Antitumor Agents, 127. Bruceoside C, a New Cytotoxic Quassinoid Glucoside, and Related Compounds from Brucea javanica

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ANTITUMOR AGENTS, 127.[1] BRUCEOSIDE C, A NEW CYTOTOXIC QUASSINOID GLUCOSIDE, AND RELATED COMPOUNDS FROM *BRUCEA JAVANICA*

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ABSTRACT.—Bruceoside C [**5**], a new quassinoid glucoside, and related compounds were isolated from *Brucea javanica*, and their structures were elucidated by spectral data. Bruceoside C showed potent cytotoxicities against KB, A-549, RPMI, and TE-671 tumor cells.

Following the isolation of the first two antileukemic quassinoid glucosides, bruceoside A and bruceoside B, as well as brusatol and cleomiscosin A from *Brucea javanica* (L.) Merr. (Simaroubaceae) ("Ya-Tan-Tzu") by Lee and co-workers (1–3), Takahashi and co-workers (4–11) reported the isolation of 16 quassinoid glucosides from this same plant. As a result of our investigations for plant-derived agents selectively cytotoxic against slow-growing solid tumors, we report herein the isolation of bruceoside C [**5**], a new cytotoxic quassinoid glucoside, from *B. javanica*. Compound **5** was isolated along with known compounds including bruceoside A [**1**], yadanzioside A [**2**], yadanzioside G [**3**], brucein E [**4**], bruceoside B [**6**], yadanzioside C [**7**], yadanzioside B [**8**], yadanzioside F [**9**], and yadanzioside L [**10**] in this study.

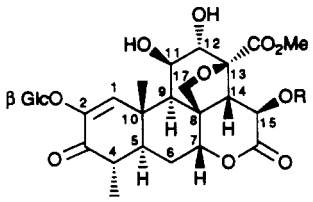
RESULTS AND DISCUSSION

Bruceoside C [**5**] was obtained as an amorphous solid. Its ir spectrum showed the presence of a hydroxy group (3400 cm^{-1}), a δ-lactone and an ester group (1740 cm^{-1}), and an α,β-unsaturated carbonyl group (1680 and 1650 cm^{-1}). The uv spectrum of **5** exhibited maximum absorption at 252 nm due to a conjugated enone system. The fdms spectrum of **5** showed pseudo-molecular ion peaks at *m/z* 721 $[M+K]^+$ and 705 $[M+Na]^+$, indicating the molecular formula to be $C_{32}H_{42}O_{16}$ (MW 682) which coincided with that of **6**. The hrsims spectrum of **5** showed the molecular formula of **5** to be $C_{32}H_{42}O_{16}$. Additionally, the aglycone **11** obtained by acid hydrolysis of **5** had a molecular formula $C_{26}H_{32}O_{11}$ as determined by hreims (found *m/z* 520.1953 $[M]^+$, calcd for $C_{26}H_{32}O_{11}$, 520.1943); it also coincided with that of **12**.

The ^1H- and ^{13}C-nmr spectra of **5** were closely similar to those of bruceoside B [**6**] except for a singlet signal that appeared at δ 2.52 in **5** and at δ 2.05 in **6**. Retention times (hplc) of **5** and **6** were also different from each other. Aglycones **11** and **12**, which were obtained by acid hydrolysis of **5** and **6**, respectively, also differed in retention time.

^1H-nmr (Table 1) and ^{13}C-nmr (Table 2) assignments for **5** were based on COSY,

[1]For part 126, see Z.Q. Wang, Y.C. Shen, H.X. Chen, J.Y. Hang, F.S. Han, Y.C. Cheng, and K.H. Lee, *J. Med. Chem.*, (in press).



