Cytotoxic Prenylated Xanthones from the Young Fruit of *Garcinia mangostana*

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Three new prenylated xanthones, mangostenones C (1), D (2), and E (3), together with 16 known xanthones 4—19, were isolated from the young fruit (7-week maturity stage) of *Garcinia mangostana*. The structural elucidation of the new compounds was mainly established on the basis of 1D and 2D NMR and HR-MS spectroscopic analysis. Compound 1 showed cytotoxic properties against three human cancer cell lines, epidermoid carcinoma of the mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187), with IC_{50} values of 2.8, 3.53, and 3.72 μg/ml, respectively. Among the isolates, α-mangostin (12), the major metabolite, exhibited the most potent effects against the BC-1 cells with an IC_{50} value of 0.92 μg/ml, an activity greater than that of the standard drug ellipticine (IC_{50}=1.46 μg/ml). Compound 12 also showed the highest activity against KB cells, while gartanin (10) displayed the strongest activity against the NCI-H187 cells at the respective IC_{50} values of 2.08 μg/ml and 1.08 μg/ml.

Key words *Garcinia mangostana*; Clusiaceae; mangostenone C; mangostenone D; mangostenone E; cytotoxicity

Biological studies on the xanthones obtained from the fruit of the tropical tree *Garcinia mangostana* L. (Clusiaceae), regarded as "the queen of fruit," have demonstrated interesting biological activities.[1,2] Studies have been conducted to examine the anticancer properties of the extracts or xanthones obtained from the fruit hulls of this plant species against colon preneoplastic lesions,[3] DNA topoisomerases I and II,[4] human leukemia (HL60, K562, NB4, U937, P3HR1, and Raji),[5,6] hepatoma (HCC36, TONG, HA22T, Hep 3B, HEpG2, and SK-HEp-1), lung (NCI-Hut 125, CH27-LC-1, H2981, and Calu-1), and gastric carcinomas (AZ521, NUGC-3, KATO-III, and AGS),[7] and human breast cancer SKBR3 cells.[8,9] Our interest has been focused on the isolation of structurally interesting prenylated xanthones and the biological activities of intermediates at various stages of fruit maturity. In our previous study, the isolation of 17 xanthones including three new xanthones, mangostenol and mangostenones A and B, from the green fruit (14-week maturity stage) of this plant and their antituberculosis activity were already described.[10,11] In a continuation of this work, the EtOAc-soluble extract obtained from the young fruit (7-week maturity stage) of *G. mangostana* was subjected to a chemical investigation leading to the isolation and structural elucidation of three new prenylated xanthones, mangostenones C (**1**), D (**2**), and E (**3**), in addition to 16 previously reported xanthones, thwaitesixanthone (**4**),[12] demethylcalabaxanthone (**5**),[11] garcinone B (**6**),[10] compound **7**,[11] β-mangostin (**8**),[10] 8-desoxygartanin (**9**),[13] gartanin (**10**),[14] garcinone E (**11**),[15] the major metabolite α-mangostin (**12**),[10] mangostinone (**13**),[10] the second major metabolite γ-mangostin (**14**),[11] mangostanol (**15**),[10] mangostanin (**16**),[11] garcinone D (**17**),[11] garcinone C (**18**),[16] and the third major metabolite 11-hydroxy-1-isomangostin (**19**).[17] We here report on the structural elucidation of the three new compounds and the *in vitro* cytotoxic activities of xanthones **1**—**19** against three human cancer cell lines, epidermoid carcinoma of the mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187).

