Cytotoxic Triterpenoids from *Acridocarpus vivy* from the Madagascar Rain Forest[1]

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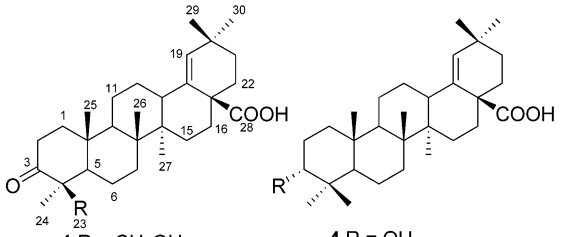
Bioassay-guided fractionation of the cytotoxic MeOH extract obtained from *Acridocarpus vivy* led to the isolation of five new triterpenoids, acridocarpusic acids A−E (**1**−**5**); three known triterpenoids, moronic acid (**6**), ursolic acid, and oleanolic acid; and two known flavonoids, 4′,5-dihydroxy-7-methoxyflavone and 4′,5-dihydroxy-3′,7-dimethoxyflavone. The structures of the new compounds **1**−**5** were established on the basis of extensive 1D and 2D NMR spectroscopic data interpretation. Compound **3** showed significant cytotoxic activity in the A2780 assay, with an IC_{50} value of 0.7 μg/mL.

In our continuing search for bioactive molecules from the Madagascar rainforests as part of an International Cooperative Biodiversity Group (ICBG) program,[2] we obtained a cytotoxic extract from the leaves and flowers of the plant *Acridocarpus vivy* J. Ar. (Malpiphiaceae) collected in Madagascar. This extract was selected for bioassay-guided fractionation on the basis of its cytotoxicity against the A2780 human ovarian cancer cell line, with an IC_{50} value of 28.9 μg/mL, and on the absence of any reported phytochemistry on the genus. The crude extract after solvent partition and reversed-phase flash chromatography, followed by reversed-phase and diol HPLC, furnished the five new triterpenoids acridocarpusic acids A−E (**1**−**5**), three known triterpenoids, and two known flavonoids.



Malpighiaceae Juss. is a pantropical plant family with about 67 genera and 1100 species. The genus *Acridocarpus* Guill. & Perr. includes about 30 species, with 11 widely distributed in Africa, six in Madagascar, and a single species disjunct in New Caledonia. Although only four species of *Acridocarpus* were recognized in the Floré de Madagascar,[3] one was subsequently described,[4] and the genus is still in need of further review. Together with the monospecific genus *Brachylophon* Oliv. from Malaysia and Sumatra, the two form a distinct clade within the Malpighiaceae.[5] *Acridocarpus vivy* J. Ar. is a medium sized tree occurring in middle elevations in eastern Madagascar; it is quite attractive with its clusters of bright yellow flowers.

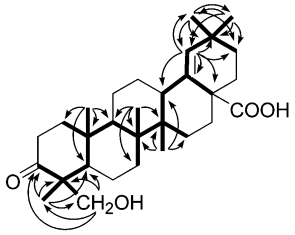


Figure 1. Key HMBC correlations of **1** (↷).

