JOURNAL OF NATURAL PRODUCTS

Volume 63, Number 11 November 2000

Full Papers

Bioactive Saponins from *Swartzia schomburgkii* from the Suriname Rainforest[1]

Maged S. Abdel-Kader,[†] Brian D. Bahler,[†] Stan Malone,[‡] Marga C. M. Werkhoven,[§] Jan H. Wisse,[⊥] Kim M. Neddermann,[∥] Isia Bursuker,[∥] and David G. I. Kingston*[,†]

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, Conservation International Suriname, Burenstrasse 7, Paramaribo, Suriname, The National Herbarium of Suriname, P.O. Box 9212, Paramaribo, Suriname, Asindopo Village, Suriname, Bedrijf Geneesmiddelen Voorziening Suriname, Commissaris Roblesweg, Geyersvlijt, Suriname, and Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492-7660

Received February 23, 2000

Bioassay-guided fractionation of the MeOH extract of *Swartzia schomburgkii* using the engineered yeast strains 1138, 1140, and 1353 as the bioassay tool resulted in the isolation of five active (**2**, **4**−**7**) and three inactive (**1**, **3**, **8**) saponins. Saponins **4** and **6** are previously unreported. The structures of all of the saponins were established based on 1D and 2D NMR spectral analysis, on acid and alkaline hydrolysis followed by TLC and GC−MS, and by comparison with literature data for known compounds. Three of the isolated compounds (**4**−**6**) showed weak cytotoxicity against the M-109 cell line.

In recent years we have been engaged in a program to discover bioactive agents from the Suriname rainforest using a mechanism-based bioassay involving genetically engineered mutants of the yeast *Saccharomyces cerevisiae*.[2,3] As a part of this program, the plant *Swartzia schomburgkii* Benth. var. *schomburgkii* (Fabaceae) was collected on an ethnobotanical basis near Asindopo village, Suriname, in June 1994, and its methanol extract was found to show reproducible activity in the yeast assay.

The genus *Swartzia* includes between 125 and 150 species from tropical South America and Africa, but only a few members have been investigated chemically.[4] Several saponins with molluscicidal activity have been isolated from two *Swartzia* species,[5] and other biologically active secondary metabolites, including pterocarpene and isoflavanones, have also been reported from the genus.[6]

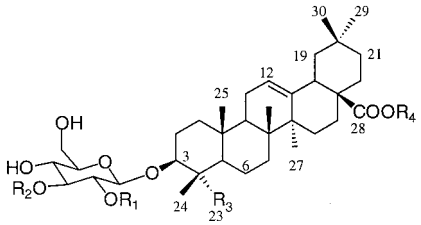
* To whom enquiries should be addressed. Tel.: (540) 231-6570. Fax: (540) 231-7702. E-mail: dkingston@vt.edu.
[†] Virginia Polytechnic Institute and State University (VPISU).
[‡] Conservation International Suriname.
[§] The National Herbarium of Suriname.
[⊥] Bedrijf Geneesmiddelen Voorziening Suriname (BGVS).
[∥] Bristol-Myers Squibb Pharmaceutical Research Institute.

Results and Discussion

The MeOH extract of *S. schomburgkii* had IC_{12} values of 4000 and 8000 μg/mL against the 1138 and 1140 yeast strains, respectively. On fractionation of this extract by liquid−liquid partition, the bioactivity was found in the aqueous MeOH phase of a hexane−80% aqueous MeOH partition and then in both phases of a $CHCl_3$−60% aqueous MeOH partition. Purification of both the $CHCl_3$-soluble and MeOH-soluble fractions using Sephadex LH-20, RP_{18}, and Si gel columns, followed by preparative TLC, resulted in the isolation of saponins **1**−**8**.

