Pergamon

Tetrahedron, Vol. 53, No. 52, pp. 17625-17632, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10231-9

Novel Cytotoxic 1*H*-Cyclopenta[*b*]benzofuran Lignans from *Aglaia elliptica*

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Abstract: Bioassay-guided fractionation of the stems and fruits of *Aglaia elliptica* using human oral epidermoid carcinoma (KB) cells, led to the isolation of five cyclopenta[*b*]benzofurans, constituted by methyl rocaglate (**1**) and four novel compounds (**2-5**), along with three known dammarane triterpenoids. Compound **5** possesses an unusual formyl ester substituent at the C-1 position. The structures of the novel compounds were established on the basis of spectroscopic methods. Compounds **1-5** were found to be very potent cytotoxic substances when evaluated against a panel of human cancer cell lines.

INTRODUCTION

In a continuation of a screening program for novel naturally occurring plant-derived anticancer agents, we have investigated the stems and fruits of *Aglaia elliptica* Bl. (Meliaceae), collected in Thailand, and found that the $CHCl_3$-soluble extracts of both these plant parts showed significant cytotoxic activity when evaluated against a panel of human cancer cell lines. This plant has not yet been subjected to any phytochemical or biological investigation, although the bark is boiled and used to treat tumors, and the leaves are applied to wounds in the Philippines.[1)] Previously, the aerial parts of *A. elaeagnoidea* var. *beddomei*,[2)] the roots and stems of *A. elliptifolia*,[3)] the leaves and twigs of *A. odorata*[4)], and the aerial parts of *A. odoratissima*[5)] were reported to have *in vivo* activity for mice bearing the P-388 lymphocytic leukemia. In addition, the leaves of *A. odorata* have shown antitumor-promoting activity in a Raji-cell line system.[6)] Cytotoxic activity was found for extracts of the roots and stems of *A. elliptifolia* (KB cell line),[3)] the leaves of *A. formosana* (KB, colon adenocarcinoma, and P-388 cell lines),[7)] and the leaves and twigs of *A. odorata* (P-388 cell line).[8)] Two antileukemic diamide derivatives, (-)-odorinol and dehydroodorin, were isolated from *A. odorata*[4)] and *A. formosana*,[7)] respectively. The absolute stereochemistry of the antileukemic cyclopenta[*b*]benzofuran derivative, rocaglamide, was unequivocally established by single-crystal X-ray analysis.[3)] Rocaglamide, along with another three congeners, desmethylrocaglamide, methyl rocaglate, and rocaglaol, was isolated from *A. odorata*, with all compounds possessing the same 1α,2α,3β-configuration and a *cis*-ring B/C junction as well as

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insecticidal activity against *Peridroma saucia* Hubner.[9,10] Methyl rocaglate (also known as aglafolin) was also reported as a selective and effective inhibitor of PAF-induced platelet aggregation in both *in vitro* and *in vivo* tests.[11] From *A. argentea,* nitrogenous and aromatic lignan derivatives were isolated, but only one of the novel compounds, didesmethylrocaglamide, was found to be active against a human oral epidermoid carcinoma (KB) cell line.[12] Recently, several cyclopenta[*b*]benzofuran derivatives from *A. odorata* were reported to be inhibitors of the growth of K-*ras*-NRK cells and to specifically inhibit protein synthesis,[13] and aglafolin and rocaglamide were obtained as cytotoxic and antiplatelet aggregative principles of *A. elliptifoia.*[14]

The present study has revealed that cyclopenta[*b*]benzofurans are highly potent cytotoxic principles of *A. elliptica* when tested against a panel of human cancer cell lines. In this communication, we report the isolation, structure elucidation, and cytotoxic activity of five cyclopenta[*b*]benzofuran lignan derivatives, constituted by methyl rocaglate (**1**) and four novel compounds (**2-5**). Also obtained from the stems of *A. elliptica* in this investigation were the three known triterpenoids, eichlerianic acid, ocotillol II, and shoreic acid, which were not significantly cytotoxic. Compounds **1-2** and **4-5** were isolated from the stems of *A. elliptica*, and compounds **1-3** from the fruits.

