

Three New Highly Oxygenated Diterpenoids from *Excoecaria cochinchinensis* LOUR.

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Chemical examination of the AcOEt extract of the leaves and twigs of *Excoecaria cochinchinensis* LOUR. collected from Xishuangbanna resulted in the isolation of the three new highly oxygenated diterpenoids **1–3**. The structures of the new diterpenoids were elucidated by a study of their physical and spectra data as (2 β ,3 β ,5 α ,6 α)-2,3-bis(acetyloxy)-8,13-epoxy-6,9-dihydroxylabd-14-en-11-one (=excolabdone A; **1**), (1 α ,5 α ,6 β ,7 β)-1,6-bis(acetyloxy)-8,13-epoxy-7,9-dihydroxylabd-14-en-11-one (=excolabdone B; **2**), and (1 α ,5 α ,6 β ,7 β)-6-(acetyloxy)-8,13-epoxy-1,7,9-trihydroxylabd-14-en-11-one (=excolabdone C; **3**).

1. Introduction. – The genus *Excoecaria* is a member of the Euphorbiaceae and comprises nearly 40 species, which are distributed throughout tropical Africa, Asia, and northwest Australia [1]. They are well-known as extreme skin irritants and tumor promoters [2]. Seven species are found in China of which *Excoecaria cochinchinensis* LOUR., *E. agallocha*, and *E. acerifolia* are commonly known [3]. Many daphane- and tiglane-type diterpene esters which cause skin irritation were isolated from the latex of *E. agallocha* [4][5]. A novel phorbol ester, an anti-HIV principle, has been recently isolated from the leaves and stems of *E. agallocha* collected in Australia [2]. Konish and co-workers have isolated a large number of new diterpenoids of different skeletons such as manoyl oxides, labdanes, beyeranes, kauranes, and diseco-diterpenes along with some known derivatives from the resinous wood of *E. agallocha* [6–13]. In primary screening, some of the diterpenes have been found to possess antitumor-promoting activity *in vivo* against mouse tumor and inhibitory effect on *Epstein–Barr* virus early antigen activation induced by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in *Raji* cells [14–16]. *E. cochinchinensis* LOUR., namely ‘Hong-bei-gui-hua’, is widely distributed in south and southwest of China and cultivated largely as a green tree, which has been used as folk medicine in the treatment of measles, parotitis, quinsy, angina, nephrocolic, and acariasis [3]. However, no work has been reported on the active constituents of this species. The preliminary pharmacological study showed the EtOH extract to have cytotoxic activity against human Hela cell lines at a concentration of 12.5 μ g/ml. A further bioassay-guided study revealed that the AcOEt fraction of the plant extract exhibited strong cytotoxic activity. The phytochemical study of this plant material led to the isolation of three new highly oxygenated

diterpenoids, named excolabdones A, B, and C (**1–3**). We herein present the structural elucidation of the three new compounds **1–3** (Fig. 1).

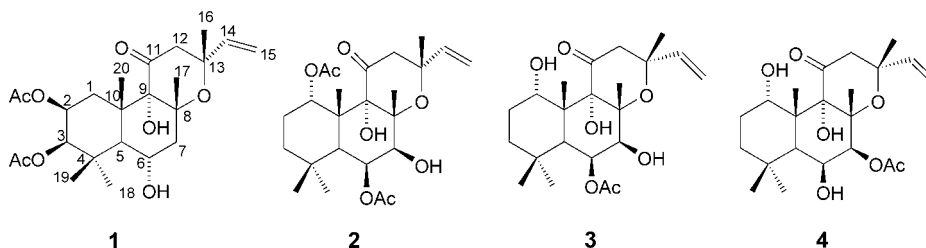


Fig. 1. Structures of compounds **1–4**

2. Results and Discussion. – Excolabdone A (**1**), obtained as colorless needles, has a molecular formula $C_{24}H_{36}O_8$ based on its HR-ESI-MS (m/z 475.2313 ($[M + Na]^+$), indicating that **1** possesses seven unsaturation degrees. The IR spectrum (KBr) showed characteristic absorption bands at 3505, 3396 (OH), 3194, 2968, 2945, 1738, 1710 (C=O), 1411, 1369, 1263, 1238, 1099, and 1054 (C–O) cm^{-1} . Detailed analysis of the 1H - and ^{13}C -NMR (Table), NOESY, 1H , 1H -COSY, and HMBC data established the structure of excolabdone A (**1**) as (2 β ,3 β ,5 α ,6 α)-2,3-bis(acetyloxy)-8,13-epoxy-6,9-dihydroxylabd-14-en-11-one.

