Cytotoxic Prenylated Xanthones and the Unusual Compounds Anthraquinobenzophenones from *Cratoxylum sumatranum*[1]

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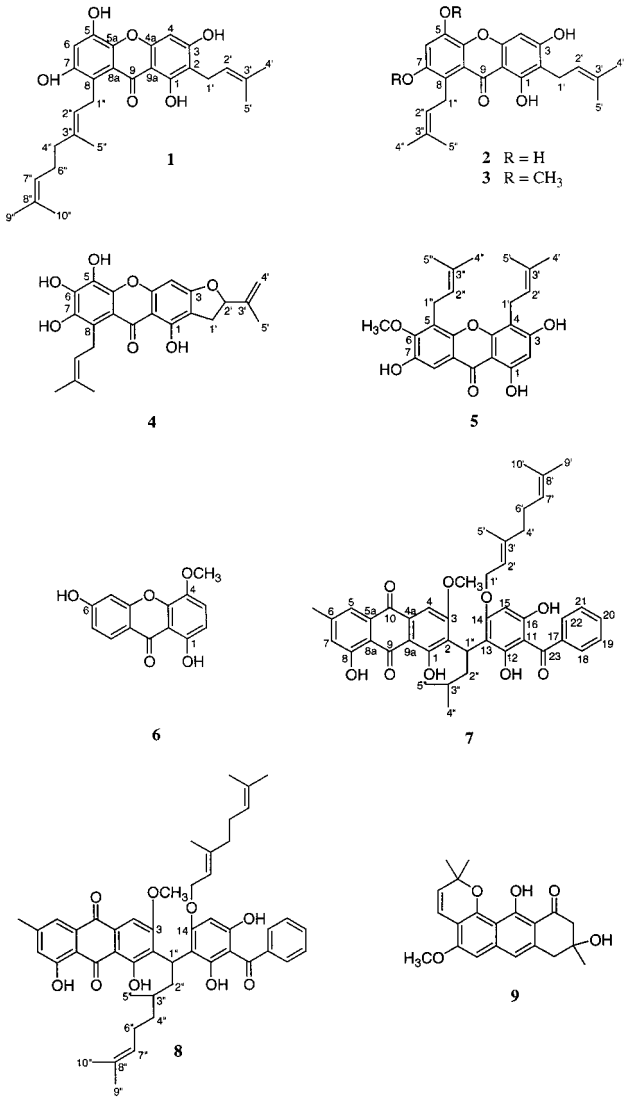
Six new xanthones, cratoxyarborenones A−F (**1**−**6**), were isolated from the leaves, twigs, and/or stem bark of *Cratoxylum sumatranum* along with the known compound, vismione B (**9**), as active constituents by bioassay-directed fractionation using the KB human cancer cell line cytotoxicity assay. In addition, two novel anthraquinobenzophenones, cratoxyarborequinones A (**7**) and B (**8**), and two known compounds, 2,4,6-trihydroxybenzophenone 4-*O*-geranyl ether and *δ*-tocotrienol, were obtained as inactive constituents.

During the course of an ongoing collaborative research program on the investigation of the plant kingdom for novel potential antitumor agents, it was found that separate chloroform-soluble fractions obtained from the leaves, twigs, and stem bark of *Cratoxylum sumatranum* Blume[2] collected in Indonesia showed considerable activity in our standard KB cytotoxicity assay. *Cratoxylum* belongs to the family Guttiferae, with at least six species of this genus distributed in several Southeast Asian countries.[3] Species of this genus have been used for their diuretic, stomachic, and tonic effects,[4] as well as for diarrhea and flatulence,[5] and for food poisoning and internal bleeding.[6] Several secondary metabolites such as xanthones,[3,4,7−9] triterpenoids,[8,10] and flavonoids[4] have been reported from various *Cratoxylum* species. However, we have been unable to find any phytochemical or biological reports dealing specifically with *C. sumatranum*. In the present investigation, separate bioassay-guided fractionation procedures on the leaves, twigs, and stem bark of *C. sumatranum* collected in Indonesia using the KB cell cytotoxicity led to the isolation of six new xanthones, namely, cratoxyarborenones A−F (**1**−**6**). In addition, two novel anthraquinobenzophenones, cratoxyarborequinones A (**7**) and B (**8**), and four known compounds, vismione B (**9**),[11] 2,4,6-trihydroxybenzophenone 4-*O*-geranyl ether,[12] *δ*-tocotrienol,[13] and betulinic acid,[14] were also isolated. The structural characterization and the cytotoxic evaluation of these compounds against KB cells are discussed herein.



Results and Discussion

Compound **1** gave a molecular ion peak at *m*/*z* 464.2207 in its HREIMS, corresponding to the elemental formula $C_{28}H_{32}O_6$. The IR spectrum showed an absorption band at 3308 cm^{-1} for one or more hydroxyl groups and at 1610

