SESQUITERPENE PYRIDINE ALKALOIDS FROM MAYTENUS ILICIFOLIA

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Abstract - Three sesquiterpene pyridine alkaloids with a dihydroagarofuran core, cangorinines W-I (**1**), W-II (**2**), and E-I (**3**) were isolated from the root bark of Maytenus ilicifolia Mart. (Celastraceae). Their structures were elucidated by spectroscopic methods.

In the course of our continuing research among Amazonian medicinal plants,[1] we have been interested in the genus Maytenus,[2-6] which were widely used as folk medicines in Amazonian basin, such as antitumor, antirheumatism and antiinflammatory by several tribes.[7,8] From Maytenus species, many characteristic bioactive compounds, such as the maytansinoids[9] with antitumor activity, cytotoxic quinoid triterpenes,[2,3,10] sesquiterpene polyesters and sesquiterpene pyridine alkaloids[4-6,11] with insect antifeedant or insecticidial activity, so far have been isolated. Recently, immunosuppressive activity for sesquiterpene pyridine alkaloids[12] and anti-tumor-promoting activity for sesquiterpene polyesters[13] were also reported on Celastraceae plants.

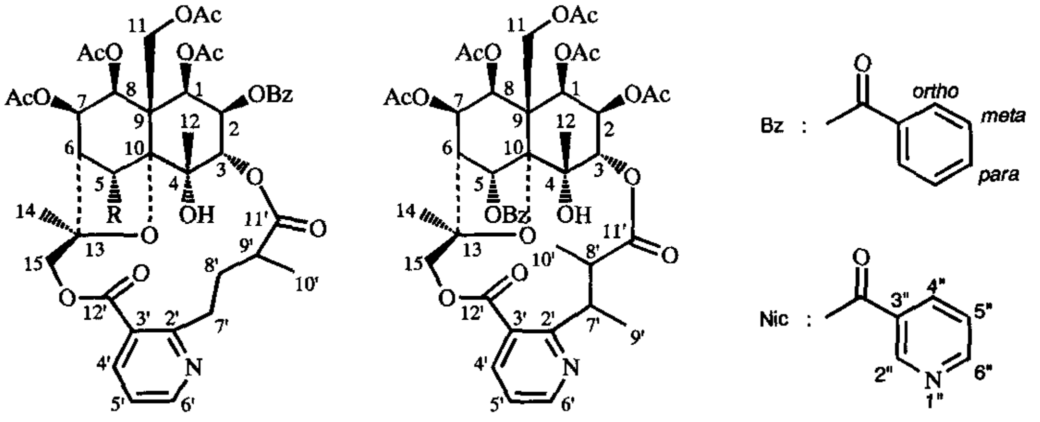
Maytenus ilicifolia Mart. is a large shrub found in Southern Brazil, Paraguay, Uruguay and Argentina. Its reddish to orangish brown root bark, known as "cangorosa" by Indian tribes and rural populations in Paraguay, is used as a fertility regulating agent.[14] In our previous examinations of this material, unique triterpene dimers named cangorosins,[2] the biogenetically important triterpene cangoronine along with some quinoid triterpenes[3] and oligo-nicotinated sesquiterpene polyesters named cangorins[6] were isolated. Further investigation of its chemical constituents resulted in the isolation of three new alkaloids.

We report herein the isolation and structural characterization of three sesquiterpene pyridine alkaloids, which we called cangorinines W-I (**1**), W-II (**2**), and E-I (**3**).

Fractionation of CH_2Cl_2 soluble phase of the MeOH extract led us to the isolation of three sesquiterpene pyridine alkaloids, cangorinines W-I (**1**), W-II (**2**) (wilfordate type[15-17]) and E-I (**3**) (evoninate type[18-20]). A combination of HMQC and HMBC[21] spectra enabled us to perform complete assignment of the ^{1}H- and ^{13}C-signals of **1**, **2** and **3**, as shown in Tables 1 and 2, respectively.