The ^{13}C - and DEPT-NMR spectra of **1** revealed the presence of 24 C-signals, which were analyzed as 2 AcO ($\delta(C)$ 170.4 and 21.2, 170.2 and 20.8), 1 C=O ($\delta(C)$ 206.7), 5 Me, 3 CH_2 , and 4 CH groups including 3 OCH groups, 5 quaternary C-atoms ($\delta(C)$ 82.7, 81.3, 75.8, 43.3, 34.2) including 3 O-bearing ones, and 1 olefinic CH_2 ($\delta(C)$ 110.5) and 1 olefinic CH group ($\delta(C)$ 147.5). The 1H -NMR spectrum exhibited signals for a vinyl group which were typical dd signals for H–C(14) at $\delta(H)$ 6.29 ($J=10.7, 17.4$ Hz) and $2dd$ for CH_2 (15) at 5.35 ($dd, J=1.5, 17.4$ Hz, 1 H) and 4.91 ($dd, J=1.5, 10.7$ Hz, 1 H). Consideration of the type of diterpenoids previously isolated from the genus and the MS fragment ions, as well as the characteristic NMR spectra, allowed us to deduce the basic skeleton of **1** as an 8,13-epoxylabdane diterpenoid having a C=C bond between C(14) and C(15). The location of the keto group at C(11) was supported by two d at $\delta(H)$ 3.48 and 2.61 (each $d, J=16.5$ Hz, 1 H) in the 1H -NMR spectrum, which showed correlations with C(11), C(13), C(16), and C(14) in the HMBC experiment. Careful analysis of the NMR spectra of **1** established that the hydroxylated quaternary C-atom at $\delta(C)$ 82.7 was C(9) which was further confirmed by the HMBC correlations C(9)/Me(17) ($\delta(H)$ 1.86, s), Me(20) ($\delta(H)$ 1.65, s), H–C(5) ($\delta(H)$ 2.73, d), and OH–C(9) ($\delta(H)$ 8.63). The 1H -NMR spectrum of **1** displayed three protons attached to O-bearing C-atoms at $\delta(H)$ 6.21 ($dd, J=3.0, 4.5$ Hz, 1 H), 6.15 ($d, J=4.5$ Hz, 1 H), and 5.02 (br. $d, J=2.5$ Hz, 1 H). The presence of AcO–C(2) and AcO–C(3) was established by the HMBC correlations H–C(2)/C(4), C(3), and MeCO, and H–C(3)/C(2), C(4), C(19), and MeCO. The clear key NOESY correlations H–C(2)/H–C(3) and Me(18), and H–C(3)/H–C(5), H–C(2), and Me(18) were consistent with the β -configurations of AcO–C(2) and AcO–C(3) (see Fig. 2). The secondary OH group at C(6) was suggested by the 1H , 1H -COSY correlation between H–C(6) ($\delta(H)$ 5.02) and OH and the HMBC correlations H–C(6)/C(7) and C(5). This OH group is α -oriented as shown by the NOESY correlations H–C(6)/Me(20) and H_β –C(1), and OH–C(6)/H–C(5), H_α –C(7), and H_α –C(1) (Fig. 2).

Excolabdone B (**2**) has the same molecular formula as **1** as determined from its HR-EI-MS (m/z 475.2309 ($[M + Na]^+$, $C_{24}H_{36}NaO_8^+$). The NMR spectra (Table) of **2** suggested that its structure was closely comparable to that of **1**. The difference between **1** and **2** was due to different substituent positions of the OH and the two AcO groups.

Table. ^1H - and ^{13}C -NMR Data for Compounds **1**–**3**. In $\text{C}_5\text{D}_5\text{N}$. δ in ppm, J in Hz.