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cm^{-1} for a conjugated carbonyl functionality which also appeared at δ_C 183.1 (C-9) in the ^{13}C NMR spectrum of **1**. This carbonyl group formed a hydrogen bond with a hydroxyl group, as evidenced by a proton signal at δ_H 13.94 (OH-1). Two aromatic proton signals were observed at δ_H 6.37 (H-4) and 6.80 (H-6), and six oxygenated aromatic carbon signals appeared at δ_C 161.7 (C-1), 162.6 (C-3), 153.5 (C-5), 155.7 (C-4a), 141.5 (C-7), and 152.2 (C-5a). These results indicated that **1** has a xanthone skeleton, which has been found to occur in compounds in other genera in the family Guttiferae including *Cratoxylum*.[3,4,7,9,10,15] The UV spectrum was also typical of the xanthone nucleus of compound **1**.[16] Signals at δ_H 3.34/δ_C 22.0 (C-1′), 5.27/123.5 (C-2′), 1.64/25.9 (C-4′), 1.77/17.9 (C-5′), and δ_C 131.3 (C-3′) were found to be due to the presence of a prenyl group, by comparison of the NMR data with literature values.[9] A geranyl group appeared at δ_H 4.20/δ_C 26.3 (C-1″), 5.33/124.4 (C-2″), 1.95/40.6 (C-4″), 1.85/16.6 (C-5″), 2.04/27.4 (C-6″), 5.04/125.2 (C-7″), 1.55/25.7 (C-9″), 1.52/17.7 (C-10″), δ_C 135.0 (C-3″), and 131.5 (C-8″). A HMBC NMR experiment was employed to determine the positions of these two side chains in compound **1**. The prenyl group was assigned to C-2 based on the HMBC correlations of H-1′/C-2 (two-bond), H-1′/C-1 (three-bond), and H-1′/C-3 (three-bond). In turn, the geranyl group was located at C-8 by the HMBC correlations of H-1″/C-8, H-1″/C-8a, and H-1″/C-7. In the ^1H NMR spectrum of **1**, the signal for H-1″ of this geranyl group appears further downfield (δ_H 4.20) than the usual values for this functionality.[17,18] This can be explained from the fact that H-1″ is in a region deshielded by the carbonyl group, which is consistent with the assigned position (C-8) of the geranyl group identified by HMBC correlations. Thus, structure **1** was assigned to the new compound cratoxyarborenone A (1,3,5,7-tetrahydroxy-2-isoprenyl-8-geranylxanthone).

Compound **2** was deduced to have an elemental formula of $C_{23}H_{24}O_6$ by HREIMS, which showed a molecular ion peak at *m/z* 396.1576. The IR spectrum showed an absorption band at 3244 cm^{-1} for one or more hydroxyl groups and 1640 cm^{-1} for a conjugated carbonyl functionality. The UV and ^1H and ^{13}C NMR spectra indicated the presence of a xanthone skeleton as in **1**. The ^1H and ^{13}C NMR spectra of **2** were similar to those of compound **1** except for the presence of signals for a prenyl group at δ_H 4.19/δ_C 26.3 (C-1″), 5.32/124.4 (C-2″), 1.65/25.9 (C-4″), 1.84/18.3 (C-5″), and δ_C 131.3 (C-3″) instead of signals for the geranyl group of **1**. The HMBC experiment was used to confirm the positions of attachment of the prenyl groups in **2**. One prenyl group was assigned to C-2 by a two-bond correlation of H-1′/C-2 and three-bond connectivities of H-1′/C-1 and H-1′/C-3. The second prenyl group was positioned at C-8, as evidenced by correlations of H-1″/C-8 (two-bond), H-1″/C-7 (three-bond), and H-1″/C-8a (three-bond). A proton signal for H-1″ appeared at δ_H 4.19, which is a more deshielded value than usually found for this functionality, due to the carbonyl group effect described for compound **1**,[17] and thus provided further evidence for the position of the prenyl group at C-8. Therefore, the structure for the compound **2** was assigned as a new prenylated xanthone, cratoxyarborenone B (1,3,5,7-tetrahydroxy-2,8-diisoprenylxanthone).

Compound **3** demonstrated a molecular ion peak at *m/z* 424.1881 in the HREIMS, corresponding to an elemental formula $C_{25}H_{28}O_6$. The IR spectrum showed absorption bands at 3232 cm^{-1} for one or more hydroxyl groups and at 1605 cm^{-1} for a conjugated carbonyl functionality. Compound **3** exhibited UV and ^1H and ^{13}C NMR spectra similar to those of compound **2**, indicating the presence of a xanthone skeleton. Additional signals for two methoxyl groups were found in the NMR spectrum of compound **3** compared to compound **2**, for which the ^1H NMR signals at δ_H 3.95 and 3.80 each integrated as three protons and showed cross-peaks with the ^{13}C NMR signals at δ_C 56.0 and 60.9, respectively, in the $^1H-^{13}C$ HMQC spectrum. The methoxyl group at δ_H 3.80 was assigned to C-7 from the HMBC correlations of H-6/C-7,C-8, H-1″/C-7,C-8,C-8a, and OCH_3-7/C-7. Another methoxyl group signal at δ_H 3.95 was positioned at C-5 by two-bond HMBC connectivities of H-6/C-5 and OCH_3-5/C-5. Two prenyl groups in the structure of **3** were assigned to C-2 and C-8 in a manner similar to compounds **1** and **2**. Accordingly, structure **3** was assigned to the new compound cratoxyarborenone C (1,3-dihydroxy-5,7-dimethoxy-2,8-diisoprenylxanthone).

Compound **4** was deduced as having an elemental formula of $C_{23}H_{22}O_7$ from its positive HRFABMS, which showed a molecular ion peak $[M + H]^+$ at *m/z* 411.1441. The IR spectrum showed an absorption band at 3335 cm^{-1} for one or more hydroxyl groups and 1615 cm^{-1} for a conjugated carbonyl functionality. The UV and ^1H and ^{13}C NMR spectra of **4** were compared to those of compounds **1**−**3** and found to have a xanthone skeleton similar to compound **2**. Signals appeared at δ_H 4.17/δ_C 26.4 (C-1″), 5.31/124.5 (C-2″), 1.63/25.0 (C-4″), 1.83/18.4 (C-5″), and 131.3 (C-3″) and indicated the presence of a prenyl group attached at C-8 in **4**, as also observed in compounds **2** and **3**. The ^1H and ^{13}C NMR spectra of **4** displayed signals at δ_H 3.07, 2.88/δ_C 30.6 (C-1′), 4.40/76.7 (C-2′), 4.94, 4.76/108.6 (C-4′), 1.83/18.3 (C-5′), and 148.3 (C-3′) for a dihydrofuran ring with an isopropenyl group. This dihydrofuran ring was positioned at C-2 and C-3 by HMBC correlations of H-1′a/C-3 (three-bond), H-1′b/C-2 (two-bond), H-1′b/C-1 (three-bond), and H-2′/C-2 (three-bond). Thus, structure **4** was assigned to the new compound cratoxyarborenone D {2,3-dihydro-1,5,6,7-tetrahydroxy-3-(1-methyethenyl)-8-prenylfuro[2,3-*b*]xanthone}.