RESULTS AND DISCUSSION

The known cyclopenta[*b*]benzofuran, methyl rocaglate (**1**), was isolated from both the stems and fruits of *A. elliptica*, and identified by comparison with literature values.[9,10]

Compound **2** was shown to possess a molecular formula of $C_{28}H_{26}O_9$ by HREIMS. Its IR spectrum showed a carbonyl absorption at 1744 cm^{-1} as well as aromatic group absorption at 1626 cm^{-1}. The ^{1}H- and ^{13}C-NMR spectra of **2** exhibited similar signals to those of **1**, suggesting that the two compounds are based on the same carbon skeleton. Analysis of the ^{1}H-NMR signal at δ 5.84 (2H, s) and a corresponding ^{13}C-NMR signal at δ 100.8 (t, SFORD, HETCOR), indicated the appearance of a methylenedioxy group, but no signals due to an aromatic methoxyl function at the C-4′ position were observed in the molecule of **2**. Other ^{1}H-NMR signals at δ 6.72 (1H, d, J=1.8 Hz), 6.70 (1H, dd, J=1.8, 8.8 Hz), and 6.61 (1H, d, J=8.8 Hz) were attributable to H-2′, H-6′, and H-5′, respectively, and suggested the replacement of the 4′-methoxy group in **1** by a 3′,4′-methylenedioxy group in the molecule of **2**. The presence of the 3′,4′-methylenedioxy group in **2** was supported in the low-resolution EIMS by the molecular ion peak at *m/z* 506 and a base peak at *m/z* 314 $[C_{17}H_{14}O_6]^+$, which resulted from the scission of C_1-C_{8b} and C_3-C_{3a}.[10] These two characteristic ion peaks were 14 amu higher than analogous data for compound **1**. In a selective INEPT NMR experiment on **2**, irradiation of the H-3 signal at δ 4.33 ($^3J_{CH}$=6 Hz) enhanced the C-1, C-1′, C-2″/C-6″, and carbonyl group signals at δ 79.5 (s), 128.1 (s), 127.7 (d), and 170.4 (s), respectively. The configuration around C-1, C-2, C-3, C-3a, and C-8b in **2** was established on the basis of similar chemical shifts and vicinal coupling constant values of the methine protons at C-1, C-2, and C-3 ($J_{1,2}$=6.6 Hz and $J_{2,3}$=14.2 Hz) to those of **1** ($J_{1,2}$=6.8 Hz and $J_{2,3}$=14.2 Hz), which indicated

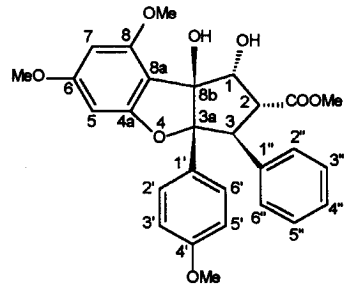
the existence of the same 1α,2α,3β-configuration and ring B/C junction in the two compounds. An nOe difference experiment on **2** confirmed the relative configurations at C-1, C-2, and C-3. Irradiation of H-1 at δ 5.02 led to the enhancement of H-2 (δ 3.92, 5.6%), but no enhancement for H-3, an observation supported by the closely comparable CD and ^{13}C-NMR spectra of **1** and **2**. Assignments of all carbons of **2** (Table 1) were made by performing appropriate ^{1}H-^{1}H COSY, NOESY, HETCOR, APT, SFORD, and selective INEPT experiments. Thus, the structure of **2** was determined as 4′-demethoxy-3′,4′-methylenedioxy-methyl rocaglate.

