J. Oriental Bot. Res 7(1) 77~88(1994)

Cangorins F–J, Five Additional Oligo-Nicotinated Sesquiterpene Polyesters from Maytenus Ilicifolia

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ABSTRACT.—The isolation and structure elucidation of five new oligo-nicotinated sesquiterpene polyesters with a dihydroagarofuran core from *Maytenus ilicifolia*, named cangorins F, G, H, I and J [**1**–**5**], is described. The structures of these compounds, which possessed nicotinyl, benzoyl, and acetyl groups as esterifying moieties, were elucidated by ^{1}H- and ^{13}C-nmr spectroscopic studies, inclusive of heteronuclear correlation, long-range correlation, and nOe spectra, along with mass and cd spectral data, and the X-ray crystallographic analysis of **1**.

We have recently been investigating the bioactive metabolites of the genus *Maytenus* in the Celastraceae (1–4), which are widely used as folk medicines in South America (5,6). From several *Maytenus* species, many characteristic bioactive compounds, such as the maytansinoids (7) with antitumor activity, cytotoxic quinoid triterpenes (1,2,8), and sesquiterpene polyesters and sesquiterpene pyridine alkaloids (3,9) with insect antifeedant or insecticidal activity, have been previously isolated. Recently, the immunosuppressive activity of sesquiterpene pyridine alkaloids (10) and the antitumor-promoting activity of sesquiterpene polyesters (11) were also reported from constituents of plants in the Celastraceae.

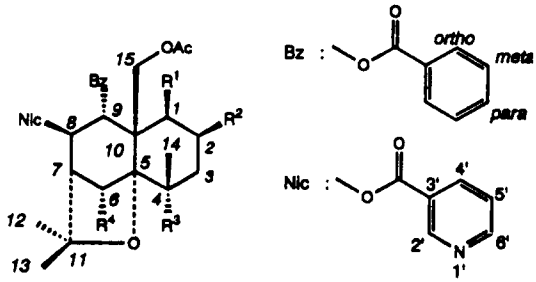
Maytenus ilicifolia Mart. is a large shrub found in southern Brazil, Paraguay, Uruguay, and Argentina. Its red- to orange-brown root bark, known as "cangorosa," is used by Indian tribes and rural populations in Paraguay as a fertility-regulating agent. In a previous paper (12), we have reported the isolation and the structure determination of five new oligo-nicotinated sesquiterpene polyesters named cangorins A–E from the $CHCl_3$-soluble portion of a MeOH extract of *M. ilicifolia*. Further investigation of its chemical constituents led to the isolation of five new oligo-nicotinated sesquiterpene polyesters named cangorins F–J [**1**–**5**]. The presence of two or three nicotinyl groups in the sesquiterpene core is characteristic of the cangorins, although sesquiterpene polyesters with only two nicotinoyl ester substituents in the molecule appear to be rare (13,14).

RESULTS AND DISCUSSION

The $CHCl_3$-soluble portion of a methanolic extract of the root bark of *M. ilicifolia* was subjected to Si gel cc. The fractions obtained were further separated by Si gel or ODS (octadecyl Si gel) medium-pressure liquid chromatography (mplc) and/or hplc to give five new sesquiterpene polyesters, cangorins F [**1**] 0.0045%, G [**2**] 0.0014%, H [**3**] 0.0006%, I [**4**] 0.0007%, and J [**5**] 0.0005%.

[1]Part 2 in the series "Alkaloids of *Maytenus ilicifolia*." For part 1, see Itokawa *et al.* (12).

Cangorin F [**1**] was obtained as plate crystals with the molecular formula $C_{38}H_{40}N_2O_{13}$. It contained two acetyl groups (δ_H 1.48, 1.96), one benzoyl group [δ_H 8.00 (o), 7.44 (m), 7.58 (p)], two nicotinyl groups [δ_H 9.25 (2′), 8.33 (4′), 7.4 (5′), 8.79 (6′); 9.28 (2″), 8.33



	R^1	R^2	R^3	R^4
1	OAc	Nic	OH	OH
2	Nic	Nic	OH	OH
3	Nic	Nic	OH	OAc
4	Nic	OAc	OH	Bz
5	OAc	Nic	H	OAc

(4″), 7.4 (5″), 8.79 (6″)], three tertiary methyl groups [δ_H 1.75 (12), 1.66 (13), 1.82 (14)], two sets of methylene protons [δ_H 2.18 (3α), 2.38 (3β); 4.76 (15α), 5.24 (15β)], six methine protons [δ_H 5.75 (1), 5.90 (2), 5.28 (6), 2.60 (7), 5.55 (8), 5.78 (9)], and two hydroxyl groups [δ_H 3.48 (4-OH); 5.28 (6-OH)]. These data indicated the presence of a sesquiterpene polyester, often found in Celastraceae plants. The orientations of the ester groups were revealed as 1βeq, 2βax, 6αeq, 8βax, and 9αax, similar to cangorins A–E (12), by means of the coupling constants exhibited by the six methine protons and one set of methylene protons, and were confirmed with nOe data from a NOESY nmr spectrum. In order to determine the position of each ester group, an HMBC nmr spectrum was recorded. This spectrum enabled the assignments of two acetyl groups located at positions 1 and 15, since one methine proton at position 1 (δ_H 5.75) and one acetyl methyl group (δ_H 1.48) gave cross-peaks with the same carbonyl carbon (δ_C 169.35), and one set of methylene protons at position 15 (δ_H 4.76, 5.24) and one acetyl methyl group (δ_H 1.96) were correlated to the same carbonyl carbon (δ_C 170.35). Cross-peaks between the 4′ proton of the nicotinyl group, as well as the oxygenated methine proton of position 8 and its corresponding carbonyl carbons ($^1H/^{13}C/^1H$ 8.33/163.91/5.55 ppm), and between the ortho-protons of the benzoyl group as well as the oxygenated methine at 9 and its carbonyl carbons (8.00/164.41/5.78 ppm) were recognized. Therefore one nicotinate and one benzoate ester were located at C-8 and C-9. (This C-9 benzoyl group gave rise to an unusual diamagnetic effect for the acetyl methyl group oriented on C-1.) The signal for the remaining nicotinyl carbonyl carbon (δ_C 164.44), which was presumably linked at positions 2 or 6, gave no cross-peaks with these methine protons.