Results and Discussion

The positive-ion mode HR-FAB-MS of compound **1** showed a pseudo molecular ion at *m/z* 443.1691 which corresponded to a molecular formula of $C_{24}H_{26}O_8$. The UV and IR spectra indicated that **1** has a xanthone skeleton. The ^{1}H-NMR spectrum of **1** (Table 1) exhibited the presence of two aromatic protons at δ 6.29 and 6.83, two phenolic hydroxyl groups at δ 6.38 and 13.92, a methoxyl at δ 3.81, and a prenyl group at δ 4.07, 5.23, 1.82, and 1.69. In the HMBC spectrum (Fig. 1), the methoxyl group at δ 3.81 showed a correlation with the C-7 (δ 143.0) and the hydroxyl proton at δ 6.38 correlated with C-6 and C-5. This methoxyl signal also exhibited NOE enhancement with H-16 at δ 4.07, H-17 at δ 5.23, and 6-OH in the NOESY spectrum (Fig. 1), confirming the placement of the methoxyl and the hydroxyl groups at C-7 and C-6, respectively. The two singlet methyls adjacent to an oxygen function (δ_H 1.40, δ_C 18.1 and δ_H 1.43, δ_C 23.7) and two oxygenated methine protons (δ_H 6.10, δ_C 82.8 and δ_H 5.29, δ_C 98.5) in the NMR data evidenced the presence of a 4-hydroxy-5-(1-hydroxy-1-methylethyl)dihydrofuran system in the side chain. The *cis* relationship of the two oxygenated methine protons was established on the basis of the coupling constant value of 6.1 Hz[12] in the ^{1}H-NMR spectrum. The correlation between these two methines and respective methyls observed in the NOESY spectrum in addition to the observation of the fragment ion at *m/z* 383 $[M-59]^+$ in the EI-MS confirmed that the 4-hydroxy-5-(1-hydroxy-1-methylethyl)dihydro furan moiety is preferable to the 4,5-dihydroxy-6,6-dimethyldihydropyran system for the partial structure of **1**. There remained the placement of the dihydrofuran ring. In the HMBC spectrum, the proton resonating at δ 5.29 (H-12) was correlated with an aromatic carbon at δ 167.0 (C-3) through ^3J, which implied that the

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Table 1. ^{1}H- (300 MHz) and ^{13}C-NMR (75 MHz) Data for Compounds **1** (in $CDCl_3$), **2** and **3** (in Acetone-d_6)[a]

Position	**1**		**2**		**3**	
	^{1}H (δ)	^{13}C (δ)	^{1}H (δ)	^{13}C (δ)	^{1}H (δ)	^{13}C (δ)
1		160.8		161.5		161.5
2		104.4[c]		110.8		111.1
3		167.0		162.6		163.3
4	6.29 s	88.1	6.38 s	93.0	6.40 s	93.2
4a		158.9		155.8		156.1[f]
5	6.83 s	101.6	6.73 s	101.3	6.84 s	102.9
6		154.7		154.0[e]		155.7[f]
7		143.0		139.8		145.5
8		137.1		122.9		137.0
8a		113.5		111.3		112.6
9		182.5		183.2		183.7
9a		105.6[c]		103.7		103.5
10a		155.7		153.9[e]		157.5
11	6.10 d (6.1)	82.8	3.34 d (6.9)	21.9	3.33 d (6.6)	21.9
12	5.29 d (6.1)	98.5	5.27 br t (6.9)	123.5	5.27 br t (6.6)	123.3
13		85.5		131.3		131.4
14	1.43 s[b]	23.7[d]	1.63 s	25.8	1.62 s	25.8
15	1.40 s[b]	18.1[d]	1.77 s	18.6	1.76 s	17.8
16	4.07 d (6.0)	26.5	3.47 t (6.6)	23.2	3.59 m	29.5
17	5.23 br t (6.0)	122.9	1.87 t (6.6)	33.2	3.69 m	79.7
18		132.3		75.2		73.2
19	1.69 s	25.7	1.34 s	26.4	1.29 s	26.1[g]
20	1.82 s	18.1				25.4[g]
1-OH	13.92 s		13.79 s		13.58 s	
3-OH			9.55 s			
6-OH	6.38 br s		8.79 s		9.86 br s	
7-OMe	3.81 s	62.0			3.85 s	60.8

a) δ in ppm, value in parentheses are coupling constant in Hz. *b*—*g*) Interchangeable within a column.