Cangorinine W-I (**1**) was obtained as an amorphous solid, and its molecular formula $C_{48}H_{51}NO_{18}$ (m/z 930.3172: M+H; $\Delta = +1.3$ mmu) was determined by means of HR-EI ms spectrum. From nmr spectroscopic data, it appeared that it contained four acetyl groups (δ_H : 1.87, 1.96, 2.12, 2.26), two benzoyl groups [δ_H :

7.48 (m), 7.60 (p), 8.05 (o); 7.48 (m), 7.58 (p), 8.23 (o)], two tertiary methyl groups (δ_H : 1.69, 1.71), two sets of methylene protons [δ_H : 3.73, 5.78 (J = 11.9 Hz); 4.48, 5.56 (J = 13.2 Hz)], seven methine protons (δ_H : 2.57, 5.13, 5.46, 5.52, 5.59, 5.82, 6.97) and one hydrogen bonded hydroxyl group (δ_H : 5.12; ν : 3450 cm^{-1}). It also appeared to contain one 2,3-disubstituted pyridine [δ_H :7.26 (5'), 8.27 (4'), 8.75 (6')], one secondary methyl group (δ_H : 1.25) coupled with one methine proton (δ_H : 2.50), and two sets of methylenes (δ_H : 2.07, 2.29; 3.01, 3.95) coupled each other. These data indicated that this was one of the sesquiterpene pyridine alkaloids derived from polyester sesquiterpenes based on a dihydro-β-agarofuran core, which have been characteristically detected in Celastraceae plants. It included one macrocycle structure formed by two ester linkages between one sesquiterpene molecule and one wilfordic acid, at positions 3 and 15. The coupling constants among the seven methine protons revealed their connections in the dihydroagarofuran core, and nOe data from NOESY spectrum confirmed its ester group orientation patterns as 1βeq, 2βax, 5αeq, 7βax and 8βeq. In order to determine the positions of ester groups, an HMBC spectrum was recorded. The methine proton (δ_H : 5.52) of position 2 and the *ortho* protons (δH : 8.05) of one benzoyl group gave cross peaks with same carbonyl carbon at δ_C 165.00, and the methine proton (δ_H : 6.97) of position 5 and the *ortho* protons (δ_H : 1.42) of another benzoyl group also gave cross peaks with same carbonyl carbon at δ_C 165.80. These data showed that the two benzoate groups located at positions 2 and 5, respectively. Consequently, the structure of cangorinine W-I was **1** (Figure 1).



cangorinine W-I (**1**) : R = OBz
cangorinine W-II (**2**) : R = ONic

cangorinine E-I (**3**)

Figure 1. The structures of cangorinines.

Cangorinine W-II (**2**) was an amorphous solid which had a molecular formula $C_{47}H_{50}N_2O_{18}$ (m/z 931.3182: M+H; Δ = -4.5 mmu). It was also a macrocyclic sesquiterpene pyridine alkaloid, and its nicotinate derivative unit in the macrocycle was wilfordic acid as same as cangorinine W-I. It contained four acetyl groups (δ_H : 1.87, 1.97, 2.18, 2.25), one benzoyl group [δ_H : 7.49 (m), 7.61 (p), 8.06 (o)], one nicotinyl group [δ_H : 9.37

(2"), 8.62 (4"), 7.43 (5"), 8.80 (6")], revealed by means of the ^{1}H-nmr spectrum. The positions of one benzoyl and one nicotinyl groups were determined by long range correlation data among the proton and the carbon obtained from an HMBC spectrum, to be the benzoate group at position 2 and the nicotinate group at position 5. That is, the presence of the cross peaks between H_2 at δ_H 5.51, $H_{Bz(o)}$ at δ_H 8.06 and the carbonyl carbon at δC 165.05, and between H_5 at δ_H 7.08, $H_{Nic(4")}$ at δ_H 8.62 and the carbonyl carbon at δC 164.62 were detected. These data showed that the structure of cangorinine W-II was as shown in Figure 1.