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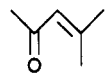

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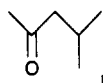

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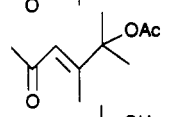

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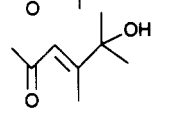

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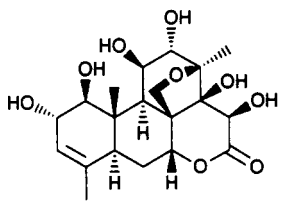

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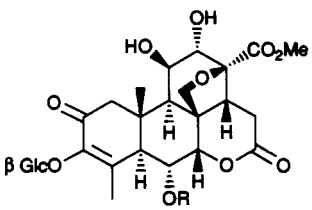

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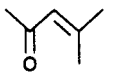

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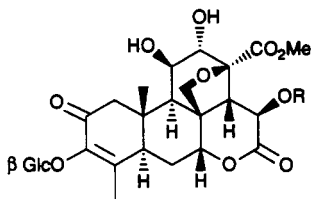

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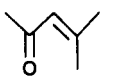

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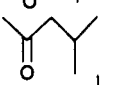

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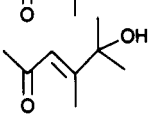


HETCOR, ROESY, and HMBC spectra. The ^{1}H-nmr spectrum of **5** disclosed the presence of a senecioyl [δ 1.59 (Me-5′), 2.12 (Me-4′), and 5.68 (H-2′)], a carbomethoxy (δ 3.65), and two methyl groups [δ 1.80 (10-Me) and 2.52 (4-Me)]. The ^{13}C-nmr spectra of **5** indicated the presence of a senecioyl group [δ 116.0 (C-2′), 158.6 (C-3′), 27.0 (C-5′), and 20.1 (C-4′)] and a β-D-glucose moiety [δ 105.1 (C-1″), 76.3 (C-2″), 78.2 (C-3″), 71.0 (C-4″), 77.9 (C-5″), and 62.2 (C-6″)]. The D-glucose moiety was also identified by gc analysis of the TMSi derivative of the hydrolyzed product by comparison with an authentic sample.

The linkage position of the sugar moiety was established by inspection of ^{1}H-nmr spectra of **5** and **11** and by long-range ^{1}H-^{13}C correlation spectroscopy of **5** as follows: In the ^{1}H-nmr spectrum of **11**, the methyl proton signal (δ 2.35) assigned to 4-Me (H-18) was shifted to higher field than that (δ 2.52) of **5**. Moreover, the HMBC spectra of **5** showed a long-range correlation peak between the anomeric proton at δ 5.44 (d, J = 7.5 Hz) and the C-3 carbon at δ 148.0. Thus, the β-D-glucose moiety was attached to the C-3 hydroxy group of **11**.

The partial structure of ring A was elucidated by the following observations. In the HMBC spectra of **5**, the proton at δ 2.56 (H-1β) showed long-range ^{1}H-^{13}C correlations with the carbonyl carbon at δ 194.1 (C-2), the olefinic carbon at δ 148.0 (C-3), the quarternary carbon at δ 39.7 (C-10), and the carbon at δ 48.1 (C-5). Additionally, long-range ^{1}H-^{13}C correlations were observed between H-1α at δ 3.35 and C-2 at δ 194.1, and between 10-Me (H-19) at δ 1.80 and C-1 at δ 51.0. These observations suggested that the structure of ring A of **5** was similar to that of **6** which had a 3-en-2-one moiety and a methylene group at C-1.