Furthermore, the signal overlapping one hydroxyl group and the methine proton at position 6 (δ_H 5.28) made the assignment of the position of the hydroxyl group attachment difficult. By comparison of ^{1}H-nmr chemical shifts between **1** and other cangorins, however, a significant upfield shift (ca. 1.5 ppm) of the methine proton at 6 was clearly evident. This enabled the conclusion to be made that the hydroxyl group was attached at C-6, and thus the nicotinyl group was positioned at C-2. Based on these

spectroscopic data, the structure of cangorin F was determined as **1**. In order to confirm the position of the attachment of the esters and the hydroxyl group, a colorless single-plate crystal of cangorin F crystallized from MeOH was subjected to X-ray analysis. The result, shown in Figure 1, confirmed the pattern of esterification proposed by the nmr spectra.

Cangorin G [**2**], an amorphous solid with a molecular formula $C_{42}H_{41}N_3O_{13}$, was

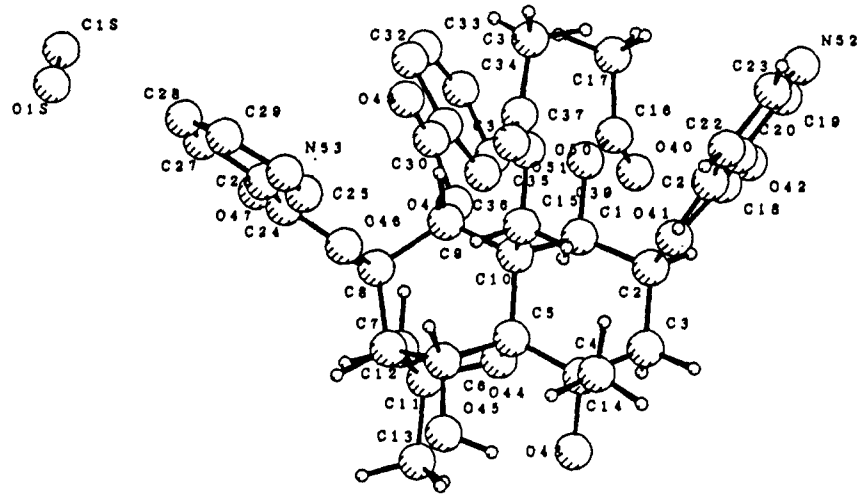


FIGURE 1. Molecular Structure of Cangorin F [**1**] by X-ray Analysis.

also a polyesterified sesquiterpene. The nmr spectrum suggested that **2** had the dihydroagarofuran core attached to one acetyl, one benzoyl, one hydroxyl, and three nicotinyl groups. In the HMBC spectrum, long-range couplings between the 4′ protons of two nicotinyl groups as well as the oxygenated methines of the sesquiterpene and their respective carbonyl carbons ($^1H/^{13}C/^1H$, 7.55/165.05/6.06 ppm for the C-1 nicotinyl; 8.35/163.91/5.58 ppm for the C-8 nicotinyl) were located, so the two nicotinate esters were placed at C-1 and C-8. By analogy, couplings between the ortho-protons of the benzoyl group as well as the methine proton at position 9 of the sesquiterpene core and its carbonyl carbon ($^1H/^{13}C/^1H$, 7.65/164.22/5.82 ppm) indicated that the benzoate ester was at C-9. A substantial upfield shift (about 1.5 ppm) of the methine proton at position 6 suggested that the hydroxyl group was attached to this carbon. While the remaining one methine and one set of methylene protons at positions 2 and 15 failed to show cross-peaks with the respective carbonyl carbon of the acetyl and the nicotinyl groups in the HMBC spectrum, the NOESYPH (phase-sensitive NOESY) nmr spectrum revealed that the acetyl group must be located at position 15 and the remaining nicotinyl group at 2, from the following evidence: the acetyl methyl group at δ_H 2.05 gave a cross-peak with the methine proton at 9αax (δ_H 5.82); the 4′ proton at δ_H 7.55 of the nicotinyl group gave cross-peaks with the tertiary methyl group at 14 (δ_H 1.89) and the methylene protons at 15 (δ_H 4.89 and 5.41). Based on these spectroscopic observations, the structure of cangorin G was determined as **2**.