Saponins **1**−**3**, **5**, **7**, and **8** were identified from chemical and spectroscopic data and by comparison with literature data as oleanolic acid-3-*O*-β-D-glucopyranoside (androseptoside A) (**1**),[7] hederagenin-3-*O*-β-D-glucopyranoside (HN-saponin D_1)(**2**),[8] oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside (randianin) (**3**),[9] oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (oleanolic acid-3-sophoroside, acutoside A) (**5**),[10] oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl]-(1→3)-β-D-glucopyranoside (anchusosid 2) (**7**),[11] and oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-xylopyranosyl]-(1→3)-β-D-glucopyranoside-28-*O*-β-D-glucopyranoside ester (aralia-

10.1021/np0000926 CCC: $19.00
Published on Web 09/07/2000



Compound	R_1	R_2	R_3	R_4
1	H	H	CH_3	H
2	H	H	CH_2OH	H
3	H	glc	CH_3	H
4	H	glc	CH_2OH	H
5	glc	H	CH_3	H
6	xyl	glc	CH_3	H
7	glc	glc	CH_3	H
8	xyl	glc	CH_3	glc

saponin IV) (**8**).[12] The ^{13}C NMR spectra for saponins **1** and **7** have not previously been reported, and they are thus reported here.

Saponin **4** was obtained as a white powder, mp 251−253 °C. The presence of two sugar molecules was indicated by its ^1H NMR spectrum, which showed signals for two anomeric protons at δ 4.46 (d, J = 7.8 Hz) and 4.56 (d, J = 7.8 Hz). An HMQC experiment correlated these two protons to two overlapped carbons at 103.8 ppm. Comparison of the ^1H and ^{13}C NMR spectra of **4** with those of **3** (Tables 1 and 2) indicated that one methyl singlet in **3** (1.06, 28.5 ppm ^1H and ^{13}C NMR) was replaced by a CH_2OH group in **4** (3.65, 63.6 ppm ^1H and ^{13}C NMR). The ^{13}C NMR chemical shift of C-3 at 82.2 ppm (90.0 ppm in **3**) indicated that the CH_2OH group had replaced the 23-CH_3 group in a 3-*O*-glycosylated aglycon.[8a] Acid hydrolysis of **4** with 3% HCl resulted in an aglycon identified by ^1H and ^{13}C NMR and by MS as hederagenin, [13] while sugar analysis by GC−MS after acetylation revealed the presence of glucose as the only sugar. These data, in addition to the observation of a sodiated molecular ion [M^+ + Na] at *m/z* 819 in FABMS indicated that **4** is hederagenin glycosylated at C-3 with two glucose units. The linkage between the two glucose units was determined to be 1→3 by comparison of the ^{13}C NMR chemical shifts of the glucose carbons with those of related compounds having the same linkage.[9,14] Acetylation of **4** gave an octaacetate, and the ^1H NMR spectrum of the glycoside part of this compound in CD_3OD was assigned by a combination of a COSY experiment and comparison with the spectrum of acetylated glucose. The COSY spectrum showed that the chemical shift of H-3′ of the inner glucose, which was at about δ 3.6 before acetylation, only moved slightly to δ 4.00 (t, J = 9.5 Hz) after acetylation. This provided further confirmation that the outer glucose is linked to C-3 of the inner glucose. The above discussion proves that **4** is hederagenin-3-*O*-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside, a previously unreported compound.

