Table 2) showed that **3** contains 21 carbon atoms: five methyls at δ 18.4, 19.2, 22.2, 23.1, and 24.5; six methylenes at δ 42.3, 19.3, 33.2, 26.4, 23.1, and 40.3; six methines at δ 49.7, 95.4, 73.5, 74.0, 72.7, and 69.3; and four quaternary carbons at δ 124.0, 135.5, 78.1, and 34.6. Complete assignments and the relative configuration of **3** were established by COSY and NOESY experiments (Figure 1). Compound **3** contains a α-L-rhamnosyl moiety, which also showed a characteristic anomeric proton signal at δ 5.52 (J = 1.6 Hz) and an anomeric ^{13}C NMR signal at δ 95.3, as compared with the NMR data of **2**.[18–21] Consequently, the structure of **3** was elucidated as γ-eudesmol 11-α-L-rhamnoside.

Table 3. In Vitro Cytotoxicity Data of Compounds **1**−**8**

	cell lines^a/IC$_{50}$ (μg/mL)	
compound	Hep G$_2$	Hep 2,2,15
1	0.22	3.8
2	0.01	0.36
3	3.9	10.6
4	1.5	0.01
5	0.22	0.54
6	6.6	1.9
7	6.2	2.4
8	8.4	3.4

^{a} Key to cell lines: Hep G$_2$, human hepatoma cell; Hep 2,2,15, Hep G$_2$ cell line transfected with hepatitis B virus (HBV).

Compound **4** was isolated and characterized as γ-eudesmol by comparing its physical and spectral data ([α]$^{25}_D$, IR, EIMS, ^{1}H and ^{13}C NMR) with those in the literature[12] and was confirmed by DEPT, COSY, NOESY, and HETCOR experiments.

Hepatocarcinoma is one of the most common cancers in Taiwan. Compounds **1**−**8** were evaluated for their cytotoxicity against two hepatocarcinoma cancer cell lines (Hep G$_2$ and 2,2,15), and the results are shown in Table 3. The data show all of the compounds were at least somewhat cytotoxic against the Hep G$_2$ and/or 2,2,15 cell lines. Furthermore, the most active compounds, **1**, **2**, **4**, and **5**, displayed potent cytotoxicity against one or both of these cell lines.

Experimental Section

General Experimental Procedures. Melting points were determined using a Yanagimoto micro-melting point apparatus and are uncorrected. The UV spectra were obtained on a Hitachi 200-20 spectrophotometer, and IR spectra were measured on a Hitachi 260-30 spectrophotometer. ^{1}H (400 MHz, using $CDCl_3$ or C_5D_5N as solvents for measurement), ^{13}C, DEPT, HETCOR, COSY, NOESY, and HMBC NMR spectra were obtained on a Varian NMR spectrometer (Unity Plus). FABMS and EIMS were collected on a JEOL JMS-SX/SX 102A mass spectrometer or a Quattro GC−MS instrument having a direct inlet system. HREIMS and HRFABMS were measured on a JEOL JMS-HX 110 mass spectrometer. Si gel 60 (Merck, 230−400 mesh) was used for column chromatography. Precoated Si gel plates (Merck, Kieselgel 60 F-254, 0.20 mm) were used for analytical TLC, and precoated Si gel plates (Merck, Kieselgel 60 F-254, 0.50 mm) were used for preparative TLC. Spots were detected by spraying with Dragendorff's reagent or 50% H_2SO_4 and then heating on a hot plate.

Plant Material. The fruits of *C. odorata* were collected from Fengshan City, Kaohsiung County, in the southern part of Taiwan, in September 1995. The plant was identified by Dr. Hsin-Fu Yen, and a voucher specimen has been deposited in the Graduate Institute of Natural Products (voucher no. Annona 10), Kaohsiung Medical University, Kaohsiung, Taiwan, Republic of China.