	1		2		3	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
$\text{CH}_2(1)$ or $\text{H}-\text{C}(1)$	2.17, 1.55 (each m , 1 H)	27.0(t)	5.96 (t -like s , 1 H)	77.6(d)	8.39 (d , $J=3.6$, $\text{OH}_\alpha-\text{C}(1)$), 5.10 (br. d , $J=2.0$, $\text{H}_\beta-\text{C}(1)$)	73.6(d)
$\text{H}-\text{C}(2)$ or $\text{CH}_2(2)$	6.21 (dd , $J=3.0, 4.5$, 1 H)	70.1(d)	2.10, 1.72 (each m , 1 H)	24.2(t)	2.21, 1.60 (each m , 1 H)	27.0(t)
$\text{H}-\text{C}(3)$ or $\text{CH}_2(3)$	6.15 (d , $J=4.5$, 1 H)	75.5(d)	1.62, 1.08 (each m , 1 H)	38.2(t)	2.12, 1.14 (each m , 1 H)	37.0(t)
$\text{C}(4)$	–	43.3(s)	–	34.1(s)	–	34.1(s)
$\text{H}_\alpha-\text{C}(5)$	2.73 (d , $J=2.8$)	42.6(d)	2.56 (d , $J=2.8$)	44.2(d)	2.76 (d , $J=2.6$)	42.8(d)
$\text{H}-\text{C}(6)$	5.02 (br. d , $J=2.5$), 8.49 (d , $J=3.6$, $\text{OH}_\alpha-\text{C}(6)$)	73.6(d)	6.21 (dd , $J=2.7, 4.5$)	73.4(d)	6.32 (t , $J=3.2, 4.0$)	73.1(d)
$\text{CH}_2(7)$ or $\text{H}-\text{C}(7)$	1.98, 1.05 (each m , 1 H)	36.8(t)	4.70 (d , $J=4.1$, 1 H)	73.6(d)	6.92 (s , $\text{OH}_\beta-\text{C}(7)$), 4.91 (d , $J=3.7$, $\text{H}_\alpha-\text{C}(7)$)	73.1(d)
$\text{C}(8)$	–	81.3(s)	–	84.5(s)	–	83.1(s)
$\text{OH}_\alpha-\text{C}(9)$	8.63(s)	82.7(s)	5.16(s)	83.0(s)	8.56(s)	82.8(s)
$\text{C}(10)$	–	34.2(s)	–	44.7(s)	–	43.3(s)
$\text{C}(11)$	–	206.7(s)	–	202.6(s)	–	207.1(s)
$\text{CH}_2(12)$	3.48, 2.61 (each d , $J=16.5$, 1 H)	49.7(t)	3.32, 2.62 (each d , $J=16.6$, 1 H)	50.0(t)	3.49, 2.66 (each d , $J=16.5$, 1 H)	49.7(t)
$\text{C}(13)$	–	75.8(s)	–	76.4(s)	–	75.3(s)
$\text{H}-\text{C}(14)$	6.29 (dd , $J=10.7, 17.3$)	147.5(d)	6.22 (dd , $J=10.6, 17.5$)	148.1(d)	6.45 (dd , $J=10.8, 17.7$)	148.1(d)
$\text{CH}_2(15)$	5.35 (dd , $J=1.5, 17.4$, 1 H), 4.91 (dd , $J=1.5, 10.7$, 1 H)	110.0(t)	5.25 (dd , $J=1.1, 17.4$, 1 H), 4.93 (dd , $J=1.1, 10.6$, 1 H)	110.8(d)	5.28 (d , $J=17.5$, 1 H), 4.97 (d , $J=10.8$, 1 H)	109.5(t)
$\text{Me}(16)$	1.43 (s)	30.8(q)	1.38 (s)	31.1(q)	1.44 (s)	30.3(q)
$\text{Me}(17)$	1.86 (s)	23.6(q)	1.90 (s)	24.0(q)	1.95 (s)	23.2(q)
$\text{Me}(18)$	0.98 (s)	32.7(q)	1.13 (s)	33.4(q)	1.20 (s)	32.8(q)
$\text{Me}(19)$	1.01 (s)	23.5(q)	1.04 (s)	24.1(q)	1.12 (s)	23.3(q)
$\text{Me}(20)$	1.65 (s)	20.0(q)	1.66 (s)	20.7(q)	1.72 (s)	20.0(q)
AcO	2.14 (s , $\text{AcO}-\text{C}(2)$)	170.4(s)	2.14 (s , $\text{AcO}-\text{C}(1)$)	22.2(q)	2.17 (s , $\text{AcO}-\text{C}(6)$)	21.6(q)
AcO	2.01 (s , $\text{AcO}-\text{C}(3)$)	170.2(s)	2.04 (s , $\text{AcO}-\text{C}(6)$)	22.4(q)		170.3(s)
		20.8(q)		171.1(s)		