Compound **3**, having a molecular formula of $C_{26}H_{24}O_7$ as determined by HREIMS, did not show any typical carbonyl group absorbance in its IR spectrum. The ^{1}H- and ^{13}C-NMR spectra of **3** exhibited very close signals to those of **2** with the exception of additional signals for an aliphatic methylene group, and no signals for a carbomethoxy group. The ^{1}H-NMR signals due to the methylene group were observed as a pair of vicinally coupled multiplets (ddd) at δ 2.24 (1H) and 2.76 (1H), and their coupling constants indicated both methylene

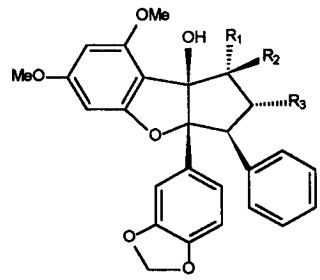
Table 1. ^{13}C-NMR spectral data for **1-5** (90.8 MHz, $CDCl_3$).*

Carbon	1	2	3	4	5
1	80.1 d	79.5 d	79.0 d	210.6 s	78.6 d
2	51.0 d	50.3 d	36.4 t	39.7 d	49.9 d
3	56.3 d	55.7 d	53.3 d	48.6 d	56.0 d
3a	102.4 s	101.8 s	103.5 s	101.2 s	101.7 s
4a	161.4 s	160.6 s	160.8 s	161.0 s	160.7 s
5	90.0 d	89.4 d	89.3 d	89.6 d	88.4 d
6	164.0 s	164.0 s	163.9 s	164.7 s	164.0 s
7	93.2 d	92.7 d	92.5 d	92.7 d	92.2 d
8	157.5 s	156.9 s	156.9 s	158.3 s	157.7 s
8a	113.3 s	107.5 s	107.2 s	106.3 s	105.8 s
8b	94.2 s	93.7 s	94.9 s	88.8 s	92.6 s
1′	127.1 s	128.1 s	128.6 s	127.5 s	128.4 s
2′	129.5 d	108.6 d	108.6 d	107.6 d	108.4 d
3′	113.3 d	146.5 s	146.5 s	146.7 s	146.5 s
4′	159.3 s	146.8 s	146.9 s	147.2 s	146.8 s
5′	113.3 d	107.4 d	107.3 d	107.6 d	107.4 d
6′	129.5 d	121.3 d	121.2 d	120.1 d	121.2 d
1″	137.4 s	136.7 s	138.5 s	137.0 s	136.4 s
2″,6″	128.2 d	127.7 d	127.7 d	127.9 d	127.6 d
3″,5″	128.4 d	127.7 d	128.0 d	127.9 d	127.9 d
4″	126.8 d	126.6 d	126.3 d	126.9 d	126.6 d
OCH_2O		100.8 t	100.8 t	100.9 t	100.9 t
4′-OMe	56.3 q				
6-OMe	55.7 q	55.7 q	55.8 q	55.8 q	55.7 q
8-OMe	55.5 q	55.0 q	55.7 q	55.6 q	55.3 q
COOMe	171.1 s	170.4 s			169.4 s
COOMe	52.6 q	52.0 q			52.3 q
1-OCHO					159.3 d

* Chemical shifts given in ppm using TMS as internal reference.



Methyl rocaglate (**1**)



	R_1	R_2	R_3
2	OH	H	COOMe
3	OH	H	H
4	=O		H
5	OCHO	H	COOMe

Figure 1. Structures of compounds **1-5**.

protons were coupled with the methine protons appearing at δ 4.79 (1H, br d, *J*=6.1 Hz) and 4.01 (1H, dd, *J*=6.6, 14.1 Hz), which were assigned to H-1 and H-3, respectively, with the aid of ^{1}H-^{1}H COSY, HETCOR, and DEPT experiments. The above evidence suggested that the methylene group should be placed at the C-2 position, between the two methines, and was confirmed by comparison of the ^{1}H- and ^{13}C-NMR data of **3** with those of rocaglaol.[10] The structure of **3** was thus assigned as 4′-demethoxy-3′,4′-methylenedioxyrocaglaol.