Cangorin H [**3**], an amorphous solid with the molecular formula $C_{44}H_{43}N_3O_{14}$, was also a sesquiterpene polyester containing two acetyl, one benzoyl and three nicotinyl groups. Its sesquiterpene core was identified as being the same as that of cangorins F and

G. The esterified positions of two acetyl groups were determined in the same manner as for cangorins F and G. However, the other ester groups were difficult to assign because of the overlapping of two carbonyl carbons in the ^{13}C-nmr spectrum, as well as an overlapping of two methine protons in the ^{1}H-nmr spectrum, and the disappearance of a cross-peak between one nicotinyl carbonyl carbon and its corresponding methine proton. These overlapped two carbonyl carbons (δ_C 164.21) belonging to one benzoyl and one nicotinyl group, showed cross-peaks with two methine protons at positions 8 and 9. Two overlapped methine protons (δ_H 6.04) assigned at positions 1 and 2 gave only one cross-peak with one nicotinyl carbonyl carbon (δ_C 163.88). The assignment of the ester groups attached to positions 1 and 2 was accomplished with a NOESY spectrum. The ortho-protons of the benzoyl group gave cross-peaks with the methyl group at position 12, the methine proton at position 8 and the overlapping methine proton 1 or 2. Thus, the benzoyl group must be located at position 9 and the nicotinyl group at position 8. The two remaining nicotinyl groups must be affixed to positions 1 and 2. [These presumptions were also verified by the fact that one nicotinyl 4′ proton gave cross-peaks with the tertiary methyl group at position 14 (δ_H 1.61) and the methylene protons at position 15 (δ_H 4.70 and 5.62), so one nicotinyl group was located at position 2, and another nicotinyl group occurred at position 1.] These data confirmed that the structure of cangorin H was **3**.

Cangorin I [**4**] was obtained as an amorphous solid, and its molecular formula was determined to be $C_{45}H_{44}N_2O_{14}$ from hrms. This cangorin derivative was identical with cangorins F, G, and H with respect to the sesquiterpene core and its structural differences were only in the esterified position of the molecule. The esterified positions were determined in the same manner as the other cangorins, but in the HMBC spectrum, a cross-peak of the methine proton at position 2 with an acetyl group was not detected, and two carbonyl carbons belonging to one benzoyl and one nicotinyl group were overlapping in the ^{13}C-nmr spectrum. These connections were clarified by a NOESY spectrum which showed that the ortho-protons of the benzoyl group gave cross-peaks with the methyl group at position 12 and methine protons at positions 1 and 9; thus this benzoyl group was located at position 9, and the other overlapping nicotinyl group must be at position 8. Therefore the remaining acetyl group was at position 2, and the structure of cangorin I was determined as **4**.

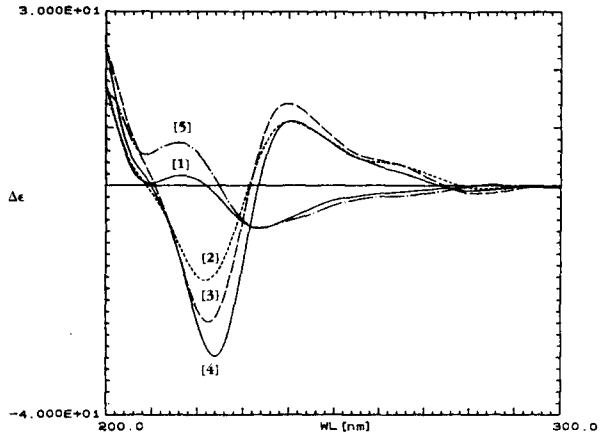


FIGURE 2. Cd Spectra of Cangorins F–J [**1–5**].

TABLE 1. ^{1}H-Nmr Chemical Shifts (ppm) for Cangorins F–J [**1**–**5**].[a]