Compound **5** showed a molecular ion peak at *m/z* 410.1723, corresponding to the elemental formula $C_{24}H_{26}O_6$. The IR spectrum showed an absorption band at 3244 cm^{-1} for one or more hydroxyl groups and 1646 cm^{-1} for a conjugated carbonyl functionality. Comparison of the UV and ^1H and ^{13}C NMR spectra of **5** with those of **2** and **3** indicated that **5** has a similar xanthone skeleton. Signals for a prenyl group appeared at δ_H 3.53/δ_C 22.3 (C-1′), 5.30/123.7 (C-2′), 131.9 (C-3′), 1.67/25.8 (C-4′), and 1.80/18.0 (C-5′). The presence of a second prenyl group was shown by signals at δ_H 3.68/δ_C 23.8 (C-1″), 5.34/123.0 (C-2″), 1.70/25.8 (C-4″), 1.84/18.1 (C-5″), and δ_C 132.8 (C-3″). The methylene protons of these two prenyl groups in **5** appeared at a more shielded region than the 1″ methylene protons in compounds **1**−**4**, indicating that neither of the two prenyl groups of **5** are attached to C-8. One prenyl group was placed at C-4, as evidenced by the HMBC correlations of H-1′/C-4 (two-bond), H-1′/C-3 (three-bond), and H-1′/C-4a (three-bond). The position of the other prenyl group was identified as C-5 by HMBC correlations of H-1″/C-5 (two-bond), H-1″/C-6 (three-bond), and H-1″/C-5a (three-bond). Signals at δ_H 3.97/δ_C 61.2 indicated the presence of a methoxyl functionality. This methoxyl group was found to be attached at C-6 from the three-bond connectivity between the proton NMR signal for the methoxyl group and C-6 in the HMBC spectrum. Thus, structure **5** was assigned to the new compound cratoxyarborenone E (1,3,7-trihydroxy-6-methoxy-4,5-diisoprenylxanthone).

Compound **6** was deduced to have an elemental formula $C_{14}H_{10}O_5$ from its HREIMS, which exhibited a molecular ion peak at *m*/*z* 258.0528. The IR spectrum showed absorption bands at 3233 cm^{-1} for one or more hydroxyl groups and at 1698 cm^{-1} for a conjugated carbonyl functionality. The UV and ^1H and ^{13}C NMR spectra demonstrated that **6** has a simple xanthone skeleton containing one methoxyl and two hydroxyl substituents. *Ortho*-coupled aromatic signals at δ_H 6.70/δ_C 110.6 and 7.44/123.1 were assigned to C-2 and C-3, respectively, by the HMBC correlations of H-2/C-1, H-2/C-9a, H-2/C-4, H-3/C-1, H-3/C-4, and H-3/C-4a. Subsequently, the methoxyl group was placed at C-4, which is in the *para*-position, with a hydrogen-bonded hydroxyl group placed at C-1 since the proton signal of the methoxyl functionality at δ_H 3.94 was correlated to C-4 as a three-bond connectivity in the HMBC spectrum. The other aromatic protons appearing at δ_H 7.62, 7.46, and 7.60 were assigned to C-5, C-7, and C-8, respectively, by the HMBC correlations of H-5/C-6, H-5/C-7, H-7/C-5, H-7/C-6, H-8/C-6, H-8/C-9, H-8/C-5a, and H-8/C-8a. These HMBC correlations also confirm the position of a hydroxyl group at C-6. Thus, structure **6** was assigned to the new compound cratoxyarborenone F (1,6-dihydroxy-4-methoxyxanthone).

The molecular formula of compound **7** was established as $C_{44}H_{46}O_9$ by HRFABMS, which showed a molecular ion peak $[M + Li]^+$ at *m*/*z* 725.3304. In the ^1H and ^{13}C NMR spectra of **7**, signals at δ_H 4.53, 4.58/δ_C 65.7 (C-1′), 5.47/119.2 (C-2′), 140.9 (C-3′), 2.11/39.7 (C-4′), 1.71/16.6 (C-5′), 2.11/26.4 (C-6′), 5.11/123.6 (C-7′), 132.0 (C-8′), 1.69/25.7 (C-9′), and 1.61/17.7 (C-10′) indicated the presence of an *O*-geranyl group. A dihydroprenyl group was apparent from resonances at δ_H 5.33/δ_C 28.9 (C-1″), 1.81, 2.00/40.7 (C-2″), 1.51/26.4 (C-3″), 0.93/22.8 (C-4″), and 0.89/22.6 (C-5″). NMR signals for a methoxyl group and a methyl functionality, both attached to aromatic systems, were observed at δ_H 2.44/δ_C 22.2 (CH_3-6) and 4.00/56.4 (OCH_3-3). In the ^{13}C NMR spectrum, three conjugated carbonyl functionalities appeared at δ_C 199.4 (C-23), 191.5 (C-9), and 181.8 (C-10), and 24 aromatic carbons were also observed. It was apparent that there were four aromatic benzene rings which were connected through the carbonyl groups or the dihydroprenyl group to each other from the following observations. The HMBC correlations of H-4/C-10, H-4/C-9a, H-5/C-10, H-5/C-8a, OH-1/C-9a, and OH-8/C-8a suggested the presence of an anthraquinone skeleton. Two other aromatic rings which were connected by one carbonyl group indicated a benzophenone skeleton provided by HMBC correlations of H-18(22)/C-23, OH-12/C-11, and OH-16/C-11. These two different skeletons were connected through a dihydroprenyl group between C-2 and C-13, as evidenced by HMBC correlations of H-1″ to C-1 (three-bond), C-2 (two-bond), C-3 (three-bond), C-12 (three-bond), C-13 (two-bond), and C-14 (three-bond). The configuration at C-1″ could not be determined. To identify the positions of the methoxyl group and the *O*-geranyl group, a ROESY NMR experiment was performed because their position could not be determined only from the HMBC spectrum, due to the overlapped ^{13}C NMR signals for C-3 and C-14 at δ_C 164.1. The proton signal at δ_H 4.00 for the methoxyl group showed a cross-peak with the signal at δ_H 7.42 for H-4 in the ROESY spectrum, indicating that the methoxyl group was attached to C-3. The *O*-geranyl group was placed at C-14 by the ROE correlation between H_2-1′ (δ_H 4.53, 4.58) and H-15 (δ_H 6.14). Therefore, structure **7** was assigned to the new compound cratoxyarborequinone A {2-[1″-[11-benzoyl-14-*O*-geranyl-12,16-dihydroxyphenyl]-3″-methylbutyl]-1,8-dihydroxy-3-methoxy-6-methyl-9,10-anthracenedione}.