The molecular formula of compound **4** was determined as $C_{26}H_{22}O_7$ by HREIMS. Its low-resolution EIMS showed a molecular ion peak at *m/z* 446, 2 amu less than that of **3**. A ketone absorbance was observed at 1750 cm^{-1} in the IR spectrum whereas no typical carbonyl group absorbance was apparent for **2**. The ^{1}H-NMR spectrum of **4** exhibited similar aromatic signals to those present in **3**, but with the absence of an H-1 signal. In the ^{13}C-NMR spectrum of **4**, signals at δ 210.2 (s) and 39.8 (t) indicated the presence of a ketone and a methylene group, as supported by APT and HMQC experiments, but typical resonances for a carbomethoxy functionality were not observed. Thus, the ketone group could be located at either the C-1 or the C-2 position. In the latter case, the proton signal due to H-3 would be expected to appear as a singlet. In the ^{1}H-NMR spectrum of **4**, a methine proton signal for H-3 was observed at δ 3.89 (1H, dd, *J*=10.2, 12.2 Hz) and coupled with the methylene protons at δ 3.01 (1H, d, *J*=10.2 Hz) and δ 3.03 (1H, d, *J*=12.2 Hz) on the basis of ^{1}H-^{1}H COSY and HMQC experiments. There was no geminal coupling constant observed between the two methylene protons. Therefore, it was apparent that the ketone group was located at the C-1 position and the methylene protons occurred at the C-2 position. Consequently, structure **4** was assigned to this isolate, 1-oxo-4′-demethoxy-3′,4′-methylenedioxyrocaglaol.

Compound **5** was assigned a molecular formula of $C_{29}H_{26}O_{10}$ as determined by HREIMS, and this isolate displayed a very similar CD spectrum as well as ^{1}H- and ^{13}C-NMR signals to those of **2**. The additional ^{1}H-NMR signal at δ 7.88 (1H, s) and ^{13}C-NMR signal at δ 159.3 (d, APT, SFORD) suggested the presence of an unusual formyloxy group in the molecule of **5**, supported by the HETCOR experiment and the low-resolution EIMS molecular ion peak at *m/z* 534, 28 amu higher than that of **2**, and other characteristic ion fragments at *m/z* 488 $[M\text{-}HCOOH]^+$ and 429 $[M\text{-}HCOOH\text{-}COOMe]^+$. The downfield shifts of ^{1}H-NMR signals due to H-1 (+1.10 ppm), H-2 (+0.17 ppm) and H-3 (+0.13 ppm) when compared with those of **2**, indicated that the formyloxy function was affixed to C-1. In a selective INEPT NMR experiment performed on **5**, irradiation ($^3J_{CH}$=6.5 Hz) of H-1 (δ 6.12) produced an enhancement of the carbonyl signal due to the formyl group at δ 159.3 (d) as well as signals at δ 101.7 (s), 92.6 (s), and 56.0 (d), attributable to C-3a, C-8b, and C-3, respectively. On the basis of the above evidence, the structure of **5** was characterized as 1-*O*-formyl-4′-demethoxy-3′,4′-methylenedioxy-methyl rocaglate.

As summarized in Table 2, compounds **1-5** demonstrated potent broad cytotoxic activity against a panel of human tumor cell lines. Compounds **3** and **4** were in general less active than other cyclopenta[*b*]benzofurans in the cell lines tested. Replacement of the 4′-methoxy group in methyl rocaglate (**1**) by a 3′,4′-methylenedioxy

group as in compound **2**, resulted in no loss of cytotoxic activity against all cell lines except for the Mel2 (melanoma) cell line. Of all the isolates, compound **2** showed the most potent cytotoxicity against the U373 (glioblastoma) and BC1 (breast cancer) cell lines, with ED_{50} values of 0.0008 and 0.0009 μg/ml, respectively. Because of the potent cytotoxic activity of these novel cyclopenta[*b*]benzofuran derivatives, a mechanistic study of their cytotoxic activity and *in vivo* testing on selected compounds are underway.