Table 1. ^{1}H-nmr chemical shifts (ppm) for cangorinines W-I, E-I and E-II.

Proton	cangorinine W-I (**1**)	cangorinine W-II (**2**)	proton	cangorinine E-I (**3**)
1-H	5.82 (d, 3.6)	5.81 (d, 3.7)	1-H	5.59 (d, 3.8)
2-H	5.52 (dd, 2.6, 3.6)	5.51 (dd, 2.6, 3.7)	2-H	5.27 (dd, 2.6, 3.8)
3-H	5.13 (d, 2.6)	5.12 (d, 2.6)	3-H	4.83 (d, 2.5)
4-OH	5.12 (br-s)	5.13 (d, 1.1)	4-OH	4.74 (br-s)
5-H	6.97 (s)	7.08 (s)	5-H	7.17 (s)
6-H	2.57 (d, 4.1)	2.56 (d, 3.9)	6-H	2.51 (d, 3.9)
7-H	5.59 (dd, 4.1, 5.8)	5.60 (dd, 3.9, 5.8)	7-H	5.54 (dd, 3.9, 5.8)
8-H	5.46 (d, 5.8)	5.46 (d, 5.8)	8-H	5.39 (d, 5.8)
11-Ha	4.48 (d, 13.2)	4.49 (d, 13.3)	11-Ha	4.56 (d, 13.5)
11-Hb	5.56 (d, 13.2)	5.54 (d, 13.3)	11-Hb	5.17 (d, 13.5)
12-CH_3	1.71 (s)	1.69 (d, 1.1)	12-CH_3	1.55 (s)
14-CH_3	1.69 (s)	1.71 (s)	14-CH_3	1.68 (s)
15-Ha	3.73 (d, 11.9)	3.71 (d, 11.8)	15-Ha	3.61 (d, 11.5)
15-Hb	5.78 (d, 11.9)	5.77 (d, 11.8)	15-Hb	6.01 (d, 11.5)
4'-H	8.27 (dd, 1.6, 7.9)	8.27 (dd, 1.8, 8.0)	4'-H	8.04 (dd, 1.5, 7.7)
5'-H	7.26 (dd, 4.8, 7.9)	7.27 (dd, 4.7, 8.0)	5'-H	7.25 (dd, 4.8, 7.7)
6'-H	8.75 (dd, 1.6, 4.8)	8.76 (dd, 1.8, 4.8)	6'-H	8.69 (dd, 1.5, 4.8)
7'-Ha	3.01 (br-ddd, 5.9, 6.9, 13.4)	3.00 (dt-like, 5.6, 13.1)	7'-H	4.70 (q, 6.8)
7'-Hb	3.95 (ddd, 6.8, 9.1, 13.4)	3.96 (ddd, 3.4, 6.2, 13.6)	----	----
8'-Ha	2.07 (m)	2.03 (m)	8'-H	2.58 (q, 7.1)
8'-Hb	2.29 (m)	2.31 (m)	----	----
9'-H	2.50 (br-dqd, 2.3, 7.0, 9.5)	2.46 (m)	9'-CH_3	1.43 (d, 6.8)
10'-CH_3	1.25 (d, 7.0)	1.24 (d, 7.0)	10'-CH_3	1.19 (d, 7.1)
1-OAc	1.87 (s)	1.87 (s)	1-OAc	1.84 (s)
2-OAc	----	----	2-OAc	2.15 (s)
OBz(*o*)	8.05 (d, 7.4)	8.06 (dd-like, 1.0, 7.9)	----	----
OBz(*m*)	7.48 (t-like, 7.4)	7.49 (t-like, 7.7)	----	----
OBz(*p*)	7.60 (t-like, 7.1)	7.61 (dt-like, 1.0, 7.1)	----	----
5-OAc	2.19 (s)	----	5-OAc	----
OBz(*o*)	8.27 (d, 7.4)	----	OBz(*o*)	8.31 (d, 7.6)
OBz(*m*)	7.48 (t-like, 7.4)	----	OBz(*m*)	7.49 (t-like, 7.6)
OBz(*p*)	7.58 (t-like, 7.1)	----	OBz(*p*)	7.58 (t-like, 7.3)
ONic(2")	----	9.37 (d, 1.6)	----	----
ONic(4")	----	8.62 (dt-like, 1.9, 8.0)	----	----
ONic(5")	----	7.43 (dd, 4.9, 7.9)	----	----
ONic(6")	----	8.80 (dd, 1.5, 4.8)	----	----
7-OAc	2.26 (s)	•2.18 (s)	7-OAc	•2.22 (s)
8-OAc	1.96 (s)	1.97 (s)	8-OAc	2.00 (s)
11-OAc	2.12 (s)	•2.25 (s)	11-OAc	•2.33 (s)