Saponin **6** was isolated in the form of a white powder, mp 244−246 °C. FABMS showed a protonated molecular ion [MH^+] at *m/z* 913, consistent with the molecular formula $C_{47}H_{76}O_{17}$, CH_2O less than saponin **7**. Signals for three anomeric protons at δ 4.81 (J = 6.6 Hz), 5.35 (J = 7.5 Hz), and 5.57 (J = 6.9 Hz) in its ^1H NMR spectrum correlated with those of two overlapped carbons at 104.6 and a carbon at 105.1 ppm by an HMQC experiment and were diagnostic for the presence of three sugar molecules. The chemical shift of the anomeric carbons and of C-3 of the triterpenoid ring system at 89.8 ppm indicated that the three sugars were attached to C-3. After complete acid hydrolysis, the aglycon was identified as oleanolic acid through comparison of ^1H and ^{13}C NMR spectra and MS with the literature data.[15] GC−MS of the sugars after acetylation indicated the presence of glucose and xylose in a ratio of 2:1. Acid hydrolysis using 3% H_2SO_4 in dry MeOH under reflux for 1 h resulted in a partial hydrolysis, where oleanolic acid, compounds **1** and **3**, and another diglycoside containing glucose and xylose were separated; the identities of the hydrolysis products were confirmed by ^1H NMR spectrometry and FABMS. The presence of two different diglycosides indicated that the inner glucose is the site of attachment to the other glucose and xylose, while the presence of compound **3** proved the presence of a glucose 1→3 glucose linkage. Acetylation of **6** resulted in a downfield shift of all sugar protons except those attached to carbons involved in the sugar aglycon and sugar linkages, which were present in a much less overlapped part of the ^1H NMR spectrum after acetylation. The ^1H NMR spectrum of acetylated **6** in pyridine-d_5 was assigned based on COSY correlations and comparison with the spectra of acetylated sugar standards. A COSY experiment on the acetylated product showed a correlation between H-1′ (δ 4.71, *d*, J = 7.6 Hz) and H-2′ (δ 4.16, *t*, J = 8.6 Hz); this latter signal was only slightly shifted from its value of about δ 4.2 (m) before acetylation. The H-2′ signal was also correlated with H-3′ (δ 4.47, *t*, J = 8.5 Hz), which was only slightly shifted from its value of δ 4.2 (m) before acetylation. These correlations indicate that both the C-2 and C-3 positions of the inner glucose are glycosylated, and because the isolation of compound **3** proves the presence of a glucose 1→3 glucose linkage, the xylose must be attached to C-2′ of the inner glucose. Two FABMS fragment ions at *m/z* 751 and 781, corresponding to the loss of glucose and xylose, respectively, were in full support of this linkage assignment. Further evidence for the structure of **6** as oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-xylopyranosyl]-(1→3)-β-D-glucopyranoside was obtained by alkaline hydrolysis of **8** in 0.5 N NaOH for 2 h at room temperature, which generated **6** (identified by ^1H NMR spectrometry and FABMS) and glucose (identified by GC−MS).

Compounds **2** and **4**−**7** showed weak activity in our yeast bioassay (Table 3), with IC_{12} values in the 0.1−1.5 millimolar range. In a cytotoxicity test at Bristol-Myers Squibb using the M-109 cell line compounds **4**−**6** showed weak cytotoxicity, with IC_{50} values against the M-109 cell line in the 25−50 micromolar range.

Experimental Section

General Experimental Procedures. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded in CD_3OD and pyridine-d_5 at 399.951 MHz for ^1H and 100.578 MHz for ^{13}C NMR, using standard Varian pulse sequence programs. FABMS were obtained on a VG 7070 E-HF mass spectrometer.

Yeast Bioassay. The bioassay was carried out as previously described.[2c]

Cytotoxicity Bioassay. The in vitro antitumor cytotoxicity assays were performed at Bristol-Myers Squibb Pharmaceutical Research Institute using the Madison lung carcinoma (M-109)[16] murine cell line as previously described.[17]

Plant Collection and Extraction. The leaves and stems of *S. schomburgkii* were collected from Asindopo, Suriname, in June 1994. A herbarium specimen was deposited in the National Herbarium of Suriname. A methanol extract of the

Table 1. Selected ^{1}H NMR Data (δ value) for Saponins **3**, **4**, and **6**[a]

position	**3**[b]	**4**[b]	**6**[c]
12	5.23 (1H, b s)	5.23 (1H, b s)	5.45 (1H, b s)
23	1.06 (3H, s)	3.65 (m)[d]	1.29 (3H, s)
24	0.93 (3H, s)	0.71 (3H, s)	0.99 (3H, s)
25	0.84 (3H, s)	0.84 (3H, s)	0.80 (3H, s)
26	0.84 (3H, s)	0.94 (3H, s)	1.05 (3H, s)
27	1.16 (3H, s)	1.16 (3H, s)	1.26 (3H, s)
29	0.90 (3H, s)	0.89 (3H, s)	0.94 (3H, s)
30	0.94 (3H, s)	0.98 (3H, s)	0.94 (3H, s)
H-1′	4.37 (d, J = 7.6 Hz)	4.46 (d, J = 7.8 Hz)	4.81 (d, J = 6.6 Hz)
H-1″	4.56 (d, J = 7.6 Hz)	4.56 (d, J = 7.8 Hz)	5.35 (d, J = 7.5 Hz)
H-1‴			4.57 (d, J = 6.9 Hz)
H-2″, H-3‴			4.03 (m)
H-3″			3.82 (b t, J = 9.8 Hz)
H-4′		3.54 (t, J = 7.7 Hz)	
H-6′			4.51 (dd, J = 10.0, 27.0 Hz)
H-6′, H-6‴		3.86 (b t, J = 12.8 Hz)	

[a] Chemical shifts in ppm from internal TMS, coupling constants in Hz. [b] Obtained in CD_3OD. [c] Obtained in pyridine-d_5. [d] Overlapped with other signals.

dried plant material was prepared at BGVS in Suriname and supplied to VPISU as BGVS M940363.