Table 2. Cytotoxic Activity of Isolates Obtained from *Aglaia elliptica*.[a)]

Compound	Cell line[b)]											
	BC1	HT	Lu1	Mel2	Col2	KB	KB-V$^+$	KB-V$^-$	A431	LNCaP	ZR-75-1	U373
1	0.01	0.009	0.006	0.03	0.009	0.009	0.03	0.03	0.02	<0.16	<0.16	0.003
2	0.0009	0.01	0.0047	0.06	0.01	0.006	0.01	0.02	0.01	<0.16	<0.16	0.0008
3	<0.16	ND	0.07	ND	<0.16	0.09	<0.16	<0.16	ND	ND	0.086	ND
4	1.4	ND	0.1	ND	0.2	0.2	0.8	0.3	ND	ND	0.07	ND
5	0.003	0.003	0.001	0.001	0.002	0.03	0.04	0.01	0.003	<0.16	<0.16	0.0026

[a] Results are expressed as ED_{50} values (μg/ml). [b] Key: BC1=human breast cancer; HT=human fibrosarcoma; Lu1=human lung cancer; Mel2=human melanoma; Col2=human colon cancer; KB=human epidermoid carcinoma in the mouth; KB-V$^+$=multidrug-resistant KB assessed in the presence of vinblastine (1 μg/ml); KB-V$^-$=multidrug-resistant KB assessed in the absence of vinblastine; A431=human epidermoid carcinoma; LNCaP=hormone-dependent human prostate cancer; ZR-75-1=hormone-dependent human breast cancer; U373=human glioblastoma. ND=Not determined.

Very recently, six insecticidal rocaglamide derivatives were reported from *A. eliptica* fruits collected in Indonesia.[15)] The fact that compounds **1-5** were not among the derivatives reported suggests the existence of separate chemical races in this species.

EXPERIMENTAL

General procedures: The UV spectra were obtained using a Beckman DU-7 spectrometer and IR spectra were recorded on a Midac Collegian FT-IR spectrometer. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. CD spectra were measured using a JASCO-600 CD polarimeter. Unless stated otherwise, ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as internal standard, employing either a Nicolet-360 or a Varian XL-300 instrument (360 MHz or 300 MHz, respectively). HMQC NMR spectra were recorded on a General Electric Omega 500 instrument. Low- and high-resolution mass spectra were obtained on a Finnigan MAT-90 instrument. Preparative TLC was performed on Merck silica gel G and Whatman reversed-phase C_{18} plates (0.5 mm and 0.25 mm layer thickness, respectively).

Plant material: The stems and fruits of *Aglaia elliptica* Bl. were collected in Khao Luang National Park, Nakorn Srithammarat, Thailand in May, 1993, and identified by one of us (T.S.). A voucher specimen for this collection (BKF 102488) has been deposited at the Royal Forest Herbarium, Bangkok, Thailand.

Extraction and isolation: The air-dried, milled stems (750 g) of the plant material were extracted with three changes of MeOH (3 x 4 l) at room temperature. The resultant extracts were combined, concentrated, and diluted with H_2O to afford an aqueous MeOH solution (80%), which was washed with hexane (3 x 300 ml). The MeOH layer was concentrated, diluted with H_2O, and partitioned between 10% MeOH solution and $CHCl_3$ (3 x 300 ml). The $CHCl_3$-soluble extract (2.8 g) exhibited significant cytotoxic activity against several cell lines tested. A portion of the $CHCl_3$-soluble extract (2.6 g) was chromatographed over a silica gel column (110 g), eluted with $CHCl_3$ and $CHCl_3$-MeOH mixtures of increasing polarity, and washed with MeOH. Ten fractions were collected and tested for cytotoxic activity against the KB cell line. The most active fraction F003 (ED_{50} 0.02 μg/ml, 280 mg) was subjected to RP-C_{18} column chromatographic separation by elution with MeOH-CH_3CN-H_2O mixtures (50:10:40→70:10:20). Subfractions 8-15 were combined and purified by silica gel column chromatography using mixtures of hexane-acetone-MeOH (6:1:0.1→3:1:0.1) as solvent systems, to yield **2** (16.4 mg) and a mixture of **1** and **5**, which was separated by preparative RP-C_{18} TLC (0.5 mm thickness), developed in MeOH-CH_3CN-H_2O (60:5:35), to afford 5.2 mg of **1** and 9.6 mg of **5**. Subfractions 16-23 were chromatographed over a silica gel column using hexane-EtOAc gradient mixtures (6:1→3:1) to yield **4** (5.8 mg). Subfractions 62-84 were purified by silica gel column chromatography employing a hexane-acetone gradient (6:1→3:1) to yield ocotillol II (12.6 mg). Fraction F005 (100 mg) was subjected to RP-C_{18} column chromatography using 40→80% MeOH in H_2O as solvent systems and purified by silica gel column chromatography, eluted with $CHCl_3$-MeOH mixtures of increasing polarity, to afford eichlerianic acid (8.6 mg) and shoreic acid (6.7 mg), respectively.