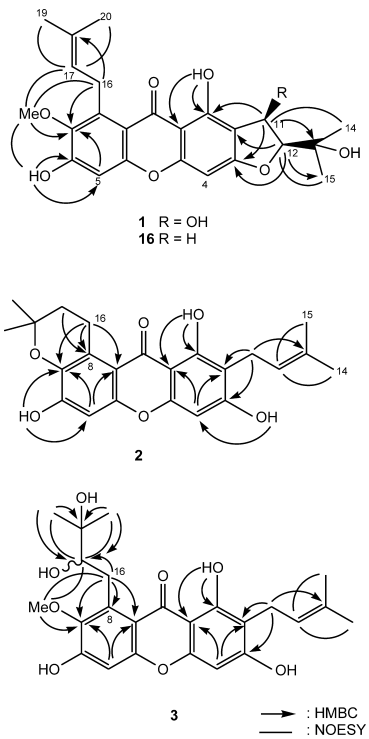

Fig. 1. Selected HMBC and NOESY Correlations for Compounds **1**—**3**

furan ring oxygen belongs to the hydroxyl group at C-3. The chemical shifts of C-11, C-12, and C-13 were in agreement with those reported for caloxanthone D.[18] Although this modification of a prenyl side chain is not common in *Garcinia*, it has been found in *Calophyllum*.[18] ^{13}C-NMR assignments (Table 2) were made by the analysis of the HMQC, HMBC, and DEPT spectra in conjuction with the comparison with those of mangostanin and caloxanthone D. The structure of mangostenone C (**1**) was therefore concluded to be 1,6-dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-4′-hydroxy-5′-(1-hydroxy-1-methylethyl)-4′,5′-dihydrofurano(2′,3′:3,2)xanthone. Due to the scarcity of compound **1**, the existing data did not permit the assignment of the absolute stereochemistry at C-11 and C-12 for this compound.

Mangostenone D (**2**) was obtained as a yellow solid. A pseudo molecular ion at *m*/*z* 397.1646 in the positive-ion HR-FAB-MS established the molecular formula of $C_{23}H_{24}O_6$. Its UV and IR data suggested that **2** also has a xanthone skeleton. In the ^{1}H-NMR spectrum, signals for two aromatic protons (δ 6.38, 6.73), a prenyl group (δ 3.34, 5.27, 1.77, 1.63), and a 2,2-dimethylchroman ring (δ 3.47, 1.87, 1.34) were observed, in addition to three hydroxyl groups (δ 13.79, 9.55, 8.79) (Table 1). The ^{1}H-NMR data of **2** were similar to those of garcinone B (**6**) except that the two doublets at H-16 (δ 8.00, J=10.2 Hz) and H-17 (δ 5.80, J=10.2 Hz) of the dimethylchromene ring in garcinone B[10] were replaced by the two triplet methylenes H-16 and H-17 in **2**. This structural assignment was confirmed by its HMBC spectrum (Fig. 1). ^{13}C-NMR assignments (Table 2) were established by comparison with those of garcinone B (**6**)[10] and mangostenone B.[10] The structure of **2** was therefore assigned to be 1,3,6-trihydroxy-2-(3-methylbut-2-enyl)-6′,6′-dimethyl-4′,5′-dihydropyrano(2′,3′:7,8)xanthone, which is a 16,17-dihydro analogue of garcinone B and designated mangostenone D.

Table 2. IC_{50} Values (μg/ml) for Cytotoxic Activities against KB, BC-1 and NCI-H187 Cancer Cell Lines of Xanthones from *G. mangostana* Fruit

Compound	KB	BC-1	NCI-H187
Mangostenone C (**1**)	2.8	3.53	3.72
Mangostenone D (**2**)	9.79	3.88	9.07
Mangostenone E (**3**)	19.96	17.53	Inactive[a)]
Thwaitesixanthone (**4**)	Inactive[a)]	Inactive[a)]	Inactive[a)]
Demethylcalabaxanthone (**5**)	10.9	2.85	3.13
Garcinone B (**6**)	Inactive[a)]	Inactive[a)]	Inactive[a)]
1,6-Dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)6′,6′-dimethyl-pyrano(2′,3′:3,2)xanthone (**7**)	3.72	3.02	2.19
β-Mangostin (**8**)	2.5	2.04	2.88
8-Desoxygartanin (**9**)	Inactive[a)]	Inactive[a)]	16.88
Gartanin (**10**)	15.63	15.54	1.08
Garcinone E (**11**)	2.67	1.44	3.74
α-Mangostin (**12**)	2.08	0.92	2.87
Mangostinone (**13**)	12.79	7.26	17.88
γ-Mangostin (**14**)	4.69	1.6	2.55
Mangostanol (**15**)	Inactive[a)]	Inactive[a)]	1.15
Mangostanin (**16**)	Inactive[a)]	Inactive[a)]	8.04
Garcinone D (**17**)	3.56	2.81	11.04
Garcinone C (**18**)	7.48	2.18	3.66
11-Hydroxy-1-isomangostin (**19**)	13.14	18.53	Inactive[a)]
Standard ellipticine	1.33	1.46	0.39

a) Inactive at 20 μg/ml.