TABLE 1. ^{1}H-nmr Spectra of Compounds **5**, **6**, and **11–14**.[a]

Proton	Compound					
	5[b]	**6**[b]	**11**[b]	**12**[b]	**13**[c]	**14**[d]
H-1α	3.35 d (16)	3.35 d (16)	3.39 d (16)	3.32 d (16)	4.35 s	3.99 s
H-1β	2.56 d (16)	2.48 d (16)	2.53 d (16)	2.58 d (16)	—	—
H-6α	—	2.28 brd (16)	—	[e]	—	—
H-6β	5.18 brs	1.66 m	5.26 brs	[e]	4.24 dd (11.5, 1.5)	4.21 dd (11, 3.9)
H-7	4.98 brs	5.04 m	5.10 brs	4.84 brs	5.70 d (1.5)	4.12 d (3.9)
H-9	3.02 brs	[e]	3.10 brs	[e]	3.00 brs	2.05 d (2.0)
H-11	4.92 brs	4.80 brs	4.88 brd (5)	[e]	5.48 brs	4.95 dd (2.0, 3.0)
H-14	2.50 m	[e]	[e]	[e]	[e]	[e]
H-15α	2.18 m	6.60 brs	[e]	[e]	6.21 brs	—
H-15β	2.49 m	—	[e]	—	—	—
H-17α	3.86 d (7.5)	3.92 d (8)	[e]	[e]	—	—
H-17β	5.10 d (7.5)	5.08 brs	[e]	[e]	—	—
4-Me	2.52 s	2.05 s	2.35 s	1.99 s	2.51 brs	2.28 brs
10-Me	1.80 s	1.72 s	1.86 s	1.66 s	1.62 s	1.09 s
13-COOMe	3.65 s	3.78 s	3.67 s	3.79 s	—	—
H-2′	5.68 s	5.90 s	5.73 brs	5.90 s	—	—
Me-4′	2.12 s	2.16 s	2.11 s	2.17 s	—	—
Me-5′	1.59 s	1.66 s	1.60 s	1.65 s	—	—
H-1″	5.44 d (7.5)	5.48 d (7)	—	—	—	—

[a]Coupling constants in Hz in parentheses.
[b]Measured at 500 MHz in C_5D_5N.
[c]Measured at 500 MHz in CD_3OD. Data in this column are from Yoshimura *et al.* (5).
[d]Measured at 400 MHz in C_5D_5N. Data in this column are from Morita *et al.* (12).
[e]Not assignable.

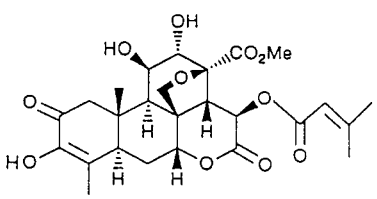
The partial structure of the δ-lactone moiety (ring D) of **5** was elucidated by the following arguments. The signal at δ 4.98 was assigned as H-7 by comparing the ^{1}H-nmr data of **5** with those of **6**. In the HMBC spectrum of **5**, the proton signal of H-7 showed long-range ^{1}H-^{13}C correlations with C-8 (δ 46.3) and C-14 (δ 42.5). The methylene proton signals that appeared at δ 2.18 (H-15α) and δ 2.49 (H-15β) showed long-range ^{1}H-^{13}C correlations with a lactone carbonyl carbon signal at δ 167.2 (C-16). Moreover, the H-15β proton signal showed long-range ^{1}H-^{13}C correlations with the C-8 signal at δ 46.3 and the C-13 signal at δ 82.8. The signals at δ 5.18 (H-6), 3.86 (H-17α), 5.10 (H-17β), and 2.50 (H-14) exhibited long-range ^{1}H-^{13}C correlations with a signal at δ 83.2 attributed to C-7. In the ROESY spectra of **5**, nOe's between H-7 and H-15β and between H-7 and H-17β indicated that H-7, H-15β, and H-17β have cis configuration. These observations indicated that the δ-lactone moiety of **5** was not substituted at C-15; this situation is different from most other quassinoids isolated from this plant, which bear an ester side chain at C-15.

