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PLANT ANTICANCER AGENTS, XXXIV. CUCURBITACINS FROM *ELAEOCARPUS DOLICHOSTYLUS*[1,2]

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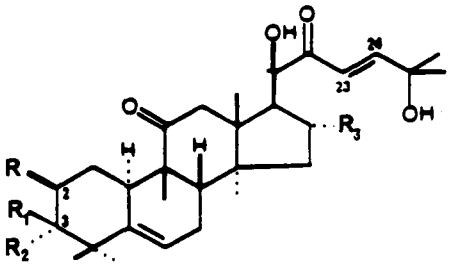
ABSTRACT.—*Elaeocarpus dolichostylus* has afforded the new cucurbitacin derivative, hexanorcucurbitacin F (**3**), whose structure was determined by spectroscopic and chemical correlation with cucurbitacin F (**1**). Cucurbitacin F (**1**) and 23,24-dihydrocucurbitacin F (**2**) were also isolated in this study.

In the course of a continuing search for tumor inhibitors of plant origin, an alcoholic extract of the stem bark of *Elaeocarpus dolichostylus* Schltr. (Elaeocarpaceae) was found to have cytotoxic activity when evaluated with cultured KB cells. A previous chemical investigation of the leaves of *E. dolichostylus* resulted in the isolation and characterization of five indolizidine alkaloids, (±)-elaeocarpine, (±)-isoelaeocarpine, elaeocarpidine, (+)-elaeocarpiline, and (−)-isoelaeocarpiline (2). Three of these alkaloids—isoeleocarpine, eleocarpine, and isoeleocarpiline—have been evaluated in the L1210 in vivo test system and found to be inactive and nontoxic when administered ip at 300-400 mg/kg body weight (3). The lack of activity of these alkaloids prompted us to re-investigate this plant in order to isolate the constituent(s) responsible for the observed cytotoxic activity.[7]

In the present work, bioactivity-directed fractionation of a MeOH extract of the stem bark of *E. dolichostylus* has led to the isolation of a cytotoxic compound, cucurbita-



	R	R_1	R_2	R_3
1	OH	H	OH	OH
4	OH	OH	H	OH
5	OAc	H	OAc	OAc

[1]For paper XXXIV in this series, see J.X. Guo, *et al.* (1).

[2]These data were presented in part, at the American Society of Pharmacognosy Annual Meeting, University, Mississippi, July, 1983.

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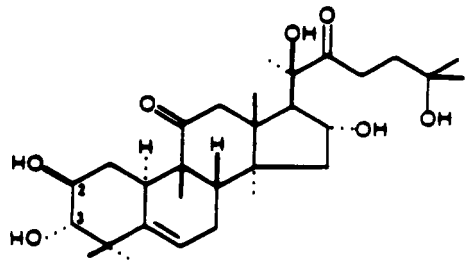
[7]Tlc analysis of the methanolic extract of the stem bark of *Elaeocarpus dolichostylus* showed it to be devoid of alkaloids, as judged by a negative reaction with Dragandorff's reagent.



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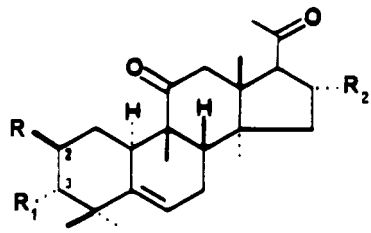

	R	R_1	R_2
3	OH	OH	OH
6	OAc	OAc	OAc

cin F (**1**). Two inactive compounds, 23,24-dihydrocucurbitacin F (**2**) and the novel cucurbitacin, hexanorcucurbitacin F (**3**) were also obtained.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were measured on a Kofler hot-stage instrument and are uncorrected. Preparative hplc was done on a Jobin-Yvon Chromatospac Prep 10/100. The adsorbent used for gravity-fed and preparative hplc was silica gel 60, particle size 0.063-0.200 mm (Merck). Tlc was performed with Analtech silica gel GHLF precoated plates (250 micron). Chromatograms were visualized with 60% H_2SO_4 in H_2O, heated at 100° for 10 min. Optical rotations were measured on a Perkin-Elmer model 241 Polarimeter. Uv spectra were obtained with a Beckman model DB-G grating spectrophotometer with MeOH as the solvent and ir spectra were obtained on a Nicolet model MX-1 Fourier Transform spectrophotometer. ^{1}H-nmr spectra were obtained on a Nicolet NT360 spectrometer with deuterated pyridine as the solvent. All values are referenced to the pyridine peak at δ 7.19 ppm and the chemical shifts are recorded in δ (ppm) units. Low resolution mass spectra were obtained with a Finnigan model 4500 mass spectrometer. High resolution mass spectra were taken on a VG 7070 mass spectrometer by peak matching.