Measurements were performed in $CDCl_3$ at 400 MHz.
Multiplicity and coupling constants (J/Hz) were in parenthesis.
• : These sets of values may be interchangeable between each group.

Table 2. ^{13}C-nmr chemical shifts (ppm) for **1**, **2** and **3**.

Carbon	**1**		**2**		**3**	
1	73.54	(d)	73.52	(d)	73.33	(d)
2	69.86	(d)	69.91	(d)	68.77	(d)
3	76.12	(d)	76.10	(d)	75.87	(d)
4	69.95	(s)	70.06	(s)	70.65	(s)
5	74.89	(d)	75.29	(d)	74.81	(d)
6	51.04	(d)	51.16	(d)	50.44	(d)
7	69.27	(d)	69.25	(d)	69.17	(d)
8	71.23	(d)	71.11	(d)	70.84	(d)
9	52.16	(s)	52.33	(s)	52.30	(s)
10	93.33	(s)	93.53	(s)	93.72	(s)
11	60.81	(t)	60.77	(t)	60.06	(t)
12	23.27	(q)	23.31	(q)	22.88	(q)
13	84.44	(s)	84.57	(s)	84.19	(s)
14	17.97	(q)	18.07	(q)	18.41	(q)
15	70.24	(t)	70.20	(t)	69.95	(t)
2'	163.74	(s)	164.03	(s)	165.24	(s)
3'	124.68	(s)	124.60	(s)	125.16	(s)
4'	138.58	(d)	138.62	(d)	137.63	(d)
5'	121.12	(d)	121.21	(d)	121.09	(d)
6'	153.04	(d)	153.26	(d)	151.48	(d)
7'	33.47	(t)	33.40	(t)	36.37	(d)
8'	33.25	(t)	33.44	(t)	45.02	(d)
9'	38.68	(d)	38.67	(d)	11.82	(q)
10'	18.48	(q)	18.70	(q)	9.59	(q)
11'	175.20	(s)	175.30	(s)	173.91	(s)
12'	167.04	(s)	167.14	(s)	168.58	(s)
1-OC=O	169.54	(s)	169.53	(s)	169.09	(s)
CH_3	20.57	(s)	20.61	(s)	*20.42	(s)
2-OC=O	165.00	(s)	165.05	(s)	168.58	(s)
CH_3	---		---		**21.00	(q)
ipso	*128.94	(s)	128.95	(s)	---	
ortho	129.85	(d)	129.96	(d)	---	
meta	*128.74	(d)	128.83	(d)	---	
para	*133.66	(d)	133.81	(d)	---	
5-OC=O	165.80	(s)	164.62	(s)	165.77	(s)
ipso	*129.34	(s)	---		129.53	(s)
ortho	130.33	(d)	---		130.31	(d)
meta	*128.85	(d)	---		128.81	(d)
para	*133.69	(d)	---		133.55	(d)
2"	---		151.64	(d)	---	
3"	---		125.49	(s)	---	
4"	---		137.91	(d)	---	
5"	---		123.91	(d)	---	
6"	---		154.12	(d)	---	
7-OC=O	170.23	(s)	170.21	(s)	170.16	(s)
CH_3	21.07	(q)	*21.12	(q)	**21.06	(q)
8-OC=O	169.00	(s)	169.06	(s)	168.95	(s)
CH_3	20.84	(q)	20.54	(q)	*20.46	(q)
11-OC=O	170.13	(s)	170.21	(s)	170.16	(s)
CH_3	21.07	(q)	*21.20	(q)	**21.40	(q)