The partial structure of the ring B moiety of **5** was elucidated based on the following evidence. In the ^{1}H-nmr spectra of **5**, a signal at δ 2.52 due to 4-Me (H-18) was shifted to a lower field than that (δ 2.05) of **6** by 0.47 ppm. Similarly, in the ^{1}H-nmr spectrum of the aglycone **11**, a singlet at δ 2.35 attributed to 4-Me (H-18) was shifted to lower field than that (δ 1.99) of **12** by 0.36 ppm. On the other hand, the ^{1}H-nmr data of **13** (5) and **14** (12), which both have a hydroxy group at C-6, indicated that the 4-Me (H-18) resonates at δ 2.51 in **13** and at δ 2.28 in **14**, respectively. Chemical shifts of the 4-Me (H-18) of **13** and **14** were close to those of **5**. These data suggested that ring B of **5** was different from that of **6**. In the HMBC spectrum of **5**, a proton signal at δ 5.18 attributed to H-6 showed long-range ^{1}H-^{13}C correlations with C-7 at δ 83.2 and C-5 at δ 48.1. In the ROESY spectra of **5**, nOe enhancements between H-6 at δ 5.18 and H-7 at δ 4.98 and between H-6 at δ 5.18 and H-17β at δ 5.10 demonstrat-

TABLE 2. ^{13}C-nmr Spectra of Compounds **5**, **6**, and **14**.

Carbon	Compound		
	5[a]	**6**[a]	**14**[b]
C-1	51.0	51.2	83.6
C-2	194.1	193.8	201.2
C-3	148.0	148.2	127.4
C-4	146.8	146.7	167.7
C-5	48.1	43.4	51.6
C-6	78.8	29.4	66.0
C-7	83.2	83.5	88.1
C-8	46.3	46.1	44.2
C-9	[c]	42.1	42.9
C-10	39.7	41.0	50.9
C-11	73.3	73.2	73.7
C-12	75.6	76.2	76.2
C-13	82.8	82.8	28.2
C-14	42.5	[c]	57.1
C-15	27.7	68.4	178.9
C-16	167.2	168.5	—
C-17	73.3	73.7	25.3
C-18	16.8	15.4	21.3
C-19	26.5	16.0	12.7
C-20	170.9	171.4	14.8
20-OMe	52.4	52.4	—
C-1′	[c]	165.4	—
C-2′	116.0	116.0	—
C-3′	158.6	158.7	—
C-4′	20.1	20.3	—
C-5′	27.0	27.1	—
C-1″	105.1	105.0	—
C-2″	76.3	75.9	—
C-3″	78.2	78.8	—
C-4″	71.0	71.6	—
C-5″	77.9	78.6	—
C-6″	62.2	62.8	—

[a]Measured at 125.7 MHz in C_5D_5N.
[b]Measured at 100 MHz in CD_3OD. Data in this column are from Morita *et al.* (12).
[c]Not assignable.



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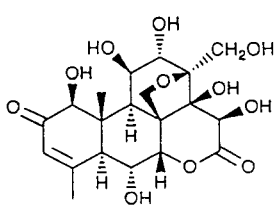

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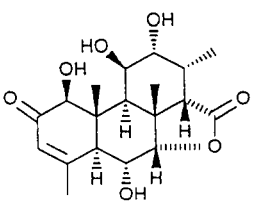

14

ed that H-7 had a cis configuration to H-6. These observations suggested that a senecioyloxy group was attached at the C-6 position and that H-6 was cis to H-7.

The long-range ^{1}H-^{13}C correlations obtained from the HMBC spectrum of **5** are depicted by arrows in Figure 1.