Results and Discussion

Acridocarpusic acid A (**1**) was obtained as a colorless powder with a molecular formula of $C_{30}H_{46}O_4$ on the basis of a quasimolecular ion peak at *m*/*z* 471.3459 $[M + H]^+$ in its HRFABMS spectrum. Its ^{1}H NMR spectrum displayed signals corresponding to six tertiary methyls (δ_H 0.79, 0.89, 0.98, 0.98, 1.00, and 1.27), one olefinic proton (δ_H 5.18, s), and one oxymethylene group (δ_H 3.43, d J = 11.2 Hz; 3.97, d J = 11.2 Hz). Its ^{13}C NMR spectrum showed signals for 30 carbons, including one ketone (δ_C 221.5), one carboxyl (δ_C 179.5), one double bond (δ_C 133.5 and 136.6), and one oxygenated methylene (δ_C 65.8); the other 25 carbons had chemical shifts from δ_C 14.8 to 55.2. On the basis of ^{1}H−^{1}H COSY, HMQC, and HMBC spectra, **1** was determined to be an oleanane-type triterpenoid bearing one double bond (C-18), an oxymethylene group (C-23), and a carboxyl group (C-28) (Figure 1). The ^{13}C NMR spectrum of **1** was similar to that of moronic acid (**6**), except for the presence of a $-CH_2O-$ group (δ_C 65.8) as well as the absence of a $-CH_3$ group (δ_C 26.7). Therefore, the planar structure of **1** was determined to be 23-hydroxymoronic acid. In the 2D NOESY spectrum of **1**, one oxymethylene proton (δ_H 3.97) correlated to C-25 (δ_H 0.89), and both the oxymethylene protons (δ_H 3.43, and 3.97) exhibited correlations to C-24 (δ_H 1.27) (Figure 2). Thus, the structure was assigned as 23β-hydroxymoronic acid (**1**).

Acridocarpusic acid B (**2**) was also obtained as a colorless powder, and the molecular formula $C_{32}H_{48}O_5$ was determined by HRFABMS and ^{13}C NMR. The ^{1}H NMR and ^{13}C NMR data were closely related to those of **1**, except for additional signals arising from an acetoxyl group (C=O:

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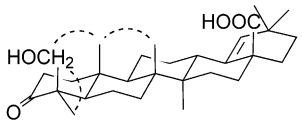

Figure 2. Key NOESY correlations of **1** (dashed curves).

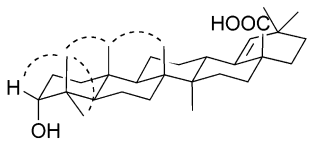

Figure 3. Key NOESY correlations of **4** (dashed curves).

δ_C 171.0; CH_3: δ_H 2.00/δ_C 20.8), which suggested that **2** is a monoacetate of **1**. This was confirmed by the downfield shifts of H_2-23 (δ_H 3.96 and 4.60) in **2**. The detailed assignments of the ^{1}H NMR and ^{13}C NMR signals were performed by ^{1}H−^{1}H COSY, HMQC, and HMBC experiments. The determination of the configuration of C-23 was based on the NOESY data of **2**, in which H_2-23 displayed a strong correlation with the β-oriented proton H_3-25. Accordingly, the structure of **2** was established as 23-β-acetoxymoronic acid.

The molecular formula of $C_{30}H_{44}O_4$ was established for acridocarpusic acid C (**3**) by HRFABMS. Inspection of the ^{1}H NMR spectrum revealed that **3** was also closely related to **1** but contained a resonance for an aldehyde proton at δ_H 9.70 instead of the oxymethylene protons at δ_H 3.43 and 3.97. The ^{13}C NMR spectrum of **3** displayed a new resonance at δ_C 201.2 and lacked the CH_2O resonance at δ_C 65.8 in **1**. The new resonance was assigned to an aldehyde group, and it correlated to H_3-24 in the HMBC spectrum of **3**. The only difference between **3** and **1** was the functional group at C-23, in which the alcohol group in **1** was replaced by the aldehyde group in **3**. The β-configuration of C-23 was assigned on the basis of NOESY correlations between H-23 and H_3-24/H_3-25 in the same manner as was done for acridocarpusic acid A (**1**). Thus, the structure of **3** was determined as shown.