The powdered air-dried fruits (450 g) of *A. elliptica* were extracted and partitioned in the same manner as described for the stems. The resultant $CHCl_3$-soluble extract (3.5 g) was fractionated by silica gel column chromatography using hexane-acetone mixtures of increasing polarity as solvent systems. Ten fractions were collected and tested against the KB cell line. The active fractions F005 and F006 were combined and chromatographed over an Al_2O_3 column eluted with hexane-acetone mixtures (5:1→3:1). Subfractions 6-8 were purified by silica gel column chromatography to afford 26 fractions, of which fractions 14-15 and 19-24 were re-purified over a silica gel column using the same solvent systems to yield compounds **1** (12.1 mg) and **2** (140 mg), in turn. Fractions 11-13 were purified by silica gel column chromatography using hexane-EtOAc-MeOH mixtures of increasing polarity as solvent systems to yield compounds **1** (4.2 mg) and **3** (8.6 mg).

Methyl rocaglate (**1**). White powder: $[\alpha]_D^{20}$ -52.0° (*c* 0.11, $CHCl_3$); UV λ_{max}^{MeOH} nm (log ε): 207 (4.37), 284 (2.42); CD (*c* 0.08, MeOH): $[\theta]_{196}$ 0, $[\theta]_{204}$ 3.60 x 10^3, $[\theta]_{209}$ 0, $[\theta]_{215}$ 2.41 x 10^3, $[\theta]_{228}$ 0; identical to methyl rocaglate by comparison with reported data (IR, ^1H NMR, ^{13}C NMR, MS).[10]

4′-Demethoxy-3′,4′-methylenedioxy-methyl rocaglate (**2**). White amorphous powder: $[\alpha]_D^{20}$ -59.8° (*c* 0.12, $CHCl_3$); UV λ_{max}^{MeOH} nm (log ε): 209 (4.58), 239 (sh), 282 (2.47); CD (*c* 0.10, MeOH): $[\theta]_{195}$ 0, $[\theta]_{203}$ 2.01 x 10^3, $[\theta]_{209}$ 0, $[\theta]_{216}$ 1.63 x 10^3, $[\theta]_{238}$ 0; IR ν_{max} (film) cm^{-1}: 3510, 2953, 1744, 1626, 1600, 1503, 1496, 1150; ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (3H, m, H-3″,4″,5″), 6.94 (2H, m, H-2″,6″), 6.72 (1H, d, *J*=1.8 Hz, H-2′), 6.70 (1H, dd, *J*=1.8, 8.8 Hz, H-6′), 6.61 (1H, d, *J*=8.8 Hz, H-5′), 6.30 (1H, d, *J*=2.0 Hz, H-5), 6.14 (1H, d, *J*=2.0 Hz, H-7), 5.86 (2H, s, OCH_2O), 5.02 (1H, d, *J*=6.6 Hz, H-1), 4.33 (1H, d, *J*=14.2 Hz, H-3), 3.92 (1H, dd, *J*=6.6, 14.2 Hz, H-2), 3.89 (3H, s, MeO-6), 3.85 (3H, s, MeO-8), 3.67 (3H, s, COOMe), 1.96 (1H, br s, HO-1); ^{13}C-NMR data: see Table 1; EIMS *m/z* (rel. int. %): 506 (19) $[M]^+$, 488 (1) $[M-H_2O]^+$, 475 (2) $[M-OMe]^+$, 429 (1) $[M-H_2O-COOMe]^+$, 404 (4), 327 (12), 314 (100), 299