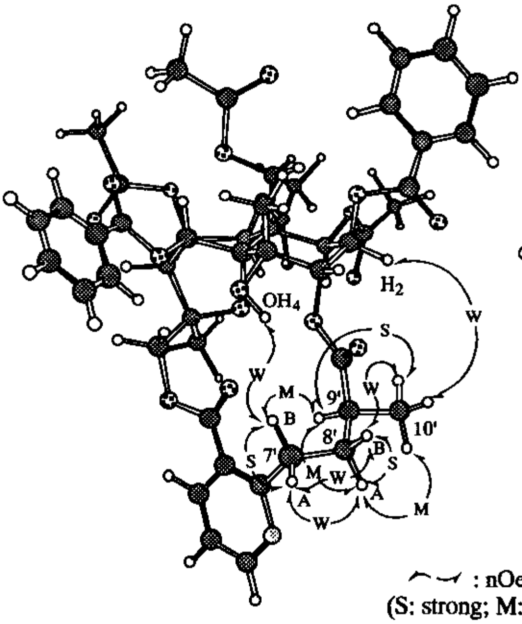
Measurements were performed in $CDCl_3$ at 100 MHz.
Multiplicity was in parenthesis.
*, ** : These sets of values may be interchangeable between each groups.

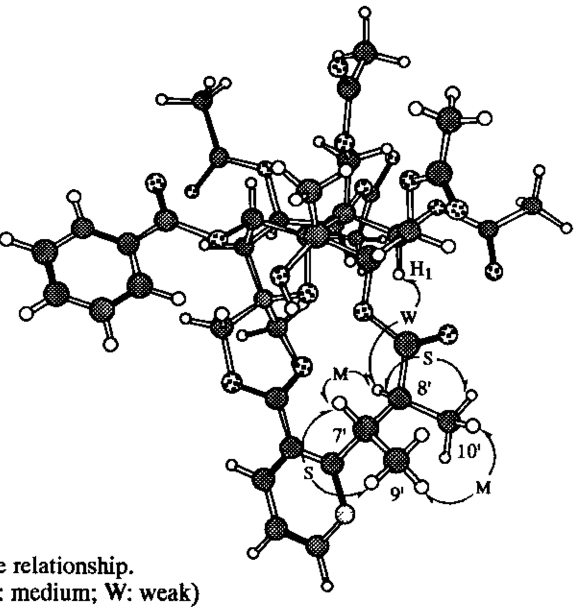
Cangorinine E-I (**3**) is an amorphous solid with the molecular formula $C_{43}H_{49}NO_{18}$ (m/z 868.3044,: M+H; Δ = -1.6 mmu). In the ^{1}H- and ^{13}C-nmr, the presence of a dihydro-β-agarofuran sesquiterpene core was observed as well as that of cangorinines W-I and W-II. Instead of the wilfordate diester,[15-17] however, an *evoninate diester*[18-20] as a dibasic acid moiety was suggested by the signals of one 2,3-disubstituted pyridine (δ_H 7.25, 8.04, 8.69), two secondary methyl groups [δ_H 1.19 (J = 7.1 Hz); 1.43 (J = 6.8 Hz)] and two methine protons [δ_H 2.58 (J = 7.1 Hz), 4.70 (J = 6.8 Hz)]. Furthermore, **3** contained five acetyl groups and one benzoyl group as indicated by ^{1}H- and ^{13}C-nmr spectral data, and these esterifying positions were confirmed clearly by means of an HMBC spectrum, which showed cross peaks among each methine protons, aromatic or acetyl methyl protons and corresponding carbonyl carbons. One of these, the benzoate group was shown to be located at position 5, by the cross peaks between H_5 (δ_H 7.17), $H_{Bz(o)}$ (δ_H 8.31) and the carbonyl carbon at δ_C 165.77. Thus, the structure of cangorinine E-I was determined as **3** (Figure 1).