Isolation of Bioactive Saponins. The bioactive MeOH extract (11.5 g) with IC_{12} 4000 and 8000 μg/mL in the 1138 and 1140 yeast strains, respectively, was dissolved in 200 mL of 80% aqueous MeOH and defatted with hexane (150 mL × 4). The aqueous MeOH fraction was diluted with H_2O until a 60% aqueous MeOH mixture was produced and was then partitioned with $CHCl_3$ (150 mL × 4) to afford 3.3 g of bioactive $CHCl_3$-soluble extract, IC_{12} 1000 μg/mL (1138). The residue left after evaporation of the 60% aqueous MeOH (7.7 g), IC_{12} 4000 μg/mL (1138), was fractionated by chromatography on RP_{18} (Whatman) using the VLC technique and eluting with H_2O−MeOH mixtures. The active fractions (1.95 g, eluted with 80−100% MeOH in H_2O) were combined with the $CHCl_3$-soluble extract according to their similarity on TLC and level of bioactivity. The combined active extracts (5.25 g) were purified by column chromatography (5 × 100 cm) on Sephadex LH-20 using CH_2Cl_2−Me_2CO (4:1, 1L), CH_2Cl_2−Me_2CO (2:3, 1L), and MeOH as eluting solvents. The active fraction (2.6 g) eluted with MeOH was separated on RP_{18} (7 cm × 8 cm, 100 g) using the VLC technique, starting with 80% MeOH in H_2O as eluent and then increasing the MeOH content; fractions 2−6 were active. Fractions 2−3 (1.19 g, 80% MeOH) were further purified on a Si gel column (2.5 cm × 50 cm, 60 g) eluted with 5% MeOH in $CHCl_3$ with a gradual increase of the MeOH content. Fractions eluted with 5% MeOH (0.3 g) afforded 120 mg of **5** (R_f value 0.5 in EtOAc−MeOH−H_2O, 30:5:4) on crystallization from MeOH. Fractions 15−26 (10% MeOH, 0.2 g) were separated by preparative TLC (Si gel, EtOAc−MeOH−H_2O, 30:5:4, double development) to obtain 30 mg of **7** (R_f value 0.44 in EtOAc−MeOH−H_2O, 30:5:4) and 15 mg of **8** (R_f value 0.31 in EtOAc−MeOH−H_2O, 30:5:4). Similar purification of fraction 4 on a Si gel column followed by preparative TLC afforded 45 mg of **6** (R_f value 0.47 in EtOAc−MeOH−H_2O, 30:5:4). Repeated crystallization of fraction 5 (0.8 g) afforded 300 mg of **3** (R_f value 0.59 in EtOAc−MeOH−H_2O, 30:5:4). Preparative TLC of the supernatant (Si gel, EtOAc−MeOH−H_2O, 30:5:4) afforded 50 mg of **3** and 90 mg of **4** (R_f value 0.55 in EtOAc−MeOH−H_2O, 30:5:4). Preparative TLC of fraction 6 (0.1 g) using the same conditions afforded 15 mg of **1** and 10 mg of **2** (R_f values 0.83 and 0.79 in EtOAc−MeOH−H_2O, 30:5:4, respectively).

Oleanolic acid-3-*O*-β-D-glucopyranoside (androseptoside A) (1): white powder; FABMS m/z 619 [M^+ + H, 40]; ^{13}C NMR data (Table 1) consistent with the assigned structure, and ^{1}H NMR data identical with literature values.[7]

Hederagenin-3-*O*-β-D-glucopyranoside (HN-saponin D_1) (2): white powder; FABMS m/z 657 [M^+ + Na, 60]; ^{13}C NMR data identical with literature values.[8]

Randianin (oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside) (3): white powder; mp 285−287 °C (MeOH) (lit.[9] 290−295 °C dec); $[\alpha]^{26}_D$ +30 ° (c 1.2, MeOH) (lit.[9] +0.22 °); ^{13}C NMR data, see Table 2.