PLANT MATERIAL.—The stem bark of *E. dolichostylus* was collected in Papua-New Guinea in 1979, by staff members of the Economic Botany Laboratory, Agricultural Research Service, BARC-East, USDA, Beltsville, MD. A voucher specimen, representative of the collection, has been deposited in the Herbarium of the National Arboretum, Washington, DC.

EXTRACTION AND FRACTIONATION.—The air-dried, milled stem bark of *E. dolichostylus* (34 kg) was extracted exhaustively with MeOH. After evaporation in vacuo, a residue (2.8 kg) was obtained that was active when evaluated with the KB cell culture test system (ED_{50}, 3.2 μg/ml).[8] This residue was partitioned between equal volumes of *n*-hexane (bp 66-69°) and H_2O-MeOH (1:2). After the addition of sufficient H_2O to increase the ratio to 1:1 (H_2O-MeOH), the solution was extracted with $CHCl_3$. After removal of the solvent, the biological activity was found to be concentrated in the $CHCl_3$ extract (KB, ED_{50}, 2.2 μg/ml). This extract (105 g) was then separated by preparative hplc over silica gel (1.5 kg). Elution

[8]Extracts, fractions and isolates were tested in the cell culture facilities, PCRPS, College of Pharmacy, University of Illinois at Chicago, essentially according to the protocols established by the Developmental Therapeutics Program of the National Cancer Institute (4) as described previously (5,6). In the P-388 or KB in vitro cell culture assays an extract or isolate is considered active if it shows ED_{50} values of $\leq$20 μg/ml or $\leq$4 μg/ml, respectively.

was effected with mixtures of $CHCl_3$ and MeOH of increasing polarity. A total of 53 one-liter fractions were collected. Fractions showing similar tlc profiles were combined, evaporated to dryness, and evaluated for cytotoxic activity. The best activity (KB, ED_{50}, 0.17 μg/ml) was found in Fraction F130, eluted from the column with $CHCl_3$-MeOH (9:1). This fraction (14.65 g) was purified by chromatography over silica gel; elution was with $CHCl_3$ and $CHCl_3$-MeOH mixtures. Of the thirteen fractions collected from this column, Fraction F147 was found to exhibit the greatest cytotoxicity (ED_{50}, 0.52 μg/ml).

ISOLATION OF CUCURBITACIN F (**1**), 23,24-DIHYDROCUCURBITACIN F (**2**) AND HEXANORCUCURBITACIN F (**3**).—Partitioning of F147 (4.3 g) between EtOAc and H_2O resulted in the formation of a precipitate (F161), which was collected. Tlc analysis of F161 (*n*-BuOH-Et_2O-HOAc, 20:60:0.8) indicated the presence of three major compounds with Rf values corresponding to 0.84, 0.75, and 0.65. Fraction F161 (1.4 g) was chromatographed over silica gel with *n*-BuOH-Et_2O-HOAc (20:60:0.8). From fractions 28-38 a white precipitate formed (Rf 0.84) which, when recrystallized from EtOH-hexane (1:1), yielded cucurbitacin F (**1**, 280 mg, 0.00082%). From fractions 57-100 a white precipitate formed which, following repeated column chromatography over silica gel 60 with *n*-BuOH-Et_2O-HOAc (20:60:0.8), resulted in the isolation of 23,24-dihydrocucurbitacin F (**2**, 5 mg, 0.000015%, Rf 0.75) and hexanorcucurbitacin F (**3**, 22 mg, 0.000065%, Rf 0.65).