(15), 283 (20), 243 (1), 223 (1), 203 (2), 192 (1), 181 (14), 149 (5), 131 (4); HREIMS *m/z*: calcd for $C_{28}H_{26}O_9$ 506.1576, found 506.1561.

4′-Demethoxy-3′,4′-methylenedioxyrocaglaol (**3**). White amorphous gum: $[\alpha]_D^{20}$ -96.3° (*c* 0.30, $CHCl_3$); UV λ_{max}^{MeOH} nm (log ε): 211 (4.06), 274 (3.09); IR ν_{max} (film) cm^{-1}: 3512, 2932, 1626, 1599, 1398; ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (3H, m, H-3″,4″,5″), 7.03 (2H, m, H-2″,6″), 6.71 (1H, d, *J*=1.8 Hz, H-2′), 6.69 (1H, dd, *J*=1.8, 8.2 Hz, H-6′), 6.59 (1H, d, *J*=1.8 Hz, H-5′), 6.28 (1H, d, *J*=2.0 Hz, H-5), 6.15 (1H, d, *J*=2.0 Hz, H-7), 5.85 (2H, s, OCH_2O), 4.79 (1H, br d, *J*=6.1 Hz, H-1), 4.01 (1H, dd, *J*=6.6, 14.0 Hz, H-3), 3.90 (3H, s, MeO-6), 3.84 (3H, s, MeO-8), 2.74 (1H, ddd, *J*=6.1, 12.2, 14.0 Hz, H-2a), 2.21 (1H, ddd, *J*=1.5, 6.6, 12.2 Hz, H-2b); ^{13}C-NMR data: see Table 1; EIMS *m/z* (rel. int.): 448 (19) $[M]^+$, 430 (7) $[M-H_2O]^+$, 366 (3), 327 (5), 314 (100), 299 (16), 283 (7), 181 (8), 169 (2), 149 (6), 111 (3); HREIMS *m/z*: calcd for $C_{26}H_{24}O_7$, 448.1522, found 446.1520.

1-Oxo-4′-demethoxy-3′,4′-methylenedioxyrocaglaol (**4**). White amorphous gum: $[\alpha]_D^{20}$ +16.5° (*c* 0.20, $CHCl_3$); UV λ_{max}^{MeOH} nm (log ε): 210 (4.56), 284 (3.02); IR ν_{max} (film) cm^{-1}: 3500, 2930, 1750, 1620, 1597, 1499, 1147; ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 (3H, m, H-3″,4″,5″), 6.99 (2H, m, H-2″,6″), 6.60 (1H, d, *J*=8.2 Hz, H-5′), 6.57 (1H, d, *J*=1.8 Hz, H-2′), 6.52 (1H, dd, *J*=1.8, 8.2 Hz, H-6′), 6.34 (1H, d, *J*=2.0 Hz, H-5), 6.11 (1H, d, *J*=2.0 Hz, H-7), 5.86, 5.84 (2H, ABq, *J*=1.5 Hz, OCH_2O), 3.89 (1H, dd, *J*=10.2, 12.2 Hz, H-3), 3.86 (3H, s, MeO-6), 3.83 (3H, s, MeO-8), 3.03 (1H, d, *J*=10.2 Hz, H-2a), 3.01 (1H, d, *J*=12.2 Hz, H-2b); ^{13}C-NMR data: see Table 1; EIMS *m/z* (rel. int.): 446 (6) $[M]^+$, 314 (100), 299 (41), 283 (8), 181 (6), 149 (20), 111 (7); HREIMS *m/z*: calcd for $C_{26}H_{22}O_7$, 446.1366, found 446.1360.