Proton	Compound				
	1	**2**	**3**	**4**	**5**
1-H	5.75 (d, 3.9)	6.06 (d, 4.1)	6.04 (br s)	5.94 (d, 3.7)	5.87 (d, 4.0)
2-H	5.90 (ddd, 2.5, 3.9, 4.2)	6.07 (ddd, 2.4, 4.0, 4.1)	6.04 (br s)	5.75 (ddd, 2.7, 3.7, 4.0)	5.95 (br dd, 4.0, 4.2)
3-Ha	2.18 (dd, 2.5, 15.1)	2.31 (dd, 2.4, 15.2)	2.25 (dd, 1.9, 15.3)	2.15 (dd, 2.7, 15.2)	1.95 (br d, 15.3)
3-Hb	2.38 (dd, 4.2, 15.1)	2.47 (dd, 4.0, 15.2)	2.48 (dd, 2.9, 15.3)	2.39 (dd, 4.0, 15.2)	2.66 (ddd, 4.2, 6.6, 15.3)
4-OH/H	3.48 (br s)	3.30 (br s)	2.81 (br s)	2.92 (s)	2.50 (dq, 6.6, 7.7)
6-H	5.28 (br s)	5.31 (s)	6.77 (s)	6.82 (s)	6.62 (s)
7-H	2.60 (d, 2.7)	2.65 (d, 2.8)	2.55 (d, 2.8)	2.72 (d, 2.8)	2.56 (d, 2.9)
8-H	5.55 (d, 2.7)	5.58 (d, 2.8)	5.60 (d, 2.8)	5.66 (d, 2.8)	5.57 (d, 2.9)
9-H	5.78 (s)	5.82 (s)	5.86 (s)	5.91 (s)	5.76 (s)
12-CH_3	1.75 (s)	1.82 (s)	1.81 (s)	1.81 (s)	1.69 (s)
13-CH_3	1.66 (s)	1.72 (s)	1.68 (s)	1.70 (s)	1.52 (s)
14-CH_3	1.82 (s)	1.89 (s)	1.61 (s)	1.56 (s)	1.23 (d, 7.7)
15-Ha	4.76 (d, 12.7)	4.89 (d, 12.6)	4.70 (d, 12.9)	4.90 (d, 12.9)	4.48 (d, 12.8)
15-Hb	5.24 (d, 12.7)	5.41 (d, 12.6)	5.62 (d, 12.9)	5.30 (d, 12.9)	5.53 (d, 12.8)
1-OAc	1.48 (s)	—	—	—	1.44 (s)
ONic (2′)	—	8.50 (d, 1.8)	8.49 (br s)	8.59 (d, 2.0)	—
ONic (4′)	—	7.55 (ddd, 1.7, 1.8, 7.9)	7.56 (ddd, 1.9, 1.9, 7.9)	7.66 (ddd, 1.6, 2.0, 7.9)	—
ONic (5′)	—	7.05 (dd, 4.8, 7.9)	7.07 (dd, 4.9, 7.9)	7.14 (dd, 4.9, 7.9)	—
ONic (6′)	—	8.56 (dd, 1.7, 4.8)	8.57 (br d, 3.6)	8.62 (dd, 1.6, 4.9)	—
2-OAc	—	—	—	2.03 (s)	—
ONic (2′)	9.25 (br s)	9.16 (d, 1.7)	9.19 (br s)	—	9.29 (br d, 2.1)
ONic (4′)	8.33 (d, 7.8)	8.23 (ddd, 1.7, 1.7, 8.0)	8.28 (ddd, 1.7, 1.7, 7.8)	—	8.38 (ddd, 1.7, 2.1, 7.9)
ONic (5′)	7.4 (m)	7.41 (dd, 4.9, 8.0)	7.41 (dd, 4.9, 7.8)	—	7.44 (dd, 4.9, 7.9)
ONic (6′)	8.79 (br s)	8.79 (dd, 1.7, 4.9)	8.79 (br s)	—	8.79 (dd, 1.7, 4.9)[b]
6-OH	5.28 (br s)	5.23 (br s)	—	—	—
OAc	—	—	2.15 (s)	—	2.13 (s)
OBz (*o*)	—	—	—	8.19 (d, 7.7)	—
OBz (*m*)	—	—	—	7.48 (t, 7.7)	—
OBz (*p*)	—	—	—	7.60 (t, 7.4)	—

TABLE 1. Continued.

Proton	Compound				
	1	**2**	**3**	**4**	**5**
8-ONic (2′)	9.28 (br s)	9.30 (d, 1.7)	9.40 (br s)	9.48 (d, 2.0)	9.41 (br d, 2.2)
ONic (4′)	8.33 (d, 7.8)	8.35 (ddd, 1.7, 1.7, 8.0)	8.44 (ddd, 1.8, 1.8, 7.8)	8.52 (ddd, 1.6, 2.0, 7.8)	8.45 (ddd, 1.7, 2.2, 7.9)
ONic (5′)	7.4 (m)	7.43 (dd, 4.9, 8.0)	7.44 (dd, 4.9, 7.8)	7.49 (dd, 4.9, 7.8)	7.44 (dd, 4.9, 7.9)
ONic (6′)	8.79 (br s)	8.82 (dd, 1.7, 4.9)	8.83 (br d, 3.8)	8.86 (dd, 1.6, 4.9)	8.82 (dd, 1.7, 4.9)[b]
9-OBz (*o*)	8.00 (d, 7.9)	7.65 (dd, 1.2, 7.6)	7.67 (dd, 1.1, 8.2)	7.70 (d, 7.8)	8.05 (dd, 1.2, 8.3)
OBz (*m*)	7.44 (t, 7.7)	7.28 (t, 7.8)	7.30 (t, 7.9)	7.30 (t, 7.8)	7.47 (t, 7.9)
OBz (*p*)	7.58 (t, 7.4)	7.51 (t, 7.6)	7.52 (t, 7.5)	7.52 (t, 7.4)	7.61 (dt, 1.2, 7.4)
15-OAc	1.96 (s)	2.05 (s)	2.12 (s)	2.18 (s)	2.08 (s)

[a]Measurements performed in $CDCl_3$ at 400 MHz. Multiplicity and coupling constants (J/Hz) given in parenthesis.
[b]These sets of values may be interchanged.

In cangorin J [**5**], an amorphous solid whose molecular formula was determined as $C_{40}H_{42}N_2O_{13}$, three acetyl, one benzoyl and two nicotinyl groups occurred, as observed from its ^{1}H- and ^{13}C-nmr spectra. Its sesquiterpene core was identified by comparison with the other cangorins, but instead of a tertiary methyl group at position 14 and a hydroxyl group at position 4, one doublet methyl group and one quartet methine proton were observed. Except for the disappearance of one cross-peak between the methine proton at position 2 and the nicotinyl carbonyl carbon, the other ester groups and methine or methylene protons were correlated by means of an HMBC spectrum as representing three acetyl groups at positions 1, 6, and 15, respectively, and one benzoyl group at position 9, and one nicotinyl group at position 8. Consequently, the structure of cangorin J was determined as **5**.