CHARACTERIZATION OF CUCURBITACIN F (**1**).—Colorless needles, mp 249-253° [lit. mp 244-245° (7), 174-178° (8)]; $[\alpha]^{25}D$ +28° (c 0.07, EtOH); ir ν max (KBr) 3437, 2973, 2952, 2919, 2879, 2850, 1687, 1633, 1390, 1375, 1366, 1285, 1167, 1090, 1056, and 1030 cm^{-1}; uv λ max (MeOH) 232 nm (log ε 4.08); ^{1}H-nmr (360 MHz, pyridine-d_5) δ 1.206 (s, -CH_3), 1.233 (s, -CH_3), 1.290 (s, -CH_3), 1.428 (s, -CH_3), 1.453 (s, -CH_3), 1.470 (s, -CH_3), 1.500 (s, -CH_3), 1.543 (d, J=10.0 Hz, 1-βH), 1.595 (s, -CH_3), 1.713 (d, J=12.8 Hz, 15-βH), 1.900 (m, 7-βH), 1.929 (d, J=8.2 Hz, 8-H), 2.332 (dm, 7-αH), 2.447 (ddd, J=3.8, 3.9, 12.1 Hz, 1-αH), 2.710 (brd, J=12.5 Hz, 10-H), 2.784 (d, J=14.6 Hz, 12-βH), 2.990 (d, J=7.0 Hz, 17-H), 3.162 (d, J=14.6 Hz, 12-αH), 3.425 (dd, J=4.7, 9.1 Hz, 3-H), 4.139 (m, 2-H), 4.986 (m, 16-H), 5.716 (brd, J=5.4 Hz, 6-H), 5.904 (s, 20-OH or 25-OH), 6.183 (d, J=5.0 Hz, 2-OH), 6.255 (d, J=4.8 Hz, 16-OH), 6.366 (d, J=4.7 Hz, 3-OH), 6.730 (s, 20-OH or 25-OH), 7.481 (d, J=15.3 Hz, 23-H), and 7.555 (d, J=15.3 Hz, 24-H); ms (20 eV) *m/z* (missing M^+), 500 (M^+-18, 0.6%), 482 (0.6), 405 (0.9), 387 (2.5), 369 (3.7), 112 (23.0), and 96 (100).

ACETYLATION OF CUCURBITACIN F (**1**).—Cucurbitacin F (**1**, 15 mg) was treated with Ac_2O-pyridine (1:1, 1 ml) at room temperature overnight. Work up in the usual manner afforded a triacetate **5** (11 mg, amorphous powder); mp 147-151°; ir ν max (KBr) 3461, 2975, 1743, 1697, 1625, 1370, 1246, 1049, 1029 cm^{-1}; ^{1}H-nmr (360 MHz, pyridine-d_5) δ 1.117 (s, -CH_3), 1.137 (s, -CH_3), 1.161 (s, -CH_3), 1.210 (s, -CH_3), 1.224 (s, -CH_3), 1.495 (d, J=10.9 Hz, 1-βH), 1.442 (d, J=12 Hz, 15-βH), 1.504 (s, -CH_3), 1.512 (s, -CH_3), 1.537 (s, -CH_3), 1.780 (dd, J=5.5, 19.4 Hz, 7-βH), 1.880 (d, J=8.2 Hz, 8-H), 1.975 (s, -$OCOCH_3$), 2.078 (s, -$OCOCH_3$), 2.13 (s, -$OCOCH_3$), 2.282 (m, 7-αH), 2.302 (ddd, J=4.1, 4.0, 12.2 Hz, 1-αH), 2.638 (d, J=14.8 Hz, 12-βH), 2.696 (brd, J=12.6 Hz, 10-H), 2.926 (d, J=14.8 Hz, 12-αH), 2.964 (d, J=7.8 Hz, 17-H), 5.045 (d, J=10.5 Hz, 3-H), 5.488 (ddd, J=4.1, 10.5, 10.9 Hz, 2-H), 5.700 (brd, J=5.5 Hz, 6-H), 5.814 (dd, J=7.8, 7.8 Hz, 16-H), 6.140 and 6.761 (1H each, s, 20-OH and 25-OH), 7.420 (d, J=15.2 Hz, 23-H), 7.537 ppm (d, J=15.2 Hz, 24-H); ms (70 eV) *m/z* (missing M^+), 584 (M^+-60, 0.4%), 566 (1.2), 531 (32.0), 524 (1.7), 471 (1.2), 455 (8.3), 411 (6.6), 369 (21.0), 351 (45.0), 309 (12.0), 219 (30.0), 96 (100).