The molecular formula of compound **8** was deduced to be $C_{49}H_{54}O_9$ by HRFABMS, which showed a molecular ion peak $[M + Na]^+$ at *m*/*z* 809.3660. The ^1H and ^{13}C NMR spectra of **8** were similar with those of compound **7** except for an additional prenyl group at δ_H 1.89/δ_C 25.6 (C-6″), 5.06/124.9 (C-7″), 131.0 (C-8″), 1.64/25.5 (C-9″), and 1.56/17.6 (C-10″). This prenyl functionality was connected to the methyl group of the dihydroprenyl group in **8** according to the HMBC correlations of H-4″/C-6″ and H-7″/C-4″ so that **8** had a 2,13-dihydrogeranyl bridge between the anthraquinone and benzophenone moieties. Thus, structure **8** was assigned to the new compound cratoxyarborequinone B {2-[1″-[11-benzoyl-14-*O*-geranyl-12,16-dihydroxyphenyl]-4″-prenyl-3″-methylbutyl]-1,8-dihydroxy-3-methoxy-6-methyl-9,10-anthracenedione}.

Compounds **1**−**9** were evaluated against the KB (human oral epidermoid) cancer cell line.[19] Compounds **1**−**6** and **9** exhibited moderate cytotoxic activity (Table 3). Values in the range of EC_{50} 1.0−4.3 μg/mL were obtained. The cytotoxicity is in all likelihood due to the presence of the basic xanthone ring in all of the compounds. The location of the various prenyl or geranyl substituents in the cratoxyarborequinones has little or no effect on the resultant cytotoxicity for KB cells. The known compounds 2,4,6-trihydroxybenzophenone 4-*O*-geranyl ether and δ-tocotrienol were inactive in this system, while betulinic acid was not tested. Due to the availability of a sufficient amount of compound, cratoxyarborenone C (**3**) was evaluated in a 25-cell-line Oncology Diverse Cell Assay (ODCA), representing a diverse group of mouse and human tumors, fibroblasts, and normal bovine endothelial cells.[20] It was found to be weakly active (a mean IC_{50} value of 13.2 μM) and displayed little cell selectivity (max/min IC_{50} ratio of <10). Cratoxyarborenone C (**3**) was also evaluated in an in vivo mouse P-388 leukemia system (ip injection).[21] When tested at 72 mg/kg/injection, cratoxyarborenone C (**3**) was inactive (T/C value of 100%).

Experimental Section

General Experimental Procedures. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter (Flanders, NJ) at 25 °C. UV and IR spectra were recorded on a Varian Cary 3G UV−visible spectrophotometer and a Shimadzu IR-460 spectrometer, respectively. ^1H, ^{13}C, DEPT, COSY, ROESY, HMQC, and HMBC NMR experiments were performed on a Bruker AMX 500 spectrometer. TMS was used as internal standard. EIMS and ESMS were recorded on HP 5989A and Finnigan LCQ instruments, respectively. HREIMS were obtained using a VGZAB-E magnetic sector instrument. Column chromatography was carried out on Si gel 60 (230−400 mesh, Merck, Darmstadt, Germany) with mild nitrogen pressure for flash chromatography or on Sephadex LH-20 (Sigma, St. Louis, MO). Fractions were monitored by TLC (silica gel 60 F_{254} plates, 0.25 mm thickness) with visualization under UV light (254 and 365 nm) and with 1% sulfuric acid in EtOH. Preparative HPLC was carried out on a Waters 3000 system controller attached to a MetaChem Inertsil ODS 3 (250 × 25 mm i.d., 3 μm) column and a MetaChem Inertsil ODS 3 (50 × 10 mm i.d., 8 μm) guard column. The peaks were detected at 254 nm using a Waters 486 tunable absorbance detector and recorded at a Waters 740 data module integrator. The flow rate was 7 mL/min.