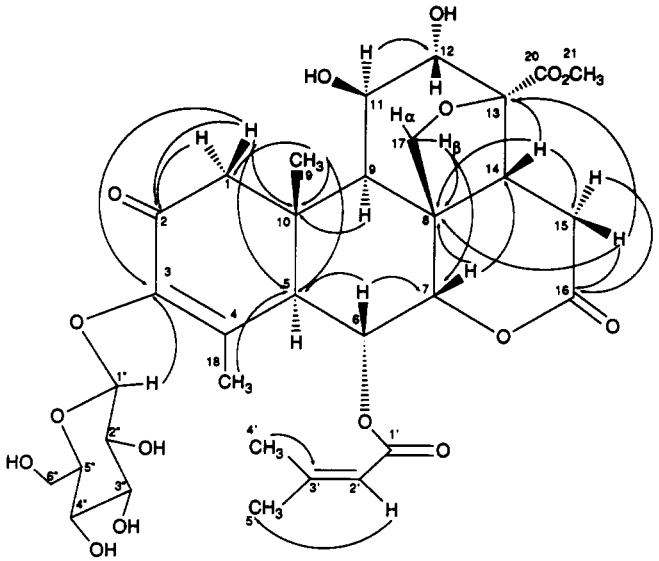

FIGURE 1. CH long-range correlations in the HMBC spectrum ($J = 8$ Hz) of **5**).

The relative stereochemistry of **5** was confirmed by the ROESY spectra. In addition to nOe enhancements mentioned above, nOe's between H-1α at δ 3.35 and H-11 at δ 4.92 and between H-9 at δ 3.02 and H-11 at δ 4.92 were observed. All results of the nOe enhancement of **5** are shown in Figure 2.

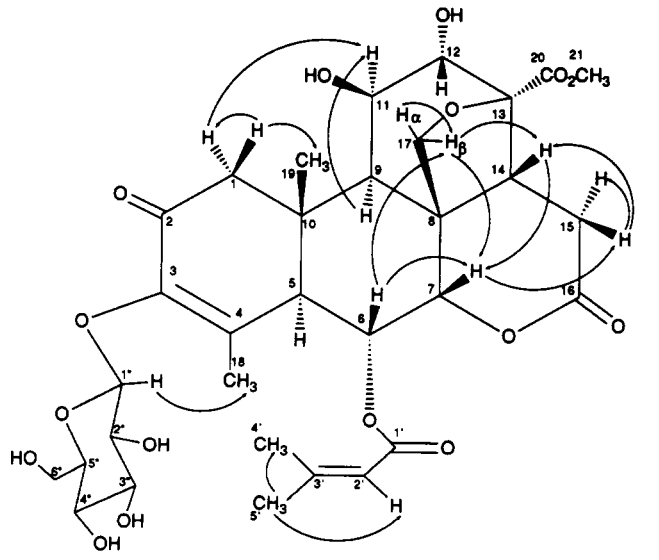

FIGURE 2. NOe correlation of **5**.

On the basis of the evidence discussed above, the structure of bruceoside C was proposed to be that of formula **5**.

Compound **5** demonstrated potent cytotoxicities against human epidermoid carcinoma of the nasopharynx (KB) ($ED_{50} < 0.1$ μg/ml), human lung carcinoma (A-549) ($ED_{50} = 0.44$ μg/ml), colon carcinoma (HCT-8) ($ED_{50} = 4.51$ μg/ml), melanoma (RPMI) ($ED_{50} < 0.1$ μg/ml), and CNS carcinoma (TE-671) ($ED_{50} = 0.29$ μg/ml), as well as murine lymphocytic leukemia (P-388) ($ED_{50} = 5.11$ μg/ml).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on an MRK air-bath type melting point apparatus and were uncorrected. Specific rotations were obtained on a YANAKO OR-50D polarimeter (L = 0.1 dm). Ir and uv spectra were recorded on a JASCO IR-810 spectrometer and a Hitachi 320-S spectrometer, respectively. Nmr (^1H, ^{13}C, COSY, ROESY, HETCOR, and HMBC) were recorded on a Varian UXR-500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C) using TMS as an internal standard. Mass spectra (eims, cims, fdms, hreims) were recorded on a Hitachi M-80 spectrometer, and the hrsims spectrum of **5** was taken on a Hitachi M-2500 instrument. Si gel (Merck, type 60, 70–230 mesh) was used for cc. Precoated Si gel plates (Merck $60F_{254}$) of 0.25 mm thickness were used for analytical tlc and plates of 1 mm and 2 mm thickness were used for preparative tlc. A mixed solvent of $CHCl_3$-MeOH-H_2O (50:14:3) (lower layer) was used both for analytical and preparative tlc. The detection of components was made by use of an uv lamp. Analytical hplc was performed on a Waters Associates liquid chromatograph (pump 6000A, uv monitor 441 set at 254 nm) equipped with a reversed-phase column (M&S PACK C18-A and/or TSK-gel ODS-80TM), using a mixed solvent of MeOH/H_2O. Preparative hplc was carried out on the same system using a DYNAMAX-60A (reversed-phase column). Gc was performed on a Shimadzu GC-mini II gas chromatograph.