CHARACTERIZATION OF 23,24-DIHYDROCUCURBITACIN F (**2**).—Colorless needles, mp 146-148° [lit. mp 128-135° (8)]; $[\alpha]^{21}D$ +41.2° (c 0.1, EtOH) [lit. value +50° (8)]; ir ν max (KBr) 3430, 2973, 2967, 2947, 2941, 2878, 1702, 1390, 1376, 1365, 1087, 1057, and 1028 cm^{-1}; uv λ max (MeOH) 208 nm (log ε 4.0); ^{1}H-nmr (360 MHz, pyridine-D_5) δ 1.206 (s, -CH_3), 1.235 (s, -CH_3), 1.312 (s, -CH_3), 1.367 (6H, s, 2-CH_3), 1.472 (s, -CH_3), 1.520 (s, -CH_3), 1.578 (s, -CH_3), 1.693 (d, J=14.4 Hz, 15-βH), 1.900 (m, 7-βH), 1.929 (d, J=7.7 Hz, 8-H), 2.231 (2H, m, 24-H_2), 2.335 (dm, J=19.0 Hz, 7-αH), 2.449 (ddd, J=3.5, 3.5, 12.4 Hz, 1-αH), 2.719 (brd, J=11.2 Hz, 10-H), 2.780 (d, J=14.7 Hz, 12-βH), 2.965 (d, J=7.1 Hz, 17-H), 3.230 (d, J=14.7 Hz, 12-αH), 3.292 (m, 23-H), 3.427 (dd, J=4.4, 9.3 Hz, 3-H), 3.500 (m, 23-H), 4.136 (m, 2-H), 4.900 (m, 16-H), 5.650 (s, 20-OH or 25-OH), 5.719 (brd, J=5.5 Hz, 6-H), 5.760 (s, 20-OH or 25-OH), 6,175 (d, J=3.9 Hz, 2-OH), 6.382 (d, J=4.4 Hz, 3-OH), and 6.460 ppm (d, J=4.7 Hz, 16-OH); ms (20 eV) *m/z* (missing M^+) 502 (M^+-18, 0.6%) 484 (0.6), 469 (1.1), 405 (2.2), 387 (3.0), 369 (1.3), 142 (4.9), 131 (15.0), 113 (100), 95 (1.3).

CHARACTERIZATION OF HEXANORCUCURBITACIN F (**3**).—Colorless needles, mp 128-130°; $[\alpha]^{25}D$ +140° (c 0.18, $CHCl_3$); ir ν max (KBr) 3441, 3412, 2968, 1697, 1432, 1390, 1374, 1359, 1207, 1192, 1055, 1027, 668 cm^{-1}; uv λ max (MeOH) 206 nm (log ε 3.92); ^{1}H-nmr (360 MHz, pyridine-d_5) δ 0.789 (s, -CH_3), 1.220 (s, -CH_3), 1.308 (s, -CH_3), 1.471 (s, -CH_3), 1.530 (m, 1-βH), 1.541 (s, CH_3), 1.802 (d, J=13.1 Hz, 15-βH), 1.880 (d, J=7.6 Hz, 8-H), 1.967 (m, 7-βH), 2.140 (s, -$COCH_3$), 2.236 (brdd, J=7.6, 19.1 Hz, 7-αH), 2.404 (ddd, J=4.0, 4.0, 12.4 Hz, 1-αH), 2.580 (d,

J=14.2 Hz, 12-βH), 2.744 (brd, J=11.5 Hz, 10-H), 3.340 (d, J=14.2 Hz, 12-αH), 3.411 (dd, J=4.2, 9.1 Hz, 3-H), 3.478 (d, J=6.5 Hz, 17-H), 4.090 (m, 2-H), 5.340 (m, 16-H), 5.715 (brd, J=5.7 Hz, 6-H), 6.159 (d, J=3.8 Hz, 2-OH), 6.398 (d, J=4.2 Hz, 3-OH), 6.780 ppm (d, J=4.2 Hz, 16-OH); ms (ei, 20 eV) *m/z* 404 (M^+, 1%), 387 (3.1), 386 (12.3), 372 (8.9), 371 (34.3), 369 (5.0), 368 (16.7), 353 (10.4), 195 (8.1), 191 (10.5), 179 (7.6), 177 (8.5), 173 (12.6), 172 (11.1), 171 (15.0), 157 (13.4), 150 (14.8), 137 (13.4), 136 (24.2), 135 (19.5), 133 (14.3), 132 (100), 125 (11.4), 111 (11.5), 107 (10.2), and 87 (17.7); ms (ci, CH_4, 70 eV), *m/z* 405 (M^++1, 10.4%), 388 (27.2), 387 (100), 385 (13.4), 370 (16.1), 369 (61.2), 351 (10.6), 237 (10.5), 219 (16.6), 179 (8.0), 177 (8.5), and 151 (9.9); Mass measurement *m/z* 404.25687 ($C_{24}H_{36}O_5$ requires 404.2561).