Extraction and Isolation. The fruits of *C. odorata* (3.5 kg) were extracted exhaustively with MeOH at room temperature. The combined MeOH extracts were evaporated under reduced pressure to yield a dark brown syrup (266.7 g). Then, the syrup was partitioned between $CHCl_3$ and water. The $CHCl_3$ solution was extracted with 3% HCl to give a further $CHCl_3$ solution (part A) (80.0 g) and an acidic aqueous layer. The latter was basified with NH_4OH and extracted with $CHCl_3$ (part B) (4.5 g). Part B gave a positive alkaloidal test with Dragendorff's reagent. The crude alkaloid portion (part B) was chromatographed over Si gel and eluted with $CHCl_3$−MeOH mixtures of increasing polarities to obtain 13 fractions. Fraction 5 (1.1 g), eluted with *n*-hexanes−EtOAc (1:1), was further separated and purified by Si gel column chromatography and preparative TLC to give cananodine (**1**) (10 mg) (*n*-hexanes−EtOAc, 1:1, R_f 0.25). The $CHCl_3$ layer (part A) was concentrated and chromatographed over Si gel using *n*-hexane−Me_2CO gradient mixtures as eluents to produce 35 fractions. Fraction 7 (1.4 g), eluted with *n*-hexanes−EtOAc (10:1), was further separated and purified by Si gel column chromatography and preparative TLC to obtain γ-eudesmol (**4**)[12] (5 mg) (*n*-hexanes−EtOAc, 1:1, R_f 0.8). Fraction 12, eluted with *n*-hexanes−EtOAc (1:8), was further separated and purified by Si gel column chromatography to yield γ-eudesmol 11-α-L-rhamnoside (**3**) (12 mg) (EtOAc, R_f 0.70). Cryptomeridiol 11-α-L-rhamnoside (**2**) (960 mg) was recrystallized from fraction 30 to afford colorless crystals (EtOAc, R_f 0.25).

Cananodine (1): yellow oil; $[\alpha]^{25}_D$ −76.2° (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 204 (4.15), 222 (sh, 4.01), 270 (3.92) nm; IR (neat) ν_{max} 3360, 2950, 1600, 1470 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectral data, see Table 1; EIMS *m/z* 233 $[M]^+$ (19), 218 (41), 200 (8), 174 (93), 160 (100), 146 (61), 132 (55), 59 (86); HREIMS *m/z* 233.1775 $[M]^+$ (calcd for $C_{15}H_{23}NO$ 233.1780).

Cryptomeridiol 11-α-L-rhamnoside (2): transparent rectangular crystals (EtOAc); mp 189−190 °C; $[\alpha]^{25}_D$ −13.3° (*c* 0.03, $CHCl_3$); IR (KBr) ν_{max} 3500, 2850, 1450, 1350 cm^{-1}; ^{1}H (C_5D_5N, 400 MHz) and ^{13}C NMR (C_5D_5N, 100 MHz) spectral data, see Table 2; EIMS *m/z* 239 $[M - C_6H_{11}O_4]^+$ (17), 223 $[M - C_6H_{11}O_5]^+$ (19), 205 (63), 149 (60), 123 (46), 85 (90), 71 (100); FABMS *m/z* 409 $[M + Na]^+$ (18), 223 (3), 205 (100), 149 (20), 123 (42), 84 (42), 71 (51); HRFABMS *m/z* 409.2586 $[M + Na]^+$ (calcd for $C_{21}H_{38}O_6Na$ 409.2576), 387.2730 (calcd for $C_{21}H_{39}O_6$ 387.2746).

Acetylation of 2. Compound **2** (10 mg) was dissolved in a mixture of dry pyridine (2 mL) and acetic anhydride (2 mL). The reaction mixture was stirred overnight at room temperature. After aqueous workup, the reaction mixture was extracted with $CHCl_3$ (5 mL × 3), and the $CHCl_3$ extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to yield a triacetate (**2a**): ^{1}H (C_5D_5N, 400 MHz) and ^{13}C NMR (C_5D_5N, 100 MHz) spectral data, see Table 2; EIMS *m/z* 334 (1), 291 (3), 273 (100), 222 (10), 205 (55), 153 (90), 111 (40).

γ-Eudesmol 11-α-L-rhamnoside (3): gum; $[\alpha]^{25}_D$ −11.5° (*c* 0.24, $CHCl_3$); IR (neat) ν_{max} 3401, 2934, 1451, 1350 cm^{-1}; ^{1}H (C_5D_5N, 400 MHz) and ^{13}C NMR (C_5D_5N, 100 MHz) spectral data, see Table 2; EIMS *m/z* 205 (46), 204 (100), 189 (41), 161 (49), 149 (66); FABMS *m/z* 391 $[M + Na]^+$ (26), 219 (14), 205 (71), 149 (100), 123 (55), 95 (68), 73 (79); HRFABMS *m/z* 391.2518 $[M + Na]^+$ (calcd for $C_{21}H_{36}O_5Na$ 391.2516).

Acid Hydrolysis of 3. Glycoside **3** (10 mg) was dissolved in 4 mL of MeOH and refluxed with 1 N HCl (4 mL) at 80 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL), with the EtOAc layer evaporated under reduced pressure. The residue was chromatographed over Si gel and eluted with increasing polarities of *n*-hexane/EtOAc to yield **4**. The water phase was neutralized with saturated aqueous $NaHCO_3$ solution, and the precipitate was filtered off. The filtrate was concentrated to dryness under reduced pressure to give 3 mg of L-rhamnose, which was identified by ^{1}H NMR comparison with the previous literature data[21−23] and with an authentic sample.

Cytotoxicity Assay. The cytotoxicity assay was carried out according to the literature.[24,25]

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