Table 2. ^{13}C NMR Data for Saponins **1**, **3**, **4**, **6**, and **7**[a]

position	**1**[b]	**3**[b]	**4**[b]	**6**[c]	**7**[c]
1	39.8	37.9	38.1	39.0	39.7
2	27.0	26.9	27.6	26.7	26.6
3	90.8	90.4	82.2	89.8	89.5
4	42.8	42.7	42.4	42.7	43.8
5	57.1	57.0	47.6	56.1	55.9
6	19.3	19.3	17.5	18.7	18.7
7	34.0	34.0	32.1	33.5	33.5
8	40.0	40.2	39.1	40.0	38.8
9	49.1	49.3	46.8	48.3	49.7
10	38.0	39.7	36.3	39.8	37.0
11	24.3	24.1	22.9	24.0	23.9
12	123.6	123.6	121.6	122.0	122.1
13	145.3	145.2	144.6	145.8	145.5
14	40.5	40.6	41.6	40.5	39.7
15	28.9	28.8	24.9	28.6	28.5
16	24.5	24.5	23.2	24.2	24.0
17	47.6	47.6	48.5	47.7	48.1
18	42.8	42.9	41.6	42.4	42.3
19	47.4	47.2	46.3	47.2	47.1
20	31.6	31.6	30.3	31.2	31.1
21	33.9	33.8	33.8	32.2	33.3
22	35.0	34.9	32.7	34.8	34.6
23	28.5	28.5	63.6	28.0	28.1
24	15.9	15.9	12.0	15.7	15.6
25	17.8	17.7	16.7	17.8	17.7
26	17.0	17.0	15.1	17.0	16.9
27	26.4	26.5	26.5	26.4	26.3
28		181.9			
29	33.9	33.6	32.4	33.7	33.6
30	24.0	24.0	22.7	24.2	24.1
glucose at C-3					
1′	106.7	106.3	103.8	104.6	105.1
2′	75.7	75.5	73.5	79.5	79.3
3′	78.3	88.1	86.8	88.6	88.4
4′	71.7	70.0	68.5	71.6	70.0
5′	77.7	77.3	76.8	78.9	78.5
6′	62.9	62.6	61.2	62.7	62.6
sugar moiety at C-2′				xylose	glucose
1″				105.1	103.7
2″				75.4	77.8
3″				77.8	76.3
4″				70.1	72.7
5″				67.2	78.5
6″					63.5
sugar moiety at C-3′					
1‴		105.2	103.8	104.6	104.6
2‴		74.9	74.0	76.1	75.4
3‴		77.8	75.9	78.4	77.8
4‴		71.5	70.1	71.5	71.5
5‴		78.1	76.3	78.6	78.6
6‴		62.9	61.2	62.3	62.3

[a] Assignment made by combination of DEPT, HMQC data. [b] Obtained in CD_3OD. [c] Obtained in pyridine-d_5.

Table 3. Cytotoxic Activities of Saponins **2** and **4**−**7**

compound	IC_{12} values (μg/mL) in *S. cerevisiae* strain			IC_{50} values (μg/mL) in the M-109 cell line
	1138	1140	1353	
2	125	200	280	NT[a]
4	400	600	1000	15.5
5	75	130	110	28.7
6	120	260	430	24.3
7	120	200	270	NT[a]

[a] NT = not tested.

Swartziadioside (hederagenin-3-*O*-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside) (4): white powder; mp 251−253 °C (MeOH); $[\alpha]^{26}_D$ +26.2° (*c* 1.2, MeOH); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m/z* 835 [M^+ + K, 31], 820 (M^+ + Na + H, 43), 819 (M^+ + Na, 100), 673 (21), 657 (9), 511 (14), 495 (16).

Oleanolic acid-3-sophoroside (5): needle crystals (EtOH), dec 215 °C (lit.[10a] dec 213 °C); $[\alpha]^{26}_D$ +34° (*c* 1, MeOH) (lit.[10a] +22°).

Swartziatrioside (oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-xylopyranosyl]-(1→3)-β-D-glucopyranoside) (6): white powder; mp 244−246 °C (MeOH); $[\alpha]^{26}_D$ +30° (*c* 1.1, MeOH); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m/z* 913 [M^+ + H, 100], 781 (34), 751 (21), 619 (34).