The cd spectra of cangorins F–J [**1–5**], which are shown in Figure 2, can be divided into two types. One type exhibited a weak split cd curve, i.e., a negative first Cotton effect around 233 nm and a positive second Cotton effect around 215 nm, which is attributable to exciton interaction (15) between the nicotinyl group at position 8 and the benzoyl group at position 9 (1,2-dichromophore; $\theta_{8-9}\approx-180°$). The other type exhibited a split cd curve, i.e., a positive first Cotton effect around 238 nm and a negative second Cotton effect around 223 nm which is attributable to exciton interactions between the nicotinyl group at position 1 and benzoyl group at position 9 (1,3-dichromophore; $\theta_{1-9}\approx+120°$), and between the nicotinyl groups at position 1 and position 2 (1,2-dichromophore; $\theta_{1-2}\approx+60°$) and between the benzoyl group at position 6 and the nicotinyl group at position 8 (1,3-dichromophore; $\theta_{6-8}\approx+90°$). This information supported the structures which were determined by nmr, and established the absolute configurations of cangorins F–J as **1–5**, respectively.

Complete assigments of the ^{1}H- and ^{13}C-nmr signals of cangorins F to J are shown in Tables 1 and 2, respectively.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps 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 spectra, uv spectra, ir spectra, and cd spectra were taken with a Hitachi M-80 spectrometer, a Hitachi 557 spectrophotometer, a Perkin Elmer 1710 spectrophotometer and a Jasco J-700 spectropolarimeter, respectively. Medium-pressure liquid chromatography (mplc) was performed with a CIG column system (22 mm i.d.×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.×250 mm, GL Science Inc., Tokyo) 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. 1D and 2D ^{1}H- and ^{13}C-nmr spectra were recorded on Bruker spectrometers (AM400 and AM500) 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 sec. The value of the delay to optimize one-bond correlations in the HMQC spectrum and suppress them in the HMBC spectrum was 3.2 msec and the evolution delay for long-range couplings in the HMBC spectrum was set to 50 msec. The nmr coupling constants (J) are given in Hz.

PLANT MATERIAL.—Root bark of *M. ilicifolia* Mart. (1140 g), commonly known as "cangorosa" among Indian tribes, was purchased at Asuncíon, Paraguay in 1987. The botanical identification was made by Dr. Tanaka (Asuncíon University). A voucher specimen has been deposited in the herbarium of the Tokyo College of Pharmacy.

EXTRACTION AND ISOLATION.—The root bark (1140 g) of *M. ilicifolia* was crushed and extracted with hot MeOH 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 Si gel cc using an *n*-hexane-EtOAc gradient system (1:0-0:1) to give 17 fractions. Non-cytotoxic fractions 12, 13, 14 and 15 were further subjected to ODS mplc with a MeOH/H_2O solvent system to give **1–5** as amorphous solids. These compounds were further purified by ODS hplc with MeOH/H_2O or MeCN/H_2O solvent systems.

Cangorin F [**1**].—Colorless plate crystals (76 mg); mp 214–217°; $[\alpha]_D$ +6.6° (c=0.59, $CHCl_3$); cd,

TABLE 2. ^{13}C-Nmr Chemical Shifts (ppm) for Cangorins F–J [**1–5**].[a]