The structure of **2** was established as $(1\alpha, 5\alpha, 6\beta, 7\beta)$ -1,6-bis(acetyloxy)-8,13-epoxy-7,9-dihydroxylabd-14-en-11-one (Fig. 1).

That the two AcO groups of **2** are attached at C(1) and C(6) rather than at C(2) and C(3) as in **1**, was deduced from HMBC correlations between the signals at $\delta(\text{H})$ 5.96 (t -like s , 1 H) with Me(20), C(2), C(3), C(5), and MeCO, and at $\delta(\text{H})$ 6.21 (dd , $J=2.7, 4.5$ Hz, 1 H, overlapping with $\text{H}-\text{C}(14)$) with C(4), C(5), C(7), C(8), and MeCO. The observation of the NOESY correlations $\text{H}-\text{C}(1)/\text{H}_\beta-\text{C}(2)$ and Me(20), and $\text{H}-\text{C}(6)/\text{H}-\text{C}(5)$ and $\text{H}-\text{C}(7)$ indicated the α -orientation of $\text{AcO}-\text{C}(1)$ and β -orientation of $\text{AcO}-\text{C}(6)$ (Fig. 2). The attribution of the hydroxylated CH group ($\delta(\text{C})$ 73.6) to $\text{OH}_\beta-(7)$ is supported by the HMBC correlations between $\text{H}-\text{C}(7)$ ($\delta(\text{H})$ 4.70 (d)) and C(6), Me(17), and C(8) and the NOESY correlations $\text{H}-\text{C}(7)/\text{H}-\text{C}(6)$, $\text{OH}-\text{C}(9)$ and $\text{H}-\text{C}(5)$.