Plant Material. Leaves, twigs, and stem barks of *C. sumatranum* were collected in August 1994 at Central Kintap, South Kalimantan Province, Indonesia. Voucher specimens

Table 1. NMR Data for Compounds **1**−**6**

	1[a]		**2**[a]		**3**[b]		**4**[b]		**5**[b]		**6**[a]	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		161.7		161.7		160.7		162.1		162.2		157.1
2		110.8		110.8		108.6		108.6	6.33 (1H, s)	98.3	6.70 (1H, d, 8.6)	110.6
3		162.6		162.7		161.5		164.4		163.3	7.44 (1H, d, 8.6)	123.1
4	6.37 (1H, s)	92.9	6.38 (1H, s)	92.9	6.26 (1H, s)	93.1	6.30 (1H, s)	94.1		107.2		143.0
5		153.5		153.5		158.1		152.7		125.0	7.62 (1H, d, 2.9)	110.9
6	6.80 (1H, s)	101.1	6.81 (1H, s)	101.1	6.71 (1H, s)	98.3		153.6		153.3		152.8
7		141.5		141.6		144.0		141.8		148.2	7.46 (1H, dd, 9.0, 2.9)	128.0
8		112.1		112.1		111.9		129.0	7.54 (1H, s)	108.4	7.60 (1H, d, 9.0)	122.2
9		183.1		183.2		182.1		183.2		181.2		184.7
4a		155.7		155.7		155.0		ND[e]		156.1		148.7
5a		152.2		152.3		155.4		156.3		149.8		156.9
8a		129.2		129.1		137.3		111.8		117.1		123.7
9a		103.8		103.7		103.8		103.6		103.3		111.4
1′	3.34 (2H, d, 6.6)	22.0	3.35 (2H, d, 7.2)	25.9	3.48 (2H, d, 7.1)	21.5	(a) 3.07 (1H, dd, 14.4, 3.0) (b) 2.88 (1H, dd, 14.4, 8.0)	30.6	3.53 (2H, d, 6.8)	22.3		
2′	5.27 (1H, brt, 6.6)	123.5	5.29 (1H, q, 7.2, 1.2)	123.5	5.28 (1H, brt, 7.1)	121.5	4.40 (1H, brd, 8.0)	76.7	5.30 (1H, q, 6.8, 1.4)	123.7		
3′		131.3		131.3		135.4		148.3		131.9		
4′	1.64 (3H, s)	25.9	1.65 (3H, s)	26.0[c]	1.77 (3H, s)	25.8[d]	(a) 4.94 (1H, brs) (b) 4.76 (1H, brs)	110.3	1.67 (3H, s)	25.8		
5′	1.77 (3H, s)	17.9	1.79 (3H, s)	17.9	1.84 (3H, s)	18.1	1.83 (3H, s)	18.3	1.80 (3H, s)	18.0		
1″	4.20 (2H, d, 6.8)	26.3	4.19 (2H, d, 6.8)	26.3	4.12 (2H, d, 5.8)	26.2	4.17 (2H, d, 6.1)	26.4	3.68 (2H, d, 6.8)	23.8		
2″	5.33 (1H, brt, 6.8)	124.4	5.32 (1H, q, 6.8, 1.5)	124.4	5.24 (1H, brt, 5.8)	123.3	5.31 (1H, brt, 6.1)	124.5	5.34 (1H, q, 6.8, 1.4)	123.0		
3″		135.0		131.3		131.7		131.3		132.8		
4″	1.95 (2H, t, 7.1)	40.6	1.65 (3H, s)	25.9[c]	1.68 (3H, s)	25.8[d]	1.63 (3H, s)	25.0	1.70 (3H, s)	25.8		
5″	1.85 (3H, s)	16.6	1.84 (3H, s)	18.3	1.85 (3H, s)	17.9	1.83 (3H, s)	18.4	1.84 (3H, s)	18.1		
6″	2.04 (2H, m)	27.4[c]										
7″	5.04 (1H, brt, 7.1)	125.2										
8″		131.5										
9″	1.55 (3H, s)	25.7										
10″	1.52 (3H, s)	17.7										
OH-1	13.94 (1H, s)		13.95 (1H, s)		13.83 (1H, s)		14.17 (1H, s)		13.02 (1H, s)		12.10 (1H, s)	
OCH_3-4											3.94 (3H, s)	59.3
OCH_3-5					3.95 (3H, s)	56.0						
OCH_3-6									3.97 (3H, s)	61.2		
OCH_3-7					3.80 (3H, s)	60.9						

[a] Run in acetone-d_6. [b] Run in $CDCl_3$. [c] Overlapped with acetone-d_6. [d] Signals may be interchangeable. [e] ND: signal not detected.