Carbon	Compound				
	1	**2**	**3**	**4**	**5**
1	70.8 (d)	72.1 (d)	72.1 (d)	72.2 (d)	71.7 (d)
2	69.1 (d)	69.3 (d)	69.4 (d)	68.2 (d)	70.5 (d)
3	41.2 (t)	41.6 (t)	42.3 (t)	42.8 (t)	31.3 (t)
4	72.4 (s)	72.4 (s)	69.9 (s)	70.2 (s)	32.6 (d)
5	91.0 (s)	91.2 (s)	91.6 (s)	91.7 (s)	89.8 (s)
6	75.4 (d)	75.5 (d)	75.5 (d)	76.0 (d)	75.0 (d)
7	54.5 (d)	54.5 (d)	53.8 (d)	53.7 (d)	53.7 (d)
8	77.9 (d)	77.8 (d)	77.9 (d)	77.7 (d)	78.3 (d)
9	72.2 (d)	72.1 (d)	73.2 (d)	72.7 (d)	73.9 (d)
10	53.2 (s)	53.4 (s)	54.8 (s)	54.9 (s)	52.7 (s)
11	83.7 (s)	84.0 (s)	83.5 (s)	83.6 (s)	81.6 (s)
12	26.4 (q)	26.5 (q)	26.0 (q)	25.9 (q)	26.1 (q)
13	30.1 (q)	30.2 (q)	29.5 (q)	29.7 (q)	30.4 (t)
14	24.4 (q)	24.6 (q)	24.9 (q)	24.3 (q)	17.2 (q)
15	66.0 (t)	66.2 (t)	66.6 (t)	66.2 (t)	66.4 (t)
1-OC=O	169.4 (s)	164.1 (s)	163.9 (s)[b]	164.0 (s)	169.4 (s)
CH_3	20.3 (q)	—	—	—	20.4 (q)
2′	—	150.4 (d)	150.5 (d)	150.5 (d)	—
3′	—	125.0 (s)	124.9 (s)	125.2 (s)	—
4′	—	136.3 (d)	136.3 (d)	136.4 (d)	—
5′	—	122.8 (d)	122.9 (d)	123.9 (d)	—
6′	—	153.4 (d)	153.4 (d)	153.4 (d)	—
2-OC=O	164.4 (s)	164.4 (s)	164.45 (s)[b]	169.6 (s)	164.8 (s)
CH_3	—	—	—	21.1 (q)	—
2′	150.9 (d)[b]	151.0 (d)	151.2 (d)	—	151.3 (d)
3′	125.5 (s)	125.2 (s)	125.2 (d)[b]	—	125.6 (s)[b]
4′	137.1 (d)	137.0 (d)	137.0 (d)	—	137.2 (s)[b]
5′	123.5 (d)[b]	123.7 (d)	123.7 (d)	—	123.4 (s)[b]
6′	153.8 (d)	154.1 (s)	154.1 (d)	—	153.9 (s)
6-OC=O	—	—	169.8 (s)	165.7 (s)	169.8 (s)
CH_3	—	—	21.5 (q)	—	21.3 (q)
ipso	—	—	—	129.6 (s)	—
ortho	—	—	—	130.3 (d)	—
meta	—	—	—	128.9 (d)	—
para	—	—	—	133.6 (d)	—
8-OC=O	163.9 (s)	163.9 (s)	164.2 (s)	164.2 (s)	164.3 (s)
2′	151.0 (d)[b]	151.1 (d)	151.4 (d)	151.5 (d)	151.4 (d)
3′	125.8 (s)	125.6 (s)	125.8 (s)[b]	125.9 (s)	126.0 (s)[b]
4′	137.3 (d)	137.4 (d)	137.4 (d)	137.6 (d)	137.4 (d)[b]
5′	123.6 (d)[b]	123.5 (d)	123.4 (d)	123.5 (d)	123.6 (d)[b]
6′	153.8 (d)	154.1 (d)	154.1 (d)	154.0 (d)	154.0 (d)
9-OC=O	164.4 (s)	164.2 (s)	164.2 (s)	164.2 (s)	164.5 (s)
ipso	128.4 (s)	128.0 (s)	128.1 (s)	128.2 (s)	128.6 (s)
ortho	130.2 (d)	130.0 (d)	130.1 (d)	130.1 (d)	130.3 (d)
meta	128.6 (d)	128.3 (d)	128.4 (d)	128.4 (d)	128.6 (d)
para	133.9 (d)	133.8 (d)	133.9 (d)	133.8 (d)	133.9 (d)
15-OC=O	170.4 (s)	170.6 (s)	170.8 (s)	170.7 (s)	170.8 (s)
CH_3	21.0 (q)	21.2 (q)	21.2 (q)	21.4 (q)	21.2 (q)

[a]Measurements performed in $CDCl_3$ at 100 MHz. Multiplicity given in parentheses.
[b]These sets of values may be interchangeable.

λ max (MeOH) (Δε) 284 (+0.1), 233 (−7.5), 216 (+1.7) and 210 (+0.4) nm; ms, *m/z* 732 $[M]^+$, 717, 595, 494, 407, 348, 124, and 105 (found $[M+H]^+$ 733.2637, $C_{38}H_{41}N_2O_{13}$ requires 733.2609); ir, ν max ($CHCl_3$) 3541 (w), 3424 (m), 1729 (br s), 1593 (s), 1423 (s), 1369 (s), and 1278 (br s) cm^{-1}; uv, λ max

TABLE 3. Refined Fractional Atomic Coordinates of Cangorin F [**1**].