Anchusosid 2 (oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl]-(1→3)-β-D-glucopyranoside) (7): white powder; dec 255 °C (MeOH); $[\alpha]^{26}_D$ +26° (*c* 1.3, MeOH) (lit.[11] +28°); ^{13}C NMR data, see Table 2; FABMS *m/z* 981 [M^+ + K, 100].

Araliasaponin IV (oleanolic acid-3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl]-(1→3)-β-D-glucopyranoside-28-*O*-β-D-glucopyranosyl ester) (8): white powder; dec 227 °C (MeOH); $[\alpha]^{26}_D$ +20.8° (*c* 1.3, MeOH) (lit.[12] +11.9°); FABMS *m/z* 1097 [M^+ + Na, 100].

Acid Hydrolysis of Glycosides. A methanolic solution of the saponin was treated with an equal volume of 3% H_2SO_4 in dry MeOH under reflux for 1 h to effect partial hydrolysis. Continuation of the refluxing for 5 h resulted in complete hydrolysis of the saponin. After hydrolysis the solution was neutralized with Na_2CO_3 and extracted with EtOAc to give an aqueous fraction containing the sugar(s) and an EtOAc fraction containing the aglycon.

Acetylation of Saponins. Acetylation of compounds **4** and **6** was performed by dissolving the saponin (5 mg) in pyridine (0.5 mL) and adding Ac_2O (0.2 mL). The mixture was allowed to stand at room temperature for 24 h, and solvent was then evaporated under a stream of N_2 to yield a chromatographically homogeneous product.

Alkaline Hydrolysis of Saponin 8. A solution of 2 mg of **8** in MeOH was kept at room temperature with an equal volume of 0.5 M methanolic solution of NaOH for 2 h. The solution was then neutralized with HCl and extracted with EtOAc, and the EtOAc fraction was evaporated to give a chromatographically homogeneous product. The aqueous layer was dried, treated with pyridine (0.5 mL) and Ac_2O (0.2 mL), allowed to stand at room temperature for 24 h, and then extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated, and the residue was analyzed by GC−MS.

Sugar Analysis by GC−MS. GC−MS runs were performed using a 30 m × 0.32 mm i.d. HP5 column (5% phenyl methyl silicone) connected to the VG7070E-HF mass spectrometer, with an initial temperature 95 °C for 1 min and then temperature programming to 285 °C at a rate of 10 °C/min. The retention times and fragmentation patterns of the analytes were compared with those of authentic sugar acetate standards.

Acknowledgment. This work was supported by an International Cooperative Biodiversity Grant, number U01 TW/CA-00313 from the Fogarty Center, NIH. We thank Mr. Kim Harich for obtaining the mass spectra.

References and Notes

(1) Biodiversity Conservation and Drug Discovery in Suriname, part 7. For part 6, see Yang et al.[2f]

(2) (a) Zhou, B.-N.; Baj, N. J.; Glass, T. E.; Malone, S.; Werkhoven, M. C. M.; van Troon, F.; David, M.; Wisse, J.; Kingston, D. G. I. *J. Nat. Prod.* **1997**, *60*, 1287−1293. (b) Abdel-Kader, M. S.; Wisse, J. H.; Evans, R.; van der Werff, H.; Kingston, D. G. I. *J. Nat. Prod.* **1997**, *60*, 1294−1297. (c) Abdel-Kader, M. S.; Bahler, B. D.; Malone, S.; Werkhoven, M. C. M.; van Troon, F.; David, M.; Wisse, J. H.; Burkuser, I.; Neddermann, K. M.; Mamber, S. W.; Kingston, D. G. I. *J. Nat. Prod.* **1998**, *61*, 1202−1208. (d) Yang, S.-W.; Zhou, B.-N.; Wisse, J. H.; Evans, R.; van der Werff, H.; Miller, J. S.; Kingston, D. G. I. *J. Nat. Prod.* **1998**, *61*, 901−906. (e) Yang, S.-W.; Abdel-Kader, M.; Malone, S.; Werkhoven, M. C. M.; Wisse, J. H.; Bursuker, I.; Neddermann, K.; Fairchild, C.; Raventos-Suarez, C.; Menendez, A. T.; Lane, K.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 976−983. (f) Yang, S.-W.; Zhou, B.-N.; Malone, S.; Werkhoven, M. C. M.; van Troon, F.; Wisse, J. H.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1173−1174.