The ^{1}H NMR spectrum of **4** showed the presence of seven methyl groups (δ_H 0.78, 0.83, 0.87, 0.93, 0.98, 0.99, 1.00), an oxygenated methine proton (δ_H 3.40, br s), and an olefinic proton (δ_H 5.19, s). ^{1}H−^{1}H COSY, HMQC, and HMBC established **4** to be an oleanane-type triterpenoid bearing a hydroxyl at C-3, a double bond at C-18, and a carboxyl group at C-28. The ^{13}C NMR values of **4** were assigned on the basis of HMQC and HMBC spectra, which closely resembled those of methyl-3-α-hydroxyolean-18-en-28-oate,[6] except for the absence of the OMe group. Acridocarpusic acid D (**4**) gave a $[M - H_2O + H]^+$ peak at *m/z* 439.3539 in the HRFABMS (calcd for $C_{30}H_{47}O_2$, 439.3576), indicating the ready loss of H_2O. The orientation of the 3-OH group was assigned as α since H-3 was a broad singlet like that of katonic acid (δ_H 3.61, br s, H-3),[7,8] rather than a doublet of doublets like that of 3β-hydroxy-3-deoxymoronic acid (δ_H 3.19, dd, J = 5.5 and 11.0 Hz, H-3).[10] In the NOESY spectrum of **4**, H-3 showed correlations to both H_3-23 and H_3-24 (Figure 3), which confirmed the above deduction.

The molecular formula of acridocarpusic acid E (**5**) was established as $C_{32}H_{50}O_4$ by HRFABMS (*m/z* 499.3820 $[M + H]^+$, calcd for $C_{32}H_{51}O_4$ 499.3787). The ^{1}H NMR and ^{13}C NMR of **5** were very similar to those of **4** (Table 1 and Experimental Section). The major difference between **4** and **5** was the presence of an extra acetate group at C-3 in **5**, which resulted in chemical shift changes in the ^{1}H NMR spectra for H-3 from δ_H 3.40 (**4**) to 4.63 (**5**) and in the ^{13}C NMR spectra for C-3 from δ_C 76.2 (**4**) to 78.3 (**5**). Other carbons in ring A were also affected, such as C-1, C-2, C-4, and C-5 (Table 1). The small coupling constant of H-3 (δ_H 4.63, apparent t, J = 3.0 Hz) with H_2-2 indicated that H-3 was equatorial,[6−8] not axial.[9,10] The NOESY spectrum of **5** was consistent with that of **4** and confirmed the orientation of the acetoxyl group to be α.

Table 1. ^{13}C NMR Spectral Data (δ) for Compounds **1**−**6**

C	**1**[a]	**2**[a]	**3**[a]	**4**[b]	**5**[a]	**6**[a,c]
1	39.6	40.6	40.0	34.4	34.2	39.7
2	34.2	34.5	34.3	25.4	22.9	33.9
3	221.5	213.6	201.2	76.2	78.3	218.3
4	50.5	52.1	63.6	37.6	36.7	47.1
5	55.2	57.6	57.5	49.2	50.4	54.7
6	19.1	19.6	19.6	18.2	18.0	19.5
7	33.5	34.8	35.9	33.5	34.3	33.4
8	40.4	40.6	40.5	40.9	40.9	40.4
9	50.2	50.7	49.7	50.9	51.0	50.3
10	36.7	37.0	37.3	37.4	37.2	36.8
11	21.8	21.4	21.6	20.8	20.7	21.4
12	26.0	25.9	25.9	26.0	26.0	25.9
13	41.5	41.3	41.3	41.4	41.4	41.3
14	42.6	42.6	42.7	42.7	42.7	42.4
15	29.3	29.4	29.3	29.3	29.4	29.2
16	33.8	33.5	33.5	33.4	33.5	33.6
17	47.9	47.9	48.0	48.0	47.9	47.8
18	136.6	136.5	136.3	136.9	136.9	136.4
19	133.5	133.7	133.6	133.3	133.5	133.0
20	32.1	32.1	32.1	32.1	32.1	31.9
21	33.4	33.4	33.5	33.5	33.4	33.3
22	33.3	33.3	33.3	33.5	33.4	33.2
23	65.8	66.1	201.2	22.1	21.7	26.7
24	22.2	20.4	17.4	28.2	27.8	20.8
25	17.5	16.7	15.7	16.5	16.5	16.4
26	15.7	16.0	16.0	16.0	16.0	15.7
27	14.8	14.9	14.8	15.0	15.1	14.7
28	179.5	178.8	179.8	179.9	179.0	182.8
29	30.3	30.4	30.4	30.4	30.3	30.2
30	29.1	29.1	29.1	29.1	29.1	29.0
C=O		171.0			170.9	
CH_3		20.8			21.4	

[a] Recorded at 125 MHz. [b]Recorded at 100 MHz. [c]Ref 6.