Atom	X 10**4		Y 10**4		Z 10**4	
C-1	3194	(3)	10512	(0)	6347	(5)
C-2	2513	(3)	10742	(5)	5790	(5)
C-3	2111	(3)	10479	(5)	6497	(5)
C-4	2218	(3)	9484	(5)	6981	(5)
C-5	2926	(3)	9285	(4)	7473	(5)
C-6	3097	(3)	8296	(5)	7975	(5)
C-7	3699	(3)	8524	(5)	8828	(5)
C-8	4215	(3)	8660	(5)	8283	(6)
C-9	4035	(3)	9332	(5)	7280	(6)
C-10	3327	(3)	9475	(4)	6695	(5)
C-11	3557	(3)	9461	(5)	9297	(5)
C-12	4106	(3)	10087	(6)	9821	(6)
C-13	3200	(3)	9295	(6)	10130	(6)
C-14	1856	(3)	8748	(5)	6182	(5)
C-15	3169	(3)	8751	(4)	5771	(5)
C-16	3731	(3)	11679	(5)	5670	(6)
C-17	4153	(4)	11823	(6)	4979	(8)
C-18	2273	(3)	10747	(6)	3889	(6)
C-19	2082	(4)	10555	(6)	1967	(6)
C-20	2073	(3)	10154	(6)	2915	(6)
C-21	1892	(4)	9214	(6)	2912	(6)
C-22	1742	(6)	8738	(7)	1978	(8)
C-23	1756	(6)	9196	(9)	1062	(8)
C-24	4868	(4)	7416	(6)	8067	(8)
C-25	4356	(5)	6179	(7)	6731	(10)
C-26	4872	(4)	6511	(6)	7445	(8)
C-27	5451	(5)	6072	(8)	7635	(10)
C-28	5427	(5)	5226	(8)	7021	(11)
C-29	4896	(6)	4929	(9)	6377	(13)
C-30	4884	(3)	10394	(7)	7459	(7)
C-31	5138	(4)	11360	(8)	7842	(7)
C-32	5771	(5)	11440	(10)	7735	(9)
C-33	5999	(7)	12419	(15)	8134	(11)
C-34	5690	(10)	13037	(14)	8491	(13)
C-35	5088	(8)	12883	(10)	8578	(13)
C-36	4811	(6)	11999	(8)	8248	(9)
C-37	3538	(5)	8311	(7)	4341	(9)
C-38	3892	(10)	8599	(14)	3628	(15)
O-39	3566	(2)	10756	(3)	5660	(4)
O-40	3584	(3)	12271	(4)	6192	(5)
O-41	2284	(2)	10247	(3)	4774	(3)
O-42	2415	(3)	11559	(4)	3891	(4)
O-43	1936	(2)	9440	(3)	7827	(4)
O-44	3148	(2)	9929	(3)	8358	(3)
O-45	2637	(2)	7899	(3)	8410	(4)
O-46	4284	(2)	7737	(3)	7838	(4)
O-47	5311	(3)	7801	(6)	8615	(8)
O-48	4332	(2)	10233	(3)	7651	(4)
O-49	5101	(3)	9841	(6)	7002	(7)
O-50	3529	(3)	8945	(4)	5069	(5)
O-51	3264	(5)	7653	(6)	4236	(8)
N-52	1921	(4)	10106	(6)	1033	(5)
N-53	4348	(5)	5354	(8)	6175	(11)
O-1S	6962	(3)	5938	(5)	9137	(5)
C-1S	7310	(8)	6773	(9)	9270	(12)

(MeOH) (log ε) 202 (4.28), 222 (4.44), 256 (3.83), 262 (3.86), 268 (3.77) and 281 (3.24) nm; ^{1}H nmr, see Table 1; ^{13}C nmr, see Table 2.

Cangorin G [**2**].—Colorless amorphous solid (16 mg); mp, 124–128°; [α]D +29.4° (*c*=1.11, $CHCl_3$); cd, λ max (MeOH) (Δε) 284 (−0.5), 260 (+4.0), 240 (+11.0), 222 (−16.6) and 207 (+2.0); ms, *m/z* 795 $[M]^+$, 780, 720, 672, 547, 470, 124 and 105 (found $[M+H]^+$ 796.2763, $C_{42}H_{42}N_3O_{13}$ requires 796.2717); ir ν max ($CHCl_3$) 3538 (w), 3425 (m), 1735 (br s), 1593 (s), 1423 (s) and 1278 (br s) cm^{-1}; uv, λ max (MeOH) (log ε) 203 (4.39), 220 (4.52), 257 (3.98), 261 (3.99), 269 (3.89) and 281 (3.33) nm; ^{1}H nmr, see Table 1; ^{13}C nmr, see Table 2.

Cangorin H [**3**].—Colorless amorphous solid (7 mg); mp 125–130°; [α]D +43.4° (*c*=0.45, $CHCl_3$); cd, λ max (MeOH) (Δε) 282 (−1.4), 259 (+4.5), 240 (+14.1), 222 (−23.8) and 208 (+4.7) nm, ms, *m/z* 837 $[M]^+$, 822, 795, 714, 672, 547, 368, 124, and 105 (found $[M+H]^+$ 838.2878, $C_{44}H_{44}N_3O_{14}$ requires 838.2823); ir, ν max ($CHCl_3$) 3540 (w), 1735 (br s), 1593 (s), 1423 (s) and 1278 (br s) cm^{-1}; uv, λ max (MeOH) (log ε) 203 (4.51), 221 (4.65), 257 (4.11), 262 (4.12), 269 (4.04) and 281 (3.46) nm; ^{1}H nmr, see Table 1; ^{13}C nmr, see Table 2.

Cangorin I [**4**].—Colorless amorphous solid (8 mg); mp 111–115°; [α]D +14.8° (*c*=0.58, $CHCl_3$); cd, λ max (MeOH) (Δε) 280 (−0.9), 241 (+11.2), 224 (−29.8) and 207 (+3.4) nm; ms, *m/z* 836 $[M]^+$, 821, 776, 713, 654, 602, 424, 355, 228 and 124 (found $[M+H]^+$ 837.2825, $C_{45}H_{45}N_2O_{14}$, requires 837.2871); ir, ν max ($CHCl_3$) 3569 (w), 1729 (br s), 1593 (s), 1423 (s), 1369 (s) and 1274 (br s) cm^{-1}; uv, λ max (MeOH) (log ε) 203 (4.44), 227 (4.59), 255 (3.92), 262 (3.93), 269 (3.87) and 281 (3.45) nm; ^{1}H nmr, see Table 1, ^{13}C nmr, see Table 2.