ACETYLATION OF HEXANORCUCURBITACIN F (**3**).—Hexanorcucurbitacin F (**3**, 11 mg) was treated with Ac_2O-pyridine (1:1, 2 ml) at room temperature for 15 h. Work up in the usual manner afforded a triacetate **6** (12 mg) as a gum, ir ν max (KBr) 2930, 1734, 1703, 1182 cm^{-1}; ^{1}H-nmr (360 MHz, pyridine-d_5) δ 0.703 (s, -CH_3), 1.116 (s, -CH_3), 1.157 (s, -CH_3), 1.210 (s, -CH_3), 1.218 (s, -CH_3), 1.401 (ddd, J=12.0, 12.0, 12.0, 1-βH), 1.560 (d, J=14.2 Hz, 15-βH), 1.791 (brd, J=5.8 Hz, 7-βH), 1.839 (d, J=8.3 Hz, 8-H), 1.975 (s, -$OCOCH_3$), 2.065 (s, -$OCOCH_3$), 2.120 (s, -$OCOCH_3$), 2.128 (s, -C-CH_3),[9] 2.260 (m, 7-αH), 2.301 (ddd, J=4.2, 4.2, 12.0 Hz, 1-αH), 2.492 (d, J=14.5 Hz, 12-αH), 2.731 (brd, J=12.0 Hz, 10-H), 3.151 (d, J=14.5 Hz, 12-αH), 3.483 (d, J=6.7 Hz, 17-H), 5.032 (d, J=10.1 Hz, 3-H), 5.431 (ddd, J=4.2, 10.1, 12.0 Hz, 2-H), 5.691 (brd, J=5.8 Hz, 6-H), and 5.990 ppm (dd, J=6.7, 7.3 Hz, 16-H); ms (ei, 20 eV) *m/z* (missing M^+), (M^+-60, 3.4%), 455 (2.6), 426 (1.4), 410 (20.0), 395 (14.0), 132 (100); ms (ci. CH_4) *m/z* 531 (M^+, 28.7%).

BIOLOGICAL ACTIVITY OF THE ISOLATES .—Cucurbitacin F (**1**) displayed significant cytotoxic activity in the KB and P-388 in vitro cell culture test systems (ED_{50} 0.074 and 0.04 μg/ml, respectively). 23,24-Dihydrocucurbitacin F (**2**) and hexanorcucurbitacin F (**3**) were both inactive in the KB and P-388 in vitro cell culture test systems (ED_{50}>50 μg/ml).

DISCUSSION

As presently described, a bioactivity-directed fractionation of a methanolic extract of the stem bark of *E. dolichostylus* has led to the isolation of a cytotoxic compound, cucurbitacin F (**1**), the known compound 23,24-dihydrocucurbitacin F (**2**), and a new compound, hexanorcucurbitacin F (**3**). The latter two isolates were inactive when evaluated in the KB and P-388 in vivo cell culture assays. The cytotoxic activities reported support the previous postulate that the double bond in the side chain of the cucurbitacin is necessary for cytotoxic activity (9-12).

Also reported herein are the 360 MHz ^{1}H-nmr assignments of these cucurbitacins obtained in pyridine-d_5. This solvent was chosen to permit the attainment of more concentrated solution, which in turn facilitated the proton assignments of these compounds, and to permit improved resolution via the shift of certain methylene and methine resonances to lower field. The 360 MHz ^{1}H-nmr in $CDCl_3$ of cucurbitacin F (**1**) has been reported previously (13).

A comparison of the physical and spectral data for compound **1** with those of known cucurbitacins indicated that compound **1** could be either cucurbitacin F (**1**) or cucurbitacin O (**4**). Selective decoupling experiments of the methine protons at carbons 2 and 3 in the 360 MHz ^{1}H-nmr spectra of compound **1** and its triacetate (**5**) showed that these protons were coupled with J values of 9.1 and 10.1 Hz, respectively; characteristic of axial-axial coupling. These results indicate that the hydroxy groups at carbons 2 and 3 in compound **1** [and therefore the acetate groups in the triacetate (**5**)] must be in the 2 β-equatorial, 3 α-equatorial *trans* configuration and that compound **1** is cucurbitacin F.[10]

Several significant differences were observed when the spectral data for compound **2** were compared with the data obtained for compound **1** (cucurbitacin F). The signals for

[9]Assignments of the resonances at δ 2.120 and 2.128 may be reversed.