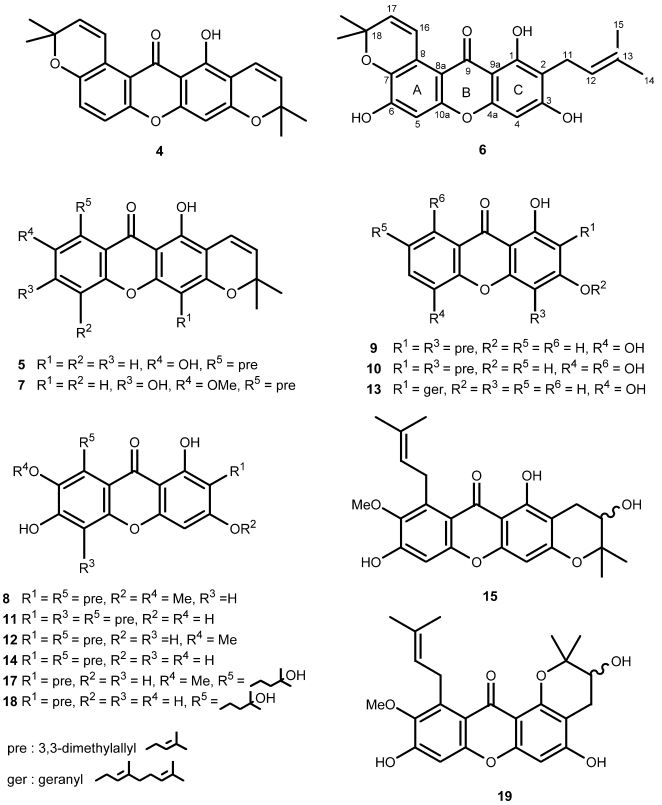

Fig. 2. Chemical Structures of Compounds **2**, **4**—**15** and **17**—**19**

Mangostenone E (**3**) was obtained as a yellow amorphous solid. The HR-FAB-MS (negative-ion mode) exhibited an $[M-H]^-$ ion at *m/z* 443.1709 compatible with the molecular formula $C_{24}H_{28}O_8$. Its UV and IR data were also indicative of a xanthone derivative. The ^{1}H-NMR spectrum (Table 1) displayed signals for a 1,3,5,6-tetraoxygenated xanthone, which included two aromatic singlets (δ 6.40, 6.84), a methoxyl (δ 3.85), a prenyl group (δ 3.33, 5.27, 1.76, 1.62), and two hydroxyl protons at δ 13.58 (chelated) and 9.86, in addition to a modified prenyl group. Comparison of the ^{1}H- and ^{13}C-NMR data of **3** with those of garcinone D (**17**)[11] suggested that **3** only differed from compound **17** in the nature of the substituent at the 8-position. In this respect, the presence of two methyls (δ_H 1.29, δ_C 26.1, 25.4), a quaternary oxygenated carbon (δ_C 73.2), an oxygenated methine (δ_H 3.69, δ_C 79.7), and a methylene signal (δ_H 3.59, δ_C 29.5) in the ^{1}H- and ^{13}C-NMR spectra (Table 1) established a 2,3-dihydroxy-3-methylbutyl moiety.[19] In the HMBC spectrum (Fig. 1) the proton resonating at δ 3.59 (H-16) showed correlations with C-7 (δ 145.5), C-8 (δ 137.0), C-8a (δ 112.6), and C-17 (δ 79.7), whereas H-17 (δ 3.69) was correlated with C-19 (δ 26.1) and C-20 (δ 25.4). Strong NOE interactions observed between the methoxyl proton and H-16 and H-17 in the NOESY spectrum (Fig. 1) further supported the placement of the 2,3-dihydroxy-3-methylbutyl group at C-8 in **3**. The chemical shifts of C-16, C-17, and C-18 of compound **3** were inconsistent with those reported for cudraxanthone N, a xanthone isolated from *Cudrania tricuspidata*.[19] ^{13}C-NMR assignments (Table 2) were established by comparison with those of garcinone D[10] and cudraxanthone N.[19] On the basis of all spectroscopic evidence, the structure of mangostenone E (**3**) was established to be 1,3,6-trihydroxy-8-(2,3-dihydroxy-3-methylbutyl)-2-(3-methylbut-2-enyl)-7-methoxyxanthone.