The structures of the known compounds were identified as moronic acid (**6**),[10] ursolic acid,[11] oleanolic acid,[12] 4′,5-dihydroxy-7-methoxyflavone,[13] and 4′,5-dihydroxy-3′,7-dimethoxyflavone[14] by comparison of their spectroscopic data with literature data.

All the isolated compounds were tested for cytotoxicity against the A2780 human ovarian cancer cell line. It was found that seven of the triterpenoids (**1**, **2**, **4**−**6**, ursolic acid, and oleanolic acid) were weakly active, with IC_{50} values from 5.9 to 15.9 μg/mL, while the flavonoids 4′,5-dihydroxy-7-methoxyflavone and 4′,5-dihydroxy-3′,7-dimethoxyflavone were inactive (Table 2). Acridocarpusic acid C (**3**), however, showed significant cytotoxic activity, with an IC_{50} value of 0.7 μg/mL (Table 2). The aldehyde group in acridocarpusic acid C (**3**) thus appears to be the functional group that makes the major contribution to the activity of the molecule.

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. IR and UV spectra were measured on MIDAC M-series FTIR and Shimadzu UV-1201 spectrophotometers, respectively. NMR spectra were obtained on a JEOL Eclipse 500 or a Unity 400 spectrometer in $CDCl_3$. Mass spectra were obtained on a JEOL JMS-HX-110 instrument. The chemical shifts are given in δ (ppm) with TMS (tetramethylsilane) as the internal reference, and coupling constants are reported in Hz. A Horizon flash chromatograph from BioTage Inc. was used for flash column

Table 2. Cytotoxicities of Isolated Compounds[a]

compound	IC_{50} (μg/mL)
1	15.9
2	11.6
3	0.7
4	5.9
5	15.3
6	13.1
ursolic acid	9.2
oleanolic acid	8.0
4′,5-dihydroxy-7-methoxyflavone	>20
4′,5-dihydroxy-3′,7-dimethoxyflavone	>20

[a] Concentration of each compound that inhibited 50% (IC_{50}) of the growth of the A2780 human ovarian cell line according to the procedure described,[15] with actinomycin D (IC_{50} 1−3 ng/mL) as the positive control.

chromatography. HPLC was performed on a Shimadzu LC-10AT instrument with a C_{18} Varian Dynamax column (5 μm, 250 ×10 mm) and a LiChrosorb diol column (5 μm, 250 × 4.6 mm).

Cytotoxicity Bioassays. The A2780 ovarian cancer cell line assay was performed at Virginia Polytechnic Institute and State University as previously reported.[15]

Plant Material. The plant sample used was a collection of leaves and flowers, designated Randrianjanaka et al. 680, and duplicates of the voucher specimens were deposited at the Missouri Botanical Garden (MO), the Muséum National d'Histoire Naturelle, Paris (P), the Départment des Recherches Forestières et Pisicoles, Madagascar (TEF), and the Centre National d'Applications et des Recherches Pharmaceutique, Madagascar. The collection was made by L. Randrianjanaka, S. Rakotonandrasana, M. Andrianjaka, B. Randriamavonju, and Rakotoson 1 km west of Mitanonoka village along the railroad to Sahamalaza, in the district of Vavatenina, in the province of Toamasina at 815 m in elevation at 17°45′28″ S, 48°45′40″ E.