Table 2. NMR Data for Compounds **7** and **8**

	7[a]				**8**[a]			
position	δ_H	δ_C	HMBC	ROESY	δ_H	δ_C	HMBC	ROESY
1		161.6 (s)				161.6 (s)		
2		126.0 (s)				126.2 (s)		
3		164.1 (s)				164.0 (s)		
4	7.42 (1H, s)	103.8 (d)	2, 10, 9a	OCH_3-3	7.41 (1H, s)	103.8 (d)	2, 3, 10, 4a, 9a	OCH_3-3
5	7.61 (1H, s)	121.4 (d)	7, 10, 8a	CH_3-6	7.61 (1H, s)	121.4 (d)	6, 7, 8a	H-6
6		148.8 (s)				148.8 (s)		H-5
7	7.07 (1H, s)	124.6 (d)	5, 8a	CH_3-6	7.07 (1H, s)	124.6 (d)	5, 8, 8a	H-7
8		162.6 (s)				162.6 (s)		H-6, OH-8
9		191.5 (s)				191.5 (s)		
10		181.8 (s)				181.8 (s)		
11		106.4 (s)				106.3 (s)		
12		158.4 (s)				158.4 (s)		
13		109.0 (s)				108.7 (s)		
14		164.1 (s)				164.1 (s)		
15	6.14 (1H, s)	93.3 (d)	11, 13, 14, 16	H-1′a	6.13 (1H, s)	93.3 (d)	11, 13, 16	H-1′, OH-16
16		162.9 (s)				163.0 (s)		
17		141.8 (s)				141.8 (s)		
18 (22)	7.66 (2H, d, 7.4)	128.3 (d)	18(22), 20, 23		7.64 (2H, d, 7.7)	128.3 (d)	18(22), 20	OH-16
19 (21)	7.43 (2H, t, 7.4)	127.8 (d)	17, 19(21)		7.42 (2H, t, 7.7)	127.8 (d)	17, 19(21)	
20	7.53 (1H, t, 7.4)	131.3 (d)	18(22)		7.51 (1H, t, 7.7)	131.2 (d)	18(22)	
23		199.4 (s)				199.4 (s)		
4a		133.0 (s)				133.0 (s)[c]		
5a		133.0 (s)				133.0 (s)[c]		
8a		113.5 (s)				113.5 (s)		
9a		110.6 (s)				110.6 (s)		
1′	(a) 4.53 (1H, dd, 11.7, 6.3)	65.7 (t)	2′, 3′	H-15, H-2′, H-5′	(a) 4.52 (1H, dd, 11.7, 6.4)	65.7 (t)	14, 2′, 3′	H-15, H-5′
	(b) 4.58 (1H, dd, 11.7, 6.3)			H-2′	(b) 4.57 (1H, dd, 11.7, 6.4)			
2′	5.47 (1H, t, 6.3)	119.2 (d)	4′, 5′	H_2-4′	5.46 (1H, t, 6.4)	119.2 (d)	4′, 5′	H-15, H-4′, OCH_3-3
3′		140.9 (s)				140.9 (s)		
4′	2.11 (2H, m)[b]	39.7 (t)	6′	H-2′, H-7′	2.09 (2H, m)	39.6 (t)	2′, 3′, 5′, 6′	H-2′, H-7′
5′	1.71 (3H, s)	16.6 (q)	3′, 4′	H-1′a	1.70 (3H, s)	16.6 (q)	2′, 3′, 4′	
6′	2.11 (2H, m)[b]	26.4 (t)	4′		2.12 (2H, m)	26.4 (t)	4′, 7′	
7′	5.11 (1H, br t, 6.6)	123.6 (d)		H_3-9′	5.10 (1H, brt, 6.6)	123.6 (d)	4′, 6′, 9′, 10′	H-9′
8′		132.0 (s)				131.9 (s)		
9′	1.69 (3H, s)	25.7 (q)	7′, 8′, 10′	H-7′	1.68 (3H, s)	25.6 (q)	7′, 8′	
10′	1.61 (3H, s)	17.7 (q)	7′, 8′, 9′		1.61 (3H, s)	17.7 (q)	7′, 8′	
1″	5.33 (1H, t, 8.2)	28.9 (d)	1, 2, 3, 12, 13, 14, 2″, 3″	OH-12, H-2″a, H-2″b, H-3″, H-4″	5.34 (1H, t, 9.0)	28.6 (d)	1, 2, 3, 12, 13, 14, 2″, 3″	H-3″, H-5″, OH-12, OCH_3-3
2″	(a) 1.81 (1H, m)	40.7 (t)	1″, 3″, 4″	OH-12	(a) 1.66 (1H, m)	38.9 (t)	13	OH-12
	(b) 2.00 (1H, m)			OH-12, CH_3-4″, CH_3-5″	(b) 2.16 (1H, m)			
3″	1.51 (1H, m)	26.4 (d)		H-1″	1.39 (1H, m)	31.0 (d)		
4″	0.93 (3H, d, 6.5)	22.8 (q)	2″, 3″, 5″	H-1″, H-2″b	(a) 1.13 (1H, m)	37.2 (t)	3″, 5″, 6″	H-7″
					(b) 1.39 (1H, m)		3″, 6″	
5″	0.89 (3H, d, 6.5)	22.6 (q)	2″, 3″, 4″	H-2″b	0.88 (3H, d, 6.3)	19.6 (q)	2″, 3″, 4″	
6″					1.89 (2H, m)	25.6 (t)		
7″					5.06 (1H, brt, 6.9)	124.9 (d)	4″, 9″	H-4″, H-9″
8″						131.0 (s)		
9″					1.64 (3H, s)	25.5 (q)	7″, 8″	H-7″
10″					1.56 (3H, s)	17.6 (q)	7″, 8″	
CH_3-6	2.44 (3H, s)	22.2 (q)	5, 6, 7		2.44 (3H, s)	22.1 (q)		
OH-1	13.32 (1H, s)		1, 2, 9a		13.31 (1H, s)			OH-12
OH-8	11.94 (1H, s)		7, 8, 8a		11.93 (1H, s)			
OH-12	7.90 (1H, s)		11, 12		7.89 (1H, s)			OH-1
OH-16	11.38 (1H, s)		11, 15, 16		11.40 (1H, s)			
OCH_3-3	4.00 (3H, s)	56.4 (q)	3		3.98 (3H, s)	56.4 (q)		H-4, H-2′

[a] Run in acetone-d_6. [b,c] Signals may be interchangeable.

(2181761) have been deposited at the Field Museum of Natural History, Chicago, IL.

Extraction and Isolation. Compounds **1**, **2**, **4**, and **5** were isolated from the leaves. Compound **6** was isolated from the twigs, and compounds **3**, **7**, and **8** were isolated from the stem bark. The dried leaves (482 g), twigs (1.1 kg), and stem bark (1.1 kg) were ground, milled, and separately extracted with MeOH (× 3) using a percolator. The MeOH solutions were

Table 3. Cytotoxic Activity of Isolates from *C. sumatranum* against the KB Cell Line

	1	2	3	4	5	6	7	8	9
KB[a]	4.3 ± 2.0	1.0 ± 0.1	1.5 ± 0.5	1.7 ± 1.0	4.3 ± 1.2	4.1 ± 0.8	IA[b]	IA[b]	1.3 ± 0.1

[a] Oral epidermoid carcinoma. Results are expressed as EC_{50} values as μg/mL (see Experimental Section). Mean ± SEM determined from three separate experiments. [b] IA: inactive.

filtered and evaporated under vacuum. Each dried MeOH extract was dissolved in 900 mL of MeOH, and then 100 mL of H_2O was added. This aqueous MeOH solution was defatted using hexane saturated with MeOH (× 3). The aqueous MeOH solution was concentrated and redissolved in $CHCl_3$−MeOH (4:1) and partitioned between H_2O (× 3). The organic fraction was washed using 1% saline solution and concentrated under vacuum to give 13.4, 9.8, and 19.3 g of residue for the leaves, twigs, and stem bark, respectively.