In our previous work,[5] we determined unknown configuration of the methyl group in the 2-methylbutanoic acid sidechain in the wilfordate-type compound as "S", with the aid of analysis of coupling constants including homodecoupling experiments and space distance relationships by nOe data from

NOESY spectra in nmr, and confirmed by means of X-ray analysis of ebenifoline W-I. In order to make sure the configuration of the position 9' about **1** and **2**, NOESY spectra of both compounds were made. In the NOESY spectra (fractional nOe data are illustrated in Figure 2), cross peaks were observed between 7'A, 8'A protons and 8'B proton, and also between 7'B, 8'A protons and 9' proton. Moreover, 10' methyl group had cross peaks with the methine protons of positions 1 and 2 of the sesquiterpene core, and 7'B proton had cross peaks with the proton of hydroxyl group at position 4 and 15B proton at the opposite site of the sidechain. The patterns of these nOe data are very similar to that of ebenifoline W-I,[10] therefore the configuration of position 9' in the wilfordate side chain of **1** and **2** were assigned as "S". Furthermore, a NOESY measurement was also done about compound (**3**). Concerning the evoninate type compounds, the configurations of the two methyl groups in the 2,3-dimethyl propanoic acid side chain have already been determined to be 2S, 3S by the hydrolysis[22] or X-ray analysis.[23] The nOe data (illustrated in Figure 3) obtained from NOESY spectrum of **3**, showed a cyclical continuative nOe correlation pattern (7' methine proton - 8' methine proton - 10' methyl group - 9' methyl group - 7' methine proton) on the sidechain, and one nOe correlation between 8' methine proton and the methine proton of position 1 of the sesquiterpene core. These data agreed with the fact that the configuration of evoninic acid is "2S, 3S".

Complete assignments of the ^{1}H and ^{13}C nmr signals of cangorinines are shown in Tables 1 and 2, respectively.





↶↷ : nOe relationship.
(S: strong; M: medium; W: weak)

Figure 2. nOe correlations and conformation of **1**.

Figure 3. nOe correlations and conformation of **3**.

EXPERIMENTAL

General Details. - Mp's were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 spectrometer and the $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Mass, uv, ir, and cd spectra were taken with a Hitachi M-80 spectrometer, a Hitachi 557 spectrophotometer, a JASCO A-302 spectrophotometer and JASCO J-700 spectropolarimeter, respectively. Medium-pressure liquid chromatography (mplc) was performed with a CIG column system (22 mm i.d. x 300 mm, Kusano Scientific Co., Tokyo) packed with 10 µm Si gel or 20 µm ODS. Hplc was performed with an Inertsil PREP-ODS column (20 mm i.d. x 250 mm, Gasukuro Kogyo Inc.) packed with 10 µm ODS. Tlc was conducted on precoated Kieselgel 60 F_{254} (Art. 5715; Merck) and the spots were detected by heating after spraying with 10% H_2SO_4. ^1H and ^{13}C nmr spectra were recorded on Bruker spectrometers (AM 400 and AM 500) at 303 K and processed on a Bruker data station with an Aspect 3000 computer. NOESYPH experiments were made with a mixing time of 0.6 s. The nmr coupling constants (J) are given in Hz.

Materials. - Reddish to orangish brown root bark of Maytenus ilicifolia Mart. (1140 g), commonly known as "cangorosa" among Indian tribes, were purchased at Asuncion, Paraguay, in 1987. The botanical identification was made by Dr. Tanaka (Asuncion University). A voucher specimen has been deposited in the herbarium of the Tokyo College of Pharmacy.