Extraction and Isolation. The dried plant sample described above (336 g) was extracted with EtOH to give 27.3 g of extract. The crude EtOH extract (527 mg) was suspended in aqueous MeOH (MeOH−H_2O, 9:1, 50 mL) and extracted with *n*-hexane (3 × 50 mL). The aqueous layer was then diluted to 70% MeOH (v/v) with H_2O and extracted with CH_2Cl_2 (3 × 50 mL). The hexanes and CH_2Cl_2 extracts (112 and 370 mg, respectively) were found to be cytotoxic and were combined on the basis of their similar activity and HPLC patterns. The combined fraction (482 mg) was separated using a Biotage Horizon flash chromatograph over a C_{18} column using MeOH−H_2O (60:40 to 100:0) and then 100% MeOH, furnishing seven fractions (I−VII), of which fraction VI was found to be active. Ten fractions (A−J) were collected from fraction VI using HPLC chromatography over C_{18} using 90% MeOH−H_2O and then 100% MeOH. The new compounds acridocarpusic acid A (**1**, 1.5 mg, t_R 16 min) and acridocarpusic acid E (**5**, 1.6 mg, t_R 43.5 min) were obtained from fractions C and I. The known terpenoids moronic acid (**6**, 4.1 mg, t_R 35 min), ursolic acid (3.2 mg, t_R 30 min), and oleanolic acid (3.5 mg, t_R 28 min) were obtained from fractions H, G, and F, respectively. 4′,5-Dihydroxy-7-methoxyflavone (0.5 mg, t_R 14 min) and 4′,5-dihydroxy-3′,7-dimethoxyflavone (0.8 mg, t_R 12 min) were obtained from fractions A and B, and could also be obtained from fraction V. The new compounds, acridocarpusic acid B (**2**, 0.5 mg, t_R 11 min), acridocarpusic acid C (**3**, 0.3 mg, t_R 13 min) and acridocarpusic acid D (**4**, 0.5 mg, t_R 13.5 min) were purified from fractions D and E on diol HPLC with the mobile phase hexanes−2-propanol (97:3).

To get enough material for the structure elucidation of compounds **2**−**4**, more crude extract (2 g) was studied, and compounds **2**−**4** (1.8, 1.2, and 1.8 mg, respectively) were purified using the above-mentioned methods.

Acridocarpusic acid A (1): colorless powder; $[\alpha]_D$ +8.2° (*c* 0.15, MeOH); UV (MeOH) λ_{max} 202 nm; IR ν_{max} 2939, 2865, 1706, 1697, 1469, 1455, 1376, 1269, 1218, 1036, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.18 (1H, s, H-19), 3.97 (1H, d, J = 11.2 Hz, H-23a), 3.43 (1H, d, J = 11.2 Hz, H-23b), 2.62 (1H, m, H-2), 2.38 (1H, m, H-2), 2.24 (1H, m, H-13), 2.18 (1H, m, H-22), 1.98 (1H, m, H-22), 1.96 (1H, m, H-16), 1.2−1.7 (17H, m), 1.27 (3H, s, H-24), 1.00 (3H, s, H-29), 0.98 (3H, s, H-30), 0.98 (3H, s, H-26), 0.89 (3H, s, H-25), 0.79 (3H, s, H-27); ^{13}C NMR ($CDCl_3$), see Table 1; HRFABMS *m/z* 471.3459 $[M + H]^+$ (calcd for $C_{30}H_{47}O_4$, 471.3474); ESIMS *m/z* 471 $[M + H]^+$, 435, 407, 247, 200, 189, 109.

Acridocarpusic acid B (2): colorless powder; $[\alpha]_D$ +4.2° (*c* 0.2, MeOH); UV (MeOH) λ_{max} 201 nm; IR ν_{max} 2930, 2865, 1769, 1706, 1697, 1455, 1376, 1232, 1036, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.19 (1H, s, H-19), 4.60 (1H, d, J = 11.2 Hz, H-23a), 3.96 (1H, d, J = 11.2 Hz, H-23b), 2.76 (1H, m, H-2), 2.34 (1H, m, H-2), 2.24 (1H, m, H-13), 2.18 (1H, m, H-22), 2.02 (1H, m, H-22), 2.00 (3H, s, Me-C═O), 1.96 (1H, m, H-16), 1.2−1.7 (17H, m), 1.15 (3H, s, H-24), 1.11 (3H, s, H-25), 1.02 (3H, s, H-26), 1.00 (3H, s, H-29), 0.98 (3H, s, H-30), 0.77 (3H, s, H-27); ^{13}C NMR ($CDCl_3$), see Table 1; HRFABMS *m/z* 513.3577 $[M + H]^+$ (calcd for $C_{32}H_{49}O_5$, 513.3580); ESI MS *m/z* 513 $[M + H]^+$, 453, 435, 407, 201.