(3) (a) Kingston, D. G. I.; Gunatilaka, A. A. L.; Zhou, B.-N.; Abdel-Kader, M.; Berger, J. M.; van der Werff, H.; Evans, R.; Famolare, L.; Mittermeier, R.; Malone, S.; Wisse, J. H. In *Biodiversity Conservation and Drug Development in Suriname*; Hostettmann, K., Gupta, M. P., Marston, A., Eds.; Harwood Academic: Amsterdam, 1999; pp 111−124. (b) Kingston, D. G. I.; Abdel-Kader, M.; Zhou, B.-N.; Yang, S.-Y.; Berger, J. M.; van der Werff, H.; Evans, R.; Mittermeier, R.; Malone, S.; Famolare, L.; Guerin-McManus, M.; Wisse, J. H.; Miller, J. S. In *Biologically Active Natural Products: Pharmaceuticals*; Cutler, S. J., Cutler, H. G., Eds.; CRC: Boca Raton, 2000; Chapter 4, pp 39−59.

(4) Schultes, R. E. *J. Ethnopharmacol.* **1979**, *1*, 79−87.

(5) (a) Borel, C.; Hostettmann, K. *Helv. Chim. Acta* **1987**, *70*, 570−576. (b) Borel, C.; Gupta, M. P.; Hostettmann, K. *Phytochemistry* **1987**, *26*, 2685−2689. (c) Suter, R.; Tanner, M.; Borel, C.; Hostettmann, K.; Freyvogel, T. A. *Acta Trop.* **1986**, *43*, 69−83.

(6) Osawa, K.; Yasuda, H.; Maruyama, T.; Morita, H.; Takeya, K.; Hokawa, H. *Chem. Pharm. Bull.* **1992**, *40*, 2970−2974.

(7) Kintya, P. K.; Piroshkova, N. M. *Khim. Prir. Soedin.* **1982**, *4*, 526−527. *Chem. Nat. Compd. (Engl. Transl.)* **1982**, *4*, 499−500.

(8) (a) Kizu, H.; Kitayama, S.; Nakatani, F.; Tomimori, T.; Namba, T. *Chem. Pharm. Bull.* **1985**, *33*, 3324−3329. (b) Aoki, T.; Tanio, Y.; Suga, T. *Phytochemistry* **1976**, 15, 781−784. (c) Oleszek W. *J. Sci. Food Agric.* **1988**, 43, 289−297.

(9) Sotheeswaran, S.; Bokel, M.; Kraus, W. *Phytochemistry* **1989**, *28*, 1544−1546.

(10) (a) Orsini, F.; Pelizzoni, F.; Ricca, G.; Verotta, L. *Phytochemistry* **1987**, *26*, 1101−1105. (b) Nagao, T.; Tanaka, R.; Iwase, Y.; Hanazono, H. Okabe, H. *Chem. Pharm. Bull.* **1991**, *39*, 599−606.

(11) Romussi, G.; Ciarrallo, G.; Falsone, G.; Schneider, C. *Liebigs Ann. Chem.* **1979**, 2028−2035.

(12) Miyase, T.; Shiokawa, K.-I.; Zhang, D. M.; Ueno, A. *Phytochemistry* **1996**, *41*, 1411−1418.

(13) Tori, K.; Seo, S.; Shimaoka, A.; Tomita, Y. *Tetrahedron Lett.* **1974**, 4227.

(14) Karl, C.; Pedersen, P. A.; Mueller, G. *Z. Naturforsch.* **1980**, *35c*, 826.

(15) *The Aldrich Library of ^{13}C and ^{1}H FTNMR Spectra*; Pouchert C. J., Behnke, J., Eds.; Aldrich Chemical Co.: Milwaukee, 1992.

(16) Marks, T. A.; Woodman, R. J.; Geran, R. I.; Billups, L. H.; Madison, R. M. *Cancer Treat.* **1977**, *61*, 1459−1470.

(17) McBrien, K. D.; Bery, R. L.; Lowes, S. E.; Neddermann, K. M.; Bursuker, I.; Huang, S.; Klohr, S. E.; Leet, J. E. *J. Antibiot.* **1995**, *48*, 1446−1452.

NP0000926