PLANT MATERIAL.—The fruit of *B. javanica* was procured and identified by C.H. Huang. A voucher specimen is available for inspection at the Herbarium of the School of Pharmacy, Kaohsiung Medical College, Kaohsiung, Taiwan.

EXTRACTION AND PARTITION OF CONSTITUENTS FROM THE FRUIT OF *B. JAVANICA*.—The fruit (45.5 kg) of *B. javanica* was ground and extracted with hot EtOH. The EtOH solution was concentrated to give a syrup, which was partitioned between H_2O and hexane. The hexane solution was evaporated to afford a hexane extract (6.86 kg) as a brown viscous oil. The aqueous solution was extracted successively with $CHCl_3$ and then *n*-BuOH. The $CHCl_3$ and *n*-BuOH solutions were concentrated to dryness to give a $CHCl_3$ extract (992 g) as a brown gum and an *n*-BuOH extract (1.45 kg) as a brown resin.

COLUMN CHROMATOGRAPHY OF THE *n*-BuOH EXTRACT.—A part (445 g) of the *n*-BuOH extract was subjected to Si gel cc using EtOAc-Et_2O (1:1) to give 4 fractions, then $CHCl_3$-MeOH-H_2O (50:14:3) to yield 11 fractions, and finally MeOH to afford one fraction. From the analytical tlc and ir spectra of each fraction, quassinoid glycosides were assumed to be in the 11 fractions obtained using $CHCl_3$/MeOH/H_2O as the eluent. The yields of the fractions 1–11 were as follows: 2.93 g, 2.93 g, 3.46 g, 2.46 g, 5.91 g, 4.41 g, 10.62 g, 21.44 g, 67.9 g, 18.75 g, 9.35 g (total 148 g, 33%).

ISOLATION OF COMPOUNDS **1–3**.—A part (2.36 g) of fractions 5–9 (which contained three major components) was subjected to preparative tlc followed by repeated preparative hplc [M&S PACK C18-A, MeOH-H_2O (1:1)] to afford compounds **1** (66.1 mg, 0.00472%), **2** (37.1 mg, 0.00265%), and **3** (32.0 mg, 0.00229%) as colorless amorphous solids. Compounds **1**, **2**, and **3** were identified as bruceoside A, yadanzioside A, and yadanzioside G, respectively, by comparing their spectral data with those of the known compounds (1,8).

ISOLATION OF COMPOUNDS **4–7**.—A part (5.25 g) of fraction 8 was subjected to preparative tlc followed by repeated preparative hplc [DYNAMAX-60A, MeOH-H_2O (1:1 then 2:3)] to give four crude compounds **4** (542 mg), **5** (115 mg), **6** (107 mg), and **7** (178 mg). Compound **4** was purified by recrystallization to yield pure brucein E (256 mg, 0.0183%). Compounds **5**, **6**, and **7** were purified by repeated preparative hplc [DYNAMAX-60A, MeOH-H_2O (2:3)] to afford pure compounds **5** (46 mg, 0.00329%), **6** (64 mg, 0.00457%), and **7** (76 mg, 0.00543%), respectively, as colorless amorphous solids. Compounds **4**, **6**, and **7** were identified as brucein E, bruceoside B, and yadanzioside B, respectively, by comparing their spectral data with those of the known compounds (1,8).