A portion of residue from the $CHCl_3$ fraction of the leaves (13 g) was subjected to Si gel column chromatography using gradient mixtures of 0→10% MeOH in $CHCl_3$ as solvents. The combined fractions that eluted with 1.5→2.5% MeOH in $CHCl_3$ were subjected to further Si gel column chromatography using hexane−acetone (90:10→0:100, gradient mixtures) as solvents. A precipitate was formed from the fractions eluted with hexane−acetone (80:20) elution to give compound **5**. Fractions eluted with hexane−acetone (60:40→50:50) were further chromatographed using Sephadex LH-20 with $CHCl_3$−MeOH (1:4) as the eluent mixture. Further Si gel column chromatography of fraction 23 using gradient mixtures of 5→25% acetone in $CHCl_3$ afforded compound **1**. Preparative HPLC of fractions 20 and 21−22 from Sephadex LH-20 column chromatography using MeOH−H_2O (90:10) afforded compounds **2** (t_R 28 min) and **4** (t_R 10.1 min), respectively.

A portion of the $CHCl_3$ fraction (9 g) of the twigs was subjected to Si gel column chromatography using gradient mixtures of 0→10% MeOH in $CHCl_3$ as solvent. Combined fractions eluted with 1.4−2.0% MeOH in $CHCl_3$ were chromatographed repeatedly over Si gel [$CHCl_3$−acetone (95:5)], Sephadex LH-20 [$CHCl_3$−MeOH (10:40)], and preparative HPLC [MeOH−H_2O (90:10)] afforded compound **6** (t_R 11.8 min).

A portion of the $CHCl_3$ fraction (19 g) from the stem bark was subjected to Si gel column chromatography using gradient mixtures of 0→10% MeOH in $CHCl_3$ as solvent. Si gel column chromatography of the combined fractions eluted with 1% MeOH in $CHCl_3$ using $CHCl_3$−acetone (90:10→50:50, gradient mixtures) as solvent followed by Sephadex LH-20 column chromatography using $CHCl_3$−MeOH (30:70) as eluent afforded compound **3**. Purification of fraction 6 from Sephadex LH-20 column chromatography followed by preparative HPLC using 1% H_2O in MeOH afforded compounds **7** (t_R 26.0 min) and **8** (t_R 43.0 min).

Cratoxyarborenone A (1): yellow powder (78 mg); mp 155−157 °C; $[\alpha]_D$ +2.5° (*c* 0.4, acetone); UV (MeOH) λ_{max} (log ϵ) 243 (4.60), 259 (4.61), 315 (4.44), 363 (4.11) nm; IR (film) ν_{max} 3308, 2916, 1726, 1610, 1457, 1386, 1366, 1287 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HMBC H-4/C-2, C-3, C-4a, C-9a, H-6/C-5, C-7, C-8, C-5a, H-1′/C-1, C-2, C-3, C-2′, C-3′, H-2′/C-4′, H-4′/C-5′, H-5′/C-4′, H-1″/C-7, C-8, C-8a, H-4″/C-2″, C-3″, H-5″/C-2″, C-3″, C-4″, H-6″/C-4″, H-7″/C-6″, H-9″/C-7″, C-10″, H-10″/C-7″, C-9″, OH-1/C-1, C-2, C-9a; EIMS *m/z* 464 [M]$^+$ (30), 339 (100), 321 (26), 257 (8); HREIMS *m/z* 464.2207 (calcd for $C_{28}H_{32}O_6$, 464.2199).

Cratoxyarborenone B (2): yellow powder (48 mg); mp 201−203 °C; $[\alpha]_D$ +5.0° (*c* 0.08, acetone); UV (MeOH) λ_{max} (log ϵ) 243 (4.59), 259 (4.59), 317 (4.43), 365 (4.08) nm; IR (film) ν_{max} 3244, 2916, 1723, 1705, 1640, 1609, 1457, 1288, 1232, 1199 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HMBC H-4/C-2, C-3, C-4a, C-9a, H-6/C-5, C-7, C-8, H-1′/C-1, C-2, C-3, C-2′, C-3′, H-2′/C-4′, C-5′, H-4′/C-2′, C-3′, H-5′/C-2′, C-3′, H-1″/C-7, C-8, C-2″, C-3″, C-8a, H-2″/C-1″, C-4″, H-4″/C-2″, C-3″, H-5″/C-3″, OH-1/C-1, C-2, C-9a; EIMS *m/z* 396 [M]$^+$ (70), 325 (85), 297 (100), 285 (31); HREIMS *m/z* 396.1576 (calcd for $C_{23}H_{24}O_6$, 396.1573).

Cratoxyarborenone C (3): yellow gum (130 mg); $[\alpha]_D$ +0.8° (*c* 0.5, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 244 (4.40), 261 (4.38), 313 (4.25) nm; IR (film) ν_{max} 3232, 2916, 1723, 1698, 1605, 1460, 1428, 1279, 1153, 1108 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HMBC H-4/C-2, C-3, C-4a, C-9a, H-6/C-5, C-7, C-8, C-9, C-5a, H-1′/C-1, C-2, C-3, C-2′, C-3′, H-4′/C-2′, C-3′, C-5′, H-5′/C-2′, C-3′, H-1″/C-7, C-8, C-8a, C-2″, H-4″/C-2″, C-3″, C-5″, H-5″/C-2″, C-3″, OH-1/C-1, C-2, C-9a, OCH_3-5/C-5, OCH_3-7/C-7; EIMS *m/z* 424 [M]$^+$ (84), 381 (100), 353 (94), 325 (60); HREIMS *m/z* 424.1881 (calcd for $C_{25}H_{28}O_6$, 424.1886).