[10]Coupling constants for the methene protons at carbons 2 and 3 in cucurbitacin O should be in the range of 2-5 Hz indicating a 2 β-equatorial, 3 β-axial diol configuration in ring A.

the 23,24-protons in compound **1** at δ 7.481 (d, J=15.3 Hz) and 7.555 (d, J=15.3 Hz), respectively, were absent in the ^{1}H-nmr of **2**, and the band at 1633 cm^{-1} for the carbon-carbon double bond of the α,β-unsaturated carbonyl was absent in the ir spectrum of compound **2**. The ion at *m/z* 502 (M^+-18) in the mass spectrum of **2** appeared at two mass units higher than the corresponding ion in **1**; as expected, the base peak in **2** was at *m/z* 113, rather than *m/z* 96 as in compound **1**. These differences suggested strongly that, unlike compound **1**, compound **2** did not contain a 23,24-carbon-carbon double bond. Hydrogenation of compound **1** (80 mg) over 10% Pd/C in EtOH for 14 h and work up in the usual manner yielded a 23,24-dihydro derivative (18 mg) whose physical and spectral data (mp, ir, ms, nmr) were identical with those of compound **2**. The ms, [α]D and uv data of **2** were also consistent with literature values for 23,24-dihydrocucurbitacin F (8). Therefore, compound **2** was identified as 23,24-dihydrocucurbitacin F.

An analysis of the 360 MHz ^{1}H-nmr of compound **3** and its triacetate (**6**) suggested that the oxygenation pattern of rings A, B, C, and D was the same as in compounds **1** and **2**. However, the nmr spectrum showed that compound **3** contained only five tertiary methyl groups in comparison with the eight present in compounds **1** and **2** and that a new signal corresponding to a methyl ketone group was present in compound **3**. Compound **3** also showed a lower molecular ion (*m/z* 404) compared with the observed parent ions (M^+-18) for compounds **1** and **2** (*m/z* 500 and 502, respectively). The difference of 96 atomic mass units between the molecular ion of compound **3** and the observed parent ion for compound **1** suggested that the side chain, characteristic of the 23,24-dehydrocucurbitacins and giving rise to a base peak at *m/z* 96 in the mass spectrum, was missing in compound **3** (14). The molecular formula ($C_{24}H_{36}O_5$) and fragmentation pattern of compound **3** were similar to those reported for 16-deoxy-Δ^{16}-hexanorcucurbitacin O (9). These findings suggested that compound **3** was a hexanor-derivative of cucurbitacin F in which the side chain had been cleaved between carbons 20 and 22 resulting in the formation of a methyl ketone at carbon 20.

The structure of compound **3** was confirmed by periodic acid cleavage of the triacetate derivative of cucurbitacin F (7, 15). To an ethanolic solution of cucurbitacin F triacetate (**5**, 25 mg in 2 ml) was added periodic acid (0.5 M, 0.3 ml) and H_2O (1.2 ml). The mixture was stirred at room temperature for 120 h. Excess periodic acid was destroyed by the addition of ethylene glycol (1 ml) and the solution was evaporated in vacuo to afford a residue. To this residue H_2O (10 ml) was added resulting in the formation of a precipitate, which was collected and subjected to preparative tlc ($CHCl_3$-EtOH, 99.4:0.6) to give a compound (0.2 mg), that was identical with **6** (tlc, ir).

Cucurbitacin F (**1**) has been isolated previously from *Cucumis angolensis* Hook. f. ex Cogn. (Cucurbitaceae) (7,16), *Crinodendron hookerianum* Gay (Elaeocarpaceae) (8) and *Datisca glomerata* Baill. (Datiscaceae) (13). 23,24-Dihydrocucurbitacin F (**2**) has been isolated from *C. hookerianum* (8), and was synthesized by hydride reduction of cucurbitacin F (7,13) or tetrahydrocucurbitacin I (17). This is the first report of the isolation of hexanorcucurbitacin F (**3**) from nature. Also, to our knowledge, this report represents the first reported isolation of cucurbitacins from the genus *Elaeocarpus* and represents only the second reported isolation from the family Elaeocarpaceae.

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