Compounds **4**—**19** were identified as thwaitesixanthone (**4**),[12] demethylcalabaxanthone (**5**),[11] garcinone B (**6**),[10] compound **7**,[11] β-mangostin (**8**),[10] 8-desoxygartanin (**9**),[13] gartanin (**10**),[14] garcinone E (**11**),[15] the major metabolite α-mangostin (**12**),[10] mangostinone (**13**),[10] the second major metabolite γ-mangostin (**14**),[11] mangostanol (**15**),[10] mangostanin (**16**),[11] garcinone D (**17**),[11] garcinone C (**18**),[16] and the third major metabolite 11-hydroxy-1-isomangostin (**19**)[17] by comparison of their ^{1}H- and ^{13}C-NMR, MS and $[\alpha]_D$ data with those reported previously.

Xanthones **1**—**19** were evaluated *in vitro* for their cytotoxicities against KB, BC-1, and NCI-H187 cells and the IC_{50} values are shown in Table 2. Based on these observations, the following conclusions can be drawn regarding these isolates: 1) For high activity, the xanthones should contain tetraoxygen functions with two C_5 units in rings A and C (as in **8**, **11**, **12**, **14**). Among these, α-mangostin (**12**), the major constituent, exhibited the most potent effects against KB and BC-1 with IC_{50} values of 2.08 and 0.92 μg/ml, respectively. In NCI screening, gartanin (**10**) demonstrated selective and the most potent activity with the IC_{50} value of 1.08 μg/ml. 2) The activity was generally reduced with the increase in the number of hydroxyl groups in the C_5 side chain (comparison of compounds **12** and **14** with **17**, **3**, and **18**). 3) The weak activity of the third major constituent **19**, compared with the highest activity of **12**, indicated the crucial role of the hydroxyl group at C-1 in the xanthone nucleus. 4) Cyclization of the C_5 group in either the 1,3,7-trioxygenated xanthone or the 1,3,6,7-tetraoxgenated nucleus resulted in decreased activity (compounds **4** and **6**). It should be noted that the pyrano and furano rings bearing the hydroxyl group attached to the xanthone nucleus (as for **1** and **15**) appear to enhance cytotoxic activity in NCI screening.

Experimental

General Procedures Melting points were determined with a Griffin melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P1010 digital polarimeter. UV spectra were run on a Shimadzu UV-2401 PC spectrophotometer. IR spectra were measured on a Perkin-Elmer FT-IR Spectrum BX spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVANCE 300 FT-NMR spectrometer, operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). For the spectra taken in $CDCl_3$ and acetone-d_6, residual nondeuterated solvent signals at δ 7.24 and 2.04 and the solvent signals at δ 77.00 and 29.80 were used as references for ^{1}H- and ^{13}C-NMR spectra, respectively. EI-MS and FAB-MS were recorded on a Thermo Finnigan Polaris Q and a Finnigan MAT 90 instrument. Unless otherwise indicated, column chromatography and TLC were carried out using Merck silica gel 60 (finer than 0.063 mm) and precoated silica gel 60 F_{254} plates, respectively. Spots on TLC were visualized under UV light and by spraying with anisaldehyde–H_2SO_4 reagent followed by heating.

Plant Material The young fruit, at 7 weeks of maturity after anthesis, of *G. mangostana* were collected from Ra-ngae district, Narathiwat province, Thailand, in 2000 and a voucher specimen (RU 0038) is deposited at the Faculty of Science, Ramkhamhaeng University, Thailand.