1-O-Formyl-4′-demethoxy-3′,4′-methylenedioxy-methyl rocaglate (**5**). White amorphous powder: $[\alpha]_D^{20}$ -102.0° (*c* 0.40, $CHCl_3$); UV λ_{max}^{MeOH} nm (log ε): 210 (4.34), 284 (3.12) ; CD (*c* 0.08, MeOH): $[\theta]_{198}$ 0, $[\theta]_{203}$ 2.60 x 10^3, $[\theta]_{214}$ 0, $[\theta]_{216}$ 7.21 x 10^2, $[\theta]_{224}$ 0; IR ν_{max} (film) cm^{-1}: 3501, 2917, 1734, 1626, 1603, 1505, 1150; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (1H, s, 1-OCHO), 7.12 (3H, m, H-3″,4″,5″), 6.99 (2H, m, H-2″,6″), 6.70 (1H, d, *J*=1.8 Hz, H-2′), 6.67 (1H, dd, *J*=1.8, 8.2 Hz, H-6′), 6.56 (1H, d, *J*=8.2 Hz, H-5′), 6.24 (1H, d, *J*=2.0 Hz, H-5), 6.12 (1H, d, *J*=6.4 Hz, H-1), 6.04 (1H, d, *J*=2.0 Hz, H-7), 5.83, 5.82 (2H, ABq, *J*=1.5 Hz, OCH_2O), 4.46 (1H, d, *J*=14.6 Hz, H-3), 4.09 (1H, dd, *J*=6.4, 14.6 Hz, H-2), 3.84 (3H, s, MeO-6), 3.76 (3H, s, MeO-8), 3.63 (3H, s, COOMe); ^{13}C-NMR data: see Table 1; EIMS *m/z* (rel. int.): 534 (46) $[M]^+$, 503 (3) $[M-OMe]^+$, 488 (7) $[M-HCOOH]^+$, 474 (4) $[M-COOMe]^+$, 429 (8) $[M-HCOOH-COOMe]^+$, 327 (33), 314 (76), 299 (27), 283 (100), 206 (13), 181 (37), 149 (12); HREIMS *m/z*: calcd for $C_{29}H_{26}O_{10}$, 534.1526, found 534.1535.

Ocotillol II. White powder: $[\alpha]_D^{20}$ +38.6° (*c* 0.23, $CHCl_3$); identical to ocotillol II by comparison with reported data (IR, ^1H NMR, ^{13}C NMR, MS).[16]

Eichlerianic acid. White powder: $[\alpha]_D^{20}$ +34.5° (*c* 0.35, $CHCl_3$); UVλ_{max}^{MeOH} nm (log ε): 204 (4.16); identical to eichlerianic acid by comparison with reported data (IR, ^1H NMR, ^{13}C NMR, MS).[17]

Shoreic acid. White powder: $[\alpha]_D^{20}$ +67.9° (*c* 0.45, $CHCl_3$); identical to shoreic acid by comparison with reported data (IR, ^1H NMR, ^{13}C NMR, MS).[17]

Bioassay evaluations: Compounds **1-8** were screened for cytotoxicity against a panel of human cancer cell lines, according to established protocols.[18] ED_{50} values of >5 μg/ml are regarded as inactive.

Acknowledgment: This investigation was supported by grant U19-CA52956 from the National Cancer Institute, NIH, Bethesda, Maryland. The award of a senior research scholarship by the Thailand Research Fund to V.R. is gratefully acknowledged. We thank Dr. J. Regaldo and Mr. R.B. Dvorak, University of Illinois at Chicago, for taxonomic assistance and for the mass spectra, respectively, as well as the Research Resources Center, University of Illinois at Chicago for the provision of NMR facilities used in this investigation.

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(*Received in USA* 9 *September* 1997; *accepted* 16 *October* 1997)