Cratoxyarborenone D (4): yellow powder (14 mg); mp 124−126 °C; $[\alpha]_D$ +1.2° (*c* 0.3 MeOH); UV (MeOH) λ_{max} (log ϵ) 243 (4.09), 259 (4.57), 315 (4.38), 365 (4.09) nm; IR (film) ν_{max} 3335, 2859, 1723, 1700, 1615, 1581, 1463, 1288, 1169 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HMBC H-4/C-9a, H-1′/C-1, C-2, C-3, C-2′, C-3′, H-2′/C-2, C-3′, C-4′, H-4′/C-2′, C-3′, C-5′, H-5′/C-3′, C-4′, H-1″/C-7, C-8, C-8a, C-2″, C-3″, H-2″/C-8, C-1″, C-5″, H-4″/C-2″, C-3″, C-5″, H-5″/C-2″, C-3″, C-4″, OH-1/C-1, C-2, C-9a; ESMS *m/z* 411 [M + 1]$^-$ (100), 340 (9), 297 (23), 285 (10); HRFABMS *m/z* 411.1441 [M + 1]$^+$ (calcd for $C_{23}H_{23}O_7$ [M + 1]$^+$, 411.1444).

Cratoxyarborenone E (5): yellow powder (51 mg); mp 220−222 °C; $[\alpha]_D$ −5.7° (*c* 0.07, acetone); UV (MeOH) λ_{max} (log ϵ) 240 (4.47), 262 (4.57), 315 (4.25), 375 (3.96) nm; IR (film) ν_{max} 3244, 2916, 1734, 1710, 1646, 1584, 1461, 1377, 1309, 1232, 1119 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HMBC H-2/C-1, C-3, C-4, C-9a, H-8/C-6, C-9, C-5a, H-1′/C-3, C-4, C-4a, C-2′, C-3′, H-2′/C-5′, H-4′/C-2′, C-3′, C-5′, H-5′/C-2′, C-3′, C-4′, H-1″/C-5, C-6, C-5a, C-2″, C-3″, H-4″/C-2″, C-3″, C-5″, H-5″/C-2″, C-3″, C-4″, OH-1/C-1, C-2, C-9a, OCH_3-6/C-6; EIMS *m/z* 410 [M]$^+$ (100), 395 (48), 342 (37), 311 (23); HREIMS *m/z* 410.1723 (calcd for $C_{24}H_{26}O_6$, 410.1729).

Cratoxyarborenone F (6): yellow powder (12 mg); mp 165−167 °C; $[\alpha]_D$ +3.3° (*c* 0.06, acetone); UV (MeOH) λ_{max} (log ϵ) 236 (4.55), 267 (4.56), 323 (3.46) nm; IR (film) ν_{max} 3233, 2359, 1723, 1698, 1488, 1385, 1339, 1235 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HMBC H-2/C-1, C-4, C-9a, H-3/C-1, C-4, C-4a, H-5/C-6, C-7, H-7/C-5, C-6, H-8/C-6, C-9, C-5a, C-8a, OH-1/C-1, C-2, C-9a, OCH_3-4/C-4; EIMS *m/z* 258 [M]$^+$ (45), 243 (100), 215 (7); HREIMS *m/z* 258.0532 (calcd for $C_{14}H_{10}O_5$, 258.0528).

Cratoxyarborequinone A (7): yellow gum (47 mg); $[\alpha]_D$ +60.8° (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 210 (4.74), 250 (4.34), 282 (4.47), 308 (4.53) nm; IR (film) ν_{max} 2957, 1622, 1477, 1306, 1229, 1187, 1133 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; ESMS *m/z* 741 [M + Na]$^+$ (100); HRFABMS *m/z* 725.3304 [M + Li]$^+$ (calcd for $C_{44}H_{46}O_9Li$, 725.3302).

Cratoxyarborequinone B (8): yellow gum (6 mg); $[\alpha]_D$ +81.2° (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 210 (4.54), 250 (4.13), 285 (4.27), 309 (4.12) nm; IR (film) ν_{max} 2977, 2325, 1622, 1488, 1269, 1207 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; ESMS *m/z* 809 [M + Na]$^+$ (100); HRFABMS *m/z* 809.3660 (calcd for $C_{49}H_{54}O_9Na$, 809.3666).

Vismione B (9): physical and spectral data were comparable with literature values.[11]

2,4,6-Trihydroxybenzophenone 4-*O*-geranyl ether: physical and spectral data were comparable with literature values.[12]

***δ*-Tocotrienol:** physical and spectral data were comparable with literature values.[13]

Betulinic acid: physical and spectral data were comparable with literature values.[14]

KB Cytotoxicity Assay. Fractions and compounds **1**−**9** and two known compounds were tested in a human oral epidermoid carcinoma (KB) cell line using established protocols.[19]

Oncology Diverse Cell Assays. Compound **3** was evaluated in a panel of 25 tumor cell lines, using MTS [3-(4,5-

dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfenyl)-2*H*-tetrazolium, inner salt] assay.[20]

In Vivo Evaluation of Compound 3. Compound **3** was evaluated in an in vivo test system using the P-388 leukemia model as described previously.[21]

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References and Notes

(1) Part of the results were presented at the 41st Annual Meeting of the American Society of Pharmacognosy in Seattle, WA, July 2000.
(2) After our initial taxonomic identification, the species name for this acquisition has been changed from *Cratoxylum arborescens* to *C. sumatranum*.
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