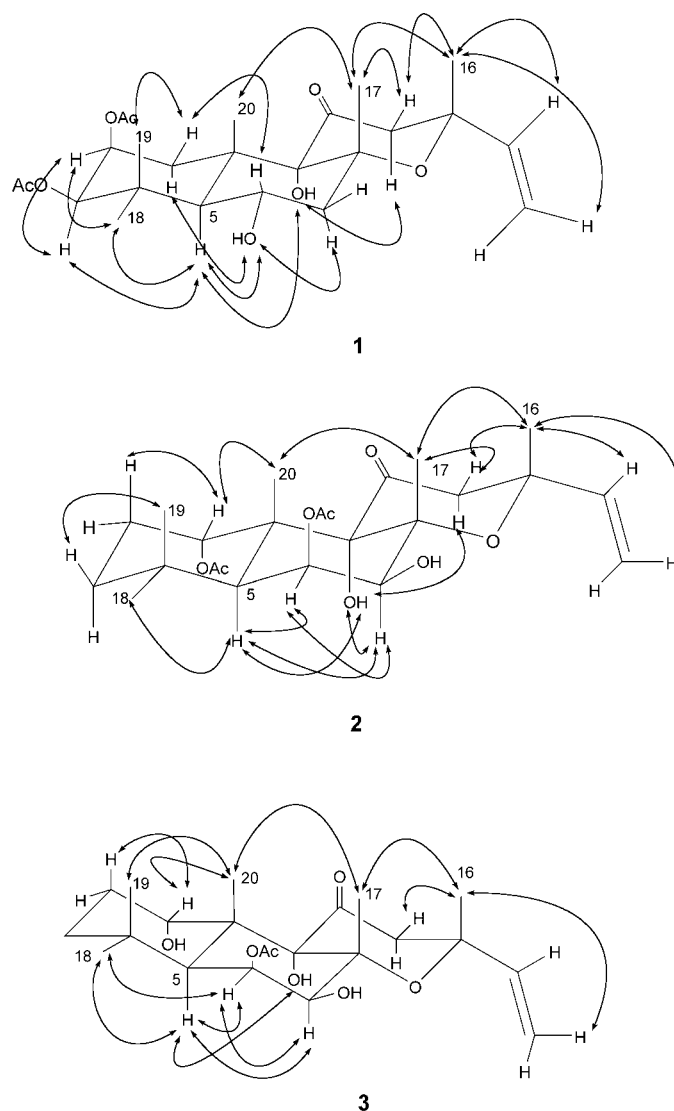


Fig. 2. Key NOESY correlations of **1**, **2**, and **3**

Excolabdone C (**3**) was found to have a molecular formula of $C_{22}H_{34}O_7$ by its molecular-ion peak in the HR-ESI-MS at m/z 433.2213 ($[M + Na]^+$). The spectral data of **3** are characteristic of the 8,13-epoxylabdane diterpenoids and were very similar to those of **2** based on a general analysis of their 2D-NMR data, the difference being the absence of an AcO group and the presence of an OH group at C(1) of **3**. The structure of **3** was established as $(1\alpha,5\alpha,6\beta,7\beta)$ -6-(acetyloxy)-8,13-epoxy-1,7,9-trihydroxyabd-14-en-11-one (Fig. 1). Compound **3** was obtained synthetically from the well-known biologically active diterpenoid forskolin (**4**) by an acyl migration of the acetate function

of **4** [17]. But as a natural product, excolabdone C (**3**) was isolated here for the first time.

The ^{13}C -NMR (DEPT) spectra (Table) of **3** showed the presence of 1 C=O, 1 AcO, 1 olefinic CH_2 ($\delta(\text{C})$ 109.5), 1 olefinic CH ($\delta(\text{C})$ 148.1), 5 tertiary Me, 3 CH_2 , and 4 CH groups including 3 OCH groups, and 5 quaternary C-atoms including 3 O-bearing ones. The HMBC correlations H–C(1) ($\delta(\text{H})$ 5.10, br. *d*)/C(5), C(2), and C(20) confirmed the OH group at C(1) ($\delta(\text{C})$ 73.6). Furthermore, the NOESY correlation H–C(1)/Me(20) and H_β –C(2) agreed with the α -orientation of OH–C(1).

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Experimental Part

General. TLC: commercial silica-gel plates (*Qing Dao Marine Chemical Group Co.*). M.p.: *XRC-1* micro melting-point apparatus; uncorrected. Optical rotation: *Horiba SEAP-300* spectropolarimeter. UV Spectra: *Shimadzu UV-2401PC* spectrophotometer; λ_{max} in nm. IR Spectra: *Bio-Rad FTS-135* IR spectrophotometer; $\tilde{\nu}_{\text{max}}$ in cm^{-1} . ^1H -, ^{13}C -NMR, and 2D-NMR Spectra: *Bruker AV-500* spectrometer; chemical shifts δ in ppm rel. to SiMe_4 , as internal standard, coupling constant *J* in Hz. EI-MS: *VG Autospec-3000* mass spectrometer, in *m/z* (rel. %).

Plant Material. The leaves and twigs of *Excoecaria cochinchinensis* LOUR. were collected in Xishuangbanna Country of Yunnan province, P. R. China, in October 2002, and identified by Prof. *Zhi-Hao Hu* of the Department of Botany, Yunnan University. A voucher specimen (200210) is deposited in the School of Pharmacy, Yunnan University.

Extraction and Isolation. The powdered plant material of *Excoecaria cochinchinensis* LOUR. (12.0 kg) was repeatedly extracted with EtOH at r.t. The extract was then evaporated to give a brown syrup, which was partitioned between H_2O and solvents to give a petroleum ether fraction (80 g), a AcOEt fraction (686 g), and a BuOH fraction (180 g). The AcOEt extract was subjected to column chromatography (silica gel, petroleum ether/AcOEt 50:1 \rightarrow 1:1, AcOEt/MeOH 10:1 \rightarrow 1:1, and MeOH): *Fractions I–XIX. Fr. I and II* were resubmitted to column chromatography (silica gel, *Sephadex LH-20*): **1** (5 mg), **2** (10 mg), and **3** (6 mg).