Compound **5**.—Colorless amorphous solid; mp 174–178°; $[\alpha]^{21}D$ −27.0° (*c* = 0.24, EtOH); uv λ max (EtOH) 252 (ε 7950) nm; ir (KBr) 3400 (OH), 1740 (δ-lactone and ester C=O), 1680 (α,β-unsaturated C=O), 1650 (C=C) cm^{-1}; ^1H nmr see Table 1; ^{13}C nmr see Table 2; HMBC see Figure 1; nOe see

Figure 2; fdms *m/z* $[M+K]^+$ 721, $[M+Na]^+$ 705. Hrsims found *m/z* $[M+H]^+$ 683.2563; calcd for $C_{32}H_{43}O_{16}$, 683.2551.

ISOLATION OF COMPOUNDS **8**, **9**, AND **10**.—For the isolation of more polar compounds, a part (9.2 g) of fraction 8 was subjected to preparative tlc followed by preparative hplc [DYNAMAX-60A, MeOH-H_2O (1:1)] to afford three crude compounds **8** (132 mg), **9** (332 mg), and **10** (506 mg). These compounds were purified by repeated preparative hplc [DYNAMAX-60A, MeOH-H_2O (1:2)] to furnish pure compounds **8** (25 mg, 0.00179%), **9** (44 mg, 0.00314%), and **10** (33 mg, 0.00236%), respectively, as colorless amorphous solids. Compounds **8**, **9**, and **10** were identified as yadanzioside B, yadanzioside F, and yadanzioside L, respectively, by comparing their spectral data with those of the known compounds (5,8).

ACID HYDROLYSIS OF COMPOUND **5**.—Compound **5** (4.8 mg, 0.007 mM) was dissolved in MeOH (1.0 ml), and 0.15 M H_2SO_4 (0.5 ml) was added dropwise to the solution while stirring at room temperature. The mixture was refluxed in an oil bath (80°) for 4 h. After reaction, the product was partitioned between H_2O and $CHCl_3$, and the $CHCl_3$ solution was washed with H_2O, dried over $MgSO_4$, and evaporated to give aglycone **11** as a colorless amorphous solid (2.4 mg, 65.5%). A sugar moiety was obtained from the H_2O layer as a colorless amorphous solid (1.6 mg) after neutralization using anion exchange resin (Amberlite IRA-400), evaporation, and drying on P_2O_5 in a desiccator. The sugar was treated with 1-(trimethylsilyl)imidazole at 90° for 1 h, and H_2O was added to the reaction mixture to decompose excess reagent. The reaction product was extracted with hexane, and the hexane solution was washed with H_2O. The hexane solution was subjected to gc for identification of the sugar moiety. The TMSi derivative showed two peaks (Rt 12.5 and 21.2 min) on gc (OV-17, 2%, i.d. 2.6 mm, length 1.4 m, 140°, N_2 40 ml/min) which were identified as the derivatives of α- and β-D-glucose by a comparison of the retention times with those of an authentic sample.

COMPOUND **11** (AGLYCONE OF **5**).—Colorless amorphous solid; mp 153–156°; ir (KBr) 3430 (OH), 1735 (δ-lactone and ester C=O), 1682 (α,β-unsaturated C=O) cm^{-1}; ^{1}H-nmr see Table 1. Hreims found *m/z* $[M]^+$ 520.1953; calcd for $C_{26}H_{32}O_{11}$, 520.1943.

BIOLOGICAL ASSAY.—The in vitro cytotoxicity assays were carried out according to procedures described in Geran *et al.* (13) and Ferguson *et al.* (14). The assays against KB (nasal pharyngeal carcinoma), TE-671 (human medulloblastoma), A-549 (human lung carcinoma), HCT-8 (human colon carcinoma), RPMI (human melanoma), and P-388 (murine leukemia) tumor cells were based on a method reported by Lee *et al.* (15).

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