Cangorin J [**5**].—Colorless amorphous solid (5 mg); mp 115–120°; [α]D +20.0° (*c*=0.26, $CHCl_3$); λ max (MeOH) (Δε) 285 (+0.2), 264 (−1.9), 234 (−7.4), 216 (+7.4) and 209 (+5.3) nm, ms, *m/z* 759 $[M+H]^+$, 679, 635, 591, 547, 503, 461, 369 and 277 (found $[M+H]^+$ 759.2761, $C_{40}H_{43}N_2O_{13}$, requires 759.2765); ir, ν max ($CHCl_3$) 1734 (br s), 1593 (s), 1423 (s), 1370 (s) and 1277 (br s) cm^{-1}; uv, λ max (MeOH) (log ε) 202 (4.37), 223 (4.48), 256 (3.88), 262 (3.90), 268 (3.82) and 281 (3.29) nm; ^{1}H nmr, see Table 1; ^{13}C nmr, see Table 2.

Crystallographic Analysis of Compound **1**.—Crystal data: Chemical formula, $C_{38}H_{40}N_2O_{13}\cdot CH_3OH$; formula weight, 764.8; crystal system, monoclinic; space group, C_2, Z=4, *a*=22.525 (36) Å, *b*=14.251 (23) Å, *c*=13.184 (20) Å, β=107.88°, V=4028 Å^3, Dx=1.261 g/cm^3. A colorless thick plate crystal of approximately 0.15×0.30×0.60 mm in size was mounted on a Nonius CAD4 diffractometer with graphite-monochromated CuKa radiation (μ=7.7 cm^{-1}) at 23°. A total of 3304 reflections, of which 146 were symmetry equivalent reflections, were observed above the 2s(I) level, with the 2q range from 6° through 156°. The structure was determined by the direct method using the SHELXS-86 program (16) and the refinement was carried out by the block-diagonal-matrix least-squared method used 3158 reflections. The final R value was 0.068. The R_F value for the symmetry equivalent reflections was 0.089. The numbers of atoms refined were 55 carbon, nitrogen, and oxygen atoms with anisotropic thermal parameters and 32 hydrogen atoms with isotropic parameters which were found on the difference electron-density map and located at the calculated positions. The refined fractional atomic coordinates are shown in Table 3.[2] The molecular structure determined by this method is illustrated in Figure 1.

LITERATURE CITED

1. H. Itokawa, O. Shirota, H. Morita, K. Takeya, N. Tomioka, and A. Itai, *Tetrahedron Lett.*, **31**, 6881 (1990).
2. H. Itokawa, O. Shirota, H. Morita, K. Takeya, and Y. Iitaka, *Phytochemistry*, **30**, 3713 (1991).
3. H. Itokawa, O. Shirota, H. Morita, and K. Takeya, *Heterocycles*, **34**, 885 (1992).
4. F.A. Flores, "Advances in Economic Botany," The New York Botanical Garden, New York, 1984, Vol. 1, pp. 1–8.
5. H. Itokawa, O. Shirota, H. Morita, K. Takeya, and Y. Iitaka, *J. Chem. Soc., Perkin Trans. I*, 1247 (1993).
6. J.G. Gonzalez, G.D. Monache, F.D. Monache, and G.B. Marini-Bettolo, *J. Ethnopharmacol.*, **5**, 73 (1982).
7. S.M. Kupchan, Y. Komoda, W.A. Court, G.J. Thomas, R.M. Smith, A. Karim, C.J. Gilmore, R.C. Haltiwanger, and R.F. Bryan, *J. Am. Chem. Soc.*, **94**, 1354 (1972).

[2]Refined fractional bond distances and bond angles for cangorin F [**1**] have been deposited at the Cambridge Crystallographic Center and may be obtained from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

8. K. Nakanishi, V.P. Gullo, I. Miura, T.R. Govindachari, and N. Visivanathan, *J. Am. Chem. Soc.*, **95**, 6473 (1973).
9. F.D. Monache, G.B. Marini-Bettolo, and E.A. Bernays, *Angew. Entomol.*, **97**, 406 (1984).
10. Y.L. Zheng, Y. Xu, and J.F. Lin, *Acta Pharm. Sin.*, **24**, 568 (1989).
11. K. Ujita, T. Fujita, Y. Takaishi, H. Tokuda, S. Nishino, and A. Iwashima, 39th Annual Meeting of the Japanese Society of Pharmacognosy, 1992, Tokyo, Abstract p. 58.
12. H. Itokawa, O. Shirota, K. Ichitsuka, H. Morita, and K. Takeya, *J. Nat. Prod.*, **56**, 1479 (1993).
13. R.L. Baxter, L. Crombie, D.J. Simmonds, and D.A. Whiting, *J. Chem. Soc., Perkin Trans. I*, 2972 (1979).
14. T. Yongqing, H. Guosheng, and M. Yongxiang, *Phytochemistry*, **32**, 458 (1993).
15. N. Harada and K. Nakanishi, "Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry," University Science Books, Mill Valley, CA, 1983.
16. G.M. Sheldrick, SHELXS-86, in; "Crystallographic Computing." Ed. by G.M. Sheldrick, C. Kruger, and R. Goddard, Oxford University Press, Oxford, UK, 1985, pp. 175–189.

Received 20 September 1993