Extraction and Isolation Air-dried and powdered fruit (2.06 kg) of *G. mangostana* was successively extracted with EtOAc and MeOH at 50 °C in a water bath for 48 h each and the solvents were evaporated to yield the EtOAc (295 g) and MeOH (251 g) extracts, respectively. The EtOAc extract, which exhibited stronger cytotoxicity against the KB and BC cell lines, was then investigated extensively. Thus the EtOAc-soluble fraction (42 g) was subjected to quick column chromatography[20] over silica gel using a gradient of hexane–CH_2Cl_2, CH_2Cl_2, CH_2Cl_2–EtOAc, EtOAc, and then EtOAc–MeOH (5% increment of polar solvent for 500 ml of each proportion) and were combined into nine main fractions by TLC examination. Fraction 1 (53 mg) was crystallized with hexane to yield thwaitesixanthone (**4**) (10 mg).[12] Fraction 2 (1.33 g) was chromatographed over silica gel using gradient elution of hexane–CH_2Cl_2 (70 : 30) and CH_2Cl_2 in 5% increments of polar solvent to give fractions 2a—m. Fractions 2c (148 mg), 2d (98 mg), and 2k (102 mg) were individually recrystallized with hexane to produce demethylcalabaxanthone (**5**) (20 mg),[11] garcinone B (**6**) (5 mg),[10] and garcinone E (**11**) (23 mg),[15] respectively. Fraction 2e (326 mg) was sequentially fractionated on a silica gel column (in hexane–CH_2Cl_2, 40 : 60 to 5 : 95) to give compound **7** (52 mg)[11] and β-mangostin (**8**) (5 mg).[10] Fractions 2f—h (189 mg) were further fractionated on a silica gel column (hexane–EtOAc, 95 : 5 to 50 : 50) and then on a Sephadex LH-20 column (in MeOH) to afford 8-desoxygartanin (**9**) (18 mg)[13] and gartanin (**10**) (18 mg).[14] Fractions 3—5 were the major metabolite, α-mangostin (**12**) (6.79 g).[10] Similar purification of fraction 6 (340 mg) on column chromatography (silica gel, CH_2Cl_2–MeOH 99.5 : 0.5 to 95 : 5 in 0.5% stepwise elution) gave mangostinone (**13**) (12 mg).[10] Fraction 7 (3.39 g) was crystallized with $CHCl_3$ to furnish γ-mangostin (**14**) (0.89 g),[11] and the filtrate was further chromatographed over silica gel (eluted with hexane–CH_2Cl_2, CH_2Cl_2, CH_2Cl_2–MeOH, and MeOH in 5% increments of polar solvent for 200 ml of each portion) to provide fractions 7a—j. Mangostanol (**15**) (9 mg),[10] mangostenone C (**1**) (4 mg), mangostenone D (**2**) (6 mg), and mangostanin (**16**) (6 mg),[11] were isolated from repeated individual column chromatography (silica gel) of fractions 7g (561 mg, using a hexane–EtOAc gradient system as eluent), 7h (203 mg, eluted with $CHCl_3$–MeOH, 99 : 1 to 5 : 95), and 7i (204 mg, eluted with CH_2Cl_2–MeOH, 99.5 : 0.5 to 90 : 10), respectively. Similar fractionation of fraction 8 (3.75 g), eluted with a gradient of CH_2Cl_2 and CH_2Cl_2–MeOH (70 : 30), yielded 11 fractions, in which garcinone D (**17**) (90 mg)[11] and garcinone C (**18**) (20 mg)[16] were obtained from subsequent column chromatography (silica gel, eluted with a gradient of CH_2Cl_2 and CH_2Cl_2–MeOH) of fraction 8h (2.29 g). Similarly, purification of fraction 9 (4.20 g) using column chromatography (silica gel, CH_2Cl_2–MeOH 99 : 1 to 30 : 70 in 3% increments of the polar solvent) gave five fractions, mangostenone E (**3**) (9 mg) and the third major isolate, 11-hydroxy-1-isomangostin (**19**) (235 mg),[17] were isolated from two successive column chromatographies (silica gel, CH_2Cl_2–MeOH 97 : 3 to 95 : 5) of fractions 9b (852 mg) and 9d (1.94 g), respectively. The MeOH extract that exhibited weak cytotoxicity contained a small quantity of a number of xanthones which had been isolated from the EtOAc extract.