Acridocarpusic acid C (3): colorless powder; $[\alpha]_D$ +7.5° (*c* 0.1, MeOH); UV (MeOH) λ_{max} 201 nm; IR ν_{max} 2944, 2869, 1720, 1708, 1697, 1450, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.70 (1H, s, H-23), 5.20 (1H, s, H-19), 2.64 (1H, m, H-2), 2.47 (1H, m, H-2), 2.25 (1H, m, H-13), 2.20 (1H, m, H-22), 2.08 (1H, m, H-22), 1.98 (1H, m, H-16), 1.2−1.7 (17H, m), 1.25 (3H, s, H-24), 1.04 (3H, s, H-25), 1.01 (3H, s, H-29), 1.00 (3H, s, H-30), 0.98 (3H, s, H-26), 0.78 (3H, s, H-27); ^{13}C NMR ($CDCl_3$), see Table 1; HRFABMS *m/z* 469.3301 $[M + H]^+$ (calcd for $C_{30}H_{45}O_4$, 469.3318); ESIMS *m/z* 469 $[M + H]^+$, 423, 309, 300, 243, 229.

Acridocarpusic acid D (4): colorless powder; $[\alpha]_D$ +17.5° (*c* 0.2, MeOH); UV (MeOH) λ_{max} 202 nm; IR ν_{max} 2939, 2865, 1697, 1455, 1376, 1236 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.19 (1H, s, H-19), 3.40 (1H, br s, H-3), 2.20 (1H, m, H-13), 2.18 (1H, m, H-22), 1.98 (1H, m, H-22), 1.96 (1H, m, H-16), 1.2−1.7 (19H, m), 1.00 (3H, s, H-29), 0.99 (3H, s, H-26), 0.98 (3H, s, H-30), 0.93 (3H, s, H-24), 0.87 (3H, s, H-25), 0.83 (3H, s, H-23), 0.78 (3H, s, H-27); ^{13}C NMR ($CDCl_3$), see Table 1; HRFABMS *m/z* 439.3539 $[M - H_2O + H]^+$ (calcd for $C_{30}H_{47}O_2$, 439.3576); ESI MS *m/z* 439 $[M - H_2O + H]^+$, 425.

Acridocarpusic acid E (5): colorless powder; $[\alpha]_D$ +2.0° (*c* 0.1, MeOH); UV (MeOH) λ_{max} 201 nm; IR ν_{max} 2939, 2869, 1693, 1451, 1388, 1375, 1264, 1233, 1204, 1066, 1038, 990, 931, 846, 735, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.20 (1H, s, H-19), 4.63 (1H, apparent triplet, J = 3.0 Hz, H-3), 2.20 (1H, m, H-13), 2.18 (1H, m, H-22), 2.08 (3H, s, CH_3−C═O), 2.00 (1H, m, H-22), 1.90 (1H, m, H-16), 1.2−1.7 (19H, m), 1.01 (3H, s, H-29), 1.00 (3H, s, H-26), 0.98 (3H, s, H-30), 0.88 (3H, s, H-25), 0.87 (3H, s, H-23), 0.834 (3H, s, H-24), 0.830 (3H, s, H-27); ^{13}C NMR ($CDCl_3$), see Table 1; HRFABMS *m/z* 499.3820 $[M + H]^+$ (calcd for $C_{32}H_{51}O_4$, 499.3787); ESI MS *m/z* 439 $[M - Ac - H_2O + H]^+$, 364.

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Supporting Information Available: ^{1}H NMR spectra for compounds **1**−**5** and structures of all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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