Excolabdone A ($= (2\beta,3\beta,5\alpha,6\alpha)$ -2,3-Bis(acetyloxy)-8,13-epoxy-6,9-dihydroxylabd-14-en-11-one $= (3R,4aR,6S,6aS,8R,9S,10aS,10bS)$ -8,9-Bis(acetyloxy)-3-ethenyldodecahydro-6,10b-dihydroxy-3,4a,7,7,10a-pentamethyl-1H-naphtho[2,1-b]pyran-1-one; **1**): Colorless needles from $\text{CHCl}_3/\text{MeOH}$. M.p. 260–261°. $[\alpha]_{\text{D}}^{25} = 22.8$ ($c = 0.20$, MeOH). UV (MeOH): 195, 202. IR (KBr): 3505, 3396 (OH), 3194, 2968, 2945, 1738, 1710 (C=O), 1411, 1369, 1263, 1238, 1099, 1054 (C–O). ^1H - and ^{13}C -NMR: Table. ESI-MS (pos.): 452 (7), 421 (15), 392 (10), $[M - \text{AcOH}]^+$, 325 (18), 235 (10), 207 (75), 165 (76), 99 (85), 81 (100). HR-ESI-MS: 475.2313 ($[M + \text{Na}]^+$, $\text{C}_{24}\text{H}_{36}\text{O}_8^+$; calc. 475.2307).

Excolabdone B ($= (1\alpha,5\alpha,6\beta,7\beta)$ -1,6-Bis(acetyloxy)-8,13-epoxy-7,9-dihydroxylabd-14-en-11-one $= (3R,4aR,5S,6S,6aS,10S,10aR,10bS)$ -6,10-Bis(acetyloxy)-3-ethenyldodecahydro-5,10b-dihydroxy-3,4a,7,7,10a-pentamethyl-1H-naphtho[2,1-b]pyran-1-one; **2**): Microcrystals from $\text{CHCl}_3/\text{MeOH}$. M.p. 245–247°. $[\alpha]_{\text{D}}^{25} = 35.5$ ($c = 2.6$, MeOH). IR (KBr): 3446 (OH), 2970, 2948, 1742, 1632 (C=O), 1399, 1365, 1245, 1174, 1054. ^1H - and ^{13}C -NMR: Table. EI-MS: 452 (3), 434 (15), 359 (15), 191 (60), 165 (100), 123 (75), 95 (95), 81 (75). HR-ESI-MS: 475.2309 ($[M + \text{Na}]^+$, $\text{C}_{24}\text{H}_{36}\text{O}_8^+$; calc. 475.2307).

Excolabdone C ($= (1\alpha,5\alpha,6\beta,7\beta)$ -6-(Acetyloxy)-8,13-epoxy-1,7,9-trihydroxylabd-14-en-11-one $= (3R,4aR,5S,6S,6aS,10S,10aR,10bS)$ -6-(Acetyloxy)-3-ethenyldodecahydro-5,10b-dihydroxy-3,4a,7,7,10a-pentamethyl-1H-naphtho[2,1-b]pyran-1-one; **3**): Microcrystals from $\text{CHCl}_3/\text{MeOH}$. M.p. 220–222°. $[\alpha]_{\text{D}}^{25} = -8.33$ ($c = 0.48$, MeOH). IR (KBr): 3443 (OH), 2926, 2856, 1721, 1632 (C=O), 1243, 1051. ^1H - and ^{13}C -NMR: Table. FAB-MS (pos.): 411 (55, $[M + 1]^+$), 393 (75), 315 (45), 297 (65), 237 (75), 193 (35), 175 (72), 121 (65), 81 (44). EI-MS: 410 (3), 392 (15), 359 (20), 221 (45), 191 (40), 165 (90), 125 (100), 81 (65). HR-ESI-MS: 433.2213 ($\text{C}_{22}\text{H}_{34}\text{O}_7\text{Na}^+$; calc. 433.2202).

Cytotoxicity Assay. The cytotoxic activity against human HeLa cell lines were assayed by using the standard MTT method *in vitro*.

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