Extraction and isolation of **1** - **3**. - The root barks (1140 g) of M. ilicifolia were crushed and extracted with a hot MeOH (12 l) to give a MeOH extract (364 g) which was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ soluble fraction (62.3 g) was subjected to silica gel cc using an n-hexane - ethyl acetate gradient system (1:0 - 0:1) to give seventeen fractions. Non-cytotoxic fractions 12, 13, 14 and 15 were further subjected to an ODS mplc with a MeOH - H_2O solvent system to give **1** (32 mg), **2** (13 mg) and **3** (30 mg), as an amorphous solid. These compounds were further purified by ODS hplc with MeOH - H_2O or acetonitrile - H_2O solvent systems.

Cangorinine W-I (**1**). - Colorless amorphous solid, mp 149-151°C, $[\alpha]_D$ +14.4° (c 0.57, $CHCl_3$), $\lambda_{max}^{(MeOH)}$/nm ($\Delta\varepsilon$) : 267(-2.9), 237(-25.7), 223(+7.0) and 211(-2.6), m/z : 929 (M^+), 856, 750, 634, 352, 206, 160 and 105 (Found : $[M+H]^+$, 930.3172 $C_{48}H_{52}NO_{18}$; requires : 930.3184), $\nu_{max}^{(CHCl_3)}$/cm^{-1} : 3450(m), 1720(br-s), 1603(s), 1586(s), 1570(s), 1462(s), 1380(s) and 1247(br-s), $\lambda_{max}^{(MeOH)}$/nm (log ε) : 203(4.50), 230(4.58) and 268(3.77), ^1H nmr ($CDCl_3$) : listed in Table 1, ^{13}C nmr ($CDCl_3$) : listed in Table 2.

Cangorinine W-II (**2**). - Colorless amorphous solid, mp 153-158°C, $[\alpha]_D$ +7.9° (c 0.24, $CHCl_3$), $\lambda_{max}^{(MeOH)}$/nm ($\Delta\varepsilon$) : 257(-2.4), 249(-1.9), 232(-16.7), 219(+4.1) and 209(-2.0), m/z : 930 (M^+), 858, 750, 429, 368, 313, 206, 124 and 105 (Found : $[M+H]^+$, 931.3182 $C_{47}H_{51}N_2O_{18}$; requires : 931.3137), $\nu_{max}^{(CHCl_3)}$/cm^{-1} : 3453(m), 1738(br-s), 1592(s), 1570(s), 1457(s), 1422(s), 1372(s) and 1215(br-s), $\lambda_{max}^{(MeOH)}$/nm (log ε) : 203(4.43), 226(4.48), 264(3.87) and 268(3.85), ^1H nmr ($CDCl_3$) : listed in Table 1, ^{13}C nmr ($CDCl_3$) : listed in Table 2.

Cangorinine E-I (**3**). - Colorless amorphous solid, mp 98-101°C, $[\alpha]_D$ -25.4° (c 0.36, $CHCl_3$), $\lambda_{max}^{(MeOH)}$/nm ($\Delta\varepsilon$) : 267(-2.0), 249(+1.8), 238(-4.5) and 224(+6.5), m/z : 867 (M^+), 847, 824, 746, 634, 262, 206 and 105 (Found : $[M+H]^+$, 868.3044 $C_{43}H_{50}NO_{18}$; requires : 868.3028), $\nu_{max}^{(CHCl_3)}$/cm^{-1} : 3501(m), 1740(br-s), 1601(s), 1583(s), 1566(s), 1451(s), 1430(s), 1369(s) and 1231(br-s), $\lambda_{max}^{(MeOH)}$/nm (log ε) : 203(4.39), 229(4.40) and 261(3.74), ^{1}H nmr ($CDCl_3$) : listed in Table 1, ^{13}C nmr ($CDCl_3$) : listed in Table 2.

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