Mangostenone C (**1**): Yellow solid; mp 126—127 °C; $[\alpha]_D^{27}$ −28.3° (c=0.12, MeOH); UV λ_{max} (MeOH) nm (log ε): 248 (4.39), 312 (3.97), 347 (3.01); IR ($CHCl_3$) cm^{-1}: 3584 (sharp), 3400, 1655, 1576, 1462, 1283, 1168, 1091; ^{1}H- and ^{13}C-NMR data, see Table 1; EI-MS *m/z*: 442 (M^+), 440, 383, 382, 381, 367, 349, 340, 339 (100), 324, 309, 149; HR-FAB-MS (positive-ion mode) *m/z*: 443.1691 $[M+H]^+$ (Calcd for $C_{24}H_{26}O_8$+H: 443.1705).

Mangostenone D (**2**): Yellow solid; mp 208—210 °C; UV λ_{max} (MeOH) nm (log ε): 244 (4.39), 260 (4.40), 317 (4.23), 362 (3.82); IR (KBr) cm^{-1}: 3510 (sharp), 3421, 1644, 1608, 1586, 1463, 1301, 1286, 1269, 1164, 1079; ^{1}H- and ^{13}C-NMR data: see Table 1; HR-FAB-MS (positive-ion mode) *m/z*: 397.1646 $[M+H]^+$ (Calcd for $C_{23}H_{24}O_6$+H: 397.1651).

Mangostenone E (**3**): Yellow amorphous solid; $[\alpha]_D^{28}$ 0.0° (c=0.13, MeOH); UV λ_{max} (MeOH) nm (log ε): 243 (4.27), 258 (4.15), 321 (3.91), 358 (2.98); IR ($CHCl_3$) cm^{-1}: 3421, 2926, 1647, 1607, 1457, 1281, 1192, 1083 cm^{-1}; ^{1}H- and ^{13}C-NMR data: see Table 1; HR-FAB-MS (negative-ion mode) *m/z*: 443.1709 $[M-H]^-$ (Calcd for $C_{24}H_{28}O_8$−H: 443.1705).

^{13}C-NMR data of the xanthones that had not been published are listed below.

Compound **4**: ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 183.9 (C-9), 160.5 (C-3), 158.0 (C-1), 157.0 (C-4a), 152.0 (C-10a), 149.5 (C-7), 132.6 (C-17), 127.2 (C-12), 124.2 (C-6), 120.8 (C-16), 118.1 (C-8), 117.7 (C-5), 115.5 (C-11), 114.5 (C-8a), 104.3 (C-2), 104.0 (C-9a), 94.2 (C-4), 78.2 (C-13), 75.4 (C-18), 28.3 (C-14, C-15), 27.3 (C-19, C-20).

Compound **9**: ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 181.0 (C-9), 160.9 (C-3), 158.6 (C-1), 152.3 (C-4a), 144.4 (C-10a), 144.2 (C-5), 136.1 (C-13), 133.5 (C-18), 123.8 (C-7), 122.1 (C-17), 121.1 (C-12), 120.8 (C-8a), 119.7 (C-6), 116.8 (C-8), 109.1 (C-2), 105.4 (C-4), 103.2 (C-9a), 25.8 (C-14), 25.6 (C-19), 22.0 (C-16), 21.6 (C-11), 17.9 (C-15 and C-20).

Compound **10**: ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 184.6 (C-9), 161.6 (C- 3), 158.0 (C-1), 153.7 (C-8), 152.4 (C-4a), 142.8 (C-5), 136.1 (C-13), 135.6 (C-10a), 133.9 (C-18), 122.8 (C-6), 121.8 (C-17), 120.9 (C-12), 109.7 (C-7), 109.4 (C-2), 107.0 (C-8a), 105.7 (C-4), 102.1 (C-9a), 25.8 (C-14), 25.6 (C-19), 21.9 (C-16), 21.5 (C-11), 17.9 (C-15 and C-20).

Cytotoxicity Bioassays The cytotoxicity of compounds **1**—**19** was determined employing the colorimetric method as described by Skehan *et al*.[21] The reference substance, ellipticine, exhibited cytotoxic activity against KB, BC-1, and NCI-H187 cells with IC_{50} values of 1.33, 1.46, and 0.39 μg/ml, respectively.

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